Strategic Applications of Named Reactions in Organic Synthesis

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Strategic Applications of Named Reactions in Organic Synthesis

Background and Detailed Mechanisms

by

László Kürti and Barbara Czakó

UNIVERSITY OF PENNSYLVANIA

250 Named Reactions



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This book is dedicated to

Professor Madeleine M. Joullié

for her lifelong commitment

to mentoring graduate students

ABOUT THE AUTHORS



Barbara Czakó was born and raised in Hungary. She received her Diploma from Lajos Kossuth University in Debrecen, Hungary (now University of Debrecen). She obtained her Master of Science degree at University of Missouri-Columbia. Currently she is pursuing her Ph.D. degree in synthetic organic chemistry under the supervision of Professor Gary A. Molander at the University of Pennsylvania.

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Professor Peter Wipf (University of Pittsburgh)

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MAIN MENU

FOREWORD

This book on "Strategic Applications of Named Reactions in Organic Synthesis" is destined to become unusually useful, valuable, and influential for advanced students and researchers in the field. It breaks new ground in many ways and sets an admirable standard for the next generation of texts and reference works. Its virtues are so numerous there is a problem in deciding where to begin. My first impression upon opening the book was that the appearance of its pages is uniformly elegant and pleasing – from the formula graphics, to the print, to the layout, and to the logical organization and format. The authors employ four-color graphics in a thoughtful and effective way. All the chemical formulas are exquisitely drawn.

The book covers many varied and useful reactions for the synthesis of complex molecules, and in a remarkably clear, authoritative and balanced way, considering that only two pages are allocated for each. This is done with unusual rigor and attention to detail. Packed within each two-page section are historical background, a concise exposition of reaction mechanism and salient and/or recent applications. The context of each example is made crystal clear by the inclusion of the structure of the final synthetic target. The referencing is eclectic but extensive and up to date; important reviews are included.

The amount of information that is important for chemists working at the frontiers of synthesis to know is truly enormous, and also constantly growing. For a young chemist in this field, there is so much to learn that the subject is at the very least daunting. It would be well neigh impossible were it not for the efforts of countless authors of textbooks and reviews. This book represents a very efficient and attractive way forward and a model for future authors. If I were a student of synthetic chemistry, I would read this volume section by section and keep it close at hand for reference and further study.

I extend congratulations to László Kürti and Barbara Czakó for a truly fine accomplishment and a massive amount of work that made it possible. The scholarship and care that they brought to this task will be widely appreciated because they leap out of each page. I hope that this wonderful team will consider extending their joint venture to other regions of synthetic chemical space. Job well done!

E. J. Corey

January, 2005

INTRODUCTION

The field of chemical synthesis continues to amaze with its growing and impressive power to construct increasingly complex and diverse molecular architectures. Being the precise science that it is, this discipline often extends not only into the realms of technology, but also into the domains of the fine arts, for it engenders unparallel potential for creativity and imagination in its practice. Enterprises in chemical synthesis encompass both the discovery and development of powerful reactions and the invention of synthetic strategies for the construction of defined target molecules, natural or designed, more or less complex. While studies in the former area –synthetic methodology– fuel and enable studies in the latter –target synthesis– the latter field offers a testing ground for the former. Blending the two areas provides for an exciting endeavor to contemplate, experience, and watch. The enduring art of total synthesis, in particular, affords the most stringent test of chemical reactions, old and new, named and unnamed, while its overall reach and efficiency provides a measure of its condition at any given time. The interplay of total synthesis and its tools, the chemical reactions, is a fascinating subject whether it is written, read, or practiced.

This superb volume by László Kürti and Barbara Czakó demonstrates clearly the power and beauty of this blend of science and art. The authors have developed a standard two-page format for discussing each of their 250 selections whereby each named reaction is concisely introduced, mechanistically explained, and appropriately exemplified with highlights of constructions of natural products, key intermediates and other important molecules. These literature highlights are a real treasure trove of information and a joy to read, bringing each named reaction to life and conveying a strong sense of its utility and dynamism. The inclusion of an up-to-date reference listing offers a complete overview of each reaction at one's fingertips.

The vast wealth of information so effectively compiled in this colorful text will not only prove to be extraordinarily useful to students and practitioners of the art of chemical synthesis, but will also help facilitate the shaping of its future as it moves forward into ever higher levels of complexity, diversity and efficiency. The vitality of the enduring field of total synthesis exudes from this book, captivating the attention of the reader throughout. The authors are to be congratulated for the rich and lively style they developed and which they so effectively employed in their didactic and aesthetically pleasing presentations. The essence of the art and science of synthesis comes alive from the pages of this wonderful text, which should earn its rightful place in the synthetic chemist's library and serve as an inspiration to today's students to discover, invent and apply their own future named reactions. Our thanks are certainly due to László Kürti and Barbara Czakó for a splendid contribution to our science.

K.C. Nicolaou

January, 2005

PREFACE

Today's organic chemist is faced with the challenge of navigating his or her way through the vast body of literature generated daily. Papers and review articles are full of scientific jargon involving the description of methods, reactions and processes defined by the names of the inventors or by a well-accepted phrase. The use of so-called "named reactions" plays an important role in organic chemistry. Recognizing these named reactions and understanding their scientific content is essential for graduate students and practicing organic chemists.

This book includes some of the most frequently used named reactions in organic synthesis. The reactions were chosen on the basis of importance and utility in synthetic organic chemistry. Our goal is to provide the reader with an introduction that includes a detailed mechanism to a given reaction, and to present its use in recent synthetic examples. This manuscript is not a textbook in the classical sense: it does not include exercises or chapter summaries. However, by describing 250 named organic reactions and methods with an extensive list of leading references, the book is well-suited for independent or classroom study. On one hand, the compiled information for these indispensable reactions can be used for finding important articles or reviews on a given subject. On the other hand, it can also serve as supplementary material for the study of organic reaction mechanisms and synthesis.

This book places great emphasis on the presentation of the material. Drawings are presented accurately and with uniformity. Reactions are listed alphabetically and each named reaction is presented in a convenient two-page layout. On the first page, a brief introduction summarizes the use and importance of the reaction, including references to original literature and to all major reviews published after the primary reference. When applicable, leading references to modifications and theoretical studies are also given. The introduction is followed by a general scheme of the reaction and by a detailed mechanism drawn using a four-color code (red, blue, green and black) to ensure easy understanding. The mechanisms always reflect the latest evidence available for the given reaction. If the mechanism is unknown or debatable, references to the relevant studies are included. The second page contains 3 or 4 recent synthetic examples utilizing the pertinent named reaction. In most cases the examples are taken from a synthetic sequence leading to the total synthesis of an important molecule or a natural product. Some examples are taken from articles describing novel methodologies. The synthetic sequences are drawn using the four-color code, and the procedures are described briefly in 2-3 sentences. If a particular named reaction involves a complex rearrangement or the formation of a polycyclic ring system, numbering of the carbon-skeleton is included in addition to the four-color code. In the depicted examples, the reaction conditions as well as the ratio of observed isomers (if any) and the reported yields are shown. The target of

the particular synthetic effort is also illustrated with colors indicating where the intermediates reside in the final product.

The approach used in this book is also unique in that it emphasizes the clever use of many reactions that might otherwise have been overlooked.

The almost 10,000 references are indexed at the end of the book and include the title of the cited book, book section, chapter, journal or review article. The titles of seminal papers written in a foreign language were translated to English. The name of the author of a specific synthetic example was chosen as the one having an asterisk in the reference.

In order to make the book as user-friendly as possible, we have included a comprehensive list of abbreviations used in the text or drawings along with the structure of the protecting groups and reagents. Also in an appendix, the named organic reactions are grouped on the basis of their use in contemporary synthesis. Thus the reader can readily ascertain which named organic reactions effect the same synthetic transformations or which functional groups are affected by the use of a particular named reaction. Finally, an index is provided to allow rapid access to desired information based on keywords found in the text or the drawings.

László Kürti & Barbara Czakó

University of Pennsylvania

Philadelphia, PA

January 2005

IV. EXPLANATION OF THE USE OF COLORS IN THE SCHEMES AND TEXT

The book uses four colors (black, red, blue, and green) to depict the synthetic and mechanistic schemes and highlight certain parts of the text. In the "**Introduction**" and "**Mechanism**" sections of the text, the title named reaction/process is highlighted in blue and typed in italics:

> "The preparation of ketones *via* the C-alkylation of esters of 3-oxobutanoic acid (acetoacetic esters) is called the *acetoacetic ester synthesis*. Acetoacetic esters can be deprotonated at either the C2 or at both the C2 and C4 carbons, depending on the amount of base used."

All other named reactions/processes that are mentioned are typed in italics:

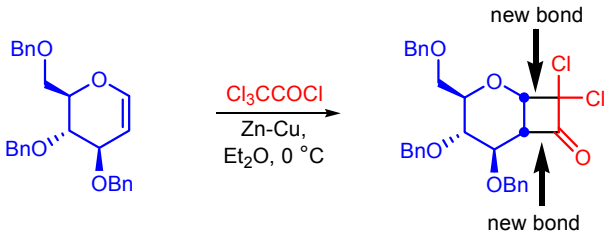
> "Dilute acid hydrolyzes the ester group, and the resulting β-keto acid undergoes decarboxylation to give a ketone (mono- or disubstituted acetone derivative), while aqueous base induces a *retro-Claisen reaction* to afford acids after protonation."

In the "**Synthetic Applications**" section, the name of the target molecule is highlighted in blue:

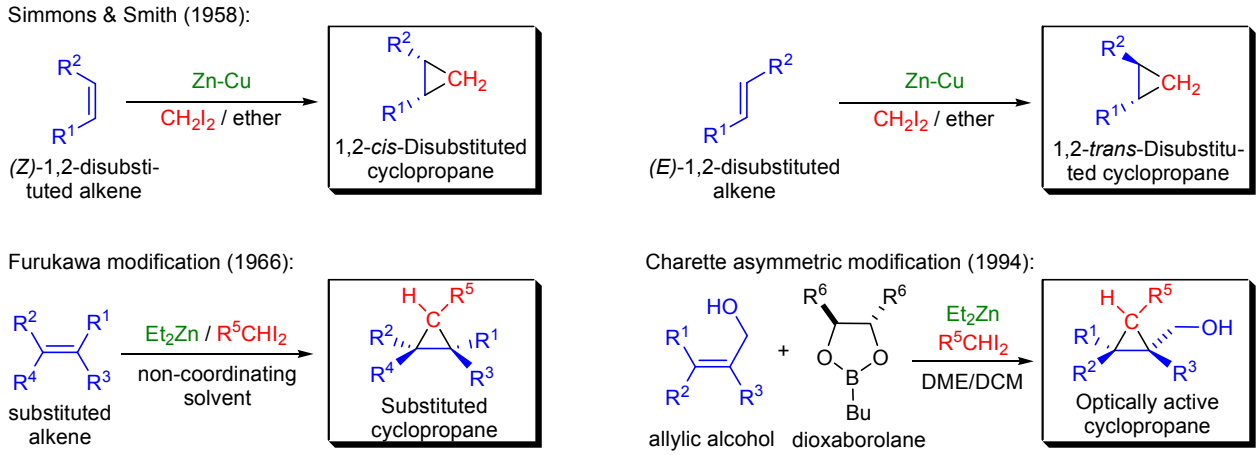
> "During the highly stereoselective total synthesis of epothilone B by J.D. White and co-workers, the stereochemistry of the alcohol portion of the macrolactone was established by applying *Davis's oxaziridine oxidation* of a sodium enolate."

In the schemes, colors are applied to highlight the changes in a given molecule or intermediate (formation and breaking of bonds). It is important to note that due to the immense diversity of reactions, it is impossible to implement a strictly unified use of colors. Therefore, **each scheme has a unique use of colors specifically addressing the given transformation**. By utilizing four different colors the authors' goal is to facilitate understanding. The authors hope that the readers will look up the cited articles and examine the details of a given synthesis. The following sample schemes should help the readers to understand how colors are used in this book.

- In most (but not all) schemes the starting molecule is colored blue, while the reagent or the reaction partner may be of any of the remaining two colors (red and green). **The newly formed bonds are always black**.



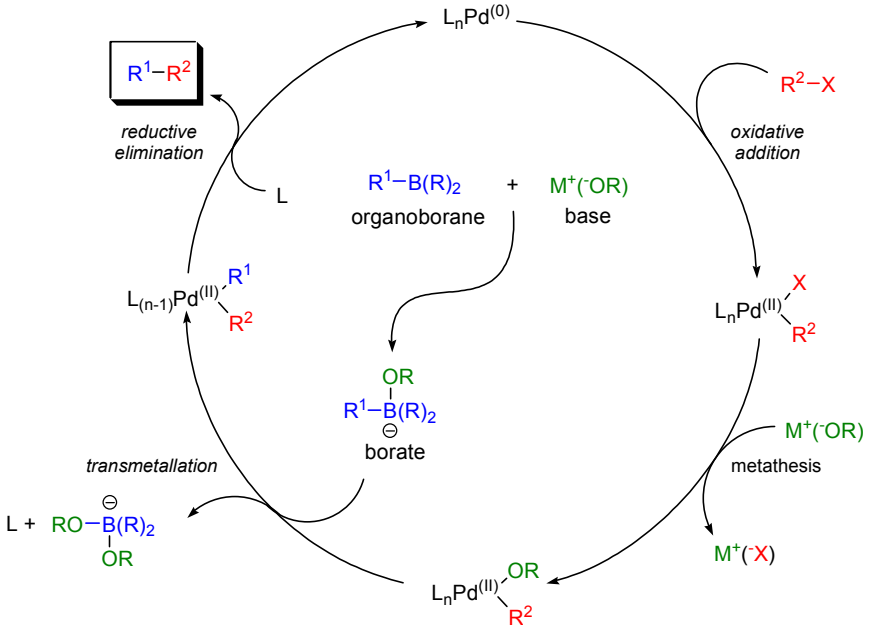
- The general schemes follow the same principle of coloring, and where applicable the same type of key reagents are depicted using the same color. (In this example the two different metal-derived reagents are colored green.)



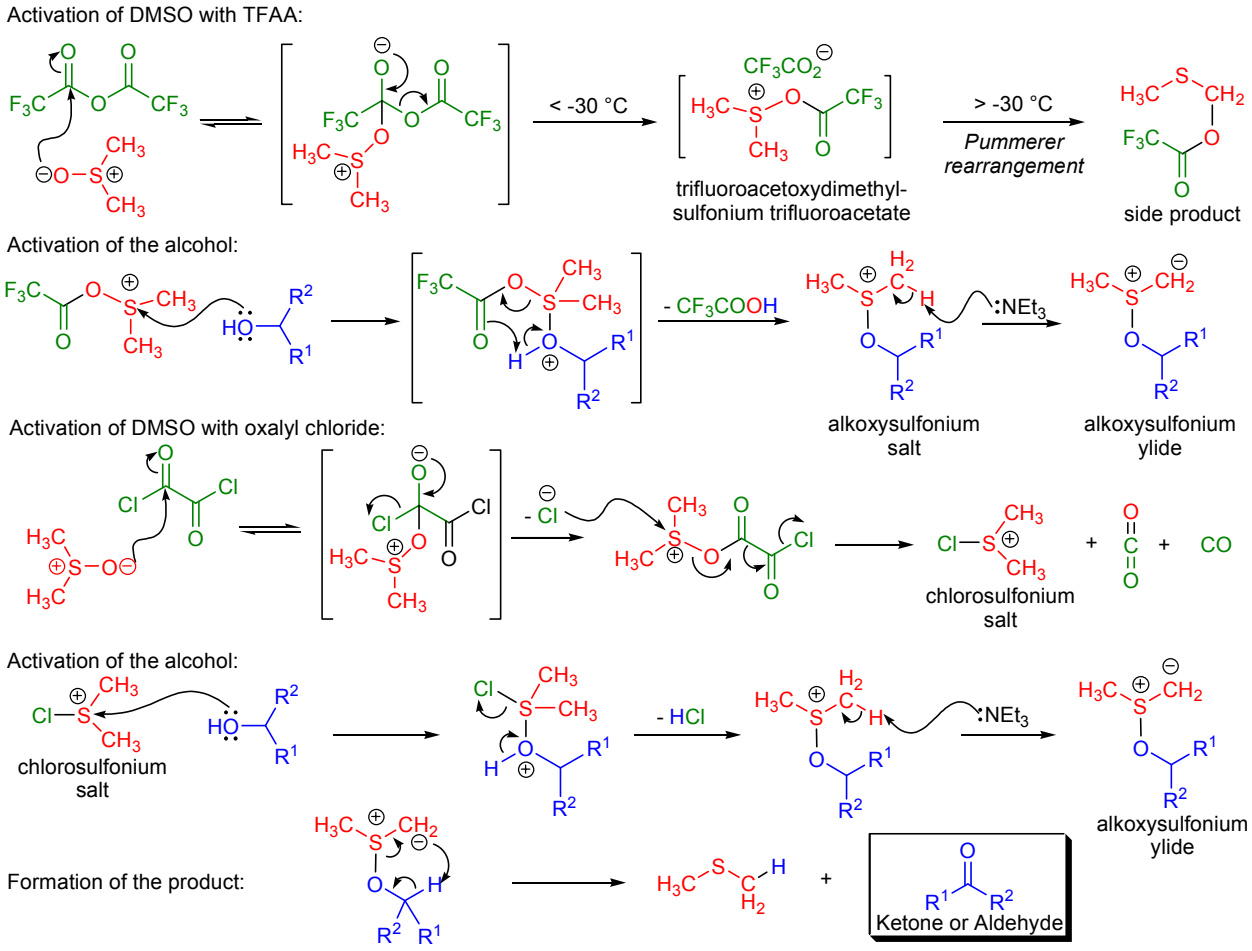
R^{1-4} = H, substituted alkyl and aryl; R^5 = H, Me, phenyl; R^6 = $CONMe_2$; non-coordinating solvent: toluene, benzene, DCM, DCE

- The mechanistic schemes benefit the most from the use of four colors. These schemes also include extensive arrow-pushing. The following two schemes demonstrate this point very well.

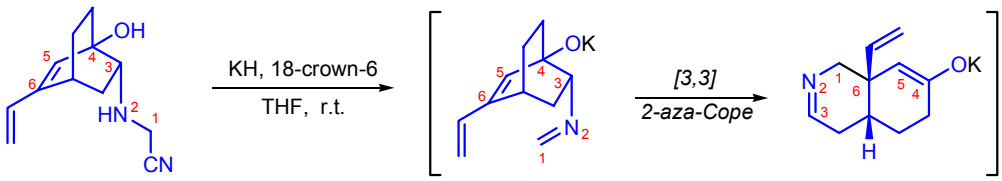
  - The catalytic cycle for the *Suzuki cross-coupling*:



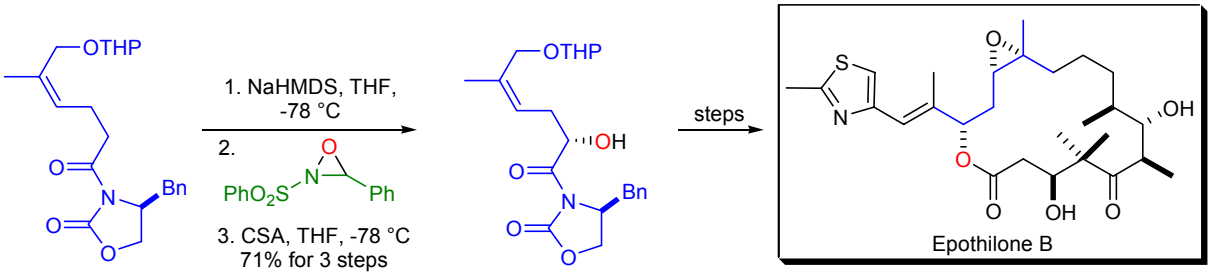
  - The mechanism of the *Swern oxidation*:



- In the case of complex rearrangements, numbering of the initial carbon skeleton has been applied in addition to the colors to facilitate understanding. Again, the newly formed bonds are black.



- In most instances, the product of a given named reaction/process will be part of a larger structure (e.g., natural product) at the end of the described synthetic effort. For pedagogical reasons, the authors decided to indicate where the building block appears in the target structure. It is the authors' hope that the reader will be able to put the named reaction/process in context and the provided synthetic example will not be just an abstract one.



- The references at the end of the book are listed in alphabetical order, and the named reaction for which the references are listed is typed in blue and with boldface (see *Dakin oxidation*). **Important: the references are listed in chronological order when they appear as superscript numbers in the text** (e.g., reference 10 is a more recent paper than reference 12, but it received a smaller reference number because it was cited in the text earlier).

Mechanism: [12,10,15-17]

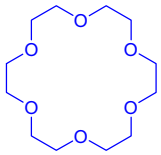
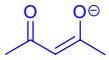
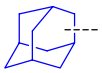
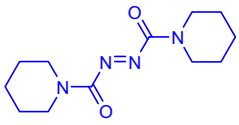
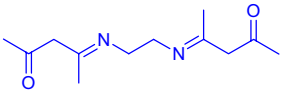
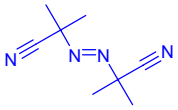
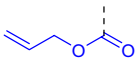
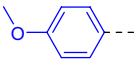
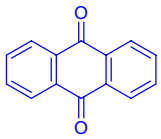
The mechanism of the *Dakin oxidation* is very similar to the mechanism of the *Baeyer-Villiger oxidation*.

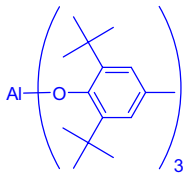
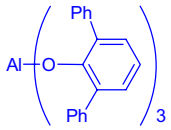
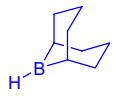
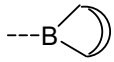
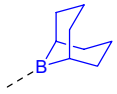
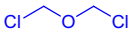
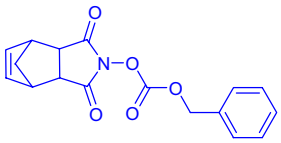
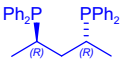
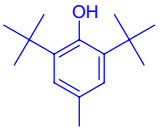
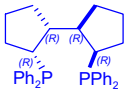
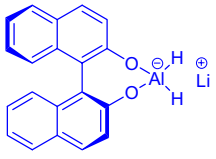
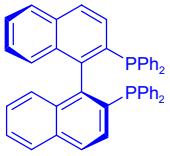
- For the *Dakin oxidation* example, the references at the end of the book will be printed in the order they have been cited, but within a group of references (e.g., 15-17) they appear in chronological order.

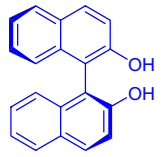
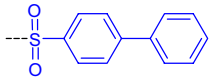
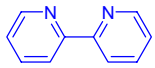
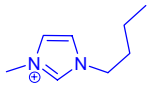
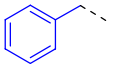
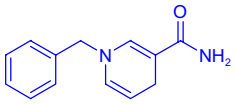
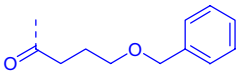
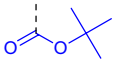
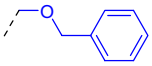
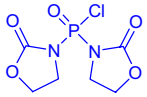
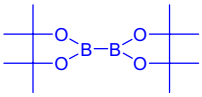
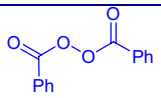
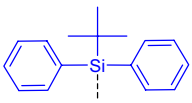
Dakin oxidation

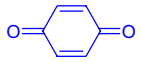
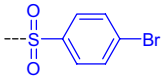
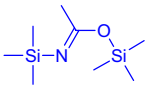
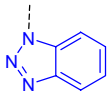
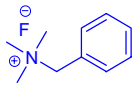
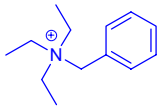
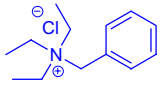
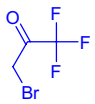
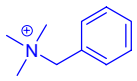
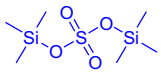
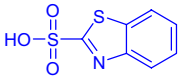
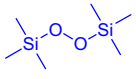
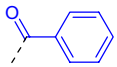
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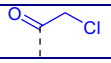
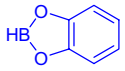
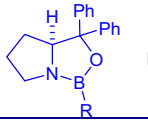
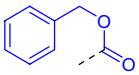
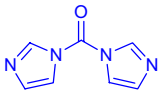
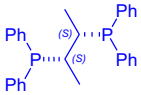
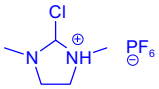
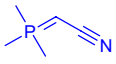
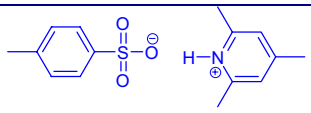
V. LIST OF ABBREVIATIONS

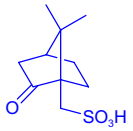
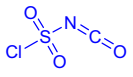
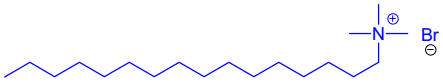
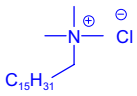
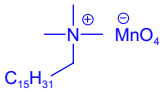
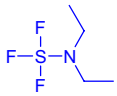
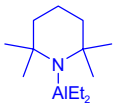
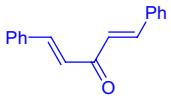
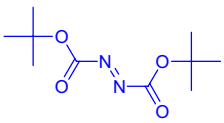
Abbreviation	Chemical Name	Chemical Structure
18-Cr-6	18-crown-6	
Ac	acetyl	
acac	acetylacetonyl	
AA	asymmetric aminohydroxylation	NA
AD	asymmetric dihydroxylation	NA
ad	adamantyl	
ADDP	1,1'-(azodicarbonyl)dipiperidine	
ADMET	acyclic diene metathesis polymerization	NA
acaen	*N,N'-bis*(1-methyl-3-oxobutylidene)ethylenediamine	
AIBN	2,2'-azo *bis*isobutyronitrile	
Alloc	allyloxycarbonyl	
Am	amyl (*n*-pentyl)	
An	*p*-anisyl	
ANRORC	anionic ring-opening ring-closing	NA
aq	aqueous	NA
AQN	anthraquinone	
Ar	aryl (substituted aromatic ring)	NA

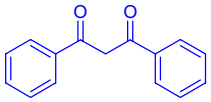
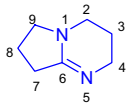
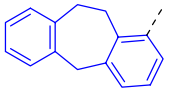
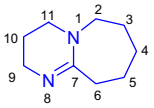
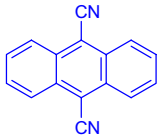
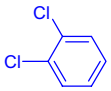
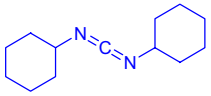
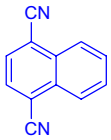
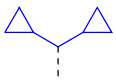
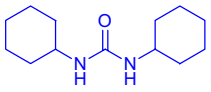
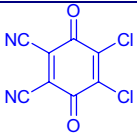
Abbreviation	Chemical Name	Chemical Structure
ATD	aluminum tris(2,6-*di*-*tert*-butyl-4-methylphenoxide)	
atm	1 atmosphere = 10^5 Pa (pressure)	NA
ATPH	aluminum tris(2,6-diphenylphenoxide)	
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)	
	9-borabicyclo[3.3.1]nonyl	
BCME	*bis*(chloromethyl)ether	
BCN	*N*-benzyloxycarbonyloxy-5-norbornene-2,3-dicarboxiimide	
BDPP	(2*R*, 4*R*) or (2*S*, 4*S*) *bis*(diphenylphosphino)pentane	
BER	borohydride exchange resin	NA
BHT	2,6-*di*-*t*-butyl-*p*-cresol (butylated hydroxytoluene)	
BICP	2(*R*)-2'(*R*)-*bis*(dipenylphosphino)-1(*R*),1'(*R*)-dicyclopentane	
BINAL-H	2,2'-dihydroxy-1,1'-binaphthyl lithium aluminum hydride	
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl	

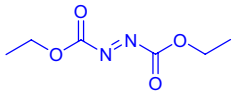
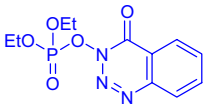
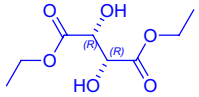
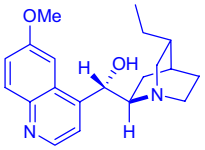
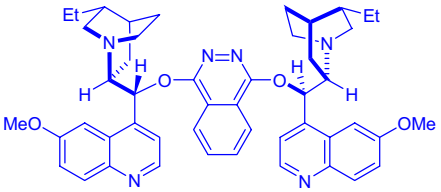
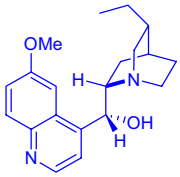
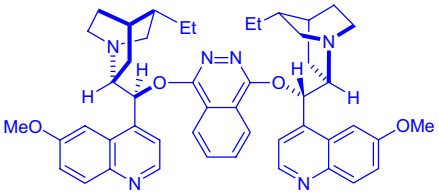
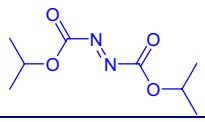
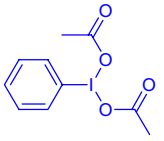
Abbreviation	Chemical Name	Chemical Structure
BINOL	1,1'-bi-2,2'-naphthol	
Bip	biphenyl-4-sulfonyl	
bipy	2,2'-bipyridyl	
BLA	Brönsted acid assisted chiral Lewis acid	NA
bmin	1-butyl-3-methylimidazolium cation	
BMS	Borane-dimethyl sulfide complex	$H_3B \cdot SMe_2$
Bn	benzyl	
BNAH	1-benzyl-1,4-dihydronicotinamide	
BOB	4-benzyloxybutyryl	
Boc	*t*-butoxycarbonyl	
BOM	benzyloxymethyl	
BOP-Cl	*bis*(2-oxo-3-oxazolidinyl)phosphinic chloride	
bp	boiling point	NA
BPD	*bis*(pinacolato)diboron	
BPO	benzoyl peroxide	
BPS (TBDPS)	*t*-butyldiphenylsilyl	

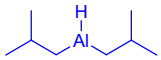
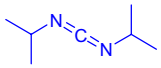
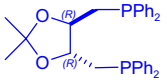
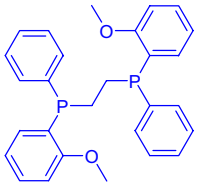
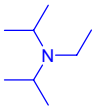
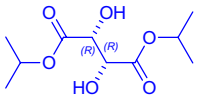
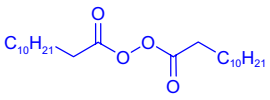
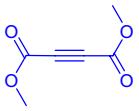
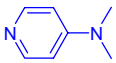
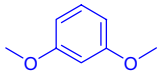
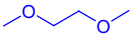
Abbreviation	Chemical Name	Chemical Structure
BQ	benzoquinone	
Bs	brosyl = (4-bromobenzenesulfonyl)	
BSA	*N,O-bis*(trimethylsilyl)acetamide	
BSA	Bovine serum albumin	NA
Bt	1- or 2-benzotriazolyl	
BTAF	benzyltrimethylammonium fluoride	
BTEA	benzyltriethylammonium	
BTEAC	benzyltriethylammonium chloride	
BTFP	3-bromo-1,1,1-trifluoro-propan-2-one	
BTMA	benzyltrimethylammonium	
BTMSA	*bis*(trimethylsilyl) acetylene	
BTS	*bis*(trimethylsilyl) sulfate	
BTSA	benzothiazole 2-sulfonic acid	
BTSP	*bis*(trimethylsilyl) peroxide	
Bz	benzoyl	
Bu (^{n}Bu)	*n*-butyl	
c	cyclo	NA

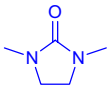
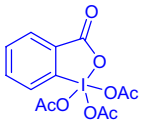
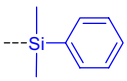
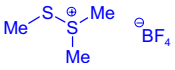
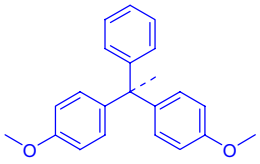
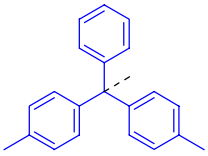
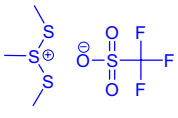
Abbreviation	Chemical Name	Chemical Structure
ca	circa (approximately)	NA
CA	chloroacetyl	
CAN	cerium(IV) ammonium nitrate (cericammonium nitrate)	$Ce(NH_4)_2(NO_3)_6$
cat.	catalytic	NA
CB	catecholborane	
CBS	Corey-Bakshi-Shibata reagent	 R = H, alkyl
Cbz (Z)	benzyloxycarbonyl	
cc. or conc.	concentrated	NA
CCE	constant current electrolysis	NA
CDI	carbonyl diimidazole	
CHD	1,3 or 1,4-cyclohexadiene	 1,3-CHD 1,4-CHD
CHIRAPHOS	2,3-*bis*(diphenylphosphino)butane	
Chx (Cy)	cyclohexyl	
CIP	2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate	
CM (XMET)	cross metathesis	NA
CMMP	cyanomethylenetrimethyl phosphorane	
COD	1,5-cyclooctadiene	
COT	1,3,5-cyclooctatriene	
Cp	cyclopentadienyl	
CPTS	collidinium-*p*-toluenesulfonate	

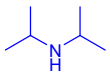
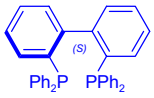
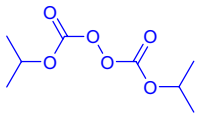
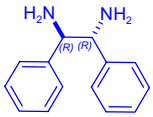
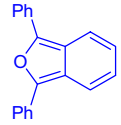
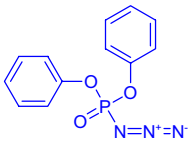
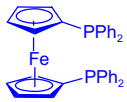
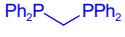
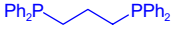
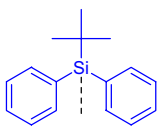
Abbreviation	Chemical Name	Chemical Structure
CRA	complex reducing agent	NA
Cr-PILC	chromium-pillared clay catalyst	NA
CSA	camphorsufonic acid	
CSI	chlorosulfonyl isocyanate	
CTAB	cetyl trimethylammonium bromide	
CTACl	cetyl trimethylammonium chloride	
CTAP	cetyl trimethylammonium permanganate	
Δ	heat	NA
d	days (length of reaction time)	NA
DABCO	1,4-diazabicyclo[2.2.2]octane	
DAST	diethylaminosulfur trifluoride	
DATMP	diethylaluminum 2,2,6,6-tetramethylpiperidide	
DBA (dba)	dibenzylideneacetone	
DBAD	*di-tert*-butylazodicarboxylate	
DBI	dibromoisocyanuric acid	

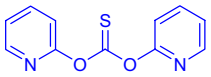
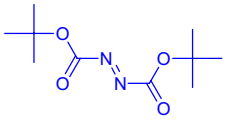
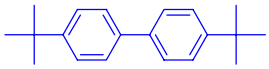
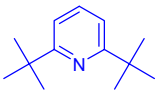
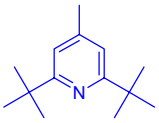
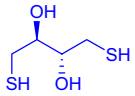
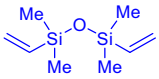
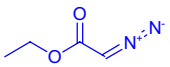
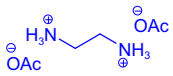
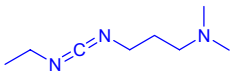
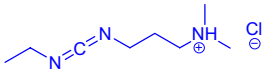
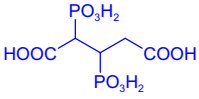
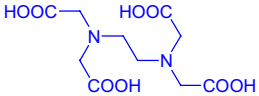
Abbreviation	Chemical Name	Chemical Structure
DBM	dibenzoylmethane	
DBN	1,5-diazabicyclo[4.3.0]non-5-ene	
DBS	dibenzosuberyl	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
DCA	9,10-dicyanoanthracene	
DCB	1,2-dichlorobenzene	
DCC	dicyclohexylcarbodiimide	
DCE	1,1-dichloroethane	
DCM	dichloromethane	CH_2Cl_2
DCN	1,4-dicyanonaphthalene	
Dcpm	dicyclopropylmethyl	
DCU	*N,N'*-dicyclohexylurea	
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	
de	diastereomeric excess	NA

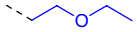
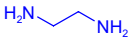
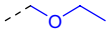
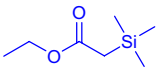
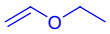
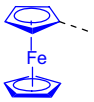
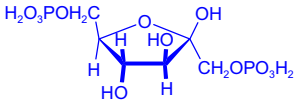
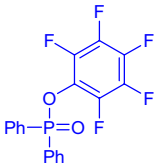
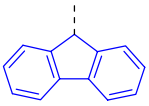
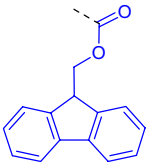
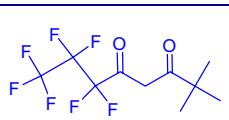
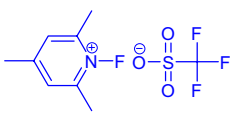
Abbreviation	Chemical Name	Chemical Structure
DEAD	diethyl azodicarboxylate	
DEIPS	diethylisopropylsilyl	
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one	
DET	diethyl tartrate	
DHP	3,4-dihydro-2*H*-pyran	
DHQ	dihydroquinine	
$(DHQ)_2PHAL$	*bis*(dihydroquinino)phthalazine	
DHQD	dihydroquinidine	
$(DHQD)_2PHAL$	*bis*(dihydroquinidino)phthalazine	
DIAD	diisopropyl azodicarboxylate	
DIB (BAIB or PIDA)	(diacetoxyiodo)benzene	

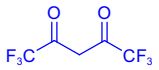
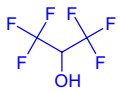
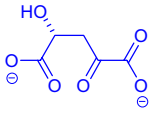
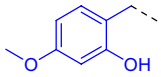
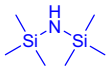
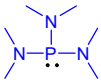
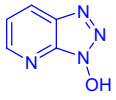
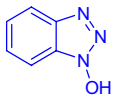
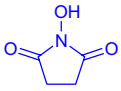
Abbreviation	Chemical Name	Chemical Structure
DIBAL (DIBAH) DIBAL-H	diisobutylaluminum hydride	
DIC	diisopropyl carbodiimide	
diop	4,5-*bis*-[(diphenylphosphanyl)methyl]-2,2-dimethyl-[1,3]dioxolane	
DIPAMP	1,2-*bis*(*o*-anisylphenylphosphino)ethane	
DIPEA (Hünig's base)	diisopropylethylamine	
DIPT	diisopropyl tartrate	
DLP	dilauroyl peroxide	
DMA (DMAC)	*N,N*-dimethylacetamide	
DMAD	dimethyl acetylene dicarboxylate	
DMAP	*N,N*-4-dimethylaminopyridine	
DMB	*m*-dimethoxybenzene	
DMDO	dimethyl dioxirane	
DME	1,2-dimethoxyethane	

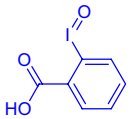
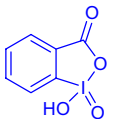
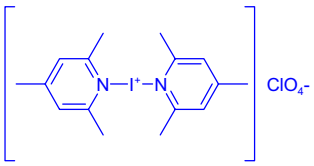
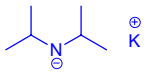
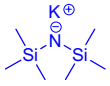
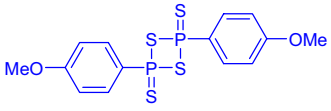
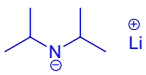
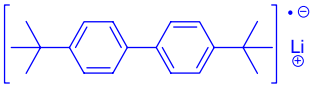
Abbreviation	Chemical Name	Chemical Structure
DMF	*N,N*-dimethylformamide	
DMI	1,3-dimethylimidazolidin-2-one	
DMP	Dess-Martin periodinane	
DMPS	dimethylphenylsilyl	
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (*N,N*-dimethyl propylene urea)	
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate	
DMS	dimethylsulfide	
DMSO	dimethylsulfoxide	
DMT	4,4'-dimethoxytrityl	
DMTMM	4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride	
DMTr	4,4'-dimethyltrityl	
DMTST	(dimethylthio)methylsulfonium trifluoromethanesulfonate	
DNA	deoxyribonucleic acid	NA

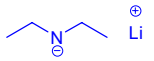
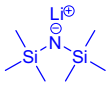
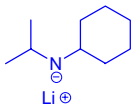
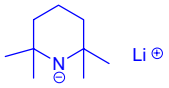
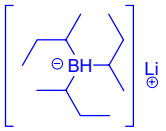
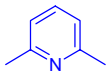
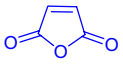
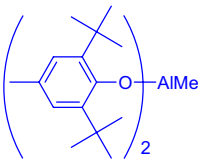
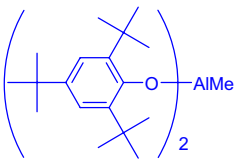
Abbreviation	Chemical Name	Chemical Structure
DPA (DIPA)	diisopropylamine	
DPBP	2,2'-*bis*(diphenylphosphino)biphenyl	
DPDC	diisopropyl peroxydicarbonate	
DPDM	diphenyl diazomethane	
DPEDA	1,2-diamino-1,2-diphenylethane	
DPIBF	diphenylisobenzofuran	
DPPA	diphenylphosphoryl azide (diphenylphosphorazidate)	
Dppb (ddpb)	1,4-*bis*(diphenylphosphino)butane	
dppe	1,2-*bis*(diphenylphosphino)ethane	
dppf	1,1'-*bis*(diphenylphosphino)ferrocene	
dppm	*bis*(diphenylphosphino)methane	
dppp	1,3-*bis*(diphenylphosphino)propane	
DPS (also TBDPS or BPS)	*t*-butyldiphenylsilyl	

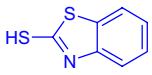
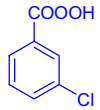
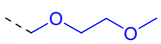
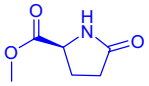
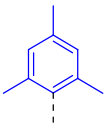
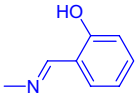
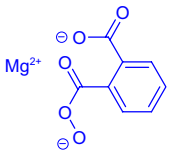
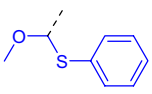
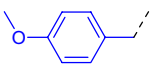
Abbreviation	Chemical Name	Chemical Structure
DPTC	*O,O'*-di(2'-pyridyl)thiocarbonate	
dr	diastereomeric ratio	NA
DTBAD (DBAD)	*di-tert*-butyl azodicarboxylate	
DTBB	4,4'-*di-tert*-butylbiphenyl	
DTBP	2,6-*di-tert*-butylpyridine	
DTBMP	2,6-*di-tert*-butyl-4-methylpyridine	
DTE	1,4-dithioerythritol	
DVS	1,3-divinyl-1,1,3,3-tetramethyldisiloxane	
E^+	electrophile (denotes any electrophile in general)	NA
E2	bimolecular elimination	NA
ED	effective dosage	NA
EDA	ethyl diazoacetate	
EDDA	ethylenediamine diacetate	
EDC (EDAC)	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (ethyldimethylaminopropylcarbodiimide)	
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride	
EDCP	2,3-*bis*-phosphonopentanedioic acid (ethylene dicarboxylic 2,3-diphosphonic acid)	
EDG	electron-donating group	NA
EDTA	ethylenediamine tetraacetic acid	

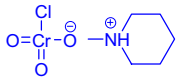
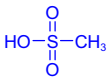
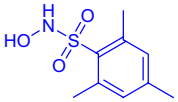
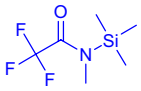
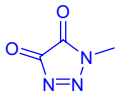
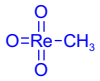
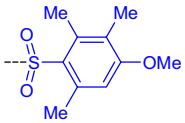
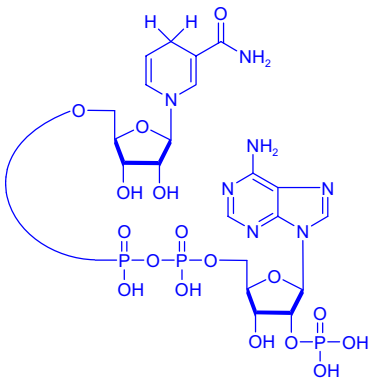
Abbreviation	Chemical Name	Chemical Structure
ee	enantiomeric excess	NA
EE	ethoxyethyl	
E_i	intramolecular *syn* elimination	NA
en	ethylenediamine	
EOM	ethoxymethyl	
ESR	electron spin resonance (spectroscopy)	NA
Et	ethyl	
ETSA	ethyl trimethylsilylacetate	
EVE	ethyl vinyl ether	
EWG	electron-withdrawing group	NA
Fc	ferrocenyl	
FDP	fructose-1,6-diphosphate	
FDPP	pentafluorophenyl diphenylphosphinate	
Fl	fluorenyl	
FMO	frontier molecular orbital (theory)	NA
Fmoc	9-fluorenylmethoxycarbonyl	
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione	
fp	flash point	NA
FSM	Mesoporous silica	NA
FTT	1-fluoro-2,4,6-trimethylpyridinium triflate	

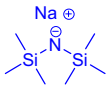
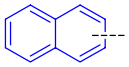
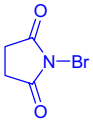
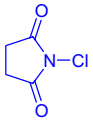
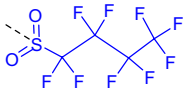
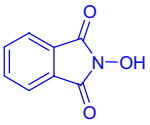
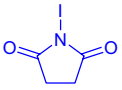
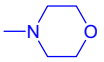
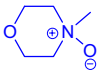
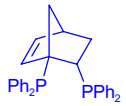
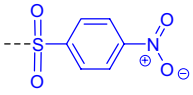
Abbreviation	Chemical Name	Chemical Structure
FVP	flash vacuum pyrolysis	NA
GEBC	gel entrapped base catalyst	NA
h	hours (length of reaction time)	NA
hν	irradiation with light	NA
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate	
Het	heterocycle	NA
hfacac	hexafluoroacetylacetone	
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol (hexafluoroisopropanol)	
HGK	4-hydroxy-2-ketoglutarate	
Hgmm	millimeter of mercury (760 Hgmm = 1 atm = 760 Torr)	NA
HLE	horse liver esterase	NA
Hmb	2-hydroxy-4-methoxybenzyl	
HMDS	1,1,1,3,3,3-hexamethyldisilazane	
HMPA	hexamethylphosphoric acid triamide (hexamethylphosphoramide)	
HMPT	hexamethylphosphorous triamide	
HOAt	1-hydroxy-7-azabenzotriazole	
HOBt (HOBT)	1-hydroxybenzotriazole	
HOMO	highest occupied molecular orbital	NA
HOSu	*N*-hydroxysuccinimide	
HPLC	high-pressure liquid chromatography	NA
HWE	Horner-Wadsworth-Emmons	NA
i	iso	NA

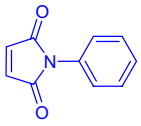
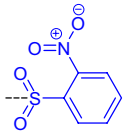
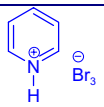
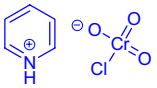
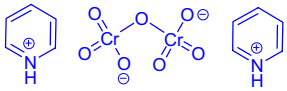
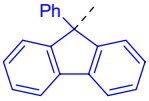
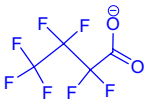
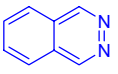
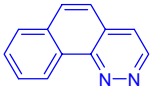
Abbreviation	Chemical Name	Chemical Structure
IBA	2-iodosobenzoic acid	
IBX	*o*-iodoxybenzoic acid	
IDCP	*bis*(2,4,6-collidine)iodonium perchlorate	
Imid (Im)	imidazole	
INOC	intramolecular nitrile oxide cycloaddition	NA
IPA	isopropyl alcohol	
Ipc	isopinocamphenyl	
IR	infrared spectroscopy	NA
K-10	a type of Montmorillonite clay	NA
KDA	potassium diisopropylamide	
KHMDS	potassium *bis*(trimethylsilyl)amide	
KSF	a type of Montmorillonite clay	NA
L	ligand	NA
L.R.	Lawesson's reagent (2,4-*bis*-(4-methoxyphenyl)-[1,3,2,4]dithiadiphosphetane 2,4-dithion)	
LA	Lewis acid	NA
LAB	lithium amidotrihydroborate	LiH_2NBH_3
LAH	lithium aluminum hydride	$LiAlH_4$
LD_{50}	dose that is lethal to 50% of the test subjects (cells, animals, humans etc.)	NA
LDA	lithium diisopropylamide	
LDBB	lithium 4,4'-*t*-butylbiphenylide	

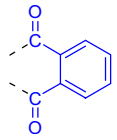
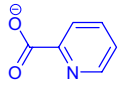
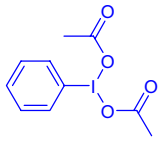
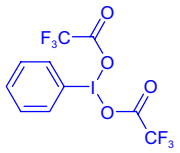
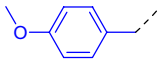
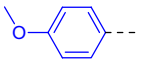
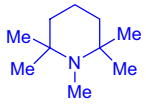
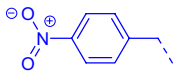
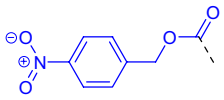
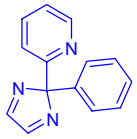
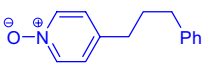
Abbreviation	Chemical Name	Chemical Structure
LDE	lithium diethylamide	
LDPE	lithium perchlorate-diethyl etherate	$LiClO_4$ - Et_2O
LHMDS (LiHMDS)	lithium *bis*(trimethylsilyl)amide	
LICA	lithium isopropylcyclohexylamide	
LICKOR (super base)	butyllithium-potassium *tert*-butoxide	BuLi - KO*t*-Bu
liq.	liquid	NA
LiTMP (LTMP)	lithium 2,2,6,6-tetramethylpiperidide	
LPT	lithium pyrrolidotrihydroborate (lithium pyrrolidide-borane)	$Li(CH_2)_4NBH_3$
L-selectride	lithium tri-*sec*-butylborohydride	
LTA	lead tetraacetate	$Pb(OAc)_4$
LUMO	lowest unoccupied molecular orbital	NA
lut	2,6-lutidine	
m	meta	NA
MA	maleic anhydride	
MAD	methyl aluminum *bis*(2,6-di-*t*-butyl-4-methylphenoxide)	
MAT	methyl aluminum *bis*(2,4,6-tri-*t*-butylphenoxide)	

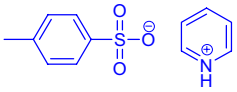
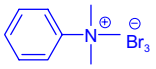
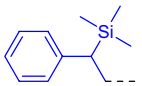
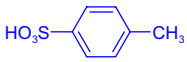
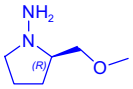
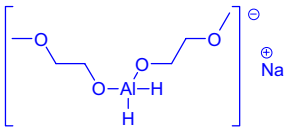
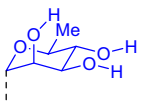
Abbreviation	Chemical Name	Chemical Structure
MBT	2-mercaptobenzothiazole	
***m*-CPBA**	*meta* chloroperbenzoic acid	
Me	methyl	
MEM	(2-methoxyethoxy)methyl	
MEPY	methyl 2-pyrrolidone-5(*S*)-carboxylate	
Mes	mesityl	
mesal	*N*-methylsalicylaldimine	
MIC	methyl isocyanate	
MMPP (MMPT)	magnesium monoperoxyphthalate	
MOM	methoxymethyl	
MoOPH	oxodiperoxomolybdenum(pyridine)-(hexamethylphosphoric triamide)	NA
mp	melting point	NA
MPa	megapascal = 10^6 Pa = 10 atm (pressure)	
MPD (NMP)	N-methyl-2-pyrrolidinone	
MPM	methoxy(phenylthio)methyl	
MPM (PMB)	*p*-methoxybenzyl	

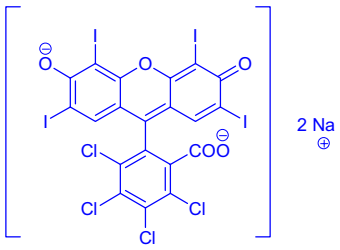
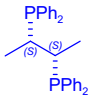
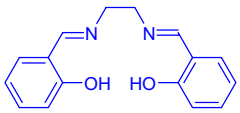
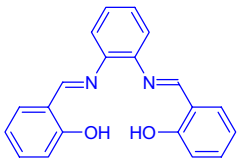
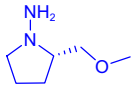
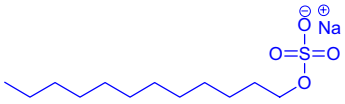
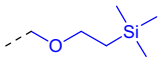
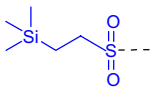
Abbreviation	Chemical Name	Chemical Structure
MPPC	*N*-methyl piperidinium chlorochromate	
Ms	mesyl (methanesulfonyl)	
MS	mass spectrometry	NA
MS	molecular sieves	NA
MSA	methanesulfonic acid	
MSH	*o*-mesitylenesulfonyl hydroxylamine	
MSTFA	*N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide	
MTAD	*N*-methyltriazolinedione	
MTEE (MTBE)	methyl *t*-butyl ether	
MTM	methylthiomethyl	
MTO	methyltrioxorhenium	
Mtr	(4-methoxy-2,3,6-trimethylphenyl)sulfonyl	
MVK	methyl vinyl ketone	
mw	microwave	NA
n	normal (e.g. unbranched alkyl chain)	NA
NADPH	nicotinamide adenine dinucleotide phosphate	

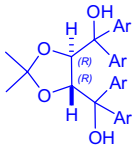
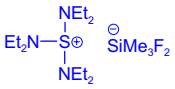
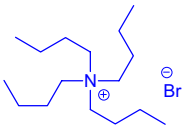
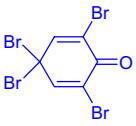
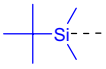
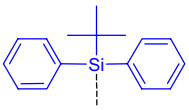
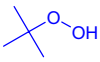
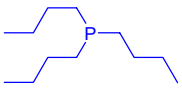
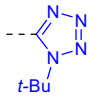
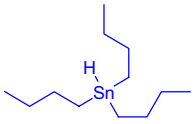
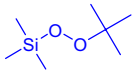
Abbreviation	Chemical Name	Chemical Structure
NaHMDS	sodium *bis*(trimethylsilyl)amide	
Naph (Np)	naphthyl	
NBA	*N*-bromoacetamide	
NBD (nbd)	norbornadiene	
NBS	*N*-bromosuccinimide	
NCS	*N*-chlorosuccinimide	
N_f	nonafluorobutanesulfonyl	
NHPI	*N*-hydroxyphthalimide	
NIS	*N*-iodosuccinimide	
NMM	*N*-methylmorpholine	
NMO	*N*-methylmorpholine oxide	
NMP	*N*-methyl-2-pyrrolidinone	
NMR	nuclear magnetic resonance	NA
NORPHOS	*bis*(diphenylphosphino)bicyclo[2.2.1]-hept-5-ene	
Nos	4-nitrobenzenesulfonyl	

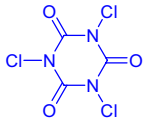
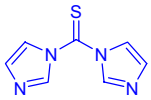
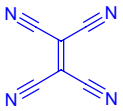
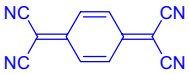
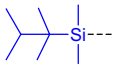
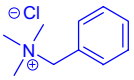
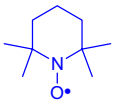
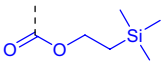
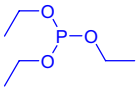
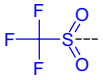
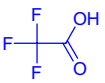
Abbreviation	Chemical Name	Chemical Structure
NPM	*N*-phenylmaleimide	
NR	no reaction	NA
Ns	2-nitrobenzenesulfonyl	
NSAID	non steroidal anti-inflammatory drug	NA
Nuc	nucleophile (general)	NA
o	ortho	NA
Oxone	potassium peroxymonosulfate	$KHSO_5$
p	para	NA
PAP	2,8,9-trialkyl-2,5,8,9-tetraaza-1-phospha-bicyclo[3.3.3]undecane	
PBP	pyridinium bromide perbromide	
PCC	pyridinium chlorochromate	
PDC	pyridinium dichromate	
PEG	polyethylene glycol	NA
Pf	9-phenylfluorenyl	
pfb	perfluorobutyrate	
Ph	phenyl	
PHAL	phthalazine	
phen	9,10-phenanthroline	

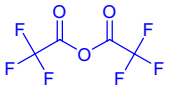
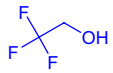
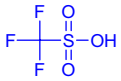
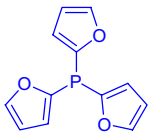
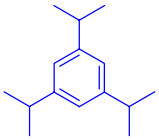
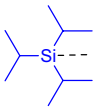
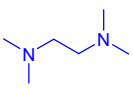
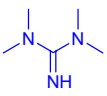
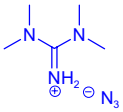
Abbreviation	Chemical Name	Chemical Structure
Phth	phthaloyl	
pic	2-pyridinecarboxylate	
PIDA (BAIB or DIB)	phenyliodonium diacetate	
PIFA	phenyliodonium *bis*(trifluoroacetate)	
Piv	pivaloyl	
PLE	pig liver esterase	NA
PMB (MPM)	*p*-methoxybenzyl	
PMP	4-methoxyphenyl	
PMP	1,2,2,6,6-pentamethylpiperidine	
PNB	*p*-nitrobenzyl	
PNZ	*p*-nitrobenzyloxycarbonyl	
PPA	polyphosphoric acid	NA
PPI	2-phenyl-2-(2-pyridyl)-2*H*-imidazole	
PPL	pig pancreatic lipase	NA
PPO	4-(3-phenylpropyl)pyridine-N-oxide	
PPSE	polyphosphoric acid trimethylsilyl ester	NA

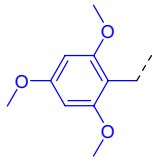
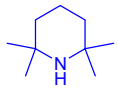
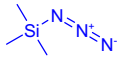
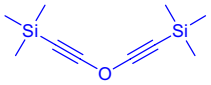
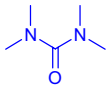
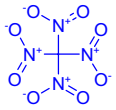
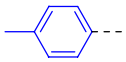
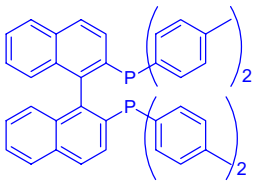
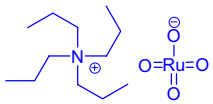
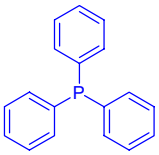
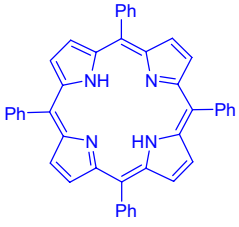
Abbreviation	Chemical Name	Chemical Structure
PPTS	pyridinium *p*-toluenesulfonate	
Pr	propyl	
psi	pounds per square inch	NA
PT	1-phenyl-1*H*-tetrazol-yl	
P.T.	proton transfer	NA
PTAB	phenyltrimethylammonium perbromide	
PTC	Phase transfer catalyst	NA
PTMSE	(2-phenyl-2-trimethylsilyl)ethyl	
PTSA (or TsOH)	*p*-toluenesulfonic acid	
PVP	poly(4-vinylpyridine)	NA
Py (pyr)	pyridine	
r.t.	room temperature	NA
rac	racemic	NA
RAMP	(*R*)-1-amino-2-(methoxymethyl)pyrrolidine	
RaNi	Raney nickel	NA
RB	Rose Bengal	See Rose bengal
RCAM	ring-closing alkyne metathesis	NA
RCM	ring-closing metathesis	NA
Rds (or RDS)	rate-determining step	NA
Red-Al	sodium *bis*(2-methoxyethoxy) aluminum hydride	
Rham	rhamnosyl	
R_f	perfluoroalkyl group	
R_f	retention factor in chromatography	NA
ROM	ring-opening metathesis	NA
ROMP	ring-opening metathesis polymerization	NA

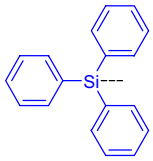
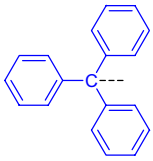
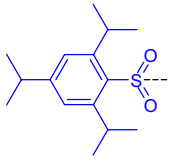
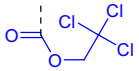
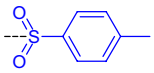
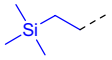
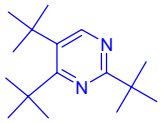
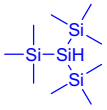
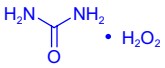
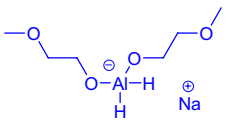
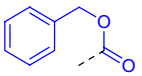
Abbreviation	Chemical Name	Chemical Structure
Rose Bengal (RB)	2,4,5,7-tetraiodo-3',4',5',6'-tetrachlorofluorescein disodium salt (a photosensitizer)	
s	seconds (length of reaction time)	NA
S,S,-chiraphos	(*S,S*)-2,3-*bis*(diphenylphosphino)butane	
Salen	*N,N'*-ethylene*bis*(salicylideneiminato) *bis*(salicylidene)ethylenediamine	
salophen	*o*-phenylene*bis*(salicylideneiminato)	
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrrolidine	
SC CO_2	supercritical carbon-dioxide	NA
SDS	sodium dodecylsulfate	
sec	secondary	NA
SEM	2-(trimethylsilyl)ethoxymethyl	
SES	2-[(trimethylsilyl)ethyl]sulfonyl	
SET	single electron transfer	NA
Sia	1,2-dimethylpropyl (secondary isoamyl)	
SPB	sodium perborate	

Abbreviation	Chemical Name	Chemical Structure
TADDOL	2,2-dimethyl-α,α,α^1, α^1-tetraaryl-1,3-dioxolane-4,5-dimethanol	
TASF	tris(diethylamino)sulfonium difluorotrimethylsilicate	
TBAB	tetra-*n*-butylammonium bromide	
TBAF	tetra-*n*-butylammonium fluoride	
TBAI	tetra-*n*-butylammonium iodide	
TBCO	tetrabromocyclohexadienone	
TBDMS (TBS)	*t*-butyldimethylsilyl	
TBDPS (BPS)	*t*-butyldiphenylsilyl	
TBH	*tert*-butyl hypochlorite	
TBHP	*tert*-butyl hydroperoxide	
TBP	tributylphosphine	
TBT	1-*tert*-butyl-1*H*-tetrazol-5-yl	
TBTH	tributyltin hydride	
TBTSP	*t*-butyl trimethylsilyl peroxide	

Abbreviation	Chemical Name	Chemical Structure
TCCA	trichloroisocyanuric acid	
TCDI	thiocarbonyl diimidazole	
TCNE	tetracyanoethylene	
TCNQ	7,7,8,8-tetracyano-para-quinodimethane	
TDS	dimethyl thexylsilyl	
TEA	triethylamine	
TEBACl	benzyl trimethylammonium chloride	
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical	
Teoc	2-(trimethylsilyl)ethoxycarbonyl	
TEP	triethylphosphite	
TES	triethylsilyl	
Tf	trifluoromethanesulfonyl	
TFA	trifluoroacetic acid	
Tfa	trifluoroacetamide	

Abbreviation	Chemical Name	Chemical Structure
TFAA	trifluoroacetic anhydride	
TFE	2,2,2-trifluoroethanol	
TFMSA	trifluoromethanesulfonic acid (triflic acid)	
TFP	tris(2-furyl)phosphine	
Th	2-thienyl	
thexyl	1,1,2-trimethylpropyl	
THF	tetrahydrofuran	
THP	2-tetrahydropyranyl	
TIPB	1,3,5-tri*iso*propylbenzene	
TIPS	triisopropylsilyl	
TMAO (TMANO)	trimethylamine *N*-oxide	
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine	
TMG	1,1,3,3-tetramethylguanidine	
TMGA	tetramethylguanidinium azide	

Abbreviation	Chemical Name	Chemical Structure
Tmob	2,4,6-trimethoxybenzyl	
TMP	2,2,6,6-tetramethylpiperidine	
TMS	trimethylsilyl	
TMSA	trimethylsilyl azide	
TMSEE	(trimethylsilyl)ethynyl ether	
TMU	tetramethylurea	
TNM	tetranitromethane	
Tol	*p*-tolyl	
tolbinap	2,2'-*bis*(di-*p*-tolylphosphino)-1,1'-binaphthyl	
TPAP	tetra-*n*-propylammonium perruthenate	
TPP	triphenylphosphine	
TPP	5,10,15,20-tetraphenylporphyrin	

Abbreviation	Chemical Name	Chemical Structure
TPS	triphenylsilyl	
Tr	trityl (triphenylmethyl)	
Trisyl	2,4,6-triisopropylbenzenesulfonyl	
Troc	2,2,2-trichloroethoxycarbonyl	
TS	transition state (or transition structure)	NA
Ts (Tos)	*p*-toluenesulfonyl	
TSE (TMSE)	2-(trimethylsilyl)ethyl	
TTBP	2,4,5-tri-*tert*-butylpyrimidine	
TTMSS	tris(trimethylsilyl)silane	
TTN	thallium(III)-trinitrate	
UHP	urea-hydrogen peroxide complex	
Vitride (Red-Al)	sodium *bis*(2-methoxyethoxy)aluminum hydride	
wk	weeks (length of reaction time)	NA
Z (Cbz)	benzyloxycarbonyl	

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VII. NAMED ORGANIC REACTIONS IN ALPHABETICAL ORDER

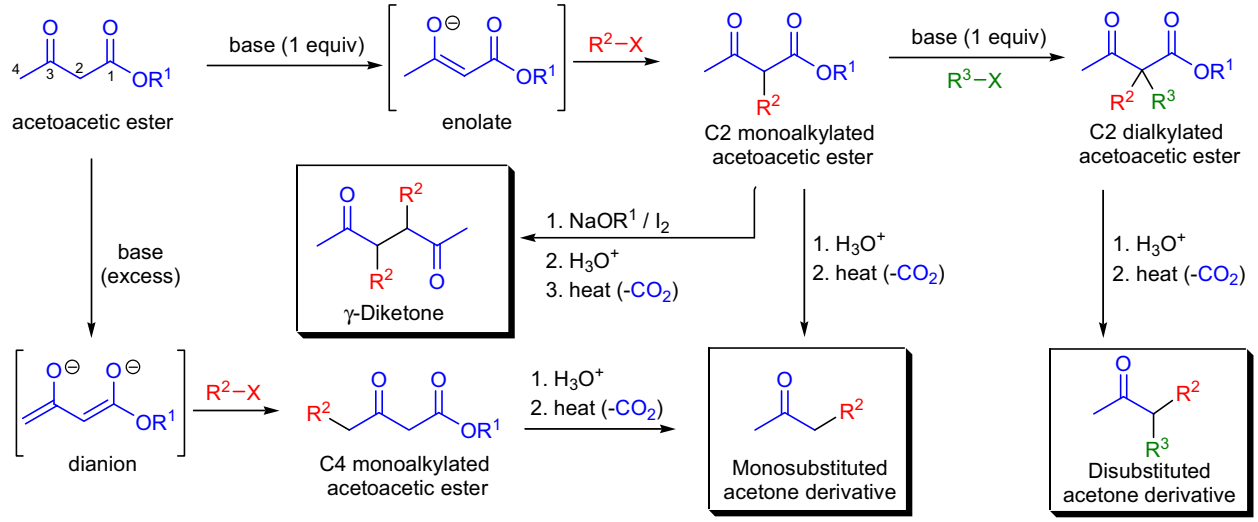
ACETOACETIC ESTER SYNTHESIS

(References are on page 531)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-9]; *Modifications & Improvements*[10-19]]

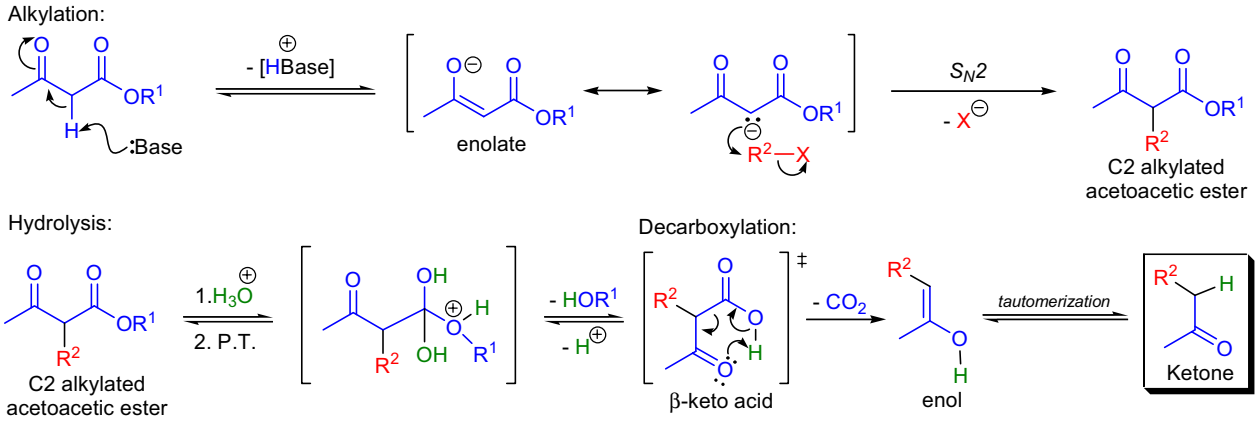
The preparation of ketones *via* the *C*-alkylation of esters of 3-oxobutanoic acid (acetoacetic esters) is called the *acetoacetic ester synthesis*. Acetoacetic esters can be deprotonated at either the C2 or at both the C2 and C4 carbons, depending on the amount of base used. The C-H bonds on the C2 carbon atom are activated by the electron-withdrawing effect of the two neighboring carbonyl groups. These protons are fairly acidic (pK_a ~11 for C2 and pK_a ~24 for C4), so the C2 position is deprotonated first in the presence of one equivalent of base (sodium alkoxide, LDA, NaHMDS or LiHMDS, etc.). The resulting anion can be trapped with various alkylating agents. A second alkylation at C2 is also possible with another equivalent of base and alkylating agent. When an acetoacetic ester is subjected to excess base, the corresponding dianion (extended enolate) is formed.[13-15,18,19] When an electrophile (e.g., alkyl halide) is added to the dianion, alkylation occurs first at the most nucleophilic (reactive) C4 position. The resulting alkylated acetoacetic ester derivatives can be subjected to two types of hydrolytic cleavage, depending on the conditions: 1) dilute acid hydrolyzes the ester group, and the resulting β-keto acid undergoes decarboxylation to give a ketone (mono- or disubstituted acetone derivative); 2) aqueous base induces a *retro-Claisen reaction* to afford acids after protonation. The hydrolysis by dilute acid is most commonly used, since the reaction mixture is not contaminated with by-products derived from ketonic scission. More recently the use of the *Krapcho decarboxylation* allows neutral decarboxylation conditions.[11,12] As with malonic ester, monoalkyl derivatives of acetoacetic ester undergo a base-catalyzed coupling reaction in the presence of iodine. Hydrolysis and decarboxylation of the coupled products produce γ-diketones. The starting acetoacetic esters are most often obtained *via* the *Claisen condensation* of the corresponding esters, but other methods are also available for their preparation.[5,8]



R^1 = 1°, 2° or 3° alkyl, aryl; R^2 = 1° or 2° alkyl, allyl, benzyl; R^3 = 1° or 2° alkyl, allyl, benzyl; base: NaH, $NaOR^1$,LiHMDS, NaHMDS

Mechanism: [3,20]

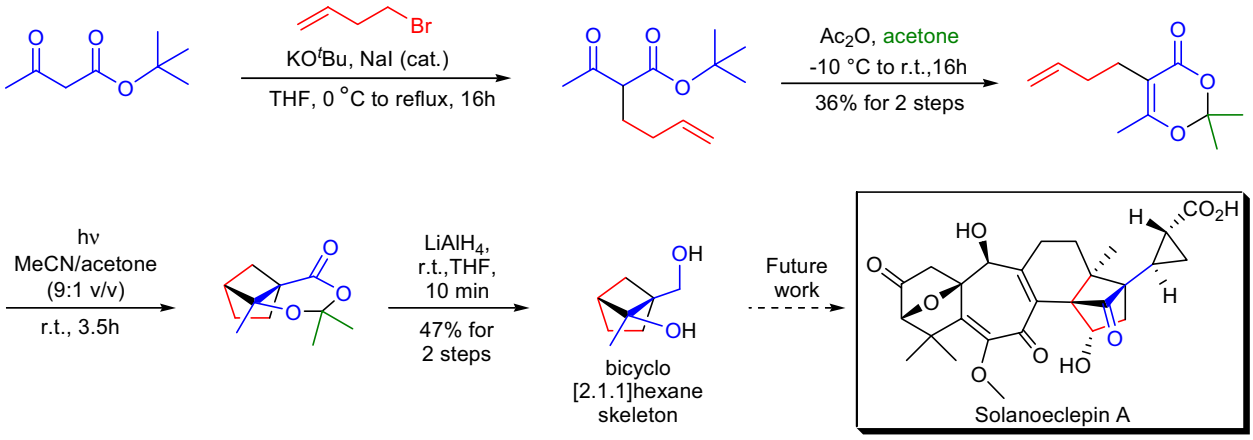
The first step is the deprotonation of acetoacetic ester at the C2 position with one equivalent of base. The resulting enolate is nucleophilic and reacts with the electrophilic alkyl halide in an S_N2 reaction to afford the C2 substituted acetoacetic ester, which can be isolated. The ester is hydrolyzed by treatment with aqueous acid to the corresponding β-keto acid, which is thermally unstable and undergoes decarboxylation *via* a six-membered transition state.



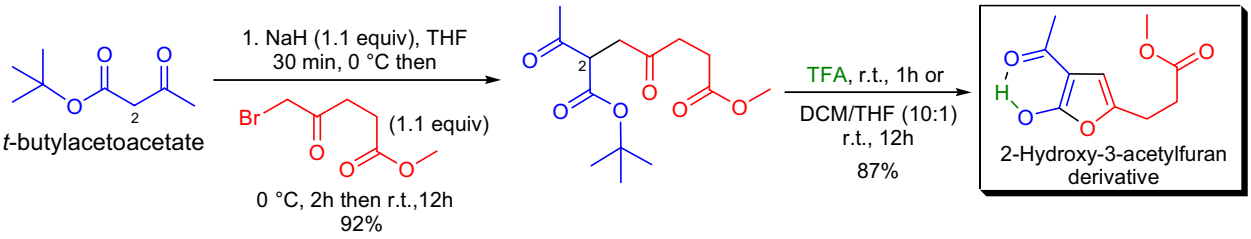
ACETOACETIC ESTER SYNTHESIS

Synthetic Applications:

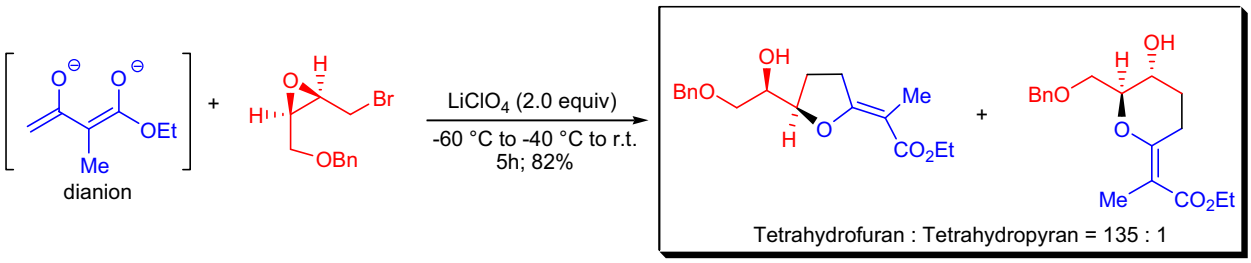
In the laboratory of H. Hiemstra, the synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A was undertaken utilizing the intramolecular photochemical dioxenone-alkene [2+2] cycloaddition reaction.[21] The dioxenone precursor was prepared from the commercially available *tert*-butyl acetoacetate using the *acetoacetic ester synthesis*. When this dioxenone precursor was subjected to irradiation at 300 nm, complete conversion of the starting material was observed after about 4h, and the expected cycloadduct was formed in acceptable yield.



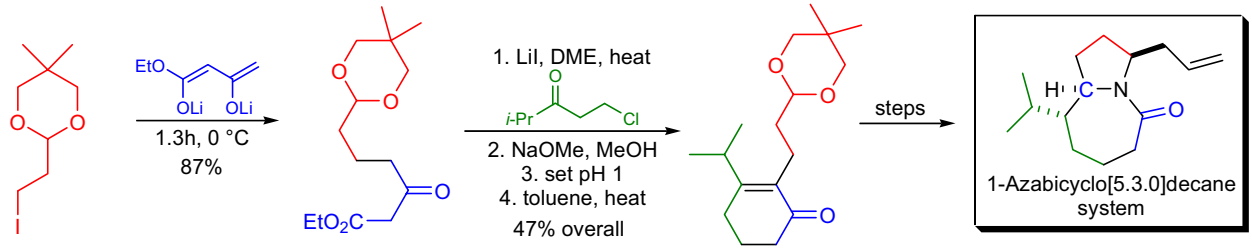
R. Neier et al. synthesized substituted 2-hydroxy-3-acetylfurans by the alkylation of *tert*-butylacetoacetate with an α-haloketone, followed by treatment of the intermediate with trifluoroacetic acid.[22] When furans are prepared from β-ketoesters and α-haloketones, the reaction is known as the *Feist-Bénary reaction*. A second alkylation of the C2 alkylated intermediate with various bromoalkanes yielded 2,2-disubstituted products, which upon treatment with TFA, provided access to trisubstituted furans.



M. Nakada and co-workers developed a novel synthesis of tetrahydrofuran and tetrahydropyran derivatives by reacting dianions of acetoacetic esters with epibromohydrin derivatives.[23] The selective formation of the tetrahydrofuran derivatives was achieved by the use of $LiClO_4$ as an additive.



A synthetic strategy was developed for the typical core structure of the *Stemona* alkaloids in the laboratory of C.H. Heathcock.[24] The precursor for the 1-azabicyclo[5.3.0]decane ring system was prepared *via* the successive double alkylation of the dianion of ethyl acetoacetate.



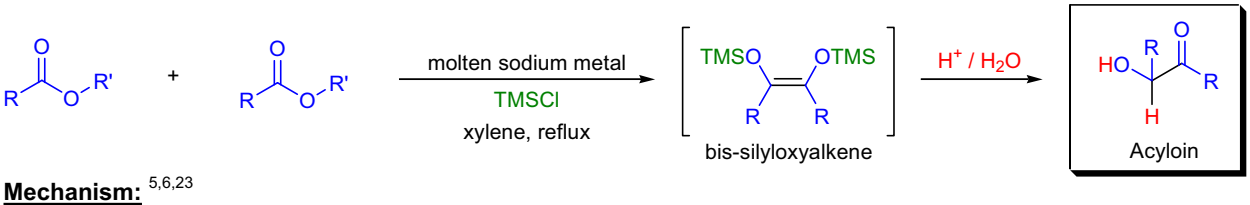
ACYLOIN CONDENSATION

(References are on page 531)

Importance:

[*Seminal Publications* [1-4]; *Reviews* [5-9]; *Modifications & Improvements*[10-22]]

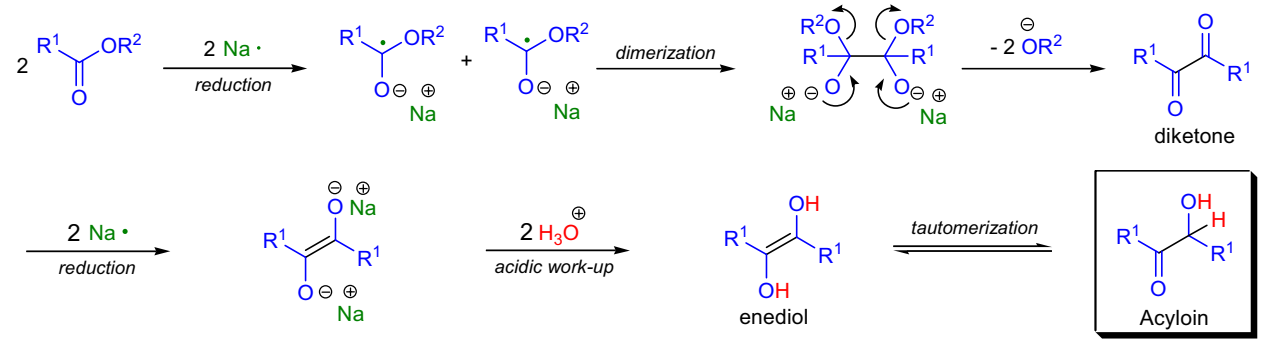
The *acyloin condensation* affords acyloins (α-hydroxy ketones) by treating aliphatic esters with molten, highly dispersed sodium in hot xylene.[8] The resulting disodium acyloin derivatives are acidified to liberate the corresponding acyloins, which are valuable synthetic intermediates. Aliphatic monoesters give symmetrical compounds, while diesters lead to cyclic acyloins. The *intramolecular acyloin condensation* is one of the best ways of closing rings of 10 members or more (up to 34 membered rings were synthesized).[6] For the preparation of aromatic acyloins (R=Ar), the *benzoin condensation* between two aromatic aldehydes is applied. The acyloin condensation is performed in an inert atmosphere, since the acyloins and their anions are readily oxidized. For small rings (ring size: 4-6), yields are greatly improved in the presence of TMSCl and by the use of ultrasound.[11,13] The addition of TMSCl increases the scope of this reaction by preventing base-catalyzed side reactions such as β-elimination, *Claisen* or *Dieckmann condensations*. The resulting bis-silyloxyalkenes are either isolated or converted into acyloins by simple hydrolysis or alcoholysis.



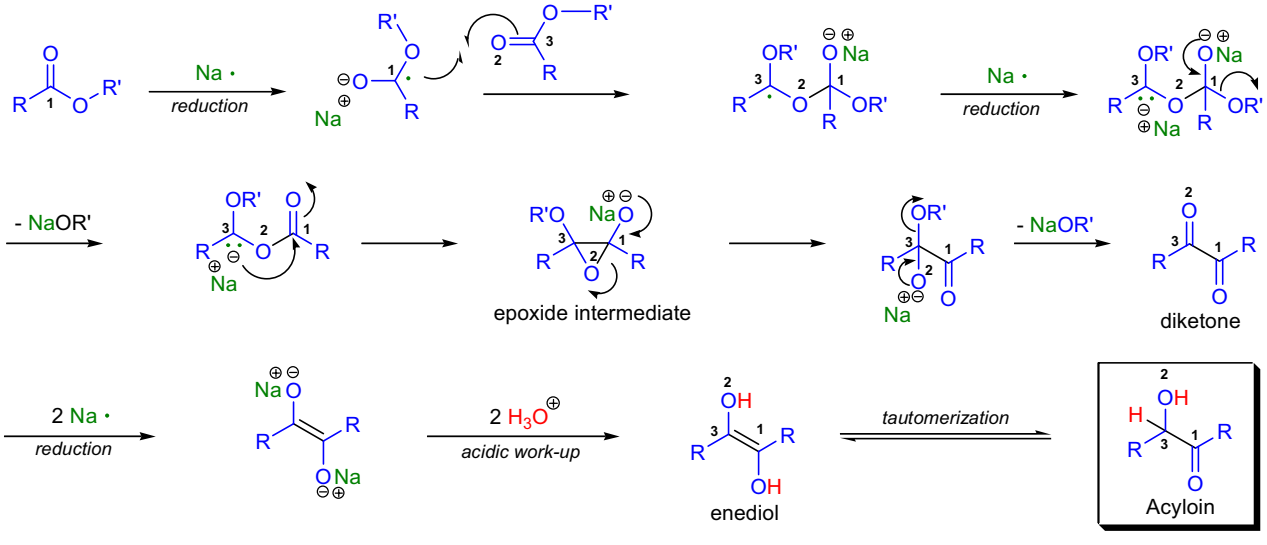
Mechanism: [5,6,23]

There are currently two proposed mechanisms for the *acyloin ester condensation* reaction. In mechanism **A** the sodium reacts with the ester in a single electron transfer (SET) process to give a radical anion species, which can dimerize to a dialkoxy dianion.[5,6] Elimination of two alkoxide anions gives a diketone. Further reduction (electron transfer from the sodium metal to the diketone) leads to a new dianion, which upon acidic work-up yields an enediol that tautomerizes to an acyloin. In mechanism **B** an epoxide intermediate is proposed.[23]

Mechanism **A**:



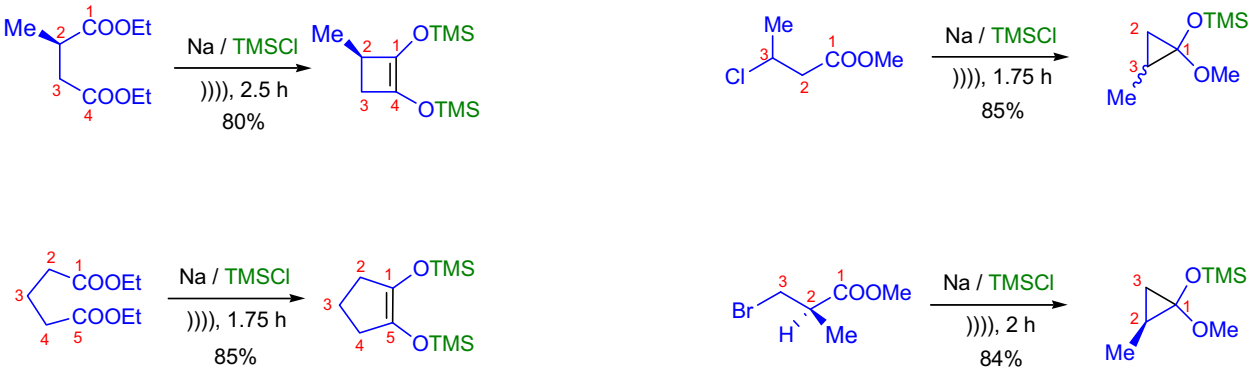
Mechanism **B**:



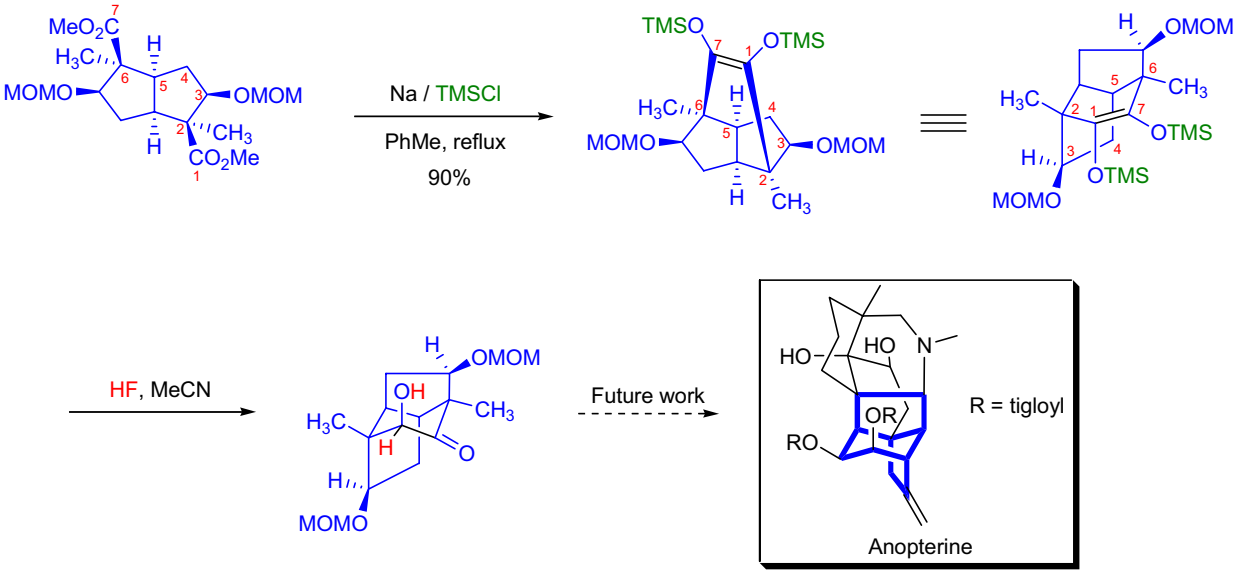
ACYLOIN CONDENSATION

Synthetic Applications:

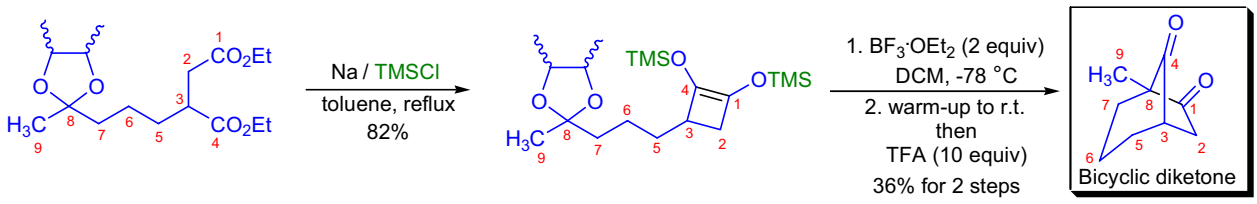
J. Salaün and co-workers studied the ultrasound-promoted *acyloin condensation* and cyclization of carboxylic esters.[13] They found that the acyloin coupling of 1,4-, 1,5-, and 1,6-diesters afforded 4-, 5- and 6-membered ring products. The cyclization of β-chloroesters to 3-membered ring products in the presence of TMSCl, which previously required highly dispersed sodium, was simplified and improved under sonochemical activation.



The diterpene alkaloids of the *Anopterus* species, of which anopterine (R=tigloyl) is a major constituent, are associated with a high level of antitumor activity. All of these alkaloids contain the tricyclo[3.3.2^{1,4}.0]decane substructure. S. Sieburth et al. utilized the *acyloin condensation* as a key step in the short construction of this tricyclic framework.[24]



D.J. Burnell et al. synthesized bicyclic diketones by Lewis acid-promoted geminal acylation involving cyclic acyloins tethered to an acetal. The required *bis*-silyloxyalkenes were prepared by using the standard *acyloin condensation* conditions.[25]



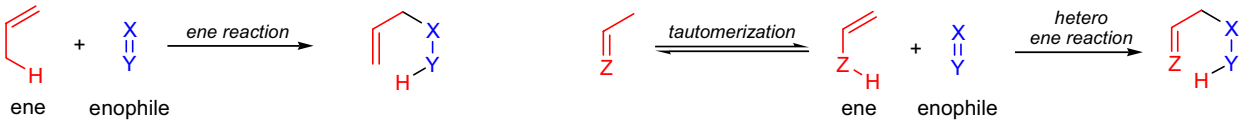
ALDER (ENE) REACTION
(HYDRO-ALLYL ADDITION)

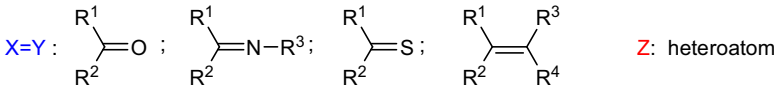
(References are on page 532)

Importance:

[*Seminal Publications*[1-6]*; Reviews*[7-33]*; Theoretical Studies*[34-44]]

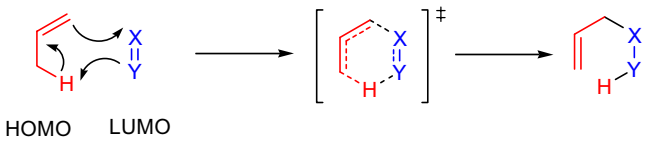
In 1943, K. Alder systematically studied reactions that involved the activation of an allylic C-H bond and the allylic transposition of the C=C bond of readily available alkenes.[4-6] This reaction is known as the *ene reaction*. Formally it is the addition of alkenes to double bonds (C=C or C=O), and it is one of the simplest ways to form C-C bonds. The *ene reaction* of an olefin bearing an allylic hydrogen atom is called "*carba-ene reaction*". For the reaction to proceed without a catalyst, the alkene must have an electron-withdrawing (EWG) substituent. This electrophilic compound is called the *enophile*. The *ene reaction* has a vast number of variants in terms of the enophile used.[7-9,11,12,45,14-16,46,18-20,24,47,27-30] Olefins are relatively unreactive as enophiles, whereas acetylenes are more enophilic. For example, under high pressure acetylene reacts with a variety of simple alkenes to form 1,4-dienes. When the enophile is a carbonyl compound, the *ene reaction* leads exclusively to the corresponding alcohol instead of the ether (*carbonyl-ene reaction*). However, thiocarbonyl compounds react mainly to give allylic sulfides rather than homoallylic thiols. Schiff bases derived from aldehydes afford homoallylic amines (*aza-ene, imino-ene* or *hetero-ene reaction*).[19] *Metallo-ene reactions* with Pd, Pt, and Ni-catalyzed versions have been successful in intramolecular systems. The *ene reaction* is compatible with a variety of functional groups that can be appended to the ene and enophile. The *ene reaction* can be highly stereoselective and by adding Lewis acids ($RAlX_2$, $Sc(OTf)_3$, $LiClO_4$, etc.), less reactive enophiles can also be used. The regioselectivity of the reaction is determined by the steric accessibility of the hydrogen. Usually primary hydrogens are abstracted faster than secondary hydrogens and tertiary hydrogens are abstracted last. Functionalization of the reacting components by introduction of a silyl, alkoxy, or amino group, thus changing the steric and electronic properties, affords more control over the regioselectivity of the reaction.





Mechanism: [48-52,31]

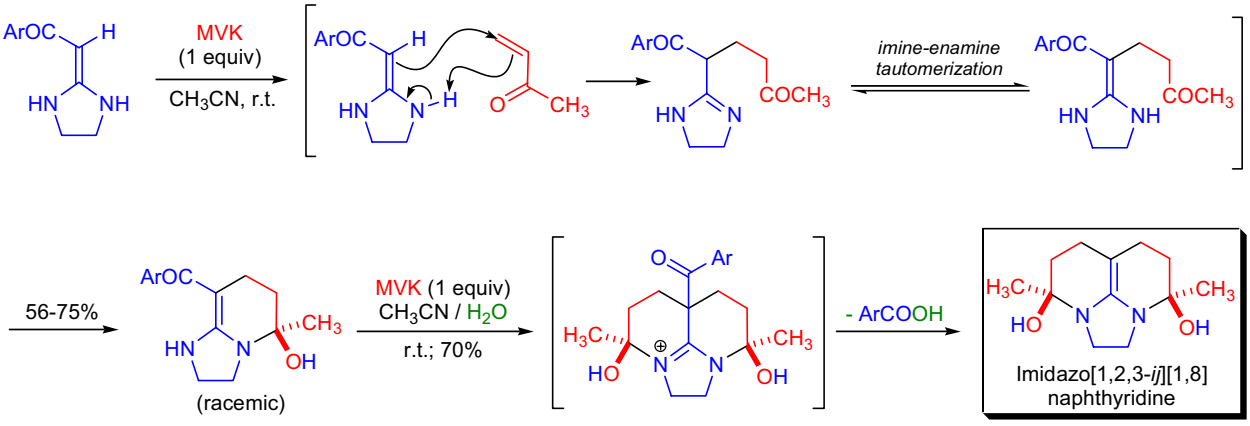
The *ene reaction* is mechanistically related to the better-known *Diels-Alder reaction* and is believed to proceed *via* a six-membered aromatic transition state.[50,51] Thermal *intermolecular ene reactions* have high negative entropies of activation, and for this reason the *ene reaction* requires higher temperatures than the *Diels-Alder reaction*. The forcing conditions were responsible for the initial paucity of *ene reactions*. However, *intramolecular ene reactions* are more facile. The enophile reacts with the ene component in a "*syn*-fashion" and this observation suggests a *concerted mechanism*. There is a frontier orbital interaction between the HOMO of the ene component and the LUMO of the enophile. The *ene-reaction* is favored by electron-withdrawing substituents on the enophile, by strain in the ene component and by geometrical alignments that position the components in a favorable arrangement. Some *thermal ene reactions*, such as the ene reaction between cyclopentene and diethyl azodicarboxylate (DEAD), are catalyzed by free radical initiators, so for these processes a *stepwise biradical pathway* had been suggested.[48,49] The mechanism of the *Lewis acid-promoted ene reaction* is believed to involve both a concerted and a cationic pathway.[53] Whether the mechanism is concerted or stepwise, a partial or full positive charge is developed at the ene component in Lewis acid-promoted reactions.



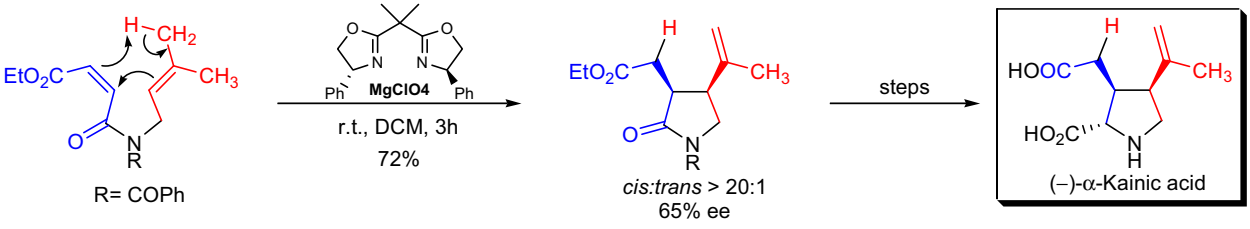
ALDER (ENE) REACTION
(HYDRO-ALLYL ADDITION)

Synthetic Applications:

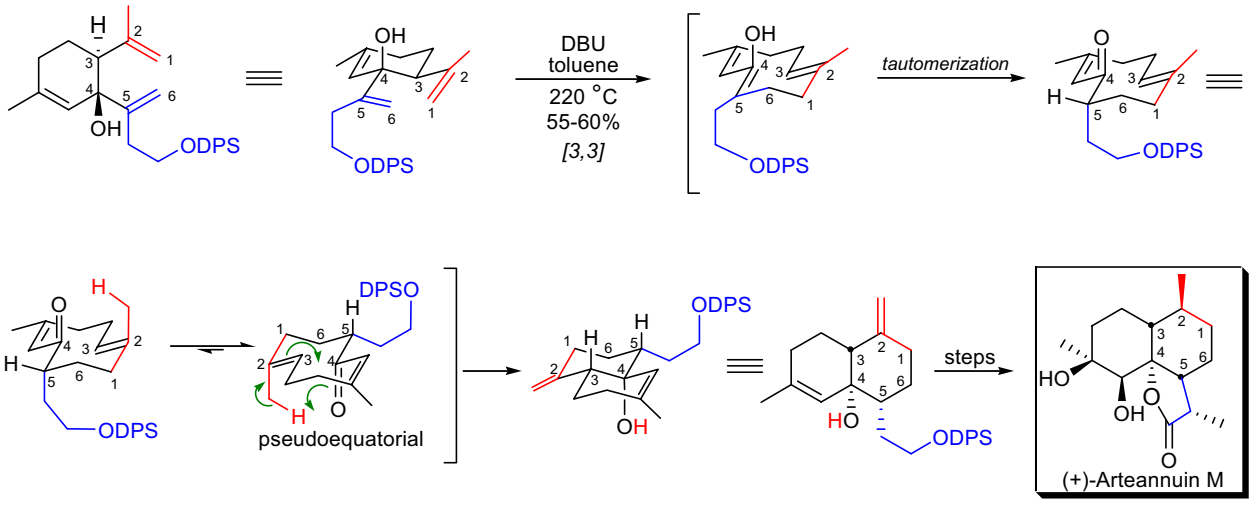
The *aza-ene* reaction recently found application in the synthesis of imidazo[1,2-*a*]pyridine and imidazo[1,2,3-*ij*][1,8]naphthyridine derivatives in the laboratory of Z.-T. Huang.[54] The reaction of heterocyclic ketene aminals with enones such as MVK proceeded *via* an *aza-ene addition*, followed by intramolecular cyclization to afford the products. The aroyl-substituted heterocyclic ketene aminals (Ar=Ph, 2-furyl, 2-thienyl) underwent two subsequent *aza-ene reactions* when excess MVK was used.



B. Ganem and co-workers accomplished the asymmetric total synthesis of (–)-α-kainic acid using an enantioselective, *metal-promoted ene cyclization*.[52] The chiral bis-oxazoline-magnesium perchlorate system strongly favored the formation of the *cis*-diastereomer in the cyclization. Enantiomerically pure kainic acid was synthesized from readily available starting materials on a 1-2 g scale in six steps in an overall yield of greater than 20%.



The first total synthesis of (+)-arteannuin M was completed by L. Barriault et al. using a tandem *oxy-Cope/transannular ene reaction* as the key step to construct the bicyclic core of the natural product.[55] The tandem reaction proceeded with high diastereo- and enantioselectivity.



ALDOL REACTION

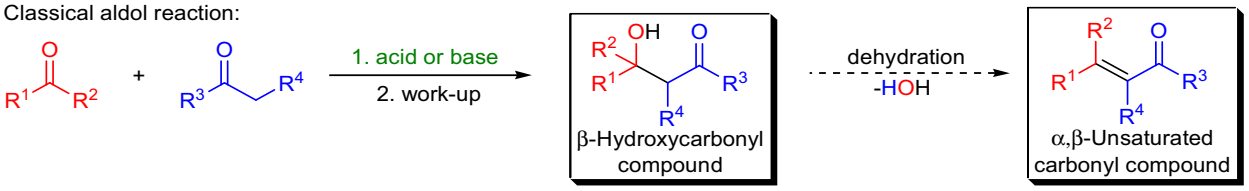
(References are on page 533)

Importance:

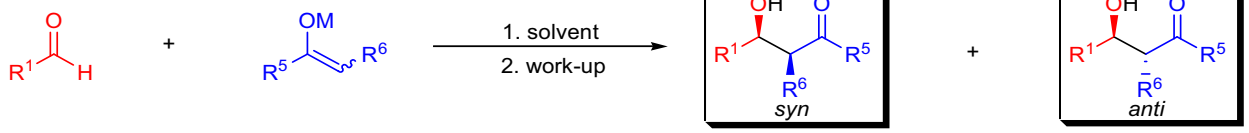
[*Seminal Publications*[1,2]; *Reviews*[3-46]; *Theoretical Studies*[47-74]]

The *aldol reaction* involves the addition of the enol/enolate of a carbonyl compound (nucleophile) to an aldehyde or ketone (electrophile). The initial product of the reaction is a β-hydroxycarbonyl compound that under certain conditions undergoes dehydration to generate the corresponding α,β-unsaturated carbonyl compound. The transformation takes its name from 3-hydroxybutanal, the acid-catalyzed self-condensation product of acetaldehyde, which is commonly called aldol. Originally the *aldol reaction* was carried out with Brönsted acid[1,2] or Brönsted base catalysis,[75,76] but these processes were compromised by side reactions such as self-condensation, polycondensation, and dehydration followed by *Michael addition*. Development of methods for the formation and application of preformed enolates was a breakthrough in the aldol methodology. Most commonly applied enolates in the aldol reaction are the lithium-,[12] boron-,[14] titanium-,[15] and silyl enol ethers, but several other enolate derivatives have been studied such as magnesium-,[12] aluminum-,[14] zirconium-,[15] rhodium-,[15] cerium-,[15] tungsten-,[15] molybdenum-,[15] rhenium-,[15] cobalt-,[15] iron-,[15] and zinc enolates.[16] Enolate formation can be accomplished in a highly regio- and stereoselective manner. The *aldol reaction* of stereodefined enolates is highly diastereoselective.[3,13] (*E*)-Enolates generally yield the *anti* product, while (*Z*)-enolates lead to the *syn* product as the major diastereomer. Lewis acid mediated *aldol reaction* of silyl enol ethers (*Mukaiyama aldol reaction*) usually provides the *anti* product.[77,78] Control of the absolute stereochemical outcome of the reaction can be achieved through the use of enantiopure starting materials (reagent control) or asymmetric catalysis.[6,7,79,8,9,22,41] Reagent control can be realized by: 1) utilizing chiral auxiliaries in the enol component, such as oxazolidinones (also see *Evans aldol*), bornanesultams, pyrrolidinones, arylsulfonamido indanols, norephedrines and *bis*(isopropylphenyl)-3,5-dimethylphenol derivatives;[80] 2) applying chiral ligands on boron enolates such as isopinocampheyl ligands, menthone derived ligands, tartrate derived boronates, and C_2-symmetric borolanes;[24,25,80] 3) using chiral aldehydes.[7,17,29,41] Direct *asymmetric catalytic aldol reactions* can be achieved *via* 1) biochemical catalysis applying enzymes or catalytic antibodies;[11,18,20,81,27] 2) chiral metal complex mediated catalysis; and 3) organocatalysis utilizing small organic molecules.[21,28,29,33,82,35-37,39]

Classical aldol reaction:



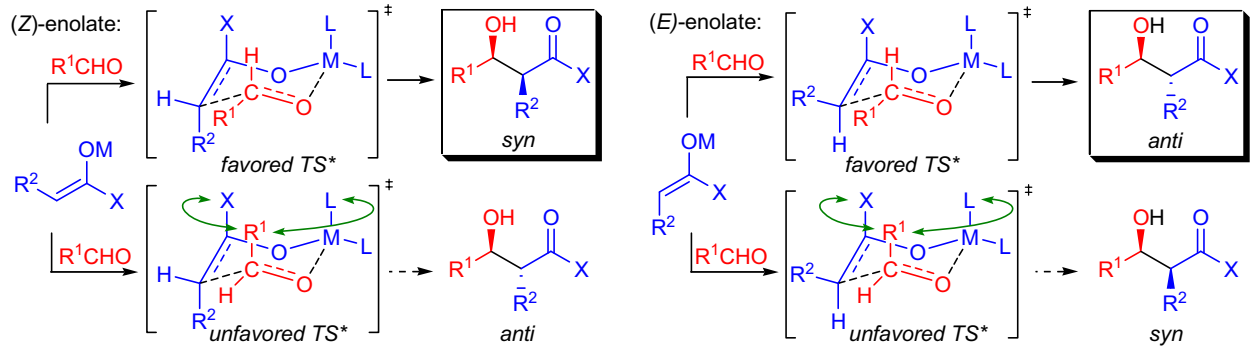
Aldol reaction through the use of preformed enolate:



R^1 = H,alkyl or aryl; R^2 = alkyl, aryl; R^3 = R^5 = alkyl, aryl, -NR_2, -OR, -SR; R^4 = R^6 = alkyl, aryl, -OR; M = Li, Na, B, Al, Si, Zr, Ti, Rh, Ce, W, Mo, Re, Co, Fe, Zn;

Mechanism:[7,12,13]

The mechanism of the classical *acid catalyzed aldol reaction* involves the equilibrium formation of an enol, which functions as a nucleophile. The carbonyl group of the electrophile is activated toward nucleophilic attack by protonation. In the base catalyzed reaction, the enolate is formed by deprotonation followed by the addition of the enolate to the carbonyl group. In both cases, the reaction goes through a number of equilibria, and the formation of the product is reversible. *Aldol reaction* of preformed enolates generally provides the products with high diastereoselectivity, (*Z*)-enolates yielding the *syn* product, (*E*)-enolates forming the *anti* product as the major diastereomer. The stereochemical outcome of the reaction can be rationalized based on the Zimmerman-Traxler model, according to which the reaction proceeds through a six-membered chairlike transition state. The controlling factor according to this model is the avoidance of destabilizing 1,3-diaxial interactions in the cyclic transition state.

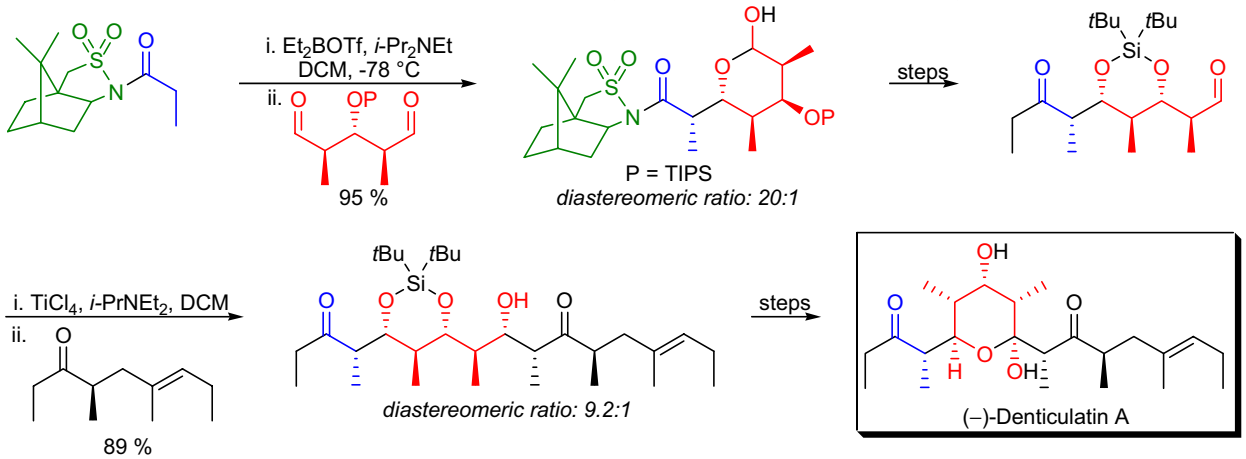


Zimmerman-Traxler model for (Z)- enolate *Zimmerman-Traxler model for (E)- enolate*

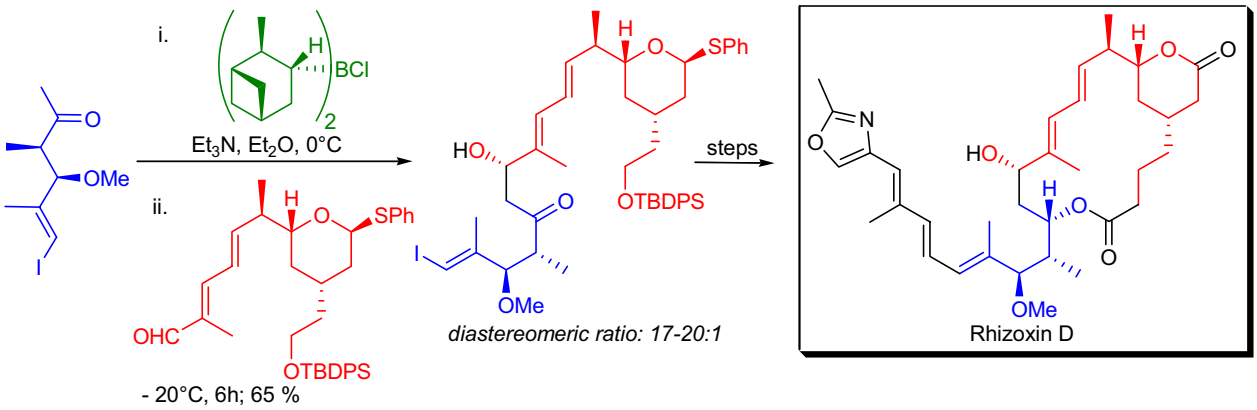
ALDOL REACTION

Synthetic Applications:

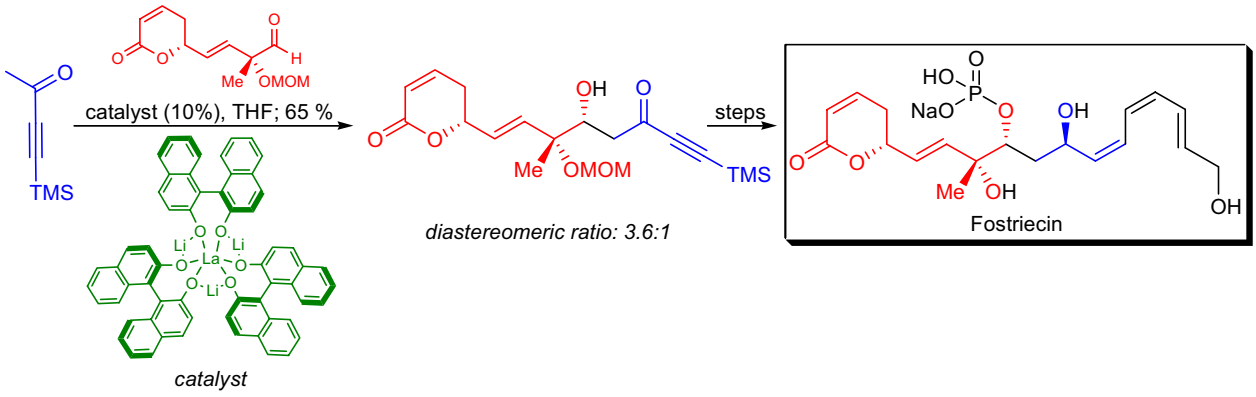
The first enantioselective total synthesis of (–)-denticulatin A was accomplished by W. Oppolzer.[83] The key step in their approach was based on enantiotopic group differentiation in a *meso* dialdehyde by an *aldol reaction*. In the *aldol reaction* they utilized a bornanesultam chiral auxiliary. The enolization of *N*-propionylbornane-10,2-sultam provided the (*Z*)-borylenolate derivative, which underwent an *aldol reaction* with the *meso* dialdehyde to afford the product with high yield and enantiopurity. In the final stages of the synthesis they utilized a second, *double-diastereodifferentiating aldol reaction*. Aldol reaction of the (*Z*)-titanium enolate gave the *anti*-Felkin *syn* product. The stereochemical outcome of the reaction was determined by the α-chiral center in the aldehyde component.



During the total synthesis of rhizoxin D by J.D. White et al., an *asymmetric aldol reaction* was utilized to achieve the coupling of two key fragments.[84] The *aldol reaction* of the aldehyde and the chiral enolate derived from (+)-chlorodiisopinocampheylborane afforded the product with a diastereomeric ratio of 17-20:1 at the C13 stereocenter. During their studies, White and co-workers also showed that the stereochemical induction of the chiral boron substituent and the stereocenters present in the enolate reinforce each other thus representing a "*matched*" *aldol reaction*.



A possible way to induce enantioselectivity in the *aldol reaction* is to employ a chiral catalyst. M. Shibasaki and co-workers developed a bifunctional catalyst, (*S*)-LLB (L=lanthanum; LB=lithium binaphthoxide), which could be successfully applied in direct *catalytic asymmetric aldol reactions*.[85] An improved version of this catalyst derived from (*S*)-LLB by the addition of water and KOH was utilized in the formal total synthesis of fostriecin.[86]



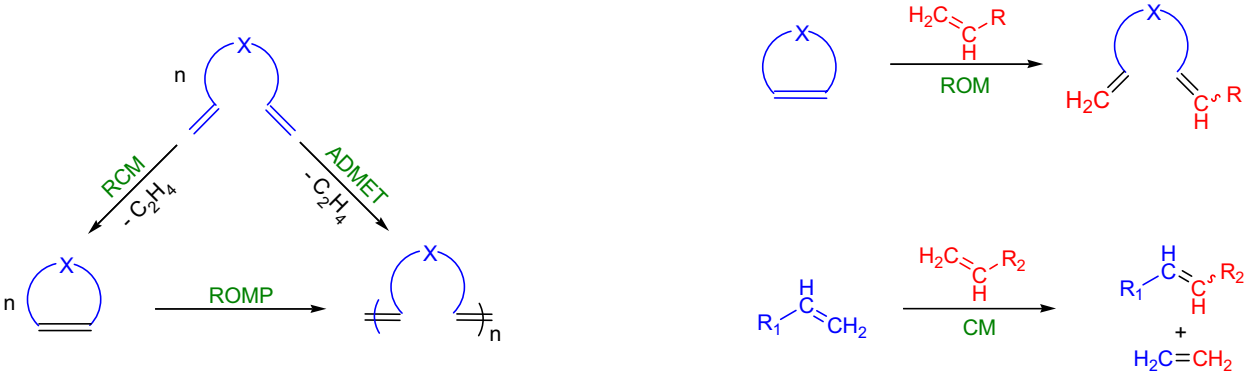
ALKENE (OLEFIN) METATHESIS

(References are on page 534)

Importance:

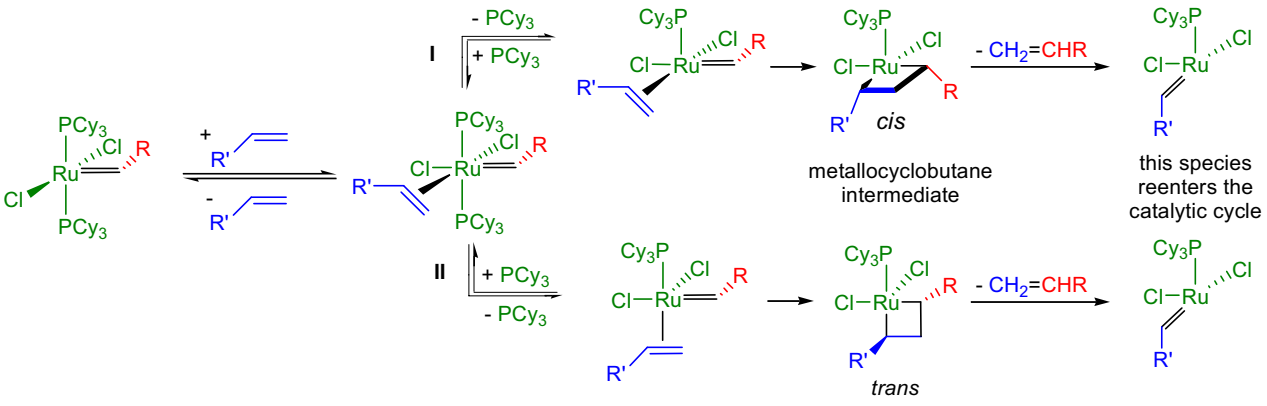
[*Seminal Publications*[1,2]; *Reviews*[3-61]; *Modifications & Improvements*[62-70]; *Theoretical Studies*[71-76]]

The metal-catalyzed redistribution of carbon-carbon double bonds is called *alkene (olefin) metathesis*. The first report of double-bond scrambling was published in 1955[1] but the term "*olefin metathesis*" was introduced only thirteen years later by N. Calderon[2] and co-workers. There are several different *olefin metathesis* reactions: *ring-opening metathesis polymerization* (ROMP), *ring-closing metathesis* (RCM), *acyclic diene metathesis polymerization* (ADMET), *ring-opening metathesis* (ROM), and *cross-metathesis* (CM or XMET). These various olefin metathesis reactions give access to molecules and polymers that would be difficult to obtain by other means. ROMP makes it possible to prepare functionalized polymers, while the application of RCM provides easy entry into medium and large carbocycles as well as heterocyclic compounds. The application of *olefin metathesis* for the synthesis of complex organic molecules did not appear until the beginning of the 1990s because the available catalysts had low performance and little functional group tolerance. In the past 10 years *olefin metathesis* has become a reliable and widely used synthetic method. The currently used $L(L')X_2Ru{=}CHR$ catalyst system is highly active, and it has sufficient functional group tolerance for most applications. However, new catalysts are still needed, because the current ones do not always perform well in several demanding transformations. Some of the problems still encountered are: 1) incompatibility with basic functional groups (nitriles and amines); 2) cross metathesis to form tetrasubstituted olefins; and 3) low stereoselectivity in CM and macrocyclic RCM reactions.



Mechanism: [77-86]

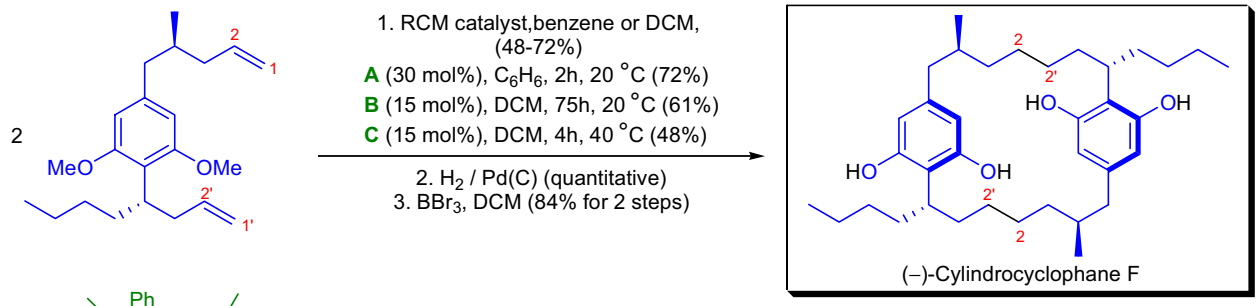
Crystal structures of the $L_2X_2Ru{=}CHR$ carbene complexes reveal that they have a distorted square pyramidal geometry with the alkylidene in the axial position and the *trans* phosphines and halides in the equatorial plane.[87,88] R. H. Grubbs and co-workers have conducted extensive kinetic studies on $L_2X_2Ru{=}CHR$ complexes and proposed a mechanism that is consistent with the observed activity trends.[89] There are two possible mechanistic pathways (**I** & **II**):

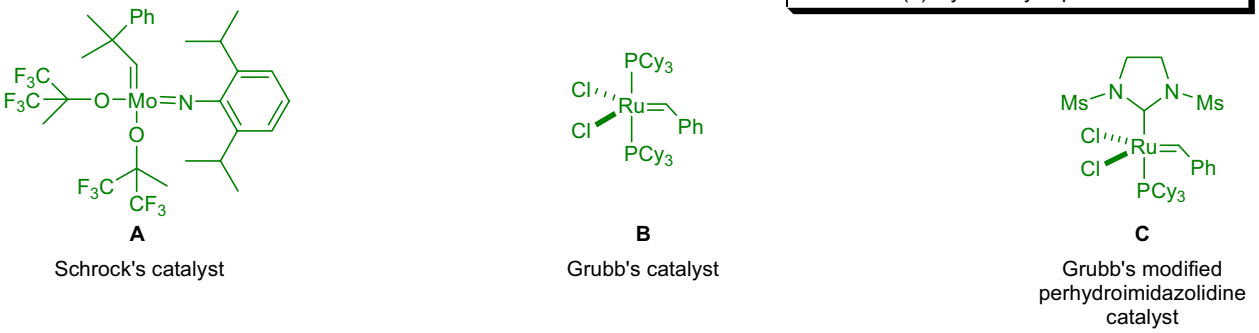


ALKENE (OLEFIN) METATHESIS

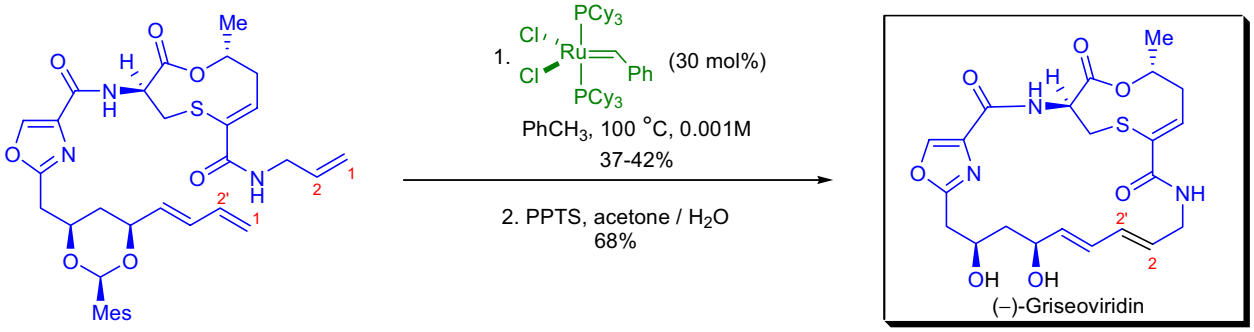
Synthetic Applications:

A.B. Smith and co-workers have devised an efficient strategy for the synthesis of the cylindrocyclophane family of natural products.[90,91] Olefin *ring-closing metathesis* was used for the assembly of the [7,7]-paracyclophane skeleton. During their investigations they discovered a remarkably efficient *CM dimerization* process, that culminated in the total synthesis of both (–)-cylindrocyclophane A and (–)-cylindrocyclophane F. They established that the *cross metathesis dimerization* process selectively led to the thermodynamically most stable member of a set of structurally related isomers. Out of three commonly used RCM catalysts, Schrock's catalyst proved to be the most efficient for this transformation.

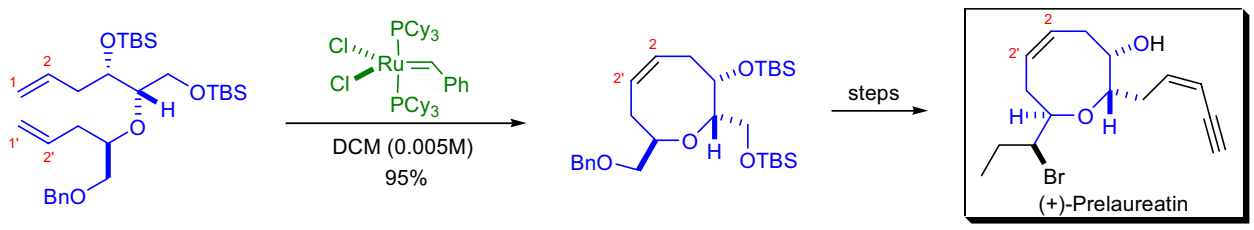




The streptogramin antibiotics are a family of compounds that were isolated from a variety of soil organisms belonging to the genus *Streptomyces*. They are active against bacteria resistant to vancomycin. In the laboratory of A.I. Meyers the first total synthesis of streptogramin antibiotics, (–)-griseoviridin and its C8 epimer, featuring a 23-membered unsaturated ring, was accomplished using a novel *RCM* that involved a highly diastereoselective triene to diene macrocyclic ring formation.[92] The metathesis was performed in 37-42% yield using 30 mol% of Grubbs catalyst. The natural product was obtained as a single diastereomer; no other olefin isomers were formed in the ring-closing step.



The first enantioselective total synthesis of (+)-prelaureatin was achieved by M.T. Crimmins et al.[93] The oxocene core of the natural product was constructed in high yield by a *RCM* reaction using the first generation Grubbs catalyst.



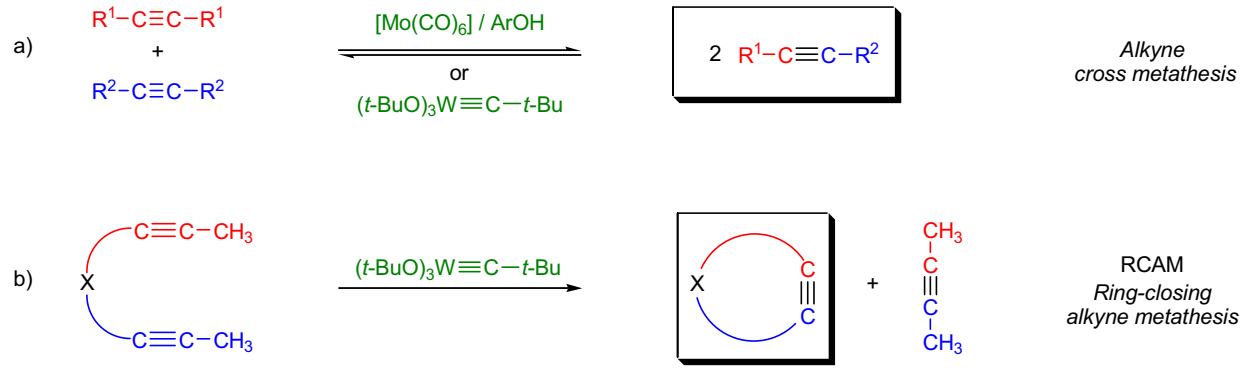
ALKYNE METATHESIS

(References are on page 536)

Importance:

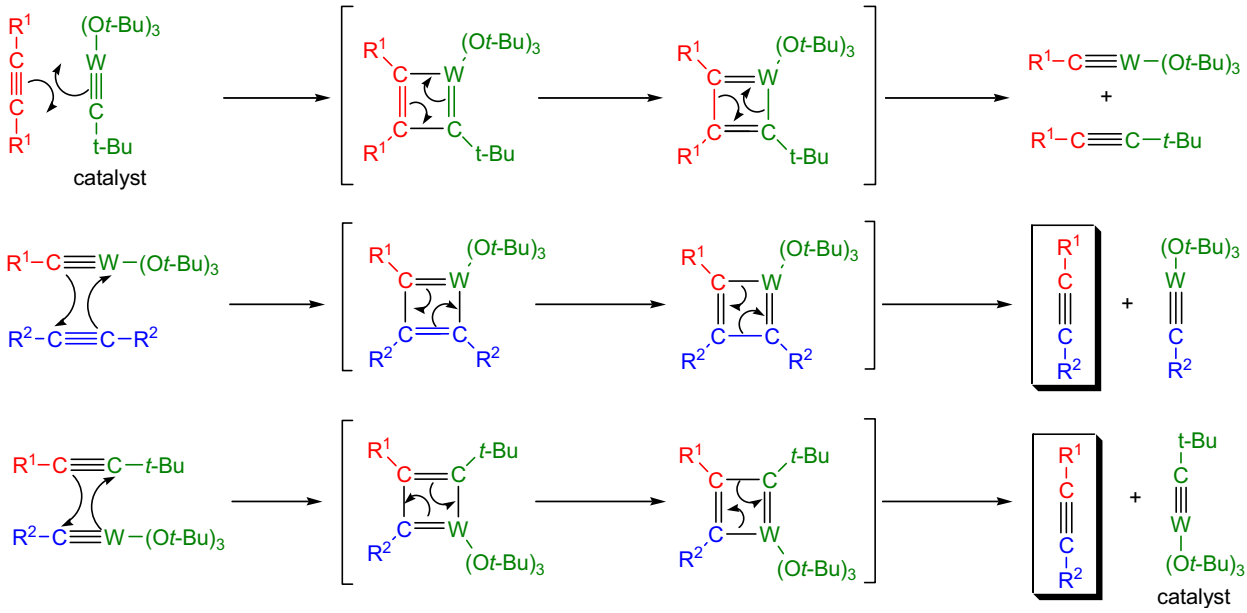
[*Seminal Publications*[1-3]; *Reviews*[4-11]]

The metal-catalyzed redistribution of carbon-carbon triple bonds is called *alkyne metathesis*. In the beginning of the 1970s, A. Mortreux and co-workers were the first to achieve the homogeneously catalyzed metathesis reaction of a C-C triple bond in which they statistically disproportionated *p*-tolylphenylacetylene to tolan (diphenyl acetylene) with an *in situ* formed [$Mo(CO)_6$]/resorcinol catalyst at 110 °C.[1] However, all attempts to convert terminal alkynes by metathesis failed with this catalyst. Cyclotrimers and complex polymers were isolated instead. A decade later, in the 1980s, the well-defined Schrock tungsten carbyne complex [(*t*-BuO)$_3$W≡C-*t*-Bu] was shown to catalyze the metathesis of terminal alkynes accompanied by the evolution of gaseous acetylene.[12] This reaction also suffered from substantial polymerization of the substrate to polyacetylenes. In the 1990s research efforts intensified to find suitable catalysts. M. Mori and co-workers successfully cross-metathesized internal alkynes in the presence of a Mortreux-type catalyst,[13,14] while in the laboratory of A. Fürstner the conditions for RCAM (ring-closing alkyne metathesis) were developed.[15] The cycloalkynes obtained by the RCAM can be stereoselectively converted into the corresponding (*Z*)- or (*E*)-alkenes by catalytic hydrogenation,[16-18] hydroboration, and subsequent protonation, as well as by other methods.[19] In the years to come *alkyne metathesis* will probably become a useful tool for organic synthesis as well as for the synthesis of polymers.



Mechanism: [20-27]

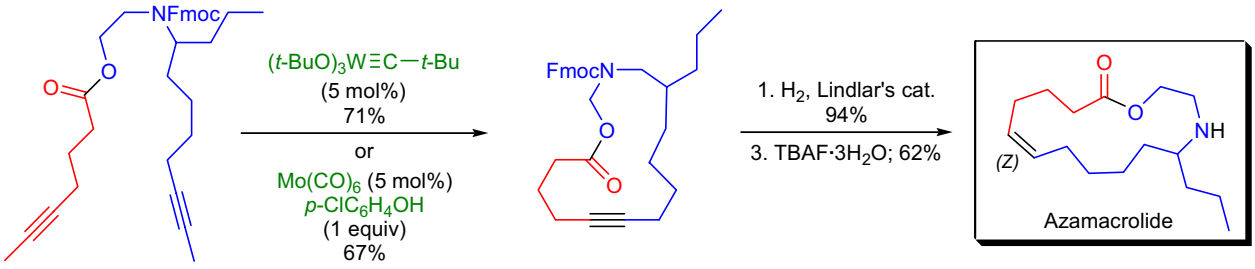
The *alkyne cross metathesis* and *metathesis polymerization* can be carried out both thermally and photochemically. The nature of the catalytically active species in the thermally and photochemically activated systems is unknown. The mechanism shown below accounts for the formation of the *alkyne cross metathesis* products, but none of the currently proposed mechanisms are supported by solid experimental evidence.



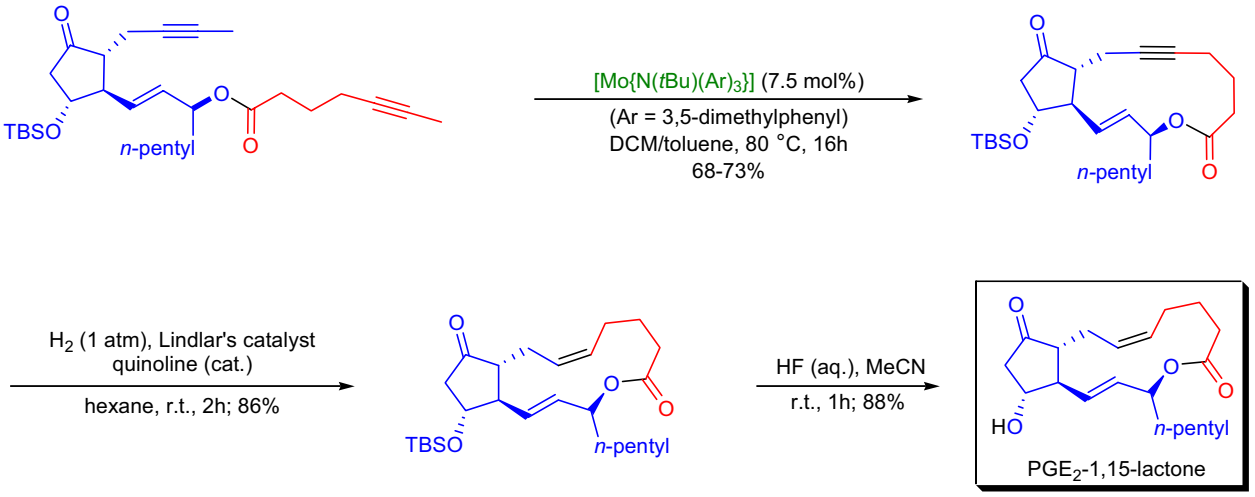
ALKYNE METATHESIS

Synthetic Applications:

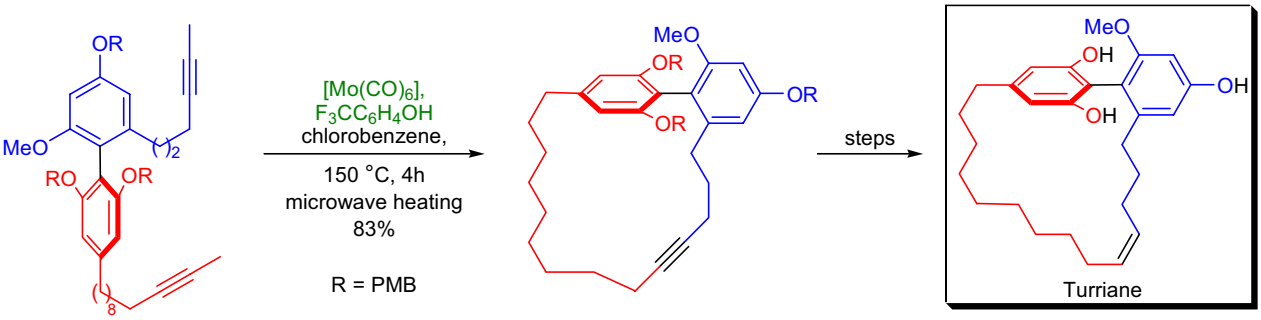
The total synthesis of the recently discovered azamacrolides was undertaken in the laboratory of A. Fürstner.[16] These compounds are the defense secretions of the pupae of the Mexican beetle *Epilachnar varivestis*, and they are the first examples of naturally occurring macrolactones containing a basic nitrogen atom in the tether that do not ring-contract to the corresponding amides. RCAM followed by Lindlar reduction provided a convenient, high-yielding, and stereoselective way to introduce the (*Z*)-double bond. (The usual RCM approach using Grubbs carbene only yielded a mixture of alkenes (*Z*) : (*E*) = 1:2.)



A. Fürstner and co-workers also showed that RCAM is indeed a very mild method, because during their stereoselective total synthesis of prostaglandin E_2-1,15-lactone, the Mo[N-(*t*-Bu)$(Ar)_3$]-derived catalyst tolerated a preexisting double bond and a ketone functionality.[17] Chromatographic inspection of the reaction mixture revealed that no racemization took place before or after the ring closure, and the *ee* of the substrate and the product were virtually identical.



The first total synthesis of three naturally occurring cyclophane derivatives belonging to the turriane family of natural products was also described by A. Fürstner et al.[28] These natural products have a sterically hindered biaryl moiety and saturated as well as unsaturated macrocyclic tethers. Stereoselective entry to this class of compounds is possible using RCAM followed by Lindlar reduction of the resulting cycloalkynes.



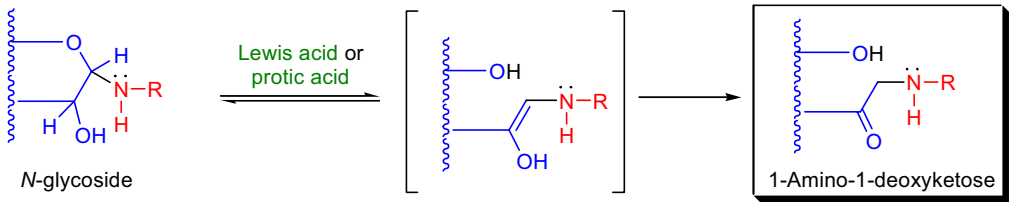
AMADORI REACTION / REARRANGEMENT

(References are on page 537)

Importance:

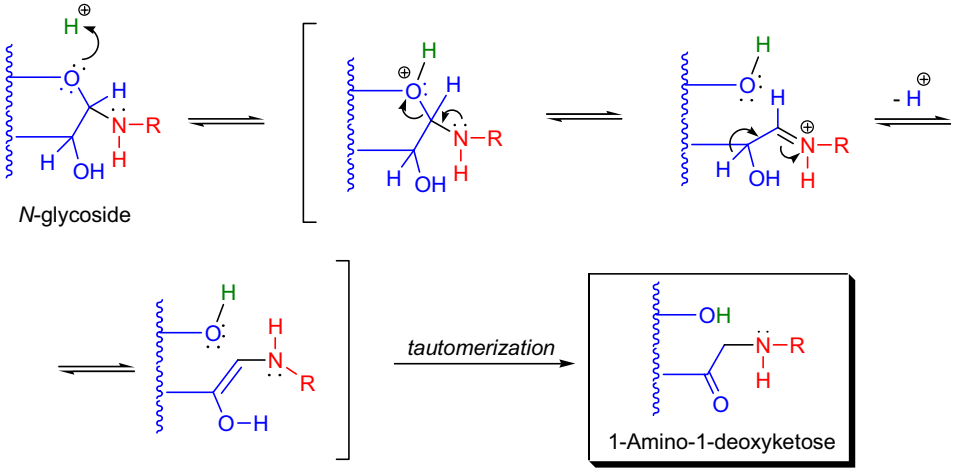
[*Seminal Publications*[1,2]; *Reviews*[3-9]]

The acid- or base-catalyzed isomerization of *N*-glycosides (glycosylamines) of aldoses to 1-amino-1-deoxyketoses is called the *Amadori reaction/rearrangement*. Both the substrates and the products are referred to as "Amadori compounds". A variety of Lewis acids ($CuCl_2$, $MgCl_2$, $HgBr_2$, $CdCl_2$, $AlCl_3$, $SnCl_4$, etc.) have been employed as catalysts to induce this rearrangement. The rearrangement takes place if an aldose is reacted with an amine in the presence of a catalytic amount of acid. The amine component can be primary, secondary, aliphatic, or aromatic. Glycosylamine derivatives are implicated in the complex *Maillard reaction*, whereby sugars, amines, and amino acids (proteins) condense, rearrange, and degrade often during cooking or preservation of food.[10] The dark-colored products formed in this reaction are responsible for the non-enzymatic browning observed with various foodstuffs.



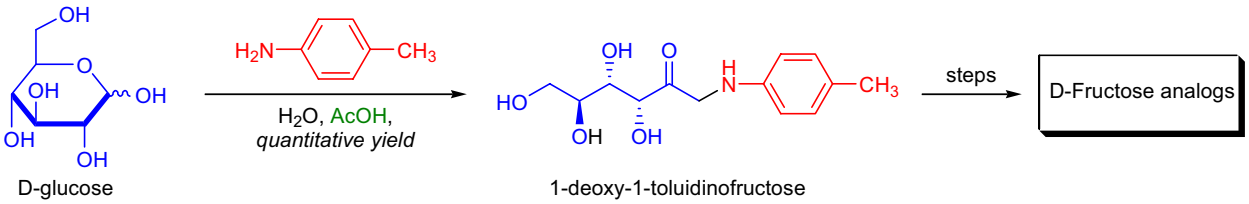
Mechanism:[11,12]

The first step of the mechanism is the coordination of the Lewis acid (proton in the scheme) to the ring oxygen atom of the *N*-glycoside. Subsequently the ring is opened, and the loss of a proton gives rise to an enolic intermediate, which in turn undergoes tautomerization to the corresponding 1-amino-1-deoxyketose.



Synthetic Applications:

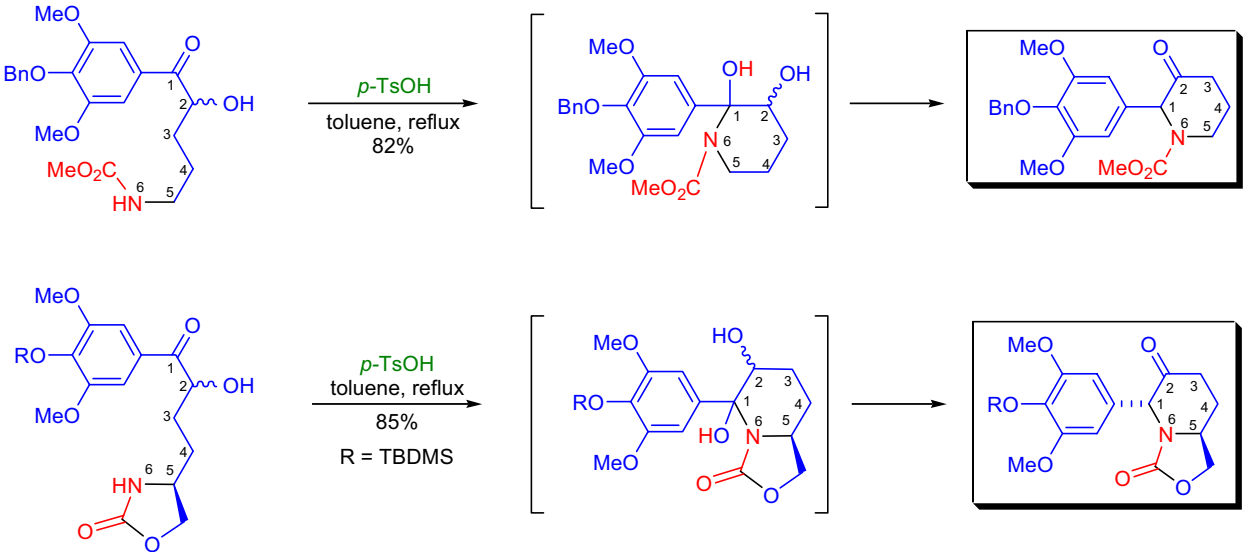
C. Blonski and co-workers utilized the *Amadori rearrangement* in the synthesis of various D-*fructose analogs* that were modified at C1, C2, or C6 positions.[13] The key intermediate, 1-deoxy-1-toluidinofructose, was obtained from D-glucose quantitatively by reacting D-glucose with *p*-toluidine in acetic acid.



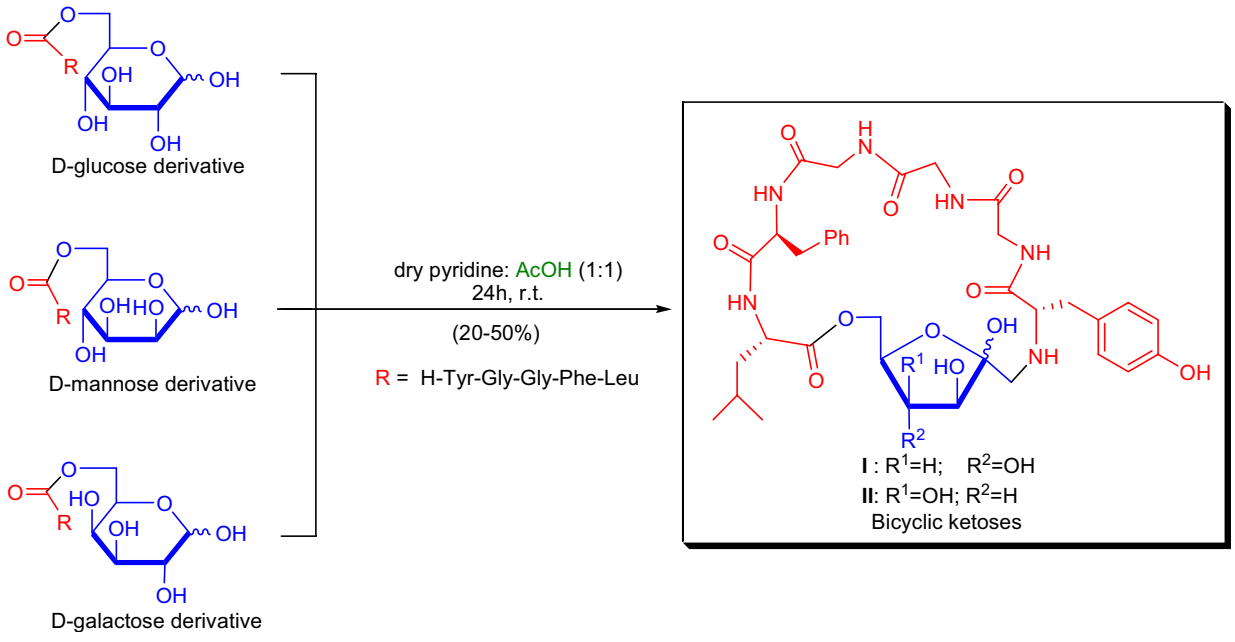
AMADORI REACTION / REARRANGEMENT

Synthetic Applications:

The synthesis of novel DNA topoisomerase II (topo II) inhibitors was undertaken in the laboratory of T.L. Macdonald.[14] Their research program dealt with the synthesis of piperidin-3-one derivatives, which were needed as synthetic intermediates for a variety of potential topo II-directed agents. The key step in their approach was the *Amadori reaction* for the preparation of highly functionalized piperidin-3-ones under mild conditions. Upon treatment with a catalytic amount of *p*-toluenesulfonic acid in toluene at reflux, the desired rearrangement took place in high yield.



S. Horvat and co-workers conducted studies on the *intramolecular Amadori rearrangement* of the monosaccharide esters of the opioid pentapeptide leucine-enkephaline.[15] The esters were prepared from either D-glucose, D-mannose or D-galactose by linking their C6 hydroxy group to the C-terminal carboxy group of the endogenous opioid pentapeptide leucine-enkephaline (H-Tyr-Gly-Gly-Phe-Leu-OH). Exposure of these monosaccharide esters to dry pyridine-acetic acid (1:1) mixture for 24h at room temperature, resulted in the desired *Amadori rearrangement* to afford novel bicyclic ketoses that are related to the furanose tautomers of 1-deoxy-D-fructose (**I**) and 1-deoxy–D-tagatose (**II**).



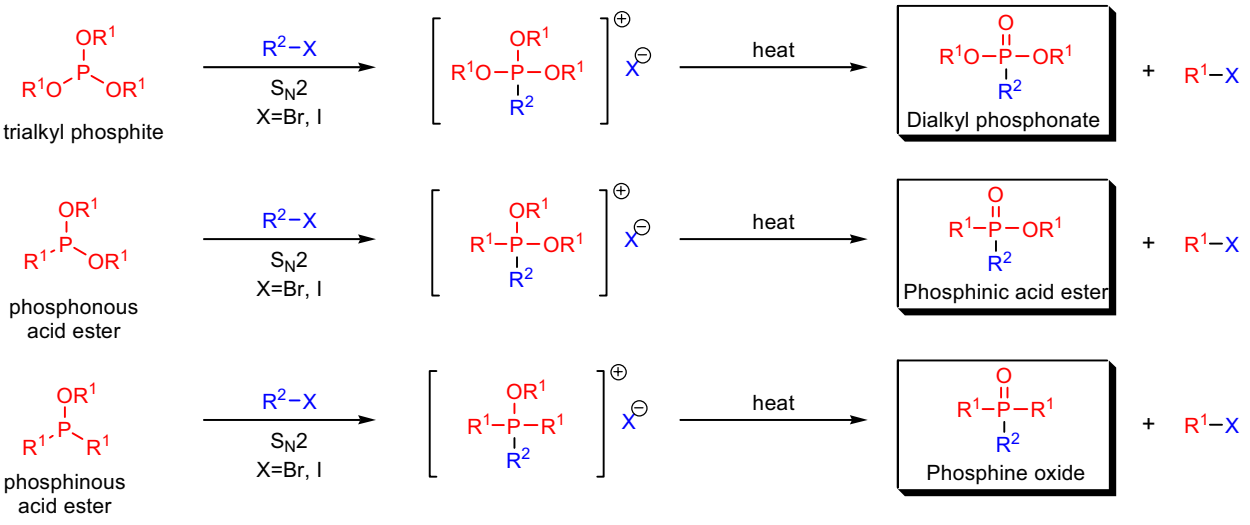
ARBUZOV REACTION
(MICHAELIS-ARBUZOV REACTION)

(References are on page 537)

Importance:

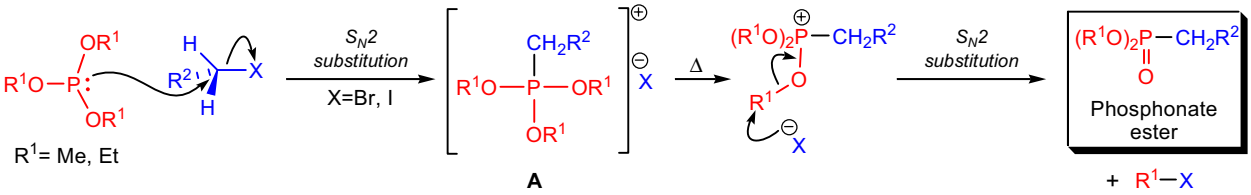
[*Seminal Publications*[1-4]; *Reviews*[5-14]; *Modifications & Improvements*[15-22]]

In 1898, A. Michaelis and R. Kaehne reported that, upon heating, trialkyl phosphites reacted with primary alkyl iodides to afford dialkyl phosphonates.[2] A few years later, A.E. Arbuzov investigated the reaction in great detail and determined its scope and limitations.[3] The synthesis of pentavalent alkyl phosphoric acid esters from trivalent phosphoric acid esters and alkyl halides is known as the *Arbuzov reaction* (also known as *Michaelis-Arbuzov reaction*). The general features of this transformation are:[9] 1) it usually proceeds well with primary alkyl halides (mainly iodides and bromides); 2) certain secondary alkyl halides such as *i*-PrI or ethyl α-bromopropionate do react, but with most secondary and tertiary alkyl halides the reaction does not take place or alkenes are formed; 3) besides simple alkyl halides, other organic halides are also good substrates for the reaction including benzyl halides, halogenated esters, acyl halides, and chloroformic acid esters; 4) aryl and alkenyl halides do not undergo S_N2 substitution, so they are unreactive under the reaction conditions; 5) activated aryl halides (e.g., heteroaryl halides: isoxazole, acridine, coumarin) do react; 6) the alkyl halides may not contain ketone or nitro functional groups, since these usually cause side reactions; 7) α-chloro- and bromo ketones undergo the *Perkow reaction* with trialkyl phosphites to afford dialkyl vinyl phosphates, but α-iodo ketones give rise to the expected Arbuzov products; 8) the trivalent phosphorous reactant can be both cyclic and acyclic; 9) in most cases the reaction takes place in the absence of a catalyst, but for certain substrates the presence of a catalyst is needed; and 10) catalysts can be various metals, metal salts, and complexes (e.g., Cu-powder, Ni-halides, $PdCl_2$, $CoCl_2$), protic acids (e.g., AcOH), or light. Phosphonates are of great importance in organic synthesis, agriculture, and chemical warfare. Organophosphoric acid esters are produced on the multiton scale and used as insecticides (e.g., methidathion, methyl-parathion, etc.). Organophosphonates also found application in chemical warfare (nerve gases such as VX, Sarin, etc.). They are potent inhibitors of the enzyme acetyl cholinesterase *via* phosphorylation and therefore extremely toxic to the parasympathetic nervous system. The *Horner-Emmons-Wadsworth modification of the Wittig reaction* (synthesis of alkenes from carbonyl compounds) utilizes phosphonates instead of phosphoranes. Phosphonates are easily deprotonated to yield ylides that are more reactive than the corresponding phosphoranes (phosphorous ylides). Phosphonates react with ketones that are unreactive toward phosphoranes.



Mechanism: [23-30,15,18]

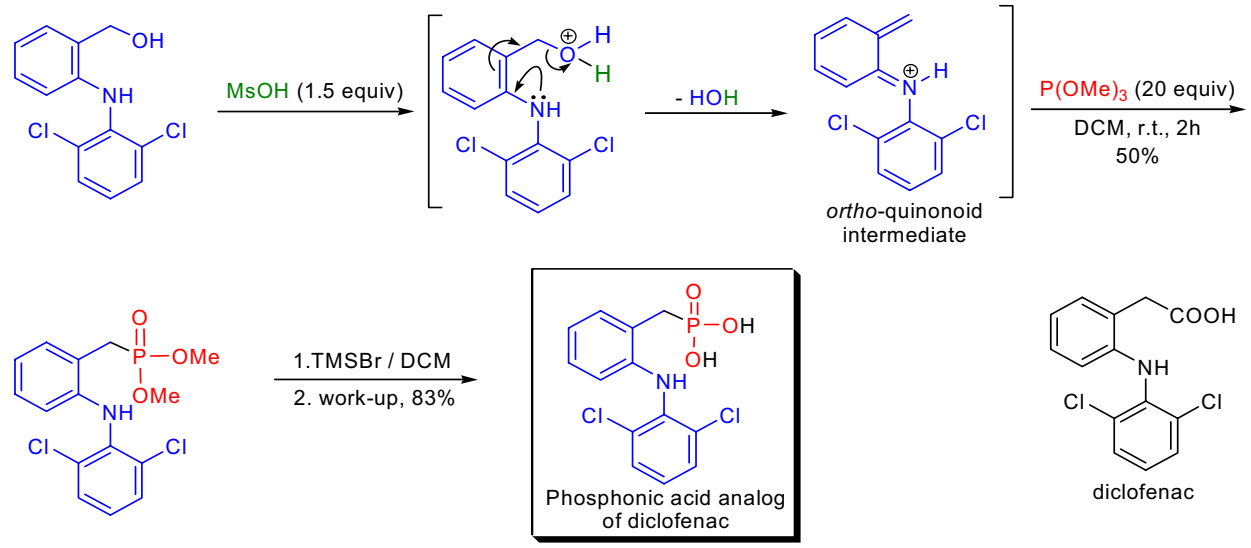
The first step of the mechanism is the nucleophilic attack (S_N2) of the alkyl halide by the phosphorous to form a phosphonium salt **A**. Under the reaction conditions (heat) the phosphonium salt **A** is unstable and undergoes a C-O bond cleavage (the halide ion (X^-) acts as a nucleophile and attacks one of the alkyl groups in an S_N2 reaction) to afford the phosphonate ester.



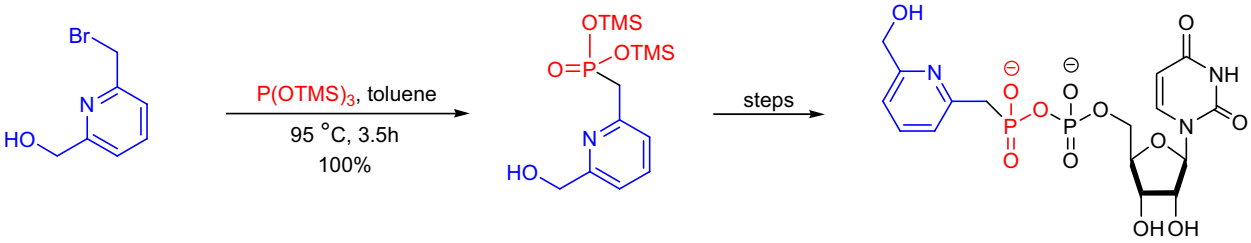
ARBUZOV REACTION
(MICHAELIS-ARBUZOV REACTION)

Synthetic Applications:

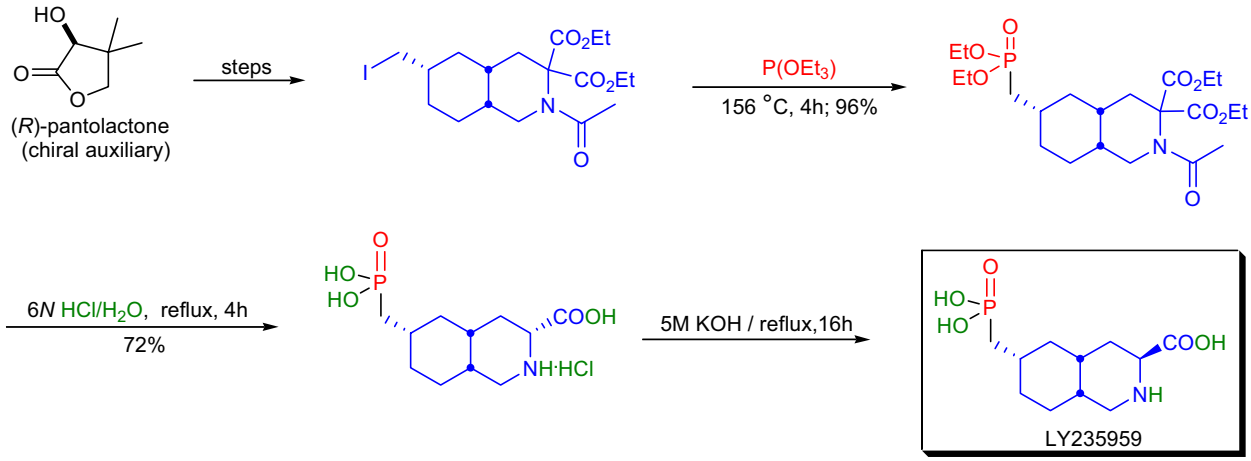
The phosphonic acid analog of NSAID (Non-Steroidal Anti-Inflammatory Drug) diclofenac® was successfully synthesized in the laboratory of B. Mugrage using a novel acid catalyzed *Arbuzov reaction* as the key step followed by a TMSBr promoted dealkylation.[31] It needs to be pointed out that the nucleophilic attack takes place on the *ortho*-quinonoid intermediate in a non-S_N2 process.



R.R. Schmidt and co-workers designed and synthesized a novel class of glycosyltransferase inhibitors.[32] The key synthetic steps involve an *Arbuzov reaction* followed by a coupling with uridine-5'-morpholidophosphate as the activated derivative.



A novel enantioselective synthesis of an antagonist of the NMDA receptor, *cis*-perhydroisoquinoline LY235959, was achieved in 13% overall yield and 17 steps from (*R*)-pantolactone in the laboratory of M.M. Hansen.[33] The phosphoric acid portion of the target was introduced by a high-yielding *Arbuzov reaction*.



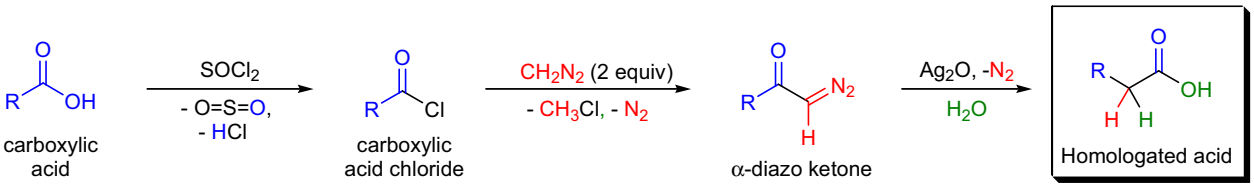
ARNDT-EISTERT HOMOLOGATION / SYNTHESIS

(References are on page 538)

Importance:

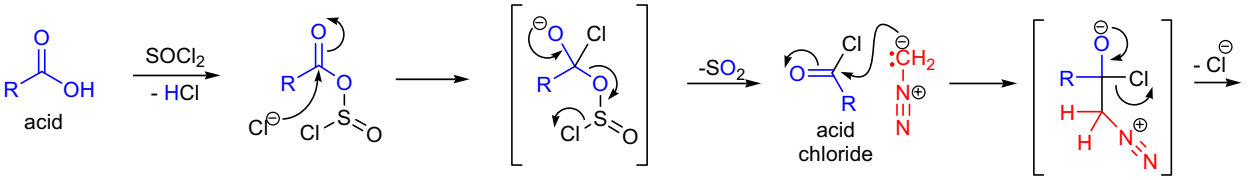
[*Seminal Publication*[1]*; Reviews*[2-4]*; Modifications & Improvements*[5-10]]

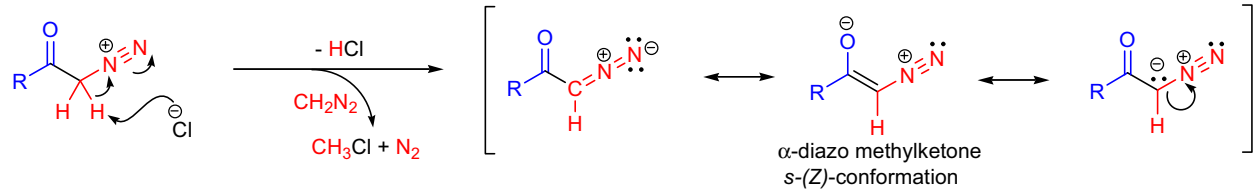
The conversion of a carboxylic acid to its homolog (one CH_2 group longer) in three stages is called the *Arndt-Eistert synthesis*. This homologation is the best preparative method for the chain elongation of carboxylic acids. In the first stage of the process the acid is converted to the corresponding acid chloride. The second stage involves the formation of a α-diazo methylketone, followed by a *Wolff rearrangement* in the third stage.[4] The third stage is conducted either in the presence of solid silver oxide/water or silver benzoate/triethylamine solution. The yields are usually good (50-80%). If the reaction is conducted in the presence of an alcohol (ROH) or amine (RNHR'), the corresponding homologated ester or amide is formed. Other metals (Pt, Cu) also catalyze the decomposition of the diazo ketones. An alternative method is to heat or photolyze the diazo ketone in the presence of a nucleophilic solvent (H_2O, ROH, or RNH_2), and in these cases no catalyst is required. The reaction tolerates a wide range of non-acidic functional groups (alkyl, aryl, double bonds). Acidic functional groups would react with diazomethane or diazo ketones.

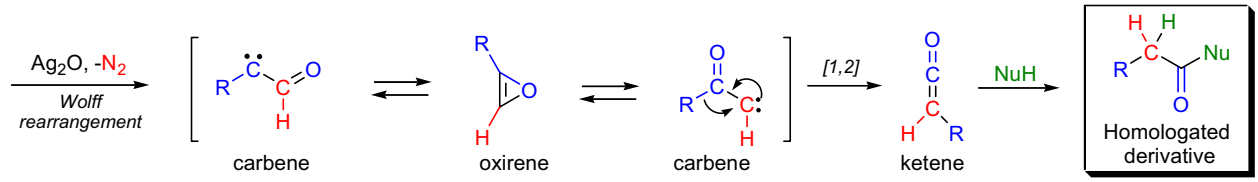


Mechanism: [2,11,4]

Since hydrogen chloride (HCl) is the by-product of the reaction between the acid chloride and diazomethane, two equivalents of diazomethane are needed so that the presence of HCl does not give side products (e.g. chloroketones). The HCl reacts with the second equivalent of diazomethane to form methyl chloride and dinitrogen. The role of the catalyst is not well understood. The diazo ketone can exist in two conformations, namely the *s-(E)* and *s-(Z)* conformations, which arise from the rotation about the C-C single bond. It has been shown that the *Wolff rearrangement* takes place preferentially from the *s-(Z)* conformation. With the loss of a molecule of nitrogen, the decomposition of the diazo ketone involves the formation of a carbene, followed by a carbene rearrangement with the intermediacy of an oxirene. The carbene undergoes a rapid *[1,2]*-shift to afford a ketene that reacts with the nucleophilic solvent to give the homologated acid derivative.



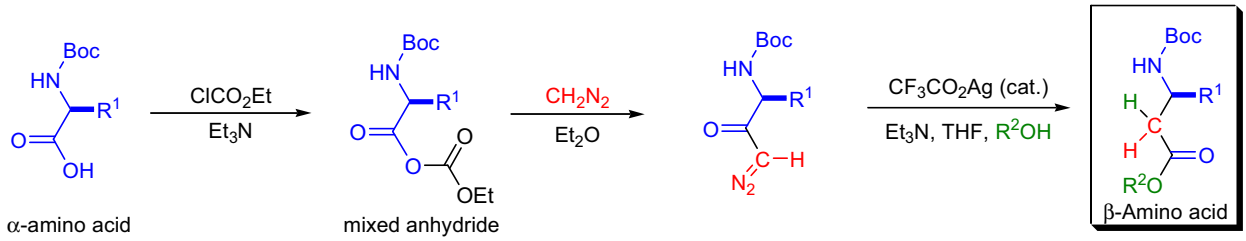




ARNDT-EISTERT HOMOLOGATION / SYNTHESIS

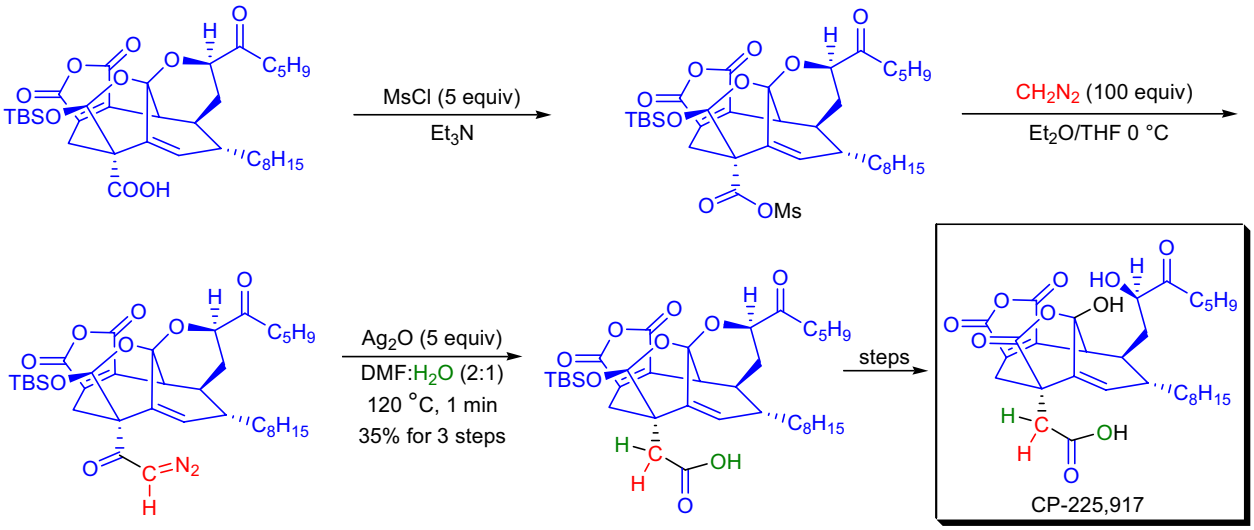
Synthetic Applications:

The oligomers of β-amino acids, as opposed to α-peptides, show a remarkable ability to fold into well-defined secondary structures in solution as well as in the solid state. The β-amino acid building blocks were synthesized from α-amino acids using the *Arndt-Eistert homologation reaction* in the laboratory of D. Seebach.[12]

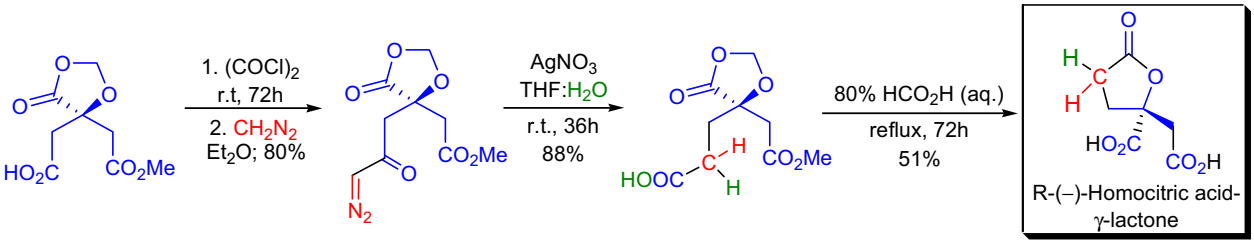


α-amino acid — mixed anhydride

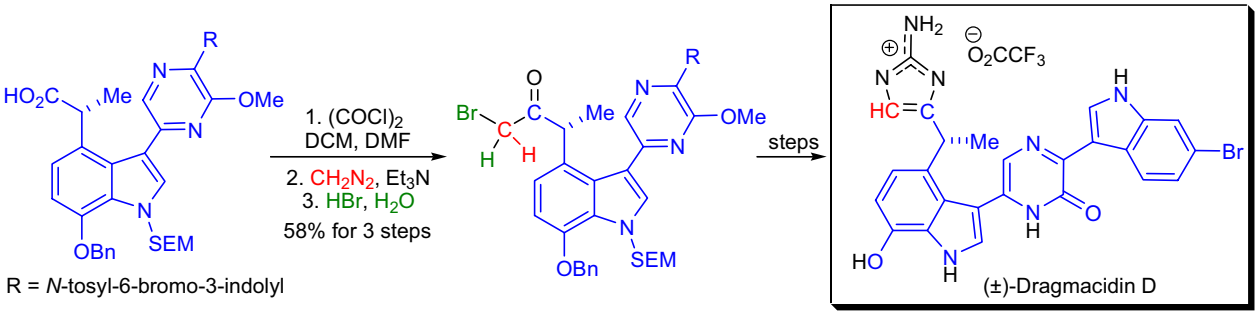
During the total synthesis of the CP molecules, K.C. Nicolaou et al. homologated a sterically hindered carboxylic acid, which was part of an advanced intermediate.[13] Due to the sensitive nature of this intermediate, the diazo ketone was prepared *via* the acyl mesylate rather than the acid chloride. The diazo ketone then was immediately dissolved in DMF:H_2O (2:1) and heated to 120 °C in the presence of excess Ag_2O for one minute to generate the homologated acid in 35% yield.



A.T. Russell and co-workers synthesized (*R*)-(–)-homocitric acid-γ-lactone in multigram quantities starting from a citric acid derivative and using the *Arndt-Eistert homologation* as the key step.[14]



In the laboratory of B.M. Stolz, the first total synthesis of the bis-indole alkaloid (±)-dragmacidin D was accomplished.[15] During the endgame, a carboxylic acid was homologated to the corresponding α-bromo ketone by treating the diazo ketone intermediate with hydrobromic acid.



R = *N*-tosyl-6-bromo-3-indolyl

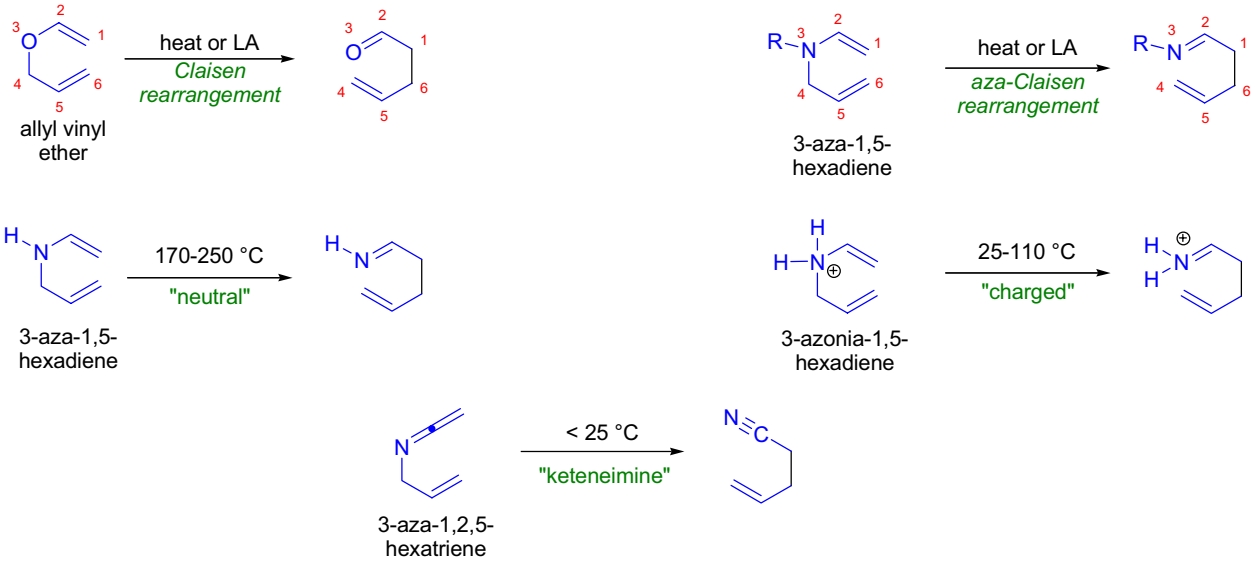
AZA-CLAISEN REARRANGEMENT
(3-AZA-COPE REARRANGEMENT)

(References are on page 538)

Importance:

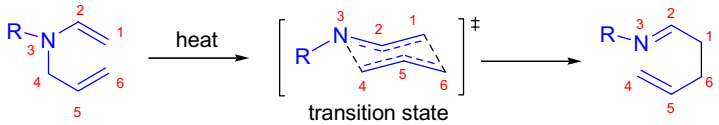
[*Seminal Publications*[1]*; Reviews*[2,3]*; Modifications & Improvements*[4-11]*; Theoretical Studies*[12]]

The thermal *[3,3]-sigmatropic rearrangement* of allyl vinyl ethers is called the *Claisen rearrangement*.[13,14] Its variant, the thermal *[3,3]-sigmatropic rearrangement* of *N*-allyl enamines, is called the *aza-Claisen rearrangement* (*3-aza-Cope* or *amino-Claisen rearrangement*). There are several known variations of the *aza-Claisen rearrangement*, and each one belongs to a subclass of this type of reaction. The rates of the rearrangement depend mainly on the structural features of the specific system, which can be: 1) *3-aza-1,5-hexadienes;* 2) *3-azonia-1,5-hexadienes*; and 3) *3-aza-1,2,5-hexatrienes*. The observed temperature trend for these reactions is that milder temperatures are required as one progresses from the "*neutral*" to the "*charged*" and finally to the *keteneimine* rearrangement. The rearrangement generally occurs between 170-250 °C for the neutral species, and between room temperature and 110 °C for the Lewis acid coordinated or quaternized molecules.



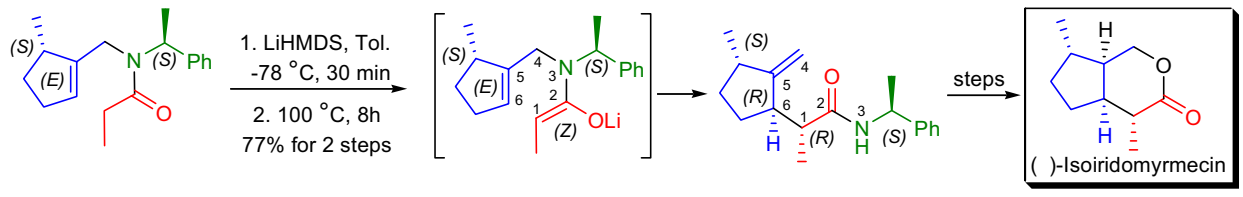
Mechanism:

The *aza-Claisen rearrangement* is a concerted process, and it usually takes place *via* a chairlike transition state where the substituents are arranged in quasi-equatorial positions. (See more details in *Claisen rearrangement*.)



Synthetic Applications:

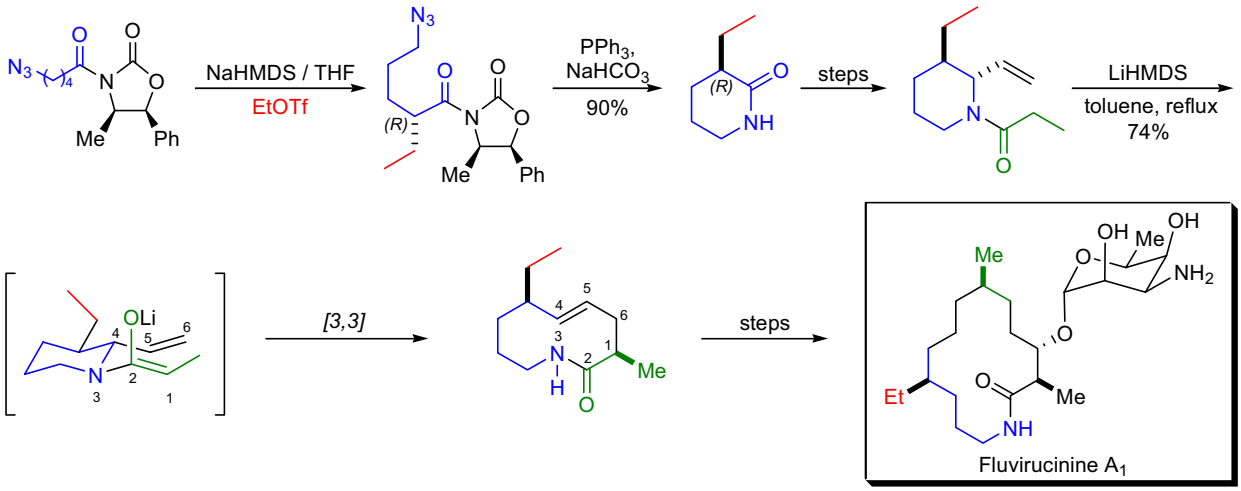
S. Ito et al. utilized the *aza-Claisen rearrangement* of carboxamide enolates for the enantioselective total synthesis of (–)-isoiridomyrmecin, which is a constituent of *Actinidia polygama* and exhibits unique bioactivity.[2] The rearrangement of the (*S,S*) stereoisomer was conducted under standard conditions, and the product was isolated as a single (*R,R*) stereoisomer in 77% yield.



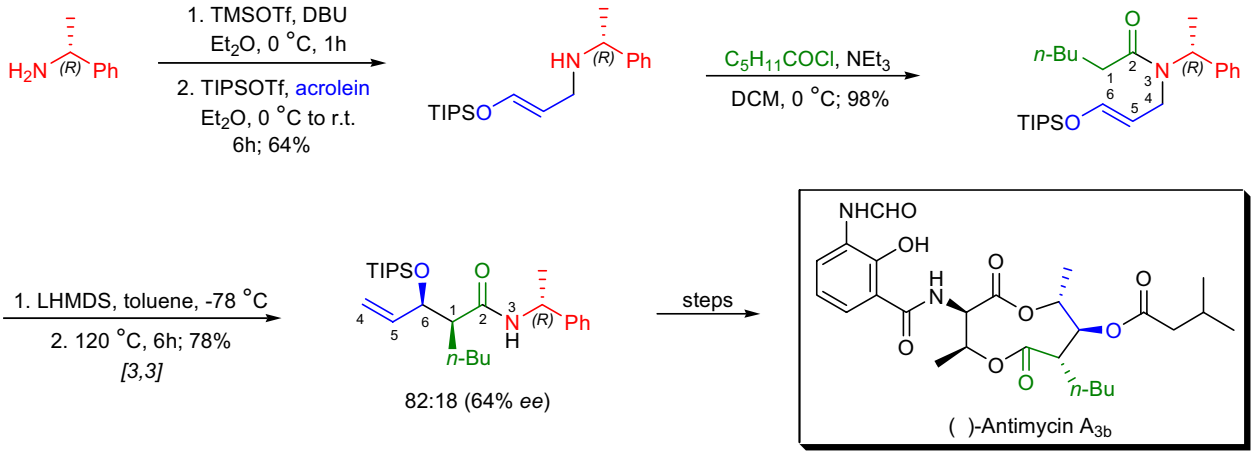
AZA-CLAISEN REARRANGEMENT
(3-AZA-COPE REARRANGEMENT)

Synthetic Applications:

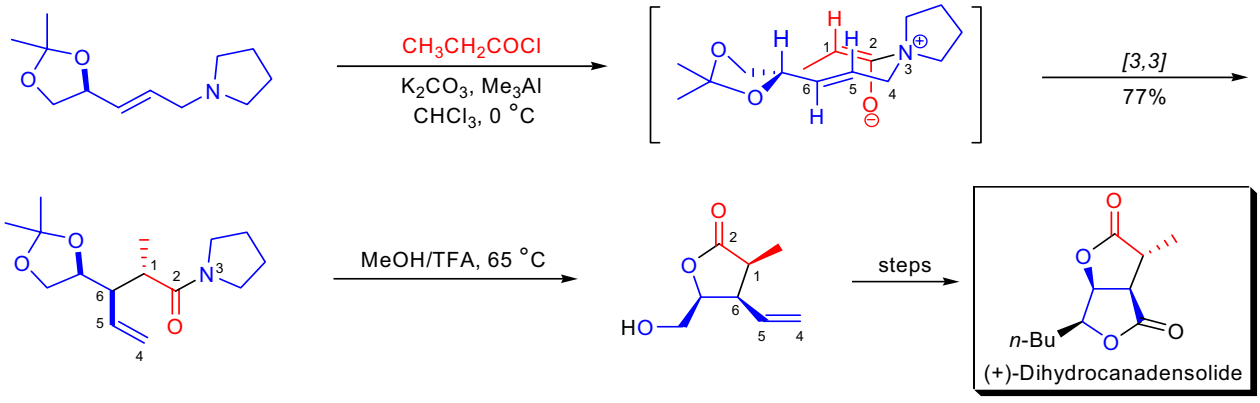
The first asymmetric synthesis of fluvirucinine A_1 was accomplished in the laboratory of Y.-G. Suh.[15] Key steps of the synthesis involved a diastereoselective vinyl addition to the amide carbonyl group as well as an *amide enolate induced aza-Claisen rearrangement*.[15]



T. Tsunoda and co-workers synthesized the antipode of natural antibiotic antimycin A_{3b} starting from (*R*)-(+)-methylbenzylamine and utilizing the *asymmetric aza-Claisen rearrangement*.[16] The amide precursor was deprotonated with LiHMDS at low temperature then the reaction mixture was refluxed for several hours to bring about the sigmatropic rearrangement.



U. Nubbemeyer et al. achieved the enantioselective total synthesis of the bicyclic tetrahydrofuran natural product (+)-dihydrocanadensolide *via* a key step utilizing the *diastereoselective zwitterionic aza-Claisen rearrangement* of an *N*-allylpyrrolidine.[17]



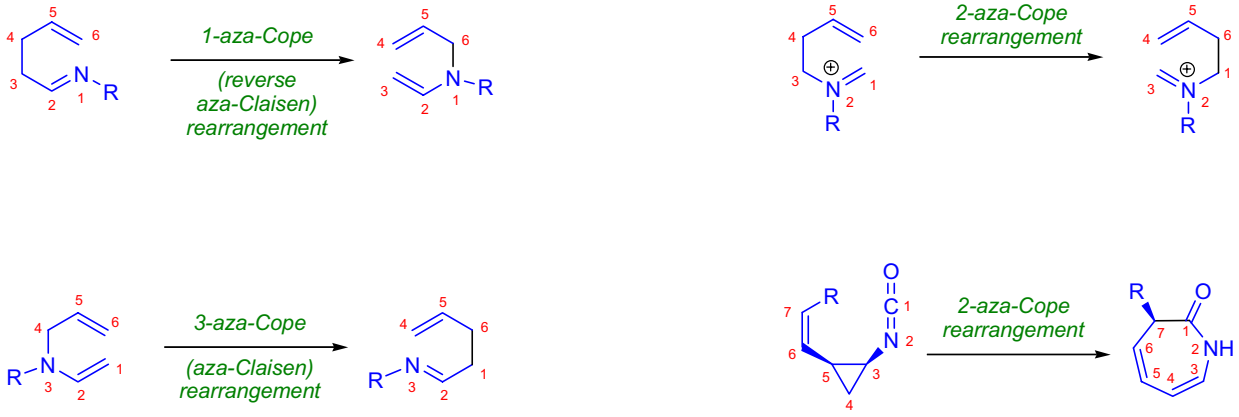
AZA-COPE REARRANGEMENT

(References are on page 538)

Importance:

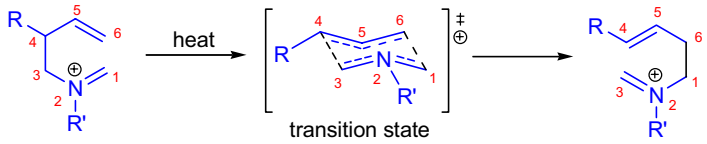
[*Seminal Publications*[1-3]*; Reviews*[4-6]*; Modifications & Improvements*[7-28]*; Theoretical Studies*[18,21,29]]

When 1,5-dienes are heated, they isomerize *via* a *[3,3]-sigmatropic rearrangement* known as the *Cope rearrangement*. The rearrangement of *N*-substituted 1,5-dienes is called the *aza-Cope rearrangement*. This reaction has many variants, namely *1-aza-*, *2-aza-*, *3-aza-* and *1,3-*, *2,3-*, *2,5-*, *3,4- diaza-Cope rearrangements*.[7,8] The *3-aza-Cope rearrangement* is also known as the *aza-Claisen rearrangement*. The rearrangement of *cis*-2-vinylcyclopropyl isocyanates to 1-azacyclohepta-4,6-dien-2-ones (*2-aza-divinylcyclopropane rearrangement*) is analogous to the well-known and highly stereospecific *cis-divinylcyclopropane rearrangement*. It is well established that the presence of an oxygen atom adjacent to the π-bond accelerates the *Cope rearrangement*. When there is a group attached to C3 or C4 with which the newly formed double bond can conjugate, the reaction takes place at a lower temperature than in the unsubstituted case. As with all *[3,3]-sigmatropic rearrangements*, the activation energies are significantly lowered when the starting diene is charged.



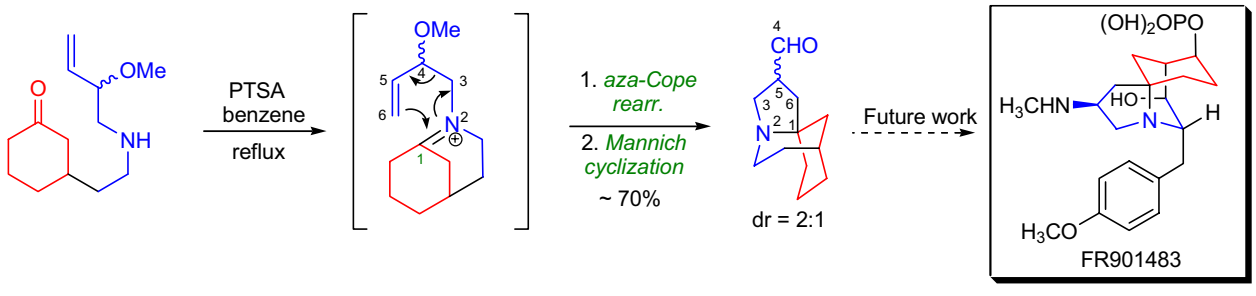
Mechanism:[30-35,18,36,21,37,38,29]

The *aza-Cope rearrangement* is a concerted process, and it usually takes place *via* a chairlike transition state where the substituents are arranged in a quasi-equatorial position. (*See more detail in Cope rearrangement.*)



Synthetic Applications:

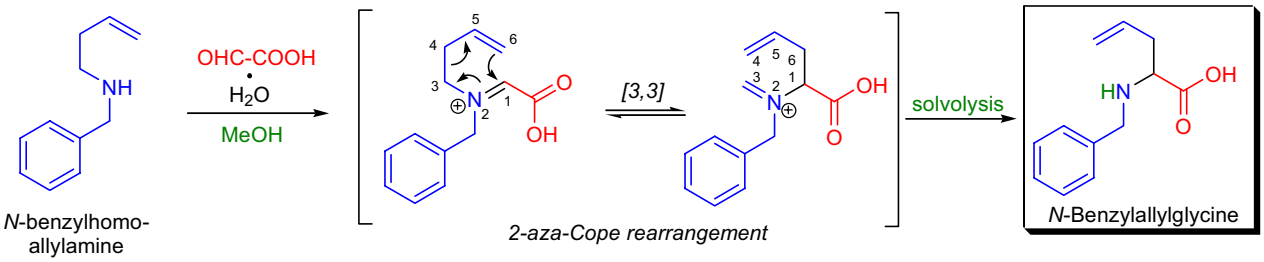
The *tandem cationic aza-Cope rearrangement* followed by a *Mannich cyclization* was applied in the synthesis of the novel tricyclic core structure of the powerful immunosupressant FR901483 in the laboratory of K. Brummond.[39] Their approach was the first synthetic example in which this tandem reaction passes through a bridgehead iminium ion.



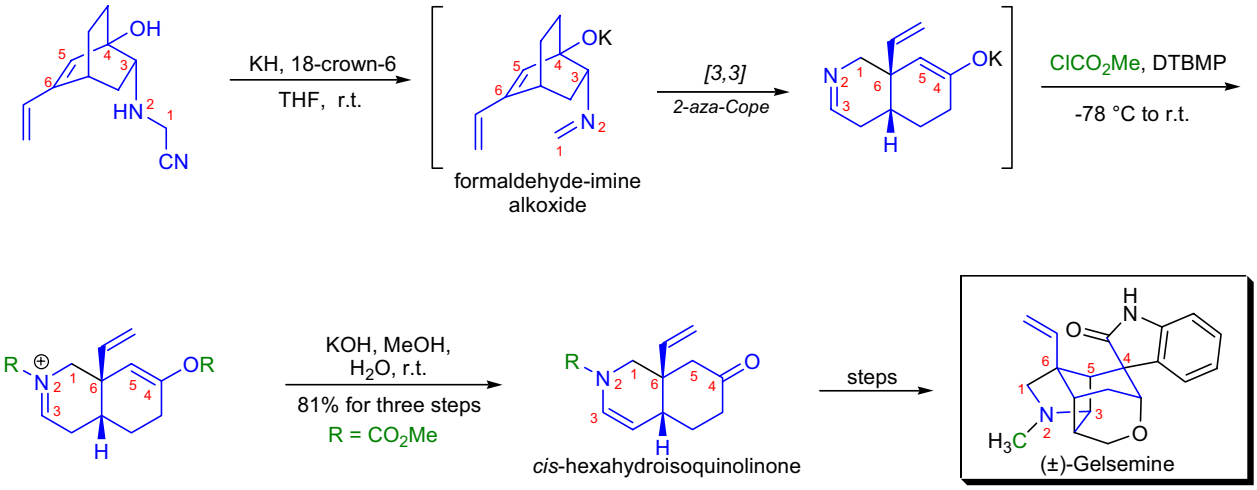
AZA-COPE REARRANGEMENT

Synthetic Applications:

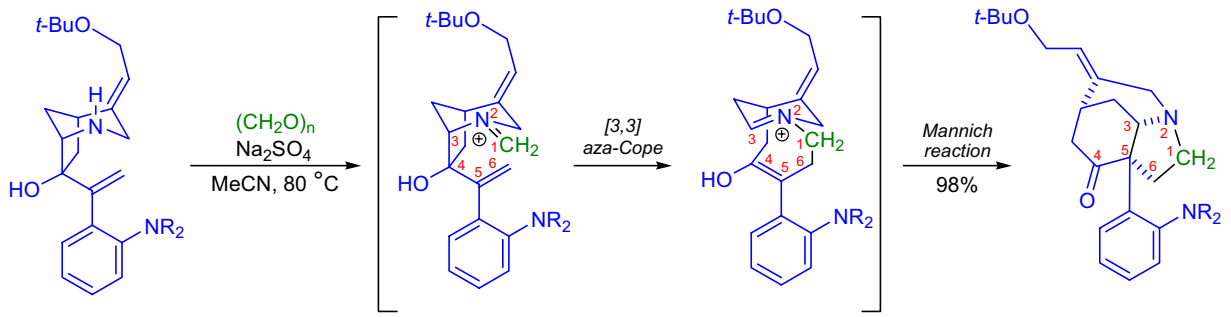
D.J. Bennett et al. developed a facile synthesis of *N*-benzylallylglycine based on a *tandem 2-aza-Cope/iminium ion solvolysis reaction*.[40] *N*-Benzylallylglycine can be prepared in good yield through a one-pot reaction of *N*-benzylhomoallylamine with glyoxylic acid monohydrate in methanol.



L.E. Overman and co-workers accomplished a total synthesis of (±)-gelsemine by a sequence where the key strategic steps are a sequential anionic 2-*aza-Cope rearrangement* and *Mannich cyclization*, an *intramolecular Heck reaction*, and a *complex base-promoted molecular reorganization* to generate the hexacyclic ring system.[41] The exposure of the bicyclic substrate to potassium hydride in the presence of 18-crown-6 initiated the anionic aza-Cope rearrangement of the bicyclic formaldehyde-imine alkoxide. The rearrangement product was quenched with excess methyl chloroformate then was treated with base to afford the desired *cis*-hexahydroisoquinolinone.



During the enantioselective total syntheses of (–)- and (+)-strychnine and the Wieland-Gumlich aldehyde, L.E. Overman and co-workers used the tandem *aza-Cope rearrangement/Mannich reaction* as a key step.[42] This central *aza-Cope/Mannich reorganization* step proceeded in 98% yield.



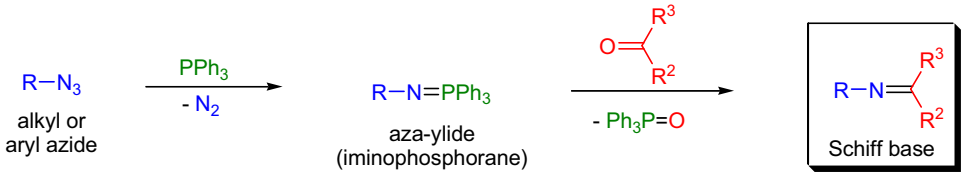
AZA-WITTIG REACTION

(References are on page 539)

Importance:

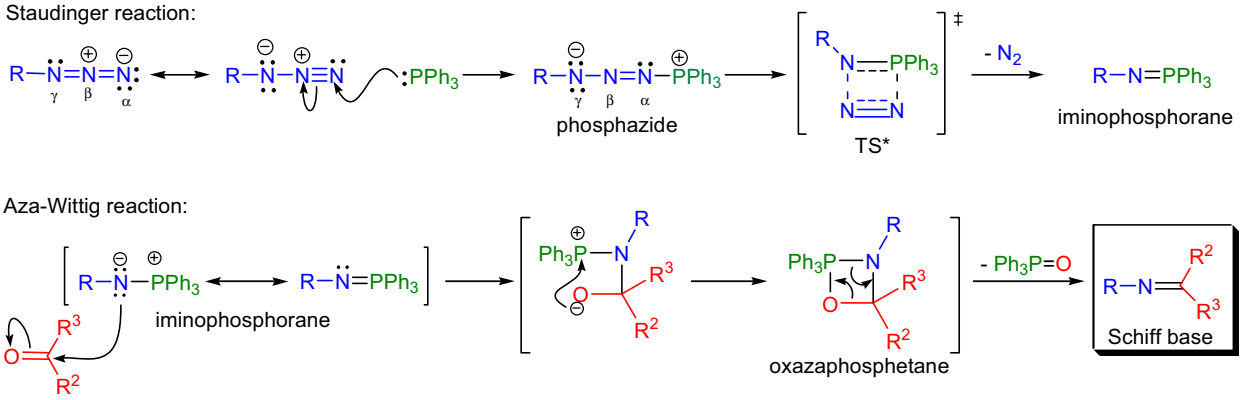
[*Seminal Publications*[1]; *Reviews*[2-11]; *Theoretical Studies*[12-17]]

In 1919, H. Staudinger and J. Meyer prepared $PhN{=}PPh_3$, an aza-ylide which was the first example of an aza-Wittig reagent.[1] By definition an ylide is "a substance in which a carbanion is attached directly to a heteroatom carrying a substantial degree of positive charge and in which the positive charge is created by the sigma bonding of substituents to the heteroatom".[4] The reaction of aza-ylides (iminophosphoranes) with various carbonyl compounds is called the *aza-Wittig reaction*. The product of the reaction is a Schiff base. Just as in the regular *Wittig reaction*, the by-product is triphenylphosphine oxide. Over the last decade, the *aza-Wittig* methodology has received considerable attention because of its utility in the synthesis of C=N double bond containing compounds, in particular, nitrogen heterocycles. The *intramolecular aza-Wittig reaction* is a powerful tool for the synthesis of 5-, 6-, 7-, and 8 membered heterocycles.



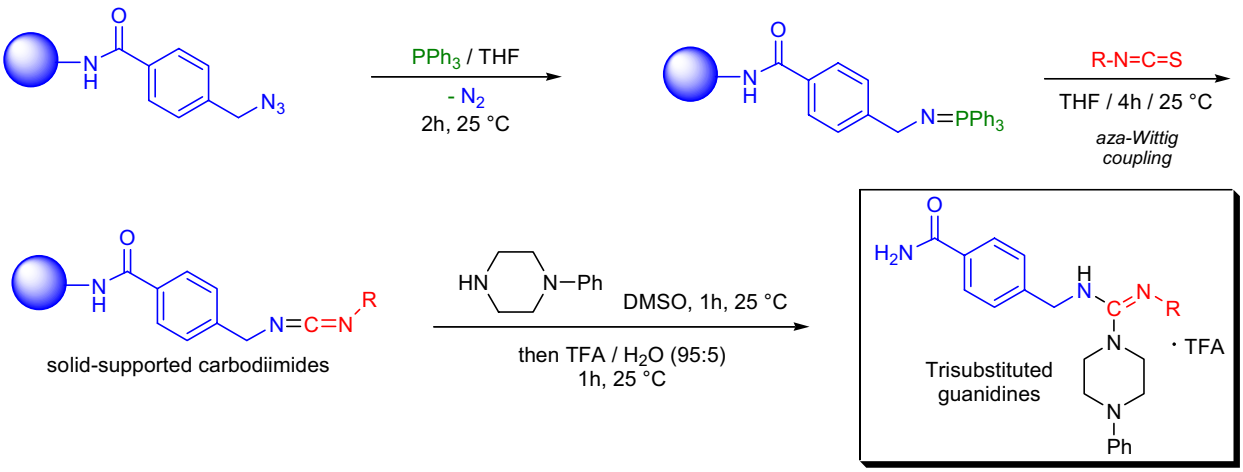
Mechanism:[18,15]

In the first step, the triphenylphosphine reacts with an alkyl azide to form an iminophosphorane with loss of nitrogen (*Staudinger reaction*). In the second step, the nucleophilic nitrogen of the iminophosphorane attacks the carbonyl group to form a four-membered intermediate (oxazaphosphetane) from which the product Schiff base and the by-product triphenylphosphine oxide are released.



Synthetic Applications:

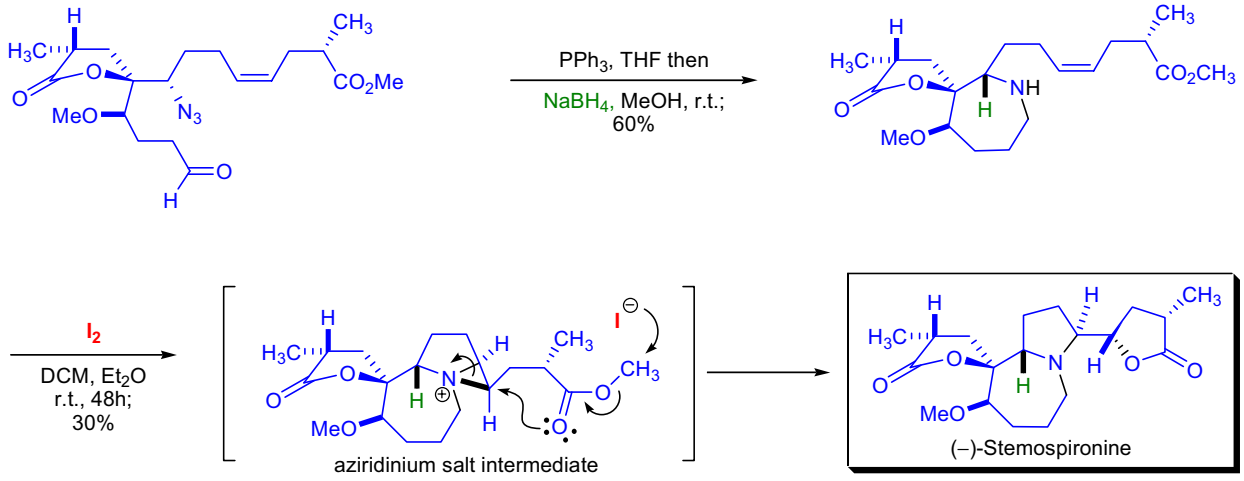
The solid phase synthesis of trisubstituted guanidines was achieved in the research group of D.H. Drewery by utilizing the *aza-Wittig reaction*. The reaction of solid-supported alkyl iminophosphorane and aryl or alkyl isothiocyanates afforded carbodiimides, which upon treatment with primary or secondary amines provided the trisubstituted guanidines.[19]



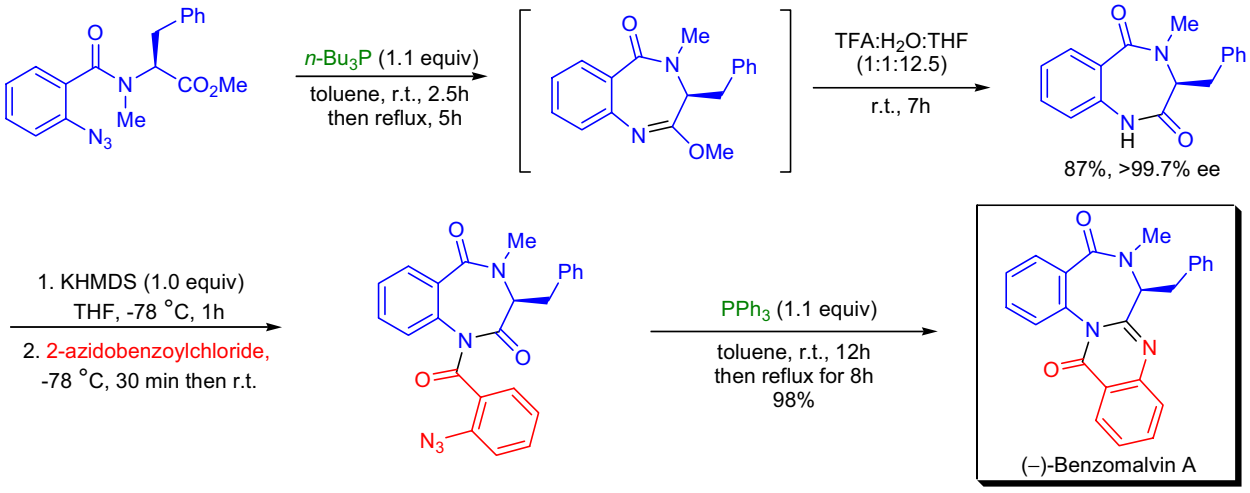
AZA-WITTIG REACTION

Synthetic Applications:

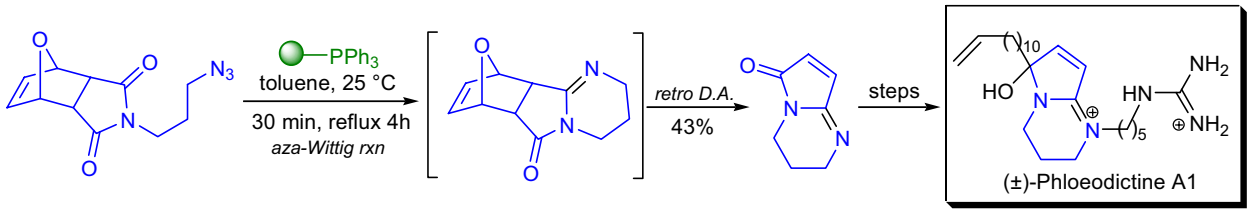
D.R. Williams and co-workers have accomplished the stereocontrolled total synthesis of the polycyclic *Stemona* alkaloid, (–)-stemospironine.[20] Key transformations included the use of a *Staudinger reaction* leading to the *aza-Wittig ring closure* of the perhydroazepine system. The *Staudinger reaction* was initiated by the addition of triphenylphosphine, leading to an aza-ylide for intramolecular condensation providing a seven-membered imine. An *in situ* reduction yielded the azepine system. Finally, (–)-stemospironine was produced by the iodine-induced double cyclization reaction in which the vicinal pyrrolidine butyrolactone was formed *via* the stereoselective intramolecular capture of an intermediate aziridinium salt.



The first total synthesis of (–)-benzomalvin A, which possesses a 4(3H)-quinazolinone and 1,4-benzodiazepin-5-one moiety, was accomplished in the laboratory of S. Eguchi.[21] Both 6- and 7-membered ring skeletons were efficiently constructed by the *intramolecular aza-Wittig reaction*. The precursors were prepared from L-phenylalanine. The reaction of the azide derivative with tributylphosphine formed the corresponding iminophosphorane intermediate, which spontaneously underwent the *aza-Wittig cyclization* to give the 7-membered ring. Finally the 6-membered ring of (–)-benzomalvin A was constructed by another *intramolecular aza-Wittig cyclization reaction*.



In the total synthesis of antitumor antibiotic (±)-phloeodictine A1 by B.B. Snider and co-workers, the key step was an *aza-Wittig reaction* followed by a *retro-Diels-Alder reaction* to afford the desired bicyclic amidine.[22] The polystyrene-supported PPh_3 made it easy to separate the product from by-products with a simple filtration.



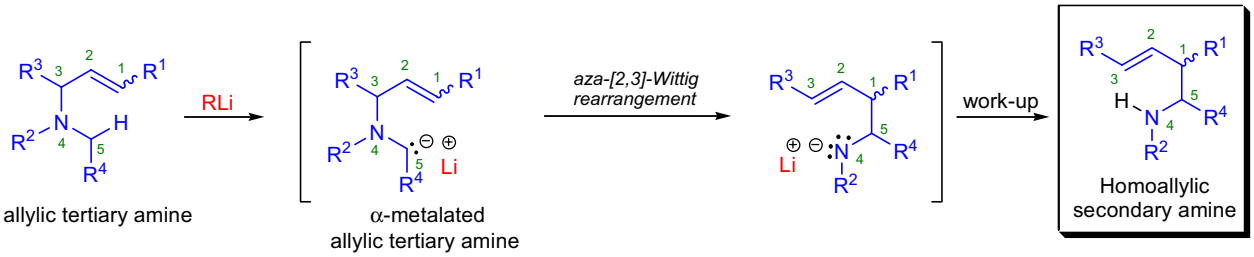
AZA-[2,3]-WITTIG REARRANGEMENT

(References are on page 540)

Importance:

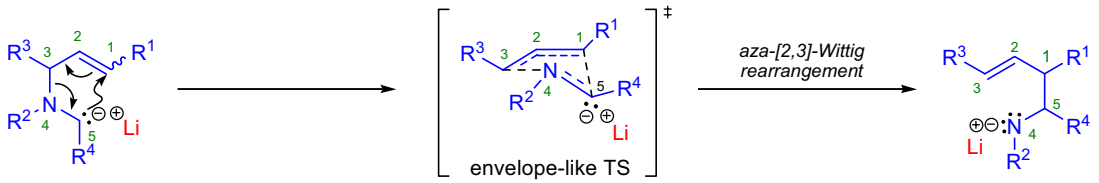
[*Seminal Publications*[1,2]*; Review*[3]; *Modifications & Improvements*[4-14]; *Theoretical Studies*[9,15]]

The highly stereoselective rearrangement of α-metalated ethers to metal alkoxides is called the *Wittig rearrangement* and was first reported by G. Wittig and L. Löhmann in 1942.[16] The product is a secondary or tertiary alcohol after hydrolytic work-up. The nitrogen analog of this reaction is the isoelectronic *aza-Wittig rearrangement* that involves the isomerization of α-metalated tertiary amines to skeletally rearranged metal amides. The corresponding homoallylic secondary amines are obtained upon work-up. It was shown that the *aza-[2,3]-Wittig rearrangement* proceeds with the inversion of configuration of the lithium bearing carbon[17] as it occurs in the oxygen series. The *aza-Wittig rearrangement* should not be confused with the *Stevens* or *Sommelet-Hauser rearrangement* that both require quaternary ammonium salts as starting materials. These two rearrangements may lead to side products (e.g., when a quaternary ammonium salt is treated with a strong base, a rearranged tertiary amine may be formed by the *Stevens rearrangement* through a vicinal alkyl migration). In the case of a benzyltrialkylammonium salt the *Sommelet-Hauser rearrangement* may also compete; it is favored at low temperatures and yields an *o*-substituted benzyldialkylamine through a *[2,3]-sigmatropic rearrangement*.[3] In general, the *aza-[2,3]-Wittig rearrangement* of α-metalated amines is considerably slower (due to the lack of a thermodynamic driving force) and less selective than that of α-metalated ethers. Exceptions are noted when the rate of rearrangement is increased due to the relief of ring strain.



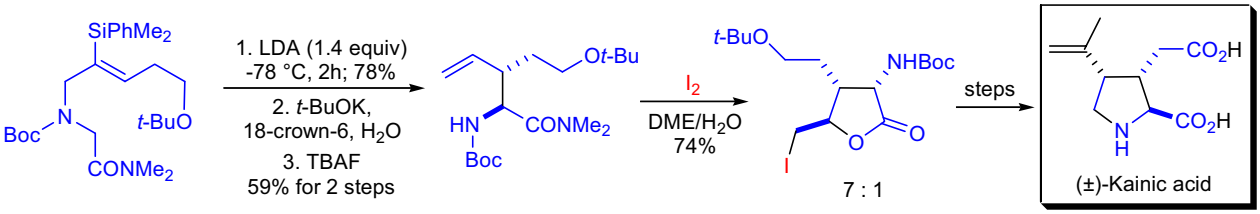
Mechanism:[18-22,9]

The *aza-[2,3]-Wittig rearrangement* proceeds by a concerted process through a six-electron, five-membered cyclic transition state of envelope-like geometry. According to the Woodward-Hoffmann rules, the *[2,3]-sigmatropic rearrangement* is a thermally allowed, concerted sigmatropic rearrangement that proceeds in a suprafacial fashion with respect to both fragments. Therefore, the *aza-[2,3]-Wittig rearrangement* is a one-step S_Ni-reaction, which results in a regiospecific carbon-carbon bond formation by suprafacial allyl inversion in which the heteroatom function gets transposed from allylic to homoallylic. The driving force for these rearrangements is the transfer of a formal negative charge from the less electronegative α-carbon to the more electronegative heteroatom.



Synthetic Applications:

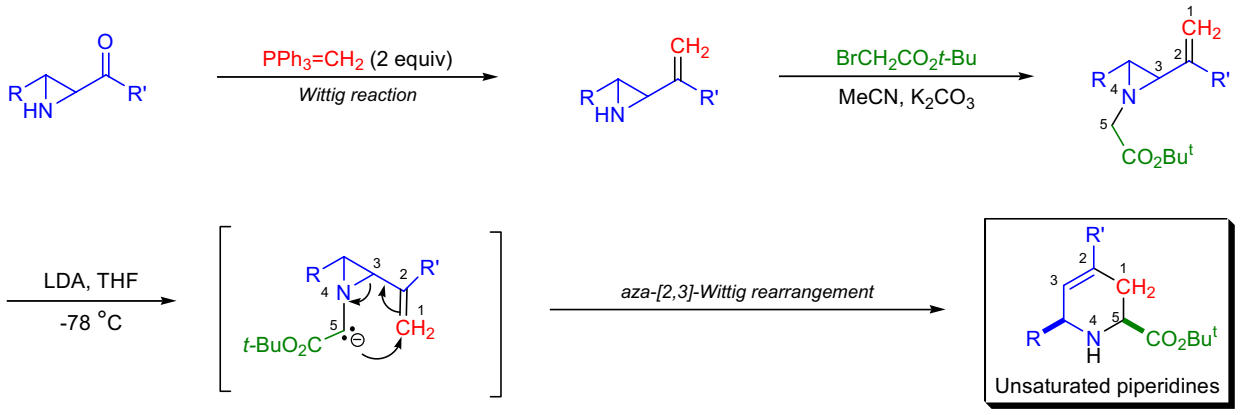
In the laboratory of J.C. Anderson, the total synthesis of (±)-kainic acid was accomplished relying on a route that utilized an *aza-[2,3]-Wittig rearrangement* as the key step to install the correct relative stereochemistry between C2 and C3.[23] The C4 stereocenter was established *via* an *iodolactonization reaction*.



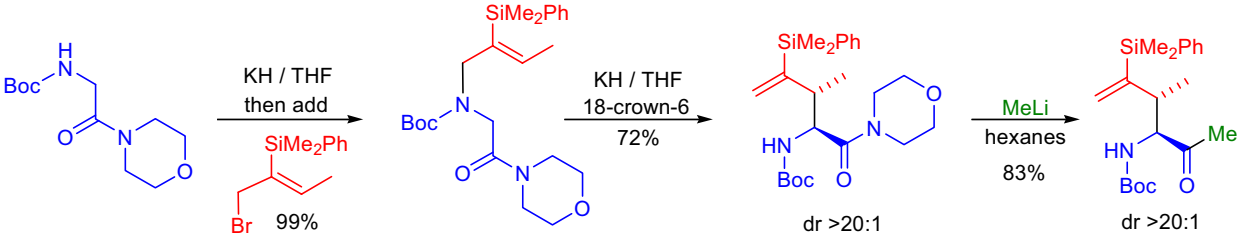
AZA-[2,3]-WITTIG REARRANGEMENT

Synthetic Applications:

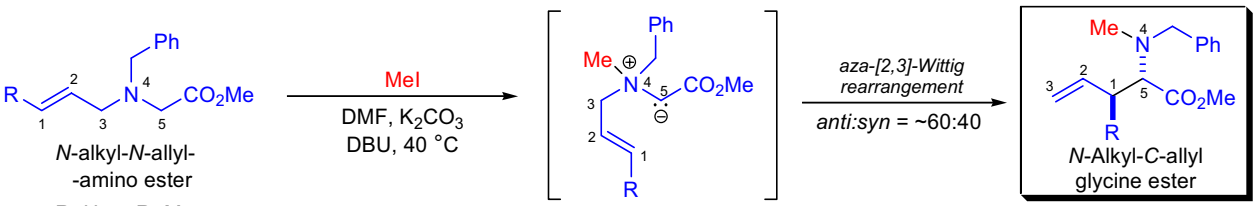
The *aza-Wittig rearrangement* of appropriately substituted vinylaziridines leads to the stereoselective formation of tetrahydropyridines, which are key intermediates in the synthesis of piperidines. A one-pot, two-step synthesis of unsaturated piperidines from 2-ketoaziridines utilizing the *aza-[2,3]-Wittig rearrangement* was reported by I. Coldham and co-workers.[24] Treatment of 2-ketoaziridines with two equivalents of a phosphonium ylide generates vinylaziridines that rearrange by a *[2,3]*-sigmatropic shift with the concomitant ring opening of the aziridines to give unsaturated piperidines.



Research by J.C. Anderson et al. has shown that the inclusion of a C2 trialkylsilyl substituent into allylic amine precursors allows the base-induced *aza-[2,3]-sigmatropic rearrangement* to proceed in excellent yield and diastereoselectivity.[14] The rearrangement precursors require a carbonyl-based nitrogen protecting group that must be stable to the excess strong base required for the reaction. The *N*-Boc and *N*-benzoyl groups are very good at stabilizing the product anion and initiating deprotonation. The migrating groups need to stabilize the initial anion by resonance and a pK_a>22 is required for the rearrangement to occur. Products are formed with high *anti* diastereoselectivity (10:1-20:1).



Tertiary amines are generally reluctant to undergo the *[2,3]-aza-Wittig rearrangement* and promotion of the rearrangement leads to unreacted starting material or *[1,2]*-rearranged products. However, in certain cases the addition of Lewis acids can lead to successful *aza-[2,3]-Wittig rearrangements*. In the laboratory of I. Coldham, the *aza-[2,3]-Wittig rearrangement* of *N*-alkyl-*N*-allyl- -amino esters to *N*-alkyl-*C*-allyl glycine esters was investigated in detail.[25] It was reported that instead of using Lewis acids, the addition of iodomethane or benzyl bromide to tertiary amines promoted quaternary ammonium salt formation. *In situ*, these salts underwent spontaneous *[2,3]*-sigmatropic rearrangement when DMF was used as the solvent along with K_2CO_3 and DBU at 40 °C. In all cases when R=Me, a 60:40 *anti:syn* ratio of diastereomers was obtained.



N-alkyl-*N*-allyl- -amino ester
R=H or R=Me

N-Alkyl-*C*-allyl glycine ester
R=H, 51%; R=Me, 63%

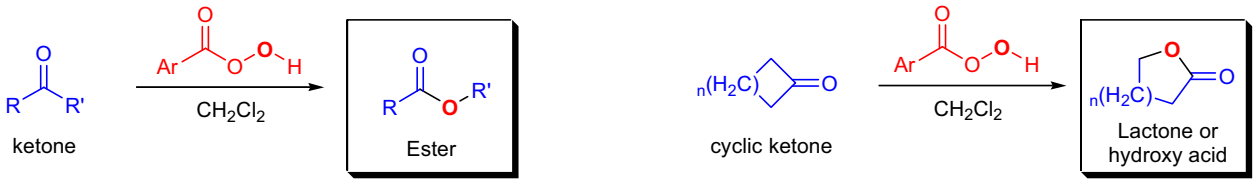
BAEYER-VILLIGER OXIDATION/REARRANGEMENT

(References are on page 540)

Importance:

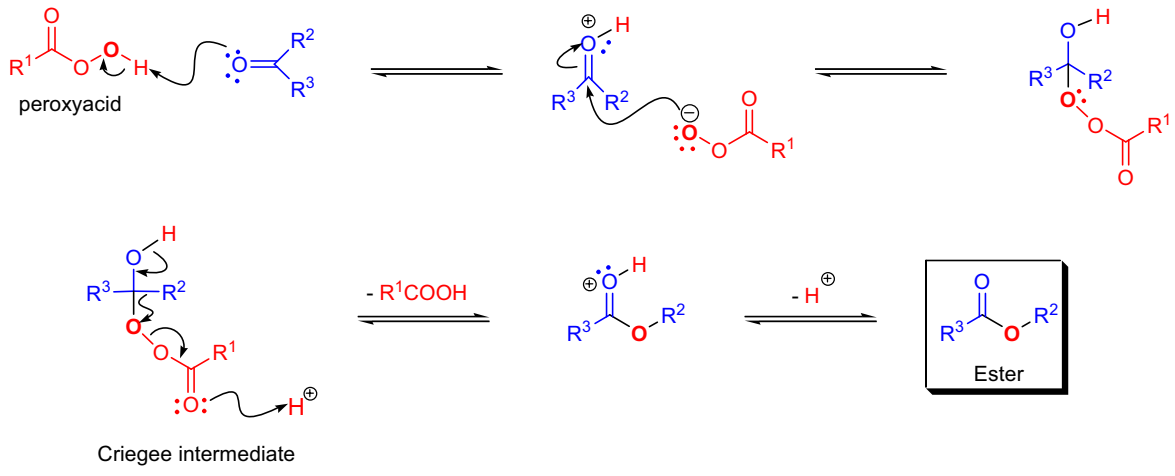
[*Seminal Publication*[1]; *Reviews*[2-25]; *Modifications & Improvements*[26-36]; *Theoretical Studies*[37-48]]

The transformation of ketones into esters and cyclic ketones into lactones or hydroxy acids by peroxyacids was discovered as early as 1899 by A. Baeyer and V. Villiger when they were investigating the ring cleavage of cyclic ketones. This reaction was later named after them as the *Baeyer-Villiger oxidation*. The oxidation of ketones using this method has the following features: 1) it tolerates the presence of many functional groups in the molecule, for example, even with α,β-unsaturated ketones, the oxidation with peroxyacids generally occurs at the carbonyl group and not at the C=C double bond; 2) the regiochemistry depends on the migratory aptitude of different alkyl groups. For acyclic compounds, R' must usually be secondary, tertiary, or vinylic. For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl > aryl > primary alkyl > methyl, and there are cases (e.g., bicyclic systems) in which various stereoelectronic aspects can influence which group migrates; 3) the rearrangement step occurs with retention of the stereochemistry at the migrating center; 4) a wide variety of peroxyacids can be used as oxidants for the reaction; and 5) the oxidation can also be performed asymmetrically on racemic or prochiral ketones using enzymes or chiral transition metal catalysts. A wide range of oxidizing agents can be used to perform the *Baeyer-Villiger oxidations* and their activity is ranked as follows: CF_3CO_3H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > *m*CPBA ~ performic acid > perbenzoic acid > peracetic acid » H_2O_2 > *t*-BuOOH.[34] Recently there has been considerable effort to make the *B.-V. oxidation* catalytic and at the same time preserve the high regio- and stereoselectivity of the reaction. Some of the most promising catalysts are substituted seleninic acids that are usually generated *in situ* from diaryl diselenides with H_2O_2 (*Syper method* of activation).[28,34]



Mechanism:[49-61]

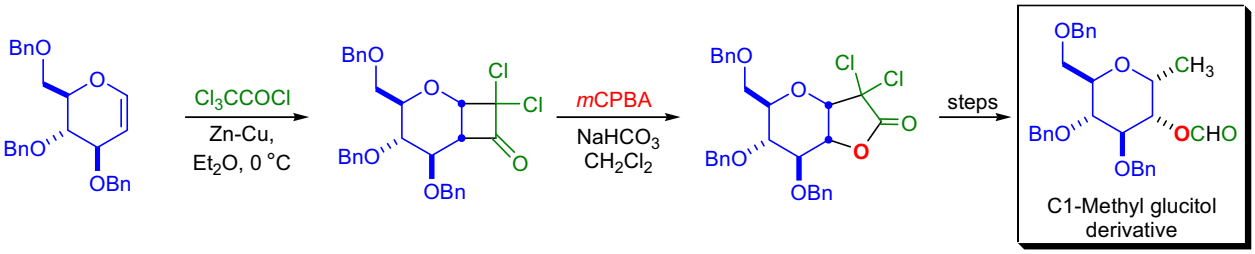
In 1953 Doering and Dorfman clarified the mechanism by performing a labeling experiment. Their experimental results confirmed Criegee's hypothesis, which he presented in 1948. In the first step, the carbonyl group is protonated to increase its electrophilicity, then the peroxyacid adds to this cationic species to form the so-called *Criegee intermediate* (adduct). When the carboxylic acid (R^1COOH) departs from this intermediate, an electron-deficient oxygen substituent is formed, which immediately undergoes an alkyl migration. This alkyl migration and the loss of the carboxylic acid both take place in a concerted process. It is assumed that the migrating group has to be in a position antiperiplanar to the dissociating oxygen-oxygen single bond of the peroxide. The FMO (frontier molecular orbital) theory states that this antiperiplanar arrangement allows the best overlap of the C-R^2 σ bond with the O-O σ* orbital (primary stereoelectronic effect). In 1998, Y. Kishi and co-workers showed that in allylic hydroperoxides the bond antiperiplanar to the dissociating peroxide bond is always and exclusively the bond that migrates, even when this migration is electronically disfavored.[57] Despite the numerous investigations of the mechanism of the *Baeyer-Villiger oxidation*, the factors that control the migratory aptitude are still not completely understood. Electron density and steric bulk strongly influence the migration ability, but the exact nature of these influences remains obscure.



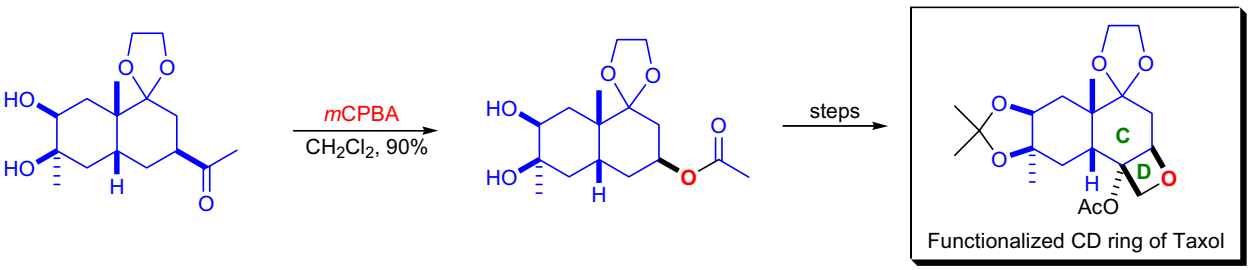
BAEYER-VILLIGER OXIDATION/REARRANGEMENT

Synthetic Applications:

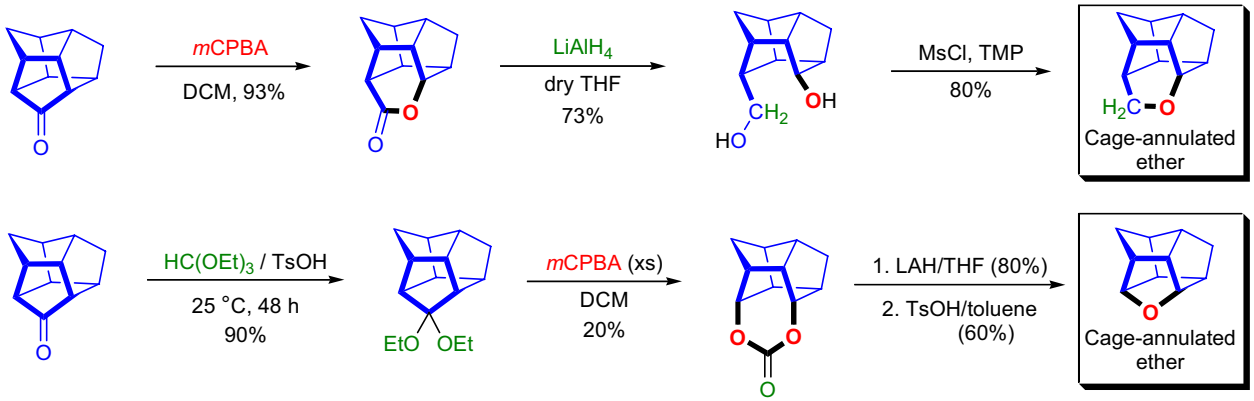
Investigations by J. Oh showed that the cycloaddition of dichloroketene to glucal followed by *Baeyer-Villiger oxidation* afforded a bicyclic γ-lactone, an α-D-*C*-glucoside, which was further transformed to a C1-methyl glucitol derivative.[62]



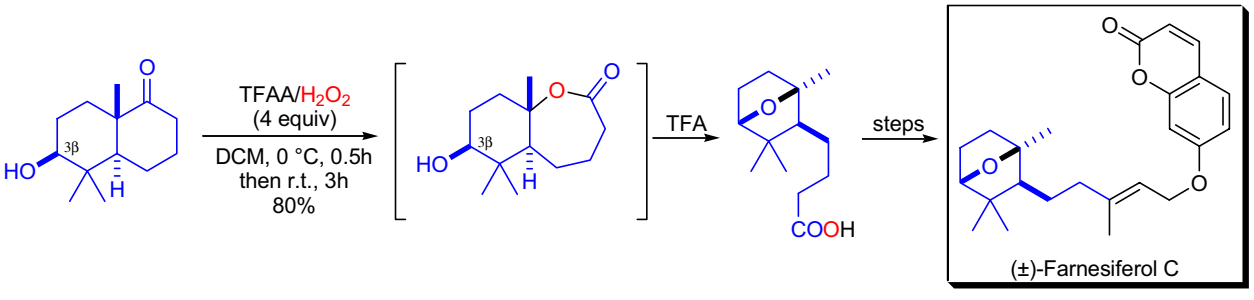
In the laboratory of T.K.M. Shing, the functionalized CD-ring of Taxol® was synthesized in 21 steps starting out from (*S*)-(+)-carvone.[63] The key steps were *Baeyer-Villiger oxidation*, *Oppenhauer oxidation*, *Meerwein-Ponndorf-Verley reduction*, a stereospecific *Grignard addition*, and an intramolecular S_N2 reaction.



Only a few methods are known for the preparation of cage-annulated ethers. A.P. Marchand and co-workers have used the *Baeyer-Villiger oxidation* for the synthesis of novel cage heterocycles and developed a general procedure that can be used to synthesize cage ethers by replacing the carbonyl group in a cage ketone by a ring oxygen atom or by a CH_2O group.[64]



An unexpected rearrangement was observed in the peroxytrifluoroacetic acid-mediated *Baeyer-Villiger oxidation* of *trans*-3β-hydroxy-4,4,10β-trimethyl-9-decalone by F.W.J. Demnitz and co-workers.[65] The initially formed ring-expanded lactone product underwent a trifluoroacetic acid-catalyzed cleavage of the lactone C-O bond, and the resulting tertiary carbocation was trapped by the free hydroxyl group to afford a 7-oxabicyclo[2.2.1]heptane derivative. This compound was then used for the total synthesis and structure proof of the sesquiterpene (±)-farnesiferol C.



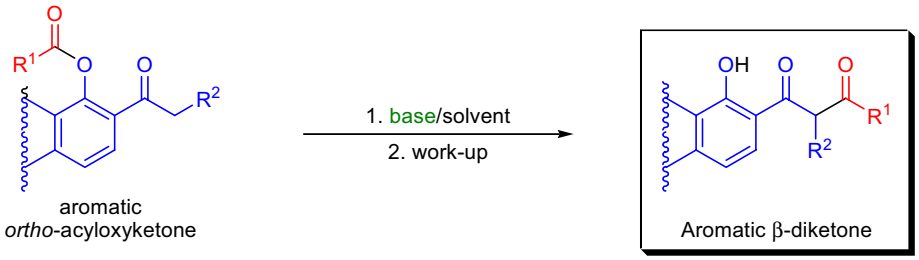
BAKER-VENKATARAMAN REARRANGEMENT

(References are on page 542)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-7]; *Modifications & Improvements*[8-17]]

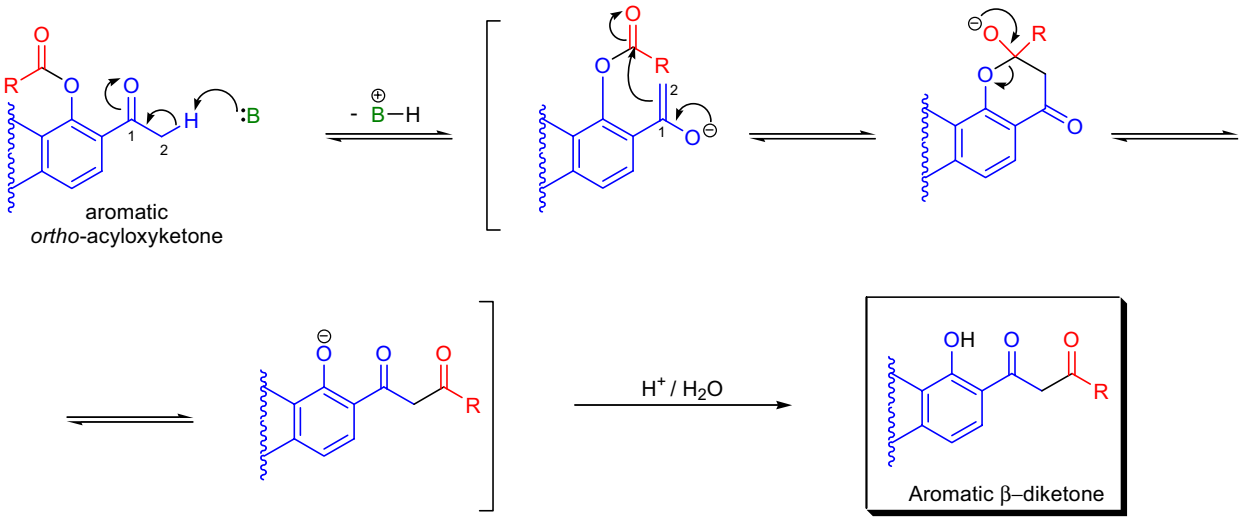
The base-catalyzed rearrangement of aromatic *ortho*-acyloxyketones to the corresponding aromatic β-diketones is known as the *Baker-Venkataraman rearrangement*. β-Diketones are important synthetic intermediates, and they are widely used for the synthesis of chromones, flavones, isoflavones, and coumarins. The most commonly used bases are the following: KOH, potassium *tert*-butoxide in DMSO, Na metal in toluene, sodium or potassium hydride, pyridine, and triphenylmethylsodium.



R^1 = alkyl, aryl, NH_2; R^2 = alkyl, aryl; base: KOH, KO*t*-Bu, NaH, Na metal, KH, C_5H_5N

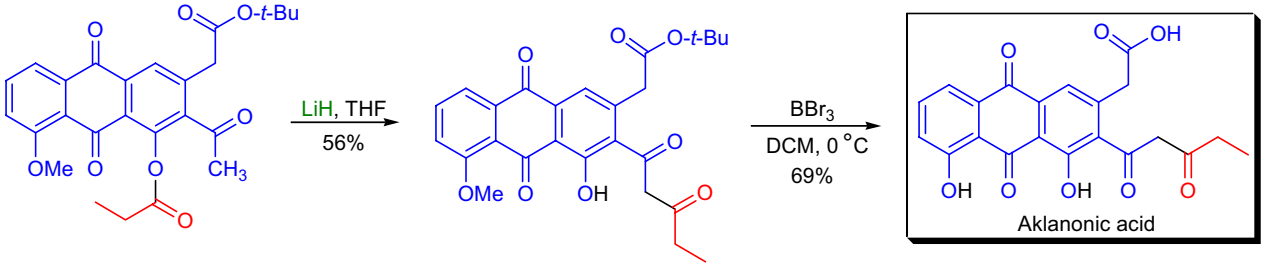
Mechanism: [18-22]

In the first step of the mechanism, the aromatic ketone is deprotonated at the α-carbon and an enolate is formed. This nucleophile attacks the carbonyl group of the acyloxy moiety intramolecularly to form a tetrahedral intermediate that subsequently breaks down to form the aromatic β-diketone.



Synthetic Applications:

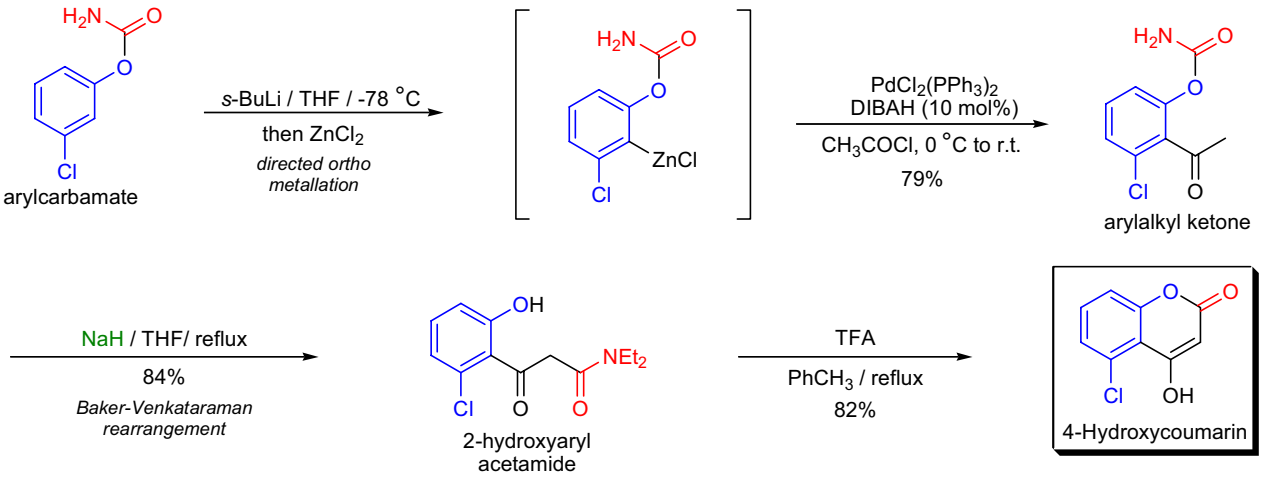
In the laboratory of K. Krohn, the total synthesis of aklanonic acid and its derivatives was undertaken, utilizing the *Baker-Venkataraman rearrangement* of *ortho*-acetyl anthraquinone esters in the presence of lithium hydride.[23] Using this method, it was possible to introduce ketide side-chains on anthraquinones in a facile manner.



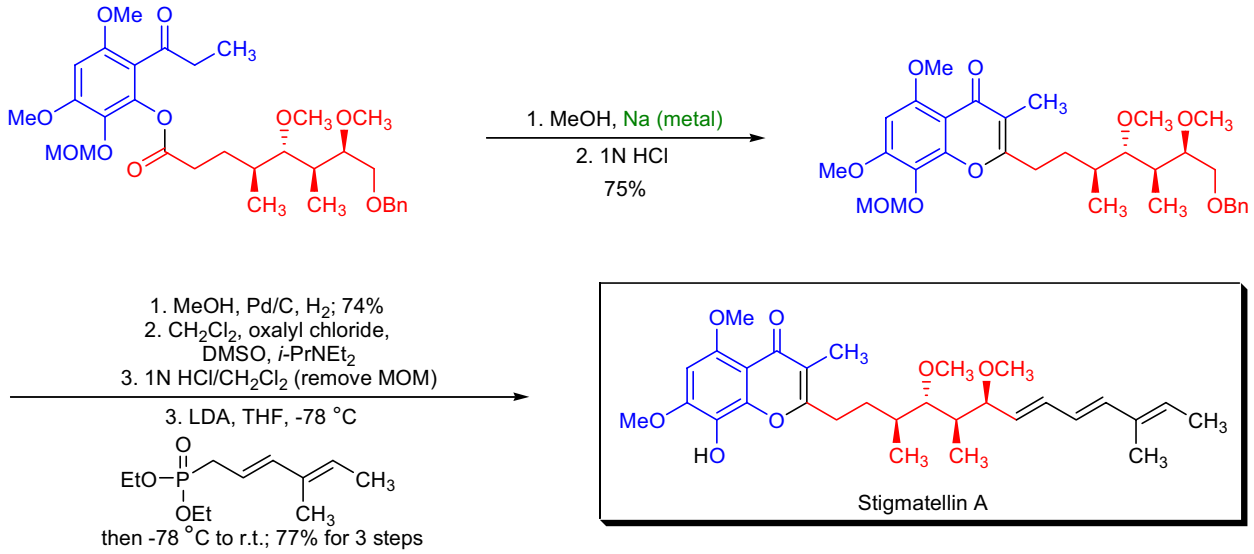
BAKER-VENKATARAMAN REARRANGEMENT

Synthetic Applications:

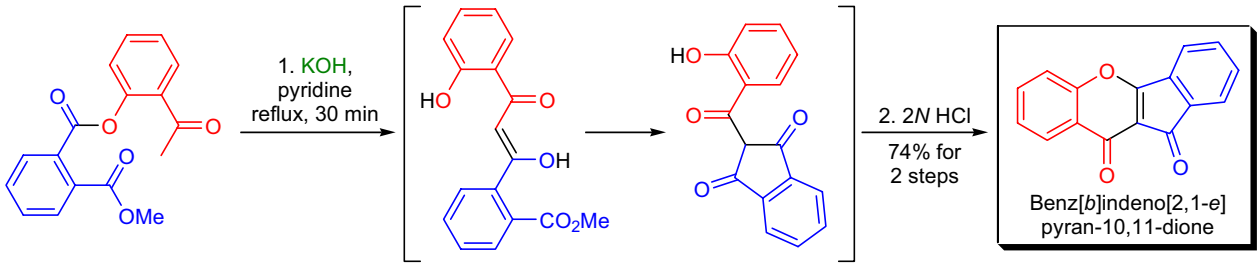
V. Snieckus and co-workers developed a new *carbamoyl Baker-Venkataraman rearrangement,* which allowed a general synthesis of substituted 4-hydroxycoumarins in moderate to good overall yields.[16] The intermediate arylketones were efficiently prepared from arylcarbamates *via directed ortho metallation* and *Negishi cross coupling*. The overall sequence provided a regiospecific anionic *Friedel-Crafts* complement for the construction of *ortho*-acyl phenols and coumarins.



Stigmatellin A is a powerful inhibitor of electron transport in mitochondria and chloroplasts. During the diastereo- and enantioselective total synthesis of this important natural product, D. Enders et al. utilized the *Baker-Venkataraman rearrangement* for the construction of the chromone system in good yield.[24]



A highly efficient and operationally simple domino reaction was developed in the laboratory of S. Ruchiwarat for the synthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones.[25] The initial aroyl-transfer was achieved by the *Baker-Venkataraman rearrangement* by subjecting the starting material to KOH in pyridine under reflux for 30 minutes.



BALDWIN'S RULES / GUIDELINES FOR RING-CLOSING REACTIONS

(References are on page 542)

Importance:

[*Seminal Publication*[1]; *Reviews*[2,3]; *Related Publications*[4-14]]

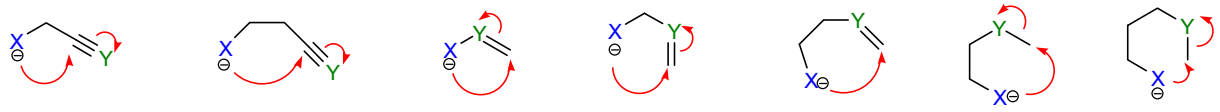
In 1976, J.E. Baldwin formulated a set of rules/guidelines governing the ease of intramolecular ring-closing reactions, the so-called *Baldwin's rules* or *Baldwin's guidelines*.[1] Baldwin used these rules/guidelines to gain valuable insight into the role of stereoelectronic effects in organic reactions and predict the feasibility of these reactions in synthetic sequences. A few years later in 1983, J.D. Dunitz and co-workers demonstrated that there are favored trajectories for the approach of one reactant molecule toward another.[15] We must note, however, that there is substantial limitation on these rules/guidelines; a large number of examples are known for which they do not apply.

Summary of most important ring closures:

(F=favored, D=disfavored)

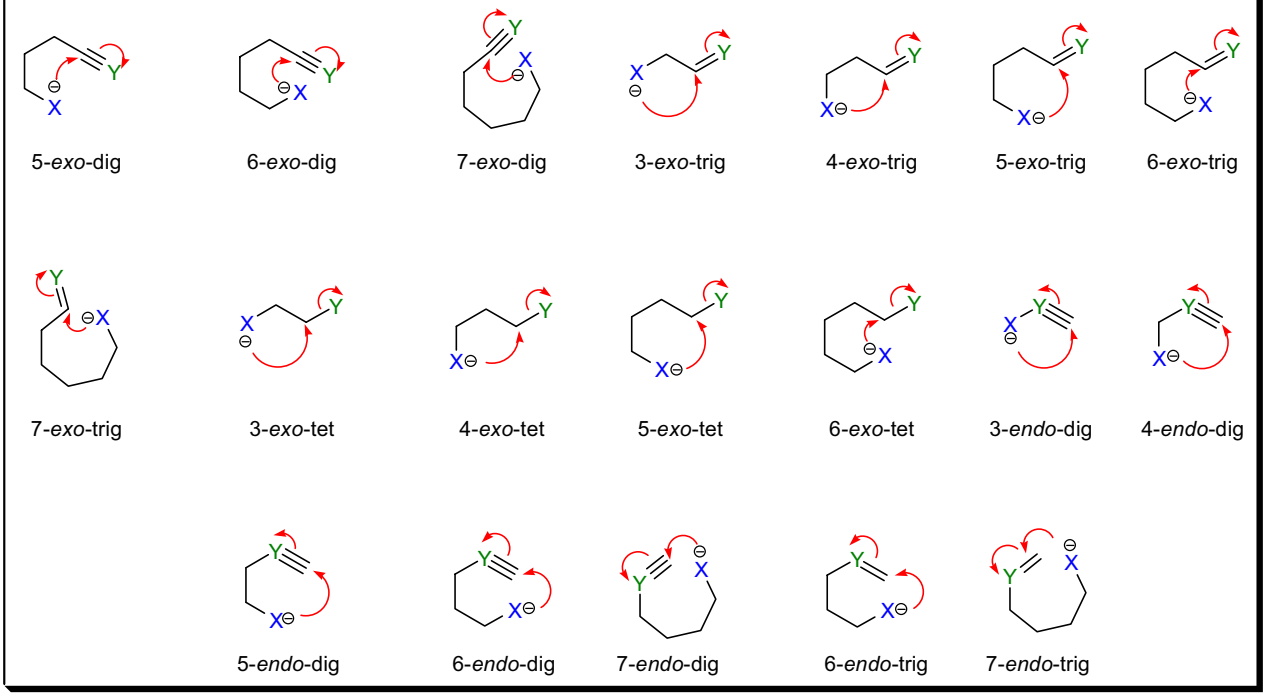
Ring size	Exo-dig	Exo-trig	Exo-tet	Endo-dig	Endo-trig	Endo-tet
3	D	F	F	F	D	-
4	D	F	F	F	D	-
5	F	F	F	F	D	D
6	F	F	F	F	F	D
7	F	F	F	F	F	-

Disfavored Processes



3-*exo*-dig, 4-*exo*-dig, 3-*endo*-trig, 4-*endo*-trig, 5-*endo*-trig, 5-*endo*-tet, 6-*endo*-tet

Favored Processes



5-*exo*-dig, 6-*exo*-dig, 7-*exo*-dig, 3-*exo*-trig, 4-*exo*-trig, 5-*exo*-trig, 6-*exo*-trig

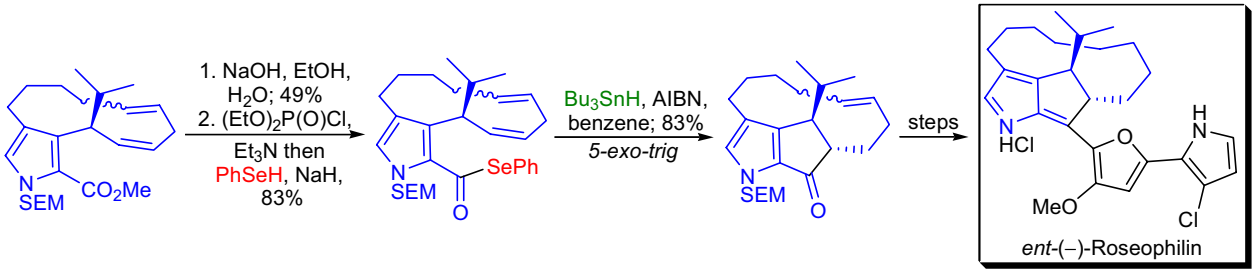
7-*exo*-trig, 3-*exo*-tet, 4-*exo*-tet, 5-*exo*-tet, 6-*exo*-tet, 3-*endo*-dig, 4-*endo*-dig

5-*endo*-dig, 6-*endo*-dig, 7-*endo*-dig, 6-*endo*-trig, 7-*endo*-trig

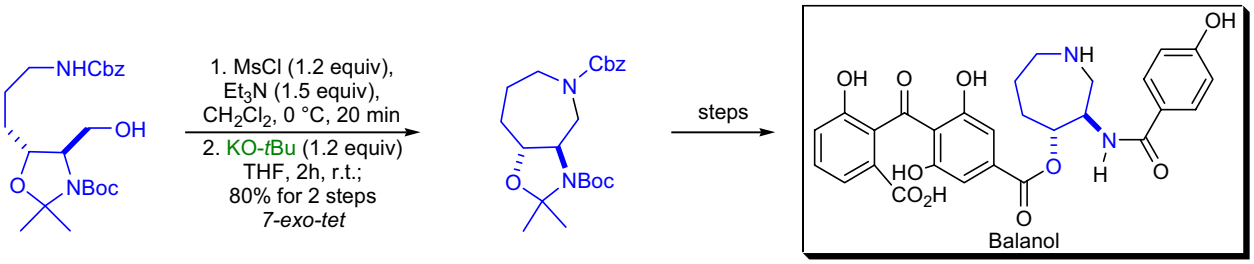
BALDWIN'S RULES / GUIDELINES FOR RING-CLOSING REACTIONS

Synthetic Applications:

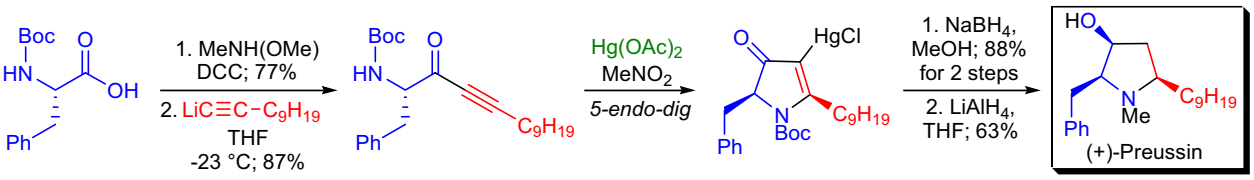
D.L Boger and co-workers reported an asymmetric total synthesis of *ent*-(–)-roseophilin, the unnatural enantiomer of a naturally occurring antitumor antibiotic.[16] Their approach featured a *5-exo-trig* acyl radical-alkene cyclization to construct the fused cyclopentanone unit. To this end, the hindered methyl ester functionality was hydrolyzed and the resulting acid was transformed to the corresponding phenyl selenoester *via* a two-step sequence. The *5-exo-trig* acyl radical-alkene cyclization was achieved by using AIBN and Bu_3SnH to provide the tricyclic *ansa*-bridged azafulvene core.



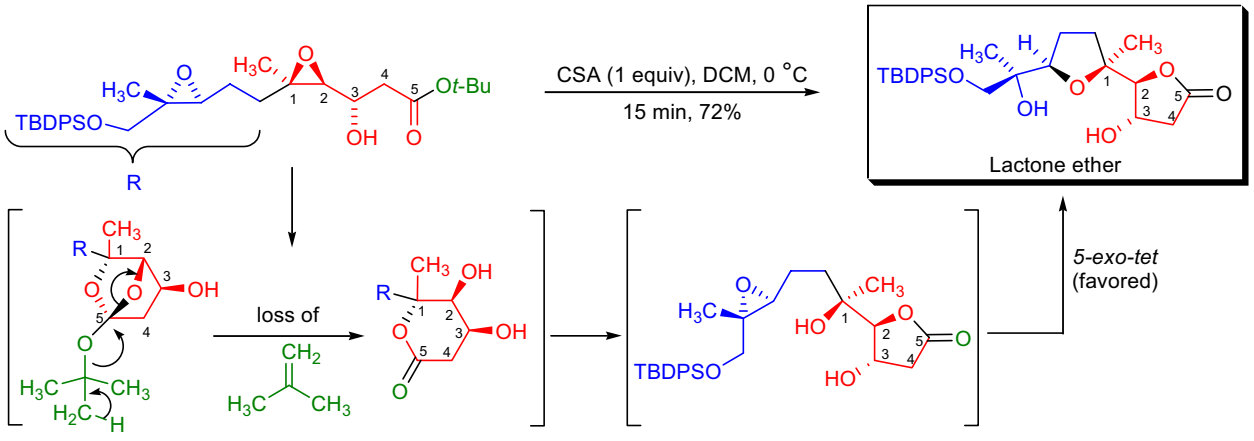
The total synthesis of balanol, a fungal metabolite was accomplished by K.C. Nicolaou *et al.*[17] For the construction of the central hexahydroazepine ring, they have utilized a *7-exo-tet* cyclization. The substitution reaction between the mesylate of the primary alcohol and the Cbz-protected amine was effected by a slight excess of base to produce the desired 7-membered ring in high yield.



The total synthesis of pyrrolidinol alkaloid, (+)-preussin was achieved in five efficient transformations from commercially available *tert*-Boc-(*S*)-phenylalanine in the laboratory of S.M. Hecht.[18] The key step involved the $Hg^{(II)}$-mediated *5-endo-dig* cyclization of ynone substrate affording the desired pyrrolidinone which, in two more steps, was converted into the natural product.



In the laboratory of K. Nacro, a cyclization process leading stereoselectively to *six- and/or five-membered ring lactones* and *lactone ethers* from optically active epoxy- or diepoxy β-hydroxyesters or diastereomeric epoxy lactones was developed.[19] The diastereomeric lactones were prepared from nerol and geraniol. The acid catalyzed cyclization of epoxyalcohols is one of the most effective methods for constructing cyclic ethers. The cyclization proceeds in the *exo* mode giving cyclic ethers with a hydroxyl group in the side chain. The regioselectivity of the cyclization is predicted by the *Baldwin's rules*; in the case shown below the ether formation takes place *via* a *5-exo-tet* cyclization.



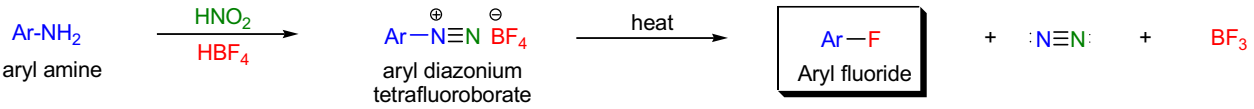
BALZ-SCHIEMANN REACTION
(SCHIEMANN REACTION)

(References are on page 543)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-6]; *Modifications & Improvements*[7-14]]

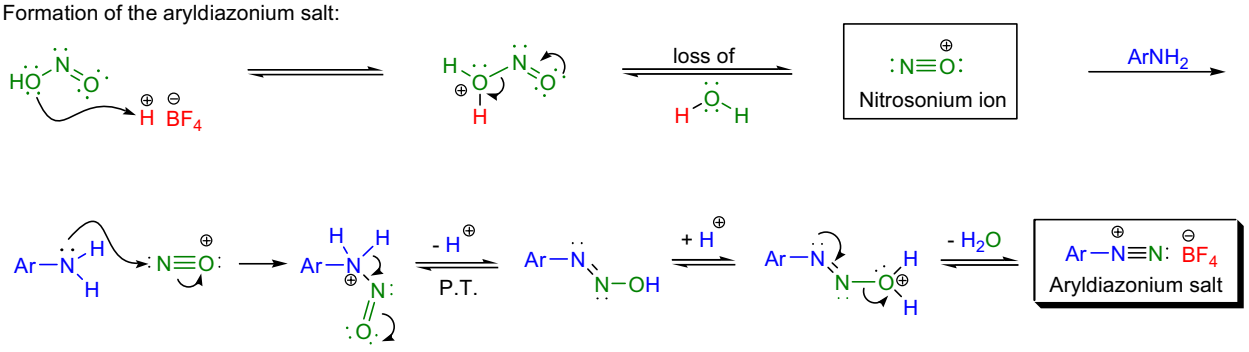
The thermal decomposition of aromatic diazonium tetrafluoroborates ($ArN_2^+BF_4^-$) to give aromatic fluorides is called the *Balz-Schiemann reaction*. Normally diazonium salts are unstable but diazonium tetrafluoroborates are fairly stable and may be obtained in high yields. Aromatic heterocyclic diazonium tetrafluoroborates may also be used. The diazonium salts are obtained from the diazotization of aromatic amines in the presence of hydrogen tetrafluoroborate (HBF_4). Improved yields of aryl fluorides may be achieved when instead of tetrafluoroborates, hexafluorophosphates (PF_6^-) or hexafluoroantimonates (SbF_6^-) are used as counterions.[7,8] One drawback of the reaction is the potential danger of explosion when large-scale thermal decomposition of the aromatic diazonium tetrafluoroborates is attempted. However, when the decomposition is carried out, either thermally or photolytically, in pyridine·HF solution, the reaction proceeds smoothly even on a larger scale. This approach is especially useful for the preparation of aryl fluorides having polar substituents (OH, OMe, CF_3, etc.).[15]



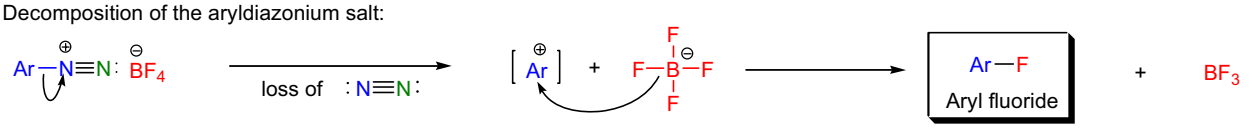
Mechanism: [16-24]

The mechanism involves a positively charged intermediate,[21] which is attacked by BF_4^- rather than the fluoride ion.[20] Both the thermal and photochemical decomposition of diazonium tetrafluoroborates afford the same product ratio, which suggests the intermediacy of the aryl cation. The decomposition follows a first-order rate law, so it is probably of S_N1 type.

Formation of the aryldiazonium salt:

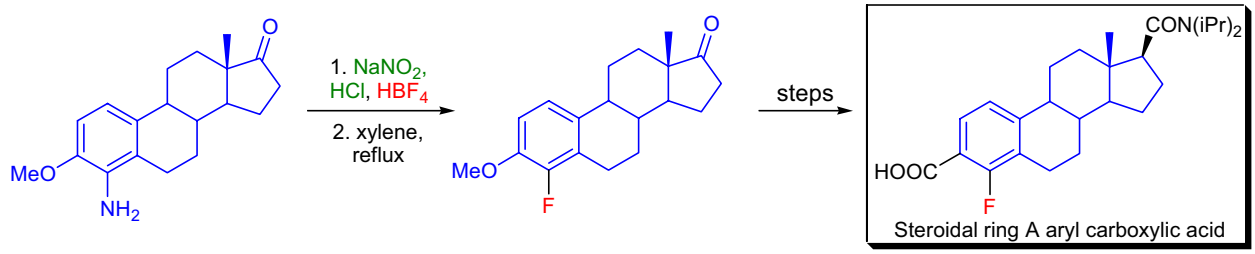


Decomposition of the aryldiazonium salt:



Synthetic Applications:

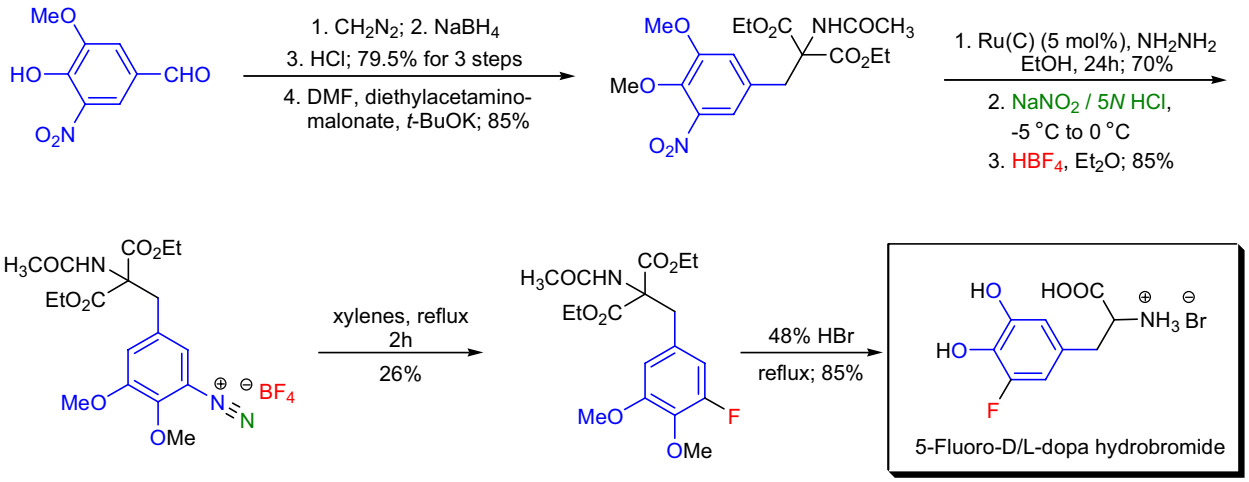
In the laboratory of D.A. Holt, the synthesis of a new class of steroid 5 -reductase inhibitors was undertaken.[25] They found that unlike the steroidal acrylates, steroidal A ring aryl carboxylic acids exhibit greatly reduced affinity for rat liver steroid 5 -reductase. The tested steroidal A ring carboxylic acids were synthesized from estrone; in one example, fluorine was incorporated into the 4-position of estrone *via* the *Balz-Schiemann reaction*.



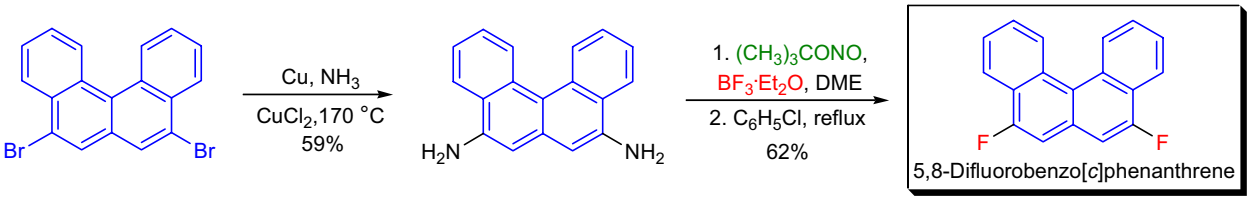
BALZ-SCHIEMANN REACTION
(SCHIEMANN REACTION)

Synthetic Applications:

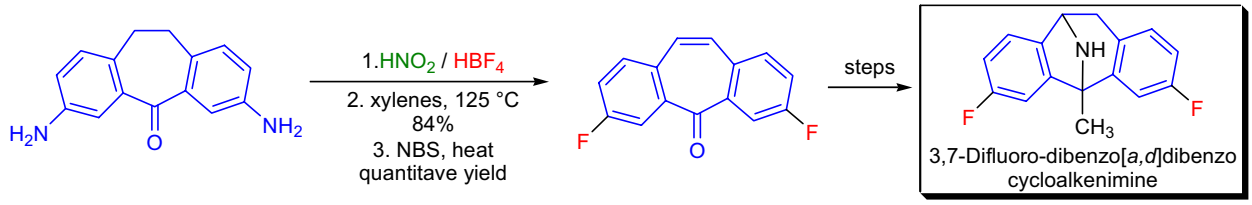
C. Wiese and co-workers have synthesized 5-fluoro-D/L-dopa and the corresponding [^{18}F]5-Fluoro-L-dopa starting from 5-nitrovanillin *via malonic ester synthesis*, the *Balz-Schiemann reaction*, and the separation of the racemic mixture [^{18}F]5-fluoro-D/L-dopa utilizing a chiral HPLC system.[26] The inactive 5-fluoro-D/L-dopa was obtained in an eight-step synthesis with an overall yield of 10%.



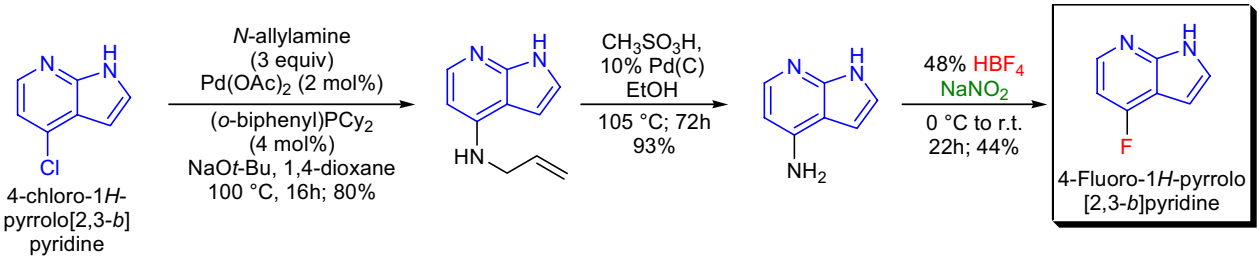
D.R. Thakker synthesized K-region monofluoro- and difluorobenzo[c]phenanthrenes using the *Balz-Schiemann reaction* in order to elucidate the metabolic activation and detoxification of polycyclic aromatic compounds.[27]



Dibenzo[*a,d*]cycloalkenimines were synthesized and pharmacologically evaluated as *N*-methyl-D-aspartate antagonists by P.S. Anderson et al.[28] A symmetrical 3,7-difluoro derivative was accessed by applying the *Balz-Schiemann reaction* on the corresponding 3,7-diamino analog.



The synthesis of 7-azaindoles is a challenging task and there are few efficient routes to substituted derivatives. In the laboratory of C. Thibault, the concise and efficient synthesis of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine was achieved.[29] The fluorination was carried out using the *Balz-Schiemann reaction*. The aromatic amine precursor was prepared *via* the *Buchwald-Hartwig coupling* of the aryl chloride with *N*-allylamine followed by deallylation. The diazonium tetrafluoroborate intermediate was generated at 0 C and it decomposed spontaneously in 48% HBF_4 solution to afford the desired aromatic fluoride.



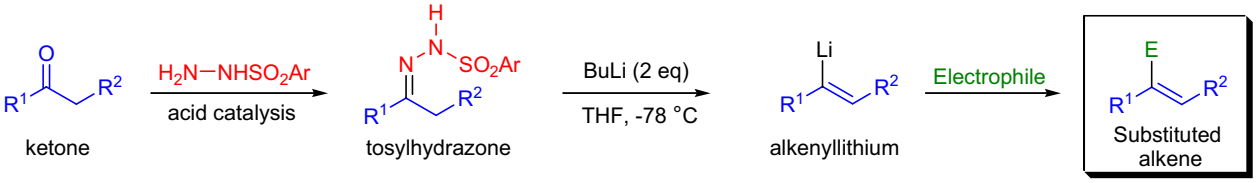
BAMFORD-STEVENS-SHAPIRO OLEFINATION

(References are on page 543)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-4]; *Modifications & Improvemens*[5-18]]

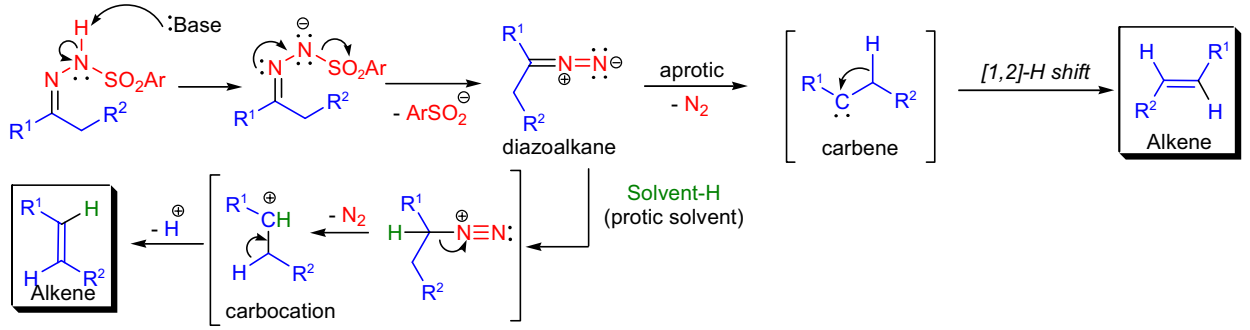
The base catalyzed decomposition of arylsulfonylhydrazones of aldehydes and ketones to provide alkenes is called the *Bamford-Stevens reaction*. When an organolithium compound is used as the base, the reaction is termed the *Shapiro reaction*. The most synthetically useful protocol involves treatment of the substrate with at least two equivalents of an organolithium compound (usually MeLi or BuLi) in ether, hexane, or tetramethylenediamine. The *in situ* formed alkenyllithium is then protonated to give the alkene. The above procedure provides good yields of alkenes without side reactions and where there is a choice, the less highly substituted alkene is predominantly formed. Under these reaction conditions tosylhydrazones of α,β-unsaturated ketones give rise to conjugated dienes. It is also possible to trap the alkenyllithium with electrophiles other than a proton.



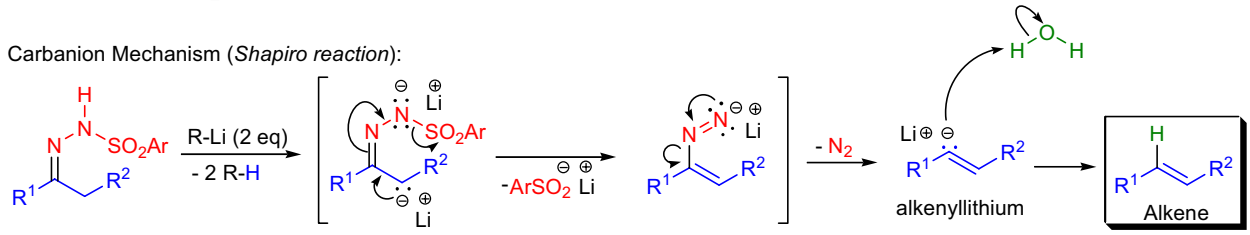
Mechanism:[19,7,20]

The reaction mechanism depends on the reaction conditions used. The reaction of tosylhydrazone with a strong base (usually metal-alkoxides) in protic solvents results in the formation of a diazo compound that in some cases can be isolated.[20] The diazo compound gives rise to a carbocation that may lose a proton or undergo a *Wagner-Meerwein rearrangement*. Therefore, a complex mixture of products may be isolated. When aprotic conditions are used, the initially formed diazo compound loses a molecule of nitrogen and a carbene intermediate is formed, which either undergoes a *[1,2]-H shift* or various carbene insertion reactions. In the case of the *Shapiro reaction*, two equivalents of alkyllithium reagent deprotonate the tosylhydrazone both at the nitrogen and the α-carbon and an alkenyllithium intermediate is formed *via* a carbanion mechanism. Subsequently, the protonation of the alkenyllithium gives rise to the alkene.

Carbene and Carbocation Mechanism:

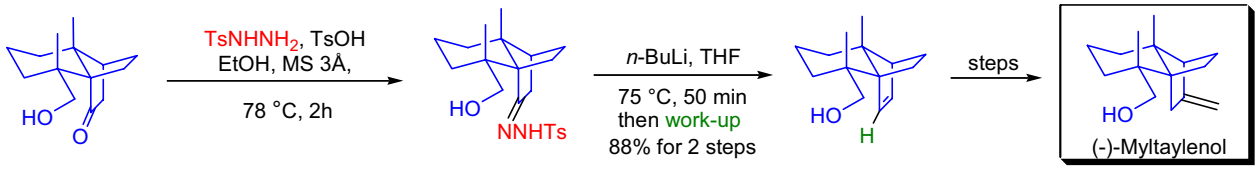


Carbanion Mechanism (*Shapiro reaction*):



Synthetic Applications:

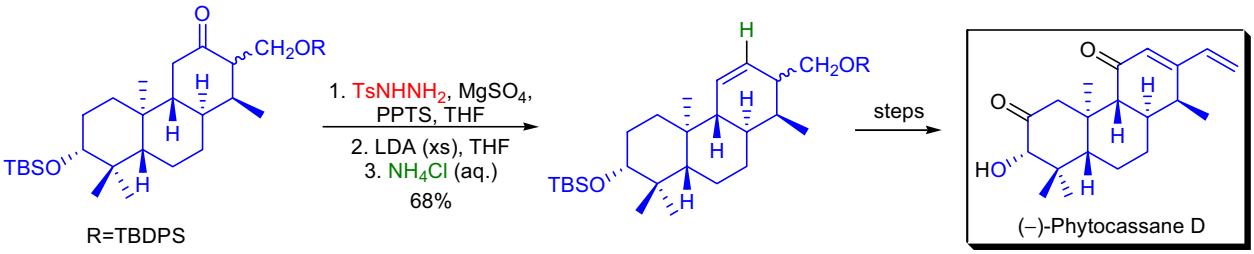
The first enantioselective total synthesis of (–)-myltaylenol was achieved in the laboratory of E. Winterfeldt.[21] The authors used an *intramolecular Diels-Alder cycloaddition* and the *Shapiro reaction* as key transformations to construct the unusual carbon framework of this sesquiterpenoid alcohol natural product, which contains three consecutive quaternary carbon atoms.



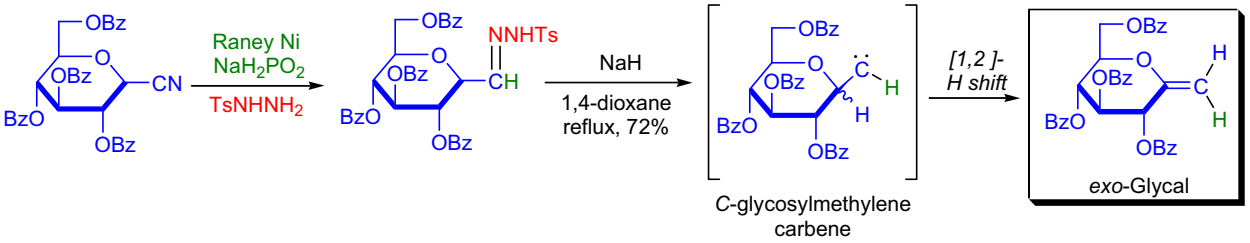
BAMFORD-STEVENS-SHAPIRO OLEFINATION

Synthetic Applications:

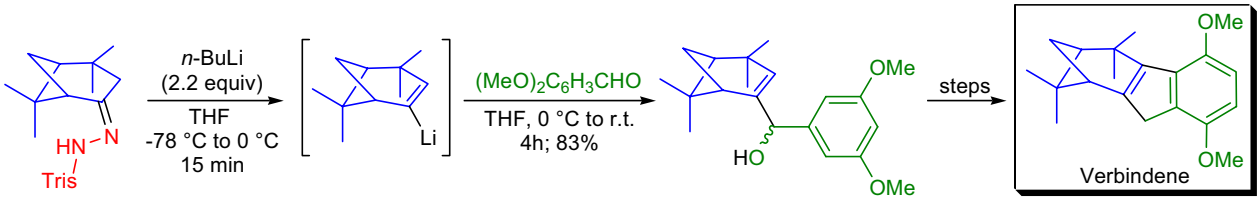
In the laboratory of K. Mori the task of determining the absolute configuration of the phytocassane group of phytoalexins was undertaken. To this end, the naturally occurring (–)-phytocassane D was synthesized from (*R*)-Wieland-Miescher ketone.[22] During the synthesis, a tricyclic ketone intermediate was subjected to the *Shapiro olefination* reaction to give the desired cyclic alkene in good yield.



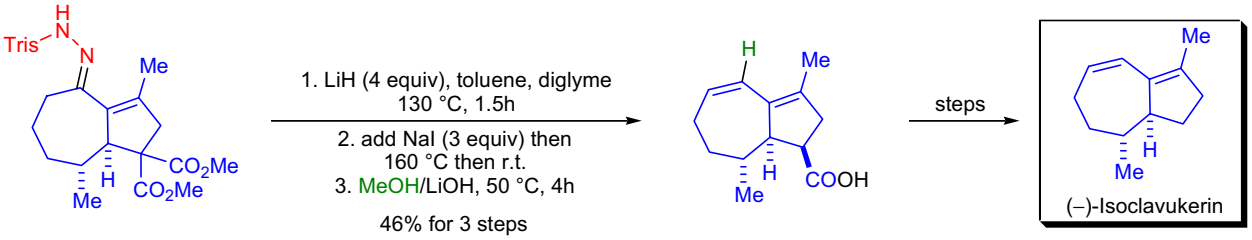
L. Somsák et al. developed a one-pot reaction to prepare exo-glycals from glycosyl cyanides.[23] In this one-pot reaction, acylated glycosyl cyanides were first converted to the corresponding aldehydes with Raney nickel-sodium hypophosphite, and then converted into 2,5- and 2,6-anhydroaldose tosylhydrazones to give *exo*-glycals under aprotic *Bamford-Stevens* conditions. During the reaction *C*-glycosylmethylene carbenes are formed and spontaneously rearrange to give the observed *exo*-glycals.



A novel class of chiral indenes (verbindenes) was prepared from enantiopure verbenone by K.C. Rupert and co-workers who utilized the *Shapiro reaction* and the *Nazarov cyclization* as the key transformations.[24] The bicyclic ketone substrate was treated with triisopropylbenzenesulfonyl hydrazide to prepare the trisyl hydrazone that was then exposed to *n*-BuLi. The resulting vinyllithium intermediate was reacted with various aromatic aldehydes to afford the corresponding allylic alcohols.



During the total synthesis of (–)-isoclavukerin A by B.M. Trost et al., the introduction of the diene moiety was achieved by the use of the *Bamford-Stevens reaction* on a bicyclic trisylhydrazone compound.[25] Interestingly, the strongly basic Shapiro conditions (e.g., alkyllithiums or LDA) led only to uncharacterizable decomposition products. However, heating of the trisylhydrazone with KH in toluene in the presence of diglyme gave good yield of the desired diene. It was also shown that the olefin formation and the following decarboxylation could be conducted in one pot. According to this procedure, excess NaI was added and the temperature was elevated to bring about the *Krapcho decarboxylation*.



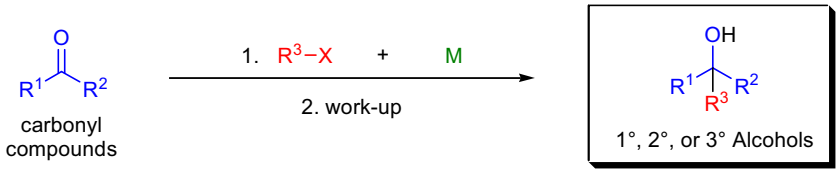
BARBIER COUPLING REACTION

(References are on page 544)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-16]; *Modifications & Improvements*[17-22]; *Theoretical Studies*[23]]

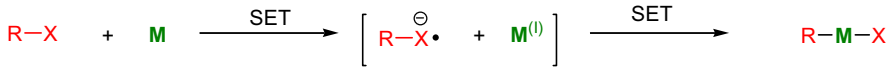
In the case of unstable organometallic reagents, it is convenient to generate the reagent in the presence of the carbonyl compound, to produce an immediate reaction. This procedure is referred to as the *Barbier reaction*. The original protocol with magnesium metal was described by P. Barbier and later resulted in the development of the well-known *Grignard reaction*. Most recently other metals (e.g., Sn, In, Zn, etc.) in aqueous solvents have been used under similar conditions with good results. The obvious advantages of these procedures are their safety and simplicity, as well as the ability to treat unprotected sugars with organometallic reagents.

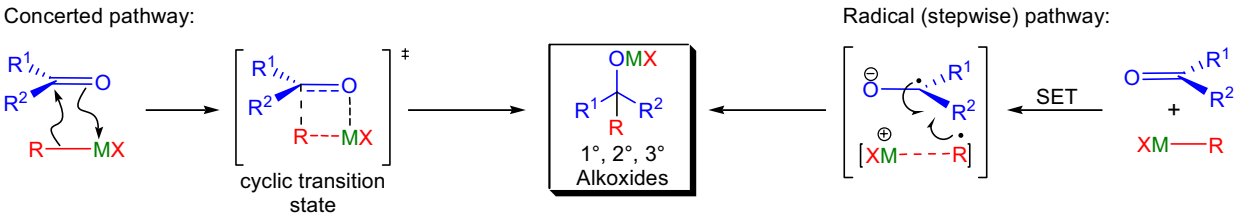


R^1, R^2 = H, alkyl, aryl; R^3 = alkyl, aryl, allyl, benzyl; X = Cl, Br, I; M = Mg, Sm, Zn, Li, etc.

Mechanism:[24-29]

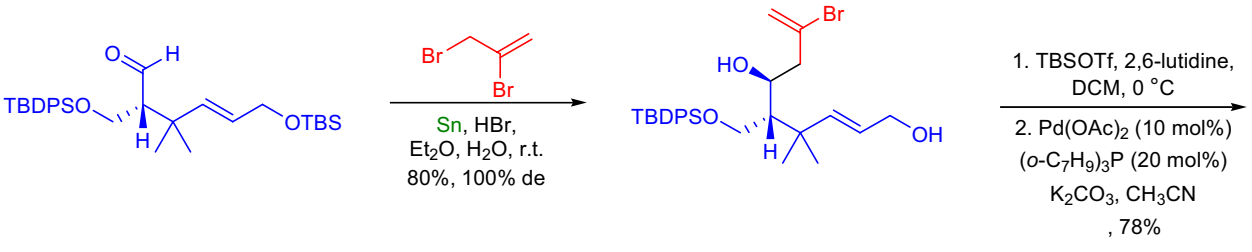
The mechanism of the formation of the organometallic reagent is identical to the formation of a *Grignard reagent*, presumably involving a single electron transfer (SET) mechanism from the metal surface to the alkyl halide. The mechanism of the addition of Grignard reagents to carbonyl compounds is not understood, but it is thought to take place mainly *via* either a concerted process or a radical pathway (stepwise).[30-32]

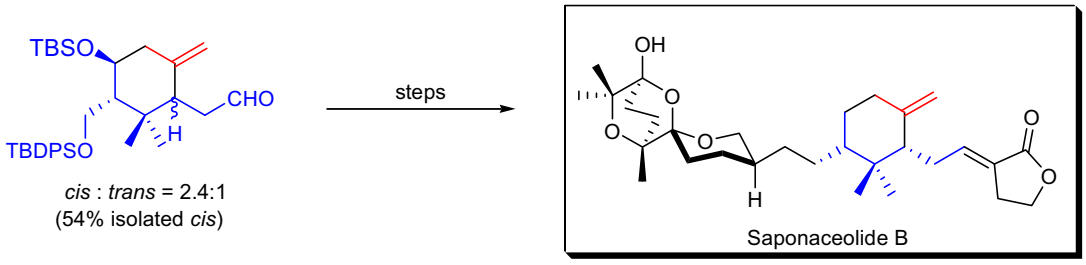




Synthetic Applications:

B.M. Trost and co-workers conducted studies toward the total synthesis of saponaceolide B, an antitumor agent active against 60 human cancer cell lines.[33,34] One of the challenging structural features of this compound was the *cis* 2,4-disubstituted 1-methylene-3,3-dimethylcyclohexane ring. The key steps to construct this highly substituted cyclohexane ring were a diastereoselective *Barbier reaction* to install a vinyl bromide moiety followed by an *intramolecular Heck cyclization reaction*.

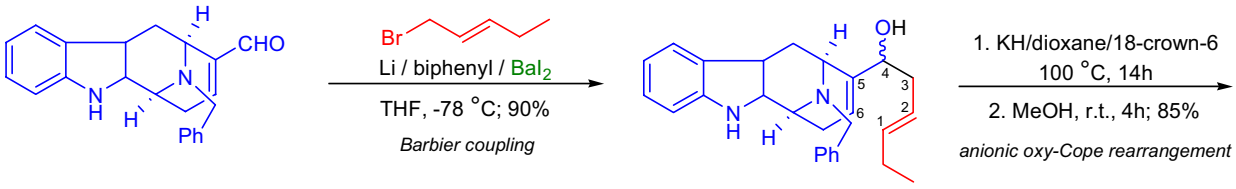


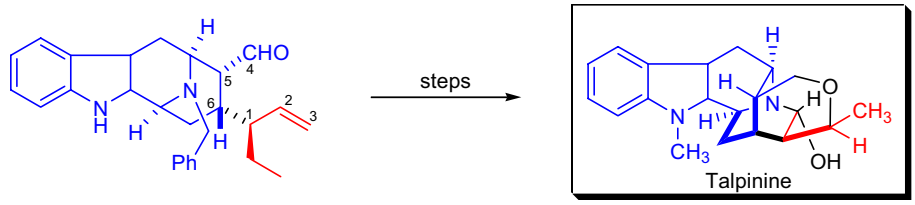


BARBIER COUPLING REACTION

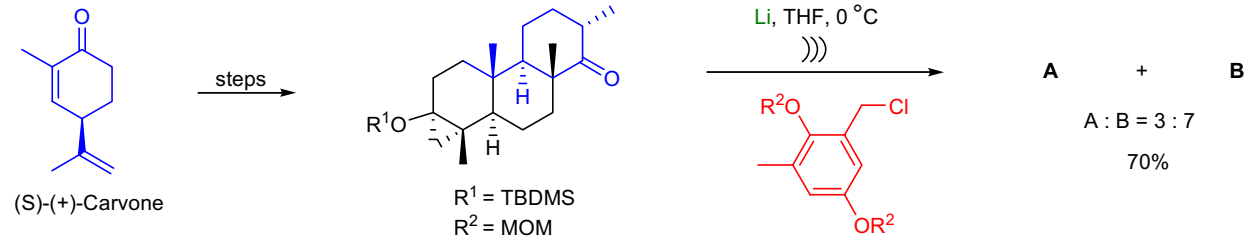
Synthetic Applications:

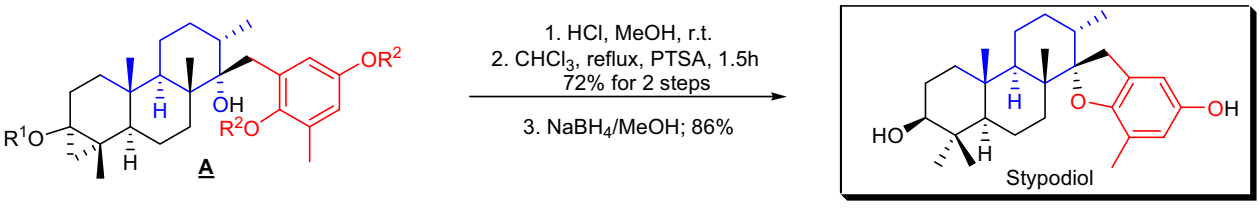
During the enantioselective total synthesis of the sarpagine-related indole alkaloids talpinine and talcarpine, J.M. Cook and co-workers prepared an important allylic alcohol precursor for an *anionic oxy-Cope rearrangement*.[35] However, the desired allylic carbanion was expected to undergo an undesired allylic rearrangement when stabilized as either a magnesium or lithium species. This problem was overcome by using the *Barbier reaction conditions,* which was a modification of the allylbarium chemistry of Yamamoto.[36,37] The mixture of the allylic bromide and the aldehyde was added to freshly prepared barium metal at -78 °C to generate the desired allylic carbanion. The resulting barium-stabilized species then added to the aldehyde, affording the 1,2-addition product in high yield, without allylic rearrangement.

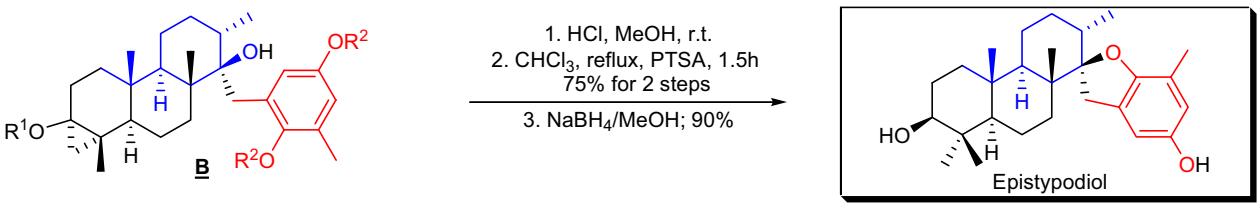




Stypodiol, epistypodiol and stypotriol are secondary diterpene metabolites produced by the tropical brown algae *Stypopodium zonale*. These compounds display diverse biological properties, including strong toxic, narcotic, and hyperactive effects upon the reef-dwelling fish. In the laboratory of A. Abad an efficient stereoselective synthesis of stypodiol and its C14 epimer, epistypodiol, was accomplished from (*S*)-(+)-carvone.[38] The key transformations in the synthesis of these epimeric compounds were an *intramolecular Diels-Alder reaction*, a *sonochemical Barbier reaction* and an *acid-catalyzed quinol-tertiary alcohol cyclization*.







BARTOLI INDOLE SYNTHESIS

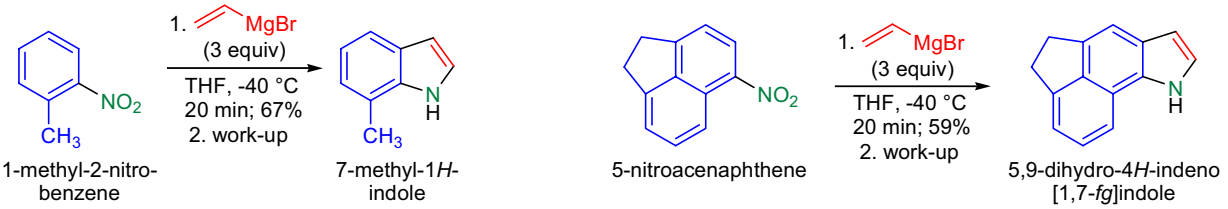
(References are on page 545)

Importance:

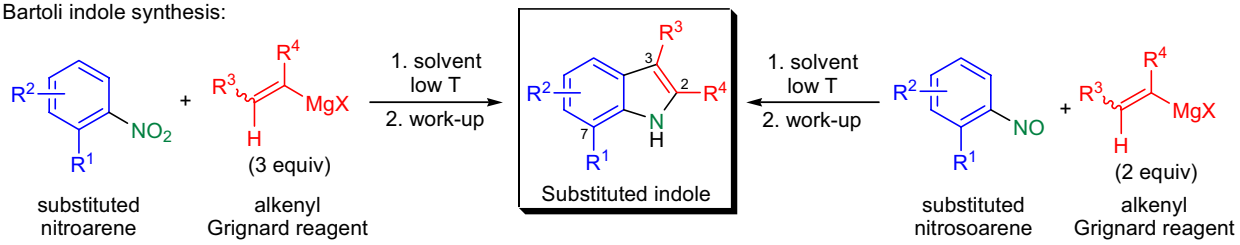
[*Seminal Publications*[1-3]; *Reviews*[4-7]; *Modifications & Improvements*[8-11]]

In 1989, G. Bartoli et al. described the reaction of substituted nitroarenes with excess vinyl Grignard reagents at low temperature to afford substituted indoles upon aqueous work-up.[2] The authors found that the highest yields were obtained with *ortho*-substituted nitroarenes. According to their procedure three equivalents of vinylmagnesium bromide were added to the cold solution of the nitroarene, which was stirred for 20 minutes, then quenched with a saturated NH_4Cl solution, followed by extraction of the product with diethyl ether. The formation of 7-substituted indoles from *ortho*-substituted nitroarenes (or nitrosoarenes) and alkenyl Grignard reagents is known as the *Bartoli indole synthesis*. The general features of this transformation are: 1) when the nitroarene does not have a substituent *ortho* to the nitro group, the reaction gives low or no yield of the desired indole; 2) the size of the *ortho* substituent also has an effect on the yield of the reaction and the sterically more demanding groups usually give higher yield of the product; 3) most often simple vinylmagnesium bromide is used but substituted alkenyl Grignard reagents can also be applied and they give rise to the corresponding indoles with substituents at the C2 or C3 positions; and 4) when nitrosoarenes are the substrates, only two equivalents of the Grignard reagent are necessary.

Bartoli (1989):



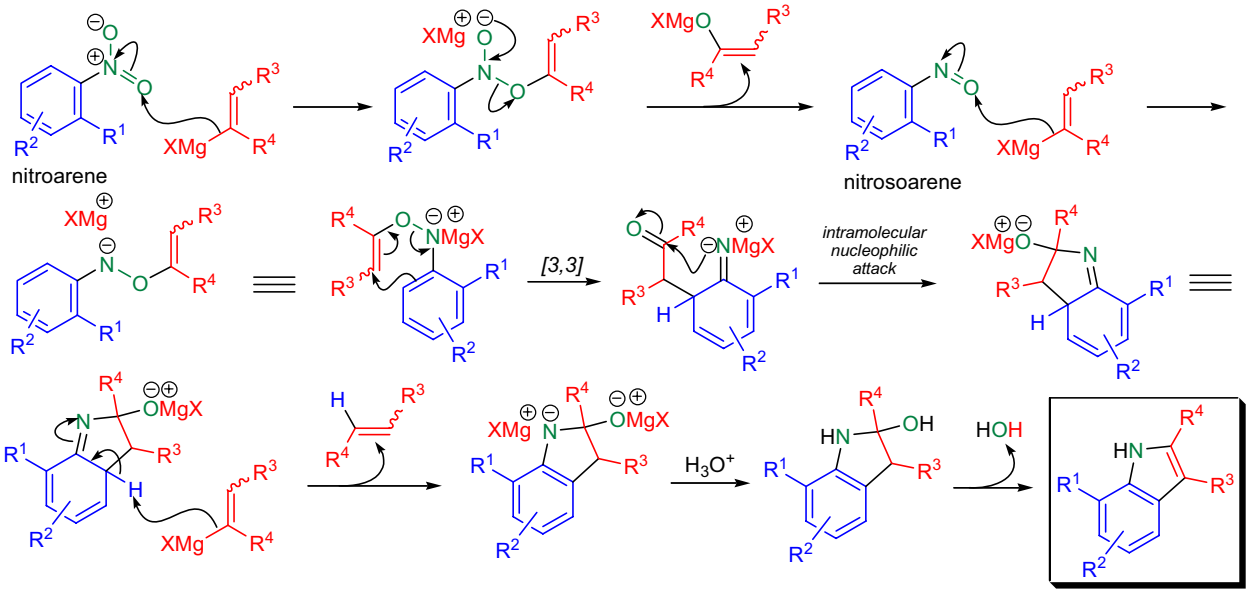
Bartoli indole synthesis:



R^1 = Me, alkyl, aryl, F, Cl, Br, I, $OSiR_3$, *O*-benzyl, *O*-*sec*-alkyl, $CH(OR)_2$; R^2 = H, alkyl, aryl, *O*-alkyl, etc.; R^{3-4} = H, alkyl, aryl, SiR_3
X = Cl, Br, I; solvent: Bu_2O, Et_2O, THF

Mechanism:[12,7]

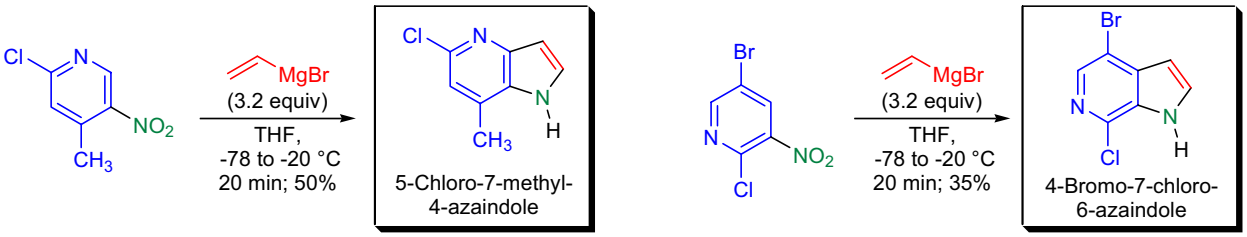
The mechanism of the *Bartoli indole synthesis* is not clear in every detail, but G. Bartoli and co-workers successfully elucidated the main steps in the process. The first step is the addition of Grignard reagent to the oxygen atom of the nitro group followed by the rapid decomposition of the resulting *O*-alkenylated product to give a nitrosoarene. The nitrosoarene is much more reactive than the starting nitroarene, and it is attacked by the second equivalent of Grignard reagent to give an *O*-alkenyl hydroxylamine derivative, which rearranges in a facile *[3,3]-sigmatropic process*. The rearranged product then undergoes intramolecular nucleophilic attack, and the proton in the ring junction is removed by the third equivalent of the Grignard reagent. Finally, acidic work-up affords the indole.



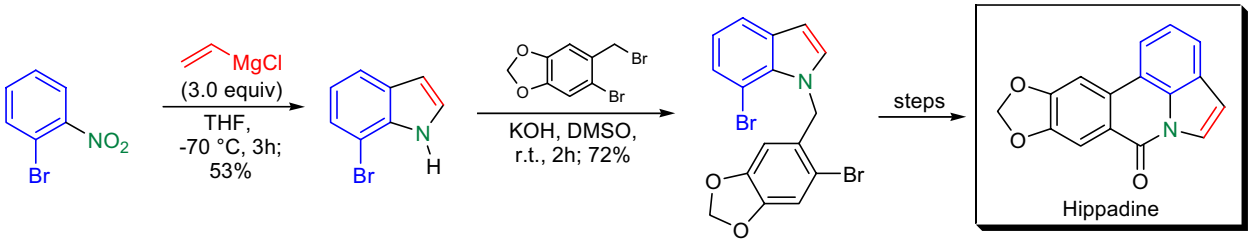
BARTOLI INDOLE SYNTHESIS

Synthetic Applications:

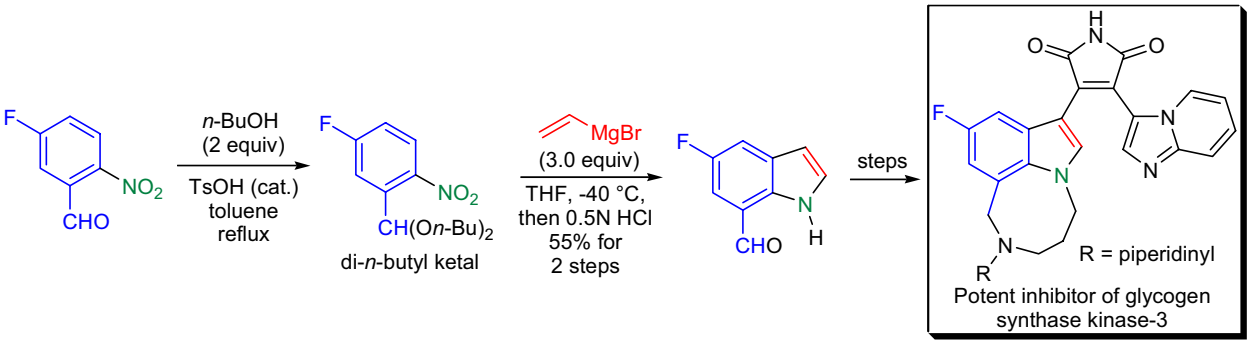
In the laboratory of T. Wang a general method for the preparation of 4- and 6-azaindoles from substituted nitropyridines based on the *Bartoli indole synthesis* was developed.[13] The substrates were treated with excess vinylmagnesium bromide according to the original procedure described by Bartoli et al. The yields were usually moderate and similarly to the simple nitroarenes, the larger the ortho substituent was, the higher yields were obtained. Interestingly, it was noted that the presence of a halogen atom at the 4-position of the pyridine ring resulted in significantly improved product yields.



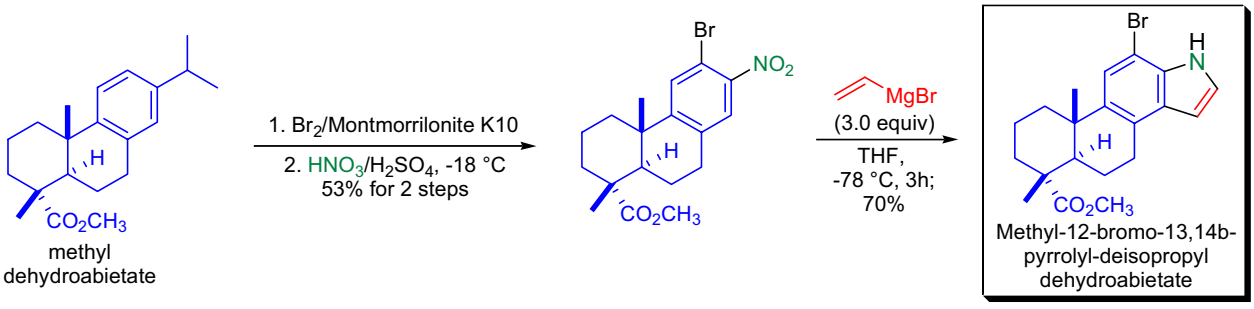
The short synthesis of the pyrrolophenanthridone alkaloid hippadine was accomplished by D.C. Harrowven and co-workers.[14] The key step of the synthetic sequence was the *Ziegler modified intramolecular Ullmann biaryl coupling* between two aryl bromides. One of the aryl halides was 7-bromoindole which was prepared using the *Bartoli indole synthesis*. The second aryl bromide was connected to 7-bromoindole *via* a simple *N*-alkylation.



The research team of T.A. Engler and J.R. Henry identified and synthesized a series of potent and selective glycogen synthase kinase-3 (GSK3) inhibitors.[15] One of the targets required the preparation of 5-fluoro-7-formylindole, which was achieved by the *Bartoli indole synthesis*. Since the unprotected formyl group is incompatible with the Grignard reagent, a two-step protocol was implemented. First, the formyl group of 5-fluoro-2-nitrobenzaldehyde was protected as the corresponding di-*n*-butyl acetal, then excess Grignard reagent was added at low temperature, and finally the acetal protecting group was removed by treatment with aqueous HCl.



Several heterocycles were prepared from dehydroabietic acid, and their antiviral properties were evaluated in the laboratory of B. Gigante.[16] Dehydroabietic acid was first esterified, then brominated. Nitrodeisopropylation was achieved using a mixture of nitric acid and sulfuric acid. The resulting *o*-bromo nitroarene was treated with excess vinyl Grignard reagent to obtain the corresponding methyl-12-bromo-13,14b-pyrrolyl-deisopropyl dehydroabietate.



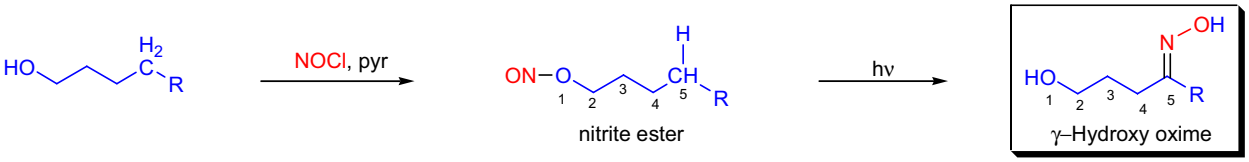
BARTON NITRITE ESTER REACTION

(References are on page 545)

Importance:

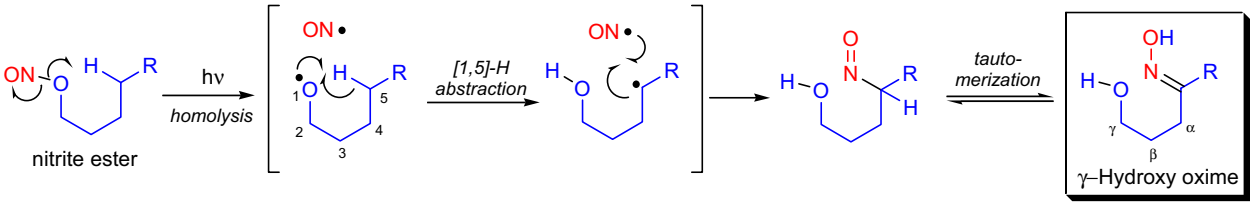
[*Seminal Publications*[1-7]; *Reviews*[8-12]; *Theoretical Studies*[13,14]]

The Barton nitrite ester reaction (*Barton reaction*) is a method for achieving remote functionalization on an unreactive aliphatic site of a nitrite ester under thermal or photolytic conditions *via* oxygen-centered radicals. The nitrite esters are converted to the corresponding γ-hydroxy oximes in the reaction. The most common way to generate an oxygen-centered radical is by the thermolysis or photolysis of nitrite, hypochlorite, or hypoiodite esters. Nitrogen-centered radicals are generated by heating the appropriate *N*-haloamines with sulfuric acid to give pyrrolidines or piperidines (*Hofmann-Löffler-Freytag reaction*). The *Barton nitrite ester reaction* was a landmark in the development of free radicals as valuable intermediates for organic synthesis. Most of the synthetic examples are from the steroid field because the *Barton reaction* occurs readily in rigid molecules. Usually skeletons with several fused rings are well-suited for remote functionalizations.



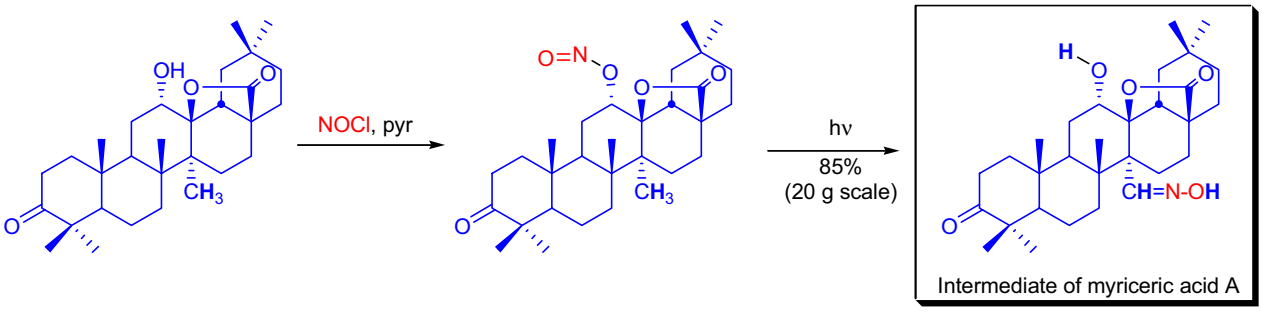
Mechanism:[15,16]

The first step in the mechanism is the homolysis of the O-N bond to form an oxygen-centered radical and a nitrogen-centered free radical. Next, the highly reactive alkoxyl radical abstracts a hydrogen atom from the δ-position (5-position) *via* a quasi chair-like six-atom transition state to generate a new carbon-centered radical that is captured by the initially formed NO free radical. If a competing radical source such as iodine is present, the reaction leads to an iodohydrin, which can cyclize to form a tetrahydrofuran derivative. Occasionally, tetrahydropyran derivatives are obtained in low yields.

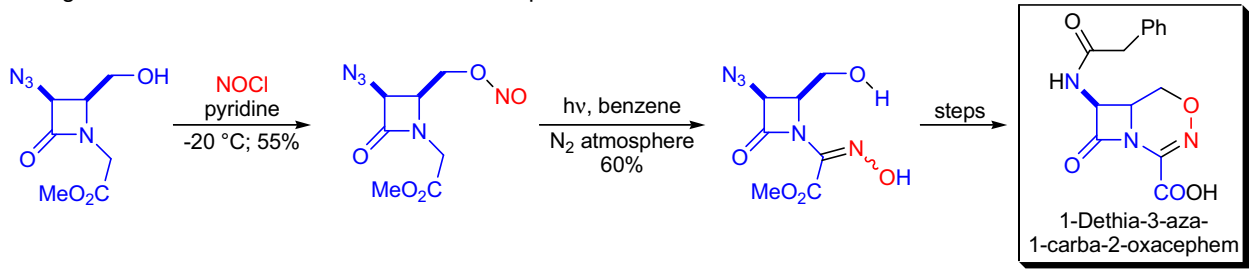


Synthetic Applications:

In the partial synthesis of myriceric acid A by T. Konoike and co-workers, the *Barton nitrite ester reaction* was utilized in a large-scale preparation of one of the intermediates.[17]



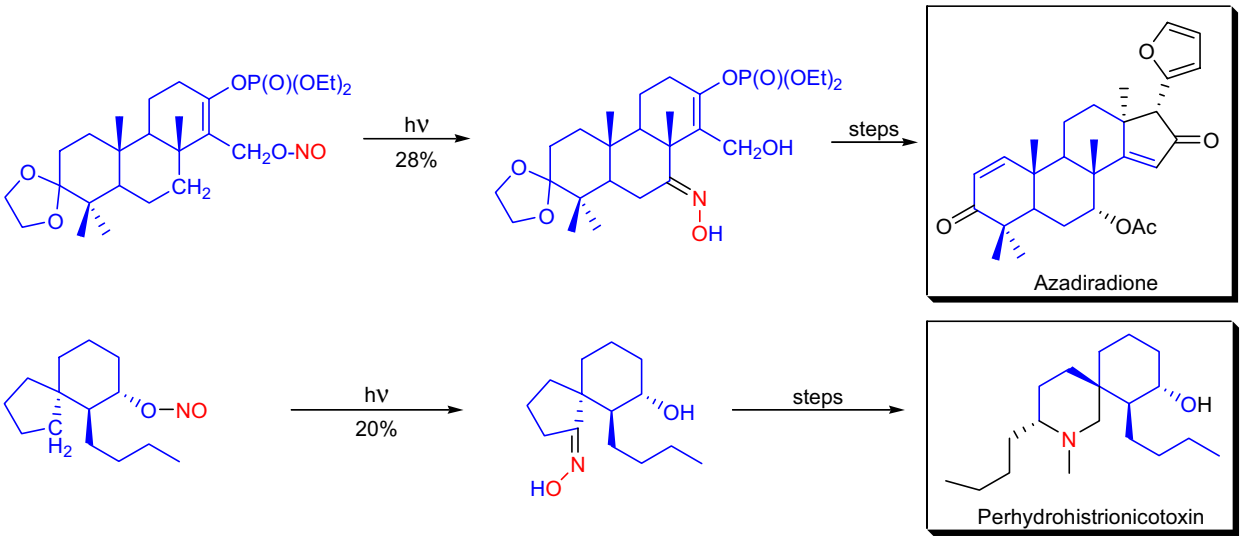
Cephalosporins are important β-lactams, but a number of pathogenic microorganisms have developed resistance to these antibiotic compounds. In order to prepare novel antibiotic cephalosporin analogs, I. Chao and co-workers synthesized 1-dethia-3-aza-1-carba-2-oxacephem, which is not a substrate of the inducible β-lactamase enzyme.[18] The key step of the synthetic sequence was the *Barton nitrite ester reaction* in which regioisomeric oximino β-lactams were generated and transformed into the desired product.



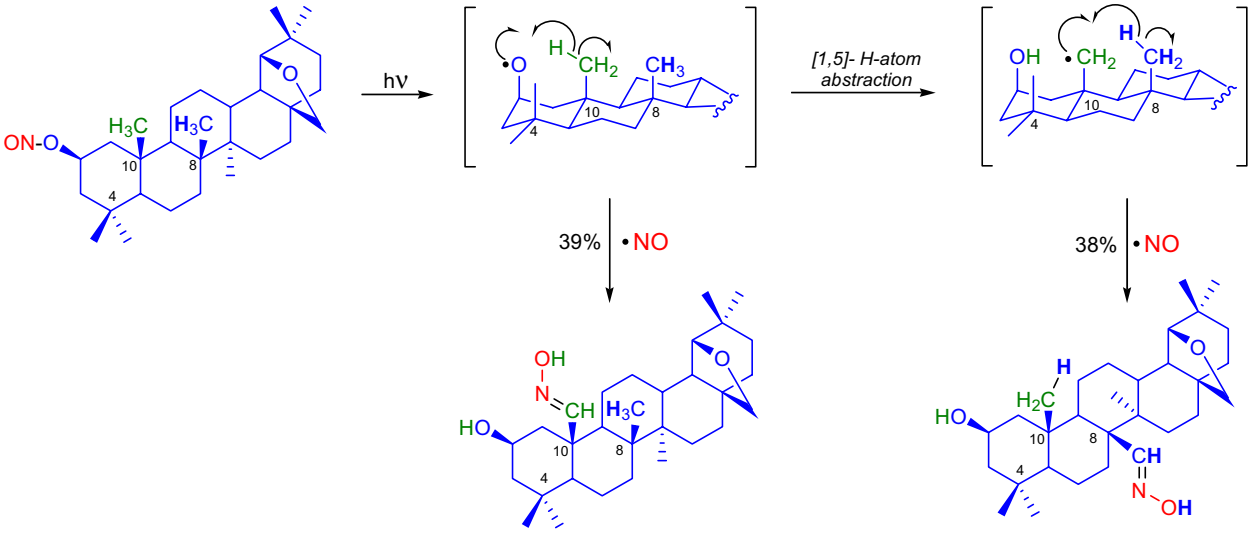
BARTON NITRITE ESTER REACTION

Synthetic Applications:

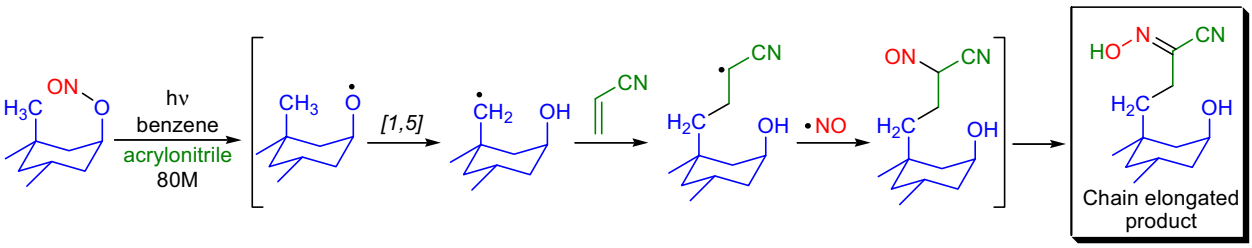
The *Barton reaction* was utilized during the synthesis of various terpenes and has played a crucial role in the elucidation of terpene structures. The *Barton nitrite ester reaction* was a key step in E.J. Corey's synthesis of azadiradione[19] and perhydrohistrionicotoxin[20]. Even though the yields were low, other ways to access the same intermediates would have been tedious, and afforded lower overall yields than in the applied *Barton reactions*.



The *Barton reaction* does not always afford only a single major product. J. Sejbal and co-workers isolated two products in a *Barton reaction* on triterpene substrates.[21] In this example, reaction at either (or both) the C4 and C10 methyl groups was expected, but oxidation of the C8 methyl group was not. This remote functionalization occured *via* two consecutive *[1,5]- H-atom transfers*.



The carbon-centered radical at the δ-position can be reacted by various trapping agents other than the nitrosyl radical. Z. ekovi and co-workers used electron-deficient olefins (Michael acceptors) such as acrylonitrile to trap the δ-carbon radial and obtain functionalized alkyl chains.[22] In order to maximize the yield of the desired chain-elongated product, a high concentration of the acrylonitrile had to be used. The final radical was trapped by the nitrosyl radical.



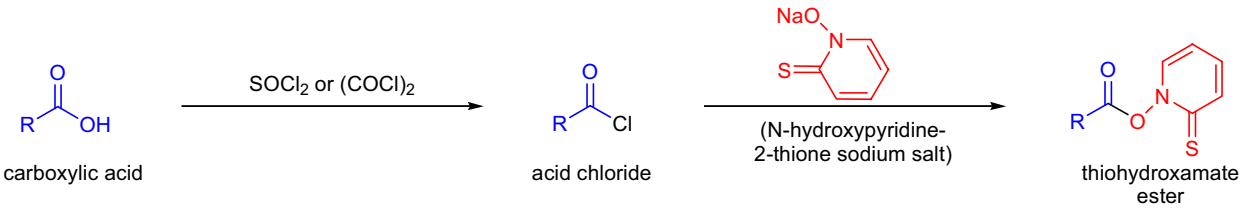
BARTON RADICAL DECARBOXYLATION REACTION

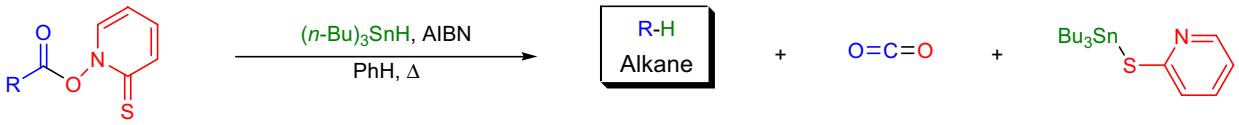
(References are on page 546)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4]; *Modifications & Improvements*[5-12]]

Conversion of a carboxylic acid to a thiohydroxamate ester, followed by heating the product in the presence of a suitable hydrogen donor such as tri-*n*-butyltin hydride, produces a *reductive decarboxylation*. This sequence of reactions is called the *Barton decarboxylation reaction* and may be used to remove a carboxylic acid and replace it with other functional groups.

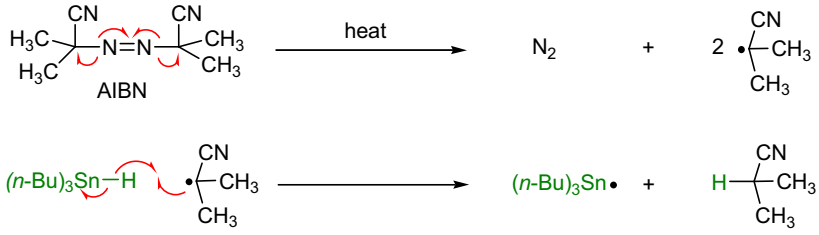




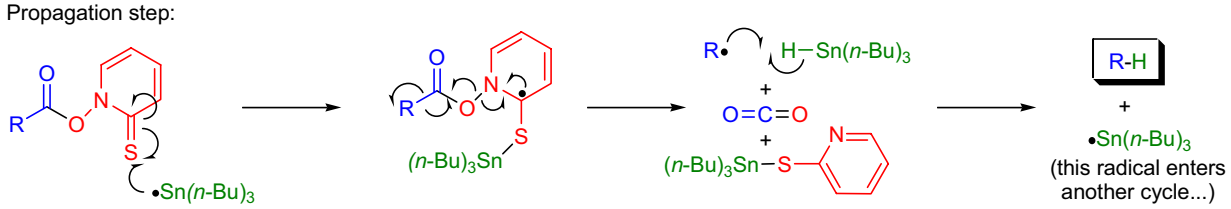
Mechanism: [13]

The first step of the reaction is the homolytic cleavage of the radical initiator AIBN upon heating. This initiation step generates the first radical to start the chain reaction. The initial radical abstracts a hydrogen atom from the tri-*n*-butyltin hydride to afford a tri-*n*-butyltin radical that attacks the sulfur atom of the thiohydroxamate ester, forming a strong Sn-S bond. Next, carbon dioxide is lost, and the released alkyl radical (R·) gets reduced to the product (R-H) by abstracting a hydrogen atom from a tri-*n*-butyltin hydride molecule. The tin radical generated in this last step enters another reaction cycle until all of the starting thiohydroxamate ester is consumed.

Initiation step:

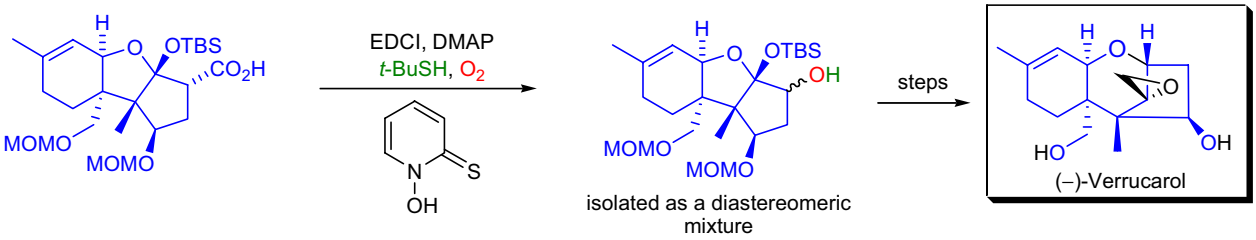


Propagation step:



Synthetic Applications:

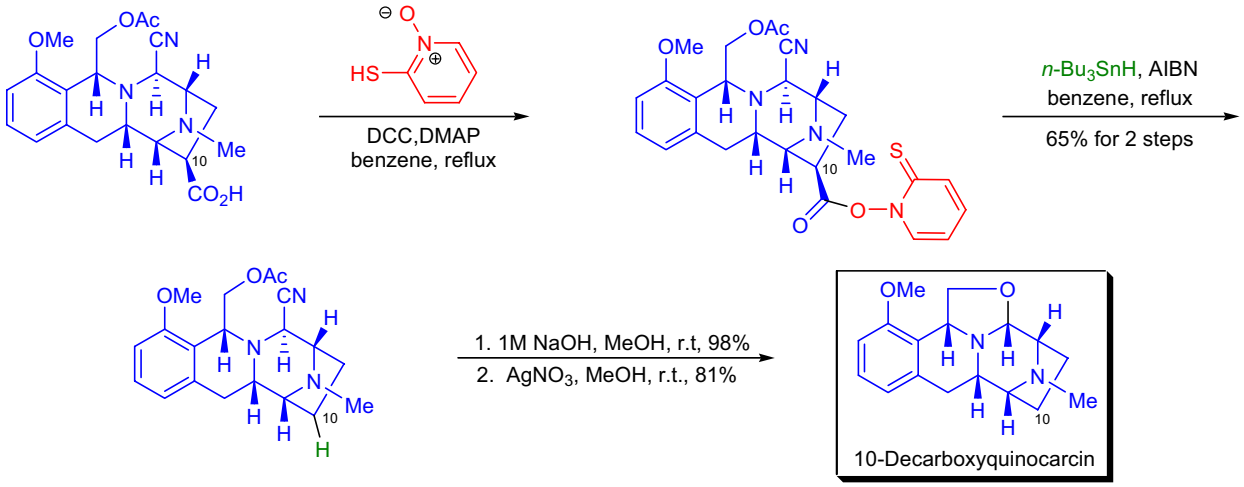
The *Barton decarboxylation procedure* was used in the total synthesis of (–)-verrucarol by K. Tadano et al. The initially formed thiohydroxamic ester was decarboxylated to leave a methylene radical on the cyclopentyl ring, which was then trapped by molecular oxygen. Reductive work-up in the presence of *t*-BuSH finally provided the hydroxylated product.[14]



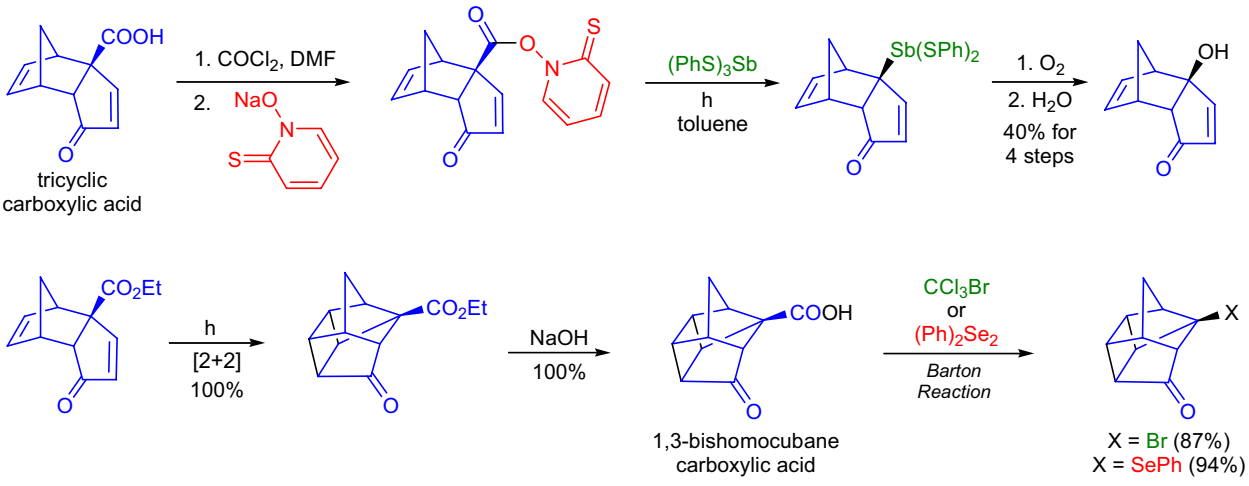
BARTON RADICAL DECARBOXYLATION REACTION

Synthetic Applications:

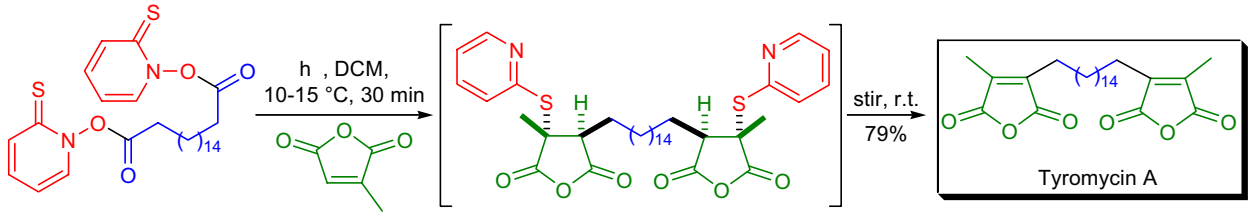
(–)-Quinocarcin exhibits notable antitumor activity against several strains of solid mammalian carcinomas. In the laboratory of S. Terashima, synthetic studies on quinocarcin and its related compounds were conducted.[15] In an effort to establish structure-activity relationships, the synthesis and *in vitro* cyctotoxicity of C10 substituted quinocarcin congeners was carried out. To prepare 10-decarboxyquinocarcin, the *Barton decarboxylation protocol* was employed. The corresponding acid was esterified with 2-mercaptopyridine-*N*-oxide, and the resulting thiohydroxamate ester was immediately subjected to *Barton radical decarboxylation* using AIBN and tributyltin hydride giving rise to the C10 decarboxylated derivative in 65% overall yield.



B. Zwanenburg and co-workers synthesized 6-functionalized tricyclodecadienones (*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones) using *Barton's radical decarboxylation reaction* from the corresponding tricyclic carboxylic acid.[16] Their work expanded the chemical scope of the tricyclodecadienone system as a synthetic equivalent of cyclopentadienone. The synthesis of functionalized cage compounds was also undertaken beginning with 1,3-bishomocubanone carboxylic acid, obtained by irradiating the tricyclic ester. After the *bromodecarboxylation* and *phenylselenodecarboxylation* of 1,3-bishomocubanone carboxylic acid under the conditions of the *Barton reaction*, the corresponding bridgehead bromide and phenylselenide were obtained in high yield.



A *double Barton radical decarboxylation* was utilized during the one-step total synthesis of tyromycin A and its analogs by M. Samadi et al.[17] The *bis*-thiohydroxamic ester was irradiated in the presence of citraconic anhydride, and the resulting product was stirred for two days at room temperature to ensure complete elimination.



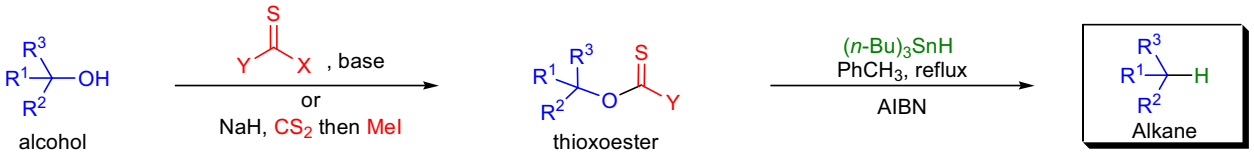
BARTON-McCOMBIE RADICAL DEOXYGENATION REACTION

(References are on page 546)

Importance:

[*Seminal Publications*[1-6]; *Reviews*[7-12]; *Modifications & Improvements*[13-24]]

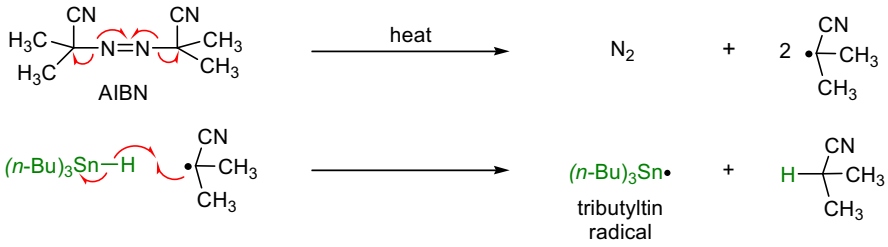
In the *Barton-McCombie radical deoxygenation* reaction the hydroxyl group of an alcohol is replaced with a hydrogen atom. Even hindered secondary and tertiary alcohols may be deoxygenated by this method. In a typical procedure the alcohol is first converted to a thioxoester derivative, which is then exposed to tri-*n*-butyltin hydride in refluxing toluene.



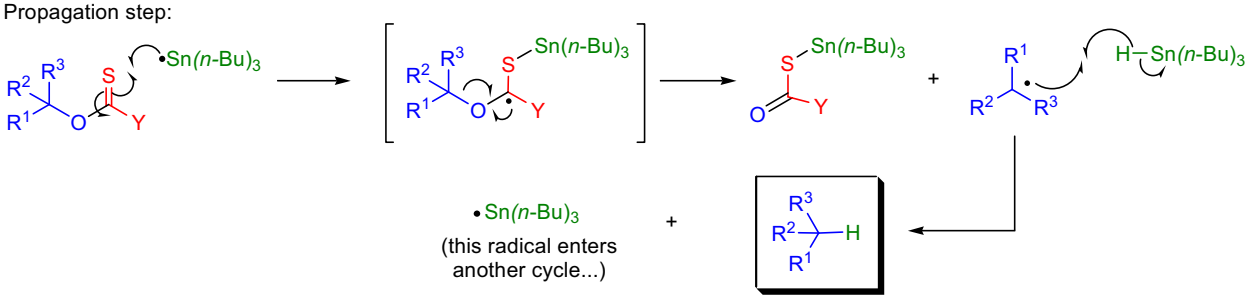
Y = SMe, imidazolyl, OPh, OMe; X = Cl, imidazolyl; base: NaH

Mechanism: [25,13,26]

Initiation step:

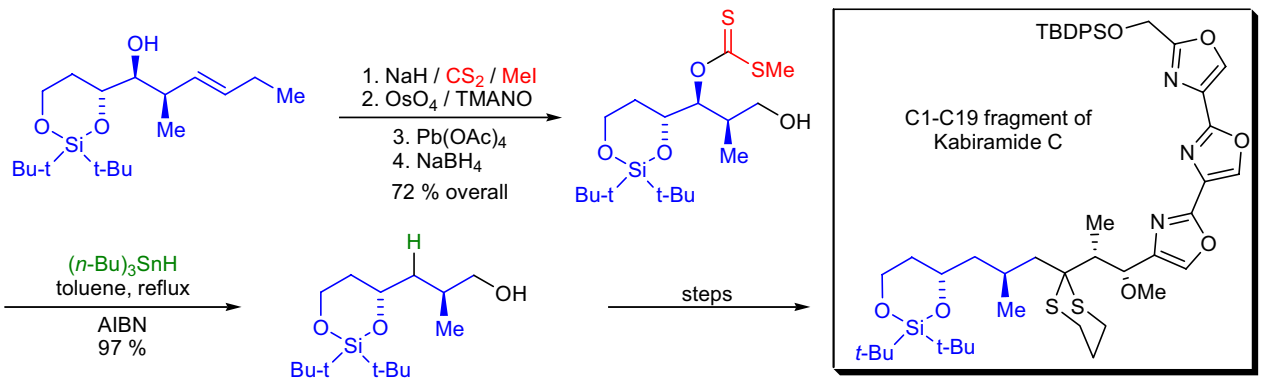


Propagation step:



Synthetic Applications:

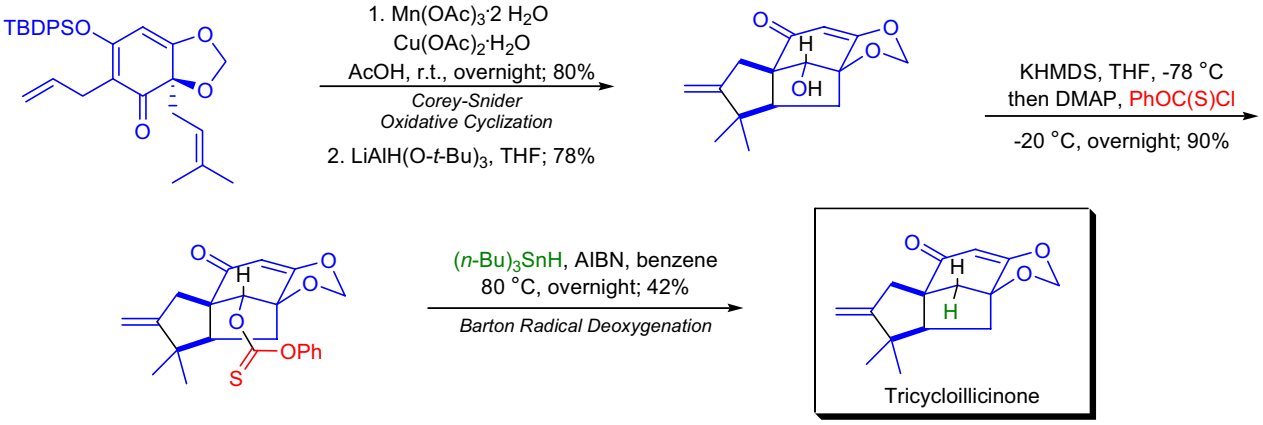
In the asymmetric synthesis of the C1-C19 fragment of kabiramide C, to complete the stereochemical array, J. Panek and co-workers used, among other methods, *the Barton-McCombie deoxygenation* protocol.[27]



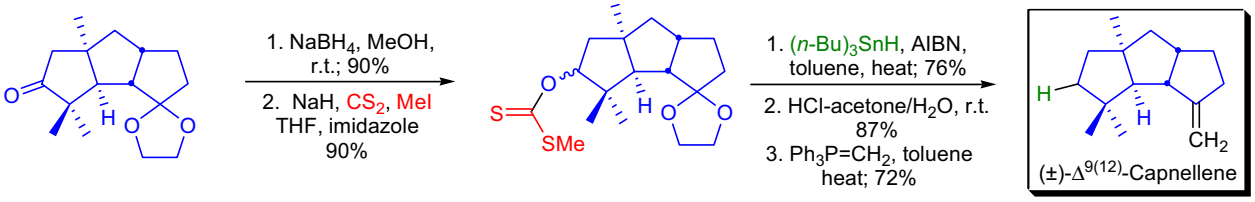
BARTON-McCOMBIE RADICAL DEOXYGENATION REACTION

Synthetic Applications:

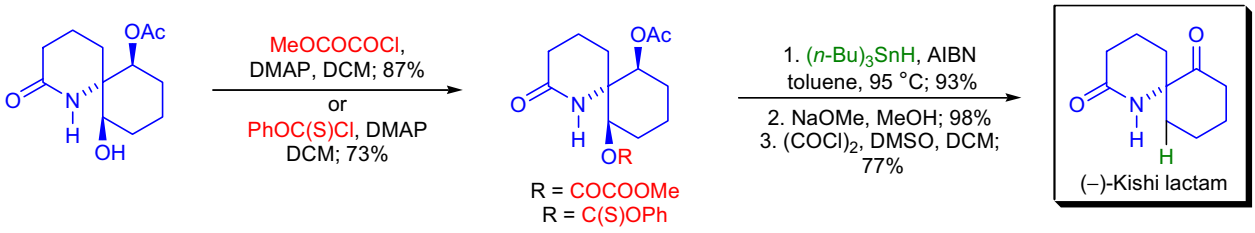
S.J. Danishefsky and co-workers developed a synthetic route to the neurotrophic illicinones and a total synthesis of the natural product tricycloillicinone.[28] Illicinones were found to enhance the action of choline acetyltransferase, which catalyzes the synthesis of acetylcholine from its precursors. The application of *Corey-Snider oxidative cyclization* and the *Barton-McCombie radical deoxygenation* provided a direct route to tricycloillicinone.



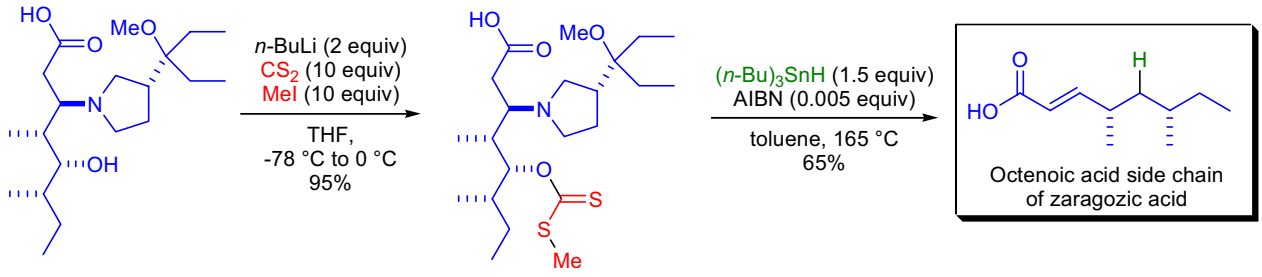
In the laboratory of V. Singh a novel and efficient stereospecific synthesis of the marine natural product (±)-$\Delta^{9(12)}$-capnellene from *p*-cresol was developed.[29] After rapidly assembling the desired carbon framework, it was necessary to remove the carbonyl group from the tricyclic intermediate which was accomplished using *Barton's deoxygenation procedure*.



F. Luzzio and co-workers devised a total synthesis for both antipodes of the (–)-Kishi lactam, which is a versatile intermediate for the synthesis of the perhydrohistrionicotoxin (pHTX) alkaloids.[30] In the final stages of the synthesis of the (-)-Kishi lactam, it was necessary to remove one of the secondary alcohol groups. The *Barton radical deoxygenation protocol* was utilized for this operation.



R.H. Schlessinger et al. have successfully synthesized the α,β-unsaturated octenoic acid side chain of zaragozic acid, which contains acyclic "skip" 1,3 dimethyl stereocenters.[31] Their approach utilized the *Barton radical deoxygenation reaction* in the last step of the total synthesis for the removal of the unnecessary hydroxyl group.



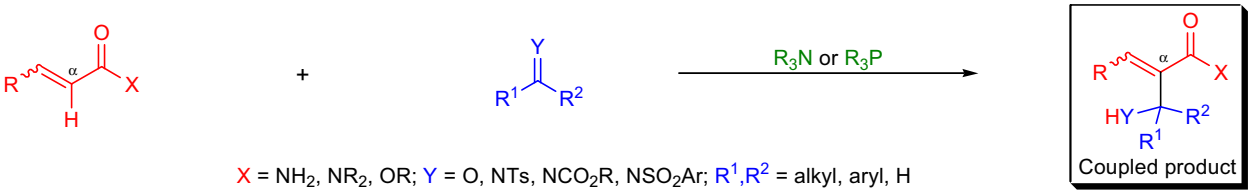
BAYLIS-HILLMAN REACTION

(References are on page 547)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-13]; *Modifications & Improvements*[14-31]]

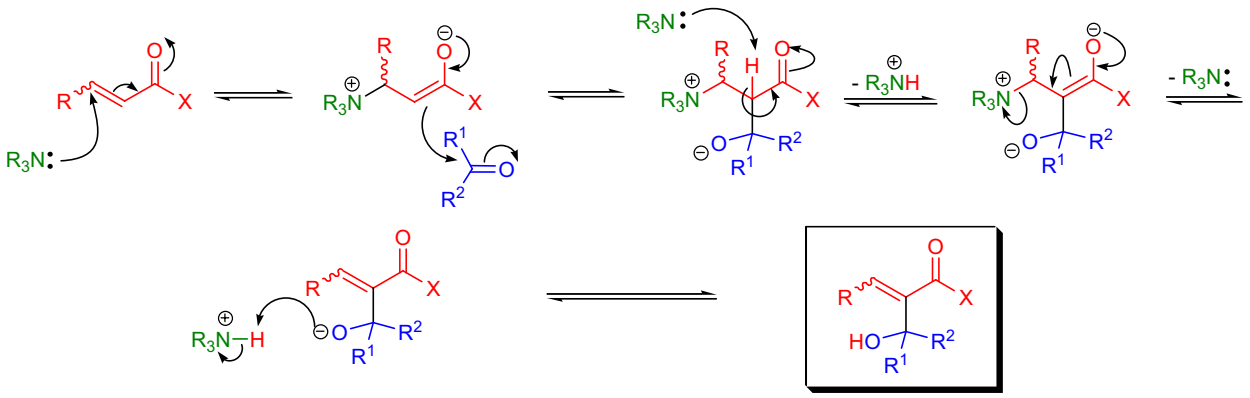
In 1968, K. Morita reported the reaction of acetaldehyde with ethyl acrylate to give α-hydroxyethylated products in the presence of tertiary phosphines.[1] Four years later A.B. Baylis and M.E.D. Hillman carried out the same transformation by using the cheaper and less toxic DABCO as the catalyst.[2] The *Baylis-Hillman reaction* involves the formation of a C-C single bond between the α-position of conjugated carbonyl compounds, such as esters and amides, and carbon electrophiles, such as aldehydes and activated ketones in the presence of a suitable nucleophilic catalyst, particularly a tertiary amine. The most frequently used catalysts are DABCO, quinuclidine, cinchona derived alkaloids and trialkylphosphines. The *asymmetric Baylis-Hillman reaction* can be mediated efficiently by hydroxylated chiral amines derived from cinchona alkaloids. The reaction works with both aliphatic and aromatic aldehydes and results in high enantioselectivities.[7] A catalytic amount of BINAP was also shown to promote the reaction with selected aldehydes.[17] The major drawbacks of the *organocatalytic Baylis-Hillman reaction* are the slow reaction rate (days and weeks) and the limited scope of substrates. However, these shortcomings may be partly overcome by using metal-derived Lewis acids.[15,16]



X = NH_2, NR_2, OR; Y = O, NTs, NCO_2R, NSO_2Ar; R^1,R^2 = alkyl, aryl, H

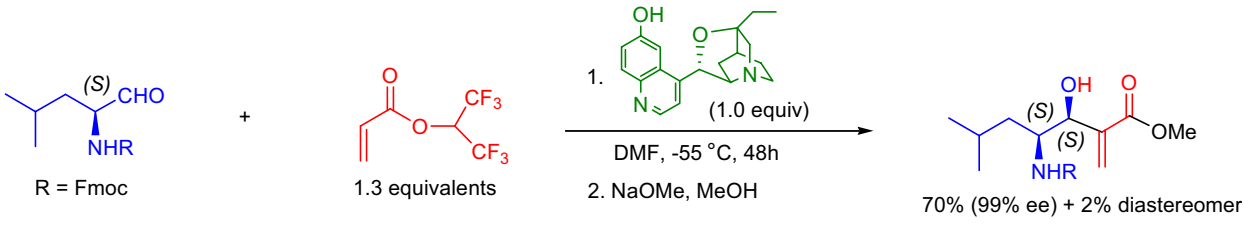
Mechanism:[32-34,17,35-38]

The currently accepted mechanism of the *Baylis-Hillman reaction* involves a *Michael addition* of the catalyst (tertiary amine) at the β-position of the activated alkene to form a zwitterionic enolate. This enolate reacts with the aldehyde to give another zwitterion that is deprotonated, and the catalyst is released. Proton transfer affords the final product.



Synthetic Applications:

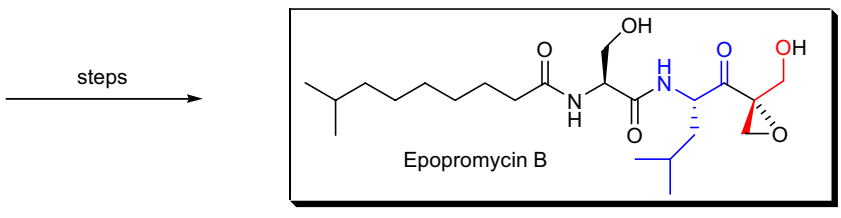
S. Hatekayama and co-workers developed a highly enantio- and stereocontrolled route to the key precursor of the novel plant cell inhibitor epopromycin B, using a *cinchona-alkaloid catalyzed Baylis-Hillman reaction* of *N*-Fmoc leucinal.[39]



R = Fmoc

1.3 equivalents

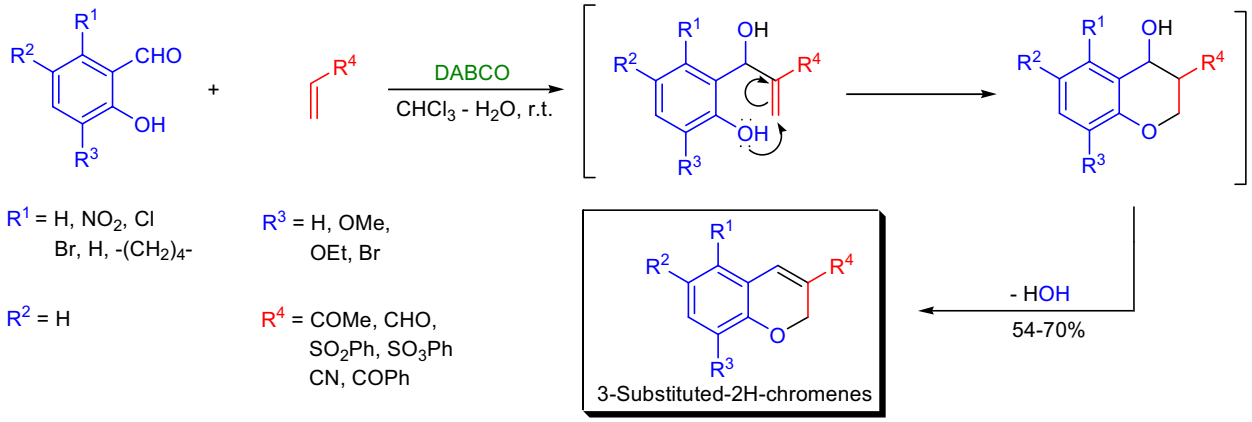
70% (99% ee) + 2% diastereomer



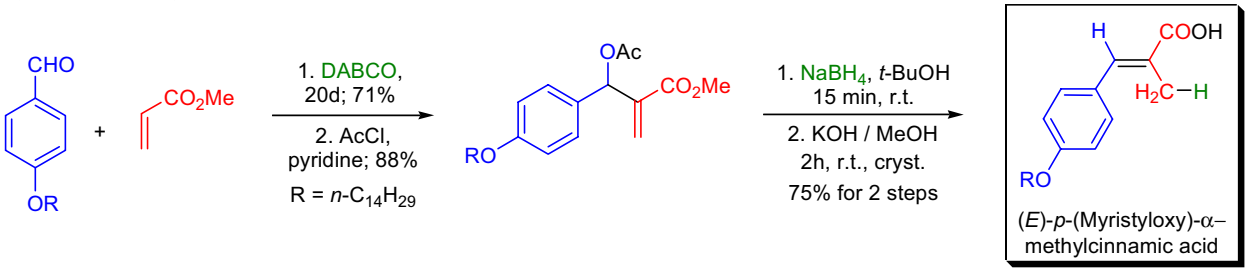
BAYLIS-HILLMAN REACTION

Synthetic Applications:

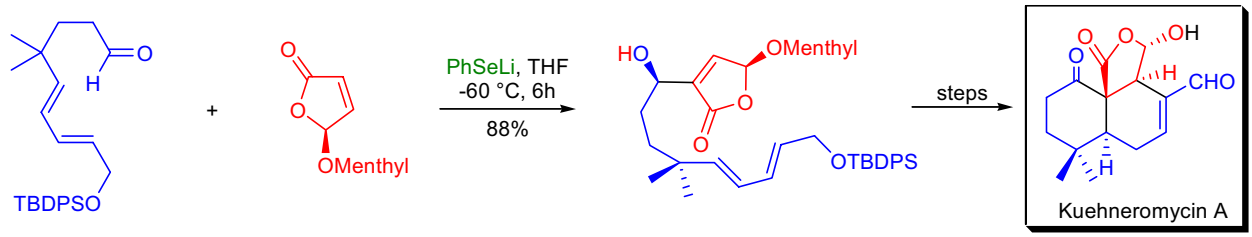
It was shown in the laboratory of P.T. Kaye that the reactions of 2-hydroxybenzaldehydes and 2-hydroxy-1-naphthaldehydes with various activated alkenes proceeded with regioselective cyclization under *Baylis-Hillman conditions* to afford the corresponding 3-substituted 2H-chromene derivatives in high yields.[40] Previous attempts to prepare 2H-chromenes chemoselectively *via* the cyclization of 2-hydroxybenzaldehyde-derived Baylis-Hillman products had proven unsuccessful. Complex mixtures containing coumarin and chromene derivatives were obtained. Good results were observed after the careful and systematic study of the various reactants and reaction conditions.



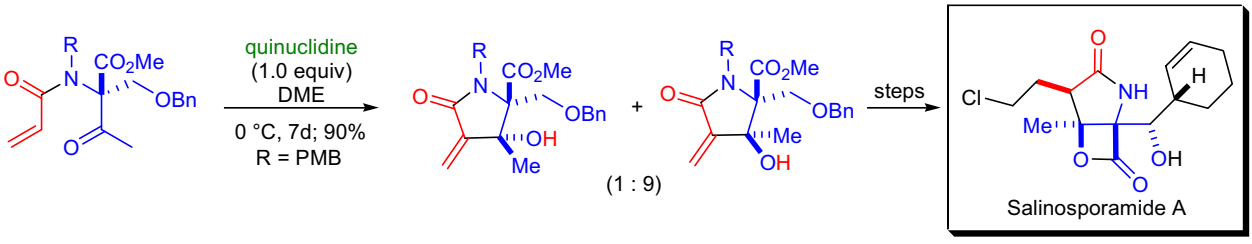
D. Basavaiah and co-workers achieved the simple and convenient stereoselective synthesis of (*E*)-α-methylcinnamic acids *via* the nucleophilic addition of hydride ion from sodium borohydride to acetates of Baylis-Hillman adducts (methyl 3-acetoxy-3-aryl-2-methylenepropanoates), followed by hydrolysis and crystallization.[41] The potential of this methodology was demonstrated in the synthesis of (*E*)-*p*-(myristyloxy)-α-methylcinnamic acid, which is an active hypolipidemic agent.



Research by J. Jauch showed that in the case of highly base-sensitive substrates the *Baylis-Hillmann reaction* can be carried out by using lithium phenylselenide, which is a strong nucleophile but only weakly basic. This variant of the reaction is highly diastereoselective and was successfully applied to the total synthesis of kuehneromycin A.[42]



In the simple stereoselective total synthesis of salinosporamide A, E.J. Corey and co-workers applied the *intramolecular Baylis-Hillman reaction* to a ketoamide substrate.[43] The reaction was catalyzed by quinuclidine and the γ-lactam product was formed as a 9:1 mixture of diastereomers favoring the desired stereoisomer.



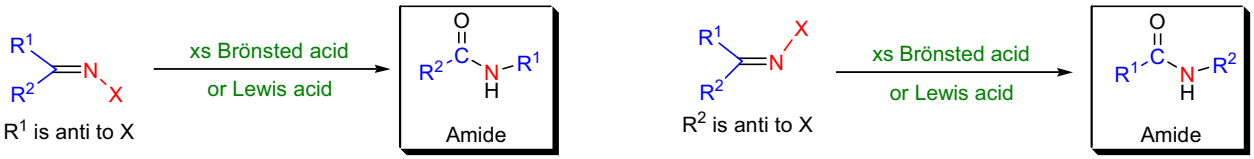
BECKMANN REARRANGEMENT

(References are on page 548)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-5]; *Modifications & Improvements*[6-17]; *Theoretical Studies*[18-27]]

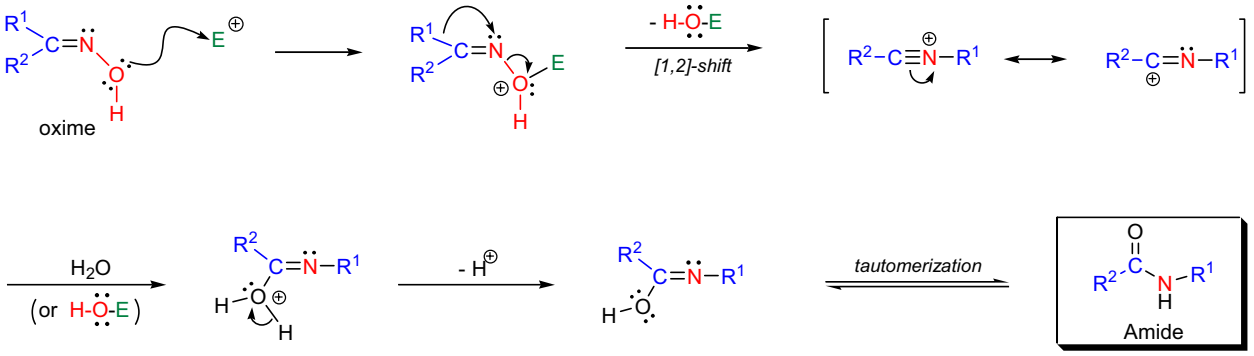
The conversion of aldoximes and ketoximes to the corresponding amides in acidic medium is known as the *Beckmann rearrangement*. It is especially important in the industrial production of ε-caprolactam, which is used as a monomer for polymerization to a polyamide for the production of synthetic fibers. The reaction is usually carried out under forcing conditions (high temperatures >130 °C, large amounts of strong Brönsted acids) and it is non-catalytic. The applied Brönsted acids are: H_2SO_4, $HCl/Ac_2O/AcOH$, etc., which means that sensitive substrates cannot be used in this process. The stereochemical outcome of this rearrangement is predictable: the R group *anti* to the leaving group on the nitrogen will migrate. If the oxime isomerizes under the reaction conditions, a mixture of the two possible amides is obtained. The hydrogen atom never migrates, so this method cannot be used for the synthesis of *N*-unsubstituted amides.



R^1, R^2 = alkyl, aryl, heteroaryl; X = OH, OTs, OMs, Cl

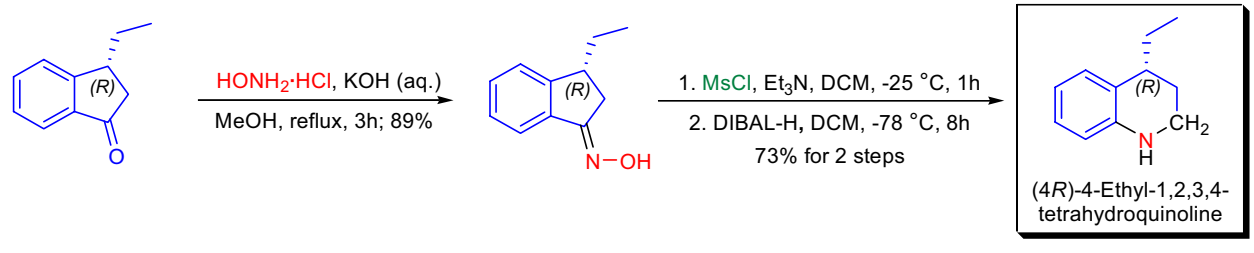
Mechanism:[28,19,22-24,29-31]

In the first step of the mechanism the X group is converted to a leaving group by reaction with an electrophile. The departure of the leaving group is accompanied by the *[1,2]*-shift of the R group, which is *anti* to the leaving group. The resulting carbocation reacts with a nucleophile (a water molecule or the leaving group) to afford the amide after tautomerization.



Synthetic Applications:

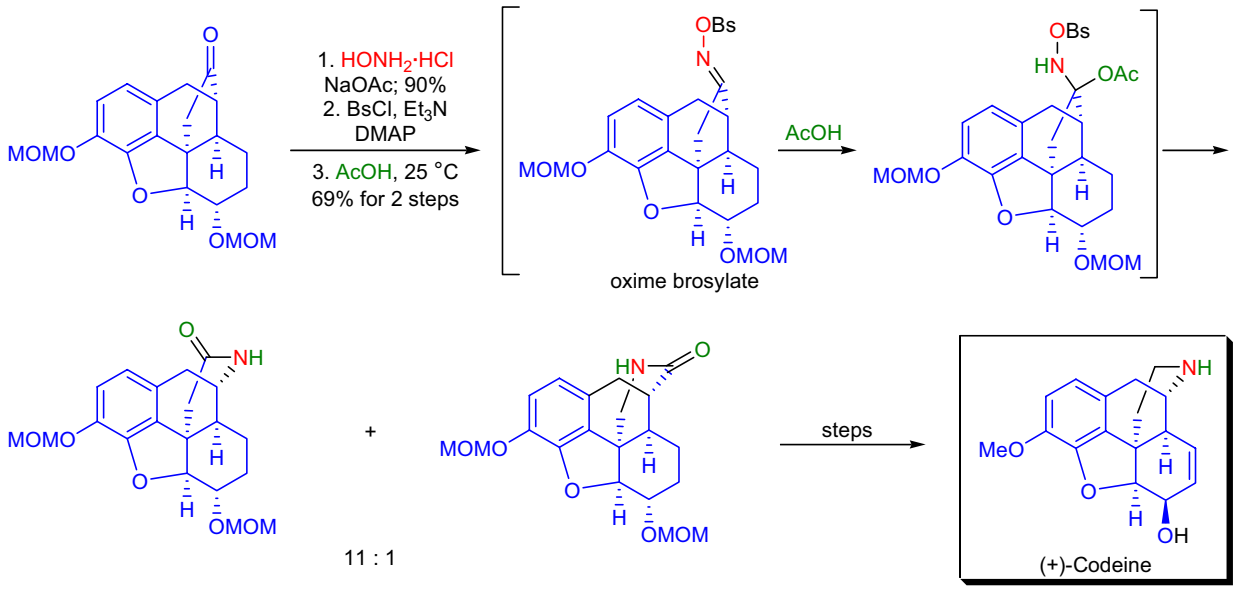
N.S. Mani and co-workers utilized the *organoaluminum promoted modified Beckmann rearrangement* during their efficient synthetic route to chiral 4-alkyl-1,2,3,4-tetrahydroquinoline. (4*R*)-4-Ethyl-1,2,3,4-tetrahydroquinoline was obtained by rearrangement of the ketoxime sulfonate of (3*R*)-3-ethylindan-1-one.[32] The resulting six-membered lactam product was reduced to the corresponding cyclic secondary amine with diisobutylaluminum hydride.



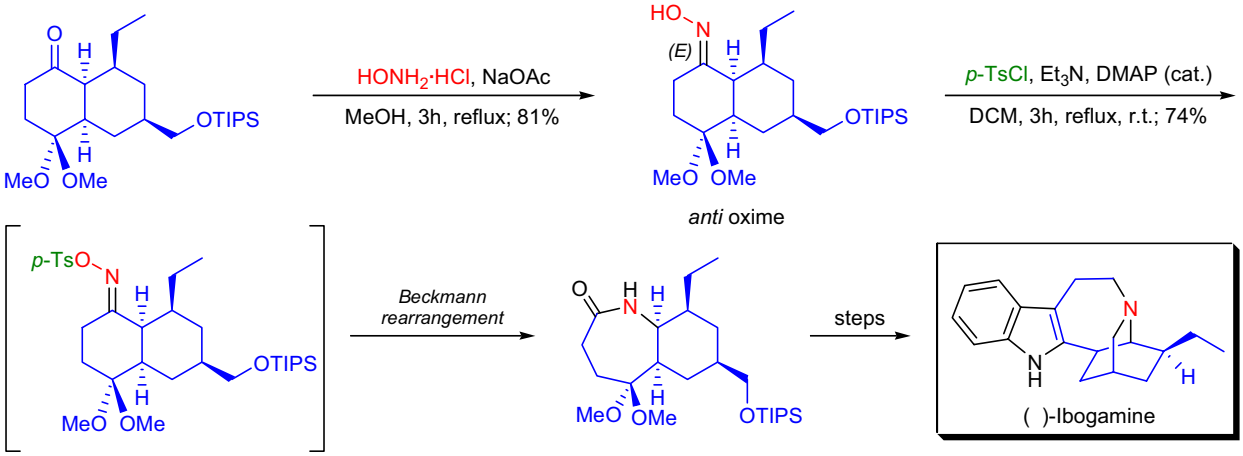
BECKMANN REARRANGEMENT

Synthetic Applications:

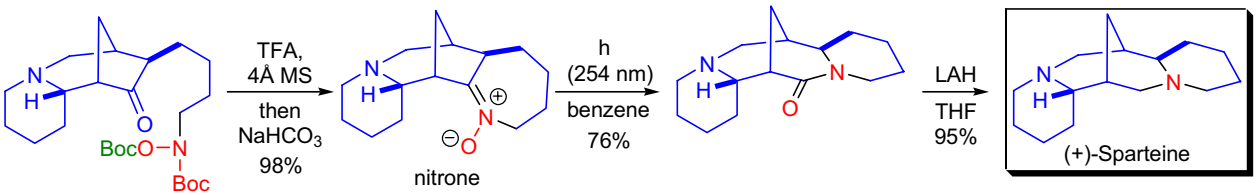
In the laboratory of J.D. White, the asymmetric total synthesis of the non-natural (+)-codeine was accomplished *via intramolecular carbenoid insertion*.[33] In the late stages of the total synthesis it was necessary to install a 6-membered piperidine moiety. This transformation was accomplished utilizing a *Beckmann rearrangement* of the cyclopentanone oxime portion of one of the intermediates. Later the 6-membered lactam was reduced to the corresponding amine with LAH. To this end, an oxime brosylate (Bs) was prepared, which underwent a smooth *Beckmann rearrangement* in acetic acid to provide a 69% yield of two isomeric lactams in an 11:1 ratio in favor of the desired isomer.



J.D. White et al. reported the total synthesis of (–)-ibogamine *via* the catalytic *asymmetric Diels-Alder reaction* of benzoquinone.[34] The azatricyclic framework of the molecule was established by converting the bicyclic ketone to the *anti* oxime and then subjecting it to a *Beckmann rearrangement* in the presence of *p*-toluenesulfonyl chloride to afford the 7-membered lactam. Elaboration of this lactam into the azatricyclic core of ibogamine and later to the natural product itself was accomplished in a few additional steps.



A novel variant of the *photo-Beckmann rearrangement* was utilized by J. Aubé and co-workers in the endgame of the total synthesis of (+)-sparteine.[35] The hydroxylamine was generated *in situ*, and reacted intramolecularly with the ketone to form a nitrone . Photolysis of the nitrone afforded the desired lactam in good yield.



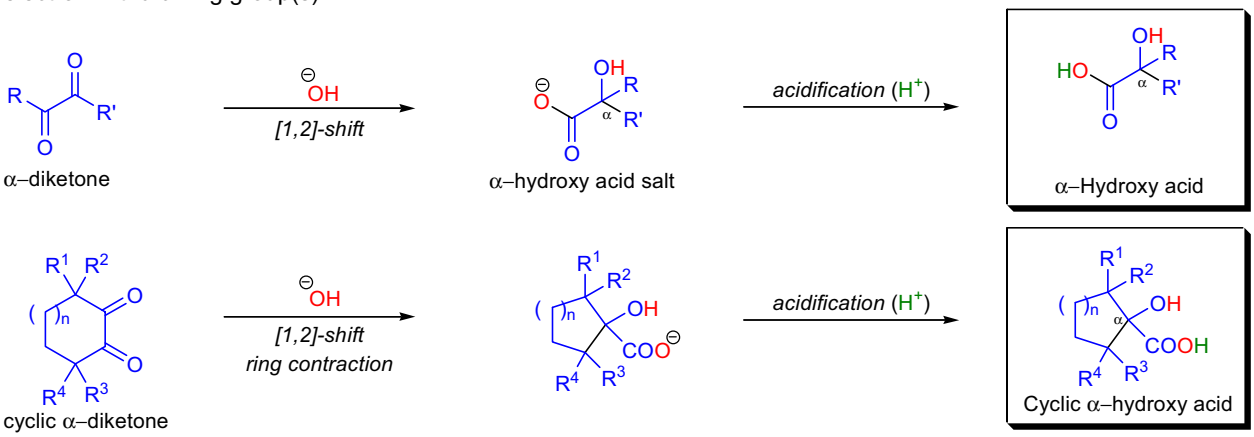
BENZILIC ACID REARRANGEMENT

(References are on page 548)

Importance:

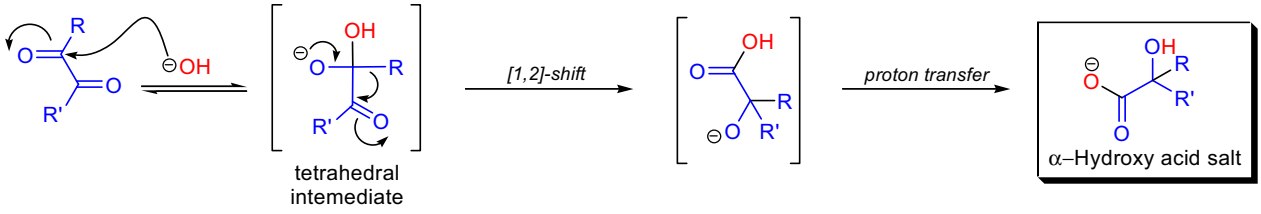
[Seminal Publications[1,2]; *Reviews*[3-6]; *Modifications & Improvements*[7-10]; *Theoretical Studies*[11]]

Upon treatment with base (e.g., NaOH), α-diketones rearrange to give salts of α-hydroxy acids. This process is called the *benzilic acid rearrangement*. The reaction takes place with both aliphatic and aromatic α-diketones and α-keto aldehydes. Usually diaryl diketones undergo *benzilic acid rearrangements* in excellent yields, but aliphatic α-diketones that have enolizable α-protons give low yields due to competing *aldol condensation* reactions. Cyclic α-diketones undergo the synthetically useful *ring-contraction benzilic acid rearrangement* reaction under these conditions. When alkoxides or amide anions are used in place of hydroxides, the corresponding esters and amides are formed. This process is called the *benzilic ester rearrangement*. Alkoxides that are readily oxidized such as ethoxide (EtO^-) or isopropoxide (Me_2CHO^-) are not synthetically useful, since these species reduce the α-diketones to the corresponding α-hydroxy ketones. Aryl groups tend to migrate more rapidly than alkyl groups. When two different aryl groups are available, the major product usually results from migration of the aromatic ring with the more powerful electron-withdrawing group(s).



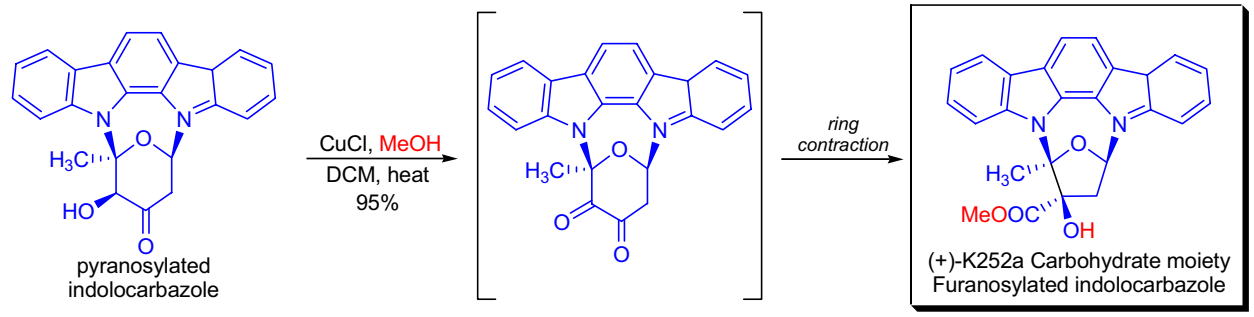
Mechanism: [12-16,11,17,18,8,6]

The *benzilic acid rearrangement* is an irreversible process. The first step of the mechanism is the addition of the nucleophile (HO^-, alkoxide, or amide ion) across the C=O bond to give a tetrahedral intermediate. The next step is aryl or alkyl migration to form the corresponding α-hydroxy acid salt.



Synthetic Applications:

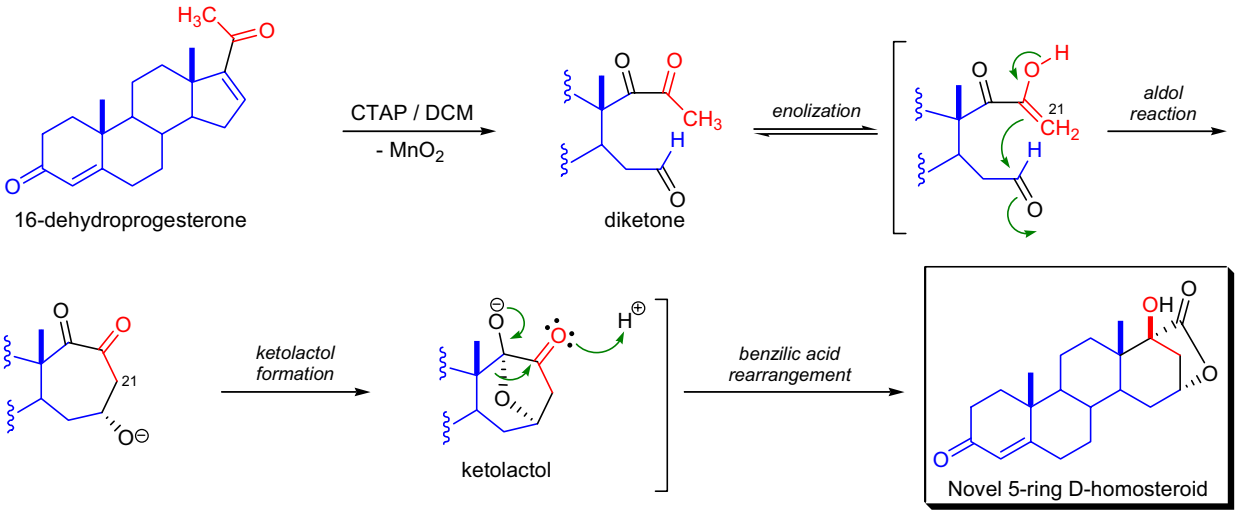
J.L. Wood et al. were able to convert a pyranosylated indolocarbazole to the carbohydrate moiety of (+)-K252a utilizing the stereoselective *ring-contraction benzilic acid rearrangement*.[19] This reaction suggested a possible biosynthetic link between furanosylated and pyranosylated indolocarbazoles.



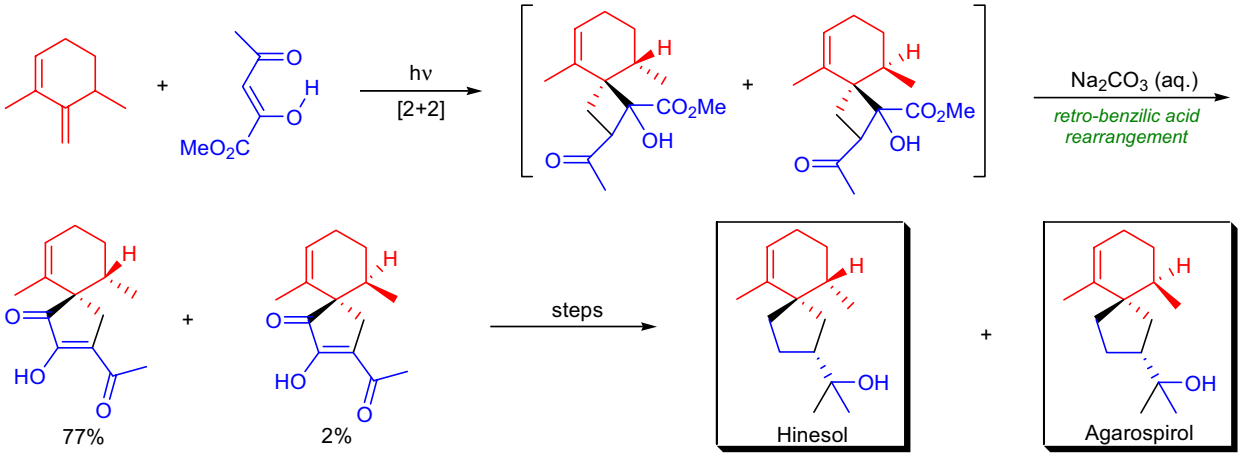
BENZILIC ACID REARRANGEMENT

Synthetic Applications:

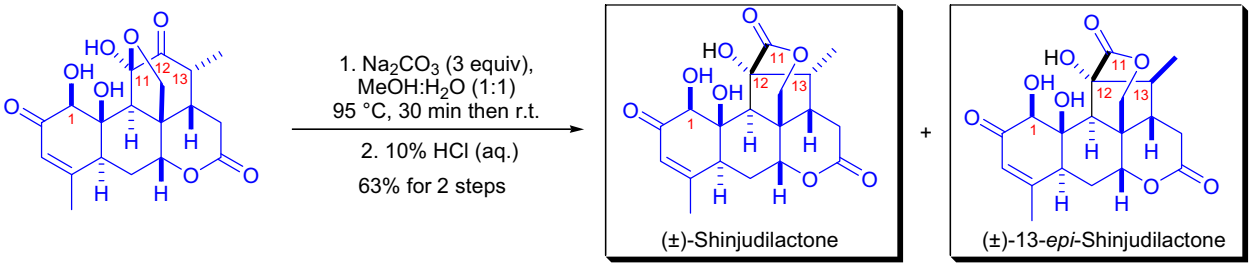
In an attempt to isolate 16α,17α-dihydroxyprogesterone by the stereoselective *cis*-dihydroxylation of 16-dehydroprogesterone using cetyltrimethylammonium permanganate (CTAP) as an oxidant, J.A. Katzenellenbogen and co-workers isolated a novel 5-ring D-homosteroid instead of the desired diol.[20] The mechanism of the final step was similar to the *benzilic acid rearrangement.* Under reaction conditions in which the permanganate concentration was high, the C21 enolate of the diketone attacked the aldehyde to form the 5-membered ketolactol. The final ring contraction was accomplished by the *benzilic acid rearrangement*.



H. Takeshita and co-workers devised a short synthesis of (±)-hinesol and (±)-agarospirol *via* a mild base-catalyzed *retro-benzilic acid rearrangement* of *proto*-[2+2] photocycloadducts to the desired spiro[4,5]decanedione framework.[21]



P.A. Grieco et al. accomplished the total synthesis of (±)-shinjudilactone and (±)-13-*epi*-shinjudilactone *via* a *benzilic acid-type rearrangement*.[22] The substrate was exposed to basic conditions and the two desired products were obtained as a 1:1 mixture. Interestingly, when the C1 position was methoxy substituted, the rearrangement failed to take place under a variety of acidic and basic conditions.



BENZOIN AND RETRO-BENZOIN CONDENSATION

(References are on page 549)

Importance:

[*Seminal Publication*[1-3]*; Reviews*[4-8]*; Modifications & Improvements*[9-16]*; Theoretical Studies*[17,18]]

Upon treating certain (but not all) aromatic aldehydes or glyoxals (α-keto aldehydes) with cyanide ion (CN^-), benzoins (α-hydroxy-ketones or acyloins) are produced in a reaction called the *benzoin condensation*. The reverse process is called the *retro-benzoin condensation*, and it is frequently used for the preparation of ketones. The condensation involves the addition of one molecule of aldehyde to the C=O group of another. One of the aldehydes serves as the donor and the other serves as the acceptor. Some aldehydes can only be donors (e.g. *p*-dimethylaminobenzaldehyde) or acceptors, so they are not able to self-condense, while other aldehydes (benzaldehyde) can perform both functions and are capable of self-condensation. Certain thiazolium salts can also catalyze the reaction in the presence of a mild base.[11,12,19] This version of the benzoin condensation is more synthetically useful than the original procedure because it works with enolizable and non-enolizable aldehydes and asymmetric catalysts may be used. Aliphatic aldehydes can also be used and mixtures of aliphatic and aromatic aldehydes give mixed benzoins. Recently, it was also shown that thiazolium-ion based organic ionic liquids (OILs) promote the benzoin condensation in the presence of small amounts of triethylamine.[12] The stereoselective synthesis of benzoins has been achieved using chiral thiazolium salts as catalysts.[11]

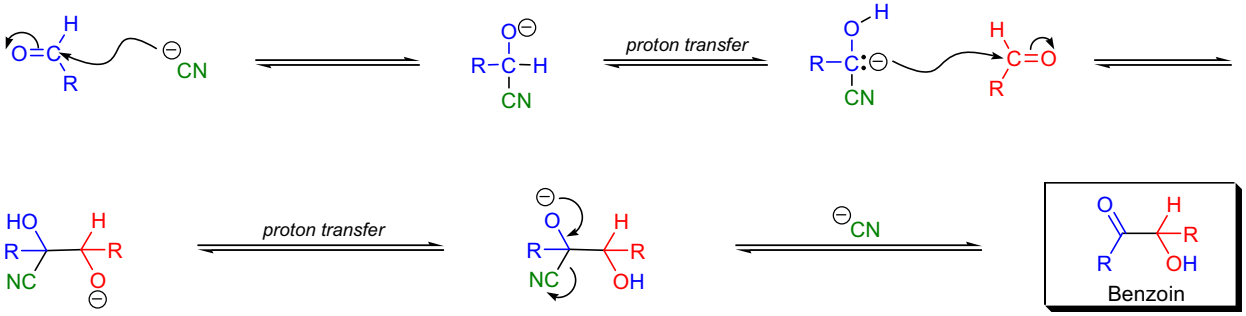


R = aryl, heteroaryl, 3° alkyl, C(=O)-alkyl; catalyst: NaCN, KCN, thiazolium salt, NHC (*N*-heterocyclic carbenes)

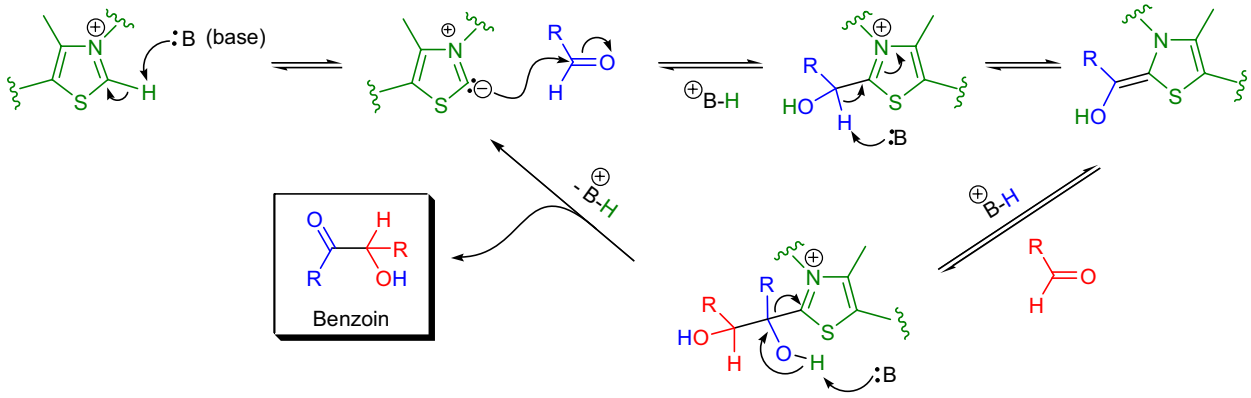
Mechanism:

[20,21,17,22-24,18,25-30,19,31]

All the steps of *the cyanide ion catalyzed benzoin condensation* are completely reversible, and the widely accepted mechanism involves the loss of the aldehydic proton in the key step. This deprotonation is possible due to the increased acidity of this C-H bond caused by the electron-withdrawing effect of the CN group. The cyanide ion is a very specific catalyst of the reaction. Cyanide is a good nucleophile, a good leaving group, and its electron-withdrawing effect enhances the acidity of the aldehyde hydrogen.



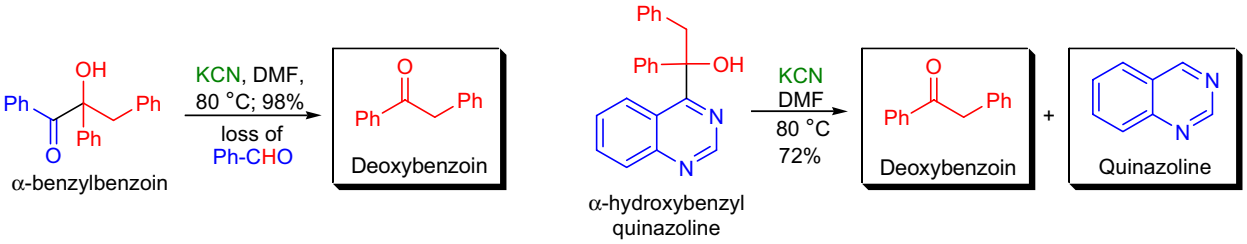
The generally accepted mechanism of the *thiazolium salt-catalyzed benzoin condensation* was first proposed by R. Breslow.[26]



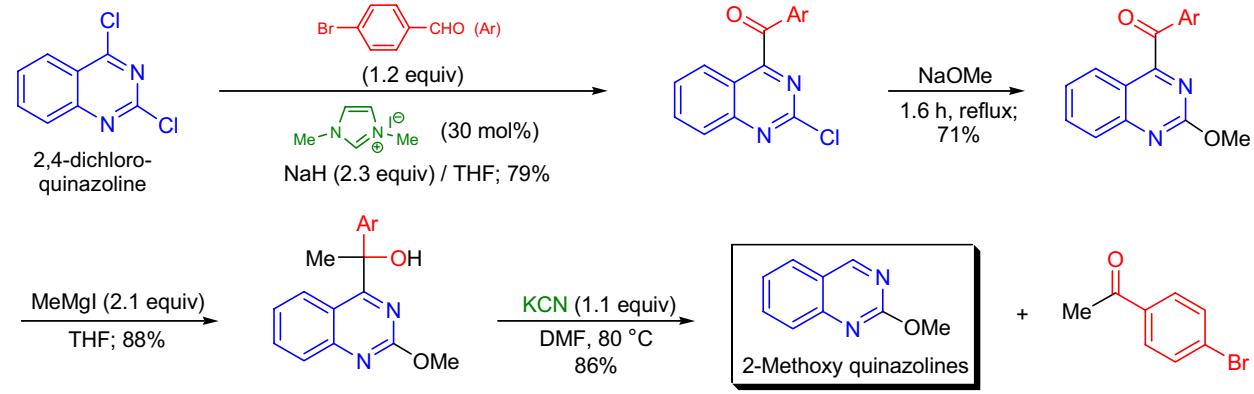
BENZOIN AND RETRO-BENZOIN CONDENSATION

Synthetic Applications:

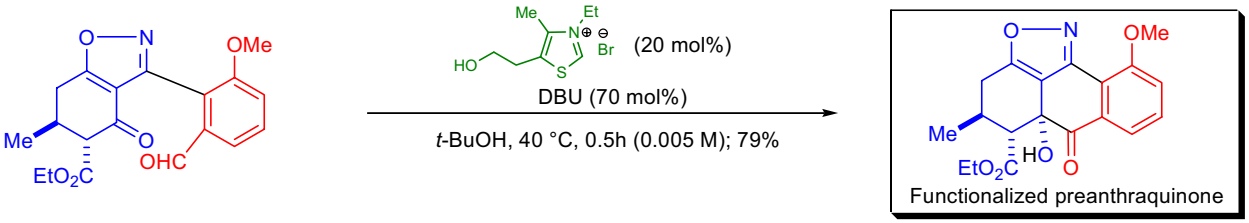
A. Miyashita and co-workers have developed a new method for the synthesis of ketones based on the concept that the *benzoin condensation* is reversible (*retro-benzoin condensation*) and affords the most stable product.[32] When α-benzylbenzoin was treated with KCN in DMF, the C-C bond was cleaved, resulting in the formation of deoxybenzoin and benzaldehyde. This method of synthesizing ketones has been applied to several α-substituted benzoins, and the corresponding ketones were formed in good yields. The authors also realized, based on the known analogy between the chemical behavior of the C=O double bond of ketones and the C=N double bond of nitrogen-containing heteroarenes, that a cyanide ion catalyzed *retro-benzoin condensation* of α-hydroxybenzylheteroarenes would also be possible.[33]



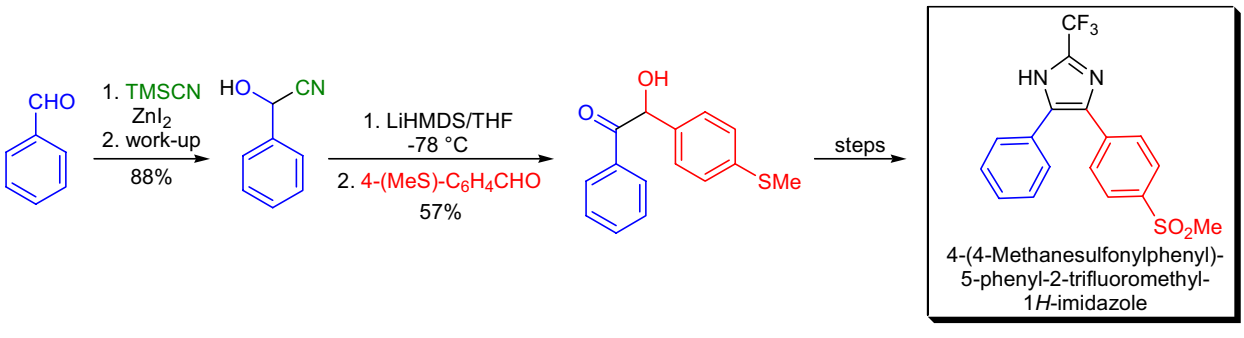
The *retro-benzoin condensation* methodology was used to synthesize 2-substituted quinazolines in good overall yield from 2,4-dichloroquinazoline. 2-Substituted quinazolines are obtained by substitution of 2-chloroquinazoline with nucleophiles, though it is difficult to prepare the starting 2-chloroquinazoline. These results indicate that the aroyl group, which may be introduced onto nitrogen-containing heteroarenes at the α-position, can be used as a protecting group. Later it can be easily removed by conversion to an α-hydroxybenzyl group, followed by a *retro-benzoin condensation*.[33]



In the laboratory of K. Suzuki, a *catalytic crossed aldehyde-ketone benzoin condensation* was developed and applied to the synthesis of stereochemically defined functionalized preanthraquinones.[15]



The *benzoin condensation* was the key carbon-carbon bond forming step during the synthesis of anti-inflammatory 4,5-diarylimidazoles by T.E. Barta and co-workers.[34] The benzaldehyde was first converted to the cyanohydrin using TMSCN. Deprotonation was followed by the addition of 4-(MeS)-benzaldehyde to afford the benzoin.



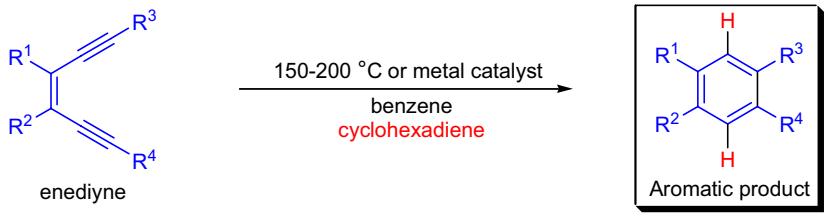
BERGMAN CYCLOAROMATIZATION REACTION

(References are on page 550)

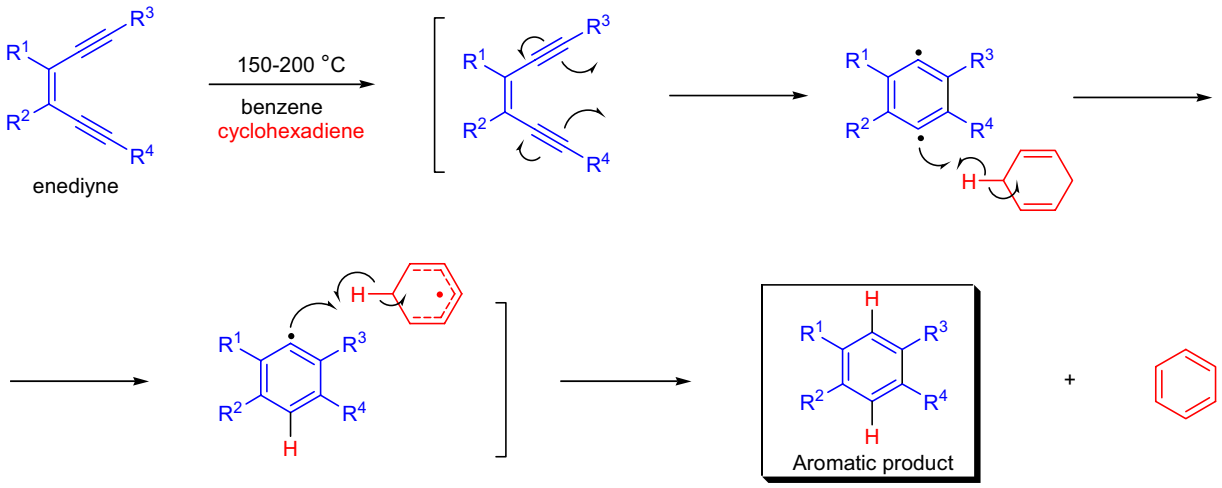
Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-14]; *Modifications & Improvements*[15-18]*; Theoretical Studies*[19-33]]

The thermal cycloaromatization of enediynes, which proceeds *via* the formation of benzenoid diradicals, is known as the *Bergman cycloaromatization reaction*. It received little attention in the 1970s when it was first reported, but it became the subject of intense research in the 1990s when certain marine natural products containing the enediyne moiety showed remarkable antitumor activity *via* the cleavage of double stranded DNA. Synthetically the *Bergman cyclization* was exploited to prepare fused ring systems by tethering alkenes to an enediyne unit and allowing the alkenes to react with the cycloaromatized species to form additional saturated rings. It is also possible to make fused aromatic ring systems, such as acenaphthenes or perylene derivatives. The *Bergman cyclization* tolerates a wide range of functional groups, many of which also increase the yield of the cycloaromatization reaction.[34] The distance between the triple bonds is crucial: the further away the triple bonds are, the higher the temperature required for the cyclization to occur. In order to observe cyclization at physiological temperatures, the enediyne unit should be part of a 10-membered ring.

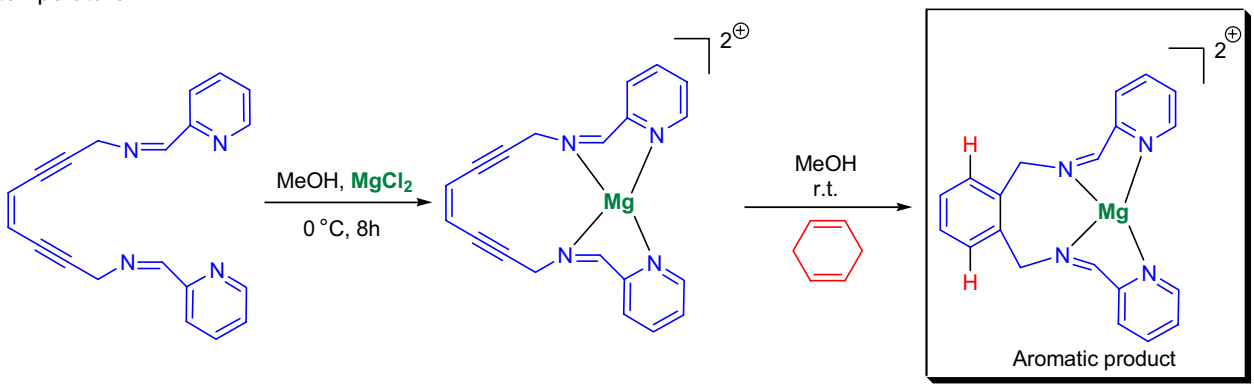


Mechanism: [35-40,26-28]



Synthetic Applications:

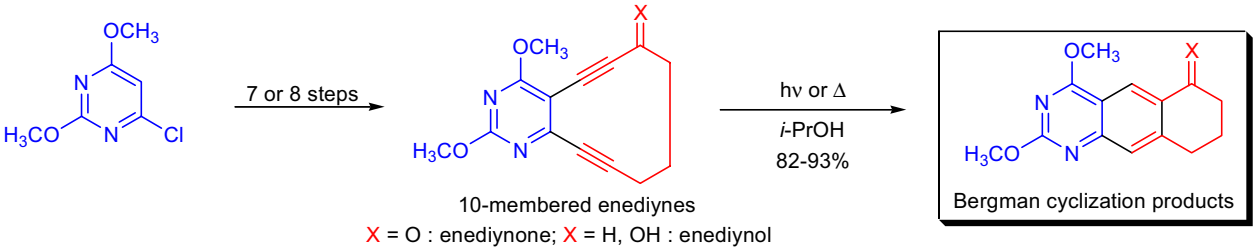
To make the *Bergman cyclization* synthetically more appealing, the reaction temperature had to be lowered significantly. J.M. Zaleski and co-workers developed a *Mg^{2+}-induced thermal Bergman cyclization* at ambient temperature.[29]



BERGMAN CYCLOAROMATIZATION REACTION

Synthetic Applications:

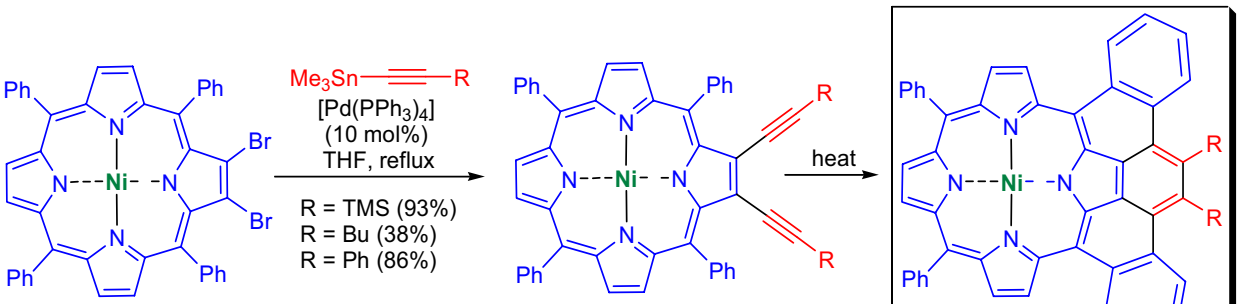
In the laboratory of K.C. Russell novel 10-membered pyrimidine enediynes were synthesized in seven and eight steps, respectively.[41] These compounds were tested for their ability to undergo the *Bergman cyclization* both thermally and photochemically. Where X=OH, the enediynol readily cyclizes both thermally and photochemically in isopropanol, while when X=O, the enediynone only cyclizes under thermal conditions to give excellent yield of the corresponding aromatic compound. The difference in reactivity between the alcohol and the ketone was assumed to arise from different excited states. Ketones are well-known to possess different excited states and different reactivity from triplet excited states that can undergo hydrogen- and electron-abstraction processes. If the *photochemical Bergman cyclization* is favored by a singlet excited state, then a triplet state ketone could interfere with the normal cyclization process and result in poor yield and conversion.



10-membered enediynes

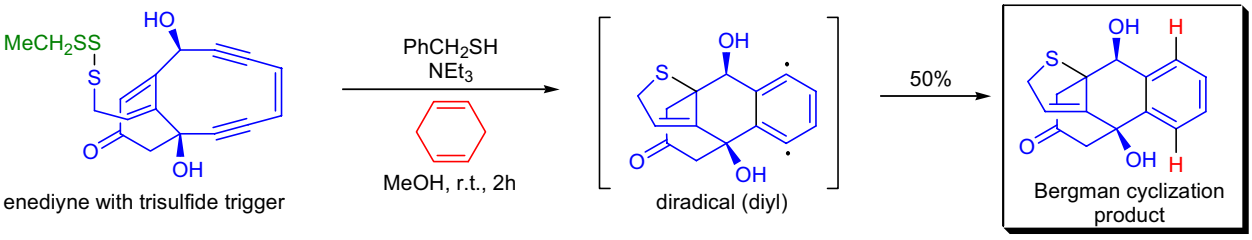
X = O : enediynone; X = H, OH : enediynol

Porphyrin chromophores have received much attention, particularly as photoelectric devices and molecular wires. Efficient π-electronic communication between porphyrin macrocycles is pivotal in various complex functions. K.M. Smith et al. showed that neighboring acetylenic units on porphyrins provide a means for the efficient construction of aromatic superstructures triggered by the *Bergman cyclization* reaction conditions and give rise to novel [n]phenacenoporphyrins, which belong to a new class of highly π-extended porphyrins.[42]



R = TMS, (190 °C, 12h, no reaction); R = H (190 °C, 8h, 89%); R = Bu (190 °C, 60h, 50%); R= Ph (280 °C, 18h, 86%)

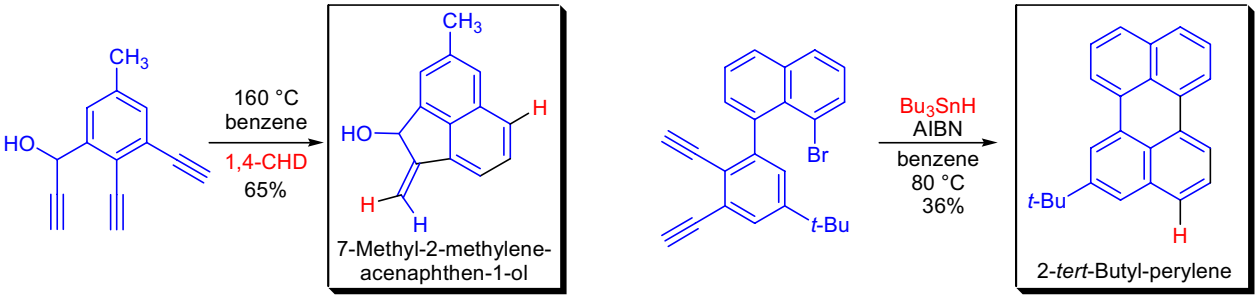
Research by S.J. Danishefsky et al. has shown that calicheamicin/esperamicin antibiotics containing an allylic trisulfide trigger can undergo a mild *Bergman cyclization* when treated with benzyl mercaptan.[43]



enediyne with trisulfide trigger

diradical (diyl)

When the enediyne substrate has functional groups that can trap the initially formed Bergman diradical, the rapid construction of complex fused ring systems becomes feasible. J.E. Anthony and co-workers prepared an acenaphthene derivative as well as a substituted perylene using this concept.[34]



BIGINELLI REACTION

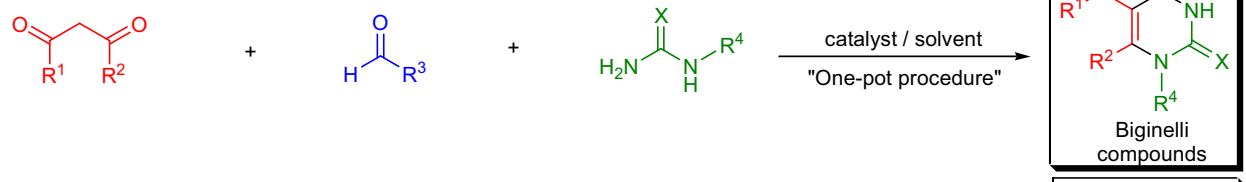
(References are on page 551)

Importance:

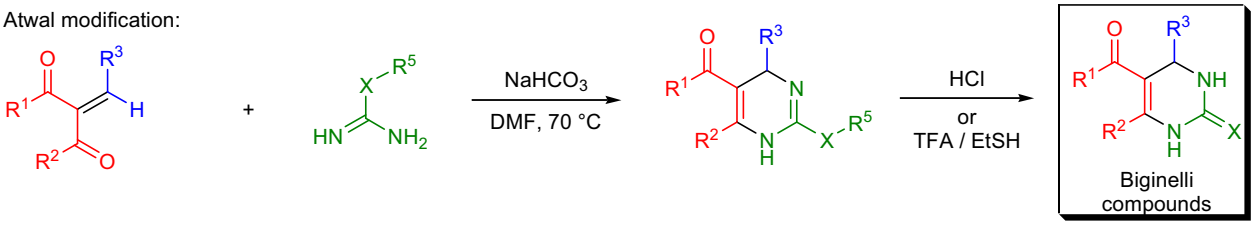
[*Seminal Publications*[1,2]*; Reviews*[3-14]*; Modifications & Improvements;*[15-38] *Theoretical Studies*[39,40]]

In 1893, P. Biginelli was the first to synthesize functionalized 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) by the one-pot three-component condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate in the presence of catalytic HCl in refluxing ethanol.[2] This process is called the *Biginelli reaction* and the products are referred to as Biginelli compounds.[5] The *Biginelli reaction* was not utilized widely until the early 1990s when the growing demand for biologically active compounds made multicomponent reactions attractive.[8] The general features of the reaction are: 1) it is usually carried out in alcohols as solvents containing a small amount of catalyst; 2) several Lewis and Brönsted acids catalyze the process: HCl, H_2SO_4, TsOH,[31] TMSI,[36] LiBr,[35], $InBr_3$,[30] $BF_3{\cdot}OEt_2$, $FeCl_3$,[21] $Yb(OTf)_3$, $Bi(OTf)_3$,[26,37] VCl_3[41] and PPE;[19] 3) the structure of all three components can be widely varied; 4) aliphatic, aromatic, or heteroaromatic aldehydes are used but with aliphatic or hindered aromatic aldehydes (*ortho*-substituted) the yields are moderate; 5) a variety of β-keto esters, including ones with chiral centers at R^2 as well as tertiary acetoacetamides have been utilized; 6) monosubstituted ureas and thioureas give exclusively *N*-1 substituted dihydropyrimidines while *N*-3 alkylated products are never formed; 7) *N,N'*-disubstituted ureas do not react under the standard *Biginelli reaction* conditions; and 8) the preparation of enantiomerically pure Biginelli compounds is currently easiest *via* resolution, and a true intermolecular asymmetric version does not yet exist.[42] There are several variations of the *Biginelli reaction*: 1) the most significant variant is called the *Atwal modification* in which an enone is reacted with a protected urea or thiourea derivative under neutral conditions to first give a 1,4-dihydropyrimidine, which is converted to the corresponding DHPM upon deprotection with acid;[15-17] 2) in the *Shutalev modification* α-tosyl substituted ureas and thioureas are reacted with enolates of 1,3-dicarbonyl compounds to afford hexahydropyrimidines, that are readily converted to DHPMs;[20] 3) solid phase synthesis with Wang resin-bound urea derivatives or with PEG-bound acetoacetate allows the preparation of DHPMs in high yield and high purity;[43,44] 4) a fluorous phase variant was developed using a fluorous urea derivative;[18] and 5) microwave-assisted and solvent-free conditions were also successfully implemented.[23,25,32]

Biginelli reaction:



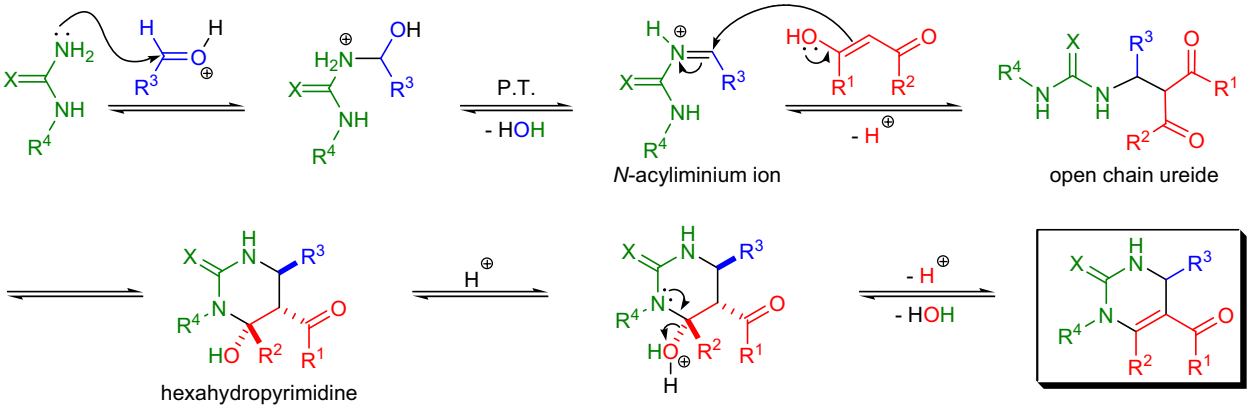
Atwal modification:



R^1 = -OEt, -NHPh, NEt_2, alkyl, -SEt; R^2 = alkyl, aryl, $-CH_2Br$; R^3 = aryl, heteroaryl, alkyl; R^4 = Me, Ph, H; X = O, S; R^5 = Me when X = O; R^5 = *p*-$OMeC_6H_4$ when X = S; <u>catalyst</u>: HCl, $FeCl_3$, $InCl_3$, PPE, $BF_3{\cdot}OEt_2$

Mechanism:[45-50,40,9]

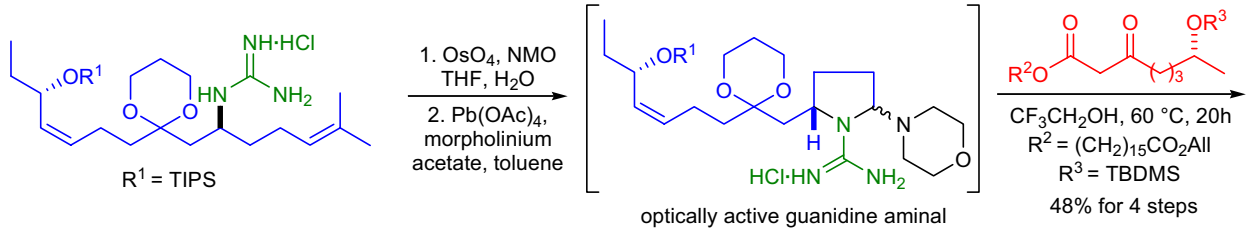
The first step in the mechanism of the *Biginelli reaction* is the acid-catalyzed condensation of the urea with the aldehyde affording an aminal, which dehydrates to an *N*-acyliminium ion intermediate. Subsequently, the enol form of the β-keto ester attacks the *N*-acyliminium ion to generate an open chain ureide, which readily cyclizes to a hexahydropyrimidine derivative.

