

Jie Jack Li, 4th editn

Jie Jack Li

more than
300
reactions!

Name Reactions

A Collection of Detailed Mechanisms
and Synthetic Applications

Fourth Edition

Buchwald-Hartwig amination
Burke boronates
Chan-Lam C-X coupling reaction
Ring-closing metathesis
Corey-Kim oxidation
Corey-Nicolaou macrolactonization
Overman rearrangement



Springer

Name Reactions

Fourth Expanded Edition

Jie Jack Li

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and Synthetic Applications

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Springer

Jie Jack Li, Ph.D.
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
USA
jack.li@bms.com

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To Vivien

Foreword

I don't have my name on anything that I don't really do.
–Heidi Klum

Can the organic chemists associated with so-called “Named Reactions” make the same claim as supermodel Heidi Klum? Many scholars of chemistry do not hesitate to point out that the names associated with “name reactions” are often not the actual inventors. For instance, the Arndt–Eistert reaction has nothing to do with either Arndt or Eistert, Pummerer did not discover the “Pummerer” rearrangement, and even the famous Birch reduction owes its initial discovery to someone named Charles Wooster (first reported in a DuPont patent). The list goes on and on...

But does that mean we should ignore, boycott, or outlaw “named reactions”? Absolutely not. The above examples are merely exceptions to the rule. In fact, the chemists associated with name reactions are typically the original discoverers, contribute greatly to its general use, and/or are the first to popularize the transformation. Regardless of the controversial history underlying certain named reactions, it is the students of organic chemistry who benefit the most from the cataloging of reactions by name. Indeed, it is with **education** in mind that Dr. Jack Li has masterfully brought the chemical community the latest edition of *Name Reactions*.

It is clear why this beautiful treatise has rapidly become a bestseller within the chemical community. The quintessence of hundreds of named reactions is encapsulated in a concise format that is ideal for students and seasoned chemists alike. Detailed mechanistic and occasionally even historical details are given for hundreds of reactions along with key references. This “must-have” book will undoubtedly find a place on the bookshelves of all serious practitioners and students of the art and science of synthesis.

Phil S. Baran
May 2009
La Jolla, California

Preface

The first three editions of this book have been warmly embraced by the organic chemistry community. Many readers have indicated that while they like the detailed mechanisms, they prefer to have more real case applications in synthesis. For this edition, we have revolutionized the format, which finally liberated more space to accomodate many more synthetic examples. As a consequence, the subtitle of the book has been changed to *A Collection of Detailed Mechanisms and Synthetic Applications*. When putting together the 4th edition, I also strived to capture the latest references, up to 2009 whenever possible. Coincidentally, my daughter Vivien, a sophomore at the University of Michigan, will take soon Organic Chemistry. I hope she finds this book useful in preparing for her exams.

I am very much indebted to the readers who have kindly written to me with suggestions, which helped transform this book into a useful reference book for senior undergraduate and graduate students around the world—the second edition was translated to both Chinese and Russian. I am grateful to my good friend Derek A. Pflum at Ash Stevens Inc. who kindly proofread the entire manuscript and provided many invaluable suggestions. Prof. Derrick L. J. Clive at University of Alberta also proofread the first half of the manuscript and offered helpful comments. I also wish to thank Prof. Phil S. Baran at Scripps Research Institute and his students, Tanja Gulder, Yoshi Ishihara, Chad A. Lewis, Jonathan Lockner, Jun Cindy Shi, and Ian B. Seiple for proofreading the final draft of the manuscript. Their knowledge and time have tremendously enhanced the quality of this book. Any remaining errors are, of course, solely my own responsibility.

As always, I welcome your critique!



Jie Jack Li
May 2009

Killingworth, Connecticut

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Abbreviations and Acronyms

	polymer support
3CC	three-component condensation
4CC	four-component condensation
9-BBN	9-borabicyclo[3.3.1]nonane
A	adenosine
Ac	acetyl
ADDP	1,1'-(azodicarbonyl)dipiperidine
AIBN	2,2'-azobisisobutyronitrile
Alpine-borane [®]	<i>B</i> -isopinocampheyl-9-borabicyclo[3.3.1]-nonane
AOM	<i>p</i> -Anisyloxymethyl = <i>p</i> -MeOC ₆ H ₄ OCH ₂ -
Ar	aryl
B:	generic base
[bimim]Cl•2AlCl ₃	1-butyl-3-methylimidazolium chloroaluminuminate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BT	benzothiazole
Bz	benzoyl
Cbz	benzyloxycarbonyl
CuTC	copper thiophene-2-carboxylate
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<i>de</i>	diastereoselective excess
DEAD	diethyl azodicarboxylate
(DHQ) ₂ -PHAL	1,4-bis(9- <i>O</i> -dihydroquinine)-phthalazine
(DHQD) ₂ -PHAL	1,4-bis(9- <i>O</i> -dihydroquinidine)-phthalazine
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMFDMA	<i>N,N</i> -dimethylformamide dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane

dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
<i>dr</i>	diastereoselective ratio
DTBAD	di- <i>tert</i> -butylazodicarbonate
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
E1	unimolecular elimination
E1cB	2-step, base-induced β -elimination <i>via</i> carbanion
E2	bimolecular elimination
EAN	ethylammonium nitrate
EDDA	ethylenediamine diacetate
<i>ee</i>	enantiomeric excess
Ei	two groups leave at about the same time and bond to each other as they are doing so.
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMTTA	1,1,4,7,10,10-hexamethyltriethylenetetramine
IBX	<i>o</i> -iodoxybenzoic acid
Imd	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	metal
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
MCRs	multicomponent reactions
Mes	mesityl
MPS	morpholine-polysulfide
Ms	methanesulfonyl
MWI	microwave irradiation
MVK	methyl vinyl ketone
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
Nos	nosylate (4-nitrobenzenesulfonyl)
<i>N</i> -PSP	<i>N</i> -phenylselenophthalimide
<i>N</i> -PSS	<i>N</i> -phenylselenosuccinimide
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl

PMB	para-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium <i>p</i> -toluenesulfonate
PT	phenyltetrazolyl
PyPh ₂ P	diphenyl 2-pyridylphosphine
Pyr	pyridine
Red-Al	sodium bis(methoxy-ethoxy)aluminum hydride
Red-Al (SMEAH)	sodium bis(methoxy-ethoxy)aluminum hydride
Salen	<i>N,N'</i> -disalicylidene-ethylenediamine
SET	single electron transfer
SIBX	Stabilized IBX
SM	starting material
SMEAH	sodium bis(methoxy-ethoxy)aluminum hydride
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
S _N Ar	nucleophilic substitution on an aromatic ring
TBABB	tetra- <i>n</i> -butylammonium bibenzoate
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAO	1,3,3-trimethyl-6-azabicyclo[3.2.1]octane
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TDS	thexyldimethylsilyl
TEA	triethylamine
TEOC	trimethylsilylethoxycarbonyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2'-bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl
TosMIC	(<i>p</i> -tolylsulfonyl)methyl isocyanide
Ts	tosyl
TsO	tosylate

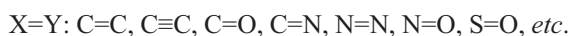
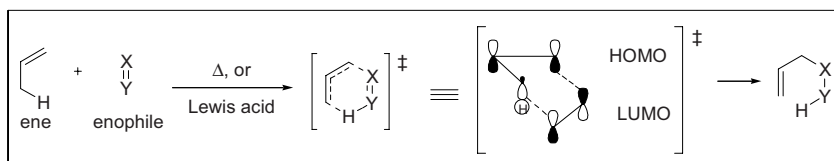
UHP

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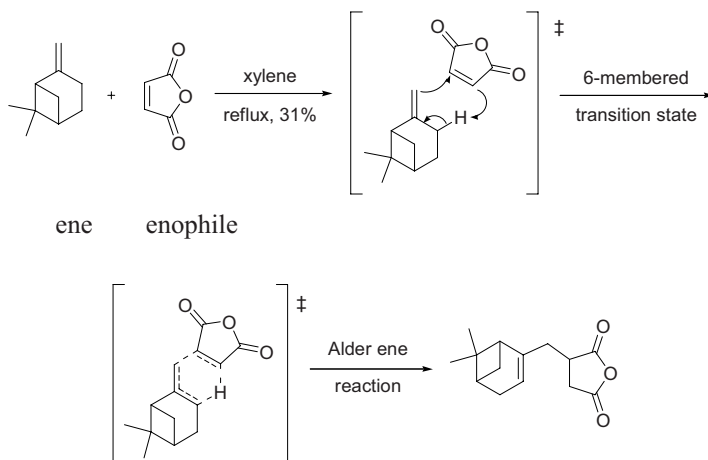
urea-hydrogen peroxide
solvent heated under reflux

Alder ene reaction

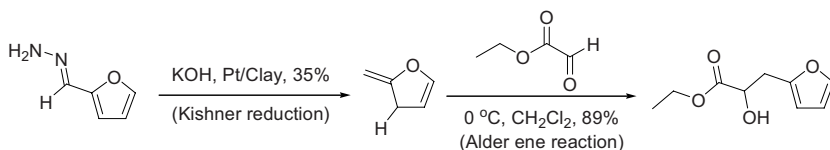
The Alder ene reaction, also known as the hydro-allyl addition, is addition of an enophile to an alkene (ene) *via* allylic transposition. The four-electron system including an alkene π -bond and an allylic C-H σ -bond can participate in a pericyclic reaction in which the double bond shifts and new C-H and C-C σ -bonds are formed.



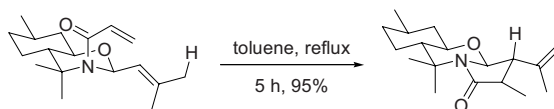
Example 1⁵

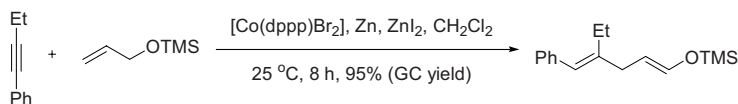
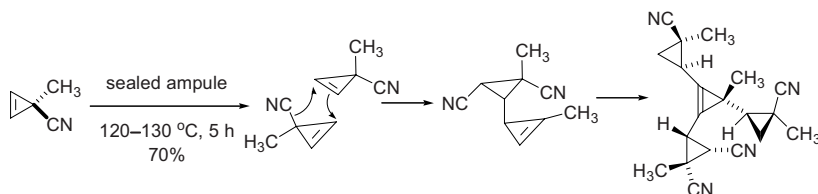
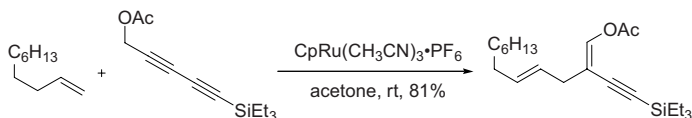


Example 2⁷



Example 3, Intramolecular Alder-ene reaction⁸



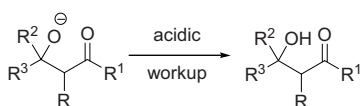
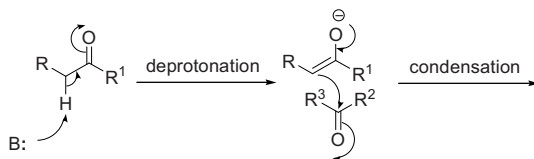
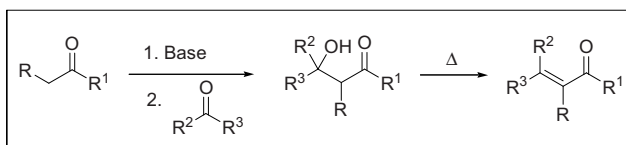
Example 4, Cobalt-catalyzed Alder-ene reaction⁹Example 5, Nitrile-Alder-ene reaction¹⁰Example 6¹¹

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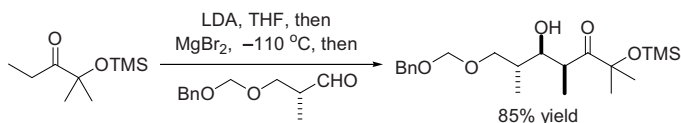
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Aldol condensation

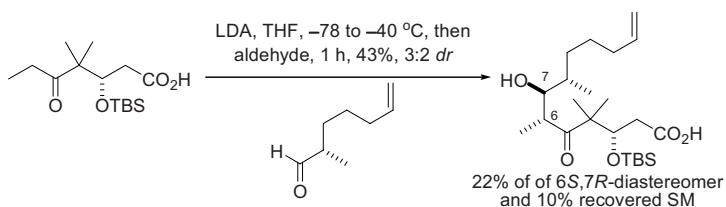
The Aldol condensation is the coupling of an enolate ion with a carbonyl compound to form a β -hydroxycarbonyl, and sometimes, followed by dehydration to give a conjugated enone. A simple case is addition of an enolate to an **aldehyde** to afford an **alcohol**, thus the name **aldol**.

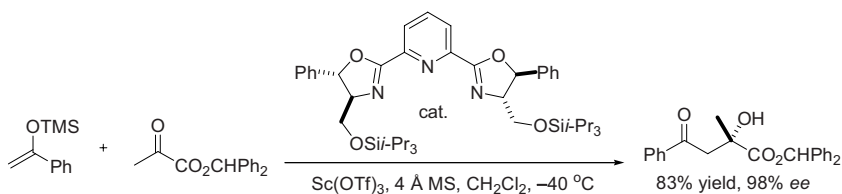
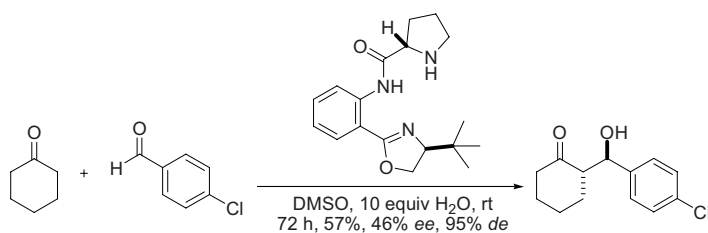
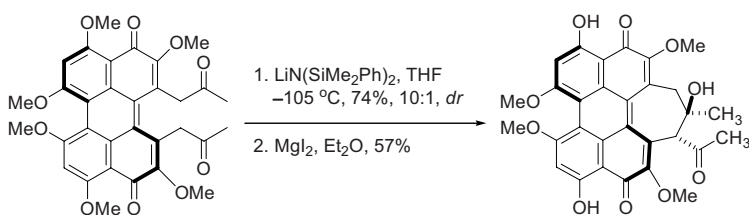


Example 1³



Example 2⁸



Example 3, Enantioselective Mukaiyama-aldol reaction¹⁰Example 4, Intermolecular aldol reaction using organocatalyst¹²Example 5, Transannular aldol reaction¹³

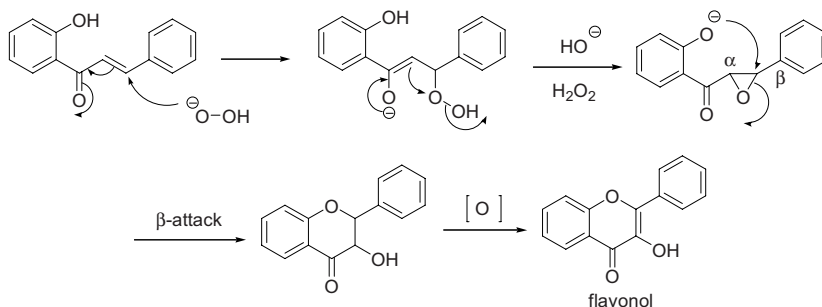
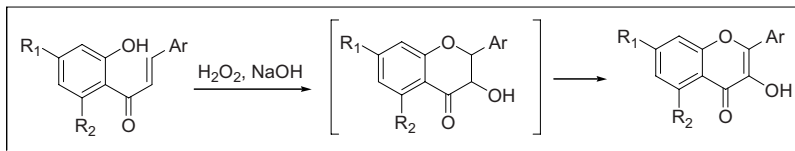
References

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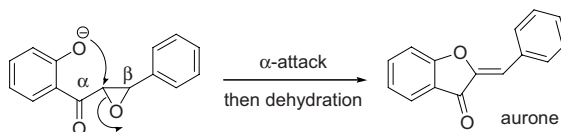
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Algar–Flynn–Oyamada Reaction

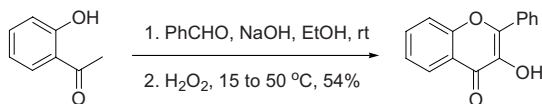
Conversion of 2'-hydroxychalcones to 2-aryl-3-hydroxy-4*H*-1benzopyran-4-ones (flavonols) by an oxidative cyclization.



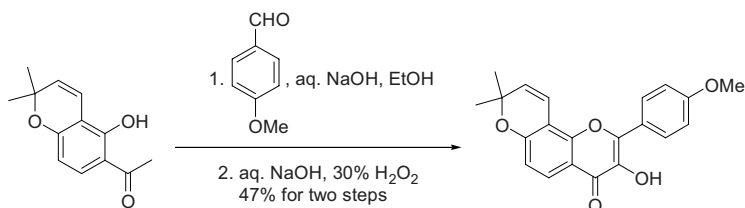
A side reaction:



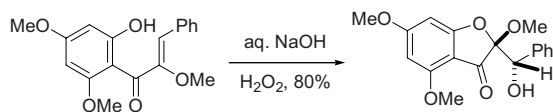
Example 1⁵



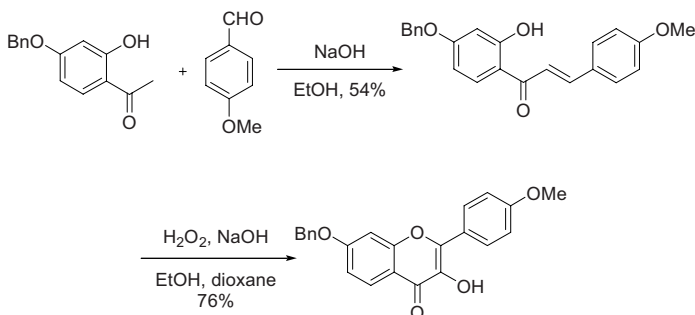
Example 2⁵



Example 3, The side reaction dominated to give the aurone derivative:⁹



Example 4¹²

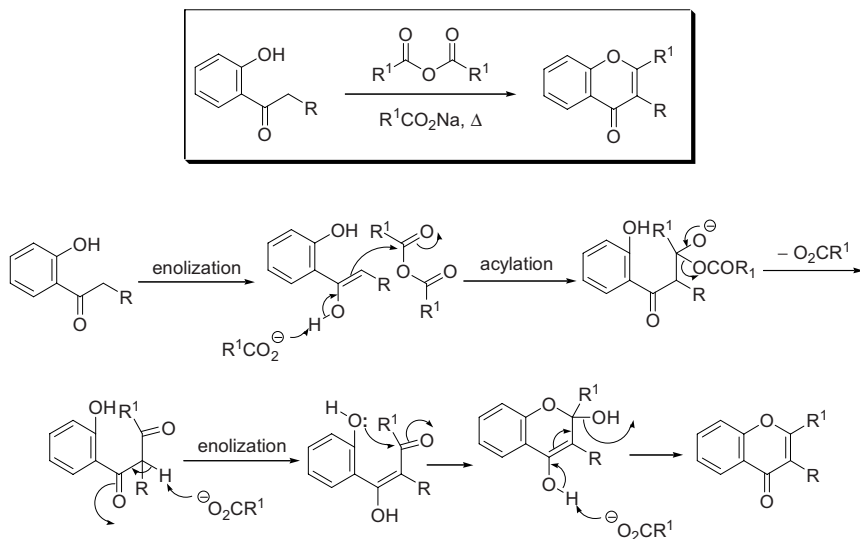


References

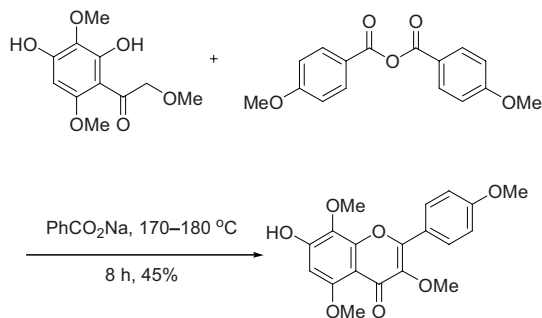
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Allan–Robinson reaction

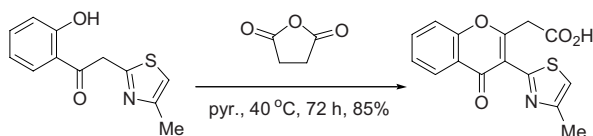
Synthesis of flavones or isoflavones by the treatment of *o*-hydroxyaryl ketones with aromatic aldehydes. *Cf.* Kostanecki reaction on page 322.

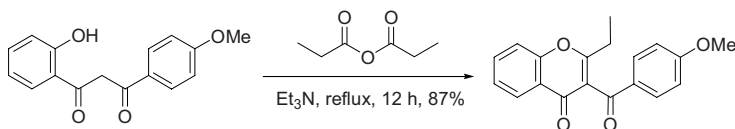


Example 1⁶



Example 2⁹



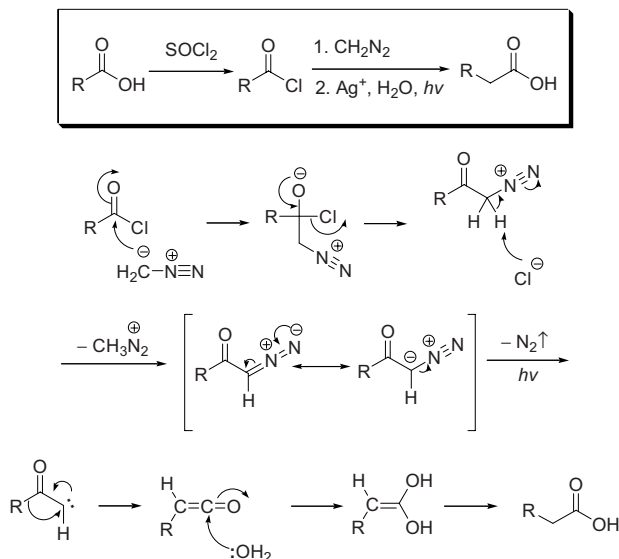
Example 3¹⁰

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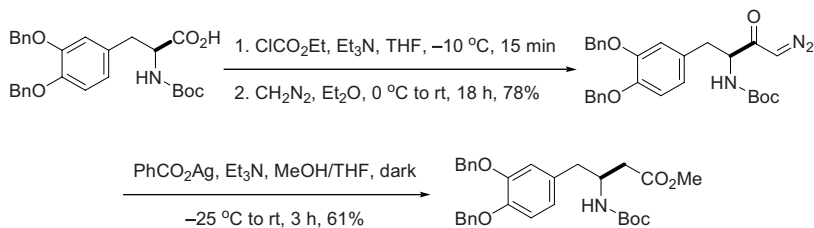
Arndt–Eistert homologation

One-carbon homologation of carboxylic acids using diazomethane.