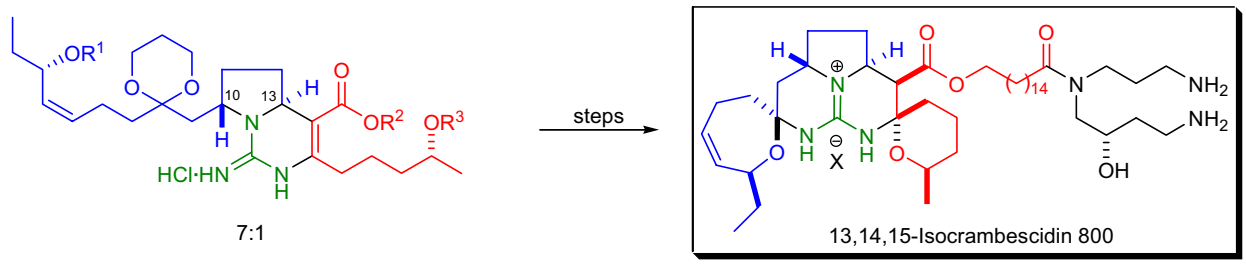


BIGINELLI REACTION

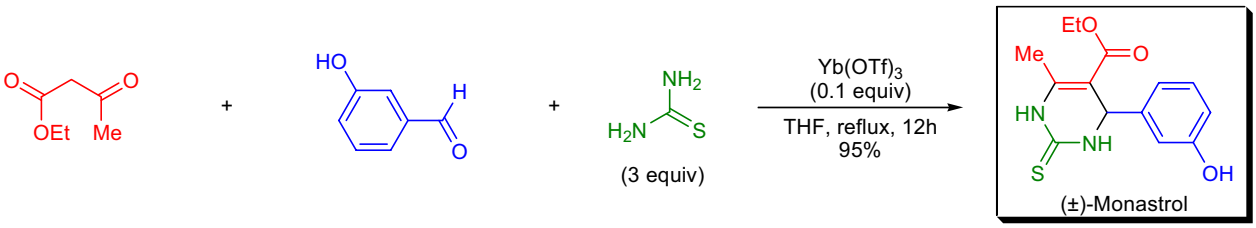
Synthetic Applications:

The only way to realize an enantioselective *Biginelli reaction* is to conduct it intramolecularly where the enantiopure urea and aldehyde portions are tethered.[51] This reaction was the key step in L.E. Overman's total synthesis of guanidine alkaloid 13,14,15-Isocrambescidin 800.[52] An optically active guanidine aminal was reacted with an enantiopure β-keto ester in trifluoroethanol to afford 1-iminohexahydropyrrolo[1,2-*c*]pyrimidine carboxylic ester with a 7:1 *trans* selectivity between C10 and C13 positions.

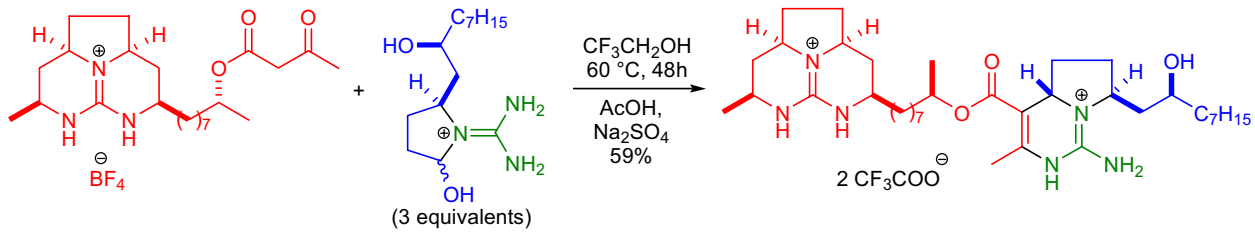




The traditional intermolecular three-component version of the *Biginelli reaction* was utilized for the improved synthesis of racemic monastrol by A. Dondoni and co-workers.[28] The one-pot $Yb(OTf)_3$ catalyzed reaction took place between 3-hydroxybenzaldehyde, ethyl acetoacetate, and thiourea. Racemic monastrol was isolated in 95% yield and was resolved on a preparative scale using diastereomeric *N*-3-ribofuranosyl amides.



The first total synthesis of batzelladine F was accomplished using the tethered version of the *Biginelli reaction* in the laboratory of L.E. Overman.[53] The assembly of complex bisguanidines was achieved by reacting an enantiopure β-keto ester with 3 equivalents of a guanidine derivative in trifluoroethanol in the presence of morpholinium acetate. The product pentacyclic bisguanidine was isolated in 59% yield after HPLC purification. To complete the total synthesis, the trifluoroacetate counterions were exchanged for BF_4^-, the final ring was closed by converting the secondary alcohol to the corresponding mesylate followed by treatment with base, and the vinylogous amide was reduced by catalytic hydrogenation. Interestingly, the choice of counterion was crucial since model studies indicated the formation of complex product mixtures when the counterion was formate, acetate or chloride.



BIRCH REDUCTION

(References are on page 552)

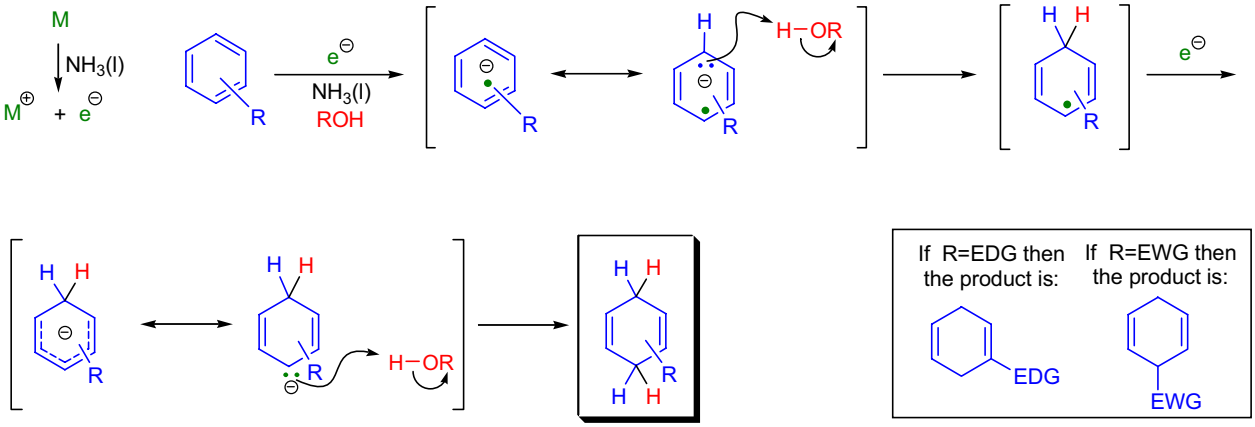
Importance:

[*Seminal Publication*[1]; *Reviews*[2-15]; *Modifications & Improvements*[16-21]; *Theoretical Studies*[22-33]]

The 1,4-reduction of aromatic rings to the corresponding unconjugated cyclohexadienes and heterocycles by alkali metals (Li, Na, K) dissolved in liquid ammonia in the presence of an alcohol is called the *Birch reduction*. Heterocycles, such as pyridines, pyrroles, and furans, are also reduced under these conditions. When the aromatic compound is substituted, the regioselectivity of the reduction depends on the nature of the substituent. If the substituent is electron-donating, the rate of the reduction is lower compared to the unsubstituted compound and the substituent is found on the non-reduced portion of the new product. In the case of electron-withdrawing substituents, the result is the opposite. Ordinary alkenes are not affected by the *Birch reduction* conditions, and double bonds may be present in the molecule if they are not conjugated with an aromatic ring. However, conjugated alkenes, α,β-unsaturated carbonyl compounds, internal alkynes, and styrene derivatives are reduced under these conditions. There are some limitations to the *Birch reduction*: electron-rich heterocycles need to have at least one electron-withdrawing substituent, so furans and thiophenes are not reduced unless electron-withdrawing substituents are present.

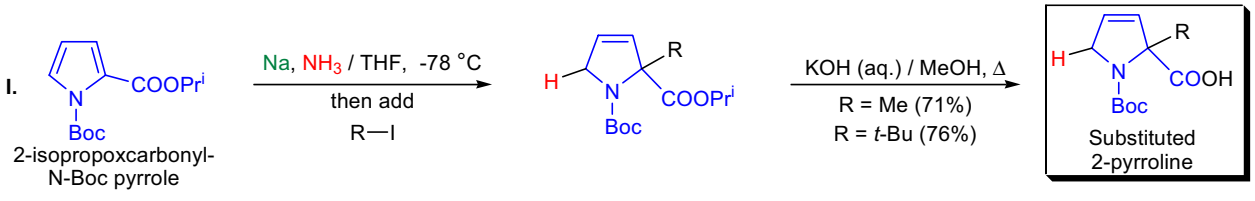


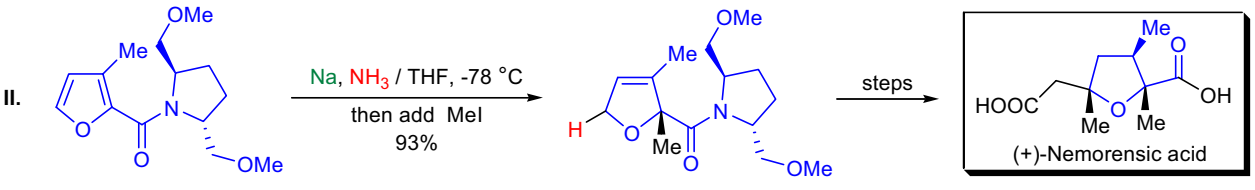
Mechanism: [34-38]



Synthetic Applications:

In the first example (**I**) T.J. Donohoe et al. utilized the *Birch reduction* to reduce then alkylate electron-deficient 2- and 3-substituted pyrroles.[39,40] This reductive alkylation method proved to be very efficient for the synthesis of substituted 3- and 2-pyrrolines, respectively. An alcohol as a proton source was not necessary for the reduction to occur. In the second example (**II**) the same researchers performed a *stereoselective Birch reduction* on a substituted furan during the enantioselective total synthesis of (+)-nemorensic acid.[41]

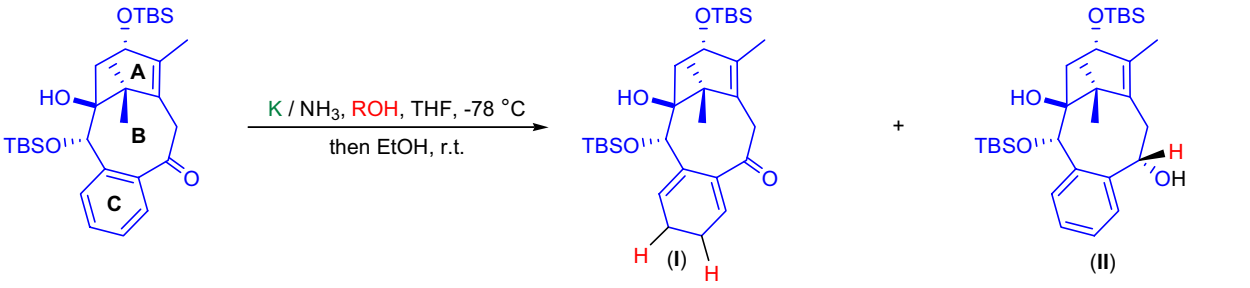


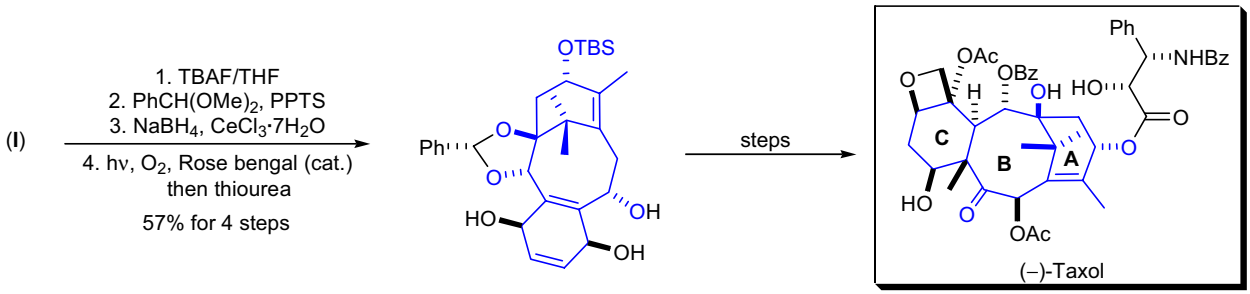


BIRCH REDUCTION

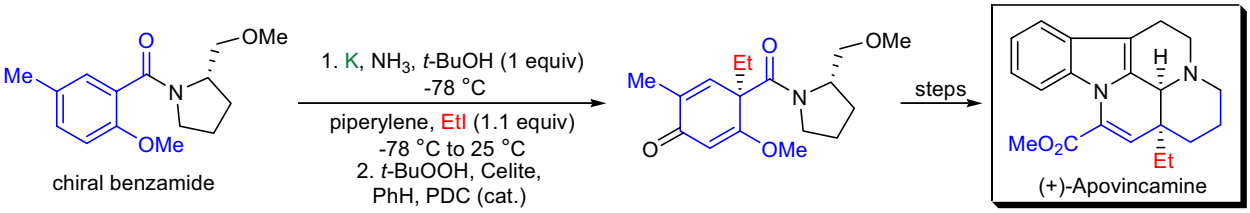
Synthetic Applications:

During the enantioselective total synthesis of (–)-taxol, I. Kuwajima and co-workers used the *Birch reduction* to elaborate an array of functional groups on the C-ring of the natural product.[42] The originally 1,2-disubstituted benzene ring was subjected to typical *Birch reduction* conditions (K/liquid ammonia/*t*-BuOH), and the resulting 1,3-cyclohexadiene (**I**) was oxygenated by singlet oxygen from the convex β-face to give the desired $C_4\beta$-$C_7\beta$ diol. The side product benzyl alcohol (**II**) was recycled as starting material *via Swern oxidation* in excellent yield providing a total conversion that was acceptable for synthetic purposes.

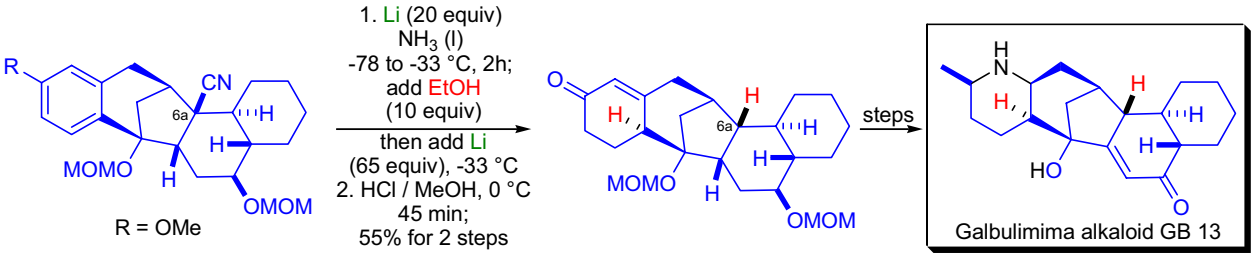




In the laboratory of A.G. Schultz during the asymmetric total synthesis of two vincane type alkaloids, (+)-apovincamine and (+)-vincamine, it was necessary to construct a crucial *cis*-fused pentacyclic diene intermediate.[43] The synthesis began by the *Birch reduction-alkylation* of a chiral benzamide to give 6-ethyl-1-methoxy-4-methyl-1,4-cyclohexadiene in a >100:1 diastereomeric purity. This cyclohexadiene was first converted to an enantiopure butyrolactone which after several steps was converted to (+)-apovincamine.



The total synthesis of galbulimima alkaloid GB 13 was accomplished by L.N. Mander and co-workers. The *Birch reduction* of a complex intermediate was necessary in order to prepare a cyclic α,β-unsaturated ketone.[44] The treatment of the substrate with lithium metal in liquid ammonia first resulted in a quantitative *reductive decyanation* of the C6a cyano group. The addition of excess ethanol to the reaction mixture reduced the aromatic ring to the corresponding enol ether that was hydrolyzed in a subsequent step to afford the unsaturated ketone.



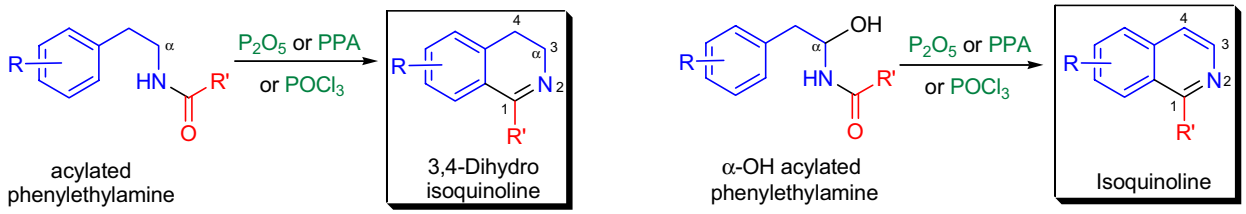
BISCHLER-NAPIERALSKI ISOQUINOLINE SYNTHESIS

(References are on page 553)

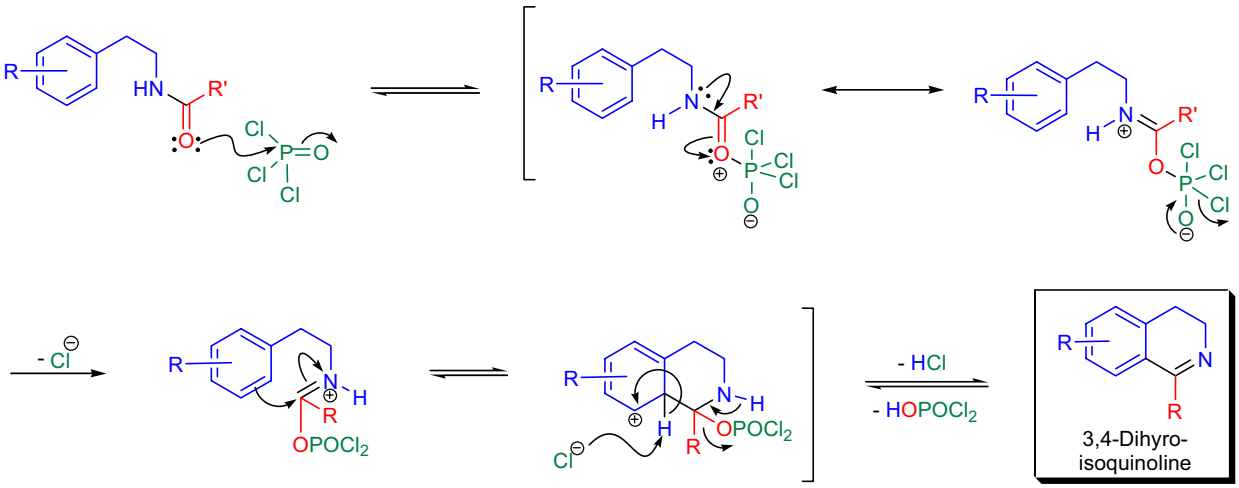
Importance:

[*Seminal Publication*[1]; *Reviews*[2-4]; *Modifications & Improvements*[5-15]]

One of the *Friedel-Crafts acylation* routes toward the synthesis of isoquinolines is the *Bischler-Napieralski synthesis*. When an acyl derivative of a phenylethylamine is treated with a dehydrating agent ($POCl_3$, P_2O_5, PPA, TFAA, or Tf_2O)[6] a *cyclodehydration reaction* takes place to form a 3,4-dihydroisoquinoline derivative. If the starting compound contains a hydroxyl group in the α-position, an additional dehydration takes place yielding an isoquinoline.

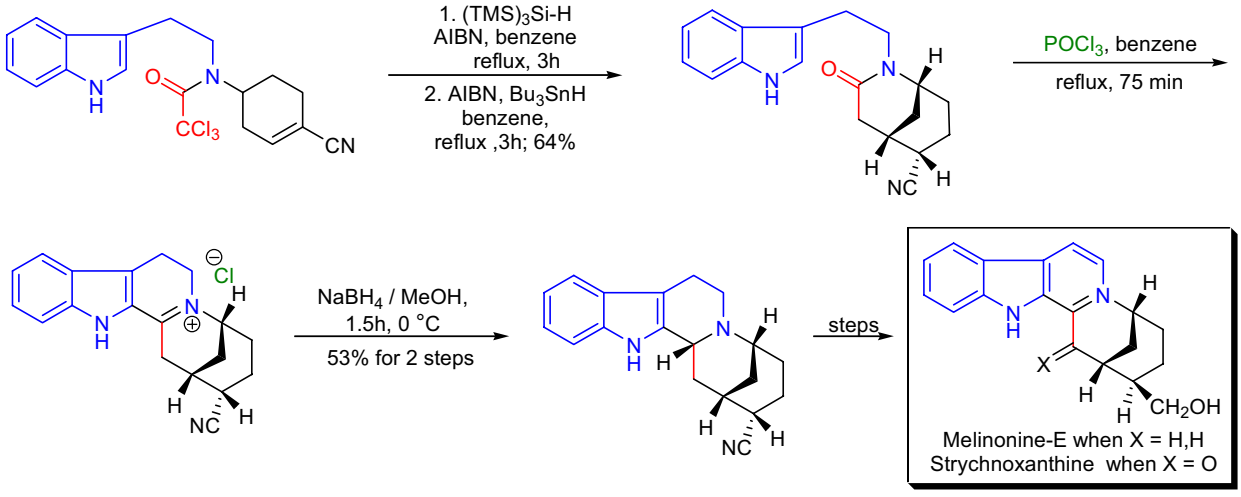


Mechanism:[16,5]



Synthetic Applications:

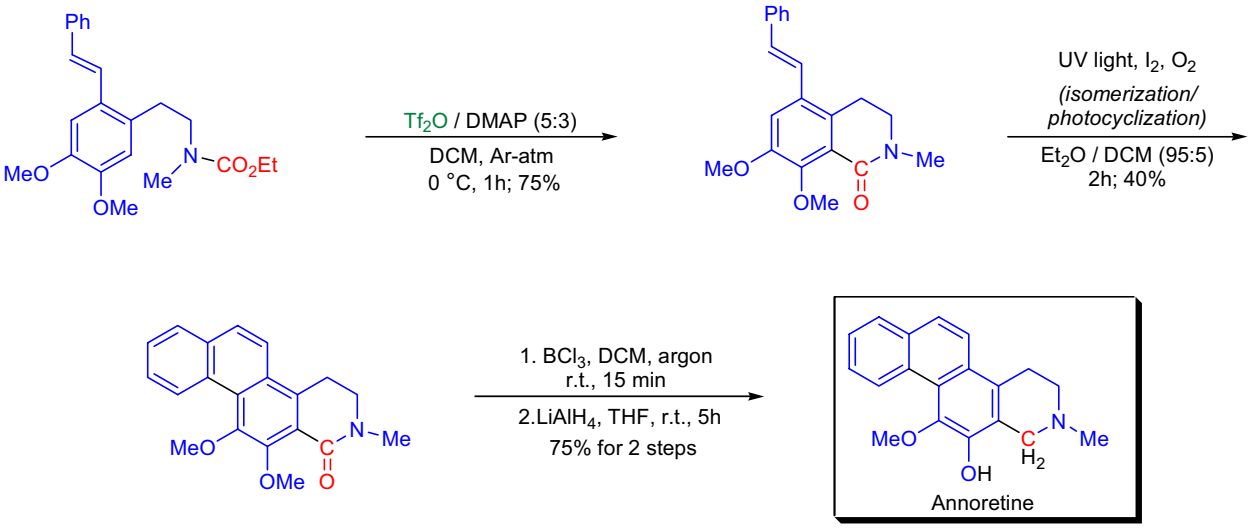
In the laboratory of J. Bonjoch the first total syntheses of the pentacyclic (±)-strychnoxanthine and (±)-melinonine-E alkaloids were accomplished using a *radical carbocyclization via* α-carbamoyldichloromethyl radical followed by the *Bischler-Napieralski cyclization*, as the two key cyclization steps.[17]



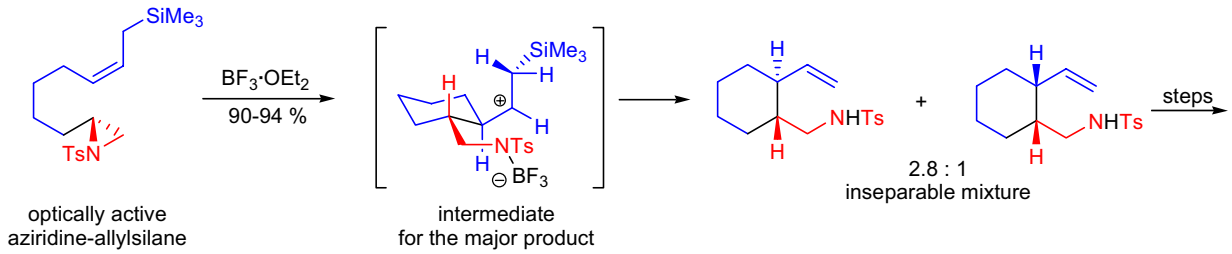
BISCHLER-NAPIERALSKI ISOQUINOLINE SYNTHESIS

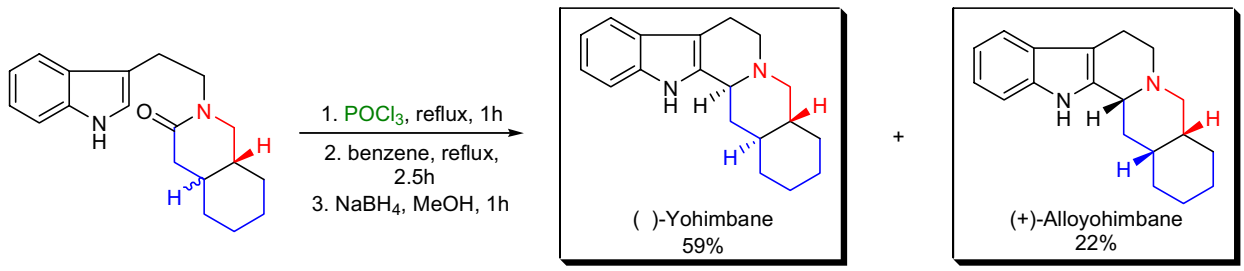
Synthetic Applications:

The first total synthesis of annoretine, an alkaloid containing the 1,2,3,4-tetrahydronaphtho [2,1-*f*]isoquinoline moiety was achieved by J.C. Estevez and co-workers.[18] The total synthesis had two key steps: first a *Bischler-Napieralski reaction* to form the 5-styrylisoquinoline unit followed by a *photocyclization* to provide the desired naphthoisoquinoline skeleton.

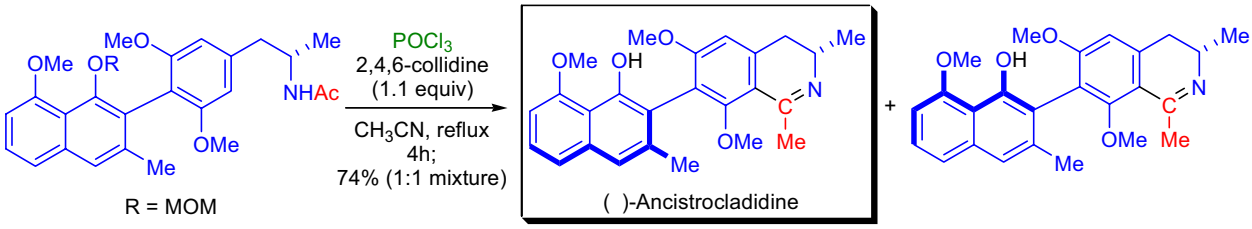


The asymmetric total synthesis of rauwolfia alkaloids (–)-yohimbane and (–)-alloyohimbane was carried out by S.C. Bergmeier et al. by utilizing a *novel aziridine-allylsilane cyclization* and the *Bischler-Napieralski isoquinoline synthesis* as key steps.[19] These alkaloids have a characteristic pentacyclic ring framework and exhibit a wide range of interesting biological activities such as antihypertensive and antipsychotic properties.





The first enantioselective total synthesis of the 7,3'-linked naphthylisoquinoline alkaloid (–)-ancistrocladidine was accomplished by J.C. Morris and co-workers.[20] The key steps of the synthesis were the *Pinhey-Barton ortho-arylation* and the *Bischler-Napieralski cyclization*. The natural product was isolated from the 1:1 mixture of atropisomers by recrystallization from toluene/petroleum ether.



BROOK REARRANGEMENT

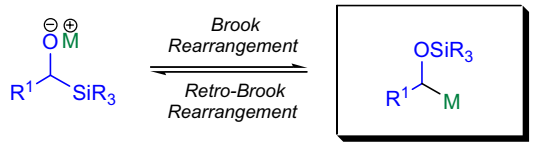
(References are on page 553)

Importance:

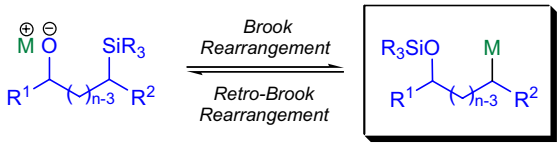
[*Seminal Publications*[1-4]*; Reviews*[5-12]*; Modifications & Improvements*[13-19]*; Theoretical Studies*[20-25]]

In the late 1950s, A.G. Brook observed the intramolecular anionic migration of silyl groups from a carbon to an oxygen atom.[1,2] This migratory aptitude of the silyl group was later found to be more general. Therefore, all the *[1,n]*-carbon to oxygen silyl migrations are referred to as *Brook rearrangements*. The reaction is based on the great susceptibility of silicon toward a nucleophilic attack and the formation of a strong silicon-oxygen bond (Si-O) from the relatively weak silicon-carbon bond. The reverse process is called the *retro-Brook rearrangement* and was first reported by J.L. Speier.[26,27]

[1,2]-Silyl migrations:



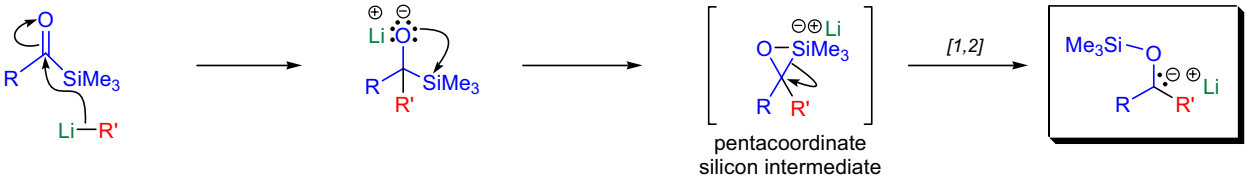
[1,n]-Silyl migrations:



R^{1-2} = alkyl, aryl; SiR_3 = $SiMe_3$, $SiEt_3$, $SiMe_2t$-Bu, etc.; n = 2-5

Mechanism:[28,29,13,30-32,25]

The mechanism is believed to involve a pentacoordinate-silicon atom.[30]

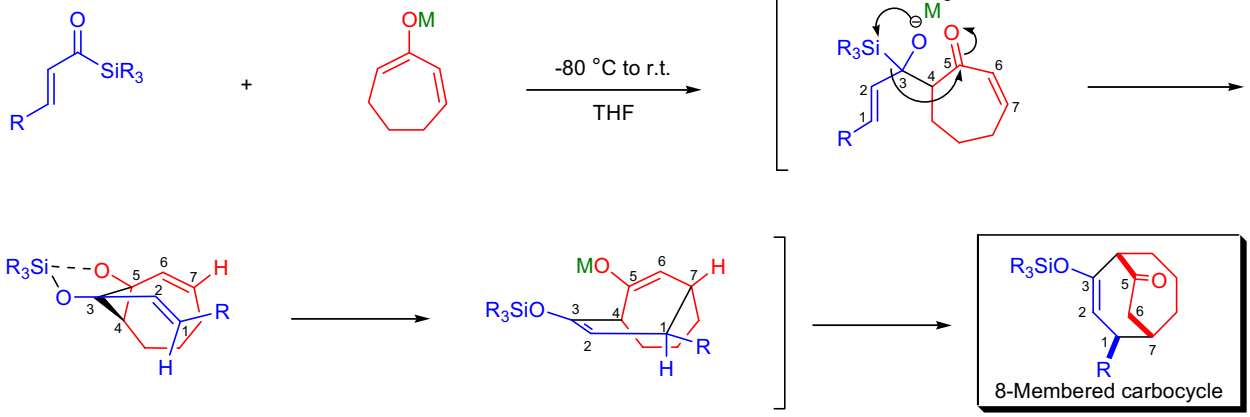


pentacoordinate silicon intermediate

Synthetic Applications:

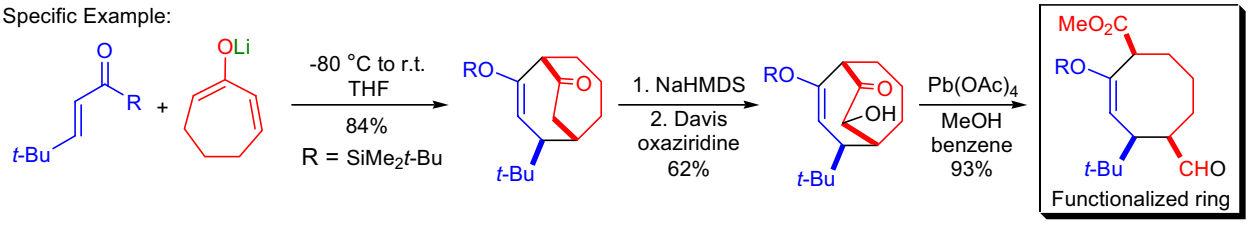
In the laboratory of K. Takeda, a new synthetic strategy was developed for the stereoselective construction of eight-membered carbocycles utilizing a *Brook rearrangement-mediated [3+4] annulation.*[33] The unique feature of this methodology is the generation, in two steps, of eight-membered ring systems containing useful functionalities from readily available compounds containing three- and four-carbon atoms.

General Scheme:



8-Membered carbocycle

Specific Example:

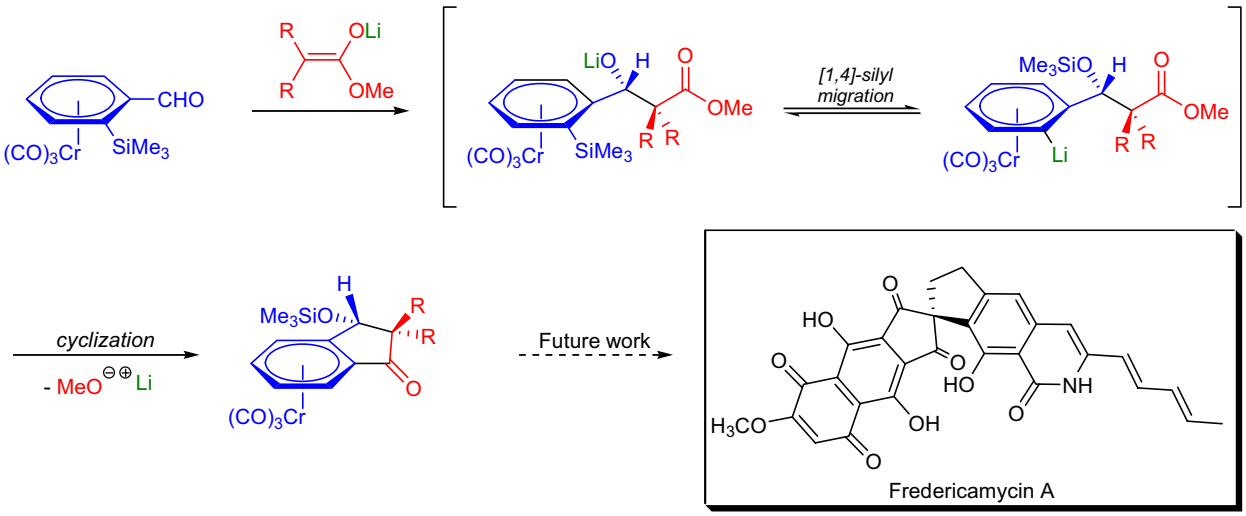


Functionalized ring

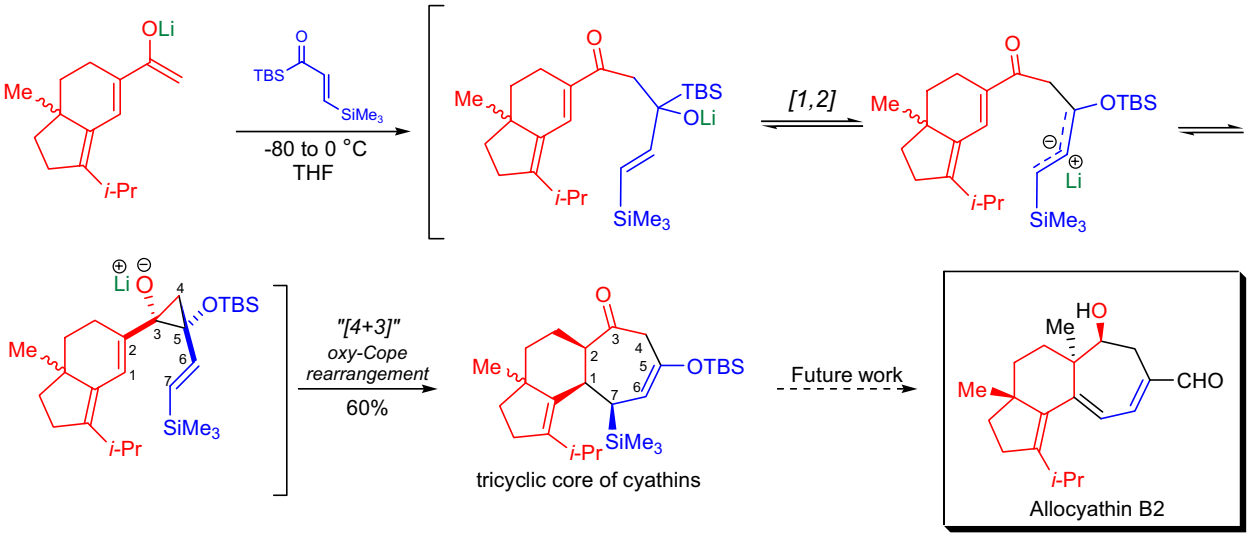
BROOK REARRANGEMENT

Synthetic Applications:

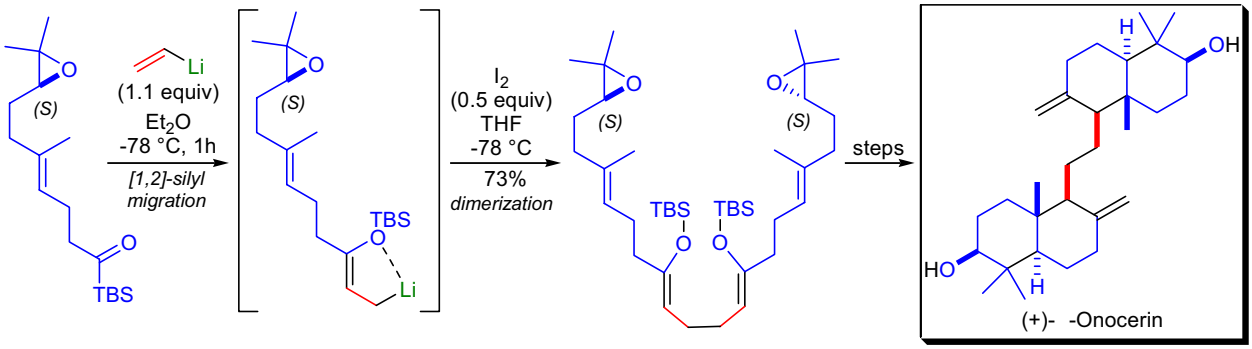
W.H. Moser and co-workers developed a new and efficient method for the stereocontrolled construction of spirocyclic compounds, including the spirocyclic core of the antitumor agent fredericamycin A.[34] The strategy involved a one-pot *aldol addition*/*Brook rearrangement*/*cyclization* sequence beginning from arene chromium tricarbonyl complexes and can formally be described as a [3+2] annulation.



Cyathins, isolated from bird nest fungi, are interesting compounds because of their unusual 5-6-7 tricyclic ring system and their important biological activities. K. Takeda and co-workers synthesized the tricyclic core of the *cyathins* using a *Brook rearrangement mediated-[4+3] annulation* reaction.[35] The seven-membered ring was formed *via* the *oxy-Cope rearrangement* of a divinylcyclopropane intermediate.



The total synthesis of (+)- -onocerin *via* four-component coupling and tetracyclization steps was achieved in the laboratory of E.J. Corey.[36] The farnesyl acetate-derived acyl silane was treated with vinyllithium, which brought about the stereospecific formation of a (*Z*)-silyl enol ether as a result of a spontaneous *Brook rearrangement*. In the same pot, the solution of I_2 was added to obtain the desired diepoxide *via oxidative dimerization*.



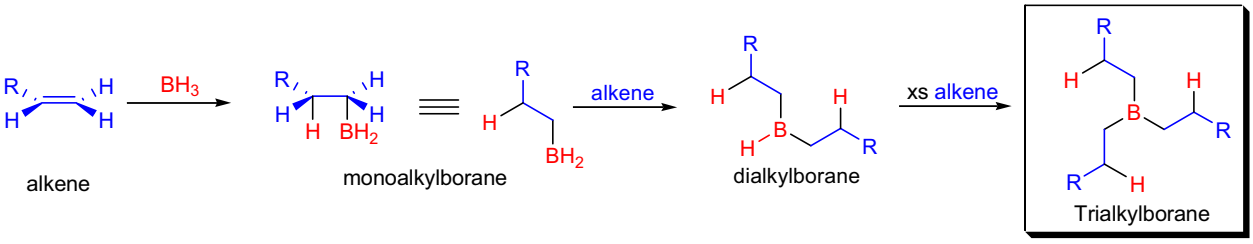
BROWN HYDROBORATION REACTION

(References are on page 554)

Importance:

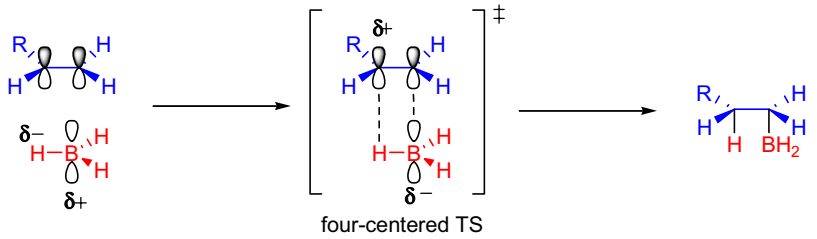
[*Seminal Publication*[1]; *Reviews*[2-21]; *Modifications & Improvements*[22-28]; *Theoretical Studies*[29-34]]

The addition of a B-H bond across a carbon-carbon double or triple bond is called the *Brown hydroboration reaction*. This process is highly regioselective and stereospecific (*syn*). The boron becomes bonded primarily to the less substituted carbon atom of the alkene (*anti-Markovnikoff product*). The resulting organoboranes are very useful intermediates in organic synthesis. The boron can be replaced for hydroxyl (*hydroboration/oxidation*), halogen, or amino groups (*hydroboration/amination*). If BH_3 is used in the hydroboration reaction, it will react with three molecules of alkenes to yield a trialkylborane (R_3B). Transition metal complexes catalyze the addition of borane to alkenes and alkynes and significantly enhance the rate of the reaction. This variant may alter the chemo-, regio-, and diastereoselectivity compared to the uncatalyzed hydroboration.[27] In the presence of a chiral transition metal complex, enantioselectivity can be achieved.[25]

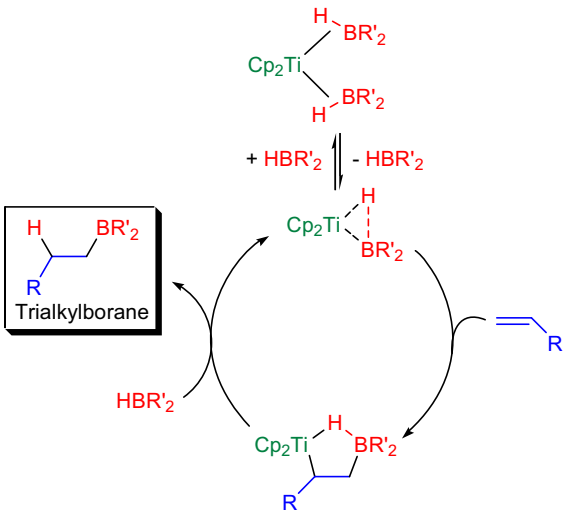


Mechanism: [35-43]

Boron has only three electrons in the valence shell, and therefore its compounds are electron deficient and there is a vacant *p*-orbital on the boron atom. Borane (BH_3) exists as a mixture of B_2H_6/BH_3, as dimerization partially alleviates the electron deficiency of the boron. This equilibrium is fast, and most reactions occur with BH_3. The addition of borane to a double bond is a concerted process going through a four-centered transition state. The formation of the C-B bond precedes the formation of the C-H bond so that the boron and the carbon atoms are partially charged in the four-centered transition state.



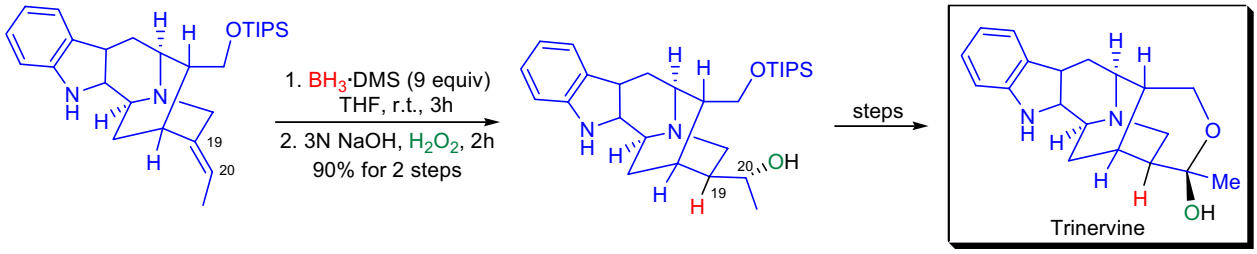
In the Cp_2TiMe_2-catalyzed hydroboration of alkenes, a titanocene bis(borane) complex is responsible for the catalysis.[43] This bis(borane) complex initially dissociates to give a monoborane intermediate. Coordination of the alkene gives rise to the alkene-borane complex, which is likely to be a resonance hybrid between an alkene borane complex and a β-boroalkyl hydride. An intramolecular reaction extrudes the trialkylborane product, and coordination of a new HBR_2 regenerates the monoborane intermediate.



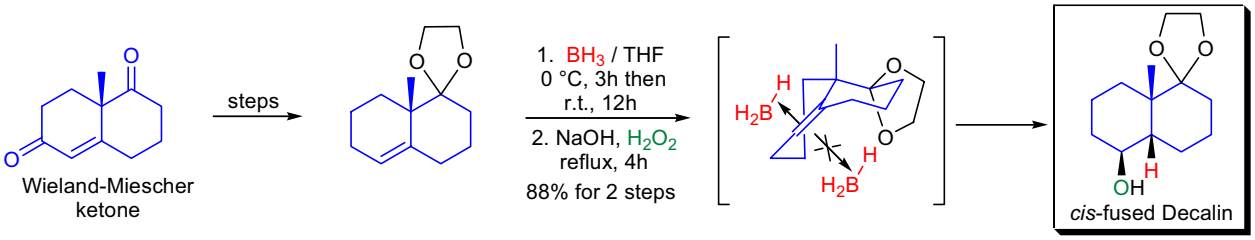
BROWN HYDROBORATION REACTION

Synthetic Applications:

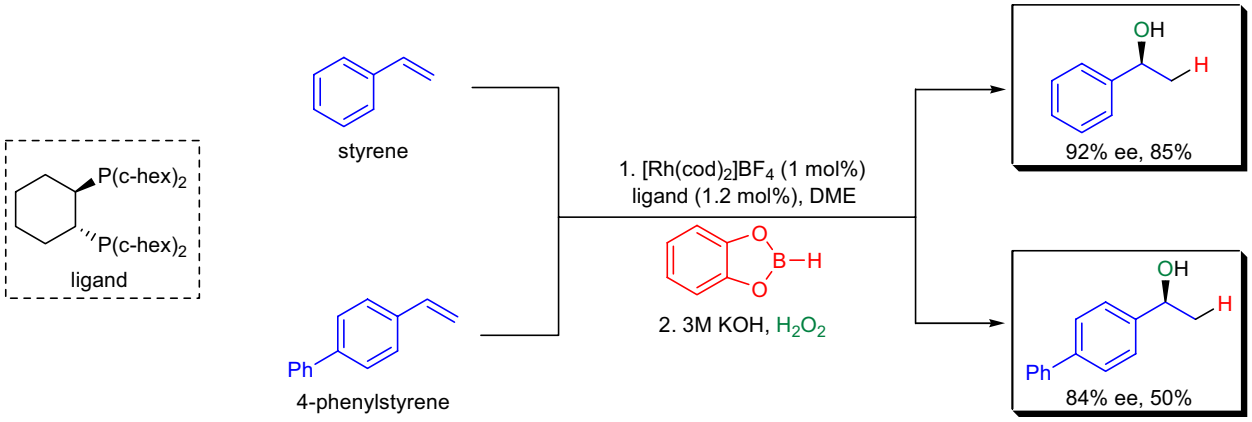
In the enantiospecific total synthesis of the indole alkaloid trinervine, J.M. Cook and co-workers used the *hydroboration/oxidation* sequence to functionalize the C19-C20 *exo* double bond with excellent regioselectivity.[44]



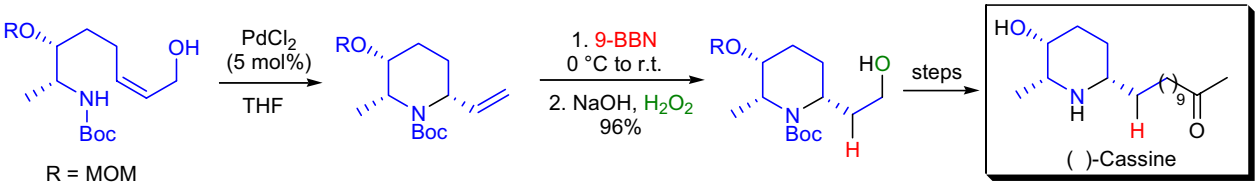
During the enantioselective synthesis of (3a*R*,4*R*,7a*S*)-4-hydroxy-7a-methylperhydro-1-indenone, a suitable CD-ring fragment for vitamin D-analogs, M. Vandewalle et al. realized that the *hydroboration/oxidation* of (1,1)-ethylenedioxy-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphtalene led to a *cis*-decalin structure instead of the literature reported *trans*-fusion.[45]



P. Knochel and co-workers used diphosphines as ligands in the rhodium-catalyzed asymmetric hydroboration of styrene derivatives.[46] The best results were obtained with the very electron rich diphosphane, and (*S*)-1-phenylethanol was obtained in 92% ee at –35 °C, with a regioselectivity greater than 99:1 (Markovnikoff product). A lower reaction temperature resulted in no reaction, while a higher temperature resulted in lower enantioselectivity and regioselectivity. The regioselectivity was excellent in all cases. Irrespective of the electronic nature of the substituents, their position and size had a profound effect on the enantioselectivity.



The enantioselective total synthesis of (–)-cassine was accomplished in the laboratory of H. Makabe.[47] The synthetic sequence involved a key, highly diastereoselective *$PdCl_2$-catalyzed cyclization* of an amino allylic alcohol. The cyclic product was then subjected to *hydroboration* with 9-BBN followed by oxidation to afford the desired primary alcohol, which was converted to (–)-cassine.



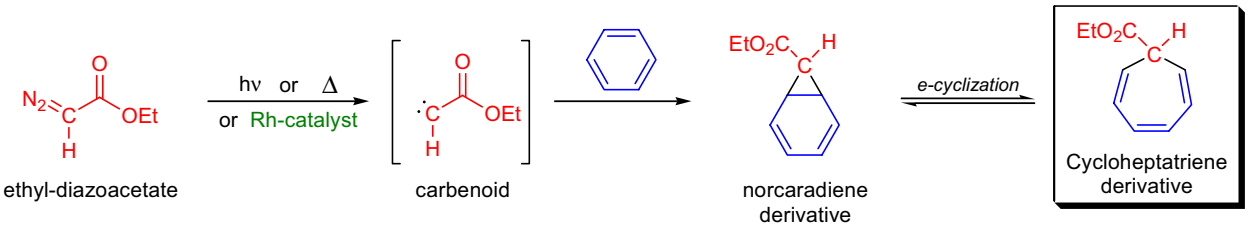
BUCHNER METHOD OF RING EXPANSION

(References are on page 555)

Importance:

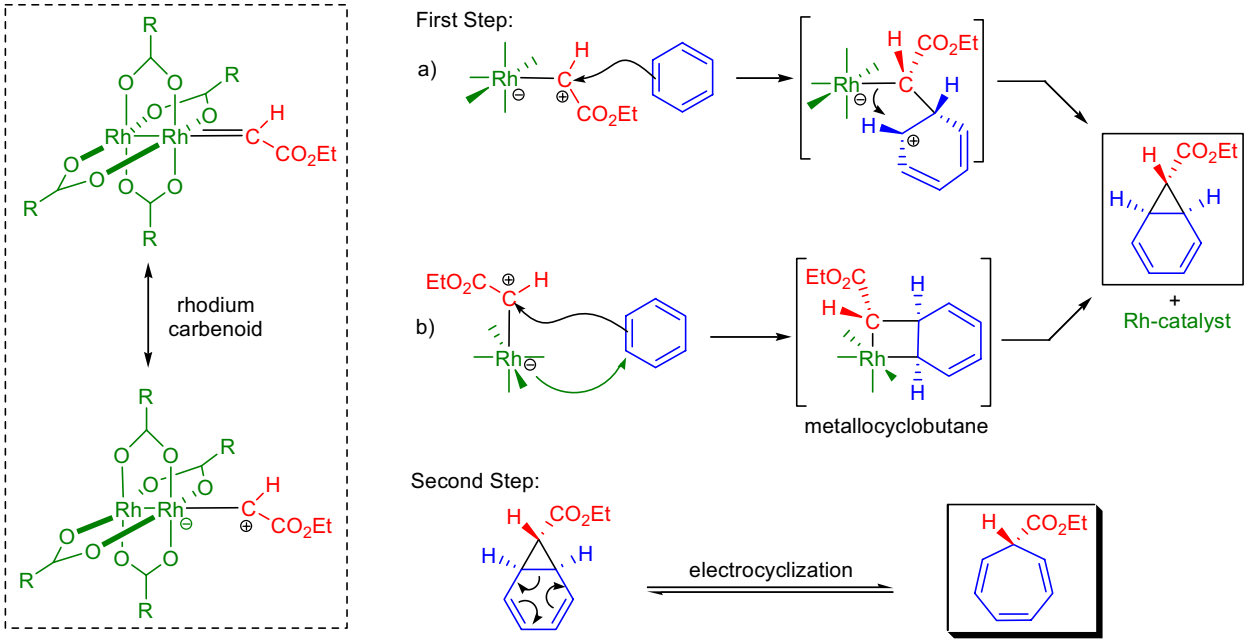
[*Seminal Publications*[1-3]; *Reviews*[4-9]; *Modifications & Improvements*[10-20]]

The thermal or photochemical reaction of ethyl diazoacetate with benzene and its homologs to give the corresponding isomeric esters of cycloheptatriene carboxylic acid (*via* the corresponding esters of norcaradienic acid) is called the *Buchner reaction*. This transformation was first reported by E. Buchner and T. Curtius in 1885, when they synthesized cycloheptatrienes from thermal and photochemical reactions of ethyl diazoacetate with benzene *via* arene cyclopropanation, followed by the electrocyclic ring opening of the intermediate norcaradiene.[1] The reaction offers a convenient entry to seven-membered carbocycles both inter- and intramolecularly. The complexity of the product mixture was significantly reduced or completely eliminated with the advent of modern transition metal catalysts: at first it was copper-based, and then in the 1980s it became almost exclusively rhodium-based (e.g., $RhCl_3 \cdot 3H_2O$, $Rh_2(OAc)_4$, Rh(II)-trifluoroacetate). For example, rhodium(II)-trifluoroacetate catalysis provides a single isomer of the cycloheptatriene in 98% yield.[11] Synthetically, it is convenient that chromium tricarbonyl-complexed aromatic rings do not undergo the *Buchner ring expansion* either inter- or intramolecularly.[20]



Mechanism:[21-23]

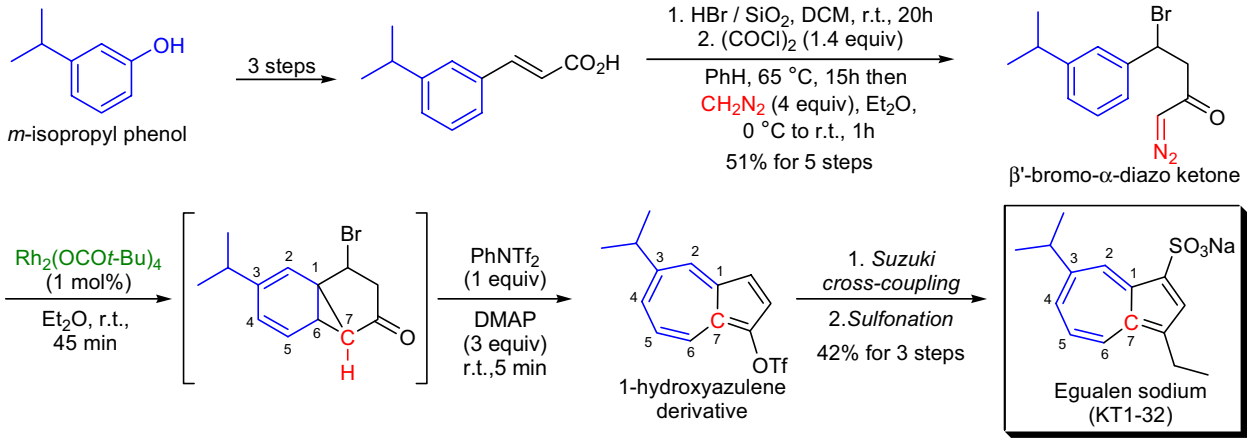
In the first step of the *Buchner reaction*, one of the π-bonds of the aromatic ring undergoes cyclopropanation catalyzed by a metal-carbenoid complex, which is the reactive intermediate. Metal carbenoids are formed when transition-metal catalysts [e.g., $Rh_2(OCOR)_4$] react with diazo compounds to generate transient electrophilic metal carbenes. The catalytic activity of the transition-metal complexes depends on the coordinative unsaturation at their metal center that allows them to react with diazo compounds as electrophiles. Electrophilic addition causes the loss of N_2 and the formation of the metal-stabilized carbene. Transfer of the carbene to electron-rich substrates completes the catalytic cycle. There are two possible scenarios for the first step: a) the intermediate can be represented as a metal-stabilized carbocation where the carbenoid α-carbon atom is the electrophilic center, that undergoes nucleophilic attack by the electron-rich double bond of olefins on route to cyclopropane; and b) the metal-carbenoid intermediate forms a rhodium-based metallocycle resulting from the nucleophilic attack of the negative charge on the rhodium atom onto one of the carbon atoms of the double bond. In the second step, the norcaradiene derivative undergoes an electrocyclization to afford the corresponding cycloheptatriene.



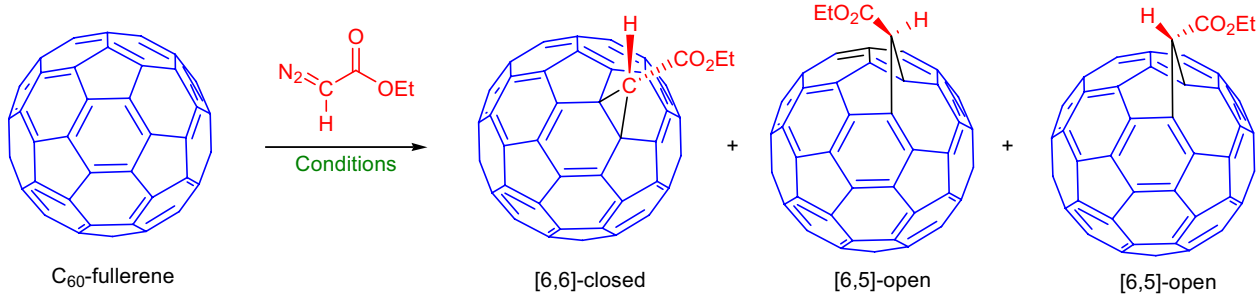
BUCHNER METHOD OF RING EXPANSION

Synthetic Applications:

R.L. Danheiser and co-workers developed a new strategy for the synthesis of substituted azulenes, which is based on the reaction of β-bromo-α-diazo ketones with rhodium carboxylates.[24] The key transformation involves the following steps: *intramolecular addition of rhodium carbenoid* to an arene double bond, *electrocyclic ring opening*, *β-elimination*, *tautomerization*, and trapping to produce 1-hydroxyazulene derivatives. The advantage of this method over previous approaches is the ability to prepare a variety of azulenes substituted on both the five- and seven-membered rings from readily available benzene starting materials. The synthetic utility of the method was demonstrated in the total synthesis of the antiulcer drug egualen sodium (KT1-32).

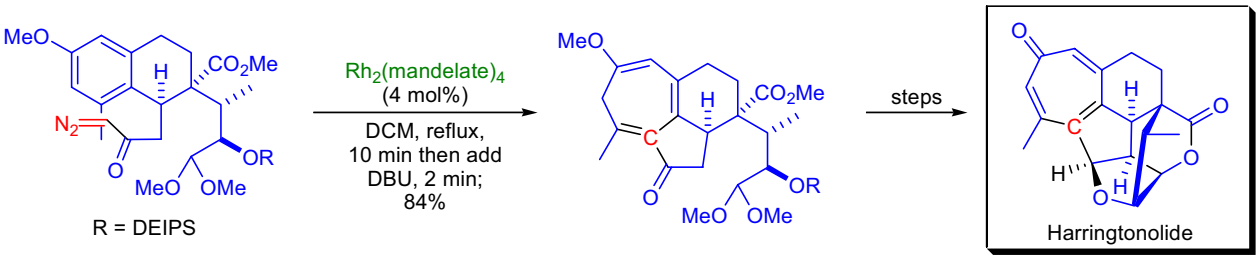


The need to prepare fullerene derivatives for possible applications to medicine and material sciences resulted in the development of novel synthetic methods for the functionalization of C_{60}. R. Pellicciari et al. reacted C_{60} with carboalkoxycarbenoids generated by the $Rh_2(OAc)_4$-catalyzed decomposition of α-diazoester precursors.[25] This reaction was the first example of a transition metal carbenoid reacting with a fullerene and the observed yields and product ratios were better than those obtained by previously reported methods. The reaction conditions were mild and the specificity was high for the synthesis of carboalkoxy-substituted[6,6]-methanofullerenes. When the same reaction was carried out thermally, the rearranged product (the [6,5]-open fullerene) was the major product.



Thermal: (110 °C, 7h; toluene; 35%)	1	:	4	:	2
$Rh_2(OAc)_4$ (stoichiometric): (r.t., 8h; 1-MeNap; 42%)	52	:	1	:	0

The total synthesis of the diterpenoid tropone, harringtonolide was accomplished in the laboratory of L.N. Mander.[26] The key step to form the seven-membered ring was the *Buchner reaction* of a complex polycyclic diazo ketone intermediate. Upon treatment with rhodium mandelate, an unstable adduct was formed and was immediately treated with DBU to afford the less labile cycloheptatriene.



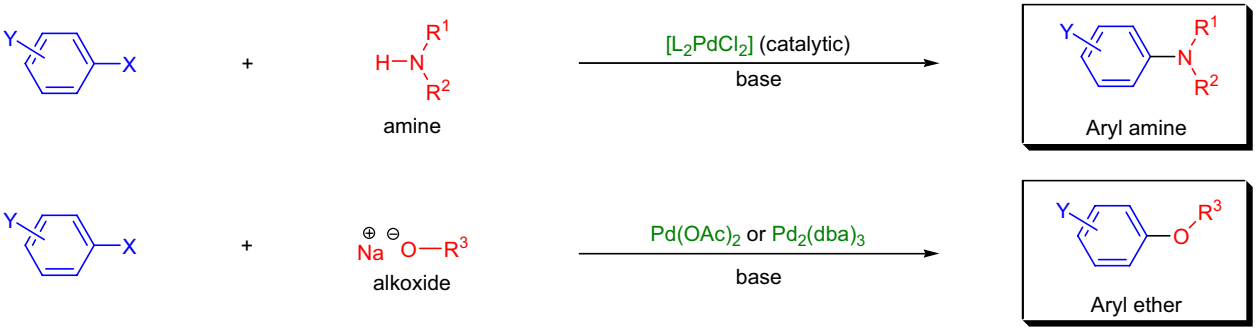
BUCHWALD-HARTWIG CROSS-COUPLING

(References are on page 556)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-15]]

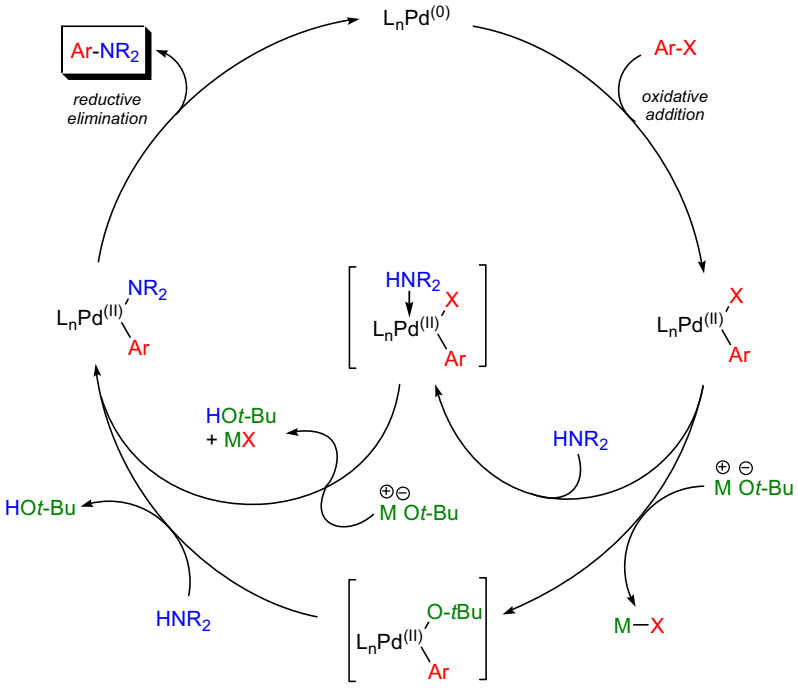
The direct Pd-catalyzed C-N and C-O bond formation between aryl halides or trifluoromethanesulfonates and amines (1° and 2° aliphatic or aromatic amines; imides, amides, sulfonamides, sulfoximines) or between aryl halides or triflates and alcohols (aliphatic alcohols and phenols) in the presence of a stoichiometric amount of base is known as the *Buchwald-Hartwig cross-coupling*. The coupling can be both inter- and intramolecular. The first palladium-catalyzed formation of aryl C-N bonds was reported by T. Migita and co-workers in 1983.[1] More than a decade later, in the laboratory of S. Buchwald, a new catalytic procedure was developed based on Migita's amination procedure.[2] The great disadvantage of these early methods was that both procedures called for the use of stoichiometric amounts of heat- and moisture-sensitive tributyltin amides as coupling partners. In 1995, S. Buchwald[16] and J. Hartwig[17] concurrently discovered that the aminotin species can be replaced with the free amine if one uses a strong base (e.g., sodium *tert*-butoxide or LHMDS), which generates the corresponding sodium amide *in situ* by deprotonating the Pd-coordinated amine. The typical procedure calls for either an aryl bromide or iodide, while the $Pd^{(0)}$-catalyst is usually complexed with chelating phosphine type ligands such as BINAP, DPPF, XANTPHOS, and DPBP or bidentate ligands such as DBA (*trans*,*trans*-dibenzylideneacetone). The base has to be present in stoichiometric amounts and the temperature for the reaction can be sometimes as low as 25 °C. Since the mid-1990s the reaction conditions for this coupling have gradually become milder, and by applying the appropriate ligand, even the otherwise unreactive aryl chlorides can be coupled with amines or alcohols.[9]



X = Cl, Br, I, OTf; Y = *o, m* or *p*-alkyl, phenacyl, amino, alkoxy; R^{1-2} = 1° or 2° aromatic or aliphatic; R^3 = 1°, 2°, or 3° aliphatic or aromatic; L = P(*o*-Tol)$_3$, BINAP, dppf, dba; base: NaO*t*-Bu, LHMDS, K_2CO_3, Cs_2CO_3

Mechanism: [3,17,4,7,9,11,14]

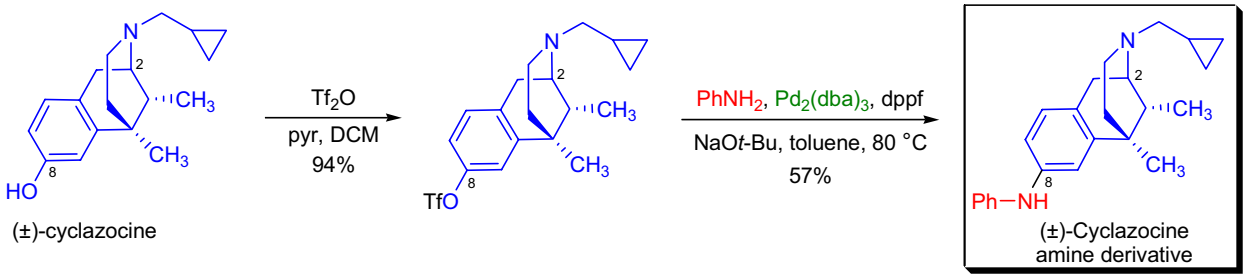
The first step in the catalytic cycle is the oxidative addition of $Pd^{(0)}$ to the aryl halide (or sulfonate). In the second step the $Pd^{(II)}$-aryl amide can be formed either by direct displacement of the halide (or sulfonate) by the amide *via* a $Pd^{(II)}$-alkoxide intermediate. Finally, reductive elimination results in the formation of the desired C-N bond and the $Pd^{(0)}$ catalyst is regenerated. Below is the catalytic cycle for the formation of an arylamine.



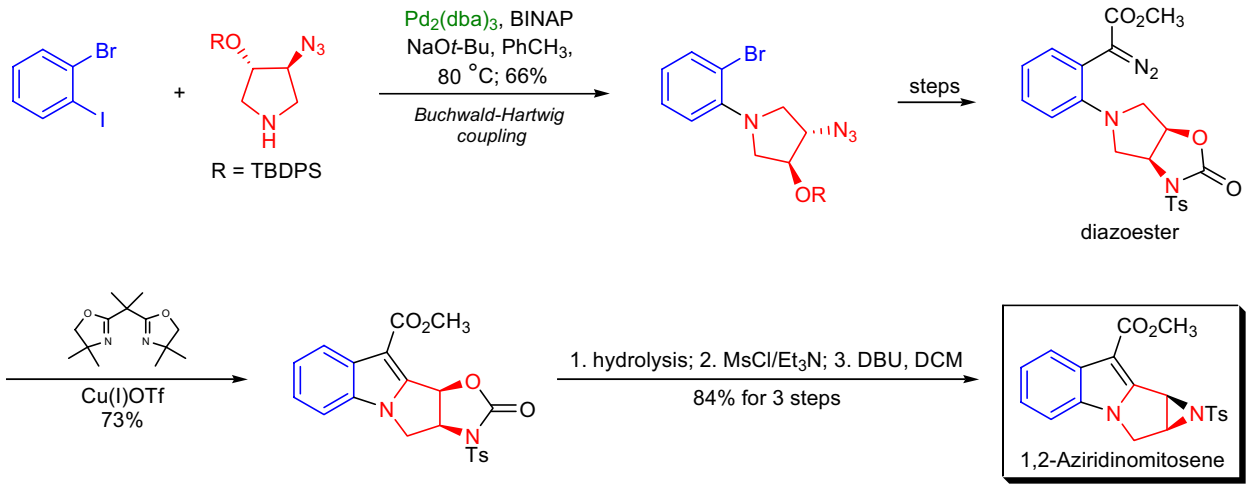
BUCHWALD-HARTWIG CROSS-COUPLING

Synthetic Applications:

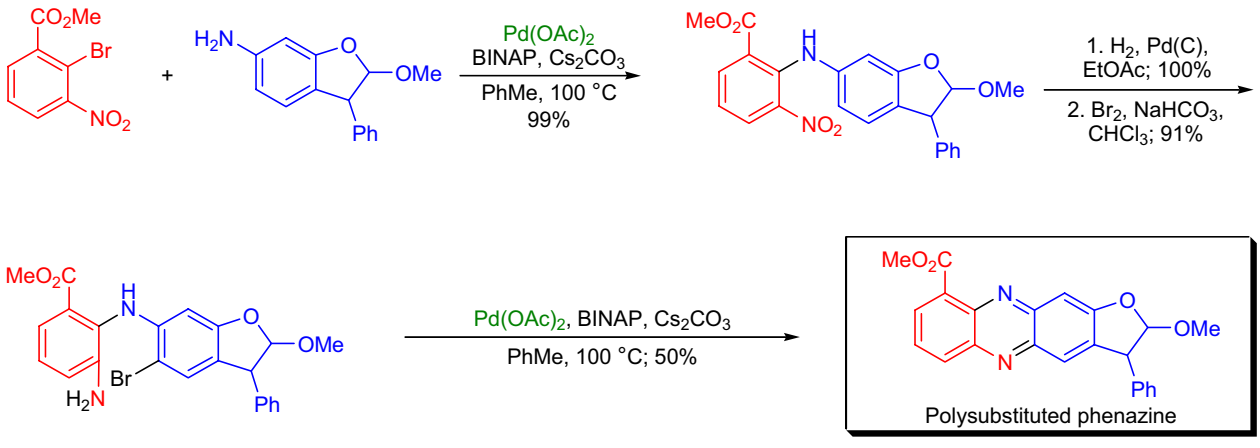
The opioid (±)-cyclazocine is known to be an analgesic and in the 1970s it was thought to prevent relapse in post-addicts of heroin. Unfortunately cyclazocine is *O*-glucuronidated in humans, and therefore it has a short duration of action. M.P. Wentland and co-workers synthesized analogues by replacing the prototypic 8-OH substituent of cyclazocine by amino and substituted amino groups using the *Buchwald-Hartwig cross-coupling reaction*.[18]



In the laboratory of G.A. Sulikowski, an enantioselective synthesis of a 1,2-aziridinomitosene, a key substructure of the mitomycin antitumor antibiotics, was developed.[19] Key transformations in the synthesis involved the *Buchwald-Hartwig cross-coupling* and chemoselective *intramolecular carbon-hydrogen metal-carbenoid insertion reaction*.



Naturally occurring phenazines have interesting biological activities but the available methods for their preparation offer only poor yields. T. Kamikawa et al. prepared polysubstituted phenazines by a new route involving two subsequent *Pd(II)-catalyzed aminations* of aryl bromides using the conditions developed by Buchwald and Hartwig.[20]



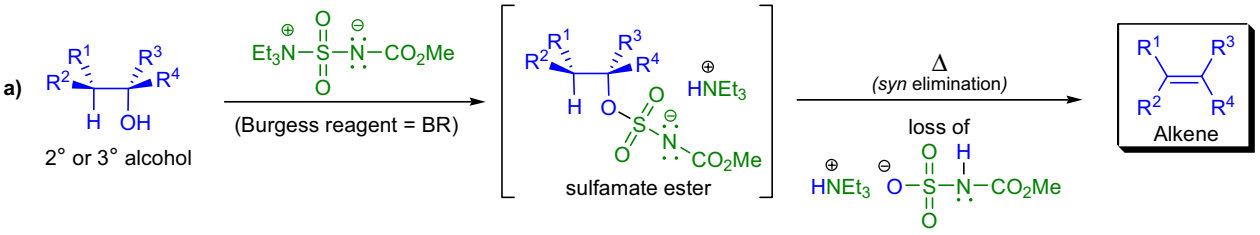
BURGESS DEHYDRATION REACTION

(References are on page 556)

Importance:

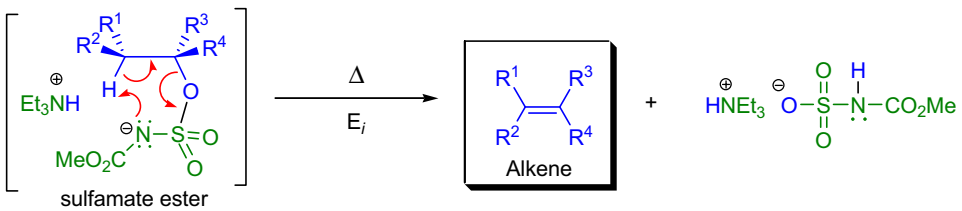
[*Seminal Publications*[1,2]*; Reviews*[3,4]*; Modifications & Improvements*[5-17]]

In the early 1970s, E.M. Burgess and co-workers discovered that secondary and tertiary alcohols could be dehydrated with the inner salt of (methoxycarbonylsulfamoyl)triethylammonium hydroxide to afford the corresponding olefins.[1] This process is now known as the *Burgess dehydration reaction* and the reagent is called the Burgess reagent. The *Burgess dehydration reaction* offers an advantage over other dehydration methods, namely it takes place under mild conditions (low temperature and neutral medium). Therefore, excellent yields can be achieved even with acid-sensitive substrates that are prone to rearrange. The elimination is *syn*-selective, but the *syn*-selectivity is higher for secondary alcohols. Tertiary alcohols tend to react faster and under milder conditions; E1 elimination products are observed when stabilized carbocations are formed. In most cases the elimination leads to the formation of the conjugated product, if conjugation with other C=C or C=O double bonds is possible. Primary alcohols are converted to the corresponding carbamates, which in turn give primary amines after hydrolysis.[5] The Burgess reagent is compatible with a wide range of functional groups, such as epoxides, alkenes, alkynes, aldehydes, ketones, alkyl halides, acetals, amides, and esters, and this enables the efficient dehydration of highly functionalized molecules. In the second half of the 1980s, the Burgess reagent was also used for dehydrating primary amides[6] and oximes[13] to the corresponding nitriles at room temperature. Other functional groups can also be dehydrated, so formamides give isonitriles,[10] ureas are converted to carbodiimides,[8] and primary nitro alkanes yield nitrile oxides[9] upon treatment with the Burgess reagent.



Mechanism:[1,2]

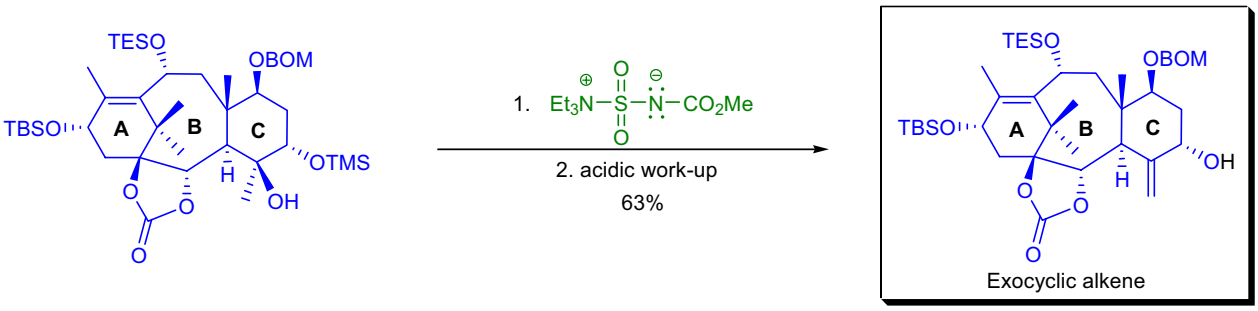
The mechanism involves a stereospecific *syn*-elimination *via* ion-pair formation from the intermediate sulfamate ester (comparable to the *Chugaev elimination* of xanthate esters). Kinetic and spectroscopical data are consistent with an initial rate-limiting formation of an ion-pair followed by a fast *cis*-β-proton transfer to the departing anion.



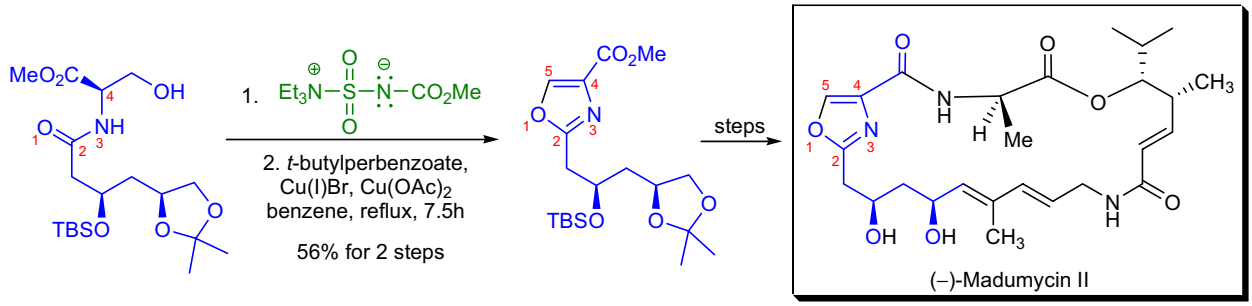
BURGESS DEHYDRATION REACTION

Synthetic Applications:

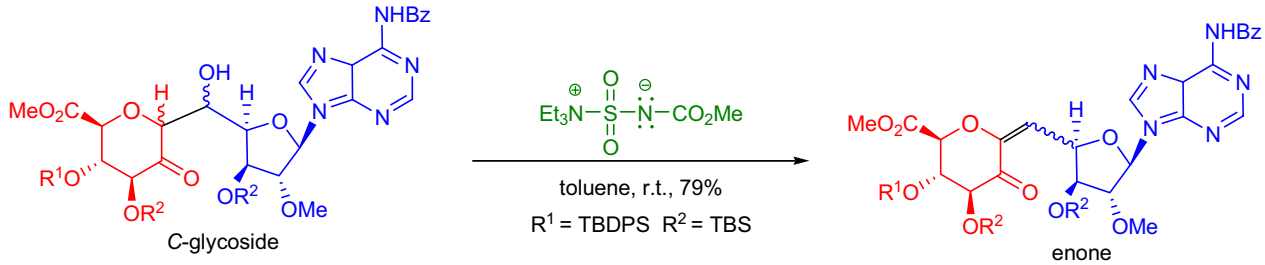
During the first total synthesis of taxol®, R. Holton and co-workers installed an *exo*-methylene group on the C ring in order to set the stage for the D ring (oxetane) formation.[18] The *Burgess dehydration reaction* was applied to a complex tricyclic tertiary alcohol intermediate (ABC rings) and the desired exocyclic alkene was isolated in 63% yield.

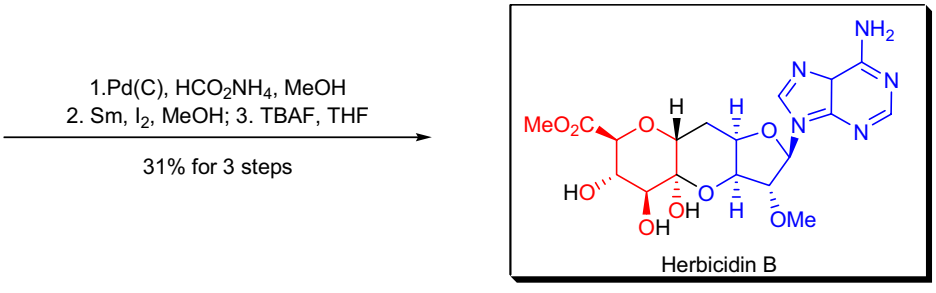


In the laboratory of A.I. Meyers, the first enantioselective total synthesis of the streptogramin antibiotic (–)-madumycin II was achieved.[19] The natural product contains an oxazole moiety, which may be considered a masked dehydropeptide. The oxazole moiety was introduced in two steps: by the *Burgess cyclodehydration reaction* followed by oxidation of the resulting oxazoline to the corresponding oxazole.



The first total synthesis of the nucleoside antibiotic herbicidin B was achieved by A. Matsuda et al. using a SmI_2 promoted *novel aldol-type C-glycosidation reaction* as the key step.[20] After the key step, the resulting secondary alcohol functionality was removed with the Burgess reagent. The corresponding α,β-unsaturated ketone was isolated in good yield. Hydrogenation of the enone double bond followed by the removal of protecting groups and cyclic ketal formation afforded herbicidin B.





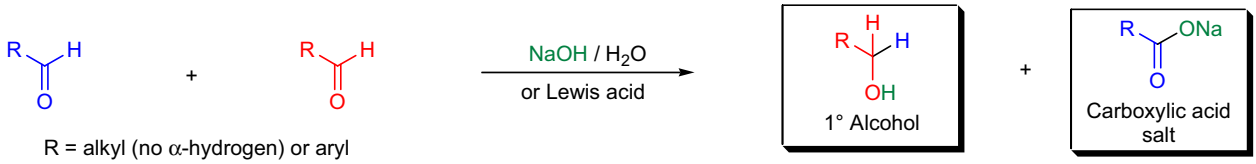
CANNIZZARO REACTION

(References are on page 557)

Importance:

[*Seminal Publication*[1,2]; *Reviews*[3]; *Modifications & Improvements*[4-14]; *Theoretical Studies*[15,16]]

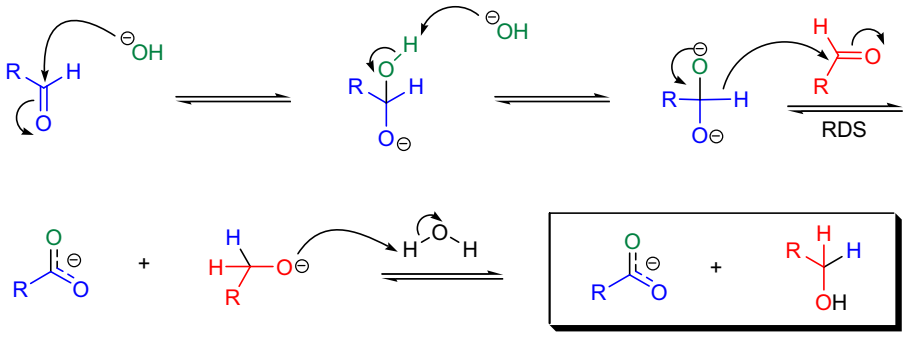
When reacted with concentrated NaOH (50 wt%) or other strong bases (e.g., alkoxides), aliphatic and aromatic aldehydes with no α-hydrogen undergo an *intermolecular hydride-transfer reaction* known as the *Cannizzaro reaction*. In this disproportionation reaction, one molecule of aldehyde oxidizes another to the corresponding carboxylic acid and is reduced to the corresponding primary alcohol in a maximum 50% yield. If the aldehyde has α-hydrogens, the *aldol reaction* will take place faster than the *Cannizzaro reaction*. Alternatively, high yields of alcohol can be obtained from almost any aldehyde when the reaction is performed in the presence of an excess of formaldehyde. This process is called the *crossed Cannizzaro reaction*. α-Keto aldehydes undergo an *intramolecular Cannizzaro reaction*. This method, however, has been rendered obsolete by the emergence of hydride reducing agents in 1946. In the presence of an appropriate Lewis acid catalyst, the *intramolecular Cannizzaro reaction* takes place with stereocontrol, yielding synthetically useful α-hydroxy esters directly from readily available glyoxals under neutral conditions.[9] It has also been shown that the reaction rates are enhanced significantly when the *Cannizzaro reaction* is performed under solvent-free conditions.[10]



R = alkyl (no α-hydrogen) or aryl

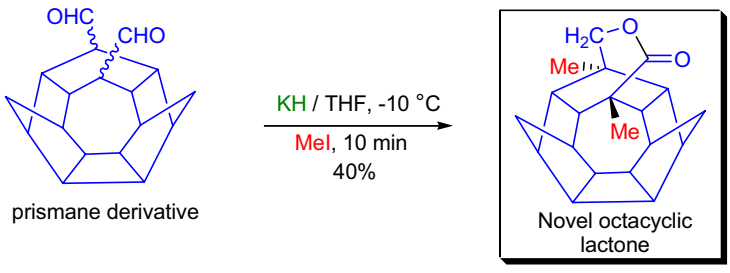
Mechanism:[17-23]

A variety of mechanisms have been proposed for this reaction, but the generally accepted mechanism of the *Cannizzaro reaction* involves a hydride transfer. First, OH^- adds across the carbonyl group, and the resulting species is deprotonated under the applied basic conditions to give the corresponding dianion. This dianion facilitates the ability of the aldehydic hydrogen to leave as a hydride ion. This leaving hydride ion attacks another aldehyde molecule in the *rate-determining step* (RDS) to afford the alkoxide of a primary alcohol, which gets protonated by the solvent (H_2O). By running the reaction in the presence of D_2O, it was shown that the reducing hydride ion came from another aldehyde and not the reaction medium, since the resulting primary alcohol did not contain a deuterium. Ashby and co-workers using resolved ESR spectra demonstrated that substituted benzaldehyde radical anions were formed in the reactions of substituted benzaldehydes with either NaOH or KO*t*-Bu. This observation suggested that the reaction proceeded by a single-electron transfer (SET) mechanism.[22]



Synthetic Applications:

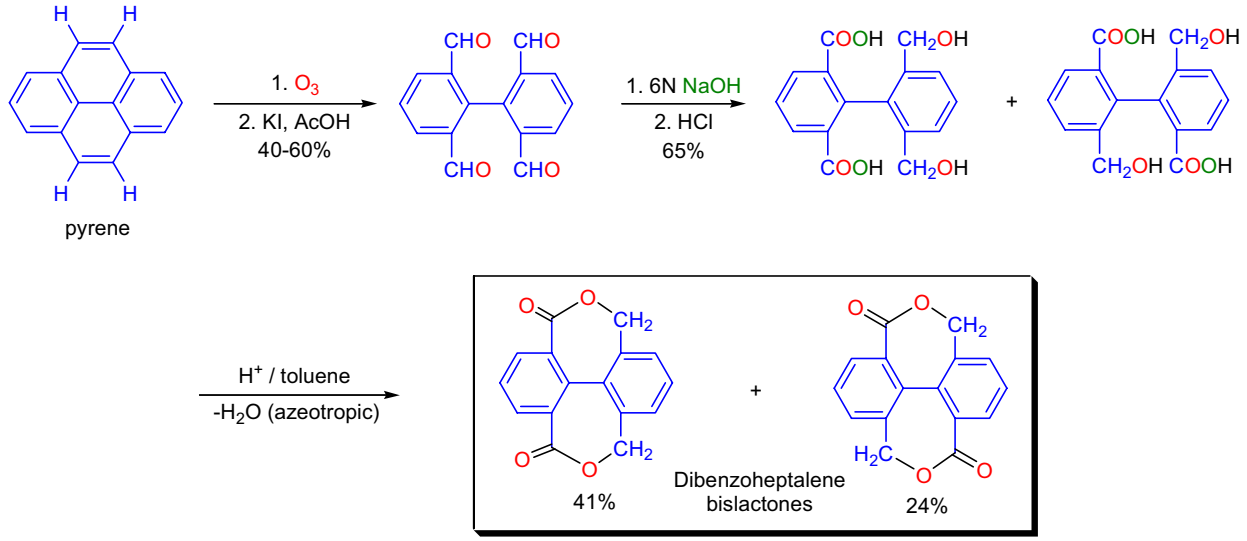
G. Mehta and co-workers unexpectedly encountered a novel *transannular Cannizzaro reaction* when 1,4-bishomo-6-seco[7]prismane dialdehyde derivative was subjected to basic conditions to yield a novel octacyclic lactone.[24] The *transannular Cannizzaro* reaction is the result of the proximity of the two reacting aldehyde groups induced by the rigid caged structure.



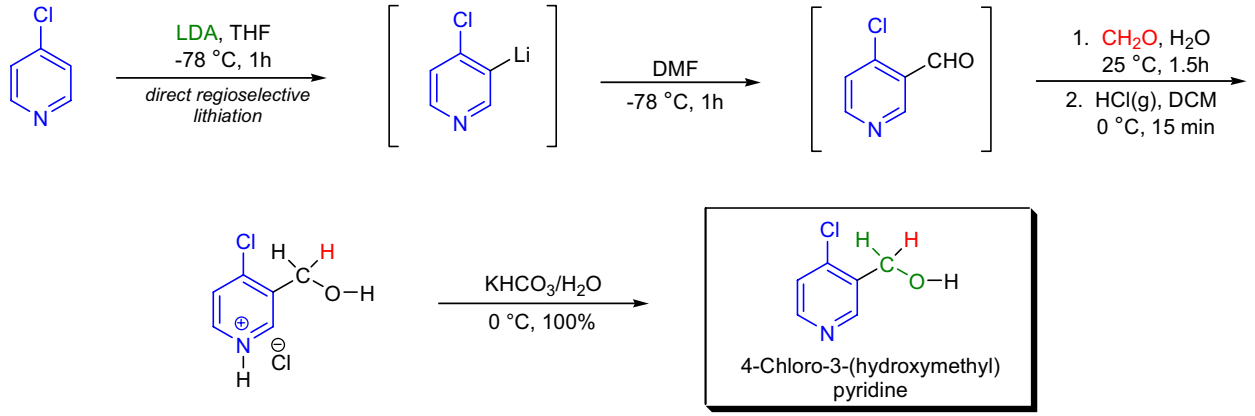
CANNIZZARO REACTION

Synthetic Applications:

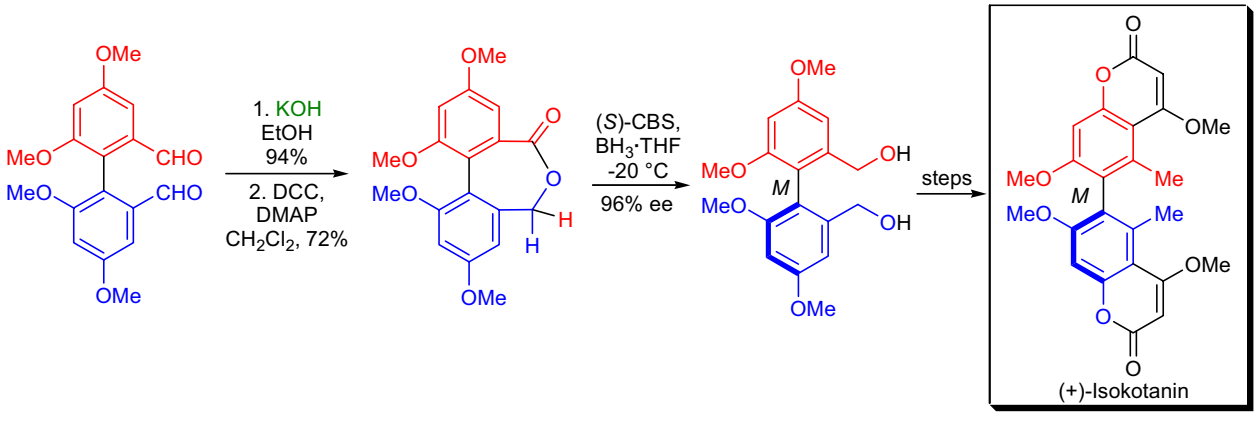
J. Rebek et al. synthesized novel dibenzoheptalene bislactones *via a double intramolecular Cannizzaro reaction* for condensation polymerization and remote catalysis studies.[25] These bislactones are chiral, atropisomeric molecules.



During the large-scale, high-yield, one-pot synthesis of 4-chloro-3-(hydroxymethyl)pyridine, a starting material for the preparation of several polyfunctionalized molecules that can be linked to cephalosporines, M. Penso and co-workers utilized the combination of *direct regioselective lithiation/formylation* and *crossed-Cannizzaro reduction* of 4-chloropyridine.[26]



An efficient atropo-enantioselective total synthesis of the axially chiral bicoumarin (+)-isokotanin was accomplished by J. Bringmann and co-workers.[27] The key steps in this synthetic approach were the formation of a configurationally stable seven-membered biaryl lactone by the *Cannizzaro reaction* of the corresponding biaryl dialdehyde followed by a *kinetic resolution* by *atroposelective ring cleavage*.



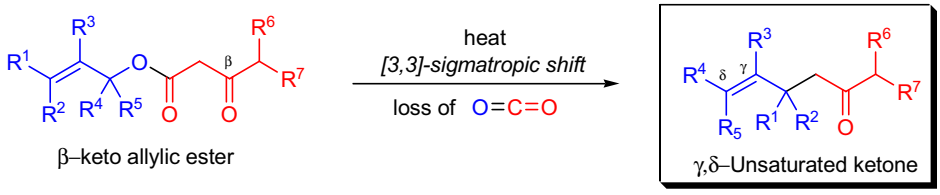
CARROLL REARRANGEMENT
(KIMEL-COPE REARRANGEMENT)

(References are on page 557)

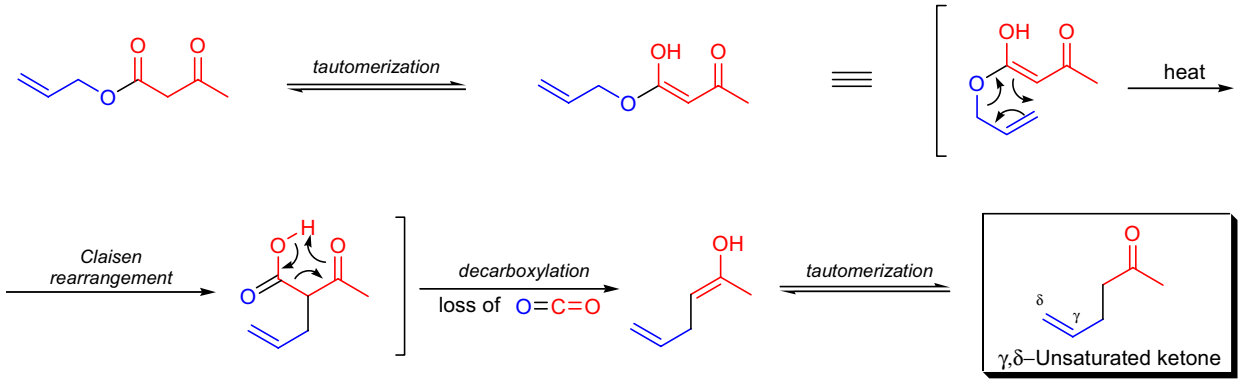
Importance:

[*Seminal Publications*[1,2]*; Reviews*[3,4]*; Modifications & Improvements*[5-12]]

The *[3,3]-sigmatropic rearrangement* of allylic β-keto esters to γ,δ-unsaturated ketones is known as the *Carroll rearrangement* (*Kimel-Cope rearrangement* or *decarboxylative Claisen rearrangement*). Although discovered in 1940, this reaction was not applied in drug synthesis until the early 1990s.[6] The reaction has found limited use in synthetic organic chemistry, since harsh conditions (130-220 °C) were needed to induce the *[3,3]-sigmatropic rearrangement*. However, these thermal barriers were lowered through modifications of the precursor β-keto ester.[6-12] Many different variations of the *Carroll rearrangement* are known, but most of them proceed with decarboxylation of the initially formed β-keto acid. The decarboxylation can be avoided by esterification or intramolecular lactonization of the β-keto acids at low temperatures, leading to the rearranged products with excellent *syn/anti* selectivities.

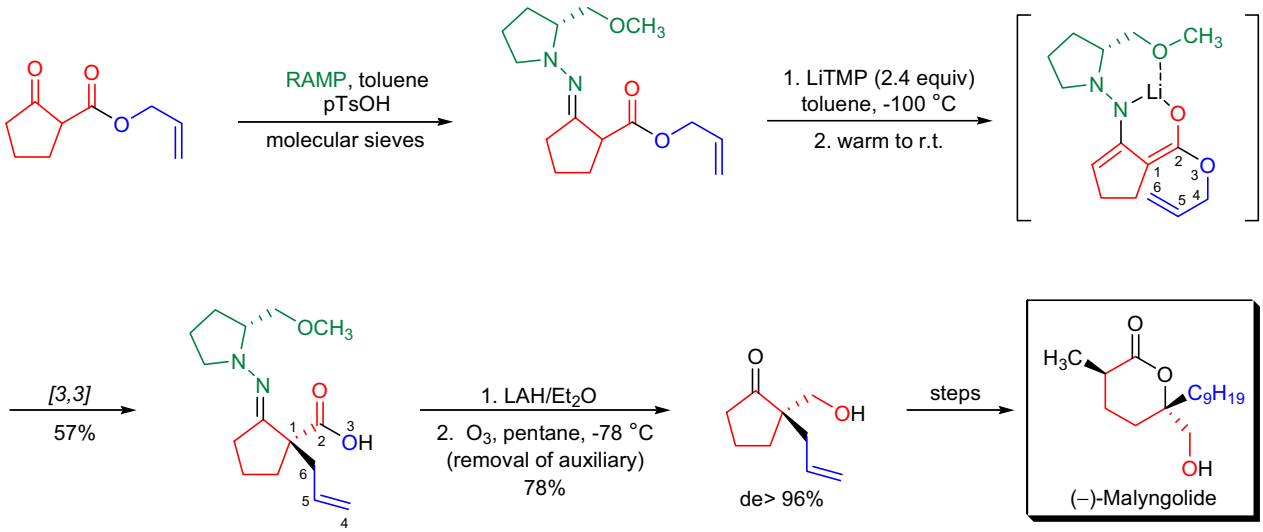


Mechanism: [13,14]



Synthetic Applications:

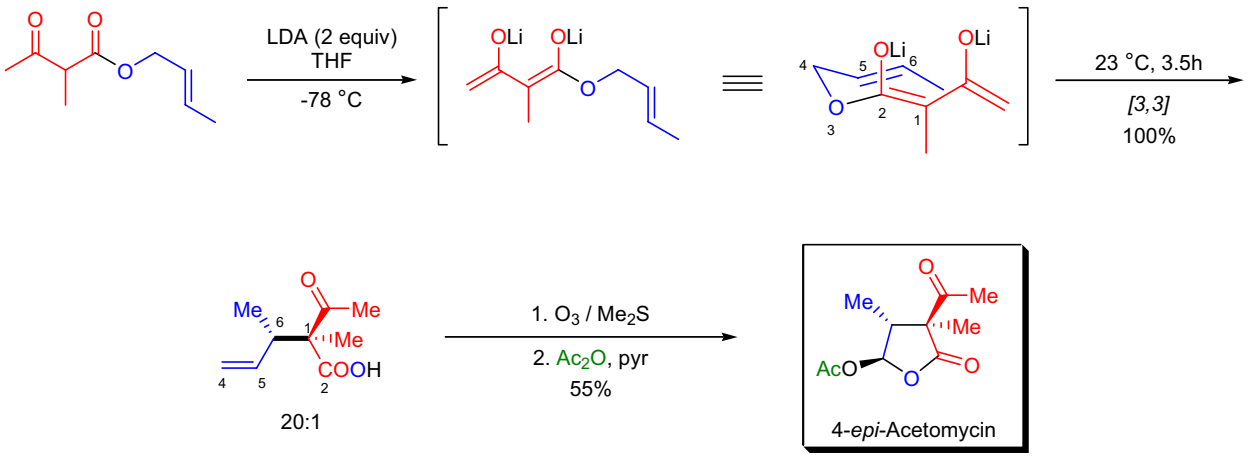
D. Enders and co-workers have achieved the enantioselective total synthesis of antibiotic (–)-malyngolide by using the *asymmetric Carroll rearrangement* as the key step.[11]



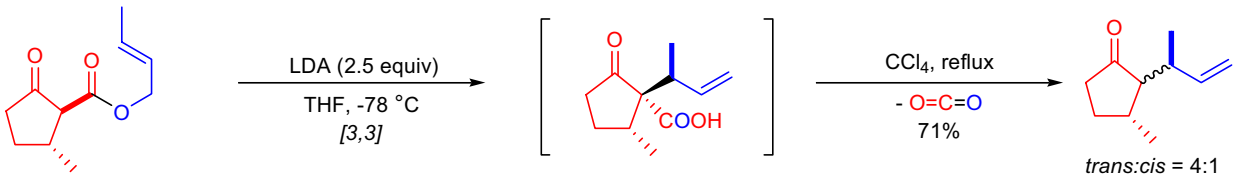
CARROLL REARRANGEMENT
(KIMEL-COPE REARRANGEMENT)

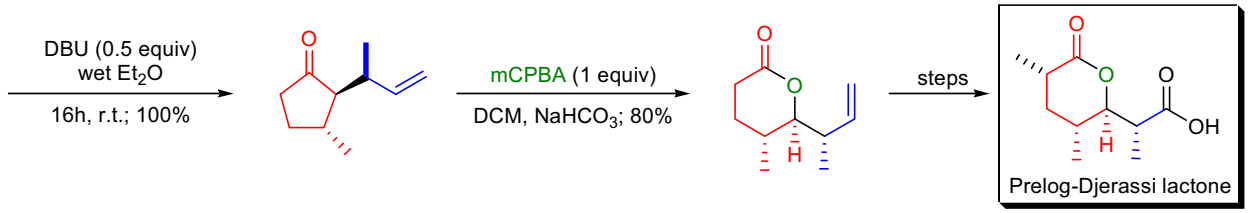
Synthetic Applications:

In the laboratory of A.M. Echavarren, the total synthesis of the antibiotic (±)-4-*epi*-acetomycin was completed by using the stereoselective *ester enolate Carroll rearrangement* of (*E*)-butenyl-2-methylacetoacetate as the key step, followed by ozonolysis and acetylation. The stereochemistry of the major isomer resulted from the rearrangement of the (*E*)-enolate through a chair-like transition state.[6]

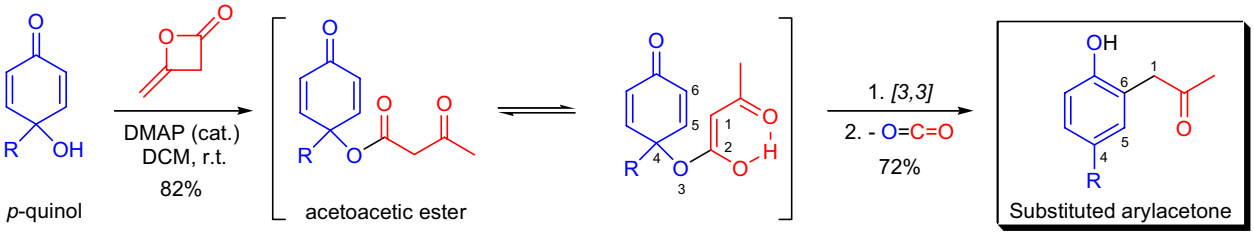


J. Rodriguez et al. have investigated the stereoselective *ester dienolate Carroll rearrangement* of (*E*)- and (*Z*)-allylic β-keto esters and found a new, attractive approach to the synthesis of the Prelog-Djerassi lactone and related compounds.[7]





K.L. Sorgi and co-workers prepared acetoacetates from substituted *p*-quinols and found that they underwent the *Carroll rearrangement* at room temperature to afford substituted arylacetones and related derivatives in moderate to good yields.[10]



CASTRO-STEPHENS COUPLING

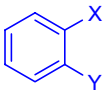
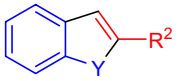
(References are on page 558)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-8]*; Modifications & Improvements*[9-13]]

The copper(I) mediated coupling of aryl or vinyl halides with aryl- or alkyl-substituted alkynes is known as the *Castro-Stephens coupling*. In the early 1960s, R.D. Stephens and C.E. Castro discovered that disubstituted (diaryl or arylalkyl) acetylenes were produced in good yield upon treatment of aryl iodides with stoichiometric amounts of copper(I) acetylides under a nitrogen atmosphere in refluxing pyridine (a).[1] The best results are obtained with electron-poor aryl halides. When aryl iodides bear a nucleophilic substituent in the *ortho* position, cyclization to the corresponding heterocycles occurs exclusively (b).[2] Vinyl iodides and bromides are also suitable partners affording enynes. Traditional copper-mediated aryl coupling reactions have several drawbacks compared to the currently used Pd-catalyzed reactions (e.g., *Sonogashira coupling*). The problems encountered are: 1) most copper(I) salts are insoluble in organic solvents, so the reactions are often heterogeneous and require high reaction temperatures; and 2) the reactions are sensitive to functional groups on the aryl halides, and the yields are often irreproducible. Recent modifications allow the use of catalytic amounts of copper(I) complexes and milder conditions for the couplings.[11,13]

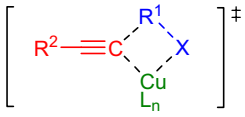
a) R^1–X + H–≡–R^2 → (Cu(I)-complex/salt; solvent, base, reflux) → R^1–≡–R^2 (Disubstituted acetylene)

b)  + H–≡–R^2 → (Cu(I)-complex/salt; solvent, base, reflux) →  (Heterocycle)

R^1 = aryl, vinyl; X = I, Br; Y = OH, NH_2; R^2 = alkyl, aryl; base: pyridine, KO*t*-Bu, NEt_3

Mechanism:[4]

The reaction is believed to proceed *via* a four-centered transition state.

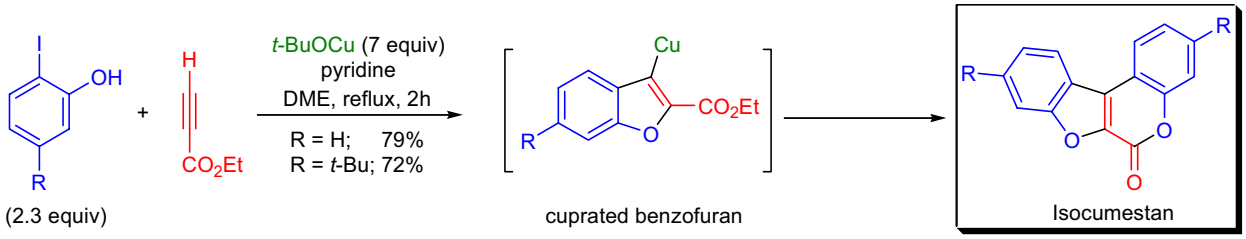
R^1–X + L_nCu–≡–R^2 ⇌  → - CuX → R^1–≡–R^2 (Disubstituted acetylene)

X = I, Br

four-centered TS*

Synthetic Applications:

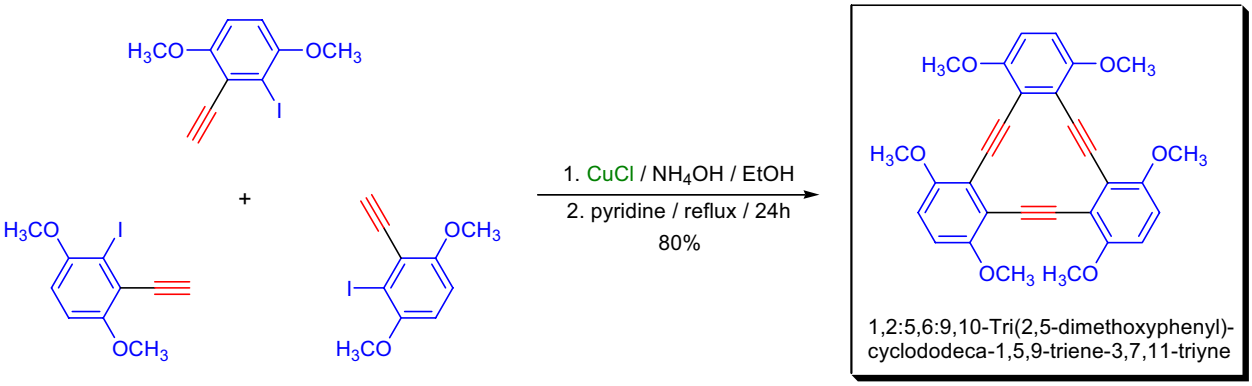
In the laboratory of M. Nilsson, a facile one-pot synthesis of isocumestans (6*H*-benzofuro[2,3-*c*][1]benzopyran-6-ones) was developed *via* a novel extension of the *Castro-Stephens coupling* utilizing *ortho*-iodophenols and ethyl propiolate.[14] The reaction can be regarded as an extended *Castro-Stephens coupling* where an intermediate cuprated benzofuran couples with a second equivalent of *ortho*-iodophenol, and the product lactonizes to isocumestan.



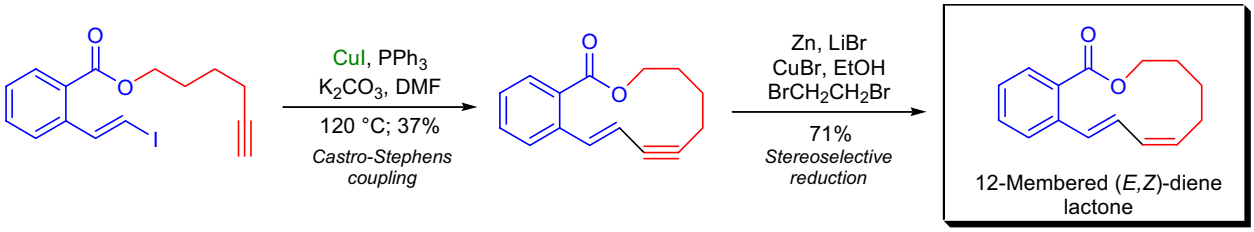
CASTRO-STEPHENS COUPLING

Synthetic Applications:

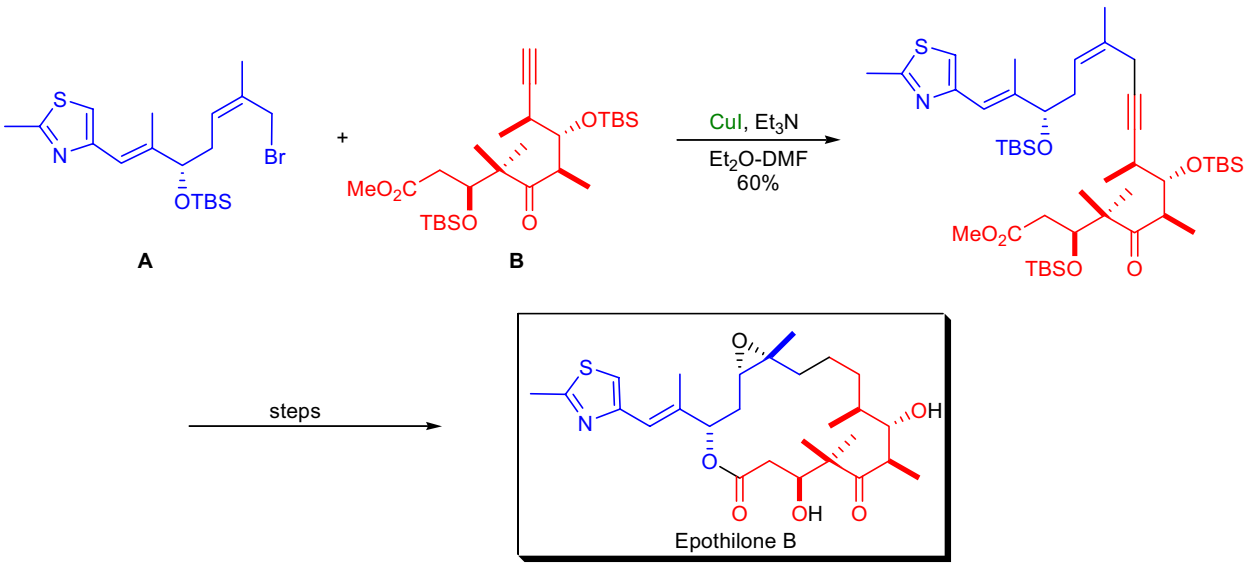
Tribenzocyclotriyne (TBC) is a planar, anti-aromatic, annelated dehydroannulene. The cavity of TBC is of sufficient size to form complexes with low oxidation state first-row transition metals. When the complex of Ni(TBC) is partially reduced with alkali metals, the complex increases its conductivity by four orders of magnitude. This remarkable property was the reason for the synthesis of cyclotriynes by W.J. Youngs et al. as precursors to conducting systems.[15] The synthesis of a methoxy-substituted tribenzocyclotriyne was accomplished starting from (2-iodo-3,6-dimethoxyphenyl)ethyne using the *Castro-Stephens coupling*. The copper acetylide was prepared by dissolving the alkyne in ethanol and adding it to an equal volume of CuCl in ammonium hydroxide. Refluxing the copper acetylide in pyridine under anaerobic conditions produced the cyclotriyne in 80% yield.



R.S. Coleman and co-workers have developed a stereoselective synthesis of the 12-membered diene and triene lactones characteristic of the antitumor agent oximidines I and II, based on an *intramolecular Castro-Stephens coupling*.[16] The effectiveness of this protocol rivals the efficiency of standard macrolactonization. The stereoselective reduction of the internal alkyne afforded the 12-membered (*E*,*Z*)-diene lactone in good yield.



During the total synthesis of epothilone B, J.D. White et al. used the *modified Castro-Stephens reaction* instead of a *Wittig reaction* for the coupling of two important subunits (**A** & **B**) to avoid strongly basic conditions.[17]



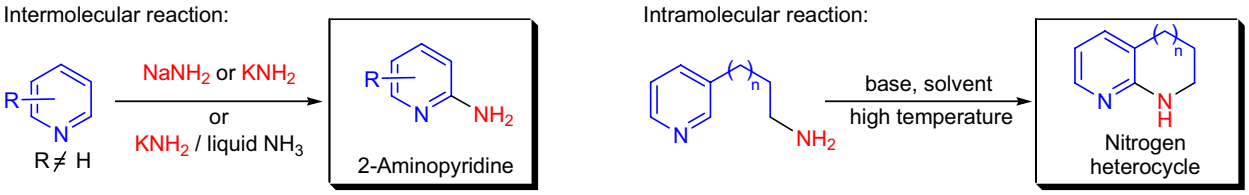
CHICHIBABIN AMINATION REACTION

(References are on page 558)

Importance:

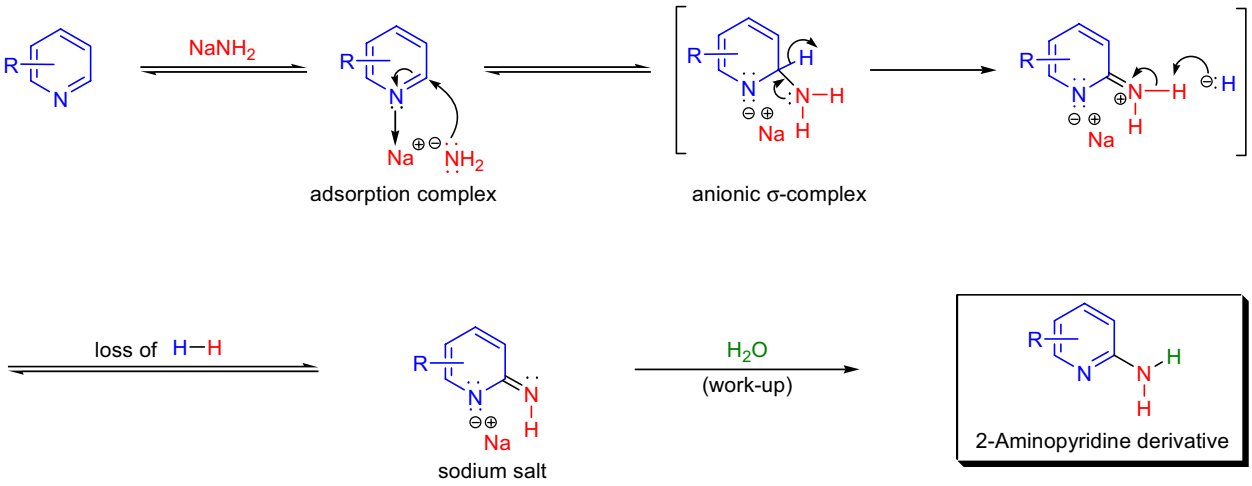
[*Seminal Publications*[1,2]*; Reviews*[3-8] *; Modifications & Improvements*[9,10]]

In the early 1900s, A.E. Chichibabin reacted pyridine with sodium amide ($NaNH_2$) in dimethylamine at high temperature (110 °C). After aqueous work-up, he isolated 2-aminopyridine in 80% yield.[1] A decade later, he added pyridine to powdered KOH at 320 °C, and after aqueous work-up 2-hydroxypyridine was isolated.[2] Similar reactions take place when pyridine or its derivatives are treated with strong nucleophiles such as alkyl- and aryllithiums to give 2-alkyl and 2-arylpyridines.[11] The direct amination of pyridine and its derivatives at their electron-deficient positions *via* nucleophilic aromatic substitution (S_NAr) is known as the *Chichibabin reaction*. This reaction is also widely used for the direct introduction of an amino group into the electron-deficient positions of many azines and azoles (e.g., quinoline is aminated at C2 & C4, isoquinoline at C1, acridine at C9, phenanthridine at C6, quinazoline at C4). Both inter- and intramolecular[12-14] versions are available, but investigations have mainly focused on intermolecular reactions. There are two procedures for conducting the *Chichibabin reaction*: **A**) the reaction is carried out at high temperature in a solvent that is inert toward $NaNH_2$ (e.g., *N,N*-dialkylamines, arenes, mineral oil, etc.) or without any solvent; or **B**) the reaction is run at low temperature in liquid ammonia with KNH_2 (more soluble than $NaNH_2$). Procedure **A** proceeds in a heterogeneous medium and the reactions effected under these conditions show strong dependence on substrate basicity, while procedure **B** proceeds in a homogeneous medium and there is no substrate dependence. Frequently, an oxidant such as KNO_3 or $KMnO_4$ is added during procedure **B** to facilitate the amination by oxidizing the hydride ion (poor leaving group) in the intermediate σ-complex.[9,6] The low temperature conditions make it possible to aminate substrates such as diazines, triazines, and tetrazines, which are destroyed at high temperatures, but pyridine itself does not undergo amination in liquid ammonia because it is not sufficiently electron-deficient.



Mechanism: [15-26,7]

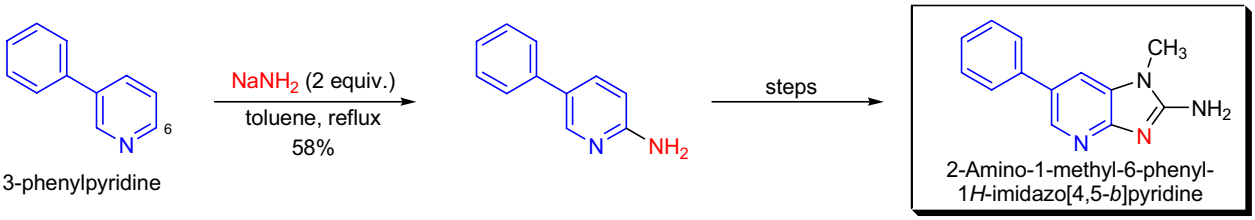
The *Chichibabin reaction* is formally the nucleophilic aromatic substitution of hydride ion (H^-) by the amide ion (NH_2^-). In the first step, an *adsorption complex* is formed with a weak coordination bond between the nitrogen atom in the heterocycle and the sodium ion (Na^+); this coordination increases the positive charge on the ring α-carbon atom, and thus facilitates the formation of an *anionic σ-complex* that can be observed by NMR in liquid ammonia solution. This σ-complex is then aromatized to the corresponding sodium salt while hydrogen gas (H_2) is evolved (a proton from an amino group reacts with the leaving group hydride ion). It is possible to monitor the progress of the reaction by the volume of the hydrogen gas evolved. However, this mechanism may not be the only one operating, since indirect evidence (formation of heterocyclic dimers) suggests that under heterogeneous conditions there is a single-electron-transfer (SET) from the amide nucleophile to the substrate.



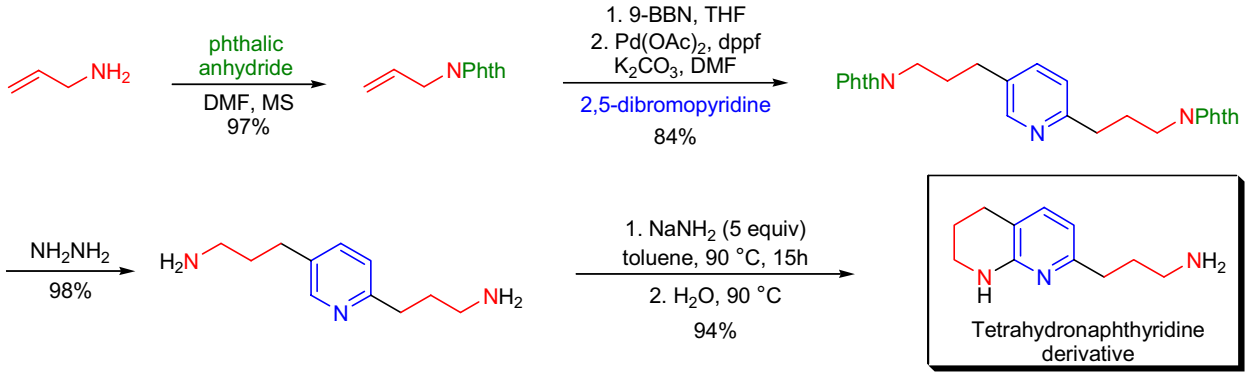
CHICHIBABIN AMINATION REACTION

Synthetic Applications:

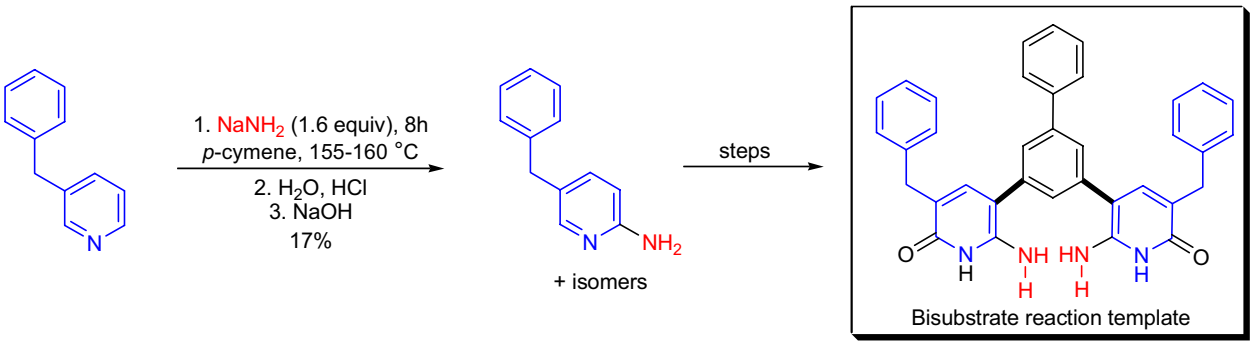
In the laboratory of J.S. Felton, the synthesis of 2-amino-1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridine (PHIP), a mutagenic compound isolated from cooked beef, and its 3-methyl isomer have been accomplished.[27] The synthesis of PHIP began with the commercially available 3-phenylpyridine, which was aminated at the 6-position with sodium amide in toluene by the *Chichibabin reaction* in 58% yield.



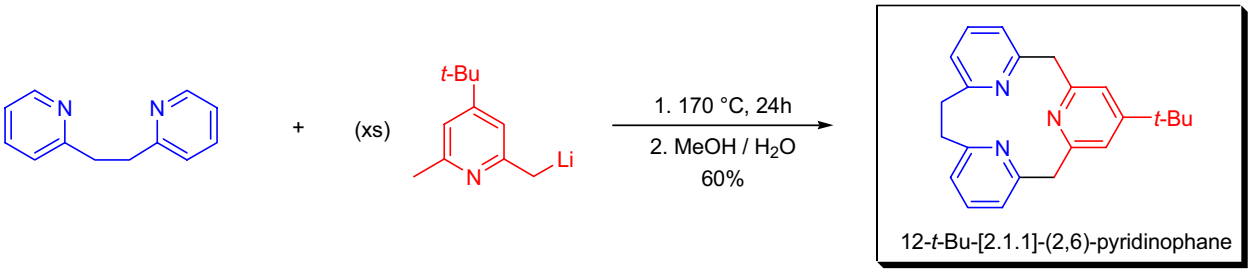
M. Palucki and co-workers synthesized 2-[3-aminopropyl]-5,6,7,8-tetrahydronaphthyridine in large quantities for clinical studies *via* a one-pot *double Suzuki reaction* followed by deprotection and a highly regioselective *intramolecular Chichibabin cyclization*.[14] This approach was amenable to scale-up unlike the traditional methods such as the *Skraup* and *Friedländer reactions* that involve carbon-carbon bond forming steps. The *Chichibabin reaction* was optimized and afforded the desired product in high yield, excellent regioselectivity, and a significant reduction in reaction time compared to literature precedent.



T.R. Kelly et al. have synthesized bisubstrate reaction templates utilizing the *Chichibabin amination reaction* during the preparation of one precursor.[28] This reaction template was designed to use hydrogen bonding to bind two substrates simultaneously but transiently, giving rise to a ternary complex, which positions the substrates in an orientation that facilitates their reaction.



A.N. Vedernikov and co-workers designed and synthesized tridentate facially chelating ligands of the [2.n.1]-(2,6)-pyridinophane family.[29] The key step in their synthesis of these tripyridine macrocycles was a *double Chichibabin-type condensation* of 1,2-*bis*(2-pyridyl)ethanes with lithiated 2,6-dimethylpyridines.



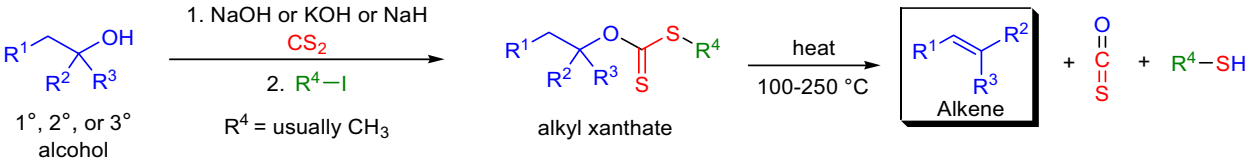
CHUGAEV ELIMINATION REACTION
(XANTHATE ESTER PYROLYSIS)

(References are on page 559)

Importance:

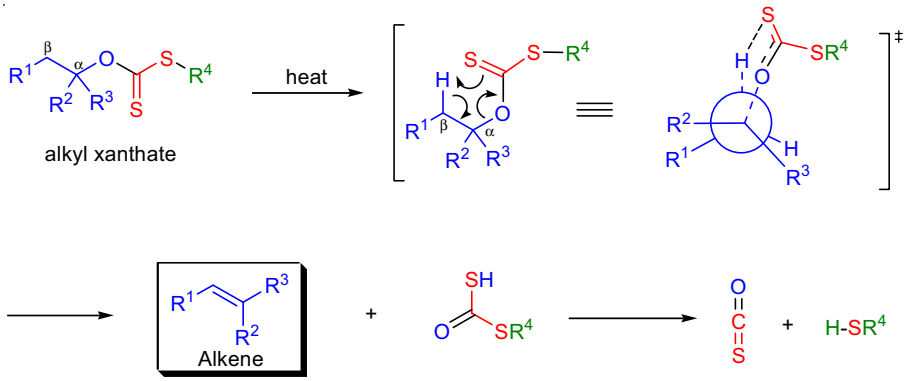
[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5-7]]

The formation of olefins by pyrolysis (100-250 °C) of the corresponding xanthates (containing at least one β-hydrogen atom) *via cis*-elimination is known as the *Chugaev elimination reaction*. This transformation was discovered by L. Chugaev in connection with his studies on the optical properties of xanthates[1] in 1899. Xanthates are prepared from the corresponding alcohols (1°, 2°, and 3°) by first deprotonating the alcohol with a base (e.g., NaH, NaOH, or KOH) and reacting the resulting alkoxide with carbon disulfide. The metal xanthate is then trapped with an alkyl iodide (often methyl iodide). Primary xanthates are usually more thermally stable than secondary and tertiary xanthates and therefore undergo elimination at much higher temperatures (>200 °C). The *Chugaev elimination* reaction of xanthates is very similar to the ester (acetate) pyrolysis, but xanthates eliminate at lower temperatures than esters and the possible isomerization of alkenes is minimized. The by-products (COS, R^4-SH) of the *Chugaev reaction* are very stable, thus making the elimination irreversible. The reaction is especially valuable for the conversion of sensitive alcohols to the corresponding olefins without rearrangement of the carbon skeleton. If the elimination of the xanthate can occur in two directions, when more than one β-hydrogen is available on each carbon atom, the utility of the *Chugaev reaction* is greatly diminished by the formation of complex mixtures of olefins.



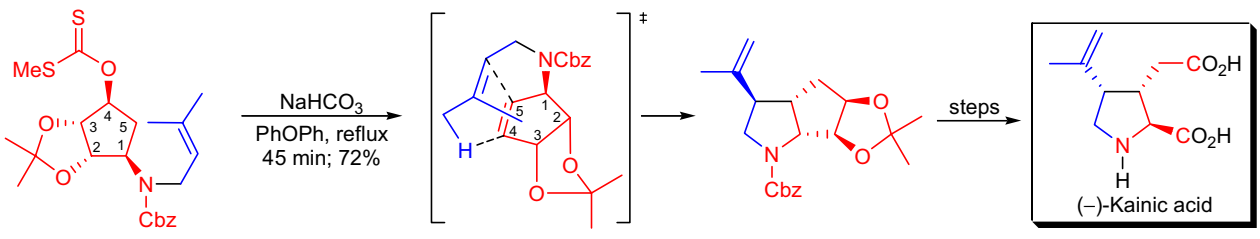
Mechanism: [8-12]

The *Chugaev reaction* is an intramolecular *syn* elimination (E_i), and it proceeds through a six-membered transition state involving a *cis*-β-hydrogen atom of the alcohol moiety and the thione sulfur atom of the xanthate. Isotopic studies involving ^{34}S and ^{13}C showed that the C=S, and not the thiol sulfur atom, closes the ring in the transition state.[12] The β-hydrogen and the xanthate group must be coplanar in the cyclic transition state.



Synthetic Applications:

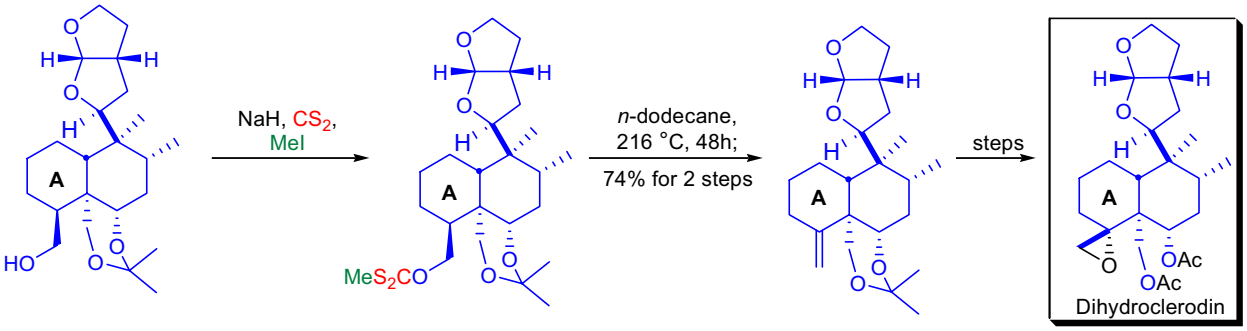
A concise route to (–)-kainic acid was developed by K. Ogasawara and co-workers by employing sequentially a *Chugaev syn-elimination* and an *intramolecular ene reaction* as the key steps.[13] After preparing the xanthate under standard conditions, the compound was heated to reflux in diphenyl ether in the presence of sodium bicarbonate. The desired tricyclic product bearing the trisubstituted pyrrolidine framework was formed as a single diastereomer in 72% yield.



CHUGAEV ELIMINATION REACTION
(XANTHATE ESTER PYROLYSIS)

Synthetic Applications:

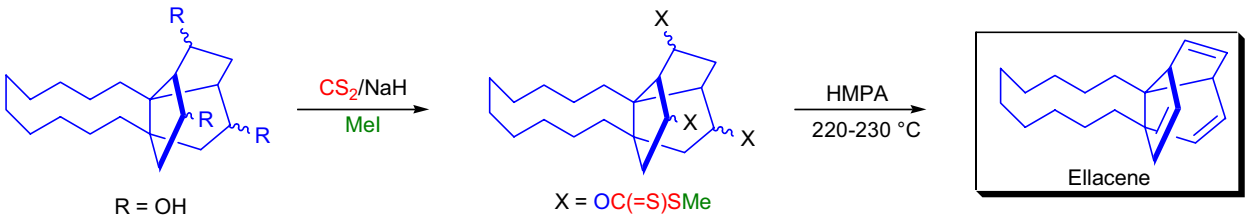
In the late stages of the total synthesis of dihydroclerodin, A. Groot and co-workers used the *Chugaev elimination reaction* to install an exocyclic double bond on ring A.[14] Before employing the xanthate ester pyrolysis, the authors tried several methods that failed to convert the primary alcohol to the exocyclic methylene functionality. The corresponding xanthate ester was prepared followed by heating to 216 °C in *n*-dodecane for 2 days to afford the desired alkene in 74% yield.



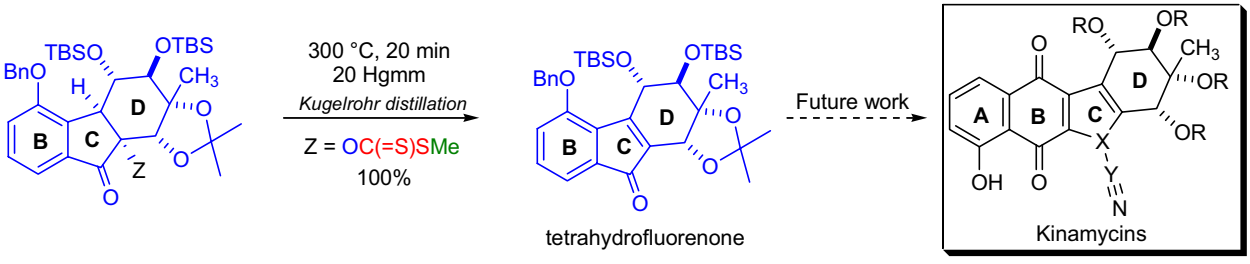
During the first total synthesis of (–)-solanapyrone E by H. Hagiwara et al., it was necessary to install the C3-C4 double bond in the decalin ring of the natural product by eliminating the C4 secondary alcohol.[15] Since the stereochemistry of the *xanthate pyrolysis* is *syn*, it was possible to install this double bond regioselectively, without observing any of the undesired C4-C5 double bond. The C4 alcohol was first converted to the xanthate in 91% yield using *t*-BuOK as a base. The double bond at C3 was then selectively introduced by heating the xanthate at 190 °C in 1-methylnaphthalene.



J.M. Cook and co-workers accomplished the total synthesis of ellacene (1,10-cyclododecanotriquinancene) by utilizing the *Weiss reaction* and the *Chugaev elimination* as key steps.[16] The elimination of the *tris*-xanthate was performed in HMPA at 220-230 °C in very high yield. This pyrolysis was superior to the elimination conducted under neat conditions.



Synthetic studies on kinamycin antibiotics in the laboratory of T. Ishikawa resulted in the elaboration of the highly oxygenated D ring with all the required stereocenters for the kinamycin skeletons.[17] The tricyclic tertiary alcohol was converted to the corresponding xanthate and then smoothly pyrolyzed under reduced pressure to yield the desired tetrahydrofluorenone system.



CIAMICIAN-DENNSTEDT REARRANGEMENT

(References are on page 559)

Importance:

[*Seminal Publications*[1-4]*; Theoretical Studies*[5]]

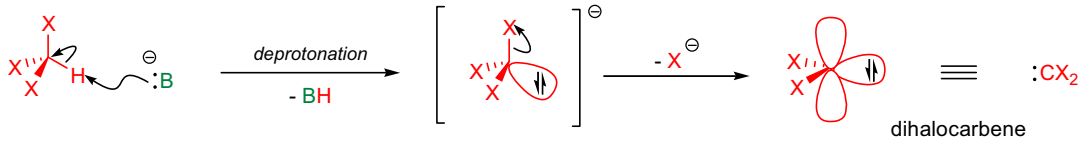
The rearrangement of pyrroles to 3-halo-pyridines upon treatment with haloforms (CHX_3 where X = Cl, Br, I) in the presence of a strong base was first described by G.L. Ciamician.[1] Its synthetic utility was later extended by M. Dennstedt to the sodium methoxide catalyzed reaction of pyrrole with methylene iodide to give pyridine.[6] Soon after the initial discovery, the methodology was also extended for the indole series to prepare substituted quinolines.[7-9] The reaction is known as the *Ciamician-Dennstedt rearrangement*, but it is also referred to as the *"abnormal" Reimer-Tiemann reaction*.



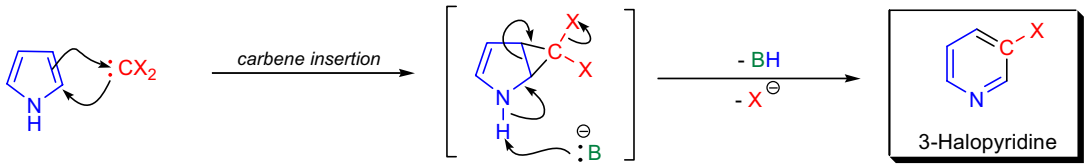
Mechanism:[10-19]

The mechanism starts with the generation of a dihalocarbene *via* an α-elimination, followed by insertion into the most electron rich π-bond of the pyrrole. The 6,6-dihalo-2-azabicyclo[3.1.0]hexane intermediate then undergoes a ring expansion to give the 3-halogen-substituted pyridine derivative triggered by the deprotonation of the pyrrole nitrogen. In the case of indoles the dihalocyclopropane intermediate interconverts with an open-ring indolyldihalomethyl anion, and therefore two different products, 3*H*-indole and quinoline, are formed.[19]

Carbene formation:

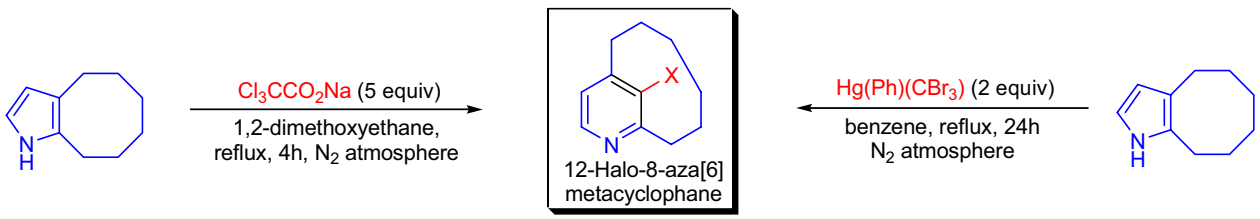


Insertion of carbene:



Synthetic Applications:

In an effort to expand the available synthetic tools for the preparation of various metacyclophanes and pyridinophanes, C.B. Reese and co-workers prepared [6](2,4)pyridinophane derivatives by treating 4,5,6,7,8,9-hexahydro-1*H*-cyclo-octa[*b*]pyrrole with dichloro- and dibromocarbene respectively.[20] The dihalocarbenes predominantly inserted into the most substituted (more electron rich) double bond of the pyrrole ring in modest to poor yields.

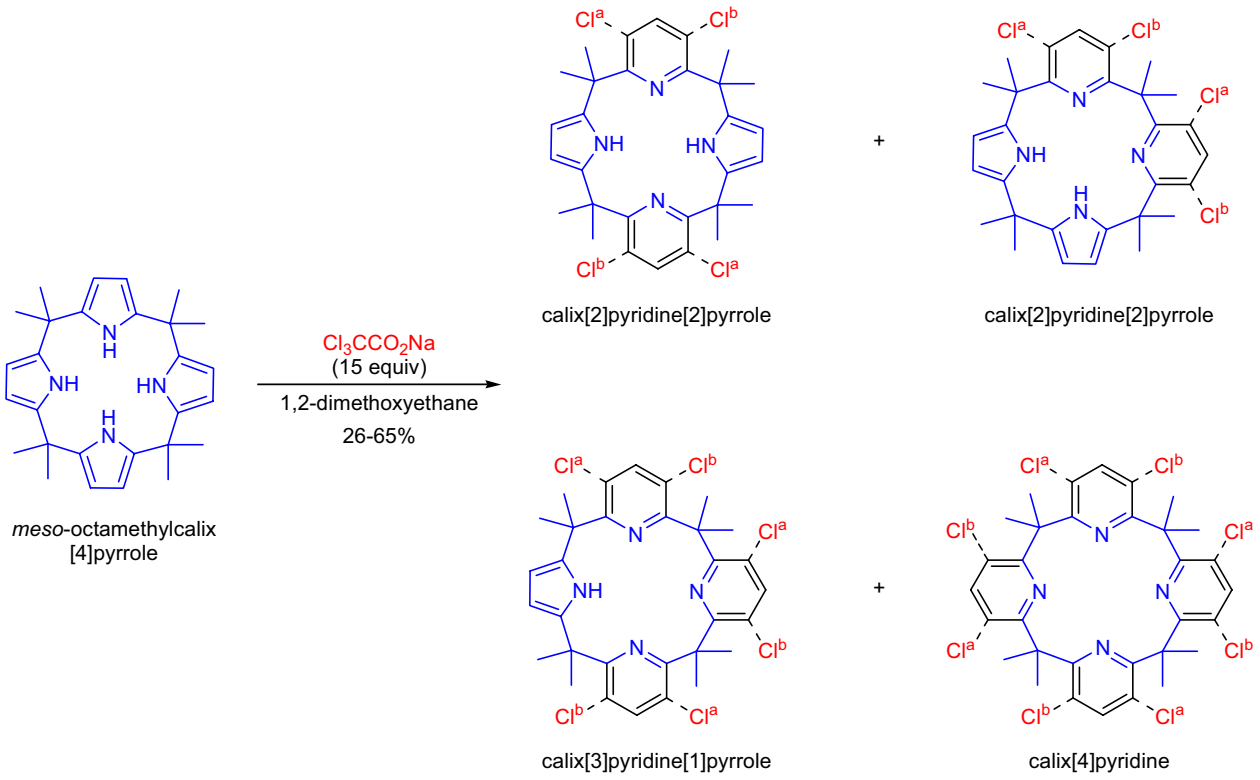


X = Cl; 28% X = Br; 6%

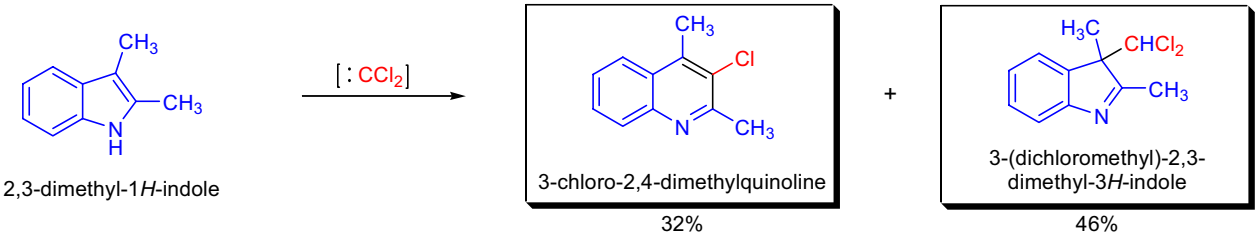
CIAMICIAN-DENNSTEDT REARRANGEMENT

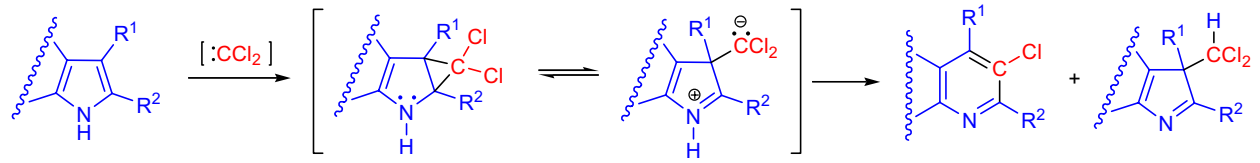
Synthetic Applications:

For a long time heterocyclic analogues of calix[4]arene such as calix[4]pyridines were unknown. In the laboratory of J.L. Sessler, a universal and easy synthetic protocol was devised for the preparation of calix[m]pyridine-[n]pyrrole (m+n=4) and calix[4]pyridine systems based on the nonmetal mediated ring expansion of pyrrole.[21] The reaction of dichlorocarbene with *meso*-octamethyl-calix[4]pyrrole brought about a pyrrole ring expansion to give chlorocalixpyridinopyrroles and chlorocalixpyridines. Using 15 equivalents of sodium trichloroacetate as the carbene source and 1,2-dimethoxyethane as the solvent afforded a 1:1:1 ratio of calix[3]pyridine[1]pyrrole : calix[4]pyridine : calix[2]pyridine[2]pyrrole. Only monochlorinated pyridines were formed but each pyridine ring gave rise to two regioisomers. Yields were between 26-65%.



The first example for the insertion of an electrogenerated dichlorocarbene into substituted indoles was described by F. De Angelis and co-workers.[19] The dichlorocarbene was generated by reduction of CCl_4, followed by fragmentation of the resulting trichloromethyl anion. Under these conditions, 2,3-dimethylindole was converted to 3-chloro-2,4-dimethylquinoline and 3-(dichloromethyl)-2,3-dimethyl-3*H*-indole in moderate yield. The study revealed that the reaction mechanism and product formation are determined by the acidity of the solvent.





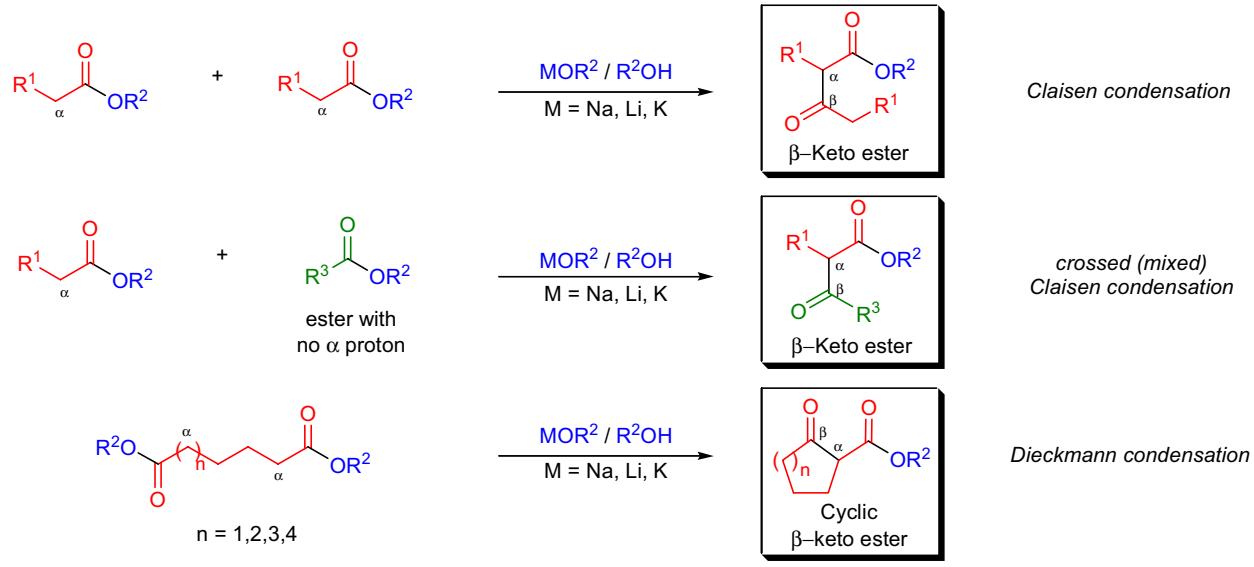
CLAISEN CONDENSATION / CLAISEN REACTION

(References are on page 559)

Importance:

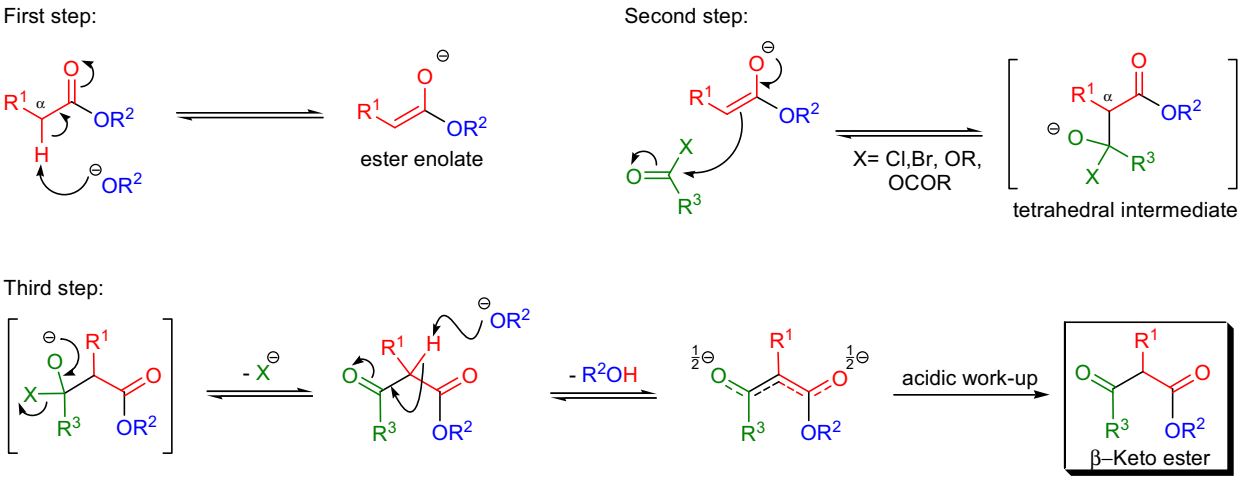
[*Seminal Publication*[1]; *Reviews*[2-8]; *Modifications & Improvements*[9-11]; *Theoretical Studies*[12-14]]

The base mediated condensation of an ester containing an α-hydrogen atom with a molecule of the same ester to give a β-keto ester is known as the *Claisen condensation*. If the two reacting ester functional groups are tethered, then a *Dieckmann condensation* takes place. The reaction between two different esters under the same conditions is called *crossed (mixed) Claisen condensation*. Since the *crossed Claisen condensation* can potentially give rise to at least four different condensation products, it is a general practice to choose one ester with no α-protons (e.g., esters of aromatic acids, formic acid and oxalic acid). The ester with no α-proton reacts exclusively as the acceptor and this way only a single product is formed. A full equivalent of the base (usually an alkoxide, LDA or NaH) is needed and when an alkoxide is used as the base, it must be the same as the alcohol portion of the ester to prevent product mixtures resulting from ester interchange. There are two other variants of this process: a) an ester enolate reacts with a ketone or aldehyde to give an β-hydroxyester, and b) a ketone or aldehyde enolate reacts with an ester to give a 1,3-diketone, both of these are referred to as the *Claisen reaction*. A useful alternative to the *Claisen condensation* is the reaction of an ester enolate with an acid chloride to generate a β-ketoester.



Mechanism:[15-23]

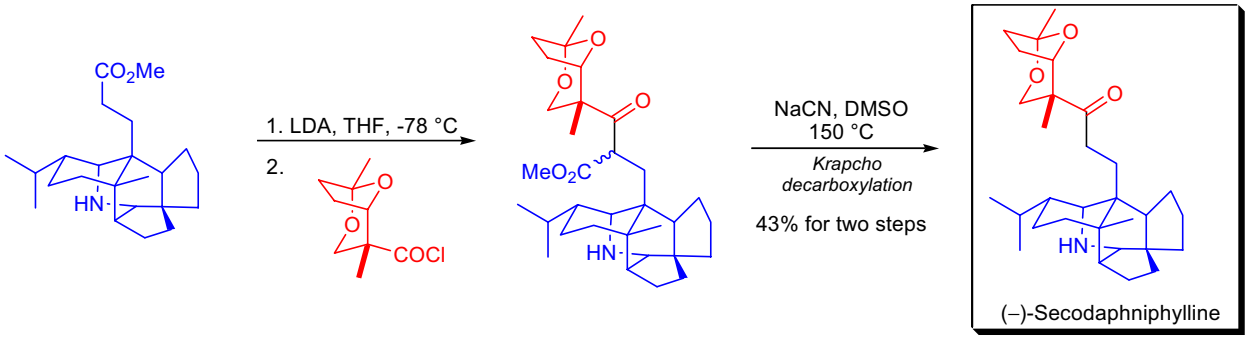
In the first step the base (usually an alkoxide, LDA, or NaH) deprotonates the α-proton of the ester to generate an ester enolate that will serve as the nucleophile in the reaction. Next, the enolate attacks the carbonyl group of the other ester (or acyl halide or anhydride) to form a tetrahedral intermediate, which breaks down in the third step by ejecting a leaving group (alkoxide or halide). Since it is adjacent to two carbonyls, the α-proton in the product β-keto ester is more acidic than in the precursor ester. Under the basic reaction conditions this proton is removed to give rise to a resonance stabilized anion, which is much less reactive than the ester enolate generated in the first step. Therefore, the β-keto ester product does not react further.



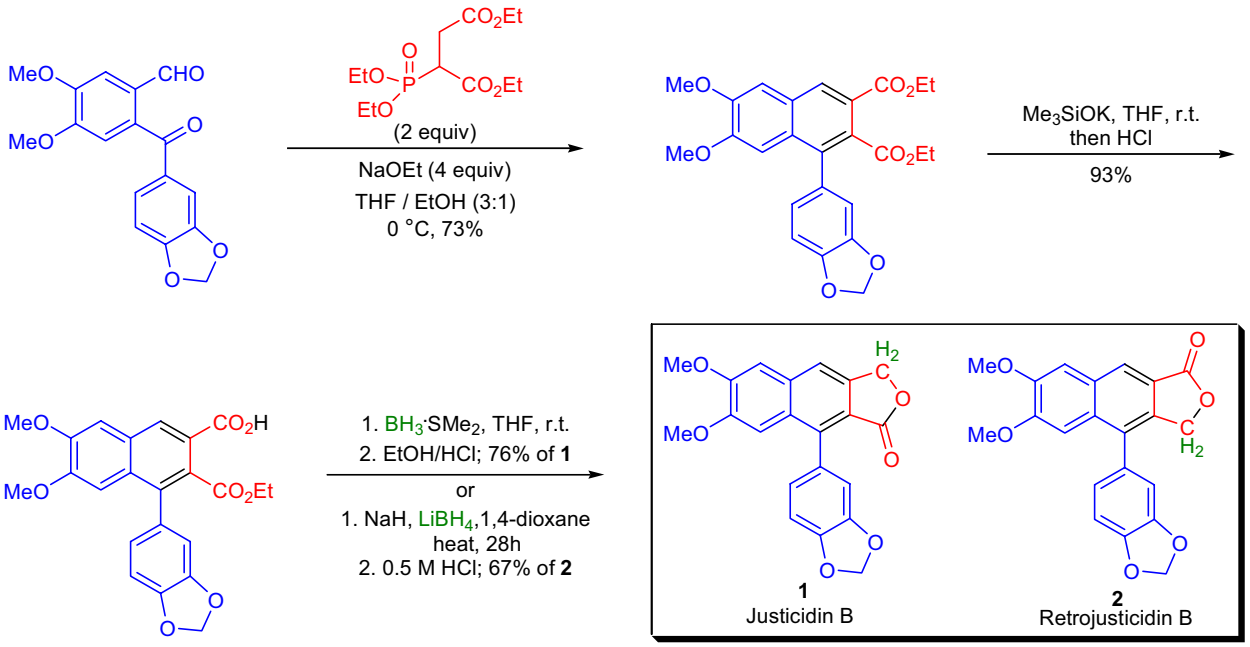
CLAISEN CONDENSATION / CLAISEN REACTION

Synthetic Applications:

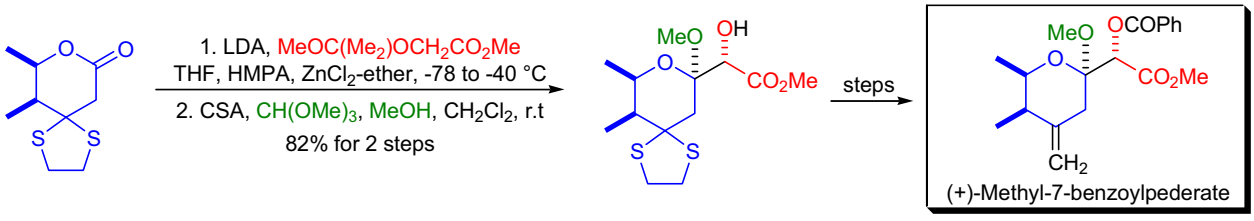
C.H. Heathcock and co-workers devised a highly convergent asymmetric total synthesis of (–)-secodaphniphylline, where the key step was a *mixed Claisen condensation*.[24] In the final stage of the total synthesis, the two major fragments were coupled using the *mixed Claisen condensation*; the lithium enolate of (–)-methyl homosecodaphniphyllate was reacted with the 2,8-dioxabicyclo[3.2.1]octane acid chloride. The resulting crude mixture of β-keto esters was subjected to the *Krapcho decarboxylation* procedure to afford the natural product in 43% yield for two steps.



The short total syntheses of justicidin B and retrojusticidin B were achieved in the laboratory of D.C. Harrowven.[25] A novel tandem *Horner-Emmons olefination/Claisen condensation* sequence was used between an aldehyde and a phosphonate tetraester to prepare the highly substituted naphthalene core of the natural products. Simultaneous addition of the aromatic ketoaldehyde and phosphonate to a cooled solution of sodium ethoxide in THF-ethanol effected the desired annulation in 73% yield. The resulting diester was then converted to justicidin B and retrojusticidin B.



T. Nakata et al. developed a simple and efficient synthetic approach to prepare (+)-methyl-7-benzoylpederate, a key intermediate toward the synthesis of mycalamides.[26] The key steps were the *Evans asymmetric aldol reaction*, *stereoselective Claisen condensation* and the *Takai-Nozaki olefination*. The *diastereoselective Claisen condensation* took place between a δ-lactone and the lithium enolate of a glycolate ester.



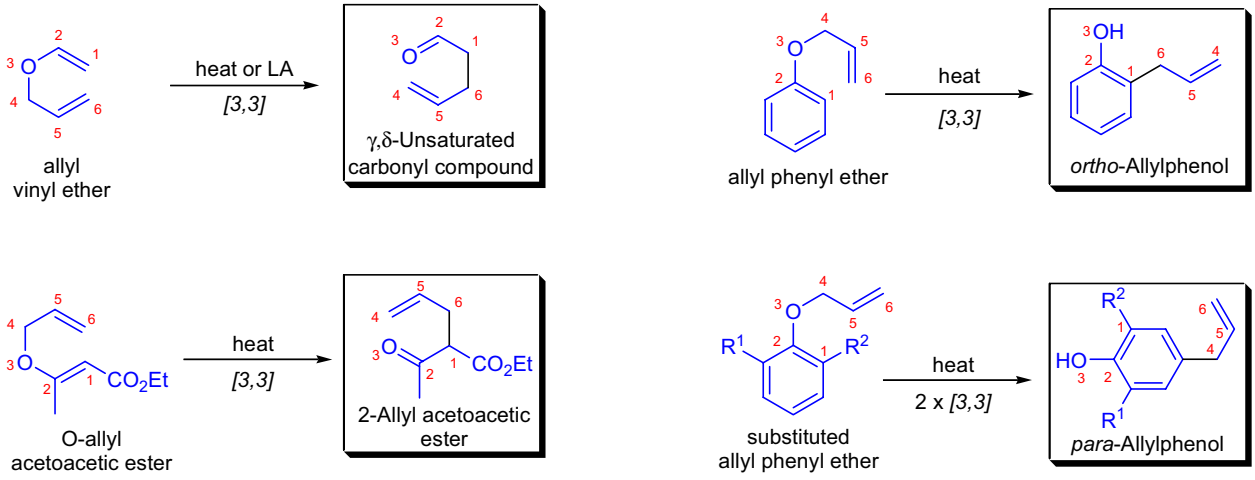
CLAISEN REARRANGEMENT

(References are on page 560)

Importance:

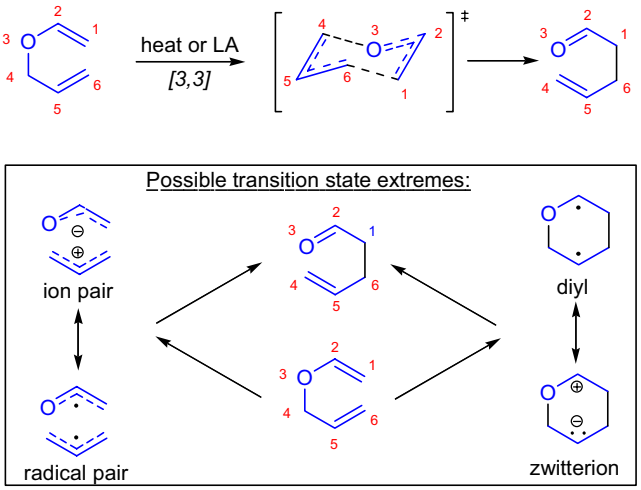
[*Seminal Publications*[1,2]; *Reviews*[3-32]; *Modifications & Variants*[33-48]; *Theoretical Studies*[49-55]]

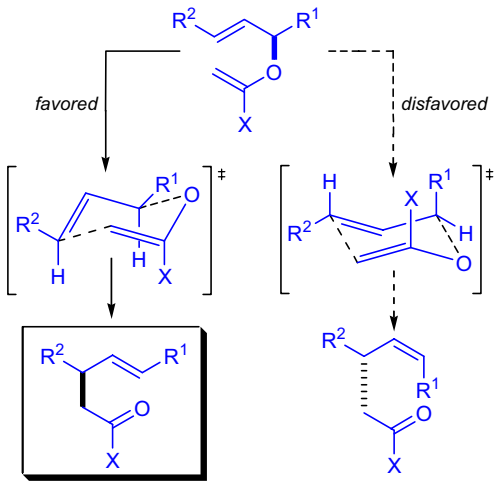
In 1912, L. Claisen described the rearrangement of allyl phenyl ethers to the corresponding *C*-allyl phenols and also described the transformation of *O*-allylated acetoacetic ester to its *C*-allylated isomer in the presence of ammonium chloride upon distillation.[1] Named after its discoverer, the thermal *[3,3]-sigmatropic rearrangement* of allyl vinyl ethers to the corresponding γ,δ-unsaturated carbonyl compounds is called the *Claisen rearrangement*. The allyl vinyl ethers can be prepared in several different ways: 1) from allylic alcohols by mercuric ion–catalyzed exchange with ethyl vinyl ether;[56,57] 2) from allylic alcohols and vinyl ethers by acid catalyzed exchange;[58,59] 3) thermal elimination;[60,61] 4) *Wittig olefination* of allyl formates and carbonyl compounds;[62,63] and 5) *Tebbe olefination* of unsaturated esters;[64,65]. It is usually not necessary to isolate the allyl vinyl ethers, since they are prepared under conditions that will induce their rearrangement.



Mechanism:[66,67,6,68-70,18,20,31]

Mechanistically the reaction can be described as a suprafacial, concerted, nonsynchronous *[3,3]-sigmatropic rearrangement*. The *Claisen rearrangement* is a unimolecular process with activation parameters (negative entropy and volume of activation) that suggest a constrained transition state.[20] Studies revealed that the stereochemical information is transferred from the double bonds to the newly formed σ-bond. Based on this observation, an early six-membered chairlike transition state is believed to be involved. There are several transition state extremes possible. The actual transition state depends on the nature of substituents at the various positions of the starting allyl vinyl ether. If a chiral allylic alcohol is used to prepare the starting allyl vinyl ether, then the chirality is transferred to the products; the stereoselectivity will depend on the energy difference between diastereomeric chairlike transition states. In acyclic systems, the observed stereoselectivity can usually be rationalized by assuming that the unfavorable 1,3-diaxial interactions are minimized in the chairlike transition state with the large groups adopting an equatorial position. When the geometry of the ring or other steric effects preclude or disfavor a chairlike structure, the reaction can proceed through a boatlike transition state.[71,72]

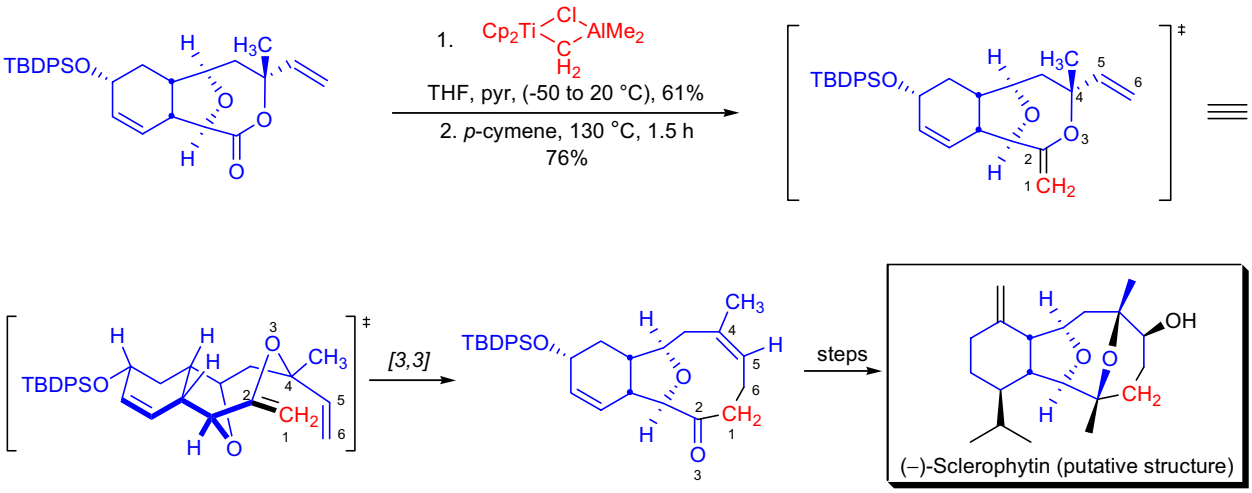




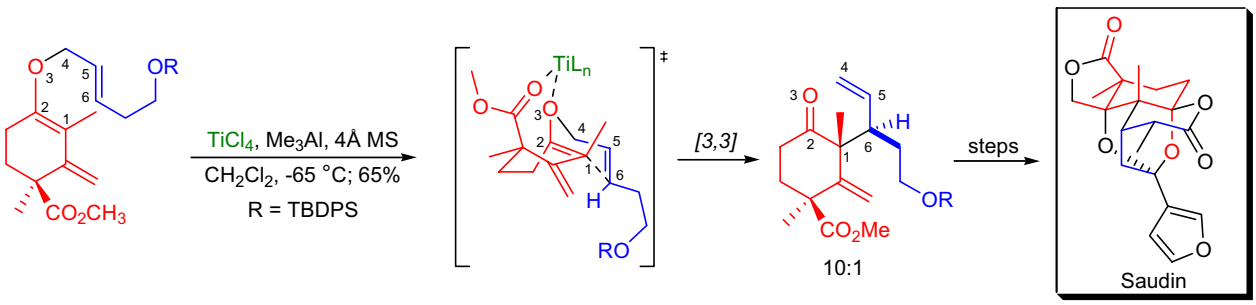
CLAISEN REARRANGEMENT

Synthetic Applications:

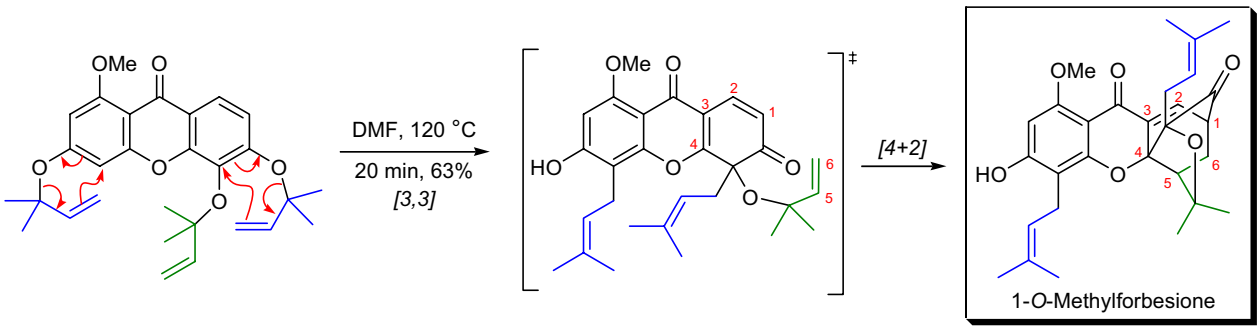
The asymmetric total synthesis of the putative structure of the cytotoxic diterpenoid (–)-sclerophytin A was realized *via* a *Tebbe-Claisen rearrangement* of a tricyclic lactone precursor in the laboratory of L.A. Paquette.[73] The tricyclic lactone was subjected to the *Tebbe methylenation* protocol to provide the allyl vinyl ether that was then heated to 130-140 °C in *p*-cymene to undergo the *Claisen rearrangement* in good yield.



In the enantioselective total synthesis of (+)- and (–)-saudin, the core of the synthetic strategy was a *Lewis acid mediated stereoselective Claisen rearrangement* to establish the correct relative stereochemistry between the C1 and C6 stereocenters.[74] R.K. Boeckman Jr. and co-workers had to overcome the stereochemical preference of the thermal rearrangement by using a bidentate Lewis acid promoter ($TiCl_4$) that coordinated to both the oxygen of the vinyl ether and the ester. This coordination enforced a boatlike conformation for the existing six-membered ring in the transition state. The rearrangement itself took place *via* a chairlike transition state.



In K.C. Nicolaou's biomimetic synthesis of 1-*O*-methylforbesione, the construction of the 4-oxatricyclo[4.3.1.0]decan-2-one framework was achieved by using a *double Claisen rearrangement* that was followed by an *intramolecular Diels-Alder reaction*.[75] This one-pot biomimetic *double Claisen rearrangement/intramolecular Diels-Alder reaction cascade* afforded the natural product in 63% yield.



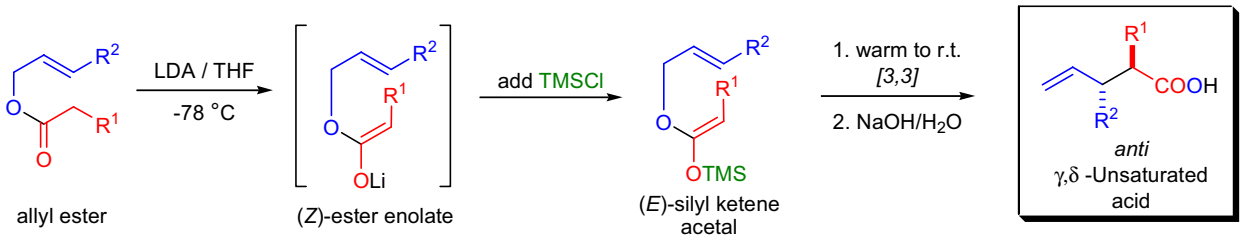
CLAISEN-IRELAND REARRANGEMENT

(References are on page 561)

Importance:

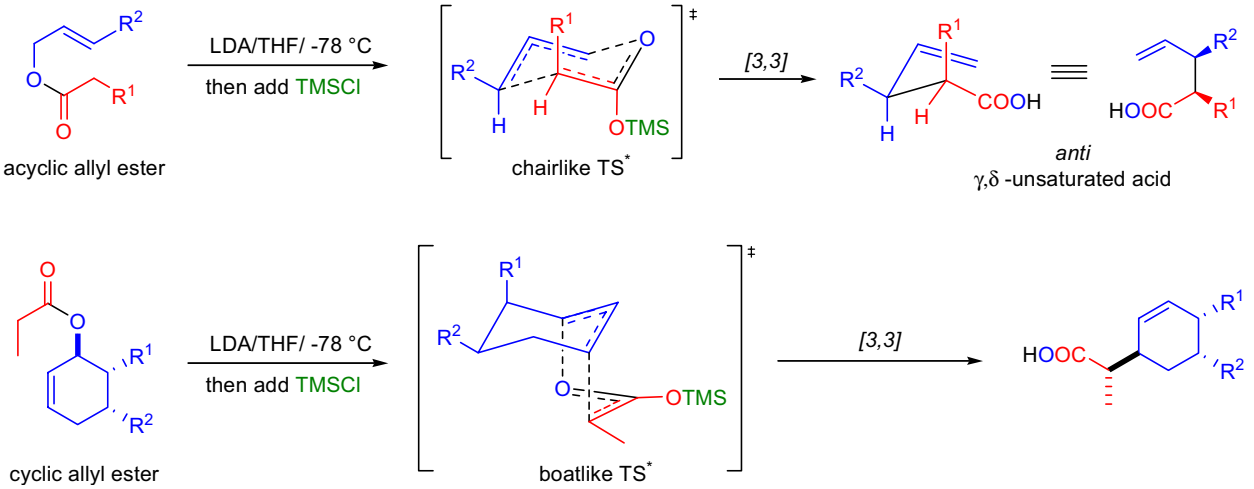
[*Seminal Publications*[1-8]*; Reviews*[9-20]*; Modifications & Improvements*[21-25]; *Theoretical Studies*[26]]

The *[3,3]-sigmatropic rearrangement* of *O*-trialkylsilylketene acetals to γ,δ-unsaturated carboxylic acids was first reported by R.E. Ireland in 1972, and it is referred to as the *Claisen-Ireland rearrangement* or *ester enolate Claisen rearrangement*.[6] Silylketene acetals are readily available by preparing the lithium enolate of allylic esters and trapping the enolate with a trialkylsilyl halide. The *Claisen-Ireland rearrangement* takes place under much milder conditions (room temperature and above) than the regular *Claisen rearrangement*. The ease of rearrangement is attributed to the highly nucleophilic enolate that generally accelerates sigmatropic processes (see *oxy-Cope rearrangement*). The reaction is very versatile, since it allows the assembly of highly functionalized structures. The conversion of a carbon-oxygen bond into a carbon-carbon bond affords a convenient way to assemble contiguous quaternary centers. Due to the highly ordered cyclic transition state, high levels of stereocontrol can be achieved. The high product stereoselectivities can be realized by efficient control of the ketene acetal geometry; deprotonation with LDA/THF leads to the kinetically favored (*Z*)-ester enolates, whereas the (*E*)-ester enolates are formed in the presence of THF/HMPA.[27,28] The rearrangement of the (*Z*)-ester enolates of (*E*)-allyl esters affords *anti*-products, whereas *syn*-products are obtained by the rearrangement of the (*E*)-ester enolates of (*E*)-allyl esters. The first asymmetric enantioselective version of the *Claisen-Ireland rearrangement* using a chiral boron reagent was reported by E.J. Corey et al.[21,23] It is also possible to achieve high levels of enantioselectivity by using chiral auxiliaries or chiral catalysts.[15,25]



Mechanism:[29,27,28,25]

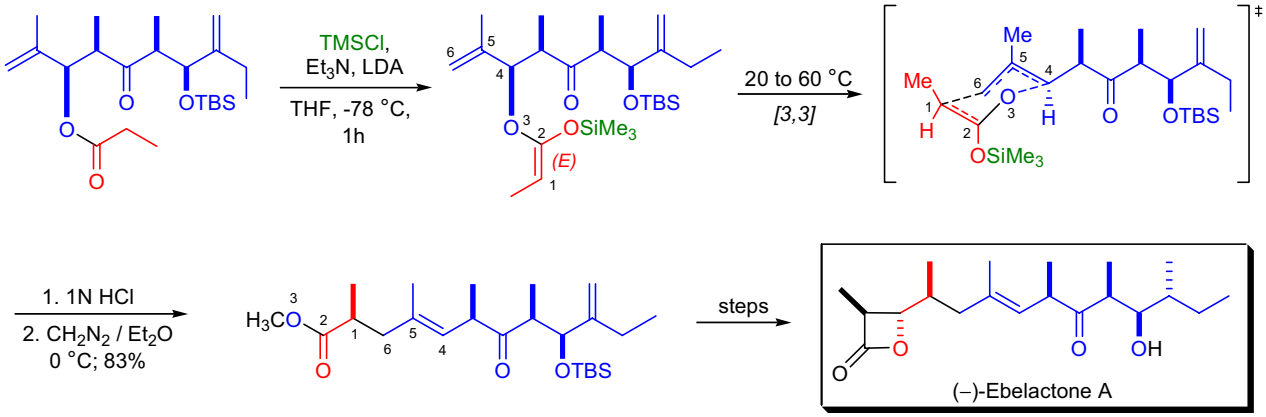
In acyclic systems the *Claisen-Ireland rearrangement* proceeds *via* a chairlike transition state (TS*). However, in cyclic systems conformational constraints can override the inherent preference for chairlike TS* and the boatlike TS* becomes dominant. One explanation for the preference of boatlike transition states in cyclic systems is the destabilizing steric interactions of the silyloxy substituent and the ring atoms in a chairlike TS*.



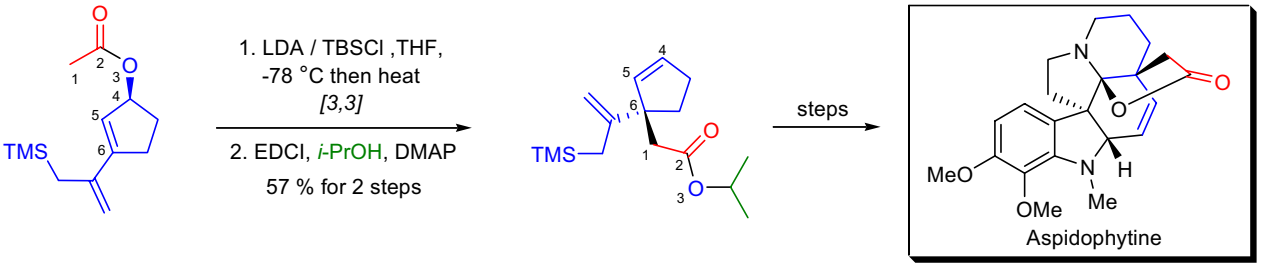
CLAISEN-IRELAND REARRANGEMENT

Synthetic Applications:

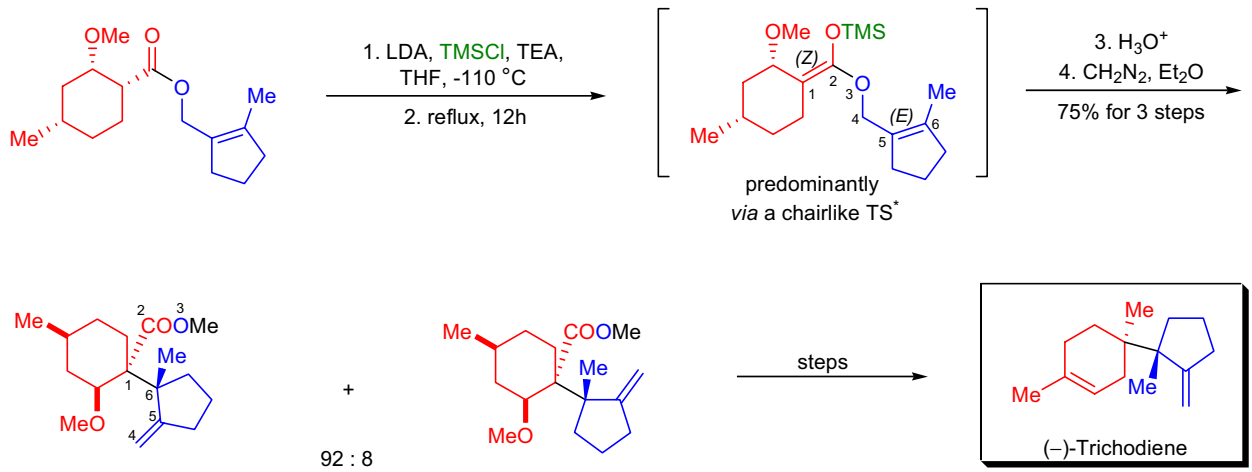
In the enantioselective total synthesis of β-lactone enzyme inhibitor (–)-ebelactone A and B, I. Paterson and co-workers constructed seven stereocenters and a trisubstituted alkene plus a very sensitive β-lactone ring.[30] The backbone of their strategy applied an *aldol reaction / Ireland-Claisen rearrangement* sequence and used minimal functional group manipulation. The *Ireland-Claisen rearrangement* was performed in the presence of an unprotected ketone moiety and set a precedent for this protocol. The diastereoselectivity was 96:4, indicating highly (*E*)-selective silylketene acetal formation.



It was nearly a quarter century after the structure determination of aspidophytine that its first convergent enantioselective total synthesis was accomplished in the laboratory of E.J. Corey.[31] The *Claisen-Ireland rearrangement* was used to construct one of the key intermediates.



The first chemical synthesis of an optically active trichodiene, (–)-trichodiene involved a *Claisen-Ireland rearrangement* as the key step to connect the vicinal quaternary centers.[32] J.C. Gilbert and co-workers found that the rearrangement occurred with complete facial selectivity and excellent diastereoselectivity to afford an advanced intermediate that was directly converted to (–)-trichodiene.



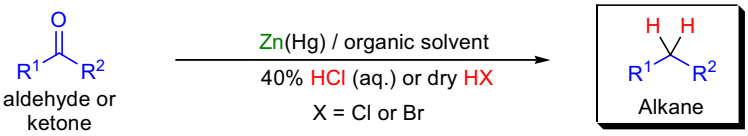
CLEMMENSEN REDUCTION

(References are on page 562)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-9]; *Modifications & Improvements*[10-13]]

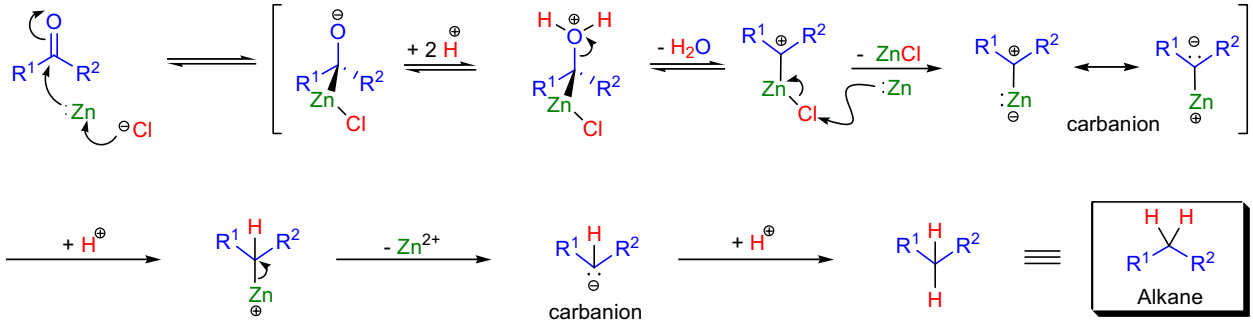
In 1913, E. Clemmensen reported that simple ketones and aldehydes were converted to the corresponding alkanes upon refluxing for several hours with 40% aqueous hydrochloric acid, amalgamated zinc (Zn/Hg), and a hydrophobic organic co-solvent such as toluene.[1] This method of converting a carbonyl group to the corresponding methylene group is known as the *Clemmensen reduction*. The original procedure is rather harsh so not surprisingly the *Clemmensen reduction* of acid-sensitive substrates and polyfunctional ketones is rarely successful in yielding the expected alkanes. The *Clemmensen reduction* has been widely used in synthesis and several modifications were developed to improve its synthetic utility by increasing the functional group tolerance. Yamamura and co-workers have developed a milder procedure which uses organic solvents (THF, Et_2O, Ac_2O, benzene) saturated with dry hydrogen-halides (HCl or HBr) and activated zinc dust at ice-bath temperature.[10-13] Compared to the original Clemmensen procedure[1] these modified reductions are complete within an hour at 0 °C and are appropriate for acid- and heat-sensitive compounds. Certain carbonyl compounds, however, have very low solubility in the usual solvents used for the *Clemmensen reduction*, so in these cases a second solvent (acetic acid, ethanol, or dioxane) is added to the reaction mixture to increase the solubility of the substrate and allow the reduction to take place. The *Clemmensen reduction* of polyfunctional ketones such as 1,2-, 1,3-, 1,4-, 1,5-diketones, α,β-unsaturated ketones and ketones with α-heteroatom substituents is less straightforward than the reduction of monofunctional substrates.[6] Usually complex mixtures are formed in these reactions, which contain a substantial amount of rearranged products.



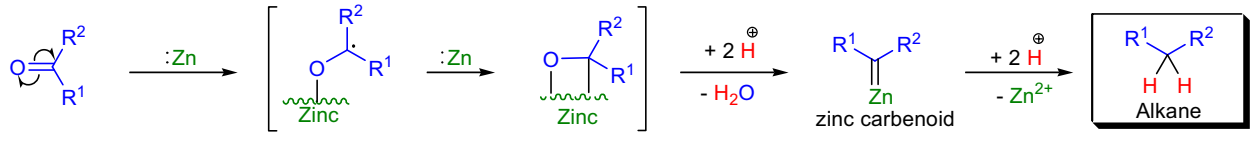
Mechanism:[14-20,6,21-25,8,26,27]

The mechanism of the *Clemmensen reduction* is not well understood. The lack of a unifying mechanism can be explained by the fact that the products formed in the various reductions are different when the reaction conditions (e.g., concentration of the acid, concentration of zinc in the amalgam) are changed. It was shown that the reduction occurs with zinc but not with other metals of comparable reduction potential. The early mechanistic papers came to the conclusion that the *Clemmensen reduction* occurs stepwise involving organozinc intermediates.[15-17] It was also established that simple aliphatic alcohols are not intermediates of these reductions, since they do not give alkanes under the usual Clemmensen conditions. However, allylic and benzylic alcohols undergo the *Clemmensen reduction*.[14,21] Currently, there are two proposed mechanisms for the *Clemmensen reduction*, and they are somewhat contradictory. In one of the mechanisms the rate determining step involves the attack of zinc and chloride ion on the carbonyl group[17] and the key intermediates are carbanions, whereas in the other heterogeneous process, the formation of a radical intermediate and then a zinc carbenoid species is proposed.[20,22]

Carbanionic mechanism:



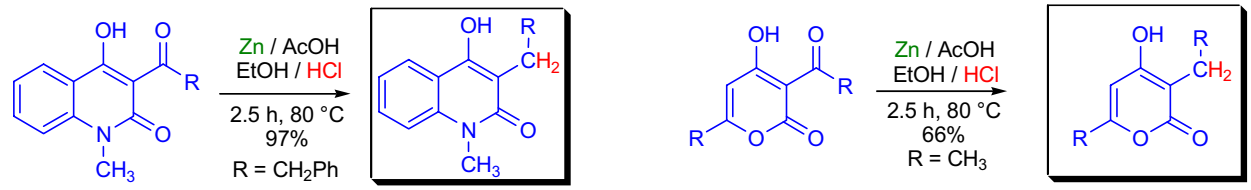
Carbenoid mechanism:



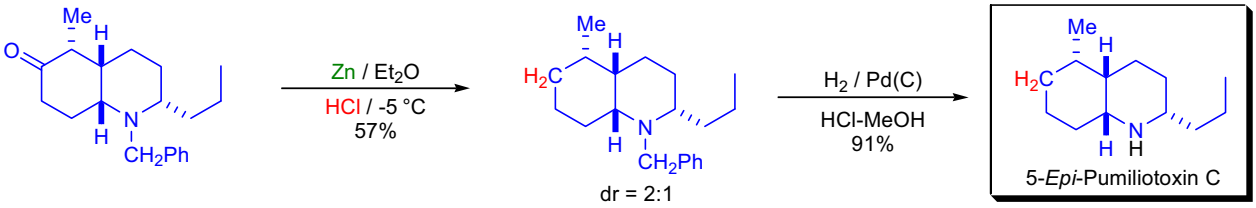
CLEMMENSEN REDUCTION

Synthetic Applications:

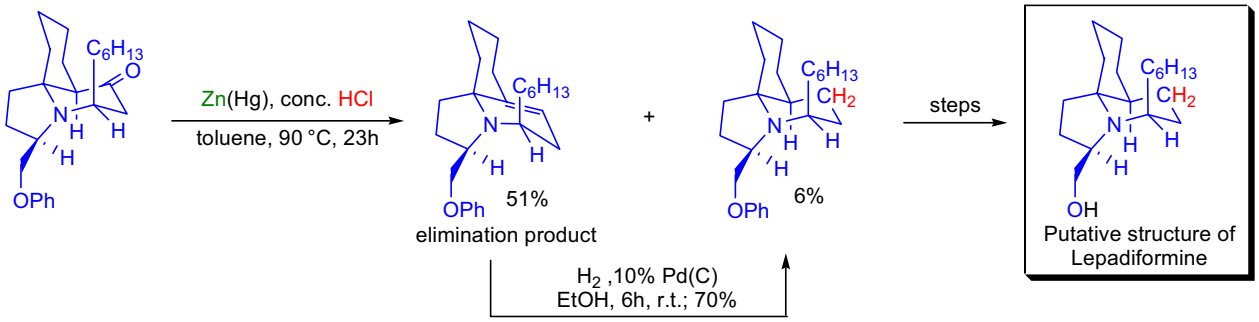
Numerous heterocyclic 1,3-dicarbonyl compounds possessing alkyl substituents at the electronegative 2-position exhibit interesting biological properties. The synthesis of these compounds is either cumbersome or calls for expensive starting materials. T. Kappe and co-workers have found a simple and effective method for the reduction of acyl substituted 1,3-dicarbonyl compounds to the corresponding alkyl derivatives.[28] For example, 3-acyl-4-hydroxy-2(1H)-quinolones and 3-acyl-4-hydroxy-6-methypyran-2-ones were reduced in good yields to 3-alkyl-4-hydroxy-2(1H)-quinolinones and 3-alkyl-4-hydroxy-6-methylpyran-2-ones, respectively, using zinc powder in acetic acid/hydrochloric acid.



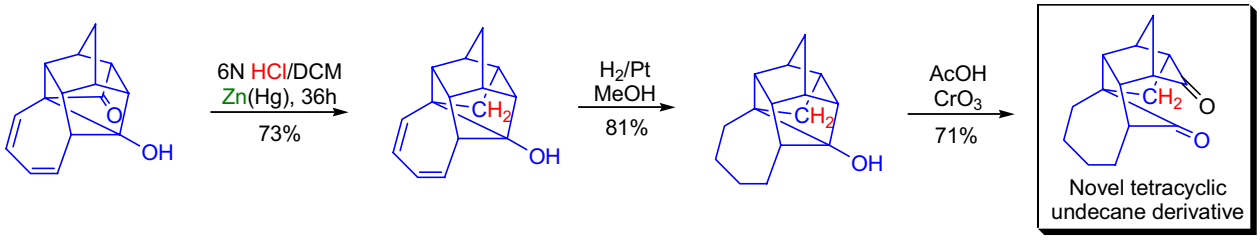
During the enantioselective total synthesis of denrobatid alkaloid (–)-pumiliotoxin C by C. Kibayashi et al., an aqueous *acylnitroso Diels-Alder cycloaddition* was used as the key step.[29] In the endgame of the total synthesis, the *cis*-fused decahydroquinolone was subjected to the *Clemmensen reduction* conditions to give a 2:1 epimeric mixture of deoxygenated products in 57% yield. Subsequent debenzylation converted the major isomer into 5-*epi*-pumiliotoxin C.



S.M. Weinreb and co-workers were surprised to find that the convergent stereoselective synthesis of marine alkaloid lepadiformine resulted in a product that gave a totally different NMR spectra than the natural product.[30] This finding led to the revision of the proposed structure of lepadiformine. In the final stages of the synthesis, they exposed a tricyclic piperidone intermediate to *Clemmensen conditions* to remove the ketone functionality. Under these conditions the otherwise minor elimination product (alkene) was formed predominantly; however, it was possible to hydrogenate the double bond to give the desired alkane.



In the laboratory of F.J.C. Martins the synthesis of novel tetracyclic undecane derivatives was undertaken. In one of the synthetic sequences the *Clemmensen reduction* was used to remove a ketone functionality in good yield.[31]



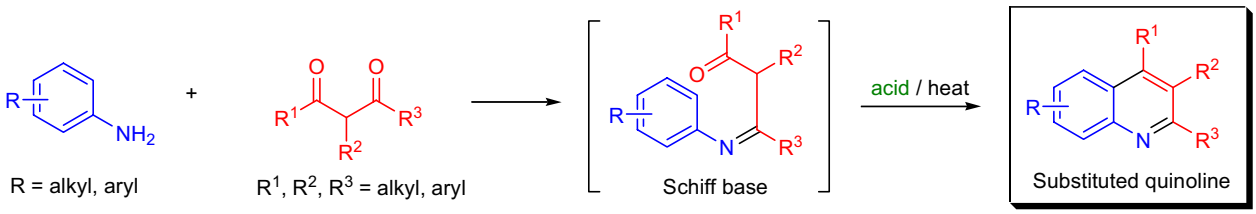
COMBES QUINOLINE SYNTHESIS

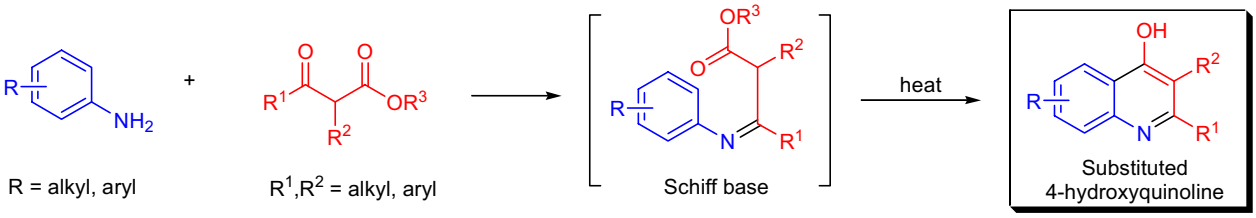
(References are on page 563)

Importance:

[*Seminal Publication*[1]*; Reviews*[2-4]*; Modifications & Improvements*[5]]

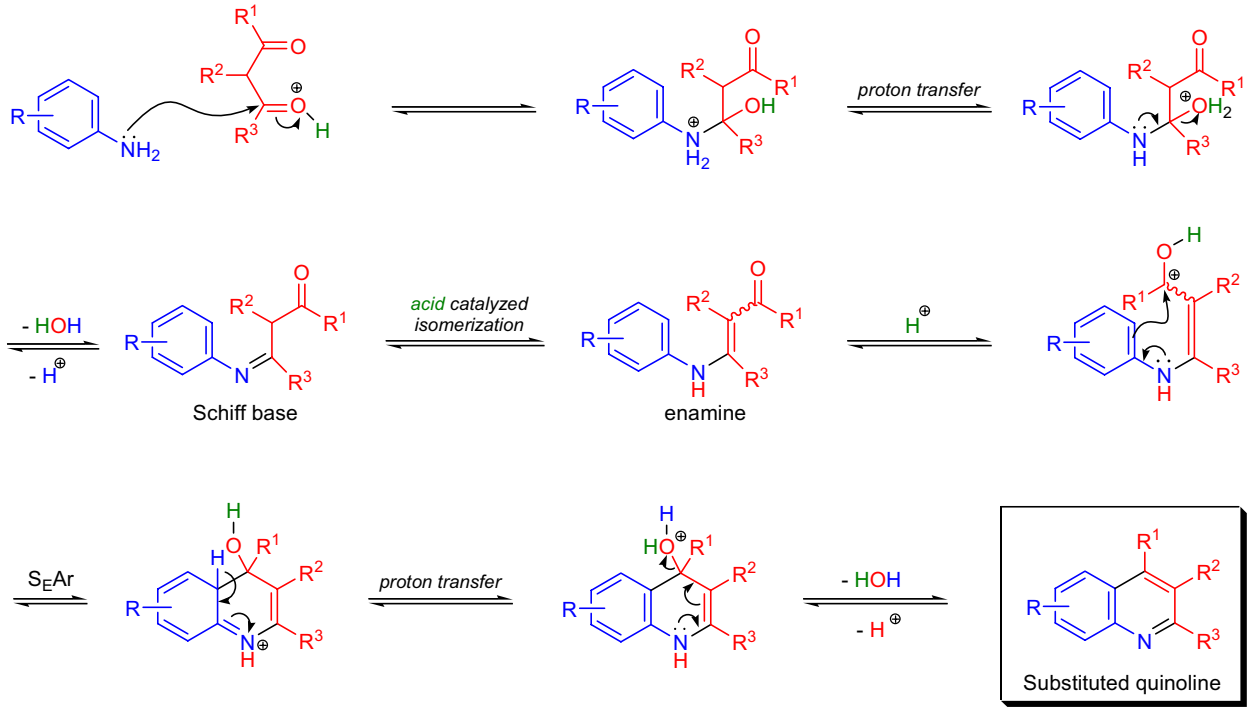
The formation of quinolines and benzoquinolines by the condensation of primary aryl amines with β-diketones followed by an acid catalyzed ring closure of the Schiff base intermediate is known as the *Combes quinoline synthesis*. The closely related reaction of primary aryl amines with β-ketoesters followed by the cyclization of the Schiff base intermediate is called the *Conrad-Limpach reaction* and it gives 4-hydroxyquinolines as products.[6-8]





Mechanism:[9]

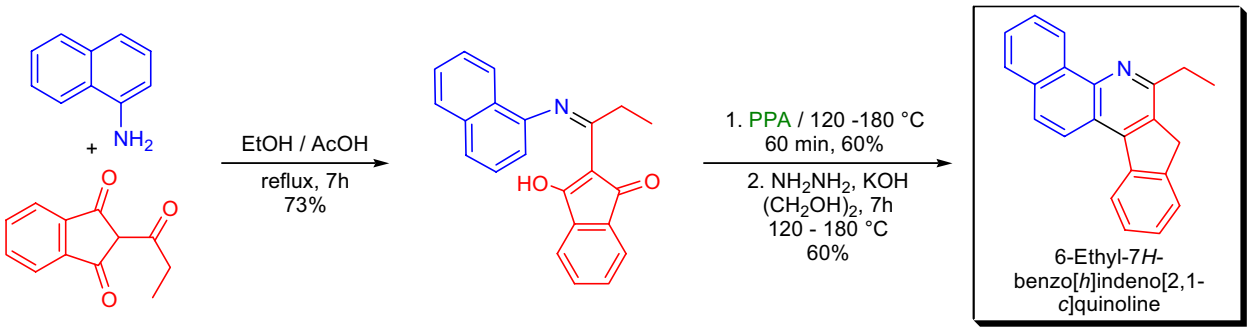
The first step in the *Combes reaction* is the acid-catalyzed condensation of the diketone with the aromatic amine to form a Schiff base (imine), which then isomerizes to the corresponding enamine. In the second step, the carbonyl oxygen atom of the enamine is protonated to give a carbocation that undergoes an electrophilic aromatic substitution. Subsequent proton transfer, elimination of water and deprotonation of the ring nitrogen atom gives rise to the neutral substituted quinoline system.



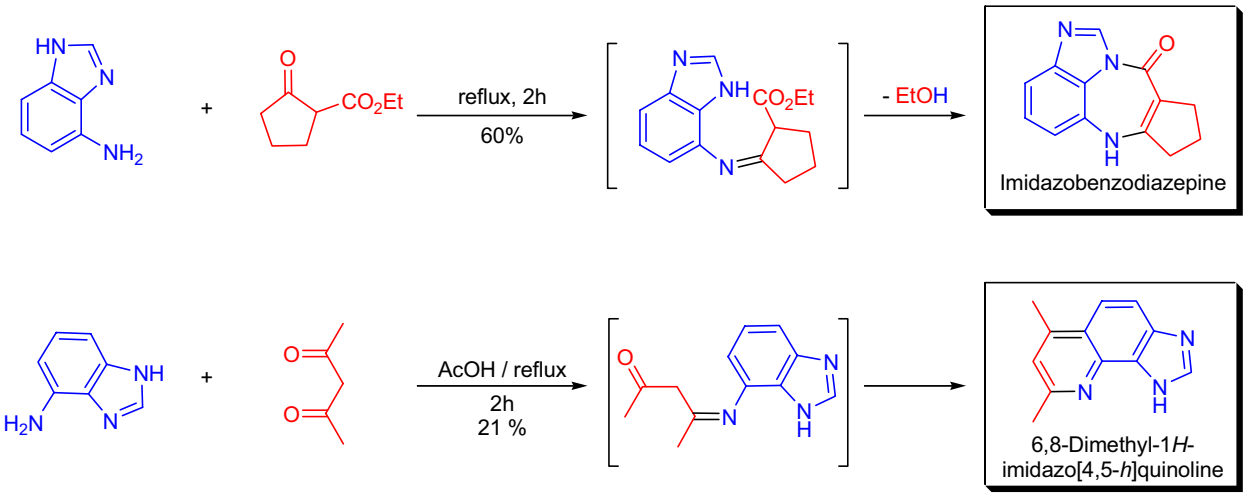
COMBES QUINOLINE SYNTHESIS

Synthetic Applications:

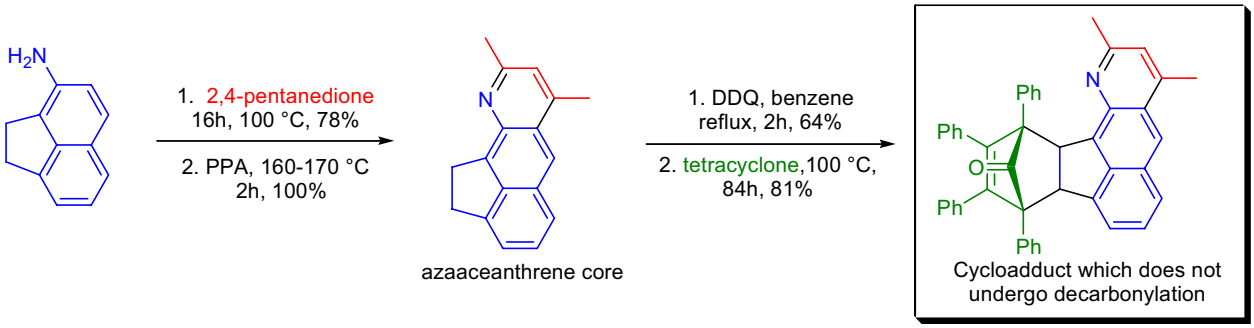
In the laboratory of S. Gupta, the synthesis of novel heterocyclic ring systems was accomplished utilizing the *Combes reaction.*[10] The condensation of 1-naphthylamine with 2-acylindan-1,3-diones produced the corresponding anils in good yield. The anils were cyclodehydrated to benz[*h*]indeno[2,1-*c*]quinoline-7-ones in the presence of polyphosphoric acid. Subsequent *Wolff-Kishner reduction* gave rise to the novel 7*H*-benzo[*h*]indeno[2,1-*c*]quinolines.



During a study of the reactivity of 4(7)-aminobenzimidazole as a bidentate nucleophile, C. Avendano and co-workers obtained 7*H*-imidazo[1,5,4-*e*,*f*][1,5]benzodiazepine-4-ones by using β-ketoesters as electrophiles.[11] The reactions were regioselective and took place with equimolar amounts of the β-ketoesters without the use of a catalyst. Isolated yields were around 50%. However, when the benzimidazole was treated with 2,4-pentanedione in a 1:5 ratio in the presence of an acid catalyst, an 1*H*-imidazo[4,5-*h*]quinoline was formed and no traces of imidazobenzodiazepines were observed.



In the attempted synthesis of twisted polycycle 1,2,3,4-tetraphenylfluoreno[1,9-*gh*]quinoline, R.A. Pascal Jr. et al. used the *Combes quinoline synthesis* to assemble the azaaceanthrene core.[12] Oxidation with DDQ was followed by a Diels-Alder reaction with tetracyclone (tetraphenylcyclopentadienone) to afford the corresponding cycloadduct. However, the last decarbonylation step of the sequence failed to work even under forcing conditions, presumably due to steric hindrance.



COPE ELIMINATION / COPE REACTION

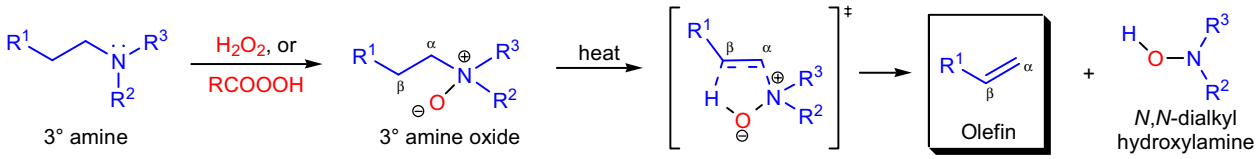
(References are on page 563)

Importance:

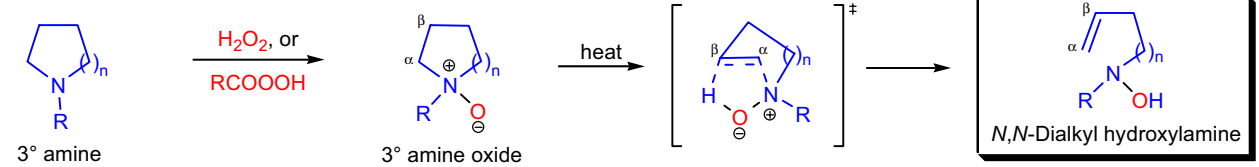
[*Seminal Publications*[1-3]*; Reviews*[4-6]*; Modifcations & Improvements*[7-11]*; Theoretical Studies*[12,13]]

In 1949, A.C. Cope and co-workers discovered that by heating trialkylamine-*N*-oxides having hydrogens in the β-position, an olefin and *N,N*-dialkylhydroxylamine are formed.[1] The transformation involving the stereoselective *syn* elimination of tertiary amine oxides is now referred to as the *Cope elimination* or *Cope reaction*. The substrates, tertiary amine oxides, are easily prepared by the oxidation of the corresponding tertiary amine with hydrogen peroxide or peroxycarboxylic acids such as *m*CPBA. Isolation of the *N*-oxides is usually not necessary; the amine is mixed with the oxidizing agent and heated. Amine oxides are very polar compounds and the oxygen serves as a base to remove the β-hydrogen atom via a *syn* conformation. The synthetic utility of the *Cope elimination* is comparable to the *Hofmann elimination* of quaternary ammonium hydroxides, but it takes place at lower temperatures (100-150 °C). The *Cope elimination* is almost free of side reactions due to the intramolecular nature of the elimination (the base is part of the molecule). However, in certain cases, the product alkene may isomerize[14] to the more stable conjugated system, and allyl- or benzyl migration[2] is sometimes observed to give O-allyl or benzyl-substituted hydroxylamines. Cyclic amine oxides (5, 7-10-membered rings, where the nitrogen is part of the ring) can also be pyrolysed but with 6-membered rings the reaction is usually low-yielding or does not occur.[15,16] The direction of the *Cope elimination* is governed almost entirely by the number of hydrogen atoms at the various β-positions, and therefore there is no preference for the formation of the least substituted alkene unlike in the *Hofmann elimination* reaction. Upon pyrolysis, *N*-cycloalkyl-substituted amine oxides give mainly the thermodynamically more stable endocyclic olefins. Cyclohexyl derivatives, however, form predominantly exocyclic olefins, since the formation of the endocyclic double bond would require the cyclohexane ring to be almost planar in the transition state.

Acyclic systems:

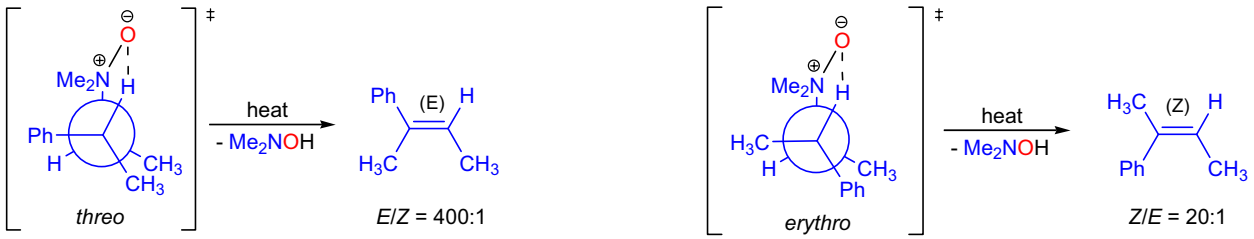


Cyclic systems:



Mechanism:[17,16,5,18-21]

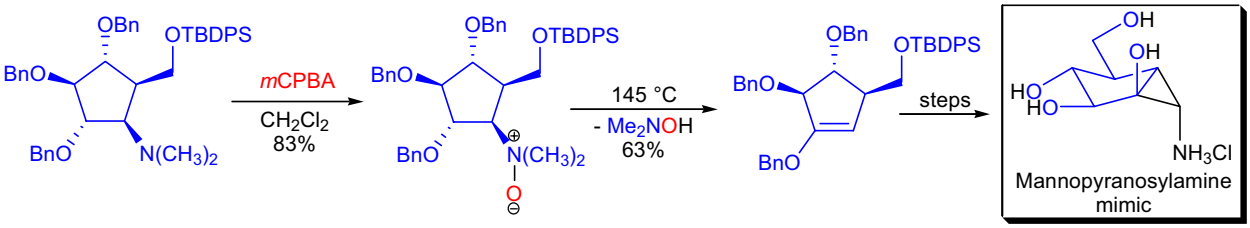
The *Cope elimination* is a stereoselective *syn* elimination and the mechanism involves a planar 5-membered cyclic transition state. There is strong resemblance to the mechanism of *ester pyrolysis* and the *Chugaev elimination*. The first evidence of the stereochemistry of the elimination was the thermal decomposition of the *threo* and *erythro* derivatives of *N,N*-dimethyl-2-amino-3-phenylbutane.[17] The *erythro* isomer gives predominantly the *(Z)*-alkene (20:1), while the *threo* isomer forms the (*E)*-olefin almost exclusively (400:1). Two decades later deuterium-labeling evidence confirmed the mechanism of the *Cope elimination* to be 100% *syn*.[18]



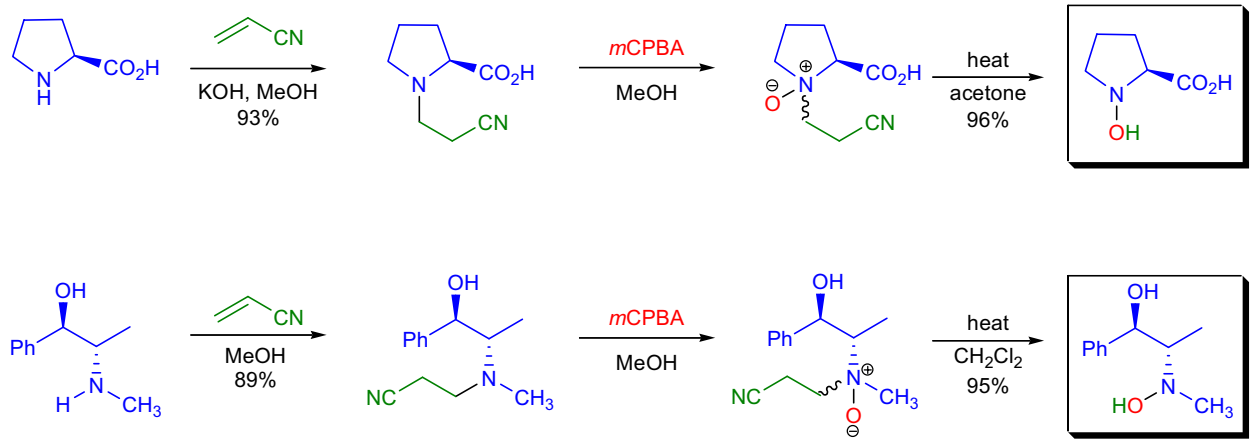
COPE ELIMINATION / COPE REACTION

Synthetic Applications:

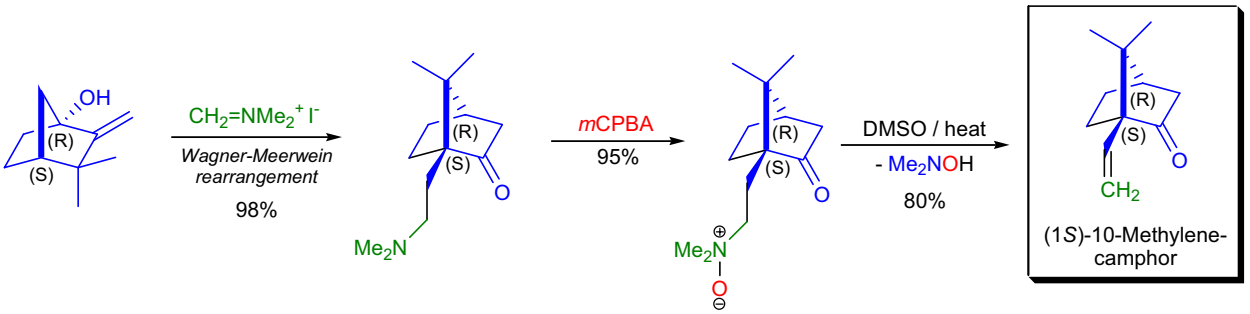
In their search for conformationally biased mimics of mannopyranosylamines, A. Vasella and co-workers planned to synthesize compounds that would inhibit β-mannosidases.[22] In order to construct the bicyclo[3.1.0]hexane framework, a five-membered *O*-silylated *N*,*N*-dimethyl-amino alcohol was synthesized. Oxidation of the tertiary amine with *m*CPBA yielded 83% of the *N*-oxide, which was subsequently subjected to the *Cope elimination* to give 69% of the desired benzyl enol ether. Cyclopropanation of this enol ether gave rise to the highly functionalized bicyclic skeleton.



A convenient synthesis of secondary hydroxylamines using secondary amines as starting material was developed in the laboratory of I.A. O'Neil.[10] Secondary amines were treated with a Michael acceptor such as acrylonitrile in methanol to give tertiary β-cyanoethyl amines in excellent yield. These tertiary amines were then oxidized with *m*CPBA to give the corresponding *N*-oxides, which underwent the *Cope elimination in situ* to generate the hydroxylamine in excellent yield. The great advantage of this method is that it works for both cyclic and acyclic systems.



A new enantiospecific synthesis of taxoid intermediate (1*S*)-10-methylenecamphor was described by A.G. Martinez utilizing the *Cope elimination* to generate the vinyl group at the bridgehead norbornane position.[23] (1*R*)-3,3-Dimethyl-2-methylenenorbornan-1-ol was treated with Eschenmoser's salt, to initiate a tandem *electrophilic carbon-carbon double bond addition*/*Wagner-Meerwein rearrangement* to give (1*S*)-10-dimethylaminomethylcamphor. This tertiary amine was oxidized to the corresponding *N*-oxide in 95% yield, and subsequent *Cope elimination* gave the desired taxoid intermediate in 80% yield.



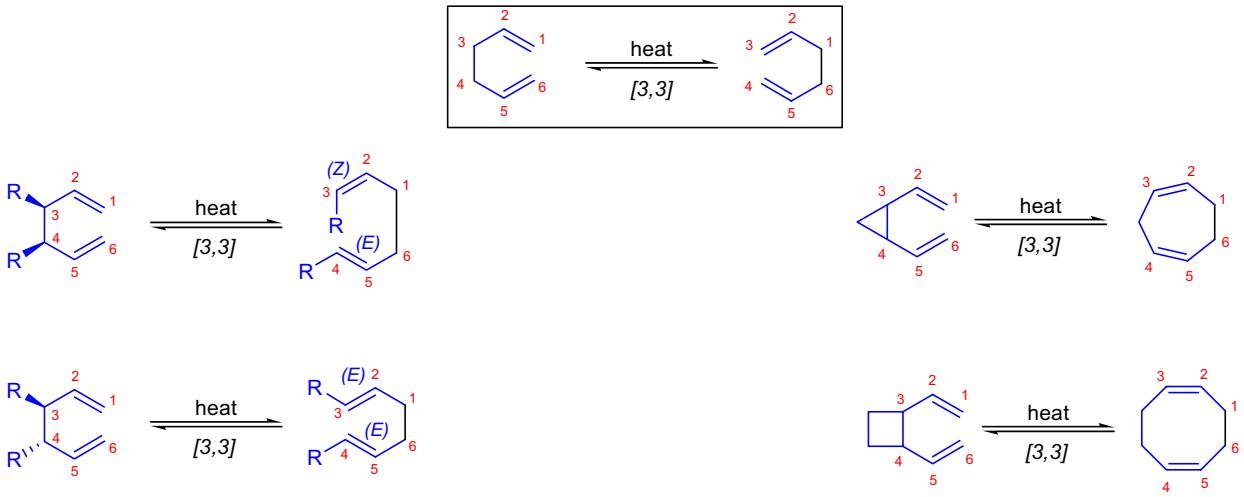
COPE REARRANGEMENT

(References are on page 564)

Importance:

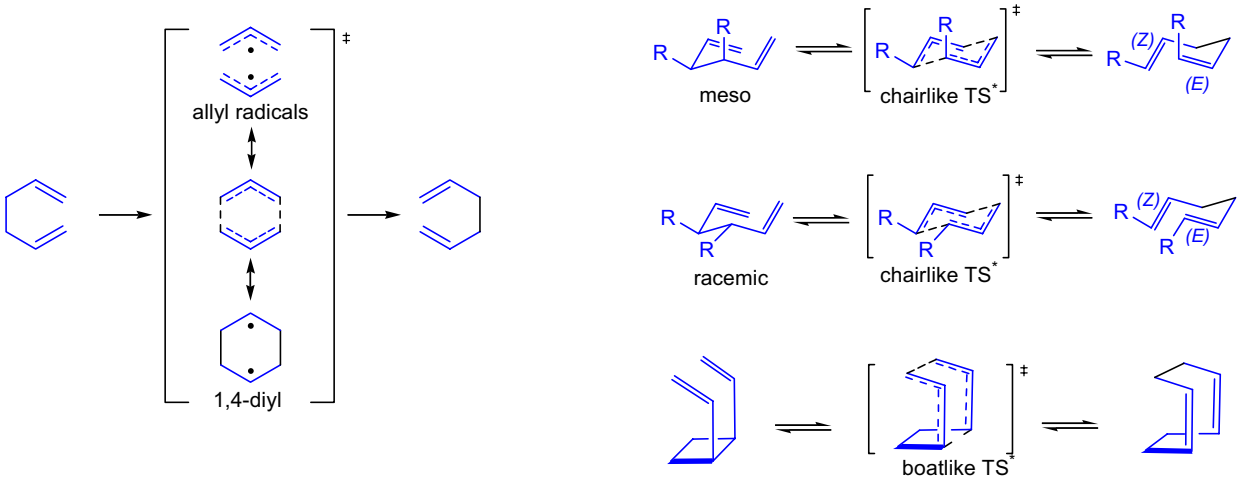
[*Seminal Publications*[1]; *Reviews*[2-14]; *Theoretical Studies*[15-28]]

In 1940, A.C. Cope observed the rearrangement of (1-methylpropenyl)allylcyanoacetate into the isomeric (1,2-dimethyl)-4-pentylidinecyanoacetate upon distillation, and he recognized that this rearrangement was similar in type to the known *Claisen rearrangement*.[1] The thermal *[3,3]-sigmatropic rearrangement* of 1,5-dienes to the isomeric 1,5-dienes is called the *Cope rearrangement*, and it can only be detected when the 1,5-diene substrate is substituted. The rearrangement is reversible because there are no changes in the number or types of bonds, and the position of the equilibrium is determined by the relative stability of the starting material and the product. When the product is stabilized by conjugation or the resulting double bond is more highly substituted, the equilibrium will be shifted toward the formation of the product. The reaction is both stereospecific and stereoselective as a result of a cyclic chairlike transition state. The typical temperature required to induce *Cope rearrangement* in acyclic dienes is 150-260 °C. The required temperature is significantly lower (room temp. or below) when: 1) the dienes are substituted in positions C3 or C4; 2) the dienes are cyclic and ring strain is relieved; or 3) the *Cope rearrangement* is catalyzed by transition metal complexes.[4] The *Cope rearrangement* of strained 1,2-divinyl cycloalkanes (cyclopropane and cyclobutane) gives convenient access to synthetically useful seven- and eight-membered carbocycles.



Mechanism:[29-43]

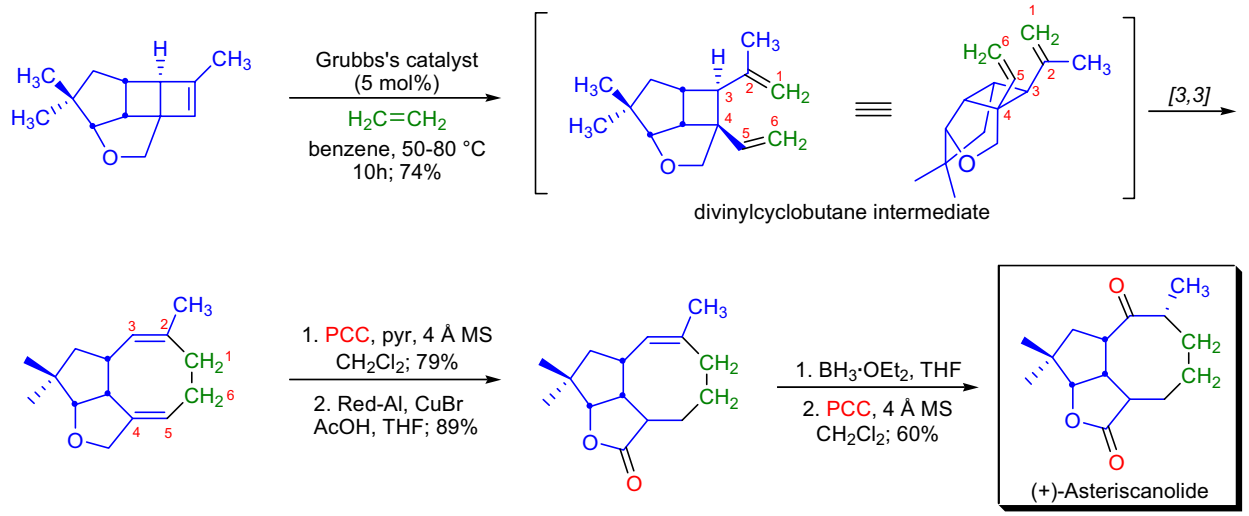
Soon after its discovery, the *Cope rearrangement* was investigated in great detail in order to establish its mechanism. In the classical sense, *[3,3] sigmatropic rearrangements* do not have observable intermediates. Therefore, in the 1960s these rearrangements were dubbed “no mechanism reactions”.[29] The *Cope rearrangement* predominantly proceeds *via* a chairlike transition state where there is minimal steric interaction between the substituents.[29,32] The exact nature of the transition state depends on the substituents and varies between two extreme forms: from two independent allyl radicals to a cyclohexane-1,4-diradical depending on whether the bond making or bond breaking is more advanced. In most cases the reactions are concerted with a relatively late transition state where the bond between C1 and C6 is well-developed.



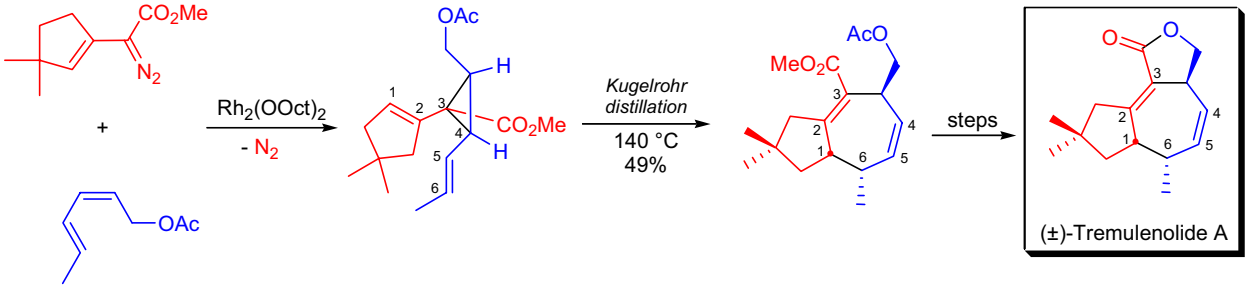
COPE REARRANGEMENT

Synthetic Applications:

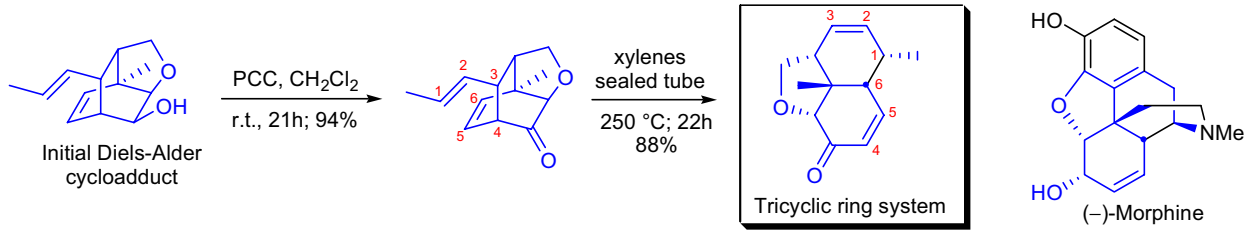
The enantioselective total synthesis of (+)- and (–)-asteriscanolide was accomplished in the laboratory of M.L. Snapper utilizing a sequential *intramolecular cyclobutadiene cycloaddition*, *ring-opening metathesis* and *Cope rearrangement*.[44] The key cycloadduct was treated with Grubbs's catalyst under an ethylene atmosphere to generate a divinylcyclobutane intermediate in a selective *ring-opening metathesis* of a strained trisubstituted cyclobutene. The divinylcyclobutane intermediate subsequently underwent a facile *Cope rearrangement* under mild conditions to afford the 8-membered carbocycle of (+)-asteriscanolide.



The Cope rearrangement of a divinylcyclopropane intermediate was the key step in the total synthesis of (±)-tremulenolide A by H.M.L. Davies et al.[45] The divinylcyclopropane intermediate was obtained by a Rh-*catalyzed stereoselective cyclopropanation* of a hexadiene. Usually the *Cope rearrangement* of divinylcyclopropanes occurs at or below room temperature, In this case, a congested boat transition state was required for the rearrangement so forcing conditions were necessary. The product cycloheptadiene was obtained by Kugelrohr distillation at 140 °C as a single regioisomer in 49% yield.



A tricyclic ring system containing all the stereogenic centers of the nonaromatic portion of (–)-morphine was prepared by T. Hudlicky and co-workers using an *intramolecular Diels-Alder cycloaddition* followed by a *Cope rearrangement*.[46] Interestingly, the initial Diels-Alder cycloadduct did not undergo the *Cope rearrangement* even under forcing conditions. However, when the hydroxyl group was oxidized to the corresponding ketone, the *[3,3]*-sigmatropic shift took place at 250 °C in a sealed tube. The driving force of the reaction was the formation of an α,β-unsaturated ketone.



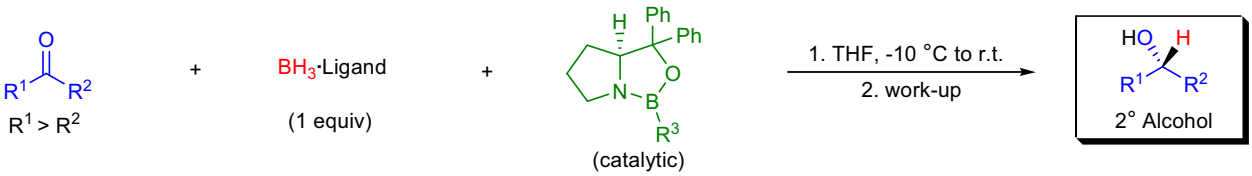
COREY-BAKSHI-SHIBATA REDUCTION (CBS REDUCTION)

(References are on page 565)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-12]*; Modifications & Improvements*[13,14]*; Theoretical Studies*[15-23]]

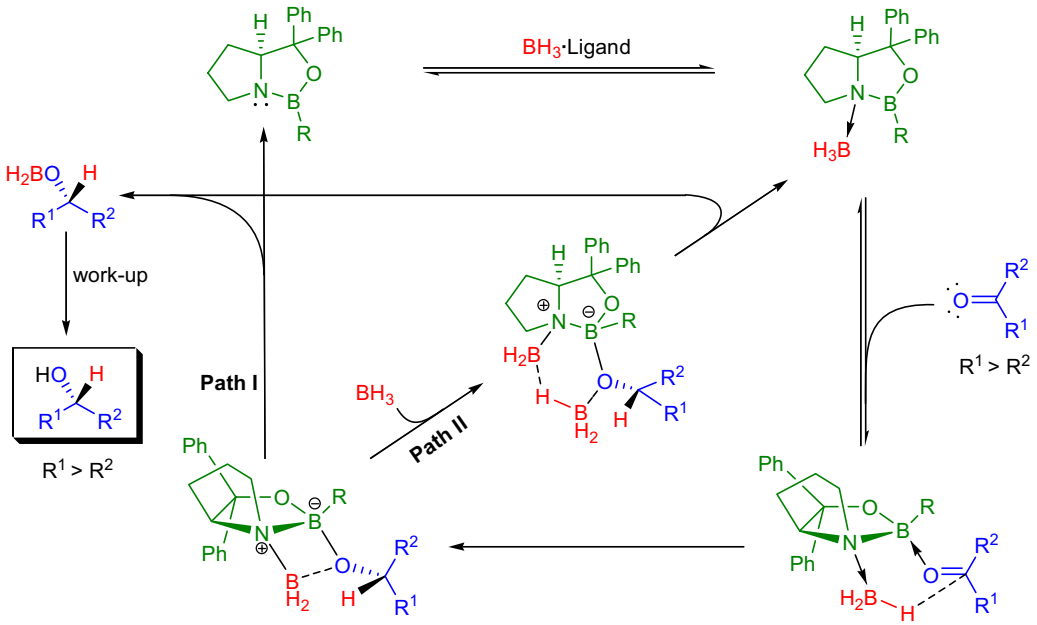
In 1981, S. Itsuno and co-workers were the first to report that stoichiometric mixtures of chiral amino alcohols and borane-tetrahydrofuran complex (BH_3·THF) reduced achiral ketones to the corresponding chiral secondary alcohols enantioselectively and in high yield.[1] Several years later, E.J. Corey and co-workers showed that the reaction of borane (BH_3) and chiral amino alcohols leads to the formation of oxazaborolidines, which were found to catalyze the rapid and highly enantioselective reduction of achiral ketones in the presence of BH_3·THF.[2,3] The enantioselective reduction of ketones using catalytic oxazaborolidine is called the *Corey-Bakshi-Shibata reduction* or *CBS reduction*. Research in the Corey group showed that the methyl-substituted oxazaborolidines (*B*-Me) were more stable and easier to prepare than the extremely air and moisture-sensitive original *B*-H analogs. The systematic study of oxazaborolidine-catalyzed reductions revealed that high enantiomeric excess (*ee*) is achieved when the oxazaborolidine has a rigid bicyclic (proline based) or tricyclic structure. More flexible ring systems resulted in lower enantioselectivities. The advantages of the CBS catalysts are: 1) ease of preparation; 2) air and moisture stability; 3) short reaction times (high catalyst turnover); 4) high enantioselectivity; 5) typically high yields; 6) recovery of catalyst precursor by precipitation as the HCl salt; and 7) prediction of the absolute configuration from the relative steric bulk of the two substituents attached to the carbonyl group.



R^{1-2} = alkyl, aryl; Ligand: THF, Me_2S, 1,4-thioxane, diethylaniline; R^3 = H, alkyl

Mechanism: [2-4,24-27]

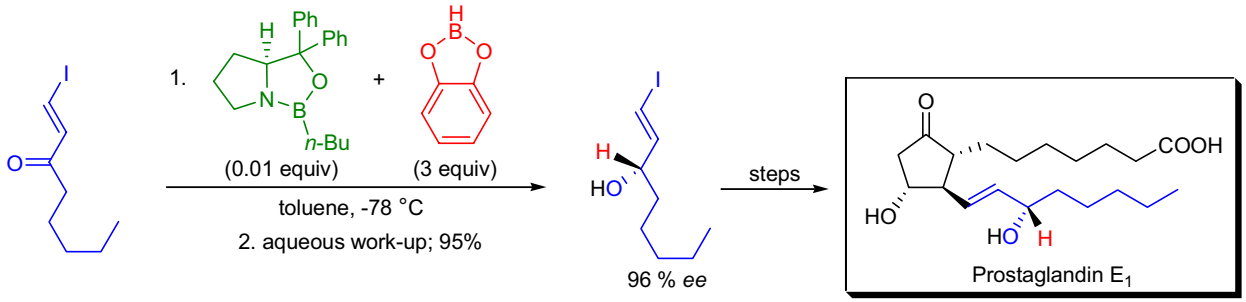
The first step of the mechanism is the coordination of BH_3 (Lewis acid) to the tertiary nitrogen atom (Lewis base) of the CBS catalyst from the -face.[27] This coordination enhances the Lewis acidity of the endocyclic boron atom and activates the BH_3 to become a strong hydride donor. The CBS catalyst-borane complex then binds to the ketone at the sterically more accessible lone pair (the lone pair closer to the smaller substituent) *via* the endocyclic boron atom. At this point the ketone and the coordinated borane in the vicinal position are *cis* to each other and the unfavorable steric interactions between the ketone and the CBS catalyst are minimal. The face-selective hydride transfer takes place *via* a six-membered transition state.[24,26] The last step (regeneration of the catalyst) may take place by two different pathways (**Path I** or **II**).[25,19,21]



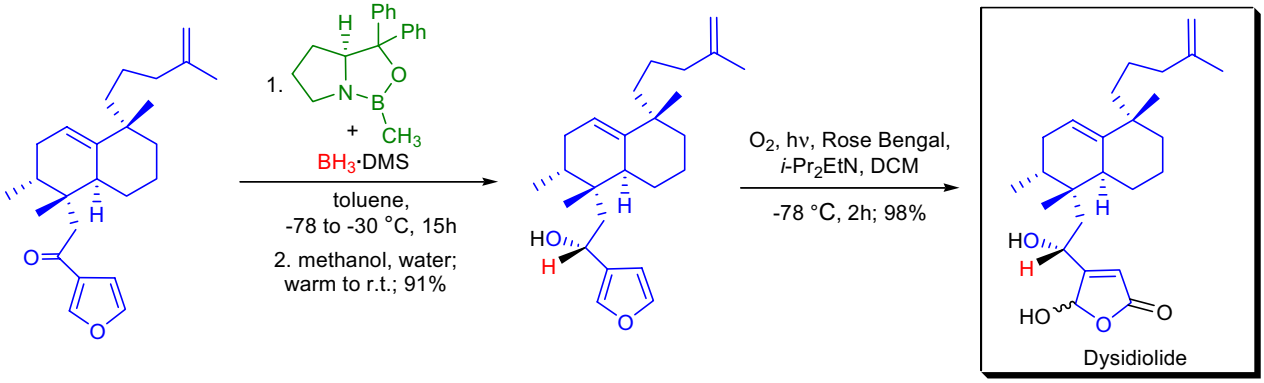
COREY-BAKSHI-SHIBATA REDUCTION (CBS REDUCTION)

Synthetic Applications:

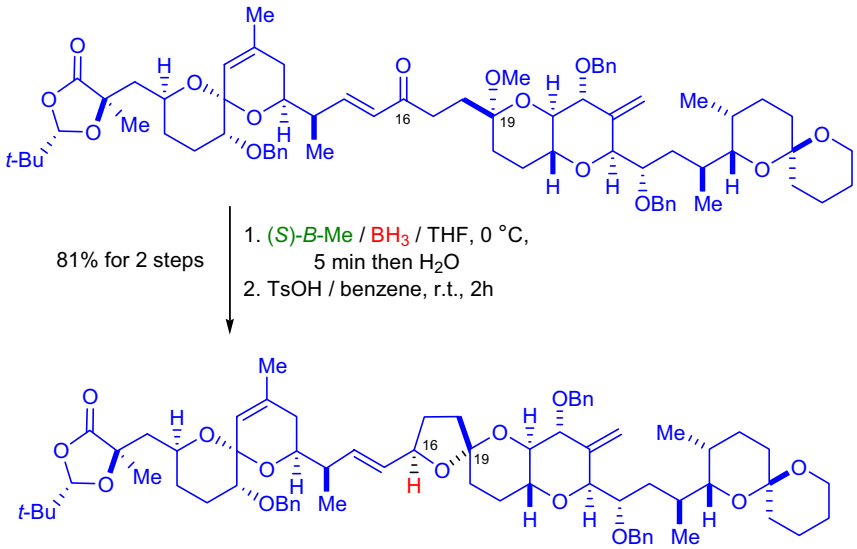
The asymmetric total synthesis of prostaglandin E_1 utilizing a *two-component coupling process* was achieved in the laboratory of B.W. Spur.[28] The hydroxylated side-chain of the target was prepared *via* the *catalytic asymmetric reduction* of a γ-iodo vinyl ketone with catecholborane in the presence of Corey's CBS catalyst. The reduction proceeded in 95% yield and >96% *ee*. The best results were obtained at low temperature and with the use of the *B*-*n*-butyl catalyst. The *B*-methyl catalyst afforded lower enantiomeric excess and at higher temperatures the *ee* dropped due to competing non-catalyzed reduction.



E.J. Corey and co-workers synthesized the cdc25A protein phosphatase inhibitor dysidiolide enantioselectively.[29] In the last phase of the total synthesis, the secondary alcohol functionality of the side-chain was established with a highly diastereoselective *oxazaborolidine-catalyzed reduction* using borane-dimethylsulfide complex in the presence of the (*S*)-*B*-methyl CBS catalyst. Finally, a *photochemical oxidation* generated the γ-hydroxybutenolide functionality. This total synthesis confirmed the absolute stereochemistry of dysidiolide.



In the final stages of the total synthesis of okadaic acid by C.J. Forsyth et al., the central 1,6-dioxaspiro[4,5]decane ring system was introduced by the enantioselective reduction of the C16 carbonyl group using (*S*)-CBS/BH_3, followed by *acid-catalyzed spiroketalization*.[30]



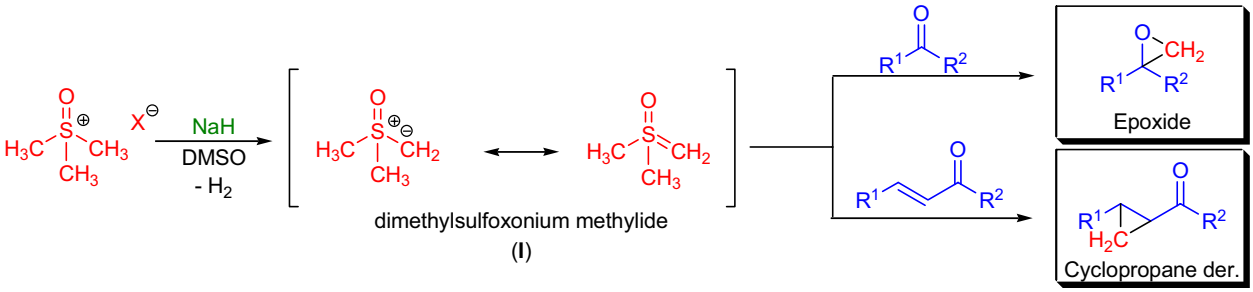
COREY-CHAYKOVSKY EPOXIDATION AND CYCLOPROPANATION

(References are on page 565)

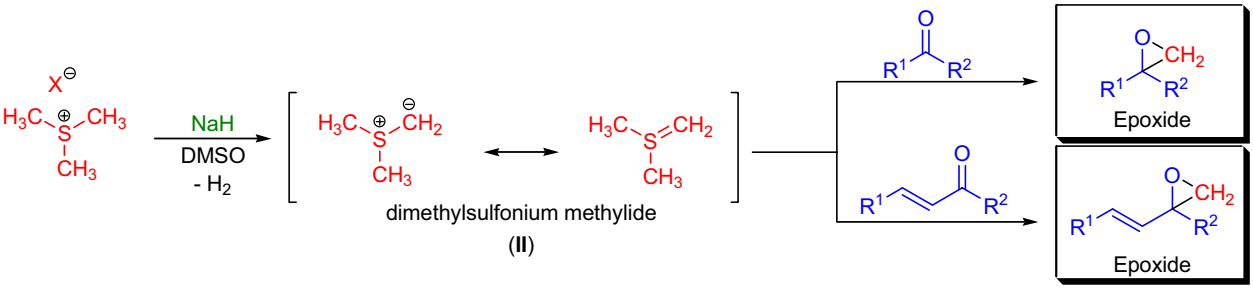
Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-11]*; Modifications & Improvements*[12-14]*; Theoretical Studies*[15-17]]

In 1962, E.J. Corey and M. Chaykovsky deprotonated trimethylsulfoxonium halides using powdered sodium hydride under nitrogen at room temperature to form a reactive compound, dimethylsulfoxonium methylide (**I**).[1] When simple aldehydes and ketones were mixed with **I**, the formation of epoxides was observed. Likewise, the reaction of dimethylsulfonium methylide (**II**) with aldehydes and ketones also resulted in epoxide formation.[2] Compounds **I** and **II** are both sulfur ylides and are prepared by the deprotonation of the corresponding sulfonium salts. The preparation of epoxides (oxiranes) from aldehydes and ketones using sulfur ylides is known as the *Corey-Chaykovsky epoxidation*. When **I** is reacted with α,β-unsaturated carbonyl compounds, a conjugate addition takes place to produce a cyclopropane as the major product. This reaction is known as the *Corey-Chaykovsky cyclopropanation*.[1] Sulfur ylide **II** is more reactive and less stable than **I**, so it is generated and used at low temperature. The reaction of substituted sulfur ylides with aldehydes is stereoselective, leading predominantly to *trans* epoxides. Asymmetric epoxidations are also possible using chiral sulfides.[12,6] The use of various substituted sulfur ylides allows the transfer of substituted methylene units to carbonyl compounds (isopropylidene or cyclopropylidene fragments) to prepare highly substituted epoxides. Since the S-alkylation of sulfoxides is not a general reaction, it is not practical to obtain the precursor salts in the trialkylsulfoxonium series. This shortcoming limits the corresponding sulfur ylides to the unsubstituted methylide. However, sulfur ylide reagents derived from sulfoximines offer a versatile way to transfer substituted methylene units to carbonyl compounds to prepare oxiranes and cyclopropanes.[12]

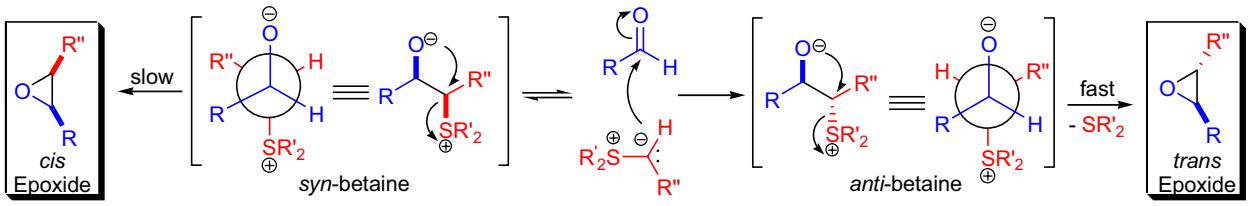


X = Cl, Br, I

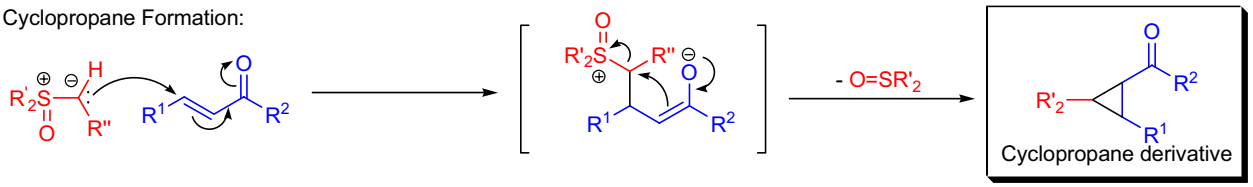


Mechanism:[18-25]

Epoxide Formation:



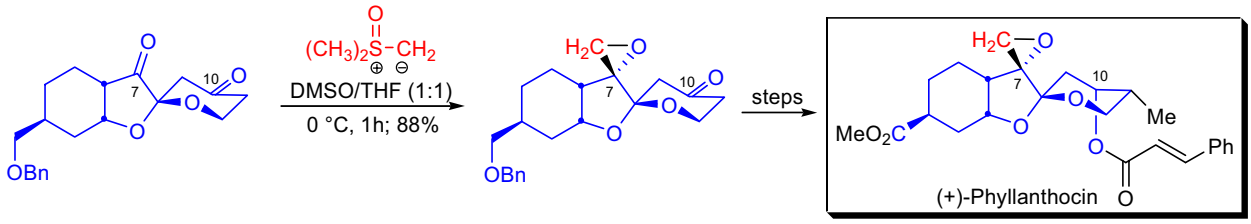
Cyclopropane Formation:



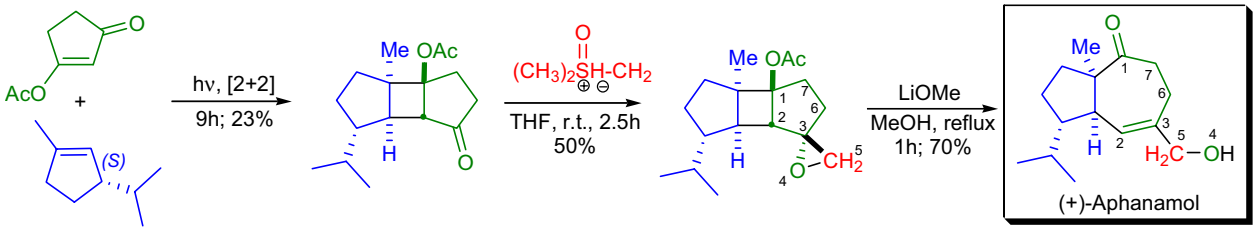
COREY-CHAYKOVSKY EPOXIDATION AND CYCLOPROPANATION

Synthetic Applications:

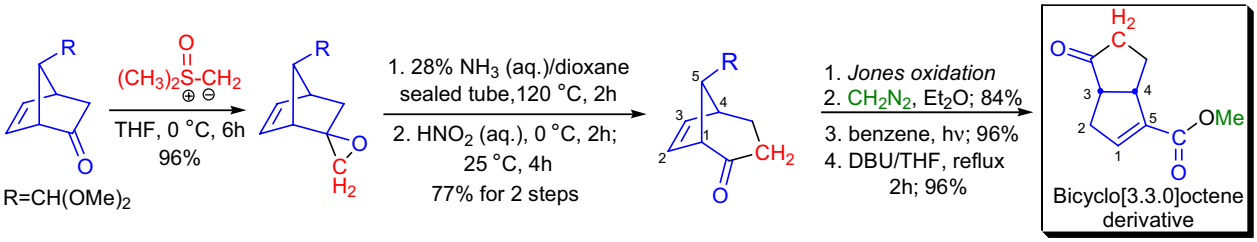
During the total synthesis of (+)-phyllanthocin, A.B. Smith and co-workers installed the epoxide functionality *chemo-* and *stereoselectively* at the C7 carbonyl group of the intermediate diketone by using dimethylsulfoxonium-methylide in a 1:1 solvent mixture of DMSO-THF at 0 °C.[26] The success of this chemoselective methylenation was attributed to the two α-alkoxy substituents, which render the C7 carbonyl group much more electrophilic than C10.



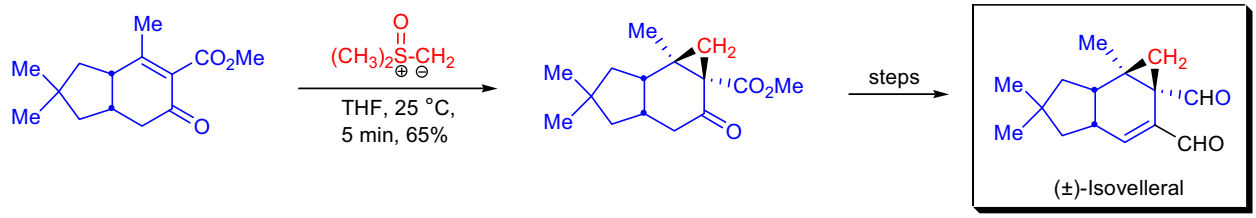
A short enantiospecific total synthesis of (+)-aphanamol I and II from limonene was achieved and the absolute stereochemistry of I and II established in the laboratory of B. Wickberg.[27] The key steps were a *de Mayo photocycloaddition*, a *Corey-Chaykovsky epoxidation* and finally a *base-catalyzed fragmentation* of the γ,δ-epoxyalcohol intermediate. Upon treating the photocycloadduct with dimethylsulfoxonium methylide, only the *endo* epoxide diastereomer was formed due to the steric hindrance provided by the methyl and isopropyl groups.



The conversion of a bicyclo[2.2.1]octenone derivative to the corresponding bicyclo[3.3.0]octenone, a common intermediate in the total synthesis of several iridoid monoterpenes, was achieved by N.C. Chang et al. The target was obtained by sequential application of the *Corey-Chaykovsky epoxidation*, *Demjanov rearrangement* and a *photochemical [1,3]-acyl shift*. [28]



One of the steps in the highly stereoselective total synthesis of (±)-isovelleral involved the cyclopropanation of an α,β-unsaturated ketone using dimethylsulfoxonium methylide.[29] C.H. Heathcock and co-workers studied this transformation under various conditions and they found that THF at ambient temperature gave superior results to DMSO, which is the most common solvent for the *Corey-Chaykovsky cyclopropanation*.



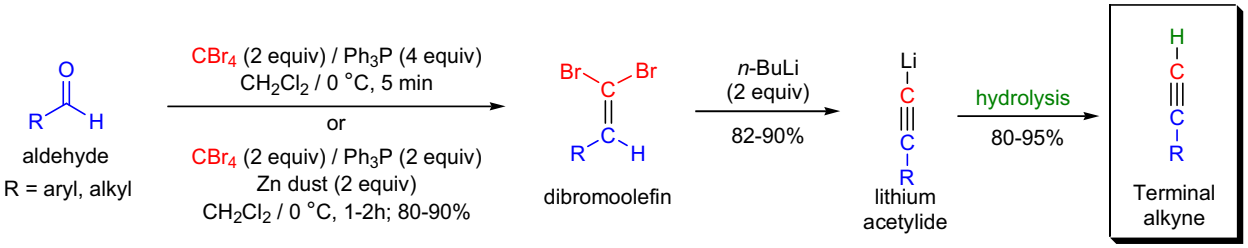
COREY-FUCHS ALKYNE SYNTHESIS

(References are on page 566)

Importance:

[*Seminal Publication*[1]*; Reviews*[2]*; Modifications and Improvements*[3-5]]

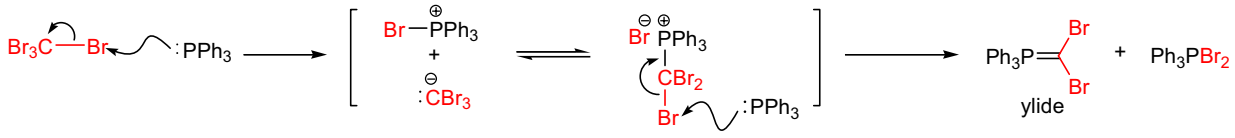
The one-carbon homologation of aldehydes to the corresponding terminal alkynes using carbon tetrabromide and triphenylphosphine is known as the *Corey-Fuchs alkyne synthesis*. In 1972, E.J. Corey and P.L. Fuchs examined the synthetic possibility of transforming aldehydes to the corresponding one-carbon chain-extended alkynes.[1] The first step of their procedure involved the conversion of the aldehyde to the corresponding homologated dibromoolefin in two possible ways: **I**) addition of the aldehyde (1 equivalent) to a mixture of triphenylphosphine (4 equivalents) and carbon tetrabromide (2 equivalents) in CH_2Cl_2, at 0 °C in 5 minutes;[6] or **II**) addition of the aldehyde to a reagent, which is prepared by mixing zinc dust (2 equivalents) with Ph_3P (2 equivalents) and CBr_4 (2 equivalents) in CH_2Cl_2 at 23 °C for 24-30h (the reaction time to form the alkyne is 1-2h). Yields are typically 80-90% for this first Wittig-type step. Procedure **II**, using zinc dust and less Ph_3P, tends to give higher yields of dibromoolefins and simplifies the isolation procedure. In the second step, the conversion of the prepared dibromoolefins to the corresponding terminal alkynes is accomplished by treatment with 2 equivalents of *n*-butyllithium at -78 °C (*lithium-halogen exchange* and elimination), followed by simple hydrolysis. The intermediate is a lithium acetylide, which can be treated with a number of electrophiles to produce a wide variety of useful derivatives. Recently, a one-pot modified procedure using *t*-BuOK/$(Ph_3PCHBr_2)Br$ followed by the addition of excess *n*-BuLi was published.[5]



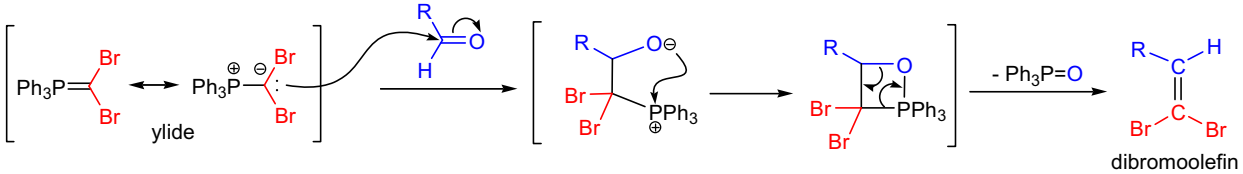
Mechanism:[6,1]

The mechanism of dibromoolefin formation from the aldehyde is similar to the mechanism of the *Wittig reaction*. However, there is very little known about the formation of the alkyne from the dibromoolefin. The mechanism below is one possible pathway to the observed product.

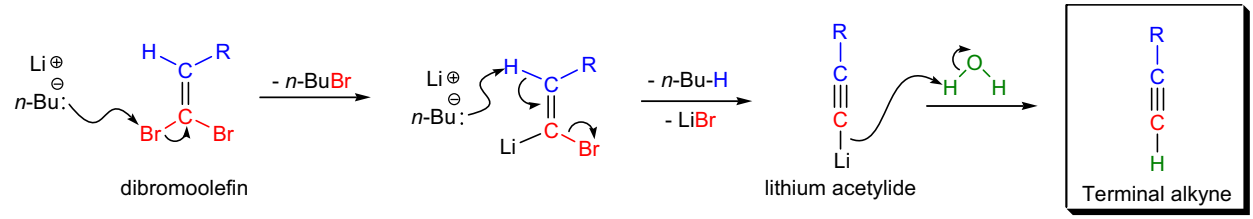
Generation of the phosphorous ylide:



Reaction of the phosphorous ylide with the aldehyde:



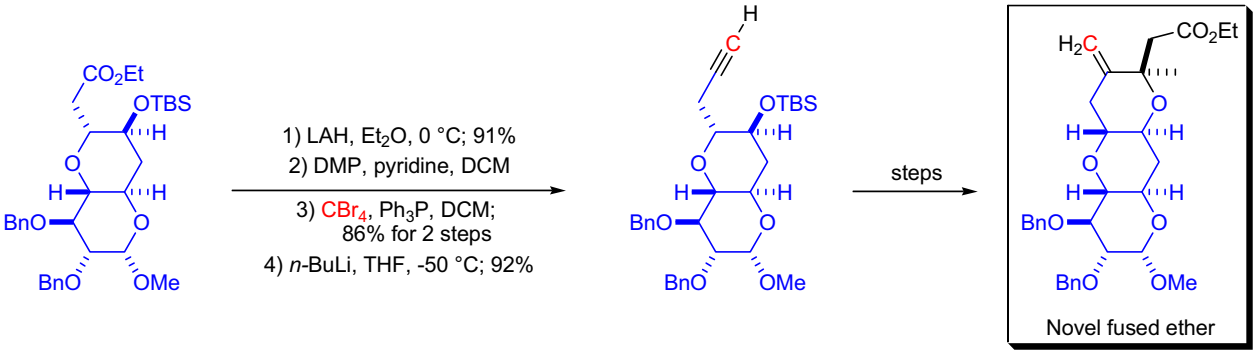
Conversion of dibromoolefin to terminal alkyne:



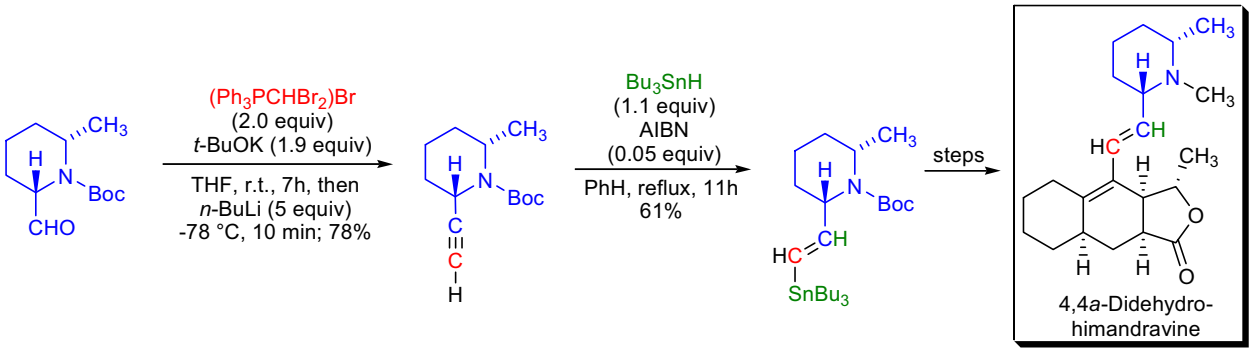
COREY-FUCHS ALKYNE SYNTHESIS

Synthetic Applications:

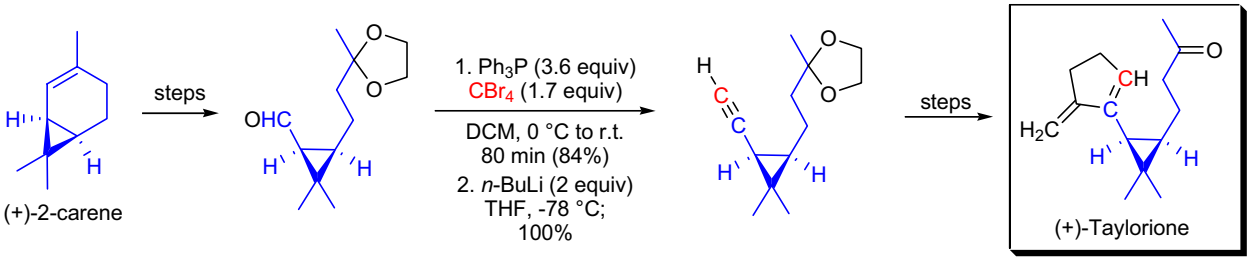
In the laboratory of J.H. van Boom, the synthesis of highly functionalized *cis*- and *trans*-fused polycyclic ethers of various ring sizes *via* radical cyclization of carbohydrate-derived β-(alkynyloxy)acrylates was developed.[7] The radical cyclization precursors were prepared iteratively and the terminal alkyne moieties were installed using the *Corey-Fuchs procedure*.



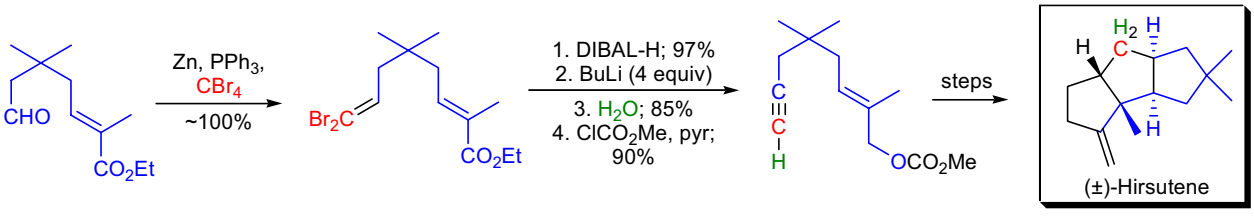
The total synthesis of Galubulimima alkaloid 4,4*a*-didehydrohimandravine, using an *intramolecular Diels-Alder reaction* and a *Stille coupling* as the key steps, was accomplished in the laboratory of M.S. Sherburn.[8] The required vinylstannane intermediate for the *Stille coupling* was prepared *via* the *one-pot Corey-Fuchs reaction*,[5] followed by *radical hydrostannylation*.



W.J. Kerr and co-workers carried out the total synthesis of (+)-taylorione starting from readily available (+)-2-carene and using a *modified Pauson-Khand annulation* with ethylene gas as the key step.[9] The key terminal alkyne intermediate was prepared by the *Corey-Fuchs reaction*. Interestingly, the ketal protecting group was sensitive to the excess of CBr_4, so the addition of this reagent had to be monitored carefully to cleanly transform the aldehyde to the desired dibromoolefin.



W. Oppolzer et al. utilized the *Corey-Fuchs alkyne synthesis* for the preparation of a key acyclic enynyl carbonate during the total synthesis of (±)-hirsutene.[10]



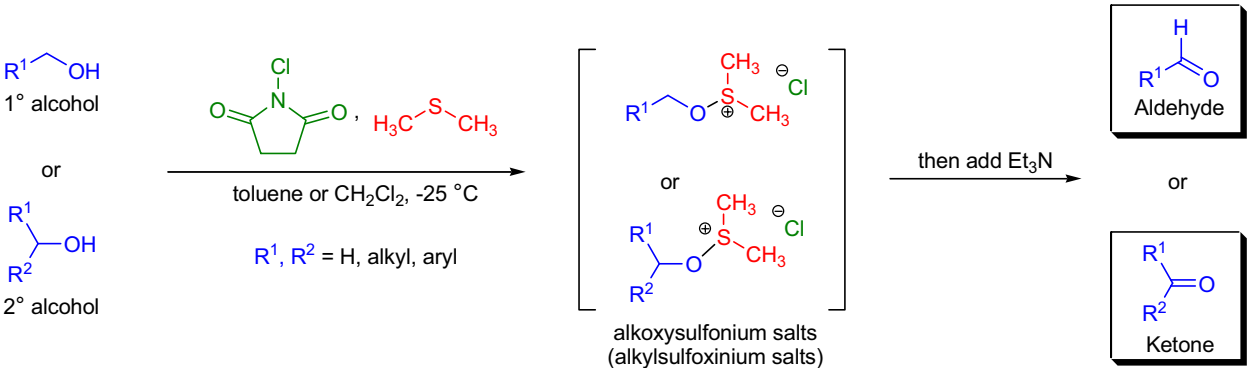
COREY-KIM OXIDATION

(References are on page 566)

Importance:

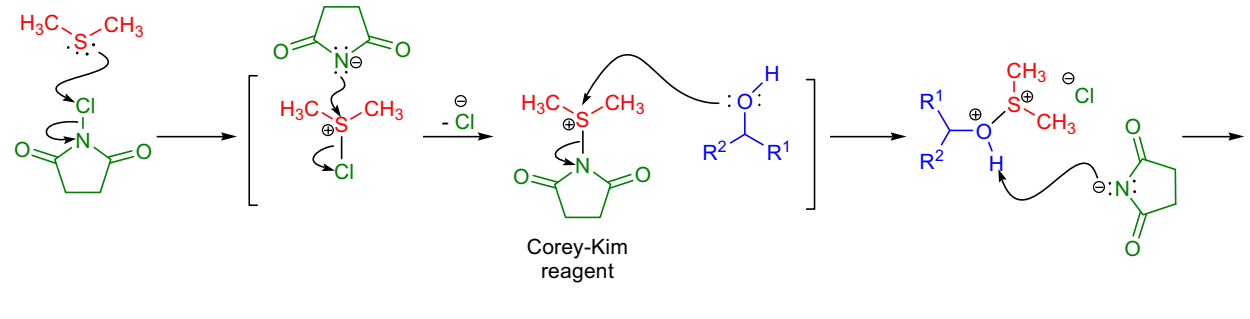
[*Seminal Publications*[1-3]*; Modifications & Improvements*[4,5]]

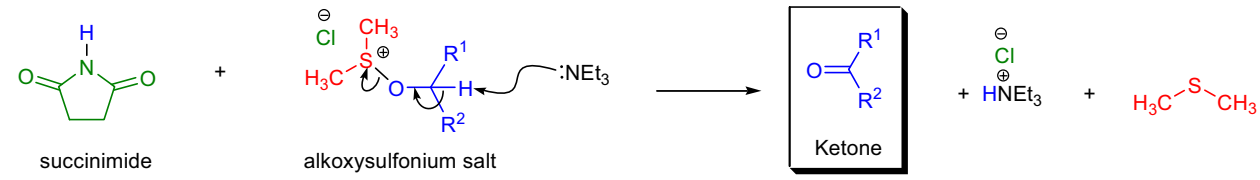
In 1972, E.J. Corey and C.U. Kim developed a new process for the efficient conversion of alcohols to aldehydes and ketones using *N*-chlorosuccinimide (NCS), dimethylsulfide (DMS) and triethylamine (TEA).[2] The oxidation of primary and secondary alcohols with NCS/DMS is known as the *Corey-Kim oxidation*. The active reagent, S,S-dimethylsuccinimidosulfonium chloride, is formed *in situ* when NCS and DMS are reacted and is called the *Corey-Kim reagent*.[1] This protocol can be used for the oxidation of a wide variety of primary and secondary alcohols except for allylic and benzylic alcohols, where the substrates are predominantly converted to the allylic and benzylic halides. In polar solvents, a side-reaction may occur in which the alcohol forms the corresponding methylthiomethyl ether ($ROCH_2SCH_3$). The reaction conditions for the *Corey-Kim oxidation* are mild and tolerate most functional and protecting groups. Therefore, the protocol can be applied to the oxidation of polyfunctionalized molecules. Recent modifications of the original procedure led to the development of the fluorous[4] and odorless[5] *Corey-Kim oxidations*. In addition to being an effective oxidant for alcohols, the *Corey-Kim reagent* has also been used to dehydrate aldoximes to nitriles,[6] convert 3-hydroxycarbonyl compounds to 1,3-dicarbonyls,[7] synthesize stable sulfur ylides from active methylene compounds[8] and to prepare 3(*H*)-indoles from 1(*H*)-indoles.[9]



Mechanism:[2,4]

The first step of the mechanism of the *Corey-Kim oxidation* is the reaction of dimethylsulfide with *N*-chlorosuccinimide to generate the electrophilic active species, *S,S*-dimethylsuccinimidosulfonium chloride (*Corey-Kim reagent*) *via* dimethylsulfonium chloride. The sulfonium salt is then attacked by the nucleophilic alcohol to afford an alkoxysulfonium salt. This alkoxysulfonium salt is deprotonated by triethylamine and the desired carbonyl compound is formed. The dimethylsulfide is regenerated, and it is easily removed from the reaction mixture *in vacuo*. In the *odorless Corey-Kim oxidation*[5] instead of dimethylsulfide, dodecylmethylsulfide is used. This sulfide lacks the unpleasant odor of DMS due to its low volatility.

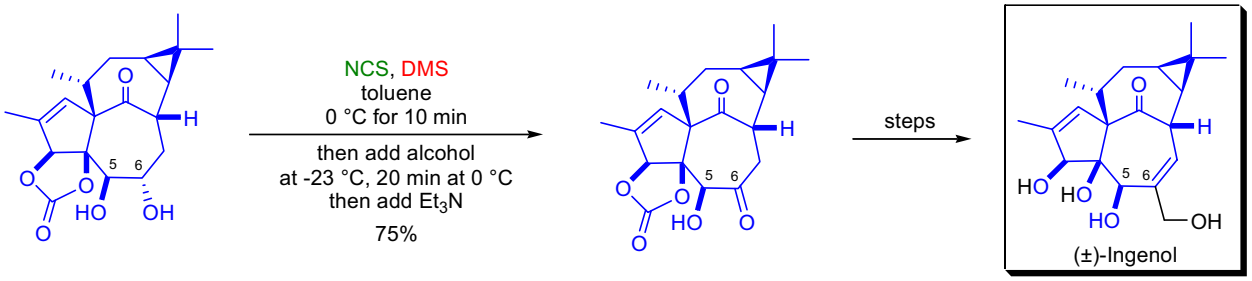




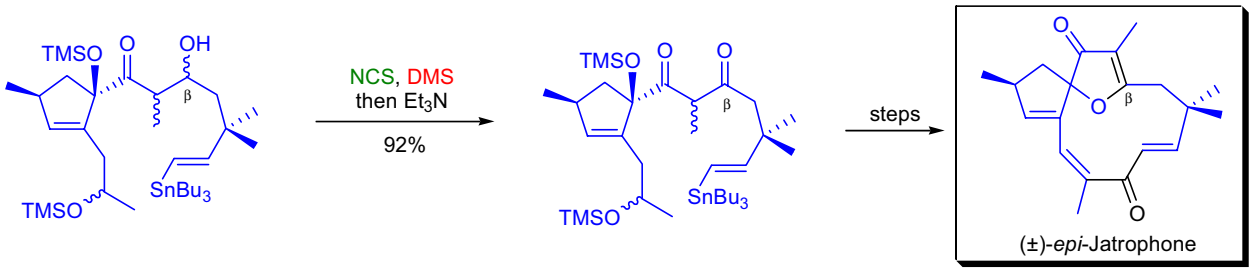
COREY-KIM OXIDATION

Synthetic Applications:

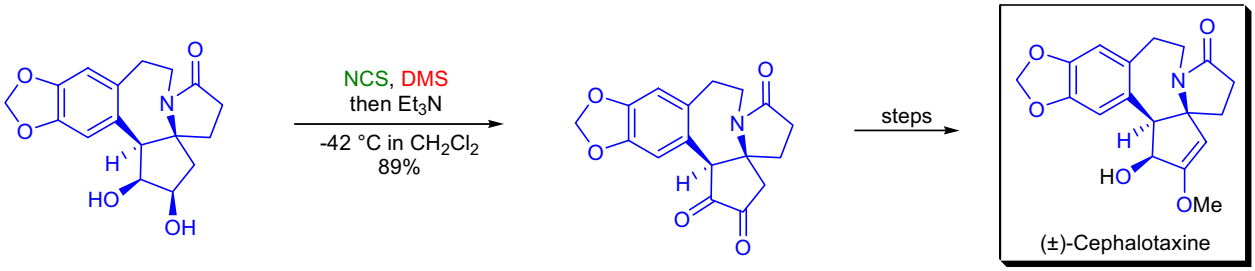
During the total synthesis of (±)-ingenol by I. Kuwajima and co-workers, an advanced tricyclic diol intermediate was selectively converted to the corresponding α-ketol utilizing the *Corey-Kim oxidation*.[10] The diol was oxidized only at the less hindered C6 hydroxyl group.



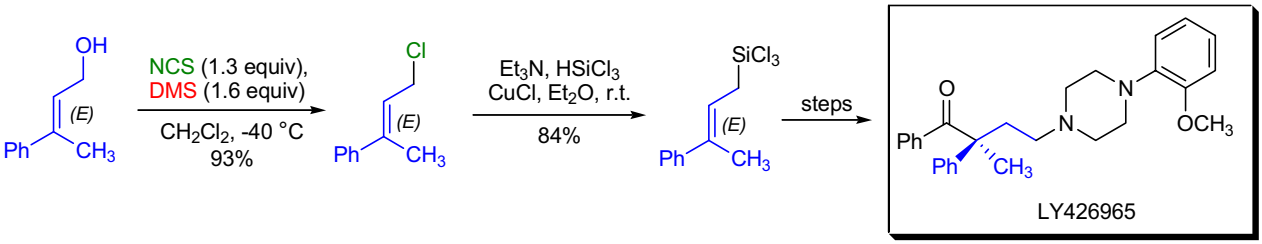
In the laboratory of L.S. Hegedus, the total synthesis of (±)-*epi*-jatrophone was accomplished using a *palladium-catalyzed carbonylative coupling* as the key step.[11] In the endgame of the synthesis, a β-hydroxy ketone moiety was oxidized in excellent yield to the corresponding 1,3-dione using the mild *Corey-Kim protocol*.



In the final stages of the total synthesis of (±)-cephalotaxine by M.E. Kuehne et al., a tetracyclic *cis*-vicinal diol was oxidized to the α-diketone.[12] Using PCC, pyridine/SO_3 or the Swern protocol did not yield the desired product. However, by applying the *Corey-Kim protocol*, NCS-DMS in dichloromethane at -42 °C, afforded the diketone in 89% yield.



The serotonin antagonist LY426965 was synthesized using *catalytic enantioselective allylation* with a chiral biphosphoramide in the laboratory of S.E. Denmark.[13] In order to prepare the necessary 3,3-disubstituted allyltrichlorosilane reagent, the (*E*)-allylic alcohol was first converted by the *Corey-Kim procedure* to the corresponding chloride.



COREY-NICOLAOU MACROLACTONIZATION

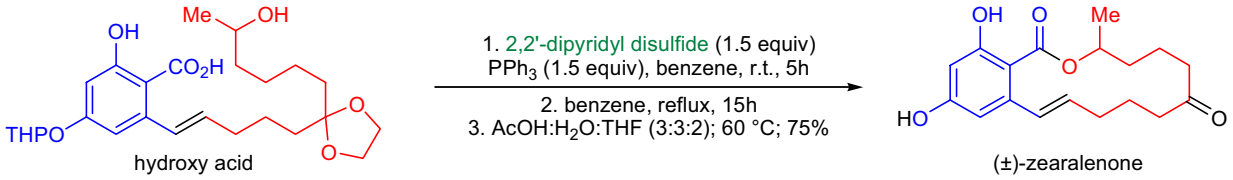
(References are on page 567)

Importance:

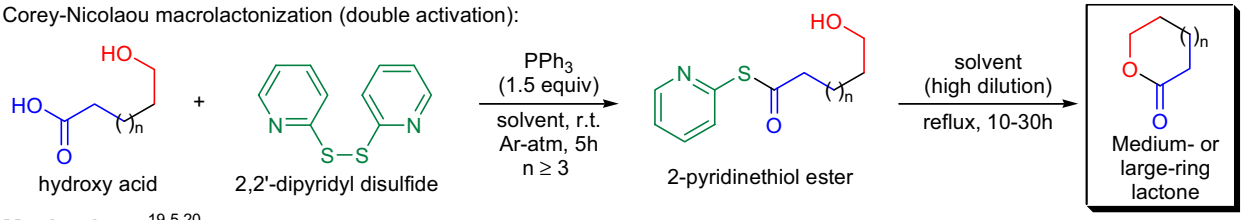
[*Seminal Publications*[1,2]; *Reviews*[3-13]; *Modifications & Improvements*[14-16]; *Theoretical Studies*[17]]

Before the 1970s there was no general way to efficiently prepare medium- and large-ring lactones from highly functionalized hydroxy acids under mild conditions. When the ring size of the target lactone is large, the probability of the hydroxyl group reacting with the carboxylic acid moiety within the same molecule is very low, and mainly intermolecular coupling occurs unless the concentration of the substrate is very low (high-dilution conditions). In 1974, E.J. Corey and K.C. Nicolaou reported a novel and mild method for the formation of macrolactones from complex hydroxy acid precursors.[1] A series of ω-hydroxy acids were lactonized by first converting them to the corresponding 2-pyridinethiol esters, which were then slowly added to xylene at reflux. The formation of lactones from hydroxy acids *via* their 2-pyridinethiol esters is known as the *Corey-Nicolaou macrolactonization*. The power of the method was first demonstrated by the total synthesis of (±)-zearalenone in which the functionalized hydroxy acid was first treated with 2,2'-dipyridyl disulfide and the resulting 2-pyridinethiol ester was heated to reflux in benzene.[1] Removal of the protecting groups furnished the natural product. The general features of this macrolactonization strategy are: 1) the reaction is conducted under neutral and aprotic conditions, so substrates containing acid- and base-labile functional groups are tolerated; 2) the formation of the 2-pyridinethiol ester is conducted in the presence of a slight excess of PPh_3 and 2,2-dipyridyl disulfide;[18] 3) the actual cyclization is usually conducted in refluxing benzene or toluene under high-dilution conditions to keep the undesired intermolecular ester formation at a minimum; 4) the lactonization is not catalyzed by acids, bases, or by-products; and 5) lactones with ring sizes 7-48 have been successfully prepared, but reaction rates strongly depend on ring-size and the functionality of the substrate. Over the past three decades several modifications of the method were introduced: 1) the use of silver perchlorate (or $AgBF_4$) to activate the 2-pyridinethiol esters by complexation; significant reduction of reaction time is observed (*Gerlach-Thalmann modification*);[14] and 2) the development of other bis-heterocyclic disulfide reagents by Corey et al.[15]

Corey & Nicolaou (1974):



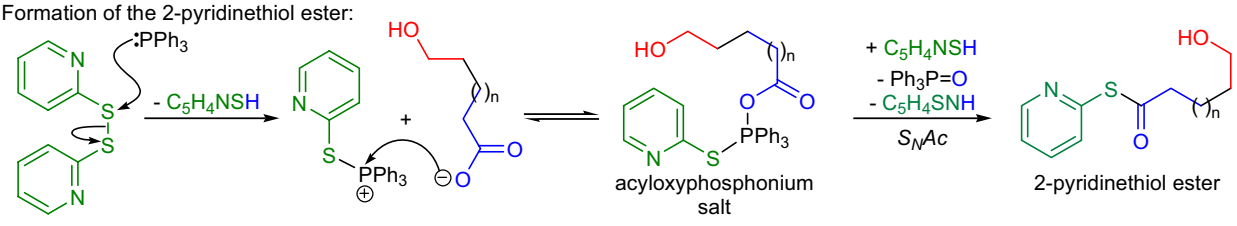
Corey-Nicolaou macrolactonization (double activation):



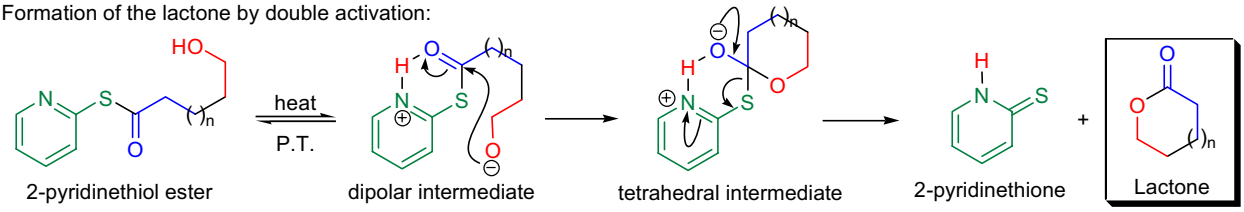
Mechanism:[19,5,20]

The 2-pyridinethiol ester undergoes an intramolecular proton transfer to give rise to a dipolar intermediate in which the carbonyl group is part of a six-membered ring held by hydrogen bonding. In this dipolar intermediate both the carbonyl group and the oxygen atom of the alcohol are activated because the carbonyl group is more electrophilic but the oxygen is more nucleophilic than before. The intramolecular attack of the alkoxide ion onto the carbonyl group is electrostatically driven and the tetrahedral intermediate collapses to yield the desired lactone as well as 2-pyridinethione. This mechanistic picture is supported by the observation that thiolesters in which the intramolecular hydrogen bonding was not possible did not undergo lactonization upon heating.

Formation of the 2-pyridinethiol ester:



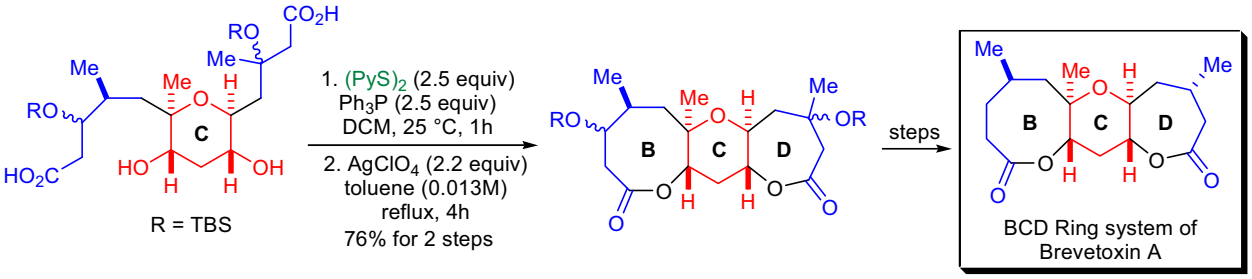
Formation of the lactone by double activation:



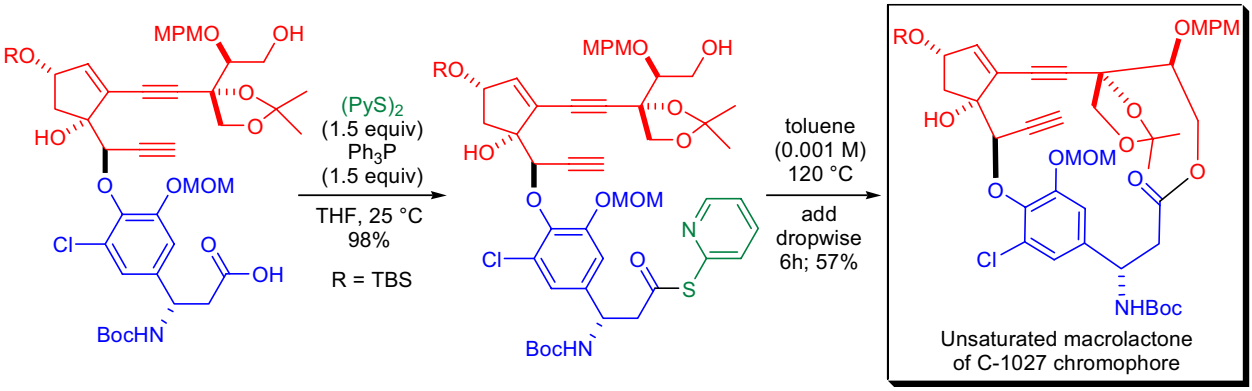
COREY-NICOLAOU MACROLACTONIZATION

Synthetic Applications:

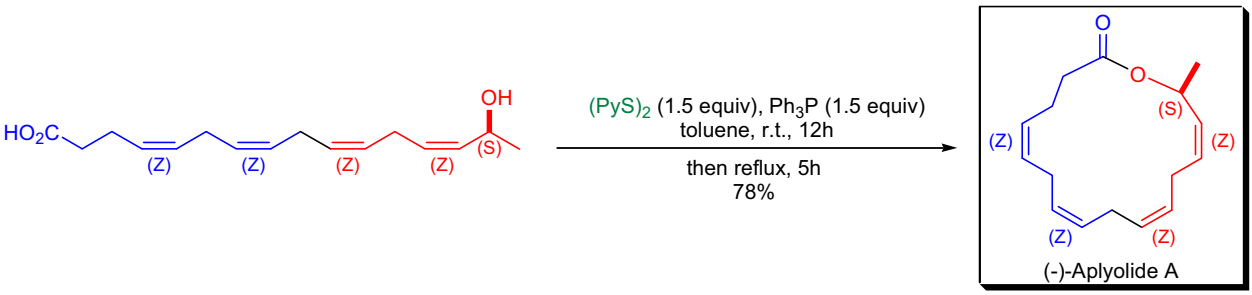
The *modified Corey-Nicolaou macrolactonization* was applied for the construction of the BCD ring system of brevetoxin A by K.C. Nicolaou and co-workers.[21] The dihydroxy dicarboxylic acid substrate was subjected to a one-pot bis-lactonization. After the formation of the bis-2-pyridinethiol ester, the lactonization was conducted at low substrate concentration (0.013 M) in toluene at reflux temperature.



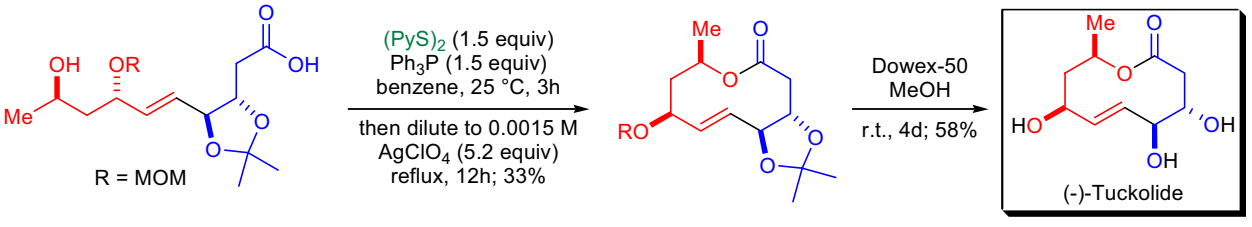
The research team of M. Hirama conducted synthetic studies toward the C-1027 chromophore, which contains a highly unsaturated 17-membered macrolactone.[22] The authors investigated several macrolactonization protocols including the *Mukaiyama-*, *Corey-Nicolaou-*, and *Yamaguchi protocols*. The Mukaiyama and *Yamaguchi macrolactonization* conditions gave dimers as the major product, but the *Corey-Nicolaou procedure* yielded the desired macrolactone as the only product, albeit in modest yield. The modification of the protecting groups in the hydroxy acid precursor helped to optimize the yield of the macrolactone which was obtained as a 1:1.1 mixture of inseparable atropisomers.



The first total synthesis of the ichthyotoxic marine natural product (–)-aplyolide A was accomplished by Y. Stenstrøm and co-workers.[23] The compound has a 16-membered lactone ring, four (*Z*)-double bonds, as well as a stereogenic center. Numerous macrolactonization protocols were tested, but most of them gave the diolide (dimer) except for the *Corey-Nicolaou procedure*.



M.B. Andrus and T.-L. Shi achieved the total synthesis of the 10-membered lactone (–)-tuckolide (decarestrictine D), which potentially inhibits cholesterol biosynthesis.[24] The lactonization was only successful under the *Corey-Nicolaou conditions*. Interestingly, the unsubstituted 9-hydroxynonanoic acid did not lactonize under these conditions.



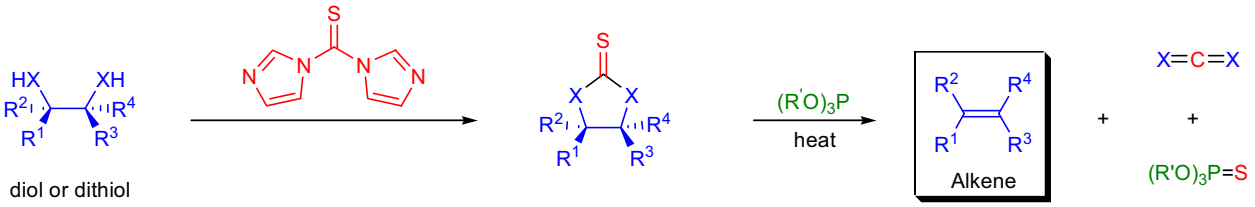
COREY-WINTER OLEFINATION

(References are on page 567)

Importance:

[*Seminal Publications*[1,2]*; Review*[3]]

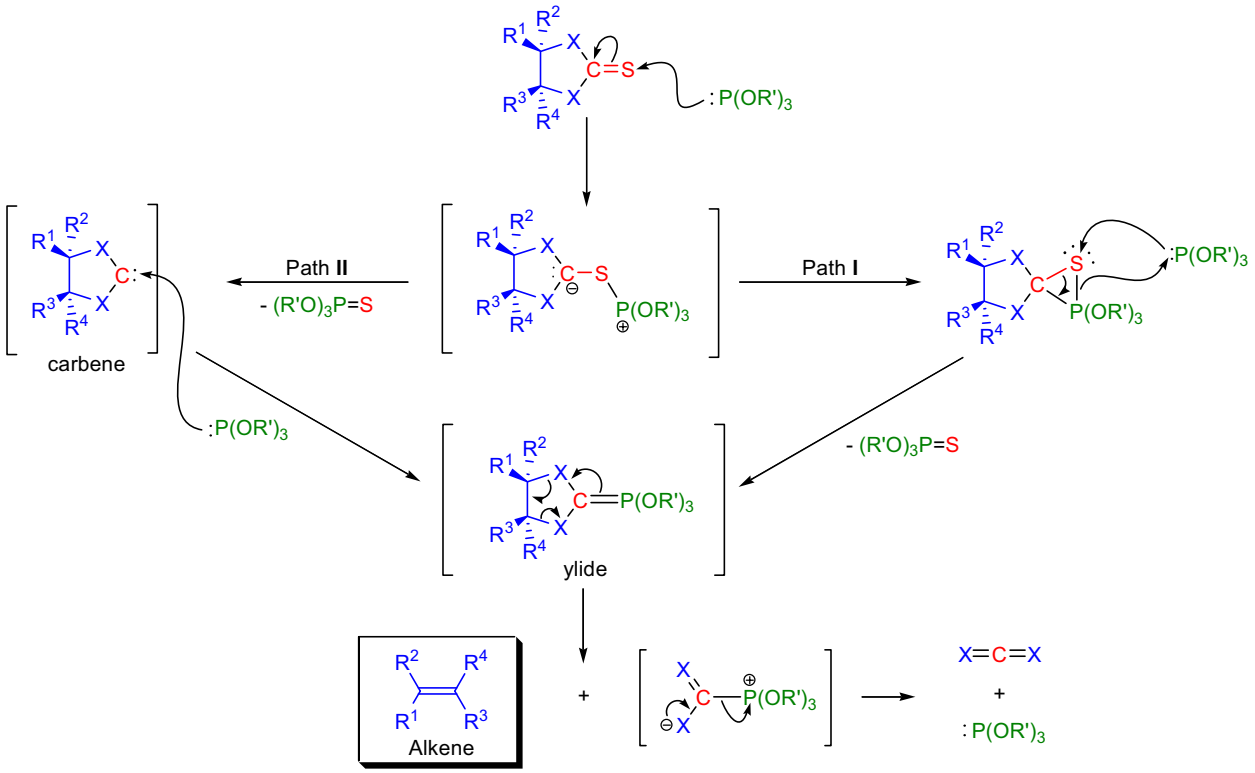
In 1963, E.J. Corey and R.A.E. Winter described a new two-step method for the stereospecific synthesis of alkenes from 1,2-diols *via* cyclic 1,2-thionocarbonates and 1,2-trithiocarbonates.[1,2,4] This method of alkene synthesis is called the *Corey-Winter olefination*. In the first step, the 1,2-diol is converted quantitatively to the corresponding cyclic thionocarbonate derivative using thiocarbonyldiimidazole. In the second step, the thionocarbonate is treated with excess trialkylphosphite [$P(OR')_3$, where R'=Me, Et or alkyl] at reflux, and a *cis*-elimination reaction takes place to yield the alkene and by-products [CO_2 and $(OR)_3P=S$]. The reaction is completely *stereospecific* and high-yielding. Even highly substituted and strained olefins (e.g., *trans*-cycloheptene)[2] can be prepared. However, no elimination is observed in those cases in which the *cis*-elimination would lead to an extremely strained structure (e.g., *trans*-cyclohexene). The stereochemistry of the product olefin is only determined by the stereochemistry of the starting 1,2-diol (*cis* or *trans*) and usually under the reaction conditions, no isomerization of the product is observed. A *cis* olefin, may be converted to *trans*-1,2-diol and subjected to the *Corey-Winter procedure* to afford the corresponding *trans* olefin. Similarly, *trans* olefins can be converted to the corresponding *cis* olefins.



R^1, R^2, R^3, R^4 = H, alkyl, aryl; R' = Me, Et; substrate: X = O (1,2-diol), X = S, 1,2-dithiol; cyclic intermediate: X = O (cyclic 1,2-thionocarbonate), X = S (cyclic 1,2-trithiocarbonate)

Mechanism:[2,5-7]

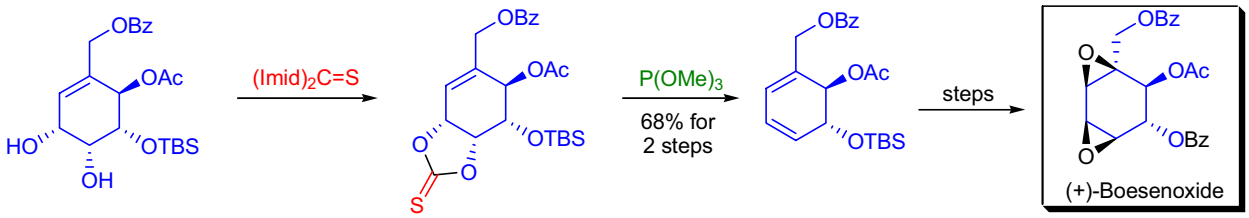
The exact mechanism of the reaction between the thionocarbonate and the trialkylphosphite is not known. There are two possible pathways (**I** and **II**) and both of them are presented. In pathway **I**, the formation of an ylide intermediate is postulated based on inhibition studies,[4] while in pathway **II** the generation of a carbenoid intermediate is assumed. There is direct experimental evidence that the elimination of the cyclic 1,2-thionocarbonate involves the formation of a carbenoid intermediate.[6]



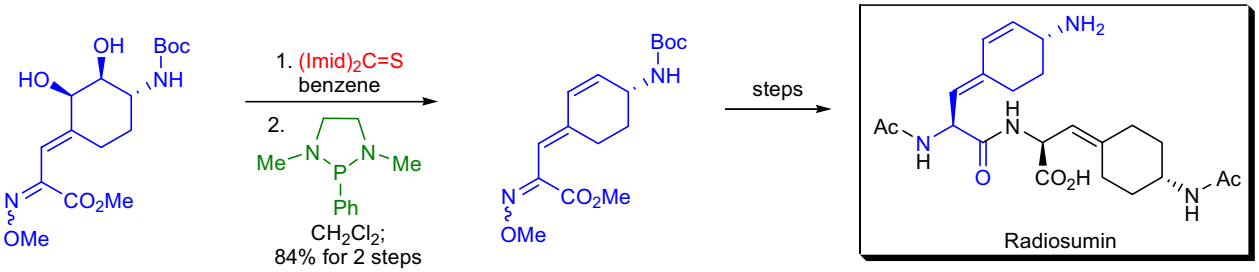
COREY-WINTER OLEFINATION

Synthetic Applications:

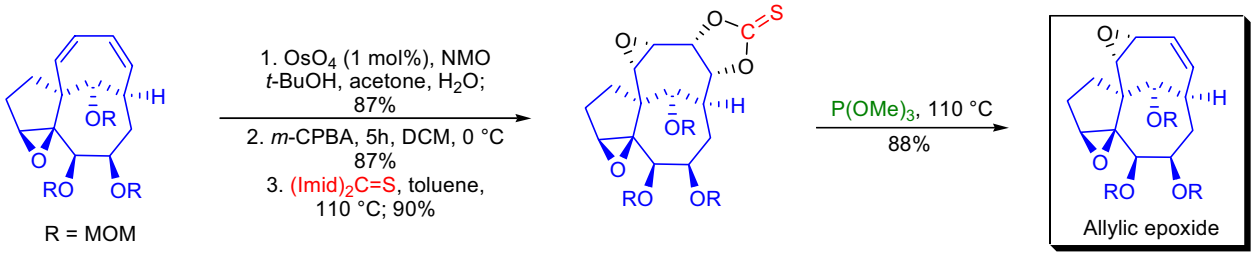
The enantiospecific synthesis of naturally occurring cyclohexane epoxides such as (+)-crotepoxide and (+)-boesenoxide was accomplished by T.K.M. Shing et al.[8] The key intermediate 1,3-cyclohexadiene was prepared using the *Corey-Winter protocol* on a *cis*-vicinal diol. The resulting diene was then converted to the natural product after several steps.



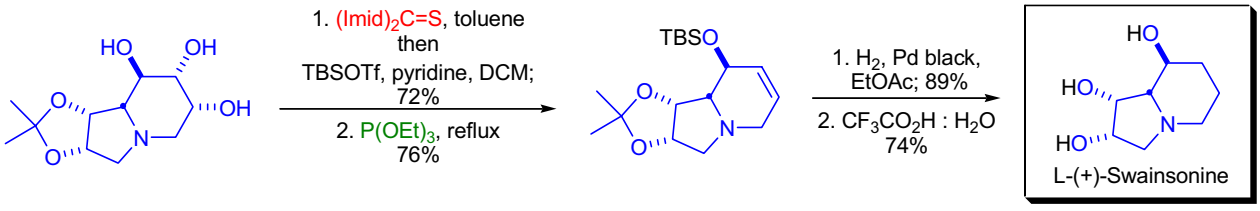
The absolute configuration of radiosumin, a novel potent trypsin inhibitory dipeptide, was determined by T. Shioiri and co-workers by carrying out the first enantioselective total synthesis of the natural product.[9] The *s-trans* 1,3-diene in one of the key synthetic intermediates was installed by the *Corey-Winter olefination* using the Corey-Hopkins reagent (1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine).



In the laboratory of J.H. Rigby, synthetic studies were undertaken on the ingenane diterpenes.[10] During these studies, it was necessary to investigate the ring opening reactions of a structurally complex allylic epoxide intermediate. This allylic epoxide was prepared from a 1,3-diene in three steps: *dihydroxylation*, *epoxidation* and *Corey-Winter olefination*.



G.W.J. Fleet and co-workers synthesized L-(+)-swainsonine and other more highly oxygenated monocyclic structures that exhibited inhibitory activity toward naringinase (L-rhamnosidase).[11] In order to remove a *cis*-vicinal diol moiety in the endgame of the synthesis, the *Corey-Winter olefination* was utilized.



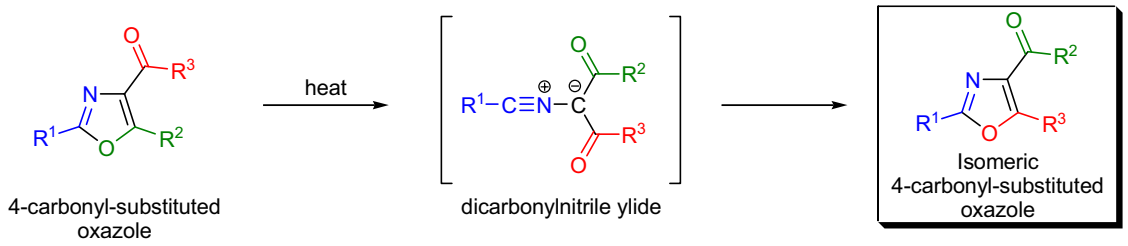
CORNFORTH REARRANGEMENT

(References are on page 567)

Importance:

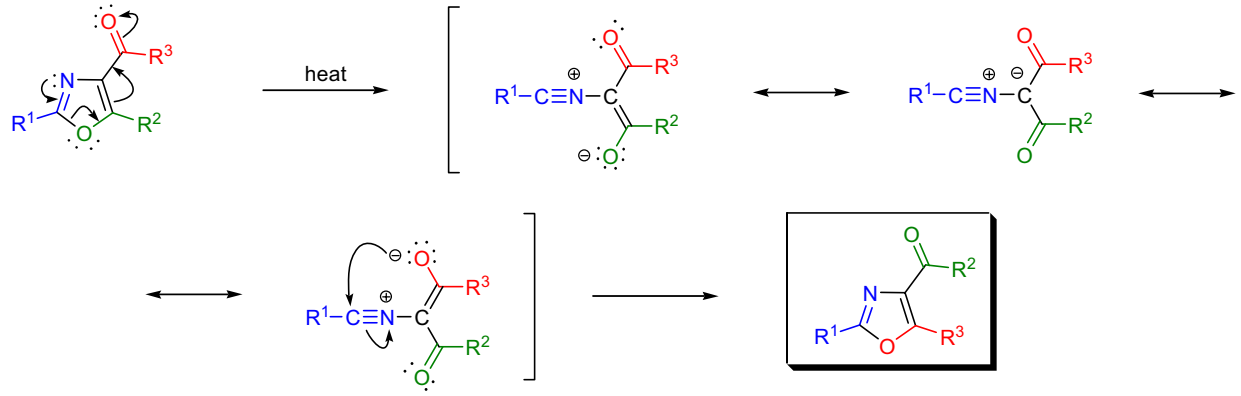
[*Seminal Publication*[1]; *Reviews*[2-7]; Modifications[8]; *Theoretical Studies*[9-11]]

In 1949 J.W. Cornforth observed that upon heating, 2-phenyl-5-ethoxyoxazole-4-carboxamide (R^1=Ph, R^2=OEt, and R^3=NH_2) rearranged to ethyl 2-phenyl-5-aminooxazole-4-carboxylate.[1] The thermal rearrangement of 4-carbonyl substituted oxazoles to their isomeric oxazoles is known as the *Cornforth rearrangement*. The extent of the rearrangement depends on the thermodynamic stability of the starting material versus the product. When R^2=R^3, the *Cornforth rearrangement* is degenerate and leads to a 1:1 equilibrium mixture.[12] In the early 1970s, the scope and limitations of the reaction were investigated in depth by M.J.S. Dewar and co-workers.[13,12] They found that the rearrangement was general and that secondary and tertiary alkyl and aryl oxazole-4-carboxamides were converted to the corresponding secondary and tertiary 5-aminooxazoles.[13] When the amide nitrogen is part of a heterocycle (R^3=N-heterocycle), the rearrangement occurs in typically excellent (>90%) yield. The *Cornforth rearrangement* was also found to be a general method for the synthesis of 5-thiooxazole-4-carboxylic esters from 5-alkoxyoxazole-4-thiocarboxylates (R^3=SAr). A special case of the rearrangement is the base-induced or pyrolytic isomerization of 4-hydroxymethylene-5-oxazolones or their potassium salts to the corresponding oxazole-4-carboxylic acids.[14]

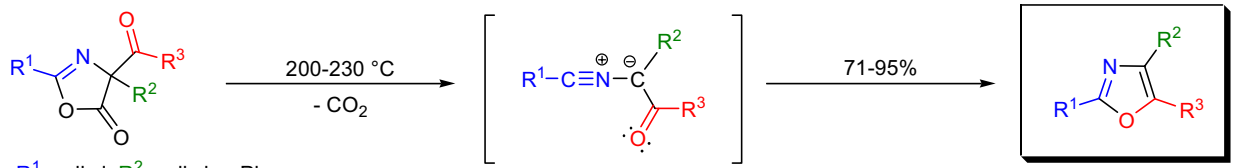


Mechanism: [15,13,3]

The mechanism involves the electrocyclic opening of the oxazole ring to a dicarbonylnitrile ylide intermediate, which undergoes a *[1,5]-dipolar electrocyclization*[3,11] to give the rearranged oxazole. The intermediate nitrile ylide cannot be isolated. To prove that the mechanism involves this intermediate, G. Höfle and W. Steglich generated carbonylnitrile ylides by a thermally induced *[1,3]-dipolar cycloreversion reaction* of 4-acyl-2-oxazolin-5-ones and found that the resulting ylides readily cyclized to oxazoles in preparatively useful yields.[16] Whether or not the rearrangement occurs depends solely on the free energy difference between the starting material and product, or more precisely on the nature of R^2 and R^3 substituents.[13,12] In aprotic solvents the rate of isomerization increases with increasing solvent polarity suggesting that only a small positive charge builds up in the transition state.[15] However, there is a substantial rate increase when the solvent is changed from an aprotic ($PhNO_2$) to a protic solvent ($PhCH_2OH$), suggesting that the negative charge in the transition state is stabilized *via* hydrogen bonding.[13]



Preparation of carbonylnitrile ylide:

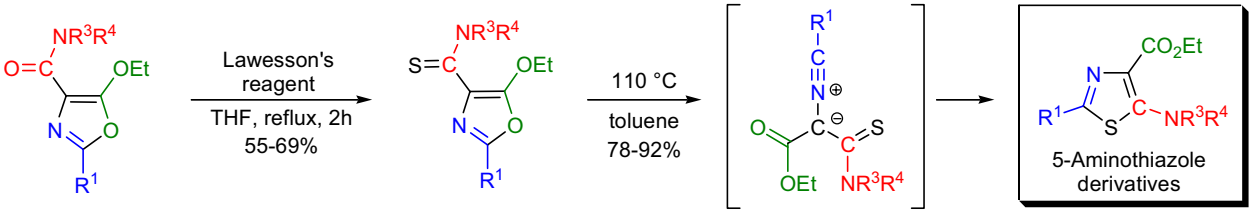


R^1 = alkyl, R^2 = alkyl or Ph
R^3 = Ph, Me, OMe, CO_2Et

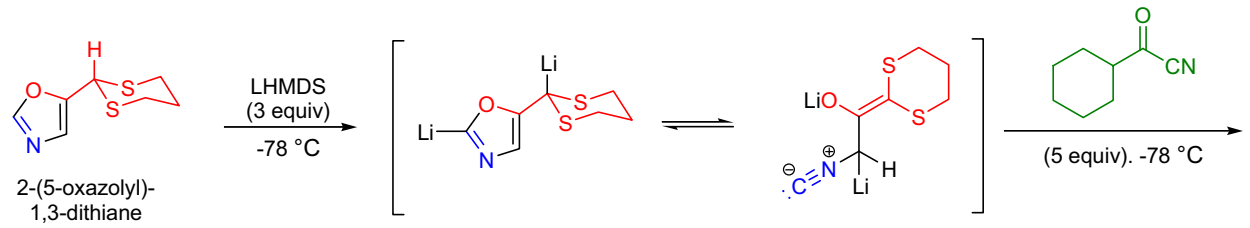
CORNFORTH REARRANGEMENT

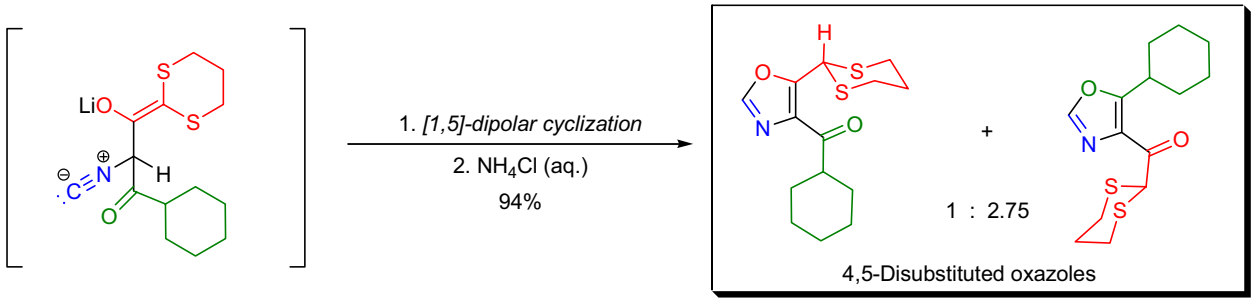
Synthetic Applications:

Substituted oxazoles are attractive starting materials for a variety of heterocyclic ring transformations due to their reactivity toward acids, bases, heat, dienophiles, and dipolarophiles. Despite the numerous ring transformations of oxazoles, the oxazole to thiazole interconversion was mainly unexplored until I.J. Turchi and co-workers examined the thermal *Cornforth rearrangement* of 4-(aminothiocarbonyl)-5-ethoxyoxazoles to 5-aminothiazoles.[17] The reaction turned out to be a simple and relatively general route to thiazoles from readily available starting materials, and the procedure is applicable to the synthesis of any 2-alkyl- or 2-aryl-4-(alkoxycarbonyl)-5-aminothiazoles.

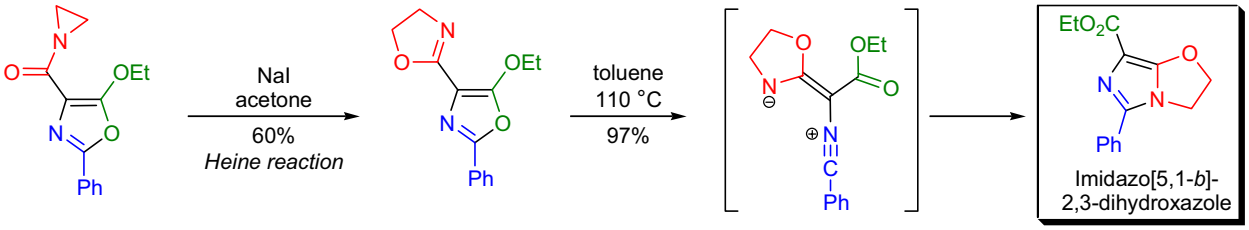


In the laboratory of D.R. Williams, a carbanion methodology for the alkylations and acylations of substituted oxazoles was investigated.[8] The study showed that the monoalkylation of the dianion generated from 2-(5-oxazolyl)-1,3-dithiane exclusively led to the substitution of the carbon adjacent to sulfur. However, acylation reactions of the dianion afforded 4,5-disubstituted oxazoles. These new products presumably arose from carbonylnitrile ylide intermediates, which were generated by the selective C-acylation of a ring-opened dianion tautomer. This is the first example of a base-induced, low-temperature *Cornforth rearrangement*.





During the investigation of the scope and limitations of the *Cornforth rearrangement*, M.J.S. Dewar and co-workers treated 2-phenyl-5-ethoxyoxazole-4-aziridinylcarboxamide with sodium iodide in acetone (*Heine reaction*) to prepare 2-(2-phenyl-5-ethoxyoxazolyl)- [2]-oxazoline in 60% yield.[12] This oxazoline was a *Cornforth rearrangement* precursor, which upon thermolysis in boiling toluene gave 5-phenyl-7-carboethoxyimidazo[5,1-*b*]-2,3-dihydrooxazole in 97% yield.



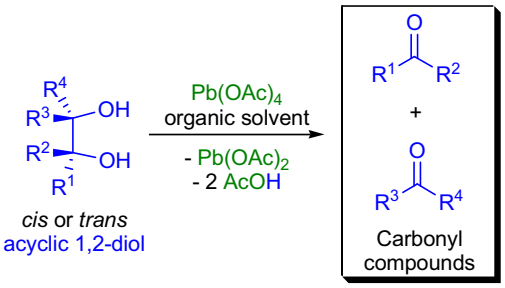
CRIEGEE OXIDATION

(References are on page 568)

Importance:

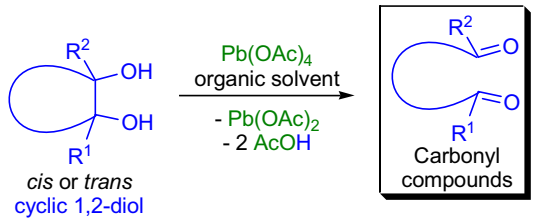
[*Seminal Publication*[1]; *Reviews*[2-5]; *Modifications & Improvements*[6-8]]

The cleavage of 1,2-diols (glycols) to the corresponding carbonyl compounds by lead tetraacetate [$Pb(OAc)_4$, LTA] in an organic solvent is known as the *Criegee oxidation*. Glycols are cleaved with ease under mild conditions and in good yield with periodic acid (HIO_4) or LTA. Other functional groups, such as β-amino alcohols, 1,2-diamines, α-hydroxy aldehydes and ketones, α-diketones and α-keto aldehydes undergo similar cleavage upon treatment with LTA. Several oxidizing agents (e.g., sodium bismuthate, manganese(III) pyrophosphate, PIDA, cerium(IV) salts, vanadium(V) salts, chromic acid, nickel peroxide, silver(I) salts, etc.) also cleave glycols, but these oxidizing agents are synthetically much less efficient. *Cis*-vicinal diols and *threo* diols are cleaved much faster than the corresponding *trans*-vicinal diols and *erythro* diols. *Cis* diols can be titrated using LTA without the interference of aliphatic glycols and *trans*-glycols on five-membered rings.[9] The *Criegee oxidation* is complementary to the *ozonolysis* of double bonds, since alkenes are easily dihydroxylated and then cleaved to afford the desired carbonyl compounds. During the past decade, the oxidative cleavage of bicyclic unsaturated diols led to the development of a new *ring-expansion/rearrangement* methodology for the preparation of densely functionalized six- and seven-membered rings from simple and well-known building blocks.[6-8]



cis or *trans* acyclic 1,2-diol

R^{1-4} = H, alkyl

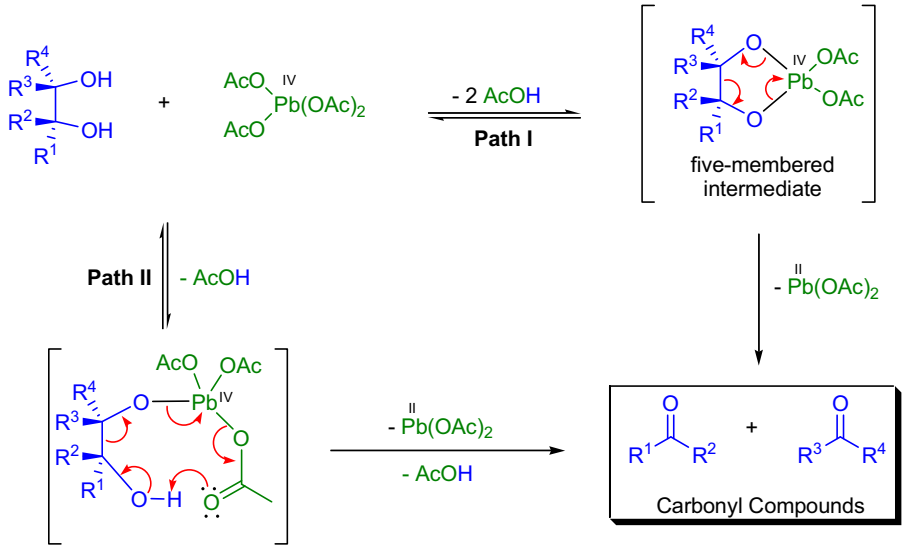


cis or *trans* cyclic 1,2-diol

R^{1-2} = H, alkyl

Mechanism:[10-20,8]

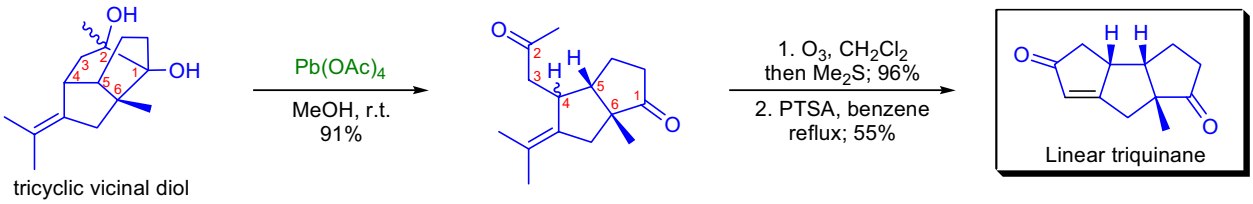
The mechanism of the *Criegee oxidation* most likely involves the formation of a bidentate metal - 1,2-glycol five-membered complex (**Path I**), which then breaks down to products *via* a two-electron process. The breakdown of the cyclic intermediate is the rate-determining step and the driving force is the electronegativity of $Pb^{(IV)}$, which abstracts the bonded electron pair of one of the O-atoms adjacent to the C-C bond and is reduced to $Pb^{(II)}$. The kinetics of the reaction is overall second order, first order in each reactant. It was found that the addition of acetic acid retards the reaction by shifting the equilibrium to the left. For substrates where the formation of the cyclic five-membered intermediate is not possible (e.g., bicyclic *trans* diols), an alternative concerted electron displacement is proposed (**Path II**) involving one of the acetate groups attached to the metal.[13]



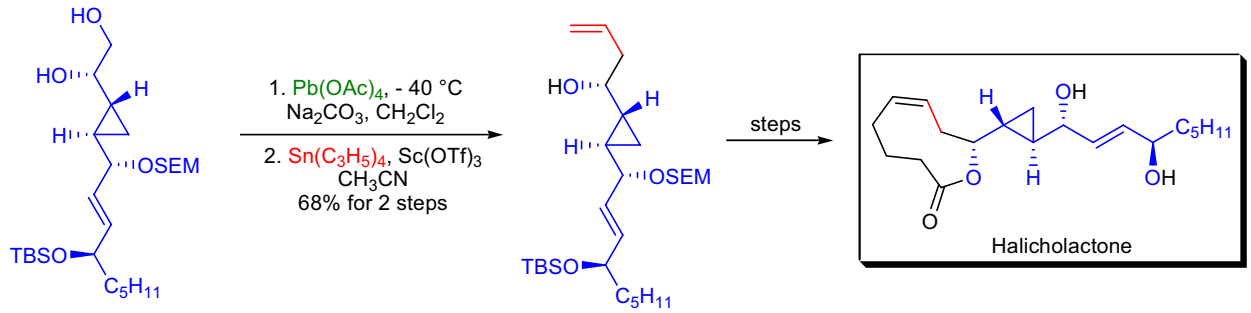
CRIEGEE OXIDATION

Synthetic Applications:

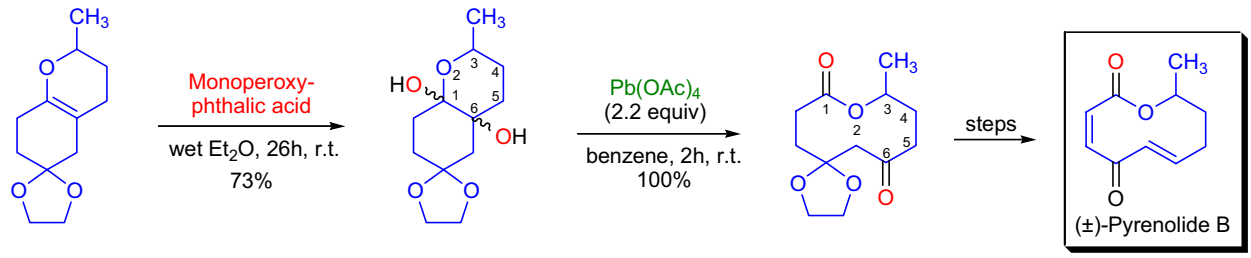
G.S.R. Rao and co-workers described the conversion of aromatic compounds to linear and angular triquinanes, which involved a *5-exo-trig allyl radical cyclization* as the key step.[21] To install the third five-membered ring of the linear triquinane, the tricyclic 1,2-diol intermediate was cleaved using the *Criegee oxidation* to afford a diketone. The remaining double bond was cleaved by ozonolysis and the resulting triketone was treated with PTSA in refluxing benzene to give the desired linear triquinane.



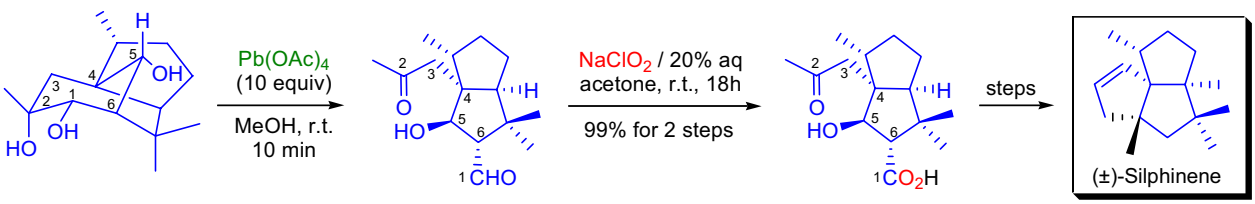
In the laboratory of Y. Takemoto, the asymmetric total synthesis of the marine metabolite, halicholactone was accomplished.[22] One advanced intermediate contained a 1,2-vicinal diol moiety which was cleaved under mild conditions to afford the corresponding aldehyde. The *Criegee oxidation* was chosen to effect this transformation at low temperature, followed by the *stereoselective allylation* of the resulting aldehyde with tetraallyltin.



M. Hesse and co-workers synthesized ( )-pyrenolide B, a macrocyclic natural product isolated from a phytopathogenic fungus.[23] The key transformation of the synthesis was the *ring enlargement reaction* of a bicyclic enol ether intermediate to the corresponding oxolactone. The ring enlargement was performed using a two-step procedure: dihydroxylation of the enol ether double bond, followed by oxidation of the resulting diol with $Pb(OAc)_4$ to quantitatively afford the ring-expanded product.



In the synthesis of angular triquinane ( )-silphinene by S. Yamamura et al., the *Criegee oxidation* was used to obtain a key bicyclic intermediate.[24]



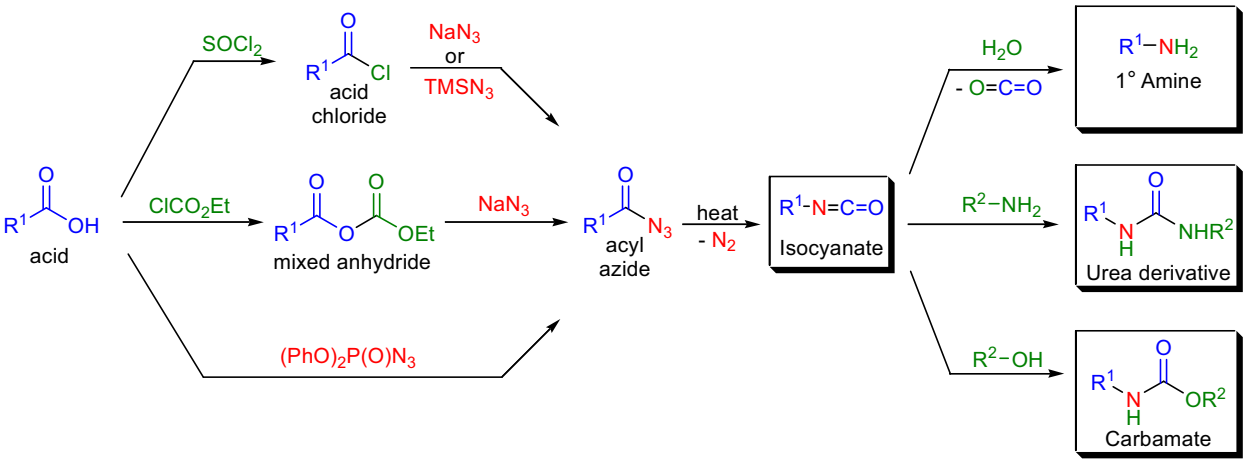
CURTIUS REARRANGEMENT

(References are on page 568)

Importance:

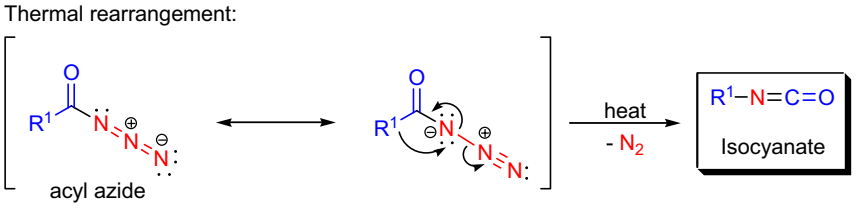
[*Seminal Publications*[1-5]; *Reviews*[6-10]; *Modifications & Improvements*[11-14]; *Theoretical Studies*[15-17]]

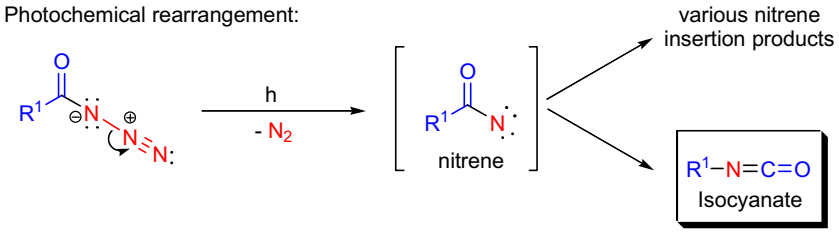
The thermal decomposition (pyrolysis) of acyl azides to the corresponding isocyanates is known as the *Curtius rearrangement*. The rearrangement is catalyzed by both protic[18] and Lewis acids and the decomposition temperature is significantly lowered compared to the uncatalyzed reaction.[19] Acyl azides can be prepared in several different ways: 1) reacting acid chlorides or mixed anhydrides[11] with alkali azide[13] or trimethylsilyl azide;[20] 2) treating acylhydrazines with nitrous acid or nitrosonium tetrafluoroborate;[21] and 3) treating carboxylic acids with diphenyl phosphoryl azide (DPPA).[12] The product isocyanate can be isolated if the pyrolysis is conducted in the absence of nucleophilic solvents. If the reaction is carried out in the presence of water, amines (R-NH_2), or alcohols (R-OH), the corresponding amines, ureas, and carbamates are formed. The *Curtius rearrangement* is a very general reaction and can be applied to carboxylic acids containing a wide range of functional groups. It is also possible to induce a *Curtius rearrangement* under photochemical conditions, but this pathway gives rise to several side-products in addition to the desired isocyanate.[22] The *photochemical Curtius rearrangement* of phosphinic azides is also known as the *Harger reaction*.[23-25]



Mechanism: [26-30]

Nitrene intermediates are formed in the pyrolysis of most alkyl azides, aryl azides, sulfonyl azides, and azidoformates. However, the mechanism of the *Curtius rearrangement* under thermal conditions is most likely a concerted process.[27] This hypothesis is based on the lack of any evidence indicating the formation of a free acyl nitrene species.[15] For example, neither insertion, addition, nor amide products are isolated in the *thermal Curtius rearrangement*, which would be expected if a nitrene intermediate is involved.[6] The values of the entropy of activation are also in good agreement with a synchronous mechanism.[28] The *photochemical Curtius rearrangement* on the other hand proceeds by the formation of nitrenes, which undergo typical nitrene reactions. This is not surprising, since the energy of the photon is high enough to break the N-N_2 bond without alkyl or aryl participation.

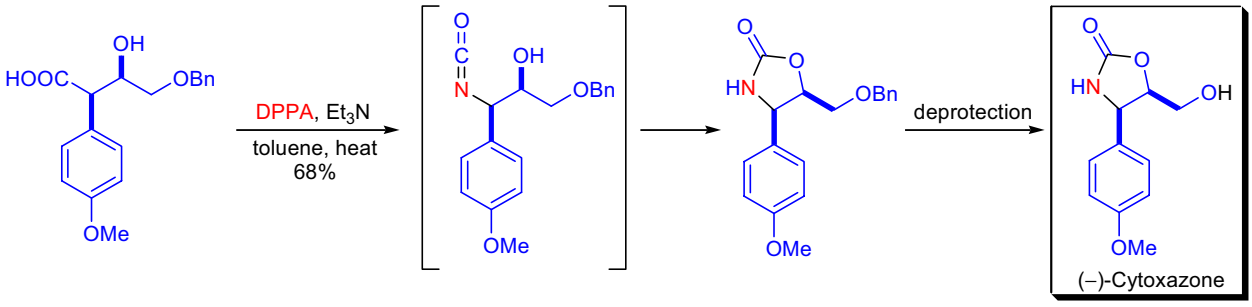




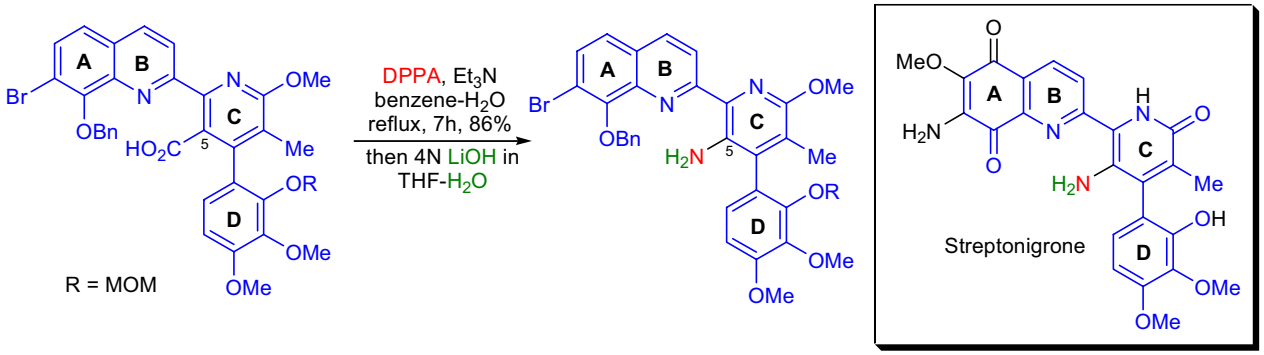
CURTIUS REARRANGEMENT

Synthetic Applications:

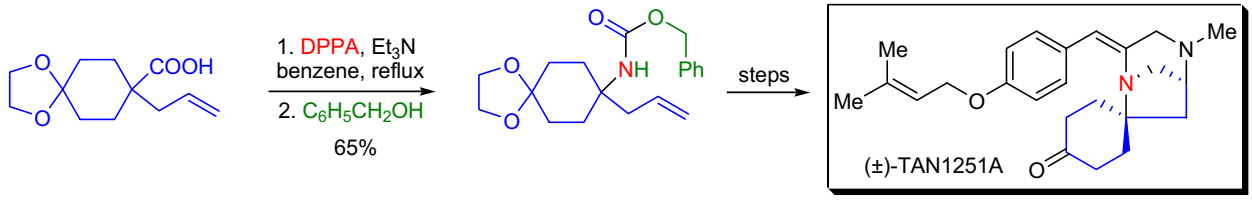
The enantioselective total synthesis of the cytokine modulator (–)-cytoxazone using a *syn-stereoselective aldol addition* and a *Curtius rearrangement* as key steps was described by J.A. Marco et al.[31] The key intermediate acid was treated with DPPA and triethylamine in toluene at reflux. This step furnished the oxazolidinone directly and in good yield through an *in situ* capture of the isocyanate group by the free secondary alcohol functionality. Removal of the protecting group led to the formation of the natural product.



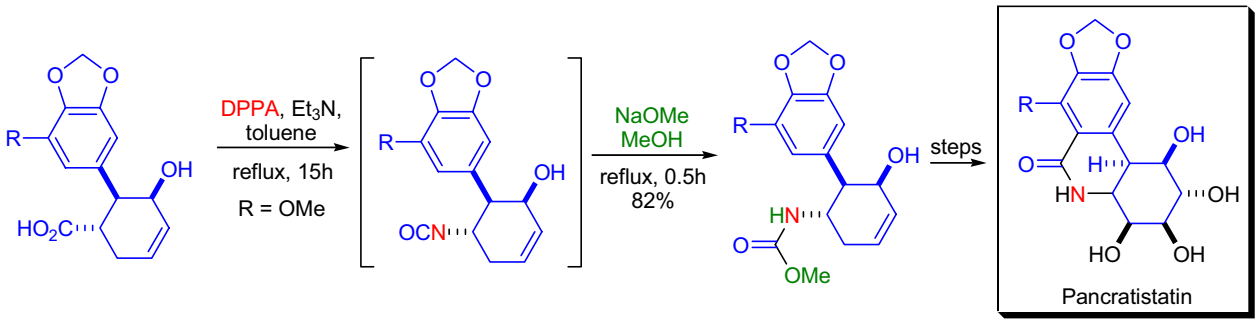
The first total synthesis of streptonigrone utilizing an *inverse electron demand Diels-Alder reaction* was accomplished in the laboratory of D.L. Boger.[32] In order to introduce the C5 pyridone amine functionality, the carboxylic acid was exposed to the Shioiri-Yamada reagent (DPPA) in benzene-water. Subsequent hydrolysis with lithium hydroxide in THF/water was necessary to complete the conversion to the primary amine.



The antimuscarinic alkaloid (±)-TAN1251A possesses a unique tricyclic skeleton that consists of a 1,4-diazabicyclo[3.2.1]octane ring and a cyclohexanone ring bonded through a spiro carbon atom. K. Murashige and co-workers introduced the nitrogen connected to the spiro carbon atom by applying the *Curtius rearrangement*.[33]



A key carbamate intermediate during the total synthesis of pancratistatin was prepared *via* the *Curtius rearrangement* of the corresponding carboxylic acid by S. Kim et al.[34] The isocyanate intermediate was rather stable and was converted to the desired carbamate in 82% overall yield by treatment with NaOMe/MeOH.



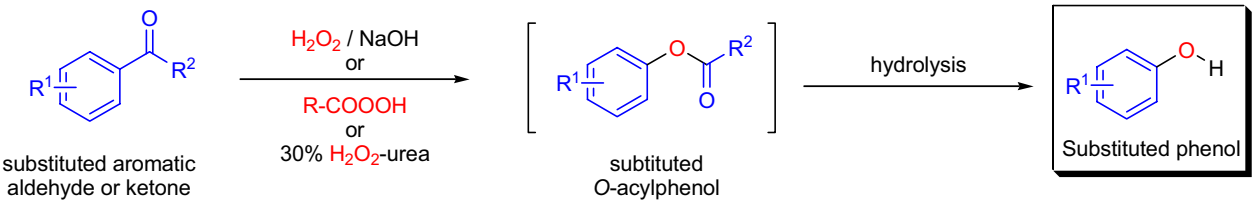
DAKIN OXIDATION

(References are on page 569)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifcations & Improvements*[8,9]]

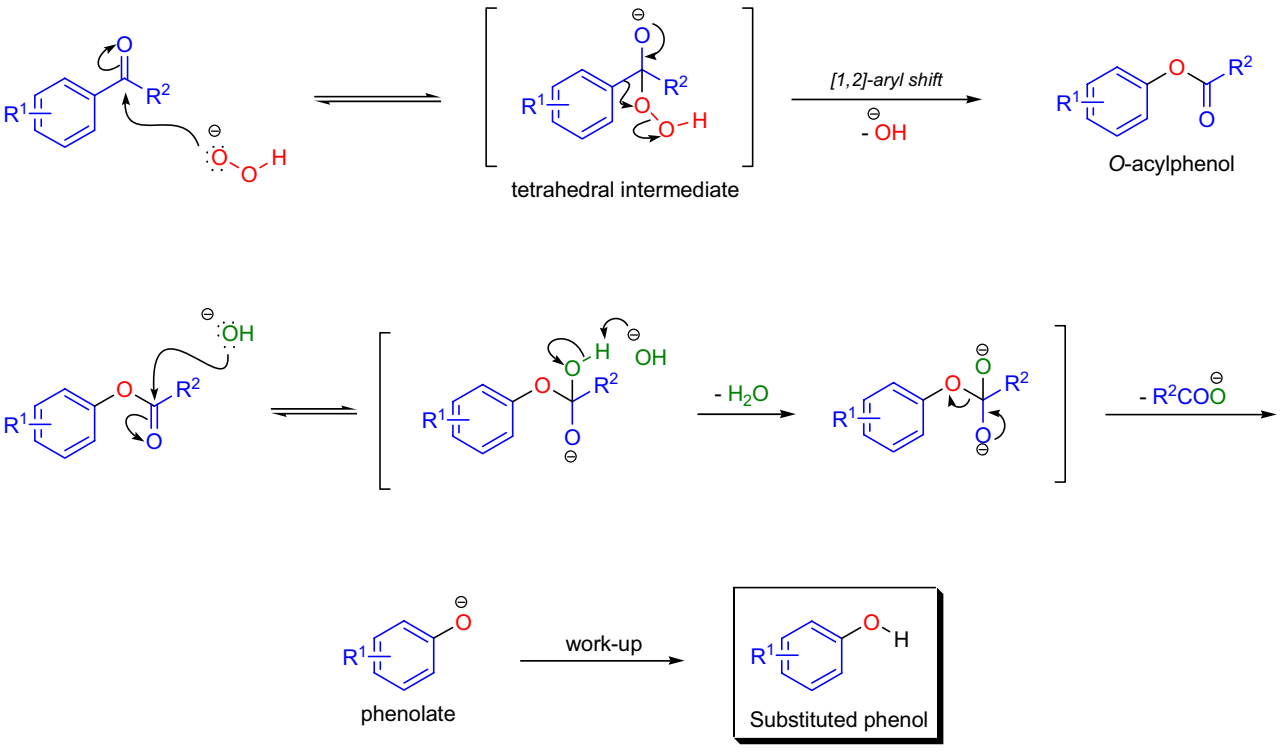
When treated with organic peracids (RCO_3H) or hydrogen peroxide (H_2O_2), aliphatic aldehydes are smoothly oxidized to carboxylic acids. Aromatic aldehydes, however, undergo a more complex reaction in which the aldehyde group is converted to the acylated phenolic hydroxyl group. In 1909, H.D. Dakin obtained high yields of pyrocatechol (1,2-dihydrohybenzene) when he oxidized *ortho*-hydroxybenzaldehyde with perbenzoic acid.[1] The oxidation of aromatic aldehydes and ketones to the corresponding phenols is known as the *Dakin oxidation*, and this transformation is very similar to the well-known *Baeyer-Villiger oxidation*. The reaction works best if the aromatic aldehyde or ketone is electron rich (-R, -OH, -OR, $-NH_2$, or -NHR substituents in the *ortho* or *para* positions). When the aromatic ring is substituted with electron-withdrawing groups, the product of the oxidation is usually the carboxylic acid. The *Dakin oxidation* is usually performed using the following reagents: alkaline H_2O_2,[5,10] acidic H_2O_2,[11] peroxybenzoic acid,[12] peroxyacetic acid,[13] sodium percarbonate,[14] 30% H_2O_2 with arylselenium compounds as activators (*Syper process*),[8] and urea-H_2O_2 (UHP) adduct.[9]



R^1 = OH, NH_2, alkyl, OR, NHR; R^2 = H, alkyl

Mechanism:[12,10,15-17]

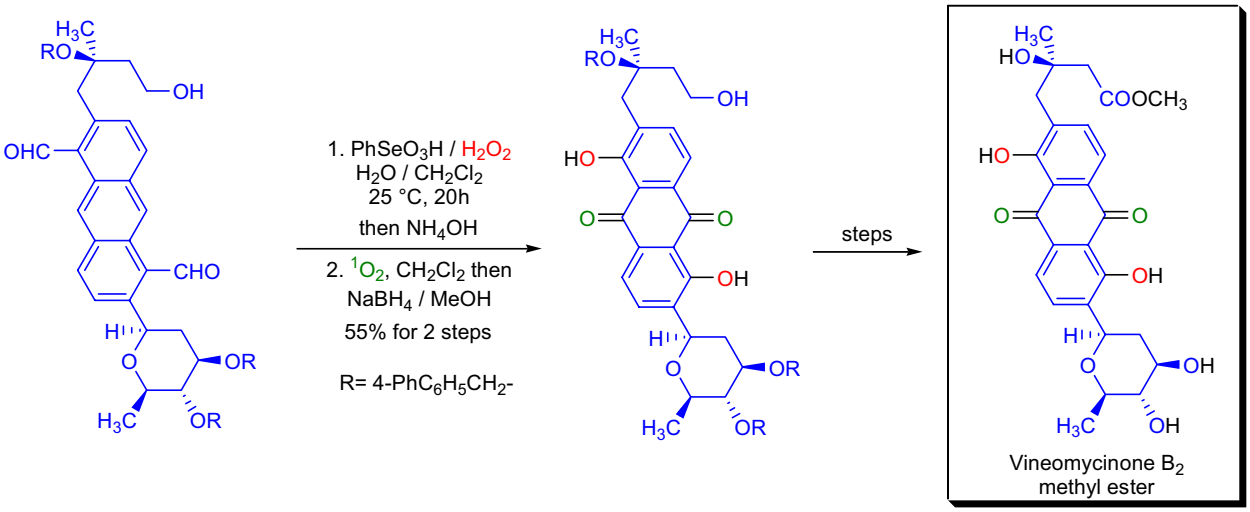
The mechanism of the *Dakin oxidation* is very similar to the mechanism of the *Baeyer-Villiger oxidation*. Under basic conditions (H_2O_2/NaOH) the hydrogen-peroxide is deprotonated to give the hydroperoxide anion (HO_2^-), which adds across the carbonyl group of the substituted aromatic aldehyde or ketone. The resulting tetrahedral intermediate undergoes a *[1,2]-aryl shift* to afford an *O*-acylphenol, which is hydrolyzed to the corresponding phenolate anion under the reaction conditions. Finally, the work-up liberates the substituted phenol from the phenolate salt.



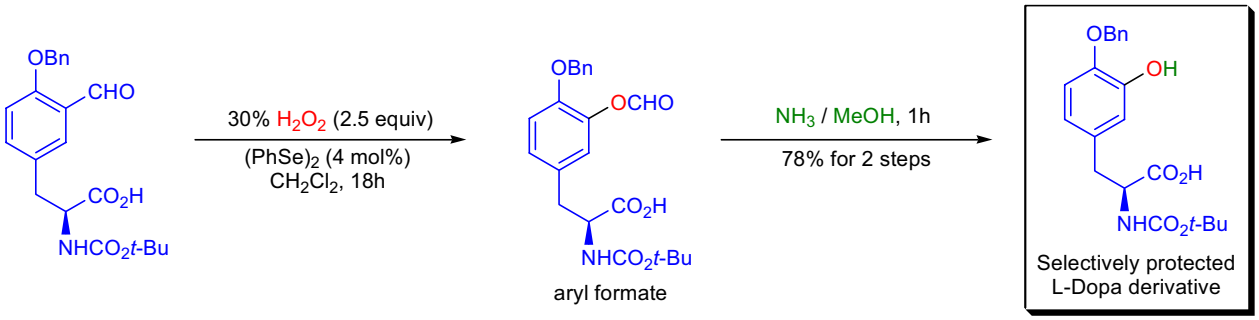
DAKIN OXIDATION

Synthetic Applications:

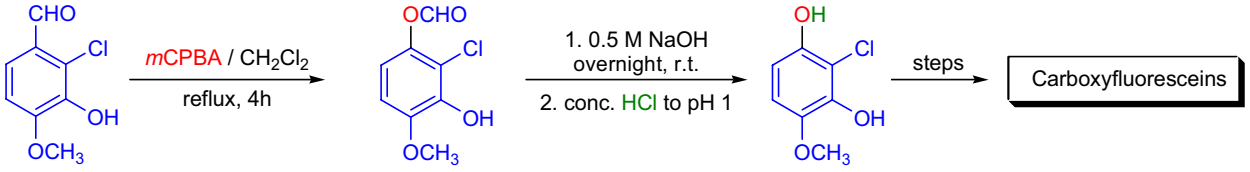
The total synthesis of vineomycinone B_2 methyl ester was accomplished in the laboratory of C. Mioskowski using a *double Bradsher cyclization*, a *modified Dakin oxidation*, and a *singlet oxygen oxidation* as key steps.[18] The substituted anthracene-dialdehyde derivative was treated under *modified Dakin oxidation* conditions, that is, with phenylselenic acid and hydrogen peroxide at 20 °C for 20h, to introduce the phenolic oxygens. This was followed by a singlet oxygen addition across the central aromatic ring with reductive work-up and air oxidation to generate the desired anthraquinone functionality.



M.E. Jung and co-workers have developed a synthesis of selectively protected L-Dopa derivatives from L-tyrosine *via* a *Reimer-Tiemann reaction* followed by the *modified Dakin oxidation*.[19] The formyl group introduced by the *Reimer-Tiemann reaction* had to be converted to the corresponding phenol. After trying many sets of conditions, the *Syper process* was chosen, which uses arylselenium compounds as activators for the oxidation. Treatment of the aromatic aldehyde with 2.5 equivalents of 30% hydrogen peroxide in the presence of 4% diphenyl diselenide in dichloromethane for 18h gave the aryl formate in excellent yield. This ester was cleaved by treatment with methanolic ammonia for 1h to afford the desired phenol in good yield.



Carboxy-functionalized fluorescein dyes are important as conjugated fluorescent markers of biologically active compounds. M.H. Lyttle et al. have used the *Dakin oxidation* on 4-methoxy-3-hydroxy-2-chloro-benzaldehyde to obtain the desired resorcinol derivative that served as an intermediate in their improved synthesis.[20]



DAKIN-WEST REACTION

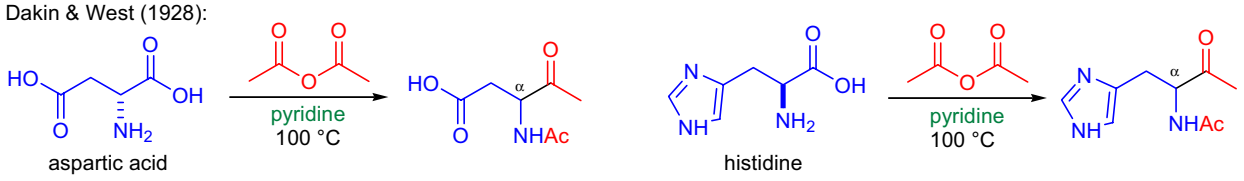
(References are on page 569)

Importance:

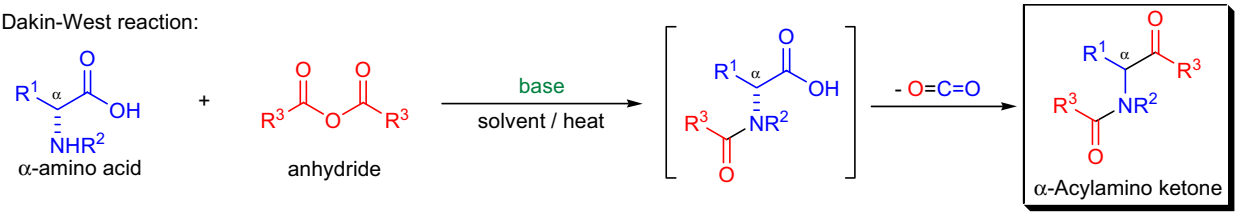
[*Seminal Publications*[1-3]; *Reviews*[4-6]; *Modifications & Improvements*[7-10]]

The conversion of carboxylic acids to ketones has been known for centuries.[6] It is therefore interesting that since the mid-1800s several chemists have claimed to have discovered this transformation (e.g., W.H. Perkin, Sr., W. Heintz, etc.).[1] In 1928, H.D. Dakin and R. West reported that when certain amino acids, such as aspartic acid and histidine, were heated in acetic anhydride in the presence of pyridine, the corresponding α-acetamido methyl ketones were formed in high yield.[2,3] The formation of α-acylamino alkyl ketones from α-amino acids and symmetrical carboxylic acid anhydrides in the presence of a base is known as the *Dakin-West reaction*. The general features of this transformation are: 1) both primary and secondary α-amino acids undergo this transformation, but β-amino acids only afford the corresponding *N*-acylated derivatives; 2) the α-amino acids need to have a proton at their α-position, otherwise they simply undergo *N*-acylation; 3) the anhydride component is most often acetic anhydride, but other anhydrides such as propionic anhydride can also be used; 4) when acetic anhydride is used, the product is an α-acetylamino methyl ketone, whereas with propionic anhydride the corresponding α-propionylamino ethyl ketone is obtained; 5) the base is usually pyridine, but various alkylpyridines and sodium acetate have been successfully employed; 6) primary α-amino acids react with anhydrides at around 100 °C, but secondary α-amino acids require significantly higher reaction temperatures; and 7) the addition of a nucleophilic catalyst such as DMAP allows the reaction to take place at room temperature.[8]

Dakin & West (1928):



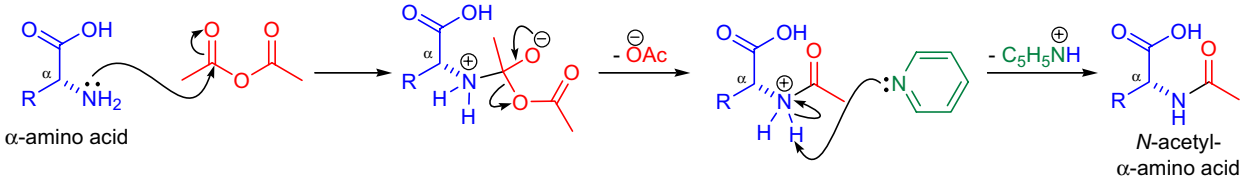
Dakin-West reaction:



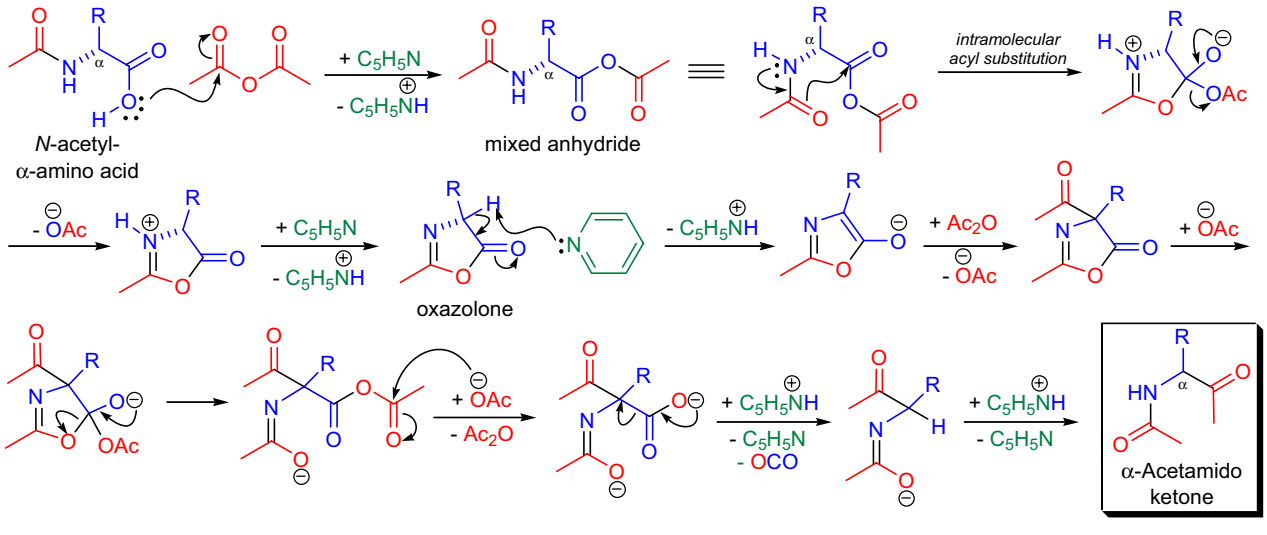
R^1 = H, alkyl, substituted alkyl; R^2 = H, alkyl, substituted alkyl, aryl, heteroaryl; R^3 = Me, Et, *n*-Pr; base: pyridine, alkylpyridine, NaOAc; solvent: pyridine, Et_3N

Mechanism:[11-26,6]

Formation of *N*-acetyl-α-amino acid:



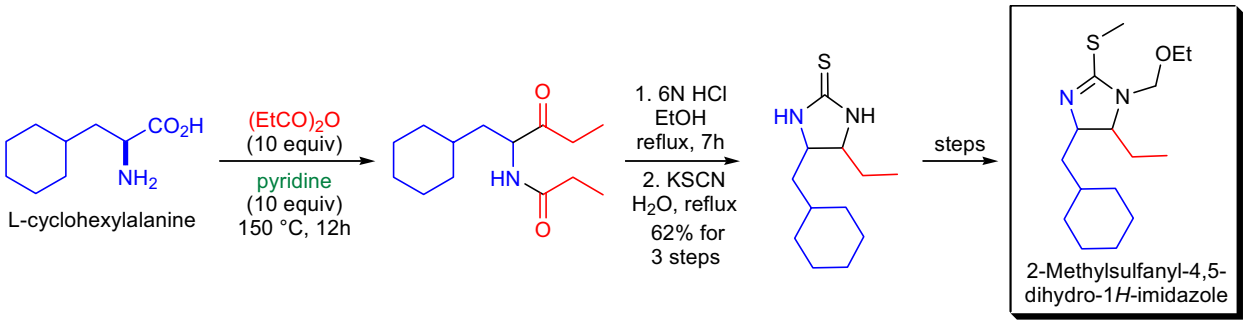
Formation of α-acetamido ketone from *N*-acetyl-α-amino acid:



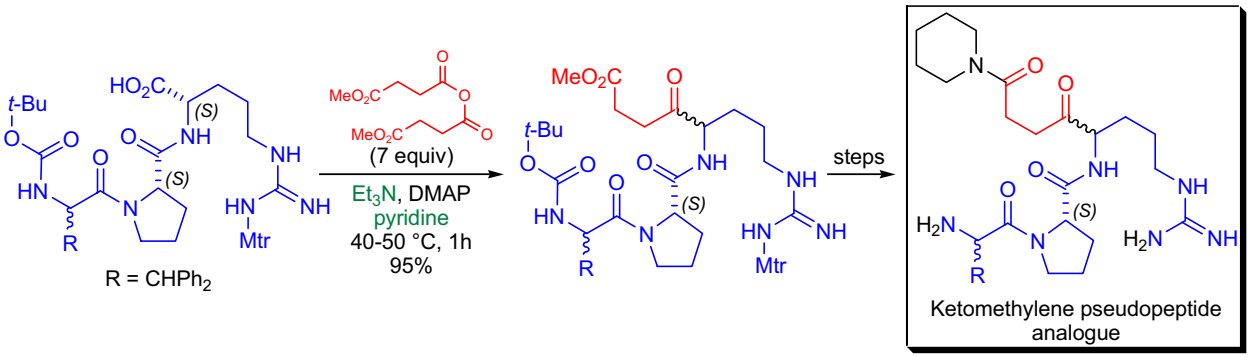
DAKIN-WEST REACTION

Synthetic Applications:

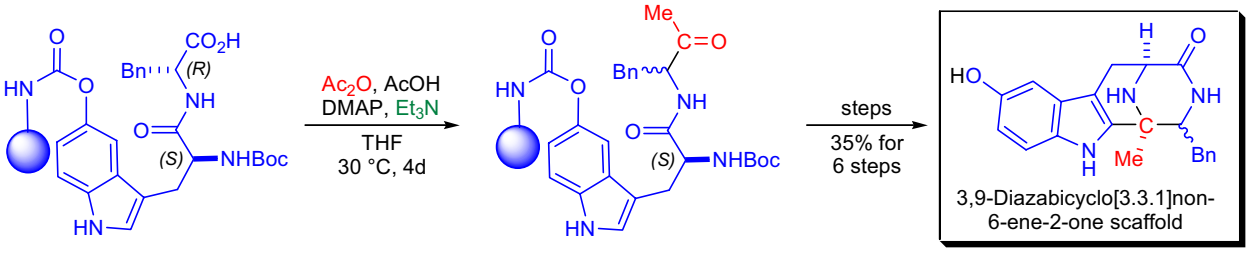
In the laboratory of E.B. Pedersen, several 2-methylsulfanyl-1*H*-imidazoles were prepared and tested for their activity against HIV-1.[27] These compounds can be regarded as novel non-nucleoside reverse transcriptase inhibitors. The required α-aminoketone hydrochloride building blocks were prepared using the *Dakin-West reaction*. L-Cyclohexylalanine was dissolved in excess pyridine and propionic anhydride and was kept at reflux overnight. The resulting α-propionylamino ethyl ketone was hydrolyzed with concentrated hydrochloric acid and the α-aminoketone hydrochloride was heated with one equivalent of potassium thiocyanate in water to afford 4-cyclohexylmethyl-5-ethyl-1,3-dihydroimidazole-2-thione. This material was then advanced to 4-cyclohexylmethyl-1-ethoxymethyl-5-ethyl-2-methylsulfanyl-1*H*-imidazole.



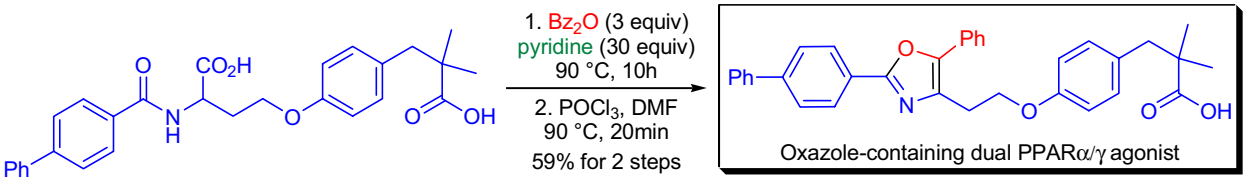
The synthesis of ketomethylene pseudopeptide analogues was accomplished by L. Cheng et al., and their biological activity as thrombin inhibitors was tested.[28] These analogues were prepared through a *modified Dakin-West reaction* under mild conditions and in almost quantitative yield. The required anhydride was prepared from monomethyl succinate, and a large excess of it was mixed with the tripeptide substrate in pyridine in addition to triethylamine and catalytic amounts of DMAP. The reaction mixture was heated for one hour at 40-50 °C.



The efficient solution and solid phase synthesis of a 3,9-diazabicyclo[3.3.1]non-6-en-2-one scaffold was developed by R. Giger and co-workers from L-tryptophan using a novel sequential *Dakin-West/intramolecular Pictet-Spengler reaction*.[10]



An improved method for the preparation of a series of oxazole-containing dual PPARα/γ agonists was reported by A.G. Godfrey et al.[29] The synthesis utilized the *Dakin-West reaction* which allowed the introduction of a phenyl ketone moiety. This ketone was subsequently converted to the corresponding oxazole using $POCl_3$/DMF.



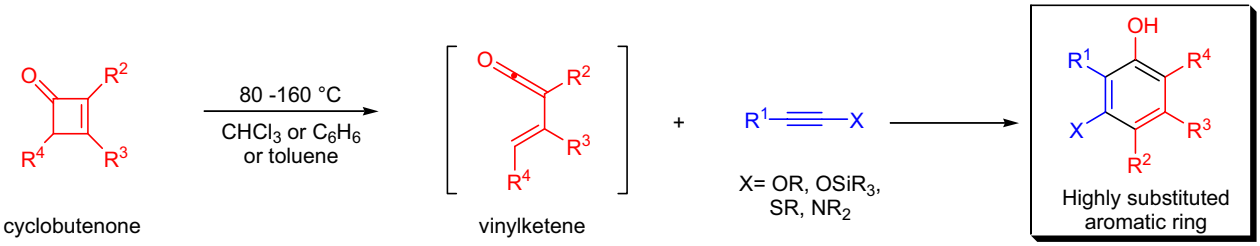
DANHEISER BENZANNULATION

(References are on page 570)

Importance:

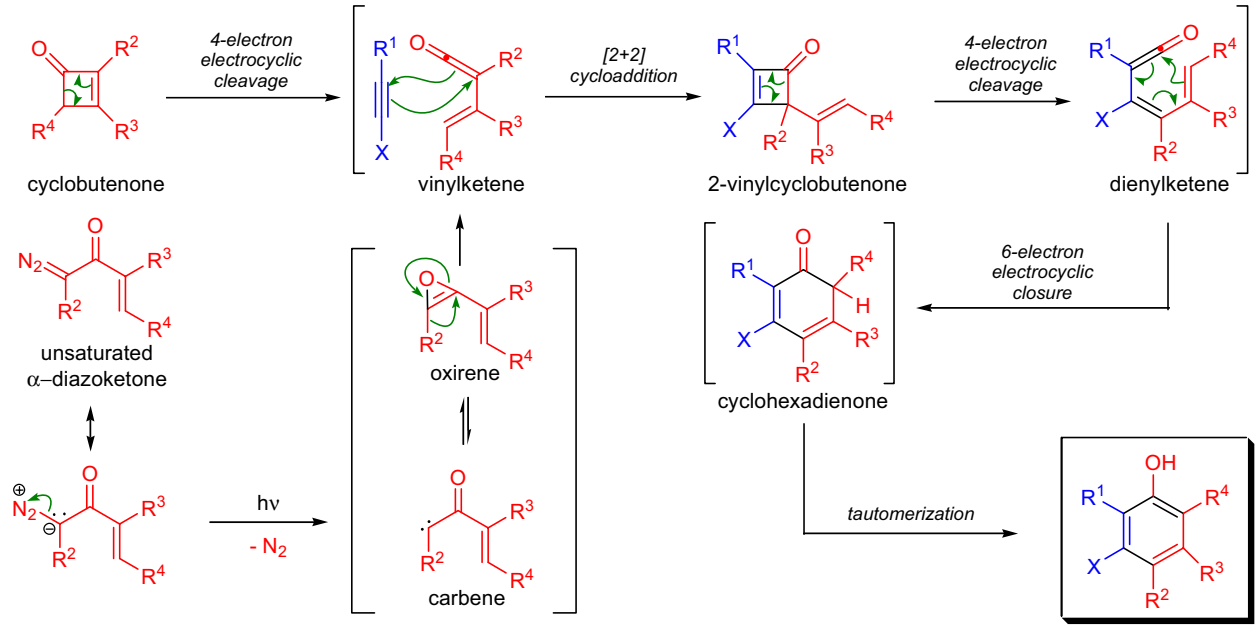
[*Seminal Publication*[1]; *Modifications & Improvements*[2]]

In 1984, R.L. Danheiser and co-workers developed a new, one-step method for the regiocontrolled synthesis of highly substituted aromatic compounds by heating cyclobutenone derivatives with activated (heterosubstituted)[1,3-5] or unactivated acetylenes. This convergent annulation process is referred to as the *Danheiser benzannulation*, and it proceeds *via* a vinylketene intermediate. Alkoxyacetylenes were found to be the best partners for this annulation, but the relatively harsh conditions required to cleave the aryl ether moiety in the products led to the use of trialkylsilyloxyalkynes instead.[4] In the typical annulation procedure, the solution of the cyclobutenone component (in $CHCl_3$, benzene, or toluene) in the presence of a slight excess of the heterosubstituted acetylene is heated to 80-160 °C in a sealed Pyrex tube.[1] Modification of the original strategy involves the generation of the vinyl- or arylketene intermediate *via* the *photochemical Wolff-rearrangement* of an unsaturated (vinyl or aryl) α-diazo ketone.[2] This new two-step *modified Danheiser benzannulation* allows the synthesis of polycyclic aromatic and heteroaromatic systems (e.g., substituted naphthalenes, benzofurans, benzothiophenes, indoles, carbazoles, etc.), which cannot be accessed using the original methodology. The advantage of this new procedure is that the various functionalized aryl and vinyl α-diazo ketones are easily accessible from a wide range of available simple ketones and carboxylic acid derivatives. The best yields are obtained when 3-alkoxy phenol derivatives are formed, and in this respect the *modified Danheiser benzannulation* complements the *Dötz benzannulation* reaction, which results in the formation of 4-alkoxy phenol derivatives.



Mechanism:[1,2]

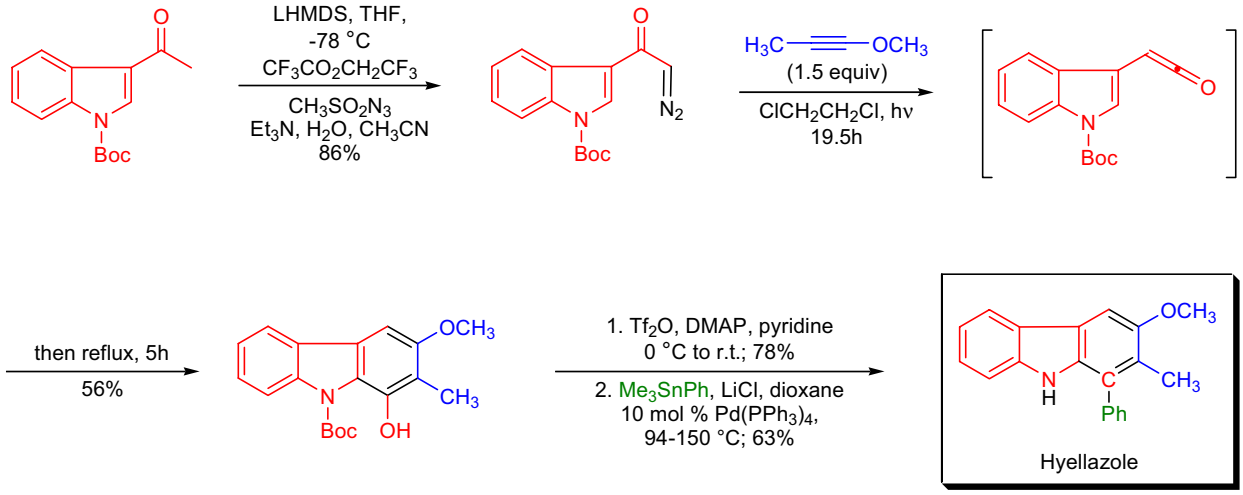
In the original version of the annulation, the vinylketene[6] intermediate is generated in a reversible *4π electrocyclic ring opening* of the cyclobutenone followed by a cascade of three more pericyclic reactions. The ketenophilic alkyne reacts with the vinylketene in a regiospecific *[2+2] cycloaddition*. The resulting 2-vinylcyclobutenone then undergoes a reversible *4π electrocyclic cleavage* to give a dienylketene, which immediately rearranges in a *six-electron electrocyclization* to afford a cyclohexadienone. The highly substituted phenol is formed after tautomerization. The *photochemical Wolff rearrangement* of the unsaturated α-diazoketone also yields the vinylketene, and most likely proceeds *via* carbene and oxirene intermediates.[7]



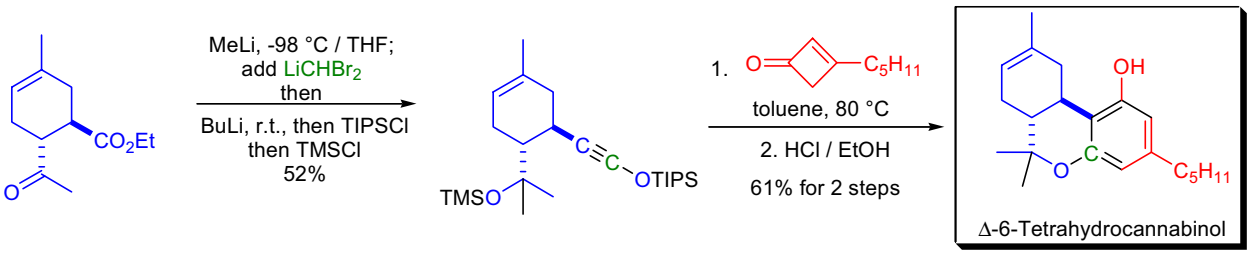
DANHEISER BENZANNULATION

Synthetic Applications:

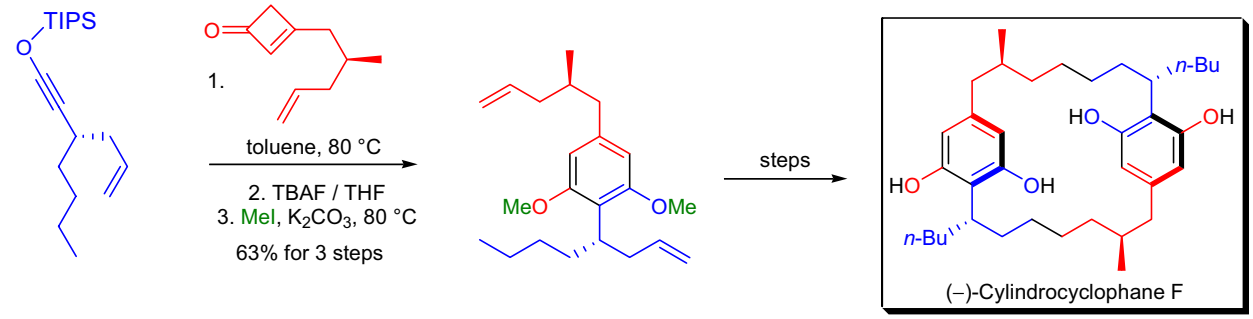
R.L. Danheiser and co-workers have used the *modified Danheiser benzannulation* for the synthesis of the marine carbazole alkaloid hyellazole.[2] The required diazoketone was prepared from the *N*-Boc derivative of 3-acetylindole using a *diazo transfer reaction*. The diazoketone was irradiated in the presence of the alkyne to afford the desired carbazole annulation product in 56% yield. Finally, in order to install the phenyl group of hyellazole at C1, the phenolic hydroxyl group was converted to the corresponding triflate and a *Stille cross-coupling* was performed.



The use of substituted alkoxyacetylenes in synthesis is fairly limited due to the lack of simple, general methods for their preparation. However, silyloxyacetylenes are easier to make and can be prepared from esters in a one-pot operation.[8] In the laboratory of C.J. Kowalski, research has shown that silyloxyacetylenes could be successfully used in the *Danheiser benzannulation*.[5] This modification was used in the total synthesis of Δ-6-tetrahydrocannabinol.



During the total synthesis of (–)-cylindrocyclophane F, A.B. Smith et al. used the *Danheiser benzannulation* to construct the advanced aromatic intermediate for an *olefin metathesis dimerization* reaction.[9] The starting material triisopropylsilyloxyalkyne was synthesized from the corresponding ethyl ester using the *Kowalski two-step chain homologation*.[8]



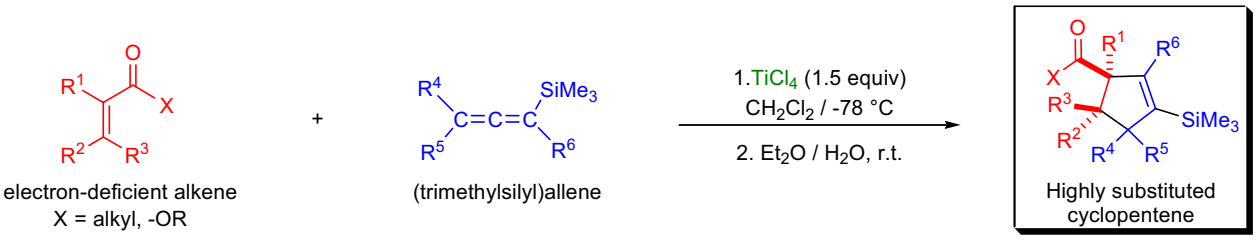
DANHEISER CYCLOPENTENE ANNULATION

(References are on page 570)

Importance:

[*Seminal Publications*[1,2]; *Modifications and Improvements*[3-8]]

The one-step regio- and stereoselective [3+2] annulation of (trimethylsilyl)allenes and electron-deficient alkenes (allenophiles) in the presence of titanium tetrachloride ($TiCl_4$) to produce highly substituted cyclopentene derivatives is referred to as the *Danheiser cyclopentene annulation*. The typical annulation involves rapid addition of 1.5 equivalents of distilled $TiCl_4$ to a methylene chloride solution containing the allenophile and 1.0-1.5 equivalents of (trimethylsilyl)allene at -78°C.[1,2] The required (trimethylsilyl)allenes are relatively easy to prepare, and the allenophiles are usually readily available α,β-unsaturated ketones. Both cyclic and acyclic enones are good reaction partners. However, other allenophiles such as α-nitro olefins only react with allenes in a *Michael type process*. α,β-Unsaturated aldehydes give complex reaction mixtures, whereas α,β-unsaturated esters react sluggishly to afford the desired cyclopentene derivative in moderate yields. The annulation works most efficiently using 1-substituted (trimethylsilyl)allenes. The addition of the allene to the allenophile is predominantly suprafacial, and as a result, the annulation is highly stereoselective. The reaction of allenylsilanes with other electrophiles results in the formation of heterocycles.[4,5,8]

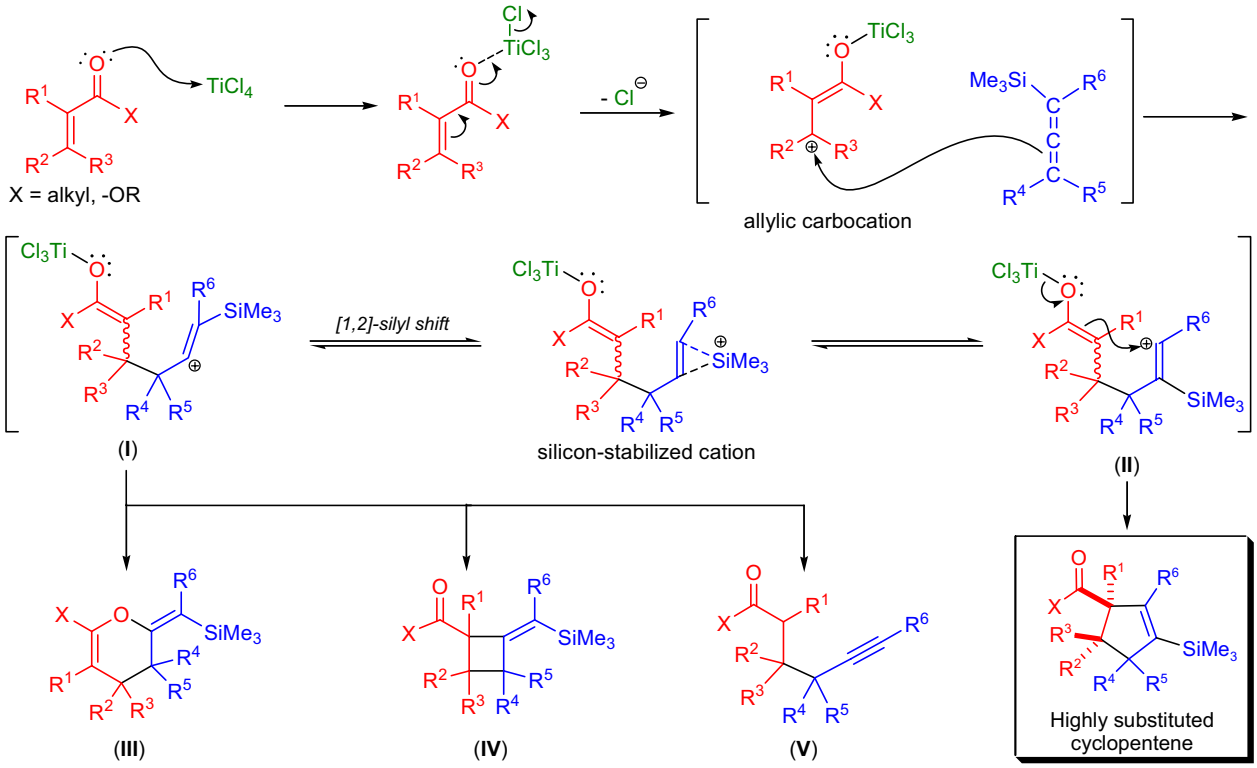


electron-deficient alkene
X = alkyl, -OR

(trimethylsilyl)allene

Mechanism:[1,2]

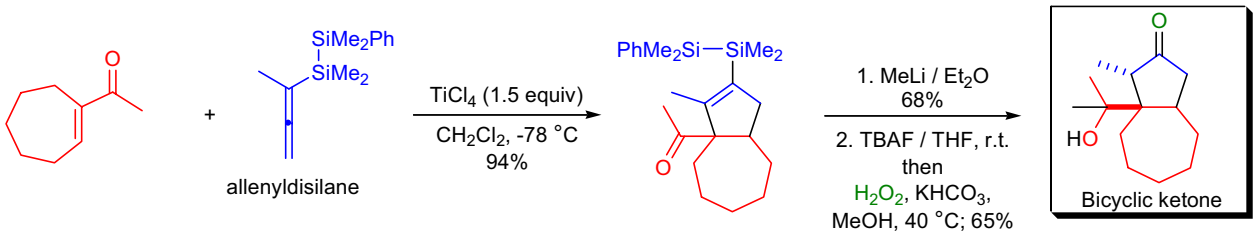
The first step of the mechanism involves the initial complexation of titanium tetrachloride to the carbonyl group of the electron-deficient alkene (enone) to give an alkoxy-substituted allylic carbocation. The allylic carbocation attacks the (trimethylsilyl)allene regiospecifically at C3 to generate vinyl cation **I**,[9] which is stabilized by the interaction of the adjacent C-Si bond. The allylic π-bond is only coplanar with the C-Si bond in (trimethylsilyl)allenes, so only a C3 substitution can lead to the formation of a stabilized cation.[1] A *[1,2]-shift* of the silyl group follows to afford an isomeric vinyl cation (**II**), which is intercepted by the titanium enolate to produce the highly substituted five-membered ring.[10,11] Side products (**III** – **V**) may be formed from vinyl cation **I**.



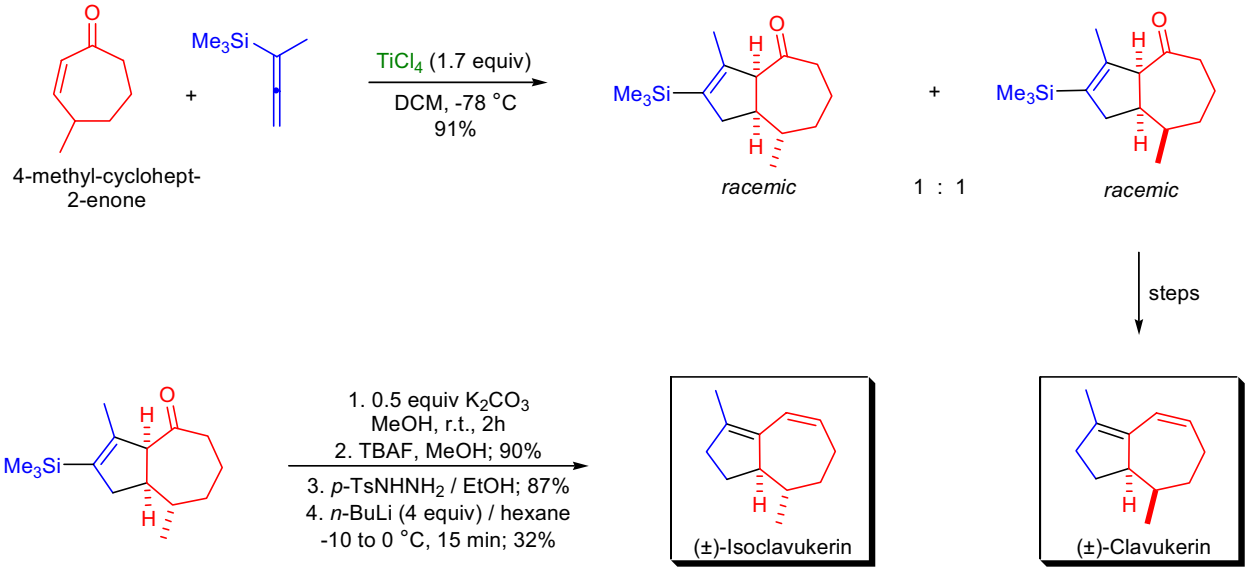
DANHEISER CYCLOPENTENE ANNULATION

Synthetic Applications:

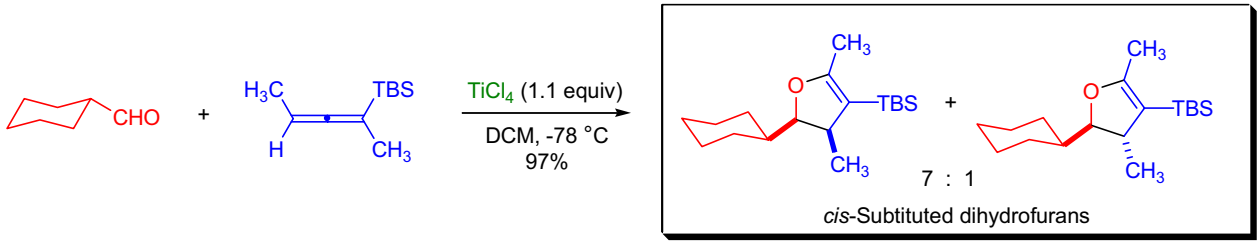
Disilanyl groups are considered the synthetic equivalent of the hydroxyl group. These groups can be easily converted in a one-pot reaction to the corresponding hydroxyl group by treatment with TBAF in THF followed by $H_2O_2/KHCO_3$ oxidation.[12] Y. Ito and co-workers have demonstrated the synthetic usefulness of the disilanyl groups in the *disilane version of the Danheiser cyclopentene annulation*. In the presence of 1.5 equivalents of $TiCl_4$, allenyldisilanes reacted with 1-acetylcycloalkenes to give bicyclic alkenyldisilanes in moderate to good yields. Then the bicyclic alkenyldisilanes were converted to the corresponding bicyclic ketones *via* oxidation.



H.J. Schäfer et al. achieved the formal total synthesis of the trinorguaiane sesquiterpenes (±)-clavukerin and (±)-isoclavukerin by using the *Danheiser cyclopentene annulation* as the key step.[13] Racemic 4-methylcyclohept-2-en-1-one was reacted with (trimethylsilyl)allene in the presence of 1.7 equivalents of $TiCl_4$ in dichloromethane at -78 °C to afford a 1:1 mixture of the *cis*-fused diastereomers, which were easily separated by HPLC. The diastereomers were then converted to key fragments of earlier total syntheses of the above mentioned natural products.



Research in the laboratory of R.L. Danheiser has shown that allenylsilanes can be reacted with electrophiles other than enones, such as aldehydes and *N*-acyl iminium ions to generate oxygen and nitrogen heterocycles.[4] Aldehydes can function as heteroallenophiles and the reaction of C3 substituted allenylsilane with the achiral cyclohexane carbaldehyde afforded predominantly *cis*-substituted dihydrofurans.



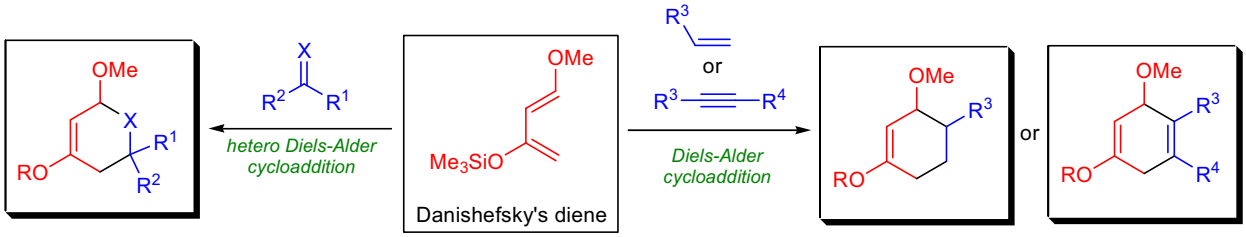
DANISHEFSKY'S DIENE CYCLOADDITION

(References are on page 570)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-5]; *Modifications and Improvements*[6-16]]

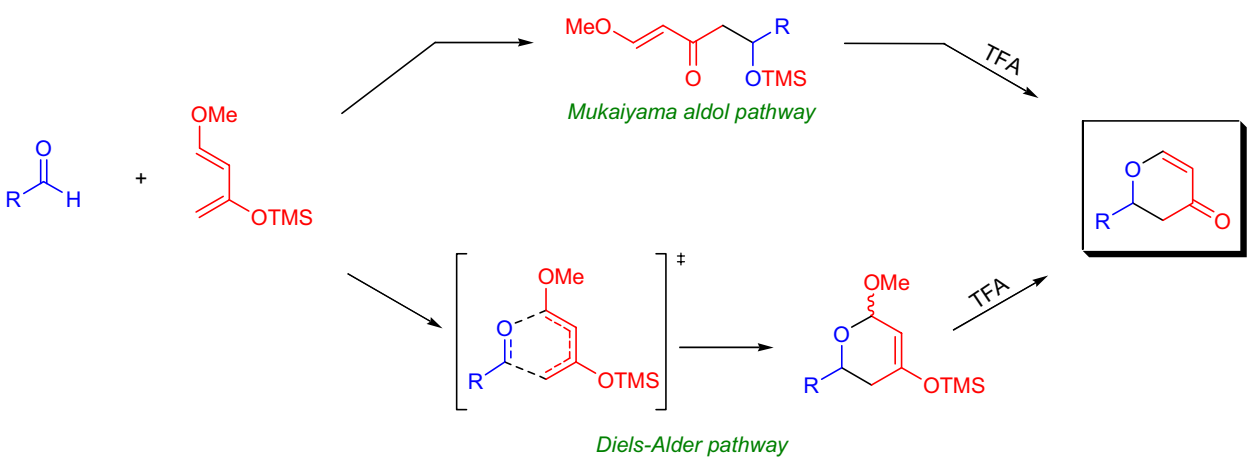
Following the discovery of the *Diels-Alder cycloaddition reaction* in 1928, a wide variety of functional groups were incorporated into the dienophile component, while the variation of substituents on the diene component was fairly limited. In 1974, S.J. Danishefsky et al. prepared an electron-rich heteroatom substituted diene, (*E*)-1-methoxy-3-(trimethylsilyloxy)-1,3-diene, which was later successfully used in *normal and hetero Diels-Alder cycloaddition* reactions.[1] Cycloaddition reactions involving this particular diene are referred to as *Danishefsky's diene cycloadditions*. Danishefsky's diene readily reacts with imines,[6,16] aldehydes,[4,11,14] alkenes, alkynes, and even with certain electron-deficient aromatic rings[17] to afford the corresponding heterocyclic and carbocyclic rings. In general, heteroatom substituents with lone pairs of electrons have the following effects on the diene component: 1) the diene becomes more electron-rich, making it more reactive toward dienophiles; 2) regioselectivity of the cycloaddition is improved when unsymmetrical dienophiles are used; and 3) the heteroatom serves as a handle for post-cycloaddition modifications (e.g., the β-alkoxy enol silyl ether is converted to the corresponding enone under acidic conditions).[18] The increase in reactivity can be explained by the FMO theory, namely that the electron-rich heteroatom increases the HOMO energy level of the diene thereby decreasing the energy difference between the diene's HOMO and the dienophile's LUMO. As a result, the transition state is stabilized, and the reaction rate is increased. Over the years, structural modifications to *Danishefsky's diene* improved the reactivity and selectivity as well as the acid and heat sensitivity of these electron-rich dienes.[7,9,10,12] The *Danishefsky's diene cycloaddition* reactions are catalyzed by various Lewis acids, and asymmetric versions have also been developed.[11,13-15]



R = TMS; X = O, NH, NR; R^1 = alkyl, aryl; R^2 = H, alkyl; R^3, R^4 = alkyl, aryl, EWG

Mechanism:[19,11,20,13]

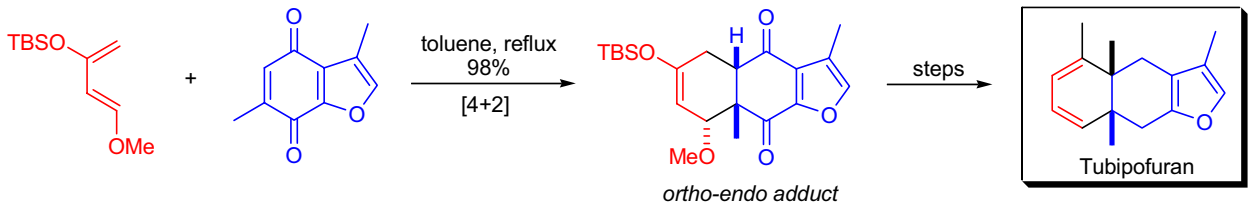
There are two different modes of cyclizations in hetero [4+2] cycloadditions involving *Danishefsky's diene*: 1) concerted (pericyclic) and 2) stepwise. When carbonyl compounds are reacted with Danishefsky's diene, the stepwise pathway is often referred to as the *Mukaiyama aldol reaction pathway*. The concerted process is called the *Diels-Alder pathway*. The mode of cyclization in the case of Lewis acid catalyzed reactions depends on the Lewis acid itself and whether it is present in stoichiometric or catalytic amounts.[19] The *Mukaiyama aldol pathway* has been observed only with titanium[21] and boron[22,23] complexes, while the *Diels-Alder pathway* occurred when aluminum,[11] chromium,[24] europium,[25] rhodium,[14] zinc,[19] and ytterbium[26] complexes were used. The scheme below shows that the intermediates of both mechanistic pathways give the same product upon treatment with acid.



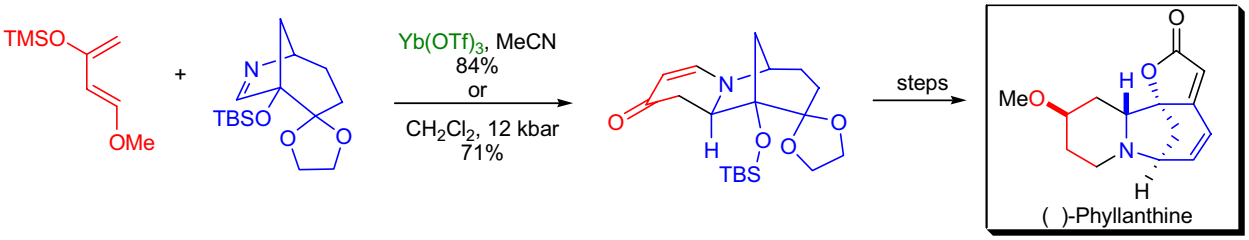
DANISHEFSKY'S DIENE CYCLOADDITION

Synthetic Applications:

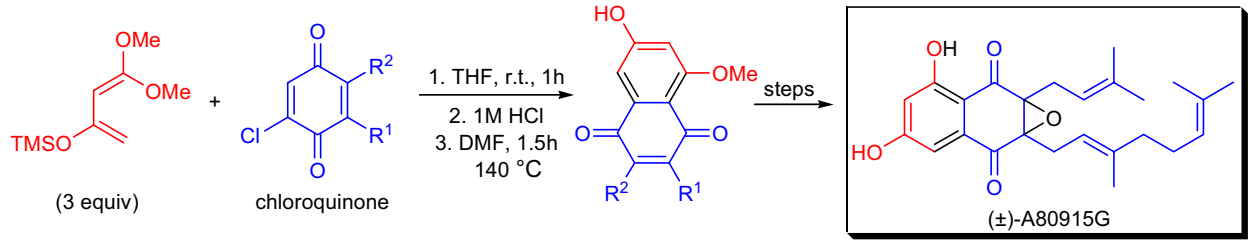
The first total synthesis of the marine furanosesquiterpenoid tubipofuran was accomplished in the laboratory of K. Kanematsu.[27] The *cis*-fused furanodecalin system was constructed by the *regioselective Diels-Alder cycloaddition* reaction of benzofuran quinone and *Danishefsky's diene* in refluxing toluene. The reaction gave an 11:1 mixture of the desired *ortho-endo* adduct versus the undesired *para-endo* product in 98% isolated yield. The major isomer then was subjected to sequential *radical deoxygenation reactions* before it was finally converted to the natural product.



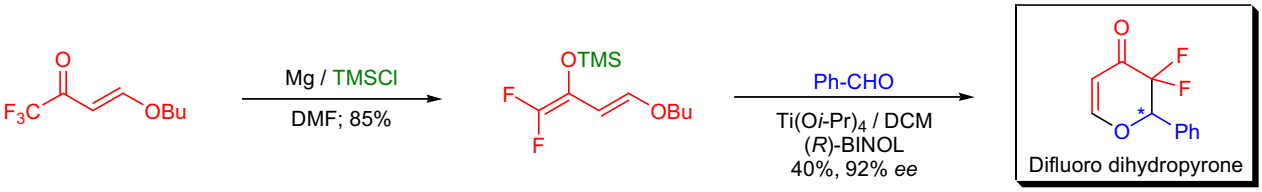
The enantioselective total synthesis of the Securinega alkaloid (–)-phyllanthine by S.M. Weinreb et al. involved a stereoselective $Yb(OTf)_3$-promoted *hetero Diels-Alder reaction* between a cyclic imine dienophile and *Danishefsky's diene*.[26] This was the first example of using an unactivated cyclic imine in this type of cycloaddition. Commonly used Lewis acid catalysts (e.g., $SnCl_2$, $TiCl_4$, etc.) produced only low yields of the desired cycloadduct. However, it was discovered that ytterbium triflate catalyzed the cycloaddition and afforded the product in 84% yield. Later they also found that the cyclization could occur at high pressure and in the absence of the catalyst, although a slightly lower yield (71%) of the product was obtained.



(±)-A80915G is a member of the napyradiomycin family of antibiotics. Its concise total synthesis was published by M. Nakata and co-workers using sequential *Stille cross-coupling* of aryl halides with allyltins and the *Diels-Alder reaction* of a chloroquinone with the *Danishefsky-Brassard diene*.[28]



A versatile C_4-building block, *difluorinated Danishefsky's diene*, was developed for the construction of fluorinated six-membered rings in the laboratory of K. Uneyama. The diene was prepared by the selective C-F bond cleavage of trifluoromethyl ketones. The reaction of this novel diene with benzaldehyde afforded the corresponding difluoro dihydropyrone in 92% *ee* in the presence of equimolar Ti(IV)-(*R*)-BINOL.[12]



DARZENS GLYCIDIC ESTER CONDENSATION

(References are on page 571)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-7]; *Modifications and Improvements*[8-16]]

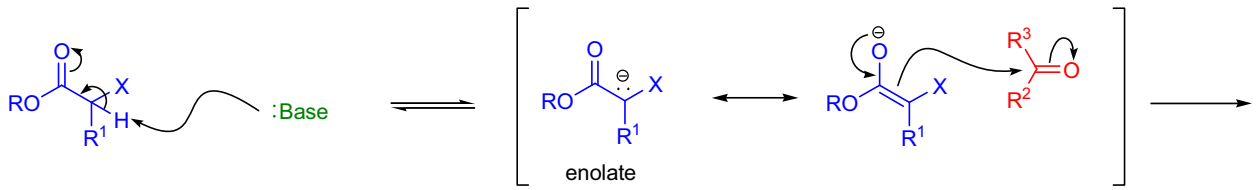
The formation of α,β-epoxy esters (glycidic esters) from aldehydes and ketones and α-halo esters under basic conditions is known as the *Darzens glycidic ester condensation*. The first report of this transformation was published by E. Erlenmeyer, and he described the condensation of benzaldehyde with ethyl chloroacetate in the presence of sodium metal.[1] During the early 1900s G. Darzens developed and generalized the reaction and found that sodium ethoxide (NaOEt) was a very efficient condensing agent.[3] Sodium amide[2] and other bases such as *N*-ethyl-*N*-(tributylstannyl)carbamate[17] can also be used to bring about the *Darzens condensation*. The reaction is general, since aromatic aldehydes and ketones, aliphatic ketones as well as α,β-unsaturated and cyclic ketones react smoothly and give good yields of the expected glycidic esters. Aliphatic aldehydes usually give lower yields, but the deprotonation of the α-halo ester with a strong kinetic base prior to the addition of the aldehyde results in acceptable yields.[18] α-Chloro esters are preferable to bromo or iodo esters, since they give higher yields. In addition to α-halo esters, α-halo sulfones,[19,15] nitriles,[20,16] ketones,[17] ketimines,[21] thiol esters,[22] or amides[14,16] can also be used to obtain the corresponding glycidic derivatives. A useful extension of the reaction is the *Darzens aziridine synthesis* (*aza-Darzens reaction*) when the α-halo esters are condensed with imines.[8] Newer versions of the *aza-Darzens reaction* allow the preparation of aziridines in optically pure form.[11,12] Glycidic esters are versatile synthetic intermediates: the epoxide functionality can be opened with various nucleophiles and upon thermolysis the intermediates undergo decarboxylation to afford the corresponding one carbon homologue of the starting aldehyde or ketone.[23]

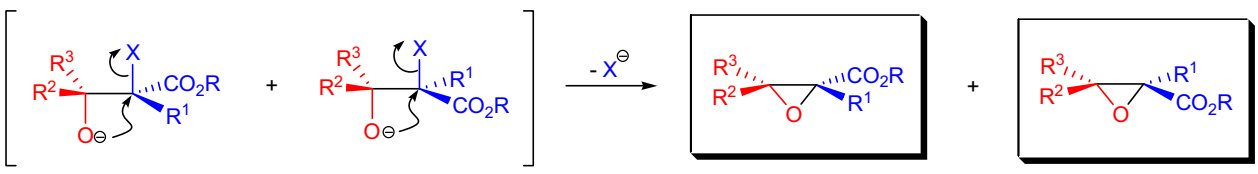


R^1 = alkyl, aryl; X = Cl, Br, I; EWG = CO_2R, CN, SO_2R, $CONR_2$, C(=O), C(=NR); R^2 = alkyl, aryl, H; R^3 = alkyl, aryl; Y = O, NR;
base = Na, NaOEt, $NaNH_2$, NaOH, K_2CO_3, NaO*t*-Bu;
when Y = O and EWG = CO_2R then the product is called glycidic ester

Mechanism:[24-26,6,27-29]

The first step of the mechanism is an *aldol reaction*: the base deprotonates the α-halo ester in a rate-determining step and the resulting carbanion (enolate) attacks the carbonyl group of the reactant aldehyde or ketone. The resulting intermediate is a halohydrin that undergoes an S_Ni reaction in the second step to form the epoxide ring. The strereochemical outcome of the *Darzens condensation* is usually in favor of the *trans* glycidic derivative. However, changing the solvents, bases, and the substituents can give either the *cis* or *trans* diastereomers. The stereochemistry of the product is determined by the initial enolate geometry and the steric requirements of the transition state.[29]



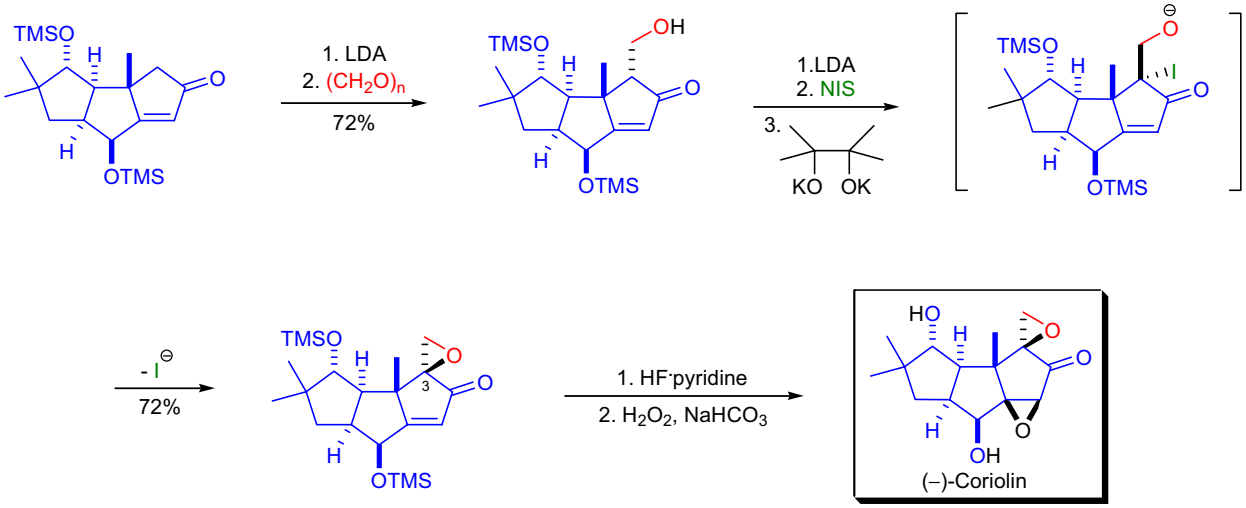


DARZENS GLYCIDIC ESTER CONDENSATION

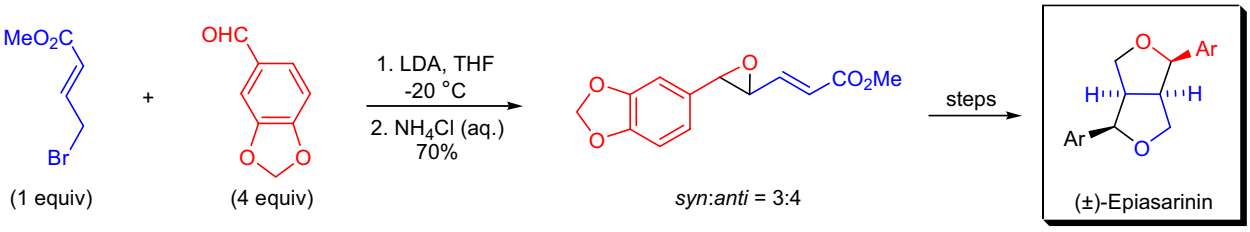
PPT topic

Synthetic Applications:

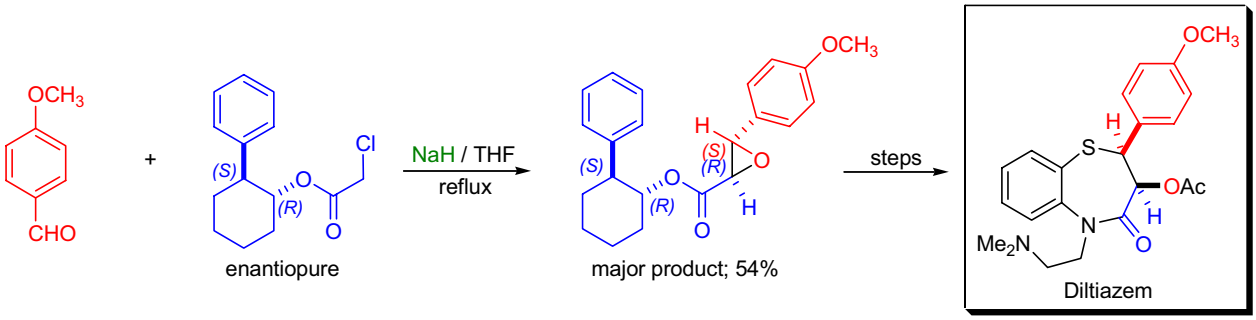
During the enantioselective total synthesis of (–)-coriolin, I. Kuwajima and co-workers used a *Darzens-type reaction* to construct the spiro epoxide moiety on the triquinane skeleton.[30] Interestingly, the usual *Darzens condensation* where the α-bromoketone was condensed with paraformaldehyde yielded a bromohydrin in which the hydroxymethyl group was introduced from the concave face of the molecule. This bromohydrin upon treatment with DBU gave the undesired stereochemistry at C3 (found in 3-*epi*-coriolin). To obtain the correct stereochemistry at C3, the substituents were introduced in a reverse manner. It was also necessary to enhance the reactivity of the enolate with potassium pinacolate by generating a labile potassium enolate in the presence of NIS. The *in situ* formed iodohydrin, then cyclized to the spiro epoxide having the desired stereochemistry at C3.



In the laboratory of P.G. Steel, a five-step synthesis of (±)-epiasarinin from piperonal was developed.[31] The key steps in the sequence involved the *Darzens condensation*, *alkenyl epoxide-dihydrofuran rearrangement* and a Lewis acid mediated cyclization. The desired vinyl epoxide intermediate was prepared by treating the solution of (*E*)-methyl-4-bromocrotonate and piperonal with LDA, then quenching the reaction mixture with mild acid (NH_4Cl).



A. Schwartz et al. synthesized several calcium channel blockers of the diltiazem group enantioselectively by using an auxiliary-induced asymmetric *Darzens glycidic ester condensation*.[32] The condensation of *p*-anisaldehyde with an enantiopure α-chloro ester afforded a pair of diastereomeric glycidic esters that possessed significantly different solubility. The major product was crystallized directly from the reaction mixture in 54% yield and in essentially enantiopure form. This major glycidic ester was then converted to diltiazem in a few more steps.



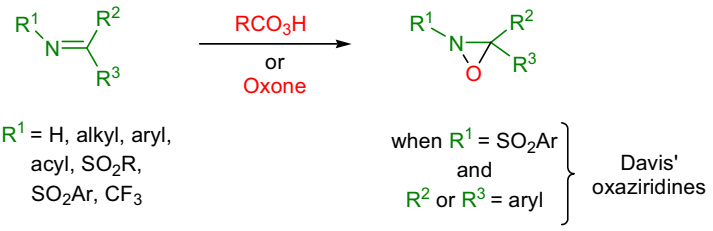
DAVIS' OXAZIRIDINE OXIDATIONS

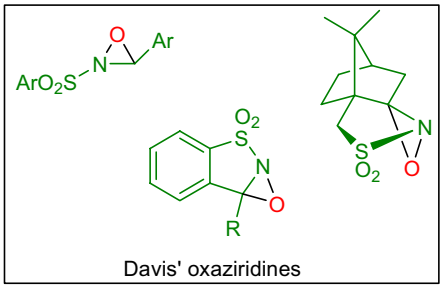
(References are on page 572)

Importance:

[*Seminal Publications*[1-9]*; Reviews*[10-17]*; Modifications & Improvements*[18-22]*; Theoretical Studies*[23-25]]

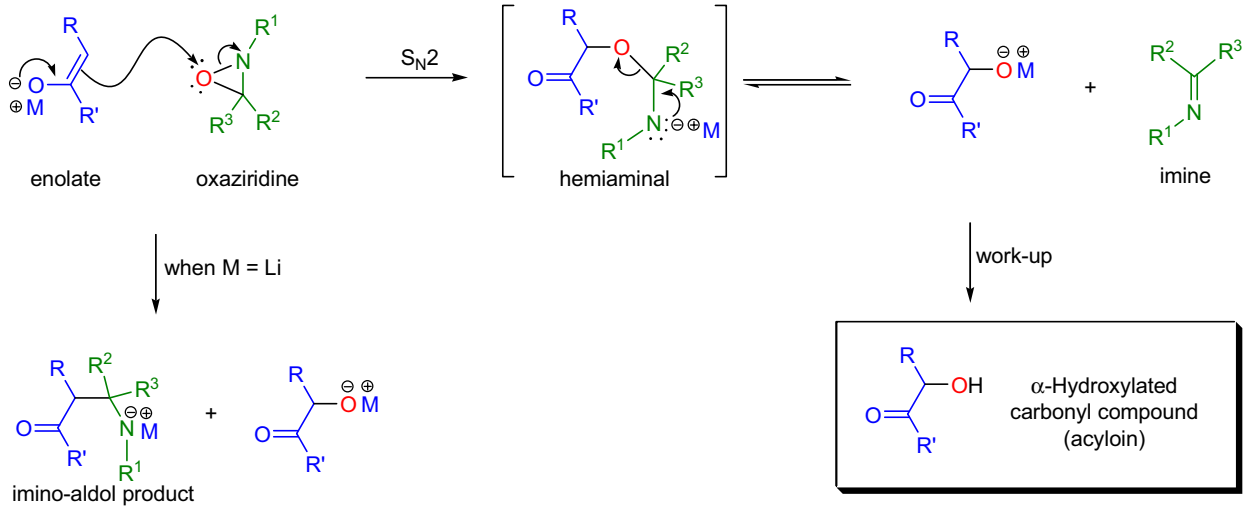
Three-membered heterocyclic compounds containing oxygen, nitrogen, and carbon atoms are called oxaziridines. The first oxaziridines were prepared by treating imines with peroxyacids in the second half of the 1950s.[26,27] Oxaziridines are highly reactive compounds due to the ring strain and the relatively weak N-O bond, and they can serve as both aminating and oxygenating agents. Nucleophiles attack at the nitrogen atom if the substituent attached to the aziridine nitrogen is small (R^1 = H, Me). However, in the case of larger substituents, the nucleophilic attack takes place at the oxygen atom instead. In the late 1970s, F.A. Davis prepared *N*-sulfonyloxaziridines, which act exclusively as oxidizing agents with nucleophiles and their rate of oxidation is comparable to peracids.[2] The oxidation reactions involving 2-arylsulfonyl-3-aryloxaziridines (Davis' reagents) are called *Davis' oxaziridine oxidations*. *N*-sulfonyloxaziridines offer two major advantages: they are highly chemoselective and also neutral, aprotic oxidizing agents. The following oxidative transformations are easily carried out: 1) sulfides and selenides to sulfoxides[28,29] and selenoxides[7] without overoxidation; 2) alkenes to epoxides;[4,6,22] 3) amines to hydroxylamines and amine oxides;[30] and 4) organometallic compounds to alcohols or phenols.[31] The most widespread application of *N*-sulfonyloxaziridines is the oxidation of enolates to α-hydroxy carbonyl compounds (acyloins).[13] Recently, the synthetic utility of a new class of oxaziridines, perfluorinated oxaziridines, is being investigated due to the unique reactivity profile of these oxidizing agents.[19]





Mechanism:[6,9,32-34,13,20,35]

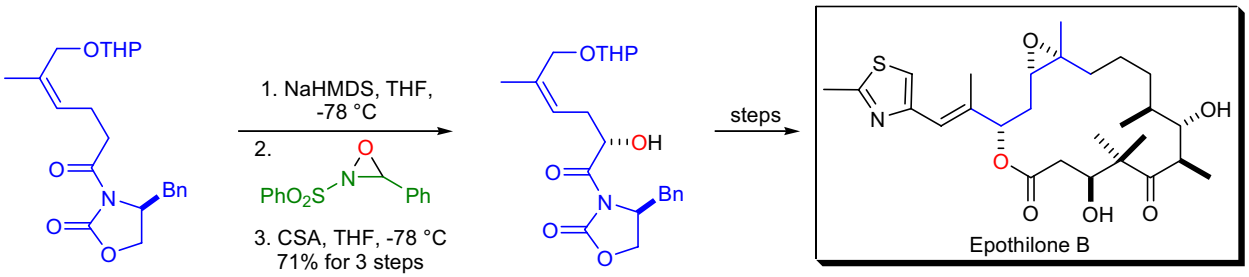
The mechanism of oxygen transfer from oxaziridines to nucleophiles is believed to involve an S_N2 type reaction and this assumption is supported by theoretical[23-25] and experimental[9] studies. When sulfides are oxidized to the corresponding sulfoxides and sulfones, the molecular recognition is steric in origin, and it is determined by the substituents on both the substrate and the oxaziridine.[9] For the oxidation of enolates, the molecular recognition is explained with an S_N2 mechanism as well as by an open (non-chelated) transition state where the nonbonded interactions are minimized.[33,36,20] The mechanism of oxygen transfer to an enolate to form the corresponding acyloin is shown below.[13]



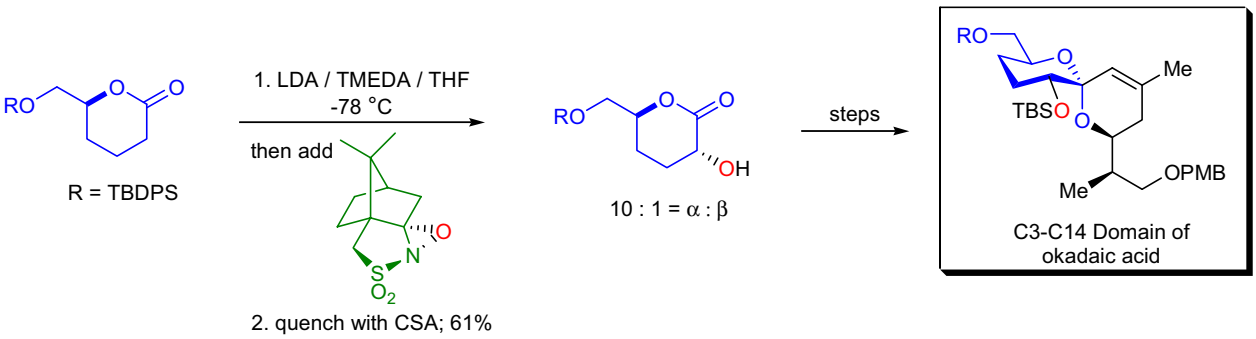
DAVIS' OXAZIRIDINE OXIDATIONS

Synthetic Applications:

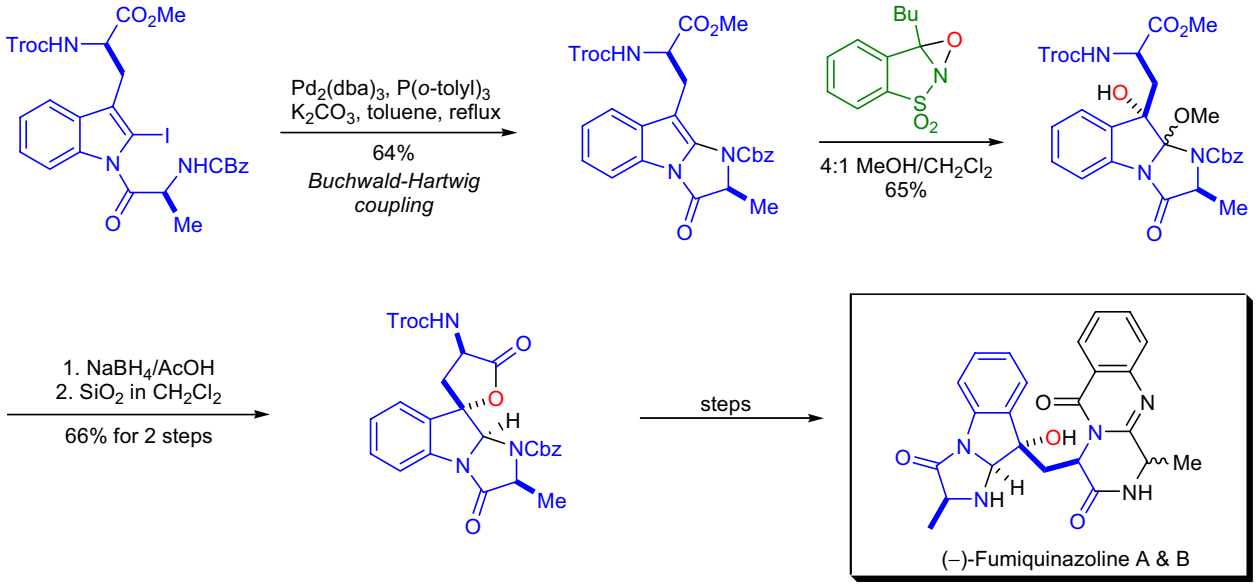
During the highly stereoselective total synthesis of epothilone B by J.D. White and co-workers, the stereochemistry of the alcohol portion of the macrolactone was established by applying *Davis' oxaziridine oxidation* of a sodium enolate.[37] The sodium enolate was generated from the corresponding chiral oxazolidinone derivative, which upon oxidation gave 71% yield of α-hydroxylated compound.



An abbreviated synthesis of a substituted 1,7-dioxaspiro[5.5]undec-3-ene system constituting the C3-C14 portion of okadaic acid was developed in the laboratory of C.J. Forsyth.[38] The C3-C8 fragment, a substituted valerolactone, was prepared in three steps. The diastereoselective α-hydroxylation of this lactone was accomplished by using *Davis' chiral camphorsulphonyl oxaziridine* on the corresponding lithium enolate at -78 °C. The isolated yield was 61% and the ratio of diastereomers was 10:1.



The first total synthesis of (–)-fumiquinazoline A and B was accomplished by B.B. Snider and co-workers using a *Buchwald-Hartwig Pd-catalyzed cyclization* of an iodoindole carbamate to construct the imidazoindolone moiety.[39] In order to set up the stereochemistry at the benzylic position of the indole fragment, the double bond was oxidized with the *saccharine-derived Davis' oxaziridine* in the presence of methanol to give the major diastereomer in 65% yield.



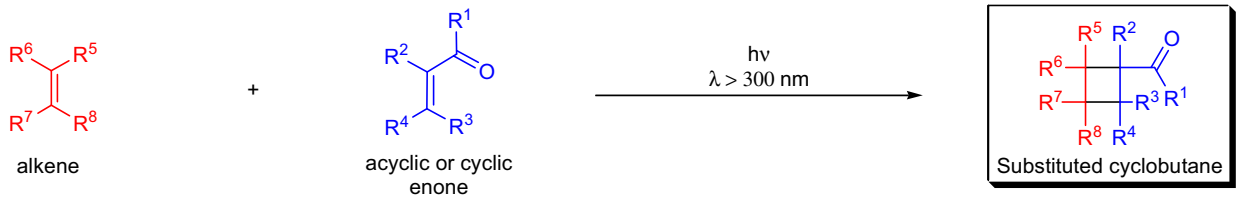
DE MAYO CYCLOADDITION (ENONE-ALKENE [2+2] PHOTOCYCLOADDITION)

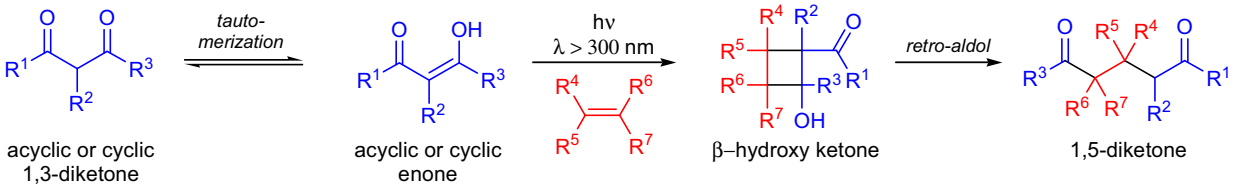
(References are on page 573)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-14]; *Modifications & Improvements*[15-18]]

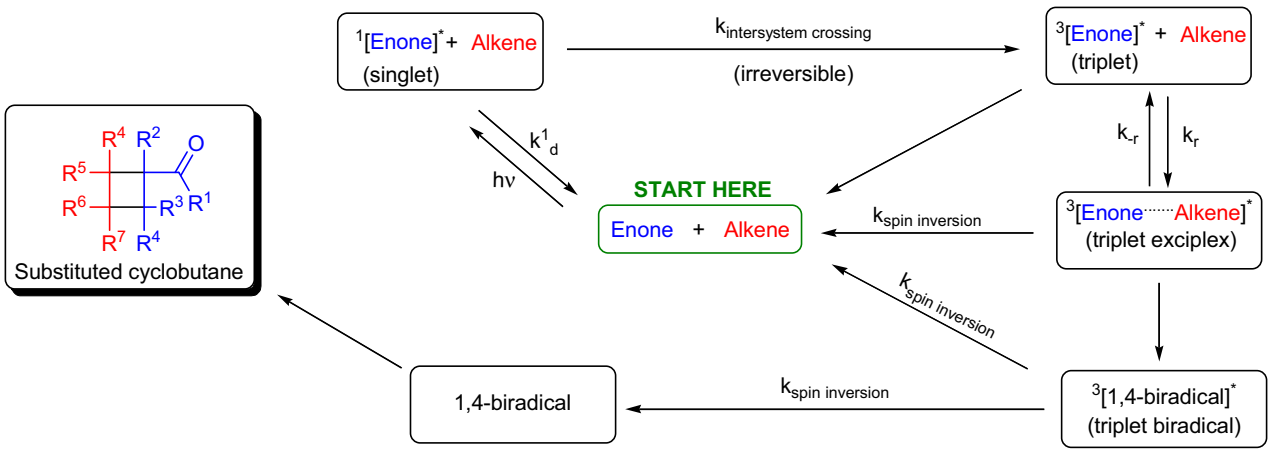
The photochemical [2+2] cycloaddition of enones (α,β-unsaturated carbonyl compounds) with alkenes is known as the *de Mayo cycloaddition*. A substituted cyclobutane is formed in the process. The first example of this transformation was the "Italian sunlight-induced" *intramolecular photoisomerization* of carvone to carvoncamphor published by G.L. Ciamician in 1908.[19] Ciamician's finding was verified by G. Büchi 50 years later.[20] It was not until the early 1960s when P. de Mayo, P.E. Eaton, and E.J. Corey demonstrated that the intermolecular *enone-alkene photocycloaddition* was possible as well.[1-4] De Mayo's first paper described the intermolecular [2+2] cycloaddition of enolized 1,3-diketones (enone) and olefins. The cycloadducts (β-hydroxy ketones) underwent a spontaneous *retro-aldol reaction* to afford 1,5-diketones.[1] The alkene (olefin) and enone reaction partners can vary widely; cycloadditions with enol esters of β-diketones, dioxolenones, vinylogous esters and amides, and with cycloalkenones have been successfully carried out. The *de Mayo cycloaddition* is highly stereo- and regioselective, but there are no simple rules available to predict the stereo- and regiochemistry of the products. In intermolecular processes, the stereochemical information carried by the alkene component is often scrambled in the product indicating that the mechanism of the cycloaddition is not concerted.[12] The cycloadducts of cyclic enones are most often *cis*-fused.[4] The regiochemical outcome of intermolecular reactions is determined by orbital coefficients. In intramolecular processes, the number of atoms connecting the two double bonds (the enone and alkene double bonds) also has an effect: two-atom tethers give rise to a mixture of regiosiomers, while tethers of three or more atoms generally yield single products.[10]





Mechanism:[2,4,21,7,22-26,12,27,28,14]

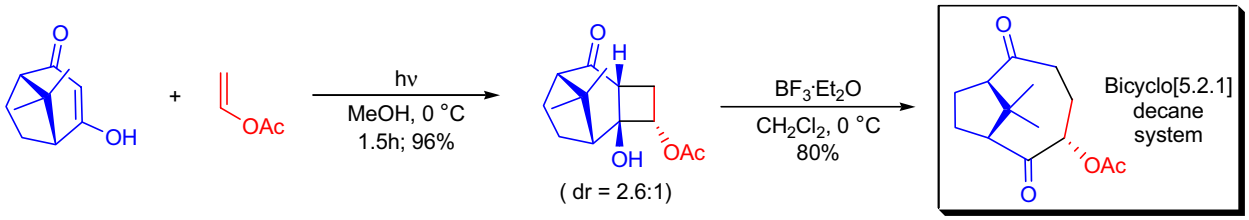
The mechanism of the *enone-alkene [2+2] photocycloaddition* presumably follows the scheme below. Upon irradiation: 1) a triplet exciplex is irreversibly formed from the triplet enone and ground state alkene; 2) the triplet exciplex collapses to one or more 1,4-biradicals.; 3) the biradicals either cyclize to the cyclobutane or revert to starting materials; and 4) the biradical reversion decreases the overall efficiency of the process.



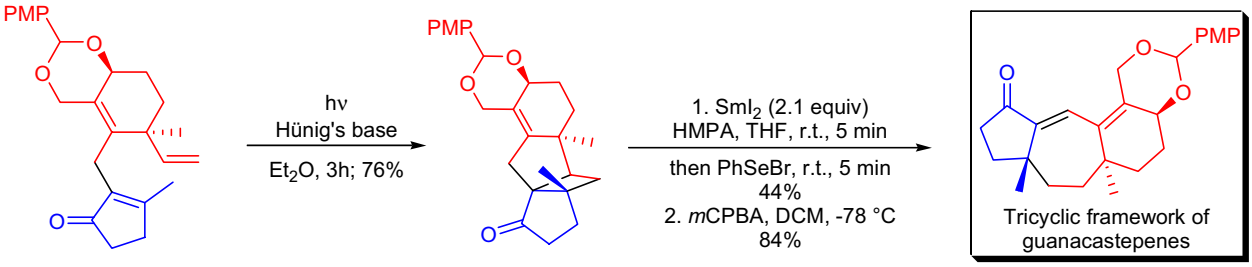
DE MAYO CYCLOADDITION (ENONE-ALKENE [2+2] PHOTOCYCLOADDITION)

Synthetic Applications:

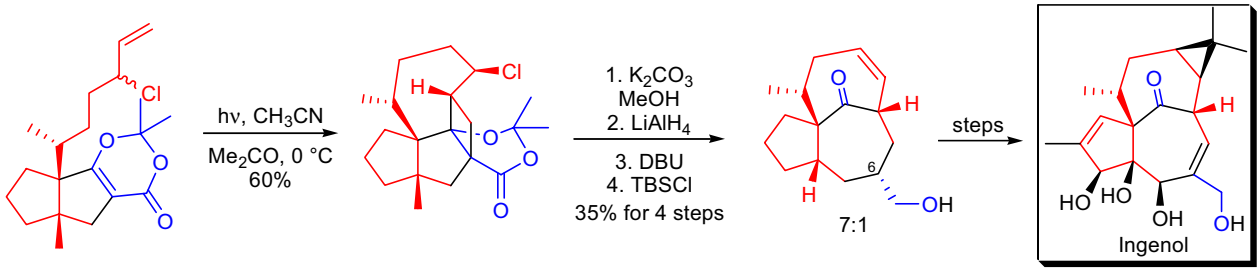
During the early 1990s, the research group of M. Fetizon was developing novel methods for the synthesis of taxane diterpenes.[29] Their goal was to construct the AB ring skeleton of taxol. The construction of the bicyclo[5.2.1]decane system was realized by the *intermolecular de Mayo cycloaddition* of an enolized bicyclic 1,3-dione and vinyl acetate followed by a *Lewis acid catalyzed ring opening reaction*. The methanolic solution of the β-diketone and vinyl acetate was irradiated (λ>245 nm) at 0 °C and a mixture of diastereomers was formed in excellent yield. The *retro-aldol reaction* was effected by treatment with BF_3 etherate in dichloromethane to afford good yields of the desired bicyclic ring system.



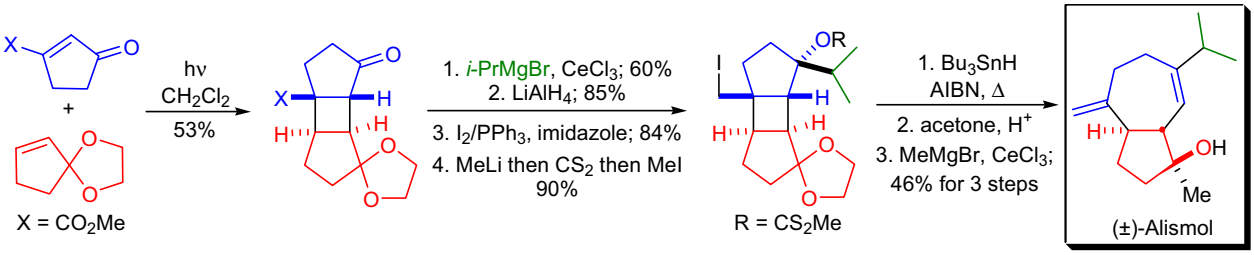
E.J. Sorensen and co-workers have synthesized the tricyclic carbon framework of guanacastepenes by applying an *intramolecular [2+2] photocycloaddition* followed by a SmI_2-induced fragmentation as key steps.[30] The enone was irradiated to effect an *intramolecular enone-olefin [2+2] cycloaddition* to afford the desired cyclobutyl ketone in 76% yield. The cyclobutane fragmentation was achieved by treatment with SmI_2 and the resulting Sm(III) enolate was trapped with a selenium electrophile. The double bond in the seven-membered ring was introduced by the oxidation of the selenium with *m*CPBA.



The first total synthesis of (±)-ingenol was accomplished in the laboratory of J.D. Winkler.[31] In order to establish the highly unusual C8 / C10 *trans* ("inside-outside") intrabridgehead stereochemistry of the BC ring system of the natural product, a *dioxenone-alkene intramolecular [2+2] photocycloaddition-fragmentation* sequence was employed. The photocycloaddition of the allylic chloride with the tethered dioxenone proceeded in 60% yield. The fragmentation was induced by methanolic potassium carbonate, followed by LAH reduction of the ester, elimination of the chloride with DBU, and silylation of the primary alcohol with TBSCl. The yield was 35% over four steps and the product was a 7:1 mixture of epimers at C6.



The total synthesis of the naturally occurring guaiane (±)-alismol was accomplished by G.L. Lange and co-workers using a *free radical fragmentation/elimination* sequence of an initial [2+2] de Mayo photocycloadduct.[32]



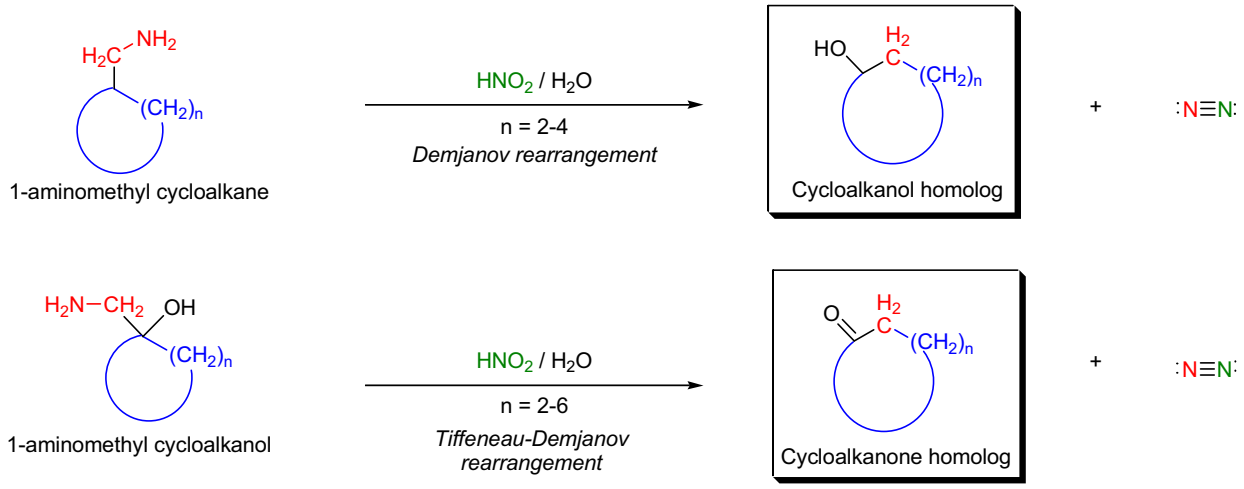
DEMJANOV AND TIFFENEAU-DEMJANOV REARRANGEMENT

(References are on page 573)

Importance:

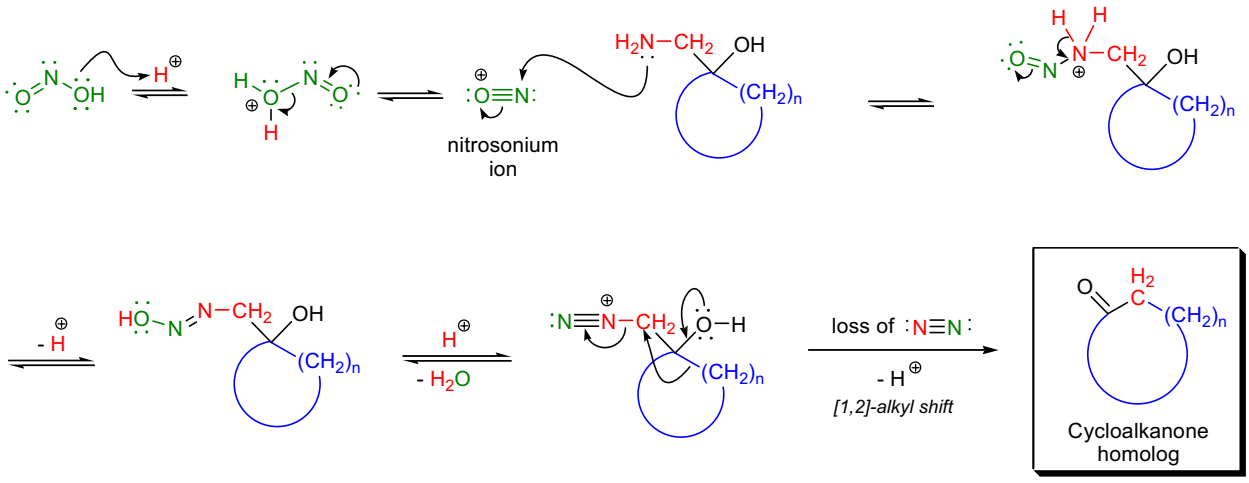
[*Seminal Publications*[1-3]; *Reviews*[4-6]; *Modifications & Improvements*[7]]

The ring enlargement of aminomethylcycloalkanes upon treatment with nitrous acid (HNO_2) to the corresponding homologous cycloalkanols is called the *Demjanov rearrangement*. This name is also given to the rearrangement of acyclic primary amines with nitrous acid. The first rearrangement of this type was observed and reported in the early 1900s.[1,2] Synthetically, the *Demjanov rearrangement* is best applied for the preparation of five-, six-, and seven-membered rings, but it is not well-suited for the preparation of smaller or larger rings due to low yields. In 1937, M. Tiffeneau observed that the treatment of 1-aminomethyl cycloalkanols (β-aminoalcohols) with nitrous acid led to the formation of the ring-enlarged homolog ketones.[3] This transformation can be regarded as a variant of the *pinacol rearrangement* (*semipinacol rearrangement*) and is known as the *Tiffeneau-Demjanov rearrangement*. This transformation can be carried out on four- to eight-membered rings, and the yields of the ring-enlarged products are always better than for the *Demjanov rearrangement*. However, the yields tend to decrease with increasing ring size.[8,9,6] If the aminomethyl carbon atom is substituted, the *Demjanov rearrangement* is significantly retarded and mostly unrearranged alcohols are formed, but the *Tiffeneau-Demjanov rearrangement* readily occurs. Substrates with substitution on the ring carbon atom to which the aminomethyl group is attached undergo facile *Demjanov rearrangement*.



Mechanism: [10-12]

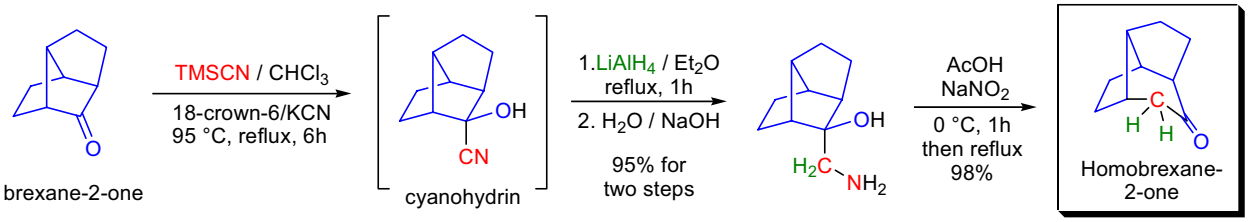
The mechanism of both the *Demjanov* and *Tiffeneau-Demjanov rearrangements* is essentially the same. The first step is the formation of the nitrosonium ion or its precursor (N_2O_3) from nitrous acid. This electrophile is attacked by the primary amino group and in a series of proton transfers the diazonium ion is formed. This diazonium ion is very labile due to the lack of stabilization and it readily undergoes a *[1,2]-alkyl shift* accompanied by the loss of nitrogen. The rearrangement is competitive with the substitution of the diazonium leaving group by the solvent (e.g., water) or with the formation of carbocations that may undergo other rearrangements (e.g., hydride shift). The ring expansion is favored in the *Demjanov rearrangement*, since the entropy of activation for *hydride shift* is higher.



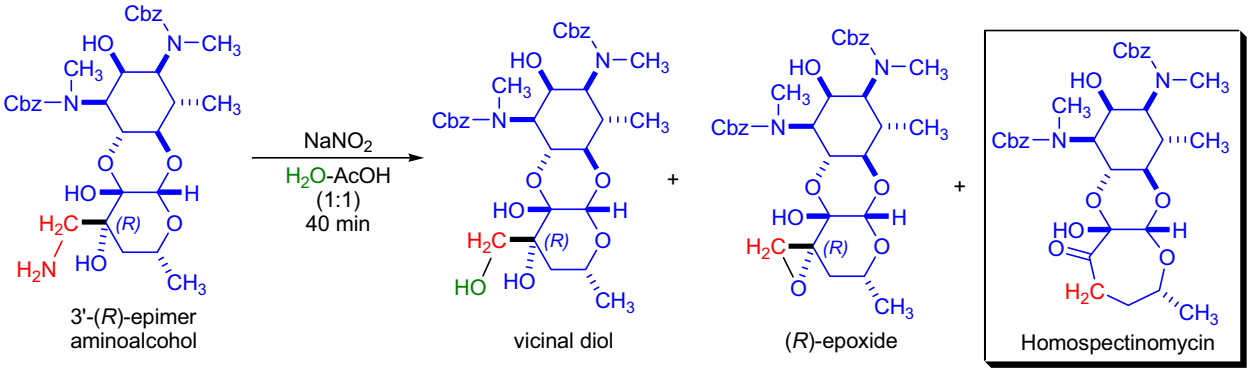
DEMJANOV AND TIFFENEAU-DEMJANOV REARRANGEMENT

Synthetic Applications:

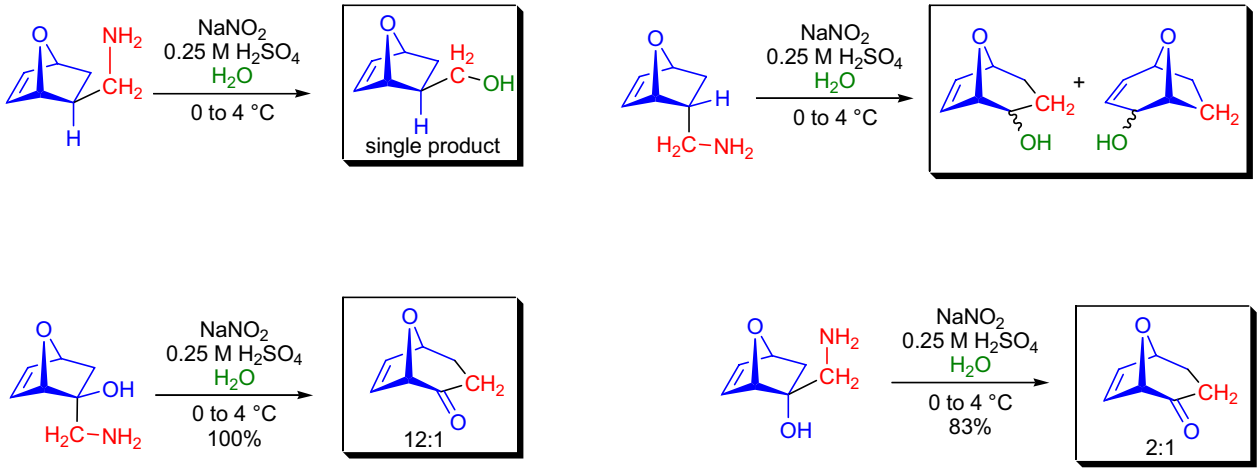
In the laboratory of A. Nickon, the syntheses of brexan-2-one (tricyclo[4.3.0.0^{3,7}]nonane-2-one) and the ring-expanded homolog (homobrexan-2-one) were undertaken.[13] Brexanes are frequently used in mechanistic studies, so an efficient and versatile method for the preparation of these molecules was necessary. The key step leading to the brexane-2-one parent molecule was an *endo-selective intramolecular Diels-Alder cycloaddition*, while the ring-expansion to the homolog was achieved using the *Tiffeneau-Demjanov rearrangement*. Toward this end the tricyclic ketone was efficiently converted to the corresponding aminoalcohol by treatment with TMSCN followed by LAH reduction. Upon treatment with HNO_2, the rearrangement proceeded in excellent yield to afford homobrexan-2-one.



To explore the biological activity of spectinomycin analogs, E. Fritzen and co-workers prepared the ring-expanded homospectinomycins containing a seven-membered carbohydrate ring.[14] The *Tiffeneau-Demjanov* ring expansion was attempted on two epimeric aminoalcohols. Surprisingly, only the (*R*)-epimer gave the desired ring-expanded ketone, while the (*S*)-epimer afforded the corresponding epoxide as the only product. Upon treatment with nitrous acid, the (*R*)-epimer gave rise to three products in equal amounts. Only one of the products was the desired ring-expanded ketone, whereas the other two products were the (*R*)-epoxide and the corresponding vicinal diol.



The stereochemistry of cyclic primary amines or aminoalcohols dramatically influences the product distribution of their respective *Demjanov* and *Tiffeneau-Demjanov rearrangements*. P. Vogel and co-workers have studied the ring-expansion of 2-aminomethyl-7-oxabicyclo[2.2.1]heptane derivatives upon treatment with nitrous acid. Some of their findings are shown below.[6]



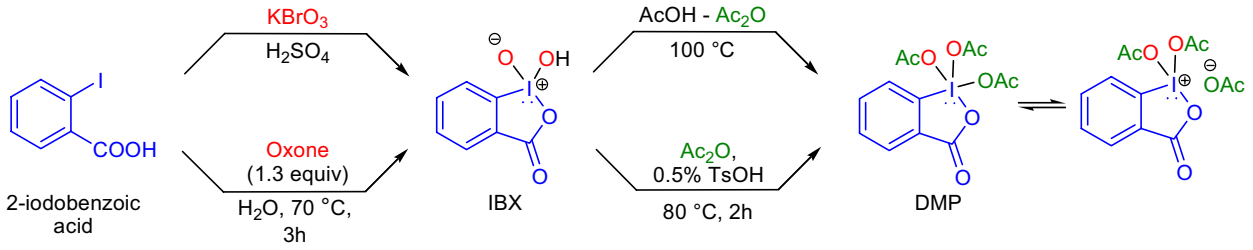
DESS-MARTIN OXIDATION

(References are on page 574)

Importance:

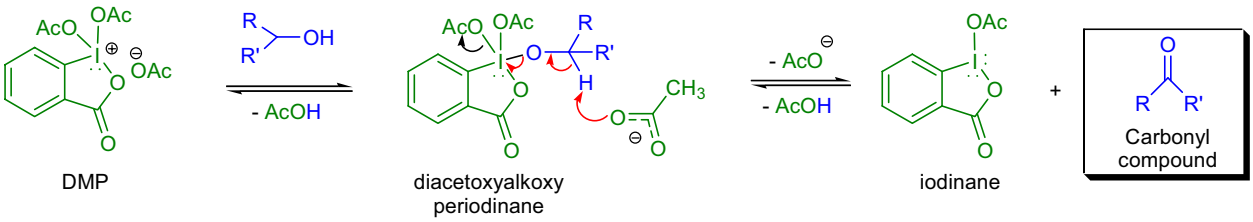
[*Seminal Publication*[1]; *Reviews*[2-8]; *Modifications & Improvements*[9-15]]

Since the early 1980s, hypervalent iodine reagents have emerged as selective, mild, and environmentally friendly oxidizing agents in organic synthesis.[7] One class of these reagents encompasses the organic derivatives of pentacoordinate iodine(V), which are called periodinanes.[16,17] The best-known members of this class are 2-iodoxybenzoic acid (IBX)[18] and *Dess-Martin periodinane* (DMP).[1] IBX has been known since 1893, but its almost complete insolubility in most organic solvents prevented its widespread use in organic synthesis.[19] In 1983, D.B. Dess and J.C. Martin reported the preparation of 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (DMP) *via* the acylation of IBX.[19] This new periodinane is far more soluble in organic solvents than IBX; since its discovery it has emerged as the reagent of choice for the oxidation of alcohols to the corresponding carbonyl compounds.[2] Oxidations using DMP are called *Dess-Martin oxidations*. Currently, DMP is commercially available, but it is rather expensive. Therefore, it is usually prepared by the oxidation of 2-iodobenzoic acid to IBX, followed by the acylation of IBX to DMP. The oxidation of 2-iodobenzoic acid can be done with potassium bromate ($KBrO_3$)[1,10,12] in aqueous sulfuric acid or with Oxone ($2KHSO_5$-$KHSO_4$-K_2SO_4)[13] in water. During the 1990s, modifications[10,13] to the original procedure were necessary because the morphology[12] and purity of the IBX strongly influenced the quality of DMP and therefore the reproducibility of DMP oxidations. The advantages of the *Dess-Martin oxidation* over the conventional oxidation of alcohols are: 1) mild reaction conditions (room temperature, neutral pH); 2) high chemoselectivity; 3) tolerance of sensitive functional groups on complex substrates; and 4) long shelf-life and thermal stability (unlike IBX, which has been found to be explosive[20]). Besides the conversion of alcohols to carbonyl compounds, the *DMP oxidation* was also successfully utilized for the oxidation of functional groups for which traditional mild oxidants failed to work: 1) allylic alcohols to α,β-unsaturated carbonyls;[21] 2) cleavage of aldoximes and ketoximes to aldehydes and ketones;[22] 3) *N*-acyl hydroxylamines to acyl nitroso compounds;[23] 4) 4-substituted anilides to *p*-quinones;[24] 5) β-amino alcohols to α-amino aldehydes without epimerization;[25] and 6) γ,δ-unsaturated aromatic amides to complex heterocycles.[26]



Mechanism:[9,11,27,28]

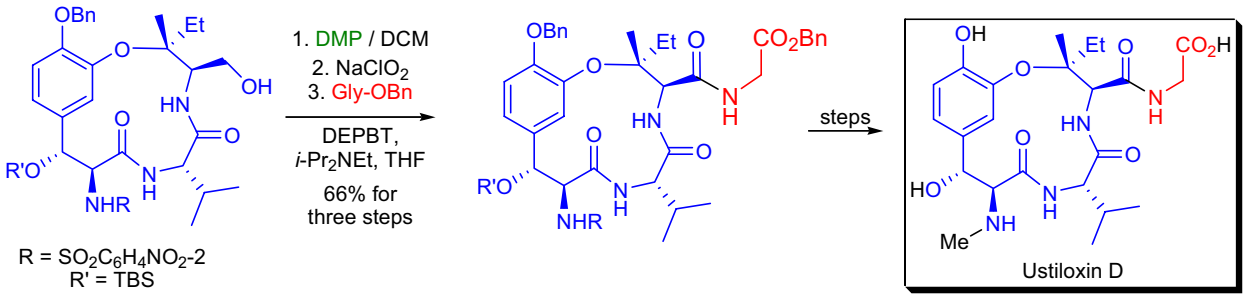
It has been shown by ^{1}H-NMR that DMP reacts rapidly with 1 equivalent of alcohol (1° or 2°) to give diacetoxyalkoxyperiodinanes, while in the presence of 2 equivalents of alcohol (or diol) a double displacement takes place to produce acetoxydialkoxyperiodinanes. Next, the α-proton of the alcohol is removed by a base (acetate), and the carbonyl compound is released along with a molecule of iodinane. When excess alcohol is present, the oxidation is much faster due to the especially labile nature of acetoxydialkoxyperiodinanes.[9] It has also been shown that added water accelerates DMP oxidations.[11]



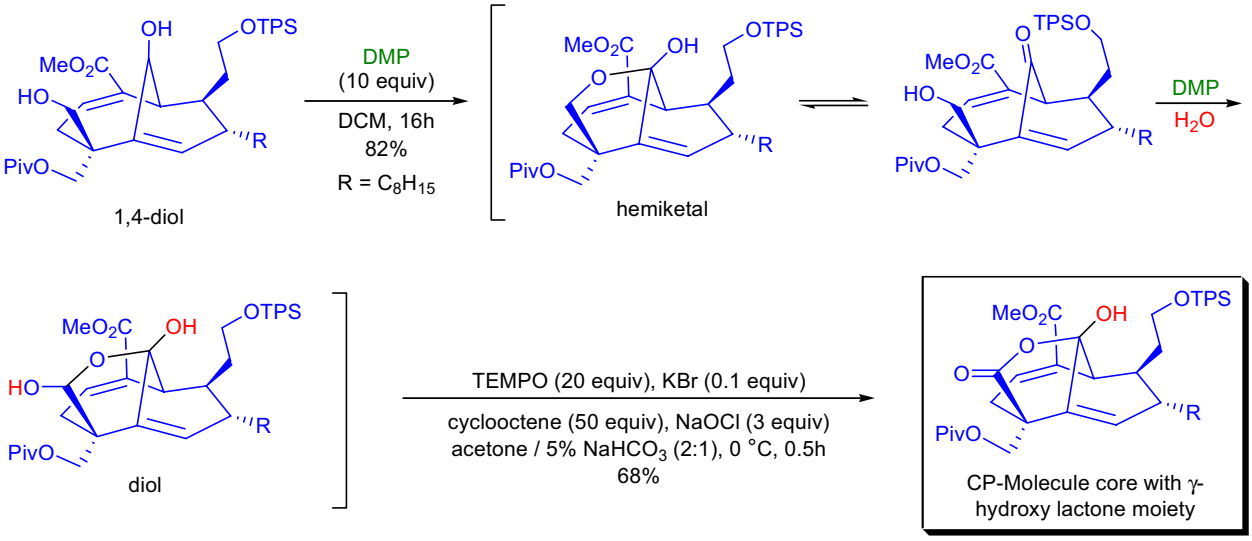
DESS-MARTIN OXIDATION

Synthetic Applications:

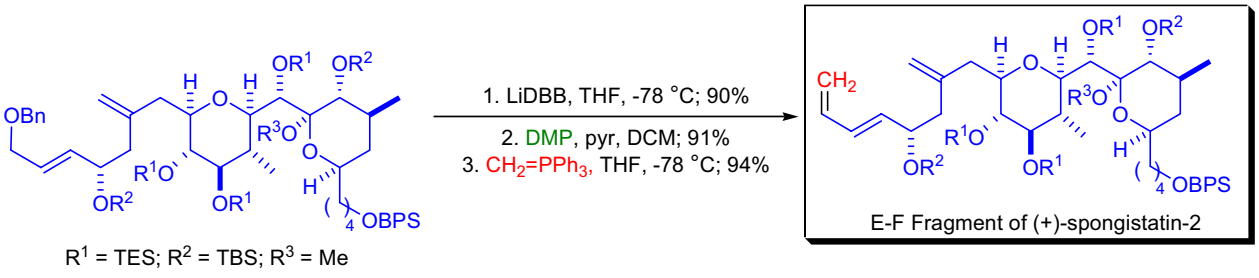
In the final stages of the total synthesis of ustiloxin D, M.M. Joullié and co-workers had to install the amide side-chain onto the already assembled macrocycle.[29] To achieve this goal, the macrocyclic primary alcohol was treated with the Dess-Martin periodinane to generate the corresponding aldehyde, which was subsequently treated with sodium chlorite to afford the carboxylic acid. The carboxylic acid was then coupled with the benzyl ester of glycine to complete the installation of the side-chain in 66% yield for three steps.



A novel one-pot *Dess-Martin oxidation* was developed for the construction of the γ-hydroxy lactone moiety of the CP-molecules in the laboratory of K.C. Nicolaou.[30] Bicyclic 1,4-diol was treated with 10 equivalents of DMP in dichloromethane for 16h to promote a tandem reaction: first, the bridgehead secondary alcohol was selectively oxidized to the ketone, followed by a ring closure to afford the isolable hemiketal, which was further oxidized by DMP to give a keto aldehyde. Trace amounts of water terminated the cascade to give a stable diol, which was not further oxidized with DMP. Subsequent TEMPO oxidation furnished the desired γ-hydroxy lactone.



For the elaboration of the dienyl side-chain of the E-F fragment of (+)-spongistatin 2, A.B. Smith et al. oxidized the sensitive primary allylic alcohol moiety using the *Dess-Martin oxidation*.[31] The resulting α,β-unsaturated aldehyde was treated with a Wittig reagent to obtain the desired 1,3-dienyl side chain.



DIECKMANN CONDENSATION

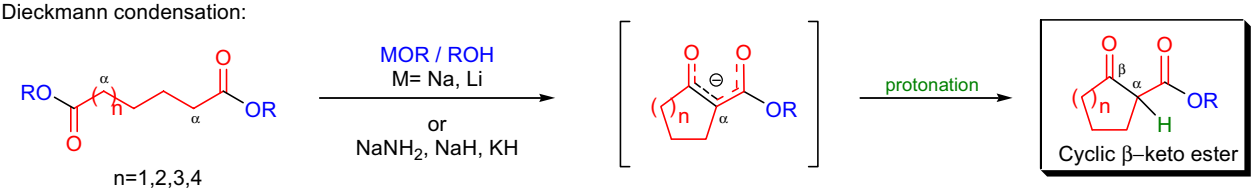
(References are on page 574)

Importance:

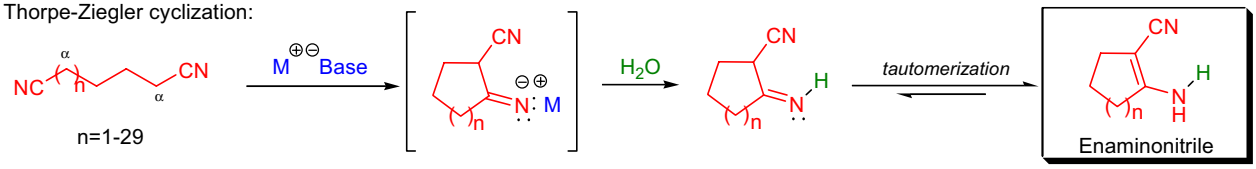
[*Seminal Publications*[1,2]*; Reviews*[3-8]; *Modifications & Improvements*[9-17]]

The base mediated condensation of an ester, containing an α-hydrogen atom, with a molecule of the same ester to give a β-keto ester is known as the *Claisen condensation*. When the two reacting ester functional groups are tethered the reaction is called the *Dieckmann condensation*, and a cyclic β-keto ester is formed. In the related *Thorpe-Ziegler condensation* the intramolecular base-catalyzed cyclization of dinitriles affords enaminonitriles.[18,19] The commonly used procedure involves prolonged treatment of the diesters with at least one equivalent of a strong base (alkoxide, sodium amide, or alkali metal hydrides)[20] in dry solvent under reflux in an inert atmosphere. The *Dieckmann condensation* forms 5-, 6-, 7-, and 8-membered rings in high yield but gives very low yields for larger rings.[21,4] It is possible, however, to effect the cyclization at high-dilution so the intramolecular reaction dominates and in certain cases the preparation of large rings (>12) is possible.[22,23] If the product β-keto ester does not have an acidic α-hydrogen, the reaction is sluggish and the *retro-Dieckmann cyclization* predominates; the equilibrium is shifted to the right if one equivalent of an alcohol-free base is used. With the *Thorpe-Ziegler cyclization* it is possible to assemble 5- to 33-membered rings and this method is superior to the *Dieckmann condensation* for the formation of 7- and 8-membered rings. Modifications of the original *Dieckmann procedure* made it possible to use mild reaction conditions: 1) dithiols (dithioesters) are treated with sodium hydride so the cyclizations take place in only 2h at room temperature;[9] 2) environmentally friendly solvent-free conditions allow the presence of air and the reaction proceeds in high yield at room temperature in 1h;[16] and 3) the use of $TiCl_4/Bu_3N$ with catalytic amounts of TMSOTf in toluene gives high yields in 2-3h at room temperature.[14,24,17]

Dieckmann condensation:

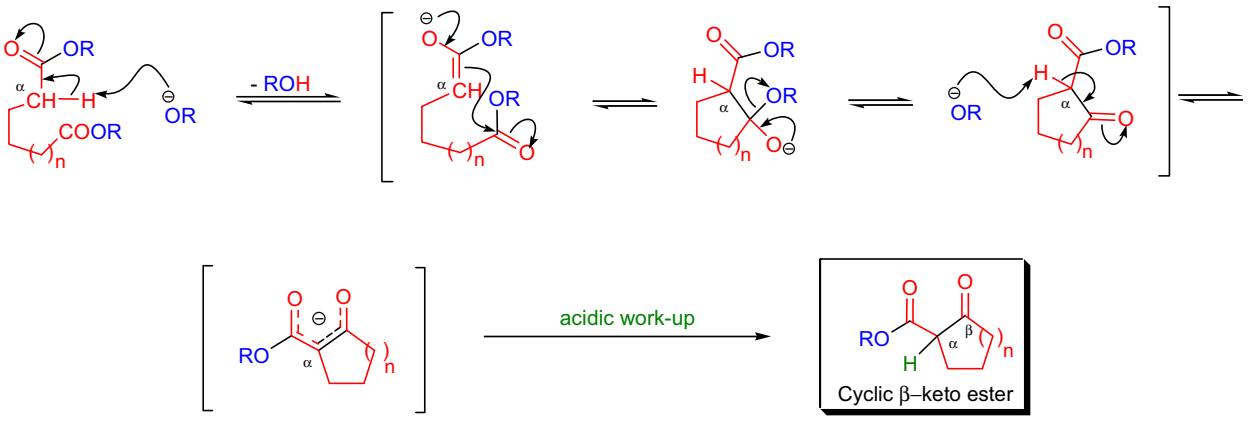


Thorpe-Ziegler cyclization:



Mechanism:[25-31]

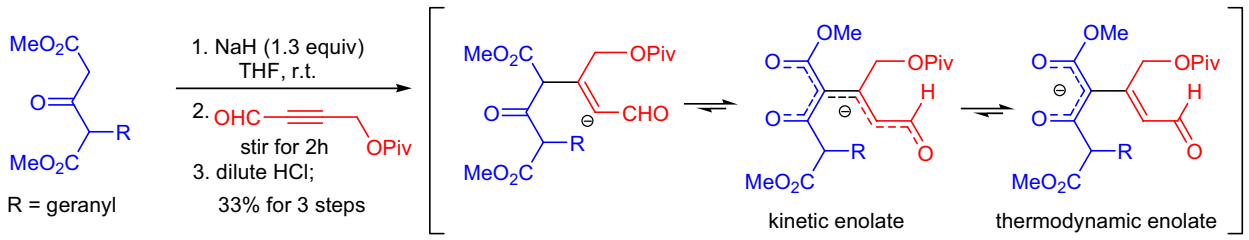
Each step of the *Dieckmann condensation* is completely reversible. The driving force of the reaction is the generation of the resonance-stabilized enolate of the product β-keto ester. As stated above, the condensation usually fails if it is not possible to generate this stable intermediate. The mechanism of the *Dieckmann condensation* is almost identical to the mechanism of the *Claisen condensation*. The rate-determining step, however, is the ring formation in which the ester enolate attacks the carbonyl group of the second ester functional group.[25,26] The resulting tetrahedral intermediate then rapidly breaks down to the enolate of the β-keto ester. Protonation of the enolate affords the final product.

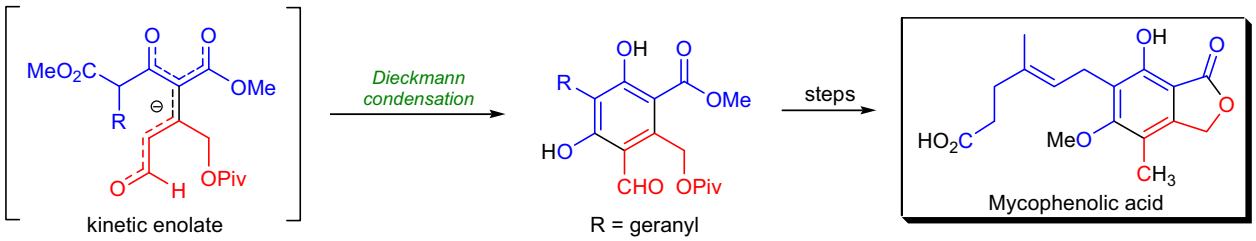


DIECKMANN CONDENSATION

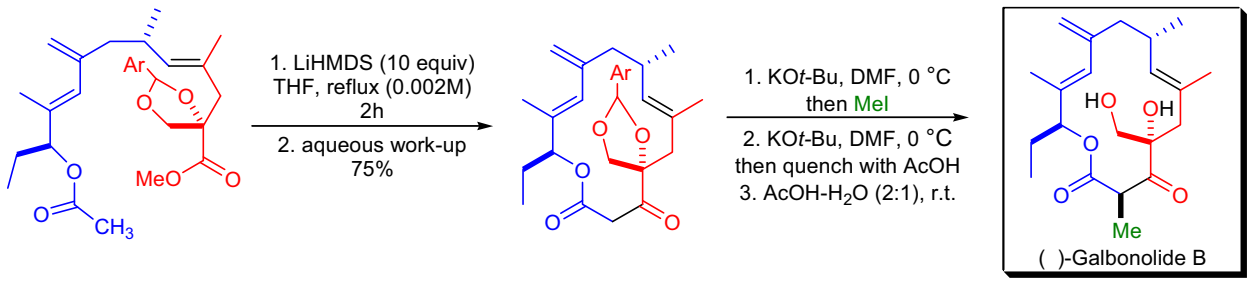
Synthetic Applications:

Mycophenolic acid is one of the highly substituted phthalide natural products and possesses many *in vitro* and *in vivo* biological activities. The synthetic strategy toward its convergent total synthesis by A. Covarrubias-Zúñiga was based on a ring annulation sequence involving a *Michael addition* and a *Dieckmann condensation* as key steps.[32] The deprotonation of 2-geranyl 1,3-acetonedicarboxylate with sodium hydride was followed by the addition of a protected alkynal to give rise to the enolate *in situ*, which cyclized to the hexasubstituted aromatic ring of the natural product in 33% yield.

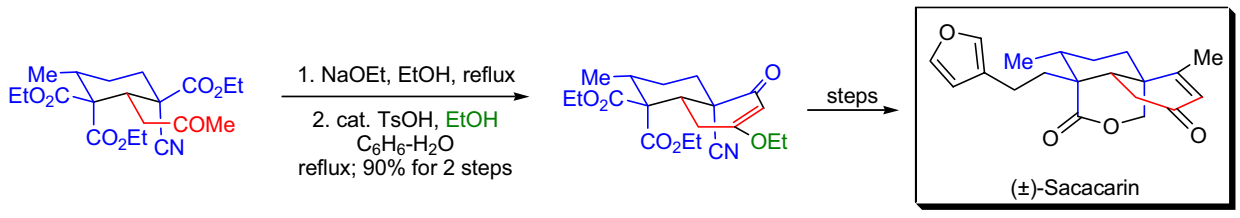




The 14-membered macrocyclic ring of (–)-galbonolide B was formed utilizing a novel *macro-Dieckmann cyclization* which was developed in the laboratory of B. Tse.[33] In order to bring about the desired macrolactonization, the secondary acetate was treated with LiHMDS in refluxing THF under high-dilution conditions to afford the desired lactone in 75% yield. It is important to note, however, that the analogous secondary propionate failed to cyclize under identical conditions.



The naturally occurring clerodane diterpenoid (±)-sacacarin has been synthesized by R.B. Grossman and co-workers in only 10 steps using a double annulation of a tethered diacid and 3-butyn-2-one.[34] The second ring of sacacarin was prepared by an *intramolecular Dieckmann condensation* of an ester and a methyl ketone in excellent yield. The resulting enol was then immediately converted to the corresponding ethyl enol ether using ethanol and an acid catalyst.



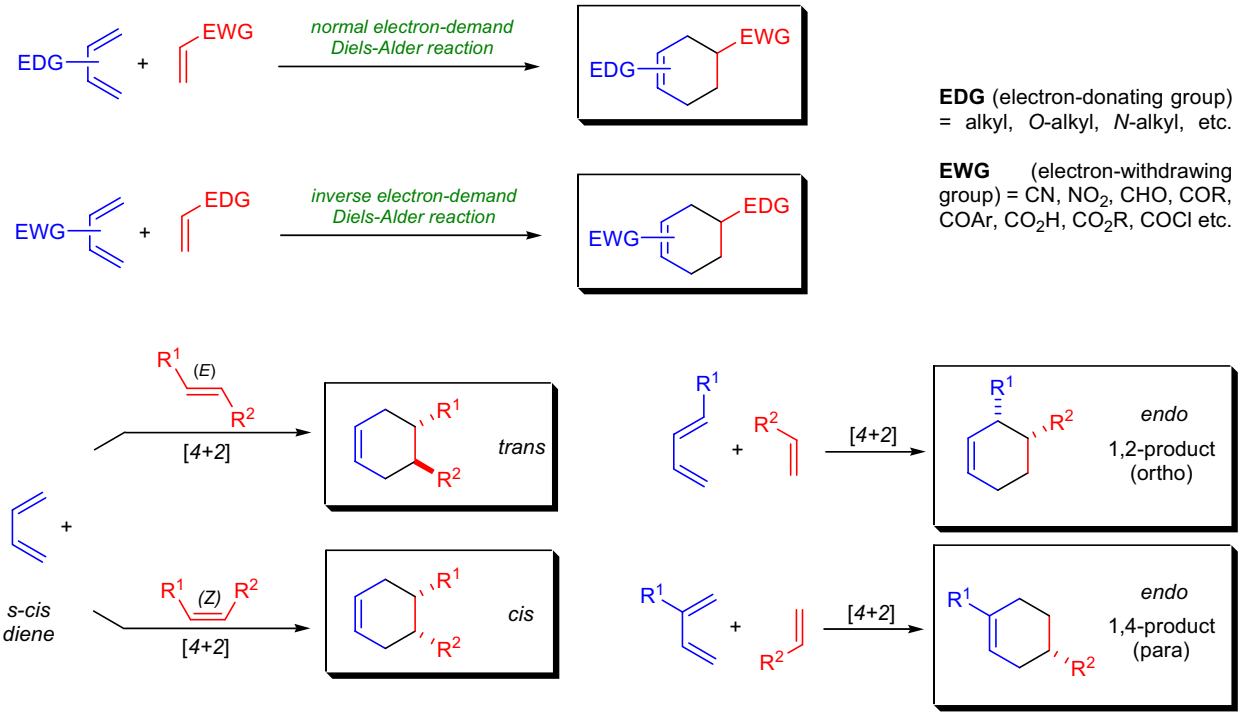
DIELS-ALDER CYCLOADDITION

(References are on page 575)

Importance:

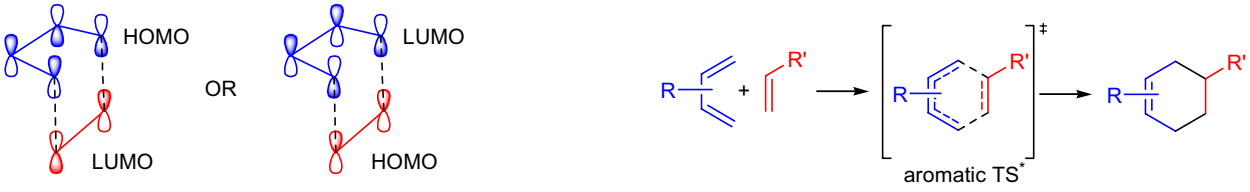
[*Seminal Publications*[1-4]; *Reviews*[5-47]; *Theoretical Studies*[48-66]]

The [4π + 2π] cyclization of a diene and alkene to form a cyclohexene derivative is known as the *Diels-Alder cycloaddition* (*D-A cycloaddition*). Reports of such cyclizations were made by H. Wieland,[67] W. Albrecht,[68] Thiele, H. Staudinger, and H.V. Euler[69] in the early 1900s, but the structures of the products were misassigned. It was not until 1928 when O. Diels and K. Alder established the correct structure of the cycloadduct of *p*-quinone and cyclopentadiene.[2] Since its discovery, the *D-A cycloaddition* has become one of the most widely used synthetic tools. The diene component is usually electron rich, while the alkene (dieneophile) is usually electron poor and the reaction between them is called the *normal electron-demand D-A reaction*. When the diene is electron poor and the dienophile is electron rich then an *inverse electron demand D-A cyclization* takes place. Besides alkenes, substituted alkynes, benzynes, and allenes are also good dienophiles. If one or more of the atoms in either component is other than carbon, then the reaction is known as the *hetero-D-A reaction*.[70] In the *retro-D-A reaction* unsaturated six-membered rings break down to yield dienes and dienophiles.[8] The synthetic value of the *D-A cycloaddition* is due to the following features: 1) it can potentially set four stereocenters in one step; 2) if unsymmetrical dienes and dienophiles react it is highly *regioselective* and *stereospecific;* 3) the regioisomers are predominantly the "*ortho*" and "*para*" products over the "*meta*" product; 4) if a disubstituted *cis* (*Z*) alkene is used, the stereochemistry of the two substituents in the product will be *cis* and when an (*E*) alkene is used, the stereochemistry in the product will be *trans*; 5) the stereochemical information (*E* or *Z*) in the diene is also transferred to the product; 6) the predominant product is the *endo* cycloadduct; 7) by using appropriate chiral catalysts the cycloaddition can be made enantioselective;[71-73,41] and 8) multiple rings can be created in one step with defined stereochemistry.



Mechanism: [23,74-78,29,79-82,38,83-85,44,86]

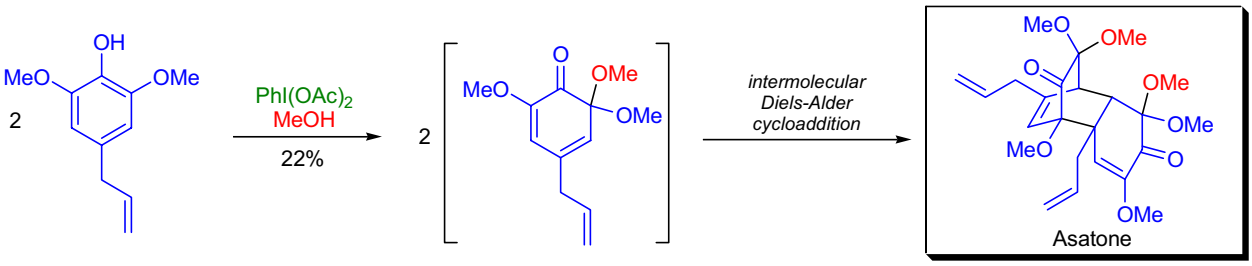
Mechanistically the D-A reaction is considered a concerted, pericyclic reaction with an aromatic transition state. The driving force is the formation of two new σ-bonds. The *endo* product is the kinetic product and its formation is explained by *secondary orbital interactions*.[80] Some of the mechanistic studies suggested that a diradical[79] or a di-ion mechanism may be operational in certain cases.[82] It was also shown that solvents and salts can influence reaction kinetics.[38]



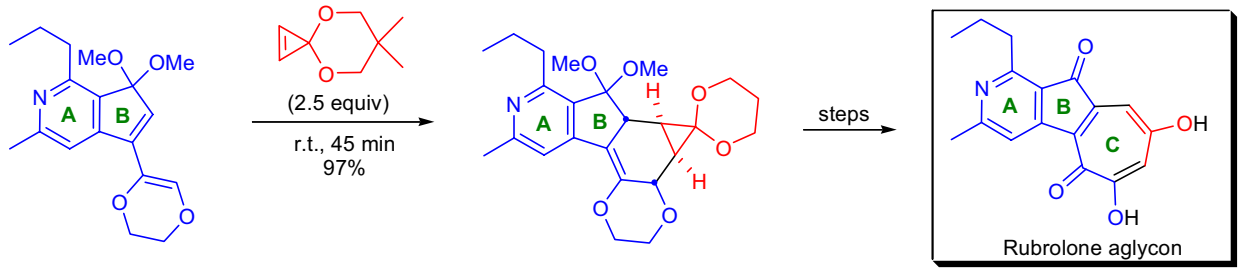
DIELS-ALDER CYCLOADDITION

Synthetic Applications:

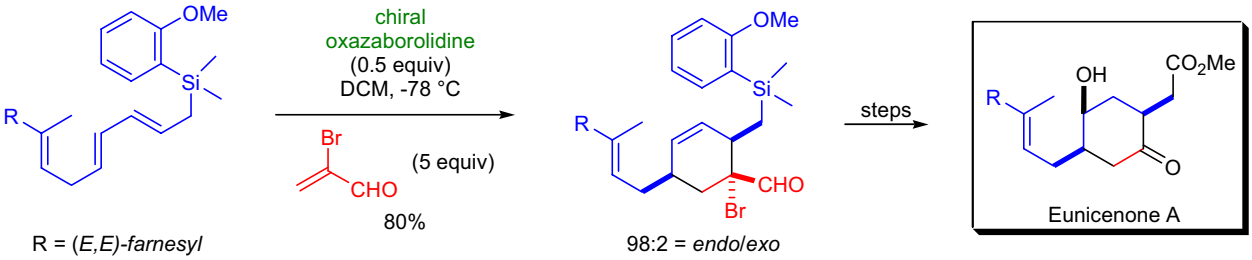
The *intramolecular Diels-Alder cycloaddition* is a very powerful synthetic tool, since it can generate molecular complexity in a single step. S. Antus and co-workers obtained reactive cyclohexa-2,4-dienones by dearomatizing *o*-methoxyphenols with hypervalent iodine reagents (e.g., PIDA). These dienones rapidly dimerized to give heavily substituted complex tricyclic compounds. The dearomatization of 2,6-dimethoxy-4-allylphenol with PIDA/methanol resulted in the formation of the natural product asatone in a single step.[87]



The total synthesis of the rubrolone aglycon was accomplished in the laboratory of D.L. Boger as part of the ongoing research to explore the cycloaddition reaction of cyclopropenone ketals.[88] The key step in the production of the seven-membered C-ring was the *intermolecular Diels-Alder reaction* of an electron-rich diene with the very strained dienophile. The cycloaddition took place in excellent yield (97%) and with complete disastereoselectivity.



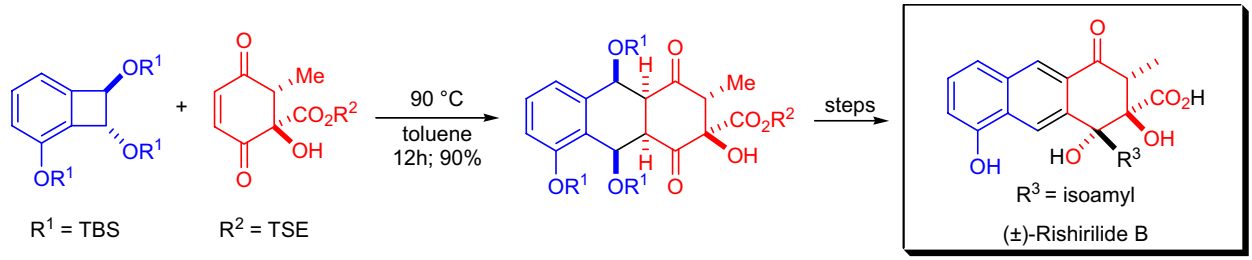
The critical step in the enantioselective and stereocontrolled total synthesis of eunicenone A by E.J. Corey et al. was the highly efficient chiral Lewis acid catalyzed *intermolecular Diels-Alder cycloaddition reaction*.[89] The diene component was mixed with 5 equivalents of 2-bromoacrolein and 0.5 equivalents of the chiral oxazaborolidine catalyst in CH_2Cl_2 at -78 °C for 48h. The reaction gave 80% of the desired cycloadduct in 97% *ee* and the *endo*/*exo* selectivity was 98:2.



R = (*E,E*)-*farnesyl*

98:2 = *endo*/*exo*

Certain functional groups can direct through hydrogen-bonding the outcome of the *intermolecular Diels-Alder cycloaddition*. This was the case in the key *Diels-Alder cycloaddition* step during the total synthesis of ( )-rishirilide B in the laboratory of S.J. Danishefsky.[90] The diene was thermally generated *in situ*.



R1 = TBS

R2 = TSE

DIENONE-PHENOL REARRANGEMENT

(References are on page 577)

Importance:

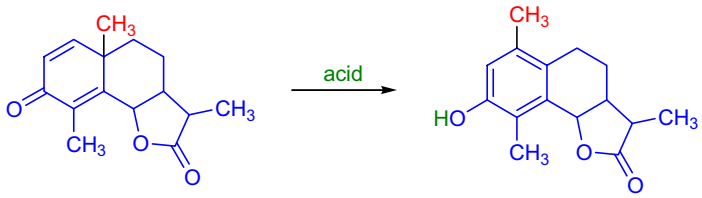
[*Seminal Publications*[1-3]; *Reviews*[4-8]; *Modifications & Improvements*[9-11]; *Theoretical Studies*[12]]

The acid- and base-catalyzed or photochemically-induced migration of alkyl groups in cyclohexadienones is known as the *dienone-phenol rearrangement*, and is widely used for the preparation of highly substituted phenols. In 1893, A. Andreocci described the rearrangement of santonin to desmotroposantonin upon acidic treatment, but it was only in 1930 that the starting material and the product of this rearrangement were carefully characterized.[1,3] The term "*dienone-phenol rearrangement*" was introduced by A.L. Wilds and C. Djerassi.[13] Cyclohexadienones (both *ortho* and *para*) can be considered as "blocked aromatic molecules" in which the migration of an alkyl group converts the non-aromatic substrate into an aromatic one.[6] *Dienone-phenol rearrangements* require only moderately strong acidic media (e.g., H_2SO_4 in acetic acid, acetic anhydride, Lewis acidic clay,[9] etc.), and they are considerably exothermic due to the formation of very stable aromatic compounds.



para cyclohexadienone

ortho cyclohexadienone

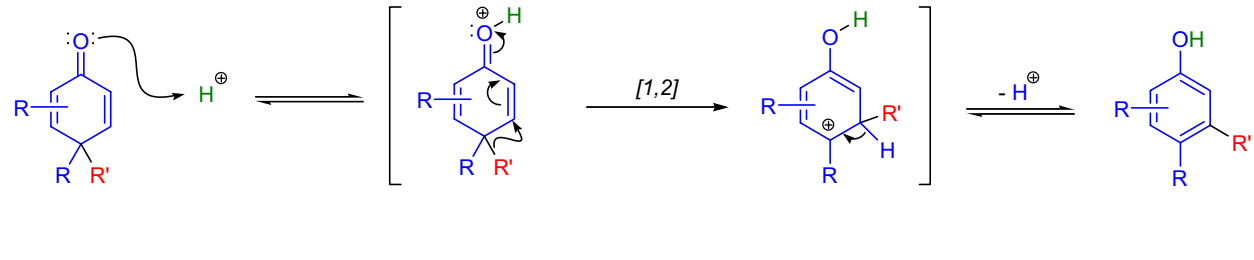


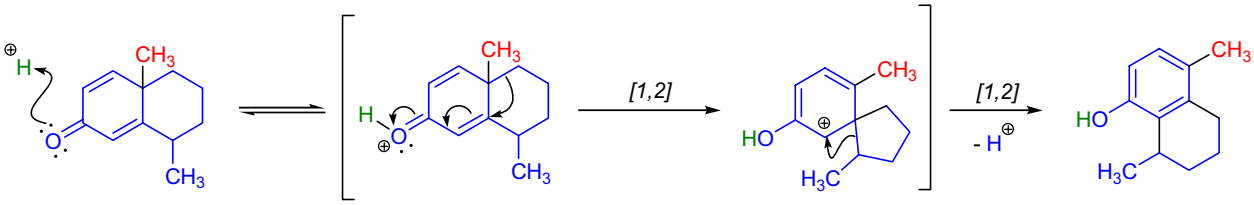
santonin

desmotroposantonin

Mechanism:[14-28]

Most *dienone-phenol rearrangements* involve acid catalysis and the products appear to be the result of sigmatropic *[1,3]-migrations* of C-C bonds. The *[1,3]-alkyl migrations* are actually the result of two subsequent *[1,2]-alkyl shifts* as was demonstrated by ^{14}C isotope labeling studies.[14,15] Depending on the nature of the migrating groups, other rearrangements such as *[1,2]*, *[1,3]*, *[1,4]*, *[1,5]*, *[3,3]*, *[3,4]*, and *[3,5]* can also take place.[6,7] When the migrating group is benzyl, the products predominantly arise from [1,5]-migrations, and the rate of these rearrangements is several orders of magnitude greater than for simple alkyl groups. If the migrating group is allyl, crotyl, or propargyl, then the main course of the rearrangement takes place *via [3,3]-shifts* rather than *[1,2]-shifts*. The scheme below depicts the mechanism of the acid-catalyzed rearrangement of *p*-cyclohexadienone to the corresponding 3,4-disubstituted phenol as well as the rearrangement of a bicyclic dienone *via* two subsequent *[1,2]-shifts*.

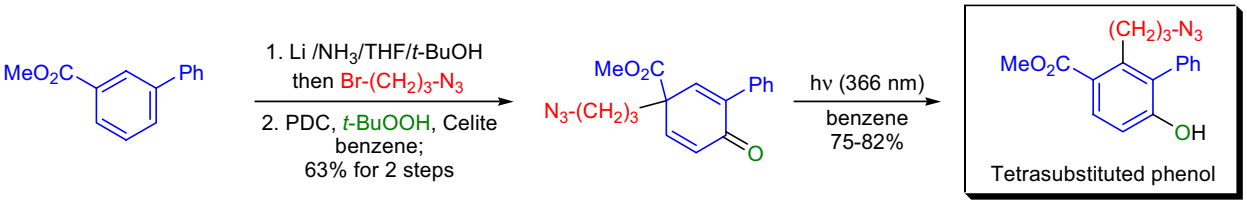




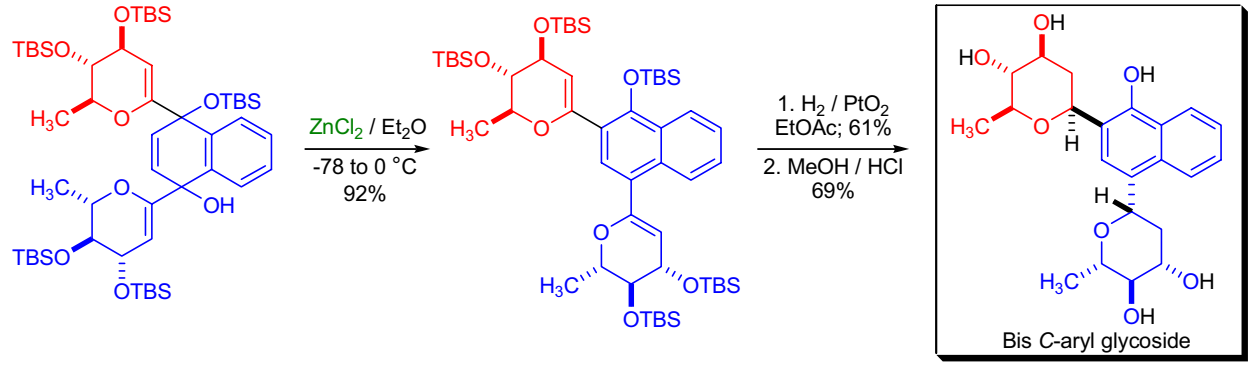
DIENONE-PHENOL REARRANGEMENT

Synthetic Applications:

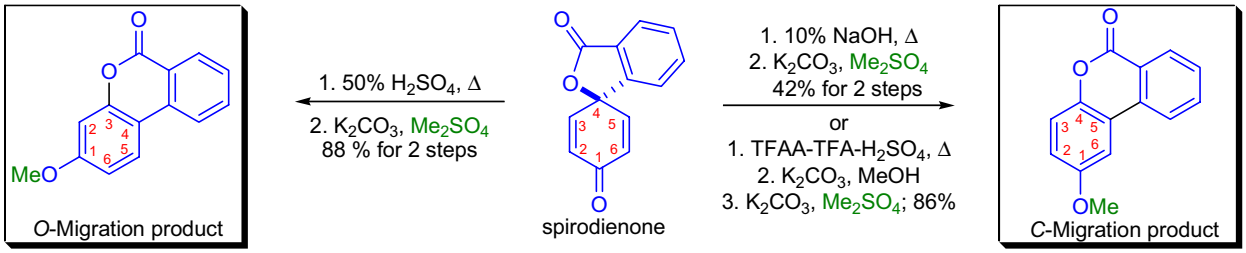
An efficient synthetic route to tetra- and pentasubstituted phenols was developed in the laboratory of A.G. Schultz by the *photochemical dienone-phenol rearrangement* of 4,4-disubstituted 2-phenyl-2,5-cyclohexadienones.[29] The photorearrangement substrates were conveniently prepared by the *Birch reduction-alkylation* of the corresponding aromatic compounds followed by the *bis allylic oxidation* of the initial diene products using *t*-butyl hydroperoxide and catalytic amounts of PDC. Upon irradiation with 366 nm light, the dienones underwent a regioselective *dienone-phenol rearrangement* to afford the phenols in high yield.

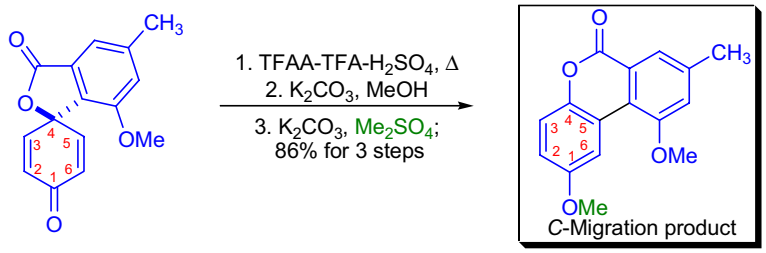


During model studies toward kidamycins, K.A. Parker and co-workers developed a methodology for the synthesis of *bis C*-aryl glycosides.[30] Phenolic *bis* glycosides were synthesized using the regiocontrolled Lewis acid mediated *dienone-phenol type rearrangement* as the key step in which a glycal undergoes a *[1,2] shift*. The resulting *bis C*-aryl glycal was first hydrogenated over PtO_2 to give the *bis* glycoside followed by global desilylation to afford the desired kidamycin model.



Rearrangement of spirodienones under a variety of conditions (both acidic and basic) afforded substituted 6*H*-dibenzo[*b*,*d*]pyran-6-ones.[31] D.J. Hart et al. showed that rearrangements in aqueous sulfuric acid gave products of formal *O*-migration, whereas rearrangements in trifluoroacetic anhydride (TFAA)/trifluoroacetic acid (TFA)/sulfuric acid mostly resulted in *C*-migration products. The *dienone-phenol rearrangement* also worked well for highly substituted spirodienone systems and afforded either the *C*- or *O*-migration products depending on the applied reaction conditions.





DIMROTH REARRANGEMENT

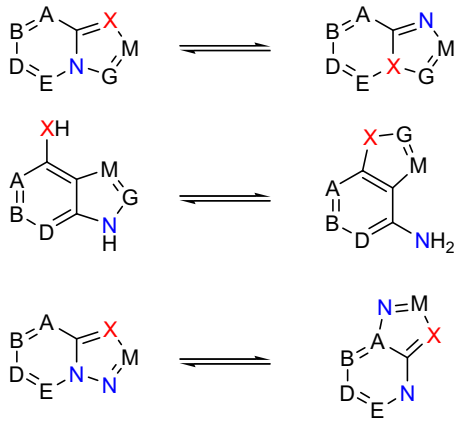
(References are on page 578)

Importance:

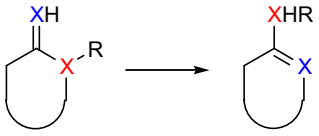
[*Seminal Publications*[1-3]*; Reviews*[4-10]*; Theoretical Studies*[11]]

The isomerization of heterocycles in which endocyclic or exocyclic heteroatoms and their attached substituents are translocated *via* a ring-opening-ring-closure sequence is known as the *Dimroth rearrangement*. The first observation of this type of rearrangement was made by B. Rathke on a triazine derivative but no rationalization was provided to explain the findings.[1] In 1909, O. Dimroth proposed the correct mechanism for the rearrangement of a triazole derivative.[2] The generality of the process was first recognized in the pyrimidine series[12,13] in the mid-1950s and later proved to be even more general; it was shown to occur in many nitrogen-containing heterocyclic systems.[10] It was in 1963 when the term *Dimroth rearrangement* was coined by D.J. Brown and J.S. Harper.[14] The rearrangement may be divided into two types: 1) translocation of heteroatoms within rings of fused systems (***Type I***) and 2) translocation of exo- and endocyclic heteroatoms in a heterocyclic ring (***Type II***). The second type of rearrangement is more common than the first. The *Dimroth rearrangement* can be catalyzed by acids,[15,16] bases (alkali),[17,18] heat, or light.[19,20] Numerous factors influence the course of the *Dimroth rearrangement* in heterocyclic systems: 1) degree of aza substitution in the rings (more nitrogen atoms in the ring lead to more facile nucleophilic attack);[21] 2) pH of the reaction medium (affects the rate of the rearrangement);[22] 3) presence of electron-withdrawing groups (give rise to more facile ring-opening); and 4) the relative thermodynamic stability of the starting material and the product.

Type I rearrangement:



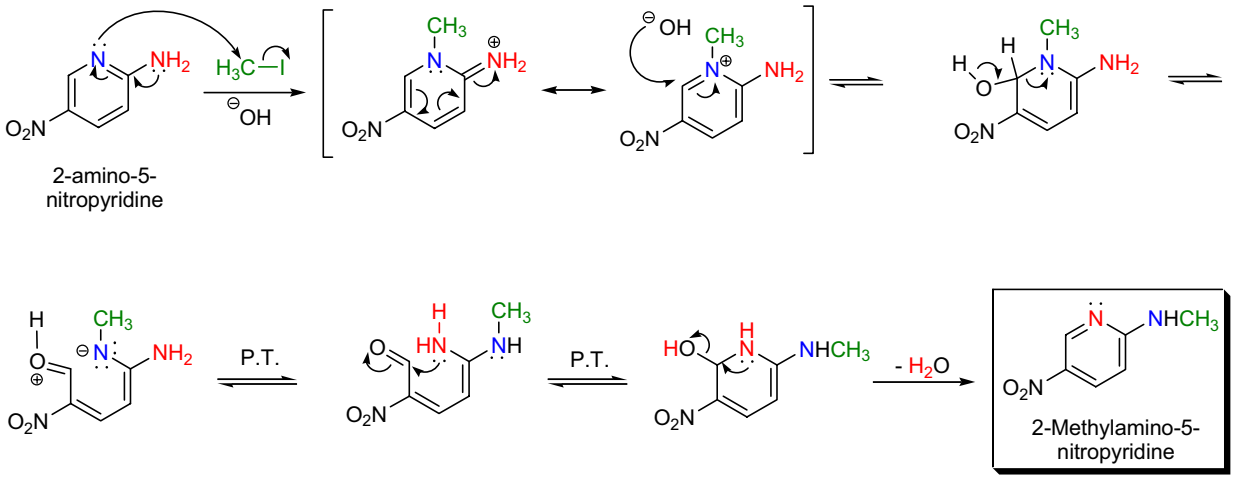
Type II rearrangement:



X = heteroatom; N = nitrogen

Mechanism:[23,24]

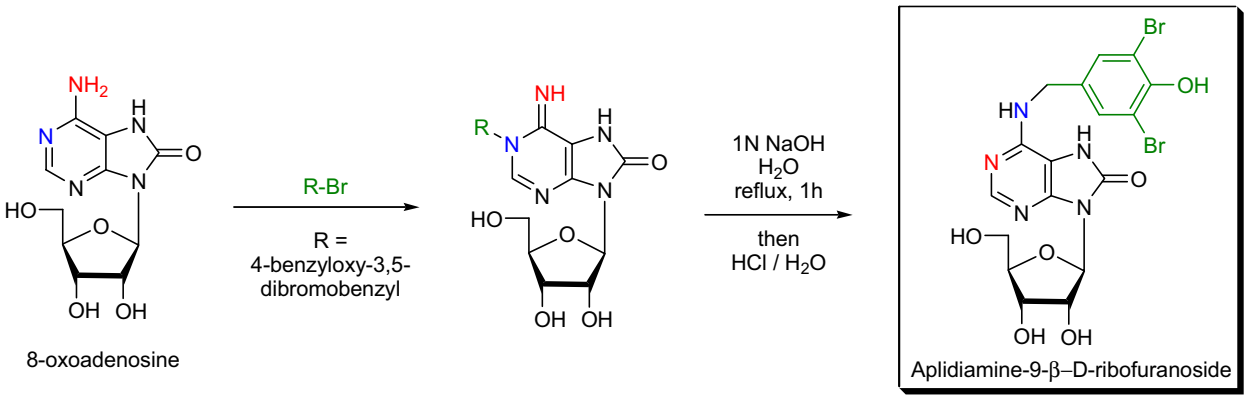
The exact pathway by which the *Dimroth rearrangement* takes place in a given heterocycle depends on many factors (see above). However, in general there are three distinct steps: 1) attack of the heterocyclic ring by a nucleophile; 2) electrocyclic ring opening followed by rotation about a single bond; and 3) ring closure. These steps are known collectively as the ANRORC mechanism. If the rearrangement takes place as a result of heat or irradiation, then the first step is the electrocyclic ring opening followed by the ring closure. The mechanism illustrates the rearrangement of 2-amino-5-nitropyridine to 2-methylamino-5-nitropyridine.



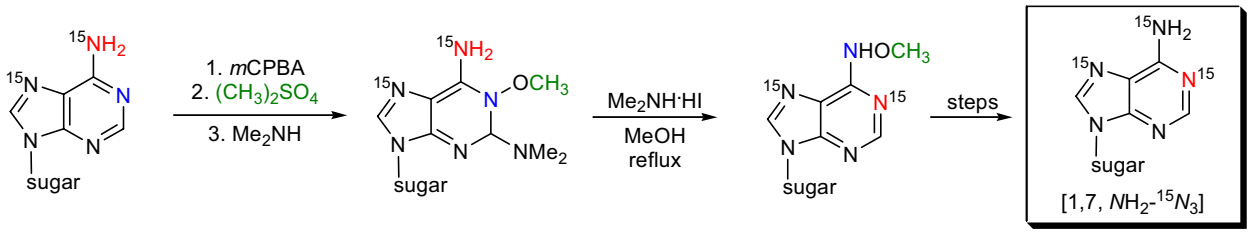
DIMROTH REARRANGEMENT

Synthetic Applications:

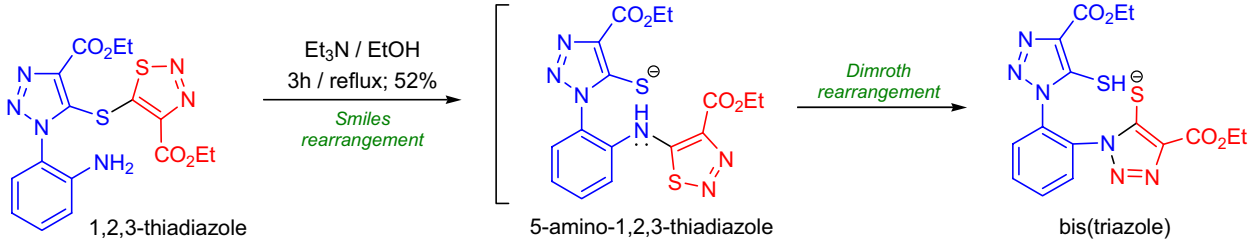
The marine ascidian metabolite purine aplidiamine-9-β-D-ribofuranoside was prepared by T. Itaya et al. by alkylation of 8-oxoadenosine with 4-benzyloxy-3,5-dibromobenzyl bromide followed by a *Dimroth rearrangement* and acid hydrolysis.[25] The rearrangement was induced by treating the nucleoside in boiling 1N NaOH for 1h. The desired rearranged nucleoside was formed in 58% overall yield.

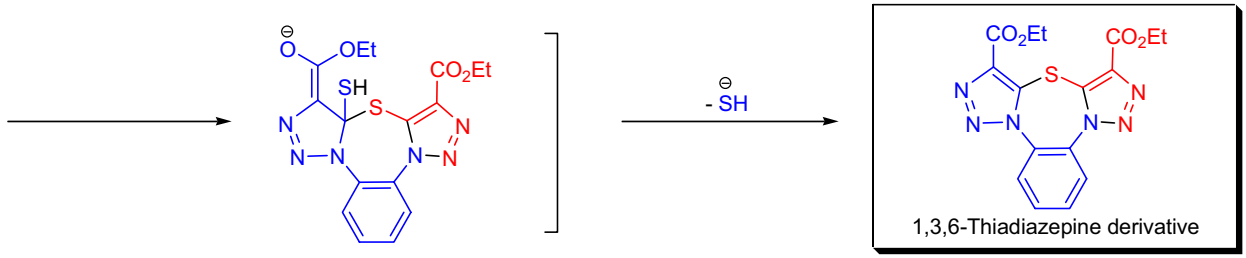


In the laboratory of R.A. Jones, N^1-methoxy derivatives of adenosine and 2'-deoxyadenosine were found to undergo a facile *Dimroth rearrangement*.[26] The high-yielding process allowed the efficient synthesis of [1,7-$^{15}N_2$]- and [1,7, NH_2-$^{15}N_3$] adenosine and 2'-deoxyadenosine that are important tools in the NMR studies of nucleic acid structure and interactions. The rearrangement was carried out in weakly acidic refluxing methanol.



A new synthetic approach to tricyclic 1,3,6-thiadiazepines was developed by V.A. Bakulev and co-workers.[27] The synthetic sequence involved a base-catalyzed *Smiles rearrangement* followed by an *in situ Dimroth rearrangement*. The starting substituted 1,2,3-thiadiazole was treated with triethylamine in refluxing ethanol. In the first step, the thiadiazole ring was transposed from the sulfur to the nitrogen atom (*Smiles rearrangement*). In the second step, the 5-amino-1,2,3-thiadiazole underwent a *Dimroth rearrangement* to form the bis(triazole) intermediate, which immediately formed the tricyclic 1,3,6-thiadiazepine accompanied by the loss of hydrogen sulfide anion.





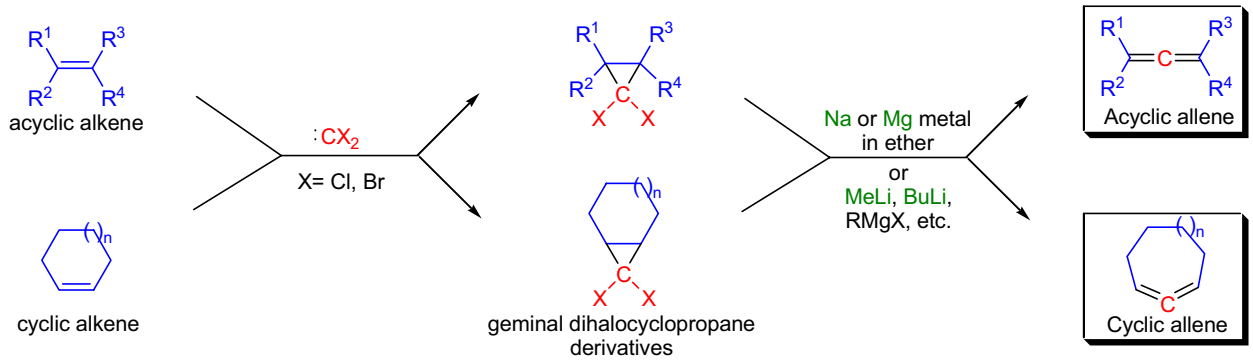
DOERING-LAFLAMME ALLENE SYNTHESIS

(References are on page 578)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-7]; *Modifications & Improvements*[8,9]]

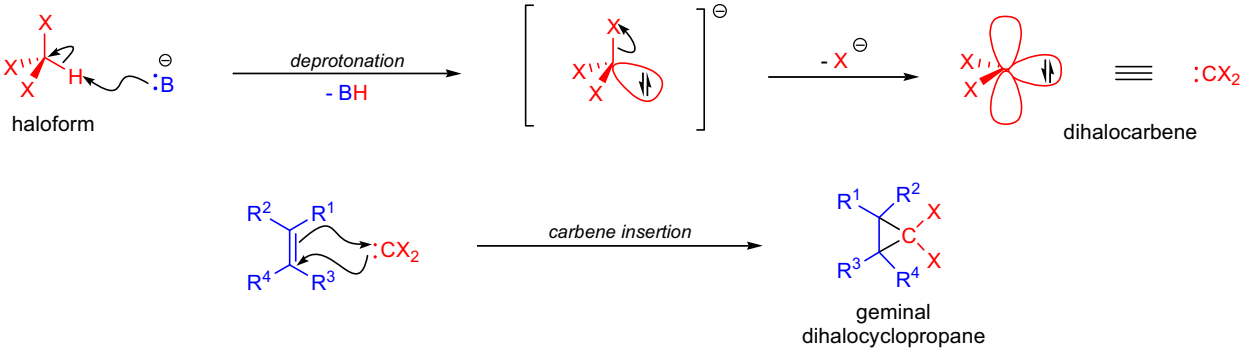
In 1958, W. Doering and P.M. LaFlamme developed a two-step one-carbon homologation procedure to prepare allenes from alkenes.[3] The first step of the synthesis involves the addition of dibromocarbene to an olefin. Then, in the second step, the 1,1-dibromocyclopropane derivative is reduced with an active metal (high surface area Na or Mg) to afford the allene in moderate to good yield. The method was shown to be general and today the preparation of allenes from olefins *via* dihalocyclopropanes is known as the *Doering-LaFlamme allene synthesis*. Geminal dihalocyclopropanes are readily available from the reaction of dihalocarbene with an olefin, as described by Doering and Hoffmann in 1954.[1] Drawbacks of the original allene synthesis are: 1) isomerization of unsaturated compounds is common with sodium metal; 2) sluggish reaction and the formation of allene-cyclopropane mixtures with magnesium metal; and 3) dichlorocyclopropanes are less reactive than the dibromo analogs. The modification of the original procedure by reacting the dihalocarbene with alkyllithiums[8,9] or Grignard reagents[10] results in higher yields of allenes. For example ethyl- and isopropylmagnesium bromide can be used at room temperature to convert dibromocyclopropanes into aliphatic and non-strained cyclic allenes.[10]



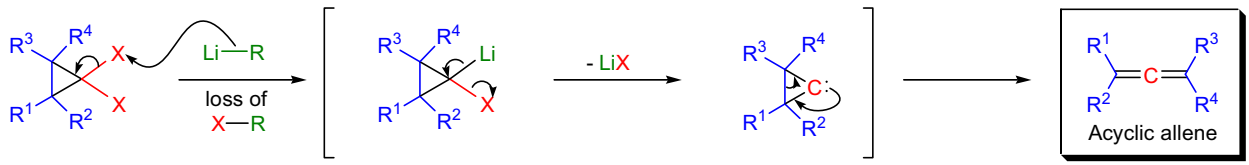
Mechanism:[3,11-14,10]

The first step of the *Doering-LaFlamme allene synthesis* is the generation of a dihalocarbene that reacts with the olefin *in situ*. First, the haloform is deprotonated by a strong base to form an unstable trihalomethyl carbanion, which undergoes a facile -elimination to the dihalocarbene. The dihalocarbene then quickly inserts into the double bond of the olefin to afford a geminal dihalocyclopropane. In the second step, the alkyllithium performs a lithium-halogen exchange with the dihalocyclopropane to form lithiobromocyclopropane, which in turn loses lithium halide to generate a cyclopropylidene or a related carbenoid. The cyclopropylidene undergoes rearrangement to the corresponding allene.

Dihalocarbene formation and insertion:



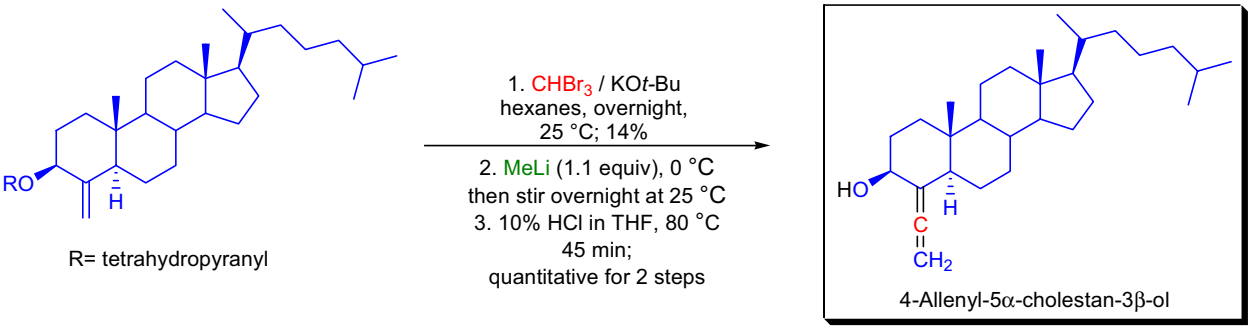
Metal-halogen exchange and rearrangement:



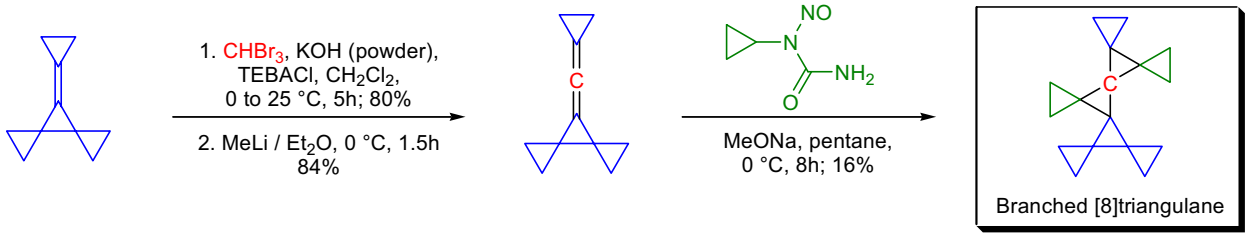
DOERING-LAFLAMME ALLENE SYNTHESIS

Synthetic Applications:

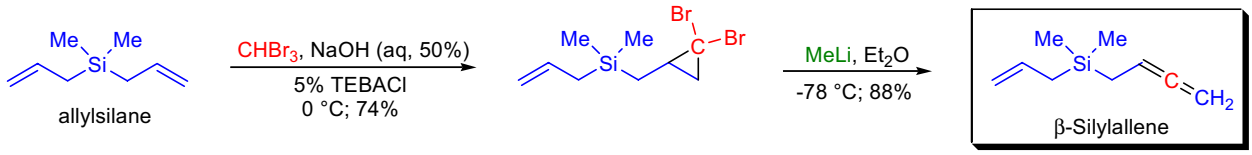
The synthesis of novel 4α-substituted sterols was undertaken in the laboratory of C.H. Robinson.[15] These compounds are potential inhibitors of sterol 4-demethylation. To prepare the desired 4-allenyl-5α-cholestan-3β-ol, the exocyclic olefin precursor was first reacted with bromoform/potassium *t*-butoxide to afford the geminal dibromo-substituted cyclopropane derivative. Next, methyllithium was used to bring about the rearrangement to afford the allene, and finally acidic conditions were applied for the removal of the THP protecting group.



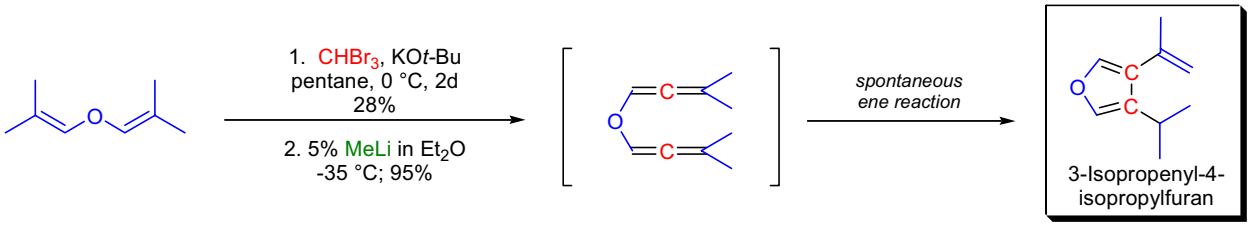
During studies of the preparation and chemical behavior of spirocyclopropanated bicyclopropylidenes, A. de Meijere and co-workers successfully synthesized a branched [8]triangulane from 7-cyclopropylidenespiro[2.0.2.1]heptane.[16] The key transformation in their approach was the *Doering-LaFlamme allene synthesis*. The 7-cyclopropylidene spiro[2.0.2.1]heptane was first dibromocyclopropanated and then treated with methyllithium to afford the key intermediate allene in good yield. Upon reaction with diazocyclopropane (generated *in situ* from *N*-nitroso-*N*-cyclopropylurea), the allene gave the desired branched [8]triangulane in modest yield.



M. Santelli et al. developed a general synthesis of β-silylallenes from allylsilanes utilizing the *Doering-LaFlamme allene synthesis*.[17]



The synthesis and thermal rearrangement of π and heteroatom bridged diallenes was investigated by S. Braverman and co-workers.[18] Bis(γ,γ-dimethylallenyl)ether was generated by the addition of dibromocarbene to diisobutenyl ether and treating the resulting dibromocyclopropane derivative with methyllithium. However, the allene proved to be impossible to isolate, since it underwent spontaneous cyclization to give 3-isopropenyl-4-isopropylfuran in high yield.



DÖTZ BENZANNULATION REACTION

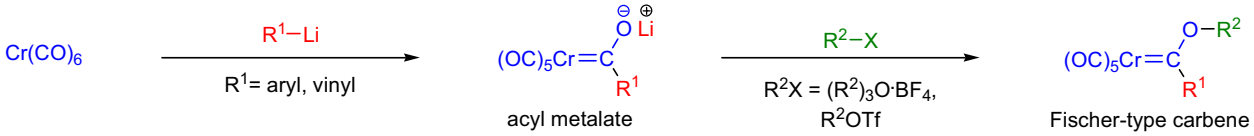
(References are on page 579)

Importance:

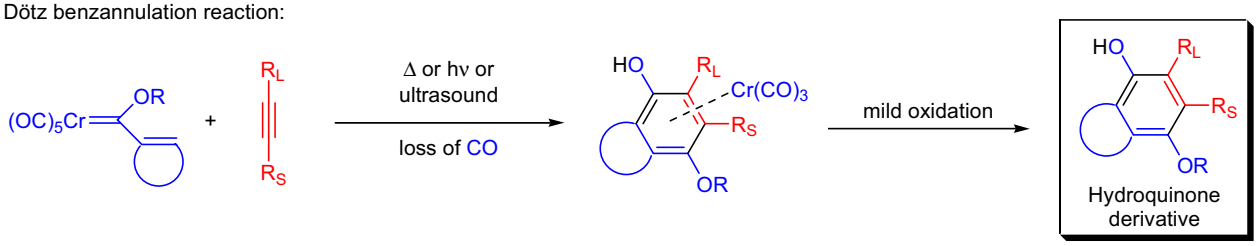
[*Seminal Publications*[1,2]; *Reviews*[3-20]; *Modifications & Improvements*[21-24]; *Theoretical Studies*[25-28]]

In 1975, K.H. Dötz reported the formal [3+2+1] cycloaddition of a chromium phenylmethoxycarbene complex with diphenylethyne that yielded primarily a chromium tricarbonyl-complexed 4-methoxy-1-naphthol upon heating in dibutyl ether at 45 °C.[1] The reaction of an α,β-unsaturated pentacarbonyl chromium carbene complex (Fischer-type carbene) with an alkyne to afford a substituted hydroquinone (1,4-dihydroxybenzene) derivative is called the *Dötz benzannulation reaction*. Since its initial discovery, the transformation has become one of the most studied reactions of chromium complexes. The nature of the products depends largely on the nature of the substituents on the carbene and the reaction conditions (solvents, temperature, concentration, etc.).[29,30] The required Fischer chromium carbenes can be prepared with ease by treating $Cr(CO)_6$ with an organolithium nucleophile followed by the *O*-alkylation of the resulting acyl metalate with a strong alkylating agent (e.g., Meerwein's salt, alkyl triflates, etc.). This process allows the preparation of a wide variety of unsaturated chromium-carbenes and is limited only by the availability of the organolithium reagent. Advantages of the *Dötz benzannulation reaction* are: 1) access to densely functionalized aromatic compounds with excellent chemo- and regioselectivity (the large alkyne substituent, R_L, always ends up *ortho* to the phenolic OH group); 2) compatibility with a variety of substituents on both the alkyne and the unsaturated carbene side chain; 3) aryl carbene complexes with electron-withdrawing or electron-donating substituents work as well as unsubstituted aryl- or heteroaryl carbenes; 4) alkynes bearing electron-donating groups give moderate to excellent yields; 5) the hydroquinone products can be oxidized to give highly substituted quinones; and 6) the annulation is also possible intramolecularly with a reversal of the regioselectivity. The disadvantages are: 1) toxicity of chromium complexes; 2) alkynes with electron-withdrawing groups give poor yields or do not react at all; 3) heterosubstituted alkynes generally give low yields; and 4) the benzannulation is often accompanied by the formation of indenes and cyclobutenones.

Preparation of α,β–unsaturated Fischer-type carbenes:

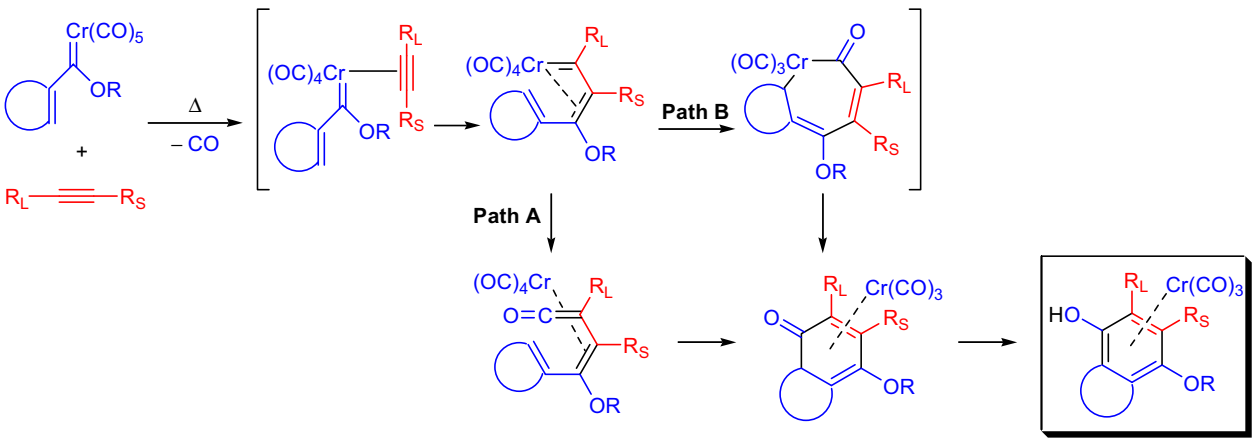


Dötz benzannulation reaction:



Mechanism:[31-34,17,35]

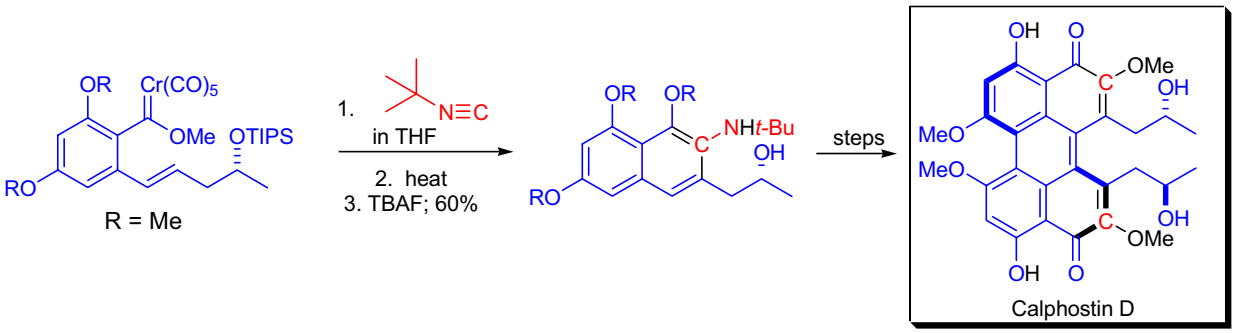
The mechanism of the *Dötz benzannulation reaction* has not been fully elucidated. The first step is the rate-determining dissociation of one carbonyl ligand from the Fischer carbene complex, which is *cis* to the carbene moiety. Subsequently, the alkyne component coordinates to the coordinatively unsaturated carbene complex, and then it inserts into the metal-carbon bond. After the alkyne insertion, a vinylcarbene is formed that can lead to the product by two different pathways (**Path A** or **Path B**).[36-39]



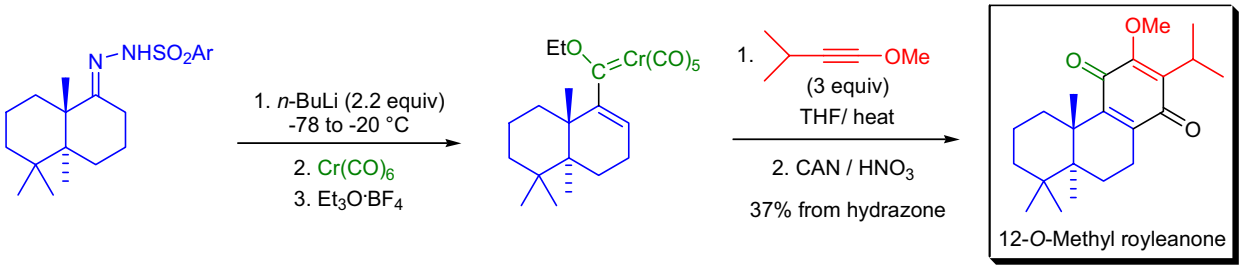
DÖTZ BENZANNULATION REACTION

Synthetic Applications:

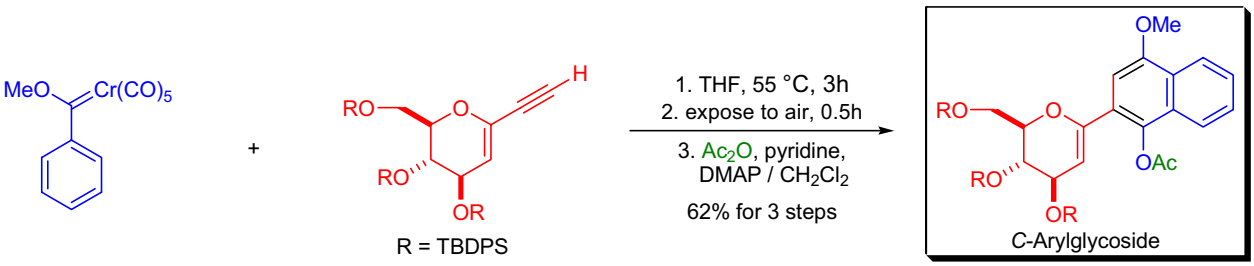
The architecturally interesting and biologically significant protein kinase C inhibitor calphostins (A-D), and their analogs were synthesized in the laboratory of C.A. Merlic.[40] The key steps in their approach were a *Dötz aminobenzannulation* utilizing an enantiopure Fischer carbene complex to prepare a pentasubstituted naphthylamine, followed by a *biomimetic oxidative dimerization* to produce the perylenequinone skeleton.



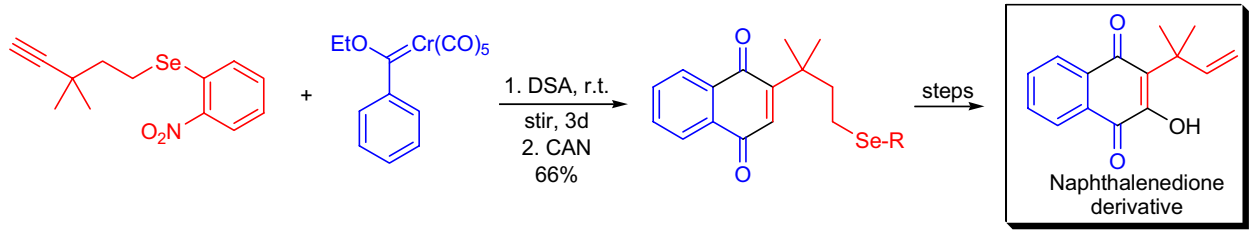
P. Quayle and co-workers utilized the *Dötz benzannulation reaction* for the synthesis of diterpenoid quinones.[41] The authors developed a novel synthetic approach to 12-*O*-methyl royleanone using a simple vinyl chromium carbene complex along with a disubstituted oxygenated acetylene. The bicyclic hydrazone was converted to the corresponding vinyllithium derivative by the *Shapiro reaction* and then functionalized to give the desired crude Fischer chromium carbene complex. The benzannulation took place in refluxing THF with excellent regioselectivity, and the natural product was obtained in 37% overall yield from the hydrazone.



C-Arylglycosides possess a stable C-C glycosidic linkage and exhibit a broad range of useful antitumor, antifungal and antibiotic properties. S.R. Pulley et al. developed a novel method for the synthesis of this important class of compounds by using the *Dötz benzannulation* reaction between alkynyl glycosides and alkoxy phenyl chromium carbenes.[42]



An exceptionally mild *Dötz benzannulation* was used by W.J. Kerr and co-workers for the total synthesis of a natural insecticide, 2-(1,1-dimethyl-2-propenyl)-3-hydroxy-1,4-naphthalenedione, by utilizing dry adsorption (DSA) techniques.[24]



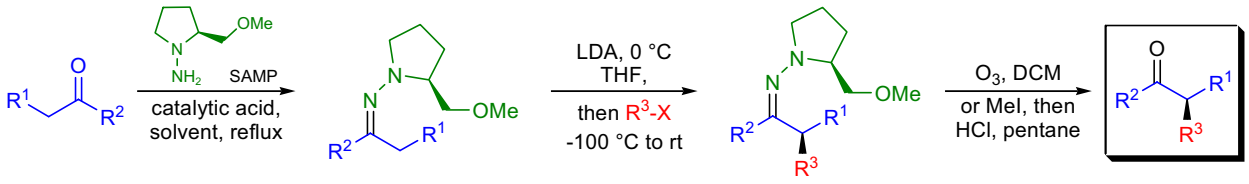
ENDERS SAMP/RAMP HYDRAZONE ALKYLATION

(References are on page 579)

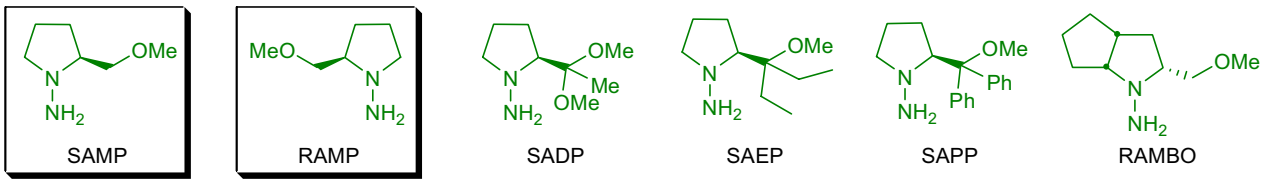
Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-15]; *Modifications & Improvements*[16-18]]

In 1976, D. Enders reported the asymmetric α-alkylation of ketones *via* the corresponding (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone derivatives.[1] According to the general procedure, the SAMP hydrazone was deprotonated with lithium diisopropylamide in tetrahydrofuran, and the corresponding lithium derivative was reacted with an alkyl halide. The product was ozonized to provide the α-alkylated ketone with high enantioselectivity. The opposite enantiomer can be obtained by using (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) as the chiral auxiliary. This transformation can also be carried out on aldehydes.[2,3] The asymmetric alkylation of ketones and aldehydes *via* their SAMP/RAMP hydrazone derivatives is referred to as the *Enders SAMP/RAMP hydrazone alkylation*. General features of the reaction are: 1) the SAMP/RAMP hydrazones of aldehydes can be formed by mixing the aldehyde with the hydrazone derivative at 0 °C, while ketones need to be heated to reflux in the presence of a catalytic amount of acid in benzene or cyclohexane under Dean-Stark conditions;[1,2] 2) the hydrazones can be purified by distillation or chromatography, although purification is not always necessary, and they can be stored at -20 °C under inert atmosphere without decomposition;[1,2] 3) cyclic and acyclic ketones and aldehydes undergo the transformation;[1,2,14] 4) deprotonation can be effected with lithium bases, most commonly with lithium diisopropylamide;[1,2,14] 5) the alkylating reagents are alkyl-, benzyl-, and allyl bromides and iodides; 6) upon completion of the alkylation, the ketone can be regenerated by ozonolysis or methylation with methyl iodide and subsequent acidic hydrolysis;[1,2] and 7) the hydrazones can be transformed into various functionalities such as nitrile,[19,20] dithiane,[21] or amine.[19,13] The SAMP chiral auxiliary can be obtained from (*S*)-proline in four steps in a 58% overall yield, while RAMP is available from (*R*)-glutamic acid in six steps in 35%.[22-24] Several related chiral auxiliaries were also developed such as SADP, SAEP, SAPP, and RAMBO.[16-18] In addition to alkyl halides, the deprotonated SAMP/RAMP hydrazones react with Michael acceptors, ketones, α-halogen substituted esters, oxiranes, and aziridines.[14]

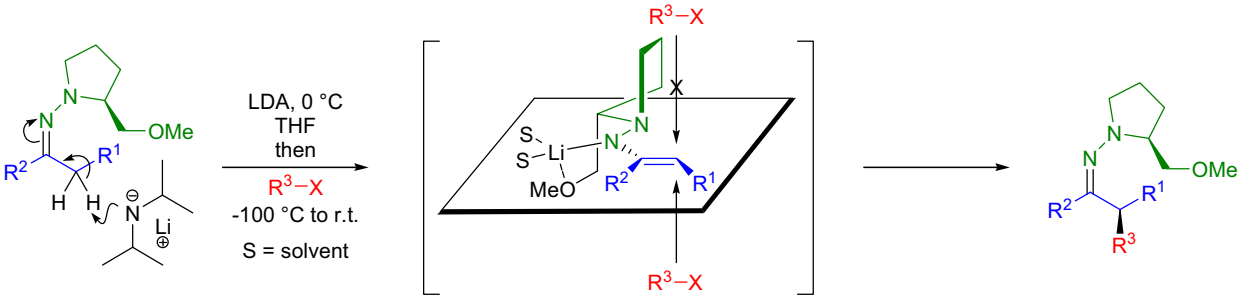


R^1 = alkyl, aryl; R^2 = H, alkyl, R^1 = R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -CH=CH$(CH_2)_2$-; R^3 = alkyl, benzyl, allyl; X = I, Br;
solvent: benzene, cyclohexane



Mechanism:[25,1,2,26,3,22,27,5,28]

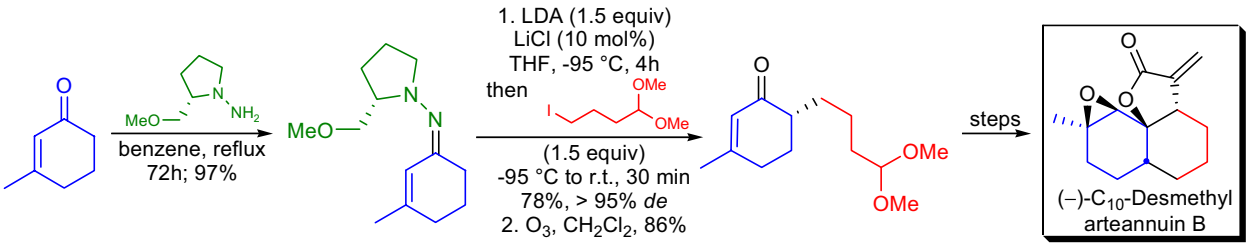
The deprotonation of the SAMP/RAMP hydrazone derivatives leads to the formation of azaenolates that can be trapped by the alkyl halide. In theory, four isomeric azaenolates can form in the deprotonation step, but it was shown that around the C-C double bond *E* stereochemistry is dominant, while around the C-N bond *Z* stereochemistry ($E_{CC}Z_{CN}$) is dominant for cyclic- and acyclic ketones. This observation was confirmed by trapping experiments,[1,2,22,27,5] MNDO calculations,[25] spectroscopic investigations,[26,3] and X-ray analysis.[28] It was also shown by freezing point depression experiments that the lithiated SAMP hydrazones exist in a monomeric form.[29] Electrophilic attack by the electrophile on this system proceeds from the sterically more accessible face with high diastereoselectivity.



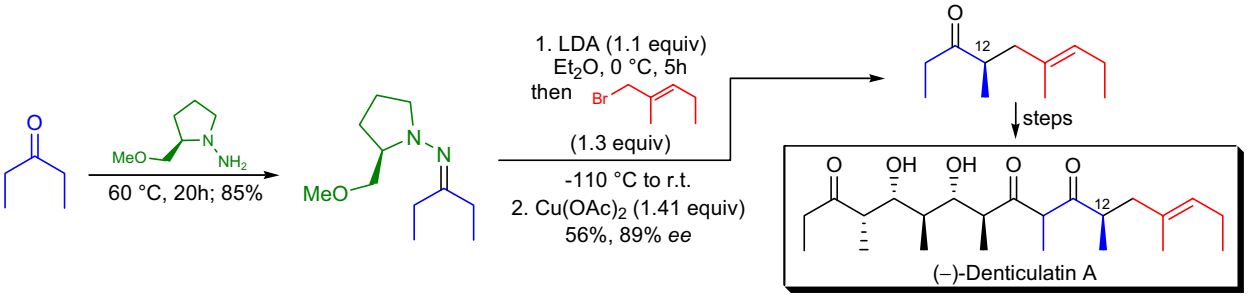
ENDERS SAMP/RAMP HYDRAZONE ALKYLATION

Synthetic Applications:

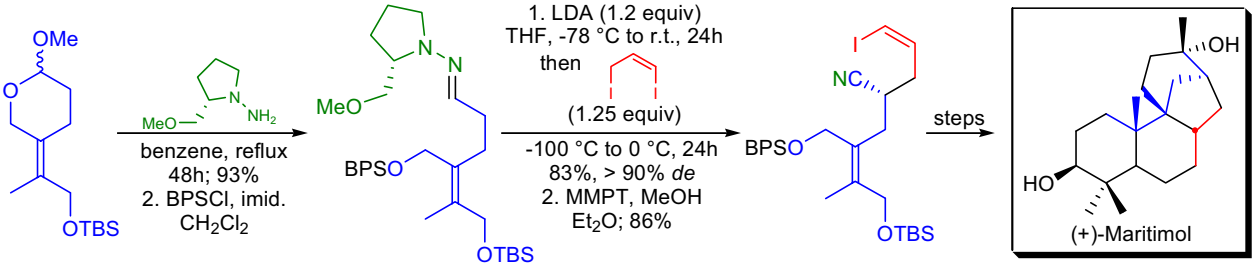
The synthesis of (–)-C_{10}-desmethyl arteannuin B, a structural analog of the antimalarial artemisinin, was developed by D. Little et al.[30] In their approach, the absolute stereochemistry was introduced early in the synthesis utilizing the *Enders SAMP/RAMP hydrazone alkylation* method. The sequence begins with the conversion of 3-methylcyclohexenone to the corresponding (*S*)-(–)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone. Deprotonation with lithium diisopropylamide, followed by alkylation in the presence of lithium chloride at -95 °C afforded the product as a single diastereomer. The SAMP chiral auxiliary was removed by ozonolysis.



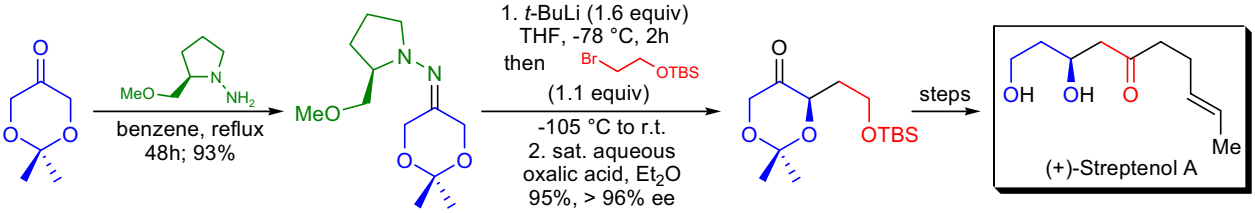
The total synthesis of (–)-denticulatin A, a polypropionate metabolite, was accomplished in the laboratory of F.E. Ziegler.[31] To establish the absolute stereochemistry at C12, they utilized the *Enders SAMP/RAMP hydrazone alkylation.* To this end, the RAMP hydrazone of 3-pentanone was successfully alkylated with 1-bromo-2-methyl-2(*E*)-pentene. Hydrolysis of the hydrazone under standard acidic conditions led to loss of the enantiomeric purity. This problem was avoided by using cupric acetate for the cleavage.



The first asymmetric total synthesis of (+)-maritimol, a diterpenoid natural product that possesses a unique tetracyclic stemodane framework was accomplished by P. Deslongchamps.[32] To introduce the C12 stereocenter, the *Enders SAMP/RAMP hydrazone alkylation* was used. This stereocenter played a crucial role in controlling the diastereoselectivity of the key transannular Diels-Alder reaction later in the synthesis. The required SAMP hydrazone was formed under standard conditions using catalytic *p*-toluenesulfonic acid. Subsequent protection of the free alcohol as a *t*-butyldiphenylsilyl ether, deprotonation of the hydrazone with LDA and alkylation provided the product in high yield and excellent diastereoselectivity. The hydrazone was converted to the corresponding nitrile by oxidation with magnesium monoperoxyphthalate.



Application of the *Enders SAMP/RAMP hydrazone alkylation method* on 1,3-dioxan-5-one derivatives leads to versatile C_3 building blocks.[33] To demonstrate the usefulness of the above method, the research group of D. Enders applied it during the first asymmetric total synthesis of both enantiomers of streptenol A.[34] To obtain the natural isomer, the RAMP hydrazone of 2,2-dimethyl-1,3-dioxan-5-one was used as starting material. This compound was deprotonated with *t*-butyllithium and alkylated with 2-bromo-1-*tert*-butyldimethylsilyloxyethane. The chiral auxiliary could be hydrolyzed under mildly acidic conditions to provide the ketone in excellent yield and enantioselectivity.



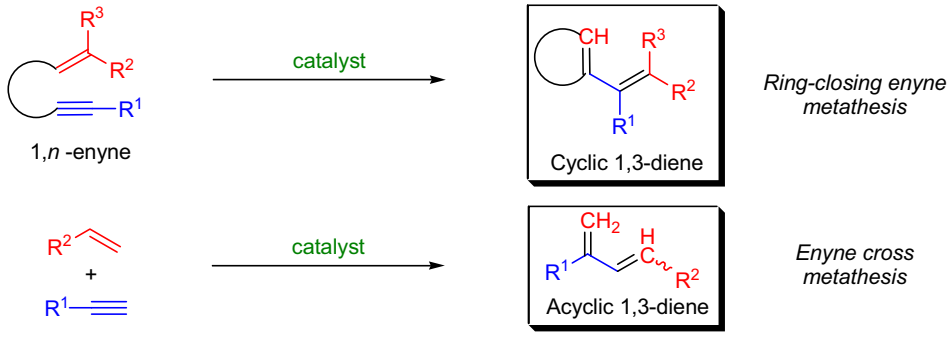
ENYNE METATHESIS

(References are on page 580)

Importance:

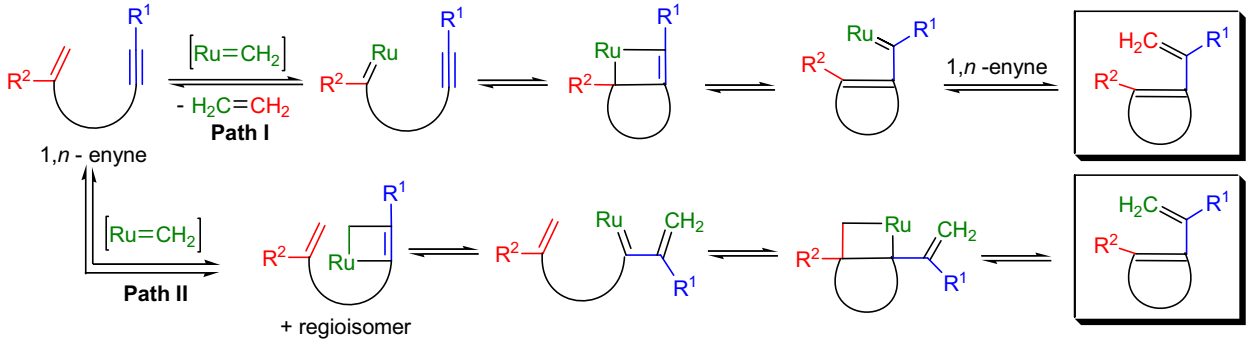
[*Seminal Publications*[1-5]*; Reviews*[6-16]*; Modifications & Improvements*[17-23]*; Theoretical Studies*[24,25]]

In 1985, T.J. Katz reported an intriguing methylene migration reaction when a biaryl 1,7-enyne was exposed to 1 mol% of a tungsten Fischer carbene complex to give a 1,3-diene as the product in 31% yield.[1] This was the first example of the metal carbene catalyzed intramolecular redistribution of carbon-carbon multiple bonds between an alkene and an alkyne. The transition metal catalyzed cycloisomerization of 1,*n*-enynes to the corresponding 1,3-dienes is known as the *intramolecular ring-closing enyne metathesis*. Another variant is the *cross enyne metathesis* between independent molecules of an alkene and an alkyne.[26] Soon after Katz's report, molybdenum, and chromium Fischer carbene complexes were also successfully utilized, but the catalysts were often required in stoichiometric amounts, and the yields were generally low due to side reactions. Besides metal carbene complexes, the *enyne metathesis* can be catalyzed by the following low-valent transition metals: Pd(II),[7] Pt(II),[27] Ru(II),[28] and Ir(I)[29] complexes.[15] The most widely used and most efficient *enyne metathesis* catalysts are ruthenium benzylidene complexes such as Grubbs first and second generation catalysts, which were originally developed for *olefin metathesis* reactions. The general features of the *ring-closing enyne metathesis* are: 1) the substituents of the olefin have a profound influence on the reaction rate, the number of different products, and their distributions;[30,31] 2) monosubstituted alkenes react faster than di- or trisubstituted ones; 3) enynes with monosubstituted olefins form exclusively the smallest possible ring size; 4) the substitution of the alkyne partner also has an influence on the reaction rate: terminal alkynes react slower than internal ones; 5) alkyl substituents on the alkyne tend to give high yields, whereas electron-withdrawing substituents usually result in lower yields; 6) the presence of ethylene gas (instead of the usual argon) may substantially increase the rate of the reaction in certain cases;[32,33] 7) reactions are usually conducted in dichloromethane, toluene, or benzene either at ambient temperature or at reflux; 8) a wide range of functional groups (esters, amides, ethers, ketones, acetals, etc.) are tolerated under the reaction conditions, but amines and alcohols need to be protected to obtain high yields; 9) the formation of a five- and six-membered ring is easily achieved, whereas 7-, 8-, and 9-membered carbocycles are not formed as readily unless the enyne tether contains a heteroatom;[12] and 10) the *enyne metathesis* in combination with other metathesis reactions and cycloadditions leads to powerful tandem reactions.



Mechanism: [34-36,17,37-39,30,27,40,31,41]

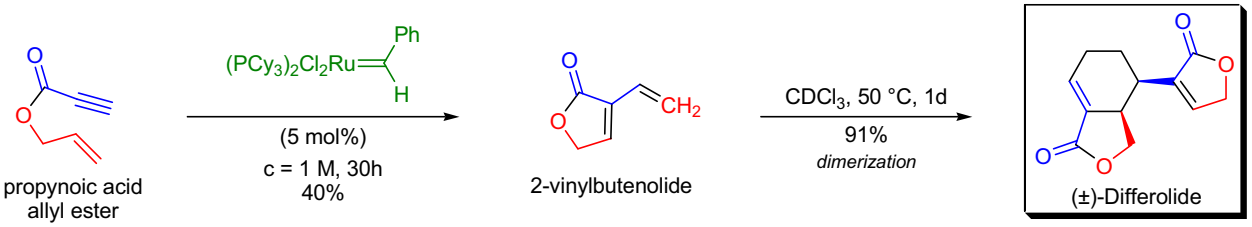
The mechanism of the *enyne metathesis* depends on the type of catalyst used while the fine details of the process are much less understood than in the case of olefin metathesis. Since the most widely used catalyst is the Grubbs's second-generation ruthenium carbene complex, the reaction mechanism of a *ring-closing enyne metathesis* employing this carbene is discussed. Two different mechanistic pathways may operate depending on whether the metal carbene first reacts with the alkene or alkyne. In **Path I** the alkene forms a metallacyclobutane intermediate that subsequently undergoes several ring openings and closures to give the final diene product. However, in **Path II** the metal carbene first reacts with the alkyne and two different dienes can be formed *via* two regioisomeric metallacyclobutenes (only one is shown).



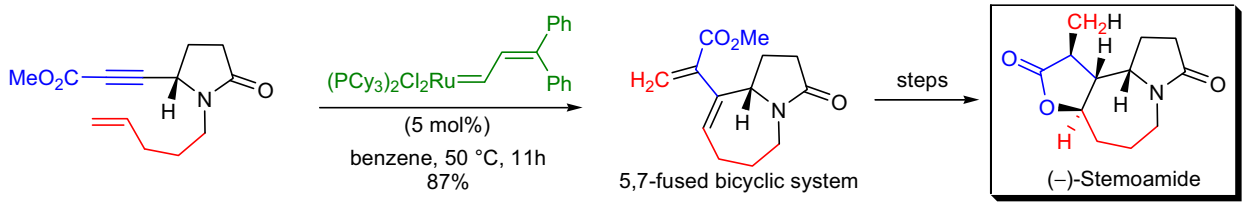
ENYNE METATHESIS

Synthetic Applications:

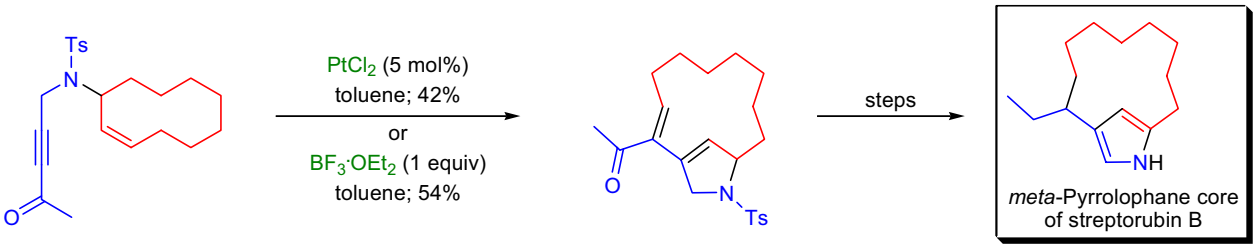
The short total synthesis of (±)-differolide based on a tandem *enyne metathesis* / [4+2] cycloaddition was accomplished by T.R. Hoye et al.[42] The *enyne metathesis* was carried out on allyl propynoate using Grubbs's first-generation metathesis catalyst. The catalyst was added to the substrate slowly to maintain high substrate and low ruthenium carbene concentrations. The initially formed 2-vinylbutenolide readily dimerized *via* a *Diels-Alder cycloaddition* in which the vinyl group participated as the dienophile to afford the natural product.



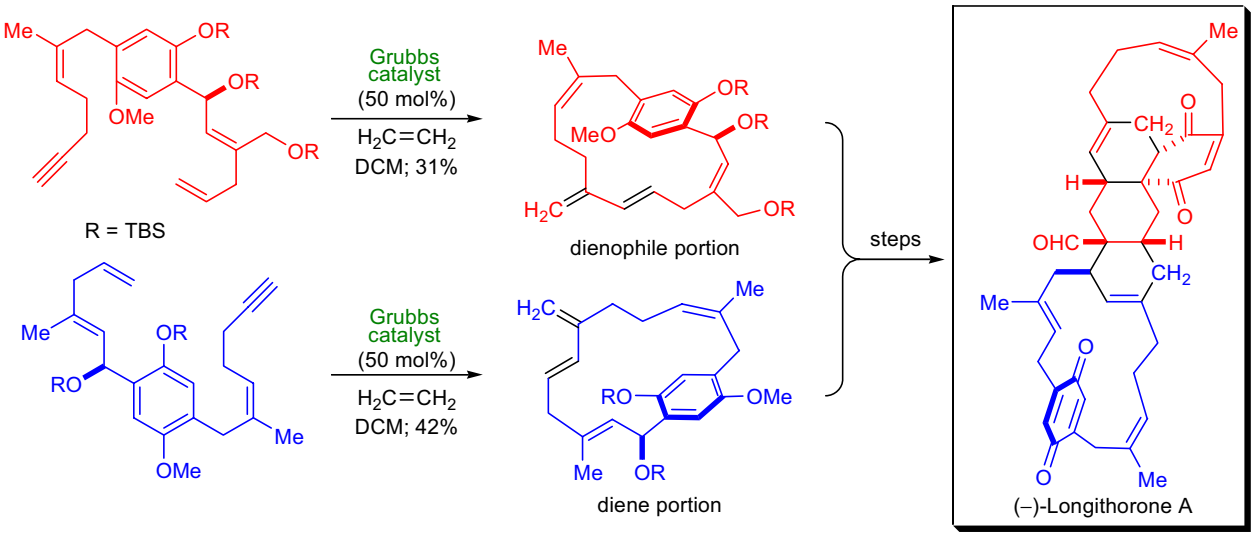
The total synthesis of polycyclic alkaloid (–)-stemoamide was achieved in the laboratory of M. Mori *via* a ruthenium carbene catalyzed *enyne metathesis*.[43] The cyclization was effected by 5 mol% of catalyst in benzene at 50 °C. After 11h of stirring under these conditions, 87% of the 5,7-fused bicyclic system was formed.



A platinum- and Lewis acid catalyzed *enyne metathesis* was used as the key step in the formal total synthesis of antibiotics streptorubin B and metacycloprodigiosin by A. Fürstner.[37] The electron-deficient enyne was cyclized with either a platinum halide or a hard Lewis acid (e.g., $BF_3{\cdot}OEt_2$) to the desired *meta*-pyrrolophane core of the target molecules. A few more steps completed the formal synthesis.



M. Shair and co-workers were the first to apply the *enyne metathesis* for macrocyclization during the biomimetic synthesis of (–)-longithorone A.[44] The two 16-membered paracyclophane building blocks, one diene and one dienophile component, were prepared using 50 mol% Grubbs's first-generation catalyst under 1 atm ethylene gas pressure. These components, after several additional steps, underwent two facile *Diels-Alder cycloaddition reactions* to afford the natural product.



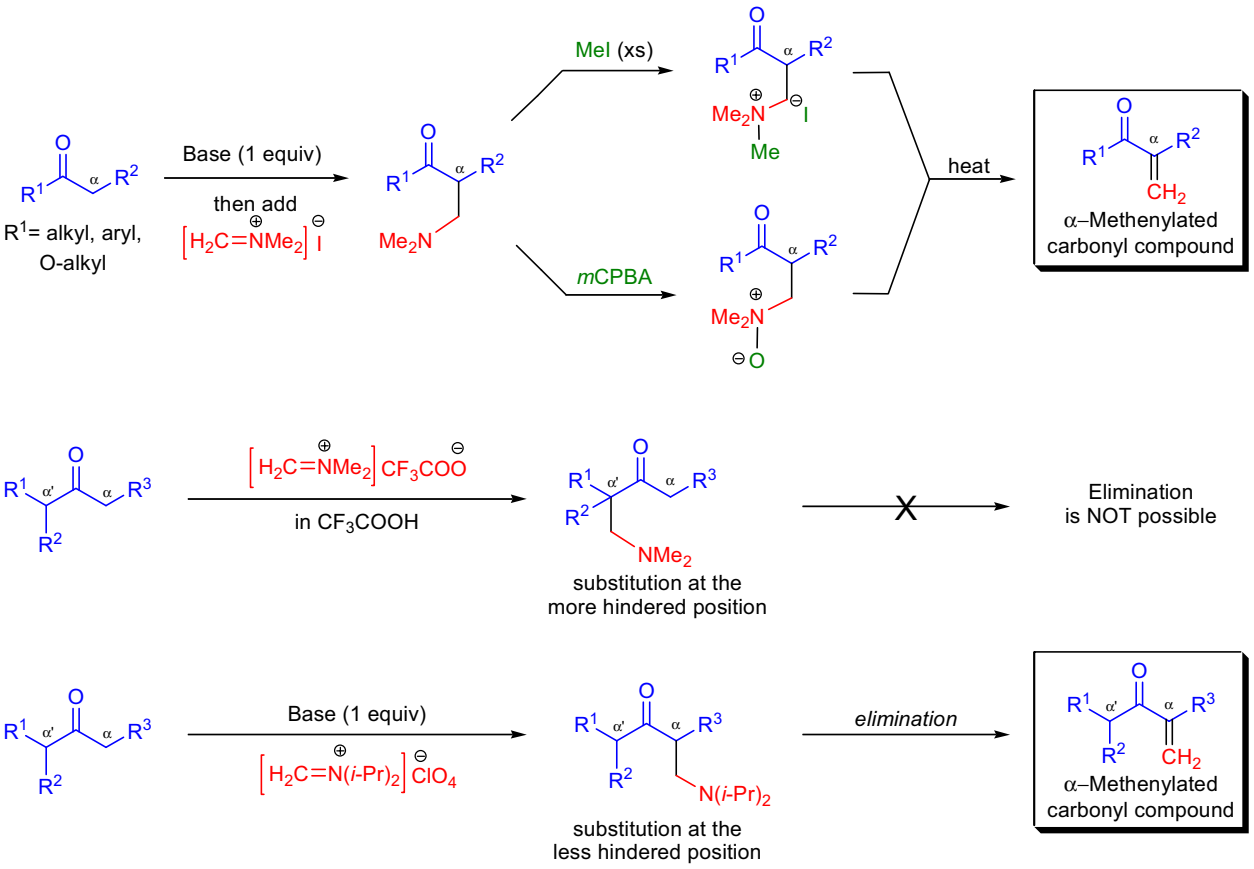
ESCHENMOSER METHENYLATION

(References are on page 581)

Importance:

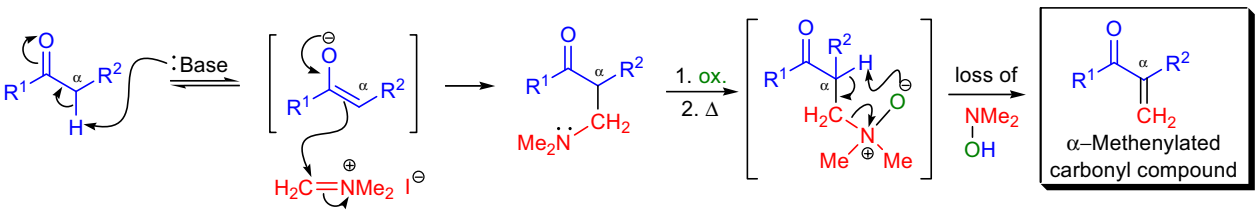
[*Seminal Publications*[1]; *Reviews*[2]; *Modifications & Improvements*[3,4]]

The introduction of a (dimethylamino)methyl group (-CH_2NMe_2) into the α-position of a carbonyl group (ketone, ester, lactone, etc.) using dimethyl(methylene)ammonium iodide, $[CH_2{=}NMe_2]^+I^-$ (Eschenmoser's salt), followed by an elimination to the corresponding α-methylene carbonyl compound is known as the *Eschenmoser methenylation*. The first step of the methenylation procedure can be regarded as a modified *Mannich reaction*, in which the enolizable carbonyl compound is reacted with a preformed iminium ion (Eschenmoser's salt). Next, the resulting α-(dimethylamino)methyl carbonyl compound can be eliminated by using one of the following methods: 1) heat; 2) conversion to the corresponding quaternary ammonium salt, which is then heated (*Hoffmann elimination*);[5] 3) conversion to the corresponding *N*-oxide to induce a *Cope elimination* upon heating;[6] or 4) treatment with base.[7] The methenylation process is most efficient when the substrates are symmetrical ketones or ketones that have only one available enolizable α-position. In the case of unsymmetrical ketones (in which both the α and α' positions are available), regioselective methenylation is possible by the use of modified versions of Eschenmoser's salt.[3,4]



Mechanism:

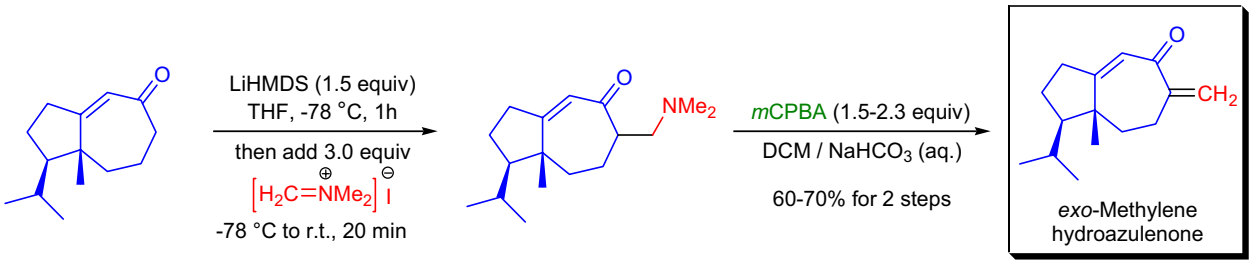
The first step of the mechanism of the *Eschenmoser methenylation* is the deprotonation of the substrate at the α-position. The resulting enolate ion then reacts with the electrophilic iminium salt to afford the α-(dimethylamino)methyl carbonyl compound. In a second operation, the elimination is carried out in one of four ways as mentioned above. The scheme shown below depicts the *Cope elimination* of the tertiary amine *N*-oxide.



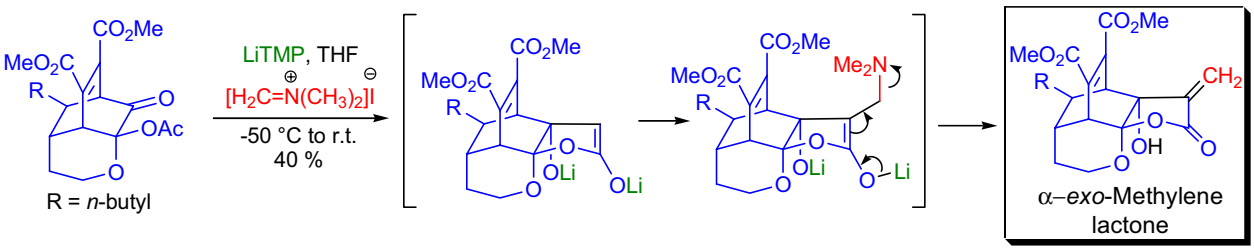
ESCHENMOSER METHENYLATION

Synthetic Applications:

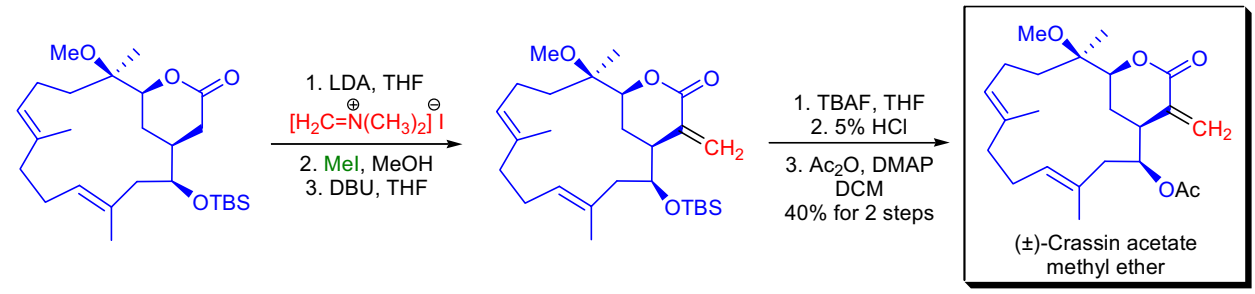
S.J. Danishefsky and co-workers identified an *exo*-methylene hydroazulenone as a versatile intermediate in efforts directed toward the total synthesis of guanacastepene.[6] The *exo*-methylene group was introduced on the hydroazulene by the two-step *Eschenmoser methenylation* procedure. The substrate was deprotonated with LiHMDS followed by the addition of 3 equivalents of Eschenmoser's salt. The resulting α-(dimethylamino)methyl ketone was treated with *m*CPBA to form the *N*-oxide, which spontaneously underwent a *Cope elimination* to afford the desired *exo*-methylene hydroazulenone.



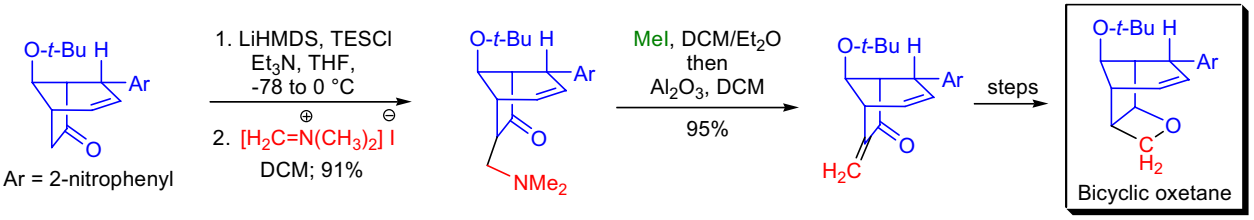
In the laboratory of J.L. Wood, an expeditious approach to the densely functionalized isotwistane core of CP-263,114 was developed.[7] For the proposed *radical cyclization*, an *exo*-methylene group was installed on a five-membered lactone ring. It was discovered that both the formation of the lactone ring and the *Eschenmoser methenylation* could be conducted in a one-pot operation by simply treating the α-acetoxy ketone with excess amounts of LiTMP and then with Eschenmoser's salt.



The total synthesis of the cembranoid diterpene (±)-crassin acetate methyl ether was accomplished by W.G. Dauben et al.[8] In the final stages of the total synthesis, the sensitive α-methylene group was introduced onto the six-membered lactone by using the *Eschenmoser methenylation* procedure. The lactone was deprotonated with LDA and then treated with Eschenmoser's salt. In the second step, the dimethylamino group was exhaustively methylated and the quaternary ammonium salt underwent a smooth *Hofmann elimination* upon deprotonation with DBU.



During the early stages of the total synthesis of (±)-gelsemine, S.J. Danishefsky et al. wanted to install a key oxetane ring on a bicyclic ketone intermediate.[9] The *Eschenmoser methenylation* was chosen to prepare the required bicyclic α-methylene ketone which was later converted to the oxetane in a few steps.



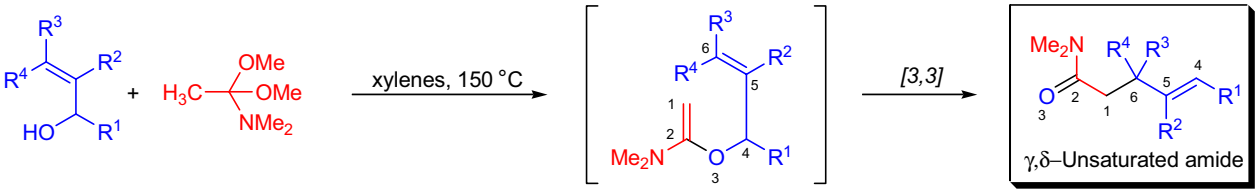
ESCHENMOSER-CLAISEN REARRANGEMENT

(References are on page 581)

Importance:

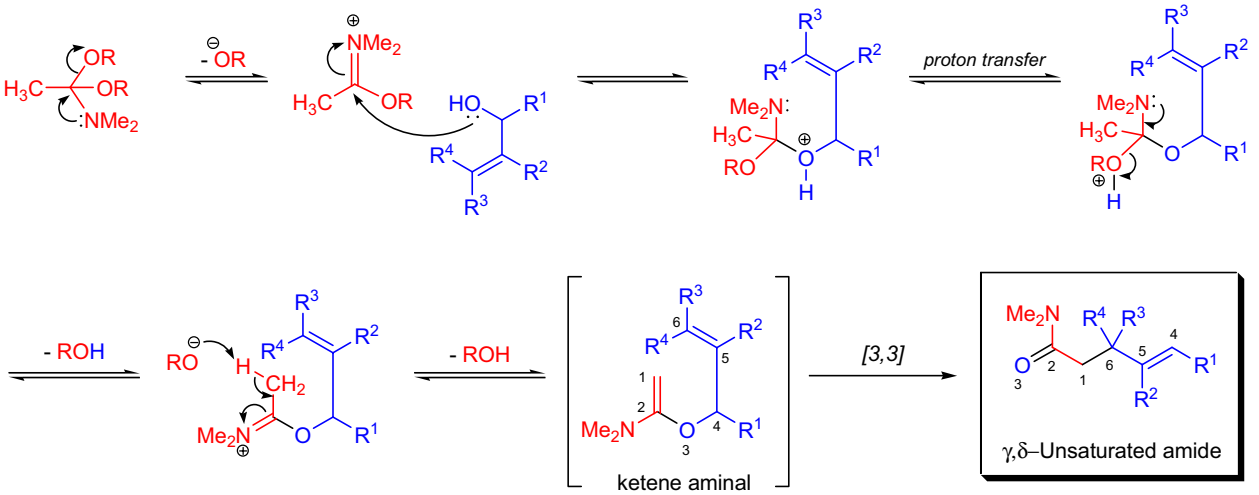
[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5]]

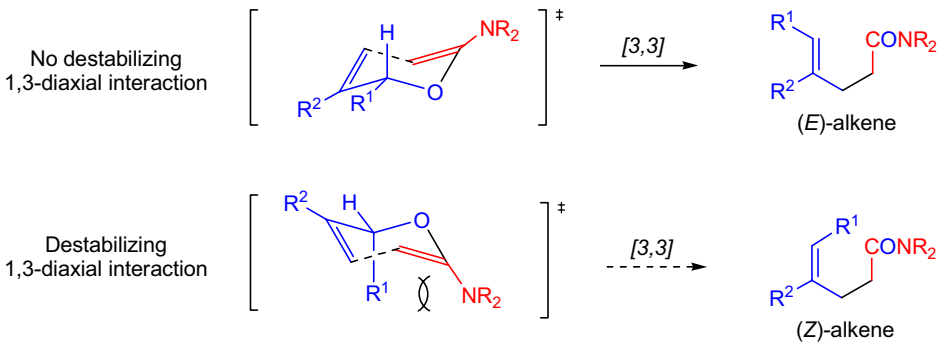
In 1964, A. Eschenmoser reported a reaction in which allylic or benzylic alcohols underwent a *Claisen-type rearrangement* when heated with *N,N*-dimethylacetamide dimethyl acetal in xylenes.[1] The rearrangement took place with a high degree of sterospecificity and generated a γ,δ-unsaturated amide as the product. Today this transformation is referred to as the *Eschenmoser-Claisen rearrangement*. The rearrangement is more (*E*)-selective and usually takes place at lower temperature (100-150 °C) than the other variants such as the *Claisen* and *Johnson-Claisen rearrangements*. Allylic alcohols substituted at the 2-position afford trisubstituted alkene products with significant levels of diastereoselection, just as in the case of the *Johnson-Claisen rearrangement*.[6] This selectivity is explained by 1,3-diaxial nonbonding interactions in the chairlike transition state.



Mechanism: [6]

The reaction does not require the presence of an acid catalyst, the allylic alcohol readily exchanges one of the alkoxy groups of *N,N*-dimethylacetamide dimethyl acetal. The resulting mixed acetal loses methanol and the ketene aminal intermediate undergoes a *[3,3]-sigmatropic shift via* a chairlike transition state in acyclic systems. In certain cases, cyclic systems may prefer a boatlike transition state due to conformational constraints. The ratio of the products will depend on the energy difference between the transition states. Generally the *Eschenmoser-Claisen rearrangement* of secondary allylic alcohols proceeds with very high (*E*)-selectivity due to destabilizing 1,3-diaxial interactions in the transition state that would lead to the (*Z*)-isomer.[6]

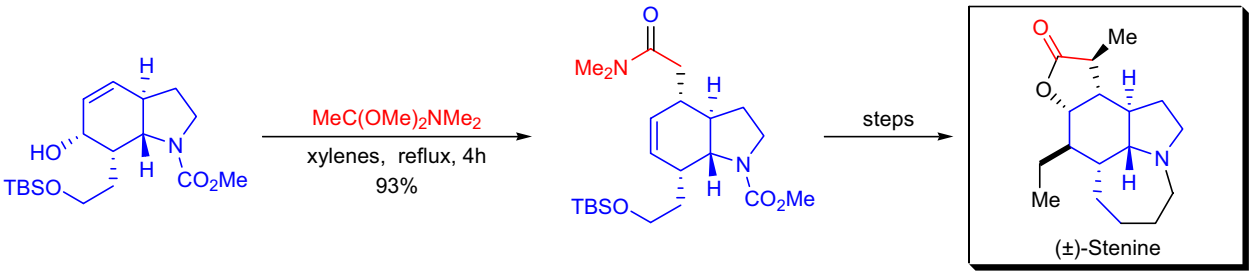




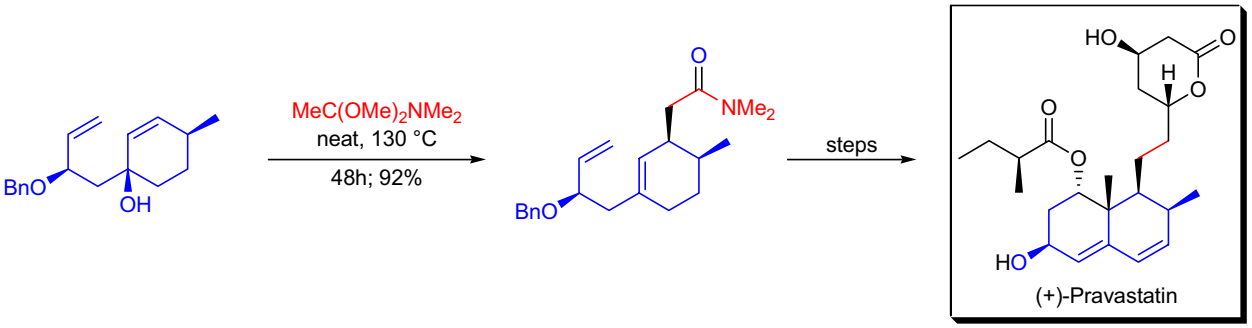
ESCHENMOSER-CLAISEN REARRANGEMENT

Synthetic Applications:

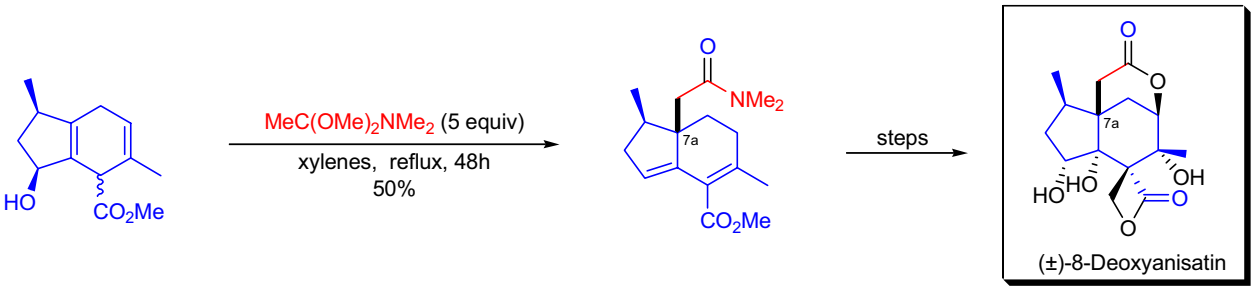
The first total synthesis of (±)-stenine has been accomplished in the laboratory of D.J. Hart.[7] The key steps were an *intramolecular Diels-Alder reaction*, an amidine variant of the *Curtius rearrangement*, an *Eschenmoser-Claisen rearrangement*, a *halolactonization*, and a *Keck allylation*. The allylic alcohol precursor and *N,N*-dimethylacetamide dimethyl acetal was heated to reflux in xylenes for 4h to afford the desired amide in 93% isolated yield. The transition state most likely adopted a boatlike conformation.



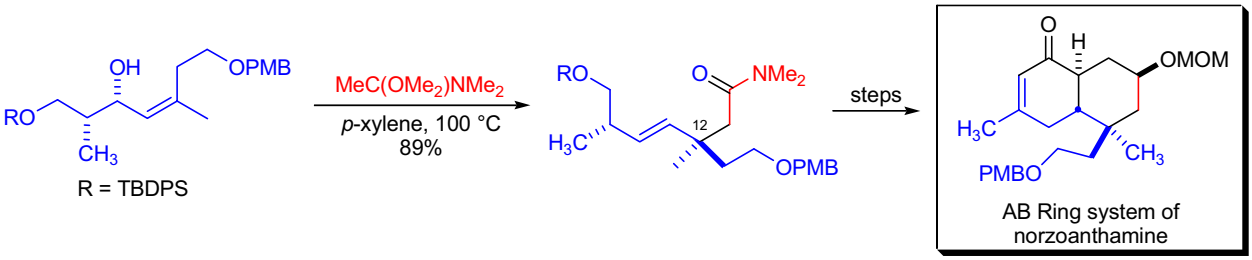
During the asymmetric total synthesis of (+)-pravastatin by A.R. Daniewski et al., one of the stereocenters was introduced with the *Eschenmoser-Claisen rearrangement*.[8] The tertiary alcohol intermediate was heated in neat *N,N*-dimethylacetamide dimethyl acetal at 130 °C for 48h, during which time the by-product methanol was distilled out of the reaction mixture to afford the desired amide in 92% yield.



In order to construct the sterically congested C7a quaternary chiral center in the natural product anisatin, T.P. Loh and co-workers developed an efficient strategy by way of an *Eschenmoser-Claisen rearrangement*.[9] The resulting amide was converted to an ε-lactone (reported by A.S. Kende) in four steps, thereby completing a concise formal synthesis of (±)-8-deoxyanisatin. Other attempted *[3,3]-sigmatropic rearrangements* to construct C7a stereocenter resulted in re-aromatized products.



D.R. Williams et al. successfully synthesized the AB ring system of norzoanthamine by the *intramolecular Diels-Alder cyclization* of an (*E*)-1-nitro-1,7,9-decatriene.[10] The key transformation for establishing the quaternary stereocenter at C12 in the cycloaddition precursor was the *Eschenmoser-Claisen rearrangement*.



ESCHENMOSER-TANABE FRAGMENTATION

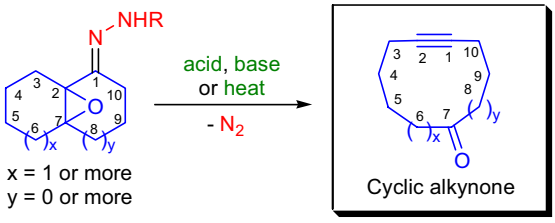
(References are on page 582)

Importance:

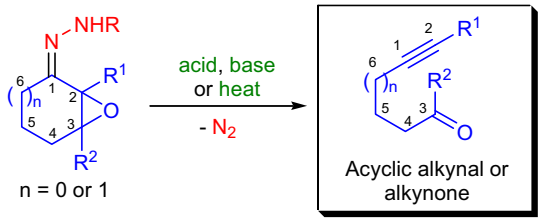
[*Seminal Publications*[1-4]; *Reviews*[5,6]; *Modifications & Improvements*[7-12]]

In 1967, A. Eschenmoser was the first to describe the fragmentation of the tosylhydrazone of an α,β-epoxy ketone to the corresponding acetylenic ketone (alkynone).[1] Soon after this initial report, M. Tanabe and J. Schreiber published their independent findings of the same fragmentation generating medium-sized cyclic alkynones.[2-4] Today, the preparation of cyclic alkynones, acyclic alkynals, and alkynones *via* cyclic epoxy ketone hydrazones is known as the *Eschenmoser-Tanabe fragmentation*. Although the fragmentation readily occurs on acyclic epoxy ketone hydrazones, from a synthetic point of view one needs to start from a cyclic epoxy ketone in order to isolate the desired cyclic or acyclic alkynones. The starting cyclic epoxy ketones are not always easy to synthesize, especially when they are sterically hindered. They are usually prepared by the epoxidation of the corresponding α,β-unsaturated ketones.[13] Next, the epoxy ketone hydrazones are exposed to base (or acid in certain cases) or heated to bring about the fragmentation, which is accompanied by the evolution of nitrogen gas. Acyclic acetylenic aldehydes can be efficiently prepared by using the 2,4-dinitrophenylhydrazone derivatives of the epoxy ketones.[10] When the preparation of the epoxy ketone is not possible or has to be avoided, treatment of the unsaturated hydrazones with excess NBS in methanol leads directly to the desired alkynones.[12] Over the last few decades, the scope of the reaction was extended, and improvements have been implemented by the use of the following epoxy ketone derivatives: 1) oximes;[14] 2) aminoaziridines;[8,9] 3) 2,4-dinitrobenzenesulfonyl hydrazones;[10] 4) 1,3,4-oxadiazolines;[11] and 5) diazirines.[7] Advantages of the *Eschenmoser-Tanabe fragmentation* are the following: 1) easy access to medium-sized cyclic ketones; 2) both terminal and disubstituted alkynes can be prepared; and 3) the fragmentation is not limited to the use of aromatic sulfonylhydrazones. Besides the fragmentation of epoxy ketone derivatives, there are only very few examples in the literature for the "*nitrogen*- and *carbon*-analogue" of the *Eschenmoser-Tanabe fragmentation*.[15-17]

Synthesis of cyclic alkynones:



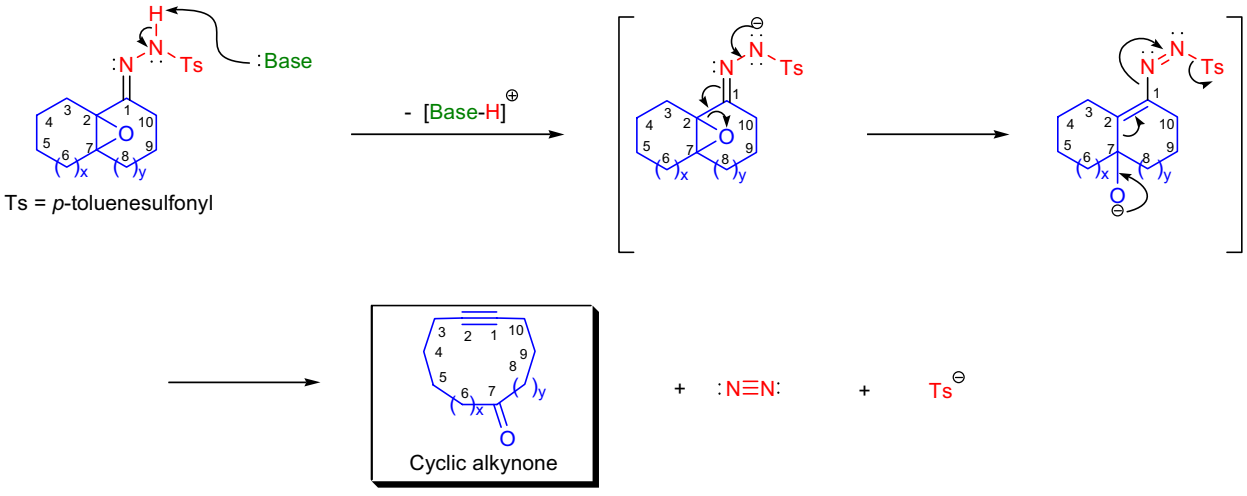
Synthesis of acyclic alkynones and alkynals:



R = tosyl, 2,4-dinitrophenyl; R^{1-2} = H, alkyl; when R^2 = H, then the product is an alkynal, and when R^2 = alkyl, then it is an alkynone

Mechanism:[1,3,6,18,19]

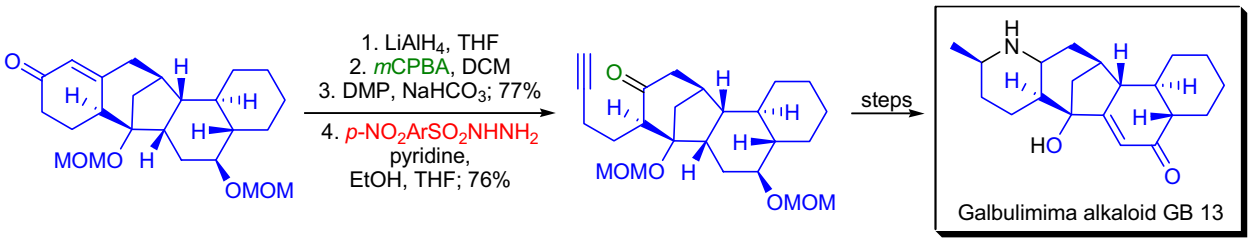
The *Eschenmoser-Tanabe fragmentation* is basically a seven-center *Grob-type fragmentation* in which the starting molecule breaks into three fragments. The mechanism is concerted for epoxy ketone hydrazones and oxadiazolinones, while the thermal decomposition of epoxy-diazirines involves a free oxiranylcarbene intermediate.[18,19] The deprotonation of the starting epoxy ketone arylhydrazone leads to the formation of an alkoxide, which rapidly undergoes fragmentation to give an alkyne, ketone, nitrogen gas, and a leaving group (usually arylsulfinate).



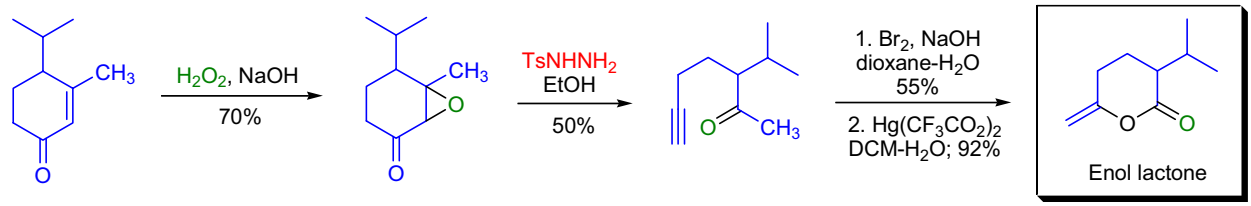
ESCHENMOSER-TANABE FRAGMENTATION

Synthetic Applications:

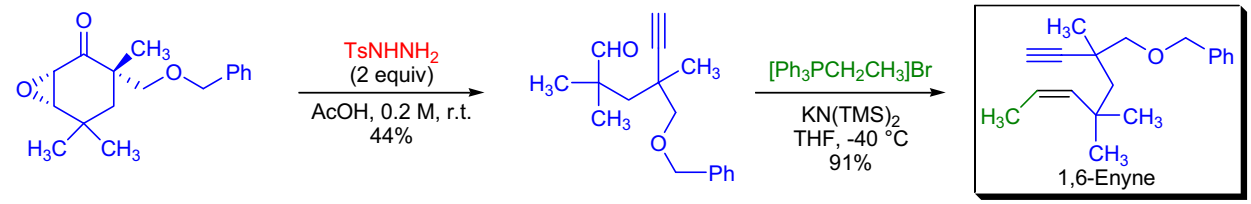
The first total synthesis of the Galbulimima alkaloid GB 13 was accomplished in the laboratory of L.N. Mander.[20] In the late stages of the synthesis, the plan was to convert the pentacyclic α,β-unsaturated ketone to the corresponding tetracyclic alkynone using the *Eschenmoser-Tanabe fragmentation*. Interestingly, the direct epoxidation of the enone was unsuccessful. Therefore, a sequence of reduction-epoxidation-oxidation gave the desired epoxy ketone in 77% yield. The treatment of this epoxy ketone with *p*-nitrobenzenesulfonylhydrazide afforded the alkynone in good yield.



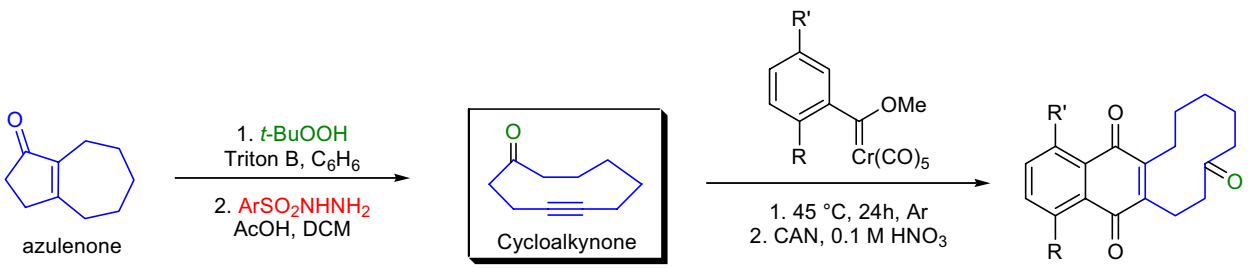
J.A. Katzenellenbogen et al. developed an efficient method for the synthesis of alkyl-substituted enol lactones that are potent inhibitors of the serine protease elastase.[21] The precursors for the enol lactones were α- and β-alkyl-substituted 5-hexynoic acids, which were prepared by the *bromoform reaction* of the corresponding alkynoic methyl ketones. These alkynones were synthesized by an *Eschenmoser-Tanabe fragmentation* of suitably substituted cyclohexenones.



During model studies for the synthesis of botrydiane sesquiterpene antibiotics, B.M. Trost and co-workers prepared a complex 1,6-enyne precursor for transition metal catalyzed *enyne metathesis* reactions.[22] The 1,6-enyne was prepared from a heavily substituted alkynal, which was synthesized *via* the *Eschenmoser-Tanabe fragmentation* of an epoxy ketone. The resulting alkynal was unstable, so it was immediately subjected to a *Wittig olefination* to afford the desired 1,6-enyne.



In the laboratory of S.J. Danishefsky, the synthesis of antibiotics containing the benz[*a*]anthracene core structure was investigated using the *Dötz benzannulation* of a cycloalkynone.[23] The required cycloalkynone was prepared from azulenone using the *Eschenmoser-Tanabe fragmentation*.



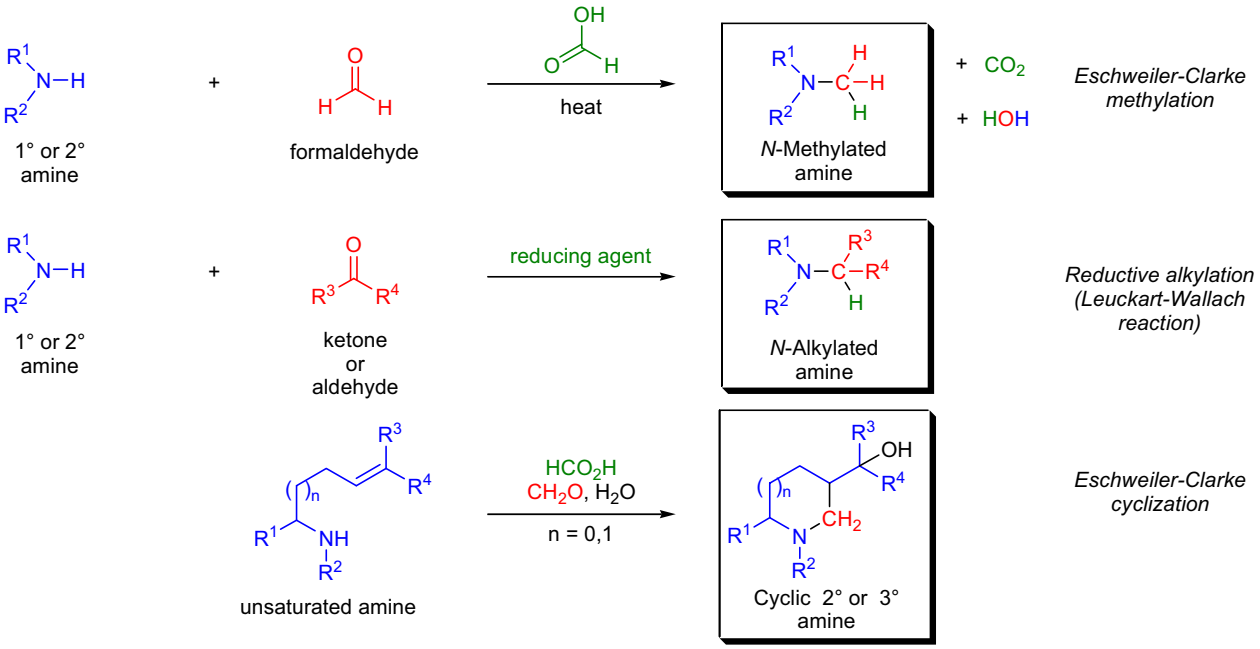
ESCHWEILER-CLARKE METHYLATION
(REDUCTIVE ALKYLATION)

(References are on page 582)

Importance:

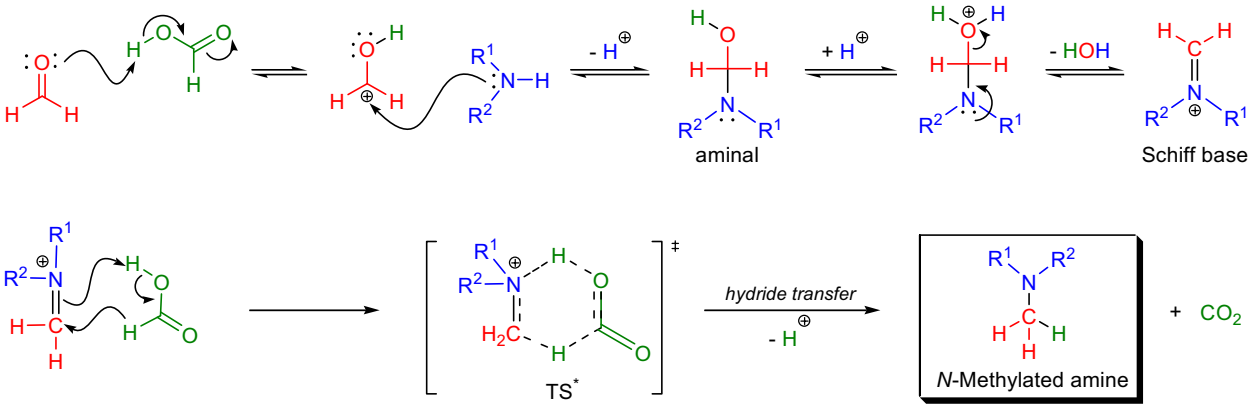
[*Seminal Publications*[1-4]*; Reviews*[5-7]*; Modifications & Improvements*[8-13]]

The one-pot reductive methylation of primary and secondary amines to the corresponding tertiary amines is known as the *Eschweiler-Clarke methylation*. This reaction falls into the category of *reductive alkylation* of amines by carbonyl compounds (aldehydes and ketones), and it is considered as a modification of the *Leuckart-Wallach reaction*.[14] The first reductive alkylation of an amine was reported by R. Leuckart in 1885, and a few years later the scope of the reaction was explored by Wallach and co-workers.[15,16] In 1905, W. Eschweiler and then in 1933, H.T. Clarke demonstrated that formaldehyde could be used along with formic acid to introduce methyl groups to primary and secondary amines to obtain tertiary amines.[1,2] Formic acid serves as a reducing agent (hydride donor), which reduces the Schiff base intermediate to the corresponding amine. Today, other reducing agents, such as sodium borohydride, sodium cyanoborohydride,[8] sodium cyanoborohydride-titanium(IV)isopropoxide [$NaBH_3CN$-$Ti(Oi\text{-}Pr)_4$)],[17] sodium triacetoxyborohydride [$NaBH(OAc)_3$],[18] borohydride exchange resin (BER),[19] formic acid derivatives (formamide, ammonium formate, etc.), or hydrogen gas/catalyst[20] are used in place of formic acid. When the amine substrate is unsaturated, it is possible to obtain a cyclic amine product under the *Eschweiler-Clarke methylation* conditions, and the process is referred to as the *Eschweiler-Clarke cyclization*.[3,4]



Mechanism: [21-26,13]

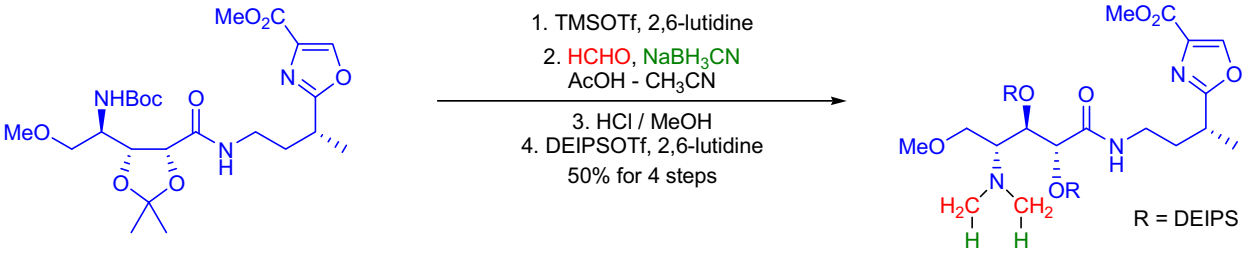
The mechanism of all of the above mentioned reactions is essentially the same. However, some steps in the mechanism are still not fully understood. The following steps are believed to be involved in the *Eschweiler-Clarke methylation*: 1) formation of a Schiff-base (imine) from the starting primary or secondary amine and formaldehyde *via* an aminoalcohol (aminal) intermediate; 2) hydride transfer from the reducing agent (e.g., formic acid, cyanoborohydride, etc.) to the imine to get the corresponding *N*-methylated amine along with the loss of CO_2; and 3) if the starting amine was primary, then steps 1 and 2 are repeated.



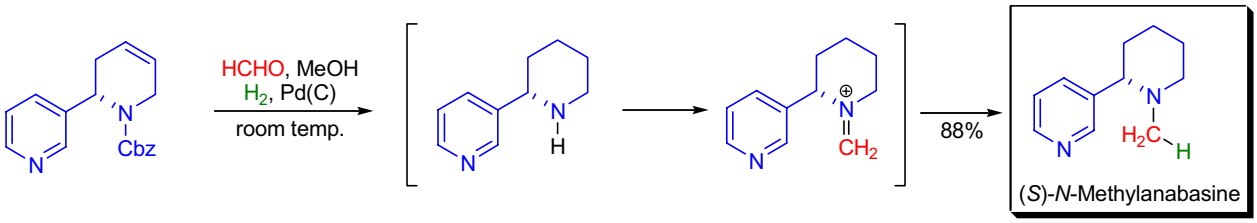
ESCHWEILER-CLARKE METHYLATION
(REDUCTIVE ALKYLATION)

Synthetic Applications:

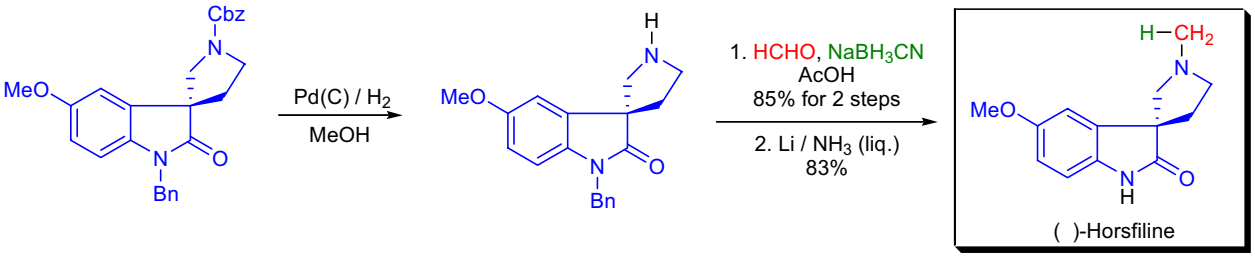
During the total synthesis of (–)-calyculin A and B, A.B. Smith and co-workers utilized a modified *Eschweiler-Clarke methylation* to convert a complex primary amine to the corresponding *N*,*N*-dimethylamino derivative.[27] The *N*-Boc protected primary amine was first deprotected using TMSOTf, followed by introduction of the two methyl groups using HCHO/$NaBH_3CN$ in AcOH/CH_3CN solvent mixture. The acetonide protecting group was subsequently removed, and the resulting diol was silylated.



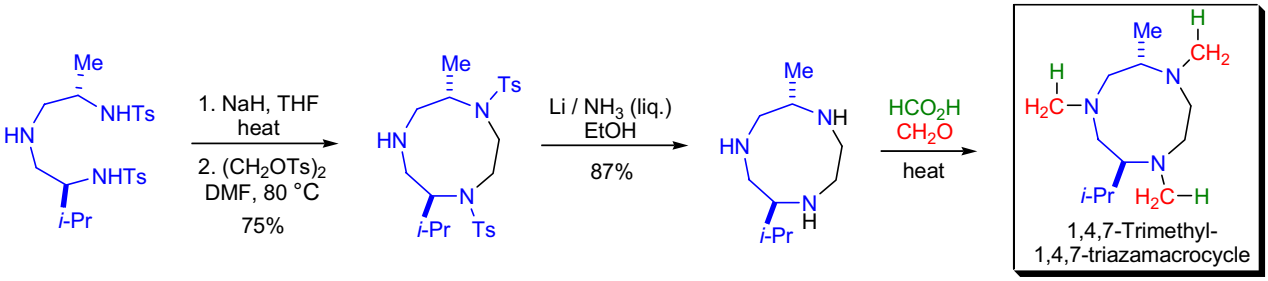
The enantioselective total syntheses of several piperidine and pyrrolidine alkaloids of tobacco were accomplished in the laboratory of J. Lebreton.[20] In the final stage of the total synthesis of (*S*)-*N*-methylanabasine, a one-pot *Cbz-deprotection-hydrogenation-Eschweiler-Clarke methylation* was carried out using a HCHO/MeOH/Pd(C)/H_2 system at room temperature with an overall 88% yield.



The oxindole alkaloid (–)-horsfiline was synthesized by K. Fuji et al. using an *asymmetric nitroolefination* as the key step.[28] During the endgame of the total synthesis, an *N*-methylation was performed on the five-membered secondary amine using the original *Eschweiler-Clarke methylation* conditions (HCO_2H/HCHO/reflux). Unfortunately, these harsh methylation conditions led to the racemization of the quaternary stereocenter. Therefore, milder modified conditions were applied ($NaBH_3CN$ as the reducing agent) to retain the optical activity of the substrate.



C.L. Gibson and co-workers developed an efficient synthesis for chiral ring annulet 2,6-disubstituted 1,4,7-trimethyl-1,4,7-triazamacrocycles. This class of molecules is capable of stabilizing transition metals in their high oxidation states and therefore can be used as oxidation catalysts.[29] The *N*-methylation of the three nitrogens in the last step was conducted using the original *Eschweiler-Clarke methylation conditions*.



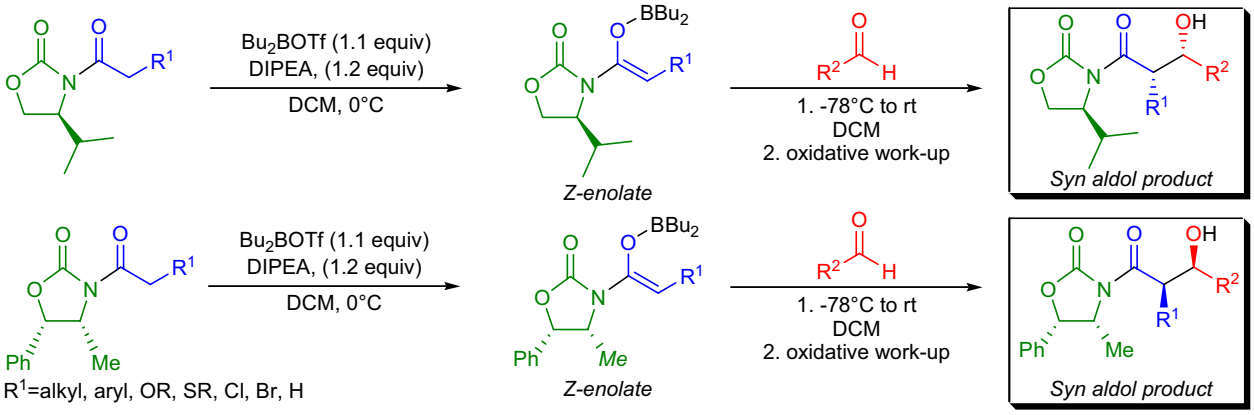
EVANS ALDOL REACTION

(References are on page 583)

Importance:

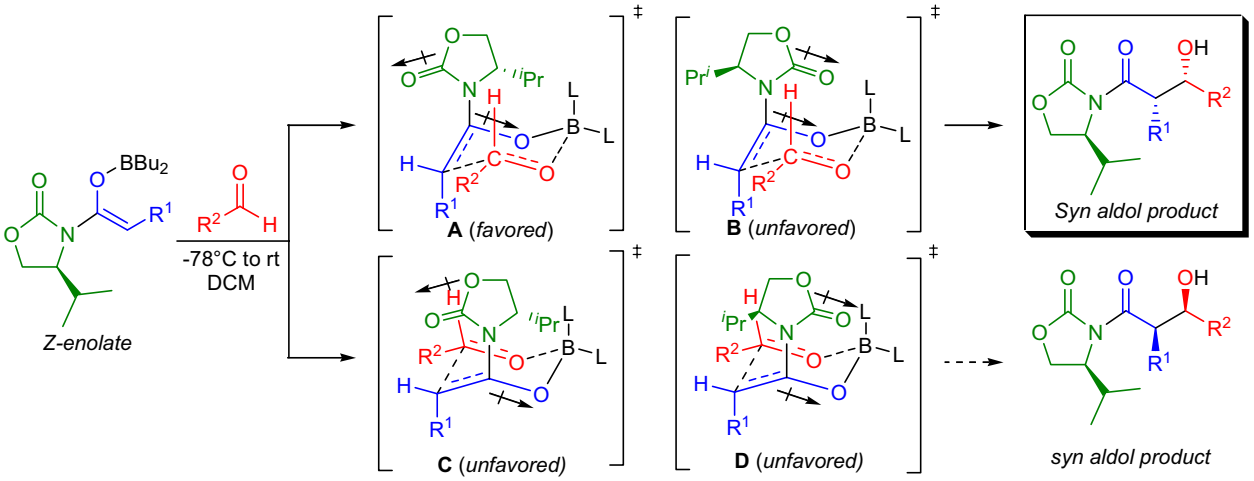
[*Seminal Publication*[1]; *Reviews*[2-10]; *Modifications & Improvements*[11-22]; *Theoretical Studies*[23-28]]

The boron mediated *aldol reaction* is a powerful method for highly stereoselective carbon-carbon bond formation. The high diastereoselectivity of this process can be attributed to the relatively short boron-oxygen bond length (1.36-1.47 Å) in the boron enolate,[29] which upon reacting with an aldehyde leads to a tight, six-membered chairlike transition state. Reaction of (*Z*)-boron enolates with aldehydes gives the *syn* aldol product while, (*E*)-boron enolates lead to formation of the *anti* aldol product with high diastereoselectivity.[30,31] Control of the absolute stereochemistry can be achieved through the application of covalently attached chiral auxiliaries in the enol component. D.A Evans and his co-workers developed a pair of oxazolidinone based chiral auxiliaries, which could be obtained from (*S*)-valinol and (1*S*,2*R*)-norephedrine with excellent enantiopurity.[1] *Asymmetric aldol reactions* relying on the application of these chiral auxiliaries are called the *Evans aldol reaction*. General features of the *Evans aldol reaction* are: 1) enolization of the *N*-acyl oxazolidinones under standard conditions (1.1 equiv Bu_2BOTf, 1.2 equiv diisopropylamine, 0 °C, 30 min) affords the (*Z*)-enolates with excellent selectivity;[1] 2) *aldol reaction* of the resulting (*Z*)-boron enolates with a wide variety of aldehydes yields the *syn* aldol product with very high diastereo- and enantioselectivity;[1] 3) when a chiral aldehyde is used, the facial bias of the enolate overrides the π-facial selectivity of the chiral aldehyde;[32] 4) aldol reaction of boron enolates derived from *N*-acetyloxazolidinone (R^1=H) provide the products with low stereoselectivity, but this can be overcome by the incorporation of a heteroatom substituent in the α-position, such as a thioalkyl group (R^1=SR), which can be reductively removed;[1] and 5) there are several methods for the nondestructive removal and recovery of the chiral auxiliary: hydrolysis and transesterification (LiOH, LiOOH, LiOR, LiSEt),[33-35] reductive removal ($LiAlH_4$),[33,36] and transamination to Weinreb amide (Me(OMe)NH, Me_3Al).[37] Since the introduction (S)-4-isopropyl-oxazolidin-2-one and (1S,2*R*)-4-methyl-5-phenyl-oxazolidin-2-one chiral auxiliaries by D.A. Evans, several modifications have been reported.[11-22] Besides the *aldol reaction*, the Evans chiral auxiliaries were successfully applied in enolate alkylation,[33] enolate acylation,[33] enolate amination,[38-41] and hydroxylation[42] processes.



Mechanism:[2]

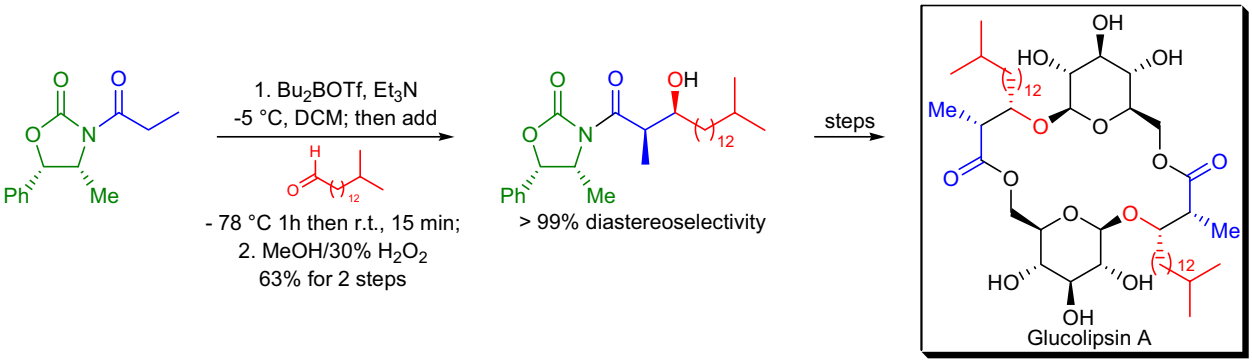
The observed stereoselectivity in the *Evans aldol reaction* can be explained by the *Zimmerman-Traxler* transition state model.[2] There are eight possible transition states, four of which would lead to the *anti* aldol product. These, however, are disfavored due to the presence of unfavorable 1,3-diaxial interactions (not depicted below). The possible transition states leading to the *syn* aldol product are shown below. The preferred transition state leading to the product is transition state **A**, where the dipoles of the enolate oxygen and the carbonyl group are opposed, and there is the least number of unfavored steric interactions.



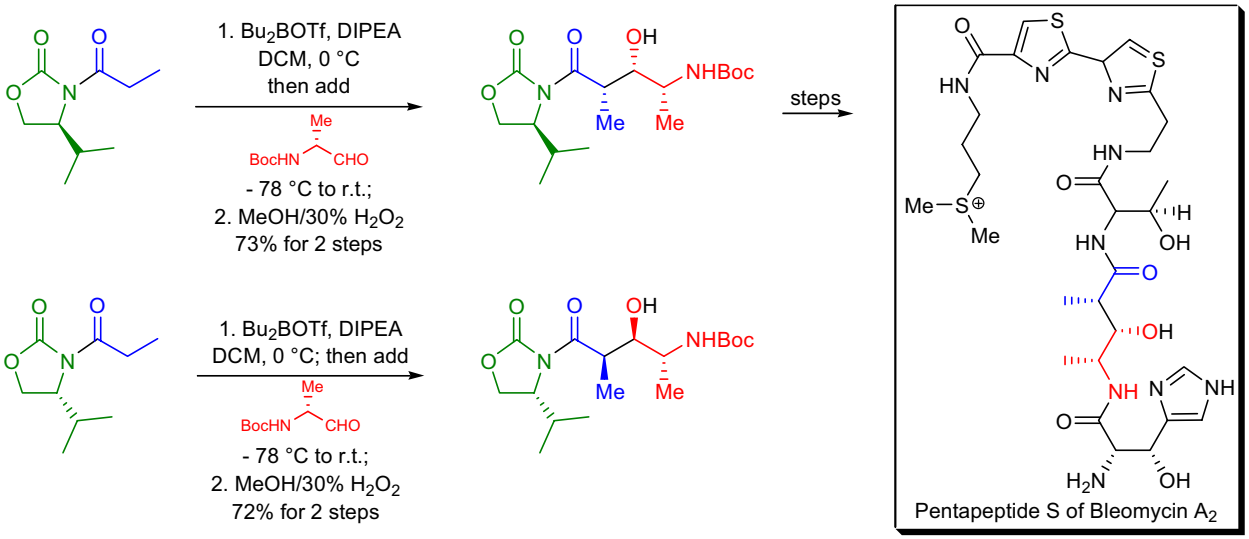
EVANS ALDOL REACTION

Synthetic Applications:

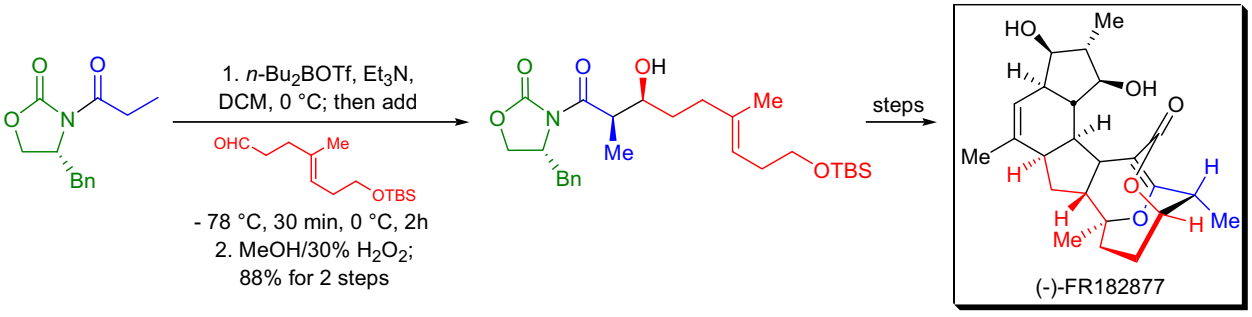
Glucolipsin A, a glycolipid possessing glycokinase-activating properties, was discovered at Bristol-Myers Squibb, but the absolute stereochemistry of the natural product remained elusive. A. Fürstner and co-workers elucidated the absolute stereochemistry *via* synthesis and spectroscopic analysis of the natural macrolide and its C_2-symmetric stereoisomers.[43] In their approach, they utilized the *Evans aldol reaction* that provided the *syn* aldol product with good yield and excellent diastereoselectivity.



D.L Boger et al. reported the total synthesis of bleomycin A_2. They devised an efficient synthesis for the construction of the tripeptide S, tetrapeptide S, and pentapeptide S subunits of the natural product.[44,45] In their strategy, they utilized an *Evans aldol* reaction between the (*Z*)-enolate derived from (*S*)-4-isopropyl-3-propionyl-oxazolidin-2-one and *N*-Boc-D-alaninal. In order to synthesize one of the diastereomers of the pentapeptide S subunit, they carried out an *Evans aldol reaction* between the same aldehyde and the (*Z*)-enolate of (*R*)-4-isopropyl-3-propionyl-oxazolidin-2-one. The formation of the diastereomeric *syn* aldol product in this reaction clearly shows that the stereochemical outcome of the transformation is determined by the chiral auxiliary.



The asymmetric total synthesis of cytotoxic natural product (–)-FR182877 was accomplished by D.A. Evans and co-workers.[46,47] To establish the absolute stereochemistry, a boron mediated aldol reaction was utilized applying (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone[48] as a chiral auxiliary to yield the *syn* aldol product.



FAVORSKII AND HOMO-FAVORSKII REARRANGEMENT

(References are on page 584)

Importance:

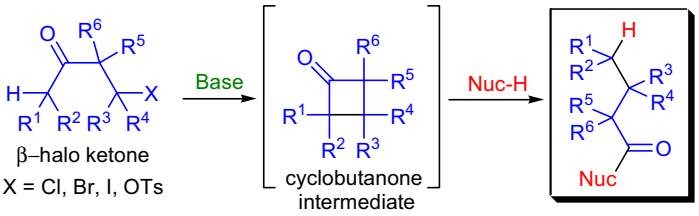
[*Seminal Publications*[1,2]*; Reviews*[3-8]*; Modifications & Improvements*[9-12]*; Theoretical Studies*[13,14]]

Treatment of α-halo ketones possessing at least one α-hydrogen with base in the presence of a nucleophile (alcohol, amine, or water) results in a skeletal rearrangement *via* a cyclopropanone intermediate to give carboxylic acids or carboxylic acid derivatives (esters or amides). This reaction is known as the *Favorskii rearrangement*, and it is widely used for the synthesis of highly branched carboxylic acids. The halogen substituent can be a chlorine, bromine or iodine, while the base is usually an alkoxide or hydroxide. Upon rearrangement, acyclic α-halo ketones give acyclic carboxylic acid derivatives, while cyclic α-halo ketone substrates undergo a ring-contraction reaction to afford one-carbon smaller cyclic carboxylic acid derivatives. The reaction is both regio- and stereoselective.[15,16,12] The rearrangement of unsymmetrical α-halo ketones leads to the product, which is formed through the cleavage of the cyclopropanone intermediate to usually give the thermodynamically more stable of the two possible carbanions. Besides α-halo ketones, other α-substituted ketones such as α-hydroxy,[9] α-tosyloxy,[17] and α,β-epoxy ketones[18,19] can undergo the rearrangement upon treatment with base. When the starting ketone is α,α'-dihalogenated, the product is an α,β-unsaturated carboxylic acid derivative and in analogous fashion trihaloketones give rise to α,β-unsaturated-α-halo acids. α-Halo ketimines are also suitable substrates for the *Favorskii rearrangement*, although they are less reactive than the corresponding α-halo ketones.[10,11] General features of the *Favorskii rearrangement* are: 1) sensitivity to structural factors (bulkiness of substituents, degree of alkyl substitution) and reaction conditions (base, solvent, temperature); 2) alkyl or aryl substitution on the halogen-bearing carbon increases the rate of rearrangement; 3) in cyclic α-halo ketones, the rearrangement is general in rings from 6-10; and 4) yields are widely varied from moderate to good. There are two important variations of the *Favorskii rearrangement*: 1) when β-halo ketones are treated with base in the presence of a nucleophile, the *homo-Favorskii rearrangement* takes place *via* a cyclobutanone intermediate;[20,21] and 2) if the α-halo ketone does not have any enolizable hydrogens ($R^{3-5} \neq H$), then the *quasi-Favorskii rearrangement* is operational.

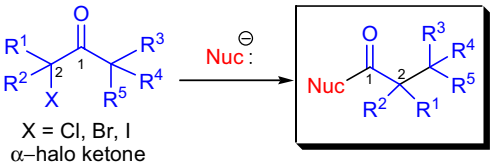
Favorskii-rearrangement:



Homo-Favorskii-rearrangement:

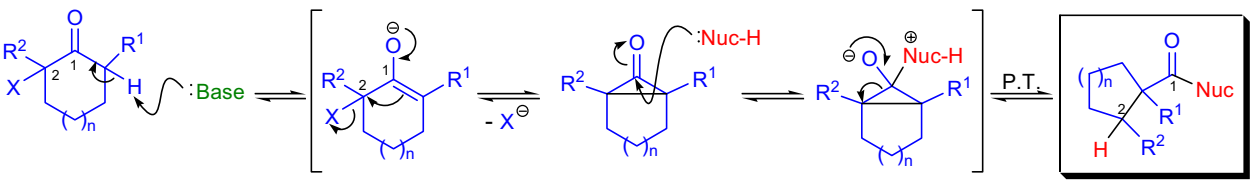


Quasi-Favorskii-rearrangement:



Mechanism: [22-26,9,27-31,10,11]

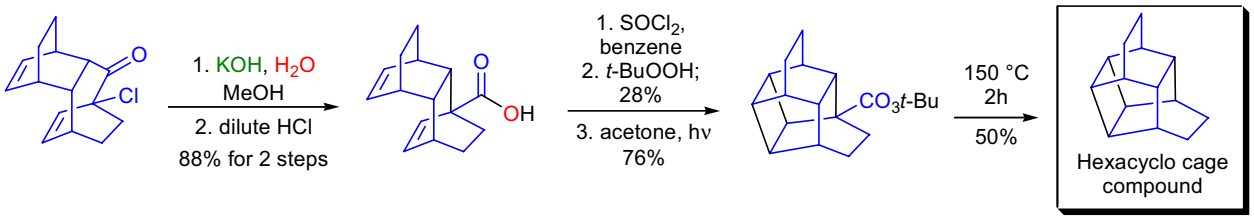
During the last century there have been numerous proposals for the mechanism of the *Favorskii rearrangement*. Currently the widely accepted mechanism involves the following steps: 1) deprotonation at the α-carbon and formation of an enolate; 2) intramolecular attack by the enolate on the α'-carbon bearing the leaving group to form a cyclopropanone intermediate; 3) regioselective opening of the intermediate to give the most stable carbanion; and 4) proton transfer to the carbanion to afford the product.



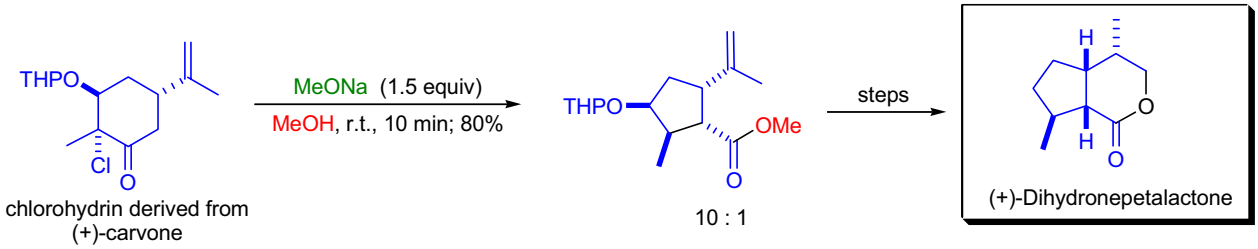
FAVORSKII AND HOMO-FAVORSKII REARRANGEMENT

Synthetic Aplications:

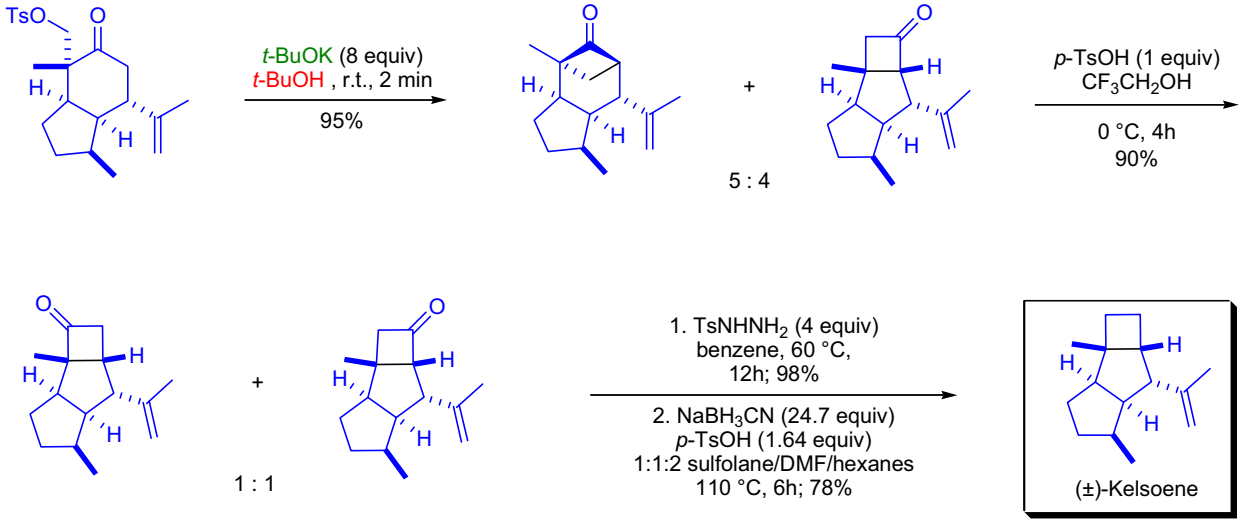
The total synthesis of the symmetrical cage compound hexacyclo[6.4.2.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$.$0^{9,12}$]tetradecene was accomplished in the laboratory of H. Takeshita by using sequential *Diels-Alder cycloaddition*, *Favorskii rearrangement* and *[2π+2π] photocycloaddition* as key steps.[32] The *Favorskii rearrangement* of a bridgehead α-halo ketone afforded the anticipated bridgehead carboxylic acid in 88% yield. Next, the acid was converted to the corresponding *tert*-butyl peroxy ester, which was subsequently photocyclized. The final step was the removal of the bridgehead carboxylic acid functionality by heating the perester in *p*-diisopropylbenzene for 2h at 150 °C.



E. Lee and co-workers demonstrated that the chlorohydrin derived from (+)-carvone undergoes a *stereoselective Favorskii rearrangement* to afford a highly substituted cyclopentane carboxylic acid derivative.[33] This intermediate was then converted to (+)-dihydronepetalactone. When the THP-protected chlorohydrin was treated with sodium methoxide in methanol at room temperature, the rearrangement took place with excellent stereoselectivity (10:1) and high yield. Interestingly, the major product was the thermodynamically less stable cyclopentanecarboxylate.



The key step in the stereocontrolled total synthesis of the tricyclic (±)-kelsoene by M. Koreeda et al. was a base-catalyzed *homo-Favorskii rearrangement* of a γ-keto tosylate to elaborate the 4-5 fused ring portion of the target molecule.[34] The bicyclic 5-6 fused γ-keto tosylate was treated with excess potassium *tert*-butoxide, which effected the desired rearrangement in less than 2 minutes at room temperature. The nucleophilic solvent was too bulky to effect the opening of the cyclobutanone intermediates, making their isolation possible. The mixture of isomeric cyclobutanones was converted to a separable 1:1 mixture of cyclobutanones with *p*-TsOH, and the ketone functionality was then removed *via* the corresponding tosylhydrazone.



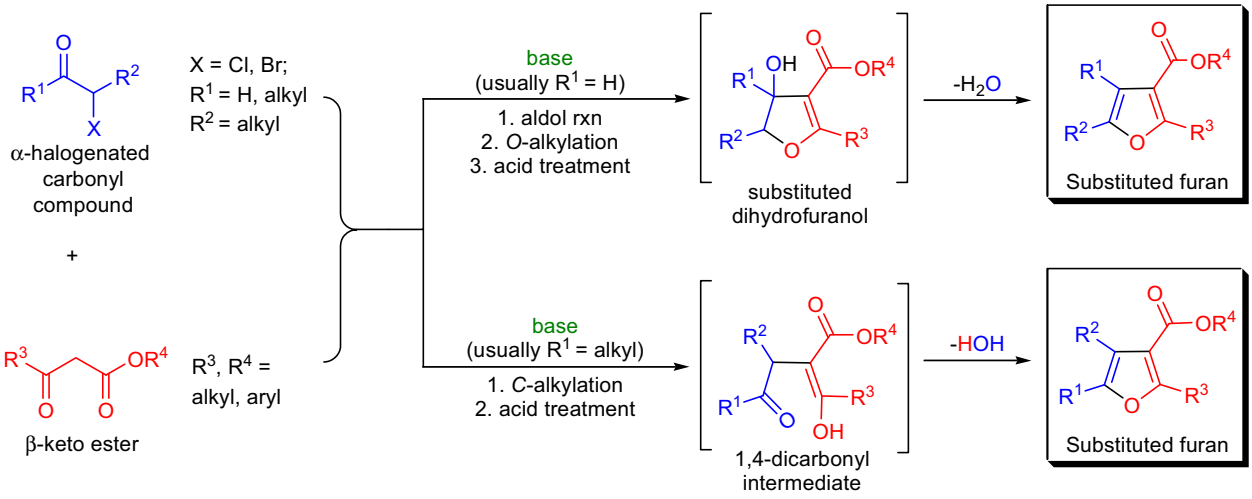
FEIST-BÉNARY FURAN SYNTHESIS

(References are on page 585)

Importance:

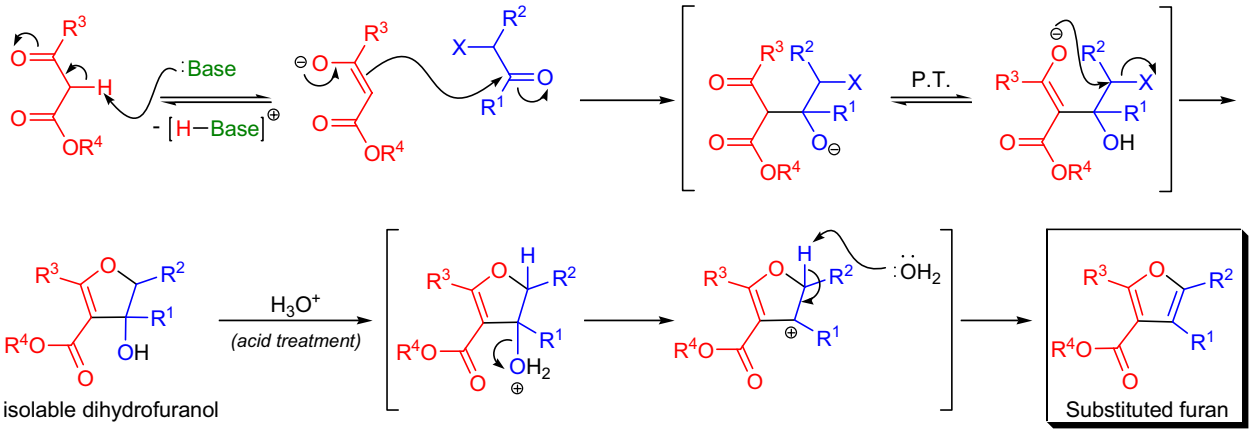
[*Seminal Publications*[1,2]*; Reviews*[3]*; Modifications & Improvements*[4-6]]

The synthesis of furans from β-keto esters and α-halogenated carbonyl compounds (aldehydes and ketones) under basic conditions is known as the *Feist-Bénary furan synthesis*. The general features of this reaction are: 1) the yields are strongly dependent on the substrates and are often moderate; 2) the initially isolated product of the reaction is usually the substituted dihydrofuranol ("*interrupted Feist-Bénary reaction*"), which is dehydrated under acid-catalyzed conditions to isolate the substituted furan;[7] 3) the regiochemical outcome depends on the reactivity of the α-halogenated carbonyl compound: α-halogenated aldehydes (R^1=H) tend to first undergo an *aldol reaction* followed by an *O*-alkylation, while α-halogenated ketones (R^1=alkyl) first *C*-alkylate the β-keto ester and then acid treatment is necessary to obtain the substituted furan;[8] 4) the following bases are often used to deprotonate the β-keto esters: NaH, NaOMe, NaOEt, aqueous NaOH, or Et_3N; 5) the reaction is general with respect to the nature of the β-dicarbonyl compound: in addition to β-keto esters, β-oxopropionates, β-diketones and β-dialdehydes can also be used;[7] and 6) the diastereoselectivity of the *interrupted Feist-Bénary reaction* depends on the basicity of the nucleophile: mainly the *cis* isomer is formed when nucleophiles derived from moderately acidic β-dicarbonyl compounds are used, while nucleophiles derived from highly acidic β-dicarbonyl compounds mainly yield the *trans* isomer.[7] There are several modifications of the original *Feist-Bénary synthesis* and they use more complex α-halogenated carbonyl compounds as reaction partners: 1) β-keto esters were condensed with 1,2-dibromoacetate to afford high yields of 2,3-disubstituted furans;[5] 2) alkylation of the sodium salts of β-keto esters with 3-halogenated alkynes (propargyl halides) in the presence of Cu(II)-salts yielded alkylidenefurans, which were isomerized to tetrasubstituted furans upon treatment with acid;[9] and 3) heating of β-keto esters with 5-hydroxy-5*H*-furan-2-one in the presence of Et_3N gave 3-alkoxy carbonylfurans.[10]



Mechanism:[11,12]

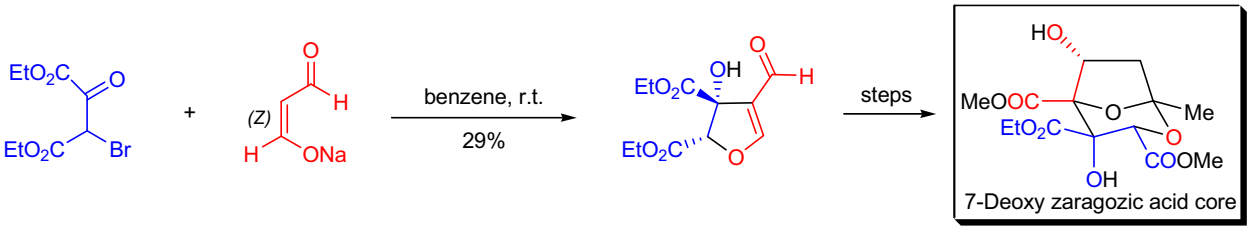
The first step of the *Feist-Bénary furan synthesis* is the deprotonation of the β-keto ester at the α-carbon atom. The resulting stabilized enolate undergoes an *aldol reaction* with the α-halogenated carbonyl compound by attacking the carbonyl group. Subsequent proton transfer generates a stable enolate anion that displaces the α-halogen atom in an intramolecular S_N2 reaction. The resulting dihydrofuranol, which often can be isolated, is treated with aqueous acid to generate the substituted furan.



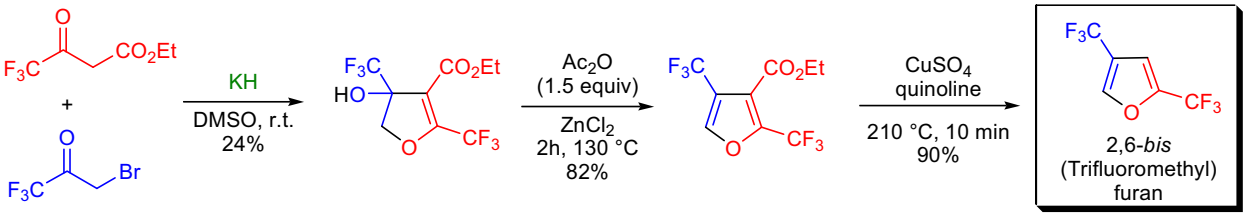
FEIST-BÉNARY FURAN SYNTHESIS

Synthetic Applications:

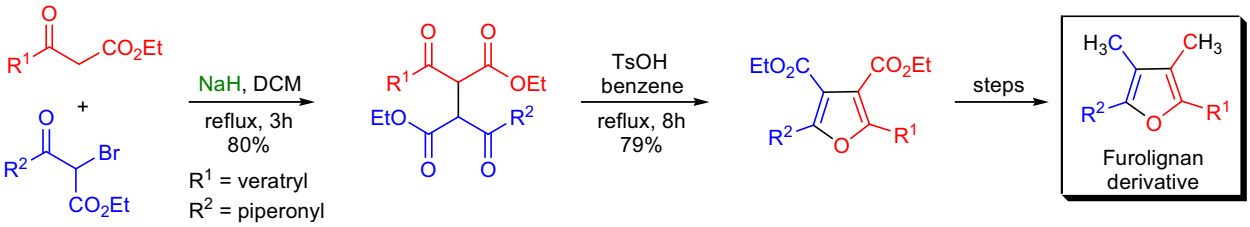
An efficient synthesis of the 7-deoxy zaragozic acid core was developed by M.A. Calter and co-workers.[13] The assembly of this complex structure was based on the *"interrupted" Feist-Bénary reaction*, which produces highly oxygenated dihydrofuranols that can be isolated. To this end, the sodium enolate of malondialdehyde was reacted with 2-bromo-3-oxo-diethyl succinate in benzene at room temperature to afford 29% of the *cis*-dihydrofuranol. This product was converted to the zaragozic acid core in four steps.



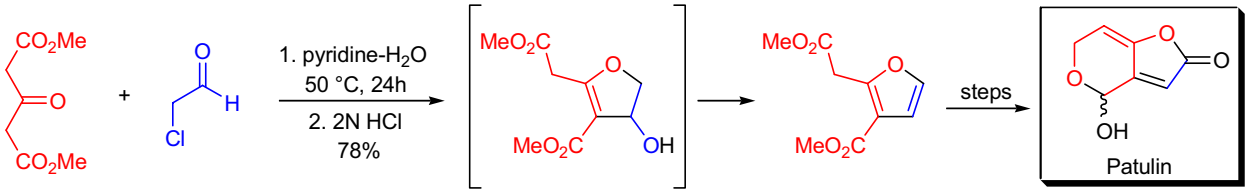
An efficient synthetic sequence for the preparation of 2,4-*bis*(trifluoromethyl)furan was developed by R. Filler and co-workers.[14] The potassium enolate of ethyl 4,4,4-trifluoroacetate was reacted with 3-bromo-1,1,1-trifluoroacetate in DMSO to afford 2,4-bis (trifluormethyl)-4-hydroxydihydro-3-furoate as a result of *O*-alkylation. Interestingly, under these conditions usually *C*-alkylation is preferred. Next, dehydration was performed to give the corresponding 2,4-*bis* (trifluoromethyl)-3-furoate in good yield. Finally, decarboxylation by heating with quinoline and $CuSO_4$ yielded the target furan in excellent yield.



Research by P. Xinfu et al. has shown that the *Feist-Bénary furan synthesis* is well-suited for the construction of furolignans having two different aryl groups.[15] 3,4-Dimethyl-2-piperonyl-5-veratrylfuran was prepared by first reacting the sodium enolate of a -keto ester derived from piperonal with an -bromo -keto ester derived from vanillin. The resulting 1,4-diketone was then subjected to acid-catalyzed cyclization with TsOH to the corresponding tetrasubstituted furan. The desired furolignan was obtained in two more steps.



The mycotoxin patulin was synthesized via the oxidation of a disubstituted furan in the laboratory of M. Tada.[16] The required 2,3-disubstituted furan was conveniently prepared *via* the *Feist-Bénary reaction* of acetonedicarboxylic acid dimethyl ester and chloroacetaldehyde in the presence of pyridine. Subsequent functional group modification and oxidation of this furan finally gave the natural product.



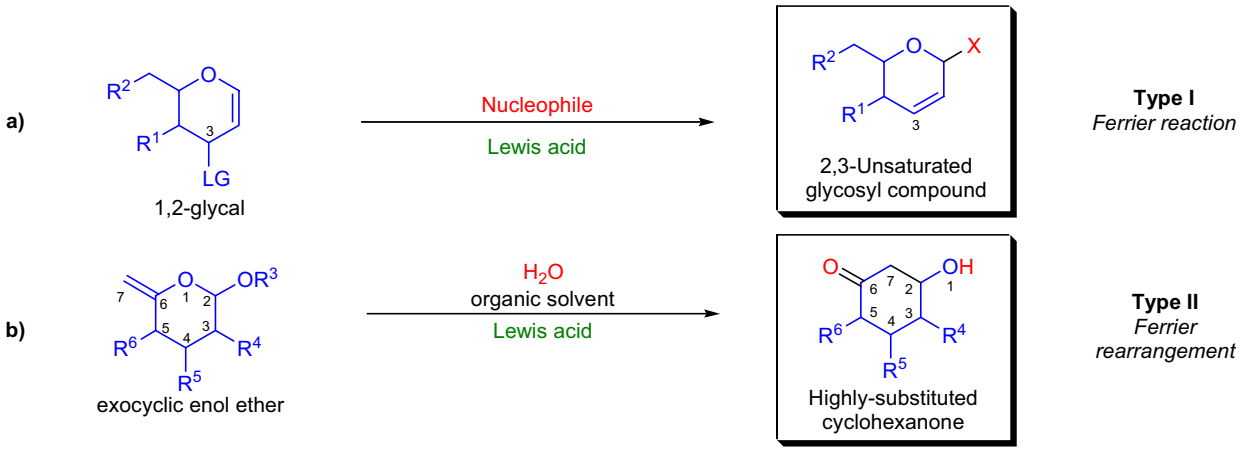
FERRIER REACTION / REARRANGEMENT

(References are on page 585)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-16]; *Modifications & Improvements*[17-24]]

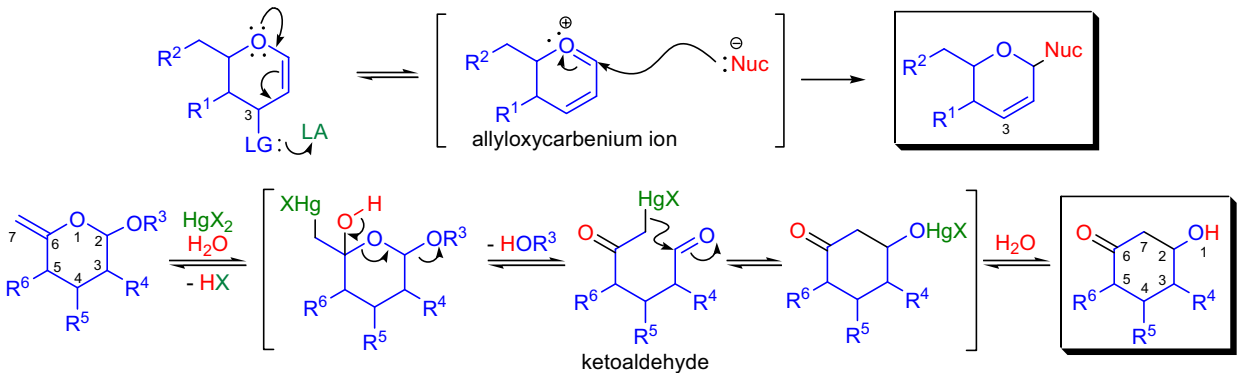
The Lewis acid promoted rearrangement of unsaturated carbohydrates is known as the *Ferrier reaction/ rearrangement*. The first report was made in 1914 by E. Fischer when he observed the allylic rearrangement of tri-*O*-acetyl-D-glucal to the corresponding 2,3-unsaturated hemiacetal upon heating with water.[1,25] The synthetic utility of this transformation was recognized by R.J. Ferrier during the early 1960s when he successfully prepared *O*-, *S*-, and *N*-linked unsaturated glycosyl compounds from 1,2-glycals and nucleophiles in the presence of Lewis acids.[2-4] This reaction is the *Type I Ferrier reaction* and its general features are: 1) substrates with good leaving groups, for example, acyloxy groups, in the 3-position (sugar nomenclature) successfully undergo the rearrangement upon heating in the presence of strong nucleophiles, such as alcohols and phenols, even in the absence of a catalyst; 2) commonly used Lewis acids are: $BF_3{\cdot}OEt_2$, $SnCl_4$, I_2,[21] $FeCl_3$,[24] TMSOTf-$AgClO_4$ [23]; 3) the hydroxyl group at C3 in the glycal can be activated under *Mitsunobu reaction* conditions without the use of a Lewis or protic acid;[20] and 4) the stereochemistry of the 2,3-unsaturated glycosyl product at the anomeric center depends on the relative stereochemistry of the groups at C3 and C4 in the starting material, but the α-anomer is usually predominant. The *Type II Ferrier rearrangement* was first reported in 1979 when exocyclic enol ethers were converted to substituted cyclohexanones upon treatment with mercury(II) salts.[5] The *Type II rearrangements* also became synthetically significant for the following reasons: 1) the precursors are readily available from carbohydrates, so the synthesis of chiral, highly-substituted cyclohexanone derivatives is possible; 2) in most reactions, single diastereomers are isolated in high yield;[7] and 3) the Lewis acid can be used in catalytic amounts and complex targets having acid sensitive functionalities can be prepared.[18] It was established that there is a strong correlation between the stereochemistry of the group at C3 and the stereochemistry of the group β to it: the newly generated OH groups and the C3 substituents are generally *trans* disposed in the product.[26]



R^1, R^2 = *O*-acyl; LG = *O*-acyl, OTs, etc.; Lewis acid: $BF_3{\cdot}OEt_2$, $SnCl_4$, I_2, H_3O^+, TMSOTf, $FeCl_3$, etc.; X = OR, SR, NR_2, CR_3
R^3 = alkyl; R^4, R^5, R^6 = *O*-alkyl, *O*-acyl; Lewis acid: $HgCl_2$, $HgSO_4$, $Hg(OCOCF_3)_2$, $PdCl_2$, $Pd(OAc)_2$, etc.

Mechanism:[27-33,15]

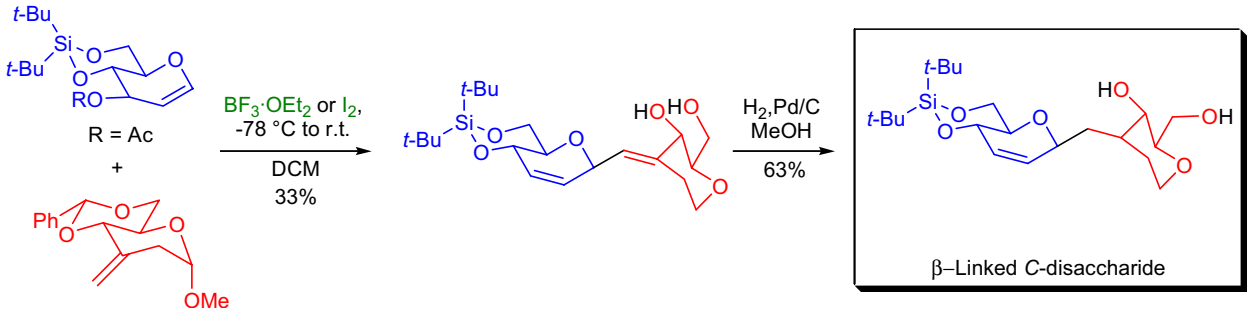
The first step of the mechanism in the *Type I Ferrier reaction* is the departure of the leaving group from the C3 position of the glycal to give an allyloxocarbenium ion upon treatment with Lewis acid. The allyloxycarbenium ion is then captured by the nucleophile to give the corresponding glycoside. In the *Type II Ferrier rearrangement*, the enol ether first undergoes regiospecific hydroxymercuration to give a ketoaldehyde. This ketoaldehyde intermediate then undergoes an *aldol-like intramolecular cyclization* to afford the product cyclohexanone.



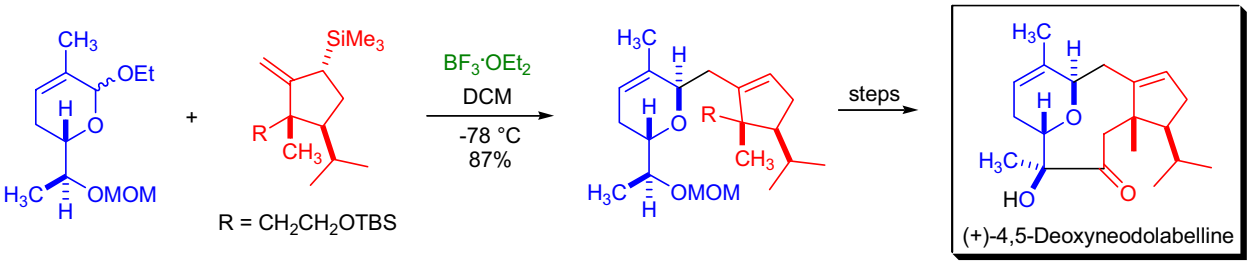
FERRIER REACTION / REARRANGEMENT

Synthetic Applications:

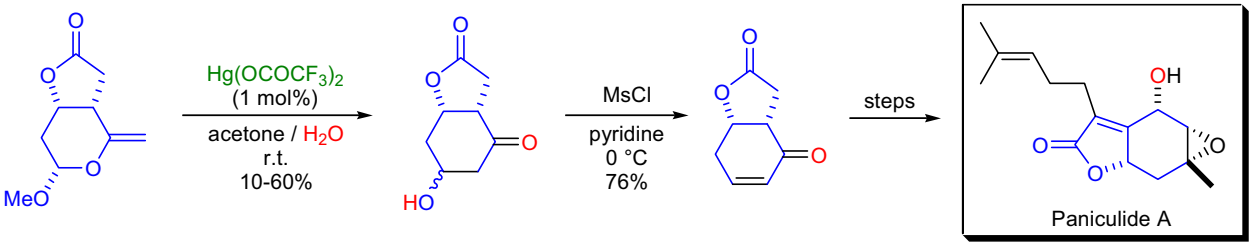
Research in the laboratory of H.M.I. Osborn showed that the use of cyclohexene derivatives as nucleophiles in the Lewis acid-mediated *Type I carbon-Ferrier reaction* of 3-*O*-acetylated glycals can be used to prepare unsaturated β-linked *C*-disaccharides.[34] The incorporation of the alkene took place with one equivalent of glucal in the presence of boron-trifluoride etherate in 33% yield. The desired *C*-disaccharide was obtained by selective hydrogenation of the exocyclic double bond in the presence of an endocyclic one.



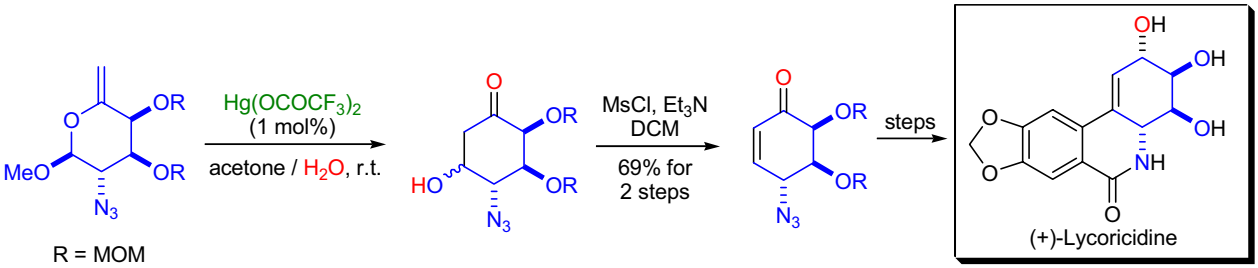
D.R. Williams and co-workers accomplished the first total synthesis of marine dolabellane diterpene (+)-4,5-deoxyneodolabelline.[35] The *Type I carbon-Ferrier reaction* was utilized to assemble the key *trans*-2,6-disubstituted dihydropyran with complete stereoselectivity (α-anomer). The macrocyclization was carried out with a vanadium-based *pinacol coupling*.



The highly oxygenated sesquiterpene paniculide A was synthesized by N. Chida et al. starting from D-glucose.[36] The key step to construct the substituted cyclohexane subunit of the natural product involved the *Type II Ferrier rearrangement*.



The stereoselective total synthesis of antimitotic alkaloid (+)-lycoricidine was accomplished by S. Ogawa and co-workers by utilizing the catalytic version of the *Type II Ferrier rearrangement* for the synthesis of the optically active substituted cyclohexenone fragment.[37] The rearrangement was effected with 1 mol% of mercuric(II)trifluoroacetate in acetone-water solvent system.



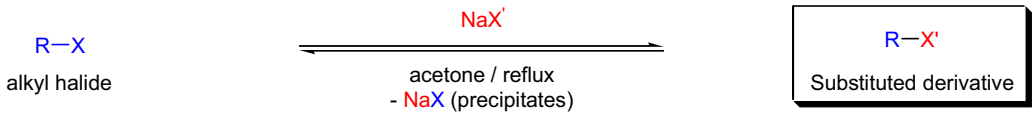
FINKELSTEIN REACTION

(References are on page 586)

Importance:

[*Seminal Publication*[1]*; Review*[2]*; Modifications & Improvements*[3-9]*; Theoretical Studies*[10-14]]

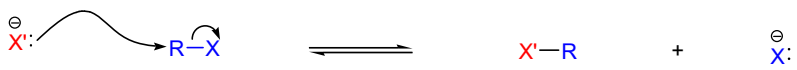
The equilibrium exchange of the halogen atom in alkyl halides for another halogen atom is known as the *Finkelstein reaction*. The first example of a halogen-exchange reaction was reported in the mid 1800s by W.H. Perkin,[15] but the systematic study of the reaction was conducted several decades later by H. Finkelstein in 1910.[1] Finkelstein observed that when various alkyl chlorides and bromides (1°, 2°, 3°, benzylic, etc.) were boiled with a 15 wt% solution of NaI in acetone, the corresponding alkyl iodides were formed in good yield. He also noted that the reaction time varied greatly, being the shortest for primary, allylic, and benzylic halides and the longest for tertiary alkyl halides. The *Finkelstein reaction* is an equilibrium process and capitalizes on the substantial solubility difference of sodium-halides in organic solvents (acetone, 2-butanone, etc.). While NaI dissolves readily in acetone, the solubility of NaBr and NaCl in organic solvents is very low. Therefore, the equilibrium can be shifted toward the direction of halogen-exchange according to the *Le Chatelier principle*: the formed NaBr and NaCl precipitates from the solution. Even today, the preparatively most important *Finkelstein reactions* are the conversion of alkyl bromides, chlorides, tosylates and mesylates to the corresponding alkyl iodides which are often difficult to prepare by other methods. Other halogenated compounds such as α-halogenated ketones and acids also undergo the *Finkelstein reaction* with ease. There are numerous modifications of the reaction: 1) solid-phase supported KI avoids the use of large excess of the reagent;[5] 2) microwave irradiation at high pressure considerably increases the rate of the reaction; [6,8] 3) alkyl fluorides can be prepared from other alkyl halides with lipophilic quaternary ammonium fluorides (TBAF) even in aprotic solvents of low polarity;[7] 4) the alkyl halide to alkyl fluoride conversion can also be done by using KF/18-crown-6 in dipolar aprotic solvents;[16] 5) the displacement of fluorine in alkyl fluorides with iodide is possible with the use of TMSI;[4] and 6) sterically hindered secondary and tertiary alkyl halides can be converted to the alkyl iodides by treatment with NaI/CS_2 in the presence of various Lewis acids ($AlMe_3$, $ZnCl_2$ $FeCl_3$, etc.).[3]



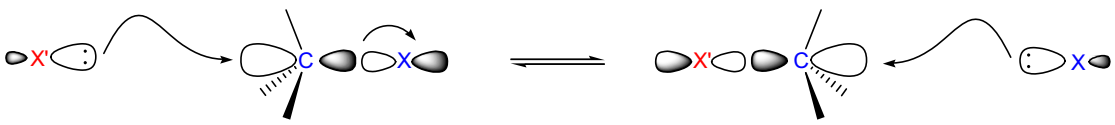
X = Cl, Br, OMs, OTs; R = 1° and 2°alkyl, allyl, benzyl; when X = Cl then X' = Br or I; when X = Br then X' = I

Mechanism: [17-27]

The mechanism of the *Finkelstein reaction* is often described as a typical S_N2 reaction where the filled orbital of the nucleophile (halide ion) interacts with the σ* orbital of the carbon-halogen bond, and the reaction proceeds with an overall inversion of configuration. This mechanistic picture depicts most transformations involving primary and secondary alkyl, allylic or benzylic halides. The driving force for the reaction is the removal of one of the nucleophiles from the equilibrium as an insoluble salt. Usually alkyl fluorides are very stable, and therefore they are sluggish to participate in nucleophilic displacement reactions unless the fluoride ion can be tied up in a stronger bond (such as Si-F) to compensate for the cleavage of the strong C-F bond. In certain cases, however, the *Finkelstein reaction* gave rise to dimeric and rearranged products, which were isolated and characterized; detailed mechanistic studies concluded that a sequential cation-free radical mechanism was operational.[22]



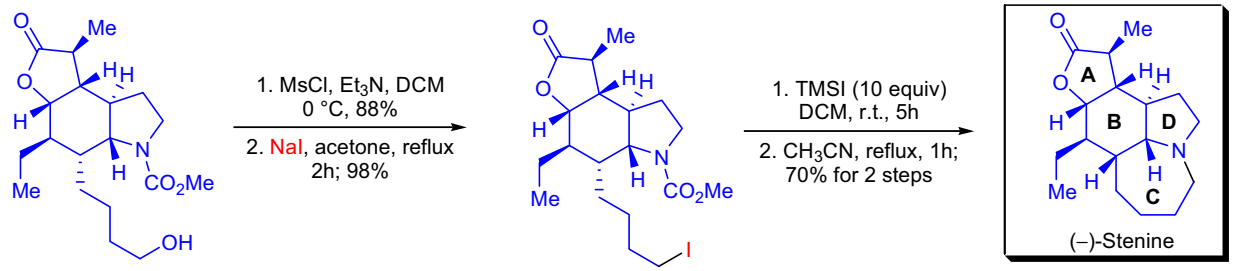
Description of the process with molecular orbitals:



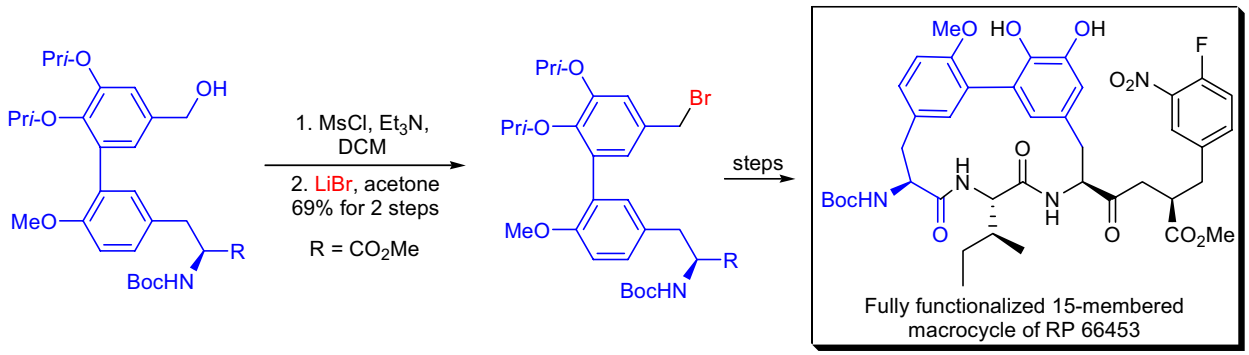
FINKELSTEIN REACTION

Synthetic Applications:

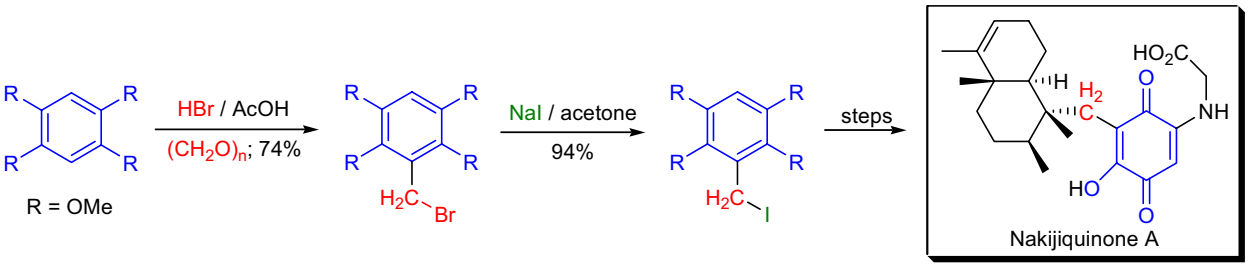
During the endgame of the total synthesis of the stemona alkaloid (–)-stenine, Y. Morimoto and co-workers utilized the *Finkelstein reaction* to prepare a primary alkyl iodide from a primary alkyl mesylate.[28] The mesylate was prepared from the corresponding primary alcohol with MsCl/Et_3N. The resulting primary alkyl iodide was used in the subsequent *intramolecular N-alkylation* to construct the final perhydroazepine C-ring of the natural product.



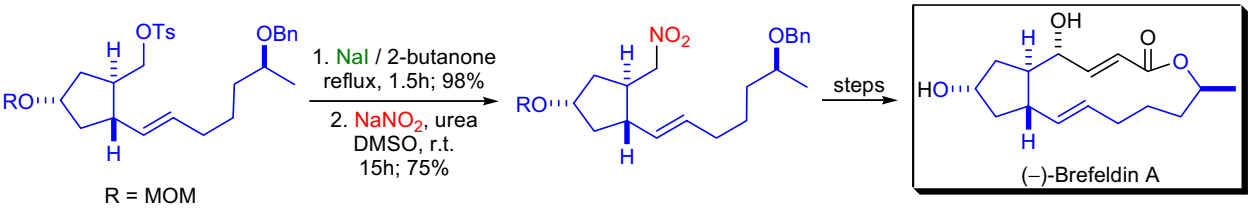
In the laboratory of J. Zhu, the synthesis of the fully functionalized 15-membered biaryl-containing macrocycle of RP 66453 was accomplished.[29] One of the key steps in their approach was *Corey's enantioselective alkylation of a glycine template* with a structurally complex biaryl benzyl bromide. This benzyl bromide was prepared from the corresponding benzyl mesylate *via* the *Finkelstein reaction* using lithium bromide in acetone.



The marine sesquiterpene nakijiquinones were synthesized and biologically evaluated by H. Waldmann et al.[30] The core structure of the natural product was assembled *via* a *reductive alkylation* of a bicyclic enone with tetramethoxybenzyl iodide. This aryl iodide was obtained in a two-step procedure: treatment of the corresponding 1,2,4,5-tetramethoxybenzene with HBr/paraformaldehyde/AcOH followed by the *Finkelstein reaction* to replace the bromide with iodide.



The key step in D. Kim's total synthesis of (–)-brefeldin A was an *intramolecular nitrile-oxide cycloaddition*.[31] In order to prepare the substrate for this cycloaddition, a *double Finkelstein reaction* was performed; first an alkyl tosylate was replaced with iodide; then the iodide was exchanged with a nitrite ion to afford the desired alkyl nitro compound.



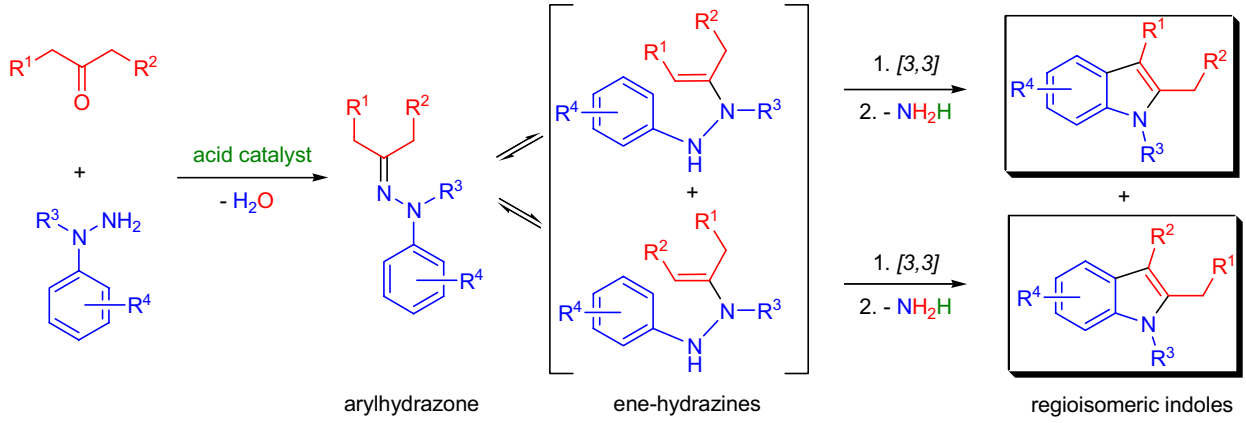
FISCHER INDOLE SYNTHESIS

(References are on page 587)

Importance:

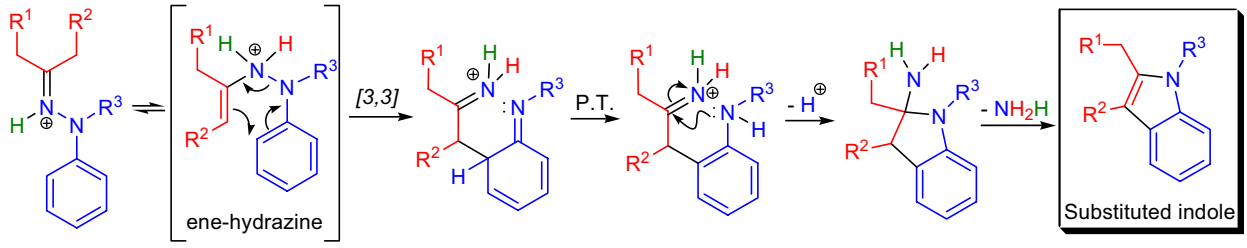
[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-13]; *Theoretical Studies*[14-21]]

In 1883, E. Fischer and F. Jourdan[1] treated pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride, and the product of this reaction was later identified as 1-methylindole-2-carboxylic acid.[2] The preparation of indoles by heating arylhydrazones of ketones or aldehydes in the presence of a protic acid or a Lewis acid catalyst is known as the *Fischer indole synthesis*. Since its discovery, it has become the most important method to prepare substituted indoles. The catalysts that successfully lead to indolization are: 1) strong acids (e.g., PTSA, PPA, HCl, H_2SO_4); 2) weak acids (e.g., pyridinium chloride, AcOH); 3) solid acids (e.g., montmorillonite KSF clay, Mordenite, Zelotite Y, ion-exchange resins); and 4) Lewis acids (PCl_3, polyphosphoric acid trimethylsilyl ester, $ZnCl_2$). The Lewis acid catalyzed reactions often proceed under milder conditions (room temperature rather than high temperature) than the reactions catalyzed by protic acids. In the case of heteroaromatic arylhydrazones, however, the use of any acid is problematic (due to the protonation of the heteroatom), and for these compounds simple heating at high temperatures (thermal non-catalytic method) can also lead to indolization. The acid catalyzed cyclizations are usually 7 to 30 times faster than the thermal reactions. The main features of the *Fischer indole synthesis* are the following: 1) it is not necessary to isolate the arylhydrazones, the indole formation can be conducted by mixing the aldehyde and hydrazine and carrying out the indolization in one-pot; 2) unsymmetrical ketones give two regioisomeric 2,3-disubstituted indoles, and the regioselectivity depends on a combination of factors: acidity of the medium, substitution of the hydrazine, steric effects in the ketone and in the ene-hydrazines; 3) with unsymmetrical ketones indolization usually occurs at the least substituted α-carbon atom in strongly acidic medium, whereas weak acids give rise to the other regioisomer; 4) indolization of α,β-unsaturated ketones is generally unsuccessful due to the formation of unreactive pyrazolines; 5) 1,2-diketones can give both mono- and *bis*-indoles and the mono-indoles are usually formed with strong acid catalysts in refluxing alcohols; 6) 1,3-diketones and β-keto esters are not ideal substrates, since their arylhydrazones form pyrazoles and pyrazol-3-ones, respectively; 7) due to their sensitivity, aldehydes are used in their protected forms (acetal, aminal, or bisulfite addition product), and they give rise to 3-substituted indoles; 8) hydrazines are often used as their HCl salt or in their Boc protected form (they are not very stable in their free base form); 9) electron-withdrawing substituents on the aromatic ring of the hydrazine causes the indolization to become low-yielding and slow; 10) *ortho*-substituted arylhydrazines generally react much slower than the *meta*-substituted ones; and 11) the *Japp-Klingemann reaction* provides an easy way to obtain the starting arylhydrazones from β-dicarbonyls and arenediazonium salts.



Mechanism:[22-39]

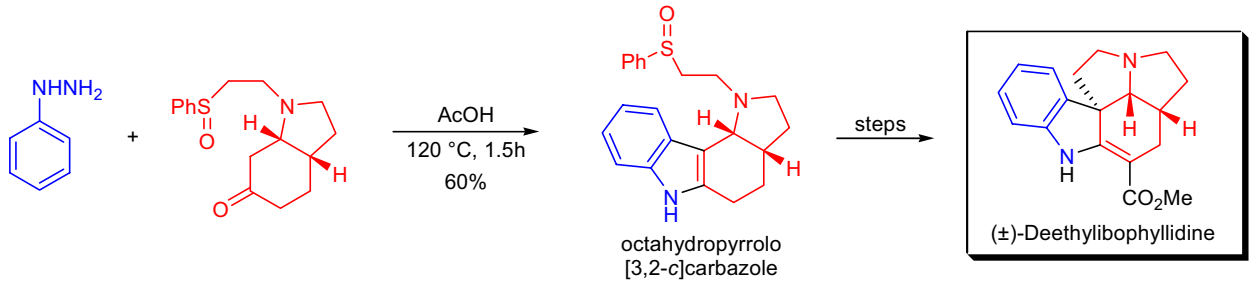
The currently accepted mechanism of the *Fischer indole synthesis* was originally proposed by R. Robinson in 1924.[22] There are five distinct steps: 1) coordination of the Lewis acid (e.g., proton) to the imine nitrogen; 2) tautomerization of the hydrazone to the corresponding ene-hydrazine; 3) disruption of the aromatic ring by a *[3,3]-sigmatropic rearrangement*; 4) rearomatization *via* a proton shift and formation of the 5-membered ring by a favored *5-exo-trig* cyclization; and 5) the loss of a molecule of ammonia to finally give rise to the indole system.



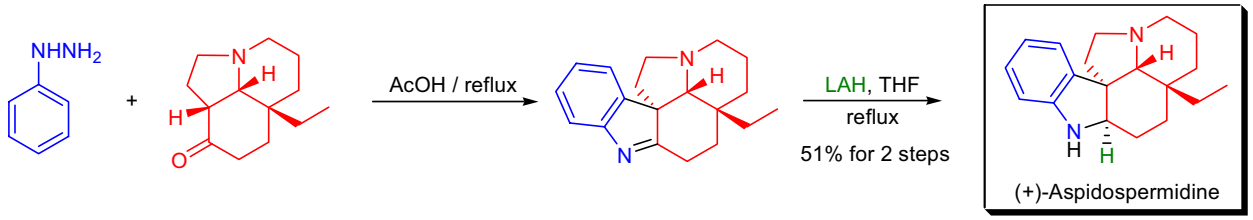
FISCHER INDOLE SYNTHESIS

Synthetic Applications:

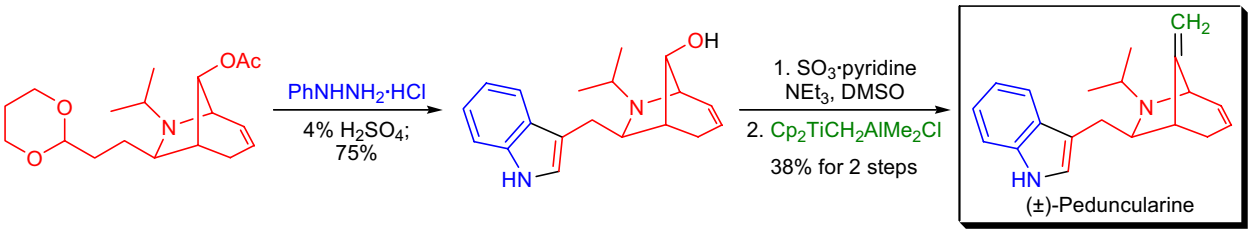
The total synthesis of (±)-deethylibophyllidine was accomplished by J. Bonjoch and co-workers, who applied a regioselective *Fischer indole synthesis* as one of the key steps to obtain octahydropyrrolo[3,2-*c*]carbazoles.[40] The indole formation was followed by a tandem *Pummerer rearrangement-thionium ion cyclization* to generate the quaternary spiro stereocenter.



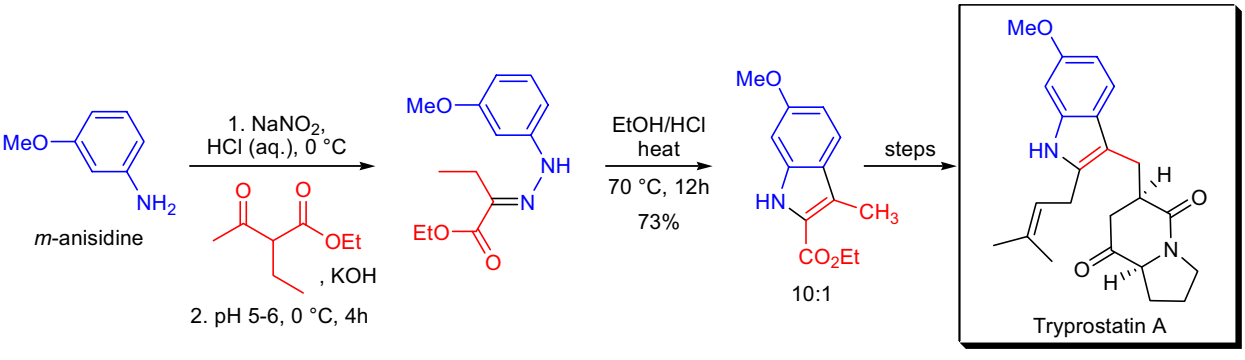
During the total synthesis of (+)-aspidospermidine by J. Aubé et al., the final steps involved an efficient *Fischer indolization* of a complex tricyclic ketone.[41] This ketone was unsymmetrical and the indole formation occurred regioselectively at the most substituted α-carbon in a weakly acidic medium (glacial AcOH).



The unusual 6-azabicyclo[3.2.1]oct-3-ene core of the alkaloid (±)-peduncularine was assembled using the [3+2] annulation of an allylic silane with chlorosulfonyl isocyanate by K.A. Woerpel and co-workers.[42] In the endgame of the total synthesis, the bicyclic aldehyde was masked as the acetal, and an efficient *Fischer indole synthesis* was performed using phenylhydrazine hydrochloride along with 4% H_2SO_4. Several subsequent steps led to the natural product.



J.M. Cook et al. accomplished the enantiospecific total synthesis of the indole alkaloid tryprostatin A.[43] The substituted indole nucleus was assembled at the beginning of the synthesis, and the necessary arylhydrazone was prepared *via* the *Japp-Klingemann reaction* using the diazonium salt derived from *m*-anisidine and the anion of ethyl-α-ethylacetoacetate. The regioselectivity of the *Fischer indole synthesis* favored the 6-methoxy-3-methylindole-2-carboxylate regioisomer in a 10:1 ratio.



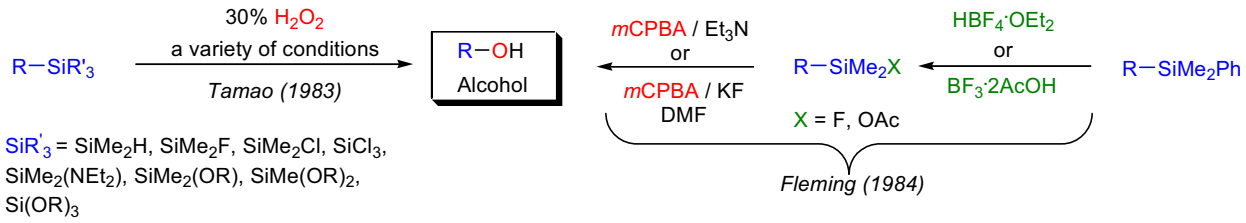
FLEMING-TAMAO OXIDATION

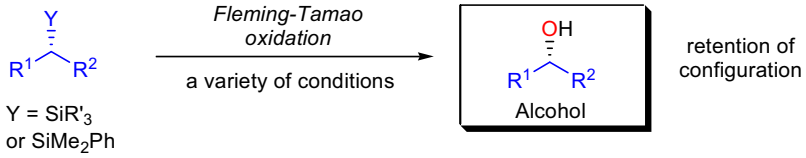
(References are on page 588)

Importance:

[*Seminal Publications*[1-7]*; Reviews*[8-12]*; Modifications & Improvements*[13-17]*; Theoretical Studies*[18,19]]

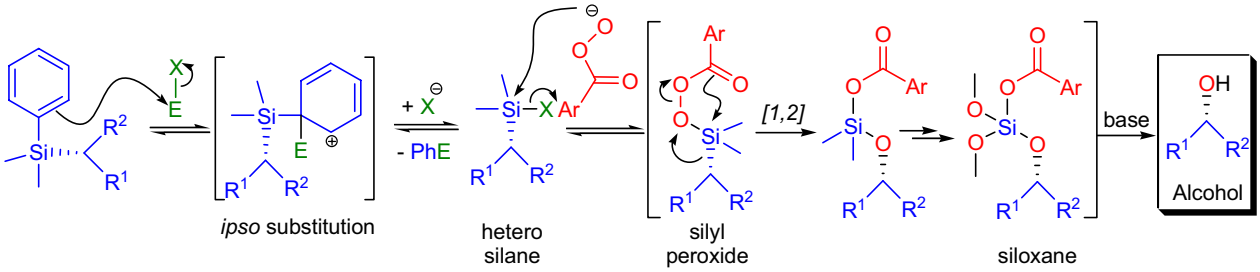
In 1983, K. Tamao and M. Kumada reported that silicon-carbon bonds can be cleaved by hydrogen peroxide, under basic conditions in the presence of bicarbonate salts, to afford the corresponding alcohols, provided that the silicon atom had at least one electron-withdrawing substituent.[3] A year later, I. Fleming and co-workers discovered that the dimethylphenylsilyl-carbon bond ($PhMe_2Si$-C) can be oxidatively cleaved in two steps to the corresponding alcohol with retention of configuration at the carbon atom to which the silicon is attached.[5] The two steps were: 1) protodesilylation of the phenyl ring using HBF_4 or BF_3·AcOH complex; and 2) treatment of the resulting silyl fluoride with a peracid (e.g., *m*CPBA, AcOOH). These early discoveries paved the way to the development of a large number of silicon-based reagents and the use of various silyl groups as the masked form of the hydroxyl group.[16] The mild, stereospecific oxidation of silicon-carbon bonds to yield the corresponding carbon-oxygen bonds (alcohols) is called the *Fleming-Tamao oxidation*. In terms of laboratory execution of the oxidation, the following facts are noteworthy: 1) phenylsilanes are more robust than alkoxysilanes, so they can be removed at the end of a long synthetic sequence; 2) aryl, heteroaryl and allyl substituents on the silicon atom behave the same way as the phenyl group, and they are all replaced by the fluoride in the first step of the oxidation; 3) in the second step fluoride additives are often needed in addition to the oxidizing agent; and 4) usually more than one equivalent of oxidizing agent is necessary for each silicon-carbon bond. Advantages of the *Fleming-Tamao oxidation* are: 1) carbon-silicon bonds can be introduced stereospecifically, and therefore the preparation of substrates is straightforward (e.g., *via* the regioselective transition metal catalyzed *hydrosilylation of olefins*); 2) by carefully choosing the substituents on the silicon atom, the oxidation of a specific silyl group is possible in the presence of other silyl groups; 3) unlike the oxygen atom, the silicon does not have lone pairs of electrons, so it does not coordinate to electrophiles or Lewis acids; 4) in the case of optically active substrates, the reaction is stereospecific, that is, there is a retention of configuration; 5) the oxidation conditions are mild enough to tolerate a wide range of functional groups even in complex substrates; 6) the two-step reaction can also be conducted in one-pot by using Hg^{2+} or Br^+ as electrophiles;[7] and 7) the isolation of the product alcohol is straightforward, since the by-products of the oxidation are usually water-soluble. There are some disadvantages as well: 1) the oxidation of silyl groups attached to tertiary carbons of cyclic systems do not always proceed with ease;[14] and 2) in the presence of tertiary amines, special conditions are required to avoid *N*-oxide formation.[19]





Mechanism:[1,11,18]

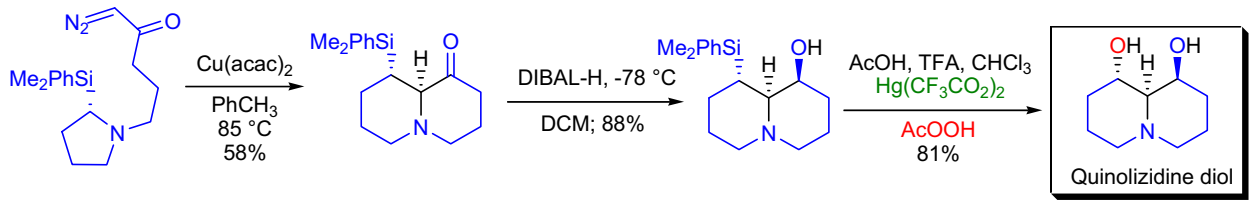
The mechanism of the *Fleming-Tamao oxidation* has four distinct steps when the silyl group is $-SiMe_2Ph$: 1) S_EAr by the electrophile on the phenyl ring in the *ipso* position affords the heteroatom-substituted silane ($-SiMe_2X$) derivative; 2) attack of the heterosilane by the peroxide to give tetracoordinated silyl peroxide; 3) *[1,2]*-alkyl shift to give a dialkoxy silane (analogous to the step in *Baeyer-Villiger oxidation*), followed by conversion to a siloxane; and 4) hydrolysis of the siloxane to the desired alcohol.



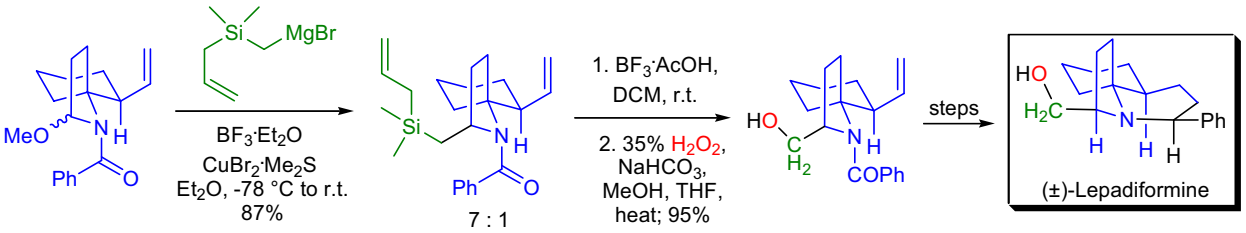
FLEMING-TAMAO OXIDATION

Synthetic Applications:

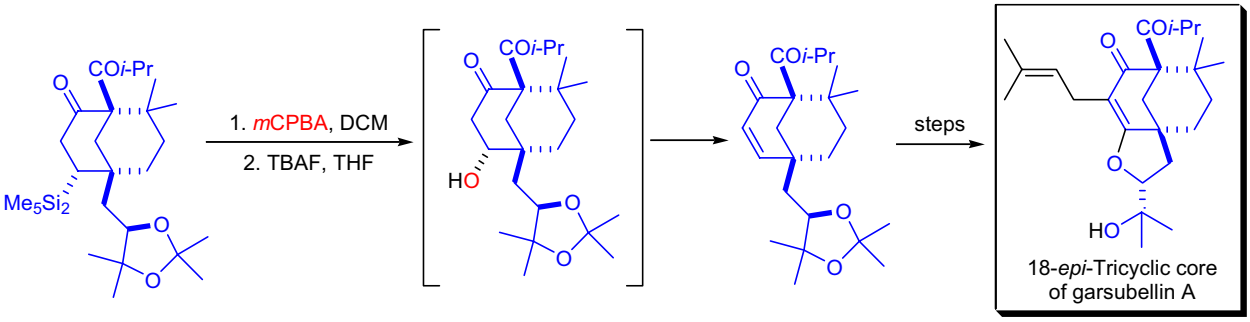
In the laboratory of F.G. West, the stereoselective *silyl-directed [1,2]-Stevens rearrangement* of ammonium ylides was investigated as a potential key step toward the enantioselective synthesis of various hydroxylated quinolizidines.[19] The dimethylphenylsilyl group served as a surrogate for one of the hydroxyl groups in the product. The *Fleming-Tamao oxidation* was performed under Denmark's conditions to avoid oxidation of the tertiary amine to the corresponding *N*-oxide, and the desired quinolizidine diol was obtained in 81% yield.[17]



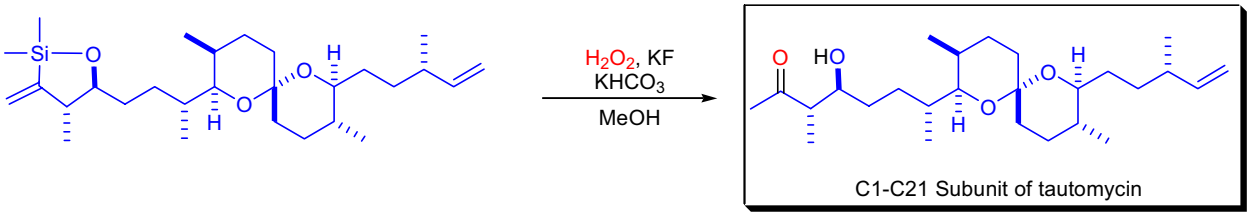
During the total synthesis of the marine alkaloid (±)-lepadiformine by S.M. Weinreb et al., one of the key bicyclic *N*-acyliminium salt intermediates was subjected to a nucleophilic attack by an organocuprate.[20] The resulting allyldimethylsilyl derivative was then treated under the *Fleming-Tamao oxidation* conditions to afford the corresponding hydroxymethyl compound in excellent yield.



M. Shibasaki and co-workers reported a concise stereocontrolled synthesis of the 18-*epi*-tricyclic core of garsubellin A.[21] In the endgame, the unmasking of an α,β-unsaturated ketone became necessary just prior to the cyclization of the third ring. The latent β-hydroxyl group was best carried through several steps as a pentamethyldisilyl substituent, which was removed by a *modified Fleming-Tamao oxidation*.[15]



The synthesis of the C1-C21 subunit of the protein phosphatase inhibitor tautomycin was accomplished by J.A. Marshall et al.[22] During the last steps of the synthetic sequence, the *hydrosilylation* of a terminal alkyne afforded a five-membered siloxane that was oxidized by the *Fleming-Tamao oxidation*. The initially formed enol tautomerized to the corresponding methyl ketone.



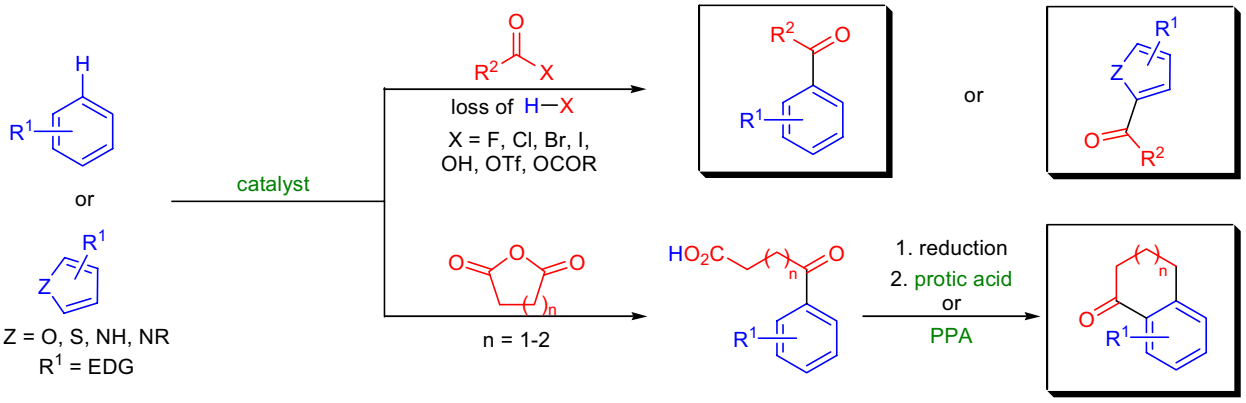
FRIEDEL-CRAFTS ACYLATION

(References are on page 588)

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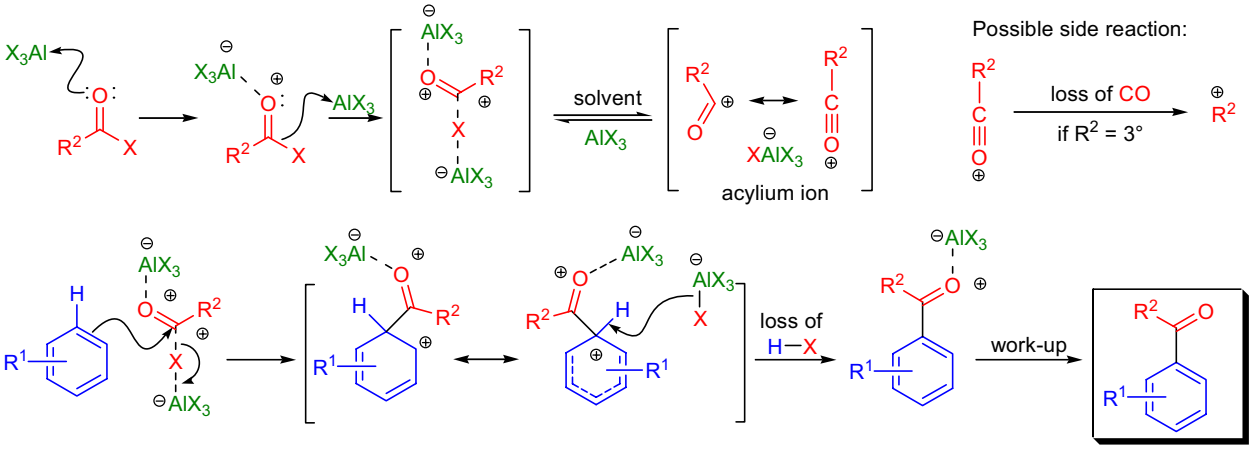
[*Seminal Publications*[1,2]*; Reviews*[3-18]*; Modifications & Improvements*[19-29]*; Theoretical Studies*[30-40]]

The introduction of a keto group into an aromatic or aliphatic substrate by using an acyl halide or anhydride in the presence of a Lewis acid catalyst is called the *Friedel-Crafts acylation*. The reaction is closely related to the *Friedel-Crafts alkylation*, which introduces alkyl groups into aromatic and aliphatic substrates. General features of the *Friedel-Crafts acylations* are the following: 1) substrates that undergo the *Friedel-Crafts alkylation* are also easily acylated and in most cases electron-rich substrates (R^1 = -OH, -NR_2, alkyl, etc.) are needed to obtain the desired ketone in good yield; 2) aromatic substrates with strongly electron-withdrawing groups (R^1 = -NO_2, -CX_3, etc.) and certain heteroaromatic compounds (e.g., quinolines, pyridines) do not undergo the acylation at all, and they may be used as solvents (these unreactive substrates, however, are efficiently acylated by the *Minisci reaction*); 3) acylating agents besides acyl halides are: aromatic and aliphatic carboxylic acids, anhydrides, ketenes and esters, as well as polyfunctional acylating agents (oxalyl halides); 4) acyl iodides are usually the most reactive, while acyl fluorides are the least reactive (I > Br > Cl > F); 5) unlike in the alkylations, *Friedel-Crafts acylations* require substantial amounts of catalyst (slightly more than one equivalent), since the acylating agent itself coordinates one equivalent of Lewis acid, and therefore excess is needed to observe catalysis; 6) most often used catalysts are: AlX_3, lanthanide triflates, zeolites, protic acids (e.g., H_2SO_4, H_3PO_4), $FeCl_3$, $ZnCl_2$, PPA; 7) in the case of very reactive acylating agents (e.g., acyloxy triflates) or very electron-rich substrates there is little or no catalyst required;[8] 8) no polyacylated products are observed, since, after the introduction of the first acyl group, the substrate becomes deactivated; 9) rearrangement of the acylating agent under the reaction conditions is rarely observed and this feature allows the preparation of straight chain alkylated aromatic compounds in a two-step process (acylation followed by reduction); 10) unprotected Lewis basic functional groups (e.g., amines) are poor substrates, since the acylation will preferentially take place on these functional groups instead of the aromatic ring; 11) the *intramolecular Friedel-Crafts acylation* is well-suited for the closure of 5-, 6- and 7-membered rings with a tendency for the formation of the 6-membered ring. One drawback of the *Friedel-Crafts acylation* is that the Lewis acid catalyst usually cannot be recovered at the end of the reaction, since it is destroyed in the work-up step. However, recent studies showed that the use of heterogeneous catalysts (mainly zeolites) makes this important reaction more feasible on an industrial scale.[41]



Mechanism:[4,42-47]

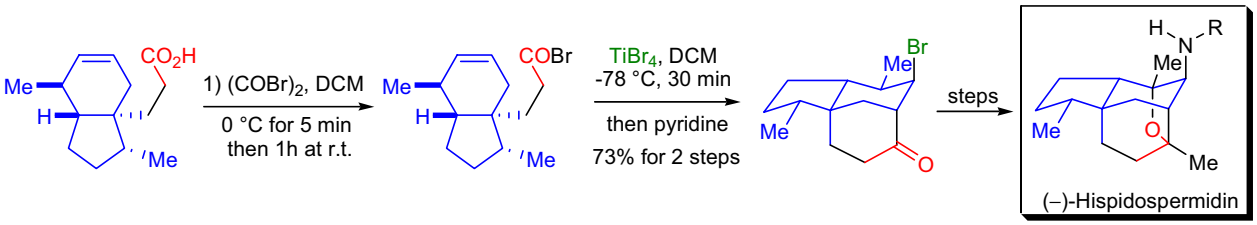
The initial step of the mechanism is the coordination of the first equivalent of the Lewis acid to the carbonyl group of the acylating agent. Next, the second equivalent of Lewis acid ionizes the initial complex to form a second donor-acceptor complex which can dissociate to an acylium ion in ionizing solvents. The typical S_EAr reaction gives rise to an aromatic ketone-Lewis acid complex that has to be hydrolyzed to the desired aromatic ketone.



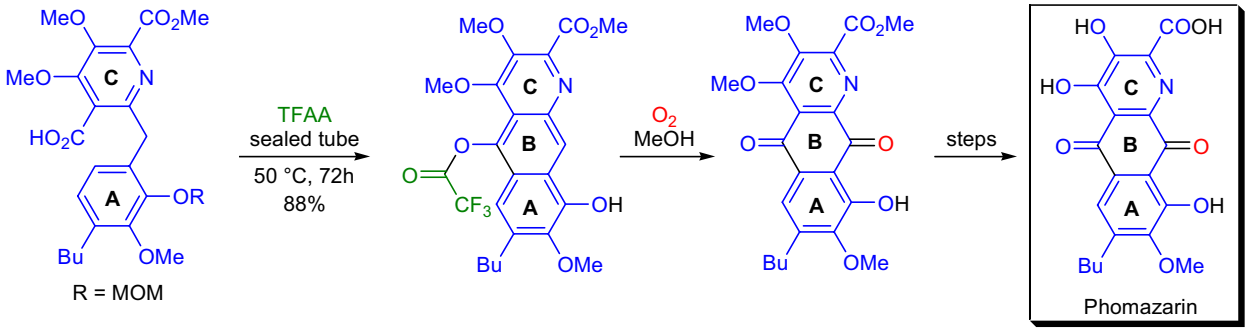
FRIEDEL-CRAFTS ACYLATION

Synthetic Applications:

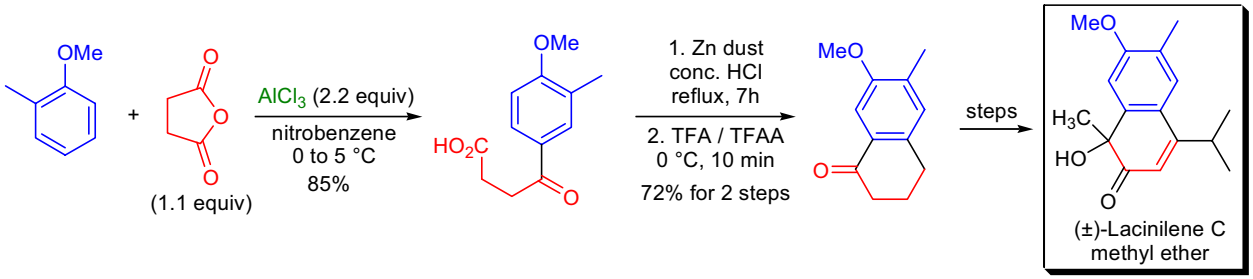
L.E. Overman et al. accomplished the enantioselective total synthesis of (–)-hispidospermidin by utilizing an *aliphatic intramolecular Friedel-Crafts acylation* as the key step to assemble the rigid tricyclic core.[48] The bicyclic acid precursor was first converted to the corresponding acid halide followed by treatment with one equivalent of titanium tetrahalide (TiX_4). Interestingly, upon cyclization with $TiCl_4$, the acid chloride gave substantial quantities of a side-product arising from a facile *[1,2]-hydride shift*. The extent of this unwanted hydride shift was greatly suppressed by first preparing the acid bromide followed by a $TiBr_4$ mediated cyclization. The authors attributed this improvement to the increased nucleophilicity of the bromide ion *vs*. chloride ion.



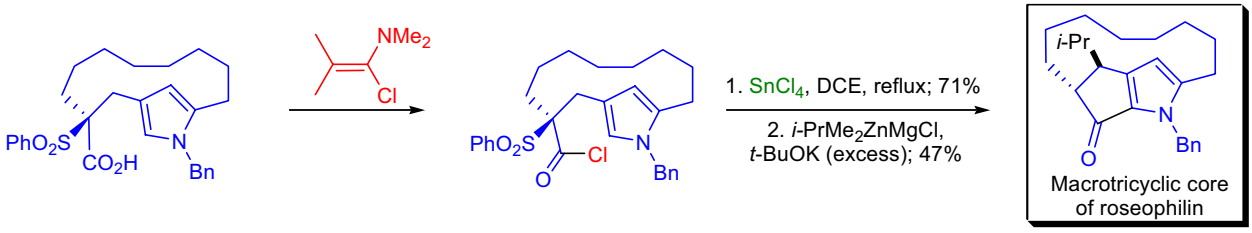
During the total synthesis of phomazarin, D.L. Boger and co-workers closed the B ring of the natural product with a *Friedel-Crafts acylation* reaction.[49] This key step provided the fully functionalized phomazarin skeleton. The carboxylic acid precursor was exposed to trifluoroacetic anhydride at 50 °C for 72h. The initial product was a C5 trifluoroacetate, which was subsequently hydrolyzed in the presence of air, which oxidized the phenol to the corresponding B-ring quinone.



In the laboratory of K. Krohn, the total synthesis of phytoalexine (±)-lacinilene C methyl ether was completed.[50] In order to prepare the core of the natural product, an *intermolecular Friedel-Crafts acylation* was carried out between succinic anhydride and an aromatic substrate, followed by an *intramolecular acylation*. After the first acylation, the 4-keto arylbutyric acid was reduced under *Clemmensen reduction* conditions (to activate the aromatic ring for the intramolecular acylation).



The first synthesis of the macrotricyclic core of roseophilin was carried out by A. Fürstner and co-workers.[51] An *intramolecular Friedel-Crafts acylation* was used to close the third ring of the macrotricycle.



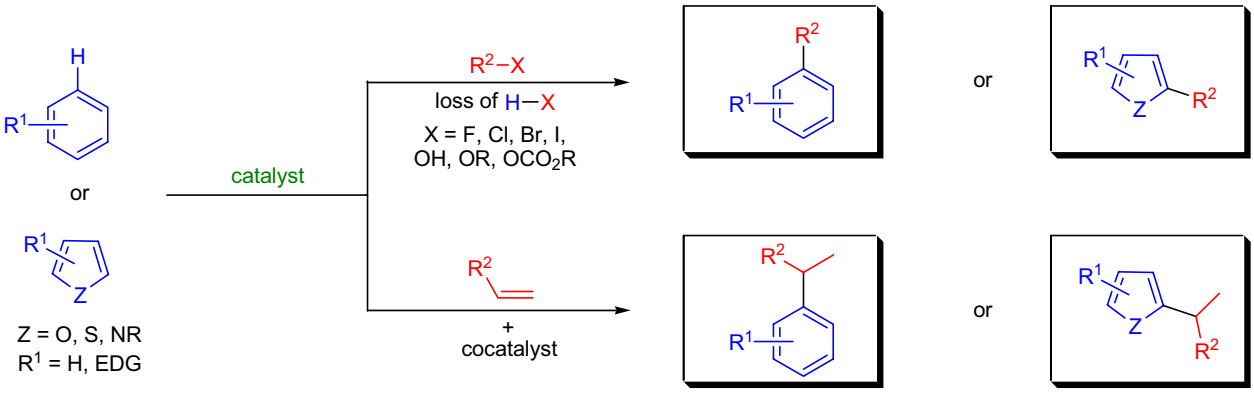
FRIEDEL-CRAFTS ALKYLATION

(References are on page 589)

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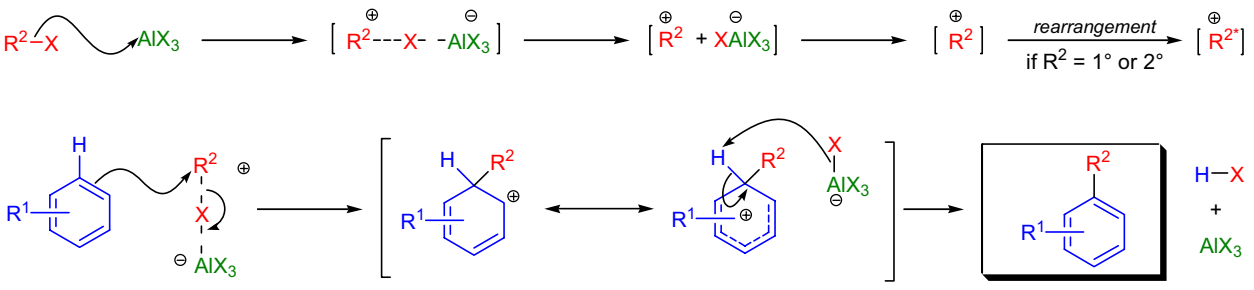
[*Seminal Publications*[1,2]; *Reviews*[3-13]; *Modifications & Improvements*[14-36]; *Theoretical Studies*[37-45]]

In 1877, C. Friedel and J.M. Crafts treated amyl chloride with thin aluminum strips in benzene and observed the formation of amylbenzene.[1,2] The reaction of alkyl halides with benzene was found to be general, and aluminum chloride ($AlCl_3$) was identified as the catalyst. Since their discovery, the substitution of aromatic and aliphatic substrates with various alkylating agents (alkyl halides, alkenes, alkynes, alcohols, etc.) in the presence of catalytic amounts of Lewis acid is called the *Friedel-Crafts alkylation*. Until the 1940s the alkylation of aromatic compounds was the predominant reaction, but later the alkylation of aliphatic systems also gained considerable importance (e.g., isomerization of alkanes, polymerization of alkenes and the reformation of gasoline). In addition to aluminum chloride other Lewis acids are also used for *Friedel-Crafts alkylations*: $BeCl_2$, $CdCl_2$, BF_3, BBr_3, $GaCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$, lanthanide trihalides, and alkylaluminum halides ($AlRX_2$). The most widely employed catalysts are $AlCl_3$ and BF_3 for alkylations with alkyl halides. When the alkylating agent is an alkene or an alkyne, in addition to the catalyst, a cocatalyst (usually a proton-releasing substance such as water, an alcohol, or a protic acid) is also necessary for the reaction to occur. Other efficient catalysts are: 1) aluminum trialkyls (e.g., AlR_3) and alkoxides [$Al(OPh)_3$]; 2) acidic oxides and sulfides; 3) modified zeolites; 4) acidic cation-exchange resins (e.g., Dowex 50); 5) Brönsted acids (e.g., HF, H_2SO_4, H_3PO_4); 6) Brönsted and Lewis superacids (e.g., $HF{\cdot}SbF_5$, $HSO_3F{\cdot}SbF_5$); 7) clay-supported metal halides;[18] and 8) enzymes.[22] The general features of the *Friedel-Crafts alkylations* are: 1) the reactivity of alkyl halides is the highest for alkyl fluorides and the lowest for alkyl iodides (F > Cl > Br > I); 2) the branching of the alkyl group has a dramatic influence, since tertiary alkyl halides are the most reactive: tertiary, benzyl > secondary > primary; 3) if the alkyl halide is polyfunctional (it has more than one halogen atom (e.g., $RCHX_2$) or has a double bond besides the halogen), a wide range of products can be formed, and the product ratio mainly depends on the type of catalyst used; 4) 1° and 2° alkyl groups tend to rearrange and therefore product mixtures are formed; 5) if the aromatic substrate is substituted, electron-donating substituents are required, and electron-poor substrates do not undergo the alkylation (e.g., $C_6H_5NO_2$); and 6) the orientation of substitution is catalyst dependent; in addition to the expected *o*- and *p*-disubstituted products, substantial amounts of *meta*-derivatives can be obtained under harsh conditions (e.g., with $AlCl_3$ at high temperature). The reaction also has disadvantages: 1) only electron-rich (usually alkyl substituted) aromatic rings can be used as substrates; 2) after the first alkyl group is introduced, the aromatic ring becomes more reactive and polyalkylation often occurs; 3) catalysts and alkylating agents that are too reactive may degrade the substrate; 4) nucleophilic functional groups (-OH, -OR, -NH_2) coordinate to the Lewis acid catalyst, thereby deactivating it; and 5) the *Friedel-Crafts alkylation* reaction is reversible, and therefore alkyl groups that are already in the substrate may migrate, rearrange, or be removed under the reaction conditions.



Mechanism:[46-54]

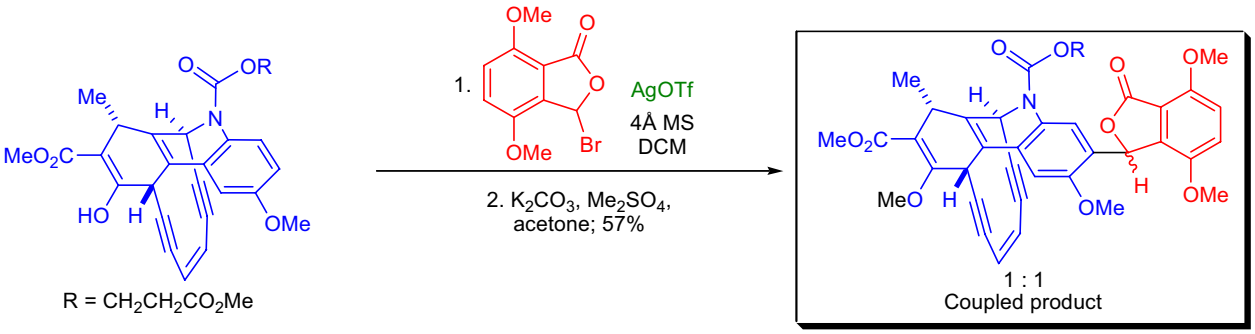
The first step of the *Friedel-Crafts alkylation* is the coordination of the Lewis acid to the alkylating agent (e.g., alkyl halide) to give a polar addition complex. The extent of polarization in this complex depends on the branching of the alkyl group and almost total dissociation is observed in the case of tertiary and benzylic compounds. The rate determining step is the formation of the -complex by the reaction of the initial complex (electrophile) and the aromatic ring; this step disrupts the aromaticity of the substrate. In the last step of the mechanism a proton is lost and the aromaticity is reestablished.



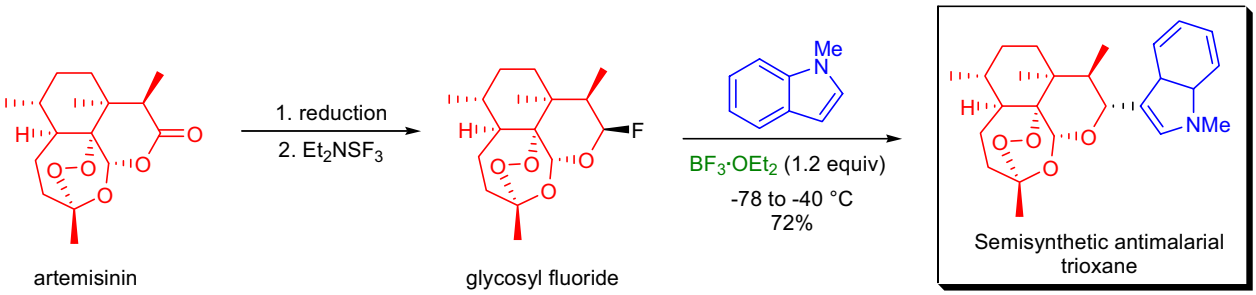
FRIEDEL-CRAFTS ALKYLATION

Synthetic Applications:

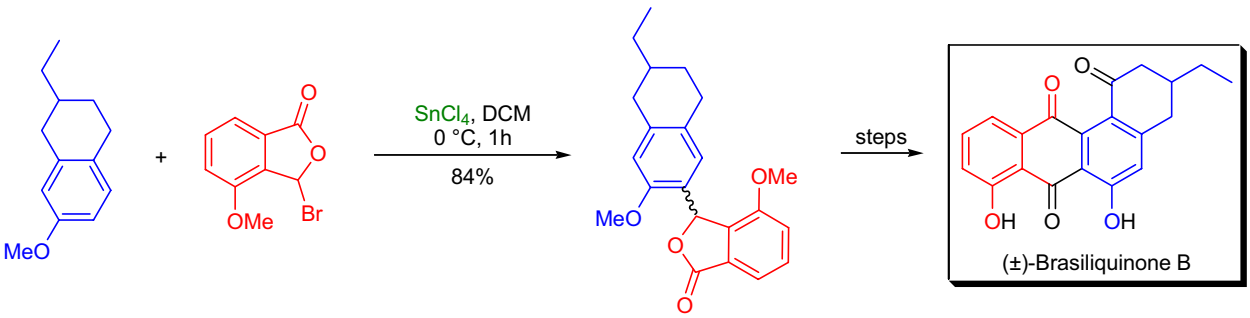
S. L. Schreiber et al. carried out the total synthesis of the potent cytotoxin (±)-tri-*O*-methyl dynemicin A methyl ester.[55] The key step was a *regioselective Friedel-Crafts alkylation* of an extremely sensitive aromatic enediyne with 3-bromo-4,7-dimethoxyphthalide. The coupling of these two fragments took place in the presence of silver triflate at 0 °C in 1 minute, and after methylation, gave a 1:1 mixture of diastereomers in 57% yield.



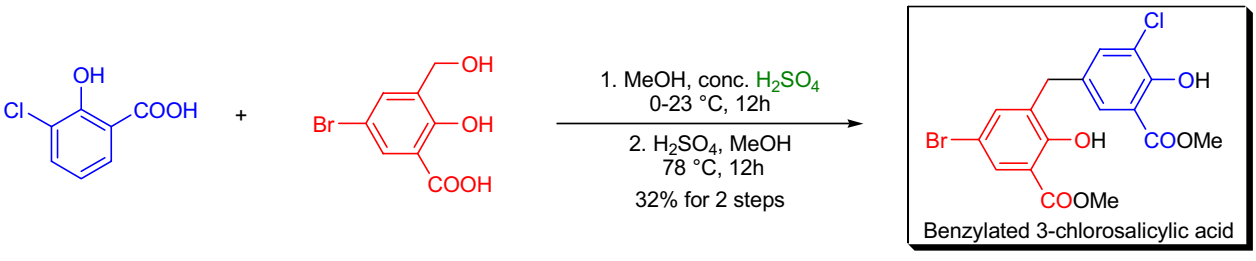
In the laboratory of G.A. Posner, semisynthetic antimalarial trioxanes in the artemisinin family were prepared *via* an efficient *Friedel-Crafts alkylation* using a pyranosyl fluoride derived from the natural trioxane lactone artemisinin.[56] The alkylating agent, pyranosyl fluoride, was prepared from the lactone in two steps: reduction to the lactol followed by treatment with diethylaminosulfur trifluoride. The highly chemoselective alkylation was promoted by $BF_3{\cdot}OEt_2$ and several electron-rich aromatic and heteroaromatic compounds were alkylated in moderate to high yield using this method.



The first total synthesis of (±)-brasiliquinone B was accomplished by V.H. Deshpande and co-workers starting from 7-methoxy-1-tetralone.[57] The key step of their synthesis was the *Friedel-Crafts alkylation* of 2-ethyl-7-methoxytetralin with 3-bromo-4-methoxyphthalide in the presence of tin tetrachloride.



During the synthesis of anti-HIV cosalane analogues, M. Cushman et al. attached substituted benzoic acid rings to the pharmacophore through methylene and amide linkers.[58] In order to assemble a complex highly substituted benzophenone derivative, 3-chlorosalicylic acid had to be benzylated. A substituted benzyl alcohol was chosen as the alkylating agent and the benzylation proceeded smoothly in methanol using sulfuric acid as the catalyst.



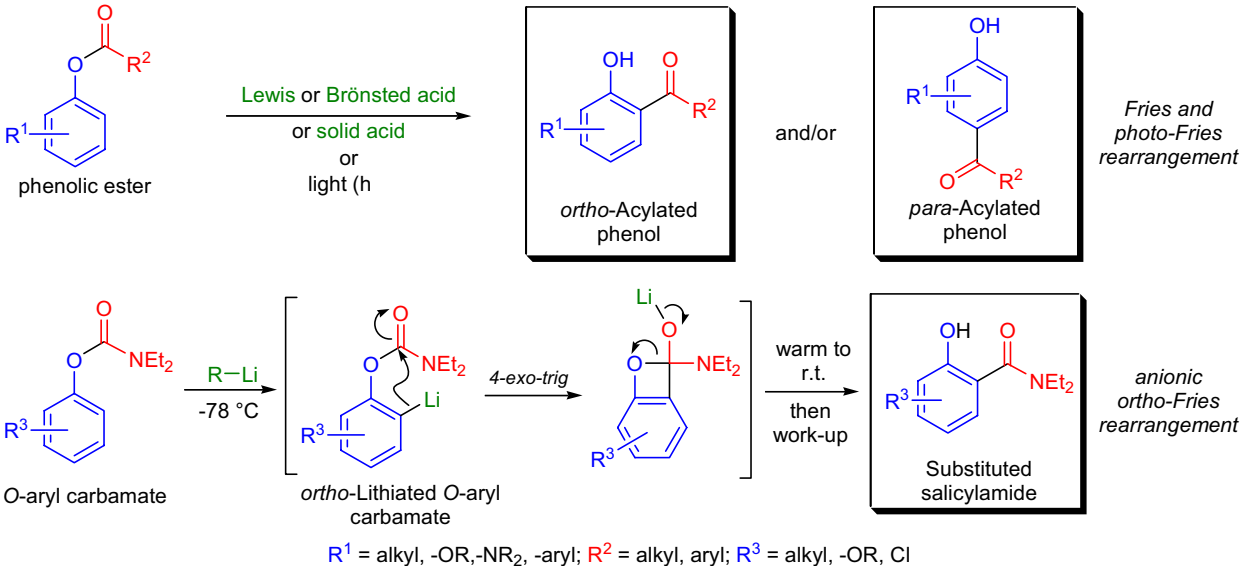
FRIES-, PHOTO-FRIES, AND ANIONIC ORTHO-FRIES REARRANGEMENT

(References are on page 590)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-14]*; Modifications & Improvements*[15-31]*; Theoretical Studies*[32-38]]

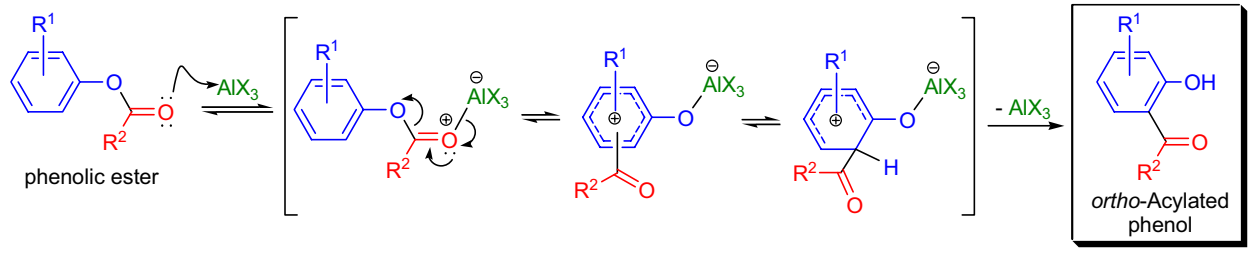
In the early 1900s, K. Fries and co-workers reacted phenolic esters of acetic and chloroacetic acid with aluminum chloride and isolated a mixture of *ortho*- and *para*-acetyl- and chloroacetyl phenols.[3,4] Reports in the literature described similar rearrangements in the presence of Lewis acids during the late 1800s,[1,2] but Fries was the one who recognized that the rearrangement of phenolic esters was general. In his honor the conversion of phenolic esters to the corresponding *ortho* and/or *para* substituted phenolic ketones and aldehydes, in the presence of Lewis or Brönsted acids is called the *Fries rearrangement*. The *Fries rearrangement* has the following general features: 1) usually it is carried out by heating the phenolic ester to high temperatures (80-180 °C) in the presence of at least one equivalent of Lewis acid or Brönsted acid (e.g., HF, $HClO_4$, PPA); 2) the reaction time can vary between a few minutes and several hours; 3) Lewis acids that catalyze the *Friedel-Crafts acylation* are all active but recently solid acid catalysts (e.g., zeolites, mesoporous molecular sieves) and metal triflates have also been used;[12,30] 4) the rearrangement is general for a wide range of structural variation in both the acid and phenol component of phenolic esters; 5) yields are the highest when there are electron-donating substituents on the phenol, while electron-withdrawing substituents result in very low yields or no reaction; 6) with polyalkylated phenols alkyl migration is often observed under the reaction conditions; 7) the *Friedel-Crafts acylation* of phenols is usually a two-step process: formation of a phenolic ester followed by a *Fries rearrangement*; 8) the selectivity of the rearrangement to give *ortho*- or *para*- substituted products largely depends on the reaction conditions (temperature, type, and amount of catalyst, solvent polarity, etc.); 9) at high temperatures without any solvent the *ortho*-acylated product dominates while low temperatures favor the formation of the *para*-acylated product; 10) with increasing solvent polarity the ratio of the *para*-acylated product increases; and 11) optically active phenolic esters rearrange to optically active phenolic ketones. There are two main variants of the *Fries rearrangement*: 1) upon irradiation with light phenolic esters undergo the same transformation, which is known as the *photo-Fries rearrangement*;[8,11] and 2) an *anionic ortho-Fries rearrangement* takes place when *ortho*-lithiated *O*-aryl carbamates undergo a facile *intramolecular [1,3]-acyl migration* to give substituted salicylamides at room temperature.[17,27]



R^1 = alkyl, -OR,-NR_2, -aryl; R^2 = alkyl, aryl; R^3 = alkyl, -OR, Cl

Mechanism:[39-49,11,50]

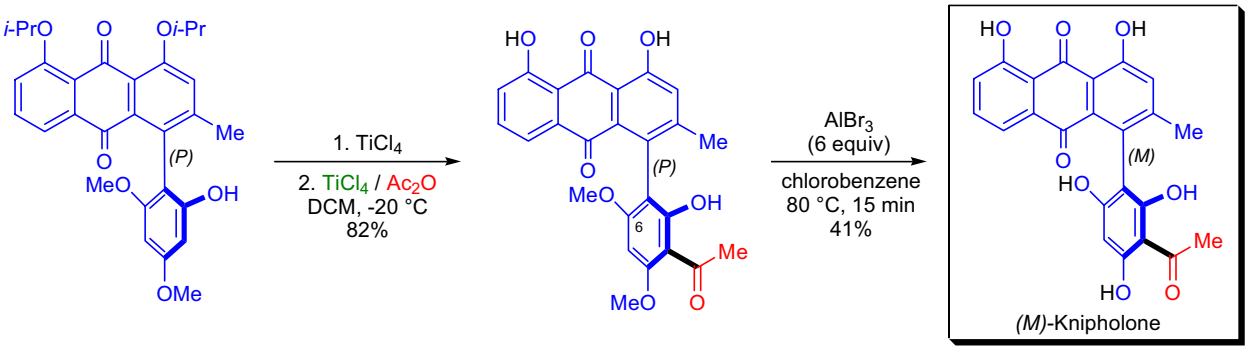
The *Fries rearrangement* proceeds *via* ionic intermediates but the exact mechanistic pathway (whether it is inter- or intramolecular) is still under debate. There are many reports in the literature that present evidence to support either of the pathways, but it appears that the exact route depends on the structure of the substrates and the reaction conditions. The scheme depicts the formation of an *ortho*-acylated phenol from a substituted phenolic ester in the presence of aluminum trihalide catalyst. The *photo-Fries rearrangement* proceeds *via* radical intermediates.[11,50,13]



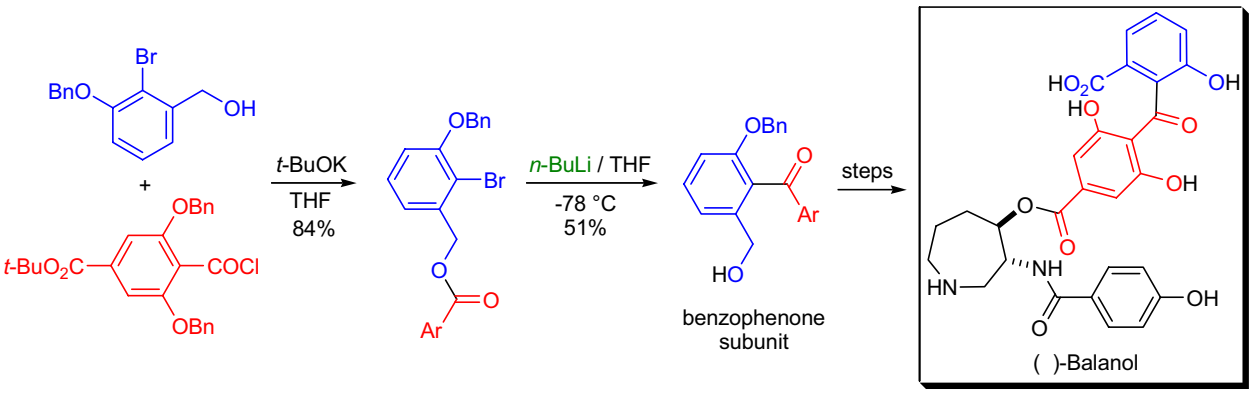
FRIES-, PHOTO-FRIES, AND ANIONIC ORTHO-FRIES REARRANGEMENT

Synthetic Applications:

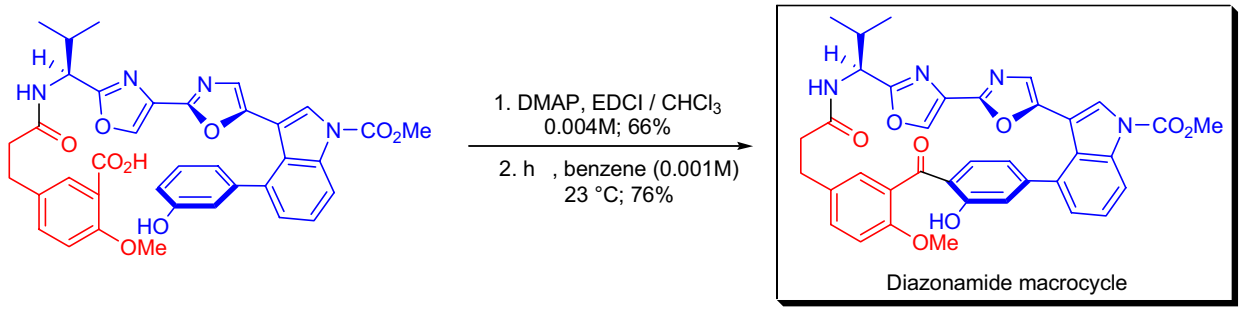
The first atropo-enantioselective total synthesis of a phenylanthraquinone natural product (*M*)-knipholone was reported by G. Bringmann et al.[51] In the late stages of the synthesis, an acetyl group had to be introduced under mild conditions. The advanced substituted anthraquinone intermediate was first deprotected with $TiCl_4$ and then acylated with Ac_2O in the presence of $TiCl_4$. A spontaneous *Fries-rearrangement* took place to afford the *ortho*-acylated product in high yield. The natural product was obtained by a mono *O*-demethylation at C6 with $AlBr_3$.



The total synthesis of the potent protein kinase C inhibitor (–)-balanol was accomplished by J.W. Lampe and co-workers.[52] They took advantage of the *anionic homo-Fries rearrangement* to prepare the sterically congested benzophenone subunit. To this end, 2-bromo-3-benzyloxy benzyl alcohol was first acylated with a 1,3,5-trisubstituted benzoyl chloride to obtain the ester precursor in 84% yield. Next, the ester was treated with *n*-BuLi at -78 °C to perform a metal-halogen exchange. The resulting aryllithium rapidly underwent the *anionic homo-Fries rearrangement* to afford the desired tetra *ortho*-substituted benzophenone in 51% yield.



Research in the laboratory of P. Magnus showed that the macrocyclic skeleton of diazonamide could be synthesized with the use of *macrolactonization* followed by a *photo-Fries rearrangement*.[53] First, the aromatic carboxylic acid and the phenol were coupled with EDCI to form the macrolactone (phenolic ester), which was then exposed to light at high-dilution to cleanly afford the macrocyclic *ortho*-acylated phenol skeleton of diazonamide.



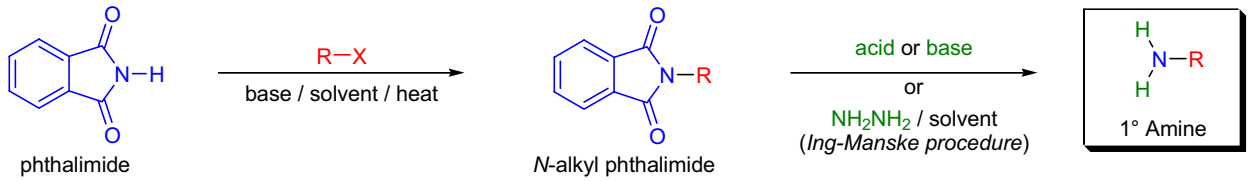
GABRIEL SYNTHESIS

(References are on page 592)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-4]; *Modifications & Improvements*[5-16]]

The mild, two-step preparation of primary amines from the corresponding alkyl halides, in which potassium phthalimide is first alkylated and the resulting *N*-alkylphthalimide is subsequently hydrolyzed, is known as the *Gabriel synthesis*. Alkylation of phthalimide with simple alkyl halides was first reported in 1884,[17] but it was not until 1887 when S. Gabriel recognized the generality of the process and came up with the two-step procedure for the synthesis of primary amines.[1] The alkylation reaction can be conducted in the absence or in the presence of a solvent.[2] The best solvent is DMF (good for S_N2 reactions), but DMSO, HMPA, chlorobenzene, acetonitrile, and ethylene glycol can also be used. The following alkylating agents give good to excellent yields during the preparation of the required *N*-alkylphthalimides: 1) sterically unhindered 1°and 2° alkyl halides give the best results with alkyl iodides being the most reactive (I > Br > Cl) followed by allylic, benzylic, and propargylic halides; 2) alkyl sulfonates (mesylates, tosylates) often give higher yields than the alkyl halides and are easier to obtain; 3) α-halo ketones, esters, nitriles, and β-keto esters (e.g., diethyl bromomalonate);[18,19] 4) *O*-alkylisoureas;[20] 5) alkoxy- and alkylthiophosphonium salts;[21] 6) 1°and 2° alcohols under the *Mitsunobu reaction* conditions (DEAD/Ph_3P/phthalimide);[12] 6) aryl halides with several electron-withdrawing groups (S_NAr reaction to prepare 1° arylamines); 7) aryl halides in the presence of Cu(I) catalysts;[6,9] 8) epoxides and aziridines (preparation of amino alcohols and diamines);[22,23] and 9) α,β-unsaturated compounds undergo facile *Michael-addition* by the phthalimide anion.[24] The original *Gabriel synthesis* had the following problems that limited its widespread application: 1) when the potassium phtalimide and the alkyl halide required high temperatures (120-240 °C) without a solvent, heat sensitive substrates could not be used; 2) the hydrolysis was usually carried out with a strong acid (e.g., H_2SO_4, HBr, HI) at high temperatures therefore substrates containing acid-sensitive functionalities were excluded; and 3) strong alkaline hydrolysis was also used and was incompatible with base-sensitive functional groups. In 1926, H.R. Ing and R.H.F. Manske came up with a modification by introducing hydrazine hydrate in refluxing ethanol for the cleavage of the *N*-alkylphthalimide under mild and neutral conditions (*Ing-Manske procedure*).[5] During the past century, several other modifications of the original procedure were introduced: 1) novel Gabriel reagents (replacement of phthalimide with other nitrogen sources) to achieve milder deprotection conditions;[4] 2) addition of catalytic amounts of a crown ether or a cryptand to the reaction mixture of alkyl halides with potassium phthalimide gives almost quantitative yields;[8,10] and 3) the use of $NaBH_4$ in isopropanol for the exceptionally mild cleavage of the phthalimide.[11] A related process is the *Gabriel-malonic ester synthesis* in which the anion of diethyl phthalimidomalonate is alkylated and after hydrolysis/decarboxylation an amino acid is obtained.[19]

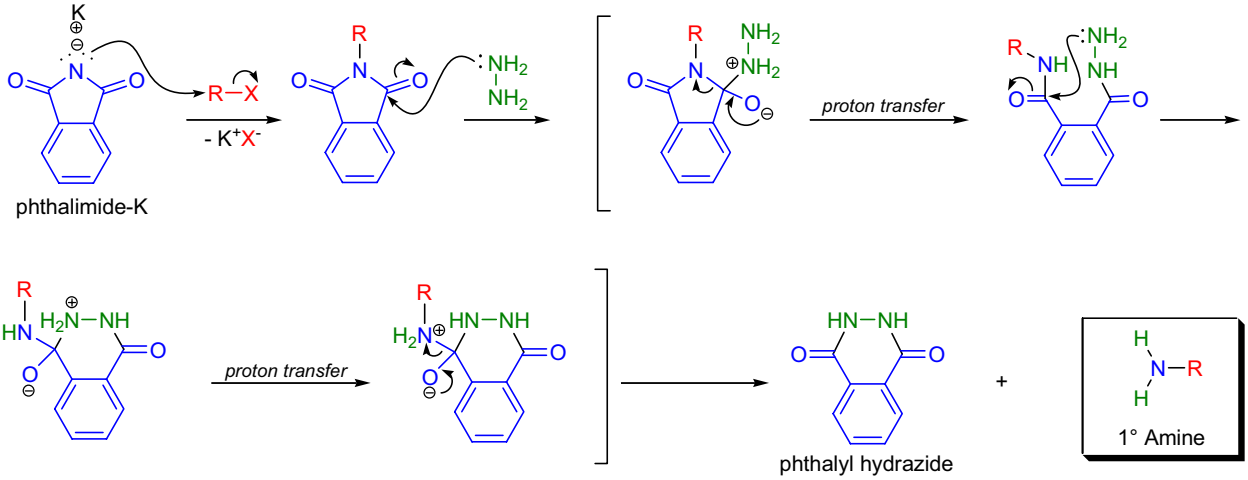


phthalimide *N*-alkyl phthalimide

X = halogen, OTf, OMs, etc.; R = 1°, 2° alkyl, allylic, benzylic, etc.

Mechanism:[2,15]

The first step of the *Gabriel synthesis*, the alkylation of potassium phthalimide with alkyl halides, proceeds *via* an S_N2 reaction. The second step, the hydrazinolysis of the *N*-alkylphthalimide, proceeds by a nucleophilic addition of hydrazine across one of the carbonyl groups of the phthalimide. Subsequently, the following steps occur: ring-opening then proton-transfer followed by an intramolecular S_NAc reaction, another proton-transfer and finally, the breakdown of the tetrahedral intermediate to give the desired primary amine and the side product phthalyl hydrazide.

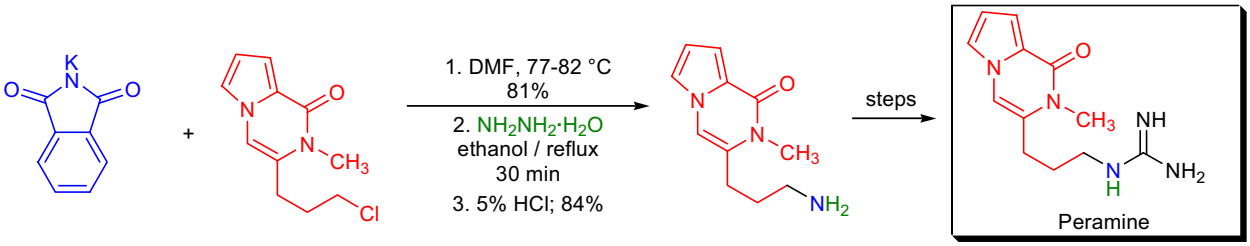


phthalimide-K phthalyl hydrazide

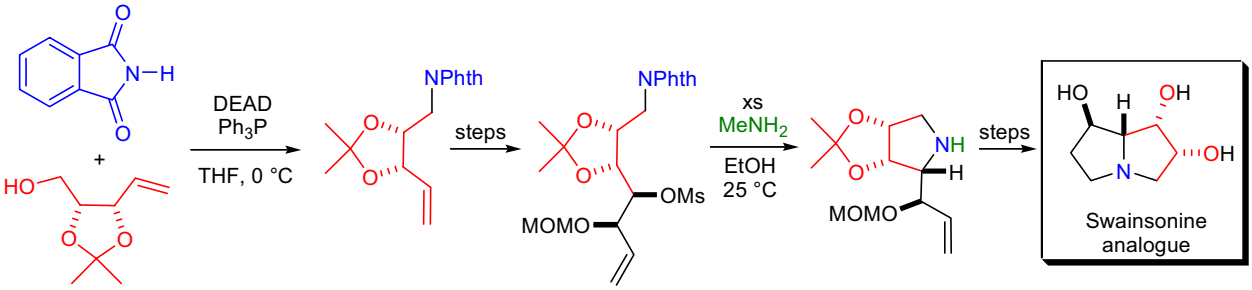
GABRIEL SYNTHESIS

Synthetic Examples:

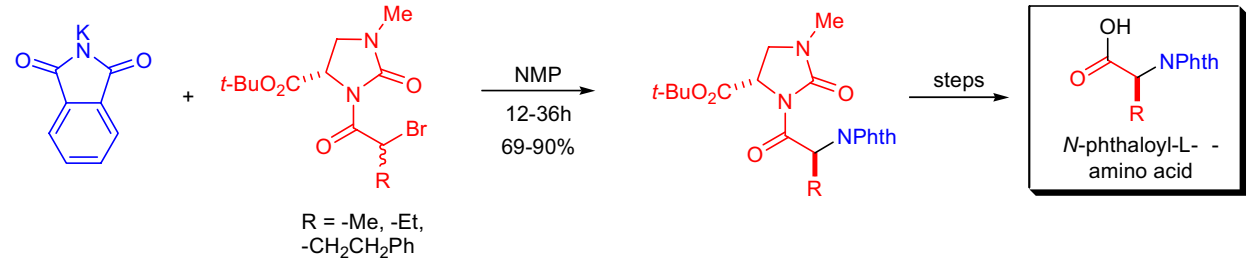
The total synthesis of the insect feeding deterrent peramine was accomplished by D.J. Dumas at du Pont laboratories.[25] The *Gabriel synthesis* was successfully employed in the last steps of the synthesis. The primary alkyl chloride was treated with potassium phthalimide in DMF at 77-82 °C for 1.5h. The resulting *N*-alkylphthalimide was cleaved in high yield using the *Ing-Manske procedure*.



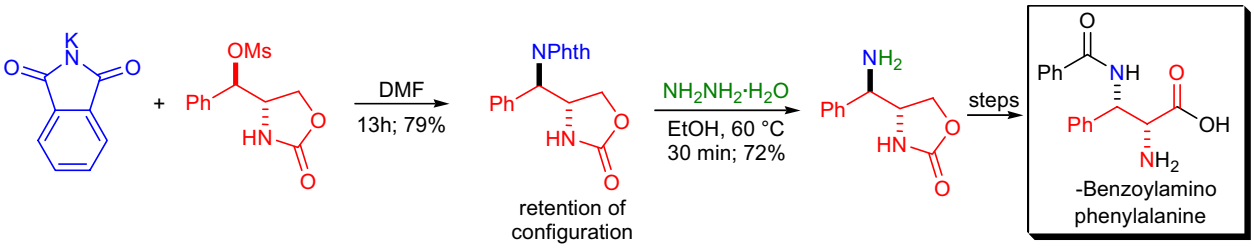
During the synthesis of swainsonine- and castanospermine analogues (amino sugars), K. Burgess et al. introduced the nitrogen atom by replacing a primary hydroxyl group using phthalimide under the *Mitsunobu reaction conditions*.[26] The phthalyl group was not immediately removed but carried over several steps. Interestingly, deprotection with hydrazine was not compatible with the terminal alkene functionality due to significant hydrogenation of the double bond by the *in situ* formed diimide. Using methylamine instead of hydrazine cleanly afforded the deprotected primary amine that readily displaced a secondary mesylate to form a substituted pyrrolidine ring.



A dynamic kinetic resolution was utilized for the highly stereoselective *Gabriel synthesis* of -amino acids by K. Nunami and co-workers.[27] The substrate, *t*-butyl-(4*S*)-1-methyl-3-2-(bromoalkanoyl)-2-oxoimidazolidine-4-carboxylate, smoothly reacted with potassium phthalimide at room temperature to give only one diastereomer in good yield. The removal of the chiral auxiliary afforded an *N*-phthaloyl-L- -amino acid.



The preparation of vicinal diamines in an enantioselective fashion is a challenging task. F.M. Rossi et al. undertook the synthesis of a -benzoylamino-phenylalanine (2,3-diamino acid), which is an analogue of the taxol side chain.[28] During their synthetic studies, the secondary alcohol of an enantiopure oxazolidinone was mesylated and displaced by potassium phthalimide in DMF. Interestingly, there was a net retention of configuration due to neighboring group participation by the oxazolidinone nitrogen atom. For this reason, the authors later decided to displace the mesylate with NaN_3 and to protect the oxazolidinone nitrogen with a TMS group to avoid participation.



GATTERMANN AND GATTERMANN-KOCH FORMYLATION

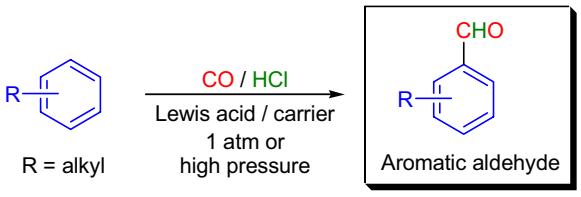
(References are on page 592)

Importance:

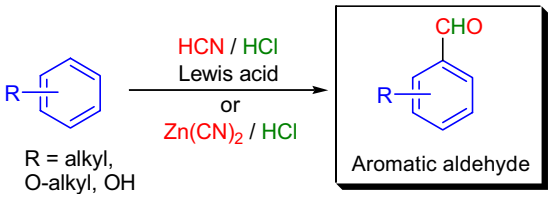
[*Seminal Publications*[1-3]*; Reviews*[4-8]*; Modifications & Improvements*[9-13]*; Theoretical Studies*[14,15]]

In 1897, L. Gattermann and J.A. Koch successfully introduced a formyl group (CHO) on toluene by using formyl chloride (HCOCl) as the acylating agent under *Friedel-Crafts acylation* conditions.[1] Although the researchers were not able to prepare the acid chloride, they assumed that by reacting carbon monoxide (CO) with hydrogen chloride (HCl), formyl chloride would be formed *in situ*, and in the presence of catalytic amounts of $AlCl_3$-Cu_2Cl_2 formylation of the aromatic ring would occur. The introduction of a formyl group into electron rich aromatic rings by applying CO/HCl/Lewis acid catalyst (AlX_3, FeX_3, where X = Cl, Br, I) to prepare aromatic aldehydes is known as the *Gattermann-Koch formylation*. The general features of this formylation reaction are: 1) at atmospheric pressure activated aromatic compounds can be used as substrates (e.g., alkylbenzenes); 2) at high CO pressure (100-250 atm) the reaction rate increases significantly and even non-activated aromatics (chlorobenzene, benzene) can be formylated; 3) deactivated aromatic compounds (having *meta*-directing substituents) cannot be formylated with this method; 4) a carrier/activator (Cu_2Cl_2, $TiCl_4$ or $NiCl_2$) for the catalyst is necessary at atmospheric pressure; however, no activator is needed at high pressure; 5) the amount and purity of the catalyst is very important and often a full equivalent of catalyst is needed; 6) monosubstituted substrates are formylated almost exclusively at the *para* position, but when there is already a *para* substituent present in the substrate, the formyl group is introduced at the *ortho* position; 7) just as in the *Friedel-Crafts reactions*, alkyl migration occurs with highly alkylated aromatic substrates; and 8) the need for high pressures renders this method mainly useful to industrial applications. The scope of the *Gattermann-Koch reaction* in terms of suitable substrates is also limited, since it is mostly restricted to alkylbenzenes. Gattermann introduced a modification where HCN is mixed with HCl in the presence of $ZnCl_2$ to formylate phenols, phenolic ethers and heteroaromatic compounds (e.g., pyrroles and indoles). This modification is called the *Gattermann formylation* (or *Gattermann synthesis*).[2,3] The main drawback of the *Gattermann formylation* was that it called for the use of anhydrous HCN, which is a very toxic compound. To avoid the handling of HCN, R. Adams generated it *in situ* along with $ZnCl_2$ by reacting $Zn(CN)_2$ with HCl in the presence of the aromatic substrate (*Adams modification*).[10] This method has since become the most widely used variant in organic synthesis. Other modifications used NaCN and CNBr successfully instead of HCN.[9] A serious limitation of both title reactions is that they cannot be used for the formylation of aromatic amines due to numerous side reactions.

Gattermann-Koch Formylation:



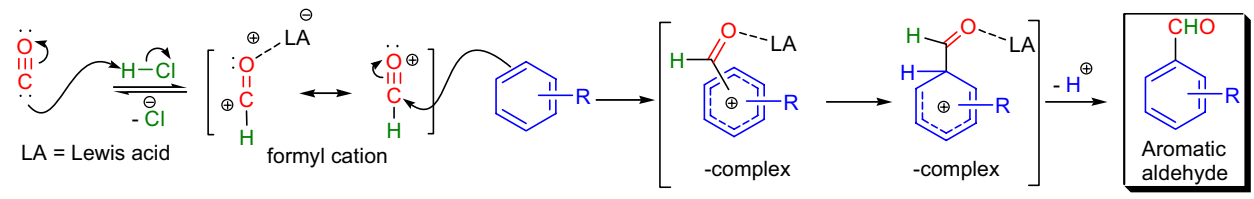
Gattermann Formylation:



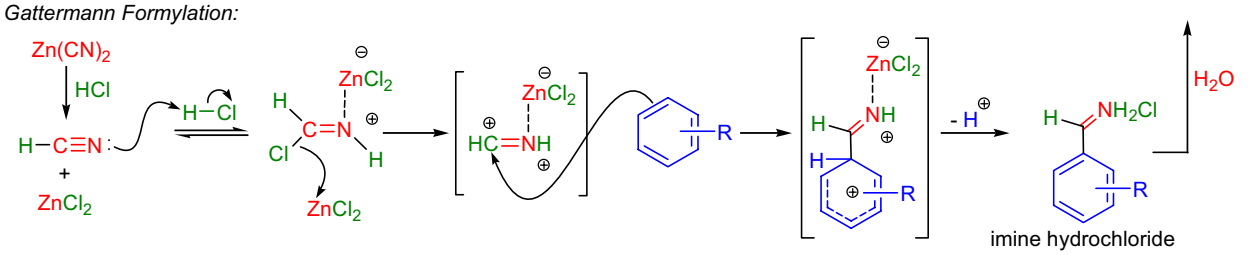
Mechanism:[16-23]

The mechanisms of the *Gattermann* and *Gattermann-Koch formylation* belong to the category of electrophilic aromatic substitution (S_EAr) but are not known in detail, since they have a tendency to vary from one substrate to another, and the reaction conditions may also play a role. When carbon monoxide is used, the electrophilic species is believed to be the formyl cation, which is attacked by the aromatic ring to form a -complex. This -complex is then converted to the aromatic aldehyde upon losing a proton. When HCN is used, the initial product after the S_EAr reaction is an imine hydrochloride, which is subsequently hydrolyzed to the product aldehyde.

Gattermann-Koch Formylation:



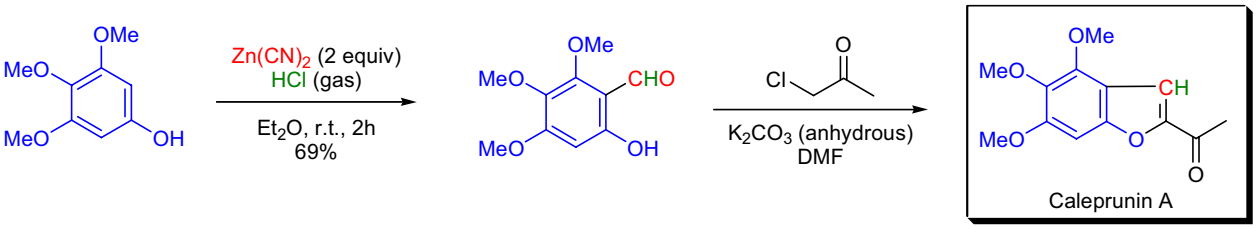
Gattermann Formylation:



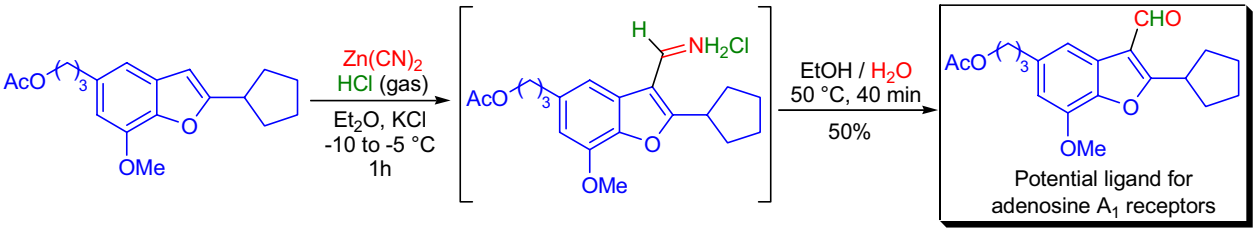
GATTERMANN AND GATTERMANN-KOCH FORMYLATION

Synthetic Applications:

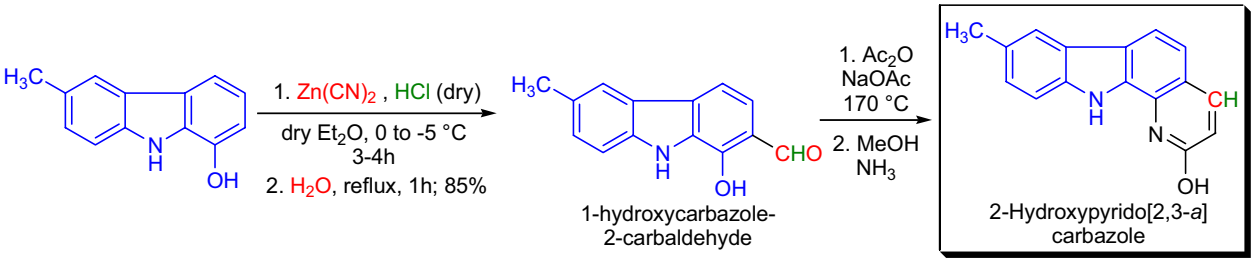
The benzofuran-derived natural product caleprunin A was synthesized by R. Stevenson et al. using the *Gattermann formylation* as the key step.[24] The starting 3,4,5-trimethoxyphenol was suspended with $Zn(CN)_2$ in ether and dry HCl gas was bubbled through the reaction mixture at room temperature for 2h. The solvent was decanted, water was added and the mixture was heated for 15 minutes. The natural product was obtained by reacting the benzaldehyde derivative with chloroacetone in DMF in the presence of anhydrous K_2CO_3.



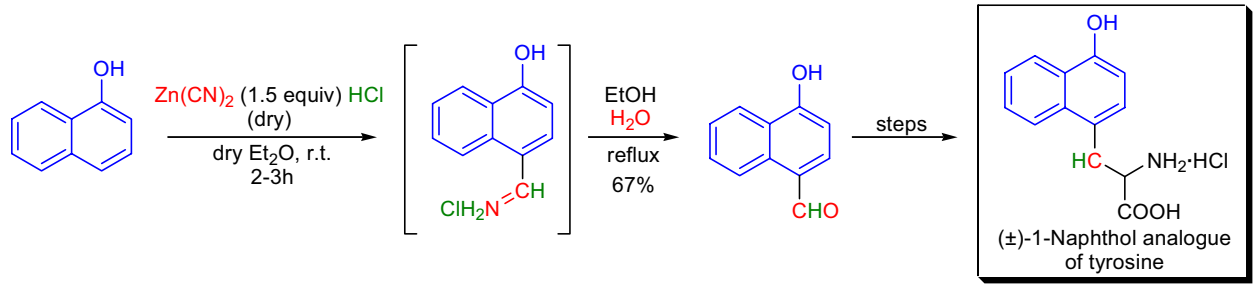
The regiospecific introduction of the formyl group into the C3 postion of 2,5-dialkyl-7-methoxy-benzo[*b*]furans was achieved by H.N.C. Wong and co-workers by using the *Adam's modification of the Gattermann formylation*.[25] A potential ligand for adenosine A_1 receptors was prepared from 2-cyclopentyl-5-(3-hydroxypropyl)-7-methoxy-benzo[*b*]furan in 50% yield by bubbling HCl gas through its etheral solution containing $Zn(CN)_2$ at -10 °C for 1h. The resulting imine hydrochloride was hydrolyzed with a water-ethanol mixture at 50 °C.



Compounds containing the pyridocarbazole ring are known to have DNA intercalating properties and therefore they are potent antitumor agents. For example, several syntheses of pyrido[2,3-*a*]carbazole derivatives have been published, but these methods are often lengthy and low-yielding. R. Prasad and co-workers synthesized 2-hydroxypyrido[2,3-a]carbazoles starting from 1-hydroxycarbazoles.[26] The key transformation was the *Gattermann formylation* of 1-hydroxycarbazoles to obtain 1-hydroxycarbazole-2-carbaldehydes, from which the target compounds could be obtained *via* a *Perkin reaction*.



Certain aromatic analogues of natural amino acids can be used as potential fluorescent probes of peptide structure and dynamics in complex environments. The research team of M.L. McLaughlin undertook the gram scale synthesis of racemic 1- and 2-naphthol analogues of tyrosine.[27] The synthesis of the 1-naphthol tyrosine analogue started with the *Gattermann formylation* of 1-naphthol using the *Adams modification* to afford the formylated product 4-hydroxy-1-naphthaldehyde in 67% yield.



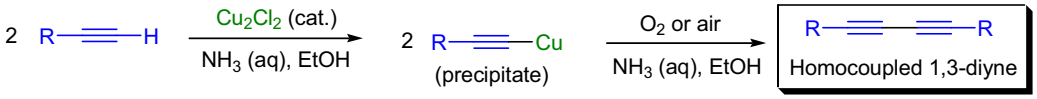
GLASER COUPLING

(References are on page 593)

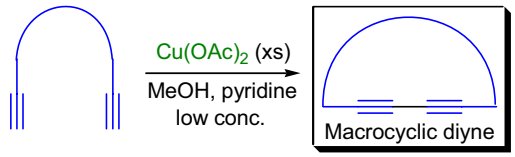
Importance:

[*Seminal Publication*[1]; *Reviews*[2-9]; *Modifications & Improvements*[10-16]]

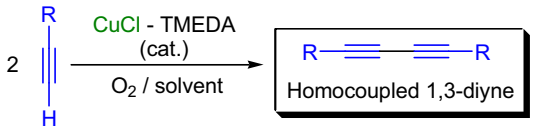
In 1869, C. Glaser discovered that when phenylacetylene was treated with a copper(I)-salt in the presence of aqueous ammonia, a precipitate formed, which after air oxidation yielded a symmetrical compound, 1,4-diphenyl-1,3-butadiyne (diphenyldiacetylene).[1] The preparation of symmetrical conjugated diynes and polyynes (linear or cyclic) by the oxidative homocoupling of terminal alkynes in the presence of copper salts is known as the *Glaser coupling*. There are numerous versions of the original procedure developed by Glaser, and these differ mainly in the type and amount of oxidants used: 1) besides oxygen and air, $CuCl_2$ and $K_3Fe(CN)_6$ are used most often as oxidizing agents; 2) Glaser's procedure was heterogeneous and slow, but G. Eglinton and A.R. Galbraith showed that using $Cu(OAc)_2$ in methanolic pyridine made the process homogeneous and faster (*Eglinton procedure*). This method was successfully applied to the synthesis of macrocyclic diynes;[10] and 3) A.S. Hay used tertiary amines such as pyridine or the bidentate ligand TMEDA as complexing agents to solubilize the $Cu^{(I)}$-salt. Next, oxygen gas was passed through this solution to give the homocoupled product in a few minutes at room temperature in almost quantitative yield (*Hay coupling conditions*).[11,12] General features of the *Glaser coupling* and related methods are: 1) it works well for acidic terminal alkynes, but the yield tends to drop when the alkyne is less acidic (e.g., alkyl- or silicon-substituted terminal alkynes); 2) the reaction rate is often increased when a small amount of DBU, which most likely serves as a strong base to deprotonate the alkyne, is added to the reaction mixture;[7] 3) the reaction conditions tolerate a wide range of functional groups as the oxidation is mostly restricted to the triple bond; 4) if the reactants or the product is oxygen sensitive, side reactions can be minimized by either running the reaction for shorter periods of time or applying an inert atmosphere and using large amounts of the $Cu^{(II)}$-salt; 5) the yield of the coupling of heterocyclic alkynes strongly depends on the solvent used, and DME was found to be the best; 6) for oligomerization reactions, *o*-dichlorobenzene is the best solvent; and 7) besides using common solvents, recent modifications employed supercritical CO_2 and ionic liquids for the couplings.[13,16] The *Glaser coupling* is not well-suited for the preparation of unsymmetrical diynes. Therefore, other methods were developed using both oxidative and non-oxidative conditions: 1) the *Chodkiewitz-Cadiot reaction* couples a terminal alkyne with a 1-bromoalkyne in the presence of a copper(I)-salt and an aliphatic amine (e.g., $EtNH_2$);[17-19] 2) copper(I)- and cobalt(I)-salts are efficient catalysts for the coupling of alkynyl Grignard derivatives with 1-haloalkynes;[4] and 3) $Pd^{(0)}$-catalyzed coupling of terminal alkynes with 1-iodoalkynes in the presence of a $Cu^{(I)}$-salt is also successful.[20]



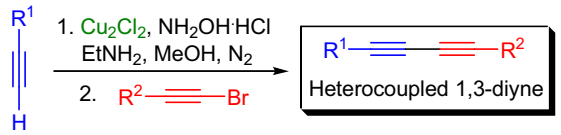
Eglinton procedure:



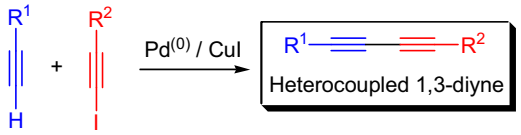
Hay's conditions:



Chodkiewitz-Cadiot heterocoupling:

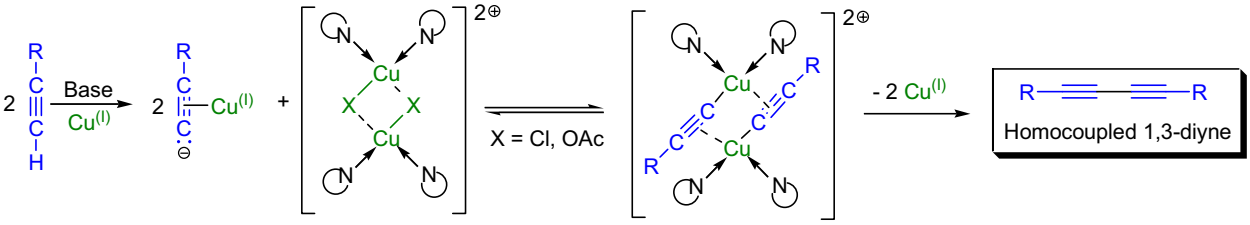


Pd-catalyzed heterocoupling:



Mechanism:[21-29]

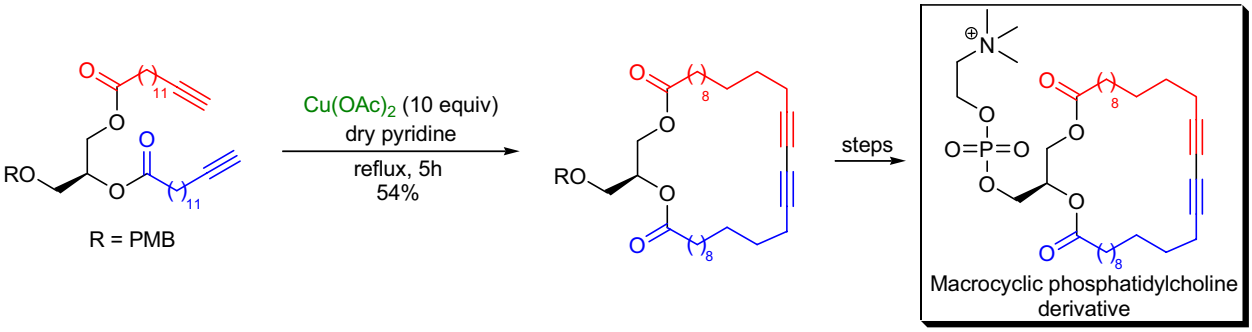
The mechanism of the *Glaser coupling* and related methods is very complex and is not fully understood. Studies revealed that the mechanism is highly dependent on the experimental conditions. The early proposal involving a radical mechanism has been rejected. The currently accepted mechanism involves dimeric copper(II)acetylide complexes.



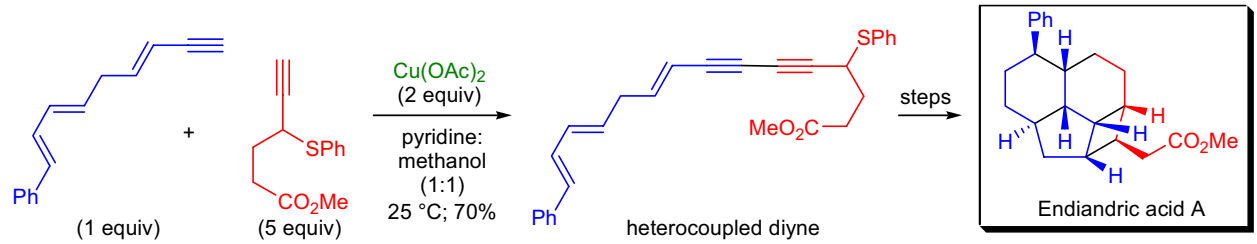
GLASER COUPLING

Synthetic Applications:

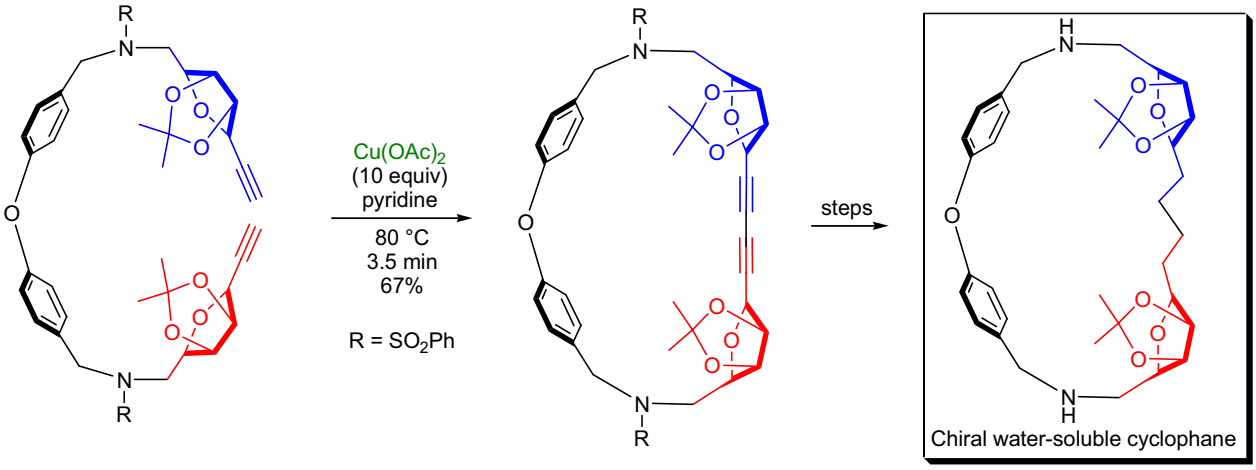
Novel polymerizable phosphatidylcholines were successfully synthesized by the research team of G. Just.[30] To prepare a 32-membered macrocyclic diyne, the *Eglinton modification* of the *Glaser coupling* was utilized. The diester-diyne starting material was slowly added to a refluxing solution containing 10 equivalents of cupric acetate in dry pyridine. The macrocycle was isolated in 54% yield after column chromatography.



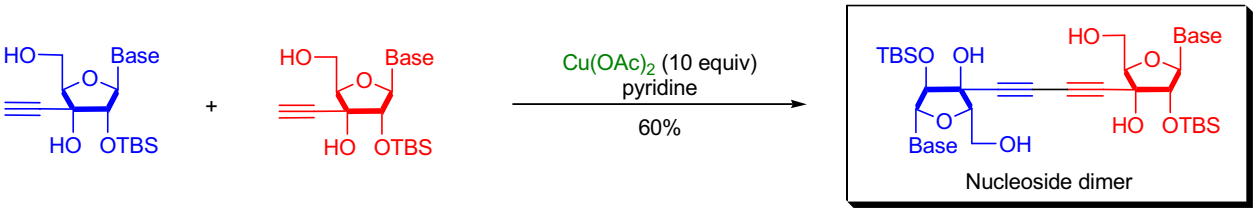
During the biomimetic total synthesis of endiandric acids A-G by K.C. Nicolaou and co-workers, the key polyunsaturated precursor was assembled *via* the *Glaser coupling* of two different terminal alkynes.[31-34] One of the alkynes was used in excess so the yield of the heterocoupled diyne could be maximized. In a solvent mixture of pyridine:methanol (1:1), the two reactant alkynes were treated with $Cu(OAc)_2$ at 25 °C to provide the desired diyne in 70% yield.



C.S. Wilcox and his research team designed and synthesized chiral water-soluble cyclophanes based on carbohydrate precursors.[35] These compounds are also dubbed as “glycophanes” and they are potentially valuable enzyme models. The key macrocyclization step utilized the *Glaser coupling* and the reaction was carried out in a thermal flow reactor at 80 °C in 67% yield.



Nucleoside dimers linked by the butadiynediyl group were prepared by A. Burger et al. using the *Eglinton modification* of the *Glaser coupling via* dimerization of 3' -C-ethynyl nucleosides.[36]



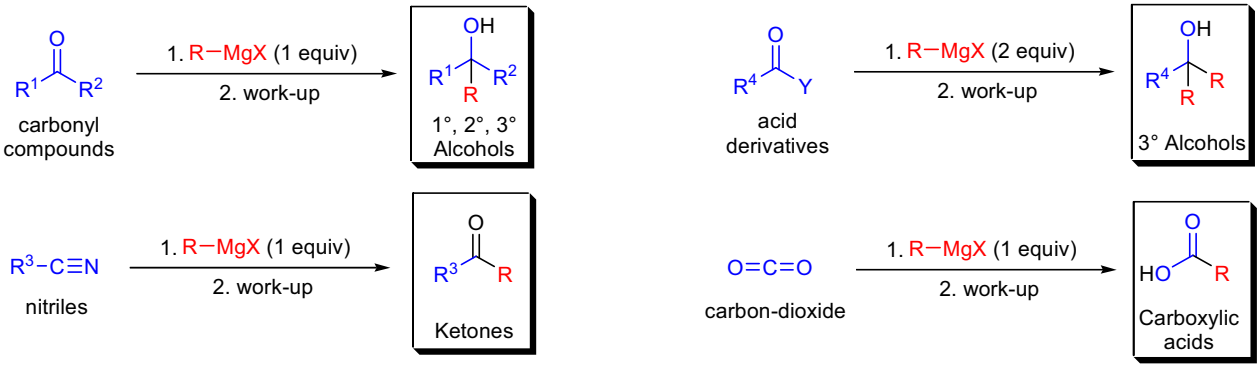
GRIGNARD REACTION

(References are on page 593)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-17]; *Modifications and Improvements*;[18-20] *Theoretical Studies*[21-26]]

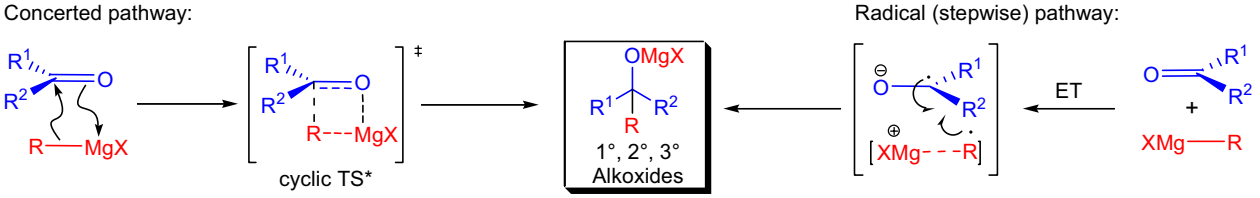
In 1900, V. Grignard reported that an alkyl halide (RX) reacts with magnesium metal (Mg) in diethyl ether to give a cloudy solution of an organomagnesium compound (RMgX), which upon reaction with aldehydes and ketones afforded secondary and tertiary alcohols, respectively.[1] These organomagnesium compounds are called *Grignard reagents*, and their addition across carbon-heteroatom multiple bonds is referred to as the *Grignard reaction*. Soon after its discovery, the *Grignard reaction* became one of the most versatile C-C bond forming tools. The general features of Grignard reagents and their reactions are: 1) the reagents are predominantly prepared by reacting alkyl, aryl, or vinyl halides with magnesium metal in aprotic nucleophilic solvents (e.g., ethers, tertiary amines); 2) the reagents are usually thermodynamically stable but air and moisture sensitive and incompatible with acidic functional groups (e.g., alcohols, thiols, phenols, carboxylic acids, 1°, 2° amines, terminal alkynes); 3) the C-Mg bond is very polar and the partial negative charge resides on the carbon atom, so Grignard reagents are excellent carbon nucleophiles (in the precursor halides the carbon has a partial positive charge so overall a reversal of polarity known as *umpolung* takes place upon formation of the reagent); 4) in most carbon-heteroatom multiple bonds the carbon atom is partially positively charged so the formation of C-C bonds with the nucleophilic Grignard reagents is straightforward; 5) addition of one equivalent of Grignard reagent followed by a work-up converts aldehydes to secondary alcohols (formaldehyde to primary alcohols), ketones to tertiary alcohols, nitriles to ketones and carbon-dioxide to acids; 6) acid derivatives react with two equivalents of Grignard reagent: esters and acyl halides (RCOX) are converted to tertiary alcohols; 7) prochiral aldehydes and ketones give rise to racemic mixtures of the corresponding alcohols upon reacting with achiral Grignard reagents, since the addition takes place on both faces of the carbonyl group; 8) chiral substrates, however, lead to diastereomeric mixtures with the predominant formation of one diastereomer as predicted by the *Felkin-Anh* or *chelation-control* models; and 9) alkyl halides can couple with Grignard reagents in a *Wurtz reaction* to give alkanes, while epoxides are opened in an S_N2 reaction at the less substituted carbon to give two-carbon homologated alcohols. Grignard reactions are often accompanied by certain side-reactions: 1) the generation of the Grignard reagent from alkyl halides can lead to undesired *Wurtz coupling* products; 2) the presence of oxygen (air) and moisture can consume some of the reagent to give alkoxides and alkanes, respectively; 3) if the carbonyl compound has a proton at the α-position, the Grignard reagent can act as a base and enolize the substrate (alkyllithium or organocerium reagents offer a solution to this problem, because they are more covalent and therefore less basic); and 4) if the reagent has a β-hydrogen and the substrate is hindered, reduction of the carbonyl group may occur by an intermolecular hydride transfer.



R^1, R^2 = alkyl, aryl, H; R^3 = alkyl, aryl; R^4 = alkyl, aryl; Y = OR, Cl, Br, I; R = alkyl, aryl; X = Cl, Br, I

Mechanism:[5,27-33,18,34]

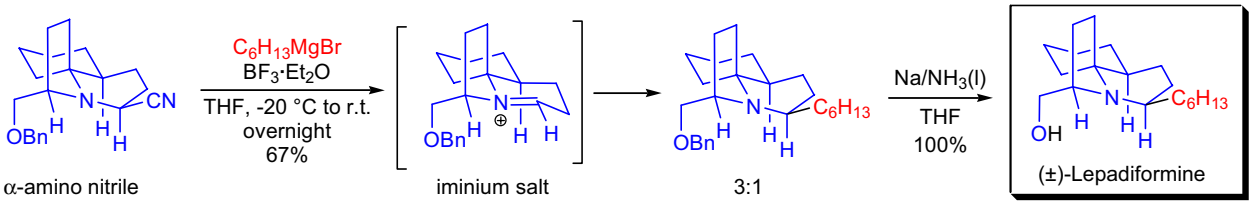
The mechanism of the formation of the Grignard reagent is most likely a single-electron-transfer (SET) process, and it takes place on the metal surface.[33] The mechanism of the addition of Grignard reagents to carbonyl compounds is not fully understood, but it is thought to take place mainly *via* either a concerted process or a radical pathway (stepwise).[5,27,29] It was found that substrates with low electron affinity react in a concerted fashion passing through a cyclic transition state. On the other hand, sterically demanding substrates and bulky Grignard reagents with weak C-Mg bonds tend to react through a radical pathway, which commences with an electron-transfer (ET) from RMgBr to the substrate.[34]



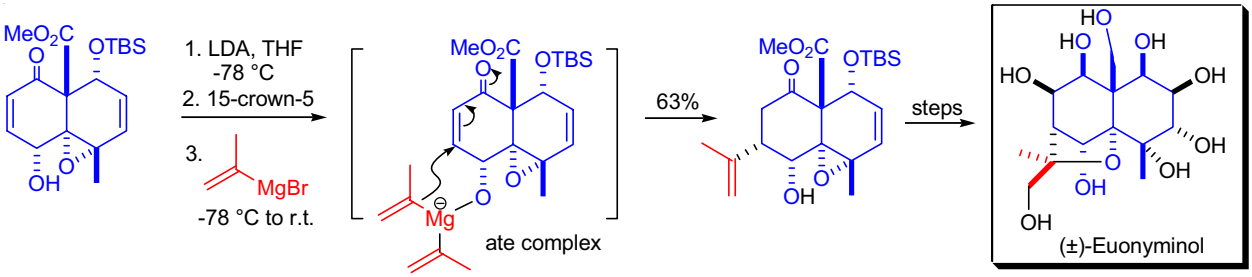
GRIGNARD REACTION

Synthetic Applications:

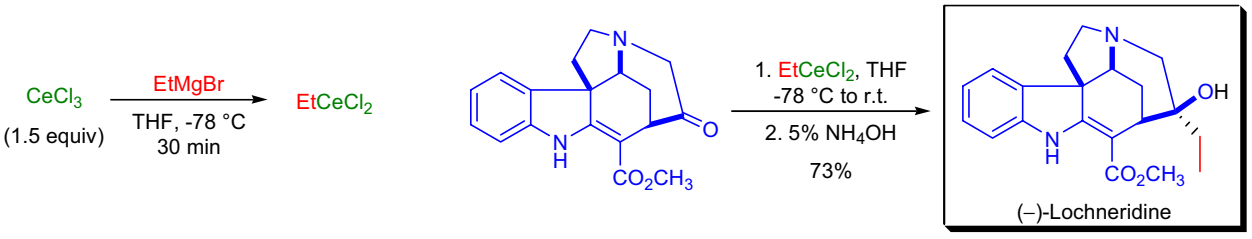
The stereoselective total synthesis of (±)-lepadiformine was accomplished in the laboratory of S.M. Weinreb.[35] The introduction of the hexyl chain in a stereoselective fashion was achieved by a *Grignard reaction* to an iminium salt during the last steps of the synthetic sequence. The iminium salt was generated *in situ* from an α-amino nitrile with boron trifluoride etherate, and the addition of hexylmagnesium bromide gave a 3:1 mixture of alkylated products favoring the desired stereoisomer. Removal of the benzyl group completed the total synthesis.



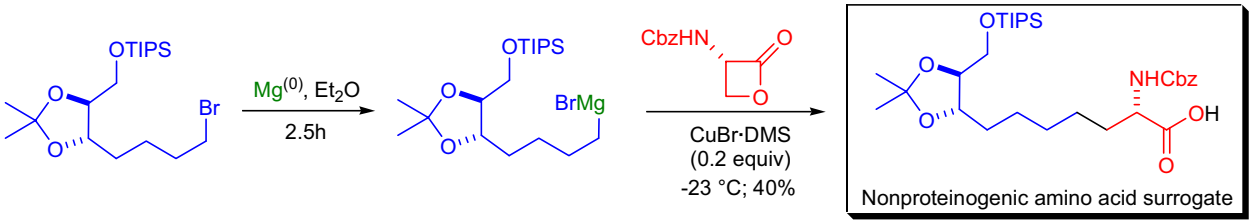
The conjugate addition of Grignard reagents to cyclic α,β-unsaturated ketones can be efficiently directed by an alkoxy substituent in the γ-position. This was the case in J.D. White's total synthesis of sesquiterpenoid polyol (±)-euonyminol in which an isopropenyl group was introduced to a bicyclic substrate *via* a chelation-controlled conjugate *Grignard addition*.[36] The γ-hydroxy unsaturated cyclic ketone was first treated with LDA and 15-crown-5 and then with isopropenylmagnesium bromide, which led to the formation of a reactive ate complex through a *Schlenk equilibrium*. From the ate complex, the isopropenyl group was intramolecularly transferred to the β-carbon of the enone.



The addition of Grignard reagents to complex molecules sometimes results in side reactions that may destroy the substrate. These side reactions are often attributed to the basicity of the reagent. Therefore, more nucleophilic derivatives must be prepared. This was the case during the total synthesis of (–)-lochneridine by M.E. Kuehne et al., when the attempted conversion of a pentacyclic ketone to the corresponding tertiary alcohol with ethylmagnesium bromide failed.[37] However, the formation of an organocerium reagent by adding the Grignard reagent to anhydrous $CeCl_3$ increased its nucleophilicity, therefore the reaction afforded the desired tertiary alcohol in 73% yield with complete diastereoselection.



During the synthesis of natural and modified cyclotetrapeptide trapoxins, S.L. Schreiber and co-workers prepared a fully functionalized nonproteinogenic amino acid surrogate *via* the ring-opening of Cbz serine β-lactone with an organocuprate derived from a Grignard reagent.[38]



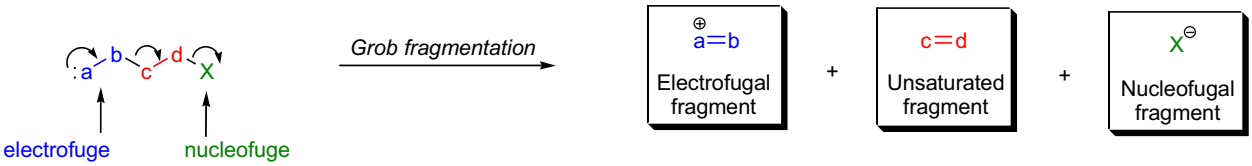
GROB FRAGMENTATION

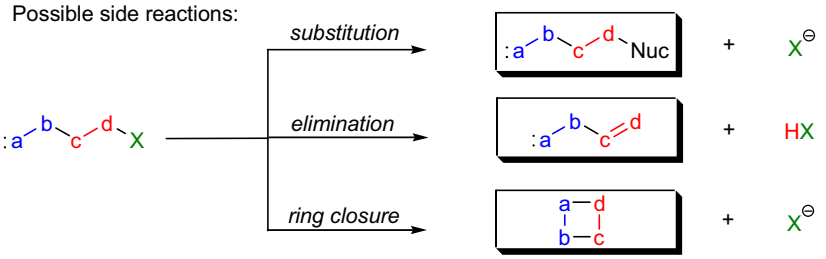
(References are on page 594)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-6]; *Theoretical Studies*[7-9]]

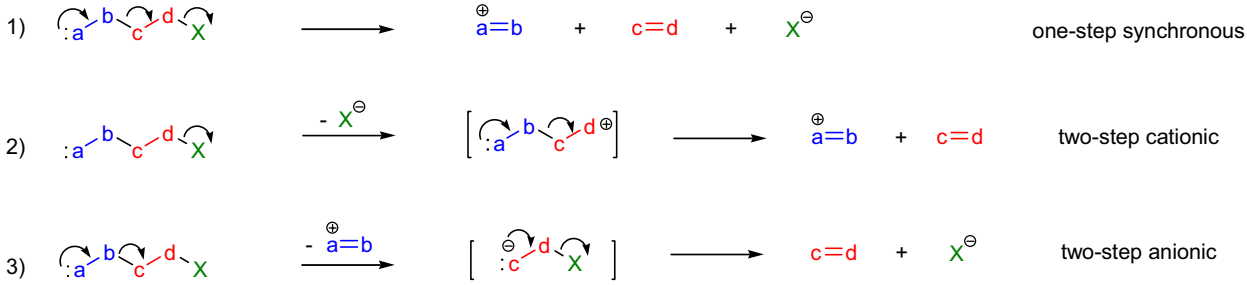
In the 1950s, C.A. Grob was the first to systematically investigate the regulated heterolytic cleavage reactions of molecules containing certain combinations of carbon and heteroatoms (e.g., B, O, N, S, P, halogens). Cleavage reactions of this type are referred to as *Grob fragmentations*, and as a result, three fragments (products) are formed. The general formula of "*a*-*b*-*c*-*d*-*X*" represents three embedded components: 1) "*a*-*b*" is the electrofuge, which leaves without the bonding electron pair and becomes the electrofugal fragment; 2) "*c*-*d*" will become the unsaturated fragment at the end of the reaction; and 3) "*X*" is the nucleofuge, which leaves with a bonding electron pair. Typical electrofugal fragments are carbonyl compounds, carbon dioxide, imonium-, carbonium- and acylium ions, olefins, and dinitrogen. Stabilization of the incipient positive charge on atom "*b*" and the inductive effect of atom "*a*" together determine how facile the formation of the electrofugal fragment is. The unsaturated fragment is usually an olefin, alkyne, imine, or nitrile while the nucleofugal fragment is often a halide, carboxylate, or sulfonate ion. The nucleofuge can have a charge (e.g., diazonium ion) before the fragmentation occurs, and that can accelerate the cleavage of the *b*-*c* and *d*-*X* bonds. The *Grob fragmentation* is often accompanied by side reactions such as substitution, elimination, or ring closure. It is most synthetically useful when it takes place in rigid bi- or polycyclic systems in a concerted and highly stereoselective fashion, so the stereochemical outcome of the product is predictable.





Mechanism:[10,5,11-13]

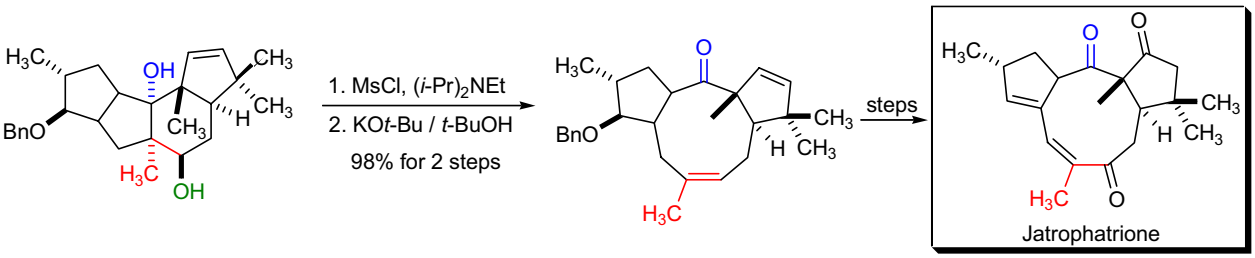
Heterolytic cleavage reactions such as the *Grob fragmentation* can take place by several different mechanisms, and the exact pathway depends on the structural, steric and electronic factors present in the substrate. There are three main mechanistic pathways: 1) one-step synchronous (concerted) cleavage in which the *a*=*b* and *X* fragments depart from the middle *c*=*d* group simultaneously; 2) two-step cleavage starting with the loss of *X* and the departure of the a=b fragment from the carbocationic intermediate; and 3) two-step cleavage starting with the departure of *a*=*b* and the loss of *X* from the carbanionic intermediate (this is rare). The synchronous mechanism has very strict structural and stereochemical requirements, since five atoms are involved in the transition state: all five atomic orbitals need to overlap. These requirements are best met in rigid polycyclic systems and the *Grob fragmentation* of these rigid molecules exhibits a significant increase in reaction rates compared to the non-concerted fragmentations (frangomeric effect). When the stereochemical arrangement for the concerted process cannot be achieved due to strain, then the so-called *syn fragmentation* or side reactions (e.g., elimination) take place.[6]



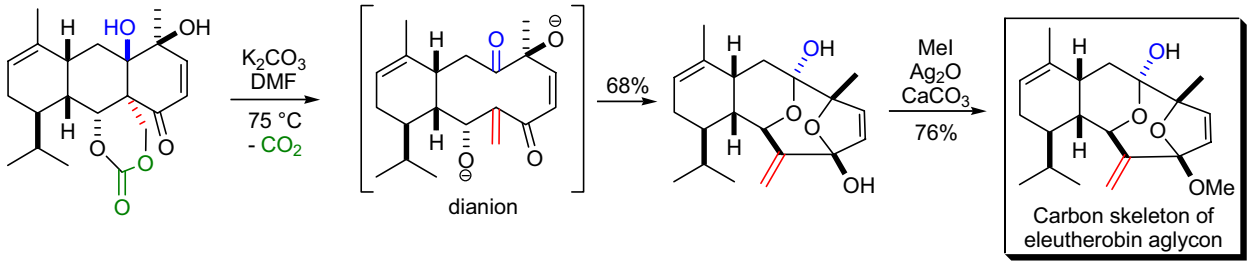
GROB FRAGMENTATION

Synthetic Applications:

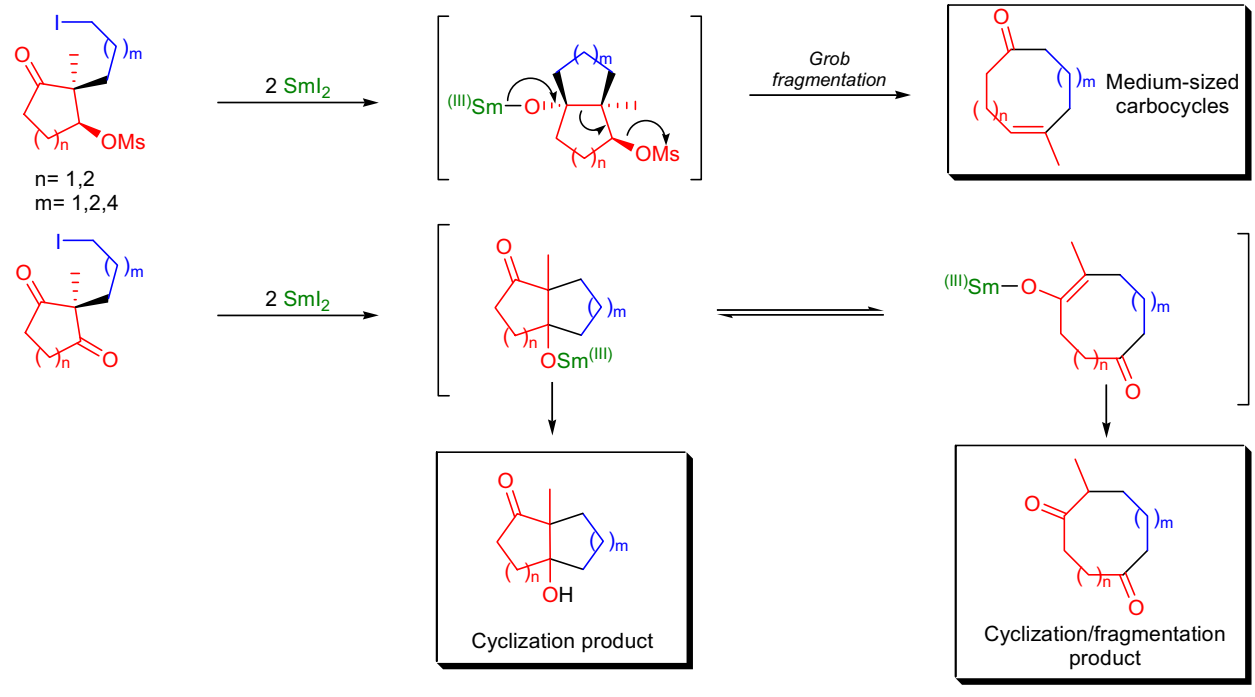
L.A. Paquette and co-workers accomplished the first total synthesis of the antileukemic agent jatrophatrione.[14] This natural product has a [5.9.5] fused tricyclic skeleton with a *trans*-B/C ring fusion. The key step in their approach was the *Grob fragmentation* to obtain the tricyclo[5.9.5] skeleton. The tetracyclic 1,3-diol was monomesylated on the less hindered hydroxyl group and then treated with potassium *tert*-butoxide, triggering the concerted fragmentation to afford the desired tricyclic product in almost quantitative yield.



In the laboratory of J.D. Winkler, the synthesis of the carbon framework of the eleutherobin aglycon was developed using a *tandem Diels-Alder reaction* and a *Grob fragmentation* as key steps.[15] The tricyclic fragmentation precursor was subjected to potassium carbonate in DMF at 75 °C to afford the fragmentation product in 68% yield *via* a dianion intermediate that underwent a spontaneous hemiketalization.



G.A. Molander et al. used samarium(II) iodide to prepare *highly functionalized stereodefined medium sized (8-, 9-, and 10-membered) carbocycles via* a domino reaction composed of a cyclization/fragmentation process.[16] The method involved the reduction of substituted keto mesylates bearing iodoalkyl, allyl, or benzyl side chains under Barbier-type conditions. The *intramolecular Barbier reaction* occurred between the iodoalkyl chain and the ketone of the cycloalkanone and generated a bicyclic alkoxide that underwent *Grob fragmentation*. The reaction proceeded in a stereoselective manner with high yields under mild conditions. The cyclization of cycloalkanediones under similar conditions was also observed, yielding functionalized polycyclic hydroxyl ketones in high yields with complete diastereoselectivity.



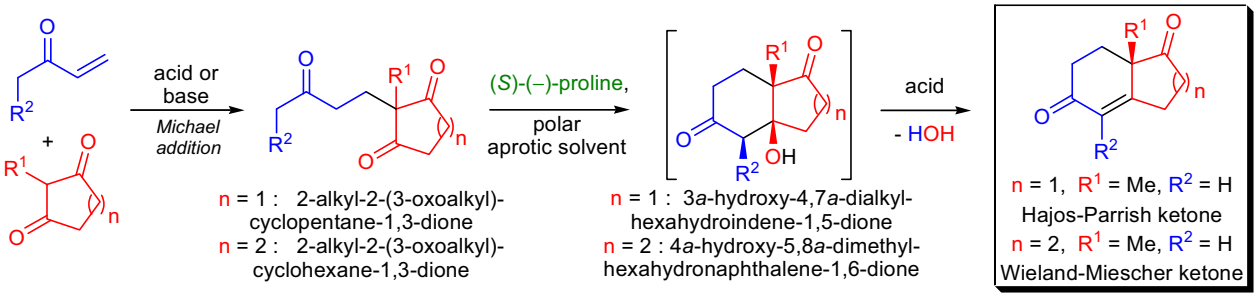
HAJOS-PARRISH REACTION

(References are on page 595)

Importance:

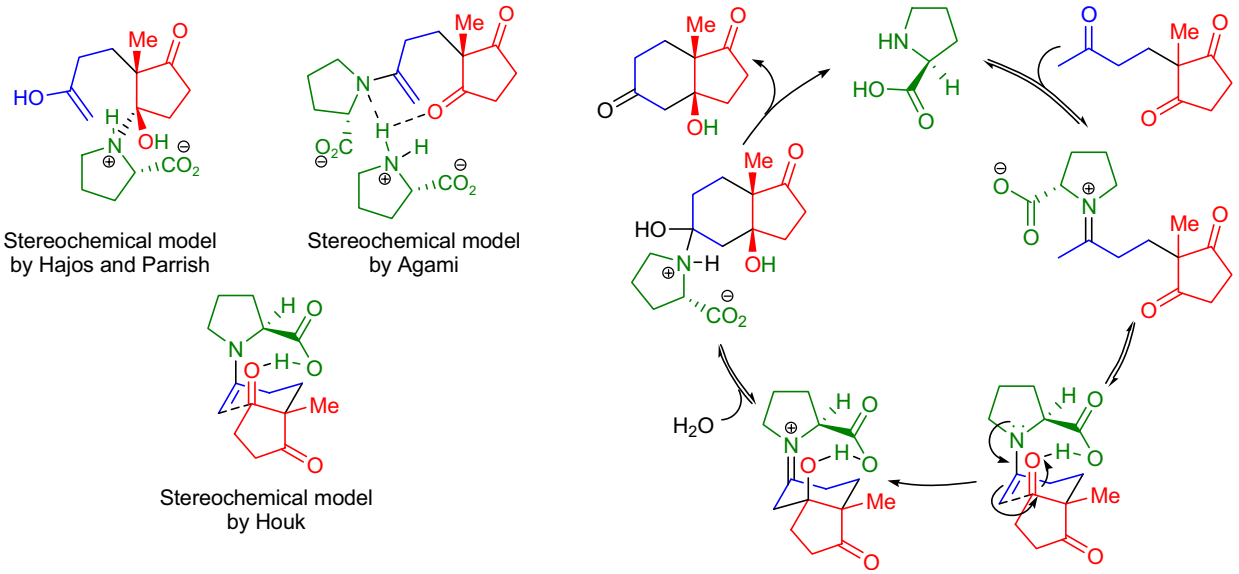
[*Seminal Publications*[1-4]*; Reviews*[5-12]*; Modifications & Improvements*[13-18]*; Theoretical Studies*[19-22]]

In the early 1970s, two industrial groups independently examined the *asymmetric intramolecular aldol reaction* of 2-alkyl-2-(3-oxoalkyl)-cyclopentane-1,3-diones using amino acids. Z.G. Hajos and D.R. Parrish at Hoffmann-LaRoche found that a catalytic quantity of (*S*)-(–)-proline was sufficient to furnish the cyclization of 2-methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione and induce enantioselectivity.[3,4] Best results were obtained when the reaction was carried out in polar aprotic solvents such as DMF at room temperature in the presence of 3 mol% (*S*)-(–)-proline yielding the product quantitatively with 93.4% *ee*. *p*-Toluenesulfonic acid catalyzed dehydration to the corresponding bicyclic enone (*Hajos-Parrish ketone*) could be realized without the loss of optical purity. R. Wiechert and co-workers showed that the enone product could be formed directly when the cyclization was performed in the presence of (*S*)-(–)-proline (10-200 mol%) and an acid co-catalyst such as $HClO_4$.[1,2] The amino acid catalyzed *intramolecular aldol reaction* of prochiral 2-alkyl-2-(3-oxoalkyl)-cyclopentane-1,3-diones is known as the *Hajos-Parrish reaction*, but it is also referred to as the *Hajos-Parrish-Eder-Sauer-Wiechert reaction*. (*S*)-(–)-Proline catalyzed *intramolecular aldol reaction* of 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione leading to 8*a*-methyl-3,4,8,8*a*-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione (*Wieland-Miescher ketone*) could also be realized in high yields, although the optical purity of the product was moderate (70%) and further recrystallization was required to obtain the product in optically pure form.[23] Since its invention, the *Hajos-Parrish reaction* was applied to the synthesis of several differently substituted hexahydroindene-1,5-dione-, 2,3,7,7*a*-tetrahydro-6*H*-indene-1,5-dione- and 3,4,8,8*a*-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione derivatives.[1-5,16,18] The most general catalyst is (*S*)-(–)-proline, but in certain cases (*S*)-(–)-phenylalanine proved to be more efficient.[24] The reaction was also studied applying polymer bound (*S*)-(–)-proline as catalyst.[15] Precursors for the *Hajos-Parrish reaction* can be easily obtained by the *Michael addition* of cyclopentane-1,3-dione and cyclohexane-1,3-dione derivatives to α,β-unsaturated ketones.



Mechanism:[4,25-28,20-22]

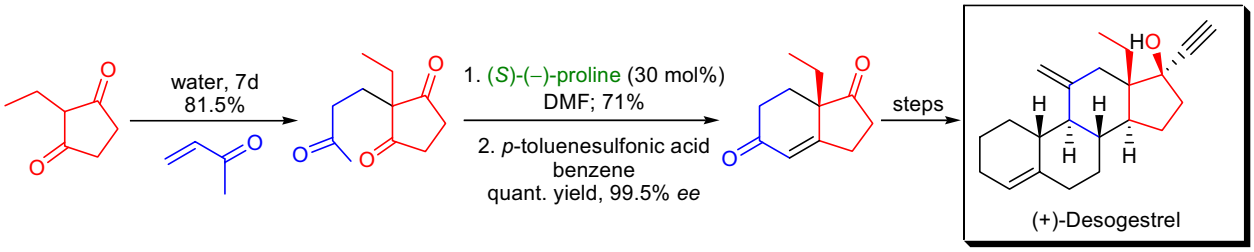
The originally proposed stereochemical model by Hajos and Parrish[4] was rejected by M.E. Jung[25] and A. Eschenmoser.[26] They proposed a one-proline aldolase-type mechanism involving a side chain enamine. The most widely accepted transition state model to account for the observed stereochemistry was proposed by C. Agami et al. suggesting the involvement of two (*S*)-(–)-proline molecules.[14,27-29] Recently, K.N. Houk and co-workers reexamined the mechanism of the intra- and intermolecular (*S*)-(–)-proline catalyzed *aldol reactions*. Their theoretical studies, kinetic, stereochemical and dilution experiments support a one-proline mechanism where the reaction goes through a six-membered chairlike transition state.[19-22]



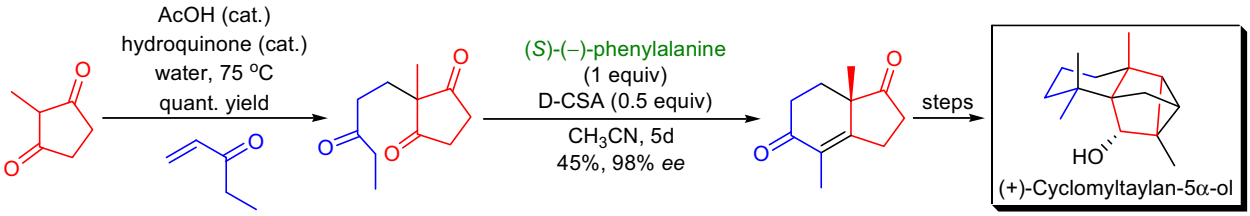
HAJOS-PARRISH REACTION

Synthetic Applications:

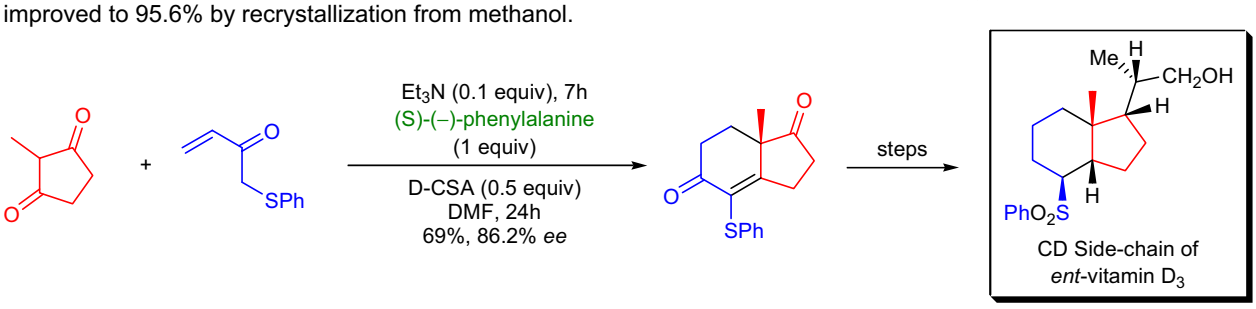
A short, enantioselective total synthesis of (+)-desogestrel, the most prescribed third-generation oral contraceptive, was accomplished by E.J. Corey et al.[30] They started out from a *Hajos-Parrish ketone* analogue (*S*)-(+)-7*a*-ethyl-2,3,7,7*a*-tetrahydro-6*H*-indene-1,5-dione, which was readily available by the original procedure by Hajos and Parrish.[4] The desired enone could be synthesized starting out from 2-ethylcyclopentane-1,3-dione that underwent *Michael addition* with methyl vinyl ketone. *Intramolecular aldol reaction* in the presence of 30 mol% (*S*)-(–)-proline followed by dehydration gave the product in high yield and excellent enantioselectivity. The product enone could be converted to desogestrel in 16 consecutive steps.



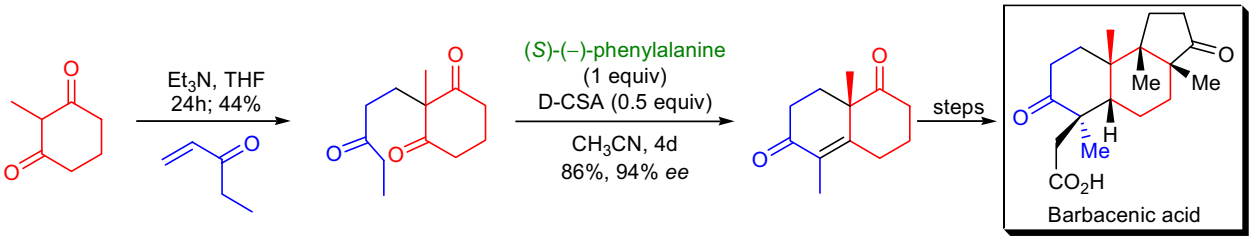
The first enantioselective total synthesis of tetracyclic sesquiterpenoid (+)-cyclomyltaylan-5α-ol, isolated from a Taiwanese liverwort, was accomplished by H. Hagiwara and co-workers.[31] They started out from *Hajos-Parrish ketone* analogue, (*S*)-(+)-4,7*a*-dimethyl-2,3,7,7*a*-tetrahydro-6*H*-indene-1,5-dione, that could be synthesized from 2-methylcyclopentane-1,3-dione and ethyl vinyl ketone in an acetic acid-catalyzed *Michael addition* followed by an *intramolecular aldol reaction*. The *intramolecular aldol reaction* was carried out in the presence of one equivalent (*S*)-(–)-phenylalanine and 0.5 equivalent D-camphorsulfonic acid. The resulting enone was recrystallized from hexane-diethyl ether to yield the product in 43% yield and 98% *ee*. Since the absolute stereochemistry of the natural product was unknown, the total synthesis also served to establish the absolute stereochemistry.



J. Wicha and co-workers reported the enantioselective synthesis of the CD side-chain portion of *ent*-vitamine D_3.[18] The key step in their approach was the amino acid mediated *asymmetric Robinson annulation* between 2-methyl-cyclopentane-1,3-dione and 1-phenylsulfanyl-but-3-en-2-one. During their optimization studies they found that the annulation is most efficient if the reaction is carried out in the presence of (S)-(–)-phenylalanine and D-camphorsulfonic acid, giving the product in 69% yield and 86.2% *ee*. The optical purity of the enone could be improved to 95.6% by recrystallization from methanol.



The first total synthesis of barbacenic acid, a bisnorditerpene containing five contiguous stereocenters, was achieved by A. Kanazawa et. al.[32,33] They started out from a *Wieland-Miescher ketone* analogue that could be synthesized with high yield and excellent enantioselectivity by the procedure of S. Takahashi. According to this procedure, the *Michael addition* product 2-methyl-2-(3-oxo-pentyl)-cyclohexane-1,3-dione was cyclized in the presence of (*S*)-(–)-phenylalanine and D-camphorsulfonic acid.



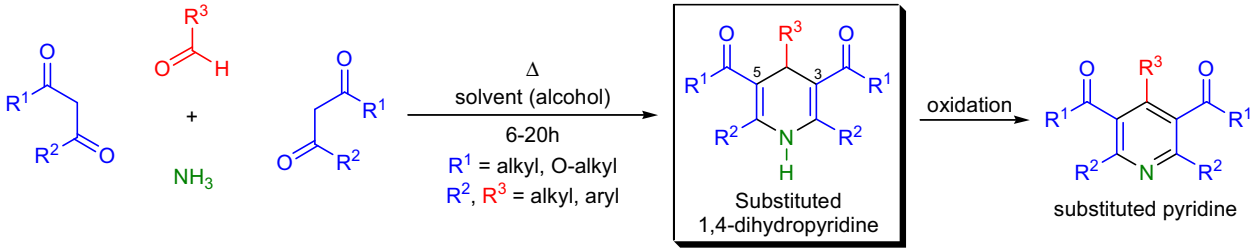
HANTZSCH DIHYDROPYRIDINE SYNTHESIS

(References are on page 595)

Importance:

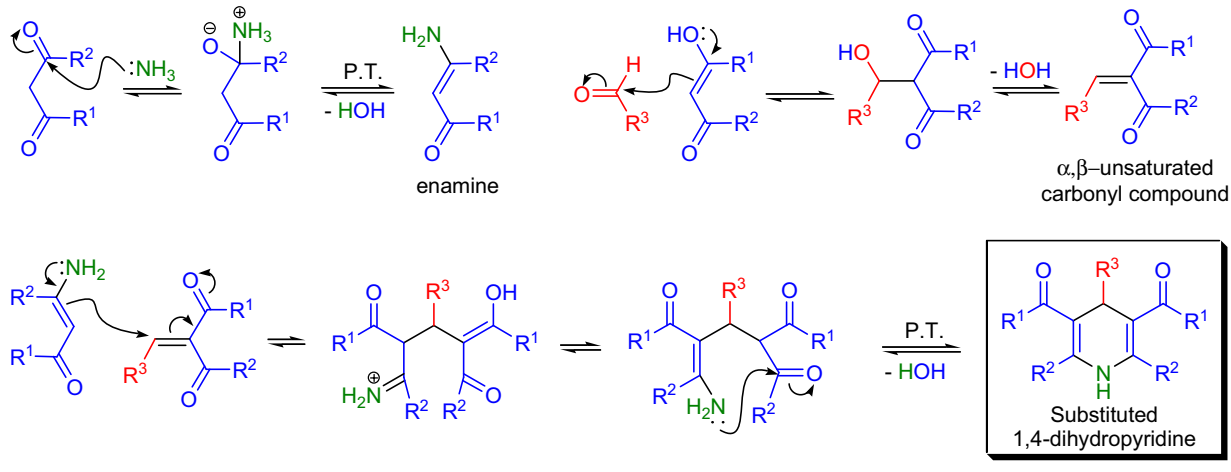
[*Seminal Publication*[1]; *Reviews*[2-13]; *Modifications & Improvements*[14-22]]

In 1882, A. Hantzsch condensed two moles of ethyl acetoacetate with one mole of acetaldehyde and ammonia to obtain a fully substituted symmetrical dihydropyridine.[1] He initially assigned the structure as a 2,3-dihydropyridine, but it was later shown to be a 1,4-dihydropyridine. The one-pot condensation of a β-keto ester or a 1,3-dicarbonyl compound with an aldehyde and ammonia to prepare 1,4-dihydropyridines is known as the *Hantzsch dihydropyridine synthesis*. Frequently, the 1,4-dihydropyridine products are spontaneously oxidized to the corresponding substituted pyridines, but in the case of stable dihydropyridines, the use of an oxidizing agent [e.g., HNO_2, HNO_3, $(NH_4)_2Ce(NO_3)_6$, MnO_2, $Cu(NO_3)_2$] is necessary.[23-30] General features of the reaction are: 1) aliphatic, aromatic, heterocyclic, and α,β-unsaturated aldehydes can be used as the aldehyde component; 2) ammonia or primary amines are suitable as the amine component; 3) the dicarbonyl component is usually an acyclic or cyclic β-keto ester, β-keto aldehyde, or a 1,3-diketone; 4) the product of the reaction is a symmetrical dihydropyridine, which is formed in good or excellent yield; 5) if the C3 and C5 substituents are electron-withdrawing (e.g., acyl, nitro, sulfonyl) the dihydropyridine is stable enough to be isolated; 6) the reaction conditions can range from basic media all the way to strongly acidic solutions, and the choice of conditions needs to be optimized for the given system; 7) good yields are obtained with substrates having electron-withdrawing groups; and 8) sterically congested aldehydes generally give low yields (e.g., *o*-substituted benzaldehyde). The original procedure only affords symmetrical products, but there are several modifications that allow the preparation of unsymmerical dihydropyridines: 1) one equivalent of a β-keto ester is condensed with an aldehyde of choice to give an α,β-unsaturated carbonyl compound (alkylidene), which in turn is treated with another β-keto ester and a nitrogen source; 2) an α,β-unsaturated carbonyl compound (derived from the condensation of active methylene compounds and aldehydes) is condensed with an enamine;[31-33] and 3) in the *Knoevenagel modification* various substituted 1,5-dicarbonyl compounds can be prepared (e.g., *Michael addition* of a 1,3-dicarbonyl compound to an α,β-unsaturated carbonyl compound under basic conditions) and reacted with a nitrogen source (usually ammonium acetate-acetic acid).[34,35]



Mechanism:[36-38]

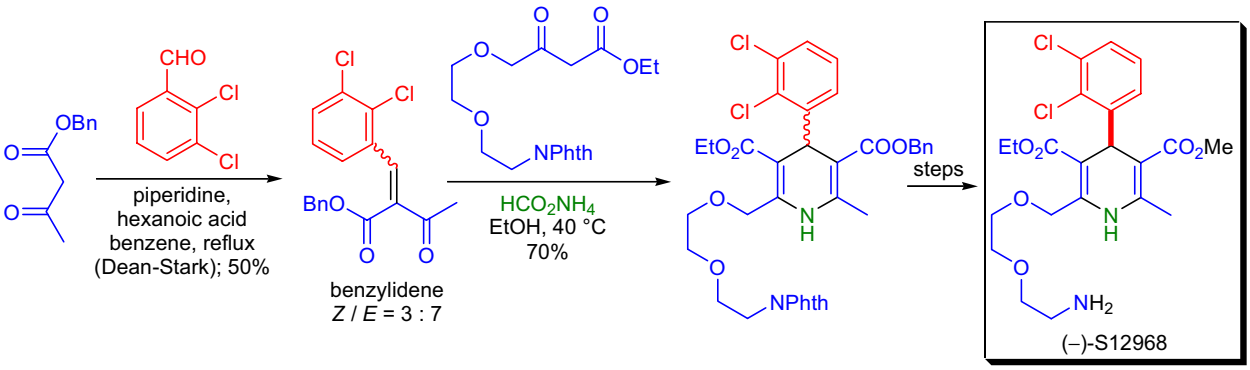
There have been many studies aiming to determine the exact mechanistic pathway of the *Hantzsch dihydropyridine synthesis*, but the ^{13}C and ^{15}N-NMR experiments conducted by A.R. Katritzky et al. were the only ones that confirmed the existence of certain intermediates.[37] All of the investigated reactions had two common intermediates: an enamine and an α,β-unsaturated carbonyl compound. The initial steps of the reaction involve a *Knoevenagel condensation* of the 1,3-dicarbonyl compound with the aldehyde to give an α,β-unsaturated carbonyl compound and a condensation of ammonia with another equivalent of the 1,3-dicarbonyl compound to give an enamine. The rate determining step is the *Michael addition* of the enamine to the α,β-unsaturated carbonyl compound. Subsequently, the addition product undergoes an intramolecular condensation of the amino and carbonyl groups to afford the desired substituted 1,4-dihydropyridine.



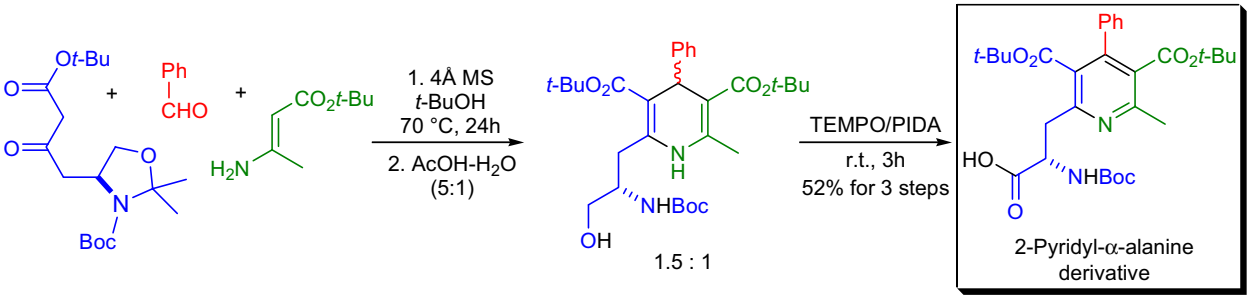
HANTZSCH DIHYDROPYRIDINE SYNTHESIS

Synthetic Applications:

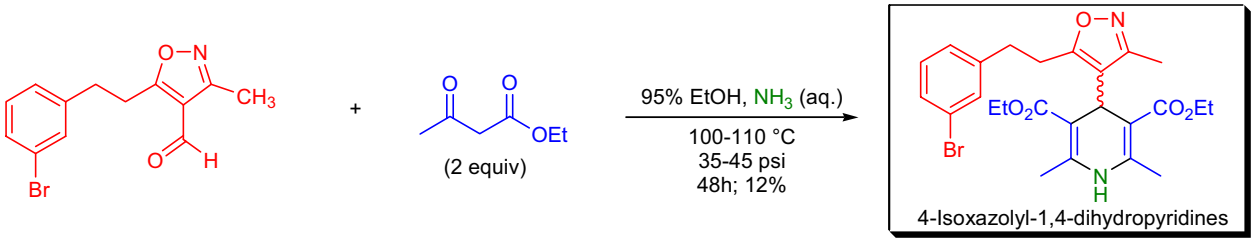
F. Dollé and co-workers synthesized (–)-S12968, an optically active 1,4-dihydropyridine that is a calcium channel antagonist.[39] The key step in their synthetic approach was a *modified Hantzsch dihydropyridine synthesis* and the resulting racemic mixture was separated by chiral HPLC. The starting β-keto ester was condensed with 2,3-dichlorobenzaldehyde under slightly acidic conditions to obtain the corresponding benzylidene derivative in 50% yield. Next, the second β-keto ester was heated in ethanol along with ammonium formate, which was the source of ammonia, to give the racemic 1,4-dihydropyridine. Finally, HPLC separation of the enantiomers followed by deprotection and esterification gave (–)-S12968.



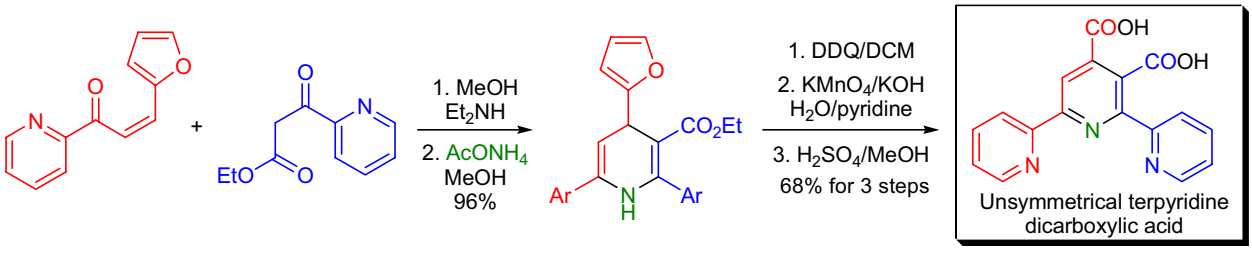
A new strategy for the synthesis of heterocyclic α-amino acids utilizing the *Hantzsch dihydropyridine synthesis* was developed in the laboratory of A. Dondoni.[40] The enantiopure oxazolidinyl keto ester was condensed with benzaldehyde and *tert*-butyl amino crotonate in the presence of molecular sieves in 2-methyl-2-propanol to give a 85% yield of diastereomeric 1,4-dihydropyridines. The acetonide protecting group was removed and the resulting amino alcohol was oxidized to the target 2-pyridyl α-alanine derivative.



Lipophilic 1,4-dihydropyridines, such as 4-aryl-1,4-dihydropyridines, exhibit significant calcium channel antagonist activity. N.R. Natale et al. have synthesized a series of 4-isoxazolyl-1,4-dihydropyridines bearing lipophilic side chains at the C5 position of the isoxazole ring.[41] The *Hantzsch synthesis* was carried out in an aerosol dispersion tube at 110 °C in ethanol in the presence of 2 equivalents of ethyl acetoacetate and aqueous ammonia solution.



M. Baley reported the first synthesis of an unsymmetrical 2,2'-6'2"-terpyridine containing two carboxylic acids using the *Hantzsch dihydropyridine synthesis* followed by an oxidation.[42] The furan ring served as a latent carboxylic acid functional group.