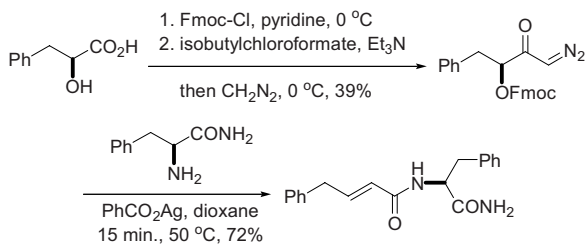


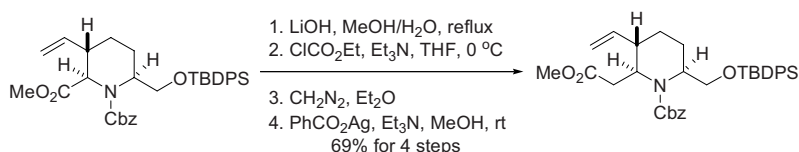
α -ketocarbene intermediate ketene intermediate

Example 1⁷



Example 2, An interesting variation⁹



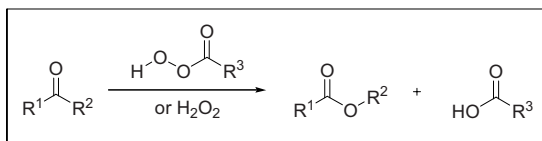
Example 3¹⁰

References

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Baeyer–Villiger oxidation

General scheme:

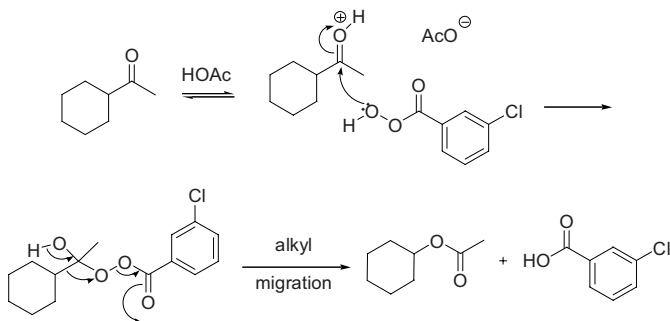


The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order: tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > methyl >> H.

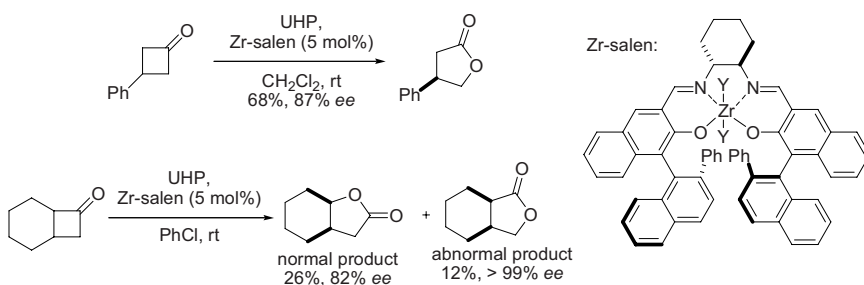
For substituted aryls:

p-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O₂N-Ar

Example 1:

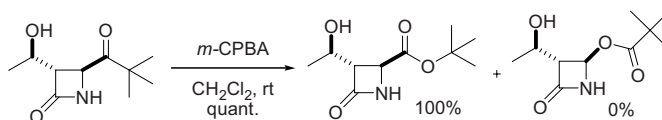


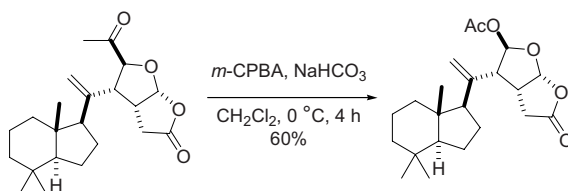
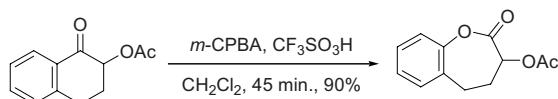
Example 2⁴



UHP = Urea-hydrogen peroxide complex

Example 3⁵



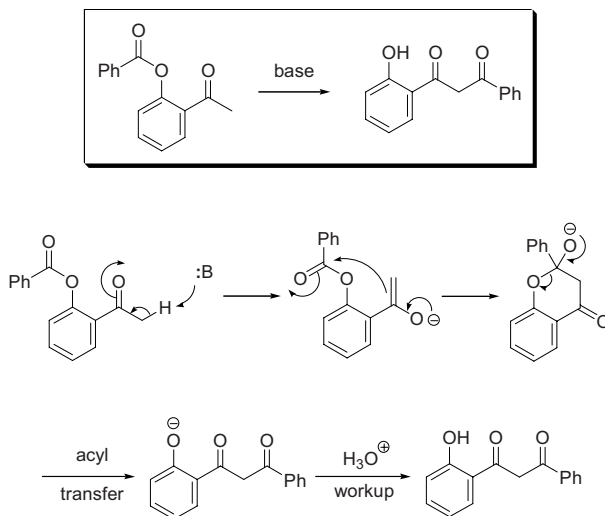
Example 4⁶Example 5⁸

References

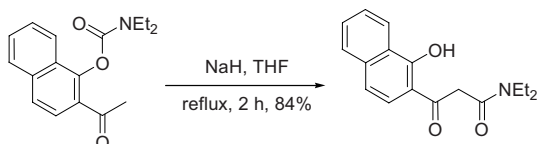
1. v. Baeyer, A.; Villiger, V. *Ber.* **1899**, *32*, 3625–3633. Adolf von Baeyer (1835–1917) was one of the most illustrious organic chemists in history. He contributed to many areas of the field. The Baeyer–Drewson indigo synthesis made possible the commercialization of synthetic indigo. Another Baeyer’s claim of fame is his synthesis of barbituric acid, named after his then girlfriend, Barbara. Baeyer’s real joy was in his laboratory and he deplored any outside work that took him away from his bench. When a visitor expressed envy that fortune had blessed so much of Baeyer’s work with success, Baeyer retorted dryly: “Herr Kollege, I experiment more than you.” As a scientist, Baeyer was free of vanity. Unlike other scholastic masters of his time (Liebig for instance), he was always ready to acknowledge ungrudgingly the merits of others. Baeyer’s famous greenish-black hat was a part of his perpetual wardrobe and he had a ritual of tipping his hat when he admired novel compounds. Adolf von Baeyer received the Nobel Prize in Chemistry in 1905 at age seventy. His apprentice, Emil Fischer, won it in 1902 when he was fifty, three years before his teacher. Victor Villiger (1868–1934), born in Switzerland, went to Munich and worked with Adolf von Baeyer for eleven years.
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Baker–Venkataraman rearrangement

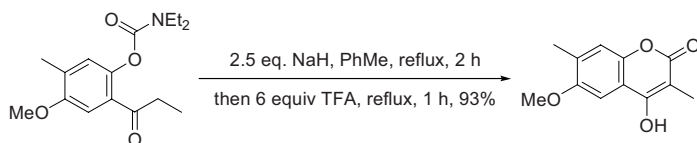
Base-catalyzed acyl transfer reaction that converts α -acyloxyketones to β -diketones.

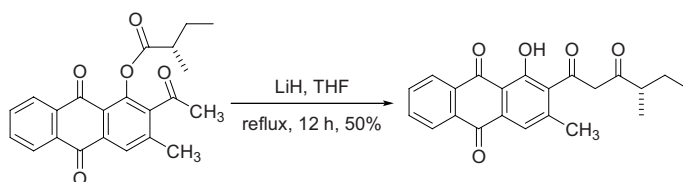
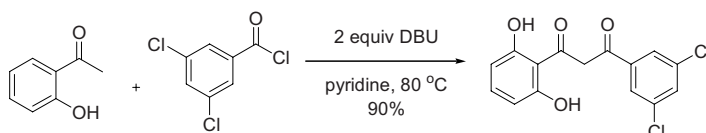


Example 1, Carbamoyl Baker–Venkataraman rearrangement⁵



Example 2, Carbamoyl Baker–Venkataraman rearrangement⁶



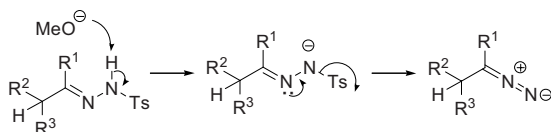
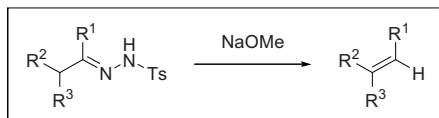
Example 3, Ester Baker–Venkataraman rearrangement⁹Example 4, Ester Baker–Venkataraman rearrangement¹⁰

References

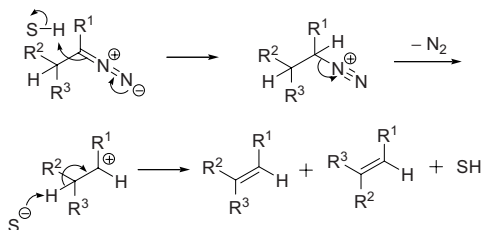
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Bamford–Stevens reaction

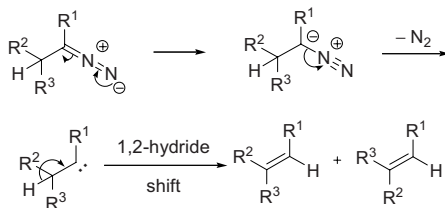
The Bamford–Stevens reaction and the Shapiro reaction share a similar mechanistic pathway. The former uses a base such as Na, NaOMe, LiH, NaH, NaNH₂, heat, *etc.*, whereas the latter employs bases such as alkyllithiums and Grignard reagents. As a result, the Bamford–Stevens reaction furnishes more-substituted olefins as the thermodynamic products, while the Shapiro reaction generally affords less-substituted olefins as the kinetic products.



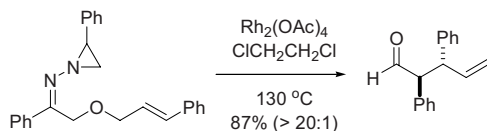
In protic solvent (S–H):



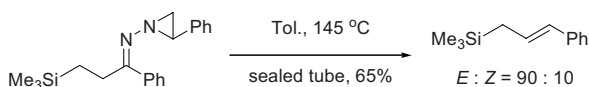
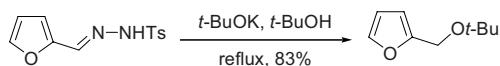
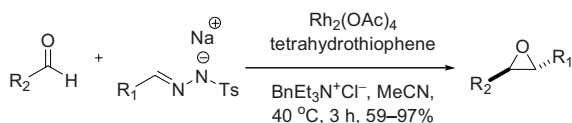
In aprotic solvent:



Example 1, Tandem Bamford–Stevens/thermal aliphatic Claisen rearrangement sequence²



The starting material *N*-aziridinyl imine is also known as Eschenmoser hydrazone.

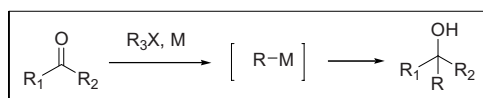
Example 2, Thermal Bamford–Stevens⁶Example 3⁷Example 4⁸

References

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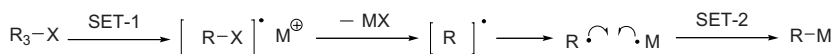
Barbier coupling reaction

In essence, the Barbier coupling reaction is a Grignard reaction carried out *in situ* although its discovery preceded that of the Grignard reaction by a year. Cf. Grignard reaction (Page 266).

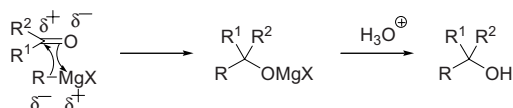


According to conventional wisdom,³ the organometallic intermediate (M = Mg, Li, Sm, Zn, La, *etc.*) is generated *in situ*, which is intermediately trapped by the carbonyl compound. However, recent experimental and theoretical studies seem to suggest that the Barbier coupling reaction goes through a single electron transfer pathway.

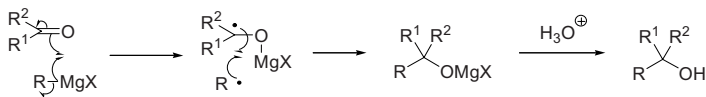
Generation of the Grignard reagent,



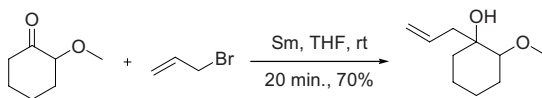
Ionic mechanism,

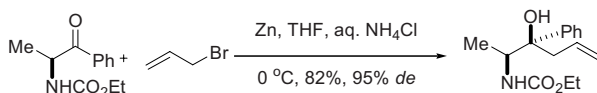
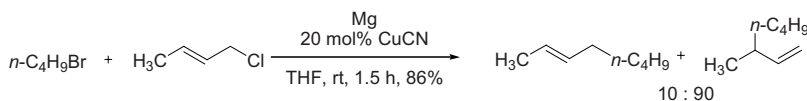
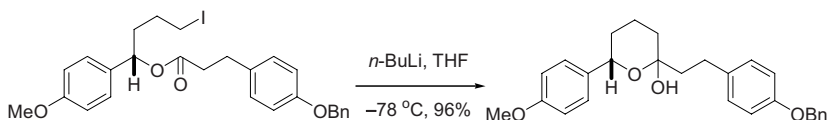


Single electron transfer mechanism,



Example 1⁶



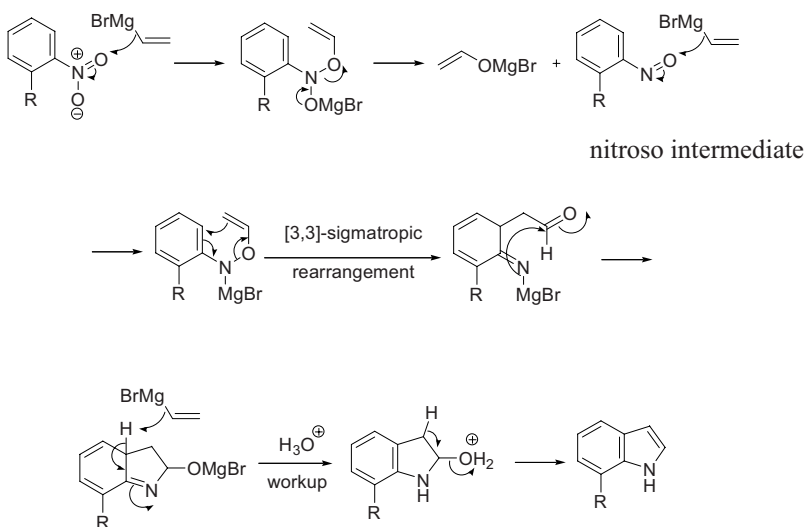
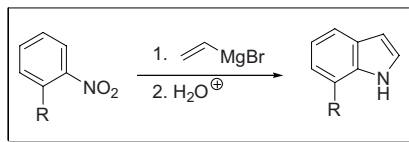
Example 2⁹Example 3¹⁰Example 4¹¹

References

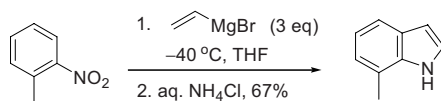
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Bartoli indole synthesis

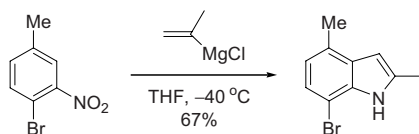
7-Substituted indoles from the reaction of *ortho*-substituted nitroarenes and vinyl Grignard reagents.

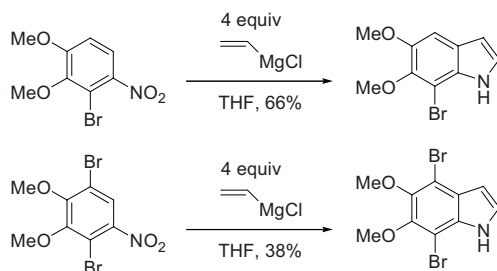
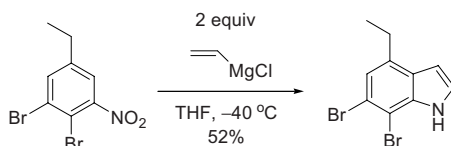


Example 1³



Example 2⁶



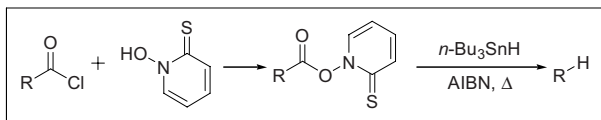
Example 3¹⁰Example 4¹¹

References

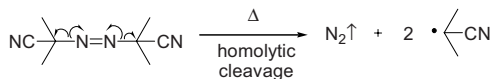
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Barton radical decarboxylation

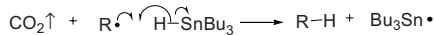
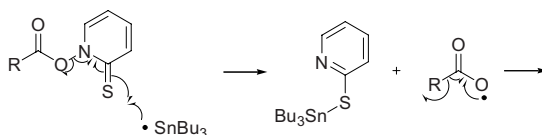
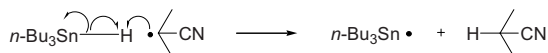
Radical decarboxylation *via* the corresponding thiocarbonyl derivatives of the carboxylic acids.



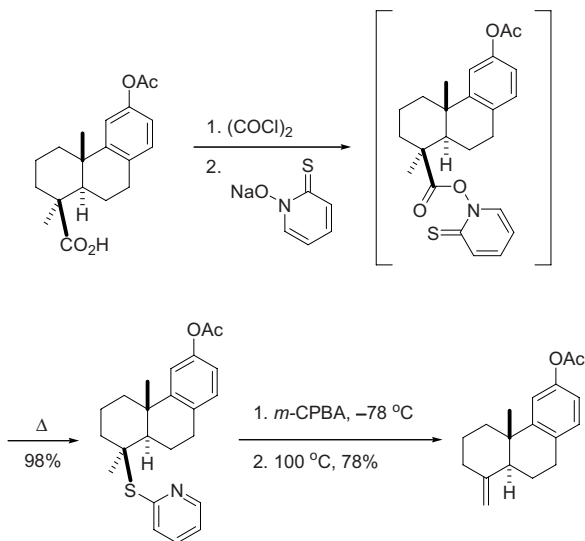
Barton ester

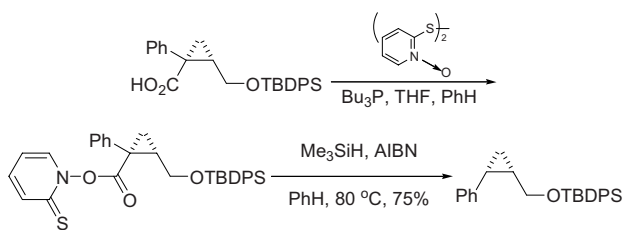
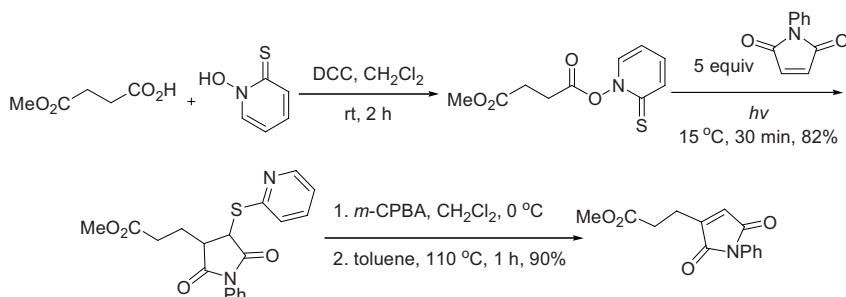


AIBN = 2,2'-azobisisobutyronitrile



Example 1³



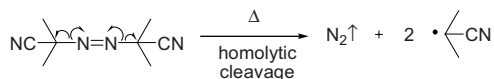
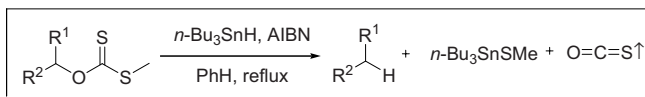
Example 2⁶Example 3⁹

References

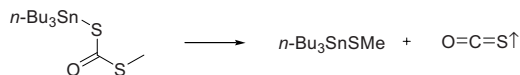
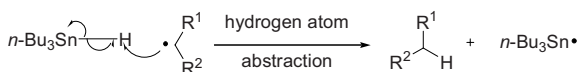
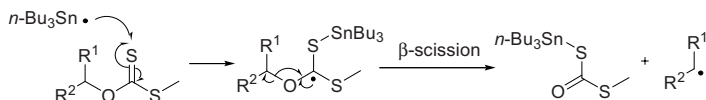
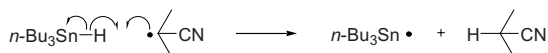
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Barton–McCombie deoxygenation

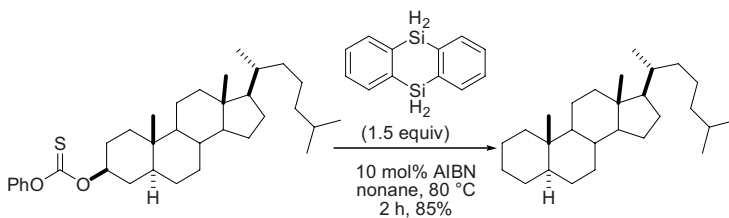
Deoxygenation of alcohols by means of radical scission of their corresponding thiocarbonyl derivatives.