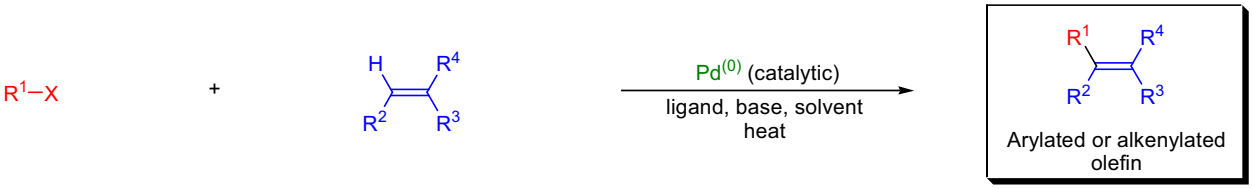
HECK REACTION

(References are on page 596)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-39]; *Modifications & Improvements*[40-47]; *Theoretical Studies*[48-54]]

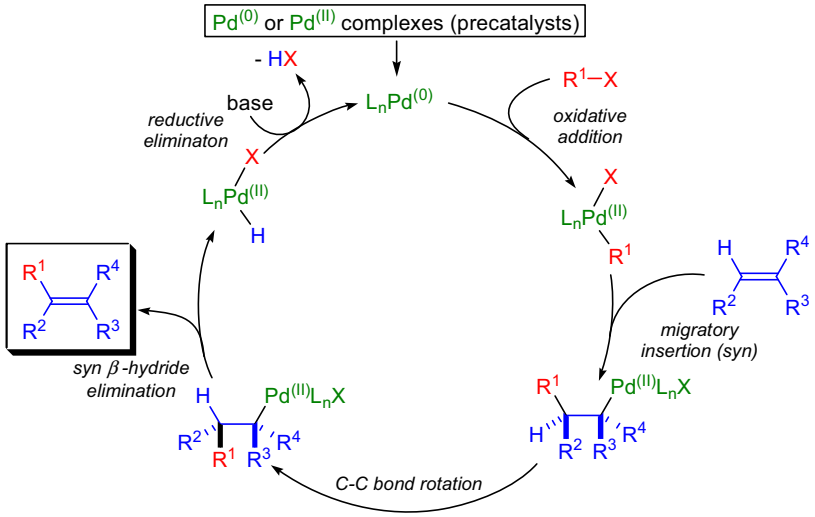
In the early 1970s, T. Mizoroki and R.F. Heck independently discovered that aryl, benzyl and styryl halides react with olefinic compounds at elevated temperatures in the presence of a hindered amine base and catalytic amount of $Pd^{(0)}$ to form aryl-, benzyl-, and styryl-substituted olefins.[1-3] Today, the palladium-catalyzed arylation or alkenylation of olefins is referred to as the *Heck reaction*. Since its discovery, the *Heck reaction* has become one of the most widely used catalytic carbon-carbon bond forming tools in organic synthesis. The general features of the reaction are: 1) it is best applied for the preparation of disubstituted olefins from monosubstituted ones; 2) the electronic nature of the substituents on the olefin only has limited influence on the outcome of the reaction; it can be either electron-donating or electron-withdrawing but usually the electron poor olefins give higher yields; 3) the reaction conditions tolerate a wide range of functional groups on the olefin component: esters, ethers, carboxylic acids, nitriles, phenols, dienes, etc., are all well-suited for the coupling, but allylic alcohols tend to rearrange; 4) the reaction rate is strongly influenced by the degree of substitution of the olefin and usually the more substituted olefin undergoes a slower *Heck reaction*; 5) unsymmetrical olefins (e.g., terminal alkenes) predominantly undergo substitution at the least substituted olefinic carbon; 6) the nature of the X group on the aryl or vinyl component is very important and the reaction rates change in the following order: I > Br ~ OTf >> Cl; 7) the R^1 group in most cases is aryl, heteroaryl, alkenyl, benzyl, and rarely alkyl (provided that the alkyl group possesses no hydrogen atoms in the β-position), and these groups can be either electron-donating or electron-withdrawing; 8) the active palladium catalyst is generated *in situ* from suitable precatalysts (e.g., $Pd(OAc)_2$, $Pd(PPh_3)_4$) and the reaction is usually conducted in the presence of monodentate or bidentate phosphine ligands and a base; 9) the reaction is not sensitive to water, and the solvents need not be thoroughly deoxygenated; and 10) the *Heck reaction* is stereospecific as the migratory insertion of the palladium complex into the olefin and the β-hydride elimination both proceed with *syn* stereochemistry. There are a couple of drawbacks of the *Heck reaction*: 1) the substrates cannot have hydrogen atoms on their β-carbons, because their corresponding organopalladium derivatives tend to undergo rapid β-hydride elimination to give olefins; and 2) aryl chlorides are not always good substrates because they react very slowly. Several modifications were introduced during the past decade: 1) asymmetric versions;[23,36] 2) generation of quaternary stereocenters in the *intramolecular Heck reaction*;[17,55,34] 3) using water as the solvent with water-soluble catalysts;[56,57,47] and 4) heterogeneous palladium on carbon catalysis.[40]



R^1 = aryl, benzyl, vinyl (alkenyl), alkyl (no β hydrogen); R^2, R^3, R^4 = alkyl, aryl, alkenyl; X = Cl, Br, I, OTf, OTs, N_2^+;
ligand = trialkylphosphines, triarylphosphines, chiral phosphines; base = 2° or 3° amine, KOAc, NaOAc, $NaHCO_3$

Mechanism:[58,59,21,22,51,53]

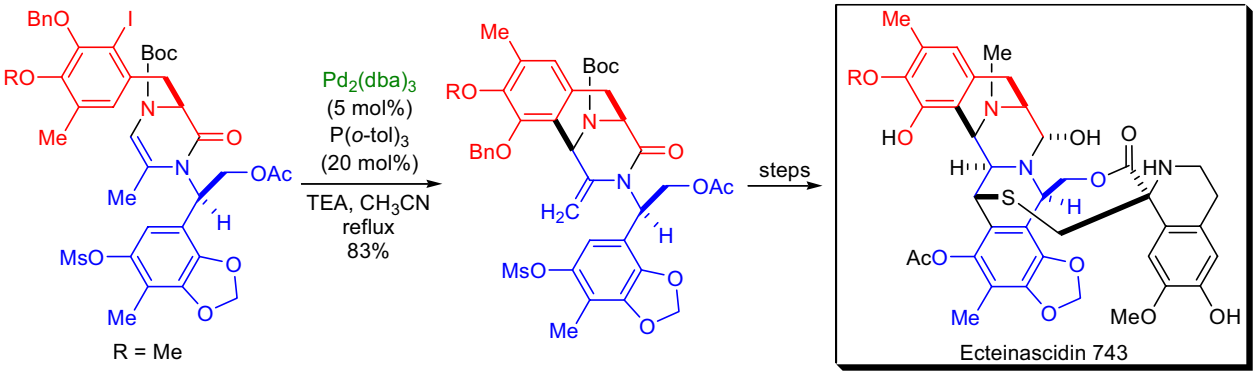
The mechanism of the *Heck reaction* is not fully understood and the exact mechanistic pathway appears to vary subtly with changing reaction conditions. The scheme shows a simplified sequence of events beginning with the generation of the active $Pd^{(0)}$ catalyst. The rate-determining step is the *oxidative addition* of $Pd^{(0)}$ into the C-X bond. To account for various experimental observations, refined and more detailed catalytic cycles passing through anionic, cationic or neutral active species have been proposed.[21,36]



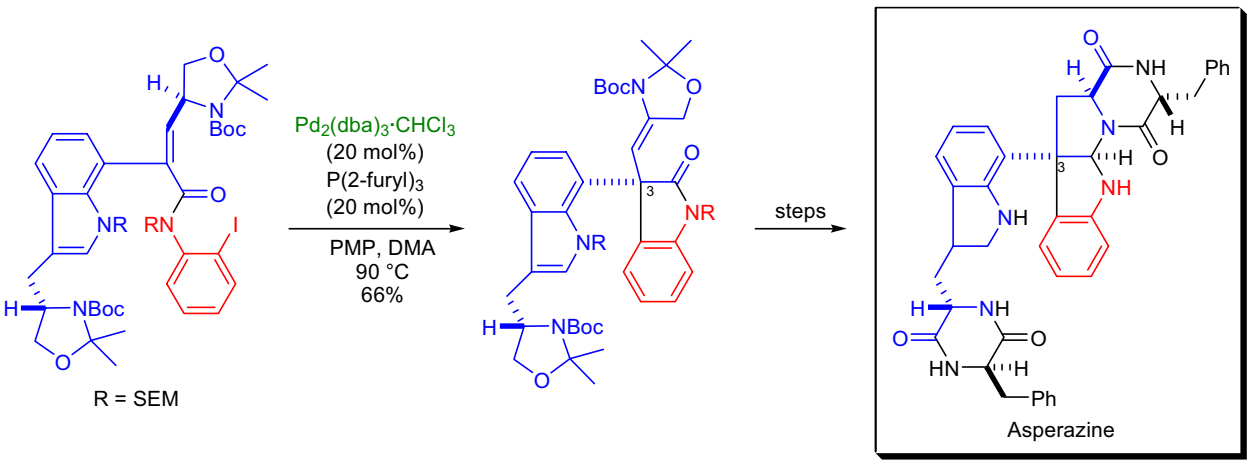
HECK REACTION

Synthetic Applications:

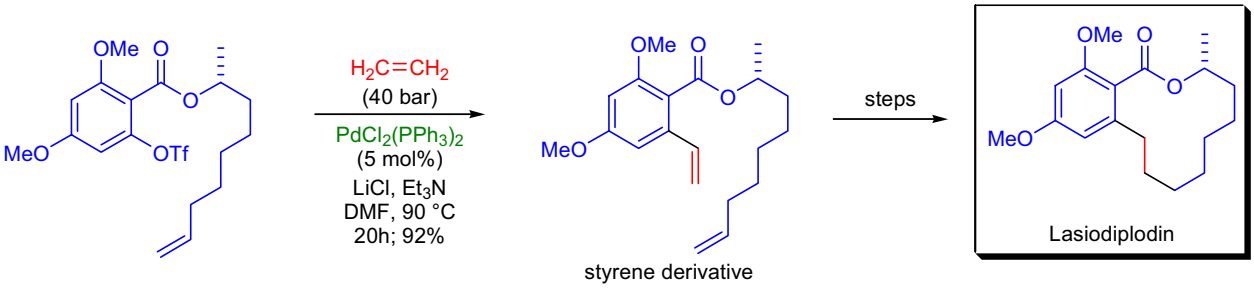
Ecteinascidin 743 is a potent antitumor agent that was isolated from a marine tunicate. T. Fukuyama et al. applied the *intramolecular Heck reaction* as the key step in the assembly of the central bicyclo[3.3.1] ring system.[60] Toward this end, the cyclic enamide precursor was exposed to 5 mol% of palladium catalyst and 20 mol% of a phosphine ligand in refluxing acetonitrile to afford the desired tricyclic intermediate in 83% isolated yield.



The introduction of the C3 quaternary center was the major challenge during the total synthesis of asperazine by L.E. Overman and co-workers.[61] To address this synthetic problem, a diastereoselective *intramolecular Heck reaction* was used. The α,β-unsaturated amide precursor was efficiently coupled with the tethered aryl iodide moiety in the presence of 20 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and one equivalent of $(2\text{-furyl})_3P$ ligand. The desired hexacyclic product was obtained as a single diastereomer in 66% yield.



The total synthesis of the potent anticancer macrocyclic natural product lasiodiplodin was achieved in the laboratory of A. Fürstner.[62] The key macrocyclization step was carried out by the *alkene metathesis* of a styrene derivative, which was prepared in excellent yield *via* an *intermolecular Heck reaction* between an aryl triflate and high-pressure ethylene gas.



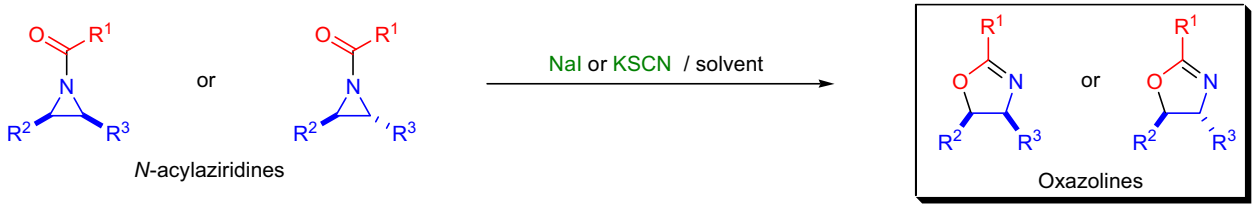
HEINE REACTION

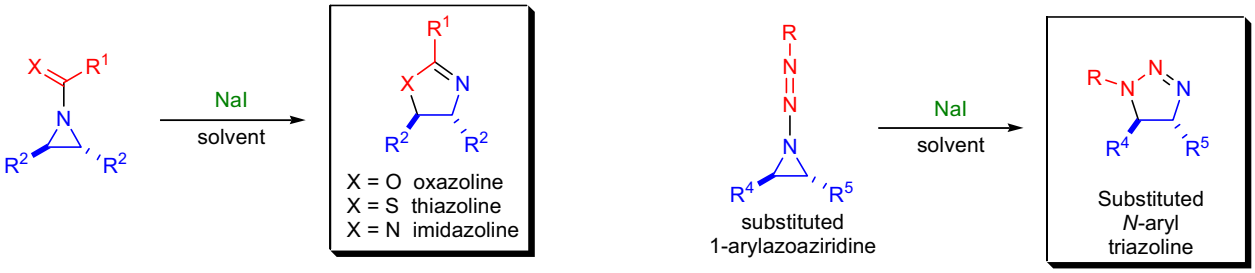
(References are on page 597)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-9]]

In 1959, H.W. Heine described the isomerization of 1-aroylaziridines to the corresponding 2-aryl-2-oxazolines in the presence of excess sodium iodide in acetone at room temperature or at reflux.[1] The isomerizations took place in almost quantitative yields. The *intramolecular ring expansion* of substituted *N*-acylaziridines by nucleophilic reagents (e.g., NaI or KSCN) to the corresponding substituted oxazolines is known as the *Heine reaction*. The isomerization of various substituted aziridines to oxazolines under acidic and thermal conditions are very well known, but the *Heine reaction* is the only reaction that induces these isomerizations under mild and neutral conditions.[5,6,9] The main features of the *Heine reaction* are: 1) iodide ion and thiocyanate ion were found to be the only nucleophiles to induce isomerizations;[2] 2) the course of the reaction is greatly influenced by the choice of solvent and acetone, acetonitrile, and 2-propanol give the best results;[2] 3) the *Heine reaction* is stereospecific; when non-racemic aziridines are used as substrates, the stereochemical outcome is a net retention of configuration; 4) 3-aryl substituted *N*-acyl aziridinecarboxylic esters (R^2 = aryl) or aryl disubstituted C_2-symmetric *N*-acyl aziridines are the best substrates, since it is essential to open the aziridine ring regiospecifically; 5) substrates for which the aziridine ring-opening is not regiospecific give rise to a mixture of products; and 6) aziridines that are substituted at C1 with electron-withdrawing groups often undergo dimerization when treated with sodium iodide.[5,6] The ring expansion of *N*-substituted aziridines (X = O, S, N) with iodide or thiocyanate ions is quite general and can lead to other five-membered heterocycles such as thiazolines, imidazolines and triazolines.

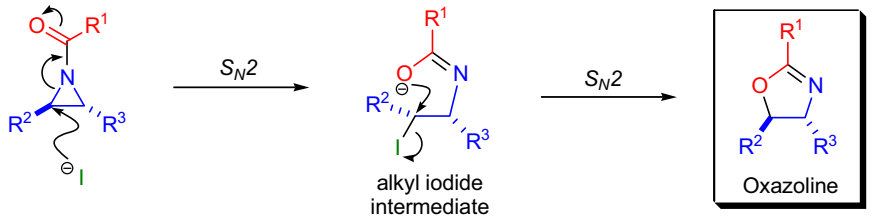




R^1 = alkyl, aryl, O-alkyl, O-aryl, *N*,*N*-dialkyl, *N*,*N*-diaryl; R^2 = aryl; R^3 = CO_2-alkyl, CO_2-aryl; R^4 = aryl; R^5 = aryl, H; X = O, S, NH, NR;
solvent = 2-propanol, acetone, acetonitrile

Mechanism:[5,6,9]

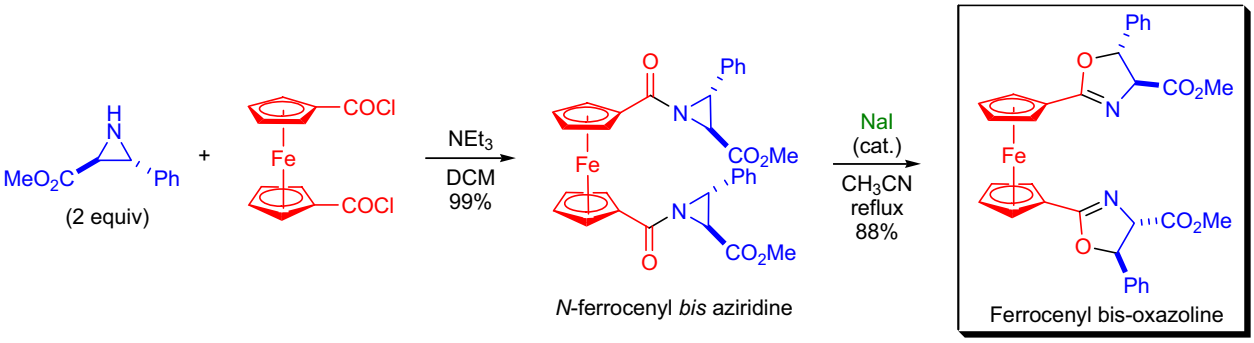
The first step of the *Heine reaction* is the regiospecific S_N2 attack of the iodide ion at the C3 carbon resulting in the ring-opening of the aziridine and the inversion of stereochemistry at C3. Next, the secondary alkyl iodide is attacked by the negatively charged oxygen atom in an S_N2 reaction causing the stereochemistry to invert once again at C3. Since two consecutive inversions (double inversion) take place at C3, the stereochemical outcome of the *Heine reaction* is a net retention.



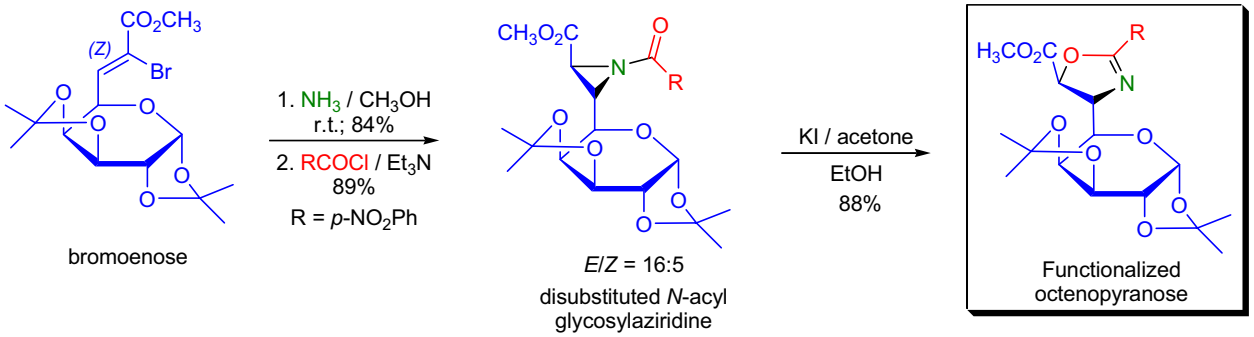
HEINE REACTION

Synthetic Applications:

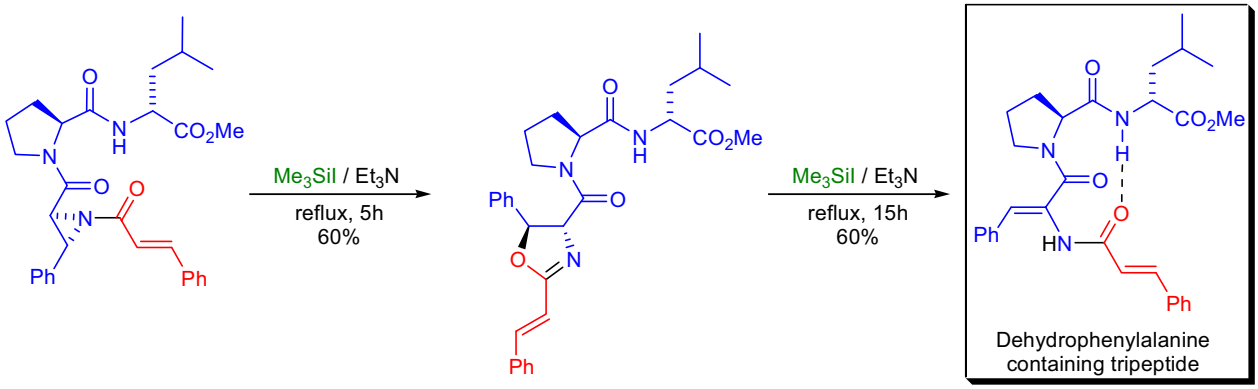
The synthesis of ferrocenyl oxazolines was accomplished in the laboratory of B. Zwanenburg using the *Heine reaction* as the key step to form the oxazoline rings.[10] *N*-Ferrocenoyl-aziridine-2-carboxylic esters were prepared by the acylation of optically active aziridines with either ferrocenecarbonyl chloride or ferrocene-1,1'-dicarbonyl dichloride and treated with catalytic amounts of NaI in boiling acetonitrile. The ring expansions proceeded in good yields affording the expected ferrocenyl oxazolines and ferrocenyl *bis*-oxazolines. The ester functionality provided a convenient handle for further modifications of the ligands by the addition of a Grignard reagent to form the corresponding ferrocenyl oxazoline carbinols.



J.M.J. Tronchet and co-workers prepared functionalized octenopyranoses to investigate the synthetic utility of glycosylaziridine derivatives.[11] The authors found that by treating bromoenoses with methanolic ammonia at room temperature, the corresponding disubstituted glycosylaziridines were formed with an *E*/*Z* ratio of 16:5. The aziridines were acylated, and the resulting *N*-acyl glycosylaziridines were subjected to a nucleophilic ring-expansion to afford oxazolines in excellent yield. As expected, the overall stereochemical outcome was a net retention of configuration.



The synthesis of proline containing tripeptides constrained with phenylalanine-like aziridine and dehydrophenylalanine residues was accomplished in the laboratory of J. Iqbal.[12] These tripeptides show -turn structure in solution and are good models for studying the mechanism of HIV protease. The aziridine rings in these tripeptides were stereoselectively transformed *via* the *Heine reaction* in two steps to the corresponding dehydrophenylalanine containing tripeptides, which also prefer to form -turn structures in solution.



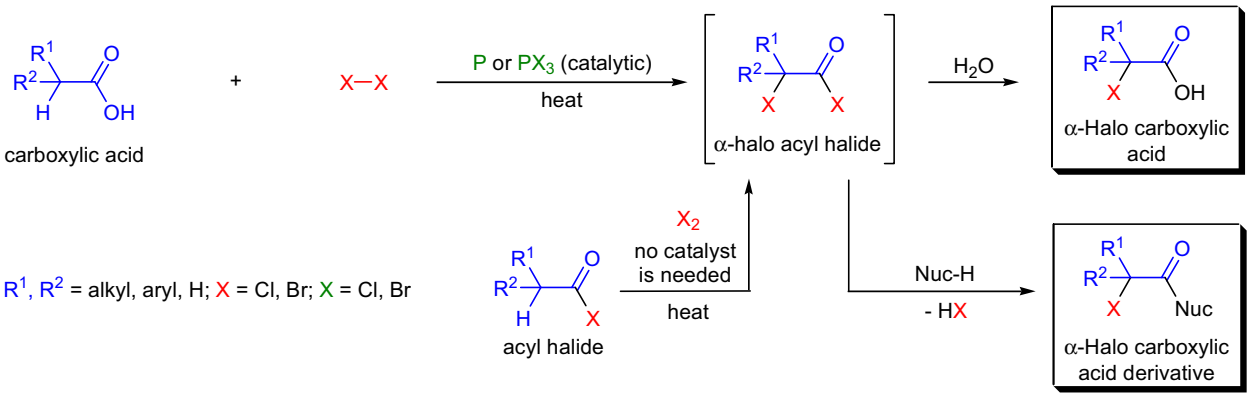
HELL-VOLHARD-ZELINSKY REACTION

(References are on page 598)

Importance:

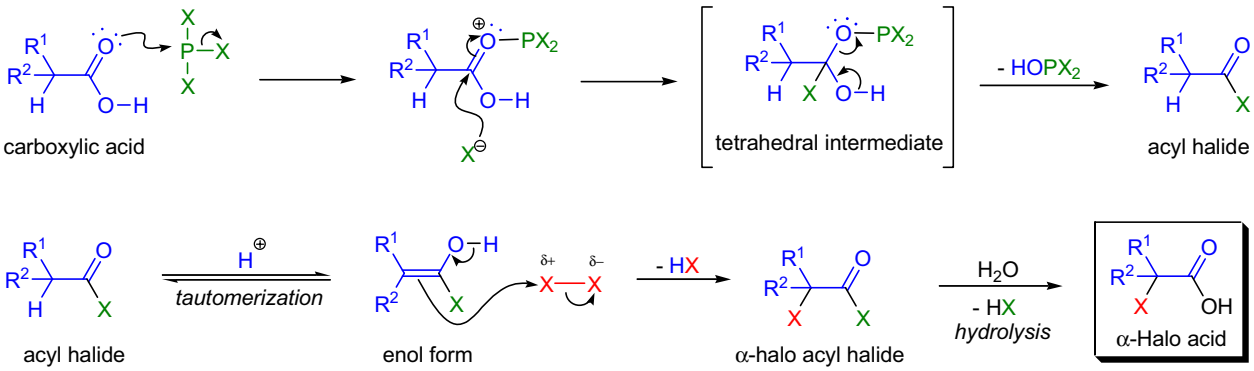
[*Seminal Publications*[1-3]; *Reviews*[4-6]; *Modifications & Improvements*[7-11]]

The preparation of α-halo carboxylic acids by treating the corresponding carboxylic acid with elemental halogen (Cl_2 or Br_2) at elevated temperatures in the presence of catalytic amounts of red phosphorous (P) or phosphorous trihalide (PCl_3 or PBr_3) is known as the *Hell-Volhard-Zelinsky reaction* (*HVZ reaction*). The reaction was first described by C. Hell[1] and was slightly modified by J. Volhard[2] and N. Zelinsky[3] a few years later. The initial product of the *HVZ reaction* is an α-halo acyl halide, which usually is hydrolyzed to the corresponding α-halo acid during the aqueous work-up. However, when the work-up is conducted in the presence of nucleophiles such as alcohols, thiols, and amines, the corresponding α-halo esters, thioesters, and amides are formed, respectively. General features of the *HVZ reaction* are: 1) reaction conditions are relatively harsh, involving high temperatures (usually above 100 °C) and extended reaction times; 2) usually less than one equivalent of P or PX_3 catalyst is needed; 3) certain activated carboxylic acids and acid derivatives (e.g. anhydrides, acyl halides, 1,3-diesters) that are readily enolized can be halogenated in the absence of a catalyst; 4) α-bromination of substrates with long alkyl chains is completely selective; however, α-chlorination competes with random free radical chlorination processes so a mixture of mono- and polychlorinated products are obtained;[12,13] 5) attempts to bring about the fluorination or iodination of carboxylic acids under HVZ conditions have not been successful (however, there are other means of introducing these elements directly into carboxylic acids);[14] and 6) conducting the reaction at too high a temperature may result in the elimination of hydrogen halide from the product resulting in the formation of α,β-unsaturated carboxylic acids.[12] To improve the low selectivity of chlorination, certain modifications were introduced: 1) passing chlorine gas through the neat aliphatic acid (chains are no longer than C_8) at 140 °C in the presence of a strong acid catalyst and a free radical inhibitor;[7,8] 2) using TCNQ as the radical initiator gives monochlorinated products of acids of any chain length;[9] and 3) treatment of acylphosphonates with SO_2Cl_2 and subsequent hydrolysis of the α-chloro acylphosphonates to the corresponding α-halo acids.[10,11]



Mechanism:[15-17,4,18,19]

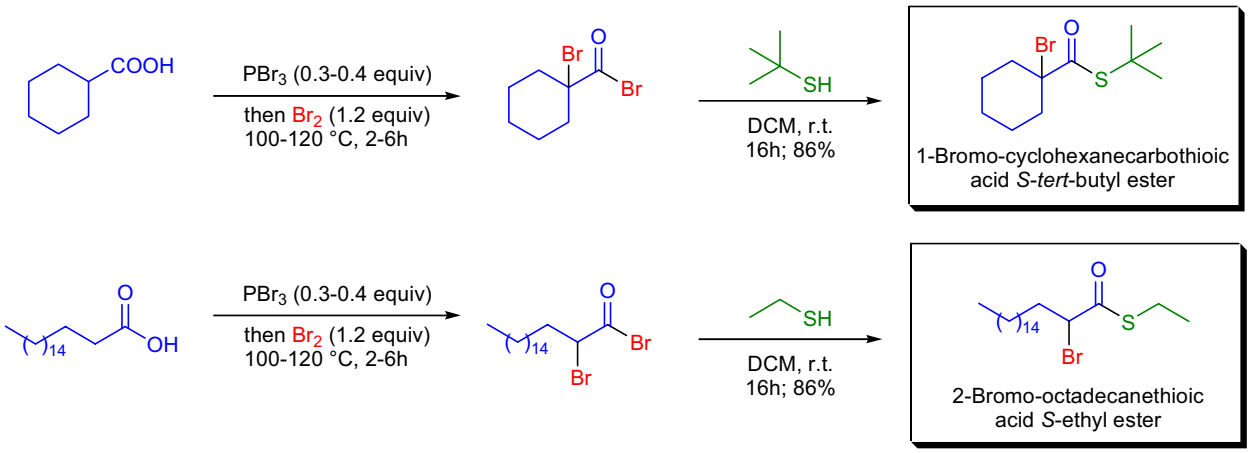
The first part of the mechanism includes the conversion of the carboxylic acid functionality to the acyl halide by the phosphorous trihalide. The acyl halide easily tautomerizes to the corresponding enol in the presence of a catalytic amount of acid.[15,4] The halogen subsequently reacts with the enol to afford the α-halo acyl halide, accompanied by the loss of a hydrogen halide. The halogen atoms in the PX_3 catalyst/reagent are not incorporated in the α-position of the acid.



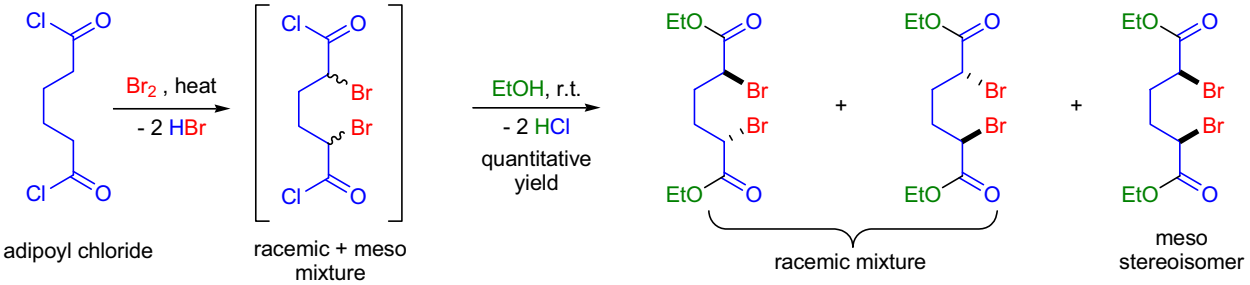
HELL-VOLHARD-ZELINSKY REACTION

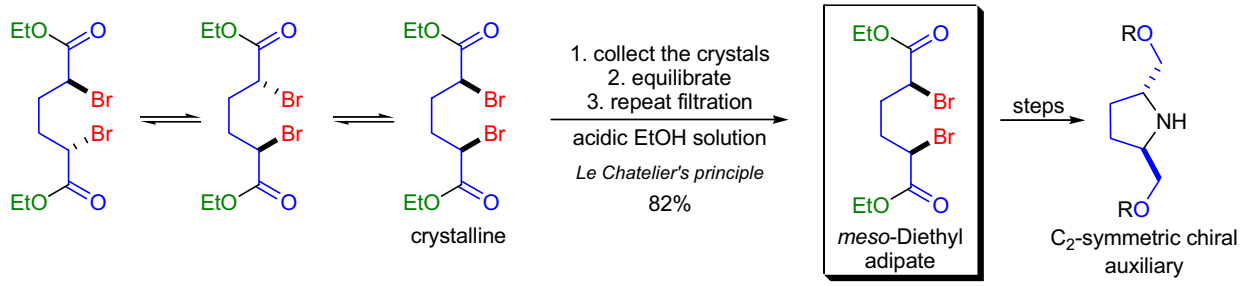
Synthetic Applications:

A convenient one-pot procedure for the preparation of α-bromo thioesters from carboxylic acids based on the *HVZ reaction* was developed by H.-J. Liu and co-workers.[20] The neat carboxylic acid was mixed with 0.4 equivalents of PBr_3, the resulting mixture was heated to 100-120 °C in an oil bath and 1.2 equivalents of liquid bromine was added in 1.5h. In the same flask, now containing the α-bromo acyl bromide, the solution of the thiol in dichloromethane was added to give the desired α-bromo thioesters in high yield.

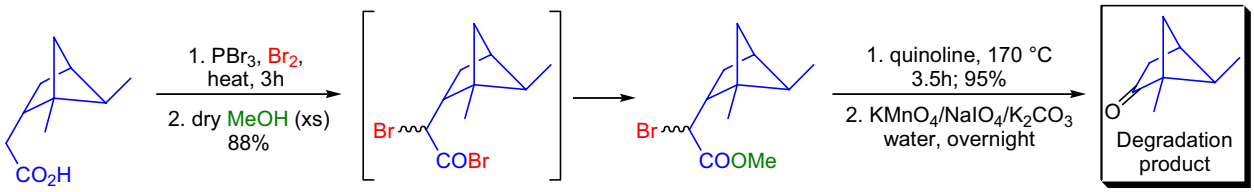


The preparation of C_2-symmetric 2,5-disubstituted pyrrolidines (utilized as chiral auxiliaries) often calls for *meso*-2,5-dibromoadipic esters as starting materials. An improvement in the synthesis of the *meso* stereoisomer was published by T. O'Neill and co-workers.[21] The authors began with the α-bromination of adipoyl chloride followed by esterification with ethanol to obtain a complex mixture of dibromo adipates (racemic + *meso*) in quantitative yield. The racemic and *meso*-dibromoadipates have very different crystalline properties, and these stereoisomers were found to be in equilibrium in an alcohol solution. Crystallizing the higher melting *meso* isomer and removing it from the equilibrium caused the remaining racemic mixture to convert to the *meso* isomer by shifting the equilibrium to the right, according to *Le Chatelier*'s *principle*.





In order to determine the structure of the photochemical rearrangement product of carvone camphor in methanol, and to prove its structure, the research team of T. Gibson subjected the bicyclic carboxylic acid product to a degradation sequence, which commenced with the *HVZ reaction*, followed by dehydrohalogenation, dihydroxylation and glycol cleavage.[22]



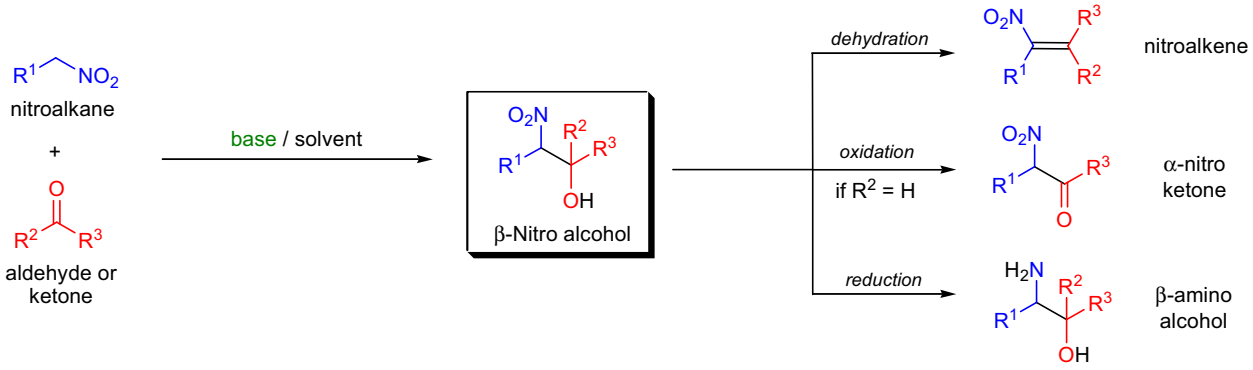
HENRY REACTION

(References are on page 598)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-18]*; Modifications & Improvements*[19-38]*; Theoretical Studies*[39]]

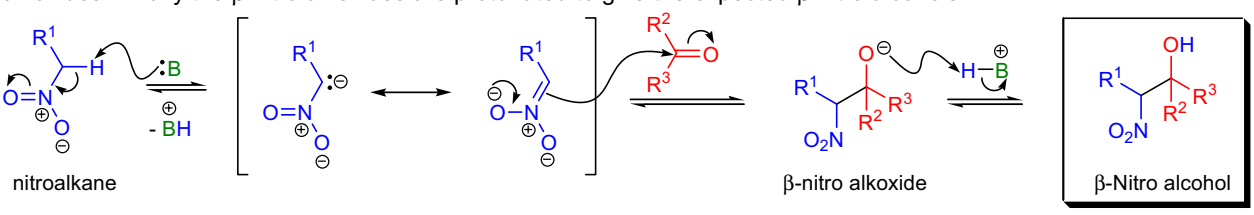
In 1895, L. Henry discovered that nitroalkanes were easily combined with aldehydes and ketones to give β-nitro alcohols in the presence of a base.[1,2] Since its discovery, the *aldol condensation* between nitroalkanes and carbonyl compounds (*nitro-aldol reaction*) has become a significant tool in the formation of C-C bonds and is referred to as the *Henry reaction*. The β-nitro alcohols are easily converted to other useful synthetic intermediates: 1) upon dehydration, nitroalkenes are formed that may be used as: a) dienes and dienophiles;[40-42] b) Michael acceptors;[43] or c) masked ketones (since the *Nef reaction* converts them to the corresponding ketones); 2) oxidation of the secondary alcohol functionality affords α-nitro ketones; 3) reduction of the nitro group gives β-amino alcohols; and 4) radical denitration affords secondary alcohols. General features of the *Henry reaction* are: 1) only a catalytic amount of base is necessary; 2) both ionic and nonionic bases may be used such as alkali metal hydroxides, alkoxides, carbonates, sources of fluoride ion (e.g., TBAF,[44] KF,[45] Al_2O_3-supported KF[46]), solid supported bases,[47] rare earth metal salts,[48] transition metal complexes[31,33,34] and nonionic organic nitrogen bases (e.g., amines,[49] TMG,[50] DBU,[51] DBN,[52] PAP[27]); 3) the solvents and bases do not have significant influence on the outcome of the reaction; 4) the steric properties of the reactants play an important role: hindered substrates (usually ketones) react slowly and side reactions often occur; 5) usually the β-nitro alcohols are formed as a mixture of diastereomers (*syn* and *anti*) but by modification of the reaction conditions high levels of diastereoselectivity can be achieved;[6,17] and 6) the stereocenter to which the nitro group is attached to is easy to epimerize. The *Henry reaction* is often accompanied by side reactions: 1) the β-nitro alcohols undergo dehydration, especially when aromatic aldehydes are used as substrates; however, by carefully chosen conditions this can be supressed; 2) with sterically hindered carbonyl compounds, a base-catalyzed self-condensation or *Cannizzaro reaction* may take place; and 3) the *retro-Henry reaction* may prevent the reaction from going to completion. Several modifications have been developed: 1) unreactive alkyl nitro compounds are converted to their corresponding dianions which react faster with carbonyl compounds;[19,20] 2) reactions of ketones are accelerated by using PAP as the base;[27] 3) high-pressure and solvent-free conditions improve chemo- and regioselectivity; 4) aldehydes react with α,α-doubly deprotonated nitroalkanes to give nitronate alkoxides that afford mainly *syn*-nitro alcohols upon kinetic protonation;[6] 5) nitronate anions on which the alcohol oxygen atom is silyl-protected give predominantly *anti*-β-nitro alcohols upon kinetic protonation;[6] 6) nitronate anions in which one oxygen atom of the nitro group is silyl-protected give mainly anti-β-nitro alcohols when reacted with aldehydes in the presence of catalytic amounts of fluoride ion;[6] 7) in the presence of chiral catalysts the *asymmetric Henry reaction* can be realized;[13,15,17,18,34] and 8) when imines are used instead of carbonyl compounds as substrates, the *aza-Henry reaction* takes place to afford nitroamines; upon the reduction of nitroamines, vicinal diamines are obtained.[28,37]



R^1 = alkyl, aryl, CO_2R, alkenyl; R^2, R^3 = alkyl, aryl, H; base = NR_3, DBU, DBN, PAP, TMG, KF, TBAF, Al_2O_3, $La_3(OR)_9$, NaOH, NaOR, amberlyst A-21, etc.

Mechanism:[53,51]

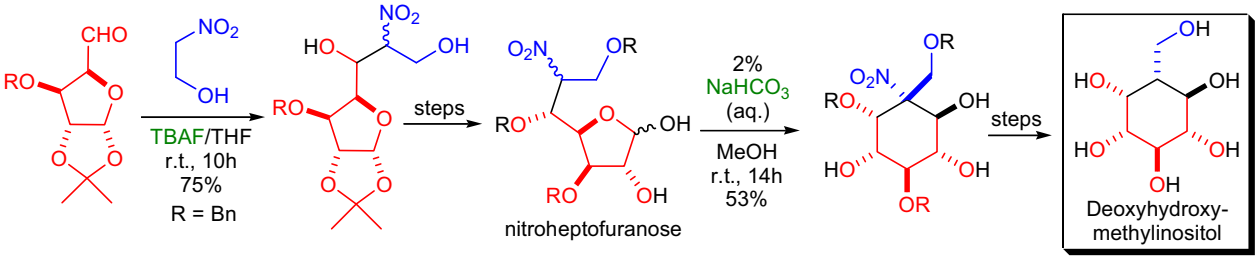
All the steps in the *Henry reaction* are completely reversible. The first step of the mechanism is the deprotonation of the nitroalkane by the base at the α-position to form the corresponding resonance stabilized anion. Next, an *aldol reaction* (*C*-alkylation of the nitroalkane) takes place with the carbonyl compound to form diastereomeric β-nitro alkoxides. Finally the β-nitro alkoxides are protonated to give the expected β-nitro alcohols.



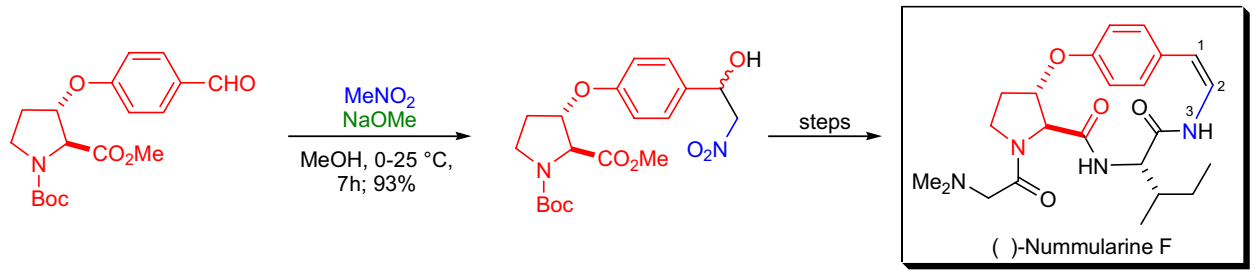
HENRY REACTION

Synthetic Applications:

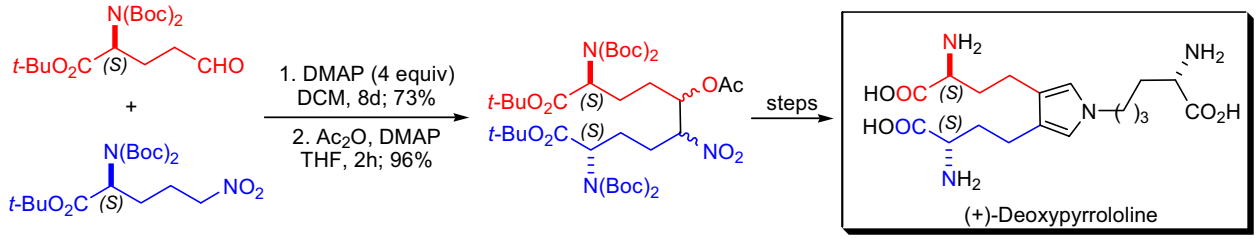
R.J. Estévez and co-workers utilized the *intramolecular Henry reaction* in their synthetic strategy to convert nitroheptofuranoses into deoxyhydroxymethylinositols.[54] The starting nitroheptofuranoses were prepared as a mixture of diastereomers from a D-glucose derivative and 2-nitroethanol using the *intermolecular Henry reaction*. The key *intramolecular Henry reaction* was brought about by treating this diastereomeric mixture with 2% aqueous sodium bicarbonate solution to afford an enantiomerically pure six-membered carbocycle. Removal of the nitro group and cleavage of the protecting groups gave the desired 1D-3-deoxy-3-hydroxymethyl-*myo*-inositol.



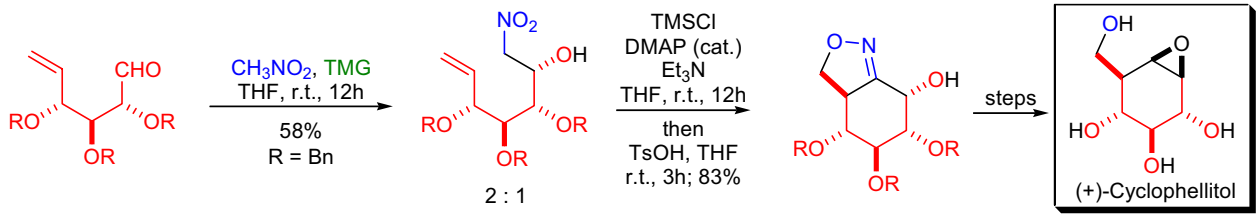
The first total synthesis of the 14-membered para ansa cyclopeptide alkaloid (–)-nummularine F was accomplished in the laboratory of M.M. Joullié.[55] The *N*3 nitrogen atom was introduced by using the *Henry reaction* between the 4-formylphenoxy group and the anion of nitromethane, followed by reduction of the nitro group to the corresponding amine. The epimeric benzyl alcohols did not pose a problem since they were dehydrated at the end of the synthetic sequence to give the C1-C2 double bond.



The bone collagen cross-link (+)-deoxypyrrololine has potential clinical utility in the diagnosis of osteoporosis and other metabolic bone diseases. Intrigued by its novel structure and its promise to allow the early discovery of various bone diseases, the research team of M. Adamczyk developed a convergent total synthesis for this 1,3,4-trisubstituted pyrrole amino acid.[56] The key step of the synthesis was the union of the nitroalkane and aldehyde fragments to obtain a diastereomeric mixture of the expected -nitro alcohol in good yield. This new functionality served as a handle to install the pyrrole ring.



The total synthesis of (+)-cyclophellitol containing a fully oxygenated cyclohexane ring was accomplished by T. Ishikawa and co-workers.[57] The synthetic strategy was based on the *intramolecular silyl nitronate [3+2] cycloaddition* reaction. The cycloaddition precursor was prepared by the *Henry reaction* starting from a D-glucose-derived aldehyde.



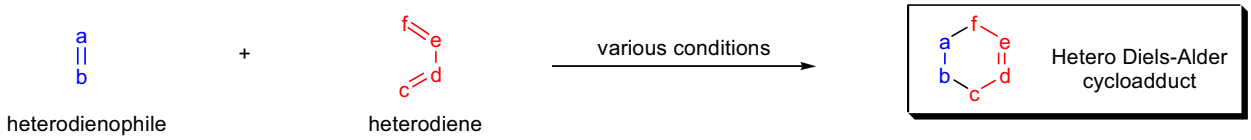
HETERO DIELS-ALDER CYCLOADDITION

(References are on page 599)

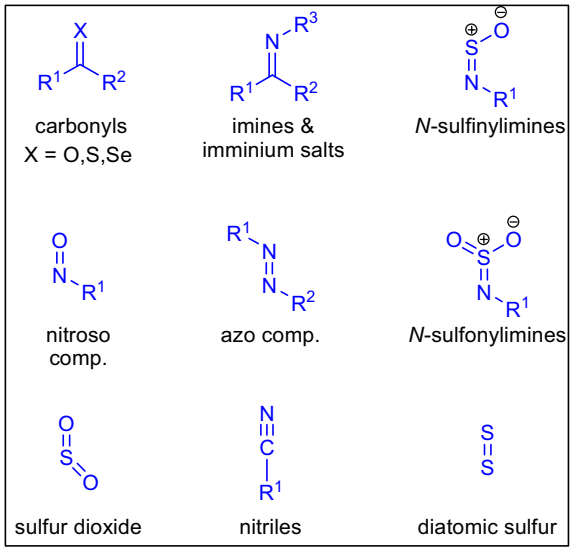
Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-43]; *Theoretical Studies*[44-59]]

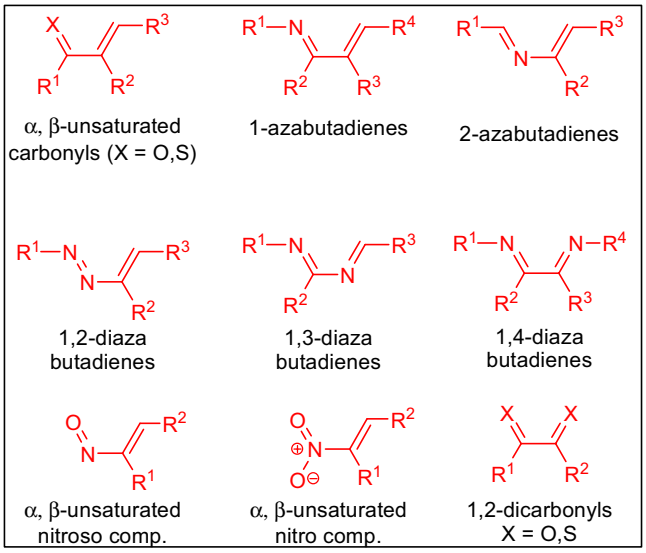
The [$4\pi + 2\pi$] cyclization of a diene and a dienophile to form a cyclohexene derivative is known as the *Diels-Alder cycloaddition* (*D-A cycloaddition*), but if one or more of the atoms in either component is other than carbon, then the reaction is referred to as the *hetero D-A cycloaddition (HDA)*. The first example of an imine participating as a heterodienophile was reported by K. Alder in 1943.[1] Since this initial report, the utilization of the *HDA reaction* in the synthesis of heterocyclic compounds has become pervasive. The general features of these reactions are: 1) high levels of regio- and diastereocontrol are observed and the outcome of the reaction can be predicted to the same extent as in the case of the *all-carbon D-A reaction*; 2) when the diene component does not contain a heteroatom and the heterodienophile is electron-deficient because of the heteroatom(s), the cycloaddition proceeds as a *normal electron-demand D-A reaction* (diene HOMO interacts with the LUMO of the heterodienophile); 3) when the diene contains one or more heteroatoms and/or electron-withdrawing substituents, it becomes electron-deficient, and therefore an electron-rich dienophile is needed and the reaction proceeds as an *inverse electron-demand D-A reaction* (heterodiene LUMO interacts with the HOMO of the dienophile); 4) when the heterodiene is substituted with one or more strongly electron-donating groups, the electron-deficient nature of the diene can be reversed and a *normal electron-demand hetero D-A reaction* can take place with a suitably electron-deficient dienophile; 5) *HDA reactions* can be catalyzed by Lewis acids, usually exhibiting higher regio- and stereoselectivities than uncatalyzed processes; and 6) by using a chiral auxiliary or catalyst the *asymmetric HDA reaction* can be realized.[22,31,38]



Most common heterodienophiles

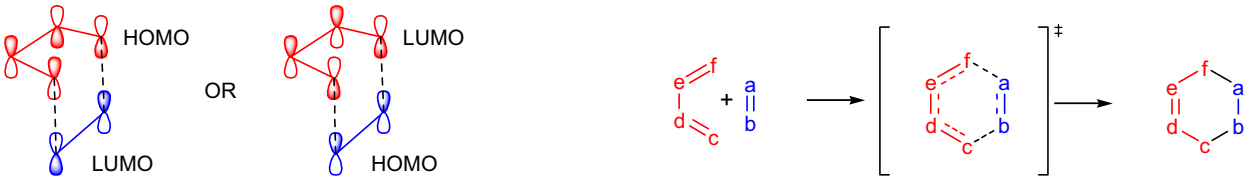


Most common heterodienes



Mechanism: [60-69,51,53]

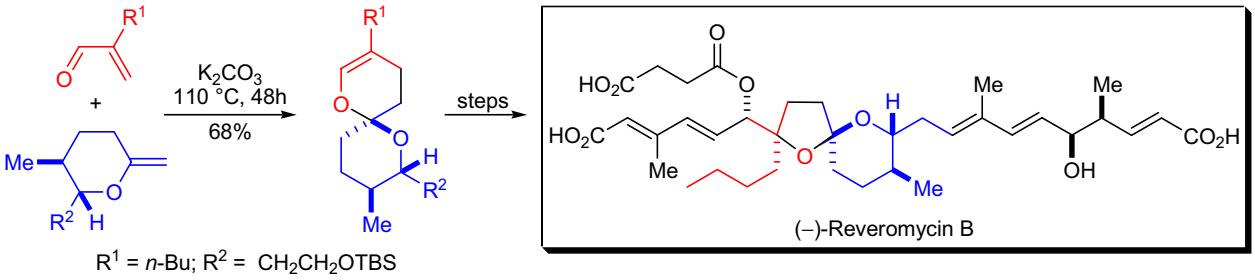
Mechanistically the *all-carbon Diels-Alder reaction* is generally considered a concerted, pericyclic reaction with an aromatic transition state, but there is also evidence for a stepwise (diradical or diion) process. For *HDA reactions*, theoretical studies revealed that the transition states are usually concerted, but less symmetrical. Depending on the reaction conditions and the number and type of substituents on the reactants, the *HDA reaction* can become stepwise, exhibiting a polar transition state.



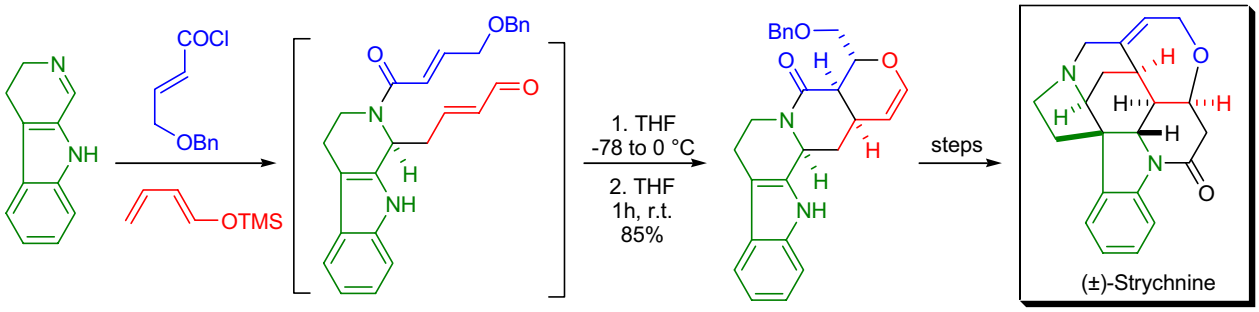
HETERO DIELS-ALDER CYCLOADDITION

Synthetic Applications:

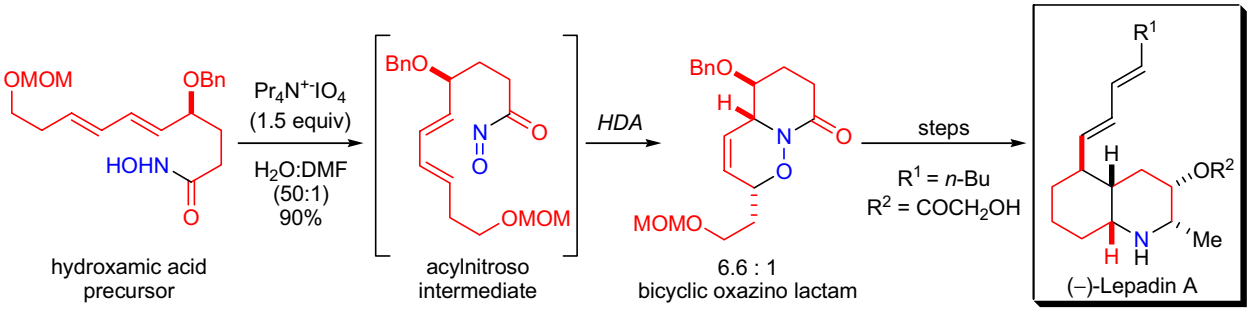
The enantioselective total synthesis of the epidermal growth factor inhibitor (–)-reveromycin B was completed by M.A. Rizzacasa and co-workers.[70] The key step to assemble the 6,6-spiroketal moiety was the *HDA reaction* between an α,β-unsaturated aldehyde (butylacrolein) and an enantiopure methylene pyran. The desired 6,6-spiroketal was obtained as a single enantiomer after heating the neat reactants in the absence of solvents at 110 °C for 2 days.



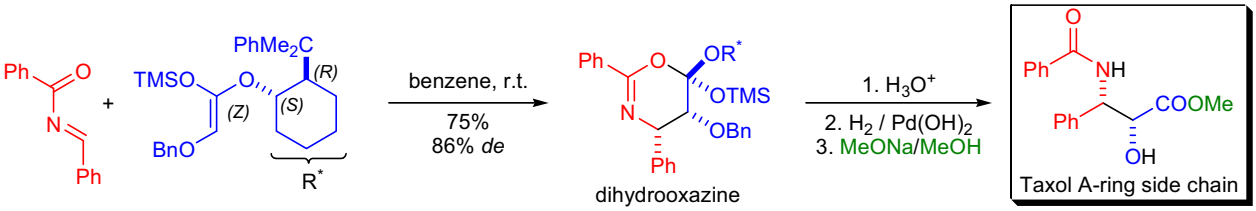
In the laboratory of S.F. Martin, a biomimetic approach toward the total synthesis of (±)-strychnine was developed by using tandem *vinylogous Mannich addition* and *HDA reaction* to construct the pentacyclic heteroyohimboid core of the natural product.[71] The commercially available 4,9-dihydro-3*H*-β-carboline was first converted to the corresponding *N*-acylium ion and then reacted with 1-trimethylsilyloxybutadiene in a *vinylogous Mannich reaction*. The resulting cycloaddition precursor readily underwent the expected *HDA reaction* in 85% yield.



The first total synthesis of the decahydroquinoline alkaloid (–)-lepadin A was reported by C. Kibayashi et al.[72] The authors' approach was based on the *intramolecular HDA reaction* of an *in situ* generated acylnitroso compound. The precursor hydroxamic acid was oxidized with $Pr_4N(IO_4)$ in water-DMF (50:1) to form an acylnitroso compound that smoothly underwent the *[4+2] cycloaddition*. The *trans* bicyclic oxazino lactam product was formed as a 6.6:1 mixture of diastereomers; a result of the hydrophobic effect.



C.H. Swindell and co-workers enantioselectively prepared the Taxol A-ring side chain by using a *thermal inverse electron-demand HDA reaction* as the key step.[73] The (*Z*)-ketene acetal was attached to a chiral auxiliary and reacted with the *N*-benzoylaldimine to give the desired dihydrooxazine in 75% yield with good diastereoselectivity.



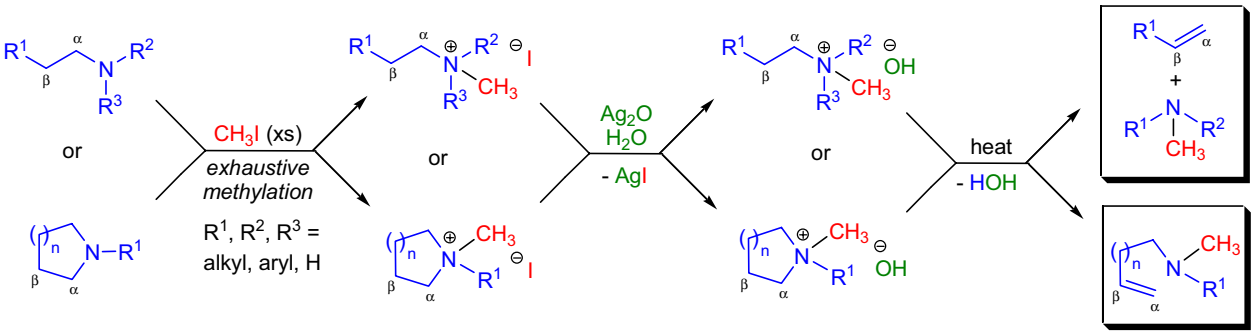
HOFMANN ELIMINATION

(References are on page 601)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-9]*; Modifications & Improvements*[10,11]*; Theoretical Studies*[12]]

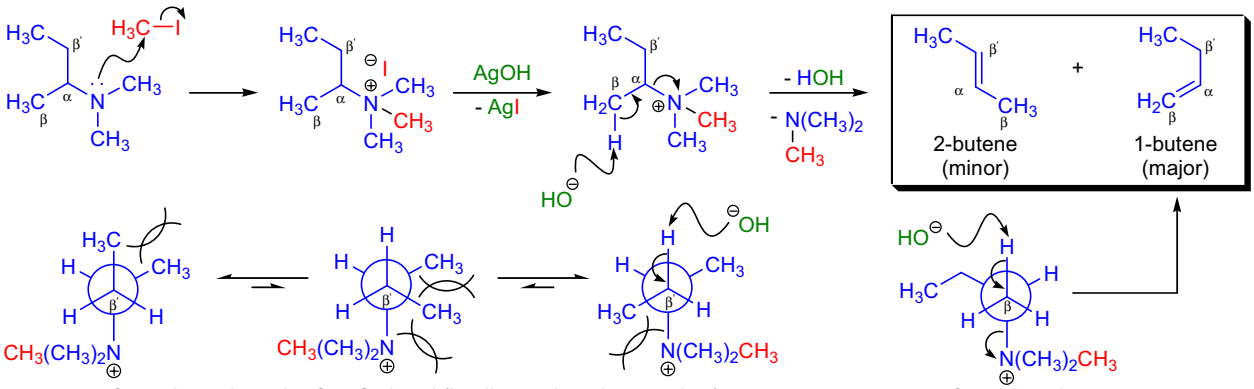
In 1851, A.W. Hofmann discovered that when trimethylpropylammonium hydroxide is heated, it decomposes to form a tertiary amine (trimethylamine), an olefin (propene), and water.[1,2] Widespread use of this transformation did not occur until 1881, when Hofmann applied this method to the study of the structure of piperidines and nitrogen-containing natural products (e.g., alkaloids).[3,4] The pyrolytic degradation of quaternary ammonium hydroxides to give a tertiary amine, an olefin and water is known as the *Hofmann elimination*. The process involves three steps: 1) exhaustive methylation of the primary, secondary or tertiary amine with excess methyl iodide to yield the corresponding quaternary ammonium iodide; 2) treatment with silver oxide and water (the iodide counterion is exchanged with hydroxide ion); and 3) the aqueous or alcoholic solution of the quaternary ammonium hydroxide is concentrated under reduced pressure and heated between 100-200 °C to bring about the elimination. Under reduced pressure, the elimination tends to take place at lower temperatures with higher yields. When the substrate is heterocyclic or the nitrogen is at a ring junction or at the bridgehead, the above steps need to be repeated multiple times to completely eliminate the nitrogen from the molecule. In the old days the number of repetitions indicated the position of the nitrogen atom in the original molecule and gave valuable structural clues about the unknown substance. The *Hofmann elimination* is a β-elimination, that is, the hydrogen is abstracted by the base (hydroxide ion) from the β-carbon atom. In the case of unsymmetrical compounds (in which more than one alkyl group attached to the nitrogen has β-hydrogen atoms), the β-hydrogen located at the least substituted carbon is abstracted by the base to form the less substituted alkene (Hofmann's rule).[1] The *Hofmann elimination* has few side reactions: occasionally the base can act as a nucleophile and substitution products are isolated. When the substrate does not have any alkyl groups with β-hydrogen, the main product of the pyrolysis is the substitution product (alcohol when water is the solvent or ether when no solvent is used).[13] An important variant of the *Hofmann elimination* is the *Wittig modification* in which the quaternary ammonium halide is treated with strong bases (alkylithiums, KNH_2/liquid NH_3, etc.) to afford an olefin and tertiary amine *via* an E_i mechanism.[11]



Mechanism:

[14-27,11,28-30,12,31-34]

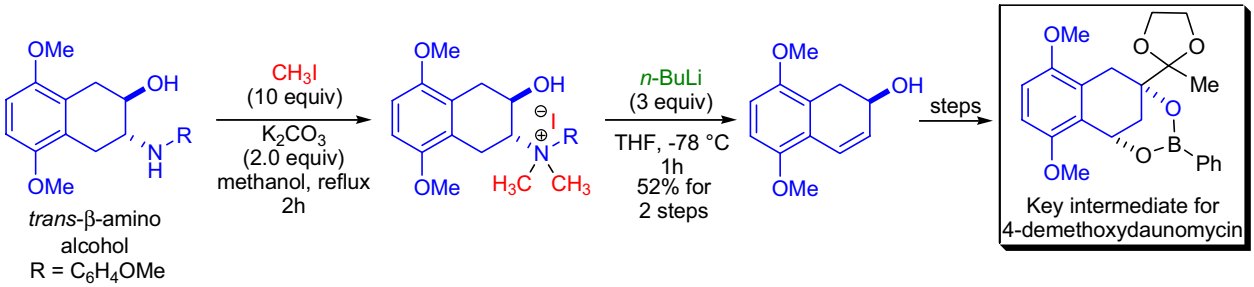
Generally the mechanism of the *Hofmann elimination* is E2, and it is an *anti* elimination (the leaving groups have to be *trans*-diaxial/antiperiplanar). However, in the case of certain substrates, the mechanism can be shifted in the carbanionic $E1_{cb}$ direction when the *trans* elimination process is unfavorable and the compounds contain sufficiently acidic allylic or benzylic β-hydrogen atoms. In acyclic substrates, the elimination gives rise to the least substituted alkene (Hofmann product). There are three factors which play a role in determining the outcome of the elimination: 1) the extent to which the double bond is developed in the transition state; 2) the acidity of the β-hydrogen atom; and 3) the influence of steric interactions in the transition state (this is the most widely accepted argument). In cycloalkyl ammonium salts, the most important factor in the elimination process is the availability of the *trans* β-hydrogen atoms. When both the β and β' trans hydrogens atoms are available in cyclic substrates, the elimination gives the most substituted alkene (*Saytzeff's rule*).



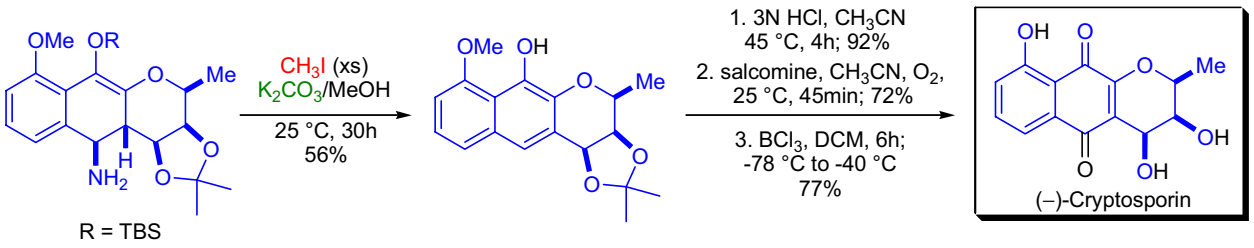
HOFMANN ELIMINATION

Synthetic Applications:

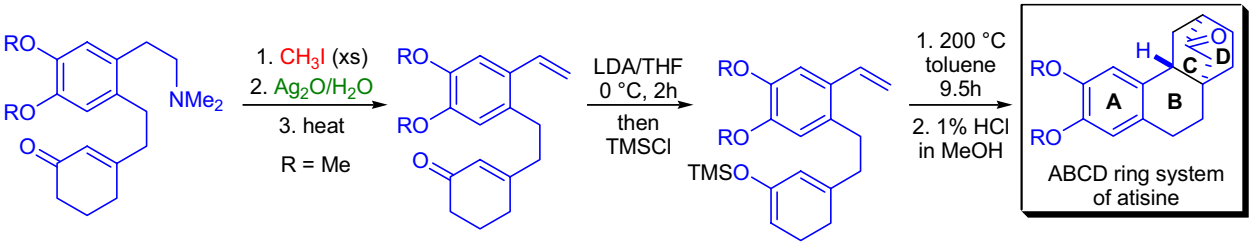
The enantioselective formal total synthesis of 4-demethoxydaunomycin was accomplished in the laboratory of M. Shibasaki.[35] The key intermediate was prepared from an enantiomerically enriched *trans*-β-amino alcohol, which was first exhaustively methylated to the corresponding quaternary ammonium salt. This salt was then treated with excess *n*-BuLi to afford the desired allylic alcohol in moderate yield.



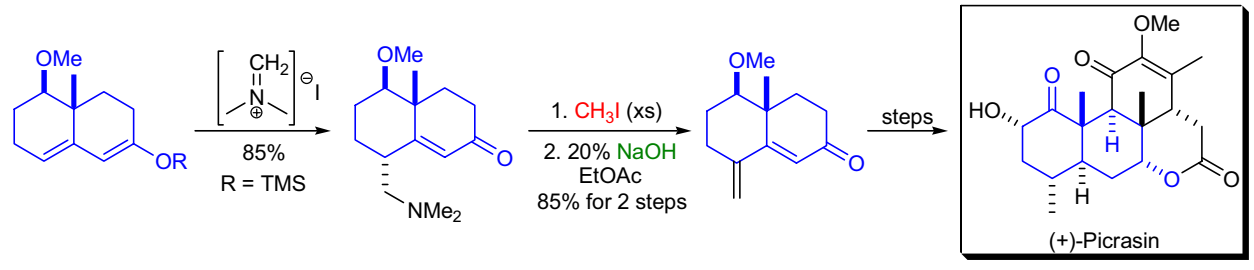
During the total synthesis of fungal metabolite (–)-cryptosporin, R.W. Franck and co-workers developed an efficient method for the regiospecific synthesis of naphtho[2,3-*b*]pyrano- and [2,3-*b*]furanoquinones using the *Bradscher cycloaddition* as the key step.[36] The *Hofmann elimination* of a primary amine located at the benzylic position, was carried out in the last steps of the synthesis. Interestingly, exhaustive methylation of the primary amine with excess MeI in MeOH/K_2CO_3 resulted in spontaneous elimination of the quaternary ammonium salt at room temperature.



The ABCD ring system of the diterpene alkaloid atisine was constructed by T. Kametani et al using an *intramolecular Diels-Alder cycloaddition* reaction as the key step.[37] The dienophile was obtained by the traditional *Hofmann degradation* of the corresponding dimethylamino precursor. The diene was prepared by the kinetic enolization of the cyclohexenone system with LDA.



In the laboratory of D.S. Watt, the enantioselective total synthesis of (+)-picrasin B was achieved from (–)-Wieland-Miescher ketone.[38] At the early stages of the synthetic effort, an exocyclic double bond was introduced in a two-step procedure by first alkylating the bicyclic conjugated TMS enol ether with Eschenmoser's salt at the γ-position, followed by *Hofmann elimination* of the dimethylamino group.



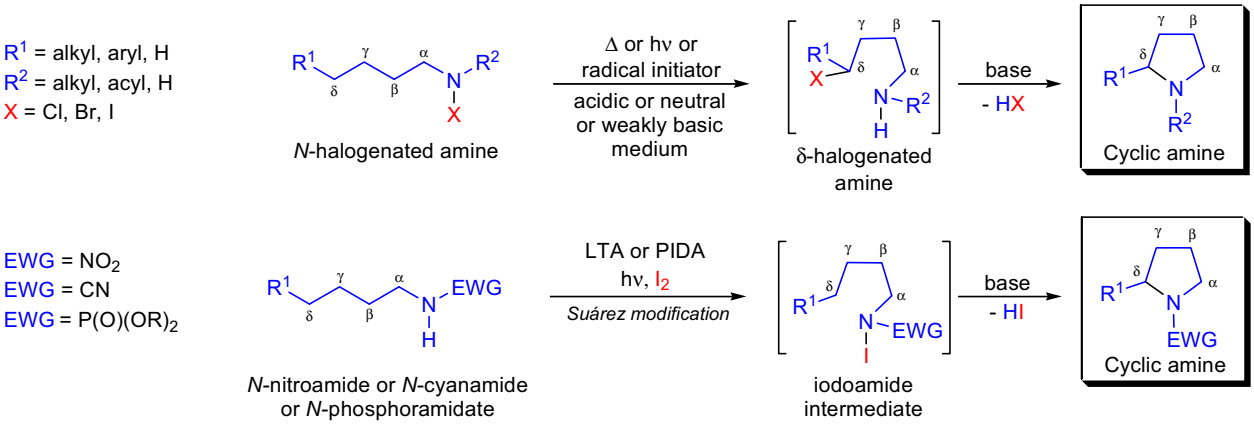
HOFMANN-LÖFFLER-FREYTAG REACTION
(REMOTE FUNCTIONALIZATION)

(References are on page 602)

Importance:

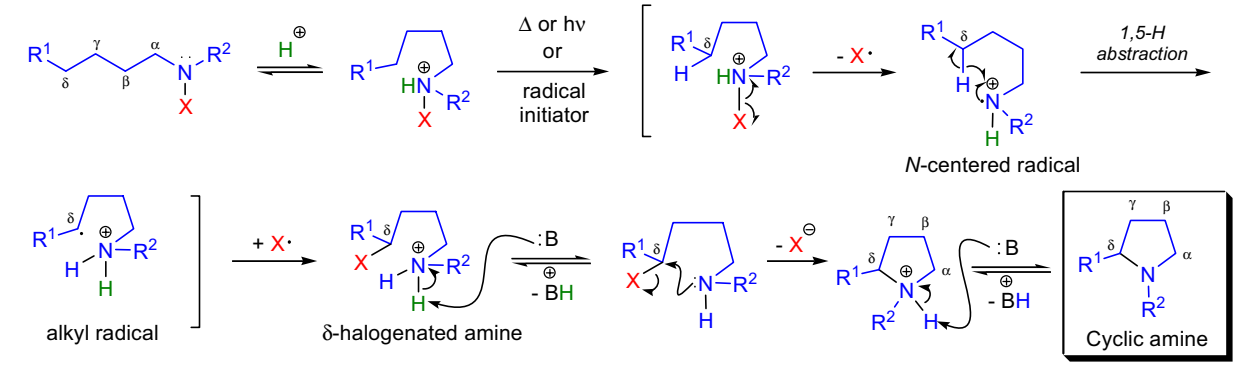
[*Seminal Publications*[1-4]*; Reviews*[5-14]*; Modifications & Improvements*[15-22]*; Theoretical Studies*[23]]

In the early 1880s, A.W. Hofmann was trying to determine if piperidine, whose structure was unknown at the time, was unsaturated by exposing it to hydrohalic acids or bromine. During these investigations he prepared various *N*-haloamines and *N*-haloamides and studied their reactions under acidic and basic conditions. The treatment of 1-bromo-2-propylpiperidine with hot sulfuric acid, followed by basic work-up, yielded octahydroindolizine, a bicyclic tertiary amine.[1-3] In 1909, K. Löffler and C. Freytag applied this transformation to simple secondary amines and realized that it was a general method for the preparation of pyrrolidines.[4] The formation of cyclic amines from *N*-halogenated amines *via* an *intramolecular 1,5-hydrogen atom transfer* to a nitrogen radical is known as the *Hofmann-Löffler-Freytag reaction* (*HLF reaction*). General features of the reactions are: 1) it may be carried out in acidic solutions, but neutral and even weakly basic reaction conditions have been applied successfully;[24,25] 2) it can be conducted under milder conditions if the intermediate alkyl radical is stabilized by a heteroatom (e.g., nitrogen);[24] 3) initiation of the radical process can be done by heating, irradiation with light or with radical initiators (e.g., dialkyl peroxides, metal salts); 4) the initially formed nitrogen-centered radical abstracts a H-atom mostly from the δ-position (or 5-position) and predominantly 5-membered rings are formed; and 5) rarely, in rigid cyclic systems, the formation of 6-membered rings is possible.[24,15] The original strongly acidic reaction conditions are often not compatible with the sensitive functional and protecting groups of complex substrates, therefore several modifications were introduced: 1) photolysis of *N*-bromoamides proceeds under neutral conditions;[26] 2) in the presence of persulfates and metal salts, sulfonamides undergo remote γ- and δ-halogenation under neutral conditions;[27] 3) the most important variant of this reaction is the *Suárez modification* in which *N*-nitroamides,[20] *N*-cyanamides,[18] and *N*-phosphoramidates[22] react with hypervalent iodine reagents in the presence of iodine (I_2) under neutral conditions to generate nitrogen-centered radicals *via* the hypothetical iodoamide intermediate. The *HLF reaction* is closely related to the well-known *Barton nitrite ester reaction*, which proceeds *via* alkoxyl radicals and has been extensively used for remote functionalization in steroid synthesis.



Mechanism: [28-31]

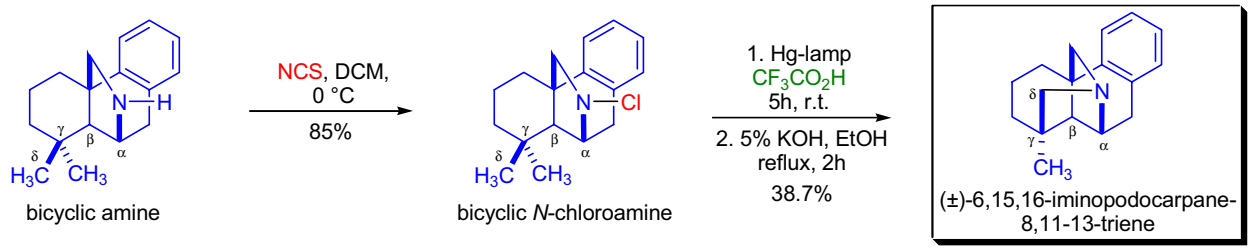
The mechanism of the *HLF reaction* is a radical chain reaction. When the reaction is conducted in acidic medium, the first step is the protonation of the *N*-halogenated amine to afford the corresponding *N*-halogenated ammonium salt. Heat, irradiation with light or treatment with radical initiators generates the nitrogen-centered radical, *via* the homolytic cleavage of the *N*-halogen bond, which readily undergoes an *intramolecular 1,5-hydrogen abstraction*. Next, the newly formed alkyl radical abstracts a halogen atom intermolecularly. Treatment of the δ-halogenated amine with base gives rise to the desired cyclic amine product.



HOFMANN-LÖFFLER-FREYTAG REACTION
(REMOTE FUNCTIONALIZATION)

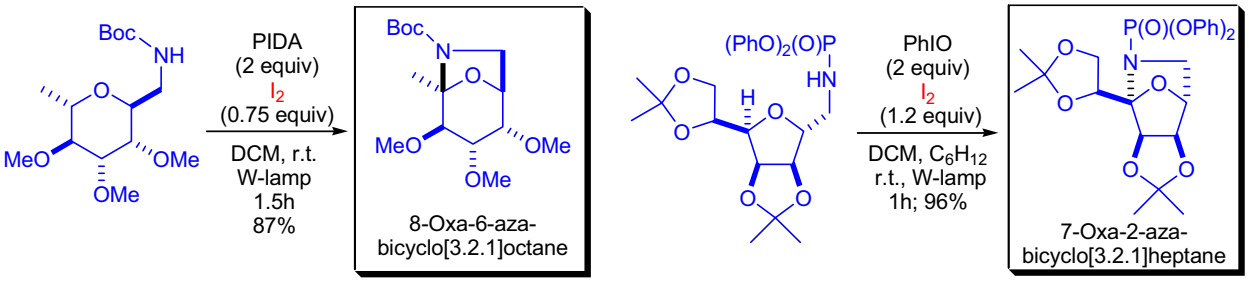
Synthetic Applications:

In the laboratory of Y. Shibanuma, a novel synthetic approach was developed to construct the bridged azabicyclic ring system of the diterpene alkaloid kobusine.[32] The bridged nitrogen structure of the target (±)-6,15,16-imino-podocarpane-8,11,13-triene was synthesized by means of a *Hofmann-Löffler-Freytag reaction* from a bicyclic chloroamine. First the bicyclic amine was converted to the corresponding *N*-chloro derivative in good yield by treatment with NCS in dichloromethane. The solution of the bicyclic *N*-chloroamine in trifluoroacetic acid was then irradiated with a 400 W high pressure Hg-lamp under nitrogen atmosphere at r.t. for several hours to afford a moderate yield of the product.



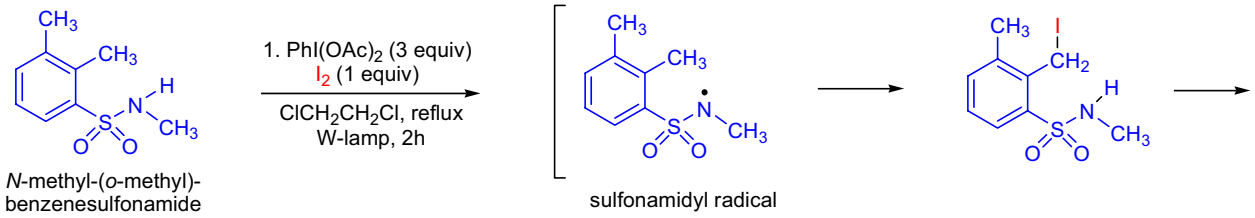
bicyclic amine — bicyclic *N*-chloroamine — (±)-6,15,16-iminopodocarpane-8,11-13-triene

E. Suárez and co-workers prepared chiral 7-oxa-2-azabicyclo[3.2.1]octane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems derived from carbohydrates *via* an intramolecular hydrogen abstraction reaction promoted by *N*-centered radicals.[22] The *N*-centered radicals were obtained under mild conditions (*Suárez modification*) from phenyl and benzyl amidophosphates and alkyl and benzyl carbamate derivatives of aminoalditols by treatment with PIDA/I_2 or PhIO/I_2. The initial *N*-radical undergoes a 1,5-hydrogen abstraction to form an alkyl radical, which is oxidized to the corresponding stabilized carbocation (oxocarbenium ion) under the reaction conditions. The overall transformation may be considered as an *intramolecular N-glycosidation* reaction.

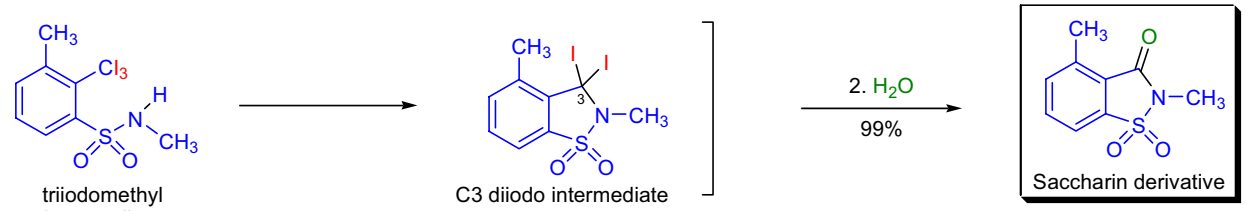


8-Oxa-6-aza-bicyclo[3.2.1]octane — 7-Oxa-2-aza-bicyclo[3.2.1]heptane

The *Suárez modification of the HLF reaction* was the basis of the new synthetic method developed by H. Togo et al.[33] The authors prepared *N*-alkyl-1,2-benzisothiazoline-3-one-1,1-dioxides (*N*-alkylsaccharins) from *N*-alkyl(*o*-methyl)-arenesulfonamides using (diacetoxyiodo)arenes in the presence of iodine *via* sulfonamidyl radicals. The transformations did not work in the dark, indicating the radical nature of the reaction. The yields varied from moderate to excellent and the nature of the aromatic substituents on both the substrate and the (diacetoxyiodo)arenes were important. It should be noted that the oxygen atom at the C3 position most likely arises from the hydrolysis of a C3 diiodo intermediate (not isolated).



N-methyl-(*o*-methyl)-benzenesulfonamide — sulfonamidyl radical



triiodomethyl intermediate — C3 diiodo intermediate — Saccharin derivative

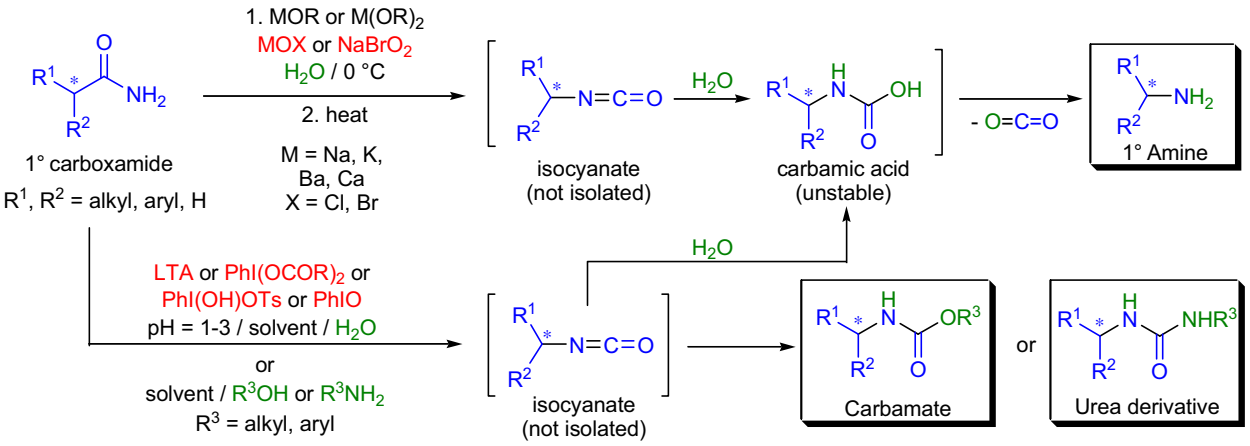
HOFMANN REARRANGEMENT

(References are on page 602)

Importance:

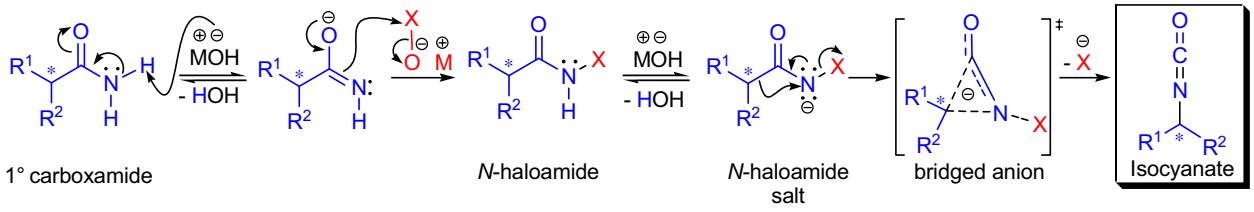
[*Seminal Publications*[1-5]; *Reviews*[6-15]; *Modifications & Improvements*[16-30]]

In 1881, A.W Hofmann found that by treating acetamide with one equivalent of bromine (Br_2) and sodium or potassium hydroxide it afforded *N*-bromoacetamide. Upon further deprotonation and heating, *N*-bromoacetamide gave an unstable salt that in the absence of water readily rearranged to methyl isocyanate.[1] However, in the presence of water and excess base the product was methylamine. The conversion of primary carboxamides to the corresponding one-carbon shorter amines is known as the *Hofmann rearrangement* (also known as the *Hofmann reaction*). According to the standard procedure, the amide is dissolved in a cold solution of an alkali hypobromite or hypochlorite and the resulting solution is heated to ~70-80 °C to bring about the rearrangement. The general features of this transformation are: 1) the hypohalite reagents are freshly prepared by the addition of chlorine gas or bromine to an aqueous solution of KOH or NaOH; 2) the amides cannot contain base-sensitive functional groups under the traditional basic reaction conditions, but acid-sensitive groups (e.g., acetals) remain unchanged; 3) the isocyanate intermediate is not isolated, since under the reaction conditions it is readily hydrolyzed (or solvolyzed) to the corresponding one-carbon shorter amine *via* the unstable carbamic acid; 4) when the reaction is conducted under phase-transfer catalysis conditions, the isocyanates may be isolated;[31,25] 5) if the starting amide is enantiopure (the carbonyl group is directly attached to the stereocenter), there is a *complete retention of configuration* in the product amine; 6) the *Hofmann rearrangement* gives high yields for a wide variety of aliphatic and aromatic amides but the best yields for aliphatic amides are obtained if the substrate has no more than 8 carbons (hydrophilic amides); and 7) α,β-unsaturated amides and amides of α-hydroxyacids rearrange to give aldehydes or ketones.[32,33] Since the discovery of the *Hofmann rearrangement*, several modifications were introduced: 1) for hydrophobic amides, the use of methanolic sodium hypobromite (bromine added to sodium methoxide in methanol) results in high yields of the corresponding methylurethanes;[6] 2) for acid- and base-sensitive substrates the use of neutral *electrochemically induced Hofmann rearrangement* was developed;[18,26,28] 3) in order to extend the scope of the reaction for base-sensitive substrates, the *oxidative Hofmann rearrangement* may be carried out with LTA or hypervalent iodine reagents (PIDA, PIFA, PhI(OH)OTs, etc.) under mildly acidic conditions;[16,23,14,29] and 4) when hypervalent iodine reagents or LTA are used in the presence of an amine or an alcohol, the generated isocyanate is *in situ* converted to the corresponding carbamate or urea derivative.[17]



Mechanism:[34-40,19,41]

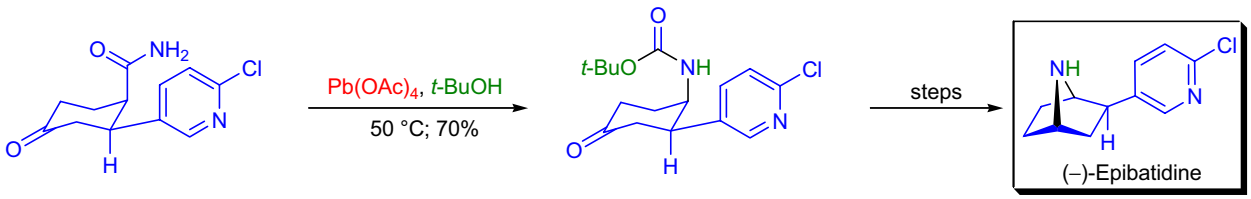
The mechanism of the *Hofmann rearrangement* is closely related to the *Curtius*, *Lossen* and *Schmidt rearrangements*. The first step is the formation of an *N*-halogen substituted amide. Next, the *N*-haloamide is deprotonated by the base to the corresponding alkali salt that is quite unstable and quickly undergoes a concerted rearrangement to the isocyanate *via* a bridged anion. This mechanistic picture is strongly supported by kinetic evidence.[36-39] As a result, the *Hofmann rearrangement* proceeds with complete retention of configuration.



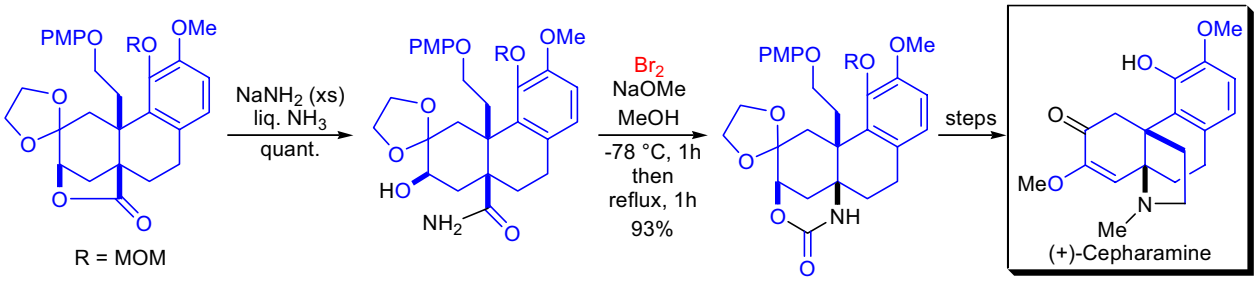
HOFMANN REARRANGEMENT

Synthetic Applications:

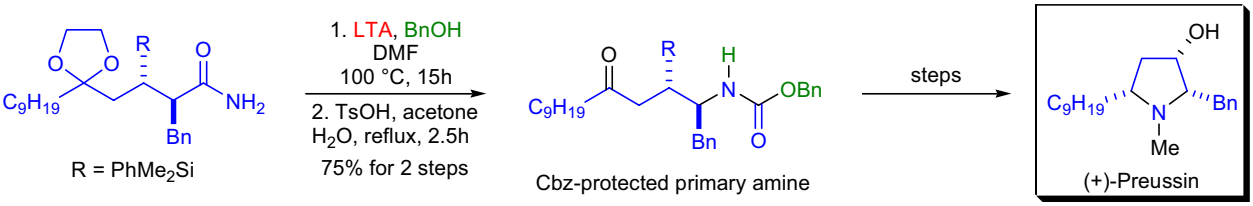
The enantioselective total synthesis of (–)-epibatidine was accomplished in the laboratory of D.A. Evans.[42] The key steps in the synthetic sequence included a *hetero Diels-Alder reaction* and a modified *Hofmann rearrangement*. The primary carboxamide was subjected to lead tetraacetate in *tert*-butyl alcohol that brought about the rearrangement and gave the corresponding *N*-Boc protected primary amine in good yield. A few more steps from this intermediate led to the completion of the total synthesis.



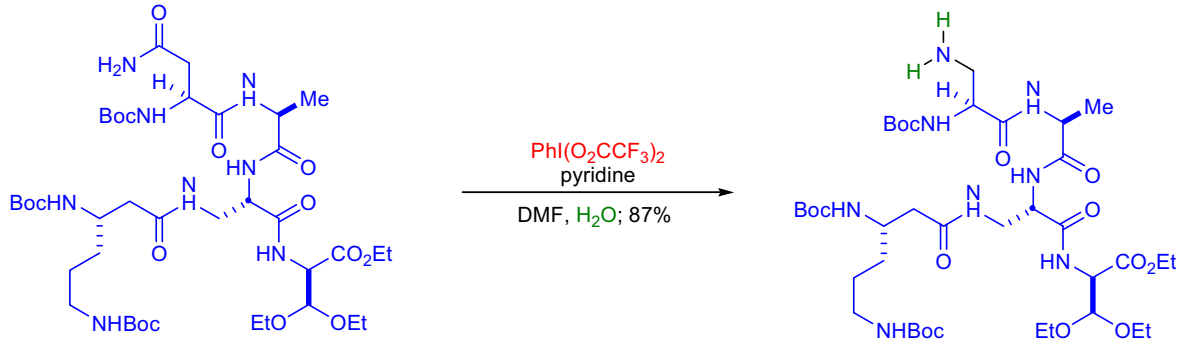
The first asymmetric total synthesis of the hasubanan alkaloid (+)-cepharamine was completed by A.G. Schultz et al.[43] In order to construct the *cis*-fused *N*-methylpyrrolidine ring, the advanced tetracyclic lactone was first converted to the primary carboxamide by treatment with sodium amide in liquid ammonia. Next the *Hofmann rearrangement* was induced with sodium hypobromite in methanol initially affording the isocyanate, which upon reacting with the free secondary alcohol intramolecularly gave the corresponding cyclic carbamate in excellent yield.



R. Verma and co-workers developed a silicon-controlled total synthesis of the antifungal agent (+)-preussin using a *modified Hofmann rearrangement* as one of the key steps in the final stages of the synthetic sequence.[44] The primary carboxamide was exposed to LTA in DMF in the presence of benzyl alcohol, which resulted in an efficient *Hofmann rearrangement* to afford the Cbz-protected primary amine. As expected, there was no loss of optical activity in the product. The silicon group was finally converted to the corresponding secondary alcohol by the *Fleming-Tamao oxidation*.



During the late stages of the asymmetric total synthesis of capreomycidine IB it was necessary to transform an asparagine residue into a diaminopropanoic acid residue.[45] R.M. Williams et al. employed a chemoselective *Hofmann rearrangement*, thereby avoiding protection and deprotection steps that would have been necessary had the diaminopropanoic acid been introduced directly. The complex pentapeptide was treated with PIFA and pyridine in the presence of water to afford the primary amine in high yield.



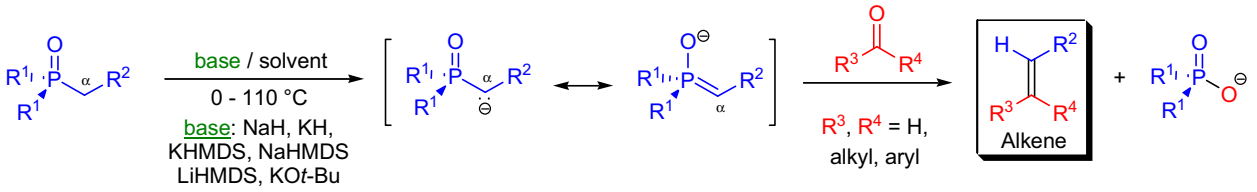
HORNER-WADSWORTH-EMMONS OLEFINATION

(References are on page 603)

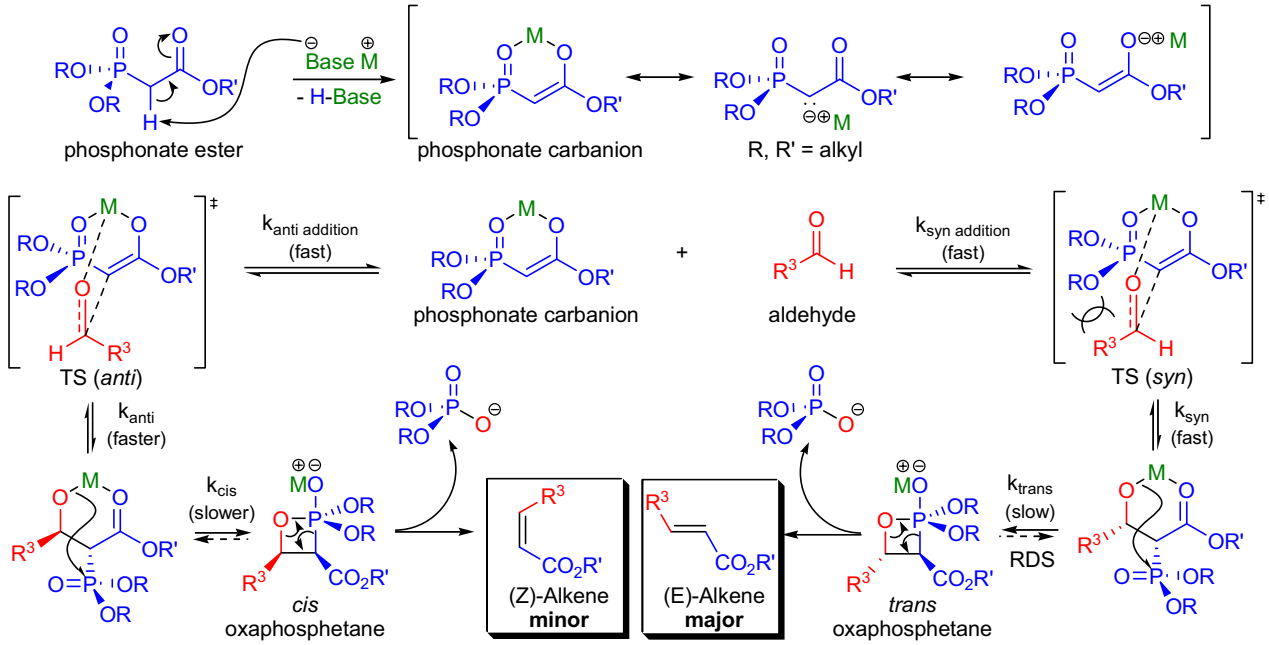
Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-24]; *Modifications & Improvements*[25-39]; *Theoretical Studies*[40-46]]

In 1958, L. Horner utilized the carbanions of alkyl diphenyl phosphine oxides (R^1=Ph) to prepare alkenes from aldehydes and ketones.[1,2] This modification of the *Wittig reaction* is known as the *Horner-Wittig reaction* (or *Horner reaction*) but its widespread use in organic synthesis became a reality only in the early 1960s when W.S. Wadsworth and W.D. Emmons studied the synthetic utility of phosphonate carbanions (R^1=O-alkyl) for the preparation of olefins.[3] In this detailed study, Wadsworth and Emmons revealed the significant advantages these phosphonate carbanions had over the traditional triphenyl phosphorous ylides used in *Wittig reactions*. The stereoselective olefination of aldehydes and ketones using phosphoryl-stabilized carbanions (most often R^1=O-alkyl and R^2=CO_2-alkyl) is referred to as the *Horner-Wadsworth-Emmons olefination (or HWE olefination)*. The *HWE olefination* has the following advantages over the traditional *Wittig olefination*: 1) the preparation of the starting alkyl phosphonates is easier (usually the *Arbuzov reaction* is used) and cheaper than the preparation of phosphonium salts; 2) the phosphonate carbanions are more nucleophilic than the corresponding phosphorous ylides, so they readily react with practically all aldehydes and ketones under milder reaction conditions; 3) hindered ketones that are unreactive in *Wittig reactions* react readily in *HWE olefinations*; 4) the α-carbon of the phosphonate anions can be further functionalized with various electrophiles (e.g., alkyl halides) prior to the olefination, but phosphorous ylides usually do not undergo smooth alkylation; 5) the by-product dialkyl phosphates are water-soluble, so it is much easier to separate them from the alkene products than from the water-insoluble triphenylphosphine oxide. General features of the *HWE olefination* are: 1) high (*E*)-selectivity for disubstituted alkenes under much milder conditions than normally used in *Wittig reactions* (R^2 needs to be able to conjugate with the incipient double bond); 2) the (*E*)-selectivity is maximized by increasing the size of the alkyl group of the R^1 or R^2 substituents (e.g., R=isopropyl is best); and 3) the stereoselectivity is strongly substrate dependent but can be reversed to form predominantly (*Z*)-olefins by using smaller alkyl groups (e.g., methyl) in the R^1 and R^2 substituents and a strongly dissociating base (e.g., KO*t*-Bu). There are a couple of important modifications of the *HWE olefination*: 1) in the *Still-Gennari modification* R^1=OCH_2CF_3 and the reaction affords (*Z*)-olefins exclusively;[27] 2) for base-sensitive substrates, the use of a metal salt (LiCl or NaI) and a weak amine base (e.g., DBU) has proven effective to avoid epimerization;[28,30,35] 3) asymmetric *HWE olefinations*;[29,36,23] 4) the *Corey-Kwiatkowski modification* uses phosphoric acid bisamides to prepare (*Z*)-alkenes stereoselectively, $(Me_2N)_2P(O)CH_2R$, where R=aryl.[25,26]



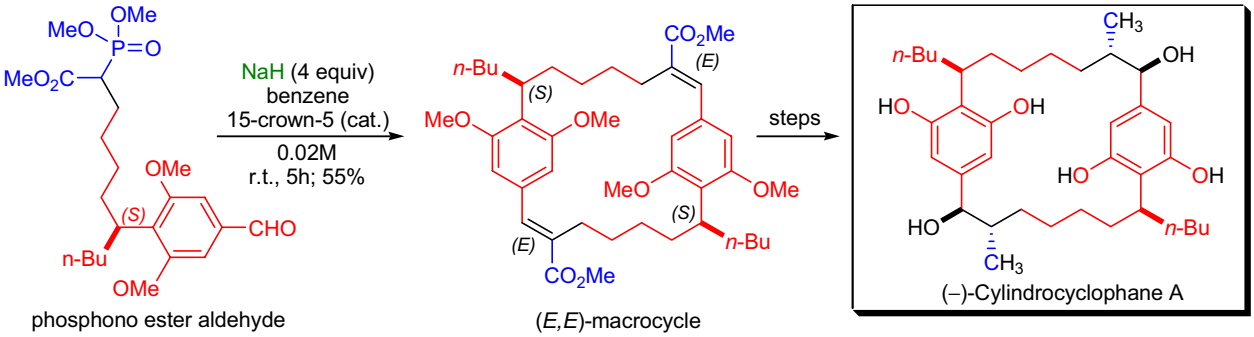
Mechanism:[47,9,48,11]



HORNER-WADSWORTH-EMMONS OLEFINATION

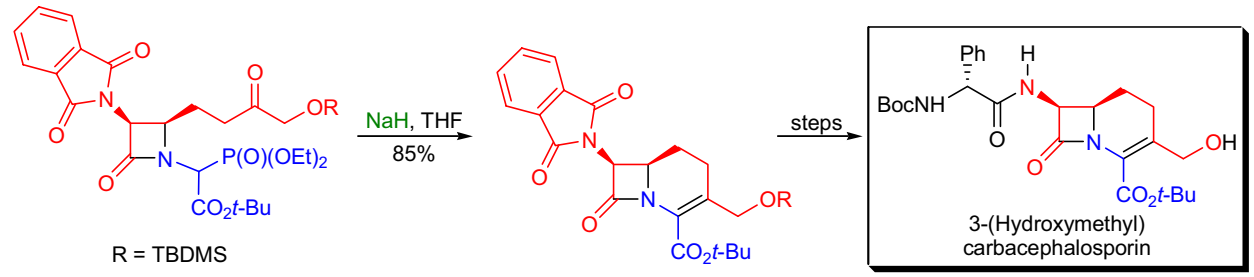
Synthetic Applications:

In the laboratory of T.R. Hoye, a *HWE macrocyclic head-to-tail dimerization* was used to construct the C_2-symmetric macrocyclic core of (–)-cylindrocyclophane A. [49] The monomer phosphono ester aldehyde was subjected to sodium hydride in benzene containing a catalytic amount of 15-crown-5 ether and 55% of the (*E,E*)-macrocyclized product was obtained. None of the (*Z,Z*) stereoisomer was observed. Macrocyclization reactions usually require high-dilution conditions but even relatively concentrated solutions (0.02M) did not decrease the yield of the product in this case.



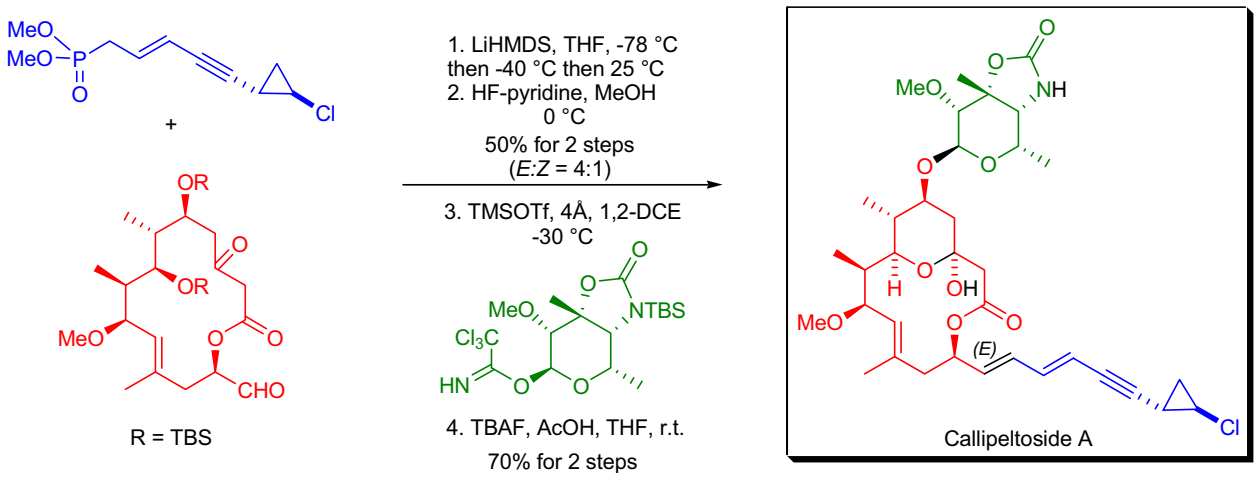
phosphono ester aldehyde (*E,E*)-macrocycle

A short, asymmetric total synthesis of an important 3-(hydroxymethyl)carbacephalosporin antibiotic was achieved by M.J. Miller and co-workers.[50] The β-lactam ring was formed *via* a *Mitsunobu cyclization*, while the six-membered unsaturated ring was constructed by a *HWE cyclization*. This intramolecular olefination afforded a single diastereomer in 85% yield.



R = TBDMS

In order to assign the absolute stereochemistry and relative configuration of *callipeltoside A*, B.M. Trost et al. devised a highly convergent total synthesis by which several stereoisomers were prepared.[51] The key steps in the synthetic sequence were a *ruthenium-catalyzed Alder-ene alkene-alkyne coupling*, a *Pd-catalyzed asymmetric allylic alkylation* and a late-stage coupling of the side chain by the *HWE olefination*. The olefination step gave the coupled product in a moderate yield and with moderate stereoselectivity (*E:Z* = 4:1).



R = TBS

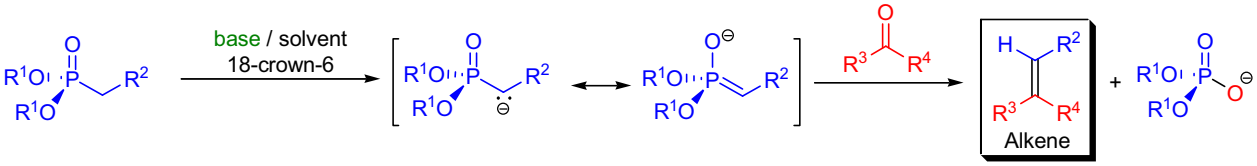
HORNER-WADSWORTH-EMMONS OLEFINATION – STILL-GENNARI MODIFICATION

(References are on page 604)

Importance:

[*Seminal Publication*[1]; *Reviews*[2,3]; *Modifications & Improvements*[4-10]; *Theoretical Studies*[11]]

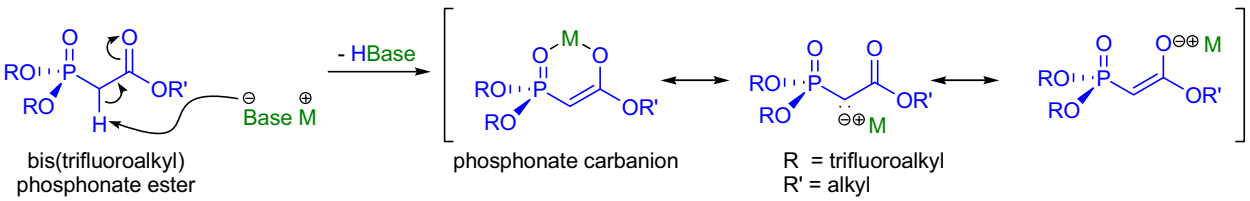
The *Horner-Wadsworth-Emmons olefination* and the *Wittig reaction* of stabilized ylides with aldehydes are the two most widely used methods for the preparation of (*E*)-alkenes. The *HWE olefination* gives rise to (*E*)-α,β-unsaturated ketones and esters, while the *trans*-selective *Wittig reaction* affords simple, unconjugated (*E*)-alkenes. In 1983, W.C. Still and C. Gennari introduced the first general way to prepare (*Z*)-olefins from aldehydes by the modification of the phosphonate reagent used in the *HWE olefination*.[1] The preparation of (*Z*)-α,β-unsaturated ketones and esters by coupling electrophilic *bis*(trifluoroalkyl) phosphonoesters in the presence of strong bases with aldehydes is known as the *Still-Gennari modification of the HWE olefination*. General features of this process are: 1) the necessary *bis*(trifluoroethyl)phosphonoesters are easily prepared from the commercially available trialkylphosphonoesters and trifluoroethanol; 2) (*Z*)-stereoselectivity is observed not only for 1,2-disubstituted but for trisubstituted alkenes as well; 3) the phosphonate reagent must have an electron-withdrawing (carbanion-stabilizing) group at its α-position, otherwise the phosphonate carbanion decomposes; 4) a well-dissociating base must be used in which the metal cation is not coordinating (this is usually achieved by adding 18-crown-6 into the reaction mixture); and 5) when R^2=CN, the (*Z*)-selectivity is high as opposed to the poor (*E*)-selectivity of α-cyano-stabilized regular phosphonates.

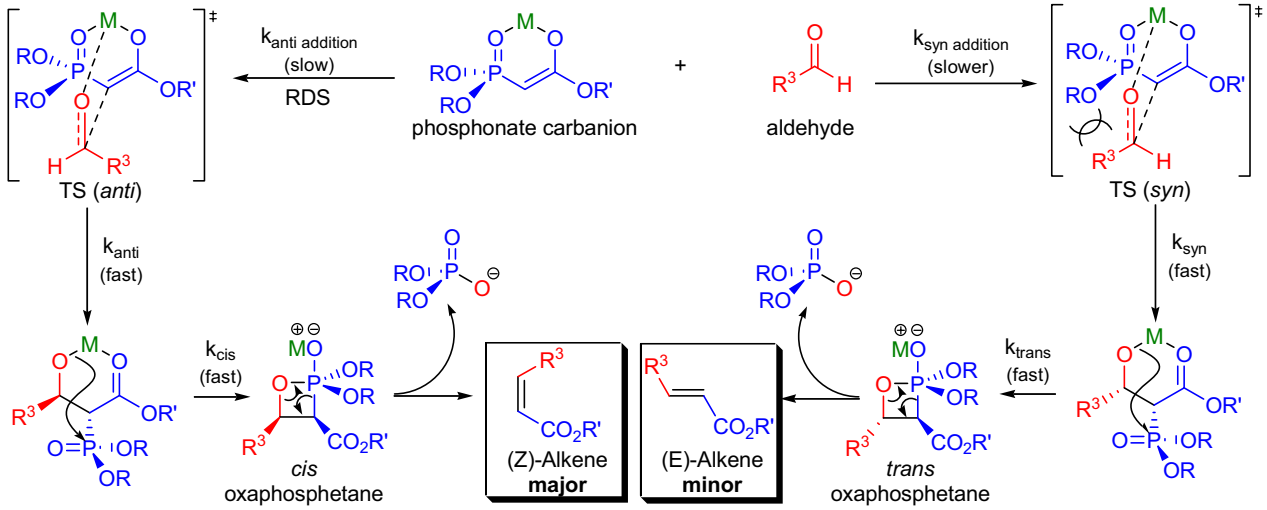


R^1 = CH_2CF_3, trifluoroalkyl; R^2 = COR, CO_2R, CN, SO_2R; R^{3-4} = H, alkyl, aryl; base = KH, KHMDS

Mechanism:[12]

The mechanism of the *HWE olefination* is not fully understood. In the *Still-Gennari modified HWE olefination* the phosphorous has two electron-withdrawing trifluoroalkoxy groups. In this case the rearrangement from the chelated adduct to form the oxaphosphetane is favored and the elimination step is faster than the initial addition, which essentially becomes irreversible (unlike in the case of the regular HWE olefination). As a result, the formation of the (*Z*)-stereoisomer is predominant.

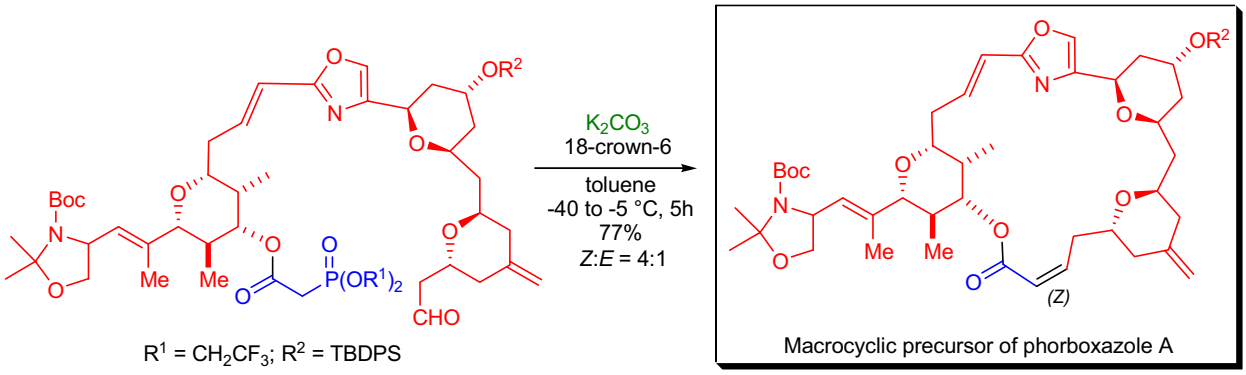




HORNER-WADSWORTH-EMMONS OLEFINATION – STILL-GENNARI MODIFICATION

Synthetic Applications:

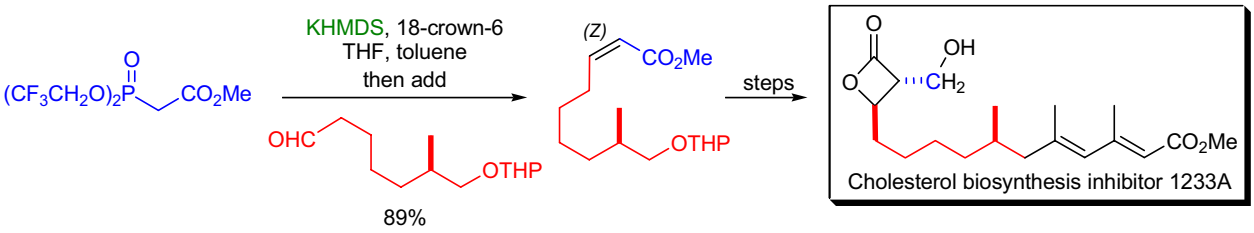
In C.J. Forsyth's total synthesis of phorboxazole A, the intramolecular version of the *Still-Gennari modified HWE olefination* was used to affect the macrocyclization of a complex *bis*(trifluoroethoxy) phosphonate-aldehyde precursor.[13] The precursor was dissolved in toluene and was exposed to K_2CO_3 in the presence of 18-crown-6. The desired C1-C3 (*Z*)-acrylate moiety was formed in 77% yield with a 4:1 (*Z*:*E*) ratio. Interestingly, when the same cyclization was carried out with the regular *bis*(dimethoxy) phosphonate, the macrocyclization was markedly slower, but the stereoselectivity was the same (4:1).



$R^1 = CH_2CF_3$; R^2 = TBDPS

Macrocyclic precursor of phorboxazole A

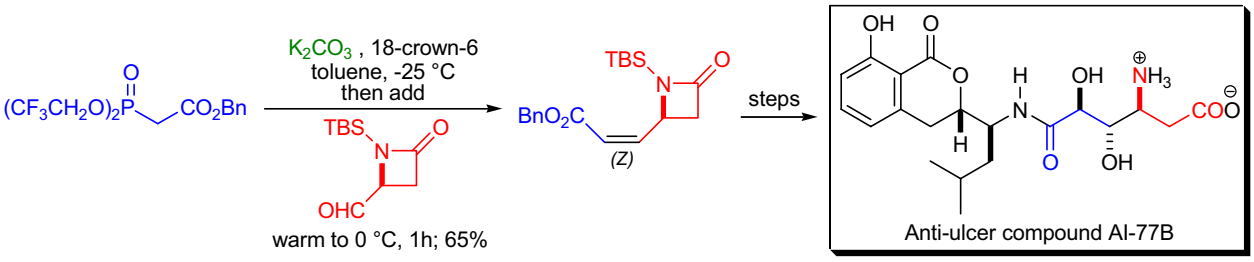
In the laboratory of S.V. Ley, the total synthesis of the β-lactone cholesterol synthase inhibitor 1233A was achieved by using the *oxidative decomplexation* of a (π-allyl)tricarbonyliron lactone as the key step.[14] The (*Z*)-alkene present in the target was introduced using the *S-G modified HWE olefination* of an aldehyde with *bis*(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate to give the desired α,β-unsaturated methyl ester in excellent yield.



89%

Cholesterol biosynthesis inhibitor 1233A

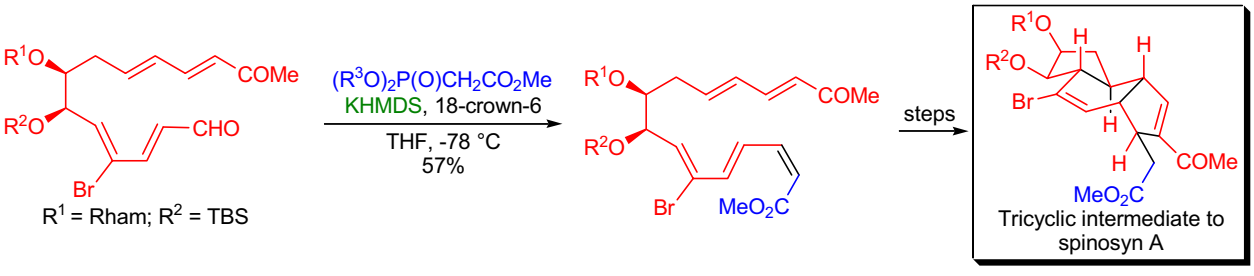
The stereoselective synthesis of the anti-ulcer 3,4-dihydroisocoumarin AI-77B was accomplished by E.J. Thomas and co-workers.[15] The key transformation was the *stereoselective dihydroxylation* of 4-(*Z*)-alkenylazetidinones that were prepared from 4-formylazetidinone *via* the *Still modified HWE olefination*. The benzyl *bis*(trifluoroethyl) phosphonoacetate was prepared from phosphonic dichloride and 2,2,2-trifluoroethanol and was alkylated using benzyl bromoacetate.



warm to 0 °C, 1h; 65%

Anti-ulcer compound AI-77B

The key tricyclic intermediate toward the total synthesis of spinosyn A was assembled by W.R. Roush et al. featuring a one-pot tandem *intramolecular Diels-Alder reaction* and an *intramolecular vinylogous Baylis-Hillman cyclization*.[16] The cyclization precursor was prepared *via* the *S-G modified HWE reaction*.



R^1 = Rham; R^2 = TBS

Tricyclic intermediate to spinosyn A

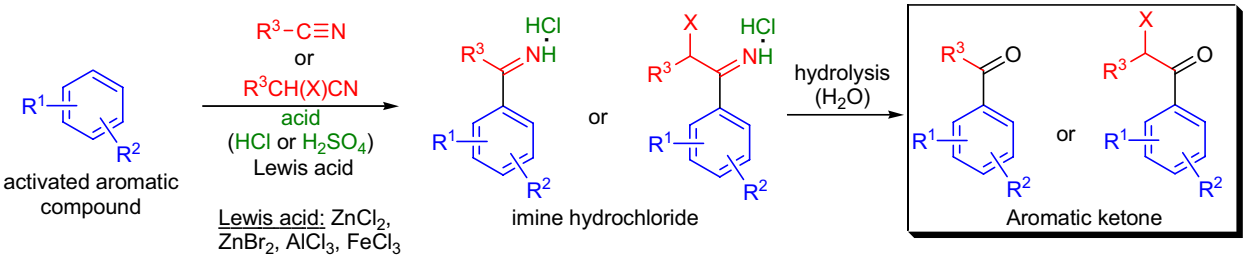
HOUBEN-HOESCH REACTION / SYNTHESIS

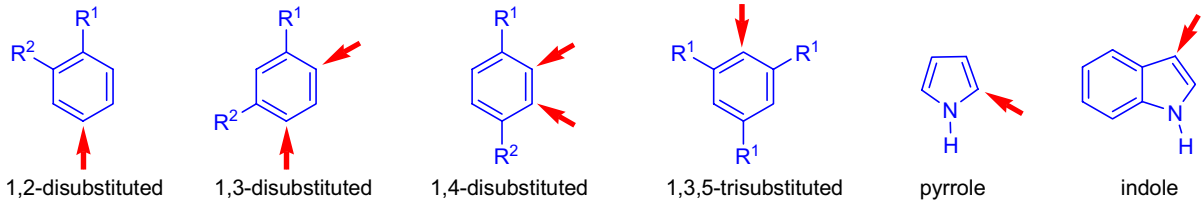
(References are on page 605)

Importance:

[*Seminal Publications*[1-5]*; Reviews*[6-10]*; Modifications & Improvements;*[11-17] *Theoretical Studies*[18]]

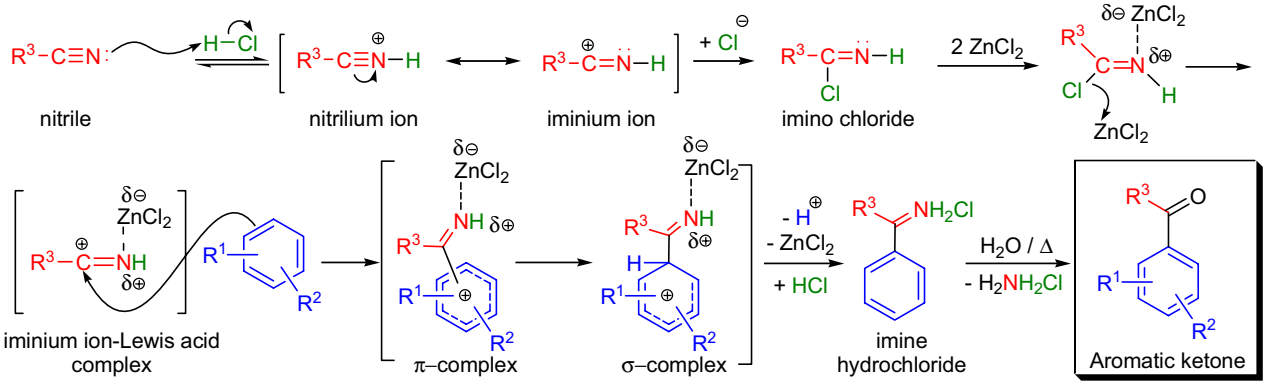
By the early 1900s the *Friedel-Crafts acylation* and the *Gattermann formylation* were widely used to prepare aromatic ketones and aldehydes, respectively. The preparation of monoacylated derivatives of highly activated (electron rich) substrates (e.g., polyphenols) was not possible, since usually more than one acyl group was introduced using the standard *Friedel-Crafts acylation* conditions. In 1915, K. Hoesch reported the extension of the *Gattermann reaction* for the preparation of aromatic ketones by using nitriles instead of hydrogen cyanide and replaced the aluminum chloride with the milder zinc chloride.[1,2] A decade later the scope and the limitation of this novel ketone synthesis was examined in great detail by J. Houben, who showed that the procedure principally worked for polyphenols or polyphenolic ethers.[3] The condensation of nitriles with polyhydroxy- or polyalkoxyphenols to prepare the corresponding polyhydroxy- or polyalkoxyacyloxyphenones is known as the *Houben-Hoesch reaction*. The general features of this reaction are: 1) only highly activated disubstituted aromatic compounds undergo the transformation (at least one of the substituents should be a hydroxy or an alkoxy group); 2) the aromatic compound can be heterocyclic so pyrroles, indoles, and furans are also substrates of this transformation; 3) the structure of the nitrile is freely variable: alkyl, aryl, and substituted alkyl groups (e.g., α-halogenonitriles, α-hydroxynitriles, and their ethers and esters) are all compatible with the reaction conditions; 4) aliphatic nitriles tend to give higher yields than aromatic nitriles; 5) the aromatic nitrile cannot have a strongly electron-withdrawing group in its *ortho*-position (no reaction is observed), but these groups in the *meta*-position have no effect on the reactivity of the aromatic nitrile; 6) the nitriles are often introduced as their hydrochloride salts;[11] 7) zinc chloride is the most widely used Lewis acid but for very electron rich substrates (e.g., phloroglucinol) no Lewis acid is needed; and 8) the initial product of the reaction is the imine hydrochloride that is hydrolyzed to afford the final product aromatic ketone. The most important modifications of the *Houben-Hoesch reaction* are: 1) by using trichloroacetonitrile, even non-activated aromatics can be acylated; and 2) switching the Lewis acid to BCl_3 the acylation of aromatic amines can be realized with high *ortho* regioselectivity.[13]





Mechanism: [19,15,20,21]

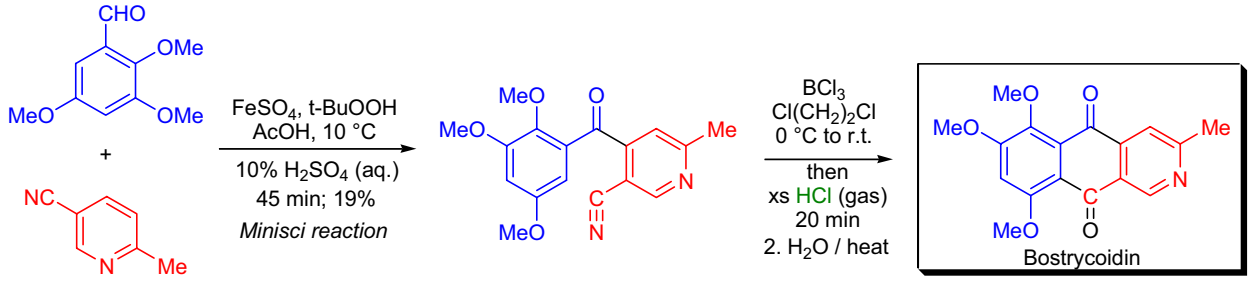
The mechanism is not fully understood, but it is very similar to the mechanism of the *Gattermann-Koch formylation*. The first step is the formation of a nitrilium chloride that is subsequently transformed to an imino chloride from which the reactive species, the iminium ion is generated.



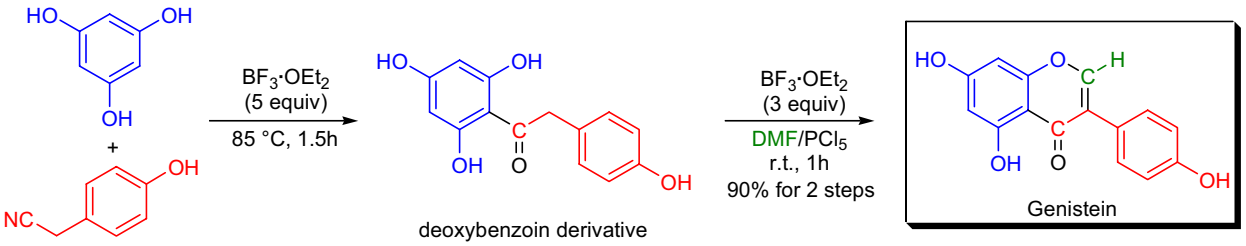
HOUBEN-HOESCH REACTION / SYNTHESIS

Synthetic Applications:

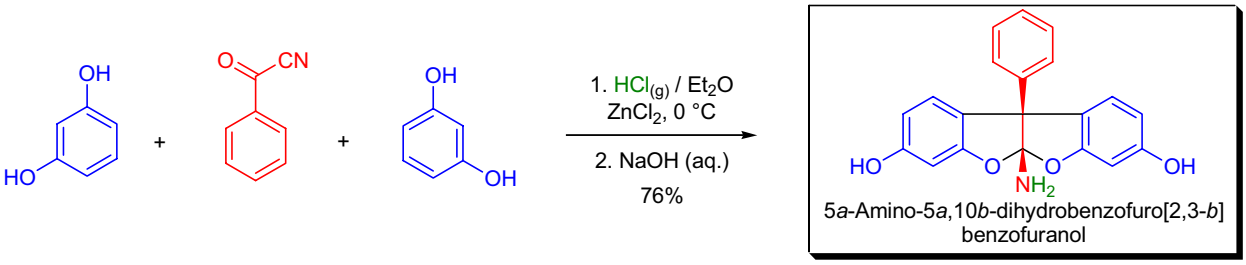
In the laboratory of D.W. Cameron the total synthesis of the azaanthraquinone natural product bostrycoidin was undertaken using the *Minisci reaction* and the *intramolecular Houben-Hoesch reaction* as the key steps.[22] It is worth noting that the synthesis of specific di- and trihydroxyazaanthraquinones by the *Friedel-Crafts acylation* is very limited due to the lack of orientational specificity and the lack of reactivity of pyridine derivatives in acylation reactions.



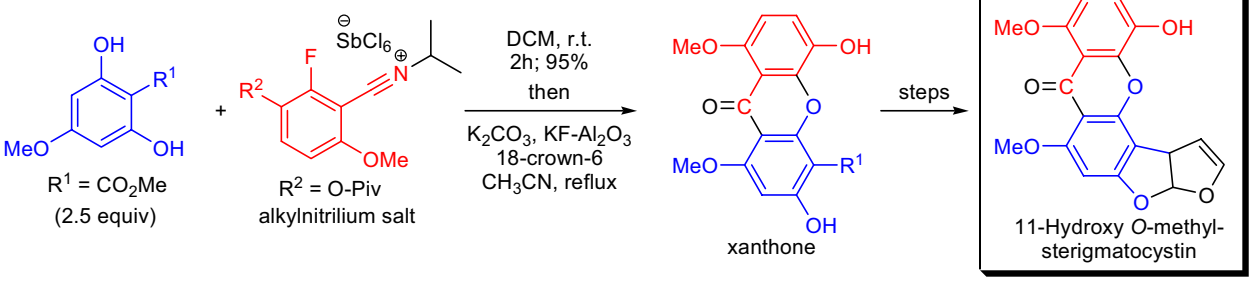
Genistein (4',5,7-trihydroxyflavone) is an important nutraceutical molecule found in soybean seeds, and it has a wide range of pharmacological effects.[23] The two-step total synthesis of genistein was achieved by M.G. Nair et al. using the *Houben-Hoesch reaction* to acylate phloroglucinol with *p*-hydroxyacetonitrile.[24] The resulting deoxybenzoin was treated with DMF/PCl_5 in the presence of $BF_3{\cdot}OEt_2$ to give genistein in 90% yield. The DMF/PCl_5 mixture was the source of the $[(Me_2N{=}CHCl)^+]Cl^-$ reagent. This synthetic sequence was suitable for the large scale (~1 metric ton) one-pot preparation of the natural product.



Nitriles having electrophilic or leaving groups in their - or -postions often lead to so-called "abnormal" Houben-Hoesch products besides the expected "normal" acylation products. Especially notorious is the reaction of -oxonitriles with phenols that afford exclusively 2*H*-1-benzopyran-2-one derivatives instead of the expected 1,2-diketones. -Halogenonitriles react with phenols to give the expected 3-benzofuranone and also the abnormal 2-benzofuranone. R. Kawecki and co-workers found that the condensation of phenols with aromatic -hydroxyiminonitriles or -oxonitriles under the Hoesch conditions leads to benzofuro[2,3-*b*]benzofuran derivatives.[25]



The synthesis of 11-hydroxy *O*-methylsterigmatocystin (HOMST) was carried out in the laboratory of C.A. Townsend by utilizing the *alkylnitrilium ion variant of the Houben-Hoesch reaction*.[17] The alkylnitrilium salt was prepared by reacting the aryl nitrile with 2-chloropropene in the presence of $SbCl_5$. Next, the phenol was added in a 2.5:1 excess. Alkaline hydrolysis then afforded the xanthone, which was subsequently converted to HOMST in few more steps.



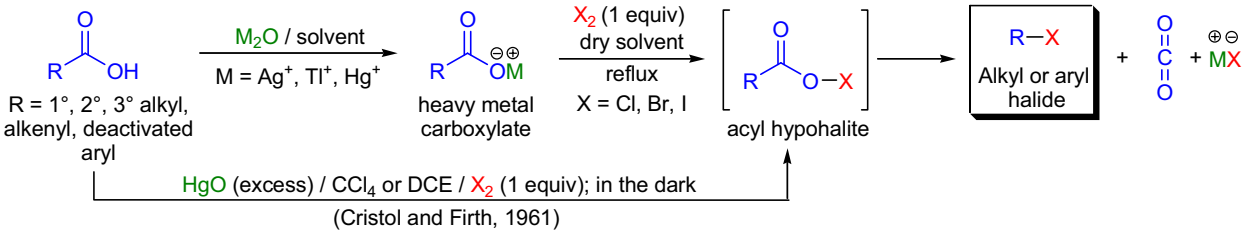
HUNSDIECKER REACTION

(References are on page 605)

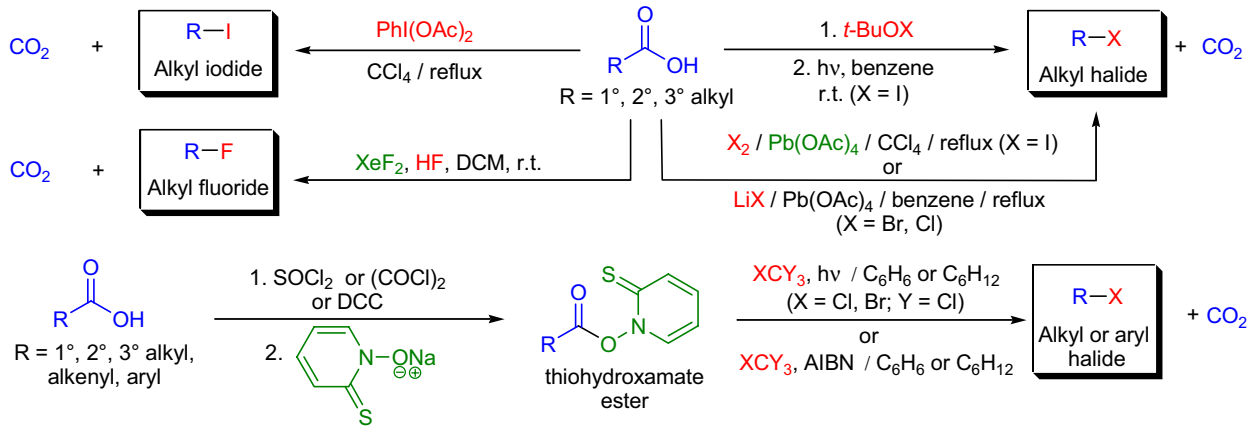
Importance:

[*Seminal Publications*[1-3]*; Reviews*[4-7]*; Modifications & Improvements*[8-30]]

In 1939, H. Hunsdiecker reported that when the dry silver salts of aliphatic carboxylic acids were treated with bromine, the corresponding one-carbon shorter alkyl bromides were obtained.[2,3] The halogenative decarboxylation of aliphatic-, α,β-unsaturated-, and certain aromatic carboxylic acids to prepare the one-carbon shorter alkyl halides is referred to as the *Hunsdiecker reaction*. The general features of this transformation are: 1) the silver salts are prepared from the corresponding carboxylic acids with silver oxide; 2) the slurry of the silver salt in carbon tetrachloride is treated with one equivalent of the halogen, and carbon-dioxide is evolved as rapidly as the halogen is added; 3) in order to obtain high yields, the silver salts must be pure and scrupulously dry, which is not easy to achieve, since the silver salt is often heat sensitive; 3) aliphatic carboxylic acids are the best substrates, but aromatic carboxylic acids with electron-withdrawing substituents are also suitable; 4) electron-rich (activated) aromatic carboxylic acids undergo electrophilic aromatic substitution under the reaction conditions; 5) instead of silver salts, the much more stable thallium(I)- and mercury(I)-salts can be used;[13] 6) functional groups that react with halogens are incompatible (e.g., alkenes, alkynes) under the reaction conditions; and 7) if optically active silver carboxylates are used, there is a significant loss of optical activity in the product alkyl halides. Due to the technical difficulties with the preparation of the silver carboxylates, numerous modifications were introduced to simplify the procedure: 1) the preparation of the silver carboxylate is avoided and higher yields are observed if one adds the solution of the acid chloride to a slurry of dry silver oxide/CCl_4/bromine at reflux temperature;[8,9] 2) the use of crystallizable thallium(I)-carboxylates instead of silver salts improve the yield;[13] 3) the *Cristol-Firth modification* uses excess red HgO and one equivalent of halogen in one-pot;[10] 4) in the *Suárez modification*, the acid is treated with a hypervalent iodine reagent in CCl_4 with remarkable functional group tolerance;[20] 5) LTA can be used directly with iodine or with lithium halides (chlorides and bromides) to produce the corresponding alkyl halides (*Kochi modification*);[11,6] 6) the *Barton modification* exploits the thermal or photolytic decomposition of thiohydroxamate esters in halogen donor solvents (e.g., $BrCCl_3$, CHI_3) and this modification is compatible with almost all functional groups;[17,19] 7) if AIBN is used in the *Barton modification*, any kind of aromatic acid (both activated and deactivated) can be decarboxylated in high yield;[31] and 8) the reaction can be made metal-free and catalytic, but this reaction probably follows a non-radical mechanistic pathway.[24,27,29]

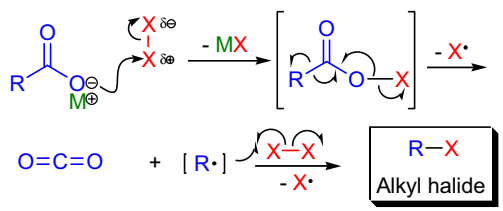


Hunsdiecker-type reactions:

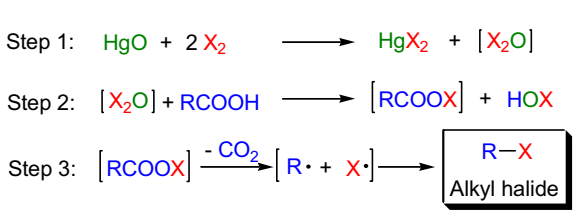


Mechanism:[4,32-37,29]

Classical Hunsdiecker reaction:



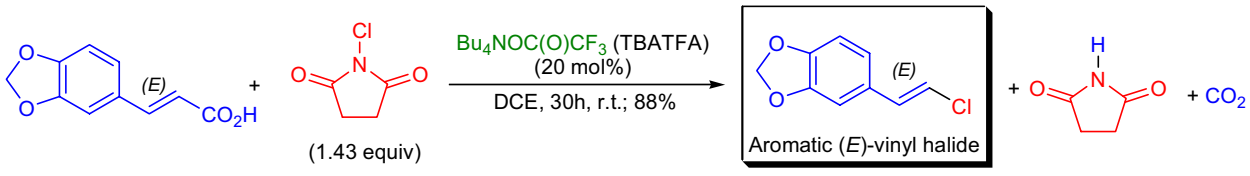
Cristol-Firth modified Hunsdiecker reaction:

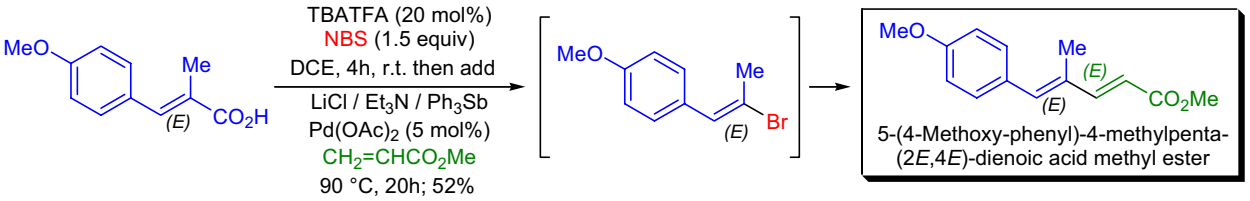


HUNSDIECKER REACTION

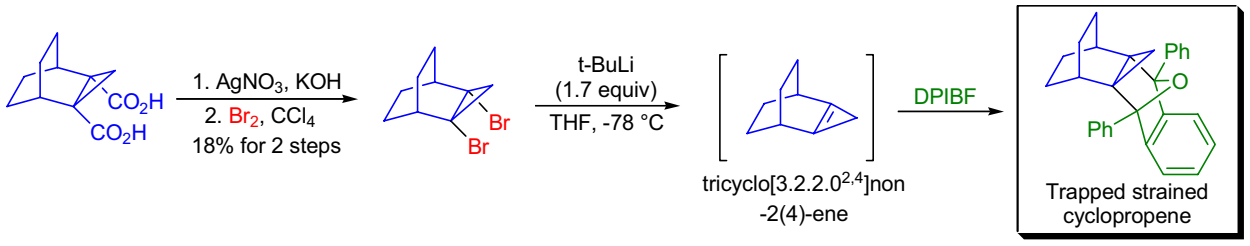
Synthetic Applications:

There are a few efficient methods for the stereoselective synthesis of vinyl halides, and this transformation remains a synthetic challenge. Research by S. Roy showed that the *Hunsdiecker reaction* can be made metal free and catalytic (*catalytic Hunsdiecker reaction*) and can be used to prepare (*E*)-vinyl halides from aromatic α,β-unsaturated carboxylic acids.[27] The unsaturated aromatic acids were mixed with catalytic amounts of TBATFA and the *N*-halo-succinimide was added in portions over time at ambient temperature. The yields are good to excellent even for activated aromatic rings which do not undergo the *classical Hunsdiecker reaction*. The fastest *halodecarboxylation* occurs with NBS, but NCS and NIS are considerably slower. The nature of the applied solvents is absolutely critical, and DCE proved to be the best. This strategy was extended and applied in the form of a *one-pot tandem Hunsdiecker reaction-Heck coupling* to prepare aryl substituted (2*E*,4*E*)-dienoic acids, esters, and amides.

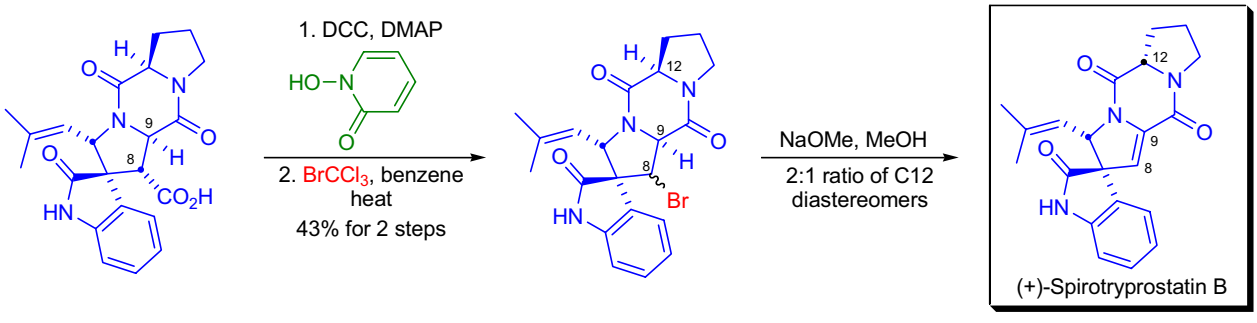




The *classical Hunsdiecker reaction* was utilized in the laboratory of P.J. Chenier for the preparation of a highly strained cyclopropene, tricyclo[3.2.2.0^{2,4}]non-2(4)-ene.[38] The *Diels-Alder cycloaddition* was used to prepare the bicyclic 1,2-diacid, which surprisingly failed to undergo the *Cristol-Firth modified Hunsdiecker reaction*, most likely due to the unreactive nature of the diacid mercuric salt. However, the classical conditions proved to work better to afford the bicyclic 1,2-dibromide in modest yield. Treatment of this dibromide with *t*-BuLi generated the desired strained cyclopropene, which was trapped with diphenylisobenzofuran (DPIBF).



During the final stages of the asymmetric total synthesis of antimitotic agents (+)- and (-)-spirotryprostatin B, the C8-C9 double bond had to be installed, and at the same time the carboxylic acid moiety removed from C8. R.M. Williams et al. found that the *Kochi- and Suárez modified Hunsdiecker reaction* using LTA or PIDA failed and eventually the *Barton modification* proved to be the only way to achieve this goal.[39] After the introduction of the bromine substituent at C8, the C8-C9 double bond was formed by exposing the compound to sodium methoxide in methanol. This step not only accomplished the expected elimination but also epimerized the C12 position to afford the desired natural product as a 2:1 mixture of diastereomers at C12. The two diastereomers were easily separated by column chromatography.



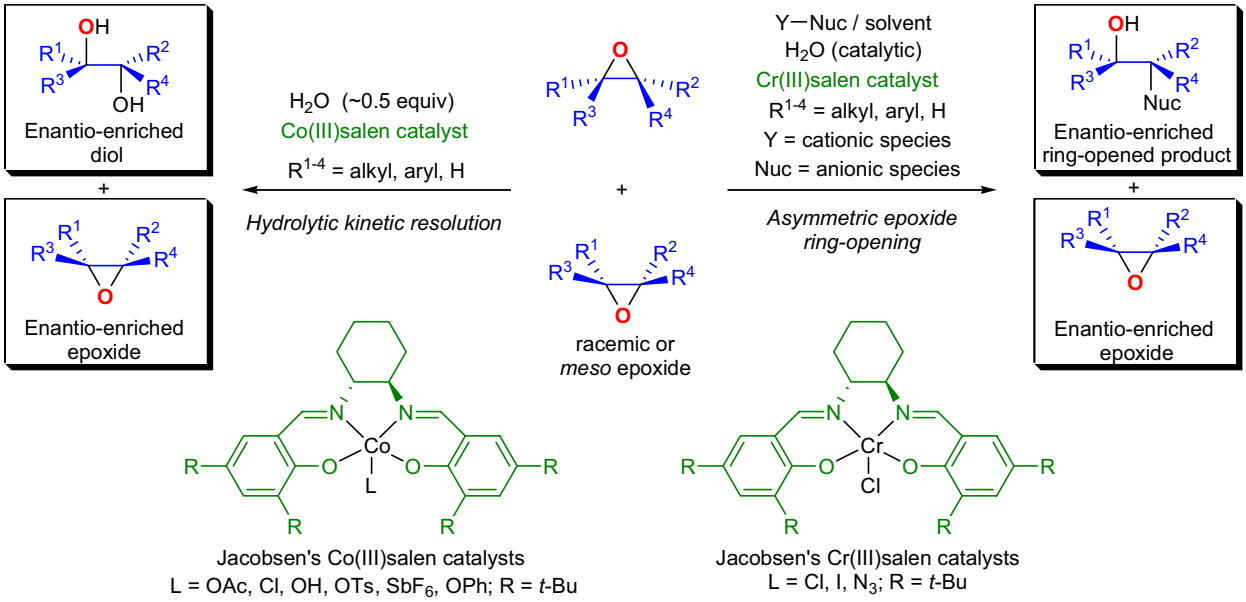
JACOBSEN HYDROLYTIC KINETIC RESOLUTION

(References are on page 606)

Importance:

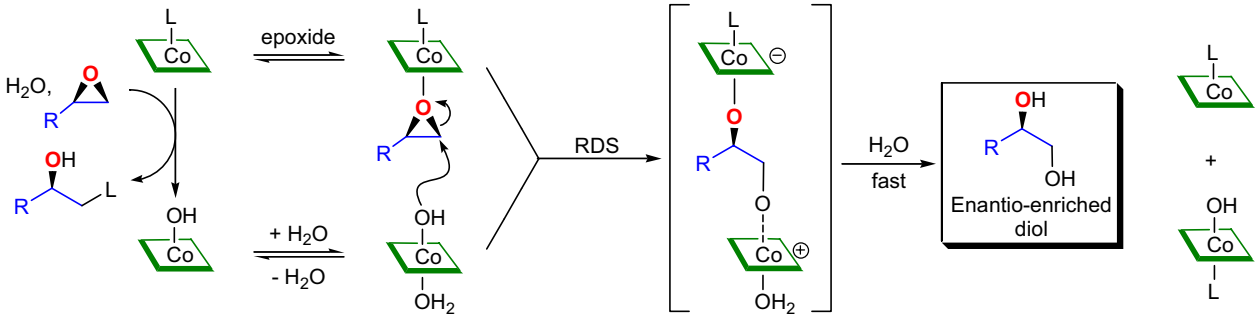
[*Seminal Publications*[1-5]; *Reviews*[6-15]; *Modifications & Improvements*[16-24]]

In 1995, a few years after the discovery of the enantioselective epoxidation of unfunctionalized olefins (*Jacobsen-Katsuki epoxidation*), E.N. Jacobsen and co-workers discovered that *meso* epoxides undergo *asymmetric ring-opening* (*ARO*) by various nucleophiles (e.g., $TMSN_3$) in the presence of catalytic amounts of chiral Cr(III)(salen) complexes.[3] Although several enantioselective ring-opening reactions of epoxides were known at the time,[1,2] it was shown that the chromium(III)-salen complex catalyzed these ring-opening reactions with an unprecedented high level of enantioselectivity. In 1997, it was discovered that Co(III)salen complexes catalyzed the reaction of racemic terminal epoxides with water to afford highly enantiomerically enriched terminal epoxides and diols. This method is known as the *Jacobsen hydrolytic kinetic resolution* (*HKR*).[5] The general features of this reaction are: 1) racemic terminal epoxides are readily available and inexpensive substrates; 2) water is the most environmentally benign reactant possible; 3) catalyst loadings are low (0.5-5 mol%); 4) both enantiomers of the catalyst are readily available; 5) the scale of the reaction has no effect on the yield and enantiomeric excess (mg to ton scale); 6) the enantioselectivity of the ring-opening is extremely high (k_{rel} = >100); 7) the scope of substrates is completely general and practically every terminal epoxide undergoes *HKR*; 8) both products of the *HKR* are isolated in a highly enantio-enriched form (>99% *ee*); 9) separation of the products is straightforward based on the large difference of boiling points and solubility of epoxides and diols; 10) the yields are generally high considering that the theoretical maximum yield for each of the products is 50%; 11) solvent-free conditions can be achieved in many cases (unless the epoxide is too hydrophobic) and generally the volumetric productivity is very high; and 12) the catalyst can be recovered and reused many times without noticeable decrease of its activity.



Mechanism: [25-28]

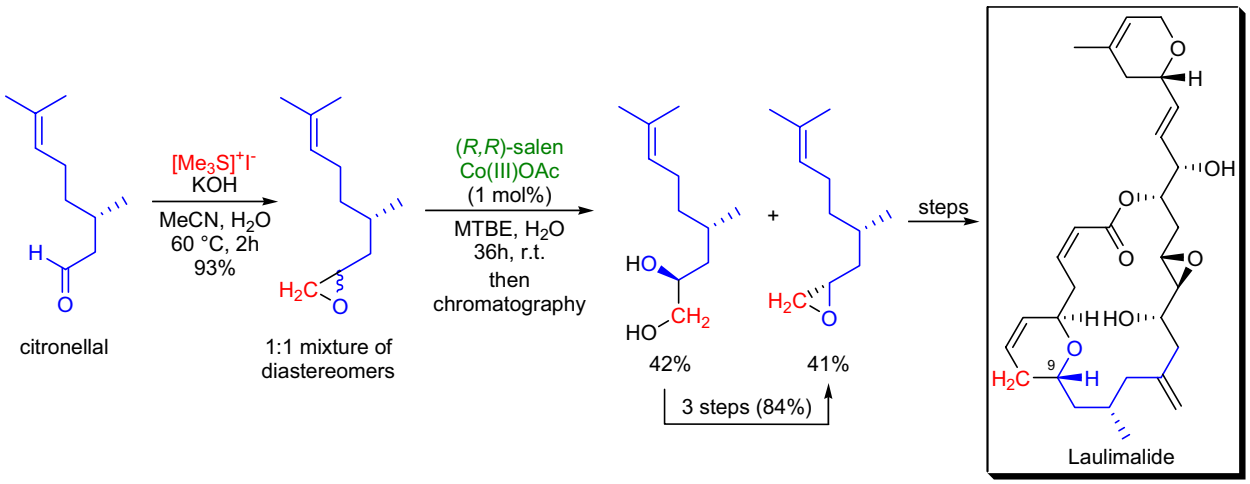
The mechanism of the *Jacobsen HKR* and *ARO* are analogous. There is a second order dependence on the catalyst and a cooperative bimetallic mechanism is most likely. Both epoxide enantiomers bind to the catalyst equally well so the enantioselectivity depends on the selective reaction of one of the epoxide complexes. The active species is the Co(III)salen-OH complex, which is generated from a complex where L OH. The enantioselectivity is counterion dependent: when L is only weakly nucleophilic, the resolution proceeds with very high levels of enantioselectivity.



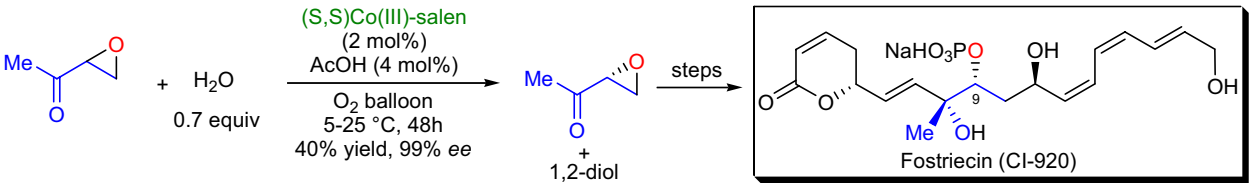
JACOBSEN HYDROLYTIC KINETIC RESOLUTION

Synthetic Applications:

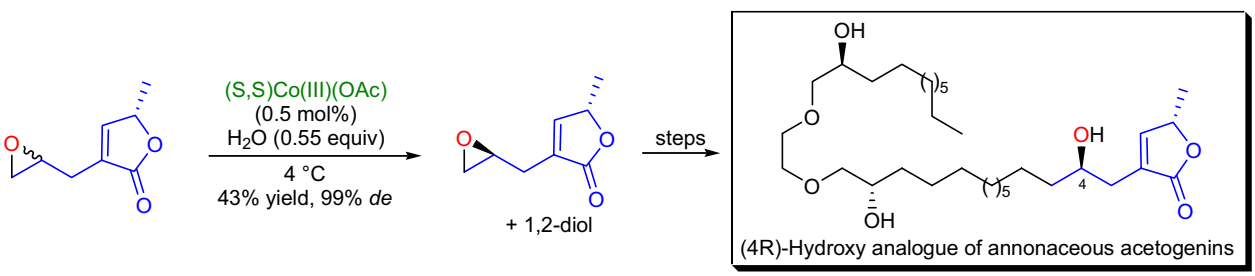
In the laboratory of J. Mulzer, the total synthesis of laulimalide, a microtubule stabilizing antitumor agent, was accomplished.[29] The C9 stereochemistry of the natural product was introduced using the *Jacobsen HKR* on a diastereomeric mixture of a terminal epoxide. The epoxide mixture was prepared *via* the *Corey-Chaykovsky epoxidation* of citronellal. The *HKR* proceeded in high yield and high selectivity at room temperature, and the products were easily separated by flash chromatography. The diol was converted into the diastereomerically pure epoxide in three steps.



The highly convergent total synthesis of the antitumor agent fostriecin (CI-920) was achieved by E.N. Jacobsen and co-workers.[30] The goal was to make the synthetic route flexible enough to prepare structural analogs of the natural product. One of the key building block terminal epoxides was prepared in enantio-enriched form by the *Jacobsen HKR*. The racemic epoxide was readily available by the epoxidation of the inexpensive methyl vinyl ketone. However, the *HKR* catalyst was easily reduced to its Co(II) form and precipitated with low substrate conversion. This problem was resolved by carrying out the reaction in the presence of oxygen, which reoxidized the inactive Co(II)salen complex to the catalytically active Co(III)salen complex. The enantiopure epoxide was the source for the C9 stereocenter of the product.



Annonaceous acetogenins have shown potent activity as inhibitors of certain tumor cells. The (4*R*)-hydroxylated analogue of the naturally occurring annonaceous acetogenin bullatacin was synthesized by Z.-J. Yao et al., and it showed enhanced cytotoxicity compared to other analogues.[31] This compound combines the advantages of bullatacin, one of the most potent naturally occurring acetogenins, and the previous analogues. The (4*R*)-hydroxylated butenolide subunit was introduced by the ring opening of a diastereomerically pure epoxide, which was prepared by the *Jacobsen HKR* in high yield and with almost perfect diastereoselectivity. This approach will allow the synthesis of other (4*R*)-hydroxylated analogs of annonaceous acetogenins.



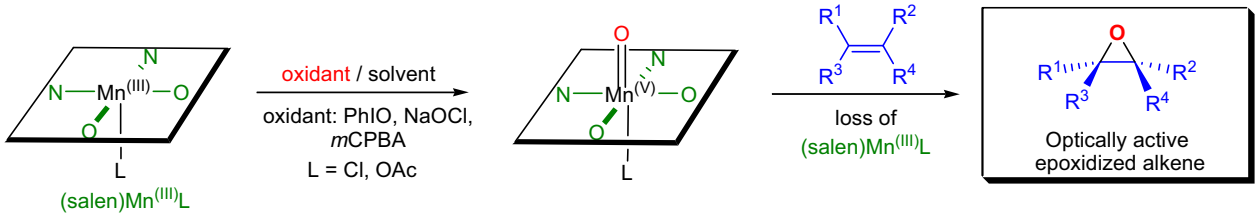
JACOBSEN-KATSUKI EPOXIDATION

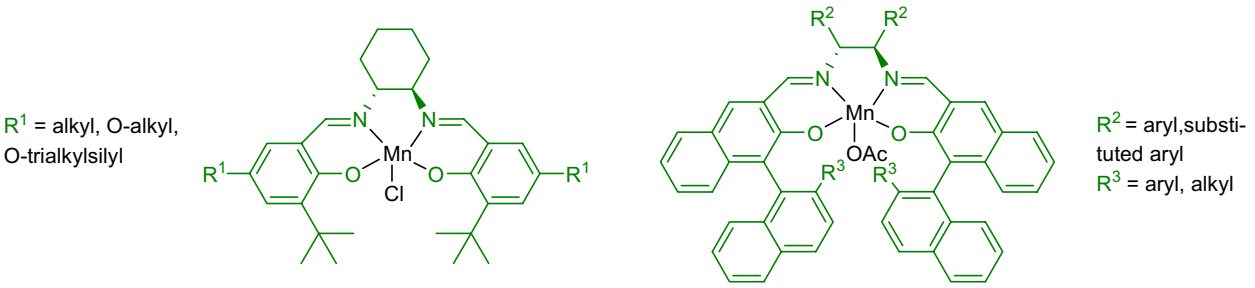
(References are on page 607)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-26]; *Modifications & Improvements*[27-31]; *Theoretical Studies*[32-40]]

In the early 1990s, E.N. Jacobsen and T. Katsuki independently reported that chiral (salen)manganese(III)-complexes were effective catalysts for the enantioselective epoxidation of unfunctionalized alkyl- and aryl-substituted olefins.[2-4] This novel catalytic asymmetric method is known as the *Jacobsen-Katsuki epoxidation*, and it was based on the initial study by J.K. Kochi and co-workers, who described the racemic epoxidation of unfunctionalized olefins using achiral cationic (salen)$Mn^{(III)}$-complexes as catalysts.[1] The chiral salen complexes show a strong structural resemblance to porphyrin-metal complexes that are well-known oxidizing agents in biological systems.[7] The general features of the *J-K epoxidation* are: 1) the chiral Schiff-base salen ligands are easily prepared by the condensation of readily available C_2-symmetric chiral diamines [e.g., (*R,R*)- or (*S,S*)-1,2-diamino-1,2-diphenylethane] and a substituted salicylaldehyde; 2) the degree of enantioselectivity is dependent on several factors: the structure of the olefinic substrate, the nature of the axial donor ligand on the active oxomanganese species and the reaction temperature; 3) conjugated alkenes are better epoxidation substrates than nonconjugated ones; 4) cyclic and acyclic (*Z*)-1,2-disubstituted olefins are epoxidized with almost 100% enantioselectivity, whereas terminal alkenes are not as good substrates; 5) (*E*)-1,2-disubstituted olefins are usually poor substrates for Jacobsen's catalysts but give higher enantioselectivities when Katsuki's catalysts are used; 6) the choice of stoichiometric oxidant is usually dependent on the reaction temperature: iodosobenzene (PhIO) and sodium hypochlorite (NaOCl) are used at room temperature while *m*CPBA is used at -78 °C; 7) other possible stoichiometric oxidants are: hydroperoxides, peroxy acids, amine-*N*-oxides, oxaziridines, Oxone, H_2O_2, and MMPP; 8) addition of Lewis basic compounds (e.g., pyridine, imidazole) to the reaction mixture increases the catalyst turnover rate and number as well as the yield of the product epoxide; 9) with "good" substrates the enantioselectivities are high (90-95% ee); and 10) styrene derivatives often lead to the formation of stereoisomeric epoxides at room temperature but at lower temperatures using *m*CPBA and in the presence of donor ligands the enantioselectivity is usually high.

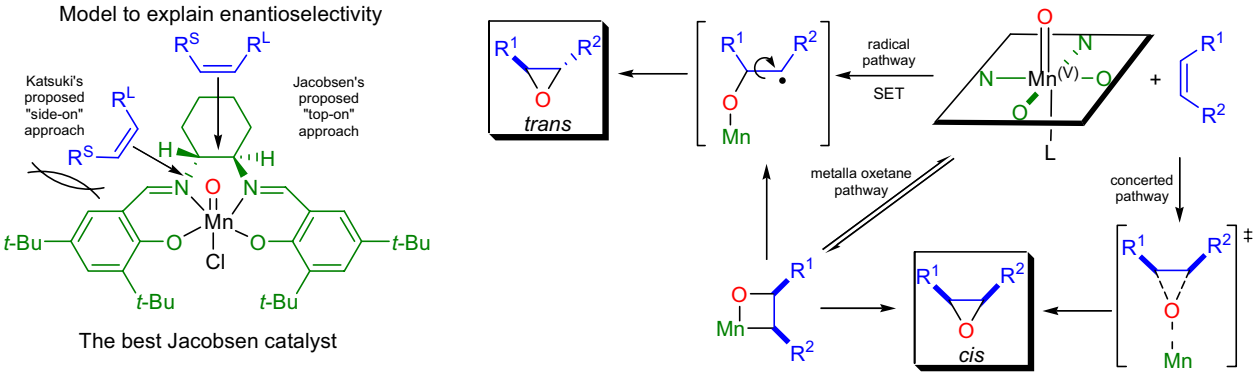




Mechanism:

[41,42,10,43-47,35,48-50]

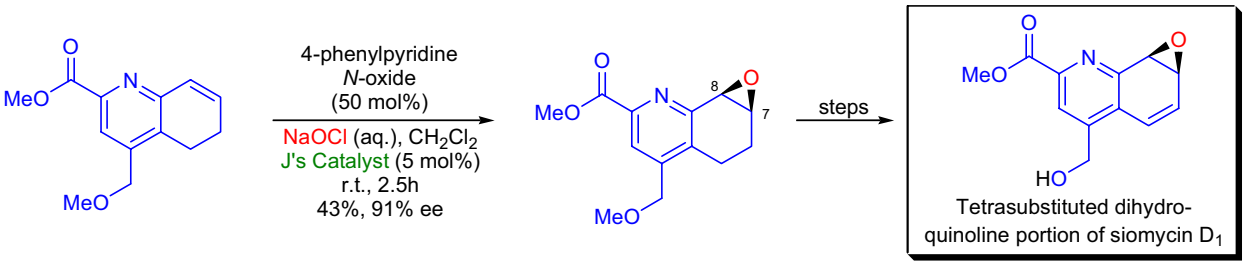
The mechanism of the *J-K epoxidation* is not fully understood, but most likely a manganese(V)-species is the reactive intermediate, which is formed upon the oxidation of the Mn(III)-salen complex. The enantioselectivity is explained by either a "top-on" approach (Jacobsen) or by a "side-on" approach (Katsuki) of the olefin. The three major mechanistic pathways are shown below. The radical intermediate accounts for the formation of mixed epoxides when conjugated olefins are used as substrates.



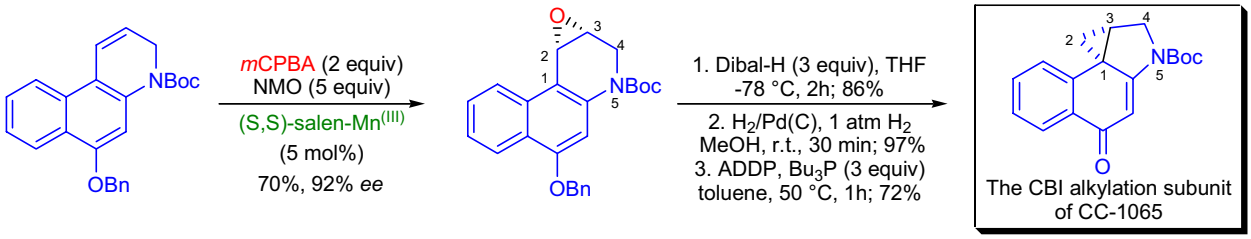
JACOBSEN-KATSUKI EPOXIDATION

Synthetic Applications:

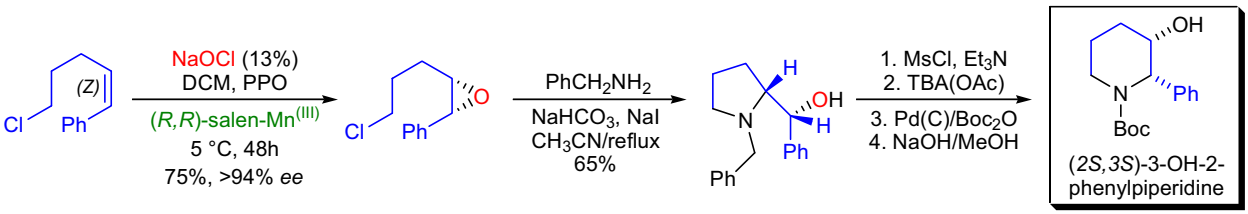
The synthesis of the tetrasubstituted dihydroquinoline portion of siomycin D_1, which belongs to the thiostrepton family of peptide antibiotics, was achieved in the laboratory of K. Hashimoto.[51] The *Jacobsen epoxidation* was utilized to introduce the epoxide enantioselectively at the C7-C8 position. The olefin was treated with 5 mol% of Jacobsen's manganese(III)-salen complex (R^1=*t*-Bu) and 4% aqueous NaOCl solution in dichloromethane. To enhance the catalyst turnover, 50 mol% of 4-phenylpyridine-*N*-oxide was added to the reaction mixture. The desired epoxide was obtained in 43% yield and with 91% *ee*.



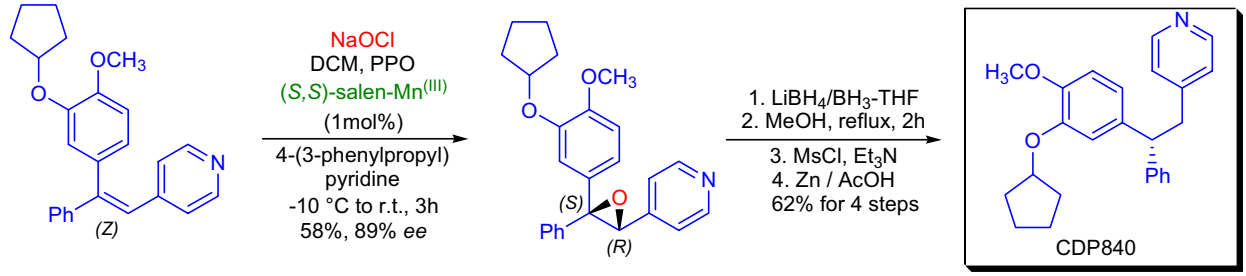
The short asymmetric synthesis of the CBI alkylation subunit of CC-1065 and duocarmycin analogs was accomplished by D.L. Boger and co-workers.[52] The tricyclic alkene substrate was exposed to *m*CPBA at -78 °C in dichloromethane in the presence of 5 mol% of Jacobsen's (*S,S*)-salen-$Mn^{(III)}$ catalyst (R^1=*t*-Bu). A nucleophilic additive, NMO, was also added to increase the yield and the enantioselectivity. Reductive opening of the epoxide with Dibal-H to the corresponding secondary alcohol was followed by the hydrogenolysis of the benzyl ether and a *transannular spirocyclization* upon *Mitsunobu activation* of the secondary alcohol.



The catalytic asymmetric synthesis of (*2S,3S*)-3-hydroxy-2-phenylpiperidine was developed by J. Lee et al. using an *intramolecular epoxide opening* (*5-exo-tet*) followed by ring expansion. The acyclic *cis*-epoxide substrate was prepared in good yield and in greater than 94% ee by the *Jacobsen epoxidation* from the corresponding (*Z*)-alkene.[53]



J.E. Lynch and co-workers reported the asymmetric total synthesis of the PDE IV inhibitor CDP840 in which they utilized the *Jacobsen epoxidation* to introduce the only stereocenter of the target.[54] The triaryl (*Z*)-olefin substrate was epoxidized with significantly higher enantiomeric excess than the triaryl (*E*)-olefin. This finding was interpreted with Jacobsen's "skewed side-on" approach model.



JAPP-KLINGEMANN REACTION

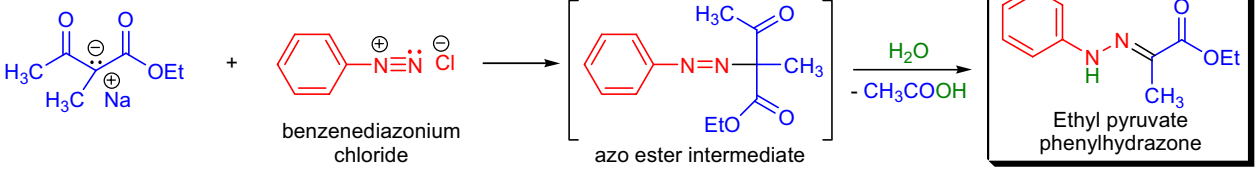
(References are on page 608)

Importance:

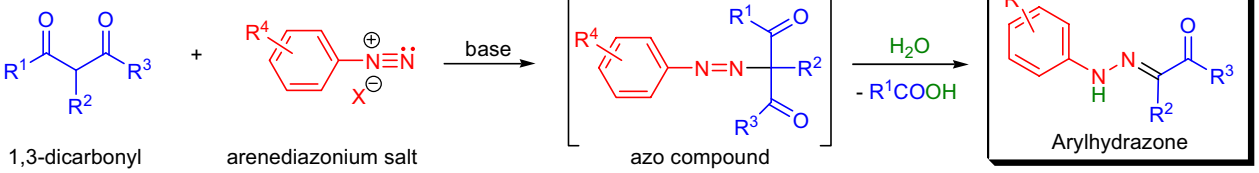
[*Seminal Publications*[1-4]*; Reviews*[5-7]*; Modifications & Improvements*[8-11]]

In 1887, F.R. Japp and F. Klingemann attempted to prepare an azo ester by coupling benzenediazonium chloride with the sodium salt of ethyl-2-methylacetoacetate.[1] However, the isolated product turned out to be the phenylhydrazone of ethyl pyruvate, which contained two carbon atoms less than the expected azo ester.[2-4] Subsequent experiments showed that the reaction was general and the initial coupling product was the azo ester, which was unstable under the reaction conditions and it rapidly rearranged to the phenylhydrazone with loss of the aliphatic acyl group. The coupling reaction between aryldiazonium salts and 1,3-dicarbonyl compounds to yield arylhydrazones is known as the *Japp-Klingemann reaction*. The general features of the reaction are: 1) the substituted arenediazonium salts are prepared from the corresponding *o*-, *m*-, and *p*-substituted anilines *via diazotization* (treatment with HNO_2); 2) the reaction works for compounds having an acidic C-H bond between two or three electron-withdrawing groups (e.g., substituted β-diketones, β-keto esters, malonic esters, cyanoacetic esters, or alkali salts of their corresponding acids); 3) if the coupling is carried out with the alkali metal salt of a β-keto acid, the carboxylate anion will undergo decarboxylation (CO_2 is lost) to give the arylhydrazone of the corresponding 1,2-diketone; 4) when a mixed β-diketone (having both an aliphatic and an aromatic acyl group) is used, the aliphatic acyl group will be cleaved preferentially; 5) when acyl derivatives of acetoacetic esters are used (R^2=acyl), the products are the monoarylhydrazones of α,β-diketo esters; 6) cyclic β-keto esters undergo ring-opening in the second stage of the reaction; 7) alkali metal salts of cyclic β-keto acids are not opened, but rather they undergo decarboxylation to give 1,2-diketone monoarylhydrazones; 8) the coupling is usually carried out in acidic or basic aqueous medium at 0 °C and if solubility of the substrate is poor, ethanol or methanol is added; 9) under basic conditions both stages of the reaction take place, whereas under acidic conditions the azo compound can be isolated, and it has to be treated with a mild base to bring about the rearrangement; 10) the rate of the reaction depends on the C-H acidity of the 1,3-dicarbonyl compound and the more activated compounds tend to react faster; 11) excess diazonium salt leads to numerous decomposition products, so the use of one equivalent is advised; 12) the reaction is easy to monitor visually, since the intermediate azo compounds are more highly colored than the product arylhydrazones; and 13) the main use of arylhydrazones is as substrates for the *Fischer indole synthesis* as well as for the synthesis of enantiopure amino acids.

Japp and Klingemann, 1877:

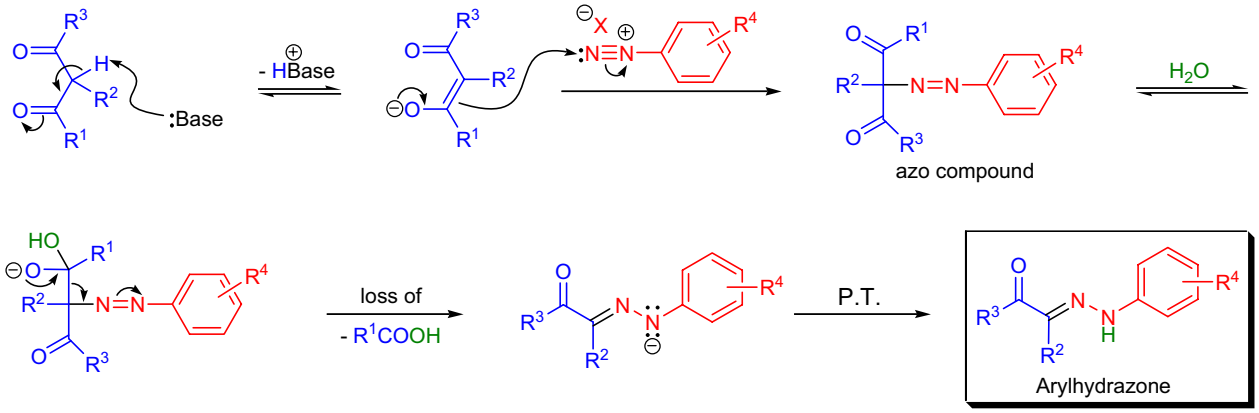


General equation:



R^1 = alkyl, aryl; R^2 = H, alkyl, aryl, acyl, CN, Cl, Br; R^3 = *O*-alkyl, *O*-aryl, OH; R^4 = electron-withdrawing or electron-donating groups

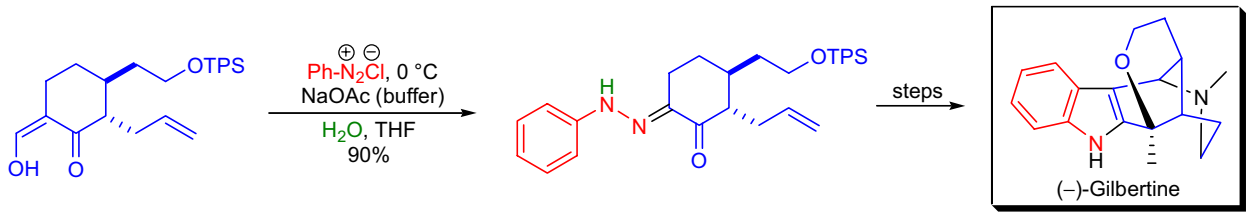
Mechanism:[12-21]



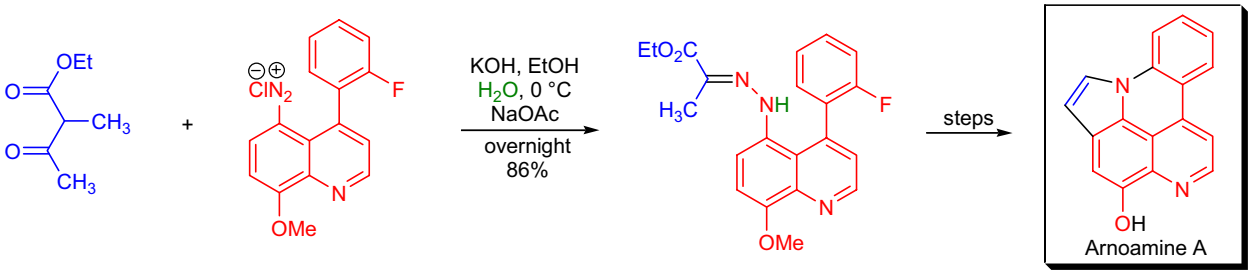
JAPP-KLINGEMANN REACTION

Synthetic Applications:

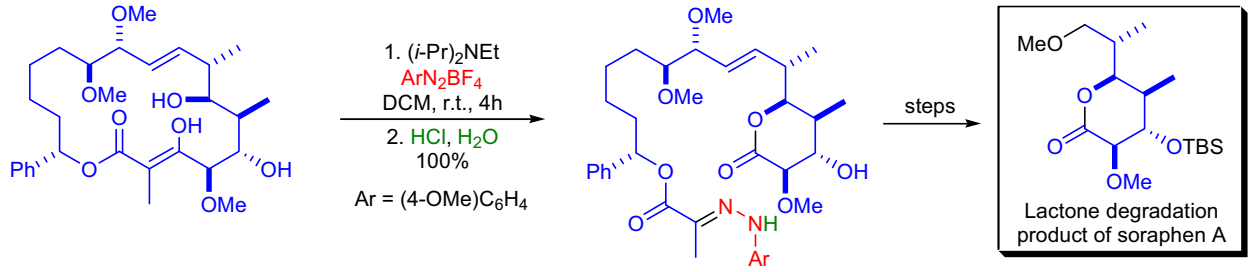
The first enantioselective total synthesis of (–)-gilbertine was accomplished by S. Blechert and co-workers using a *cationic cascade cyclization* as the key step.[22] The indole moiety was introduced by first applying the *modified Japp-Klingemann reaction* on a substituted formylcyclohexanone precursor followed by the *Fischer indole synthesis* of the resulting phenylhydrazone. The benzenediazonium chloride was prepared prior to the reaction by treating aniline with concentrated HCl/ aqueous $NaNO_2$. Then the strongly acidic solution was buffered by the addition of NaOAc before the formylcyclohexanone derivative was added. The buffering increased the yield of the phenylhydrazone from 10% to 90%!



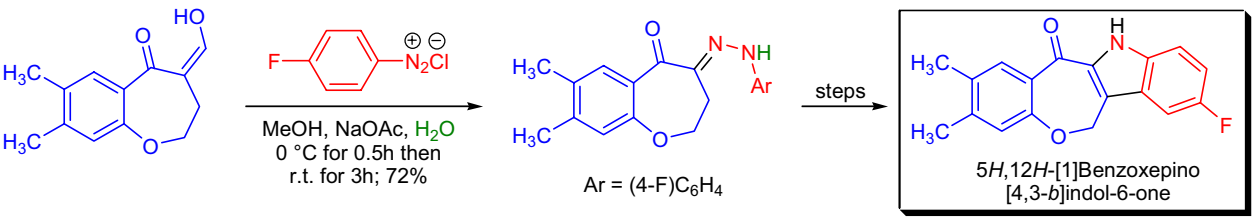
The *Japp-Klingemann reaction* was the key step during the first synthesis of the pentacyclic pyridoacridine marine cytotoxic alkaloid arnoamine A by E. Delfourne et al.[23] The diazonium salt was added to a vigorously stirred solution of ethyl-2-methyl-3-oxobutyrate in ethanol containing KOH, NaOAc and water. The resulting hydrazone was exposed to polyphosphoric acid to form the indole ring.



The macrolide soraphen A was shown to exhibit potent fungicidal activity against a variety of plant pathogenic fungi. In the laboratory of J.-L. Sinnes, a new approach was undertaken in which the natural product was degraded to a key lactone, which was used to build several simplified analogs of soraphen A.[24] The key degradation step was the *Japp-Klingemann reaction* of the macrocyclic β-keto ester in its enol form. Treatment of this enol with 4-(methoxyphenyl)diazonium tetrafluoroborate under mildly basic conditions resulted in the quantitative cleavage of the C-C bond of the macrocycle. Since the natural product was very sensitive to strong acids and bases, this approach was a mild alternative to a *retro-Claisen reaction*, which would have required the use of strongly acidic or basic conditions.



A new heterocyclic ring system, 5*H*,12*H*-[1]Benzoxepino[4,3-*b*]indol-6-one, was prepared by the *Fischer indole cyclization* of a substituted benzoxepin-5b-one phenylhydrazone by G. Primofiore and co-workers.[25] The phenylhydrazone precursor was prepared *via* the *Japp-Klingemann reaction* of the corresponding 3,4-dihydro-4-hydroxymethylene[1]benzoxepin-5(2*H*)-one.



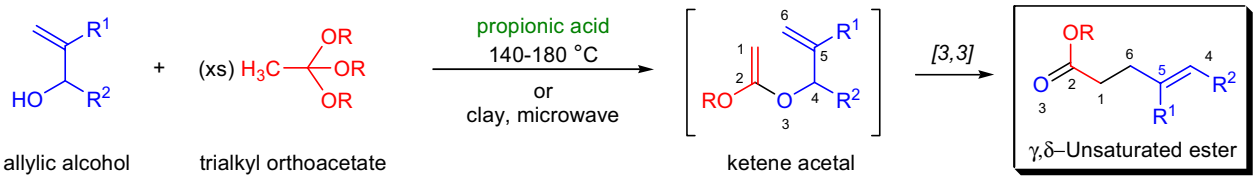
JOHNSON-CLAISEN REARRANGEMENT

(References are on page 609)

Importance:

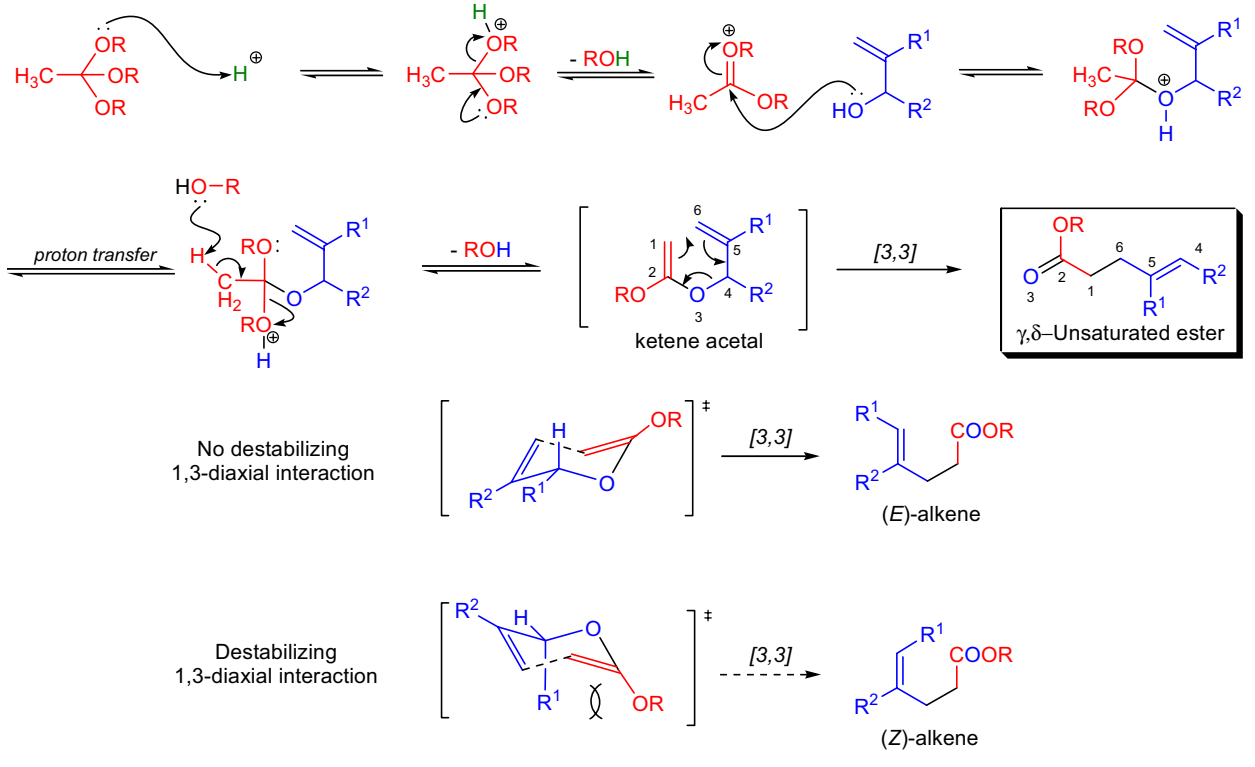
[*Seminal Publication*[1]; *Reviews*[2-6]]

In 1970, W.S. Johnson reported a reaction in which allylic alcohols were heated in the presence of excess triethyl orthoacetate under weakly acidic conditions (e.g., catalytic amounts of propionic acid).[1] The initial product was a ketene acetal that underwent a facile *[3,3]-sigmatropic rearrangement* to afford γ,δ-unsaturated esters. This method is a modification of the original *Claisen rearrangement*, and is referred to as the *Johnson-Claisen-* or *ortho ester Claisen rearrangement*. The reaction is highly stereoselective and is well-suited for the synthesis of *trans*-disubstituted olefinic bonds. The temperature required for the transformation is usually 100-180 °C. The rearrangement can be significantly accelerated by clay-catalyzed microwave thermolysis.[7] While the traditional *Claisen rearrangement* has excellent acyclic stereocontrol, the *Johnson-Claisen rearrangement* exhibits only modest levels of acyclic stereoselection when the double bond is disubstituted. However, using allylic alcohols substituted at the 2-position affords trisubstituted alkene products with significant levels of diastereoselection.[8] This is explained by 1,3-diaxial nonbonding interactions in the chairlike transition state. Therefore, the *Johnson-Claisen rearrangement* of (*E*)-allylic alcohols mainly give *syn* products while (*Z*)-allylic alcohols predominantly give *anti* products.



Mechanism:[1,8]

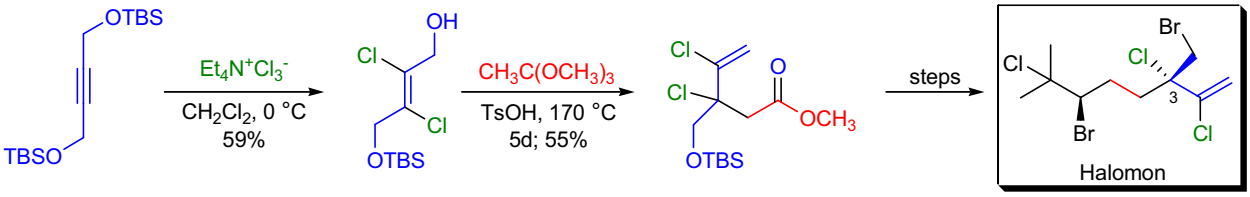
The reaction starts with the exchange one of the alkoxy groups of the ortho ester for the allylic alcohol under acid catalysis. The resulting mixed ortho ester then eliminates a molecule of alcohol to afford an unstable ketene acetal, which undergoes a *[3,3]-sigmatropic shift*. In all of the known Claisen rearrangements, acyclic systems prefer chairlike transition states, whereas cyclic systems may prefer boatlike transition states due to conformational constraints. The ratio of the products will depend on the energy difference between the transition states. The *Johnson-Claisen rearrangements* of secondary allylic alcohols proceed with high *(E)*-selectivity due to the destabilizing 1,3-diaxial interactions in the transition state, which would lead to the (*Z*)-isomer.



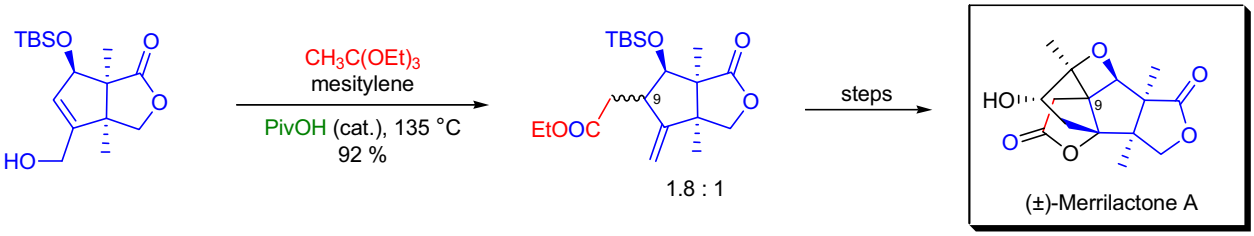
JOHNSON-CLAISEN REARRANGEMENT

Synthetic Applications:

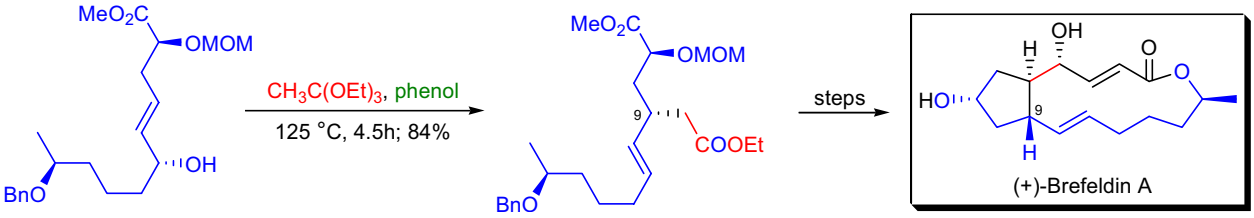
The potent antitumor agent halomon has a tertiary chlorinated carbon stereocenter at C3, which also contains an α-chlorovinyl group. C. Mioskowski and co-workers developed a strategy that enabled them to prepare a wide range of analogs and establish the correct stereochemistry at C3.[9] These operations were achieved by using a *Johnson-Claisen rearrangement* of a *trans*-dichlorinated allylic alcohol. The reaction was carried out in trimethyl orthoacetate as the solvent and using *p*-toluenesulfonic acid instead of the usual propionic acid as the catalyst. Interestingly, no other *[3,3]-sigmatropic rearrangements* (*Cope*, *Stevens*, *Claisen* or *Ireland-Claisen*) were successful to bring about the same transformation. Halomon was synthesized in 13 steps starting from 2-butyne-1,4-diol with an overall yield of 13%.



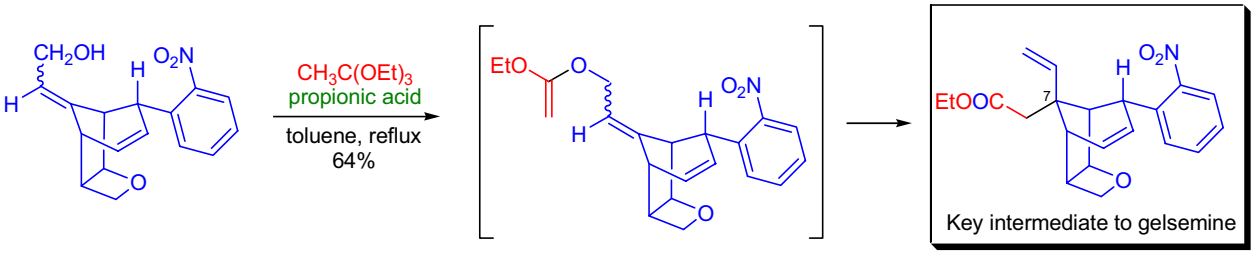
During the total synthesis of the pentacyclic sesquiterpene dilactone (±)-merrilactone A by S.J. Danishefsky et al., a two-carbon unit was introduced at C9 by a *Johnson-Claisen rearrangement*.[10] This high yielding transformation was carried out in the presence of catalytic 2,2-dimethyl propanoic acid at 135 °C using mesitylene as the solvent. A mixture of diastereomeric esters were formed, which were later hydrolyzed and subjected to *iodolactonization* to form the second lactone ring present in merrilactone A. The natural product was synthesized in 20 steps with an overall yield of 10.7%.



The enantioselective total synthesis of the 13-membered macrolide fungal metabolite (+)-brefeldin A was accomplished using a *triple chirality transfer process* and *intramolecular nitrile oxide cycloaddition* in the laboratory of D. Kim.[11] To set the correct stereochemistry at C9, the stereoselective *ortho ester Claisen rearrangement* was applied on a chiral allylic alcohol precursor. The rearrangement was catalyzed by phenol and it took place at 125 °C in triethyl orthoacetate to give 84% isolated yield of the desired diester.



The C7 quaternary stereocenter of (±)-gelsemine was established utilizing a *Johnson-Claisen rearrangement* by S.J. Danishefsky and co-workers.[12] The starting stereoisomeric allylic alcohols were individually subjected to the rearrangement conditions, and each gave rise to the same γ,δ-unsaturated ester.



JONES OXIDATION / OXIDATION OF ALCOHOLS BY CHROMIUM REAGENTS

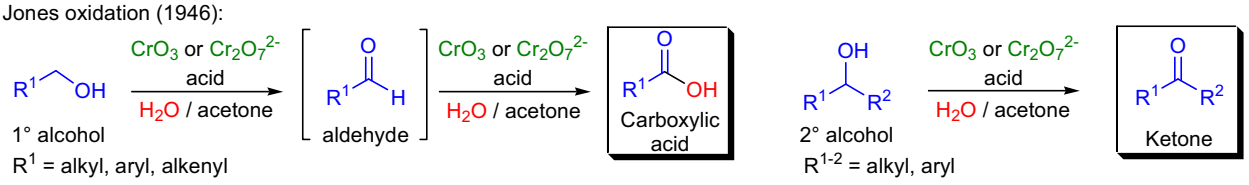
(References are on page 609)

Importance:

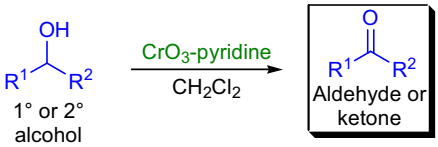
[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-20]]

In 1946, E.R.H. Jones and co-workers successfully converted alkynyl carbinols with chromic acid (CrO_3 mixed with dilute sulfuric acid) to the corresponding alkynyl ketones without oxidizing the sensitive triple bond.[1] The reaction was carried out in acetone by slowly adding the aqueous chromic acid to the substrate at ambient temperature, and the product was isolated in high yield. The oxidation of primary and secondary alcohols with chromic acid is referred to as the *Jones oxidation*. The general features of the reaction are: 1) the chromic acid (H_2CrO_4) can be prepared by dissolving chromic trioxide (CrO_3) or a dichromate salt ($Cr_2O_7^{2-}$) in acetic acid or in dilute sulfuric acid; 2) the oxidation is usually carried out in acetone, which serves a dual purpose: it dissolves most organic substrates, and it reacts with any excess oxidant so it protects the product from overoxidation; 3) in practice the alcohol substrate is titrated with the aqueous solution of the oxidant; 4) excess of the reagent should be avoided because other functional groups of the substrate may be oxidized; 5) the process is amenable to large-scale oxidations; 6) primary alcohols are converted to carboxylic acids with the intermediacy of aldehydes that sometimes can be isolated by distillation if the aldehyde is volatile; 7) secondary alcohols are converted to the corresponding ketones; 8) allylic and benzylic alcohols are efficiently oxidized to the corresponding aldehydes with little or no over-oxidation; 9) glycols and acyloins often suffer C-C bond cleavage under the reaction conditions, but in certain cases the addition of Mn^{2+} or Ce^{3+} salts prevents this side reaction;[10] 10) isolated double and triple bonds remain unchanged, but α,β-unsaturated aldehyde products may undergo double bond isomerization; 11) in rigid cyclic systems axial alcohols tend to react faster than the equatorial alcohols; 12) acid sensitive protecting groups are easily removed under the reaction conditions; and 13) free amines are often incompatible with the *Jones oxidation*, and they need to be protected as the corresponding perchlorate salts prior to the oxidation. For particularly acid sensitive or otherwise delicate substrates the use of the strongly acidic *Jones reagent* is clearly not the best method of oxidation, so several mildly acidic CrO_3-derived oxidizing agents were developed: 1) Sarett prepared CrO_3-(pyridine)$_2$ and carried out the oxidations in pyridine as the solvent;[8] 2) due to difficulties during work-up and with the isolation of products, the *Sarett oxidation* was modified by Collins by using the macrocrystalline form of the reagent that was soluble in dichloromethane and made the oxidations very fast at room temperature (*Collins oxidation*) and highly tolerant toward a wide range of functional groups;[11] 3) Corey et al. developed the mildly acidic pyridinium chlorochromate (PCC) and the neutral pyridinium-dichromate (PDC) reagents that rapidly oxidize 1° and 2° alcohols, as well as allylic and benzylic alcohols in dichloromethane to the corresponding aldehydes and ketones;[12,16] and 4) a large number of other very mild CrO_3-amine reagents have been developed.[5,7]

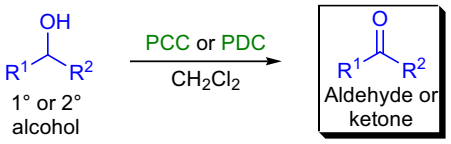
Jones oxidation (1946):



Sarett and Collins oxidations (1953 & 1968):



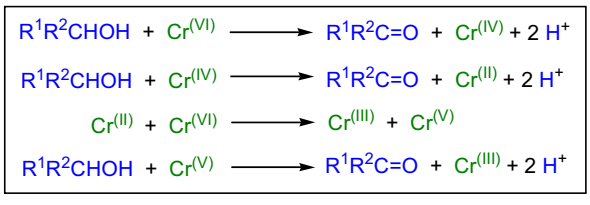
PCC and PDC oxidations (Corey, 1975 & 1979):



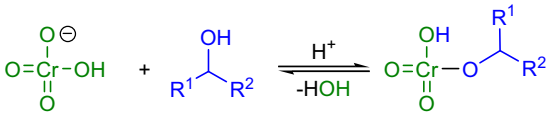
Mechanism:[21,9,22-24]

The concentration and the pH determines the form of $Cr^{(VI)}$ in aqueous solutions: in dilute solution the monomoeric form ($HCrO_4^-$) dominates while in concentrated solution the dimeric form ($HCr_2O_7^-$) is prevalent. The alcohol substrate is first converted to the corresponding chromate ester, which suffers a rate-determining deprotonation by a base to release the $Cr^{(IV)}$ species. This mechanism is supported by a large kinetic isotope effect observed during the oxidation of an α-deuterated alcohol substrate.[21]

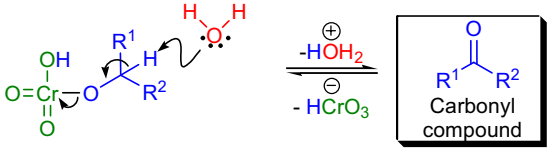
Complete mechanism which accounts for the observed stoichiometry:



Step #1:



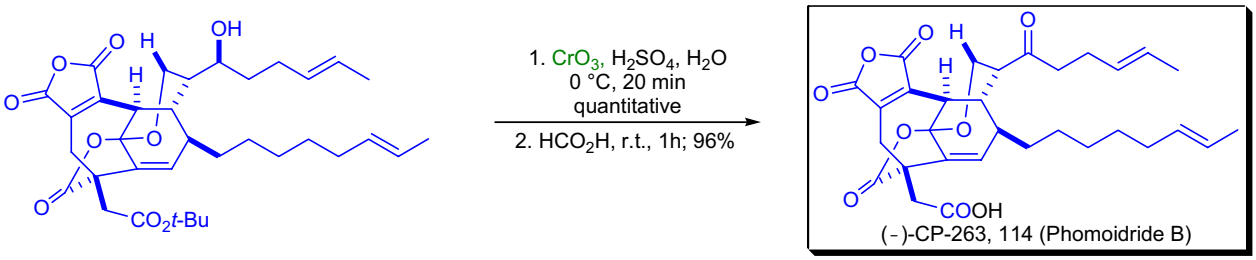
Step #2:



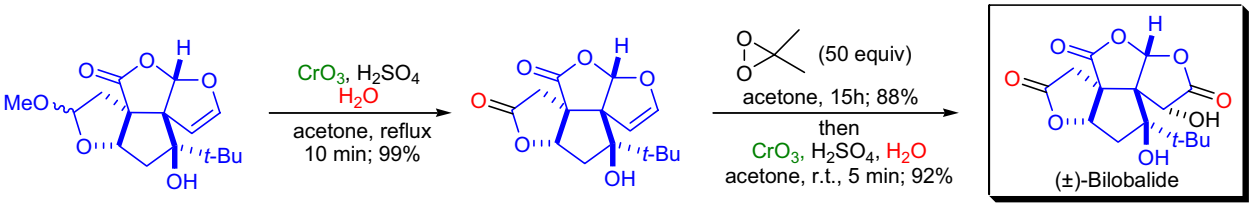
JONES OXIDATION / OXIDATION OF ALCOHOLS BY CHROMIUM REAGENTS

Synthetic Applications:

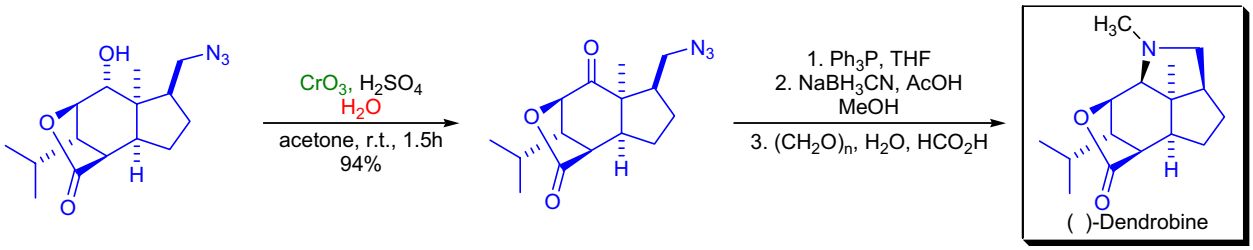
The *Jones oxidation* was used during the endgame of the total synthesis of (–)-CP-263,114 (Phomoidride B) by T. Fukuyama and co-workers.[25] The secondary alcohol functionality of the side chain on the fully elaborated carbon skeleton was exposed to excess CrO_3 in H_2SO_4 for 20 minutes to afford the corresponding ketone in quantitative yield. The last step was the removal of the *tert*-butyl ester with formic acid to give the natural product in 96% yield.



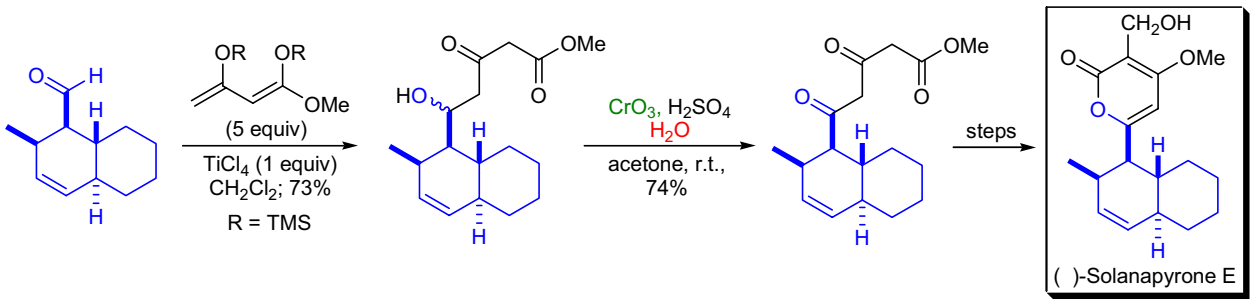
The total synthesis of (±)-bilobalide, a C15 ginkgolide, was accomplished in the laboratory of M.T. Crimmins using a *[2+2] photocycloaddition* as the key step to secure most of the stereocenters.[26] In the final stages of the total synthesis the *Jones oxidation* was used twice. First, the five-membered acetal moiety was oxidized with Jones reagent to the corresponding lactone in refluxing acetone. Next, the five-membered enol ether was epoxidized with excess DMDO and the resulting epoxide was treated with Jones reagent to afford the natural product.



An *-carbonyl radical cyclization* was the key step in C.-K. Sha's enantioselective total synthesis of the alkaloid (–)-dendrobine.[27] The five-membered nitrogen heterocycle was installed during the final stages of the synthetic effort. The bicyclic azido alcohol intermediate was oxidized using the Jones reagent to give the corresponding azido ketone, which was converted in three steps to the natural product.



In the laboratory of H. Hagiwara, the first total synthesis of the polyketide natural product (–)-solanapyrone E was achieved.[28] The installation of the pyrone moiety required the addition of the *bis*(trimethylsilyl) enol ether of methyl acetoacetate to a bicyclic aldehyde precursor in the presence of titanium tetrachloride. The resulting -hydroxy- -ketoester was oxidized with the Jones reagent to afford the corresponding -diketoester in good yield.



JULIA-LYTHGOE OLEFINATION

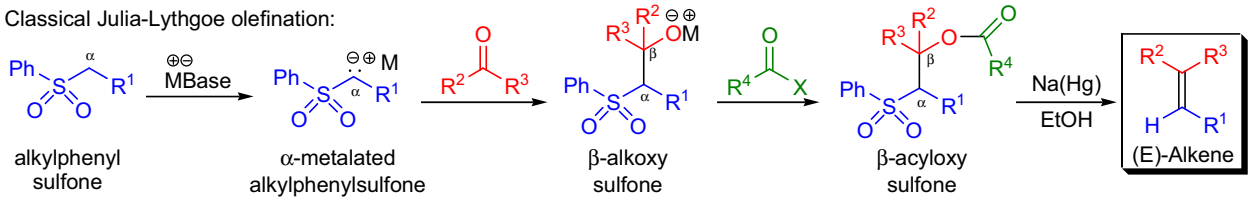
(References are on page 610)

Importance:

[*Seminal Publication*[1]*; Reviews*[2-9]*; Modifications & Improvements*[10-22]]

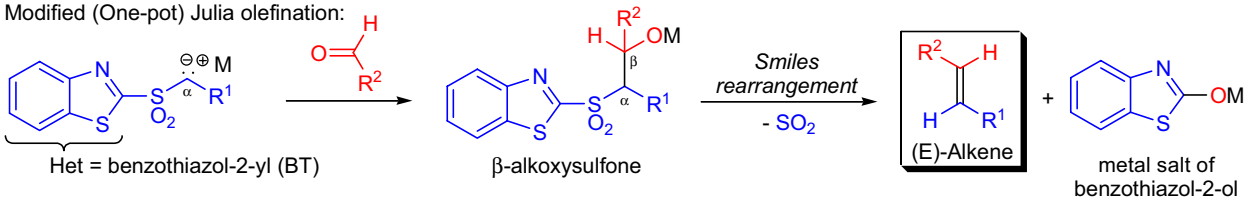
In 1973, M. Julia and J.-M. Paris reported a novel olefin synthesis in which β-acyloxysulfones were reductively eliminated to the corresponding di-, tri-, or tetrasubstituted alkenes.[1] This olefin synthesis requires the following steps: 1) addition of an α-metalated phenylsulfone to an aldehyde or ketone; 2) acylation of the resulting β-alkoxysulfone; and 3) reductive elimination of the β-acyloxysulfone with a single-electron donor to yield the desired alkene. Not long after the seminal publication, B. Lythgoe and P.J. Kocienski explored the scope and limitation, and today this olefination method is known as the *Julia-Lythgoe olefination*.[10-13] The classical *Julia-Lythgoe olefination* has the following general features: 1) high (*E*)-stereoselectivity; 2) the (*E*)-selectivity is increased with increasing chain branching around the newly formed double bond; and 3) the relative stereochemistry in the intermediate β-acyloxysulfones does not influence the geometry of the alkene product. Since the classical procedure was quite tedious (3 steps) to carry out in the laboratory, a more convenient *one-pot modification* was developed by S.A. Julia and co-workers who added α-metalated heteroarylsulfones to carbonyl compounds instead of the traditional phenylsulfones.[15] The initial intermediate β-alkoxy heteroarylsulfone is very labile, and it quickly undergoes the *Smiles rearrangement* in which the heterocycle is transferred from the sulfur to the oxygen atom to afford yet another unstable intermediate, a sulfinate salt. This sulfinate salt readily decomposes to the desired (*E*)-alkene, sulfur dioxide and the metal salt of benzothiazol-2-ol. Several heteroaromatic activators were examined, and it was revealed that not all heteroarylsulfones worked equally well in terms of product yield and stereoselectivity.[8] The BT-sulfones react with α,β-unsaturated or aromatic aldehydes to give conjugated 1,2-disubstituted (*E*)-alkenes. Kocienski found that the PT-sulfone (1-phenyl-1*H*-tetrazol-5-yl sulfone) provides nonconjugated 1,2-disubstituted alkenes with high (*E*)-selectivity if no significant electronic or steric bias is present (*Kocienski-modified Julia olefination*).[17] For the preparation of conjugated 1,2-disubstituted (*Z*)-alkenes, the use of allylic or benzylic TBT-sulfones (1-*t*-butyl-1*H*-tetrazol-5-yl sulfones) is recommended.[18]

Classical Julia-Lythgoe olefination:



R^1 = H, alkyl, aryl; R^2, R^3 = H, alkyl, aryl, alkenyl; R^4 = alkyl, aryl; X = Cl, Br, OCOR

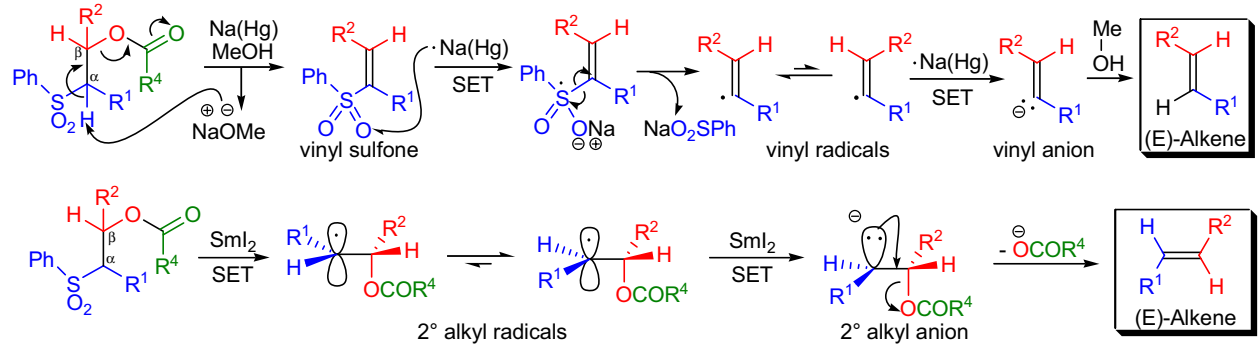
Modified (One-pot) Julia olefination:



R^1 = H, alkyl, aryl; R^2 = alkyl, aryl,alkenyl; Het = benzothiazol-2-yl (BT), pyridin-2-yl (PYR), 1-phenyl-1*H*-tetrazol-5-yl (PT)

Mechanism:[11,13,3,16]

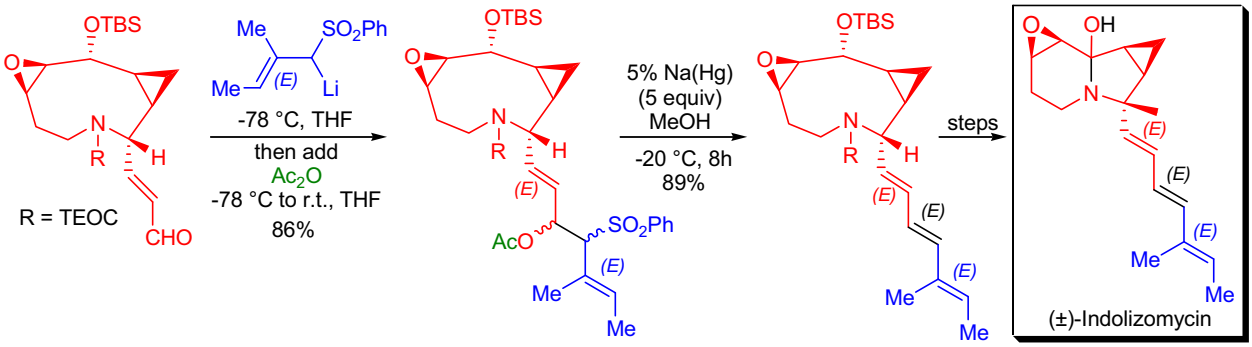
The exact mechanistic pathway of the *classical J-L olefination* is unknown. Deuterium-labeling studies showed that the nature of the reducing agent (sodium amalgam or SmI_2) determines what type of intermediate (vinyl radical or secondary alkyl radical) is involved.[16] Both intermediates are able to equilibrate to the more stable isomer before conversion to the product. The high (*E*)-selectivity of the *Kocienski-modified reaction* is the result of kinetically controlled irreversible diastereoselective addition of metalated PT-sulfones to nonconjugated aldehydes to yield *anti*-β-alkoxysulfones which stereospecifically decompose to the (*E*)-alkenes.



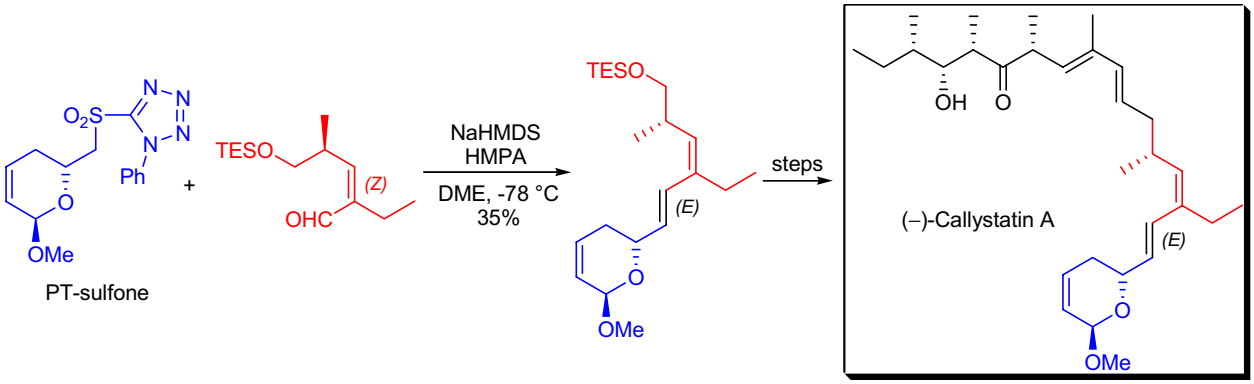
JULIA-LYTHGOE OLEFINATION

Synthetic Applications:

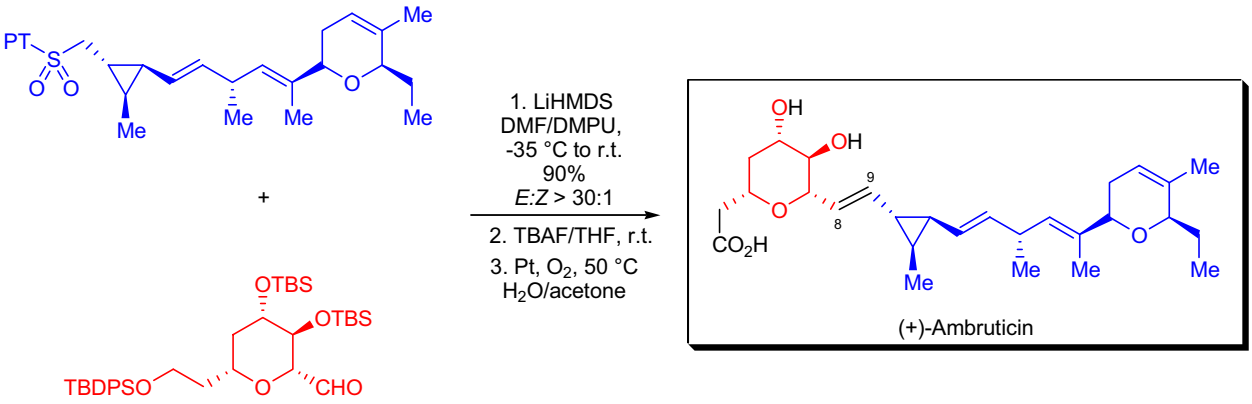
The first total synthesis of racemic indolizomycin was accomplished by S.J. Danishefsky et al.[23] The natural product's trienyl side chain was elaborated using the classical *J-L olefination*. The macrocyclic α,β-unsaturated aldehyde was treated with an (*E*)-allylic lithiated sulfone to give epimeric acetoxy sulfones upon acetylation. The mixture of epimers was exposed to excess sodium amalgam in methanol to afford the desired (*E,E,E*) triene stereospecifically.



In the asymmetric total synthesis of (–)-callystatin A by A.B. Smith and co-workers, two separate *Julia olefinations* were used to install two (*E*)-alkene moieties.[24] The C6-C7 (*E*)-alkene was installed using the *Kocienski-modified process* in which the PT-sulfone was dissolved along with the α,β-unsaturated aldehyde in DME and treated with NaHMDS in the presence of HMPA. The (*E*)-olefin was the only product but due to the relative instability of the starting PT-sulfone, the isolated yield of the product was only modest.



The novel antifungal agent (+)-ambruticin was synthesized in the laboratory of E.N. Jacobsen.[25] The key coupling step in this convergent synthesis was the formation of the C8-C9 (*E*)-alkene *via* the *Kocienski modified Julia olefination*. Interestingly, the coupling showed great selectivity for either the (*E*)- or (*Z*)-stereoisomers depending on the base or solvent used. When NaHMDS was used in THF, the (*Z*)-olefin was formed predominantly (8:1), whereas when LiHMDS was used in DMF/DMPU, the (*E*)-olefin was formed with very high stereoselectivity.



KAGAN-MOLANDER SAMARIUM DIIODIDE-MEDIATED COUPLING

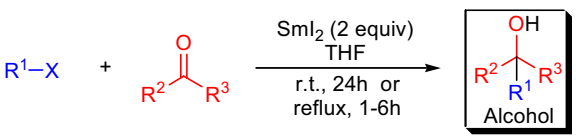
(References are on page 610)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-26]]

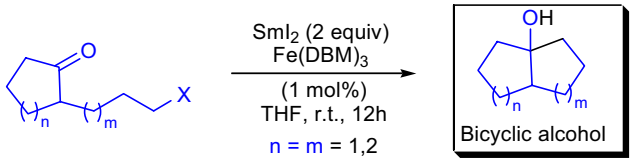
During the late 1970s, H. Kagan systematically examined the reducing properties of lanthanide(II) iodides. During his studies he found that in the presence of two equivalents of samarium diiodide, alkyl bromides, iodides and tosylates react with aldehydes and ketones to provide the corresponding alcohols.[2] The original transformation was carried out in tetrahydrofuran at room temperature for 24 hours or at reflux for a few hours. Kagan also noted that the addition of catalytic amounts of ferric choride significantly decreased the reaction time. This method was later extensively studied by G.A. Molander. In 1984, he reported the first intramolecular version of this transformation.[3,27] He also discovered that ω-iodoesters undergo intramolecular acyl substitution in the presence of samarium diiodide and catalytic amounts of iron(III) salts.[28] Tandem reactions leading to complex carbocycles were also developed.[29] Today, these transformations are referred to as the *Kagan-Molander samarium diiodide-mediated coupling*. The reaction can be performed in two different ways: 1) adding the ketone to a preformed solution of the organosamarium that is prepared by treating the alkyl halide with two equivalents of samarium diiodide (*samarium Grignard reaction*); and 2) reacting the alkyl halide with samarium diiodide in the presence of the ketone (*samarium Barbier reaction*). The most common method for the preparation samarium diiodide is to react the finely ground samarium metal with diiodomethane, diiodoethane or iodine in tetrahydrofuran.[30,5,10] The general features of the reaction are:[19] 1) it is usually carried out in tetrahydrofuran by employing two equivalents of samarium diiodide in the presence of additives or catalysts; 2) in some cases, tetrahydropyran, alkylnitriles, and benzene were used as solvents; 3) under standard conditions, alkyl bromides and iodides undergo the transformation, but alkyl chlorides are unreactive; 4) reaction of alkyl choride under visible light irradiation was reported; 5) the substrate scope of organic bromides and iodides is wide: primary alkyl-, secondary alkyl, allylic and benzylic halides, iodoalkynes, α-heterosubstituted alkyl halides, and α-halogeno carbonyl compounds (*samarium Reformatsky reaction*) undergo the reaction; 6) aryl, vinyl, and tertiary halides are not viable substrates; they are reduced to the radical stage but are usually not reduced further by samarium diiodide; they instead abstract a hydrogen atom from tetrahydrofuran; and 7) the reaction of aryl chlorides with ketones was reported in benzene as a solvent, where hydrogen abstraction is not feasible. The reactions in most cases are relatively slow in tetrahydrofuran, and the addition of co-solvents or catalysts is necessary. The most commonly used co-solvent is HMPA, which dramatically improves the reducing ability of samarium diiodide ($E°_{(Sm(II)/Sm(III) \text{ in THF})}$ = -1.33V; $E°_{(Sm(II)/Sm(III)/4 \text{ equiv HMPA in THF})}$ = -2.05V).[31] DMPU is also often used as an additive.[19] Several transition metal salts proved to be efficient catalysts for this transformation: iron(III) salts, copper(I)- and copper(II) salts, nickel(II) salts, vanadium trichloride, silver(I) halides, cobalt dibromide, zirconium tetrachloride, and Cp_2ZrCl_2.[19]

Intermolecular reaction (Kagan 1980)

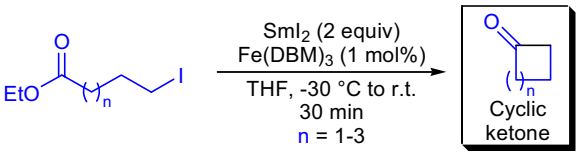


R^1 = alkyl, allyl, benzyl, propargyl; R^2 = H, alkyl, aryl;
R^3 = alkyl aryl; X=Br, I, OTs

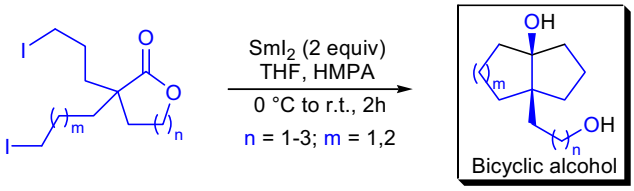
Intramolecular reaction (Molander 1984)



Nucleophilic acyl substitution (Molander 1993):

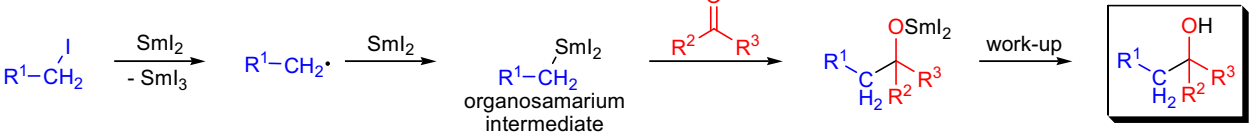


Tandem reactions (Molander 1995):



Mechanism:[32-34,7,35-37,31,38-45]

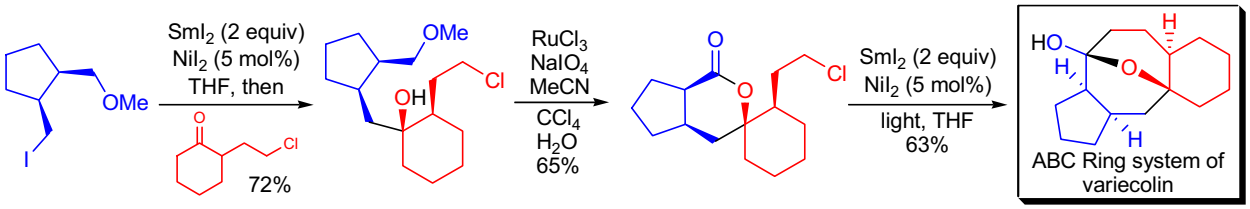
Samarium diiodide is a one electron reductant that is capable of reducing both alkyl halides and carbonyl compounds. The rate of the reduction depends on the nature of the substrate and the reaction conditions. The mechanism of the addition of alkyl halides to carbonyls was extensively studied.[33,7,35] In case of the *samarium Grignard processes*, it was concluded that the reaction proceeds through an organosamarium intermediate. However, the mechanism of the samarium Barbier processes is not fully understood and there is no unambiguous evidence in favor of any of the possible pathways.



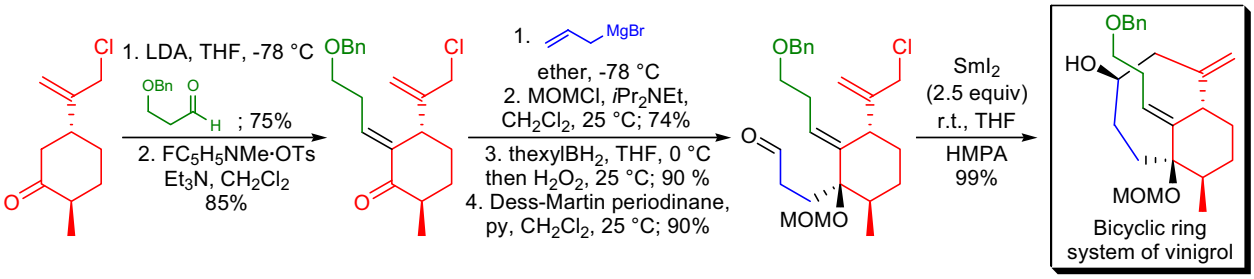
KAGAN-MOLANDER SAMARIUM DIIODIDE-MEDIATED COUPLING

Synthetic Applications:

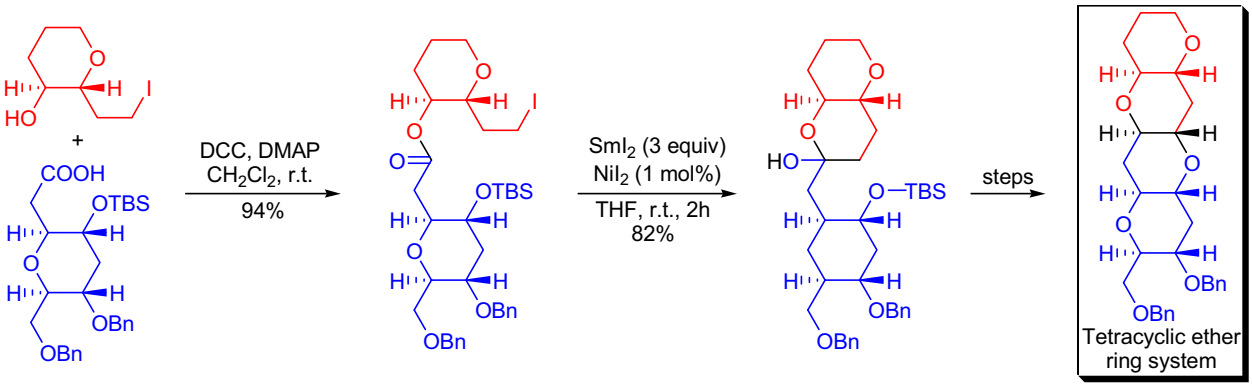
The ABC ring system of the carbocyclic skeleton of variecolin, a sesterterpenoid natural product was accomplished by G.A. Molander and co-workers.[46] In their approach, they utilized two samarium diiodide mediated processes. First, a primary alkyl iodide was reacted with a ketone substrate in the presence of two equivalents of samarium diiodide and catalytic nickel(II) iodide under *samarium Grignard* conditions. Subsequent oxidation and lactone formation provided the chlorolactone substrate. As alkyl chlorides are less reactive than alkyl bromides and iodides, the second samarium diiodide mediated process, an intramolecular nucleophilic acyl substitution, required visible light irradiation.



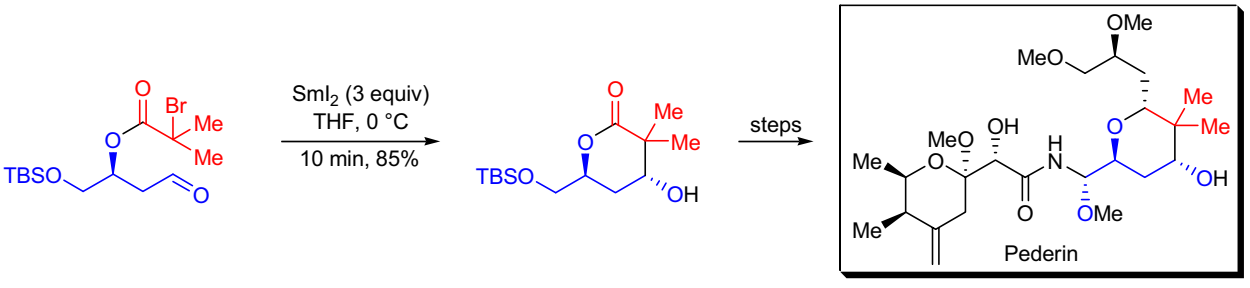
Vinigrol is a tricyclic diterpene with interesting biological activity such as antihypertensive activity and platelet aggregation inhibition property. The eight-membered framework of this natural product was synthesized by F. Matsuda et al. utilizing an *intramolecular Kagan-Molander coupling reaction*.[47] The substrate for the cyclization was prepared starting out from chlorodihydrocarvone in six steps. The samarium diiodide mediated cyclization took place within minutes in tetrahydrofuran using HMPA as the co-solvent.



The research group of T. Nakata developed a convergent synthesis for the construction of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system, a subunit, which is present in several polycyclic marine ether natural products.[48] Late in their synthesis, they utilized a *samarium diiodide mediated nucleophilic acyl substitution* as the key step to form one of the tetrahydropyran rings.



The total synthesis of pederin, a potent insect toxin was achieved by T. Takemura and co-workers.[49] One of the key steps of the synthesis was an *intramolecular samarium diiodide induced Reformatsky reaction* to construct the lactone subunit of the molecule. The transformation was carried out in tetrahydrofuran at 0 °C without the use of additives or catalysts.



KAHNE GLYCOSIDATION

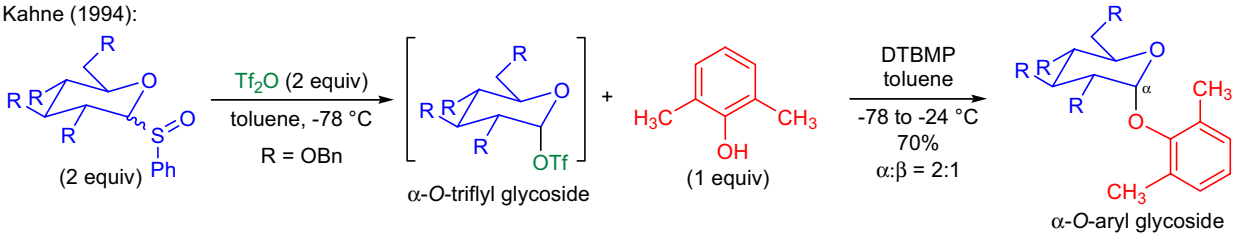
(References are on page 611)

Importance:

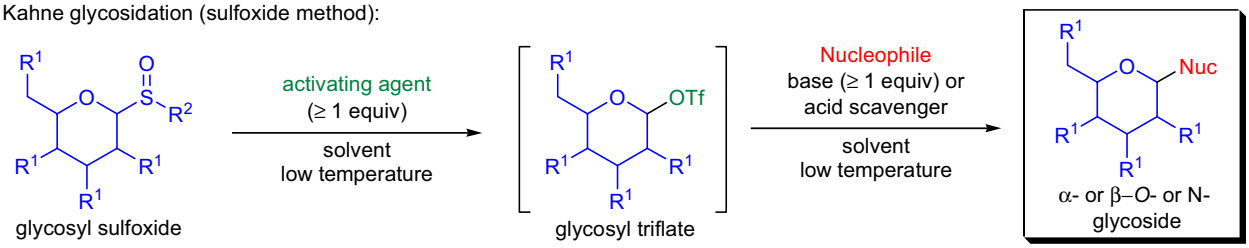
[*Seminal Publications*[1]; *Reviews*[2-9]; *Modifications & Improvements*[10-19]; *Theoretical Studies*[20,21]]

The efficient preparation of glycosides from sterically hindered or otherwise unreactive substrates using standard glycosidation methods (e.g., *Koenigs-Knorr glycosidation*, thioglycoside method, etc.) was a significant challenge until the late 1980s. In 1989, D. Kahne and co-workers developed a novel glycosidation method in which they treated glycosyl sulfoxides with trifluoromethanesulfonic anhydride in toluene at low temperature and to the resulting reaction mixture they added the solution of the nucleophile (alcohols, phenols, or amides) and a base also in toluene.[1] The products were the corresponding *O*- or *N*-glycosides with predominantly α-stereochemistry in the absence of neighboring group participation and with predominantly β-stereochemistry when anchimeric assistance was involved. The highly stereoselective preparation of *O*-, *S*-, or *N*-glycosides *via* the activation of glycosyl sulfoxides is known as the *Kahne glycosidation* (*sulfoxide method*). The general features of this transformation are:[8] 1) the sulfoxides are usually prepared *via* the oxidation of the corresponding thioglycosides (axial thioglycosides are oxidized to give a single sulfoxide diastereomer while equatorial thioglycosides give rise to a mixture of diastereomeric sulfoxides);[22-24] 2) the most common oxidizing agents are *m*CPBA and MMPP; 3) both alkyl and aryl sulfoxides can be used as substrates; 4) the reactivity of aryl glycosyl sulfoxides can be modulated by placing electron-donating or electron-withdrawing substituents on the aromatic ring (multicomponent couplings are possible this way[25]); 5) primary-, secondary and tertiary alcohols, phenols, trialkylstannylated phenols, silylated amides can be used as nucleophiles; 6) the method is especially well-suited for the glycosidation of sterically hindered alcohols, which are unreactive under other glycosidation methods; 7) the most common activating agent is triflic anhydride (Tf_2O) and trimethylsilyl triflate (TMSOTf), but occasionally Lewis acids (e.g., $Cp_2ZrCl_2/AgClO_4$)[16] and mineral acids[14,15] can be used as activating agents; 8) since triflic acid or phenylsulfenyl triflate is generated in the reaction, the use of a hindered, non-nucleophilic base to buffer the reaction mixture is recommended (sometimes the use of a base results in the formation of an orthoester instead of a glycoside, a problem that is resolved by simply omitting the base); 9) the reaction is conducted at low temperatures and is usually complete in a matter of minutes or a few hours; and 10) the stereochemical outcome of the coupling is a function of the solvent and the protecting groups in both the glycosyl donor and acceptor.

Kahne (1994):



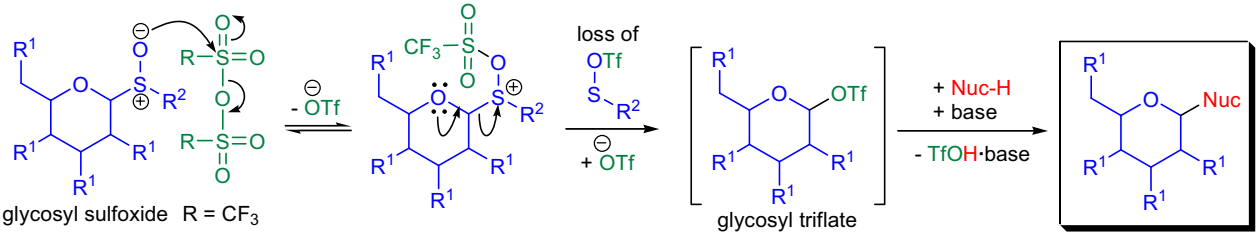
Kahne glycosidation (sulfoxide method):



R^1 = *O*-alkyl, *O*-aryl, *O*-acyl; R^2 = alkyl, aryl; triflate activator: Tf_2O, TMSOTf, TfOH; solvent: toluene, CH_2Cl_2, Et_2O, EtOAc, EtCN; base: DTBMP, DTBP, TTBP; acid scavenger: methyl propiolate, allyl-1,2-dimethoxybenzene, $P(OMe)_3$, $P(OEt)_3$; Nucleophile: 1°, 2° and 3° alcohols, phenols, thiols, silylated amides, *O*-trialkylstannyl phenols

Mechanism:[26,20,27,21,8]

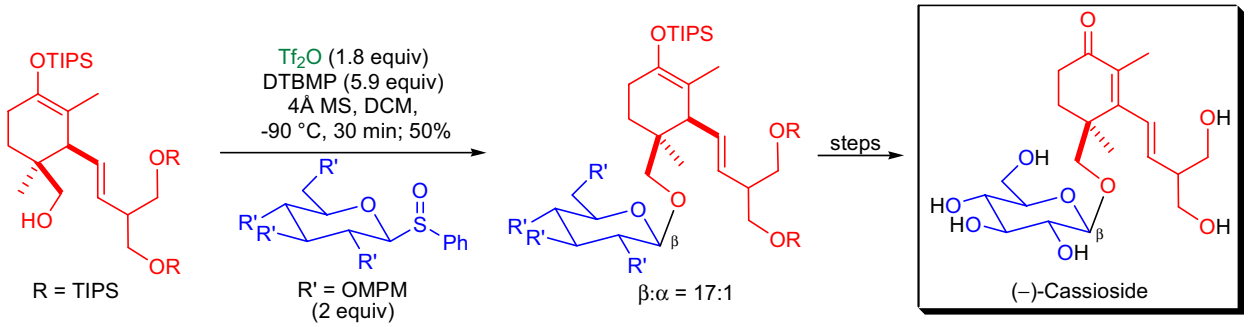
The precise mechanism of the glycosidic bond formation in the *Kahne glycosidation* is not known. NMR studies have revealed that when the activating agent is a triflate, glycosyl triflates are formed and act as glycosyl donors.[26] It is not clear whether the nucleophile displaces the leaving group in an S_N2 reaction or oxocarbenium/triflate contact ion pairs trap it stereoselectively. There is no structural information on the active species, which are generated upon activation by Lewis acids.



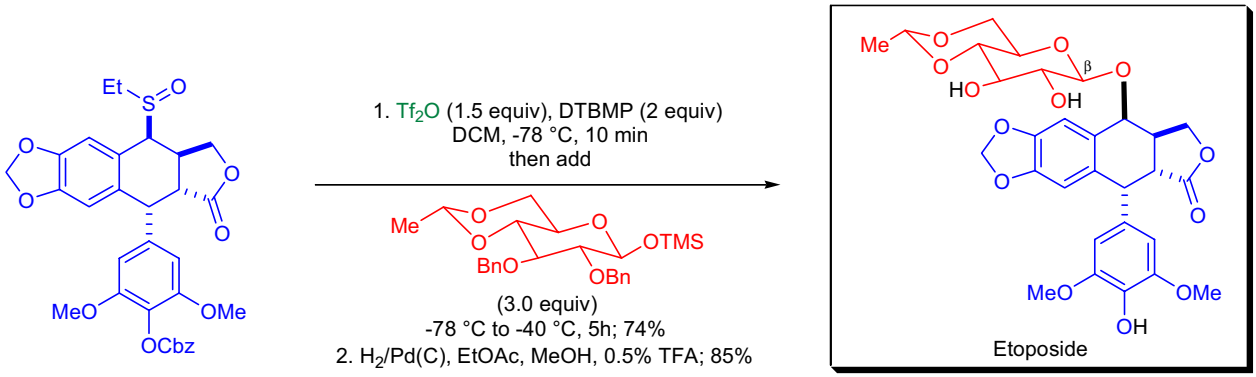
KAHNE GLYCOSIDATION

Synthetic Applications:

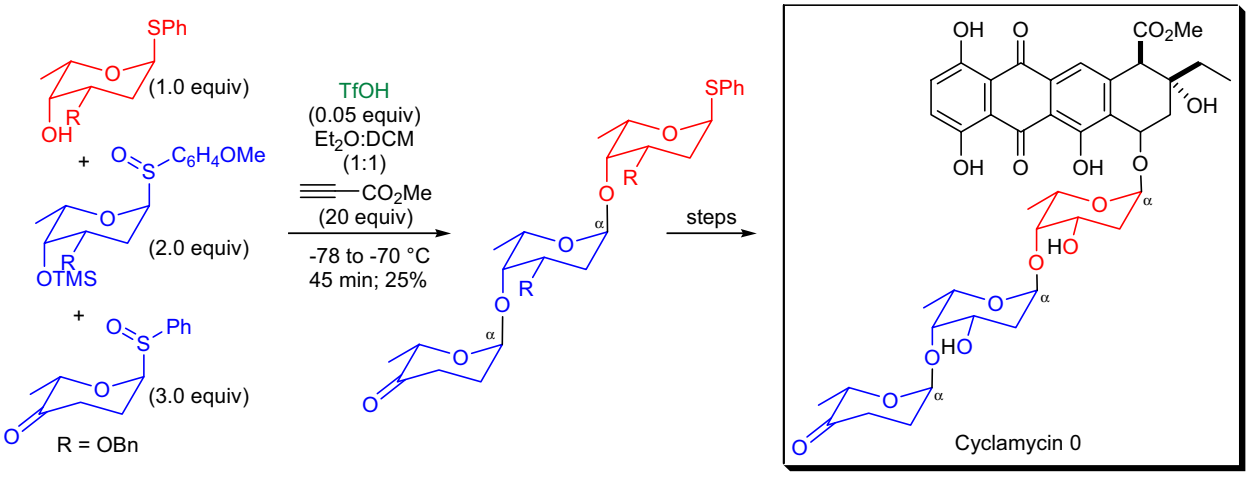
The first enantioselective total synthesis of the potent antiulcerogenic glycoside (–)-cassioside was accomplished in the laboratory of R.K. Boeckman Jr.[28] The natural product features a β-glycosidic bond to the extremely hindered neopentyl alcohol functionality of the aglycon. The *Kahne glycosidation* proved to be well-suited for the challenging glycosidation step at the final stages of the synthetic effort. The choice of the protecting groups proved to be important, since the authors found that after the coupling the removal of the benzyl groups failed in the presence of the unsaturations present in the coupled product. The tetrakis(MPM)glucosylphenyl sulfoxide was activated with Tf_2O at -90 °C. The resulting reactive intermediate was unstable at -78 °C, so the addition of the nucleophile was performed at -90 °C.



When the alkyl or aryl sulfoxide functionality is placed on the aglycon, a useful variant of the *Kahne glycosidation* arises which is known as the *reverse Kahne glycosidation*. D.B. Berkowitz and co-workers utilized this method for the total synthesis of etoposide, a semisynthetic glucoconjugate of epipodophyllotoxin, which has been used as an antineoplastic agent.[12] The activation of the phenyl sulfoxide occurred at low temperature, and after the addition of excess glycosyl acceptor, the reaction mixture was warmed to -40 °C in 5 hours and quenched. The coupled product was exclusively the β anomer, which was isolated in good yield. The final step was the removal of the benzyl and Cbz groups.



D. Kahne et al. developed a one-pot multicomponent stereoselective synthesis for the trisaccharide portion of cyclamycin 0 using the *Kahne glycosidation*.[25,29] The reactivity of the glycosyl donor was tuned (the rate limiting step is the triflation of the sulfoxide) and the *p*-methoxyphenyl sulfoxide was activated first. The trisaccharide was obtained in an overall 25% yield with complete α-selectivity.



KECK ASYMMETRIC ALLYLATION

(References are on page 612)

Importance:

[*Seminal Publication*[1-3]*; Reviews*[4-11]*; Modifications & Improvements*[12-19]]

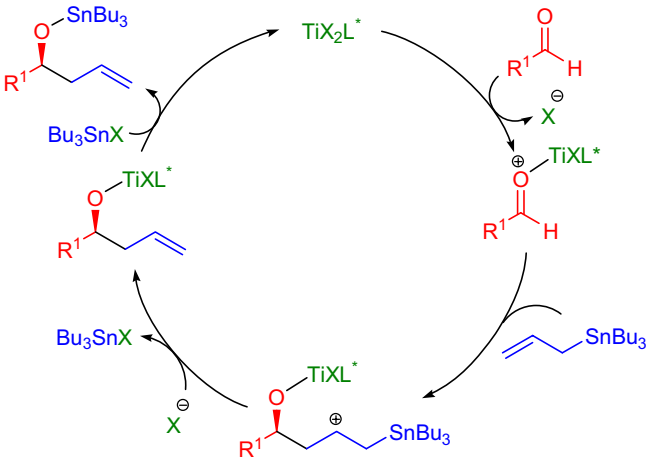
The formation of chiral secondary homoallylic alcohols *via* the enantioselective addition of allylic nucleophiles to aldehydes is an important tool in organic synthesis. An efficient way to achieve this transformation is to use allylic organometallic reagents in the presence of chiral Lewis acid catalysts. The most widely studied catalysts in the area are the 1,1'-binaphthalene-2,2'-diol (BINOL) complexes of titanium$^{(IV)}$. The first application of a Ti$^{(IV)}$-BINOL complex for enantioselective allylation was reported by K. Mikami in 1993.[20] According to this procedure, the catalyst was prepared from $TiCl_2(O\textit{i}\text{-}Pr)_2$ and (*S*)-BINOL in the presence of 4Å molecular sieves *in situ*. The addition of allylsilanes and allylstannanes to glyoxylate in the presence of 10% of the catalyst provided the products with low enantio- and diastereoselectivity. The same year, G.E. Keck independently reported the application of the BINOL/Ti$^{(IV)}$ catalyst system for asymmetric allylation.[1-3] He utilized allyltributylstannane as the nucleophile, and reacted it with aliphatic, aromatic, and unsaturated aldehydes in the presence of 10 mol% catalyst. The catalyst was prepared by combining two equivalents of the (*R*)- or (*S*)-BINOL ligand with one equivalent of $Ti(O\textit{i}\text{-}Pr)_4$ in dichloromethane, and the mixture was kept at room temperature for five minutes to an hour. The reaction of unbranched aliphatic, aromatic and unsaturated aldehydes with allyltributylstannane in the presence of 10% catalyst provided the homoallylic alcohols with high yields and enantioselectivity; α-branched aldehydes gave the products with lower yields and enantioselectivity. Today, this reaction is referred to as the *Keck asymmetric allylation*. About the same time, the research group of E. Tagliavini reported similar results using BINOL/Ti$^{(IV)}$ complexes for asymmetric allylation.[21] His procedure for the preparation of the catalyst system was similar to Mikami's original method, except that they used a slight excess of the BINOL ligand. The high selectivity and wide applicability of the above method stimulated further studies and several modifications of the original catalyst system were reported: 1) instead of the original BINOL ligand, derivatives of BINOL were utilized;[16,17] 2) dendritic BINOL ligands were applied for easy separation of the reaction mixture from the catalyst;[15] 3) racemic BINOL and enantiopure diisopropyl tartrate was combined to prepare the catalyst;[12] 4) bidentate catalysts prepared by mixing $Ti(O\textit{i}\text{-}Pr)_4$, BINOL, and aromatic diamines showed improved reactivity and selectivity;[18,19] and 6) rate enhancement could be achieved by the addition of stoichiometric amounts of additives such as *i*-PrSSiMe, *i*-PrSBEt$_2$, *i*-PrSAlEt$_2$, and $B(OMe)_3$.[13,14] The scope of the reaction was extended to β-substituted allylic stannanes.[22-25]



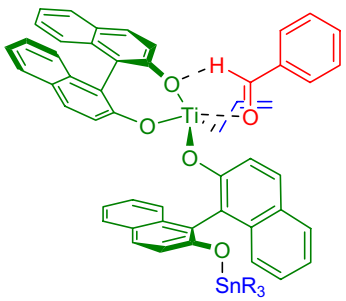
R^1 = alkyl, aryl, alkenyl; R^2 = alkyl, O-alkyl; Mikami's catalyst: $TiCl_2(O\textit{i}\text{-}Pr)_2$ + (*S*)-BINOL (0.3 equiv) + 4Å MS in CH_2Cl_2, toluene, 1h, r.t.; Keck's catalyst: $Ti(O\textit{i}\text{-}Pr)_4$ + (*R*)-BINOL (2 equiv) + 4Å mol sieves in CH_2Cl_2, 1h, r.t.; Tagliavini's catalyst: $TiCl_2(O\textit{i}\text{-}Pr)_2$ + (*S*)-BINOL (slight excess) + 4Å mol. sieves in CH_2Cl_2, 2h, r.t.;

Mechanism:[2,26,12,27]

The exact course of the mechanism of the allylation is not fully understood. The chiral Lewis acid presumably activates the aldehyde toward nucleophilic attack by the allyltributyltin. After loss of the tributyltin group, the homoallylic titanium$^{(IV)}$ alkoxide forms. Subsequently, the Ti$^{(IV)}$ Lewis acid is regenerated through transmetallation. This process can be facilitated by additives such as *i*-PrSSiMe$_3$.[13] Investigation of the mechanism of the enantioselective process revealed a positive nonlinear effect that suggests the involvement of a dimeric titanium complex $(BINOL)_2Ti_2X_4$.[2,12] To account for the absolute stereochemistry, a stereochemical model was proposed by E.J. Corey and co-workers. They postulated that a C-H···O hydrogen bond in the transition state assembly is a key factor in determining the absolute stereochemistry.[27]



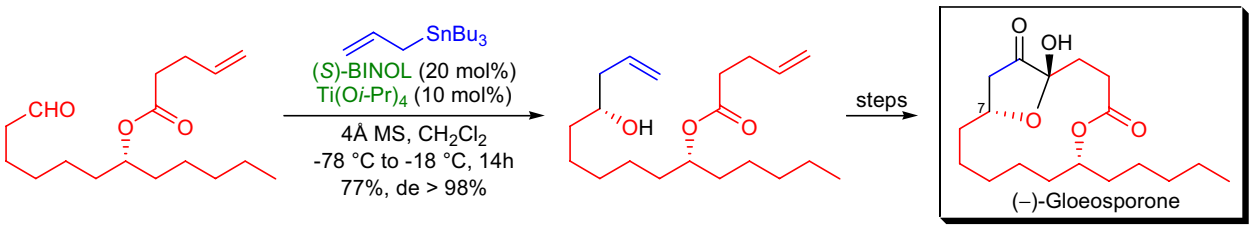
Corey's stereochemical model:



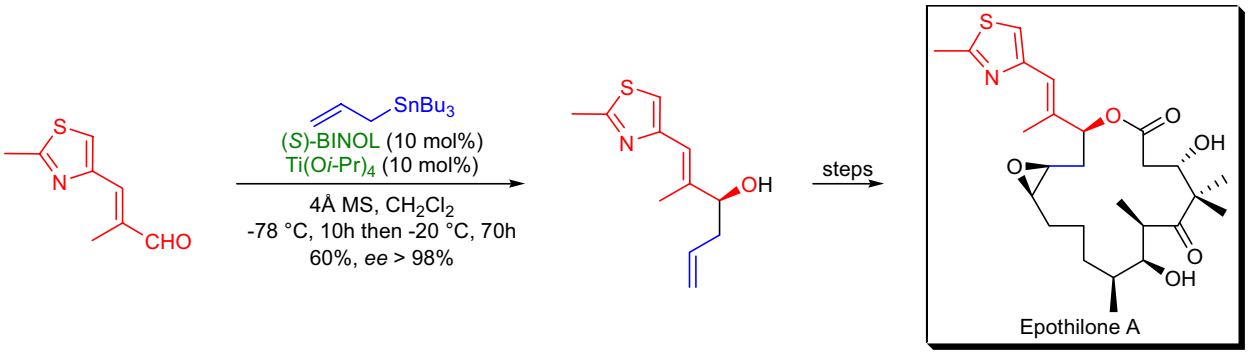
KECK ASYMMETRIC ALLYLATION

Synthetic Applications:

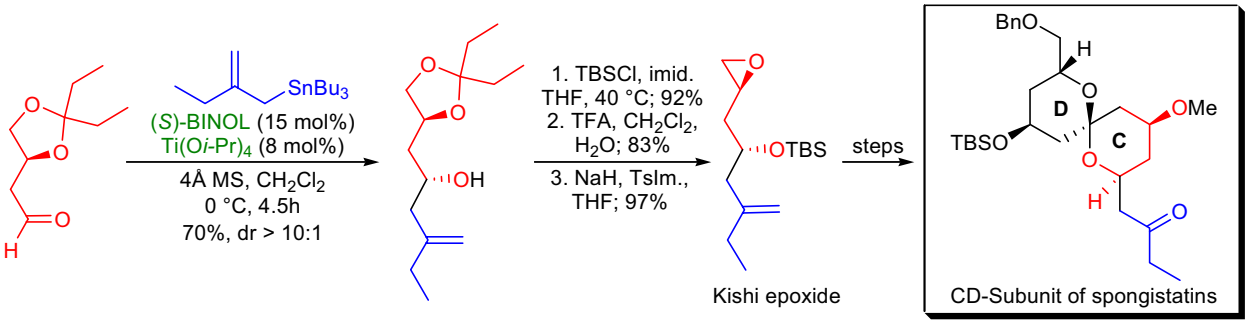
A. Fürstner and co-workers devised an efficient synthesis of (–)-gloeosporone, a fungal germination inhibitor.[28] They utilized the *Keck asymmetric allylation* method to create the 7(*R*)-homoallylic alcohol subunit. The reaction of the substrate aldehyde in the presence of the *in situ* generated catalyst provided the product with high yield and as the only diastereomer. It is important to note that it was essential to use freshly distilled Ti(*i*-OPr)$_4$ for the preparation of the catalyst in order to get high enantioselectivity and reproducible results.



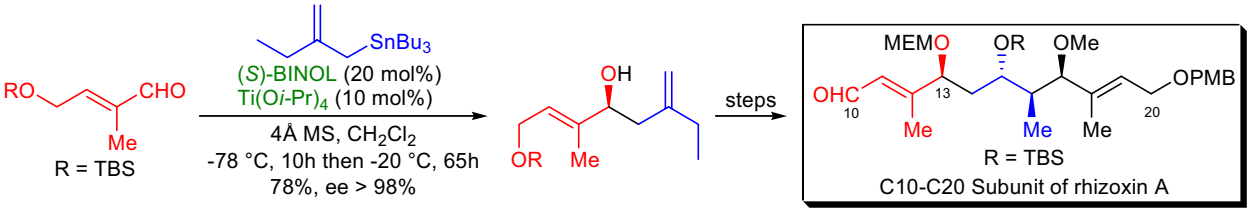
A convergent, stereocontrolled total synthesis of the microtubule-stabilizing macrolides, epothilones A *and* B was achieved in the laboratory of S.J. Danishefsky.[29] During their investigations, they examined several approaches to construct these natural products. One possible strategy to introduce the C15-hydroxyl group in an enantioselective fashion was to use Keck's asymmetric allylation method. Under standard conditions, the reaction provided the desired homoallylic alcohol in good yield and excellent enantioselectivity.



The spongistatins are a family of architecturally complex bisspiroketal macrolides, which display extraordinary cytotoxicity. During the second generation synthesis of the ABCD subunit of *spongistatin 1*, A.B. Smith and co-workers utilized the Keck allylation to construct the Kishi epoxide.[30] The allylation was carried out under standard conditions, using tributyl-(2-ethylallyl)-stannane as the allylstannane reactant. The desired product was formed in high yield and a diastereomeric ratio greater than 10:1.



Rhizoxin is a macrocyclic natural product possessing antibiotic and antifungal properties, and it also exhibits antitumor activity. G.E. Keck and co-workers described a synthetic approach for the construction of this natural product, where they utilized the catalytic asymmetric allylation method as a key strategic element to establish the C13 stereochemistry.[31]



KECK MACROLACTONIZATION

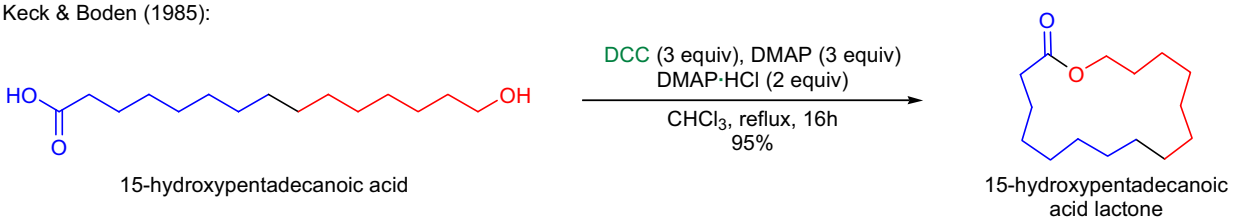
(References are on page 613)

Importance:

[*Seminal Publications*[1]*; Reviews*[2,3]*; Modifications & Improvements*[4]]

The introduction of the *Corey-Nicolaou macrolactonization* in the mid-1970s had a tremendous impact in the field of natural product total synthesis, and it was followed by numerous other macrolactonization procedures.[2] By the early 1980s the total synthesis of several very complex macrolide antibiotics was achieved. In 1985, G.E. Keck and E.P. Boden were trying to develop a new macrolactonization protocol in which the activated ester derived from the hydroxy acid substrate is generated *in situ* and does not need to be isolated.[1] At the outset of their studies they attempted to use the conditions of the *Steglich esterification* (DMAP/DCC)[5] for the formation of macrolactones, but even in the presence of excess reagents the experiments failed. However, when a proton source such as the hydrochloride salt of dimethylamino pyridine (DMAP·HCl) was added to mediate the crucial proton-transfer step, the macrocyclizations occurred in good to excellent yields. The formation of medium- and large-ring lactones from hydroxy acids using a combination of a dialkyl carbodiimide, an amine hydrochloride, and an amine base is known as the *Keck macrolactonization*. The general features of this transformation are: 1) as with other macrolactonization procedures the reaction requires high-dilution conditions (≤ 0.03 M); 2) the substrate is usually dissolved in an aprotic solvent and added to the refluxing solution of the reagents *via* a syringe pump over several hours; 3) the activating agent is a *N,N'*-dialkyl carbodiimide (DCC or EDCI) that prevents small amounts of water from destroying the activated acyl derivative; the process is essentially self-drying; 4) the carbodiimide reagent is typically used in several fold excess to ensure high conversion of the starting material; and 5) the use of DMAP·HCl prolongs the lifetime of the activated acyl intermediate and suppresses the formation of the undesired *N*-acyl urea by-product. The main disadvantage of the method is the need to use excess amounts of the carbodiimide reagent. At the end of the reaction, the excess carbodiimide must be destroyed with AcOH/MeOH and the product has to be separated from large amounts of dialkylurea. The most important modification of the *Keck macrolactonization* utilizes polymer-bound DCC to simplify the work-up.[4]

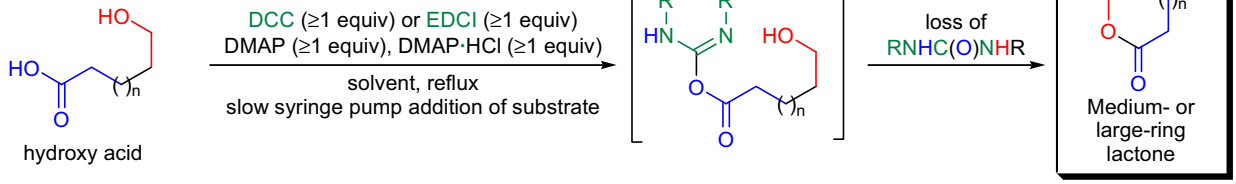
Keck & Boden (1985):



15-hydroxypentadecanoic acid

15-hydroxypentadecanoic acid lactone

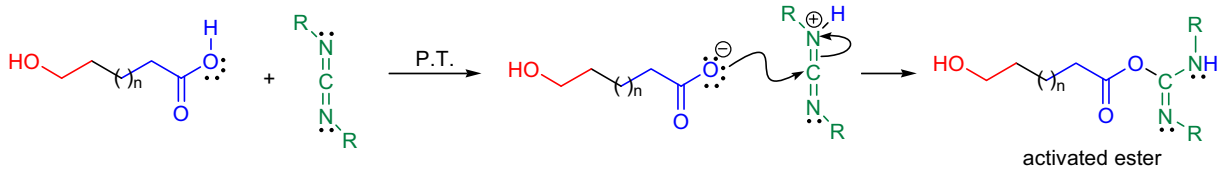
Keck macrolactonization:



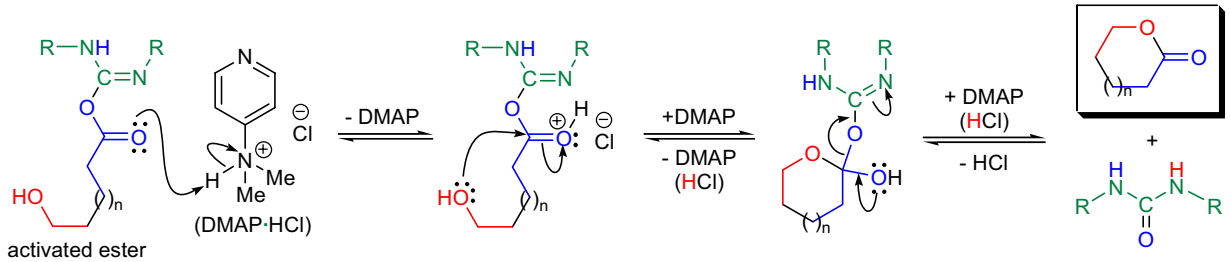
hydroxy acid

Mechanism:

Formation of the activated ester intermediate:



Formation of the macrolactone and the N,N'-dialkylurea by-product:

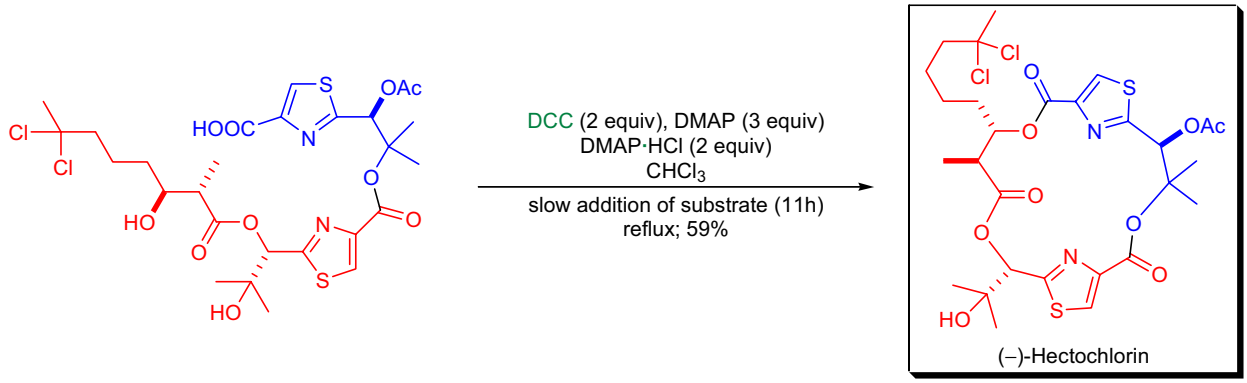


activated ester

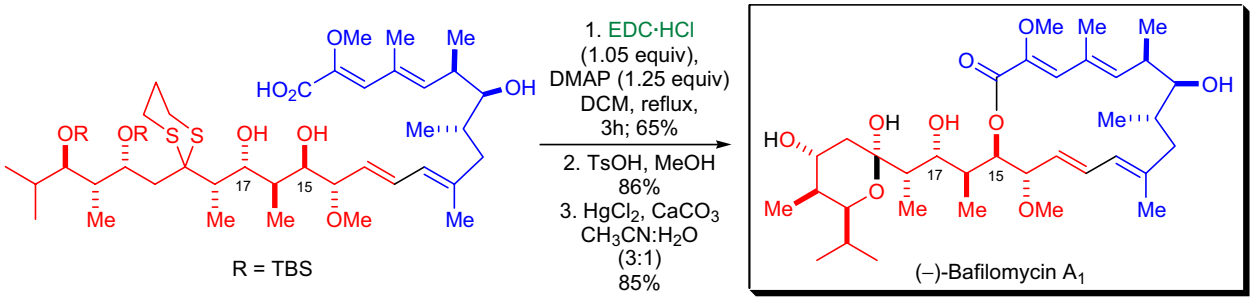
KECK MACROLACTONIZATION

Synthetic Applications:

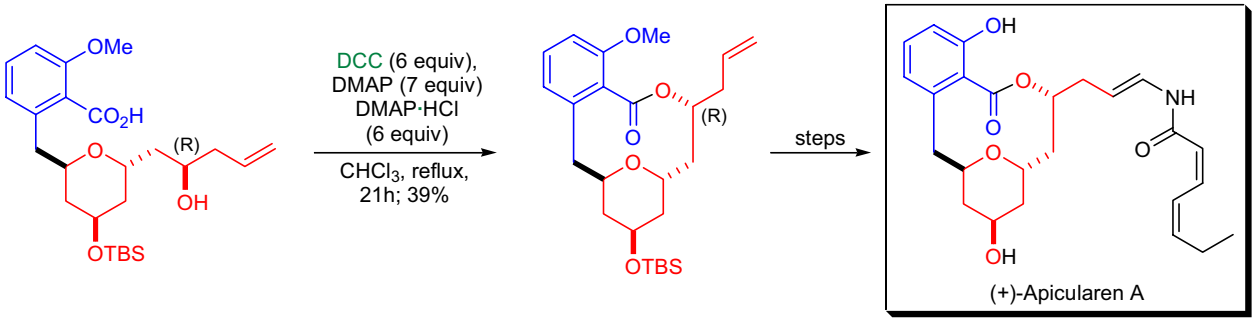
The total synthesis of a novel fungicidal natural product, (–)-hectochlorin, was accomplished by J.R.P. Cetusic and co-workers.[6] The final step in their synthetic route was the *Keck macrolactonization* under the original conditions developed by Keck et al. The substrate hydroxy acid was dissolved in ethanol-free $CHCl_3$ and was slowly added to a chloroform solution of DCC, DMAP and DMAP·HCl at reflux temperature.



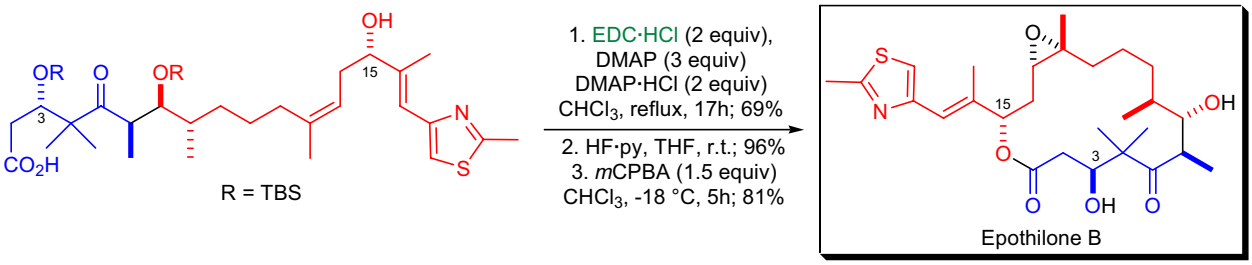
The 16-membered tetraenic macrolactone (–)-bafilomycin A_1 was synthesized in the laboratory of S. Hanessian.[7] The key macrolactonization step was conducted under the *modified Keck conditions* using EDCI instead of DCC. Interestingly, model studies on the macrocyclization of the hydroxy acid containing the entire bafilomycin A_1 carbon framework yielded a mixture of products. However, if the hydroxy acid did not contain the pseudosugar moiety, the macrolactonization took place uneventfully, and the thermodynamically more stable 16-membered lactone ring (with the C15 hydroxyl group) was formed exclusively.



The *Keck macrolactonization* was used by R.J.K. Taylor et al. to close the 10-membered ring of (+)-apicularen A.[8] The lactonization was attempted using both the Yamaguchi and Mitsunobu procedures and neither gave even a trace of the cyclic product. However, when the *Keck conditions* were applied, the desired lactone was isolated in moderate yield.



The total synthesis of the microtubule stabilizing antitumor drug epothilone B was achieved by J. Mulzer et al. who cyclized the 16-membered macrocycle using the *Keck macrolactonization*.[9]



KECK RADICAL ALLYLATION

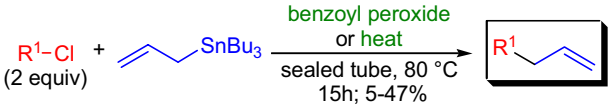
(References are on page 613)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-8]]

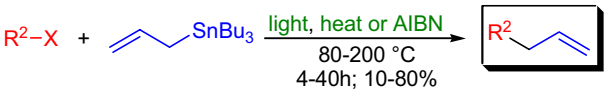
During the total synthesis of perhydrohistrionicotoxin, G.E. Keck and co-workers faced a challenge to replace a halogen with an allyl moiety.[9] They solved this problem by applying a free radical chain process, namely reacting an alkyl halide with allyltributyltin. The reaction was carried out in benzene, at 80 °C in the presence of catalytic amounts of AIBN as a radical initiator. Since this report, the coupling of an alkyl halide with allyltributyltin under radical conditions to introduce the allyl functionality is referred to as the *Keck radical allylation*. Keck examined the scope of the reaction and he found the following:[4] 1) the reaction is general for primary-, secondary-, and tertiary alkyl bromides: 2) it tolerates a wide range of functional groups such as free hydroxyl groups, esters, ethers, epoxides, acetals, ketals, and sulfonate esters; 3) the reaction is highly chemoselective: aldehydes that readily undergo allylation with allyltributyltin under acidic conditions, were not affected under the reaction conditions; 4) the process is tolerant of steric hindrance; 5) in addition to alkyl bromides, alkyl chlorides, phenylselenides, and thioacylimidazole derivatives also react; and 6) to initiate the process, a catalytic amount of AIBN proved to be the most efficient, but photoinitiation can also be used. Although this transformation was studied and extended by Keck, it should be noted that the first example of such a reaction was reported independently by M. Kosugi[2] and J. Grignon[1,3] in 1973. For the initiation, they utilized benzoyl peroxide, pyrolysis, or photoinitiation, and the isolated yields of the products were low to moderate.

Kosugi's procedure (1973):



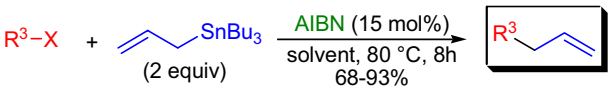
R^1 = -CCl_3, -$CHCl_2$, -CH_2CO_2Me, -CH_2CCl_3

Grignon's procedure (1973, 1975):



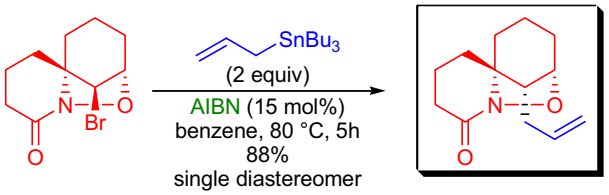
R^2 = -CCl_3, -$CHCl_2$, - CH_2Cl, -CH_2CO_2Et, -CCl_2CO_2Et, -CCl_2CHO, -CBr_2CHO, -$CH(CH_3)CO_2Me$, *n*-propyl, *i*-Pr, *t*-Bu, allyl, *t*-butylcyclohexyl, aryl; X = Cl, Br

Keck's general process (1982):



R^3 = 1°, 2°, and 3° alkyl; X = Cl, Br, SePh, thioacylimidazole; solvent = benzene, toluene;

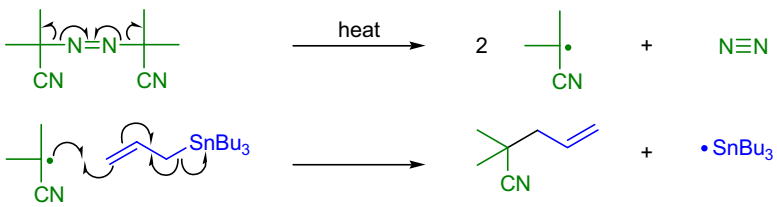
Keck's specific example (1982):



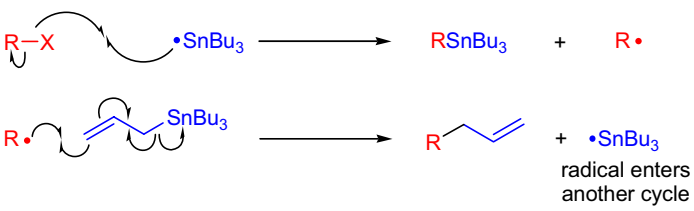
Mechanism:[1-3]

The mechanism of this transformation was examined by M. Kosugi.[2] He found that the reaction was promoted by benzoyl peroxide, a radical initiator and was retarded by *p*-quinone, a radical scavenger. These results are in accordance with a free radical chain mechanism. The initiation of the reaction may take place *via* a variety of possible pathways, one possibility is depicted below.

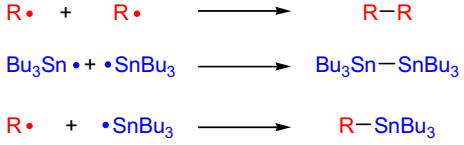
Initiation step:



Propagation step:



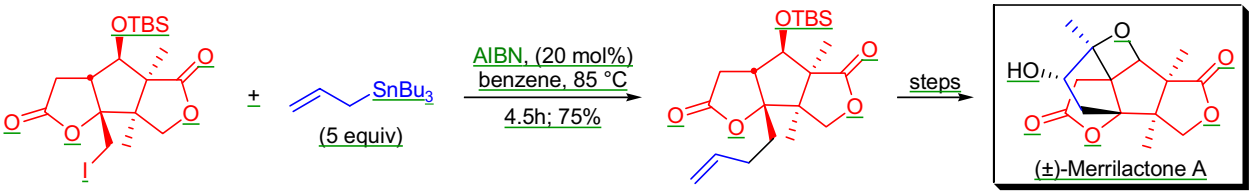
Termination steps



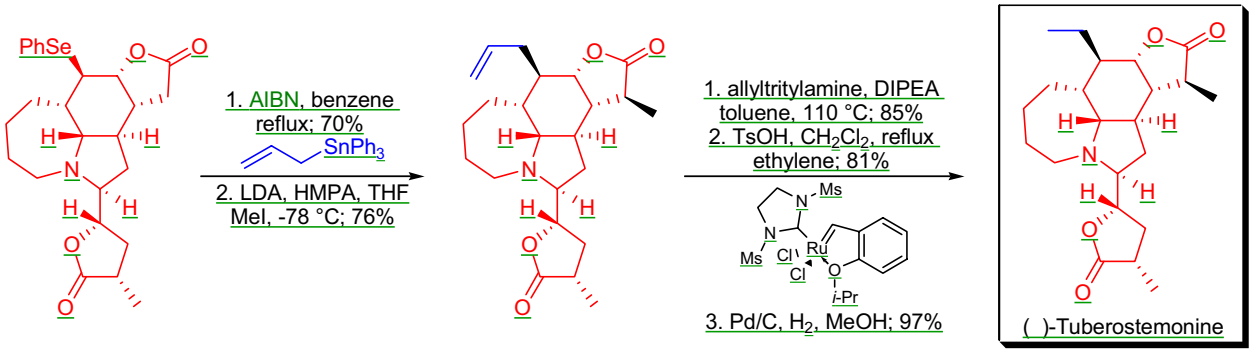
KECK RADICAL ALLYLATION

Synthetic Applications:

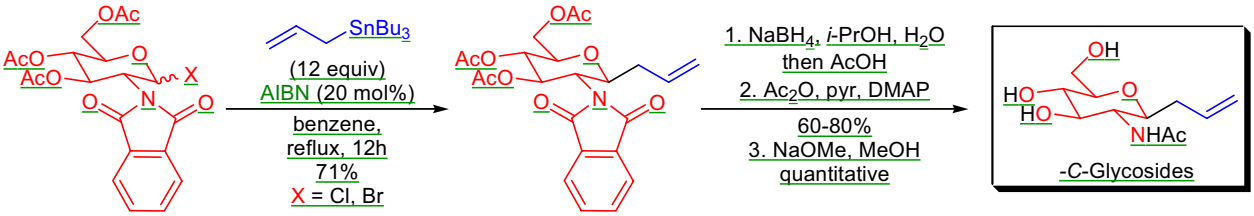
S.J. Danishefsky and co-workers reported the total synthesis of pentacyclic sesquiterpene dilactone, merrilactone A.[10] In their approach, they utilized *Keck's radical allylation* method to achieve the required chain extension. This sidechain was later used to construct one of the cyclopentane rings of the natural product.



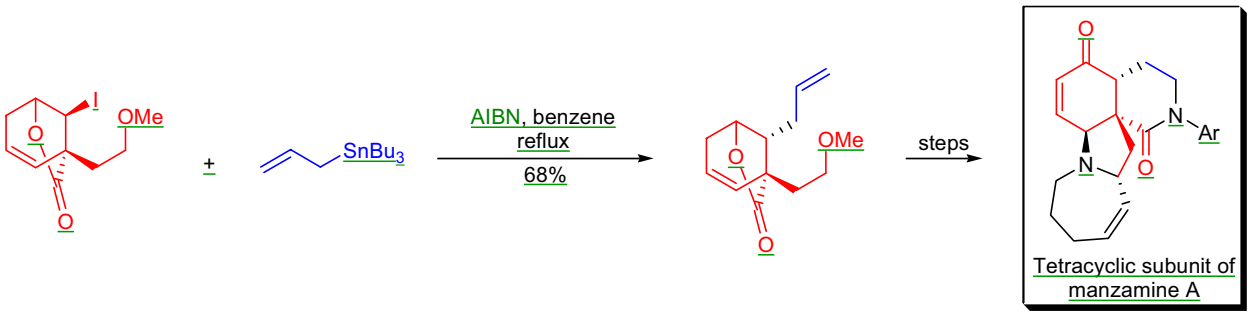
The total synthesis of *Stemona* alkaloid (–)-tuberostemonine was accomplished by P. Wipf.[11] Late in the synthesis, the introduction of an ethyl sidechain was required. This could be achieved in a novel four-step sequence. First, the allyl sidechain was introduced by the *Keck radical allylation*. To this end, the secondary alkyl phenylselenide substrate was treated with allyltriphenyltin in the presence of catalytic amounts of AIBN. This was followed by the introduction of a methyl group onto the lactone moiety. The allyl group then was transformed into the desired ethyl group as follows: the terminal double bond was isomerized to the internal double bond by the method of R. Roy. This was followed by ethylene cross metathesis and catalytic hydrogenation to provide the desired ethyl sidechain.



Oligosaccharides are structurally diverse biopolymers that play an important role in many biological processes. To examine the biological function of these compounds and develop therapeutic agents, the construction of synthetic polysaccharides is essential. Carbon-linked glycosides, called *C-glycosides*, are hydrolytically stable carbohydrate mimetics that were widely studied for their biological activity. C.R. Bertozzi and co-workers reported the synthesis of -C-glycosides of N-acetylglucosamine *via* the *Keck radical allylation*.[12] This transformation was carried out on the corresponding bromide- and chloride derivatives, using a large excess of allyltributyltin. In case of the chloride substrate, higher temperature (110 °C) was required to effect the transformation.



Manzamine A is an alkaloid that was shown to inhibit the growth of P-388 mouse leukemia cells. The synthesis of the tetracyclic substructure of this natural product was reported by D.J. Hart.[13] For the construction of the perhydroisoquinoline moiety, he utilized the *Keck radical allylation*. This transformation was carried out under standard conditions, reacting a secondary alkyl iodide with allyltributyltin.



KNOEVENAGEL CONDENSATION

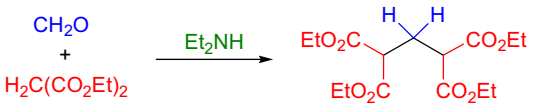
(References are on page 613)

Importance:

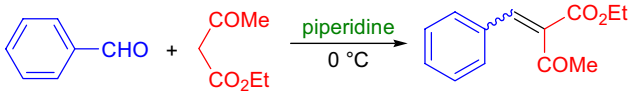
[*Seminal Publications*[1,2]; *Reviews*[3-10]; *Modifications & Improvements*[11-41]]

In 1894, E. Knoevenagel reported the diethylamine-catalyzed condensation of diethyl malonate with formaldehyde in which he isolated the *bis* adduct.[1] He found the same type of *bis* adduct when formaldehyde and other aldehydes were condensed with ethyl benzoylacetate or acetylacetone in the presence of primary and secondary amines. Two years later in 1896, Knoevenagel carried out the reaction of benzaldehyde with ethyl acetoacetate at 0 °C using piperidine as the catalyst and obtained ethyl benzylidene acetoacetate as the sole product.[2] The reaction of aldehydes and ketones with active methylene compounds in the presence of a weak base to afford α,β-unsaturated dicarbonyl or related compounds is known as the *Knoevenagel condensation*. The general features of the reaction are: 1) aldehydes react much faster than ketones; 2) active methylene compounds need to have two electron-withdrawing groups and typical examples are malonic esters, acetoacetic esters, malonodinitrile, acetylacetone, etc.; 3) the nature of the catalyst is important, usually primary, secondary, and tertiary amines and their corresponding ammonium salts, certain Lewis acids combined with a tertiary amine (e.g., $TiCl_4/Et_3N$), potassium fluoride, or other inorganic compounds such as aluminum phosphate are used; 4) the by-product of the reaction is water and its removal from the reaction mixture by means of azeotropic distillation, the addition of molecular sieves, or other dehydrating agents shifts the equilibrium toward the formation of the product; 5) the choice of solvent is crucial and the use of dipolar aprotic solvents (e.g., DMF) is advantageous, since protic solvents inhibit the last 1,2-elimination step; 6) the dicarbonyl product can be hydrolyzed and decarboxylated to afford the corresponding α,β-unsaturated carbonyl compounds; 7) when R^3 and R^4 or R^5 and R^6 are different, the product is obtained as a mixture of geometrical isomers, and the selectivity is dictated by steric effects; and 8) usually the thermodynamically more stable compound is formed as the major product.

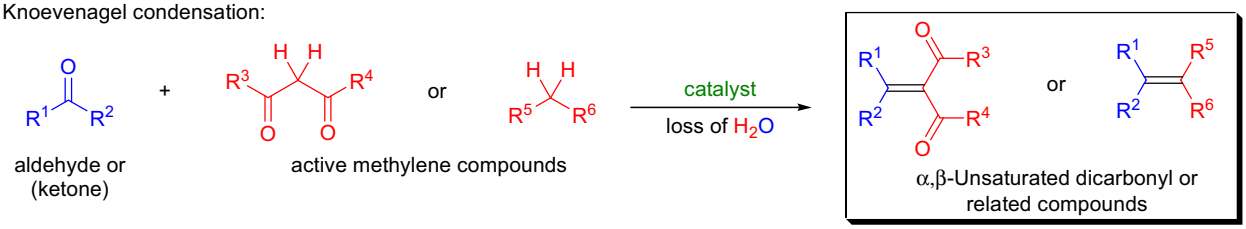
Knoevenagel (1894):



Knoevenagel (1896):



Knoevenagel condensation:

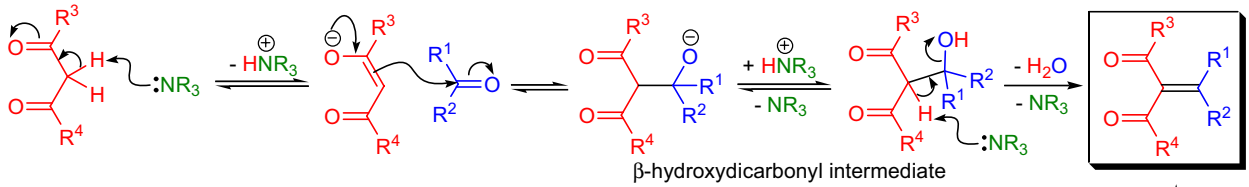


R^1 = H, alkyl, aryl; R^2 = H, alkyl, aryl; R^{3-4} = alkyl, aryl, OH, *O*-alkyl, *O*-aryl, NH-alkyl, NH-aryl *N*-dialkyl, *N*-diaryl; R^{5-6} = CO_2H, CO_2-alkyl, CO_2-aryl, C(O)NH-alkyl, C(O)NH-aryl, C(O)N-dialkyl, C(O)N-diaryl, C(O)-alkyl, C(O)-aryl, CN, $CNNR_2$, $PO(OR)_2$, SO_2OR, SO_2NR_2, SO_2R, SOR, SiR_3; catalyst: 1°, 2° or 3° amines, R_3NHX such as $[H_3NCH_2CH_2NH_3](OAc)_2$, piperidinium acetate/AcOH, NH_4OAc, KF, CsF, RbF, $TiCl_4/R_3N$ (*Lehnert modification*), pyridine/piperidine (*Doebner modification*), dry alumina (*Foucaud modification*), $AlPO_4/Al_2O_3$, xonotlite with KO*t*-Bu, $Zn(OAc)_2$

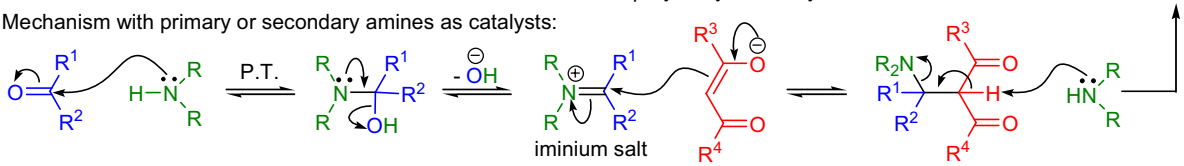
Mechanism:[42,4,43-49,7,50-55]

The *Knoevenagel condensation* is a base-catalyzed *aldol-type reaction*, and the exact mechanism depends on the substrates and the type of catalyst used. The first proposal for the mechanism was set forth by A.C.O. Hann and A. Lapworth (*Hann-Lapworth mechanism*) in 1904.[42] When tertiary amines are used as catalysts, the formation of a β-hydroxydicarbonyl intermediate is expected, which undergoes dehydration to afford the product. On the other hand, when secondary or primary amines are used as catalyst, the aldehyde and the amine condense to form an iminium salt that then reacts with the enolate. Finally, a 1,2-elimination gives rise to the desired α,β-unsaturated dicarbonyl or related compounds. The final product may undergo a *Michael addition* with the excess enolate to give a *bis* adduct.

Hann-Lapworth mechanism with tertiary amines as catalysts:



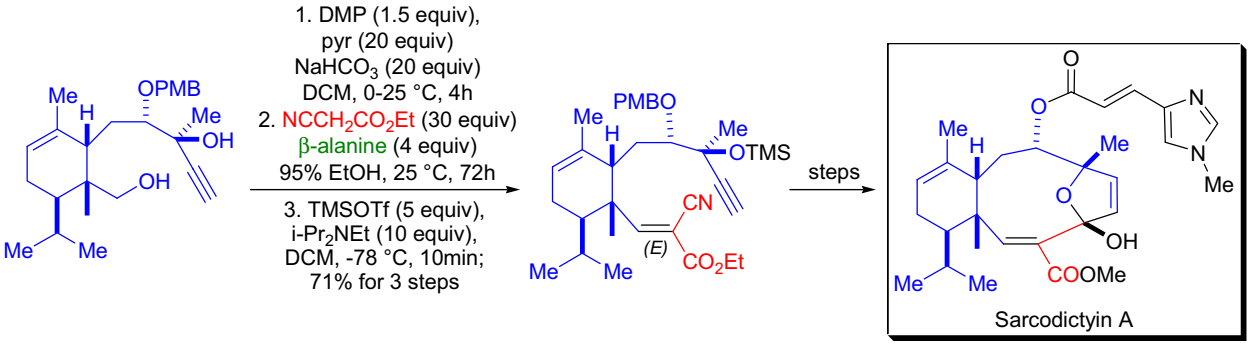
Mechanism with primary or secondary amines as catalysts:



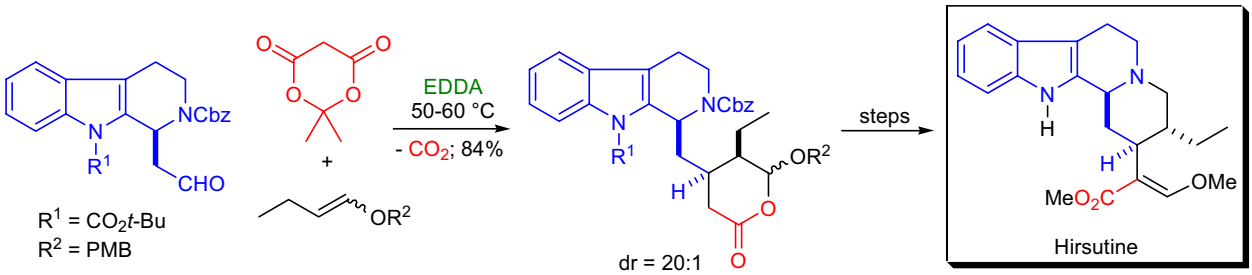
KNOEVENAGEL CONDENSATION

Synthetic Applications:

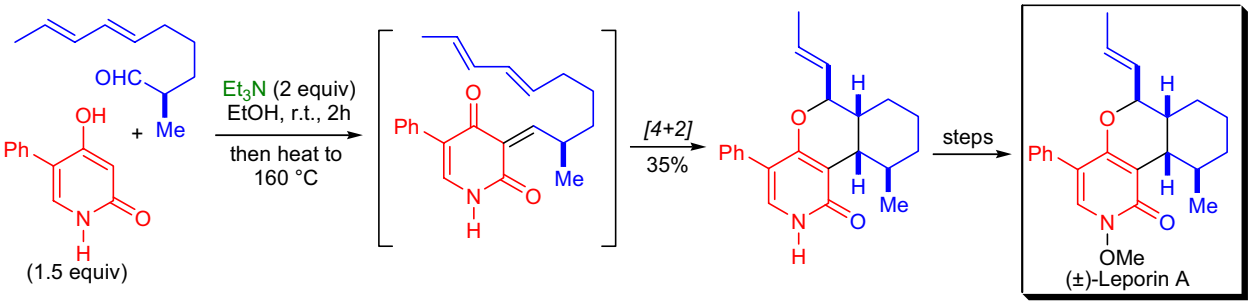
The total synthesis of the marine-derived diterpenoid sarcodictyin A was accomplished in the laboratory of K.C. Nicolaou.[56] The most challenging part of the synthesis was the construction of the tricyclic core, which contains a 10-membered ring. This macrocycle was obtained by the intramolecular 1,2-addition of an acetylide anion to an α,β-unsaturated aldehyde. This unsaturated aldehyde moiety was installed by utilizing the *Knoevenagel condensation* catalyzed by β-alanine. The Knoevenagel product was exclusively the (*E*)-cyanoester.



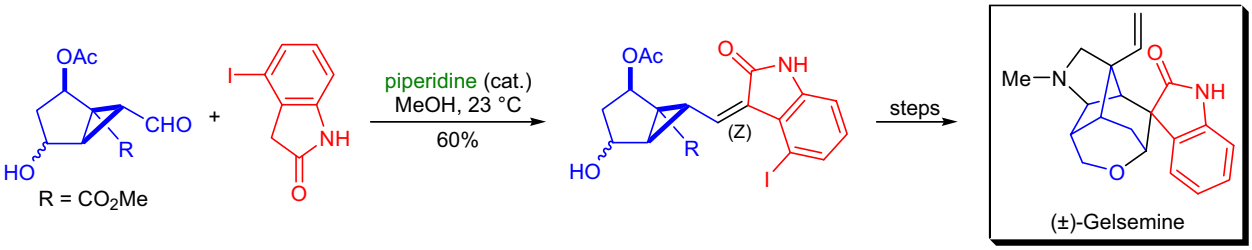
The domino *Knoevenagel condensation/hetero-Diels-Alder reaction* was used for the enantioselective total synthesis of the active anti-influenza A virus indole alkaloid hirsutine and related compounds by L.F. Tietze and co-workers.[57] The *Knoevenagel condensation* was carried out between an enantiopure aldehyde and Meldrum's acid in the presence of ethylenediamine diacetate. The resulting highly reactive 1-oxa-1,3-butadiene underwent a *hetero-Diels-Alder reaction* with 4-methoxybenzyl butenyl ether (*E*/*Z* = 1:1) *in situ*. The product exhibited a 1,3-asymmetric induction greater than 20:1.



During the total synthesis of (±)-leporin A, a tandem *Knoevenagel condensation/inverse electron demand intramolecular hetero-Diels-Alder reaction* was employed by B.B. Snider et al. to construct the key tricyclic intermediate.[58] The condensation of pyridone with the enantiopure acyclic aldehyde in the presence of triethylamine as catalyst afforded an intermediate that underwent a [4+2] cycloaddition to afford the tricyclic core of the target.



The stereocontrolled total synthesis of (±)-gelsemine was accomplished by T. Fukuyama and co-workers using the *Knoevenagel condensation* to prepare a precursor for the key *divinylcyclopropane-cycloheptadiene rearrangement*.[59] The use of 4-iodooxindole as the active methylene component allowed the preparation of the (*Z*)-alkylidene indolinone product as a single stereoisomer.



KNORR PYRROLE SYNTHESIS

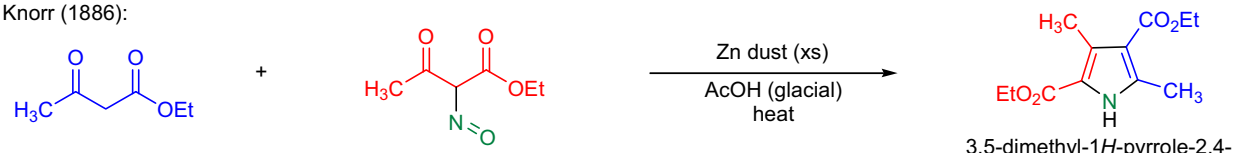
(References are on page 614)

Importance:

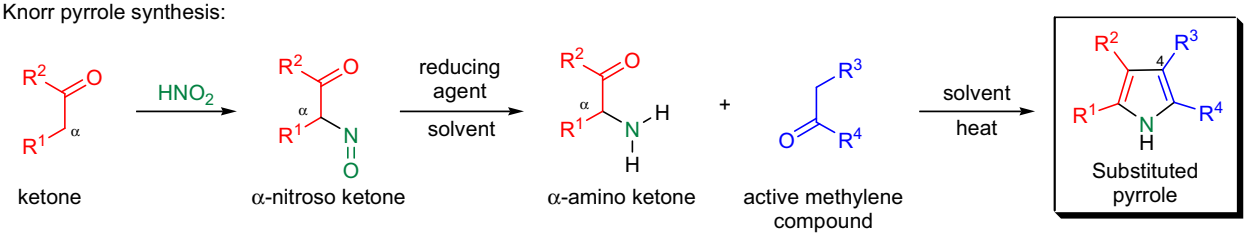
[*Seminal Publications*[1,2]; *Reviews*[3-8]; *Modifications & Improvements*[9-17]]

In 1886, L. Knorr reported that by heating the mixture of α-nitroso ethyl acetoacetate and ethyl acetoacetate in glacial acetic acid with zinc dust, a tetrasubstituted pyrrole is formed. The nitroso compound underwent reduction under the reaction conditions, and the resulting α-amino-β-ketoester reacted with the acetoacetic ester to afford the highly substituted pyrrole product. The condensation of an α-amino ketone or an α-amino-β-ketoester with an active methylene compound is known as the *Knorr pyrrole synthesis*. The general features of the transformation are: 1) the reaction can be conducted under both acidic and basic conditions; 2) α-amino ketones are often quite labile and tend to undergo self-condensation (to form the corresponding pyrazines), so it is common to prepare them by first nitrosating the ketone and then reducing the resulting α-nitroso ketone *in situ*; 3) the reduction of the α-nitroso ketone (or α-oximino ketone in its tautomerized form) is conducted using zinc powder in acetic acid, aqueous solution of sodium dithionate ($Na_2S_2O_4$), or catalytic hydrogenation under which conditions ketones and esters are not reduced; 4) the hydrochloride salts of α-amino ketones are stable, and they can be used directly and the HCl can be neutralized *in situ*; 5) carbonyl-protected (e.g., acetal) derivatives of α-amino ketones are often utilized to avoid self-condensation; 6) alternatively the required α-amino ketones can be prepared by the *Neber rearrangement* of *O*-acylated ketoximes; 7) *N*-substituted pyrroles are formed when a secondary amino ketone is used; 8) the active methylene component is usually a 1,3-diketone, β-ketoester or a β-cyanoester; 9) if the active methylene compound is not reactive enough, the formation of the pyrrole will be slow and the self-condensation of the α-amino ketone becomes predominant; and 10) when non-symmetrical ketones are used, there is a modest regioselectivity favoring the regioisomer in which the bulkier group is part of the acyl substituent at C4.

Knorr (1886):



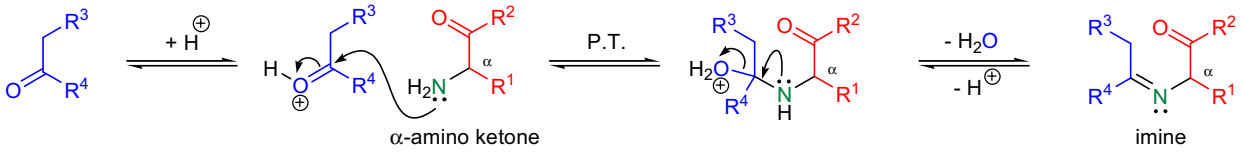
Knorr pyrrole synthesis:



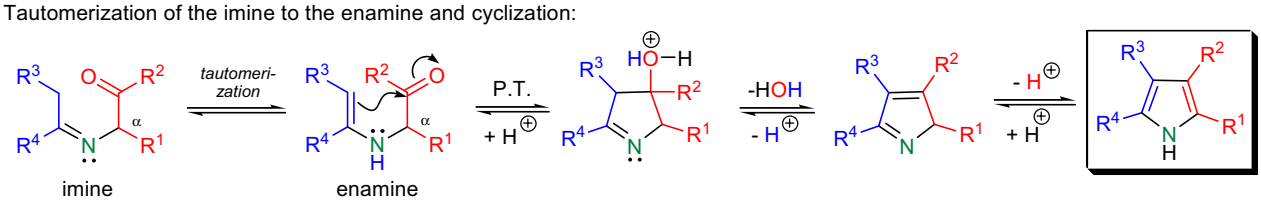
R^1 = H, aryl, CO_2R; R^2 = alkyl, aryl; R^3 = electron-withdrawing group (EWG) = COR, CO_2R, CN, SO_2R; R^4 = H, alkyl, aryl, CO_2R;
reducing agent: Zn/AcOH, $Na_2S_2O_4$, Pd(C)/H_2; solvent: AcOH, H_2O

Mechanism:[18-20]

Condensation of the amino ketone and ketone to give an imine:



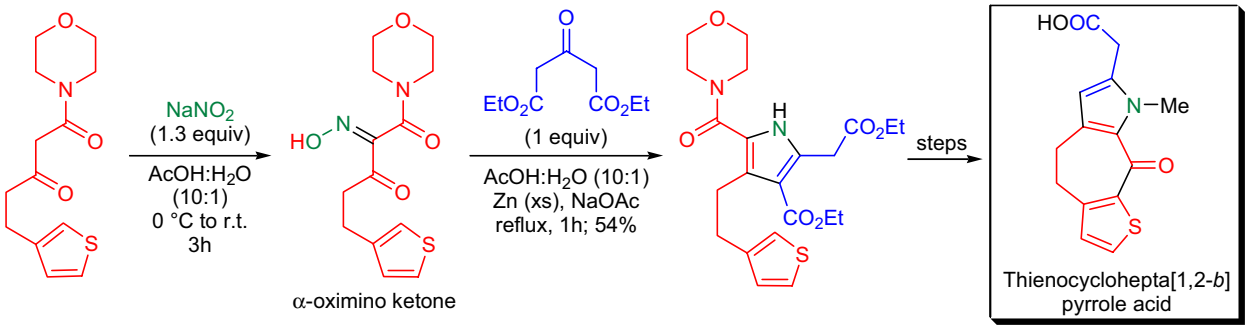
Tautomerization of the imine to the enamine and cyclization:



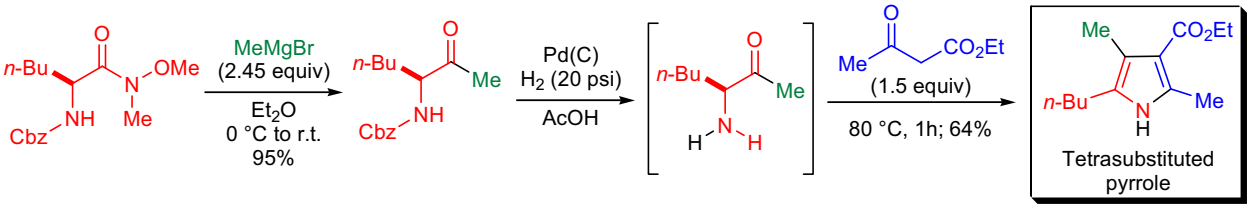
KNORR PYRROLE SYNTHESIS

Synthetic Applications:

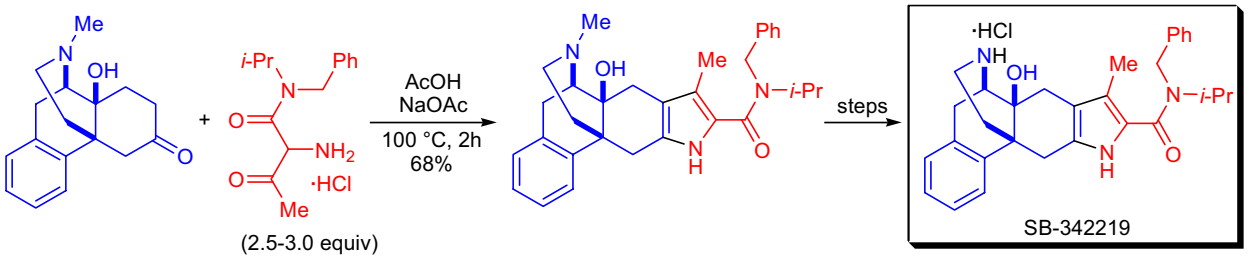
A new anti-inflammatory/analgesic agent, 4,5,8,9-tetrahydro-8-methyl-9-oxothieno[3',3':5,6]cyclohepta[1,2-*b*]-pyrrole-7-acetic acid, was synthesized by H.E. Rosenberg and R.W. Ward et al. using the *Knorr pyrrole synthesis* for the construction of the highly substituted pyrrole ring.[21] The starting β-ketoamide was first nitrosated under standard conditions in acetic acid/water to afford the corresponding α-oximino ketone. This was followed by the addition of diethyl acetone-1,3-dicarboxylate, zinc powder, and sodium acetate, and the resulting mixture was heated at reflux. The cyclization to obtain the desired tricyclic ketone was achieved under Vilsmeier-Haack conditions using $POCl_3$.



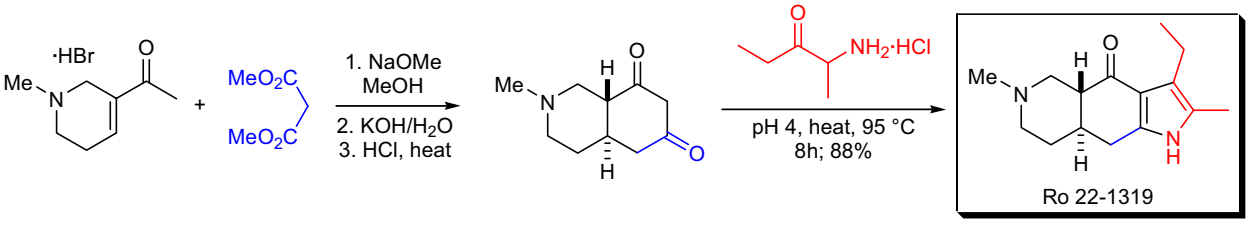
A useful modification of the *Knorr pyrrole synthesis* was developed in the laboratory of J.M. Hamby for the construction of tetrasubstituted pyrroles. The necessary α-amino ketones were prepared from *N*-methoxy-*N*-methylamides of amino acids (Weinreb amides).[13] These Weinreb amides were prepared by the mixed anhydride method and treated with excess methylmagnesium bromide in ether to afford the corresponding Cbz-protected α-amino ketones in excellent yield. The Cbz group is removed by catalytic hydrogenation in the presence of the active methylene compound (e.g., acetoacetic ester), the catalyst is then filtered and the resulting solution is heated to reflux to bring about the condensation.



The large-scale synthesis of a potent δ-opioid antagonist, SB-342219, was accomplished by the research team of J.S. Carey.[22] The route developed by medicinal chemists could not be fully adapted for the large-scale preparation, since it required the addition of finely divided zinc powder in portions to a hot and flammable solvent containing a phenylhydrazone and a low concentration of the resulting α-amino ketone had to be maintained. Therefore, a procedure was sought that avoided the use of zinc metal altogether. The tricyclic ketone was mixed with an excess of the amino ketone hydrochloride in acetic acid and heated. Only one regioisomer of the pyrrole was formed in good yield, which was then converted to the final compound in a few steps.



The two-step one-pot total synthesis of Ro 22-1319, an antipsychotic agent featuring a rigid pyrrolo[2,3-*g*]isoquinoline skeleton, was accomplished by D.L. Coffen and co-workers.[23] The cyclic 1,3-diketone precursor was prepared from arecoline and dimethyl malonate, and in the same reaction vessel an amino ketone hydrochloride was added. The pH of the reaction mixture was adjusted to 4 in order to initiate the formation of the pyrrole.



KOENIGS-KNORR GLYCOSIDATION

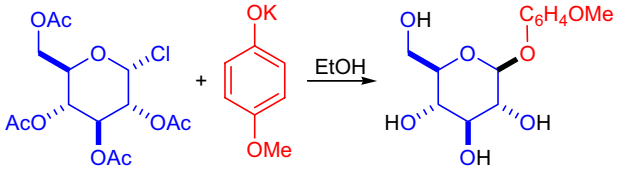
(References are on page 615)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-21]*; Modifications & Improvements*[22-34]*; Theoretical Studies*[35-37]]

The first synthesis of a glycoside was reported by A. Michael in 1879, when he treated 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride with the potassium salt of 4-methoxy phenol in absolute ethanol.[1] The product was the corresponding β-D-*O*-phenyl glycoside, but the acetyl groups were hydrolyzed under the strongly basic reaction conditions. This procedure could only be used for the synthesis of aryl glycosides, and the integrity of the acetyl functionality could not be preserved. Two decades later, in 1901, W. Koenigs and E. Knorr modified the procedure and by taking tetra-*O*-acetyl-α-D-glucopyranosyl bromide and treating it with excess silver carbonate in methanol they isolated the corresponding β-D-*O*-methyl glycoside with all the acetyl groups intact.[2] The synthesis of alkyl- and aryl *O*-glycosides from glycosyl halides and alcohols or phenols in the presence of heavy metals salts or Lewis acids is known as the *Koenigs-Knorr glycosidation*. The general features of this transformation are: 1) the preparation of glycosyl halides can be achieved typically by the exchange of the anomeric hydroxyl group with halogenating agents; 2) the various glycosyl halide substrates may have very different reactivities and stabilities, and these mainly depend on the nature of the halogen atom and the substituents on the carbohydrate scaffold: chlorides are more stable than bromides, while iodides are usually very unstable and electron-withdrawing protecting groups tend to increase the stability; 3) the reactivity of the glycosyl halide is also influenced by the choice of solvent, the temperature and the nature of the coactivator (Lewis acid or heavy metal salt); 4) the reaction is regiospecific, since the substitution always takes place at the anomeric carbon (C1) and can be highly diastereoselective; 5) formation of α-*O*-glycosides can be aided by the anomeric effect when neighboring group participation is not operational (if R^4=*O*-alkyl); 6) formation of β-*O*-glycosides is usually achieved from α-glycosyl halides when neighboring group participation is operational (e.g., R^4=*O*-acyl); 7) the coactivator or catalyst is typically a silver- or mercury salt dissolved in an aprotic solvent and the by-product acid is usually trapped by a base (e.g., Ag_2CO_3, collidine); and 8) due to the relatively low thermodynamic stability of glycosyl halides, reactions are conducted at or below room temperature. Disadvantages of the procedure are: 1) harsh conditions are needed for the preparation of the glycosyl halides, which are thermally not very stable; 2) glycosyl halides can undergo hydrolysis or 1,2-elimination; and 3) the coactivators are usually required in equimolar quantities, and they are often toxic and sometimes explosive. Numerous significant modifications and variants of the reaction exist.[22-34]

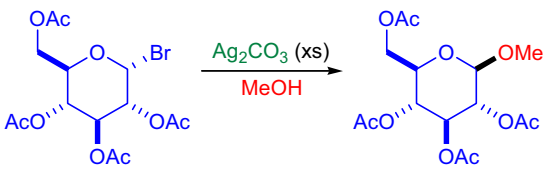
Michael (1879):



tetra-*O*-acetyl-α-D-glucopyranosyl chloride

β-D-*O*-phenyl glycoside

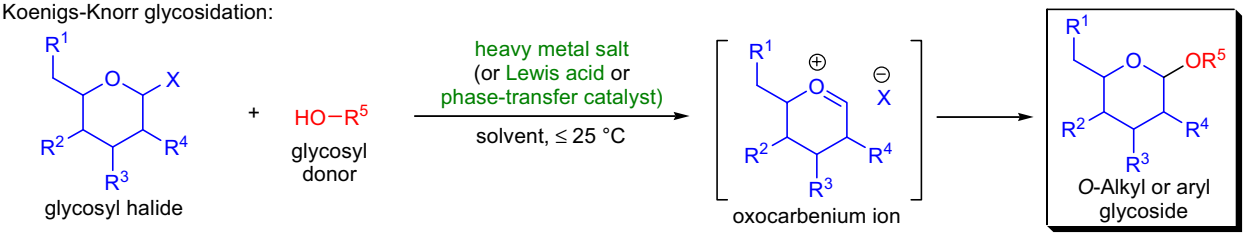
Koenigs & Knorr (1901):



tetra-*O*-acetyl-α-D-glucopyranosyl bromide

β-D-*O*-methyl glycoside

Koenigs-Knorr glycosidation:



glycosyl halide

glycosyl donor

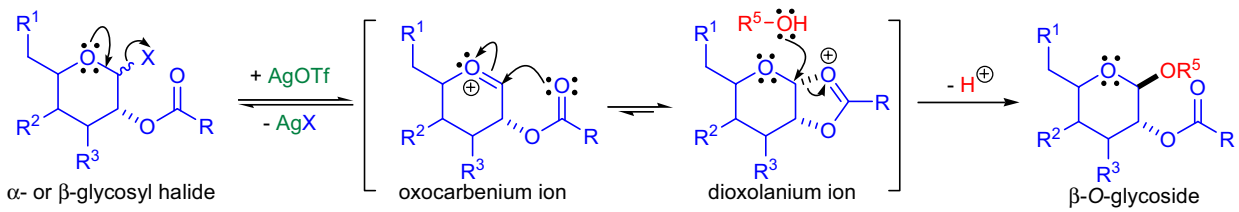
oxocarbenium ion

R^{1-4} = *O*-alkyl, *O*-acyl, alkyl ,aryl; X = Cl, Br, I; R^5 = alkyl, aryl, heteroaryl; heavy metal salts: AgOTf, Ag_2O, Ag_2CO_3, $AgNO_3$, $AgClO_4$, HgI_2, $HgCl_2$, $HgBr_2$, $Hg(CN)_2$; Lewis acids: $Sn(OTf)_2$, $Sn(OTf)_2$-collidine, $Sn(OTf)_2$-TMU, $SnCl_4$, TrCl-$ZnCl_2$; Phase-transfer catalysts: $(Bu_4N)Br$, $(Et_3NCH_2Ph)Br$, $(Et_3NCH_2Ph)Cl$; solvent: DCM, cyclohexane, petroleum ether, etc.

Mechanism:[38-42]

In order to achieve high levels of diastereoselectivity, the attack of the nucleophile should proceed *via* an S_N2 type mechanism. This is the case when the acyloxy group at C2 forms a dioxolanium ion with the oxocarbenium ion.

Glycosidation with neighboring group participation:



α- or β-glycosyl halide

oxocarbenium ion

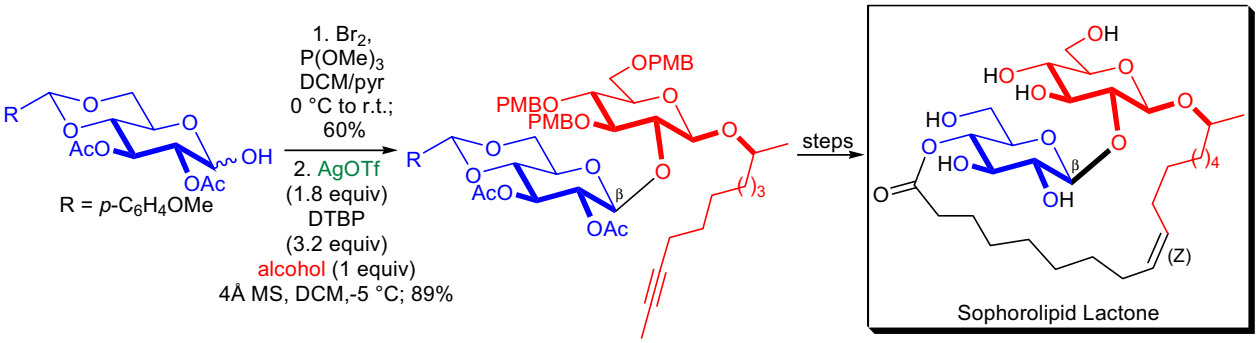
dioxolanium ion

β-*O*-glycoside

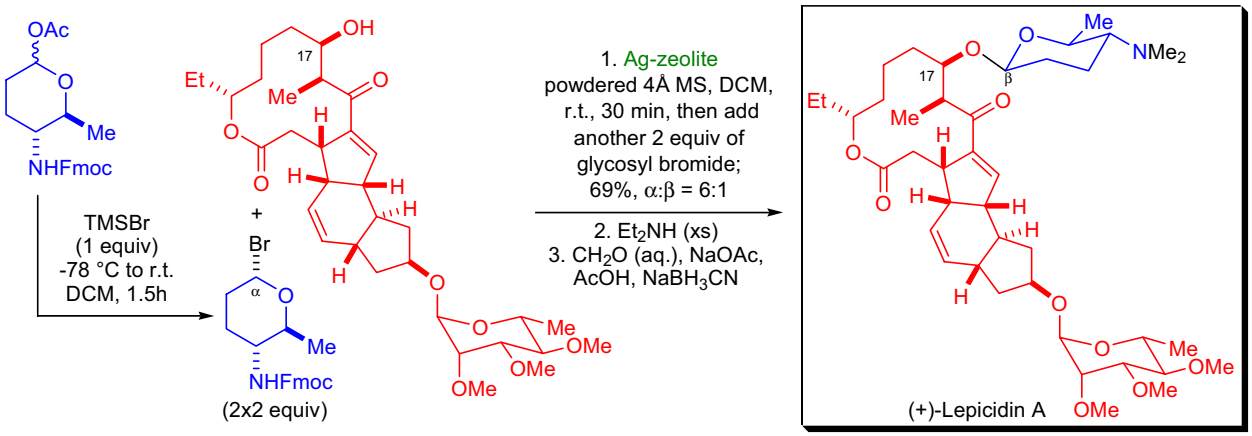
KOENIGS-KNORR GLYCOSIDATION

Synthetic Applications:

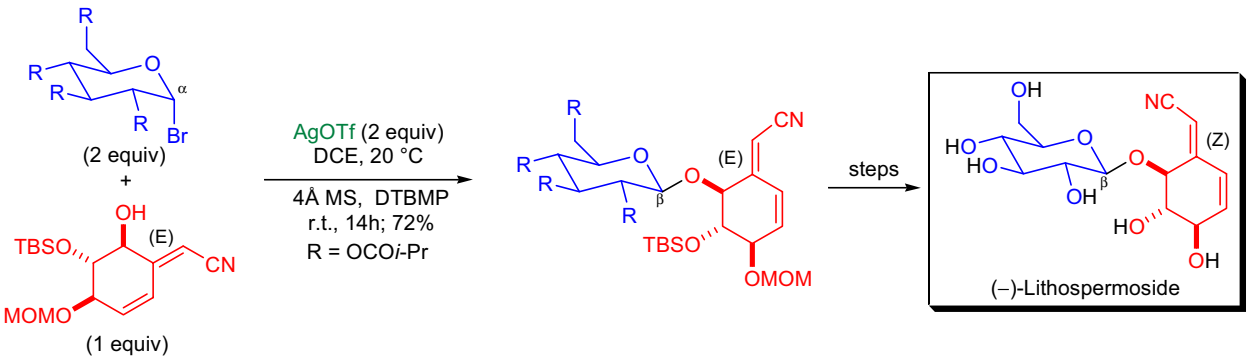
The first total synthesis of the major component of the microbial biosurfactant sophorolipid, sophorolipid lactone, was accomplished in the laboratory of A. Fürstner.[43] The natural product features a 26-membered ring, a (Z)-double bond, and two β-glycosidic linkages. The macrocyclization was achieved *via ring-closing alkyne metathesis* followed by hydrogenation of the alkyne in the presence of Lindlar's catalyst and finally the glycosidic linkages were installed using a *modified Koenigs-Knorr glycosidation*. In order to preserve the labile *p*-methoxybenzaldehyde dimethylacetal functionality, the anomeric hydroxyl group was converted to the corresponding glycosyl bromide under neutral conditions. The glycosidation was performed in the presence of excess silver triflate and base to afford an excellent yield of the desired β-*O*-glycoside. Interestingly, coactivators other than AgOTf gave inferior results.



The macrolide insecticide (+)-lepicidin A (or (+)-A83543A) was first synthesized by D.A. Evans and co-workers. In the final stages of the total synthesis, the β-selective glycosidation of the C17 alcohol was required. The task was made even more difficult by the fact that a 2''-deoxy-β-glycosidic linkage had to be formed. The strategy was to take an α-glycosyl halide and its S_N2 inversion would afford the desired β-glycoside. The glycosyl bromide was generated prior to the reaction from the corresponding glycosyl acetate, but it was not purified due to its instability. NMR spectra confirmed that it was exclusively the α-anomer. The α:β selectivity was poor, and the yield could only be improved by using as much as 4 equivalents of the glycosyl bromide. The reaction was conducted several times and the anomers were separated providing enough β-glycoside to complete the total synthesis. The last two steps were the removal of the Fmoc protecting group under mildly basic conditions (Et_2NH) and reductive alkylation of the free amino group under the *Eschweiler-Clarke methylation* conditions.



The naturally occurring noncyanogenic cyanoglucoside (–)-lithospermoside was prepared by C. Le Drian et al.[44] The key *Koenigs-Knorr glycosidation* step was very sensitive to steric hindrance, so the protecting groups on the aglycon had to be carefully chosen to obtain a reasonable yield.



KOLBE-SCHMITT REACTION

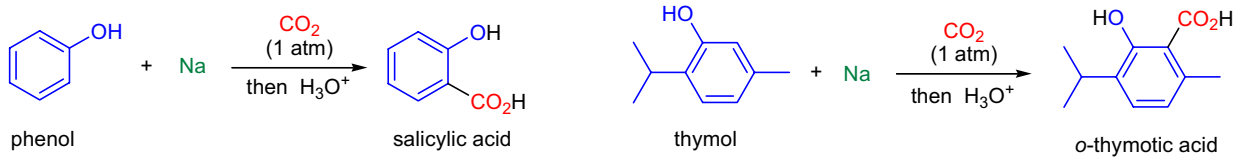
(References are on page 616)

Importance:

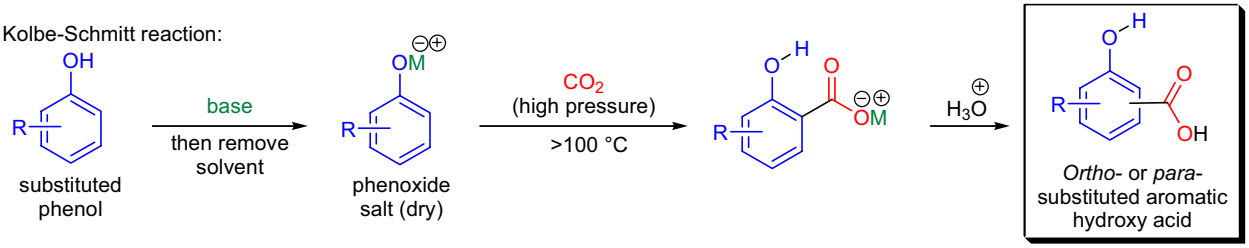
[*Seminal Publications*[1-4]; *Reviews*[5,6]; *Modifications & Improvements*[7-15]; *Theoretical Studies*[16,17]]

In 1860, J. Kolbe and E. Lautemann reported the successful synthesis of salicylic acid (2-hydroxybenzoic acid) by heating phenol and sodium metal in an atmosphere of carbon dioxide.[1-3] The same year, they published similar transformation of *p*-cresol and thymol to obtain the corresponding *p*-cresotinic acid and *o*-thymotic acid, respectively.[4] This initial procedure was capricious and the yields varied greatly. In 1884, R. Schmitt found that exposing dry sodium phenoxide to a high-pressure of CO_2 in a sealed tube and heating it above 100 °C gave quantitative yields of the corresponding salicylic acid derivatives.[7,8] These conditions worked equally well for substituted phenols and naphthols. The preparation of *ortho*- or *para*-substituted aromatic hydroxy acids from the corresponding phenols under basic conditions using gaseous CO_2 is referred to as the *Kolbe-Schmitt reaction*. The general features of this transformation are: 1) phenols, substituted phenols, naphthols, and electron-rich heteroaromatic compounds (e.g., hydroxypyridine, carbazole, etc.) are good substrates; 2) monohydric phenols are first converted to the corresponding alkali or alkali earth phenoxides (e.g., Na, K, Mg, Ca, Ba), dried and then heated in the presence of pressurized CO_2 (5-100 atm); 3) di- or polyhydric phenols (with more than two hydroxyl groups) can be carboxylated with carbon dioxide at atmospheric pressure; 4) simple acidification of the reaction mixture affords the desired aromatic hydroxy acid; 5) the size of the alkali metals greatly influences the position of attack, the use of large alkali metal ions such as Rb^+ or Cs^+ gives rise to *p*-hydroxybenzoic acid derivatives, whereas smaller alkali metal ions (Na^+ or K^+) afford salicylic acid derivatives;[14] and 6) the presence of even trace amounts of water significantly decreases the yield of the product, so the reactants, reagents, and the solvents should be thoroughly dried before use.

Kolbe & Lautemann (1860):



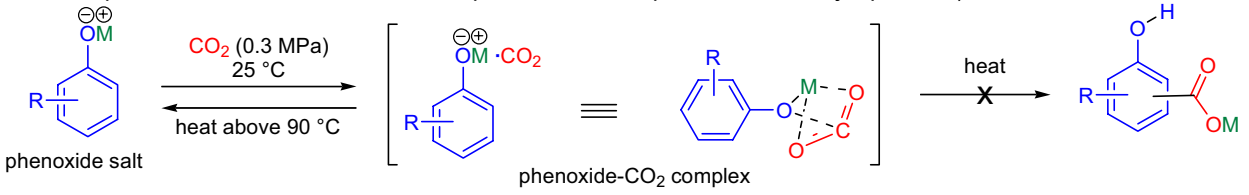
Kolbe-Schmitt reaction:



R = H, alkyl, aryl, OH, *O*-alkyl, NR_2; base: alkali metal hydroxides (e.g., NaOH, KOH, CsOH), K_2CO_3, $KHCO_3$

Mechanism:[8,18,5,19-24,15]

The mechanism of the *Kolbe-Schmitt reaction* was investigated since the late 1800s, but the mechanism of the carboxylation could not be elucidated for more than 100 years. For a long time, the accepted mechanism was that the carbon dioxide initially forms an alkali metal phenoxide-CO_2 complex, which is then converted to the aromatic carboxylate at elevated temperature.[8,18] The detailed mechanistic study conducted by Y. Kosugi et al. revealed that this complex is actually not an intermediate in the reaction, since the carefully prepared phenoxide-CO_2 complex started to decompose to afford phenoxide above 90 °C.[17] They also demonstrated that the carboxylated products were thermally stable even at around 200 °C.[17] The CO_2 electrophile attacks the ring directly to afford the corresponding *ortho*- or *para*-substituted products. (When the counterion is large (e.g., cesium) the attack of CO_2 at the *ortho*-position is hindered; therefore, the *para*-substituted product is the major product.)



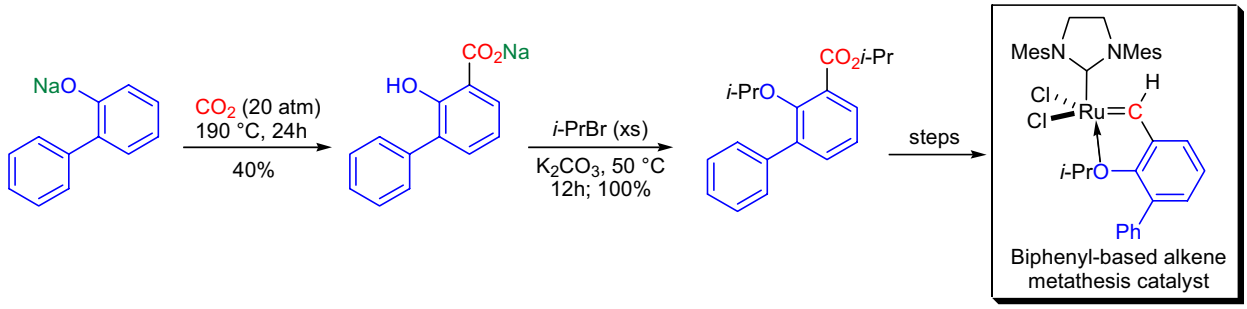
Direct attack of CO_2 on the aromatic ring:



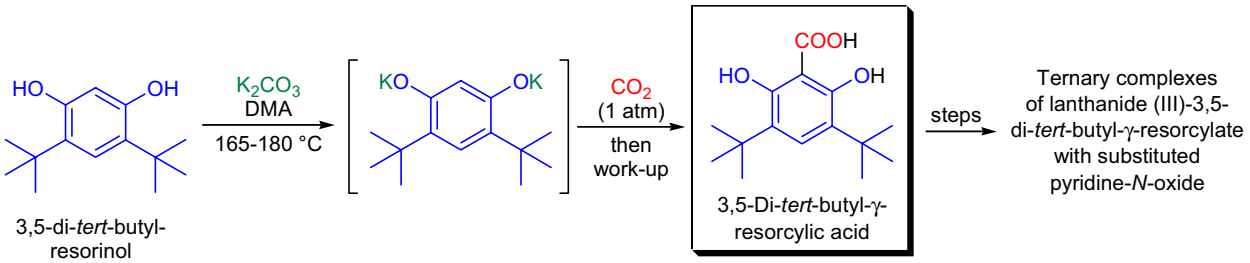
KOLBE-SCHMITT REACTION

Synthetic Applications:

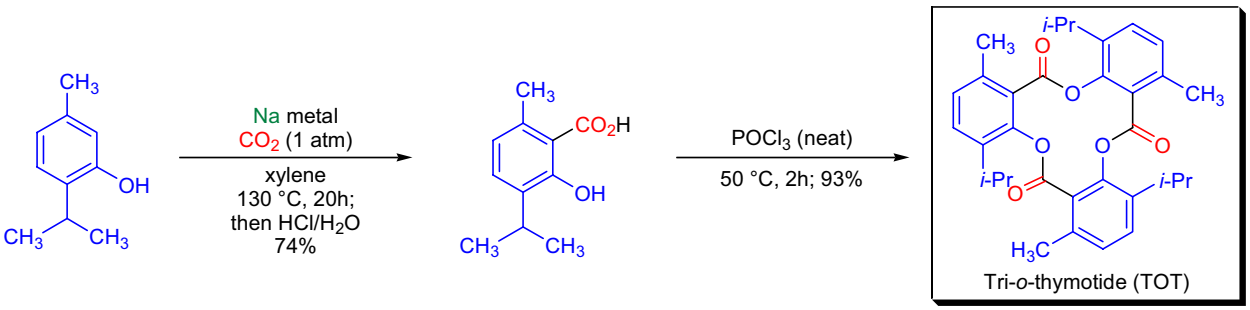
In the laboratory of S. Blechert, the large-scale synthesis of a new and highly efficient alkene metathesis catalyst was achieved.[25] The catalyst was a biphenyl-based ruthenium alkylidene complex, and it was ideal for the ring-opening cross-metathesis of substrates that contain unprotected chelating atoms. The starting material 2-hydroxybiphenyl was first deprotonated, and the resulting dry sodium salt subjected to the *Kolbe-Schmitt reaction* conditions. The crude carboxylation product was alkylated with excess isopropyl bromide to afford the corresponding isopropyl ester that in three steps was converted to a vinyl derivative and finally to the desired ruthenium alkylidene complex.



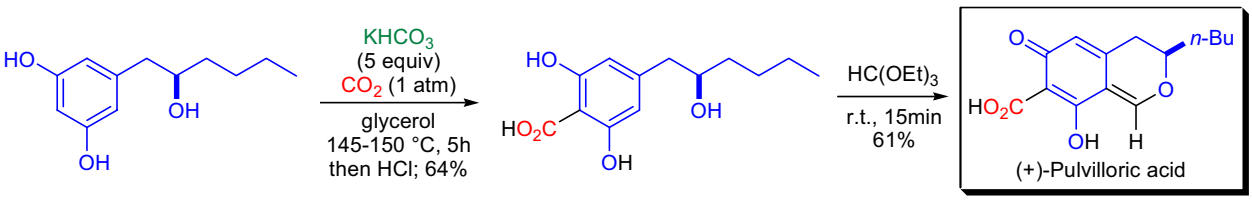
Phenols that have more than one hydroxyl group may be carboxylated with CO_2 at atmospheric pressure under basic conditions. The research team of Y.-C. Gao synthesized 3,5-di-*tert*-butyl-γ-resorcylic acid from 4,6-di-*tert*-butyl resorcinol using the *Kolbe-Schmitt reaction* under these conditions.[26] The resorcylic acid derivative was needed in order to prepare ternary complexes of lanthanide(III)-3,5-di-*tert*-butyl-γ-resorcylate with substituted pyridine-*N*-oxide.



B.S. Green and co-workers developed an improved preparation of the clathrate host compound tri-*o*-thymotide (TOT) and other trisalicylide derivatives.[27] The synthesis began with the preparation of *ortho*-thymotic acid from thymol using the *Kolbe-Schmitt reaction*. The authors found that the yield of the product was dramatically increased when the reactants, solvents, and reagents were dried before use. Thus, thymol was dissolved in dry xylene, sodium metal was added and the temperature was kept at 130 °C for 20h in a dry carbon dioxide atmosphere. The desired carboxylated product was isolated in good yield. Finally, cyclodehydration with $POCl_3$ afforded TOT in almost quantitative yield.



The first enantioselective total synthesis of the fungal metabolite (+)-pulvilloric acid was accomplished by H. Gerlach et al.[28] At the final stages of the synthetic effort the carboxylic acid moiety was installed *via* the *Kolbe-Schmitt reaction* using CO_2 at atmospheric pressure. The final formylation and ring-closure were achieved with triethyl orthoformate.



KORNBLUM OXIDATION

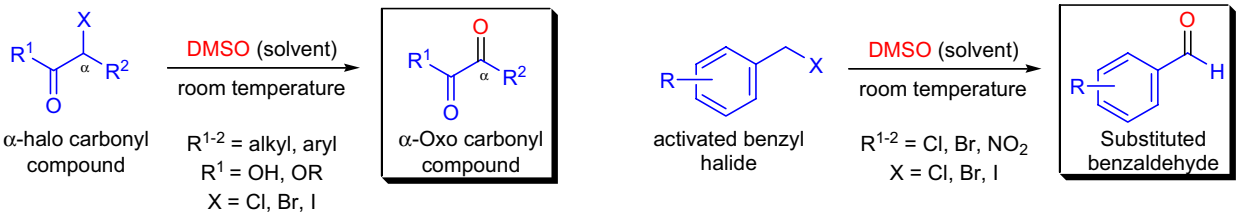
(References are on page 616)

Importance:

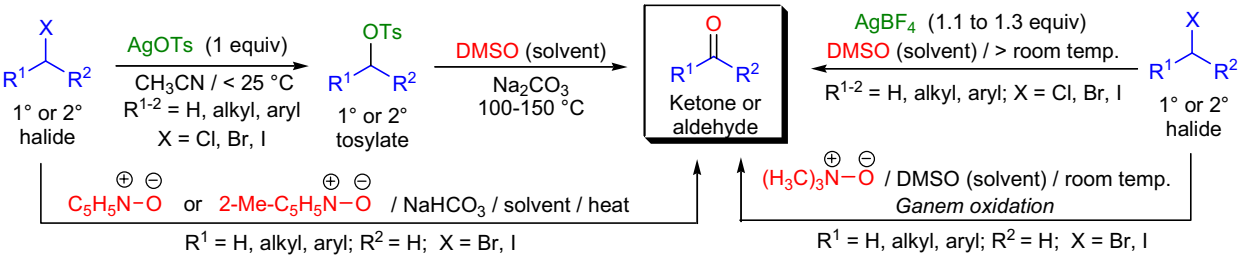
[*Seminal Publications*[1,2]*; Reviews*[3-8]*; Modifications & Improvements*[9-16]]

In 1957, N. Kornblum and co-workers discovered that activated primary benzyl bromides and α-bromo aromatic ketones are efficiently oxidized to the corresponding aldehydes and phenylglyoxals by simply dissolving the substrates in dimethyl sulfoxide (DMSO).[1] The drawback of this procedure was that it gave low yields for benzyl bromides having no electron-withdrawing groups, and less reactive halides, such as aliphatic alkyl halides, did not get oxidized at all. It was quickly recognized that the unreactive alkyl halides first had to be converted to the more reactive tosylates, which were oxidized readily in hot DMSO in the presence of a base (e.g., Na_2CO_3).[2] The oxidation of alkyl halides to the corresponding carbonyl compounds using DMSO as the oxidant is known as the *Kornblum oxidation*. The general features of the reaction are: 1) the typical procedure calls for the heating of the activated primary or secondary alkyl halide in DMSO in the presence of a base; 2) for unactivated alkyl halides the process requires two steps: first the addition of silver tosylate forms the tosylate, which is heated in DMSO in the presence of a base; 3) for primary alkyl halides the oxidation usually gives high yield of the carbonyl product, but with secondary alkyl halides, elimination of HX to form olefins is often a side reaction; 4) for sterically hindered substrates the yields are only moderate; 5) tertiary alkyl halides do not react; 6) the relative reactivity of the substrates is the following: tosylate>iodide>bromide>chloride; 7) the base plays a dual role: it neutralizes the hydrogen halide to avoid the oxidation of HX by DMSO (X_2 can lead to side reactions), as well as facilitates the deprotonation of the alkoxysulfonium intermediate; and 7) for substrates that dissolve poorly in DMSO a co-solvent is needed (e.g., DME). There are a number of variants and alternatives of the *Kornblum oxidation*: 1) silver-assisted DMSO oxidations;[11] 2) the use of amine oxides as oxidants (occasionally called the *Ganem oxidation*);[13] 3) the use of pyridine *N*-oxide or 2-picoline *N*-oxide and a base;[17,18] 4) the use of metal nitrates;[19,9,20,21] 5) *Sommelet oxidation*;[22] and 6) *Kröhnke oxidation*.[23]

Original procedure (Kornblum, 1957):



Improved procedure (Kornblum, 1959):

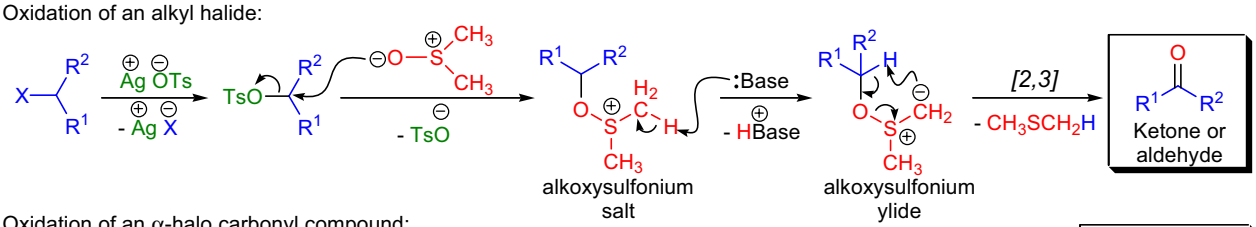


Improved procedure (Ganem, 1974):

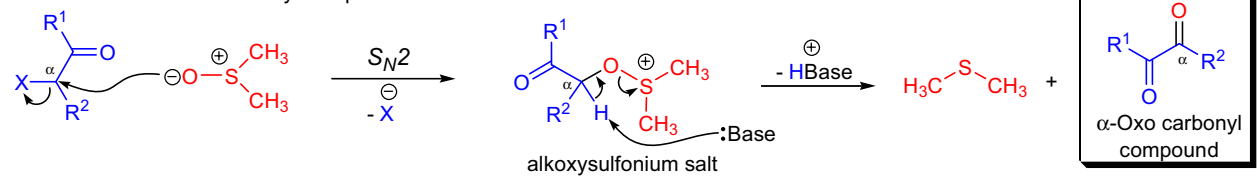
Mechanism:[4,6-8]

With alkyl halide substrates, the first step of the oxidation is the S_N2 displacement of the halide with tosylate anion. Next the alkyl tosylate undergoes a second S_N2 reaction with the nucleophilic oxygen atom of the DMSO to form the alkoxysulfonium salt that undergoes deprotonation to give the alkoxysulfonium ylide, which upon a *[2,3]-sigmatropic shift* affords the carbonyl compound. In the case of α-halo carbonyl substrates, the deprotonation takes place at the more acidic α-carbon instead of the methyl group attached to the sulfur atom of the alkoxysulfonium salt.

Oxidation of an alkyl halide:



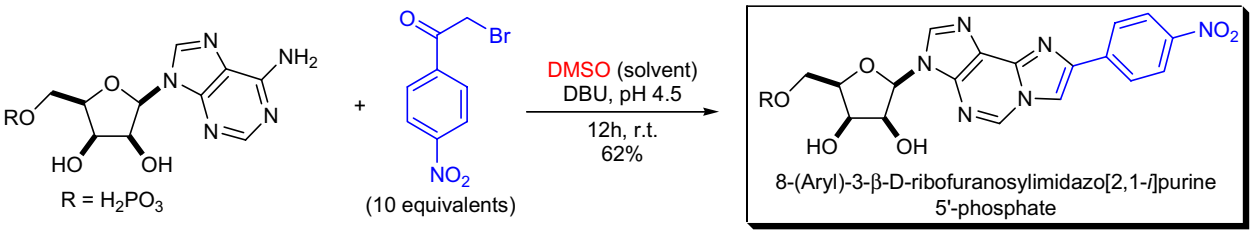
Oxidation of an α-halo carbonyl compound:



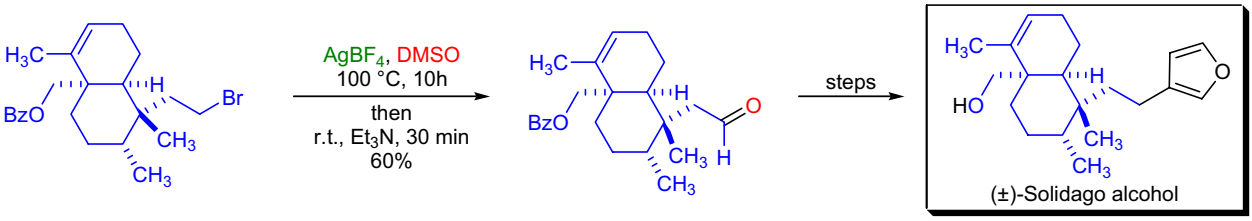
KORNBLUM OXIDATION

Synthetic Applications:

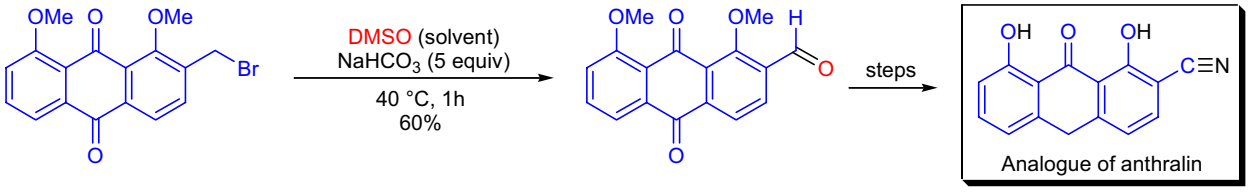
A tandem *Kornblum oxidation*/imidazole formation reaction was used during the preparation of new fluorescent nucleotides by B. Fischer and co-workers.[24] The adenosine monophosphate free acid was mixed with 10 equivalents of 2-bromo-(*p*-nitro)-acetophenone and dissolved in DMSO. The required pH value was maintained with the addition of DBU which also served as a base. The *Kornblum oxidation* of the alkyl halide yielded the glyoxal, which reacted *in situ* with the aromatic amine to form the desired imidazole derivative.



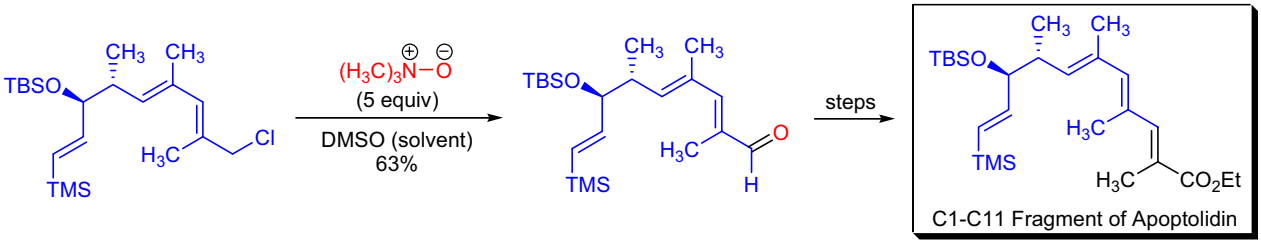
The first total synthesis of the clerodane alkaloid solidago alcohol was achieved in the laboratory of H.-S. Liu, using a highly diastereoselective *Diels-Alder cycloaddition* as the key step.[25] The installation of the 3-furyl side chain required the conversion of the bicyclic primary alkyl bromide to the corresponding aldehyde. This was accomplished by the *modified Kornblum oxidation*, which employed silver tetrafluoroborate to activate the substrate.



A number of simple analogs of the antipsoriatic agent anthralin (dithranol) were prepared by K. Müller and co-workers by changing the positions of the hydroxyl groups as well as adding new functional groups into various positions of the anthracenone nucleus.[26] The benzyl bromide functionality was converted to the corresponding aldehyde by the *Kornblum oxidation* in fair yield.



A novel synthetic approach was developed by R.E. Taylor et al. for the preparation of the triene portion of the biologically active polyketide apoptolidin.[27] The allylic chloride substrate was prepared from an allylic alcohol *via* a *thionyl chloride mediated rearrangement*. Next, the allylic chloride was subjected to the *Ganem oxidation* by treating it with five equivalents of trimethylamine *N*-oxide (*TMANO*) in DMSO at room temperature to obtain the desired α,β-unsaturated aldehyde. Interestingly, the original *Kornblum oxidation* conditions were not well suited for this system because of the required high reaction temperature.



KRAPCHO DEALKOXYCARBONYLATION (KRAPCHO REACTION)

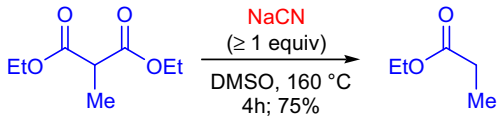
(References are on page 617)

Importance:

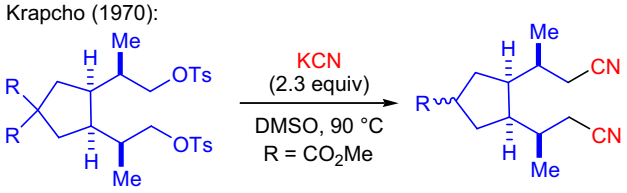
[*Seminal Publications*[1-6]*; Reviews*[7-9]*; Modifications & Improvements*[10-15]]

In 1967, A.P. Krapcho reported that upon heating geminal dicarbethoxy compounds with sodium cyanide in dimethyl sulfoxide, the corresponding ethyl esters were obtained in high yield.[5] The products could be purified by distillation following an aqueous work-up. The discovery of this transformation happened serendipitously during an attempted conversion of a ditosylate to the corresponding dinitrile with potassium cyanide in hot DMSO, and the product of the reaction was the demethoxycarbonylated dinitrile (this result was reported only in 1970).[6] The dealkoxycarbonylation of β-keto esters, α-cyano esters, malonate esters, and α-alkyl- or arylsulfonyl esters to the corresponding ketones, nitriles, esters, and alkyl- or arylsulfones is known as the *Krapcho dealkoxycarbonylation* (also *Krapcho reaction* or *Krapcho decarboxylation*). The general features of this reaction are:[8,9] 1) this nucleophilic dealkoxycarbonylation process is general for methyl- or ethyl esters of carboxylic acids, which have an electron-withdrawing group (CO_2-alkyl, CN, CO-alkyl, SO_2-alkyl, etc.) at their α-position; 2) this one-pot procedure obviates the need to perform the multistep decarboxylation of geminal diesters to the corresponding monoesters, which involves the following steps: basic or acidic hydrolysis of the ester followed by the decarboxylation of the resulting diacid and the esterification of the final carboxylic acid to obtain the desired monoester; 3) the reaction conditions are essentially neutral, so both acid- and base-sensitive substrates can be used and the otherwise frequent acid-catalyzed rearrangements are avoided; 4) the chemoselectivity and the functional group tolerance of the method is very high; 5) double bonds are not isomerized and in the overwhelming majority of cases labile stereocenters are not racemized; 6) the choice of specific reaction conditions is always dependent on the substitution pattern of the substrate; 7) monosubstituted malonic esters are dealkoxycarbonylated in hot dipolar aprotic solvent containing at least one equivalent of water; 8) as a rule of thumb when the substrate has at least one proton at the α-position, the dealkoxycarbonylation can be achieved with wet DMSO at reflux in the absence of a salt; 9) disubstituted malonic esters, however, are dealkoxycarbonylated only in the presence of at least one equivalent of a salt (e.g., KCN, LiCl, etc.) in wet DMSO at reflux; 10) the presence of a salt tends to accelerate the rate of the dealkoxycarbonylation of many (but not all) substrates; 11) besides DMSO, other dipolar aprotic solvents can be used such as dimethylacetamide, HMPT and DMF; 12) methyl esters are dealkoxycarbonylated faster than ethyl esters; and 13) vinylogous β-keto esters are also dealkoxycarbonylated in high yield.

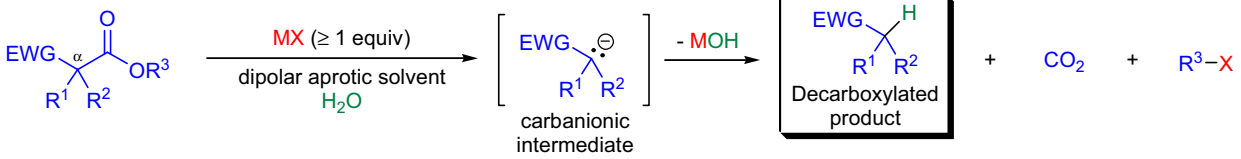
Krapcho (1967):



Krapcho (1970):



Krapcho dealkoxycarbonylation:

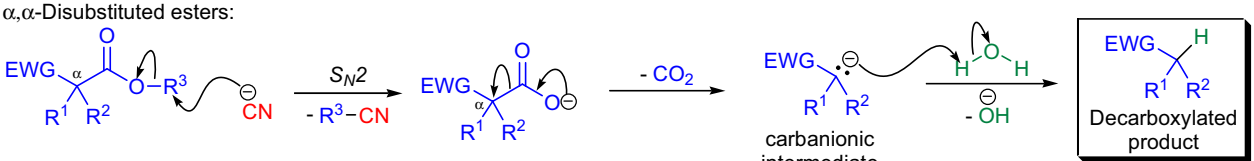


EWG = CO_2-alkyl, CO_2-aryl, CN, CO-alkyl, SO_2-alkyl, SO_2-aryl; R^{1-2} = H, alkyl, aryl; R^3 = Me, Et; MX = NaCN, KCN, LiCl, NaCl, NaBr, NaI, LiI·H_2O, Na_2CO_3·H_2O, Na_3PO_4·12H_2O, Me_4NOAc ; solvent: DMSO, DMF, DMA, HMPT

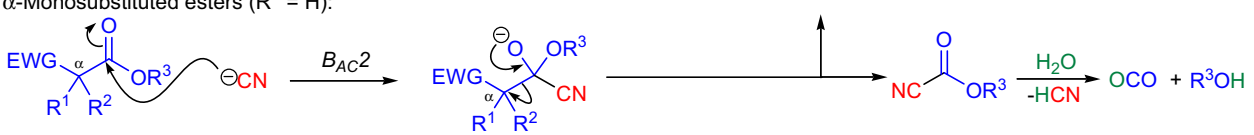
Mechanism:[16,17,9,18,19]

The mechanism of the *Krapcho dealkoxycarbonylation* is dependent on the structure of the substrate ester and the type of anion used. In the case of α,α-disubstituted diesters (especially the methyl esters), the anion from the salt (cyanide ion in the scheme) attacks the alkyl group of the ester in an S_N2 fashion and the decarboxylation results in the formation of a carbanionic intermediate that is quenched by the water. In the case of α-monosubstituted diesters the cyanide attacks the carbonyl group to form a tetrahedral intermediate, which breaks down to give the same carbanionic intermediate and a cyanoformate, which is hydrolyzed to give carbon dioxide and an alcohol.

α,α-Disubstituted esters:



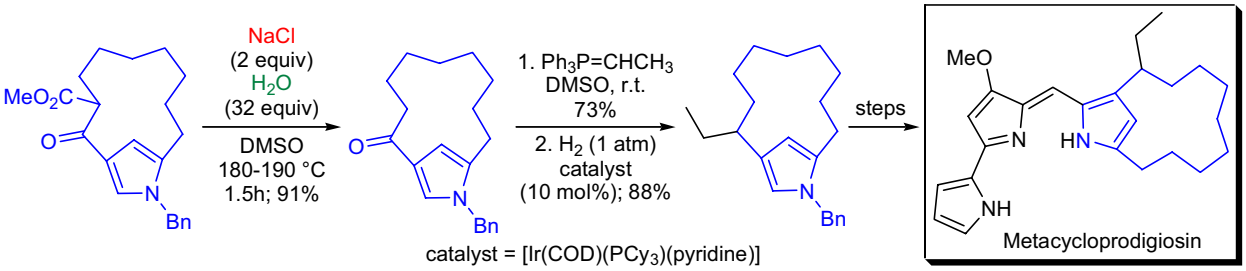
α-Monosubstituted esters (R^2 = H):



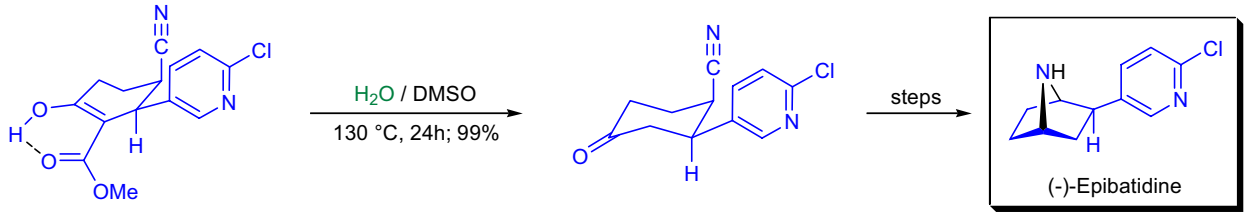
KRAPCHO DEALKOXYCARBONYLATION (KRAPCHO REACTION)

Synthetic Applications:

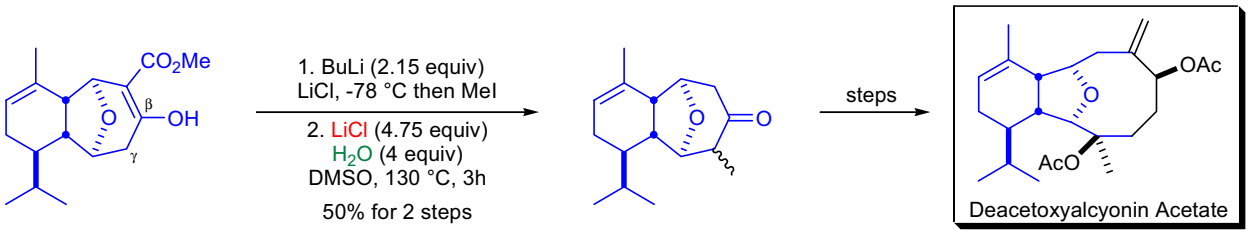
In the laboratory of A. Fürstner, a practical synthesis of the immunosuppressive alkaloid metacycloprodigiosin and its functional derivatives was developed.[20] Toward the end of the synthetic sequence a *meta*-pyrrolophane β-keto ester was decarboxylated under standard Krapcho conditions. The substrate was dissolved in wet DMSO, and two equivalents of sodium chloride were added and the reaction mixture was heated to 180 °C to afford the desired *meta*-pyrrolophane ketone in excellent yield. This ketone functionality was first converted to an ethyl group and then the product was advanced to metacycloprodigiosin.



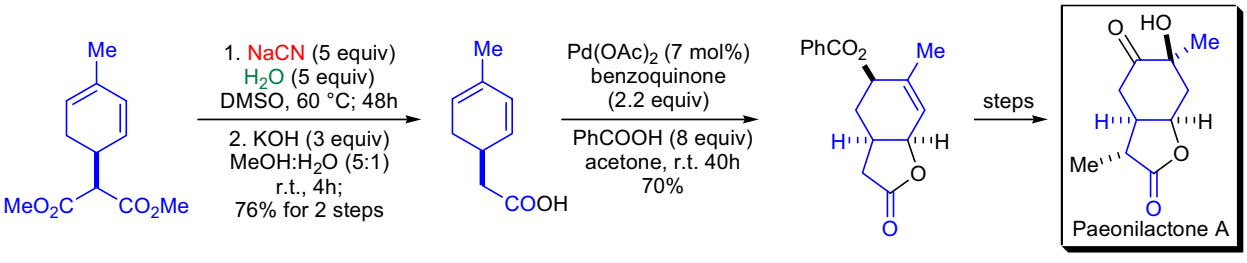
A highly *exo*-selective asymmetric *hetero Diels-Alder reaction* was the key step in D.A. Evans' total synthesis of (–)-epibatidine.[21] The bicyclic cycloadduct was then subjected to a fluoride-promoted fragmentation that afforded a β-keto ester, which was isolated exclusively as its enol tautomer. The removal of the ethoxycarbonyl functionality was achieved using the *Krapcho decarboxylation*. Interestingly, the presence of a metal salt was not necessary in this transformation. Simply heating the substrate in wet DMSO gave rise to the decarboxylated product in quantitative yield.



A general synthetic route toward the marine metabolite eunicellin diterpenes was developed by G.A. Molander and co-workers.[22] The power of this method was demonstrated by the completion of the asymmetric total synthesis of deacetoxyalcyonin acetate. A tricyclic β-keto ester intermediate was methylated in the γ-position with complete diastereoselectivity using dianion chemistry and the crude product was subjected to the *Krapcho decarboxylation*. This was one of the rare cases when the transformation did not only remove the methoxycarbonyl group, but at the same time epimerized the newly formed stereocenter to yield a separable mixture of methyl ketones.



The first enantioselective formal total synthesis of paeonilactone A was reported by J.E. Bäckvall who used a palladium(II)-catalyzed 1,4-oxylactonization of a conjugated diene as the key step.[23] The lactonization precursor diene acid was obtained from an enantiopure dimethyl malonate derivative *via* sequential *Krapcho decarboxylation* and ester hydrolysis.



KRÖHNKE PYRIDINE SYNTHESIS

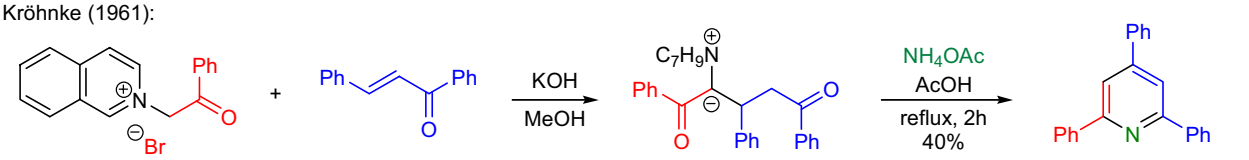
(References are on page 617)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3]; *Modifications and Improvements*[4,5]]

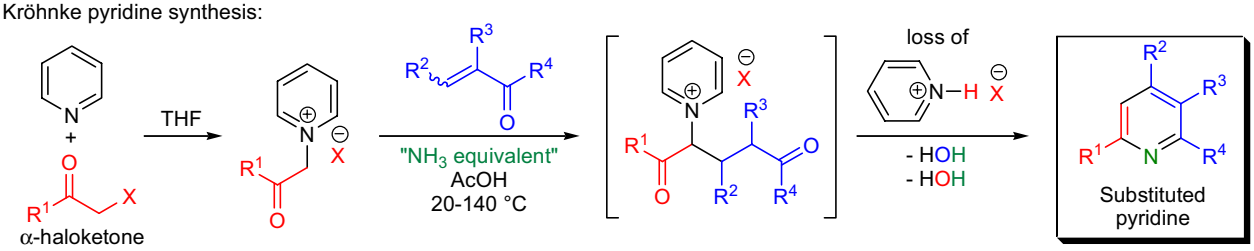
In 1961, F. Kröhnke and W. Zeher reported that phenacyl isoquinolinium bromide reacted with benzalacetophenone under basic conditions to afford an isoquinolinium betaine, which upon treatment with ammonium acetate in acetic acid at reflux temperature yielded 2,4,6-triphenylpyridine in moderate yield.[1,2] This synthetic sequence was a new and efficient way to access highly substituted pyridines. The condensation of acylmethylpyridinium salts with α,β-unsaturated ketones and ammonia to give substituted pyridines is known as the *Kröhnke pyridine synthesis*. The general features of the transformation are:[3] 1) α-haloketones are prepared from the corresponding methyl ketones using standard halogenation conditions (e.g., Br_2, Bu_4NBr_3, etc.); 2) α-haloketones are mixed with pyridine to afford the required acylmethylpyridinium salts that are considered 1,3-diketone equivalents; 3) treatment of the acylmethylpyridinium salt with ammonium acetate (or other ammonia equivalents) in acetic acid in the presence of an α,β-unsaturated ketone gives rise to a Michael adduct (a 1,5-diketone), which undergoes cyclization with ammonia to produce the substituted pyridine; 4) the great advantage of the method is that unlike in the *Hantzsch dihydropyridine synthesis*, oxidation (dehydrogenation) is not necessary, since the pyridine is formed directly; 5) the substitution pattern of the two components can be varied widely ranging from simple alkyl all to way to substituted aryl and heteroaryl groups; 6) the α,β-unsaturated ketones can be used directly or in the form of the corresponding Mannich bases, which undergo cleavage under the reaction conditions to afford the α,β-unsaturated ketones; 7) in most cases the reaction is used to prepare 2,4,6-trisubstituted pyridines, but occasionally higher substitution (at C3 and C5) can be achieved; 8) if R^4=CO_2H, 2-carboxypyridines are formed that can be decarboxylated thermally to afford 2,4-disubstituted pyridines; and 9) the preparation of symmetrically or unsymmetrically substituted bi- and oligopyridines (up to seven pyridine units) is accomplished with ease unlike with other methods that are less straightforward and require many steps.

Kröhnke (1961):



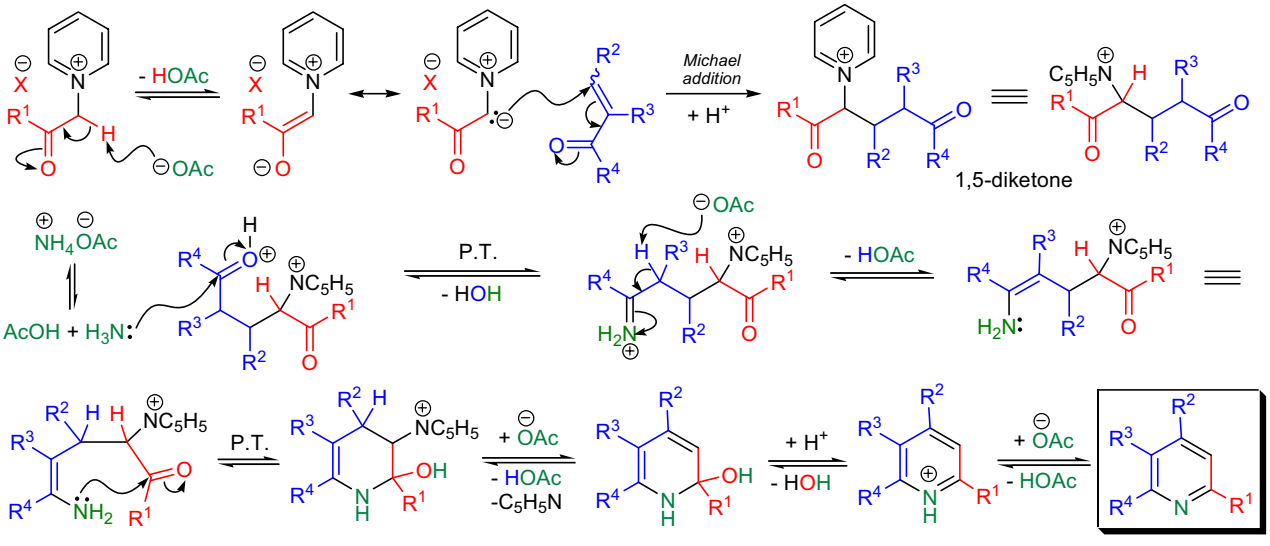
N-phenacyl isoquinolinium bromide | benzalacetophenone | isoquinolinium betaine | 2,4,6-triphenylpyridine

Kröhnke pyridine synthesis:



R^1 = alkyl, substituted aryl, heteroaryl; X = Cl, Br, I; R^2 = H, alky, aryl, heteroaryl; R^3 = H, (alkyl, aryl, heteroaryl); R^4 = alkyl, aryl, heteroaryl, CO_2^-, CO_2-alkyl; NH_3 equivalent: NH_4OAc, $HCONH_2$, CH_3CONH_2

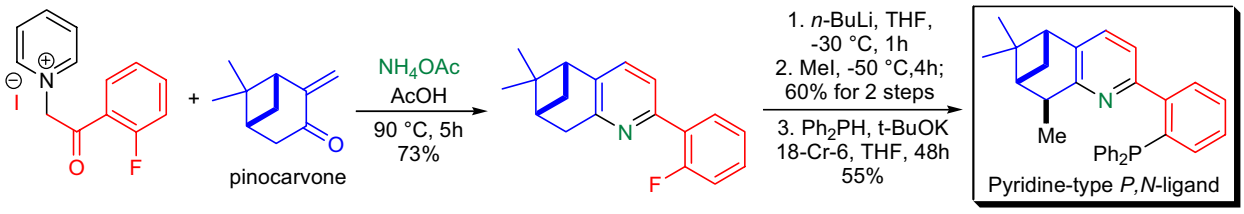
Mechanism:[6-9]



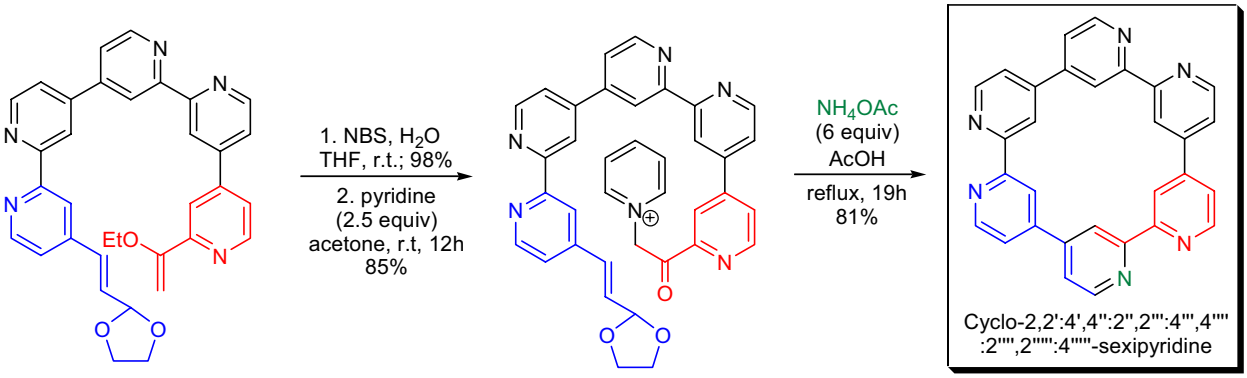
KRÖHNKE PYRIDINE SYNTHESIS

Synthetic Applications:

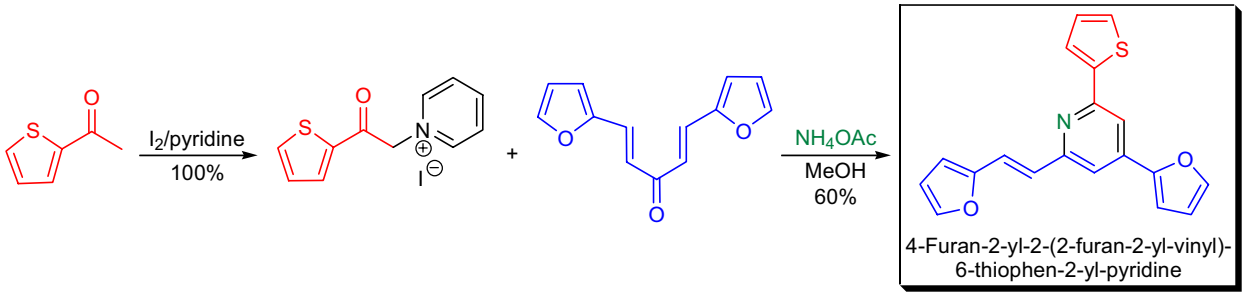
In the laboratory of P. Kočovský, novel pyridine-type *P,N*-ligands were prepared from various monoterpenes.[10] The key step was the *Kröhnke pyridine synthesis*, and the chirality was introduced by the α,β-unsaturated ketone component, which was derived from enantiopure monoterpenes. One of these ligands was synthesized from (+)-pinocarvone which was condensed with the acylmethylpyridinium salt under standard conditions to give good yield of the trisubstituted pyridine product. The benzylic position of this compound was deprotonated with butyllithium, and upon addition of methyl iodide the stereoselective methylation was achieved. The subsequent nucleophilic aromatic substitution (*S*$_N$*Ar*) gave rise to the desired ligand.



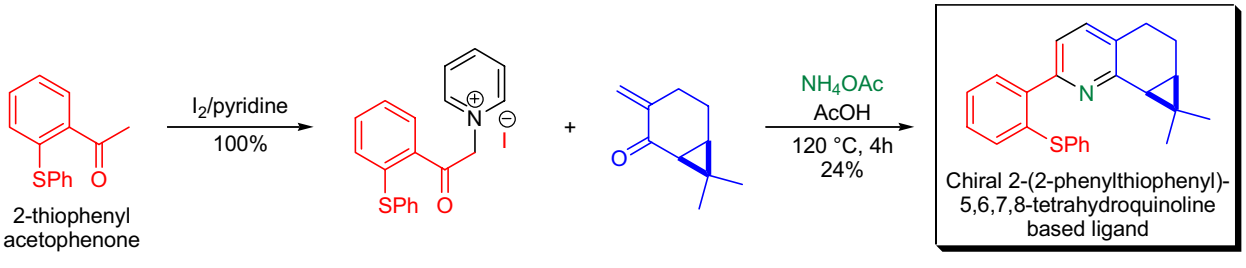
The synthesis of cyclo-2,2':4',4":2",2"':4"',4"":2"",2""':4"""'-sexipyridine was accomplished by T.R. Kelly and co-workers by using multiple *Stille cross-couplings* and the *Kröhnke pyridine synthesis* for the final macrocyclization.[11] The bromination of the quinquepyridine was conducted with wet *N*-bromosuccinimide in THF, and the resulting α-bromoketone was immediately converted to the corresponding acylmethylpyridinium salt by strirring it with excess pyridine in acetone overnight. The crucial macrocyclization took place in the presence of excess ammonium acetate in acetic acid at reflux. Interestingly, other macrocyclization attempts using the *Ullmann biaryl coupling* or the *Glaser coupling* all failed.



The research team of E.-S. Lee synthesized and evaluated several 2,4,6-trisubstituted pyridine derivatives as potential topoisomerase I inhibitors.[12] One of these compounds, 4-furan-2-yl-2-(2-furan-2-yl-vinyl)-6-thiophen-2-yl-pyridine, was prepared by the *Kröhnke pyridine synthesis* and showed strong topoisomerase I inhibitory activity.



Novel, tetrahydroquinoline-based *N,S*-type ligands were prepared by the *Kröhnke pyridine synthesis* and their catalytic activity was assessed by G. Chelucci et al.[13] The acylmethylpyridinium iodide was reacted with a cyclic α,β-unsaturated ketone derived from 2-(+)-carene.



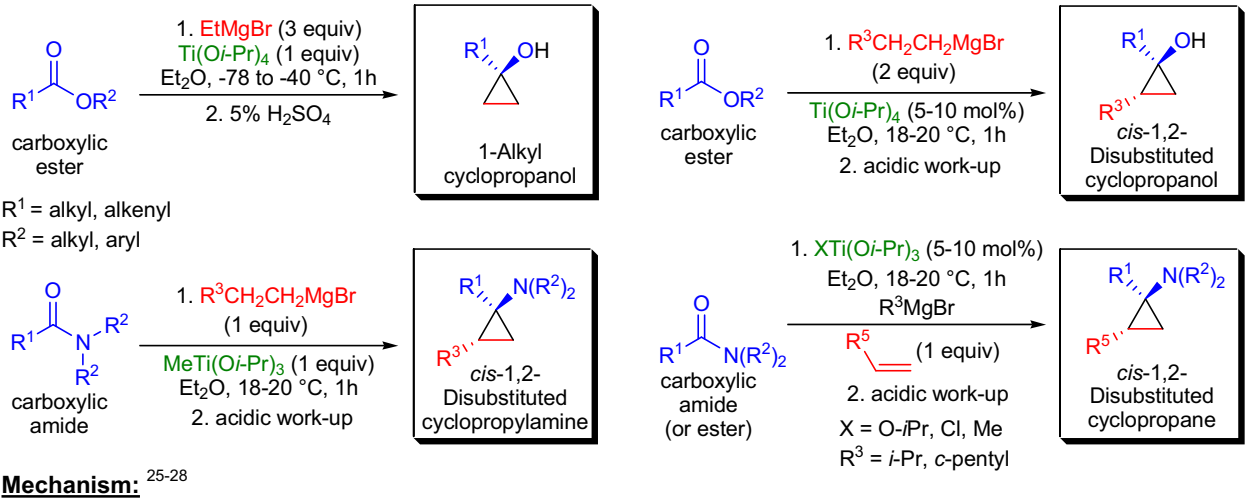
KULINKOVICH REACTION

(References are on page 618)

Importance:

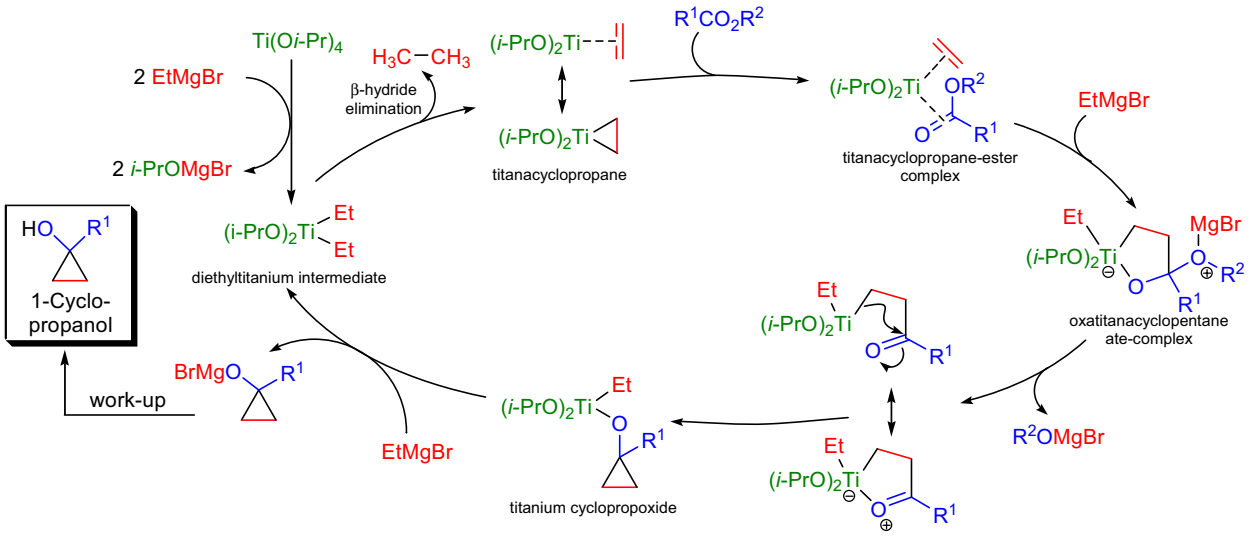
[*Seminal Publications*[1,2]*; Reviews*[3-15]*; Modifications & Improvements*[16-23]*; Theoretical Studies*[24]]

In 1989, O.G. Kulinkovich reported that 1-alkylcyclopropanols were formed when an excess of ethylmagnesium bromide was added to simple carboxylic esters in the presence of one equivalent of titanium tetraisopropoxide.[1] The reaction could also be carried out with catalytic amounts of Ti(O*i*-Pr)$_4$ and only two equivalents of Grignard reagent was necessary. The titanium(II)-mediated one-pot conversion of carboxylic esters and amides to the corresponding 1-alkylcyclopropanols and 1-alkylcyclopropylamines is known as the *Kulinkovich reaction*. The general features of the reaction are: 1) the active species is a titanacyclopropane intermediate that acts as a 1,2-dicarbanion equivalent and doubly alkylates the carbonyl group; 2) more complex Grignard reagents yield 1,2-*cis* disubstituted cyclopropanols with good diastereoselectivity; 3) the observed *cis*-selectivity is lower for the formation of 1,2-disubstituted cyclopropylamines from amides; 4) the reaction is sensitive to the nature of the R^1 group (aromatic esters do not react) and steric crowding (α-branched R^1 groups and too bulky R^2 groups) give lower yields); 5) when terminal alkenes are added into the reaction mixture, these are incorporated into the cyclopropane products. There are several important modifications of the procedure, which helped to expand the scope of the reaction.[16-23]



Mechanism:[25-28]

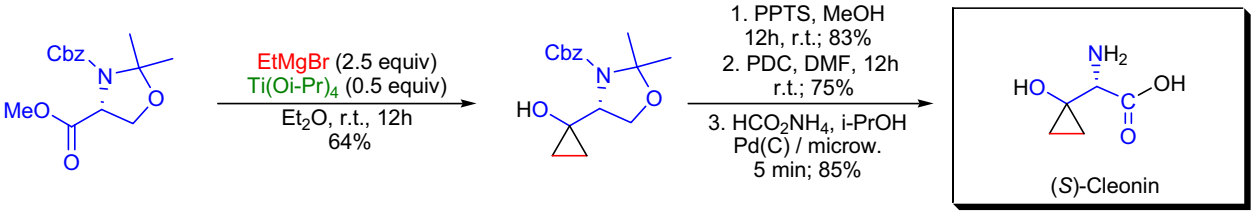
The catalytic cycle of the *Kulinkovich reaction* begins with the dialkylation of the Ti(O*i*-Pr)$_4$ with two equivalents of ethylmagnesium bromide to form the thermally unstable diethyltitanium intermediate, which quickly undergoes a β-hydride elimination to give ethane and titanacyclopropane. This titanacyclopropane acts as a 1,2-dicarbanion equivalent when it reacts with the carboxylic ester, and it performs a double alkylation. The addition of ethylmagnesium bromide to the titanium in the titanacyclopropane-ester complex triggers the formation of the first C-C bond formation and leads to the oxatitanacyclopentane ate-complex. At this point, the alkoxy group of the original ester is eliminated as its magnesium salt and the second C-C bond is formed to generate the cyclopropane ring. The resulting titanium cyclopropoxide undergoes alkylation at the titanium by ethylmagnesium bromide, and thus the diethyltitanium intermediate is regenerated and the product magnesium cyclopropoxide is formed. Upon aqueous/acidic work-up, the 1-cyclopropanol is isolated. For carboxylic amides the mechanism is slightly different.



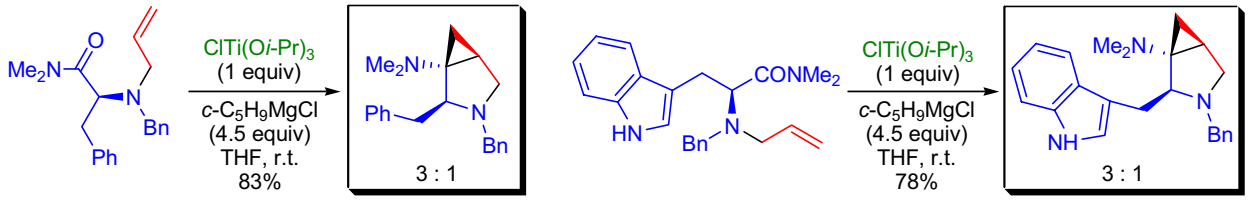
KULINKOVICH REACTION

Synthetic Applications:

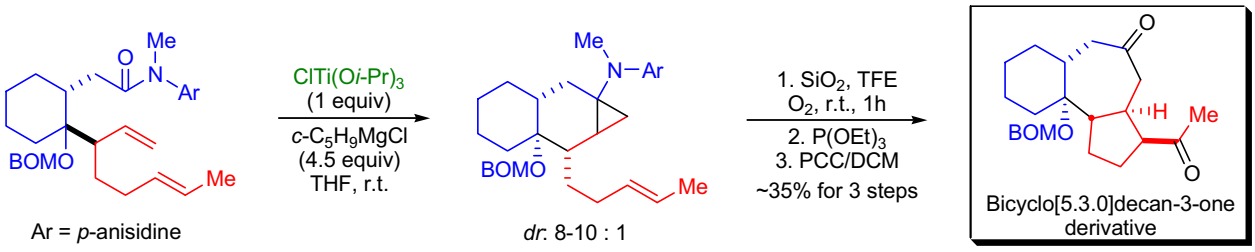
The key component of the antitumor antibiotic cleomycin, (*S*)-cleonin, was prepared from (*R*)-serine using the *Kulinkovich reaction* as the key step in the laboratory of M. Taddei.[29] The methyl ester of *N*-Cbz serine acetonide was exposed to freshly prepared ethylmagnesium bromide in the presence of substoichiometric amounts of titanium tetraisopropoxide to afford the desired cyclopropylamine in good yield. Subsequent functional group manipulations gave (*S*)-cleonin.



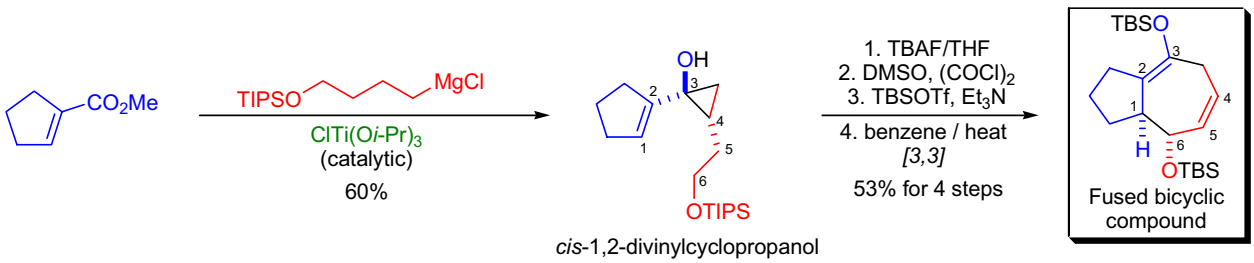
Cyclopropylamines and their substituted derivatives are important building blocks in a large number of biologically active compounds. The synthesis of potentially biologically active *N,N*-dimethyl bicyclic cyclopropylamines from *N*-allylamino acid dimethylamides by the *intramolecular variant of the Kulinkovich reaction* was accomplished by M.M. Joullié and co-workers.[30]



J.K. Cha et al. developed a stereocontrolled synthesis of bicyclo[5.3.0]decan-3-ones from readily available acyclic substrates.[31] Acyclic olefin-tethered amides were first subjected to the *intramolecular Kulinkovich reaction* to prepare bicyclic aminocyclopropanes. This was followed by a *tandem ring-expansion-cyclization sequence* triggered by *aerobic oxidation*. The reactive intermediates in this tandem process were aminium radicals (radical cations). The *p*-anisidine group was chosen to lower the amine oxidation potential. This substituent was crucial for the generation of the aminium radical (if Ar = phenyl, the ring aerobic oxidation is not feasible).



A general diastereoselective synthesis of fused bicyclic compounds using a sequential *Kulinkovich cyclopropanation* and an *oxy-Cope rearrangement* was achieved by J.K. Cha and co-workers.[32] *cis*-1,2-Divinylcyclopropanes have found significant synthetic utility as substrates for *[3,3]-sigmatropic rearrangements*. The *Kulinkovich reaction* offered a straightforward and facile synthesis of *cis*-1,2-dialkenylcyclopropanols that gave fused bicyclic carbocycles upon *oxy-Cope rearrangement*.



KUMADA CROSS-COUPLING

(References are on page 619)

Importance:

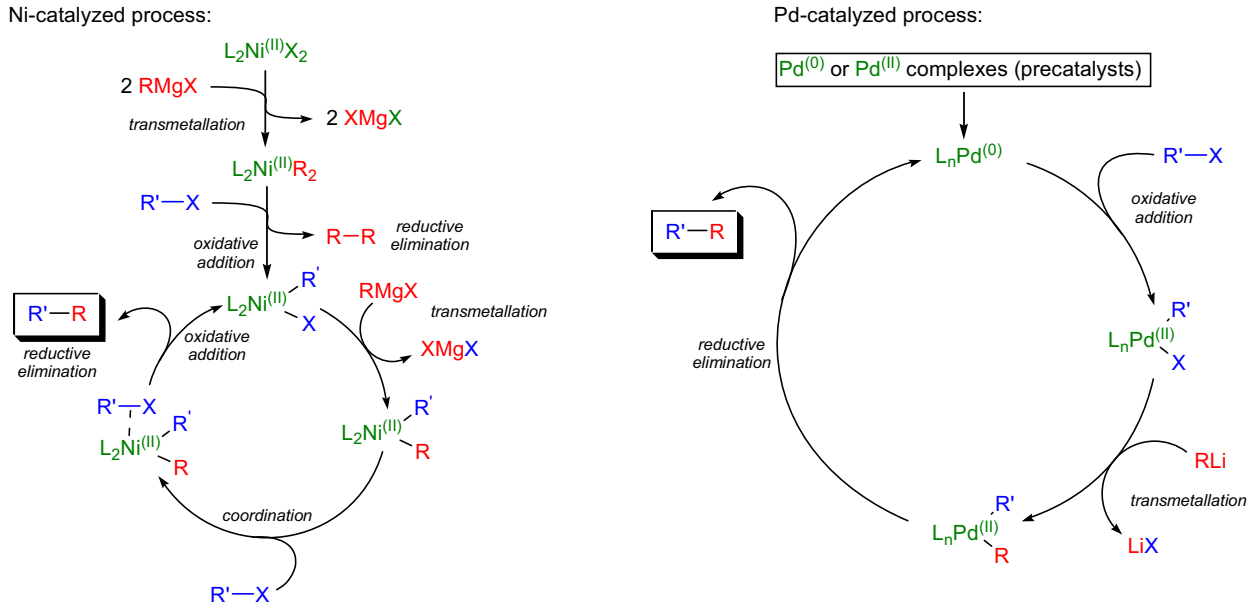
[*Seminal Publications*[1-4]; *Reviews*[5-18]; *Modifications & Improvements*[19-30];]

During the 1970s a great deal of research effort was focused on the transition metal-catalyzed carbon-carbon bond forming reactions of unreactive alkenyl and aryl halides.[31,32] In 1972, M. Kumada and R.J.P. Corriu independently discovered the stereoselective cross-coupling reaction between aryl- or alkenyl halides and Grignard reagents in the presence of a catalytic amount of a nickel-phosphine complex. In the following years, Kumada explored the scope and limitation of the reaction. Consequently, this transformation is now referred to as the *Kumada cross-coupling*. Nickel catalysis only worked for Grignard reagents and excluded the highly versatile organolithium reagents. Therefore, the use of alternative catalysts such as various palladium complexes was explored.[19-24,26] The characteristic features of the *Kumada cross-coupling* are: 1) in the Ni-catalyzed process the catalytic activity depends largely on the nature of the phosphine ligand, and the following reactivity trend is observed: $Ni(dppp)Cl_2$ > $Ni(dppe)Cl_2$ > $Ni(PR_3)_2Cl_2$ ~ $Ni(dppb)Cl_2$; 2) even alkyl (sp^3) Grignard reagents having β-hydrogens can selectively undergo cross-coupling reactions without any undesired β-hydride elimination; 3) with *sec*-alkyl Grignard reagents the alkyl group tends to isomerize to the corresponding primary alkyl group, and this isomerization is dependent on the basicity of the phosphine ligand and the nature of the aromatic halide; 4) the use of the *dppf* ligand slows the β-hydride elimination considerably and accelerates the reductive elimination, thereby allowing the coupling of *sec*-Grignard reagents without isomerization;[24] 5) chlorinated aromatic compounds react with ease and even fluorobenzene can undergo Ni-catalyzed cross-coupling;[16] 6) the coupling is stereoselective and the stereochemistry of the starting vinyl halides is preserved; 7) the Pd-catalyzed process is more chemo- and stereoselective and has a much broader scope with carbanions than the Ni-catalyzed reaction. However, the coupling does not take place with aryl chlorides, only with aryl bromides and iodides; 8) organomagnesium and organolithium reagents are used most often. However, the coupling will take place with organosodium (RNa), organocopper (R_2CuLi), organoaluminum, organozinc, organotin, organozirconium, and organoboron compounds;[14] 9) organolithiums are by far the most versatile, since these reagents can be prepared in many different ways including the direct lithiation of hydrocarbons;[9] and 10) functional groups that are base-sensitive are not tolerated because of the polar nature of the organomagnesium and organolithium compounds (this tolerance is greatly improved in the *Negishi cross-coupling* by using much less basic organozinc compounds). There are not many side-reactions except for the occasional isolation of homocoupled and reduction products that can be avoided by observing the following precautions: 1) the organolithium should be added slowly because fast addition produces α-bromo alkenyllithiums that undergo rearrangement to give lithium acetylides, thus lowering the overall yield; 2) the $Pd^{(0)}$ catalyst should be clean to ensure high activity; and 3) no reagents should be added in excess.[33,14]



R^{1-3} = H, alkyl, aryl, alkenyl; X = F, Cl, Br, I. OTf; R^4 = alkyl, aryl, alkenyl; X = Br, I; L = PPh_3 or L_2 = dppp, dppe, dppb

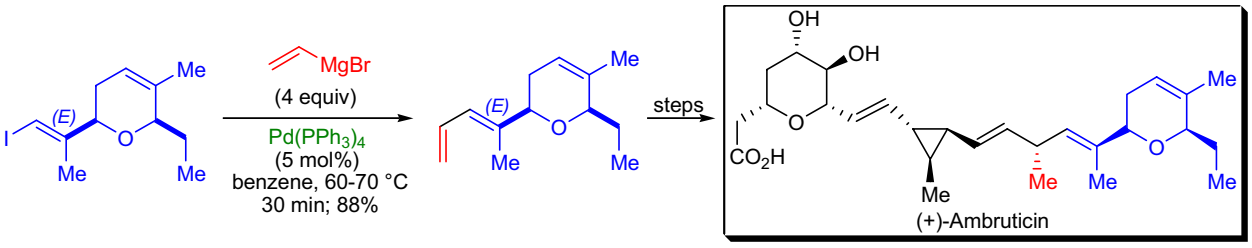
Mechanism:[34-38]



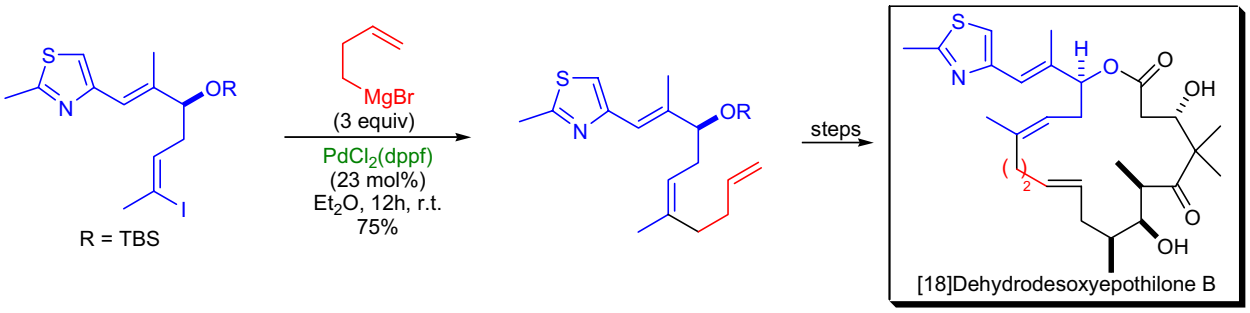
KUMADA CROSS-COUPLING

Synthetic Applications:

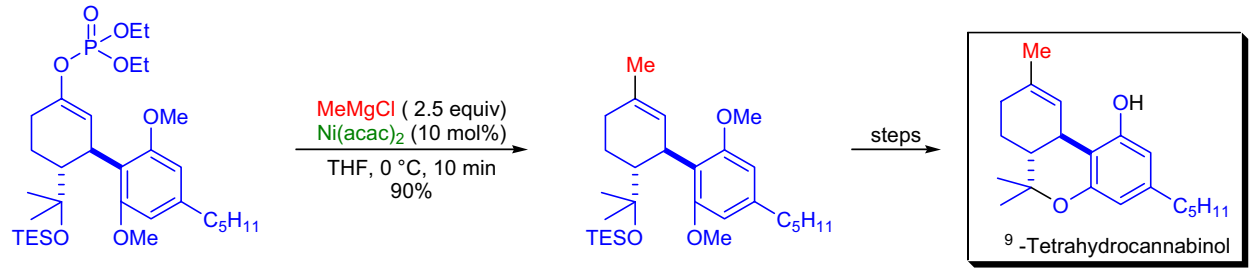
The enantioselective total synthesis of (+)-ambruticin was accomplished in the laboratory of E.N. Jacobsen. The *Kumada cross-coupling* was utilized to convert an (*E*)-vinyl iodide intermediate to the corresponding conjugate diene in good yield.[39] The stereochemistry of the vinyl iodide was completely preserved.



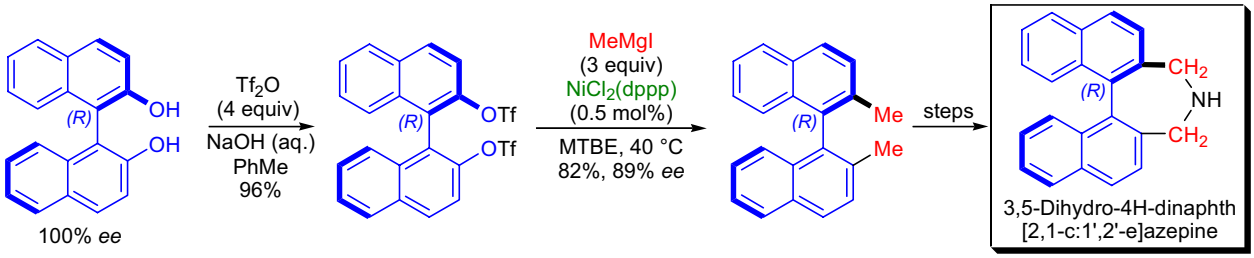
The highly concise synthesis of [18]dehydrodesoxyepothilone B, the 18-membered ring homologue of 10,11-dehydro-12,13-desoxyepothilone B, was based on a convergent *RCM* strategy.[40] S.J. Danishefsky et al. assembled the metathesis precursor by first converting a (*Z*)-vinyl iodide precursor to the corresponding 1,5-diene *via* the *Kumada cross-coupling*.



Enol phosphates were used as substrates for the *Kumada cross-coupling* during the final stages of the total synthesis of tetrahydrocannabinol and several of its analogs.[41] Y. Kobayashi and co-workers developed an indirect three-step 1,4-addition strategy to functionalize -iodinated cyclohexanones with the addition of cuprates. The resulting enolates were trapped as corresponding phosphates, which underwent facile *Kumada cross-coupling* with methylmagnesium chloride in the presence of $Ni(acac)_2$.



Research by M. Ikunaka showed that C_2-symmetrical chiral quaternary ammonium salts can serve as asymmetric phase-transfer catalysts.[42] To prepare significant quantities of (*R*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine, a novel short and scalable synthetic approach was undertaken. The synthesis commenced with the triflation of (*R*)-binol to give the *bis*-*O*-triflate. The *Kumada cross-coupling* was used to install two methyl groups in good yield.



LAROCK INDOLE SYNTHESIS

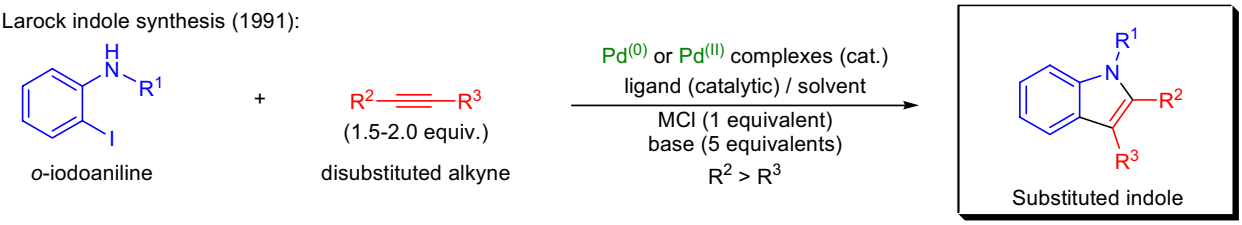
(References are on page 620)

Importance:

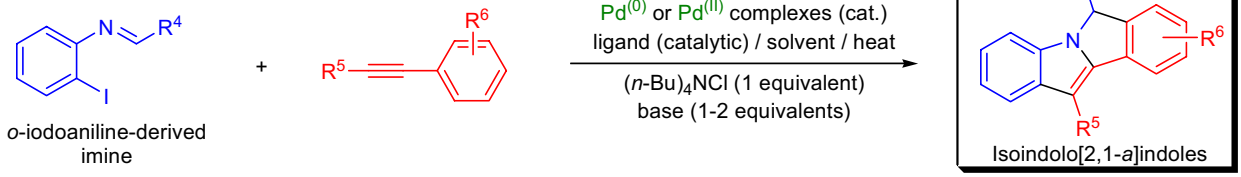
[*Seminal Publications*[1]; *Reviews*[2-11]; *Modifications & Improvements*[12-20]]

In 1991, R.C. Larock reported the synthesis of indoles *via* the Pd-catalyzed coupling of 2-iodo anilines and disubstituted alkynes.[1] In the following years, the scope and limitation of the method were further explored by Larock and co-workers.[21] The one-pot Pd-catalyzed heteroannulation of *o*-iodoanilines and internal alkynes to give 2,3-disubstituted indoles is known as the *Larock indole synthesis* (*Larock heteroannulation*). The general features of the reaction are: 1) a wide variety of disubstituted alkynes can be used as coupling partners, and the substitution pattern of R^2 and R^3 groups does not have a marked effect on the efficiency of the reaction; 2) the nitrogen atom on the aniline can also be diversely substituted; 3) only *o*-iodoanilines are good substrates for the coupling and *o*-bromoanilines were found to be unreactive under the reaction conditions; 4) the coupling is highly regioselective: the larger alkyne substituent (R^2) almost always becomes located at the 2-position of the indole;[17] 5) when R^2=SiR_3, 2-silylindoles are obtained that can be protodesilylated, halogenated, or coupled with alkenes *via* a Pd-catalyzed reaction; 6) usually an excess (1.5-2 equivalents) of the alkyne coupling partner is needed. However, in the case of volatile alkynes, multiple equivalents are needed to achieve high yields; 7) the use of a full equivalent of LiCl and excess base was found to be necessary for the reproducibility of the reaction; and 8) typically DMF is used as the solvent at 100 °C. There are several modifications of the *Larock indole synthesis*: 1) the coupling of imines derived from *o*-iodoanilines with disubstituted alkynes gives rise to isoindolo[2,1-*a*]indoles;[14,15] 2) the *o*-iodoanilines can be replaced with vicinal iodo-substituted heterocyclic amines to prepare 5-,6- or 7-azaindoles,[13] pyrrolo[3,2-c]quinolines, tetrahydroindoles and 5-(triazolylmethyl)tryptamine analogs;[5] and 3) the coupling partner alkynes can be replaced with substituted allenes to synthesize 3-methyleneindolines.[12]

Larock indole synthesis (1991):

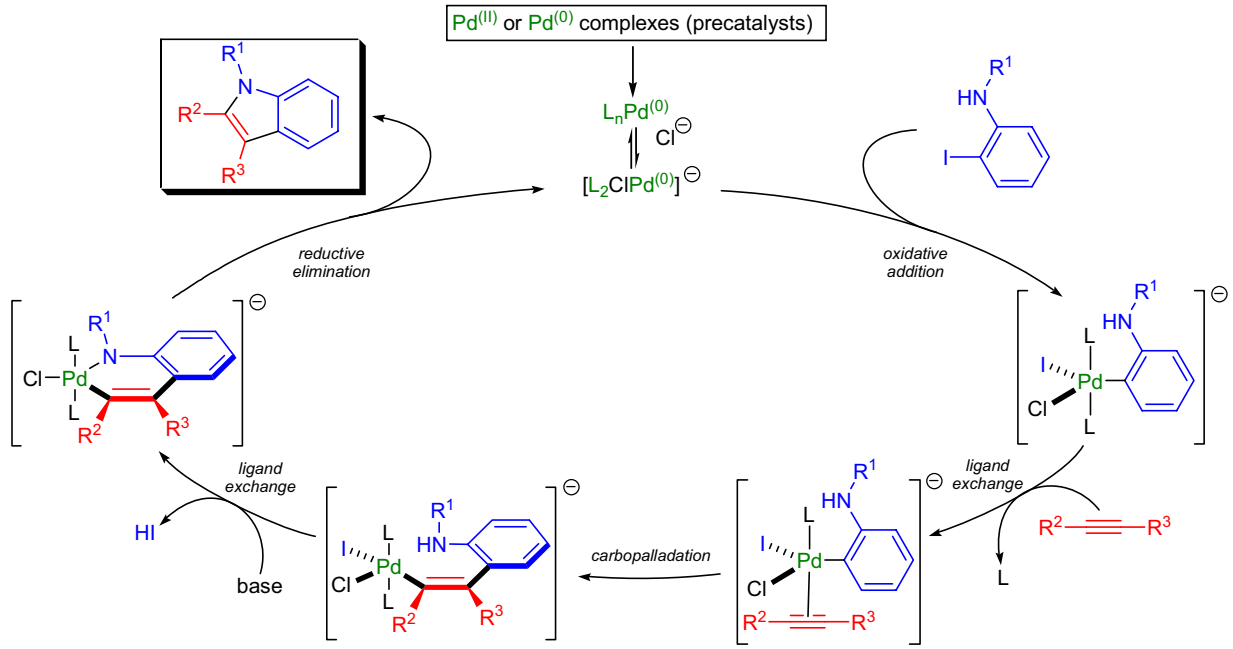


Modified Larock indole synthesis for fused systems (1999):



R^1 = alkyl, acyl, SO_2Ar; R^{2-3} = 1°, 2°, 3° alkyl, aryl, alkenyl, CH_2OH, SiR_3; M = $(n\text{-Bu})_4N^+$, Li; base = Na_2CO_3, K_2CO_3, KOAc
R^4 = alkyl, aryl; R^5 = 1°, 2°, 3° alkyl, aryl, CH_2OH, CO_2R; R^6 = EWG or EDG; base = Na_2CO_3, *i*-Pr_2NEt

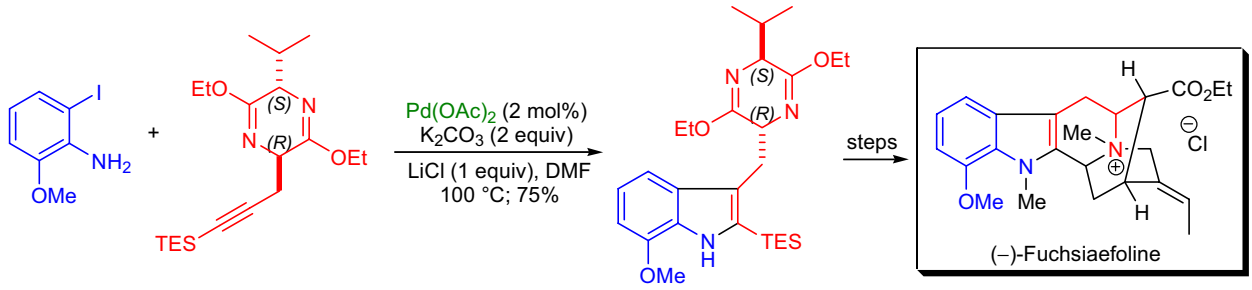
Mechanism:[21]



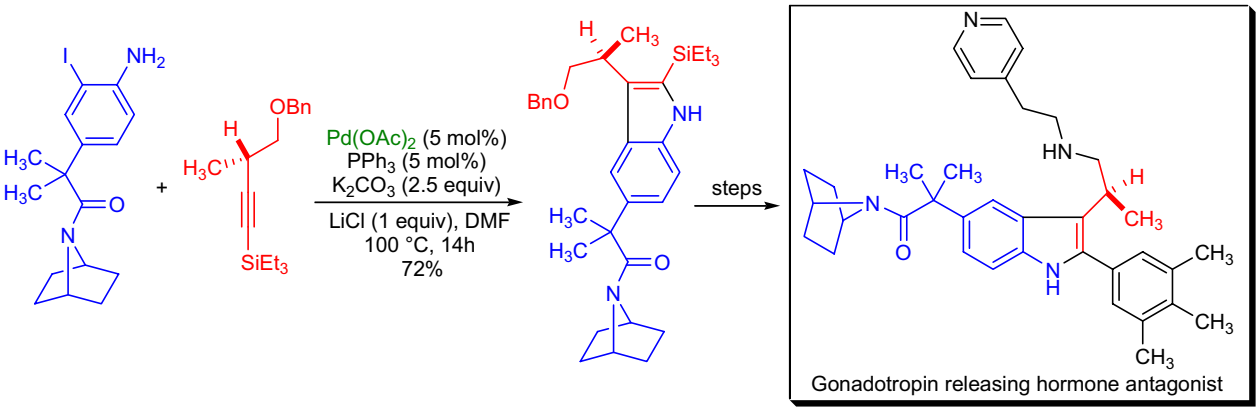
LAROCK INDOLE SYNTHESIS

Synthetic Applications:

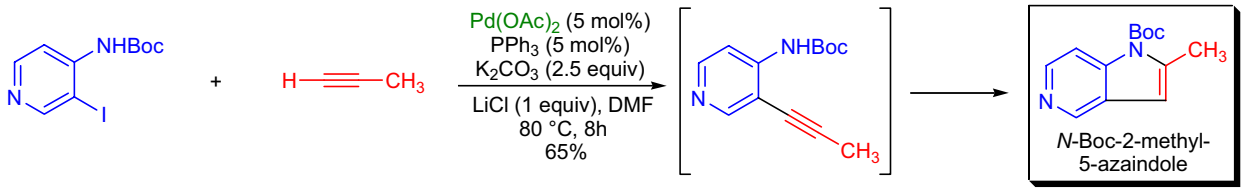
The total synthesis of (–)-fuchsiaefoline was accomplished in the laboratory of J.M. Cook using the *Larock indole synthesis* to prepare the key precursor 7-methoxy-D-tryptophan in enantiopure form.[22] The propargyl-substituted Schöllkopf chiral auxiliary was reacted with 2-iodo-6-methoxyaniline in the presence of 2 mol% $Pd(OAc)_2$ to give the expected indole in good yield. Interestingly, the *Bartoli indole synthesis* gives 7-substituted indoles only in moderate yield.



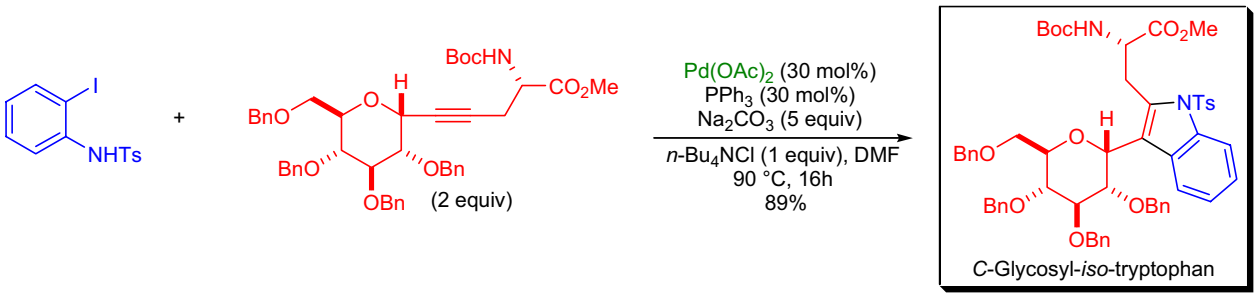
T.F. Walsh and co-workers synthesized two (*S*)-β-methyl-2-aryltryptamine based gonadotropin hormone antagonists *via* a consecutive *Larock indole synthesis* and *Suzuki cross-coupling*. The required (*S*)-β-methyltryptophol derivatives were prepared by coupling 4-substituted *o*-iodoanilines with optically active internal alkynes under standard conditions. The resulting 2-trialkylsilyl substituted indoles were then subjected to a *silver-assisted iododesilylation reaction* to afford the 2-iodo-substituted indoles that served as coupling partners for the *Suzuki cross-coupling* step.



The preparation of diversely substituted azaindoles is fairly difficult, and there are no generally applicable strategies in the literature. Research by L. Xu et al. showed that 2-substituted-5-azaindoles could be synthesized by the Pd-catalyzed coupling of aminopyridyl iodides with terminal alkynes.[13] The coupling reaction proceeded in good yield under the conditions originally developed by Larock. Therefore, this example can be considered an extension of the *Larock indole synthesis*. By stopping the reaction early it was shown that the intermediate was an internal alkyne.



A complete reversal of regioselectivity was observed by M. Isobe and co-workers during the *Larock heteroannulation* of *o*-iodoaniline with α-C-glucosylpropargyl glycine in an attempt to prepare *C*-glycosyltryptophan.[14]



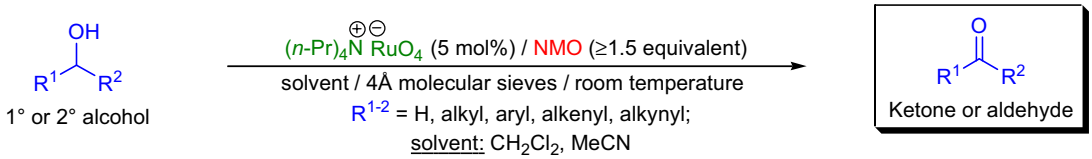
LEY OXIDATION

(References are on page 620)

Importance:

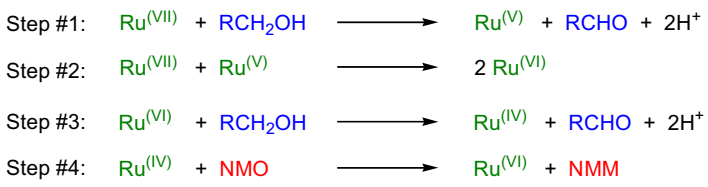
[*Seminal Publications*[1,2]; *Reviews*[3-12]; *Modifications & Improvements*[13-18]]

There are only two elements in the periodic table, ruthenium (Ru), and osmium (Os), which can sustain the uniquely high +8 oxidation state in their complexes containing strongly σ- and π-donating oxo (O^{2-}) ligands. Both metals can have eleven different oxidation states (d^0 to d^{10}), and any of these oxidation states can be stabilized with the appropriate choice of ligands. At any given oxidation state ruthenium complexes are more potent oxidizing agents than the corresponding osmium complexes (e.g., OsO_4 does not cleave double bonds, while RuO_4 does).[6] The greater lability of ruthenium complexes makes it possible to participate in catalytic processes. Despite the unselective nature of RuO_4 as an oxidant, it was possible to design ruthenium complexes with lower oxidation states which were less reactive and therefore more selective toward organic substrates containing several different functional groups.[5] The organic salts of perruthenate ion with large cations, $R[RuO_4]$, ($R=Pr_4N^+$ or Bu_4N^+) are soluble in organic solvents and are milder oxidizing agents than RuO_4.[1,2,13] In 1987, S.V. Ley and co-workers introduced tetrapropylammonium perruthenate (TPAP) as a selective and mild oxidant of primary and secondary alcohols without the undesired cleavage of double bonds. The oxidation takes place with catalytic amounts (5-10 mol%) of TPAP when a co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO) is used. The catalytic process to convert primary and secondary alcohols to the corresponding aldehydes and ketones with TPAP/NMO is referred to as the *Ley oxidation*. The general features of the reagent and reaction are: 1) TPAP is an air stable and non-volatile dark green solid and can be stored indefinitely when kept in the freezer (it decomposes when heated over 150 °C); 2) TPAP is soluble in a wide range of organic solvents, but in practice dichloromethane or acetonitrile (or their mixture) are used almost exclusively; 3) in a typical procedure, 5 mol% of TPAP is added to the solution of the substrate alcohol (1 equivalent) and NMO (1.5 equivalent) in CH_2Cl_2/MeCN in the presence of finely ground 4Å molecular sieves (0.5 g/mmol of substrate); 4) oxidations take place at room temperature in a few minutes or a couple of hours and the isolated yield of products is usually good or excellent (the catalyst turnover number is ~250); 5) the oxidations are vigorous, especially when the co-oxidant is not NMO (e.g., TMAO) and in these cases the TPAP should be added slowly to the reaction mixture in small portions; 6) the process works well on both small and large scale (e.g., *Swern oxidation* is difficult to run on a scale of a few milligrams); 7) due to the rapid nature of this oxidation, there is a danger of a runaway reaction (explosion) on multigram scale, so adequate cooling is necessary and the TPAP should be added to the reaction mixture slowly and portionwise; 8) the reaction rate and efficiency is improved when finely ground 4Å molecular sieves are added to the reaction mixture; 9) if pure CH_2Cl_2 is used as the solvent, the oxidations may not go to completion on a large scale but the addition of 10% (by volume) acetonitrile to the reaction mixture drives the oxidation to full conversion; 10) the work-up is very simple when the solvent is pure dichloromethane: the reaction mixture is filtered through a pad of silica-gel (or a short column), the silica-gel is washed with EtOAc and the filtrate is evaporated in vacuo; and 11) when the reaction is carried out in a mixture of CH_2Cl_2/acetonitrile, the solvent is first removed on a rotary evaporator, the residue is dissolved in dichloromethane or EtOAc and filtered through a pad of silica-gel (this is necessary, since acetonitrile can co-elute some residual TPAP, which contaminates the product).



Mechanism:[19,6,20-25]

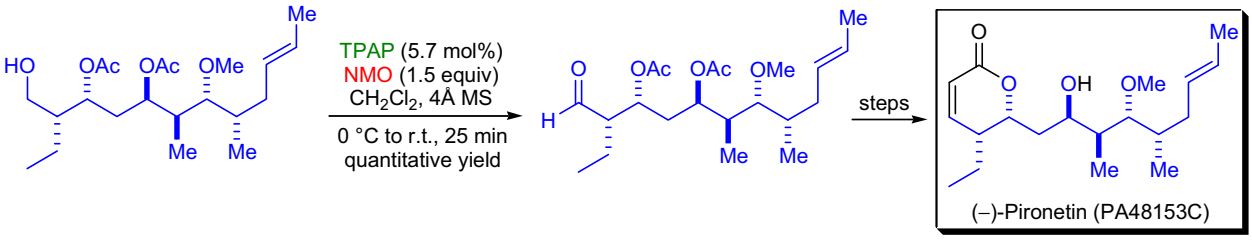
The mechanism of the *Ley oxidation* is complex and the exact nature of the species involved in the catalytic cycle is unknown. The difficulty in establishing an exact mechanism arises from the fact that the complexes of $Ru^{(VIII)}$, $Ru^{(VII)}$, $Ru^{(VI)}$, $Ru^{(V)}$ and $Ru^{(IV)}$ are all capable of stoichiometrically oxidizing alcohols to carbonyl compounds.[6] The TPAP reagent can oxidize alcohols stoichiometrically as a three-electron oxidant and can also be used as a catalyst when a co-oxidant is present (e.g., NMO, TMAO, or hydroperoxides). Data suggests that the oxidation proceeds *via* the formation of a complex between the alcohol and TPAP (ruthenate ester).[21] It was also found that the stoichiometric oxidation of isopropyl alcohol with TPAP is autocatalytic and the catalyst is suspected to be colloidal RuO_2. Small amounts of water decrease the degree of autocatalysis. This observation is supported by the finding that the addition of molecular sieves improves the efficiency of the reaction.



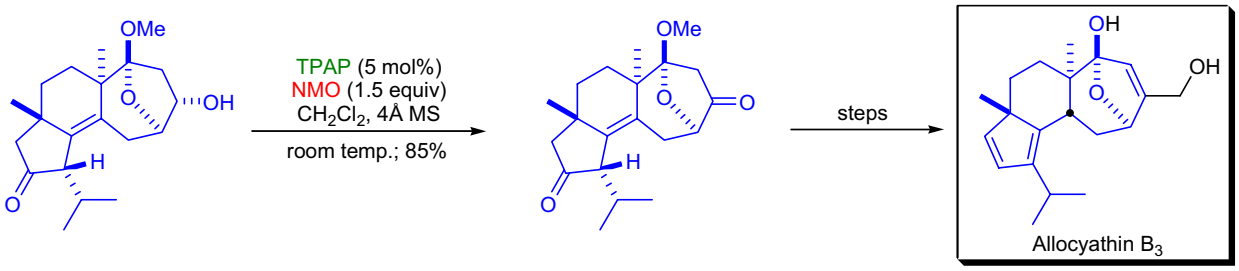
LEY OXIDATION

Synthetic Applications:

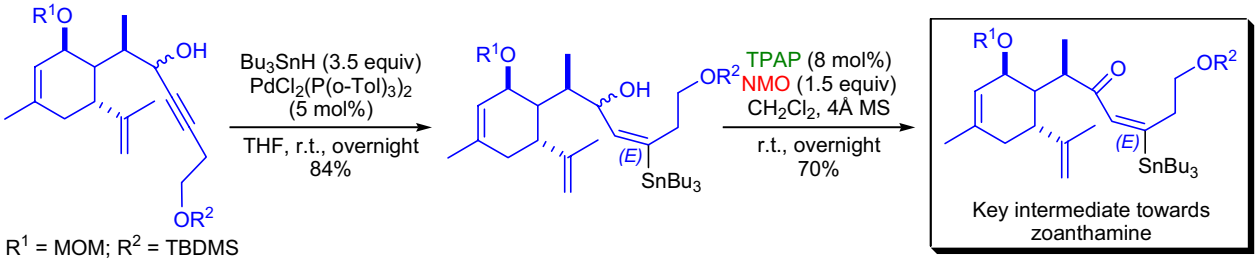
The total synthesis of the immunosuppressant (–)-pironetin (PA48153C) was accomplished by G.E. Keck and co-workers.[26] The six-membered α,β-unsaturated lactone moiety was installed using a *lactone annulation reaction* by reacting the advanced aldehyde intermediate with the lithium enolate of methyl acetate. The aldehyde was prepared by the *Ley oxidation* of the corresponding primary alcohol and was used without purification in the subsequent annulation step.



D.E. Ward et al. reported a general approach to cyathin diterpenes and the total synthesis of allocyathin B_3. The tetracyclic secondary alcohol was converted to the corresponding ketone using TPAP/NMO in good yield.[27]

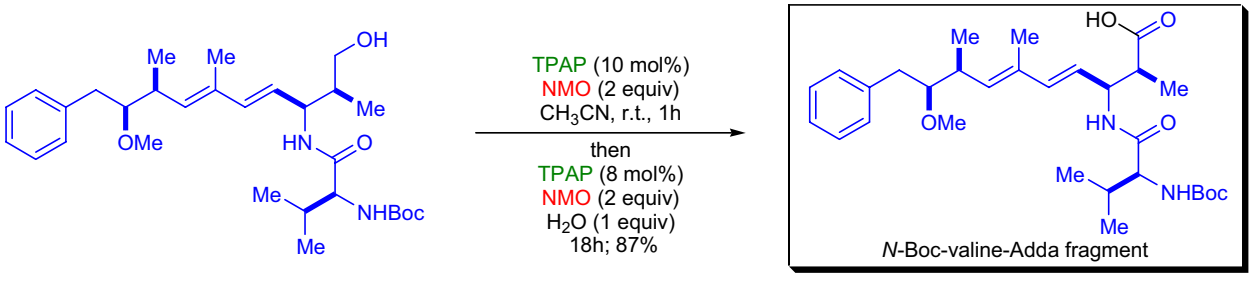


In the laboratory of D. Tanner, a novel method was developed for the stereoselective synthesis of (*E*)-tributylstannyl-α,β-unsaturated ketones in two steps from secondary propargylic alcohols.[28] The first step was the highly regio- and stereoselective *Pd-catalyzed hydrostannylation* of the triple bond followed by a mild *Ley oxidation*. This method was utilized for the construction of a key intermediate for the total synthesis of zoanthamine.



R^1 = MOM; R^2 = TBDMS

During the total synthesis of (–)-motuporin by J.S. Panek et al., the *modified Ley oxidation* was utilized in the preparation of the key *N*-Boc-valine-Adda fragment.[29] In order to obtain the carboxylic acid, the TPAP and NMO were administered twice, and the second portion of TPAP/NMO was accompanied by the addition of water. The water formed aldehyde hydrate which was oxidized to the carboxylic acid. The oxidation is so mild that the labile α-stereocenter was left intact.



LIEBEN HALOFORM REACTION

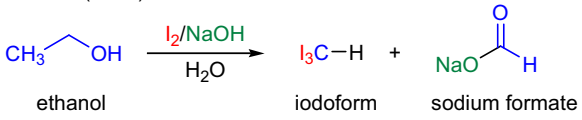
(References are on page 621)

Importance:

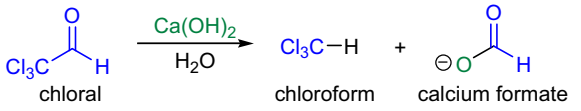
[*Seminal Publications*[1-3]; *Reviews*[4-8]; *Modifications & Improvements*[9-13]]

In 1822, Serullas discovered that when iodine crystals were added to the mixture of an alkali and ethyl alcohol, a yellow precipitate was formed that he identified as "hydroiodide of carbon", but it was actually iodoform (CHI_3).[1] The discovery of chloroform ($CHCl_3$) came a decade later, when J. Liebig reacted chloral (trichloroacetaldehyde) with aqueous calcium hydroxide solution.[2] The reaction did not attract attention until 1870 when A. Lieben studied the action of iodine and alkali on many carbonyl compounds and formulated the rules that provide the basis of the so-called iodoform test.[3] Before spectroscopic methods became widely available for structural elucidation, the use of the iodoform test provided crucial information regarding the structure of organic compounds.[14] Presently, the reaction is more useful as a method of synthesizing carboxylic acids with one less carbon atom. The formation of haloforms from organic compounds upon treatment with hypohalites is known as the *Lieben haloform reaction* (or *haloform reaction*). The general features of this reaction are: 1) compounds containing the methyl ketone (CH_3-CO) functional group or compounds that get oxidized under the reaction conditions to methyl ketones will undergo the transformation; 2) in addition to methyl ketones and methyl carbinols, mono-, di-, and trihalogenated methyl ketones also give rise to haloforms; 3) the reaction is usually conducted in aqueous alkali, but for compounds that are insoluble in water the addition of a co-solvent such as dioxane or THF is necessary; 4) the halogen can be chlorine, bromine, and iodine, but elemental fluorine gas cannot be used due to its immense reactivity; 5) the reaction is sensitive to steric hindrance, so when the R^1 group is bulky, the hydrolysis of the trihalomethyl ketone usually does not take place, and the reaction stops; 6) certain side reactions such as the α-halogenation and subsequent cleavage of the other alkyl group is possible.

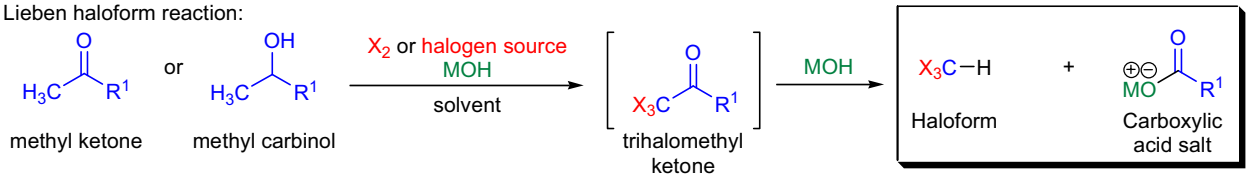
Serullas (1822):



Lieben (1831):



Lieben haloform reaction:

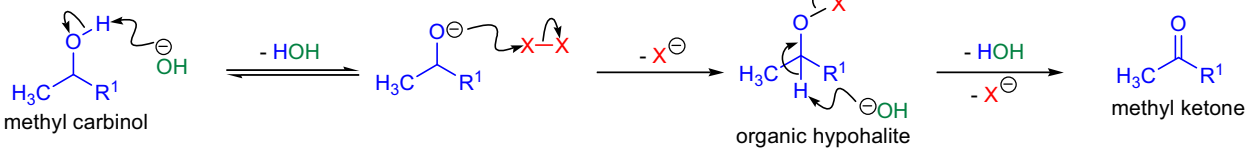


R^1 = H, alkyl, aryl; X_2 = Cl_2, Br_2, I_2; halogen source: NaOCl, NaOBr, NaOI, ICN; X_3C = F_3C, Cl_3C,Br_3C, I_3C; MOH = NaOH, KOH; solvent: H_2O, dioxane/H_2O, THF/MeOH

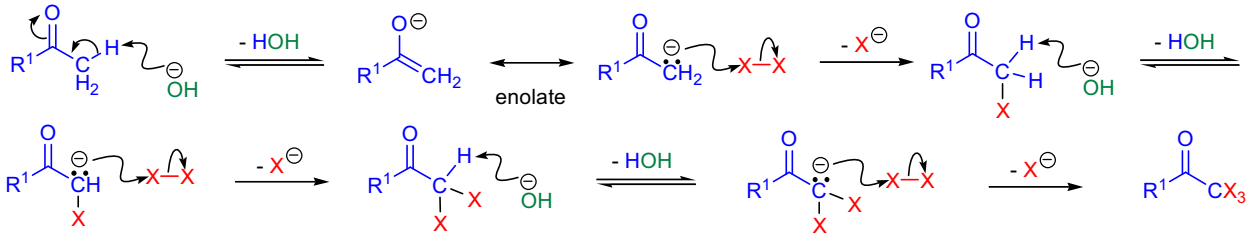
Mechanism:[15,4,16,5,17]

The mechanism of the *haloform reaction* has been extensively studied, and it can be concluded that it is a very complex process. The exact mechanistic pathway is dependent on the structure of the substrate and the specific reaction conditions.[17] The scheme depicts the oxidation of a methyl carbinol to the corresponding methyl ketone *via* an organic hypohalite. The methyl ketone then undergoes deprotonation, and three sequential α-halogenations take place to afford the trihalomethyl ketone. This compound undergoes rapid hydrolysis to afford the haloform and a carboxylate.

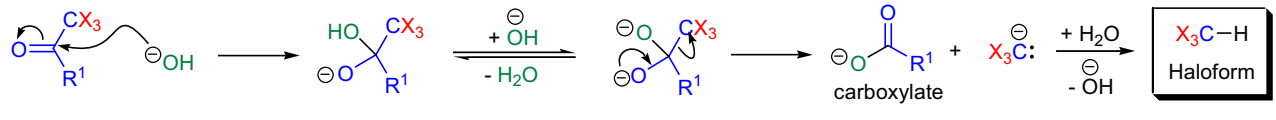
Oxidation of the carbinol to the methyl ketone:



Sequential halogenation of the methyl group:



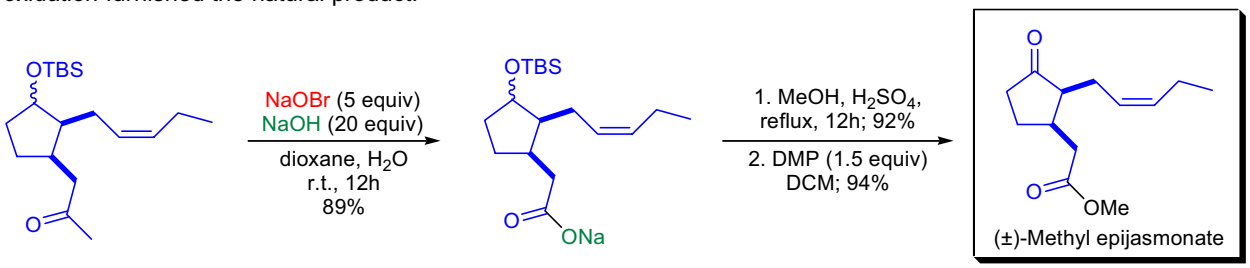
Hydrolysis of the trihalomethyl ketone:



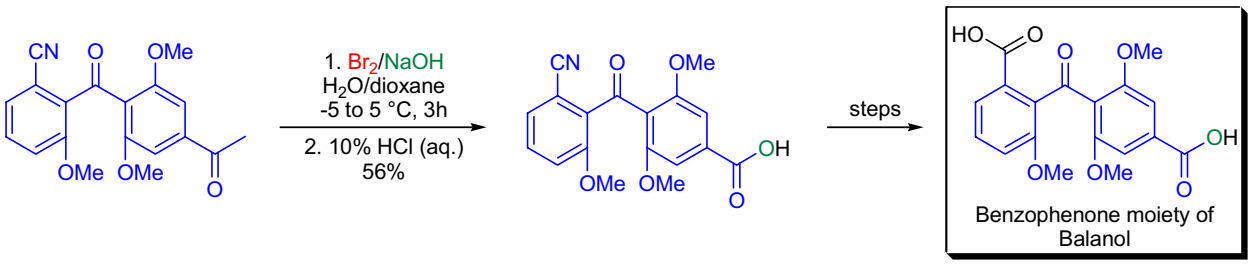
LIEBEN HALOFORM REACTION

Synthetic Applications:

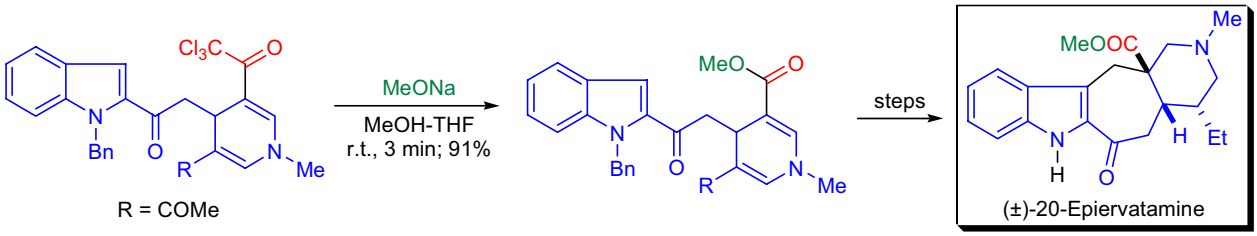
The blossoms of many flowers contain methyl jasmonates that are frequently used as ingredients in perfumes. It is noteworthy that the methyl epi-isomers have greater biological activity, and they play a role in inducing gene expression, mediate plant defense mechanisms, and signal transmission. The total synthesis of (±)-methyl epijasmonate was undertaken by H.C. Hailes and co-workers, who used a highly regioselective *Diels-Alder reaction* to install the required 2,3-*cis* stereochemistry.[18] After the ozonolysis of the cyclohexene double bond, the resulting methyl ketone moiety had to be transformed to a methyl ester, which was accomplished by using the *Lieben haloform reaction*. The aqueous solution of sodium hypobromite (prepared by adding Br_2 to sodium hydroxide) was slowly added to the solution of substrate in dioxane. The resulting carboxylate salt was converted to the methyl ester using *Fischer esterification* conditions under which the silyl protecting group was also removed. A final *Dess-Martin oxidation* furnished the natural product.



A novel synthetic route for the preparation of unsymmetrically substituted benzophenones was developed in the laboratory of C.-M. Andersson utilizing an iron-mediated aromatic substitution as one of the key steps.[19] The power of this method was demonstrated by the formal synthesis of the benzophenone moiety of the protein kinase C inhibitor balanol. In the late stages of the synthesis, it became necessary to convert the aromatic methyl ketone functionality of the highly substituted benzophenone substrate to the corresponding carboxylic acid. Bromine was added to sodium hydroxide solution, and the resulting sodium hypobromite solution was slowly added to the substrate at low temperature. Upon acidification the desired carboxylic acid was obtained in fair yield.

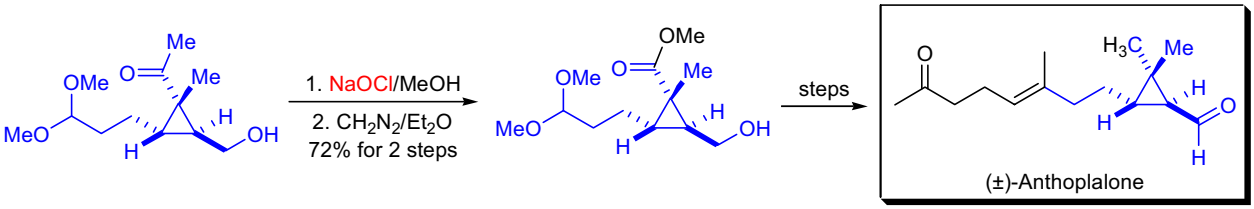


The biomimetic total synthesis of (±)-20-epiervatamine was accomplished by J. Bosch et al.[20] The authors used the addition of 2-acetylindole enolate to a 3-acylpyridinium salt as akey step to connect the two main fragments. The *in situ* formed 1,4-dihydropyridine was trapped with trichloroacetic anhydride to afford the corresponding trichloroacetyl-substituted 1,4-dihydropyridine derivative. The conversion of the trichloroacetyl group to a methyl ester was achieved by treatment with sodium methoxide. This transformation can be regarded as the second step of the *haloform reaction*.



R = COMe

During the total synthesis of (±)-anthoplalone by K. Fukumoto et al. one of the intermediates was a cyclopropyl methyl ketone, and the synthetic sequence required the conversion of this functionality to the corresponding cyclopropane carboxylic acid methyl ester.[21] This transformation was accomplished via the *haloform reaction* using bleach in methanol. The methyl ester and some carboxylic acid was obtained after this step, so the product mixture was treated with diazomethane to convert the acid side product to the methyl ester.



LOSSEN REARRANGEMENT

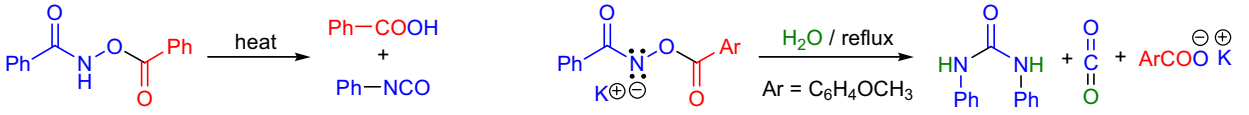
(References are on page 621)

Importance:

[*Seminal Publications*[1-3]*; Reviews*[4-9]*; Modifications & Improvements*[10-19]]

In 1872, W. Lossen reported that the pyrolysis of benzoyl benzohydroxamate (the mixed anhydride derived from phenylhydroxamic acid and benzoic acid) gave phenyl isocyanate and benzoic acid.[2] A few years later, he observed that the potassium salt of anisoyl benzohydroxamate was readily converted to diphenylurea, potassium anisoate, and carbon dioxide in boiling water. In this latter transformation the initial product was phenyl isocyanate, half of which reacted with water to afford aniline and carbon dioxide, and the other half reacted with aniline to form diphenylurea. The conversion of *O*-acyl hydroxamic acids to the corresponding isocyanates is known as the *Lossen rearrangement*. The general features of the reaction are: 1) hydroxamic acids can be readily prepared in several different ways:[4,5,7] a) from the corresponding carboxylic acids by first conversion to acid chlorides or mixed anhydrides then reaction with hydroxylamine; b) from esters with hydroxylamine; c) from aliphatic and aromatic carboxamides with hydroxylammonium chloride; 2) the free hydroxamic acids do not undergo the *Lossen rearrangement* under any condition, so the activation of the oxygen atom is necessary for the rearrangement to take place; 3) the acylation of the hydroxyl group of hydroxamic acids can be carried out with the following types of reagents: anhydrides,[4,5] acyl halides,[4,5] $SOCl_2$, SO_3·Et_3N,[11] dialkylcarbodiimides,[10] activated aromatic halides[14] (e.g., 2,4-dinitrochlorobenzene), under *Mitsunobu reaction* conditions[12] (PPh_3, DEAD, ROH) and silylation;[13] 4) the rearrangement is usually initiated by heating the *O*-activated hydroxamic acids with bases (e.g., NaOH, DBU) in the presence of water or other nucleophiles (e.g., amines, alcohols); 5) the more active *O*-sulfonyl and *O*-phosphoryl derivatives, however, tend to rearrange spontaneously; 6) the initial product of the rearrangement is an isocyanate that after reacting with water gives an unstable carbamic acid, which breaks down to give a primary amine and carbon dioxide; 7) when an amine is present as the nucleophile, the product of the reaction is a substituted urea; 8) when there is a neighboring nucleophilic functional group (e.g., NH_2, OH, COOH) within the molecule, it will react with the isocyanate; and 9) the stereocenter adjacent to the hydroxamic acid functional group remains intact during the rearrangement (optical activity is unchanged). The *Lossen rearrangement* is closely related to the *Hofmann and Curtius rearrangements*, but its main advantage over the other methods is the mild reaction conditions, since it does not require the use of concentrated strong bases or intense heat.

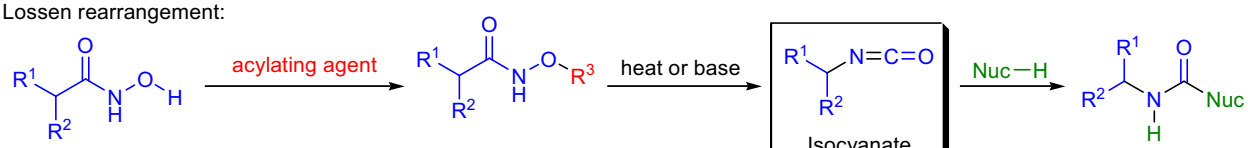
W. Lossen (1872):



benzoyl benzohydroxamate

potassium salt of anisoyl benzohydroxamate

Lossen rearrangement:



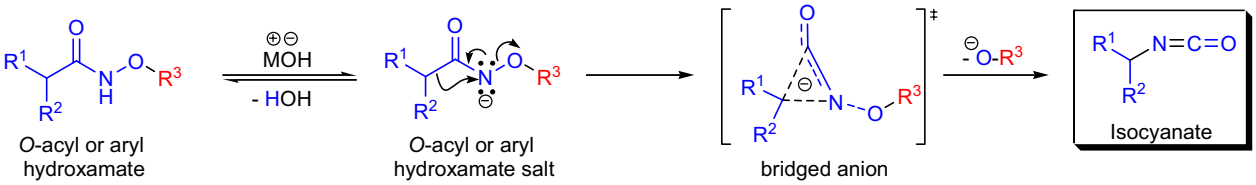
hydroxamic acid

O-acyl or aryl hydroxamate

R^{1-2} = alkyl, aryl ; acylating agent: anhydrides, acyl halides ($RCOCl$, RSO_2Cl, RPO_2Cl), $SOCl_2$, activated aromatic halides, RNCNR (carbodiimides); R^3 = CO-alkyl, CO-aryl, Cl, SiR_3, $C_6H_3(EWG)_2$(O-aryl), PO_2R, SO_2R, C=NR(NHR); base: NaOH, KOH, DBU, $(i\text{-}Pr)_2NEt$; nucleophile: H_2O, ROH, RNH_2

Mechanism:[20,10,21-23]

The mechanism of the *Lossen rearrangement* is closely related to the *Curtius-*, *Hofmann-*, and *Schmidt rearrangements*. The first step is the deprotonation of the *O*-acyl hydroxamate at the nitrogen atom by the base to the corresponding alkali salt, which is quite unstable and quickly undergoes a concerted rearrangement to the isocyanate *via* a bridged anion. The rate of the rearrangement strongly depends on the electronic nature of the substituents: the more electron-withdrawing R^3 is and the more electron-donating R^1 and R^2 are, the higher the rate is.



O-acyl or aryl hydroxamate

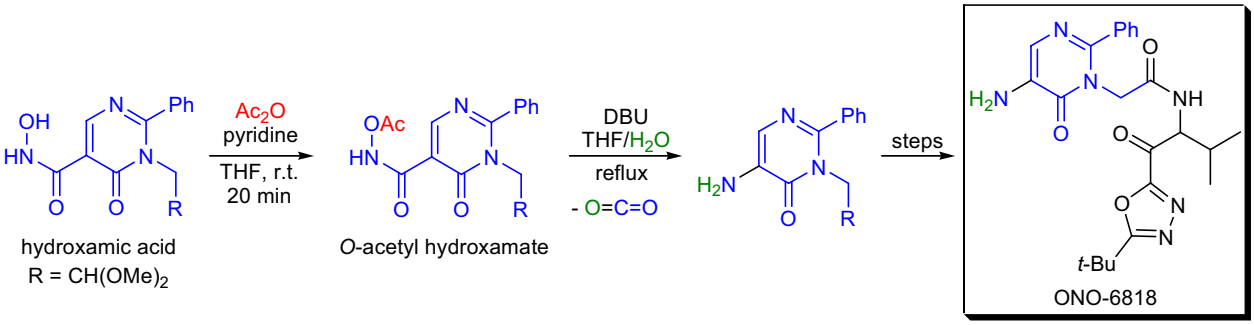
O-acyl or aryl hydroxamate salt

bridged anion

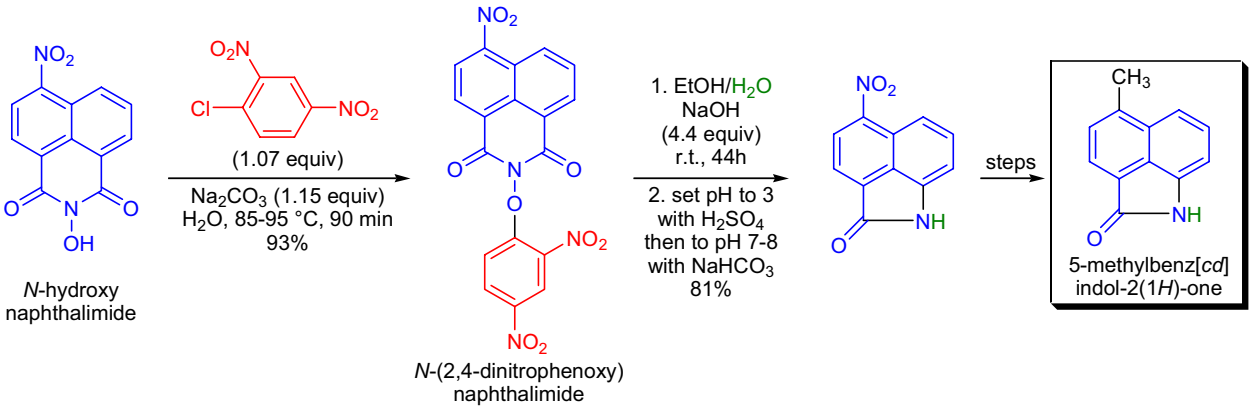
LOSSEN REARRANGEMENT

Synthetic Applications:

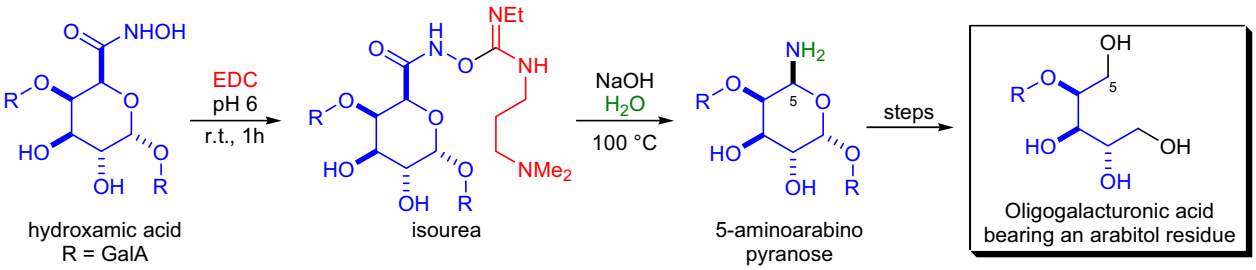
An improved synthesis of ONO-6818, a new nonpeptidic inhibitor of human neutrophil elastase, was developed by K. Ohmoto and co-workers.[24] The main difference between this new synthesis and the previous ones is that a dangerous (explosive) *Curtius rearrangement* of an acyl azide was replaced with a safer *Lossen rearrangement*. The required hydroxamic acid was prepared from a carboxylic acid by first converting it to the mixed anhydride with isobutyl chloroformate followed by the addition of hydroxylamine. The hydroxamic acid then was acetylated using acetic anhydride and the resulting *O*-acetyl hydroxamate was exposed to DBU in the presence of water. The intermediate isocyanate reacted with water to give the corresponding amine and CO_2.



5,6-Disubstituted benz[*cd*]indoles have been shown to be effective inhibitors of the enzyme thymidylate synthase. The improved large scale synthesis of 5-methylbenz[*cd*]indol-2(1*H*)-one was accomplished by G. Marzoni et al.[25] The *Lossen rearrangement* was the key step to set up the ring system of the target compound. The cyclic hydroxamic acid (*N*-hydroxynaphthalimide) was deprotonated and used in a nucleophilic aromatic substitution with 2,4-dinitrochlorobenzene to afford *N*-(2,4-dinitrophenoxy)naphthalimide. The rearrangement took place under basic conditions with complete regioselectivity so that the amine was formed on the more electron rich aromatic ring. The cyclization of the resulting γ-amino acid to the amide was achieved by adjusting the pH to 3 with concentrated sulfuric acid.



Pectins are important in cell wall assembly and detailed information of their structure will help to elucidate the relationship between the structures and physical properties. One possible approach is the chemical degradation of pectins. The specific degradation of the methyl esterified galacturonic acid residues of pectin to the corresponding oligogalacturonic acids bearing an arabitol residue was carried out in the laboratory of P.W. Needs.[26] The esters were first converted to the hydroxamic acids then reacted with EDC to give isoureas that upon the *Lossen rearrangement* and hydrolysis afforded 5-aminoarabinopyranose derivatives.



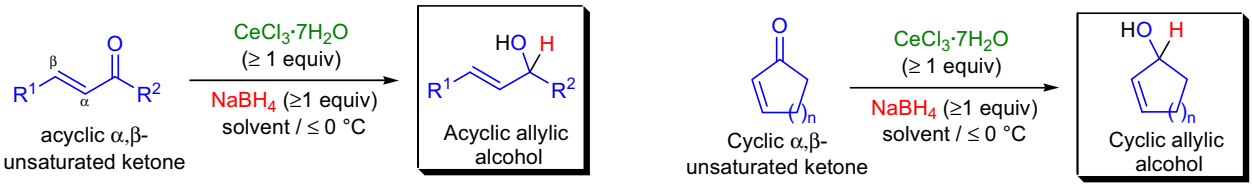
LUCHE REDUCTION

(References are on page 622)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-15]; *Theoretical Studies*[16]]

In 1978, J.L. Luche reported the selective conversion of α,β-unsaturated ketones to allylic alcohols using a mixture of lanthanide chlorides and sodium borohydride ($NaBH_4$).[1,2] Later the scope and limitation of the reaction was determined, and it was found that the 1,2-reduction of enones was best achieved by the use of $CeCl_3{\cdot}7H_2O/NaBH_4$ in ethanol or methanol.[4] The transformation of enones to the corresponding allylic alcohols using the combination of cerium chloride/sodium borohydride is known as the *Luche reduction*. The discovery by Luche was a breakthrough in the reduction of unsaturated carbonyl compounds, since metal hydrides usually give a mixture of 1,2- and 1,4-reduction products, and it was rare to obtain the 1,2-reduction product exclusively and in good yield. Usually hard metal hydrides (containing more ionic metal-H bonds) deliver the hydride mostly to the carbonyl group (1,2-addition), whereas soft metal hydrides (containing a more covalent metal-H bonds) favor conjugate addition. Alkali metal borohydrides are softer reducing agents than aluminum hydrides, so they are expected to favor the conjugate reduction of enones. Borohydrides can be made harder by the replacement of some of the hydride ligands with alkoxy groups so that the 1,2-selectivity will be larger. The general features of the *Luche reduction* are: 1) both acyclic and cyclic enones are reduced to the corresponding allylic alcohols in high yield with no or little 1,4-reduction by-product; 2) among various lanthanide salts, the heptahydrate of $CeCl_3$ was found to give the highest 1,2-selectivity; 3) under the reaction conditions most functional groups (such as carboxylic acids, esters, amides, alkyl halides, tosylates, acetals, sulfides, azides, epoxides, nitriles, nitro compounds) are unaffected; 4) the reactions are usually conducted at or below room temperature, and the reduction is complete within 5-10 minutes; 5) the reaction vessel and the solvents do not need to be dried, the regioselectivity and the yield is unaffected by water content up to 5% by volume; 6) the cerium chloride can be used directly as its heptahydrate and no drying is needed; 7) no inert atmosphere is required as the reaction is not sensitive to the presence of oxygen; 7) the best solvent is methanol, since the reaction rates are the highest, but occasionally ethanol and isopropanol are used, even though the reduction is slower in these solvents; 8) steric hindrance has little or no effect on the regioselectivity; 8) the combination of $CeCl_3/NaBH_4$ is excellent for the chemoselective reduction of ketones in the presence of aldehydes, since under these conditions aldehydes undergo rapid *acetalization*, which prevents their reduction; 9) substituted cyclohexenones undergo mainly an axial attack of hydride, so equatorial alcohols are obtained; 10) in rigid cyclic or polycyclic systems the hydride delivery occurs from the least hindered face of the carbonyl group; 11) conjugated or aromatic aldehydes are reduced preferentially in the presence of isolated aliphatic aldehydes; and 12) the lowering of the reaction temperature well below zero (e.g., -78 °C) usually increases the diastereoselectivity of the reduction of chiral substrates.

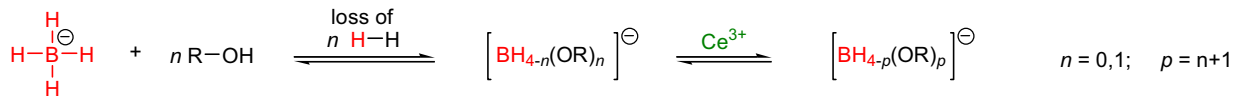


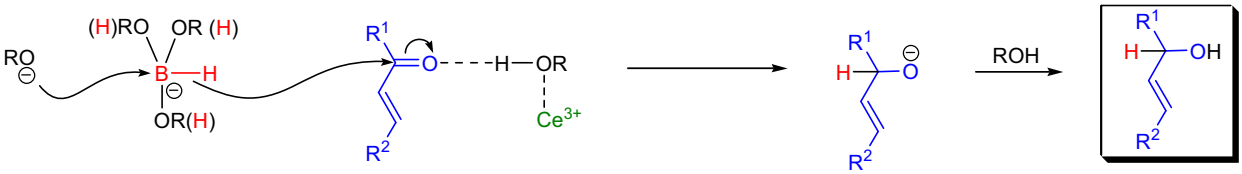
$R^{1\text{-}2}$ = H, alkyl, aryl; n = 1-3; solvent = methanol, ethanol, isopropanol

Mechanism:[17,4,18]

As mentioned above, $NaBH_4$ is a soft reducing agent and it has a tendency to reduce enones at the β-position of the double bond. The active species during the *Luche reduction* is believed to be an alkoxy borohydride, which in combination with the hard cerium cation acts as a hard reducing agent. The involvement of cerium borohydrides have been discounted based on experimental evidence.[19] The mechanism is complicated by the fact that more than one type of borohydride is formed. The role of the cerium is twofold: 1) catalysis of the formation of alkoxyborohydrides; and 2) increasing the electrophilicity of the carbonyl carbon atom. By coordinating to the oxygen atom of the solvent, cerium increases the acidity of the medium and helps activating the carbonyl of the enone indirectly (lanthanoid ions were shown to preferentially coordinate to alcohols rather than carbonyl groups by NMR spectroscopy).[20]

Formation of alkoxyborohydrides:

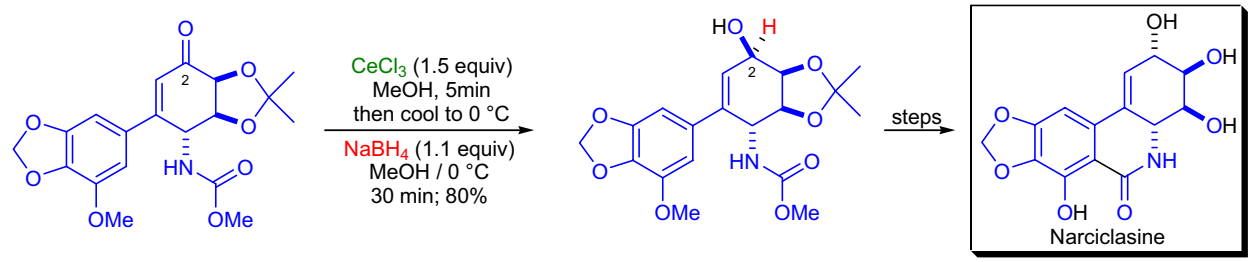




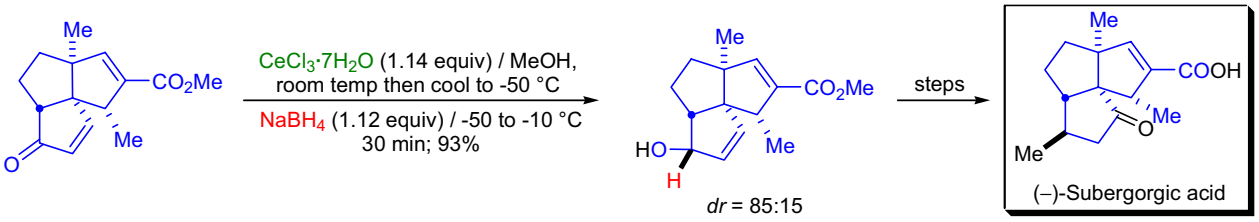
LUCHE REDUCTION

Synthetic Applications:

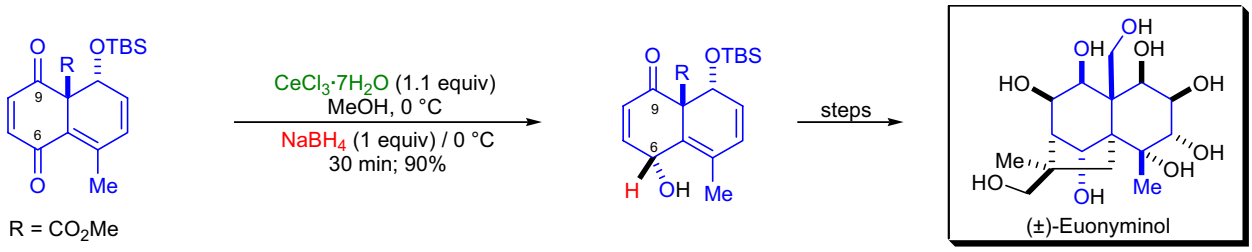
The total synthesis of several *amaryllidaceae alkaloids* including that of narciclasine was accomplished in the laboratory of T. Hudlicky.[21] The C2 stereochemistry was established by a two-step sequence: *Luche reduction* of the α,β-unsaturated cyclic ketone followed by a *Mitsunobu reaction*. The ketone was first mixed with over one equivalent of $CeCl_3$ in methanol and then the resulting solution was cooled to 0 °C, and the sodium borohydride was added. In 30 minutes the reaction was done, and the excess $NaBH_4$ was quenched with AcOH. The delivery of the hydride occurred from the less hindered face of the ketone and the allylic alcohol was obtained as a single diastereomer.



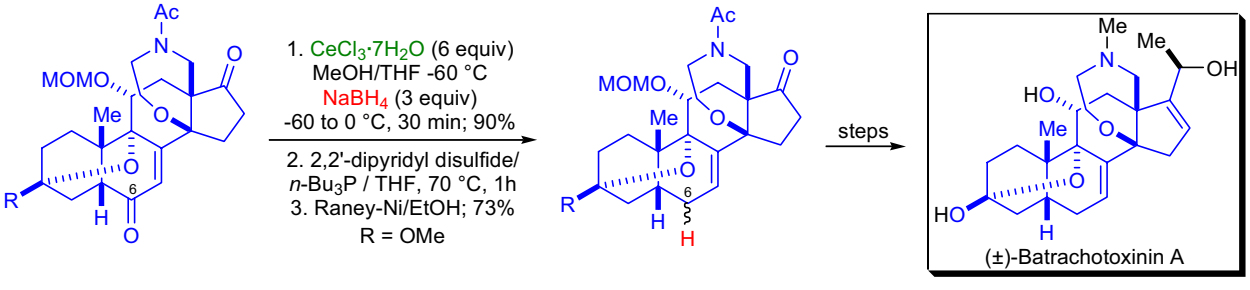
During the final stages of the total synthesis of (–)-subergorgic acid by L.A. Paquette and co-workers, the transposition of a tricyclic enone was needed.[22] The enone was exposed to the *Luche conditions* and an 85:15 mixture of diastereomers was obtained. In order to achieve this level of diastereoselectivity, the reaction temperature had to be lowered to -50 °C instead of the usual 0 °C. The major product was formed *via* the *exo* attack of the carbonyl group by the hydride. The allylic alcohol was later converted to the corresponding sulfoxide followed by a *Mislow-Evans rearrangement* to the isomeric allylic alcohol.



A general synthetic route to several polyhydroxylated agarofurans was developed by J.D. White and co-workers and the total synthesis of (±)-euonyminol was achieved.[23] The key intermediate was prepared *via* a *Diels-Alder reaction* between a diene and a substituted benzoquinone. The resulting bicyclic homoannular diene was reduced under the Luche conditions with excellent regio- and stereoselectivity at C6. The substrate was mainly in the boat conformation and the β-face of the ketone was more exposed to hydride attack. The C6 ketone was also more sterically accessible and more basic than the C9 ketone functionality.



The deoxygenation of the C6 position of an advanced intermediate was accomplished in a two-step procedure by Y. Kishi et al. in their synthesis of (±)-batrachotoxinin A.[24] The *Luche reduction* was followed by the formation of the C6 pyridylthioether, which was desulfurized using Raney nickel.



MADELUNG INDOLE SYNTHESIS

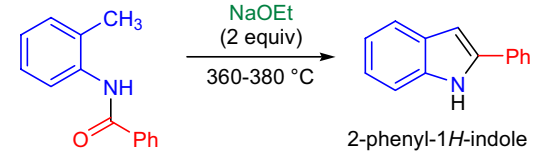
(References are on page 622)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-20]]

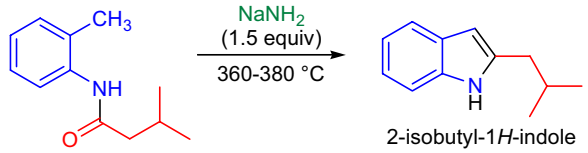
In 1912, W. Madelung reported that *N*-benzoyl-*o*-toluidine was converted to the corresponding 2-phenylindole when heated with two equivalents of sodium ethoxide at high temperatures in the absence of air.[2] Madelung also showed that the yields could be improved by using the alkoxides of higher aliphatic alcohols such as *n*-amyl alcohol. The intramolecular cyclization of *N*-acylated-*o*-alkylanilines to the corresponding substituted indoles in the presence of a strong base is known as the *Madelung indole synthesis*. A decade later in 1924, A. Verley demonstrated that sodium amide ($NaNH_2$) was a more general reagent and a wide range of *N*-acylated-*o*-toluidines could be converted to the corresponding 2-substituted indoles.[8,9] The general features of the transformation are: 1) when $NaNH_2$ or sodium alkoxides are used as bases, usually temperatures over 250 °C are required; 2) the use of alkyllithiums allows the reaction to take place at ambient or slightly higher temperatures; 3) high yields are observed when the aromatic ring has electron-donating substituents, while electron-withdrawing substituents tend to give lower yields; 4) the efficiency of the reaction is dependent of the steric bulk of the R^2 substituent; and 5) when the methyl group is substituted with an electron-withdrawing group (e.g., CN), the cyclization takes place at lower temperatures.[13] One of the most important modifications of the *Madelung indole synthesis* was introduced by A.B. Smith et al. who metalated substituted *N*-TMS-o-toluidines with *n*-BuLi. The resulting benzylic anion was reacted with non-enolizable esters or lactones to afford *N*-lithioketamine intermediates that first underwent *intramolecular heteroatom Peterson olefination* to give indolinines, and then tautomerized to the corresponding 2-substituted indoles. This modification is referred to as the *Smith indole synthesis*.[6]

Madelung (1912):



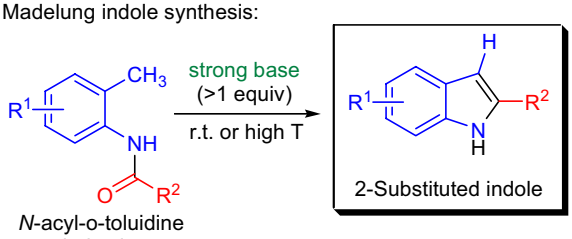
N-benzoyl-o-toluidine — 2-phenyl-1*H*-indole

Verley (1924 & 1925):



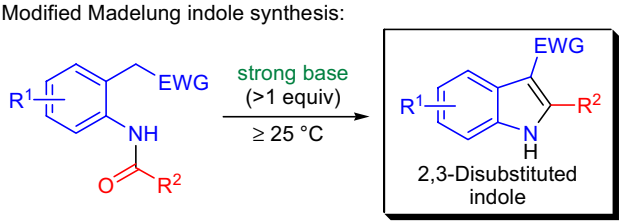
N-(3-methyl-butyryl)-*o*-toluidine — 2-isobutyl-1*H*-indole

Madelung indole synthesis:

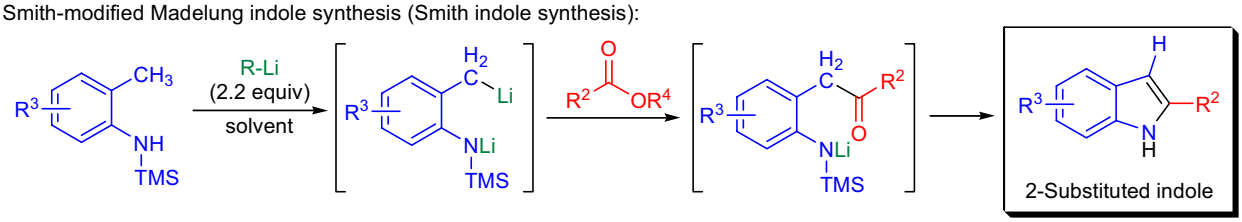


N-acyl-o-toluidine derivative

Modified Madelung indole synthesis:



Smith-modified Madelung indole synthesis (Smith indole synthesis):

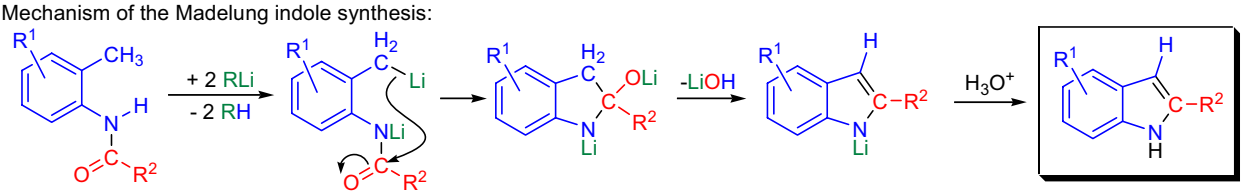


R^1 = H, alkyl, aryl, typically EDG; R^2 = alkyl, aryl; R^3 = alkyl, O-alkyl, O-aryl, Cl, F; R^4 = Me, Et; EWG = CN, CO_2R

strong base: KOEt, NaOEt, $NaNH_2$, Na(O-alkyl); alkyllithium, aryllithium; solvent: hexanes, THF

Mechanism:[4,11]

Mechanism of the Madelung indole synthesis:



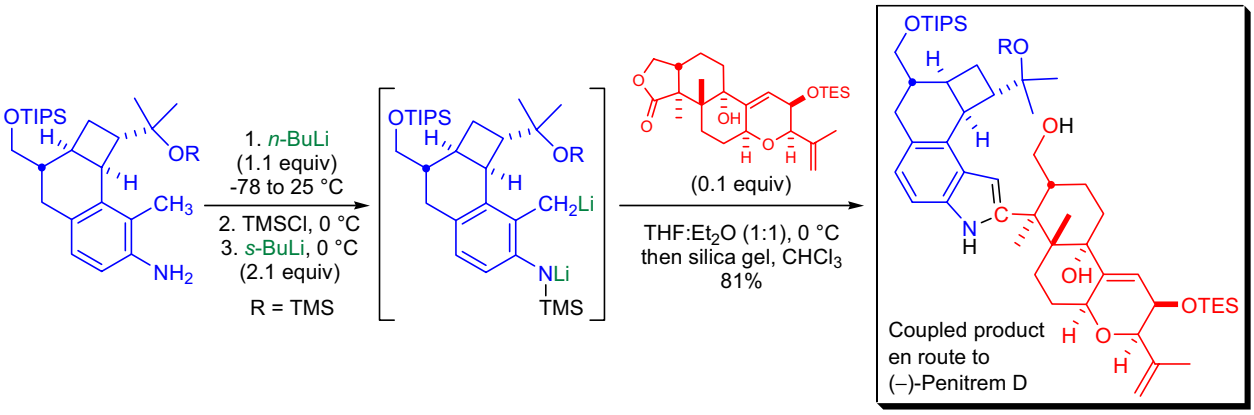
Mechanism of the Smith indole synthesis:



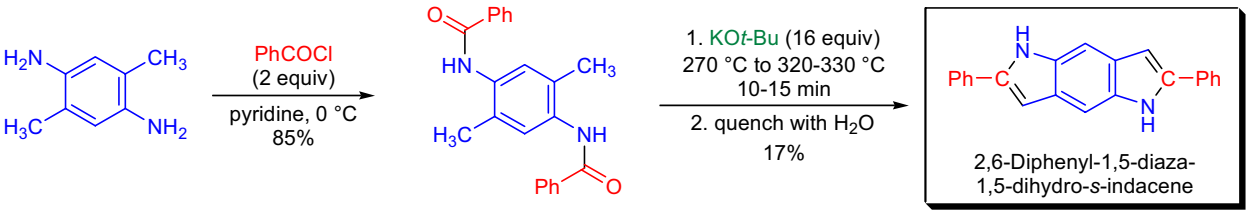
MADELUNG INDOLE SYNTHESIS

Synthetic Applications:

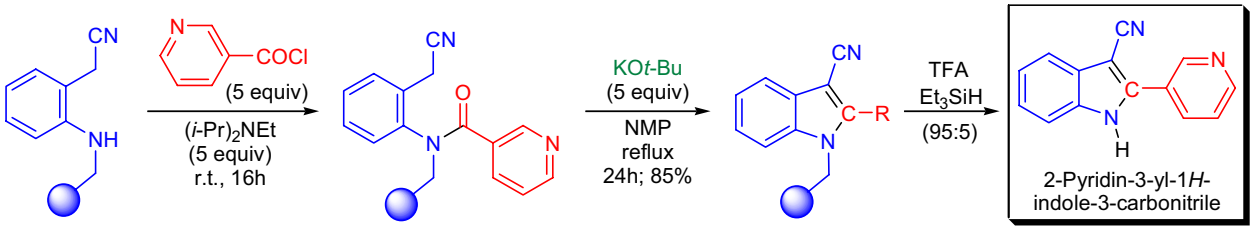
In the laboratory of A.B. Smith, the total synthesis of (–)-penitrem D, one of the most architecturally complex indole alkaloids, was accomplished.[21] The *Smith-modified Madelung indole synthesis* was utilized for the coupling of the two main fragments to form the desired 2-substituted indole ring. The *o*-toluidine derivative was first *N*-silylated and then treated with 2.1 equivalents of *sec*-BuLi. In the same pot, the addition of the lactone furnished an initial coupled product. In order to facilitate the final *heteroatom Peterson olefination*, exposure to silica gel was necessary and the indole was formed in high yield. It is worth noting that the use of large excess of the lithiated *o*-toluidine fragment was necessary to achieve the full conversion of the lactone.



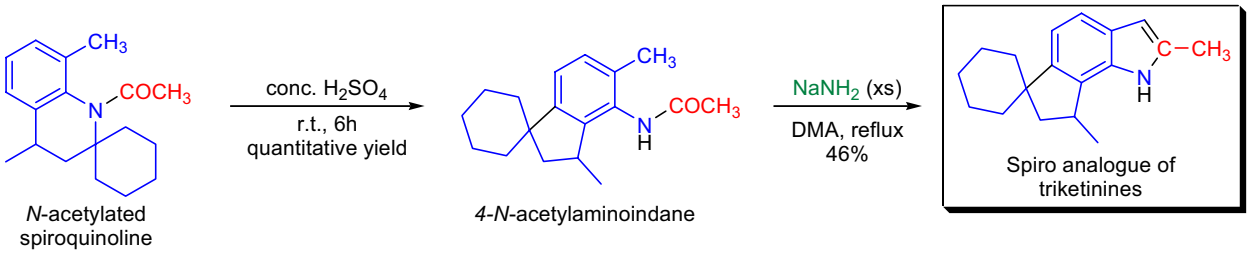
The synthesis of a novel indacene (2,6-diphenyl-1,5-diaza-1,5-dihydro-*s*-indacene) was completed by H.J. Geise and co-workers.[22] This compound had a great potential to be used as an organic light-emitting diode based on its optical and electroluminescent properties. The authors chose the conditions of the original high-temperature *Madelung indole synthesis*. First, 2,5-dimethyl-4-amino aniline was benzoylated then mixed with a large excess of potassium-*tert*-butoxide and heated to high temperatures in a preheated oven.



The *solid-phase version of the Madelung indole synthesis* was developed by D.A. Wacker et al. for the preparation of 2,3-disubstituted indoles.[20] The *ortho*-substituted aniline substrate was first attached to the Bal resin using reductive amination. The resin-bound aniline was then acylated and the cyclization was brought about with a variety of bases to afford high yields of the disubstituted indoles. The products were quantitatively removed from the resin with TFA:Et_3SiH (95:5).



A practical synthetic route to the spiro analogues of triketinins was devised by V. Kouznetsov and co-workers utilizing the *Madelung indole synthesis* in the final step.[23] The starting *N*-acetylated spiroquinolines were rearranged to 4-*N*-acetylaminoindanes, which were finally converted to the desired indoles.



MALONIC ESTER SYNTHESIS

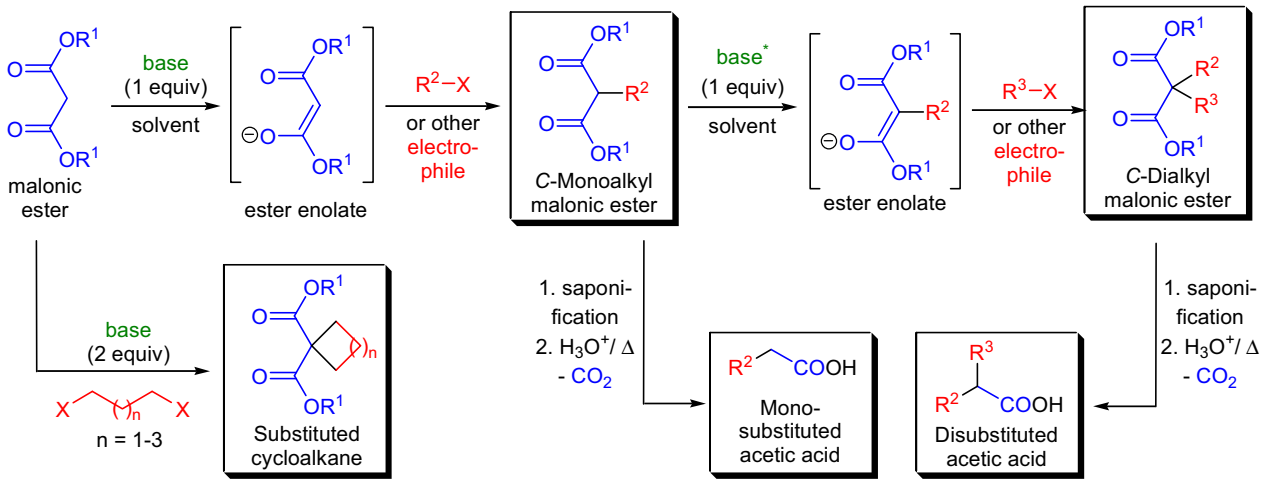
(References are on page 623)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-6]; *Modifications & Improvements*[7-16]]

In 1863, Geuther was the first investigator to perform the *C*-alkylation of an enolate derived from an active methylene compound (a methylene or methine group with two electron-withdrawing groups attached to it). Namely, he deprotonated ethyl acetoacetate and reacted the resulting sodium enolate with ethyl iodide and isolated the corresponding ethyl α-ethyl acetoacetate.[17] More than a decade later, J. Wislicenus investigated the reaction between the sodium enolates of malonic esters and primary and secondary alkyl halides and made the observation that primary alkyl halides reacted faster than secondary ones.[1,2] The alkylation of malonic ester enolates with various organic halides and the subsequent decarboxylation of the alkylated products to yield substituted acetic acid derivatives is known as the *malonic ester synthesis*. The general features of the transformation are:[4] 1) the alcohol component of the malonic ester substrates is primarily derived from aliphatic alcohols (e.g., OMe, OEt, O*t*-Bu); 2) the pK_a of the methylene group is usually between 9-11, so relatively weak bases are sufficient for the generation of the reactive ester enolate; 3) the base most often corresponds to the alcohol component of the substrate to avoid the generation of mixtures of esters (e.g., dimethyl malonate is deprotonated with NaOMe in MeOH); 4) the applied solvent can vary from hydroxylic solvents (e.g., alcohols) all the way to dipolar aprotic solvents (e.g., DMF) and nonpolar aprotic solvents (e.g., benzene); 5) the reaction is bimolecular (S_N2) for 1° and 2° alkyl halides, especially in dipolar aprotic solvents, so high concentration of both the enolate and the organic halide results in faster alkylation; 6) allylic and benzylic halides may also react in a monomolecular fashion (S_N1); 7) 1° and 2° alkyl halides and allylic and benzylic halides react the fastest, while tertiary alkyl halides mainly give elimination products; 8) the order of reactivity of the halides is I ~ OTs > Br > Cl; 9) *C*-monoalkyl malonic esters are less acidic than unsubstituted ones, so the use of a stronger base is needed to effect the second deprotonation, and the alkylation of the corresponding enolates is slower; 10) when α,ω-dihalides are used as the alkylating agents, cycloalkanes are obtained and the formation of five-, six-, and seven-membered rings is favored; and 11) saponification of the mono- or disubstituted malonic ester with base affords a 1,3-diacid, which undergoes decarboxylation upon heating with an acid to give substituted acetic acids.

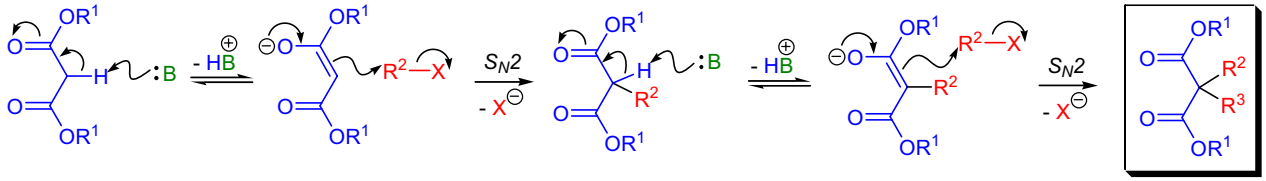
Monoalkylation of malonic ester: Dialkylation of malonic ester:



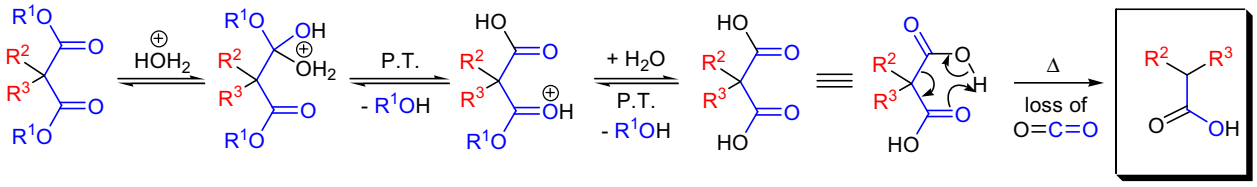
R^1 = alkyl, aryl; R^{2-3} = 1° or 2° alkyl, allyl, benzyl, activated aryl, acyl; X = Cl, Br, I, OTs; electrophile: epoxide, dialkyl sulfate, alkyl sulfonate, alkyl nitrate; base = $NaOR^1$, NaH; base* = KO*t*-Bu, conc. NaOEt, NaH; solvent = R^1OH, *t*-BuOH, benzene, ether, DMF

Mechanism:[18,4]

Mechanism of mono- and dialkylation:



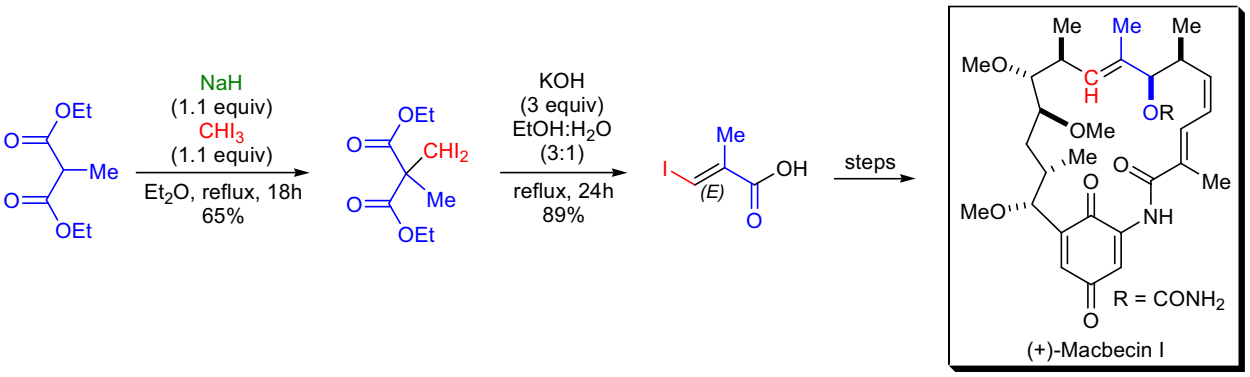
Mechanism of acidic hydrolysis and decarboxylation:



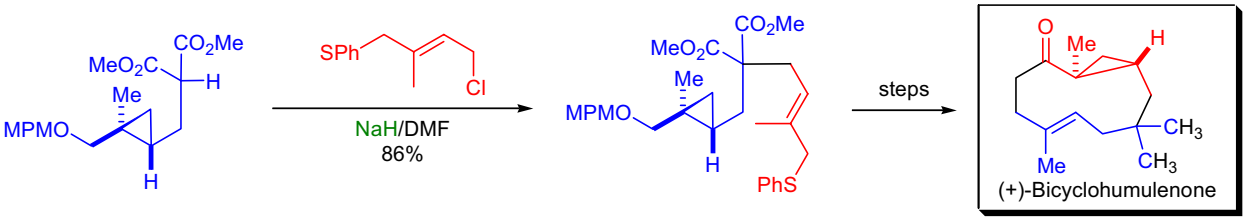
MALONIC ESTER SYNTHESIS

Synthetic Applications:

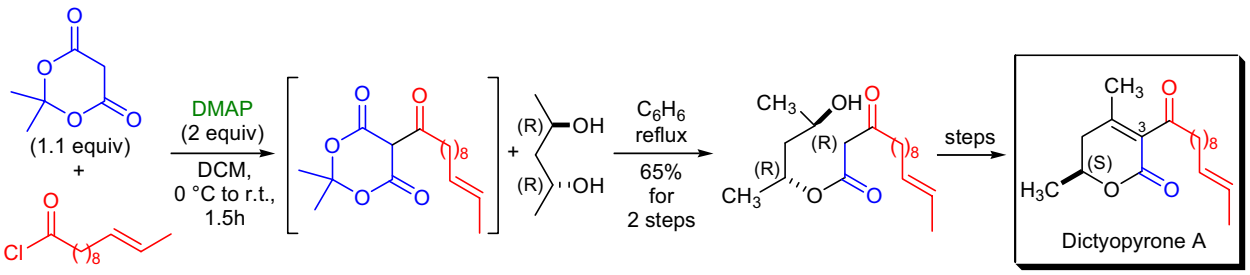
The first enantioselective total synthesis of (+)-macbecin I was accomplished by R. Baker and co-workers.[19] A key vinyl iodide precursor was prepared stereoselectively using the *malonic ester synthesis*. Diethyl methylmalonate was treated with *in situ* generated diiodocarbene in ether at reflux to afford diiodomethylmethylmalonate in good yield. This dialkylated malonic ester then was converted to (*E*)-3-iodo-2-methyl-2-propenoic acid by reacting it with aqueous KOH. The saponification was accompanied by a concomitant decarboxylation.



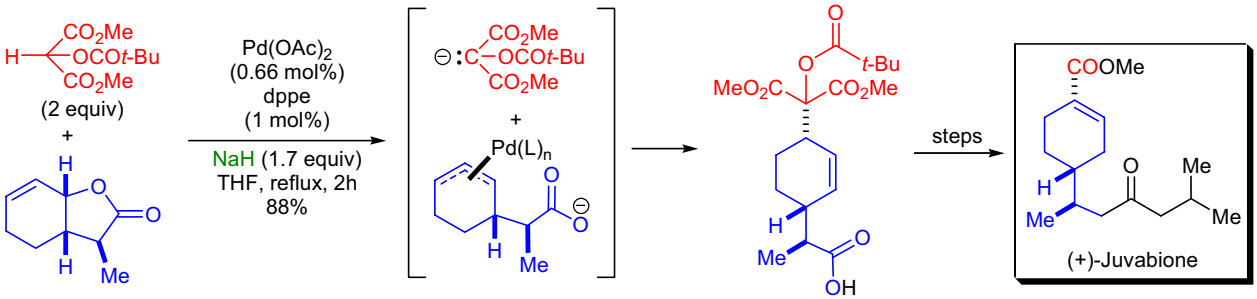
The novel humulane-type sesquiterpene (+)-bicyclohumulenone was synthesized for the first time in the laboratory of M. Kodama.[20] The natural product features a cyclodecenone ring fused to a cyclopropane ring, having two stereocenters at the ring junction. The cyclopropane moiety was installed using a stereoselective *Simmons-Smith cyclopropanation* reaction, while the 10-membered ring was formed *via* an intramolecular alkylation of an α-sulfenyl carbanion with an epoxide. The two main fragments were united by the *malonic ester synthesis* in which the monosubstituted dimethyl malonate was alkylated with an allylic chloride.



The structural elucidation of the secondary metabolites of *Dictyostellium* cellular slime molds was achieved by Y. Oshima et al.[21] The total synthesis of a novel compound, dictyopyrone A, which possesses a unique α-pyrone moiety with a side-chain at the C3 position, was successfully carried out using the *malonic ester synthesis*. Meldrum's acid was acylated and the product was subjected to transesterification with an optically active diol. Specific rotation of the final product was identical with that of the natural product, so the absolute configuration was established as (S).



The key step in total synthesis of (+)-juvabione by G. Helmchen and co-workers was the *Pd-catalyzed allylic substitution* with the anion of (pivaloyloxy)malonate.[22] The substitution proceeded with very high regio- and stereoselectivity.



MANNICH REACTION

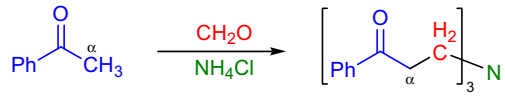
(References are on page 623)

Importance:

[*Seminal Publications*[1-3]*; Reviews*[4-23]*; Modifications & Improvements*[24-36]*; Theoretical Studies*[37-49]]

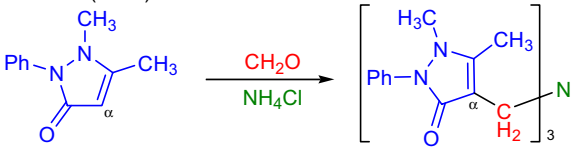
In 1903, B. Tollens and von Marle made the observation that the reaction of acetophenone with formaldehyde and ammonium chloride led to the formation of a tertiary amine.[1] In 1917, C. Mannich also isolated a tertiary amine by exposing antipyrine to identical conditions and recognized the generality of this reaction.[2,3] The condensation of a CH-activated compound (usually an aldehyde or ketone) with a primary or secondary amine (or ammonia) and a non-enolizable aldehyde (or ketone) to afford aminoalkylated derivatives is known as the *Mannich reaction*. More generally, it is the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines. The product of the reaction is a substituted β-amino carbonyl compound, which is often referred to as the Mannich base. The general features of the reaction are: 1) the CH-activated component (activated at their α-position) is usually an aliphatic or aromatic aldehyde or ketone, carboxylic acid derivatives, β-dicarbonyl compounds, nitroalkanes, electron-rich aromatic compounds[12] such as phenols (activated at their *ortho* position) and terminal alkynes;[13] 2) only primary and secondary aliphatic amines or their hydrochloride salts can be used since aromatic amines tend not to react; 3) the non-enolizable carbonyl compound is most often formaldehyde; 4) when the amine component is a primary amine, the initially formed β-amino carbonyl compound can undergo further reaction to eventually yield a *N,N*-dialkyl derivative (a tertiary amine); however, with secondary amines overalkylation is not an issue; 5) the reaction medium is usually a protic solvent such as ethanol, methanol, water, or acetic acid to ensure sufficiently high concentration of the electrophilic iminium ion, which is responsible for the aminoalkylation; 6) unsymmetrical ketones usually give rise to regioisomeric Mannich bases, but the product derived from the aminoalkylation of the more substituted α-position tends to be dominant; and 7) Mannich bases are useful synthetic intermediates, since they can undergo a variety of transformations: β-elimination to afford α,β-unsaturated carbonyl compounds (Michael acceptors), reaction with organolithium, or Grignard reagents to yield β-amino alcohols and substitution of the dialkylamino group with nucleophiles to generate functionalized carbonyl compounds. There have been several improvements to the original three-component *Mannich reaction.* The use of preformed iminium salts is the most significant modification because it allows faster, more regioselective, and even stereoselective transformations under very mild conditions.[18]

Tollens and von Marle (1903):



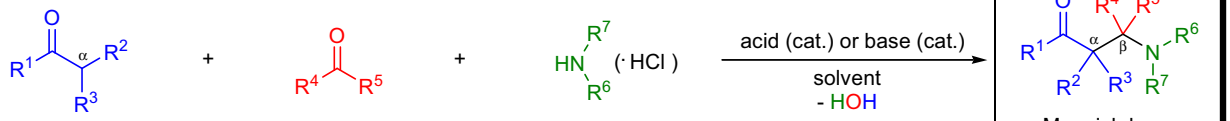
acetophenone — 3° amine

Mannich (1917):



antipyrine — 3° amine

Mannich reaction:



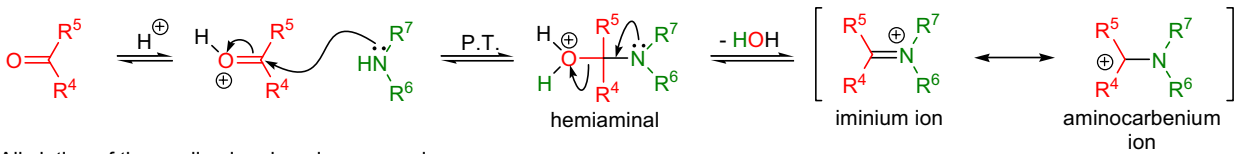
enolizable carbonyl compound + non-enolizable aldehyde or ketone + 1° or 2° amine or its hydrochloride → Mannich base

R^1 = H, alkyl, aryl, OR; R^{2-3} = H, alkyl, aryl; R^{4-5} = H, alkyl, aryl; R^6 = H, alkyl, OH, NH_2; R^7 = H, alkyl; solvent = ROH, H_2O, AcOH

Mechanism:[6,50,12-14]

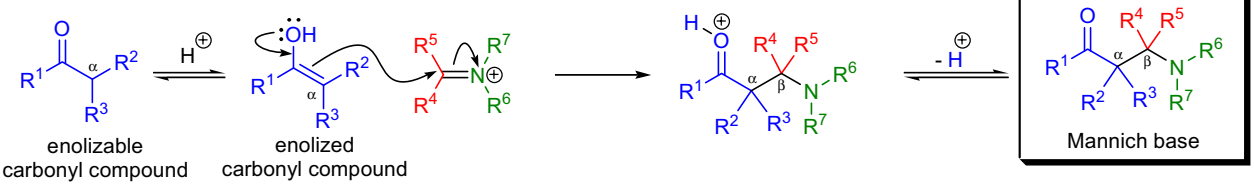
The mechanism of the *Mannich reaction* has been extensively investigated. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion.[50] This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its α-carbon in an *aldol-type reaction* to give rise to the Mannich base.

Formation of the reactive iminium ion under acidic conditions:



hemiaminal — iminium ion — aminocarbenium ion

Alkylation of the enolized carbonyl compound:

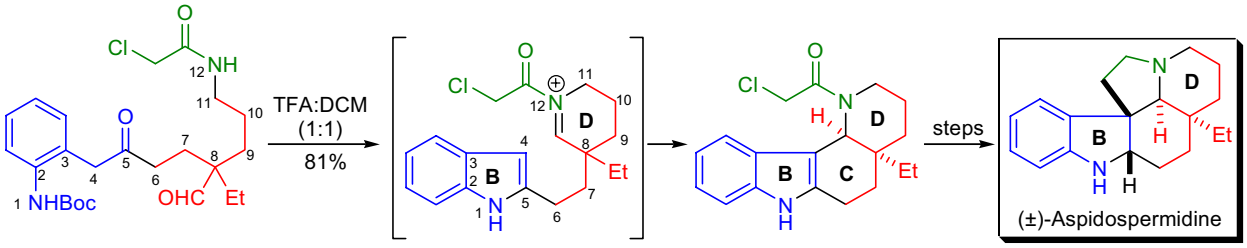


enolizable carbonyl compound — enolized carbonyl compound — Mannich base

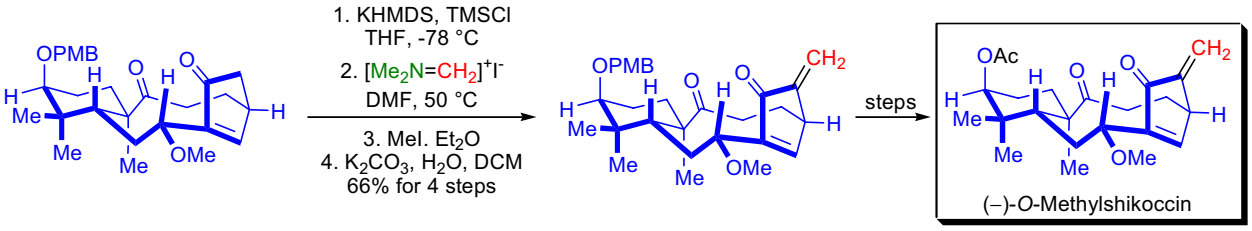
MANNICH REACTION

Synthetic Applications:

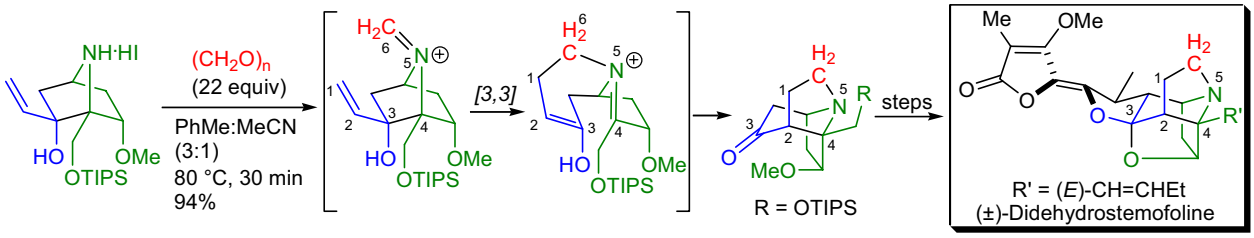
The total synthesis of (±)-aspidospermidine was accomplished by C.H. Heathcock and co-workers.[51] The synthetic strategy relied on an intramolecular cascade reaction, which simultaneously formed the B, C, and D rings of the natural product. As we mentioned previously, the CH-activated component of the *Mannich reaction* can also be an electron-rich aromatic ring such as an indole. The starting material was subjected to TFA in dichloromethane which first resulted in the formation of an indole (B ring) and an acylammonium ion (D ring) that *in situ* underwent an *intramolecular Mannich-type cyclization* giving rise to the C ring.



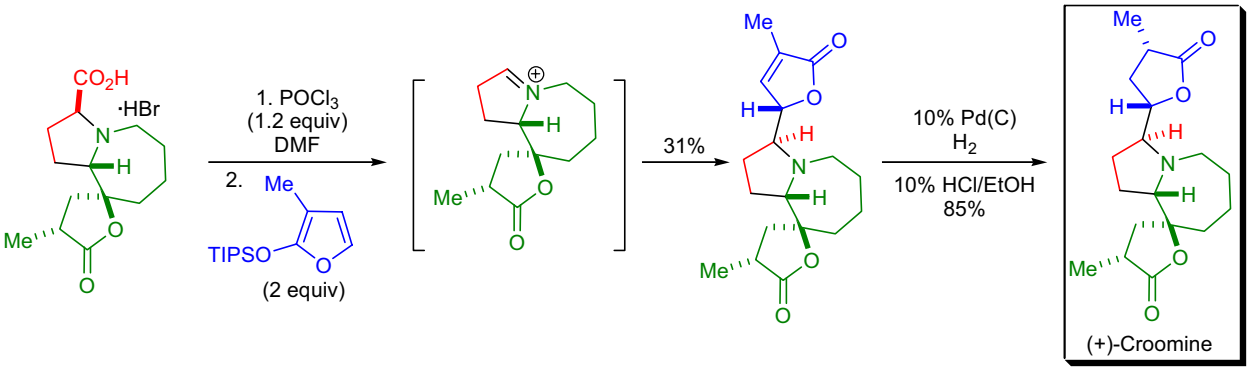
When preformed iminium salts are utilized in *Mannich reactions*, the reaction medium no longer needs to be a protic solvent, so the use of aprotic solvents allows the transformation of sensitive intermediates such as metal enolates. L.A. Paquette et al. carried out the highly regioselective introduction of an *exo*-methylene functionality during the total synthesis of (–)-*O*-methylshikoccin by reacting a potassium enolate with the Eschenmoser salt.[52] The resulting β-*N,N*-dimethylamino ketone was converted to the corresponding quaternary ammonium salt and elimination afforded the desired α,β-unsaturated ketone (*Eschenmoser methenylation*).



One of the most well-known applications of the *Mannich reaction* is its use in a tandem fashion with the *aza-Cope rearrangement* to form heterocycles. This reaction was the cornerstone of the strategy in the research group of L.E. Overman during the total synthesis of (±)-didehydrostemofoline (asparagamine A).[53] The bicyclic amine hydrogen iodide salt was exposed to excess paraformaldehyde, which led to the formation of the first iminium ion intermediate that underwent a facile *[3,3]-sigmatropic rearrangemen*t. The resulting isomeric iminium ion spontaneously reacted with the enol in an *intramolecular Mannich cyclization*.



In the laboratory of S.F. Martin, the *vinylogous Mannich reaction* (VMR) of a 2-silyloxyfuran with a regioselectively generated iminium ion was utilized as the key step in the enantioselective construction of (+)-croomine.[54,55] The carboxylic acid moiety of the starting material was converted to the acid chloride which spontaneously underwent decarbonylation to give the corresponding iminium ion. Reaction of this iminium ion with the 2-silyloxyfuran afforded the desired *threo* butenolide isomer as the major product.



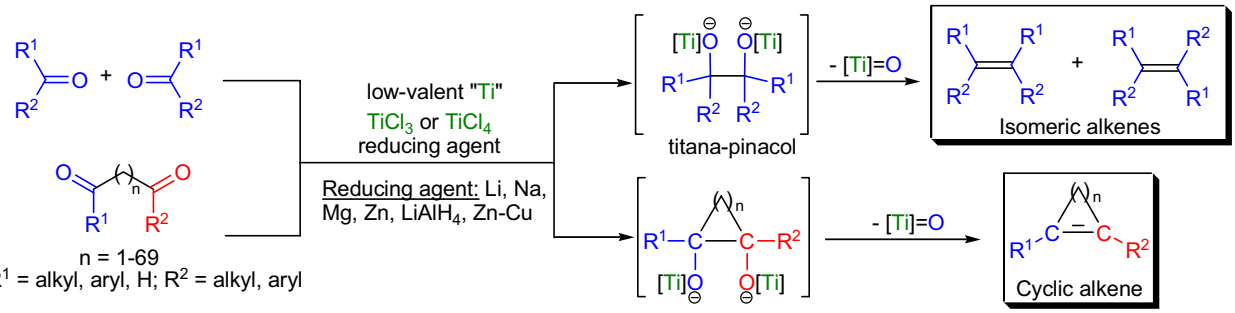
McMURRY COUPLING

(References are on page 624)

Importance:

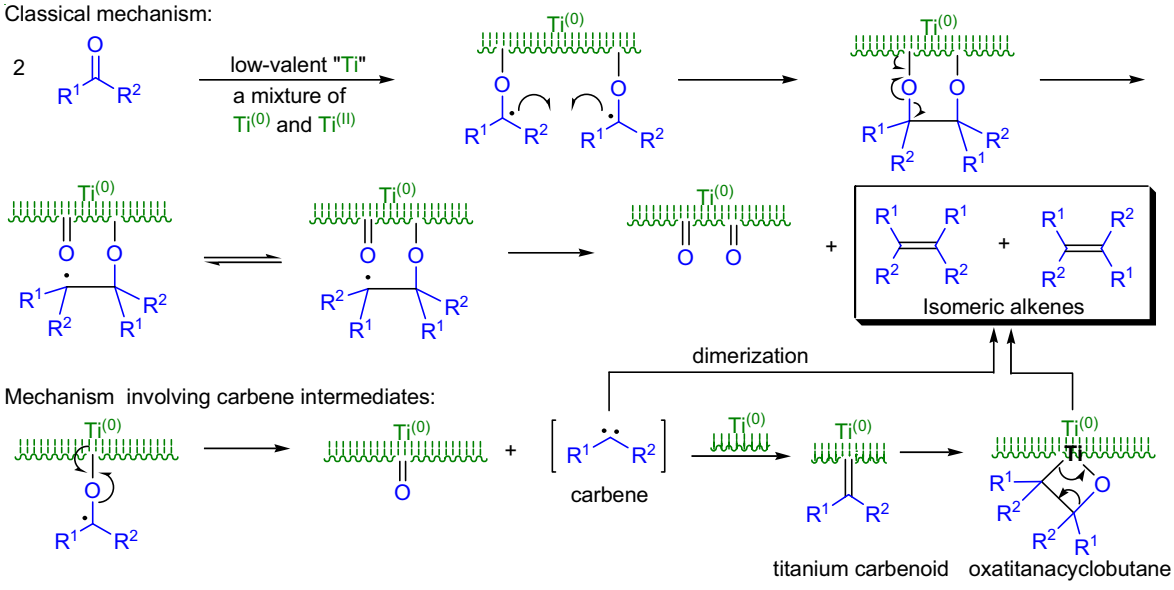
[*Seminal Publications*[1-5]*; Reviews*[6-19]*; Modifications & Improvements*[20-28]*; Theoretical Studies*[29]]

In the early 1970s, the research groups of T. Mukaiyama,[3] S. Tyrlik,[4] and J.E. McMurry[5] independently discovered that the treatment of carbonyl compounds with low-valent titanium led to olefinic coupled products. In the following years, McMurry investigated the scope and limitation of the process,[20] and today the reductive coupling of carbonyl compounds using low-valent titanium complexes to form the corresponding alkenes is known as the *McMurry coupling*. The general features of this coupling reaction are: 1) it is used most often for the homocoupling of aldehydes and ketones to afford alkenes. However, mixed coupling is feasible if one component is used in excess or one of the coupling partners is a diaryl ketone; 2) the low-valent titanium reducing agent can be prepared in many ways but the most common is the reduction of $TiCl_3$ with a zinc-copper couple (Zn-Cu) in DME;[20] 3) if the reaction is conducted at low temperature, the pinacol intermediate may be isolated; 4) at high temperature the alkenes are formed directly; 5) sterically hindered and/or strained olefins, which cannot be prepared by other means, are formed in high yield; 6) even sterically hindered tetrasubstituted alkenes can be prepared; 7) macrocyclization under high-dilution conditions is successful for the synthesis of medium and large rings and the yields are independent of the ring size unlike in other macrocyclizations (e.g., *acyloin condensation*); 8) intramolecular reactions are the fastest for the formation of five- and six-membered rings and the formation of eight- or higher-membered rings is considerably slower; 9) the reaction conditions do not tolerate the presence of easily reducible functional groups (e.g., epoxides, α-halo ketones, unprotected 1,2-diols; allylic and benzylic alcohols, quinones, halohydrins, aromatic and aliphatic nitro compounds, oximes, and sulfoxides), but most other functional groups are compatible; 10) aldehydes react much faster than ketones so the coupling of two aldehydes in the presence of a ketone can be performed chemoselectively; 11) the alkene product is formed with poor stereoselectivity, although there is a slight preference for the formation of (*E*)-alkenes in intermolecular reactions; and 12) in the presence of a chlorosilane the *McMurry reaction* becomes catalytic.[18]



Mechanism:[30,20,31-38,13,39,40]

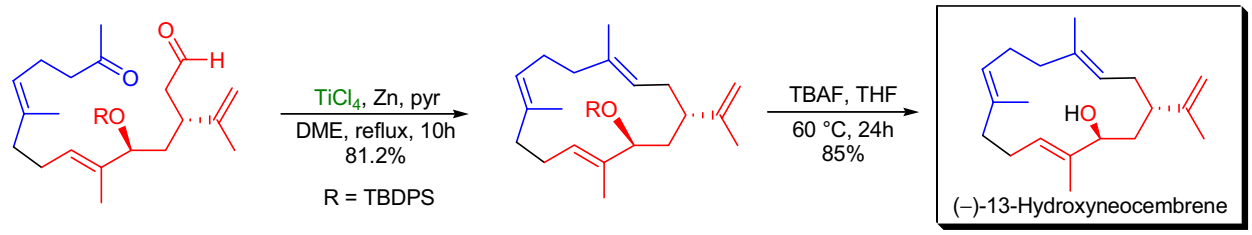
The mechanism of the *McMurry coupling* is not entirely clear, but it is composed of two distinct steps: 1) pinacol formation and 2) deoxygenation to the alkene. Extensive research showed that the low-valent titanium is most likely a mixture of $Ti^{(II)}$ and $Ti^{(0)}$, and the ratio of these species depends on the method of preparation (solvent, temperature, reducing agent, etc.). Recent findings suggest that the reaction possibly involves the formation of a carbene or a metal carbenoid.[34-36,13] The nature of the intermediates is strongly dependent on the structure of the carbonyl substrate and the reaction conditions, which is why the reaction is "tricky" and yields are difficult to reproduce in the laboratory.



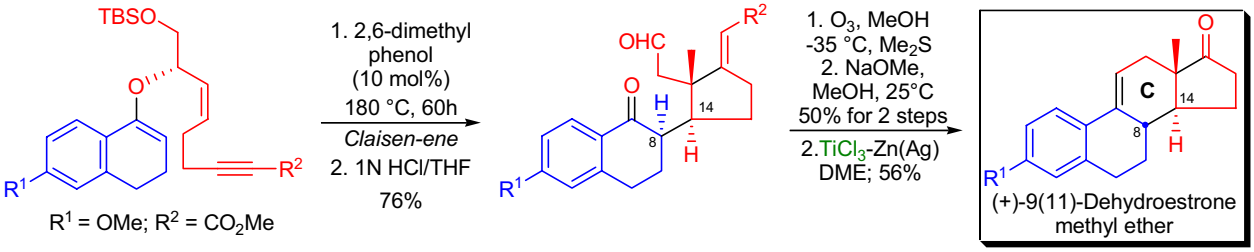
McMURRY COUPLING

Synthetic Applications:

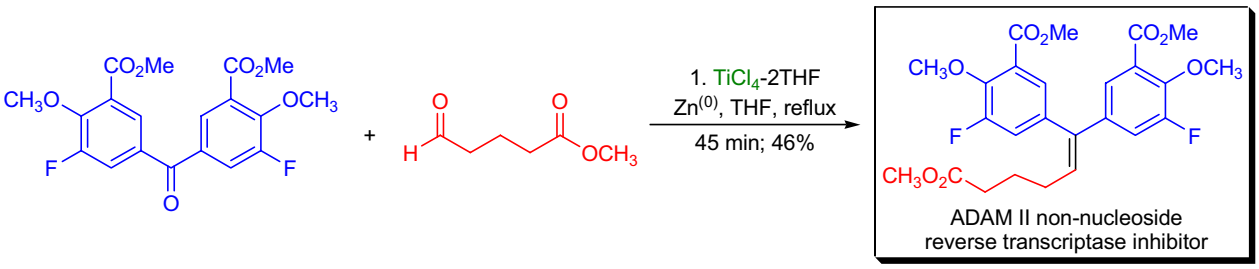
The first enantioselective total synthesis of (–)-13-hydroxyneocembrene using an *intramolecular McMurry coupling* as the key macrocyclization step was accomplished by Y. Li and co-workers.[41] To avoid any intermolecular coupling, high-dilution conditions were used. The cyclization precursor was added slowly *via* a syringe pump to a suspension of low-valent titanium reagent ($TiCl_4$/Zn) in refluxing DME. The reaction favored the formation of the (*E*)-olefin, the *E/Z* ratio was 2.5:1. The final step was the removal of the silyl protecting group with TBAF.



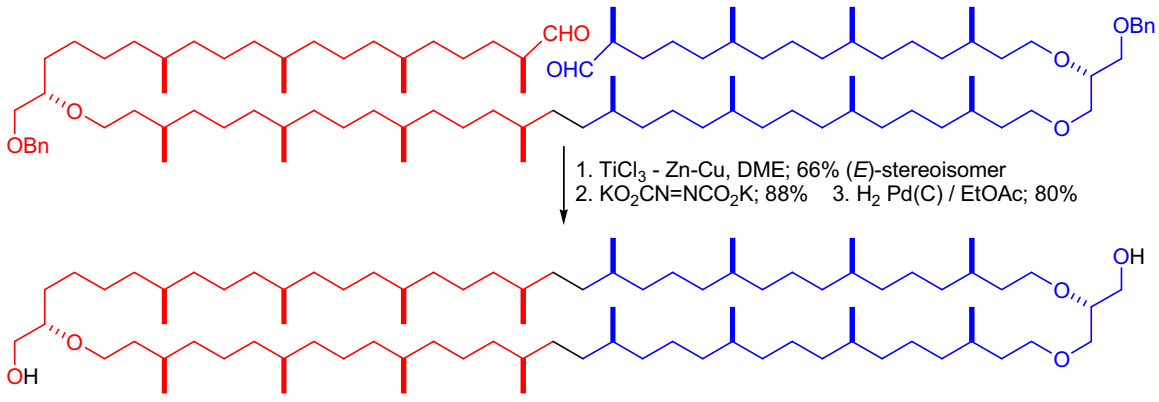
In the laboratory of T. Nakai, the asymmetric tandem *Claisen-rearrangement-ene reaction* sequence followed by a *modified McMurry coupling* was used to access (+)-9(11)-dehydroestrone methyl ether.[42] The Claisen-ene product was subjected to ozonolysis and epimerization to the 8,14-*anti* configuration. The C-ring was constructed by treating the tricyclic diketo aldehyde with $TiCl_3$-Zn(Ag) in DME to afford the desired final product in 56% yield.



Several ADAM (alkenyldiarylmethane) II non-nucleoside reverse transcriptase inhibitors were prepared by M. Cushman and co-workers.[43] The *McMurry reaction* was the key transformation that enabled the coupling of the diaryl ketone with a variety of aldehydes in good yield. The commercially available $TiCl_4$-THF (2:1) and zinc dust was used to prepare the low-valent titanium reagent in refluxing THF. To this suspension was added the diaryl ketone and the aldehyde successively.



The impressive synthetic power of the *McMurry coupling* was demonstrated by K. Kakinuma et al. when they synthesized archaeal 72-membered macrocyclic lipids.[44] The final macrocyclization between the dialdehyde proceeded in 66% yield, giving rise to a single diastereomer.



MEERWEIN ARYLATION

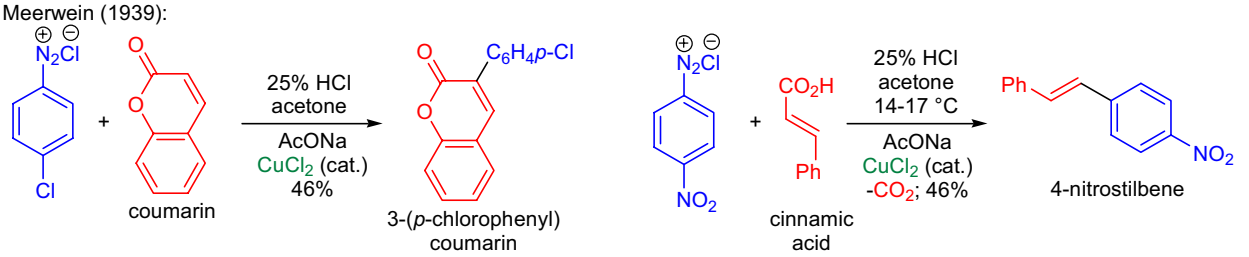
(References are on page 625)

Importance:

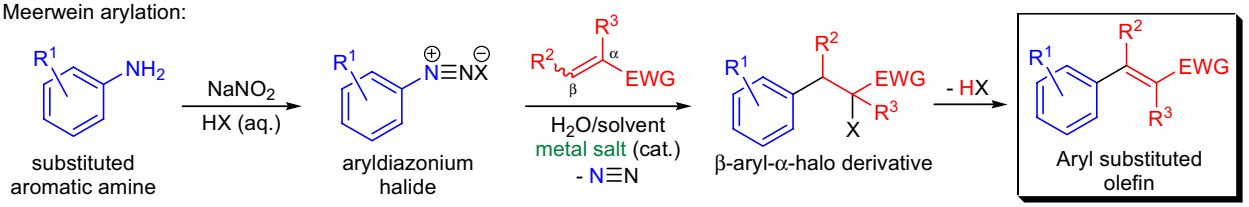
[*Seminal Publications*[1]; *Reviews*[2-7]; *Modifications & Improvements*[8-18]; *Theoretical Studies*[19-21]]

In 1939, H. Meerwein and co-workers reported in an extensive study that aromatic diazo compounds reacted with α,β-unsaturated carbonyl compounds in which the aryl group added across the double bond and a molecule of nitrogen was lost.[1] In one experiment, coumarin was reacted with *p*-chlorodiazonium chloride in the presence of catalytic amounts of copper(II)chloride, and the corresponding 3-(*p*-chlorophenyl)coumarin was isolated in moderate yield. When the unsaturated reaction partner was cinnamic acid, a molecule of carbon dioxide was lost in addition to nitrogen and the product was the corresponding styrene derivative. The arylation of substituted alkenes with aryldiazonium halides (formally the addition of an aryl halide to a carbon-carbon double bond) in the presence of a metal salt catalyst is known as the *Meerwein arylation*. The general features of this reaction are: 1) the procedure is simple; no special laboratory equipment is needed; 2) the aryldiazonium halides are prepared by the diazotization of aromatic amines using sodium nitrite and aqueous hydrohalic acids and are not isolated, rather immediately reacted with the alkenes in the presence of an organic solvent (e.g., acetone, acetonitrile); 3) the presence of electron-withdrawing substituents on the aromatic ring tends to increase the yield, whereas electron-donating groups often give lower yields; 4) the alkene component usually has an electron-withdrawing substituent and mostly α,β-unsaturated carbonyl compounds are used; 5) if there are two electron-withdrawing substituents on the double bond, and they are attached to the same carbon and then the aryl group will add to the other sp^2 hydbridized carbon atom; 6) when each of the olefin carbon atoms has an electron-withdrawing substituent, regioisomeric products may be formed; however, the major product will arise from the most resonance stabilized radical intermediate; 7) cinnamic acids and maleic acids are arylated at the α-carbon, and the reaction is accompanied by decarboxylation which is a pH-dependent process; 8) alkynes with electron-withdrawing substituents also react, but the yields are often poor; 9) furan derivatives are arylated with ease under the reaction conditions; and 10) the initial product of the reaction is a substitution product (alkyl halide), which can be dehydrohalogenated under basic conditions to afford the corresponding aryl substituted olefin. The *Meerwein arylation* is not free of side reactions (e.g., *Sandmeyer reaction,* formation of azo compounds, etc.), which are the primary cause of the often moderate product yields.

Meerwein (1939):



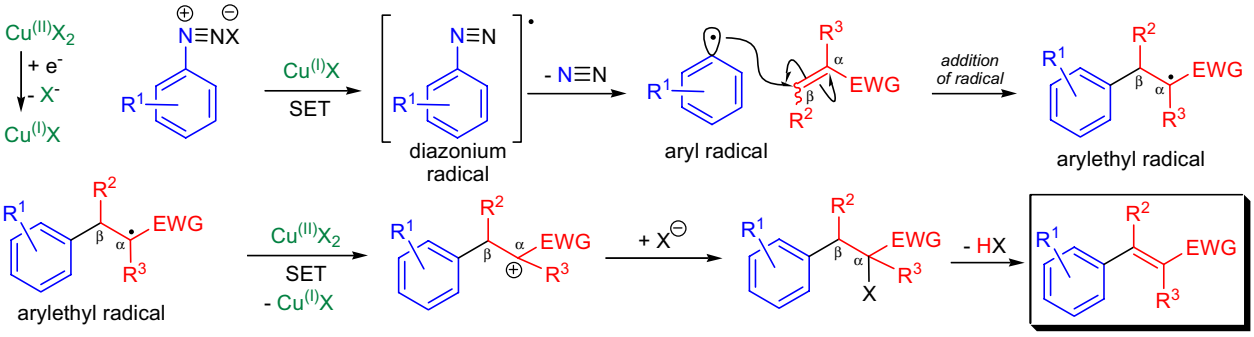
Meerwein arylation:



R^1 = H, alkyl, aryl, *O*-alkyl, Cl, Br, I, CO_2-alkyl, CONHR, SO_2R, NO_2, CF_3; R^{2-3} = H, alkyl, aryl; EWG = CHO, CO-alkyl, CO_2-alkyl, CO_2H, CO_2NH_2, CO_2NR_2, CN, alkenyl, Cl, Br; HX: HCl, HBr; solvent: acetone, acetonitrile; metal salt: $CuCl_2$, $CuBr_2$

Mechanism:[22-24,4,21]

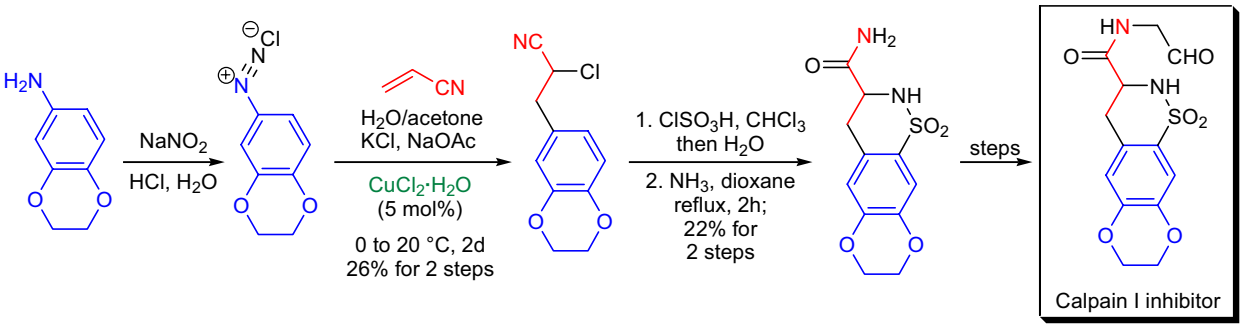
The mechanism of the *Meerwein arylation* is not completely understood. In his seminal paper, Meerwein proposed the involvement of aryl cations, however, this hypothesis was soon eliminated when J.K. Kochi suggested that aryl radicals are formed under the reaction conditions.[22] The actual catalyst is a copper(I) species, which is formed *in situ* from copper(II) salts and carbonyl compounds (e.g., acetone which is often used as a solvent).[23]



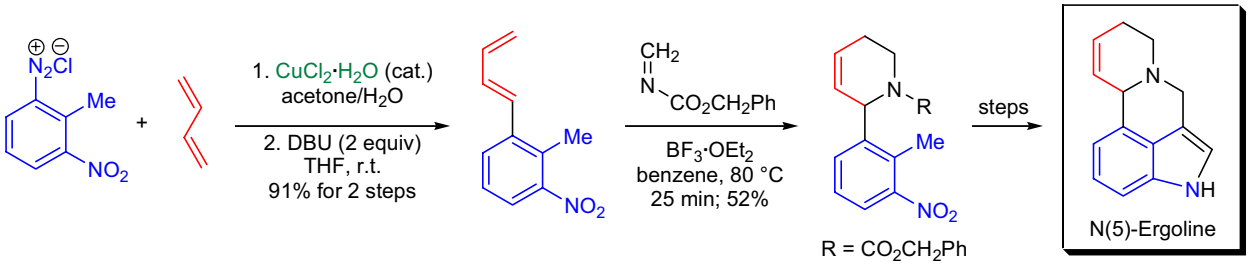
MEERWEIN ARYLATION

Synthetic Applications:

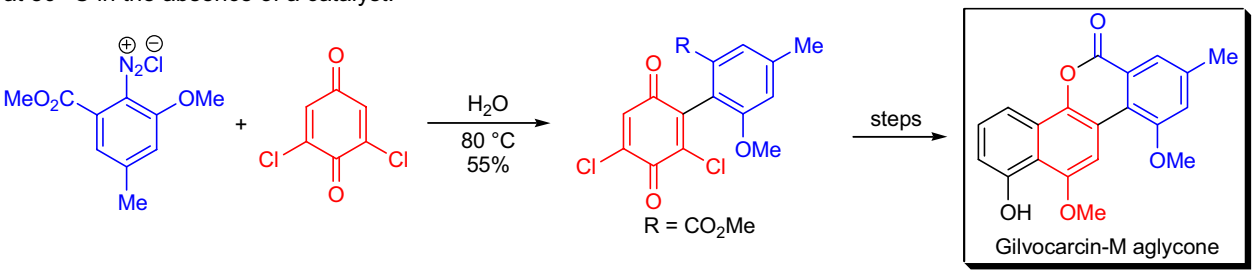
In the laboratory of R. Bihovsky, a series of peptide mimetic aldehyde inhibitors of calpain I was prepared in which the P_2 and P_3 amino acids were replaced with substituted 3,4-dihydro-1,2-benzothiazine-3-carboxylate-1,1-dioxides.[25] The synthesis began with the diazotization of the substituted aniline substrate using sodium nitrite and hydrochloric acid. The aqueous solution of the corresponding diazonium chloride product was added dropwise to the solution of acrylonitrile in a water-acetone mixture, which contained catalytic amounts of copper(II) chloride. This *Meerwein arylation* step afforded the chloronitrile derivative, which was subjected to sulfonation with chlorosulfonic acid, and the resulting sulfonyl chloride was treated with the solution of ammonia in dioxane to give the desired 3,4-dihydro-1,2-benzothiazine-2-carboxamide.



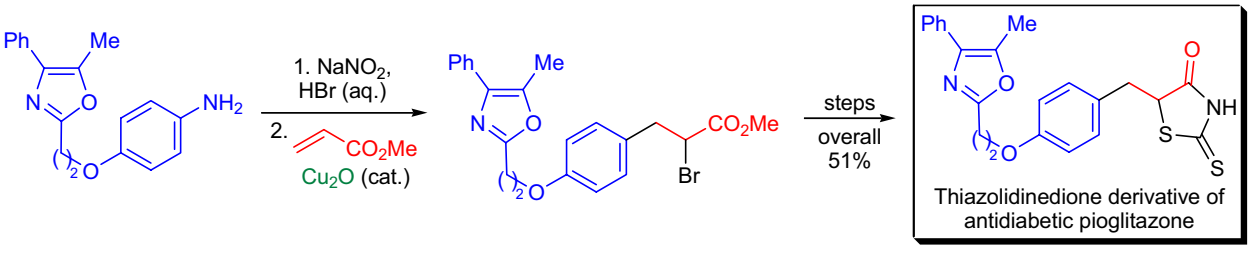
The research team of J.E. Baldwin developed the first synthetic sequence for the preparation of N(5)-ergolines.[26] The key step was a *hetero-Diels-Alder reaction* of a substituted phenyl butadiene to form the piperidine ring. The phenyl butadiene substrate was prepared *via* the *Meerwein arylation* of 1,4-butadiene and a diazonium salt derived from 2,6-dinitrotoluene. The initially formed chlorinated product was subjected to dehydrochlorination using DBU as the base.



The synthesis of the aglycone of the antibiotic gilvocarcin-M was accomplished by T.C. McKenzie et al. by a sequential *Meerwein arylation-Diels-Alder cycloaddition*.[27] The anthranilic methyl ester substrate was first subjected to diazotization and then the resulting diazonium chloride was coupled to 2,6-dichlorobenzoquinone in water to afford the quinone product in moderate yield. It is important to mention that the *Meerwein arylation* was conducted in water at 80 C in the absence of a catalyst.



T. Sohda and co-workers prepared a series of novel thiazolidinedione derivatives of the potent antidiabetic pioglitazone (AD-4833, U-72, 107).[28] The *para*-substituted aniline was diazotized with $NaNO_2$/HBr, and the diazonium bromide was used to arylate methyl acrylate in the presence of copper(II) oxide. The bromopropionate product was first treated with thiourea, and the resulting iminothiazolidinone hydrolyzed with aqueous hydrochloric acid to afford the desired thiazolidinedione derivative.



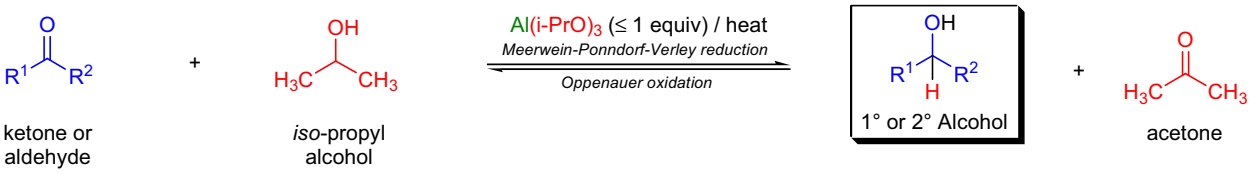
MEERWEIN-PONNDORF-VERLEY REDUCTION

(References are on page 626)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-18]; *Modifications & Improvements*[19-31]; *Theoretical Studies*[32,33]]

In the mid-1920s, three researchers independently described reduction of carbonyl compounds with the use of aluminum alkoxides: 1) in 1925, H. Meerwein successfully reduced aldehydes with ethanol in the presence of aluminum ethoxide;[1] 2) during the same year, A. Verley reduced ketones with aluminum ethoxide as well as aluminum isopropoxide but found that sterically hindered ketones (e.g., camphor) reacted very slowly;[2] and 3) in 1926, W. Ponndorf demonstrated that the reduction of aldehydes and ketones was general for a variety of metal alkoxides (e.g., alkali metal and aluminum alkoxides) derived from secondary alcohols, and he found the process completely reversible.[3] The reduction of aldehydes and ketones by metal alkoxides (mainly by aluminum isopropoxide) is known as the *Meerwein-Ponndorf-Verley reduction* (*MPV reduction*).[34] The reverse reaction, the oxidation of alcohols to aldehydes and ketones, is referred to as the *Oppenauer oxidation*. The general features of the *MPV reduction* are: 1) the reaction is completely reversible and the removal of the low boiling ketone or the addition of excess isopropyl alcohol shifts the equilibrium to the right according to *Le Chatelier's principle*; 2) the reduction takes place in boiling isopropanol under mild conditions, and it is very chemoselective for aldehydes and ketones, whereas other functional groups (e.g., double bond, esters, acetals, etc.) remain unchanged, and this is the greatest advantage over the use of metal hydride reducing agents; 3) the most popular metal alkoxides are aluminum alkoxides, and these are often used in stoichiometric amounts (one or more equivalents for ketones), but Ln(III) alkoxides (e.g., Sm(O*t*-Bu)I_2) can be applied in catalytic amounts;[21,22] 4) aluminum alkoxides are readily soluble in both alcohols and hydrocarbon solvents, whereas other metal alkoxides have limited solubility; 5) aldehydes react faster than ketones; 6) keto aldehydes are reduced to hydroxy ketones, whereas α,β-unsaturated aldehydes and ketones give the corresponding allylic alcohols; 7) cyclic diketones usually give rise to hydroxyl ketones unless an aromatic ring can be formed *via hydrogen transfer*; 8) β-diketones or β-keto esters cannot be reduced due to the formation of stable β-enolate chelate complexes with metal alkoxides, but when these compounds do not have enolizable hydrogens at the α-position, the reduction proceeds smoothly; 9) the method is sensitive to steric hindrance, so sterically hindered ketones and aldehydes are reduced more slowly than unhindered ones; 10) to increase the rate of reduction for slow reactions, the alcohol solvents may be mixed with higher boiling solvents (e.g., toluene, xylene) or multiple equivalents of aluminum alkoxide should be applied; 11) the reaction rate is significantly increased by the addition of protic acids (e.g., TFA, HCl, propionic acid);[19,24,25] 12) in rigid cyclic substrates, the reduction proceeds with high diastereoselectivity; 13) catalytic asymmetric versions are known, but currently only the *intramolecular asymmetric MVP reduction* gives high *ee*'s;[15] and 14) both small-, and large-scale reduction can be carried out with ease (few milligrams to several hundred grams). The most important side reactions are: 1) *aldol condensation* of aldehyde substrates, which have an α-hydrogen atom to form β-hydroxy aldehydes and/or α,β-unsaturated aldehydes, but with ketones this side reaction is not common; 2) *Tishchenko reaction* of aldehyde substrates with no α-hydrogen atom, but this can be suppressed by the use of anhydrous solvents; 3) dehydration of the product alcohol to an olefin, especially at high temperature; and 4) the migration of the double bond during the reduction of α,β-unsaturated ketones.

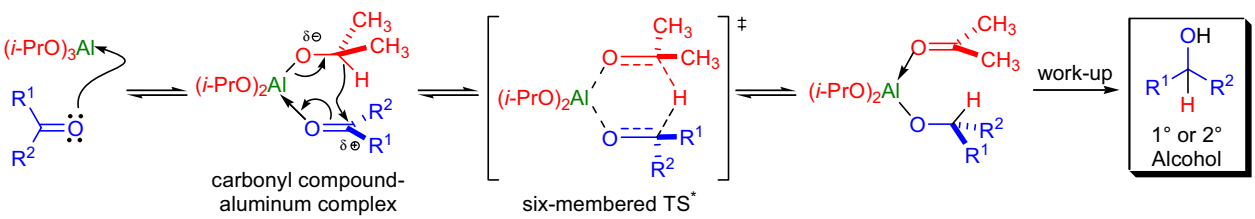


ketone or aldehyde + *iso*-propyl alcohol ⇌ 1° or 2° Alcohol + acetone

R^1 = alkyl, aryl, alkenyl; R^2 = H, alkyl, aryl, alkenyl

Mechanism:[35-40,19,41-48]

The currently accepted concerted mechanism that goes through a chairlike six-membered transition state was first proposed by Woodward.[35] The special activity of aluminum alkoxides for the *MVP reduction* can be explained as a result of the activation of both the hydride donor and the hydride acceptor. For aromatic ketones the involvement of radicals was suggested, but for aliphatic carbonyl compounds there is no evidence for a SET mechanism.[44]

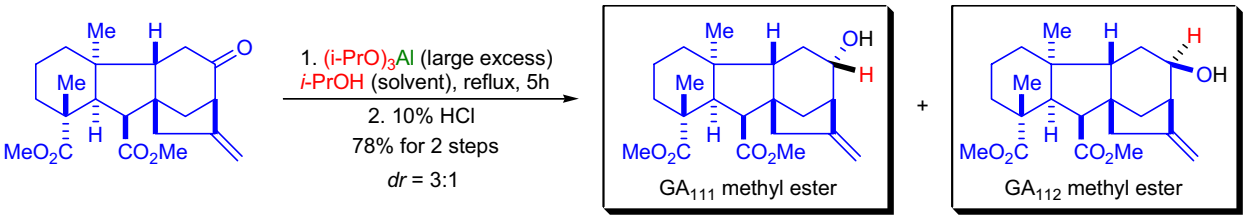


carbonyl compound-aluminum complex — six-membered TS‡

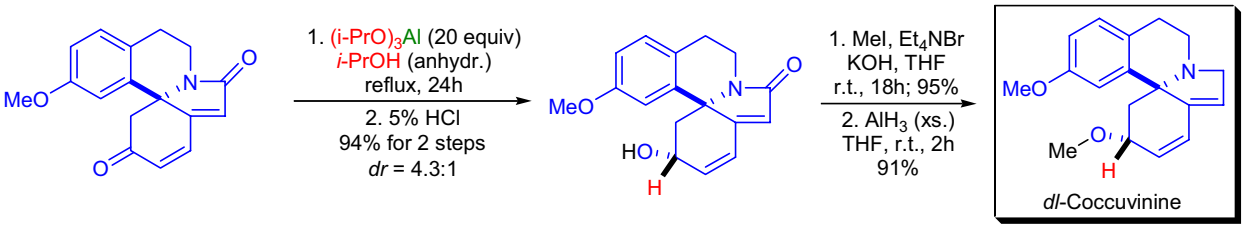
MEERWEIN-PONNDORF-VERLEY REDUCTION

Synthetic Applications:

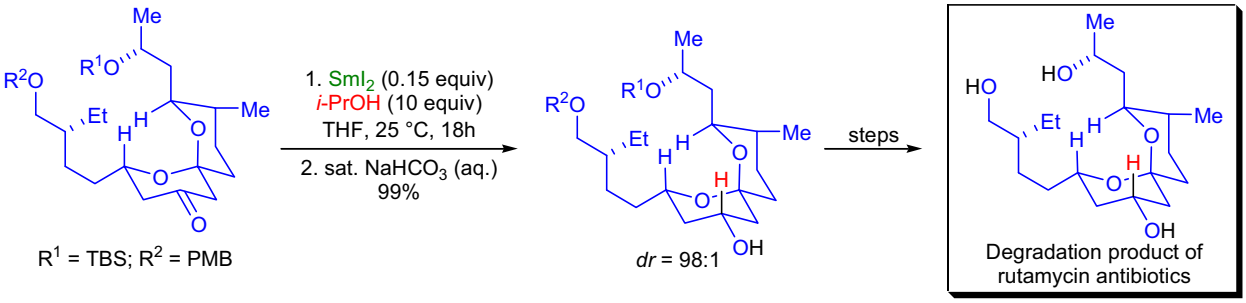
The highly stereoselective formal total synthesis of GA_{111} and GA_{112} methyl esters was accomplished using the combination of a *Pd-catalyzed cycloalkenylation reaction* and *inverse-electron demand Diels-Alder cycloaddition* in the laboratory of M. Ihara.[49] The final step of the synthesis was the reduction of the tetracyclic ketone to obtain both diastereomers of the corresponding secondary alcohols. It was found, however, that the hydride reduction of this ketone gave GA_{112} methyl ester exclusively as a single diastereomer. When the reduction was carried out in the presence of large excess of aluminum isopropoxide, both diastereomers were formed, but the GA_{111} methyl ester was the major product.



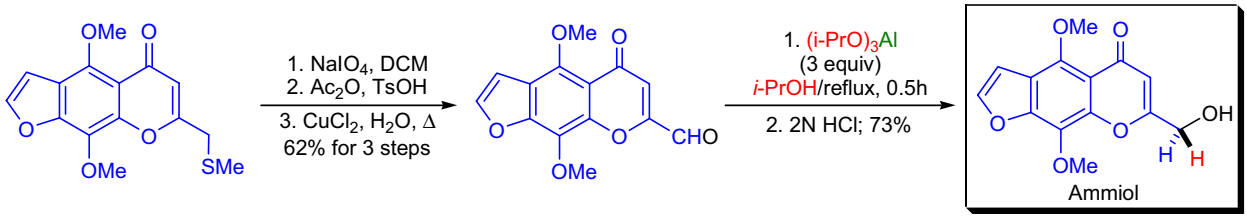
The *MPV reduction* was used in a highly stereoselective fashion during the final stages of the total synthesis of *dl*-coccuvinine and *dl*-coccolinine by T. Sano et al.[50] The α,β-unsaturated ketone moiety was selectively reduced in the presence of an α,β-unsaturated lactam to give the β-allylic alcohol in good yield. The methylation of the allylic alcohol under phase-transfer conditions (*Williamson ether synthesis*) was followed by the reduction of the lactam carbonyl group to the corresponding methylene group with excess allane to afford the natural product.



The absolute stereochemistry of the rutamycin antibiotics was established through asymmetric synthesis of the known bicyclic degradation product by D.A. Evans and co-workers.[51] The introduction of the equatorial secondary alcohol functionality turned out to be problematic when traditional metal hydrides were used for the reduction of the ketone. For example, $LiAlH_4$ gave only a 1:1 mixture of axial and equatorial diastereomers. The use of the *samarium(II)-catalyzed MVP reduction* gave a 98:1 mixture of diastereomers favoring the equatorial alcohol. Subsequent examination of this highly stereoselective reduction revealed that the reaction operated under kinetic control, and the observed product was formed due to the coordination of the reducing agent to the axial spiroketal oxygen atom.



The synthesis of the rare furochromone ammiol was achieved by R.B. Gammill starting from (methylthio)furochromone in four steps.[52] The last step was the selective conversion of the aldehyde moiety of a six-membered 1,4-dicarbonyl compound using the *MVP reduction*.



MEISENHEIMER REARRANGEMENT

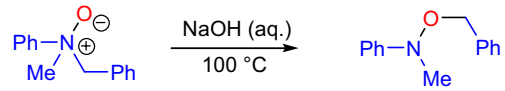
(References are on page 627)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-5]*; Modifications & Improvements*[6-13]*; Theoretical Studies*[14-17]]

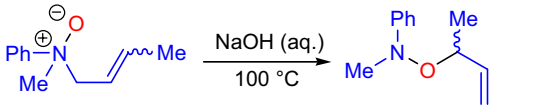
In 1919, J. Meisenheimer reported that upon heating in an aqueous sodium hydroxide solution, *N*-benzyl-*N*-methyl aniline-*N*-oxide underwent a facile isomerization to afford *O*-benzyl-*N*-methyl-*N*-phenyl hydroxylamine.[1] Three decades later, A.C. Cope and co-workers reinvestigated the rearrangement to explore its mechanism.[18] They discovered that the isomerization of *N*-crotyl-*N*-methyl aniline *N*-oxide occurred with the inversion of the allylic system to give *N*-methyl-*O*-(1-methyl-allyl)-*N*-phenylhydroxylamine. This result suggested that the isomerization occurred *via* a five-membered cyclic transition state analogous to the mechanism of the *Claisen rearrangement*. The thermal rearrangement of certain tertiary amine *N*-oxides to the corresponding *O*-substituted-*N,N*-disubstituted hydroxylamines is known as the *Meisenheimer rearrangement*. The general features of the reaction are: 1) the rearrangement takes place in both open-chain and cyclic systems; 2) the *[1,2]-* and *[2,3]-shift* of substituents are the two different modes of the transformation; 3) the *[1,2]-shift* occurs when one of the substituents is capable of stabilizing radicals (R^1 = benzyl, diphenylmethyl, etc.); 4) the *[2,3]-shift* is common when one of the substituents is allylic; 5) during the *[1,2]-shift*, the stereocenter on the migrating group suffers extensive racemization;[3] 6) the *[2,3]-shift* usually takes place much faster than the *[1,2]-shift* and the transfer of chirality of the migrating group is possible; 7) when any of the R^2,R^3 or R^6,R^7 are alkyl groups that have a hydrogen atom at their β-position, the *Cope elimination* becomes competitive; 8) the *N*-oxides of *N*-benzyl and *N*-allyl cyclic amines mainly undergo *[1,2]-shifts* to afford the corresponding *O*-benzyl and *O*-allyl hydroxylamines, respectively; 9) the *N*-oxides of 2-aryl-, 2-heteroaryl, and 2-vinyl cyclic amines predominantly undergo ring-enlargement to give 1,2-oxazaheterocycles; and10) the ring-enlargement is general for four- to ten-membered cyclic amine *N*-oxides.[5]

Meisenheimer (1919):



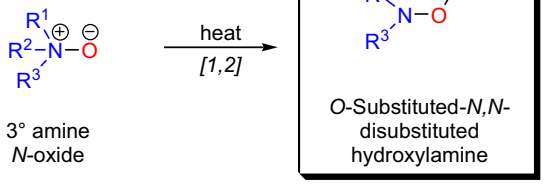
N-benzyl-*N*-methyl aniline-*N*-oxide → *O*-benzyl-*N*-methyl-*N*-phenylhydroxylamine

Cope and Kleinschmidt (1944):



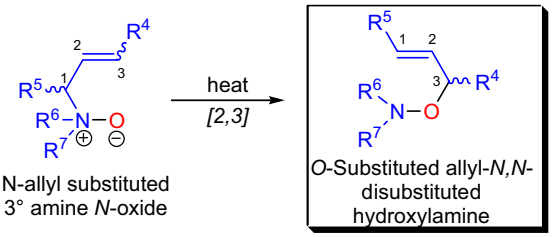
N-crotyl-*N*-methyl aniline-*N*-oxide → *N*-Methyl-*O*-(1-methyl-allyl)-*N*-phenyl-hydroxylamine

[1,2]-Meisenheimer rearrangement in acyclic systems:



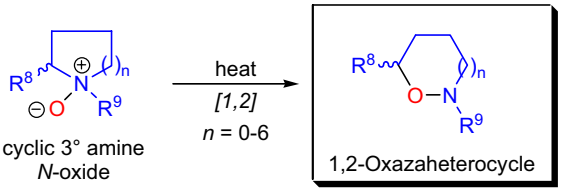
3° amine *N*-oxide → *O*-Substituted-*N,N*-disubstituted hydroxylamine

[2,3]-Meisenheimer rearrangement in acyclic systems:



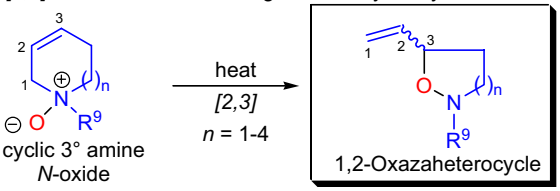
N-allyl substituted 3° amine *N*-oxide → *O*-Substituted allyl-*N,N*-disubstituted hydroxylamine

[1,2]-Meisenheimer rearrangement in cyclic systems:



cyclic 3° amine *N*-oxide → 1,2-Oxazaheterocycle

[2,3]-Meisenheimer rearrangement in cyclic systems:

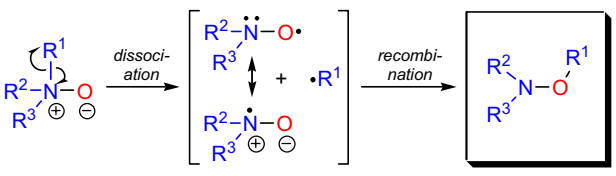


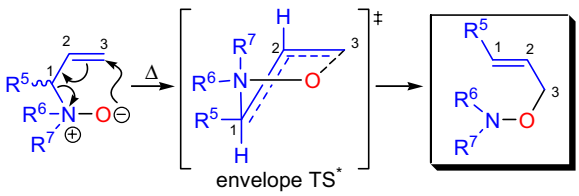
cyclic 3° amine *N*-oxide → 1,2-Oxazaheterocycle

R^1 = CH_2Ph, $CHPh_2$, CH_2Ar, allyl; R^{2-3} = alkyl with no β-hydrogen, aryl; R^{4-5} = H, alkyl, aryl; R^{6-7} = alkyl with no β-hydrogen, aryl; R^8 = alkenyl, aryl; R^9 = alkyl with no β-hydrogen

Mechanism:[18,3,19,20,6,13]

The *[1,2]-Meisenheimer rearrangement* most likely proceeds *via* a *homolytic dissociation-recombination* mechanism,[19] whereas the *[2,3]-Meisenheimer rearrangement* is a concerted sigmatropic process that goes through a five-membered envelopelike transition state.

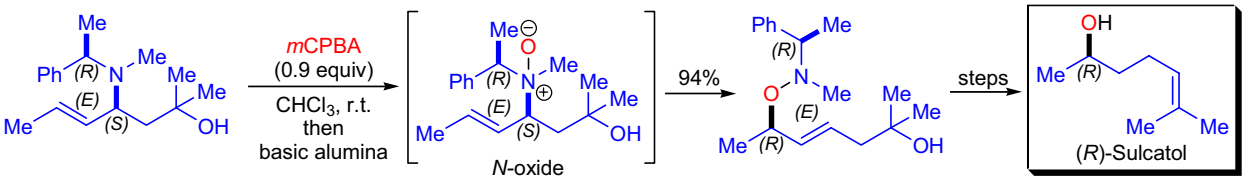




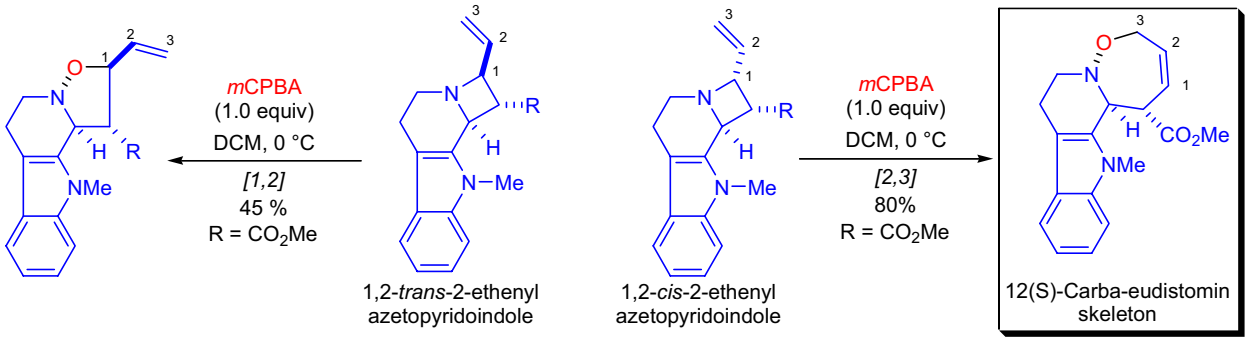
MEISENHEIMER REARRANGEMENT

Synthetic Applications:

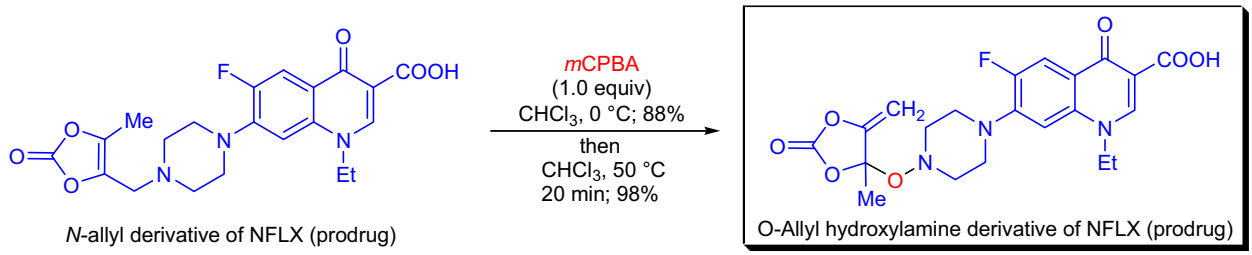
The natural product (*R*)-sulcatol is a male-produced aggregation pheromone of the ambrosia beetle. This insect can devastate entire forests when its population is out of control.[21] Various studies revealed that different species respond to the compound in different enantiomeric excess. The asymmetric synthesis of (*R*)-sulcatol was accomplished in the laboratory of S.G. Davies using a *stereospecific [2,3]-Meisenheimer rearrangement* as the key step. The treatment of the allylic amine substrate with *m*CPBA followed by the filtration of the reaction mixture through deactivated basic alumina afforded the desired hydroxylamine as a single diastereomer.



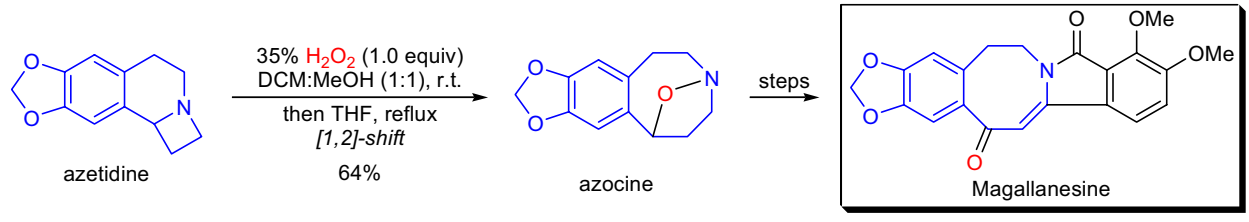
A new route to the 12(S)carba-eudistomin skeleton was developed by T. Kurihara et al.[22] The key substrate for this new route was a 1,2-*cis*-2-ethenylazetopyridoindole, which was readily oxidized at 0 °C to afford the corresponding *N*-oxide. This *N*-oxide spontaneously underwent a *[2,3]-Meisenheimer rearrangement* to afford the desired oxazepine derivative. Interestingly, when the 1,2-*trans*-2-ethenylazetopyridoindole was subjected to identical conditions, the *[1,2]-Meisenheimer rearrangement* occurred exclusively and gave rise to an isoxazolidine derivative.



In the laboratory of H. Kondo, various prodrugs of the clinically effective antibacterial agent norfloxacin (NFLX) were synthesized.[23] The *N*-masked derivatives of NFLX were efficiently unmasked *in vivo*, and they exhibited equal or higher activity than NFLX itself. In order to reveal the mode of action of these prodrugs, the *N*-allylic derivative of NFLX was subjected to *m*CPBA at low temperatures. The resulting *N*-oxide was then heated to bring about a *[2,3]-Meisenheimer rearrangement* to afford the corresponding *O*-allyl-hydroxylamine derivative. This hydroxylamine derivative also acted as a prodrug, since it liberated a higher concentration of NFLX in plasma and had a higher activity than NFLX itself.



The *[1,2]-Meisenheimer rearrangement* and a *Heck cyclization* were the key steps in T. Kurihara's synthesis of magallanesine.[24] The azetidine was exposed to H_2O_2, and the resulting azetidine *N*-oxide was refluxed in THF to afford the desired azocine derivative. Other usual oxidants such as *m*CPBA or MMPP gave rise to complex mixtures.



MEYER-SCHUSTER AND RUPE REARRANGEMENT

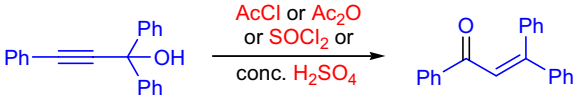
(References are on page 627)

Importance:

[*Seminal Publications*[1-7]*; Reviews*[8]*; Modifications & Improvements*[9-15]*; Theoretical Studies*[16-21]]

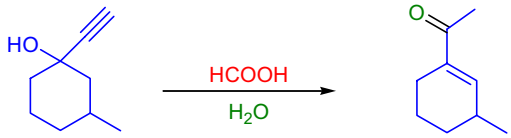
In 1922, K.H. Meyer and K. Schuster reported that the attempted conversion of 1,1,3-triphenyl-2-propynol to the corresponding ethyl ether with concentrated sulfuric acid and ethanol afforded 1,3,3-triphenyl propenone, an α,β-unsaturated ketone.[1] The authors showed that the use of other reagents such as acetic anhydride and acetyl chloride also brought about the same reaction. A few years later, H. Rupe and co-workers investigated the acid-catalyzed rearrangement of a large number of α-acetylenic (propargylic) alcohols.[2-7] The acid-catalyzed isomerization of secondary and tertiary propargylic alcohols, *via* a *[1,3]*-shift of the hydroxyl group, to the corresponding α,β-unsaturated aldehydes or ketones is known as the *Meyer-Schuster rearrangement*. The general features of this transformation are: 1) when the substrate contains a terminal alkyne, the product is an aldehyde, whereas substrates containing disubstituted alkynes yield ketones; 2) the substrates, 2° or 3° propargylic alcohols, may not have a proton at their α-position so that the initial propargylic cation can isomerize to an allenyl cation, which provides the product carbonyl compound; 3) the rearrangement can be catalyzed by both protic and Lewis acids under anhydrous or aqueous conditions. The related acid-catalyzed rearrangement of tertiary propargylic alcohols, *via* a formal *[1,2]*-shift of the hydroxyl group, yielding the corresponding α,β-unsaturated ketones is called the *Rupe rearrangement*. The most important features of this reaction are: 1) the product is always the α,β-unsaturated ketone regardless of the substitution of the triple bond; 2) the substrates are tertiary propargylic alcohols that have hydrogen atoms available at their α-position; 3) most often strong protic acids mixed with alcohol solvents are used to bring about the rearrangement, but certain Lewis acid such as mercury(II)-salts and even dehydrating agents ($SOCl_2$, P_2O_5, etc.) were shown to be effective; 4) the nature of the acid catalyst does not affect the course of the rearrangement. The disadvantages of the above two rearrangements are: 1) certain substrates may give rise to a mixture of *Rupe and Meyer-Schuster rearrangement* products; 2) low yields are observed when the product (especially aldehydes) undergoes self-condensation, or is readily oxidized under the reaction conditions; 3) acid-sensitive functionalities in the substrate may give undesired elimination products; and 4) the initial propargylic cation occasionally undergoes *Wagner-Meerwein or Nametkin rearrangement*.

Meyer and Schuster (1922):



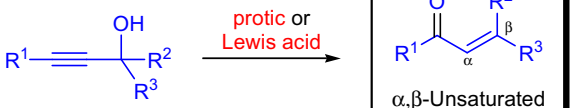
1,1,3-triphenyl-2-propynol — 1,3,3-triphenyl-propenone

Rupe (1924-1928):



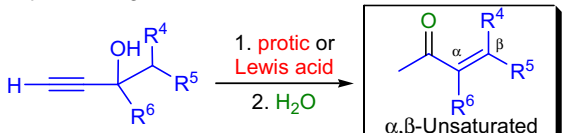
1-ethynyl-3-methyl-cyclohexanol — 1-(3-methyl-1-cyclohexenyl)-ethanone

Meyer-Schuster rearrangement:



2° or 3° propargylic alcohol — α,β-Unsaturated aldehyde or ketone

Rupe rearrangement:

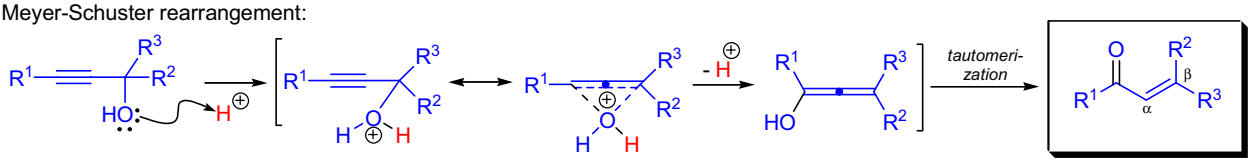


3° propargylic alcohol — α,β-Unsaturated ketone

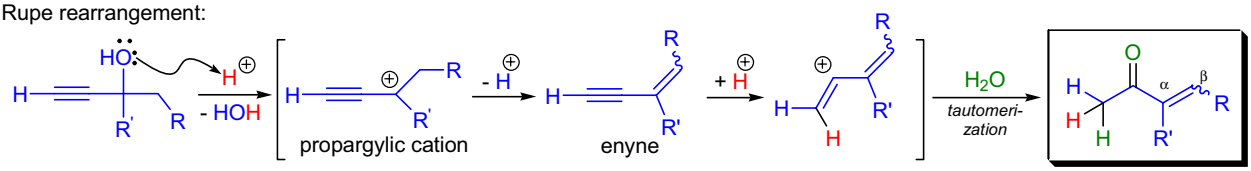
R^1 = H, alkyl, aryl; R^{2-3} = H, aryl or alkyl with no H atoms adjacent to the α-carbon; R^{4-6} = alkyl, aryl; protic acid: H_2SO_4, AcOH, HCO_2H, Dowex-50/HCO_2H, HCl/2-propanol, HCl/Et_2O, *p*-TsOH. etc.; Lewis acid: $HgSO_4$/EtOH, $POCl_3$/pyridine, $HgSO_4/H_2SO_4$

Mechanism:[22,8,23]

Meyer-Schuster rearrangement:



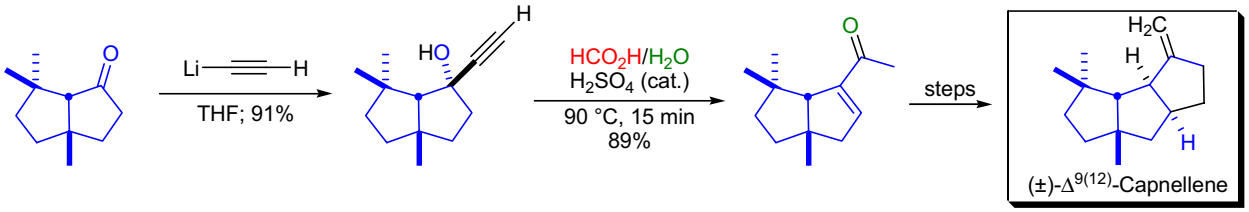
Rupe rearrangement:



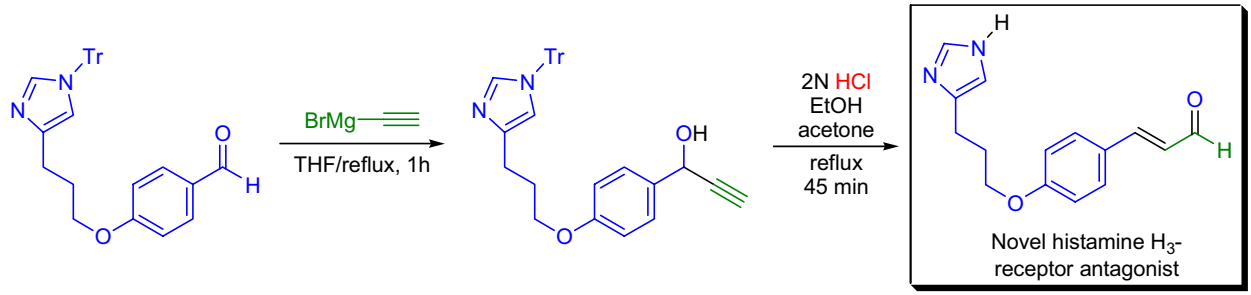
MEYER-SCHUSTER AND RUPE REARRANGEMENT

Synthetic Applications:

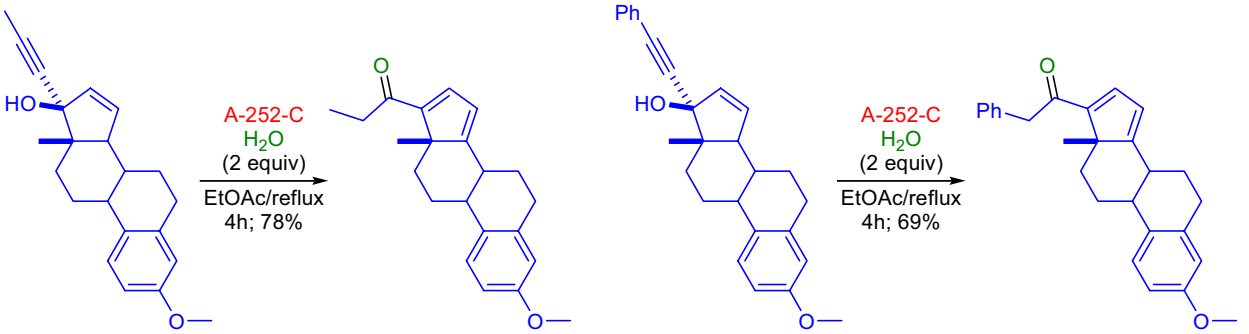
The first fully stereoselective total synthesis of the linear triquinane sesquiterpene (±)-capnellene was achieved by L.A. Paquette et al.[24] The C-ring is a fused cyclopentenone moiety, and the authors tried to assemble it using the *Nazarov cyclization*. However, the dienone precursor failed to undergo the cyclization under a variety of conditions, so an alternative strategy was sought that was based on the *Rupe rearrangement*. The treatment of the bicyclic tertiary propargylic alcohol substrate with formic acid and trace amounts of sulfuric acid afforded high yield of the α,β-unsaturated methyl ketone product. Interestingly, the double bond of the enone did not end up in the most substituted position as it is expected in most cases.



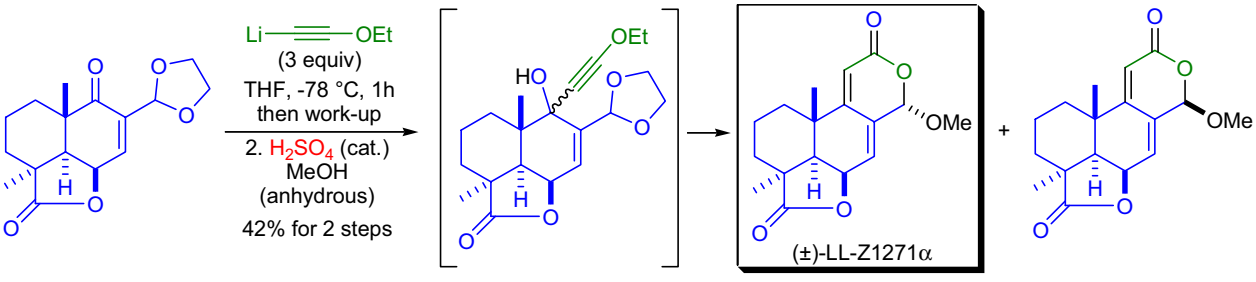
H. Stark and co-workers prepared novel histamine H_3-receptor antagonists with carbonyl-substituted 4-[(3-phenoxy)propyl]-1*H*-imidazole structures.[25] The *Meyer-Schuster rearrangement* was used for the synthesis of one of the compounds. The *p*-hydroxybenzaldehyde derivative was reacted with ethynylmagnesium bromide to afford a secondary propargylic alcohol. Upon hydrolysis with 2N HCl in a refluxing ethanol/acetone mixture, the corresponding *p*-hydroxy cinnamaldehyde was obtained.



One of the disadvantages of the *Rupe rearrangement* is the harsh reaction conditions needed, making it very difficult to adapt the reaction to large-scale synthesis of unsaturated ketones. The research team of H. Weinmann investigated the rearrangement of a steroidal tertiary propargylic alcohol using a variety of acid catalysts.[15] They found that the macroporous Amberlyst-type resin A-252C in refluxing ethyl acetate containing 2 equivalents of water were ideal for the rearrangement in a pilot plant on a 64 kg scale.



In the laboratory of S.C. Welch, the *Meyer-Schuster rearrangement* was the key step in the stereoselective total synthesis of the antifungal mold metabolite (±)-LL-Z1271α.[26] A tricyclic enone acetal was treated with lithium ethoxyacetylide, and the crude product was exposed to H_2SO_4 in anhydrous methanol, which brought about the rearrangement and afforded the desired product in 30% yield along with 12% of an epimer.



MICHAEL ADDITION/REACTION

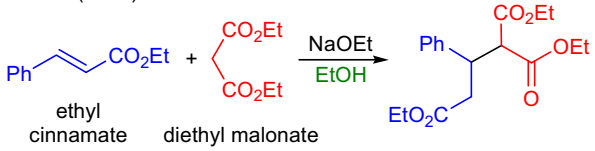
(References are on page 628)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-26]; *Modifications & Improvements*[27-46]; *Theoretical Studies*[47-66]]

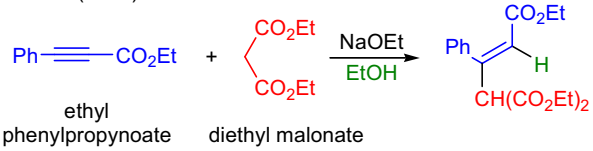
The first example of a carbon nucleophile adding to an electron-deficient double bond was published in 1883 by T. Komnenos, who observed the facile addition of the anion of diethyl malonate to ethylidene malonate.[1] However, it was not until 1887 that A. Michael systematically investigated the reaction of stabilized anions with α,β-unsaturated systems; during this study he found that diethyl malonate added across the double bond of ethyl cinnamate in the presence of sodium ethoxide to afford a substituted pentanedioic acid diester.[2] A few years later, in 1894, he demonstrated that not only electron-deficient double bonds but also triple bonds can serve as reaction partners for carbon nucleophiles.[4] This method of forming new carbon-carbon bonds became exceedingly popular by the early 1900s and today the addition of stabilized carbon nucleophiles to activated π-systems is known as the *Michael addition* (or *Michael reaction*) and the products are called Michael adducts. Currently, however, all reactions that involve the 1,4-addition (conjugate addition) of virtually any nucleophile to activated π-systems are also referred to as the *Michael addition*. The general features of this reaction are: 1) the nucleophile (Michael donor) can be derived by the deprotonation of CH-activated compounds such as aldehydes, ketones, nitriles, β-dicarbonyl compounds, etc. as well as by the deprotonation of heteroatoms; 2) depending on the type and strength of the electron-withdrawing group (negative charge stabilizing group), the use of even relatively weak bases is possible (e.g., NEt_3); 3) it is possible to carry out the reaction using only catalytic amount of base, so when a full equivalent base is used, the product is an anion that can be reacted further with various electrophiles; 4) the structure of the activated alkene or alkyne (Michael acceptor) can be varied greatly; virtually any electron-withdrawing group could be used; 5) the reaction may be conducted in both protic and aprotic solvents; 6) both inter- and intramolecular versions exist; 7) the reaction can be highly diastereoselective when both the Michael donor and acceptor have defined stereochemistry; and 8) asymmetric versions have been developed.[28,30,31,41,25] The main drawback of the *Michael addition* is that other processes may compete with the desired 1,4-addition such as 1,2-addition and self-condensation of the carbon nucleophile, but the careful choice of reaction medium and the use of additives can suppress these undesired reactions.

Michael (1887):



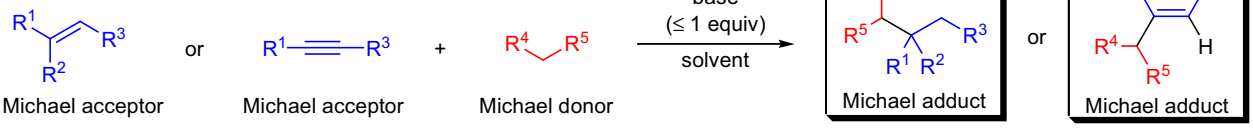
ethyl cinnamate + diethyl malonate

Michael (1894):



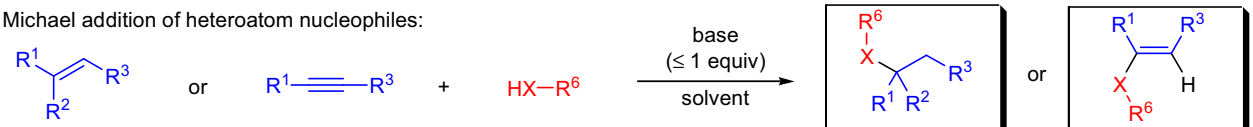
ethyl phenylpropynoate + diethyl malonate

Michael addition of carbon nucleophiles:



Michael acceptor | Michael acceptor | Michael donor

Michael addition of heteroatom nucleophiles:

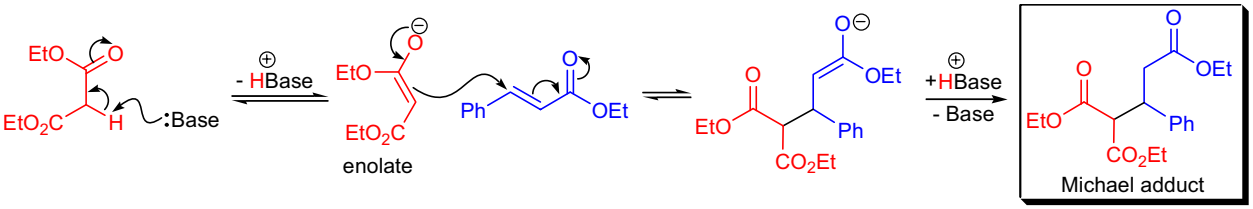


Michael acceptor | Michael acceptor | Michael donor

R^{1-2} = H, alkyl, aryl; R^3 = C(=O)-alkyl, C(=O)-aryl, CO_2-alkyl, CO_2-aryl, $C(=O)NR_2$, CN, CHO, NO_2, S(=O)R, $[PR_3]^+$, $PO(OR)_2$, heteroaryl (e.g. pyridine); R^4 = H, alkyl, aryl, C(=O)-alkyl, C(=O)-aryl, CO_2-alkyl, CO_2aryl, $C(=O)NR_2$, CN, CHO, NO_2; R^5 = C(=O)-alkyl, C(=O)-aryl, CO_2-alkyl, CO_2-aryl, CN, CHO; R^6 = H, alkyl, aryl; X = O, S, NH, NR, etc.; base: piperidine, NEt_3, NaOH, KOH, NaOEt, KO*t*-Bu; solvent: EtOH, *t*-BuOH, etc. or aprotic solvents such as THF, acetonitrile, benzene, etc.

Mechanism:[9,11,67,17]

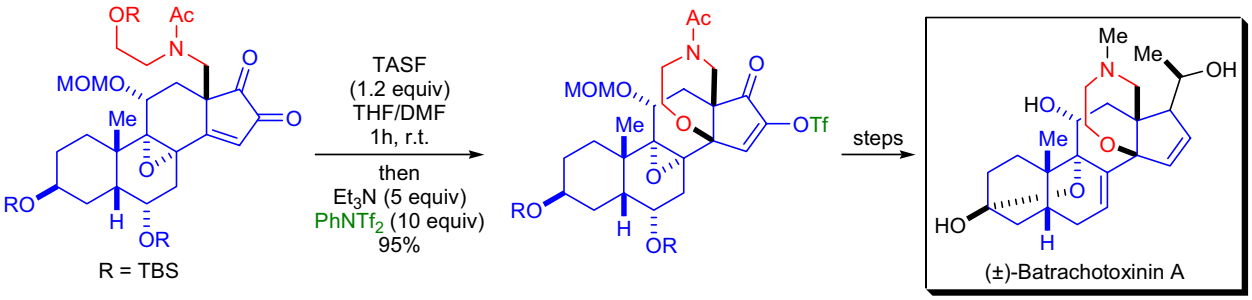
The mechanism is illustrated with the addition of a malonate anion across the double bond of ethyl cinnamate. The reaction is reversible in protic solvents and the thermodynamically most stable product usually predominates. When organometallic reagents are used as Michael donors (e.g., copper-catalyzed organomagnesium additions) SET-type mechanisms may be operational.



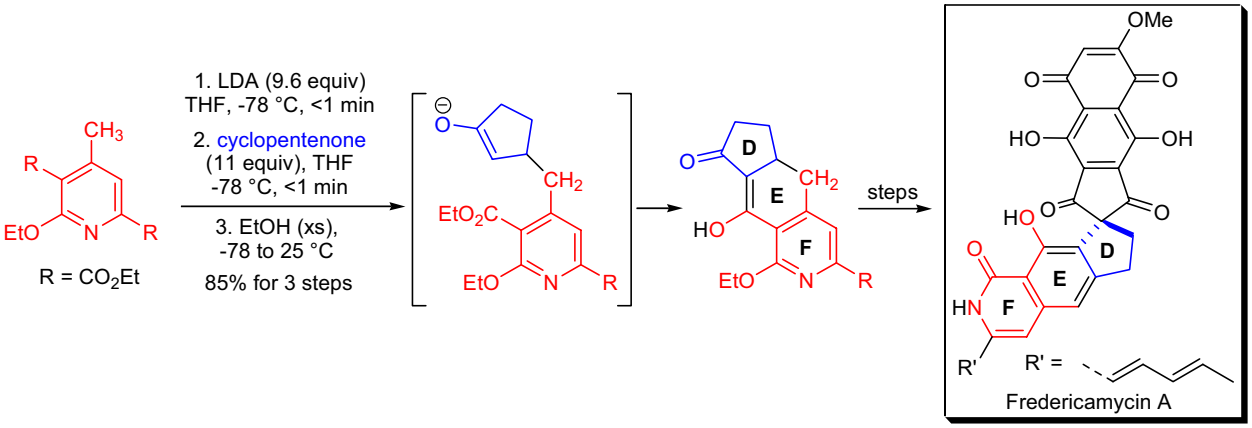
MICHAEL ADDITION/REACTION

Synthetic Applications:

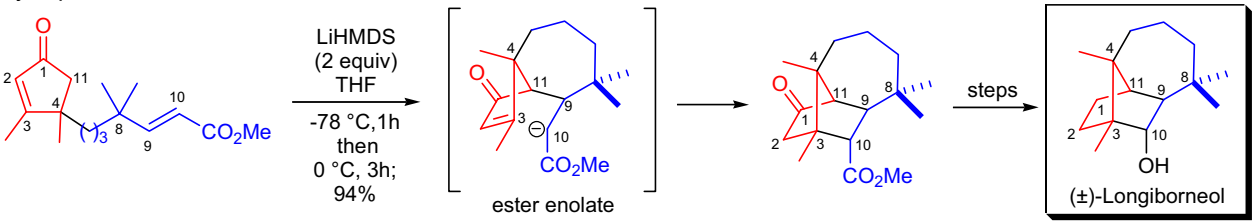
A unique class of steroidal alkaloids, the batrachotoxinins, is isolated in small quantities from the skins of poison arrow frogs and also from the feather of a New Guinea bird. One of the key steps during the total synthesis of (±)-batrachotoxinin A by Y. Kishi et al. was a *Michael addition* to form a seven-membered oxazapane ring.[68] The removal of the primary TBS protecting group was achieved by treatment with TASF and the resulting alkoxide attacked the enone at the β-position to afford an enolate as the Michael adduct. The enolate was trapped with phenyl triflimide as the enol triflate.



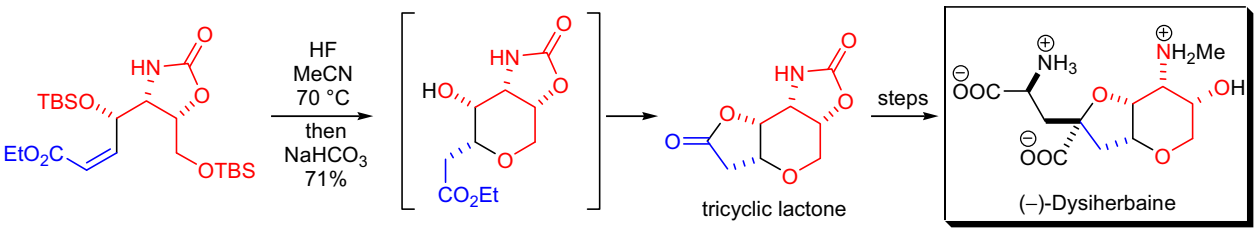
The synthesis of both enantiomers of the antitumor-antibiotic fredericamycin A was achieved in the laboratory of D.L. Boger.[69] The DE ring system of the natural product was assembled *via* a tandem *Michael addition-Dieckmann condensation*. The highly substituted 4-methylpyridine precursor was treated with excess LDA followed by the addition of the Michael acceptor cyclopentenone. The Michael adduct underwent an intramolecular acylation with the ester functionality *in situ* to afford the desired DEF tricycle.



M. Ihara and co-workers utilized an *intramolecular double Michael addition* for the efficient and completely stereoselective construction of the tricyclo[6.3.0.0^{3,9}]undecan-10-one framework during the total synthesis of (±)-longiborneol.[70] The substituted cyclopentenone precursor was exposed to several different reaction conditions, and the highest yield was obtained when LHMDS was used as the base. The first deprotonation took place at C11; the resulting enolate added to C9, and the ester enolate (negative charge located at C10) in turn added to the cyclopentenone at C3.



The potent neurotoxin (–)-dysiherbaine was synthesized by S. Hatekayama et al. who assembled the central pyran ring *via* an *intramolecular Michael addition* of a primary alcohol to an α,β-unsaturated ester.[71] The sole product of this key cyclization was a tricyclic lactone, which was isolated in good yield.



MIDLAND ALPINE-BORANE® REDUCTION (MIDLAND REDUCTION)

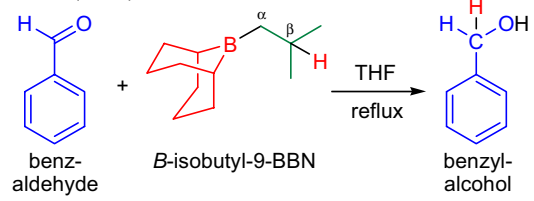
(References are on page 630)

Importance:

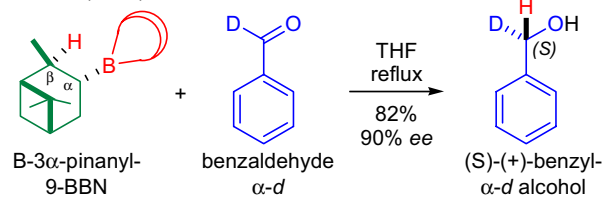
[*Seminal Publications*[1-7]; *Reviews*[8-14]; *Modifications & Improvements*[15-20]; *Theoretical Studies*[21]]

In the late 1970s, M.M. Midland and co-workers reported a surprising observation that certain B-alkyl-9-borabicyclo[3.3.1]nonanes reduced benzaldehyde to benzyl alcohol in THF solution at reflux.[3] The rate of the reaction was strongly dependent on the structure of the B-alkyl group, and it was found that increasing substitution at the β-position significantly increased the rate of reduction. Soon after this initial communication, the asymmetric version was developed by the same authors using B-3α-pinanyl-9-BBN as the reducing agent, which was easily available by reacting (+)-α-pinene with 9-BBN.[2] The asymmetric induction was comparable to that of an enzyme catalyzed reduction. This new reducing agent was later commercialized by Aldrich Co. under the name Alpine-Borane®. The asymmetric reduction of carbonyl compounds (mostly ketones) using either enantiomer of Alpine-Borane® is known as the *Midland reduction* (or *Midland Alpine-Borane reduction*). The general features of this transformation are: 1) since both enantiomers of α-pinene are available, the corresponding chiral reducing agents are readily available by reaction with 9-BBN; 2) suitable substrates are prochiral ketones and aldehydes (e.g., deutero aldehydes); 3) by using one enantiomer of Alpine-Borane® the carbonyl compounds are reduced consistently to give the same absolute configuration of the corresponding alcohol; 4) alcohols of the opposite absolute configuration may be obtained by using the other enantiomer of Alpine-Borane®; 5) the reduction takes place under mild conditions at room temperature or slightly above using 40-100% excess of the reducing agent; 6) the rate of reduction is the greatest for aldehydes, whereas ketones are reduced at significantly slower rates depending on the steric bulk of the substituents; 7) when the reaction is conducted under high-pressure conditions, the rate is increased as well as the level of asymmetric induction; 8) the level of asymmetric induction is usually very high (>90% *ee*), and existing stereocenters in the substrates usually do not influence the outcome of the reduction; 9) Alpine-Borane® exhibits a remarkable degree of chemoselectivity for aldehydes and ketones. Other functional groups remain unchanged unless forcing condition induce a dehydroboration process to form 9-BBN and α-pinene.

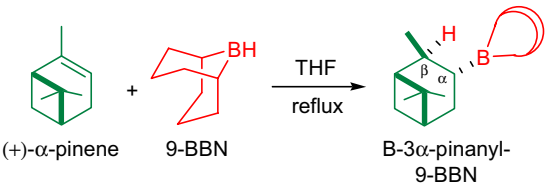
Midland (1977):



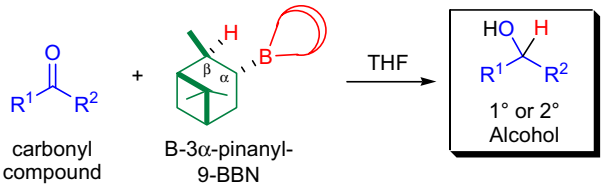
Midland (1977):



Preparation of B-3α-pinanyl-9-BBN (Alpine-Borane):



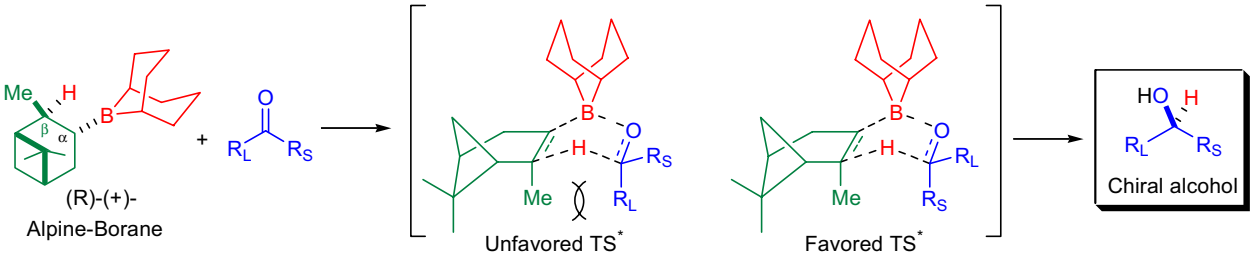
Midland reduction:



R^1 = alkyl, aryl, alkenyl, alkynyl; R^2 = H, D, alkyl, aryl, CO_2-alkyl

Mechanism:[22,23,9,24,25]

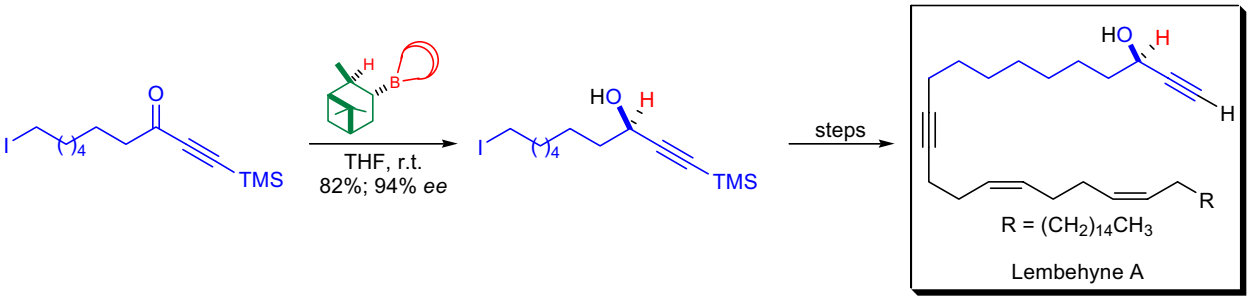
Kinetic studies of the *Midland reduction* confirmed that the reduction of aldehydes is a bimolecular process and the changes in ketone structure have a marked influence on the rate of the reaction (e.g., the presence of an EWG in the *para* position of aryl ketones increases the rate compared to an EDG in the same position).[23] However, when the carbonyl compound is sterically hindered, the rate becomes independent of the ketone concentration and the structure of the substrate. The mechanism with sterically unhindered substrates involves a cyclic boatlike transition structure (similar to what occurs in the *Meerwein-Ponndorf-Verley reduction*). The favored transition structure has the larger substituent (R_L) in the equatorial position, and this model correctly predicts the absolute stereochemistry of the product.



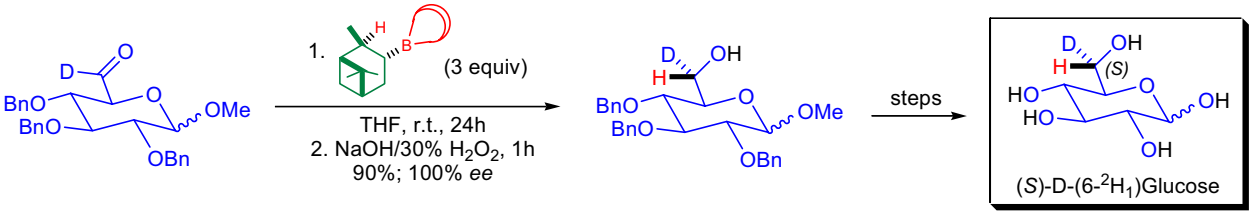
MIDLAND ALPINE-BORANE® REDUCTION (MIDLAND REDUCTION)

Synthetic Applications:

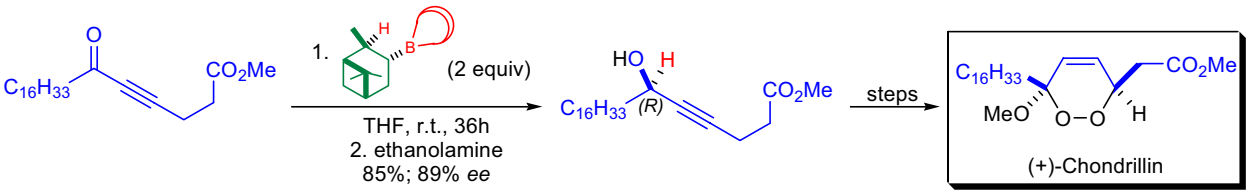
The first total synthesis of the neuritogenic spongean polyacetylene lembehyne A was accomplished by M. Kobayashi and co-workers.[26] The single stereocenter of the molecule was introduced *via* the *Midland reduction* of a propargylic ketone using an Alpine-Borane®, which was prepared from (+)-α-pinene and 9-BBN.



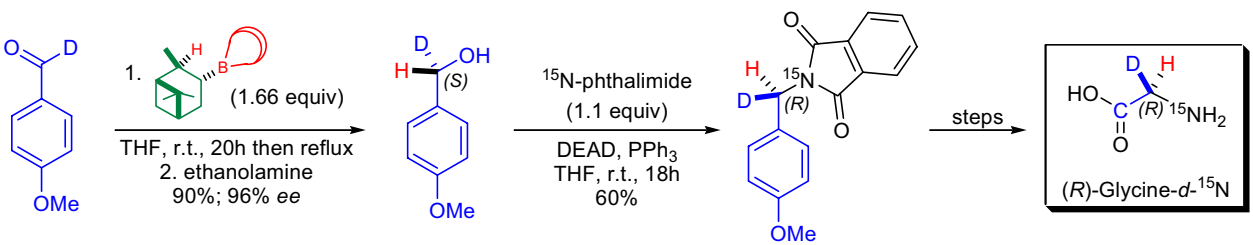
Chirally deuterated sugars are useful in elucidating mechanisms of biosynthesis and chemical reactions. In the laboratory of N.P.J. Price, the stereoselective synthesis of chirally deuterated (*S*)-D-(6-$^2H_1$)glucose was achieved utilizing (*R*)-(+)-Alpine-Borane to reduce a deutero aldehyde precursor stereoselectively.[27] The substrate was dissolved in dichloromethane, and at room temperature the solution of the reducing agent was added in THF in excess. When all the starting material was consumed, the excess reagent was destroyed with acetaldehyde and the reaction mixture was worked-up oxidatively using $NaOH/H_2O_2$.



The cyclic peroxide natural product (+)-chondrillin was prepared by P.H. Dussault and co-workers using a *singlet oxygenation/radical rearrangement* sequence as the key step.[28] The first stereocenter was introduced *via* the *Midland reduction* of an ynone substrate.



Stable, isotope-labeled amino acids are often utilized in the elucidation of protein structures and in probing the mechanism of enzyme catalyzed processes as well as revealing the metabolic pathways of amino acids. When deuterium is introduced, the protein in which the labeled amino acids are incorporated can be studied by NMR techniques. For instance, the absence of signal in the ^{1}H-NMR spectrum simplifies the assignment of peaks. An improved synthesis of the doubly labeled (*R*)-glycine-d-^{15}N was developed by R.W. Curley Jr. et al.[29] The current synthetic sequence introduced chirality by reducing a deutero aldehyde with (*R*)-(+)-Alpine-Borane. The resulting benzyl alcohol was subjected to a *Mitsunobu reaction* using ^{15}N-phthalimide, which inverted the stereochemistry and introduced the labeled nitrogen atom (overall a *Gabriel synthesis*).



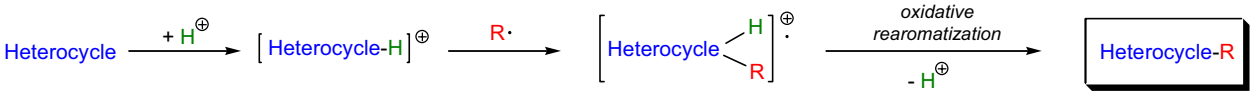
MINISCI REACTION

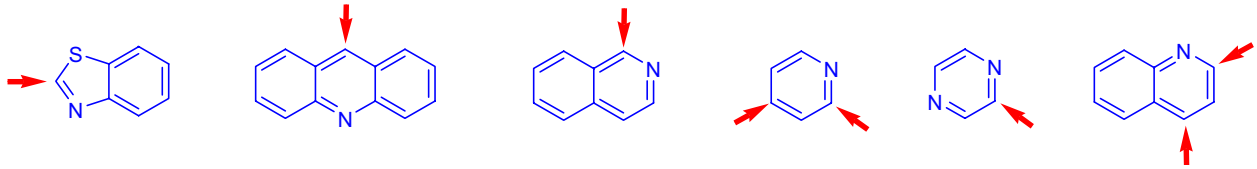
(References are on page 630)

Importance:

[*Seminal Publications*[1-11]*; Reviews*[12-16]]

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals is known as the *Minisci reaction*, named after its discoverer F. Minisci. In the late 1960s, radical processes were generally not considered selective, and their synthetic use was limited to simple molecules. In 1968, Minisci demonstrated that selective substitutions could be realized by reacting nucleophilic carbon-centered radicals with electron-deficient substrates (olefin conjugated with EWG, protonated heteroaromatic bases, quinines, etc.).[1] This transformation was especially important because it resembled the *Friedel-Crafts aromatic substitution*, but with opposite reactivity and selectivity. The *Minisci reaction* introduces acyl groups directly into heteroaromatic rings, a reaction that would be impossible under the ususal Friedel-Crafts reaction conditions. Pyridines,[5,17,18] pyrazines,[19] quinolines,[4,5] diazines,[20] imidazoles,[21] benzothiazoles[22] and purines were shown to selectively react with a wide range of nucleophilic radicals, at the positions α- and γ to the nitrogen. All heteroaromatic bases in which at least one α- or γ position is free undergo this reaction. The reactivity and the selectivity generally increase with the number of heteroatoms in the aromatic rings or polycyclic heterocycles. The observed high selectivity is due to polar effects, and is strictly related to the nucleophilic character of carbon-centered radicals. The radicals may be generated from a wide range of compounds (alkanes, alkenes, alkylbenzenes, alcohols, ethers, aldehydes, ketones, carboxylic acids, esters, amides, amines, alkyl halides, peroxides, *N*-chloroamines, oxaziridines, etc.), making the reaction synthetically useful.[1,23-26,15,27,16,28,29] Most of the Minisci substitution reactions occur in aqueous or mixed aqueous media (e.g., methanol-water) under acidic conditions at room temperature. The reactions are immediate, and isolation of the organic products is convenient.

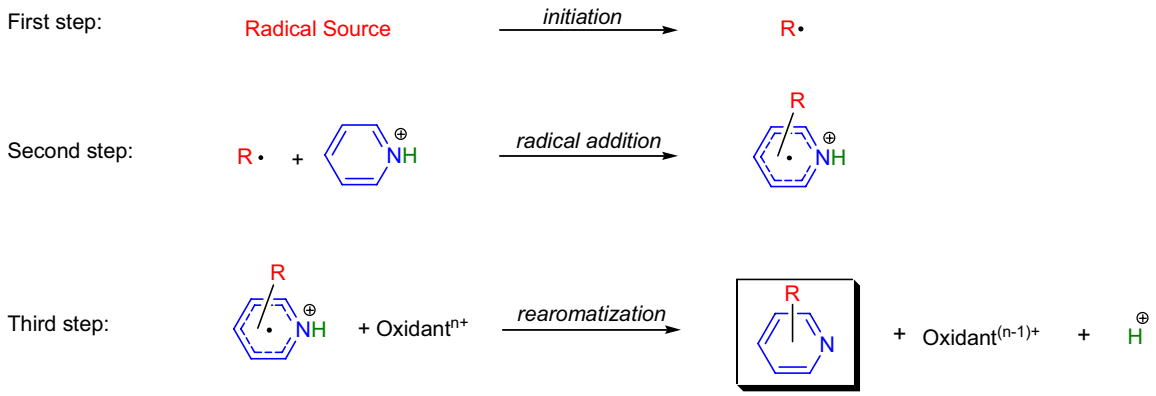




benzothiazole acridine isoquinoline pyridine pyrazine quinoline

Mechanism:[1,5,6,23,30-33,24,34-36]

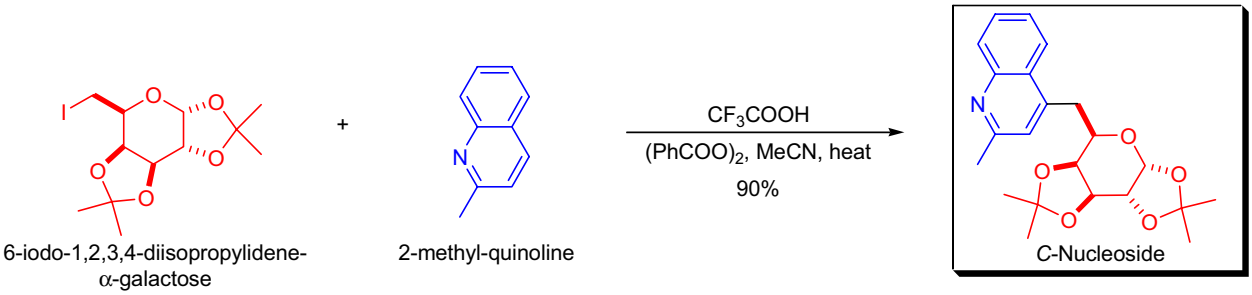
In the first step, the carbon centered radical is generated. The second step involves the addition of this radical to the protonated ring. The third step consists of the rearomatization of the radical adduct by oxidation. The rates of addition of alkyl and acyl radicals to protonated heteroaromatic bases are much higher than those of possible competitive reactions, particularly those with solvents. Polar effects influence the rates of the radical additions to the heteroaromatic ring by decreasing the activation energy as the electron deficiency of the heterocyclic ring increases.



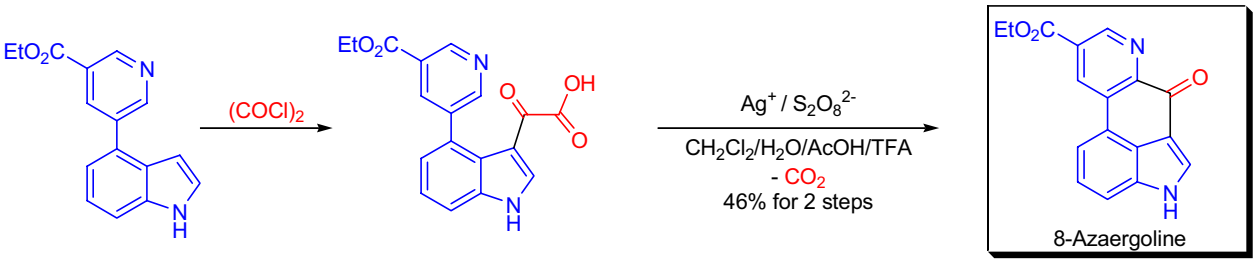
MINISCI REACTION

Synthetic Applications:

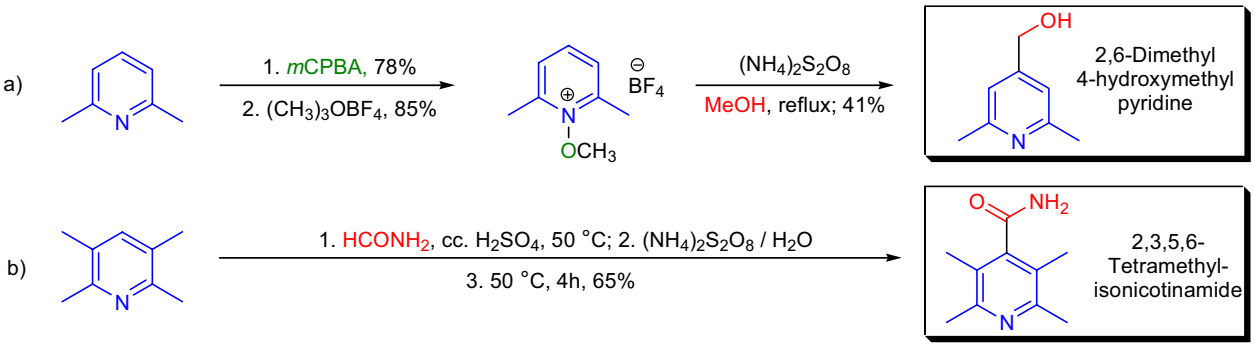
F. Minisci and co-workers generated alkyl radicals from alkyl iodides under simple conditions (thermal decomposition of dibenzoyl peroxide) and used it for selective C-C bond formation on protonated heterocycles.[37] The method was successfully applied to complex substrates, such as 6-iodo-1,2,3,4-diisopropylidene-α-galactose, which was reacted with protonated 2-methylquinoline to give the corresponding *C*-nucleoside in excellent yield.



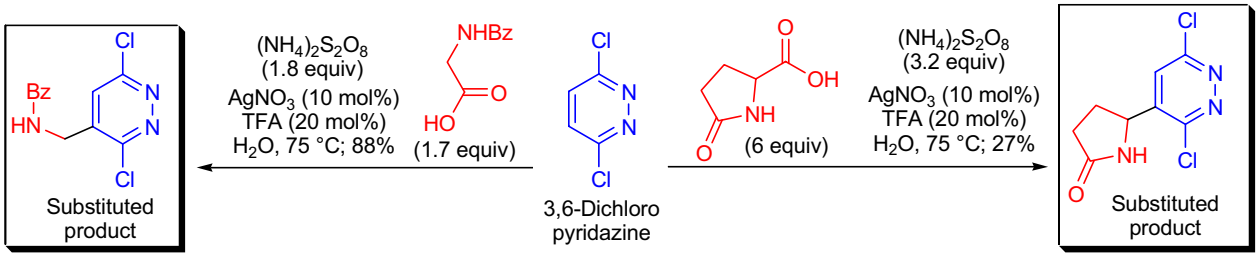
In the course of synthetic and pharmacological investigations, some non-natural azaergoline analogs were efficiently synthesized in the laboratory of M.K.H Doll.[38] Previous syntheses of these analogs were too long to be practical. Therefore, an *intramolecular tandem decarboxylation-cyclization Minisci reaction* was developed to achieve a short synthesis of the 8-azaergoline ring system. Starting from simple, commercially available precursors, the target tetracycle was obtained in four steps with an overall yield of 28%.



In order to evaluate fluoroheteroaromatic compounds as intracellular pH probes, R.A.J. Smith and co-workers prepared monofunctionalized polymethylated pyridines.[28] To this end, *radical Minisci-type substitution reactions* were used on substituted pyridines. Reaction of hydroxymethyl radicals with *N*-methoxy 2,4- and 2,6-dimethylpyridinium salts gave 2,4,6-substituted hydroxymethylpyridines. Similar reactions with 2,3,5,6-tetramethylpyridine and derivatives failed, but substitution at the 4-position could be achieved using a carbamoyl radical to yield 2,3,5,6-tetramethyl isonicotinamide, which suggested that steric and reactivity restrictions can be overcome by appropriate choice of the reactive radical intermediate.



Commercially available glycine derivatives were used by C.J. Cowden to generate 1-amidoalkyl radicals for the alkylation of 3,6-dichloropyridazine in moderate to good yields.[39]



MISLOW-EVANS REARRANGEMENT

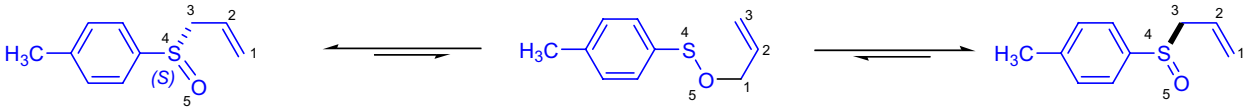
(References are on page 631)

Importance:

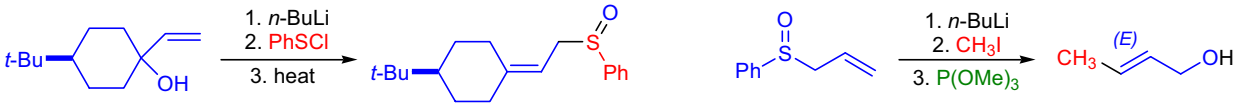
[*Seminal Publications*[1-3]; *Reviews*[4-8]; *Modifications & Improvements*[9-12]; *Theoretical Studies*[13,14]]

In 1968, K. Mislow and co-workers reported that upon heating, enantiomerically pure allylic sulfoxides underwent facile thermal racemization, while enantiopure allylic sulfenates afforded optically active sulfoxides.[1] Mechanistic studies revealed that these transformations were closely related, reversible, and concerted intramolecular processes that could be classified as *[2,3]*-sigmatropic rearrangements.[2] Soon after this discovery, D.A. Evans et al. recognized the synthetic potential of this rearrangement by converting allylic sulfoxides to allylic alcohols in the presence of a sulfenate ester trapping agent (thiophile) and demonstrated that it was general for a wide range of substrates.[3] The reversible 1,3-transposition of allylic sulfoxide and allylic alcohol functionalities is known as the *Mislow-Evans rearrangement*. The general features of the reaction are: 1) it is used mainly for the stereoselective synthesis of allylic alcohols from sulfoxides; 2) sulfoxides can be synthesized in variety of ways for example from the corresponding sulfides *via* oxidation or by the thermal rearrangement of sulfenate esters and can be obtained in enantiomerically pure form;[3] 3) allylic sulfoxides are regioselectively deprotonated at the α-position, and the resulting sulfoxide-stabilized allylic carbanion can be alkylated regioselectively α to the sulfur; 4) the formation of the allylic carbanion is achieved by the use of a strong base such as *n*-BuLi or LDA at low temperatures; 5) the alkylation of the allylic carbanion is conducted also at low temperatures with a variety of alkyl, allylic, and benzylic halides; 6) in the presence of a thiophile the allylic sulfoxides are cleanly transformed into the rearranged allylic alcohol products; 7) when heated in the absence of a thiophile, α,α'-disubstituted allylic sulfoxides may undergo rearrangement to afford the thermodynamically more stable isomers;[4] 8) the reaction is stereoselective, the chirality of the sulfur atom can be transferred to the carbon and *vice versa* allowing the preparation of allylic alcohols with defined double bond geometries; 9) the choice of thiophile can alter the stereochemical outcome of the rearrangement depending on the relative rates of the *sulfoxide-sulfenate ester rearrangement* and *sulfenate ester cleavage* by the thiophile;[15] 10) phosphite and amine thiophiles favor the almost exclusive formation of the (*E*) stereoisomer; 11) usually no purification of the intermediate products is required; after work-up the allylic alcohol product is isolated in good to excellent yield; and 12) propargyl sulfenates also undergo the rearrangement to give allenic sulfoxides.[6]

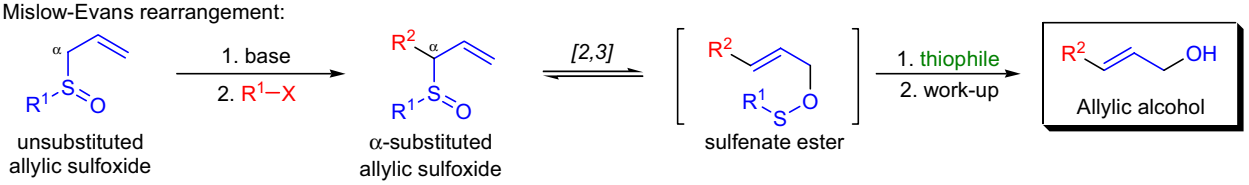
The thermal racemization of allylic sulfoxides (Mislow, 1968):



Conversion of allylic alcohols to allylic sulfoxides and allylic sulfoxides to allylic alcohols (Evans, 1971):

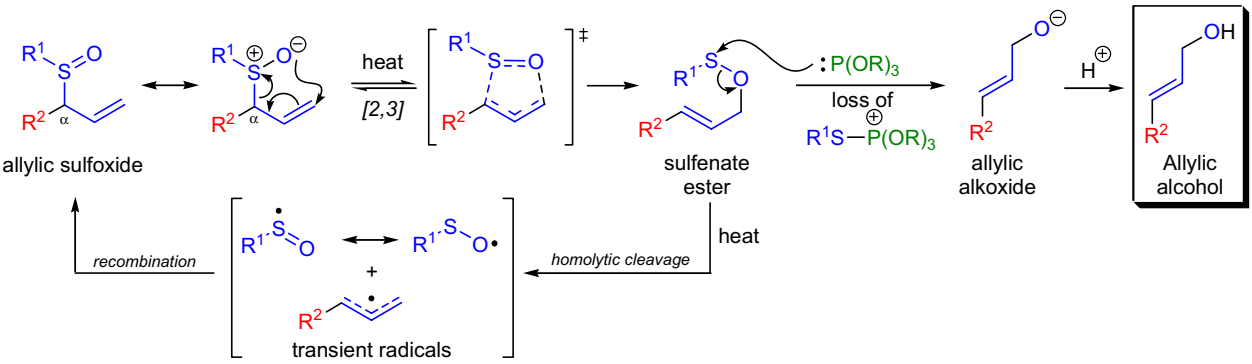


Mislow-Evans rearrangement:



R^1 = alkyl, aryl; R^2 = alkyl, allyl, propargyl, benzyl; base: alkyllithiums, LDA; thiophile: PhSNa, $P(OMe)_3$, $P(OEt)_3$, $P(NEt_2)_3$, Et_2NH

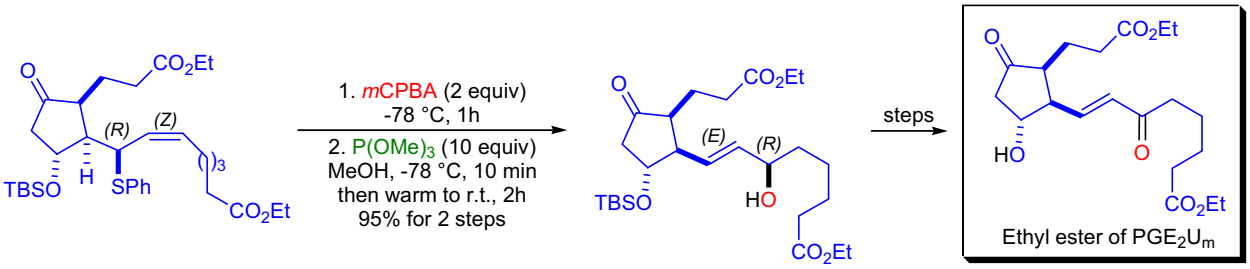
Mechanism:[1,2,15,5,16]



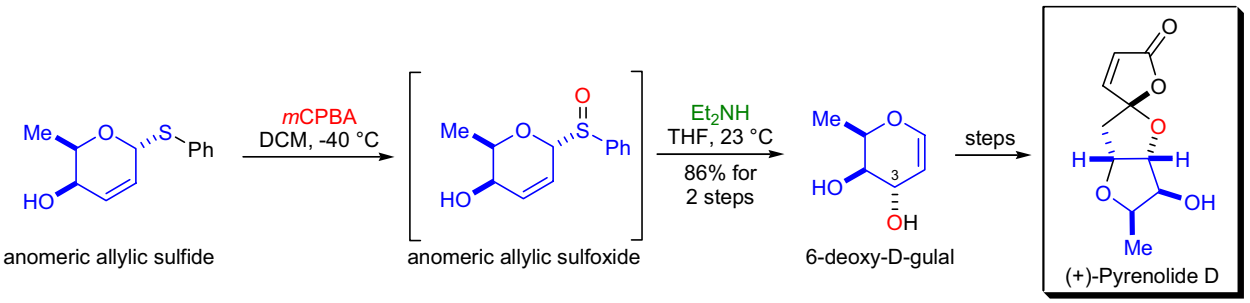
MISLOW-EVANS REARRANGEMENT

Synthetic Applications:

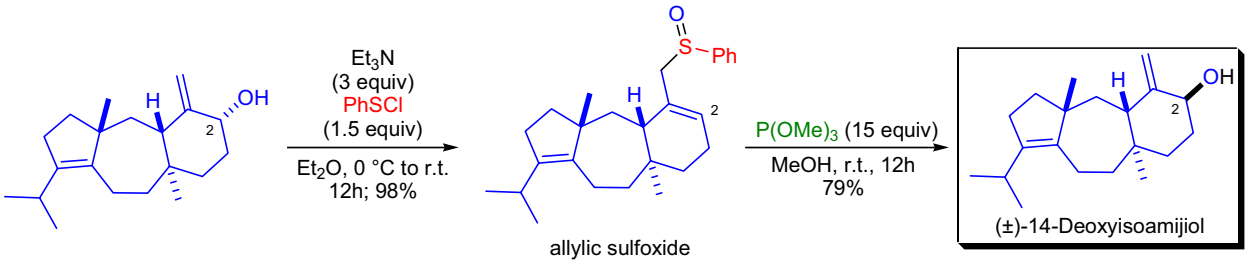
Prostaglandin E_2 is one of the most important members of the mammalian hormone prostaglandins that exhibit a wide range of biological activity. The quantification of the total amount of prostaglandin E_2 produced in humans is best achieved by assessing the accumulation of the major urinary metabolite PGE_2U_m. Since the supply of this material for assays has been depleted, the total synthesis of the ethyl ester of the major urinary metabolite of prostaglandin E_2 (PGE_2U_m) was undertaken by D.F. Taber et al.[17] In order to ensure the (*E*) stereochemistry of the double bond, the *Mislow-Evans rearrangement* was utilized. The phenyl sulfide substrate was first oxidized to the corresponding sulfoxide with *m*CPBA, and without purification, it was treated with trimethyl phosphite to produce the desired (*E*)-allylic alcohol in excellent yield.



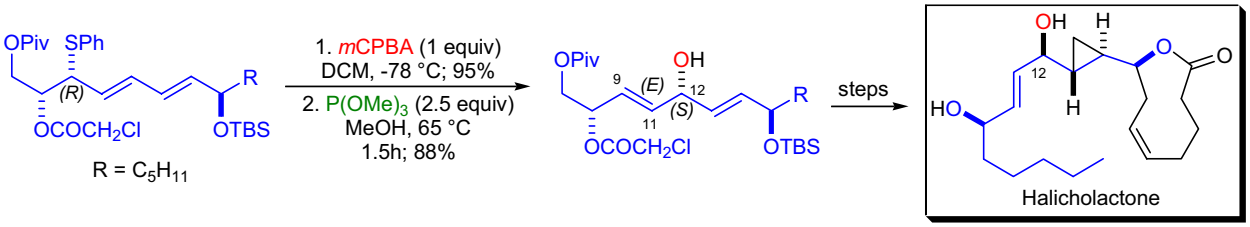
The first asymmetric total synthesis of the macrocyclic lactone metabolite (+)-pyrenolide D was accomplished in the laboratory of D.Y. Gin.[18] The natural product has a densely functionalized polycyclic structure and its absolute configuration had to be established. The key step of the synthesis was a *stereoselective oxidative ring-contraction* of a 6-deoxy-D-gulal, which was prepared from anomeric allylic sulfoxide *via* the *Mislow-Evans rearrangement*.



In the stereoselective total synthesis of (±)-14-deoxyisoamijiol by G. Majetich et al., the last step was the epimerization of the C2 secondary allylic alcohol functionality.[19] The *Mitsunobu reaction* resulted only in a poor yield (30%) of the inverted product, so the well-established *sulfoxide-sulfenate rearrangement* was utilized. The allyic alcohol was first treated with benzenesulfenyl chloride, which afforded the thermodynamically more stable epimeric sulfenate ester *via* an allylic sulfoxide intermediate. The addition of trimethyl phosphite shifted the equilibrium to the right by consuming the desired epimeric sulfenate ester and produced the natural product.



The *Mislow-Evans rearrangement* was chosen by T. Tanaka and co-workers to create the C12 stereocenter of halicholactone and ensure the (*E*) stereochemistry of the C9-C11 double bond.[20]



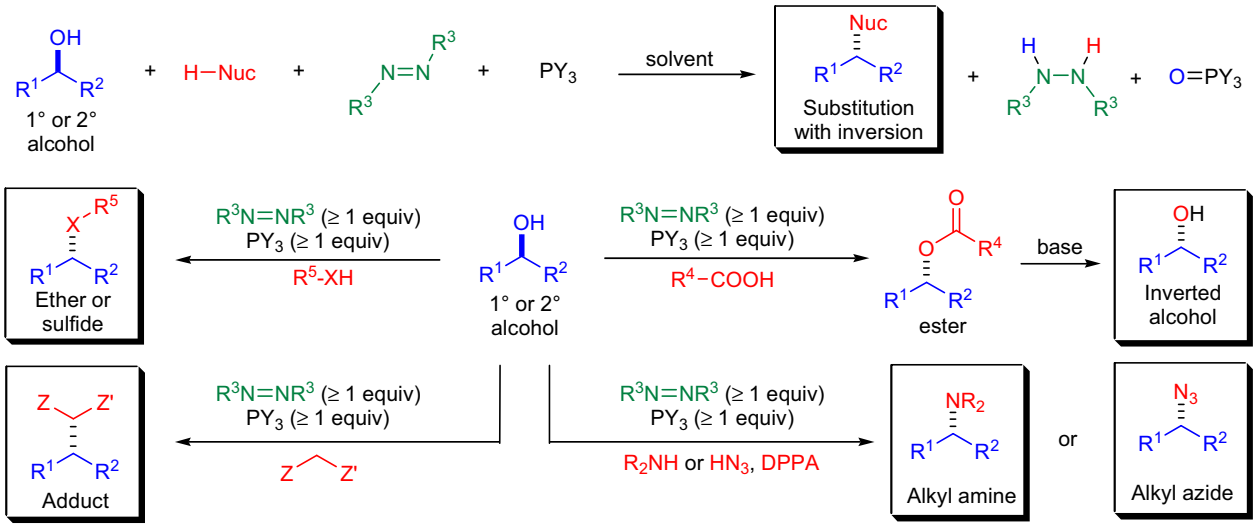
MITSUNOBU REACTION

(References are on page 632)

Importance:

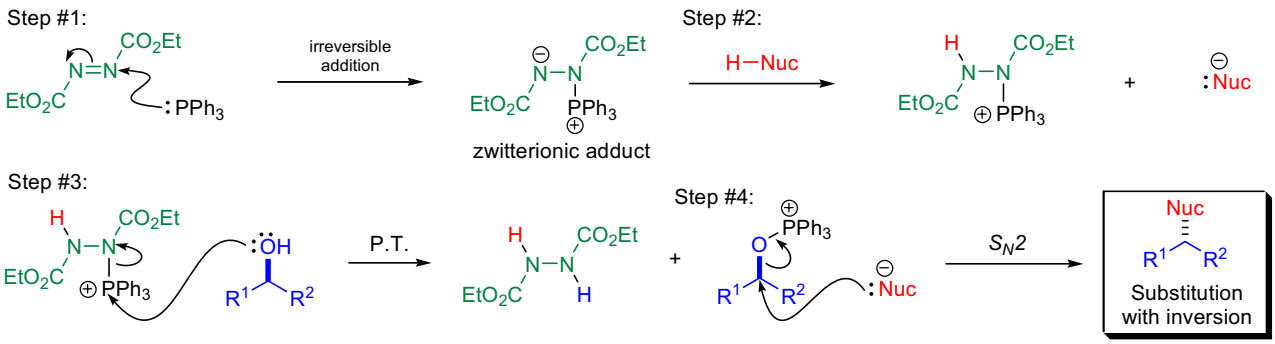
[*Seminal Publications*[1,2]; *Reviews*[3-12]; *Modifications & Improvements*[13-24]]

In 1967, O. Mitsunobu et al. reported that secondary alcohols could be efficiently acylated with carboxylic acids in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine.[1,2] A few years later it was shown that optically active secondary alcohols underwent complete inversion of configuration under the reaction conditions. Later the procedure was found to be general for the synthesis of optically active amines, azides, ethers, thioethers, and even alkanes. The substitution of primary and secondary alcohols with nucleophiles in the presence of a dialkyl azodicarboxylate and a trialkyl- or triaryl phosphine is known as the *Mitsunobu reaction*. The general features of this transformation are:[3-5] 1) primary and secondary alcohols are the best substrates and secondary alcohols undergo complete inversion of configuration; 2) tertiary alcohols do not undergo the reaction, but certain tertiary propargylic alcohols have been successfully converted; 3) the nucleophile is a relatively acidic compound ($pK_a \leq 15$); 4) among oxygen nucleophiles carboxylic acids give rise to esters, alcohols, and phenols to ethers, while thiols and thiophenols afford thioethers; 5) common nitrogen nucleophiles include imides, hydroxamates, nitrogen heterocycles, and hydrazoic acid; 6) the formation of carbon-carbon bonds is also possible, but the nucleophiles in this case are mainly active methylene compounds (β-diketones, β-keto esters, etc.); however, β-diesters are not reactive enough; 7) the reaction is also feasible intramolecularly, 3-,4-,5-,6-, and 7-membered cyclic ethers and cyclic amines can be prepared; 8) when halide ion sources (e.g., alkyl and acyl halides, zinc halides) are used along with DEAD/PPh_3, the alcohol substrates are converted to the corresponding primary and secondary alkyl halides;[4] 9) the reaction is usually conducted in THF, but dioxane and DCM are also used; 10) PPh_3 or P(*n*-Bu)$_3$ are the most commonly used phosphines; 11) the azodicarboxylate reagents are most often DEAD and DIAD, which can be used interchangeably; 11) the reaction temperature is usually between 0 °C and 25 °C, but certain sterically hindered substrates may require higher temperatures; and 12) in the typical procedure the mixture of the phosphine, alcohol, and the nucleophile are dissolved and the solution of the azodicarboxylate is added dropwise; alternatively, the azodicarboxylate is first reacted with the phopshine, and the solution of the alcohol and the nucleophile is added drowpwise. An important variant of the *Mitsunobu reaction* was developed by T. Mukaiyama, who described the preparation of inverted *tert*-alkyl carboxylates from chiral tertiary alcohols *via* alkoxydiphenylphosphines formed *in situ* using 2,6-dimethyl-1,4-benzoquinone.[20,23]



R^{1-2} = alkyl ,aryl, heteroaryl, alkenyl; H-Nuc: *O*-, *S*-, *N*- and *C*-nucleophiles; R^3 = CO_2Et (DEAD), CO_2*i*-Pr (DIAD), $CON(CH_2)_5$ (ADDP), $CONMe_2$ (TMAD); Y = alkyl, aryl, heteroaryl, O-alkyl; solvent: THF, dioxane, DCM, $CHCl_3$, DMF, toluene, benzene, HMPA; R^4 = H, CH_3, Ph, 4-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$, alkyl, aryl; R^5 = alkyl, aryl, heteroaryl; X = O, S; Z & Z' = CO-alkyl, CO-aryl, CO_2-alkyl, CO_2-aryl, CN

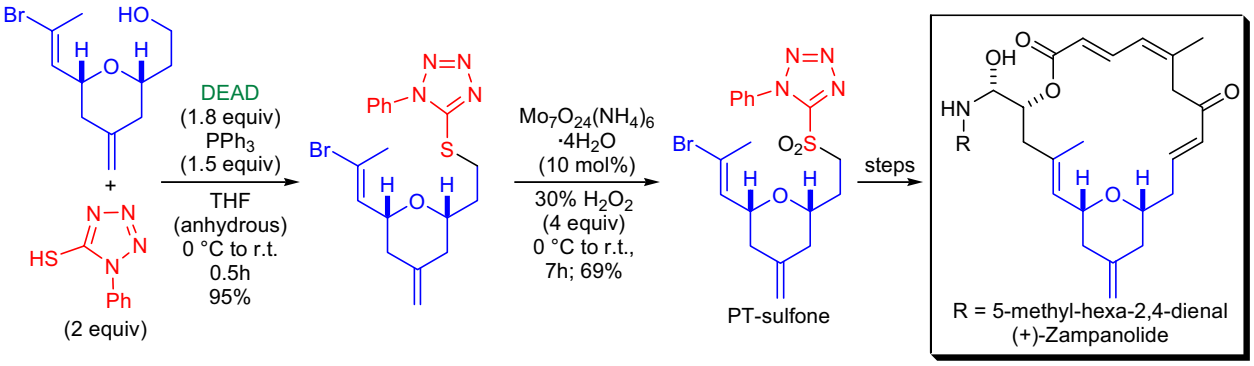
Mechanism:[25-45]



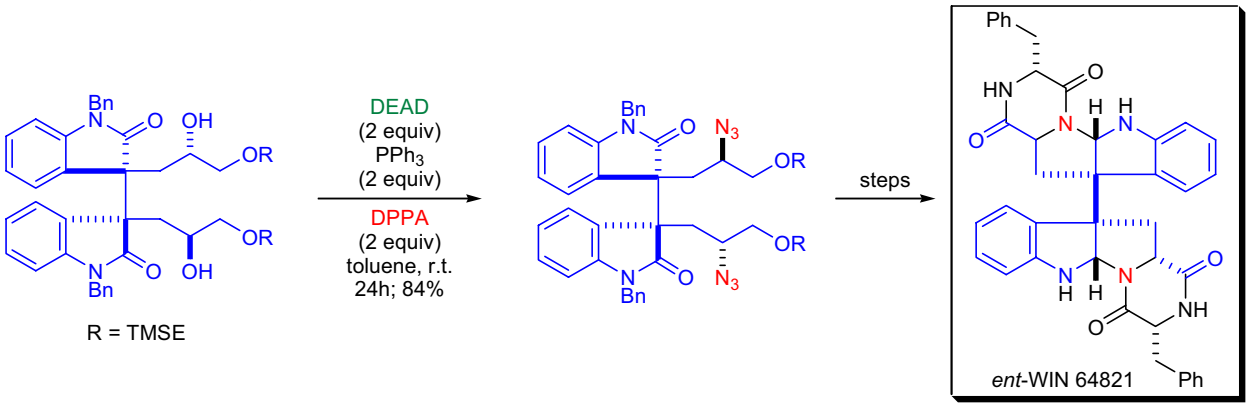
MITSUNOBU REACTION

Synthetic Applications:

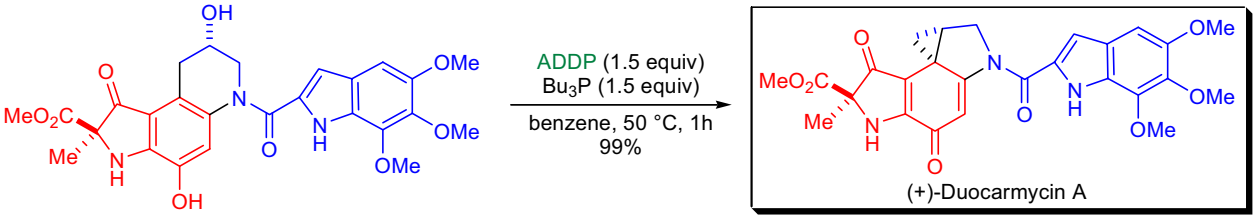
The architecturally novel macrolide (+)-zampanolide was synthesized in the laboratory of A.B. Smith.[46] The C8-C9 (*E*)-olefin moiety was constructed using the *Kocienski-modified Julia olefination*. The required PT-sulfone was prepared from the corresponding primary alcohol *via* a two-step protocol employing sequential *Mitsunobu reaction* and sulfide-sulfone oxidation. The primary alcohol and two equivalents of 1-phenyl-1*H*-tetrazolo-5-thiol was dissolved in anhydrous THF at 0 °C and treated sequentially with triphenylphosphine and DEAD. The desired tetrazolo sulfide was isolated in nearly quantitative yield.



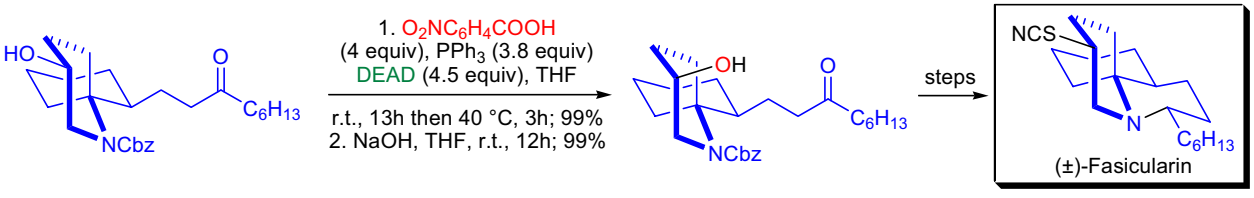
The enantioselective total synthesis of the complex bioactive indole alkaloid *ent*-WIN 64821 was accomplished by L.E. Overman and co-workers.[47] This natural product is a representative member of the family of the C_2-symmetric bispyrrolidinoindoline diketopiperazine alkaloids. The stereospecific incorporation of two C-N bonds was achieved using the *Mitsunobu reaction* to convert two secondary alcohol functionalities to the corresponding alkyl azides with inversion of configuration. The azides subsequently were reduced to the primary amines and cyclized to the desired *bis*-amidine functionality.



The naturally occurring potent antitumor antibiotic (+)-duocarmycin A, its epimer, and unnatural enantiomers were prepared by D.L. Boger et al.[48] The last step of the synthesis was the elaboration of the reactive cyclopropane moiety, which was carried out *via* a *transannular spirocyclization* using Mitsunobu conditions. This is a special case when the *Mitsunobu reaction* is utilized to create new carbon-carbon bonds.



The first total synthesis of the tricyclic marine alkaloid (±)-fasicularin was completed by the research team of C. Kibayashi.[49] The secondary alcohol functionality was inverted using the Mitsunobu protocol. The resulting *p*-nitro benzoate was readily hydrolyzed under basic conditions.



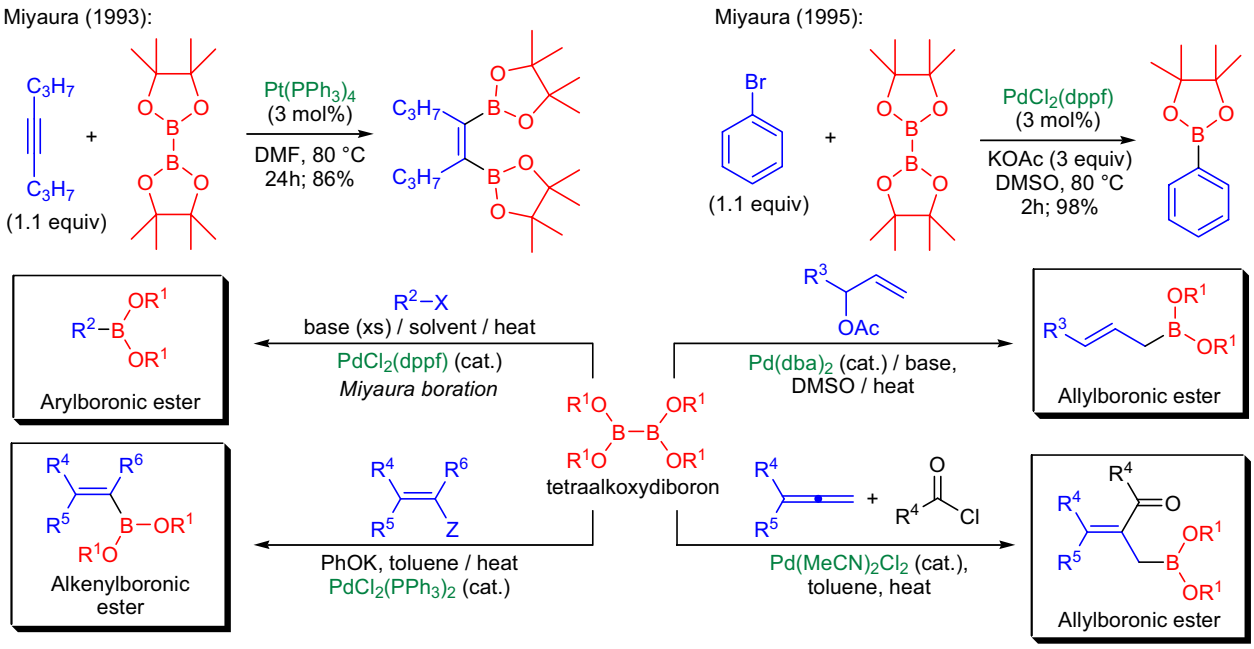
MIYAURA BORATION

(References are on page 633)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-12]; *Modifications & Improvements*[13-31]; *Theoretical Studies*[32]]

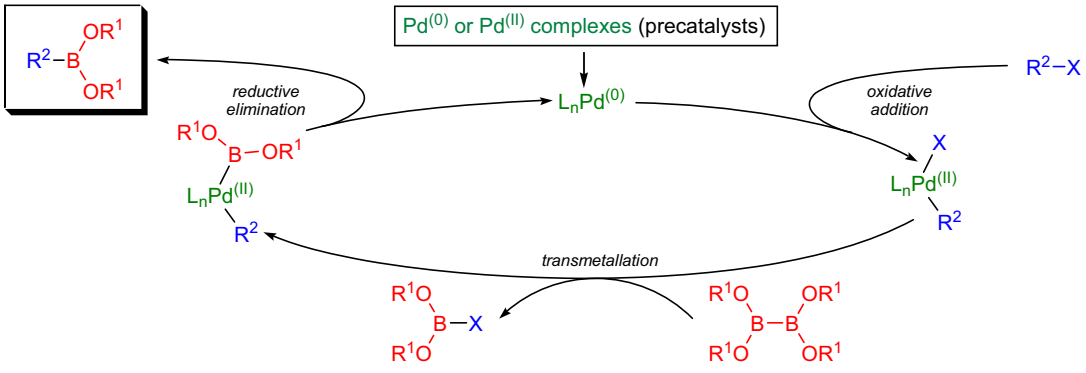
In 1993, N. Miyaura and co-workers found that alkynes could be efficiently *cis*-diborated with the pinacol ester of diboronic acid (abbreviated as B_2pin_2 or pinB-Bpin) in the presence of catalytic amounts of platinum tetrakistriphenylphosphine.[1] Later, in 1995, the same authors discovered that tetraalkoxydiboron compounds could be coupled with aromatic halides in the presence of catalytic amounts of $PdCl_2$(dppf) to afford arylboronic esters, which are important substrates for the *Suzuki cross-coupling* and *Ullmann biaryl ether synthesis*.[2] Surprisingly, only Pd-based catalysts were effective; other metal complexes did not catalyze the reaction at all. The palladium-catalyzed cross-coupling reaction of aromatic and heteroaromatic halides or triflates with tetraalkoxyboron compounds to give arylboronic and heteroarylboronic esters is referred to as the *Miyaura boration*. The general features of this transformation are: 1) the one-pot coupling proceeds under mild conditions, which is a significant improvement over the traditional synthesis of arylboronic esters and acids (the reaction between trialkyl borates and arylmagnesium halides or aryllithiums); 2) most functional groups are tolerated under the mildly basic reaction conditions; 3) the best substrates are aryl bromides and iodides, but recently aryl triflates[15,3] and aryldiazonium tetrafluoroborates[21] have also been used; 4) the aryl group may have either electron-donating or electron-withdrawing substitutents; 5) electron-rich aryl bromides tend to react slower than electron-rich aryl iodides, and the chemoselective boration of an aryl iodide in the presence of an aryl bromide can be achieved in high yield; 6) the use of palladium(0)-tricyclohexylphosphine as the catalyst allows the coupling of the much less reactive aryl chlorides;[23] and 7) the presence of potassium acetate (KOAc) as the base in the reaction mixture is critical for the successful coupling of aryl halides, and it not only accelerates the reaction but also prevents the formation of biaryl by-products (*Suzuki cross-coupling*). A number of synthetically useful variants of this reaction have been developed.[13-31]



R^1 = alkyl; R^2 = aryl, heteroaryl; R^3 = H, alkyl, aryl; R^{4-6} = alkyl, aryl; X = Br, I, (or Cl) OTf, N_2BF_4; Z = I, Br, OTf; base: KOAc; solvent: DMF, DMSO, dioxane, toluene

Mechanism:[2,32]

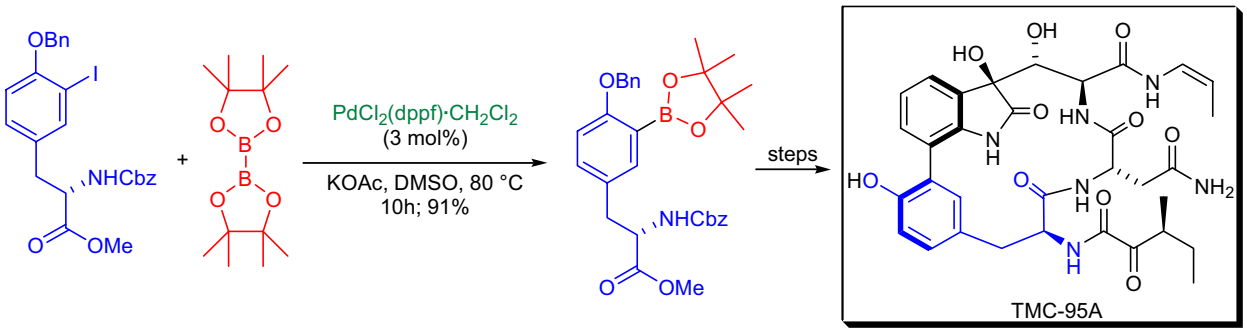
The first step of the *Miyaura boration* is the oxidative addition of the $Pd^{(0)}$-complex into the C-X bond of the aryl halide. Next, a transmetallation takes place, the exact mechanism of which depends on the nature of the substrate, and finally the reductive elimination affords the product.



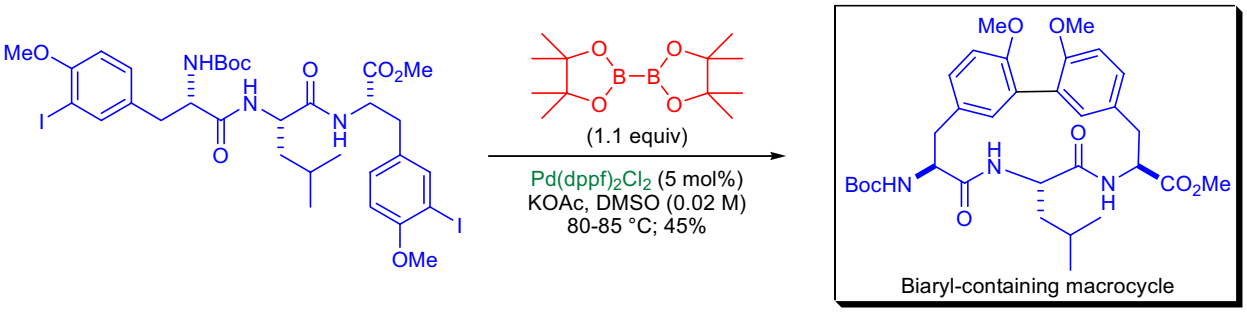
MIYAURA BORATION

Synthetic Applications:

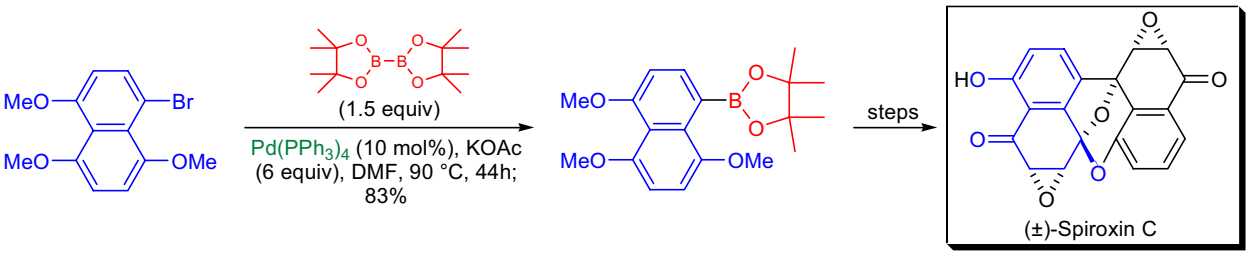
The total synthesis of the proteasome inhibitor cyclic peptide TMC-95A was accomplished by. S.J. Danishefsky and co-workers.[33] The biaryl linkage in the natural product was constructed by a *Suzuki cross-coupling* between an aryl iodide and an arylboronic ester derived from L-tyrosine. The required arylboronic pinacolate substrate was prepared using the *Miyaura boration*. The aryl iodide was exposed to *bis*(pinacolato)diboron in the presence of a palladium catalyst and potassium acetate in DMSO. The coupling proceeded in high yield and no symmetrical biaryl by-product was observed.



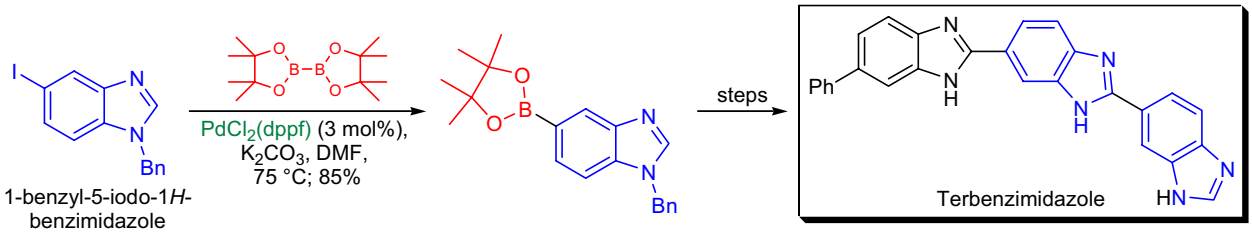
A novel macrocyclization reaction was developed based on a domino *Miyaura boration/intramolecular Suzuki cross-coupling* sequence in the laboratory of J. Zhu.[34] This strategy was applied in the synthesis of biaryl-containing macrocycles. The diiodide substrate was dissolved in degassed DMSO, and then the catalyst and the base were added. Successful macrocyclization required extensive experimentation, and the authors determined that the concentration and the nature of the base were the two most important factors. Interestingly, potassium carbonate is not suitable as a base in the *Miyaura boration*, since it tends to give biaryl by-products, but in this particular macrocyclization reaction it proved to be completely ineffective because the reaction failed to take place.



The first total synthesis of the potent antibiotic marine natural product ( )-spiroxin C was completed by T. Imanishi et al., who employed a *TBAF-activated Suzuki cross-coupling* as the key step to form the biaryl linkage.[35] The coupling partner naphthylborate ester was prepared using the *Miyaura boration*.



The efficient synthesis of a potent topoisomerase I poison terbenzimidazole was developed in the laboratory of P.J. Smith.[36] The desired aryl-aryl bonds were created *via* iterative *Suzuki-cross couplings*. The arylboronic ester was derived from 1-benzyl-5-iodo-1*H*-benzimidazole using the *Miyaura boration*.



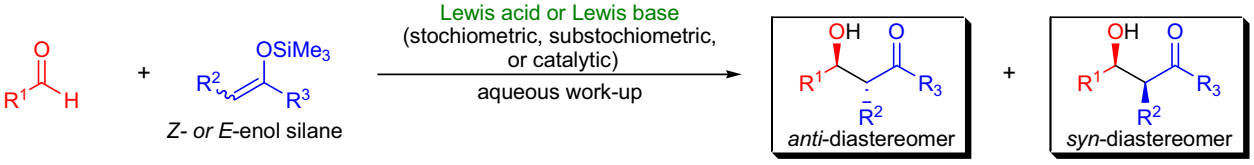
MUKAIYAMA ALDOL REACTION

(References are on page 633)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-22]*; Theoretical Studies*[23]]

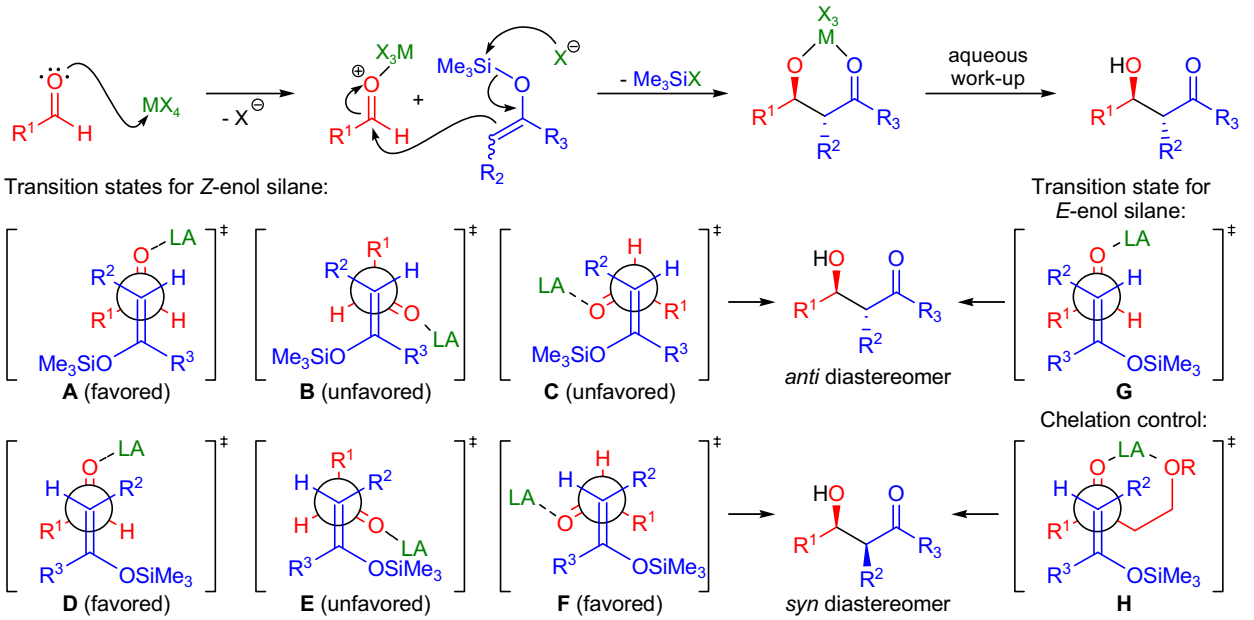
The *crossed aldol reaction* between preformed enolates and carbonyl compounds is among the most important carbon-carbon bond forming reactions. A powerful version of this transformation is the Lewis acid mediated addition of enol silanes to carbonyl compounds, a process that was discovered by T. Mukaiyama in the early 1970's[1,2] and today is referred to as the *Mukaiyama aldol reaction*. The general features of the reaction are: 1) according to the original procedure, stoichiometric quantities of the Lewis acid such as $TiCl_4$, $SnCl_4$, $AlCl_3$, $BCl_3{\cdot}OEt_2$, and $ZnCl_2$ were required to effect the transformation;[1,2] 2) lately, several catalytic versions were developed utilizing Lewis acids such as $Sn^{(IV)}$, $Sn^{(II)}$, $Mg^{(II)}$, $Zn^{(II)}$, $Li^{(I)}$, $Bi^{(III)}$, $In^{(III)}$, $Ln^{(III)}$, $Pd^{(II)}$, $Ti^{(IV)}$, $Zr^{(IV)}$, $Ru^{(II)}$, $Rh^{(II)}$, $Fe^{(II)}$, $Al^{(III)}$, $Cu^{(II)}$, $Au^{(I)}$, R_3SiX, Ar_3C^+, and clay as catalyst;[6,10,11,13,14,16] 3) several Lewis base catalyzed transformations were also developed;[24-27] 4) the enol silane component can be derived from aldehydes, ketones, esters, and thioesters;[4] 5) the reactions of unsubstituted, mono- and disubstituted enol silanes were examined;[4] and 6) the most commonly used carbonyl reactants are aldehydes, but ketones and acetals also react under appropriate reaction conditions.[4] The diastereoselectivity of the *Mukaiyama aldol reaction* can be controlled if substrates and conditions are carefully chosen. The diastereochemical outcome of monosubstituted enol silanes is usually as follows: 1) when R^2 is small and R^3 is bulky, the reaction leads to the *anti* product independent of the double bond geometry; 2) when R^2 is large, *syn* diastereoselection predominates independent of the enol silane geometry; and 3) when the aldehyde is capable of chelation, the formation of the *syn*-diastereomer is preferred.[14] Control of the absolute stereoselectivity can be achieved by utilizing chiral enol silanes or chiral aldehydes.[14] The fastest-growing area in the *Mukaiyama aldol* methodology is the development of asymmetric catalytic processes, utilizing chiral Lewis acid complexes and Lewis bases.[13]



R^1 = alkyl, aryl, -OR; R^2 = H, alkyl, aryl; R^3 = alkyl, aryl, -OR, -SR, H; Lewis acid = $Sn^{(IV)}$, $Sn^{(II)}$, $Mg^{(II)}$, $Zn^{(II)}$, $Li^{(I)}$, $Bi^{(III)}$, $In^{(III)}$, $Ln^{(III)}$, $Pd^{(II)}$, $Ti^{(IV)}$, $Zr^{(IV)}$, $Ru^{(II)}$, $Rh^{(II)}$, $Fe^{(II)}$, $Al^{(III)}$, $Cu^{(II)}$, $Au^{(I)}$, R_3SiX, Ar_3C^+, clay; Lewis base = F^-, $(R_2N)_3PO$;

Mechanism:[3,28-39,14]

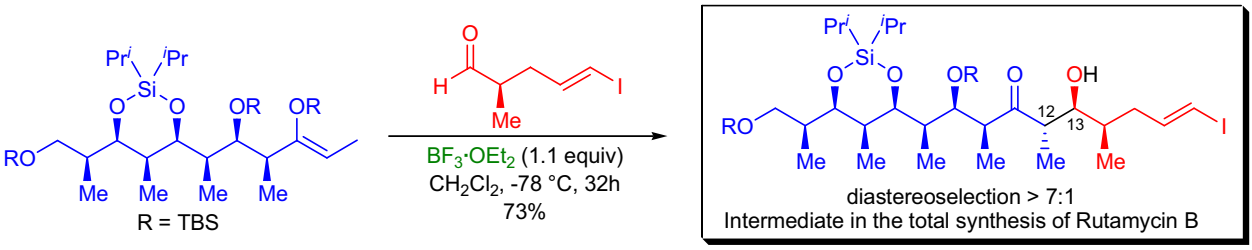
The mechanism of the *Mukaiyama aldol reaction* largely depends on the reaction conditions, substrates, and Lewis acids. Under the classical conditions, where $TiCl_4$ is used in equimolar quantities, it was shown that the Lewis acid activates the aldehyde component by coordination[30,31,35] followed by rapid carbon-carbon bond formation. Silyl transfer may occur in an intra- or intermolecular fashion. The stereochemical outcome of the reaction is generally explained by the open transition state model, and it is based on steric- and dipolar effects.[14] For *Z*-enol silanes, transition states **A**, **D**, and **F** are close in energy. When substituent R^2 is small and R^3 is large, transition state **A** is the most favored and it leads to the formation of the *anti*-diastereomer.[34] In contrast, when R^2 is bulky and R^3 is small, transition state **D** is favored giving the *syn*-diastereomer as the major product. When the aldehyde is capable of chelation, the reaction yields the *syn* product, presumably *via* transition state **H**.[29,32,36]



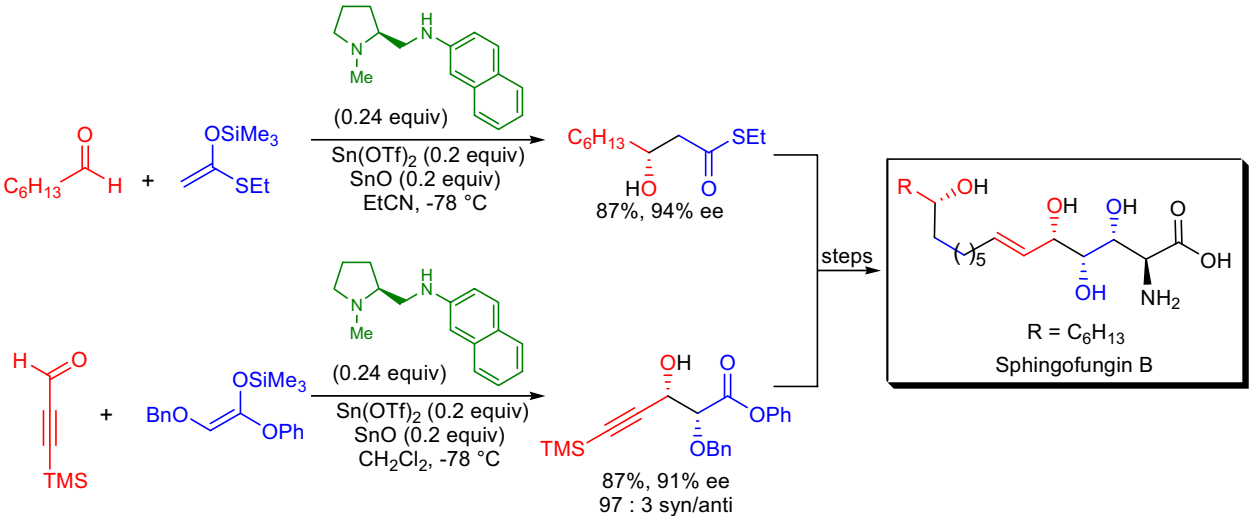
MUKAIYAMA ALDOL REACTION

Synthetic Applications:

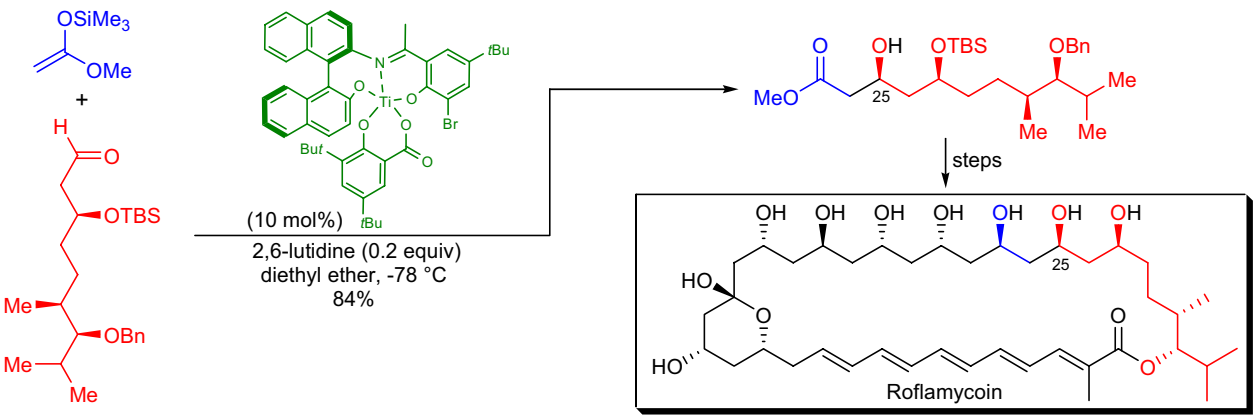
The asymmetric total syntheses of rutamycin B and oligomycin C was accomplished by J.S. Panek et al.[40] In the synthesis of the C3-C17 subunit, they utilized a *Mukaiyama aldol reaction* to establish the C12-C13 stereocenters. During their studies, they surveyed a variety of Lewis acids and examined different trialkyl silyl groups in the silyl enol ether component. They found that the use of $BF_3{\cdot}OEt_2$ and the sterically bulky TBS group was ideal with respect to the level of diastereoselectivity. The stereochemical outcome was rationalized by the open transition state model, where the orientation of the reacting species was *anti* to each other, and the absolute stereochemistry was determined by the chiral aldehyde leading to the *anti* diastereomeric Felkin aldol product.



Tin(II) mediated asymmetric *aldol reactions* are among the first chiral Lewis acid controlled *Mukaiyama aldol reactions*.[41,42] A catalytic version of this method was utilized during the total syntheses of sphingofungins B and F by S. Kobayashi.[43] The *asymmetric tin catalyzed Mukaiyama aldol reaction* provided the two main fragments of the molecule with excellent enantio- and diastereoselectivities. Combination of the two fragments and subsequent steps led to the total synthesis of sphingofungins B and F.



A convergent total synthesis of polyene macrolide roflamycoin was achieved by S.D. Rychnovsky and co-workers.[44] In their approach, they introduced the C25 stereocenter *via* an asymmetric catalytic *Mukaiyama aldol reaction* utilizing Carreira's chiral titanium catalyst.[45]



MYERS ASYMMETRIC ALKYLATION

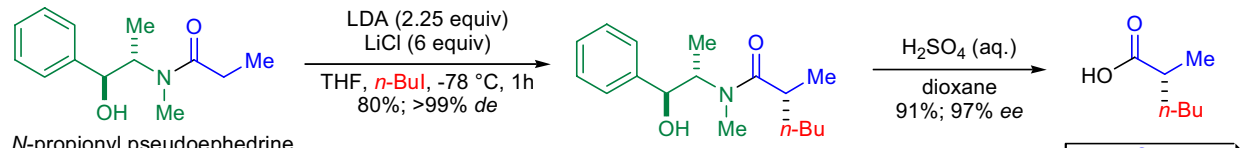
(References are on page 634)

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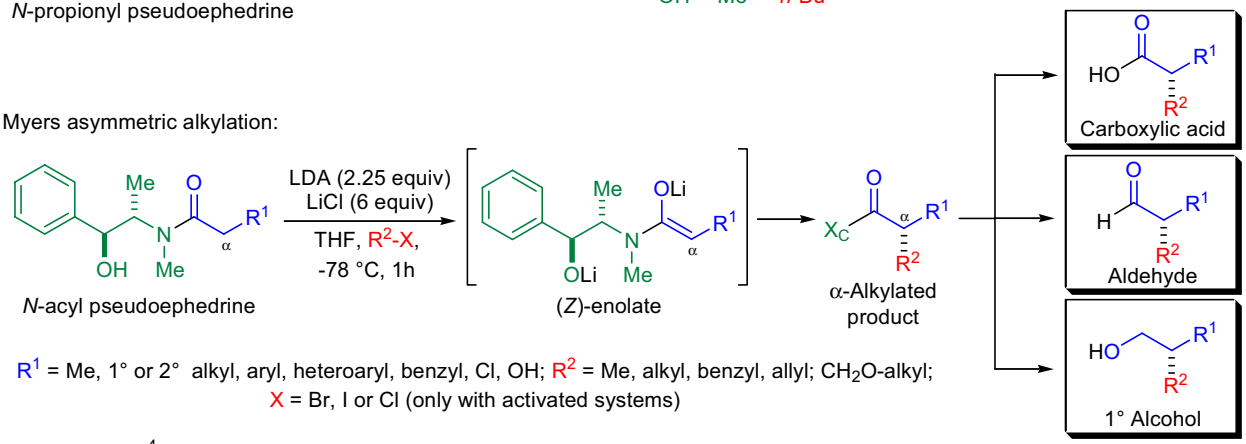
[*Seminal Publications*[1-4]*; Reviews*[5-7]*; Modifications & Improvements*[8]]

In 1978, M. Larcheveque and co-workers reported that the *N*-acylation of commercially available D- or L-ephedrine led to highly crystalline *N,N*-disubstituted amides that could be alkylated in high yield and with good diastereoselectivity.[1,2] The alkylated products were easily converted to the corresponding optically active α-substituted ketones and carboxylic acids. Almost two decades later, A.G. Myers et al. developed an efficient alkylation of *N*-acylated pseudoephedrines (the diastereomers of ephedrine) to obtain enantiomerically enriched α-alkylated, aldehydes, ketones, carboxylic acids, and alcohols.[3] This transformation is known as the *Myers asymmetric alkylation*. The general features of this alkylation are:[4] 1) both enantiomers of pseudoephedrine are inexpensive and commercially available commodity chemicals; 2) the *N*-acylation can be achieved in almost quantitative yields using symmetrical and mixed anhydrides or acid chlorides and the *N*-acyl derivatives (tertiary amides) are usually highly crystalline materials; 3) the alkylation of these tertiary amides is achieved by first deprotonation with lithium diisopropylamide and the resulting (*Z*)-enolate undergoes highly diastereoselective alkylation at the α-position; 4) allylic, benzylic, as well as the less reactive alkyl halides (including β-branched alkyl iodides and β-oxygenated *n*-alkyl halides) are all good alkylating agents, since the enolates are highly nucleophilic (unlike imide enolates that react only with highly reactive halides); 5) the α-alkylated products are often crystalline and can be enriched by recrystallization to get >99% *de*; 6) there are two general procedures to conduct the alkylation: in the first the alkylating agent is used in slight excess, while in the second the enolate is used in excess; 7) in order to obtain high yields and high levels of diastereoselectivity, the use of a large excess (6-10 equivalents) of anhydrous lithium chloride is necessary; 8) the role of the LiCl is twofold: it accelerates the rate of the alkylation and suppresses the *O*-alkylation of the pseudoephedrine hydroxyl group; 9) when β-branched alkyl iodides are used as alkylating agents the transformation leads to 1,3-dialkyl substituted alkyl chains (*syn* or *anti*), a common motif in a large number of natural products; 10) the 1,3-*syn* products represent matched cases demonstrating that the diastereofacial bias exerted by this chiral auxiliary overrides the secondary effects originating from the existing stereocenter in the alkyl iodide; 11) substrates that are both β-alkyl branched and β-alkoxy substituted react very slowly, albeit the diastereoselectivity of the alkylation remains high; and12) the removal of the chiral auxiliary from the alkylated tertiary amide products gives rise to the following useful functionalities: simple acidic, basic or Lewis acid catalyzed hydrolysis affords carboxylic acids, reduction with lithium pyrrolidide-borane (LPT) or with lithium amidotrihydroborate (LAB) gives primary alcohols, reduction with lithium triethoxyaluminum hydride results in aldehydes, while the addition of alkyllithium reagents followed by an aqueous work-up leads to ketones.

Myers (1994):



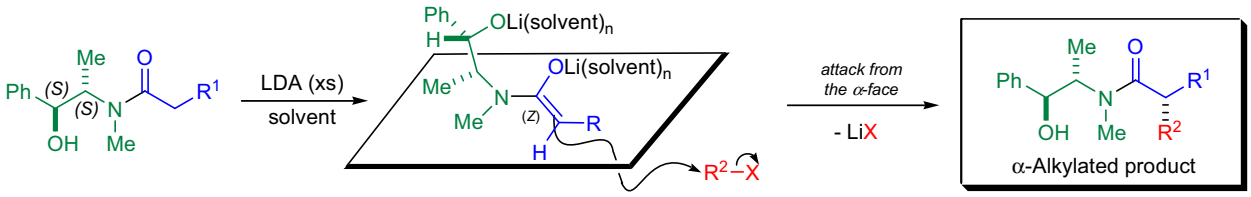
Myers asymmetric alkylation:



R^1 = Me, 1° or 2° alkyl, aryl, heteroaryl, benzyl, Cl, OH; R^2 = Me, alkyl, benzyl, allyl; CH_2O-alkyl; X = Br, I or Cl (only with activated systems)

Mechanism:[4]

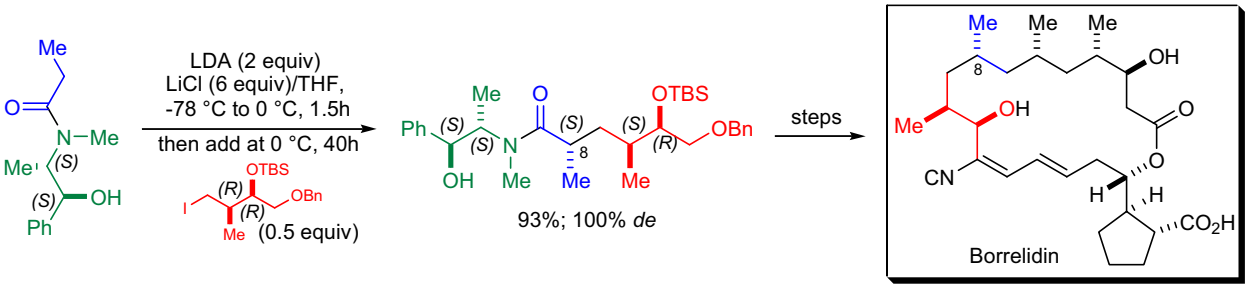
The origin of the high diastereoselectivity in this alkylation is not fully understood. The stereochemical outcome is consistent with a model in which the (*Z*)-enolate is alkylated from the α-face while the β-face is blocked by the solvated lithium alkoxide.



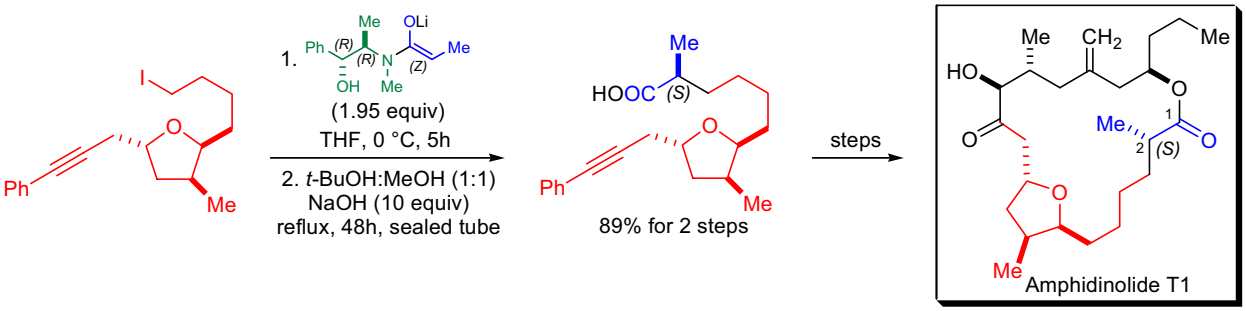
MYERS ASYMMETRIC ALKYLATION

Synthetic Applications:

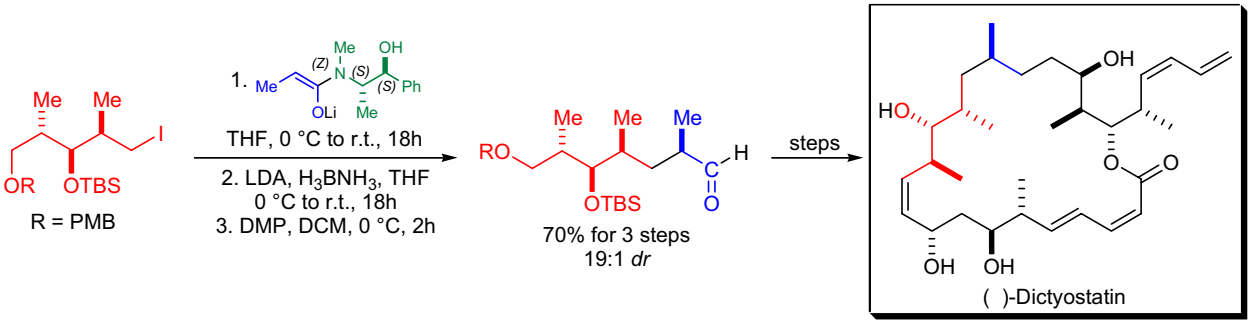
The enantioselective total synthesis of borrelidin, a structurally unique macrolide with angiogenesis inhibitory activity, was completed by J.P. Morken and co-workers.[9] The *Myers asymmetric alkylation* was used to set the C8 stereocenter. *N*-Propionyl pseudoephedrine was deprotonated with LDA in the presence of excess lithium chloride. It is well known that when excess enolate is used and the alkyl halide is the limiting reagent, yields tend to be higher than in those cases where the enolates are used as the limiting reagent. The authors used twice as much enolate as the alkyl iodide, and the product was isolated in excellent yield and with complete diastereoselectivity. Subsequently, the auxiliary was removed reductively using LAB as the reducing agent.



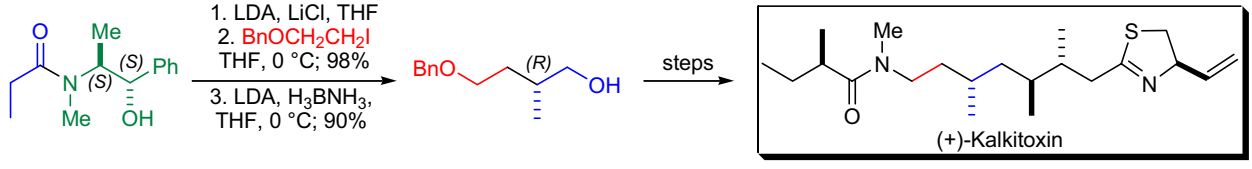
In the laboratory of T.F. Jamison, the synthesis of amphidinolide T1 was accomplished utilizing a catalytic and stereoselective macrocyclization as the key step.[10] The *Myers asymmetric alkylation* was chosen to establish the correct stereochemistry at the C2 position. In the procedure, the alkyl halide was used as the limiting reagent and almost two equivalents of the lithium enolate of the *N*-propionyl pseudoephedrine chiral auxiliary was used. The alkylated product was purified by column chromatography and then subjected to basic hydrolysis to remove the chiral auxiliary.



The total synthesis of the potent cytotoxic macrolide ( )-dictyostatin was accomplished by I. Paterson et al.[11] This natural product exhibits a powerful growth-inhibitory activity against a number of human cancer cell lines at nanomolar concentrations and it is active against Taxol-resistant cancer cells that express active P-glycoprotein. In order to create the C16 stereocenter, the *Myers asymmetric alkylation* was chosen as the method that achieved the desired three-carbon homologation of the -branched alkyl iodide substrate. The alkylated product was removed reductively using LAB and the resulting primary alcohol was oxidized to the corresponding aldehyde by the *Dess-Martin oxidation*.



The neurotoxic lipopeptide (+)-kalkitoxin was prepared by J.D. White et al., who installed one of the stereocenters *via* the *Myers asymmetric alkylation* followed by reductive workup to obtain the enantiopure primary alcohol.[12]



NAGATA HYDROCYANATION

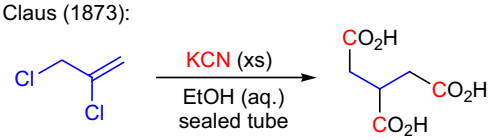
(References are on page 635)

Importance:

[*Seminal Publications*[1-6]; *Reviews*[7]; *Modifications & Improvements*[8,9]]

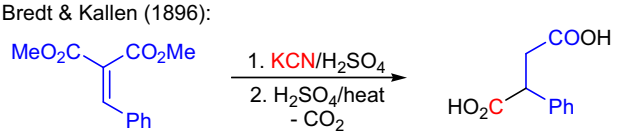
In 1873, A. Claus reported that tricarballic acid (1,2,3-propanetricarboxylic acid) was isolated when an ethanolic solution of 2,3-dichloropropene was heated with excess potassium cyanide in a sealed tube.[1] Although Claus did not realize at that time, this observation was the first example of a 1,4-addition of hydrogen cyanide to an activated alkene. Two decades later in 1896, J. Bredt and J. Kallen observed that the treatment of benzalmalonate with KCN and sulfuric acid followed by hydrolysis and decarboxylation (see *malonic ester synthesis*) gave rise to 2-phenylsuccinic acid.[2] In the first half of the 1900s, many research groups used the conjugate hydrocyanation in organic synthesis, but the method was far from being efficient, and it was plagued by numerous side reactions. A breakthrough in efficiency occurred in 1962, when W. Nagata and co-workers developed a new hydrocyanation method in which they added α,β-unsaturated ketones to a mixture of triethylaluminum and HCN in THF and observed that the reaction took place considerably faster and with much higher selectivity than under the original reaction conditions.[3] Later it was found that dialkylaluminum cyanides were even better reagents for conjugate hydrocyanations. The formation of β-cyano ketones and esters from α,β-unsaturated ketones and esters using dialkylaluminum cyanides (or HCN with Al-based Lewis acids) is known as the *Nagata hydrocyanation*. The general features of this transformation are: 1) in the overwhelming majority of cases the carbonyl compound is a ketone and rarely the aldehyde (since it undergoes 1,2-addition); 2) α,β-unsaturated esters and nitriles are also good substrates; 3) when HCN is used in conjunction with aluminum trialkyls or with alkylaluminum halides, the order of reactivity is as follows: $EtAlCl_2$>Me_3Al>Et_3Al>Et_2AlCl; 4) the reaction is almost exclusively conducted in a dipolar aprotic solvent such as THF, hydrocarbon solvents are not suitable, since the HCN reacts with AlX_3 immediately in nonpolar media; 5) a small amount of water in the reaction medium accelerates the hydrocyanation when HCN/$AlMe_3$ is used (substrates with free hydroxyl groups have the same effect); 6) in the case of less reactive substrates, the trialkylaluminum and the HCN are both used in excess, but always more of the aluminum reagent is applied to prevent the polymerization of HCN; 7) the reactivity of the dialkylaluminum cyanide reagent is strongly dependent on the basicity of the solvent and increases with decreasing solvent basicity: THF>dioxane>*i*-Pr_2O>benzene>toluene; and 8) the rate of hydrocyanation is much faster with the dialkylaluminum cyanide than with the other reagent combination (HCN/AlX_3).

Claus (1873):



2,3-dichloro-propene — 1,2,3-propane-tricarboxylic acid

Bredt & Kallen (1896):



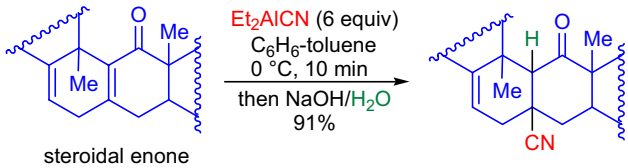
benzalmalonate — 2-phenylsuccinic acid

Nagata (1962):



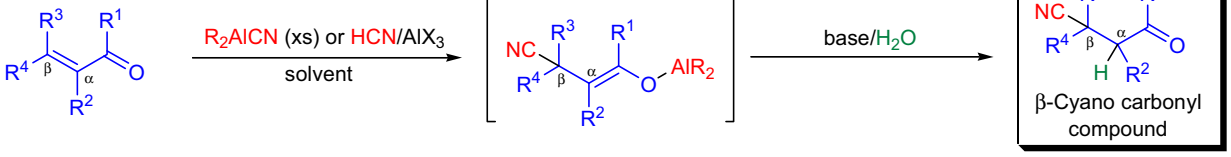
cis:*trans* = 1:24

Nagata (1966):



steroidal enone

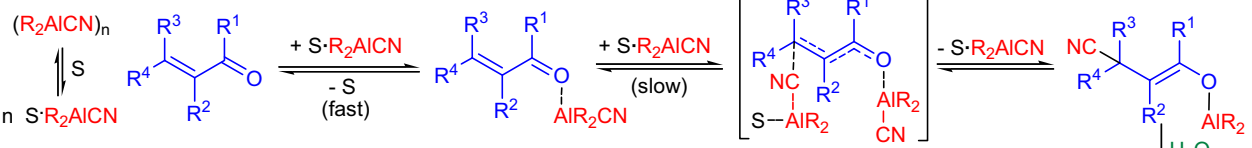
Nagata hydrocyanation:



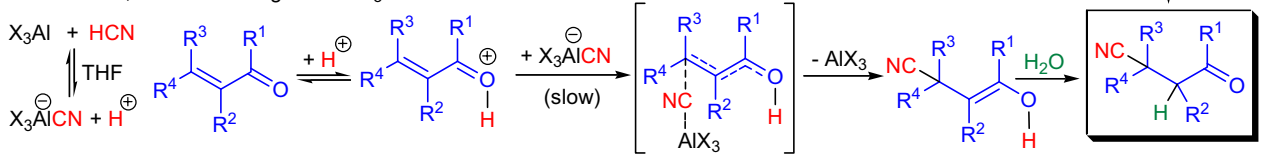
R^1 = alkyl, aryl, *O*-alkyl, *O*-aryl, (NR_2); R^{2-4} = H, alkyl, aryl; R = Me, Et, *i*-Bu; AlX_3 = $EtAlCl_2$, Me_3Al, Et_3Al, Et_2AlCl

Mechanism:

Reversible 1,4-addition using dialkylaluminum cyanide (S = solvent):



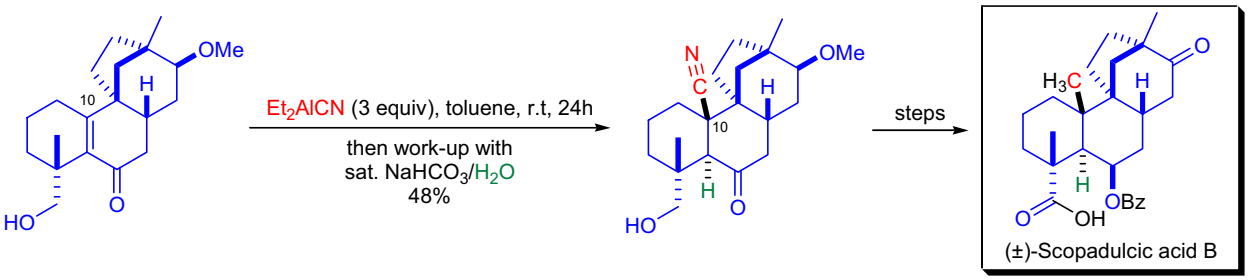
Irreversible 1,4-addition using HCN/AlX_3:



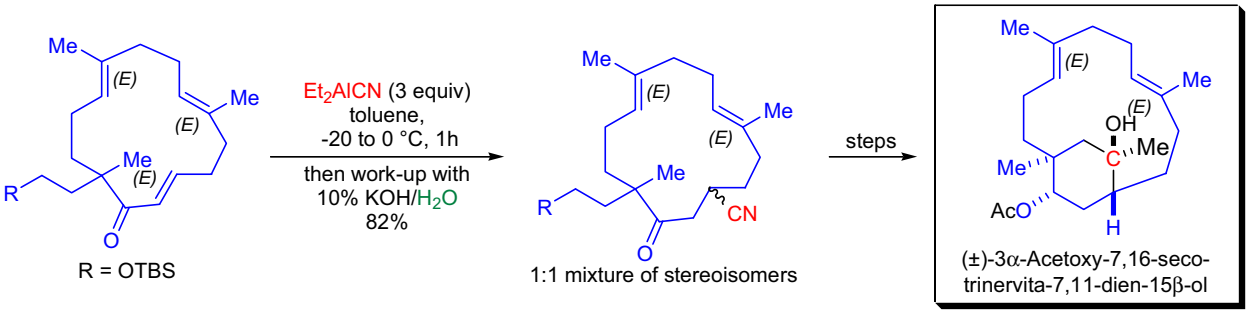
NAGATA HYDROCYANATION

Synthetic Applications:

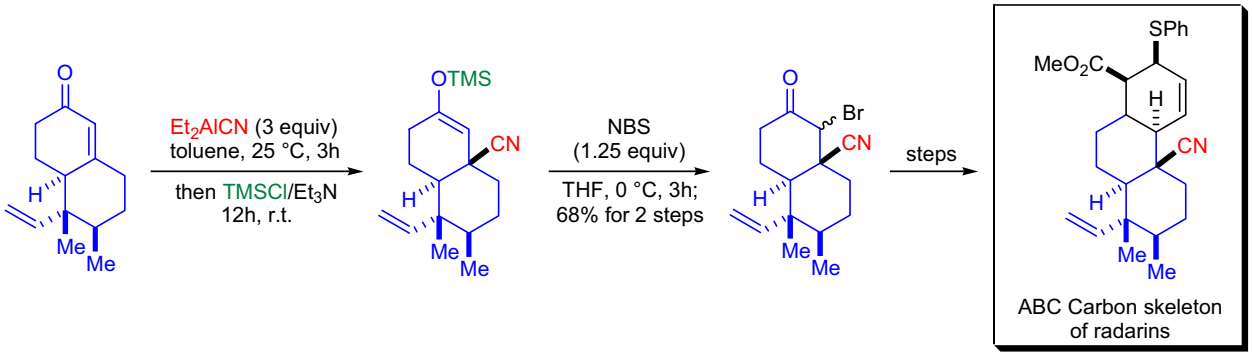
The total synthesis of (±)-scopadulcic acid B was completed by L.E. Overman et al. who used a *double-Heck cyclization* as the key step.[10] In the endgame of the synthetic effort, the stereoselective introduction of the quaternary methyl group at the C10 position was required. The authors anticipated that the pentacyclic β,β-disubstituted enone would be a poor Michael acceptor. However, they were surprised that virtually none of the standard conjugate addition procedures worked, giving rise only to 1,2-adducts and large amounts of recovered starting material. Fortunately, the *Nagata hydrocyanation* protocol using diethylaluminum cyanide was able to effect the desired conjugate addition. Since in rigid bicyclic systems the cyano group is usually delivered from the axial position, the stereochemical outcome of the *Nagata hydrocyanation* was first assigned tentatively. Later it was confirmed that indeed the addition occurred from the axial position. Subsequently, the cyano group was reduced to the corresponding methyl group in two steps.



Termite soldiers produce a large number of different chemical defense agents. Several of these molecules are unusual bioactive terpenoids such as the secotrinervitanes that have been isolated and their structure elucidated. In the laboratory of T. Kato, the total synthesis of (±)-3α-acetoxy-7,16-secotrinervita-7,11-dien-15β-ol was accomplished.[11] The *Nagata hydrocyanation* was used to introduce a carbon at the β-position of a macrocyclic enone intermediate. The substrate was treated with excess diethylaluminum cyanide in dry toluene and the addition resulted in the formation of a 1:1 mixture of diastereomers, which could be readily separated by column chromatography. The cyano group was later converted to the corresponding methyl ester.



The highly stereoselective synthesis of the tricyclic diterpene moiety of radarins was achieved by K. Fukumoto and co-workers, who utilized an *intramolecular Diels-Alder cycloaddition* to construct the B and C rings simultanaeously.[12] Radarins are indole alkaloids that exhibit potent cytotoxicity against solid tumor cells. The preparation of the Diels-Alder cycloaddition precursor commenced with the *Nagata hydrocyanation* of a known bicyclic enone. The ring fusion of the decalin system had to be *trans*, so the hydrocyanation was conducted under thermodynamic conditions using diethylaluminum cyanide. The choice of the cyano group at the ring junction was strategic for two reasons: 1) a cyano group can be easily converted to the corresponding methyl group, which is actually required in the natural product; and 2) in the cycloaddition, the small steric bulk of the cyano group avoids the substantial 1,3-diaxial interactions that would have occurred if a methyl group was present. The enolate formed in the hydrocyanation step was trapped as the silyl enol ether, and was subsequently halogenated at the α-position with NBS. The resulting α-bromo ketone was converted to the corresponding α-hydroxy ketone, which was subsequently cleaved in a *Criegee-type oxidation*.



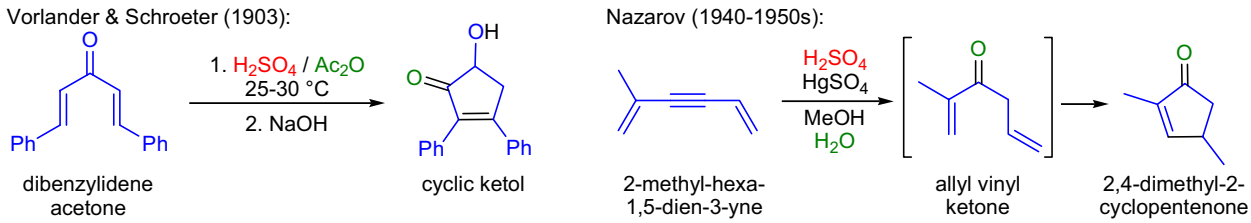
NAZAROV CYCLIZATION

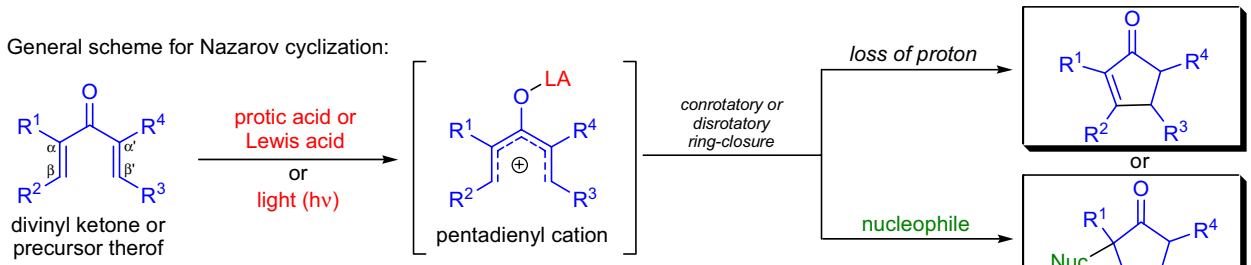
(References are on page 635)

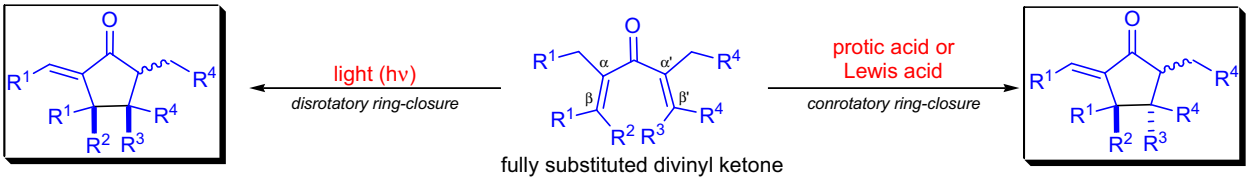
Importance:

[*Seminal Publications*[1-6]; *Reviews*[7-11]; *Modifications & Improvements*[12-28]; *Theoretical Studies*[29-31]]

In 1903, D. Vorländer and co-workers found that treatment of dibenzylideneacetone with concentrated sulfuric acid and acetic anhydride followed by hydrolysis by sodium hydroxide yielded a cyclic ketol, the structure of which was unknown at the time.[1] In the 1930s, the research group of C.S. Marvel examined the acid-catalyzed hydration of dienynes.[2,3] Later, in the 1940s and 1950s, I.N. Nazarov et al. revisited the topic and extensively studied the cyclization of the intermediate allyl vinyl ketones to the corresponding 2-cyclopentenones.[4-6] The protic- or Lewis acid catalyzed ring-closure of divinyl ketones (and their acid-labile precursors) *via* pentadienylic cations is known as the *Nazarov cyclization*. The general features of the reaction are:[8,10] 1) in a broader sense, any compound that affords the key pentadienylic cation or its equivalent is a viable substrate for the transformation; 2) allyl vinyl ketones are isomerized *in situ* to the corresponding divinyl ketones; 3) electron-donating substituents in the α and α' positions accelerate the cyclization, whereas rate retardation is observed when they are in the β and β'-positions; 4) fused cyclic systems are formed when one or both of the groups attached to the ketone are cyclic; and 5) the introduction of trialkylsilyl (or trialkylstannyl) groups in the β or β'-position ensures the controlled collapse of the cyclopentenylic cation thus undesired *Wagner-Meerwein rearrangements* are avoided, the final double bond is formed regioselectively, and the stereocenters at the ring fusion are preserved (*silicon-directed Nazarov cyclization*).[13]

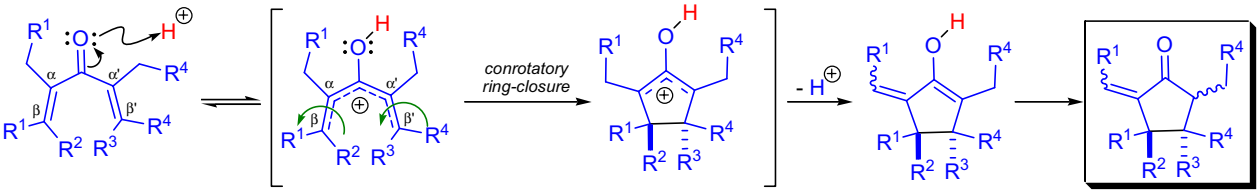






Mechanism: [32-37,15,10]

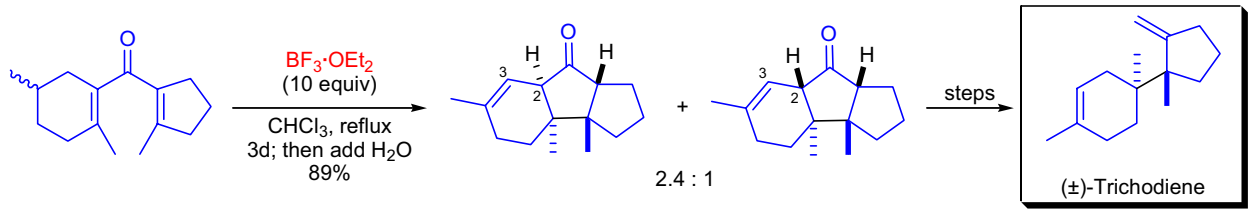
The mechanism of the *Nazarov cyclization* was not clarified until 1952, when it was realized that the cyclization proceeded *via* carbocation intermediates.[32] The *Nazarov cyclization* is a pericyclic reaction that belongs to the class of 4π electrocyclizations. The first step is the coordination of the Lewis acid to the carbonyl group of the substrate and the formation of the pentadienylic cation, which undergoes a conrotatory ring closure to give a cyclic carbocation that may be captured by a nucleophile, may undergo deprotonation, or further rearrangement may take place. The electrocyclization step may proceed in a clockwise or counterclockwise fashion (torquoselectivity) generating two diastereomers when the divinyl ketone substrate is chiral. The sense of torquoselection is primarily controlled by steric factors such as the torsional and nonbonding interactions between the substituents in the vicinity of the newly forming bond. Under photochemical conditions the cyclization proceeds in a disrotatory fashion.



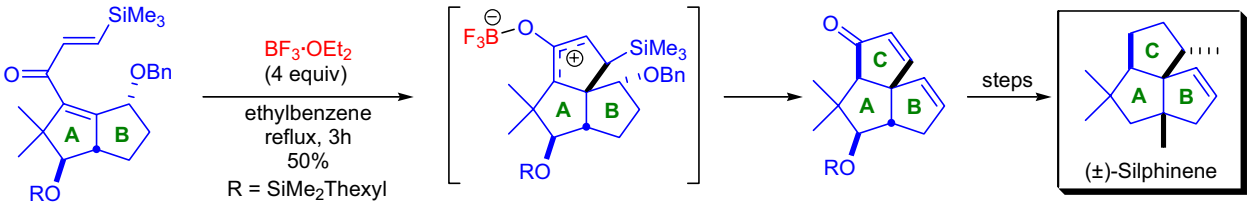
NAZAROV CYCLIZATION

Synthetic Applications:

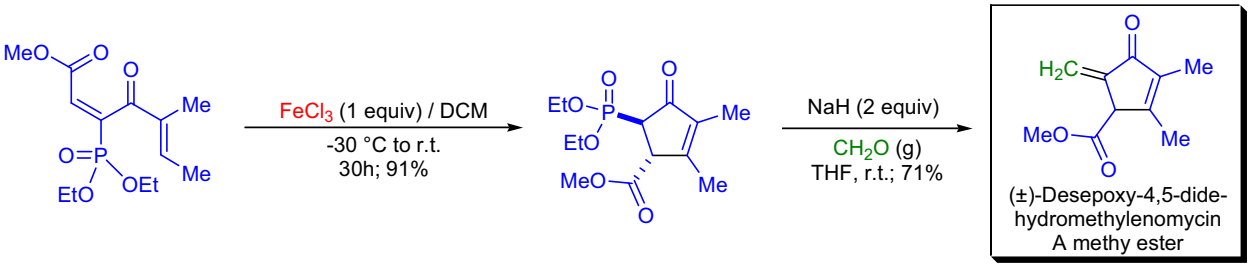
The stereoselective synthesis of (±)-trichodiene was accomplished by K.E. Harding and co-workers.[38] The synthesis of this natural product posed a challenge, since it contains two adjacent quaternary stereocenters. For this reason, they chose a stereospecific electrocyclic reaction, the *Nazarov cyclization*, as the key ring-forming step to control the stereochemistry. The cyclization precursor was prepared by the *Friedel-Crafts acylation* of 1,4-dimethyl-1-cyclohexene with the appropriate acid chloride using $SnCl_4$ as the catalyst. The *Nazarov cyclization* was not efficient under protic acid catalysis (e.g., TFA), but in the presence of excess boron trifluoride etherate high yield of the cyclized products was obtained. It is important to note that the mildness of the reaction conditions accounts for the fact that both of the products had an intact stereocenter at C2. Under harsher conditions, the formation of the C2-C3 enone was also observed.



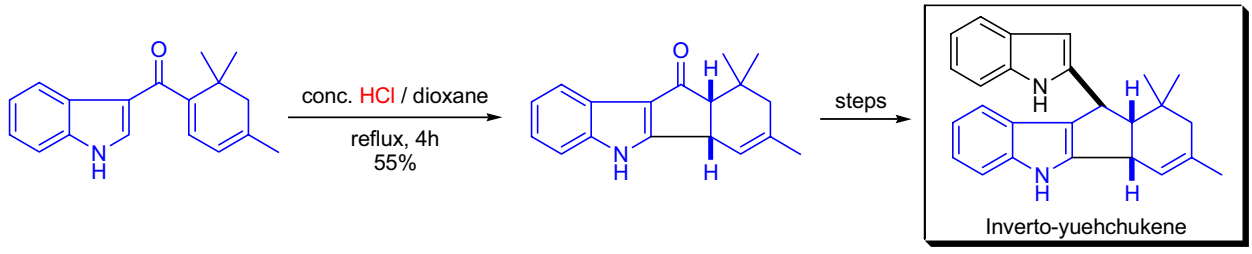
In the laboratory of M. Miesch, the *silicon-directed Nazarov cyclization* was utilized in the synthesis of the angular triquinane (±)-silphinene.[39] The cyclization precursor was prepared by the addition of a Grignard reagent derived from bromovinylsilane to the α,β-unsaturated aldehyde on the A ring, followed by MnO_2 oxidation of the resulting allylic alcohol. The addition of large excess of boron trifluoride etherate in refluxing ethylbenzene brought about the *Nazarov cyclization* to form the C ring of the natural product. The benzyloxy group on the B ring was also eliminated during the cyclization step.



The six-step synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A methyl ester from diethyl methanephosphonate was reported by M. Mikolajczyk et al.[40] The key ring-forming step was the *Nazarov cyclization* of an α-phosphoryl dienone to afford the corresponding cyclopentenone in high yield. In the product, the phosphoryl and carboxymethyl groups were exclusively *trans* disposed to each other. The double bond was found to be also exclusively at the C2 and C3 positions. The final step of the synthetic sequence was the introduction of the exo-methylene functionality by using the *Horner-Wittig reaction*.



The naturally occurring *bis*-indole yuehchukene is considered the dimer of 3-didehydroprenylindole and exhibits potent anti-implantation activity in rats. Part of an SAR study, K.-F. Cheng and co-workers synthesized inverto-yuehchukene, which can be considered as the dimer of 2-didehydroprenylindole.[41] The five-membered ring of the target was constructed by the *Nazarov cyclization* of the corresponding divinyl ketone in a refluxing dioxane solution containing concentrated hydrocholoric acid.



NEBER REARRANGEMENT

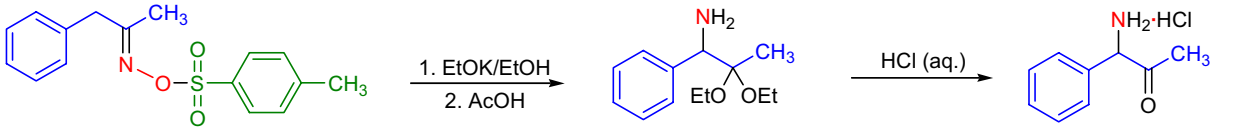
(References are on page 636)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-11]; *Modifications & Improvements*[12-19]]

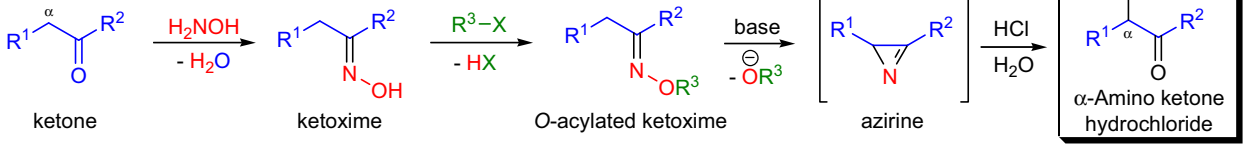
In 1926, during the investigation of the *Beckmann rearrangement*, P.W. Neber and A. Friedolsheim reported that the successive treatment of ketoxime tosylates with potassium ethoxide, acetic acid, and hydrochloric acid yielded the hydrochloride salts of α-amino ketones.[1] The base-induced rearrangement of *O*-acylated ketoximes to the corresponding α-amino ketones is known as the *Neber rearrangement*. Since its discovery, the rearrangement has become an important synthetic tool in the synthesis of heterocycles in which amino ketones are used as key intermediates. The general features of the reaction are: 1) acylated ketoximes derived from both acyclic and cyclic ketones can be used; 2) the required oximes are readily prepared from the ketones by reacting them with hydroxylamine under acidic conditions; 3) *O*-acylation of the oximes is conducted using acyl halides or anhydrides in the presence of a mild base (e.g., pyridine); 4) the rearrangement is usually carried out in an alcohol solution containing equimolar quantities of an alkali alkoxide; 5) when two methylene groups are available at the α- and α'-positions, the rearrangement mainly gives rise to a product in which the amino group is located on the more electrophilic carbon; 6) the rearrangement is not stereospecific, since the stereochemistry of the substrate (*syn* or *anti*) usually does not influence the outcome of the reaction, and this is in sharp contrast with the stereospecificity of the *Beckmann rearrangement*; and 7) the product amino ketones have a tendency to dimerize, so they often need to be prepared in a protected form as their amino acetals or hydrochloride salts (e.g., the amino acetals are prepared from the 2*H*-azirine intermediates by treatment with acidic alcohols). There are a few limitations to the *Neber rearrangement*: 1) *O*-acylated aldoximes do not yield α-amino ketones upon treatment with base, but rather undergo *E2 elimination* to afford the corresponding nitriles or isonitriles; and 2) the substrate must have a methylene group in the α-position in the overwhelming majority of the cases. Other types of compounds having at least one α-hydrogen atom also undergo the *Neber rearrangement* upon treatment with base: 1) ketone dimethylhydrazonium halides;[20] 2) *N,N*-dichloro-*sec*-alkyl amines;[21,22] 3) *N*-chloroimines;[12] and 4) *N*-chloroimidates.[13,23]

Rearrangement of ketoxime tosylates (Neber, 1926):



1-phenylpropan-2-one oxime tosylate — 2,2-diethoxy-1-phenylpropylamine — 1-amino-1-phenylpropan-2-one hydrochloride

Neber rearrangement of O-acylated ketoximes:

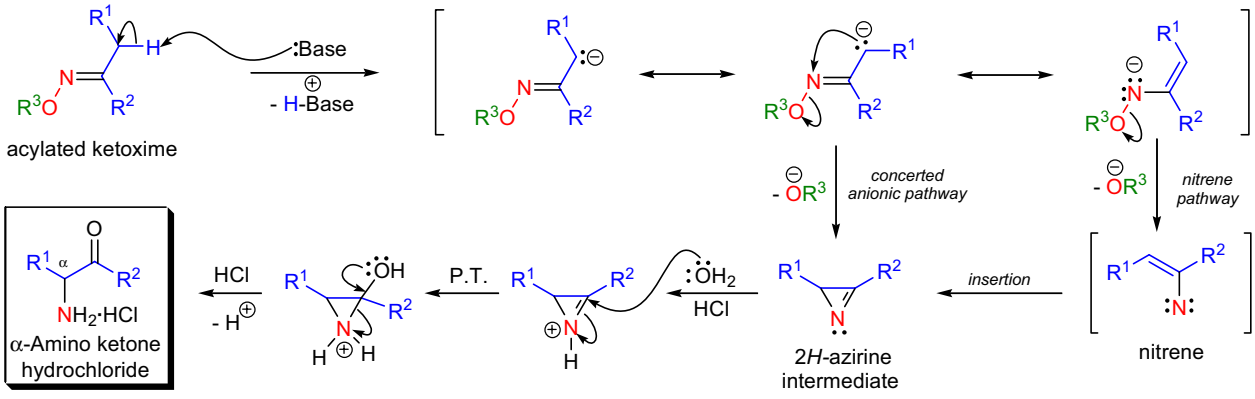


ketone — ketoxime — *O*-acylated ketoxime — azirine — α-Amino ketone hydrochloride

R^1 = H, alkyl, aryl; R^2 = alkyl, aryl, O-alkyl, NH_2, NH-alkyl; R^3 = $SO_2C_6H_4CH_3$, SO_2CH_3; base: NaOEt, KOEt

Mechanism:[24,25,22,26-28,19]

The first step of the mechanism is the deprotonation of the *O*-acylated ketoxime at its α-position, which gives rise to the corresponding enolate. This enolate then can react *via* two possible pathways: 1) a concerted anionic pathway in which the leaving group is directly displaced to give the isolable 2*H*-azirine or 2) a nitrene pathway that leads to the same 2*H*-azirine intermediate *via nitrene insertion*. The nitrene pathway has not been disproved experimentally.

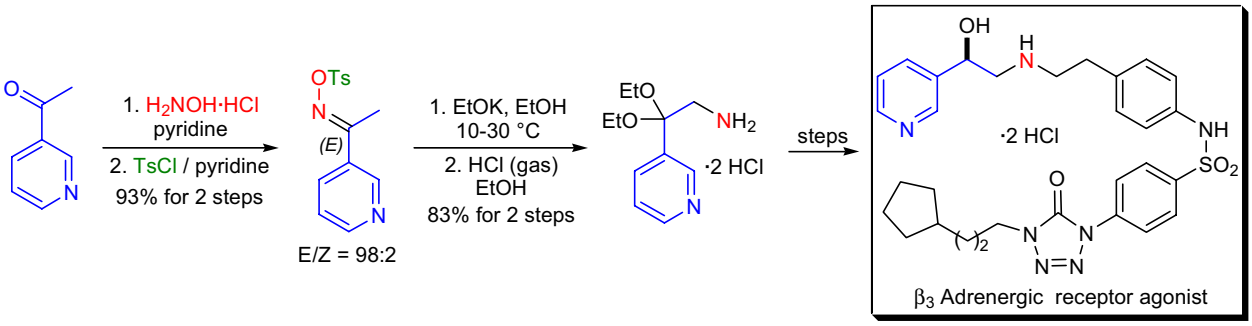


acylated ketoxime

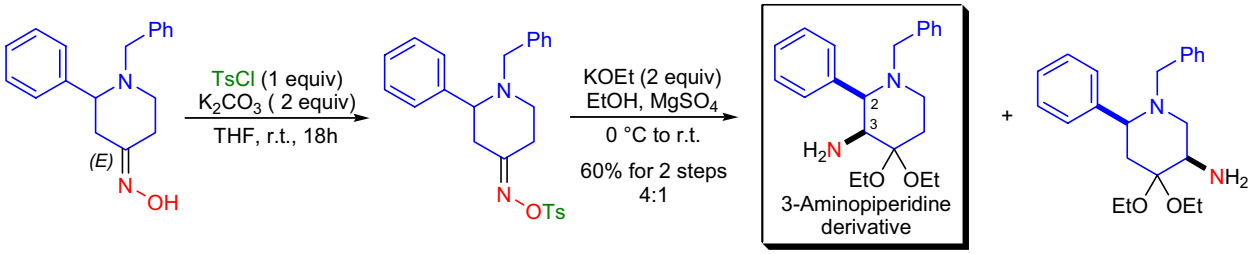
NEBER REARRANGEMENT

Synthetic Applications:

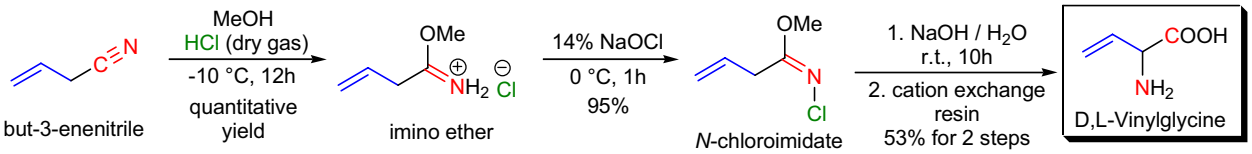
The chemoenzymatic synthesis of a β_3 adrenergic receptor agonist was developed by J.Y.L. Chung and co-workers.[29] The key chiral 3-pyridylethanolamine intermediate was prepared *via* the *Neber rearrangement* of the ketoxime tosylate derived from 3-acetylpyridine. The oxime formation and the tosylation were carried out in a one-pot process using pyridine as the solvent. The solution of the ketoxime tosylate in ethanol was then cooled to 10 °C and potassium ethoxide was added. After the TsOK salt was removed from the reaction mixture, HCl gas was bubbled through the solution until the pH reached ~2 and the 3-pyridylaminomethyl ketal was isolated as its di-HCl salt.



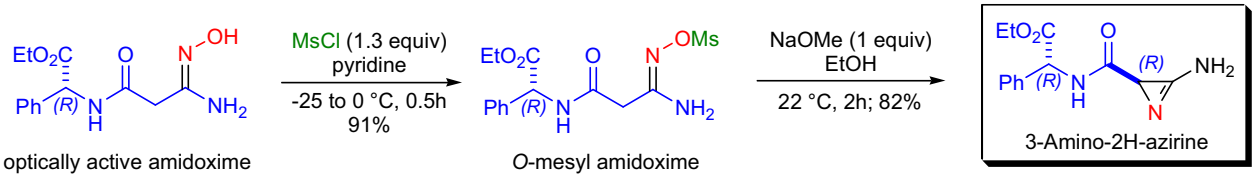
In the laboratory of M. Rubiralta, the general synthesis of the potential substance P antagonist 3-aminopiperidines was accomplished.[30] The (*E*)-oxime of 2-phenyl-2-piperidone was first tosylated and the resulting ketoxime tosylate was immediately subjected to KOEt/EtOH in the presence of anhydrous $MgSO_4$. The resulting regioisomeric aminopiperidines were formed in a 4:1 ratio. The major regioisomer was identified as the 2,3-*cis* diastereomer. Interestingly, when the (*Z*)-oxime was rearranged under identical conditions, the other regioisomer was the major product. This finding suggested that the intermediate 2*H*-azirine was formed *via* the *anti* displacement of the tosyl group.



The short synthesis of L- and D-vinylglycine was achieved by D.H.G. Crout and co-workers using the *Neber rearrangement* of an *N*-chloroimidate prepared from but-3-enenitrile.[23] The synthesis started with the *Pinner reaction*, which gave rise to the imino ether in quantitative yield. Oxidation of the imino ether with sodium hypochlorite afforded the *N*-chloroimidate, which was then exposed to aqueous NaOH to induce the *Neber rearrangement*. The racemic vinylglycine was isolated in 53% yield using a cation exchange resin. The resolution of this racemic product was carried out by a *papain-catalyzed enantioselective esterification* in a two-phase system.



The synthesis of optically active 3-amino-2*H*-azirines was carried out using a *modified Neber rearrangement* in the laboratory of I.P. Piskunova.[16] The optically active amidoximes were acylated using mesyl chloride to give *O*-mesyl derivatives that upon treatment with sodium methoxide afforded the desired product with high diastereoselectivity.



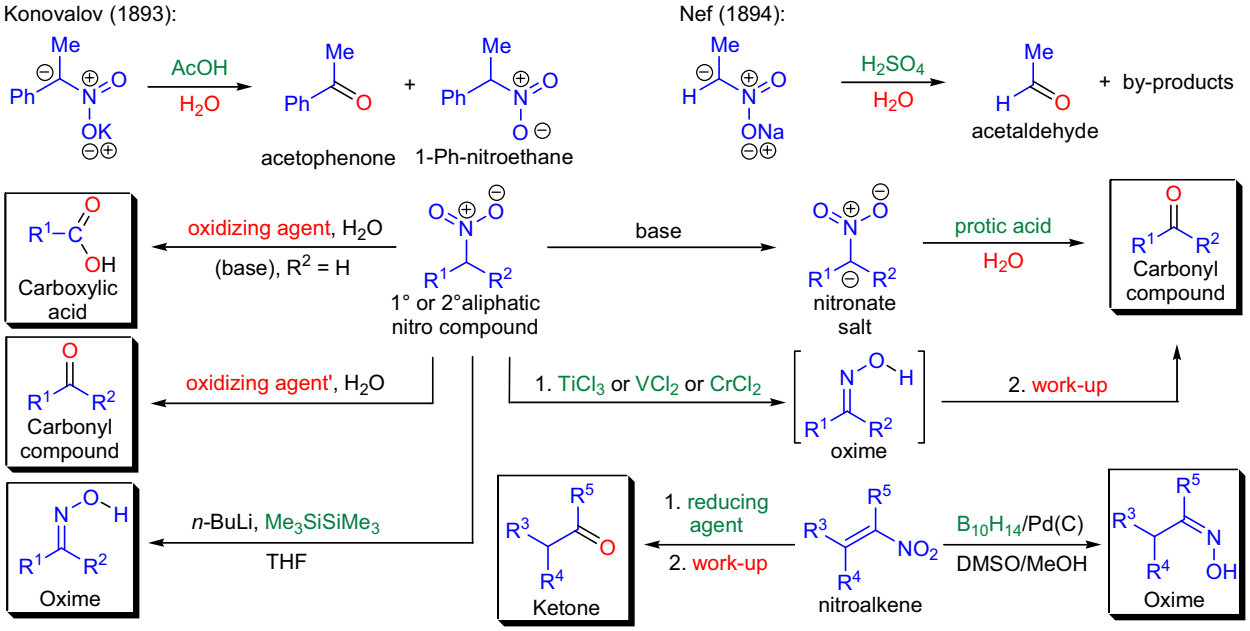
NEF REACTION

(References are on page 636)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-9]*; Modifications & Improvements*[10-30]]

In 1893, M. Konovalov observed that the treatment of the potassium salt of 1-phenylnitroethane with dilute acid (AcOH, H_2SO_4) led to the formation of 1-phenylnitroethane and acetophenone.[1] In 1894, J.U. Nef systematically studied the acidic hydrolysis of several nitroparaffin sodium salts, while he was completely unaware of Konovalov's experiments, and showed that the major product of all these reactions were the corresponding carbonyl compounds.[2] Since Nef demonstrated the generality of this transformation, which he discovered independently, the conversion of nitroalkanes into the corresponding carbonyl compounds is known as the *Nef reaction*. The general features of the reaction are: 1) the product distribution is strongly influenced by the acid concentration, and for best results the pH need to be smaller than unity; 2) when the pH>1, a number of by-products such as oximes and hydroxynitroso compounds can be formed; and 3) original reaction conditions required the addition of the nitronate salt to the solution of the acid to avoid the formation of undesired products. To make the reaction more chemoselective and tolerant toward many functional groups, several modifications have been developed during the past three decades: 1) oxidative methods allow the conversion of primary nitroalkanes into aldehydes or carboxylic acids, while secondary nitroalkanes are converted to ketones;[11,13,21,23,24,27] 2) reductive methods are available for the direct preparation of nitroalkanes to aldehydes, ketones, or oximes;[10,12,17,26] 3) carbonyl compounds and oximes can also be prepared from nitroolefins (nitroalkenes) using various reducing agents.[14,15,18,25]

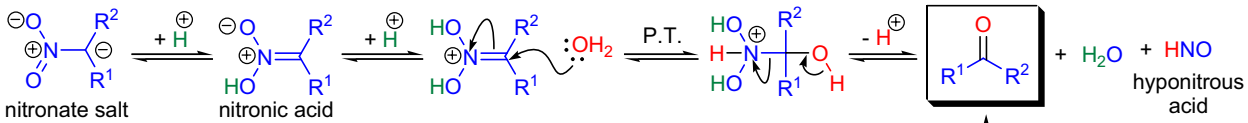


R^{1-2} = H, alkyl, aryl; R^{3-5} = H, aryl, alkyl; oxidizing agent: $KMnO_4$ (at pH~11), Oxone, $(OTMS)_2$, TPAP/NMO, $Cu(OAc)_2/O_2$, $NaNO_2$/AcOH/DMSO; oxidizing agent': to get aldehydes (R^2 = H) use DMDO, $Na_2CO_3 \cdot 1.5\ H_2O_2$, $KMnO_4$ while for ketones use any of the above oxidants; reducing agent: Al powder/$NiCl_2 \cdot 6H_2O$, Zn dust/TFA, Mg powder/$CdCl_2$; protic acid: HCl, H_2SO_4, AcOH

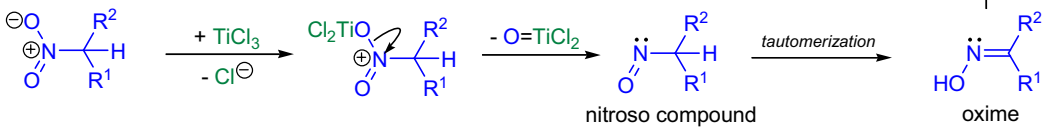
Mechanism:[31-39,4,5,40,41]

The mechanism of the *Nef reaction* has been extensively studied. Under the original reaction conditions, the nitronate salt is first protonated to give the nitronic acid, which after further protonation is attacked by a molecule of water. The process is strongly dependent on the pH of the reaction medium. Weakly acidic conditions favor the regeneration of the nitro compound and by-product formation (oximes and hydroxynitroso compounds), whereas strongly acidic medium (pH 1) promotes the formation of the carbonyl compound. The most popular reductive method ($TiCl_3$) proceeds *via* a nitroso compound that tautomerizes to form an oxime and finally upon work-up the desired product is obtained.

Nef reaction under acidic conditions:



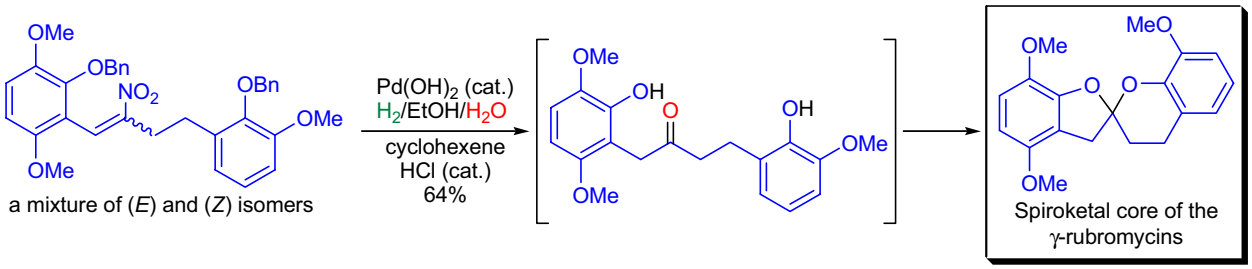
Nef reaction under reductive conditions:



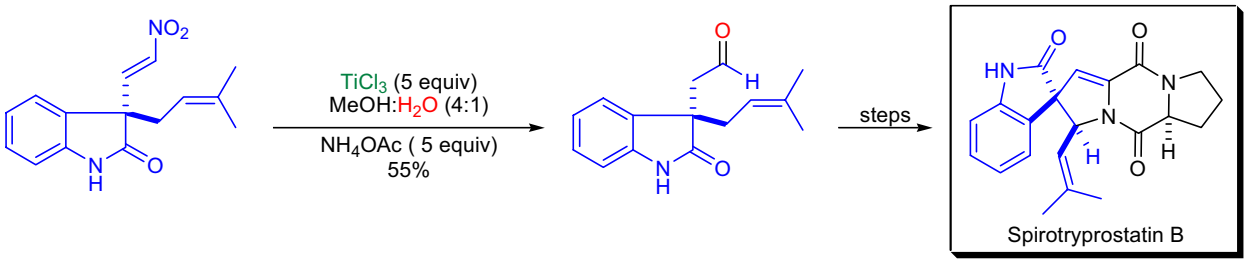
NEF REACTION

Synthetic Applications:

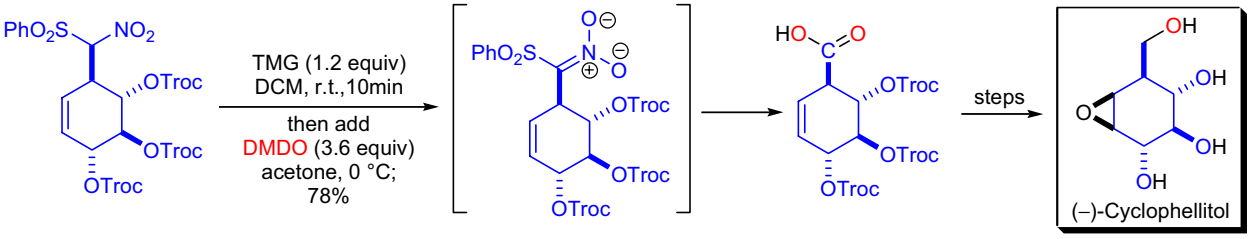
The synthesis of the bisbenzannelated spiroketal core of the γ-rubromycins was achieved by the research team of C.B. de Koning.[42] The key step was the *Nef reaction* of a nitroolefin, which was prepared by the *Henry reaction* between an aromatic aldehyde and a nitroalkane. The nitroolefin was a mixture of two stereoisomers, and it was subjected to catalytic hydrogenation in the presence of hydrochloric acid. The hydrogenation accomplished two different tasks: it first converted the nitroalkene to the corresponding oxime and removed the benzyl protecting groups. The oxime intermediate was hydrolyzed to a ketone that underwent spontaneous spirocyclization to afford the desired spiroketal product.



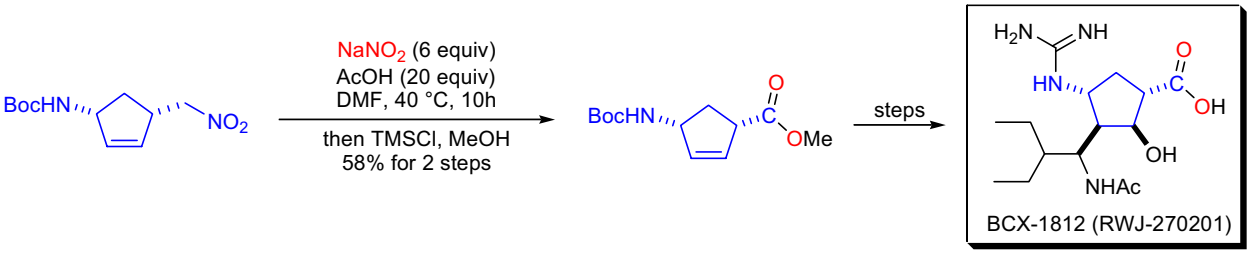
The total synthesis of spirotryprostatin B was accomplished by K. Fuji et al using an *asymmetric nitroolefination* to establish the quaternary stereocenter.[43] The conversion of the nitroolefin to the corresponding aldehyde was carried out under reductive conditions using excess titanium(III) chloride in aqueous solution. The initially formed aldehyde oxime was hydrolyzed *in situ* by the excess ammonium acetate.



In the laboratory of B.M. Trost, the second generation asymmetric synthesis of the potent glycosidase inhibitor (–)-cyclophellitol was completed using a *Tsuji-Trost allylation* as the key step.[44] The synthetic plan called for the conversion of the α-nitrosulfone allylation product to the corresponding carboxylic acid or ester. Numerous oxidative *Nef reaction* conditions were tested, but most of them caused extensive decomposition of the starting material or no reaction at all. Luckily, the nitrosulfone could be efficiently oxidized with dimethyldioxirane under basic conditions (TMG) to afford the desired carboxylic acid in high yield.



In order to treat influenza infections, the development of neuraminidase inhibitors is required. The currently available compounds are not potent enough, and they have a number of side effects. The stereoselective total synthesis of one potent inhibitor, BXC-1812 (RWJ-270201), was achieved by M.J. Müller and co-workers.[45] The key intermediate substituted nitromethane was prepared *via* a Pd-catalyzed allylation of nitromethane under basic conditions. The transformation of this nitroalkane to the corresponding carboxylic acid methyl ester was carried out in two steps. The *Nef reaction* was conducted in DMF instead of the usual DMSO because DMSO as the solvent caused extensive epimerization of the product. The initially formed carboxylic acid was then esterified.



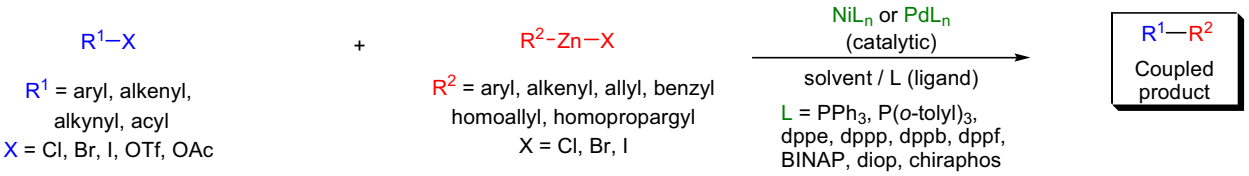
NEGISHI CROSS-COUPLING

(References are on page 637)

Importance:

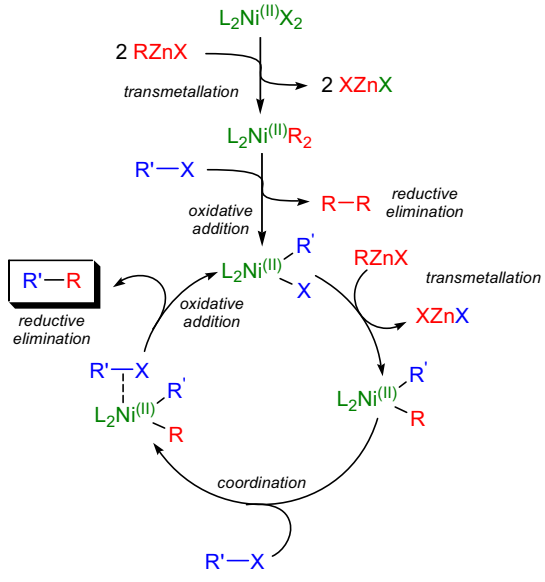
[*Seminal Publications*[1-6]; *Reviews*[7-24]; *Modifications & Improvements*[25-32]]

In 1972, after the discovery of Ni-catalyzed coupling of alkenyl and aryl halides with Grignard reagents (*Kumada cross-coupling*), it became apparent that in order to improve the functional group tolerance of the process, the organometallic coupling partners should contain less electropositive metals than lithium and magnesium. In 1976, E. Negishi and co-workers reported the first stereospecific Ni-catalyzed alkenyl-alkenyl and alkenyl-aryl cross-coupling of alkenylalanes (organoaluminums) with alkenyl- or aryl halides.[1,2] Extensive research by Negishi showed that the best results (reaction rate, yield, and stereoselectivity) are obtained when organozincs are coupled in the presence of $Pd^{(0)}$-catalysts.[3,4,7] The Pd- or Ni-catalyzed stereoselective cross-coupling of organozincs and aryl-, alkenyl-, or alkynyl halides is known as the *Negishi cross-coupling*. The general features of the reaction are: 1) both Ni- and Pd-phosphine complexes work well as catalysts. However, the Pd-catalysts tend to give somewhat higher yields and better stereoselectivity, and their functional group tolerance is better; 2) the active catalysts are relatively unstable $Ni^{(0)}$- and $Pd^{(0)}$-complexes but these can be generated *in situ* from more stable $Ni^{(II)}$- and $Pd^{(II)}$-complexes with a reducing agent (e.g., 2 equivalents of DIBAL-H or *n*-BuLi); 3) in the absence of the transition metal catalyst, the organozinc reagents do not react with the alkenyl halides to any appreciable extent; 4) the most widely used ligand is PPh_3, but other achiral and chiral phosphine ligands have been successfully used; 5) the various organozinc reagents can be prepared by either direct reaction of the organic halide with zinc metal or activated zinc metal or by transmetallation of the corresponding organolithium or Grignard reagent with a zinc halide (ZnX_2);[33,34] 6) the use of organozinc reagents allows for a much greater functional group tolerance in both coupling partners than in the *Kumada cross-coupling* where organolithiums and Grignard reagents are utilized as coupling partners; 7) other advantages of the use of organozincs include: high reactivity, high regio-, and stereoselectivity, wide scope and applicability, few side reactions and almost no toxicity; 8) the reaction is mostly used for the coupling of two $C(sp^2)$ carbons but $C(sp^2)$-C(sp) as well as $C(sp^2)$-$C(sp^3)$ couplings are well-known; 9) besides organozincs, compounds of Al and Zr can also be utilized; 10) if the organoaluminum and organozirconium derivatives are not sufficiently reactive, they can be transmetallated by the addition of zinc salts, and this protocol is referred to as the *double metal catalysis*;[35] and 11) of all the various organometals (Al, Zr, B, Sn, Cu, Zn), organozincs are usually the most reactive in Pd-catalyzed cross-coupling reactions and do not require the use of additives (e.g., bases as in *Suzuki cross-couplings*) to boost the reactivity;[20] Some of the limitations of the *Negishi cross-coupling* are: 1) propargylzincs do not couple well but homopropargylzincs do; 2) secondary and tertiary alkylzincs may undergo isomerization, but cross-couplings of primary alkyl- and benzylzincs give satisfactory results; and 3) due to the high reactivity or organozincs, CO insertion usually does not happen unlike in the case of less reactive organotins (see *carbonylative Stille cross-coupling*).

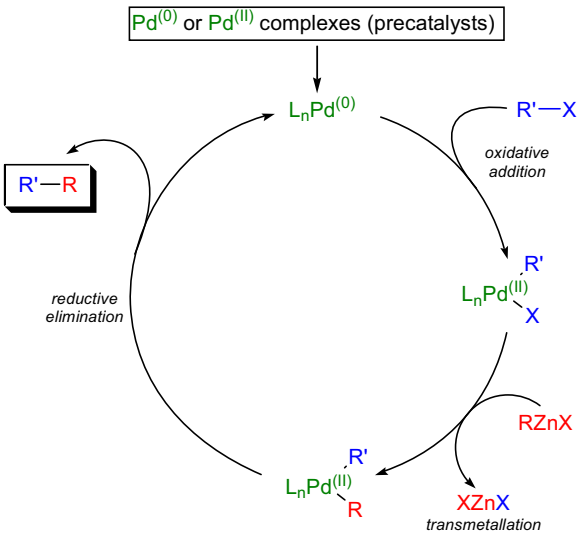


Mechanism:[10]

Ni-catalyzed process:



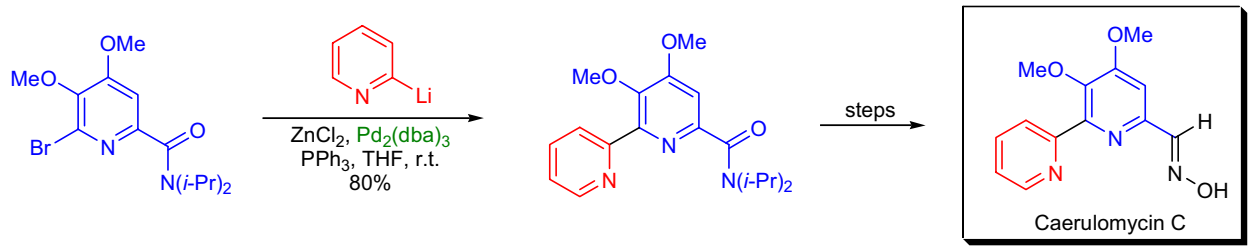
Pd-catalyzed process:



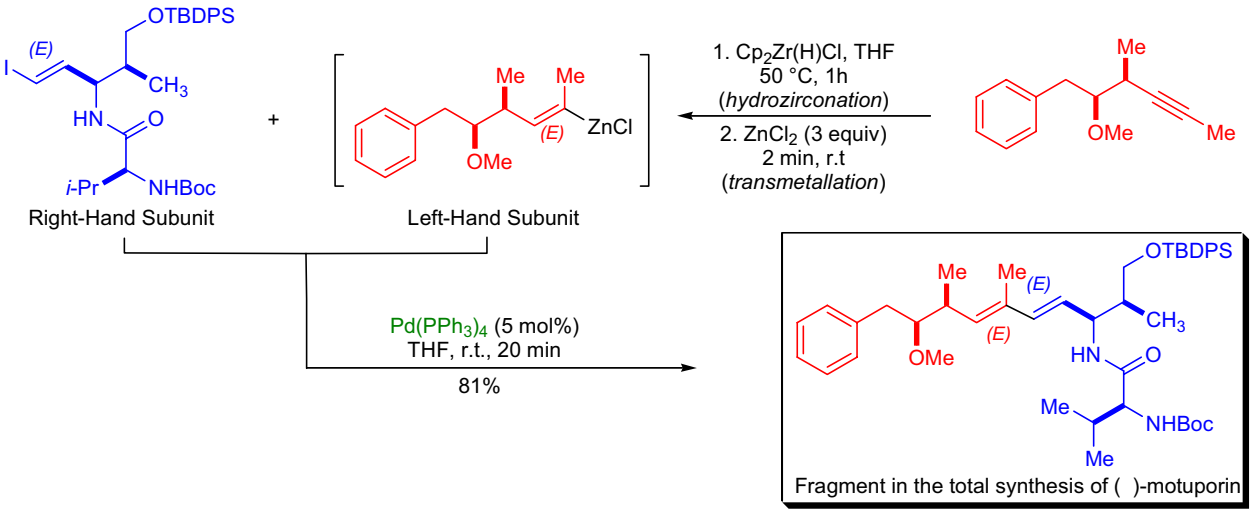
NEGISHI CROSS-COUPLING

Synthetic Applications:

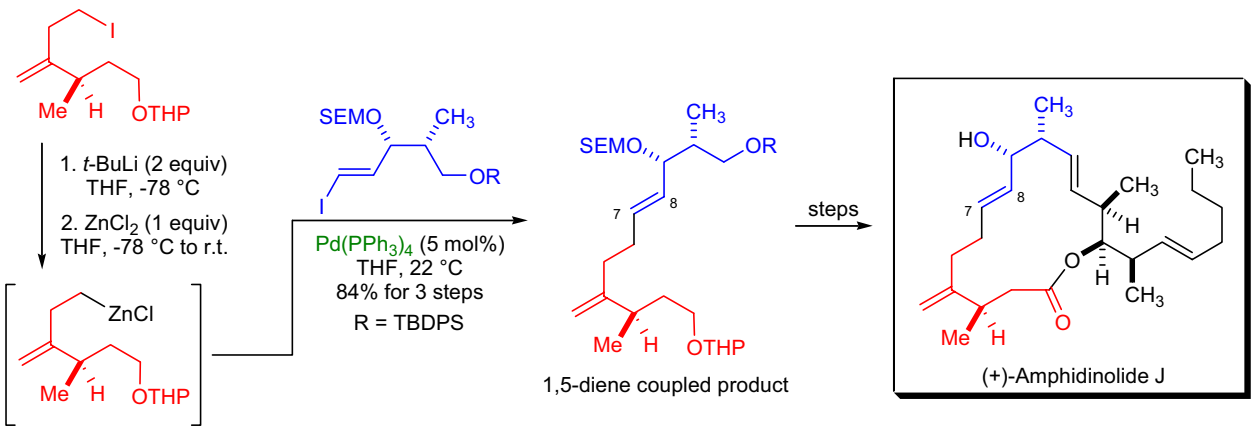
The *Negishi cross-coupling* was utilized during the final stages of the total synthesis of caerulomycin C for the preparation of the bipyridyl system by T. Sammakia et al.[36] The highly substituted 6-bromopyridine was coupled, in the presence of $Pd_2(dba)_3/PPh_3$ catalyst system, with 2-lithiopyridine, which was transmetallated by $ZnCl_2$ *in situ* to the corresponding organozinc reagent. Interestingly, the analogous *Stille cross-coupling* using 2-tributylstannyl pyridine was far less efficient and gave a low yield of the desired product.



The *modified Negishi protocol* was used in J.S. Panek's total synthesis of (–)-motuporin to couple the left-hand subunit organozinc compound with the right-hand subunit (*E*)-vinyl iodide.[37] The left-hand subunit was prepared by the *Schwartz hydrozirconation* of a disubstituted alkyne to give an (*E*)-trisubstituted zirconate, which was subsequently transmetalated with anhydrous $ZnCl_2$. The resulting vinylzinc species was immediately treated with one equivalent of the (*E*)-vinyl iodide in the presence of 5 mol% $Pd(PPh_3)_4$ to afford the (*E,E*)-diene coupled product with complete stereoselectivity.



The convergent and stereocontrolled synthesis of (+)-amphidinolide J was achieved in the laboratory of D.R. Williams.[38] To install the (*E*)- C7-C8 double bond stereoselectively, a homoallylic alkylzinc reagent was coupled with an (*E*)-vinyl iodide using the *Negishi reaction*. The very stable homoallylic alkylzinc species was prepared in one pot from the corresponding homoallylic iodide by treatment with two equivalents of *t*-BuLi followed by transmetallation with $ZnCl_2$. The addition of the (*E*)-vinyl iodide in the presence of catalytic amounts $Pd(PPh_3)_4$ gave the coupled 1,5-diene product in high yield.



NENITZESCU INDOLE SYNTHESIS

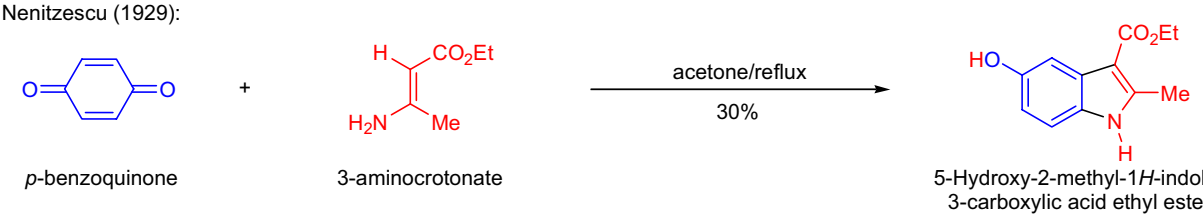
(References are on page 638)

Importance:

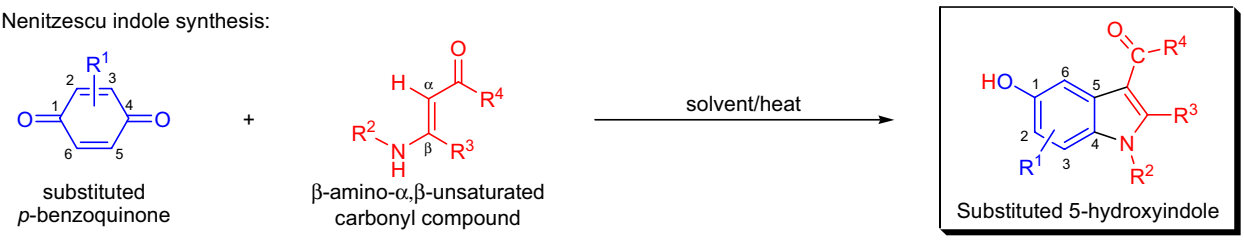
[*Seminal Publications*[1]; *Reviews*[2-6]; *Modifications & Improvements*[7-20]]

In 1929, C.D. Nenitzescu described the reaction of *p*-benzoquinone with 3-aminocrotonate in acetone at reflux temperature from which he isolated a 2-methyl-5-hydroxyindole derivative.[1] For the next two decades, the reaction was not explored further, but during the 1950s the scope and limitation of the transformation was thoroughly investigated and applied to the synthesis of melanin-related compounds. The condensation of a 1,4-benzoquinone with enamines to afford substituted 5-hydroxyindole derivatives is known as the *Nenitzescu indole synthesis*. The general features of the reaction are:[3] 1) the benzoquinone component can be unsubstituted, mono-, di-, or trisubstituted; 2) the degree of substitution does not have a significant effect on the rate of the reaction; 3) the structure of the enamine component may be varied widely: β-aminocrotonates (R^3=Me and R^4=O-alkyl), β-aminoacrylates, β-aminoacrylamides (R^4=NH_2 or NR_2), and even β-amino-α,β-unsaturated ketones can be used; 4) when R^4=O-alkyl, the resulting 3-alkoxycarbonyl indoles can be easily decarboxylated; 5) in most instances the R^3 substituent should be other than hydrogen; 6) yields can be very high, but occasionally low yields are observed (varies from substrate to substrate); 7) the reaction is regioselective, and the regioselectivity is strongly influenced by the nature of the substituents on the quinone component; 8) an electron-donating group (e.g., R^1=OH, O-alkyl) at the C2 position deactivates the C3 position and directs the attack of the nucleophile to C5; 9) an electron-withdrawing group (e.g., R^1=CO_2-alkyl, CF_3) at C2 directs the attack of the nucleophile preferentially to the C3 position; 10) a small substituent at C2, which is moderately electron-donating (e.g., R^1=Me, Cl) results in possible nucleophilic attack at either C5 or C6 and the formation of a mixture of regioisomeric indoles is expected; 11) when the C2 substituent is sterically demanding (e.g., R^1=*t*-Bu), the nucleophile is expected to attack at C5 preferentially; 12) besides 5-hydroxyindoles, other heterocycles such as benzofurans can be prepared using the *Nenitzescu reaction* between *N,N*-dialkylaminocrotonates and benzoquinones;[17] and 13) instead of the *p*-benzoquinone, the corresponding quinone imides and quinone diimides can also be used.[7,9]

Nenitzescu (1929):



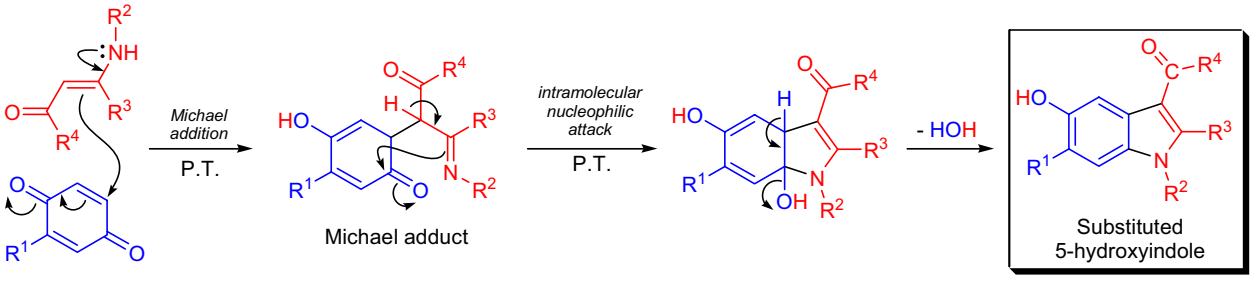
Nenitzescu indole synthesis:



R^1 = H, alky, aryl, OH, *O*-alkyl, *O*-aryl, Cl, Br, CF_3, CO_2-alkyl, etc.; R^2 = H, alkyl, cycloalkyl, aryl, benzyl; R^3 = alkyl, aryl, CO_2-alkyl, *O*-alkyl; R^4 = alkyl, aryl, *O*-alkyl, NH_2, NR_2; solvent: acetone, EtOH, $MeNO_2$, AcOH, $CHCl_3$

Mechanism:[21-27]

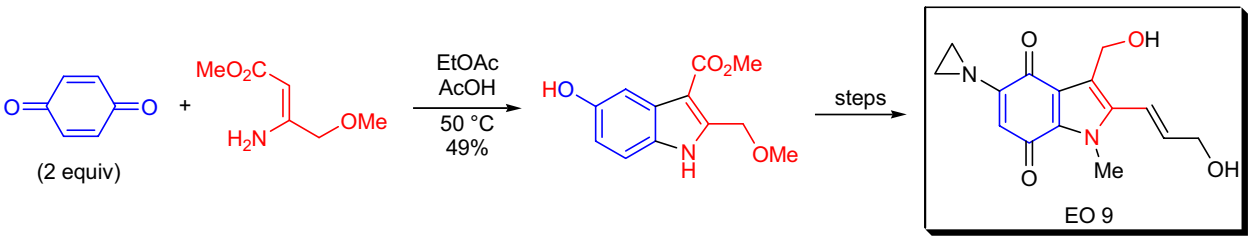
The mechanism of the *Nenitzescu indole synthesis* is not fully understood. The most likely first step is a *Michael addition* of the enamine to the *p*-quinone. In the resulting Michael adduct, the imine nitrogen attacks the proximal carbonyl group of the quinone and the bicyclic hemiaminal and then undergoes dehydration to give the 5-hydroxyindole product. In an alternative mechanism, an oxidation-reduction mechanism is proposed: the Michael adduct tautomerizes to the corresponding hydroquinone, which is oxidized by the starting *p*-quinone to another *p*-quinone, which undergoes intramolecular cyclization to qive a quinonimmonium intermediate. This intermediate in turn is a viable oxidant of the hydroquinone and itself gets reduced to give the 5-hydroxyindole product.[27]



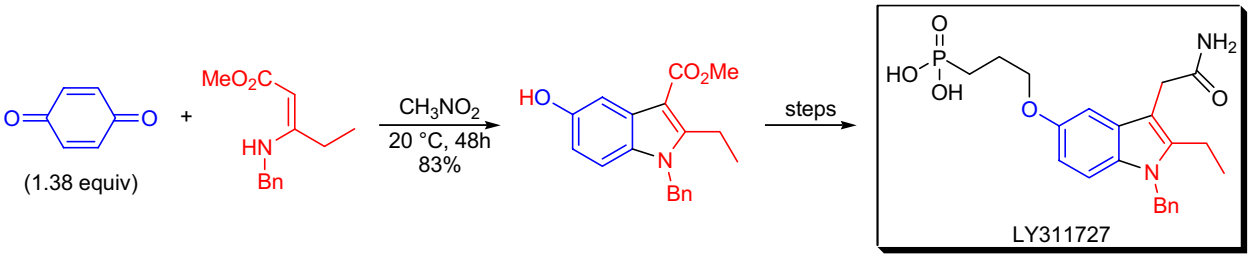
NENITZESCU INDOLE SYNTHESIS

Synthetic Applications:

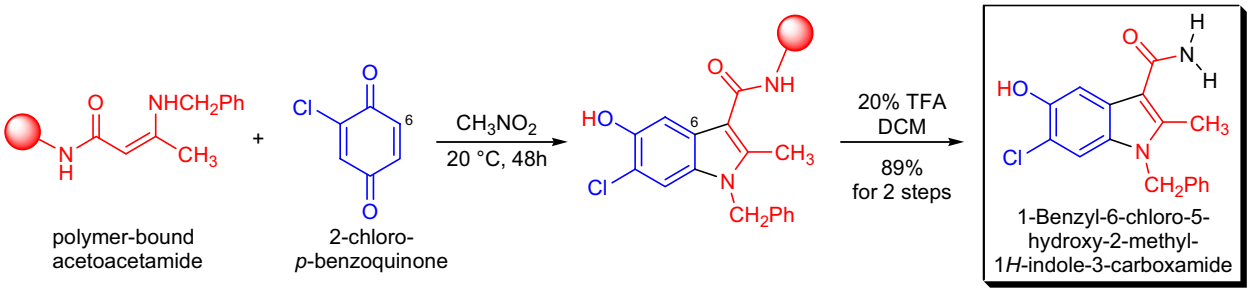
A facile synthesis of the key intermediate of EO 9, a novel and fully synthetic bioreductive alkylating indolequinone, was accomplished by M. Kasai et al.[28] The authors' goal was to develop a short and efficient synthesis in order to prepare large quantities of the target. The highly functionalized indole nucleus was constructed in one step using the *Nenitzescu indole synthesis*. The benzoquinone and the enamine were dissolved in the solvent mixture and heated to afford the desired methyl-5-hydroxy-2-methoxymethylindole-3-carboxylate in moderate yield. In the work-up step, the excess benzoquinone was destroyed with sodium dithionate ($Na_2S_2O_4$) and the product was crystallized thus obviating the need for chromatographic separation.



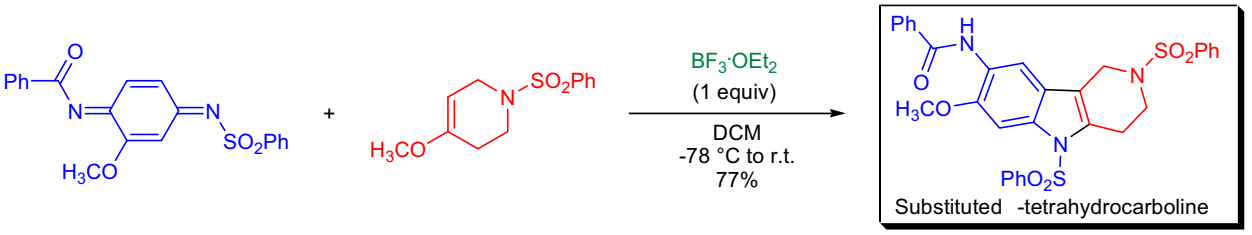
The synthesis of the first potent and selective secretory phospholipase A_2 (s-PLA_2) inhibitor, LY311727, was carried out in the laboratory of M.J. Martinelli.[29] The indole core of the target was prepared by the *Nenitzescu indole synthesis*, which proceeded in high yield. The enamine component was readily prepared from methyl propionylacetate (3-oxo-pentanoic acid methyl ester) and benzylamine in the presence of catalytic amounts of TsOH. A thorough screening of various solvents pinpointed nitromethane as the optimal solvent for the transformation, since the product crystallized from the reaction mixture and was easily removed by filtration.



The *Nenitzescu indole synthesis* can be formally regarded as a one-pot three-component condensation where all the components are readily available: -keto esters, primary amines, and *p*-benzoquinones. This observation prompted the research team of D.M. Ketcha to develop the *solid-phase version of the Nenitzescu indole synthesis* for the preparation of 5-hydroxyindole-3-carboxamides.[30] The process began with the acetoacetylation of ArgoPore -Rink-NH_2 resin with diketene to obtain a polymer-bound acetoacetamide, which was then converted to the corresponding enamine upon condensation with primary amines and in the presence of trimethyl orthoformate (dehydrating agent). The indole formation generally took place in nitromethane much more efficiently than in acetone, and it was completely regioselective, giving rise exclusively to the C6 regioisomer.



An interesting variant of the *Nenitzescu indole synthesis,* involving the Lewis acid-directed coupling of enol ethers with benzoquinone mono- and *bis*-imides, was developed by T.A. Engler et al. for the synthesis of substituted - and -tetrahydrocarbolines.[31]



NICHOLAS REACTION

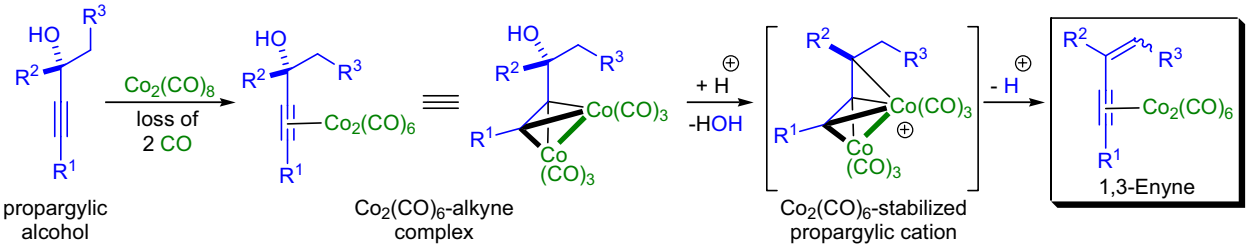
(References are on page 639)

Importance:

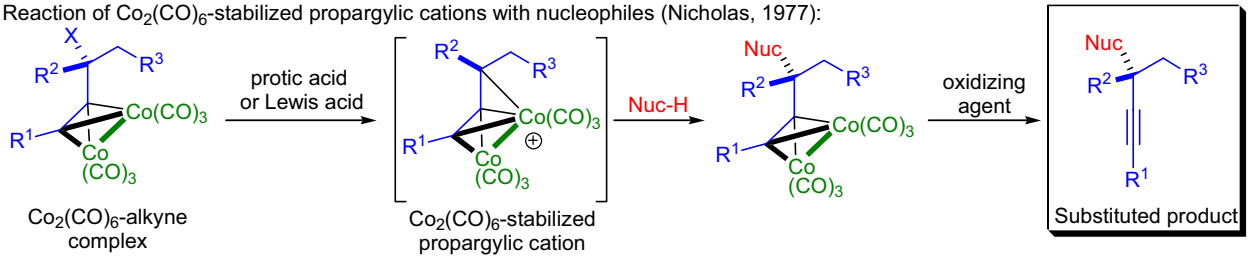
[*Seminal Publications*[1-4]; *Reviews*[5-14]; *Modifications & Improvements*[15-19]; *Theoretical Studies*[20,21]]

In 1972, K.M. Nicholas and R. Pettit reported that dicobalt hexacarbonyl-complexed propargylic alcohols were easily dehydrated upon treatment with acid to form the corresponding 1,3-enynes. However, uncomplexed propargylic alcohols did not react under identical conditions.[2] This finding suggested that the intermediates of these reactions were the dicobalt hexacarbonyl-stabilized propargylic cations, which in fact could be isolated and were shown to have significant stability.[3] The trapping of dicobalt hexacarbonyl-stabilized propargylic cations with various nucleophiles is known as the *Nicholas reaction*. The alkyne functionality of the resulting substituted products can be regenerated by a mild oxidation. The general features of the *Nicholas reaction* are: 1) propargylic alcohols are easily prepared by the addition of acetylides to ketones and aldehydes and readily converted to various derivatives; 2) the alkyne complexes are obtained in almost quantitative yields by reacting the propargyl derivatives with $Co_2(CO)_8$ in an appropriate solvent (ether, pentane, hexane, benzene, etc.);[1] 3) the cobalt-alkyne complexes are red, brown, or purple solids or oils that are moderately air stable and can be purified with flash chromatography; 4) the stabilized propargylic cations are either generated by the addition of Brönsted or Lewis acids to propargylic derivatives or by the addition of electrophiles to 1,3-enyne-cobalt hexacarbonyl complexes; 5) a wide range of nucleophiles reacts with the resulting propargylic cations including C-, O-, N-, and S-nucleophiles (see scheme); 6) after the substitution the cobalt complexes can be decomplexed either oxidatively (most common) or reductively; 7) *oxidative decomplexation* regenerates the triple bond, while *reductive decomplexation* (e.g., Li/liquid ammonia, H_2/Rh-catalyst, or Wilkinson catalyst) yields the corresponding alkene; 8) when the cobalt complex is not removed, it can be used in a subsequent Pauson-Khand reaction; 9) the reaction can be both inter- and intramolecular, and even macrocyclization can be achieved; and 10) there are no allene side products that often complicates the reactions of uncomplexed propargylic substrates.

Nicholas & Pettit (1972):

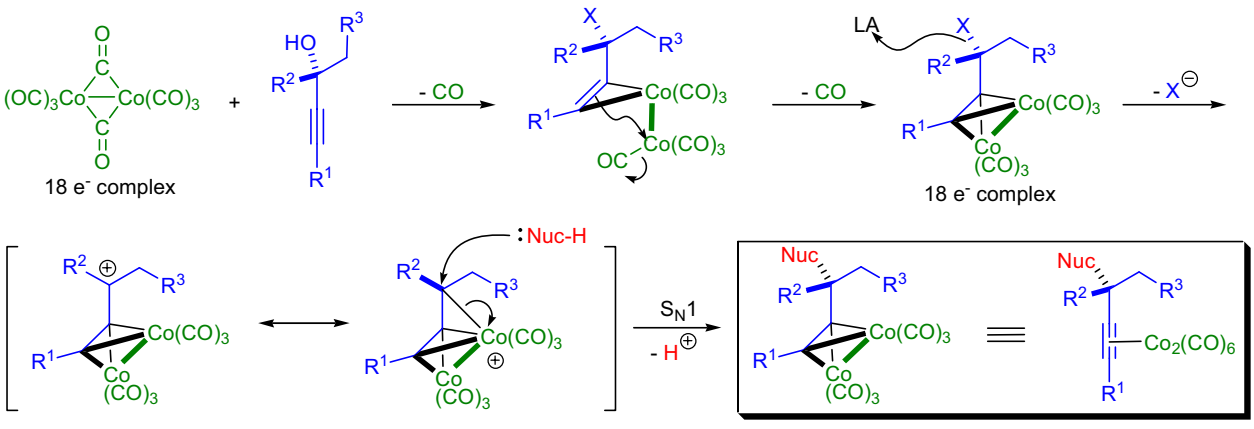


Reaction of $Co_2(CO)_6$-stabilized propargylic cations with nucleophiles (Nicholas, 1977):



R^{1-3} = H, alkyl, aryl; X = OH, O-alkyl, O-benzyl, O-silyl, acetal, OAc, OCOAr, OCO*t*-Bu, OMs, OTf, Cl; Nuc-H = e-rich aromatics, simple alkenes, allylsilanes, allylstannanes, enol ethers, silylketene acetals, ROH, N_3^-, RNH_2, RR'NH, RSH, HS(R)SH, F^-; oxidizing agent: CAN, $Fe(NO_3)_3$, NMO, TMANO, TBAF, C_5H_5N/air/ether, DMSO/H_2

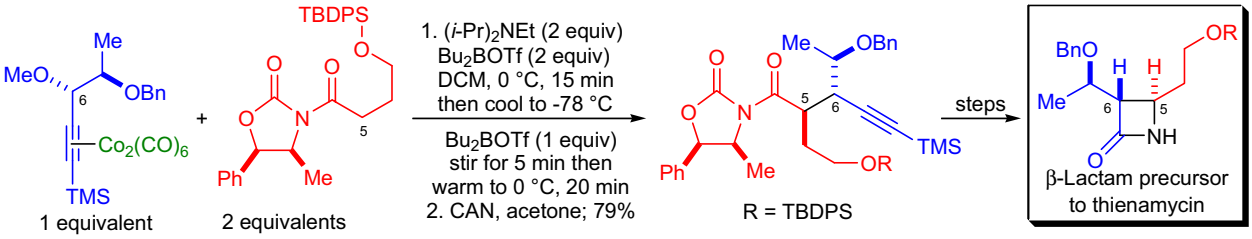
Mechanism:[2,22,20,23]



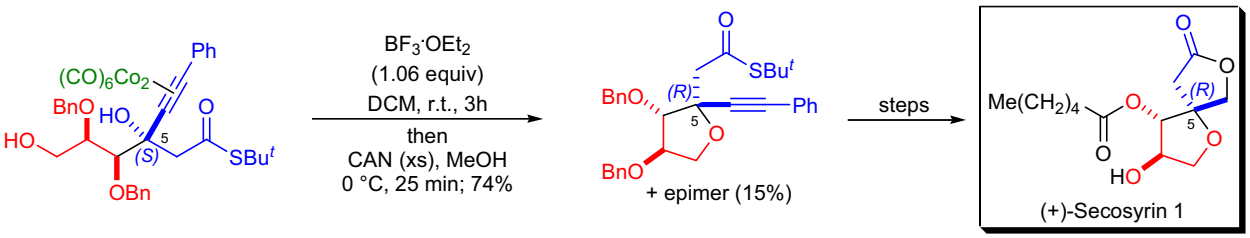
NICHOLAS REACTION

Synthetic Applications:

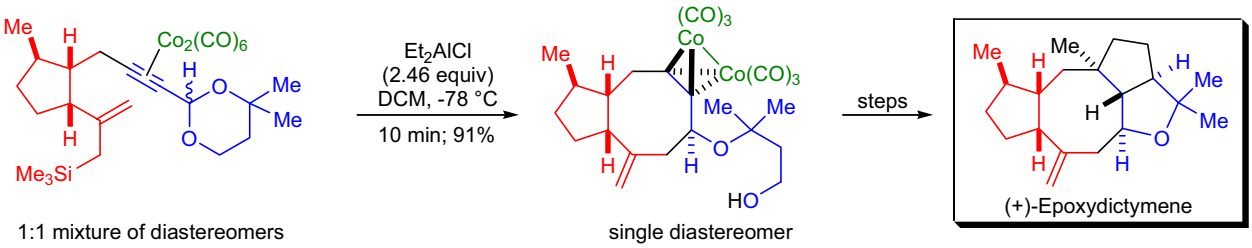
The *Nicholas reaction* was used to synthesize the β-lactam precursor of thienamycin in the laboratory of P.A. Jacobi and thereby accomplish its formal total synthesis.[24] The necessary β-amino acid was prepared by the condensation of a boron enolate (derived from an acylated oxazolidinone) with the cobalt complex of an enantiopure propargylic ether. The resulting adduct was oxidized with ceric ammonium nitrate (CAN) to remove the cobalt protecting group from the triple bond, and the product was obtained with a 17:1 *anti:syn* selectivity and in good yield.



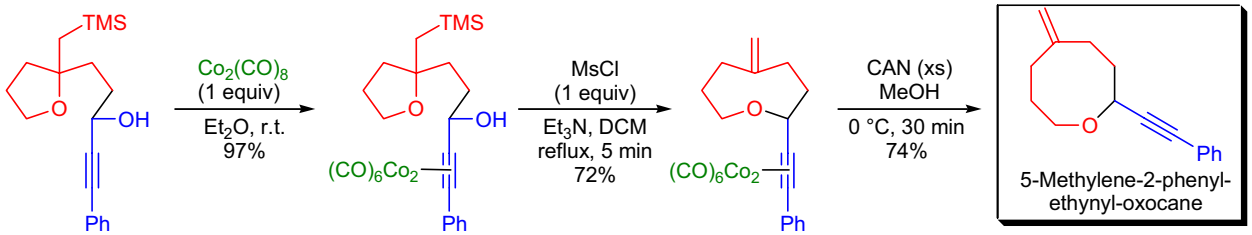
The total syntheses of (+)-secosyrins 1 and 2 was achieved and their relative and absolute stereochemistry was unambiguously established by C. Mukai and co-workers.[25] To construct the spiro skeleton of these natural products, the *intramolecular Nicholas reaction* was utilized. The alkyne substrate was first converted to the dicobalt hexacarbonyl complex by treatment with $Co_2(CO)_8$ in ether. Exposure of the resulting complex to boron trifluoride etherate at room temperature brought about the ring closure with inversion of configuration at C5 to afford the expected tetrahydrofuran derivative. The minor product was the C5 epimer which was formed only in 15% yield.



The tandem use of the *intramolecular Nicholas reaction* and the *Pauson-Khand reaction* was featured in S.L. Schreiber's total synthesis of (+)-epoxydictymene.[26] The propargylic acetal, a 1:1 mixture of diastereomers at the acetal carbon, was readily converted to the $Co_2(CO)_6$-complex in excellent yield. The treatment of this complex with a stoichiometric amount of Et_2AlCl afforded the 5-8 fused bicyclic ring system of the natural product as a single diastereomer in 91% yield. The allylsilane served as the nucleophile to capture the stabilized propargylic cation. The alkyne protecting group was not removed as later this cobalt-alkyne complex was utilized in the *Pauson-Khand reaction*.



The application of the *intramolecular Nicholas reaction* by C. Mukai et al. made it possible to develop a novel procedure for the construction of oxocane derivatives.[27] Interestingly, several Lewis and Brönsted acids gave rise to complex mixtures. However, the use of mesyl chloride/triethylamine in refluxing DCM afforded the desired oxocane as the sole product.



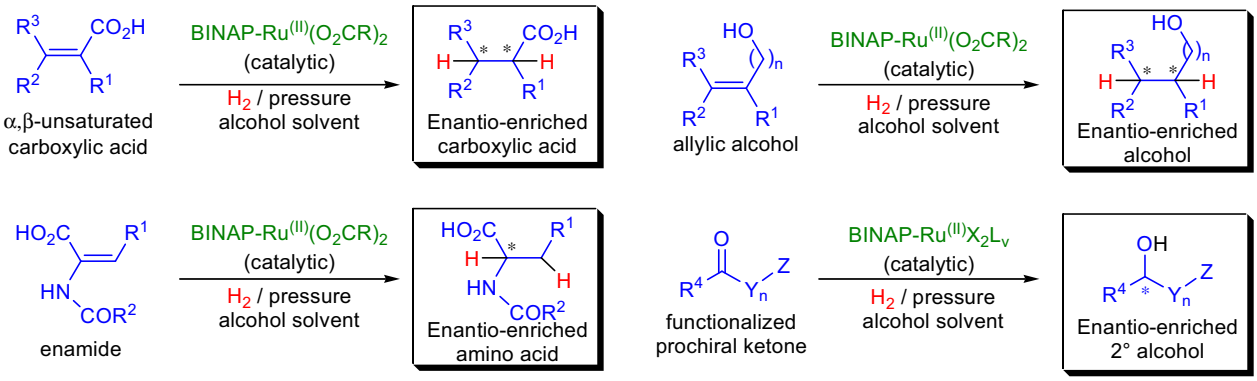
NOYORI ASYMMETRIC HYDROGENATION

(References are on page 640)

Importance:

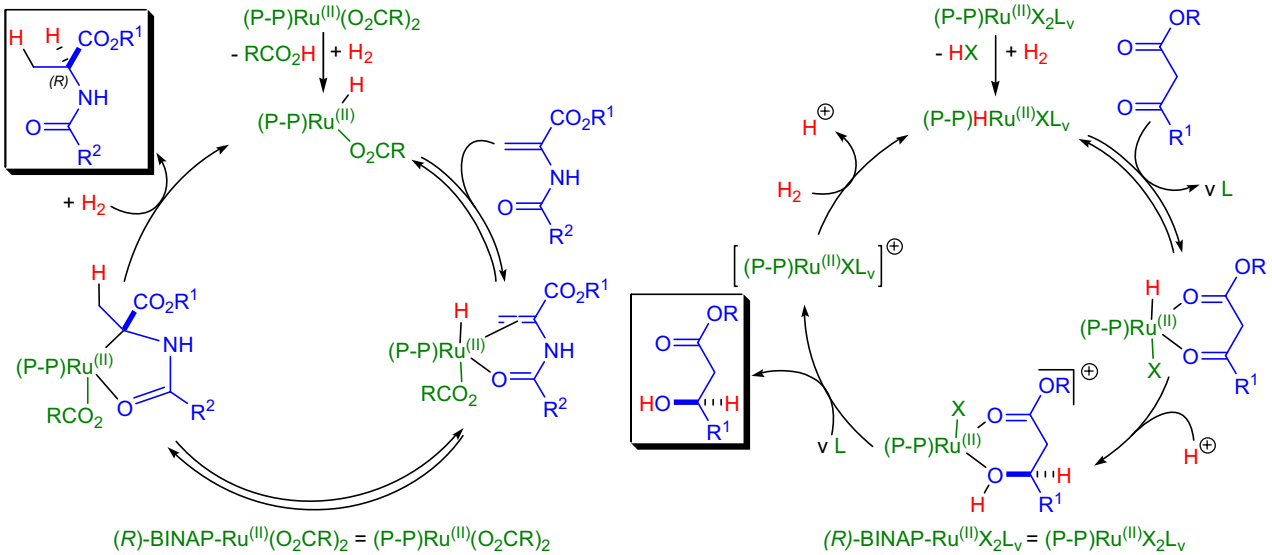
[*Seminal Publications*[1-4]; *Reviews*[5-32]; *Modifications & Improvements*[33-37]; *Theoretical Studies*[38,39]]

In 1980, T.S.R. Noyori and co-workers reported that cationic BINAP-Rh complexes catalyzed the *asymmetric hydrogenation* of α-(acylamino) acrylic acids or esters to give the corresponding amino acid derivatives in high enantiomeric excess.[1] However, these rhodium catalysts could be used only for the synthesis of amino acids, the rate of hydrogenation was very slow, and the reaction conditions had to be chosen very carefully for each substrate to achieve high enantioselectivity. A few years later, the preparation of BINAP-Ru$^{(II)}$ dicarboxylate complexes proved to be generally applicable for the asymmetric hydrogenation of a wide range of functionalized olefins.[2] Oligomeric halogen-containing BINAP-Ru$^{(II)}$ complexes were found to be efficient catalysts for the asymmetric hydrogenation of functionalized ketones in which coordinative nitrogen, oxygen, and halogen atoms near the C=O functionality direct the reactivity and the absolute stereochemistry of the product.[3,4] The reduction of functionalized olefins and ketones with hydrogen gas (H_2) using BINAP-Ru$^{(II)}$ complexes as catalyst is known as the *Noyori asymmetric hydrogenation*. The general features of the reaction are: 1) BINAP, a conformationally flexible atropisomeric C_2-symmetric diphosphane ligand is available in both enantiomeric forms;[40,41] 2) the various BINAP-Ru$^{(II)}$ complexes are easily prepared and the catalyst loadings are small; 3) hydrogenation of α,β-unsaturated and β,γ-unsaturated carboxylic acids takes place in alcohol solvents, where the sign and degree of enantioselection are highly dependent on the substitution pattern and hydrogen pressure;[42] 4) allylic and homoallylic alcohols are hydrogenated with high enantioselectivity;[43] 5) substituted enamides give rise to enantio-enriched α- or β-amino acids;[44,45] 6) the sense of chirality is predictable in the hydrogenation of functionalized ketones and preexisting stereogenic centers in the substrate significantly influence the outcome;[3] 7) the double hydrogenation of 1,3-diones *via* chiral β-hydroxy ketones give rise to *anti* 1,3-diols in almost 100% ee;[3] 8) β-keto esters are the best substrates for asymmetric hydrogenation;[46] and 9) racemic β-keto esters with a configurationally labile α-stereocenter can be transformed into a single stereoisomer with high selectivity by undergoing an *in situ* inversion of configuration in the presence of a base (*dynamic kinetic resolution*).[47,48]



R^{1-3} = H, alkyl, aryl; R^4 = alkyl, aryl; Z = nitrogen, oxygen, halogen; Y = sp^2 or sp^3 hybridized carbon; n =1-3; X = halogen; L = neutral ligand or solvent; R = alkyl, aryl

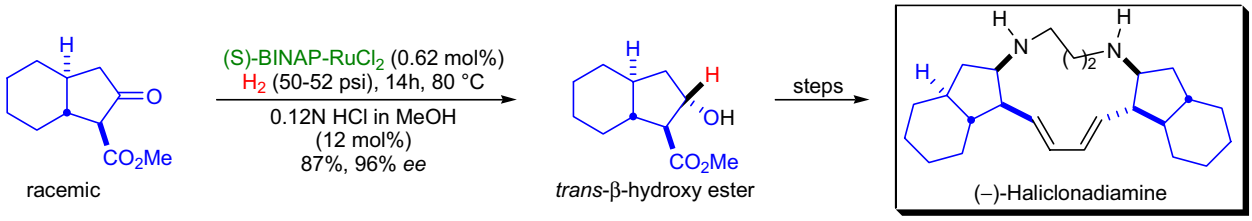
Mechanism:[1,49-64]



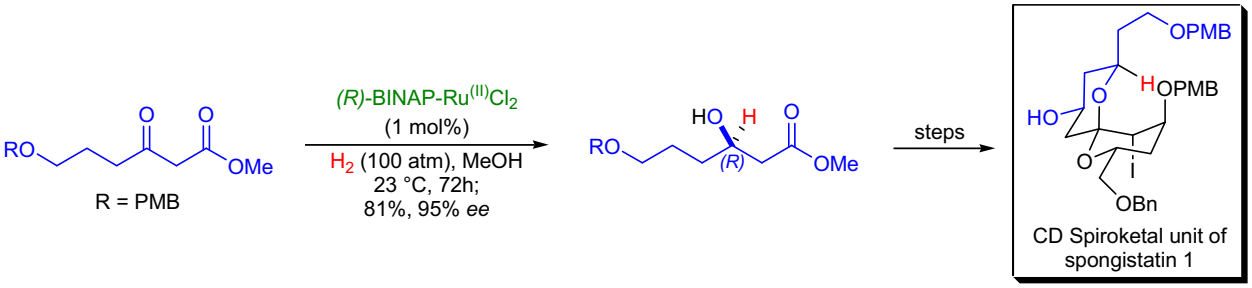
NOYORI ASYMMETRIC HYDROGENATION

Synthetic Applications:

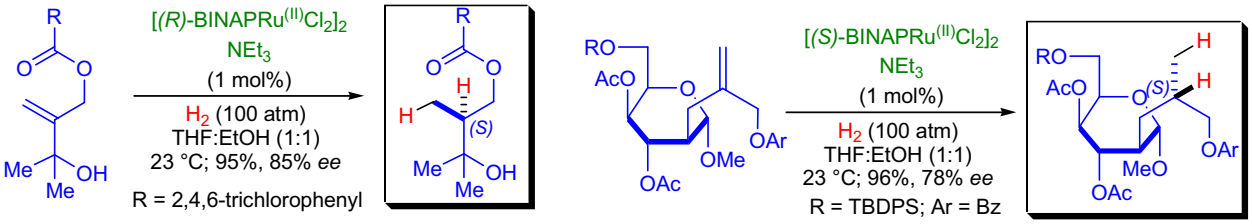
The total synthesis of pentacyclic alkaloid (–)-haliclonadiamine was accomplished by D.F. Taber and co-workers.[65] The *Noyori asymmetric hydrogenation* was used to prepare a bicyclic β-hydroxy ester intermediate in enantiopure form from a racemic bicyclic β-keto ester *via* kinetic resolution. It was found that the hydrogenation only took place in the presence of added HCl and by optimizing the amount of HCl added, the proportion of the total reduced ketone could be controlled. About 87% of the "matched" ketone was reduced, while the other β-keto ester enantiomer was not significantly converted to the reduced product. Interestingly, the diastereoselectivity of the hydrogenation depended on the nature of the added acid: with HCl, the *trans* diastereomer was the major product, while with AcOH the *cis* diastereomer was dominant.



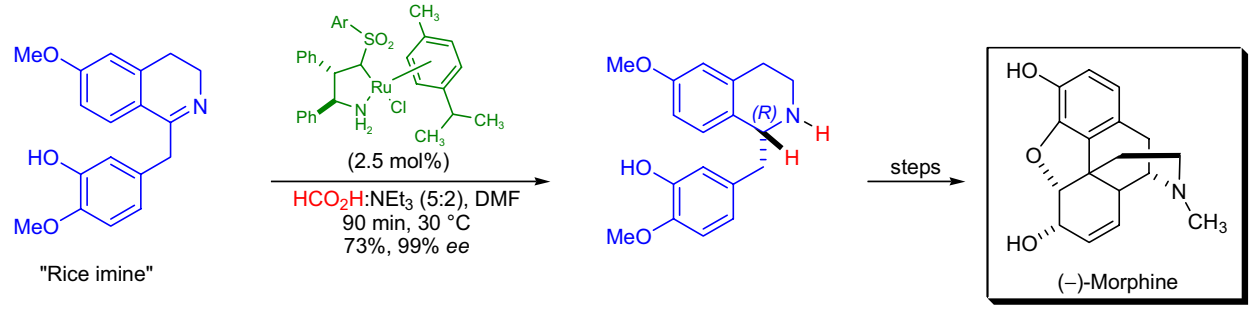
The convergent and stereocontrolled synthesis of the C17-C28 fragment (CD spiroketal unit) of spongistatin 1 was achieved in the laboratory of W.R. Roush.[66] One of the building blocks was prepared by using the *Noyori asymmetric hydrogenation* of a readily available β-keto ester, which gave rise to the corresponding β-hydroxy ester in 81% yield and 95% *ee*.



A pronounced enhancement of stereoselectivity was observed in the *asymmetric hydrogenation* of 2-substituted 2-propen-1-ols by *transient acylation* in the laboratory of O. Mitsunobu.[67] The aroylation of the allylic alcohol hydroxyl group prior to the hydrogenation gave the best results.



The *Noyori asymmetric transfer hydrogenation* was utilized in the synthesis of the chiral 1,2,3,4-tetrahydroisoquinolines by R.A. Sheldon et al.[68] These compounds are important intermediates in the Rice and Beyerman routes to morphine. The "Rice imine" was exposed to a series of chiral $Ru^{(II)}$ complexes, which was prepared from η^6-arene-$Ru^{(II)}$ chloride dimeric complexes and *N*-sulfonated 1,2-diphenylethylenediamines along with the azeotropic mixture of $HCOOH/NEt_3$. With the best catalyst the desired tetrahydroisoquinoline was isolated in 73% yield and the enantiomeric excess was 99%.



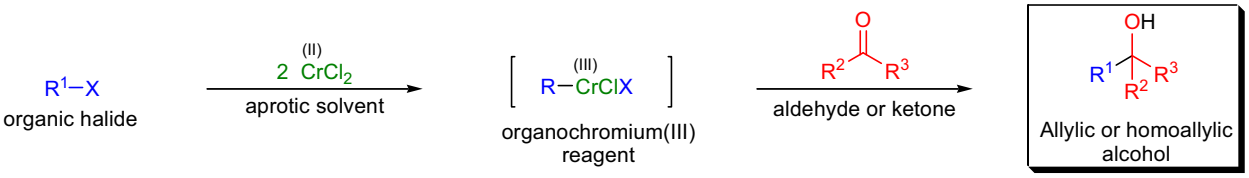
NOZAKI-HIYAMA-KISHI REACTION

(References are on page 641)

Importance:

[*Seminal Publications*[1-7]; *Reviews*[8-16]; *Modifications & Improvements*[17-30]]

In 1977, H. Nozaki and T. Hiyama et al. reacted aldehydes and ketones with organochromium(III) reagents, which were generated *in situ* from allyl and vinyl halides upon treatment with $CrCl_2$ under aprotic and oxygen-free conditions, and obtained the corresponding allylic and homoallylic alcohols with high chemospecificity and stereoselectivity.[1,2] In 1986, Y. Kishi and H. Nozaki independently discovered that traces of nickel salts catalyzed the formation of carbon-chromium(III) bonds, even from otherwise less reactive substrates (e.g., vinyl and aryl halides). This modification helped to make the process more reliable.[6,7] The one-pot *Barbier-type addition* of alkenyl, alkynyl, aryl, allyl, or vinylchromium compounds to aldehydes or ketones is known as the *Nozaki-Hiyama-Kishi (NHK) reaction*. Since its discovery, the *NHK reaction* has become a powerful synthetic tool for the chemoselective formation of carbon-carbon bonds under very mild conditions and has been applied to the total synthesis of a number of complex natural products. The general features of the reaction are: 1) the $CrCl_2$ is either purchased commercially or prepared by the reduction of $CrCl_3$ prior to the reaction; 2) $Cr^{(II)}$ is a one-electron donor, and therefore two moles of the chromium(II) salt are required to reduce one mol of organic halide to the corresponding organochromium(III) reagent; 3) it can take place both inter- and intramolecularly, and the thermodynamic driving force is the formation of a strong O-$Cr^{(III)}$ bond; 4) aldehydes react markedly faster than ketones, so when both functional groups are present, the reaction of the organochromium species with aldehydes proceeds with complete chemoselectivity; 5) because of their low basicity, organochromium reagents are compatible with a wide range of sensitive functional groups; 6) it is possible to maintain the integrity of the various electrophilic functional groups within polyfunctional organochromium reagents; and 7) the addition of crotylchromium(III) reagents to aldehydes is highly diastereoselective and stereoconvergent: in all cases, the *anti* homoallylic alcohol is favored, independent of the configuration of the starting crotyl halide. The drawbacks of the *NHK reaction* are: 1) the nickel and chromium salts are very toxic; 2) the redox potential of $Cr^{(II)}$ shows a significant dependence on the solvents used as the reaction medium and solvent mixtures need to be used for optimum results; 3) usually a large excess of $CrCl_2$ is required, especially in macrocyclization reactions; and 4) the Lewis acidic salts formed during the preparation of $CrCl_2$ may alter the stereochemical outcome of the reaction for polyfunctional substrates where chelation control determines the stereochemical course.

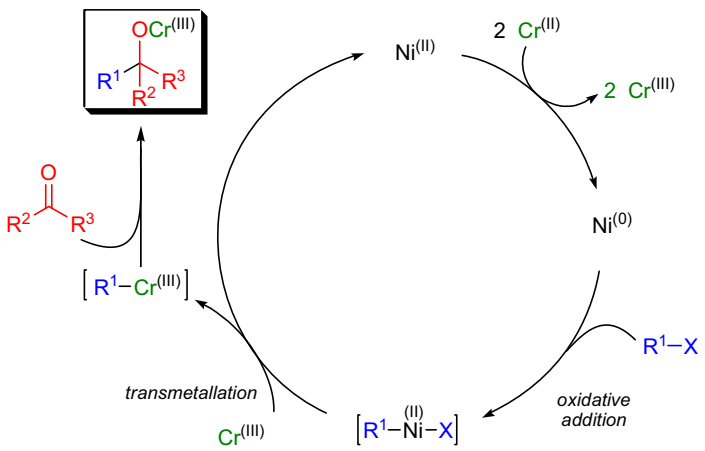


R^1 = alkenyl, aryl, allyl, vinyl, propargyl, alkynyl, allenyl; X = Cl, Br, I, OTf, etc.; R^2, R^3 = alkyl, aryl, alkenyl, H;
solvent: DMF, DMSO, THF

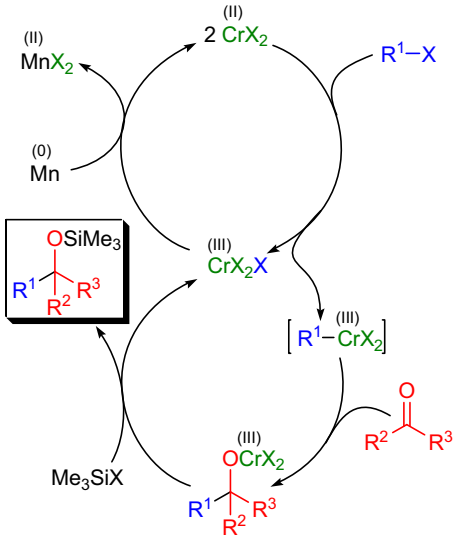
Mechanism:[6,18,19,9,10,13]

In the nickel(II)-catalyzed *NHK reaction*, the first step is the reduction of $Ni^{(II)}$ to $Ni^{(0)}$ that inserts into the halogen-carbon bond *via* an oxidative addition. The *organonickel species* transmetallates with $Cr^{(III)}$ to form the organochromium(III) nucleophile, which then reacts with the carbonyl compound. To make the process environmentally benign, a chromium-catalyzed version was developed where a chlorosilane was used as an additive to silylate the chromium alkoxide species in order to release the metal salt from the product.[18,19] The released $Cr^{(III)}$ is reduced to $Cr^{(II)}$ with manganese powder.

$Ni^{(II)}$-catalyzed process:



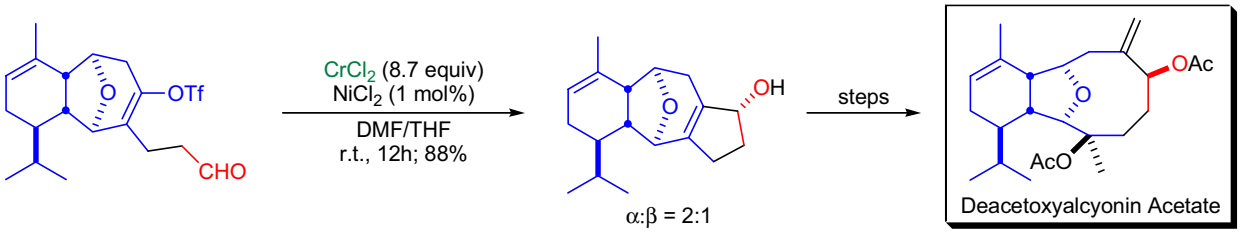
Chromium-catalyzed process:



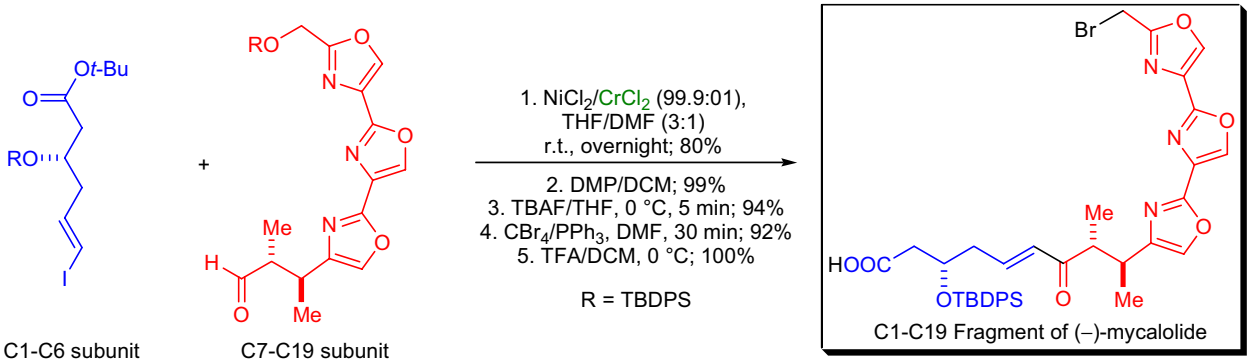
NOZAKI-HIYAMA-KISHI REACTION

Synthetic Applications:

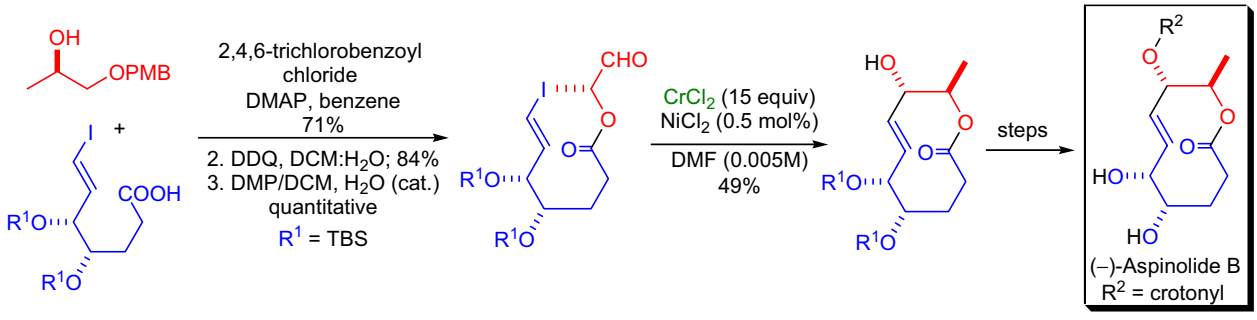
In the laboratory of G.A. Molander, a general route for the synthesis of eunicellin diterpenes was developed and was applied for the asymmetric total synthesis of deacetoxyalcyonin acetate.[31] One of the key steps was an *inramolecular NHK coupling* reaction between an enol triflate and an aldehyde. The cyclopentenol product was formed in high yield as a 2:1 mixture of diastereomers. The undesired diastereomer could be transformed to the desired one using a *Mitsunobu reaction*.



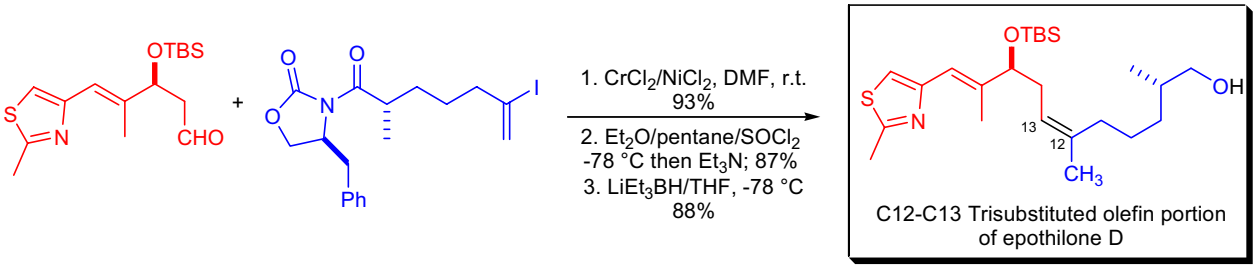
The C1-C19 fragment of (-)-mycalolide was assembled by J.S. Panek et al. *via* the *NHK coupling* between the C1-C6 vinyl iodide and C7-C19 aldehyde subunits.[32] The desired allylic alcohol was obtained as a 1:1 mixture of stereoisomers and was oxidized to the corresponding ketone using Dess-Martin periodinane. The synthesis of the C1-C19 fragment was completed in three more steps.



One of the key steps during the first total synthesis of (–)-aspinolide B by A. de Meijere and co-workers was the *NHK reaction* to form the ten membered lactone ring.[33] The precursor for this key macrocyclization step was prepared by forming an ester from a three-carbon monoprotected diol fragment and a seven-carbon vinyl iodide fragment. Deprotection of the primary alcohol and its subsequent oxidation afforded the desired vinyl iodide aldehyde precursor. Exposure of this precursor to 15 equivalents of $CrCl_2$ doped with 0.5% of $NiCl_2$ at high dilution in DMF afforded the desired diastereomer in a 1.5:1 ratio.



A novel approach to the elaboration of the C12-C13 trisubstituted olefin portion of epothilone D was developed by R.E. Taylor et al.[34] The authors used sequential *NHK coupling* and a thionyl chloride induced *allylic rearrangement* followed by the reductive removal of the chiral auxiliary.



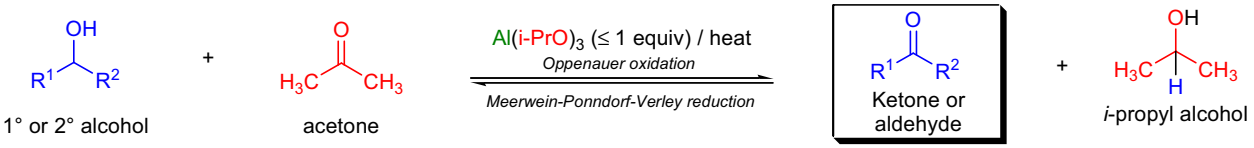
OPPENAUER OXIDATION

(References are on page 642)

Importance:

[*Seminal Publications*[1]*; Reviews*[2-7]*; Modifications & Improvements*[8-17]*; Theoretical Studies*[18,17]]

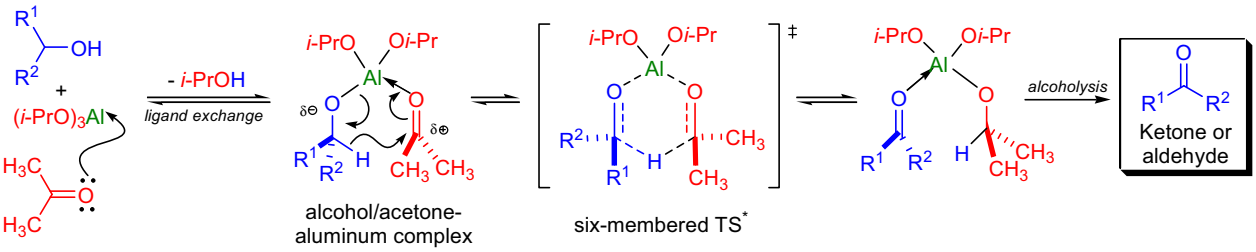
In 1937, R.V. Oppenauer oxidized steroids with secondary alcohol functionality to the corresponding ketones using acetone in benzene in the presence of catalytic amounts of aluminum *tert*-butoxide.[1] This oxidation proved to be high yielding and superior to other existing oxidation methods due to its mildness. Oppenauer's method came more than a decade after three researchers independently described reduction of carbonyl compounds with the use of aluminum alkoxides: 1) in 1925, H. Meerwein successfully reduced aldehydes with ethanol in the presence of aluminum ethoxide;[19] 2) during the same year A. Verley reduced ketones with aluminum ethoxide as well as aluminum isopropoxide but found that sterically hindered ketones (e.g., camphor) reacted very slowly;[20] and 3) in 1926, W. Ponndorf demonstrated that the reduction of aldehydes and ketones was general for a variety of metal alkoxides (e.g., alkali metal and aluminum alkoxides) derived from secondary alcohols, and he found the process completely reversible.[21] The oxidation of primary and secondary alcohols with ketones in the presence of metal alkoxides (e.g., aluminum isopropoxide) to the corresponding aldehydes and ketones is known as the *Oppenauer oxidation*.[22] The reverse reaction, the reduction of aldehydes and ketones to alcohols, is referred to as the *Meerwein-Ponndorf-Verley reduction.* The general features of the *Oppenauer oxidation* are: 1) the reaction is completely reversible and can be driven to completion according to *Le Chatelier's principle* by adding large excess of the ketone (e.g., acetone) to the reaction mixture; 2) the reaction conditions are mild, since the substrates are usually heated in acetone/benzene mixtures; 3) most functional groups are tolerated (alkenes, alkynes, esters, amides, etc.), but if the substrate contains basic nitrogen atoms, the use of alkali metal alkoxides is necessary in place of aluminum alkoxides;[23] 4) in order to achieve reasonable reaction rates, stoichiometric amounts of the aluminum alkoxide needs to be used; 5) most commonly aluminum isopropoxide, *t*-butoxide, and phenoxide are used; 6) a wide range of primary and secondary alcohols are oxidized under the reaction conditions; 6) secondary alcohols are oxidized much faster than primary alcohols, so complete chemoselectivity can be achieved (this feature makes the *Oppenauer oxidation* unique compared to other oxidations); 7) overoxidation of aldehydes to carboxylic acids never happens; 8) the oxidation of 1,4- and 1,5-diols usually yields lactones; 9) acetone is used most often as the oxidant, but aromatic and aliphatic aldehydes are suitable as oxidants due to their low reduction potentials; 10) addition of protic acids dramatically increases the rate of oxidation;[9] and 11) the oxidation can be conducted using heterogeneous catalysts (e.g., alumina, zeolites), which has one great advantage over the traditional homogeneous variant: the catalyst can be easily separated from the reaction mixture.[12,5] The most important side reactions are: 1) *aldol condensation* of aldehyde products, which have an α-hydrogen atom to form β-hydroxy aldehydes and/or α,β-unsaturated aldehydes, but with ketones this side reaction is not common; 2) *Tishchenko reaction* of aldehyde products with no α-hydrogen atom, but this can be suppressed by the use of anhydrous solvents; and 3) the migration of the double bond during the oxidation of allylic and homoallylic alcohol substrates.[4]



R^1 = alkyl, aryl, alkenyl; R^2 = H, alkyl, aryl, alkenyl

Mechanism:[24-29]

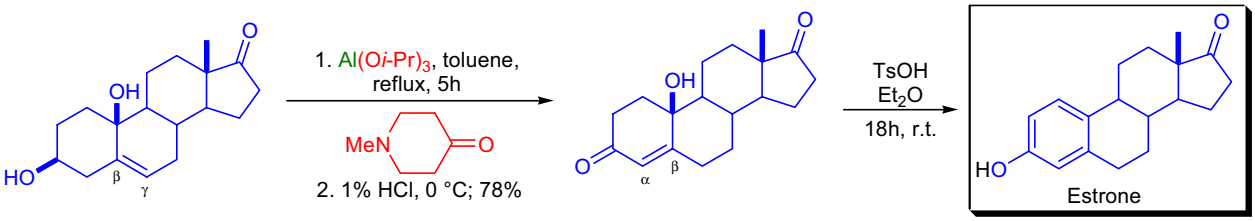
Both the oxidant carbonyl compound (acetone) and the substrate alcohol are bound to the metal ion (aluminum). The alcohol is bound as the alkoxide, whereas the acetone is coordinated to the aluminum which activates it for the hydride transfer from the alkoxide. The hydride transfer occurs *via* a six-membered chairlike transition state. The alkoxide product may leave the coordination sphere of the aluminum *via* alcoholysis, but if the product alkoxide has a strong affinity to the metal, it results in a slow ligand exchange, so a catalytic process is not possible. That is why often stoichiometric amounts of aluminum alkoxide is used in these oxidations.



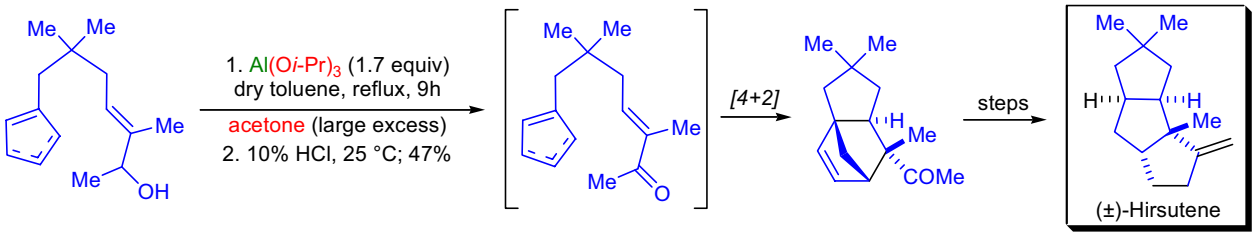
OPPENAUER OXIDATION

Synthetic Applications:

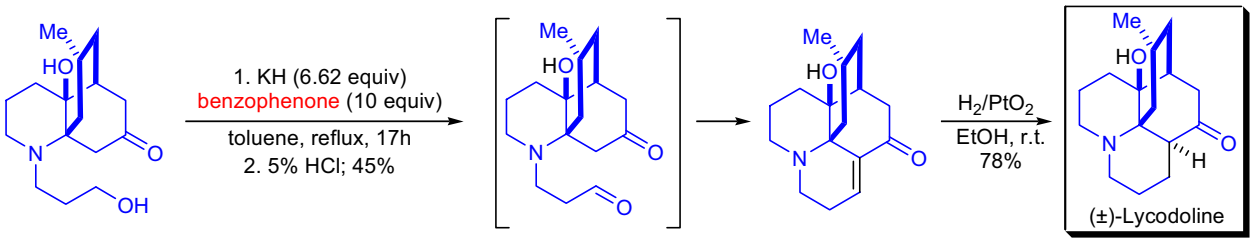
The *modified Oppenauer oxidation* was used in the synthesis of estrone by P. Kočovský et al.[30] The tetracyclic diol was exposed to aluminum isopropoxide and *N*-methyl-piperidine-4-one (oxidizing agent)[8] to obtain the corresponding enone in good yield. The formation of the enone involved the migration of the initial β,γ-double bond. The treatment of this enone with TsOH overnight in ether led to the formation of estrone by aromatization.



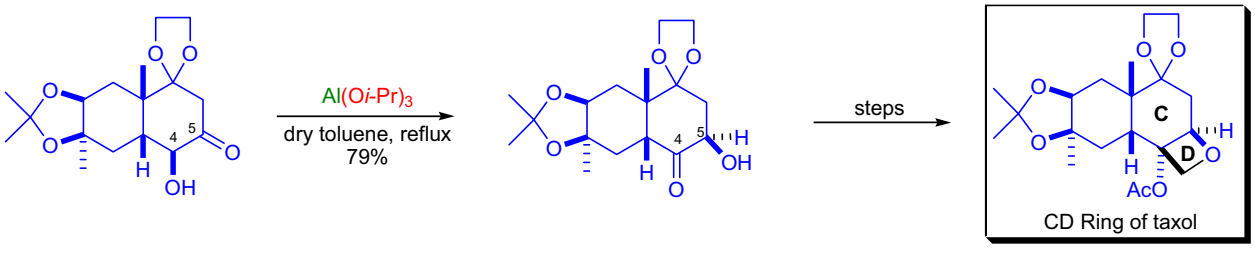
An *intramolecular Diels-Alder reaction* was the key step in D.D. Sternbach's total synthesis of the linearly fused triquinane (±)-hirsutene.[31] The cycloaddition took place between a cyclopentadiene ring and an α,β-unsaturated ketone that was generated *in situ* by using the *Oppenauer oxidation*.



The total synthesis of several lycopodium alkaloids was accomplished by C.H. Heathcock and co-workers.[32] At the final stages of the synthesis of (±)-lycodoline, a *modified Oppenauer oxidation* was planned to carry out the transformation of a primary alcohol to the corresponding aldehyde. However, when the substrate was treated with potassium *t*-butoxide and benzophenone in refluxing benzene, the only product was an *N*-dealkylated tricyclic amino ketone (via *retro Michael reaction*). This problem was resolved by substituting the KO*t*-Bu with potassium hydride which efficiently removed the protons from both the primary and tertiary alcohols, thereby preventing the *retro Michael reaction*. The oxidation product aldehyde quickly underwent a facile *aldol condensation* to form the tricyclic enone.



The tricyclic ring system containing the fully functionalized CD ring of taxol was prepared from (*S*)-(+)-carvone by T.K.M. Shing et al.[33] The bicyclic α-hydroxy ketone (4-hydroxy-5-one) was isomerized by an *intramolecular redox reaction* in the presence of catalytic amounts of aluminum isopropoxide. This example was a special case where both reactants were in the same molecule: the ketone was the oxidant for the *Oppenauer oxidation*, whereas the secondary alcohol was the hydride donor for the *MVP reduction*. The conversion to the thermodynamically more stable 5-hydroxy-4-one proceeded in good yield.



OVERMAN REARRANGEMENT

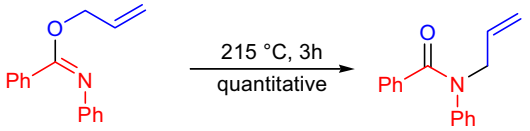
(References are on page 643)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-8]; *Modifications & Improvements*[9-20]; *Theoretical Studies*[21]]

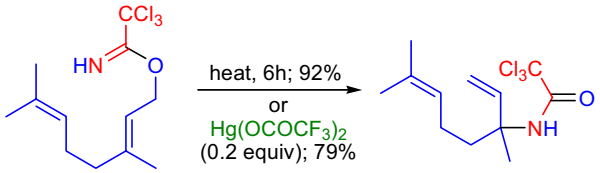
In 1937, O. Mumm and F. Möller, while investigating the mechanism of the *Claisen rearrangement*, observed that the thermal rearrangement of *N*-phenyl-benzimidic acid allyl ester afforded *N*-allyl-*N*-phenyl-benzamide in quantitative yield.[1] They also showed that the termini of the allyl group were switched as a result of the transformation. For the next few decades, several research groups reported similar rearrangements of allylic imidates, but the preparation of the substrates were low yielding, and the relatively harsh conditions did not allow these reactions to become synthetically useful.[4] In 1974, L.E. Overman described the facile thermal and mercuric ion catalyzed rearrangement of allylic trichloroacetimidates to afford the corresponding trichloroacetamides.[2] The 1,3-transposition of alcohol and amine functionalities *via* the *[3,3]*-sigmatropic rearrangement of allylic trichloroacetimidates is known as the *Overman rearrangement*. The general features of the reaction are: 1) the allylic trichloroacetimidates are easily prepared in almost quantitative yield by reacting allylic alcohols with trichloroacetonitrile in the presence of catalytic amounts of base (e.g., NaOR, KOR, DBU);[22,23] 2) heating the crude trichloroacetimidates in a solvent (e.g., xylenes) usually between 25-140 °C for several hours or exposure to certain metal catalysts results in a *[3,3]*-sigmatropic rearrangement;[23,15,18-20] 3) isolated yield of the allylic trichloroacetamides is usually high; 4) the allylic trichloroacetamides can be hydrolyzed under basic conditions (3*M* NaOH solution at room temperature) to afford the corresponding allylic amines; 5) the rearrangement is completely regiospecific, therefore no trichloroacetamide product with an unrearranged carbon skeleton is formed; 6) the rearrangement of trichloroacetimidates derived from secondary allylic alcohols proceeds with a high level of stereoselectivity and preferentially the (*E*)-alkenes are formed; 7) the metal catalysts are usually $Hg^{(II)}$-salts, which are used in 10-20 mol% quantities; 8) the mercury(II)-salts can be removed from the product by flash chromatography or by complexation with pyridine or PPh_3; 9) the metal catalysis, however, usually works well only for imidates derived from 3-substituted primary allylic alcohols and in all other cases the thermal conditions are preferred; 10) the imidates of certain cyclohexenyl allylic alcohols may undergo a competitive elimination;[3] 11) propargylic trichloroacetimidates rearrange to give trichloroacetamido-1,3-dienes;[9] and 12) the trichloroacetamide functionality can be used as a radical precursor or transformed into acylureas or guanidine derivatives.[24,25]

Mumm & Moller (1937):



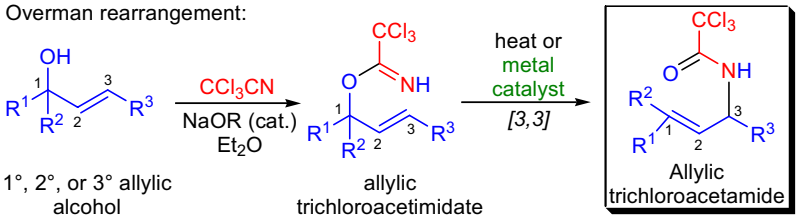
N-Phenyl-benzimidic acid allyl ester → *N*-allyl-*N*-phenyl-benzamide

Overman (1974):



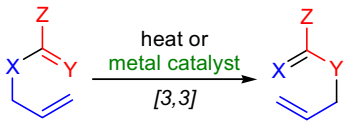
geranyl trichloroacetimidate → geranyl trichloroacetamide

Overman rearrangement:



1°, 2°, or 3° allylic alcohol → allylic trichloroacetimidate → Allylic trichloroacetamide

Claisen-type rearrangements:

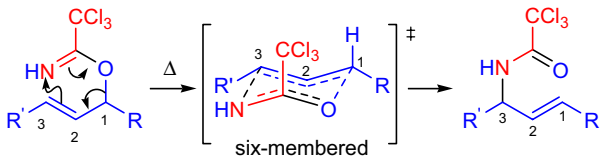


R^{1-3} = H, alkyl, aryl; metal catalyst: $Hg(OCOCF_3)_2$, $Hg(NO_3)_2$, $Pd^{(II)}$-salts; X = O,S, *N*-alkyl, *N*-aryl; Z = CCl_3; Y = NH, *N*-alkyl, *N*-aryl

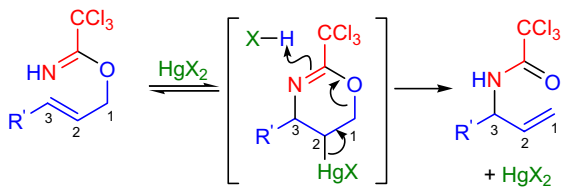
Mechanism:[2,3,26,27]

Similarly to the mechanism of the *Claisen rearrangement*, the *Overman rearrangement* is a suprafacial, concerted, nonsynchronous *[3,3]*-sigmatropic rearrangement. The reaction is irreversible, which is the result of the significant driving force associated with the formation of the amide functionality. The mechanism of the metal catalyzed reaction is believed to proceed *via* an *iminomercuration-deoxymercuration* sequence and it is only formally a *[3,3]-sigmatropic shift*.

Mechanism of the thermal rearrangement:



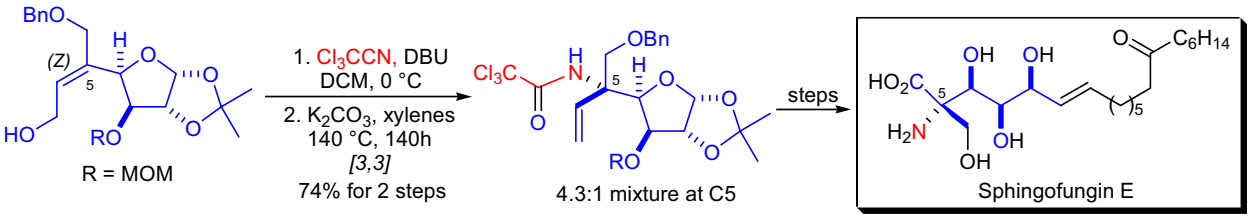
Mechanism of the $Hg^{(II)}$-catalyzed rearrangement:



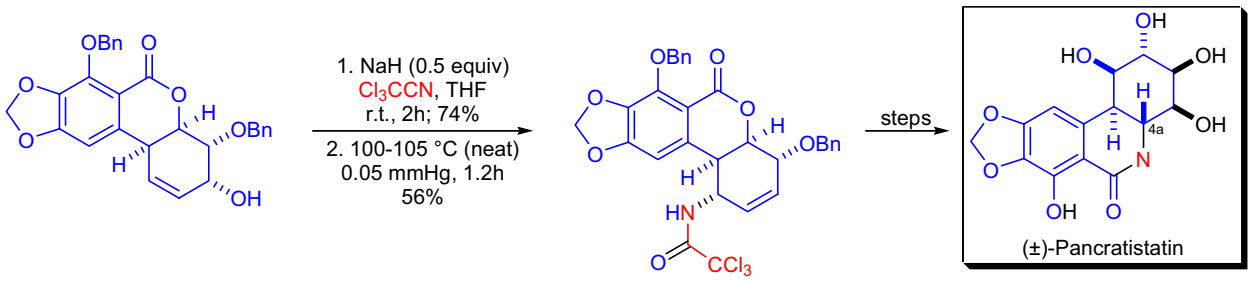
OVERMAN REARRANGEMENT

Synthetic Applications:

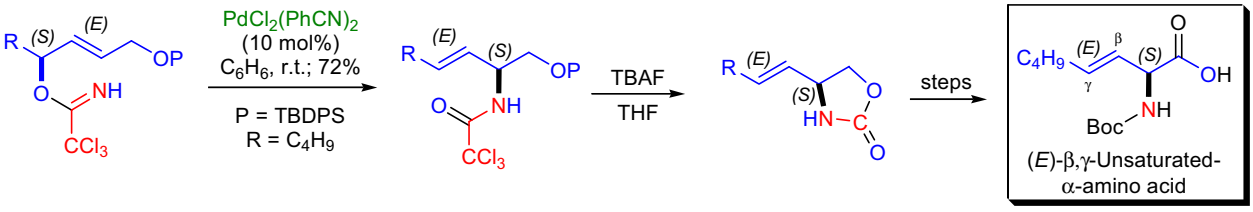
The total synthesis of sphingofungin E from D-glucose was described by N. Chida and co-workers.[28] The stereocenter at C5 was constructed using the *Overman rearrangement* of an allylic trichloroacetimidate derived from diacetone-D-glucose. The (*Z*)-allylic alcohol was reacted with trichloroacetonitrile in the presence of DBU and the resulting crude trichloroacetimidate was heated in xylenes for six days to afford a 4.3:1 ratio of C5 epimers. Interestingly, the rearrangement of the trichloracetimidate derived from the (*E*)-allylic alcohol gave only moderate yield of the C5 epimers in a 1:4 ratio.



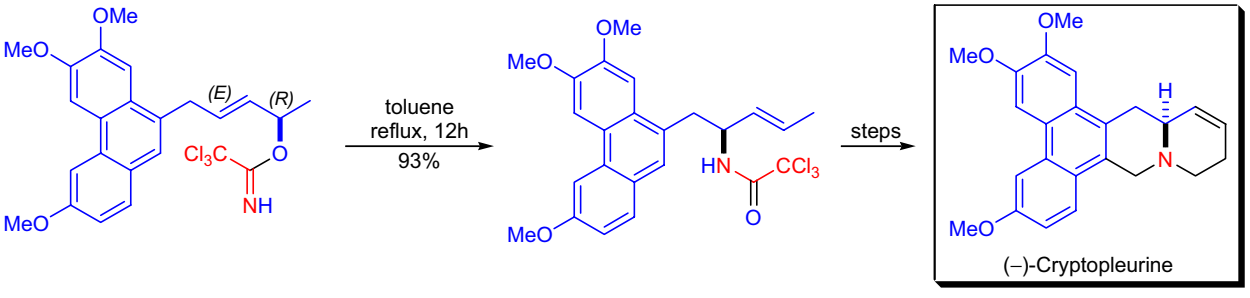
The *Overman rearrangement* was used by S.J. Danishefsky et al. to introduce the nitrogen atom stereoselectively at the C4a position of (±)-pancratistatin.[29] The cyclic allylic alcohol was converted to the trichloroacetimidate in the presence of sodium hydride. The compound was heated as a neat liquid under high vacuum, which afforded the desired rearranged product in reasonable yield.



The *transition metal catalyzed Overman rearrangement* allows the reaction to take place at or around room temperature, so thermally sensitive substrates can be used. In the laboratory of M. Mehmandoust, this approach was applied for the synthesis of enantiomerically pure (*E*)-β,γ-unsaturated α-amino acids, which are potent enzyme inhibitors.[30] The trichloroimidate substrates were derived from optically pure monoprotected diallylalcohols and were exposed to 10 mol% of $Pd^{(II)}$-salt. The rearrangements took place rapidly at room temperature with complete transfer of chirality.



The asymmetric total synthesis of the phenanthroquinolizidine alkaloid (–)-cryptopleurine was reported by S. Kim et al.[31] One of the key steps in the sequence was the *thermal Overman rearrangement* which took place in refluxing toluene in nearly quantitative yield and without any loss of the optical purity of the allyl trichloroimidate substrate.



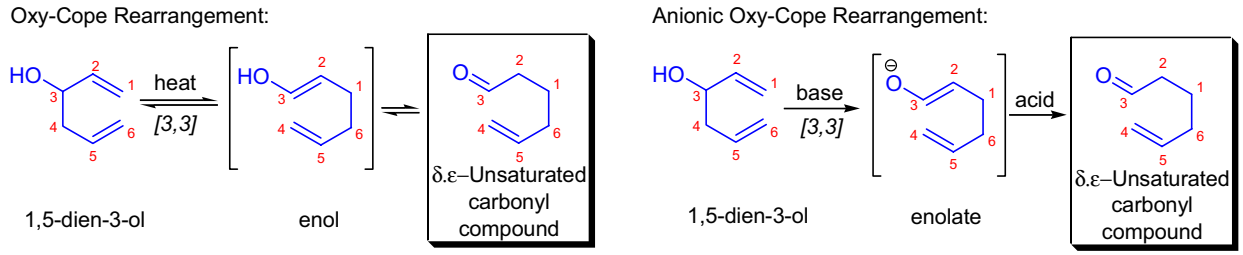
OXY-COPE REARRANGEMENT AND ANIONIC OXY-COPE REARRANGEMENT

(References are on page 643)

Importance:

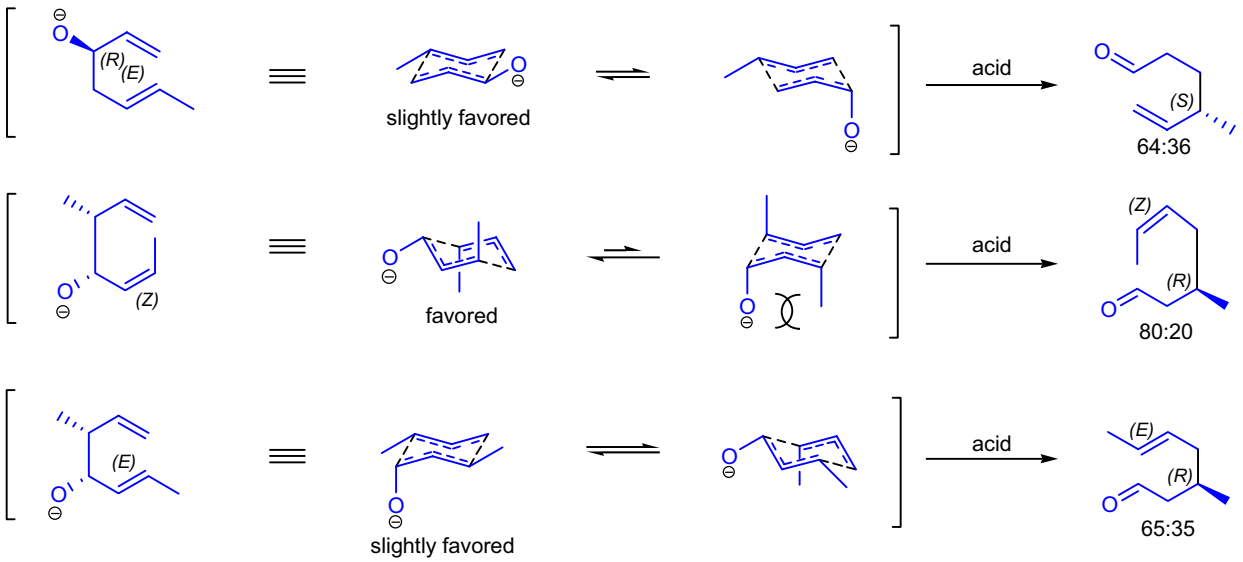
[*Seminal Publications*[1,2]; *Reviews*[3-14]; *Modifcations & Improvements*[15,16]; *Theoretical Studies*[17,18]]

The thermal *[3,3]-sigmatropic rearrangement* of 1,5-dienes is known as the *Cope rearrangement*. When 1,5-dienes are substituted with a hydroxyl group at the C3 position, they undergo a similar rearrangement to first give enols that are subsequently converted to the corresponding δ,ε-unsaturated carbonyl compounds. The formation of the carbonyl compound is the driving force for the reaction.[19] The *[3,3]-sigmatropic rearrangement* of 1,5-diene-3-ols is called the *oxy-Cope rearrangement*, a term coined by J.A. Berson in 1964.[2] A decade later in 1975, a major improvement in the *oxy-Cope rearrangement* was made when it was found that conversion of the 1,5-diene alcohol to the corresponding potassium alkoxides resulted in 10^{10}-10^{17} rate acceleration of the rearrangement.[15] The *base accelerated oxy-Cope rearrangements* are called *anionic-oxy-Cope rearrangements*. Besides the enormous rate acceleration, there was a considerable drop in the temperature required to bring about the rearrangements. In this anionic rearrangement an enolate anion is first formed, which renders the process irreversible. Potassium bases are used most often along with 18-crown-6 to effect greater charge separation and the maximization of the acceleration. The preparation of the 1,5-diene-3-ol substrates usually involves the 1,2-addition of vinyl organometallics to β,γ-unsaturated aldehydes or ketones or the 1,2-addition of allyl anions to α,β-unsaturated carbonyl compounds. Just as in the parent *Cope rearrangement*, the *oxy-Cope* and *anionic-oxy-Cope rearrangements* are both stereospecific and stereoselective as a result of a cyclic highly ordered transition state. It is worth noting that the use of the *anionic-oxy-Cope rearrangement* in synthesis is advantageous over the *Cope rearrangement* because it does not require high temperature at which side reactions more frequently occur.



Mechanism:[1,5,9,12,20]

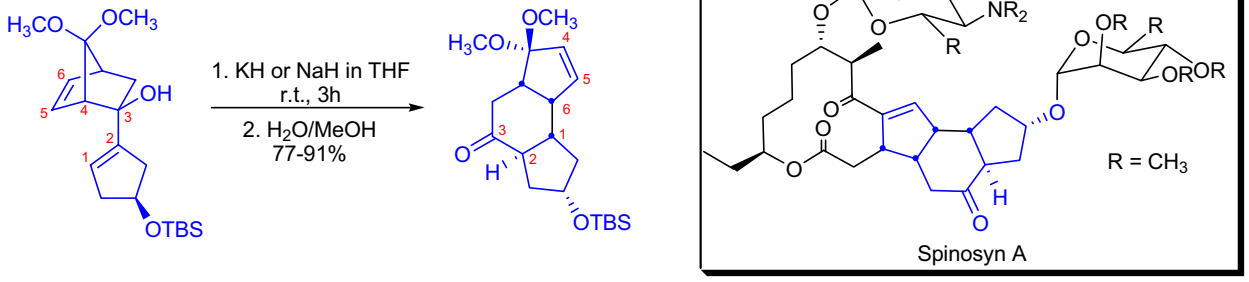
The *oxy-Cope* and *anionic-oxy-Cope rearrangements* involve highly ordered cyclic transition states, so the asymmetry is almost completely transferred from the substrate to the product. Most commonly in acyclic systems as in other *[3,3]-sigmatropic rearrangements*, the transition states are chairlike and the substituents adopt a quasiequatorial position to minimize unfavorable steric interactions. In unsubstituted substrates the diastereoselection is low, but the introduction of an alkyl substituent at C4 improves the diastereoselectivity. In (*Z*)-1-substituted alkenes there is preference for the oxyanionic bond to be pseudo-equatorial, whereas in (*E*)-1-substituted alkenes it tends to be pseudo-axial.[21] Due to conformational constraints in some cyclic substrates, a boatlike transition state may be preferred.



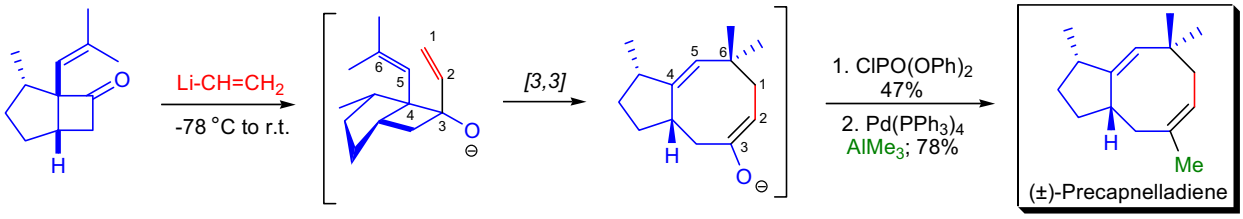
OXY-COPE REARRANGEMENT AND ANIONIC OXY-COPE REARRANGEMENT

Synthetic Applications:

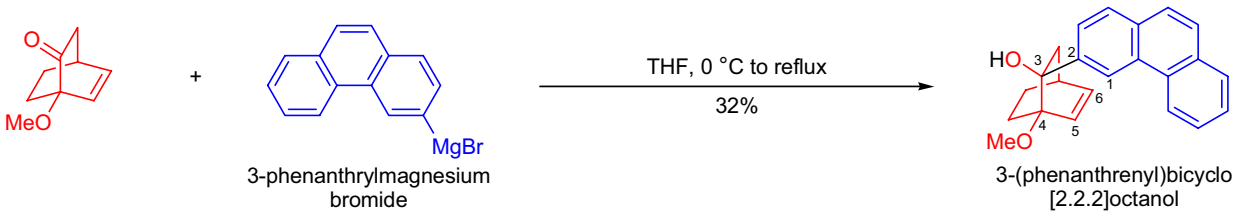
The enantioselective construction of a key tricyclic intermediate of spinosyn A utilizing a highly stereocontrolled *anionic oxy-Cope rearrangement* was accomplished in the laboratory of L.A. Paquette.[22] The precursor tertiary alcohol was treated with potassium hydride in THF and the *oxy-Cope rearrangement* was complete within 3 hours at room temperature. Interestingly, the yield varied between 77 and 91% depending on the source of KH.

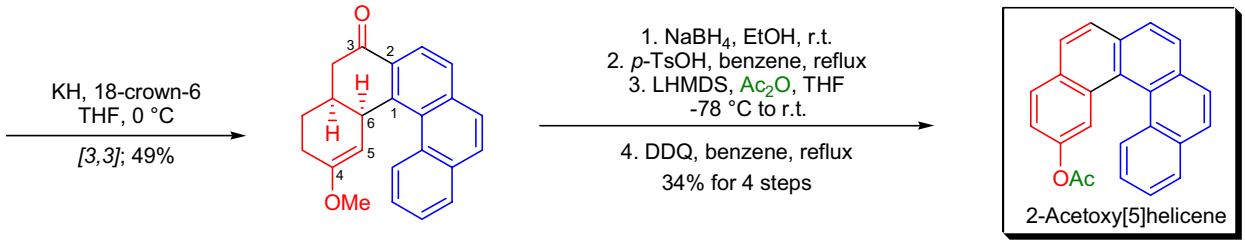


The 1,2-addition of vinyllithium to the carbonyl group of dialkyl squarate-derived bicycloheptenones initiates a low-temperature anion-accelerated *oxy-Cope rearrangement* to afford bicyclo[6.3.0]undecadienone. H.W. Moore and co-workers accomplished the total synthesis of (±)-precapnelladiene using this methodology.[23]



Helicenes are helical compounds consisting of *ortho*-fused aromatic rings. These compounds are potentially useful as catalysts or as platforms for molecular recognition. The currently used syntheses are not practical and do not allow the preparation of helicenes on large scale. M. Karikomi et al. have developed a sequential *double aromatic oxy-Cope rearrangement* strategy for the synthesis of 2-acetoxy[5]helicene.[24] First, 3-phenanthrylmagnesium bromide was synthesized using an *aromatic oxy-Cope rearrangement*. The Grignard reagent was then used to obtain 3-(phenanthrenyl)bicyclo[2.2.2]octanol, which underwent a second *aromatic oxy-Cope rearrangement* upon treatment with KH and one equivalent of 18-crown-6 in THF at 0 °C.