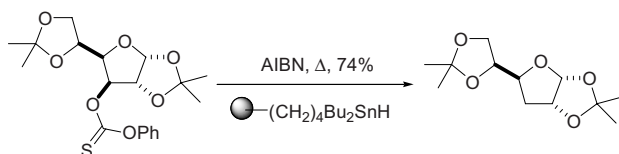
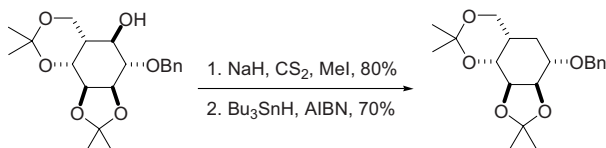
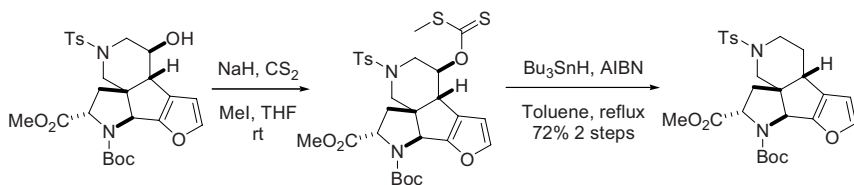


AIBN = 2,2'-azobisisobutyronitrile



Example 1²



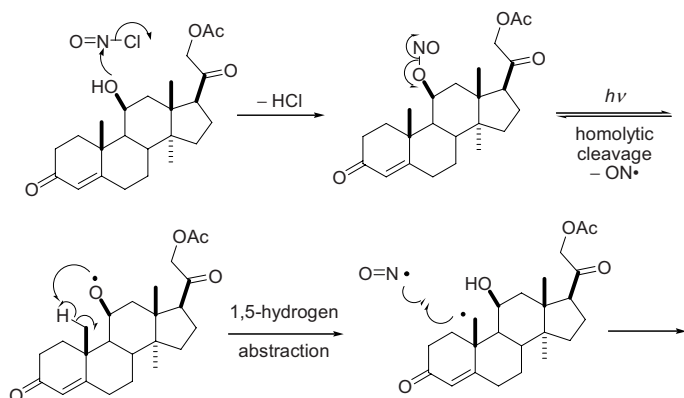
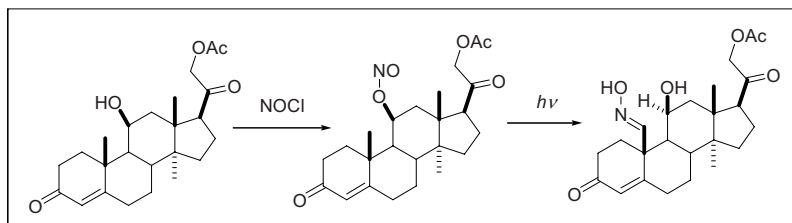
Example 2⁶Example 3¹⁰Example 4¹¹

References

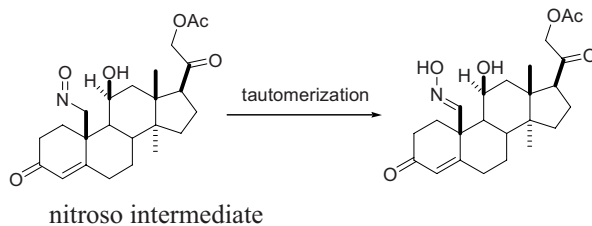
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Barton nitrite photolysis

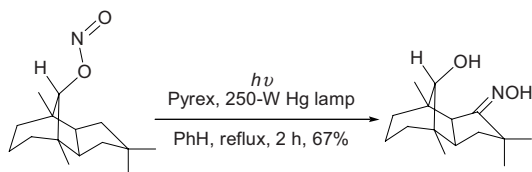
Photolysis of a nitrite ester to a γ -oximino alcohol.

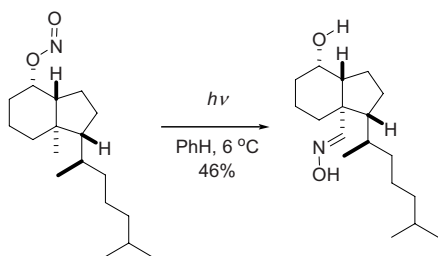
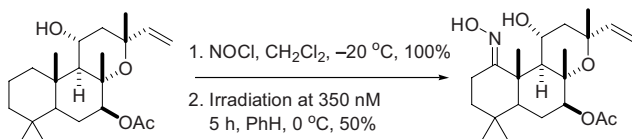


Nitric oxide radical is a stable and therefore, long-lived radical



Example 1²



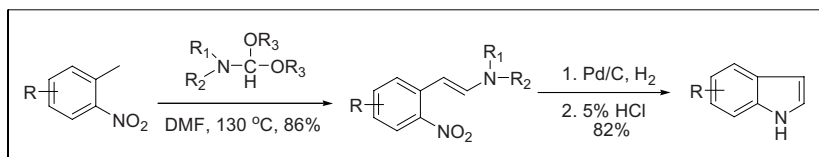
Example 2⁶Example 3⁷

References

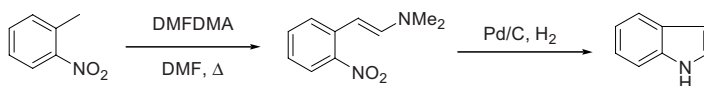
1. (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, 82, 2640–2641. In 1960, Derek Barton took a “vacation” in Cambridge, Massachusetts; he worked in a small research institute called the Research Institute for Medicine and Chemistry. In order to make the adrenocortical hormone aldosterol, Barton invented the Barton nitrite photolysis by simply writing down on a piece of paper what he thought would be an ideal process. His skilled collaborator, Dr. John Beaton, was able to reduce it to practice. They were able to make 40 to 50 g of aldosterol at a time when the total world supply was only about 10 mg. Barton considered it his most satisfying piece of work. (b) Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc.* **1960**, 82, 2641–2641. (c) Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc.* **1961**, 83, 4083–4089. (d) Barton, D. H. R.; Lier, E. F.; McGhie, J. M. *J. Chem. Soc., (C)* **1968**, 1031–1040.
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Batcho–Leimgruber indole synthesis

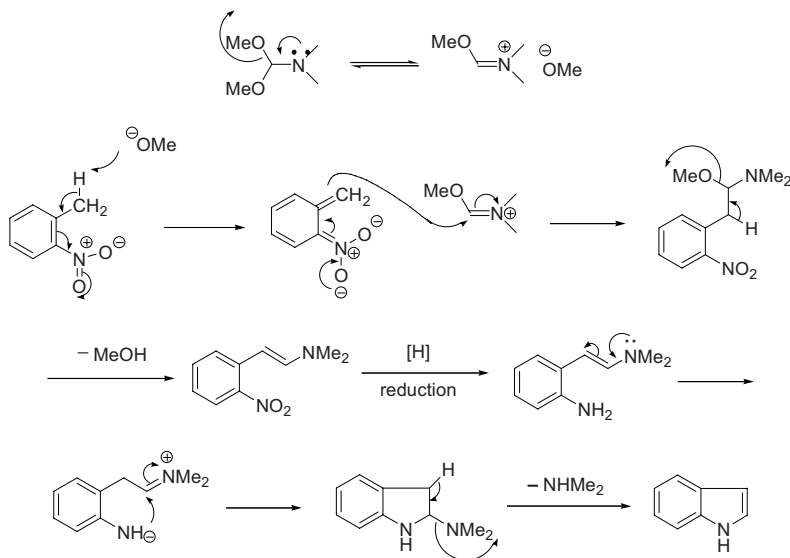
Condensation of *o*-nitrotoluene derivatives with formamide acetals, followed by reduction of the *trans*- β -dimethylamino-2-nitrostyrene to furnish indole derivatives.



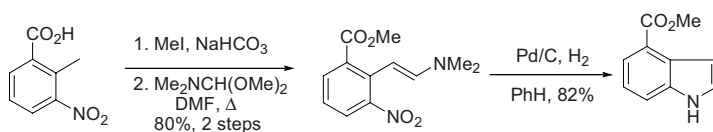
Example 1⁴

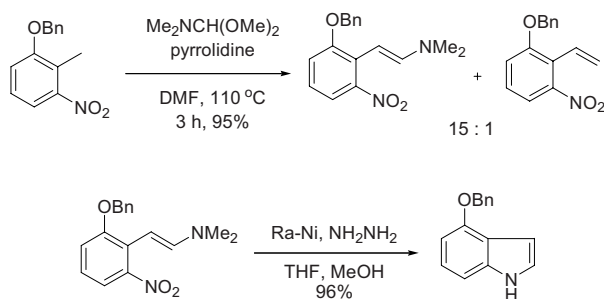
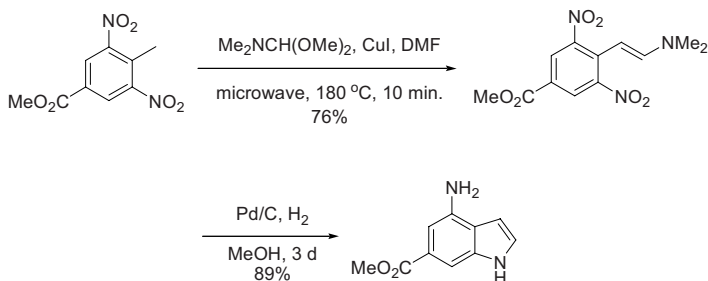


DMFDMA = *N,N*-dimethylformamide dimethyl acetal, $\text{Me}_2\text{NCH}(\text{OMe})_2$



Example 2⁴



Example 3⁵Example 4¹⁰

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Baylis–Hillman reaction

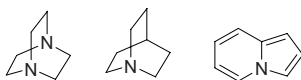
Also known as Morita–Baylis–Hillman reaction. It is a carbon–carbon bond-forming transformation of an electron-poor alkene with a carbon electrophile. Electron-poor alkenes include acrylic esters, acrylonitriles, vinyl ketones, vinyl sulfones, and acroleins. On the other hand, carbon electrophiles may be aldehydes, α -alkoxycarbonyl ketones, aldimines, and Michael acceptors.

General scheme:

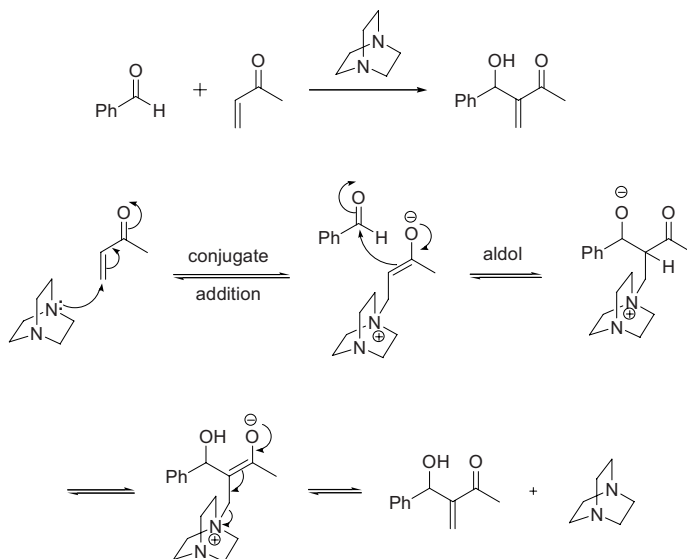


X = O, NR₂, EWG = CO₂R, COR, CHO, CN, SO₂R, SO₃R, PO(OEt)₂, CONR₂, CH₂=CHCO₂Me

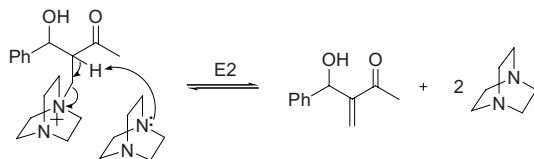
Alternative catalytic tertiary amines:



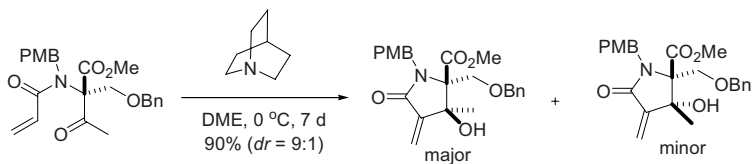
Example 1:



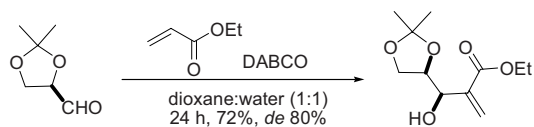
E2 (bimolecular elimination) mechanism is also operative here:



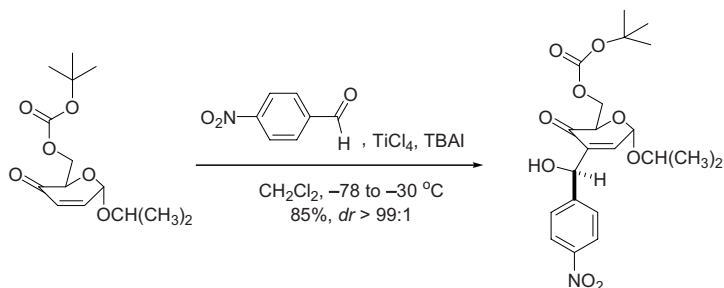
Example 2, Intramolecular Baylis–Hillman reaction⁶



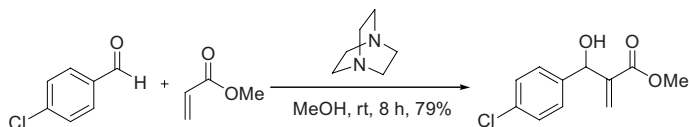
Example 3⁷

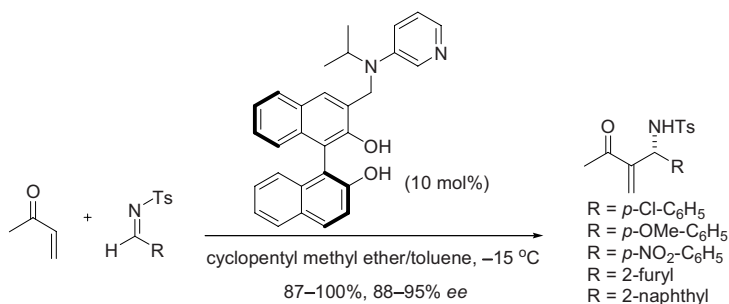


Example 4⁸



Example 5⁹



Example 6¹⁰

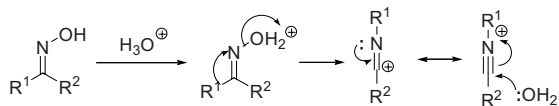
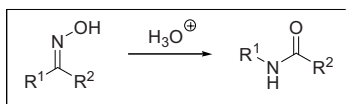
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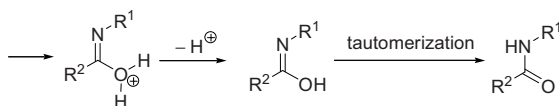
Beckmann rearrangement

Acid-mediated isomerization of oximes to amides.

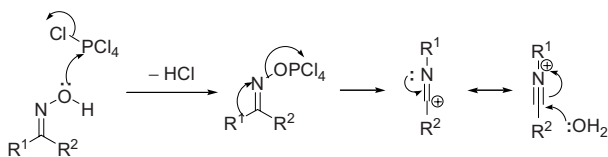
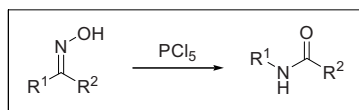
In protic acid:



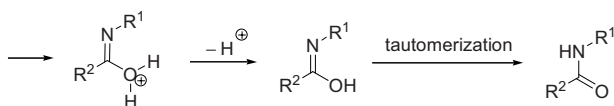
the substituent *trans* to the leaving group migrates



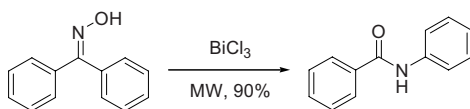
With PCl_5 :

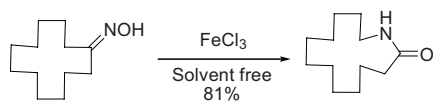
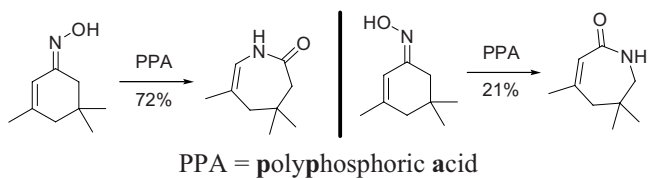
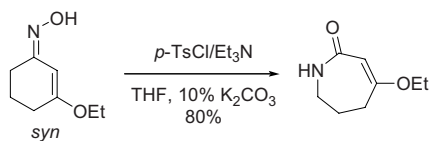


Again, the substituent *trans* to the leaving group migrates

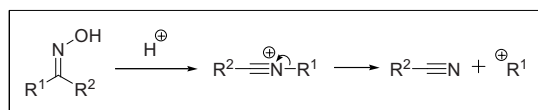
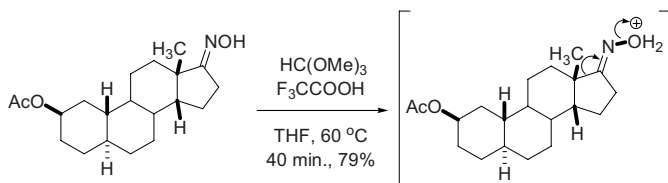


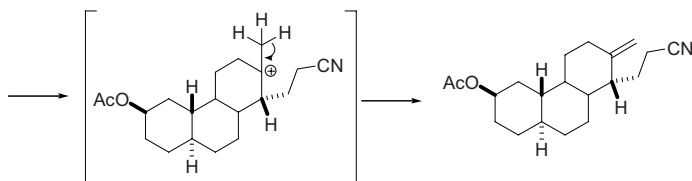
Example 1, Microwave (MW) reaction³



Example 2⁴Example 3⁶Example 4⁸

Abnormal Beckmann rearrangement is when the migrating substituent fragment (e.g., R^1) departs from the intermediate, leaving a nitrile as a stable product.

Example 1⁹

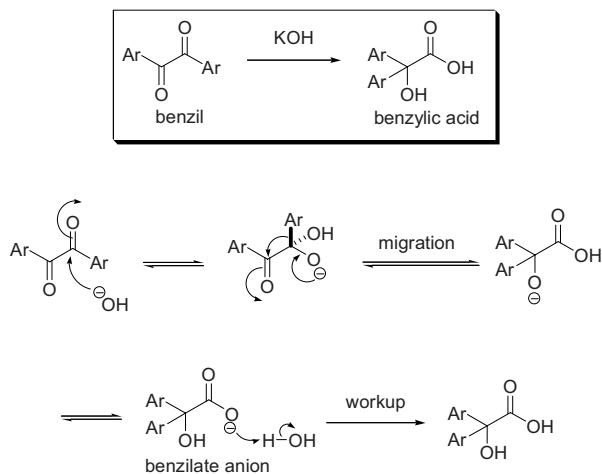


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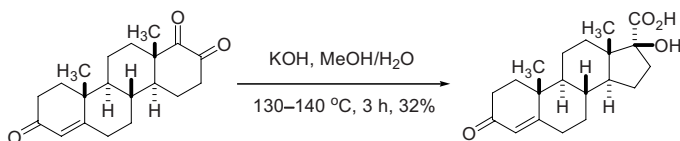
Benzilic acid rearrangement

Rearrangement of benzil to benzylic acid *via* aryl migration.

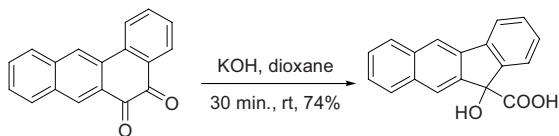


Final deprotonation of the carboxylic acid drives the reaction forward.

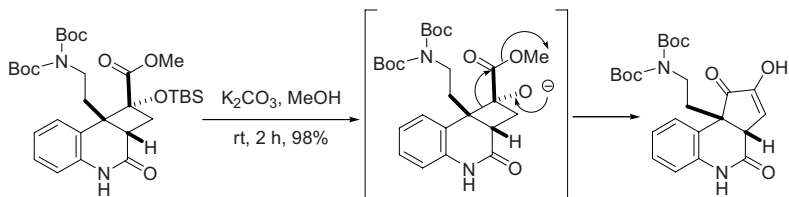
Example 1³



Example 2⁶



Example 3, Retro-benzilic acid rearrangement⁷

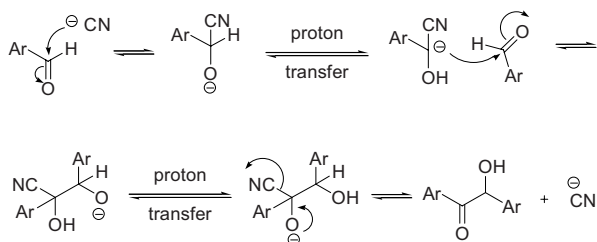
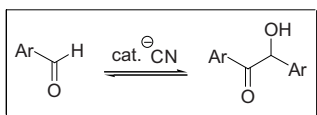


References

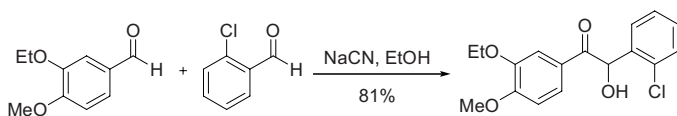
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Benzoin condensation

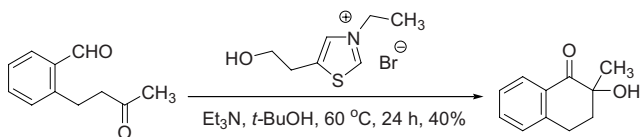
Cyanide-catalyzed condensation of aryl aldehyde to benzoin. Now cyanide is mostly replaced by a thiazolium salt. *Cf.* Stetter reaction.



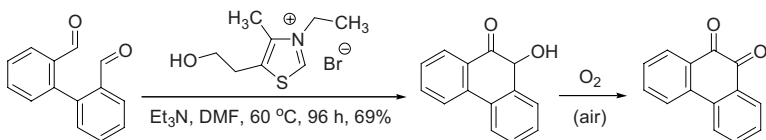
Example 1²

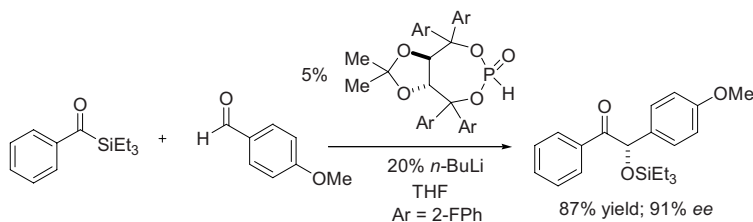
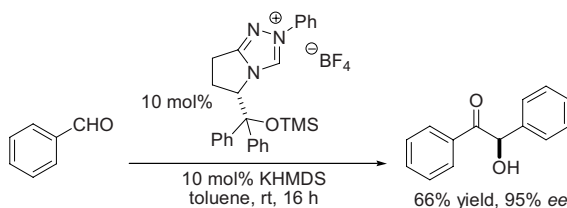


Example 2⁷



Example 3⁷



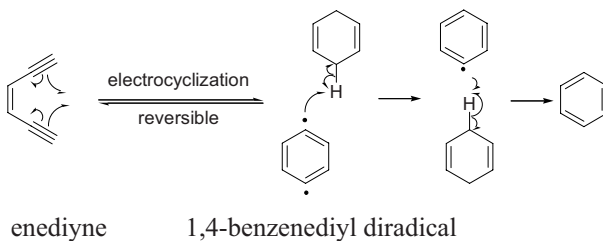
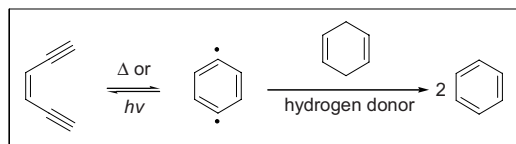
Example 4⁹Example 5¹⁰

References

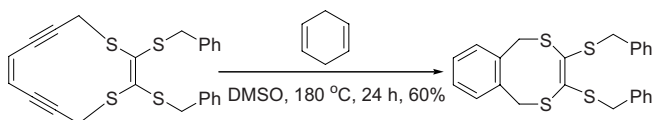
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Bergman cyclization

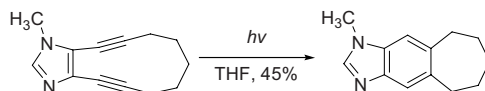
1,4-Benzenediyl diradical formation from enediyne *via* electrocyclicization.