PAAL-KNORR FURAN SYNTHESIS

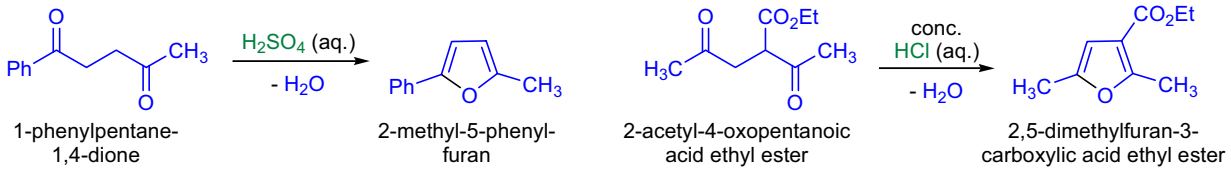
(References are on page 644)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-6]; *Modifications & Improvements*[7,8]]

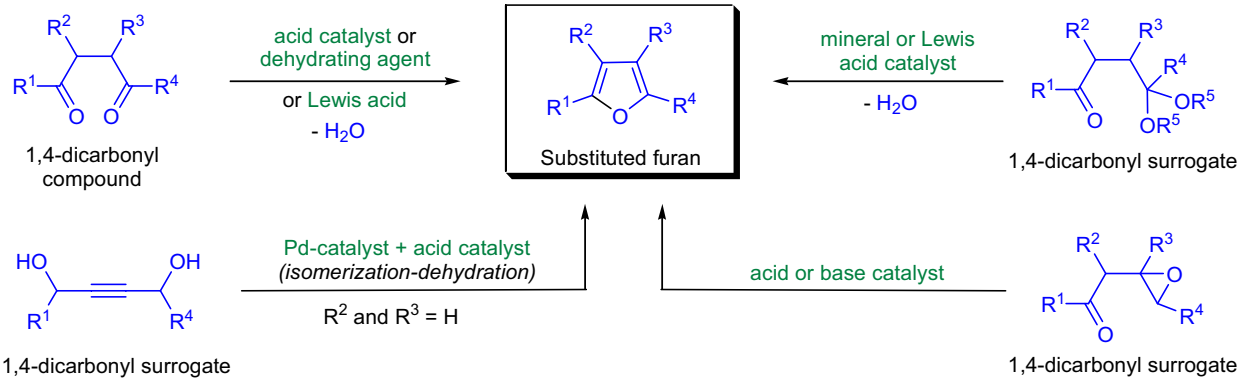
In 1884, C. Paal and L. Knorr almost simultaneously reported that 1,4-diketones upon treatment with strong mineral acids underwent dehydration to form substituted furans.[1,2] This transformation soon became widely used and now it is referred to as the *Paal-Knorr furan synthesis*. The general features of the method are:[5] 1) virtually any 1,4-dicarbonyl compound (mainly aldehydes and ketones) or their surrogates[9-12] are suitable substrates; 2) the dehydration is affected by strong mineral acids such as hydrochloric acid or sulfuric acid, but often Lewis acids and dehydrating agents (e.g., phosphorous pentoxide, acetic anhydride, etc.) can be used; and 3) the yields are usually moderate to good. The two major drawbacks of the reaction are the relative difficulty to obtain the 1,4-dicarbonyl substrates, and the sensitivity of many functionalities to acidic conditions.

Paal & Knorr (1884):



1-phenylpentane-1,4-dione — 2-methyl-5-phenyl-furan — 2-acetyl-4-oxopentanoic acid ethyl ester — 2,5-dimethylfuran-3-carboxylic acid ethyl ester

Paal-Knorr furan synthesis:



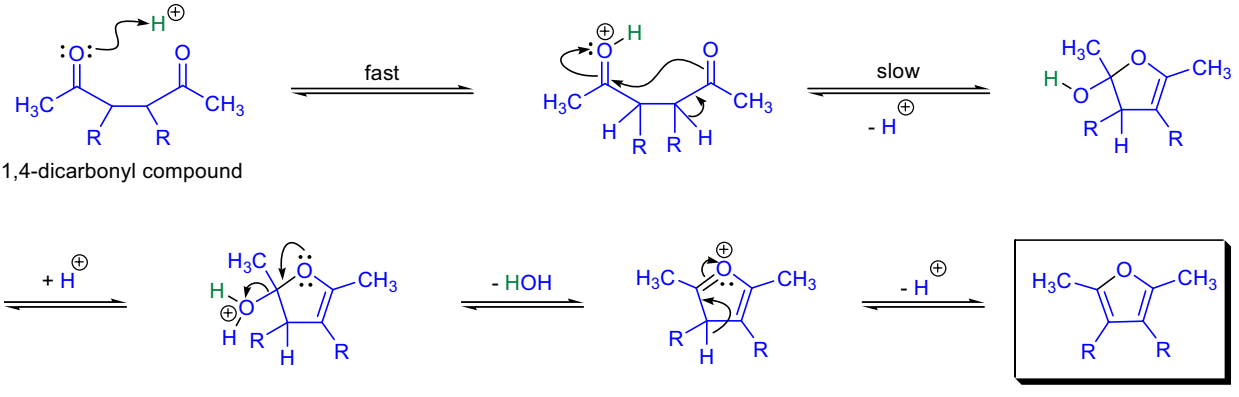
1,4-dicarbonyl compound — Substituted furan — 1,4-dicarbonyl surrogate

1,4-dicarbonyl surrogate — 1,4-dicarbonyl surrogate

R^1 = H, alkyl, aryl; R^{2-3} = H, alkyl, aryl, CO_2-alkyl, CO_2-aryl; R^4 = H, alkyl, aryl; R^5 = CH_3, C_2H_5; acid catalyst: HCl, H_2SO_4, PPA, *p*-TsOH, $(COOH)_2$, Amberlyst 15; Lewis acid: $ZnBr_2$, ZnC_2, $BF_3{\cdot}Et_2O$; dehydrating agent: P_2O_5, Ac_2O

Mechanism:[13,5]

Even though the *Paal-Knorr furan synthesis* has been around for 120 years, its precise mechanism was not known until 1995 when V. Amarnath et al. investigated the intermediates of the reaction and determined the most likely mechanistic pathway.[13] The formation of furans was studied on various racemic and *meso*-3,4-diethyl-2,5-hexane-diones. The authors found that the rate of cyclization was different for the racemic and *meso* compounds and that the configuration of the unreacted dione was not affected. This observation strongly suggested that the widely accepted mechanism, involving the ring-closure of a monoenol followed by the loss of water, is incorrect. The most likely pathway involves the rapid protonation of one of the carbonyl groups followed by the attack of the forming enol at the other carbonyl group (rate-determining step). This pathway accounts for the difference in reaction rates for the substrate diastereomers.

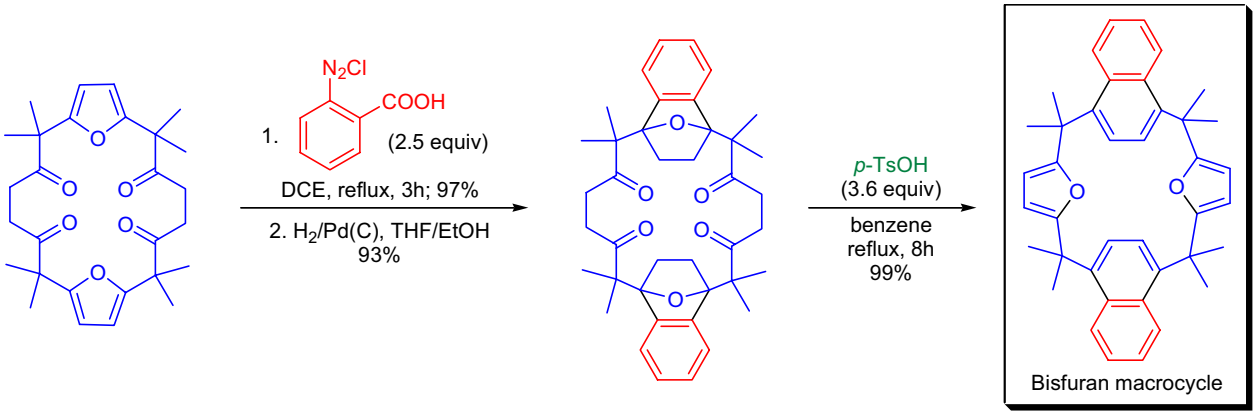


1,4-dicarbonyl compound

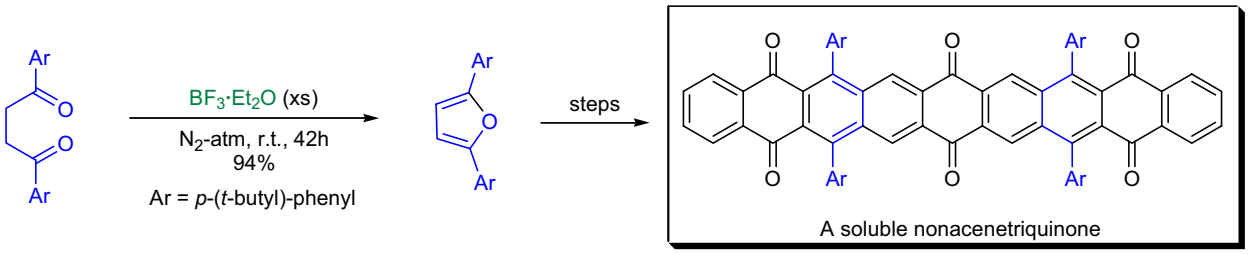
PAAL-KNORR FURAN SYNTHESIS

Synthetic Applications:

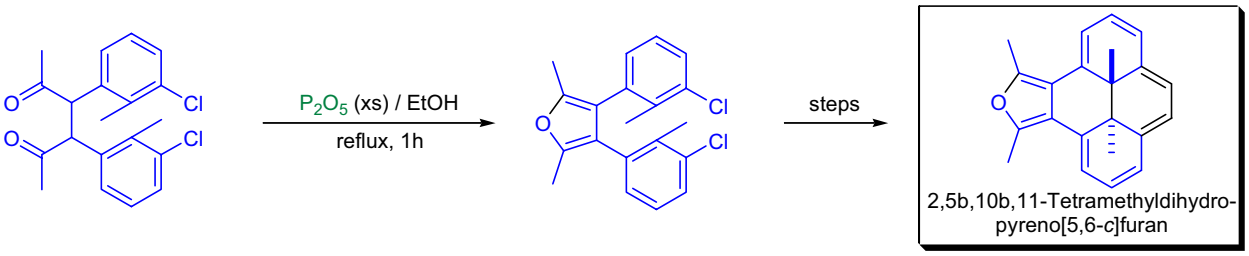
In the laboratory of H. Hart, the synthesis of various furan macrocycles was accomplished.[14] The preparation of a bisfuran macrocycle, which also contained two naphthalene rings, began with the *Diels-Alder cycloaddition* of the tetraketone substrate with excess benzyne. The benzyne was generated *in situ* from benzenediazonium carboxylate hydrochloride, and it reacted with the two furan rings to afford the corresponding oxabicyclic derivative. The double bond in the newly formed ring was saturated by catalytic hydrogenation. The formation of the desired furan rings was achieved with the *Paal-Knorr furan synthesis* in the presence of *p*-toluenesulfonic acid. Under the reaction conditions the oxabicycles were converted to the naphthalene rings.



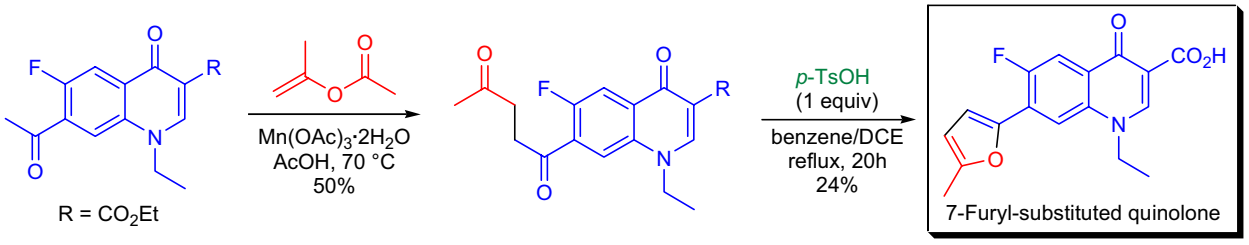
The synthesis of a soluble nonacenetriquinone based on the well-known *Diels-Alder reaction* of 1,3-diarylisobenzofurans was developed by L.L. Miller and co-workers.[15] The preparation of the 1,3-diarylisobenzofuran commenced with the *Paal-Knorr furan synthesis*. The substrate was an aromatic 1,4-diketone, which was treated with excess neat boron trifluoride etherate for almost two days to afford the desired 2,5-diarylfuran in almost quantitative yield. Interestingly, this cyclization could not be achieved efficiently by using the more traditional acid catalysts such as H_2SO_4 or PPA.



The first furan-isoannelated [14]annulene was prepared by Y.-H. Lai et al.[16] The furan moiety was installed by the *Paal-Knorr furan synthesis*. The 1,4-diketone substrate was synthesized *via* an oxidative coupling using MnO_2/AcOH. The dehydration to the furan was effected by phosphorous pentoxide in ethanol.



C.S. Cooper and co-workers synthesized several quinolones containing five- and six-membered heterocyclic substituents at the 7-position and tested their antibacterial activities.[17] The 1,4-diketone substrate was prepared *via* the oxidative coupling of isopropenyl acetate and an acetophenone derivative. The *Paal-Knorr furan synthesis* was conducted in the presence of *p*-TsOH.



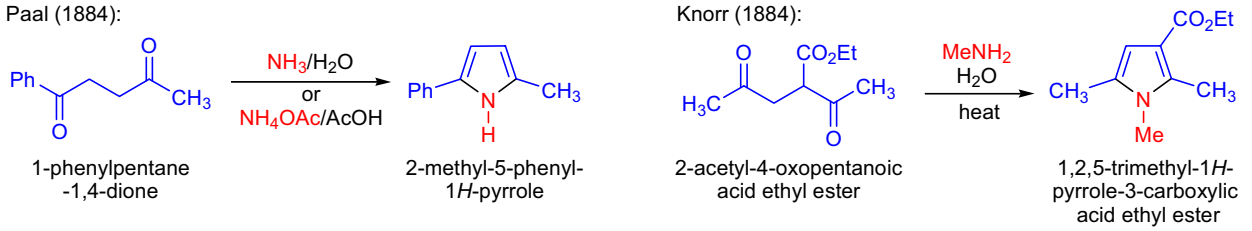
PAAL-KNORR PYRROLE SYNTHESIS

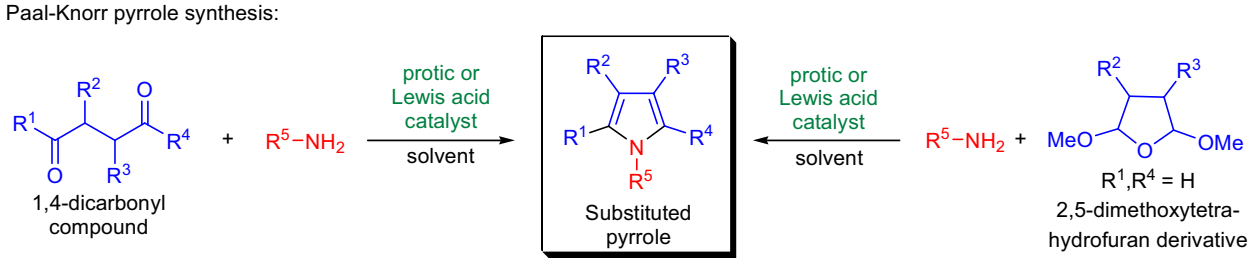
(References are on page 644)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-8]; *Modifications & Improvements*[9-20]]

In 1884, C. Paal and L. Knorr almost simultaneously reported that the treatment of 1,4-diketones with concentrated aqueous ammonia or ammonium acetate in glacial acetic acid gave rise to 2,5-disubstituted pyrroles in good yield.[1,2] It was also shown that besides ammonia, primary amines also react with 1,4-diketones to afford *N*-alkyl substituted pyrroles. The preparation of substituted pyrroles by the condensation of 1,4-dicarbonyl compounds with ammonia or primary amines is known as the *Paal-Knorr pyrrole synthesis*. The general features of the transformation are: 1) practically any 1,4-dicarbonyl compound (mainly 1,4-diketones) or their surrogates are good substrates for the reaction; 2) 1,4-dialdehydes or keto aldehydes are used less often mainly because of their relative instability and the lack of general methods for their preparation; 3) the structure of the amine component can be varied widely, since ammonia, aliphatic primary amines, both electron-rich and electron-poor aromatic amines, and heterocyclic amines (e.g., aminopyridines, aminothoazoles, etc.) can be used; 4) α,ω-diamines afford dipyrryl derivatives tethered *via* their nitrogen atoms; 5) ammonia can be introduced either as a concentrated aqueous solution, as ammonium acetate in an alcohol solvent or ammonium carbonate in DMF at high temperature; 6) the relatively basic alkylamines do not react if the acidity of the reaction medium is below pH 5.5, while aromatic amines usually undergo cyclization only when pH<8.2 and the highest yields are observed between pH 4.5 and 5.5; 7) besides protic acids, certain Lewis acids such as Ti(O*i*-Pr)$_4$, as well as layered zirconium phosphate also catalyze the reaction; 8) the solvent of choice depends on the type of amine used, and it can range from polar protic to dipolar aprotic all the way to nonpolar solvents; and 9) yields range from good to excellent and occasionally can be close to quantitative.

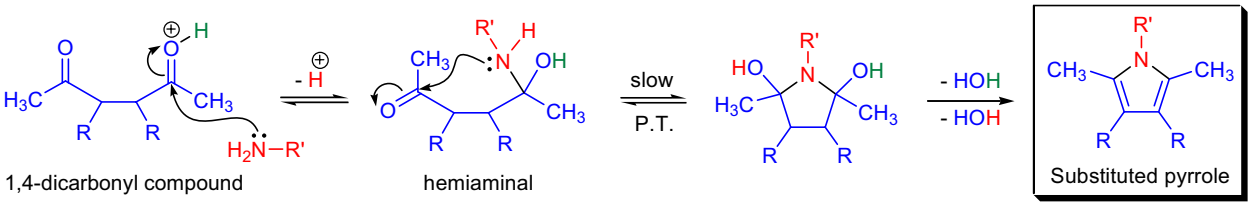




R^1 = H, alkyl, aryl; R^{2-3} = H, alkyl, aryl, CO_2-alkyl, CO_2-aryl; R^4 = H, alkyl, aryl; R^5 = H, 1°, 2° or 3° alkyl, aryl, heteroaryl, NR_2, NHR, NH_2, OH; ammonia precursors: NH_4OAc, $(NH_4)_2CO_3$; catalyst: zeolite, Al_2O_3, *p*-TSOH, CSA, zirconium phosphate, Ti(O*i*-Pr)$_4$, microwave; solvent: MeOH, EtOH, H_2O, toluene, DMF, ionic liquid

Mechanism:[21,22]

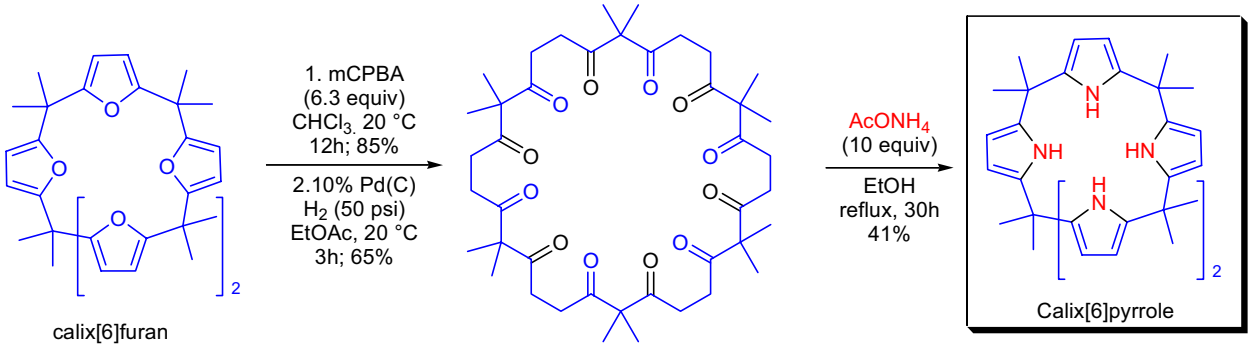
Even though the *Paal-Knorr pyrrole synthesis* has been around for 120 years, its precise mechanism was the subject of debate. In 1991, V. Amarnath et al. investigated the intermediates of the reaction and determined the most likely mechanistic pathway.[23] The formation of pyrroles was studied on various racemic and *meso*-3,4-diethyl-2,5-hexanediones. The authors found that the rate of cyclization was different for the racemic and *meso* compounds and the racemic isomers reacted considerably faster than the *meso* isomers. There were two crucial observations: 1) the stereoisomers did not interconvert under the reaction conditions; and 2) there was no primary kinetic isotope effect for the hydrogen atoms at the C3 and C4 positions. These observations led to the conclusion that the cyclization of the hemiaminal intermediate is the rate-determining (slow) step.



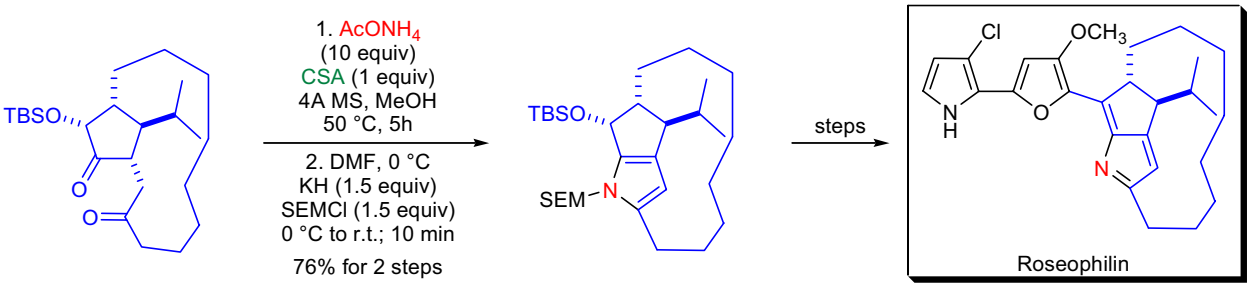
PAAL-KNORR PYRROLE SYNTHESIS

Synthetic Applications:

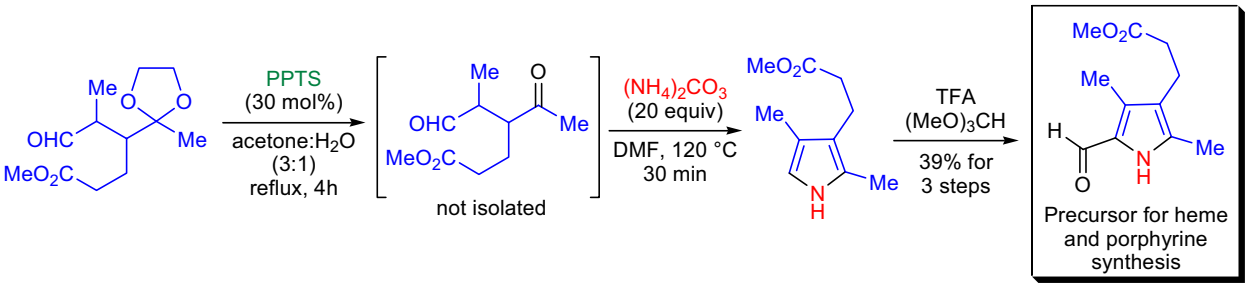
F.H. Kohnke and co-workers prepared novel heterocyclophanes from cyclic poly-1,4-diketones, which were obtained by the oxidation of calix[6]furan and calix[4]furan.[24] One of the heterocyclophanes, calix[6]pyrrole, was prepared by the *Paal-Knorr pyrrole synthesis* from the corresponding dodecaketone. The substrate was heated with excess ammonium acetate in absolute ethanol. Interestingly, the analogous synthesis of calix[4]pyrrole under identical conditions failed, while calix[5]pyrrole is obtained only in 1% yield.[25,26]



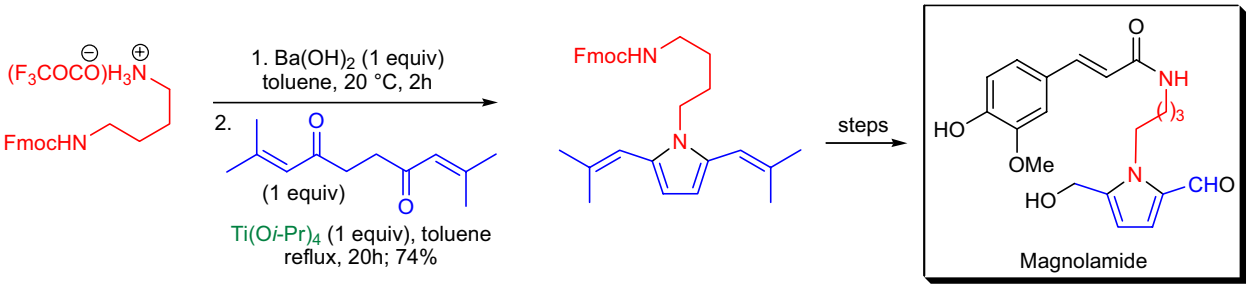
The formal total synthesis of roseophilin was accomplished by B.M. Trost et al. who used the *Paal-Knorr pyrrole synthesis* to install the trisubstituted pyrrole moiety.[27] The 1,4-diketone substrate was reacted with various primary amines to obtain *N*-substituted pyrroles. The best yield was obtained when benzylamine was used as the amine component, but the *N*-deprotection of the product proved to be problematic. This forced the researchers to prepare the otherwise unstable *N*-unprotected pyrrole under carefully controlled conditions and protect it immediately with SEM-chloride.



In the laboratory of D.F. Taber, the large-scale preparation of a tetrasubstituted pyrrole, a key precursor for the preparation of hemes and porphyrins, was achieved.[28] The 1,4-dicarbonyl substrate was generated from a ketal *via* hydrolysis and was immediately subjected to the *Paal-Knorr pyrrole synthesis* by heating it with ammonium carbonate in DMF. The resulting 1*H*-pyrrole was formylated with trimethyl orthoformate in trifluoroacetic acid.



The titanium isopropoxide mediated *Paal-Knorr pyrrole synthesis* was used as the key step in the first total synthesis of magnolamide by W. Le Quesne et al.[29]



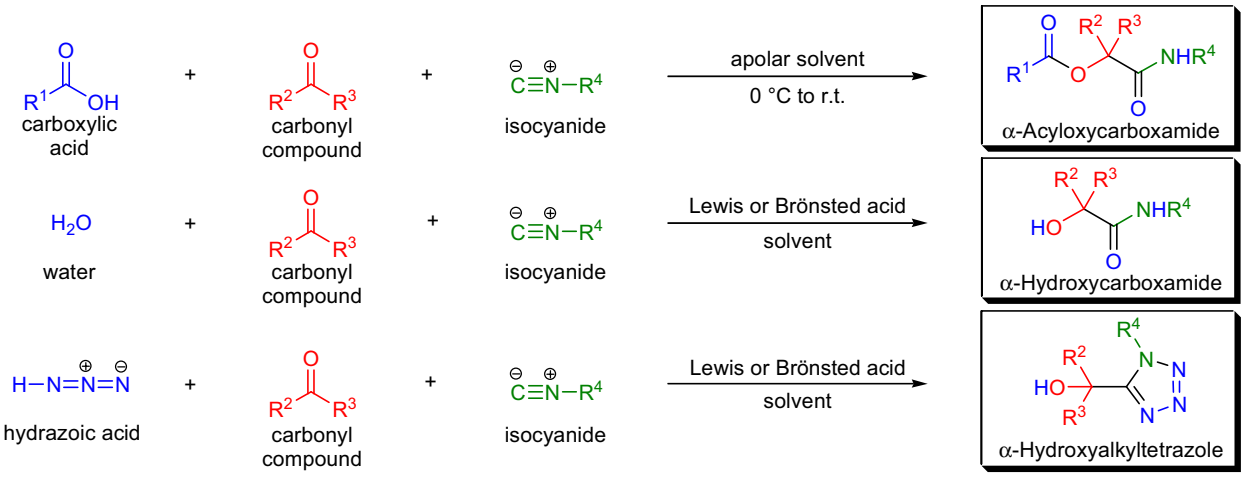
PASSERINI MULTICOMPONENT REACTION

(References are on page 645)

Importance:

[*Seminal Publications*[1]; *Reviews*[2-12]; *Modifications & Improvements*[13-28]]

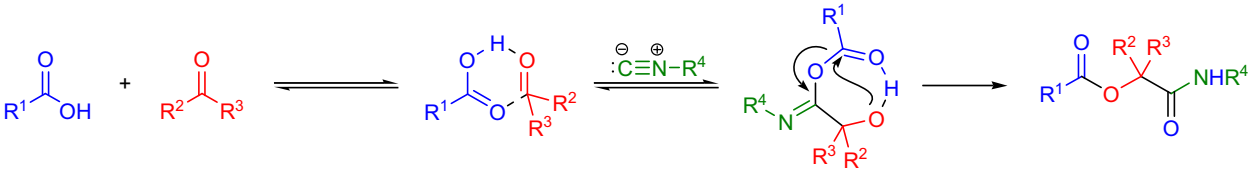
Isocyanides, also known as isonitriles, are a unique class of organic compounds. The carbon center of the isocyanide group is formally divalent, and it can react with electrophiles and nucleophiles. The first synthetically useful reaction of isocyanides was described by M. Passerini, who reported that isocyanides react with carboxylic acids and carbonyl compounds in one step to provide α-acyloxycarboxamides.[1] This transformation is known today as the *Passerini multicomponent reaction* (MCR). The synthetic power of the *Passerini reaction* is that three reaction partners are combined in one pot under mild conditions (three component reaction or P-3CR) and the product incorporates most atoms of all three starting materials. These types of transformations coupled with combinatorial chemistry and parallel synthesis techniques allow the quick assembly of a wide array of compounds from simple starting materials.[7,9,10] The general features of the classical *Passerini reaction* are: 1) it is carried out at high concentrations of the starting materials in inert solvents at or below room temperature;[1] 2) it is accelerated in apolar solvents;[2] 3) a wide variety of aldehydes and ketones undergo the reaction; 4) there are rare limitations to the carbonyl component, only sterically hindered ketones and α,β-unsaturated ketones are unreactive;[29,16] 5) in addition to C-isocyanides, trimethylsilyl isocyanide also undergoes the reaction;[18] 6) when water is used as the nucleophilic component instead of carboxylic acid, the reaction gives the corresponding α-hydroxycarboxamide under acid catalyzed conditions;[13,15] 7) when hydrazoic acid is combined with the isocyanide and the carbonyl compound under acidic conditions, α-hydroxyalkyltetrazole is the product;[15-17] and 8) catalytic asymmetric variants of the reaction were also developed.[26-28] By choosing the proper starting materials, the *Passerini reaction* often does not stop at the α-acyloxycarboxamide product and it leads to the formation of heterocycles:[20-22,24,25] 1) the reaction of α-oxoaldehydes with carboxylic acids and isocyanides leads to the formation of oxazoles;[20] 2) when cyanoacetic acid is used as the acid component along with α-oxoaldehydes and isocyanides, 2-hydroxyfurans form;[21] and 3) the reaction of β-oxothioamide with isocyanides leads to benzo[c]thiophenes.[22] When bifunctional starting materials incorporating the carbonyl and the carboxylic acid functionality are used, lactones of various ring sizes can be formed.[14] The reaction of α-chloroketones with carboxylic acids and isocyanides under basic conditions leads to the formation of β-lactams.[19,23] In the absence of the carboxylic acid component, this transformation leads to the formation of α-epoxylactones.[19]



R^1 = alkyl, aryl; R^2 = alkyl, aryl; R^4 = alkyl, aryl; R^3 = H, alkyl, aryl; Brönsted acid: HCl, HNO_3, H_3PO_4, H_2SO_4; Lewis acids: $BF_3{\cdot}OEt_2$, $TiCl_4$

Mechanism:[13,30,31,2,32-37]

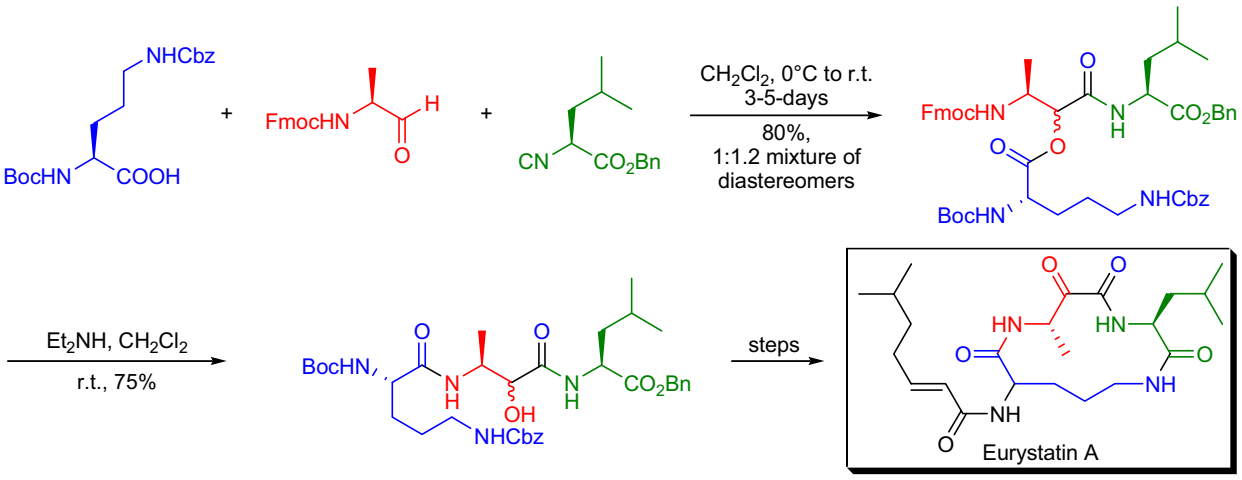
The mechanism of the *Passerini reaction* was widely examined. A plausible mechanism that is consistent with experimental data is as follows: First, the carbonyl compound and the carboxylic acid forms a hydrogen bonded adduct. Subsequently, the carbon atom of the isocyanide group attacks the electrophilic carbonyl carbon, and also reacts with the nucleophilic oxygen atom of the carboxylic acid. The resulting intermediate cannot be isolated as it rearranges to the more stable α-acyloxycarboxamide in an intramolecular transacylation.



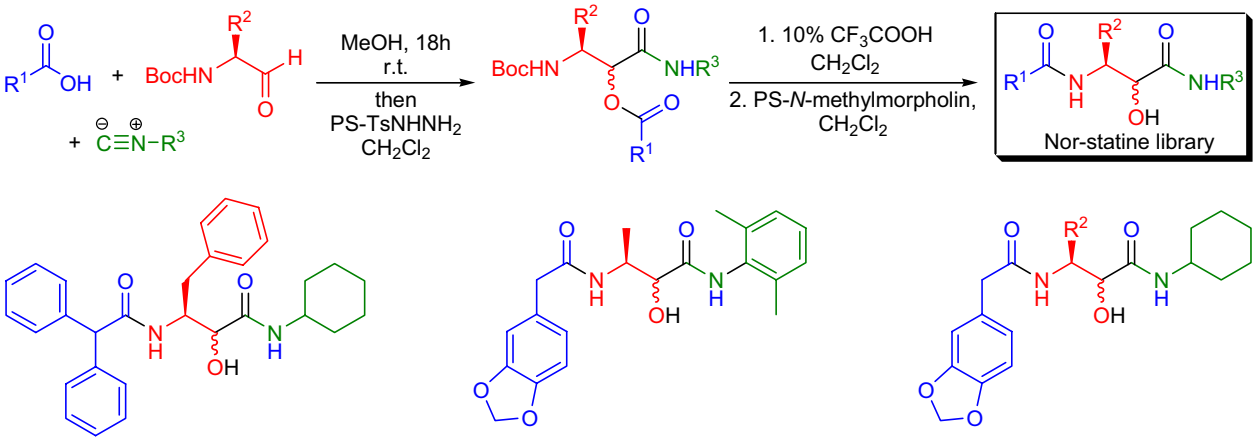
PASSERINI MULTICOMPONENT REACTION

Synthetic Applications:

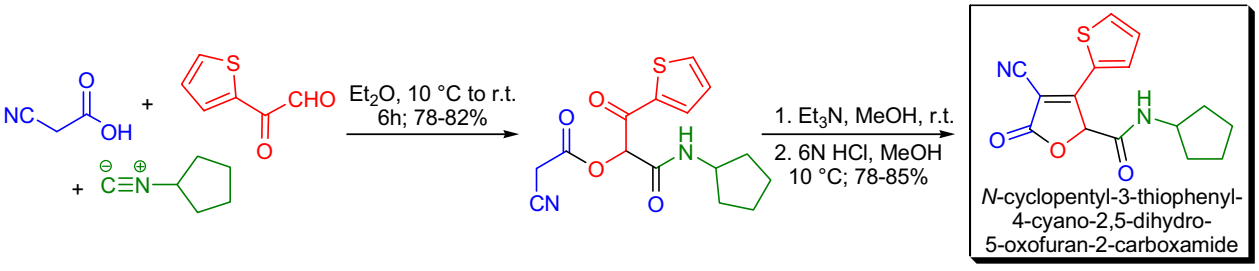
Eurystatin A is a 13-membered macrocyclic natural product featuring a leucine, ornithine, and an α-ketoalanine amide subunit. This compound exhibits serine protease prolyl endopeptidase inhibition. The total synthesis of this compound was accomplished by E. Semple et al.[38] The key reaction in their approach was the *Passerini reaction* between an *N*-protected ornithine fragment, *N*-α-Fmoc alaninal and a protected leucine isonitrile to give the desired α-acyloxycarboxamide under mild, neutral conditions in high yield and multigram quantities, and as 1:1.2 mixture of diastereomers. Subsequent Fmoc deprotection led to a smooth *O*- to *N*- acyl migration providing the entire acyclic skeleton of the natural product.



L. Banfi and co-workers utilized the *Passerini three component reaction* to prepare a 9600 member hit generation library of nor-statines.[39,40] These compounds are potential transition state mimetics for the inhibitors of aspartyl proteases. The authors produced the library by starting out from eight *N*-Boc-α-aminoaldehydes, twenty isocyanides and sixty carboxylic acids. The key *Passerini reaction* occurred under mild conditions. This transformation was followed by removal of the Boc protecting group and acyl transfer. Three representative examples of the library are shown.



R. Bossio and co-workers developed a novel method for the synthesis of tetrasubstituted furan derivatives.[21] The *Passerini reaction* between arylglyoxals, isocyanides, and cyanoacetic acids led to the formation of *N*-substituted 3-aryl-2-cyanoacetoxy-3-oxopropionamides, which in the presence of amine bases underwent a *Knoevenagel condensation* providing *N*-substituted 3-aryl-cyano-2,5-dihydro-5-oxofuran-2-carboxamides.



PATERNO-BÜCHI REACTION

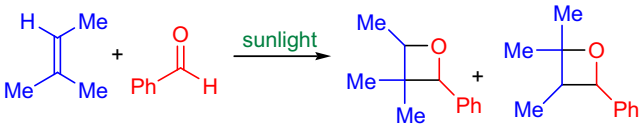
(References are on page 646)

Importance:

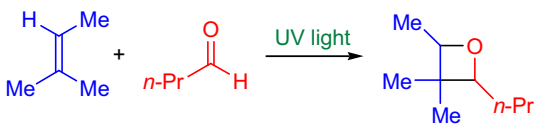
[*Seminal Publications*[1-4]; *Reviews*[5-18]; *Theoretical Studies*[19-26]]

In 1909, E. Paterno and G. Chieffi reported an interesting reaction that took place between benzaldehyde and 2-methyl-2-butene upon exposure to sunlight.[2] The authors isolated two isomeric compounds that they characterized as trimethylene oxides (oxetanes). The reaction went largely unnoticed until 1954, when G. Büchi decided to reinvestigate Paterno's findings and determine the exact structure of the products.[4] The photochemical cycloaddition between aldehydes and alkenes to form oxetanes is known as the *Paterno-Büchi reaction*. The general features of this transformation are:[7,10] 1) the carbonyl substrate is the energy-absorbing component in the process, and it becomes excited upon irradiation; 2) the carbonyl compound can be either an aldehyde or a ketone; 3) the alkene substrate is most often electron-rich by virtue of one or more electron-donating substituents (e.g., alkoxy, thioalkyl, or alkylamino); 4) the reaction is highly regio- and stereoselective, and the regiochemical outcome can be predicted based on the most stable 1,4-biradical intermediate, which is formed when the excited carbonyl compound adds across the carbon-carbon double bond; 5) the degree of regioselectivity depends on the nature and the position of the substituents on the alkene and, for example, alkenyl sulfides afford the oxetane products with higher regioselectivity than the corresponding enol ethers[27] and also 1,1-disubstituted alkenes give rise to highly regiochemically pure products; 6) when stereochemically pure (*E*) or (*Z*) alkenes are used, the stereochemical information is usually lost and the conformational preference in the 1,4-biradical intermediate results in the predominant formation of the *trans* oxetane product; 7) when cyclic alkenes are used, only the *cis* oxetanes are formed in the case of five- and six-membered alkenes, whereas larger cyclic olefins give rise to a mixture of *cis*- and *trans* oxetanes; 8) conjugated dienes (1,3-dienes and styrenes) and certain five-membered heterocycles (e.g., furans, pyrroles, imidazoles, and indoles) also react to give the corresponding oxetanes; and 9) the facial diastereoselectivity can be induced either with chiral auxiliaries attached to the carbonyl compounds or with the use of chiral alkenes.

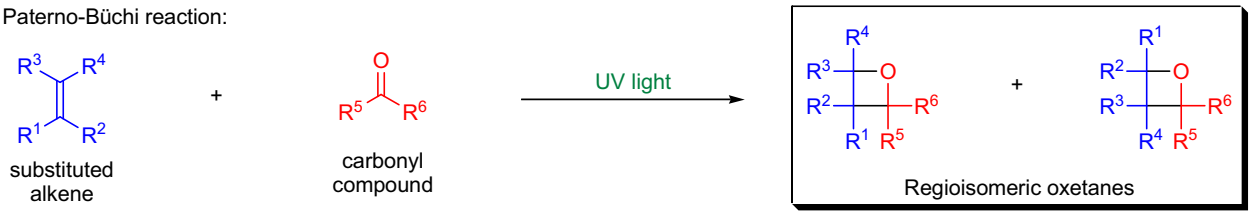
Paterno (1909 & 1911):



Büchi (1954):



Paterno-Büchi reaction:

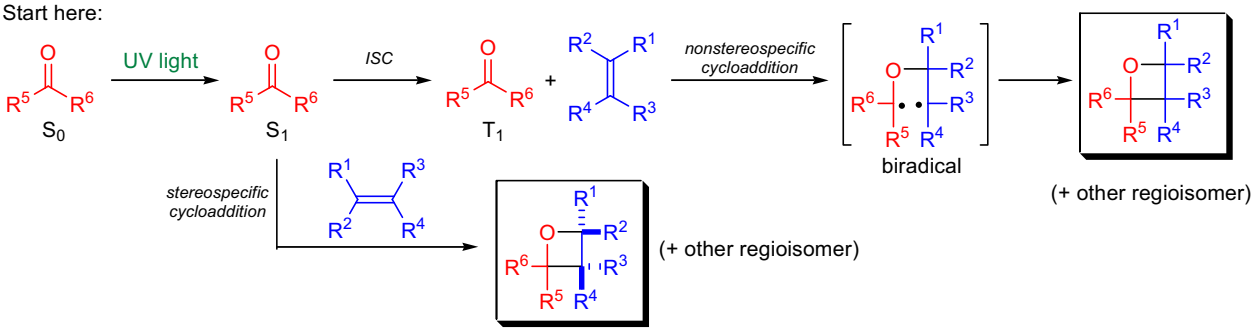


$R^{1\text{-}4}$ = H, alkyl ,aryl, O-alkyl, S-alkyl, NR_2; $R^{5\text{-}6}$ = H, alkyl ,aryl

Mechanism:[28-51]

The mechanism of the *Paterno-Büchi reaction* has been extensively studied. The current understanding of the process involves the following steps: 1) the carbonyl functionality (S_0) is excited by a UV photon *via* n *-absorption to afford the corresponding singlet state (S_1); 2) the carbonyl singlet state can be converted to the carbonyl triplet state (T_1) *via* intersystem crossing (ISC); 3) when the carbonyl singlet reacts with the alkene (mostly in the case of aliphatic aldehydes and ketones and a very high alkene concentration is required in order to quench the singlet state efficiently) the photocycloaddition is stereospecific and the stereochemical information of the alkene substrate is translated into the oxetane product; 4) in the overwhelming majority of the *Paterno-Büchi reactions*, however, the intersystem crossing gives rise to the carbonyl triplet state, which upon addition to the alkene affords a 1,4-biradical (these species have been studied spectroscopically);[33] and 5) finally the most stable 1,4-biradical conformer collapses to the oxetane product.

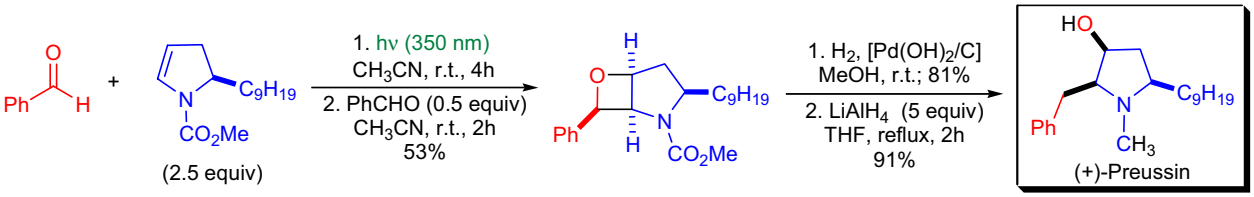
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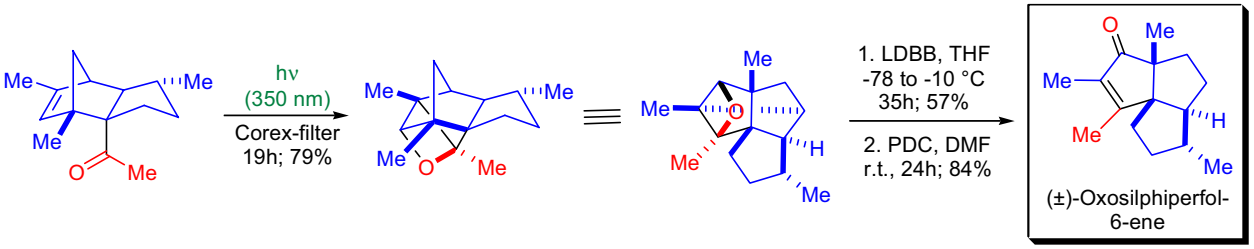
PATERNO-BÜCHI REACTION

Synthetic Applications:

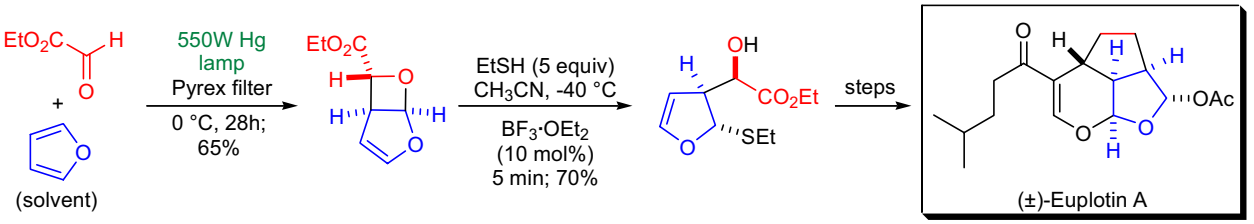
In the laboratory of T. Bach, the *Paterno-Büchi reaction* of chiral 2-substituted 2,3-dihydropyrroles with benzaldehyde was used in the total synthesis of the antifungal agent (+)-preussin.[52,53] Benzaldehyde was mixed with excess dihydropyrrole substrate in acetonitrile and was irradiated at room temperature at 350 nm UV light. Once all the benzaldehyde was consumed, half an equivalent of benzaldehyde was added and the irradiation continued for another two hours. The addition of the photoexcited benzaldehyde proceeded in a *syn* fashion and the thermodynamically less stable *endo* oxetane was formed as the major product. The oxetane ring was then cleaved under catalytic hydrogenation conditions in the presence of Pearlman's catalyst to form the all-*cis* pyrrolidinol. Finally the reduction of the *N*-carboxymethyl group to the corresponding *N*-methyl group was achieved using lithium aluminum hydride.



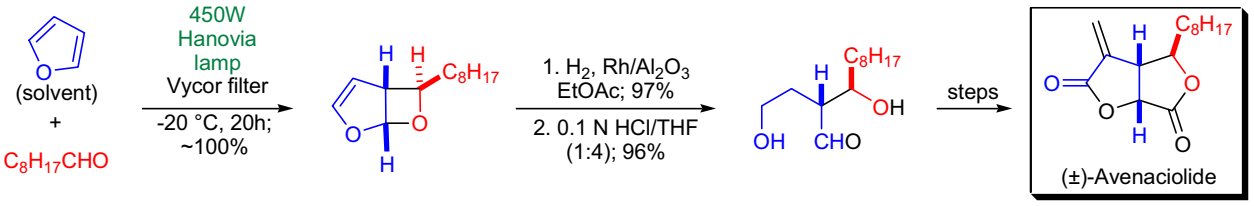
A unique *intramolecular Paterno-Büchi reaction/fragmentation* sequence was utilized during the short total synthesis of the angular triquinane (±)-oxosilphiperfol-6-ene by V.H. Rawal et al.[54] The photocycloaddition substrate was prepared *via* a highly *regio*-, *endo*-, and diastereofacially selective *Diels-Alder cycloaddition* between 1,3-dimethylcyclopentadiene and 1-acetyl-3-methylcyclopentene. The cycloadduct was then irradiated with Corex-filtered light to obtain the strained cage-like product. Reductive cleavage of the oxetane ring with LDBB yielded an allylic alcohol, which was oxidized to the desired α,β-unsaturated ketone with PDC.



The first total synthesis of the cytotoxic agent (±)-euplotin A was completed by the research team of R.L. Funk.[55] The key step of the synthetic effort was the *intramolecular hetero Diels-Alder cycloaddition* of a 3-acyl oxadiene (generated from 5-acyl-4*H*-1,3-dioxins *via* thermal retrocycloaddition) with a substituted dihydrofuran to afford the tricyclic skeleton of the natural product. The correct relative stereochemistry of the required dihydrofuran substrate was established using the *Paterno-Büchi reaction* between ethyl glyoxylate and furan. Subsequently, the oxetane ring was opened stereoselectively under Lewis acid catalysis.



The *Paterno-Büchi reaction* of furan and various aldehydes was shown to be a highly stereoselective photochemical version of the *aldol reaction* by S.L. Schreiber and co-workers in which the furan serves as an enolate equivalent.[56] This strategy was applied to the total synthesis of the antifungal metabolite (±)-avenaciolide.[57] The photocycloaddition of nonanal with excess furan proceeded in nearly quantitative yield, and the two out of the three required stereocenters were created in a single step. The photocycloadduct was first hydrogenated then hydrolyzed under acidic conditions.



PAUSON-KHAND REACTION

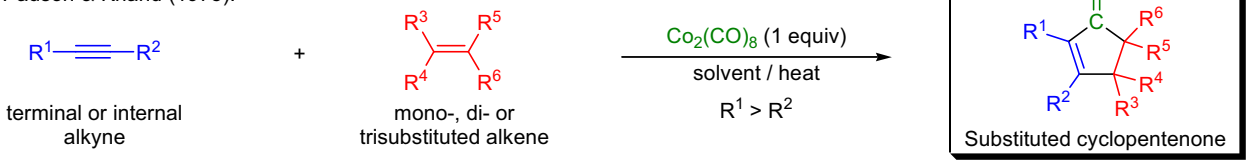
(References are on page 647)

Importance:

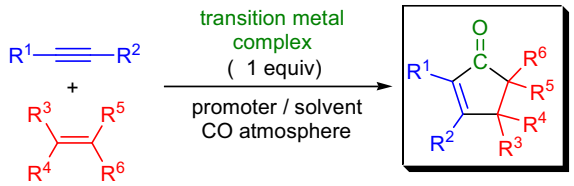
[*Seminal Publication*[1]; *Reviews*[2-31]; *Modifications & Improvements*[32-35]; *Theoretical Studies*[36-47]]

In 1973, I.U. Khand and P.L. Pauson reported that various acetylenehexacarbonyl dicobalt complexes reacted with alkenes in hydrocarbon or ether solvents to give cyclopentenones in good yield.[1] The scope and limitation of this reaction was determined by the research group of P.L. Pauson in the 1970s. The transition metal (cobalt) catalyzed formal *[2+2+1]* cycloaddition of alkynes, alkenes, and carbon-monoxide to form substituted cyclopentenones is referred to as the *Pauson-Khand reaction*. The general features of this process are: 1) the reaction is feasible both inter- and intramolecularly; 2) acetylene and terminal as well as internal alkynes are all substrates for the reaction. However, derivatives of propynoic acid do not react; 3) the required alkyne-cobalt complexes are easily prepared by reacting alkynes with dicobalt octacarbonyl; 4) internal alkynes tend to give lower yields of the product than terminal alkynes; 5) a wide range of alkenes are feasible reaction partners and, generally, strained cyclic alkenes react the fastest; 6) the order of reactivity is significantly influenced by the substitution pattern of the alkene substrate: strained cyclic alkene > terminal alkene > disubstituted alkene >> trisubstituted alkene, and tetrasubstituted alkenes do not react; 7) alkenes with strongly electron-withdrawing groups give poor or no reaction; 8) the reaction is highly regioselective: the larger alkyne substituent (R^1) ends up next to the carbonyl group in the product, but the regioselectivity with respect to the alkene is less predictable in intermolecular reactions; 9) with cyclic alkenes the reaction is highly stereoselective and the *exo* product is formed preferentially; 10) intramolecular reactions proceed with excellent regio- and stereoselectivity; 11) with the use of chiral auxiliaries the reaction conditions are compatible with a large number of different functional groups. However there are certain functionalities that are only partially tolerated: alkyl and aryl halides, vinyl ethers, and vinyl esters; 12) the reaction can be accelerated by the addition of various promoters (such as tertiary amine oxides, high-intensity light, etc.), which help to open a coordination site at one of the cobalt atoms for the alkene to coordinate; 13) it is possible to run the cyclization catalytically but only in the presence of a high pressure atmosphere of CO; and 14) besides $Co_2(CO)_8$, other transition metal complexes also efficiently catalyze the cyclization (e.g. $Fe(CO)_5$, $Ru_2(CO)_{12}$, etc.)

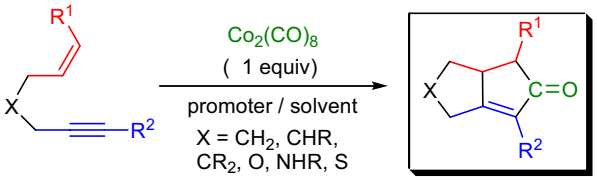
Pauson & Khand (1973):



Modified P-K reaction:



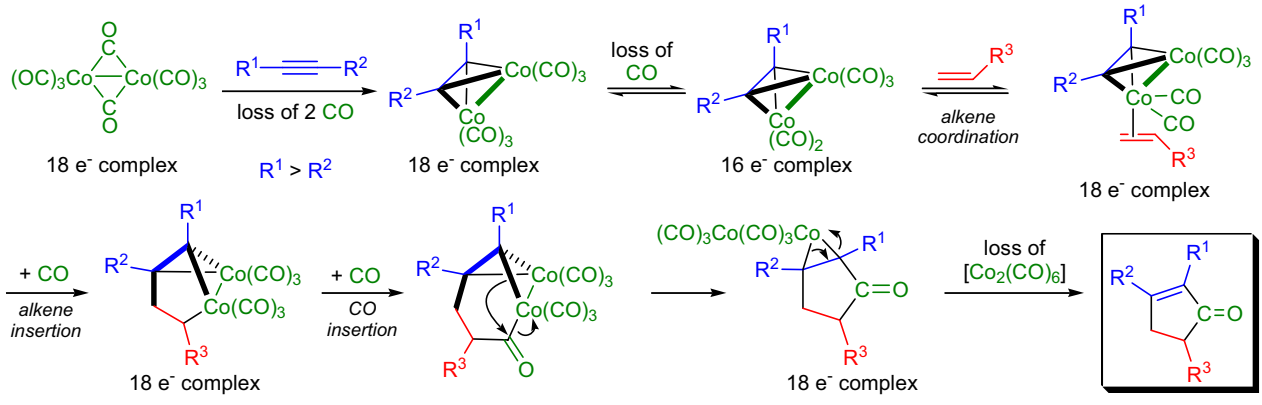
Intramolecular variant:



R^{1-6} = H, alkyl, aryl, substituted alkyl and aryl; transition metal complex: $Co_2(CO)_8$, $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2, $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$; promoter: NMO, TMAO, $RSCH_3$, high-intensity light/photolysis, "hard" Lewis base

Mechanism:[48-62]

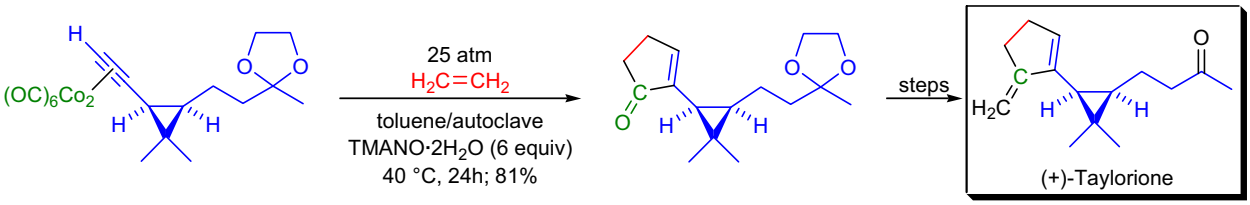
The mechanism of the *Pauson-Khand reaction* has not been fully elucidated. However, based on the regio- and stereochemical outcome in a large number of examples, a reasonable hypothesis has been inferred.



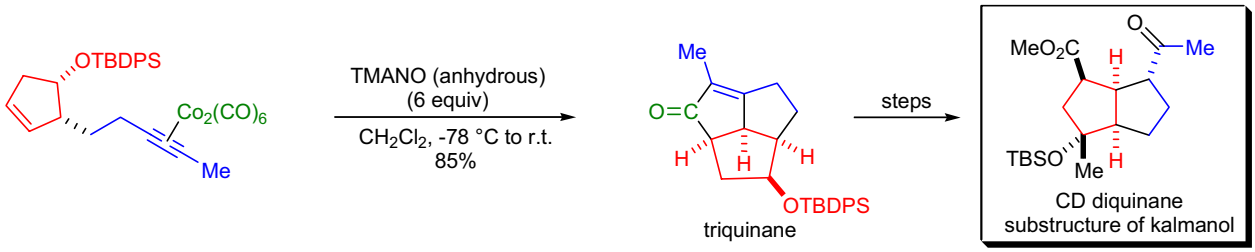
PAUSON-KHAND REACTION

Synthetic Applications:

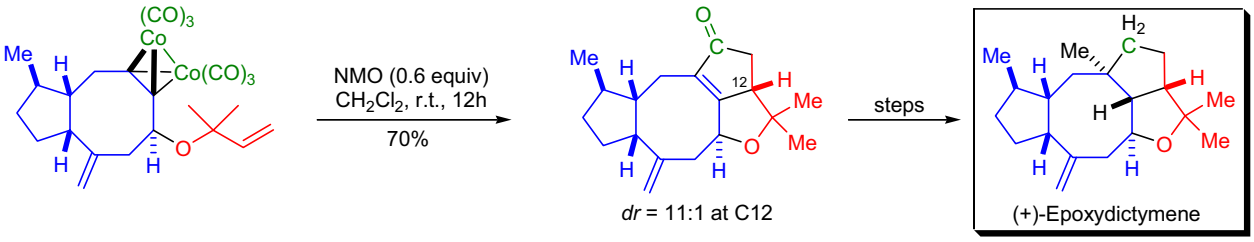
The total synthesis of the sesquiterpene (+)-taylorione was achieved in the laboratory of J.G. Donkervoort who used the *modified Pauson-Khand reaction* to prepare the five-membered ring of the natural product.[63] The preformed alkyne-cobalt complex was exposed to excess triethylamine-*N*-oxide, which oxidized off two CO ligands to free up a coordination site for the ethylene. The optimum pressure of the ethylene gas had to be at 25 atm, and the reaction was conducted in an autoclave.



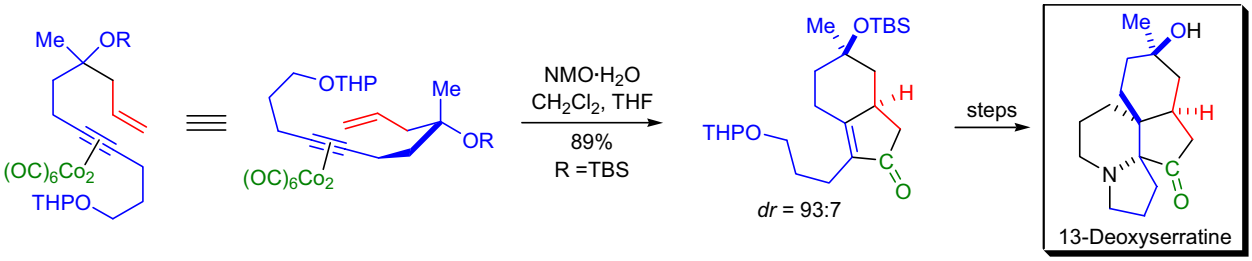
During the synthetic studies toward the natural product kalmanol, L.A. Paquette and co-workers prepared the CD diquinane substructure by using an *intramolecular Pauson-Khand reaction*.[64] The use of an *N*-oxide promoter for the cyclization resulted in very mild conditions and afforded the desired triquinane in good yield and as a single diastereomer.



In the laboratory of S.L. Schreiber, the total synthesis of (+)-epoxydictymene was accomplished by the tandem use of cobalt-mediated reactions as key steps.[65] The eight-membered carbocycle was formed *via* a *Nicholas reaction*, while the five-membered ring was annulated by the *Pauson-Khand reaction*. Several *P.-K.* conditions were explored and the best diastereoselectivity was observed when NMO was used as a promoter. The annulated product was isolated as an 11:1 mixture of diastereomers.



The key bicyclo[4.3.0]nonenone intermediate in the total synthesis of ( )-13-deoxyserratine was prepared by a highly diastereoselective *intramolecular Pauson-Khand reaction* of a functionalized enyne-cobalt complex in the laboratory of S.Z. Zard.[66] The reactive conformation of this complex is one in which the OTBS group occupies the pseudoequatorial position. The observed diastereoselectivity was high as the alternative conformer was significantly higher in energy. The concave shape of the bicyclic product was exploited in controlling the introduction of the remaining three stereocenters.



PAYNE REARRANGEMENT

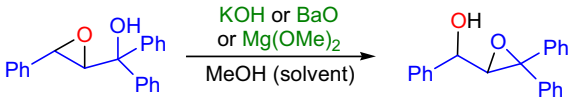
(References are on page 649)

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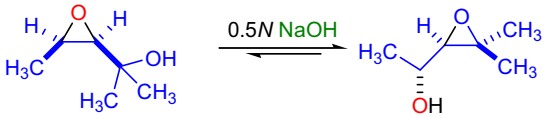
[*Seminal Publications*[1-4]*; Reviews*[5-8]*; Modifications & Improvements*[9-12]*; Theoretical Studies*[13-15]]

In 1935, E.P. Kohler and C.L. Bickel described the unusual properties of certain 2,3-epoxy alcohols (β-oxanols), which underwent a rearrangement in the presence of catalytic amounts of a strong base (e.g., alkali hydroxides, barium oxide, magnesium methylate, etc.) to give isomeric 2,3-epoxy alcohols.[1] Three decades later in 1962, G.B. Payne reported that aqueous sodium hydroxide at room temperature was sufficient to bring about the isomerization-equilibration of 2,3-epoxy alcohols, a transformation, which he found to be general and termed as "*epoxide migration*".[4] The base-catalyzed intramolecular nucleophilic displacement of 2,3-epoxy alcohols to give the isomeric 2,3-epoxy alcohols is known as the *Payne rearrangement*. The general features of the reaction are:[7] 1) enantiopure epoxide substrates are accessible most conveniently by the *Sharpless asymmetric epoxidation* of allylic alcohols; 2) the stereochemistry at C2 undergoes inversion; 3) the base needs to be strong and in most cases the use of a protic solvent such as water or an alcohol is necessary; 4) the direction of epoxide equilibration is influenced by both steric and electronic effects; 5) the most substituted epoxide isomer is favored; 6) *trans* epoxides are more stable than *cis* epoxides; 7) vinylyl and phenyl substituents on the oxirane have a stabilizing effect, while EWG are destabilizing; 8) the epoxide isomer with a primary hydroxyl group is favored; and 9) in cyclic systems the favored epoxide is the one that has more pseudoequatorial groups. The two main variants of the reaction are the *aza- and thia-Payne rearrangement* in which aziridines and thiiranes are formed, respectively.[10,5]

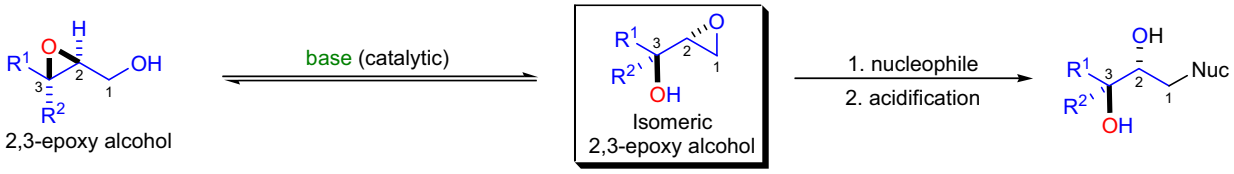
Kohler & Bickel (1935):



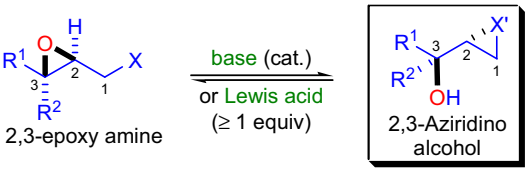
Payne (1962):



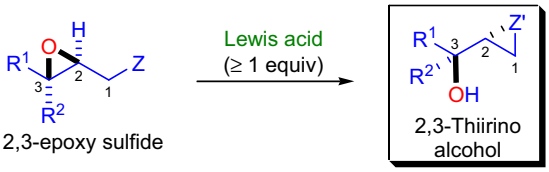
Payne rearrangement followed by nucleophilic epoxide ring-opening:



Aza-Payne rearrangement (can be true equilibrium):



Thia-Payne rearrangement (only forward direction):

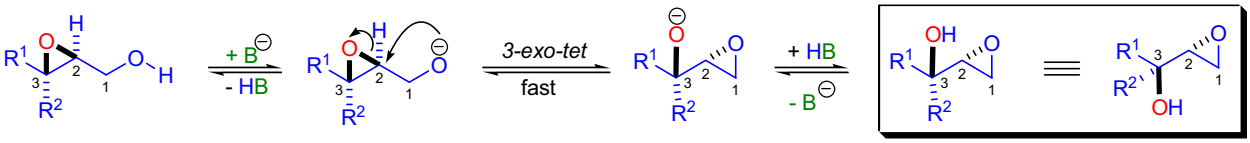


R^{1-2} = H, alkyl, aryl; when X = NR_2, X' = NR_2^+; when X = NHMs, X' = NMs; when Z = SAc, Z' = S; when Z = SR, Z' = SR^+

base: NaOH, KOH, NaOR, NaH, KH; Lewis acid: $AlMe_3$, TMSOTf, $PhB(OH)_2$, $BF_3{\cdot}OEt_2$, $Ti(O\textit{i}\text{-}Pr)_4$

Mechanism: [5,7]

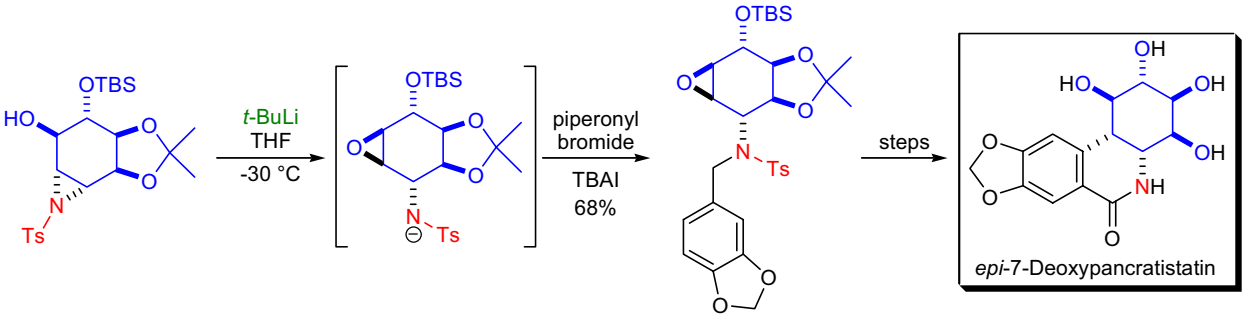
The currently accepted mechanism was first proposed by S.J. Angyal and P.T. Gilham in 1957.[3] The first step of the process is the deprotonation of the hydroxyl group at C1 by the strong base and the resulting alkoxide undergoes an S_Ni reaction (*3-exo-tet process*) to open the adjacent epoxide at C2. As a result, a new epoxide is formed at C1 and C2 in which the C2 stereochemistry is inverted. The alkoxide anion at C3 is protonated by the solvent to afford the product. It is worth noting that the success of the rearrangement in most cases depends on the nature of the solvent. Generally, strong bases in aprotic solvents (e.g., NaH/THF) do not affect the reaction, but strong bases in protic solvents (e.g., $NaOH/H_2O$) do. According to theoretical studies, the product of the *Payne rearrangement* is formed under kinetic control, since the thermodynamically most stable species would be an oxetane, which has never been observed in solution-phase reaction mixtures (only in the mass spectrometer).[13,14] When the reaction is conducted in the presence of a nucleophile so that the equilibrating epoxides are opened *in situ* with a nucleophile (slow step), the product distribution is governed by the Curtin-Hammett principle and exclusive ring-opening at the least substituted carbon of the less substituted epoxide can be achieved. The mechanism of the *aza-Payne rearrangement* is more complex and the outcome is influenced both by the structure of the substrate and the nature of the base or Lewis acid.[5]



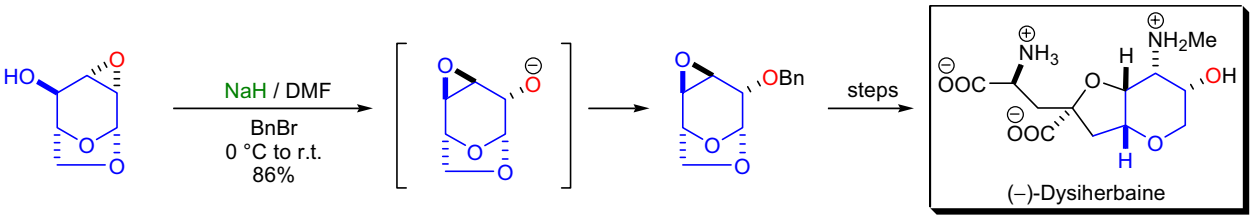
PAYNE REARRANGEMENT

Synthetic Applications:

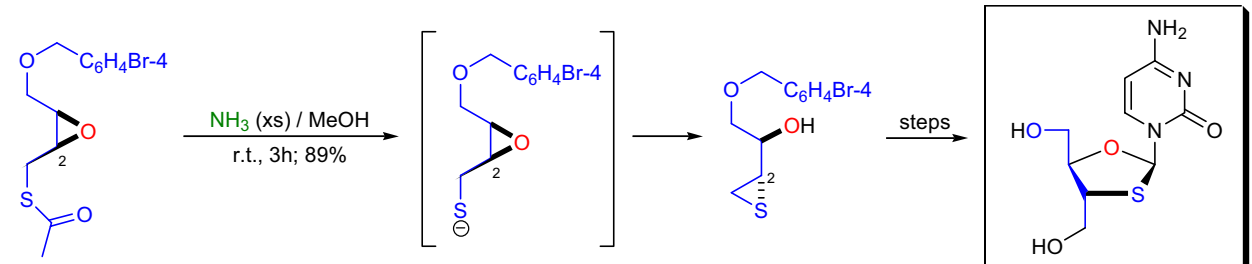
The Lewis acid-catalyzed *aza-Payne rearrangement* was utilized in the total synthesis of *epi*-7-deoxypancratistatin by T. Hudlicky and co-workers.[16] The 2,3-aziridino alcohol was treated with *t*-BuLi, to generate the epoxy amide that was trapped with piperonyl bromide.



A novel neuroexcitotoxic amino acid, (–)-dysiherbaine, was synthesized starting from a carbohydrate precursor in the laboratory of M. Sasaki.[17] Under benzylation conditions, the cyclic 2,3-epoxy alcohol underwent a facile *Payne rearrangement* and the rearranged alkoxide was trapped with benzyl bromide.

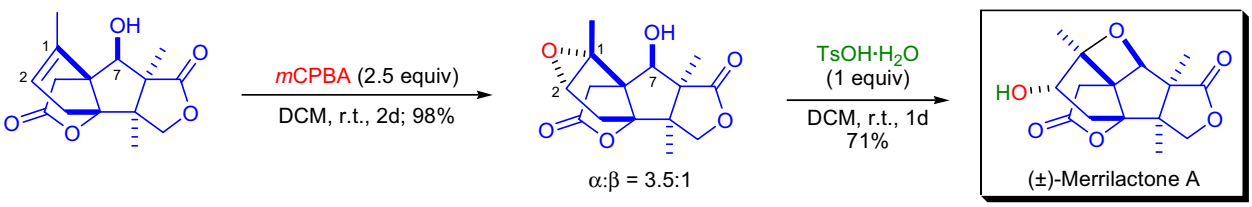


I. Kvarnström et al. prepared novel nucleosides with potential HIV-1 inhibitor acitivity using the *thia-Payne rearrangement* to install the sulfur atom stereoselectively. The 2,3-epoxy alcohol was first converted to the corresponding thioacetate then treated with methanolic ammonia solution to effect the rearrangement to afford the thiirane in excellent yield. As expected, inversion of configuration at C2 occured. The authors also found, that under mild acidic conditions (silica gel), the thioacetate yielded a thiirane with a net retention of configuration at the C2 stereocenter. This result can be explained with the neighboring group participation of the acetate, which opened the protonated epoxide (with inversion at C2) to give a 1,3-oxathiolan-2-ylium ion. This carbocation then rearranged to the more stable 1,3-dioxolan-2-ylium ion. Subsequently, the sulfur nucleophile at C1 attacked C2 for the second time with inversion of configuration to afford the thiirane with a net retention of configuration.



2,3-epoxy thioacetate

The total synthesis of (±)-merrilactone A was accomplished by S.J. Danishefsky and co-workers.[18] The last step of the sequence was an acid-induced *homo-Payne rearrangement*. The tetracyclic homoallylic alcohol precursor was first epoxidized using *m*CPBA. The epoxidation was expected to occur from the same face as the C7 hydroxyl group, but due to the congested nature of the C1-C2 double bond at its β-face, the epoxide was formed predominantly on the α-face. The epoxide substrate then was exposed to *p*-toluenesulfonic acid at room temperature to afford the desired oxetane ring of the natural product.



α:β = 3.5:1

PERKIN REACTION

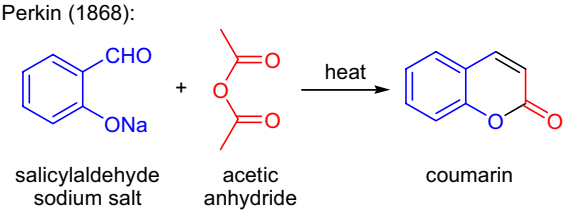
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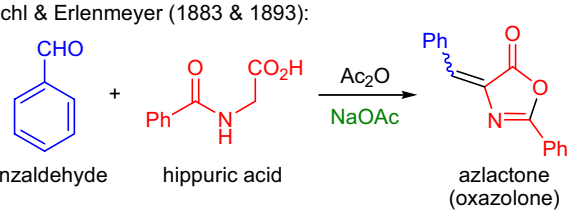
[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5-22]]

In 1868, W.H. Perkin described the one-pot synthesis of coumarin by heating the sodium salt of salicylaldehyde in acetic anhydride.[1] After this initial report, Perkin investigated the scope and limitation of the process and found that it was well-suited for the efficient synthesis of cinnamic acids.[2] The condensation of aromatic aldehydes with the anhydrides of aliphatic carboxylic acids in the presence of a weak base to afford α,β-unsaturated carboxylic acids is known as the *Perkin reaction* (or *Perkin condensation*). The general features of the transformation are:[3,4] 1) the aldehyde component is most often aromatic, but aliphatic aldehydes with no α-hydrogens as well as certain α,β-unsaturated aldehydes can also be used;[17] 2) the reaction is more facile and gives higher yield of the product when the aromatic aldehyde has one or more electron-withdrawing substituents; 3) aliphatic aldehydes are not suitable for the reaction, since they often give enol acetates and diacetates when heated with acetic anhydride; 4) the anhydride should be derived from an aliphatic carboxylic acid, which has at least two hydrogen atoms at their α-position (if there is only one α-hydrogen atom, a β-hydroxy carboxylic acid is obtained); 5) the weak base is most often the alkali metal salt of the carboxylic acid corresponding to the applied anhydride or a tertiary amine (e.g., Et_3N); 6) the usual procedure requires heating of the aldehyde in the anhydride (often used as the solvent) at or above 150 °C; and 7) the stereochemistry of the newly formed double bond is typically (*E*). There are two important modifications of the *Perkin reaction*: 1) the condensation of an aromatic aldehyde or ketone with an *N*-acyl glycine in acetic anhydride in the presence of NaOAc to obtain azlactones (oxazolones), which are important intermediates for the synthesis of α-amino acids (*Erlenmeyer-Plöchl azlactone synthesis*);[6-9,15,22] and 2) the condensation of aromatic aldehydes with α-arylacetic acids in acetic anhydride and in the presence of a weak base (proceeding *via* mixed anhydrides generated *in situ*) to obtain α-arylcinnamic acids (*Oglialoro modification*).[5]

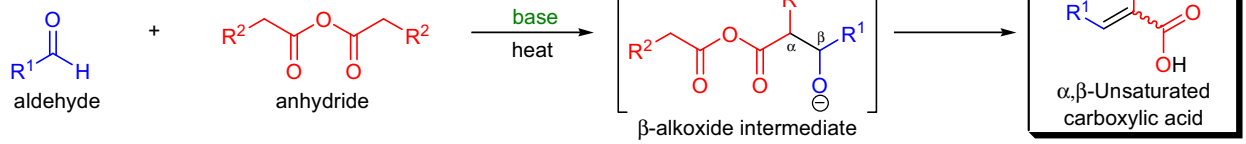
Perkin (1868):



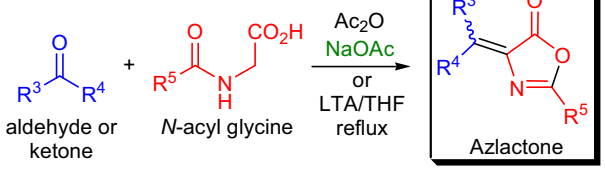
Plöchl & Erlenmeyer (1883 & 1893):



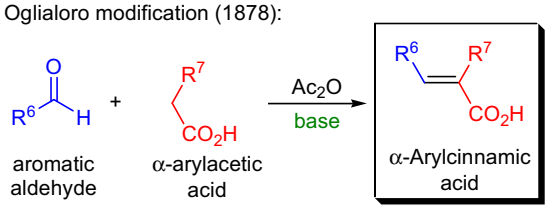
Perkin reaction:



Erlenmeyer-Plöchl azlactone synthesis:

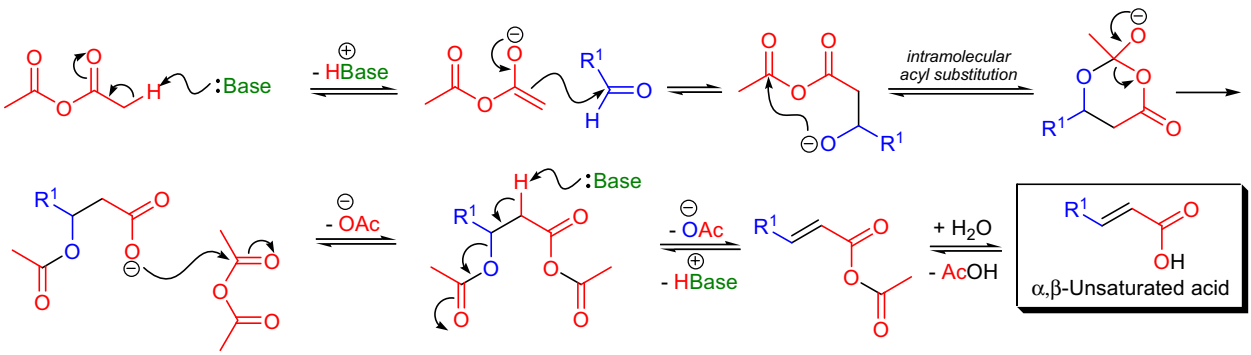


Oglialoro modification (1878):



R^1 = aromatic, heteroaromatic, alkenyl, alkyl group with no α-hydrogen atom; R^2 = H, alkyl, aryl; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; R^6 = aryl, heteroaryl; base: NaOAc, KOAc, CsOAc, Et_3N, pyridine, piperidine, K_2CO_3

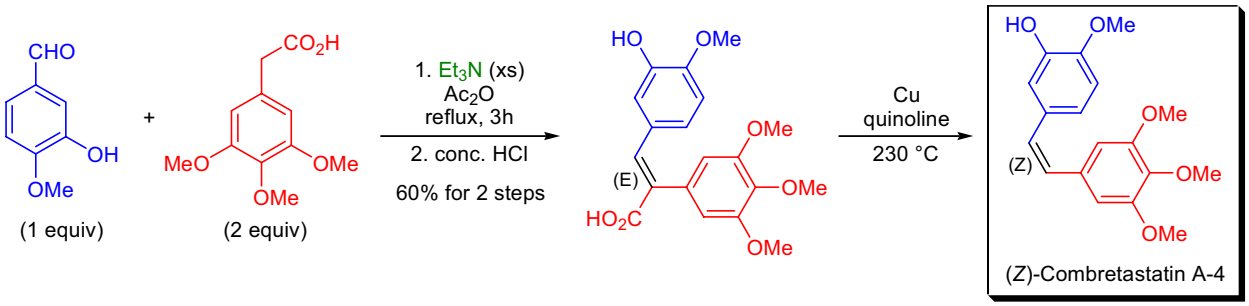
Mechanism:[23,3,24-31,4,32-35]



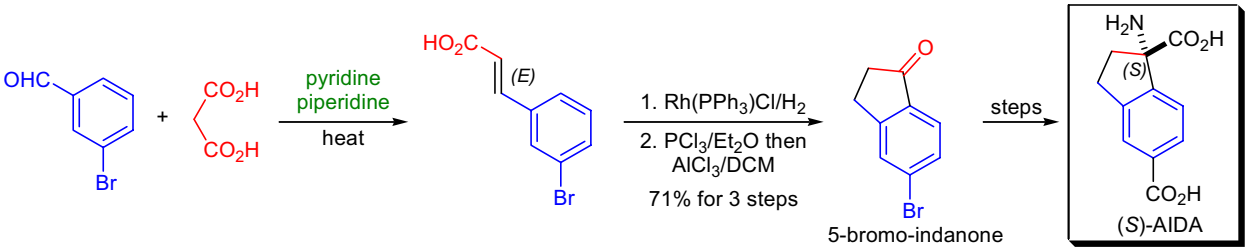
PERKIN REACTION

Synthetic Applications:

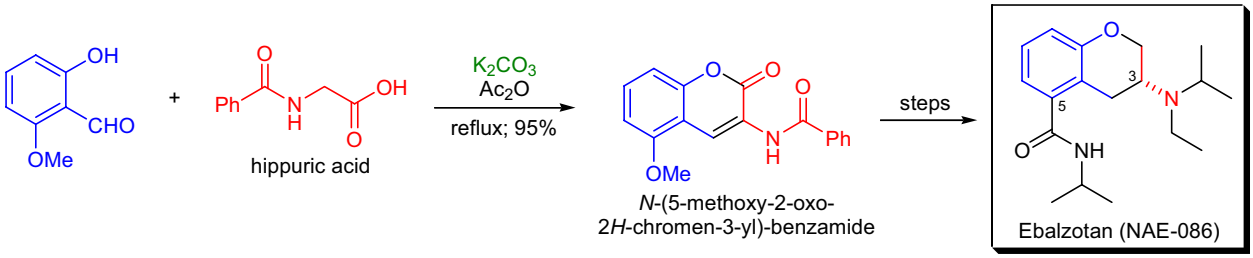
The combretastatins are a group of antimitotic agents isolated from the bark of the South African tree *Combretum caffrum*. A novel and highly stereoselective total synthesis of both the *cis* and *trans* isomers of combretastatin A-4 was developed by J.A. Hadfield and co-workers.[36] The (*Z*)-stereoisomer was prepared using the *Perkin reaction* as the key step in which 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxbenzaldehyde was heated with triethylamine and acetic anhydride at reflux for several hours. The α,β-unsaturated acid was isolated in good yield after acidification and had the expected (*E*) stereochemistry. Decarboxylation of this acid was effected by heating it with copper powder in quinoline to afford the natural product (*Z*)-combretastatin A-4.



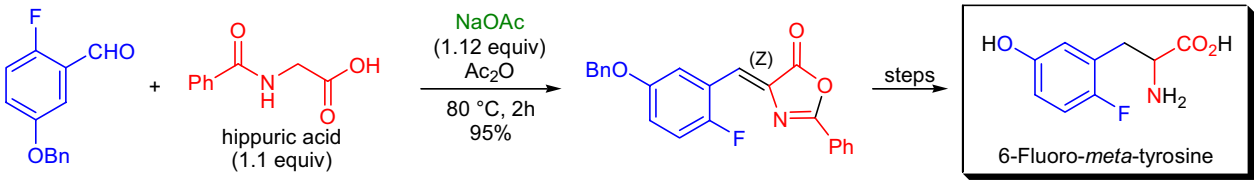
In the laboratory of D. Ma, the asymmetric synthesis of several metabotropic glutamate receptor antagonists derived from α-alkylated phenylglycines was undertaken.[37] The preparation of (*S*)-1-aminoindan-1,5-dicarboxylic acid (AIDA) started with the *Perkin reaction* of 3-bromobenzaldehyde and malonic acid. The resulting (*E*)-cinnamic acid derivative was hydrogenated and the following *intramolecular Friedel-Crafts acylation* afforded the corresponding indanone, which was then converted to (*S*)-AIDA.



The large-scale pilot plant preparation of the chiral aminochroman antidepressant ebalzotan (also known as NAE-086) was developed by H.J. Federsel and co-workers.[38] The structural features of the target included a disubstituted chroman skeleton, a stereocenter, as well as a non-symmetrical tertiary amine moiety at the C3 position and a secondary carboxamide group at C5. The backbone of the target molecule was constructed using the *Perkin condensation* of 2-hydroxy-6-methoxybenzaldehyde with hippuric acid under mild conditions.



Fluorinated analogs of naturally occurring biologically active compounds, such as amino acids, often exhibit unique physiological properties, and therefore there is substantial interest in their convenient and high-yielding preparation. The research team of K.L. Kirk synthesized 6-fluoro-*meta*-tyrosine and several of its metabolites employing the *Erlenmeyer-Plöchl azlactone synthesis*.[39] Hippuric acid and 2-benzyloxy-5-fluorobenzaldehyde were condensed in the presence of sodium acetate in acetic anhydride to isolate the corresponding azlactone, which was converted to the target fluorinated amino acid in three steps.



PETASIS BORONIC ACID-MANNICH REACTION

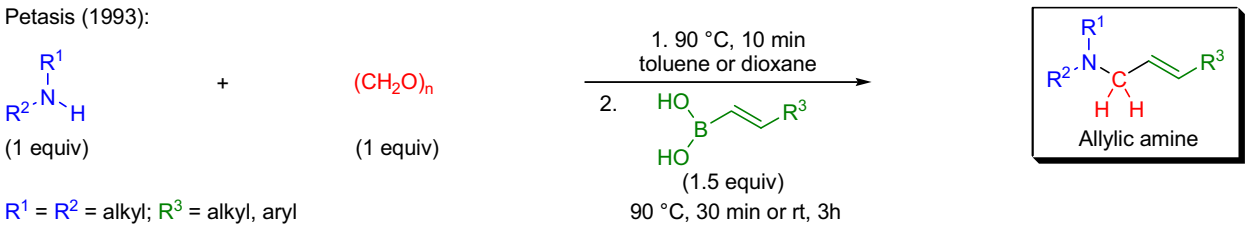
(References are on page 650)

Importance:

[*Seminal Publications*[1]; *Reviews*[2-7]; *Modifications & Improvements*[8-16]]

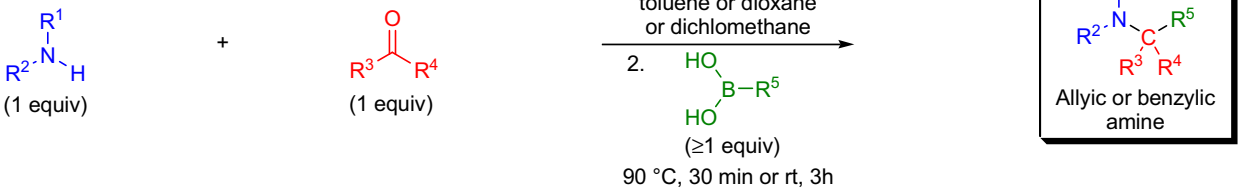
Allylic amines are synthetically useful building blocks and several derivatives possess diverse biological properties. In 1993, N.A. Petasis and co-workers reported an efficient synthesis of these compounds based on a modified *Mannich reaction* where vinylboronic acids served as the nucleophilic component. This transformation is referred to as the *Petasis boronic acid-Mannich reaction*. The general features of the reaction are: 1) according to the original procedure, the reaction is convenient to carry out: the mixture of paraformaldehyde and a secondary amine are heated to 90 °C in toluene or dioxane for ten minutes followed by the addition of the vinylboronic acid and stirring the reaction mixture at room temperature for several hours or heating to 90 °C for 30 minutes; 2) the work-up procedure includes an acid-base extraction to remove the unreacted vinylboronic acid; 3) the addition of the boronic acid to the amine-paraformaldehyde adduct occurs with complete retention of the geometry of the double bond; 4) the resulting allylamines form with high stereoselectivity; 4) originally, formaldehyde was used as the aldehyde component, but other aldehydes and ketones also undergo the transformation;[8,9] 5) when glyoxylic acid or α-keto acids are used as the carbonyl component, α-amino acids are obtained;[8,9] 5) the boronic acids can be prepared by the condensation of catecholborane with terminal alkynes and subsequent hydrolysis of the vinylboronate esters; 6) vinylboronate esters can also participate in the reaction, but purification of the product is more difficult;[1] 7) arylboronate esters[8] and potassium organotrifluoroborates[15,16] are also viable substrates; 8) in addition to secondary amines, tertiary aromatic amines,[14] substituted hydrazines,[12] substituted hydroxylamines, and sulfinamides[13] undergo the transformation; and 9) upon Lewis acid activation, 2-hydroxy- and 2-alkoxy derivatives of *N*-protected pyrrolidines and piperidines also react.[10] A solid phase version of the reaction was also developed.[11]

Petasis (1993):



R^1 = R^2 = alkyl; R^3 = alkyl, aryl

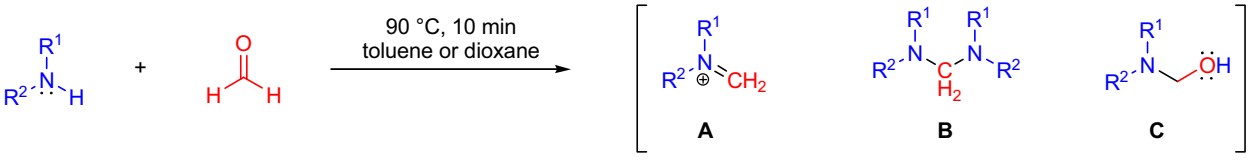
General scheme:

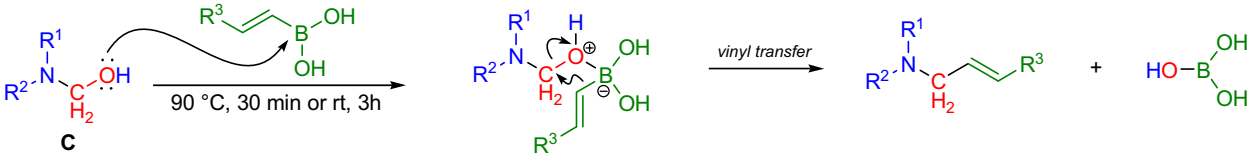


R^1 = alkyl; R^2 = alkyl; OH, *O*-alkyl, -SO^{t}Bu, NHCOO^{t}Bu; R^3 = H, alkyl, R^4 = H, -COOH, aryl; R^5 = alkenyl, aryl, heteroaryl

Mechanism:[1]

The mechanism of the *Petasis boronic acid-Mannich reaction* is not fully understood. In the first step of the reaction, upon mixing the carbonyl and the amine components, three possible products can form: iminium salt **A**, diamine **B**, and α-hydroxy amine **C**. It was shown that preformed iminium salts do not react with boronic acids. This observation suggests that the reaction does not go through intermediate **A**. Both intermediate **B** and **C** can promote the formation of the product. Most likely, the reaction proceeds through intermediate **C**, where the hydroxyl group attacks the electrophilic boron leading to an "ate"-complex. Subsequent vinyl transfer provides the allylic amine along with the boronic acid sideproduct.

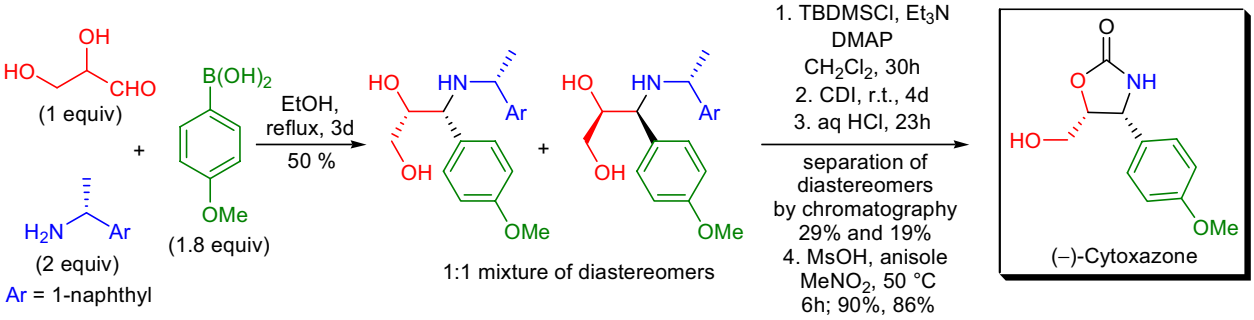




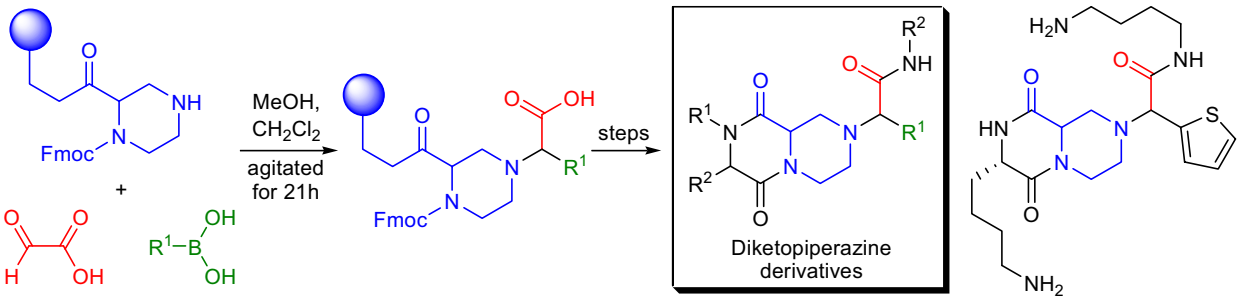
PETASIS BORONIC ACID-MANNICH REACTION

Synthetic Applications:

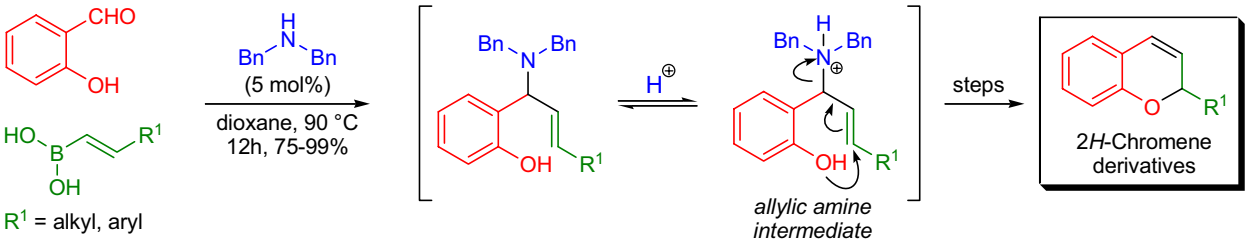
(–)-Cytoxazone is a novel cytokine modulator. The total synthesis of this natural product and its enantiomer was accomplished by S. Sugiyama.[17] The 3-amino-1,2-propanediol moiety was synthesized by a *Petasis boronic acid-Mannich* reaction between DL-glyceraldehyde, (*R*)-1-(1-naphthyl)ethylamine and 4-methoxyphenylboronic acid to provide a 1:1 mixture of the diastereomeric products. The diastereomers could be separated at a later stage in the synthesis and transformed into (–)- and (+)-cytoxazone.



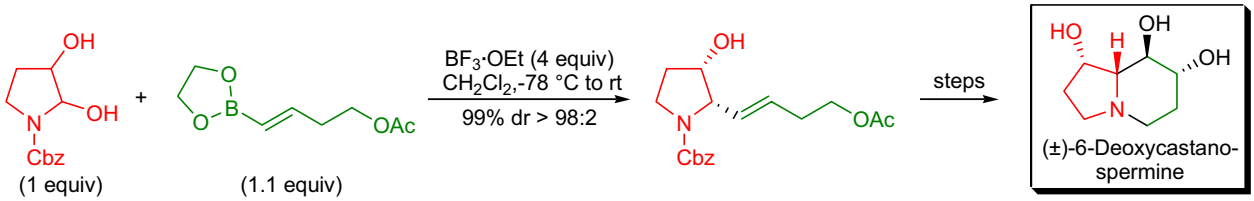
In the laboratory of A. Golebiowski, the high throughput synthesis of diketopiperazines was accomplished.[18] These compounds can serve as β-turn mimetics. The key step in this approach was a *Petasis boronic acid-Mannich reaction* between the Merrifield resin-bound piperazine-2-carboxylic acid, glyoxylic acid, and a wide range of commercially available boronic acids to provide a 1:1 mixture of the products. A specific example is shown below.



M.G. Finn and co-workers developed a procedure for the preparation of 2*H*-chromene derivatives that includes a Petasis three-component reaction between salicylaldehyde, vinylic- and aromatic boronic acids, and dibenzylamine.[19] The hydroxyl group of the salicylic aldehyde is essential for the activation of the boronic acid. The initially formed allylic amine undergoes a cyclization upon ejecting the dibenzylamine, thus rendering the process catalytic in the amine.



R.A. Batey and co-workers developed a modification of the *Petasis-boronic acid-Mannich reaction* that occurs via *N*-acyliminium ions derived from *N*-protected-2,3-dihydroxypyrrolidine and 2,3-dihydroxypiperidine derivatives.[10] This method was utilized in the total synthesis of (±)-deoxycastanospermine. The formation of the *N*-acyliminium ion was achieved by treating *N*-Cbz-2,3-pyrrolidine with $BF_3{\cdot}OEt_2$.[20] Subsequent vinyl transfer from the alkenylboronic ester provided the product with excellent yield and diastereoselectivity.



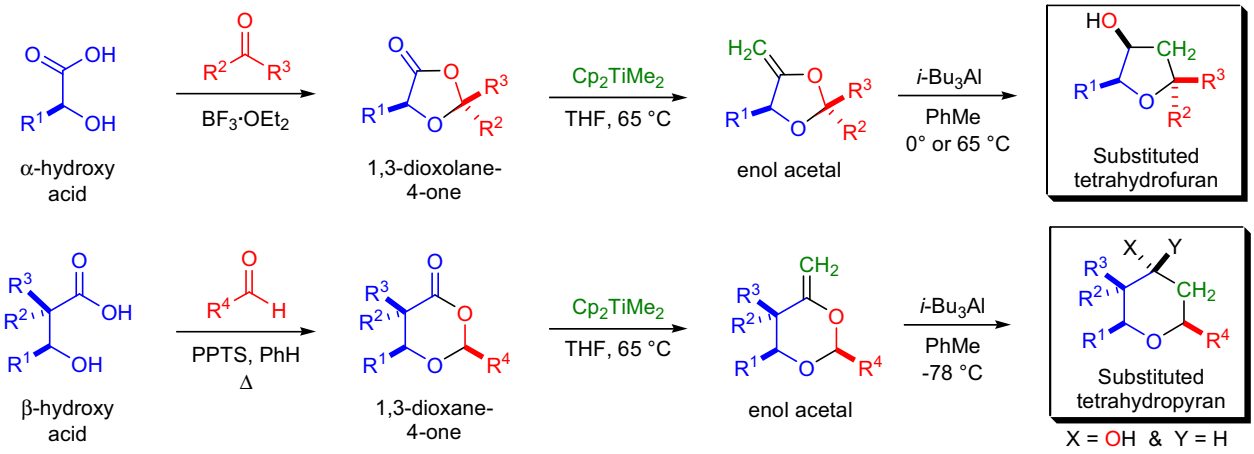
PETASIS-FERRIER REARRANGEMENT

(References are on page 650)

Importance:

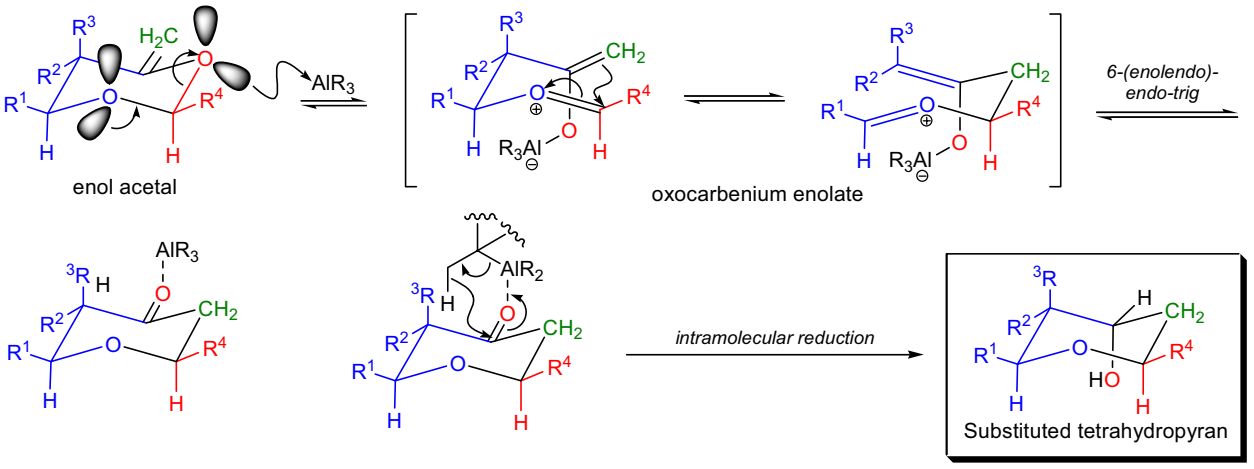
[*Seminal Publications*[1,2]*; Modifications & Improvements*[3,4]]

In 1995, N.A. Petasis reported the Lewis acid-promoted rearrangement of five-membered enol acetals to substituted tetrahydrofurans and in 1996, the similar rearrangement of six-membered enol acetals to the corresponding substituted tetrahydropyrans.[1,2] The rearrangement proceeds *via* an oxocarbenium ion intermediate similar to the one which is involved in a *Type II Ferrier rearrangement*. Therefore, the stereocontrolled Lewis acid-promoted rearrangement of cyclic enol acetals to the corresponding substituted tetrahydrofurans and tetrahydropyrans is called the *Petasis-Ferrier rearrangement*. In laboratory practice, the rearrangement is a three-step procedure: 1) highly stereoselective preparation of 1,3-dioxolane-4-ones and 1,3-dioxane-4-ones from α- and β-hydroxy acids and aldehydes, respectively; 2) methenylation of the carbonyl group with dimethyl titanocene (Cp_2TiMe_2) to afford the enol acetals; and 3) treatment of the enol acetals with an aluminum-based Lewis acid to bring about the transposition of an O-atom with a C-atom on the ring. It was not until 1999 that this rearrangement was modified and utilized for the total synthesis of complex natural products by A.B. Smith and co-workers.[3-7] The general features of the *Petasis-Ferrier rearrangement* are: 1) the straightforward construction of the substrate enol acetals allows the stereocontrolled assembly of complex fragments in a linchpin fashion; 2) the configuration of the acetal carbon is retained or enhanced during the rearrangement; 3) the rearrangement of five-membered enol acetals takes place at a much higher temperature than for the six-membered substrates; 4) trialkylaluminums were found to be the most effective reagents to mediate the rearrangement (*i*-Bu_3Al, Me_3Al, Me_2AlCl being the most common); 5) the stereoselectivity of the aluminum-mediated carbonyl reduction (very last step) depends on the substitution pattern and occurs when *i*-Bu_3Al is used (the reduction does not take place with Me_2AlCl); and 6) a drawback of the procedure is that the olefination step can lead to a mixture of olefin stereoisomers when the applied titanocene is other than dimethyl titanocene.



Mechanism: [1,2]

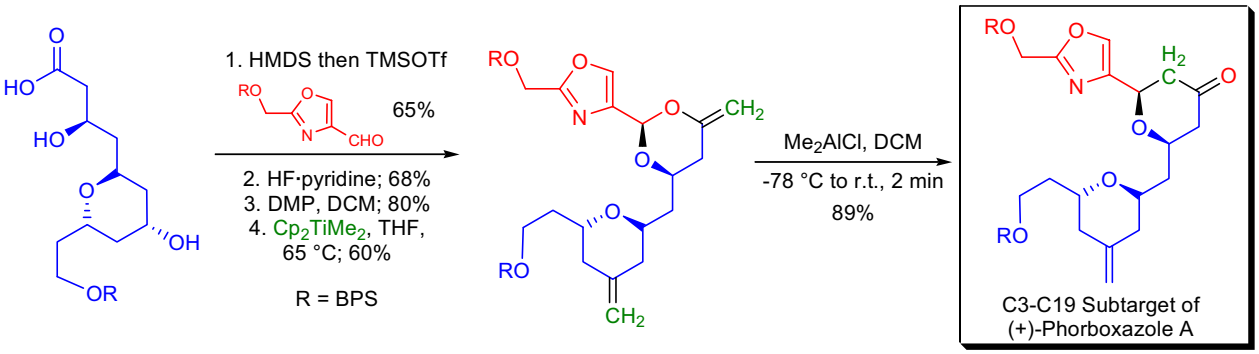
The aluminum-mediated *Petasis-Ferrier rearrangement* is a stepwise *[1,3]-sigmatropic process*. The first step is the coordination of the Lewis-acid to the O-atom of the enol. Coordination to the ether O-atom is reversible and non-productive. Cleavage of the adjacent C-O-bond, assisted by the antiperiplanar lone pair of the etheral O-atom, stereospecifically gives rise to an oxocarbenium enolate species, which cyclizes to the desired oxacycle. The rate difference in the rearrangement for the five- *versus* six-membered series can be explained by the more facile *6-(enolendo)-endo-trig* cyclization.[8,9] The last step is the intramolecular equatorial hydride delivery.



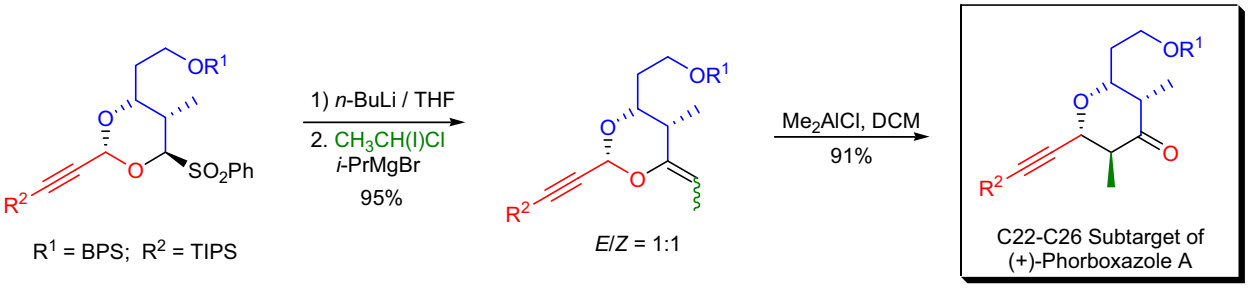
PETASIS-FERRIER REARRANGEMENT

Synthetic Applications:

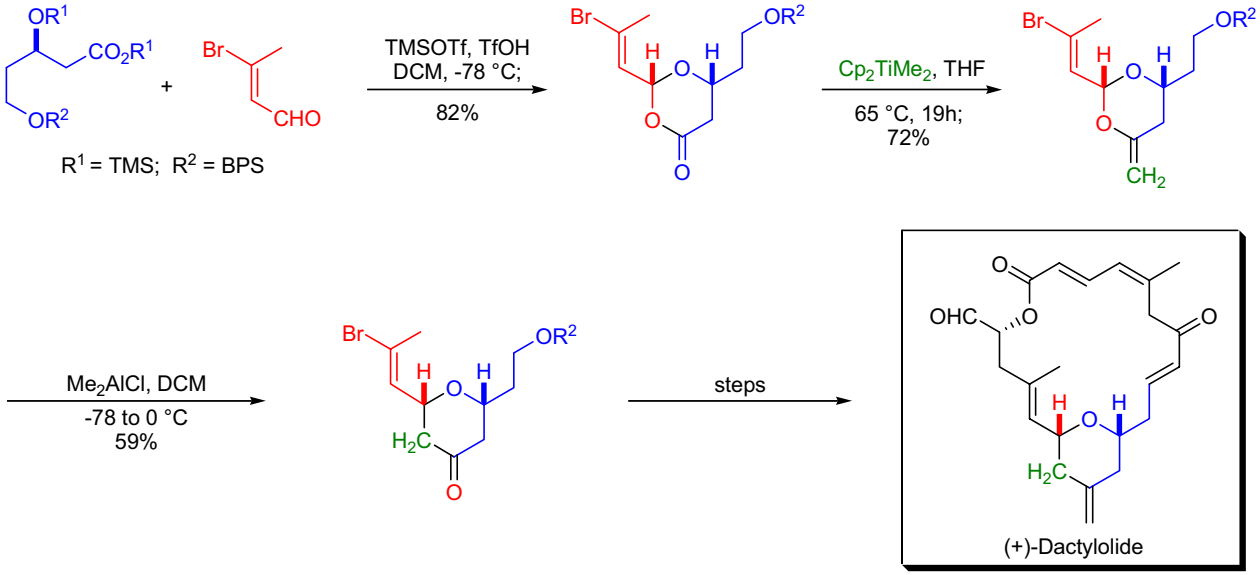
During the total synthesis of (+)-phorboxazole A by A.B. Smith and co-workers, the *modified Petasis-Ferrier rearrangement* was successfully employed for the preparation of the C11-C15 and C22-C26 *cis*-tetrahydropyran rings.[5] The rearrangement using the conditions prescribed by Petasis (with *i*-Bu_3Al) failed to produce the desired 2,6-*cis*-tetrahydropyran, so Me_2AlCl was investigated. Treatment of the substrate with Me_2AlCl at ambient temperature provided the C3-C19 subtarget of phorboxazole as a single isomer in 89% yield.



Similarly, the C22-C26 fully substituted central tetrahydropyran ring of phorboxazole was prepared using the *modified Petasis-Ferrier rearrangement*.[5] Based on the known mechanistic model, the enol acetal moiety of the rearrangement substrate required the (*Z*)-configuration. The synthesis of this enol ether was not possible with either the *Takai*- or *Petasis-Tebbe olefinations*. Utilization of the *Type-II Julia olefination* afforded the desired enol acetal, but with no *E*/*Z* selectivity. Upon treatment of these enol ethers with Me_2AlCl, the rearrangement afforded only the desired tetrahydropyran in excellent yield.



The first total synthesis of (+)-zampanolide and (+)-dactylolide was achieved in the laboratory of A.B. Smith.[6,7] The key step of these syntheses was the application of the *modified Petasis-Ferrier rearrangement* to construct the central *cis*-2,6-disubstituted tetrahydropyran moiety in a stereocontrolled fashion. The treatment of the enol acetal with 1 equivalent of Me_2AlCl at -78 °C effected the rearrangement to furnish the desired *cis*-tetrahydropyranone in 59% yield.



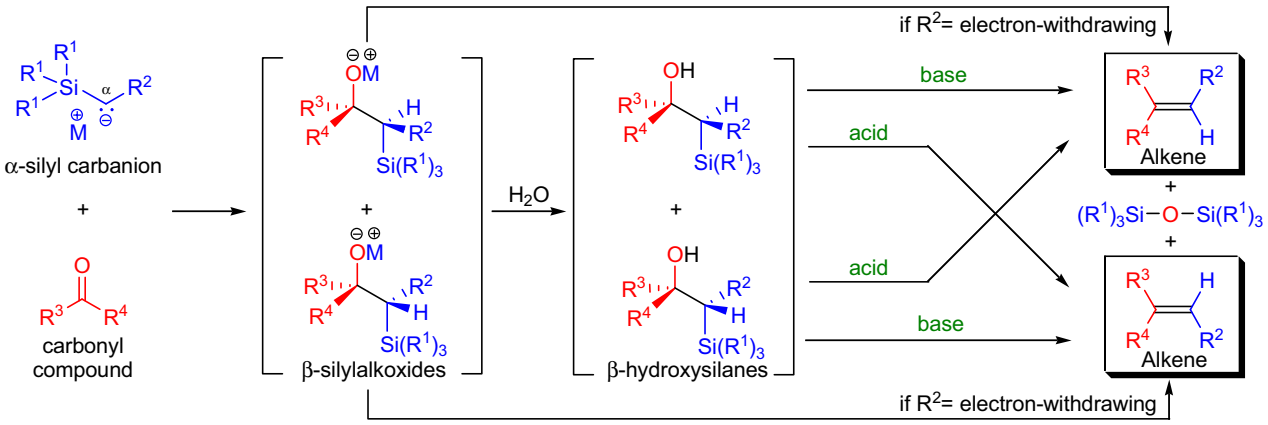
PETERSON OLEFINATION

(References are on page 650)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-23]; *Modifications & Improvements*[24-30]; *Theoretical Studies*[31-34]]

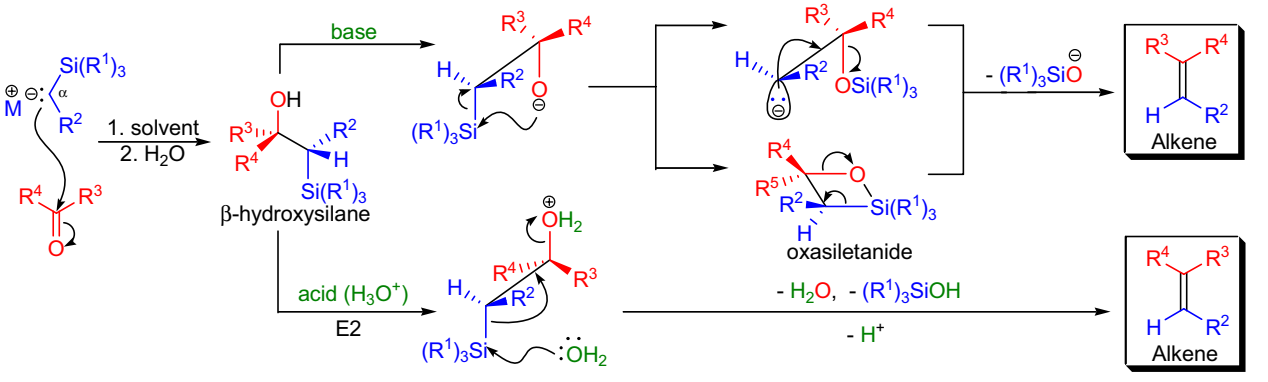
In 1968, D.J. Peterson demonstrated in a detailed study that α-trimethylsilyl-substituted organometallic compounds could be used to convert carbonyl compounds *via* β-silylcarbinols to the corresponding olefins.[3] Similar transformations prior to Peterson's publication were reported but the scope of the reaction was not investigated.[1,2] The preparation of alkenes from α-silyl carbanions and carbonyl compounds is known as the *Peterson olefination* and it is considered to be the silicon-variant of the *Wittig-type reactions*. The general features of the reaction are: 1) the α-silyl carbanions are prepared in a variety of ways, including metal-halogen exchange of the α-halogenated alkylsilanes or the direct deprotonation of alkylsilanes at the α-position; 2) the addition of the α-silyl carbanions to carbonyl compounds gives rise to a mixture of diastereomeric β-silylcarbinols, which can be isolated and separated only if the R^2 substituent in the α-silyl carbanion is not electron-withdrawing; 3) when the R^2 substituent is an electron-donating group (e.g., alkyl) the intermediate β-silylcarbinols can be isolated and the diastereomers can be separated by means of chromatography; 4) upon treatment with base (NaH, KH, KO*t*-Bu), the β-silylcarbinols undergo a stereospecific *syn*-elimination, while treatment with dilute acid or a Lewis acid (AcOH, H_2SO_4, $BF_3{\cdot}OEt_2$) results in a stereospecific *anti*-elimination; and 5) either the (E) or (Z)-alkene can be obtained from a diastereomerically pure β-silylcarbinol by choosing acidic or basic conditions, so the stereoselectivity of the reaction depends on the availability of the diastereomerically pure β-silylcarbinol. Since the preparation of a specific α-silyl carbanion is not always possible, a variety of methods were developed to access α-silylcarbinols in a diastereomerically pure form: 1) the stereoselective addition of nucleophiles to α-silyl ketones, aldehydes, and esters;[35,36] 2) ring-opening of α,β-epoxysilanes with nucleophiles;[37,38,22] 3) *aldol reaction* of enolates derived from α-silyl ketones with aldehydes and ketones;[39] and 4) *stereoselective dihydroxylation* of vinylsilanes.[40,17] Related reactions in which the silicon group (SiR_3) has been replaced with groups containing other elements (SbR_2, AsR_2, SnR_3, HgR, etc.) also form alkenes, but usually the corresponding α-carbanions are harder to prepare and the elimination requires special and often harsh conditions.[9]



R^1=alkyl, aryl; R^2 = alkyl, aryl, CO_2R, CN, $CONR_2$, CH=NR, SR, SOR, SO_2R, SeR, SiR_3, OR, BO_2R_2; R^3,R^4=alkyl, aryl, H

Mechanism: [41-44,9,45-50,21]

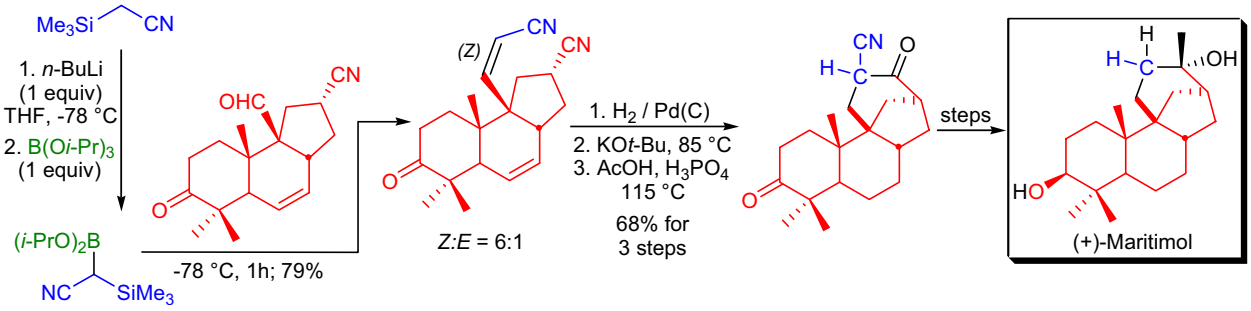
The exact pathway of the *Peterson reaction* is still not clear despite the intensive research effort.[9,21] Most of the mechanistic studies suggest that both the stepwise and concerted pathways are feasible under basic conditions. In the concerted pathway a pentacoordinate 1,2-oxasiletanide is formed. The stepwise pathway is expected when chelation control operates in the reaction. The driving force is the formation of a very strong Si-O bond. Under acidic conditions the β-hydroxysilane undergoes an *E2 elimination* to afford the other alkene isomer.



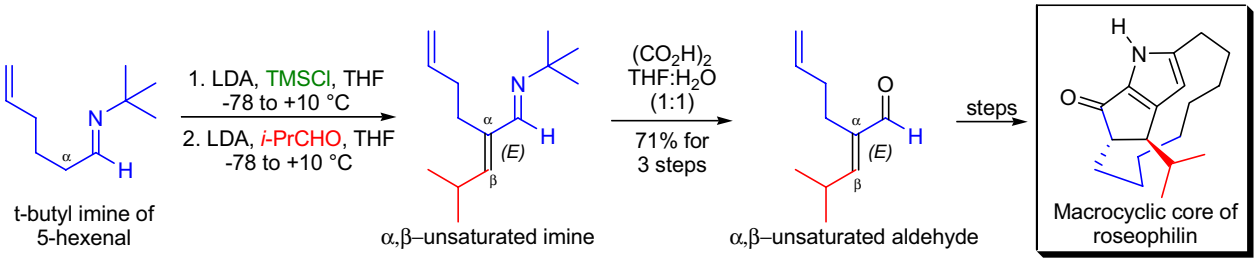
PETERSON OLEFINATION

Synthetic Applications:

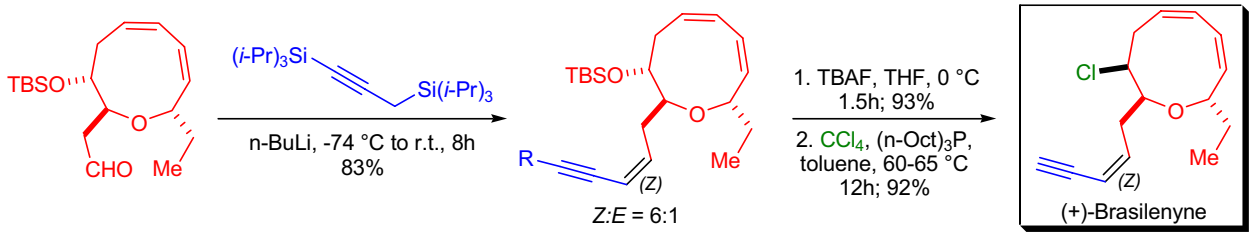
In the laboratory of P. Deslongchamps, the first asymmetric total synthesis of (+)-maritimol, a member of the stemodane diterpenoids, was accomplished using the *Peterson olefination* as the key step.[51] Close to the end of the synthetic sequence, the D ring of the natural product had to be installed via the *Thorpe-Ziegler annulation* of the corresponding 1,5-dinitrile. This dinitrile was prepared using the *Peterson olefination*. The tricyclic aldehyde was treated with the solution of an α-silyl boronate derived from trimethylsilylacetonitrile. The resulting 6:1 mixture of *cis*- and *trans*-enenitriles was reduced to the desired saturated 1,5-dinitrile.



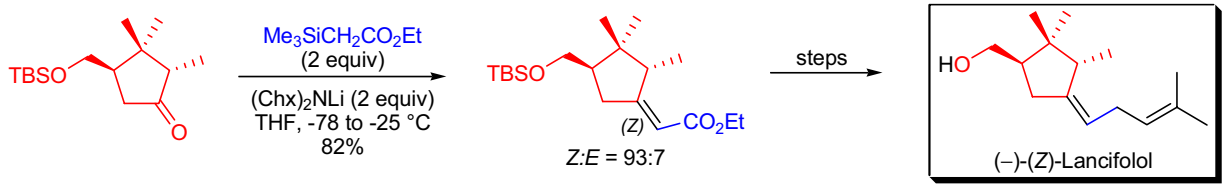
M.A. Tius et al. reported a formal total synthesis of the macrocyclic core of roseophilin.[52] The aliphatic five-membered ring of this core was prepared *via* a variant of the *Nazarov cyclization*. The precursor for this cyclopentannelation reaction is an (*E*)-α,β-unsaturated aldehyde, which was prepared using the *Peterson olefination* on the *t*-butylimine of 5-hexenal. First the α-TMS derivative of the imine was generated; then after a second deprotonation, the additon of isobutyraldehyde gave the (*E*)-α,β-unsaturated imine upon aqueous work-up. Acidic hydrolysis of this imine gave the desired (*E*)-α,β-unsaturated aldehyde in good yield.



In the final stages of the total synthesis of (+)-brasilenyne by S.E. Denmark and co-workers, the introduction of the (*Z*)-enyne side chain was accomplished with the *Peterson olefination*.[53] The aldehyde was treated with lithiated 1,3-*bis*(triisopropylsilyl)propyne at low temperature followed by slow warming of the reaction mixture to ambient temperature to give a 6:1 (*Z:E*) ratio of the desired enyne.



A (Z)-selective *Peterson olefination* was the key step in the first enantioselective total synthesis of both enantiomers of lancifolol in the laboratory of H. Monti.[54] This synthetic approach allowed the correlation of the relationship between absolute configuration and specific rotation. It is important to mention that no other olefination method could be applied successfully in installing this (Z)-alkene moiety.



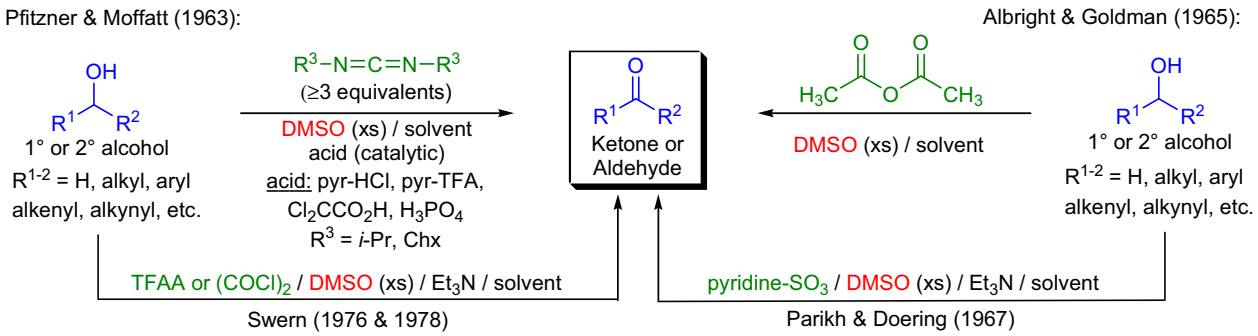
PFITZNER-MOFFATT OXIDATION

(References are on page 652)

Importance:

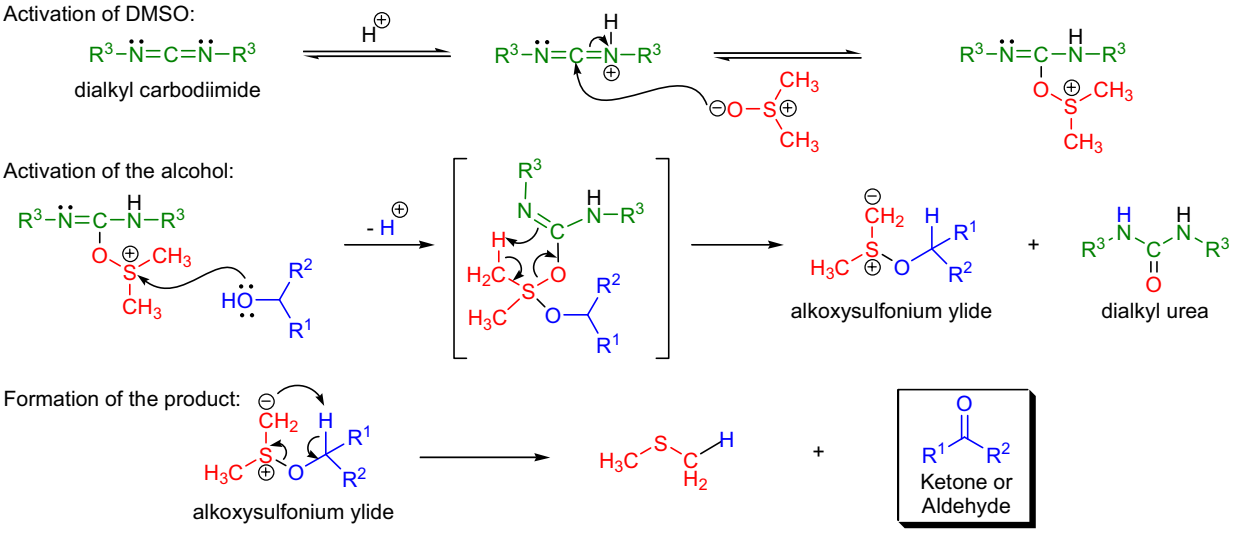
[*Seminal Publications*[1-3]; *Reviews*[4-9]; *Modifications & Improvements*[10-18]]

In 1963, J.G. Moffatt and K.E. Pfitzner observed that primary and secondary alcohols were efficiently oxidized to the corresponding aldehydes and ketones in a solution of dimethyl sulfoxide (DMSO) upon the addition of dicyclohexyl carbodiimide (DCC) and catalytic amounts of anhydrous phosphoric acid (H_3PO_4).[1] This transformation is known as the *Pfitzner-Moffatt oxidation* (*Moffatt oxidation*) and falls into the general category of activated dimethyl sulfoxide mediated oxidations.[8,9] The scope and limitation of the *P-M oxidation* was quickly established, and it was clear that this procedure was a good alternative to chromium(VI)-based oxidations (using PCC and PDC) to oxidize sensitive alcohol substrates under mild and weakly acidic condition.[2,3] The general features of the reactions are: 1) the necessary reagents are all inexpensive and easy to handle, and the execution of the oxidation does not require special equipment; 2) the yield of the product is generally high on both small and large scale; 3) there are only a few side reactions: the occasional formation of methylthiomethyl ether by-products and the isomerization of β,γ-unsaturated carbonyl compounds under the reaction conditions; 4) most functional groups are tolerated, but unprotected tertiary alcohols are often eliminated; 5) DCC is the most widely used activating agent that needs to be applied in excess (usually 3 equivalents or more); 5) the DMSO can serve as the solvent, but inert co-solvents (e.g., EtOAc, benzene) can also be used to make the isolation of the product easier; 6) the oxidation only works with catalysts that are only moderately acidic compounds such as *ortho*-phosphoric acid (H_3PO_4), dichloroacetic acid and the pyridinium salts of strong acids; and 7) in the presence of strong organic and mineral acids, the oxidation is very slow or it does not take place at all. The main drawbacks of the *P-M oxidation* are: 1) the by-product dialkyl urea is often difficult to remove from the product completely, but the use of water soluble or polymer-bound carbodiimides resolves any purification problem;[15] and 2) the excess DCC has to be removed from the product as well, but this issue can be resolved by the addition of oxalic acid during the work-up. Other well-known ways to activate DMSO involve the use of: 1) acetic anhydride (*Albright and Goldman procedure*);[13] 2) pyridine-SO_3 complex (*Parikh-Doering oxidation*);[14] and 3) oxalyl chloride or trifluoroacetic anhydride (*Swern oxidation*).[16,17]



Mechanism:[2,19,20,6,21,8,9]

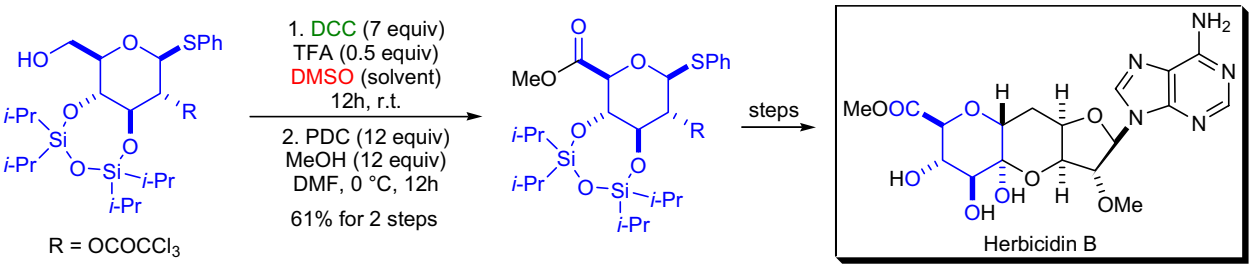
The mechanism of the *P-M oxidation* consists of three distinct steps: 1) activation of the DMSO by a protonated dialkyl carbodiimide; 2) activation of the alcohol substrate and the formation of the key alkoxysulfonium ylide intermediate; and 3) the intramolecular decomposition of the alkoxysulfonium ylide to afford the product ketone or aldehyde and the dialkyl urea by-product (established by isotopic labeling studies). The alkoxysulfonium ylide is a common intermediate in all other oxidations using activated DMSO.



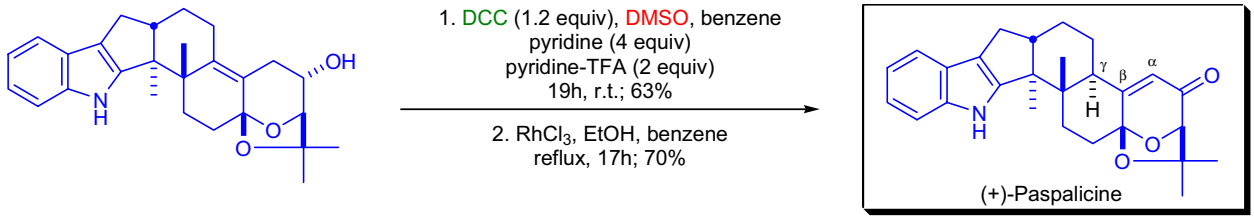
PFITZNER-MOFFATT OXIDATION

Synthetic Applications:

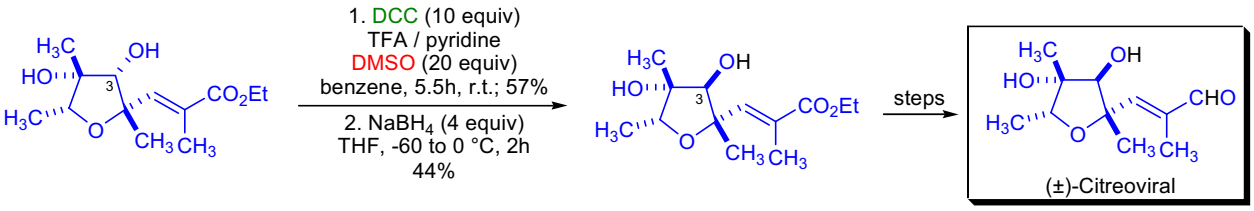
The first total synthesis of the nucleoside antibiotic herbicidin B was accomplished in the laboratory of A. Matsuda.[22] The key step was a novel *aldol-type C-glycosidation reaction* promoted by SmI_2 between a 1-phenylthio-2-ulose derivative and a 1-β-D-xylosyladenine-5'-aldehyde derivative. During the preparation of the phenylthio sugar subunit, the *Moffatt oxidation* was applied to convert the primary alcohol to the corresponding aldehyde, which was immediately oxidized with PDC in DMF/MeOH to the methyl ester. The reaction conditions were completely compatible with the silyl protecting group as well as the thioacetal functionality.



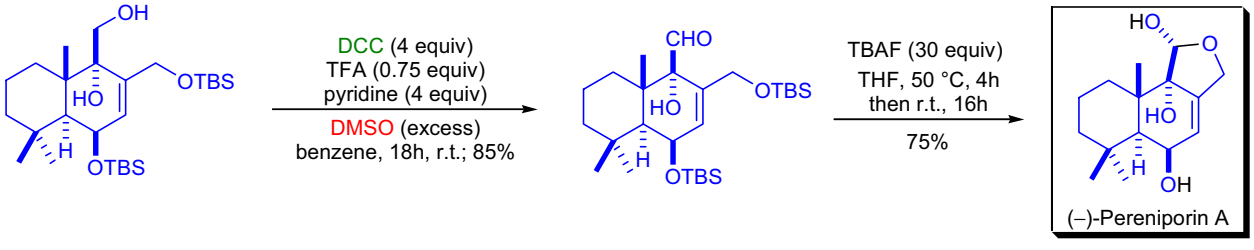
The *Moffatt oxidation* was utilized in the endgame of the total synthesis of (+)-paspalicine by A.B. Smith et al.[23] The advanced intermediate hexacyclic homoallylic alcohol was subjected to the *Moffatt oxidation* conditions using pyridinium trifluoroacetate as the acid catalyst. Under these conditions, the desired β,γ-unsaturated ketone and the rearranged α,β-unsaturated ketone (paspalicine) were formed in a 5:1 ratio. The final step was the *Rh-catalyzed isomerization* of the β,γ-unsaturated ketone to the natural product.



The complex polyene hydroxyl-substituted tetrahydrofuran metabolite (±)-citreoviral was synthesized by G. Pattenden and co-workers.[24] All four carbons on the tetrahydrofuran ring are chiral, and in the final stages of the synthetic effort the stereochemistry of the C3 secondary homoallylic alcohol had to be inverted. This step was best achieved by a *Moffatt oxidation*/$NaBH_4$ reduction sequence.



The total synthesis of the antimicrobial drimane-type sesquiterpene (–)-pereniporin A was achieved by the research team of K. Mori.[25] The advanced intermediate bicyclic primary alcohol was first oxidized to the corresponding aldehyde using the *Moffatt oxidation*. Interestingly, the sensitive α-hydroxy aldehyde moiety in the product remained unchanged. The final step was a global deprotection followed by a spontaneous lactol formation.



PICTET-SPENGLER TETRAHYDROISOQUINOLINE SYNTHESIS

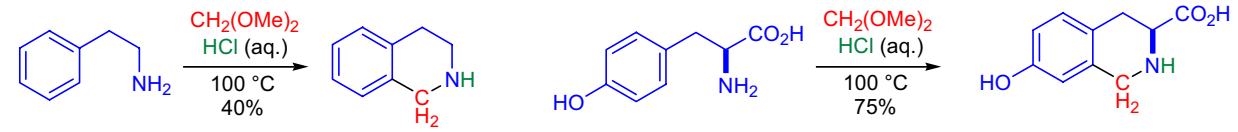
(References are on page 652)

Importance:

[*Seminal Publications*[1]*; Reviews*[2-13]*; Modifications & Improvements*[14-27]*; Theoretical Studies*[28]]

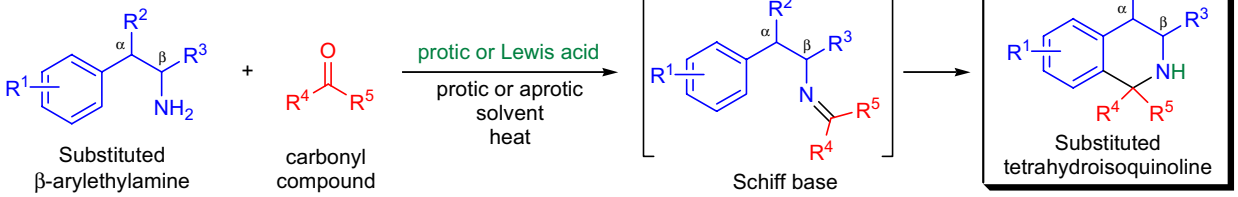
In 1911, A. Pictet and T. Spengler reported the condensation of phenylethylamine and methylal (dimethoxymethane) in concentrated hydrochloric acid to afford 1,2,3,4-tetrahydroisoquinoline in moderate yield.[1] The authors observed a similar transformation when tyrosine and phenylalanine were subjected to identical conditions. The condensation of a β-arylethylamine with a carbonyl compound in the presence of a protic or Lewis acid to give rise to a substituted tetrahydroisoquinoline is known as the *Pictet-Spengler tetrahydroisoquinoline synthesis* (or *Pictet-Spengler reaction*). The general features of the transformation are: 1) only β-arylethylamines with electron-donating substituents afford high yields; 2) the carbonyl compound can be an aldehyde or a ketone or any acid-labile surrogate; 3) the most frequently used aldehyde is formaldehyde or its dimethyl acetal; 4) the number of electron-donating groups on the aromatic ring influences the ease of the reaction, and, for example, the presence of two alkoxy groups allows the *Pictet-Spengler reaction* to proceed under physiological conditions (this is important in the biosynthesis of alkaloids); 5) the reaction is usually carried out with a slight excess of the carbonyl compound (to ensure the complete consumption of the amine) in either protic or aprotic medium; and 6) since the reaction goes through the intermediacy of a Schiff base, the Schiff base can be prepared separately and subjected to a protic or Lewis acid to afford the cyclized tetrahydroisoquinoline product.

Pictet & Spengler (1911):



phenylethylamine — 1,2,3,4-tetrahydro-isoquinoline — tyrosine — 7-hydroxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid

Pictet-Spengler reaction:

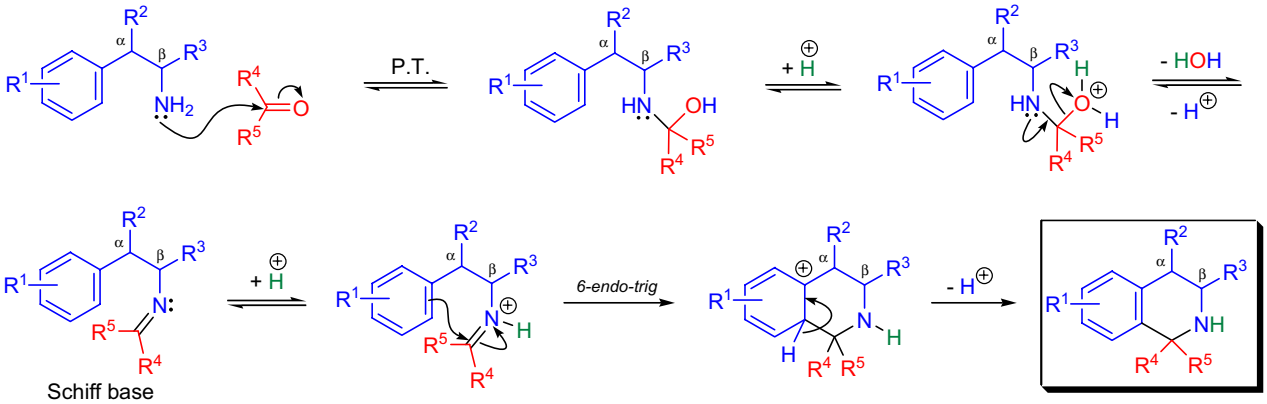


Substituted β-arylethylamine + carbonyl compound → Schiff base → Substituted tetrahydroisoquinoline

R^1 = H, alkyl , aryl, *O*-alkyl, usually an electron-donating group (EDG); R^{2-3} = H, alkyl ,aryl; R^{4-5} = H, alkyl ,aryl; protic acid: HCl, H_2SO_4, TFA, silica gel; Lewis acid: $BF_3{\cdot}OEt_2$

Mechanism:[2,9]

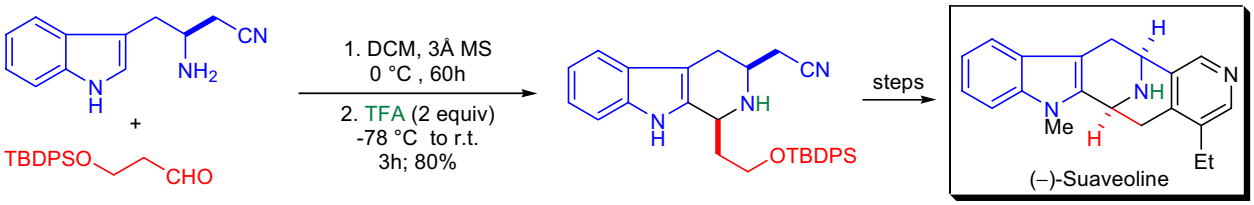
The first step of the *Pictet-Spengler reaction* is the formation of a Schiff base. The amine and aldehyde give rise to an aminal, which is dehydrated under acidic conditions to afford the corresponding imine. Protonation of the imine results in the formation of an iminium ion, which reacts with the electron-rich aromatic ring in a *6-endo-trig* cyclization to afford the six-membered heterocycle. The same type of reactive intermediate is involved in the *Bischler-Napieralski isoquinoline synthesis*, but that cationic species is more electrophilic and the aromatic ring does not need to be activated to achieve cyclization. The loss of proton restores the aromatic ring, thus giving rise to the product.



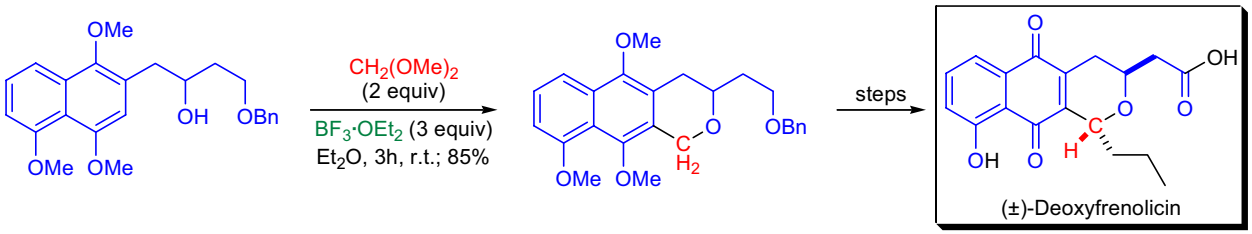
PICTET-SPENGLER TETRAHYDROISOQUINOLINE SYNTHESIS

Synthetic Applications:

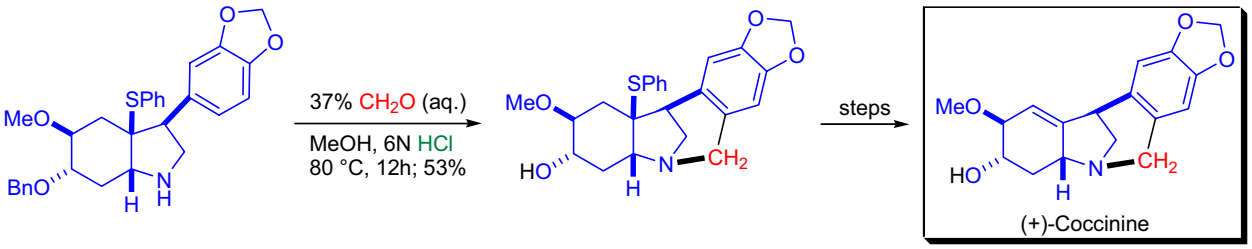
An important variant of the *Pictet-Spengler reaction* occurs when the aromatic substrate is an indole. In the laboratory of P.D. Bailey the enantioselective total synthesis of the indole alkaloid (–)-suaveoline was accomplished. The authors utilized a *cis*-selective *Pictet-Spengler reaction*.[29] The indole substrate was mixed with an aliphatic aldehyde in dichloromethane in the presence of molecular sieves and stirred for more than two days. Once the formation of the Schiff base was complete, TFA was added at low temperature to bring about the cyclization. Interestingly, no *trans* isomer of the carboline was generated and the *cis* isomer was isolated in high yield. Presumably the aromatic rings of the TBDPS protecting group interacted with the indole ring (π-stacking) during the cyclization causing the high observed *cis*-selectivity.



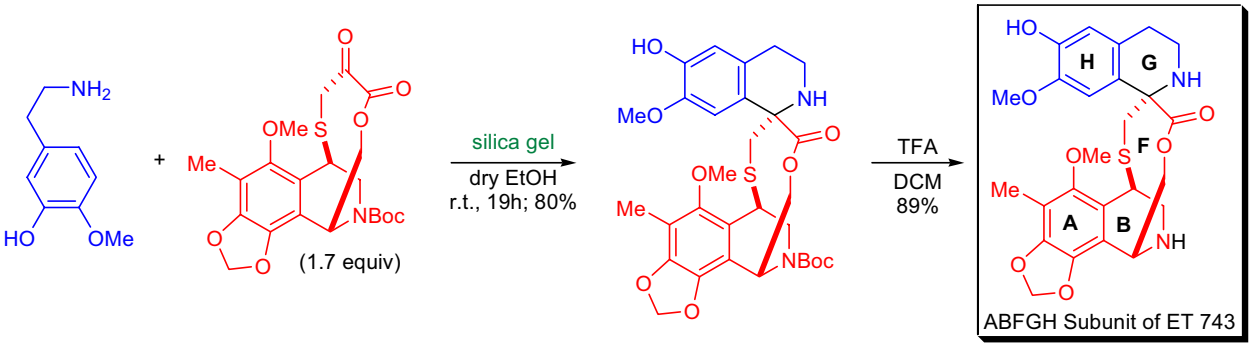
The formal total synthesis of the pyranonaphthoquinone natural product (±)-deoxyfrenolicin was achieved by Y.-C. Xu and co-workers.[30] The naphthopyran intermediate was prepared *via* the *oxa-Pictet-Spengler reaction* between a substituted naphthalene and dimethoxymethane in the presence of $BF_3{\cdot}OEt_2$. The natural product has a 1,3-*trans* relationship between the two substituents of the pyran ring, and surprisingly the use of an aliphatic aldehyde only gave rise to the 1,3-*cis* naphthopyran product. For this reason, the stereoselective introduction of the three carbon side chain was accomplished by a *DDQ-induced oxidative carbon-carbon bond formation* using allyltriphenyltin as the source of the allyl group.



One of the key steps during the enantioselective total synthesis of the montanine-type alkaloid (+)-coccinine by W.H. Pearson et al. was the *Pictet-Spengler reaction* of a highly substituted perhydroindole intermediate.[31] The substrate was exposed to the aqueous solution of formaldehyde in methanol in the presence of 6N hydrochloric acid. The cyclization took place overnight at reflux temperature to afford the pentacyclic product in moderate yield. It is worth noting that under the cyclization conditions the benzyl protecting group was removed.



The research group of S.J. Danishefsky investigated model systems in an effort directed toward the total synthesis of ET 743 and its analogues.[32] The stereoselective formation of the spiro stereocenter of the ABFGH subunit of ET 743 was installed *via* a *Pictet-Spengler reaction*. The electron-rich phenylethylamine was mixed with a slight excess of the ketone substrate and the cyclization took place at room temperature in the presence of silica gel.



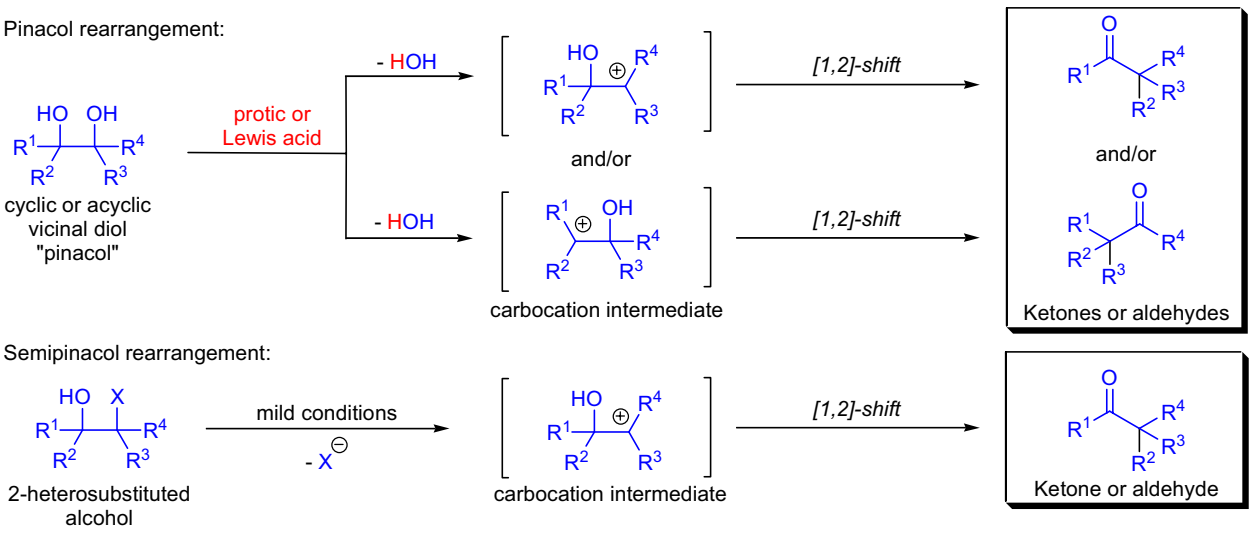
PINACOL AND SEMIPINACOL REARRANGEMENT

(References are on page 653)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-15]; *Modifications & Improvements*[16-32]; *Theoretical Studies*[33-38]]

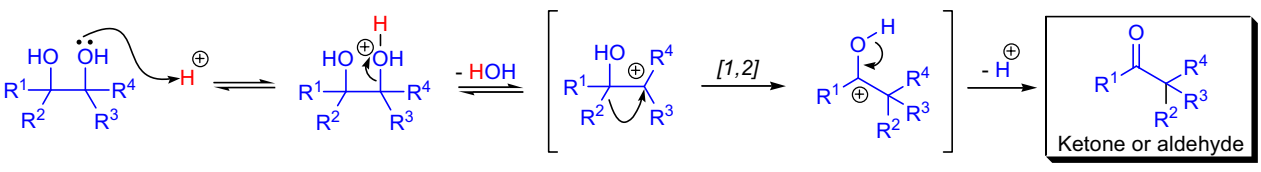
In 1860, R. Fittig reported that treatment of pinacol (2,3-dimethylbutane-2,3-diol) with sulfuric acid gave pinacolone (3,3-dimethylbutane-2-one).[1,39] The reaction was shown to be general for acyclic and cyclic vicinal diols (also known as glycols or 1,2-diols), which, upon treatment with catalytic amounts of acid, undergo dehydration with concomitant *[1,2]*-alkyl,- aryl- or hydride shift to afford ketones or aldehydes. This acid-catalyzed transformation of vicinal diols is known as the *pinacol rearrangement*. The general features of the reaction are: 1) virtually any cyclic or acyclic vicinal glycol can undergo the rearrangement, and, depending on the substitution pattern, aldehydes and/or ketones are formed; 2) when all four substituents are identical, the rearrangement yields a single product; 3) when the four substituents are not identical, product mixtures are formed; 4) the product is usually formed *via* the most stable carbocation intermediate when the glycol substrate is unsymmetrical; 5) the reaction can be highly regioselective and the regioselectivity is determined by the relative migratory aptitudes of the substituents attached to the carbon adjacent the carbocation center; 6) the substituent that is able to stabilize a positive charge better (better electron donor) tends to migrate preferentially; 7) the relative migratory aptitudes are: aryl ~ H ~ vinyl (alkenyl) > *t*-Bu >> cyclopropyl > 2° alkyl > 1° alkyl; 8) the *pinacol rearrangement* can also be stereoselective especially when complex cyclic vicinal diols are involved; 9) cyclic systems may rearrange *via* both ring-expansion and ring-contraction and the course of the rearrangement is strongly influenced by the ring size; 10) most often a cold aqueous solution of sulfuric acid (25% H_2SO_4) is used to effect the rearrangement; however, other acids such as perchloric acid and phosphoric acid have also been utilized;[10] and 11) besides protic acids, Lewis acids (e.g., $BF_3{\cdot}OEt_2$, TMSOTf) are also used. The drawbacks of the *pinacol rearrangement* are: 1) it is generally not easy to prepare complex vicinal diols; 2) in the case of unsymmetrical substrates, the regioselective formation of only one carbocation is usually not trivial, so product mixtures are obtained; 3) side reactions such as β-eliminations yielding dienes and allylic alcohols are often observed; 4) the intermediate carbocations may undergo equilibration; and 5) various conformational effects and neighboring group participation in cyclic systems are complicating factors. When one of the hydroxyl groups is converted to a good leaving group, the regioselective generation of the carbocation intermediate is possible. Similarly selective generation of carbocations can be realized when 2-heterosubstituted alcohols (e.g., halohydrins, 2-amino alcohols, 2-hydroxy sulfides, etc.) are used as substrates. The *pinacol-type rearrangement* of these compounds is referred to as the *semipinacol rearrangement*, a term first coined by M. Tiffeneau.[2] Owing to its predictability and the mild reaction conditions, the s*emipinacol rearrangement* is almost exclusively utilized in complex molecule synthesis.



$R^{1\text{-}4}$ = H, alkyl, aryl, acyl; X = Cl, Br, I, SR, OTs, OMs, N_2^+ (*Tiffeneau-Demjanov rearrangement*); protic acid: H_2SO_4, $HClO_4$, H_3PO_4, TFA, TsOH; Lewis acid: $BF_3{\cdot}OEt_2$, TMSOTf; mild conditions: $LiClO_4$/THF/$CaCO_3$, Et_3Al/DCM, Et_2AlCl/DCM, etc.

Mechanism:[40-54]

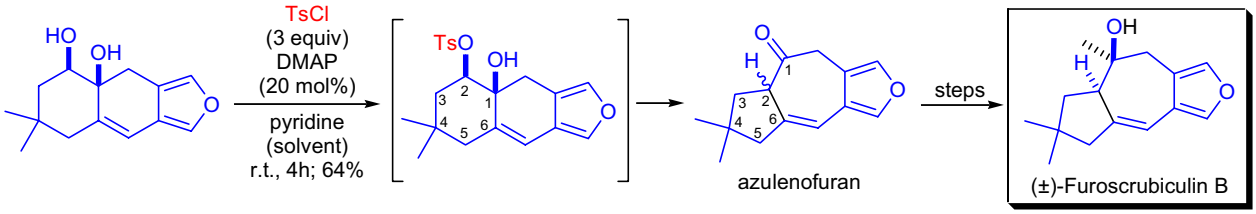
The first step of the process is the protonation of one of the hydroxyl groups, which results in the loss of a water molecule to give a carbocation intermediate. This intermediate undergoes a *[1,2]*-shift to give a more stable carbocation that upon the loss of proton gives the product. The pinacol rearrangement was shown to be exclusively intramolecular, and both inversion and retention were observed at the migrating center.



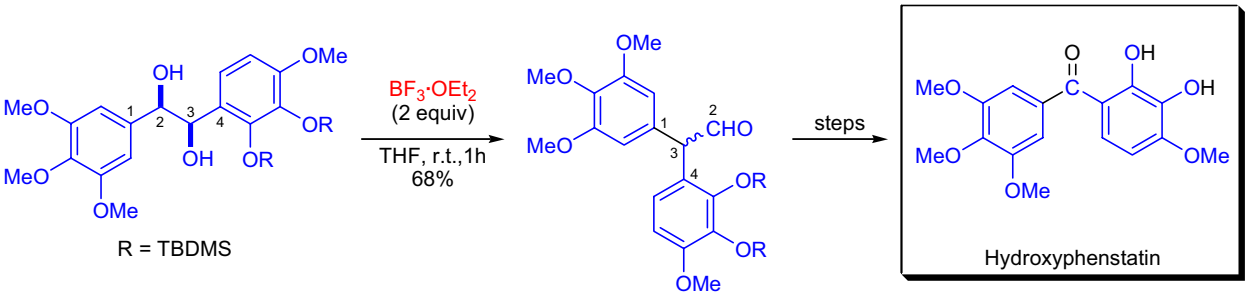
PINACOL AND SEMIPINACOL REARRANGEMENT

Synthetic Applications:

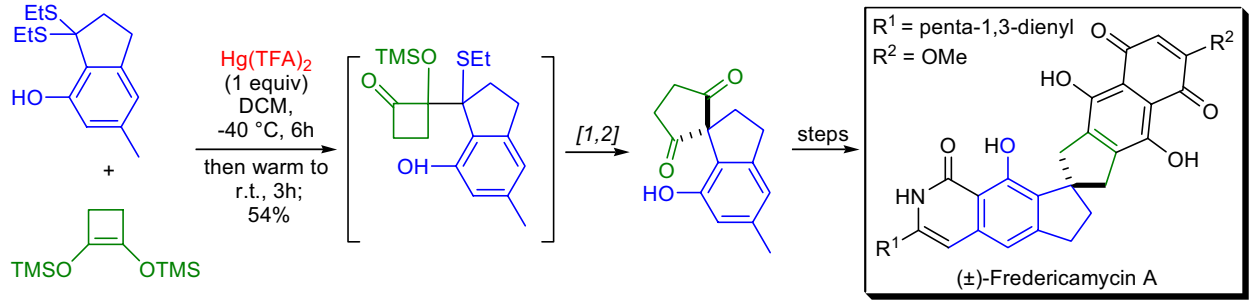
The total synthesis of (±)-furoscrobiculin B, a lactarane sesquiterpene isolated from basidiomycetes of mushrooms, was accomplished in the laboratory of H. Suemune and K. Kanematsu using a *furan ring transfer reaction* and a *semipinacol rearrangement* as key steps.[55] The secondary hydroxyl group of the tricyclic *cis*-vicinal diol substrate was converted to the corresponding tosylate that *in situ* underwent a ring-expansion reaction to afford an azulenofuran in good yield.



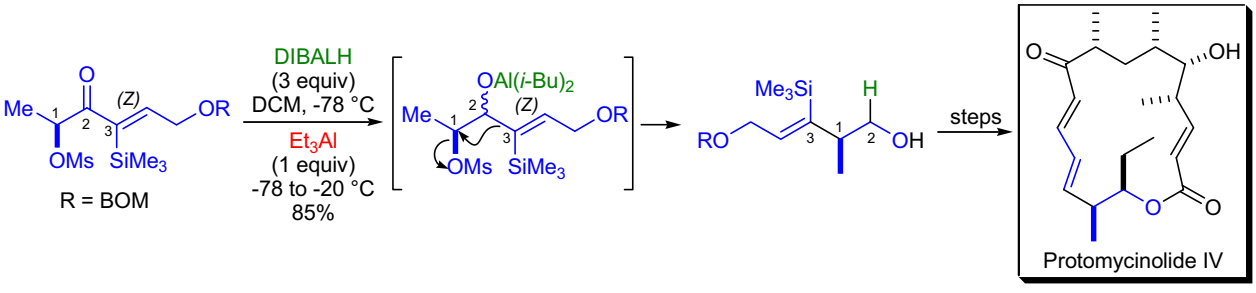
G.R. Pettit and co-workers converted a highly substituted *trans*-stilbene derivative to the strong cancer cell growth inhibitor and antimitotic agent hydroxyphenstatin.[56] The key step of the synthesis was a $BF_3{\cdot}OEt_2$-catalyzed *pinacol rearrangement* of an optically active vicinal diol to afford a substituted diphenylacetaldehyde in racemic form. From this key intermediate, several derivatives were prepared in addition to the target molecule.



During the total synthesis of (±)-fredericamycin A, the spiro 1,3-dione center was introduced by R.D. Bach et al. utilizing a mild *mercury-mediated semipinacol rearrangement* that involved a *[1,2]*-acyl shift.[57] The indanone dithioacetal was reacted with 1,2-*bis*[(trimethylsilyl)oxy]cyclobut-1-ene in the presence of mercuric trifluoroacetate and the rearrangement took place *in situ*.



The stereocontrolled asymmetric total synthesis of protomycinolide IV was achieved, based on the *organoaluminum-promoted stereospecific semipinacol rearrangement*, by K. Suzuki and co-workers.[58] The excess DIBALH reduced the C2 carbonyl group to the corresponding aluminum alkoxide, which was immediately treated with one equivalent of Et_3Al to bring about the *[1,2]*-alkenyl shift. The initially formed aldehyde was reduced by the excess reducing agent to afford the primary alcohol upon work-up. There was no E/Z isomerization of the alkenyl group.



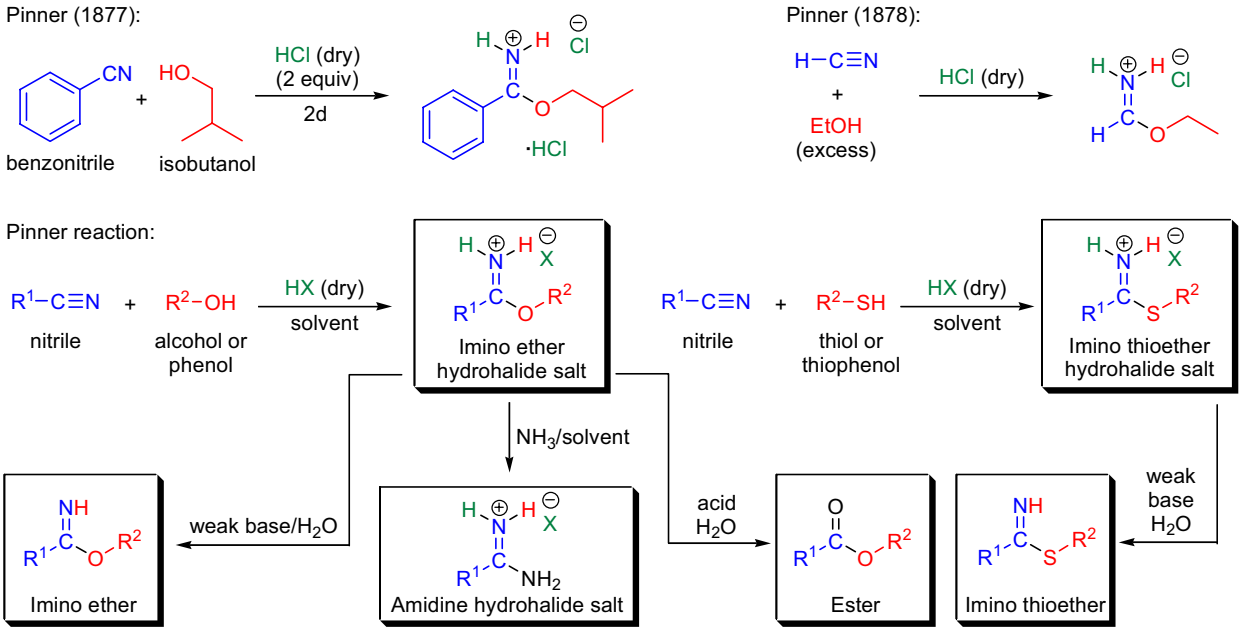
PINNER REACTION

(References are on page 654)

Importance:

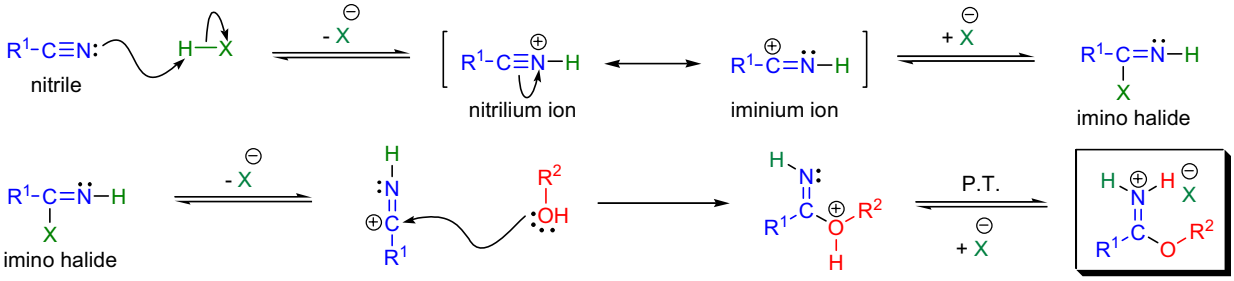
[*Seminal Publications*[1-3]; *Reviews*[4-8]; *Modifications & Improvements*[9-15]]

In 1877, A. Pinner and Fr. Klein reported that when dry hydrogen chloride gas was bubbled through the mixture of benzonitrile and isobutanol, a crystalline compound was formed that was characterized as the addition product of all three reactants.[1] A year later in 1878, a similar addition product was isolated by reacting hydrogen cyanide with absolute ethanol and HCl.[2] The condensation of nitriles with alcohols and phenols in the presence of anhydrous hydrogen chloride or hydrogen bromide to afford imino ethers (also referred to as imidates or imino esters) is known as the *Pinner reaction* (or *Pinner synthesis*). The general features of this transformation are:[4-8] 1) the reactants are usually dissolved in an anhydrous solvent (e.g., benzene, chloroform, nitrobenzene, dioxane, etc.), and dry hydrogen chloride gas is bubbled through the solution at 0 C°; 2) if the reaction is conducted at higher than 0 C°, the product imino ether salt may decompose to give an amide and an alkyl halide; 3) in some cases the use of solvent tends to lower the yield of the product, so the neat reactants are simply mixed and treated with dry HCl gas; 4) the structure of the nitrile can vary widely so aliphatic, aromatic, and heteroaromatic nitriles are all good substrates; 5) when the nitrile is sterically hindered (e.g., *ortho*-substituted benzonitrile) the *Pinner reaction* may not take place; 6) the alcohol component is usually methanol and ethanol, but many primary and secondary alcohols have been used successfully; 7) monohydric phenols also react, however, dihydric- or polyhydric phenols may undergo the *Houben-Hoesch reaction* to afford aromatic ketones; 8) thiols and thiophenols also react with nitriles in an analogous fashion to form imino thioethers (thioimidates); 9) the initial product is usually the imino ether hydrohalide salt, which can be easily converted to the corresponding free imino ether by treatment with a weak base; 10) imino ethers are generally not very stable compounds, they undergo rapid hydrolysis to form esters when treated with water and acid (this is especially true for imino ethers generated by the reaction of aliphatic nitriles); 11) if the nitrile and alcohol are treated with aqueous hydrochloric acid, the esters are formed directly; 12) upon treatment with excess alcohol, imino ethers are converted to ortho esters (this can be a side reaction during the preparation when excess alcohol is used); and 13) imino ether hydrohalide salts can be transformed into an amidine hydrohalide salt by treatment with ammonia.



R^1 = H, alkyl, aryl; R^2 = Me, Et, 1° and 2° alkyl, aryl; HX = HCl, HBr; solvent: $CHCl_3$, benzne, nitrobenzene, dioxane, (EtOH, MeOH); base: $NaHCO_3$, Na_2CO_3; acid: HCl, H_2SO_4

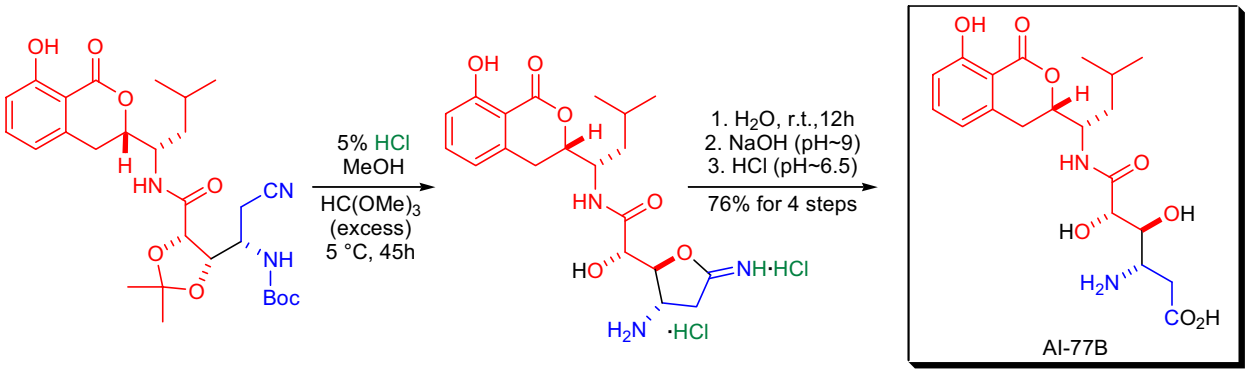
Mechanism:[16,17,6,18]



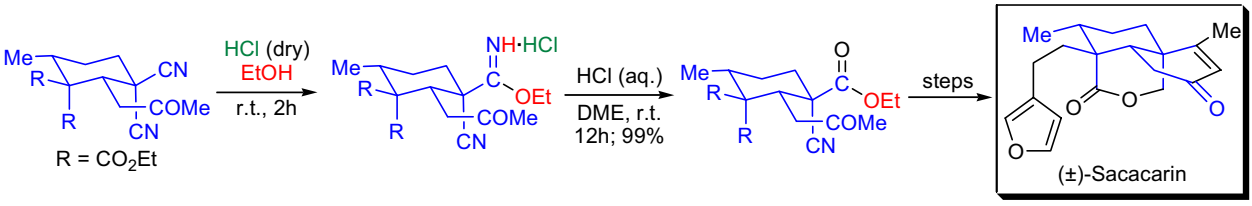
PINNER REACTION

Synthetic Applications:

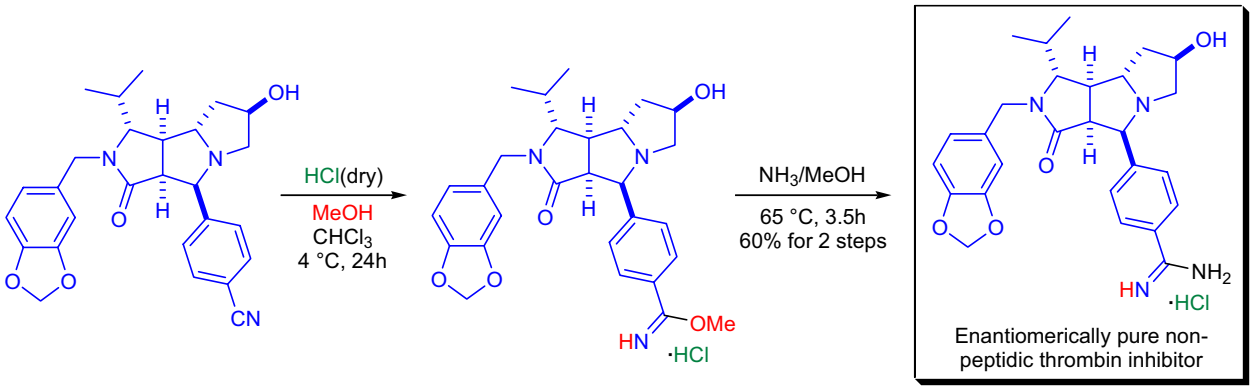
The first stereoselective total synthesis of AI-77B, a gastroprotective substance, was accomplished by Y. Hamada and co-workers.[19] In the final stages of the synthetic effort, the *intramolecular Pinner reaction* was utilized to convert the cyano group into the corresponding carboxylic acid. The nitrile substrate was dissolved in 5% HCl in methanol, and excess trimethyl orthoformate was added at 5 °C and the reaction mixture was stirred at this temperature for almost two days. Next, the cyclic imino ether hydrochloride salt was treated with water at room temperature followed by basic hydrolysis. Finally, the pH was adjusted with HCl to obtain the natural product.



In the laboratory of R.B. Grossman both the putative and the actual structure of the naturally occurring clerodane diterpenoid (±)-sacacarin was prepared.[20] A cyclic geminal dinitrile intermediate was subjected to the conditions of the *Pinner reaction* by passing dry HCl gas through the solution of the substrate in absolute ethanol at room temperature. Under these conditions, only the equatorial cyano group was converted to the imino ethyl ether hydrochloride salt. Most likely the axial cyano group was too sterically hindered, therefore it did not react. The imino ether then was hydrolyzed with concentrated aqueous hydrochloric acid to give the corresponding ethyl ester.



The synthesis of enantiomerically pure nonpeptidic inhibitors of thrombin, a key serine protease in the blood-coagulation cascade, was carried out by F. Diederich et al.[21] These ligands have a conformationally rigid tricyclic core, and the appended substituents fill the major binding pockets at the thrombin active site. The required amidine functionality on the aromatic ring of one of these inhibitors was prepared from the corresponding aromatic nitrile *via* the *Pinner reaction*. The substrate was dissolved in a mixture of dry methanol and chloroform, and dry HCl gas bubbled through the solution for 10 minutes until saturation. The reaction mixture then was stored at 4 °C for one day, and then the imino ether was isolated by filtration. The methanolic solution of ammonia was added to the solution of the imino ether in methanol, and the resulting solution was heated at 65 °C for a few hours to achieve complete conversion to the amidinium salt.



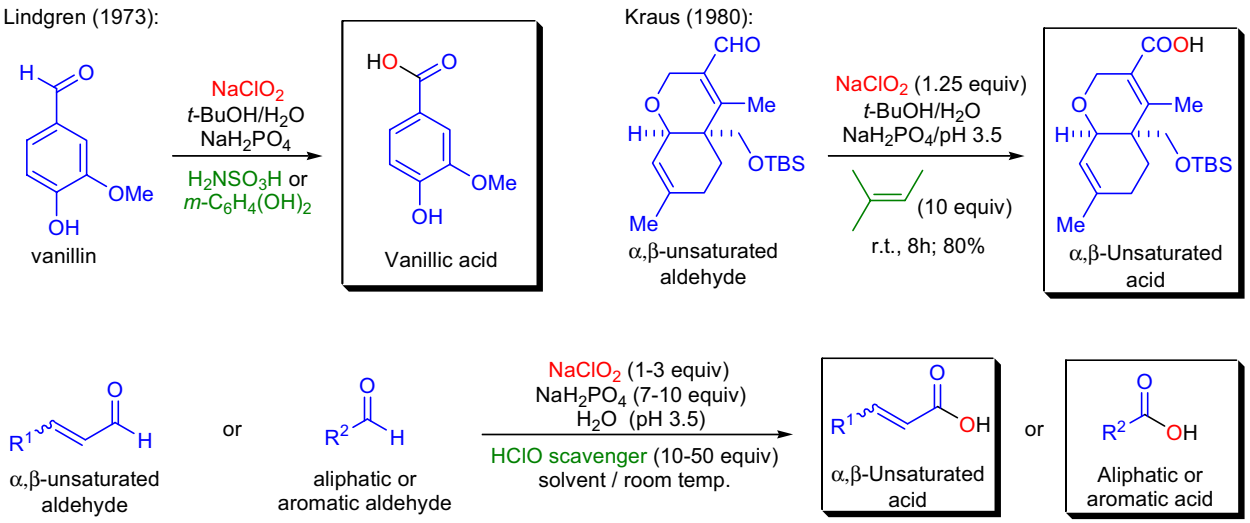
PINNICK OXIDATION

(References are on page 655)

Importance:

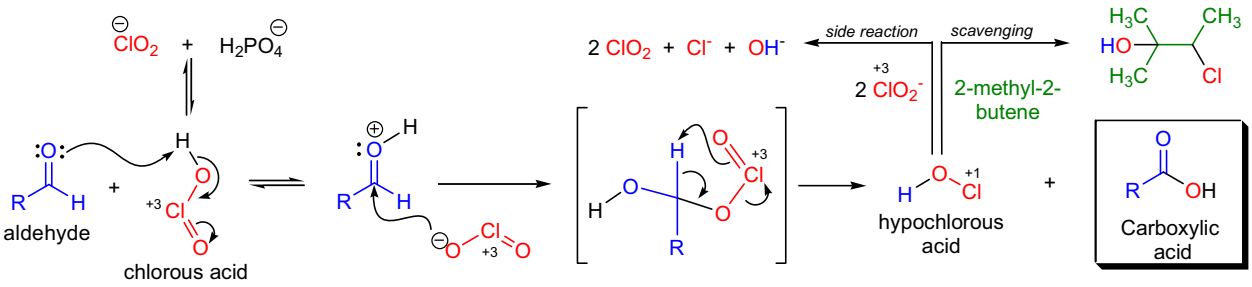
[*Seminal Publications*[1-4]; *Reviews*[5]; *Modifications & Improvements*[6,5,7]]

The oxidation of aldehydes to the corresponding carboxylic acids is a very important transformation in organic synthesis. Until the early 1970s most methods required expensive reagents and complex reaction conditions, the functional group tolerance was limited, and the selectivities were low. In 1973, B.O. Lindgren was the first to apply the inexpensive sodium chlorite ($NaClO_2$) in combination with hypochlorous acid (HClO) and scavengers (e.g., sulfamic acid, resorcinol) to convert vanillin to the corresponding vanillic acid under mild conditions.[1] The HClO is formed as a by-product of the oxidation process, and it can cause side reactions such as consumption of the $NaClO_2$ to form chlorine oxide (ClO_2) or reacting with C=C double bonds. A few years later, G.A. Kraus and co-workers were the first to use 2-methyl-2-butene as a scavenger under buffered conditions for the oxidation of an aliphatic- and an α,β-unsaturated aldehyde.[2,3] In 1981, H.W. Pinnick showed that the $NaClO_2$/2-methyl-2-butene system was generally applicable to the oxidation for a wide range of α,β-unsaturated aldehydes without affecting any of the double bonds present. Today, this transformation of aldehydes (aliphatic, aromatic, saturated, or unsaturated) to the corresponding carboxylic acids is referred to as the *Pinnick oxidation*.[4] The general features of the reaction are: 1) in a typical procedure, the aldehyde is dissolved in *tert*-butanol (often in combination with another solvent such as THF) along with the large excess of the scavenger followed by the dropwise addition of the aqueous solution of sodium dihydrogen phosphate buffer (NaH_2PO_4) and $NaClO_2$ at room temperature; 2) the scavenger is most often 2-methyl-2-butene, which has to be added in large excess (caution: the boiling point is low therefore the container should be cold before opening); 3) to ensure a constant pH value, the use of several equivalents of NaH_2PO_4 is recommended; 4) usually slightly more than one equivalent of $NaClO_2$ is necessary, which should be dissolved in water (by itself or together with the phosphate buffer) only prior to the oxidation, since exposure to light or the presence of impurities (e.g., Fe^{2+} and Fe^{3+} complexes) tend to decompose the reagent;[8] 5) with certain substrates the purity of the reagents is crucial, and the oxidation sometimes stops after a few percent of conversion:[9] a) due to the sensitivity/instability of the $NaClO_2$ in acidic medium in the presence of transition metal complexes the use of a steel needle for the addition of the oxidant should be avoided (use a Pasteur pipette instead); b) neat 2-methyl-2-butene or 2M solution in THF should be used instead of the 90% technical grade reagent; 6) when 2-methyl-2-butene is used as the scavenger, none of the double bonds in the substrate will be chlorinated, but with other scavengers, such as H_2O_2, side reactions involving isolated double bonds do occur; 7) stereocenters at the α-position of aldehydes are unaffected; and 8) functional group tolerance is excellent, and hydroxyl groups do not need to be protected.



R^1 = H, alkyl, aryl, alkenyl, allyl; R^2 = alkyl, aryl, allyl, homoallyl; scavenger = 2-methyl-2-butene, H_2O_2, H_2NSO_3H, *m*-$C_6H_4(OH)_2$, DMSO; solvent = *t*-BuOH, *t*-BuOH/THF

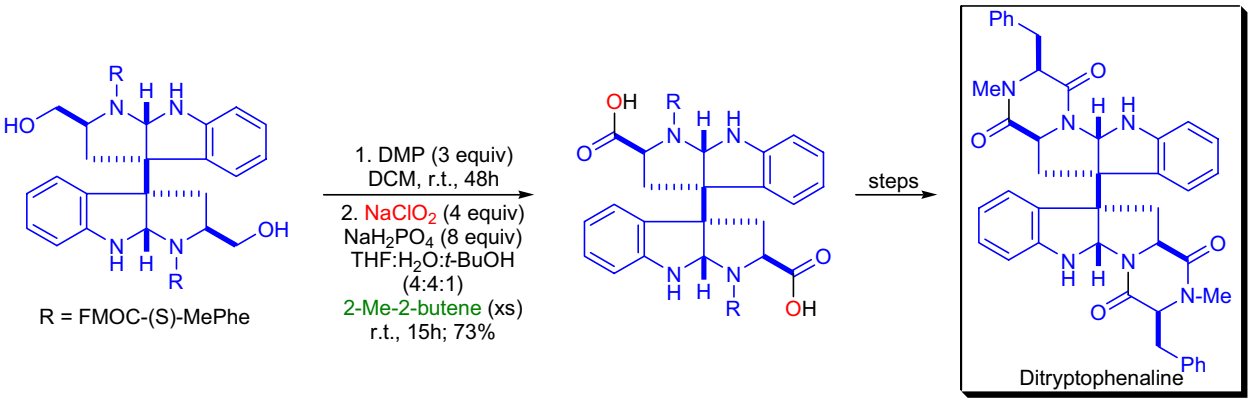
Mechanism:[10,6]



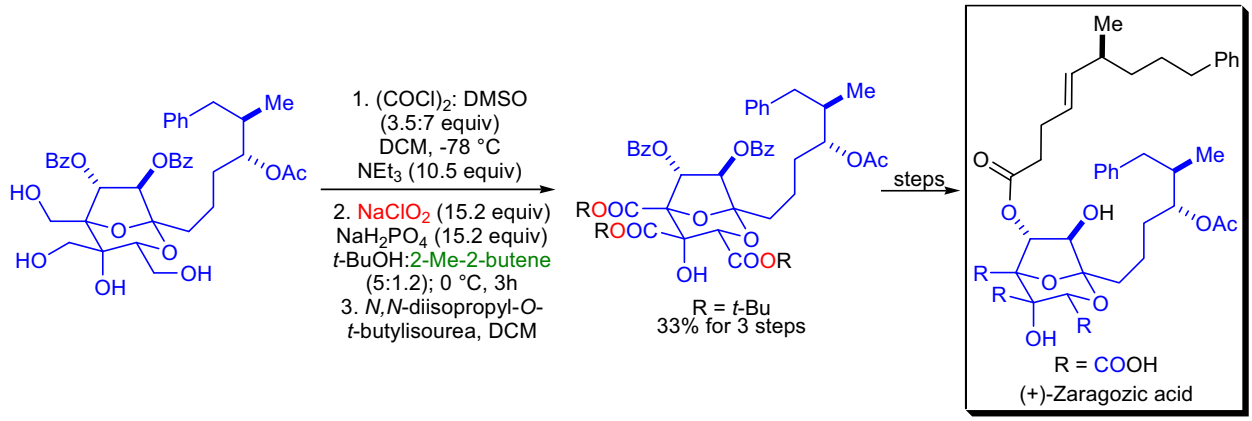
PINNICK OXIDATION

Synthetic Applications:

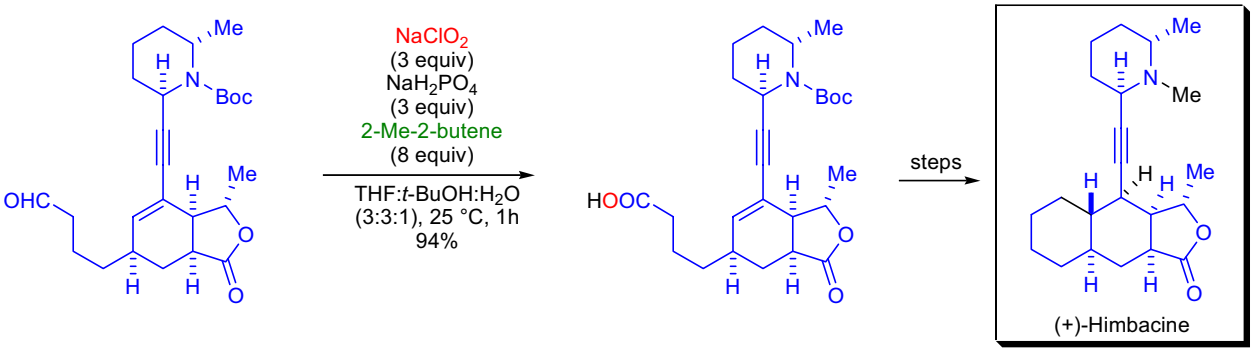
The total synthesis of the complex bioactive indole alkaloid ditryptophenaline, having two contiguous quaternary stereocenters related by C_2 symmetry, was accomplished in the laboratory of L.E Overman.[11] In the late stages of the synthetic effort the complex diol substrate was oxidized to the dicarboxylic acid using a two-step procedure: first, a *Dess-Martin oxidation* to the dialdehyde followed by the *Pinnick oxidation*. The mild reaction condition ensured that the integrity of the stereocenters at the α-positions was preserved.



A novel triple oxidation procedure was applied by A. Armstrong et al. to install the tricarboxylic acid moiety during the total synthesis of (+)-zaragozic acid C.[12] The bicyclic triol substrate was first exposed to the *Swern oxidation* conditions to afford the corresponding trialdehyde. Several different oxidations (e.g., *Jones oxidation*, *modified Ley oxidation*) were tried on the crude trialdehyde to convert it to the triacid, but all of these attempts resulted in a complex mixture of products. A clean and high-yielding solution to this problem was to use the *Pinnick oxidation* that gave rise to the desired triacid. Esterification to the tri-*tert*-butyl ester was conducted by using *N,N*-diisopropyl-*O*-*tert*-butylisourea in dichloromethane.



The formal total synthesis of the selective muscarinic receptor antagonist (+)-himbacine was accomplished by M.S. Sherburn and co-workers using an *intramolecular Diels-Alder reaction*, a *Stille cross-coupling*, and a *6-exo-trig acyl radical cyclization* as the key steps.[13] In order to prepare the selenoate ester precursor for the radical cyclization step, the aldehyde-enyne substrate was converted to the carboxylic acid *via* the *Pinnick oxidation* without affecting the delicate enyne moiety.



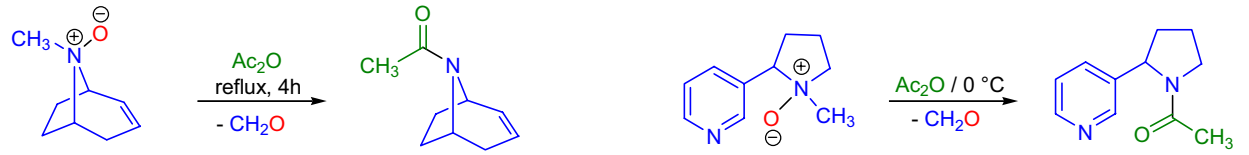
POLONOVSKI REACTION

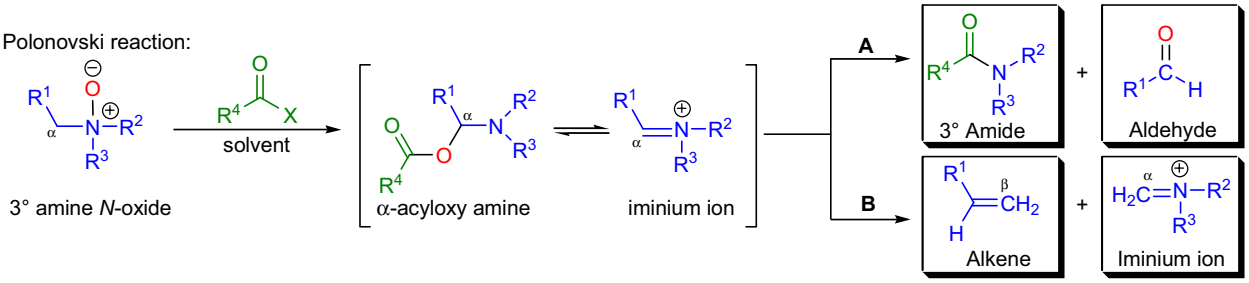
(References are on page 655)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-9]*; Modifications & Improvements*[10-16]]

In 1927, the Polonovski brothers reported that certain alkaloid *N*-oxides, upon treatment with acetic anhydride or acetyl chloride, underwent a rearrangement in which one of the alkyl groups attached to the nitrogen was cleaved and the *N*-acetyl derivative of the alkaloid was obtained.[1] For several decades, the procedure was used, almost exclusively, for the *N*-demethylation of tertiary amines because it took place under much milder conditions than other methods available at the time. The activation of tertiary amine *N*-oxides with acyl halides or anhydrides to form the corresponding iminium ion intermediates is known as the *Polonovski reaction*. The general features of the reaction are: 1) the *N*-oxide substrates are usually prepared from the corresponding tertiary amines by oxidation; 2) the activation of *N*-oxides is effected by acyl halides or anhydrides, but in the majority of the cases acetic anhydride (Ac_2O) is used; 3) when trifluoroacetic anhydride (TFAA) is used, the reaction proceeds under mild reaction conditions (*Polonovski-Potier reaction*) and the reaction can be stopped at the iminium ion stage;[10,6] 4) besides anhydrides, various iron salts and sulfur dioxide can be used as activating agents;[11,12] 5) when formic-acetic or formic-pivalic anhydride is employed as the acylating agent, the *N*-oxide is simply reduced to the amine;[17,18] 6) the initially formed iminium ions are versatile intermediates (e.g., *Mannich* and *Pictet-Spengler reactions*), which can be converted to other important classes of compounds such as enamines, tertiary amides and/or secondary amines, and aldehydes;[8,9] 7) depending on the nature of the activating agent and the reaction conditions, there are two main reaction pathways available for the iminium ions: **A**) reaction with a nucleophile at the α carbon or **B**) *Grob-type* C_α-C_β cleavage to afford alkenes and new iminium ions (only when it is activated by an adjacent electron-donating center and the C_α-C_β bond is antiperiplanar with the N-O bond);[8,9] 8) when more than one group attached to the nitrogen has a hydrogen at the α position, regioisomeric iminium ions are formed; however, the regioselectivity can be controlled, and the thermodynamically more stable iminium ion is formed with TFAA, while with Ac_2O the kinetically more acidic α position is deprotonated; 9) the acidity of the α C-H bond is increased if R^1=EWG; 10) when the 3° amine *N*-oxide is cyclic, the reaction takes place only for five- and six-membered rings, and the endocyclic iminium ions are formed in preference to exocyclic ones; and 11) when the iminium ion is too reactive, the corresponding α-cyanoamines (iminium ion equivalents) can be prepared in high yield.[13,16]

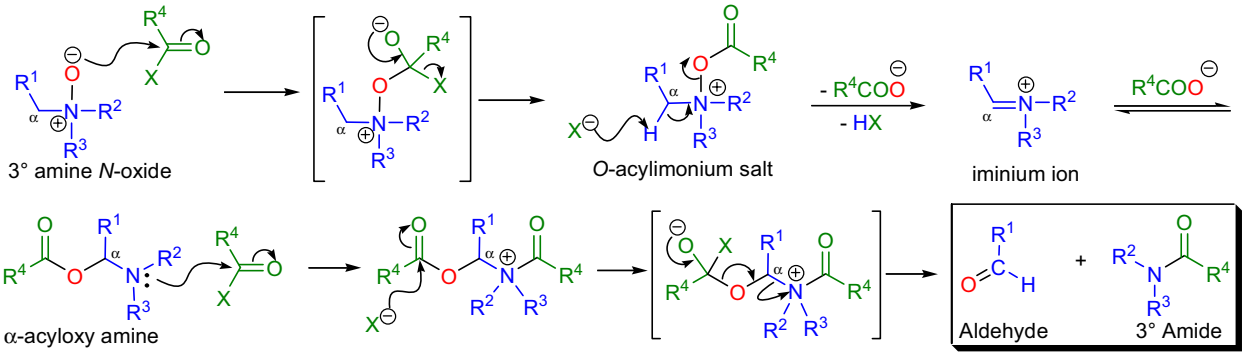




R^1 = H, alkyl, aryl, heteroaryl; $R^{2\text{-}3}$ = CH_3, alkyl, aryl; R^4 = CH_3, CF_3 (*Polonovski-Potier rxn*); X = Cl, Br, $OCOR^4$, BF_4^-, ClO_4^-, SbF_6^-

Mechanism:[19-22,8,9,23,24]

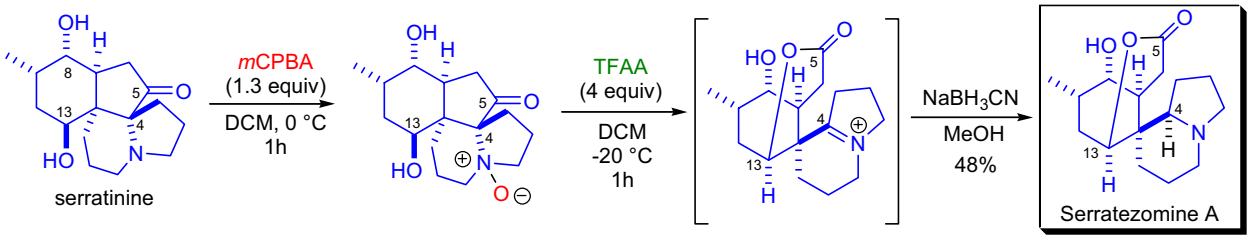
The conversion of the *O*-acylimonium salt to the imine proceeds *via* an *E2-type elimination*. The hydrogen that is antiperiplanar to the N-O bond is usually removed preferentially. When the *N*-oxide is activated with iron salts, a SET mechanism is operational, while with SO_2 an intramolecular ionic mechanism is most likely.[11,12]



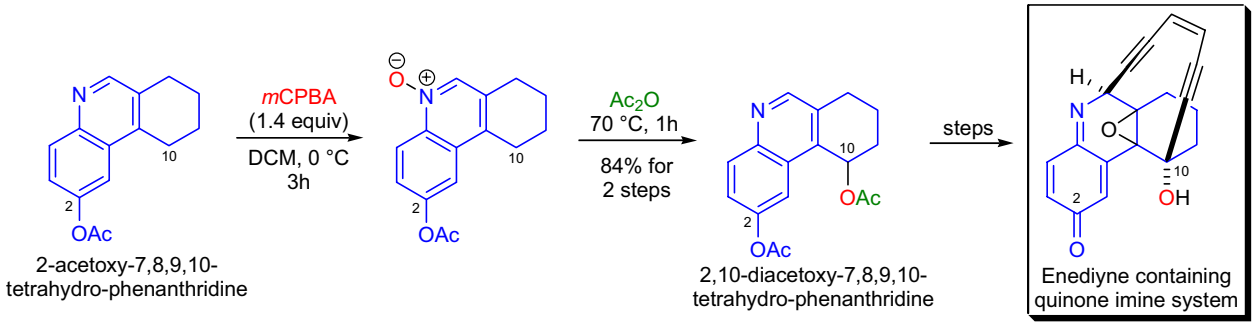
POLONOVSKI REACTION

Synthetic Applications:

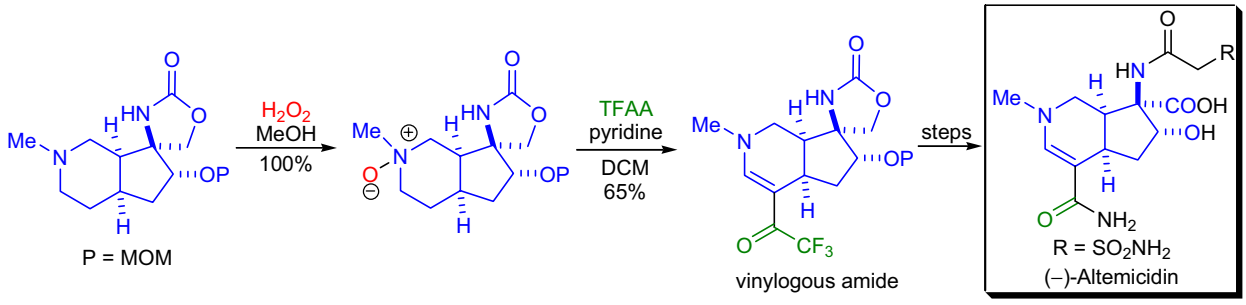
In the laboratory of J. Kobayashi, the biomimetic one-pot transformation of serratinine into serratezomine A was accomplished using the *Polonovski-Potier reaction*.[25] Serratinine was first treated with *m*-chloroperbenzoic acid to obtain the *N*-oxide, and then excess TFAA was added. The iminium ion was formed in the following fashion: the C13 hydroxyl group formed a hemiacetal with the C5 carbonyl group and simultaneously with the formation of the C5-C13 lactone the C4-C5 bond was broken. The iminium ion was then reduced with sodium cyanoborohydride to afford the tertiary amine functionality. Besides serratezomine A, another lactone (between the C8 hydroxyl and C5 carbonyl) was formed in 27% yield.



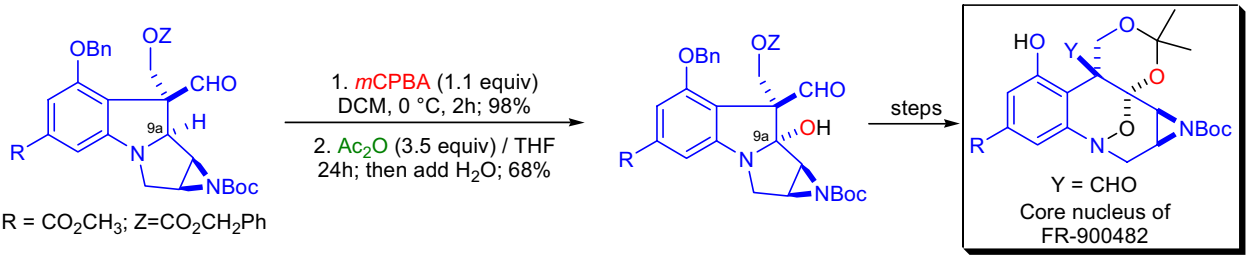
The total synthesis of (±)-dynemicin A was achieved by S.J. Danishefsky et al.[26] As part of the synthetic studies, highly sensitive enediyne containing quinone imine systems were prepared, and their biological properties were evaluated. The first step in the sequence leading to one such quinone imine began with the oxidation of the nitrogen of the phenanthridine substrate, and the resulting *N*-oxide was heated in neat acetic anhydride to induce the *Polonovski reaction*.



The naturally occurring sulfonamide (–)-altemicidin is the first 6-azaindene monoterpene alkaloid isolated as a metabolite of microorganisms. A.S. Kende utilized the *Polonovski-Potier reaction* in the key step to introduce the carbamoyl enamine functionality.[27] The tertiary amine was oxidized to the *N*-oxide by H_2O_2 followed by treatment with excess TFAA to afford the desired vinylogous trifluoromethyl amide.



The core nucleus of the mitomycinlike antitumor agent FR-900482 was synthesized by F.E. Ziegler and co-workers.[28] The selective oxygenation of the C9a position was achieved by the *Polonovski reaction*.



POMERANZ-FRITSCH REACTION

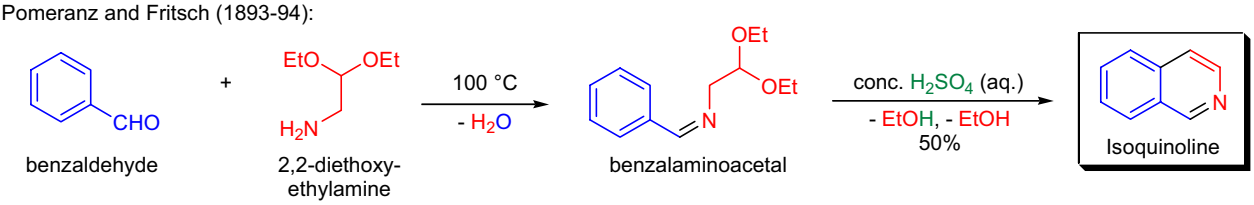
(References are on page 655)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-11]; *Modifications & Improvements*[12-19]]

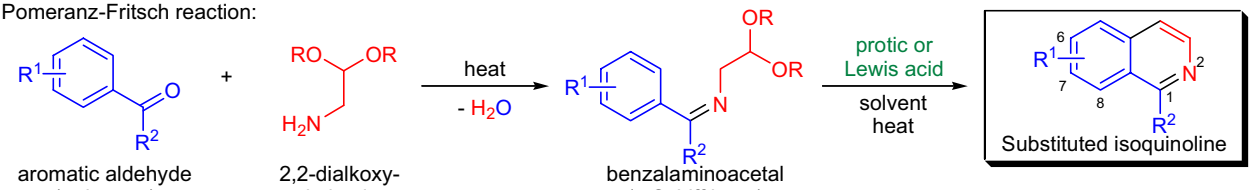
In 1893, C. Pomeranz and P. Fritsch independently reported a new synthesis of isoquinoline by heating a benzalaminoacetal, prepared by the condensation of benzaldehyde and 2,2-diethoxyethylamine, in concentrated sulfuric acid.[1,2] During the 1890s, these authors successfully prepared a wide range of structurally diverse isoquinolines.[3-5] The acid-catalyzed cyclization of benzalaminoacetals (these are Schiff bases) to give substituted isoquinolines is known as the *Pomeranz-Fritsch reaction*. The general features of the transformation are: 1) the benzalaminoacetals are prepared by reacting 2,2-dialkoxyethylamines with substituted aromatic aldehydes or rarely with aromatic ketones; 2) the structural variation of the 2,2-dialkoxyethylamines is very restricted, and, in the overwhelming majority of the cases, the dimethyl or diethyl acetals are used without any substituents on the C1 carbon (C1-substituted analogues tend to fail to undergo the reaction); 3) aromatic aldehydes give rise to C1-unsubstituted isoquinolines, usually in good yield, while aromatic ketones afford C1-substituted isoquinolines albeit in low yield; 4) the highest yields are obtained when the substituents on the aromatic ring are electron-donating; 5) strongly electron-withdrawing substituents (e.g., NO_2) on the aromatic ring prevent the formation of isoquinolines and the corresponding oxazoles are obtained instead;[20] 6) when both of the *ortho*-positions (relative to the carbonyl group) are unoccupied, a regioisomeric mixture of isoquinolines is obtained; 7) the most commonly used protic acids are sulfuric acid and hydrochloric acid, but Lewis acids such as $BF_3{\cdot}OEt_2$, trifluoroacetic anhydride and lanthanide triflates have been used occasionally;[15,17] 8) unless the aromatic ring is highly electron-rich, heating of the reaction mixture is required in order to achieve cyclization. Two of the most important modifications are: 1) when a substituted benzylamine is condensed with glyoxal hemiacetal, the resulting Schiff base is efficiently cyclized to give the corresponding C1-substituted isoquinoline (*Schlittler-Müller modification*);[12] 2) hydrogenation of the benzal-aminoacetal and the acid-catalyzed cyclization of the resulting amine gives rise to a tetrahydroisoquinoline (*Bobbitt-modification*).[13,21,19]

Pomeranz and Fritsch (1893-94):



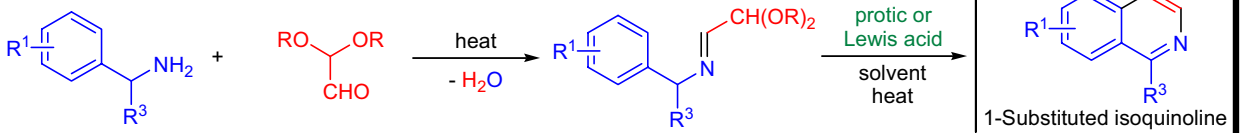
benzaldehyde | 2,2-diethoxy-ethylamine | benzalaminoacetal

Pomeranz-Fritsch reaction:



aromatic aldehyde (or ketone) | 2,2-dialkoxy-ethylamine | benzalaminoacetal (a Schiff base)

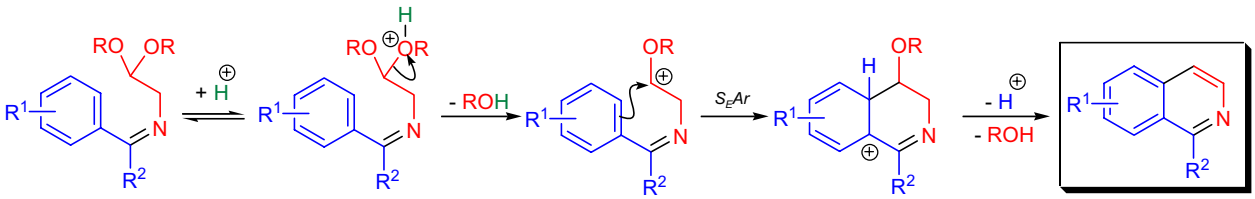
Schlittler-Müller modification (1948):



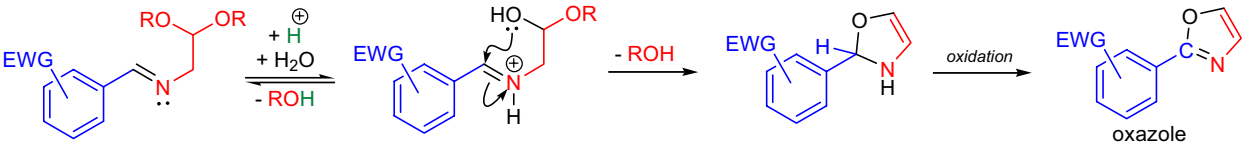
substituted benzylamine | glyoxal hemiacetal | Schiff base

R^1 = usually an electron-donating group (EDG), H, alkyl, aryl, O-alkyl, Cl, Br; R^{2-3} = H, alkyl; R = Me, Et; protic acid: H_2SO_4, HCl, PPA; Lewis acid: $BF_3{\cdot}OEt_2$

Mechanism:[20,7]



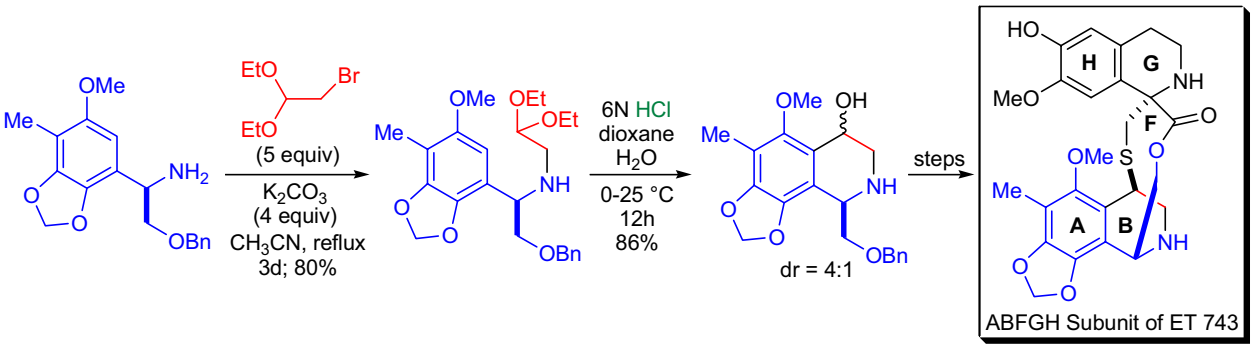
Formation of oxazole if R^1 = EWG (the oxidation is performed by the conc. H_2SO_4):



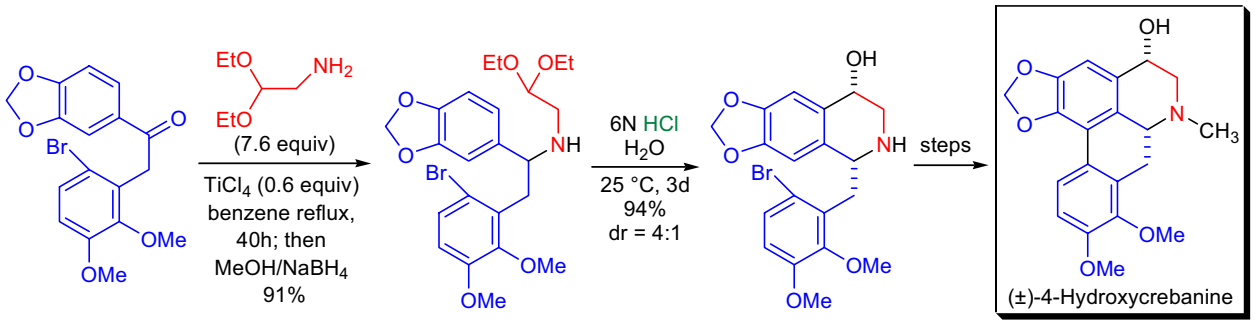
POMERANZ-FRITSCH REACTION

Synthetic Applications:

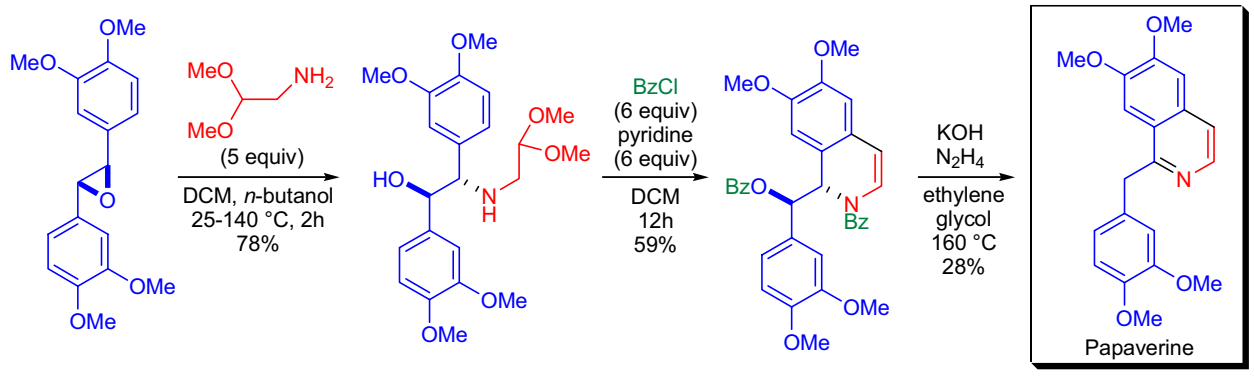
The *Bobbitt modified Pomeranz-Fritsch reaction* allows the preparation of enantiopure tetrahydroisoquinolines. During the studies directed toward the total synthesis of ET 743 and its analogues, S.J. Danishefsky and co-workers utilized this transformation for the preparation of a key tetrahydroisoquinoline intermediate.[22] The cyclization precursor was efficiently synthesized from the enantiopure benzylamine derivative by *N*-alkylation with excess diethylbromoacetal. The resulting compound was subjected to 6*N* hydrochloric acid at 0 °C and slowly warmed to ambient temperature overnight. The desired tetrahydroisoquinoline was formed as a 4:1 mixture of diastereomers.



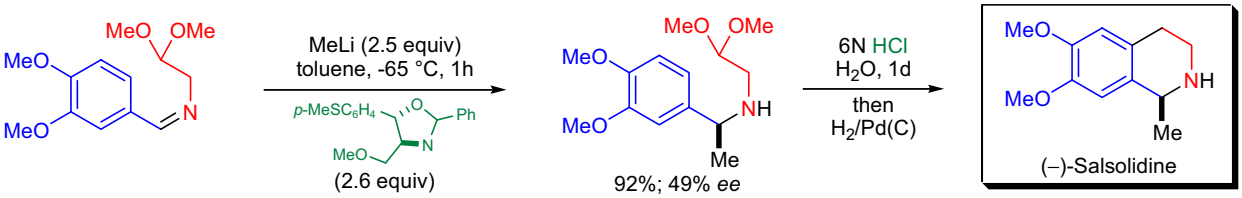
The total synthesis of (±)-4-hydroxycrebanine was accomplished by J.-I. Kunitomo et al., who used the *Bobbitt modification of the Pomeranz-Fritsch reaction* as the key ring-forming step.[23] The aromatic ketone substrate was first condensed with aminoacetaldehyde diethylacetal to afford a Schiff base that was immediately reduced to the corresponding amino compound in high yield. Exposure of this intermediate to concentrated HCl for several days gave rise to the tetrahydroisoquinoline as a mixture of two diastereomers.



The shortest synthesis of papaverine was achieved in the laboratory of R. Hirsenkorn starting from racemic stilbene oxide and using a *modified Pomeranz-Fritsch reaction*.[24] The aminolysis of the stilbene oxide led to the formation of the cyclization precursor, which upon treatment with excess benzoyl chloride, underwent cyclization to give the *N*-benzoyl 1,2-dihydroisoquinoline derivative. Reduction under Wolff-Kishner conditions afforded papaverine.



The *asymmetric variant of the Pomeranz-Fritsch reaction* was used by D. Rozwadowska and co-workers in the total synthesis of (–)-salsolidine.[21]



PRÉVOST REACTION

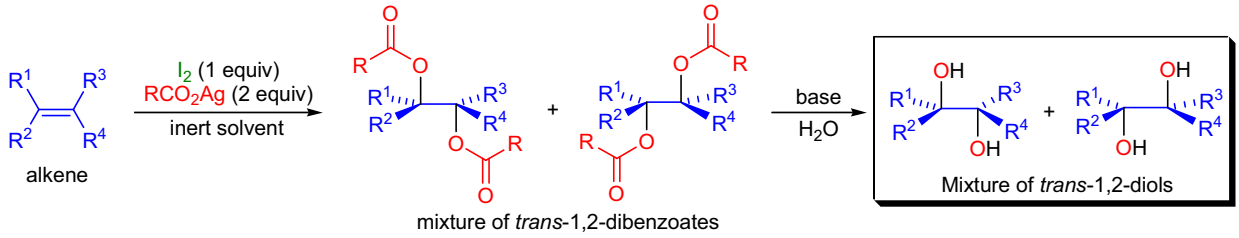
(References are on page 656)

Importance:

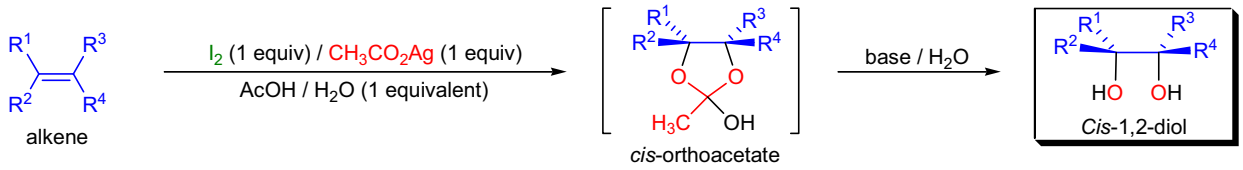
[*Seminal Publications*[1-3]; *Reviews*[4-7]; *Modifications & Improvements*[8-16]]

In 1933, C. Prévost reported that the treatment of styrene with silver benzoate and iodine (I_2) in dry benzene gave the dibenzoate ester of the corresponding glycol that upon hydrolysis afforded the 1,2-diol.[1] This two-step transformation of olefins leads to 1,2-*trans* diols, and it is referred to as the *Prévost reaction*. The general features of this reaction are: 1) both acyclic and cyclic alkenes are good substrates; 2) the initial products are diastereomeric *trans*-1,2-dicarboxylates, which are hydrolyzed under basic conditions to the *trans*-1,2-diols *(anti* products); 3) in rigid cyclic systems the reaction is highly diastereoselective; 4) the most commonly used reagent is silver benzoate (R=Ph), but this can be replaced with other silver carboxylates or thallium(I)acetate;[11] 5) when conjugated and isolated double bonds are both present in the molecule, the dihydroxylation usually takes place on the isolated double bond. The most important modification of the *Prévost reaction* was introduced by Woodward and Brutcher, who used wet acetic acid to obtain *cis*-1,2-diols. This modification was based on the observation by Winstein et al., who reported the erosion of *trans* selectivity of the *Prévost reaction* by small amounts of water.[17,18]

Trans-dihydroxylation of olefins (Prévost, 1933):

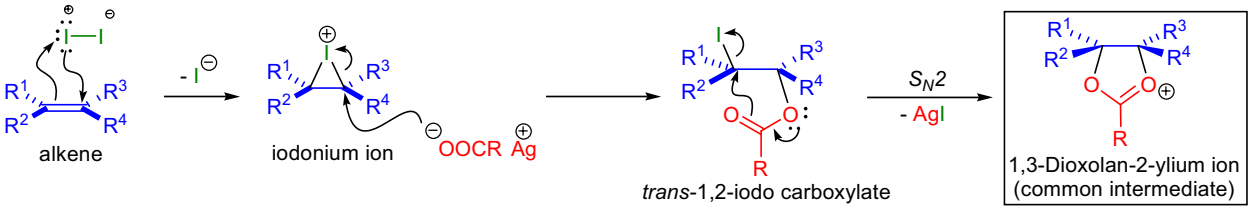


Woodward-Brutcher modification to prepare *cis*-diols (1958):

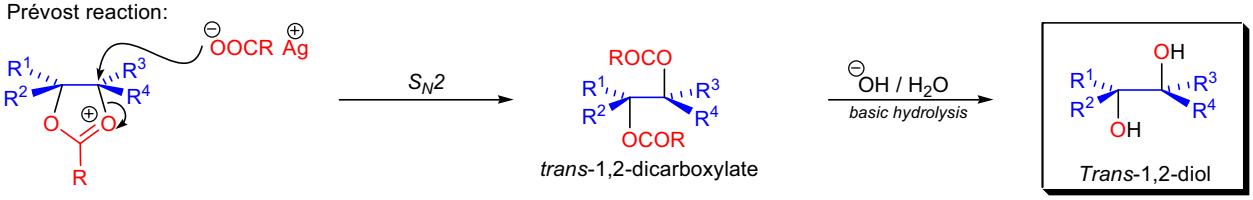


Mechanism:[17-20]

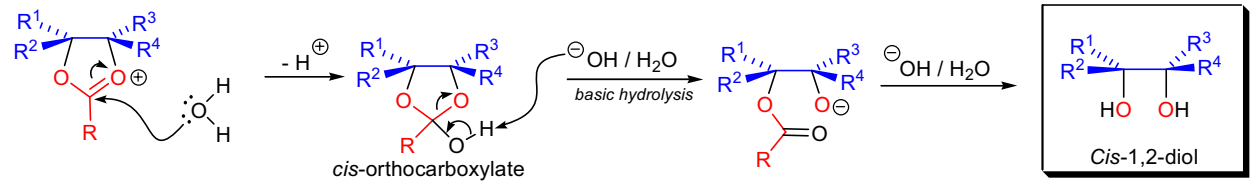
The first step of the *Prévost reaction* is the reaction of the alkene with iodine to form the cyclic iodonium ion. Next, the iodonium ion is stereospecifically opened by the silver carboxylate to form the corresponding *trans*-1,2-iodo carboxylate. The iodine is displaced intramolecularly by the carbonyl group of the carboxylate (anchimeric assistance) to form a cyclic cationic intermediate. In the absence of water, this cation is opened with the inversion of configuration by the second equivalent of silver carboxylate to afford the *trans*-1,2-dicarboxylate. However, in the presence of water (*Woodward-Brutcher modification*) the common intermediate is converted to a *cis*-orthocarboxylate which is hydrolyzed to the corresponding *cis*-1,2-diol.



Prévost reaction:



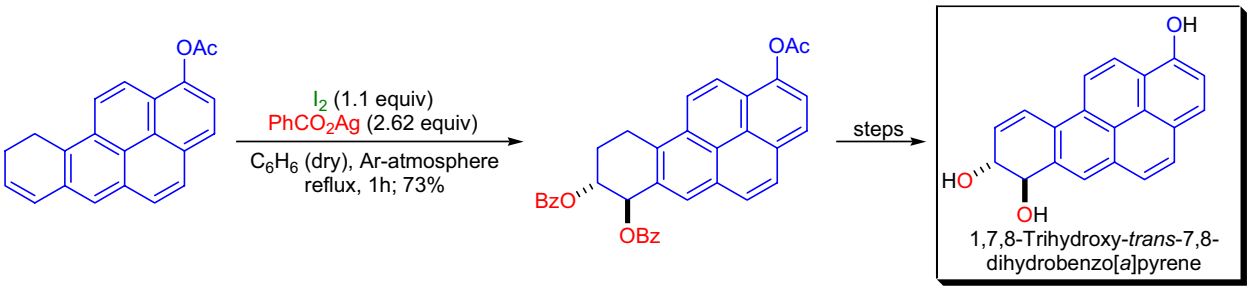
Woodward-Brutcher modification:



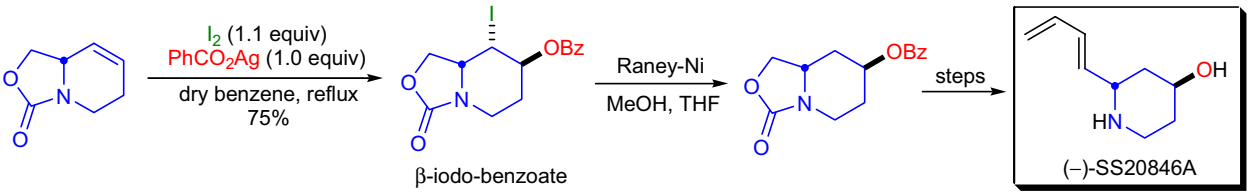
PRÉVOST REACTION

Synthetic Applications:

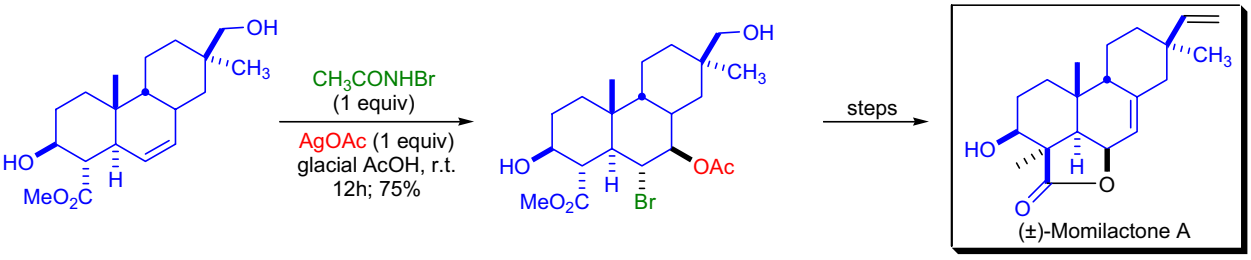
In the laboratory of S. Kumar, the synthesis of phenolic derivatives of *trans*-7,8-dihydroxy -7,8-dihydrobenzo[*a*]pyrene, a highly tumorigenic compound, was accomplished.[21] The *trans*-vicinal diol functionality was introduced by using the "dry" Prévost conditions. The alkene was subjected to a mixture of iodine and silver benzoate in dry refluxing benzene to give a good yield of the corresponding *trans*-7,8-dibenzoate derivative.



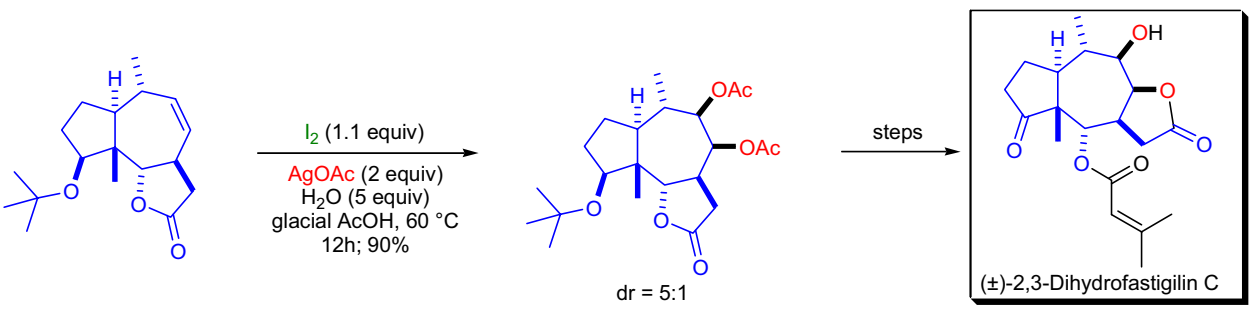
The total synthesis of (–)-SS20846A, a 2-alkyl-4-hydroxypiperidine natural product exhibiting antibacterial and anticonvulsant properties, was achieved by C.R. Johnson and co-workers.[22] The key transformations included an alkene metathesis for the preparation of the piperidine ring and the *Prévost reaction* for the installation of the 4-hydroxy substituent.



The key steps in the first total synthesis of (±)-momilactone A by P. Deslongchamps et al. were a highly diastereoselective *transannular Diels-Alder cycloaddition* and the *Prévost reaction*.[23] The β-ketolactone moiety was installed by first treating the tricyclic alkene with *N*-bromo acetamide and silver acetate to obtain the *trans* bromoacetate with excellent diastereoselectivity. The *cis* stereochemistry of the lactone was achieved a few steps later by the intramolecular nucleophilic displacement of the bromide with the carboxylate ion on the adjacent six-membered ring.



The *Woodward-Brutcher modification of the Prévost reaction* was used by P.T. Lansbury to install the *cis* vicinal diol moiety of (±)-2,3-dihydrofastigilin C.[24] The *cis* vicinal diacetate was formed in high yield and with good diastereoselectivity (5:1) when the reaction was conducted in wet acetic acid.



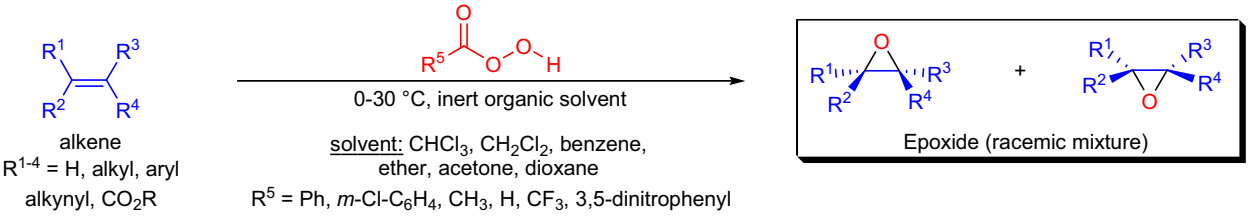
PRILEZHAEV REACTION

(References are on page 656)

Importance:

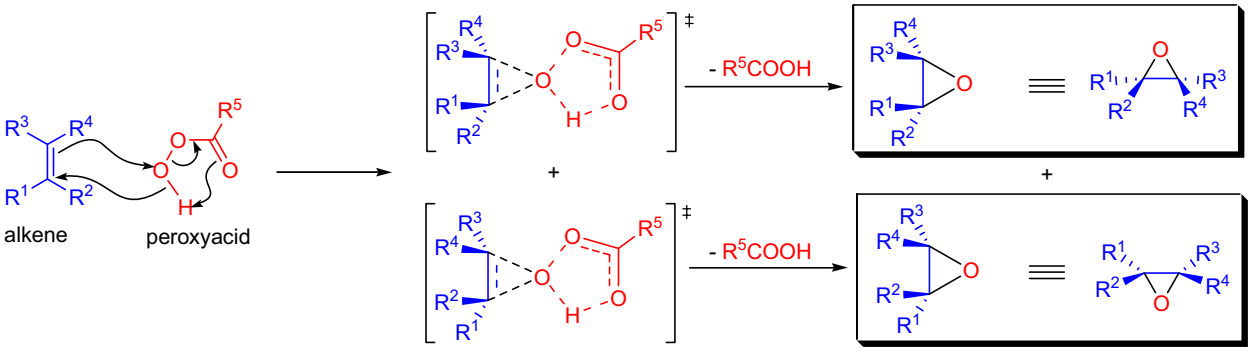
[*Seminal Publications*[1-3]*; Reviews*[4-12]*; Modifications & Improvements*[13-23]; *Theoretical Studies*[24-33]]

In 1909, N. Prilezhaev was the first to use peroxycarboxylic acids to oxidize isolated double bonds to the corresponding oxiranes (epoxides).[1] This transformation is referred to as the *Prilezhaev reaction*. The use of peroxyacids for the preparation of epoxides is one of the most widely used methods unless the epoxide is needed in an enantiomerically pure form for which other methods are available (e.g., *Sharpless, Jacobsen, and Shi asymmetric epoxidation*). The general features of the *Prilezhaev reaction* are: 1) the reaction is stereospecific, since the stereochemistry of the alkene substrate is retained in the epoxide product (*trans* alkene yields the *trans* epoxide, while *cis* alkene affords *cis* epoxide); 2) the reaction rate increases if the substituents on the alkene are electron-donating and decreases if they are electron-withdrawing; 3) an electron-withdrawing substituent (R^5) on the peroxyacid increases the rate of epoxidation; 4) substrates with multiple isolated double bonds can be epoxidized regioselectively, since the more electron-rich double bond reacts faster with the peracid (terminal alkenes are the least reactive, so a disubstituted alkene is selectively epoxidized in the presence of a terminal one); 5) alkenes that have preexisting chiral centers theoretically give rise to two diastereomeric epoxides, but in practice high diastereoselectivities may be achieved by preferentially epoxidizing the less sterically hindered face of the alkene (substrate-directed synthesis);[34] 6) alkenes with no chiral centers give rise to a 1:1 mixture of enantiomeric epoxides (racemic mixture); 7) the steric demand of the peroxyacid is almost negligible, so even very sterically hindered substrates may be epoxidized; 8) cup-shaped molecules are usually epoxidized from the less hindered convex side; 9) if a functional group adjacent to the double bond can coordinate to the peroxyacid, the natural steric bias will be overridden and the epoxidation will occur from that face of the double bond where the coordinating functional group is located (e.g., OH>CO_2H>CO_2R>OCOR) and this phenomenon is called the *neighboring group effect*; 10) the reagent peroxyacids can be prepared (by reacting carboxylic acids with hydrogen peroxide) or purchased from commercial sources; 11) most widely used peroxyacid is *m*CPBA, which is a relatively stable solid with good solubility in most organic solvents; 12) less frequently used (and not very stable) peroxyacids are generated *in situ* (e.g., peroxyacetic and performic acid); 13) the peroxyacids are much less acidic than the carboxylic acids, so acid-catalyzed side reactions (e.g., epoxide ring-opening) are rare; 14) when the product is very acid sensitive, the reaction mixture needs to be buffered since the by-product is a strong carboxylic acid; 15) epoxidations with *m*CPBA are usually carried out at or below ambient temperature, and a mildly basic work-up ensures the removal of the benzoic acid by-product from the epoxide product; 16) the reaction tolerates most functional groups, but free amines are readily oxidized, so they must be protected; 17) ketones may undergo a competing *Baeyer-Villiger oxidation*; 18) α,β-unsaturated esters are epoxidized, while α,β-unsaturated ketones remain unchanged under the reaction conditions; and 19) alkynes react 10^3 times slower than alkenes, so alkenes are selectively epoxidized in the presence of alkynes. When the use of peroxyacids is not suitable for the substrates or the products, alternative epoxidizing agents may be applied:[11] 1) peroxycarboximidic acids (by mixing nitriles with H_2O_2);[13,19] 2) magnesium monoperoxyphthalate hexahydrate (MMPP);[16] 3) dimethyldioxirane or dialkyldioxiranes;[17,23] 4) alkyl hydroperoxides in the presence of a transition metal catalyst;[35] 5) molecular oxygen and light (*photoepoxidation*);[15] and 6) inorganic peroxo acids (e.g., peroxoselenic acid).[10,11]



Mechanism:[36,7,37-47]

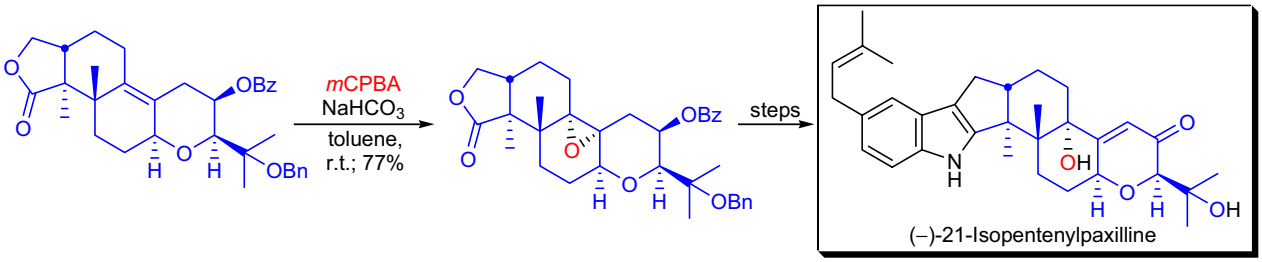
The *Prilezhaev reaction* is stereospecific, and a *syn* addition of the oxygen to the double bond is observed in all cases. This observation supports the assumption that the epoxidation of alkenes by peroxyacids is a concerted process. The reaction takes place at the terminal oxygen atom of the peroxyacid, and the π HOMO of the olefin approaches the σ^* LUMO of the O-O bond at an angle of 180° (butterfly transition structure).



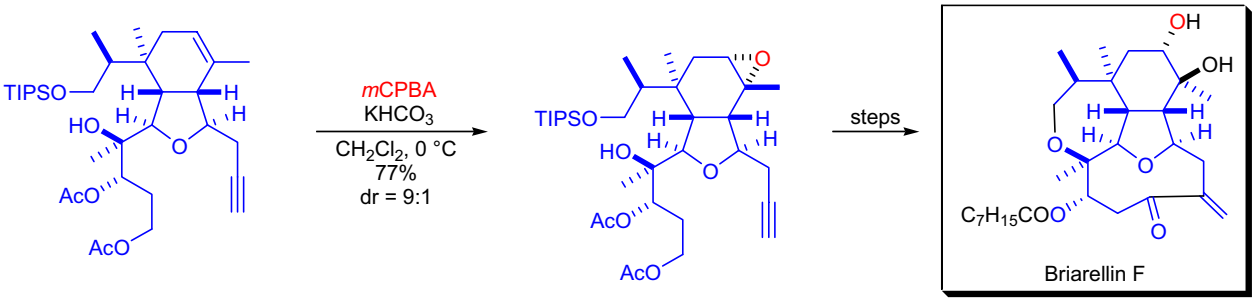
PRILEZHAEV REACTION

Synthetic Applications:

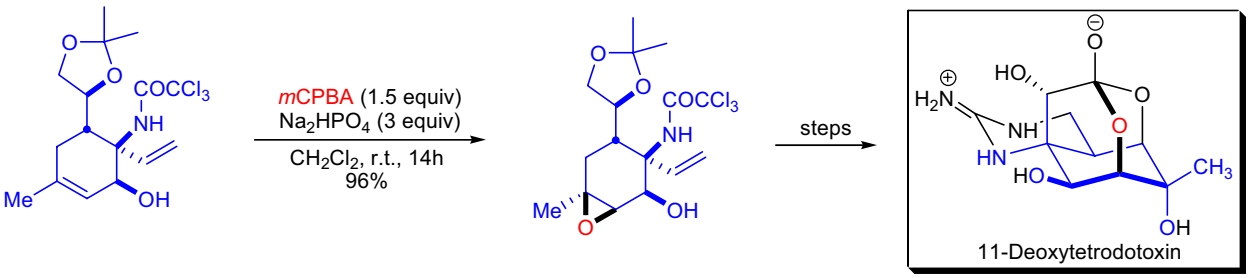
A *diastereoselective epoxidation* of a tetrasubstituted double bond was accomplished with *m*CPBA in the total synthesis of (–)-21-isopentenylpaxilline by A.B. Smith et al.[48] The tetracyclic lactone substrate containing the tetrasubstituted double bond was exposed to *m*CPBA in toluene at room temperature. The reaction mixture also contained sodium bicarbonate to neutralize the by-product *m*-chloro benzoic acid. The epoxidation exclusively took place from the less hindered α-face of the molecule. At a later stage, this epoxide was converted to the γ-hydroxy enone moiety present in the natural product.



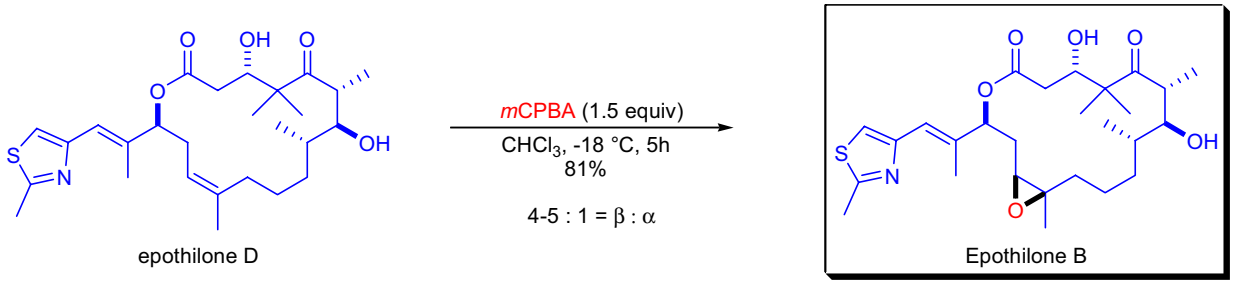
During the first total synthesis of briarellin diterpenes, briarellins E and F, L.E. Overman and co-workers utilized the large reactivity difference between a triple and a double bond in peroxyacid oxidations to selectively epoxidize a trisubstituted double bond in the presence of a terminal alkyne.[49] The epoxidation with *m*CPBA was carried out in DCM in the presence of a base to afford the α-epoxide in a 9:1 diastereomeric ratio.



The *hydroxyl group-directed epoxidation* was utilized by M. Isobe et al. in their total synthesis of 11-deoxytetrodotoxin.[50] The six-membered cyclic allylic alcohol was treated with *m*CPBA in the presence of a phosphate buffer to afford an almost quantitative yield of the desired β-epoxide.



The final step in J. Mulzer's total syntheses of epothilones B and D was the oxidation of the C12-C13 double bond of epothilone D *via* a highly diastereoselective *Prilezhaev reaction* to obtain epothilone B.[51] The same *m*CPBA oxidation endgame was chosen by R. E. Taylor et al. in the total synthesis of these two natural products.[52]



PRINS REACTION

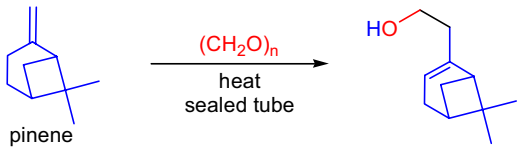
(References are on page 658)

Importance:

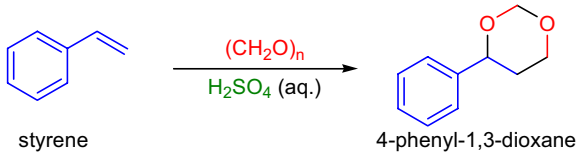
[*Seminal Publications*[1-4]; *Reviews*[5-8]; *Modifications & Improvements*[9-14]; *Theoretical Studies*[15]]

In 1899, O. Kriewitz reported that upon heating with paraformaldehyde in a sealed tube, β-pinene gave rise to an unsaturated alcohol (nopol).[1,2] It was not until two decades later that H.J. Prins conducted the first comprehensive study on the sulfuric acid-catalyzed reactions of various alkenes (e.g., styrene, pinene, camphene) with formaldehyde.[3,4] In his honor, the acid-catalyzed condensation of alkenes with aldehydes is referred to as the *Prins reaction*. The general features of the reaction are: 1) potentially a large number of different products can be formed; however, the careful control of the reaction conditions allows the formation of a given product with good selectivity; 2) besides allylic alcohol products, the formation of 3-substituted alcohols, 1,3-diols, and 1,3-dioxanes is possible, depending on what type of nucleophilic species are present in the reaction mixture; 3) a variety of protic and Lewis acids may be employed to catalyze the reaction: H_2SO_4, HCl, HOCl, HNO_3, *p*-TsOH, BF_3, $AlCl_3$, $ZnCl_2$, $TiCl_4$, etc.; 4) when the reaction is conducted under anhydrous conditions, the *carbonyl ene reaction* takes place (*See Ene reaction*), and the corresponding homoallylic alcohols are formed exclusively; 5) the reaction is fastest with formaldehyde and with highly substituted alkenes; 6) both acyclic and cyclic alkenes are substrates for the transformation; 7) the addition of the protonated aldehyde across the double bond of the alkene follows *Marknovnikoff's rule*, and the fate of the resulting carbocation determines what type of products are formed; and 8) with cyclic alkenes, the products often have *anti* stereochemistry due to neighboring group participation.

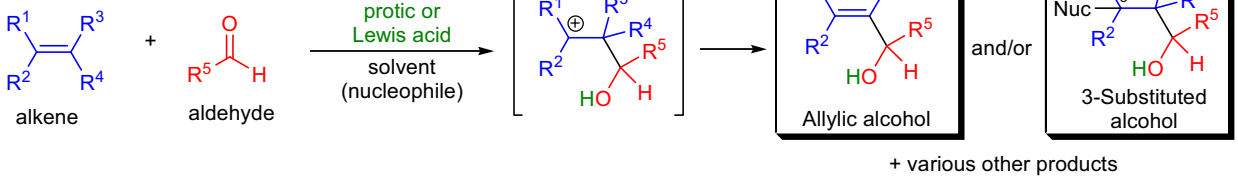
Kriewitz (1899):



Prins (1919):



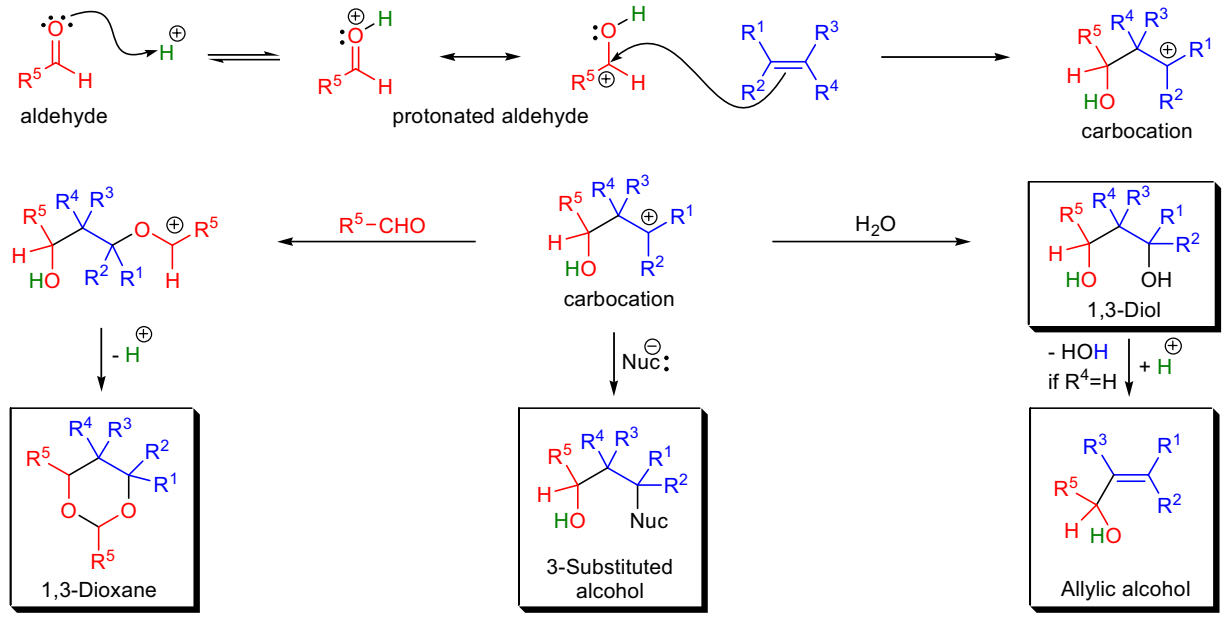
Prins reaction:



+ various other products

R^{1-4} = H, alkyl, aryl, heteroaryl; R^5 = H, alkyl, aryl; protic acid: dilute aqueous H_2SO_4, HCl, H_3PO_4, HOCl, *p*-TsOH, HNO_3; Lewis acid: BF_3, $AlCl_3$, $ZnCl_2$, $TiCl_4$, cation-exhange resin; solvent: H_2O, ROH, benzene; nucleophile: could be the solvent or the conjugate base derived from the protic acid; other products: dienes, 1,3-dioxanes, 1,3-diols, etc.

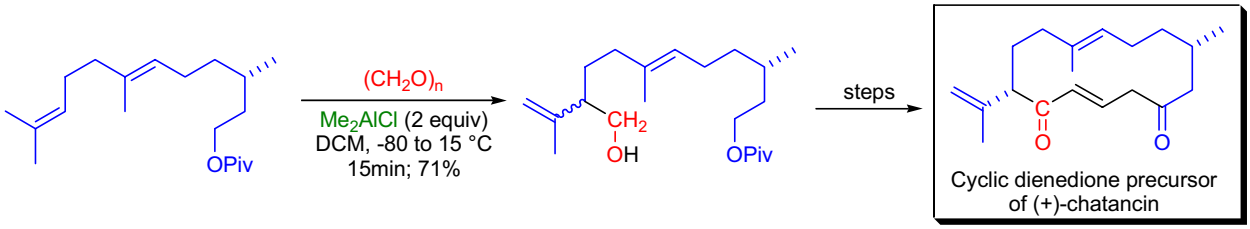
Mechanism:[16-29]



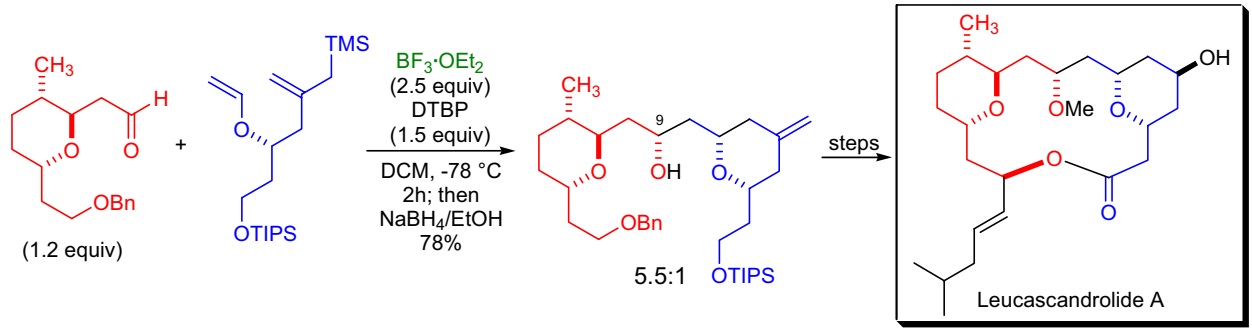
PRINS REACTION

Synthetic Applications:

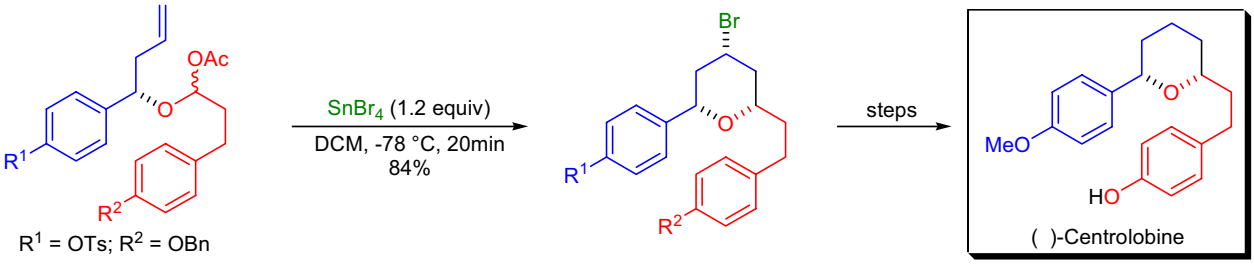
Studies toward the biomimetic total synthesis of (+)-chatancin were conducted by P. Deslongchamps et al.[30] The authors planned to use a *transannular Diels-Alder reaction* of a pyranophane intermediate as the key ring forming step. The cyclic dienedione precursor for this transformation was prepared using the *Prins reaction* on a substrate derived from *trans-trans* farnesol.



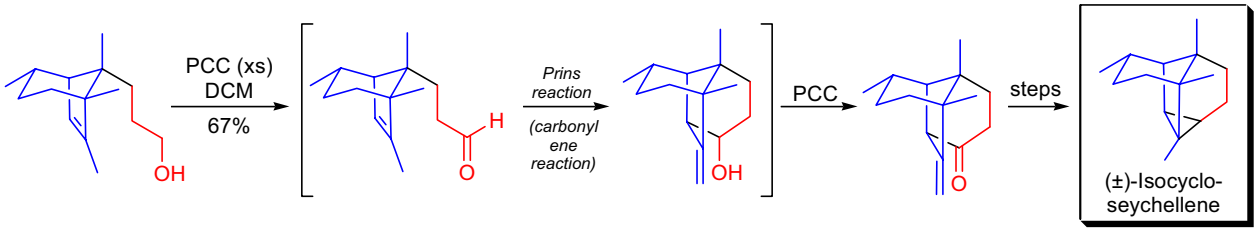
The tandem *Mukaiyama aldol reaction-Prins cyclization* was utilized during the formal total synthesis of leucascandrolide A by S.D Rychnovsky.[31] The addition of the activated aldehyde to the enol ether resulted in the formation of an oxocarbenium ion, which was captured intramolecularly by the allylsilane moiety to form a new tetrahydropyran ring. The reduction of the crude reaction mixture with $NaBH_4$ was performed to remove the unreacted aldehyde starting material, thereby facilitating the chromatographic purification of the product. The product was isolated as a 5.5:1 mixture of epimers at C9.



In the laboratory of R.D. Rychnovsky, the *segment-coupling Prins cyclization* was utilized for the total synthesis of (–)-centrolobine.[32] This approach avoided the common side reactions, such as side-chain exchange and partial racemization by reversible *2-oxonia Cope rearrangement*, associated with other *Prins cyclization reactions*. The substrate -acetoxy ether was subjected to $SnBr_4$ in DCM, which brought about the formation of the all-equatorial tetrahydropyran in good yield.



The stereoselective total synthesis of ( )-isocycloseychellene was achieved by S.C. Welch and co-workers.[33] One of the key ring forming reactions was an *oxidative Prins reaction* that took place without the need of a catalyst (*carbonyl ene reaction*) to afford the desired tricyclic ketone.



PRINS-PINACOL REARRANGEMENT

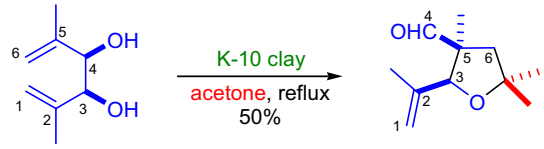
(References are on page 658)

Importance:

[*Seminal Publications*[1-6]*; Reviews*[7-9]*; Modifications & Improvements*[10-14]]

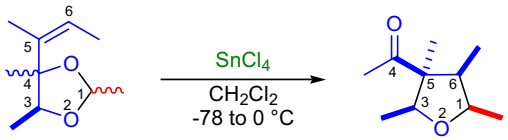
In 1969, G. Mousset and co-workers attempted to prepare the acetonide of a *meso* allylic 1,2-diol by refluxing it with acetone in the presence of an acidic clay catalyst.[1] To their surprise, instead of the expected acetal, they isolated a highly substituted tetrahydrofuran derivative. The authors proposed that the acetone condensed with the diol to give an oxocarbenium ion that underwent a *Prins cyclization* to afford a β-hydroxy carbenium ion intermediate, which gave rise to the tetrahydrofuran derivative *via* a *pinacol rearrangement*. Almost two decades later in 1987, L.E. Overman et al. investigated the Lewis acid mediated rearrangement of 4-alkenyl-1,3-dioxolanes (allylic acetals) to afford 3-acyltetrahydrofurans.[3] Subsequent studies conducted by the Overman group demonstrated that the transformation was general and had a broad scope.[9] The formation of oxacyclic and carbocyclic ring systems by terminating *Prins cyclizations* with the *pinacol rearrangement* in a tandem fashion is known as the *Prins-pinacol rearrangement*. The general features of the reaction are:[9] 1) it is completely stereoselective and results in the formation of two C-C bonds, one C-O bond, and two new stereocenters; 2) protic and Lewis acids are the most common in promoting the reaction; 3) most widely used solvents are nitromethane and dichloromethane; 4) alkenyl-substituted cyclic acetals derived from 1,2-diols give rise to highly substituted 3-acyltetrahydrofurans; 5) 1-alkenylcycloalkane-1,2-diols condense with aldehydes and ketones and afford annulated 3-acyltetrahydrofurans accompanied by ring-enlargement; 6) when the double bond of the starting alkenyl diol is part of a ring, a variety of differently annulated polycyclic ethers can be prepared upon condensation with aldehydes and ketones; 7) in the majority of cases, both the *syn* and *anti* acetal stereoisomers afford the same tetrahydrofuran adduct; 8) the acyl substituent at C3 will be preferentially *cis*-disposed to both the C2 and C5 substituents; 9) if the oxocarbenium ion intermediate is external to the ring formed in the *Prins cyclization* step, the formation of a carbocyclic ring takes place;[13] and 10) besides substituted alkenes, terminal alkynes also participate in the rearrangement.[9]

Mousset (1969):



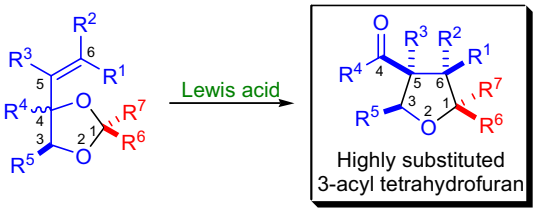
allylic 1,2-diol → substituted tetrahydrofuran

Overman (1987):

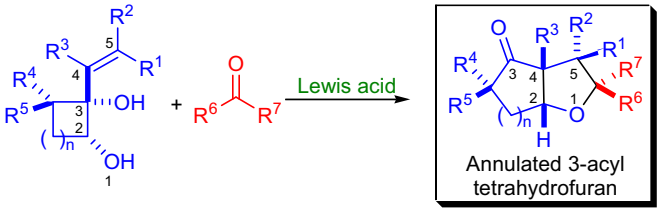


allylic acetal → acyl tetrahydrofuran

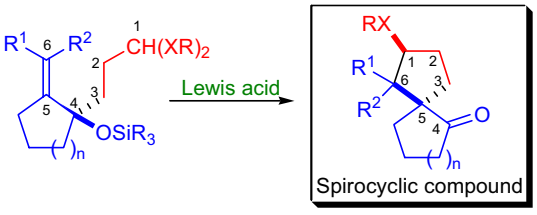
Formation of substituted tetrahydrofurans:



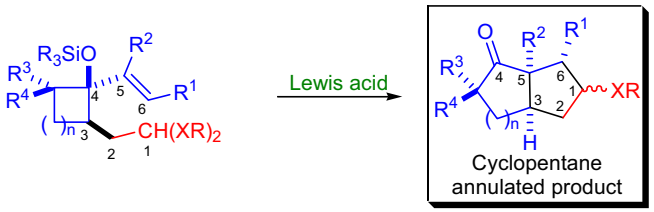
Tetrahydrofuran annulation accompanied by ring-enlargement:



Cyclopentane spiroannulation:



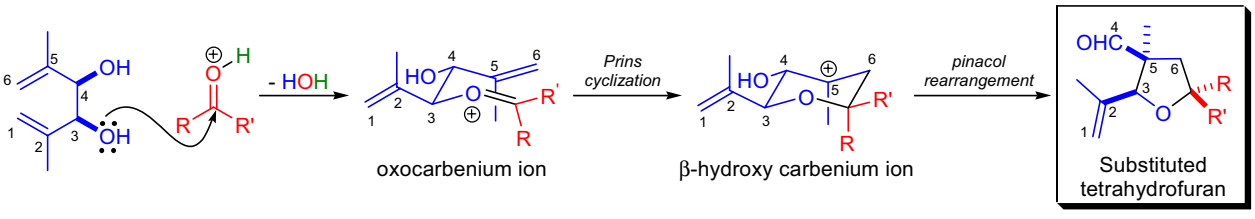
Cyclopentane annulation accompanied by ring-enlargement:



R^{1-5} = H, alkyl, aryl; R^{6-7} = H, alkyl, aryl, alkenyl; n = 1-3; XR = SEt, OMe; SiR_3 = TMS, TES, TBDMS; Lewis acid: BCl_3, $SnCl_4$, BF_3

Mechanism:[10-12,15,16,9]

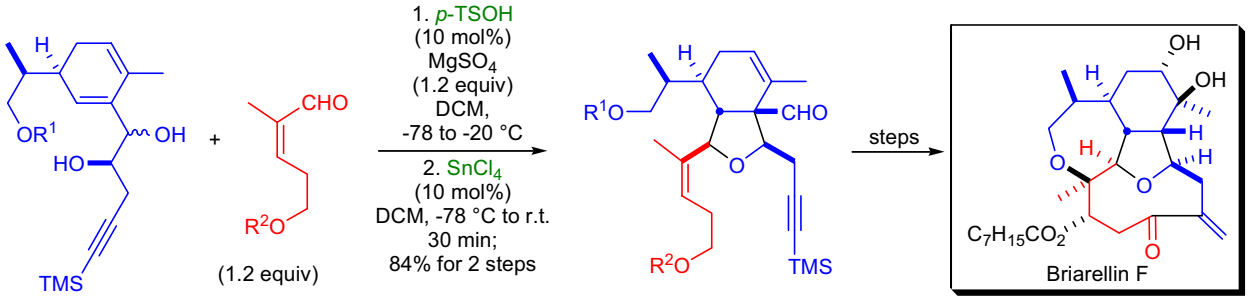
Originally, the reaction was thought to proceed by an *oxonia-Cope rearrangement* followed by *aldol cyclization*, but this hypothesis was rejected based on the observation that enantiomerically enriched acetals gave rise to tetrahydrofurans of high enantiomeric purity and not a racemic mixture as was expected.[9]



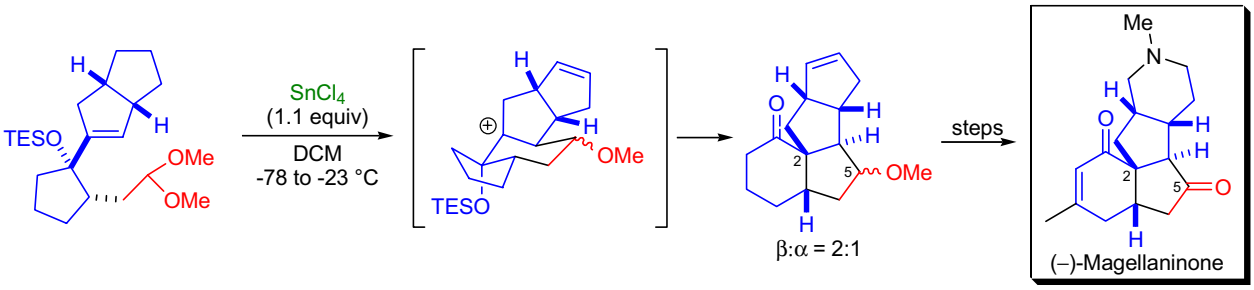
PRINS-PINACOL REARRANGEMENT

Synthetic Applications:

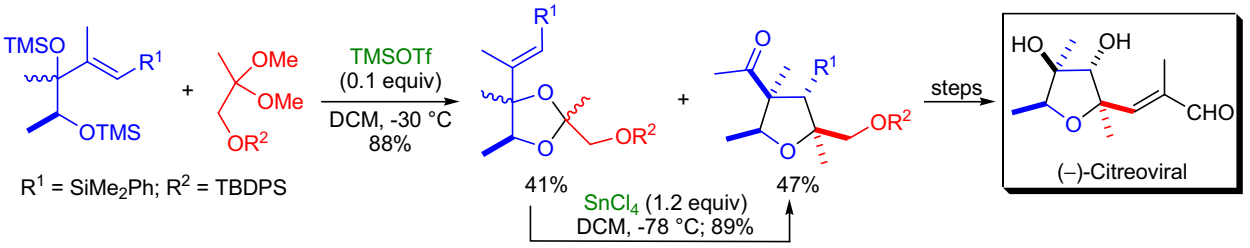
The *Prins-pinacol rearrangement* was utilized during the first enantioselective total synthesis of briarellin diterpenes by L.E. Overman and co-workers.[17] The cyclohexadienyl diol substrate was condensed with a (*Z*)-α,β-unsaturated aldehyde at low temperature in the presence of catalytic amounts of acid and $MgSO_4$ as dehydrating agent. The initially formed acetal was then exposed to 10 mol% of $SnCl_4$ to afford the desired tetrahydroisobenzofuran as a single stereoisomer that was later converted to briarellin F.



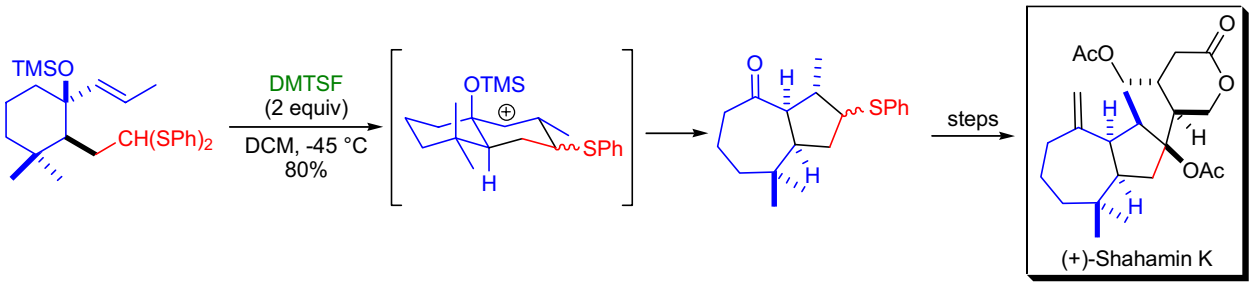
The first total synthesis of *lycopodium* alkaloids of the magellanane group was achieved in the laboratory of L.E. Overman.[18] The angularly fused all-carbon tetracyclic framework of (–)-magellaninone was constructed using the *ring-enlargement Prins-pinacol rearrangement* as the key step. The dienyl acetal substrate was treated with 1.1 equivalents of $SnCl_4$, which gave rise to the desired tetracycle as a mixture of methoxy epimers at C5. The *Prins cyclization* of the oxocarbenium ion took place from the less hindered convex face of the *cis*-bicyclooctadiene moiety and the subsequent *pinacol rearrangement* installed the quaternary stereocenter at C2.



The enantioselective total synthesis of the polysubstituted tetrahydrofuran (–)-citreoviral, the unnatural enantiomer, was synthesized by L.E. Overman et al.[15] The *Prins-pinacol rearrangement* of an allylic 1,2-diol with an unsymmetrical ketone proceeded with high stereoselectivity. The *bis*(trimethylsilyl)-1,2-diol was condensed with the dimethyl acetal of the unsymmetrical ketone in the presence of catalytic amounts of TMSOTf, which yielded a nearly 1:1 mixture of the corresponding acetal and rearrangement product. The acetal was converted to the desired tetrahydrofuran product upon exposure to tin tetrachloride.



The *thio-Prins-pinacol rearrangement* was the key transformation in L.E. Overman's enantioselective total synthesis of (+)-shahamin K.[19] Treatment of the dithioacetal substrate with DMTSF brought about the rearrangement, which gave rise to the *cis*-hydroazulene core of the natural product.



PUMMERER REARRANGEMENT

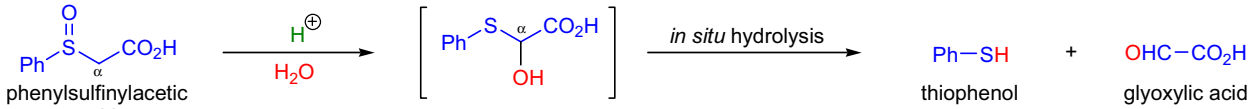
(References are on page 659)

Importance:

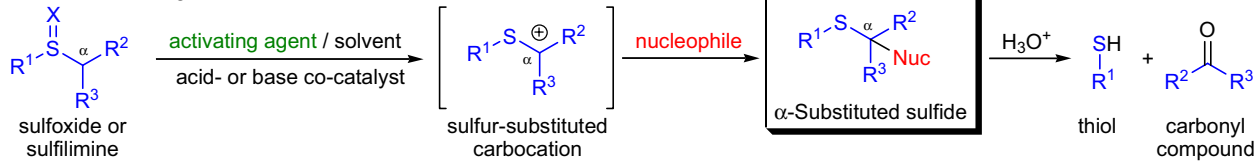
[*Seminal Publications*[1,2]; *Reviews*[3-25]; *Modifications & Improvements*[26-36]; *Theoretical Studies*[37]]

In 1909, R. Pummerer observed that by heating phenylsulfinylacetic acid with mineral acids (e.g., HCl, H_2SO_4), thiophenol and glyoxylic acid were formed.[1] Later this transformation was shown to be general, and today the formation of α-substituted sulfides from the corresponding sulfoxides is referred to as the *Pummerer rearrangement*.[38] The general features of the reaction are: 1) the sulfoxide substrates must have at least one hydrogen atom at their α-position; 2) acetic anhydride (Ac_2O) is the most widely used activating reagent for the rearrangement, and it is often applied as the solvent in combination with other solvents such as benzene or ethyl acetate; 3) the use of acid co-catalysts (e.g., TsOH, AcOH, TFAA) is common to minimize side reactions and increase the product yields; 4) Ac_2O can be replaced with TFAA, which is a stronger reagent and allows for milder reaction conditions;[26] 5) the most common product of the reaction is an α-acetoxy sulfide; 6) upon acidic hydrolysis, the α-acetoxy sulfide affords a thiol and a carbonyl compound that can be easily separated; 7) upon treatment with base, vinyl sulfides are formed *via* a β-elimination; 8) the rearrangement is regioselective when the sulfoxide has hydrogens at both the α- and α'-positions and the more acidic position will get preferentially substituted; 9) the regioselectivity can be altered by steric factors especially in cyclic systems: isomeric sulfoxides often give rise to different products; and 10) the rearrangement can take place both inter- and intramolecularly. Drawbacks of the reaction are: 1) substrates with unprotected hydroxyl or amino groups result in side rections with the activating reagent; 2) unreactive substrates may undergo undesired sulfenic acid elimination if harsh conditions are necessary; 3) fragmentation products are observed when stable carbocations (e.g., allylic, benzylic) can be formed by the heterolytic cleavage of the C-S bond; 4) when the nucleophile is a primary or secondary alcohol, reduction of the sulfoxide to the sulfide may occur along with the oxidation of the alcohol (see *Swern oxidation*). There are several variants of the rearrangement:[12] 1) when selenoxides are the substrates, the *seleno-Pummerer rearrangement* takes place; 2) *sila-Pummerer rearrangement* occurs with sulfoxides bearing a TMS group on the α-carbon, which spontaneously rearrange to α-silyloxy sulfides, and no activating reagents are needed;[39] 3) vinyl sulfoxide substrates may undergo the *additive- and vinylogous Pummerer rearrangement*; 4) chirality transfer from enantiopure sulfoxides to the α-carbon is possible, and it constitutes the *asymmetric Pummerer rearrangement*, but this process is limited in scope.[15]

Pummerer (1909):



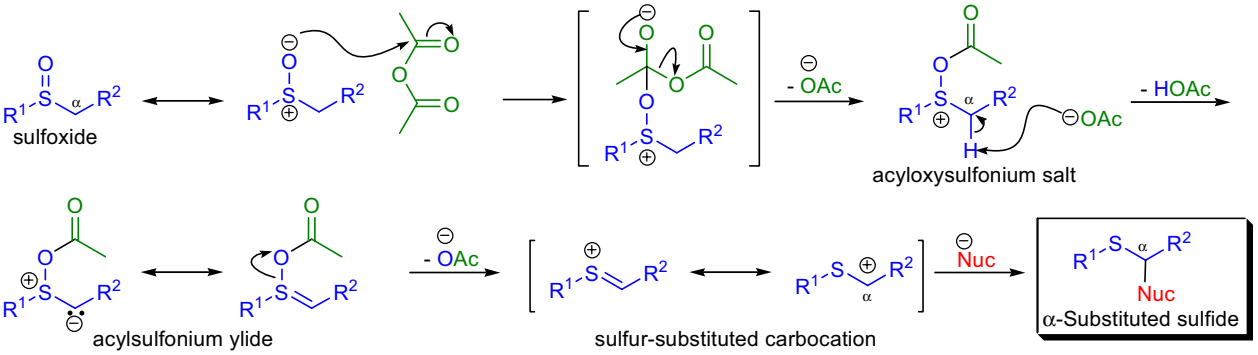
Pummerer rearrangement:



R^1 = alkyl, aryl; R^{2-3} = H, alkyl, aryl; X = O, NR; activating agent: HCl, H_2SO_4, TsOH, I_2/MeOH, Ac_2O, TFAA, *t*-BuBr, Me_3SiX, PCl_3, PCl_5, $Sn(OTf)_2$; nucleophile: H_2O, ROH, RCO_2^-; Nuc: OH, *O*-alkyl, *O*-aryl, O_2CR, F, Cl, Br, SR, NR_2; co-catalysts: AcOH, TsOH, TFAA, NaOAc

Mechanism:[9,15,21]

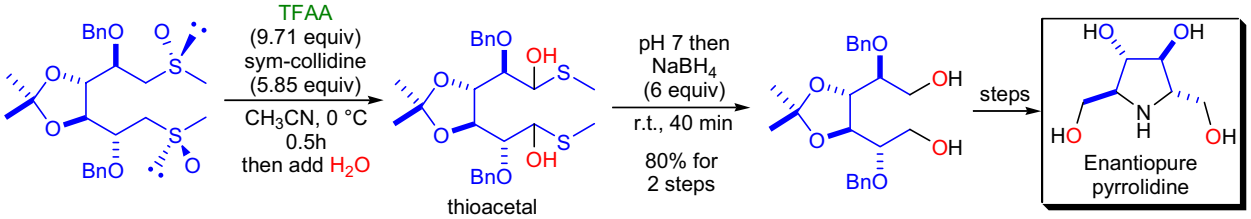
The mechanism of the *Pummerer rearrangement* consists of four steps: 1) acylation of the sulfoxide oxygen to form an acyloxysulfonium salt; 2) loss of a proton from the α-carbon to afford an acylsulfonium ylide; 3) cleavage of the sulfur-oxygen bond to give sulfur-substituted carbocation (RDS); and 4) capture of the nucleophile by the carbocation.



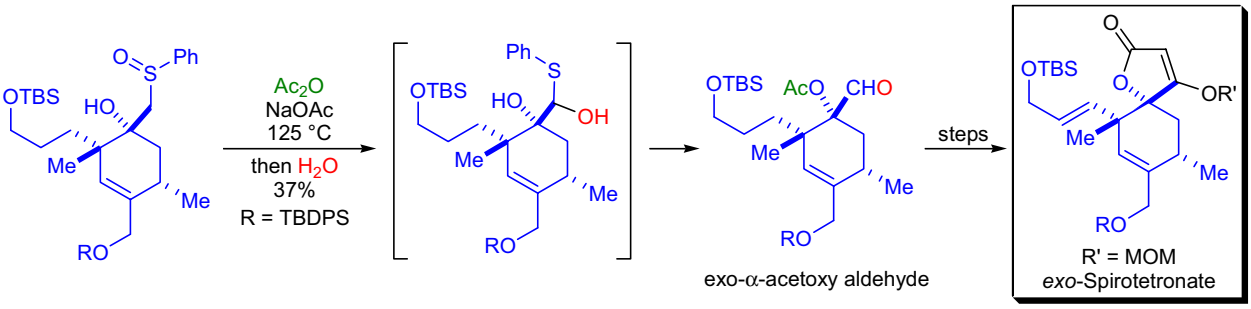
PUMMERER REARRANGEMENT

Synthetic Applications:

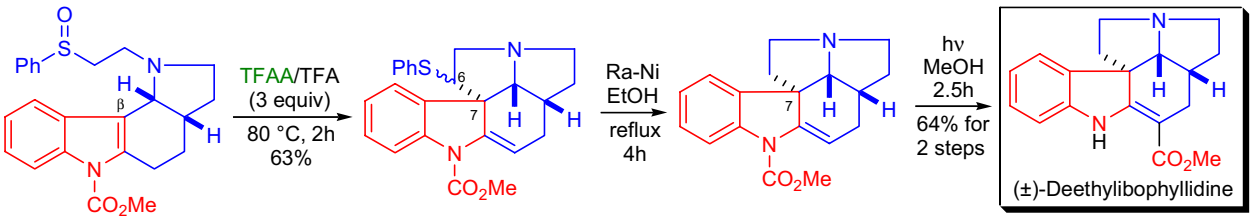
An enantioselective approach to polyhydroxylated compounds using chiral sulfoxides was developed in the laboratory of G. Solladié and was applied for the synthesis of enantiomerically pure *myo*-inositol and pyrrolidine derivatives.[40] The presence of the chiral sulfoxide directed the reduction of two carbonyl groups in one of the intermediates. In order to form the six-membered ring of *myo*-inositol, the removal of these sulfoxides under mild conditions was necessary. To this end, a one-pot *Pummerer rearrangement*-sodium borohydride reduction was performed using TFAA as the activating reagent. The initially formed thioacetal was reduced with $NaBH_4$ at pH 7 to afford the corresponding diol.



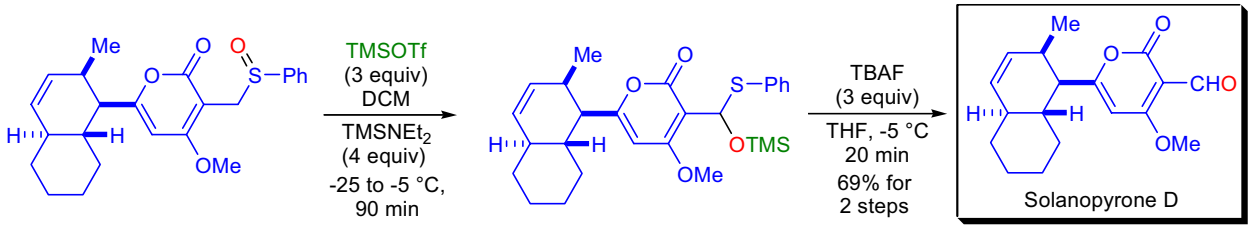
Quartromicins are complex C_2 symmetric macrocyclic natural products that have significant activity against a number of human viral targets.[41] The diastereoselective synthesis of the *endo*- and *exo*-spirotetronate subunits of the quartromicins was accomplished by W.R. Roush and co-workers. The preparation of the *exo*-α-acetoxy aldehyde involved the *Pummerer rearrangement* of a sulfoxide using acetic anhydride as the activating reagent and NaOAc as the co-catalyst. The yield of this transformation was modest and all attempts to improve its efficiency failed.



The total synthesis of (±)-deethylibophyllidine was achieved by J. Bonjoch et al. using a tandem *Pummerer rearrangement/thionium ion cyclization* to generate the quaternary spiro center.[42] The sulfoxide was exposed to an equimolar mixture of TFA/TFAA and heated for 2h to form the quaternary stereocenter at C7 with the desired stereochemistry, but at C6 a mixture of epimers were formed. Reductive desulfurization with Raney-Ni followed by photochemical rearrangement afforded the natural product.



The *Pummerer rearrangement* was utilized to introduce the formyl group into the pyrone ring during H. Hagiwara's total synthesis of solanopyrone D.[43] Extensive screening revealed that the best way to activate the sulfoxide was to use the combination of TMSOTf as the *O*-silylating agent and $TMSNEt_2$ as a mild base. The addition of TBAF in THF afforded the formylated pyrone ring.



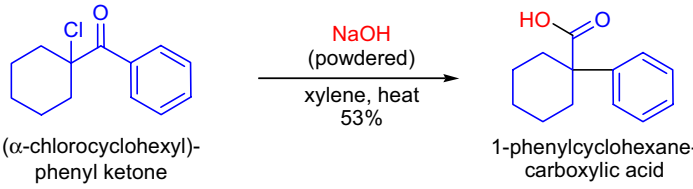
QUASI-FAVORSKII REARRANGEMENT

(References are on page 660)

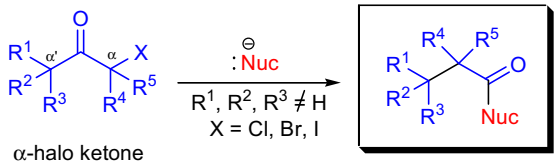
Importance:

[*Seminal Publications*[1-3]*; Review*[4]]

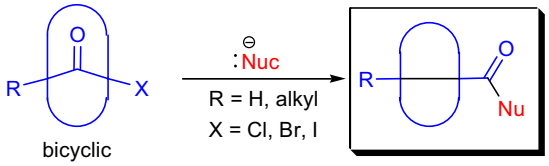
In 1939, B. Tchoubar et al. reported that upon treatment with powdered sodium hydroxide in ether, α-chlorocyclohexyl phenyl ketone gave a 40% yield of 1-phenylcyclohexanecarboxylic acid *via* a *semibenzilic type rearrangement*.[1] In 1952, C.L. Stevens and E. Farkas obtained a higher yield when they repeated the same reaction in refluxing xylene. They predicted that the stereochemistry of the rearrangement would involve an inversion at the halogen-bearing carbon.[3] Upon treatment with certain nucleophiles, α-halo ketones with no hydrogen atom at the α'-position or bicyclic α-halo ketones with an α'-hydrogen atom at the bridgehead carbon atom undergo a skeletal rearrangement known as the *quasi-Favorskii rearrangement*. The product of the rearrangement is a carboxylic acid or a carboxylic acid derivative, depending on the nature of the nucleophile. Probably the most well-known example of the *quasi-Favorksii rearrangement* is the key step in the synthesis of cubane by P.E. Eaton et al.[5,6] In addition to nucleophiles, the rearrangement can be initiated by the ionization of the α-halo ketones upon treatment with salts of heavy metals (e.g., $AgNO_3$, $AgSBF_6$, etc.).[2,7] Substrate preparation is primarily carried out in the following three ways: 1) direct α-halogenation of substituted acyclic and cyclic ketones; 2) *Robinson annulation* of cyclic α-halo ketones with methyl vinyl ketone (MVK);[8,9] and 3) *[4+3] cycloaddition* of cyclic α,α'-dihalo ketones with cyclic dienes.[10,11] The analogous reaction of α-halo ketones (having at least one enolizable hydrogen atom in the α'-position) with base in the presence of a nucleophile is called the *Favorskii rearrangement*. The general features of the *quasi-Favorskii rearrangement* are: 1) acyclic and monocyclic α-halo ketones that do not have hydrogens in their α'-positions are good substrates; 2) the reaction is stereospecific (inversion at the carbon to which the halogen is attached); and 3) monocyclic and bicyclic substrates undergo ring-contraction to give the corresponding cyclic or bicyclic homologue.



(α-chlorocyclohexyl)-phenyl ketone → 1-phenylcyclohexane-carboxylic acid



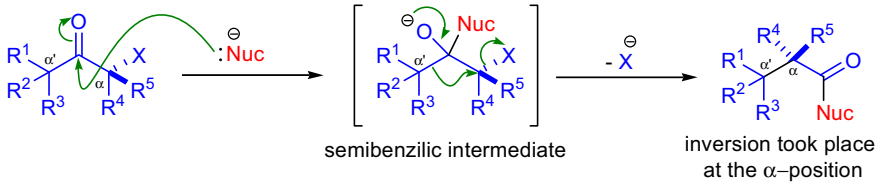
α-halo ketone (no α' hydrogen)

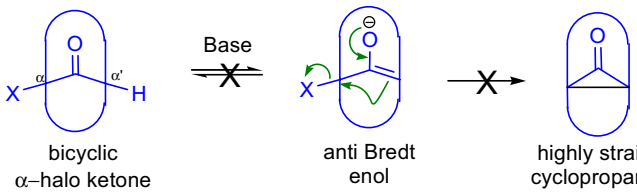


bicyclic α-halo ketone

Mechanism:[12,13,7,14,15]

The mechanism of the *quasi-Favorskii rearrangement* involves the following steps: 1) attack of the nucleophile on the carbonyl carbon atom to form a tetrahedral intermediate; 2) next, this anionic intermediate undergoes a facile *1,2-alkyl shift*, similar to the mechanism of the *benzilic acid rearrangement*, and as a result, the halogen attached to the α-carbon is displaced with the inversion of configuration. When the substrate is bicyclic and there is a hydrogen in the α'-position, enolization is not possible because the double bond of the enol would be incorporated in the bridgehead and this reaction would violate Bredt's rule. The cyclopropanone intermediate of the *Favorskii rearrangement* would be highly strained (and sterically congested) and therefore its formation is highly disfavored. (This is valid for bicyclic systems in which the *trans* double bond would be part of a ring having less than 8 carbons; however, systems with rings larger than 8 carbons could be enolized.)

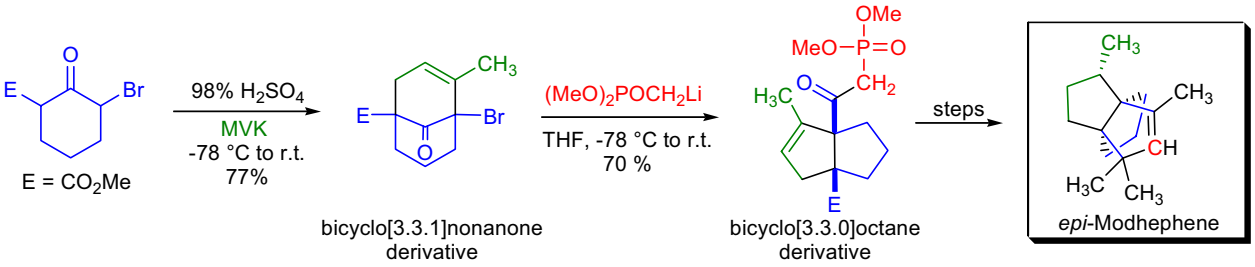




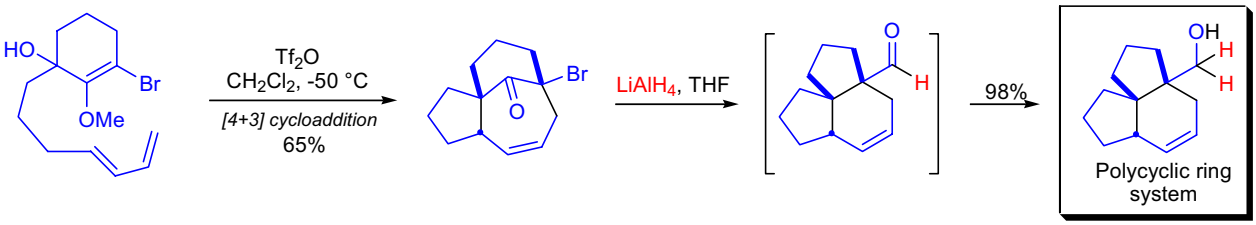
QUASI-FAVORSKII REARRANGEMENT

Synthetic Applications:

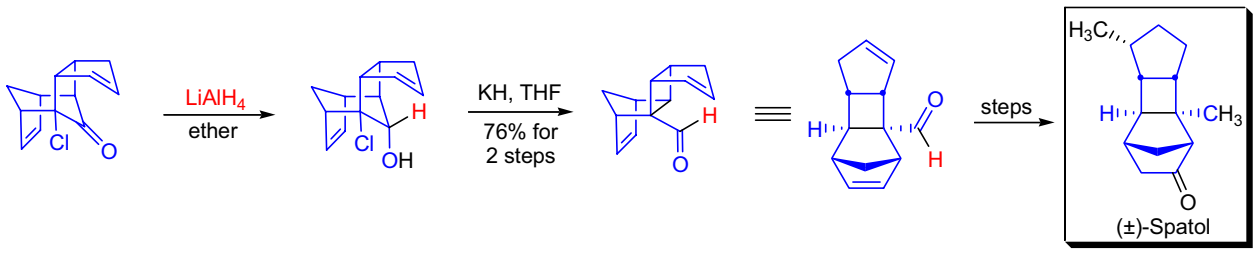
G.A. Kraus and co-workers utilized the *quasi-Favorskii rearrangement* of a bicyclic bridgehead bromide as the key step in their formal total synthesis of *epi*-modhephene.[8,9] The required bicyclo[3.3.1]nonenone bridgehead bromide precursor was prepared by a *Robinson annulation* reaction between 3-bromo-2-oxocyclohexanecarboxylate and MVK. Upon treatment with lithiated dimethyl methylphosphonate, the bicyclic bromo ketone underwent a facile *quasi-Favorskii rearrangement* to afford the key intermediate bicyclo[3.3.0]octane derivative.



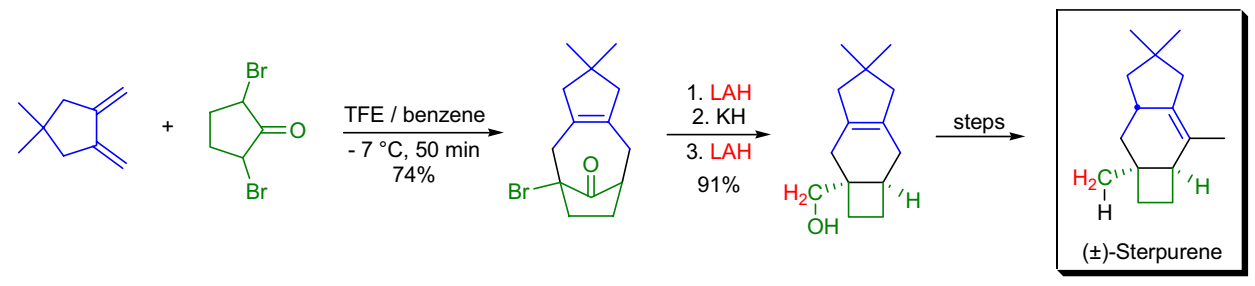
In the laboratory of M. Harmata, a novel methodology utilizing a sequential *[4+3] cycloaddition–quasi-Favorskii rearrangement* was developed for the rapid construction of polycyclic ring systems.[11] The *intramolecular [4+3] cycloaddition* of a halogenated allylic alcohol gave 65% of the expected tricyclic bridgehead α-bromo ketone precursor as a single diastereomer. Upon treating this bromo ketone with LAH in THF, a *quasi-Favorskii rearrangement* took place in nearly quantitative yield to afford a 5-6-5 fused tricyclic product.



A formal total synthesis of racemic spatol was accomplished by M. Harmata et al. using an *intermolecular [4+3] cycloaddition* of a halogenated cyclopentenyl cation with cyclopentadiene followed by a *quasi-Favorskii rearrangement* as the key steps.[16]



M. Harmata and co-workers successfully synthesized racemic sterpurene using an *intermolecular [4+3] cycloaddition* to prepare the key *quasi-Favorskii rearrangement* precursor.[17] The tricyclic bridgehead α-bromo ketone was first treated with LAH at 0 °C to get the corresponding secondary alcohol. Treatment of this alcohol with KH triggered the expected ring-contraction to afford the 5-6-4 fused tricyclic aldehyde, which was then reduced to the primary alcohol with LAH.



RAMBERG-BÄCKLUND REARRANGEMENT

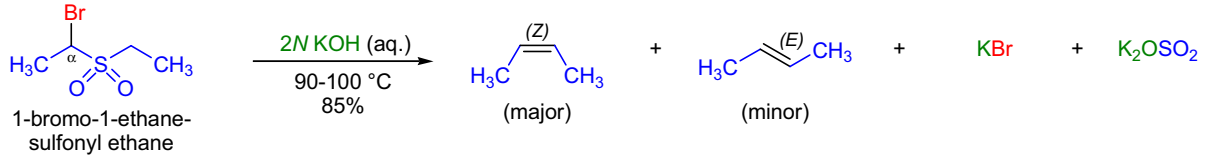
(References are on page 660)

Importance:

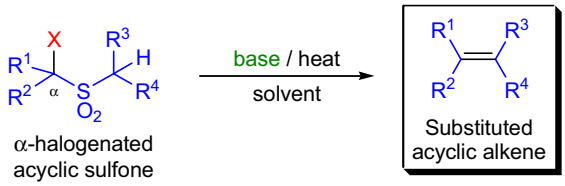
[*Seminal Publications*[1]; *Reviews*[2-9]; *Modifications & Improvements*[10-20]]

In 1940, L. Ramberg and B. Bäcklund described an interesting reaction in which 1-bromo-1-ethanesulfonyl ethane (an α-bromo sulfone) was predominantly converted to (*Z*)-2-butene when treated with a boiling aqueous KOH solution.[1] There was no work published on this transformation until the early 1950s, when F.G. Bordwell and co-workers conducted a thorough kinetic investigation and elucidated the reaction mechanism.[21,22] The base-induced rearrangement of α-halogenated sulfones *via* episulfone intermediates to produce alkenes is referred to as the *Ramberg-Bäcklund rearrangement*. The general features of the reaction are:[5,6,8] 1) the precursor halogenated sulfones can be easily prepared by the halogenation of the corresponding sulfones and the sulfones themselves are usually prepared by the oxidation of sulfides; 2) the reaction is well-suited for the preparation of 1,1- or 1,2-di, tri-, and tetrasubstituted alkenes; 3) the position of the newly formed double bond is unambiguous and under the reaction conditions no double bond migration takes place; 4) both acyclic and cyclic substrates can be used and the reaction is especially useful for the preparation of strained cycloalkenes *via* ring-contraction; 5) the stereochemical outcome of the rearrangement depends on both the base and the solvent, but the temperature is not decisive; 6) aqueous base (e.g., KOH) favors the formation of (Z)-alkenes but strong bases in aprotic solvents (e.g., KO*t*-Bu/DMSO) predominantly give rise to (*E*)-alkenes; and 7) base-sensitive functional groups need to be protected.

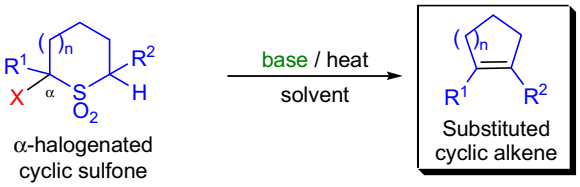
Ramberg and Bäcklund (1940):



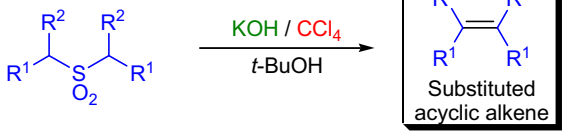
Rearrangement in acyclic systems:



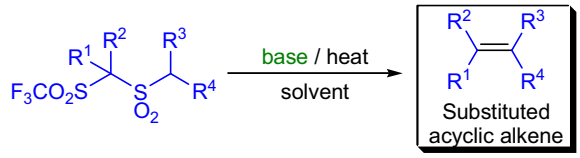
Rearrangement in cyclic systems (ring-contraction):



Meyers modification (*in situ* halogenation):



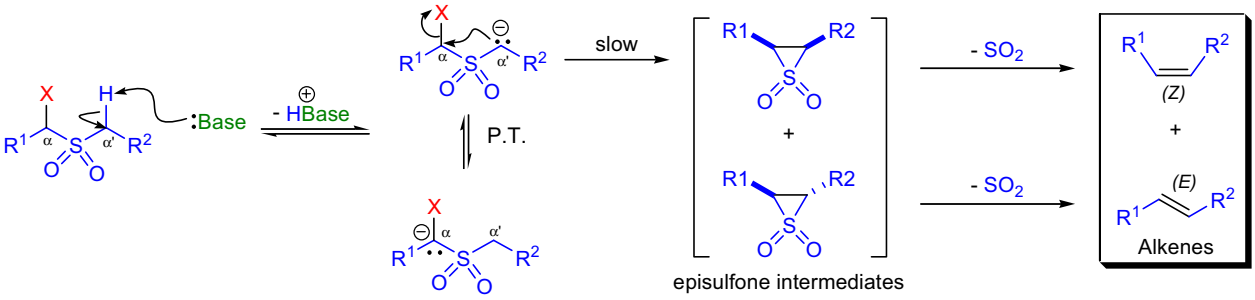
Hendrickson modification (triflinate leaving group):



R[1-4] = H, alkyl, aryl, heteroaryl, CO_2R; n = 0-12; X = Cl, Br, I, OTs; base: KOH, NaOH, KO*t*-Bu; solvent: THF, *t*-BuOH/DCM

Mechanism:[21,22,3,23-31]

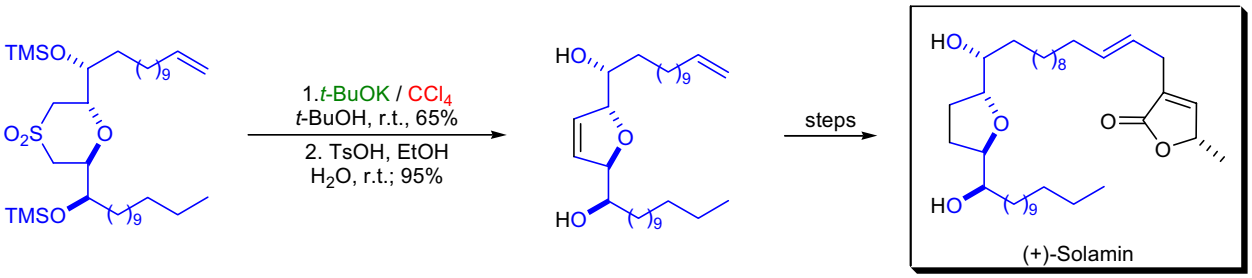
The mechanistic details of the rearrangement were investigated in detail predominantly by the research groups of F.G. Bordwell and L.A. Paquette who established that the transformation consists of three distinct steps:[3] 1) the first step of the process is the deprotonation of the sulfone at the α- or α'-position, which undergoes rapid equilibration; 2) only the carbanion at the α'-position results in an intramolecular displacement reaction (S_Ni attack) on the carbon bearing the X group to give the reactive intermediate episulfones (thiirane 1,1-dioxides), which are generally formed as mixtures of *cis*- and *trans* stereoisomers (slow step); and 3) the final step is the loss of SO_2 either thermally or under base catalysis to give a mixture of alkene stereoisomers. The overall stereochemical outcome of the reaction is determined in the second step.



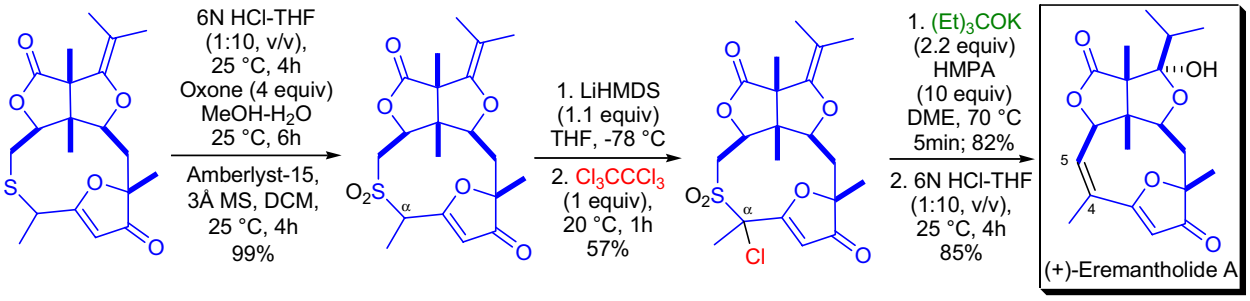
RAMBERG-BÄCKLUND REARRANGEMENT

Synthetic Applications:

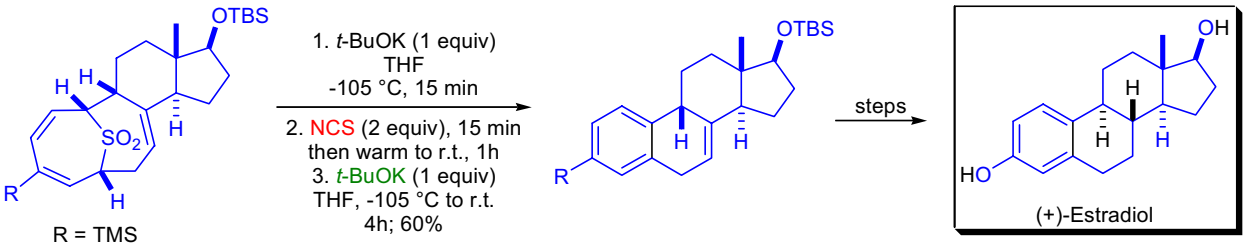
A concise convergent synthetic strategy was developed by B.M. Trost and co-workers for the synthesis of acetogenins, a class of compounds with a wide breadth of biological activity.[32] The authors chose (+)-solamin as the target to demonstrate the utility of their strategy, which relied on the *Meyers modification of the Ramberg-Bäcklund rearrangement* as the key step. As the chlorination of the sulfone failed, the *in situ* chlorination-rearrangement was attempted and led to the successful conversion of the oxasulfone precursor to the desired 2,5-dihydrofuran core.



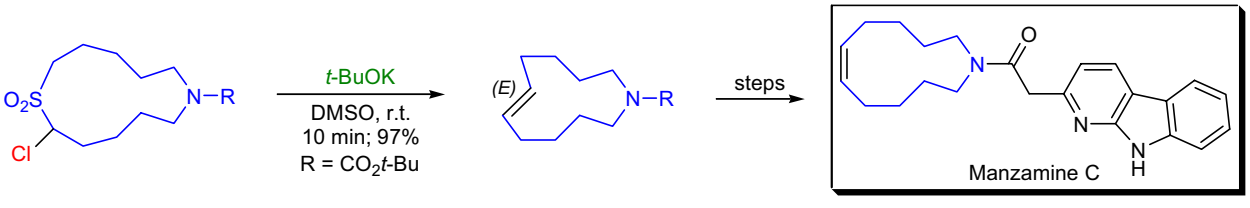
In the laboratory of R.K. Boeckman, the total synthesis of (+)-eremantholide A was accomplished using the *Ramberg-Bäcklund rearrangement* for the crucial ring-contraction step at the end of the synthetic sequence.[33] The nine-membered macrocyclic core of the natural product is highly strained since the C4-C5 double bond is twisted 88° out of the plane of the 3(2*H*)-furanone ring. The ring-contraction precursor 10-membered macrocyclic sulfide was sequentially treated with 6N HCl, Oxone and Amberlyst 15 resin to afford the corresponding sulfone. The chlorination of this sulfone took place exclusively at the more substituted α-position, and upon treatment with a strong base, the rearrangement yielded the desired product in good yield.



A novel benzannulation strategy featuring a [6+4] cycloaddition followed by *Ramberg-Bäcklund rearrangement* was employed for the total synthesis of (+)-estradiol by J.H. Rigby et al.[34] The higher-order cycloaddition took place between a seven-membered TMS-substituted η^6-thiepin 1,1-dioxide $(CO)_3Cr$-complex and a highly substituted diene to afford directly the bicyclic sulfone rearrangement precursor. The ring-contraction was induced by the sequential treatment with *t*-BuOK and *N*-chlorosuccinimide at very low temperatures followed by the addition of another equivalent of the base.



The *Ramberg-Bäcklund rearrangement* was the key step in the total synthesis of the marine alkaloid manzamine C by D.I. MaGee and E.J. Beck.[35] The azacycloundecene ring was stereoselectively formed by exposing the α-chloro sulfone to a strong base. The use of weaker bases either resulted in no reaction or gave rise to mixtures of (*E*)- and (*Z*)-alkenes.



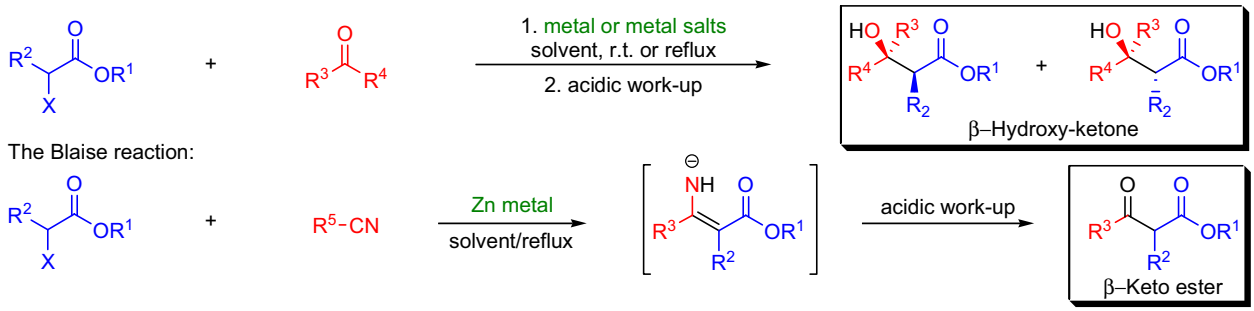
REFORMATSKY REACTION

(References are on page 661)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-19]; *Modifications & Improvements*[20-37]; *Theoretical Studies*[38-40]]

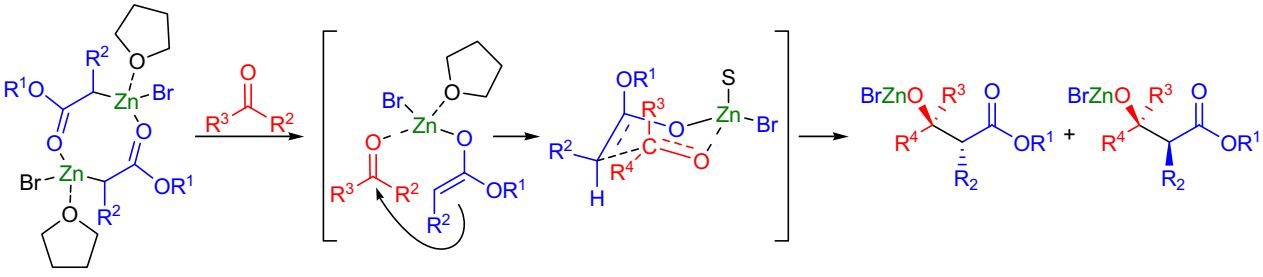
In 1887, S. Reformatsky, reported that in the presence of zinc metal, iodoacetic acid ethyl ester reacted with acetone to yield 3-hydroxy-3-methylbutyric acid ethyl ester.[1] Since this initial report, the classical *Reformatsky reaction* was defined as the zinc-induced reaction between an α-halo ester and an aldehyde or ketone. The scope of the reaction, however, extends far beyond this original definition, and today, the metal-induced reaction of α-carbonyl halides with a wide range of electrophiles are referred to as the *Reformatsky reaction*. The reaction is a two stage process: first the activated zinc metal inserts into the carbon-halogen bond, and this is followed by the reaction of the zinc enolate (Reformatsky reagent) with the carbonyl compound in an *aldol reaction*. The general features of the *Reformatsky reaction* are:[5,7,9] 1) the reaction is most commonly carried out in a single step by addition of the α-halo ester and the carbonyl compound to the suspension of the activated zinc, but preforming the organozinc reagent prior to the addition of the electrophile is also possible; 2) most often ether solvents are used such as diethyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane, but mixtures of these solvents with aromatic hydrocarbons and more polar solvents such as acetonitrile, dimethyl formamide, dimethyl sulphoxide, and hexamethylphosphoric triamide are also used; 3) organozinc reagents can be formed from 2-bromoalkanoates, α-bromo ketones, alkyl 2-bromomethyl-2-alkenoates,[41] and alkyl 4-bromo-2-alkenoates[42]; and 4) in addition to aldehydes and ketones, *Reformatsky reagents* also react with esters,[43] acid chlorides,[44] epoxides,[43] nitrones,[45] aziridines,[46] imines,[47] and nitriles[48] (*Blaise reaction*). The scope of the *Reformatsky reaction* was considerably extended by the development zinc-activation procedures. Activated zinc metal can be formed in two ways:[7] 1) by removal of the deactivating zinc oxide layer from the metal surface employing reagents such as iodine, 1,2-dibromoethane, copper(I) halides, mercuric halides or by using zinc-copper or zinc-silver couple;[2,5,7,9,12] and 2) by reduction of zinc halides in solution by various reducing agents such as potassium[49] (*Rieke zinc*), sodium-[50] or lithium naphthalide[51] and potassium-graphite laminate[52] (C_8K) to form finely dispersed zinc metal. Metals other than zinc were also used including lithium,[22] magnesium,[20] cadmium,[28] barium,[37] indium,[21,34] germanium,[36] nickel,[31] cobalt,[35] and cerium.[24] A major breakthrough in the *Reformatsky reaction* was the application of metal salts with favorable reduction potentials, the most important ones being samarium(II) iodide,[23,32,33] chromium(II) chloride,[29] and titanium(II) chloride.[25] These reactions often can be carried out under mild conditions and afford the products with high stereoselectivity. In addition to these metal salts, cerium(III) halides,[30] disodium telluride,[30] trialkylantimony/iodine,[26,27] and diethylaluminum chloride[26,27] can also be employed. The main advantages of the *Reformatsky reaction* over the classical *aldol reaction* are the following: 1) the reaction succeeds even with highly substituted ketone substrates; 2) the ester enolate can be formed in the presence of highly enolizable aldehyde and ketone functionalities; and 3) the reaction is uniquely suited for intramolecular reactions.



X = Cl, Br, I; R^1 = alkyl; R^2 = H, alkyl, aryl; R^3, R^4 = H, alkyl, aryl; R^5 = alkyl, aryl; solvent: Et_2O, THF, 1,4-dioxane, DME, benzene, toluene, MeCN, DMF, DMSO; metal: Zn, Mg, Cd, Ba, In, Ge, Co, Ni, Ce; metal salt: SmI_2, $CrCl_2$, $TiCl_2$, CeX_3, Na_2Te, R_3SnLi, R_3Sb/I_2, Et_2AlCl;

Mechanism:[53-57]

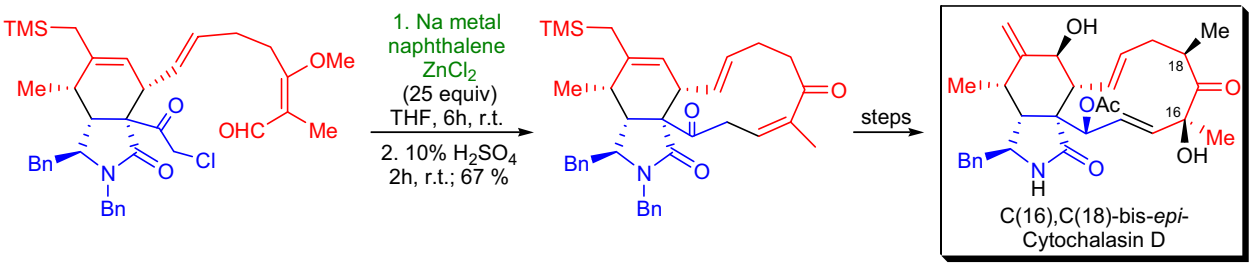
Spectroscopic[53,56] and crystallographic[54,55] studies of Reformatsky reagents derived from α-halo esters showed that the enolate is present in the *C*-enolate form and in ether solvents they form dimers. Enolates derived from α-halo ketones prefer the *O*-metal enolate form.[57] It is assumed, based on theoretical calculation,[38] that the zinc enolate dimers are dissociated by the action of the carbonyl compound and converted to the corresponding *O*-zinc enolates. Subsequently, the reaction goes through six-membered chairlike transition state.



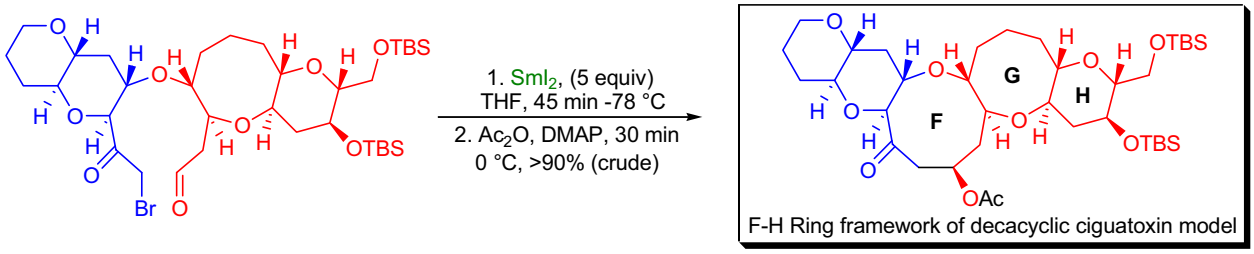
REFORMATSKY REACTION

Synthetic Applications:

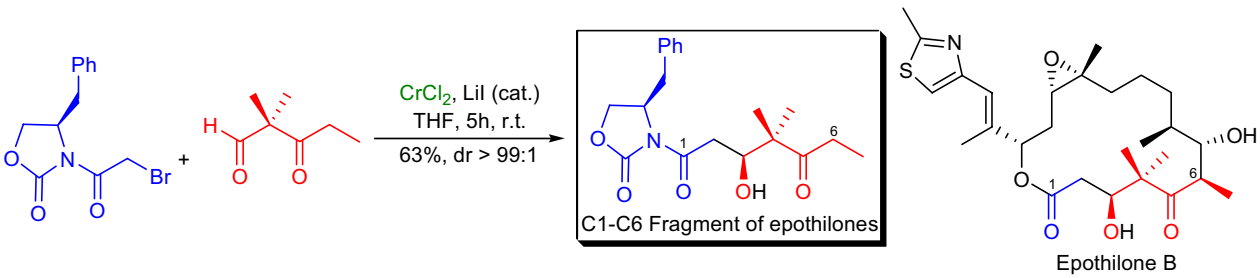
Cytochalasins are macrocyclic natural products possessing a broad range of biological activity. During the synthesis of C16, C18-bis-*epi*-cytochalasin D, E. Vedejs and co-workers utilized the *Reformatsky reaction* to close the twelve-membered macrocyclic ring.[58] The reaction was induced by finely dispersed zinc metal, which was formed by the reduction of $ZnCl_2$ by sodium naphthalide. The cyclization was carried out at room temperature by the slow addition of the substrate to the above metal suspension. To effect full elimination of the hydroxyl group and hydrolyze the methyl enol ether subunit, the product was treated with 10% H_2SO_4 upon work-up. Subsequent steps led to the formation of C(16),C(18)-bis-*epi*-cytochalasin D, the structure of which was proven by spectroscopic methods and X-ray crystallography.



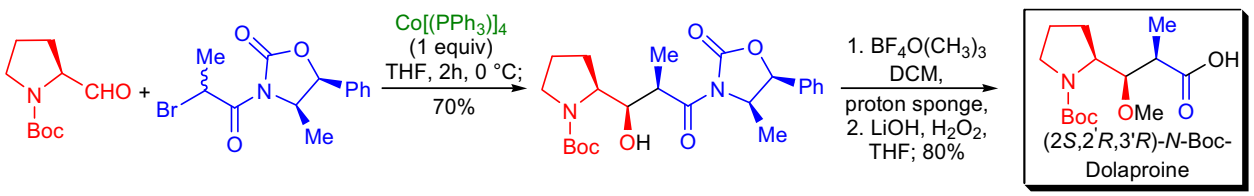
Ciguatoxin and its congeners are naturally occurring polycyclic ethers, which exhibit high affinity binding to voltage-sensitive sodium channels (VSSC). The scarcity of these compounds from natural sources and their structural complexity necessitated the construction of more accessible model systems in order to investigate their interaction with VSSC and conduct structure-activity relationship studies. In the laboratory of M Sakasi, a highly convergent synthesis of the decacyclic ciguatoxin model containing the F-M ring framework was accomplished.[59] To construct the fused oxononane ring system, a SmI_2-mediated intramolecular *Reformatsky reaction* was utilized. The reaction was carried out at -78 °C in THF to give the desired oxacyclic ring with high yield and as a single diastereomer. The resulting hydroxyl group was protected *in situ* as an acetate ester.



L. Wessjohn and co-workers successfully applied the $CrCl_2$-mediated *Reformatsky reaction* for the synthesis of C1-C6 fragment of epothilones.[60] In their approach, they utilized the Evans (*R*)-4-benzyl-oxazolidinone chiral auxiliary to control the absolute stereochemistry. The chromium-*Reformatsky reaction* between the (R)-4-benzyl-3-(2-bromoacetyl)-oxazolidinone and 2,2-dimethyl-3-oxo-pentanal occurred with complete chemoselection providing the product with 63% yield and as a single diastereomer.



G.R. Pettit and co-workers used a novel *tetrakis*(triphenylphosphine)cobalt(0)-promoted *Reformatsky reaction* for the synthesis of a dolastatin 10 unit, dolaproine in a Boc-protected form.[61]



REGITZ DIAZO TRANSFER

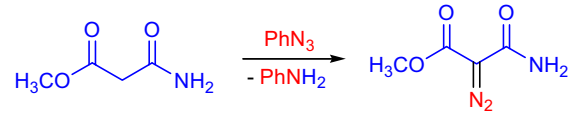
(References are on page 662)

Importance:

[*Seminal Publications*[1-6]; *Reviews*[7-13]; *Modifications & Improvements*[14-32]]

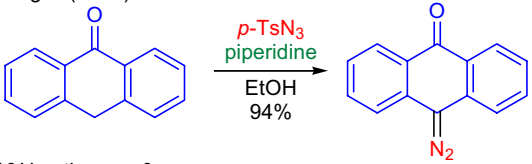
In 1910, O. Dimroth reported that the treatment of malonamic acid methyl ester with phenyl azide yielded the corresponding 2-diazomalonamic acid methyl ester.[1] This reaction remained largely unnoticed for more than fifty years until 1964, when M. Regitz et al. investigated the reaction of arylsulfonyl azides with 1,3-diketones to afford α-diazo-β-dicarbonyl compounds.[2] The transfer of a diazo group to active methylene compounds using alkyl- or arylsulfonyl azides is known as the *Regitz diazo transfer*. The general features of the transformation are: 1) both cyclic and acyclic 1,3-diketones and β-keto esters undergo the diazo transfer in the presence of weak bases such as triethylamine, diethylamine, or piperidine, but if the acidity of the methylene group is not sufficient, the use of stronger bases (e.g., NaOEt, KOH) becomes necessary; 2) the azide reagent most often is an arylsulfonyl azide such as *p*-toluenesulfonyl azide, and these reagents can be easily prepared from the corresponding arylsulfonyl halides *via halogen-azide exchange*; 3) simple cyclic and acyclic ketones usually do not react directly with sulfonyl azides, so they need to be activated by formylation (*Claisen reaction*), and the resulting α-formyl ketone is treated with the sulfonyl azide in the presence of a base to give the corresponding α-diazo ketones (*deformylative diazo transfer*);[15] 4) when the substrate is base-sensitive, instead of formylation, trifluoroacetylation can be used, which improves the yield of the diazo ketone considerably;[19] and 5) the side product of the reaction is a sulfonamide which in some cases is fairly difficult to remove from the reaction mixture (especially *p*-$TsNH_2$), so several water-soluble and lipophilic analogues have been developed.[14] The product α-diazo carbonyl compounds are versatile intermediates and can be used in the following applications:[19] 1) *Wolff rearrangement* of α-diazo ketones to give ketenes and products derived from ketenes; and 2) transition metal catalyzed C-H, N-H, O-H insertion reactions and cyclopropanations.

Dimroth (1910):



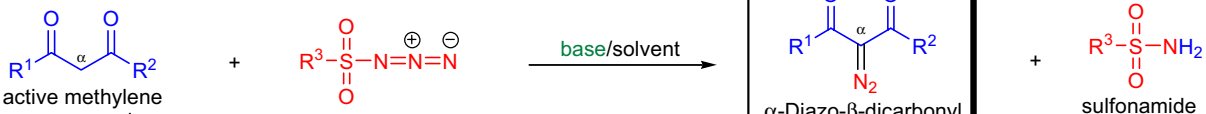
malonamic acid methyl ester → 2-diazomalonamic acid methyl ester

Regitz (1964):



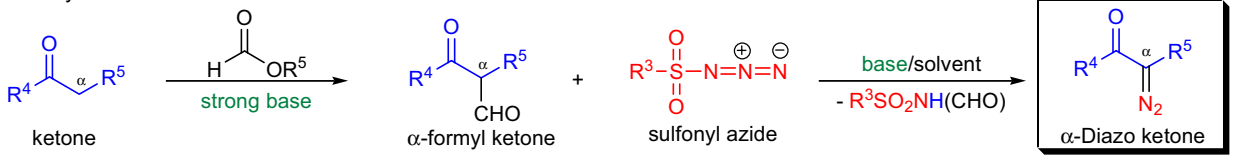
10*H*-anthracen-9-one → 10-diazo-10*H*-anthracen-9-one

Regitz diazo transfer:



active methylene compound + sulfonyl azide → α-Diazo-β-dicarbonyl compound + sulfonamide

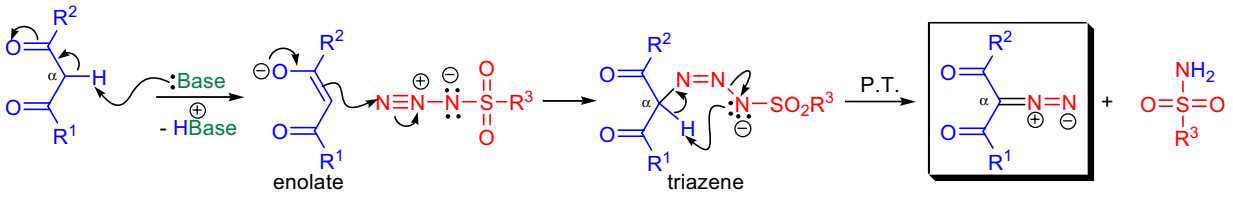
Deformylative diazo transfer:



ketone → α-formyl ketone; + sulfonyl azide → α-Diazo ketone

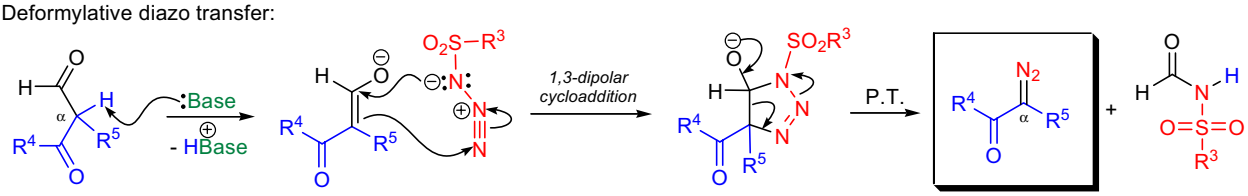
R^{1-2} = aryl, alkyl, *O*-alkyl, *O*-aryl, NH_2, NR_2; R^3 = Me, *p*-tolyl, *p*-CO_2H-phenyl; R^4 = alkyl, aryl; R^5 = H, alkyl, aryl; base: piperidine, NEt_3, $HNEt_2$, KOEt, KOH; solvent: MeOH, EtOH, EtOH-H_2O, Et_2O, CH_2Cl_2, $CHCl_3$, acetonitrile

Mechanism:[7,9,33]



enolate → triazene

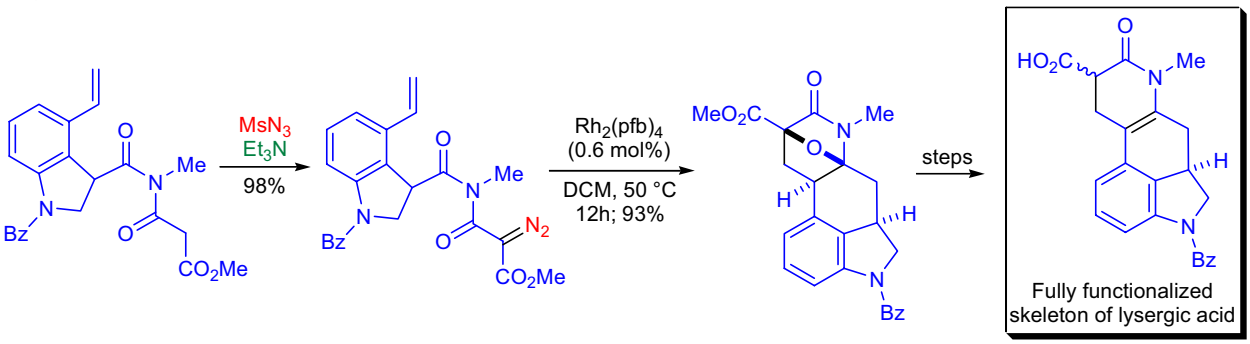
Deformylative diazo transfer:



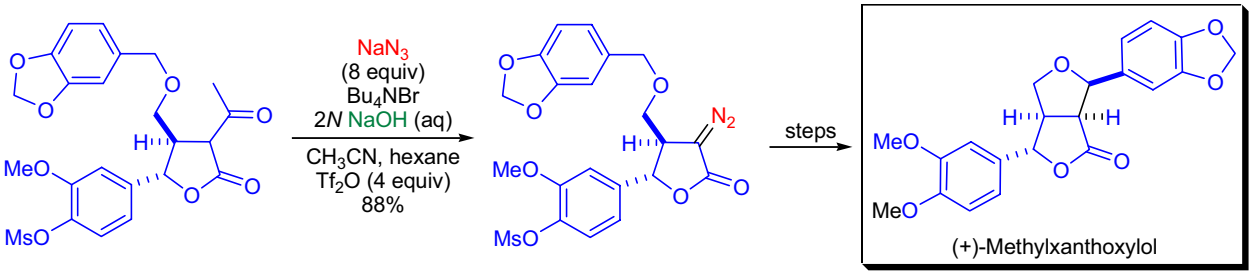
REGITZ DIAZO TRANSFER

Synthetic Applications:

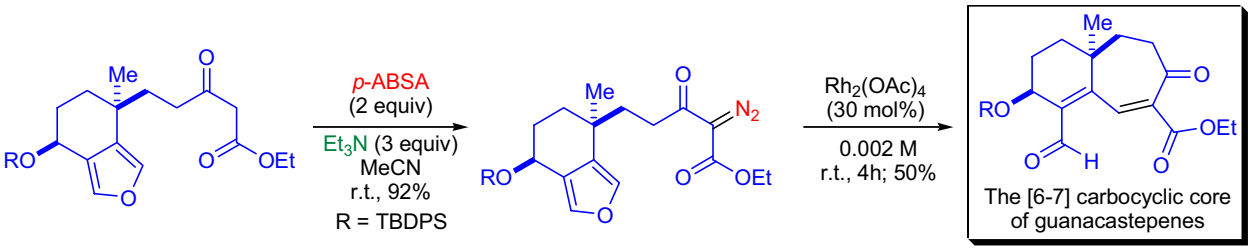
In the laboratory of A. Padwa, a novel synthetic approach to the fully functionalized core of lysergic acid was developed utilizing an *intramolecular isomünchone cycloaddition* pathway.[34] The key cycloaddition precursor diazo imide was prepared using the standard *Regitz diazo tranfer* conditions. The diazo imide then was heated with catalytic amouts of rhodium(II)-perfluorobutyrate in dichloromethane to afford the desired cycloadduct as a single diastereomer and in excellent yield. The only reason the authors were not able to complete the total synthesis of lysergic acid was that they could not affect the isomerization of the double bond between the two six-membered rings.



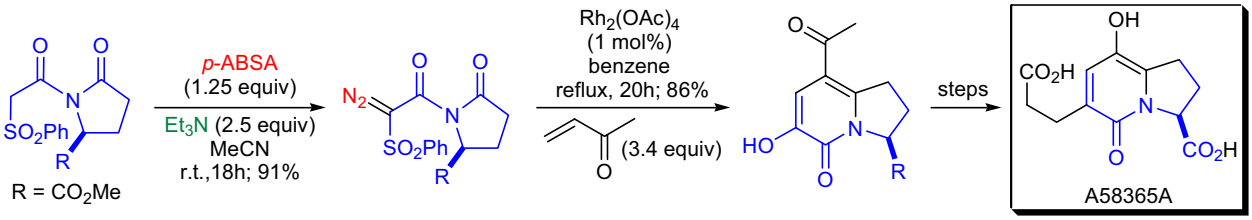
A versatile stereoselective synthesis of *endo,exo*-furofuranones was accomplished by R.C.D. Brown and co-workers.[35] One of the key steps was a Rh(II)-catalyzed C-H insertion reaction and the required diazo lactone was prepared *via* the *Regitz diazo transfer* reaction. The 2-acetyl substituted lactone substrate proved to be recalcitrant toward the *deacylative diazo transfer* under standard conditions. Eventually the authors decided to use the very reactive triflyl azide (TfN_3), which was generated *in situ* under phase-transfer conditions to afford the desired α-diazo lactone. The C-H insertion product was then converted to (+)-methylxanthoxylol.



The carbocyclic [6-7] core of guanacastepenes was prepared by. D. Trauner et al. using the intramolecular reaction between carbenoids derived from diazo carbonyl compounds and furans.[36] The required diazo carbonyl substrate was synthesized using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) as the diazo-donor component in the *Regitz diazo transfer* reaction.



N-Alkyl substituted pyridones are known to exhibit both antibacterial and antifungal activity. The pyridone acid A58365A is a potent angiotensin-converting enzyme inhibitor and it was synthesized in the laboratory of A. Padwa using a *[3+2] cycloaddition* of a phenylsulfonyl substituted isomünchone intermediate with methyl vinyl ketone.[37] The isomünchone intermediate was generated from the corresponding diazo imide which was prepared *via* a *Regitz diazo transfer* reaction.



REIMER-TIEMANN REACTION

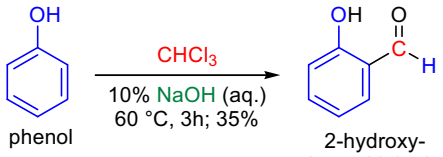
(References are on page 663)

Importance:

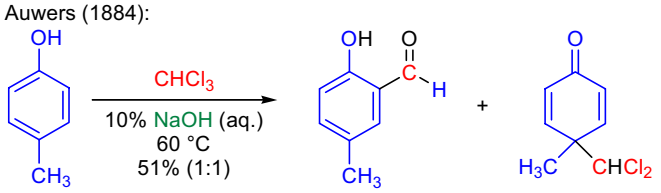
[*Seminal Publications*[1-3]*; Reviews*[4-7]*; Modifications & Improvements*[8-20]*; Theoretical Studies*[21,22]]

In 1876, K. Reimer and F. Tiemann discovered that the treatment of phenol with chloroform in 10% NaOH solution led to the formation of the corresponding *o*-hydroxy benzaldehyde as the major product.[1-3] The formylation of phenols and heterocyclic phenols using chloroform in an aqueous alkaline medium is known as the *Reimer-Tiemann reaction*. Soon after the disclosure of these seminal findings, several research groups investigated the effect of the same reaction conditions on substituted phenols and electron-rich heterocycles.[6] In the 1880s, K. Auwers reported the isolation of chlorine-containing substituted cyclohexadienones that were generated in the formylation of various alkylphenols.[23,24] These cyclohexadienones were later coined as abnormal Reimer-Tiemann products. Also in the early 1880s, G.L. Ciamician and M. Dennstedt found that under the original Reimer-Tiemann conditions the potassium salt of pyrrole underwent ring-expansion to afford 3-chloropyridine, a transformation known today as the *Ciamician-Dennstedt rearrangement* (also called as the *abnormal Reimer-Tiemann reaction*). The general features of the *Reimer-Tiemann reaction* are: 1) it is the only electrophilic aromatic substitution reaction that occurs under basic conditions in a protic solvent; 2) phenols, naphthols, alkyl-, alkoxy-, and halogenated phenols, salicylic acid derivatives, heterocyclic phenols such as hydroxyquinolines and hydroxypyrimidines, as well as pyrroles and indoles undergo formylation under the reaction conditions; 3) typically the substrate (phenol) is dissolved in 10-40% alkali hydroxide, excess chloroform is added, and the biphasic solution is vigorously stirred at elevated temperatures; 4) besides $CHCl_3$, other dichlorocarbene precursors such as chloral, trichloronitromethane, etc. can be used; 5) yields are usually moderate; 6) the regioselectivity is not high, but *ortho*-formyl products tend to predominate; 7) when the *ortho*-position is already substituted, *para*-formyl phenols are obtained; 8) in the case of pyrroles, when the *ortho* substituent is a CO_2H or CO_2R group, decarboxylation is observed and the *o*-formyl product is formed (similar findings were reported for an *o*-alkoxy phenol where the alkoxy group was eliminated to give an *o*-formyl phenol);[11,12] and 9) when the reaction is conducted in the presence of cyclodextrins, the *p*-formyl product is formed predominantly.

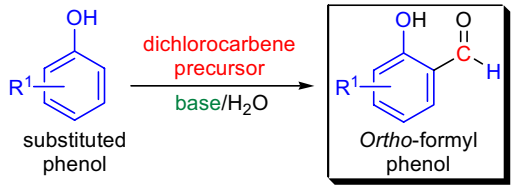
Reimer & Tiemann (1876):



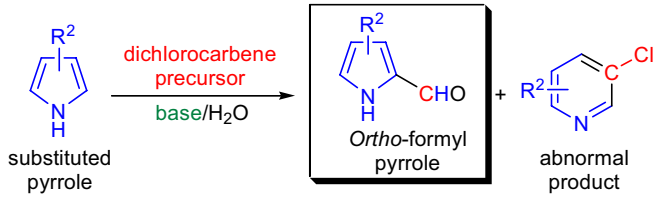
Auwers (1884):



Reimer-Tiemann reaction of phenols:



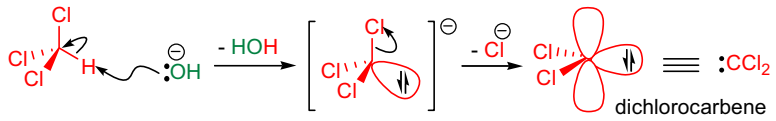
Reimer-Tiemann reaction of pyrroles:



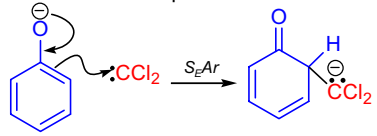
R^1 = H, alkyl, OH, *O*-alkyl, CO_2H, NO_2, Cl, Br, I; R^2 = H, alkyl; dichlorocarbene precursor: $CHCl_3$, Cl_3CCO_2H, Cl_3CCHO, Cl_3CNO_2; base: NaOH, KOH, CsOH;

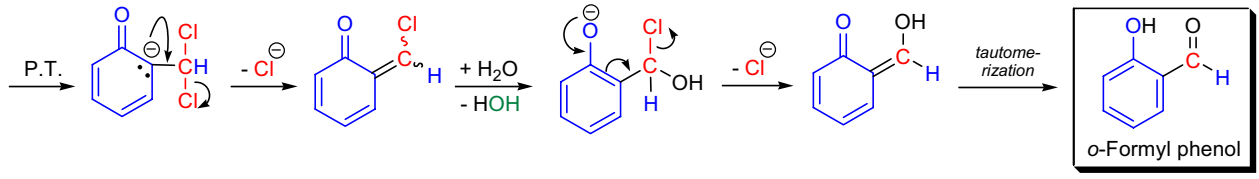
Mechanism:[4,25,6,7]

Dichlorocarbene formation:

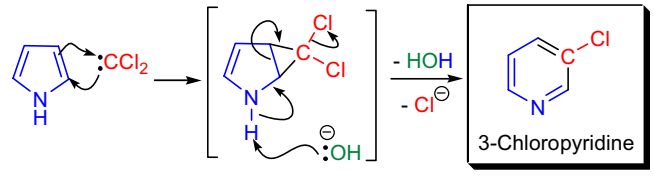


Reaction with the phenol:

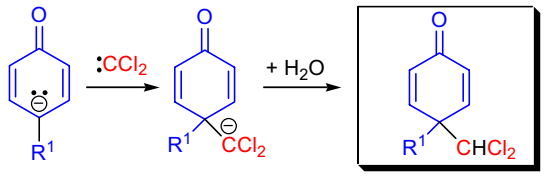




Formation of the abnormal product from pyrrole:



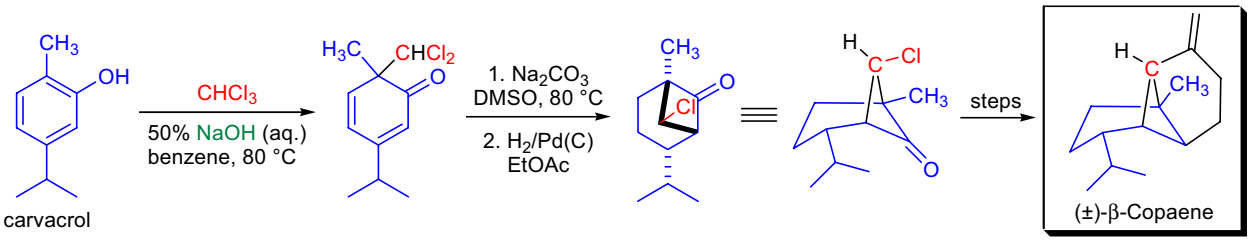
Formation of the abnormal product from alkylphenols:



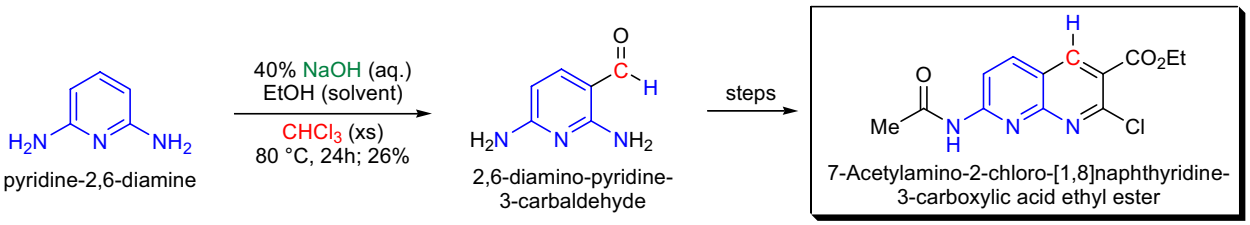
REIMER-TIEMANN REACTION

Synthetic Applications:

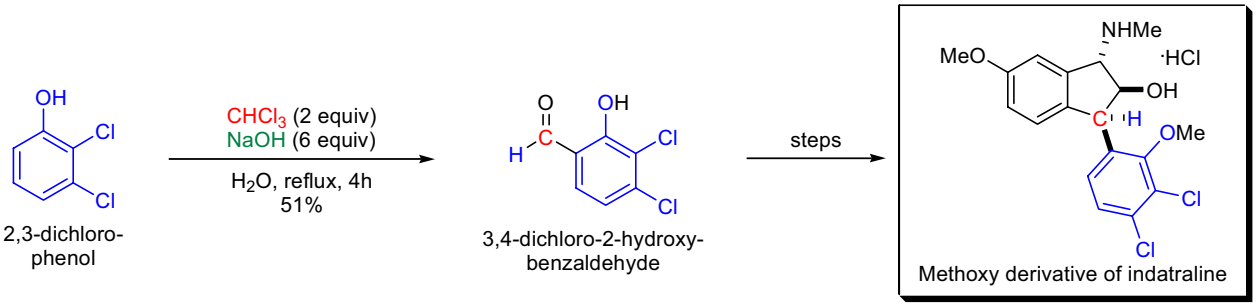
The total synthesis of the tricyclic sesquiterpene (±)-β-copaene was accomplished by E. Wenkert and co-workers. The required bicyclic starting material was prepared in three steps from carvacrol. In the first step, carvacrol was subjected to typical Reimer-Tiemann conditions. The abnormal Reimer-Tiemann product, 6-dichloromethyl-3-isopropyl-6-methyl-cyclohexa-2,4-dienone, was obtained, and upon treatment with sodium carbonate in DMSO, cyclization occurred to afford a bicyclic halo ketone. The double bonds were then hydrogenated in the presence of Pd(C) catalyst.



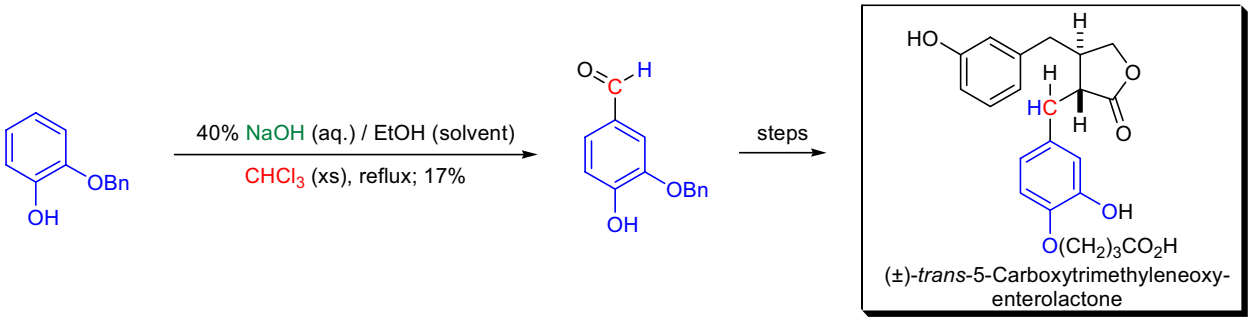
S.C. Zimmermann et al. developed an efficient synthesis of 2-amino-1,8-naphthyridines that can serve as building blocks for host-guest and self-assembling systems. The synthesis commenced with the *Reimer-Tiemann formylation* of 2,6-diaminopyridine to afford 2,6-diaminopyridine-3-carbaldehyde in modest yield. Next, the *Friedländer reaction* using activated ketones gave rise to the target compounds.



A series of indatraline derivatives containing methoxy groups were synthesized and their monoamine transporter binding site affinities were measured in the laboratory of K.C. Rice.[26] The synthetic effort began with the preparation of the required substituted benzaldehydes. The *Reimer-Tiemann formylation* of 2,3-dichlorophenol was carried out by treating the phenol with excess base and chloroform in water, and heating the mixture at reflux for several hours. Upon acidification of the reaction mixture the product was isolated as a single regioisomer.



The development of a novel hapten for radioimmunoassay of the lignan, enterolactone in plasma (serum) was accomplished by T. Mäkelä et al.[27] The essay utilized enterolactone derivatives that have a carboxylic acid moiety for the production of antiserum and tracer. The preparation of (±)-*trans*-5-carboxytrimethylenoxyenterolactone utilized the *Reimer-Tiemann reaction* for the formylation of 2-benzyloxyphenol.



RILEY SELENIUM DIOXIDE OXIDATION

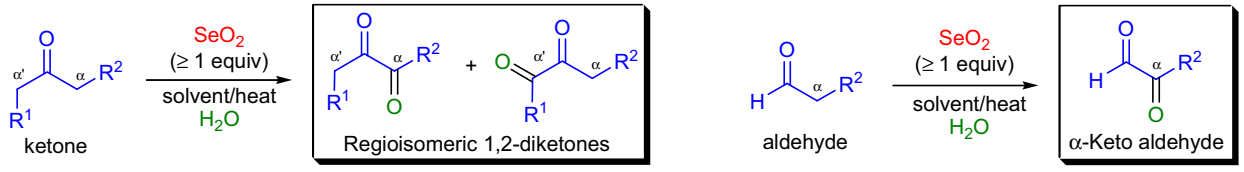
(References are on page 663)

Importance:

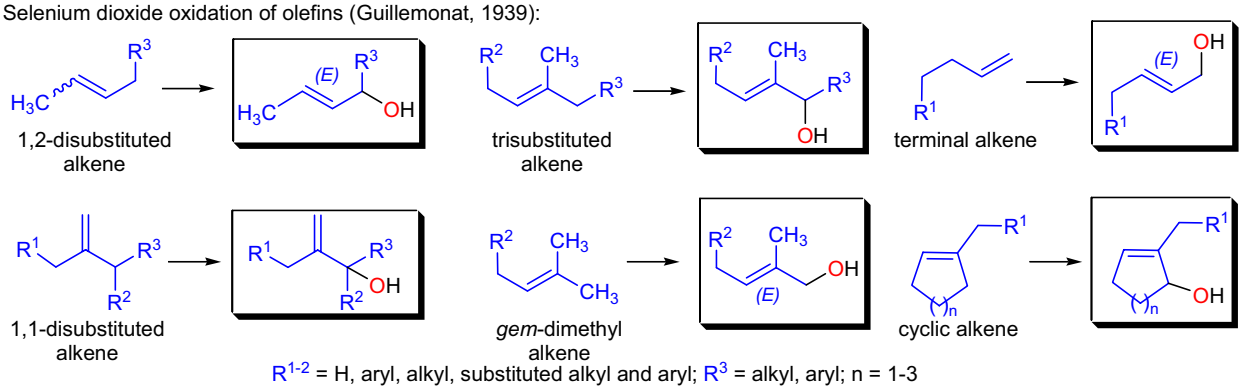
[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-22]; *Theoretical Studies*[23]]

In 1932, H.L. Riley and co-workers reported the first general synthetic use of selenium dioxide (SeO_2) as an oxidant of aldehydes and ketones.[1] The various ketones and aldehydes having an α-methylene group were converted to the corresponding 1,2-dicarbonyl compounds in moderate to good yield. Since this initial discovery, the use of SeO_2 rapidly expanded, and it was shown that besides carbonyl compounds, olefinic substrates were oxidized at the allylic position (*allylic oxidation*) to the corresponding allylic alcohols or enones.[2] The oxidation of the methylene group adjacent to a carbonyl group or the double bond of olefins (allylic or benzylic position) with selenium-dioxide is collectively referred to as the *Riley oxidation*. The general features of these transformations are: 1) ketones and aldehydes with low molecular weights are more reactive than the higher homologs; 2) ketones with available α- and α'-positions will give rise to a mixture of regioisomers; 3) the sterically less hindered α-position is oxidized faster, therefore the methyl group of methyl ketones (R^1=H) is preferentially oxidized over the other available α-position; 4) the allylic positions in acyclic olefins are oxidized at very different rates and the reactivity depends on the substitution pattern of the substrate: a) in 1,2-disubstituted alkenes the trend is: CH > CH_2 > CH_3; b) in geminally disubstituted alkenes the trend is: CH > CH_2 > CH_3; c) in trisubstituted alkenes the oxidation takes place at the more substituted end of the double bond and the trend is CH_2 > CH_3 > CH; d) terminal olefins yield primary allylic alcohols due to the allylic rearrangement of the double bond; 5) the oxidation of acyclic olefins primarily gives rise to (*E*)-allylic alcohols; 6) the oxidation of cyclic olefins occur in the ring and α to the more substituted carbon of the double bond rather than in the side chain; 7) in cyclic olefins where the double bond is unsubstituted the reactivity trend is: CH_2 > CH; 8) for bicyclic olefins in which none of the rings contain more than 7 carbon atoms, the oxidation will not take place at the bridgehead position (Bredt's rule); 9) *gem*-dimethyl olefins exclusively give rise to the (*E*)-allylic alcohols or (*E*)-α,β-unsaturated aldehydes; and 10) rearrangement may occur if the preferred allylic position is adjacent to a quaternary carbon or a cyclopropyl ring.

Selenium dioxide oxidation of ketones and aldehydes (Riley, 1932):



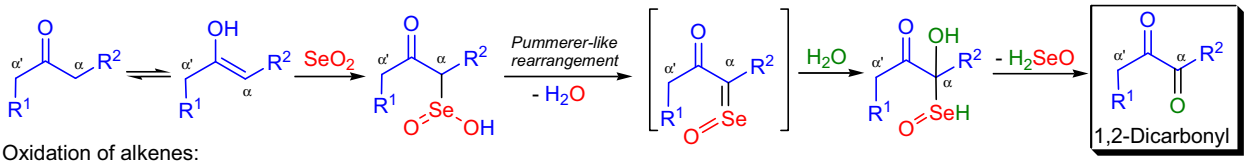
Selenium dioxide oxidation of olefins (Guillemonat, 1939):



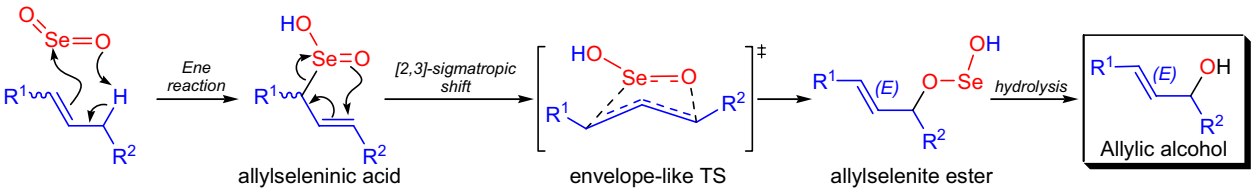
R^{1-2} = H, aryl, alkyl, substituted alkyl and aryl; R^3 = alkyl, aryl; n = 1-3

Mechanism:[24-41]

Oxidation of carbonyl compounds:



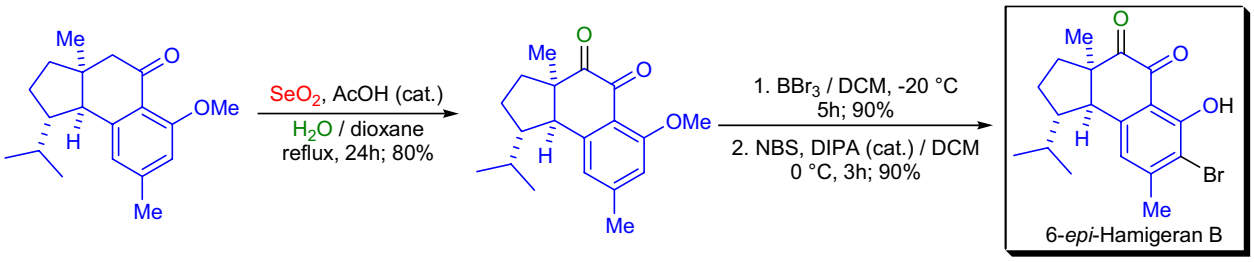
Oxidation of alkenes:



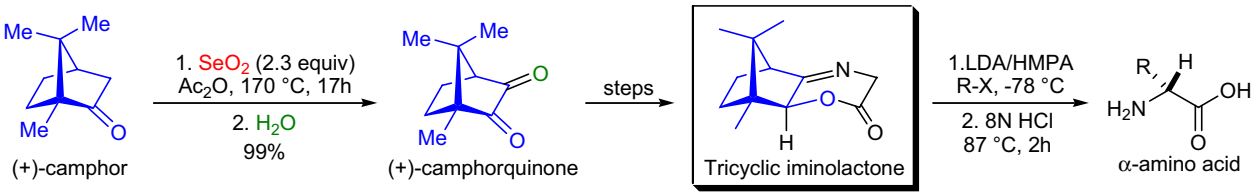
RILEY SELENIUM DIOXIDE OXIDATION

Synthetic Applications:

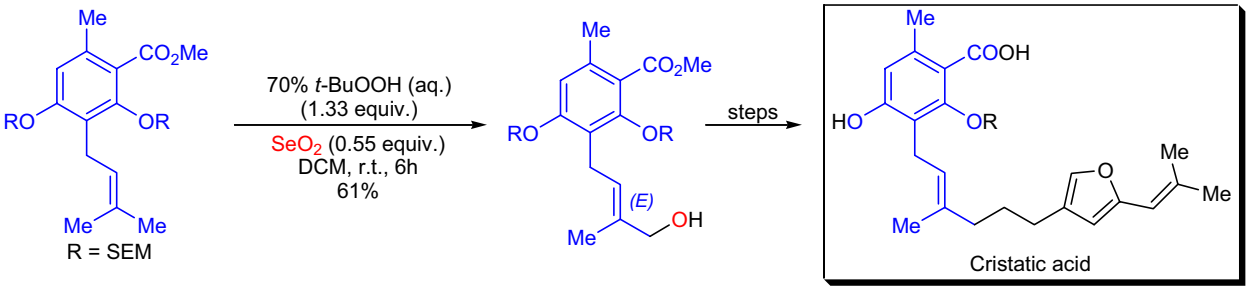
The antiviral natural product hamigeran B has a unique tricarbocyclic skeleton in which the aromatic nucleus is fused to a hydrindane framework bearing three stereogenic centers. G. Mehta and co-workers accomplished the total synthesis of 6-*epi*-hamigeran B by using an *intramolecular Heck reaction* as the key step to form the six-membered middle ring.[42] At the final stages of the synthesis, the introduction of the 1,2-diketone moiety was performed by using the *Riley oxidation*. The cyclohexanone had only one available α-position, so the oxidation proceeded cleanly and in high yield.



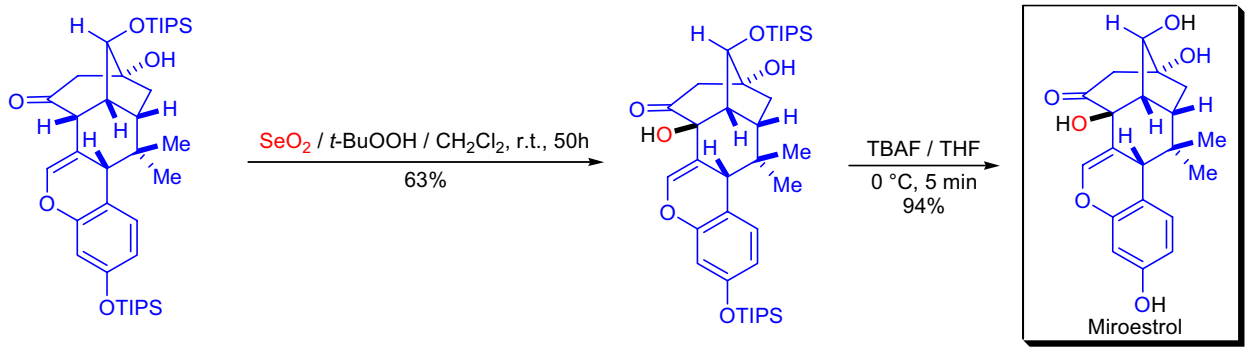
In the laboratory of T.-J. Lu, a highly stereoselective method for the asymmetric synthesis of α-amino acids was developed by the alkylation of a chiral tricyclic iminolactone derived from (+)-camphor.[43] The iminolactone can be considered a glycine equivalent. The synthesis commenced with the *Riley oxidation* of (+)-camphor to obtain the corresponding (+)-camphorquinone. Amino acids are obtained by first alkylating the α-position of the lactone with various alkyl halides and then hydrolyzing the monosubstituted products. The advantage of this technique was that the chiral auxiliary could be fully recovered without the loss of any optical activity.



The first total syntesis of cristatic acid, a potent antibiotic against Gram-positive bacteria, was reported by A. Fürstner et al.[44] The prenylated aromatic substrate (trisubstituted *gem*-dimethyl alkene) was subjected to a SeO_2-catalyzed allylic oxidation to obtain stereospecifically the (*E*)-allylic alcohol.



During the enantioselective total synthesis of miroestrol by E.J. Corey and co-workers, the introduction of a hydroxyl group was required at one of the bridgehead positions.[45] This position was α to a ketone and was also the allylic position to a double bond. The oxidation was effected by selenium dioxide/*tert*-butyl hydroperoxide at 25 °C.



RITTER REACTION

(References are on page 664)

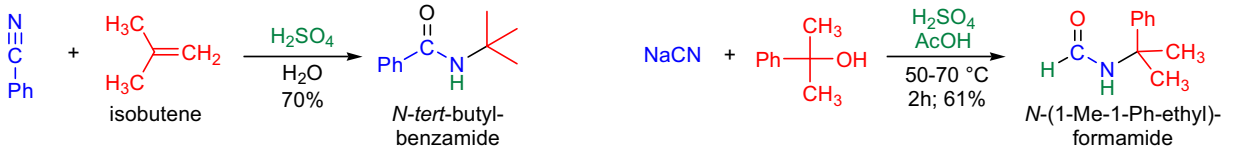
PPT topic

Importance:

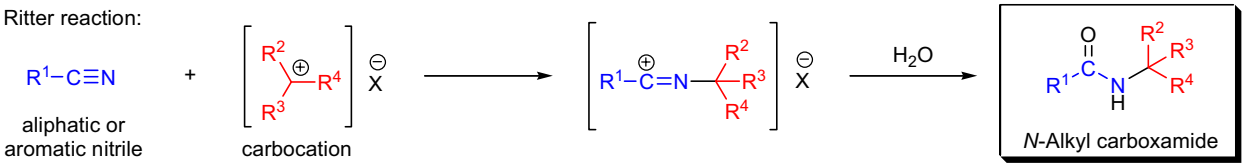
[*Seminal Publications*[1,2]; *Reviews*[3-10]; *Modifications & Improvements*[11-26]; *Theoretical Studies*[27,28]]

In 1948, J.J. Ritter and P.P. Minieri reported that treatment of nitriles with alkenes or tertiary alcohols under acidic conditions resulted in the formation of *N*-*tert*-alkylamides.[1,2] When hydrogen cyanide was used as the nitrile component, *N*-tert-alkyl formamides were obtained, which could be easily hydrolyzed with base to give the corresponding *tert*-alkylamines.[1] The formation of *N*-alkyl carboxamides from aliphatic- or aromatic nitriles and carbocations is known as the *Ritter reaction*. Since its discovery the *Ritter reaction* has enjoyed an enormous success, and it is widely used for the preparation of acyclic amides as well as heterocycles (e.g., lactams, oxazolines, dihydroisoquinolines, etc.). The general features of this transformation are:[5,8] 1) the carbocation can be generated in a variety of ways from tertiary-, secondary, or benzylic alcohols, alkenes or alkyl halides; 2) the classical reaction conditions involve the dissolution of the nitrile substrate in the mixture of acetic acid and concentrated sulfuric acid followed by the addition of the alcohol or alkene at slightly elevated temperatures (50-100 °C); 3) alcohols that are easily ionized (e.g., 2° and 3° alcohols, benzylic alcohols) give the best results; 4) 1,1-disubstituted alkenes give rise to regioisomerically pure products, but with 1,2-disubstituted alkenes a mixture of regioisomers may be formed; 5) the initially formed carbocation (which can be obtained from a large number of different functionalities)[5,8] may undergo a *Wagner-Meerwein rearrangement* to give rise to the most stable carbocation before reacting with the nitrile; 6) besides protic acids, Lewis acids (e.g., $SnCl_4$, $BF_3{\cdot}OEt_2$, $AlCl_3$, etc.) have been successfully employed in the *Ritter reaction* to generate the required carbocations; 7) the structure of the nitrile component can be varied widely and most substrates containing a cyano group will undergo the reaction, so, for example, besides aliphatic and aromatic nitriles, compounds like cyanogen and cyanamide will also react; and 8) the nitrile substrate may not contain acid-sensitive functional groups that would be destroyed under the strongly acidic reaction conditions, but modifications (*Ritter-type reactions*) that proceed under neutral conditions expanded the scope of the substrates.

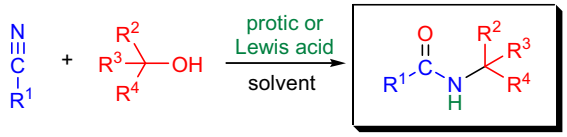
Ritter & Minieri (1948)



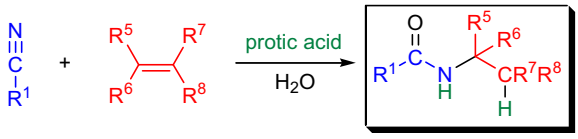
Ritter reaction:



Ritter reaction with alcohols:



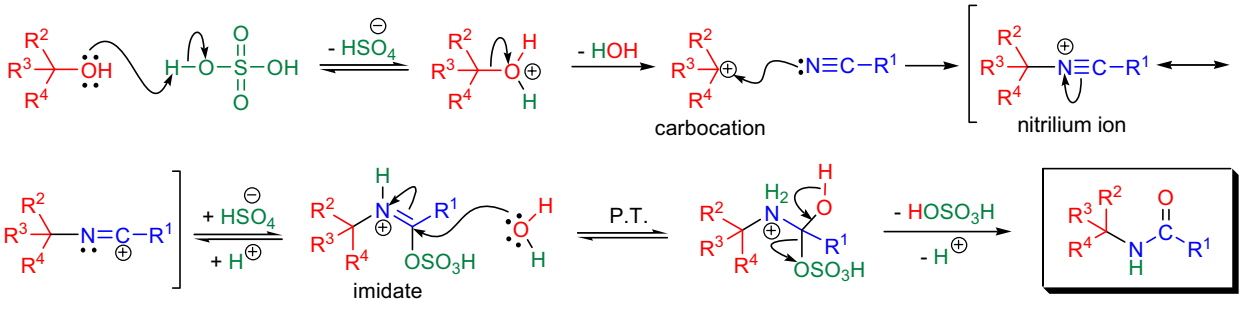
Ritter reaction with alkenes:



R^1 = H, 1°, 2° or 3° alkyl, alkenyl, alkynyl, aryl, heteroaryl; R^2 = alkyl, aryl, heteroaryl; R^{3-4} = H, alkyl, aryl; R^{5-6} = alkyl, aryl; R^{7-8} = H, alkyl, aryl; protic acid: H_2SO_4, $HClO_4$, PPA, HCO_2H, RSO_3H; Lewis acid: $AlCl_3$, $BF_3{\cdot}OEt_2$, $SbCl_5$; solvent: glacial AcOH, H_2SO_4 (conc.), Ac_2O, $CHCl_3$, CH_2Cl_2, *n*-Bu_2O, $PhNO_2$

Mechanism:[29-40]

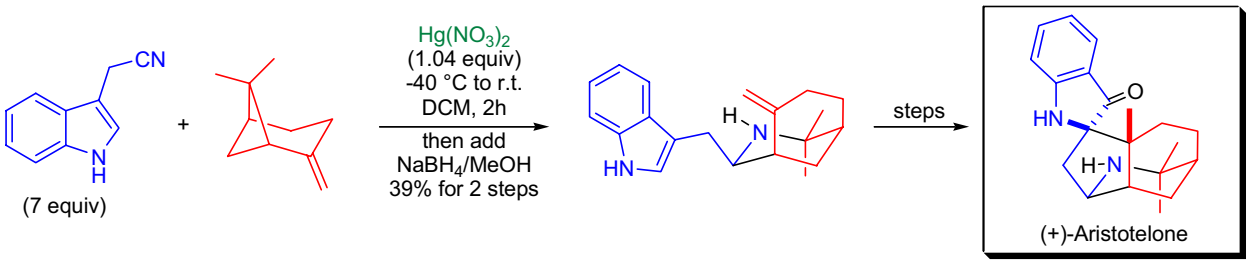
The mechanism of the *Ritter reaction* has been intensely studied. When alcohols are used to generate the carbocation, the hydroxyl group is protonated then under the reaction conditions the C-O bond is heterolytically cleaved to generate a carbocation. This cation is then attacked by the nitrogen atom of the nitrile to form a nitrilium ion, which upon reacting with the conjugate base of the acid (hydrogen sulfate anion in the scheme) gives rise to an imidate. Finally, hydrolysis produces the desired *N*-alkyl carboxamide.



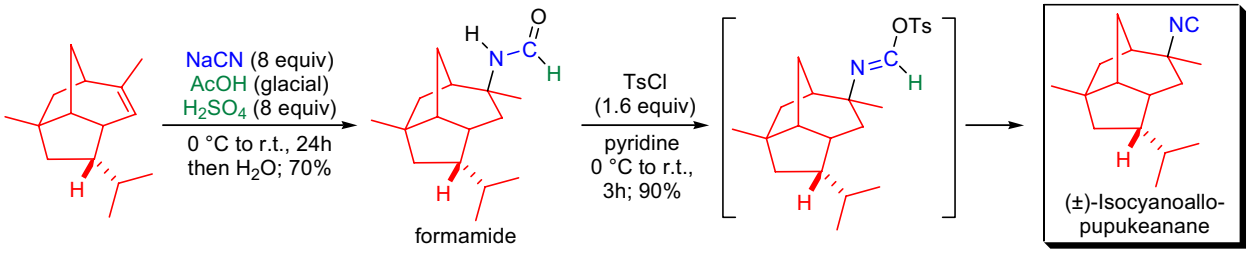
RITTER REACTION

Synthetic Applications:

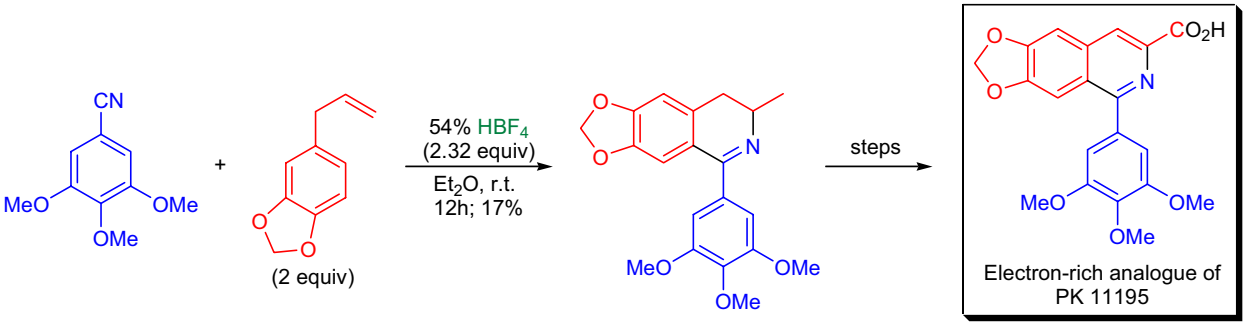
The enantioselective biomimetic total synthesis of the alkaloid (+)-aristotelone was accomplished by C.H. Heathcock and co-workers.[41] The synthetic sequence commenced with a $Hg(NO_3)_2$-mediated *Ritter reaction* between (1S)-(–)-β-pinene and 3-indolylacetonitrile. Upon protonation, the pinene underwent a *Wagner-Meerwein rearrangement* to generate a tertiary carbocation which reacted with the cyano group. The initially formed imine product was reduced to the corresponding amine by sodium borohydride in methanol.



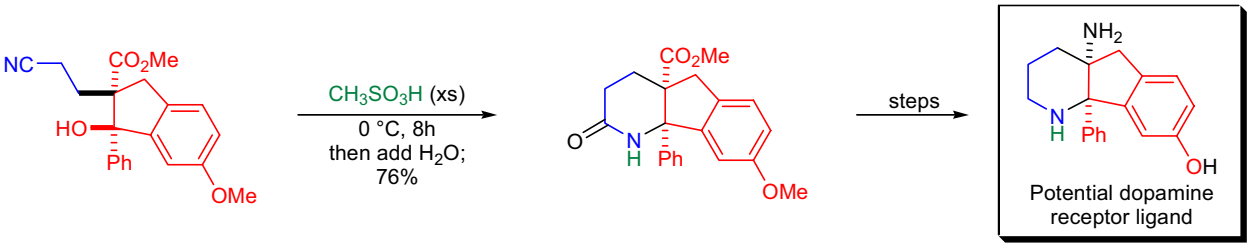
In the laboratory of T.-L. Ho, the total synthesis of the novel marine sesquiterpene (±)-isocyanoallopupukeanane was completed.[42] In the endgame of the synthesis, it was necessary to install the isocyano group onto the tricyclic trisubstituted alkene substrate so that it will occupy the more substituted carbon atom (according to Markovnikov's rule). The *Ritter reaction* was chosen to form the required carbon-nitrogen bond. The alkene substrate was dissolved in glacial acetic acid and first excess sodium cyanide followed by concentrated sulfuric acid was added at 0 °C. The reaction mixture was stirred at ambient temperature for one day and then was subjected to aqueous work-up. The product *N*-alkyl formamide was subsequently dehydrated with tosyl chloride in pyridine to give rise to the desired tertiary isocyanide which indeed was identical with the natural product.



A *modified Ritter reaction* was used by Y.L. Janin et al. for the preparation of electron rich 1-aryl-3-carboxylisoquinolines, which are considered to be the electron-rich analogues of PK 11195, a falcipain-2 inhibitor.[26] Interestingly, the standard *Ritter reaction* conditions (strong acid) led to extensive decomposition of both starting materials, but the use of HBF_4 in ether gave rise to the desired dihydroisoquinoline, albeit in poor yield.



The *intramolecular Ritter reaction* was utilized by F. Compernolle and co-workers for the synthesis of a potential dopamine receptor ligand.[43] The six-membered lactam ring was formed upon treatment of the tertiary benzylic alcohol substrate with methansulfonic acid. The benzylic carbocation was captured by the nitrogen of the cyano group.



ROBINSON ANNULATION

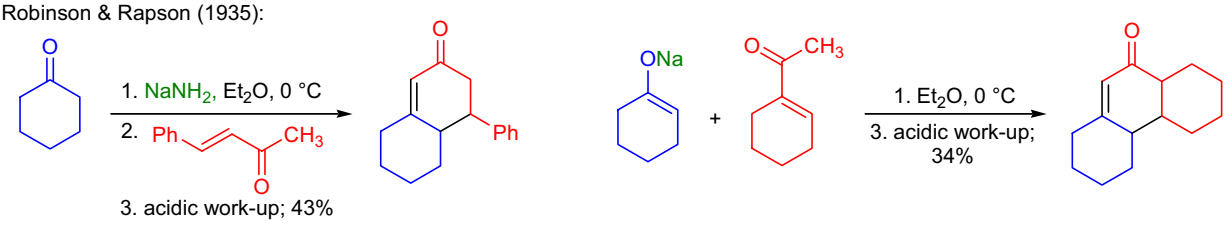
(References are on page 665)

Importance:

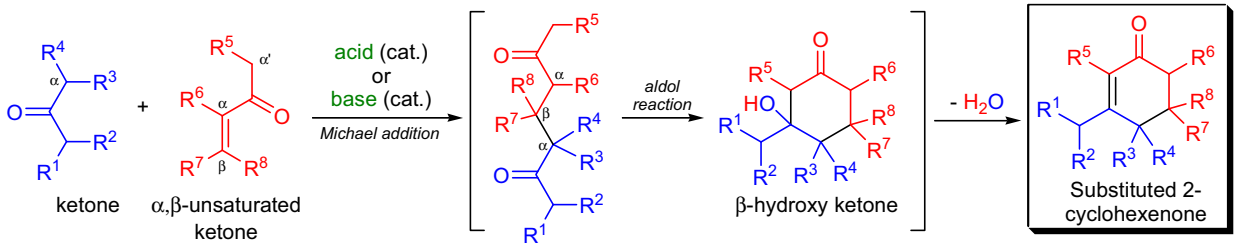
[*Seminal Publications*[1,2]*; Reviews*[3-9]*; Modifications & Improvements*[10-36]]

In 1935, R. Robinson and W.S. Rapson were preparing substances related to the sterols when they found that the sodium enolate of cyclohexanone reacted with various acyclic and cyclic α,β-unsaturated ketones to afford substituted cyclohexenones.[1] Robinson recognized the generality of this transformation, which was quickly adapted by the synthetic community, and today it is widely used in the synthesis of complex natural products. The reaction of a ketone (most often a cyclic one) with an α,β-unsaturated ketone to give a substituted cyclohexenone derivative is known as the *Robinson annulation*. The general features of the reaction are: 1) it is a combination of three reactions: *Michael addition*, *intramolecular aldol reaction*, and dehydration; 2) it can be both acid- and base-catalyzed, but predominantly the reaction is conducted under basic conditions; 3) acyclic enones and cyclic ketones afford bicyclic enones, whereas cyclic enones and cyclic ketones give rise to polycyclic fused enones; 4) methyl vinyl ketone (MVK) and its various derivatives and surrogates are used most often as the enone component; 5) can be conducted as a one-pot process, but yields tend to be higher when the Michael adduct is isolated and then subjected to the *aldol reaction*; 6) the alkylation of an unsymmetrical ketone occurs regioselectively at the most substituted α-position unless severe steric interference dictates otherwise; 7) regioselective cyclization can also be achieved by using pre-formed enolates or enamines under non-equilibrium conditions; 8) the annulation can generate as many as five stereocenters, but in the dehydration step two of these chiral centers are lost; 9) the relative stereochemistry between R^3 and R^7 (*cis* or *trans*) is dependent on the reaction conditions (e.g., solvent);[11] and 10) the enantioselective version is known as the *Hajos-Parrish reaction*.[10,13]

Robinson & Rapson (1935):



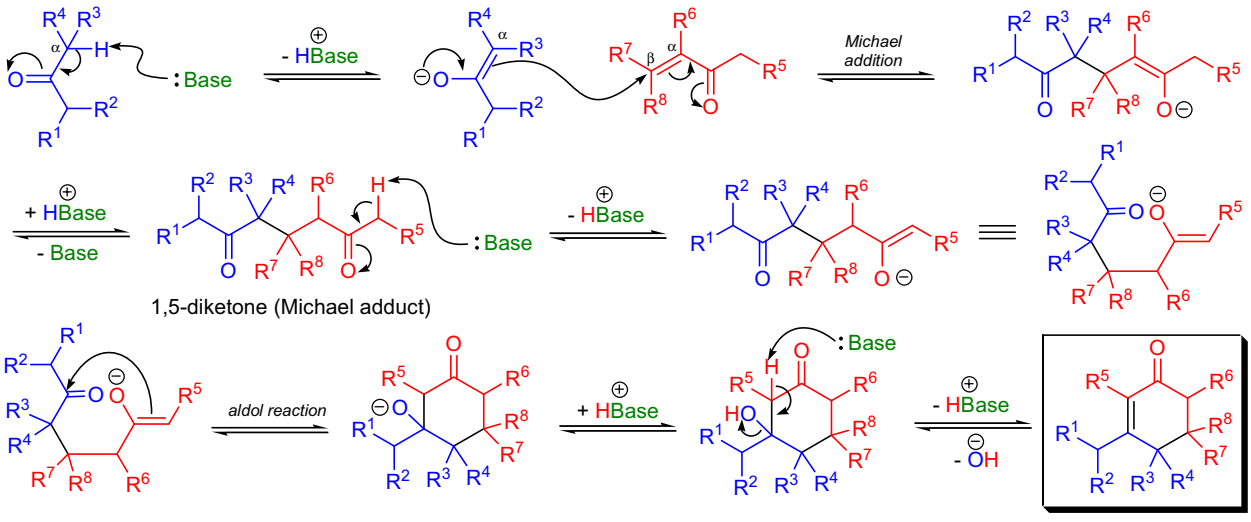
Robinson annulation:



R^{1-4} = H, alkyl, aryl; R^5 = H, alkyl, aryl; R^6 = H, alkyl, aryl, SiR_3; R^{7-8} = H, alkyl, aryl

Mechanism:[11,15,4]

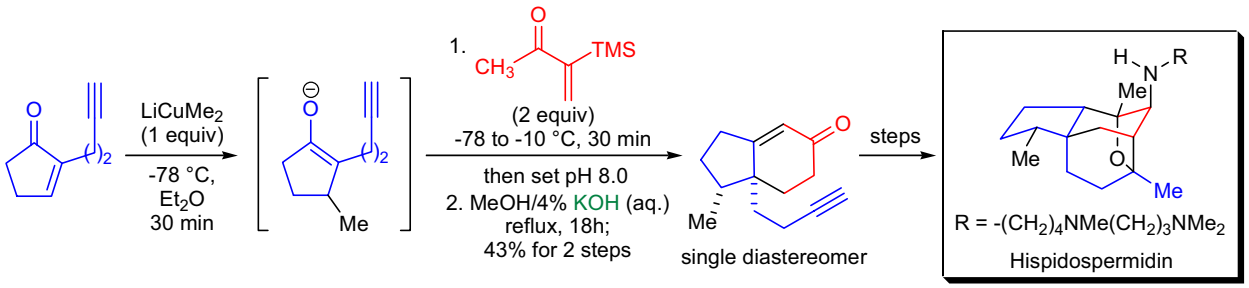
The *Robinson annulation* has three distinct steps: the *Michael addition* of the enol or enolate across the double bond of the α,β-unsaturated ketone to produce a 1,5-diketone (Michael adduct), followed by an *intramolecular aldol reaction*, which affords a cyclic β-hydroxy ketone (keto alcohol), and finally a base-catalyzed dehydration which gives rise to the substituted cyclohexenone. An alternative mechanism *via* disrotatory electrocyclic ring closure is possible.[11]



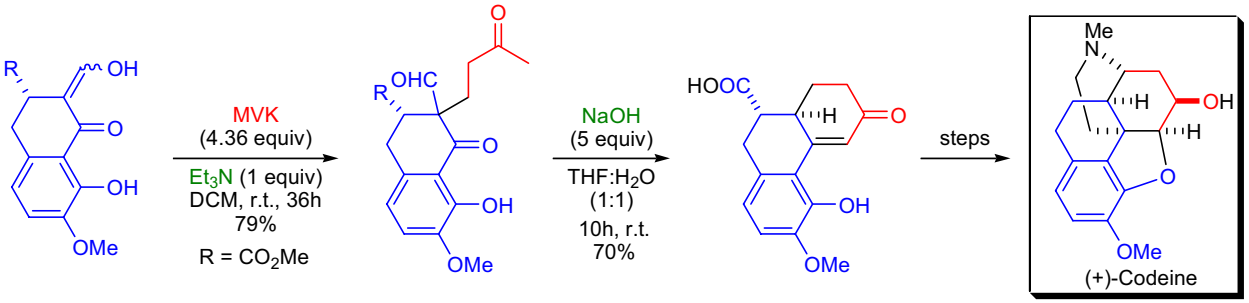
ROBINSON ANNULATION

Synthetic Applications:

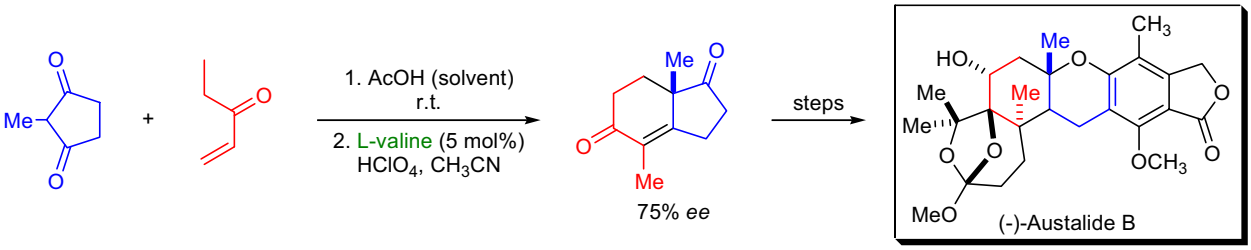
A *conjugate cuprate addition-Robinson annulation* sequence was utilized in the highly stereoselective total synthesis of hispidospermidin by S.J. Danishefsky et al.[37] It is a well-known fact that the MVK has a great tendency to polymerize under aprotic basic conditions that are used when the integrity of the enolate reaction partner has to be maintained. In order to avoid complications arising from the likely polymerization of MVK, α-trimethylsilyl methyl vinyl ketone (a base-stable surrogate of MVK developed by G. Stork and co-workers[12,14]) was chosen as the reaction partner. The 2-substituted cylopentenone was treated with lithium dimethyl cuprate, and the resulting enolate was trapped with α-trimethylsilyl MVK in a *Michael addition*. The crude Michael adduct was refluxed with aqueous KOH in methanol, which resulted in the desired hydrindenone as a single diastereomer.



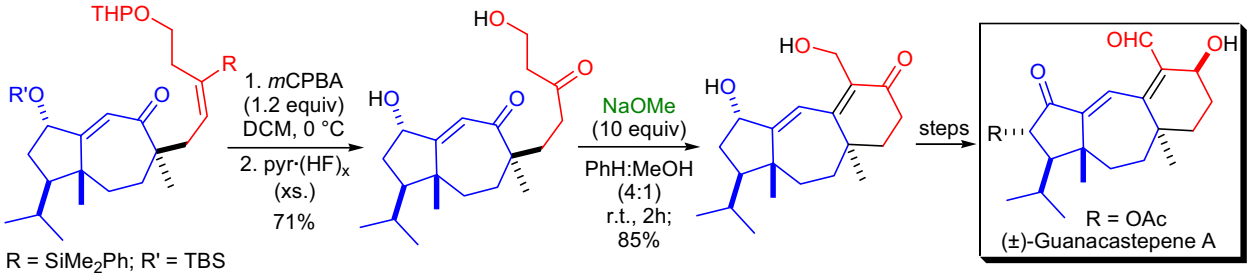
In the laboratory of J.D. White, the asymmetric total synthesis of (+)-codeine was accomplished.[38] The *Robinson annulation* was the method of choice to build a phenanthrenone precursor starting from a substituted tetralone derivative. As it is usually the case, the isolation of the Michael adduct allowed the *intramolecular aldol reaction* to proceed cleanly and to afford a higher yield of the annulated product.



The *Hajos-Parrish reaction* can be regarded as the enantioselective version of the *Robinson annulation*. In the early stages of the synthetic effort targeting the mixed polyketide-terpenoid metabolite (–)-austalide B, L.A. Paquette and co-workers used this transformation to prepare the key bicyclic precursor in enantiopure form.[39] Ethyl vinyl ketone was reacted with 2-methyl-1,3-cyclopentanedione in the presence of catalytic amounts of L-valine to afford the bicyclic diketone with a 75% *ee*.



A novel variant of the *Stork-Jung modified Robinson annulation* was developed and applied to the formal total synthesis of (±)-guanacastepene A by the research group of B.B. Snider.[40] Instead of using MVK directly, they prepared the necessary 1,5-diketone by alkylating the ketone with an allylsilane and generating the ketone functionality *via* a *Fleming-Tamao oxidation*.



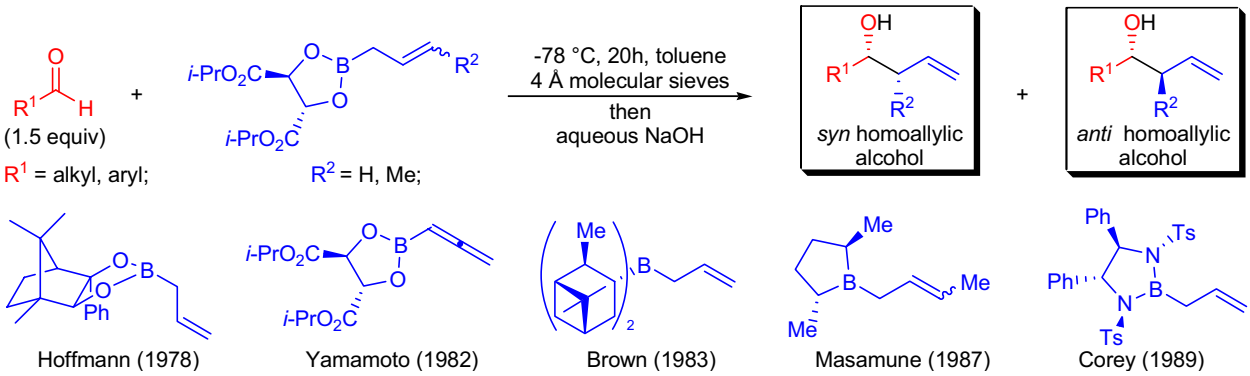
ROUSH ASYMMETRIC ALLYLATION

(References are on page 666)

Importance:

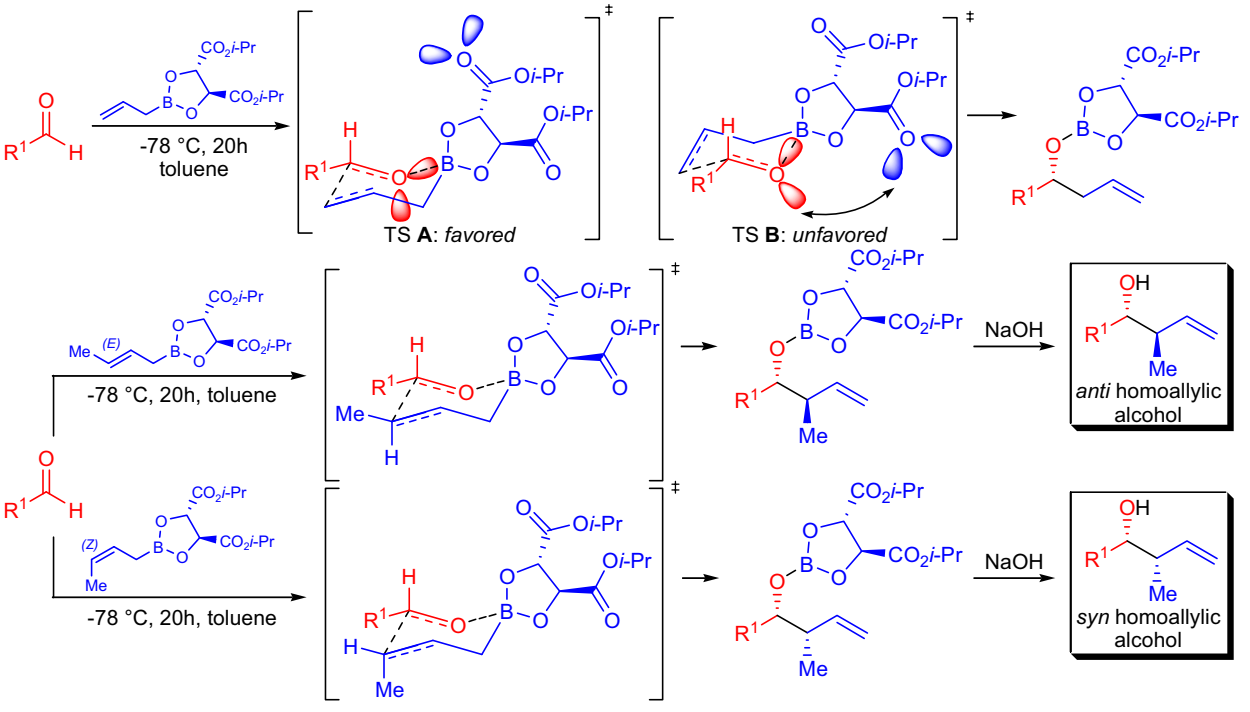
[*Seminal Publications*[1-5]*; Reviews*[6-11]*; Modifications & Improvements*[12-22]*;Theoretical studies*[23-27]]

The first example of the enantioselective synthesis of homoallylic alcohols *via* chiral nonracemic allylboronic esters was reported by R. W. Hoffmann in 1978.[1] He studied the reaction between (+)-camphor derived allylboronic ester and a series of aliphatic aldehydes. The resulting homoallylic alcohols formed with excellent yield but moderate enantioselectivity. A few years later, W.R. Roush examined the reaction of allylboronates with aldehydes and he found that diisopropyltartrate ester derived allylboronates reacted with aldehydes to give the products in good yield and enantioselectivity.[2-5] This reaction is referred to as the *Roush asymmetric allylation.* The synthesis of these allylboronates may be achieved by esterification of allylboronic acid or by transesterification of triisopropyl-allylboronate with the appropriate tartrate ester. The general features of the allylation reaction are: 1) the reaction is typically carried out in toluene, in the presence of 4Å molecular sieves at -78 °C; 2) this method provides access to both enantiomers of the homoallylic alcohol product by selecting the proper enantiomer of the diisopropyltartrate ester for the preparation of the reagent; 3) this reaction exhibits high levels of matched and mismatched diastereoselection in the case of chiral aldehydes; 4) both aliphatic and aromatic aldehydes are suitable substrates; 5) (*E*)-crotylboronate derivatives lead to the formation of the *anti* diastereomer as the major product, while (*Z*)-crotylboronates give the *syn* product; and 6) (*E*)-crotylboronates usually exhibit higher enantioselectivities than (*Z*)-crotylboronates. In addition to the *Roush asymmetric allylation*, several other methods were developed for the asymmetric synthesis of homoallylic alcohols utilizing chiral allylboranes and allylboronates: 1) H.C. Brown reported the application of *B*-allyldiisopinocampheylborane;[13,16,19,21,22] 2) E.J. Corey described the application of 1,2-diamino-1,2-diphenylethane derived allylboranes;[18,20] 3) S. Masamune developed a method where he utilized (*E*)- and (*Z*)-crotyl-2,5-dimethylborolanes;[15] and 4) chiral nonracemic allenylboronates were also utilized to form the corresponding propargyl alcohols enantioselectively.[12,14,20]



Mechanism:[2]

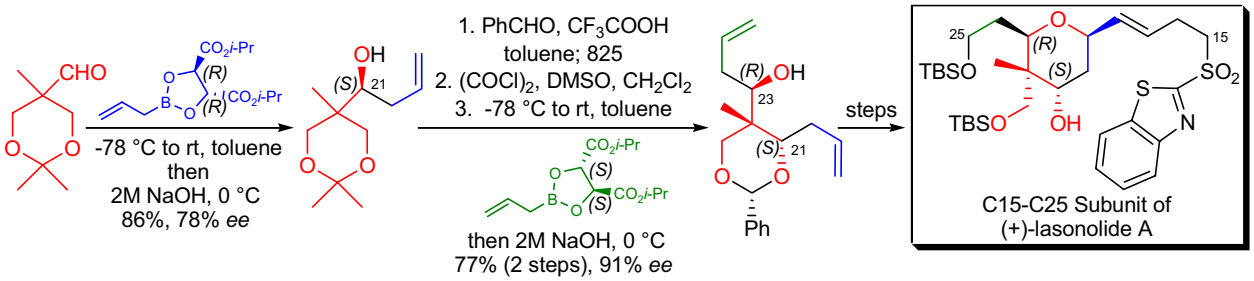
According to Roush, the asymmetric induction can be explained by an unfavorable electronic repulsive interaction between the nonbonding electron pair of the aldehyde and ester that destabilizes transition state **B** relative to **A**.[2]



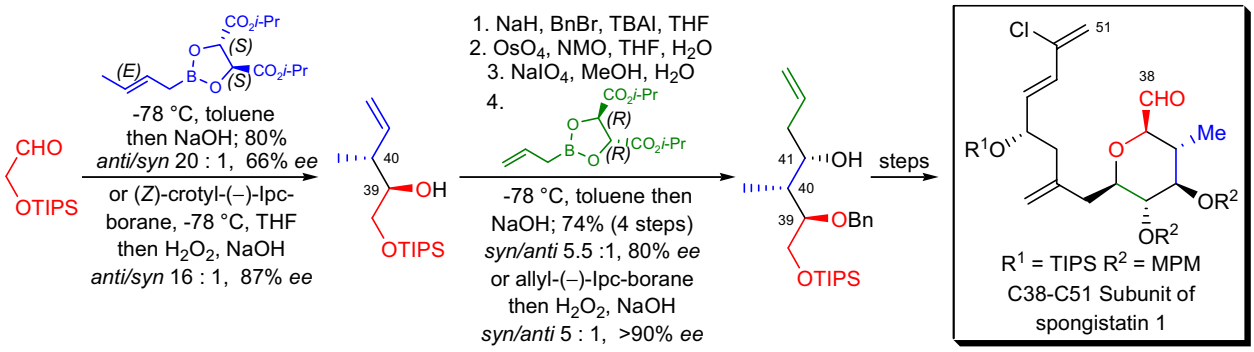
ROUSH ASYMMETRIC ALLYLATION

Synthetic Applications:

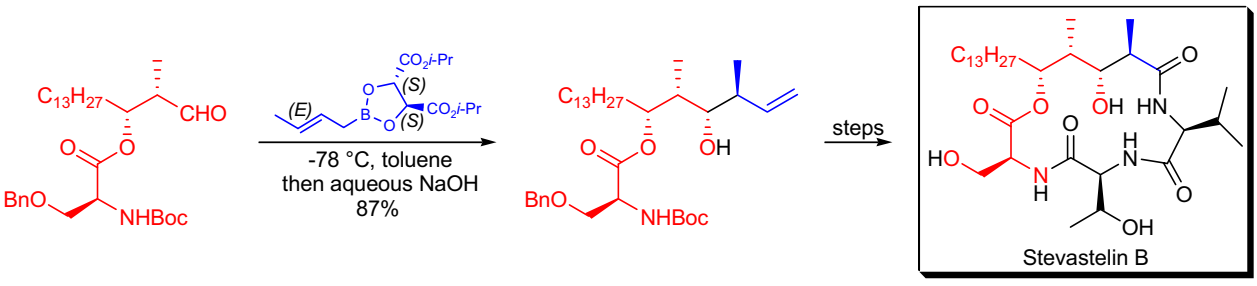
The total synthesis of the 20-membered macrolide *(+)-lasonolide-A* was undertaken by S.H. Kang and co-workers.[28] During the construction of the C15-C25 subunit, they utilized the *Roush asymmetric allylation* reaction to introduce the C21 and C23 stereocenters. First, (*R,R*)-diisopropyltartrate derived allylboronate was used to provide the (*S*)-homoallylic alcohol with 78% *ee*. A second asymmetric allylation was achieved utilizing the (*S,S*)-diisopropyltartrate-derived allylboronate to form the (*R*)-homoallylic alcohol with a 91% *ee*.



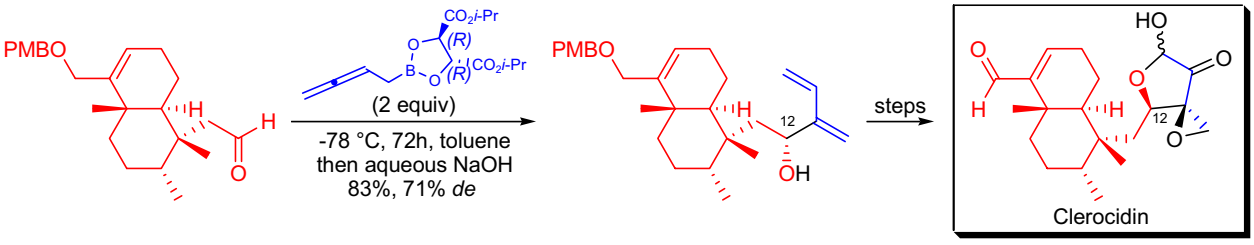
Y. Kishi and coworkers accomplished the total synthesis of *spongistatin 1*.[29] In their approach, they applied the *Roush asymmetric allylation reaction* twice during the synthesis of the C38-C51 fragment of the natural product to construct the C39, C40 and C41 stereocenters. In the first allylation, they utilized (*S,S*)-diisopropyltartrate-derived (*E*)-crotylboronate, while in the second reaction they used the (*R,R*)-diisopropyltartrate-modified allyl boronate. During their studies, they compared Roush's method with the allylation developed by H.C. Brown utilizing the corresponding crotyl- and allyldiisopinocampheylboranes. They concluded that Brown's method proceeded with higher enantioselectivity, but the ratio of the *syn* and *anti* diastereomers was higher in the *Roush asymmetric allylation*.



Stevastelins are depsipeptides exhibiting immunosuppressant activity. The first total synthesis of *stevastelin B* was described by Y. Yamamoto and co-workers.[30] To construct four consecutive stereocenters, the *Evans aldol reaction* and the *Roush asymmetric allylation* were utilized. In the allylation step, the authors used (*S,S*)-diisopropyltartrate-derived (*E*)-crotyl boronate. The *anti* homoallylic alcohol product formed as the only diastereomer.



E.A. Theodorakis and co-workers reported the total synthesis of *clerocidin*, a diterpenoid antibiotic.[31] To form the C12 stereocenter and the diene moiety, they applied an asymmetric homoallenylboration method.[32] The reaction of the aldehyde and (*S,S*)-diisopropyltartrate-derived homoallenyl boronate provided the alcohol with a 6:1 diastereoselectivity and 83% yield.



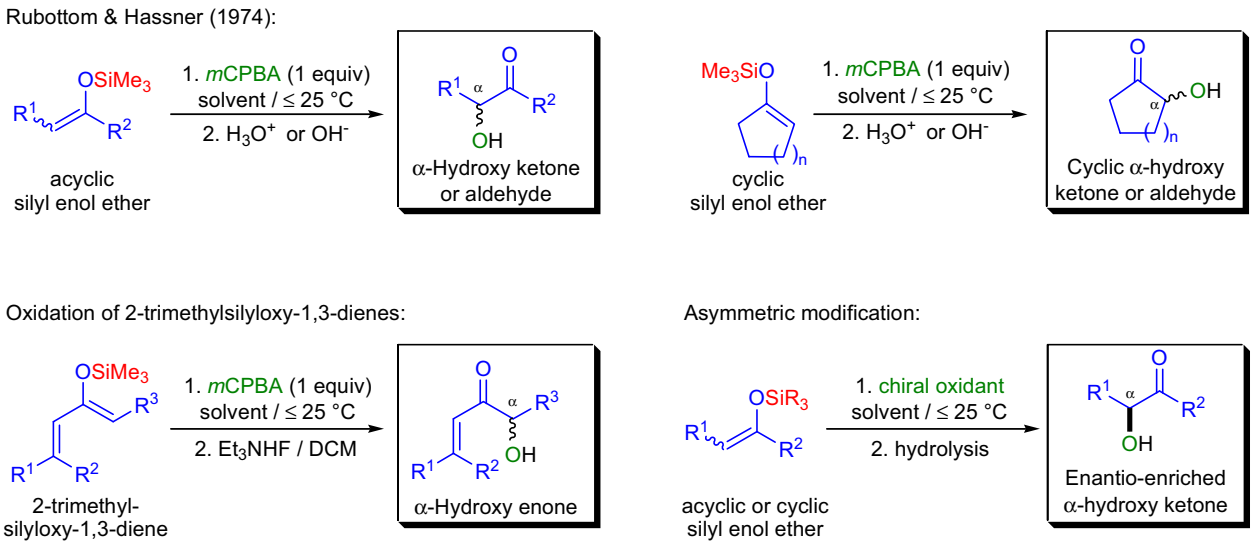
RUBOTTOM OXIDATION

(References are on page 667)

Importance:

[*Seminal Publications*[1-3]*; Modifications & Improvements*[4-14]]

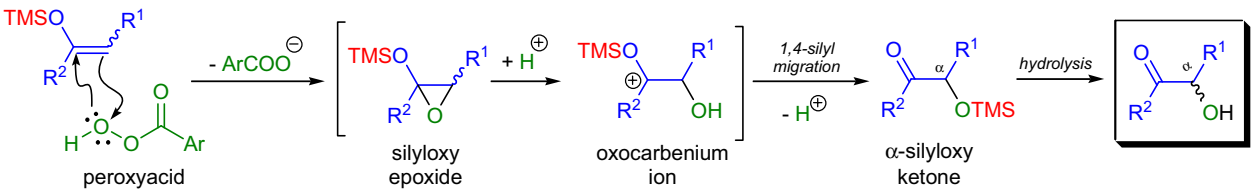
In 1974, the research groups of G.M. Rubottom and A. Hassner independently developed a general and high-yielding preparation of α-hydroxy ketones (acyloins) and α-hydroxy aldehydes by the oxidation of silyl enol ethers with *m*CPBA.[2,3] The first observation of this transformation, however, was made by A.G. Brook and co-workers the same year.[1] Today the α-hydroxylation of carbonyl compounds *via* the peroxyacid oxidation of the corresponding silyl enol ethers is known as the *Rubottom oxidation*. The general features of this reaction are: 1) the silyl enol ether substrates can be prepared efficiently and regioselectively from ketones and aldehydes;[15,16] 2) both acyclic and cyclic enol ethers undergo the oxidation; 3) the oxidation readily takes place at or below room temperature (predominantly using dichloromethane as the solvent) and the reaction mixture is worked up with either acid or base to afford the α-hydroxy carbonyl compounds in good yield; 4) the silyl enol ethers derived from α,β-unsaturated ketones (2-trimethylsilyloxy-1,3-dienes) are regioselectively oxidized at the more electron-rich double bond to afford α-hydroxy or α-acyloxy enones depending on the workup conditions;[4] 5) often the initial product of the oxidation is the α-silyloxy carbonyl compound, which is readily hydrolyzed to the corresponding α-hydroxy derivative; 6) in the case of bicyclic silyl enol ethers, the reaction has to be buffered and the use of a completely non-polar solvent (e.g., pentane, toluene) is required to avoid the extensive hydrolysis of the starting material;[8] and 7) the introduction of the α-hydroxyl functionality is stereoselective in the case of bicyclic and polycyclic substrates.[8] There are a number of modifications of the *Rubottom oxidation*, and they mainly differ in the applied oxidizing agent: 1) the use of chiral oxidants such as Davis' chiral oxaziridines,[5] Shi's D-fructose-derived chiral ketone in combination with Oxone[9,12] or manganese(III)-(Salen)complexes[10] gives rise to enantiomerically enriched α-hydroxy ketones; 2) hydrogen peroxide efficiently oxidizes silyl enol ethers in the presence of MTO (methyltrioxorhenium) to give high yields of the corresponding α-hydroxy and α-silyloxy ketones;[11] and 3) HOF-acetonitrile complex (made directly from F_2 and aqueous acetonitrile) not only oxidizes silyl enol ethers but also silyl ketene acetals (derived from esters) to afford α-hydroxy ketones and esters, respectively.[17]



R^{1-3} = H, alkyl, aryl, substituted alkyl and aryl; SiR_3 = $SiMe_3$, $SiMe_2$(t-Bu), $SiEt_3$; solvent: CH_2Cl_2, pentane, toluene; n = 1-3;
chiral oxidant: Davis' chiral oxaziridine, Shi's D-fructose derived ketone/Oxone, (Salen)manganese(III)-complexes/NaOCl or PhIO

Mechanism:[18,1,19]

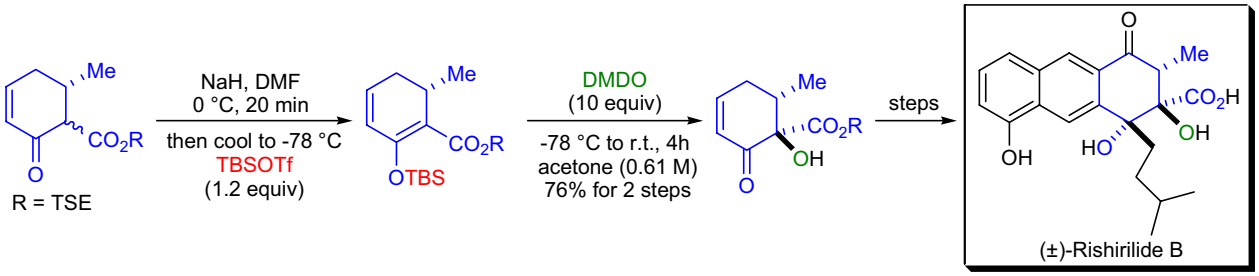
The *Rubottom oxidation* proceeds through the intermediacy of a silyloxy epoxide. The epoxide ring opens under the acidic conditions to afford a stable oxocarbenium ion, which undergoes a *1,4-silyl migration* (*Brook rearrangement*)[1] to give an α-silyloxy ketone. The α-silyloxy ketone is readily hydrolyzed to the product. Until recently the silyloxy epoxide could not be isolated or observed but when the oxidation was conducted with neutral epoxidizing agents, the silyloxy epoxide intermediate could be isolated.



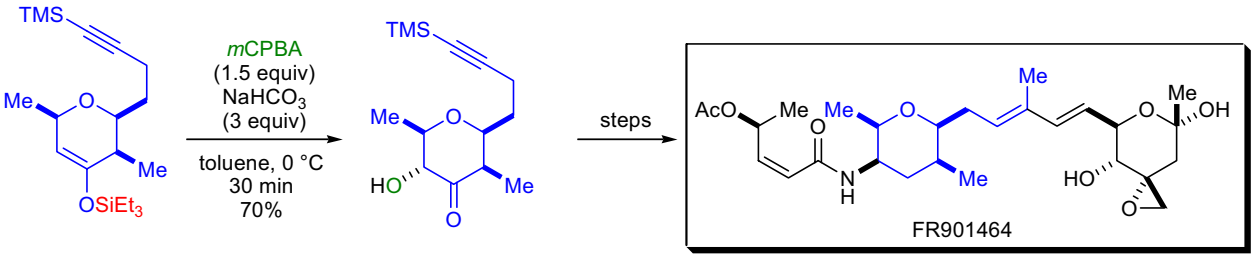
RUBOTTOM OXIDATION

Synthetic Applications:

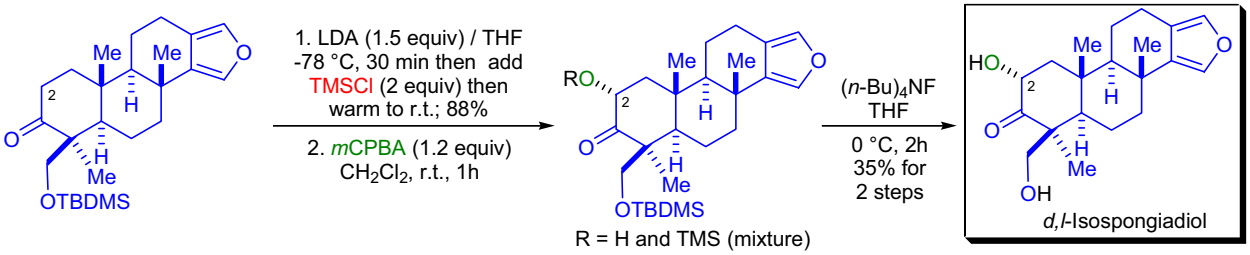
The highly potent antithrombotic (±)-rishirilide B was synthesized in the laboratory of S.J. Danishefsky.[20] One of the tertiary alcohol functionalities was introduced *via* the *Rubottom oxidation* of a six-membered silyl dienol ether with dimethyl dioxirane (DMDO). The oxidation was completely stereoselective, and it was guided by the proximal secondary methyl group. Subsequently, the enone was converted to the enedione, which was used as a dienophile in the key *intermolecular Diels-Alder cycloaddition* step.