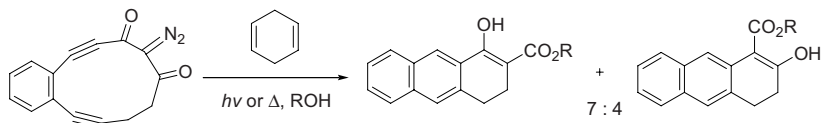
Example 1⁶

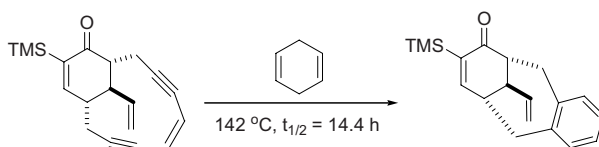


Example 2⁷



Example 3, Wolff rearrangement followed by the Bergman cyclization⁸



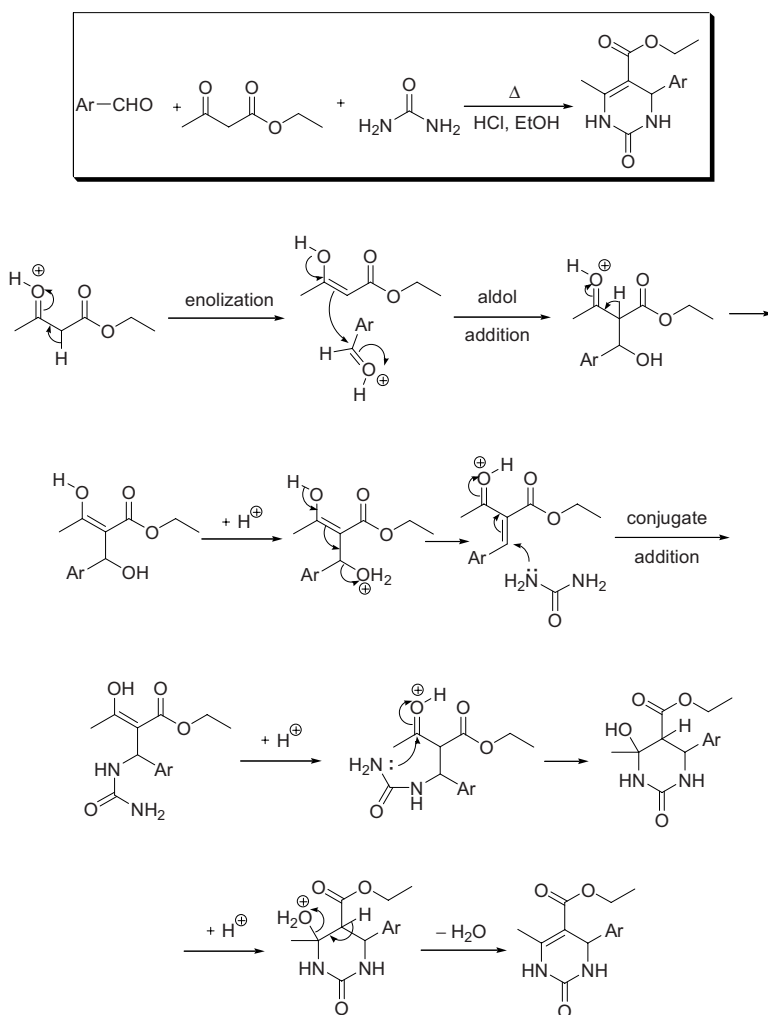
Example 4¹⁰

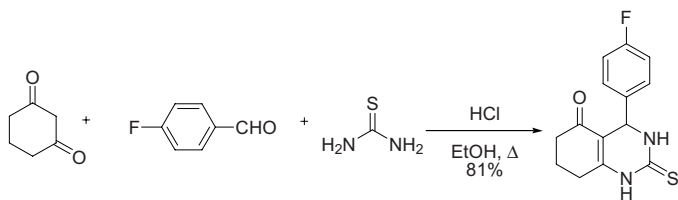
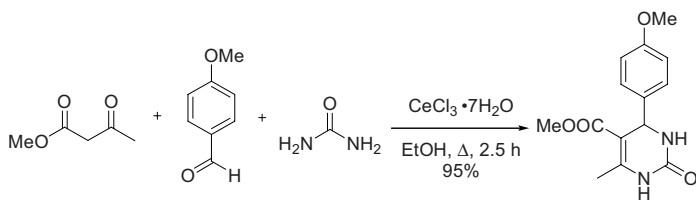
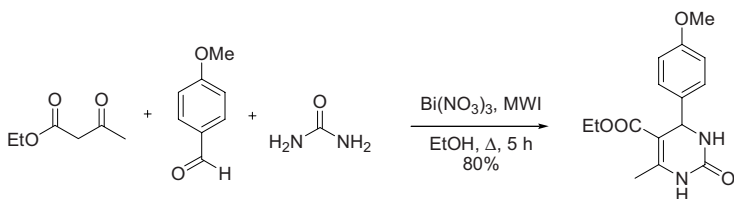
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Biginelli pyrimidone synthesis

One-pot condensation of an aromatic aldehyde, urea, and β -dicarbonyl compound in the acidic ethanolic solution and expansion of such a condensation thereof. It belongs to a class of transformations called multicomponent reactions (MCRs).



Example 1⁴Example 2⁵Example 3, Microwave-induced Biginelli condensation (MWI = microwave irradiation)⁹

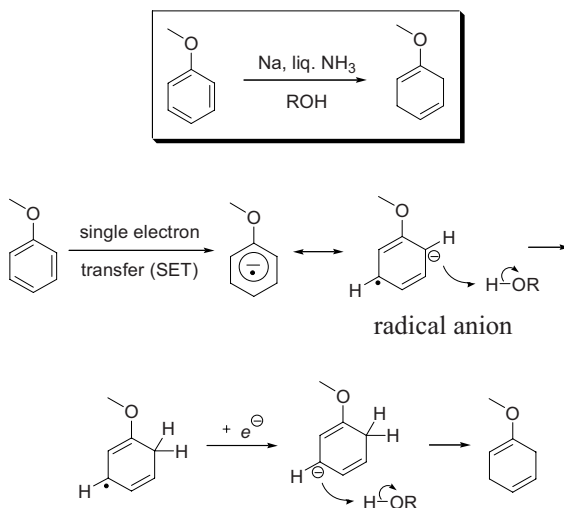
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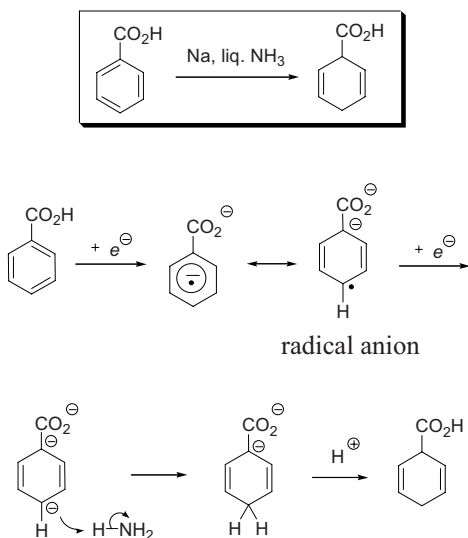
Birch reduction

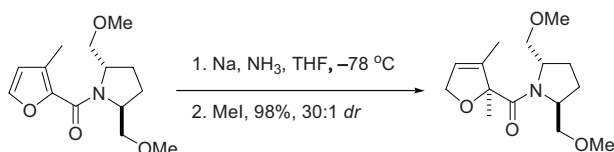
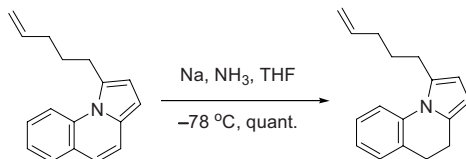
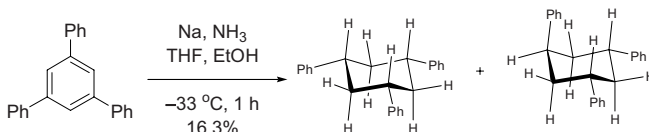
The Birch reduction is the 1,4-reduction of aromatics to their corresponding cyclohexadienes by alkali metals (Li, K, Na) dissolved in liquid ammonia in the presence of an alcohol.

Benzene ring bearing an electron-donating substituent:



Benzene ring with an electron-withdrawing substituent:



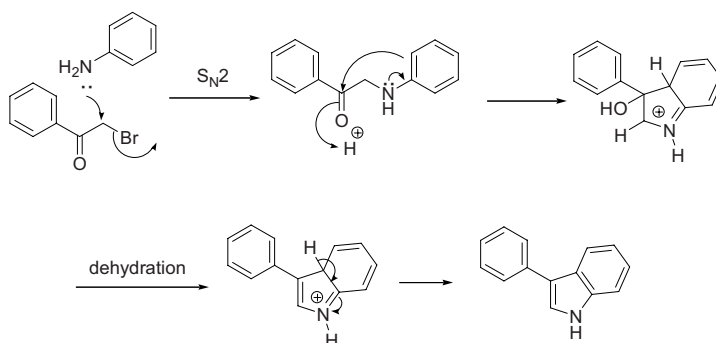
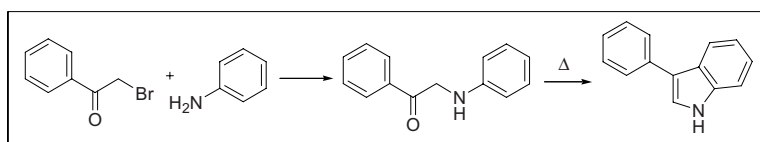
Example 1⁴Example 2⁷Example 3⁸

References

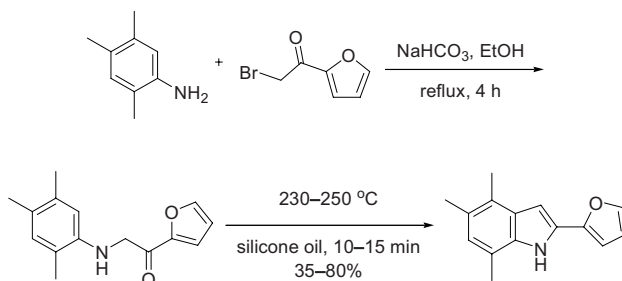
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Bischler–Möhlau indole synthesis

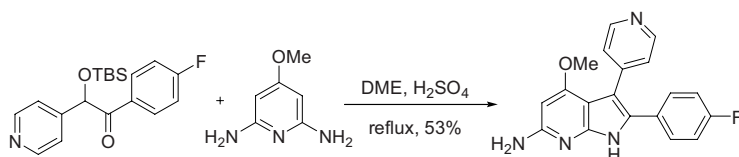
The Bischler–Möhlau indole synthesis, also known as the Bischler indole synthesis, refers to the synthesis of 3-arylindoles from the cyclization of ω -arylamino-ketones and excess anilines.

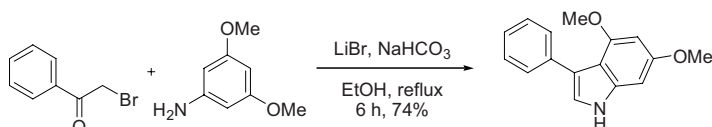
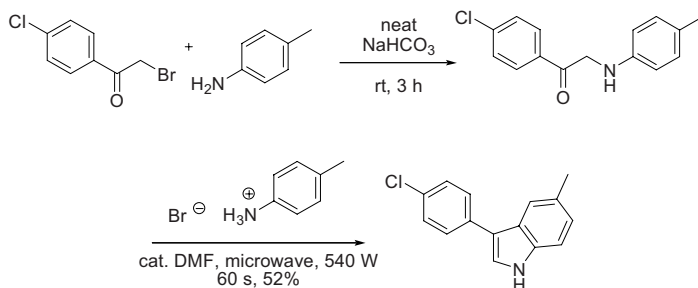


Example 1⁵



Example 2⁹



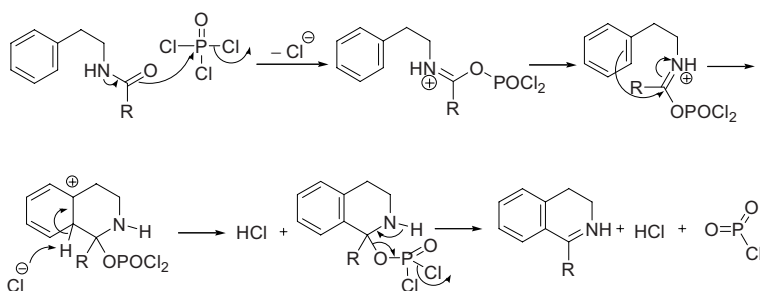
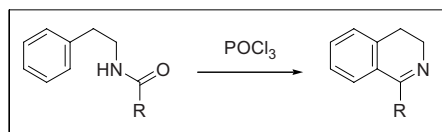
Example 3¹⁰Example 4, Microwave-assisted, solvent-free Bischler indole synthesis¹¹

References

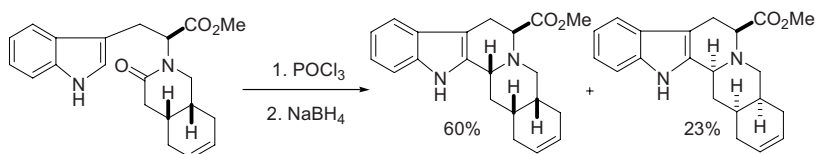
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Bischler–Napieralski reaction

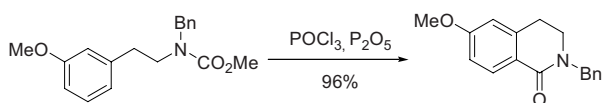
Dihydroisoquinolines from β -phenethylamides in refluxing phosphorus oxychloride.



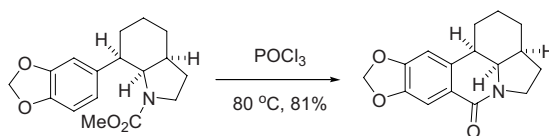
Example 1²

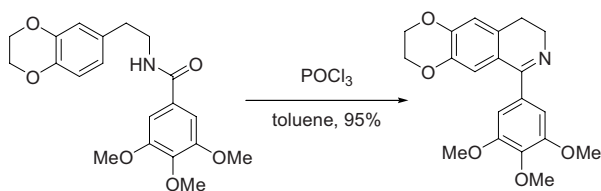
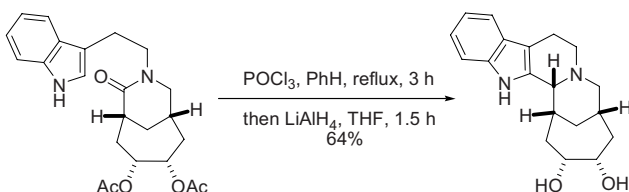


Example 2⁴



Example 3⁶



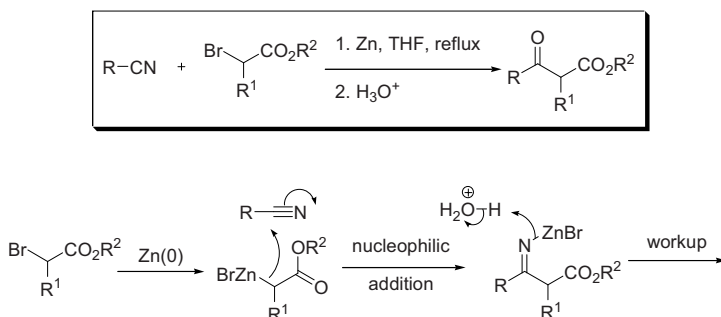
Example 4⁷Example 5⁹

References

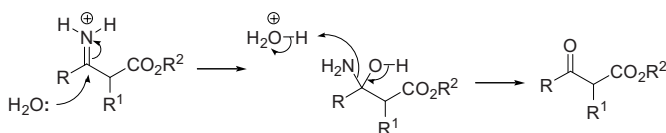
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Blaise reaction

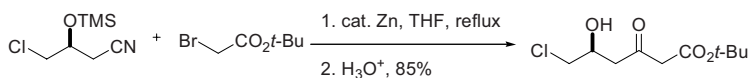
β -Ketoesters from nitriles, α -haloesters and Zn. Cf. Reformatsky reaction.



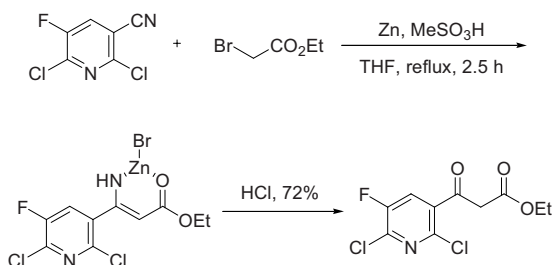
The Zn enolate itself is a *C*-enolate (in the crystal form), but for the reaction to occur, it equilibrates back into an *O*-enolate

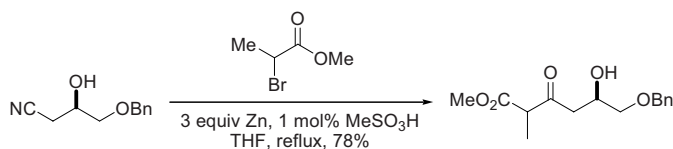
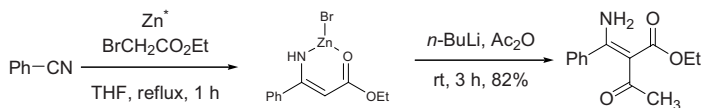


Example 1, Preparation of the statin side chain⁵



Example 2⁶



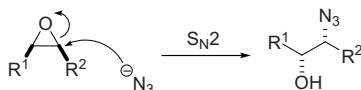
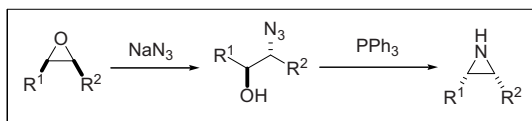
Example 3⁷Example 4, The first chemoselective tandem acylation of the Blaise reaction intermediate⁹

References

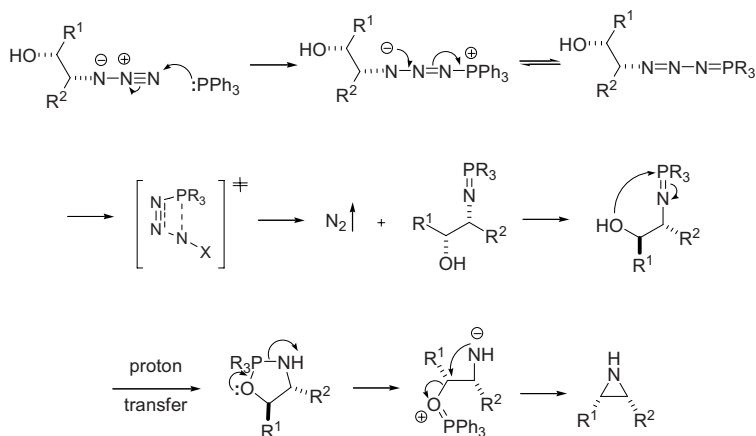
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Blum–Ittah aziridine synthesis

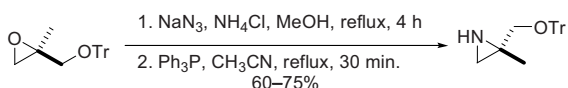
Ring opening of oxiranes using azide followed by PPh_3 -reduction of the intermediate azido-alcohol to give the corresponding aziridines.



Regardless of the regioselectivity of the $\text{S}_{\text{N}}2$ reaction of the azide, the ultimate stereochemical outcome for the aziridine is the same.

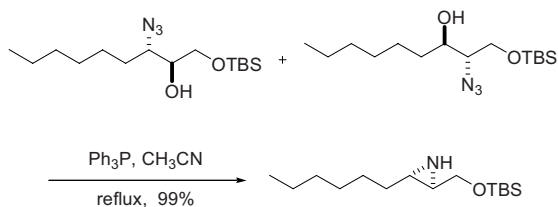
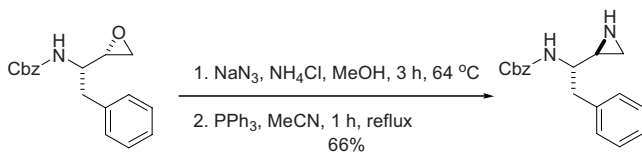
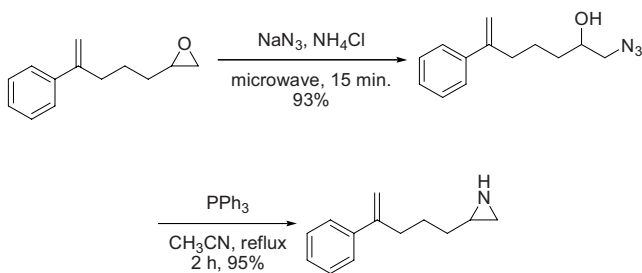


Example 1³



Example 2⁵



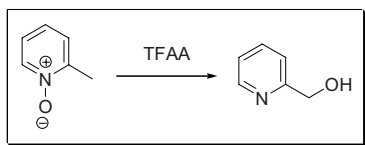
Example 3⁷Example 4⁸

References

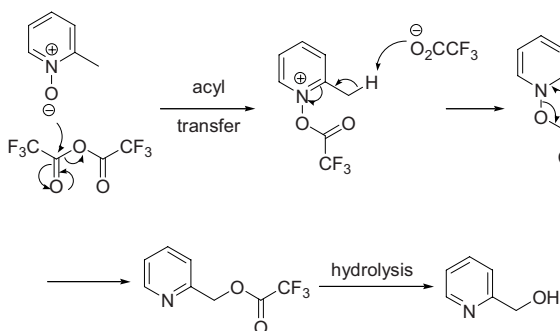
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Boeckelheide reaction

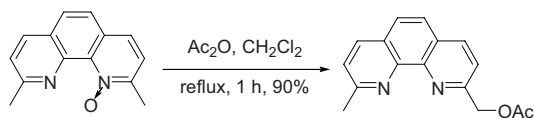
Treatment of 2-methylpyridine *N*-oxide with trifluoroacetic anhydride, or acetic, anhydride gives rise to 2-hydroxymethylpyridine.