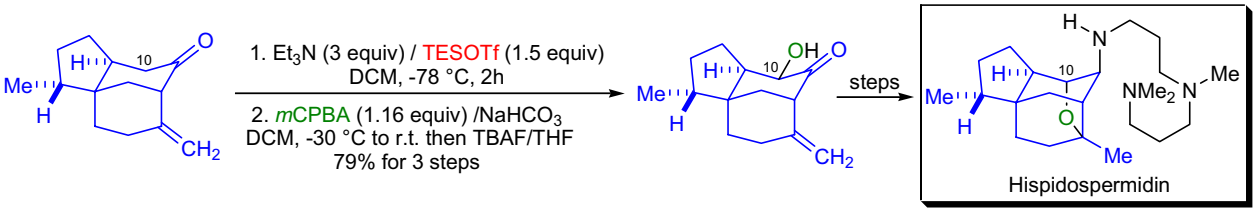
The total synthesis of the antitumor antibiotic FR901464 was accomplished by E.N. Jacobsen et al.[21] The preparation of the central six-membered fragment was achieved *via* a highly *enantioselective hetero Diels-Alder reaction* between a diene and an aldehyde. The resulting silyl enol ether was subjected to a modified *Rubottom oxidation* condition (buffer and nonpolar solvent) with mCPBA to afford the desired α-hydroxy ketone with complete diastereoselectivity.



The key step in the total synthesis of the furanoditerpene *d,l*-isospongiadiol by P.A. Zoretic and co-workers was an *oxidative free-radical cyclization*, which gave rise to the tricyclic skeleton of the natural product.[22] The last stereocenter at C2 was introduced using the *Rubottom oxidation* on the fully elaborated tetracyclic intermediate. The product was a mixture of α-hydroxy and silyloxy ketone and the last step was a global deprotection with TBAF to afford the natural product.



In the highly stereoselective synthesis of hispidospermidin, the oxygenation of the C10 position was achieved *via* a *Rubottom oxidation* by S.J. Danishefsky et al.[23] The tricyclic ketone was first converted to the TES enol ether, which was readily oxidized with *m*CPBA to give the corresponding α-hydroxy ketone as a single diastereomer.



SAEGUSA OXIDATION

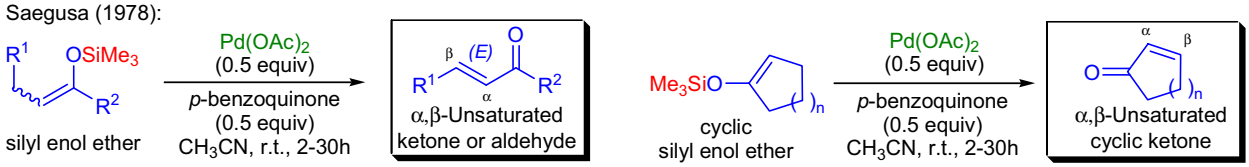
(References are on page 667)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-11]]

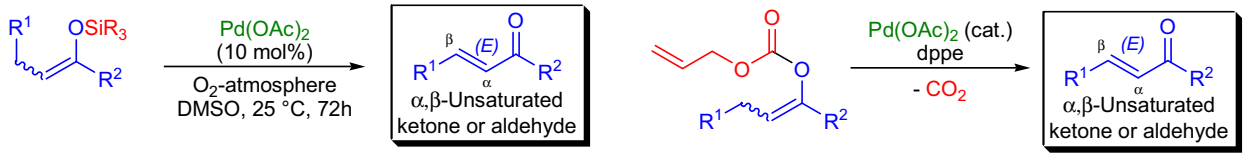
In 1978, T. Saegusa and co-workers reported that silyl enol ethers reacted with substoichiometric amounts of $Pd(OAc)_2$ and *p*-benzoquinone in acetonitrile at room temperature to afford the corresponding α,β-unsaturated carbonyl compounds.[2] The regioselective introduction of the α,β carbon-carbon double bond to cyclic and acyclic ketones *via* the Pd-mediated oxidation of the corresponding silyl enol ethers is known as the *Saegusa oxidation*. The general features of the transformation are: 1) the reaction is usually carried out using 0.5 equivalents of $Pd(OAc)_2$ and 0.5 equivalents of *p*-benzoquinone (co-oxidant) at room temperature; 2) when stoichiometric amounts of $Pd(OAc)_2$ are used, no co-oxidant is needed. However, less than 0.25 equivalents of $Pd(OAc)_2$ results in a substantial decrease in the reaction rate as well as isolated yield of the product; 3) the starting silyl enol ethers are easily obtained by trapping metal enolates with TMSCl (the metal enolates are either obtained by the regioselective deprotonation of ketones and aldehydes with LiHMDS or LDA or by the conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds);[12,13] 4) both acyclic and cyclic silyl enol ethers undergo the transformation; 5) the oxidation proceeds with high stereoselectivity, because in acyclic systems the stereochemistry of the newly formed double bond is predominantly (*E*) even if the starting silyl enol ether was a mixture of (*E*) and (*Z*) stereoisomers; and 6) cyclic silyl enol ethers (*n*=1-7) are efficiently oxidized, and when the ring size allows, the newly introduced double bond will have the (*E*) stereochemistry. The main drawback of the *Saegusa oxidation* is the high cost of the palladium acetate. However, methods employing truly catalytic amounts of $Pd^{(II)}$- and $Pd^{(0)}$ complexes have been developed.[11] There are several modifications of the process: 1) an environmentally friendly catalytic version using only 10 mol% of $Pd(OAc)_2$ and oxygen atmosphere in DMSO (*Larock modification*);[11] 2) instead of silyl enol ethers, enol acetates can also be used when they are heated with allyl methyl carbonate, catalytic amounts of $Pd(OAc)_2$ and $MeOSnBu_3$;[10] and 3) allyl enol carbonates also undergo oxidation with catalytic amounts of $Pd(OAc)_2$/dppe.[8,7] Alternatively, silyl enol ethers can be efficiently oxidized by IBX and IBX-*N*-oxides to the corresponding enones (*Nicolaou oxidation*).[14]

Saegusa (1978):



Catalytic process (*Larock modification*,1995):

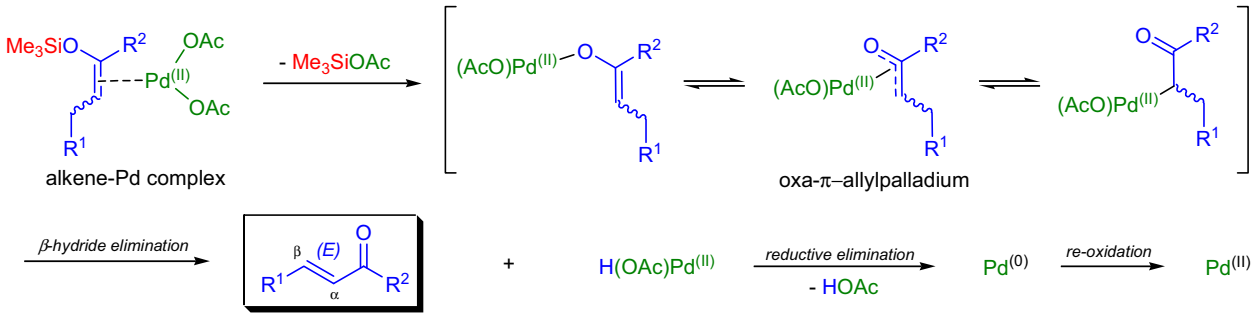
Allyl enol carbonate modification:



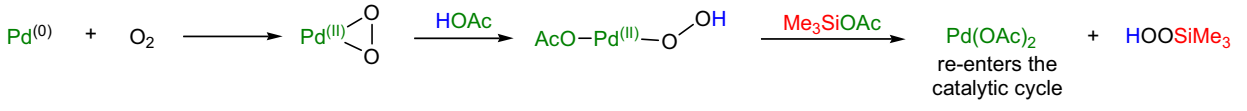
R^{1-2} = H, alkyl, aryl; SiR_3 = TMS, TBDMS; n = 1-7

Mechanism:[15,7]

When substoichiometric/stoichiometric amounts of $Pd(OAc)_2$ is used:



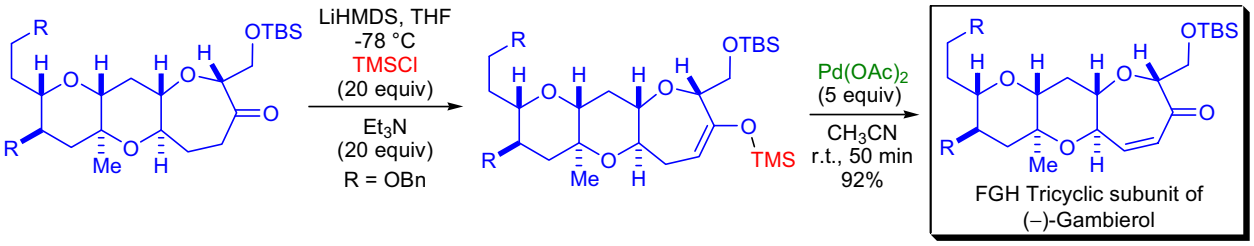
When the oxidation takes place under an oxygen atmosphere with catalytic amounts of $Pd(OAc)_2$:



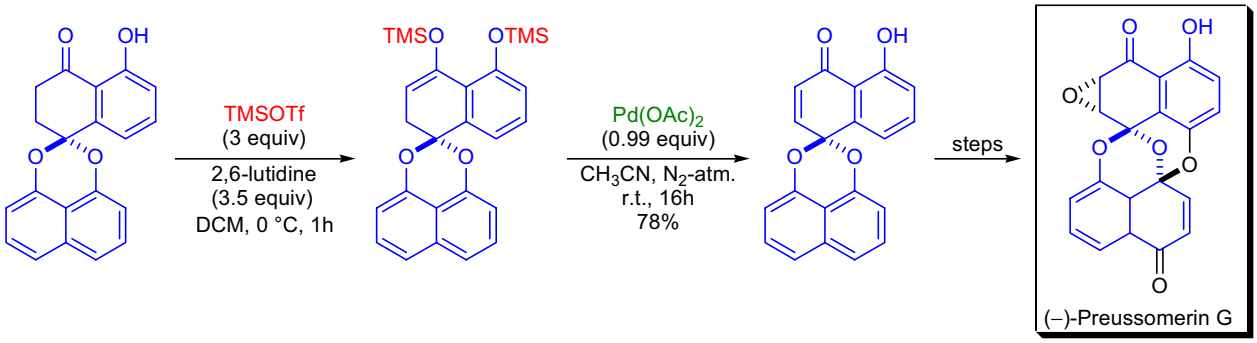
SAEGUSA OXIDATION

Synthetic Applications:

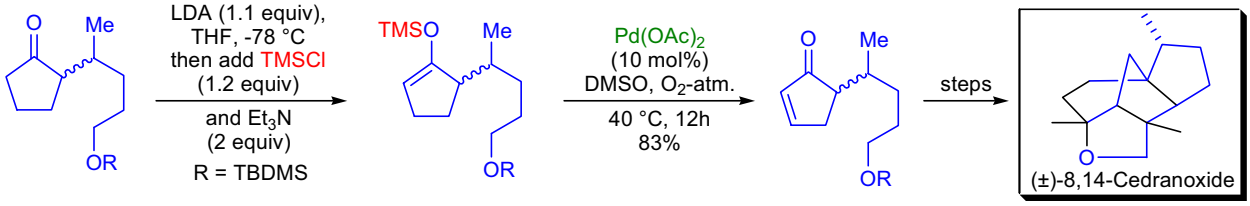
The first total synthesis of the marine polycyclic ether toxin (–)-gambierol was accomplished in the laboratory of M. Sasaki.[16] The introduction of the α,β-unsaturation into the seven-membered H ring of the FGH tricyclic subunit proved to be problematic, because both the conventional selenium-based method and the *Nicolaou oxidation* with IBX failed. However, when the seven-membered ketone was treated with LiHMDS in the presence of TMSCl and Et_3N, the corresponding silyl enol ether was formed, which was oxidized under Saegusa conditions to give the desired cyclic enone in high yield. Because of the small scale of the reaction, a large excess of $Pd(OAc)_2$ was used in acetonitrile so the presence of a co-oxidant was not necessary.



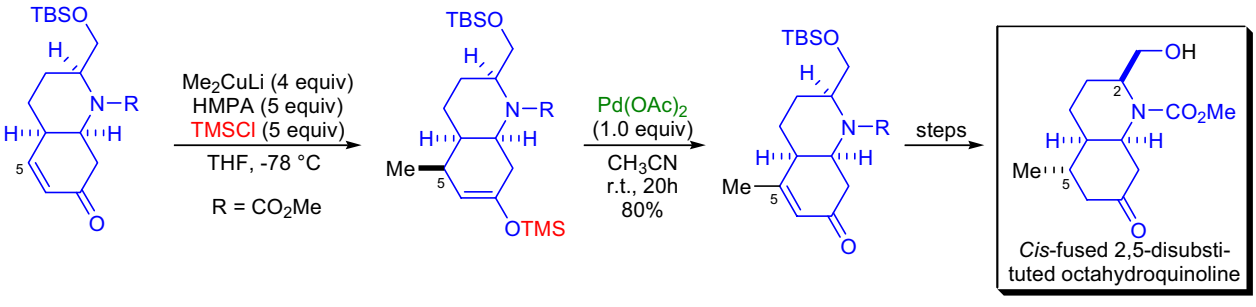
A.G.M. Barrett and co-workers reported the first total synthesis of (–)-preussomerin G.[17] In the late stages of the synthesis, the introduction of the desired cyclohexenone moiety was achieved using the *Saegusa oxidation*. The ketone was first converted to the silyl enol ether with trimethylsilyl triflate, and then it was treated with stoichiometric amounts of $Pd(OAc)_2$.



The *Larock modified Saegusa oxidation* conditions were utilized in the total synthesis of (±)-8,14-cedranoxide by M. Ihara et al.[18] The main strategy was to apply an *intramolecular double Michael addition* reaction to assemble the tricyclic cedranoid skeleton. The precursor five-membered enone was prepared in high yield from the corresponding substituted cyclopentanone in two steps.



A stereodivergent synthesis was developed by H. Nemoto and co-workers for the preparation of *cis*-fused 2,5-disubstituted octahydroquinolines, which constitute the core structure of certain dendrobatid alkaloids.[19] The installation of the C5 methyl group was achieved by 1,4-cuprate addition and the resulting enolate was trapped with TMSCl. The silyl enol ether was then oxidized to the enone with $Pd(OAc)_2$.



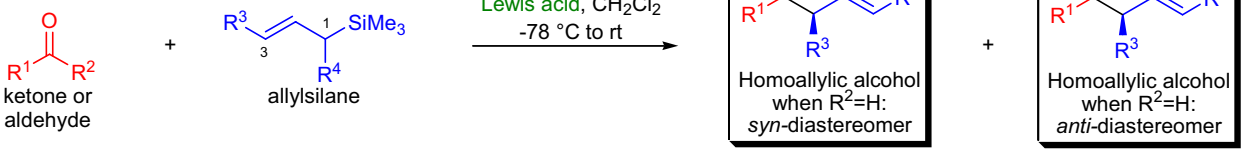
SAKURAI ALLYLATION

(References are on page 668)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-23]; *Theoretical Studies*[24,25]]

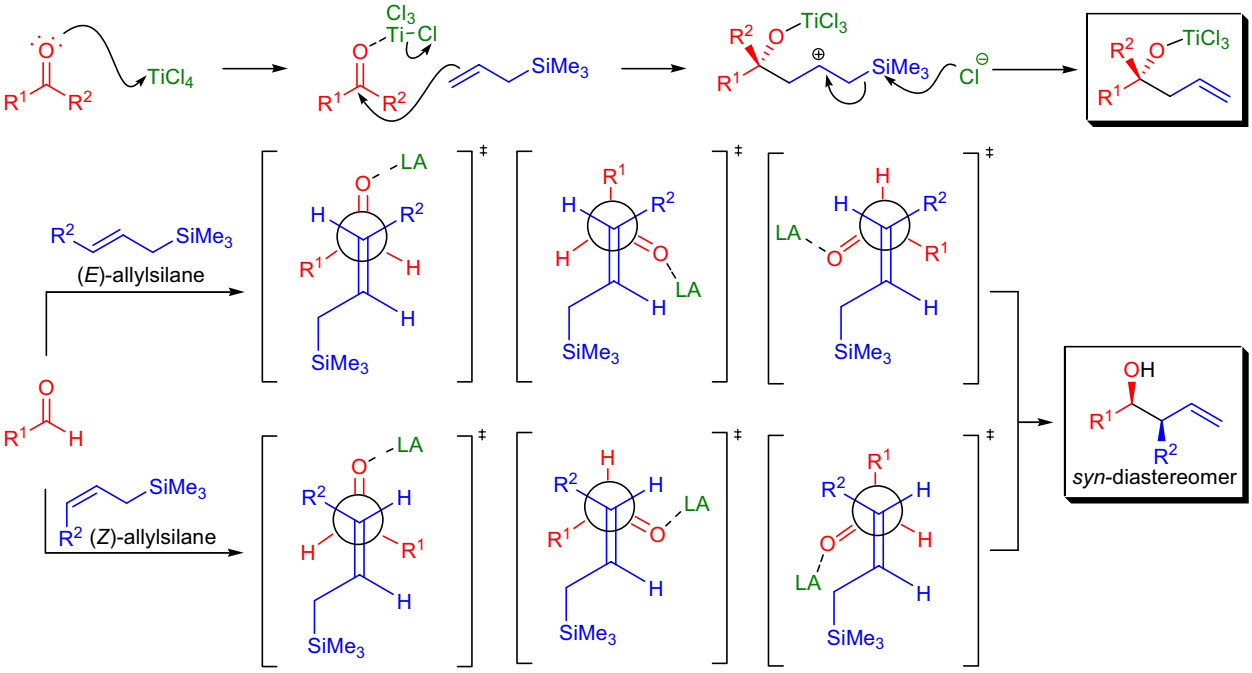
In 1976, H. Sakurai reported that allylsilanes react with a wide variety of aldehydes and ketones in the presence of stoichiometric quantities of $TiCl_4$ to form the corresponding homoallylic alcohols. Today, this transformation is referred to as the *Sakurai allylation*, and it is one of the most important carbon-carbon bond forming reactions. The general features of the reaction are: 1) typically, it is carried out in dichloromethane under nitrogen atmosphere at a temperature range between -78 °C and 25 °C; 2) in addition to $TiCl_4$, several other Lewis acids can be used such as $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $EtAlCl_2$;[1,2] 3) most commonly trimethylallylsilanes and phenyldimethylallylsilanes are utilized as the allylsilane reactant;[4,6] 4) the reaction is highly regioselective, the electrophile attacking at the C3 terminus of the allylsilane;[1,2,4] 5) C1 substituted allylsilanes give the (*E*)-alkene product;[26] 6) allenyl-,[27] propargyl-,[28] vinyl-,[29] and ethynylsilanes[29] also undergo the reaction in the presence of Lewis acids; 7) the most commonly used electrophiles are aldehydes and ketones, but acetals and ketals[30] are also often utilized; 8) dithioacetals,[31] monothioacetals,[32] alkoxymethyl-,[33] and phenylthiomethyl chlorides[34] undergo the allylation reaction; 9) α,β-unsaturated aldehydes react at the carbonyl group, while α,β-unsaturated ketones undergo conjugate addition;[35,36] 10) intramolecular reactions are also feasible;[37] and 11) C3 monosubstituted allysilanes give the *syn*-diastereomer as the major product.[38] Common side reactions in the *Sakurai allylation* are the following: 1) protodesilylation;[39] 2) allylic alcohol products, especially tertiary allylic alcohols can undergo ionization;[40] and 3) in the case of 1,1-disubstituted allylsilanes, the trisubstituted alkene product may react further.[41] Side reactions usually can be avoided by carefully controlled conditions or utilizing acetal or ketal substrates. Catalytic versions of the *Sakurai allylation* are known as well, utilizing TMSOTf,[10] TMSI,[11] Ph_3CClO_4,[12] $Cp_2Ti(CF_3SO_3)_2$,[14] TMSOMs,[19] and $InCl_3$/TMSCl[20] as catalysts. Recently, catalytic asymmetric versions were developed.[15,22,23]



R^1 = alkyl, aryl; R^2 = H, alkyl, aryl; R^3 and R^4 = H, alkyl, aryl; Lewis acid = $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $EtAlCl_2$

Mechanism:[42,43,38,44-46]

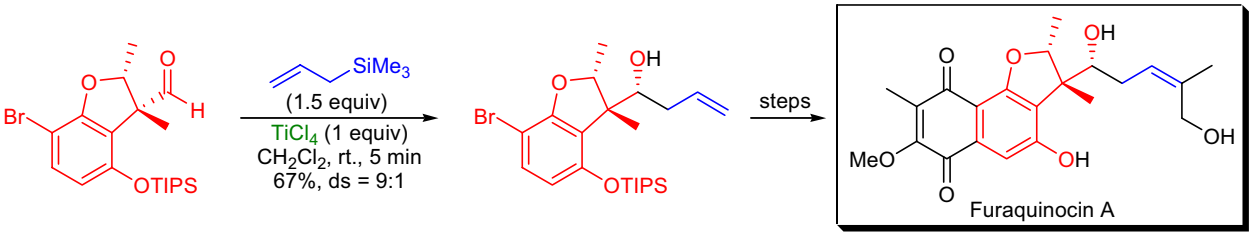
The reaction starts with the activation of the carbonyl group by the Lewis acid. Subsequent carbon-carbon bond formation leads to a silyl-stabilized carbocation,[45] which after loss of the trimethylsilyl group, gives the double bond. From studies conducted on chiral allylsilanes, it was concluded that the incoming electrophile attacks the double bond on the surface opposite to the silyl group.[42] The reaction of aldehydes with C3 substituted allylsilanes leads to the *syn*-diastereomer as the major product, and (*E*)-allylsilanes give higher diastereoselectivities than (*Z*)-allylsilanes. The reaction presumably goes through an open transition state.[38] The possible transition states leading to the *syn*-diastereomer are depicted below.[43,44]



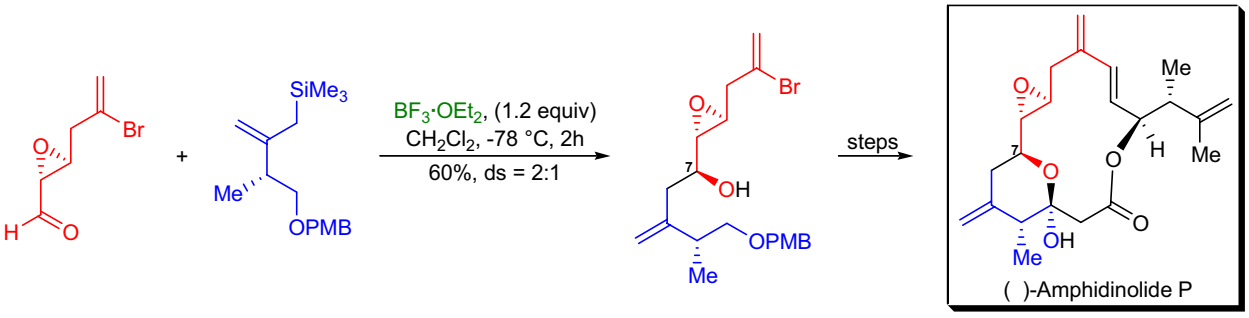
SAKURAI ALLYLATION

Synthetic Applications:

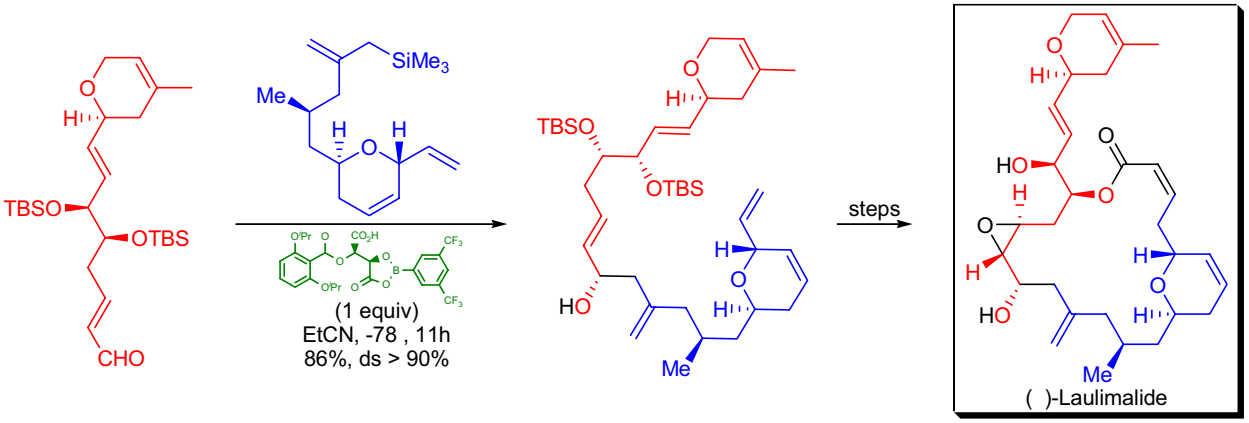
In the laboratory of B.M. Trost, a modular approach toward the total syntheses of furaquinocins was developed.[47] To introduce the homoallylic side chain in a diastereoselective fashion, they utilized the *Sakurai allylation reaction*. During their studies they found that the highest diastereoselectivity can be achieved using 1 equivalent of $TiCl_4$ at room temperature. Application of other Lewis acids such as $BF_3{\cdot}OEt_2$ gave the product with lower selectivity. Attempts to perform the allylation using catalytic amounts of Lewis acids such as $FeCl_3$ or $Sc(OTf)_3$ led to no conversion. The resulting homoallylic alcohol served as a common intermediate toward the syntheses of both furaquinocin A and B.



A convergent total synthesis of 15-membered macrolactone, (–)-amphidinolide P was reported by D.R. Williams and coworkers.[48] In their approach, they utilized the *Sakurai allylation* to introduce the C7 hydroxyl group and the homoallylic side chain. The transformation was effected by $BF_3{\cdot}OEt_2$ at -78 °C to provide the homoallylic alcohol as a 2:1 mixture of diastereomers. The desired alcohol proved to be the major diastereomer, as it resulted from the Felkin-Ahn controlled addition of the allylsilane to the aldehyde. The minor diastereomer was converted into the desired stereoisomer *via* a *Mitsunobu reaction*.



A highly convergent, enantioselective total synthesis of structurally novel, cancer therapeutic lead, (–)-laulimalide was achieved by P.A. Wender and co-workers.[49] During the synthesis, they performed an unprecedented complex asymmetric *Sakurai allylation reaction* as a key step to form the C14-C15 carbon-carbon bond. In this transformation, they utilized a chiral, nonracemic (acyloxy)borane Lewis acid that was developed by H. Yamamoto.[15] According to Yamamoto's original procedure, only a catalytic amount (10-20 mol%) of the Lewis acid was needed to bring about the desired transformation with high yield and enantioselectivity. However, in this case, one equivalent of the Lewis acid was necessary to effect the allylation. The reaction was carried out in propionitrile at -78 °C, and the product was obtained in high yield and as the only detectable diastereomer by spectroscopic methods.



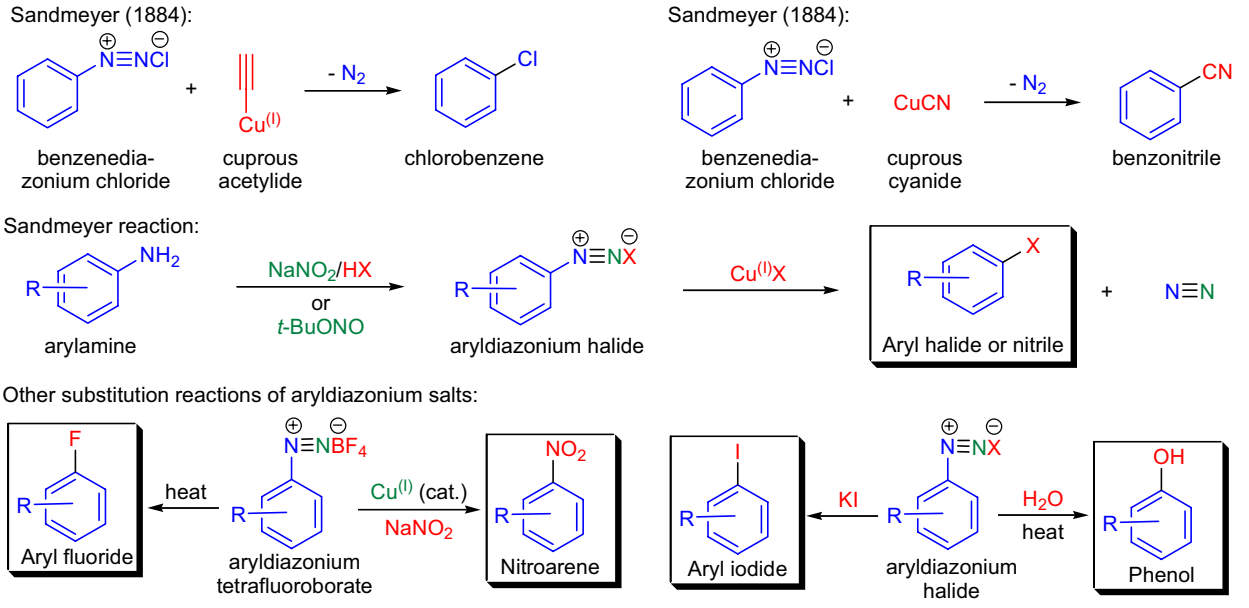
SANDMEYER REACTION

(References are on page 669)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-19]]

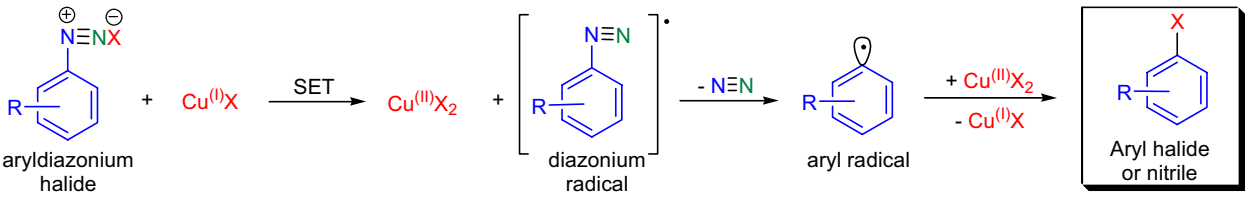
In 1884, T. Sandmeyer intended to prepare phenylacetylene by reacting benzenediazonium chloride with copper(I) acetylide, but the major product of the reaction was chlorobenzene, and no trace of the desired product was detected.[3] Careful examination of the reaction conditions revealed that copper(I) chloride was formed *in situ* and it catalyzed the replacement of the diazonium group with a chlorine atom.[4] Sandmeyer also showed that bromobenzene was formed by using copper(I) bromide, and copper(I) cyanide led to benzonitrile. The substitution of aryldiazonium salts with halides or pesudohalides is known as the *Sandmeyer reaction*. The general features of this transformation are: 1) the required aryldiazonium halides are usually prepared from arylamines *via* diazotization using either $NaNO_2$/hydrohalic acid in water or alkyl nitrites (e.g., *tert*-butyl nitrite) under anhydrous conditions; 2) the aryldiazonium halides are not isolated but reacted in the same pot with copper(I) chloride, bromide or cyanide to obtain the corresponding aryl chloride, aryl bromide, and aryl nitrile, respectively; 3) the counterion of the copper(I) salt has to match the conjugate base of the hydrohalic acid otherwise product mixtures are formed; 4) the preparation of aryl iodides does not require the use of a copper(I) salts; simply adding potassium iodide brings about the substitution accompanied by the loss of dinitrogen; and 5) the substitution pattern on the aromatic amine can be widely varied, both electron-donating and electron-withdrawing groups are tolerated. There are other useful substitution reactions of aryldiazonium salts, but these are referred to with different names (or with no specific name):[8] 1) when the aryldiazonium halides are treated with hydrogen chloride or hydrogen bromide in the presence of copper metal to afford aryl chlorides and bromides, the process is called the *Gattermann reaction*; 2) the thermal decomposition of aryldiazonium tetrafluoroborates to give aryl fluorides is known as the *Balz-Schiemann reaction*; 3) aryldiazonium tetrafluoroborates react with sodium nitrite in the presence of catalytic amounts of copper(I) salt to give nitroarenes;[20,21] and 4) aryldiazonium salts can also be converted to phenols by heating with trifluoroacetic acid, aqueous sulfuric acid, or with aqueous solution of copper salts (occasionally called the *Sandmeyer hydroxylation*).[22-24]



R = H, alkyl, aryl, electron-withdrawing groups (EWG) or electron-donating groups (EDG); HX: HCl, HBr; X = Cl, Br, CN

Mechanism: [25-32,9,33,34,16,35,36,19,24]

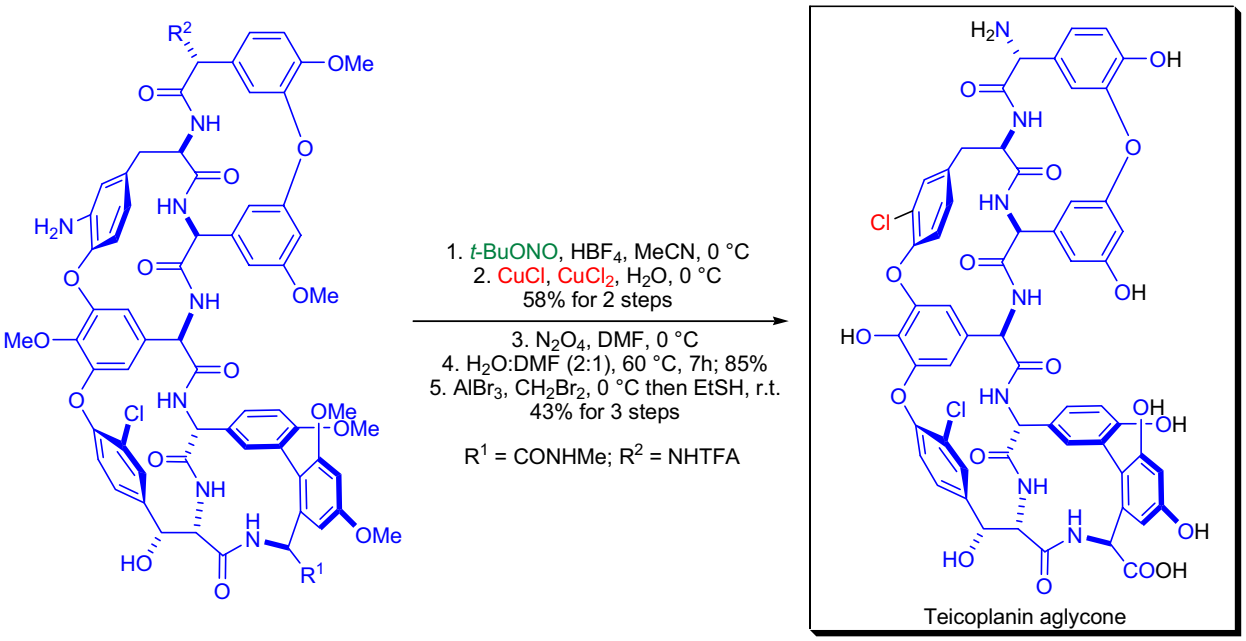
The mechanism of the *Sandmeyer reaction* is not completely understood. For a long time it was believed to proceed *via* aryl cations, but later W.A. Waters and then later J.K. Kochi proposed a radical mechanism which was catalytic for the copper(I) salt.[25,26] In a single electron-transfer event the diazonium halide is reduced to a diazonium radical which quickly loses dinitrogen to afford an aryl radical. A final ligand transfer from the copper(II) salt completes the catalytic cycle and regenerates the copper(I) species.



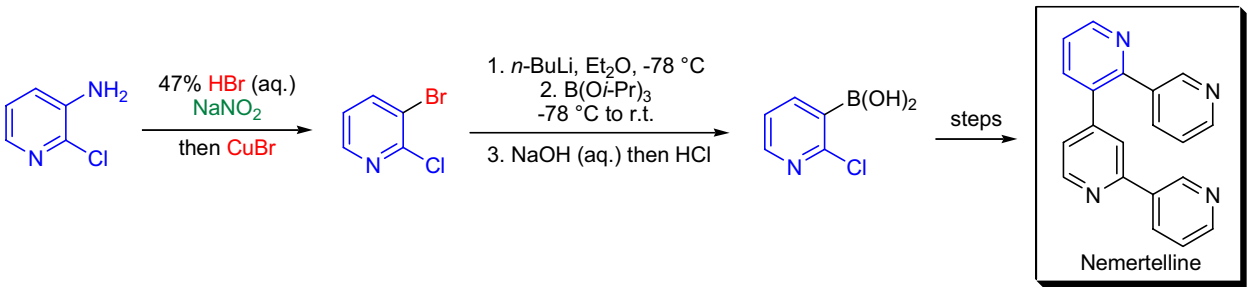
SANDMEYER REACTION

Synthetic Applications:

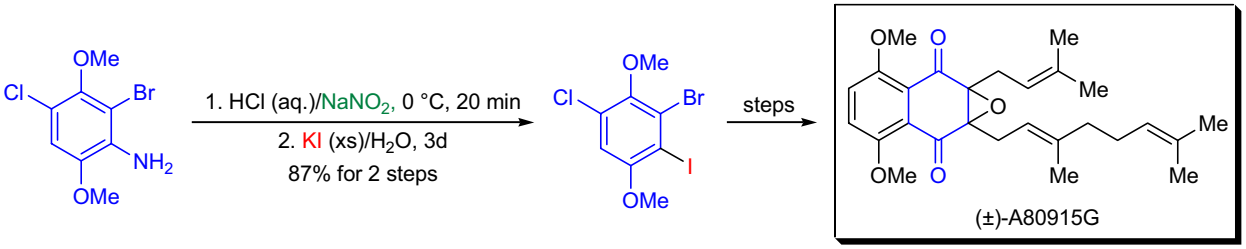
In the laboratory of D.A. Evans the total synthesis of the teicoplanin aglycon was accomplished.[37] In the endgame of the synthetic effort the introduction of the required chloro substituent on ring-2 under mild conditions was necessary. The authors chose the *Sandmeyer reaction* to bring about the desired transformation of the aromatic amine moiety. First the substrate was diazotized with *t*-butyl nitrite and HBF_4 in acetonitrile and then in the same pot a mixture of copper(I) chloride and copper(II) chloride in large excess was added at low temperature. The desired aryl chloride was isolated in moderate yield. To complete the synthesis, the following steps had to be carried out: 1) deprotection of the carboxy-terminal *N*-methylamide with N_2O_4 followed by a pH neutral hydrolysis; and 2) global demethylation at room temperature using $AlBr_3$/EtSH with concomitant *N*-terminal trifluoroacetamide hydrolysis.



The neurotoxic quaterpyridine natural product nemertelline was successfully synthesized by S. Rault et al. using a *Suzuki cross-coupling* as the key step. The boronic acid coupling partner, required for the *Suzuki reaction*, was prepared by first subjecting 3-amino-2-chloropyridine to the conditions of the *Sandmeyer reaction* followed by a lithium-halogen exchange and trapping the lithiopyridine derivative with triisopropylborate.



M. Nakata and co-workers completed the concise total synthesis of ( )-A80915G, which belongs to the napyradiomycin family of antibiotics.[38] There were two key carbon-carbon bond forming reactions in the synthetic sequence: a *Stille cross-coupling* between an aromatic trihalide and geranyl tributyltin and a *Diels-Alder cycloaddition* employing the Danishefsky-Brassard diene. A *Sandmeyer reaction* was used to introduce the iodine substituent to the 2-bromo-4-chloro-3,6-dimethoxy-aniline substrate in order to obtain the required trihalogenated 1,4-dimethoxy-benzene precursor.



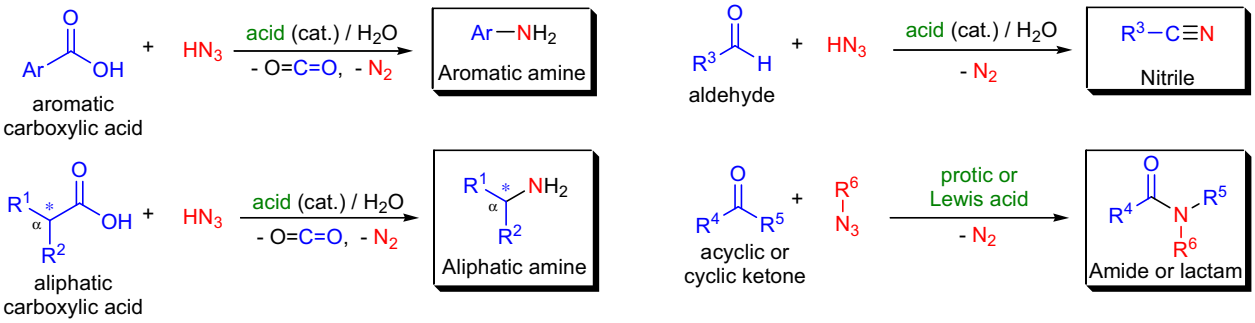
SCHMIDT REACTION

(References are on page 670)

Importance:

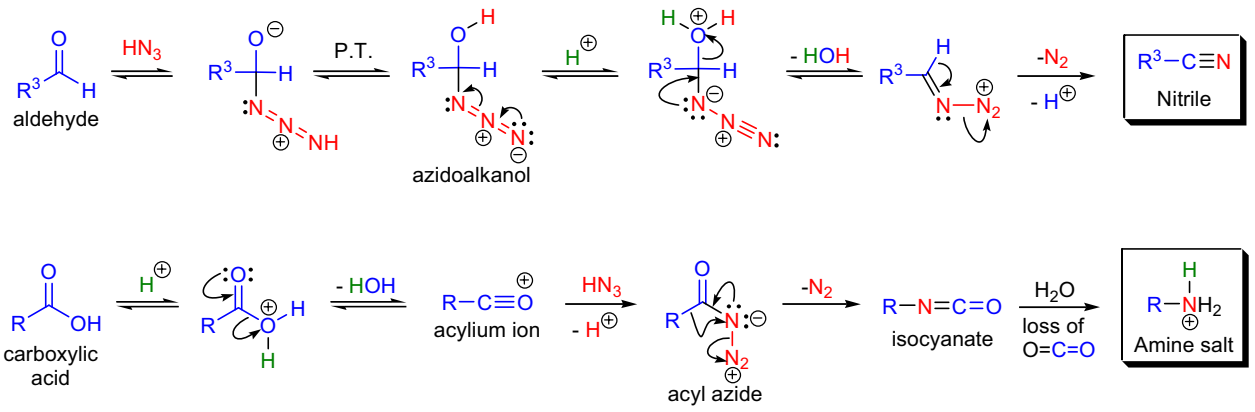
[*Seminal Publications*[1,2]; *Reviews*[3-10]; *Modifications & Improvements*[11-17]; *Theoretical Studies*[18-21]]

In 1923, K.F. Schmidt reported that heating hydrazoic acid (HN_3) with benzophenone in the presence of sulfuric acid, afforded benzanilide in quantitative yield.[1] Later this transformation was shown to be general for ketones, aldehydes, and carboxylic acids that underwent similar reactions with HN_3 to give amides, nitriles, and amines, respectively. The reaction of carbonyl compounds with hydrazoic acid or alkyl azides in the presence of acid catalysts is known as the *Schmidt reaction*. The general features of the *Schmidt reaction* are: 1) the transformation occurs in a single stage from carboxylic acids unlike the related *Curtius and Hoffmann rearrangements*; 2) the reaction conditions are mild, the reagents are readily available, the procedure is simple, and does not require special equipment; 3) protic acids are used as acid catalysts (e.g., H_2SO_4, PPA, trichloroacetic acid/H_2SO_4, TFA, TFAA), and sulfuric acid is by far the most widely used; 4) hydrogen azide is handled either as a solution in an inert solvent (e.g., $CHCl_3$) or generated *in situ* by adding NaN_3 to the acidic reaction mixture; 5) HN_3 is known to be toxic and explosive (especially on large scale); 6) in the case of carboxylic acids, the best results are obtained with aliphatic and sterically hindered aromatic substrates; 7) the product amines are one-carbon shorter homologs of the substrates due the loss of CO_2; 8) aromatic acids with electron-withdrawing groups require the use of very strong acid catalysts (e.g., conc. H_2SO_4 or oleum) and very electron-poor heterocyclic acids usually do not react; 9) the α-stereocenter remains unaffected and the product amine is obtained with retention of configuration; 10) carboxylic acids that are fully alkyl or aryl substituted at the α-position (have no α hydrogen atom) may undergo side reactions due to the decarboxylation of the acid to a stable carbocation; 11) 1,3-dicarboxylic acids react at only one of the carboxylic acid fuctional groups; 12) α-amino acids do not react; 13) α,β-unsaturated carboxylic acids are not good substrates, since they give rise to complex reaction mixtures; 14) aldehydes and ketones react with hydrazoic acid faster than carboxylic acids so good chemoselectivity can be achieved with keto acids; 15) aliphatic aldehydes are unstable in sulfuric acid, so mainly aromatic aldehydes are used; 16) the main product with aldehydes is the corresponding nitrile, but the formation of formamides is often a side reaction; 17) symmetrical ketones give rise to *N*-substituted amides; 18) in unsymmetrical ketones such as alkyl aryl ketones, the aryl group migrates preferentially so *N*-aryl amides are obtained; 19) cyclic ketones undergo ring-enlargement to afford cyclic amides; 20) Lewis acids are effective catalysts when alkyl azides are employed; and 21) the reaction works efficiently intramolecularly and affords *N*-substituted lactams. The disadvantages of the *Schmidt reaction* are: 1) carbonyl compounds and carboxylic acids that are unstable in aqueous acid cannot be used as substrates; 2) the reaction medium has to be fairly acidic to achieve high yields; 3) when ketones are reacted with excess HN_3, tetrazoles are formed in significant amounts; and 4) in addition to the carbonyl group, several other functional groups such as nitriles, imines, diimides, certain alkenes, and alcohols (which are dehydrated to alkenes in the acidic medium) react with HN_3.



$R^{1\text{-}2}$ = alkyl, aryl; Ar = substituted aryl or heteroaromatic; R^3 = Me, substituted aryl; R^4 = alkyl, substituted alkyl; R^5 = aryl; R^6 = H, alkyl or aryl; Lewis acid: $TiCl_4$, TFA, CH_3SO_3H; acid catalyst: H_2SO_4, PPA, Cl_3CCO_2H/H_2SO_4, TFA, TFAA

Mechanism:[22-25,7,26-28]



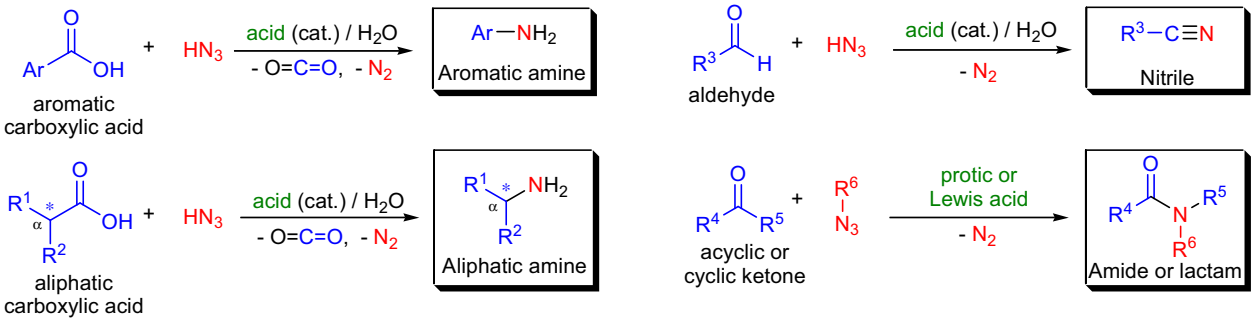
SCHMIDT REACTION

(References are on page 670)

Importance:

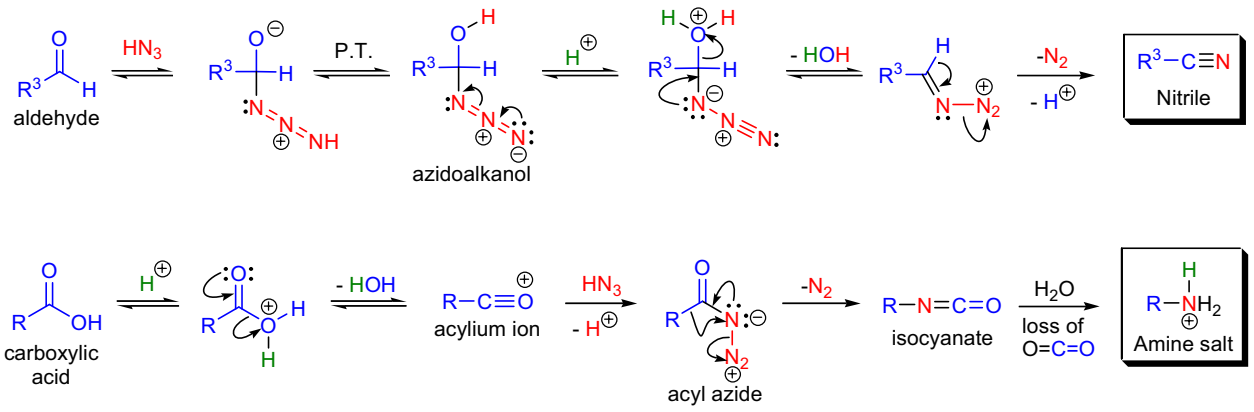
[*Seminal Publications*[1,2]; *Reviews*[3-10]; *Modifications & Improvements*[11-17]; *Theoretical Studies*[18-21]]

In 1923, K.F. Schmidt reported that heating hydrazoic acid (HN_3) with benzophenone in the presence of sulfuric acid, afforded benzanilide in quantitative yield.[1] Later this transformation was shown to be general for ketones, aldehydes, and carboxylic acids that underwent similar reactions with HN_3 to give amides, nitriles, and amines, respectively. The reaction of carbonyl compounds with hydrazoic acid or alkyl azides in the presence of acid catalysts is known as the *Schmidt reaction*. The general features of the *Schmidt reaction* are: 1) the transformation occurs in a single stage from carboxylic acids unlike the related *Curtius and Hoffmann rearrangements*; 2) the reaction conditions are mild, the reagents are readily available, the procedure is simple, and does not require special equipment; 3) protic acids are used as acid catalysts (e.g., H_2SO_4, PPA, trichloroacetic acid/H_2SO_4, TFA, TFAA), and sulfuric acid is by far the most widely used; 4) hydrogen azide is handled either as a solution in an inert solvent (e.g., $CHCl_3$) or generated *in situ* by adding NaN_3 to the acidic reaction mixture; 5) HN_3 is known to be toxic and explosive (especially on large scale); 6) in the case of carboxylic acids, the best results are obtained with aliphatic and sterically hindered aromatic substrates; 7) the product amines are one-carbon shorter homologs of the substrates due the loss of CO_2; 8) aromatic acids with electron-withdrawing groups require the use of very strong acid catalysts (e.g., conc. H_2SO_4 or oleum) and very electron-poor heterocyclic acids usually do not react; 9) the α-stereocenter remains unaffected and the product amine is obtained with retention of configuration; 10) carboxylic acids that are fully alkyl or aryl substituted at the α-position (have no α hydrogen atom) may undergo side reactions due to the decarboxylation of the acid to a stable carbocation; 11) 1,3-dicarboxylic acids react at only one of the carboxylic acid fuctional groups; 12) α-amino acids do not react; 13) α,β-unsaturated carboxylic acids are not good substrates, since they give rise to complex reaction mixtures; 14) aldehydes and ketones react with hydrazoic acid faster than carboxylic acids so good chemoselectivity can be achieved with keto acids; 15) aliphatic aldehydes are unstable in sulfuric acid, so mainly aromatic aldehydes are used; 16) the main product with aldehydes is the corresponding nitrile, but the formation of formamides is often a side reaction; 17) symmetrical ketones give rise to *N*-substituted amides; 18) in unsymmetrical ketones such as alkyl aryl ketones, the aryl group migrates preferentially so *N*-aryl amides are obtained; 19) cyclic ketones undergo ring-enlargement to afford cyclic amides; 20) Lewis acids are effective catalysts when alkyl azides are employed; and 21) the reaction works efficiently intramolecularly and affords *N*-substituted lactams. The disadvantages of the *Schmidt reaction* are: 1) carbonyl compounds and carboxylic acids that are unstable in aqueous acid cannot be used as substrates; 2) the reaction medium has to be fairly acidic to achieve high yields; 3) when ketones are reacted with excess HN_3, tetrazoles are formed in significant amounts; and 4) in addition to the carbonyl group, several other functional groups such as nitriles, imines, diimides, certain alkenes, and alcohols (which are dehydrated to alkenes in the acidic medium) react with HN_3.



$R^{1\text{-}2}$ = alkyl, aryl; Ar = substituted aryl or heteroaromatic; R^3 = Me, substituted aryl; R^4 = alkyl, substituted alkyl; R^5 = aryl; R^6 = H, alkyl or aryl; Lewis acid: $TiCl_4$, TFA, CH_3SO_3H; acid catalyst: H_2SO_4, PPA, Cl_3CCO_2H/H_2SO_4, TFA, TFAA

Mechanism:[22-25,7,26-28]



SCHOTTEN-BAUMANN REACTION

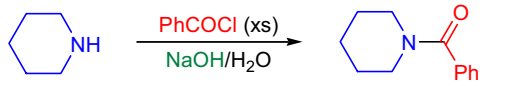
(References are on page 670)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5-21]; *Theoretical Studies*[22]]

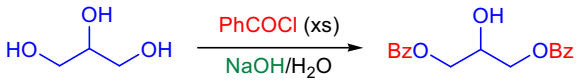
In 1884, C. Schotten reported an efficient method for the preparation of *N*-benzoyl piperidine from piperidine and benzoyl chloride in water and in the presence of sodium hydroxide.[1] In 1886, E. Baumann showed that the same reaction conditions were suitable for the preparation of benzoic acid esters from alcohols and benzoyl chloride.[2] The neat alcohol and benzoyl chloride were mixed in water, then the resulting mixture was treated with aqueous sodium hydroxide. The product esters were frequently crystalline and could be isolated in high yield. Baumann demonstrated the power of this method by benzoylating several polyhydroxy compounds such as glucose and glycerol. The synthesis of esters from alcohols and amides from amines with acyl halides or anhydrides in the presence of aqueous base is known as the *Schotten-Baumann reaction*. The general features of these transformations are: 1) the reaction is especially well-suited for the preparation of simple amides; 2) in the typical procedure the alcohol or ester is mixed with excess acyl halide or anhydride in the presence of aqueous sodium hydroxide or saturated aqueous sodium bicarbonate while the reaction mixture is stirred vigorously; 3) the order of reactivity for alcohols is: 1°>2°>3°, which means that sterically hindered secondary and tertiary alcohols are usually acylated sluggishly; 4) the order of reactivity of the amines is determined by their basicity and generally the more basic amine is acylated faster; 5) the success of the process depends on the reactivity of the acyl halide, and in general acyl halides that are less reactive give higher yields of the product (since less reactive acyl halides do not undergo rapid hydrolysis by water); 6) aromatic acyl halides are more stable under aqueous conditions than aliphatic acyl halides, so they are more suitable for acylation under the Schotten-Baumann conditions; 7) in the acylation of primary alcohols the presence of a base is not always necessary (but it is recommended to achieve high yields), since the by-product hydrogen halide in certain cases does not hydrolyze the product ester; 8) the use of a base is required during the acylation of secondary and tertiary alcohols; and 9) during the acylation of amines the presence of a base is crucial, since the substrate amine is rendered unreactive upon protonation by the acid by-product (the base applied must be stronger than the substrate amine). Several modifications were developed for the acylation of sterically hindered substrates. Today, the majority of acylation reactions is conducted in aprotic organic solvents in the presence of organic bases (e.g., pyridine, DMAP, etc.) and/or Lewis acids, and they can all be considered as modifications of the original Schotten-Baumann conditions.

Schotten (1884):



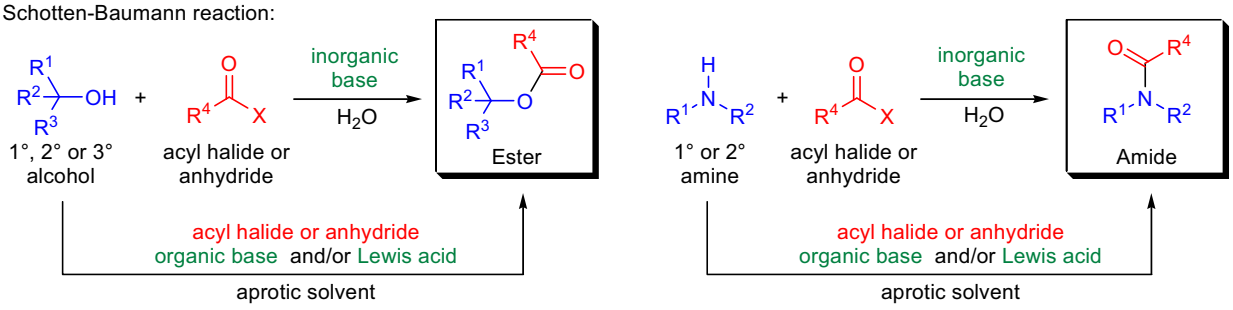
piperidine — *N*-benzoyl piperidine

Baumann (1886):



glycerol — 1,3-*O*-dibenzoyl glycerol

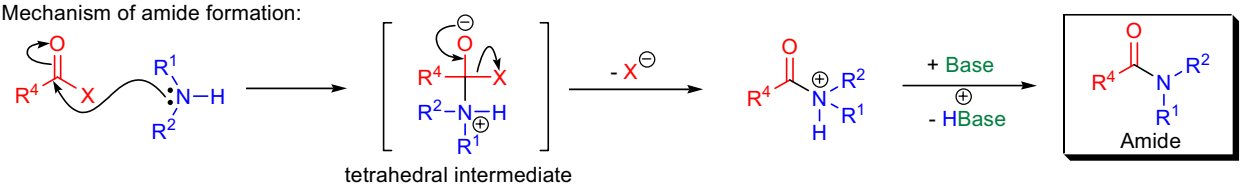
Schotten-Baumann reaction:



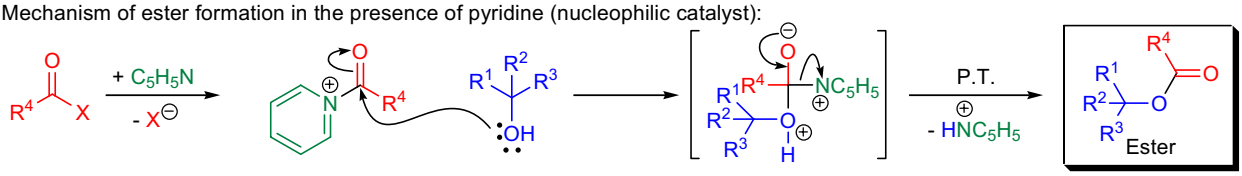
R^{1-3} = H, alkyl, aryl, heteroaryl; R^4 = alkyl, aryl; X = F, Cl, Br, $OCOR^4$; inorganic base: NaOH, KOH, Na_2CO_3, $NaHCO_3$; organic base: pyridine, DMAP, Et_3N, $(i\text{-}Pr)_2NEt$, PPh_3; Lewis acid: $MgBr_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, TMSOTf

Mechanism:[23,24,4,25-27]

Mechanism of amide formation:



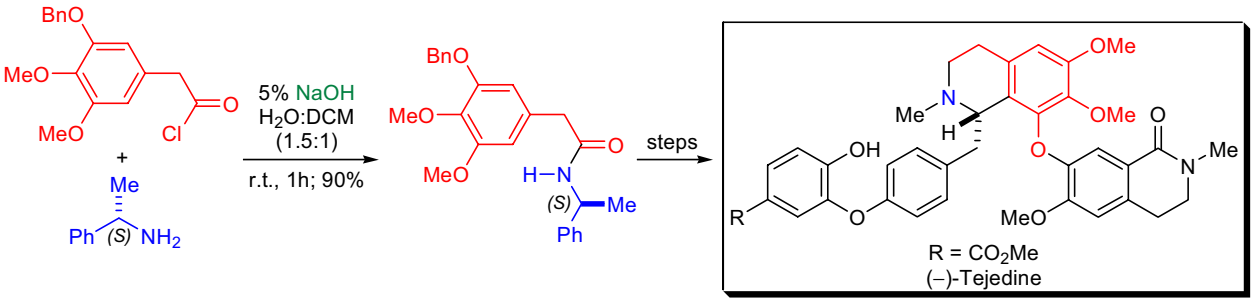
Mechanism of ester formation in the presence of pyridine (nucleophilic catalyst):



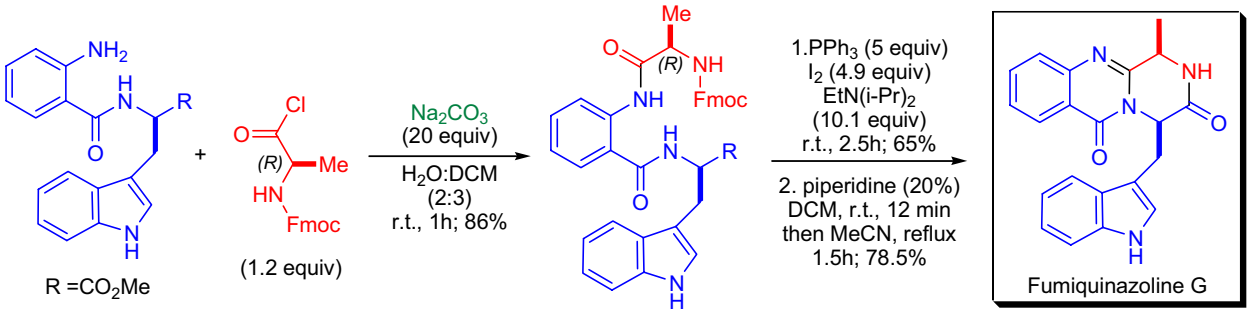
SCHOTTEN-BAUMANN REACTION

Synthetic Applications:

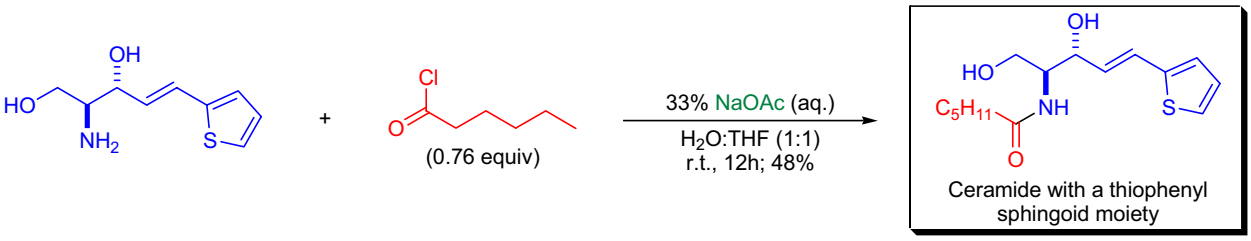
The first enantioselective total synthesis of (–)-tejedine was completed by P.E. Georghiou using a chiral auxiliary-assisted diastereoselective *Bischler-Napieralski cyclization* as one of the key steps.[28] The chiral auxiliary was the commercially available (*S*)-α-methylbenzylamine, which was coupled to the substrate using the original *Schotten-Baumann acylation* conditions. The acid chloride was reacted with the chiral amine in a solvent mixture containing aqueous sodium hydroxide and dichloromethane and the desired amide was isolated in excellent yield.



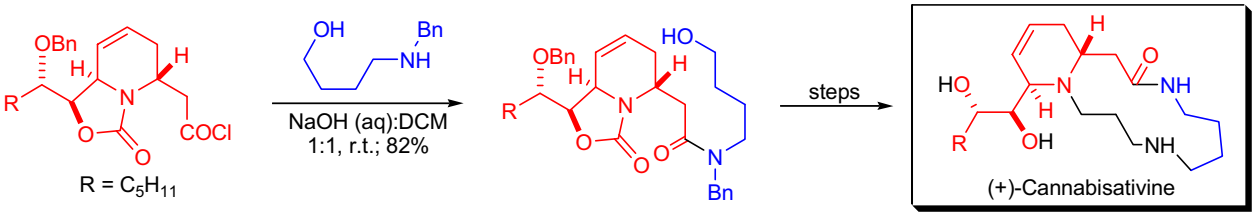
In the laboratory of A. Ganesan the short biomimetic total synthesis of the fumiquinazoline alkaloid fumiquinazoline G was accomplished.[29] The key step in the synthetic sequence was the dehydration of the anthranilamide residue in a linear tripeptide to the corresponding benzoxazine by reacting it with triphenylphosphine, iodine and Hünig's base. The authors initially prepared the linear tripeptide by condensing Fmoc-D-alanine with PyBroP as the acylating agent, but the product was formed only in a poor yield. When the peptide bond was formed under two-phase *Schotten-Baumann conditions* using sodium carbonate as the base, the desired tripeptide was isolated in high yield.



One of the intermediates in sphingolipid biosynthesis and degradation is ceramide, which influences certain cellular processes such as apoptosis and cell differentiation. The research team of P. Herdwijn prepared several ceramide analogues with substituted aromatic rings in the sphingoid moiety and evaluated their biological activity in hippocampal neurons.[30] The ceramide analogue with a thiophenyl sphingoid moiety was prepared by the *Schotten-Baumann acylation* of an amino diol with hexanoyl chloride. Since the nucleophilicity of the amino group is far greater than that of the hydroxyl groups, the acylation took place selectively to form the corresponding amide.



The first asymmetric synthesis of (+)-cannabisativine was achived by D.L. Comins et al. using the addition of metallo enolates to a chiral 1-acylpyridinium salt as one of the key steps.[31] The amide bond was created under the *Schotten-Baumann conditions* from a bicyclic acid chloride and a 1,4-amino alcohol.



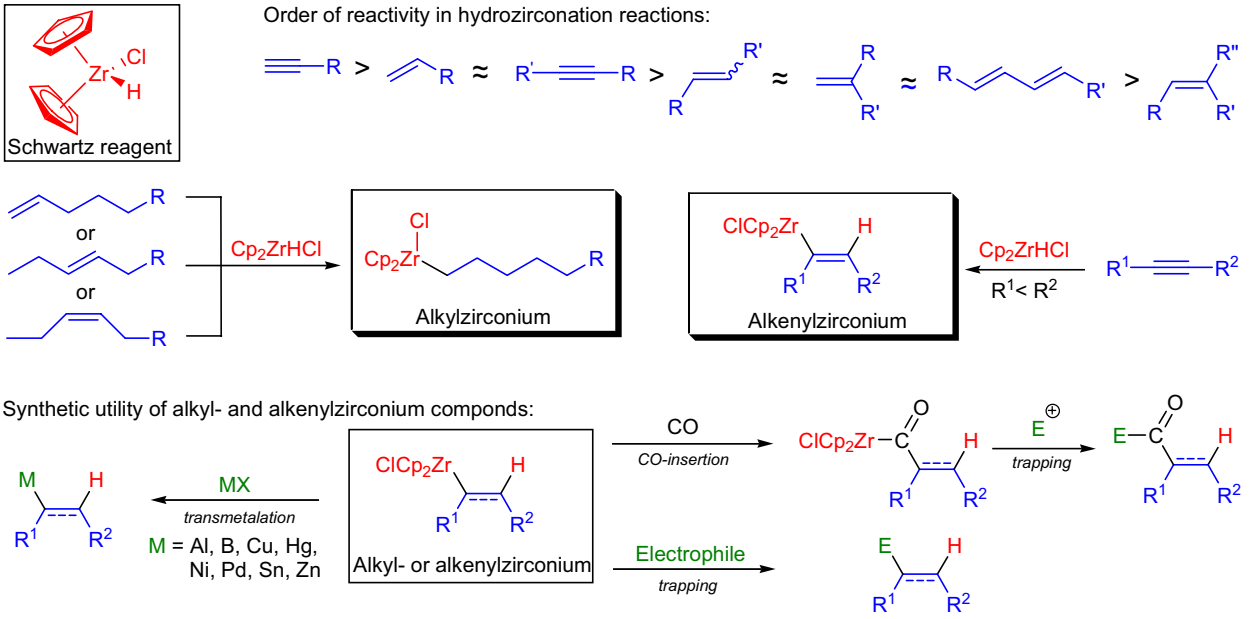
SCHWARTZ HYDROZIRCONATION

(References are on page 671)

Importance:

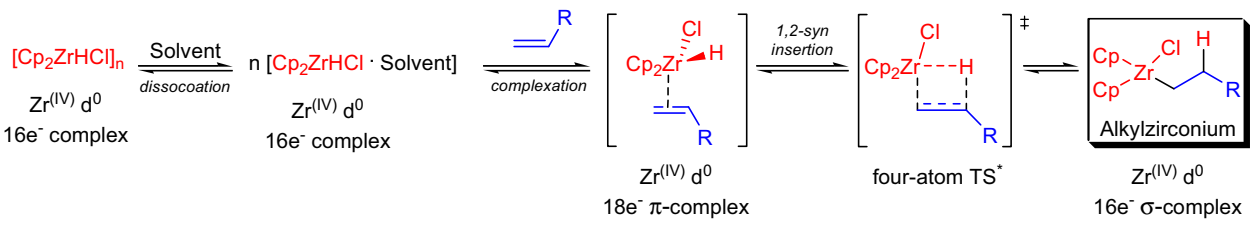
[*Seminal Publications*[1-4]; *Reviews*[5-18]; *Modifications & Improvements*[19-22]; *Theoretical Studies*[23-29]]

In 1970, P.C. Wailes and H. Weigold were the first to prepare zirconocene hydrochloride[2] (Cp_2ZrHCl) by the reduction of Cp_2ZrCl_2, but it was J. Schwartz who examined its reactions with a wide range of substrates and developed it as a useful reagent for organic synthesis.[3] The reaction of Cp_2ZrHCl (*Schwartz reagent*) with multiple bonds to form alkyl- and alkenylzirconium compounds is called the *Schwartz hydrozirconation*. The general features of the reaction are: 1) the hydrozirconation of alkenes and alkynes takes place at room temperature; 2) the reaction rate is orders of magnitude faster in ether solvents (e.g., THF, oxetane) than in hydrocarbon solvents such as hexanes and benzene; 3) under thermodynamic control, terminal or internal alkenes all give the terminal alkylzirconium compound because a rapid "chain walk" takes place to relieve the steric crowding;[12] 3) the order of reactivity for alkenes and alkynes are: terminal alkyne > terminal monosubstituted alkene ≈ internal alkyne > internal disubstituted alkene ≈ 2,2-disubstituted terminal alkene ≈ conjugated polyene > trisubstituted alkene; 4) tetrasubstituted alkenes generally do not react; 5) internal alkynes react regioselectively to give an alkenylzirconium compound in which the zirconium is located on the carbon closer to the smaller substituent; 6) conjugated dienes are hydrozirconated at the sterically less hindered double bond; and 7) the alkyl- and alkenylzirconium compounds are easily transmetallated to other useful organometallic compounds that can be used in various coupling reactions (e.g., *Negishi cross-coupling*) or can be trapped with small electrophiles (e.g., halogens, CO, isonitrile, H^+, etc.) with retention of configuration at carbon.



Mechanism: [30-32,25,33,34,12,35]

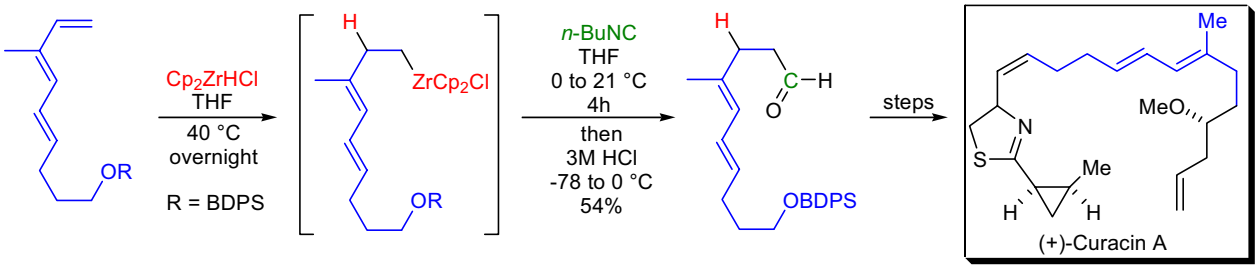
The *Schwartz hydrozirconation* is closely related to the *Brown hydroboration* reaction, but its mechanistic details are poorly understood mainly because of the oligomeric character of the Schwartz reagent, which makes the elucidation of the reaction kinetics very difficult. The fact that solvents with donor heteroatoms (e.g., THF, oxetane) accelerate hydrozirconations suggests that there is a rate-limiting dissociation of the oligomer before the addition to the multiple bond takes place. In THF the reaction is zero order in Schwartz reagent, while in oxetane it is first order both in the reagent and the alkene (or alkyne) substrate. The hydrozirconation proceeds *via* a four-atom concerted transition state (formally symmetry allowed due to the vacant d-orbitals on Zr), while the hydroboration is formally symmetry-forbidden.[25] The insertion into C-C multiple bonds takes place with *syn* stereochemistry. The *ab initio* study of hydrozirconation revealed that the attack of alkene at Zr is the most favorable between the Cl and H ligands. The alkene-Zr 18-electron π-complex is not stabilized by metal to olefin back-donation, because the zirconium has no d-electrons. Interestingly, the 16-electron alkylzirconium σ-complex is thermodynamically more stable (~10 kcal/mol) than the alkene-Zr complex, which is the driving force for hydrozirconation. (The alkene complexes of late-transition metals, however, are more thermodynamically stable. Therefore, they rarely undergo hydrometallation reactions.)



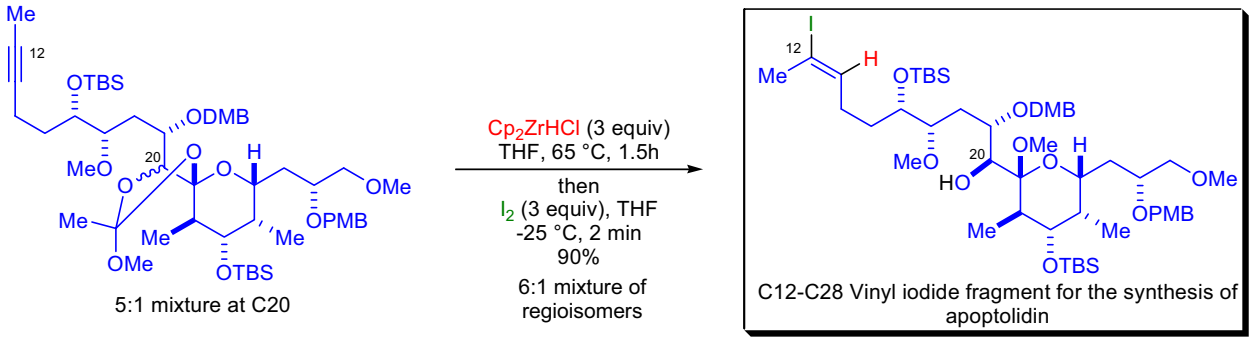
SCHWARTZ HYDROZIRCONATION

Synthetic Applications:

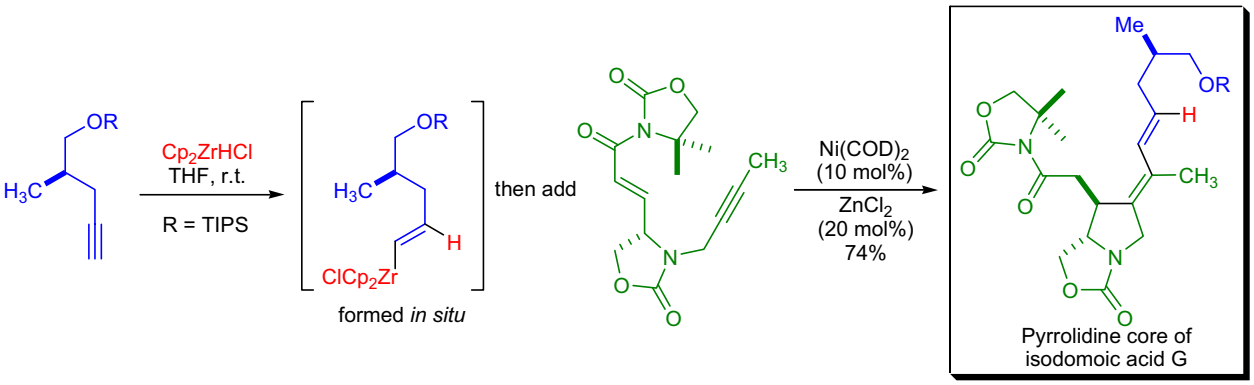
The *hydrozirconation* of polyunsaturated substrates can be plagued by extensive isomerization of double bonds. However, under carefully controlled reaction conditions, synthetically useful functionalization of conjugated polyenes can be realized. During the total synthesis of curacin A by P. Wipf and co-workers, a one-carbon homologation of conjugated triene substrate was achieved by *hydrozirconation* followed by an electrophile-trapping step.[36] The rate of formation of the desired terminal alkylzirconocene derivative was slow but was accomplished by heating the reaction mixture at 40 °C overnight. The treatment of the alkylzirconocene with *n*-butyl isocyanide and subsequent hydrolysis of the corresponding iminoylzirconocene with HCl gave the expected aldehyde in 54% yield.



The total synthesis of apoptolidin was accomplished in the laboratory of K.C. Nicolaou.[37] The key C12-C28 vinyl iodide fragment was prepared using the *Schwartz hydrozirconation* of an internal alkyne followed by trapping of the alkenylzirconium intermediate with iodine (I_2). The vinyl iodide was formed as a 6:1 mixture of regioisomers. Under the reaction conditions, the methyl orthoester was converted to the methyl glycoside moiety at C21, which was presumably facilitated by the complexation of Zr with the pyranoside oxygen atom.



J. Montgomery and co-workers established the stereochemistry of isodomoic acid G through its first total synthesis.[38] The key step to construct the pyrrolidine ring was the nickel-catalyzed coupling of an alkynyl enone with an *in situ* formed alkenylzirconium. The terminal alkyne was then exposed to the Schwartz reagent, and subsequently the alkynyl enone was added along with catalytic amounts of $Ni(COD)_2$ and $ZnCl_2$. The initial alkenylzirconium regioselectively added across the internal alkyne and was first transmetallated to an organozinc and subsequently to an organonickel intermediate. This organonickel compound underwent an *intramolecular 1,4-addition* with the enone to form the pyrrolidine ring. This one-pot operation set all the necessary stereocenters of the natural product including the stereoselective formation of the highly substituted 1,3-diene side-chain.



SEYFERTH-GILBERT HOMOLOGATION

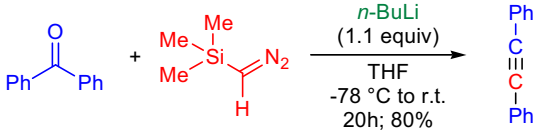
(References are on page 672)

Importance:

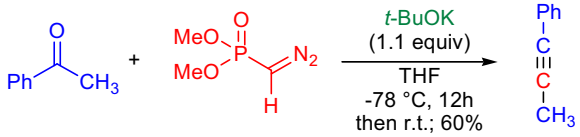
[*Seminal Publications*[1-7]; *Reviews*[8-10]; *Modifications & Improvements*[11-17]]

In 1973, E.W. Colvin and B.J. Hamill reported a convenient one-step conversion of aldehydes and ketones to acetylenes using trimethylsilyldiazomethane or dimethylphosphonodiazomethane (a compound first synthesized by D. Seyferth[2]) under basic conditions. In a subsequent paper, the authors noted that the transformation worked well only for non-enolizable carbonyl compounds such as diaryl ketones and aromatic aldehydes with electron-withdrawing groups. In 1979, J.C. Gilbert and U. Weerasooriya disclosed an improved procedure that dramatically increased the scope of the reaction.[6] The one-pot conversion of carbonyl compounds to the corresponding terminal or internal alkynes using α-diazophosphonates under basic conditions is known as the *Seyferth-Gilbert homologation*. The general features of this transformation are: 1) the phosphonate reagents are not commercially available, but they can be prepared readily;[18] 2) in the original procedure developed by Gilbert, the dialkylphosphonodiazomethane (DAMP) was deprotonated with a strong base such as an alkyllithium or potassium *tert*-butoxide, and the carbonyl compound was added at low temperature under an inert atmosphere. The product alkyne was isolated upon a simple aqueous work-up (this procedure is only rarely used, since base-sensitive substrates do not tolerate the strongly basic conditions); 3) in the *Ohira-Bestmann modification* the dimethyl-1-diazo-2-oxopropylphosphonate is added to a solution of K_2CO_3 and the aldehyde in methanol at room temperature. After several hours of stirring, the product is isolated upon aqueous work-up in excellent yield (this modified procedure is by far the most popular). The key features of the *Ohira-Bestmann protocol* are: 1) the reaction conditions are mild, and most functional groups are tolerated; 2) highly sensitive enantiopure α-alkoxy aldehydes do not undergo racemization; 3) aliphatic, aromatic, as well as arylalkyl aldehydes are homologated to the corresponding terminal alkynes in excellent yields; 4) substrates containing highly C-H acidic bonds are homologated in high yields; and 5) α,β-unsaturated aldehydes do not undergo the transformation and the expected enynes are not formed (rather the homopropargylic methyl esters are obtained).

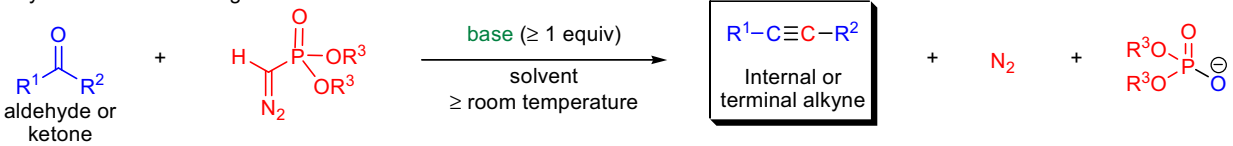
Colvin & Hamill (1973):



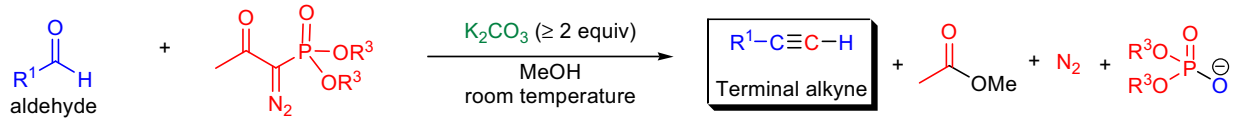
Gilbert & Weerasooriya (1979):



Seyferth-Gilbert homologation:



Modification for the synthesis of terminal alkynes (Ohira & Bestmann):

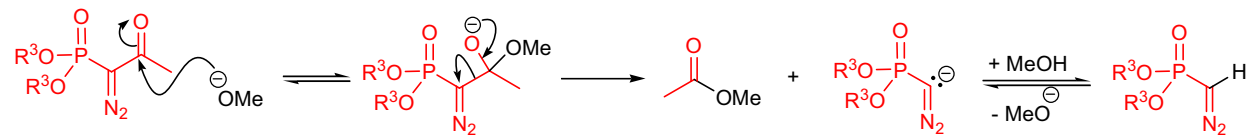


R^1 = alkyl, aryl, heteroaryl; R^2 = H, aryl, heteroaryl; R^3 = Me, Et; base: *n*-BuLi, KO-*t*Bu

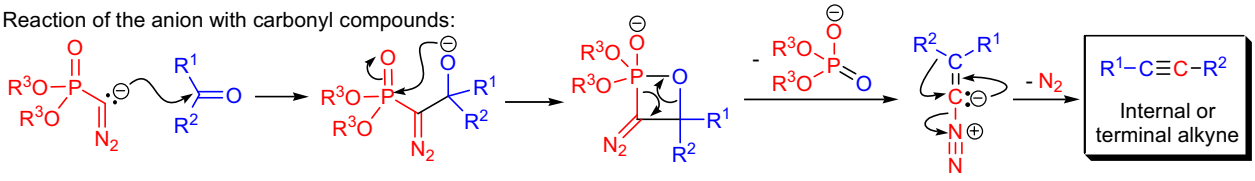
Mechanism:[7]

In the *Ohira-Bestmann modified procedure* the first step is the deacylation of the reagent by a methoxide ion. The resulting carbanion (nucleophile) attacks the carbonyl group of the aldehyde or ketone and an oxaphosphetane-type intermediate is formed (just like in the *HWE olefination*), which breaks down to afford a thermally unstable diazoalkene. The diazoalkene loses dinitrogen (α-elimination) and the resulting alkylidenecarbene undergoes a 1,2-shift to give rise to the alkyne.

Formation of the dialkylphosphonodiazomethane from dialkyl-1-diazo-2-oxopropylphosphonate:



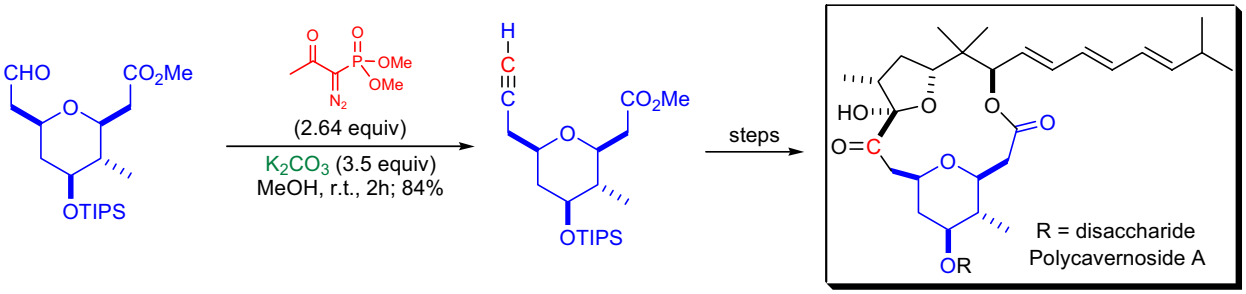
Reaction of the anion with carbonyl compounds:



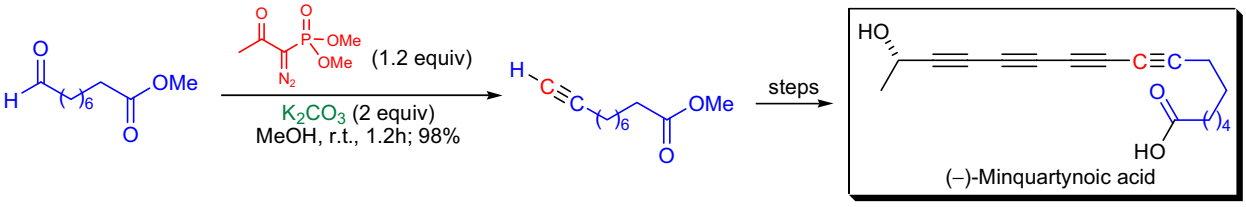
SEYFERTH-GILBERT HOMOLOGATION

Synthetic Applications:

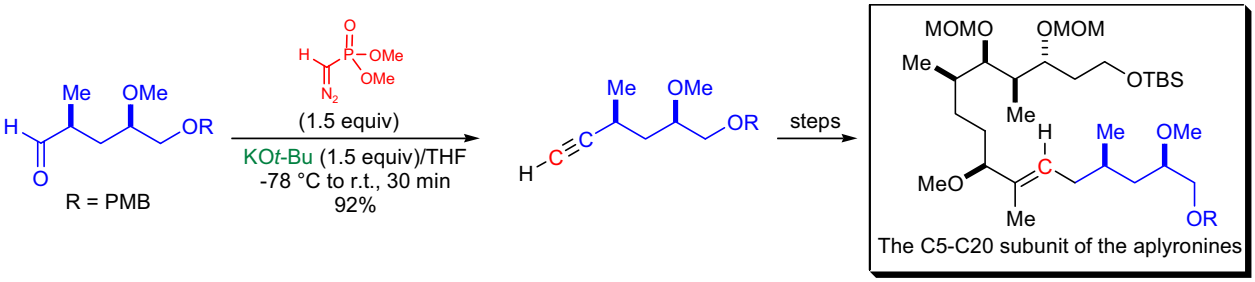
The total synthesis of the marine toxin polycavernoside A was achieved by J.D. White and co-workers.[19] In order to couple the central pyran moiety in a *Nozaki-Hiyama-Kishi reaction*, the aldehyde side chain had to be first homologated to the corresponding terminal alkyne and subsequently transformed into a vinyl bromide. The aldehyde substrate was treated under the *Ohira-Bestmann protocol*, and the desired alkyne product was obtained in high yield.



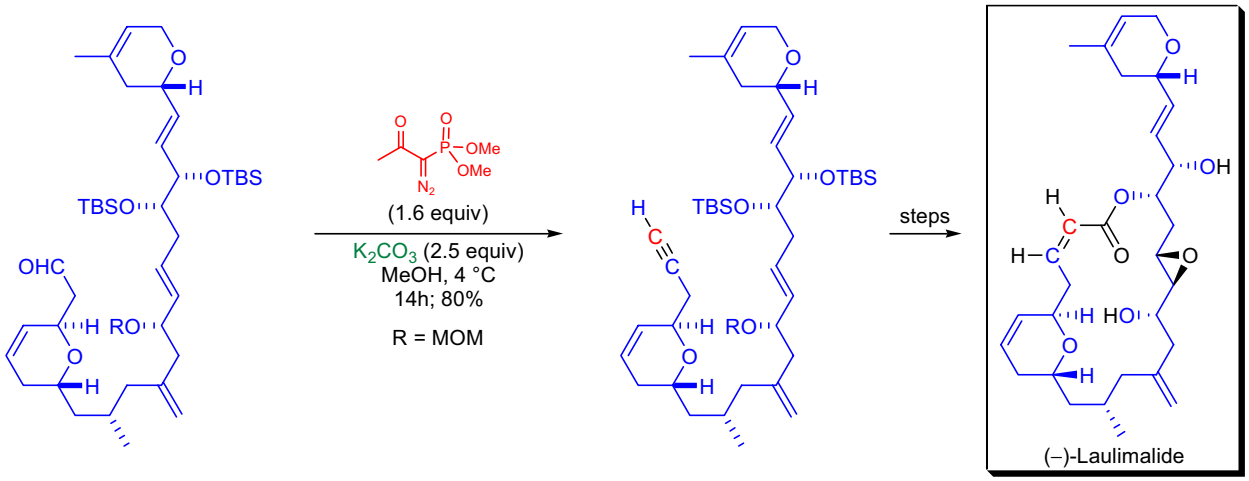
The tetraacetylenic compound (–)-minquartynoic acid was synthesized in the laboratory of B.W. Gung from commercially available azelaic acid monomethyl ester using a one-pot three-component *Cadiot-Chodkiewitz reaction* as the key step.[20] This natural product shows strong anti-cancer and anti-HIV activity. One of the alkyne components was prepared using the *modified Seyferth-Gilbert homologation*.



The stereoselective synthesis of the C5-C20 subunit of the aplyronine family of polyketide marine macrolides was accomplished by J.A. Marshall and co-workers.[21] The C15-C20 moiety was prepared using the original *Seyferth-Gilbert homologation* conditions. The diazophosphonate was deprotonated with potassium *tert*-butoxide at low temperature, and then the solution of the aldehyde was added slowly also at low temperature. Interestingly, the alternative *Corey-Fuchs alkyne synthesis* was unsuccessful on this substrate, since extensive decomposition was observed.



A structurally novel cancer therapeutic agent, (–)-laulimalide, was isolated from Pacific marine sponges in trace amounts, and it was shown to promote abnormal tubulin polymerization. P.A. Wender et al. applied the *modified Seyfert-Gilbert homologation* on a complex substrate in the endgame of the total synthesis to obtain the desired terminal alkyne.[22]



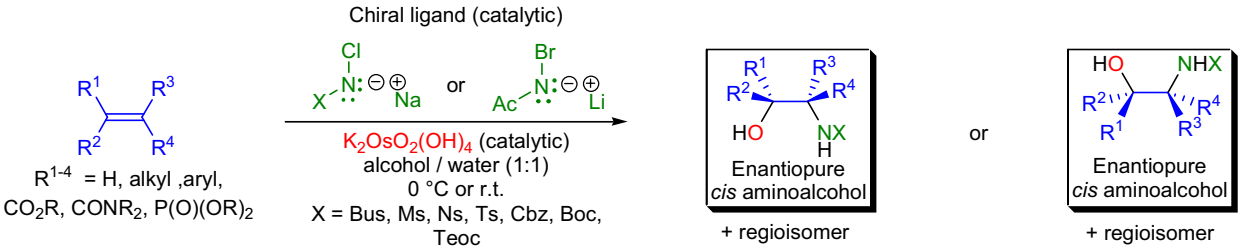
SHARPLESS ASYMMETRIC AMINOHYDROXYLATION

(References are on page 673)

Importance:

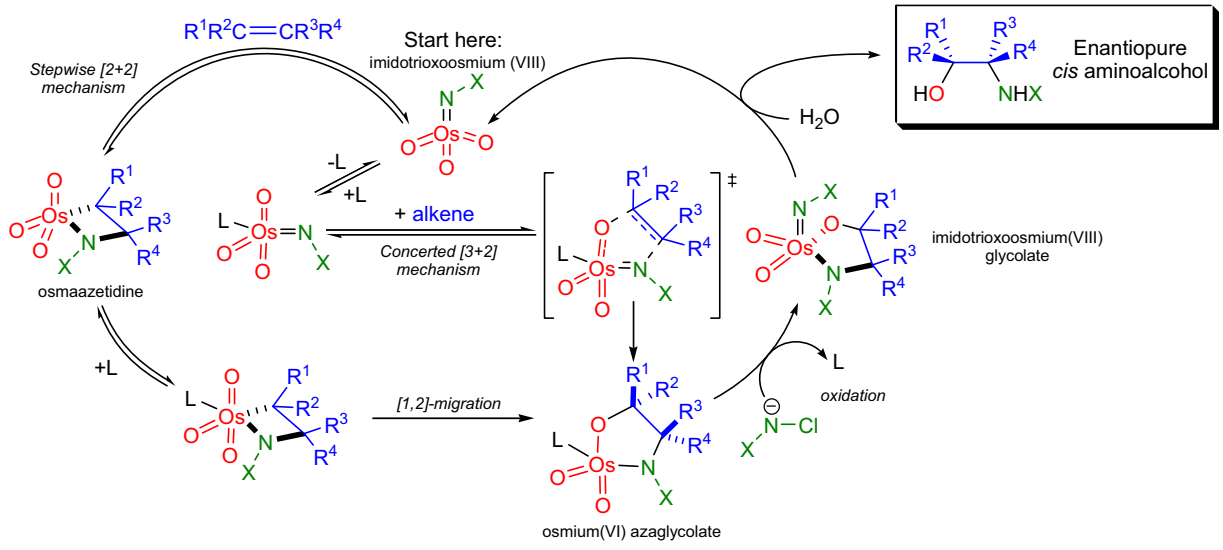
[*Seminal Publications*[1]*; Reviews*[2-8]*; Modifications & Improvements*[9-21]*; Theoretical Studies*[22]]

In 1996, K.B. Sharpless et al. reported the one-pot enantioselective synthesis of protected vicinal amino alcohols from simple alkenes.[1] This transformation is known as the *Sharpless asymmetric aminohydroxylation* (*SAA*), which complements the other asymmetric methods such as the *Sharpless asymmetric epoxidation (SAE) and dihydroxylation (SAD)* using olefins as substrates. The *SAA* is closely related to the *SAD*, since it uses the same chiral tertiary amine ligands and the factors that determine the enantioselectivity are similar. The β-amino alcohol moiety is an important pharmacophore, since it is a common structural motif in many biologically active compounds. This fact alone makes the *SAA* extremely valuable as a synthetic tool to access such compounds in good yield and with high enantioselectivity. The general features of the *SAA* are: 1) most olefins are substrates for the reaction: the best substrates have an electron-withdrawing group (e.g., CO_2R, $P(O)(OR)_2$, $CONR_2$) and tetrasubstituted alkenes do not react; 2) unlike in the *SAD*, there is no preformed reagent mixture (such as the AD-mixes) available, but the necessary components are the same except for the nitrogen source; 3) generally the nitrogen source is the alkali metal salt of an *N*-halogenated sulfonamide (X = Ms, Ns, Ts),[1,23] alkyl carbamate (X = Cbz, Boc, Teoc),[10,13,14] or amide (X = Ac);[9,24] 4) in the case of sulfonamides and acetamides, the *N*-haloamine salt is prepared from the corresponding *N*-haloamides while carbamates are prepared *in situ* by using *t*-BuOCl/NaOH; 5) the smaller the substituent (X) on the nitrogen source, the higher is the enantiopurity of the product; 6) to achieve the highest possible yield, a large excess (~3-6 equivalents) of the nitrogen source should be applied; 7) when sulfonamides are used, the substrate scope is limited to alkenes with electron-withdrawing groups, but the use of carbamates increases the substrate scope considerably; 8) just as in the *SAD,* the use of chiral bidentate tertiary amine ligands (DHQ- and DHQD-derived) give enantio-complementary results; 9) the absolute stereochemistry can be predicted with the "mnemonic device" proposed for the *SAD* and the asymmetric induction is of the same sense and similar magnitude for structurally related substrates; 10) the regioselectivity is hard to predict, since it is influenced by many factors but in the case of unsymmetrical alkenes the nitrogen generally adds to the less substituted carbon, while cinnamate esters react to give preferentially the β-amino ester product; 11) the nature of the ligand and the solvent system usually has a dramatic effect on the regioselectivity for styrene substrates;[14] 12) diols are often side-products in the *SAA* reactions, but there are several ways to reduce the extent of the dihydroxylation.[14,24,25]



Mechanism: [23,18,24-26]

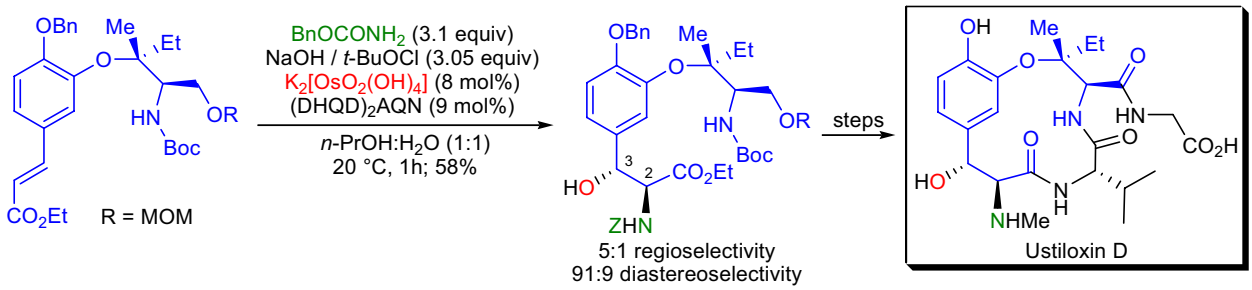
The mechanisms of the SAD and SAA are similar. The first step in mechanism of the SAA is the formal *[2+2] or [3+2] cycloaddition* of the imidotrioxoosmium(VIII) species with the olefin in a *syn*-stereospecific fashion to give eventually an osmium(VI) azaglycolate intermediate. This azaglycolate is then oxidized by the nitrogen source, while the ligand is lost and subsequent hydrolysis affords the 1,2-*cis* amino alcohol product and the imidotrioxoosmium(VIII) species which reenters the catalytic cycle.



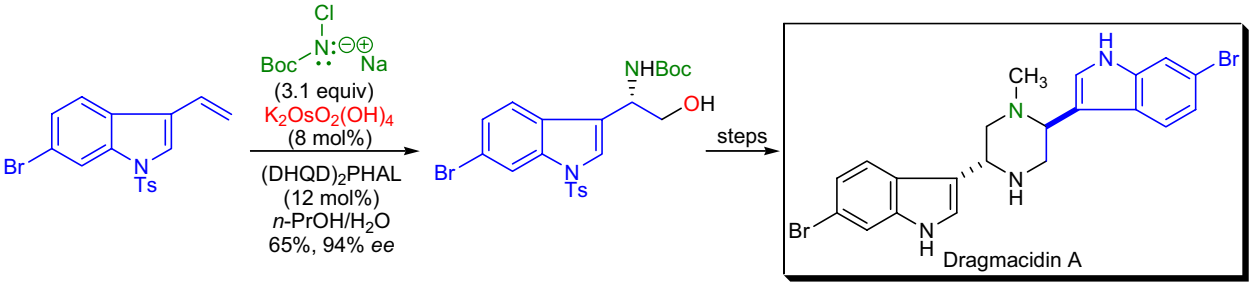
SHARPLESS ASYMMETRIC AMINOHYDROXYLATION

Synthetic Applications:

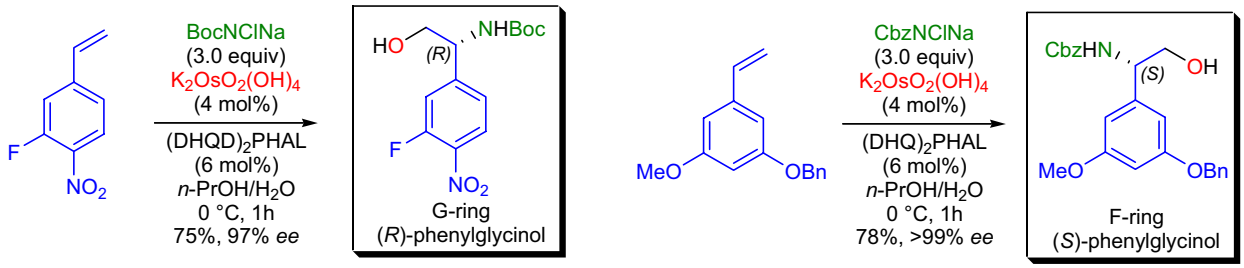
The *Sharpless regioreversed asymmetric aminohydroxylation* protocol was used as a key step in the total synthesis of ustiloxin D by M.M. Joullié and co-workers.[27] The (*E*)-ethyl cinnamate derivative was subjected to *in situ* generated sodium salt of the *N*-Cbz chloroamine in the presence of catalytic amounts of the anthraquinone-based chiral ligand to afford the desired *N*-Cbz protected (2*S*,3*R*)-β-hydroxy amino ester in good yield and with good diastereoselectivity.



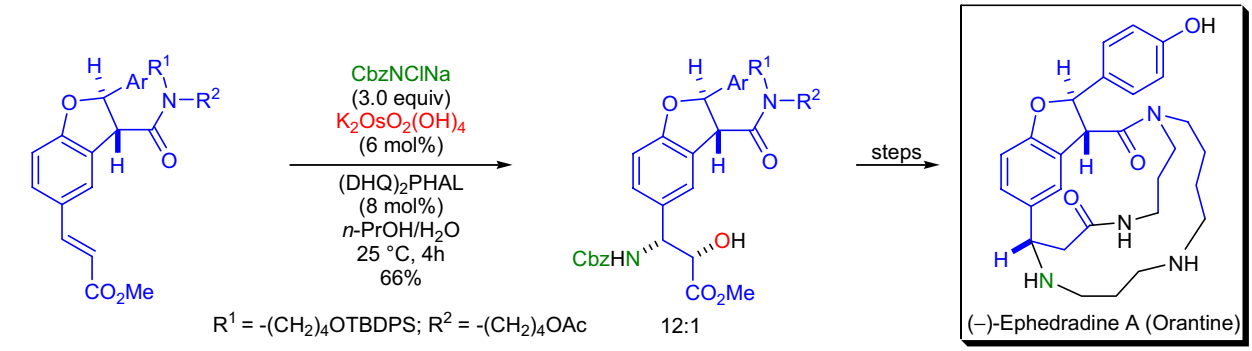
Research by B. Jiang et al. showed that the *asymmetric aminohydroxylation* of vinyl indoles can afford (*S*)-*N*-Boc protected α-indol-3-ylglycinols in moderate to good yield and with up to 94% *ee*.[28] The use of these enantiopure intermediates allowed the short enantioselective total synthesis of bisindole alkaloids, such as dragmacidin A, which contains a piperazine moiety between the indole rings.



During the total synthesis of the teicoplanin aglycon, the *Sharpless asymmetric aminohydroxylation* was used twice to prepare the required G- and F-ring phenylglycine precursors by D.L. Boger and co-workers.[29] For the G-ring precursor the (DHQD)$_2$PHAL ligand was used to obtain the *N*-Boc protected (*R*)-phenylglycinol, while the use of the pseudo enantiomer (DHQ)$_2$PHAL ligand afforded the *N*-Cbz protected (*S*)-phenylglycinol.



The stereocontrolled total synthesis of (–)-ephedradine A was accomplished by the research group of T. Fukuyama.[30] The highly stereoselective incorporation of the nitrogen atom at the benzylic position was achieved by using the *SAA*. Subsequently, the hydroxyl group was removed in two steps: first by conversion to the corresponding alkyl chloride, and then by subjecting the alkyl chloride to *transfer hydrogenation* to afford the β-amino ester.



R^1 = -$(CH_2)_4$OTBDPS; R^2 = -$(CH_2)_4$OAc

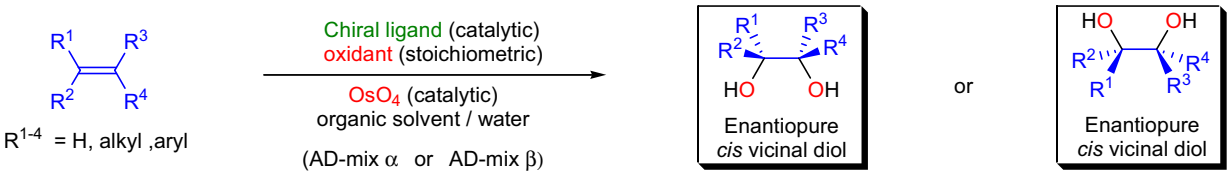
SHARPLESS ASYMMETRIC DIHYDROXYLATION

(References are on page 673)

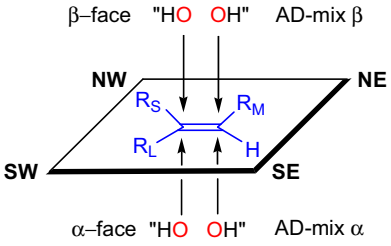
Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-21]*; Modifications & Improvements*[22-33]*; Theoretical Studies*[34-49]]

The reaction of osmium tetroxide (OsO_4) with olefins to give *cis* vicinal diols was discovered in the early 1900s[50] and since then it has undergone substantial developement.[51] At the beginning of the 1980s, the research group of K.B. Sharpless reported the first asymmetric dihydroxylation reaction of olefins with osmium tetroxide in the presence of dihydroquinine acetate, a chiral tertiary amine ligand that belongs to the family of *Chinchona* alkaloids. Today, this transformation is known as the *Sharpless asymmetric dihydroxylation* (*SAD*).[1] Sharpless's experiment was based on the observation of Criegee that certain tertiary amines (e.g., pyridine) accelerated the reaction of OsO_4 with olefins.[52] At this point the reaction was catalytic for OsO_4 but stoichiometric amount of the ligand was needed. When chiral tertiary diamines (e.g., $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$) were introduced as ligands, it became feasible to use only sub-stoichiometric amounts of them, since these ligands considerably accelerated the rate of dihydroxylation compared to the monodentate chiral amines.[2] The phenomenon of rate acceleration caused by ligands is known as the *ligand accelerated catalysis* (*LAC*). The general features of the *SAD* are: 1) practically all alkenes are substrates for the reaction, but no other functional groups are affected; 2) electron-rich alkenes tend to react faster than electron-deficient ones; 3) the enantioselectivity is moderate for *cis*-disubstituted olefins having substituents that are similar in size (facial differentiation by the catalyst becomes very difficult); 4) all the reagents are solids, and they are commercially available as preformulated mixtures: AD-mix α and AD-mix β containing the necessary bidentate chiral ligand, stoichiometric oxidant, and the osmium tetroxide in the form of dipotassium osmate dihydrate ($K_2OsO_4(OH)_4$); 5) to predict the absolute configuration of the product, an empirical model (mnemonic device) was developed by Sharpless et al.[24] in which one has to examine the substrate and rank the substituents (R_S = small, R_M = medium and R_L = large) and place the large substituent in the southwestern corner (SW); to dihydroxylate from the bottom face (α-face) one should use AD-mix α and to dihydroxylate from the top face (β-face) AD-mix β should be used; and 6) the reaction is usually conducted in *tert*-butanol/water = 1:1 at room temperature and 1.4g of the necessary AD-mix is added for each mmol of the olefinic substrate.

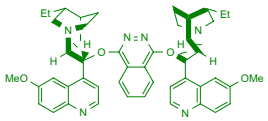


Empirical model (mnemonic device):

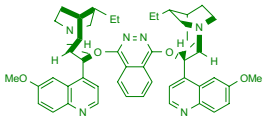


AD-mix α: $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

AD-mix β: $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$

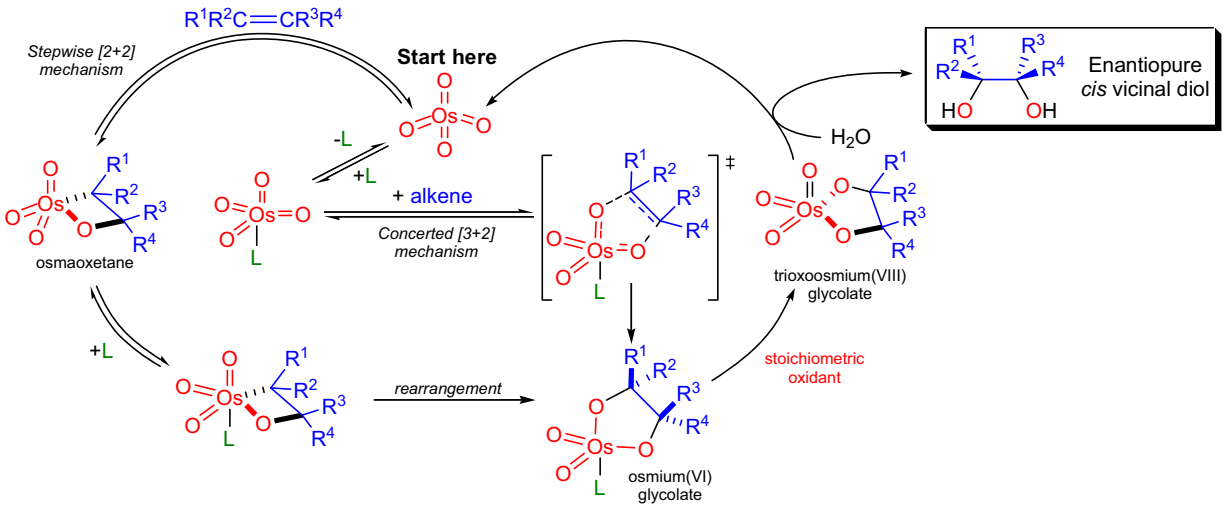


$(DHQ)_2PHAL$



$(DHQD)_2PHAL$

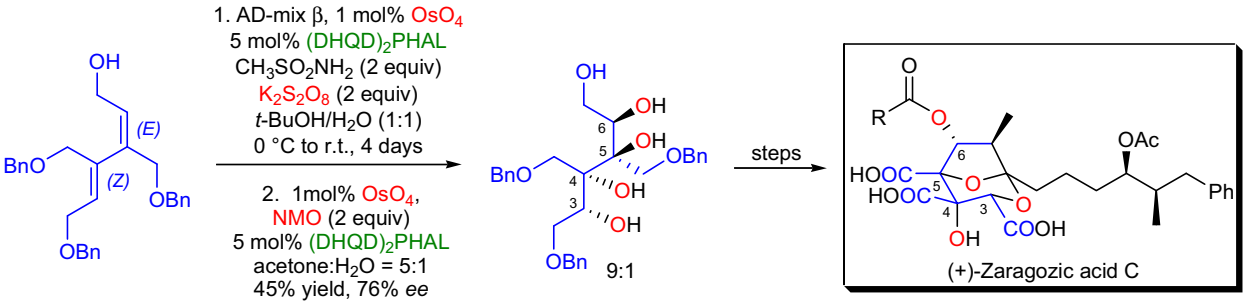
Mechanism:[53-77]



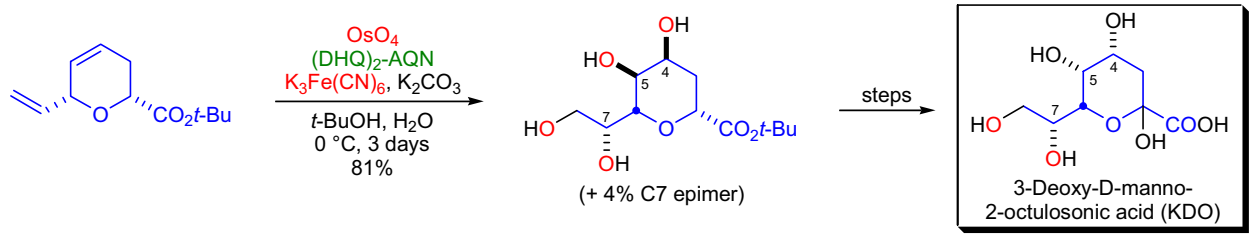
SHARPLESS ASYMMETRIC DIHYDROXYLATION

Synthetic Applications:

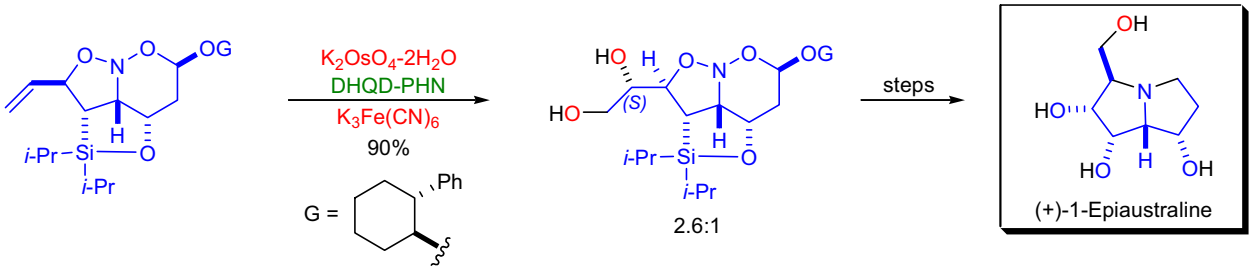
The total synthesis of (+)-zaragozic acid C was accomplished in the laboratory of A. Armstrong using a double *Sharpless asymmetric dihydroxylation* of a diene as the key step.[78] The stereochemistry of four contiguous stereocenters (C3 to C6) were controlled this way. Interestingly, the double dihydroxylation could not be performed efficiently (low yield, low *ee*) in one-pot, so it was conducted in two separate steps. In the first step, the diene was subjected to Super AD-mix β (commericial AD-mix supplemented with extra ligand and osmium tetroxide) for 4 days to afford regioisomeric triols in 78% yield. In the second step NMO was used as the stoichiometric oxidant, which afforded the desired pentaol with good diastereoselectivity. This two-step procedure was conducted on multigram scale, which allowed the completion of the total synthesis.



The key component of the cell wall lipopolysaccharide of Gram-negative bacteria, KDO (3-deoxy-D-manno-2-octulosonic acid), was synthesized by S.D. Burke and co-workers.[79] One of the key transformations in the synthetic sequence was a double *SAD* of a 6-vinyldihydropyran-2-carboxylate template. This 1,4-diene was cleanly converted to a mixture of two C7 epimeric tetraols in a 20:1 ratio. The endocyclic olefin had an intrinsic preference for dihydroxylation from the β-face and not from the desired α-face. This stereofacial bias was impossible to override with any ligand normally used in the *SAD*, so later in the synthesis these two stereocenters had to be inverted in order to give the required stereochemistry at C4 and C5.



The total synthesis of (+)-1-epiaustraline, a tetrahydroxypyrrolizidine alkaloid, was achieved by S.E. Denmark et al. who used a tandem *intramolecular [4+2] / intermolecular [3+2] nitroalkene cycloaddition* as the key ring forming reaction.[80] During the endgame of the synthesis, the last stereocenter was installed by the *SAD* of the terminal olefin moiety on the tricyclic intermediate. It was found that most ligands in the dihydroxylation gave the undesired stereoisomer as the major product. Eventually, after exhaustive screening, a DHQD ligand with a phenanthracene spacer (DHQD-PHN) was found to produce the desired stereoisomer with good selectivity.



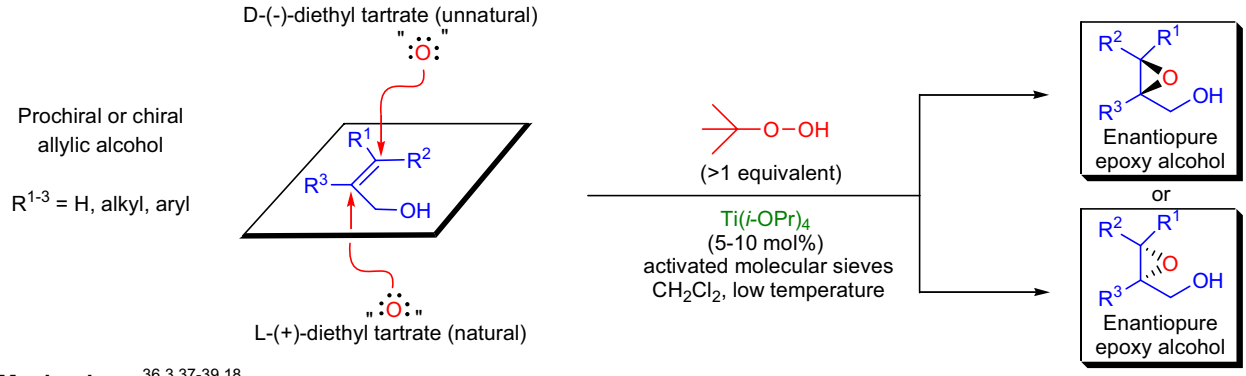
SHARPLESS ASYMMETRIC EPOXIDATION

(References are on page 675)

Importance:

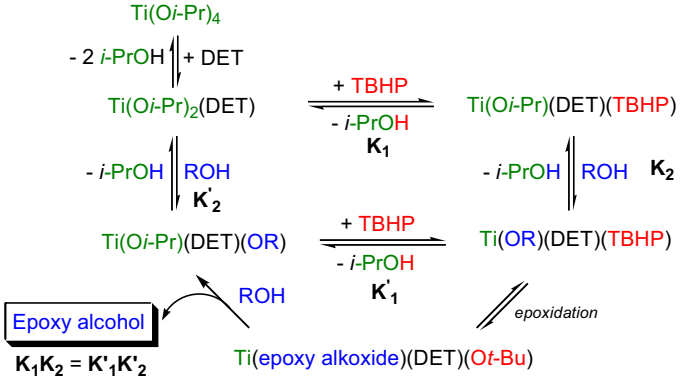
[*Seminal Publications*[1]; *Reviews*[2-24]; *Modifications & Improvements*[25-27]; *Theoretical Studies*[28-33]]

In 1980, K.B. Sharpless and T. Katsuki reported the first practical method for asymmetric epoxidation.[1] They discovered that the combination of $Ti^{(IV)}$ tetraisopropoxide, optically active diethyl tartrate (DET) and *tert*-butyl hydroperoxide (TBHP) was capable of epoxidizing a wide variety of allylic alcohols in high yield and with excellent enantiomeric excess (>90% *ee*). The $Ti^{(IV)}$ alkoxide-catalyzed epoxidation of prochiral and chiral allylic alcohols in the presence of a chiral tartrate ester and an alkyl hydroperoxide to give enantiopure 2,3-epoxy alcohols is known as the *Sharpless asymmetric epoxidation* (*SAE*). The general features of this method are: 1) only allylic alcohols are good substrates for this method, since the presence of the hydroxyl group is essential; 2) allylic alcohols are epoxidized with high chemoselectivity in the presence of other olefins; 3) the epoxidation is totally reagent controlled: by using either (+)- or (-)-DET the corresponding enantiomer of the product 2,3-epoxy alcohol can be obtained; 4) the inherent diastereofacial bias of chiral allylic alcohols is overridden: in the "matched case" the reagent reinforces the inherent selectivity of the substrate and the epoxidation proceeds with extremely high stereoselectivity, while in the "mismatched case" the diastereofacial preference of the substrate and the reagent is opposite and the level stereoselectivity for the epoxidation is lower than in the matched case, but it is synthetically still useful;[34,35] 5) the enantiofacial selectivity of the *SAE* can be predicted for all prochiral allylic alcohols (no exceptions found to date!) using the scheme below; 6) if there is a chiral center at C1 (attached to OH group) the *SAE* will proceed with substantially different rates for the two enantiomers, so it can be used for the kinetic resolution of a racemic allylic alcohols; 7) the addition of catalytic amounts of molecular sieves to the reaction mixture allows the use of only catalytic amounts (5-10 mol%) of the Ti-tartrate complex; in the absence of molecular sieves, a full equivalent of this complex is needed;[25] 8) if the product is too reactive or its solubility properties make it difficult to isolate, the *in situ* derivatization (conversion to the corresponding ester) can be used to preserve the integrity of the epoxide and make the isolation easier;[26] 9) the reaction conditions tolerate most functional groups except for free amines; carboxylic acids, thiols, and phosphines; 10) in order to achieve high yield and enantiomeric excess, it is crucial to prepare the catalyst fresh by mixing the solutions of $Ti(Oi\text{-}Pr)_4$ and DET followed by the addition of TBHP at -20 °C and age the resulting mixture for 20-30 minutes prior to adding the allylic alcohol substrate; 11) the solvent of choice is alcohol-free dichloromethane; 12) most often DET is used, but occasionally DMT and DIPT are utilized; 13) titanium tetra *t*-butoxide is applied if the product epoxy alcohol (e.g., 2-substituted epoxy alcohols) is sensitive to ring-opening by the alkoxide; and 14) the molecular sieves must be activated (heat at 200 °C for 3h) and generally 3-5 Å molecular sieves are sufficient to remove any interfering amounts water.

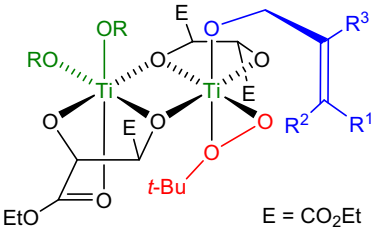


Mechanism:[36,3,37-39,18]

The first step is the rapid ligand exchange of $Ti(Oi\text{-}Pr)_4$ with DET. The resulting complex undergoes further ligand exchange with the allylic alcohol substrate and then TBHP. The exact structure of the active catalyst is difficult to determine due to the rapid ligand exchange but it is likely to have a dimeric structure. The hydroperoxide and the allylic alcohol occupy the axial coordination site on the titanium and this model accounts for the enantiofacial selectivity.



Transition state of epoxidation:

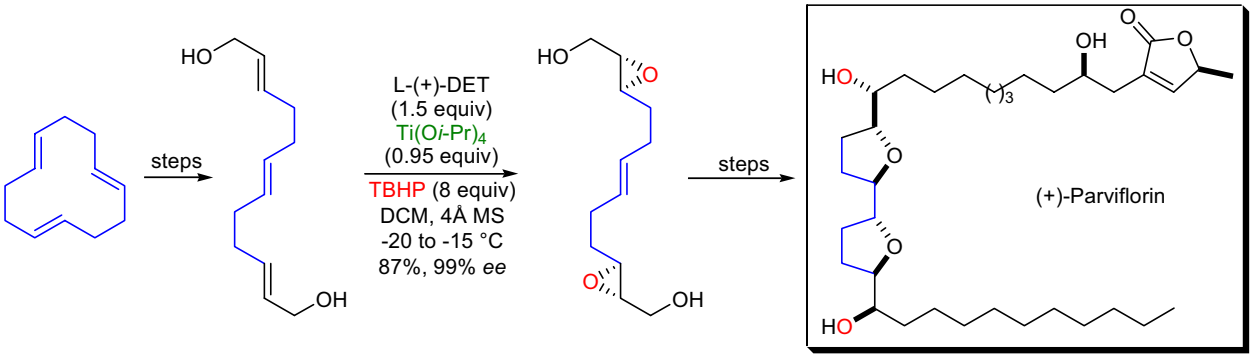


$$\text{Rate} = \frac{[Ti(Oi\text{-}Pr)_2(DET)]\,[TBHP]\,[ROH]}{[i\text{-}PrOH]^2}$$

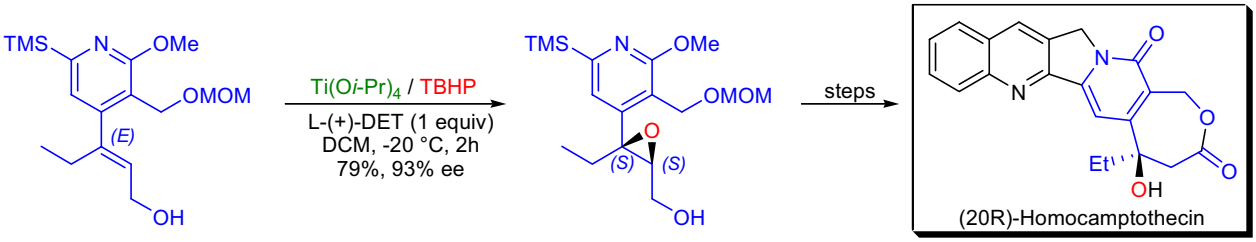
SHARPLESS ASYMMETRIC EPOXIDATION

Synthetic Applications:

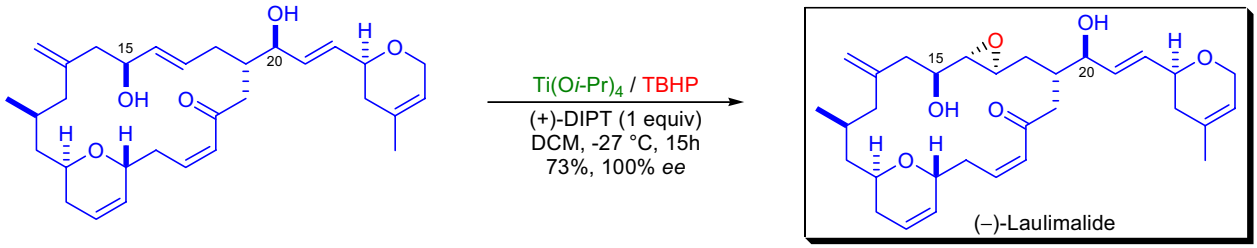
The enantioselective total synthesis of the annonacenous acetogenin (+)-parviflorin was accomplished by T.R. Hoye and co-workers.[40] The *bis*-tetrahydrofuran backbone of the natural product was constructed using a sequential double *Sharpless asymmetric epoxidation* and *Sharpless asymmetric dihydroxylation*. The *bis* allylic alcohol was epoxidized using L-(+)-DET to give the essentially enantiopure *bis* epoxide in 87% yield.



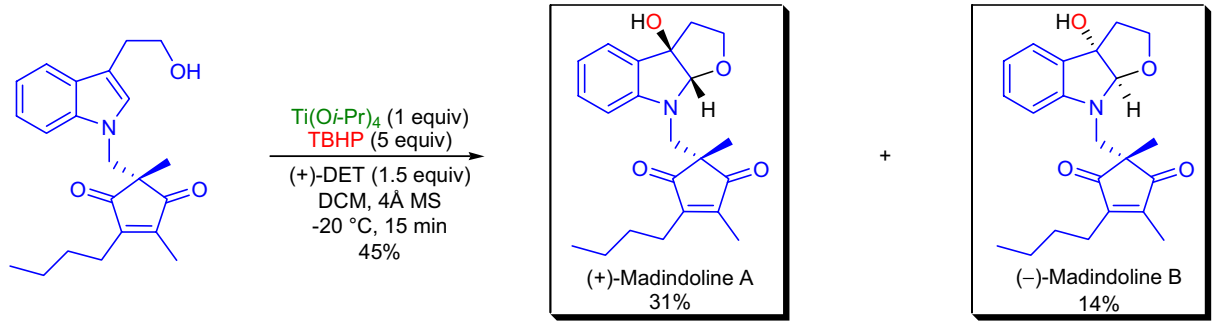
In the laboratory of D.P. Curran, the asymmetric total synthesis of (20*R*)-homocamptothecin was achieved using the *Stille coupling* and the *SAE* as key steps.[41] The *SAE* was used to install the key C20 stereocenter. The (*E*)-allylic alcohol was epoxidized rapidly in the presence of stoichiometric amounts of L-(+)-DET and TBHP at -20 °C to afford the corresponding epoxide in 93% *ee*. Interestingly, the (Z)-allylic alcohol reacted with D-(-)-DET sluggishly and gave the epoxide in very low yield and with only 31% ee.



The last and key step during the total synthesis of (–)-laulimalide by I. Paterson et al. was the *Sharpless asymmetric epoxidation*.[42] The success of the total synthesis relied on the efficient kinetic differentiation of the C_{15} and C_{20} allylic alcohols during the epoxidation step. When the macrocyclic diol was oxidized in the presence of (+)-DIPT at -27 °C for 15h, only the C_{16}-C_{17} epoxide was formed.



(+)-Madindoline A and (–)-madindoline B are potent and selective inhibitors of interleukin 6. The relative and absolute configuration of these natural products was determined by means of their total synthesis by A.B. Smith and S. Omura.[43] The key step was the *SAE* of the indole double bond, which led to the formation of the hydroxyfuroindole ring of both compounds.



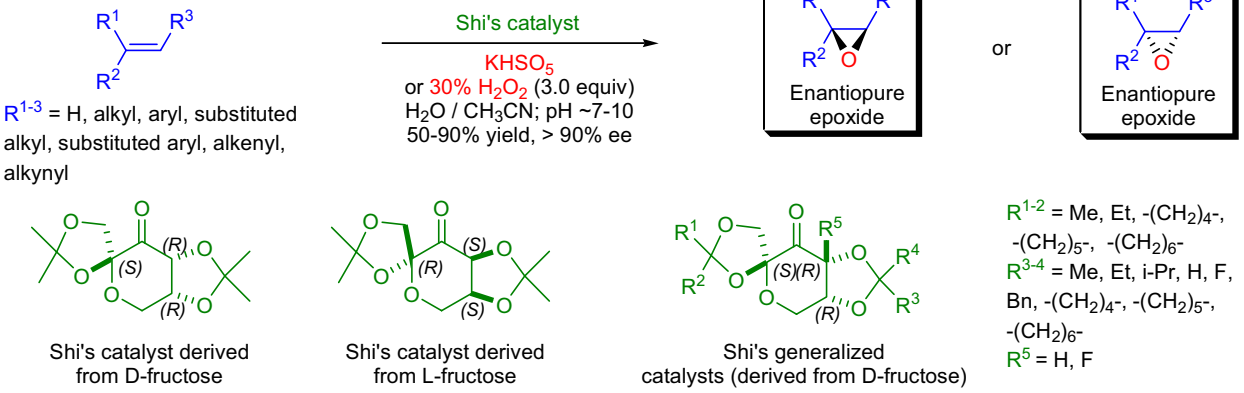
SHI ASYMMETRIC EPOXIDATION

(References are on page 676)

Importance:

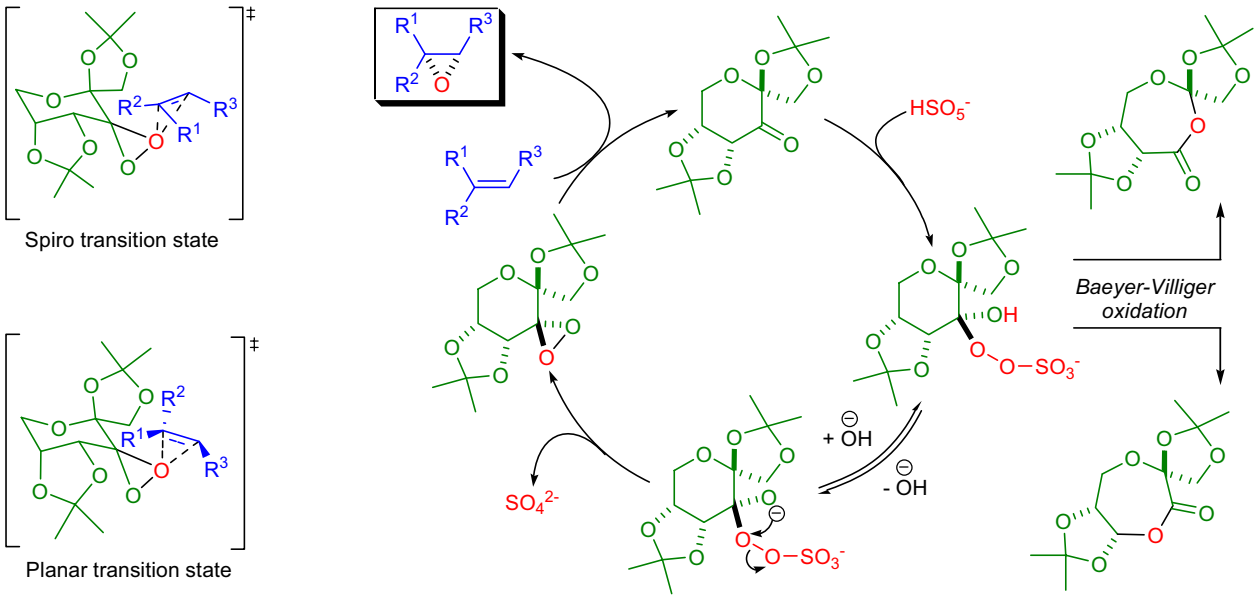
[*Seminal Publications*[1-4]*; Reviews*[5-15]*; Modifications & Improvements*[16-28]; *Theoretical Studies*[29,30]]

When ketones are treated with Oxone (potassium peroxymonosulfate, $KHSO_5$), dioxiranes are formed that are capable of transferring an oxygen atom to a wide variety of substrates, and the ketones are regenerated after the oxygen-transfer.[13] For this reason dioxiranes are considered to be environmentally friendly and versatile oxidizing agents. Recently, dioxiranes have found use in asymmetric oxidation reactions such as epoxidation of alkenes. In 1984, R. Curci and co-workers reported the first chiral ketone-catalyzed asymmetric epoxidation of unfunctionalized olefins.[1] During the following decade several new chiral ketones (mainly biphenyl and binaphthyl-based ketones) were developed and tested as catalysts in asymmetric epoxidations.[8] In 1996, a fructose-derived ketone catalyst was prepared by Y. Shi and co-workers that showed very high enantioselectivities in epoxidation reactions.[2] Today, this transformation is known as the *Shi asymmetric epoxidation*. The general features of the reaction are: 1) either enantiomer of the catalyst can be prepared easily from D- or L-fructose in two steps;[31,2,4] 2) the pH of the reaction medium has a crucial effect on the outcome of the reaction: at high pH the oxidant (Oxone) decomposes rapidly, while at lower pH values the catalyst is decomposed *via* a *Baeyer-Villiger oxidation*, and this neccesitates the use of large amounts of catalyst;[3] 3) by keeping the pH at an optimum (~10.5), the epoxidation usually takes place with high enantiomeric excess at low catalyst loadings (20-30 mol%) without the need to use large excess of Oxone; 4) at the optimum pH the epoxide products are more stable than at lower pH values; 5) a wide variety of alkene substrates are epoxidized efficiently with high *ee*: homoallylic and bishomoallylic alcohols,[32] unsymmetrical dienes are epoxidized regioselectively to give vinyl epoxides,[16] conjugated enynes yield propargylic epoxides,[22] silyl enol ethers give α-hydroxy ketones;[19] and 6) *trans*-disubstituted and trisubstituted olefins give high enantioselectivities, whereas for *cis*-disubstituted and terminal olefins the *ee*'s are lower.[4]



Mechanism:[2,33,4,34,20,8]

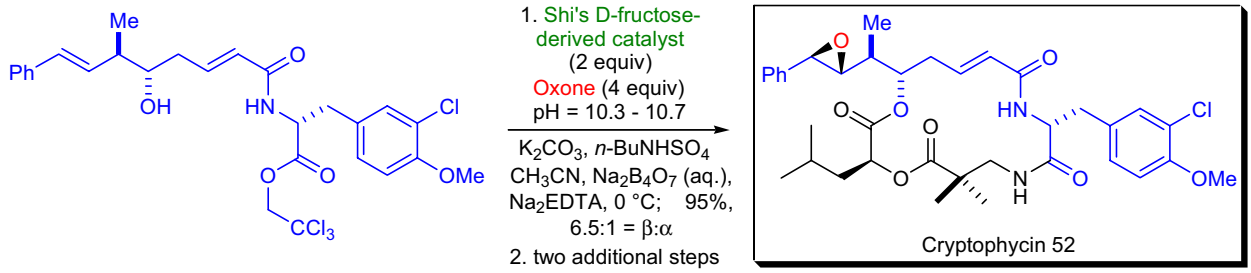
There are two possible transition states: spiro and planar. Nearly every example of *trans*-disubstituted and trisubstituted olefins which were studied with Shi's catalyst is consistent with the spiro transition state.[8] The extent of the involvement of the competing planar transition state depends on the nature of the substituents on the olefins.



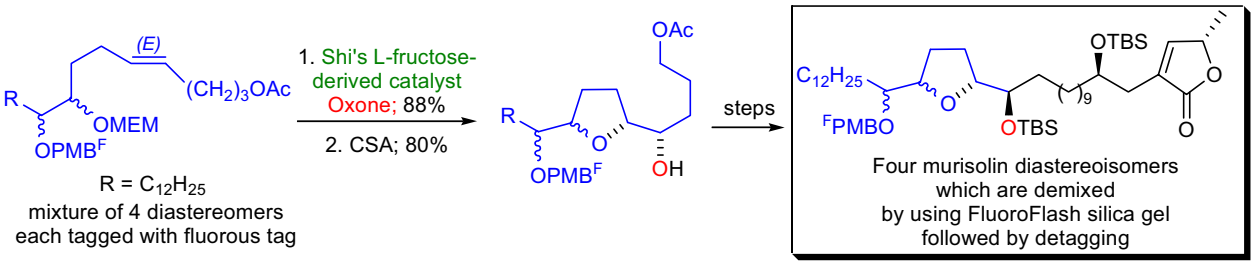
SHI ASYMMETRIC EPOXIDATION

Synthetic Applications:

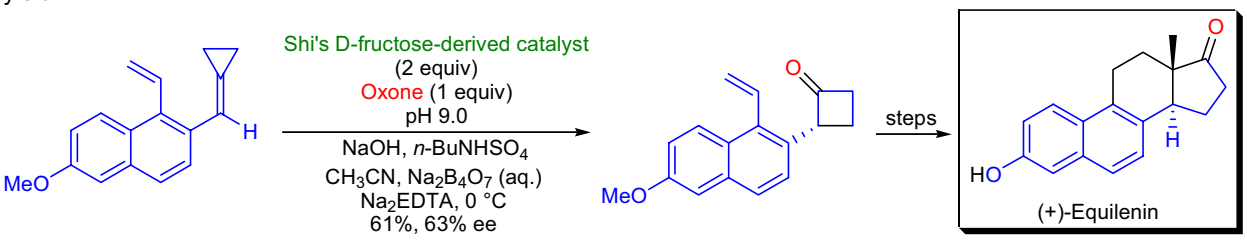
The synthesis of cryptophycin 52 was accomplished by E.D. Moher et al. using the *Shi epoxidation* as the key step to install the epoxide moiety diastereoselectively.[35] In the previous syntheses of this molecule, the epoxide moiety was always introduced in the last step, using common oxidants such as mCPBA or DMD, and with poor diastereoselectivity. Interestingly, the usual alkene precursor was a very poor substrate for the *Shi epoxidation*, so an earlier intermediate was subjected to the epoxidation conditions in which the pH was very carefully controlled. The desired epoxide was obtained as a 6.5:1 mixture of diastereomers.



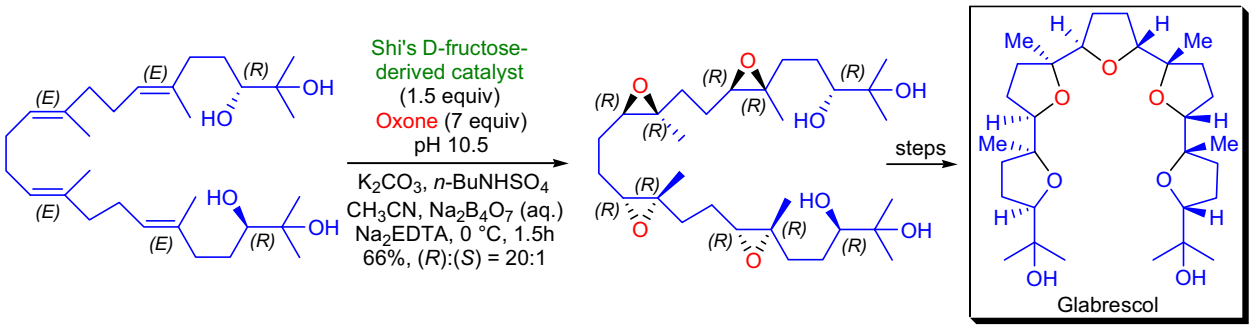
The *Shi epoxidation* employing the L-fructose derived catalyst was used during the total syntheses of (+)-murisolin and a library containing 15 of its diastereoisomers by D.P. Curran and co-workers.[36] The 4-mix/4-split strategy relied on the solution phase technique of fluorous mixture synthesis. One of the (*E*)-alkene substrates was subjected to the *Shi epoxidation* conditions to give 88% yield of the corresponding epoxide followed by ring-closure to the tetrahydrofuran by CSA. At the end of the synthesis, the four murisolin diastereomers were demixed by using FluoroFlash silica gel followed by detagging.



A novel *asymmetric epoxidation-ring expansion* strategy was used for the total synthesis of (+)-equilenin in the laboratory of M. Ihara.[37] This strategy involved the *Shi asymmetric epoxidation* of an aryl-substituted cyclopropylidene derivative to form a chiral oxaspiropentane followed by its enantiospecific rearrangement to the corresponding chiral cyclobutanone. The D-fructose-derived catalyst had to be used in large excess because the optimum yield and ee could be reached only at pH ~9 where the catalyst decomposed fairly rapidly. The authors also showed that by using the *Jacobsen epoxidation*, the enantiomeric excess could be slightly increased along with a slight decrease in the yield.



The *Shi epoxidation* was the key step in E.J. Corey's total synthesis of the chiral C_2-symmetric pentacyclic oxasqualenoid glabrescol.[38,39] Four epoxides were introduced in one step with an (*R*):(*S*) selectivity of 20:1.



SIMMONS-SMITH CYCLOPROPANATION

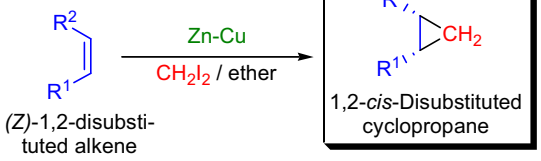
(References are on page 677)

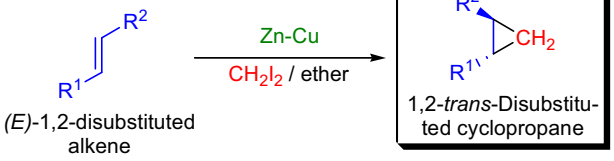
Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-16]; *Modifications & Improvements*[17-33]; *Theoretical Studies*[34-45]]

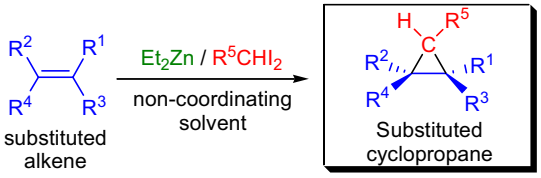
In 1958, H.E. Simmons and R.D. Smith were the first to utilize diiodomethane (CH_2I_2) in the presence of zinc-copper couple (Zn-Cu) to convert unfunctionalized alkenes (e.g., cyclohexene, styrene) to cyclopropanes stereospecifically.[1] This transformation proved to be general and has become the most powerful method of cyclopropane formation: it bears the name of its discoverers and is referred to as the *Simmons-Smith cyclopropanation*. The most important features of the reaction are: 1) a wide range of alkenes can be used: simple alkenes, α,β-unsaturates ketones and aldehydes, electron rich alkenes (enol ethers, enamines, etc.); 2) due to the electrophilic nature of the reagent, the rate of cyclopropanation is faster with more electron rich alkenes. However, highly substituted alkenes may react slower due to the increased steric hindrance; 3) the cyclopropanation is stereospecific, so the stereochemical information in the alkene substrates is translated to the products; 4) when a substituted methylene group is transferred to the alkene ($R^5 \neq H$) a preference for *syn* stereochemistry is typically observed;[17] 5) in case of chiral substrates, the cyclopropanation is highly diastereoselective and occurs from the less hindered face of the double bond; 6) when the alkene has functional groups containing heteroatoms (e.g., OH, OAc, OMe, OBn, NHR), a strong directing effect is observed and the delivery of the alkylidene occurs from the face of the double bond having the closer proximity of the functional group; 7) in cycloalkenols, the stereochemical outcome depends on the ring size: 5-, 6-, and 7-membered rings give rise to high *cis*-diastereoselectivity, while large ring cycloalkenols exhibit high levels of *anti* diastereoselectivity; 8) usually no serious side reactions are observed (e.g., C-H insertion), and the reaction conditions are tolerant of most functional groups; and 9) non-coordinating solvents (e.g., DCM, DCE) are recommended, because the use of basic solvents decrease the rate of the reaction. Today the preparation of the zinc-copper couple is more convenient (treatment of zinc powder with $CuSO_4$ solution) than described in the original procedure. However, there have been several modifications to generate the active reagent: 1) zinc-silver couple tends to give higher yields and shorter reaction times;[18] 2) the use of diethylzinc with CH_2I_2 gives very reproducible results (*Furukawa modification*);[17] 3) iodo- or chloromethylsamarium iodide ($Sm/Hg/CH_2I_2$) is the reagent of choice for the chemoselective cyclopropanation of allylic alcohols in the presence of other olefins (*Molander modification*);[21] and 4) dialkyl(iodomethyl)aluminum ($i\text{-}Bu_3Al/CH_2I_2$) exclusively cyclopropanates unfunctionalized olefins in the presence of allylic alcohols.[46] *Asymmetric Simmons-Smith cyclopropanations* can be achieved several different ways:[11] 1) the use of cleavable chiral auxiliaries (e.g., chiral allylic ethers, acetals, boronates); 2) by the addition of stoichiometric amounts of chiral additives, such as dioxaborolane prepared from tetramethyltartaric acid diamide and butylboronic acid (*Charette asymmetric modification*). However, this method is only applicable to allylic alcohols;[25] and 3) the use of chiral catalysts, such as the chiral disulfonamide ligand derived from *trans*-cyclohexanediamine, gives high *ee*'s for allylic alcohols.[26,27]

Simmons & Smith (1958):

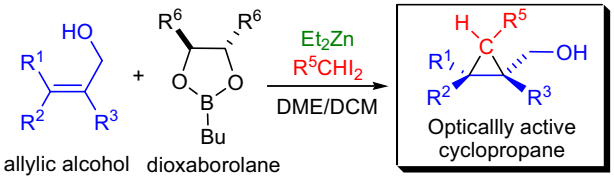




Furukawa modification (1966):



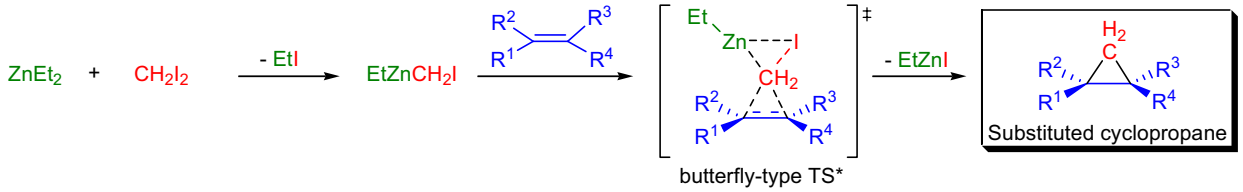
Charette asymmetric modification (1994):



$R^{1\text{-}4}$ = H, substituted alkyl and aryl; R^5 = H, Me, phenyl; R^6 = $CONMe_2$; non-coordinating solvent: toluene, benzene, DCM, DCE

Mechanism:[47,11,48,13,15,33]

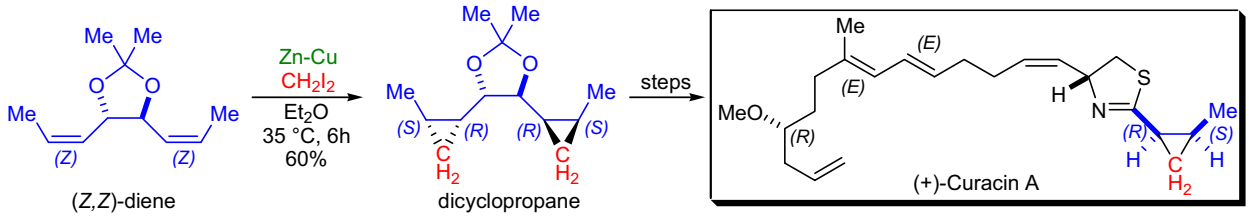
The *Simmons-Smith cyclopropanation* is a concerted process, and it proceeds *via* a three-centered "butterfly-type" transition state. This is in agreement with the result of theoretical studies as well as the stereochemical outcome of a large number of reactions.



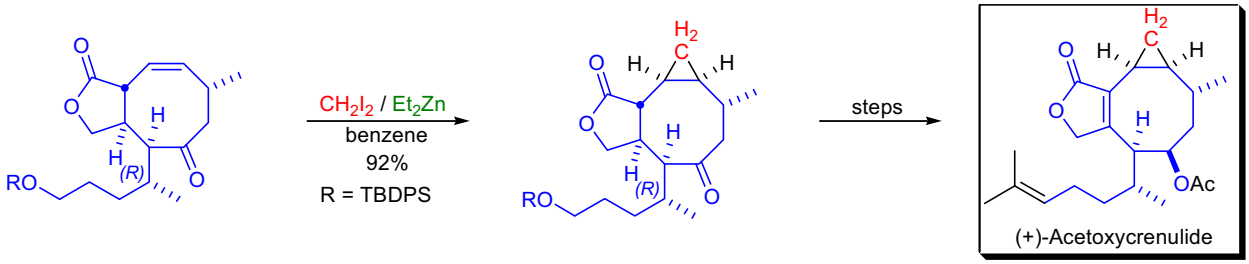
SIMMONS-SMITH CYCLOPROPANATION

Synthetic Applications:

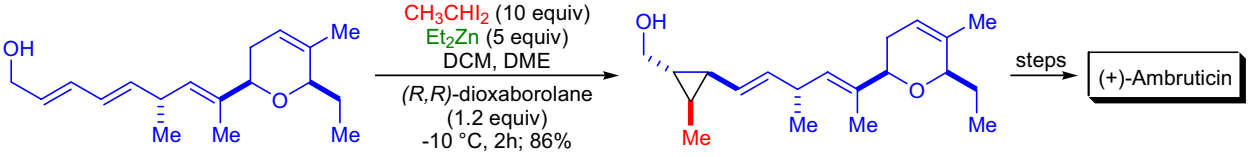
The highly stereocontrolled total synthesis of the antimitotic agent (+)-curacin A was achieved by S. Iwasaki and co-workers.[49] The main structural feature of this natural product is a disubstituted thiazoline ring bearing a cyclopropane ring and an aliphatic side chain. Diethyl L-tartrate was converted to a (*Z*,*Z*)-diene in several steps, which was subjected to a *double directed Simmons-Smith cyclopropanation reaction*. The dicyclopropane was obtained as a single diastereomer in good yield. Subsequent periodate cleavage of the diol moiety followed by oxidation led to the desired 2-methylcyclopropanecarboxylic acid, which was used to form the thiazoline portion of curacin A.



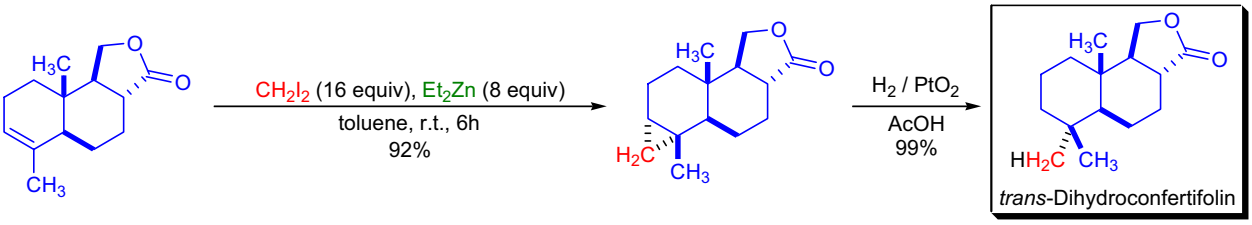
The secondary marine metabolite (+)-acetoxycrenulide has unprecedented structural features which prompted L.A. Paquette et al. to embark on its total synthesis.[50] The eight-membered carbocycle of the target was constructed *via* a *Claisen rearrangement*. The bicyclic β,γ-unsaturated lactone was subjected to Simmons-Smith conditions, that delivered the cyclopropyl ring exclusively from the β-face of the molecule as a result of the predominant ground-state conformation.



The *asymmetric Simmons-Smith cyclopropanation* (*Charette modification*) was used for the ethylidenation of an allylic alcohol moiety during the total synthesis of (+)-ambruticin in the laboratory of E.N. Jacobsen.[51] Diethylzinc was added to the solution of 1,1-diiodoethane to form the active reagent $Zn(CH_3CH_2I)_2 \cdot DME$, which was transferred to a solution of the substrate containing dioxaborolane (chiral ligand). The central cyclopropane ring was installed with high diastereoselectivity.



The *lactone-directed intramolecular Diels-Alder cycloaddition* was the key step in D.F. Taber's synthesis of *trans*-dihydroconfertifolin.[52] During the endgame, the *Simmons-Smith cyclopropanation* was utilized to install the *gem*-dimethyl group at C4. The trisubstituted alkene was cyclopropanated in excellent yield and the resulting cyclopropane was subjected to catalytic hydrogenation.



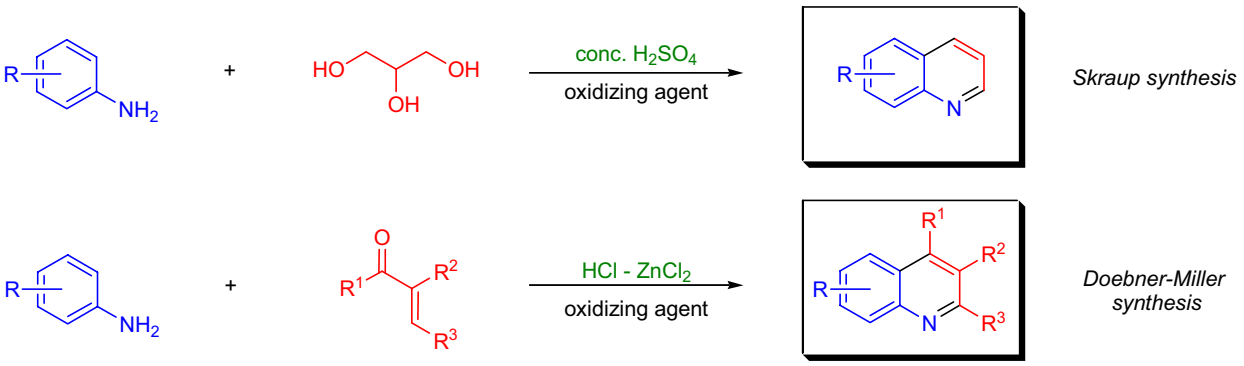
SKRAUP AND DOEBNER-MILLER QUINOLINE SYNTHESIS

(References are on page 678)

Importance:

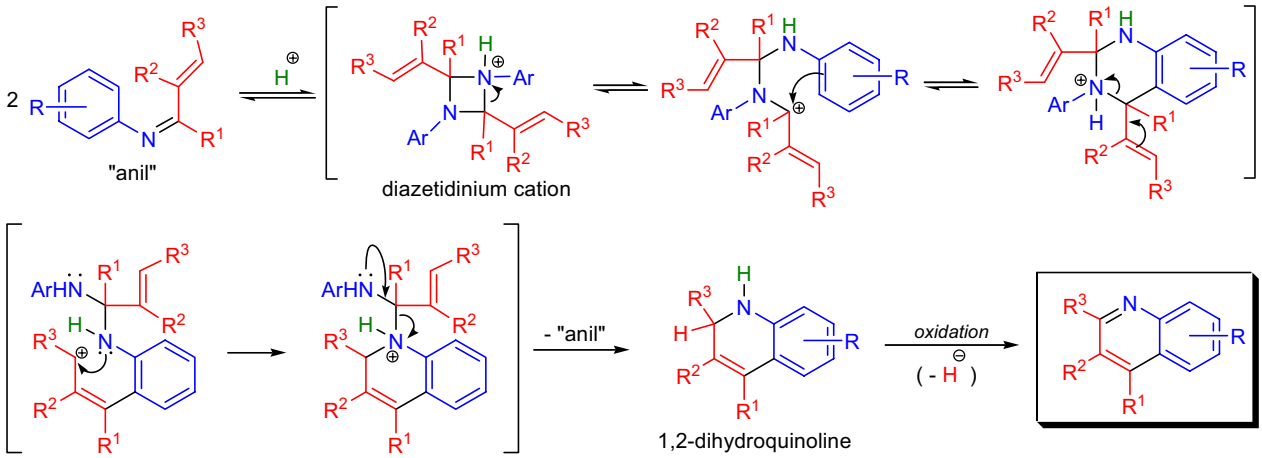
[*Seminal Publications*[1-3]; *Reviews*[4,5]; *Modifications & Improvements*[6,7]]

In 1880, Z.H. Skraup reported the formation of quinoline by heating aniline with glycerol (1,2,3-propanetriol), sulfuric acid and an oxidizing agent (As_2O_5, $ArNO_2$, *m*-$NO_2C_6H_5SO_3H$, etc.).[2] Shortly after Skraup's discovery, O. Doebner and W. Miller successfully modified and generalized Skraup's method by using α,β-unsaturated aldehydes, ketones or 1,2-diols instead of glycerol.[3] In addition, the sulfuric acid component was replaced by HCl and zinc chloride. This modification allowed the preparation of substituted quinolines. Today these methods are known as the *Skraup* and *Doebner-Miller quinoline synthesis*. The *Skraup procedure* gives easy access to quinolines substituted on the benzene ring (containing only those substituents which were on the aniline component), while the *Doebner-Miller modification* can introduce substituents on the pyridine ring as well. A great advantage of these methods is that structurally complex quinoline derivatives can be prepared in a simple operation. However, there are a few drawbacks: 1) the carbonyl component undergoes polymerization under the strongly Lewis acidic conditions; consequently the yields are often moderate; 2) the rate of addition of the aldehyde influences the yield; 3) isolation of the product from the complex reaction mixtures is often tedious; and 4) large-scale reactions are usually impractical. A recent modification of the *Doebner-Miller synthesis* in a two-phase solvent system allows the clean preparation of the desired quinoline derivative on a large scale.[6] If the aniline substrate is unsubstituted, the oxidizing agent is usually nitrobenzene, since it is conveniently converted to aniline in the process. There are two related well-known quinoline syntheses: 1) *Friedländer synthesis*, which is the condensation of *o*-aminobenzaldehydes with α-methylene ketones to give 3-substituted quinolines;[8,9] and 2) *Combes quinoline synthesis*, which is the condensation of primary arylamines with β-diketones followed by the acid catalyzed ring-closure of the resulting Schiff base.



Mechanism:[10-15]

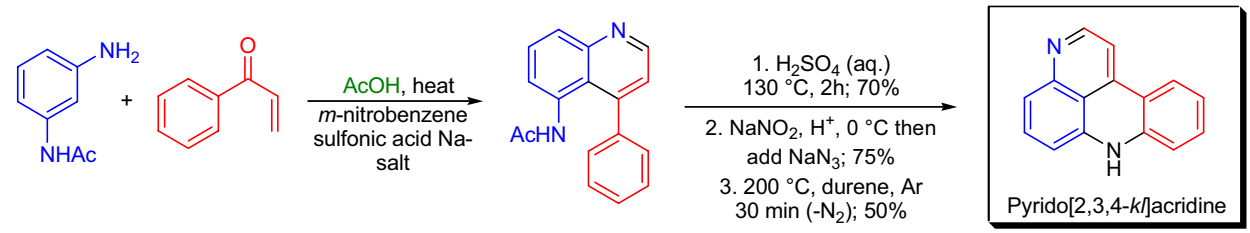
The detailed mechanism of the *Skraup* and *Doebner-Miller quinoline synthesis* has not been fully explored.[15] The two reactions are closely related, and it is assumed that the glycerol in the *Skraup procedure* is dehydrated to form acrylaldehyde (α,β-unsaturated aldehyde) or the 1,2-diol is first dehydrated to acetaldehyde, which undergoes an *aldol condensation* to afford crotonaldehyde in the *Doebner-Miller reaction*. The mechanism most likely involves the following steps: 1) condensation of the carbonyl component with the arylamine to form a Schiff-base (anil) (this step is not shown); 2) formation of a labile 1,3-diazetidinium cation intermediate from two anils; 3) ring-opening of the 1,3-diazetidinium ion to form a carbocation, which undergoes an S_EAr reaction with the aromatic ring; 4) formation of a substituted-1,2-dihydroquinoline; 5) hydride transfer (oxidation) to give a substituted quinoline.



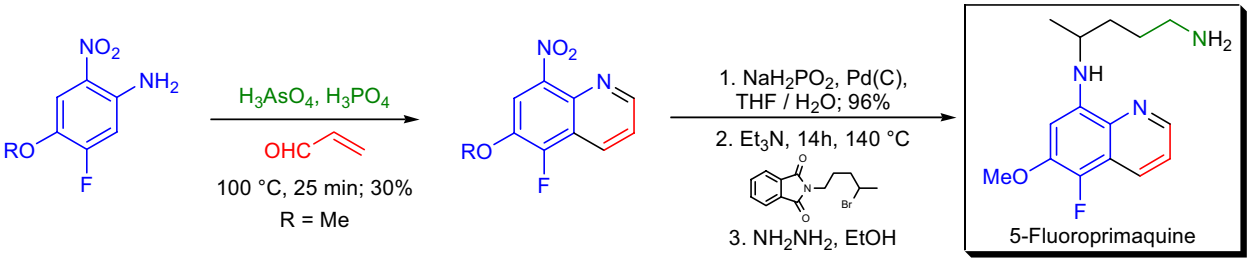
SKRAUP AND DOEBNER-MILLER QUINOLINE SYNTHESIS

Synthetic Applications:

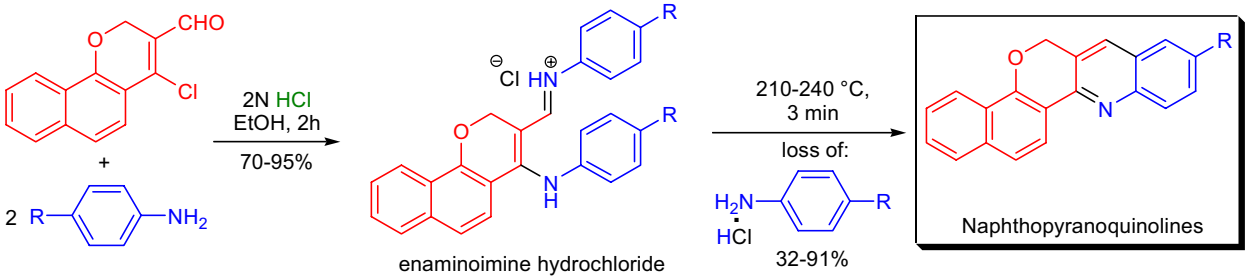
A new synthesis was developed by Y. Kashman et al. for the preparation of the parent pyrido[2,3,4-*kl*]acridine skeleton utilizing the *Doebner-Miller synthesis*.[16] In the first step, 3-aminoacetanilide was reacted with vinyl phenyl ketone in the presence of *m*-nitrobenzenesulfonic acid sodium salt and acetic acid to afford the corresponding 4-phenylquinolines. The acetamido group was then converted to the corresponding aryl azide, which underwent *intramolecular nitrene insertion* upon thermolysis to give the desired heterocyclic skeleton.



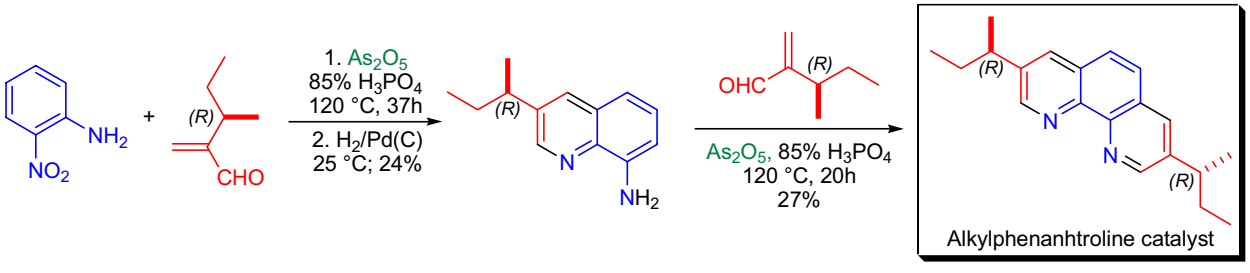
The synthesis of the antimalarial 5-fluoroprimaquine by P.M. O'Neil and co-workers involved a *Doebner-Miller reaction* of 5-fluoro-4-methoxy-2-nitroaniline with acrolein.[17] In this modified procedure 80% phosphoric acid, acrolein and arsenic acid were employed to allow a shorter reaction time and lower temperature than in the original procedure.



The short and convenient synthesis of novel naphthopyranoquinolines from naphthopyran chloroaldehydes *via* the *Doebner-Miller synthesis* was developed in the laboratory of J.K. Ray.[18] The chloroaldehydes were treated with 2.5 equivalents of a substituted aniline in ethanol in the presence of 2N HCl to afford enaminoimine hydrochlorides in good yield. These hydrochloride salts were exposed to heat at a temperature slightly above their melting point, resulting in ring-closure and elimination of one equivalent of arylamine hydrochloride.



A 3,8-dialkyl phenanthroline-based asymmetric transfer hydrogenation catalyst was prepared by S. Gladiali and co-workers using two consecutive *Doebner-Miller reactions*.[19] The synthesis of the ligand commenced with the reaction between 2-nitro aniline and enantiomerically pure 2-*sec*-butylacrolein. The resulting nitroquinoline was hydrogenated to give the corresponding aminoquinoline which was subjected to the second *Doebner-Miller reaction* to afford the enantiopure phenanhroline catalyst.



SMILES REARRANGEMENT

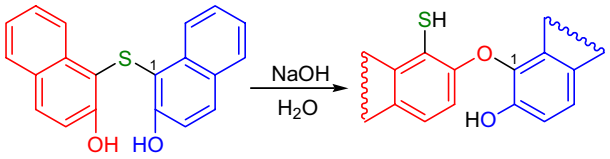
(References are on page 678)

Importance:

[*Seminal Publications*[1-8]; *Reviews*[9-17]; *Modifications & Improvements*[18-26]; *Theoretical Studies*[27-31]]

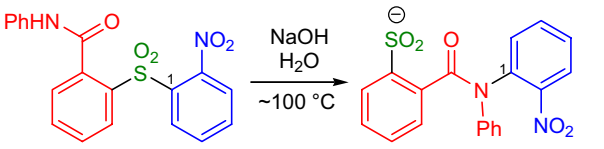
In 1894, R. Henriques reported that the base treatment of *bis*-(2-hydroxy-1-naphthyl) sulfide afforded an isomeric compound, 2-hydroxy-2'-mercapto-*bis*-(1-naphthyl) ether.[1] Two decades later, O. Hinsberg carried out similar experiments with the corresponding sulfones,[2,3] but it was S. Smiles and co-workers who established the structure of the products.[5-8] Smiles recognized that the transformations belonged to a new type of intramolecular nucleophilic aromatic rearrangement, which is known as the *Smiles rearrangement*. The general features of the reaction are:[11] 1) the aromatic ring needs to be activated by electron-withdrawing groups at the *ortho*- or *para* positions (e.g. NO_2, SO_2R); 2) if there is more than one activating group (when R^2=EWG), the rate of the rearrangement increases; 3) electron-withdrawing groups in the *meta* position usually do not activate the aromatic ring sufficiently; 4) in the absence of activating groups or when R^1 and R^2 are electron-donating, the rearrangement is slow or does not occur; 5) besides substituted benzene rings, the aromatic ring can also be heteroaromatic such as pyridine or pyrimidine; 6) in the presence of a strong base, when Y=SO_2 and XH=CH_3, no activating group is necessary and the process is called *Smiles-Truce rearrangement*);[18] 7) the nucleophilicity of the XH group and the ability of the Y group to function as a good leaving group are two factors that are interconnected and their combined effect have a dramatic influence on the rate of the rearrangement; 8) when XH=NH_2, usually no base is required and Y does not have to be a good leaving group for the reaction to take place; 9) the more stabilization of the negative charge is possible on Y, the faster the reaction will proceed (e.g., Y = SO_2 > SO > S); 10) when the Z groups are part of an aromatic ring (e.g., biaryl systems), electron-withdrawing substituents on this second ring tend to accelerate the reaction; 11) substituents at the 6-position of the second ring (*ortho* to Y) also accelerate the reaction because it forces the substrate to be predominantly in the reactive conformation, where the migrating ring is perpendicular to the plane of the other aromatic ring; 12) when the Y and the XH groups have very similar negative charge stabilizing abilities, the *Smiles rearrangement* becomes a reversible process. There are several modifications of the transformation: 1) the *Smiles-Truce rearrangement* utilizes a carbon-centered anion as the nucleophile and that can be generated by using a strong base (e.g., alkyllithium, KO*t*-Bu) is necessary;[18,11] 2) *photochemical Smiles rearrangement*;[21,32] and 3) rearrangement of phosphonium zwitterions, generated by the addition of an aryne to an alkylidene triarylphosphorane, affords P-substituted aromatic compounds.[19,20]

Henriques & Hinsberg (1894 & 1914):



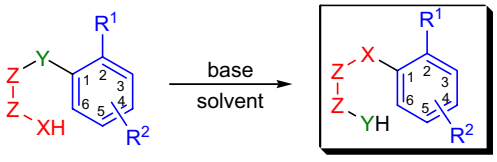
bis-(2-hydroxy-1-naphthyl) sulfide — 2-hydroxy-2'-mercapto-*bis*-(1-naphthyl) ether

Smiles (1930-1936):

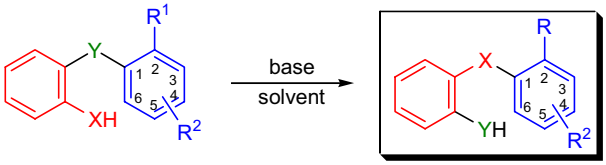


2-(2-nitro-benzenesulfonyl)-*N*-phenyl-benzamide — 2-[(2-nitro-phenyl)-phenyl-carbamoyl]-benzenesulfinate

Smiles rearrangement (general equation):



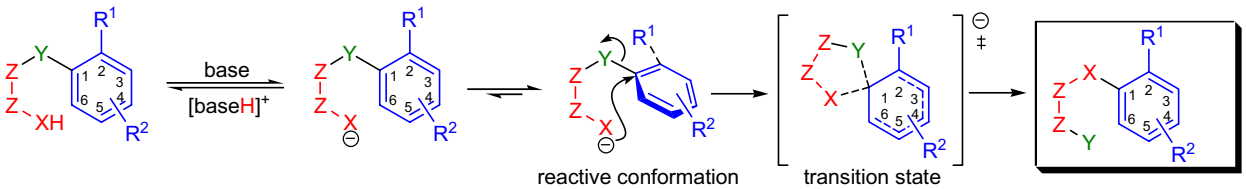
Smiles rearrangement of biaryl systems:



XH = $NHCOR$, $CONH_2$, SO_2NH_2, OH, NH_2, SH, SO_2H, CH_3 (*Smiles-Truce rearrangement*); Z = sp^2 or sp^3 hybridized substituted- or unsubstituted carbon, C=O, sp^3 nitrogen; Y = S, O, SO_2, S=O, CO_2, SO_3, I^+, P^+; R^1 = EWG = NO_2, SO_2R, Cl; R^2 = alkyl, halogen, NO_2, acyl; base: NaOH, KOH, RONa, RLi, K_2CO_3/DMSO

Mechanism:[33-47]

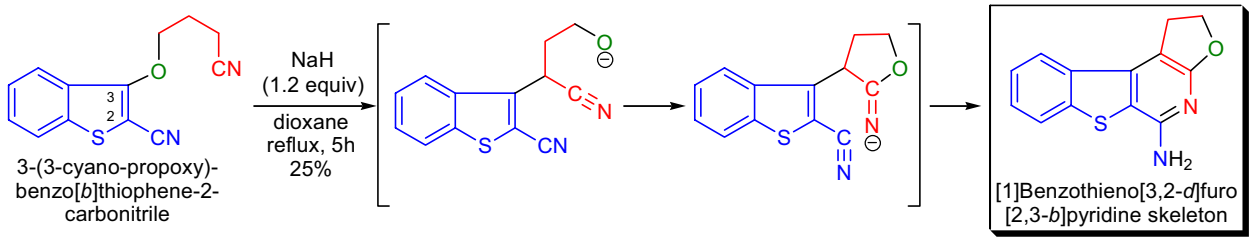
The first step of the reaction is the formation of the nucleophile by deprotonation. The substrate then has to adopt the reactive conformation in which the plane of the migrating ring is perpendicular to the Z-Z bond. The nucleophile attacks the ring in an *ipso* fashion to form a five-membered transition state that affords the product.



SMILES REARRANGEMENT

Synthetic Applications:

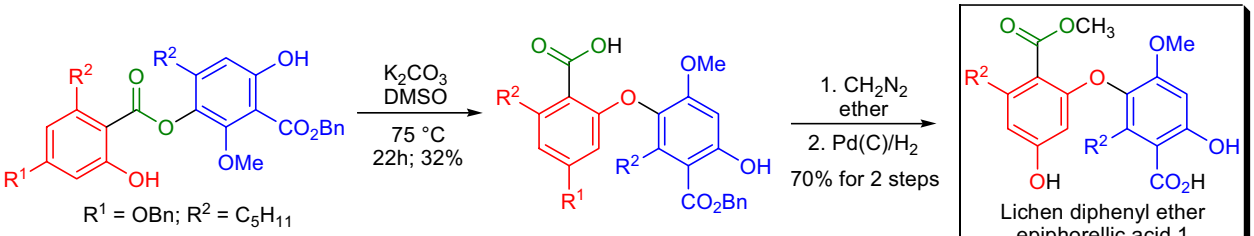
Frequently, the anionic product of the *Smiles rearrangement* can undergo further reaction if there are electrophilic functional groups on the aromatic ring. This approach was utilized by T. Hirota to prepare complex fused *N*-heterocyclic compounds such as the [1]benzothieno[3,2-*d*]furo[2,3-b]pyridine skeleton.[48] The substrate, cyanopropoxy-substituted benzo[*b*]thiophene, was exposed to sodium hydride in refluxing dioxane that induced the *Smiles rearrangement*. The resulting alkoxide attacked the cyano group to form an imine salt, which in turn added across the nitrile at the 2-position.



3-(3-cyano-propoxy)-benzo[*b*]thiophene-2-carbonitrile

[1]Benzothieno[3,2-*d*]furo[2,3-*b*]pyridine skeleton

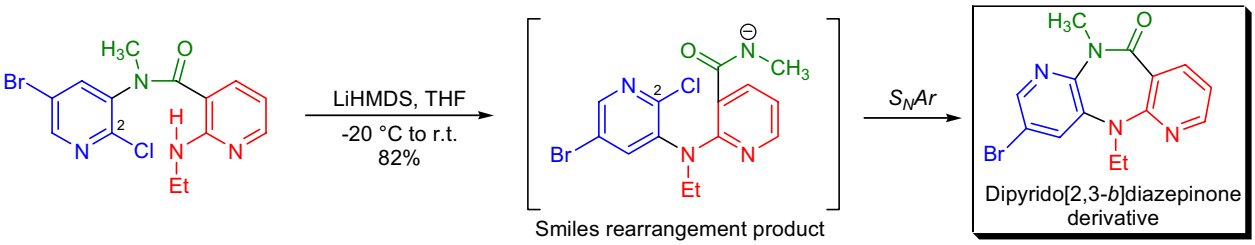
The total synthesis of the lichen diphenyl ether epiphorellic acid 1 was achieved in the laboratory of J.A. Elix using the *Smiles rearrangement* as the key step.[49] The diaryl phenolic ester substrate was heated in dry DMSO in the presence of potassium carbonate, which brought about the rearrangement. The resulting carboxylic acid was converted to the methyl ester with diazomethane and was debenzylated under catalytic hydrogenation conditions.



R^1 = OBn; R^2 = C_5H_{11}

Lichen diphenyl ether epiphorellic acid 1

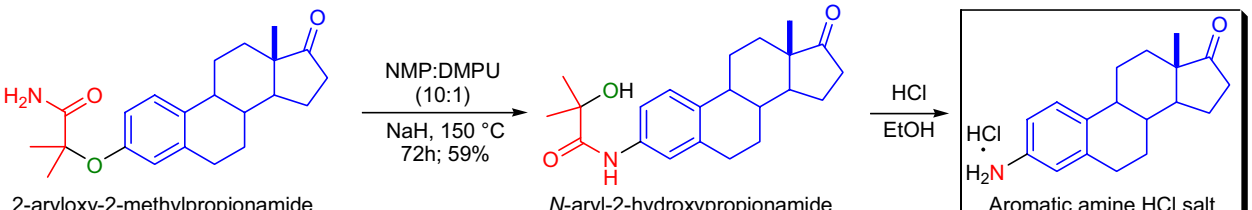
Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase, dipyrido[2,3-*b*]diazepinones, were prepared by J.R. Proudfoot and co-workers.[50] These compounds are isomeric to the potent inhibitor nevirapine and available *via* the *Smiles rearrangement* of substrates that are intermediates used for the synthesis of nevarpine analogs. The deprotonated amide functionality in the rearrangement products displaces the chlorine at the 2-position to give the desired heterocycles in moderate to good yield.



Smiles rearrangement product

Dipyrido[2,3-*b*]diazepinone derivative

A one-pot procedure was developed for the preparation of aromatic amines from phenols *via* a one-pot *Smiles rearrangement* by N.P. Peet et al.[51] This new approach can be considered as an alternative of the *Bucherer reaction* which only works well for naphthalene derivatives and gives very poor yields for substituted benzene derivatives. In the current procedure, the phenol was reacted with 2-bromo-2-methylpropionamide to give 2-aryloxy-2-methylpropionamide which upon treatment with base underwent the *Smiles rearrangement*. The hydrolysis of the resulting *N*-aryl-2-hydroxypropionamide afforded the aromatic amine.



2-aryloxy-2-methylpropionamide

N-aryl-2-hydroxypropionamide

Aromatic amine HCl salt

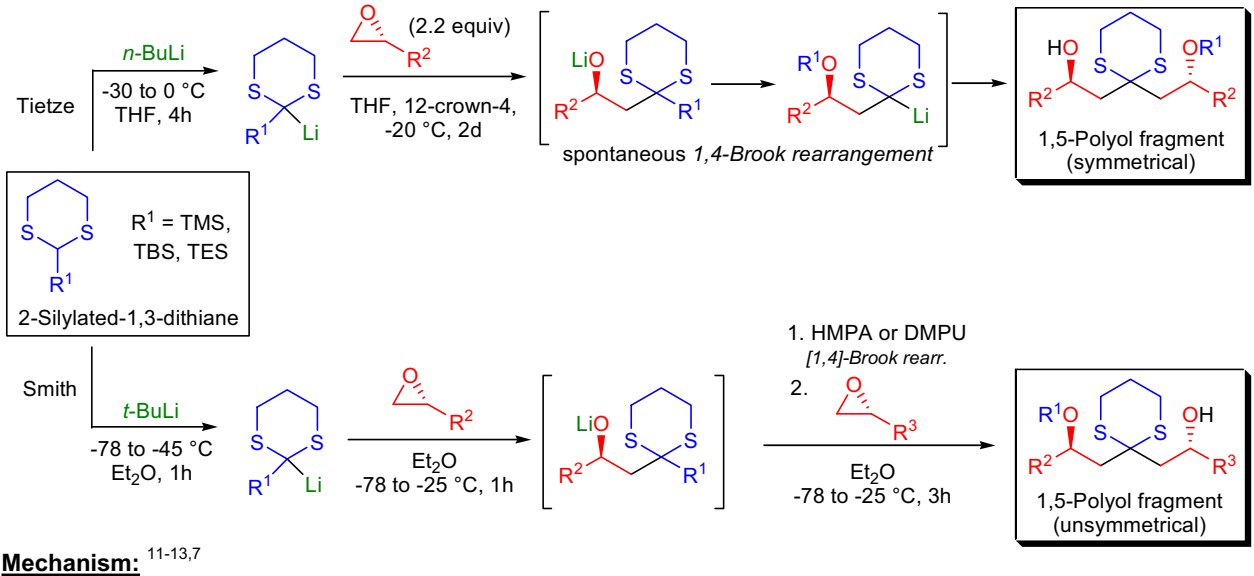
SMITH-TIETZE MULTICOMPONENT DITHIANE LINCHPIN COUPLING

(References are on page 679)

Importance:

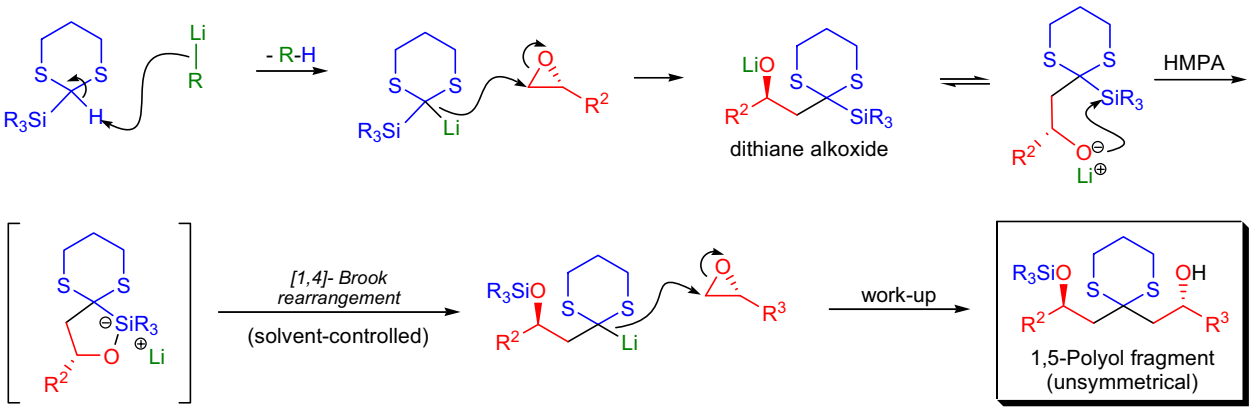
[*Seminal Publications*[1-3]; *Review*[4]; *Modifications & Improvements*[5-9]]

The one-pot multicomponent coupling of 2-silylated-1,3-dithianes with epoxides is referred to as the *Smith-Tietze coupling*. The first application of 2-lithio-1,3-dithianes as "carbonyl anion" equivalents was described by E.J. Corey and D. Seebach in the mid-1960s.[10] In 1994, L.F. Tietze and co-workers successfully synthesized C_2-symmetrical enantiopure 1,5-diols, 3-oxo-1,5-diols and 1,3,5-triols by the symmetrical *bis*-alkylation of lithiated 2-trialkylsilyl-1,3-dithianes with epoxides.[2] Tietze's protocol began with the deprotonation of the 2-trialkylsilyl-1,3-dithiane with an alkyllithium followed by the addition of 2.2 equivalents of epoxide in the presence of one equivalent of crown ether. After the opening of the first epoxide, the resulting alkoxide intermediate underwent a spontaneous *[1,4]-Brook rearrangement*, thus generating a second dithiane anion that reacted with the remaining excess epoxide. This multicomponent coupling protocol, however, had a long reaction time, and it was unsuitable for unsymmetrical couplings. A.B. Smith et al. used HMPA or DMPU as an additive in the solvent, which significantly increased the rate of the reaction and allowed two different electrophiles (epoxides) to be coupled with the dithiane in a one-pot operation.[3] The *Smith-Tietze coupling* has the following advantages: 1) optically active terminal epoxides can be readily prepared by known methods; 2) the epoxide ring-opening is completely regioselective, the nucleophile attacks on the least substituted carbon; 3) the exact timing of the *Brook rearrangement* is possible by the addition of HMPA or DMPU to the reaction mixture (*solvent-controlled Brook rearrangement*) and the formation of symmetrical adducts can be completely avoided; 4) altering the absolute configuration of the epoxides and the stereoselective reduction of the ketone moiety after the removal of the dithiane can give rise to 1,3-polyols of any desired configuration; 5) after the second epoxide has reacted, the resulting unsymmetrical adduct has its hydroxyl groups differentiated by one of them being silylated; and 6) the use of an enantiopure *bis*-epoxide as the second epoxide component allows for a one-pot *five-component linchpin coupling*.



Mechanism:[11-13,7]

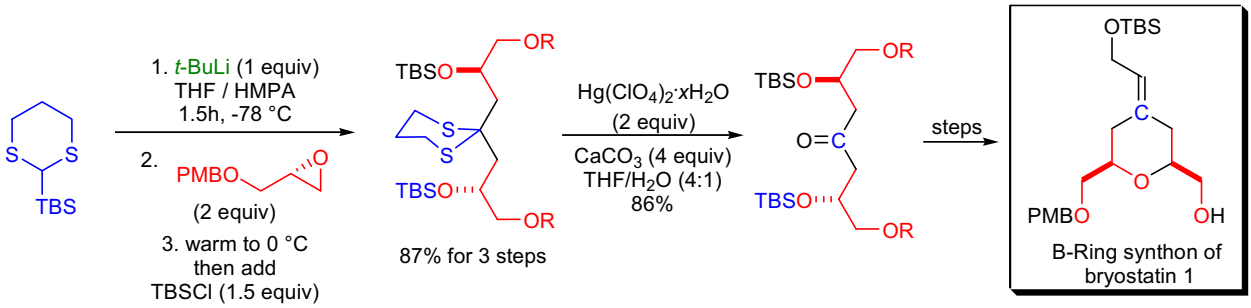
The key step of the mechanism is the solvent-controlled *[1,4]-Brook-rearrangement*, which proceeds through an intermediate having a pentacoordinate-silicon atom. This rearrangement does not take place until HMPA is added to the solvent. A similar solvent effect has been observed by K. Oshima, K. Utimoto and co-workers.[11,13] The rearrangement was found to be completely intramolecular based on the results of a crossover experiment by A.B. Smith et.al.[7]



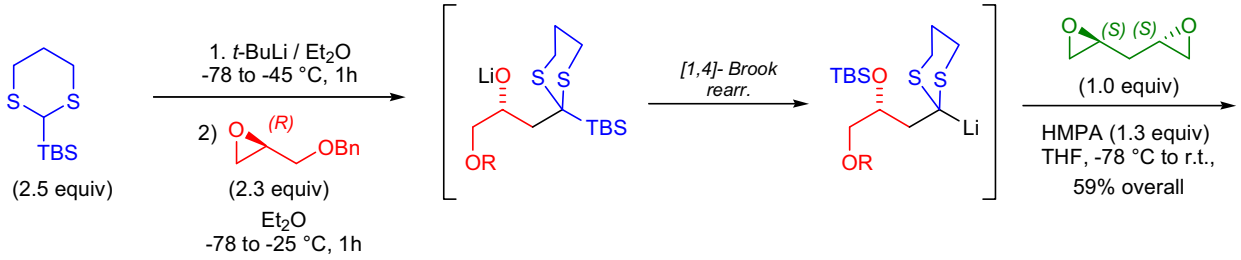
SMITH-TIETZE MULTICOMPONENT DITHIANE LINCHPIN COUPLING

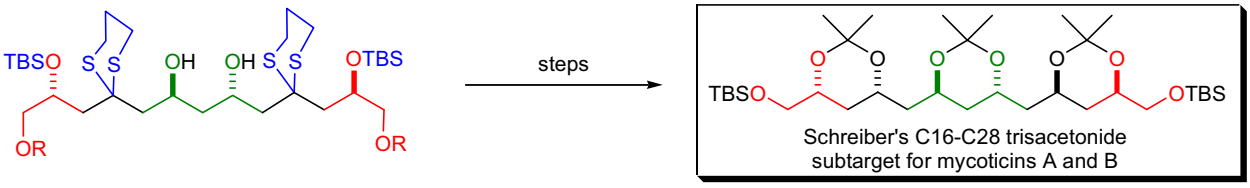
Synthetic Applications:

The stereocontrolled enantioselective synthesis of an advanced B-ring synthon of bryostatin 1 was achieved in the laboratory of K.J. Hale.[14] The key step was a *Smith-Tietze coupling* of 2-lithio-2-TBS-1,3-dithiane with a homochiral epoxide in the presence of HMPA. The resulting dithiane alkoxide was trapped with TBSCl *in situ* followed by deprotection of the dithiane moiety to give a C_2-symmetrical ketone. This ketone was then further elaborated into the target B-ring synthon.

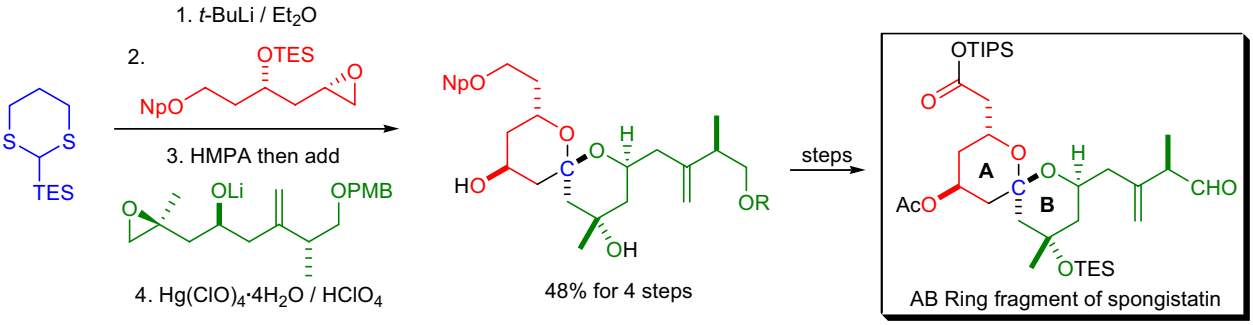


A *one-pot five-component dithiane linchpin coupling* was applied as the key synthetic transformation in A.B. Smith's approach to Schreiber's C16-C28 trisacetonide subtarget for mycoticins A and B.[7] To prevent a premature *Brook rearrangement*, ether was used instead of THF as a solvent for the initial deprotonation of 2-TBS-1,3-dithiane. The third component in the linchpin coupling was (*S*,*S*)-diepoxypentane that was added to the reaction mixture along with HMPA in THF.





The *three-component dithiane linchpin coupling* was the key bond forming reaction during the second-generation synthesis of an advanced ABCD intermediate for spongistatins by A.B. Smith et al.[15] Both the AB and CD fragments were accessed by this multicomponent coupling. Interestingly, one of the epoxide components had to be added into the reaction mixture as its lithium alkoxide to avoid the formation of elimination products. Upon deprotection of the dithiane moiety, an *in situ* spiroketalization took place. The target AB fragment was realized in several subsequent steps.



SNIECKUS DIRECTED ORTHO METALATION

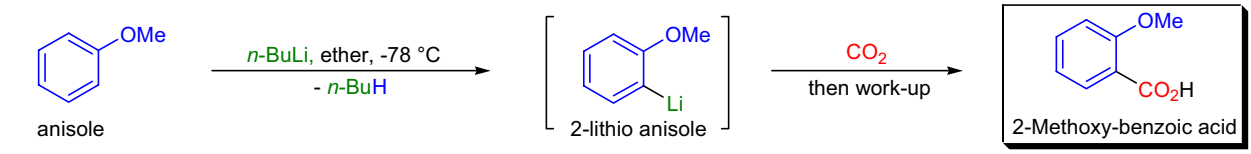
(References are on page 680)

Importance:

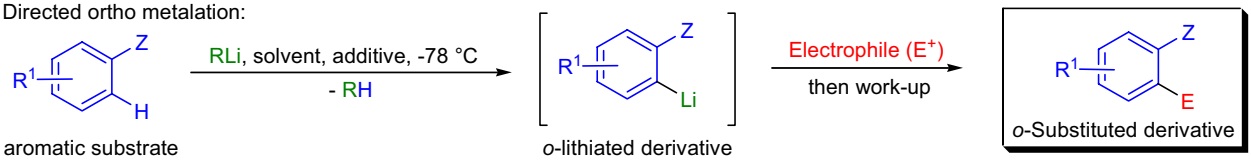
[*Seminal Publications*[1,2]; *Reviews*[3-27]; *Modifications & Improvements*[28-33]; *Theoretical Studies*[34-36]]

In the late 1930s, the research groups of H. Gilman and G. Wittig independently discovered that the treatment of anisole (methoxybenzene) and other heteroatom-substituted aromatic compounds with *n*-BuLi resulted in the exclusive deprotonation at the *ortho* position to afford the corresponding 2-lithio derivatives.[1,2] During the 1970s alkyllithiums became commercially available, and this resulted in the widespread use of the *ortho* metallation protocol to functionalize aromatic and heteroaromatic compounds.[7] *Directed metalation* is defined as the deprotonation of an sp^2 hybridized carbon atom positioned α to a heteroatom-containing substituent on an aromatic or olefinic substrate.[8] The contributions by V. Snieckus and co-workers over the last two decades significantly expanded the scope of this method, which is often referred to as the *Snieckus directed ortho metalation* (*DoM*). Before the advent of *DoM*, the preparation of contiguously substituted (e.g., 1,2-, 1,2,3- or 1,2,3,4-) aromatic compounds, using the directing effect of the various substituents in S_EAr reactions, was a major challenge and required many steps to accomplish. The general features of *DoM* reaction are: 1) the directed metalation group (Z group) must be resistant to nucleophilic attack by the metalating reagent (e.g., alkyllithiums), and it must contain at least one heteroatom, which can coordinate with the incipient *ortho* metal atom forming a 4-, 5-, or 6-membered intermediate; 2) the formation of a 5-membered intermediate is the most favorable; 3) the best Z groups are sterically demanding or charge deactivated or exhibit both of these properties at the same time; 4) the Z groups can be classified depending on the atom through which the group is attached to the aromatic ring: there are carbon linked (e.g., $CONR_2$), nitrogen linked (e.g., NHCOR), oxygen linked (e.g., $OCONR_2$), sulfur linked (e.g., SO_2R) etc. Z groups; 5) the most popular Z groups are tertiary amides and *O*-carbamates; 6) the Z groups can be ranked according to the strength of their directing effects (based on competition experiments), but the ranking changes considerably depending on the solvent, temperature and the base used to generate the metalated species: SO_2t-Bu > $CON(i\text{-}Pr)_2$ > $OCON(i\text{-}Pr)_2$ > OMOM was the hierarchy of metalation when *n*-BuLi/THF/-78 °C were used;[15] 6) in a typical procedure, the solution of the substrate is treated with the alkyllithium reagent at -78 °C under inert atmosphere followed by the addition of the electrophile; 7) substrates with Z groups having an acidic proton require the addition of at least two equivalents of the alkylithium reagent; 8) since alkyllithiums exist predominantly as aggregates in hydrocarbon solvents, the addition of basic solvents such as ethers and tertiary amines or bidentate ligands (e.g., TMEDA) is necessary to break down the aggregates to monomers and dimers to enhance their basicity; and 9) when the Z group is a carbamate ($OCONR_2$), a facile *1,3-acyl shift* occurs after the *ortho* lithiation is complete to afford a salicylamide (*anionic ortho-Fries rearrangement*). One shortcoming of the *DoM* is that the most powerful Z groups require harsh reaction conditions for their removal making it unsuitable for sensitive substrates. To address this issue, easily removable Z groups have been developed: 1) the CON(Cumyl) group is removed under mildly acidic conditions (TFA) to afford a primary amide;[31] 2) *N*-cumyl-*O*-carbamate can also be removed with mild acids.[23]

Gillman and Wittig (1939 & 1940):



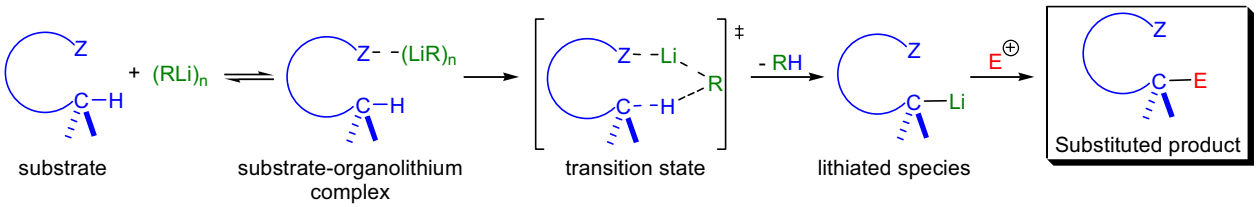
Directed ortho metalation:



Z = directed metalation group = $CONR_2$, CONHR, CONH(Cumyl), CSNHR, 2-oxazolino, 2-imidazolino, CF_3, CH=NR, $(CH_2)_nNR_2$ where n=1 or 2, CH_2OH, NMe_2, NHCOR, $NHCO_2R$, OMe, OCH_2OMe, OCH(Me)OEt, $OCONR_2$, OSEM, $OP(O)NR_2$, SO_2NR_2, SO_2NHR, SO_2R; R = *n*-Bu, *sec*-Bu, *t*-Bu; solvent = THF, Et_2O, hexanes, benzene or combinations of these; additive: TMEDA

Mechanism:[37,27]

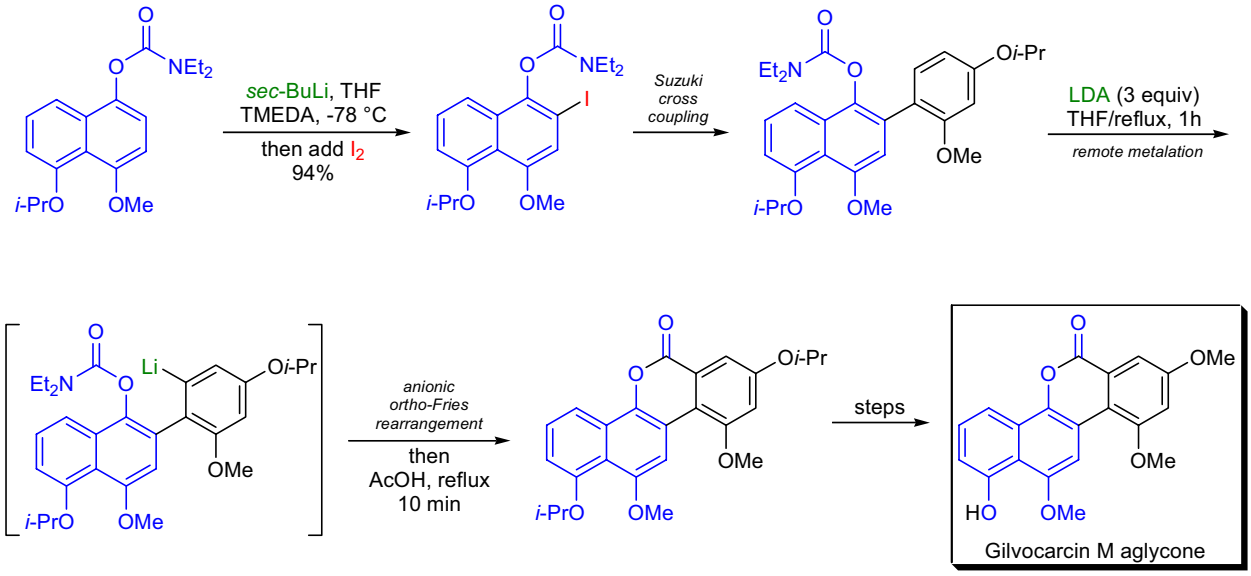
The *directed ortho metalation* is fundamentally a complex-induced proximity effect (CIPE) in which the formation of a pre-metalation complex brings reactive groups into proximity for directed deprotonation.



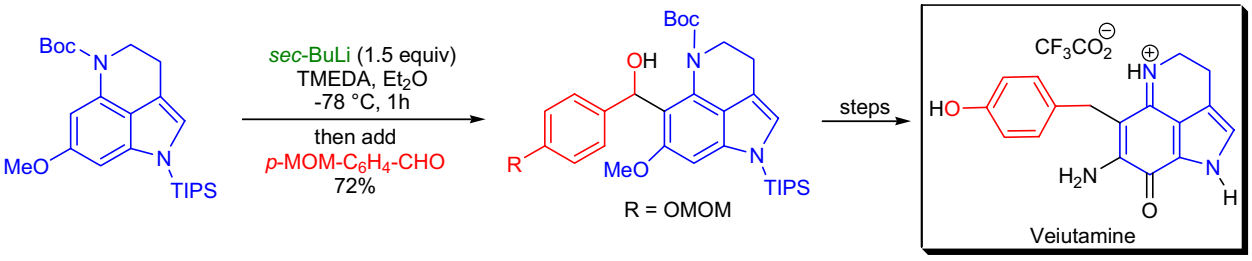
SNIECKUS DIRECTED ORTHO METALATION

Synthetic Applications:

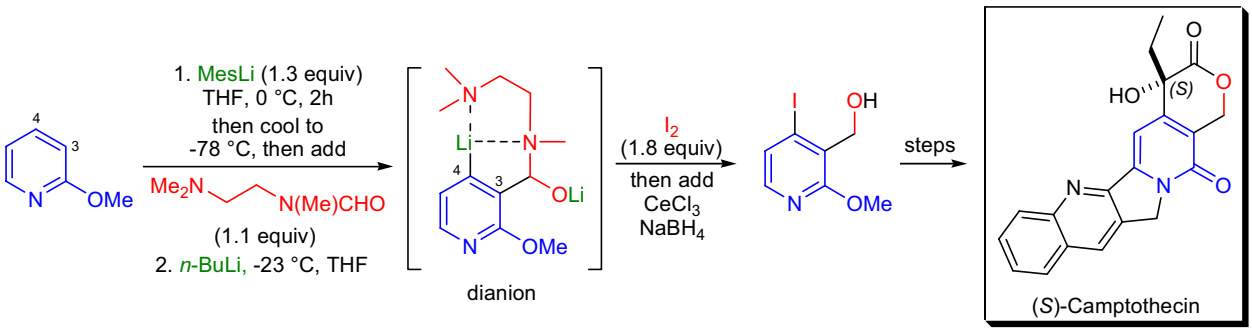
The synthesis of the aglycons of gilvocarcin V, M and E by V. Snieckus and co-workers involved the use of directed *o*-metalation and *remote metalation* (*anionic ortho-Fries rearrangement*).[38] The trioxygenated naphthalene ring was first *o*-metalated and the resulting lithiated species was iodinated. The 2-iodo compound was then subjected to a *Suzuki cross-coupling* to obtain a biaryl compound that was treated with excess LDA in refluxing THF to induce the remote metalation. Exposure to refluxing acetic acid gave the corresponding lactone, which was subsequently converted to the gilvocarcin M aglycone.



In the laboratory of M. Iwao, the first total synthesis of a new pyrroloiminoquinone marine alkaloid veiutamine was accomplished.[39] The key step was the selective functionalization of the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus *via* an *N*-Boc *directed ortho metalation* at the C6 position. The resulting 6-lithiated compound was trapped with MOM-protected *p*-hydroxybenzaldehyde.



A practical six-step synthesis of (*S*)-camptothecin was developed by D.L. Comins and co-workers.[40] In order to prepare the DE ring fragment, 2-methoxypyridine was lithiated at C3 with mesityllithium and treated with *N*-formyl-*N,N',N'*-trimethyl ethylenediamine to form an -amino alkoxide *in situ*. In the same pot, the addition of *n*-BuLi brought about a *directed lithiation* at C4 to afford a dianion, which was trapped with iodine and treated with $NaBH_4/CeCl_3$ to give the desired 4-iodo-2-methoxy-3-hydroxymethyl pyridine in 46% yield.



SOMMELET-HAUSER REARRANGEMENT

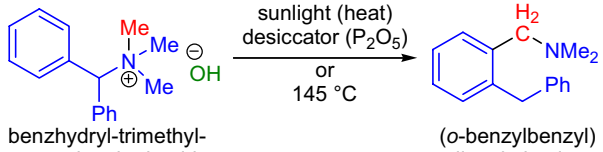
(References are on page 681)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-17]; *Theoretical Studies*[18-20]]

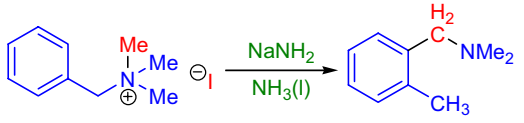
In 1937, M. Sommelet reported that benzhydryltrimethylammonium hydroxide rearranged to give (*o*-benzylbenzyl)dimethylamine in modest yield when kept in the desiccator over P_2O_5 exposed to sunlight.[1] The same result was obtained when the substrate was heated to 145 °C, which suggested that the sunlight only provided the heat necessary for the transformation. During the following decade several research groups reported products from similar rearrangements which accompanied the well-known *Stevens rearrangement* of quaternary ammonium salts; however, it was C.R. Hauser and co-workers who investigated this new rearrangement extensively. Hauser et al. treated benzyltrimethylammonium iodide with $NaNH_2$ in liquid ammonia and isolated dimethyl-(2-methylbenzyl)-amine as the sole product in excellent yield.[2] They also demonstrated that methyl groups could be successively introduced into the aromatic ring by exhaustively methylating the product and exposing it to $NaNH_2/NH_3$. The *[2,3]-sigmatropic rearrangement* of benzylic quaternary ammonium salts in the presence of a strong base is known as the *Sommelet-Hauser rearrangement* (*S.-H. rearrangement*). The general features of this transformation are: 1) the quaternary ammonium salts are easily available by the alkylation of the corresponding tertiary amines with alkyl halides; 2) the aromatic ring can be either a substituted benzene ring or a substituted heteroaromatic ring; 3) the deprotonation of the quaternary ammonium salt to generate the reactive nitrogen ylide intermediate is most often achieved by treatment with alkali metal amides in liquid ammonia, however, there are alternative methods available for the generation of the reactive intermediate; 4) when there are two possible sites of deprotonation, usually the more stable ylide is formed (derived from the more stable carbanion); 5) when it is not possible to form the ylide by deprotonation because the initial benzylic carbanion is significantly stabilized (e.g., R^1=EWG group such as CN, NO_2, Cl, Br), the rearrangement may not occur; 6) when the alkyl groups attached to the nitrogen contain a hydrogen atom at their β-position, the *Hofmann elimination* may compete; 7) cyclic quaternary ammonium salts react by ring-expansion; 8) one major competing reaction is the *Stevens rearrangement*; 8) in systems where both the *Stevens*- and *S.-H. rearrangements* are possible, the choice of reaction conditions allow control over which of these competing processes dominate; 9) low temperatures and polar solvents (e.g., NH_3, DMSO, HMPA) usually favor the *S.-H. rearrangement*, whereas higher temperatures and nonpolar solvents (e.g., hexanes, ether) facilitate the *Stevens rearrangement*; and 10) since most quaternary ammonium salts are insoluble in nonpolar organic solvents, the use of alkyllithiums as bases is limited. There are several modifications of the *S.-H. rearrangement*: 1) when benzylsulfonium salts are deprotonated, sulfonium ylides are formed that undergo analogous rearrangement and allow an asymmetric version;[10] and 2) the generation of nitrogen ylides is possible under neutral conditions by fluoride-induced desilylation of (trimethylsilyl)methyl ammonium halides.[12,13]

Sommelet (1937):



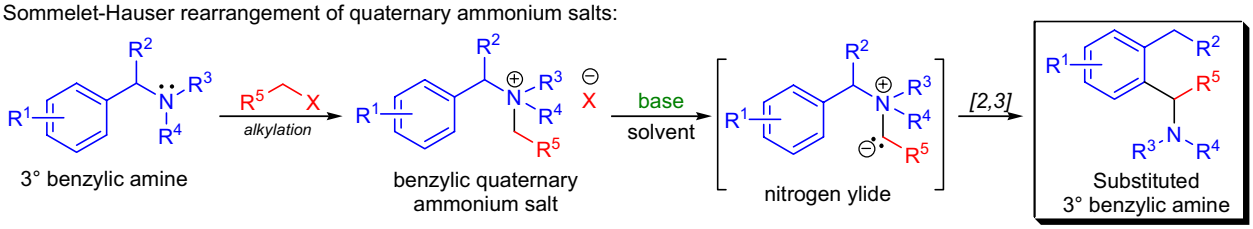
benzhydryl-trimethyl-ammonium hydroxide → (*o*-benzylbenzyl) dimethylamine

Hauser (1951):



benzyltrimethyl-ammonium iodide → dimethyl (2-methyl-benzyl)-amine

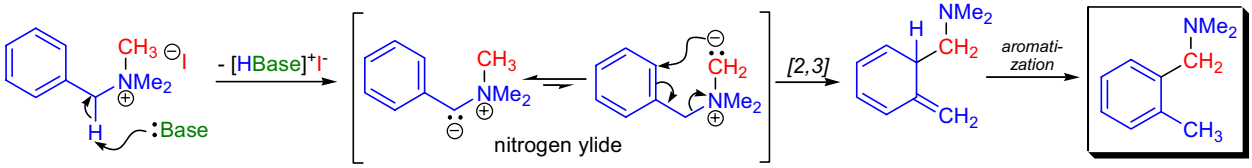
Sommelet-Hauser rearrangement of quaternary ammonium salts:



3° benzylic amine → benzylic quaternary ammonium salt → nitrogen ylide → Substituted 3° benzylic amine

R^1 = usually EDG = H, alkyl, aryl, *O*-alkyl; R^2 = H, alkyl, aryl; R^{3-4} = CH_3, alkyl with no β-hydrogen, aryl; R^5 = most often H, 3° alkyl; X = Cl, Br, I; base = $NaNH_2$, KNH_2, alkyllithium; solvent = NH_3 (liquid), DMSO, HMPA

Mechanism:[21-25]

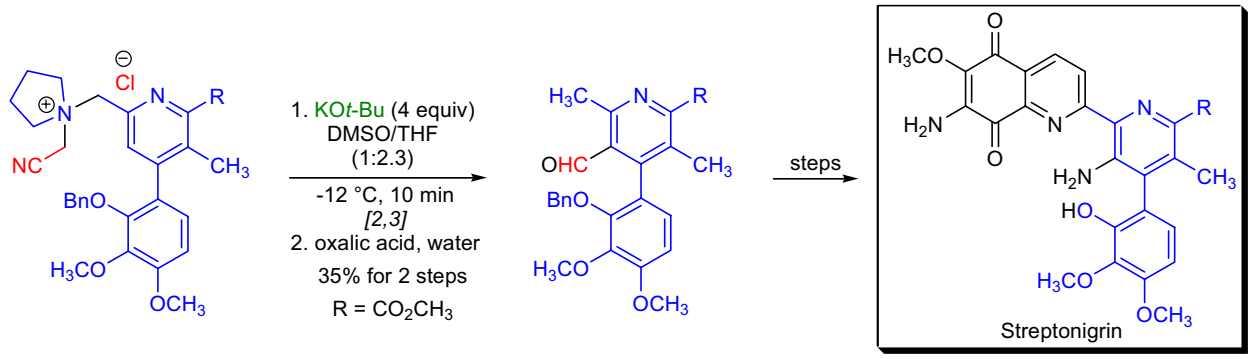


nitrogen ylide

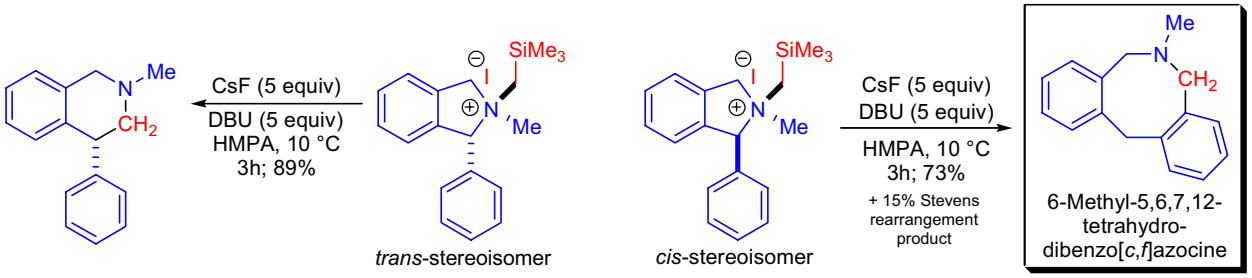
SOMMELET-HAUSER REARRANGEMENT

Synthetic Applications:

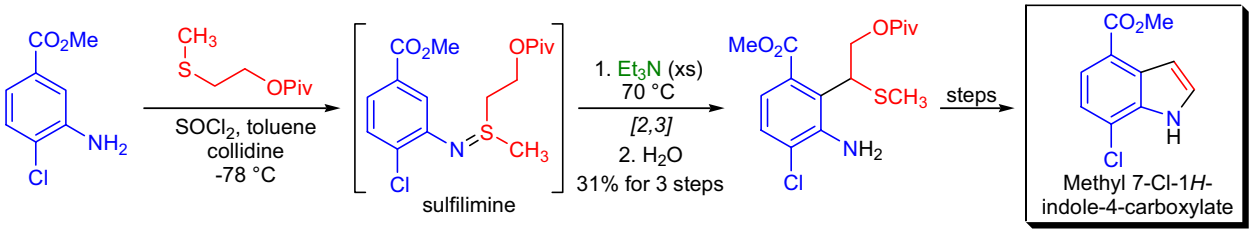
In the laboratory of S.M. Weinreb, the total synthesis of the potent antibiotic natural product streptonigrin was accomplished.[26] In order to obtain a fully substituted pyridine moiety under mild conditions, the *modified Sommelet-Hauser rearrangement* was utilized. The quaternary ammonium salt was derived from *N*-(cyanomethyl)pyrrolidine which could be efficiently deprotonated using KO*t*-Bu. Upon deprotonation the expected *[2,3]-sigmatropic shift* took place, and the resulting amino nitrile was immediately hydrolyzed to afford the corresponding aldehyde.



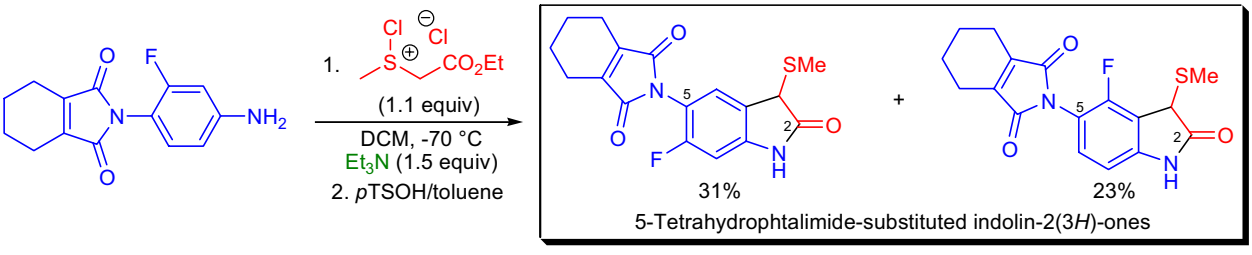
In the traditional strong base-promoted *S.-H. rearrangement*, the regioselective deprotonation of the ammonium salts is often difficult and other processes become competitive. A nonbasic modification may be accomplished when the desired nitrogen ylide is generated regiospecifically by means of fluoride ion-induced desilylation. Y. Sato and co-workers utilized this method for the ring-expansion of cyclic ammonium salts.[27] They showed that the stereochemistry of the substrate had a dramatic effect on the course of the reaction. The *cis*-stereoisomer gave predominantly the *[2,3]*-rearranged product, while the *trans*-stereoisomer gave exclusively the *Stevens rearrangement* product.



P.B. Alper and co-workers developed a practical approach for the synthesis of 4,7-disubstituted indoles based on the *Sommelet-Hauser rearrangement* of aryl sulfilimines.[28] The multihundred-gram preparation of methyl 7-chloroindole-4-carboxylate was achieved. The synthesis commenced with the activation of a sulfide precursor with $SOCl_2$ and coupling the intermediate with 3-amino-4-chlorobenzoate to afford an aromatic sulfilimine. This sulfilimine was exposed to excess triethylamine and heated to generate the sulfonium ylide that underwent the rearrangement.



Novel regioisomeric tetrahydrophthalimide-substituted indoline-2(3*H*)-ones were prepared as potential herbicides by G.M. Karp et al. utilizing the sulfonium ylide version of the *Sommelet-Hauser rearrangement* [29] The unsymmetrical aniline substrate was treated with the chlorosulfonium salt of ethyl (methylthio)acetate and triethylamine at low temperature. The resulting regioisomeric amino esters were cyclized to the regioisomeric indoline-2(3*H*)-ones that were separated by column chromatography.



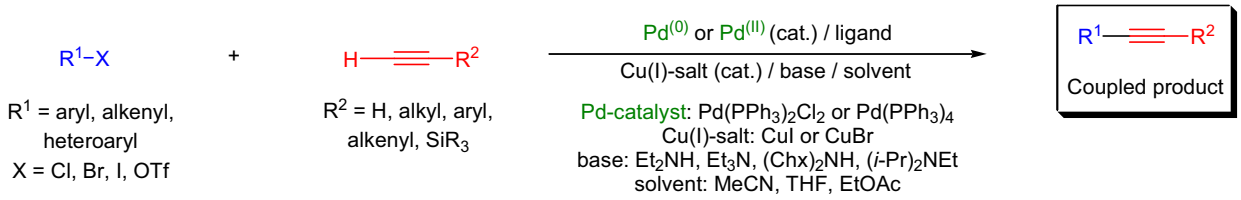
SONOGASHIRA CROSS-COUPLING

(References are on page 681)

Importance:

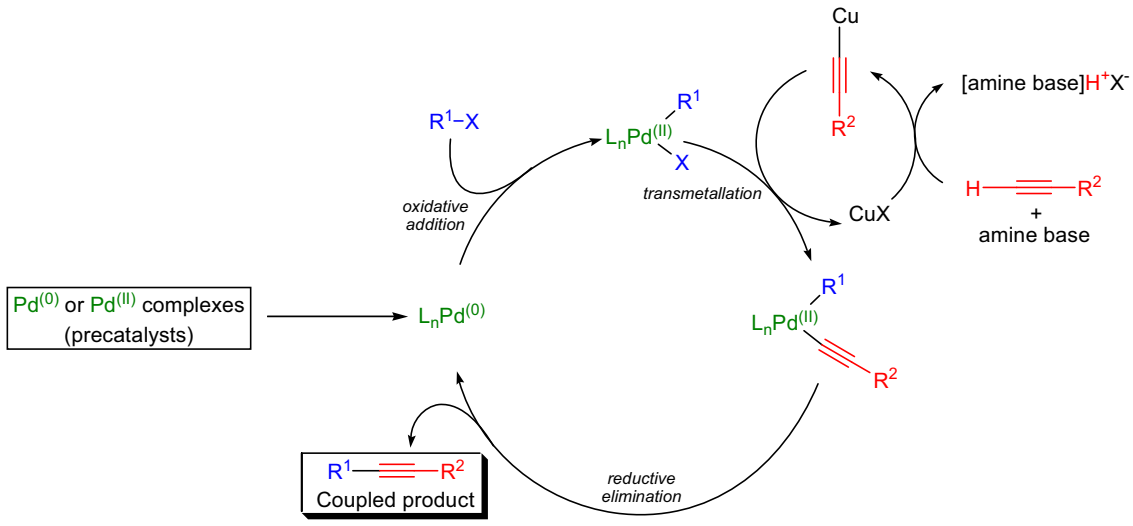
[*Seminal Publications*[1-3]; *Reviews*[4-30]; *Modifications & Improvements*[31-46]]

In 1975, K. Sonogashira and co-workers reported that symmetrically substituted alkynes could be prepared under mild conditions by reacting acetylene gas with aryl iodides or vinyl bromides in the presence of catalytic amounts of $Pd(PPh_3)Cl_2$ and cuprous iodide (CuI).[3] During the same year the research groups of both R.F. Heck and L. Cassar independently disclosed similar Pd-catalyzed processes, but these were not using copper co-catalysis, and the reaction conditions were harsh.[1,2] The copper-palladium catalyzed coupling of terminal alkynes with aryl and vinyl halides to give enynes is known as the *Sonogashira cross-coupling* and can be considered as the catalytic version of the *Castro-Stephens coupling*. The general features of the reaction are: 1) the coupling can usually be conducted at or slightly above room temperature, and this is a major advantage over the forcing conditions required for the alternative *Castro-Stephens coupling*; 2) the handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I) salt; 3) the copper(I) salt can be the commercially available CuI or CuBr and are usually applied in 0.5-5 mol% with respect to the halide or alkyne; 4) the best palladium catalysts are $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$; 5) the solvents and the reagents do not need to be rigorously dried. However, a thorough deoxygenation is essential to maintain the activity of the Pd-catalyst; 6) often the base serves as the solvent but occasionally a co-solvent is used; 7) the reaction works well on both very small and large scale (>100g); 8) the coupling is stereospecific; the stereochemical information of the substrates is preserved in the products; 9) the order of reactivity for the aryl and vinyl halides is I ≈ OTf > Br >> Cl; 10) the difference between the reaction rates of iodides and bromides allows selective coupling with the iodides in the presence of bromides; 11) almost all functional groups are tolerated on the aromatic and vinyl halide substrates. However, alkynes with conjugated electron-withdrawing groups (R^2=CO_2Me) give *Michael addition* products and propargylic substrates with electron-withdrawing groups (R^2= CH_2CO_2Me or NH_2) tend to rearrange to allenes under the reaction conditions;[5] and 12) the exceptional functional group tolerance of the process makes it feasible to use this coupling for complex substrates in the late stages of a total synthesis. The coupling of sp^2-C halides with sp-C metal derivatives is also possible by using other reactions such as the *Negishi-, Stille-, Suzuki-, and Kumada cross-couplings*. In terms of functional group tolerance, the *Negishi cross-coupling* is the best alternative to the *Sonogashira reaction*. There are certain limitations on the *Sonogashira coupling*: 1) aryl halides and bulky substrates that are not very reactive require higher reaction temperature; and 2) at high temperatures terminal akynes undergo side reactions.



Mechanism:[47-50,27]

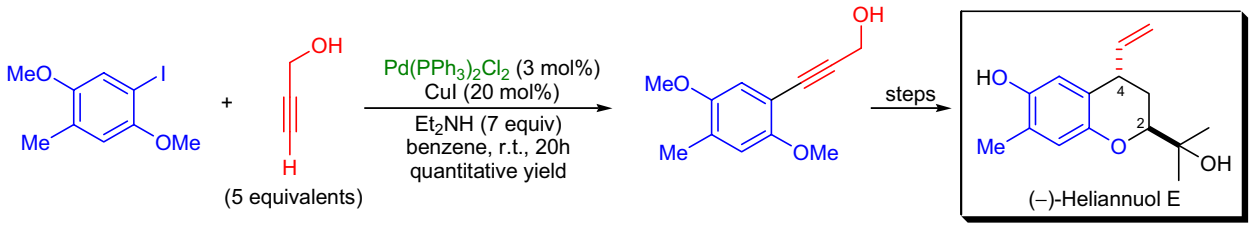
The mechanism of the *Sonogashira cross-coupling* follows the expected oxidative addition-reductive elimination pathway. However, the structure of the catalytically active species and the precise role of the CuI catalyst is unknown. The reaction commences with the generation of a coordinatively unsaturated $Pd^{(0)}$ species from a $Pd^{(II)}$ complex by reduction with the alkyne substrate or with an added phosphine ligand. The $Pd^{(0)}$ then undergoes oxidative addition with the aryl or vinyl halide followed by transmetallation by the copper(I)-acetylide. Reductive elimination affords the coupled product and the regeneration of the catalyst completes the catalytic cycle.



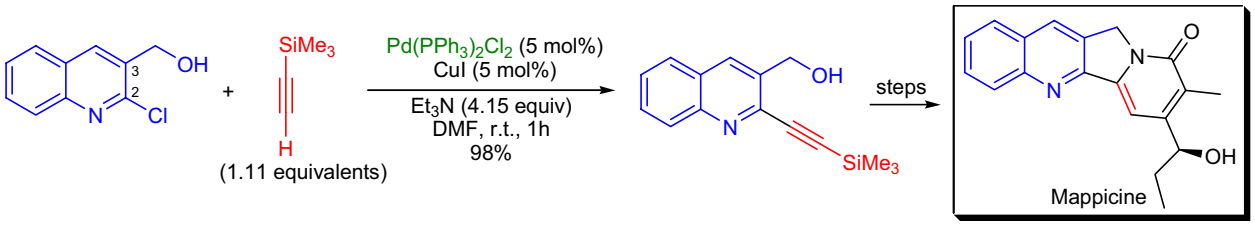
SONOGASHIRA CROSS-COUPLING

Synthetic Applications:

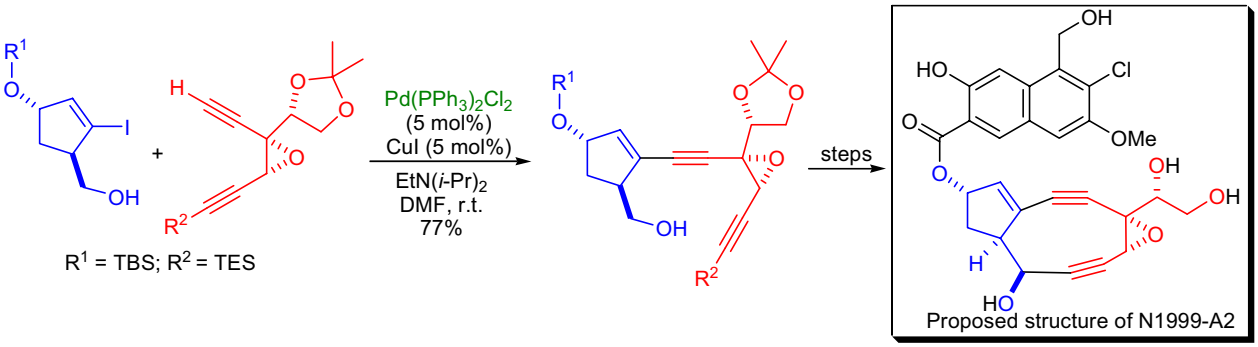
The novel heliannane-type sesquiterpenoid (–)-heliannuol E was synthesized in the laboratory of K. Shishido.[51] Interest in the total synthesis of this natural product was not only spurred by its irregular terpenoid structure and significant biological activity but the need to establish the absolute stereochemistry at the C2 and C4 stereocenters. The *Sonogashira reaction* was utilized to prepare the 3-arylpropargyl alcohol by coupling of a heavily substituted aryl iodide with an unprotected propargyl alcohol in quantitative yield.



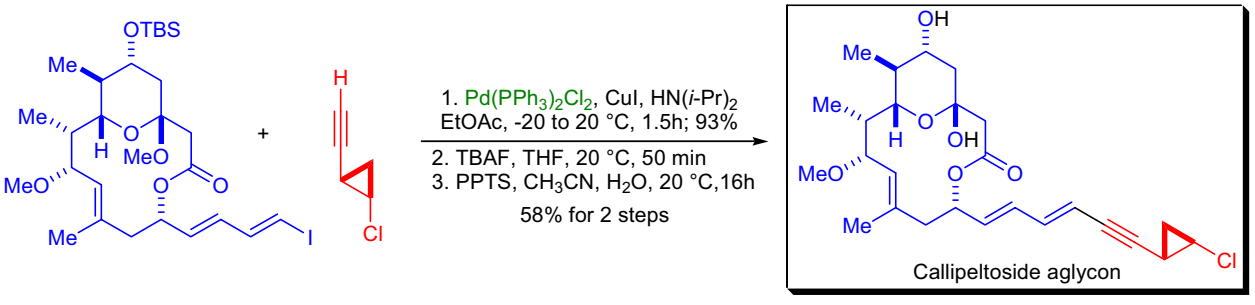
The concise formal total synthesis of mappicine was accomplished using an *intramolecular hetero Diels-Alder reaction* as the key step by M. Ihara and co-workers.[52] Introduction of the necessary acetylenic moiety at the C2 position was achieved by the *Sonogashira cross-coupling* of a 2-chloroquinoline derivative with TMS-acetylene. Several substituents at the C3 position were investigated, and it was found that the unprotected hydroxymethyl substituent gave almost quantitative yield of the desired disubstituted alkyne product.



A novel member of the highly strained nine-membered enediyne antibiotic family, N1999-A2, exhibits remarkable antitumor activity against various tumor cell lines. Because the absolute configuration has not been established, the goal of the synthetic effort by M. Hirama et al. was to prove the stereochemistry unambiguously.[53] The cyclopentenyl iodide fragment was efficiently coupled with the epoxydiyne fragment under the *Sonogashira coupling* conditions. Unfortunately, the spectrum of the final product did not match the spectrum of the natural product so the proposed structure needs to be revised.



The expedient total synthesis of the callipeltoside aglycon was achieved by I. Paterson and co-workers.[54] The authors utilized a late-stage S*onogashira coupling* between a dienyl iodide and an alkynyl cyclopropane derivative. Interestingly, the use of $Pd(PPh_3)_4$ as a catalyst did not give any of the desired coupling product. However, switching the catalyst to $Pd(PPh_3)_2Cl_2$ afforded the desired dieneyne in excellent yield.



STAUDINGER KETENE CYCLOADDITION

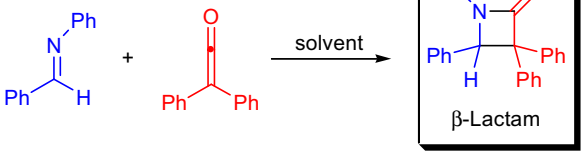
(References are on page 682)

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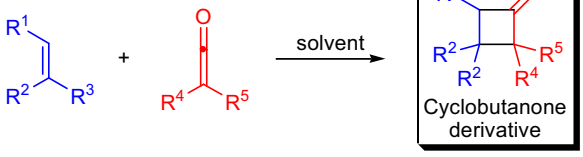
[*Seminal Publications*[1-8]; *Reviews*[9-33]; *Theoretical studies*[34-48]]

In 1908, ketene (CH_2=C=O) was independently prepared by the research groups of F. Chick and H. Staudinger.[3,6] At the same time, Staudinger exhaustively studied the reactivity of ketene and ketene derivatives, and he found that diphenylketene reacts with alkenes, ketones, and imines.[1,2,4-8,49,50] Today, the thermal [2+2] cycloaddition reaction of ketenes with carbon-carbon, carbon-oxygen, and carbon-nitrogen double bonds is referred to as the *Staudinger ketene cycloaddition*. The most common methods for the preparation of ketenes are: 1) dehydrohalogenation of acid chlorides by trialkylamines;[51] 2) dehalogenation of α-halo acid chlorides by zinc or zinc-copper alloy to form dihaloketenes;[52,53] 3) thermal[54] or photochemical[55] opening of cyclobutenones;[54] 4) *Wolff rearrangement* of α-diazoketones;[54] 5) pyrolysis of anhydrides followed by bulb to bulb distillation;[9] 6) pyrolysis of esters;[56-58] and 7) cracking commercially available diketene at atmospheric pressure leads to ketene.[9] The general features of the reaction of ketenes with alkenes are:[24] 1) the reaction leads to cyclobutanones; 2) the order of reactivity with simple alkenes is *trans* olefin < *cis* olefin < cyclic olefin< linear diene < cyclic diene; 3) the stereochemistry around the double bond is retained; 4) regiochemistry is determined by the polarization of the double bond; 5) as ketene itself is not reactive toward double bonds; usually dichloroketene is used instead, followed by dehalogenation by zinc-copper alloy; 6) in case of perfluorinated ketenes and alkoxybutadienes, the reaction may lead to the [4+2] cycloadducts; and 7) in addition to simple alkenes, allenes, enamines, and enol ethers also undergo the cycloaddition, although the yields are generally lower. The general features of the reaction of ketenes with aldehydes and ketones are:[24] 1) the reaction leads to the formation of 2-oxetanones (also called as β-lactones); 2) these reactions usually require Lewis acid activation, and the most common Lewis acids are boron trifluoride etherate, aluminum chloride, and zinc chloride; 3) amines can also be utilized as catalysts; 4) carbonyls bearing strongly electron-withdrawing substituents do not require activation; 4) a wide array of ketene substrates can be used, although aryl- and diarylketenes are generally unreactive; and 5) asymmetric versions of the cycloaddition have been developed by utilizing chiral amine bases as catalysts. The general features of the reaction of ketenes with imines are:[23,29,30,32,33] 1) the reaction is of particular importance because it leads to the formation of azetidinones (also called as β-lactams); 2) the reaction is usually carried out thermally or photochemically using acid chloride and triethylamine or α-diazoketones as the ketene precursors; 3) the diastereoselectivity of the resulting β-lactams is generally high; 4) asymmetric versions were developed by employing chiral auxiliaries attached to the imine or the ketene; 5) asymmetric catalytic methods utilizing chiral amine bases were also developed; and 6) when the reaction is carried out in sulfur dioxide, it leads to the formation of 2,3-diphenylthiazolidin-4-one-1,1-dioxide derivatives.[59] In addition to the above compounds, acetylenes, thiocarbonyls, isocyanates, carbodiimides, *N*-sulfinylamines, nitroso- and azo compounds also undergo a formal [2+2] cycloaddition with ketenes.[24]

H. Staudinger (1907):

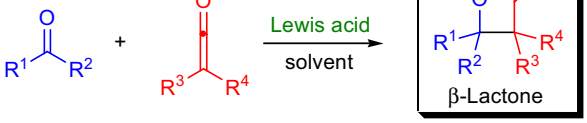


Reaction of ketenes with alkenes:



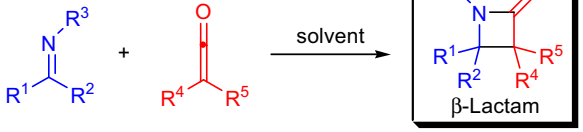
R^1 = R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, vinyl, -OR, -NR_2; R^4 = H, alkyl, aryl, -Cl, -Br; R^5 = alkyl, aryl, -Cl, -Br, -OR;

Reaction of ketenes with aldehydes and ketones:



R^1 = H, alkyl, aryl ; R^2 = H, alkyl, aryl, vinyl; R^3 = H, alkyl, -Cl, -Br; R^4 = alkyl, aryl, -Cl, -Br, -OR -$SiMe_3$; Lewis acid = $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnCl_2$

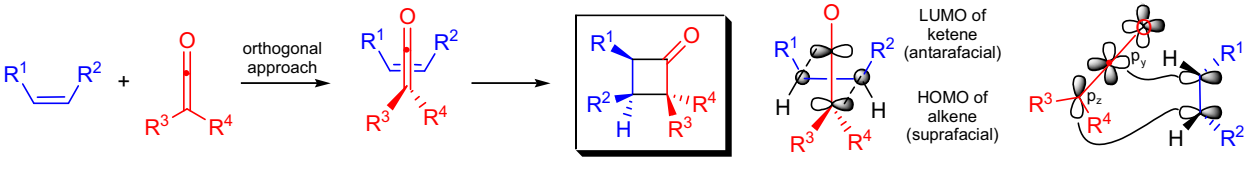
Reaction of ketenes with imines:



R^1 = H, alkyl, aryl; R^2 = alkyl, aryl; R^3 = alkyl, benzyl, aryl, -$SiMe_3$; R^4 = H, alkyl; R^5 = alkyl, -OR, -NR_2;

Mechanism:[60-67]

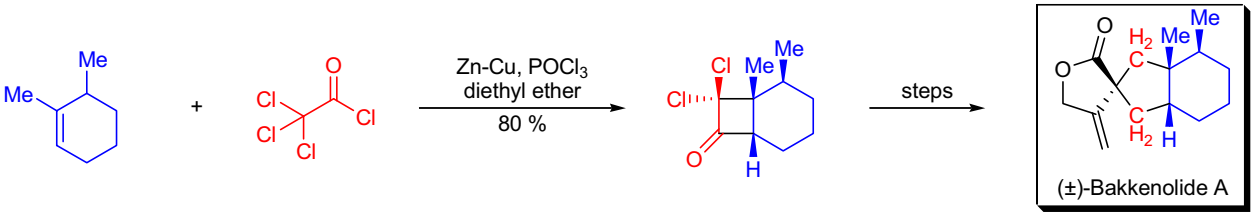
The reaction of ketenes with alkenes is assumed to occur *via* a concerted nonsynchronous mechanism, where the approach of the reacting partners is orthogonal.[60-66] As a consequence, the bulkier substituent of the ketene will end up on the sterically more crowded face of the cyclobutanone product. There are two descriptions that explain the experimental results: 1) according to the Woodward-Hoffmann rules, the LUMO of the ketene reacts antarafacially with the HOMO of the alkene that reacts suprafacially;[24] 2) the HOMO of the alkene forms a bond with the p_z orbital of the terminal carbon and the p_y orbital of the central carbon of the ketene.[67] The reaction of ketenes with carbonyls and imines follows a stepwise mechanism.



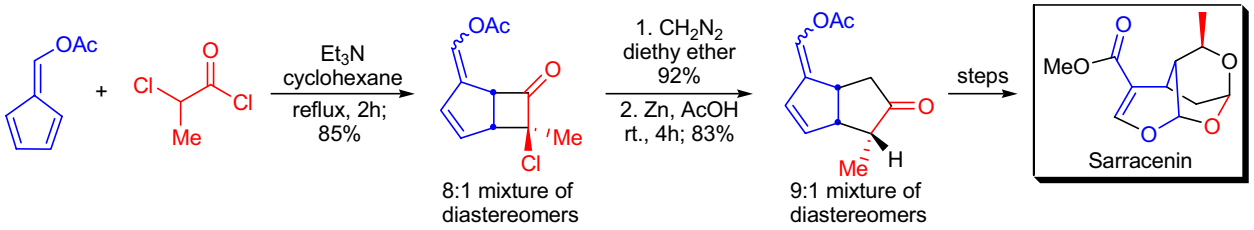
STAUDINGER KETENE CYCLOADDITION

Synthetic Applications:

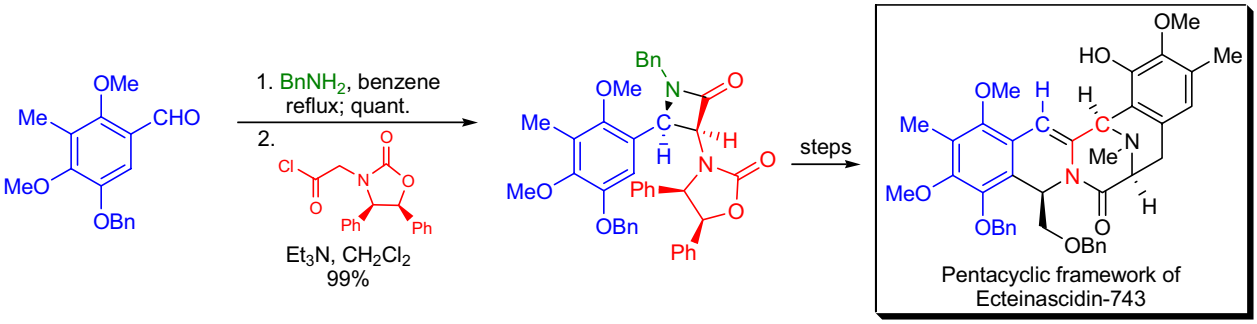
The *Staudinger ketene cycloaddition* was utilized as the key reaction in the synthesis of a number of bakkane natural products in the laboratory of A.E. Greene.[68] Dichloroketene was generated *in situ* from trichloroacetyl chloride by zinc-copper alloy in the presence of phosphorous oxychloride. The *[2+2] cycloaddition* between dichloroketene and 1,6-dimethylcyclohexene gave the product in high yield and excellent regio- and diastereoselectivity. The cycloadduct was successfully converted to (±)-bakkenolide A.



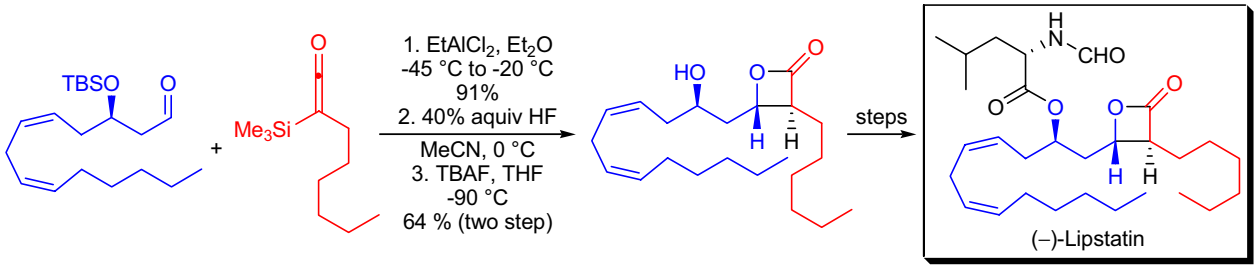
N.C. Chen and co-workers devised an efficient synthesis of the *cis*-bicyclo[3.3.0]octane ring system that was a key intermediate in the synthesis of iridoid monoterpene natural products loganin and sarracenin.[69] In their approach, they utilized a *[2+2] ketene cycloaddition* between a fulvene derivative and methylchloroketene that was generated *in situ* from 2-choropropanoyl chloride by treatment with triethylamine. The cycloaddition reaction provided the product with excellent regioselectivity and as a 8:1 mixture of diastereomers. Subsequent ring expansion and dehalogenation by zinc metal in acetic acid gave the key intermediate as a 9:1 mixture of diastereomers.



Ecteinascidin (ET)-743 is a marine natural product that exhibits potent antitumor activity. R.M. Williams and co-workers developed an approach for the synthesis of the pentacyclic framework of the molecule.[70] At an early stage in the synthesis, they used a *ketene-imine cycloaddition* utilizing a chiral *N*-protected ketene derivative to control the stereoselectivity. Subsequently, the chiral auxiliary was removed and the intermediate β-lactam was converted to the target structure.



(–)-Lipstatin is a natural product that exhibits potent inhibitor activity of the pancreatic lipase, and therefore it is a potential lead for the development of antiobesity agents. P.J. Kocienski developed a synthesis for this compound that incorporates an *aldehyde-ketene cycloaddition* as the key step.[71] The reaction between the aldehyde and silylketene derivative was carried out in the presence of $EtAlCl_2$ that served as the Lewis acid activator. This transformation led to the formation of four diastereomers in 91% yield, but after desilylation, the desired stereoisomer could be isolated in 64% yield from the mixture.



STAUDINGER REACTION

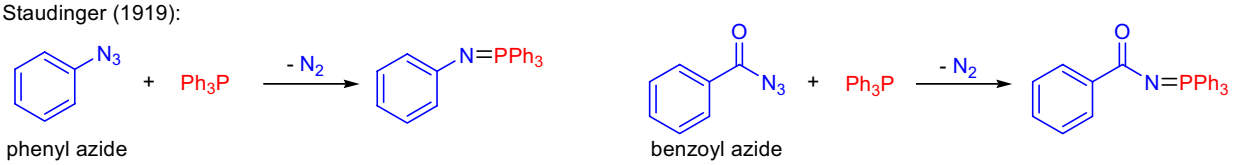
(References are on page 684)

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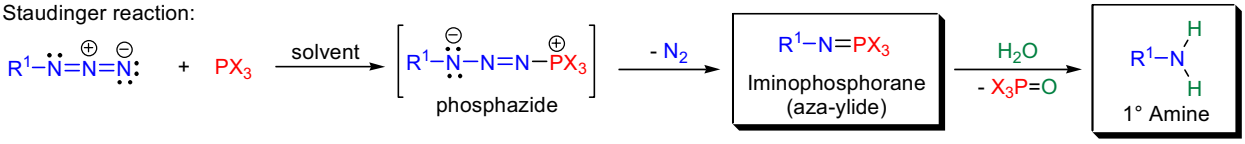
[*Seminal Publications*[1]; *Reviews*[2-15]; *Modifications & Improvements*[16-32]; *Theoretical Studies*[33-35]]

In 1919, H. Staudinger and J. Meyer reported the reaction between phenyl azide and triphenylphosphine, which afforded a novel compound, phosphinimine (also known as aza-ylide or iminophosphorane), in quantitative yield accompanied by the evolution of nitrogen gas.[1] It was found that benzoyl azide reacted with triphenylphosphine in an analogous fashion to afford the corresponding benzoyl aza-ylide. The authors also investigated the reactivity of phosphinimines and demonstrated that the reaction of carbon dioxide with phenyl aza-ylide gave rise to phenyl isocyanate and triphenylphosphine oxide, which is the first example of an *aza-Wittig reaction*. The reaction of organic azides with trivalent phosphorous compounds (e.g., trialkyl- or triarylphosphines) to afford the corresponding aza-ylides is known as the *Staudinger reaction*. The general features of this transformation are:[4,6,9,10] 1) the reaction is usually very fast and takes place in almost quantitative yield without the formation of side products; 2) virtually any trivalent phosphorus compound undergoes the reaction; 3) the structure of the azide component can also be widely varied; and 4) the iminophosphorane products derived from alkyl- or arylazides and trialkyl- and triarylphosphines are stable compounds that can be isolated, but alkoxy groups on the P atom tend to undergo alkyl migration. The iminophosphoranes are versatile synthetic intermediates: 1) hydrolysis with water gives rise to primary amines (this reduction of azides is highly chemo- and stereoselective); 2) inter- or intramolecular reaction with carbonyl or thiocarbonyl compounds affords imines (*aza-Wittig reaction*); 3) carboxylic acids convert iminophosphoranes to *N*-substituted amides; 4) acyl halides condense to generate imydoyl halides; and 5) ozonolysis produces nitro compounds.

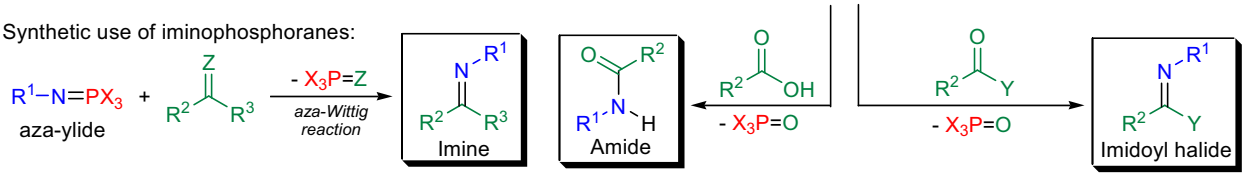
Staudinger (1919):



Staudinger reaction:



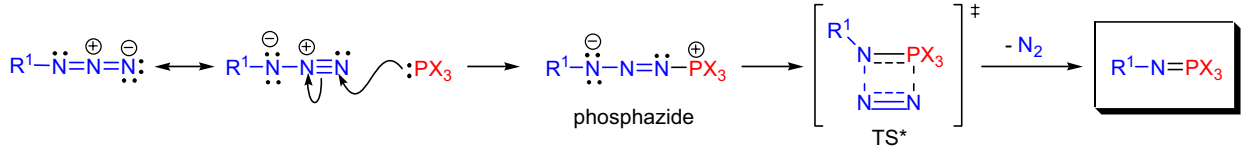
Synthetic use of iminophosphoranes:



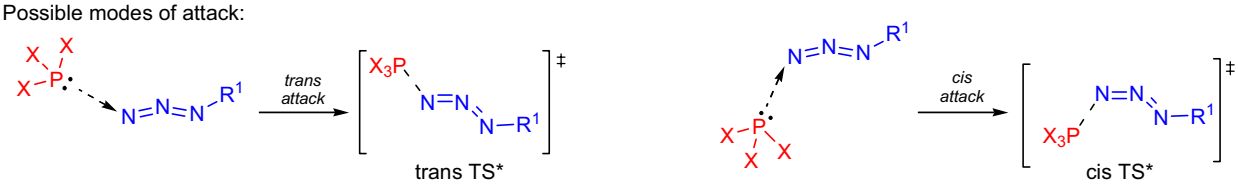
R^1 = alkyl, aryl, heteroaryl, RC(O), RSO_2, RP(O), R_2P, R_3Si, R_3Sn, R_3Ge; R^{2-3} = H, alkyl, aryl, heteroaryl; X = alkyl, aryl, O-alkyl, O-aryl, NH_2, NR_2, Cl, F, NCO, (also the combination of these ligands); Y = Cl, Br; Z = O, S; solvent: THF, Et_2O

Mechanism:[36-42]

The mechanism of the *Staudinger reaction* has been subject to a number of kinetic and theoretical studies[35] and at this point the exact mechanism remains unclear. All experimental data shows, however, that free radicals or nitrenes are not intermediates in this transformation. The first step of the mechanism is the attack of trivalent phosphorous by the unsubstituted nitrogen atom (N) of the azide to give the corresponding phosphazide (which occasionally can be isolated) with retention of configuration at the phosphorous atom. Next, the phosphazide goes through a four-membered transition state, which upon losing dinitrogen affords the iminophosphorane. A subtle point in the mechanism is the exact mode of attack of the phosphorous at N , since the PN N N backbone is not linear. Instead, the A_{NNN} angle is approximately 170 . There are two possible trajectories of the phosphorous atom to approach N : 1) from the same side of the R^1 substituent on N *trans attack*); and 2) from the opposite side of the R^1 substituent on N *cis attack*). Investigations within DFT showed that the reaction prefers a *cis* TS due to the extra interaction between the P atom and N



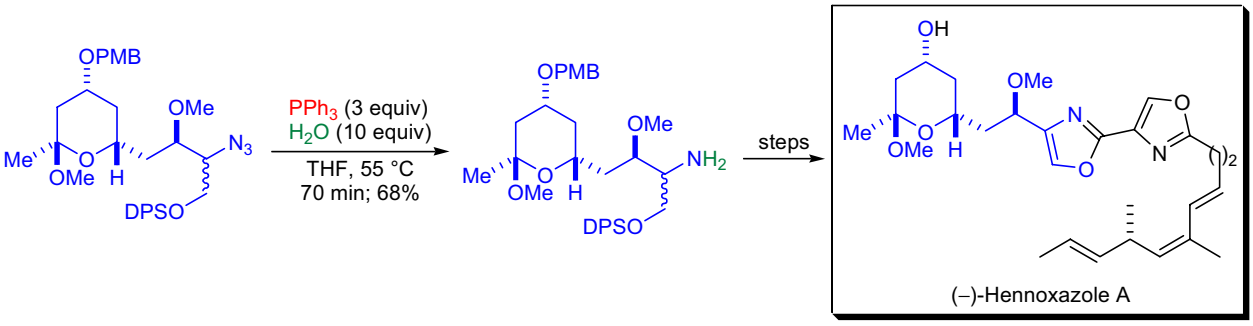
Possible modes of attack:



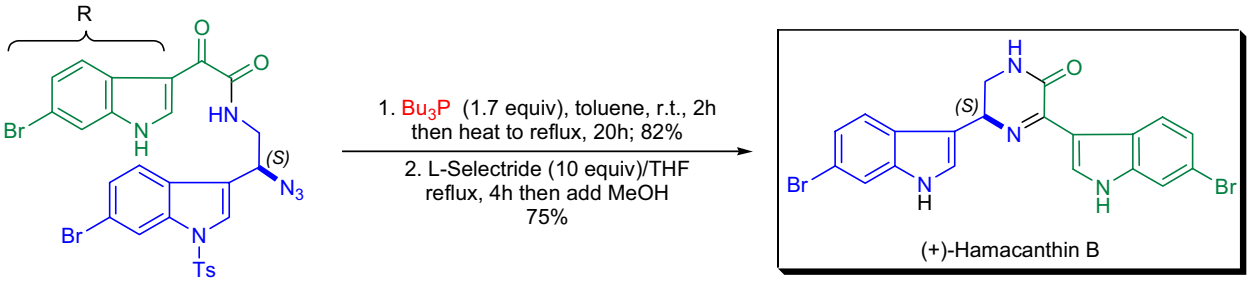
STAUDINGER REACTION

Synthetic Applications:

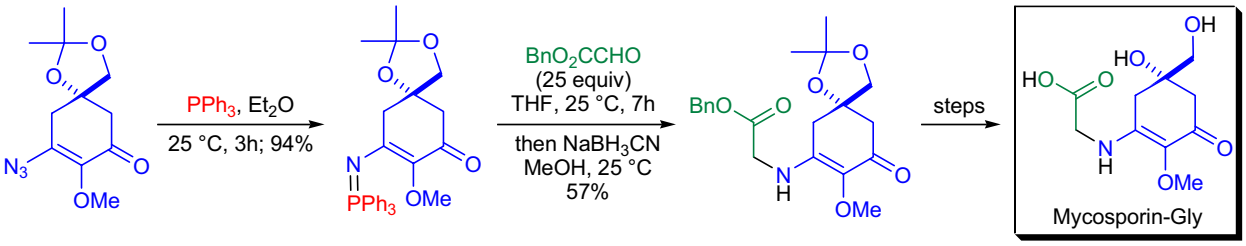
The total synthesis of the antiviral marine natural product (–)-hennoxazole A was accomplished by F. Yokokawa and co-workers.[43] The mild reduction of a secondary alkyl azide at C9 was carried out using triphenylphosphine in a THF/water mixture at slightly elevated temperature. The corresponding primary amine was obtained in good yield and was subsequently acylated and converted to one of the oxazole rings of the natural product.



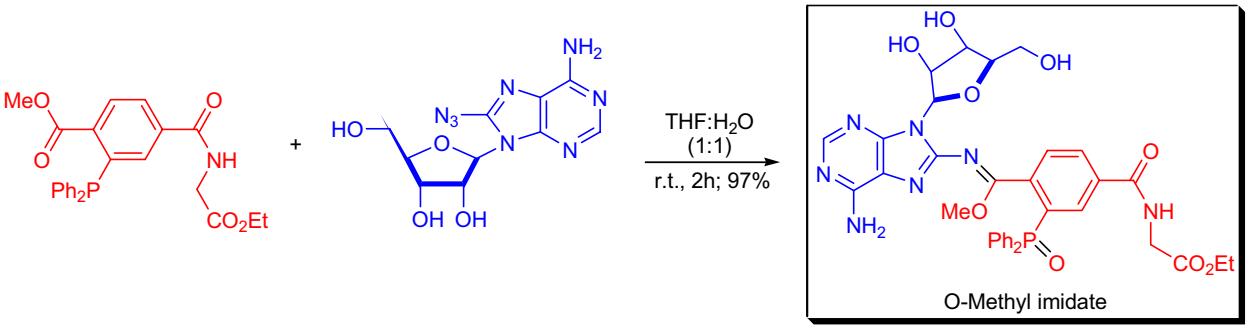
The marine indole alkaloid (+)-hamacanthin B was prepared by B. Jiang et al. using a tandem *Staudinger reaction/intramolecular aza-Wittig reaction* to convert a secondary azide to the corresponding iminophosphorane, which upon prolonged heating cyclized to the central pyrazinone ring.[44] The reduction of the azide was conducted with a slight excess of tributylphosphine in anhydrous toluene at room temperature while the *aza-Wittig cyclization* required the reflux temperature.



The absolute configuration of the structurally unique fungal metabolite mycosporins was determined in the laboratory of J.D. White by means of enantioselective total synthesis.[45] In the endgame of the synthetic effort, the *Staudinger reaction* was used to elaborate the side chain. The cyclic vinyl azide was first converted to a stable vinyl iminophosphorane, which was subsequently reacted with benzyl glyoxylate to afford the corresponding Schiff base. Reduction of the imine was achieved with sodium cyanoborohydride.



The research team of S.R. Rajski demonstrated that *o*-carboalkoxy triarylphosphines react with aryl azides to afford *Staudinger ligation* products bearing O-alkyl imidate linkages.[27] In comparison, the reaction of alkyl azides with o-carbalkoxy triarylphosphines usually gives rise to amide linkages. The importance of this technique lies in its ability to couple abiotic reagents under biocompatible conditions.



STEPHEN ALDEHYDE SYNTHESIS (STEPHEN REDUCTION)

(References are on page 685)

Importance:

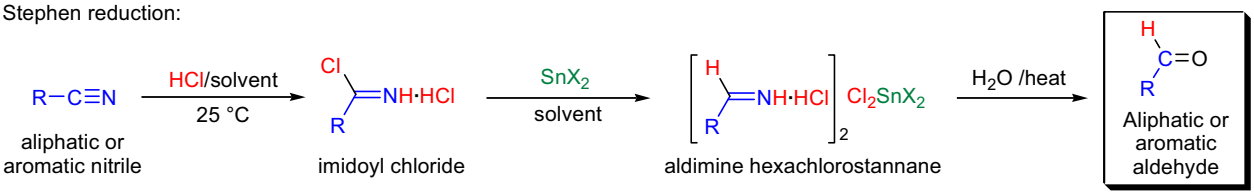
[*Seminal Publications*[1]; *Reviews*[2-7]; *Modifications & Improvements*[8,9]; *Theoretical Studies*[10]]

In 1925, H. Stephen reported that when aromatic or aliphatic nitriles were added to a solution of stannous chloride ($SnCl_2$) in diethyl ether saturated with anhydrous hydrogen chloride gas, imine hydrochlorides were obtained that readily underwent hydrolysis in warm water to give the corresponding aldehydes in good yield.[1] The preparation of aldehydes by the reduction of nitriles with the combination of stannous halide/HCl in an organic solvent is known as the *Stephen aldehyde synthesis* or *Stephen reduction*. The general features of this transformation are:[4] 1) the original procedure has been modified: first the nitrile is dissolved in an inert solvent and the resulting solution is saturated with anhydrous HCl gas at 0 °C, then a solution of SnX_2/HCl in the same solvent is added; 2) if the substrate is insoluble in a given solvent, the use of a mixture of inert solvents is recommended; 3) most common solvents for the transformation are diethyl ether, dioxane, ethyl acetate, and chloroform; 4) the reduction products are aldimine hexachlorostannanes which usually precipitate from the reaction mixture as crystalline complexes and are readily hydrolyzed to the corresponding aldehydes with warm water; 5) the best substrates are aromatic nitriles that give moderate to good yields of the aldehyde; 6) aliphatic nitriles tend to give lower yields primarily due to the formation of *N,N'*-alkyliden*bis*acylamides, which are trimeric side products; 7) the yield drops sharply for aliphatic nitriles having more than six carbon atoms; 8) seldom does the *Stephen reduction* stop at the aldimine stage, but the reduction proceeds all the way to form the primary amine product; 9) yields are also strongly influenced by steric factors, so *ortho*-substituted aromatic nitriles rarely give high yield of the corresponding aldehyde; 10) the functional group tolerance is low, which renders this method only useful for robust substrates that do not have acid sensitive functional groups; and 11) if a large excess of the stannous halide is used, aromatic nitro groups also undergo reduction to yield the corresponding aromatic amines. Alternatively, nitriles can be reduced to the corresponding aldehydes by the following methods:[11-18] 1) catalytic hydrogenation with Raney nickel/H_2 in the presence of one equivalent of an acid (e.g., H_2SO_4, HCO_2H); and 2) use of metal hydride reagents (e.g., DIBAL-H, $LiAlH(OR)_3$, etc.).

Stephen (1925):



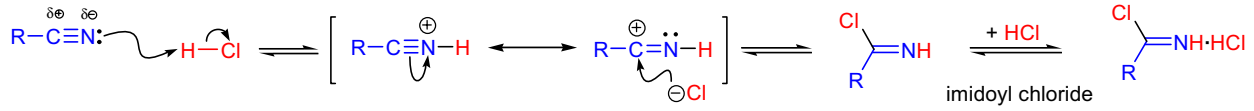
Stephen reduction:



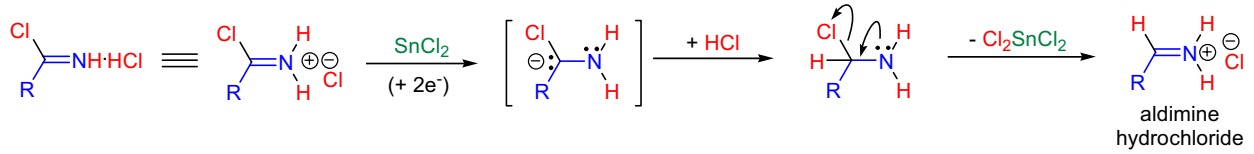
R = 1°, 2° or 3° alkyl, aryl, heteroaryl; solvent: Et_2O, dioxane, $CHCl_3$, EtOAc; X = Cl, Br

Mechanism:[4,7]

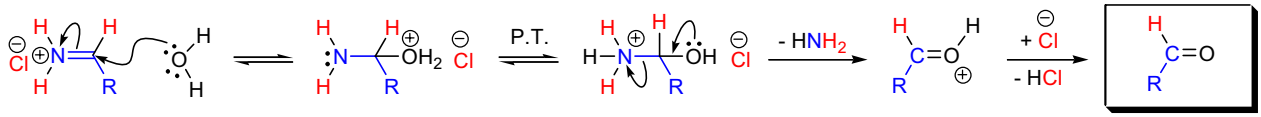
Formation of the imidoyl chloride intermediate:



Reduction of the imidoyl chloride to the aldimine:



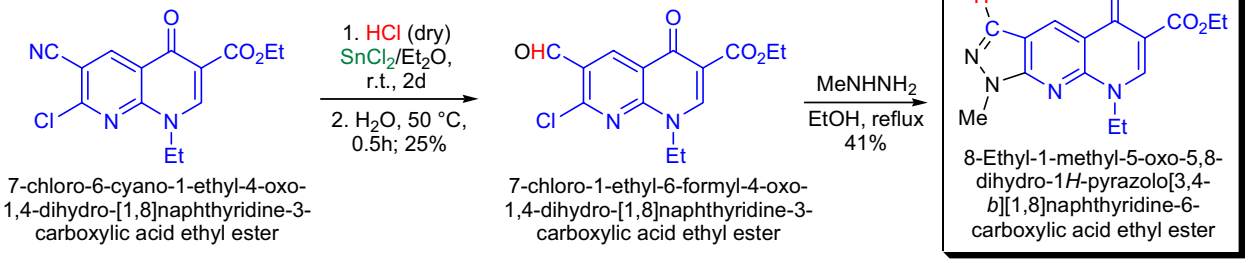
Hydrolysis of the aldimine to the corresponding aldehyde with water:



STEPHEN ALDEHYDE SYNTHESIS (STEPHEN REDUCTION)

Synthetic Applications:

In the laboratory of N. Suzuki, the synthesis of several heterocyclic condensed 1,8-naphthyridine derivatives with potential antimicrobial activity was executed.[19] The preparation of pyrazolo[3,4-*b*][1,8]naphthyridines required 7-chloro-6-formyl-3-ethyl ester as the precursor that was obtained by the *Stephen reduction* of the corresponding aromatic nitrile. The solution of the aromatic nitrile in chloroform was added to the solution of $SnCl_2$/dry HCl gas in ether. After two days of stirring, the aldimine hexachlorostannane product was treated with warm water to obtain the desired aromatic aldehyde in modest yield. Heating of the aldehyde with methyl hydrazine afforded the pyrazole derivative.

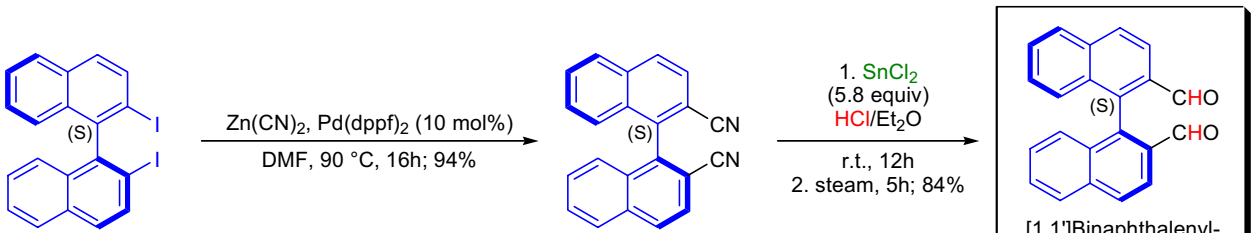


7-chloro-6-cyano-1-ethyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester

7-chloro-1-ethyl-6-formyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester

8-Ethyl-1-methyl-5-oxo-5,8-dihydro-1*H*-pyrazolo[3,4-*b*][1,8]naphthyridine-6-carboxylic acid ethyl ester

The stereoselective cyanation of [1,1']-binaphthalenyl-2,2'-diiodide was developed by M. Putala and co-workers using zinc cyanide and catalytic amounts of $Pd(dppf)_2$.[20] The resulting dinitrile was converted to the corresponding [1,1']-binaphthalenyl-2,2'-dicarbaldehyde in high yield using the *Stephen reduction*.

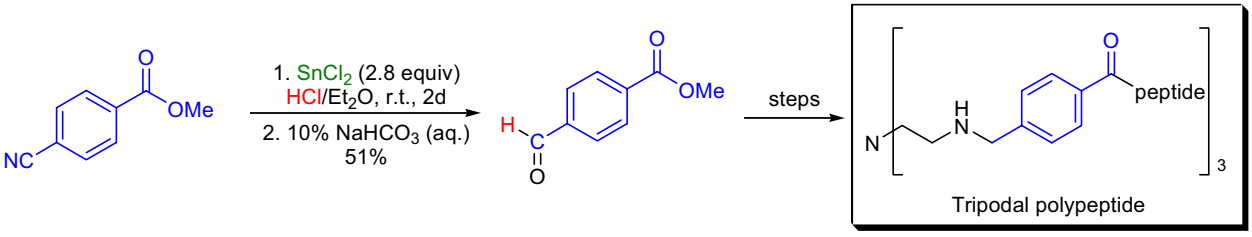


>96% *ee*

92% *ee*

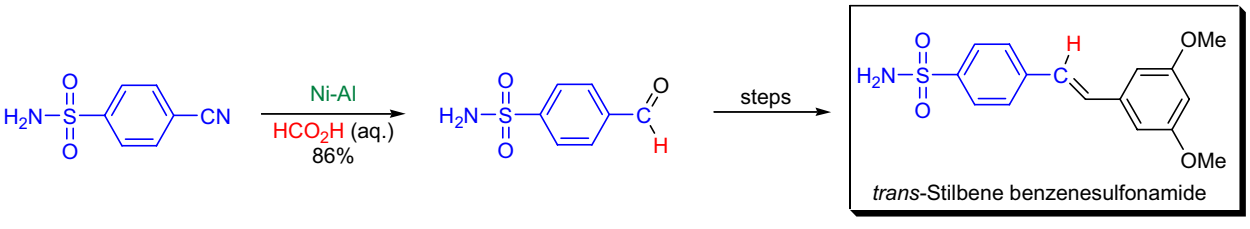
[1,1']Binaphthalenyl-2,2'-dicarbaldehyde

Research by P. Scrimin and U. Tonellato et al. showed that $Zn^{(II)}$ was an allosteric regulator of liposomal membrane permeability induced by synthetic template-assembled tripodal polypeptides.[21] Several copies of peptide sequences from the peptaibol family were connected to *tris*(2-aminoethyl)amine (TREN), which is a tripodal metal ion ligand. The resulting tripodal polypeptides were capable of modifying the permeability of liposomal membranes, and their activity was tunable upon metal ion coordination of the TREN subunit. The synthesis of the TREN-based template began with the *Stephen reduction* of 4-cyanomethylbenzoate followed by the reductive amination of the resulting aldehyde with TREN.



Tripodal polypeptide

L.-M. Yang and co-workers designed and synthesized a new series of *trans*-stilbene benzenesulfonamide derivatives as potential antitumor agents.[22] A common precursor diethylphosphonate was prepared from commercially available sulfanilamide in six steps. The aromatic nitrile-to-aldehyde reduction was affected by the *modified Stephen reduction* using Raney nickel alloy in aqueous formic acid. The corresponding aldehyde was obtained in high yield.



trans-Stilbene benzenesulfonamide

STETTER REACTION

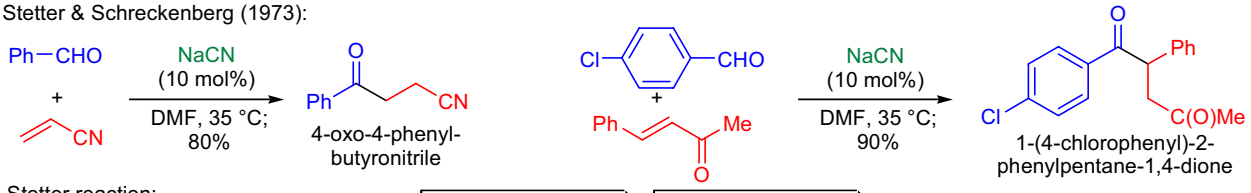
(References are on page 685)

Importance:

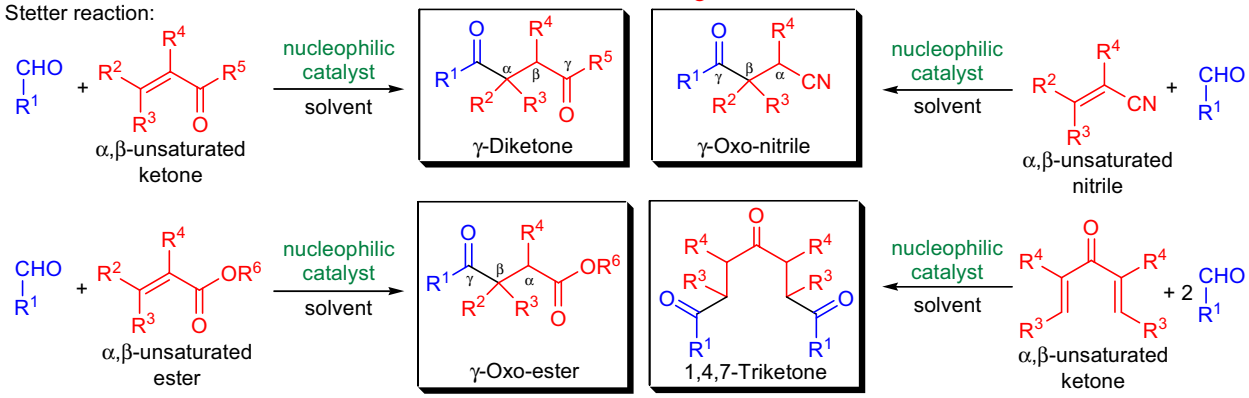
[*Seminal Publications*[1]; *Reviews*[2-9]; *Modifications & Improvements*[10-24]]

In 1973, H. Stetter and M. Schreckenberg found that in the presence of catalytic amounts of sodium cyanide, aromatic aldehydes such as benzaldehyde and *p*-chlorobenzaldehyde added smoothly to α,β-unsaturated nitriles and ketones to afford the corresponding γ-oxo nitriles and and γ-diketones, respectively.[1] The method was later expanded to aliphatic aldehydes by the use of catalytic amounts of thiazolium salts in the presence of bases. The addition of aliphatic and aromatic aldehydes across activated double bonds in the presence of a nucleophilic catalyst is known as the *Stetter reaction*. The general features of this transformation are:[2,5] 1) when the reaction is catalyzed by cyanide ions, dipolar aprotic solvents (e.g., DMF, DMSO) should be used, but with thiazolium salts protic solvents (e.g. EtOH) may also be used; 2) the reaction temperature is usually above 30 °C and the reaction time is a few hours (~1-4h); 3) the cyanide catalyzed reaction is restricted to aromatic aldehydes, since aliphatic aldehydes undergo an undesired *aldol condensation*; 4) the thiazolium salts are actually precatalysts since the added base (e.g., Et_3N, NaOAc) deprotonates the highly acidic C-H bond between the nitrogen and sulfur atoms to generate an ylide structure *in situ* (this ylide behaves the same way as cyanide ions do); 5) since the mechanism involves the rapid, reversible formation of benzoins from aromatic aldehyde substrates, benzoins can be used instead of the aldehydes (aliphatic aldehydes cannot be replaced with acyloins); 6) a wide variety of activated alkene substrates can be used, and the yields are especially high with α,β-unsaturated ketones; 7) straight chain aldehydes tend to give higher yields than α-branched aldehydes; 8) the aldehyde substrates may also be α,β-unsaturated and may have isolated double or triple bonds; and 9) the reaction fails with aromatic aldehydes that have nitro substituents as well as with 2,6-disubstituted aromatic aldehydes (due to steric hindrance).

Stetter & Schreckenberg (1973):



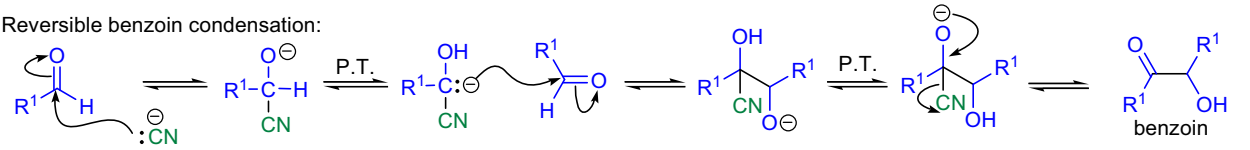
Stetter reaction:



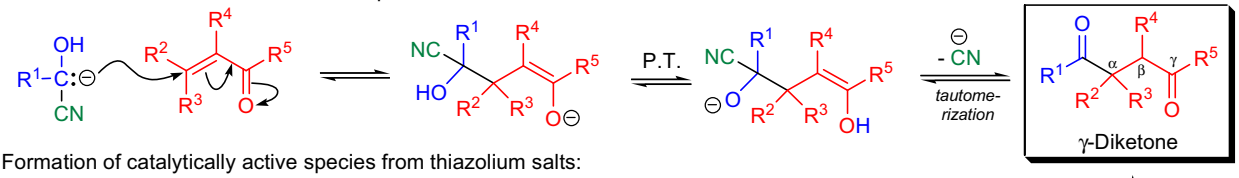
R^1 = alkyl, aryl, heteroaryl, alkenyl; R^{2-5} = H, alkyl, aryl, heteroaryl; R^6 = alkyl, aryl; nucleophilic catalyst: NaCN, KCN, thiazolium salts/base; solvent: DMF, DMSO

Mechanism:[2,5]

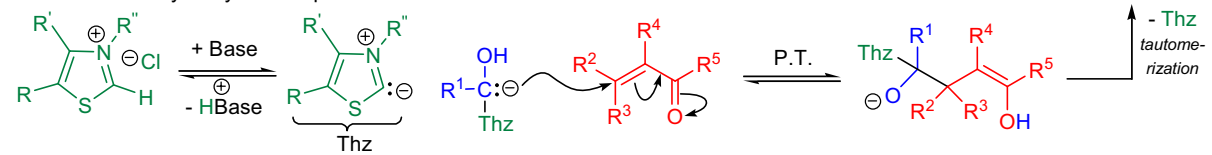
Reversible benzoin condensation:



Irreversible addition to the Michael acceptor:



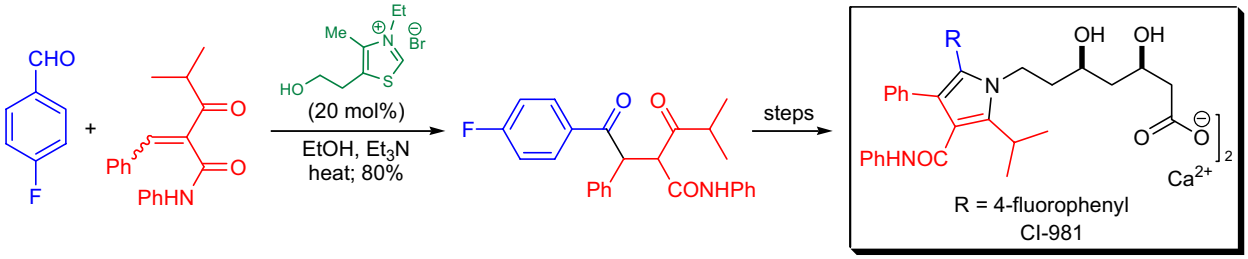
Formation of catalytically active species from thiazolium salts:



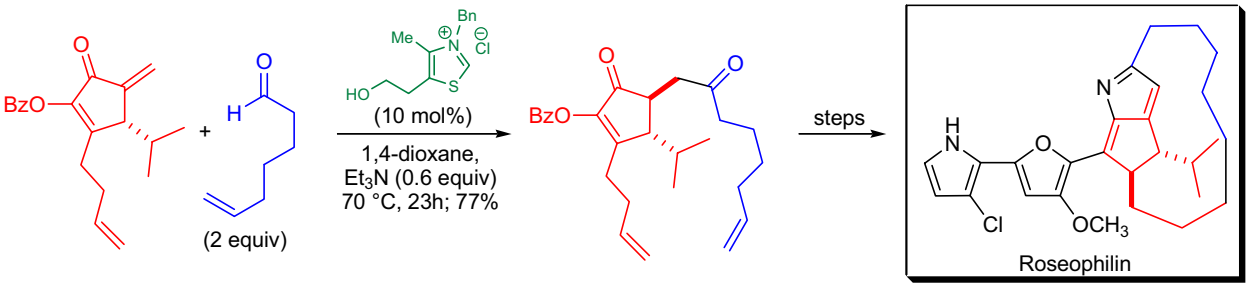
STETTER REACTION

Synthetic Applications:

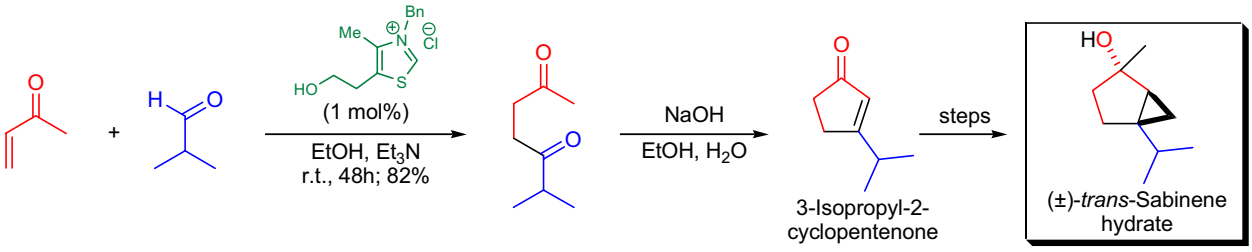
In the laboratory of A. Millar, the convergent enantioselective synthesis of CI-981, a potent and tissue-selective inhibitor of HMG-CoA reductase was achieved.[25] The central tetrasubstituted pyrrole ring was prepared *via* the *Paal-Knorr pyrrole synthesis*. The required 1,4-diketone precursor was efficiently prepared by the *Stetter reaction* between *p*-fluorobenzaldehyde and an unsaturated amide. Interestingly, the *N*-benzyl thiazolium chloride catalyst afforded only the *benzoin condensation* product and none of the desired diketone. However, when the *N*-ethyl thiazolium bromide catalyst was employed, under anhydrous and concentrated reaction conditions, the 1,4-diketone was formed in good yield. The authors also noted that the simple dilution of the reaction mixture resulted in a dramatic increase in the formation of the undesired benzoin condensation product.



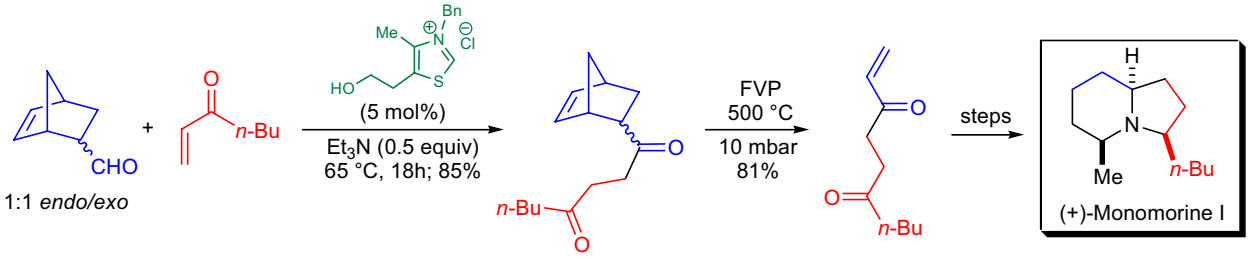
The absolute stereochemistry of natural roseophilin was determined by means of asymmetric total synthesis by M.A. Tius and co-workers.[26] The trisubstituted pyrrole moiety of the natural product was installed using the *Paal-Knorr pyrrole synthesis* starting from a macrocyclic 1,4-diketone. This diketone was prepared by reacting an exocyclic α,β-unsaturated ketone with excess 6-heptenal in the presence of 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride as the catalyst. The major product was the *trans* diastereomer and the macrocyclization was achieved *via alkene metathesis*. It is worth noting that when the aldehyde was tethered to the cyclopentenone, all attempts to close the macrocycle in an *intramolecular Stetter reaction* failed.



The short synthesis of (±)-*trans*-sabinene hydrate, an important flavor chemical found in a variety of essential oils from mint and herbs, was developed by C.C. Galopin.[27] The key intermediate of the synthetic sequence was 3-isopropyl-2-cyclopentenone. Initially a *Nazarov cyclization* of a dienone substrate was attempted for the synthesis of this compound, but the cyclization did not take place under a variety of conditions. For this reason, a sequential *Stetter reaction*/*intramolecular aldol condensation* approach was successfully implemented.



The concise enantioselective total synthesis of (+)-monomorine I, a 3,5-dialkyl-substituted indolizidine alkaloid, was completed by S. Blechert et al. using a sequential *cross-metathesis*/*double reductive cyclization* strategy.[28] The enedione substrate was prepared in two steps. The *Stetter reaction* between the masked equivalent of acrolein and butyl vinyl ketone was followed by a *retro Diels-Alder reaction* under flash vacuum pyrolysis (FVP) conditions.



STEVENS REARRANGEMENT

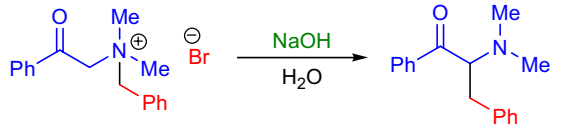
(References are on page 686)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-14]; *Modifications & Improvements*[15-25]; *Theoretical Studies*[26-34]]

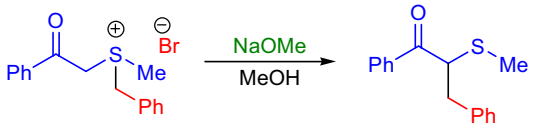
In 1928, T.S. Stevens reported that phenacylbenzyldimethylammonium bromide could be converted to 1-benzoyl-2-benzyldimethylamine upon treatment with aqueous sodium hydroxide.[1] A few years later he observed an analogous transformation by exposing a sulfonium salt to sodium methoxide that rearranged to the corresponding sulfide.[4] The base-promoted transformation of sulfonium or quaternary ammonium salts to the corresponding sulfides or tertiary amines involving the [*1,2*]-*migration* of one of the groups on the nitrogen or sulfur atom is known as the *Stevens rearrangement*. The general features of this reaction are: 1) the quaternary ammonium salts are readily available by the alkylation of the corresponding tertiary amines; 2) the sulfonium salts are usually prepared by the direct alkylation of the corresponding sulfides; 3) the key intermediate of the rearrangement is the nitrogen- or sulfur ylide; 3) the R^1 group has to be able to stabilize carbanions, so it is often an electron-withdrawing group; 4) depending on the nature of R^1, the acidity of the adjacent C-H bond varies so the type of base used for the deprotonation must be chosen accordingly; 5) when R^1=aryl or heteroaryl, the *Sommelet-Hauser rearrangement* becomes competitive; 6) R^2 and R^3 groups of ammonium salts cannot contain a hydrogen at their β-position, since the *Hofmann elimination* may compete; 7) the migrating group (R^4) is usually capable of stabilizing a carbon-centered radical; 8) the migratory aptitude of benzyl groups depends on the substituents on the phenyl ring and decrease in the following order: *p*-NO_2>*p*-halogen>*p*-Me>*p*-OMe; 9) when the migrating group has a stereocenter, it is transferred with retention of configuration at the migrating terminus; 10) the degree of the retention of configuration is influenced by the nature of substituents present on the migrating group; 11) in the case of sulfonium salts, the retention of configuration at the migrating terminus occurs to a lesser extent than in the case of quaternary ammonium salts; and 12) in addition to nitrogen to carbon migrations, there are nitrogen to heteroatom migrations as well (when Y=NH).[16,35] When the regioselective deprotonation of the ammonium and sulfonium salts is problematic, the use of fluoride ion catalyzed desilylation of (trimethylsilyl)methyl ammonium- and sulfonium salts under nonbasic conditions gives the required ylides directly and with complete regioselectivity.[17,18]

Stevens (1928):



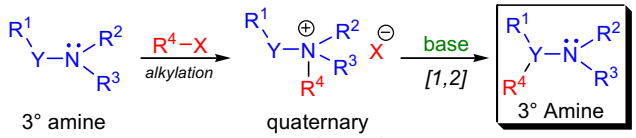
phenacylbenzyldimethyl ammonium bromide — 1-benzoyl-2-benzyl dimethylamine

Stevens (1932):



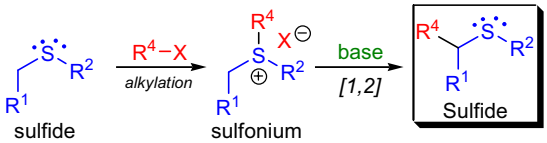
phenacylbenzylmethyl sulfonium bromide — 2-methylsulfanyl-1,3-diphenyl-propan-1-one

Stevens rearrangement of quaternary ammonium salts:



3° amine — quaternary ammonium salt

Stevens rearrangement of sulfonium salts:

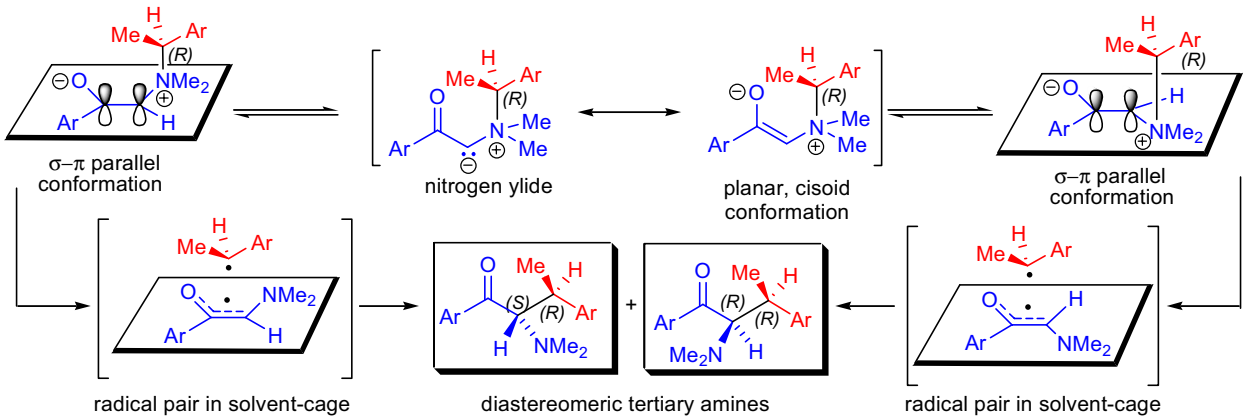


sulfide — sulfonium salt

R^1 = EWG = Ar, heteroaryl, COR, COOR, CN; Y= CH_2, CHR, NH; R^{2-3} = alkyl with no β-hydrogen, aryl; R^4 = CH_3, alkyl, allyl, benzyl, CH_2COAr; X = Cl, Br, I, OTs, OMs; base: NaH, KH, RLi, ArLi, RONa, ROK

Mechanism: [36,37,26,38-41,11,42]

If the *Stevens rearrangement* is a concerted reaction, it is a symmetry-forbidden process based on the *Woodward-Hoffmann rules*. Indeed, it was shown to occur *via* an intramolecular *homolytic cleavage-radical pair recombination* process, which explains the lack of crossover products and the observed retention of configuration at the migrating terminus.[41] The radicals are held in a solvent-cage in which there is a lack of rotation, and they recombine quickly.



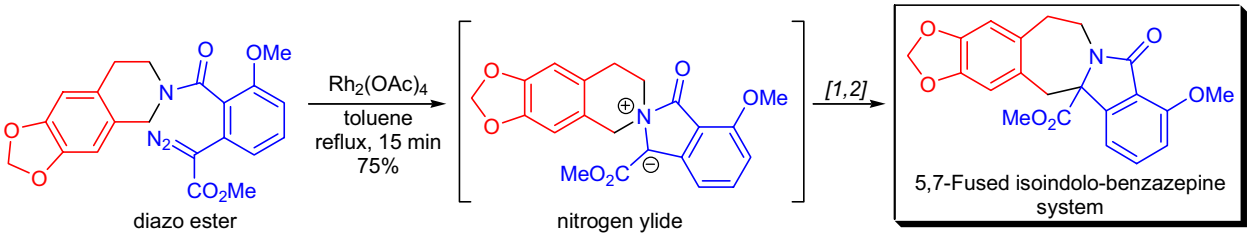
σ–π parallel conformation — nitrogen ylide — planar, cisoid conformation — σ–π parallel conformation

radical pair in solvent-cage — diastereomeric tertiary amines — radical pair in solvent-cage

STEVENS REARRANGEMENT

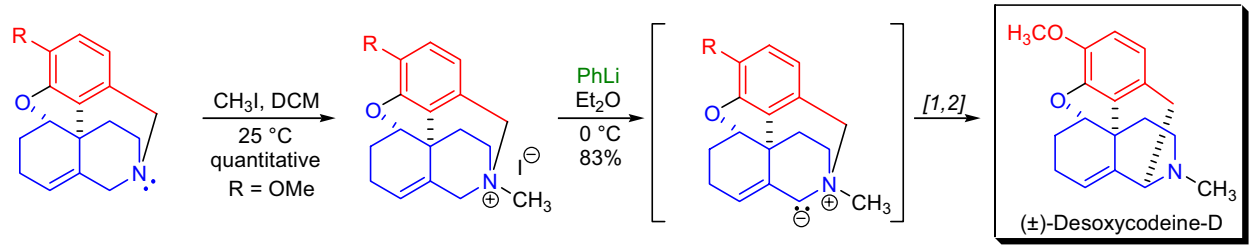
Synthetic Applications:

The nitrogen ylides required for the *Stevens rearrangement* can be accessed in a direct manner by using the transition metal catalyzed decomposition of an α-diazo carbonyl functionality tethered to tertiary amines. This tandem *ylide formation*/*Stevens rearrangement* strategy was used by A. Padwa et al. as a novel approach toward the preparation of isoindolo-benzazepines.[43] The diazo ester was added to a refluxing solution of rhodium(II) acetate in toluene, generating the nitrogen ylide *in situ*, which underwent a facile *[1,2]-benzyl shift* to afford the 5,7-fused heterocyclic ring system.

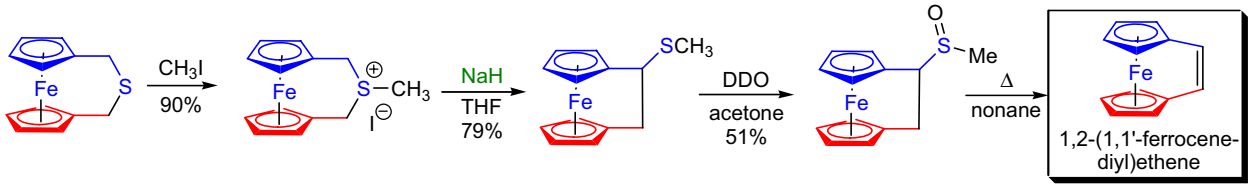


diazo ester — nitrogen ylide

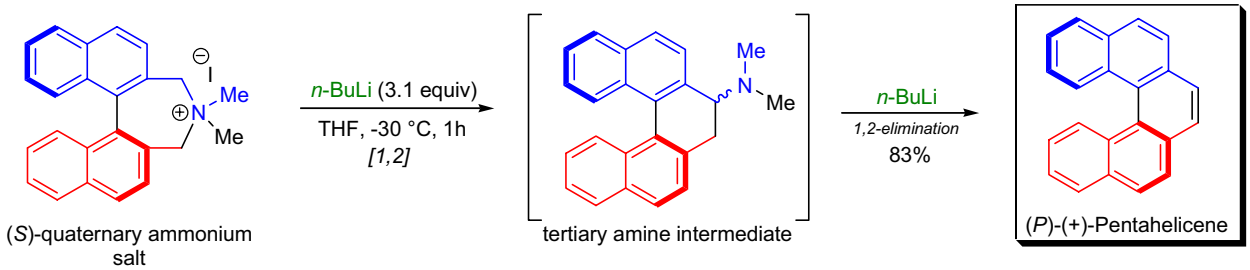
A new approach to the morphine skeleton was demonstrated by the total synthesis of (±)-desoxycodeine-D by C.-Y. Cheng and co-workers.[44] The key step was the formation of the B ring by the *Stevens rearrangement* of a tetrahydroisoquinoline-derived quaternary ammonium salt upon treatment with phenyllithium.



The first synthesis of 1,2-(1,1'-ferrocenediyl)ethene was accomplished in the laboratory of V.K. Aggarwal in six steps from ferrocene.[45] In order to construct the strained two-carbon bridge, several methods were tested including the *McMurry coupling* and the *Ramberg-Bäcklund rearrangement*. Unfortunately, under the McMurry conditions only intermolecularly coupled products were obtained. The α-chlorination of the sulfide or sulfone failed, therefore the α-chloro sulfone precursor for the *Ramberg-Bäcklund rearrangement* could not be prepared. Alternatively, the *Stevens rearrangement* of a sulfonium salt was successful in providing the desired ring-contracted product.



The transfer of axial chirality to central chirality during the *Stevens rearrangement* of binaphthyl compounds was investigated by I.G. Stará et al.[42] They found that the stereochemical course of the *Stevens rearrangement* of axially chiral onium salts is significantly structure-dependent. Their findings were utilized in a novel enantioselective synthesis of pentahelicene. The treatment of the optically pure binaphtyl ammonium salt with an excess of butyllithium brought about the expected *[1,2]- benzyl shift*, and the tertiary amine intermediate underwent an *in situ* base-induced 1,2-elimination to afford the optically pure pentahelicene. Interestingly, the rearrangement of analogous sulfur ylides proceeded with considerably lower stereoselectivity.



(*S*)-quaternary ammonium salt — tertiary amine intermediate

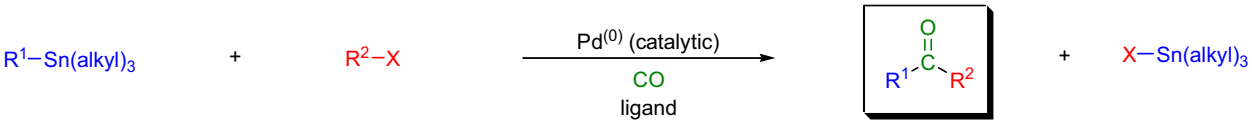
STILLE CARBONYLATIVE CROSS-COUPLING

(References are on page 687)

Importance:

[*Seminal Publications*[1-5]*; Reviews*[6,7]*; Modifications & Improvements*[8,9]]

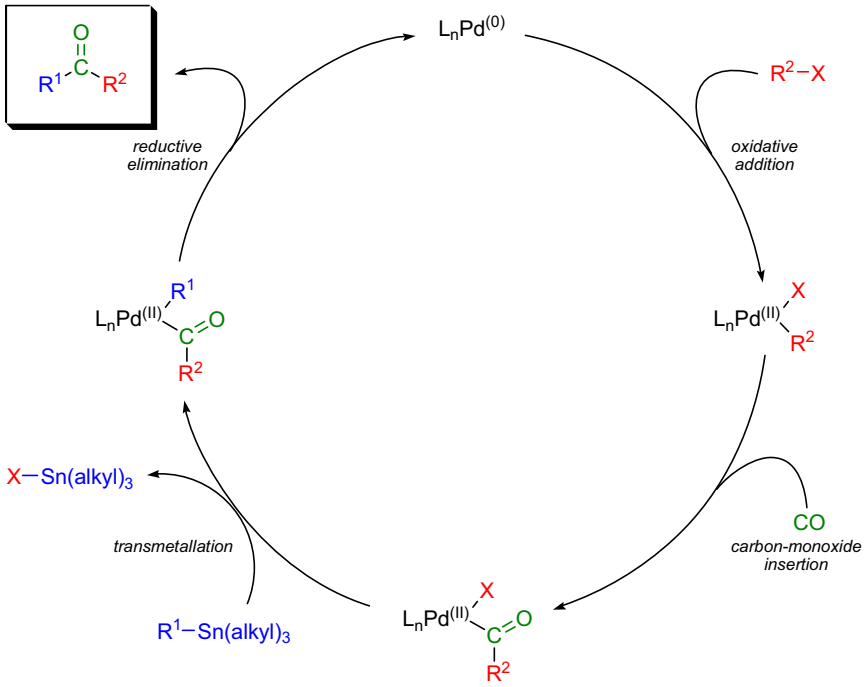
The synthesis of ketones using the *Stille cross-coupling* initially called for the use of acid chlorides as coupling partners. However, acid chlorides are not always readily available, and their preparation is often not compatible with sensitive functional groups. To widen the scope of the synthesis of ketones, the transition metal catalyzed carbonylative cross-coupling of organic halides and pseudohalides was extensively investigated in the 1980s. The $Pd^{(0)}$-catalyzed coupling between an organostannane, carbon monoxide, and an organic electrophile to form two new C-C sigma bonds is called the Stille carbonylative cross-coupling. Advantages of this method are: 1) many organic halides are commercially available or easily prepared and indefinitely stable; 2) the coupling occurs not only with *chemo- and regioselectivity*, but also with *stereoselectivity*, generally retaining the configuration at the substituted position of both the vinyl/aryl halide and the organostannane; 3) allyl and benzyl chlorides react, and they give the corresponding ketones with inversion of configuration;[2] 4) the reaction of alkenyl iodides and alkenyltins takes place under neutral and mild conditions; and 5) the use of heterostannanes (alkoxy, thioalkoxy, and aminostannanes) allows the preparation of the corresponding carboxylic acid derivatives.[8] Disadvantages are: 1) direct coupling without CO insertion and the need to use high pressures of CO to suppress this side reaction;[10] 2) the occasional *Z*/*E* isomerization of alkenyl groups from both reaction components, especially with (*Z*)-alkenyl derivatives;[3] and 3) aryl chlorides react only slowly compared to aryl bromides and iodides.



R^1 = alkyl, allyl, alkenyl, aryl; R^2 = alkenyl, aryl; X = Cl, Br, I, OTf, $OPO(OR)_2$

Mechanism: [11]

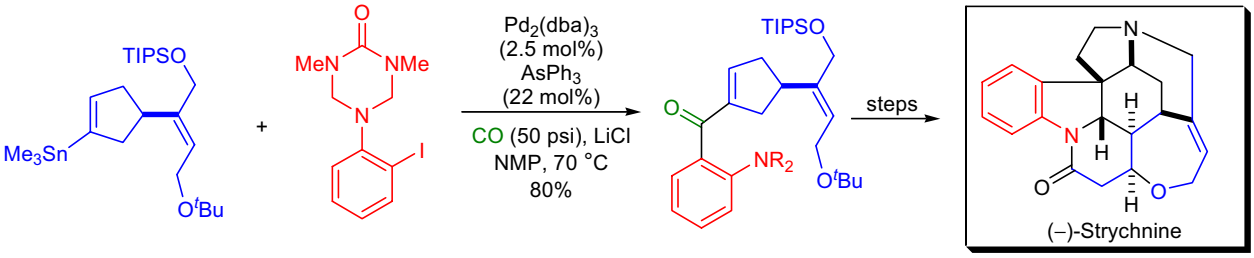
The mechanism of the *Stille carbonylative cross-coupling* is very similar to the regular *Stille cross-coupling*. The only difference between the two couplings is that a carbon-monoxide (CO) insertion takes place between the oxidative-addition step and the transmetallation step. The rate determining step is the transmetallation, so transferable groups attached to the tin atom may have -hydrogens attached to sp^3 carbons, because the steps following the transmetallation are very fast and no -hydride elimination is expected.



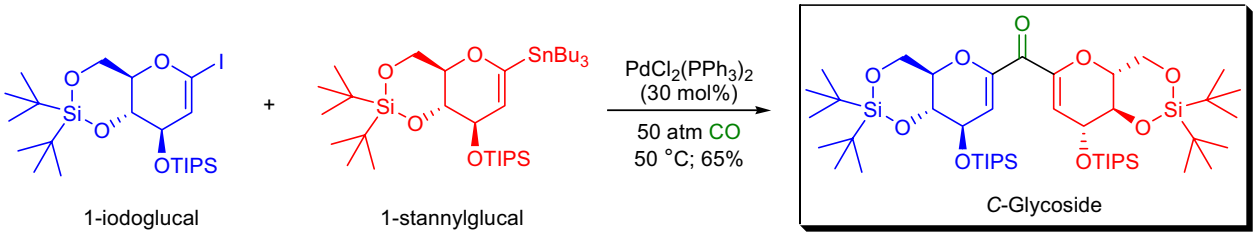
STILLE CARBONYLATIVE CROSS-COUPLING

Synthetic Examples:

The first enantioselective total synthesis of (–)-strychnine was achieved by L.E. Overman and co-workers.[12] The carbon skeleton of the main precursor for the key *aza-Cope rearrangement*/*Mannich cyclization* was assembled by applying a $Pd^{(0)}$-catalyzed *carbonylative Stille coupling reaction*. Thus, the cyclic vinylstannane was coupled with the triazinone-protected *ortho*-iodoaniline to afford 80% yield of the aromatic enone using $Pd_2(dba)_3$ as the catalyst in the presence of carbon monoxide.

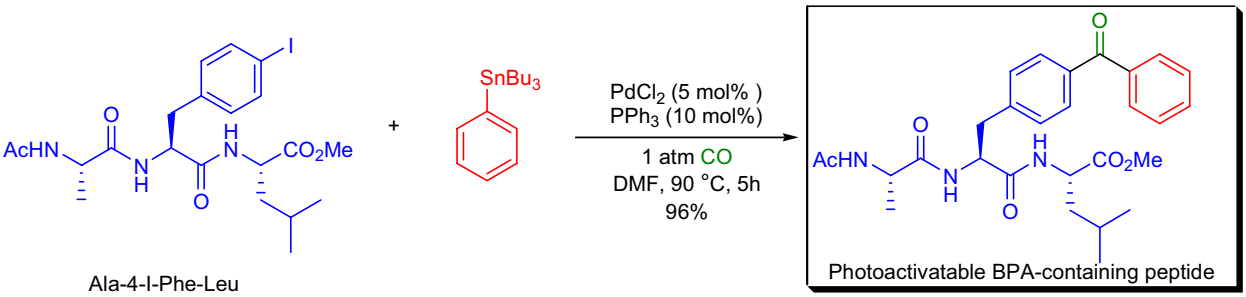


C-Disaccharides (*C*-glycosides) have an advantage over *O*-glycosides as they resist acidic and enzymatic hydrolysis. They can therefore serve as potential glycosidase inhibitors. In the laboratory of P. Vogel, a novel approach was developed for the synthesis of *C*-glycosides by a *Stille carbonylative coupling reaction* between 1-stannylglucals and 1-iodoglucals.[13]



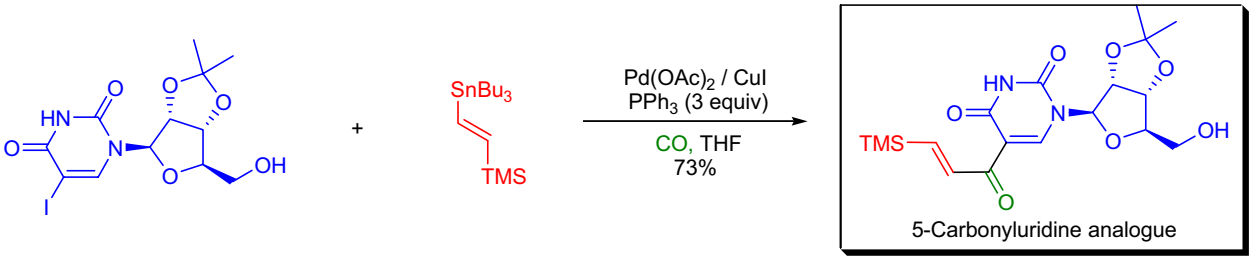
1-iodoglucal 1-stannylglucal

A concise synthesis of photoactivatable 4-benzoyl-L-phenylalanines and related peptides was described by G. Ortar et al. using a *carbonylative Stille cross-coupling* as the key step.[14] Surprisingly, when the coupling was attempted with tyrosine triflate derivatives, it proved to be unsuccessful. However, 4-iodo-phenylalanine derivatives reacted smoothly under standard conditions to give the corresponding 4-benzoyl derivatives.



Ala-4-I-Phe-Leu

Systematic evolution of ligands by exponential enrichment (SELEX) is a procedure that generates nucleic acid ligands capable of high-affinity binding to both protein and small molecule targets. In order to synthesize a wide range of these ligands, B.E. Eaton and co-workers used the *carbonylative Stille coupling* to obtain 5-carbonyluridine analogues.[15]



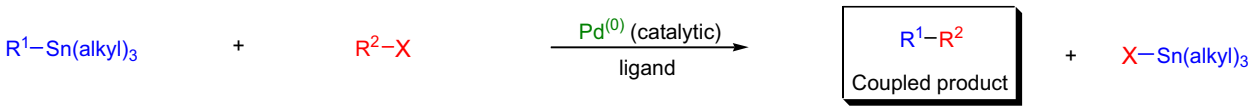
STILLE CROSS-COUPLING
(MIGITA-KOSUGI-STILLE COUPLING)

(References are on page 687)

Importance:

[*Seminal Publications*[1-8] *; Reviews*[9-27]*; Modifications*[28-40]]

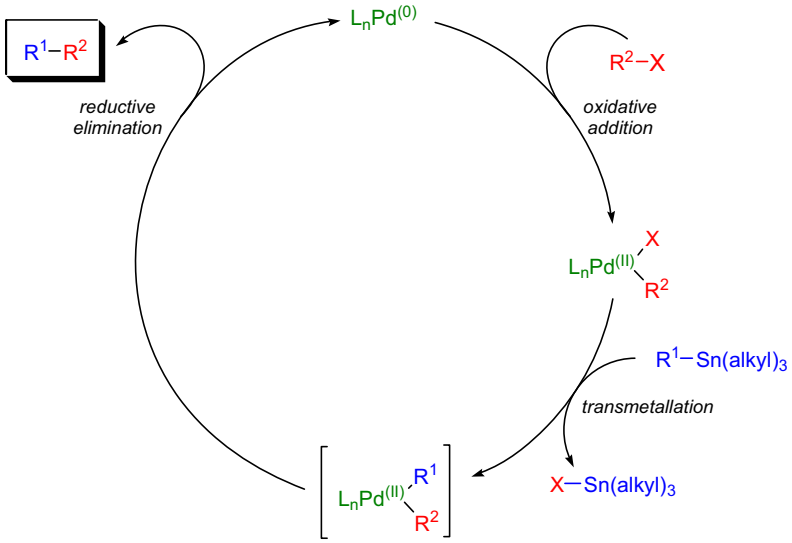
In 1976, the first palladium catalyzed reaction of organotin compounds (organostannanes) was published by C. Eaborn et al.[1] A year later in 1977, M. Kosugi and T. Migita reported transition-metal-catalyzed C-C-bond forming reactions of organotins with aryl halides[2] and acid chlorides.[3,4] In 1978, J.K. Stille used organotin compounds for the synthesis of ketones under reaction conditions much milder than Kosugi's and with significantly improved yields.[5] In the early 1980s, Stille pioneered the use of this method.[10] The $Pd^{(0)}$-catalyzed coupling reaction between an organostannane and an organic electrophile to form a new C-C sigma bond is known as the Stille cross coupling. The precursor organotin compounds have many advantages because they: 1) tolerate a wide variety of functional groups; 2) are not sensitive to moisture or oxygen unlike other reactive organometallic compounds; and 3) are easily prepared, isolated, and stored. The main disadvantages are their toxicity and the difficulty to remove the traces of tin by-products from the reaction mixture. In the past two decades, the *Stille reaction* has become one of the most powerful synthetic tools in organic chemistry, and it finds many uses in preparative chemistry. The success of the *Stille coupling* is largely attributed to the mild conditions of the method. The reaction conditions are compatible with many types of functional groups (carboxylic acid, amide, ester, nitro, ether, amine, hydroxyl, ketone, and formyl groups) and high levels of stereochemical complexity can be tolerated by both coupling partners. The only major side reaction associated with the *Stille coupling* is the oxidative homocoupling of the organostannane reagent and under harsh conditions allylic and (*Z*)-alkenyl components may undergo double bond migration and isomerization.[41,42] Metals other than palladium such as manganese,[33] nickel,[29,36] and copper[28,30-35,37] have also been found to catalyze the reaction and procedures, using only catalytic amounts of tin have been developed.[38-40]



R^1 = allyl, alkenyl, aryl; R^2 = alkenyl, aryl, acyl; X = Cl, Br, I, OTf, $OPO(OR)_2$

Mechanism: [6,7,41,43-46,12,47-53,27,54]

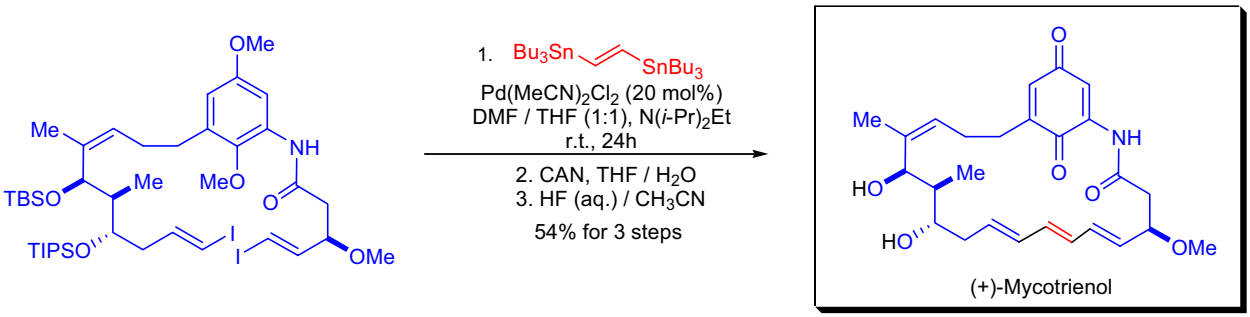
The catalytic cycle for the Stille coupling reaction was first proposed for the reaction with benzylic and aryl halides in 1979,[6,7] although the detailed mechanism is still a matter of some debate.[12,27] The catalytic cycle has three steps: 1) oxidative addition; 2) transmetallation; and 3) reductive elimination. The active catalyst is believed to be a 14-electron $Pd^{(0)}$-complex which can be generated *in situ*. Palladium(0)-catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$, with or without an added ligand, are often used. Alternatively, $Pd^{(II)}$-complexes such as $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $(PdCl_2(PPh_3)_2$, $BnPdCl(PPh_3)_2$, etc. are also used as precursors for the catalytically active $Pd^{(0)}$ species, as these compounds are reduced by the organostannane[48] or by an added phosphine ligand prior to the main catalytic process. The transmetallation step is the rate-determining step in the catalytic cycle.[46,47,49,50] Different groups on the tin coupling partner transmetallate to the $Pd^{(II)}$ intermediate at different rates and the order of migration is: alkynyl > vinyl > aryl > allyl ~ benzyl »» alkyl. The very slow migration rate of the alkyl substituents allows the transfer of aryl or vinyl groups when mixed organostannanes containing three methyl or butyl groups are used.



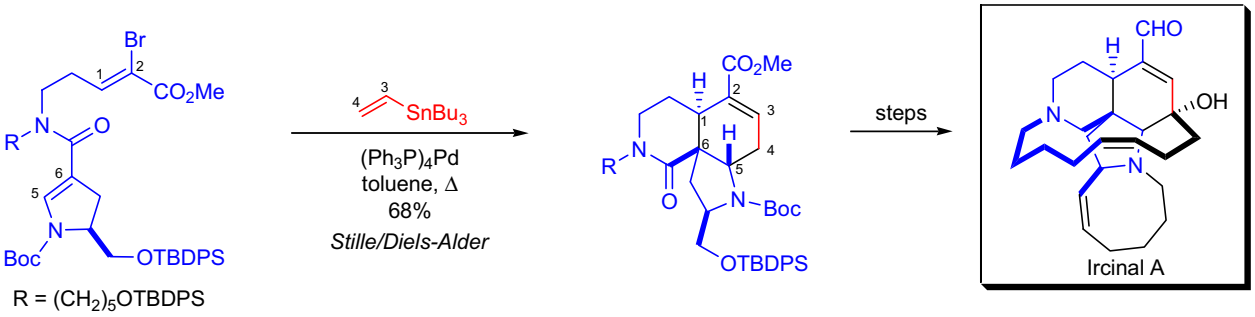
STILLE CROSS-COUPLING
(MIGITA-KOSUGI-STILLE COUPLING)

Synthetic Applications:

The total synthesis of (+)-mycotrienol was accomplished by J. Panek and co-workers using a $Pd^{(0)}$-catalyzed *Stille coupling reaction* to incorporate the (*E*,*E*,*E*)-triene unit with simultaneous macrocyclization.[55] After macrocyclization, the aromatic core was oxidized with CAN and the protecting groups were removed to provide the natural product.

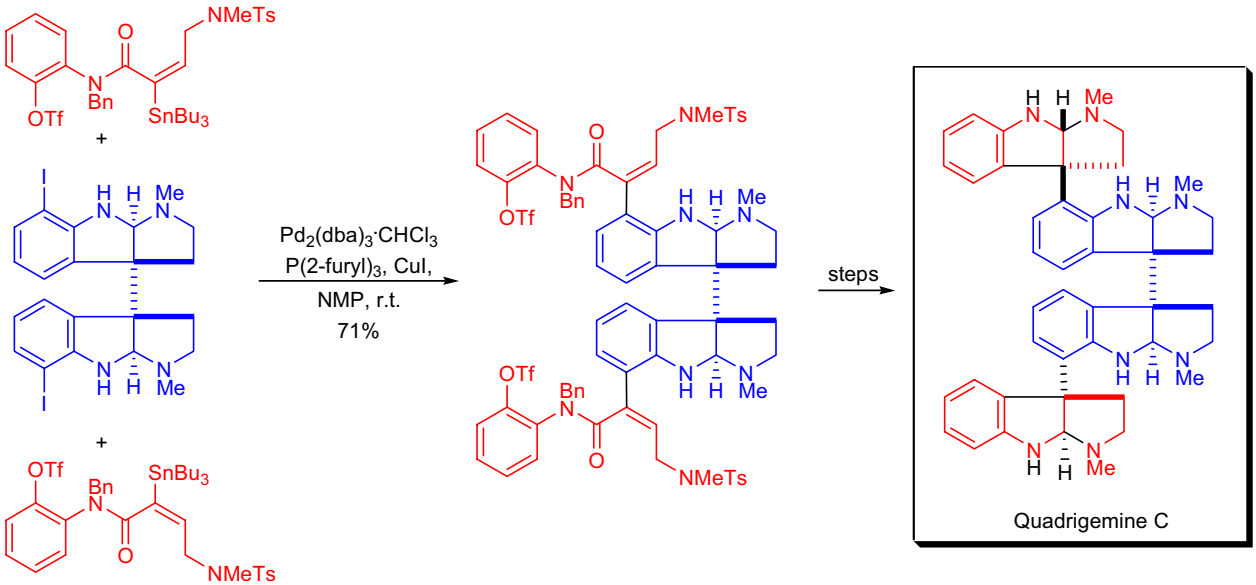


The enantioselective total synthesis of the manzamine alkaloid ircinal A was completed in the laboratory of S.F. Martin utilizing a novel strategy. A *domino Stille/Diels-Alder reaction* was used to assemble the ABC ring core of the natural product.[56] The vinyl bromide intermediate reacted with vinyl tributylstannane in the presence of $Pd^{(0)}$ to afford the 1,3-diene moiety, which cyclized *via* an *intramolecular Diels-Alder reaction* to give the ABC core.



R = $(CH_2)_5OTBDPS$

The first total synthesis of quadrigemine C, a higher-order member of the polypyrrolidinoindoline alkaloid family was published by L. Overman et al.[57] Key steps included a *double Stille cross coupling* and *catalyst-controlled double Heck cyclization*.



STILLE-KELLY COUPLING

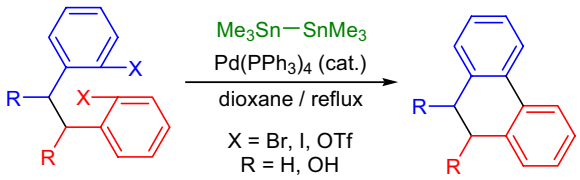
(References are on page 688)

Importance:

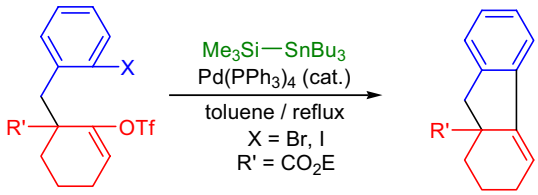
[*Seminal Publications*[1,2]; *Reviews*[3-6]; *Modifications & Improvements*[7,8]]

The Pd-catalyzed synthesis of arylstannes ($ArSnR_3$) from aryl halides with distannanes (R_3SnSnR_3) was discovered by C. Eaborn et al. in 1976. A decade later J.K. Stille reported that aryl triflates (ArOTf) also undergo a *Pd-catalyzed cross-coupling reaction* with distannanes to form the corresponding aryltrialkylstannanes.[1] These arylstannanes are important substrates for the *Stille-cross coupling* reaction with aryl halides for the preparation of biaryl compounds. The combination of the above mentioned protocols, the intramolecular Pd-catalyzed tandem *stannylation/aryl halide coupling*, was developed by T.R. Kelly and co-workers for the synthesis of dihydrophenanthrenes in the early 1990s.[2] The Pd-catalyzed intramolecular biaryl coupling of aryl halides or aryl triflates in the presence of distannanes is known as the *Stille-Kelly coupling*. The general features of the reaction are: 1) aryl iodides, bromides, and triflates work best, but there are no examples for this coupling with aryl chlorides; and 2) usually the newly formed ring is five- or six-membered, but there are cases when the formation of larger rings and even macrocycles is possible.[9] A useful extension of the *Stille-Kelly coupling* was reported by M. Shibasaki and M. Mori in which they accomplished the intramolecular *Pd-catalyzed tandem transmetallation-cyclization* of an aryl halide and a vinyl triflate using a trimethylsilyltributylstannane ($Bu_3Sn\text{-}SiMe_3$).[7]

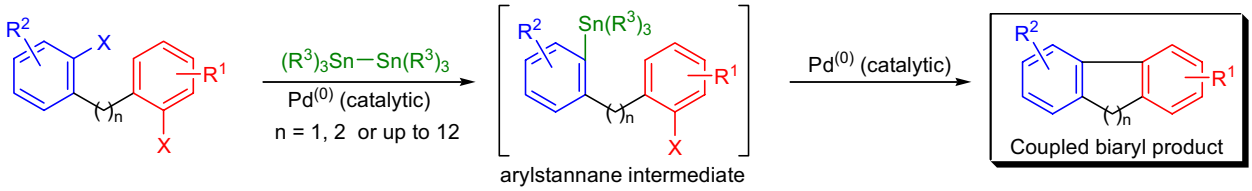
(Kelly, 1991)
Intramolecular coupling of aryl halides:



(Shibasaki & Mori, 1991)
Intramolecular coupling of aryl halides and vinyl triflates:



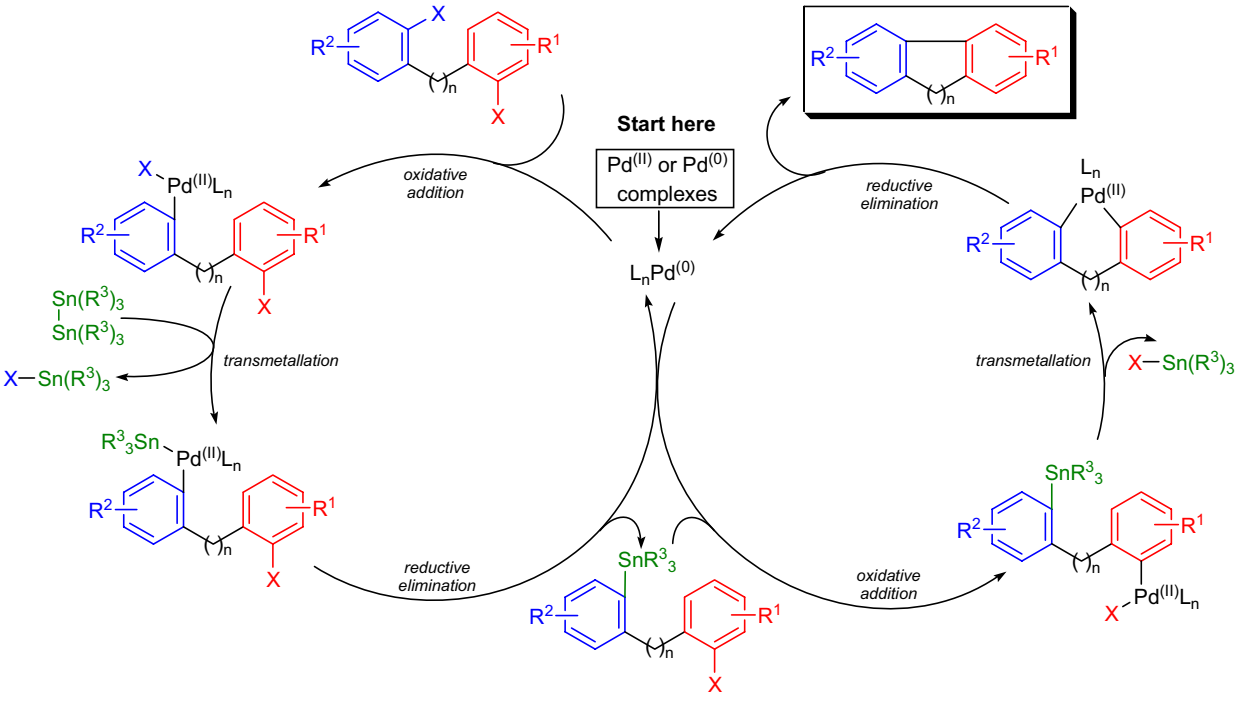
Stille-Kelly coupling:



R^1, R^2 = alkyl, aryl, electron-withdrawing or electron-donating; R^3 = Me, *n*-Bu; X = Br, I, OTf

Mechanism:[2,10]

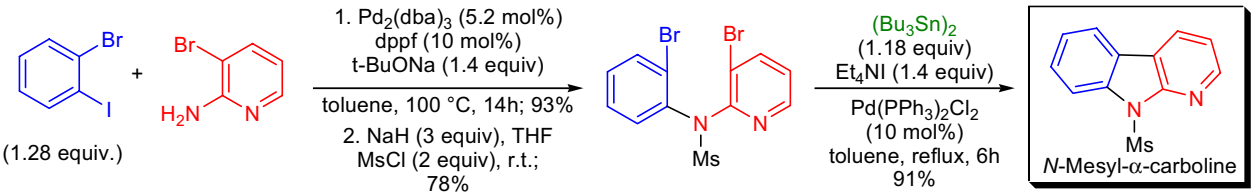
The *Stille-Kelly coupling* consists of two connected catalytic cycles and the following steps: 1) the *oxidative addition* of the $Pd^{(0)}$ complex into one of the C-X bond of the aryl halide; 2) *transmetallation* with the distannane followed by reductive elimination to afford the organostannane; 3) *oxidative addition* of the $Pd^{(0)}$ complex into the C-X bond of the organostannane; 4) *intramolecular transmetallation*; and 5) *reductive elimination* to give the coupled product.



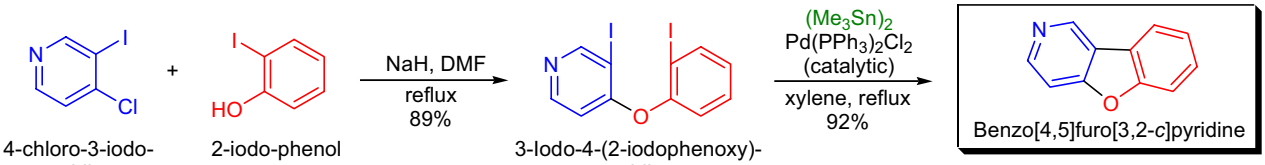
STILLE-KELLY COUPLING

Synthetic Applications:

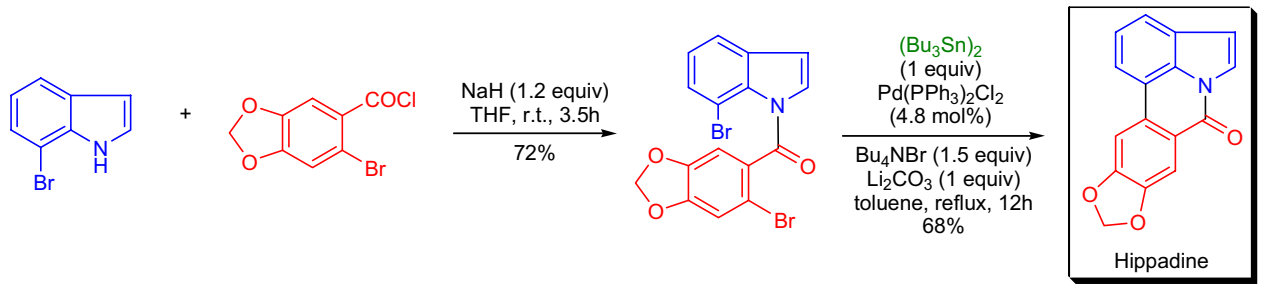
A novel strategy was developed by T. Sakamoto et al. for the synthesis of carbolines and carbazoles based on Pd-catalyzed amination (*Buchwald-Hartwig coupling*) and arylation (*Stille-Kelly coupling*) reactions.[11] The required *ortho*-bromo-substituted anilinopyridines were prepared by the *Buchwald-Hartwig coupling* of iodobenzenes with aminopyridines. The *Stille-Kelly coupling* was only possible when the secondary amine functionality was converted to the corresponding *N*-methanesulfonyl (mesyl) derivative prior to the cyclization.



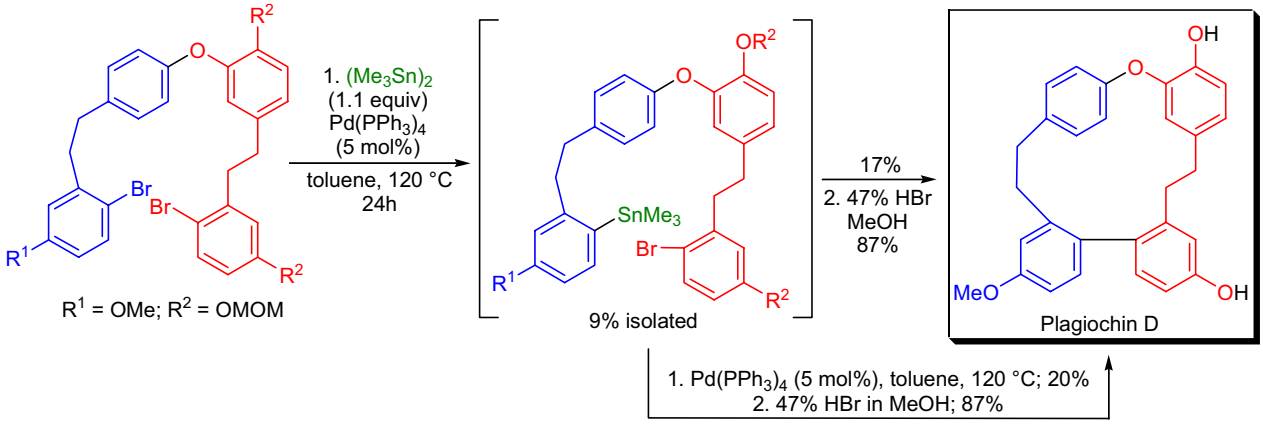
J.J. Li and co-workers synthesized all four possible benzo[4,5]furopyridines *via* two different Pd-catalyzed approaches.[12] In one of the routes the precursor biaryl compound was prepared by the S_NAr *reaction* of 3-iodo-4-chloropyridine with *ortho*-iodophenoxide. The resulting diiodo heterobiaryl ether was cyclized under *Stille-Kelly coupling* conditions in refluxing xylene.



The total synthesis of the pyrrolophenanthridine alkaloid, hippadine, was accomplished in the laboratory of T. Sakamoto.[13] The last and key step of the synthetic sequence was the *Stille-Kelly coupling* of the *N*-benzoylated indole precursor in 68% yield.



The cyclic *bis*(benzyl) macrocyclic natural product, plagiochin D, was prepared by Y. Fukuyama using the *Stille-Kelly coupling* as the key macrocyclization step.[9] The precursor dibromide was subjected to various cross-coupling conditions but only under the Stille-Kelly conditions was any coupling product obtained. The yield was low (17%) and 9% stannylated intermediate was isolated besides the condiderable amount of recovered starting material (45%). The stannylated intermediate could be exposed to $Pd^{(0)}$ catalyst to afford 20% of the desired cyclized product. Finally, removal of the MOM protecting groups was affected by concentrated HBr solution in methanol.



STOBBE CONDENSATION

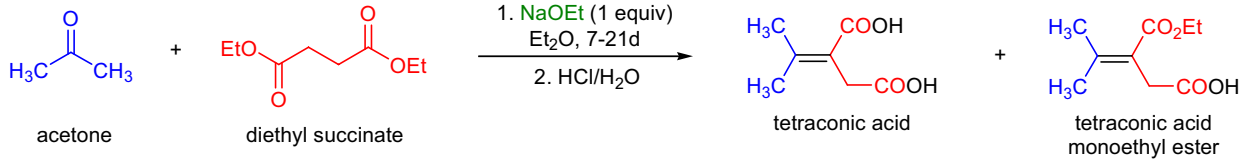
(References are on page 689)

Importance:

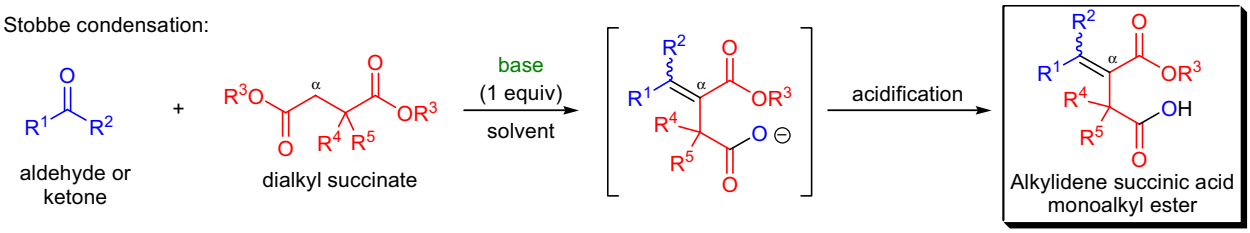
[*Seminal Publications*[1]; *Reviews*[2,3]; *Modifications & Improvements*[4-16]]

In 1893, H. Stobbe reported an unexpected reaction between acetone and diethyl succinate in the presence of a full equivalent of sodium ethoxide.[1] Upon acidification of the reaction mixture the major isolated product was found to be tetraconic acid, an α,β-unsaturated carboxylic acid, and its monoethyl ester. This result was surprising since the authors expected the formation of a 1,3-diketone *via* a *Claisen reaction*. A subsequent extensive study by Stobbe and co-workers revealed that the transformation was general for esters of succinic acid with aldehydes and ketones. The formation of alkylidene succinic acids or their monoesters by the base-mediated condensation of ketones and aldehydes with dialkyl succinates is known as the *Stobbe condensation*. The general features of the reaction are: 1) there is no restriction on the carbonyl component it may have hydrogens at its α-position; 2) aromatic-, α,β-unsaturated aldehydes and ketones as well as aliphatic ones are commonly used; 3) the diesters are mainly limited to succinic esters and their substituted derivatives, but certain α,ω-diesters that do not undergo competitive *Dieckmann condensation* will afford Stobbe products; 4) upon mild acidic work-up the primary product is an alkylidene succinic acid monoester; 5) when symmetrical ketones are condensed, only one alkene stereoisomer is formed, but unsymmetrical ketones afford a mixture of alkene stereoisomers; and 6) when the carbonyl component has α-protons, a variety of products may be formed as a result of double bond migration under the reaction conditions. There are a few drawbacks of the *Stobbe condensation*: 1) self-condensation of the aldehyde or ketone substrate; 2) *Cannizzaro reaction* of aromatic aldehydes; 3) if the ketone is highly enolizable under the reaction conditions yields tend to be low; 4) too reactive ketones may undergo acylation (*Claisen reaction*) at their α-position by the dialkyl succinate; 5) when NaOEt is used as the base, substantial reduction of the ketone substrate is usually observed due to the oxidation of ethoxide to acetaldehyde (this side reaction is minimized by using KO*t*-Bu).

Stobbe (1893):



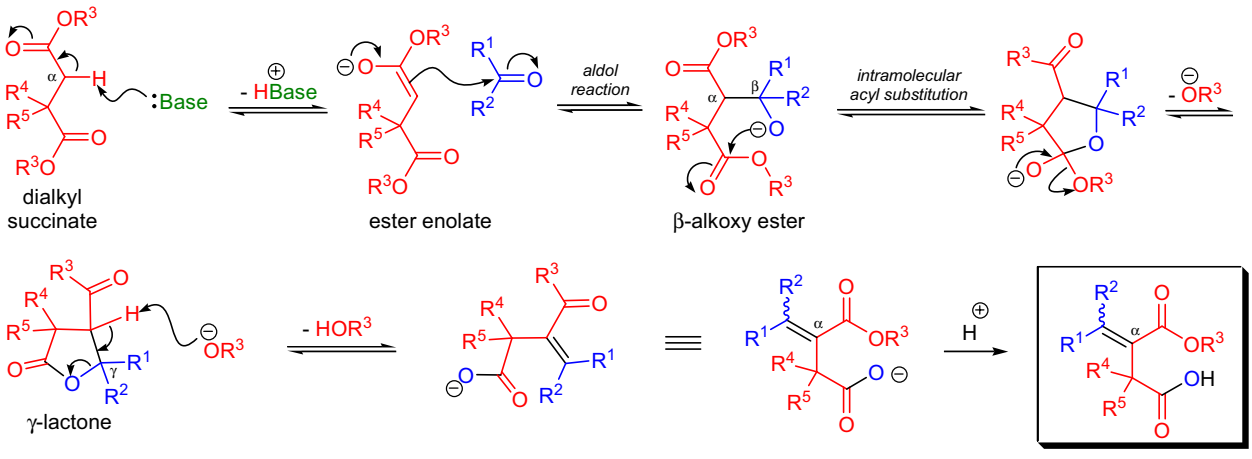
Stobbe condensation:



R^{1-2} = H, alkyl, aryl,alkenyl, acyl, CH(R)CO_2alkyl, CH(R)CN; R^3 = alkyl, aryl; R^{4-5} = H, alkyl, aryl, alkylidene; base: $NaOR^3$, KO*t*-Bu, NaH, NaOEt, Na metal, $NaCPh_3$; solvent: Et_2O, EtOH, *t*-BuOH

Mechanism:[17-22]

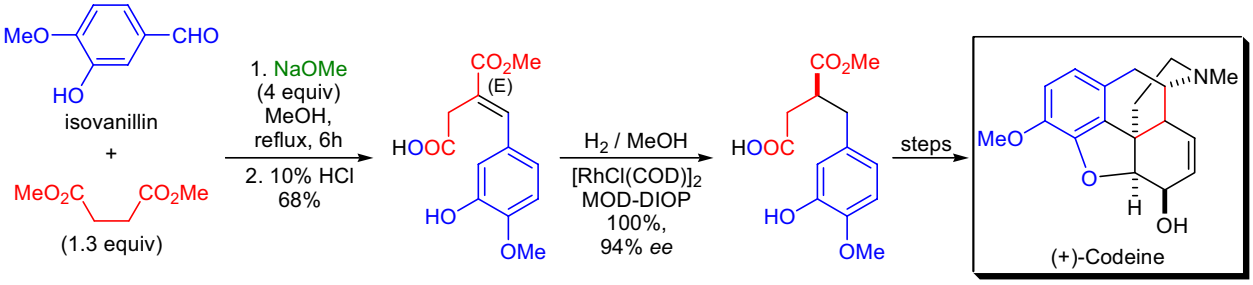
The first step of the *Stobbe condensation* is the deprotonation of the succinate at the α-carbon to afford an ester enolate that *in situ* undergoes an *aldol reaction* with the carbonyl compound to form a β-alkoxy ester intermediate. The following *intramolecular acyl substitution* gives rise to a γ-lactone intermediate which undergoes ring-opening and concomittant double bond formation upon deprotonation by the alkoxide ion. Under certain conditions the lactone intermediate can be isolated.



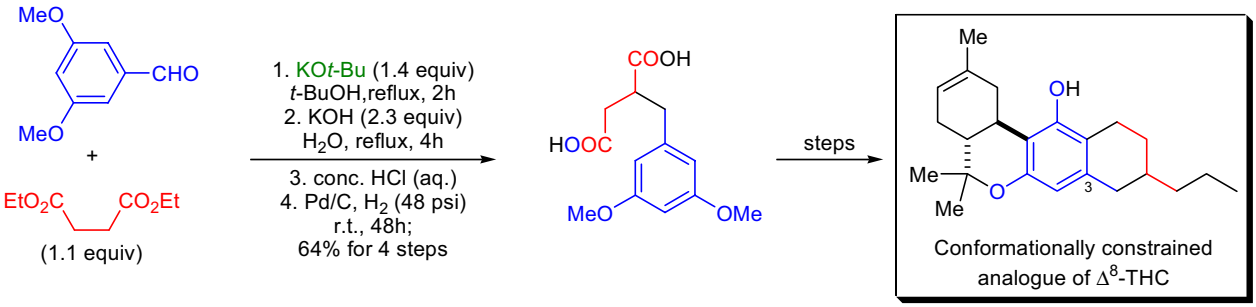
STOBBE CONDENSATION

Synthetic Applications:

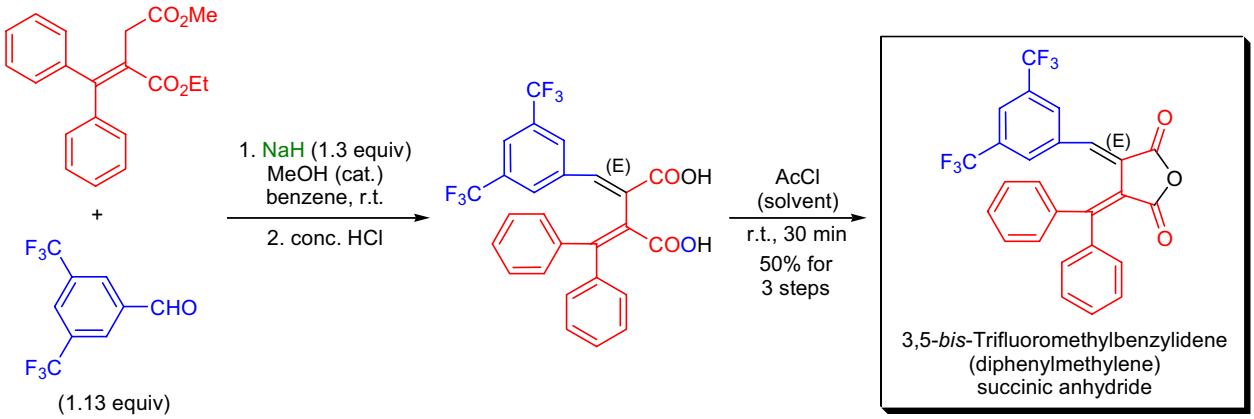
The asymmetric total synthesis of (+)-codeine, the unnatural enantiomer, was accomplished by J.D. White and co-workers using an *intramolecular carbenoid insertion* as the key step.[23] The first stereogenic center that directed all subsequent stereochemical events was installed by the *asymmetric hydrogenation* of an alkylidene succinate that was obtained using the *Stobbe condensation*. Dimethyl succinate and isovanillin were reacted in the presence of excess sodium methoxide at reflux and the resulting reaction mixture was acidified to obtain the monomethyl ester.



The SAR data regarding the potency of various cannabinoids show that one of the most important variables is the length and substitution pattern of the alkyl side chain at C3. In order to investigate the effect of side chain conformation upon receptor affinity, J.W. Huffman et al. designed and synthesized a conformationally constrained analog of Δ^8-THC.[24] The *Stobbe condensation* was applied to prepare the tetralin moiety of the target by reacting diethyl succinate in *tert*-butyl alcohol and using KO*t*-Bu as the base. The initially formed alkylidene compound was not purified but immediately subjected to *in situ* catalytic hydrogenation, and the resulting diacid was cyclized to afford a substituted tetralone, which was subsequently converted to the target.



In the laboratory of J. Liu it was shown unambiguously by single crystal X-ray diffraction, that the *Stobbe condensation* of diphenylmethylenesuccinate with aromatic aldehydes proceeded with perfect (*E*)-stereoselectivity.[25] For many decades, the product of this reaction was believed to have the (Z) stereochemistry on the basis of extreme steric crowding. The authors demonstrated that the nature and the position of the substituents on the aromatic rings of substituted benzaldehydes had no effect on the stereoselectivity of the reaction. This result was surprising, since the product was highly crowded but apparently a noncovalent π stacking interaction was operational between the two stacked aromatic rings. The condensation of ethyl methyl diphenylmethylenesuccinate with 3,5-*bis*(trifluoromethyl) benzaldehyde was carried out in benzene using sodium hydride as the base. Upon acidic work-up the corresponding diacid was obtained, which was immediately subjected to dehydration employing neat acetyl chloride.



STORK ENAMINE SYNTHESIS

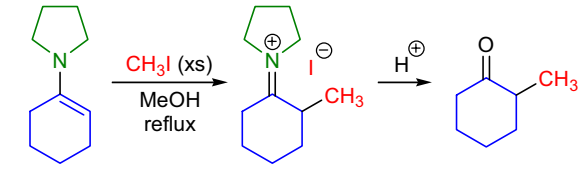
(References are on page 689)

Importance:

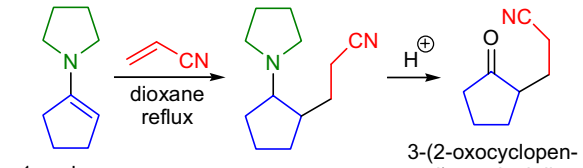
[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-21]; *Theoretical Studies*[22]]

In 1936, C. Mannich and H. Davidson reported that in the presence of a dehydrating agent (K_2CO_3 or CaO), secondary amines underwent facile condensation with aldehydes or ketones to afford enamines (non-charged enolate equivalents).[23] At that time the reaction of enamines with electrophiles was not investigated, but it was established that enamines were relatively labile compounds that underwent facile hydrolysis upon exposure to dilute aqueous acid. Two decades later, in 1954, G. Stork and co-workers discovered that the reaction of enamines with alkyl- or acyl halides followed by acidic hydrolysis constituted a novel way for the α-alkylation or α-acylation of carbonyl compounds.[3,4] The synthesis of α-alkyl- or acyl carbonyl compounds *via* the alkylation or acylation of the corresponding enamines is known as the *Stork enamine synthesis*. The general features of this method are: 1) the enamines are prepared by reacting the aldehyde or ketone with one equivalent of secondary amine (e.g., piperidine, morpholine or pyrrolidine) in the presence of a catalyst (or dehydrating agent); 2) with unsymmetrical ketones the formation of enamine regioisomers is expected but usually the less substituted regioisomer is favored; 3) the preparation of aldehyde enamines is often accompanied by the formation of aminals, which can be converted to the desired enamines by destructive distillation;[9] 4) activated alkyl and acyl halides are the best reaction partners (e.g., allyl-, benzyl-, propargylic-, or activated aryl halides); 5) tertiary alkyl halides do not alkylate the enamines but rather undergo elimination; 6) other electrophiles such as Michael acceptors and epoxides can also be used; and 7) the bulkier the ketone and the amine components, the better the yields of the monoalkylated product, but the reaction rates tend to drop. Advantages of the *Stork enamine synthesis* are: 1) the alkylation of the enamine takes place under neutral conditions, which is important when the substrate is base or acid sensitive; 2) polyalkylated products are seldom observed; 3) the alkylation takes place on the less substituted side of the ketone; and 4) an asymmetric version utilizing chiral enamines is also available.

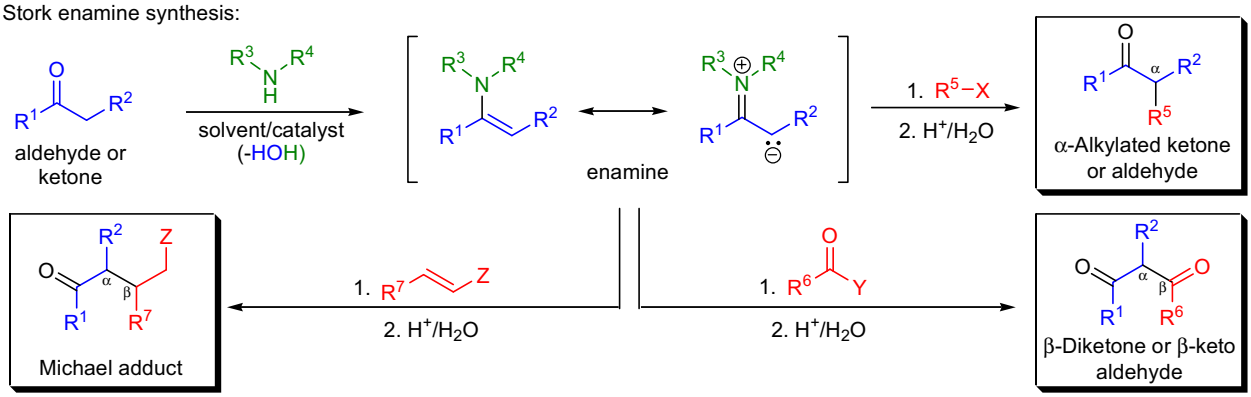
Stork, Terrell & Szmuszkovicz (1954):



Stork & Landesman (1956):



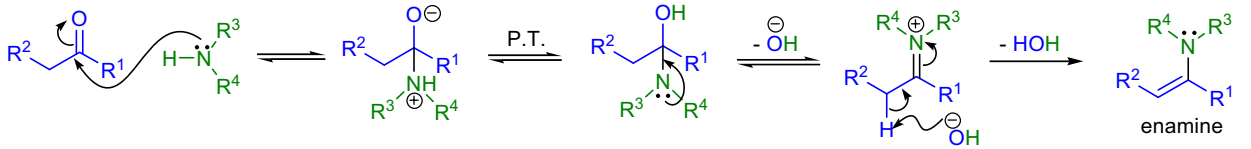
Stork enamine synthesis:



R^1 = H, alkyl, substituted alkyl; R^2 = H, alkyl, aryl; R^{3-4} = alkyl, aryl; R^5 = 1° or 2° alkyl, allylic, benzyl, CH_2CO_2R, CH_2CN, propargylic; R^6 = alkyl, aryl, OR, H; R^7 = H, alkyl, aryl; X = Cl, Br, I, OTs; Y =OCOR, CN, Cl, Br, I; Z = CN, COR, CO_2R, NO_2

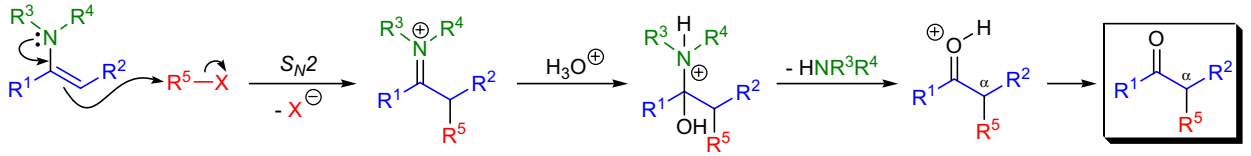
Mechanism:[24,25]

Formation of the enamine:



Alkylation of the enamine:

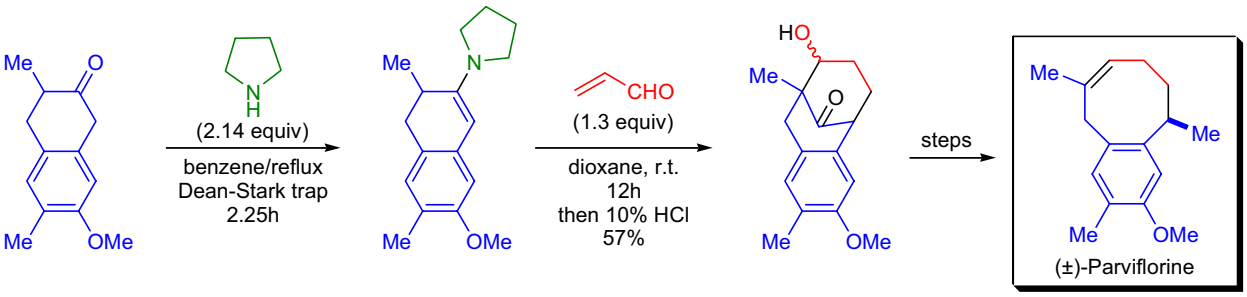
Hydrolysis with dilute acid:



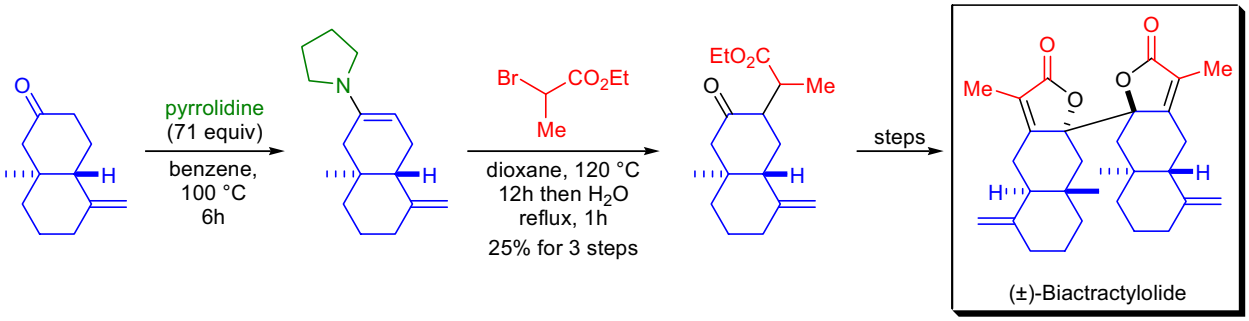
STORK ENAMINE SYNTHESIS

Synthetic Applications:

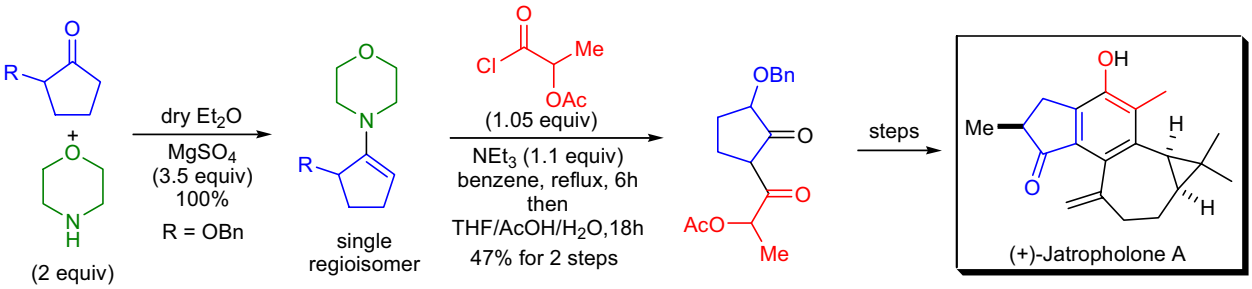
The total synthesis of the phenolic sesquiterpene (±)-parviflorine was accomplished by L.A. Maldonado and co-workers.[26] The key step in the synthetic sequence was the reaction of an enamine with acrolein to form a bicyclic intermediate, which was subjected to a *Grob fragmentation* to afford the eight-membered ring of the natural product. The bicyclic ketone substrate was refluxed in benzene using a Dean-Stark trap and the resulting enamine was taken to the next step as crude material.



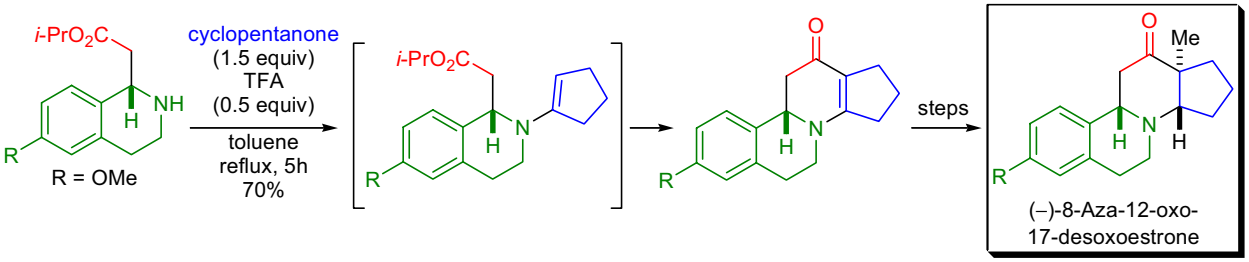
The biomimetic synthesis of the structurally novel bisesquiterpenoid (±)-biatractylolide was reported by J.E. Baldwin et al.[27] The cornerstone of the synthetic strategy was the radical dimerization of two atractylolide units. The atractylolide precursor was prepared from a bicyclic ketone using the *Stork enamine synthesis*. The pyrrolidine enamine was generated using large excess of pyrrolidine in refluxing benzene (the excess pyrrolidine was removed under reduced pressure). The alkylation of the crude enamine with ethyl α-bromopropionate took place in refluxing dioxane and afforded a mixture of ethyl ester diastereomers.



In the laboratory of A.B. Smith, the synthesis of (+)-jatropholone A and B was achieved using a *high-pressure Diels-Alder cycloaddition* between a tetrasubstituted furan and a homochiral enone. During the preparation of the furan component, the *Stork enamine synthesis* was used. The α-benzyloxy cyclopentanone was converted to the corresponding morpholine enamine in quantitative yield. The enamine was isolated as a single regioisomer. In contrast, the corresponding piperidine or pyrrolidine enamines were obtained always as a mixture of regioisomers. The acylation of the enamine with *O*-acetoxyacetyl chloride yielded a 1,3-diketone, which was converted to the desired tetrasubstituted furan component.



An intramolecular variant of the *Stork enamine synthesis* was utilized during the asymmetric total synthesis of (–)-8-aza-12-oxo-17-desoxoestrone by A.I. Meyers et al.[28]



STRECKER REACTION

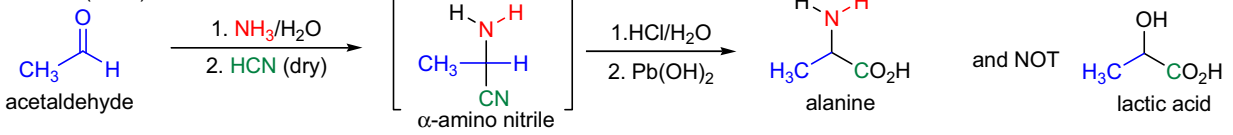
(References are on page 690)

Importance:

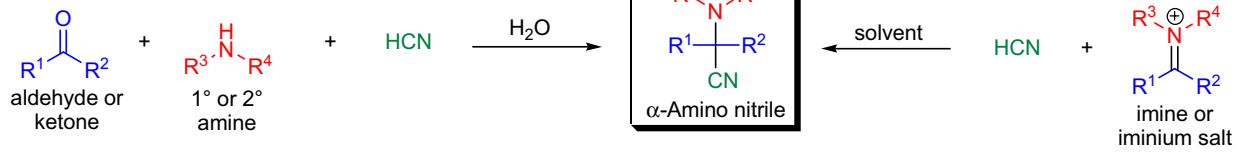
[*Seminal Publications*[1,2]; *Reviews*[3-28]; *Modifications & Improvements*[29-42]; *Theoretical Studies*[43-46]]

In 1850, A. Strecker attempted the synthesis of lactic acid by treating acetaldehyde first with aqueous ammonia followed by the addition of hydrogen cyanide and hydrolyzing the resulting amino nitrile intermediate with aqueous acid.[1] To his surprise he did not isolate any of the desired lactic acid but instead obtained alanine. This discovery constituted the first laboratory preparation of an α-amino acid. The condensation of an aldehyde or ketone with a primary amine or ammonia and hydrogen cyanide (or their equivalents) to afford the corresponding α-amino nitrile is known as the *Strecker reaction*. The most well-known use of α-amino nitriles is their hydrolysis under acidic or basic conditions to obtain α-amino acids (*Strecker amino acid synthesis*). The general features of the *Strecker reaction* are: 1) the transformation is a one-pot three-component coupling; 2) due to the extreme toxicity of HCN, various alkali cyanides (e.g., KCN, NaCN) in buffered aqueous media are used; 3) both aldehydes and ketones are good substrates; 3) the amine component can be ammonia, primary, or secondary amine; 4) the addition of HCN to preformed aldimines and ketimines (even iminium salts) or to oximes and hydrazones leads to *N*-substituted α-amino nitriles; 5) hydrolysis of α-amino nitriles gives α-amino acids, reduction with metal hydrides affords 1,2-diamines, while strong bases can deprotonate at the α-carbon (if R^2=H) and the resulting carbanion can be trapped with a variety of electrophiles (umpolung);[22] and 6) upon treatment with heavy metal salts (e.g., $AgNO_3$), Brönsted or Lewis acids, α-amino nitriles undergo a loss of cyanide ion to form iminium ions, which can be trapped with various nucleophiles (if the nucleophile is an organometallic reagent, the transformation is called the *Bruylants reaction*). It is now possible to conduct the *Strecker reaction* asymmetrically: 1) the use of optically active amines generate chiral imines, which give rise to enantio-enriched α-amino nitriles upon the addition of cyanide ions;[8,11] and 2) asymmetric induction may be achieved by the use of organocatalysts or chiral metal catalysts.[25,27]

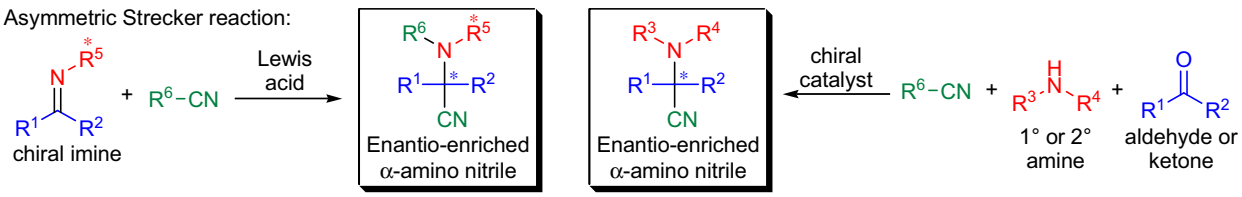
Strecker (1850):



Strecker reaction:



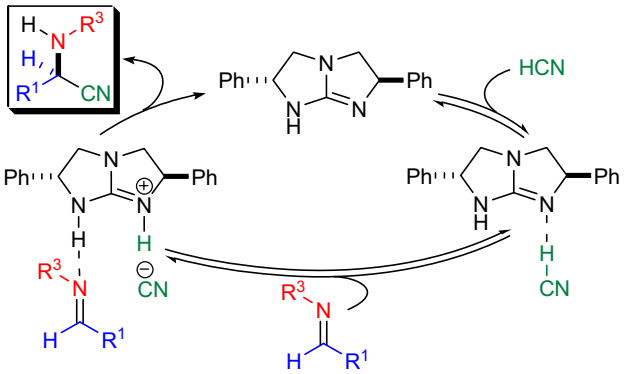
Asymmetric Strecker reaction:



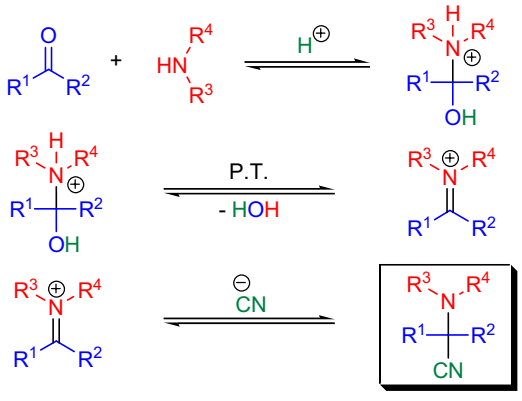
R^1 = alkyl, aryl, heteroaryl; R^2 = H, alkyl, aryl, heteroaryl; R^{3-4} = H, alkyl, aryl, heteroaryl; R^5 = group having a chiral center; R^6 = H, TMS; chiral catalyst: chiral metal catalyst or organocatalyst

Mechanism:[47-54]

Mechanism in the presence of an organocatalyst (Corey, 1999):



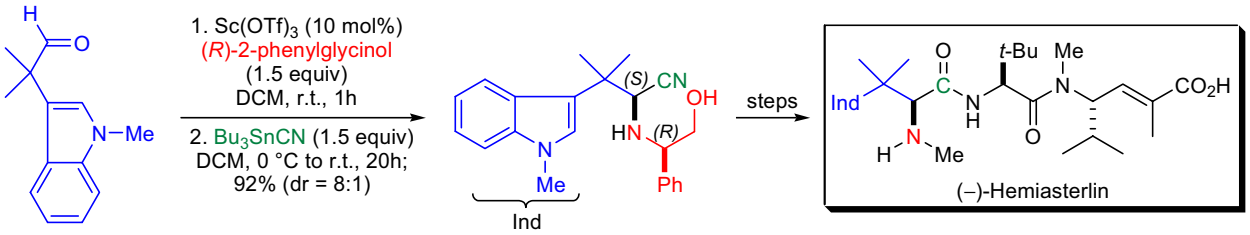
Mechanism of the classical Strecker reaction:



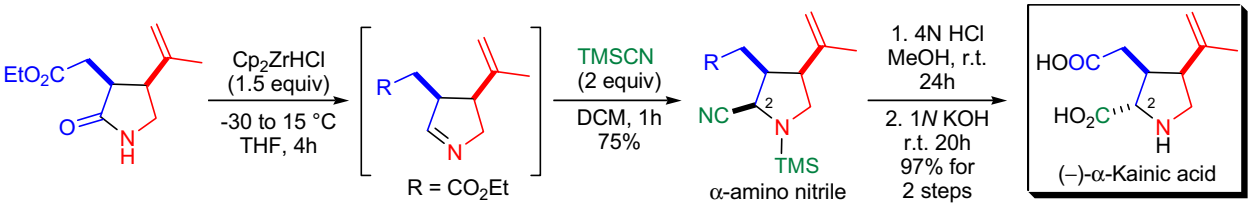
STRECKER REACTION

Synthetic Applications:

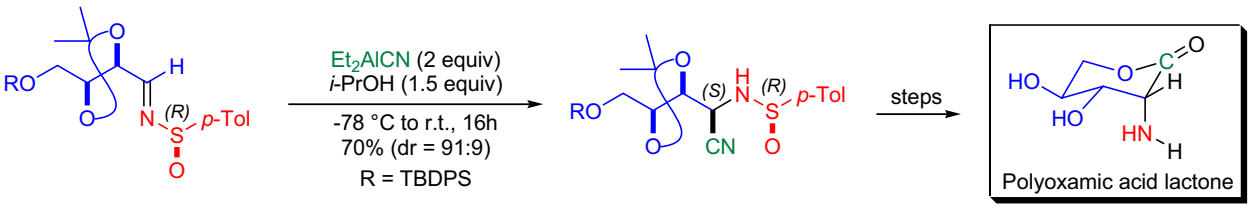
The enantioselective total synthesis of (–)-hemiasterlin, a marine tripeptide with cytotoxic and antimitotic activity, was achieved by E. Vedejs and co-workers.[55] The *asymmetric Strecker reaction* was used to construct the key tetramethyltryptophan subunit. The aldehyde substrate was first converted to the corresponding chiral imine with (*R*)-2-phenylglycinol under scandium triflate catalysis. The addition of tributyltin cyanide resulted in the formation of α-amino nitriles as an 8:1 mixture of diastereomers. Subsequently the cyano group was converted to a primary amide, and the chiral auxiliary was removed under catalytic hydrogenation conditions.



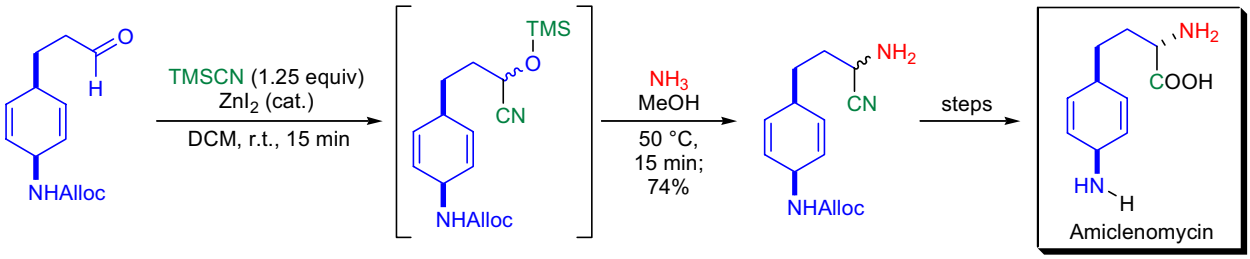
In the laboratory of B. Ganem, the asymmetric total synthesis of (–)-α-kainic acid was accomplished starting from very simple precursors. A highly stereoselective *zirconium-mediated Strecker reaction* was used to install the α-amino acid moiety of the natural product. The five-membered lactam substrate was treated with excess Schwartz reagent at low temperature which generated the corresponding cyclic imine *in situ*. This cyclic imine was not isolated but was immediately reacted with cyanotrimethylsilane to afford the all *cis* α-amino nitrile. In order to convert this intermediate to kainic acid, the cyano group was first converted by the *Pinner reaction* to a methyl ester. The resulting diester was hydrolyzed with aqueous KOH solution to give the corresponding dicarboxylic acid with complete epimerization at C2.



The *sulfinimine-mediated asymmetric Strecker reaction* was developed by F.A. Davis et al. This method involves the addition of ethylaluminumcyanoisopropoxide to functionalized sulfinimines and the resulting diastereomeric α-amino nitriles are easily separated. Subsequent hydrolysis directly affords the enantiopure α-amino acids. This protocol was applied for the synthesis of polyoxamic acid lactone.[56]



The first total synthesis of amiclenomycin, an inhibitor of biotin biosynthesis, was completed by A. Marquet and co-workers.[57] In order to prove its structure unambiguously, both the *cis* and *trans* isomers were prepared. The L-amino acid functionality was installed by a *Strecker reaction* using TMSCN in the presence of catalytic amounts of ZnI_2. The resulting O-TMS protected cyanohydrin was exposed to saturated methanolic ammonia solution, which gave rise to the corresponding α-amino nitrile. Enzymatic hydrolysis with immobilized pronase afforded the desired L-amino acid.



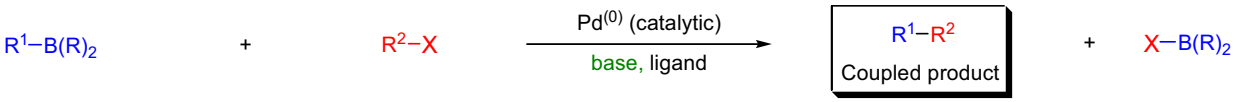
SUZUKI CROSS-COUPLING
(SUZUKI-MIYAURA CROSS-COUPLING)

(References are on page 691)

Importance:

[*Seminal Publications*[1-3] *; Reviews*[4-38]*; Modifications & Improvements*[39-49]]

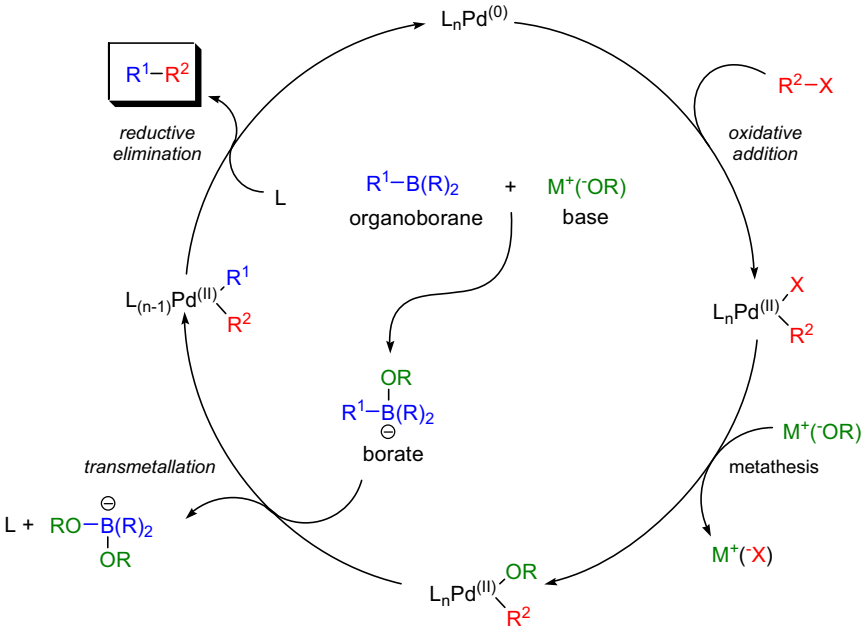
In 1979, A. Suzuki and N. Miyaura reported the stereoselective synthesis of arylated (*E*)-alkenes by the reaction of 1-alkenylboranes with aryl halides in the presence of a palladium catalyst.[1] The palladium-catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates provides a powerful and general method for the formation of carbon-carbon bonds known as the *Suzuki cross-coupling*. There are several advantages to this method: 1) mild reaction conditions; 2) commercial availability of many boronic acids; 3) the inorganic by-products are easily removed from the reaction mixture, making the reaction suitable for industrial processes; 4) boronic acids are environmentally safer and much less toxic than organostannanes (see *Stille coupling*); 5) starting materials tolerate a wide variety of functional groups, and they are unaffected by water; 6) the coupling is generally *stereo-* and *regioselective;* and 7) sp^3-hybridized alkyl boranes can also be coupled by the *B-alkyl Suzuki-Miyaura cross-coupling*. Some disadvantages are: 1) generally aryl halides react sluggishly; 2) by-products such as self-coupling products are formed because of solvent-dissolved oxygen; 3) coupling products of phosphine-bound aryls are often formed; and 4) since the reaction does not proceed in the absence of a base, side reactions such as racemization of optically active compounds or aldol condensations occur. Improvements of the *Suzuki cross-coupling* include the development of catalysts facilitating coupling of unreactive aryl halides,[39,40] the ability to react sp^3-hybridized alkyl halides,[42,44,50] and the use of alkyl, alkenyl, aryl, and alkynyl trifluoroborates in place of boronic acids.[45-47]



R^1 = alkyl, allyl, alkenyl, alkynyl, aryl; R = alkyl, OH, O-alkyl; R^2 = alkenyl, aryl, alkyl; X = Cl, Br,I, OTf, $OPO(OR)_2$ (enol phosphate);
base = Na_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3, K_2CO_3, TlOH, KF, CsF, Bu_4F, NaOH, $M^+(^-O\text{-alkyl})$

Mechanism:[51-55,24,56,57,50,58-60]

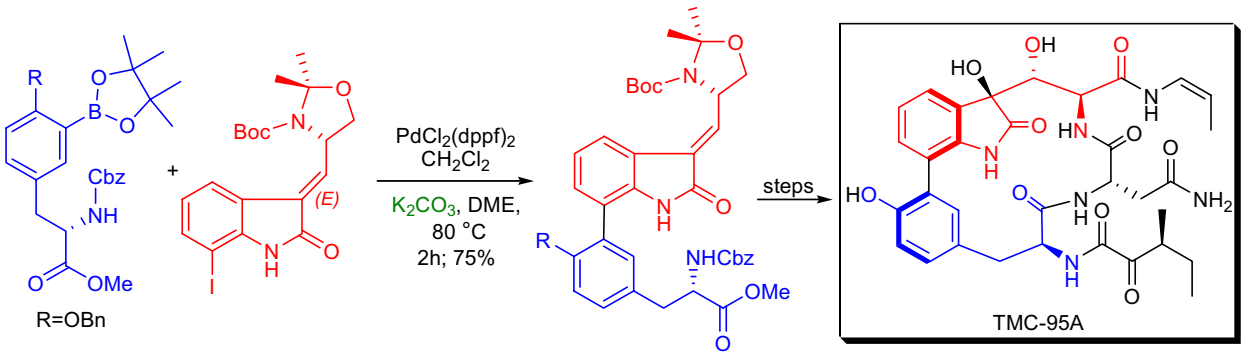
The mechanism of the Suzuki cross-coupling is analogous to the catalytic cycle for the other cross-coupling reactions and has four distinct steps: 1) oxidative addition of an organic halide to the $Pd^{(0)}$-species to form $Pd^{(II)}$; 2) exchange of the anion attached to the palladium for the anion of the base (metathesis); 3) transmetallation between $Pd^{(II)}$ and the alkylborate complex; and 4) reductive elimination to form the C-C sigma bond and regeneration of $Pd^{(0)}$. Although organoboronic acids do not transmetallate to the $Pd^{(II)}$-complexes, the corresponding ate-complexes readily undergo transmetallation. The quaternization of the boron atom with an anion increases the nucleophilicity of the alkyl group and it accelerates its transfer to the palladium in the transmetallation step. Very bulky and electron-rich ligands (e.g., $P(t\text{-Bu})_3$) increase the reactivity of otherwise unreactive aryl chlorides by accelerating the rate of the oxidative addition step.



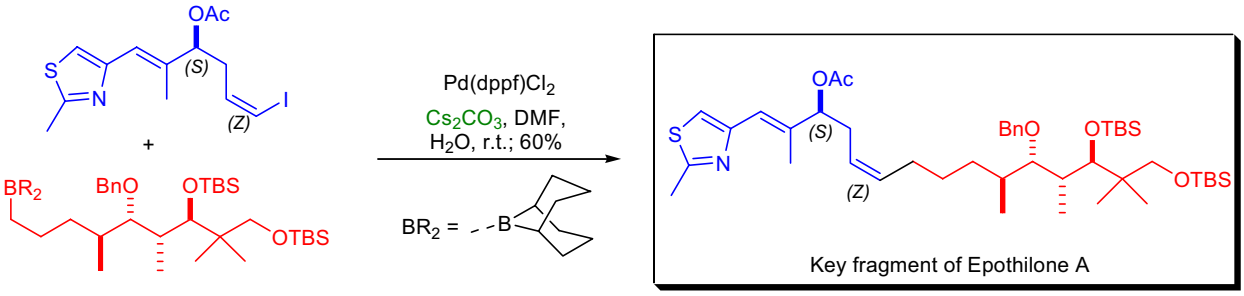
SUZUKI CROSS-COUPLING
(SUZUKI-MIYAURA CROSS-COUPLING)

Synthetic Applications:

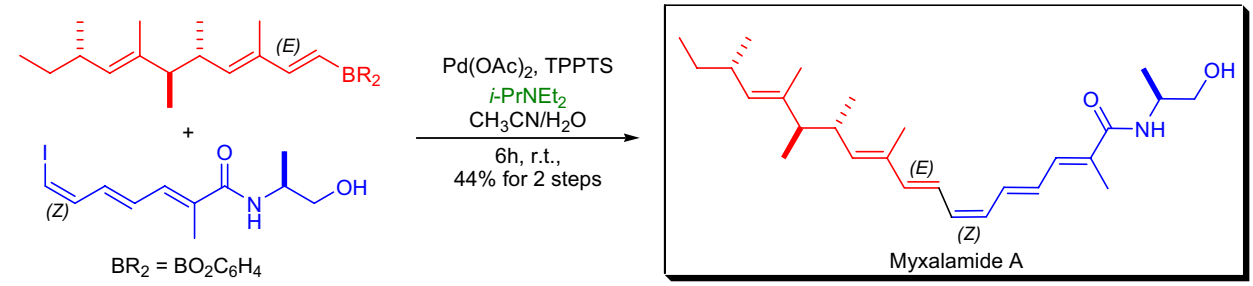
During the total synthesis of the proteosome inhibitor TMC-95A by S.J. Danishefsky et al., the biaryl moiety of the compound was assembled in good yield by the *Suzuki cross-coupling* of an aryl iodide and an arylboron intermediate.[61]



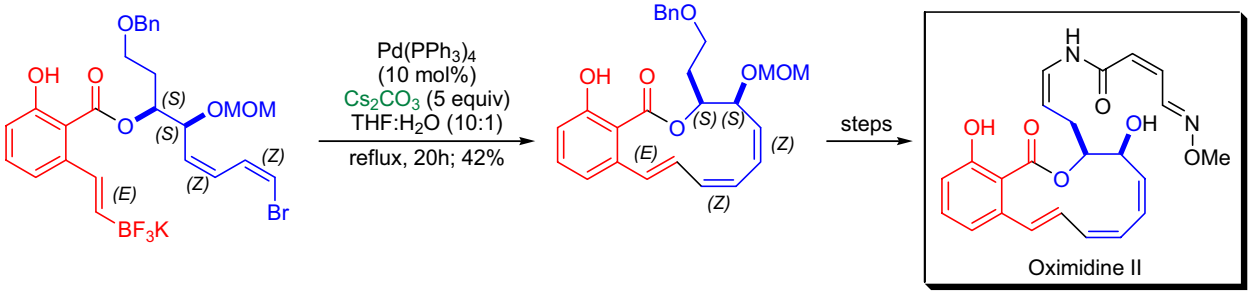
The antitumor natural product epothilone A was synthesized in the laboratory of J.S. Panek.[62] They utilized the *B-alkyl Suzuki cross-coupling* between an sp^3-hybridized alkylborane and a (*Z*)-iodoalkene for the construction of the main fragment. The alkylborane was prepared by hydroborating the terminal alkene with 9-BBN and the (*Z*)-iodoalkene was added along with the palladium catalyst and the base.



The last and key step in the total synthesis of myxalamide A by C.H. Heathcock et al. was a *Suzuki cross-coupling* between an (*E*)-vinylborane and a (*Z*)-iodotriene.[63] The (*E*)-vinylborane was prepared prior to the coupling by reacting the precursor enyne with 2 equivalents of cathecholborane. Upon completion of the hydroboration, it was combined with the (*Z*)-iodotriene and catalytic amounts of palladium acetate.



A formal total synthesis of oximidine II was achieved by G.A. Molander et al., using an *intramolecular Suzuki-type cross-coupling* between an alkenyl potassium trifluoroborate and an alkenyl bromide to construct the highly strained, polyunsaturated 12-membered macrolactone core of the natural product.[64] The stability of potassium trifluoroborates was exploited in order to establish the best conditions for the macrocyclization.



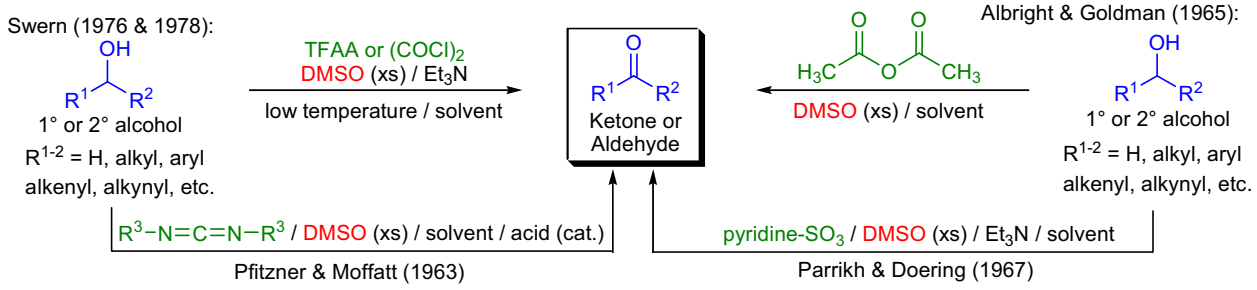
SWERN OXIDATION

(References are on page 692)

Importance:

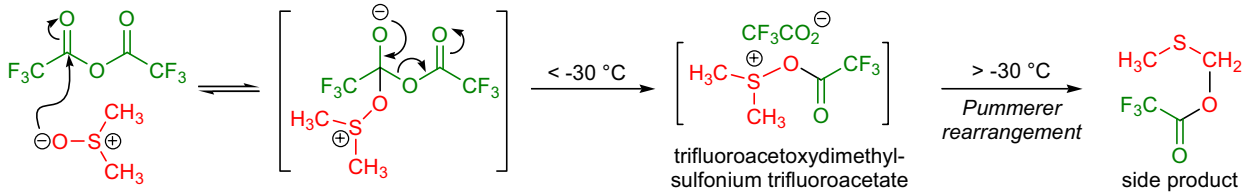
[*Seminal Publications*[1-6]; *Reviews*[7-10]; *Modifications & Improvements*[11-16]]

In 1976, D. Swern and co-workers reported that treatment of dimethyl sulfoxide (DMSO) with trifluoroacetic anhydride (TFAA) below -50 °C in methylene chloride gave trifluoroacetoxydimethylsulfonium trifluoroacetate, which reacted rapidly with primary and secondary alcohols.[3] The resulting alkoxydimethylsulfonium trifluoroacetates, upon addition of triethylamine, afforded the corresponding aldehydes and ketones in good yield.[3] In 1978, oxalyl chloride was found to be more effective than TFAA as an activating agent for DMSO in the oxidation of alcohols.[5,6] The oxidation of primary and secondary alcohols using DMSO and TFAA or oxalyl chloride is referred to as the *Swern oxidation*. The general features of this oxidation are: 1) when no solvent is used, DMSO reacts with TFAA or oxalyl chloride violently (explosion!), so great care should be exercised while running the reaction; 2) the most common solvent is DCM; 3) when TFAA is used, the initial intermediate is unstable above -30 °C and a side product is formed *via* the *Pummerer rearrangement*; 4) when oxalyl chloride is used, the initial intermediate is unstable above -60 °C, so the oxidation is usually conducted at -78 °C; 5) the typical procedure begins with the reaction of DMSO with TFAA or oxalyl chloride at low temperature followed by the slow addition of the alcohol, then a tertiary amine; 6) the addition of a tertiary amine (e.g., DIPA, TEA) is necessary to facilitate the decomposition of the alkoxysulfonium salt; 7) the efficiency of the oxidation is not influenced by the steric hindrance of the substrate; and 8) the use of TFAA may give rise to trifluoroacetate side products, whereas in the case of oxalyl chloride side reactions are extremely rare.

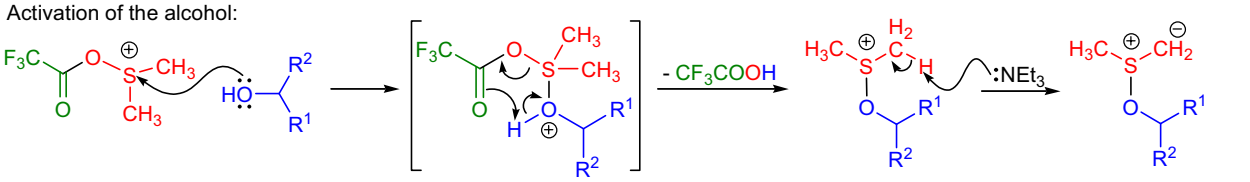


Mechanism:[6-9]

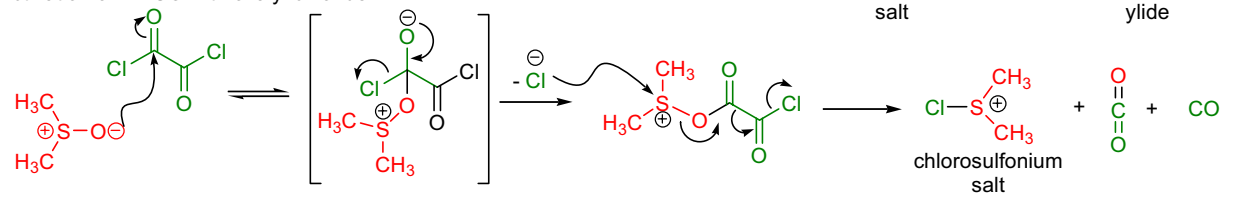
Activation of DMSO with TFAA:



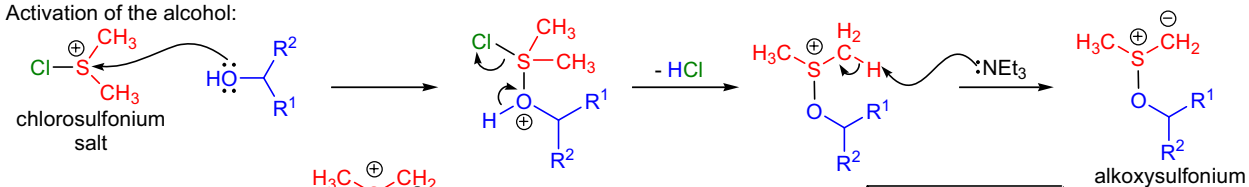
Activation of the alcohol:



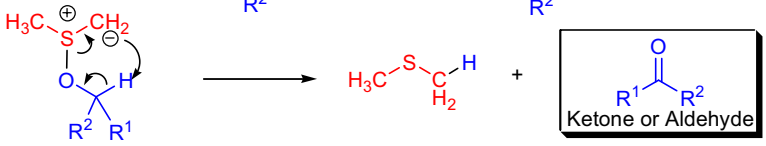
Activation of DMSO with oxalyl chloride:



Activation of the alcohol:



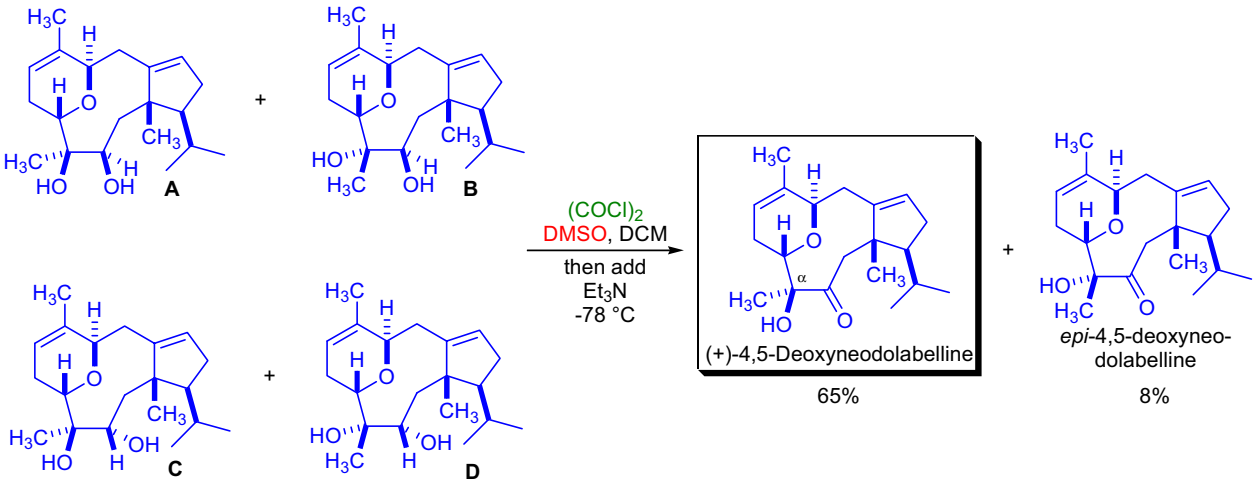
Formation of the product:



SWERN OXIDATION

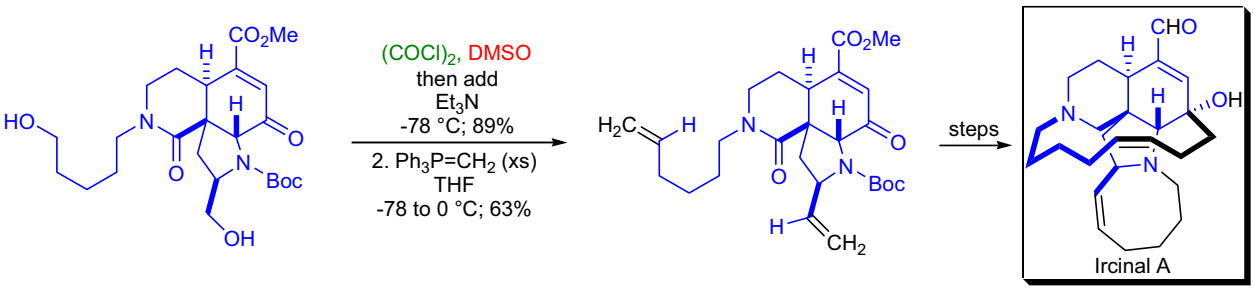
Synthetic Applications:

The first total synthesis of the marine dolabellane diterpene (+)-deoxyneodolabelline was achieved in the laboratory of D.R. Williams.[17] In the final step of the synthetic sequence, the oxidation of a secondary alcohol functionality of a 1,2-diol to the corresponding α-hydroxy ketone was required. Such 1,2-diols are known to be unstable under most oxidation conditions, and often *glycol cleavage* is observed. Indeed, when *Dess-Martin and Ley oxidations* were tried, the substrate suffered carbon-carbon bond cleavage. However, under the *Swern oxidation* conditions, the desired α-hydroxy ketone was isolated in a 65% yield. Interestingly, the substrate was a mixture of four inseparable diastereomeric diols (obtained in a *McMurry reaction*), which gave two easily separable ketone products, one of which was the natural product.

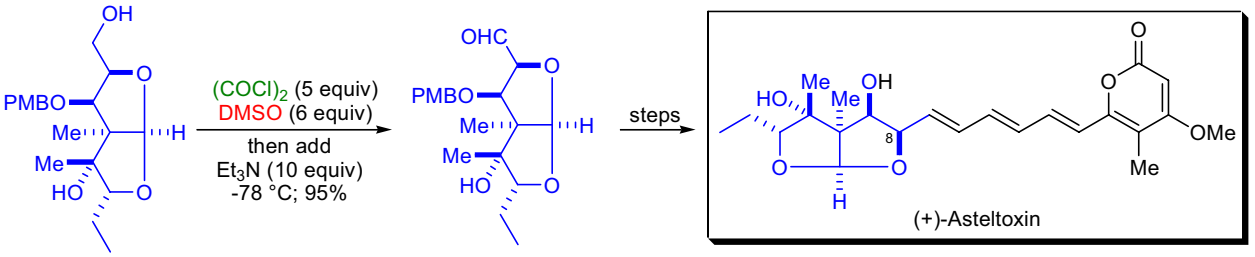


a mixture of four diastereomers (A:B:C:D = 8:2:1:1

S.F. Martin and co-workers utilized a *double Swern oxidation* in their synthesis of ircinal A and related manzamine alkaloids.[18] The advanced tricyclic diol intermediate was first subjected to the *Swern oxidation* conditions at -78 °C to afford the corresponding dialdehyde in excellent yield. In the next step, the dialdehyde was exposed to excess Wittig reagent under salt-free conditions to form the two terminal alkenes.



The convergent total synthesis of the mytotoxic (+)-asteltoxin was accomplished by J.K. Cha et al.[19] The coupling of the two main fragments was achieved by the *HWE olefination* of a *bis*(tetrahydrofuran) aldehyde with an α-pyrone phosphonate. The *bis*(tetrahydrofuran) aldehyde was prepared by the *Swern oxidation* of the corresponding *bis*(tetrahydrofuran) primary alcohol. Interestingly, under the oxidation conditions there was no epimerization of the α-stereocenter, but during the *HWE olefination* a small amount of C8 epimer was formed.



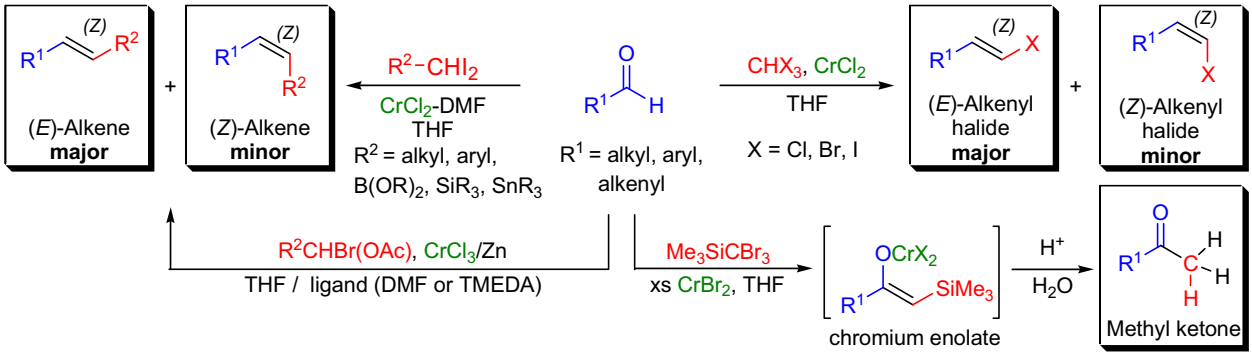
TAKAI-UTIMOTO OLEFINATION (TAKAI REACTION)

(References are on page 693)

Importance:

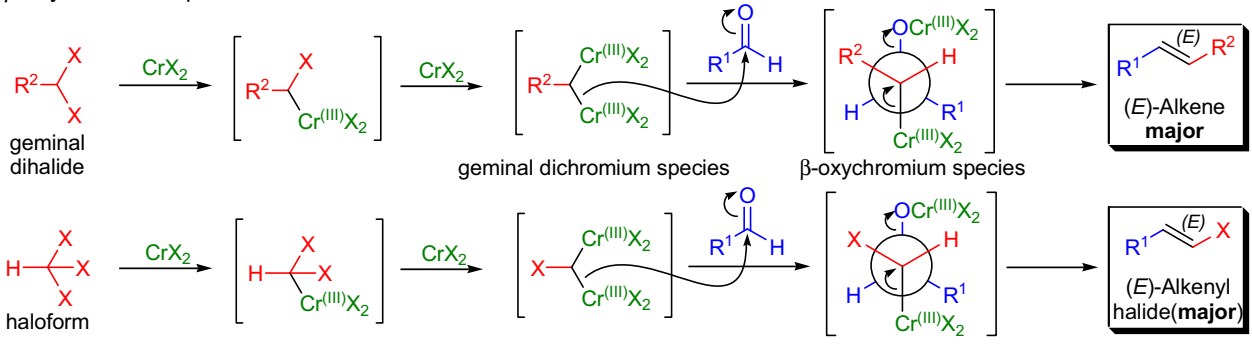
[*Seminal Publications*[1,2]; *Reviews*[3-8]; *Modifications & Improvements*[9-17]]

Until the second half of the 1980s there was no general method available for the stereoselective preparation of alkenyl halides from carbonyl compounds. In 1987, K. Takai and K. Utimoto introduced a simple and stereoselective method for the conversion of aldehydes to the corresponding (*E*)-alkenyl halides by treating the aldehydes with a haloform-chromium(II)-chloride (CHX_3-$CrCl_2$) system.[1] The chromium(II)-mediated one-carbon homologation of aldehydes with haloform to give the corresponding (*E*)-alkenyl halides is known as the *Takai-Utimoto olefination* (*Takai reaction*). General features of the reaction are: 1) the anhydrous $CrCl_2$ can be dissolved in the solvent just prior to the reaction or can be generated by reacting $CrCl_3$ with $LiAlH_4$; 2) aldehydes react much faster than ketones, so the chemoselective transformation of aldehydes in the presence of ketones is possible; 3) for aliphatic and aromatic aldehydes the major product is the (*E*)-alkenyl halide but for α,β-unsaturated aldehydes the stereoselectivity is usually poor; 4) the rate of the reaction is a function of the haloform used: I>Br>Cl; 5) iodoform reacts rapidly at low temperatures (~0 °C), while other haloforms require higher temperatures to react; 6) the (*E*/*Z*) ratio is also dependent on the haloform used (Cl>Br>I) and the best (*E*)-selectivity is observed when X=Cl; 7) when $CHBr_3/CrCl_2$ is used, a mixture of alkenyl chlorides and bromides is obtained due to a *Finkelstein reaction* of $CrCl_2$ with bromide (Br^-). However, by preparing $CrBr_2$ from $CrBr_3/LiAlH_4$ this problem is eliminated;[1,18] 8) reducing agents other than Cr(II) give unsatisfactory or no yield of the desired alkenyl halides; 9) in certain cases the applied solvent is critical to achieve good yield and stereoselectivity; 10) the reaction conditions tolerate almost any functional group; and 11) the reaction conditions are mild enough (the reagent is practically nonbasic) that even highly enolizable substrates do not racemize at their α-position. There are several important modification of the *T-U olefination*: 1) instead of haloforms, 1,1-geminal dihalides are used to afford predominantly (*E*)-olefins;[2] 2) instead of 1,1-geminal dihalides, α-acetoxy bromides can be used, which are more stable and easier to prepare and handle than 1,1-geminal dihalides;[11] and 3) one-carbon homologation of aldehydes *via* chromium enolates to the corresponding methyl ketones using $TMSCBr_3/CrBr_2$.[12] When 1,1-geminal dihalides are used, the following can be expected: 1) the (*E*)-selectivity is especially high for aliphatic substrates, and it increases with the size of R^1; 2) only 1,1-geminal diiodoalkanes are suitable; the dichlorides and dibromides undergo reduction under the reaction conditions; 3) CH_2I_2 is the most reactive. The higher homologs react slower and give lower yields; 4) aldehydes react faster than ketones; 5) the reaction can be carried out with catalytic amounts of $CrCl_3$ in the presence of samarium metal or samarium diiodide;[19] and 6) the R^2 substituent can contain heteroatoms so the preparation of alkenyl silanes,[13,15] -boronates,[14] –stannanes,[10] and sulfides[9] is possible. The use of α-acetoxy bromides has the following features: 1) the *in situ* preparation of the chromium(II) reagent and donor ligand such as DMF or TMEDA should be present; 2) high (*E*)-selectivity; and 3) exclusive reaction with aldehydes.[11]



Mechanism: [20,21,2,3,15,7]

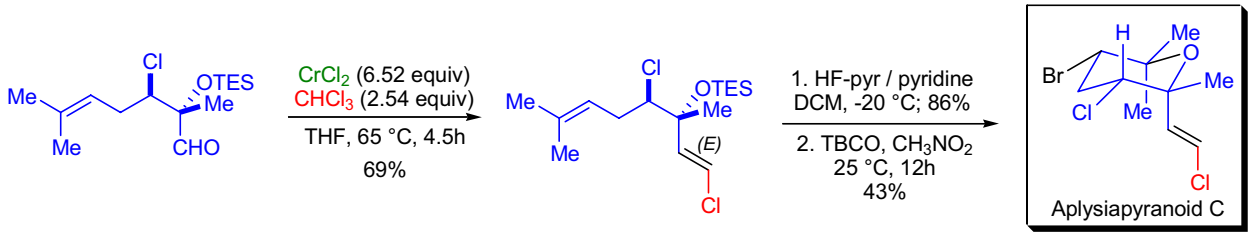
The exact mechanistic pathway is not known. However, it is believed that the *T-U olefination* proceeds *via* geminal-dichromium intermediates that are nucleophilic and attack the carbonyl compound. The (*E*)-alkene is formed from the β-oxychromium species.



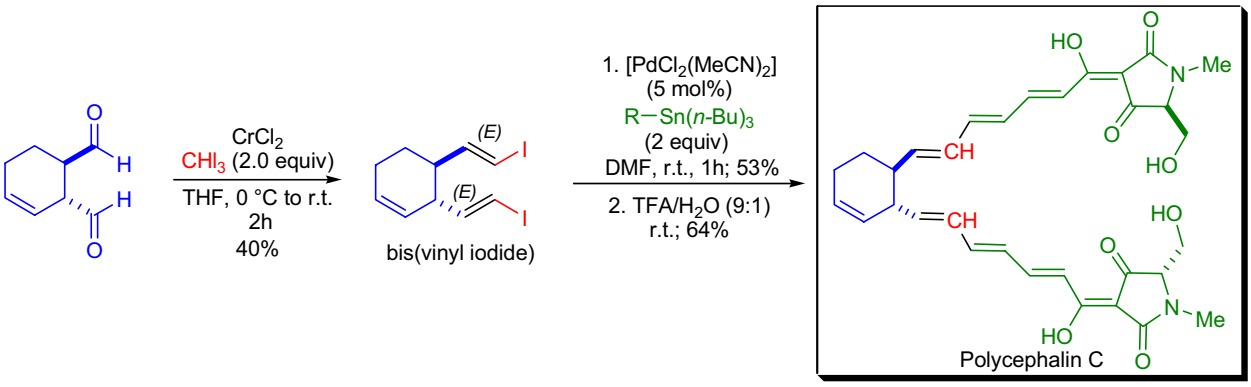
TAKAI-UTIMOTO OLEFINATION (TAKAI REACTION)

Synthetic Applications:

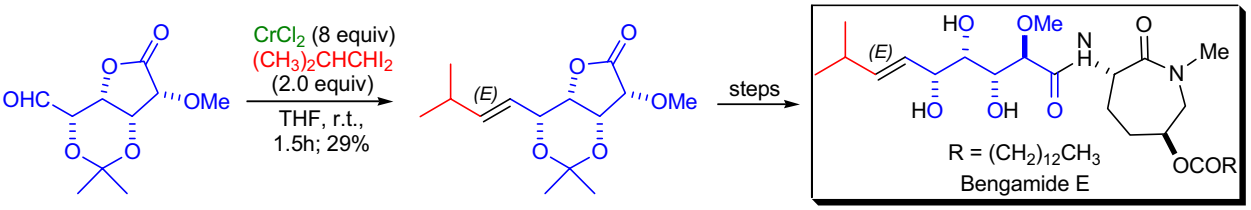
The first total synthesis of the cytotoxic marine natural product aplysiapyranoid C was accomplished by M.E. Jung et al.[22] The special structural feature of this natural product is the (*E*)-vinyl chloride moiety, which was introduced in high yield *via* the *Takai reaction* in the late stages of the synthetic effort. The removal of the silicon protecting group and cyclization of the dichlorodienol with TBCO (tetrabromocyclohexadienone) in nitromethane gave a mixture of four products, one of which was the desired product that was isolated in 43% yield.



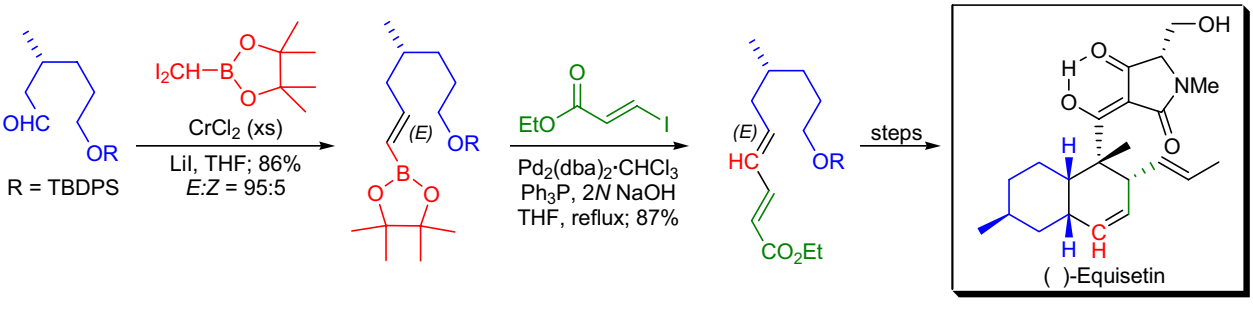
Polycephalin C is a bis(trienoyltetramic acid) linked by an unusual asymmetric cyclohexene ring. At the time of isolation and structure elucidation the absolute configuration at the C3 and C4 positions was not established. S.V. Ley and co-workers carried out the total synthesis of this natural product based on a *double Takai olefination* followed by a *double Stille cross-coupling*.[23] The dialdehyde substrate for the *Takai olefination* was prepared by the *asymmetric Diels-Alder cycloaddition* of dimenthyl fumarate with butadiene. The *double Takai olefination* proceeded with high (E)-stereoselectivity to afford the bisiodide, albeit in only 40% yield. Subsequent *double Stille coupling* proceeded in good yield and after a global deprotection the target compound was obtained.