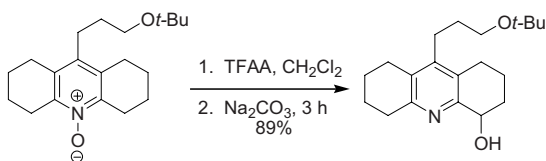
TFAA, trifluoroacetic anhydride



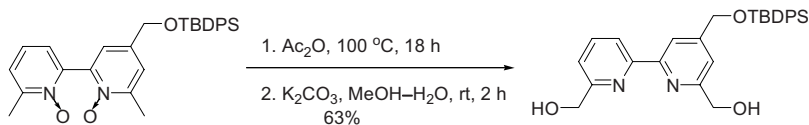
Example 1⁴

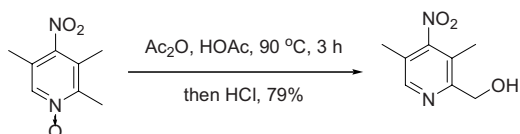


Example 2⁶



Example 3⁸



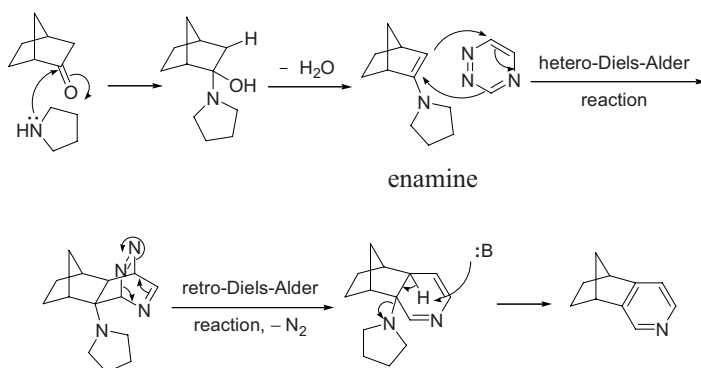
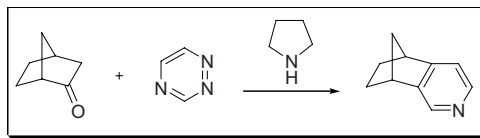
Example 4⁹

References

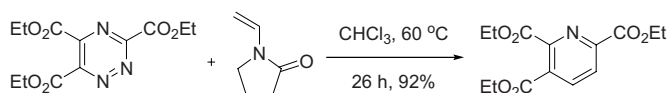
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Boger pyridine synthesis

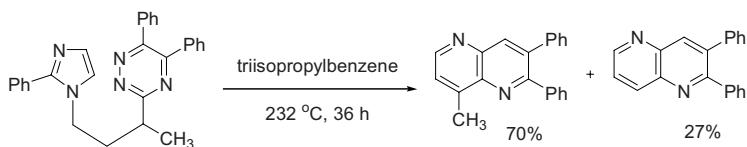
Pyridine synthesis *via* hetero-Diels–Alder reaction of 1,2,4-triazines and dienophiles (e.g., enamine) followed by extrusion of N₂.

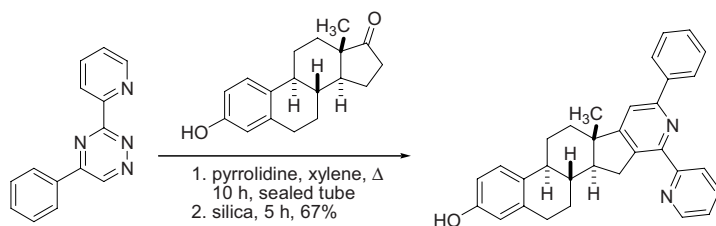
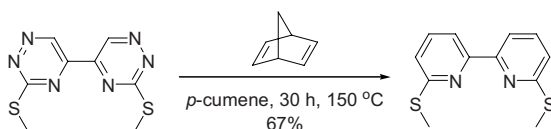


Example 1³



Example 2, Intramolecular Boger pyridine synthesis⁸



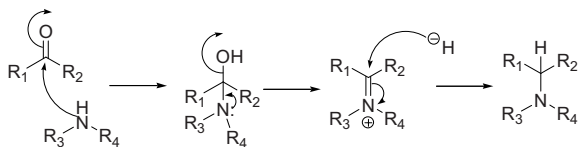
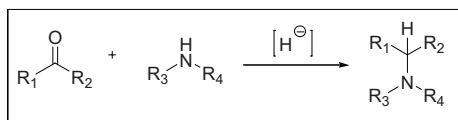
Example 3¹⁰Example 4¹¹

References

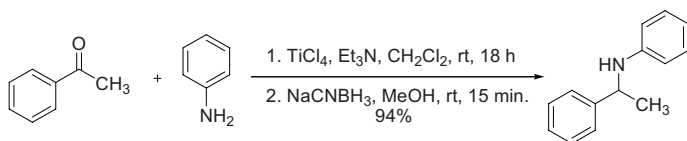
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Borch reductive amination

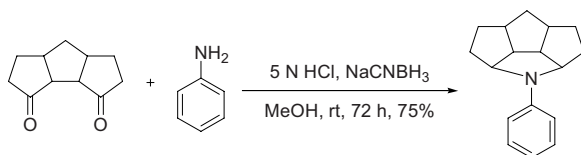
Reduction (often using NaCNBH_3) of the imine, formed by an amine and a carbonyl, to afford the corresponding amine—basically, reductive amination.



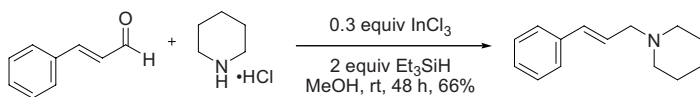
Example 1⁴

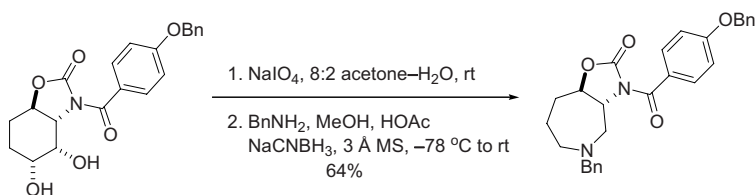


Example 2⁵



Example 3⁸



Example 4⁹

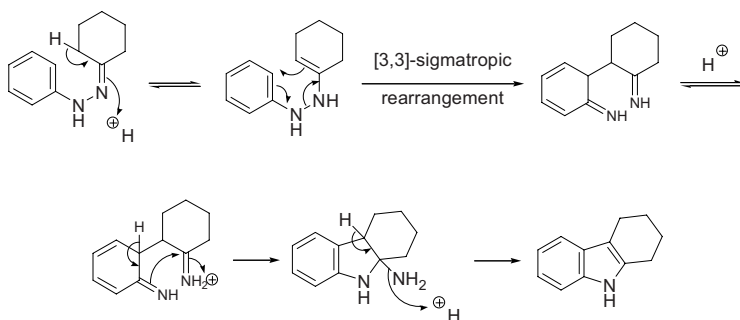
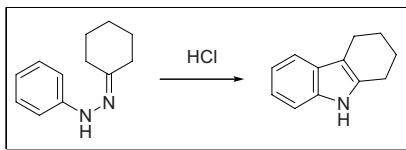
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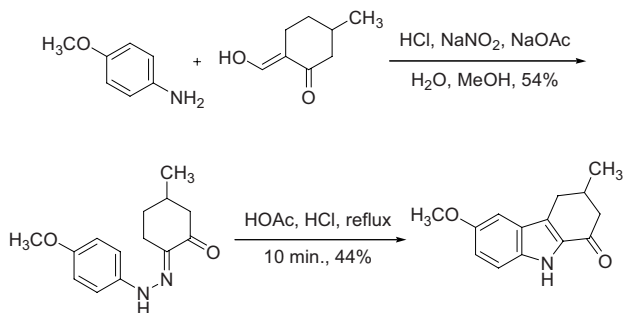
Borsche–Drechsel cyclization

Tetrahydrocarbazole synthesis from cyclohexanone phenylhydrazone.

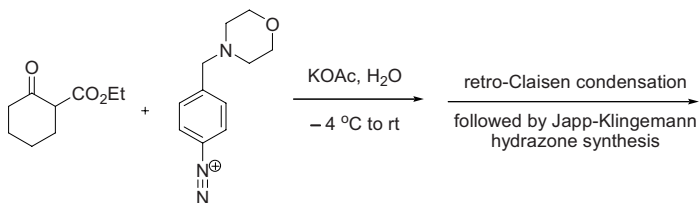
Cf. Fischer indole synthesis.

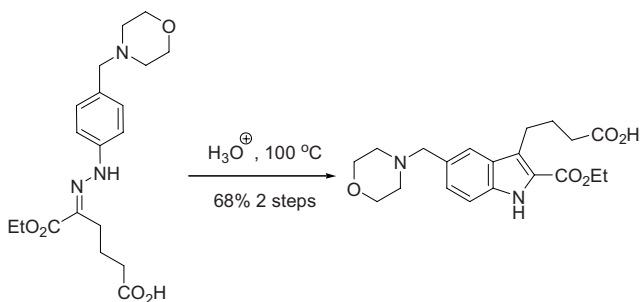
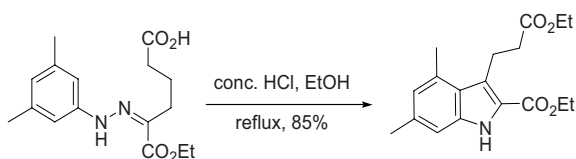


Example 1⁶



Example 2¹⁰



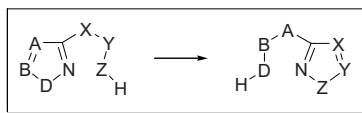
Example 3¹⁰

References

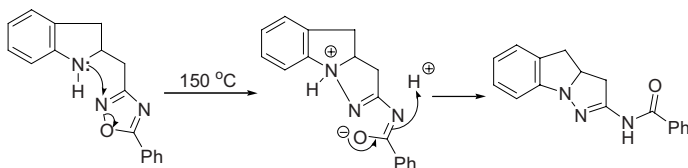
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Boulton–Katritzky rearrangement

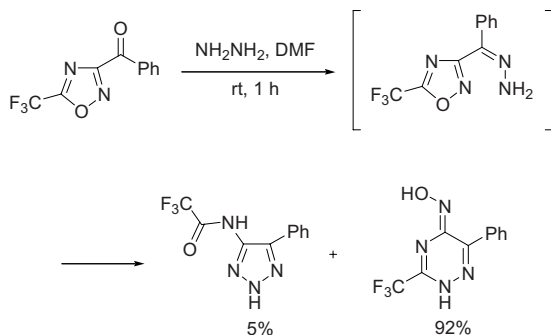
Rearrangement of one five-membered heterocycle into another under thermolysis.



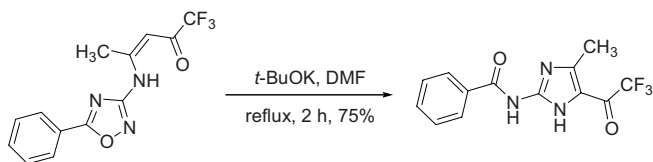
Example 1⁴



Example 2, Hydrazinolysis⁷



Example 4³

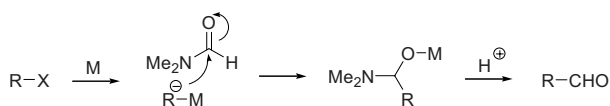
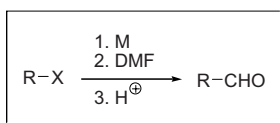


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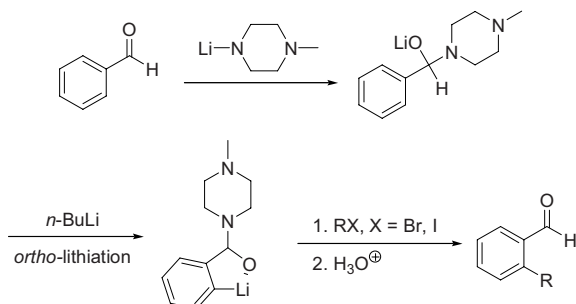
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Bouveault aldehyde synthesis

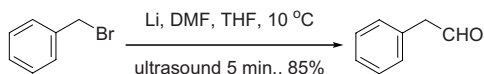
Formylation of an alkyl or aryl halide to the homologous aldehyde by transformation to the corresponding organometallic reagent then addition of DMF (M = Li, Mg, Na, and K).



Comins modification:⁴



Example³

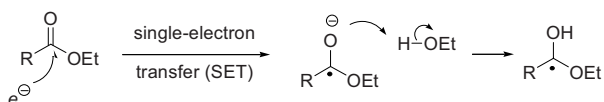
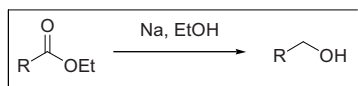


References

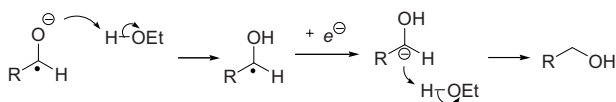
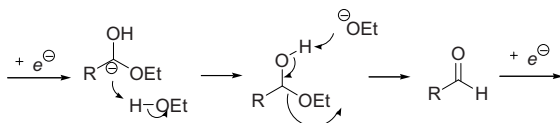
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Bouveault–Blanc reduction

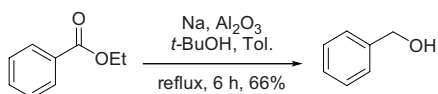
Reduction of esters to the corresponding alcohols using sodium in an alcoholic solvent.



ketyl (radical anion)



Example²

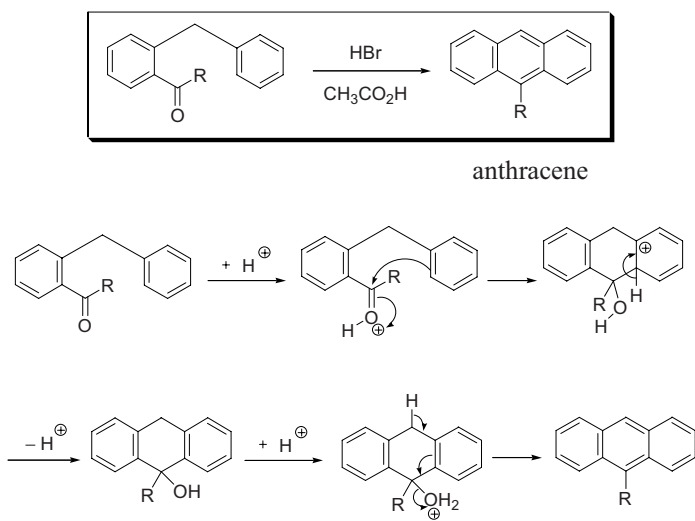


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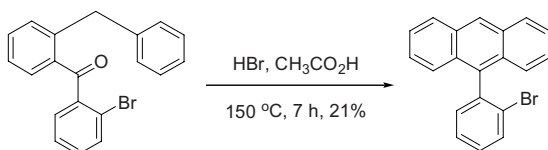
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Bradsher reaction

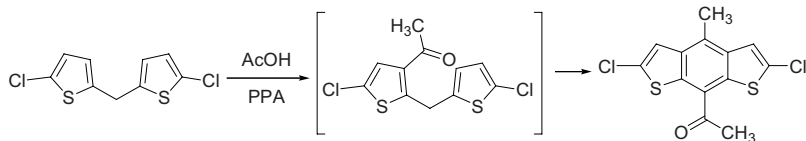
The intramolecular Bradsher cyclization refers to the acid-catalyzed aromatic cyclodehydration of *ortho*-acyl diarylmethanes to form anthracenes. On the other hand, the intermolecular Bradsher cycloaddition often involves the Diels–Alder reaction of a pyridium with a vinyl ether or vinyl sulfide.

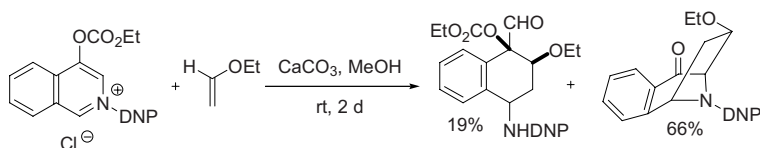
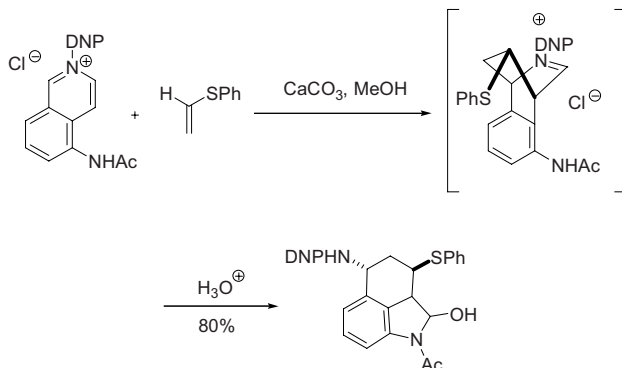


Example 1, Intramolecular Bradsher reaction²



Example 2, Intramolecular Bradsher reaction⁵



Example 3, Intermolecular Bradsher cycloaddition (DNP = dinitrophenyl)⁸Example 4, Intermolecular Bradsher cycloaddition¹⁰

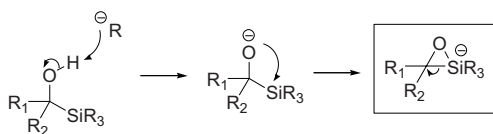
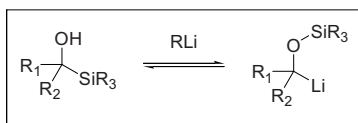
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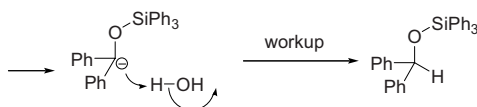
Brook rearrangement

Rearrangement of α -silyl oxyanions to α -silyloxy carbanions *via* a reversible process involving a pentacoordinate silicon intermediate is known as the [1,2]-Brook rearrangement, or [1,2]-silyl migration.

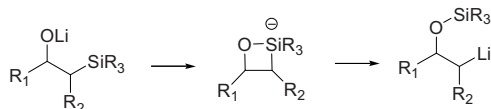
[1,2]-Brook rearrangement



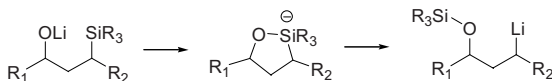
pentacoordinate silicon intermediate



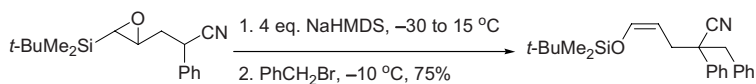
[1,3]-Brook rearrangement



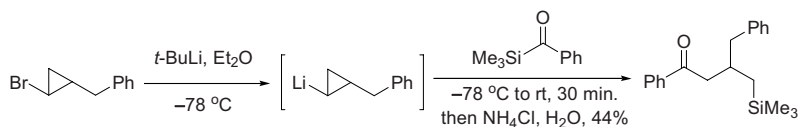
[1,4]-Brook rearrangement



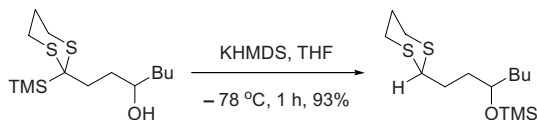
Example 1⁶



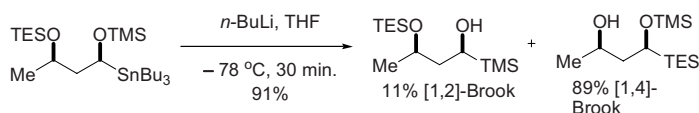
Example 2, [1,2]-Brook rearrangement followed by a retro-[1,5]-Brook rearrangement⁸



Example 3, [1,5]-Brook rearrangement⁹



Example 4, Retro-[1,4]-Brook rearrangement¹⁰

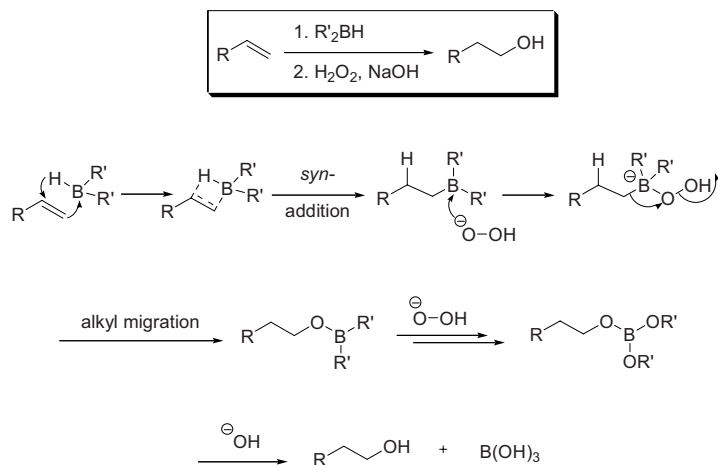


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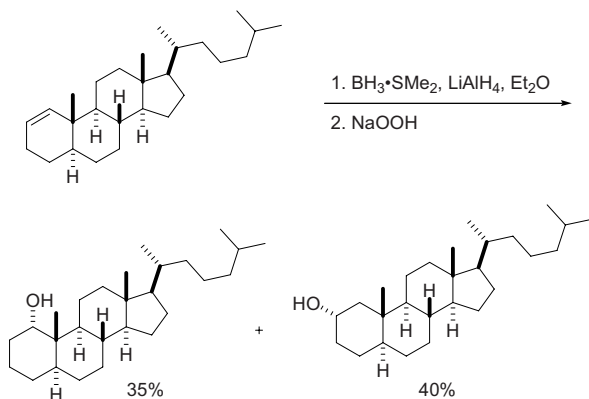
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Brown hydroboration

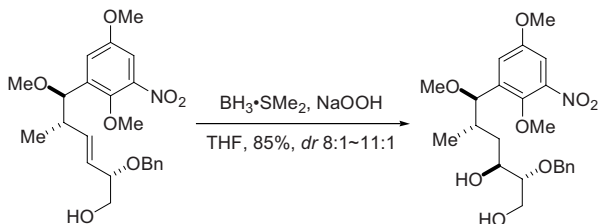
Addition of boranes to olefins followed by alkaline oxidation of the organoborane adducts to afford alcohols.

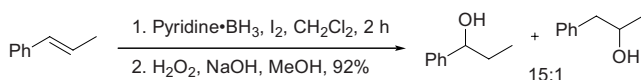
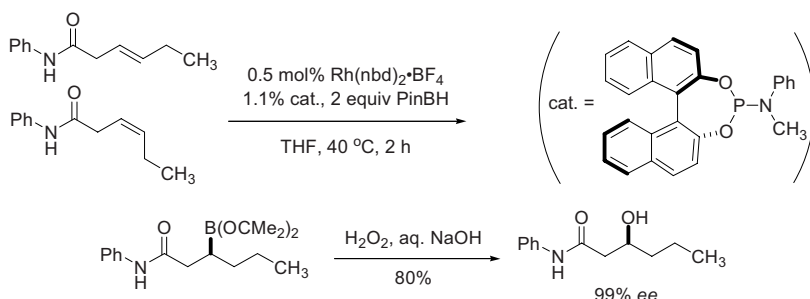
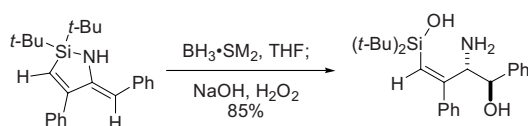


Example 1²



Example 2⁷



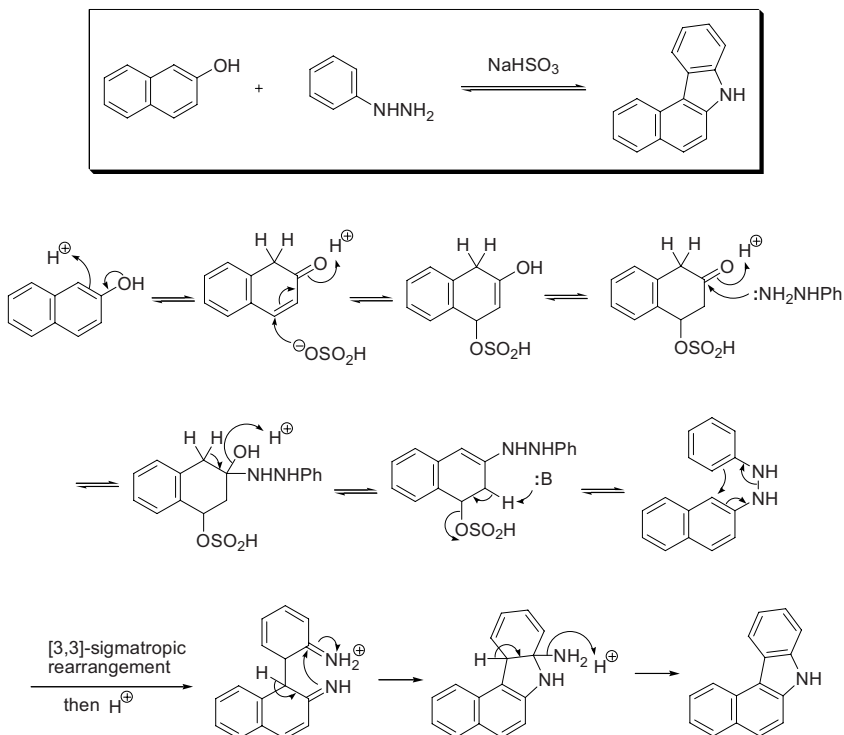
Example 3⁸Example 4, Asymmetric hydroboration¹⁰Example 5¹¹

References

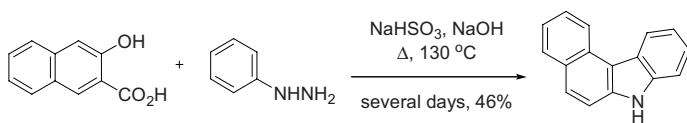
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Bucherer carbazole synthesis

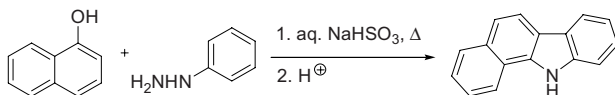
Carbazole formation from naphthols and aryl hydrazines promoted by sodium bisulfite. Another variant of the Fischer indole synthesis.

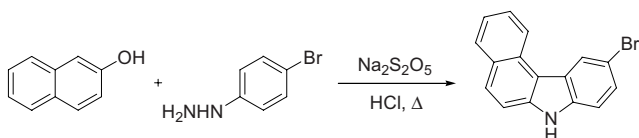
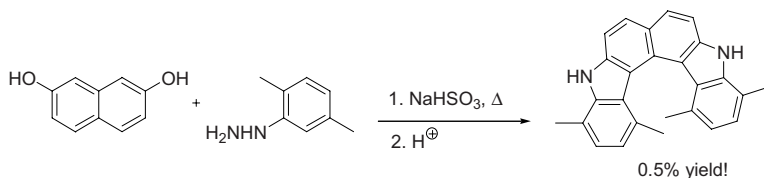


Example 1²



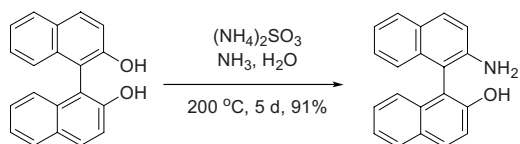
Example 2³



Example 3⁷Example 3⁴

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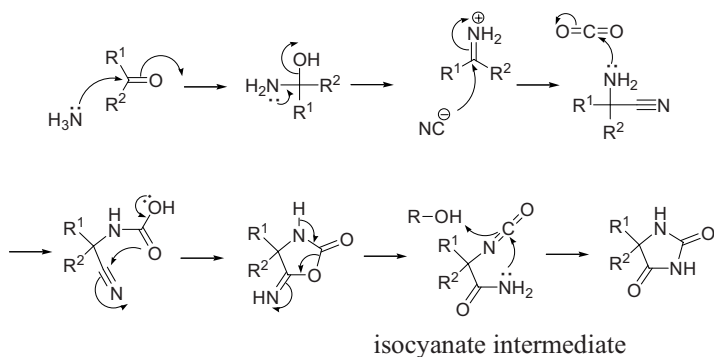
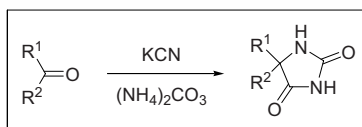
Example 3⁸

References

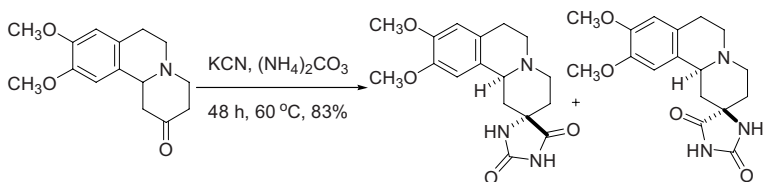
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Bucherer–Bergs reaction

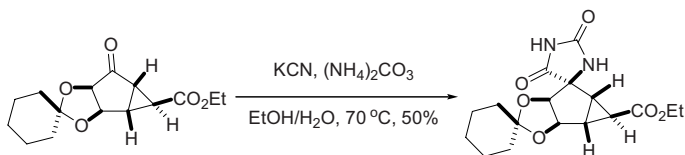
Formation of hydantoins from carbonyl compounds with potassium cyanide (KCN) and ammonium carbonate $[(\text{NH}_4)_2\text{CO}_3]$ or from cyanohydrins and ammonium carbonate. It belongs to the category of multiple component reactions (MCRs).

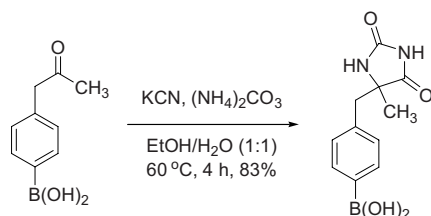
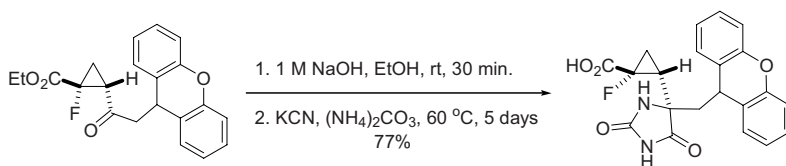


Example 1⁵



Example 2⁶



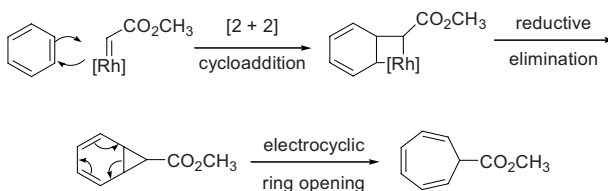
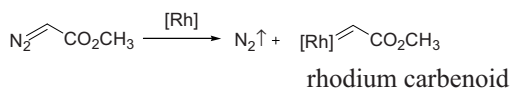
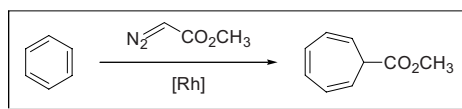
Example 3⁷Example 4⁹

References

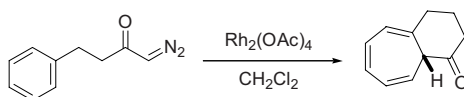
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Büchner ring expansion

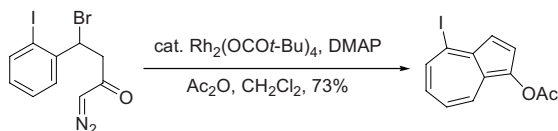
Reaction of a phenyl ring with diazoacetic esters to give cyclohepta-2,4,6-trienecarboxylic acid esters. Intramolecular Büchner reaction is more useful in synthesis. *Cf.* Pfau–Platter azulene synthesis.



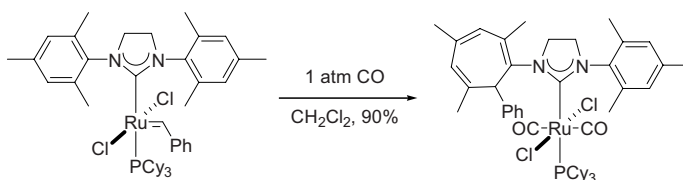
Example 1, Intramolecular Büchner reaction⁷

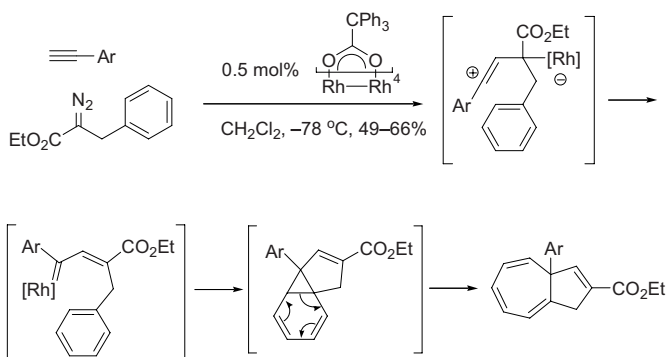


Example 2, Intramolecular Büchner reaction⁸



Example 3, An intramolecular Büchner reaction within the Grubbs' catalyst!⁹



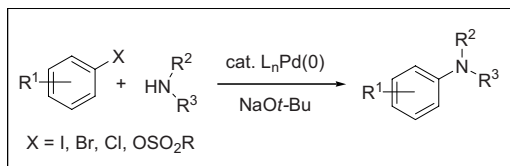
Example 4¹⁰

References

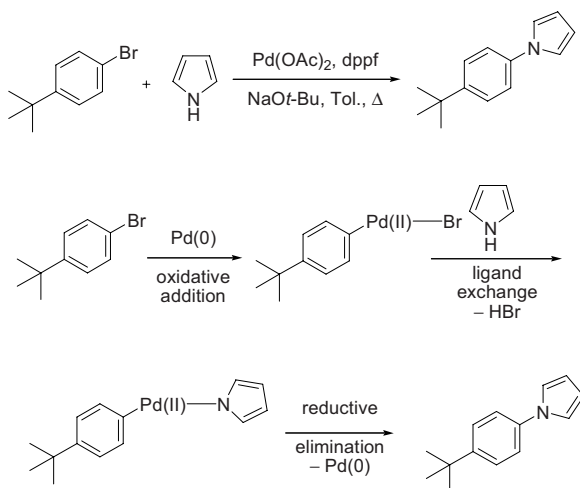
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Buchwald–Hartwig amination

The Buchwald–Hartwig amination is an exceedingly general method for generating an aromatic amine from an aryl halide or an aryl sulfonates. The key feature of this methodology is the use of catalytic palladium modulated by various electron-rich ligands. Strong bases, such as sodium *tert*-butoxide, are essential for catalyst turnover.

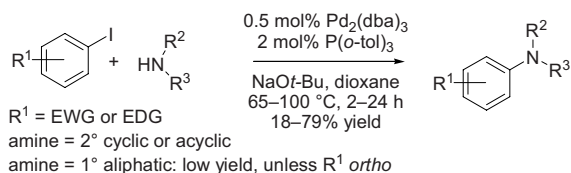


Mechanism:

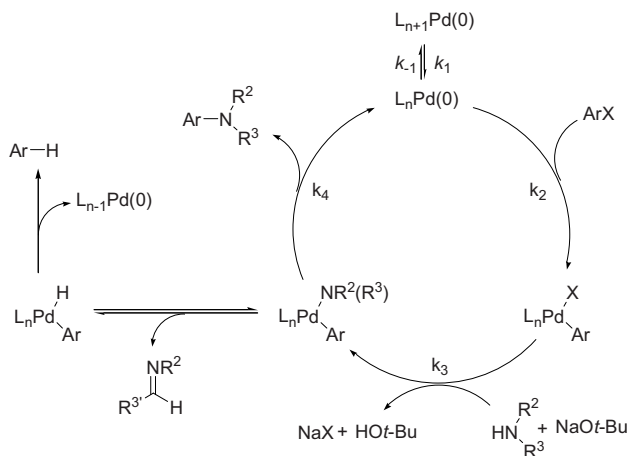


The catalytic cycle is shown on the next page.

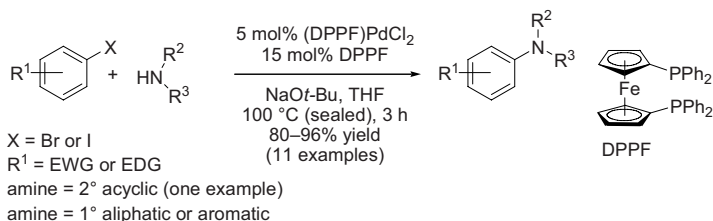
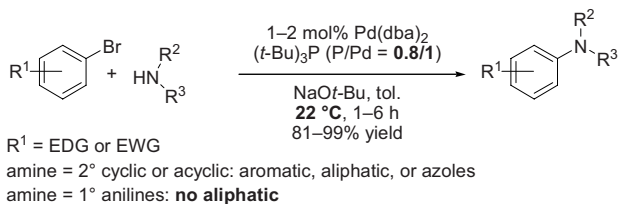
Example 1³

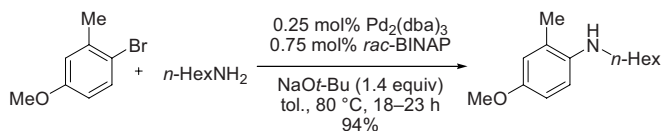
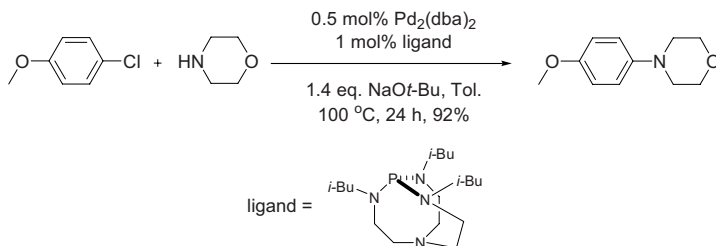
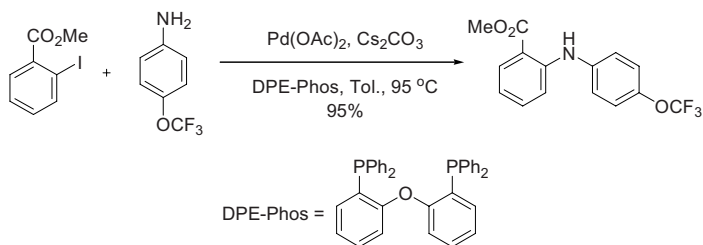
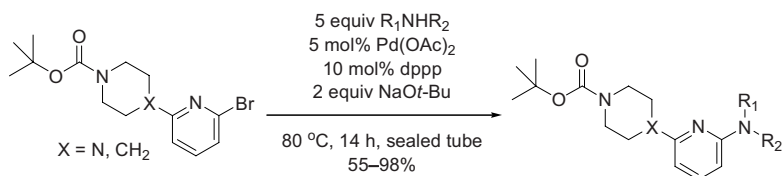
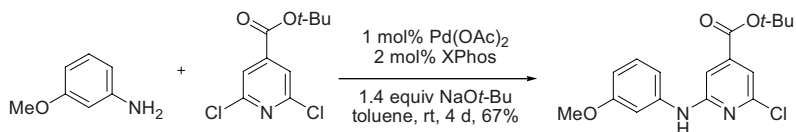


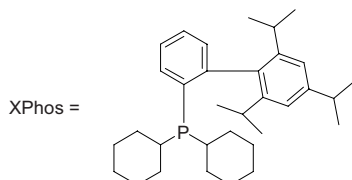
Catalytic cycle:

Pd(BINAP)₂ catalyzed

$$\frac{-d[\text{ArX}]}{dt} = \frac{k_1 k_2}{k_{-1} [\text{L}]} [\text{ArX}][\text{Pd}]$$

Example 2⁴Example 3, Room temperature Buchwald–Hartwig amination⁹

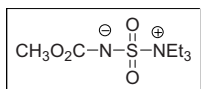
Example 4¹⁰Example 5¹¹Example 6¹²Example 7, Amination of volatile amines¹⁴Example 8¹⁵



References

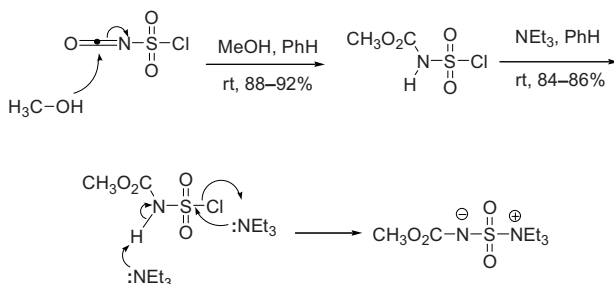
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Burgess reagent

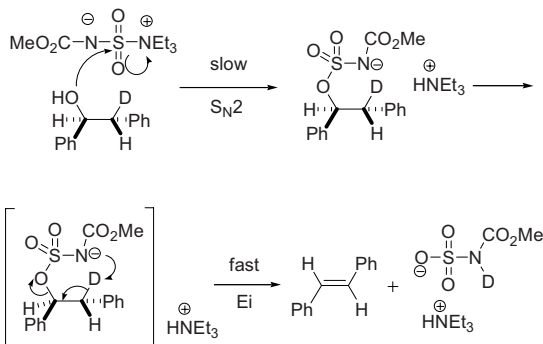


The Burgess reagent [(methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt], a neutral, white crystalline solid, is efficient at generating olefins from secondary and tertiary alcohols where the first-order thermolytic E_i (during the elimination takes place—the two groups leave at about the same time and bond to each other concurrently) mechanism prevails.