In the laboratory of F.R. Kinder Jr., the total synthesis of cytotoxic marine natural product bengamide E was completed.[24] The *Takai-Utimoto olefination* was used to introduce the (*E*)-disubstituted double bond. The aldehyde was exposed to a $CrCl_2$ solution in THF in the presence of 1,1-diiodo-2-methylpropane, and the desired olefin was obtained in 29% yield.



The diastereoselective Me_3Al-mediated *intramolecular Diels-Alder reaction*, a highly (*E*)-selective *Takai olefination* and a *Suzuki coupling* were the key steps in the enantioselective total synthesis of (–)-equisetin by K. Shishido et al.[25] It should be noted that the type of *T-U olefination* utilized allowed the preparation of functionalized heterosubstituted (*E*)-alkenes.



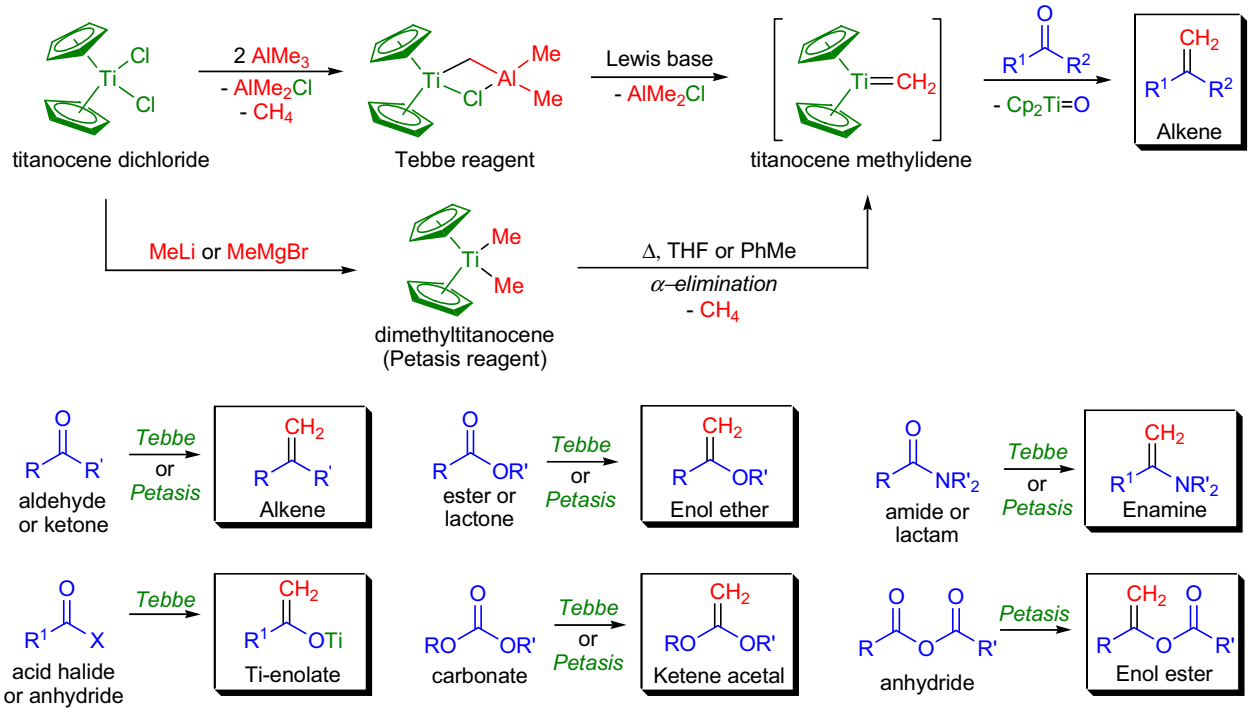
TEBBE OLEFINATION / PETASIS-TEBBE OLEFINATION

(References are on page 693)

Importance:

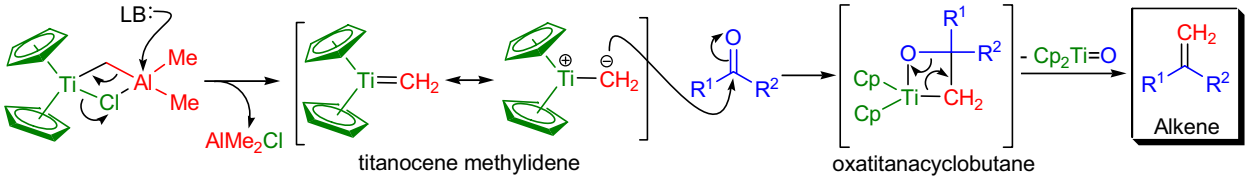
[*Seminal Publications*[1-3]; *Reviews*[4-15]; *Modifications & Improvements*[16-20]]

In 1976, R.R. Schrock discovered, during his studies of *alkene metathesis*, that the neopentylidene complex of tantalum was structurally analogous to phosphorous ylides (*Wittig reagents*), and it not only olefinated aldehydes and ketones but esters and amides as well.[1] In 1978, F.N. Tebbe et al. reported that titanocene dichloride reacted with two equivalents of $AlMe_3$ to produce a methylene-bridged titanium-aluminum complex (*Tebbe reagent*), which transferred a methylene group (CH_2) efficiently to various carbonyl compounds to afford olefins.[2] It was shown early on that the Tebbe reagent converted carboxylic esters, lactones, and amides to the corresponding enol ethers and enamines in high yield. The one-carbon homologation (methylenation) of carbonyl compounds using the Tebbe reagent is known as the *Tebbe olefination*. The *Tebbe reaction* has the following general features: 1) the active species (titanocene methylidene) is more nucleophilic and much less basic than the corresponding Wittig reagents. Consequently, less reactive (bulkier) and enolizable carbonyl compounds can be readily olefinated; 2) the Tebbe reagent is stable in solution and reacts at low temperature with the various carbonyl groups in the following order: aldehydes>ketones>esters>amides; 3) acid halides and anhydrides do not undergo methenylation. Instead, the corresponding titanium enolates are formed, which can be used in subsequent *aldol reactions*;[21] 4) only methenylations can be performed; higher alkenyl groups cannot be introduced with this method; 5) a wide range of functional groups are tolerated. However, the presence of the Lewis acidic aluminum may cause complications with certain substrates. The thermal decomposition of dimethyltitanocene also generates titanocene methylidene without the Lewis acidic aluminum, and it is capable of olefinating very sensitive substrates such as anhydrides, silyl esters, and acylsilanes.[18] This method is known as the *Petasis-Tebbe olefination* or *Petasis olefination*.[3]



Mechanism:[4,22,7,23-30]

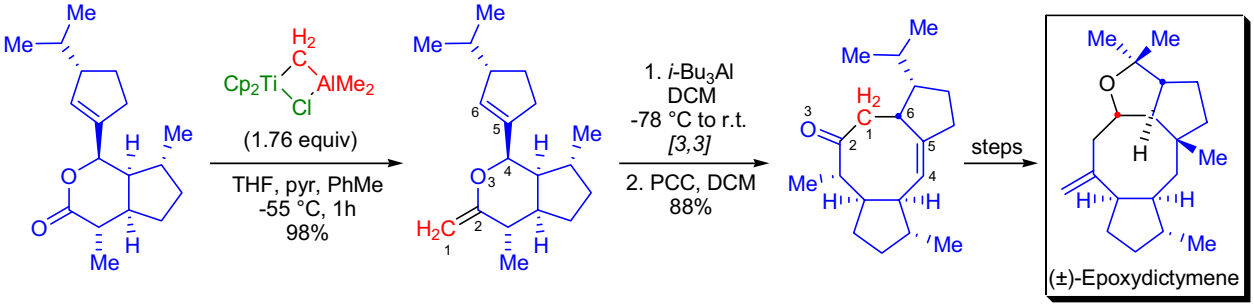
The active species in the *Tebbe olefination* is believed to be the nucleophilic (Schrock-type) titanocene methylidene, which is formed from the Tebbe reagent upon coordination of the aluminum with a Lewis base (e.g., pyridine). This methylidene in its uncomplexed form, however, has never been isolated or observed spectroscopically owing to its extreme reactivity. The same intermediate can also be generated by other means.[4] The titanocene methylidene reacts with the carbonyl group to form an oxatitanacyclobutane intermediate that breaks down to titanocene oxide and the desired methenylated compound (alkene). The driving force is the formation of the very strong titanium-oxygen bond.



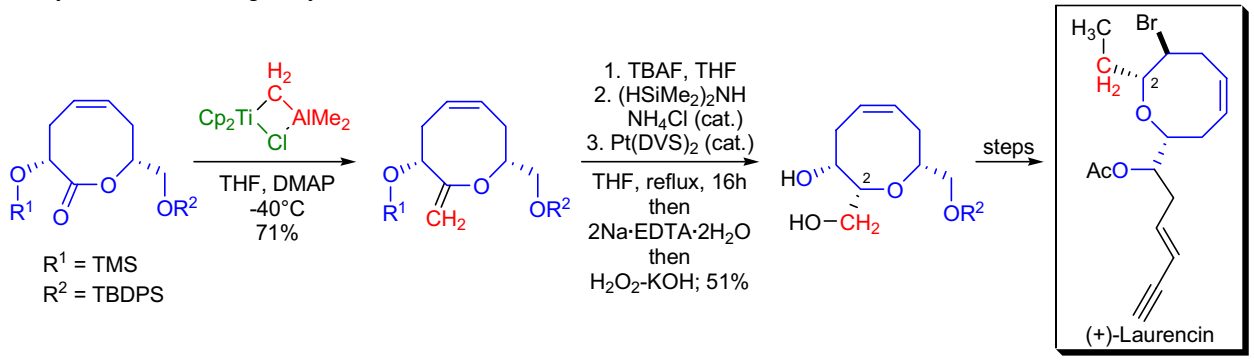
TEBBE OLEFINATION / PETASIS-TEBBE OLEFINATION

Synthetic Applications:

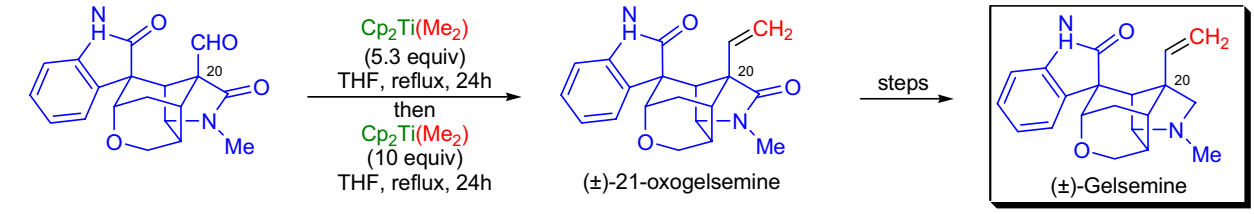
The enantioselective total synthesis of the cyclooctanoid natural product (+)-epoxydictymene was accomplished in the laboratory of L.A. Paquette.[31] The entire tricyclic framework was constructed by the application of a *Claisen rerrangement* via a chairlike transition state. The precursor for this *[3,3]*-sigmatropic rearrangement was obtained by treating a lactone precursor with the solution of the Tebbe reagent in the presence of pyridine. The corresponding enol ether was formed in almost quantitative yield, and immediately after isolation it was treated with triisobutylaluminum to effect the *Claisen rearrangement*.



The unsaturated medium ring ether (+)-laurencin was synthesized by A.H. Holmes and co-workers.[32] Halfway into the synthetic sequence the ethyl side chain had to be introduced at C2. This task was accomplished by using sequential *Tebbe methenylation*, *diastereoselective intramolecular hydrosilation*, and displacement of a primary tosylate with dimethyl cuprate. The eight-membered lactone was exposed to the Tebbe reagent in the presence of DMAP to afford the cyclic enol ether in good yield.



In the final step of the total synthesis of ( )-21-oxogelsemine and ( )-gelsemine by D.J. Hart et al., the introduction of the C20 vinyl group was unsuccessful when the cagelike aldehyde was treated with (methylidene)triphenylphosphorane (*Wittig reaction*).[33] This failure was attributed to two factors, namely, steric hindrance and neighboring group participation of the oxindole carbonyl group. However, when the Petasis reagent was used in refluxing tetrahydrofuran, the desired olefin was obtained in 87% yield. Since ( )-21-oxogelsemine has been converted to ( )-gelsemine before, this synthesis was also a formal total synthesis of ( )-gelsemine.



It is possible to methenylate the carbonyl group of amides and lactams provided that the nitrogen atom is substituted with an electron-withdrawing group. This was the case when A.R. Howell and co-workers successfully converted a wide range of *N*-substituted -lactams to the corresponding 2-methyleneazetidines.[34] In the two examples it is noteworthy that the -lactam carbonyl group reacted preferentially in the presence of the ester carbonyl group.



TISHCHENKO REACTION

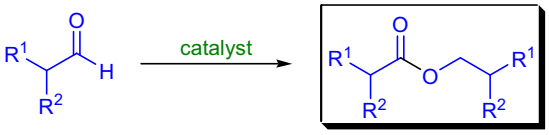
(References are on page 694)

Importance:

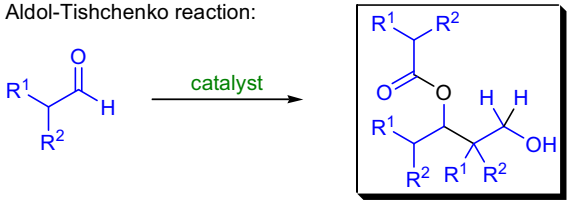
[*Seminal Publications*[1-9]*; Reviews*[10-12]*; Modifications & Improvements*[13-27]*;Theoretical studies*[28]]

In 1887, L. Claisen reported the formation of benzyl benzoate from benzaldehyde in the presence of sodium alkoxides.[1] Nearly thirty years later, W.E. Tishchenko found that both enolizable and non-enolizable aldehydes can be converted to the corresponding esters in the presence of magnesium- or aluminum alkoxides.[2-9] The reaction involves a hydride shift from one aldehyde to another that leads to the formation of the ester product. This transformation is known today as the *Tishchenko reaction*. The general features of the reaction are: 1) in the traditional transformation, the reaction takes place between the same aldehydes;[11] 2) in the *crossed Tishchenko reaction*, two different aldehydes are reacted to form the ester product;[13] 3) the reaction can take place in an intramolecular fashion, yielding the corresponding lactone;[21] and 4) common side reactions are the *aldol reaction*, *Cannizzaro reaction*, *Merwein-Ponndorf-Verley reduction,* and *Oppenauer oxidation*.[11] The most general catalysts in the traditional *Tishchenko reaction* are aluminum alkoxides, but a wide-variety of catalysts can be used:[11] 1) alkali- and alkali earth metal oxides[26] and alkoxides;[18] 2) transition metal-based catalysts such as ruthenium complexes ($RuH_2(PPh_3)_4$;[22] certain rhodium-,[18] iridium-,[19] and iron complexes,[14,15] and metallocenes of group IV metals (Cp_2MH_2 M = Hf, Zr);[22] and 3) lanthanide based catalyst such as lanthanide amides ($Ln[NSiMe_2)_3]$, Ln = La, Sm, Y),[24] organolanthanoid halides (EtLnX, Ln = Pr, Nd, Sm, X = I)[16] and SmI_2.[17] A modification of the *Tishchenko reaction* is the *aldol-Tishchenko reaction* where the aldehyde first undergoes an aldol reaction followed by the *Tishchenko reaction* to form monoesters of 1,3-diols.[11,12] In the *homo aldol-Tishchenko reaction*, the same aldehyde molecules react.[29] In the *hetero aldol-Tishchenko reaction*, a ketone or aldehyde reacts with two equivalents of a different aldehyde over the catalyst.[23,25] The most widely used modification of the *Tishchenko reaction* is the *Evans-Tishchenko reaction*.[20] In this transformation, a chiral β-hydroxy ketone reacts with an aldehyde in the presence of catalytic SmI_2 to provide the *anti* 1,3-diol monoester product with excellent diastereoselectivity.

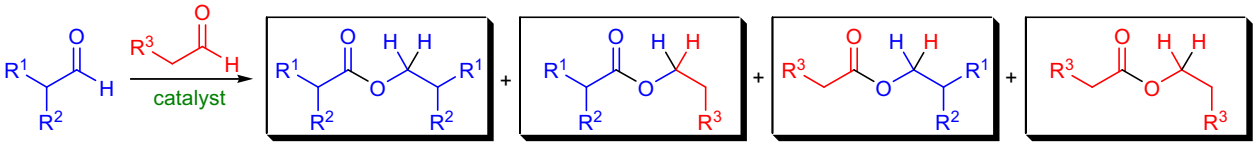
Traditional Tishchenko reaction:



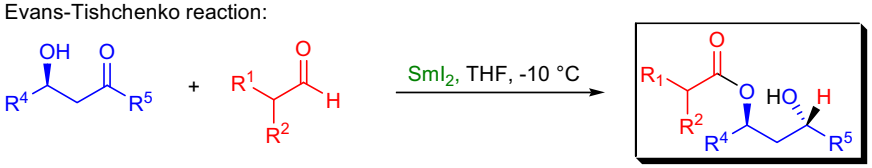
Aldol-Tishchenko reaction:



Crossed- (mixed-) Tishchenko reaction:



Evans-Tishchenko reaction:

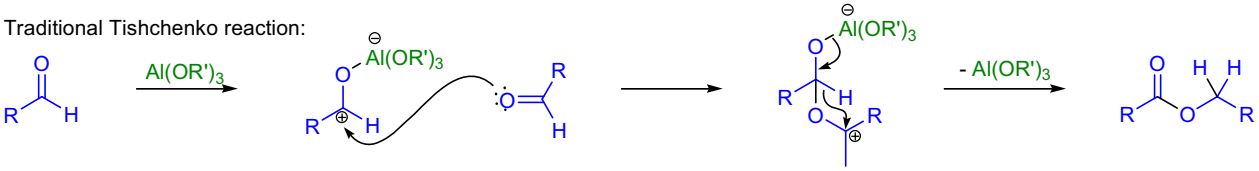


R^1, R^2, R^3 = H, alkyl, aryl; R^4, R^5 = alkyl, aryl; catalyst: $AlOR_3$; NaOR; MO, M = Ba, Sr, Mg; $RuH_2(PPh_3)_4$; $[\eta^4\text{-}C_4Ph_4\text{-}CO)Ru(CO)_3]_2$; $CpMH_2$, M = Hf, Zr; $Na_2Fe(CO)_4$; $ROIr(CO)(PPh_3)_2$; $Ln[N(SiMe_2)_3]$, Ln = La, Sm, Y; EtLnI, Ln = Pr, Nd, Sm; SmI_2

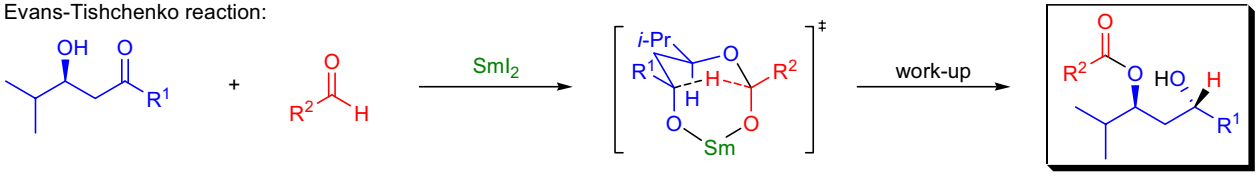
Mechanism:[13,30,31,22,11]

The mechanism of the Tishchenko reaction was extensively studied and there were three different mechanisms proposed. The most commonly accepted mechanism is depicted below.[13] According to this proposal, first the aluminum alkoxide coordinates to the aldehyde. This is followed by the attack of a second molecule of aldehyde. Subsequent hydride shift leads to the regeneration of the catalyst and formation of the product.

Traditional Tishchenko reaction:



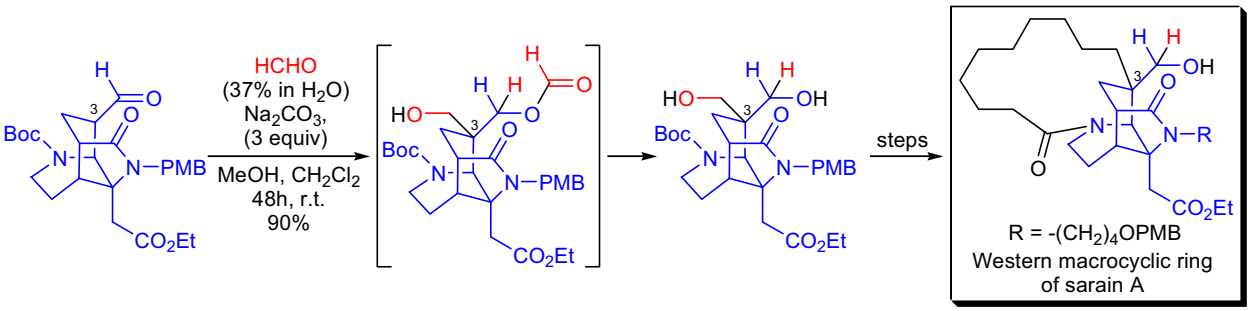
Evans-Tishchenko reaction:



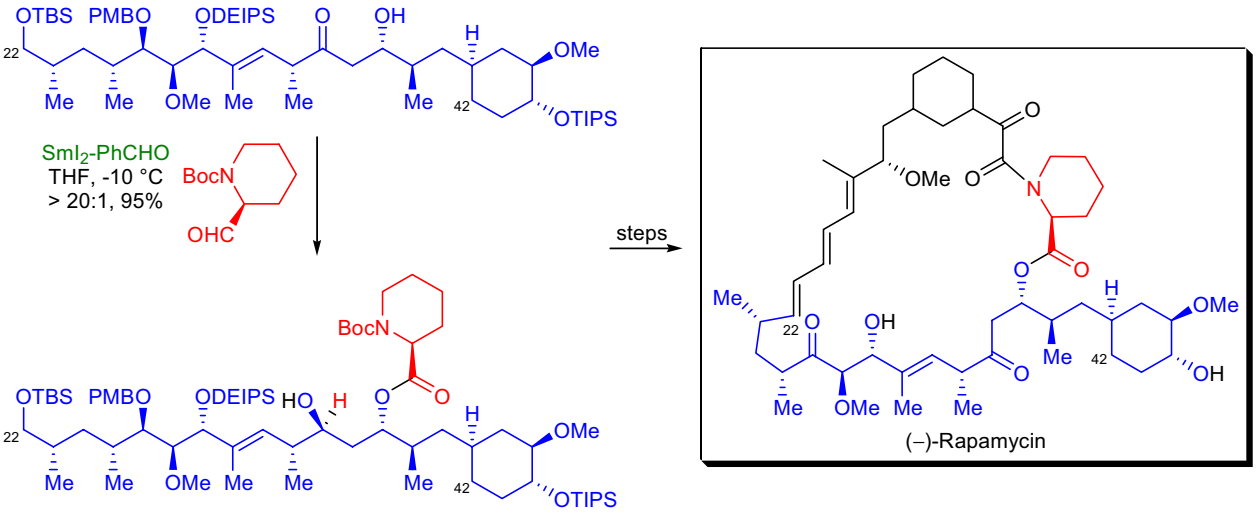
TISHCHENKO REACTION

Synthetic Applications:

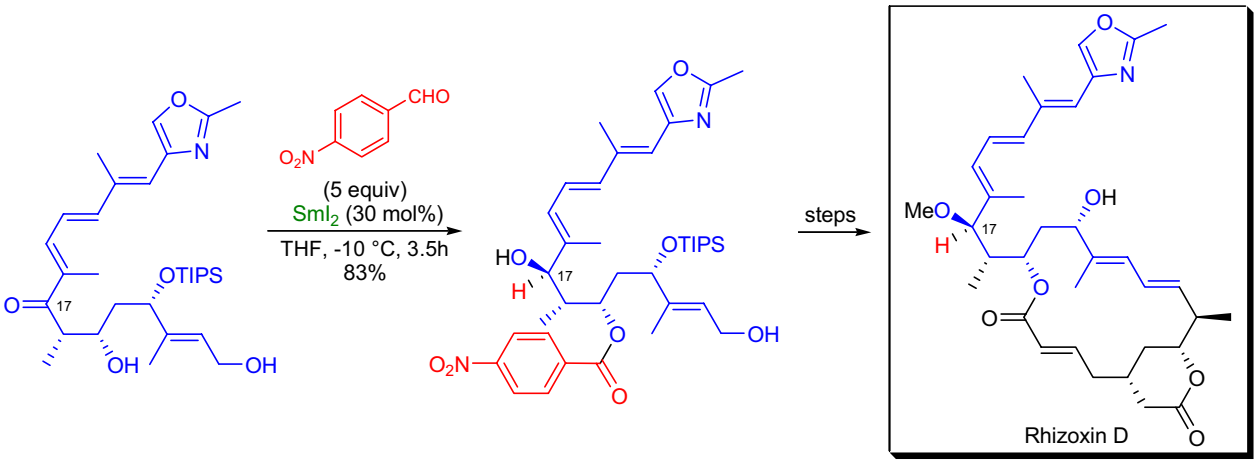
Sarains A-C are a family of alkaloids isolated from marine sponges. J.K. Cha and co-workers accomplished the synthesis of the western macrocyclic ring of sarain A.[32] To establish the C3 quaternary stereocenter, they treated the aldehyde substrate with formaldehyde in the presence of sodium carbonate. The aldehyde substrate underwent an *aldol reaction* followed by a *Tishchenko reaction* to provide the formate ester of the 1,3-diol product. This ester was hydrolyzed *in situ* under the reaction conditions and the 1,3-diol was isolated.



S.L. Schreiber and co-workers accomplished the total synthesis of (–)-rapamycin.[33] In their approach, they utilized an *Evans-Tishchenko reaction* of C22-C42 fragment and Boc pipecolinal. The reaction provided the product with excellent yield and as a >20:1 mixture of the *anti* and *syn* diastereomers.



Rhizoxin D, a natural product possessing potent antitumor and antifungal activity, was synthesized by J.W. Leahy and co-workers.[34] To establish the C17 stereocenter, they utilized the *Evans-Tishchenko reaction.* To this end, the 3-hydroxyketone substrate was reacted with *p*-nitrobenzaldehyde in the presence of catalytic SmI_2. The reaction yielded the monoester of the *anti* 1,3-diol as a single product.



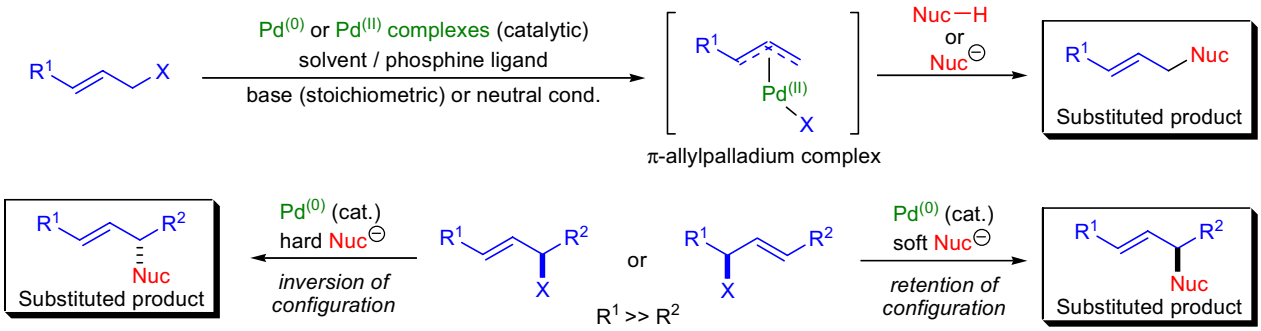
TSUJI-TROST REACTION / ALLYLATION

(References are on page 695)

Importance:

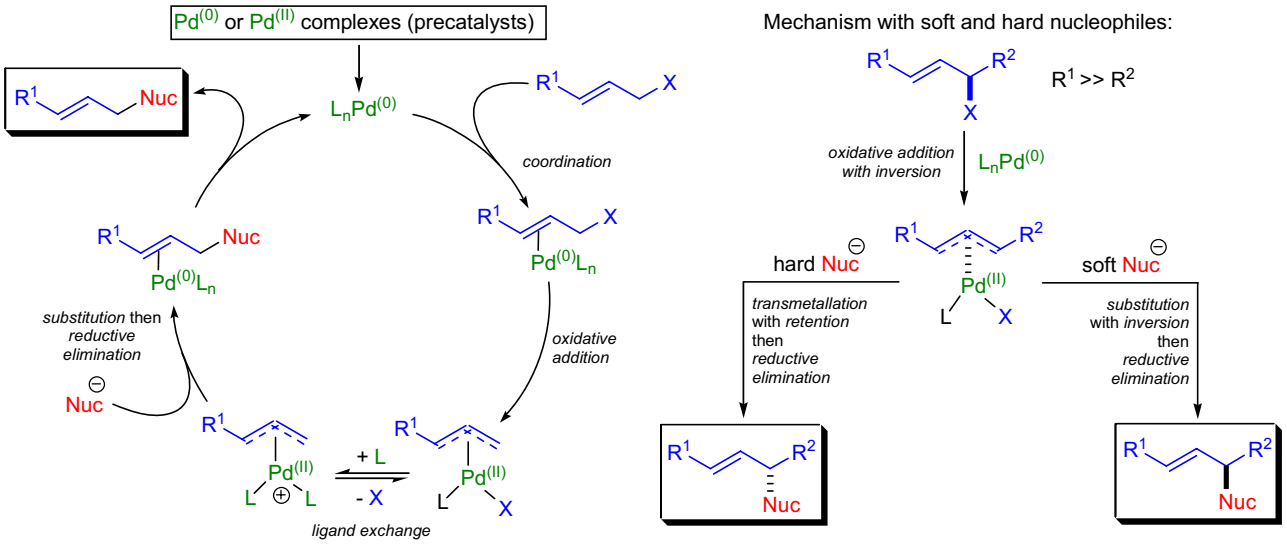
[*Seminal Publications*[1-4]; *Reviews*[5-24]; *Modifications & Improvements*[25-30]; *Theoretical Studies*[31-37]]

In 1965, J. Tsuji demonstrated that π-allylpalladium chloride could be substituted with certain nucleophiles such as enamines and the anions derived from diethyl malonate and ethyl acetoacetate.[1] Soon after this initial report, the catalytic version of this transformation was developed.[2] In 1973, B.M. Trost reported that alkyl-substituted π-allylpalladium complexes could be alkylated with soft carbon nucleophiles with complete regio- and stereoselectivity. However, hard nucleophiles (e.g., alkylithiums, alkylmagnesium halides) failed to react.[4] The Pd-catalyzed allylation of carbon nucleophiles with allylic compounds *via* π-allylpalladium complexes is called the *Tsuji-Trost reaction*. The general features of this transformation are: 1) a wide range of leaving groups (X) can be utilized to form π-allylpalladium complexes (e.g., halides, acetates, ethers, sulfones, carbonates, carbamates, epoxides, and phosphates); 2) there is a marked difference in the reactivity of the various leaving groups with the following trend: Cl > OCO_2R > OAc >> OH; 3) in the case of most substrates, the use of a stoichiometric amount of base is necessary to generate the soft nucleophiles. However, allylic carbonates undergo decarboxylation, and in the process a sufficiently basic alkoxide is formed so no extra base is needed; 4) the range of possible soft carbon nucleophiles is also wide: active methylene compounds with two electron-withdrawing groups (R^3 and R^4), enamines and enolates; 5) the catalytically active $Pd^{(0)}$ species is introduced in either the form of $Pd^{(0)}$ or by the *in situ* reduction of $Pd^{(II)}$ complexes; 6) the addition of the nucleophiles to the unsymmetrical π-allylpalladium complexes is regioselective and favors the least substituted allyl terminus regardless of the initial position of the leaving group; 7) occasionally the regioselectivity can be influenced by the nature of the ligand and the nucleophile; 8) *bis* allylic substrates having two different leaving groups can be substituted with high regioselectivity; and 9) optically active substrates are substituted by soft nucleophiles with an overall retention of configuration (double inversion), while hard nucleophiles give rise to products with an overall inversion of configuration (π-allylpalladium complexes are transmetallated). Nitrogen-, oxygen-, and sulfur-based soft nucleophiles can also be used in *Tsuji-Trost allylation* reactions.



R^{1-2} = H, alkyl, aryl; X = OH, OPh, OCOR, OCONHR, OCO_2R, $OP(O)(OR)_2$, Cl, NO_2, SO_2Ph, NR_2, NR_3X, SR_2X
soft Nuc-H = $R^3R^4CH_2$, enamines, enolates; R^{3-4} = CO_2R, CN, NO_2, SO_2Ph, COR, NC, N=(CMe_2), SPh, alkenyl
Pd-complexes: $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $[Pd(allyl)Cl]_2$; ligands: PPh_3, dba

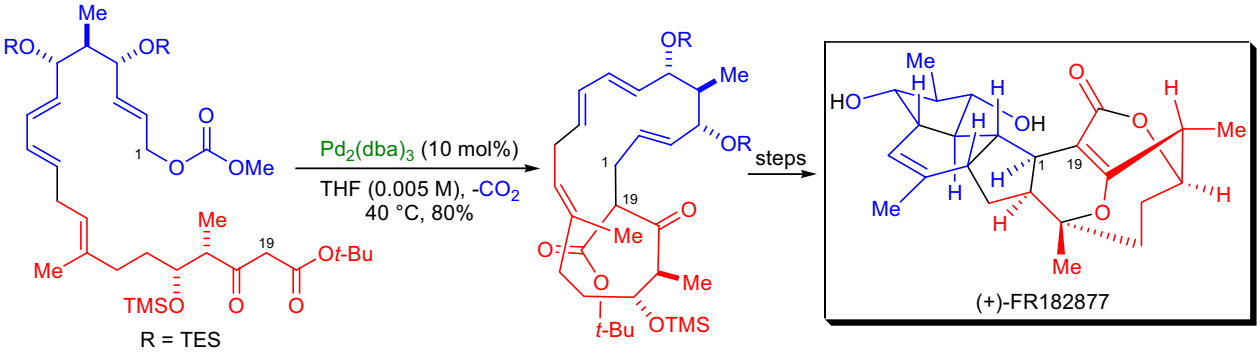
Mechanism:[38,5,39,40]



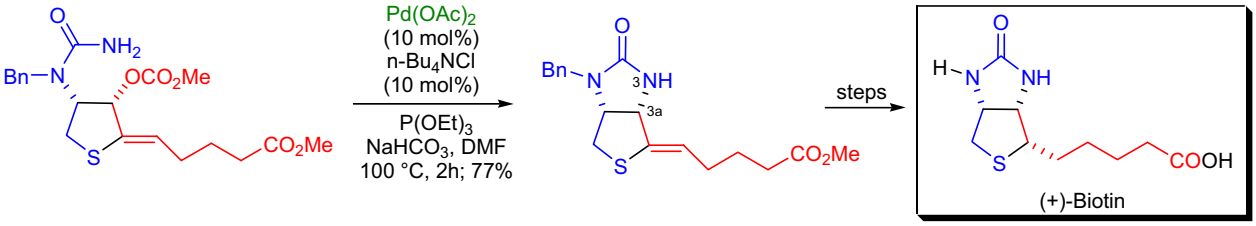
TSUJI-TROST REACTION / ALLYLATION

Synthetic Applications:

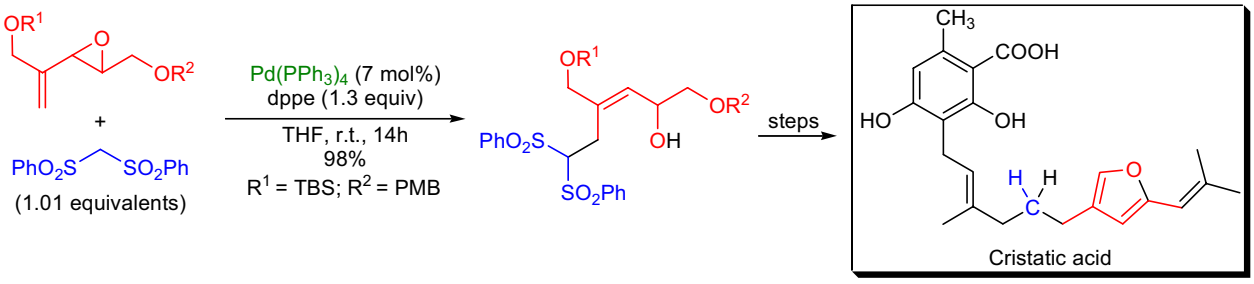
The scalable total synthesis of the cytotoxic natural product (+)-FR182877 was accomplished in the laboratory of E.J. Sorensen.[41] The key steps of the synthetis were an *intramolecular Tsuji-Trost allylation* to prepare the 19-membered macrocyclic pentaene followed by a double *transannular Diels-Alder cycloaddition* to obtain the desired pentacyclic structure. The allylic carbonate was exposed to 10 mol% of the Pd-catalyst under high dilution conditions in THF. The new bond between C1 and C19 was formed with complete diastereoselectivity and in good yield, although the configuration at C19 was not determined.



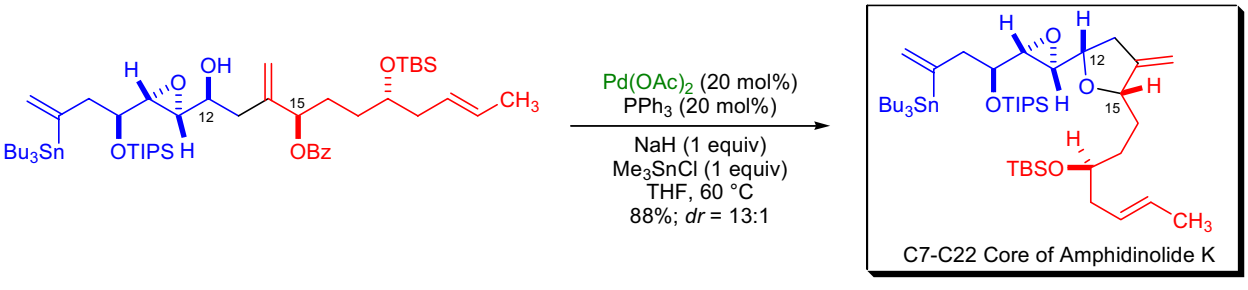
The water soluble vitamin (+)-biotin was synthesized by M. Seki and co-workers from L-cysteine in only 11 steps using inexpensive reagents and mild reaction conditions.[42] The key ring forming step was an *intramolecular allylic amination* (*Tsuji-Trost reaction* using a nitrogen nucleophile) of a *cis* allylic carbonate. As expected with a soft nucleophile, the allylation took place with an overall retention of configuration.



The first total synthesis of cristatic acid, a compound of considerable cytotoxic activity, was reported by A. Fürstner et al.[43] The disubstituted furan moiety was constructed by the *Tsuji-Trost allylation* of a vinyl epoxide intermediate by *bis*(phenylsulfonyl)methane. The resulting 1,4-diol was obtained in an almost quantitative yield.



The *Tsuji-Trost reaction* using an oxygen-based soft nucleophile was applied to the synthesis of *cis*-2,5-disubstituted-3-methylenetetrahydrofurans in the laboratory of D.R. Williams.[44] This method was the basis for the preparation of the C7-C22 core of amphidinolide K. The addition of Me_3SnCl served two purposes: it accelerated the reaction and insured that the oxygen was strongly nucleophilic during the ring-closure, and it suppressed an undesired acyl migration.



TSUJI-WILKINSON DECARBONYLATION REACTION

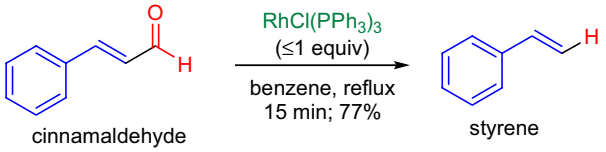
(References are on page 696)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-18]]

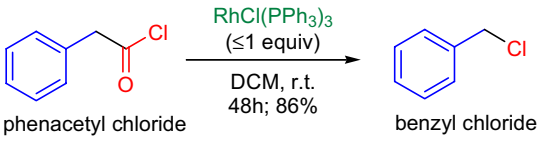
In 1965, J. Tsuji and K. Ono reported that aldehydes reacted with a stoichiometric amount of chloro-*tris*(triphenylphosphine)rhodium (Wilkinson's catalyst) to form chloro-carbonyl*bis*(triphenylphosphine)rhodium and the corresponding C-H compound.[1] Numerous aliphatic, aromatic, and α,β-unsaturated aldehydes were decarbonylated in good yield at or above room temperature. A few years later, the method was extended to the decarbonylation of acyl halides that afforded the corresponding halides.[3] The decarbonylation of aldehydes and acyl halides using Wilkinson's catalyst is known as the *Tsuji-Wilkinson decarbonylation reaction*. The general features of this transformation are:[7,10] 1) several transition metal complexes (e.g., Pd-complexes)[17] are capable of decarbonylating aldehydes and acyl halides, but the most efficient complex was found to be Wilkinson's catalyst; 2) the catalyst is employed in stoichiometric amounts, but the resulting carbonyl complex can be isolated and the catalyst recovered; 3) if the reaction temperature is raised above 200 °C, the reaction becomes catalytic because carbon monoxide is released from the coordination sphere of the rhodium, and the catalyst is regenerated; 4) the substrate can be an aldehyde, acyl halide, acyl cyanide,[16] or 1,2-diketone;[13] 5) for aliphatic substrates the order of reactivity is primary>secondary>tertiary; 6) in most cases the reaction takes place under mild conditions and at relatively low temperature (room temperature or at reflux temperature of the applied solvent); 7) the decarbonylation is stereospecific: the configuration of the stereocenter to which the formyl group is attached to is retained;[19] 8) the decarbonylation of α,β-unsaturated substrates proceeds without interference from the double bond; and 9) if the acyl halide contains β-hydrogen atoms the final product is an alkene rather than an alkane due to facile β-elimination.

Tsuji & Ono (1965):



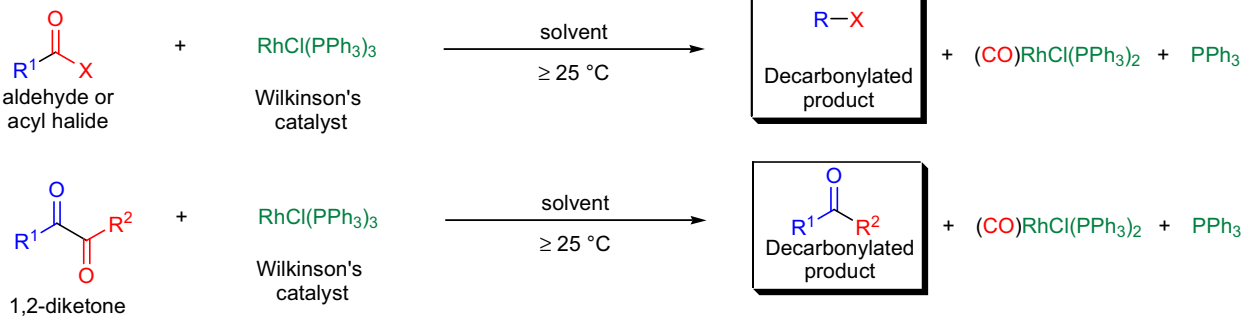
cinnamaldehyde — styrene

Tsuji & Ono (1968):



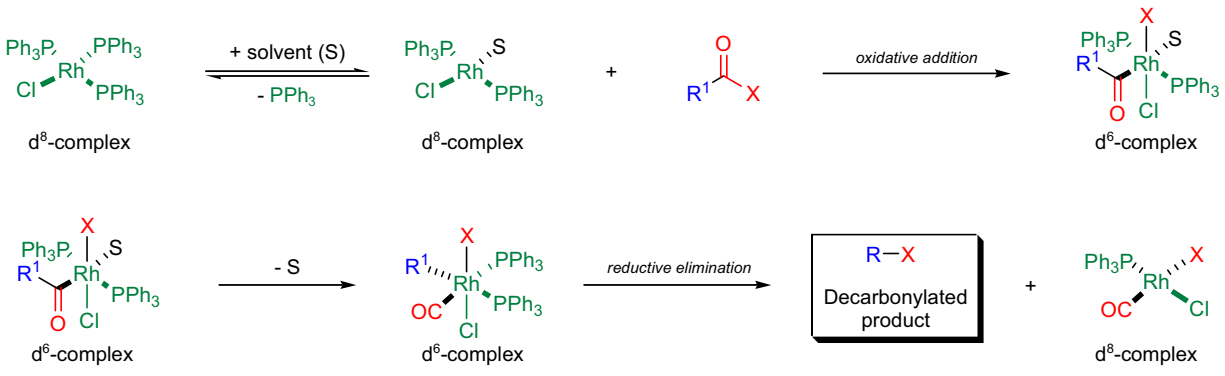
phenacetyl chloride — benzyl chloride

Tsuji-Wilkinson decarbonylation:



R^1 = 1°, 2° and 3° alkyl, aryl, alkenyl; X = H, Cl, Br, CN, CO-alkyl, CO-aryl, CH_2CO_2Me; R^2 = alkyl, aryl, alkenyl; solvent: C_6H_6, toluene, xylenes, acetonitrile, benzonitrile, DCM

Mechanism:[20-27,10]



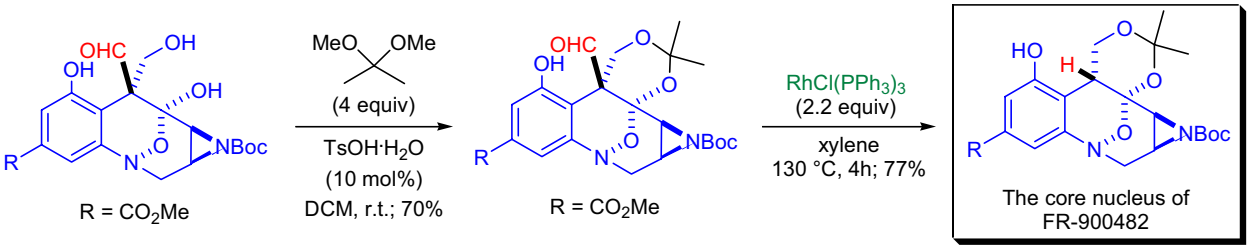
d8-complex — d8-complex — d6-complex

d6-complex — d6-complex — d8-complex

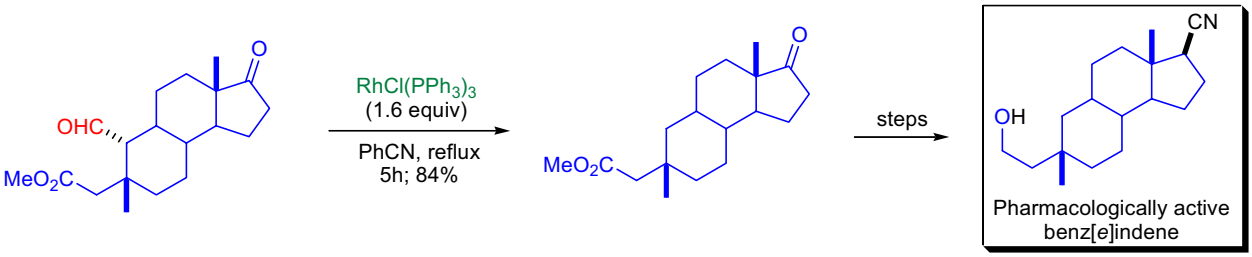
TSUJI-WILKINSON DECARBONYLATION REACTION

Synthetic Applications:

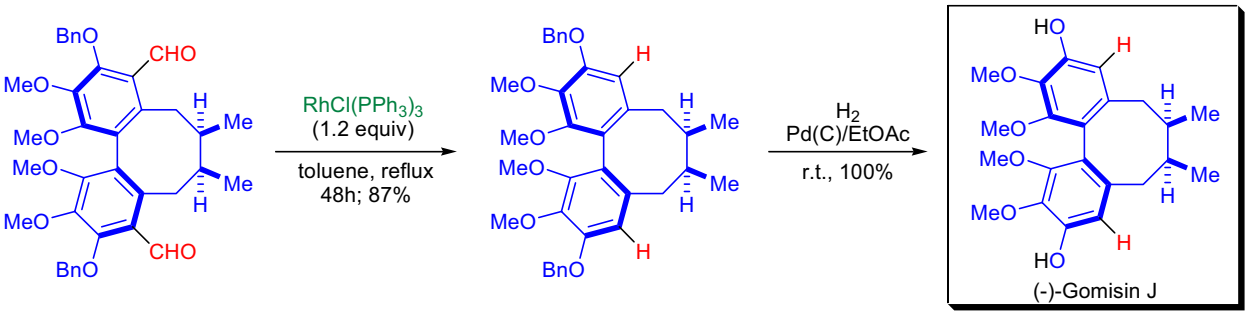
In the laboratory of F.E. Ziegler, the synthesis of the core nucleus of FR-900482 was accomplished.[28] In the final stages of the synthetic effort, the removal of the formyl group from the C7 quaternary center was necessary. The authors chose the *Tsuji-Wilkinson decarbonylation protocol* to effect the transformation. The 1,3-diol functionality was protected as the acetonide prior to the decarbonylation. Usually the rate of decarbonylation is slowest for aldehydes that have the formyl group attached to a quaternary carbon, so it was necessary to use more than two equivalents of the catalyst to effect the decarbonylation at the reflux temperature of xylene.



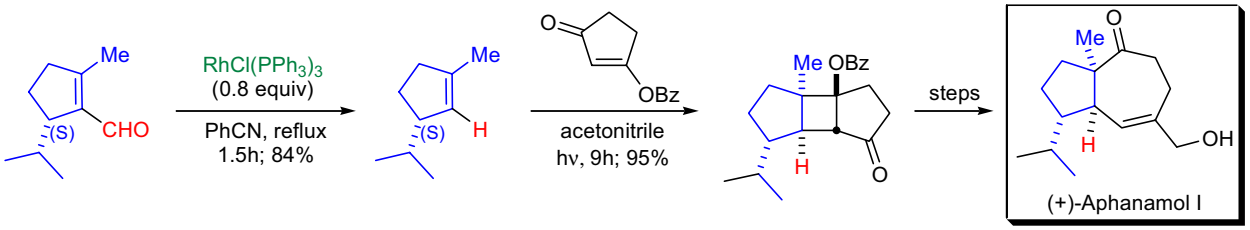
The research team of D.F. Covey developed a synthetic route to convert 5β-methyl-3-ketosteroids into 7(S)-methyl substituted analogues of neuroactive benz[*e*]indenes.[29] The synthesis began with 19-nortestosterone, in which the α,β-unsaturated cyclic ketone moiety was degraded to afford a tricyclic aldehyde. This aldehyde was unstable and could not be stored. For this reason it was immediately subjected to the *Tsuji-Wilkinson decarbonylation* to afford the decarbonylated product in high yield.



The total synthesis of (–)-gomisin J, a biologically active dibenzocyclooctane lignan, was completed by M. Tanaka and co-workers.[30] At the end of the synthesis, the removal of two aromatic formyl groups was needed. The exposure of the dialdehyde substrate to a little more than one equivalent of Wilkinson's catalyst and heating at reflux for two days afforded the deformylated product in excellent yield. The removal of the benzyl groups under catalytic hydrogenation conditions provided the natural product. Interestingly, the authors found that the decarbonylation could also be achieved *via* a *retro-Friedel-Crafts reaction*, which is a successful strategy only with electron-rich aromatic compounds.



The isodaucane sesquiterpene (+)-aphanamol I was synthesized in the laboratory of B. Wickberg using the *DeMayo cycloaddition* as the key step.[31] The required starting material 3(*S*)-isopropyl-1-methylcyclopentene was prepared by the *Tsuji-Wilkinson decarbonylation* of the corresponding α,β-unsaturated aldehyde.



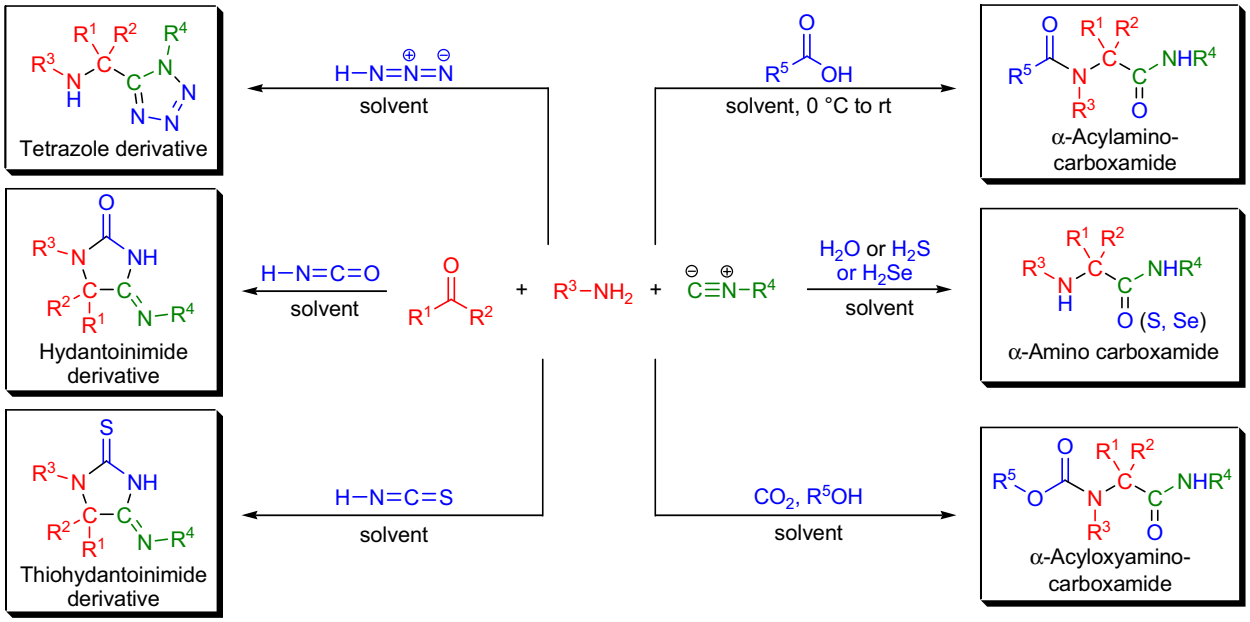
UGI MULTICOMPONENT REACTION

(References are on page 696)

Importance:

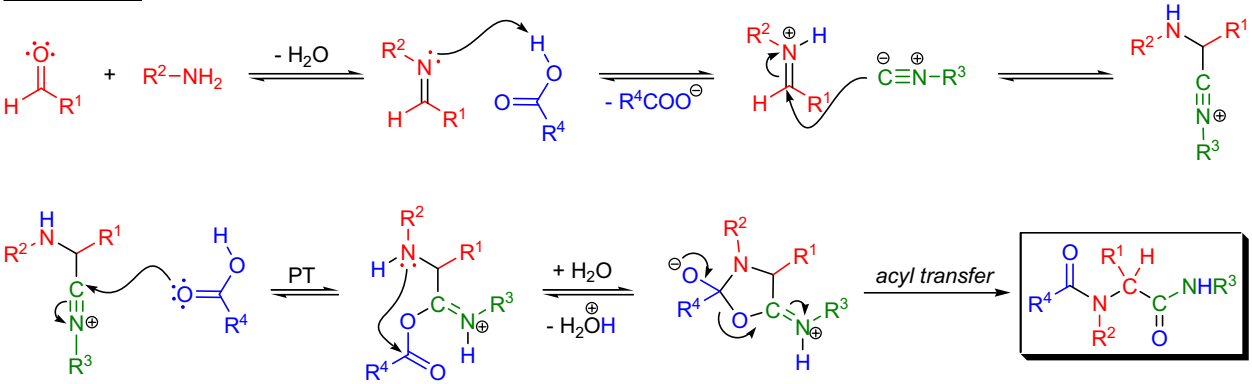
[*Seminal Publications*[1-3]*; Reviews*[4-35]*; Modifications & Improvements*[36-42,28,29,33,35]]

In 1959, I. Ugi reported that isocyanides undergo a four-component reaction (4-CR) in the presence of an amine, aldehyde or ketone and a nucleophile to provide a single condensation product.[1-3] The most commonly used nucleophiles are carboxylic acids, but hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, salts of secondary amines, water, hydrogen sulfide, and hydrogen selenide can also be used.[1-3] Today, this transformation is referred to as the *Ugi four-component reaction* (U-4CR). The general features of the reaction are:[16] 1) it is very easy to carry out, usually, the isocyanide is added to a stirring and well cooled solution of the other three components; 2) in case of less reactive aldehydes and ketones, it is advisable to precondense the carbonyl compounds and the amine to form the imine; 3) as the reaction is very exothermic, adequate cooling is necessary; 4) methanol is generally a suitable solvent, although many other solvents can be used; 5) the reaction typically is carried out between -80 °C to 80 °C and it may take from a few minutes to a week to go to completion; 6) the amine component can be any compound with a sufficiently nucleophilic NH group such as ammonia, primary and secondary amines, hydrazine and derivatives,[36-38,40] diaziridines[42] as well as hydroxylamine;[39] 7) diarylamines are usually not nucleophilic enough to undergo the reaction; 8) with the exception of diarylketones, almost all aldehydes and ketones are suitable for the U-4CR; 9) a wide range of C-isocyanides undergo the transformation; and 10) when nonpolar solvents are used, or the reacting components are bulky, the *Passerini reaction* may occur as a side reaction leading to the formation of α-acyloxycarboxamides.[12] The Ugi reaction is a powerful synthetic transformation, where the four reaction partners are combined in one pot under mild conditions. One of the earliest and most important application of the U-4CR is peptide coupling and α-amino acid synthesis;[4,7-14,17-19,23] Several modifications of the original transformation leading to the formation of heterocyclic compounds were developed.[28,29,33,35] The *Ugi reaction* also found a widespread application in combinatorial chemistry, where the synthetic power of the reaction coupled with modern techniques allows the quick assembly of a large number of molecules from simple starting materials.[20,27,28,31-33]



R^1 = alkyl, aryl; R^2 = H, alkyl; R^3 = alkyl, aryl; R^4 = alkyl, aryl; R^5 = alkyl, aryl; solvent: MeOH, EtOH, CF_3CH_2OH, DMF, $CHCl_3$, CH_2Cl_2,THF, dioxane, Et_2O

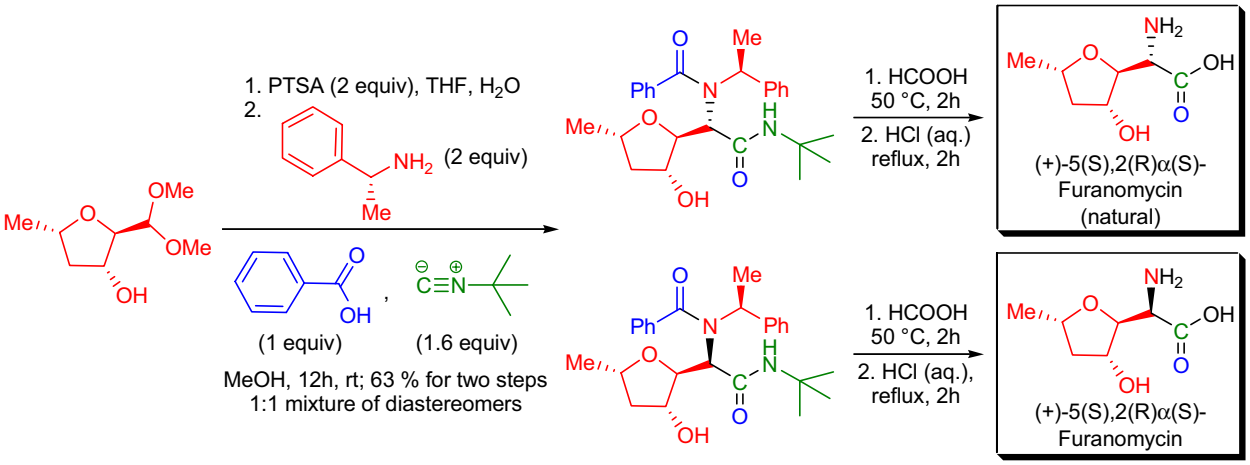
Mechanism:[43-45]



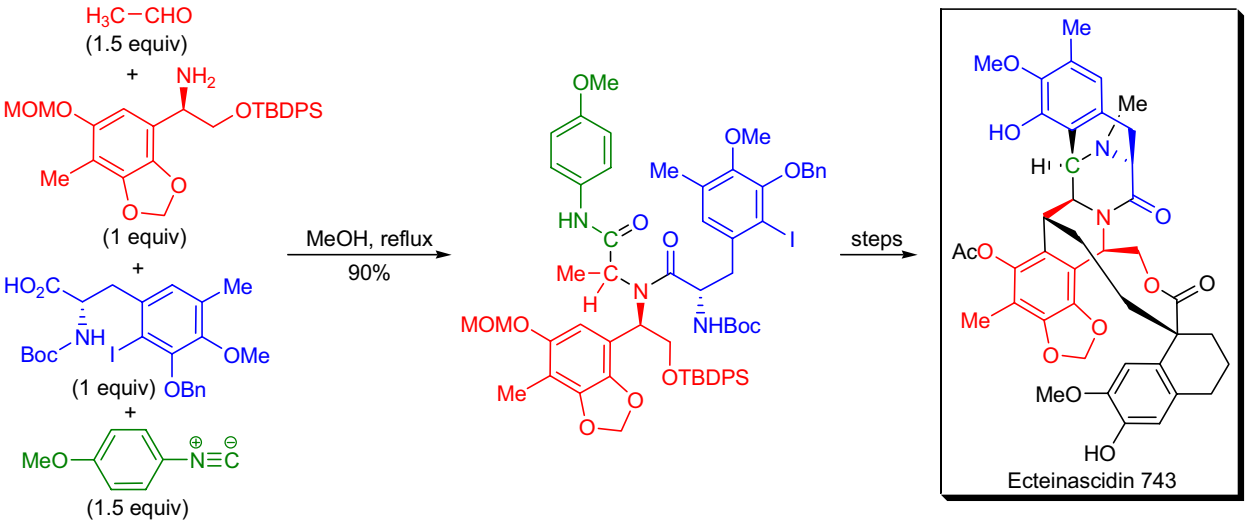
UGI MULTICOMPONENT REACTION

Synthetic Applications:

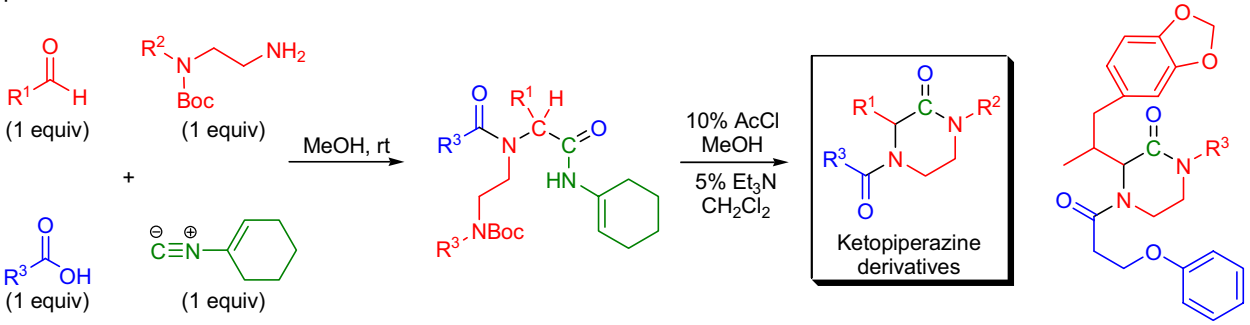
The potential application of the *Ugi four-component reaction* for amino acid and polypeptide natural product synthesis was recognized and utilized early on by M.M. Joullié.[46,47] A representative example is the total synthesis of (+)-furanomycin, a naturally occurring antibiotic. As the exact stereochemistry of the compound was not confirmed, total synthesis of the natural product and its stereoisomers was used to elucidate the stereochemistry.



Ecteinascidin 743 is an extremely potent antitumor agent isolated from a marine tunicate. The total synthesis of this natural product was realized in the laboratory of T. Fukuyama.[48] To achieve the synthesis of the key dipeptide fragment, they utilized the *Ugi four-component reaction*. The transformation was carried out under mild conditions providing the product with excellent yield.



Ketopiperazines are biologically active molecules, they are antagonists of the platelet glycoprotein IIb-IIIa, and they exhibit hypocolesteremic activity.[49,50] The solution phase synthesis of ketopiperazine libraries was achieved by C. Hulme and co-workers using a *Ugi reaction/Boc-deprotection/cyclization* strategy. The four-component coupling was performed in methanol at room temperature. The deprotection and conversion of the enamide into the corresponding methyl ester was effected by acetyl chloride in methanol. Subsequent cyclization in the presence of diethylamine in dichloromethane provided the products with a 30-97% yield for the overall process. A representative ketopiperazine product is shown below.



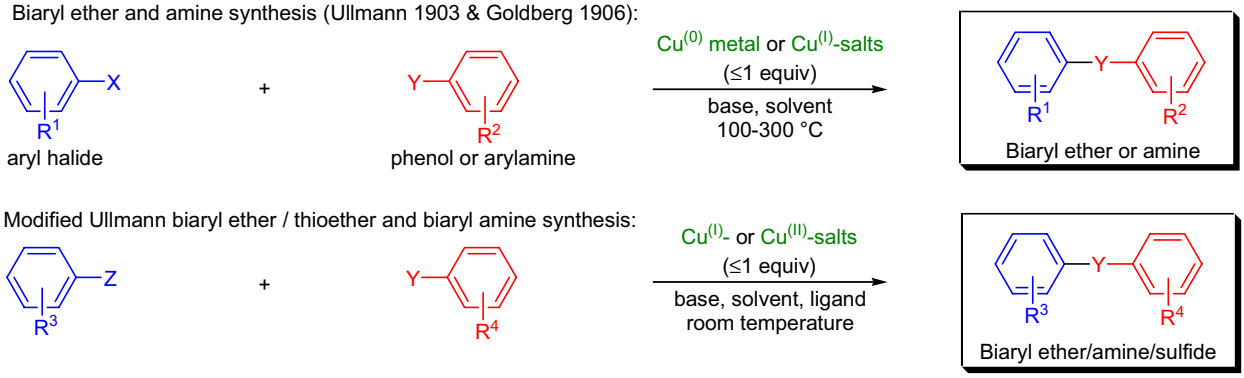
ULLMANN BIARYL ETHER AND BIARYL AMINE SYNTHESIS / CONDENSATION

(References are on page 697)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-46]]

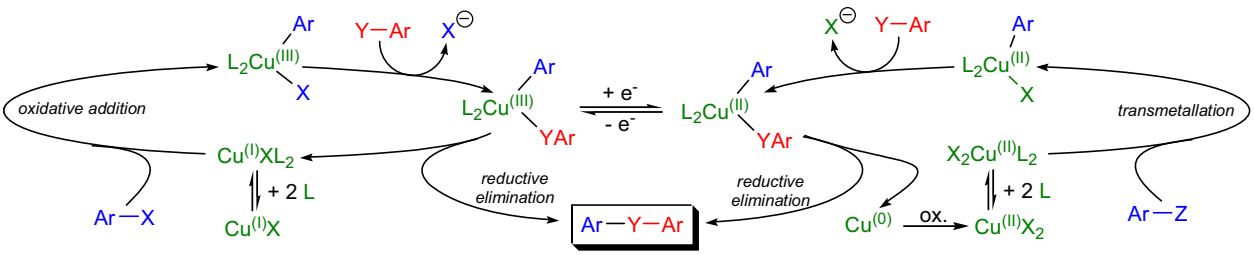
In 1904, F. Ullmann observed that the reaction of aryl halides with phenols to give biaryl ethers was significantly improved in the presence of copper powder.[2] The copper mediated synthesis of biaryl ethers is known as the *Ullmann condensation* (*Ullmann biaryl ether synthesis*). In 1906, I. Goldberg disclosed the copper-mediated formation of an arylamine by reacting an aryl halide with an amide in the presence of K_2CO_3/CuI (*Goldberg reaction*/*Goldberg modified Ullmann condensation*). The general features of the *Ullmann condensation* are: 1) aryl iodides, bromides, and chlorides are all good substrates with the following reactivity trend: I > Br > Cl >> F (the opposite trend is observed in uncatalyzed S_NAr reactions); 2) aryl fluorides usually do not react under the reaction conditions; 3) the introduction of several aryloxy groups is possible in a stepwise manner; 4) the aromatic halide can contain many different substituents and even reactive functional groups (e.g., OH, NH_2, CHO) need not be protected unlike in the *Ullmann biaryl coupling*; 5) electron-withdrawing substituents (e.g., NO_2, CO_2R, COO^-) in the *ortho* and *para* positions have a marked activating effect and the yields for these substrates are excellent; 6) electron-donating substituents anywhere on the aromatic ring do not significantly decrease the reactivity of the aryl halide compared to the unsubstituted aryl halide; 7) the required temperature ranges from 100 to 300 °C in the presence of copper metal or a copper-derived catalyst and with or without the use of solvents; 8) the catalytic activity of the copper depends on the method of preparation; 9) a wide variety of solvents work well and most of them contain a heteroatom with a lone pair of electrons; 10) the solvent helps to solubilize the catalytically active copper species by way of complexation; 11) the phenol component can be introduced in the form of free phenols or phenolate salts; 12) when free phenols are used, a base (K_2CO_3) is added to the reaction mixture, but other salts proved to be ineffective; 13) if Cu_2O or CuO is used instead of copper, no base is required, since these substances serve as bases; and 14) since phenols and phenolates are sensitive to oxidation, the use of an inert atmosphere is often required. There are few typical side reactions of the aryl halide component: 1) *reductive dehalogenation* especially when the phenol is relatively unreactive; 2) *Ullmann biaryl homocoupling*; and 3) exchange of halogens with the Cu(I)-salt. Several modifications have been introduced to improve the somewhat harsh original reaction conditions (high temperatures, often low yields and the use of stoichiometric amounts of copper), which primarily utilize coupling partners other than aryl halides: 1) arylboronic acids in the presence of Et_3N, molecular sieves and $Cu(OAc)_2$ (*Chan-Evans-Lam modification*);[23-25] 2) potassium aryltrifluoroborates (*Batey modification*);[42,43] 3) aryl iodonium salts (*Beringer-Kang modification*);[12,29] 4) aryl lead compounds (*Barton plumbane modification*);[17] and 5) aryl bismuth compounds (*Barton modification*).[15,16,18]



R^{1-4} = H, CN, NO_2, CO_2R, I, Br, Cl, I; X = I, Br, Cl, SCN; Y = OH, NH_2, NHR, NHCOR; solvent: DMF, pyridine, quinoline, DMSO, nitrobenzene, glycol, diglyme, dioxane; base: K_2CO_3, Et_3N, pyridine; $Cu^{(I)}$- and $Cu^{(II)}$-salts: CuI, Cu_2O, $Cu(OAc)_2$; ligand: diamines
When Y = NH_2, OH, SH and Z = $B(OH)_2$ (*Chan-Evans-Lam modification*), Z = BF_3K (*Batey mod.*), Z = $Si(OMe)_3$ or $Sn(alkyl)_3$ (*Lam mod.*), Z = $(I\text{-aryl})^+BF_4^-$ (*Beringer-Kang mod.*), Z = $Pb(OAc)_3$ (*Barton plumbane mod.*), Z = $BiPh_2X_2$ (*Barton mod.*)

Mechanism:[47,16,48,24,49,10]

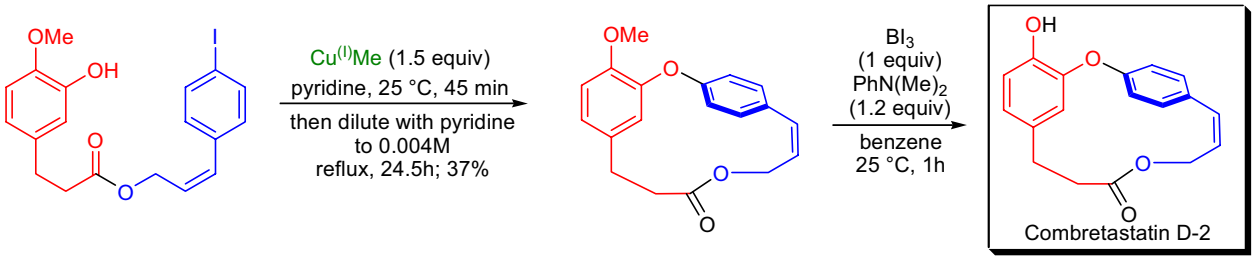
The exact nature (oxidation state) of the Cu-intermediate is not known, but radical mechanisms have been ruled out based on radical scavenger experiments. Two possible (speculated) pathways are shown.



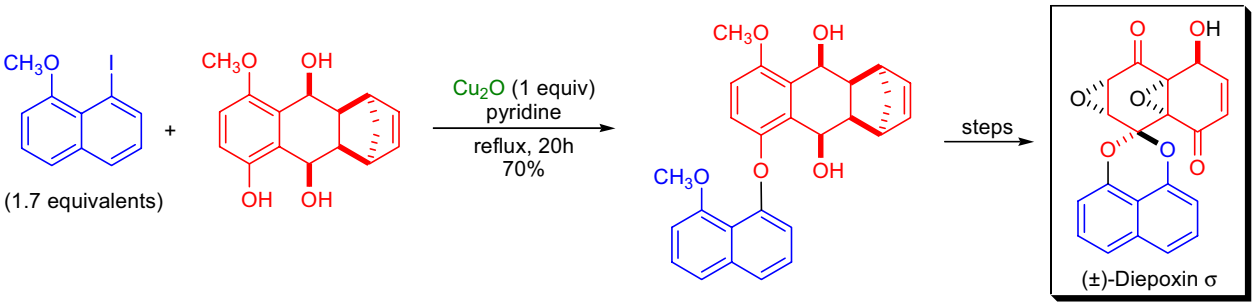
ULLMANN BIARYL ETHER AND BIARYL AMINE SYNTHESIS / CONDENSATION

Synthetic Applications:

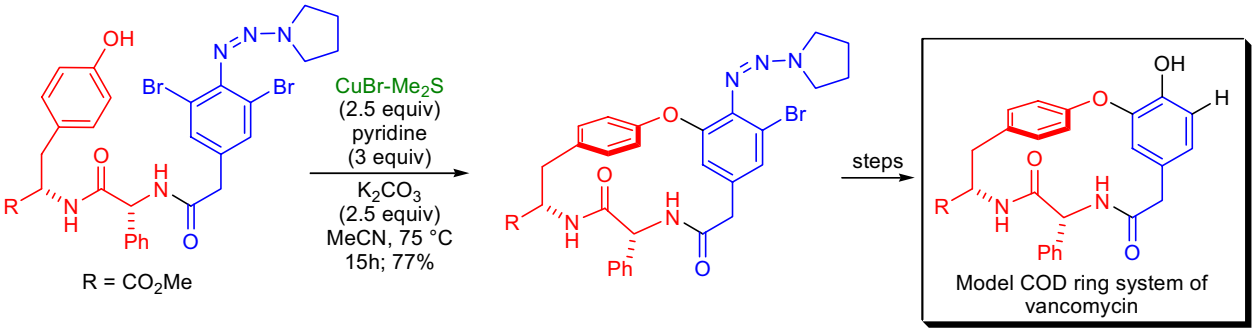
The *intramolecular Ullmann condensation* was used by D.L. Boger and co-workers to form the 15-membered macrocyclic ring of the cytotoxic natural product, combretastatin D-2.[50] This compound possesses unusual meta- and paracyclophane subunits, which are also found in a range of antitumor antibiotics. The first approach where the final step was a *macrolactonization* was unsuccessful, so the researchers chose to form the biaryl ether moiety as the key macrocyclization step. Methylcopper was found to mediate the cyclization and gave moderate yield of the corresponding biaryl ether. Finally *boron triiodide mediated demethylation* afforded the natural product.



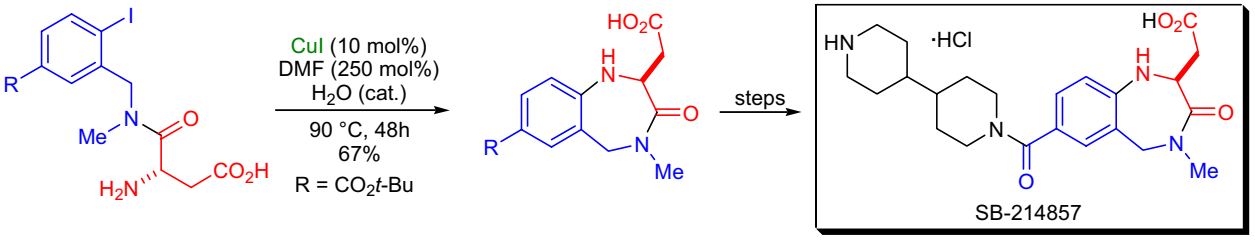
The highly oxygenated antifungal/anticancer natural product (±)-diepoxin σ was prepared in the laboratory of P. Wipf.[51] The coupling of the two substituted naphthalene rings was achieved *via* the *Ullmann condensation* of a phenolic compound with 1-iodo-8-methoxynaphthalene. The aryl iodide coupling partner was used in excess and the condensation was conducted in refluxing pyridine in the presence of a full equivalent of copper(I)-oxide.



In the laboratory of K.C. Nicolaou, a novel mild method for the preparation of biaryl ethers was developed.[22] The di-*ortho*-halogenated aromatic triazenes underwent efficient coupling with phenols in the presence of CuBr. This mild *modified Ullmann condensation* was utilized in the synthesis of the DOE and COD model ring systems of vancomycin.



The *Ullmann biaryl amine condensation* was used in the synthesis of SB-214857, a GPIIb/IIIa receptor antagonist.[52] D. Ma and co-workers coupled aryl halides with β-amino acids and esters under relatively mild conditions using CuI as a true catalyst.



ULLMANN REACTION / COUPLING / BIARYL SYNTHESIS

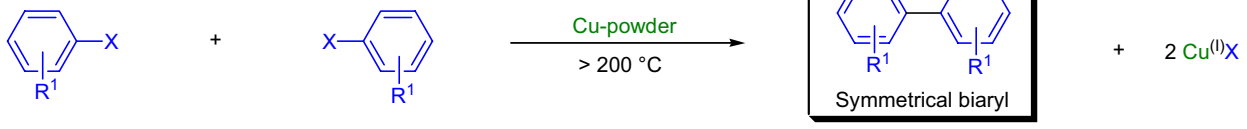
(References are on page 699)

Importance:

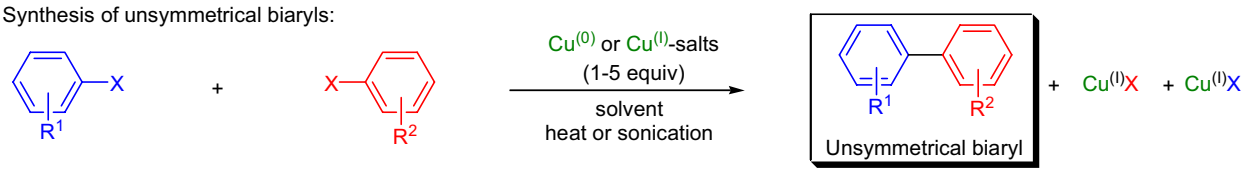
[*Seminal Publications*[1,2]*; Reviews*[3-9]*; Modifications & Improvements*[10-21]]

In 1901, F. Ullmann reported the reaction of two equivalents of an aryl halide with one equivalent of finely divided copper at high temperature (>200 °C) to afford a symmetrical biaryl and copper halide.[1] This condensation of two aryl halides in the presence of copper to give symmetrical or unsymmetrical biaryls is now referred to as the *Ullmann reaction* (*Ullmann biaryl synthesis* or *Ullmann coupling*). Since its discovery, the *Ullmann reaction* has become a general method for the synthesis of numerous symmetrical and unsymmetrical biaryls. The general features of this reaction are: 1) halogenated benzene rings as well as halogenated heteroaromatic compounds are substrates for the coupling; 2) the order of reactivity is I > Br >> Cl, but aromatic fluorides are totally inert; 3) the reaction can take place both inter- and intramolecularly and has been used to form macrocycles (4- to 24-membered rings);[6] 4) electron-withdrawing groups (e.g., NO_2, CO_2Me, CHO) *ortho* to the halogen substituent increase the reactivity of the aryl halide; 5) generally substituents in the *ortho* position, which have a lone pair increase the reactivity regardless whether they are EWG or EDG, but these substituents have no noticeable activating effect in the *meta* or *para* positions;[22] 6) substrates that are very electron rich (e.g., multiple alkyl or alkoxy groups) tend to give lower yield of the biaryl; 7) certain unprotected functional groups (e.g., OH, NH_2, CO_2H, SO_2NH_2) open alternative reaction pathways therefore inhibit the coupling;[23] 8) bulky groups located *ortho* to the halogen tend to retard or inhibit the coupling reaction due to steric hindrance; 9) when unsymmetrical biaryls are prepared, the highest yield is obtained when one of the aryl halides is activated (more electron rich), while the other is less reactive; 10) in order to achieve good results, activated copper (preferably prepared prior to use) must be used;[17] 11) highly active copper metal can be prepared by reducing CuI with lithium naphthalenide or by reducing $CuSO_4$ with Zn powder; 12) usually temperatures over 100 °C are necessary to initiate the coupling but the use of highly active Cu-powder allows lower temperatures; 13) the most common solvent is DMF, but for higher temperatures $PhNO_2$ or *p*-$NO_2C_6H_4CH_3$ are used;[10,11] 14) sonication often improves the efficiency of the coupling;[18,19] 15) Cu(I)-salts (e.g., Cu_2O, Cu_2S) also mediate the coupling although they are less active than the activated copper metal;[12] and 16) Cu(I) thiophene 2-carboxylate (CuTC) was found to be an efficient mediator under mild conditions (usually room temperature) in NMP.[21] There are a few modifications: 1) the reaction conditions of the *Ullmann coupling* become significantly milder when $Ni^{(0)}$ complexes are used in place of copper metal;[13,9] and 2) for the preparation of highly substituted biaryls the use of preformed aryl copper species has been successful (*Ziegler modification*).[16,20]

Synthesis of symmetrical biaryls (Ullmann, 1901):



Synthesis of unsymmetrical biaryls:

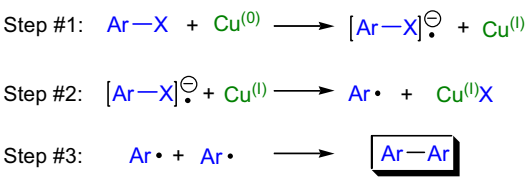


R^1, R^2 = H, CN, NO_2, CO_2R, I, Br, Cl; X = I, Br, Cl, SCN; solvent: DMF, pyridine, quinoline, nitrobenzene, *p*-nitro toluene

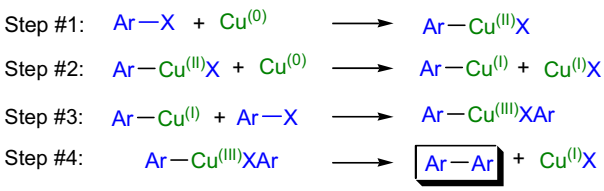
Mechanism:[24-26,14,27-32,9]

The exact mechanistic pathway of the *Ullmann coupling* is not known. There are two main pathways possible: 1) formation of aryl radicals or 2) the formation of aryl copper [$ArCu^{(I)}$, $ArCu^{(II)}$ and $ArCu^{(III)}$] intermediates. Currently the most widely accepted mechanism assumes the formation of aryl copper intermediates, since many of these species can be isolated and they can react with aryl halides to give biaryls.

Pathway involving aryl radicals:



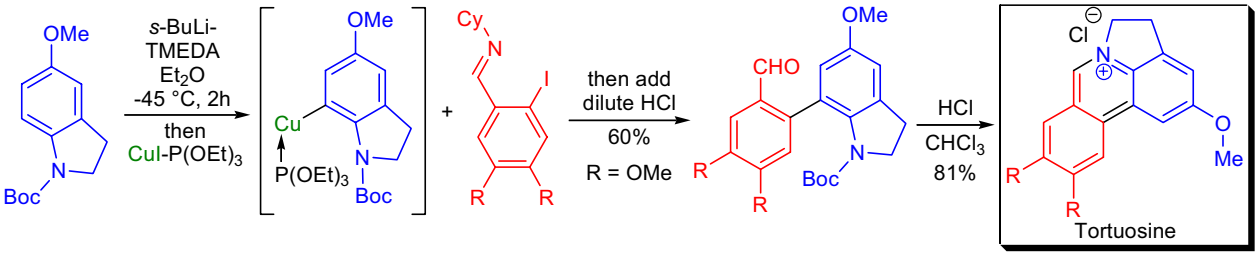
Pathway involving arylcopper intermediates:



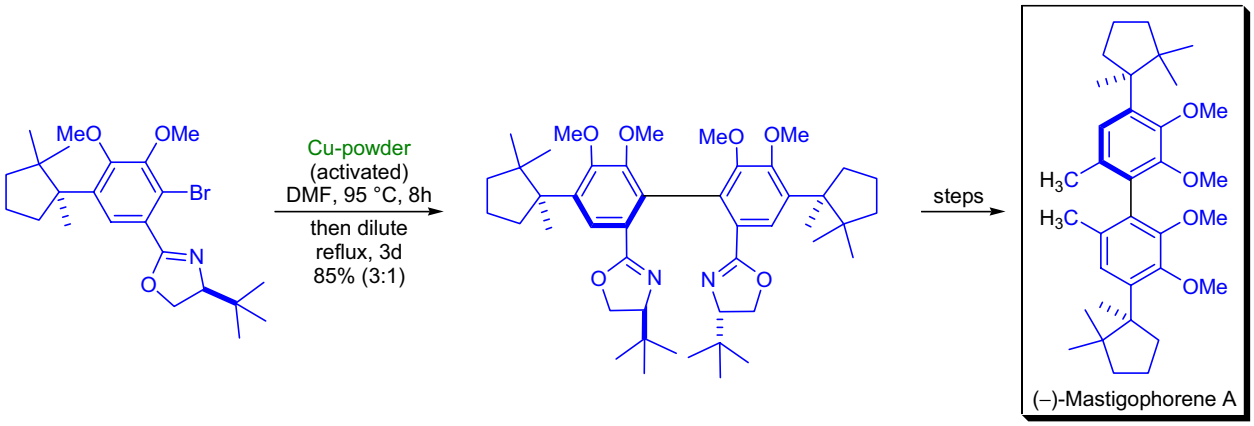
ULLMANN REACTION / COUPLING / BIARYL SYNTHESIS

Synthetic Applications:

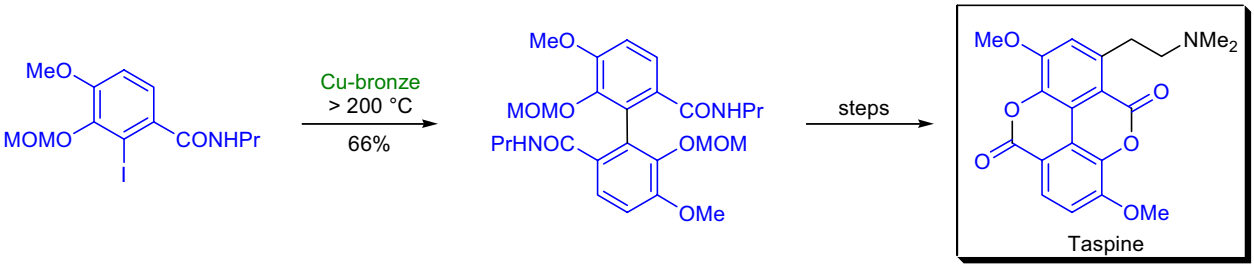
The *Ziegler-modified Ullmann reaction* was used for the total synthesis of pyrrolophenanthridinium alkaloid tortuosine by L.A. Flippin and co-workers.[33] First, *N*-Boc-5-methoxyindoline was lithiated at C7 with *s*-BuLi in the presence of TMEDA, and then it was transmetallated to the corresponding organocopper species that smoothly underwent the *Ullmann reaction* with a 3-iodoaryl imine. The resulting biaryl product was treated with anhydrous HCl in chloroform, which promoted the cyclization followed by dehydration to give the natural product.



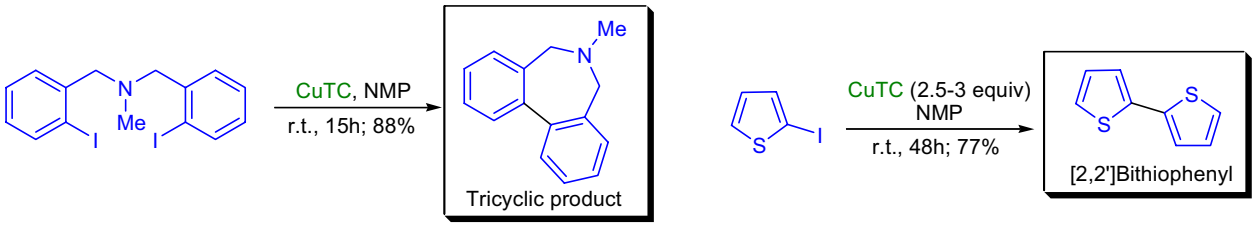
In the laboratory of A.I. Meyers, the oxazoline-mediated *asymmetric Ullmann coupling* was utilized to establish the chirality about the biaryl axis of mastigophorenes A and B.[34] The key coupling step was conducted in DMF in two stages: first the reaction mixture (0.66M) containing freshly prepared activated Cu-powder was heated at 95 °C for 8h, and then it was diluted with DMF (0.11M) and refluxed for 3 days. Interestingly, during these studies it was revealed that smaller chiral auxiliaries lead to higher atroposelection, a fact which was not previously recognized.



The first total synthesis of taspine was accomplished by T.R. Kelly and co-workers.[35] The central biaryl link was established by a classical *Ullmann coupling* using activated copper bronze. It is noteworthy that no other cross-coupling strategy was successful to make the C-C bond between the aromatic rings due to the severe steric hindrance.



L.S. Liebeskind et al. demonstrated that CuTC could be efficiently used to mediate the *Ullmann reaction* at room temperature under very mild conditions tolerating a wide variety of functional groups.[21] One of the examples features an intramolecular process while the other demonstrates the coupling of halogenated heteroaromatics.



VILSMEIER-HAACK FORMYLATION

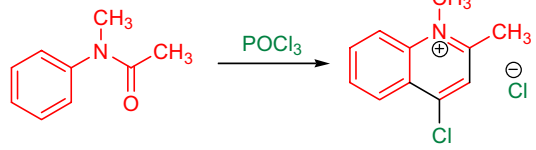
(References are on page 699)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-16]; *Modifications & Improvements*[17-30]; *Theoretical Studies*[31-33]]

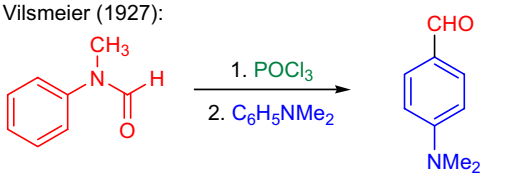
In 1925, A. Vilsmeier and co-workers reported that upon treatment with phosphoryl chloride ($POCl_3$), *N*-methylacetanilide gave rise to a mixture of products among which 4-chloro-1,2-dimethylquinolinium chloride was one of the major products.[1] Further investigation revealed that the reaction between *N*-methylformanilide and $POCl_3$ gave rise to a chloromethyliminium salt (Vilsmeier reagent), which readily reacts with electron-rich aromatic compounds to yield substituted benzaldehydes.[2] The introduction of a formyl group into electron-rich aromatic compounds using a Vilsmeier reagent is known as the *Vilsmeier-Haack formylation* (*Vilsmeier reaction*). The general features of this transformation are:[8,11] 1) the Vilsmeier reagent is prepared from any *N,N*-disubstituted formamide by reacting it with an acid chloride (e.g., $POCl_3$, $SOCl_2$, oxalyl chloride); 2) most often the combination of DMF and $POCl_3$ is used and the resulting Vilsmeier reagent is usually isolated before use; 3) mostly electron-rich aromatic or heteroaromatic compounds[8] as well as electron-rich alkenes and 1,3-dienes[11] are substrates for the transformation, since the Vilsmeier reagent is a weak electrophile; 4) the relative reactivity of five-membered heterocycles is pyrrole > furan > thiophene; 5) the solvent is usually a halogenated hydrocarbon, DMF or $POCl_3$ and the nature of the solvent has a profound effect on the electrophilicity of the reagent, so it should be carefully chosen; 6) the required reaction temperature varies widely depending on the reactivity of the substrate and it ranges from below 0 °C up to 80 °C; 7) the initial product is an iminium salt, which can be hydrolyzed with water to the corresponding aldehyde, treated with H_2S to afford thioaldehydes, reacted with hydroxylamine to afford nitriles, or reduced to give amines; 8) the transformation is regioselective favoring the less sterically hindered position (this means the *para* position on a substituted benzene ring); but electronic effects can also influence the product distribution; and 9) vinylogous chloromethyliminium salts undergo similar reaction to afford the corresponding α,β-unsaturated carbonyl compounds upon hydrolysis.

Vilsmeier (1925):



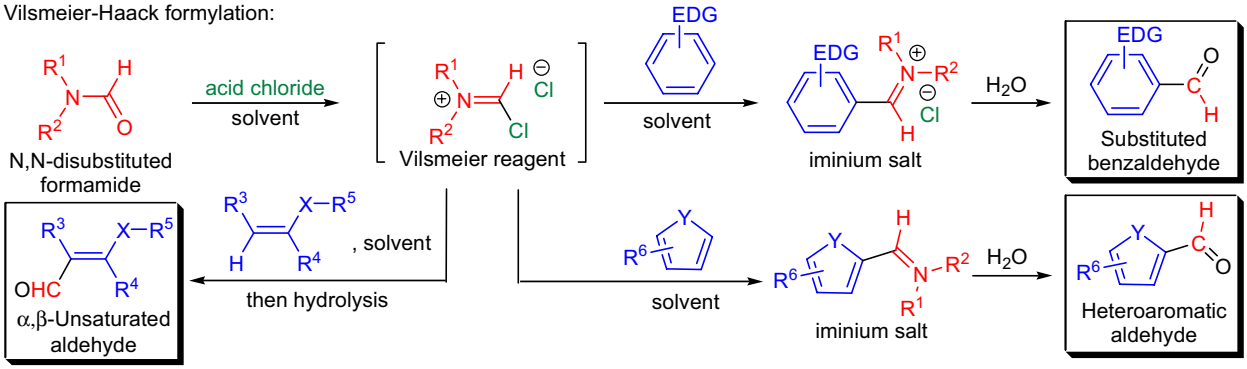
N-methyl-*N*-phenyl-acetamide → 4-chloro-1,2-dimethyl-quinolinium chloride

Vilsmeier (1927):



N-methyl-*N*-phenyl-formamide → 4-dimethylamino benzaldehyde

Vilsmeier-Haack formylation:

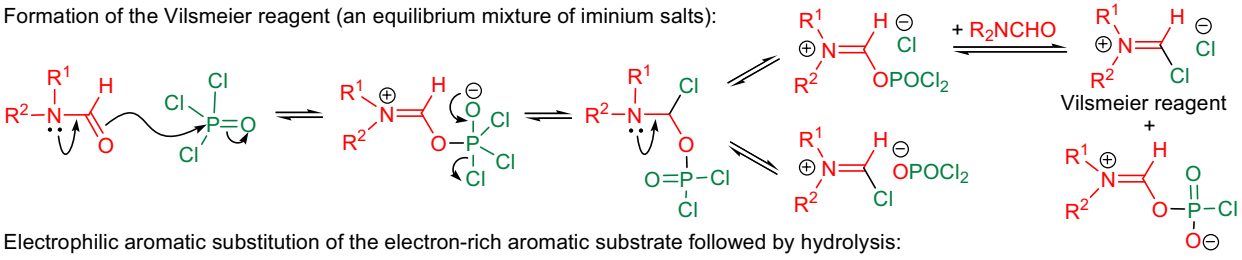


N,N-disubstituted formamide

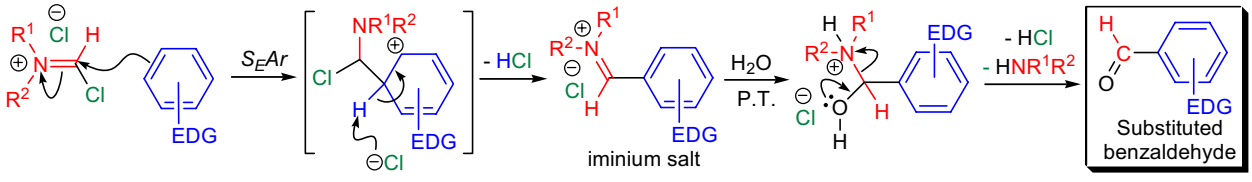
R^{1-2} = alkyl, aryl; acid chloride: $POCl_3$, $SOCl_2$,$COCl_2$, $(COCl)_2$, Ph_3PBr_2, 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, $POCl_3$; EDG = OH, *O*-alkyl, *O*-aryl, NR_2; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH_2, CR_2; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

Mechanism:[34-41,8,42,11]

Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):



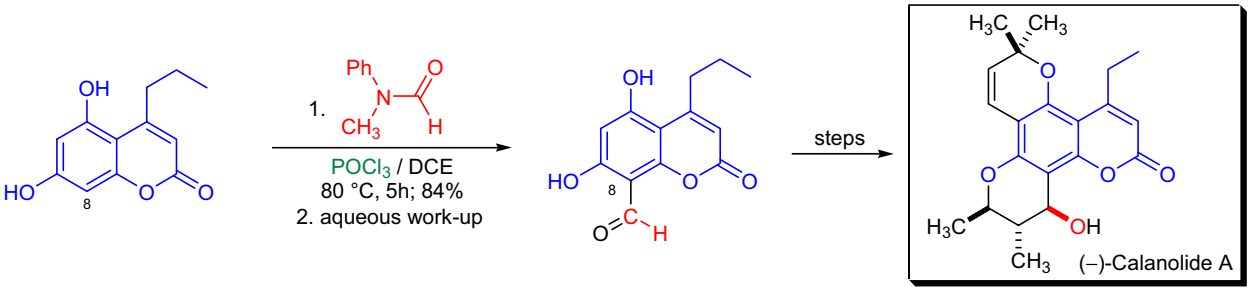
Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:



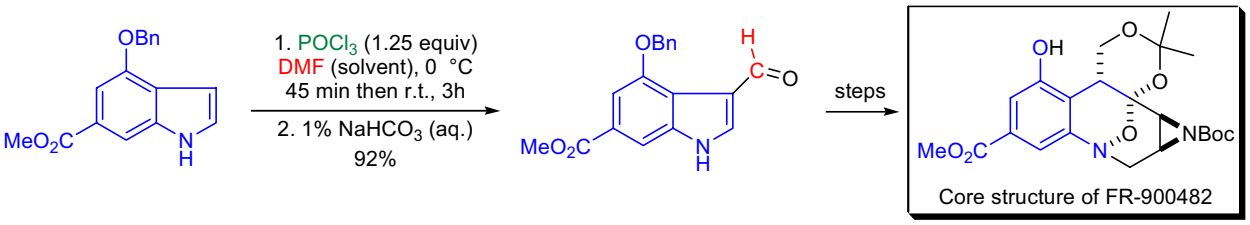
VILSMEIER-HAACK FORMYLATION

Synthetic Applications:

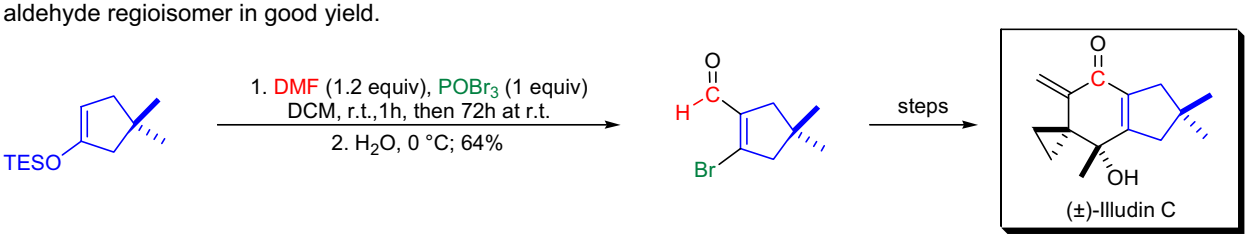
The total synthesis of the calophylium coumarin (–)-calanolide A was accomplished by D.C. Baker and co-workers.[43] This compound attracted considerable attention because it is a potent inhibitor of HIV-1 reverse transcriptase. In order to introduce a formyl group at C8, a regioselective *Vilsmeier reaction* was employed on a coumarin lactone substrate.



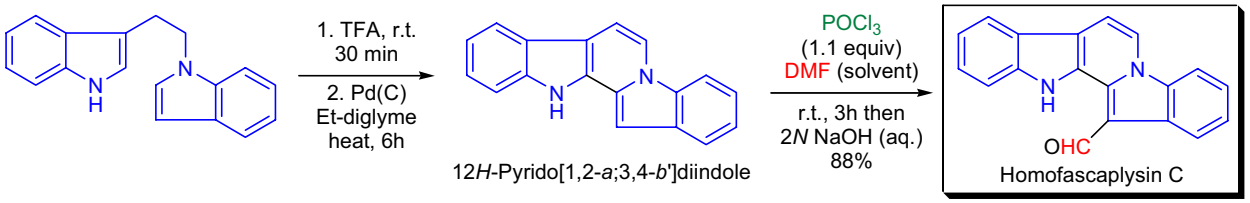
In the laboratory of F.E. Ziegler, the cyclization of a chiral aziridinyl radical into an indole nucleus was utilized to prepare the core nucleus of the potent antitumor agent FR-900482.[44] In the early stages of the synthetic effort, the *Vilsmeier-Haack formylation* was chosen to install an aldehyde functionality at the C3 position of a substituted indole substrate. The initial iminium salt was hydrolyzed under very mildly basic conditions to minimize the hydrolysis of the methyl ester moiety. Eventually the formyl group was removed from the molecule *via decarbonylation* using Wilkinson's catalyst.



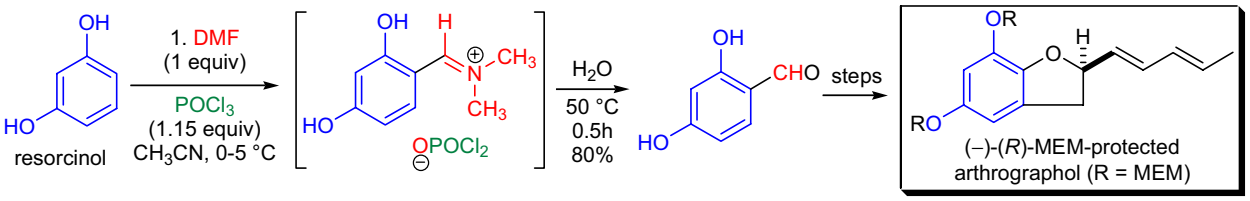
Since the *Vilsmeier-Haack formylation* is feasible on electron-rich alkenes such as enol ethers, it was a method of choice to prepare an α,β-unsaturated aldehyde during the total synthesis of (±)-illudin C by R.L. Funk et al.[45] The TES enol ether was treated with several reagent combinations (e.g., PBr_3/DMF/DCM), but unfortunately only regioisomeric product mixtures were obtained. However, the use of $POBr_3$/DMF/DCM allowed the clean preparation of the desired aldehyde regioisomer in good yield.



The marine sponge pigment homofascaplysin C was synthesized by the research team of G.W. Gribble.[46] The natural product had a novel 12*H*-pyrido[1,2-a:3,4-b']diindole ring system and a formyl group at the C13 position. The *Vilsmeier reaction* allowed the introduction of this substituent in excellent yield.



The total synthesis of (–)-(*R*)-MEM-protected arthrographol was accomplished by G.L.D. Krupadanam et al.[47] The authors used sequential *Vilsmeier reaction*/*Dakin oxidation* to prepare a 1,2,4-trihydroxybenzene derivative.



VINYLCYCLOPROPANE-CYCLOPENTENE REARRANGEMENT

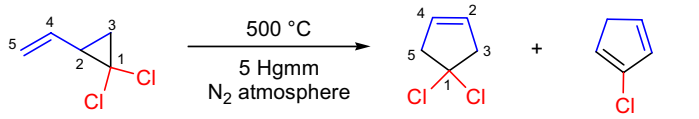
(References are on page 700)

Importance:

[*Seminal Publications*[1-3]*; Reviews*[4-10]*; Modifications & Improvements*[9,11,12]*; Theoretical Studies*[13-30]]

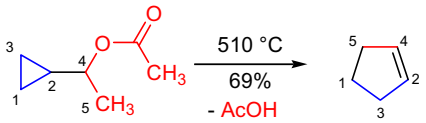
In 1959, N.P. Neureiter investigated the reactivity of 1,1-dichloro-2-vinylcyclopropane, which he prepared by the addition of dichlorocarbene to 1,3-butadiene.[1] Surprisingly, this compound was very stable and was recovered intact after being exposed to a variety of oxidizing and reducing agents. However, under flash vacuum thermolysis conditions it cleanly underwent a rearrangement to afford a mixture of five-membered chloroolefins. A year later, C.G. Overberger and A.E. Borchert reported a novel thermal rearrangement during the acetate pyrolysis of 2-cyclopropyl ethyl acetate, which yielded cyclopentene as the major product. The transformation of substituted vinylcyclopropanes to the corresponding substituted cyclopentenes is known as the *vinylcyclopropane-cyclopentene rearrangement*. The general features of the reaction are:[4-10] 1) thermal-, photochemical-, transition metal-mediated, as well as Lewis acid-mediated conditions can be applied to affect the transformation; 2) the photochemical process works well only for a limited number and type of substrates and is mainly of mechanistic interest; 3) the rearrangement of vinylcyclopropanes under thermal conditions is the most important transformation and it may take two major pathways: conversion to cyclopentenes or formation of open-chain alkenes or dienes; 4) the pathway taken depends on many factors such as the nature of substituents on the cyclopropane ring as well as the orientation of the π-system of the vinyl group relative to the cyclopropane ring (e.g., *cis*-alkylvinylcyclopropanes tend to undergo *[1,5]-sigmatropic H-shift* (*retro-ene reaction*) rather than forming cyclopentenes); 5) the rearrangement usually requires high temperatures (often this means running the reaction in a flash vacuum pyrolysis apparatus), but the degree of substitution and the presence of extended conjugation and heteroatoms lower the activation energy and also the required temperature; 6) heteroatom substitution (e.g., *O*-alkyl, NH_2, *S*-alkyl, etc.) on the cyclopropane moiety has a dramatic activation energy-lowering effect, whereas substitution on the vinylic moiety does not have a significant influence; 7) the rearrangement can be highly regio- and stereoselective provided that the cyclopropane is opened regioselectively; 8) predictions can be made regarding which cyclopropane bond is cleaved preferentially and the prediction is based on the donor/acceptor properties of the various substituents on the cyclopropane ring; and 9) the stereochemical outcome of the rearrangement is determined by the energetics of the substituted cyclopentene product.

Neureiter (1959):

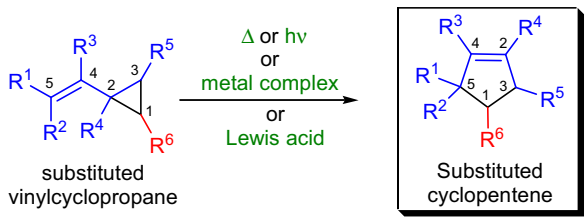


1,1-dichloro-2-vinylcyclopropane — 4,4-dichloro-cyclopentene + 2-chlorocyclo-penta-1,3-diene

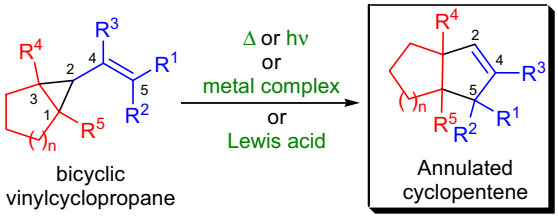
Overberger & Borchert (1960):



2-cyclopropyl-ethyl acetate → cyclopentene



substituted vinylcyclopropane → Substituted cyclopentene

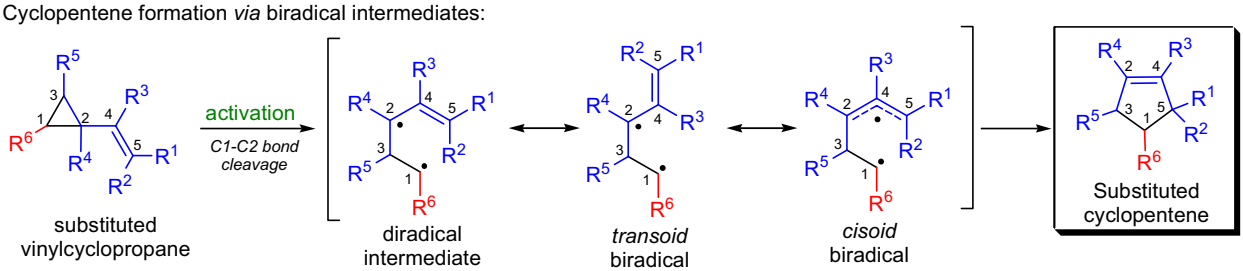


bicyclic vinylcyclopropane → Annulated cyclopentene

R^{1-5}, R^6 = H, alkyl, alkenyl, aryl, O-alkyl, NH_2, NH-alkyl, NR_2; n = 1-3

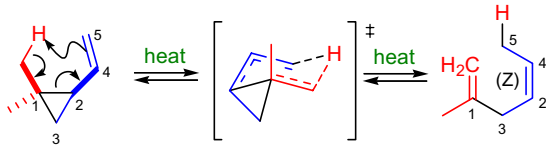
Mechanism:[31-61]

Cyclopentene formation *via* biradical intermediates:

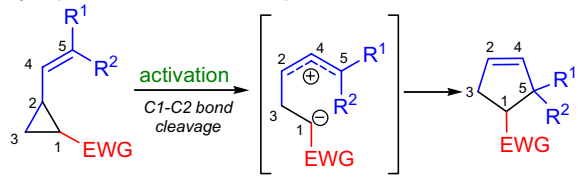


substituted vinylcyclopropane → diradical intermediate ↔ *transoid* biradical ↔ *cisoid* biradical → Substituted cyclopentene

Competing retro-ene reaction (reversible process):



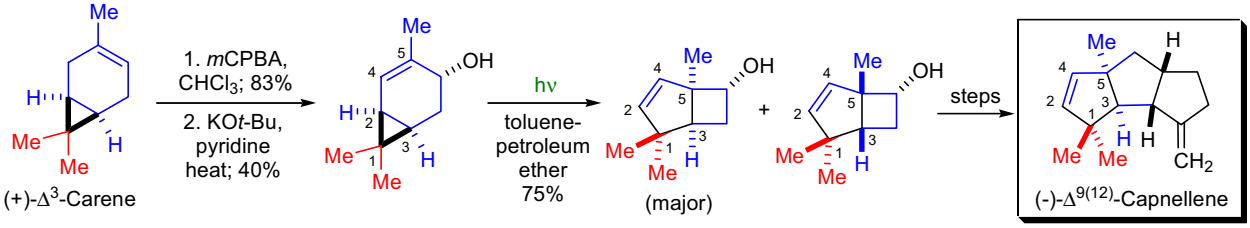
Cyclopentene formation *via* dipolar intermediates:



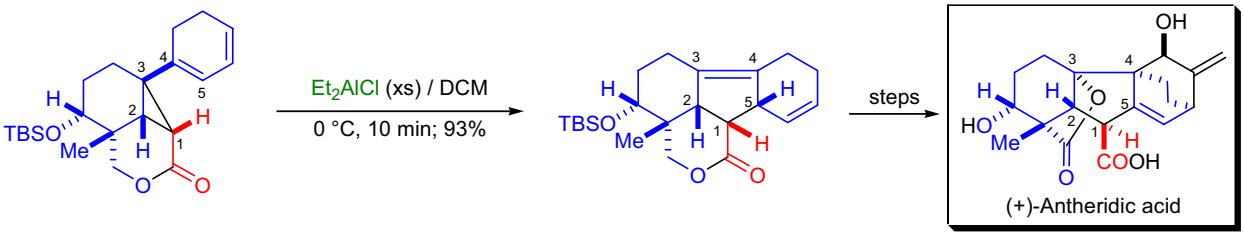
VINYLCYCLOPROPANE-CYCLOPENTENE REARRANGEMENT

Synthetic Applications:

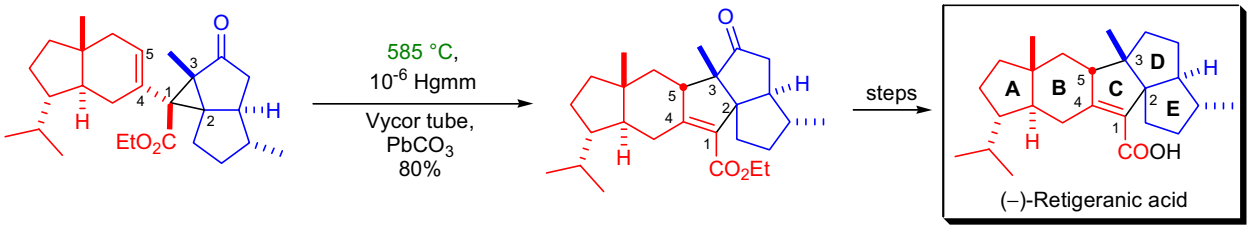
In the laboratory of H.R. Sonawane, both enantiomers of $\Delta^{9(12)}$-capnellene were prepared using the *photoinduced vinylcyclopropane-cyclopentene rearrangement*.[62] The conversion of (+)-Δ^3-carene to the corresponding enantiopure allylic alcohol was achieved by a two-step sequence of a *Prilezhaev reaction* and *base-induced epoxide ring-opening*. The photochemical rearrangement of the *cis*-alkyl vinylcyclopropane intermediate proceeded without the occurrence of the competing *retro-ene reaction* and gave rise to a diastereomeric mixture of cyclopentene-annulated products.



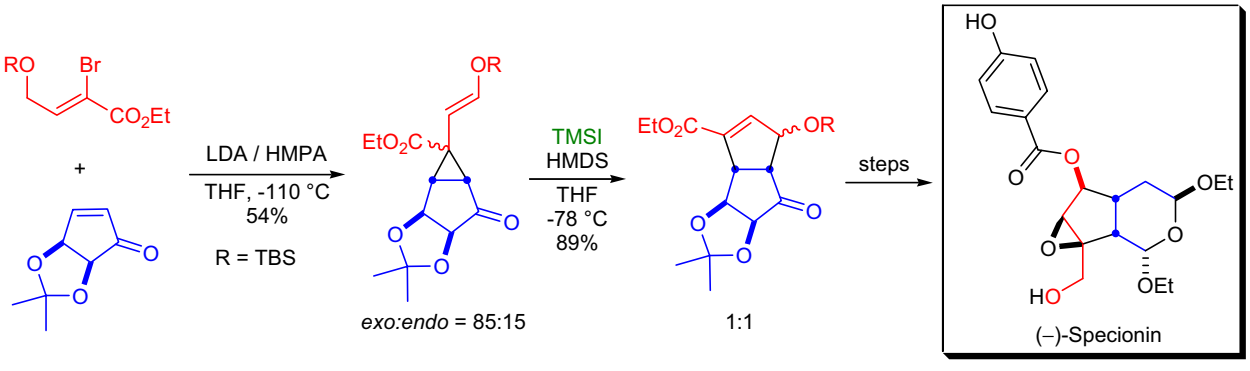
The enantioselective total synthesis of (+)-antheridic acid was accomplished by E.J. Corey and co-workers using the *Lewis-acid-mediated vinylcyclopropane-cyclopentene rearrangement* as the key step.[63] This key transformation was not possible under thermal conditions; however, the use of excess diethylaluminum chloride in DCM gave rise to the rearranged product in excellent yield.



T. Hudlicky et al. achieved the short enantioselective total synthesis of (-)-retigeranic acid.[64] The C ring of the natural product was assembled *via* the *thermal vinylcyclopropane-cyclopentene rearrangement* for which the precursor was prepared by the *vinylcyclopropanation* of a bicyclic enone with a dienolate. The vinylcyclopropane was evaporated at 585 °C in high vacuum through a Vycor tube conditioned with $PbCO_3$ (flash vacuum pyrolysis) to afford the annulated product in good yield.



The iridoid sesquiterpene (–)-specionin, an antifeedant to the spruce budworm, was synthesized by T. Hudlicky et al. using the *low-temperature vinylcyclopropane-cyclopentene rearrangement* as the key step.[65] The substituted cyclopentenone precursor was first exposed to the lithium dienolate derived from ethyl 4-(dimethyl-*tert*-butylsilyloxy)-2-bromocrotonate at -110 °C to afford silyloxyvinylcyclopropanes as a mixture of *exo* and *endo* isomers (with respect to the vinyl group). The mixture was not separated but immediately subjected to TMSI/HMDS, and the corresponding tricyclic ketones were obtained in good yield. Similar results were obtained when TBAF in THF was used instead of TMSI.



VON PECHMANN REACTION

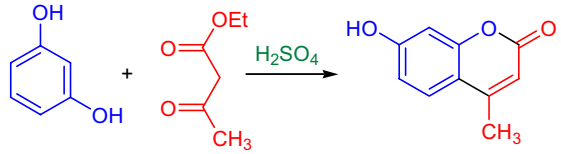
(References are on page 702)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3,4]; *Modifications & Improvements*[5-26]]

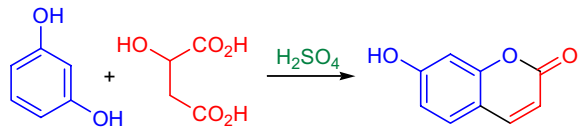
In 1883, H. von Pechmann and C. Duisberg reported that when ethyl acetoacetate was mixed with resorcinol in the presence of concentrated sulfuric acid, 4-methyl-7-hydroxycoumarin was formed.[1] He obtained a similar result upon reacting resorcinol with malic acid and isolated 7-hydroxycoumarin as the major product.[2] The condensation of phenols with β-keto esters in the presence of protic or Lewis acids to afford substituted coumarins is known as the *von Pechmann reaction* (also as *Pechmann reaction* or *Pechmann condensation*). The general features of this transformation are: 1) the best substrates are electron-rich mono-, di-, and trihydric phenols having electron-donating substituents; 2) phenols with strongly electron-withdrawing substituents (e.g., NO_2 or CO_2H) often fail to react; 3) the position of the substituents on the phenol also has an influence on the reactivity and therefore on the rate of the condensation; 4) *ortho* substituents tend to inhibit the reaction completely, *para* substituents usually do not interfere much, and substituents in the *meta* position give the best results; 5) both cyclic and acyclic β-keto esters undergo the reaction; 6) malic acid, fumaric, and maleic acids also react, but the scope of phenolic substrates is somewhat limited with these reactants; 7) β-keto esters yield coumarins that have substituents at the C4 position while malic acid affords coumarins which are unsubstituted at C4; 8) the nature of the protic or Lewis acid catalyst has a profound effect on the outcome of the reaction: if the reaction does not take place in the presence of one particular catalyst, it may proceed in high yield in the presence of another; 9) during the 1900s the most popular catalyst was concentrated sulfuric acid, but for highly functionalized and sensitive substrates milder condensation conditions have been developed; and 10) for highly reactive phenols heating of the reaction mixture is usually not necessary, but for less reactive substrates heating is often required. There are some drawbacks of the *von Pechmann reaction*: 1) in the overwhelming majority of the cases the catalyst has to be used in excess so the process is not catalytic; and 2) extended reaction times at high temperatures can lead to side reactions such as to the formation of chromones in addition to coumarins. Numerous modifications have been developed and several of them allow the synthesis of coumarins under mild conditions and even using truly catalytic amounts of condensing agent.[27]

Pechmann (1883):



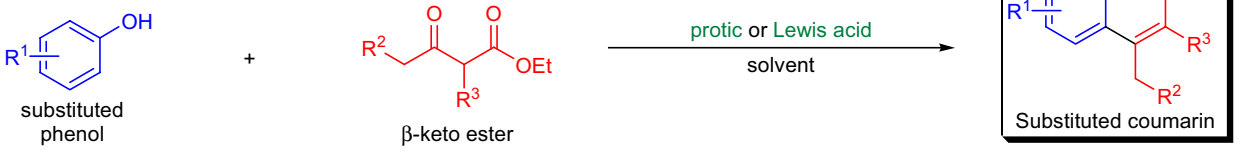
resorcinol — ethyl acetoacetate — 4-methyl-7-hydroxy-coumarin

Pechmann (1884):



resorcinol — malic acid — 7-hydroxycoumarin

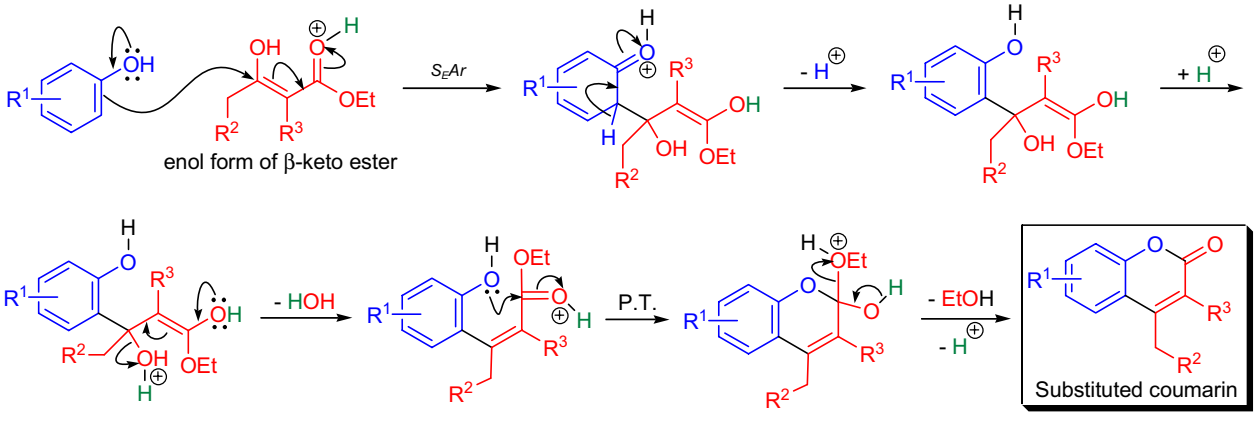
von Pechmann reaction:



substituted phenol — β-keto ester

R^1 = H, OH, *O*-alkyl, NH_2, NHR, NR_2; R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, Cl; protic acid: H_2SO_4, HCl, H_3PO_4; Lewis acid: $POCl_3$, $ZnCl_2$, $AlCl_3$, $FeCl_3$, $InCl_3$, $Yb(OTf)_3$, $SnCl_2$, $TiCl_4$, $SiCl_4$, PPA

Mechanism:[28,29]

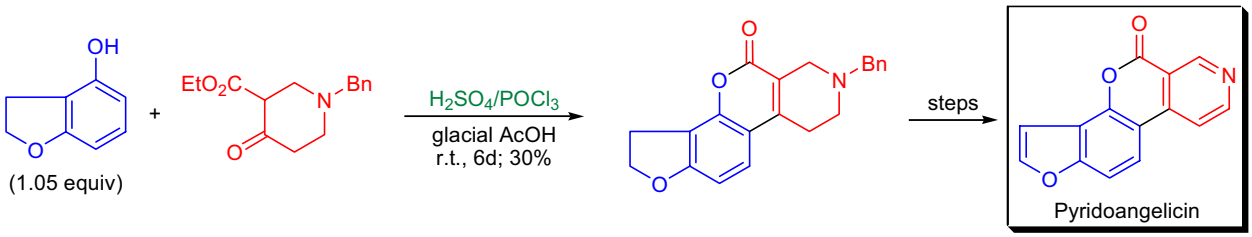


enol form of β-keto ester

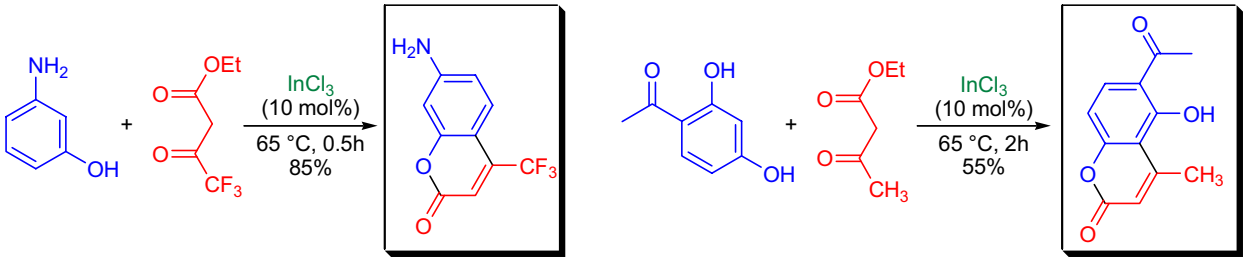
VON PECHMANN REACTION

Synthetic Applications:

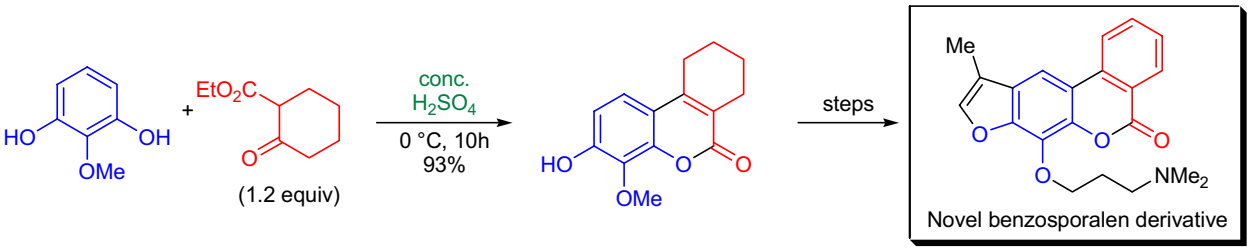
In the laboratory of J. Moron, the synthesis of two pyridoangelicins, the angular isomers of pyridopsoralens, was accomplished. The authors demonstrated in previous publications that pyridopsoralens exhibit high affinity toward DNA, so it was a logical next step to prepare the angular isomers and test their affinities. The skeleton of the desired compound was assembled by the *von Pechmann reaction*. The reaction between 2,3-dihydro-4-hydroxybenzofuran and 1-benzyl-3-ethoxycarbonylpiperidin-4-one was conducted in glacial acetic acid at room temperature in the presence of sulfuric acid and phosphorous oxychloride ($POCl_3$). When only hydrochloric acid was used as the condensing agent, the yield was very poor.



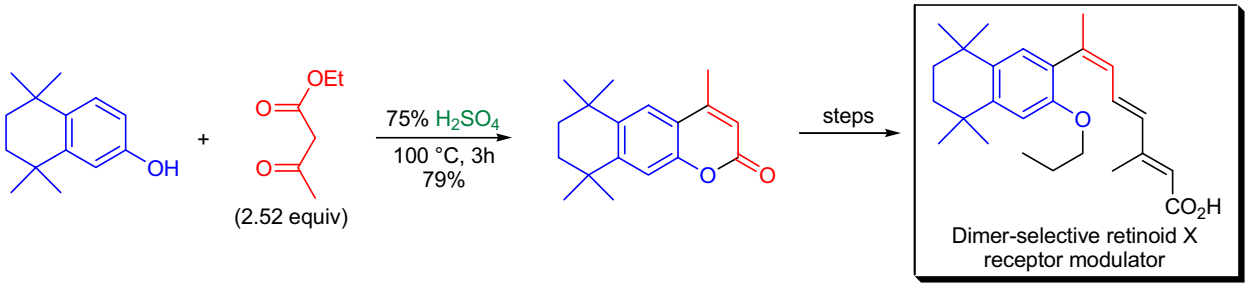
One of the mildest conditions for the *von Pechman reaction* was developed by D.S. Bose and co-workers who used indium(III) chloride as the catalyst.[27] A large number of 4-substituted coumarins were prepared in high yield by this method. Under the reaction conditions most functional groups are tolerated. In the typical procedure the substrates are heated in the presence of 10 mol% of $InCl_3$ and the reaction mixture was poured onto crushed ice which caused the product to precipitate.



Photochemotherapy is an efficient way to treat hyperproliferative diseases. Especially the so-called PUVA therapy (psoralen + UVA light) is very common in which the psoralen is irradiated with UVA light to give rise to a covalent adduct with the pyrimidine bases of DNA by means of a photoaddition reaction. There are several undesired side effects for the patients as a result of this therapy, so the synthesis and photobiological evaluation of novel benzosporalen derivatives was undertaken by the research team of L.D. Via.[30] The key step in their synthetic sequence was the *von Pechman reaction* of 2-methoxyresorcinol with ethyl 2-oxocyclohexanecarboxylate.



The short and efficient stereospecific synthesis of the dimer-selective retinoid X receptor modulator was carried out in the laboratory of L.G. Hamann.[31] The synthetic sequence began with the *von Pechmann reaction* between tetramethyltetrahydronaphthol and ethyl acetoacetate in 75% sulfuric acid solution. The desired coumarin was formed regioselectively and isolated in high yield.



WACKER OXIDATION

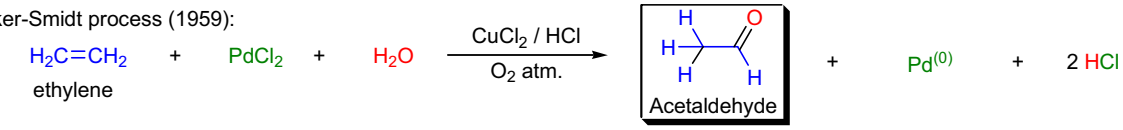
(References are on page 702)

Importance:

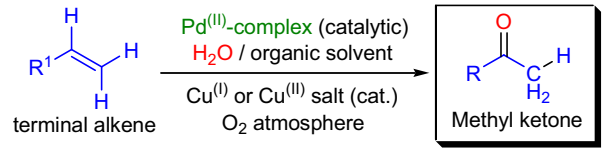
[*Seminal Publications*[1-5]; *Reviews*[6-24]; *Modifications & Improvements*[25-45]; *Theoretical Studies*[46-56]]

The industrial oxidation of ethylene to ethanal (acetaldehyde) under an atmosphere of oxygen using $PdCl_2$ and $CuCl_2$ as catalysts is known as the *Wacker-Smidt process*. The first report of the oxidation of ethylene with stoichiometric amounts of $PdCl_2$ in an aqueous solution was made by F.C. Phillips in 1894 and later the precipitation of Pd metal from a $PdCl_2$ solution was used as a test for the presence of olefins.[1] In 1959, J. Smidt et al. (at Wacker Chemie in Germany) showed that the $Pd^{(0)}$ metal could be re-oxidized to the active $PdCl_2$ with the use of $CuCl_2$.[2,3] This discovery first turned the reaction into a commercially feasible process, and it opened the door for applications in organic synthesis.[4,5,57] The one-pot oxidation of olefins to the corresponding ketones with catalytic amounts of $Pd^{(II)}$ salts is known as the *Wacker oxidation*. The general features of this reaction are: 1) the reaction is carried out in an aqueous medium in the presence of HCl; 2) terminal alkenes react much faster than internal or 1,1-disubstituted alkenes and they are almost exclusively converted to the corresponding methyl ketones; 3) terminal alkenes can be viewed as masked ketones for synthetic purposes; 4) under the reaction conditions, internal alkenes are not oxidized to any appreciable extent; 5) α,β-unsaturated ketones and esters are oxidized regioselectively to the corresponding β-keto compounds using catalytic amounts of Na_2PdCl_4 and TBHP or H_2O_2 as co-oxidants; 6) allylic- and homoallylic ethers are regioselectively oxidized to give the corresponding β- and γ-alkoxyketones; and 7) when the oxidation is carried out in the presence of nucleophiles other than water, the process is called the *Wacker-type oxidation*, which can take place both inter- and intramolecularly.

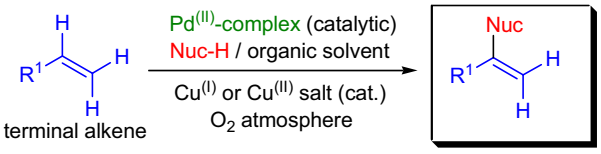
Wacker-Smidt process (1959):

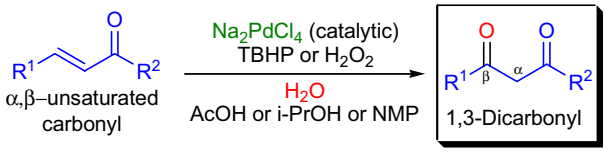


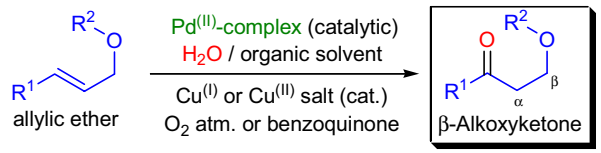
Wacker oxidation:



Wacker-type oxidation:



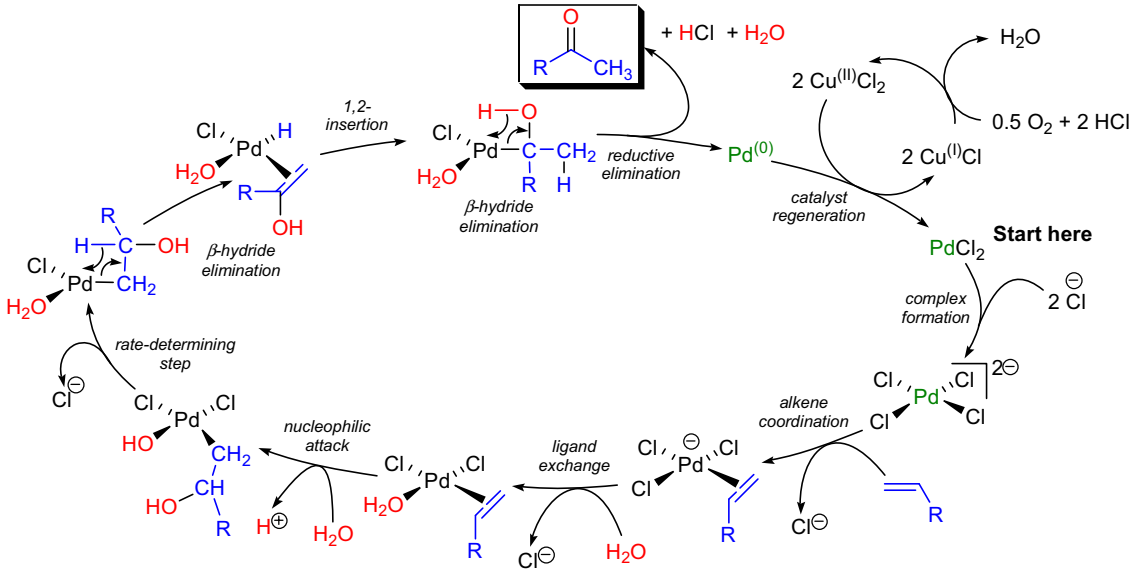




R^1 = alkyl, substituted alkyl; R^2 = alkyl, aryl, O-alkyl

Mechanism:[58-75,37,19]

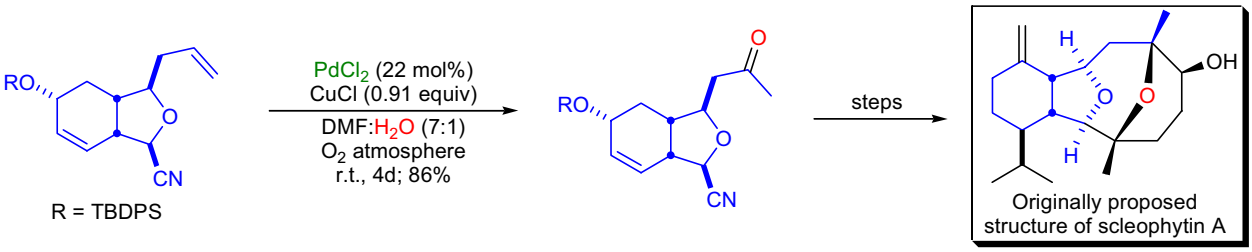
Certain steps in the mechanism of the *Wacker oxidation* are still unclear despite intensive research. One of these steps, the attack of the coordinated alkene by the nucleophile (OH^- or H_2O), could be both intra- or intermolecular as the observed rate law is consistent with either possibility. One of the plausible catalytic cycles is presented.



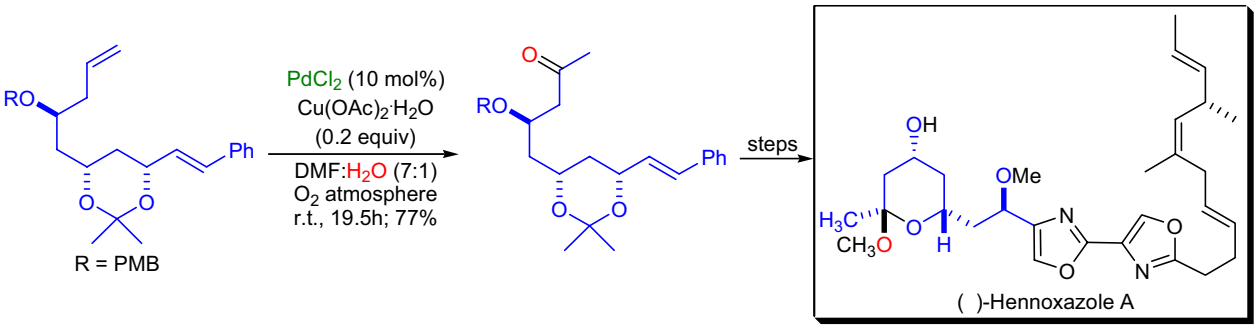
WACKER OXIDATION

Synthetic Applications:

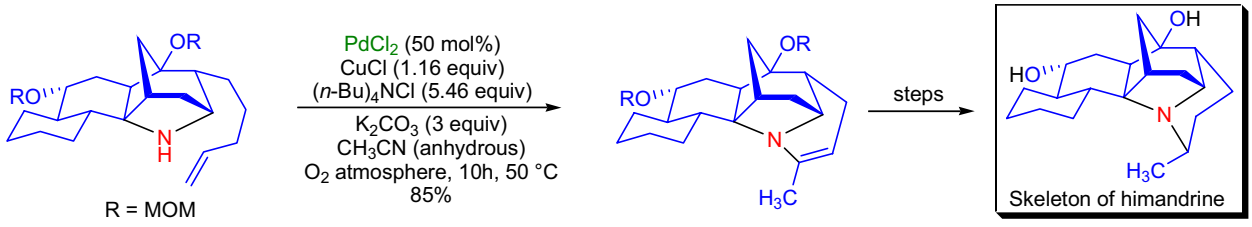
The asymmetric total synthesis of the putative structure of the cytotoxic diterpenoid (-)-sclerophytin A was accomplished by L.A. Paquette and co-workers.[76] At the beginning of the synthesis, a bicyclic intermediate was subjected to the *Wacker oxidation* to oxidize its terminal alkene into the corresponding methyl ketone. The oxidation took place in high yield, although the reaction time was long. The spectra obtained for the final product (proposed structure) did not match that of the natural product, consequently a structural revision was necessary.



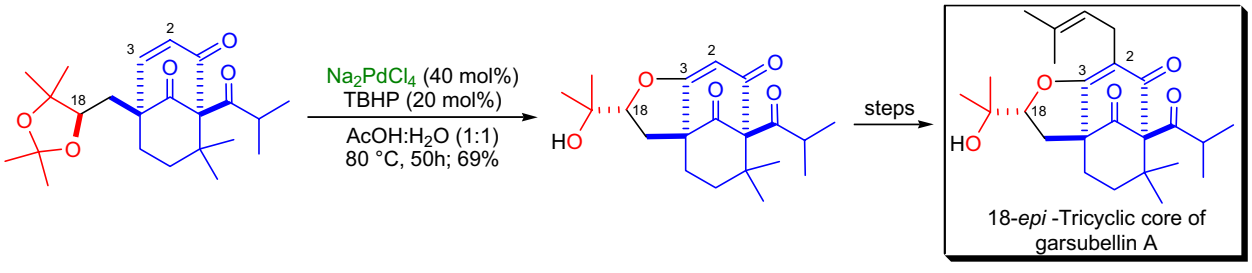
The antiviral marine natural product, (–)-hennoxazole A, was synthesized in the laboratory of F. Yokokawa.[77] The highly functionalized tetrahydropyranyl ring moiety was prepared by the sequence of a *Mukaiyama aldol reaction*, *chelation-controlled 1,3-syn reduction*, *Wacker oxidation*, and an *acid catalyzed intramolecular ketalization*. The terminal olefin functionality was oxidized by the *modified Wacker oxidation*, which utilized $Cu(OAc)_2$ as a co-oxidant.[34] Interestingly, a similar terminal alkene substrate, which had an oxazole moiety, failed to undergo oxidation to the corresponding methyl ketone under a variety of conditions.



The first synthesis of the hexacyclic himandrine skeleton was achieved by L.N. Mander and co-workers.[78] The last six-membered heterocycle was formed *via* an intramolecular *Wacker-type oxidation* in which the terminal alkene side-chain reacted with the secondary amine functionality. The oxidation was conducted in anhydrous acetonitrile to insure that the Pd-alkene complex was substituted exclusively by the internal nucleophile. The resulting six-membered enamine was then hydrogenated and the MOM protecting groups removed to give the desired final product.



Studies in the laboratory of M. Shibasaki toward the total synthesis of garsubellin A led to the stereocontrolled synthesis of the 18-*epi*-tricyclic core of the natural product.[79] During the final stages of the synthetic sequence, the tetrahydrofuran ring was installed using a *Wacker-type process*. The reaction conditions insured that the acetonide protecting group was first removed and the C18 secondary alcohol moiety served as the internal nucleophile to form the tricyclic product.



WAGNER-MEERWEIN REARRANGEMENT

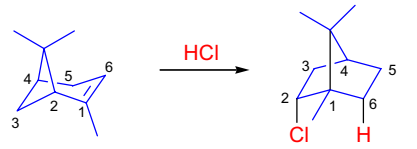
(References are on page 704)

Importance:

[*Seminal Publications*[1-3]; *Reviews*[4-18]; *Modifications & Improvements*[19-25]; *Theoretical Studies*[26-30]]

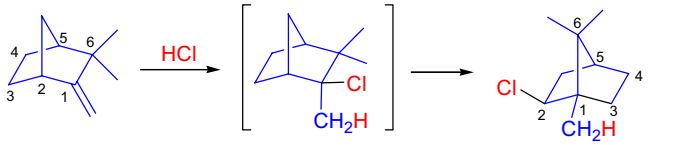
In 1899, G. Wagner and W. Brickner reported the rearrangement of α-pinene to bornyl chloride in the presence of hydrogen chloride.[1] The transformation baffled chemists at the time, since it contradicted the classical structural theory that was based on the postulate of skeletal invariance.[31] It was not until 1922, when H. Meerwein and co-workers revealed the ionic nature of the rearrangement, that an explanation was offered.[3] The generation of a carbocation followed by the *[1,2]*-shift of an adjacent carbon-carbon bond to generate a new carbocation is known as the *Wagner-Meerwein rearrangement*. Originally this name referred only to skeletal rearrangements in bicyclic systems, but today it is used to describe all *[1,2]*-shifts of hydrogen, alkyl, and aryl groups. Occasionally the *[1,2]-methyl shift* in bridged bicyclic monoterpenoids and related systems is referred to as the *Nametkin rearrangement*. The general features of the *Wagner-Meerwein rearrangement* are: 1) the generation of the initial carbocation can be achieved in a variety of ways (e.g., protonation of alkenes, alcohols, epoxides or cyclopropanes, solvolysis of secondary and tertiary alkyl halides, or sulfonates in a polar protic solvent (*semipinacol rearrangement*), deamination of amines with nitrous acid (*Tiffeneau-Demjanov rearrangement*), treatment of an alkyl halide with Lewis acid, etc.; 2) the initial carbocation has a tendency to rearrange to a thermodynamically more stable structure, a change that may occur in several different ways: e.g., *[1,2]-alkyl, -aryl- or hydride shift* to afford a more stable carbocation, ring-expansion of strained small rings such as cyclopropanes and cyclobutanes to give more stable five- or six-membered products, collapse by fragmentation, etc.; 3) several consecutive *[1,2]*-shifts are possible if the substrate contains multiple structural elements that allow the formation of gradually more stable structures; 4) the various competing rearrangement pathways limit the synthetic utility of the *Wagner-Meerwein rearrangement*, since one needs to install all the structural features that will drive the rearrangement in the desired direction; 5) the final most stable carbocation's fate may be the loss of a proton to afford an alkene or capture by a nucleophile present in the reaction mixture (solvent or conjugate base of the acid used to promote the rearrangement); and 6) the stereochemistry of the migrating group is retained, which is in accordance of the *Woodward-Hofmann rules*.

Wagner & Brickner (1899):



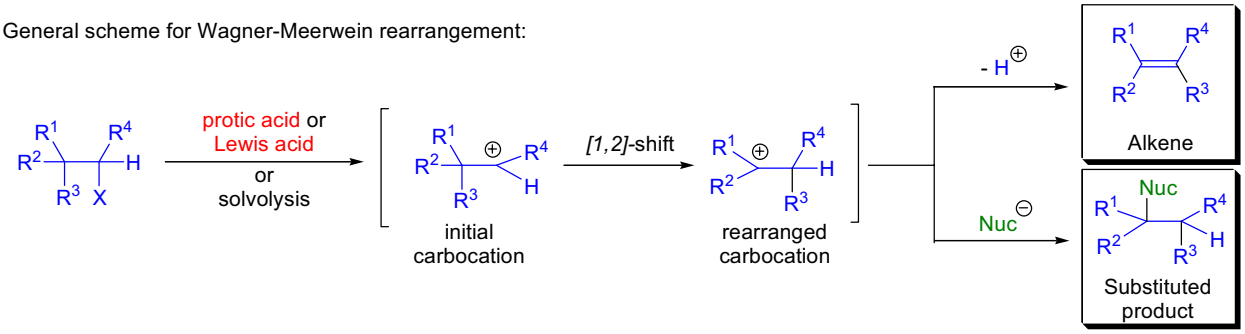
α-pinene bornyl chloride

Meerwein, Ermster & Jussen (1922):



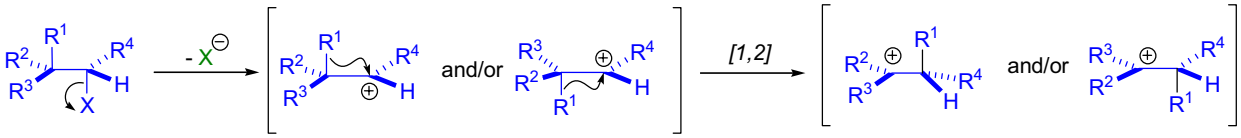
camphene camphene hydrohcloride isobornyl chloride

General scheme for Wagner-Meerwein rearrangement:



Mechanism: [32,13,15-17]

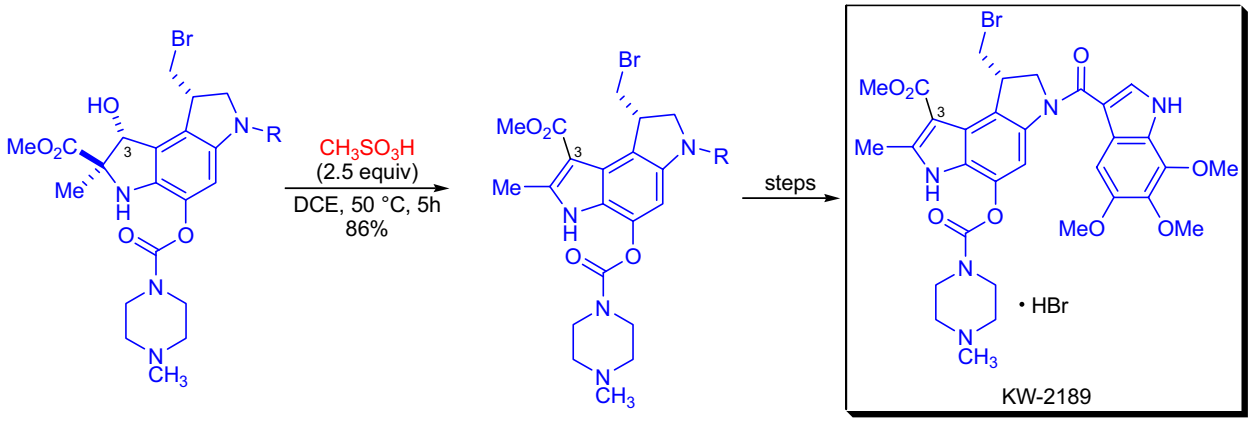
The *Wagner-Meerwein rearrangement* has been the subject of a large number of mechanistic investigations, making it probably one of the most thoroughly studied reactions in organic chemistry. Depending on the structure and stereochemistry of the substrate, the rearrangement may proceed in a concerted or stepwise fashion. When the leaving group and the migrating groups are antiperiplanar to each other, the rearrangement is concerted (especially in rigid polycyclic sytems), but in most other cases the formation of a carbocation intermediate is expected.



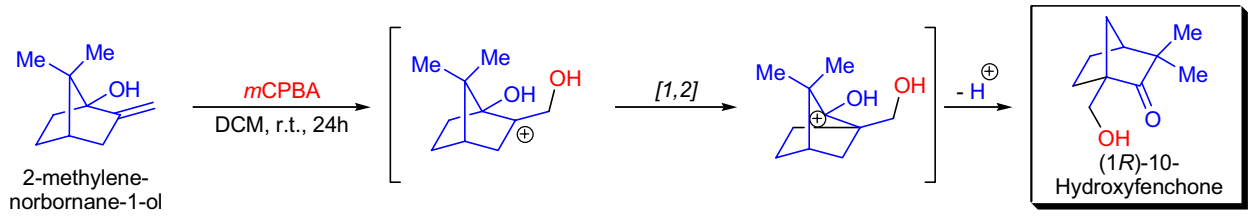
WAGNER-MEERWEIN REARRANGEMENT

Synthetic Applications:

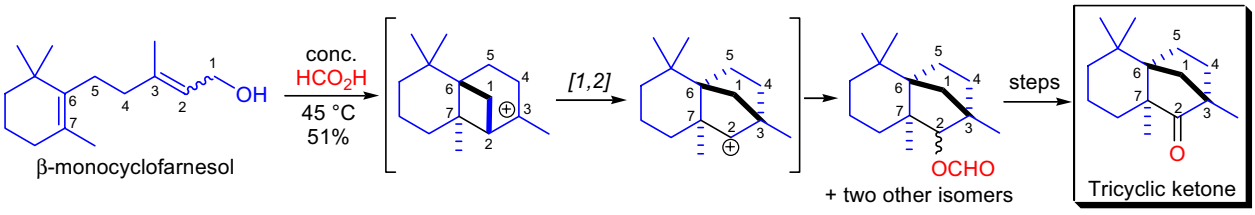
The large-scale synthesis of the potent antitumor agent KW-2189, derived from the antitumor antibiotic duocarmycin B2, was accomplished by T. Ogasa and co-workers who utilized the *Wagner-Meerwein rearrangement* as the key step.[33] The synthetic strategy avoided the use of protecting groups. The key rearrangement step was investigated in detail and the authors found that both protic and Lewis acids were effective. The best results were obtained with methanesulfonic acid in dichloroethane. Protonation of the 2° alcohol at C3 resulted in the loss of a water molecule and the formation of a secondary carbocation. The adjacent carboxymethyl group at C2 underwent a *[1,2]*-shift to form the more stable tertiary carbocation at C2, which was also stabilized by the lone pair of the nitrogen atom and finally the loss of proton afforded the indole nucleus.



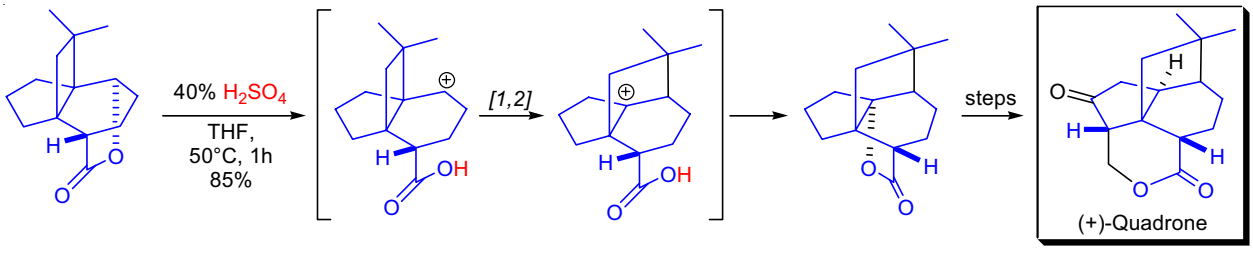
The short enantiospecific synthesis of (1*R*)-10-hydroxyfenchone from fenchone based on two consecutive *Wagner-Meerwein rearrangements* was developed in the laboratory of A.G. Martinez.[34] The preparation of this target is of great importance, since 10-hydroxyfenchone is a convenient intermediate for C10-*O*-substituted fenchones. The key intermediate in the synthetic sequence is 2-methylenenorbornan-1-ol, obtained from fenchone *via* a *Wagner-Meerwein rearrangement* (steps not shown), which was exposed to *m*CPBA at room temperature. The initially formed epoxide was protonated by *m*CPBA, generating a tertiary carbocation that underwent a facile *[1,2]-alkyl shift* to produce the more stable oxygen-stabilized carbocation.



The research team of G. Fráter investigated the acid catalyzed rearrangement of β-monocyclofarnesol for the synthesis of tricyclic ketones with sesquiterpene skeleton. The substrate β-monocyclofarnesol, prepared from dihydro-β-ionone in two steps, was exposed to concentrated formic acid, which resulted in the formation of a mixture of three different formates.



The *Wagner-Meerwein rearrangement* was one of the key steps in the total synthesis of (+)-quadrone by A.B. Smith and co-workers.[35] The propellane substrate was treated with 40% sulfuric acid, which resulted in the *[1,2]-alkyl shift* of the initially formed cyclobutylcarbinyl system.



WEINREB KETONE SYNTHESIS

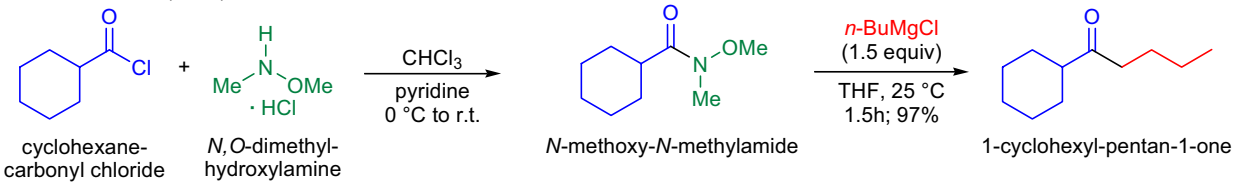
(References are on page 705)

Importance:

[*Seminal Publications*[1]; *Reviews*[2-5]; *Modifications & Improvements*[6-23]]

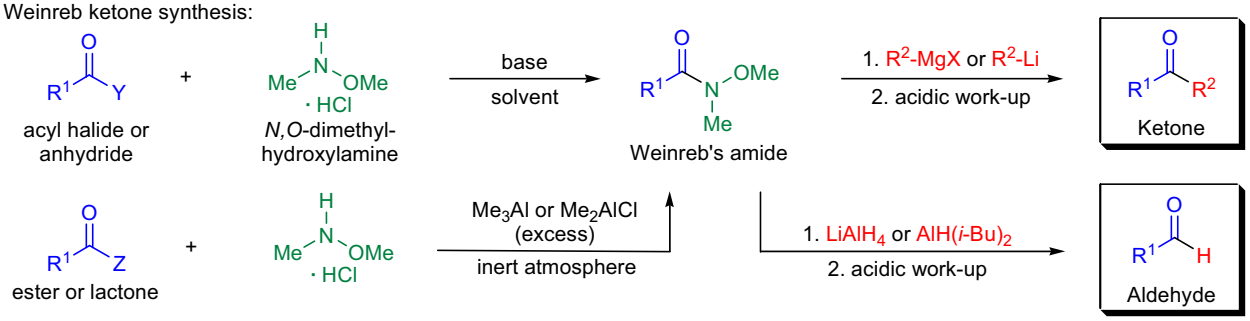
In 1981, S.M. Weinreb and S. Nahm discovered that the addition of excess Grignard reagent or organolithium species to *N*-methoxy-*N*-methylamides resulted in the formation of ketones upon acidic work-up. This observation was significant because at that time there was no general procedure available for the efficient synthesis of ketones from carboxylic acid derivatives and the then existing methods all required carefully controlled reaction conditions, and overaddition (to produce tertiary alcohols) was a major side reaction. The synthesis of ketones from *N*-methoxy-*N*-methylamides (Weinreb's amides) with organometallic reagents is known as the *Weinreb ketone synthesis*. The general features of this transformation are: 1) the Weinreb's amides can be easily prepared from activated carboxylic acid derivatives (e.g., acid chlorides or anhydrides) and *N,O*-dimethylhydroxylamine hydrochloride in the presence of a base; 2) the conversion of less active carboxylic acid derivatives such as esters and lactones to the corresponding Weinreb's amide require the use of several equivalents of trimethylaluminum (Me_3Al) or dimethylaluminum chloride (Me_2AlCl);[6,9] 3) carboxylic acids can also be converted to Weinreb's amides by the use of standard activating agents (DCC, EDCI, CBr_4/PPh_3, etc.); 4) Weinreb's amides are stable compounds; they do not require special handling, are easily purified by flash chromatography or crystallization and can be stored indefinitely; 5) the addition of at least 1.1 equivalents of Grignard reagent or organolithium species to the solution of Weinreb's amide in an ether solvent at low temperatures results in the formation of a strongly chelated metal complex, which prevents the addition of more than one equivalent of the reagent; 5) work-up with dilute aqueous acid (HCl) affords the ketone and usually does not interfere with other functional groups or protecting groups; 6) virtually any alkyl, alkenyl, alkynyl, aryl, and heteroaryl organomagnesium- or organolithium reagent can be used; 7) side reactions such as overaddition of the reagent or the epimerization of the stereocenter at the α-position are extremely rare; 8) the treatment of Weinreb's amides with excess metal hydride (e.g., LAH, DIBAL-H) results in the formation of aldehydes; and 9) the use of DIBAL-H tends to give higher yields than LAH. All the above features render the *Weinreb ketone synthesis* extraordinarily well-suited for use in the synthesis of complex molecules. One important limitation of the procedure occurs when highly basic or sterically hindered organometallic reagents are used since these are capable of removing a proton from the O-Me group resulting in the formation of *N*-methylamides.

Weinreb & Nahm (1981):



cyclohexane-carbonyl chloride + *N,O*-dimethyl-hydroxylamine → *N*-methoxy-*N*-methylamide → 1-cyclohexyl-pentan-1-one

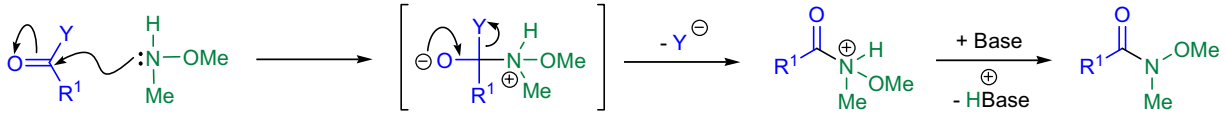
Weinreb ketone synthesis:



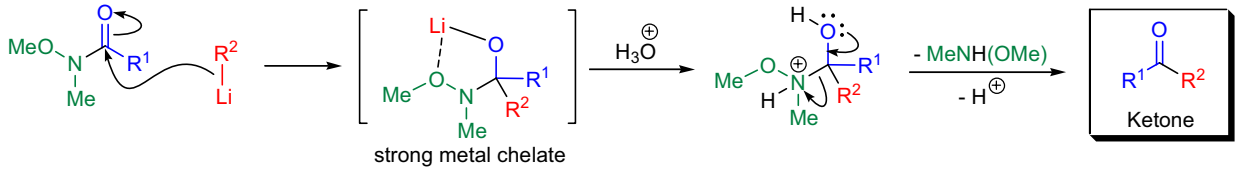
R^1 = alkyl, aryl, heteroaryl; Y = Cl, Br, OCOR'; Z = *O*-alkyl, *O*-aryl, oxazolidine; R^2 = alkyl, alkenyl, alkynyl, aryl; base: pyridine, Et_3N

Mechanism:[1]

Formation of Weinreb's amide:



Reaction of the organometallic species with Weinreb's amide:

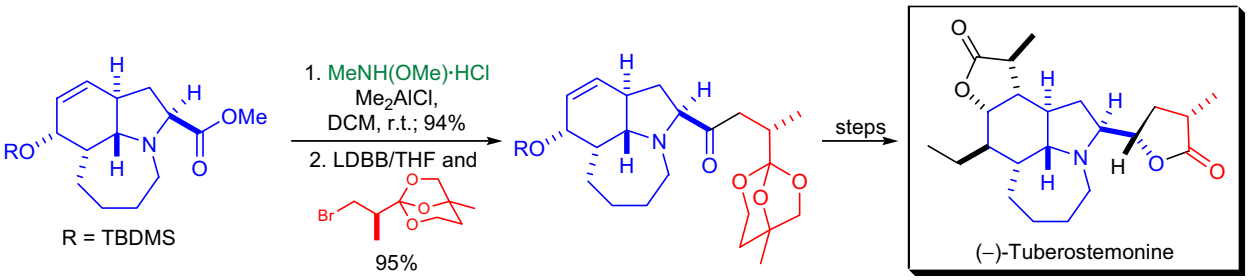


strong metal chelate

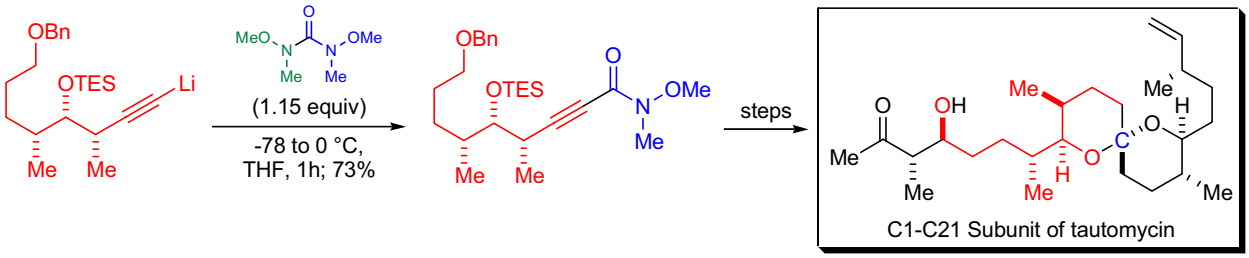
WEINREB KETONE SYNTHESIS

Synthetic Applications:

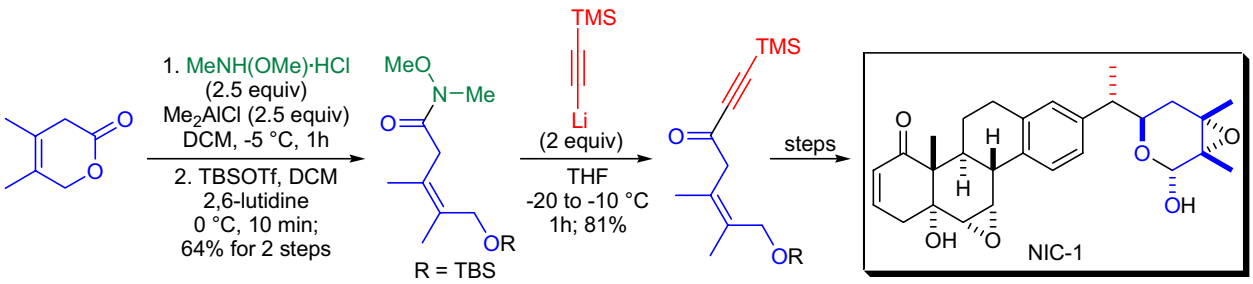
The first total synthesis of the *Stemona* alkaloid (–)-tuberostemonine was accomplished by P. Wipf and co-workers.[24] The installation of the butyrolactone moiety commenced with the preparation of a Weinreb's amide from a methyl ester. The tricyclic methyl ester substrate was exposed to *N,O*-dimethylhydroxylamine hydrochloride and Me_2AlCl and the tertiary amide was isolated in excellent yield. Next, the bromo ortho ester was treated with LDBB in THF to generate the corresponding primary alkyllithium species, which cleanly and efficiently added to the Weinreb's amide to afford the desired ketone.



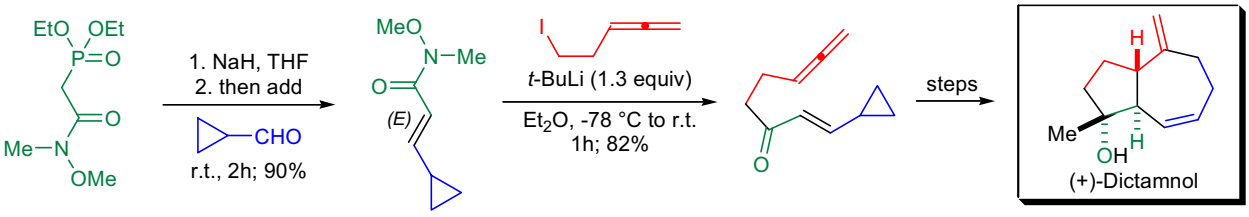
The preparation of the C1-C21 subunit of the protein phosphatase inhibitor tautomycin was completed by J.A. Marshall et al., and it constituted a formal total synthesis of the natural product.[25] The spiroketal carbon of the target was introduced by the *Weinreb ketone synthesis* between a lithioalkyne and *N*-methoxy-*N*-methylurea (a carbon monoxide equivalent). The triple bond of the resulting Weinreb's amide was first reduced under catalytic hydrogenation conditions to yield the corresponding saturated amide, which was reacted with another lithium acetylide to afford an ynone.



In the laboratory of E.J. Corey, the first synthesis of nicandrenones (NIC), a structurally complex steroid-derived family of natural products, was accomplished.[26] The side chain of NIC-1 was constructed from the known six-membered lactone which was converted to the Weinreb's amide by treating it with excess MeNH(OMe)·HCl and trimethyl-aluminum. The resulting primary alcohol was protected as the TBS ether. The ethynylation of this amide was carried out by reaction with two equivalents of lithium trimethylsilylacetylide to afford an ynone, which was reduced enantioselectively to the corresponding propargylic alcohol using *CBS reduction*.



The *rhodium-catalyzed intramolecular [5+2] cycloaddition* of an allene and vinylcyclopropane was the key step in the asymmetric total synthesis of the trinorguaiane sesquiterpene (+)-dictamnol by P.A. Wender and co-workers.[27] The cyclization precursor allene-cyclopropane was assembled starting from commercially available cyclopropane-carbaldehyde. Using the *HWE olefination*, the Weinreb's amide moiety was installed and subsequently reacted with a primary alkyllithium that was generated *via* lithium-halogen exchange.



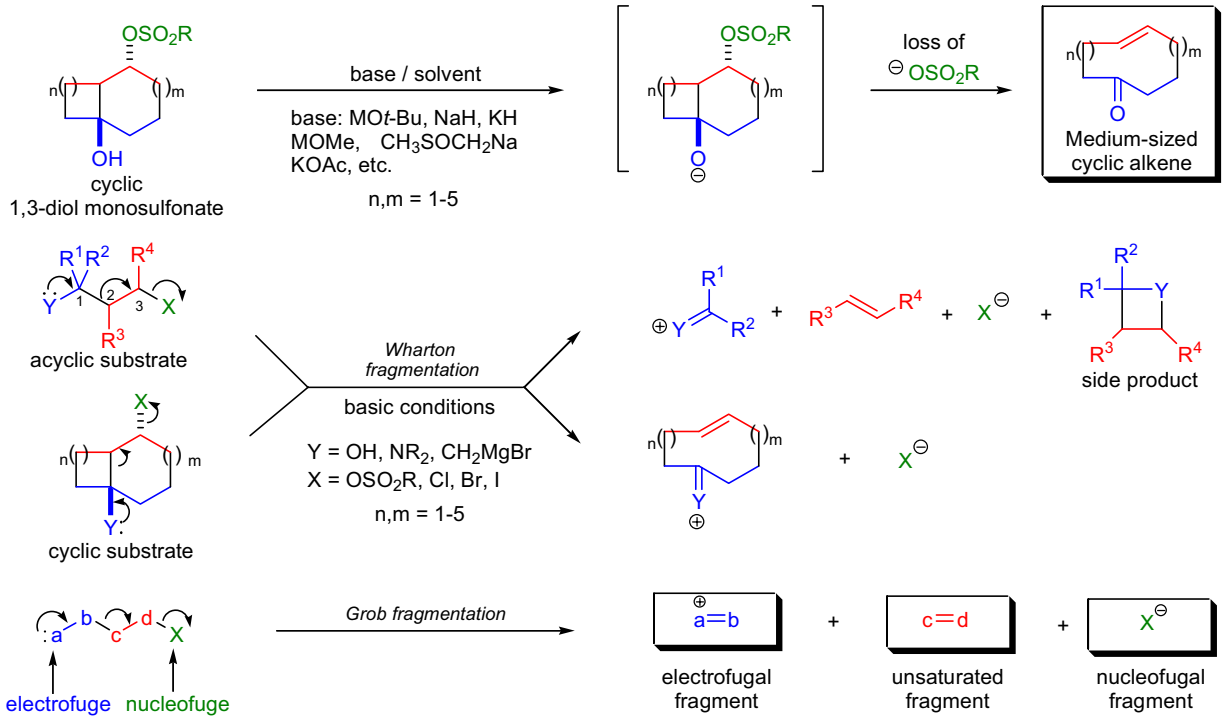
WHARTON FRAGMENTATION

(References are on page 705)

Importance:

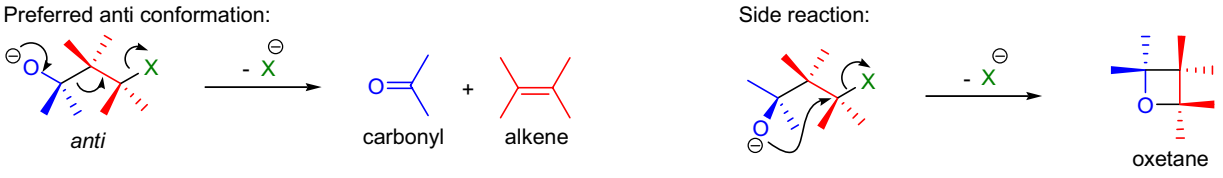
[*Seminal Publications*[1-5]; *Reviews*;[6-11] *Modifications & Improvements*[12-17]]

In 1961, P.S. Wharton investigated the potassium-*tert*-butoxide-induced heterolytic fragmentation of a bicyclic 1,3-diol monomesylate ester (functionalized decalin system), to form a 10-membered cyclic alkene stereospecifically.[2] The base-induced stereospecific fragmentation of cyclic 1,3-diol monosulfonate esters (X=OSO_2R; Y=OH) to form medium-sized cyclic alkenes is known as the *Wharton fragmentation*. Wharton and co-workers contributed to this area extensively by uncovering the stereoelectronic requirements for the reaction as well as demonstrating its synthetic utility. This fragmentation, however, falls into the category of *Grob-type fragmentations* in which carbon chains with a variety of combinations of nucleophilic atoms (heteroatoms) and leaving groups give rise to three fragments.[18] The general features of the *Wharton fragmentation* are the following: 1) synthetically, cyclic 1,3-diol derivatives are the most useful substrates, since acyclic precursors often give rise to side-products (e.g., oxetanes, Y=O) resulting from an intramolecular displacement; 2) cyclic 1,3-hydroxy monotosylates and monomesylates are the most widely used substrates, and they are prepared by treating the unsymmetrical 1,3-diol with one equivalent of MsCl or TsCl; 3) the rate of the fragmentation depends on the concentration of the anion derived from the 1,3-diol derivative; 3) strong and less nucleophilic bases favor the fragmentation, whereas more nucleophilic bases favor intramolecular substitution and elimination of the leaving group; 4) KO*t*-Bu/*t*-BuOH and dimsylsodium/DMSO are the most often used base/solvent combination; 5) if the substrate has considerable ring strain (e.g., n=1), even weaker bases (e.g., NEt_3) will initiate successful fragmentation; 6) when the fragmentation product is labile (e.g., aldehyde), $LiAlH_4$ can serve as both a basic initiator and a reducing agent, since it instantly traps (reduces) the initial product avoiding undesired side reactions (e.g., *aldol condensation*); 7) alkenes are generated stereospecifically from cyclic substrates in high yield; 8) fragmentations leading to ketones occur more readily than those that give aldehydes; 9) more highly substituted alkenes are formed faster than less substituted ones; and 10) substrates with more ring strain generally fragment faster.



Mechanism:[4,19,10]

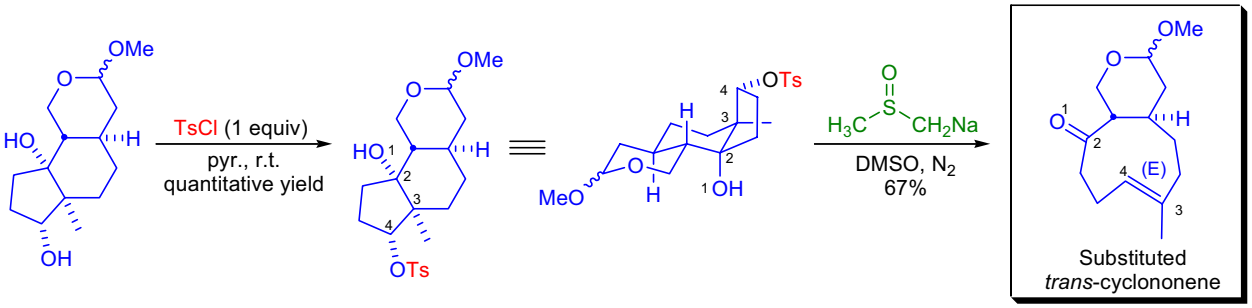
The *Wharton fragmentation* is a concerted reaction and the stereoelectronic requirement is that the bonds that are undergoing the cleavage must be *anti* to each other. This requirement is easily met in cyclic systems; however, acyclic systems have much larger conformational freedom, so side reactions may arise when the conformation of the bonds undergoing cleavage is *gauche*. In cyclic systems the fragmentation becomes slow and complex product mixtures are formed when the conformation of the bonds undergoing cleavage is *gauche*.



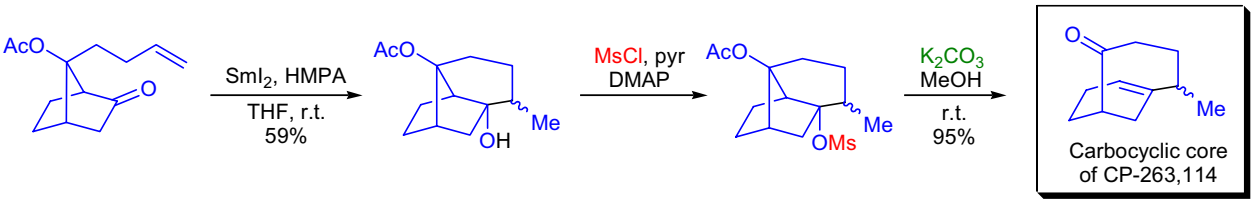
WHARTON FRAGMENTATION

Synthetic Applications:

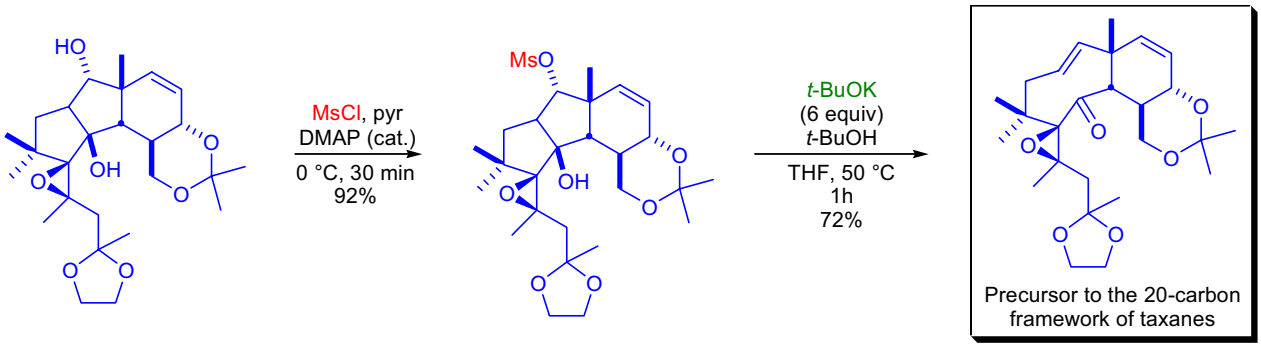
The *Wharton fragmentation* was used as a key step in an approach toward the total synthesis of xenicanes by H. Pfander et al.[20] Two optically active substituted *trans*-cyclononenes were synthesized starting from (-)-Hajos-Parrish ketone. First, the bicyclic 1,3-diol was protected regioselectively on the less sterically hindered hydroxyl group with *p*-toluenesulfonyl chloride in quantitative yield. Next, the monosulfonate ester was exposed to dimsylsodium in DMSO, which is a strong base, to initiate the desired heterolytic fragmentation.



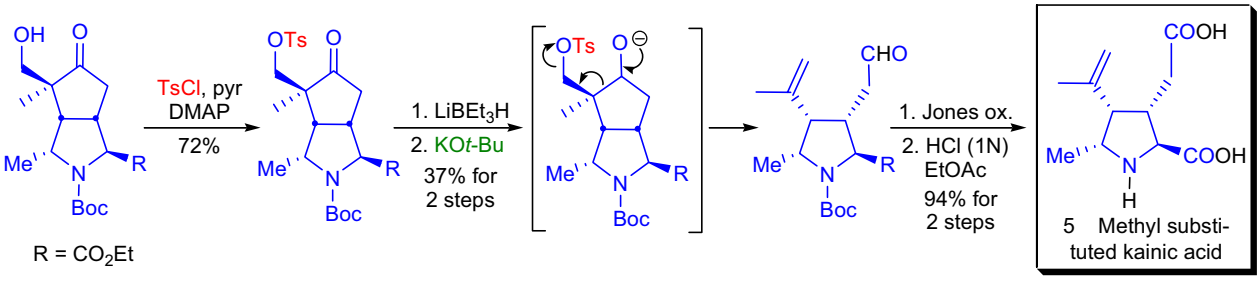
A novel synthetic approach was developed for the norbornane-based carbocyclic core of CP-263,114 in the laboratory of J.L. Wood.[21] Initial attempts to prepare the core using the *oxy-Cope rearrangement* failed even under forcing conditions, so an alternative approach utilizing the *Wharton fragmentation* was chosen. The tricyclic 1,3-diol substrate was prepared by the SmI_2-mediated 5-exo-trig *ketyl radical cyclization*. The resulting tertiary alcohol was mesylated and subjected to methanolysis, which afforded the *Wharton fragmentation* product in an almost quantitative yield.



Research by S. Arseniyadis and co-workers showed that the *aldol-annelation-fragmentation* strategy could be used for the synthesis of complex structures, which are precursors of a variety of taxoid natural products.[22] This strategy allows the preparation of the twenty-carbon framework of taxanes from inexpensive and simple starting materials.



The stereocontrolled synthesis of 5 -substituted kainic acids was achieved by A. Rubio et al.[23] The C3 and C4 substituents were introduced by the *Wharton fragmentation* of a bicyclic monotosylated 1,3-diol. When this secondary alcohol was exposed to KO*t*-Bu, the corresponding fragmentation product was obtained in moderate yield. *Jones oxidation* of the aldehyde to the carboxylic acid followed by hydrolysis of the ester and removal of the Boc group resulted in the desired substituted kainic acid.



WHARTON OLEFIN SYNTHESIS (WHARTON TRANSPOSITION)

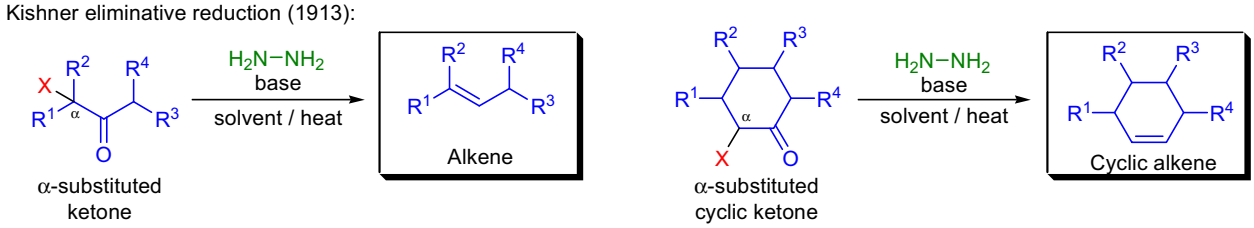
(References are on page 706)

Importance:

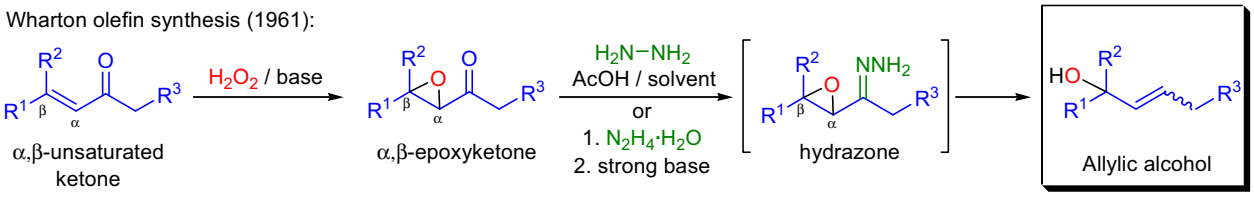
[*Seminal Publications*[1-4]*; Reviews*[5]*; Modifications & Improvements*[6-8]]

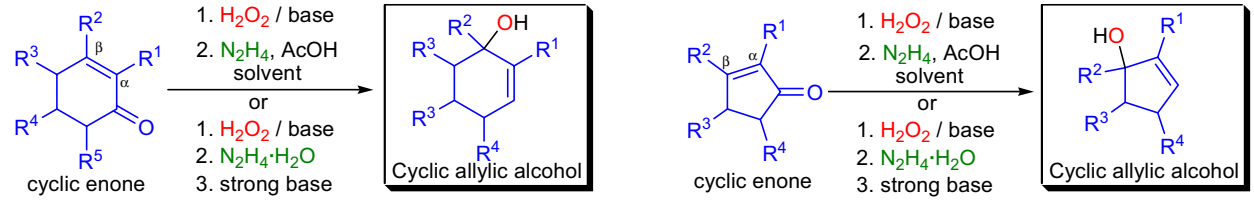
In 1913, N. Kishner reported that treating 2-hydroxy-2,6-dimethyloctan-3-one under standard *Wolff-Kishner reduction* conditions (N_2H_4/KOH/glycol/heat) gave the corresponding reductive elimination product 2,6-dimethyl-2-octene.[1] This transformation is known as the *Kishner eliminative reduction*. It was shown to work with a wide variety of α-substituted ketones, so it offers a convenient and regioselective introduction of a double bond into acyclic and cyclic ketones.[9,10] In 1961, an extension of this method was introduced independently by P.S. Wharton and Huang-Minlon when they described the rearrangement of α,β-epoxyketones to allylic alcohols *via* the corresponding epoxyhydrazones. Today, this transformation is referred to as the *Wharton olefin synthesis* or *Wharton transposition*.[3,4] The general features of this transformation are the following:[8] 1) the epoxidation of α,β-unsaturated ketones is achieved usually by basic hydrogen peroxide solution in high yield; 2) according to the classical Wharton conditions, the epoxyketone was treated with 2-3 equivalents of hydrazine hydrate in the presence of substoichiometric amounts of acetic acid, and the allylic alcohol product formed in a matter of minutes; 3) the classical reaction conditions are not free of water, which is unsuitable for sensitive substrates; 4) stable epoxyhydrazones can be prepared by treating the epoxyketones with hydrazyne hydrate in CH_2Cl_2, and in a separate step a strong base (e.g., KDA, KO*t*-Bu) is added at low temperature to afford the desired products; 5) unstable epoxyhydrazones can be prepared and rearranged when the corresponding epoxyketones are added to the solution of an *in situ* generated hydrazine (hydrazine salt + NEt_3), which is anhydrous; and 6) in acyclic systems there is no marked selectivity for the configuration of the new double bond.

Kishner eliminative reduction (1913):



Wharton olefin synthesis (1961):

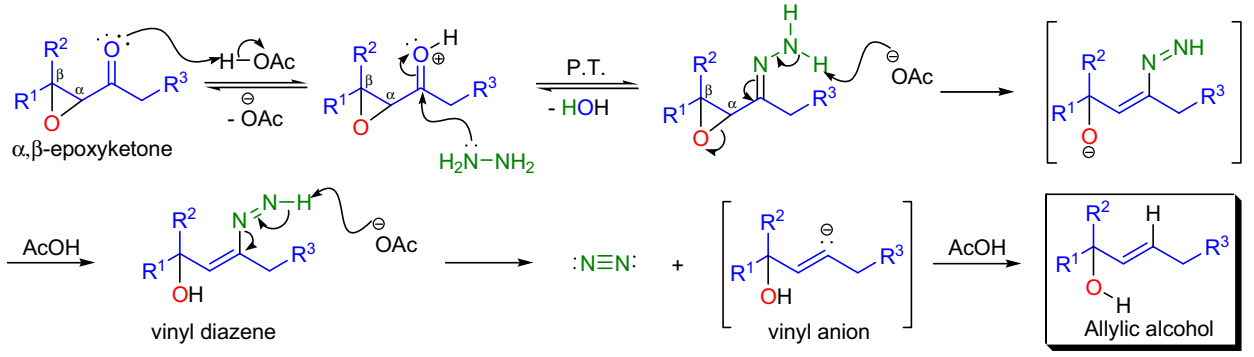




X = OH, *O*-alkyl, OPh, NR_2, *S*-alkyl, OCO-alkyl, Cl, Br, I; R^1,R^2,R^3,R^4, R^5 = H, alkyl, aryl

Mechanism:[4,6,8]

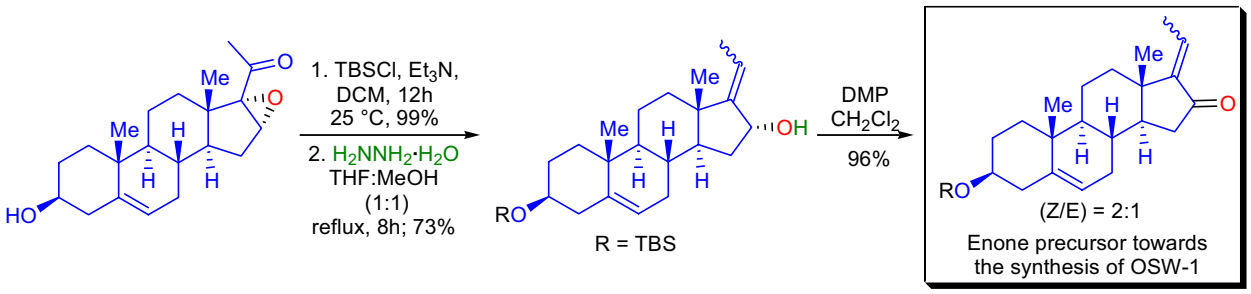
The mechanism of the *Wharton transposition* is very similar to that of the *Wolff-Kishner reaction*. The epoxyhydrazone is first deprotonated, which triggers the facile and irreversible epoxide ring-opening. The C-N bond of the resulting vinyl diazene[11,12] is broken upon another deprotonation, releasing N_2 and a vinyl anion, which in turn affords the desired allylic alcohol. Alternatively, the formation of a vinyl radical has been proposed.[6]



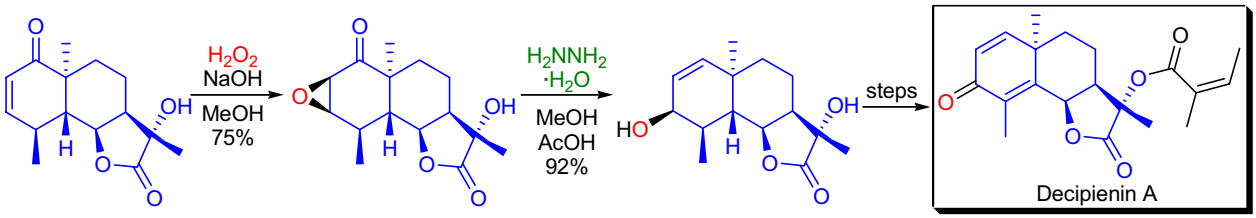
WHARTON OLEFIN SYNTHESIS (WHARTON TRANSPOSITION)

Synthetic Applications:

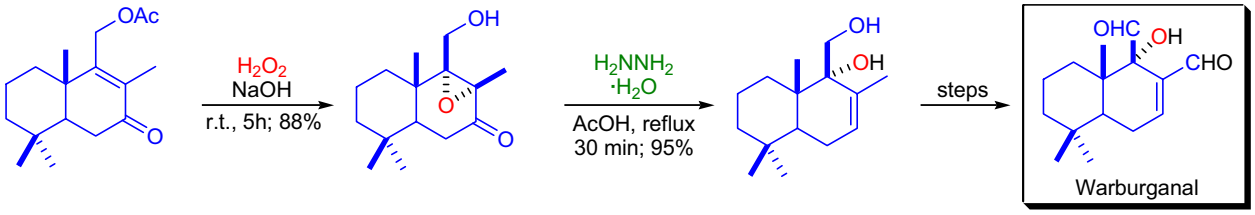
During the total synthesis of the anticancer natural product OSW-1, Z. Jin and co-workers explored several approaches to prepare a crucial steroid enone precursor with high stereoselectivity.[13] In one of the approaches, the commercially available 5-pergnen-16,17-epoxy-3β-ol-20-one was protected with a TBS group and was subjected to the *Wharton transposition*. The epoxyketone was treated with hydrazine hydrate in THF/MeOH under reflux to give the expected allylic alcohol in good yield. The desired enone was obtained by the *Dess-Martin oxidation* of the allylic alcohol with a slight preference for the (*Z*)-stereoisomer.



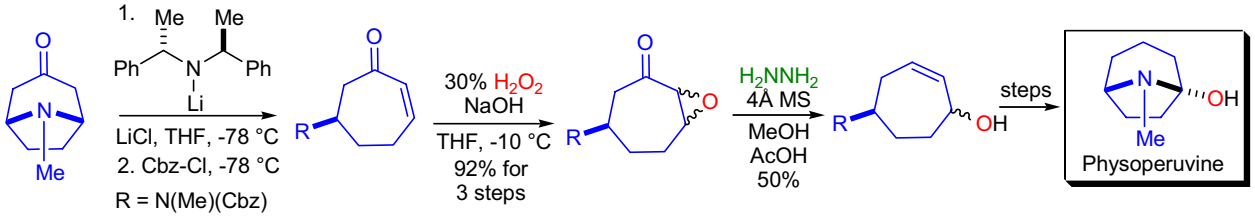
The racemic synthesis of decipienin A was accomplished in the laboratory of G.M. Massanet.[14] In the late stages of the total synthesis, the tricyclic enone lactone was converted to the corresponding α,β-epoxyketone by treatment with hydrogen peroxide in the presence of NaOH. The epoxyketone was subjected to the conditions of the *Wharton transposition* to afford the cyclic allylic alcohol in excellent yield. Several subsequent steps completed the total synthesis.



The synthesis of the bioactive natural product warburganal from (-)-sclareol was carried out by A.F. Barrero et al.[15] The bicyclic allylic acetate was epoxidized and deacetylated under basic conditions. Next, the solution of the ketoepoxide in glacial acetic acid was treated with hydrazine hydrate and the resulting mixture was heated at reflux for 30 minutes to afford the bicyclic allylic diol in excellent yield.



Research by M. Majewski et al. showed that the enantioselective ring opening of tropinone allowed for a novel way to synthesize tropane alkaloids such as physoperuvine.[16] The treatment of tropinone with a chiral lithium amide base resulted in an enantioslective deprotonation, which resulted in the facile opening of the five-membered ring to give a substituted cycloheptenone. This enone was subjected to the *Wharton transposition* by first epoxidation under basic conditions followed by addition of anhydrous hydrazine in MeOH in the presence of catalytic amounts of glacial acetic acid.



WILLIAMSON ETHER SYNTHESIS

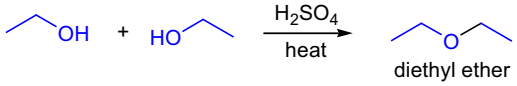
(References are on page 706)

Importance:

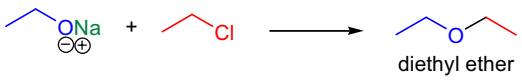
[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-19]; *Theoretical Studies*[20]]

In 1851, W. Williamson was the first to establish the correct formula of diethyl ether, which was first prepared by V. Cordus in 1544 by heating ethanol with sulfuric acid.[1] Williamson synthesized diethyl ether from sodium ethoxide and ethyl chloride. The reaction of aliphatic or aromatic alkoxides with alkyl, allyl, or benzyl halides to afford the corresponding ethers is known as the *Williamson ether synthesis*. The general features of this transformation are: 1) alkali metal alkoxides of simple aliphatic primary, secondary and tertiary alcohols are easily prepared by the use of strong bases such as NaH, KH, LHMDS, or LDA; 2) preparation of alkali metal salts of phenols (hydroxy-substituted aromatic or heteroaromatic compounds) are accomplished by reacting them with weak bases such as sodium- or potassium hydroxide or alkali metal carbonates such as potassium- or cesium carbonate, since phenols are more acidic than aliphatic alcohols; 3) alternatively, the alcohol can be directly reacted with alkali metals such as sodium or potassium at ambient or elevated temperatures in the neat substrate or at low temperature in liquid ammonia; the pure alkoxides are obtained by evaporating the excess alcohol or the liquid ammonia; 4) most alkali metal alkoxides and phenoxides can be obtained in crystalline form and stored indefinitely under an inert gas atmosphere and in the absence of moisture; 5) the reaction is usually carried out in a dipolar aprotic solvent such as DMF or DMSO to minimize side products as a result of dehydrohalogenation; 6) the choice of the alkyl halide component is critical to the success of the reaction: primary alkyl, methyl, allylic, and benzylic halides give the highest yields, since these undergo S_N2 type halide displacement by the alkoxide nucleophile; 7) the order of reactivity for the halides regarding the alkyl group: Me>allylic~benzylic>1° alkyl>2°alkyl while under standard conditions tertiary alkyl halides undergo E2 elimination to afford the corresponding alkenes; 8) the order of reactivity is also influenced by the nature of the leaving group: OTs~I>OMs>Br>Cl; and 9) when alkyl dihalides containing two different halogen atoms (such as Cl or I) are employed in the reaction, the chemoselective displacement of the better leaving group will occur. The preparation of diaryl ethers from phenoxides and unactivated aryl halides is not possible under the reaction conditions of the *Williamson ether synthesis*, but in the presence of copper metal or Cu(I)-salt catalysts, diaryl ethers are obtained (see *Ullmann biaryl ether synthesis*). When the aryl halide is activated (strongly electron-withdrawing substituents are present) the displacement of the halogen atom by the alkoxide is possible in the absence of catalyst (nucleophilic aromatic substitution). There are a few limitations of *Williamson ether synthesis*: 1) tertiary alkyl halides or sterically hindered primary or secondary alkyl halides tend to undergo E2 elimination in the presence of the alkoxide that in addition to being a nucleophile also acts as a base; and 2) alkali phenoxides may undergo *C*-alkylation in addition to expected *O*-alkylation.

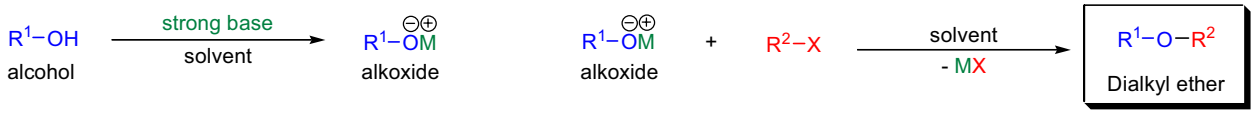
Valerius Cordus (1544):



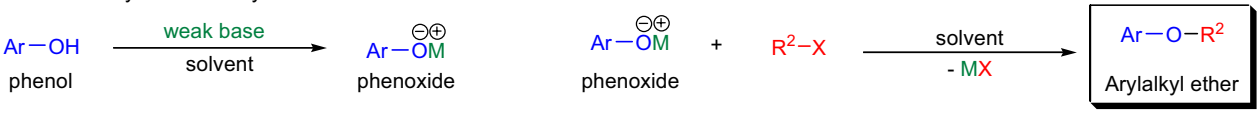
Williamson (1851):



Williamson synthesis of dialkyl ethers:



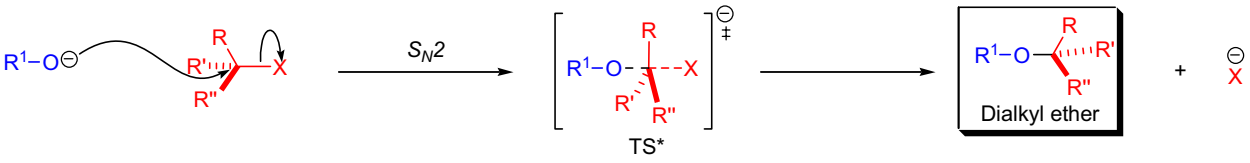
Williamson synthesis of aryl ethers:



R^1 = 1°, 2° or 3° alkyl, allyl, benzyl; Ar = aryl, heteroaryl; M = Li, Na, K, Cs; R^2 = 1° or 2° alkyl, allyl, benzyl; X = Cl, Br, I, OMs, OTs; strong base: alkali metals/liquid ammonia, metal hydrides, LHMDS, LDA; weak base: NaOH, KOH, K_2CO_3, Cs_2CO_3; solvent: usually dipolar aprotic such as DMSO, DMF

Mechanism:[21-24]

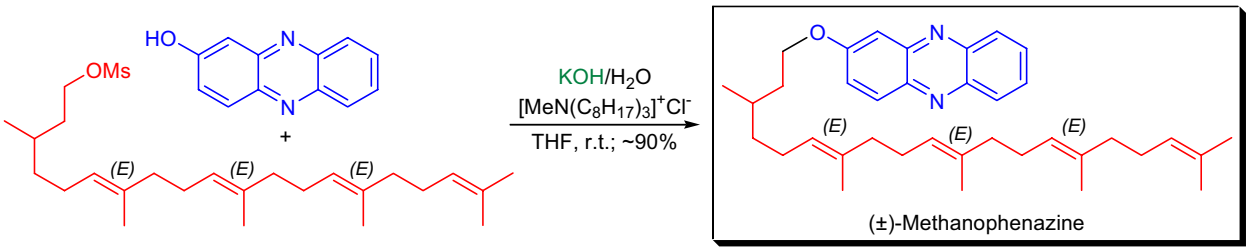
In the case of most alkoxides and primary or secondary alkyl halides, the mechanism of the *Williamson ether synthesis* proceeds *via* an S_N2 process. When the alkyl halide is secondary (R"=H) with a given absolute configuration, the product ether will have a complete inversion of configuration at that particular stereocenter. E.C. Ashby demonstrated, however, that the reaction between lithium alkoxides and alkyl iodides proceeds *via* single-electron transfer.[22]



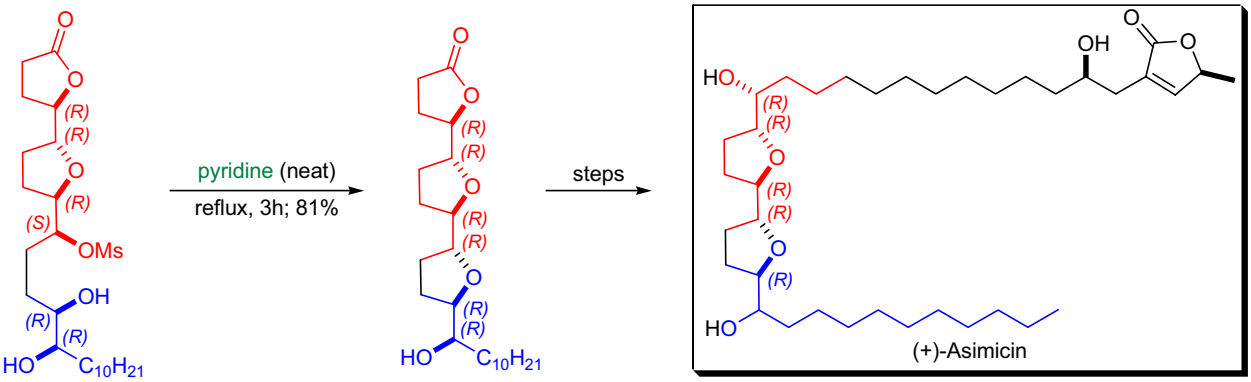
WILLIAMSON ETHER SYNTHESIS

Synthetic Applications:

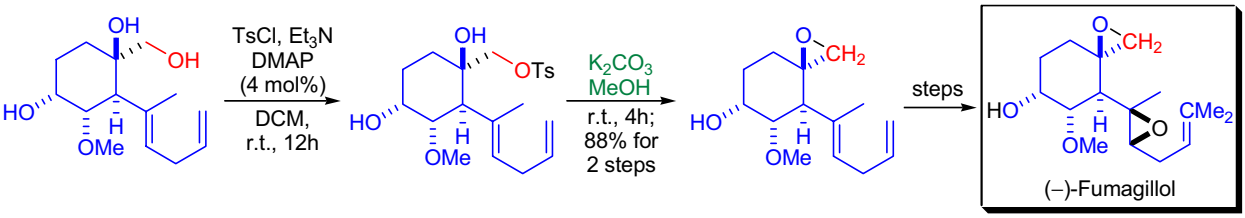
The redox-active natural product (±)-methanophenazine (MP) is the first phenazine to be isolated from archea. This compound is able to mediate the electron transport between membrane-bound enzymes and was characterized as the first phenazine derivative involved in the electron transport of biological systems. The research team of U. Beifuss prepared this natural product by using the *Williamson ether synthesis* in the last step of the synthetic sequence.[25] The etherification was conducted under phase-transfer conditions in a THF/water system in the presence of methyltrioctyl-ammonium chloride and using potassium hydroxide as a base.



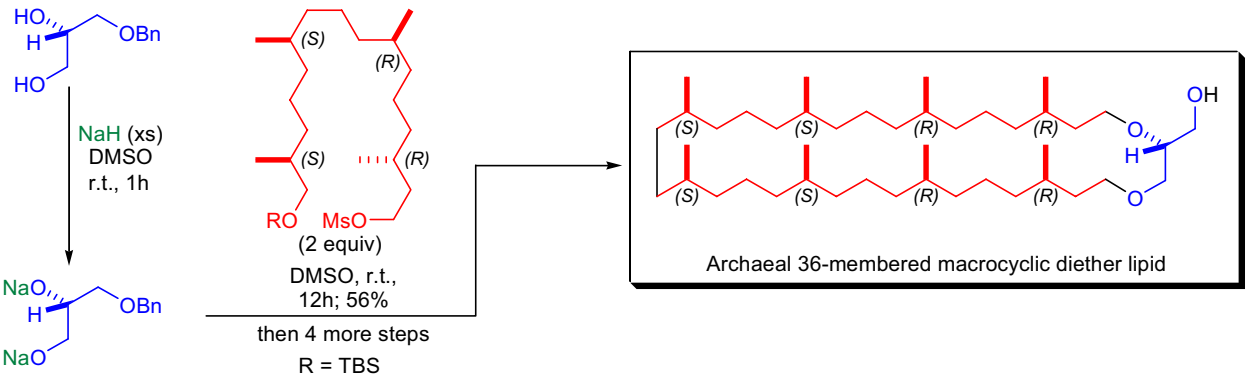
The total synthesis of (+)-asimicin, which belongs to the family of Annonaceous acetogenins, was completed by E. Keinan and co-workers.[26] In order to create one of the tetrahydrofuran rings stereospecifically, an *intramolecular Williamson ether synthesis* was performed between a secondary alcohol and a secondary mesylate using pyridine as the base.



In the laboratory of D. Kim, the asymmetric total synthesis of (–)-fumagillol, the hydrolysis product of fumagillin, was accomplished.[27] The stereoselective introduction of the sensitive 1,1-disubstituted epoxide moiety took place in the final stages of the synthesis. The primary alcohol portion of the vicinal diol functionality was first selectively converted to the corresponding tosylate. Upon treatment with K_2CO_3/MeOH the epoxide formation occurred smoothly.



The two key ether linkages during the total synthesis of archaeal 36-membered macrocyclic diether lipid by K. Kakinuma and co-workers were formed using the *Williamson ether synthesis*.[28] Two equivalents of the enantiopure isoprenoid mesylate was added to the dialkoxide derived from 1-*O*-benzyl-glycerol and the corresponding diether was isolated in good yield. Four more steps including a *McMurry coupling* completed the synthetic sequence.



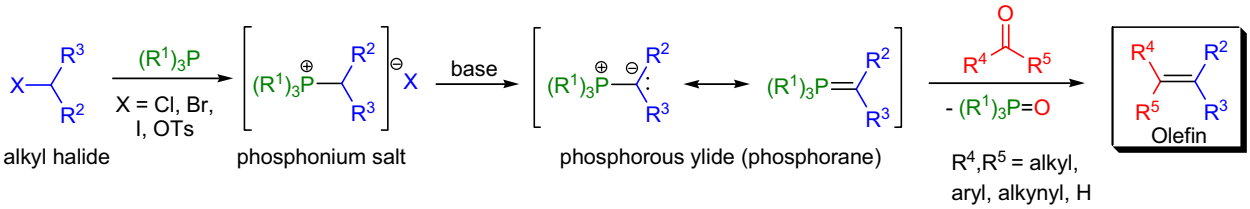
WITTIG REACTION

(References are on page 707)

Importance:

[*Seminal Publications*[1-5]; *Reviews*[6-40]; *Modifications & Improvements*[41-54]; *Theoretical Studies*[55-70]]

In the early 1950s, G. Wittig and G. Geissler investigated the chemistry of pentavalent phosphorous and described the reaction between methylenetriphenylphosphorane ($Ph_3P{=}CH_2$) and benzophenone, which gave 1,1-diphenylethene and triphenylphosphine oxide ($Ph_3P{=}O$) in quantitative yield.[3] Wittig recognized the importance of this observation and conducted a systematic study in which several phosphoranes were reacted with various aldehydes and ketones to obtain the corresponding olefins.[4,5] The formation of carbon-carbon double bonds (olefins) from carbonyl compounds and phosphoranes (phosphorous ylides) is known as the *Wittig reaction*. From a historical point of view it is important to note that Wittig was not the first to prepare a phosphorane, since Staudinger and Marvel had reported the synthesis of such compounds three decades before.[1,2] Since its discovery, the *Wittig reaction* has become one the most important and most effective method for the synthesis of alkenes. The active reagent in this transformation is the phosphorous ylide, which is usually prepared from a triaryl- or trialkylphosphine and an alkyl halide (1° or 2°) followed by deprotonation with a suitable base (e.g., RLi, NaH, NaOR, etc.). There are three different types of ylides depending on the nature of the R^2 and R^3 substituents: 1) in the "*stabilized*" ylides the alkyl halide component has at least one strong electron-withdrawing group (-CO_2R, -SO_2R, etc.), which stabilizes the formal negative charge on the carbon; 2) "semi-stabilized" ylides have at least one aryl or alkenyl substituents as the R^2 or R^3 groups, which are less stabilizing; and 3) "nonstabilized" ylides usually have only alkyl substituents, which do not stabilize the formal negative charge on the carbon. The general features of the *Wittig reaction* are: 1) the phosphonium salts are usually prepared using triphenylphosphine, and the phosphorous ylides are generated before the reaction or *in situ*; 2) the ylides are water as well as oxygen-sensitive; 3) the phosphorous ylides chemoselectively react with aldehydes (fast) and ketones (slow), other carbonyl groups (e.g., esters, amides) remain intact during the reaction; 4) the stereoselectivity, *E*-or *Z*-selectivity, is influenced by many factors: type of ylide, type of carbonyl compound, nature of solvent, and the counterion for the ylide formation; 5) "nonstabilized" ylides under salt-free conditions in a dipolar aprotic solvent with aldehydes afford olefins with high (*Z*)-selectivity; 6) "stabilized" ylides give predominantly (*E*)-olefins with aldehydes under the same salt-free conditions; 7) "semi-stabilized" ylides usually give alkenes with poorer steroselectivity; and 8) ether solvents such as THF, Et_2O, DME, MTBE, or toluene are used. The *Wittig reaction* has several important variants: 1) the *Horner-Wittig reaction* takes place when the phosphorous ylides contain phosphine oxides in place of triarylphosphines;[71] 2) the use of stabilized alkyl phosphonate carbanions is known as the *Horner-Wadsworth-Emmons reaction* in which (*E*)-α,β-unsaturated esters are formed;[72] 3) in the *Schlosser modification*, "nonstabilized" ylides can give pure (*E*)-alkenes when two equivalents of Li-halide salt is present in the reaction mixture;[73] 4) *asymmetric Wittig reaction* were also developed;[53] and 5) *Wittig reaction* on solid support allows easy separation of the products from triphenylphosphine oxide.[42]



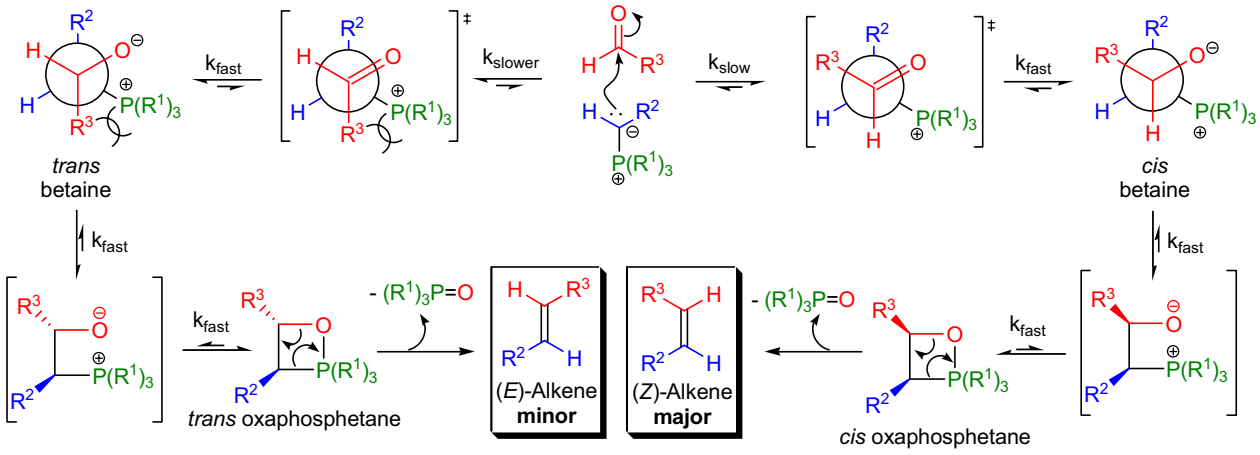
if R^1 = aryl and R^2, R^3 = alkyl, H ⇨ "nonstabilized" ylide

if R^1 = aryl and R^2, R^3 = aryl, alkenyl, benzyl, allyl, H ⇨ "semi-stabilized" ylide

if R^1 = aryl and R^2, R^3 = -CO_2R, -SO_2R, -CN, -COR ⇨ "stabilized" ylide

Mechanism:

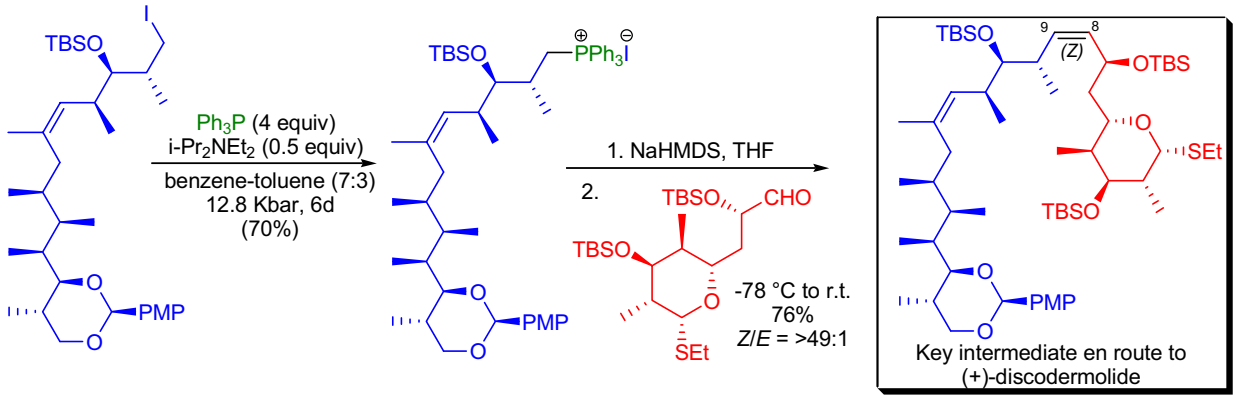
9,23,74-77,28,78-82,37



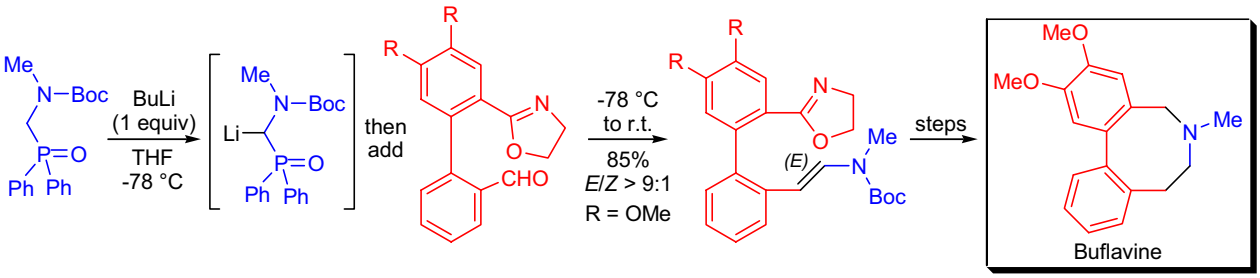
WITTIG REACTION

Synthetic Applications:

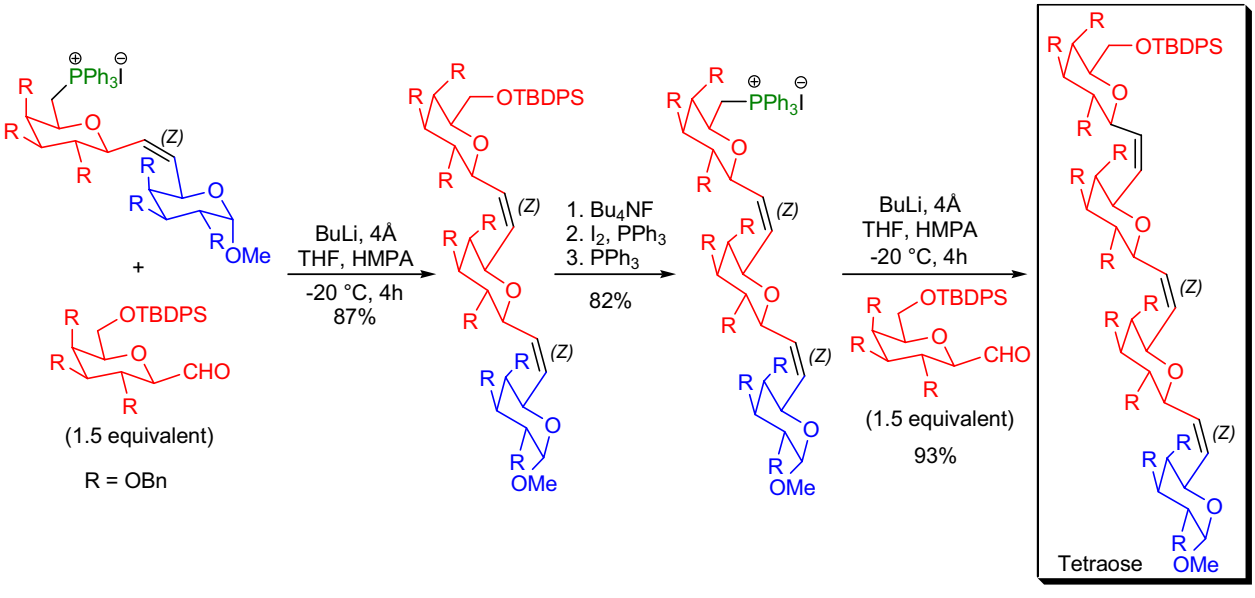
In the late stages of the gram-scale synthesis of (+)-discodermolide, A.B. Smith and co-workers utilized the highly *Z*-*selective Wittig reaction* to couple two advanced intermediates, a phosphonium salt and an aldehyde.[83] The phosphonium salt was prepared using the primary alkyl iodide, triphenylphosphine, Hünig's base, and high pressure. This procedure was necessary because the traditional methods led to the formation of substantial amounts of side-products and decomposition. The Hünig's base trapped any HI that was generated during the process and prevented the formation of decomposition products. The phosphonium salt was deprotonated with NaHMDS which, upon reacting with the aldehyde, afforded the desired C8-C9 alkene with high *Z*-selectivity.



The total synthesis of amaryllidaceae alkaloid buflavin was achieved in the laboratory of A. Couture by utilizing a *Horner-Wittig reaction* between a biaryl aldehyde and a metalated carbamate.[84] The diphenyl phosphine oxide carbamate was deprotonated with *n*-BuLi. To the resulting metalated carbamate was added the solution of the biaryl aldehyde in THF. The reaction afforded the corresponding (*Z*)- and (*E*)-enecarbamates in good yield and with high *E*-selectivity.



The *iterative Wittig olefination* was used to assemble -D-C-(1,6)-linked oligoglucoses and oligogalactoses, which are connected through olefinic bridges. The strategy by A. Dondoni et al. involved the coupling of the sugar aldehyde building block with a substrate having a phosphorous ylide functionality at C6.[85] The yields were good in each step, and oligosaccharides up to pentaoses were prepared. The synthesis of a tetraose is illustrated.



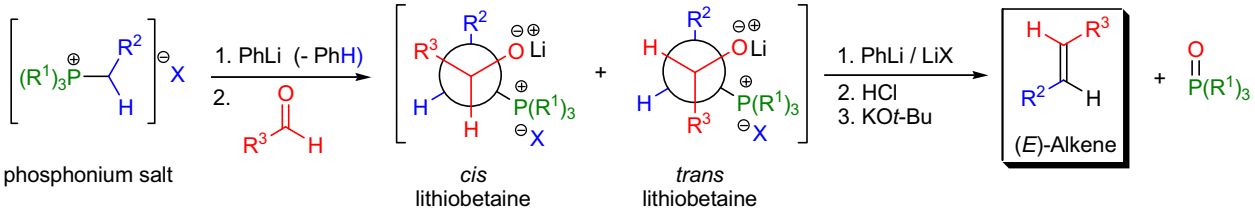
WITTIG REACTION - SCHLOSSER MODIFICATION

(References are on page 708)

Importance:

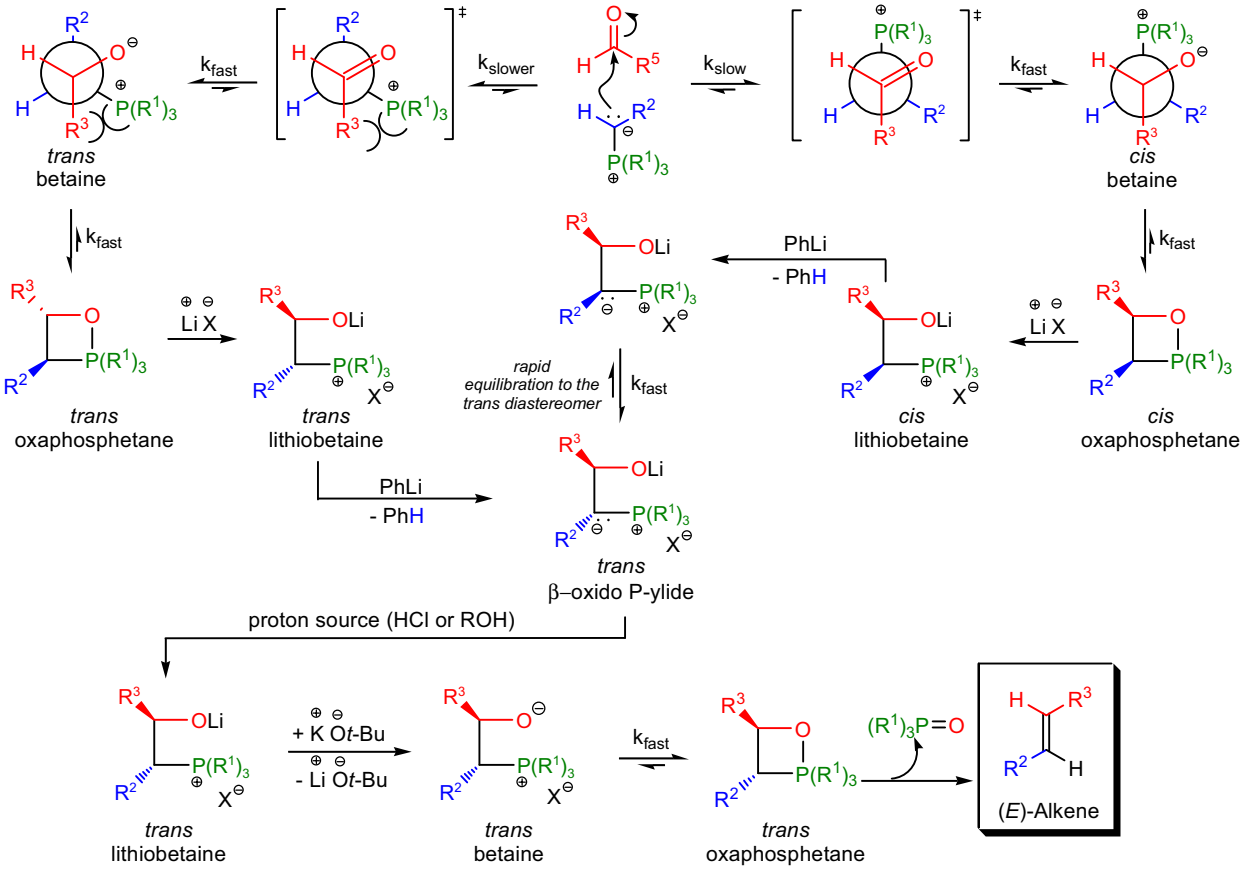
[*Seminal Publication*[1]; *Reviews*[2-6]; *Modifications & Improvements*[7-10]]

The one-pot multistep preparation of (*E*)-alkenes from "nonstabilized" phosphorous ylides and carbonyl compounds by the equilibration of the intermediate lithiobetaines is known as the *Schlosser modification of the Wittig reaction*. In the decade following the disclosure of a novel olefin synthesis using phosphorous ylides and carbonyl compounds by G. Wittig and G. Geissler,[11-13] intensive research was conducted to reveal what intermediates were involved in the reaction and what factors influenced the stereoselectivity. It was established early on that the so-called oxaphosphetanes (four-membered heterocycles containing a P-O bond) were the key intermediates, and the *cis*- and *trans* diastereomers decompose *via* cycloreversion to the corresponding *cis* and *trans* alkenes. In 1966, M. Schlosser reported that in the presence of excess lithium halide, the P-O bond of the oxaphosphetanes was rapidly cleaved and the corresponding diastereomeric lithiobetaines were formed.[1] At low temperature the lithiobetaines (pK_a = ~20) were deprotonated at their α-positions with alkyl- or aryllithiums[14] (PhLi, n-BuLi, etc.), and the resulting β-oxido phosphorous ylides rapidly equilibrated to give the thermodynamically more stable *trans* diastereomer. At this point, the diastereomerically pure *trans* β-oxido phosphorous ylide was protonated stereospecifically with one equivalent of a proton source (HCl in ether or alcohol) or an electrophile[7-10] to afford the pure *trans* lithiobetaine and the excess lithium halide was removed with KO*t*-Bu. The resulting *trans* betaine gave the corresponding (*E*)-alkene *via* the *trans* oxaphosphetane.



R^1 = aryl; R^2 = alkyl, H; R^3 = alkyl, aryl; X = Cl, Br, I

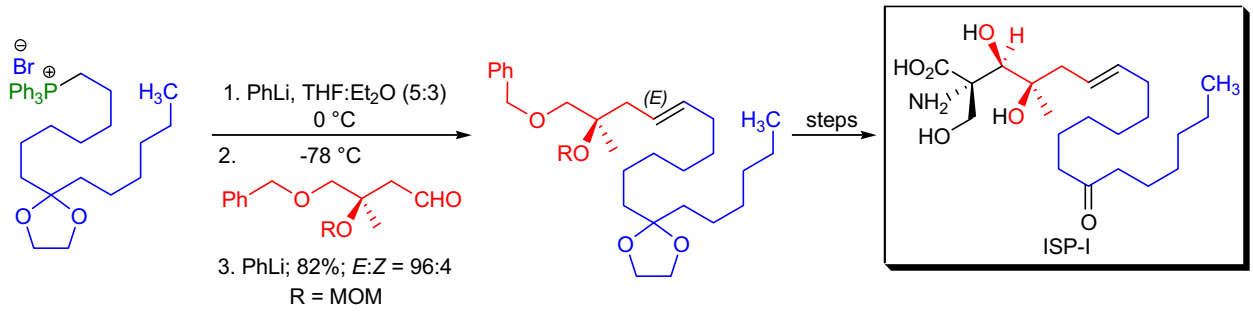
Mechanism:[2,15,14]



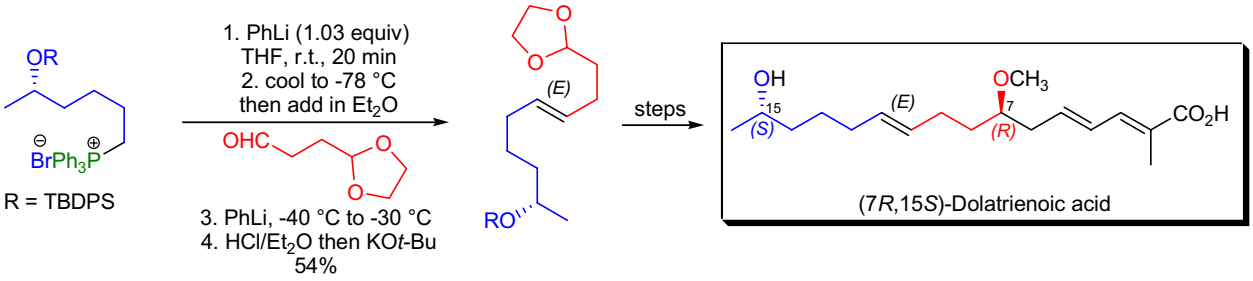
WITTIG REACTION - SCHLOSSER MODIFICATION

Synthetic Applications:

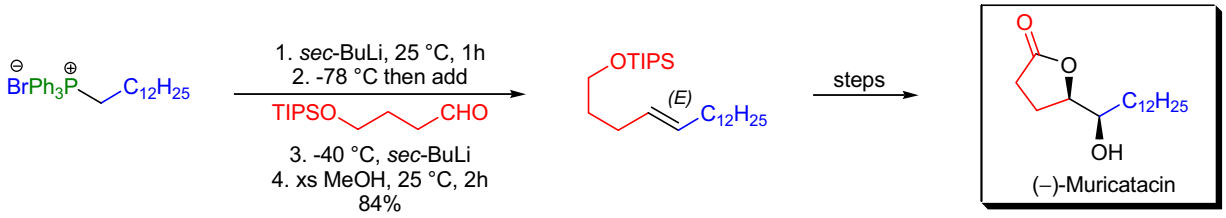
The asymmetric total synthesis of ISP-I (myriocin, thermozymocidin) was accomplished by utilizing the *Schlosser modified Wittig reaction* as one of the key steps in the laboratory of Y. Nagao.[16] The phosphonium bromide fragment was treated with PhLi at 0 °C to generate the phosphorous ylide which was reacted with the aldehyde at -78 °C. The resulting mixture of lithiobetaines was treated with PhLi at 0 °C to afford the desired (*E*)-alkene with excellent stereoselectivity.



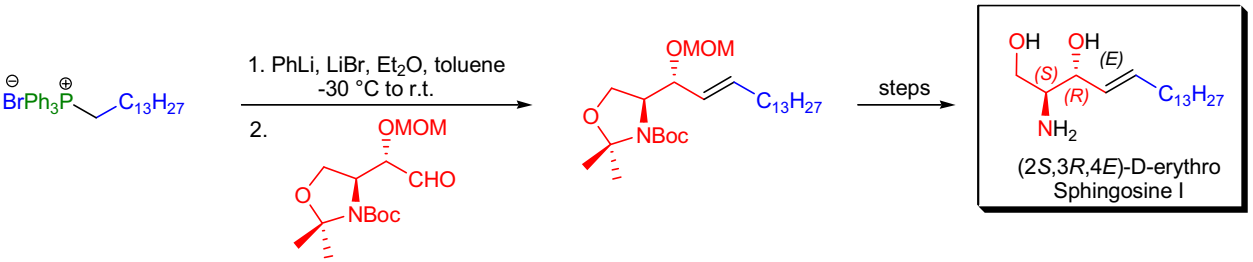
During the stereospecific total synthesis of (7*S*,15*S*) and (7*R*, 15*S*)-dolatrienoic acid by G.R. Pettit et al., the C7-C10 and C11-C16 subunits were coupled using the highly (*E*)-selective *Wittig-Schlosser reaction*.[17] The traditional Wittig conditions resulted in a mixture of alkenes in which the (*Z*)-stereoisomer was predominant. When the *Schlosser conditions* were applied, the stereoselectivity was reversed in favor of the (*E*)-alkene.



A simple and efficient method was developed by E.A. Couladouros and co-workers for the synthesis of optically pure five- or six-membered hydroxylactones.[18] The method begins from γ-butyrolactone and uses the following key transformations: reduction, *Wittig-Schlosser reaction*, *Sharpless asymmetric dihydroxylation*, oxidation, and lactonization. The preparation of antitumor agent (–)-muricatacin was achieved in 6 steps and in 43% overall yield.



In the laboratory of M. Martin-Lomas, a short and enantiodivergent synthetic route was designed and carried out to both D-*erythro* and L-*threo*-sphingosine I and II.[19] The *trans* double bond was introduced using the *Schlosser modified Wittig reaction* by coupling tetradecyltriphenylphosphonium bromide and a chiral aldehyde. Other olefination methods proved inferior: coupling *via* the traditional *Wittig reaction* afforded mostly the *cis* olefin and the *Julia-Lythgoe olefination* gave low yield and low selectivity.



WITTIG-[1,2]- AND [2,3]-REARRANGEMENT

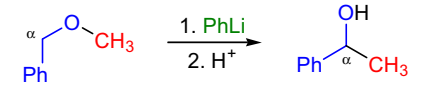
(References are on page 709)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-20]; *Modifications & Improvements*[21-25]; *Theoretical Studies*[26-40]]

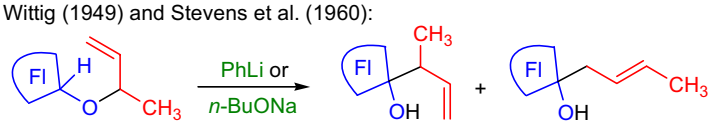
In 1942, G. Wittig and L. Löhmann reported that the deprotonation of benzyl methyl ether with phenyllithium afforded 1-phenylethanol upon work-up.[1] Subsequent studies showed that the transformation was general for α-lithiated aryl alkyl ethers that undergo a facile rearrangement to give lithio alkoxides in an overall *[1,2]-alkyl shift*. The rearrangement of aryl alkyl ethers to the corresponding secondary or tertiary alcohols in the presence of stoichiometric amount of a strong base is known as the *[1,2]-Wittig rearrangement*.[16,18] The most important features are: 1) the R^1 substituent has to be able to stabilize the carbanion; 2) the chiral center in the migrating group retains its configuration; 3) yields are usually moderate due to the harsh reaction conditions and the competing *[1,4]*-pathway; 4) at low temperatures, the formation of the [1,4]-product is favored, while at higher temperatures the [1,2]-product dominates. During the course of early mechanistic studies of this process, the research groups of G. Wittig and T.S. Stevens found that upon deprotonation, allylic ethers mainly underwent a *[2,3]-sigmatropic shift* to afford homoallylic alcohols, a process that is now referred to as the *[2,3]-Wittig rearrangement*.[2,4] The general features of the *[2,3]-rearrangement* are: 1) it proceeds under milder conditions and gives higher yields than the *[1,2]-rearrangement*; 2) virtually any α-(allyloxy)carbanion can udergo the rearrangement; the only limitation lies with the chemist's ability to generate a particular anion with currently available methods; 3) the R^4 substituent should be a carbanion-stabilizing group; 4) the *[1,2]-* and *[2,3]*-shifts often compete, and the amount of each product depends strongly on the structure of the substrate and the reaction temperature; 5) by carefully optimizing the reaction temperature, the formation of the *[1,2]*-rearranged product can be avoided; 6) for acyclic and cyclic substrates, the anions can be generated by a variety of different methods: with a strong base (e.g., LDA, *n*-BuLi) at -60 to -85 °C, *via* a *tin-lithium exchange reaction* (*Still variant*)[21] and by *reductive lithiation* of *O,S*-acetals; 7) because of the highly ordered cyclic transition state, the rearrangement is stereoselective with respect to the stereochemistry of the new double bond and the two new stereocenters;[15] 8) in acyclic substrates, the chirality of the C1 stereocenter of the substrate gets transferred to the product in a predictable fashion, consistent with the orbital symmetry conservation rules;[15,17] 9) the newly formed double bond generally has the (*E*)-stereochemistry, but the *Still variant* (R^4=SnR_3) gives predominantly (*Z*)-olefins; 10) the highest (*E*)-selectivity is achieved when the allylic moiety is only monosubstituted (R^5=alkyl and R^6=H); 11) the diastereoselectivity with respect to the newly created vicinal chiral centers is high: (*Z*)-substrates give *erythro* products with high levels of selectivity, while (*E*)-substrates afford *threo* products with lower selectivity, but the nature of the R^4 substituent also has a profound effect on the level of diastereoselectivity;[17] and 12) five different asymmetric versions of the rearrangement have been identified.[17]

Wittig and Löhmann (1942):



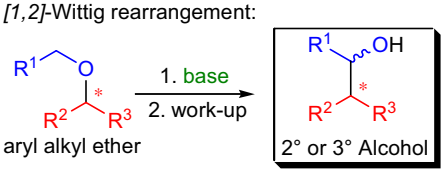
benzyl methyl ether — 1-phenylethanol

Wittig (1949) and Stevens et al. (1960):



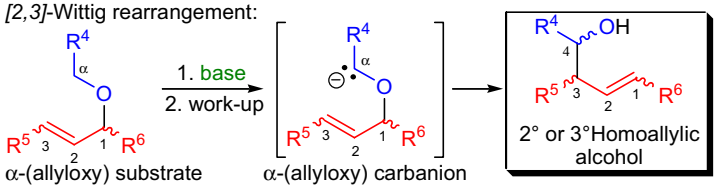
allyl fluorenyl ether — *[1,2]*-rearranged *(minor)* product — *[2,3]*-rearranged *(major)* product

[1,2]-Wittig rearrangement:



aryl alkyl ether — 2° or 3° Alcohol

[2,3]-Wittig rearrangement:

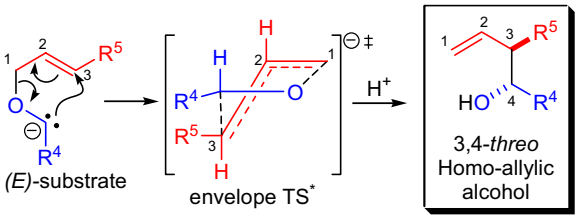


α-(allyloxy) substrate — α-(allyloxy) carbanion — 2° or 3°Homoallylic alcohol

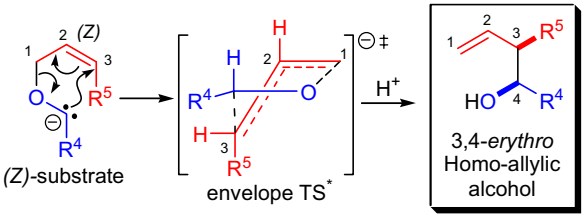
R^1 = aryl, alkenyl, alkynyl; R^{2-3} = H, alkyl; R^4 = carbanion stabilizing = aryl, alkenyl, alkynyl, COR, CN, CO_2R, $CONR_2$; when R^4 = SnR_3 (*Still variant*); R^{5-6} = H, alkyl; base: LDA, *n*-BuLi, PhLi, ROLi, $NaNH_2/NH_3$

Mechanism:[41-45,10,26,46,15]

The *[1,2]-Wittig rearrangement* proceeds *via* a radical-pair dissociation-recombination mechanism, while the *[2,3]-Wittig rearrangement* is a concerted, thermally allowed sigmatropic process proceeding *via* an envelope-like transition state in which the substituents are pseudo-equatorial.



(*E*)-substrate — envelope TS* — 3,4-*threo* Homo-allylic alcohol

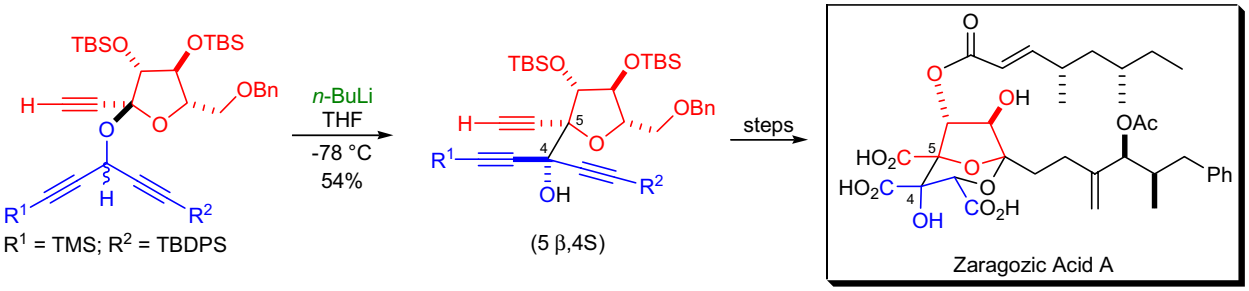


(*Z*)-substrate — envelope TS* — 3,4-*erythro* Homo-allylic alcohol

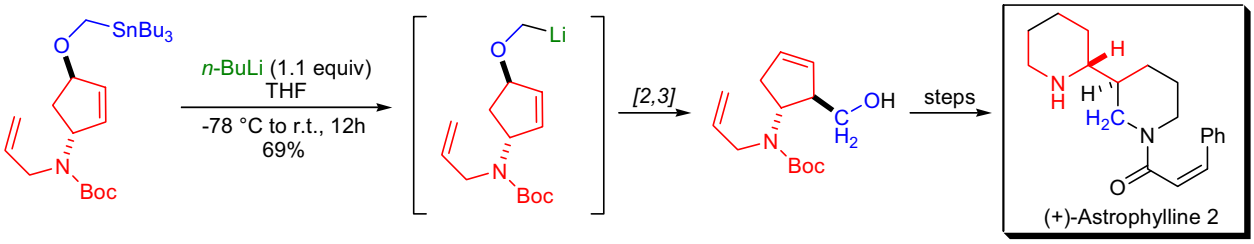
WITTIG-[1,2]- AND [2,3]-REARRANGEMENT

Synthetic Applications:

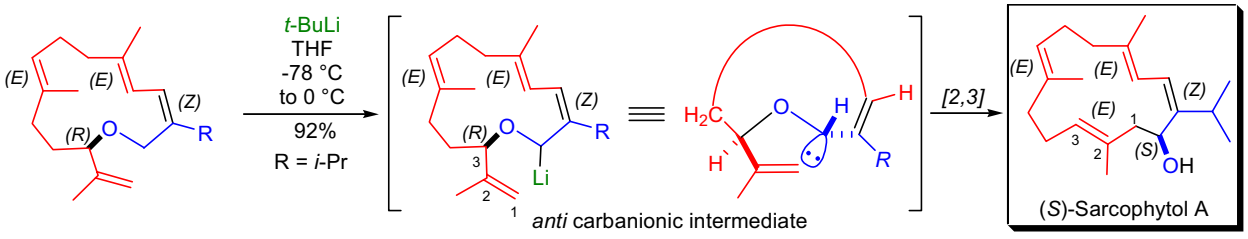
The *acetal version of the [1,2]-Wittig rearrangement* was utilized in the stereoselective total synthesis of zaragozic acid A by K. Tomooka and co-workers.[47] The acetal-protected *bis*(ethynyl)methanol was treated with *n*-BuLi, which brought about the sigmatropic *[1,2]-shift*. Thus, the chiral centers at C5 and C6 were established with high diastereoselectivity (95% β at C5 and 84% d.r. at C4). It is worth noting, that the intermediate anomeric radical could efficiently discriminate between the enantiotopic faces of prochiral *bis*(ethynyl)methanol radical (TMS vs. TBDPS) during the radical recombination process.



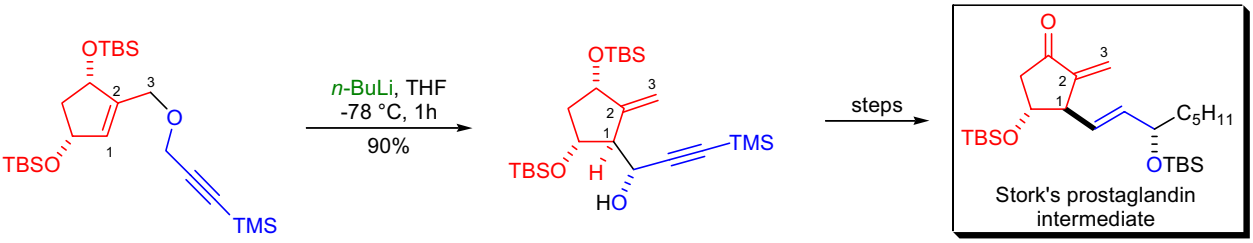
The first asymmetric total synthesis of (+)-astrophylline was accomplished in the laboratory of S. Blechert.[48] The *Still variant of the [2,3]-Wittig rearrangement* was used to generate the 1,2-*trans* relationship between the substituents of the key cyclopentene intermediate. The tributylstannylmethyl ether substrate was transmetalated with *n*-BuLi, which initiated the desired *[2,3]-sigmatropic shift* to afford the expected homoallylic alcohol as a single enantiomer.



The last and key step in the total synthesis of both enantiomers of sarcophytols A and T by Y. Fukuyama et al. was a *stereospecific [2,3]-Wittig rearrangement*.[49] The deprotonation of the macrocyclic bis-allylic ether precursor occurred with complete regioselectivity at the less substituted position. The rearrangement proceeded in excellent yield and exhibited an unexpectedly high level of stereospecificity even though the substrate was highly flexible. The reaction could occur either *via* a *syn* or *anti* carbanionic intermediate, but the (*S*)-stereochemistry of the product indicated that the *anti* carbanion was operational.



A novel approach to the asymmetric synthesis of Stork's prostaglandin intermediate was developed by T. Nakai et al.[50] This was the first example of an *asymmetric [2,3]-Wittig rearrangement*, in which three contiguous chiral centers were created in a cyclic system. Upon deprotonation, the rearrangement of the allyl propargyl ether substrate took place in excellent yield and gave rise to a single stereoisomer. Interestingly, when the TMS group was replaced with an amyl group (C_5H_{11}), the stereoselectivity diminished to only 3:1.



WOHL-ZIEGLER BROMINATION

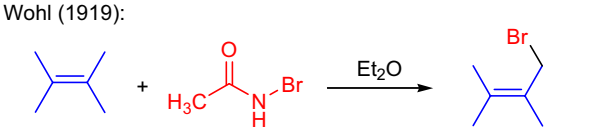
(References are on page 710)

Importance:

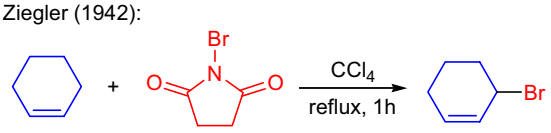
[*Seminal Publications*[1-3]*; Reviews*[4-6]*; Modifications & Improvements*[7-12]*; Theoretical Studies*[13-15]]

In 1919, A. Wohl studied the reaction between 2,3-dimethyl-2-butene and *N*-bromoacetamide in cold diethyl ether and found that the double bond of the substrate remained intact and one of the methyl groups was substituted with a single bromine atom.[1] This observation was interesting because such a transformation was previously possible only by the reaction of alkenes with elemental bromine at high temperature, but it went unnoticed for almost two decades. In 1942, K. Ziegler and co-workers conducted a detailed study on the allylic bromination of olefins using *N*-bromosuccinimide (NBS) as a new and stable brominating agent and demonstrated the preparative value of such a halogenation process. A few years later, P. Karrer found that the addition of 5-10 mol% of dibenzoyl peroxide to the reaction mixture results in significant increase in the reaction rate and allowed the bromination of substrates that were unreactive under the original reaction conditions.[7] The introduction of a bromine substituent at the allylic position of olefins or at the benzylic position of alkylated aromatic or heteroaromatic compounds in known as the *Wohl-Ziegler bromination*. The general features of this transformation are: 1) NBS is a commercially available reagent, and it is stable when kept in the dark and away from moisture; 2) various other *N*-bromo amides and *N*-bromo imides can also be used for bromination, but NBS is by far the most effective of all, and its use is accompanied by the least amount of side products; 3) when the olefin has two allylic positions, the bromination is regioselective and favors the bromination of the more substituted position (the more stable allylic radical); 4) alkylated aromatic and heteroaromatic compounds are selectively brominated at their respective benzylic positions (on the carbon directly attached to the aromatic ring) and no halogenation on the ring takes place; 5) the best solvents are carbon tetrachloride and benzene but recent environmentally friendly modifications use ionic liquids as the reaction medium, and even solvent-free conditions have been developed;[12] 6) the reaction is usually carried out at the boiling point of the solvent in the presence of 5-20 mol% of a radical initiator (AIBN or dibenzoyl peroxide); 7) alternatively the bromination can also be conducted at lower temperatures while the reaction mixture is irradiated with UV light; and 8) when the formation of polybrominated products is a side reaction, the use of a slight excess of the olefin substrate is recommended.

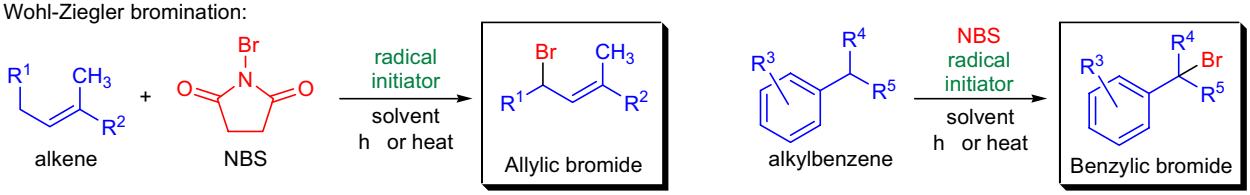
Wohl (1919):



Ziegler (1942):



Wohl-Ziegler bromination:

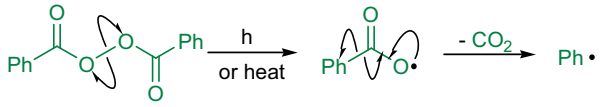


R^1 = alkyl; R^2 = H, alkyl, COR, CO_2R; R^3 = H, alkyl, aryl, O-alkyl, NR_2; R^{4-5} = H, alkyl, aryl; radical initiator: ROOR, $(Bz)_2O_2$, AIBN

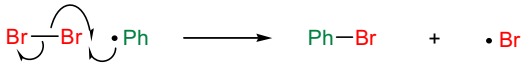
Mechanism:[16-27]

The mechanism of the *Wohl-Ziegler bromination* involves bromine radicals (and not imidoyl radicals). The radical initiator is homolytically cleaved upon irradiation with heat or light, and it reacts with Br_2 (which is always present in small quantities in NBS) to generate the Br· radical, which abstracts a hydrogen atom from the allylic (or benzylic) position. The key to the success of the reaction is to maintain a low concentration of Br_2 so that the addition across the C=C double bond is avoided. The Br_2 is regenerated by the ionic reaction of NBS with the HBr by-product.

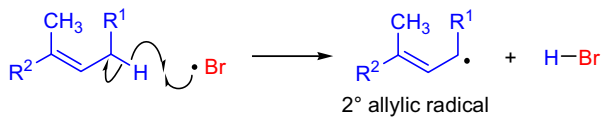
Initiation step:



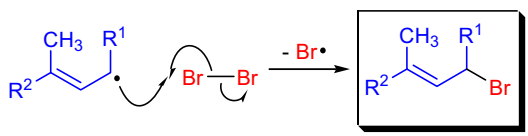
Formation of the bromine radical:



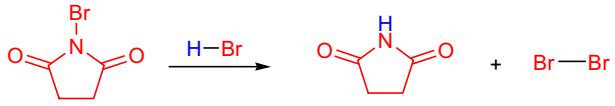
Abstraction of hydrogen atom:



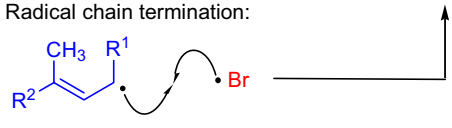
Propagation of the radical chain:



Regeneration of Br_2 (to maintain the required low concentration):



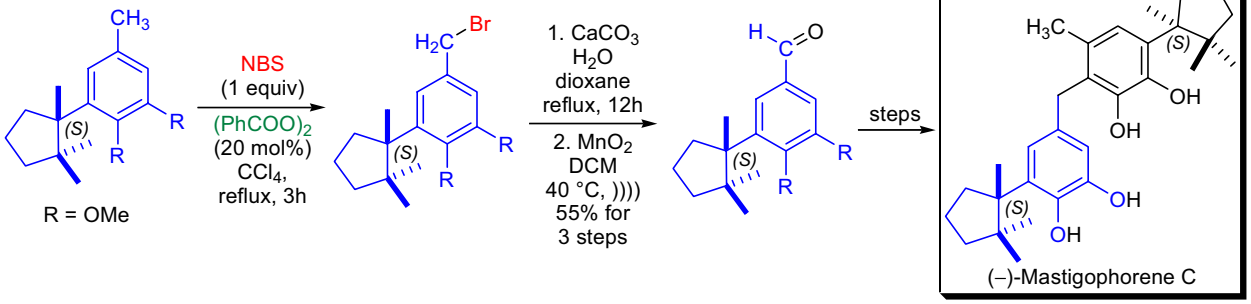
Radical chain termination:



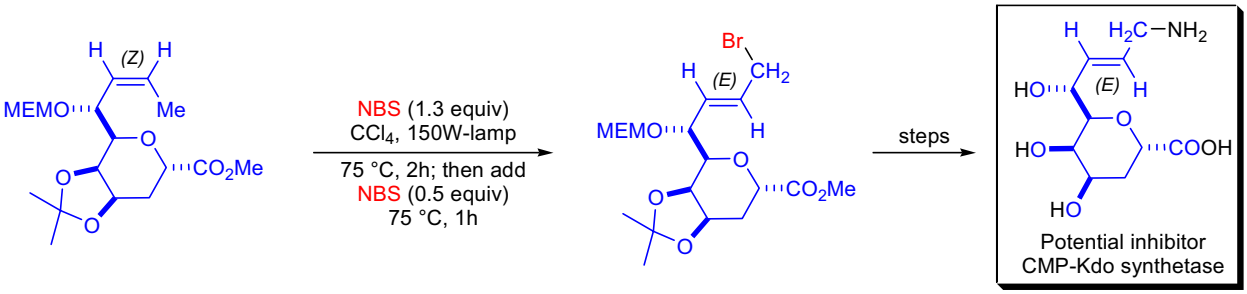
WOHL-ZIEGLER BROMINATION

Synthetic Applications:

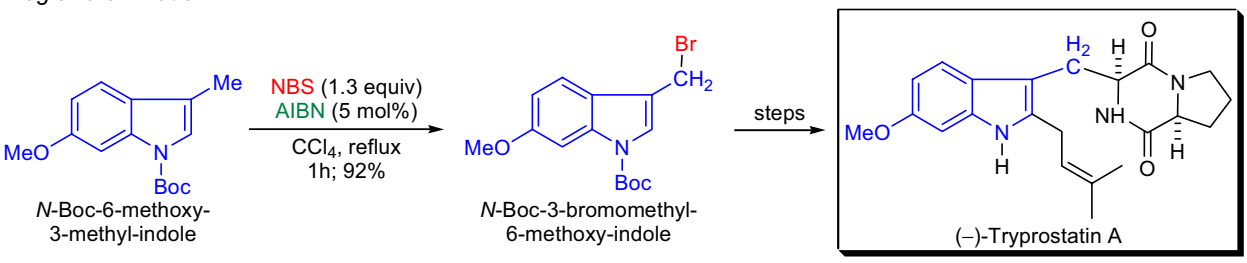
The first total synthesis of the novel sesquiterpene (–)-mastigophorene C was completed by G. Bringmann and co-workers.[28] This natural product has a negative effect on the growth of nerve cells. The synthetic strategy relied on the *Wohl-Ziegler bromination* to install the side-chain bromide on herbertenediol dimethyl ether. The substrate was dissolved in carbon tetrachloride; one equivalent of NBS and 20 mol% of dibenzoyl peroxide were added and the resulting mixture was heated at reflux for a few hours. The crude benzylic bromide was then hydrolyzed to the benzylic alcohol with water, which in turn was oxidized with MnO_2 to obtain the corresponding benzaldehyde derivative.



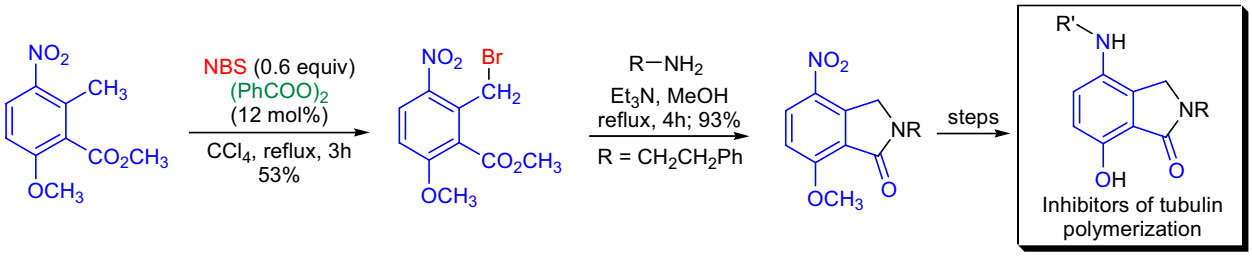
The research team of J. Tadanier prepared a series of C8-modified 3-deoxy-β-D-*manno*-2-octulosonic acid analogues as potential inhibitors of CMP-Kdo synthetase.[29] One of the derivatives was prepared from a functionalized olefinic carbohydrate substrate by means of the *Wohl-Ziegler bromination*. The stereochemistry of the double bond was (*Z*), however, under the reaction conditions a *cis-trans* isomerization took place in addition to the bromination at the allylic position (no yield was reported for this step). It is worth noting that the authors did not use a radical initiator for this transformation, the reaction mixture was simply irradiated with a 150W flood lamp. Subsequently the allylic bromide was converted to an allylic azide, which was then subjected to the *Staudinger reaction* to obtain the corresponding allylic amine.



In the laboratory of J.M. Cook, the first enantioselective total synthesis of (–)-tryprostatin A was accomplished.[30] This natural product was isolated as a secondary metabolite of the marine fungal strain BM939 and was shown to inhibit cell cycle progression. The chiral center of the 2-isoprenyltryptophan moiety was introduced by the alkylation of the Schöllkopf chiral auxiliary. The alkylating agent was prepared from *N*-Boc-6-methoxy-3-methylindole using the *Wohl-Ziegler bromination*.



Conformationally restricted analogues of lavendustin A were prepared by M. Cushman and co-wokers as cyctotoxic inhibitors of tubulin polymerization.[31]



WOLFF REARRANGEMENT

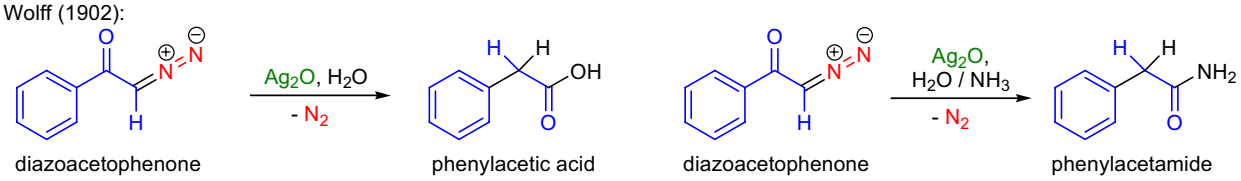
(References are on page 711)

Importance:

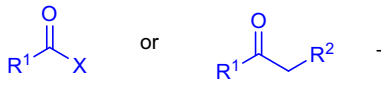
[*Seminal Publications*[1-3]; *Reviews*[4-15]; *Modifications & Improvements*[16-23]; *Theoretical Studies*[24-56]]

In 1902, L. Wolff was studying the chemistry of α-diazo ketones when he observed that upon treatment with silver oxide and water, diazoacetophenone rearranged to give phenylacetic acid.[1] When the reaction medium contained aqueous ammonia, phenylacetamide was formed. A few years later G. Schröter published similar findings in an independent study, but the reaction remained unexplored for the next three decades due to the lack of general methods for the preparation of α-diazo ketones.[2] The conversion of α-diazo ketones into ketenes and products derived from ketenes is known as the *Wolff rearrangement*. The substrate α-diazo ketones can be prepared by various methods: 1) reaction of an acyl halide or anhydride with two equivalents of diazomethane in ether or DCM solution at room temperature or below (*Arndt-Eistert homologation*);[4] however, only one equivalent is needed of higher diazoalkanes, and low temperatures are necessary due to competing *azo coupling*; 2) sequential treatment of *N*-acyl-α-amino ketones (prepared by the *Dakin-West reaction*) with N_2O_3 and sodium methoxide in methanol affords secondary α-diazo ketones, so the cumbersome use of higher diazoalkanes is avoided; 3) transfer of the diazo group from an organic azide (e.g., tosyl azide) to a substrate containing an active methylene group (e.g., β-keto ester or β-keto nitrile) in the presence of a base (*Regitz diazo transfer*);[57-60] 4) simple diazo monoketones are synthesized from ketones by the introduction of a formyl group at the α-position *via* a *Claisen reaction* and then treatment of the resulting α-formyl derivative with tosyl azide and a tertiary amine (*deformylative diazo-transfer*);[61,62] 5) oxidation of α-ketoximes with chloramine;[63] and 6) hydroxide ion assisted decomposition of tosylhydrazones.[64] The general features of the *Wolff rearrangement* are: 1) the reaction can be initiated thermally, photolytically, or by transition metal catalysis; 2) thermal conditions are not used frequently, since delicate substrates may degrade and side reactions are frequent (e.g., direct displacement of the diazo group without rearrangement); 3) the use of transition metal complexes does not only reduce the required reaction temperature considerably compared to the thermal process, but also changes the reactivity of the α-keto carbene intermediate by the formation of less reactive metal carbene complexes (Rh- and Pd-complexes usually prevent the *Wolff rearrangement* from taking place); 4) freshly prepared silver(I)oxide or silver(I)benzoate are best suited for the reaction; 5) photochemical activation is convenient, and it takes place even at low temperatures, but it can be problematic if the product is photolabile; 6) if the migrating group has a stereocenter, the stereochemistry remains unchanged (net retention of configuration) after the migration; 7) the ketene products are electrophilic and can react with various nucleophiles as well as undergo [2+2] cycloaddition reactions with alkenes; 8) cyclic diazo ketones undergo ring-contraction, and the process is well-suited for the preparation of strained ring systems; 9) α,β-unsaturated diazo ketones undergo the *vinylogous Wolff rearrangement* to give skeletally rearranged γ,δ-unsaturated esters (alternative to *Claisen-type rearrangements*);[16] and 10) since α-diazo ketones are very reactive compounds, numerous side reactions are possible that can be avoided or minimized by the careful choice of reaction conditions.[9]

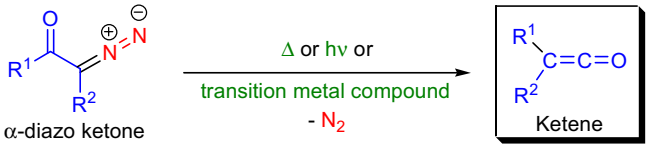
Wolff (1902):



Preparation of the α-diazo ketone:

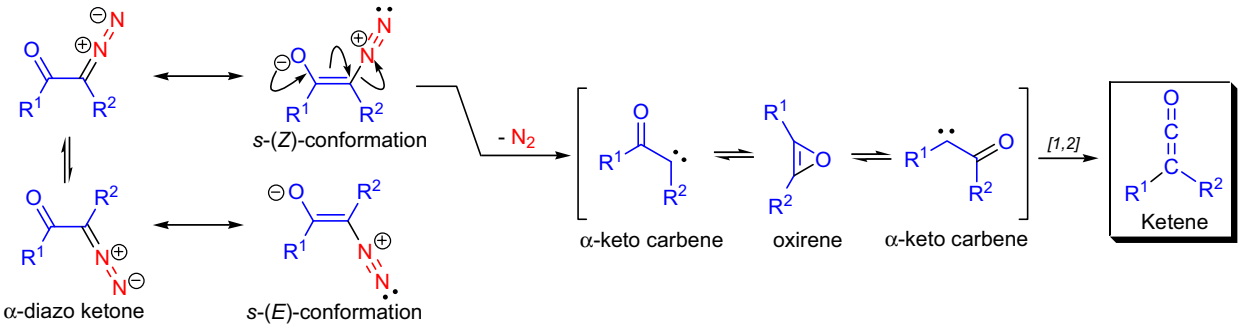


Wolff rearrangement:



R^1 = alkyl, aryl, heteroaryl; R^2 = alkyl, aryl, H, CN, CHO, C(O)-alkyl, SO_2R, CO_2R; X = Cl, Br, OCOR

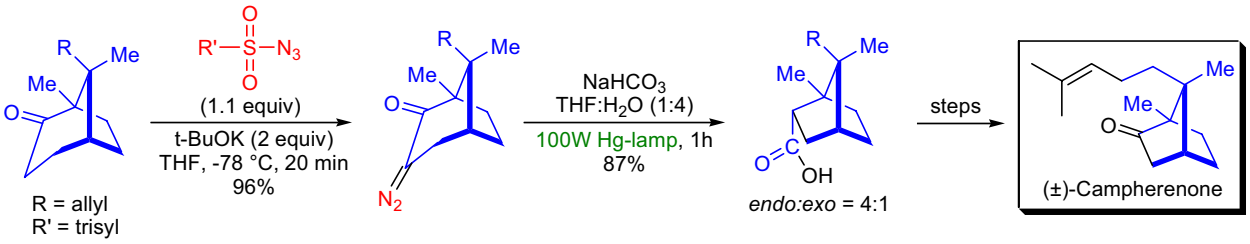
Mechanism:[65,9,13]



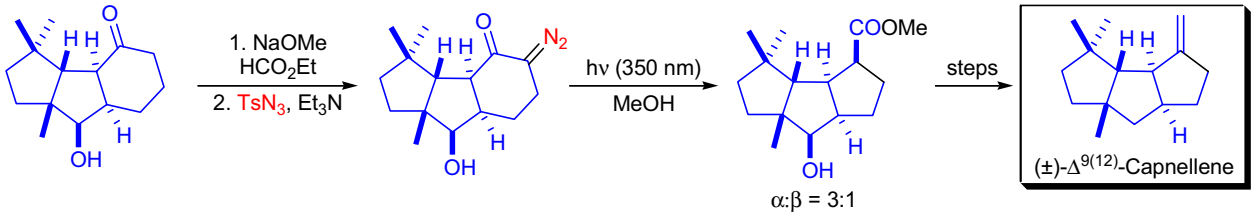
WOLFF REARRANGEMENT

Synthetic Applications:

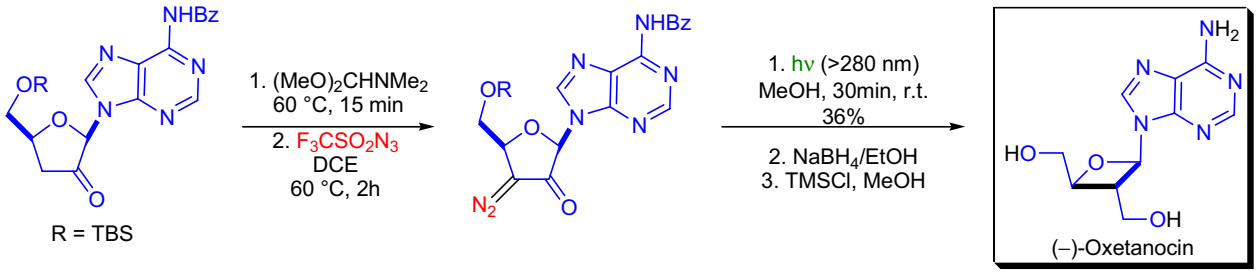
The stereoselective total synthesis of (±)-campherenone was accomplished by T. Uyehara and co-workers based on a *photochemical Wolff rearrangement*.[66] The bicyclic ketone was treated with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) under homogeneous basic conditions and the α-diazo ketone was obtained in excellent yield. The photochemical rearrangement of the diazo ketone was conducted in a THF-water mixture using a high-pressure 100 W mercury lamp. The ring-contracted acid was isolated as a 4:1 mixture of *endo* and *exo* products.



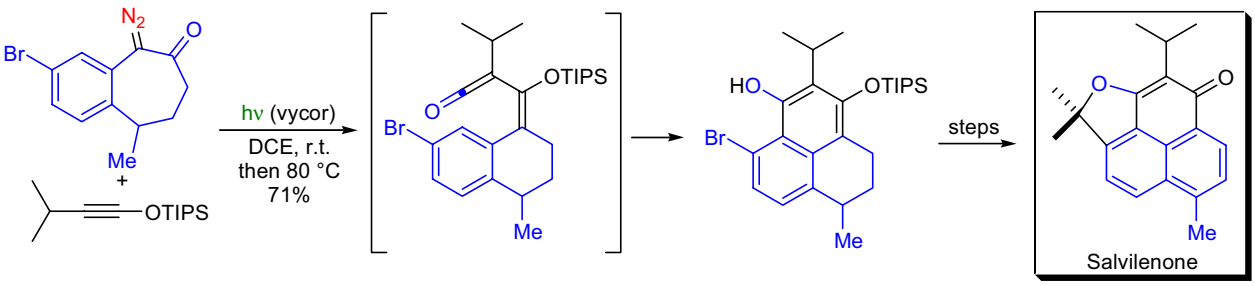
In the laboratory of K. Fukumoto, the stereoselective total synthesis of (±)-$\Delta^{9(12)}$-capnellene was carried out using an *intramolecular Diels-Alder reaction* to obtain a tricyclic 5-5-6 system.[67] Since the target molecule was a triquinane, the six-membered ring had to be converted to a five-membered one, a transformation achieved by a *Wolff rearrangement.* The required α-diazo ketone was prepared *via* a *deformylative diazo transfer reaction* and was photolyzed in methanol. The ring-contracted methyl ester was isolated as a 3:1 mixture of separable isomers favoring the α-isomer.



The natural product (–)-oxetanocin is an unprecedented oxetanosyl-*N*-glycoside that inhibits the *in vitro* replication of human immunodeficiency virus (HIV). In order to prepare multigram quantities of the compound, D.W. Norbeck et al. devised a short and efficient synthetic strategy.[68] The cornerstone of the strategy was the *Wolff rearrangement* of a five-membered diazo ketone. The diazo transfer was achieved by first converting the ketone to an enamino ketone followed by treatment with triflyl azide. Upon irradiation with a 450 W Pyrex filtered Hanovia lamp, the isomeric oxetanes (α:β = 2:1) were obtained in 36% yield.



R.L. Danheiser and co-workers generated a key vinylketene intermediate *via* tandem *Wolff rearrangement*-ketene-alkyne cycloaddition to utilize it in a *photochemical aromatic annulation reaction* (*Danheiser benzannulation*) for the total synthesis of the phenalenone diterpene salvilenone. [69]



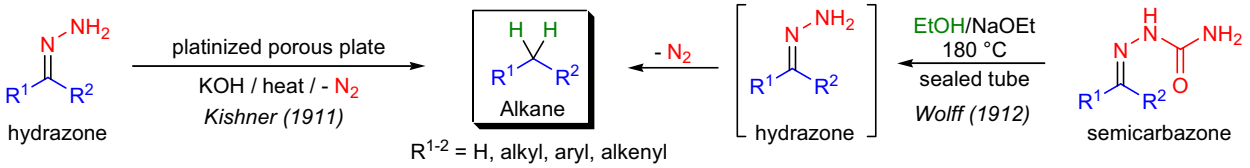
WOLFF-KISHNER REDUCTION

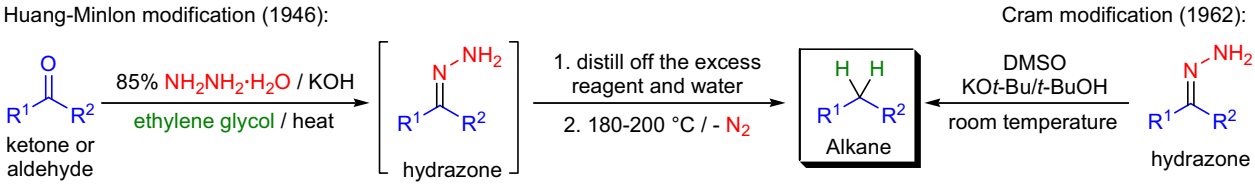
(References are on page 712)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-6]; *Modifications & Improvements*[7-20]; *Theoretical Studies*[21]]

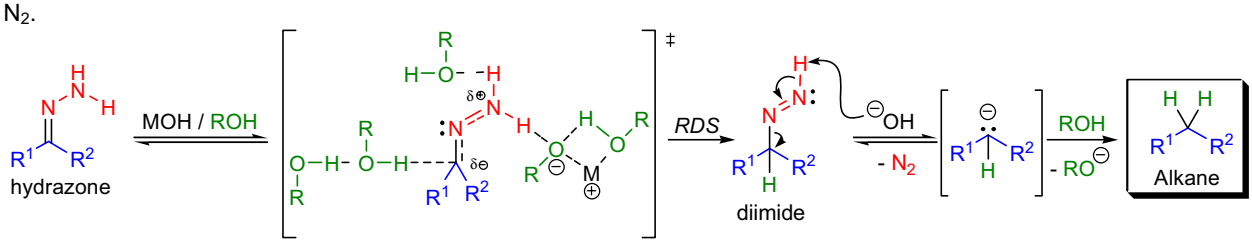
In 1911, N. Kishner reported that by adding a hydrazone dropwise onto a mixture of hot potassium hydroxide and platinized porous plate the corresponding hydrocarbon was formed.[1] A year later L. Wolff independently showed that heating the ethanol solution of semicarbazones and hydrazones in a sealed tube at ~180 °C in the presence of sodium ethoxide gives rise to the same result. The deoxygenation of aldehydes and ketones to hydrocarbons *via* the corresponding hydrazones or semicarbazones under basic conditions is known as the *Wolff-Kishner reduction* (*W-K reduction*). Since the seminal reports, the original procedure has been substantially modified to make the reaction conditions milder and improve the yields.[3,6] The standard procedure for a long time was to mix the carbonyl compound with 100% hydrazine in a high-boiling solvent (e.g., ethylene- or triethylene glycol) in the presence of excess base (sodium metal, NaOEt, etc.) and keep the reaction mixture at reflux for a couple of days. One of the main problems encountered was the temperature-lowering effect of the water generated during the formation of the hydrazone, and this resulted in long reaction times (50-100h) and the need to use an excess of the reagents and solvents. In the *Huang-Minlon modification*, the water and the excess hydrazine are removed by distillation (once the hydrazone is formed *in situ*) so the reaction temperature could rise to ~200 °C, which dramatically shortened the reaction time (3-6h), increased the yields and also allowed the use of the cheaper hydrazine hydrate along with water-soluble bases (KOH or NaOH).[9] The general features of the reaction are: 1) the reduction is usually carried out in a high boiling solvent (~180-200 °C) so that the use of a sealed tube can be avoided;[7,8,17] 2) for base-sensitive substrates better yields are achieved when the hydrazone is preformed and the base is added to the substrates at lower temperatures (e.g., 25 °C) followed by refluxing the reaction mixture; 3) esters, lactones, amides, and lactams are hydrolyzed under the reaction conditions; 4) sterically hindered carbonyl compounds are deoxygenated more slowly than unhindered ones, so higher reaction temperatures are required (*Barton modification*);[11,14] 5) the use of DMSO instead of glycols as the reaction medium containing KO*t*-Bu, followed by the slow addition of preformed hydrazones, allows the reduction to take place at room temperature (*Cram modification*). However, on small scale this method is inconvenient, and good results are very substrate dependent;[12] 6) preformed hydrazones can also be mixed with KO*t*-Bu and refluxed in toluene (~110 °C) to effect the reduction (*Henbest modification*);[13] 7) for α,β-unsaturated carbonyl compounds, the use of preformed semicarbazones is advised (hydrazine tends to give pyrazolines with these substrates), which undergo reduction under the original or most of the modified reaction conditions;[3] and 8) certain aromatic carbonyl compounds (e.g., benzophenone, benzaldehyde) do not require the use of a strong base for reduction, they are reduced when heated with excess hydrazine hydrate.[3] A powerful alternative of the *W-K reduction* is the treatment of tosylhydrazones with hydride reagents to obtain the corresponding alkanes (*Caglioti reaction*).[22] A few side reactions have been observed: 1) formation of azines; 2) reduction of ketone substrates to alcohols when the reaction is unsuccessful; 3) isomerization of double bonds especially in the case of α,β-unsaturated carbonyl compounds ; 4) elimination of the α-heteroatom substituent to afford alkenes (*Kishner-Leonard elimination*);[23,24] and 5) cleavage or rearrangement of strained rings adjacent to the carbonyl group.





Mechanism:[25-32]

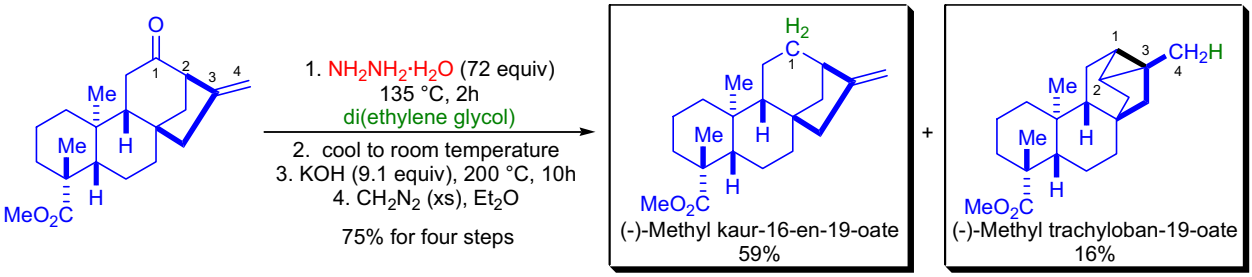
The rate-determining step is the proton capture at the carbon terminal. This process takes place in a concerted fashion with the solvent-induced proton abstraction at the nitrogen terminus to form a diimide that undergoes a loss of N_2.



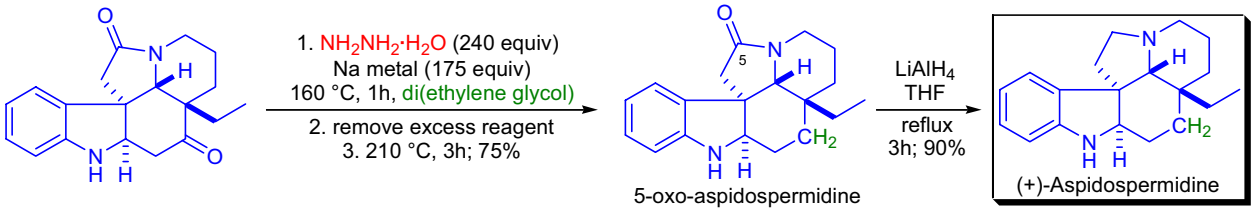
WOLFF-KISHNER REDUCTION

Synthetic Applications:

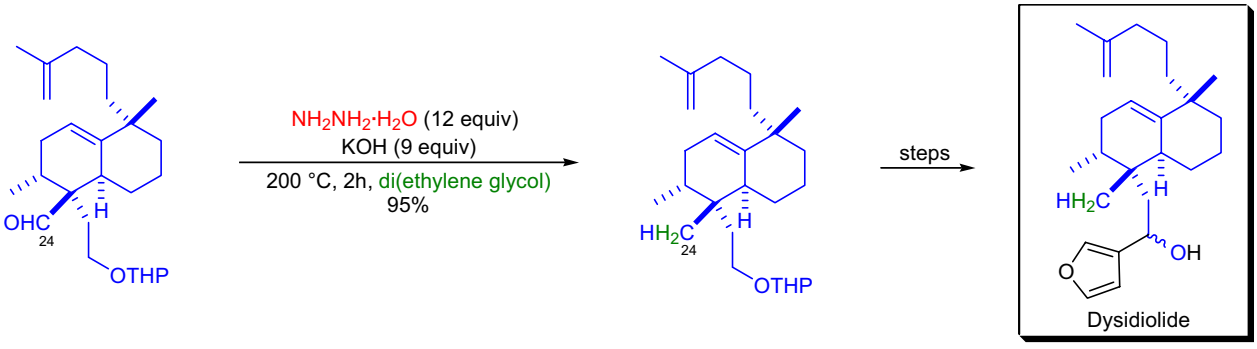
The asymmetric syntheses of (-)-methyl kaur-16-en-19-oate and (-)-methyl trachyloban-19-oate was achieved by M. Ihara and co-workers.[33] One of the last transformations was the deoxygenation of the ketone carbonyl group of the tetracyclic intermediate, which was effected by the *Wolff-Kishner reduction*. Under the strongly basic conditions the ester functionality was hydrolyzed, so an esterification using diazomethane was necessary as the final step. The major deoxygenated product was (-)-methyl kaur-16-en-19-oate (59%). The minor product was identified as (-)-methyl trachyloban-19-oate (16%).



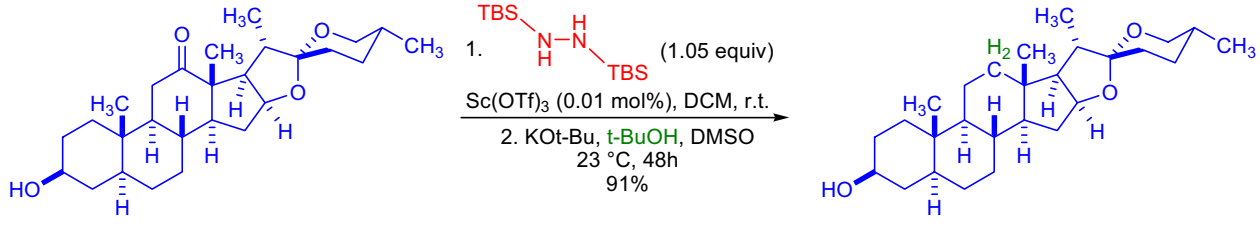
The total synthesis of (+)-aspidospermidine was accomplished in the laboratory of J.P. Marino using a novel *[3,3]-sigmatropic rearrangement* of chiral vinyl sulfoxide with a ketene as the key step.[34] During the endgame of the synthesis the pentacyclic ketone was deoxygenated using the *Wolff-Kishner reduction*. Because the ketone was sterically hindered, harsh reaction conditions had to be applied: after the formation of the hydrazone, the water and the excess hydrazine were removed and the temperature was raised to 210 °C. The final step in the synthetic sequence was the reduction of the five-membered lactam to the corresponding tertiary amine with LAH.



Dysidiolide is the first compound found to be a natural inhibitor of protein phosphatase cdc25A that is essential for cell proliferation. Y. Yamada et al. developed a novel total synthesis of this natural product using an *intramolecular Diels-Alder cycloaddition* as the key step.[35] Deoxygenation of the advanced bicyclic intermediate at the C24 position was achieved under *Wolff-Kishner reduction* conditions to afford the C24 methyl group.



A novel two-step one-pot *modified Wolff-Kishner reduction* protocol was developed in the laboratory of A.G. Myers (*Myers modification*).[20] The carbonyl compound was first converted to the *N*-TBS-hydrazone followed by the addition of KO*t*-Bu/*t*-BuOH in DMSO at or above room temperature.



WURTZ COUPLING

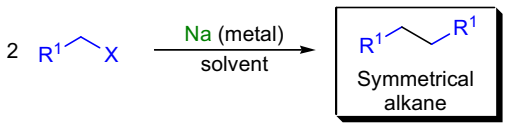
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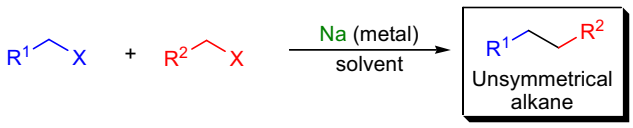
[*Seminal Publications*[1,2]; *Reviews*[3-7]; *Modifications & Improvements*[8-16]]

In 1855, A. Wurtz treated alkyl halides with sodium metal, and he isolated the corresponding symmetrical alkane dimers.[1,2] The coupling of two sp^3-carbon centers by the treatment of alkyl or benzyl halides with sodium metal is known as the *Wurtz coupling*. When metals other than sodium are used, this transformation is referred to as a *Wurtz-type coupling*. The coupling of an alkyl and an aryl halide in the presence of sodium metal to get the corresponding alkylated aromatic compound is called the *Wurtz-Fittig reaction*. Today, the synthetic significance of the *Wurtz coupling* is fairly limited and often in widely used reactions (e.g., *Grignard reactions*) involving highly reactive organometals, such as allyl- and benzylmetals, this is the side reaction. The general features of the *Wurtz coupling* are: 1) the classical reaction is heterogeneous and relatively low-yielding, because it is plagued by side reactions such as elimination and rearrangements; 2) best results are achieved with finely dispersed sodium metal; 3) alkyl halides can be coupled both inter- and intramolecularly; 4) the order of reactivity for alkyl halides is: I >> Br >> Cl, and by far primary alkyl iodides are the best substrates; 5) secondary alkyl halides are generally poor substrates and should be avoided; 6) the method works reasonably well for intermolecular homocouplings, but the heterocoupling of two different alkyl halides often results in a statistical mixture of products in low yields; 7) intramolecularly, the coupling can give rise to strained rings as well as macrocycles (e.g., cyclopropanes, cyclobutanes, and cyclophanes) in moderate to good yield, and it has been applied extensively for the preparation of such compounds;[17,4] and 8) the *Wurtz-Fittig reaction* gives high yields of the desired product without significant side reactions mainly because aryl halides do not usually dimerize under the reaction conditions. Because of the limited synthetic value of the classical reaction conditions, several modifications were introduced: 1) the most widespread reaction condition (*Müller modification*) is to treat the alkyl halide with sodium metal in THF at -78 °C in the presence of catalytic amounts of tetraphenylethylene (TPE), which solubilizes the sodium and makes the reaction homogeneous; [8] 2) metals other than sodium[18] as well as various metal complexes have been used successfully to improve the yields and suppress side reactions: activated Cu,[13] $Mn_2(CO)_{10}$,[15] Li metal/ultrasound, Na(Hg),[10] Na-K alloy, Zn;[16] and 3) the use of sonication (ultrasound) in general improves the yield, since the metal becomes highly dispersed and as a result its reactivity increases.[11,12,14]

Wurtz homocoupling (dimerization):

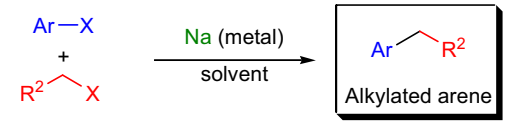


Wurtz heterocoupling (cross-coupling):

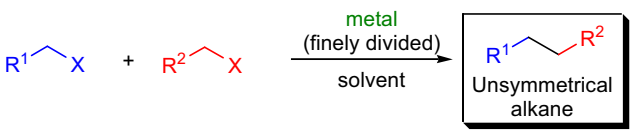


+ homocoupled products

Wurtz-Fittig reaction:



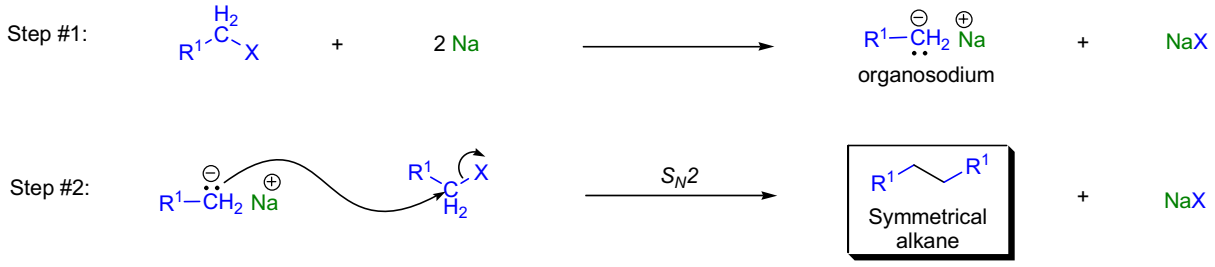
Wurtz-type coupling:



R^1 = 1° alkyl, aryl; R^2 = 1° alkyl, aryl; Ar = electron-rich and electron-poor substituted aryl; metal = K, Mg, Zn, Cu etc.; solvent = THF, Et_2O, dioxane, xylenes

Mechanism:[19-30]

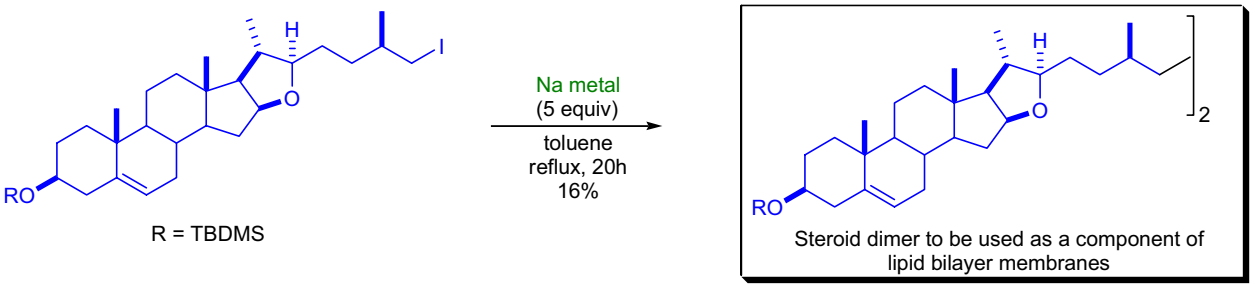
The mechanism of the *Wurtz coupling* is not well understood, and the currently accepted mechanism involves two steps: 1) formation of a carbanionic organosodium compound *via* metal-halogen exchange; and 2) the displacement of the halide ion by the organosodium species in an S_N2 reaction. Alternatively, a radical process can also be envisioned, although to date there has been no experimental evidence to support this assumption.



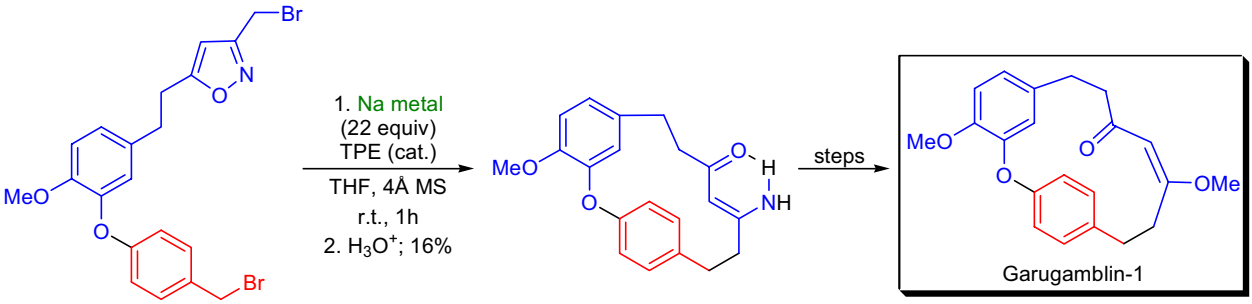
WURTZ COUPLING

Synthetic Applications:

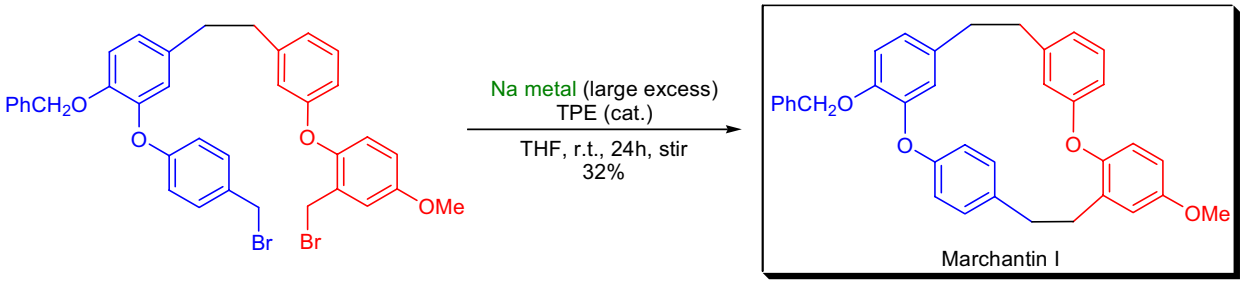
J.W. Morzycki and co-workers described the synthesis of dimeric steroids to be used as components of artificial lipid bilayer membranes.[31] The key coupling of two steroid derivatives was achieved by the *Wurtz reaction*. The steroid primary alkyl iodide was dissolved in anhydrous toluene and treated with an excess of sodium metal. After 20h of reflux, the desired homocoupled product was obtained in moderate yield along with a considerable amount (36%) of the reduced compound.



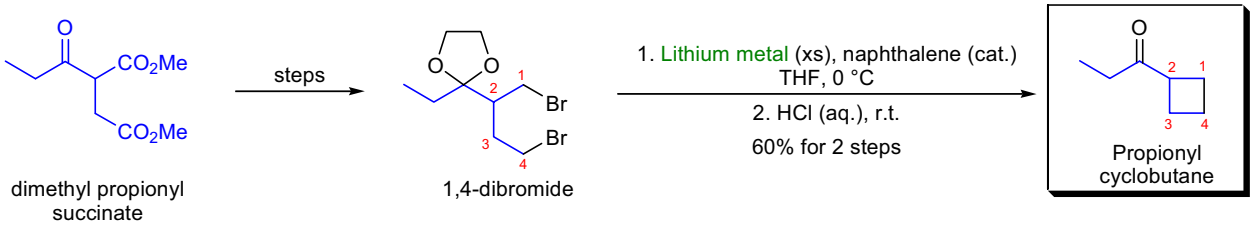
The total synthesis of the diarylheptanoid garugamblin 1 was achieved by M. Nógrádi et al. using the *modified Wurtz coupling* as the key macrocyclization step.[32] The dibromide was treated with sodium metal at room temperature in the presence of TPE to afford the desired macrocycle in moderate yield. The N-O bond of the isoxazole ring was cleaved under the reaction conditions.



The structure of the macrocyclic bis(benzylether) natural product marchantin I was confirmed in the laboratory of M. Nógrádi.[33] The last and key step of the synthesis was the *modified Wurtz coupling* in which the 18-membered ring was formed.



The classical preparation of cyclobutyl ketones involves the base-catalyzed reaction of 1,3-dihaloalkanes with malonate esters. However, the initial product of this reaction is a cyclobutane carboxylic acid. S.D. Van Arnum and co-workers showed that cyclobutyl ketones can be efficiently synthesized starting from acyl succinates and using the *Wurtz reaction* as the key cyclization step.[34] The cyclization was catalyzed by naphthalene.



YAMAGUCHI MACROLACTONIZATION

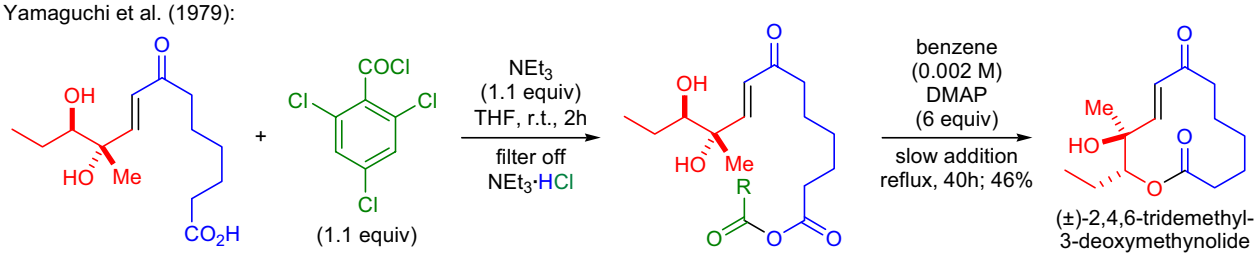
(References are on page 714)

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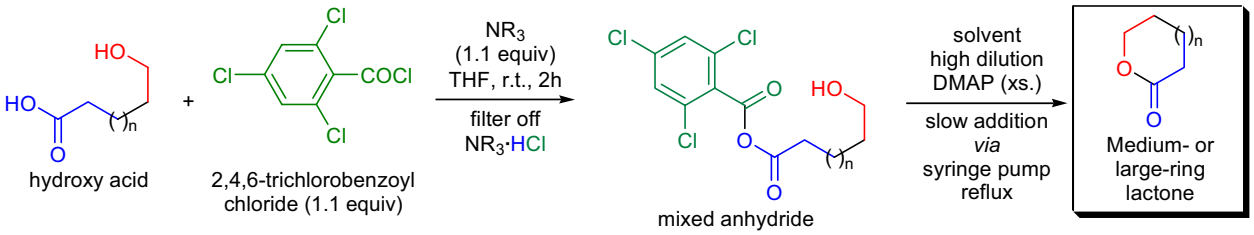
[*Seminal Publications*[1]*; Reviews*[2-4]*; Modifications & Improvements*[5,6]]

In 1979, M. Yamaguchi and co-workers developed a novel procedure for the rapid preparation of esters and lactones under mild conditions *via* the alcoholysis of the corresponding mixed anhydrides.[1] As a result of their thorough study, they found that 2,4,6-trichlorobenzoyl chloride/DMAP was the best reagent combination in terms of both the high reaction rate as well as the high product yield. The procedure was put to the test and used for the lactonization of a very acid sensitive substrate that was known to rapidly decompose on contact with catalytic amounts of HCl. The substrate hydroxy acid was treated with 2,4,6-trichlorobenzoyl chloride in the presence of NEt_3, and the by-product triethylamine hydrochloride was removed. The resulting mixed anhydride was diluted with toluene and slowly added to a refluxing solution of DMAP in toluene under high dilution conditions (~0.002 M). The desired macrolactone, (±)-2,4,6-tridemethyl-3-deoxymethynolide, was obtained without the formation of any decomposition product. The formation of medium- and large-ring lactones from hydroxy acids using 2,4,6-trichlorobenzoyl chloride/DMAP is known as the *Yamaguchi macrolactonization*. The general features of this transformation are: 1) the substrate is first converted to the corresponding mixed anhydride with 2,4,6-trichlorobenzoyl chloride in the presence of a tertiary amine to activate the carboxylic acid functionality; 2) aromatic hydrocarbons such as benzene and toluene are the best solvents; 3) the reaction is conducted under high-dilution conditions to minimize intermolecular coupling; 4) the mixed anhydride is dissolved and slowly added (*via* a syringe pump) to a refluxing solution of DMAP in benzene or toluene; and 5) usually several equivalents of DMAP, a known catalyst for acyl transfer reactions, is used. The main advantages of the *Yamaguchi macrolactonization* over other existing methods are its operational simplicity, its high reaction rate and the lack of by-products.

Yamaguchi et al. (1979):

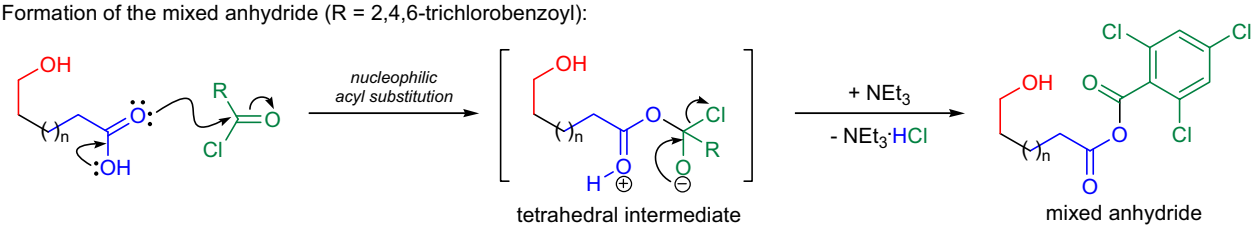


Yamaguchi macrolactonization:

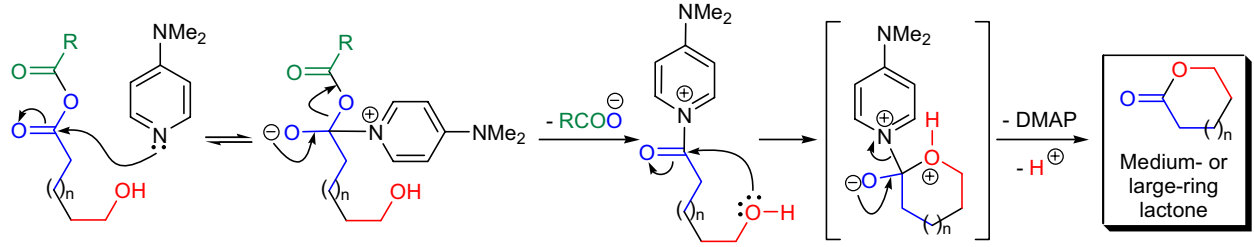


Mechanism:

Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):



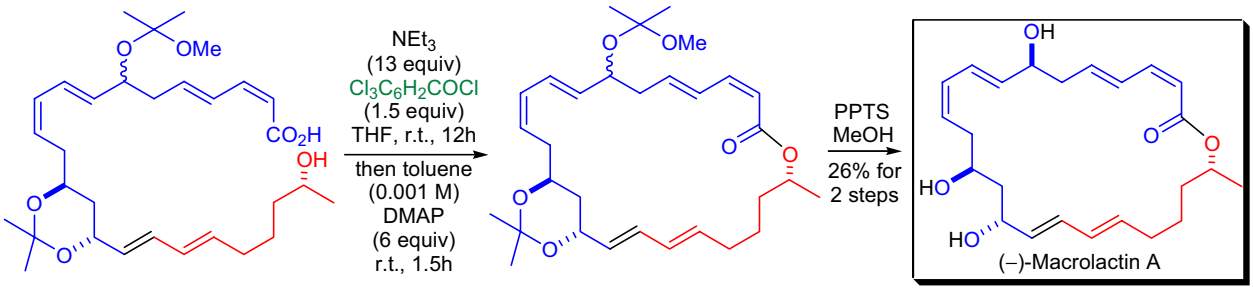
Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



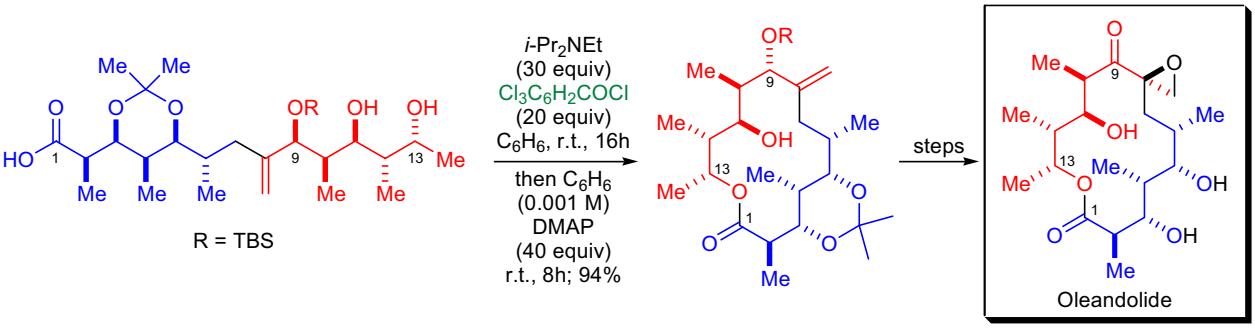
YAMAGUCHI MACROLACTONIZATION

Synthetic Applications:

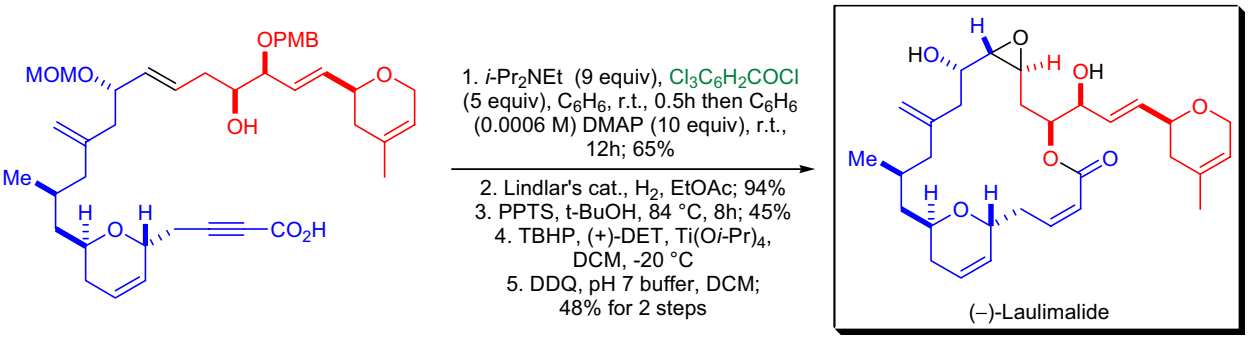
The stereocontrolled total synthesis of (–)-macrolactin A, a 24-membered macrolide, was achieved by J.P. Marino and co-workers.[7] The key macrocyclization step was carried out using the *Yonemitsu modification of the Yamaguchi macrolactonization*.[6] In this procedure, the mixed anhydride is added to the highly dilute solution of DMAP rapidly (in one portion) at room temperature. The final step of the total synthesis was the removal of the protecting groups under acidic condition.



The convergent enantioselective synthesis of oleandolide, the aglycon of the macrolide antibiotic oleandomycin, was reported by J.S. Panek et al.[8] The key macrocyclization was carried out by a *modified Yamaguchi macrolactonization* protocol. The azeotropically dried dihydroxy acid was first treated with a large excess of 2,4,6-trichlorobenzoyl chloride and Hünig's base, and the resulting mixed anhydride was diluted with benzene (~0.001 M). To this dilute solution was added in one portion a large excess of DMAP. The desired 14-membered lactone was isolated in nearly quantitative yield and no trace of the undesired 12-membered lactone was detected. The unusually high efficiency of the cyclization was attributed to the strong conformational preference induced by the large substituent at C9.



The microtubule-stabilizing and potent antitumor 18-membered macrolide, (–)-laulimalide, was synthesized in the laboratory of A.K. Ghosh.[9] The macrolactonization of the α,β-unsaturated (*Z*)-hydroxy acid under *Yamaguchi conditions* caused isomerization of the double bond. Presumably this undesired isomerization was due to the reversible *Michael addition* of the DMAP catalyst to the active acylating agent. Unfortunately, no other reaction conditions were found that could decrease the extent of the double bond isomerization, so an alternative strategy was sought. Therefore, the macrolactonization of a hydroxy alkynoic acid was performed and the triple bond was efficiently hydrogenated to the desired (*Z*)-double bond with Lindlar's catalyst. In order to complete the total synthesis, selective removal the MOM protecting group was achieved by treatment with excess PPTS in *t*-butanol at reflux. The epoxide was installed using the *Sharpless epoxidation*, which afforded the epoxide as a single diastereomer. The final step was the removal of the PMB group with DDQ.



VIII. APPENDIX

8.1 Brief explanation of the organization of this section 502

8.2 List of named reactions in chronological order of their discovery 503

8.3 Reaction categories - Categorization of named reactions in tabular format 508

8.4 Affected functional groups – Listing of transformations in tabular format 518

8.5 Preparation of functional groups – Listing of transformations in tabular format 526

8.1 Brief explanation of the organization of this section

The primary function of this section is to help advanced undergraduate students and first year graduate students in organizing the large amount of information available on various chemical transformations. It is important to note that the categorization of named reactions is a subjective one and has been addressed differently in other textbooks.

The categorization of named reactions is mainly based on the mechanism of the various processes. To make studying more friendly, we included a brief description of each named reaction and the page number for that particular transformation.

Because a large number of functional group transformations are affected by the reactions covered in the book, we felt that tables showing the interconversion of functional groups should be included.

Various functional groups are listed in alphabetical order in the first column and the functionalities that can be created from them are shown in the second column. The names of all reactions that can bring about these transformations are listed in the third column.

In the second table we listed the target functional groups in alphabetical order in the first column and showed the substrate functionalities in the second column. In the third column the names of these transformations are listed.

A note of caution: none of these tables were created with the intent to be comprehensive, since that would be beyond the scope of this book. The reader should always check the details for each reaction to find out the true scope and limitations of a given transformation. We welcome any suggestions on how to make this section more effective in future editions.

8.2 LIST OF NAMED REACTIONS IN CHRONOLOGICAL ORDER OF THEIR DISCOVERY

YEAR OF DISCOVERY	NAME OF THE TRANSFORMATION	PAGE #
1822	Lieben Haloform Reaction	264
1838	Benzilic Acid Rearrangement	52
1839	Aldol Reaction	8
1844	Dieckmann Condensation	138
1850	Strecker Reaction	446
1851	Hofmann Elimination	206
1852	Williamson Ether Synthesis	484
1853	Cannizzaro Reaction	74
1855	Wurtz Coupling	498
1860	Kolbe-Schmitt Reaction	248
1860	Pinacol and Semipinacol Rearrangement	350
1861	Acyloin Condensation	4
1861	Hunsdiecker Reaction (Borodin Reaction)	218
1868	Perkin Reaction	338
1869	Glaser Coupling Reaction	186
1869	Lossen Rearrangement	266
1876	Reimer-Tiemann Reaction	378
1877	Friedel-Crafts Acylation	176
1877	Friedel-Crafts Alkylation	178
1877	Malonic Ester Synthesis	272
1877	Pinner Reaction	352
1879	Koenigs-Knorr Glycosidation	246
1880	Skraup and Doebner-Miller Reaction	414
1881	Ciamician-Dennstedt Rearrangement	84
1881	Fries-, Photo-Fries and Anionic *Ortho*-Fries Rearrangement	180
1881	Hell-Volhard-Zelinsky Reaction	200
1881	Hofmann Rearrangement	210
1882	Hantzsch Dihydropyridine Synthesis	194
1883	Combes Quinoline Synthesis	94
1883	Fischer Indole Synthesis	172
1883	Hofmann-Löffler-Freytag Reaction	208
1883	Michael Addition	286
1883	von Pechmann Reaction	472
1884	Paal-Knorr Furan Synthesis	326
1884	Paal-Knorr Pyrrole Synthesis	328
1884	Sandmeyer Reaction	394
1884	Schotten-Baumann Reaction	398
1885	Buchner Method of Ring Enlargement (Buchner Reaction)	68
1885	Curtius Rearrangement	116
1886	Beckman Rearrangement	50
1886	Knorr Pyrrole Synthesis	244
1887	Claisen Condensation/(Claisen Reaction)	86
1887	Gabriel Synthesis	182
1887	Japp-Klingemann Reaction	224
1887	Reformatsky Reaction	374
1887	Tishchenko Reaction	456
1888	Dimroth Rearrangement	144
1891	Biginelli Reaction	58
1892	Darzens Glycidic Ester Condensation	128
1893	Bischler-Napieralski Isoquinoline Synthesis	62
1893	Dienone-Phenol Rearrangement	142

YEAR OF DISCOVERY	NAME OF THE TRANSFORMATION	PAGE #
1893	Pomeranz-Fritsch Reaction	358
1893	Stobbe Condensation	442
1894	Favorskii Rearrangement and Homo-Favorskii Rearrangement	164
1894	Knoevenagel Condensation	242
1894	Nef Reaction	308
1894	Smiles Rearrangement	416
1894	Wacker Oxidation	474
1895	Henry Reaction	202
1897	Arbuzov Reaction (Michaelis-Arbuzov Reaction)	16
1897	Gattermann and Gattermann-Koch Formylation	184
1898	Chugaev Elimination (Xanthate Ester Pyrolysis)	82
1899	Baeyer-Villiger Oxidation/Rearrangement	28
1899	Barbier Coupling Reaction	38
1899	Prins Reaction	364
1899	Wagner-Meerwein Rearrangement	476
1900	Grignard Reaction	188
1901	Demjanov Rearrangement and Tiffeneau-Demjanov Rearrangement	134
1901	Ullmann Reaction/Coupling/Biaryl Synthesis	466
1902	Feist-Bénary Furan Synthesis	166
1902	Wolff Rearrangement	494
1903	Benzoin and Retro-Benzoin Condensation	54
1903	Mannich Reaction	274
1903	Nazarov Cyclization	304
1903	Ullmann Biaryl Ether and Biaryl Amine Synthesis/Condensation	464
1905	Eschweiler-Clarke Methylation	160
1908	Staudinger Ketene Cycloaddition	426
1909	Acetoacetic Ester Synthesis	2
1909	Dakin Oxidation	118
1909	Paterno-Büchi Reaction	332
1909	Prilezhaev Reaction	362
1909	Pummerer Rearrangement	368
1910	Finkelstein Reaction	170
1910	Regitz Diazo-Transfer Reaction	376
1911	Pictet-Spengler Tetrahydroisoquinoline Synthesis	348
1911	Wolff-Kishner Reduction	496
1912	Madelung Indole Synthesis	270
1913	Claisen Rearrangement	88
1913	Clemmensen Reduction	92
1913	Wharton Olefin Synthesis (Wharton Transposition)	482
1914	Chichibabin Amination Reaction (Chichibabin Reaction)	80
1914	Ferrier Reaction/Ferrier Rearrangement	168
1915	Houben-Hoesch Reaction/Synthesis	216
1919	Aza-Wittig Reaction	24
1919	Meisenheimer Rearrangement	282
1919	Staudinger Reaction	428
1919	Wittig Reaction	486
1919	Wohl-Ziegler Bromination	492
1921	Passerini Multicomponent Reaction	330
1922	Meyer-Schuster and Rupe Rearrangement	284
1923	Schmidt Reaction	396
1925	Amadori Reaction/Rearrangement	14
1925	Meerwein-Ponndorf-Verley Reduction	280
1925	Stephen Aldehyde Synthesis	430
1926	Diels-Alder Cycloaddition	140
1926	Neber Rearrangement	306

YEAR OF DISCOVERY	NAME OF THE TRANSFORMATION	PAGE #
1927	Balz-Schiemann Reaction (Schiemann Reaction)	34
1928	Dakin-West reaction	120
1928	Stevens Rearrangement	434
1929	Nenitzescu Indole Synthesis	312
1931	Criegee Oxidation	114
1932	Riley Selenium Dioxide Oxidation	380
1933	Baker-Venkataraman Rearrangement	30
1933	Prévost Reaction	360
1935	Arndt-Eistert Homologation/Synthesis	18
1935	Payne Rearrangement	336
1935	Robinson Annulation	384
1937	Claisen-Ireland Rearrangement	90
1937	Oppenauer Oxidation	320
1937	Sommelet-Hauser Rearrangement	422
1939	Meerwein Arylation	278
1939	Quasi-Favorskii Rearrangement	370
1939	Snieckus Directed *Ortho* Metalation	420
1940	Carrol Rearrangement (Kimel-Cope Rearrangement)	76
1940	Cope Rearrangement	98
1940	Ramberg-Bäcklund Rearrangement	372
1942	Wittig-[1,2]- and [2,3]-Rearrangement	490
1943	Alder (Ene) Reaction	6
1943	Hetero Diels-Alder Reaction (HDA)	204
1944	Birch Reduction	60
1946	Jones Oxidation/Oxidation of Alcohols by Chromium Reagents	228
1947	Peterson Olefination	344
1948	Ritter Reaction	382
1949	Cope Elimination/(Cope Reaction)	96
1949	Cornforth Rearrangement	112
1952	Bamford-Stevens-Shapiro Olefination	36
1952	Grob Fragmentation	190
1952	Wharton Fragmentation	480
1954	Stork Enamine Synthesis	444
1955	Alkene (Olefin) Metathesis	10
1956	Brown Hydroboration Reaction	66
1957	Kornblum Oxidation	250
1958	Brook Rearrangement	64
1958	Doering-LaFlamme Allene Synthesis	146
1958	Horner-Wadsworth-Emmons Olefination	212
1958	Simmons-Smith Cyclopropanation	412
1959	Heine Reaction	198
1959	Ugi Multicomponent Reaction	462
1959	Vilsmeier-Haack Formylation	468
1959	Vinylcyclopropane-Cyclopentene Rearrangement	470
1960	Barton Nitrite Ester Reaction	42
1961	Kröhnke Pyridine Synthesis	254
1962	Barton Radical Decarboxylation Reaction	44
1962	Corey-Chaykovsky Epoxidation and Cyclopropanation	102
1962	DeMayo Cycloaddition (Enone-Alkene [2+2] Photocycloaddition)	132
1962	Nagata Hydrocyanation Reaction	302
1963	Castro-Stevens Coupling	78
1963	Corey-Winter Olefination	110
1963	Pfitzner-Moffatt Oxidation	346
1964	Eschenmoser-Claisen Rearrangement	156
1964	Oxy-Cope Rearrangement/Anionic Oxy-Cope Rearrangement	324

YEAR OF DISCOVERY	NAME OF THE TRANSFORMATION	PAGE #
1965	Tsuji-Trost Reaction/(Allylation)	458
1965	Tsuji-Wilkinson Decarbonylation	460
1966	Wittig Reaction-Schlosser Modification	488
1967	Aza-Claisen Rearrangement (3-Aza-Cope Rearrangement)	20
1967	Aza-Cope Rearrangement	22
1967	Eschenmoser-Tanabe Fragmentation	158
1967	Krapcho Dealkoxycarbonylation	252
1967	Mitsunobu Reaction	294
1967	Seyferth-Gilbert Homologation	402
1968	Baylis-Hillman Reaction	48
1968	Heck Reaction	196
1968	Minisci Reaction	290
1968	Mislow-Evans Rearrangement	292
1969	Prins-Pinacol Rearrangement	366
1969	Schwartz Hydrozirconation	400
1970	Burgess Dehydration Reaction	72
1970	Johnson-Claisen Rearrangement	226
1971	Aza-[2,3]-Wittig Rearrangement	26
1971	Corey-Kim Oxidation	106
1971	Eschenmoser Methenylation	154
1971	Hajos-Parrish Reaction	192
1971	Nicholas Reaction	314
1972	Bergman Cycloaromatization Reaction	56
1972	Corey-Fuchs Alkyne Synthesis	104
1972	Kumada Cross Coupling Reaction	258
1972	McMurry Coupling	276
1972	Saegusa Oxidation	390
1973	Julia-Lythgoe Olefination	230
1973	Mukaiyama Aldol Reaction	298
1973	Pauson-Khand Reaction	334
1973	Pinnick Oxidation	354
1973	Polonovski Reaction	356
1973	Stetter Reaction	432
1974	Overman Rearrangement	322
1974	Alkyne Metathesis	12
1974	Corey-Nicolau Macrolactonization	108
1974	Danishefsky's Diene Cycloaddition	126
1974	Rubottom Oxidation	388
1974	Swern Oxidation	450
1975	Barton-McCombie Radical Deoxygenation Reaction	46
1975	Dötz Benzannulation Reaction	148
1975	Sonogashira Cross-Coupling	424
1976	Enders SAMP/RAMP Hydrazone Alkylation	150
1976	Negishi Cross-Coupling	310
1976	Sakurai Allylation	392
1976	Stille Cross-Coupling (Migita-Kosugi-Stille Coupling)	438
1976	Tebbe Olefination/Petasis-Tebbe Olefination	454
1977	Davis Oxaziridine Oxidation	130
1977	Nozaki-Hiyama-Kishi Coupling	318
1978	Bartoli Indole Synthesis	40
1978	Luche Reduction	268
1978	Roush Asymmetric Allylation	386
1979	Midland Alpine Borane Reduction	288
1979	Suzuki Cross-Coupling (Suzuki-Miyaura Cross-Coupling)	448
1979	Yamaguchi Macrolactonization	500

YEAR OF DISCOVERY	NAME OF THE TRANSFORMATION	PAGE #
1980	Kagan-Molander Samarium-Diiodide Coupling	232
1980	Noyori Asymmetric Hydrogenation	316
1980	Sharpless Asymmetric Dihydroxylation Reaction	406
1980	Sharpless Asymmetric Epoxidation Reaction	408
1981	Corey-Bakshi-Shibata (CBS) Reduction	100
1981	Danheiser Cyclopentene Annulation	124
1981	Evans Aldol Reaction	162
1981	Weinreb Ketone Synthesis	478
1983	Buchwald-Hartwig Cross-Coupling	70
1983	Dess-Martin Oxidation	136
1983	Fleming-Tamao Oxidation	174
1983	Horner-Wadsworth-Emmons Olefination (Still-Gennari modification)	214
1984	Danheiser Benzannulation	122
1984	Stille Carbonylative Cross-Coupling	436
1985	Enyne Metathesis	152
1985	Keck Macrolactonization	238
1985	Ley Oxidation	262
1986	Takai-Utimoto Olefination (Takai Reaction)	452
1987	Stille-Kelly Coupling	440
1989	Kahne Glycosidation	234
1989	Kulinkovich Reaction	256
1990	Jacobsen-Katsuki Epoxidation	222
1991	Larock Indole Synthesis	260
1993	Keck Asymmetric Allylation	236
1993	Keck Radical Allylation	240
1993	Petasis Boronic Acid-Mannich reaction	340
1994	Myers Asymmetric Alkylation	300
1994	Smith-Tietze Multicomponent Dithiane Linchpin Coupling	418
1995	Jacobsen Hydrolytic Kinetic Resolution of Epoxides	220
1995	Miyaura Boration Reaction	296
1995	Petasis-Ferrier Rearrangement	342
1996	Sharpless Asymmetric Aminohydroxylation Reaction	404
1996	Shi Asymmetric Epoxidation	410

8.3 REACTION CATEGORIES

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
CARBOCYCLE FORMATION			
	Acyloin condensation	Formation of cyclic α-hydroxy ketones from diesters.	**4**
	Alkene metathesis	Formation of cyclic alkenes from dienes.	**10**
	Alkyne metathesis	Formation of cyclic alkynes from diynes.	**12**
	Danheiser cyclopentene annulation	Formation of cyclopentenes from enones and allenes.	**124**
	Danishefsky's diene cycloaddition	Formation of six-membered carbocycles using 1-methoxy-3-trimethylsilyloxy-1,3-butadiene.	**126**
	Dieckmann condensation	Formation of cyclic β-keto esters from diesters.	**138**
	Diels-Alder cycloaddition	The [4+2] cycloaddition of alkenes and dienes to afford substituted cyclohexenes.	**140**
	Hajos-Parrish reaction	Enantio-enriched bicyclic enones from 1,5-diketones.	**192**
	Nazarov cyclization	Cyclopentenones and cyclopentanones from divinyl ketones.	**304**
	Pauson-Khand reaction	Formation of cyclopentenones from alkenes, alkynes and CO.	**334**
	Robinson annulation	Formation of bicyclic enones from 1,5-diketones.	**384**
CYCLO-AROMATIZATION			
	Bergman cycloaromatization reaction	Thermal or photochemical cycloaromatization of enediynes to form substituted benzene rings.	**56**
	Danheiser benzannulation	Reaction of cyclobutenones with alkynes to give highly substituted benzene rings.	**122**
	Dötz benzannulation	Reaction of Fischer chromium carbenes with alkynes to give substituted hydroquinone derivatives.	**148**
DEGRADATION			
	Hofmann rearrangement	Conversion of primary carboxamides to one-carbon shorter primary amines.	**210**
	Hunsdiecker reaction	Conversion of carboxylic acids to one-carbon shorter alkyl, alkenyl or aryl halides.	**218**
	Lieben haloform reaction	Conversion of methyl ketones to one-carbon shorter carboxylic acids.	**262**
ELECTROPHILIC ADDITION TO C-C MULTIPLE BONDS			
Addition to alkenes			
cyclopropanation	Simmons-Smith cyclopropanation	Formation of cyclopropanes from alkenes.	**412**
epoxidation	Davis' oxaziridine oxidation	Formation of epoxides from alkenes using oxaziridines.	**130**
epoxidation	Jacobsen-Katsuki epoxidation	Formation of epoxides from alkenes using metal salen complexes.	**222**
epoxidation	Prilezhaev reaction	Formation of epoxides from alkenes using peracids.	**362**
epoxidation	Sharpless asymmetric epoxidation	Formation of epoxy alcohols from allylic alcohols.	**408**
epoxidation	Shi asymmetric epoxidation	Formation of epoxides from alkenes.	**410**
hydrogenation	Noyori asymmetric hydrogenation	Formation of enantio-enriched carboxylic acids, alcohols and amino acids from unsaturated carboxylic acids, allylic alcohols and enamides, respectively.	**316**
hydrometalation	Brown hydroboration reaction	Formation of alkylboranes from alkenes.	**66**
hydrometalation	Schwartz hydrozirconation	Formation of alkylzirconium compounds from alkenes.	**400**
Addition to alkynes			
hydrometalation	Brown hydroboration reaction	Formation of alkenylboranes from alkynes.	**66**
hydrometalation	Schwartz hydrozirconation	Formation of alkenylzirconium compounds from alkynes.	**400**
ELECTROPHILIC AROMATIC SUBSTITUTION			
	Bischler-Napieralski isoquinoline synthesis	Preparation of isoquinolines from acylated phenylethylamines.	**62**
	Combes Quinoline synthesis	Preparation of quinolines from aryl amines and 1,3-diketones.	**94**
	Friedel-Crafts acylation	Synthesis of aromatic ketones using acyl halides or anhydrides.	**176**
	Friedel-Crafts alkylation	Synthesis of alkylbenzenes using alkyl halides.	**178**
	Fries rearrangement	Synthesis of acylated phenols from *O*-acyl phenols.	**180**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
ELECTROPHILIC AROMATIC SUBSTITUTION			
	Gattermann and Gattermann-Koch formylation	Synthesis of aromatic aldehydes using HCN or CO.	**184**
	Houben-Hoesch reaction	Synthesis of aromatic ketones from activated aromatic compounds (e.g. phenols) and nitriles.	**216**
	Kolbe-Schmitt reaction	Synthesis of salicylic acid der. from phenols and CO_2.	**248**
	Pictet-Spengler tetrahydro-isoquinoline synthesis	Synthesis of tetrahydroisoquinolines and isoquinolines from β-arylethylamines.	**348**
	Pomeranz-Fritsch reaction	Synthesis of isoquinolines from aromatic aldehydes and 2,2-dialkoxyethylamine.	**358**
	Reimer-Tiemann reaction	Preparation of formylated phenols from substituted phenols	**378**
	Vilsmeier-Haack formylation	Synthesis of substituted benzaldehydes and heteroaromatic aldehydes using chloromethyliminium salts.	**468**
	von Pechmann reaction	Preparation of coumarins from phenols and β-keto esters.	**472**
ELIMINATION REACTIONS			
	Burgess dehydration	Preparation of alkenes from 2° and 3° alcohols.	**72**
	Chugaev elimination	Thermal *syn* elimination of xanthate esters to form alkenes.	**82**
	Cope elimination	Thermal *syn* elimination of 3° amine N-oxides to form alkenes.	**96**
	Hofmann elimination	Formation of alkenes from quaternary ammonium salts.	**206**
FRAGMENTATION REACTIONS			
	Eschenmoser-Tanabe fragmentation	Formation of alkynals or alkynones from epoxy ketone hydrazones.	**158**
	Grob fragmentation	Regulated heterolytic cleavage of certain types of molecules to form three different fragments.	**190**
	Wharton fragmentation	Base-induced formation of medium-sized cyclic alkenes from 1,3-diol monosulfonates.	**480**
HETEROCYCLE FORMATION			
	Bartoli indole synthesis	Formation of 7-substituted indoles from ortho-substituted nitro- or nitrosoarenes.	**40**
	Biginelli reaction	One-pot three component formation of 3,4-dihydropyrimidin-2(1H)-ones from aromatic aldehydes, keto esters and urea.	**58**
	Bischler-Napieralski isoquinoline synthesis	Preparation of isoquinolines from acylated phenylethylamines.	**62**
	Ciamician-Dennstedt rearrangement	Synthesis of 3-halopyridines from pyrroles and 2-haloquinolines from indoles.	**84**
	Combes quinoline synthesis	Preparation of quinolines from aryl amines and 1,3-diketones.	**94**
	Dimroth rearrangement	Isomerization of heterocycles in which endocyclic or oxocyclic heteroatoms and their attached substituents are translocated via a ring-opening-ring-closure sequence.	**144**
	Feist-Bénary furan synthesis	Synthesis of furans from β-keto esters and α-halogenated carbonyl compounds under basic conditions.	**166**
	Fischer indole synthesis	Preparation of indoles from arylhydrazones of ketones and aldehydes in the presence of protic or Lewis acid catalyst.	**172**
	Hantzsch dihydropyridine synthesis	Preparation of dihydropyridines from 1,3-diketones, aldehydes and ammonia.	**194**
	Heine reaction	Intramolecular ring expansion of substituted N-acylazirdines to the corresponding substituted oxazolines.	**198**
	Hetero Diels-Alder reaction	The [4+2] cyclization of a diene or heterodiene and a dienophile or heterodienophile.	**204**
	Hofmann-Löffler-Freytag reaction	Formation of cyclic amines from N-halogenated amines via an intramolecular 1,5-hydrogen atom transfer to a nitrogen radical.	**208**
	Knorr pyrrole synthesis	Condensation of an α-amino ketone or an α-amino-β-ketoester with an active methylene compound to afford substituted pyrroles.	**244**
	Kröhnke pyridine synthesis	Condensation of an unsaturated ketone with an α-halo ketone to give highly substituted pyridines.	**254**
	Larock indole synthesis	Preparation of 2,3-disubstituted indoles from *ortho*-iodoanilines and disubstituted alkynes.	**258**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
HETEROCYCLE FORMATION			
	Madelung indole synthesis	The intramolecular cyclization of N-acylated-*ortho*-alkylanilines to afford 2,3-disubstituted indoles.	**270**
	Paal-Knorr furan synthesis	Dehydration of 1,4-diketones to the corresponding substituted furans.	**326**
	Paal-Knorr pyrrole synthesis	Condensation of primary amines with 1,4-dicarbonyl compounds to form substituted pyrroles.	**328**
	Paterno-Büchi reaction	Formation of oxetanes by the photocycloaddition of alkenes and carbonyl compounds.	**332**
	Pictet-Spengler tetrahydroisoquinoline synthesis	Condensation of a β-arylethylamine with carbonyl compounds to form tetrahydroisoquinolines.	**348**
	Pomeranz-Fritsch reaction	The acid catalyzed cyclization of benzalaminoacetals to form isoquinolines.	**358**
	Skraup and Doebner-Miller quinoline synthesis	Condensation of enones with substituted anilines to afford isoquinolines.	**414**
	von Pechman reaction	Condensation of phenols with β-keto esters to give substituted coumarins.	**472**
HOMOLOGATION			
	Arndt-Eistert homologation	One-carbon homologation of carboxylic acids.	**18**
	Corey-Fuchs alkyne synthesis	One-carbon homologation of aldehydes to form the corresponding terminal alkynes.	**104**
	Doering-LaFlamme allene synthesis	Preparation of allenes from olefins.	**146**
	Seyferth-Gilbert homologation	Synthesis of alkynes from aldehydes.	**402**
	Takai-Utimoto olefination	The chromium(II)-mediated one-carbon homologation of aldehydes to the corresponding (*E*)-alkenyl halides.	**452**
	Tebbe olefination	One-carbon homologation of carbonyl compounds to afford the corresponding 1,1-disubstituted alkenes.	**454**
METATHESIS			
	Alkene metathesis	Metal catalyzed redistribution of carbon-carbon double bonds.	**10**
	Alkyne metathesis	Metal catalyzed redistribution of carbon-carbon triple bonds.	**12**
	Enyne metathesis	Transition metal catalyzed cycloisomerization of [1,n]-enynes to the corresponding 1,3-dienes.	**152**
NUCLEOPHILIC AROMATIC SUBSTITUTION			
	Chichibabin amination reaction	Direct amination of pyridine via S_NAr reaction.	**80**
	Smiles rearrangement	Intramolecular nucleophilic aromatic rearrangement of activated aromatic substrates.	**416**
NUCLEOPHILIC SUBSTITUTION			
	Finkelstein reaction	Equilibrium exchange of the halogen atom in alkyl halides for another halogen atom.	**170**
	Gabriel synthesis	Two-step preparation of primary amines from the corresponding alkyl halides using phthalimide as the nitrogen source.	**182**
	Heine reaction	Intramolecular ring expansion of substituted N-acylaziridines by nucleophilic reagents to the corresponding substituted oxazolines.	**198**
	Kahne glycosidation	Preparation of *O*-, *S*- or *N*-glycosides via the activation of glycosyl sulfoxides.	**234**
	Koenigs-Knorr glycosidation	Synthesis of alkyl or aryl *O*-glycosides from glycosyl halides and alcohols or phenols, respectively.	**246**
	Krapcho dealkoxycarbonylation	Decarboxylation of β-keto esters using alkali metal salts.	**252**
	Mitsunobu reaction	Substitution of primary and secondary alcohols with nucleophiles in the presence of dialkyl azodicarboxylate and trialkyl- or triarylphosphine.	**294**
	Myers asymmetric alkylation	Alkylation of *N*-acylated pseudoephedrines to obtain enantio-enriched α-alkylated carbonyl compounds.	**300**
	Nicholas reaction	Trapping of dicobalt hexacarbonyl-stabilized propargylic cations with various nucleophiles.	**314**
	Payne rearrangement	Base-catalyzed intramolecular displacement of 2,3-epoxy alcohols to give isomeric 2,3-epoxy alcohols.	**336**
	Stork enamine synthesis	Alkylation of enamines with alkyl halides to afford α-alkylated aldehydes or ketones.	**444**
	Williamson ether synthesis	Alkylation of alkali alkoxides with primary or secondary alkyl halides to form ethers.	**484**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
OXIDATION			
	Baeyer-Villiger oxidation	Formation of esters from ketones upon peracid oxidation.	**28**
	Corey-Chaykovsky epoxidation	Preparation of epoxides from aldehydes and ketones.	**102**
	Corey-Kim oxidation	Oxidation of primary and secondary alcohols with NCS/DMS to afford aldehydes and ketones, respectively.	**106**
	Criegee oxidation	Cleavage of 1,2-diols (glycols) to the corresponding carbonyl compounds using LTA.	**114**
	Dakin oxidation	Conversion of aromatic aldehydes and ketones to the corresponding phenols.	**118**
	Davis' oxaziridine oxidation	Oxidation of electron-rich substrates (e.g. alkenes, enolates, enol ethers etc.) with oxaziridines.	**130**
	Dess-Martin oxidation	Oxidation of alcohols and oximes to afford the corresponding carbonyl compounds using DMP.	**136**
	Fleming-Tamao oxidation	Mild stereospecific oxidation of silicon-carbon bonds to the corresponding carbon-oxygen bonds	**174**
	Jacobsen-Katsuki epoxidation	Enantioselective epoxidation of unfunctionalized alkyl- and aryl-substituted olefins.	**222**
	Jones oxidation	Oxidation of primary and secondary alcohols with chromic acid to give the corresponding carboxylic acids and ketones.	**228**
	Kornblum oxidation	Oxidation of alkyl halides to the corresponding carbonyl compounds using DMSO as the oxidant.	**250**
	Ley oxidation	Oxidation of primary and secondary alcohols with TPAP/NMO to give the corresponding aldehydes and ketones.	**260**
	Oppenauer oxidation	Oxidation of primary and secondary alcohols with ketones in the presence of metal alkoxides to afford the corresponding aldehydes and ketones.	**320**
	Pfitzner-Moffatt oxidation	Oxidation of primary and secondary alcohols with DCC/DMSO to give the corresponding aldehydes and ketones.	**346**
	Pinnick oxidation	Mild oxidation of aldehydes directly to the corresponding carboxylic acids using $NaClO_2$ as the oxidant.	**354**
	Prilezhaev reaction	Oxidation of alkenes to epoxides using peroxycarboxylic acids.	**362**
	Riley selenium dioxide oxidation	Oxidation of the methylene group adjacent to a carbonyl group or the double bond of olefins (allylic or benzylic position) with SeO_2.	**380**
	Rubottom oxidation	Oxidation of silyl enol ethers with *m*CPBA to give -hydroxy ketones or -hydroxy aldehydes.	**388**
	Saegusa oxidation	Regioselective introduction of the carbon-carbon double bond to cyclic and acylic ketones via Pd-mediated oxidation of the corresponding silyl enol ethers.	**390**
	Sharpless asymmetric aminohydroxylation	One-pot enantioselective synthesis of protected vicinal amino alcohols from simple alkenes.	**404**
	Sharpless asymmetric dihydroxylation	One-pot enantioselective synthesis of vicinal diols from simple alkenes.	**406**
	Sharpless asymmetric epoxidation	Ti-alkoxide-catalyzed epoxidation of prochiral and chiral allylic alcohols in the presence of a chiral tartrate ester and an alkyl hydroperoxide.	**408**
	Shi asymmetric epoxidation	Chiral-ketone catalyzed epoxidation of unfunctionalized olefins.	**410**
	Swern oxidation	Oxidation of primary and secondary alcohols using DMSO/TFAA or oxalyl chloride to afford the corresponding aldehydes and ketones.	**450**
	Tishchenko reaction	Conversion of aldehydes to the corresponding esters in the presence of metal alkoxides.	**456**
	Wacker oxidation	One-pot oxidation of olefins to the corresponding ketones in the presence of catalytic amounts of Pd(II)-salts	**474**
PERICYCLIC REACTIONS			
	Alder (ene) reaction	Activation of an allylic C-H bond and the concomitant allylic transposition of the C=C double bond of alkenes. (Formally the addition of alkenes to C=C and C=O bonds.)	**6**
cycloaddition	Danishefsky's diene cycloaddition	Formation of six-membered carbocycles and heterocycles using 1-methoxy-3-trimethylsilyloxy-1,3-butadiene.	**126**
cycloaddition	DeMayo cycloaddition	Photochemical [2+2] cycloaddition of enones and alkenes to give substituted cyclobutanes.	**132**
cycloaddition	Diels-Alder cycloaddition	The [4+2] cycloaddition of alkenes and dienes to afford substituted cyclohexenes.	**140**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
PERICYCLIC REACTIONS			
cycloaddition	Hetero Diels-Alder cycloaddition	The [4+2] cyclization of a diene or heterodiene and a dienophile or heterodienophile.	**204**
cycloaddition	Paterno-Büchi reaction	Formation of oxetanes by the photocycloaddition of alkenes and carbonyl compounds.	**332**
cycloaddition	Staudinger ketene cycloaddition	Formation of cyclobutanones from alkenes and ketenes.	**426**
electrocyclization	Cornforth rearrangement	Thermal rearrangement of 4-carbonyl substituted oxazoles to their isomeric oxazoles.	**112**
electrocyclization	Nazarov cyclization	Thermal or photochemical ring-closure of divinyl ketones.	**304**
sigmatropic rearr.	Aza-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of *N*-allyl enamines.	**20**
sigmatropic rearr.	Aza-Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of *N*-substituted 1,5-dienes.	**22**
sigmatropic rearr.	Aza-Wittig rearrangement	Thermal [3,3]-sigmatropic rearrangement of allylic tertiary amines to give homoallylic secondary amines.	**26**
sigmatropic rearr.	Carroll rearrangement	Thermal [3,3]-sigmatropic rearrangement of allylic β-keto esters to afford γ,δ-unsaturated ketones.	**76**
sigmatropic rearr.	Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of allyl vinyl ethers to give γ,δ-unsaturated carbonyl compounds.	**88**
sigmatropic rearr.	Claisen-Ireland rearrangement	Thermal [3,3]-sigmatropic rearrangement of *O*-trialkylsilylketene acetals to γ,δ-unsaturated carboxylic acids.	**90**
sigmatropic rearr.	Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of 1,5-dienes to the isomeric 1,5-dienes.	**98**
sigmatropic rearr.	Eschenmoser-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement to generate γ,δ-unsaturated amides from allylic alcohols and *N,N*-dimethylacetamide dimethyl acetal.	**156**
sigmatropic rearr.	Johnson-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of allyl ketene acetals to afford γ,δ-unsaturated esters.	**226**
sigmatropic rearr.	Meisenheimer rearrangement	Thermal rearrangement of certain tertiary amine N-oxides to the corresponding *O*-substituted-*N,N*-disubstituted hydroxylamines.	**282**
sigmatropic rearr.	Mislow-Evans rearrangement	Reversible 1,3-transposition of allylic sulfoxide and allylic alcohol functionalities.	**292**
sigmatropic rearr.	Overman rearrangement	The 1,3-transposition of alcohol and amine functionalities *via* the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates.	**322**
sigmatropic rearr.	Oxy-Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of 1,5-diene-3-ols to afford δ,ε-unsaturated carbonyl compounds.	**324**
sigmatropic rearr.	Sommelet-Hauser rearrangement	The thermal [2,3]-sigmatropic rearrangement of benzylic quaternary ammonium salts in the presence of a strong base.	**422**
sigmatropic rearr.	Wittig rearrangement	Thermal [1,2]-rearrangement of aryl alkyl ethers and also the thermal [2,3]-rearrangement of allyl alkyl ethers.	**490**
PHOTOCHEMICAL REACTIONS			
	Bergman cycloaromatization reaction	Thermal or photochemical cycloaromatization of enediynes to form substituted benzene rings.	**56**
	Buchner method of ring expansion	Thermal or photochemical reaction of ethyl diazoacetate with benzenes and its homologs to give the isomeric esters of cycloheptatriene carboxylic acid.	**68**
	Curtius rearrangement	Thermal or photochemical rearrangement of acyl azides to give isocyanates.	**116**
	DeMayo cycloaddition	Photochemical [2+2] cycloaddition of enones and alkenes to give substituted cyclobutanes.	**132**
	Fries rearrangement	Conversion of phenolic esters to the corresponding phenolic ketones and aldehydes.	**180**
	Nazarov cyclization	Thermal or photochemical ring-closure of divinyl ketones.	**304**
	Paterno-Büchi reaction	Formation of oxetanes by the photocycloaddition of alkenes and carbonyl compounds.	**332**
	Vinylcyclopropane-cyclopentene rearrangement	Thermal or photochemical rearrangement of substituted vinylcyclopropanes to substituted cyclopentenes.	**470**
	Wolff rearrangement	Thermal or photochemical rearrangement of α-diazo ketones to form ketenes.	**494**
RADICAL REACTIONS			
alkylation	Minisci reaction	Substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals.	**290**
allylation	Keck radical allylation	Coupling of alkyl halides with allyltributyltin in the presence of a radical initiator (e.g. AIBN)	**240**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
RADICAL REACTIONS			
arylation	Meerwein arylation	Arylation of unsaturated carbonyl compounds using diazonium salts.	**278**
decarboxylation	Barton radical decarboxylation reaction	Reductive decarboxylation of thiohydroxamate esters to give alkanes.	**44**
decarboxylation	Hunsdiecker reaction	Halogenative decarboxylation of carboxylic acids to give one-carbon shorter alkyl halides.	**218**
deoxygenation	Barton-McCombie radical deoxygenation	Reductive deoxygenation of thioxoesters to give the corresponding alkanes.	**46**
halogenation	Sandmeyer reaction	Formation of aryl halides from the corresponding diazonium salts *via* an aryl radical.	**394**
halogenation	Wohl-Ziegler bromination	Bromination of alkenes and alkylbenzenes at the allylic or benzylic position.	**492**
remote functionalization	Barton nitrite ester reaction	Thermal or photolytic reaction of nitrite esters to afford γ-hydroxy oximes.	**42**
remote functionalization	Hofmann-Löffler-Freytag reaction	Thermal or photolytic reaction of *N*-halogenated amines to form cyclic amines.	**208**
REACTIONS INVOLVING CARBENES			
	Buchner method of ring expansion	Thermal or photochemical reaction of ethyl diazoacetate with benzenes and its homologs to give the isomeric esters of cycloheptatriene carboxylic acid.	**68**
	Ciamician-Dennstedt rearrangement	Synthesis of 3-halopyridines from pyrroles and 2-haloquinolines from indoles.	**84**
	Doering-LaFlamme allene synthesis	Preparation of allenes from olefins.	**146**
	Reimer-Tiemann reaction	Preparation of formylated phenols from substituted phenols	**378**
	Wolff rearrangement	Thermal or photochemical rearrangement of α-diazo ketones to form ketenes.	**494**
REACTIONS INVOLVING CARBONYL COMPOUNDS			
	Aldol reaction	Addition of an enol/enolate of a carbonyl compound to an aldehyde or ketone to form a β-hydroxycarbonyl compound.	**8**
	Barbier coupling reaction	Metal-mediated addition of alkyl, allyl or benzyl halides to carbonyl compounds.	**38**
	Baylis-Hillman reaction	Formation of a C-C single bond between the α-position of conjugated carbonyl compounds or conjugated carboxylic acid derivatives and aldehydes or ketones.	**48**
	Benzoin and retro-benzoin condensation	Reaction of aldehydes to form α-hydroxy ketones in the presence of a nucleophilic catalyst (e.g. cyanide ion).	**54**
	Corey-Chaykovsky epoxidation	Preparation of epoxides from aldehydes and ketones using sulfur ylides.	**102**
	Corey-Fuchs alkyne synthesis	One-carbon homologation of aldehydes to form the corresponding terminal alkynes.	**104**
	Dakin oxidation	Conversion of aromatic aldehydes and ketones to the corresponding phenols.	**118**
	Eschweiler-Clarke methylation	One-pot reductive methylation of primary and secondary amines to the corresponding tertiary amines using formaldehyde and a reducing agent.	**160**
	Evans aldol reaction	Reaction of boron enolates with aldehydes to afford *syn* aldol products.	**162**
	Grignard reaction	Addition of organomagnesium species to aldehydes and ketones to form secondary alcohols and tertiary alcohols, respectively.	**188**
	Hantzsch dihydropyridine synthesis	Preparation of dihydropyridines from 1,3-diketones, aldehydes and ammonia.	**194**
	Henry reaction	Aldol condensation between nitroalkanes and carbonyl compounds to form β-nitro alcohols.	**202**
	HWE olefination	Stereoselective olefination of aldehydes and ketones using phosphoryl-stabilized carbanions.	**212**
	HWE olefination-Still modification	Preparation of (Z)-α,β-unsaturated ketones and esters by coupling electrophilic *bis*(trifluoroalkyl) phosphonoesters with aldehydes and ketones in the presence of a strong base.	**214**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
REACTIONS INVOLVING CARBONYL COMPOUNDS			
	Kagan-Molander coupling	SmI_2-mediated addition of alkyl, allyl or benzyl halides to carbonyl compounds.	**232**
	Keck asymmetric allylation	The reaction of aldehydes with allyltributylstannane in the presence of Lewis acid catalysts to form homoallylic alcohols.	**236**
	Knoevenagel condensation	Condensation of aldehydes and ketones with active methylene compounds to afford α,β-unsaturated dicarbonyl or related compounds.	**242**
	Mannich reaction	The condensation of CH activated compound with a primary or secondary amine and a non-enolizable carbonyl compound to afford aminoalkylated derivatives.	**274**
	Mukaiyama aldol reaction	Lewis acid mediated addition of enol silanes to carbonyl compounds.	**298**
	Passerini multicomponent reaction	Condensation of isocyanides with carboxylic acids and carbonyl compounds to afford α-acyloxycarboxamides.	**330**
	Perkin reaction	Condensation of aromatic aldehydes with the anhydrides of aliphatic carboxylic acids to afford α,β-unsaturated carboxylic acids.	**338**
	Peterson olefination	Preparation of alkenes from α-silyl carbanions and carbonyl compounds.	**344**
	Pictet-Spengler tetrahydro-isoquinoline synthesis	Synthesis of tetrahydroisoquinolines and isoquinolines from β-arylethylamines.	**348**
	Prins reaction	Acid-catalyzed condensation of alkenes with aldehydes.	**364**
	Reformatsky reaction	Zinc-induced reaction between an α-halo ester and an aldehyde or ketone to afford a β-hydroxy ketone.	**374**
	Robinson annulation	Formation of bicyclic enones from 1,5-diketones.	**384**
	Roush asymmetric allylation	Reaction of allylboronates with aldehydes to give homoallylic alcohols.	**386**
	Sakurai allylation	Reaction of allylsilanes with a variety of aldehydes and ketones in the presence of a Lewis acid.	**392**
	Seyferth-Gilbert homologation	Preparation of alkynes from aldehydes and ketones.	**402**
	Stetter reaction	Formation of 1,4-diketones from aldehydes and α,β-unsaturated carbonyl compounds in the presence of a nucleophilic catalyst.	**432**
	Stobbe condensation	Formation of alkylidene succinic acids or their monoesters from dialkyl succinates and carbonyl compounds.	**442**
	Strecker reaction	The condensation of carbonyl compounds with amines and nitriles to afford α-amino nitriles.	**446**
	Takai-Utimoto olefination	The chromium(II)-mediated one-carbon homologation of aldehydes to the corresponding (*E*)-alkenyl halides.	**452**
	Tebbe olefination	One-carbon homologation of carbonyl compounds to afford the corresponding 1,1-disubstituted alkenes.	**454**
	Wittig reaction	Formation of carbon-carbon double bonds from carbonyl compounds and phosphorous ylides.	**486**
	Wittig reaction-Schlosser modification	One-pot multistep preparation of (*E*)-alkenes from "nonstabilized" phosphorous ylides and carbonyl compounds by the equilibration of the intermediate lithiobetaines.	**488**
REARRANGE-MENTS			
anionic	Baker-Venkataraman rearrangement	Base-catalyzed rearrangement of aromatic *ortho*-acyloxyketones to aromatic β-diketones.	**30**
anionic	Benzilic acid rearrangement	Rearrangement of 1,2-diketones to give the salts of α-hydroxy acids.	**52**
anionic	Brook rearrangement	Intramolecular anionic [1,*n*]-migration of silyl groups from a carbon to an oxygen atom.	**64**
anionic	Ciamician-Dennstedt rearrangement	Synthesis of 3-halopyridines from pyrroles and 2-haloquinolines from indoles.	**84**
anionic	Favorskii rearrangement	Skeletal rearrangement of α-halo ketones via a cyclopropanone intermediate to give carboxylic acids or carboxylic acid derivatives.	**164**
anionic	Hofmann rearrangement	Conversion of primary carboxamides to one-carbon shorter primary amines.	**210**
anionic	Lossen rearrangement	Conversion of *O*-acyl hydroxamic acids to the corresponding isocyanates.	**266**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
REARRANGE-MENTS			
anionic	Payne rearrangement	The base-catalyzed intramolecular nucleophilic displacement of 2,3-epoxy alcohols to give the isomeric 2,3-epoxy alcohols.	**336**
anionic	Quasi-Favorskii rearrangement	Skeletal rearrangement of bicyclic α-halo ketones in which the halogen is located at the bridgehead position to afford carboxylic acids or carboxylic acid derivatives.	**370**
anionic	Ramberg-Bäcklund rearrangement	Base-induced rearrangement of α-halogenated sulfones via episulfone intermediates to produce alkenes.	**372**
anionic	Smiles rearrangement	Intramolecular nucleophilic aromatic rearrangement of activated aromatic substrates.	**416**
anionic	Wittig rearrangement	Thermal [1,2]-rearrangement of aryl alkyl ethers and also the thermal [2,3]-rearrangement of allyl alkyl ethers.	**490**
ANRORC	Dimroth rearrangement	Isomerization of heterocycles in which endocyclic or oxocyclic heteroatoms and their attached substituents are translocated via a ring-opening-ring-closure sequence.	**144**
biradical or dipolar	Vinylcyclopropane-cyclopentene rearrangement	Thermal or photochemical rearrangement of substituted vinylcyclopropanes to substituted cyclopentenes.	**470**
cationic	Amadori reaction/rearrangement	The acid- or base-catalyzed isomerization of *N*-glycosides of aldoses to form 1-amino-1-deoxy ketoses.	**14**
cationic	Beckmann rearrangement	Conversion of aldoximes and ketoximes to the corresponding amides in acidic medium.	**50**
cationic	Demjanov and Tiffeneau-Demjanov rearrangement	The ring enlargement of 1-aminomethyl cycloalkanes to the corresponding cycloalkanols and the ring-enlargement of 1-aminomethyl cycloalkanols to the corresponding cycloalkanones.	**134**
cationic	Dienone-phenol rearrangement	Acid-catalyzed migration of alkyl groups in cyclohexadienones to afford substituted phenols.	**142**
cationic	Ferrier reaction	Lewis acid promoted rearrangement of unsaturated carbohydrates (glycals) in the presence of nucleophiles to the corresponding 2,3-unsaturated glycosyl compounds.	**168**
cationic	Fries rearrangement	Synthesis of acylated phenols from *O*-acyl phenols.	**180**
cationic	Meyer-Schuster and Rupe rearrangement	Acid-catalyzed isomerization of secondary and tertiary propargylic alcohols to the corresponding α,β-unsaturated aldehydes or ketones.	**284**
cationic	Petasis-Ferrier rearrangement	Lewis acid-promoted rearrangement of cyclic enol acetals to the corresponding substituted tetrahydrofurans and tetrahydropyrans.	**342**
cationic	Pinacol rearrangement	Acid-catalyzed transformation of 1,2-diols to give the corresponding rearranged ketones or aldehydes.	**350**
cationic	Prins-Pinacol rearrangement	Formation of oxacyclic and carbocyclic ring systems by terminating Prins cyclizations with the pinacol rearrangement in a tandem fashion.	**366**
cationic	Pummerer rearrangement	Formation of α-substituted sulfides from the corresponding sulfoxides.	**368**
cationic	Schmidt reaction	Reaction of carboxylic acids and carbonyl compounds with hydrazoic acid or alkyl azides to afford the corresponding amines, nitriles or amides, respectively.	**396**
cationic	Wagner-Meerwein rearrangement	Generation of a carbocation followed by the [1,2]-shift of an adjacent carbon-carbon bond to generate a new carbocation.	**476**
concerted	Baeyer-Villiger oxidation/rearrangement	Transformation of ketones to esters and cyclic ketones to lactones by peroxyacids.	**28**
dipolar	Cornforth rearrangement	Thermal rearrangement of 4-carbonyl substituted oxazoles to their isomeric oxazoles.	**112**
neutral	Curtius rearrangement	Thermal or photochemical rearrangement of acyl azides to give isocyanates.	**116**
neutral	Wolff rearrangement	Thermal or photochemical rearrangement of α-diazo ketones to form ketenes.	**494**
radical pair	Stevens rearrangement	Base-promoted transformation of sulfonium or quaternary ammonium salts to sulfides or tertiary amines.	**434**
sigmatropic (neutral)	Aza-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of *N*-allyl enamines.	**20**
sigmatropic (neutral)	Aza-Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of *N*-substituted 1,5-dienes.	**22**
sigmatropic (anionic)	Aza-Wittig rearrangement	Thermal [3,3]-sigmatropic rearrangement of allylic tertiary amines to give homoallylic secondary amines.	**26**
sigmatropic (neutral)	Carroll rearrangement	Thermal [3,3]-sigmatropic rearrangement of allylic β-keto esters to afford γ,δ-unsaturated ketones.	**76**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
REARRANGE-MENTS			
sigmatropic (neutral)	Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of allyl vinyl ethers to give γ,δ-unsaturated carbonyl compounds.	**88**
sigmatropic (neutral)	Claisen-Ireland rearrangement	Thermal [3,3]-sigmatropic rearrangement of O-trialkylsilylketene acetals to γ,δ-unsaturated carboxylic acids.	**90**
sigmatropic (neutral)	Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of 1,5-dienes to the isomeric 1,5-dienes.	**98**
sigmatropic (neutral)	Eschenmoser-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement to generate γ,δ-unsaturated amides from allylic alcohols and *N,N*-dimethylacetamide dimethyl acetal.	**156**
sigmatropic (neutral)	Johnson-Claisen rearrangement	Thermal [3,3]-sigmatropic rearrangement of allyl ketene acetals to afford γ,δ-unsaturated esters.	**226**
sigmatropic anionic for [2,3] and radical for [1,2]	Meisenheimer rearrangement	Thermal rearrangement of certain tertiary amine *N*-oxides to the corresponding *O*-substituted-*N,N*-disubstituted hydroxylamines.	**282**
sigmatropic (anionic)	Mislow-Evans rearrangement	Reversible 1,3-transposition of allylic sulfoxide and allylic alcohol functionalities.	**292**
sigmatropic (neutral)	Overman rearrangement	The 1,3-transposition of alcohol and amine functionalities *via* the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates.	**322**
sigmatropic (anionic)	Oxy-Cope rearrangement	Thermal [3,3]-sigmatropic rearrangement of 1,5-diene-3-ols to afford δ,ε-unsaturated carbonyl compounds.	**324**
sigmatropic (anionic)	Sommelet-Hauser rearrangement	The thermal [2,3]-sigmatropic rearrangement of benzylic quaternary ammonium salts in the presence of a strong base.	**422**
REDUCTION			
	Birch reduction	1,4-Reduction of aromatic rings using alkali metals dissolved in liquid ammonia as reducing agents.	**60**
	Clemmensen reduction	Conversion of a carbonyl group to the corresponding methylene group using Zn(Hg)/HCl.	**92**
	Corey-Bakshi-Shibata reduction	Enantioselective reduction of ketones with BH_3 using oxazaborolidines as catalysts.	**100**
	Eschweiler-Clarke methylation	One-pot reductive methylation of primary and secondary amines to the corresponding tertiary amines using formaldehyde and a reducing agent.	**160**
	Luche reduction	Reduction of enones to the corresponding allylic alcohols using $CeCl_3/NaBH_4$.	**268**
	Meerwein-Ponndorf-Verley reduction	The reduction of aldehydes and ketones by metal alkoxides to the corresponding alcohols	**280**
	Midland Alpine borane reduction	Enantioselective reduction of ketones using Alpine borane.	**288**
	Noyori asymmetric hydrogenation	Formation of enantio-enriched carboxylic acids, alcohols and amino acids from unsaturated carboxylic acids, allylic alcohols and enamides, respectively.	**316**
	Staudinger reduction	Reduction of azides with triphenylphosphine.	**428**
	Stephen aldehyde synthesis	Reduction of nitriles with $SnCl_2$/HCl to give the corresponding aldehydes.	**430**
	Tishchenko reaction	Conversion of aldehydes to the corresponding esters in the presence of metal alkoxides.	**456**
	Wolff-Kishner reduction	Deoxygenation of aldehydes and ketones under basic conditions to give hydrocarbons via the corresponding hydrazones or semicarbazones.	**496**
RING CONTRACTION			
	Benzilic acid rearrangement	Rearrangement of 1,2-diketones to give the salts of α-hydroxy acids.	**52**
	Favorskii rearrangement	Skeletal rearrangement of α-halo ketones via a cyclopropanone intermediate to give carboxylic acids or carboxylic acid derivatives.	**164**
	Quasi-Favorskii rearrangement	Skeletal rearrangement of bicyclic α-halo ketones in which the halogen is located at the bridgehead position to afford carboxylic acids or carboxylic acid derivatives.	**370**
RING EXPANSION			
	Buchner method of ring expansion	Thermal or photochemical reaction of ethyl diazoacetate with benzenes and its homologs to give the isomeric esters of cycloheptatriene carboxylic acid.	**68**

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
RING EXPANSION			
	Ciamician-Dennstedt rearrangement	Synthesis of 3-halopyridines from pyrroles and 2-haloquinolines from indoles.	**84**
	Demjanov and Tiffeneau-Demjanov rearrangement	The ring enlargement of 1-aminomethyl cycloalkanes to the corresponding cycloalkanols and the ring-enlargement of 1-aminomethyl cycloalkanols to the corresponding cycloalkanones.	**134**
TRANSITION METAL CATALYZED COUPLINGS			
Cu-catalyzed	Castro-Stevens coupling	The copper(I)-mediated coupling of aryl or vinyl halides with aryl- or alkyl-substituted alkynes to afford disubstituted alkynes or enynes.	**78**
Cu-catalyzed	Glaser coupling	Preparation of symmetrical conjugated diynes and polyynes by the oxidative homocoupling of terminal alkynes in the presence of copper salts.	**186**
Cu-catalyzed	Ullmann biaryl ether synthesis	Cu-mediated synthesis of biaryl ethers by coupling aryl halides and phenols.	**464**
Cu-catalyzed	Ullmann reaction	Cu-mediated coupling of two aryl halides to afford symmetrical or unsymmetrical biaryls.	**466**
Pd-catalyzed	Buchwald-Hartwig cross-coupling	Direct Pd-catalyzed C-N and C-O bond formation between aryl halides and amines or alcohols.	**70**
Pd-catalyzed	Heck reaction	Pd-catalyzed arylation or alkenylation of olefins.	**196**
Pd- or Ni-catalyzed	Kumada cross-coupling	Cross-coupling of alkenyl- or aryl halides and Grignard reagents or organolithium species.	**258**
Pd-catalyzed	Larock indole synthesis	Preparation of 2,3-disubstituted indoles from *ortho*-iodoanilines and disubstituted alkynes.	**260**
Pd-catalyzed	Miyaura boration	Pd-catalyzed cross-coupling of aromatic and heteroaromatic halides or triflates with tetraalkoxydiboron compounds to give arylboronic and heteroarylboronic esters.	**296**
Pd- or Ni-catalyzed	Negishi cross-coupling	Pd- or Ni-catalyzed cross-coupling of organozincs and aryl- or alkenyl- or alkynyl halides.	**310**
Pd and Cu-catalyzed	Sonogashira cross-coupling	Cu-Pd-catalyzed coupling of terminal alkynes with aryl and vinyl halides to give enynes.	**424**
Pd-catalyzed	Stille carbonylative cross-coupling	Pd-catalyzed coupling of organostannanes and alkenyl- or aryl halides and CO to form ketones.	**436**
Pd-catalyzed	Stille cross-coupling	Pd-catalyzed coupling of organostannanes and alkenyl- or aryl halides.	**438**
Pd-catalyzed	Stille-Kelly coupling	Pd-catalyzed intramolecular biaryl coupling of aryl halides or aryl triflates in the presence of distannanes.	**440**
Pd-catalyzed	Suzuki cross-coupling	Pd-catalyzed coupling between organoboron compounds and organic halides and triflates.	**448**
Pd-catalyzed	Tsuji-Trost allylation	Pd-catalyzed allylation of carbon nucleophiles with allylic compounds via -allylpalladium complexes.	**458**

8.4 AFFECTED FUNCTIONAL GROUPS

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ACETAL		
	γ,δ-unsaturated amide	Eschenmoser-Claisen rearrangement
ALCOHOL		
1° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
1° alcohol	aldehyde	Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation
1° alcohol	alkane	Barton-McCombie radical deoxygenation
1° alcohol	alkene	Chugaev elimination
1° alcohol	amine	Mitsunobu reaction
1° alcohol	azide	Mitsunobu reaction
1° alcohol	carboxylic acid	Jones oxidation
1° alcohol	ester	Mitsunobu reaction
1° alcohol	ether	Mitsunobu reaction, Williamson ether synthesis
1° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
1° alcohol	nitrile	Mitsunobu reaction
1° alcohol	sulfide	Mitsunobu reaction
2° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
2° alcohol	alkane	Barton-McCombie radical deoxygenation
2° alcohol	alkene	Burgess dehydration, Chugaev elimination
2° alcohol	amine	Mitsounobu reaction
2° alcohol	azide	Mitsunobu reaction
2° alcohol	ester	Mitsunobu reaction, Schotten-Baumann reaction
2° alcohol	ether	Mitsunobu reaction, Williamson ether synthesis
2° alcohol	ketone	Corey-Kim oxidation, Dess-Martin oxidation, Jones oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation
2° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
2° alcohol	nitrile	Mitsunobu reaction
2° alcohol	sulfide	Mitsunobu reaction
3° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
3° alcohol	alkane	Barton-McCombie radical deoxygenation
3° alcohol	alkene	Burgess dehydration, Chugaev elimination, Grob fragmentation
3° alcohol	amide	Ritter reaction
3° alcohol	ester	Schotten-Baumann reaction
3° alcohol	ether	Williamson ether synthesis
3° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
allylic alcohol	γ,δ-unsaturated amide	Eschenmoser-Claisen rearrangement
allylic alcohol	γ,δ-unsaturated ester	Johnson-Claisen rearrangement
allylic alcohol	allylic amide	Overman rearrangement
allylic alcohol	epoxy alcohol	Sharpless asymmetric epoxidation
allylic alcohol	saturated enantio-enriched alcohol	Noyori asymmetric hydrogenation
propargylic alcohol	α,β-unsaturated ketone	Meyer-Schuster and Rupe rearrangement
propargylic alcohol	propargyl-substituted compound	Nicholas reaction
ALDEHYDE		
	α,β-epoxy ester	Darzens glycidic ester condensation
	α,β-unsaturated carboxylic acid	Perkin reaction
	α-amino nitrile	Strecker reaction
	β-nitro alcohol	Henry reaction
	γ-oxo ester	Stetter reaction
	γ-oxo nitrile	Stetter reaction
	1,3-diol	Prins reaction
	1,4,7-triketone	Stetter reaction
	1,4-diketone	Stetter reaction
	alkane	Tsuji-Wilkinson decarbonylation

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ALDEHYDE		
	alkene	McMurry coupling, Wittig reaction, Wittig reaction-Schlosser modification, Bamford-Stevens-Shapiro reaction, HWE olefination, HWE olefination-Still modification, Julia-Lythgoe olefination, Peterson olefination, Takai reaction, Tebbe olefination, Stobbe condensation, Perkin reaction, Knoevenagel condensation
	alkyne	Corey-Fuchs alkyne synthesis, Seyferth-Gilbert homologation
	allylic alcohol	Baylis-Hillman reaction
	amide	Passerini reaction, Ugi multicomponent reaction
	amine	Eschweiler-Clarke methylation, Baylis-Hillman reaction, Petasis boronic acid-Mannich reaction
	carboxylic acid	Jones oxidation, Cannizzaro reaction, Pinnick oxidation
	epoxide	Corey-Chaykovsky epoxidation
	ester	Tishchenko reaction, Dakin oxidation (aromatic aldehydes only)
	homoallylic alcohol	Sakurai allylation, Roush asymmetric allylation, Keck asymmetric allylation
	imine	Aza-Wittig reaction
	nitrile	Schmidt reaction
	nitroalkene	Henry reaction
	primary alcohol	Meerwein-Ponndorf-Verley reduction, Cannizzaro reaction
	secondary alcohol	Barbier coupling reaction, Grignard reaction, Aldol reaction, Evans aldol reaction, Nozaki-Hiyama-Kishi reaction, Sakurai allylation, Roush asymmetric allylation, Keck asymmetric allylation
	tetrahydroisoquinoline	Pictet-Spengler tetrahydroisoquinoline synthesis
ALKENE		
	1,2-diol	Sharpless asymmetric dihydroxylation, Prévost reaction
	1,3-diene	Enyne metathesis, Heck reaction
	1,3-diol	Prins reaction
	1,5-diketone	DeMayo cycloaddition
	alcohol	Brown hydroboration reaction/oxidation
	alkylborane	Brown hydroboration
	alkylzirconium	Schwartz hydrozirconation
	allene	Doering-LaFlamme allene synthesis
	allylic alcohol	Baylis-Hillman reaction
	allylic alcohol	Riley selenium dioxide oxidation, Prins reaction
	allylic bromide	Wohl-Ziegler bromination
	amide	Ritter reaction
	amino alcohol	Sharpless asymmetric aminohydroxylation
	arylated alkene	Heck reaction, Meerwein arylation
	cyclic alkene	Alkene metathesis, Diels-Alder cycloaddition
	cyclobutane	DeMayo cycloaddition
	cyclobutanone	Staudinger ketene cycloaddition
	cyclopentenone	Pauson-Khand reaction
	cyclopropane	Simmons-Smith cyclopropanation
	epoxide	Jacobsen-Katsuki epoxidation, Sharpless asymmetric epoxidation, Davis' oxaziridine oxidation, Prilezhaev reaction, Shi asymmetric epoxidation
	heteroatom-substituted alkene	Wacker oxidation
	methyl ketone	Wacker oxidation
	oxetane	Paterno-Büchi reaction
	unsymmetrically substituted alkene	Alkene metathesis
ALKYNE		
	1,3-diene	Enyne metathesis
	1,3-diyne	Glaser coupling
	2,3-disubstituted indole	Larock indole synthesis
	aldehyde	Brown hydroboration/oxidation
	aryl substituted alkyne	Castro-Stephens coupling, Sonogashira cross-coupling
	cyclopentenone	Pauson-Khand reaction
	disubstituted alkyne	Alkyne metathesis
	enyne	Sonogashira cross-coupling
	highly substituted benzene ring	Danheiser benzannulation, Dötz benzannulation

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ALKYNE		
	ketone	Brown hydroboration/oxidation
	macrocyclic alkyne	Alkyne metathesis
	substituted 1,4-cyclohexadiene	Diels-Alder cycloaddition, Danishefsky's diene cycloaddition
	vinylborane (alkenylborane)	Brown hydroboration
ALLENE		
	substituted cyclopentene	Danheiser cyclopentene annulation
AMIDE		
1° amide	carbamate	Hofmann rearrangement
1° amide	primary amine	Hofmann rearrangement
1° amide	substituted amidine	Aza-Wittig reaction
1° amide	substituted urea	Hofmann rearrangement
2° amide	2,3-disubstituted indole	Madelung indole synthesis
2° amide	3,4-dihydro isoquinoline	Bischler-Napieralski isoquinoline synthesis
2° amide	isoquinoline	Bischler-Napieralski isoquinoline synthesis
2° amide	N-substituted enamine	Tebbe olefination
3° amide	α,β-unsaturated aldehyde	Vilsmeier-Haack formylation
3° amide	α-alkylated aldehyde	Myers asymmetric alkylation
3° amide	α-alkylated amide	Myers asymmetric alkylation
3° amide	α-alkylated carboxylic acid	Myers asymmetric alkylation
3° amide	α-diazo amide	Regitz diazo transfer
3° amide	β-hydroxy carbonyl compound	Evans aldol reaction
3° amide	ketone	Weinreb ketone synthesis
3° amide	*N,N*-disubstituted cyclopropylamine	Kulinkovich reaction
3° amide	*N,N*-disubstituted enamine	Tebbe olfination
3° amide	substituted benzaldehyde	Vilsmeier-Haack formylation
3° amide	β-alkylated primary alcohol	Myers asymmetric alkylation
AMINE		
1° amine	α-acylamino carboxamide	Ugi multicomponent reaction
1° amine	α-amino carboxamide	Ugi muticomponent reaction
1° amine	α-amino nitrile	Strecker reaction
1° amine	amide	Schotten-Baumann reaction
1° amine	cycloalkanol	Demjanov rearrangement
1° amine	cycloalkanone	Demjanov and Tiffeneau-Demjanov rearrangement
1° amine	hydantoinimide	Ugi multicomponent reaction
1° amine	tetrahydroisoquinoline	Pictet-Spengler tetrahydroisoquinoline synthesis
1° amine	Mannich base	Mannich reaction
1° amine	secondary aromatic amine	Buchwald-Hartwig cross-coupling, Chichibabin amination reaction
1° amine	tetrazole	Ugi multicomponent reaction
1° amine	thiohydantoinimide	Ugi multicomponent reaction
2° amine	α-acylamino carboxamide	Ugi multicomponent reaction
2° amine	α-amino carboxamide	Ugi multicomponent reaction
2° amine	α-amino nitrile	Strecker reaction
2° amine	allylic amine	Petasis boronic acid-Mannich reaction
2° amine	amide	Schotten-Baumann reaction
2° amine	hydroxylamine	Davis' oxaziridine oxidation
2° amine	Mannich base	Mannich reaction
2° amine	tertiary aromatic amine	Buchwald-Hartwig cross-coupling
2° amine	tetrazole	Ugi muticomponent reaction
3° amine	alkene	Cope elimination
3° amine	homoallylic secondary amine	Aza-Wittig rearrangement
3° amine	*N,N*-dialkyl hydroxylamine	Cope elimination
3° amine	*N*-oxide	Davis' oxaziridine oxidation
3° amine	rearranged tertiary amine	Stevens rearrangement
allylic amine	1,2-oxazaheterocycle	Meisenheimer rearrangement
allylic amine	homoallylic amine	Aza-[2,3]-Wittig rearrangement
allylic amine	imine	Aza-Claisen rearrangement

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
AMINE		
allylic amine	*O*-allyl-*N,N*-disubstituted hydroxylamine	Meisenheimer rearrangement
aryl amine	amide	Ugi multicomponent reaction
aryl amine	aryl bromide	Sandmeyer reaction
aryl amine	aryl chloride	Sandmeyer reaction
aryl amine	aryl fluoride	Balz-Schiemann reaction
aryl amine	aryl iodide	Sandmeyer reaction
aryl amine	aryl substituted alkene	Meerwein arylation
aryl amine	diaryl amine	Buchwald-Hartwig cross-coupling, Ullmann biaryl amine synthesis
aryl amine	*N*-aryl substituted pyrrole	Paal-Knorr pyrrole synthesis
aryl amine	*N*-methyl aryl amine	Eschweiler-Clarke methylation
aryl amine	*N*-oxide	Davis' oxaziridine oxidation
aryl amine	*ortho*-acyl aryl amine	Houben-Hoesch reaction
aryl amine	substituted quinoline	Combes quinoline synthesis, Skraup and Doebner-Miller quinoline synthesis
aryl amine	thiohydantoinimide	Ugi multicomponent reaction
N-halo amine	amine	Hofmann-Löffler-Freytag reaction
ANHYDRIDE		
	α,β-unsaturated carboxylic acid	Perkin reaction
	α-halogenated anhydride	Hell-Volhard-Zelinsky reaction
	aromatic ketone	Friedel-Crafts acylation
	enol ether	Petasis-Tebbe olefination
	tertiary amide	Polonovski reaction
	titanium enolate	Tebbe olefination
AZIDE		
acyl azide	isocyanate	Curtius rearrangement
alkyl azide	imine	Aza-Wittig reaction
alkyl azide	iminophosphorane	Staudinger reaction
aryl azide	imine	Aza-Wittig reaction
aryl azide	iminophosphorane	Staudinger reaction
CARBONATE		
	allylated products	Tsuji-Trost allylation
	ketene acetal	Tebbe olefination
CARBOXYLIC ACID		
	α-acyloxycarboxamide	Passerini multicomponent reaction
	α-bromo acid bromide	Hell-Volhard-Zelinsky reaction
	alkane	Barton radical decarboxylation reaction
	alkyl bromide	Hunsdiecker reaction
	homologated carboxylic acid	Arndt-Eistert homologation
	isocyanate	Curtius rearrangement
	lactone	Keck macrolactonization, Corey-Nicolaou macrolactonization, Yamaguchi macrolactonization
	primary amine	Curtius rearrangement, Schmidt reaction
CYCLOPROPANE		
vinylcyclopropane	cyclopentene	Vinylcyclopropane-cyclopentene rearrangement
DIENE		
1,5-diene	1,5-diene	Cope rearrangement
1,3-diene	aryl substituted diene	Heck reaction
1,3-diene	six-membered heterocycle	Hetero Diels-Alder cycloaddition
1,3-diene	substituted cyclohexene	Diels-Alder reaction, Danishefsky's diene cycloaddition
ENAMINE		
	α-alkylated aldehyde	Stork enamine synthesis
	α-alkylated ketone	Stork enamine synthesis
	β-diketone	Stork enamine synthesis
ENAMIDE		
	enantio-enriched amino acid	Noyori asymmetric hydrogenation

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ENOL ETHER		
	α,β-unsaturated ketone	Saegusa oxidation
	β-hydroxy carbonyl compound	Mukaiyama aldol reaction
	α-hydroxy ketone	Rubottom oxidation, Davis' oxaziridine oxidation
	substituted cyclohexanone	Ferrier reaction/rearrangement
ENONE		
	1,3-dicarbonyl compound	Wacker oxidation
	1,4-diketone	Stetter reaction
	allylic alcohol	Baylis-Hillman reaction
	allylic alcohol	Luche reduction
	arylated enone	Meerwein arylation
	cyclopropane	Corey-Chaykovsky cyclopropanation
	Michael adduct	Michael addition
	phenol	Dienone-Phenol rearrangement
	quinoline	Skraup and Doebner-Miller quinoline synthesis
	substituted enone	Heck reaction
	substituted pyridine	Kröhnke pyridine synthesis
ENYNE		
	1,3-diene	Enyne metathesis
EPOXIDE		
	allylated product	Tsuji-Trost allylation
	enantiomerically pure epoxide	Jacobsen hydrolytic kinetic resolution
	polyol	Smith-Tietze multicomponent dithiane coupling
ESTER		
α,β-unsaturated ester	allylic alcohol	Baylis-Hillman reaction
α-halo ester	β-hydroxy ketone	Reformatsky reaction
β-keto ester	α-diazo-β-keto ester	Regitz diazo transfer
β-keto ester	alkylated β-keto ester	Acetoacetic ester synthesis
β-keto ester	ketone	Krapcho dealkoxycarbonylation
β-keto ester	substituted coumarin	von Pechmann reaction
β-keto ester	substituted furan	Feist-Benary furan synthesis
β-keto ester	substituted pyrrole	Knorr pyrrole synthesis
carboxylic acid ester	α,β-epoxy ester	Darzens glycidic ester condensation
carboxylic acid ester	γ,δ-unsaturated acid	Claisen-Ireland rearrangement
carboxylic acid ester	alcohol	Kagan-Molander samarium-diiodide coupling
carboxylic acid ester	cyclopropanol	Kulinkovich reaction
carboxylic acid ester	enol ether	Tebbe olefination, Petasis-Tebbe olefination
carboxylic acid ester	tertiary alcohol	Grignard reaction
diester	α-hydroxy ketone	Acyloin condensation
diester	β-keto ester	Claisen condensation, Dieckmann condensation
diester	substituted malonic ester	Malonic ester synthesis
nitrite ester	hydroxy oxime	Barton nitrite ester reaction
phenolic ester	acylated phenol	Fries rearrangement
phosphonate ester	alkene	HWE olefination, HWE olefination-Still modification
thiohydroxamate ester	alkane	Barton radical decarboxylation of thiohydroxamate esters
xanthate ester	alkene	Chugaev elimination reaction
ETHER		
	alcohol	Wittig rearrangement
allylic ether	γ,δ-unsaturated carbonyl compound	Claisen rearrangement
allylic ether	β-alkoxyketone	Wacker oxidation
allylic ether	homoallylic alcohol	Wittig-[2,3]-rearrangement
HALIDE		
α,ω-dihalide	substituted cycloalkane	Malonic ester synthesis
1,1-geminal dihalide	alkene	Takai-Utimoto olefination
1,1-geminal dihalide	allene	Doering-LaFlamme allene synthesis
acyl halide	alkyl halide (one carbon shorter)	Tsuji-Wilkinson decarbonylation

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
HALIDE		
acyl halide	amide	Schotten-Baumann reaction
acyl halide	aromatic ketone	Friedel-Crafts acylation
acyl halide	ketone	Negishi cross-coupling
alkyl halide	1° or 2° alkyl halide	Finkelstein reaction
alkyl halide	alcohol	Barbier coupling reaction, Molander-Kagan samarium-diiodide coupling
alkyl halide	aldehyde	Kornblum oxidation
alkyl halide	alkane	Wurtz coupling
alkyl halide	alkylated β-keto ester	Acetoacetic ester synthesis
alkyl halide	alkylated 1,3-diester	Malonic ester synthesis
alkyl halide	alkylated aromatic compound	Friedel-Crafts alkylation
alkyl halide	alkylated heteroaromatic compound	Minisci reaction
alkyl halide	alkylated ketone	Stork enamine synthesis
alkyl halide	amine	Gabriel synthesis
alkyl halide	ether	Williamson ether synthesis
aryl halide	ketone	Kornblum oxidation
aryl halide	phosphonate ester	Arbuzov reaction
aryl halide	rearranged carbon skeleton	Wagner-Meerwein rearrangement
aryl halide	substituted alkene	Heck reaction
aryl halide	aryl ether	Buchwald-Hartwig cross-coupling
aryl halide	aryl substituted alkene	Kumada cross-coupling, Stille cross-coupling, Suzuki cross-coupling
aryl halide	biaryl amine	Ullmann biaryl amine synthesis
aryl halide	biaryl ether	Ullmann biaryl ether synthesis
aryl halide	biaryls	Kumada cross-coupling, Stille cross-coupling, Negishi cross-coupling, Stille-Kelly coupling, Suzuki cross-coupling, Ullmann biaryl synthesis
allylic halide	allyl-substituted products	Tsuji-Trost allylation
allylic halide	*C*-allyl substituted acetoacetic ester	Acetoacetic ester synthesis
allylic halide	*C*-allyl substituted malonic ester	Malonic ester synthesis
allylic halide	homoallylic alcohol	Barbier coupling reaction, Nozaki-Hiyama-Kishi coupling
HYDRAZONE		
	α-alkylated aldehyde	Enders SAMP/RAMP hydrazone alkylation
	α-alkylated hydrazone	Enders SAMP/RAMP hydrazone alkylation
	α-alkylated ketone	Enders SAMP/RAMP hydrazone alkylation
	alkane	Wolff-Kishner reduction
	alkene	Bamford-Stevens-Shapiro reaction
	allylic alcohol	Wharton olefin synthesis
	substituted indole	Fischer indole synthesis
IMIDE		
	cyclic imine	Aza-Wittig reaction
	primary amine	Gabriel amine synthesis
IMINE		
	α-amino nitrile	Strecker reaction
	quinoline	Combes quinoline synthesis
	six-membered azaheterocycle	Hetero Diels-Alder cycloaddition
ISOCYANATE		
	carbodiimide	Aza-Wittig reaction
ISONITRILE		
	α-acyloxycarboxamide	Passerini multicomponent reaction
	α-hydroxycarboxamide	Passerini multicomponent reaction
	α-hydroxyalkyltetrazole	Passerini multicomponent reaction
KETONE		
α-halo ketone	rearranged amide	Favorskii rearrangement
α-halo ketone	rearranged ester	Favorskii rearrangement
α-halo ketone	ring-contracted ester	Favorskii rearrangement, Quasi-Favorskii rearrangement
α-halo ketone	substituted furan	Feist-Bénary furan synthesis
α-halo ketone	substituted pyridine	Kröhnke pyridine synthesis

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
KETONE		
1,2-diketone	α-hydroxy acid	Benzilic acid rearrangement
1,2-diketone	ketone	Tsuji-Wilkinson decarbonylation
1,3-diketone	α-diazo-1,3-diketone	Regitz diazo transfer
1,3-diketone	quinoline	Combes quinoline synthesis
1,5-diketone	substituted 2-cyclohexenone	Hajos-Parrish reaction, Robinson annulation
cyclic ketone	lactone	Baeyer-Villiger reaction
diazo ketone	carboxylic acid	Wolff rearrangement
diazo ketone	highly substituted aromatic ring	Danheiser benzannulation
diazo ketone	ketene	Wolff rearrangement
ketone	α,β-epoxy ester	Darzens glycidic ester condensation
ketone	β-nitro alcohol	Henry reaction
ketone	alkene	McMurry coupling, Wittig reaction, Wittig reaction-Schlosser modification, Bamford-Stevens-Shapiro reaction, HWE olefination, HWE olefination-Still modification, Julia-Lythgoe olfination, Peterson olefination, Takai-Utimoto olefination, Tebbe olefination
ketone	amide	Schmidt reaction
ketone	epoxide	Corey-Chaykovsky epoxidation
LACTONE		
	tertiary alcohol	Grignard reaction
	cyclic enol ether	Tebbe olefination
NITRILE		
aliphatic nitrile	aldehyde	Stephen aldehyde synthesis
aliphatic nitrile	aromatic ketone	Houben-Hoesch reaction
aliphatic nitrile	ester	Pinner reaction
aliphatic nitrile	imino ether	Pinner reaction
aliphatic nitrile	imino thioether	Pinner reaction
aliphatic nitrile	*N*-alkyl carboxamide	Ritter reaction
aliphatic nitrile	six-membered azaheterocycle	Hetero Diels-Alder cycloaddition
aromatic nitrile	aldehyde	Stephen aldehyde synthesis
aromatic nitrile	ester	Pinner reaction
aromatic nitrile	imino ether	Pinner reaction
aromatic nitrile	imino thioether	Pinner reaction
aromatic nitrile	*N*-alkyl carboxamide	Ritter reaction
NITRO COMPOUNDS		
aliphatic nitro cmpd.	β-nitro alcohol	Henry reaction
aliphatic nitro cmpd.	1,2-oxazaheterocycle	Hetero Diels-Alder cycloaddition
aliphatic nitro cmpd.	carbonyl compound	Nef reaction
aliphatic nitro cmpd.	carboxylic acid	Nef reaction
aliphatic nitro cmpd.	oxime	Nef reaction
aromatic nitro cmpd.	7-substituted indole	Bartoli indole synthesis
NITROALKENE		
	ketone	Nef reaction
	oxime	Nef reaction
OXIME		
	amide	Beckmann rearrangement
	α-amino ketone	Neber rearrangement
PHENOL		
	acyl-substituted phenol	Fries rearrangement
	aryl alkyl ether	Williamson ether synthesis
	biaryl ether	Ullmann biaryl ether synthesis
	ortho-formyl phenol	Reimer-Tiemann reaction
	substituted coumarin	von Pechmann reaction
	substituted salicylamide	anionic *ortho*-Fries rearrangement
	substituted salicylic acid	Kolbe-Schmitt reaction
SILANE		
acyl silane	*O*-silylated alcohol	Brook rearrangement
alkyl silane	alcohol	Fleming-Tamao oxidation

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
SILANE		
allylic silane	homoallylic alcohol	Sakurai allylation
aryl silane	alcohol	Fleming-Tamao oxidation
SULFIDE		
	sulfoxide	Davis' oxaziridine oxidation
SULFONE		
α-halo sulfone	alkene	Ramberg-Bäcklund rearrangement
aliphatic sulfone	alkene	Julia-Lythgoe olefination
SULFOXIDE		
	α-substituted sulfide	Pummerer rearrangement
	aldehyde	Pummerer rearrangement
	allylic alcohol	Mislow-Evans rearrangement
	glycoside	Kahne glycosidation
	ketone	Pummerer rearrangement
	sulfenate ester	Mislow-Evans rearrangement
allylic sulfoxide	allylic alcohol	Mislow-Evans rearrangement
allylic sulfoxide	sulfenate ester	Mislow-Evans rearrangement

8.5 PREPARATION OF FUNCTIONAL GROUPS

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ALCOHOL		
	α,β-epoxy alcohol	Payne rearrangement
	aldehyde	Grignard reaction, Barbier coupling reaction, Nozaki-Hiyama-Kishi reaction, Baylis-Hillman reaction, Cannizzaro reaction, Henry reaction, Keck asymmetric allylation, MPV reduction, Prins reaction, Roush asymmetric allylation, Sakurai allylation, Kagan-Molander coupling
	alkene	Sharpless asymmetric aminohydroxylation
	alkenyl halide or triflate	Nozaki-Hiyama-Kishi coupling
	aryl alkyl ether	Wittig-[1,2]-rearrangement
	enol ether and silyl enol ether	Davis' oxaziridine oxidation
	ketone	Grignard reaction, Barbier coupling reaction, Nozaki-Hiyama-Kishi reaction, Baylis-Hillman reaction, Henry reaction, Keck asymmetric allylation, MPV reduction, Prins reaction, Roush asymmetric allylation, Sakurai allylation, CBS reduction, Luche reduction, Midland Alpine borane reduction, Molander-Kagan coupling, Noyori asymmetric hydrogenation
	nitroalkane	Henry reaction
	organomagnesium species	Grignard reaction
	2° alcohol	Mitsunobu reaction
	silane	Fleming-Tamao oxidation
allylic alcohol	aldehyde	Baylis-Hillman reaction, Grignard reaction, Prins reaction, Nozaki-Hiyama-Kishi coupling
allylic alcohol	alkene	Prins reaction, Riley selenium dioxide oxidation
allylic alcohol	allylic sulfoxide	Mislow-Evans rearrangement
allylic alcohol	enone	Luche reduction, Baylis-Hillmann reaction
allylic alcohol	epoxyhydrazone	Wharton olefin synthesis
allylic alcohol	epoxyketone	Wharton olefin synthesis
allylic alcohol	ketone	Baylis-Hillman reaction, Grignard reaction, Nozaki-Hiyama-Kishi coupling, Wharton olefin synthesis
homoallylic alcohol	aldehyde	Grignard reaction, Barbier coupling reaction, Keck asymmetric allylation, Roush asymmetric allylation, Sakurai allylation
homoallylic alcohol	alkyl allyl ether	Wittig-[2,3]-rearrangement
homoallylic alcohol	ketone	Grignard reaction, Barbier coupling reaction, Keck asymmetric allylation, Roush asymmetric allylation, Sakurai allylation
propargylic alcohol	aldehyde	Barbier reaction, Grignard reaction
propargylic alcohol	ketone	Barbier reaction, Grignard reaction
ALDEHYDE		
aliphatic	aliphatic nitro compound	Nef reaction
aliphatic	cyclic epoxy hydrazone	Eschenmoser-Tanabe fragmentation
aliphatic	cyclic epoxy ketone	Eschenmoser-Tanabe fragmentation
aliphatic	3° amine *N*-oxide	Polonovski reaction
aliphatic/aromatic	1° or 2° alkyl halide	Kornblum oxidation
aliphatic/aromatic	1,2-diol	Criegee oxidation
aliphatic/aromatic	nitrile	Stephen aldehyde synthesis
aliphatic/aromatic	1° alcohol	Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Swern oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation
aromatic	activated benzyl halide	Kornblum oxidation
aromatic	electron-rich heteroaromatic ring	Vilsmeier-Haack formylation
aromatic	electron-rich substituted benzene	Vilsmeier-Haack formylation, Reimer-Tiemann reation
aromatic	*N,N*-disubstituted formamide	Vilsmeier-Haack formylation
aromatic	substituted benzene	Gatterman formylation and Gatterman-Koch formylation
ALKENE		
	α-halo sulfone	Ramberg-Bäcklund rearrangement
	1,2-diol	Corey-Winter olefination
	1,3-diol monosulfonate ester	Wharton fragmentation, Grob fragmentation
	1,5-diene	Cope rearrangement
	2° or 3° alcohol	Burgess dehydration, Chugaev elimination

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ALKENE		
	aldehyde	HWE olefination, HWE olefination-Still modification, Wittig reaction, Wittig reaction-Schlosser modification, Tebbe olefination, Julia olefination, Peterson olefination, Takai-Utimoto olefination
	alkyl phenyl sulfone	Julia-Lythgoe olefination
	diene	Alkene metathesis
	ketone	Bamford-Stevens-Shapiro olefination, HWE olefination, HWE olefination-Still modification, Wittig reaction, Wittig reaction-Schlosser modification, Tebbe olefination, Julia-Lythgoe olefination, Peterson olefination, Takai-Utimoto olefination
	nitroalkane	Henry reaction
	phosphonate ester	HWE olefination, HWE olefination-Still modification
	quaternary ammonium salt	Hofmann elimination
	3° amine *N*-oxide	Cope elimination, Polonosvki reaction
	tosylhydrazone	Bamford-Stevens-Shapiro olefination
	xanthate ester	Chugaev elimination
ALKYNE		
	aldehyde	Corey-Fuchs alkyne synthesis, Seyferth-Gilbert homologation
	cyclic epoxy ketone	Eschenmoser-Tanabe fragmentation
	diyne	Alkyne metathesis
	ketone	Seyferth-Gilbert homologation
ALLENE		
	alkene	Doering-LaFlamme allene synthesis
	geminal dihalocyclopropane	Doering-LaFlamme allene synthesis
AMIDE		
	α-diazo ketone	Wolff rearrangement
	3° alcohol	Ritter reaction
	3° amine *N*-oxide	Polonovski reaction
	acyl halide	Schotten-Baumann reaction
	alcohol	Ugi multicomponent reaction
	aldehyde	Passerini reaction, Ugi multicomponent reaction
	alkene	Ritter reaction
	allylic alcohol	Eschenmoser-Claisen rearrangement, Overman rearrangement
	amine	Schotten-Baumann reaction, Ugi multicomponent reaction
	anhydride	Schotten-Baumann reaction
	carboxylic acid	Passerini reaction, Ugi multicomponent reaction
	ketone	Passerini reaction, Schmidt reaction, Ugi multicomponent reaction
	nitrile	Ritter reaction, Ugi multicomponent reaction
	O-aryl carbamate	Fries rearrangement
	oxime	Beckmann rearrangement
AMINE		
	1° or 2° amine	Eschweiler-Clarke methylation
	acyl azide	Curtius rearrangement
	alkyl halide	Gabriel amine synthesis
	amide	Kulinkovich reaction, Hofmann rearrangement
	aryl halide	Buchwald-Hartwig cross-coupling, Ullmann diaryl amine synthesis
	3° benzylic amine	Sommelet-Hauser rearrangement
	benzylic quarter. ammonium salt	Sommelet-Hauser rearrangement
	carboxylic acid	Schmidt reaction
	N-halogenated amine	Hofmann-Löffler-Freytag reaction
	quaternary ammonium salt	Stevens rearrangement
allylic amine	α,β-unsaturated carboxylic acid derivative	Baylis-Hillman reaction
allylic amine	2° amine	Petasis boronic acid-Mannich reaction
allylic amine	aldehyde	Petasis boronic acid-Mannich reaction
allylic amine	allylic azide	Staudinger reaction
allylic amine	imine	Baylis-Hillman reaction

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
AMINE		
allylic amine	ketone	Petasis boronic acid-Mannich reaction
allylic amine	vinylboronic acid	Petasis boronic acid-Mannich reaction
homoallylic amine	allylic 3° amine	Aza-Wittig rearrangement
AZIDE		
alkyl azide	1° or 2° alcohol	Mitsunobu reaction
CARBOXYLIC ACID		
	α-diazo ketone	Wolff rearrangement
	aldehyde	Cannizzaro reaction, Jones oxidation, Pinnick oxidation
	anhydride	Perkin reaction
	carboxylic acid	Arndt-Eistert homologation
	methyl ketone	Lieben haloform reaction
CYCLOPROPANE		
	alkene	Simmons-Smith cyclopropanation
	amide	Kulinkovich reaction
	enone	Corey-Chaykovsky cyclopropanation
	ester	Kulinkovich reaction
DIAZO KETONE		
	β-keto ester	Regitz diazo transfer
	1,3-diketone	Regitz diazo transfer
DIENE		
1,5-diene	1,5-diene	Cope rearrangement
cyclic 1,4-diene	alkyne	Diels-Alder cycloaddition
cyclic 1,4-diene	aromatic compound	Birch reduction
α,ω-diene	cyclic alkene	Alkene metathesis
1,3-diene	enyne	Enyne metathesis
DIKETONE		
	α,β-unsaturated ester	Wacker oxidation
	α,β-unsaturated ketone	Stetter reaction, Wacker oxidation
	aldehyde	Stetter reaction
	aromatic *ortho*-acyloxyketone	Baker-Venkataraman rearrangement
	cyclic 1,2-diol	Criegee oxidation
	enamine	Stork enamine synthesis
	ketone	Riley selenium dioxide oxidation
DIOL		
	aldehyde	Prins reaction
	alkene	Prévost reaction, Prins reaction, Sharpless asymmetric dihydroxylation
	racemic epoxide	Jacobsen hydrolytic kinetic resolution
DIYNE		
	terminal alkyne	Glaser coupling
ENAMINE		
	amide	Tebbe olefination
ENYNE		
	terminal alkyne	Castro-Stephens coupling, Sonogashira cross-coupling
ENOL ETHER		
	ester	Tebbe olefination
ENONE		
	1,5-diketone	Hajos-Parrish reaction, Robinson annulation
	alkene	Pauson-Khand reaction
	alkyne	Pauson-Khand reaction
	divinyl ketone	Nazarov cyclization
	enyne	Nazarov cyclization
	propargylic alcohol	Meyer-Schuster and Rupe rearrangement
	silyl enol ether	Saegusa oxidation

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
EPOXIDE		
	α-halo ester	Darzens glycidic ester condensation
	aldehyde	Corey-Chaykovsky epoxidation
	alkene	Prilezhaev reaction, Davis' oxaziridine oxidation, Shi asymmetric epoxidation, Jacobsen-Katsuki epoxidation
	allylic alcohol	Sharpless asymmetric epoxidation
	ketone	Corey-Chaykovsky epoxidation, Darzens glycidic ester condensation
ESTER		
	α-diazo ketone	Wolff rearrangement
	1° or 2° alcohol	Mitsunobu reaction
	1°, 2° or 3° alcohol	Schotten-Baumann reaction
	acyl halide	Schotten-Baumann reaction
	aldehyde	Stobbe condensation, Tishchenko reaction
	allylic alcohol	Johnson-Claisen rearrangement
	anhydride	Schotten-Baumann reaction
	ketone	Baeyer-Villiger oxidation
	nitrile	Pinner reaction
ETHER		
	1° or 2° alcohol	Mitsunobu reaction
	1° or 2° alkyl halide	Williamson ether synthesis
	1° or 2° or 3° alcohol	Williamson ether synthesis
	aryl halide	Ullmann biaryl ether synthesis, Buchwald-Hartwig cross-coupling
	phenol	Williamson ether synthesis, Ullmann biaryl ether synthesis
HALIDE		
alkyl halide	1° or 2° alkyl halide	Finkelstein reaction
alkyl halide	acyl chloride	Tsuji-Wilkinson decarbonylation
alkyl halide	carboxylic acid	Hunsdiecker reaction
aryl halide	aryl amine	Sandmeyer reaction
aryl halide	aryldiazonium halide	Sandmeyer reaction
aryl halide	aryldiazonium tetrafluoroborate	Balz-Schiemann reaction
HYDROXY KETONE		
	α-halo ester	Reformatsky reaction
	aldehyde	Aldol condensation, Reformatsky reaction, Benzoin condensation
	enol ether	Davis' oxaziridine oxidation, Rubottom oxidation
	ester	Acyloin condensation
	ketone	Aldol condensation, Reformatsky reaction
	metal enolate	Davis' oxaziridine oxidation
IMINE		
	aldehyde	Aza-Wittig reaction
	allyl vinyl amine	Aza-Cope rearrangement
	ketone	Aza-Wittig reaction
	phenol	Houben-Hoesch reaction
IMINE		
	nitrile	Houben-Hoesch reaction
ISOCYANATE		
	acyl azide	Curtius rearrangement
	O-acyl hydroxamate	Lossen rearrangement
KETENE		
	α-diazo ketone	Wolff rearrangement
KETONE		
	α-amino acid	Dakin-West reaction
	1,2-diol	Pinacol rearrangement
	1,2-dione	Tsuji-Wilkinson decarbonylation
	1,3-diol monosulfonate	Wharton fragmentation
	2° alcohol	Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Swern oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
KETONE		
	2-hetero substituted alcohol	Semipinacol rearrangement
	alkene	Wacker oxidation
	nitroalkane	Nef reaction
	N-methoxy-*N*-methyl amide	Weinreb ketone synthesis
	substituted benzene	Friedel-Crafts acylation
	sulfoxide	Pummerer rearrangement
KETO ESTER		
	diester	Dieckmann condensation
	ester	Claisen condensation
LACTONE		
	cyclic ketone	Baeyer-Villiger oxidation
	hydroxy acid	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
NITRILE		
	3-aza-1,2,5-hexatriene	Aza-Claisen rearrangement
	aldehyde	Schmidt reaction
	aldehyde	Strecker reaction
	ketone	Strecker reaction
NITROALKENE		
	aldehyde	Henry reaction
	ketone	Henry reaction
	nitroalkane	Henry reaction
OXIME		
	nitrite ester	Barton nitrite ester reaction
PHENOL		
	aromatic ketone	Dakin oxidation
	chromium carbene	Dötz benzannulation
	dienone	Dienone-phenol rearrangement
	disubstituted alkyne	Dötz benzannulation
	phenolic ester	Fries rearrangement
PHOSPHONATE ESTER		
	alkyl halide	Arbuzov reaction
	trialkyl phosphite	Arbuzov reaction
SULFIDE		
	1 or 2 alcohol	Mitsunobu reaction
	1 or 2 alkyl halide	Williamson ether synthesis
	1 or 2 or 3 thiol	Williamson ether synthesis
SULFOXIDE		
	sulfide	Davis's oxaziridine oxidation

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Acyloin Condensation 4

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Alder (Ene) Reaction (Hydro-Allyl Addition) 6

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Baker-Venkataraman Rearrangement 30

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Balz-Schiemann Reaction (Schiemann Reaction) 34

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Bartoli Indole Synthesis 40

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Related reactions: *Hofmann-Löffler-Freytag reaction;*

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Buchwald-Hartwig Cross-Coupling 70

Related reactions: Ullmann biaryl ether and biaryl amine synthesis;

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Related reactions: Chugaev elimination, Cope elimination, Hofmann elimination;

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Related reactions: Meerwein-Ponndorf-Verley reduction, Oppenauer oxidation, Tishchenko reaction;

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Carroll Rearrangement (Kimel-Cope Rearrangement).....76

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Castro-Stephens Coupling.....78

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Chugaev Elimination Reaction (Xanthate Ester Pyrolysis).....82

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Ciamician-Dennstedt Rearrangement.....84

Related reactions: *Buchner method of ring expansion;*

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Claisen Condensation/Claisen Reaction 86

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Related reactions: *Carroll rearrangement, Claisen-Ireland rearrangement, Eschenmoser-Claisen rearrangement, Johnson-Claisen rearrangement;*

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Claisen-Ireland Rearrangement 90

Related reactions: Carroll rearrangement, Claisen rearrangement, Eschenmoser-Claisen rearrangement, Johnson-Claisen rearrangement;

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Clemmensen Reduction 92

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Combes Quinoline Synthesis 94

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Cope Elimination / Cope Reaction 96

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Cope Rearrangement.....98

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Corey-Bakshi-Shibata Reduction (CBS Reduction) 100

Related reactions: *Luche reduction, Midland alpine borane reduction, Noyori asymmetric reduction;*

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Corey-Chaykovsky Epoxidation and Cyclopropanation 102

Related reactions: *Simmons-Smith cyclopropanation, Darzens glycidic ester condensation;*

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Corey-Fuchs Alkyne Synthesis 104

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Corey-Kim Oxidation 106

Related reactions: *Dess-Martin oxidation, Jones oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation;*

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Corey-Nicolaou Macrolactonization 108

Related reactions: *Keck macrolactonization, Yamaguchi macrolactonization;*

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Cornforth Rearrangement 112

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Curtius Rearrangement 116

Related reactions: Hofmann rearrangement, Lossen rearrangement, Schmidt reaction;

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Related reactions: Jacobsen-Katsuki epoxidation, Prilezhaev oxidation, Rubottom oxidation, Sharpless asymmetric epoxidation, Shi epoxidation;

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Related reactions: Pinacol and semipinacol rearrangement;

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Dess-Martin Oxidation 136

Related reactions: Corey-Kim oxidation, Jones oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation;

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Related reactions: *Bergman cycloaromatization reaction, Danheiser benzannulation;*

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Related reactions: *Myers' asymmetric alkylation,*

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Related reactions: *Mannich reaction;*

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Eschenmoser-Claisen Rearrangement 156

Related reactions: *Carroll rearrangement, Claisen rearrangement, Claisen-Ireland rearrangement, Johnson-Claisen rearrangement;*

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Eschenmoser-Tanabe Fragmentation 158

Related reactions: *Grob fragmentation, Wharton fragmentation;*

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Related reactions: Aldol reaction, Mukaiyama aldol reaction, Reformatsky reaction;

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Grignard Reaction 188

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Grob Fragmentation 190

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Hajos-Parrish Reaction 192

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Hantzsch Dihydropyridine Synthesis 194

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Hofmann-Löffler-Freytag Reaction (Remote Functionalization) 208

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Hofmann Rearrangement 210

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Horner-Wadsworth-Emmons Olefination 212

Related reactions:, Horner-Wadsworth-Emmons olefination - Still-Gennari modification, Julia-Lithgoe olefination, Peterson olefination, Takai-Utimoto olefination, Tebbe olefination, Wittig reaction, Wittig reaction – Schlosser modification;

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Related reactions: Horner-Wadsworth-Emmons olefination, Julia olefination, Peterson olefination, Takai-Utimoto olefination, Tebbe olefination, Wittig reaction, Wittig reaction – Schlosser modification;

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Related reactions: Davis oxaziridine oxidation, Prilezhaev reaction, Sharpless asymmetric epoxidation, Shi asymmetric epoxidation;

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Related reactions: Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Pinnick oxidation;

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Keck Macrolactonization 238

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Larock Indole Synthesis.....260

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Ley Oxidation 262

Related reactions: Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Jones oxidation;

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Lossen Rearrangement 266

Related reactions: Curtius rearrangement, Hofmann rearrangement, Schmidt reaction;

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Related reactions: *Michael addition;*

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Negishi Cross-Coupling 310

Related reactions: Kumada cross-coupling, Stille cross-coupling, Suzuki cross-coupling;

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Oppenauer Oxidation

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Overman Rearrangement 322

Related reactions: *Claisen rearrangement;*

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Related reactions: *Knorr pyrrole synthesis;*

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Petasis-Ferrier Rearrangement 342

Related reactions: Ferrier reaction;

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Peterson Olefination 344

Related reactions: Horner-Wadsworth-Emmons olefination, Horner-Wadsworth-Emmons olefination - Still-Gennari modification, Julia-Lithgoe olefination, Takai-Utimoto olefination, Tebbe olefination, Wittig reaction, Wittig reaction – Schlosser modification;

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Roush Asymmetric Allylation 386

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Sakurai Allylation.....392

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Related reactions: *Davis oxaziridine oxidation, Jacobsen-Katsuki epoxidation, Prilezhaev reaction, Sharpless asymmetric epoxidation;*

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Stille Cross-Coupling (Migita-Kosugi-Stille Coupling).....438

Related reactions: Kumada cross-coupling, Negishi cross-coupling, Suzuki cross-coupling;

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Suzuki Cross-Coupling (Suzuki-Miyaura Cross-Coupling).....448

Related reactions: *Kumada cross-coupling, Negishi cross-coupling, Stille cross-coupling;*

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Swern Oxidation.....450

Related reactions: Corey-Kim oxidation, Dess-Martin oxidation, Jones oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation;

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Related reactions: Horner-Wadsworth-Emmons olefination, Horner-Wadsworth-Emmons olefination - Still-Gennari modification, Julia-Lithgoe olefination, Peterson olefination, Tebbe olefination, Wittig reaction, Wittig reaction – Schlosser modification;

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Related reactions: Horner-Wadsworth-Emmons olefination, Horner-Wadsworth-Emmons olefination - Still-Gennari modification, Julia-Lithgoe olefination, Peterson olefination, Takai-Utimoto olefination, Tebbe olefination, Wittig reaction – Schlosser modification;

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Related reactions: Horner-Wadsworth-Emmons olefination, Horner-Wadsworth-Emmons olefination - Still-Gennari modification, Julia-Lithgoe olefination, Peterson olefination, Takai-Utimoto olefination, Tebbe olefination, Wittig reaction;

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