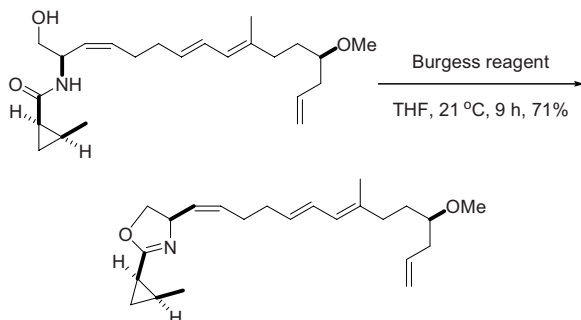
Preparation²



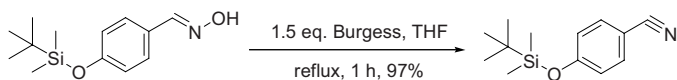
Mechanism⁵



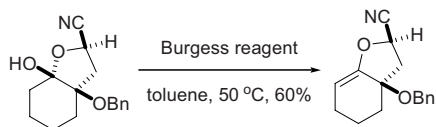
Example 1, On primary alcohols, the hydroxyl group does not eliminate but rather undergoes substitution³



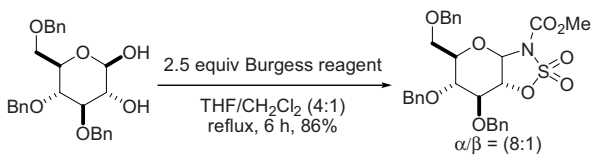
Example 2⁶



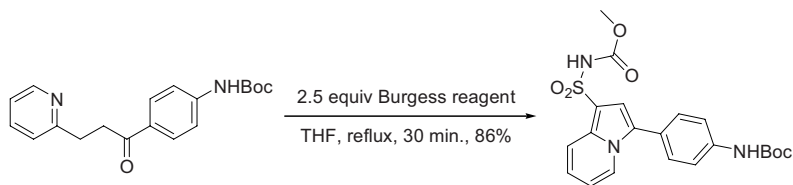
Example 3⁷



Example 4⁸



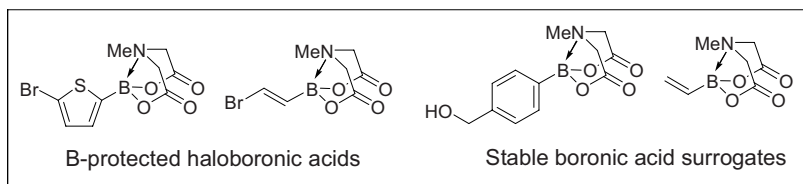
Example 5¹⁰



References

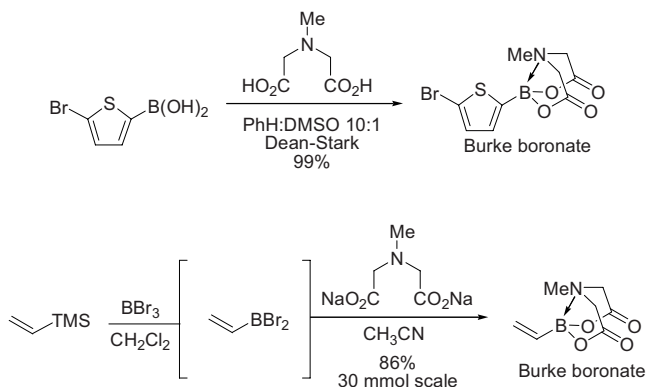
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Burke boronates



Burke boronates can serve as B-protected haloboronic acids for a wide variety of applications in iterative cross-coupling.^{1–6} The corresponding boronic acids can be liberated using mild aqueous bases such as NaOH or NaHCO₃.^{1–4} Burke boronates are also compatible with many synthetic reagents, enabling the synthesis of complex boronic acids from simple B-containing starting materials.^{3,6} They can also serve as stable building blocks for cross-coupling, i.e., under aqueous basic conditions, the corresponding boronic acid is released and coupled *in situ*.^{2,3,7} Moreover, Burke boronates are highly crystalline, monomeric, free-flowing solids that are indefinitely stable to benchtop storage under air and compatible with silica gel chromatography.^{1–3,6}

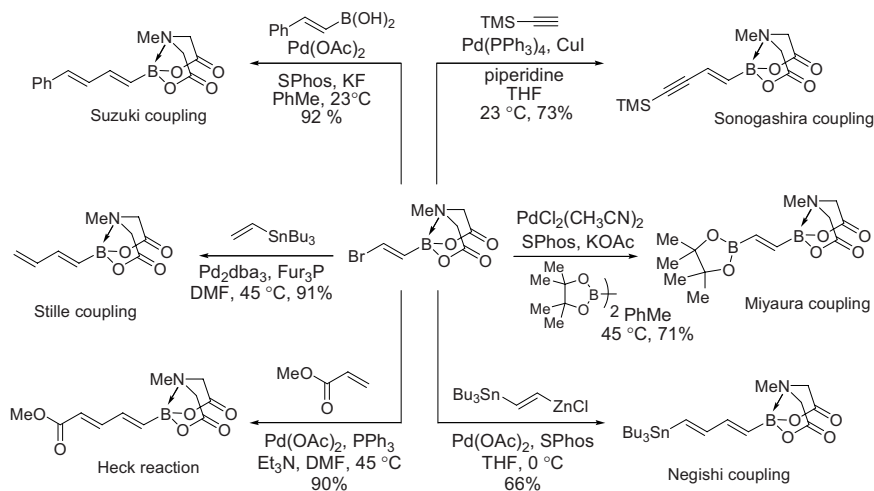
Preparation:^{1,2,4,6}



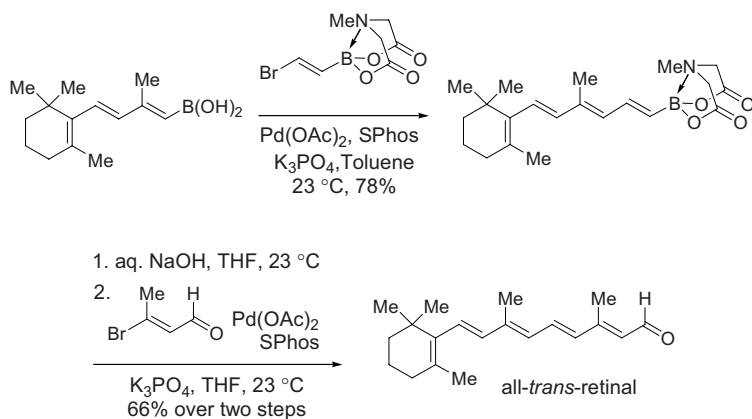
Burke boronates can be conveniently prepared from the corresponding boronic acids via complexation with *N*-methyliminodiacetic acid (MIDA)^{1,4} or from dibromoboranes via complexation with MIDA^{2–Na}.^{2,6} Alternatively, many of these building blocks are now commercially available.

Example 1²

A wide range of selective couplings can be performed at the halide terminus of a B-protected haloboronic acid.

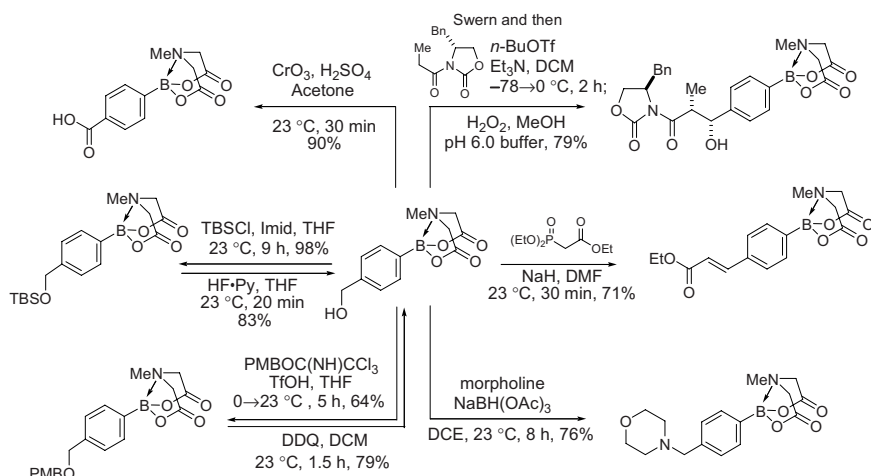
Example 2²

Small molecule natural products can be prepared via iterative cross-coupling with B-protected haloboronic acids.

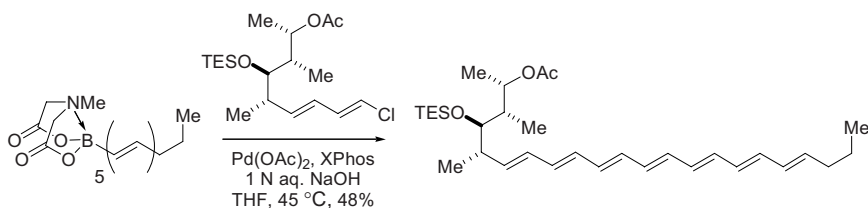


Example 3³

Burke boronates are stable to a wide range of synthetic reagents, including acids, non-aqueous bases, oxidants, reductants, electrophiles, and soft nucleophiles. This reagent compatibility enables multistep synthesis of complex boranes from simple boron-containing starting materials.

Example 4²

Burke boronates can be hydrolyzed *in situ* under aqueous basic coupling conditions, as evidenced by this synthesis of the complex polyene skeleton of amphoterin B.



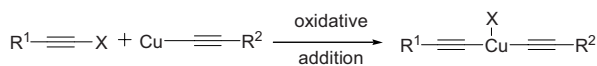
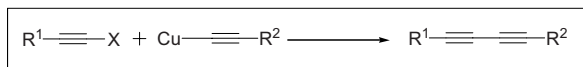
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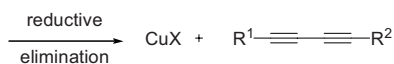
Cadiot–Chodkiewicz coupling

Bis-acetylene synthesis from alkynyl halides and alkynyl copper reagents.

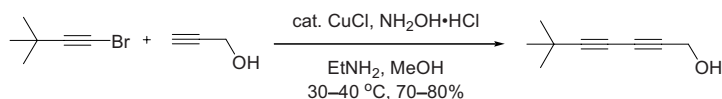
Cf. Castro–Stephens reaction.



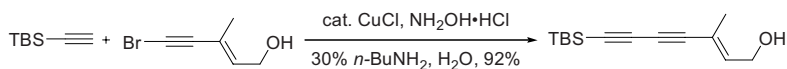
Cu(III) intermediate



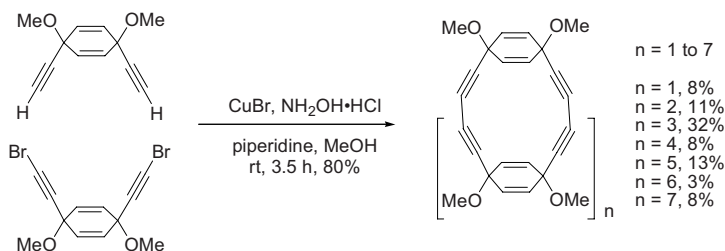
Example 1³



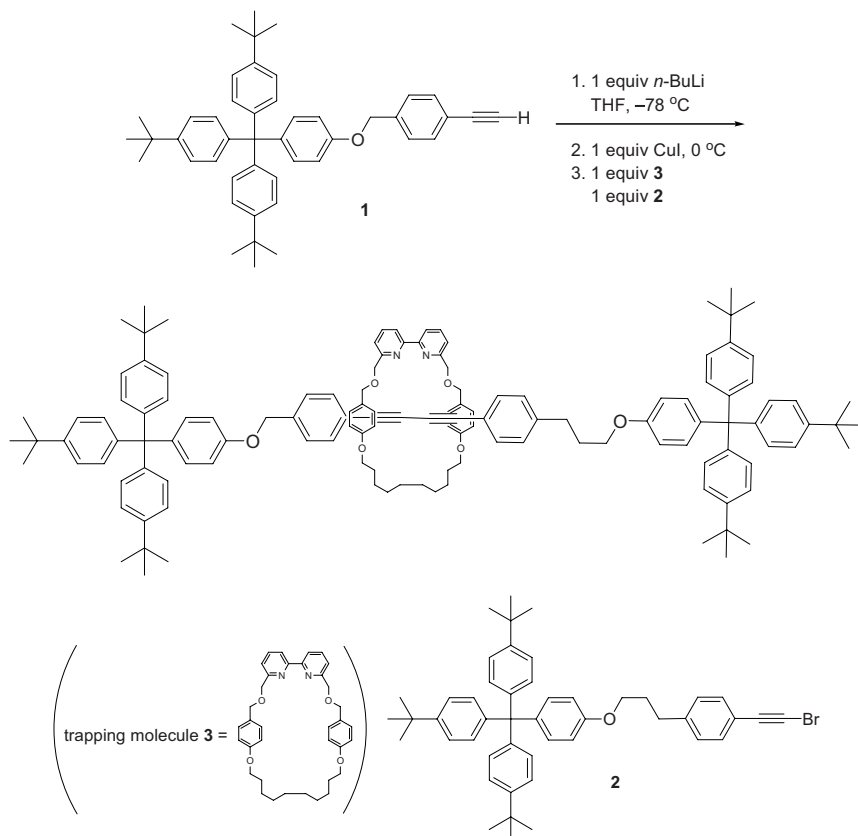
Example 2⁷



Example 3⁹



Example 4, Cadiot–Chodkiewicz active template synthesis of rotaxanes and switchable molecular shuttles with weak intercomponent interactions¹⁰

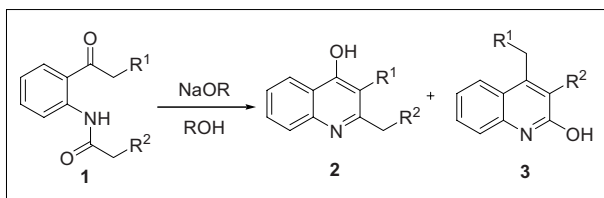


References

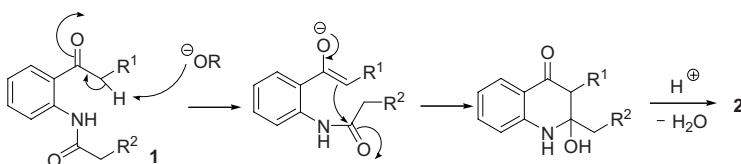
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Camps quinoline synthesis

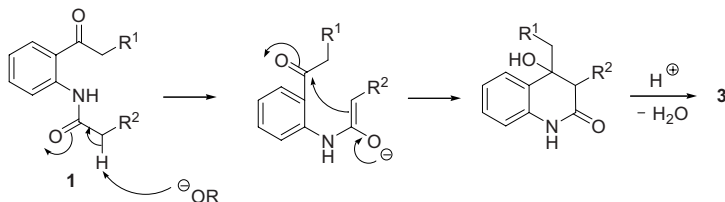
Base-catalyzed intramolecular condensation of a 2-acetamido acetophenone (**1**) to a 2-(and possibly 3)-substituted-quinolin-4-ol (**2**), a 4-(and possibly 3)-substituted-quinolin-2-ol (**3**), or a mixture.



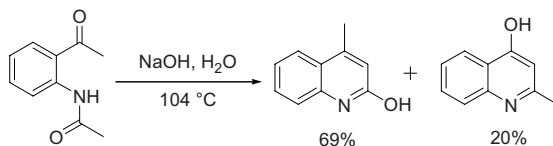
Pathway A:

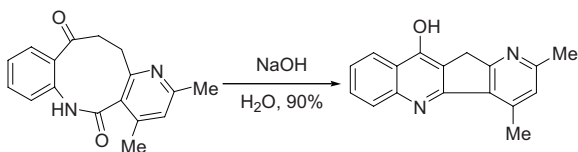


Pathway B:



Example 1¹



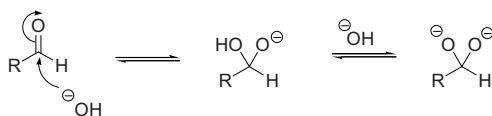
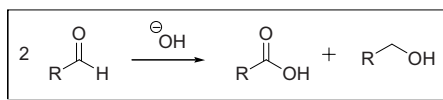
Example 2⁶

References

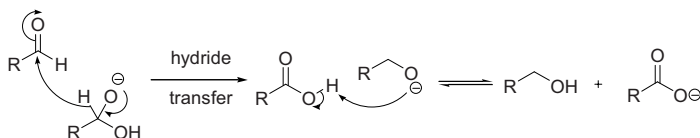
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Cannizzaro reaction

Redox reaction between aromatic aldehydes, formaldehyde or other aliphatic aldehydes without α -hydrogen. Base is used to afford the corresponding alcohols and carboxylic acids.

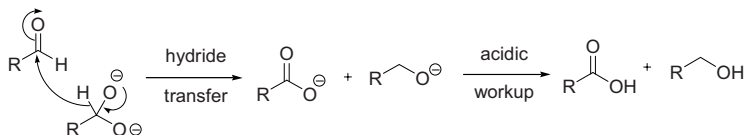


Pathway A:

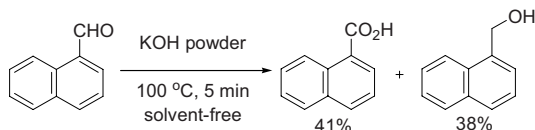


Final deprotonation of the carboxylic acid drives the reaction forward.

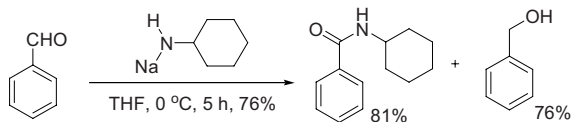
Pathway B:



Example 1⁴

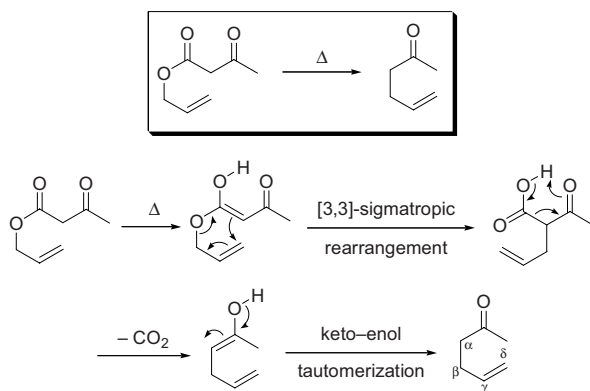


Example 2⁶

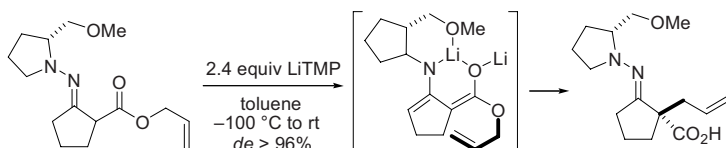


Carroll rearrangement

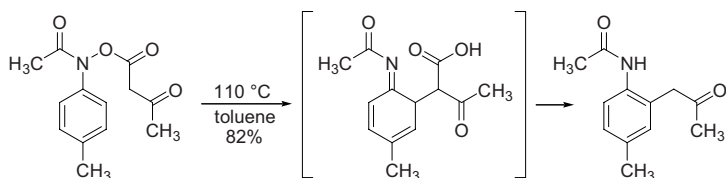
Thermal rearrangement of β -ketoesters followed by decarboxylation to yield γ -unsaturated ketones *via* anion-assisted Claisen rearrangement. It is a variant of the Claisen rearrangement (page 117).



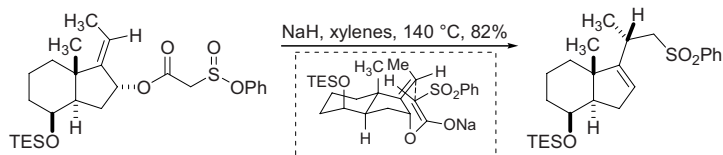
Example 1, Asymmetric Carroll rearrangement^{4,5}

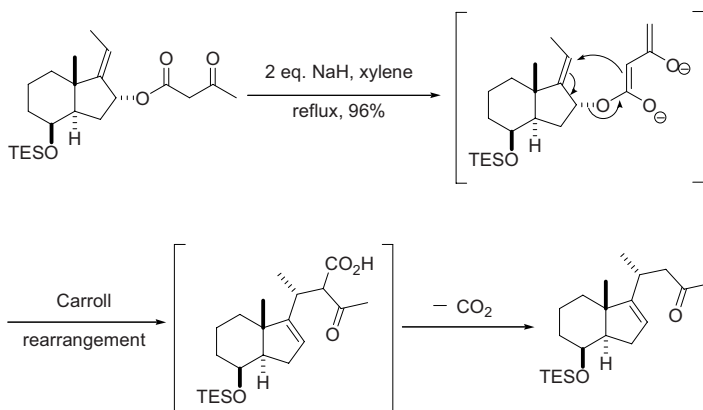
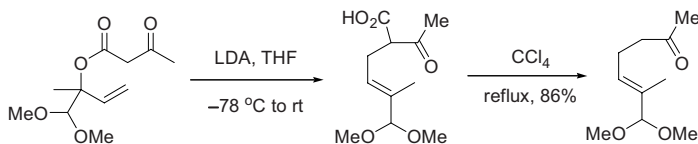


Example 2, Hetero-Carroll rearrangement⁶



Example 3⁷



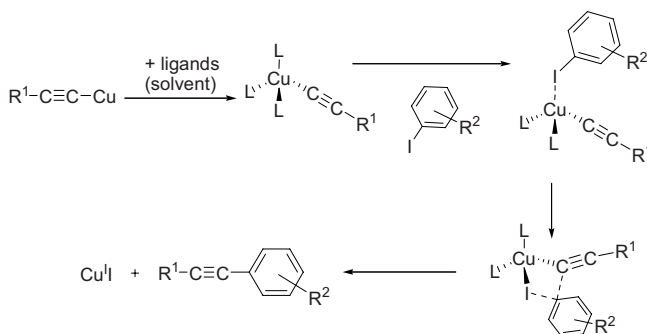
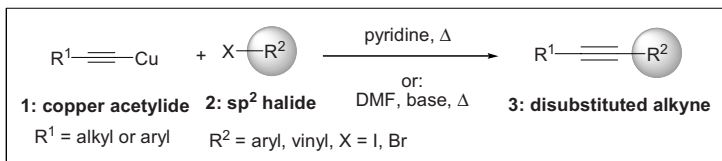
Example 4, Similar to Example 3⁷Example 5⁸

References

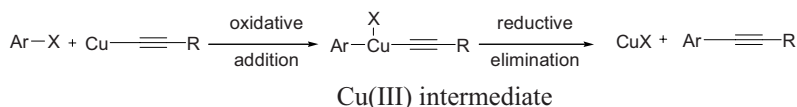
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Castro–Stephens coupling

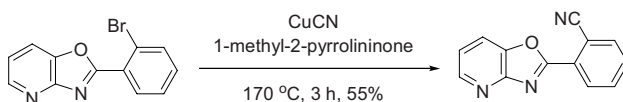
Aryl–acetylene synthesis, *Cf.* Cadiot–Chodkiewicz coupling and Sonogashira coupling. The Castro–Stephens coupling uses stoichiometric copper, whereas the Sonogashira variant uses catalytic palladium and copper.



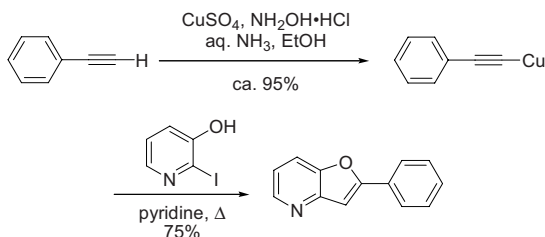
An alternative mechanism similar to that of the Cadiot–Chodkiewicz coupling:

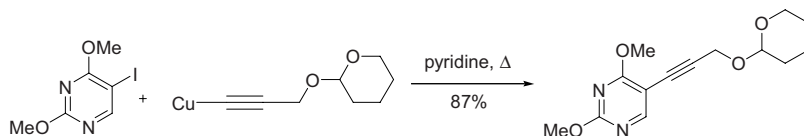
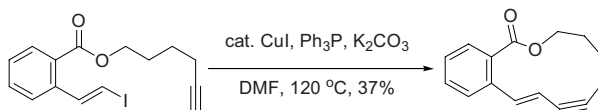
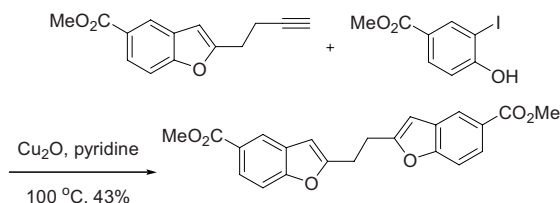


Example 1, A variant, also known as the Rosenmund–von Braun synthesis of aryl nitriles²



Example 2⁴



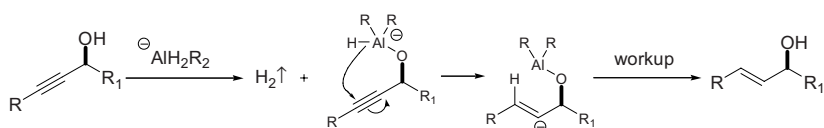
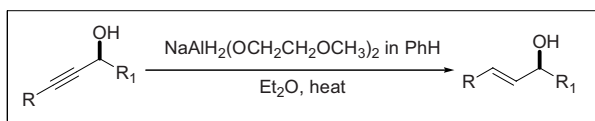
Example 3⁵Example 4⁸Example 5, *In situ* Castro–Stephens reaction¹⁰

References

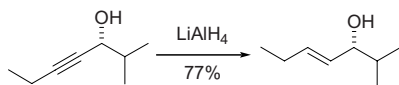
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Chan alkyne reduction

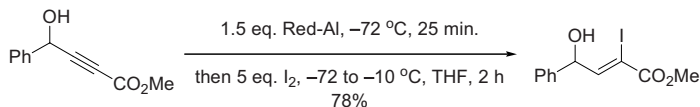
Stereoselective reduction of acetylenic alcohols to *E*-allylic alcohols using sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, also known as Red-Al) or LiAlH_4 .



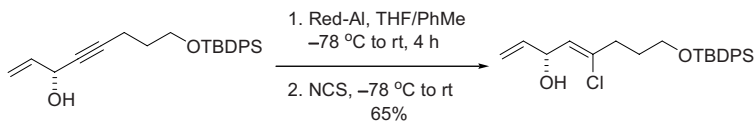
Example 1³



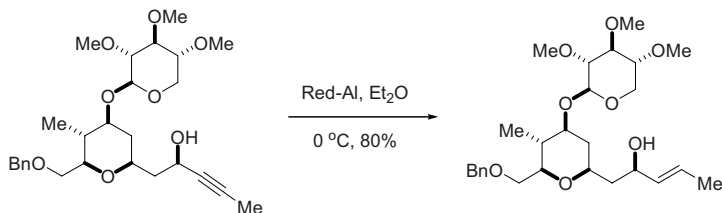
Example 2⁴



Example 3⁶



Example 4⁷

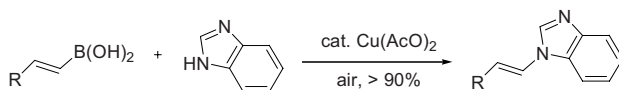
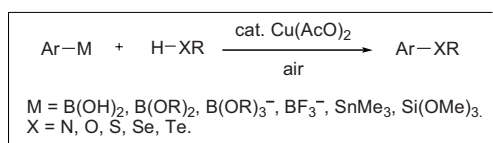


References

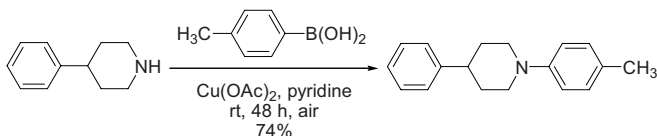
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Chan–Lam C–X coupling reaction

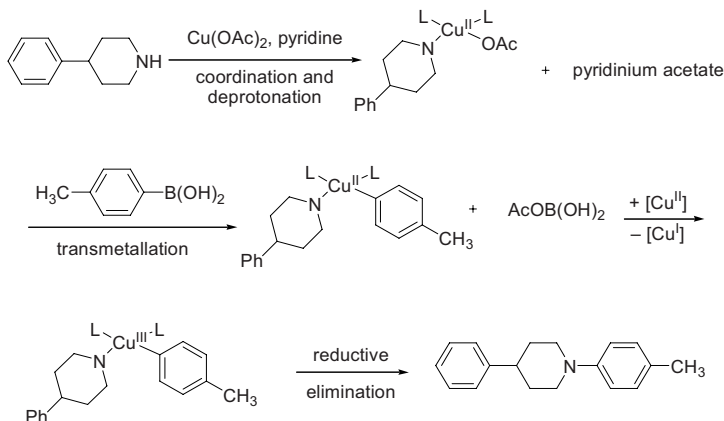
Arylation of a wide range of NH/OH/SH substrates by oxidative cross-coupling with boronic acids in the presence of catalytic cupric acetate and either triethylamine or pyridine at room temperature in air. The reaction works for amides, amines, anilines, azides, hydantoins, hydrazines, imides, imines, nitroso, pyrazinones, pyridones, purines, pyrimidines, sulfonamides, sulfinates, sulfoximines, ureas, alcohols, phenols, and thiols. It is also the mildest method for *N/O*-vinylation. The boronic acids can be replaced with siloxanes or stannanes. The mild condition of this reaction is an advantage over Buchwald–Hartwig’s Pd-catalyzed cross-coupling. The Chan–Lam C–X bond cross-coupling reaction is complementary to Suzuki–Miyaura’s C–C bond cross-coupling reaction.

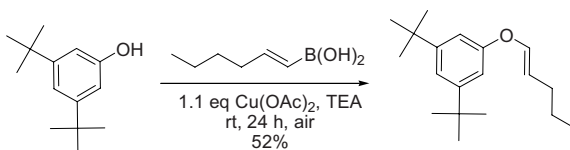
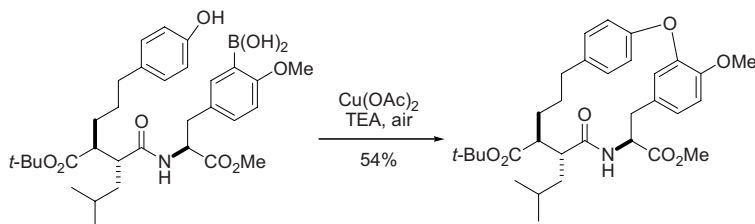
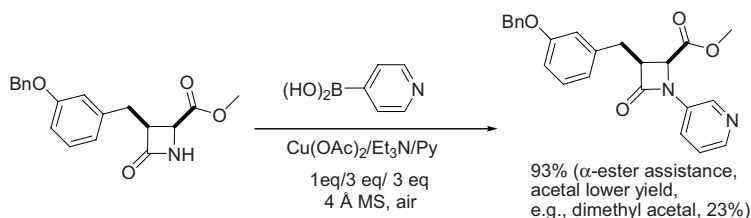
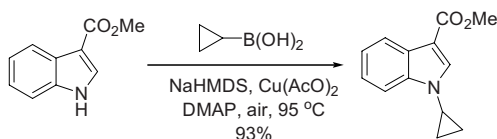
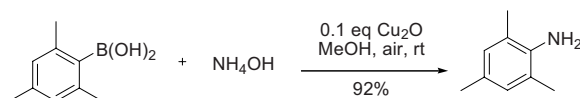


Example 1^{1a,d}



Mechanism:^{1c,d,17}



Example 2⁴Example 3⁵Example 4¹³Example 5¹⁴Example 6¹⁵

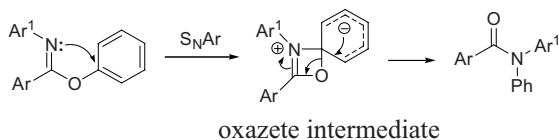
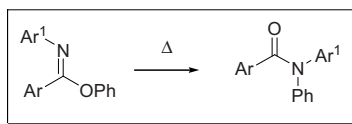
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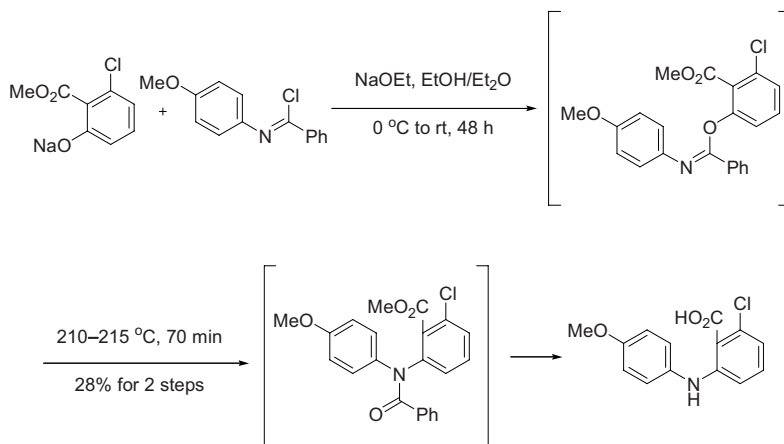
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Chapman rearrangement

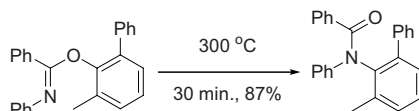
Thermal aryl rearrangement of *O*-aryliminoethers to amides.

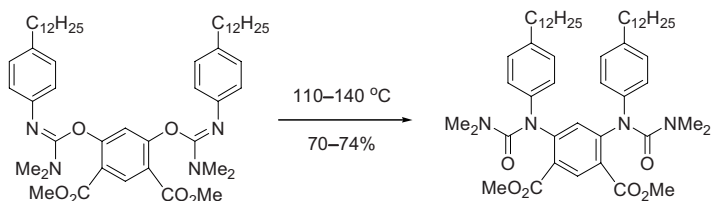
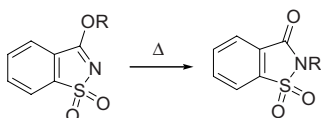


Example 1²



Example 2⁴



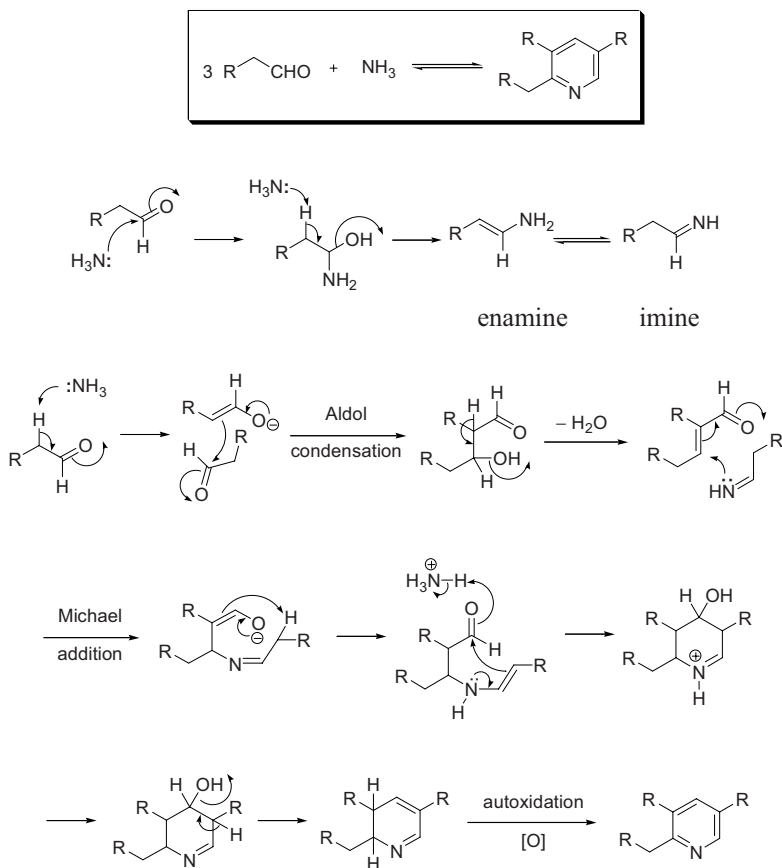
Example 3, Double Chapman rearrangement¹⁰Example 4, Chapman-like thermal rearrangement¹¹

References

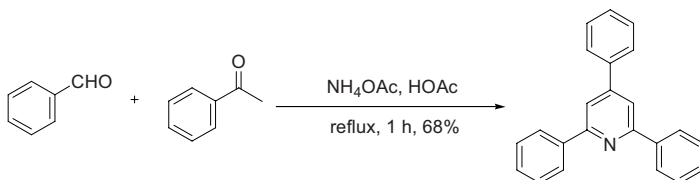
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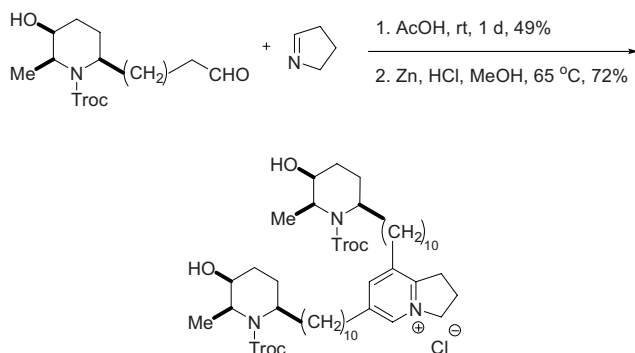
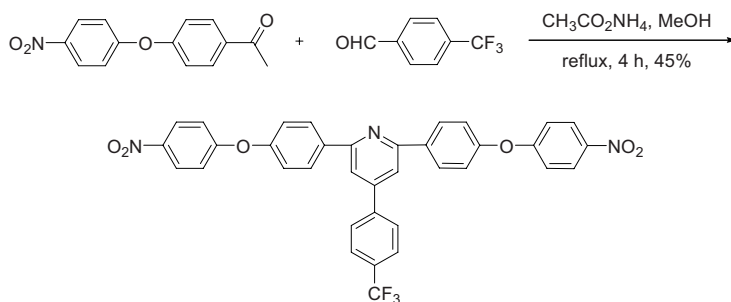
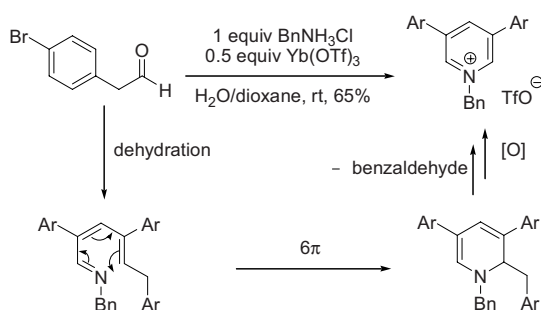
Chichibabin pyridine synthesis

Condensation of aldehydes with ammonia to afford pyridines.



Example 1⁴



Example 2⁸Example 3⁹Example 4, An abnormal Chichibabin reaction¹⁰

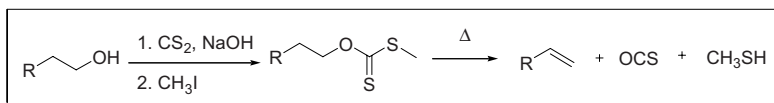
References

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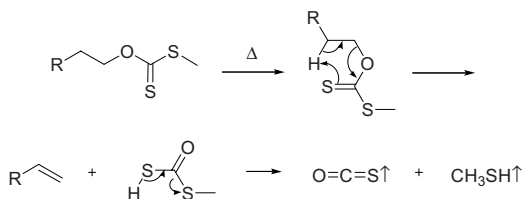
- want to cooperate with the pupil and gave Chichibabin a negative judgment on his Ph.D. work, earning Chichibabin the nickname “the self-educated man.”
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Chugaev elimination

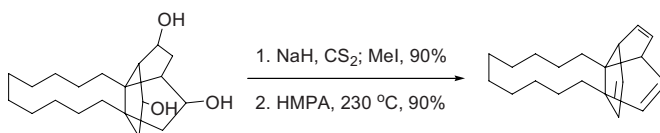
Thermal elimination of xanthates to olefins.



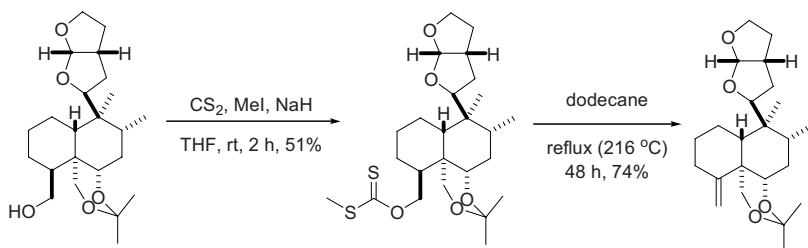
xanthate



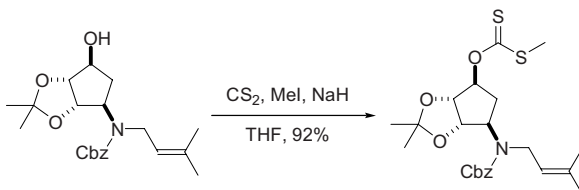
Example 1⁴

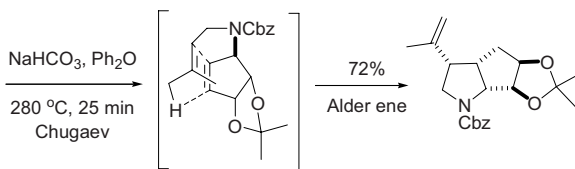


Example 2⁵



Example 3, Chugaev *syn*-elimination is followed by an intramolecular ene reaction⁶



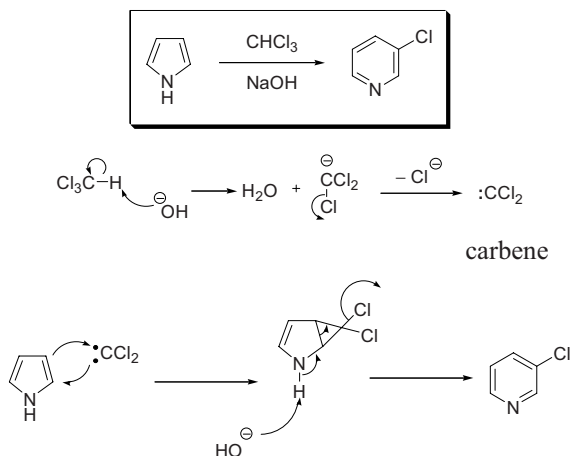


References

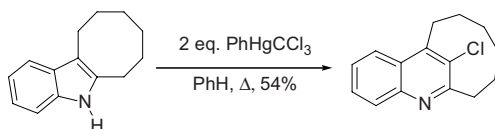
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Ciamician–Dennsted rearrangement

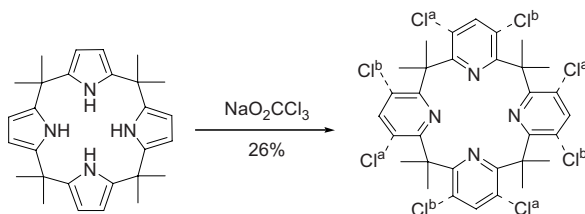
Cyclopropanation of a pyrrole with dichlorocarbene generated from CHCl_3 and NaOH . Subsequent rearrangement takes place to give 3-chloropyridine.



Example 1⁴



Example 2⁵

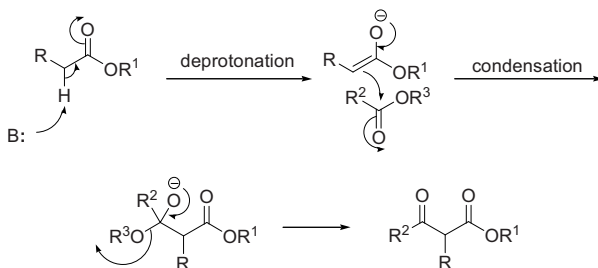
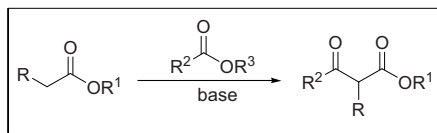


References

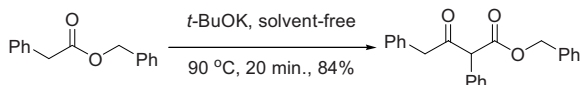
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Claisen condensation

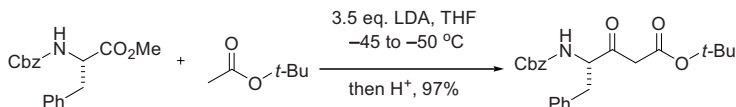
Base-catalyzed condensation of esters to afford β -keto esters.



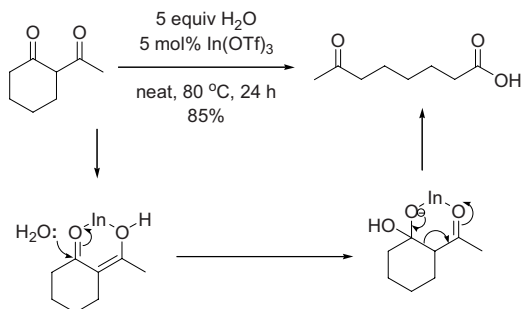
Example 1⁴

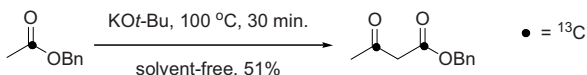


Example 2⁶



Example 3, Retro-Claisen condensation⁹



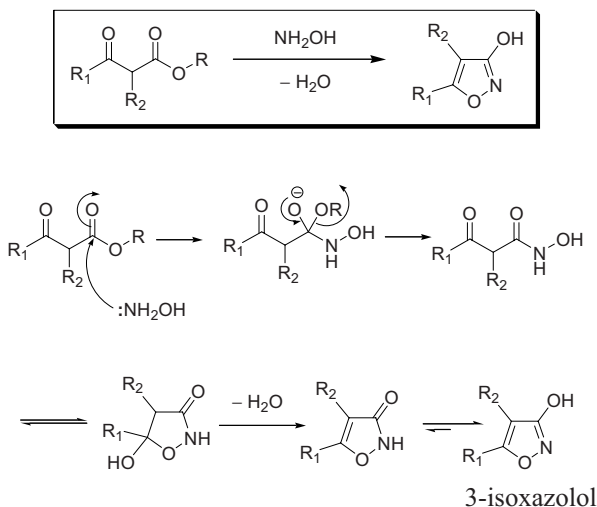
Example 4, Solvent-free Claisen condensation¹⁰

References

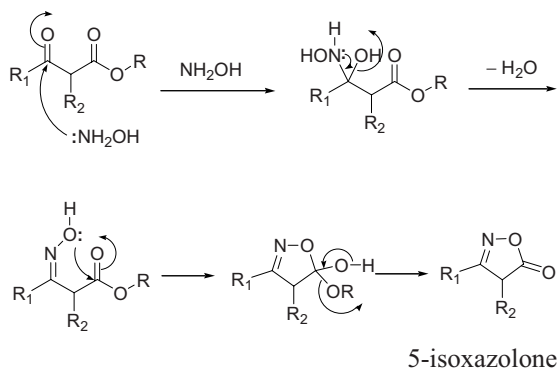
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Claisen isoxazole synthesis

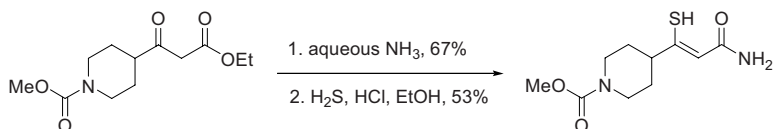
Cyclization of β -keto esters with hydroxylamine to provide 3-hydroxy-isoxazoles (3-isoxazolols).

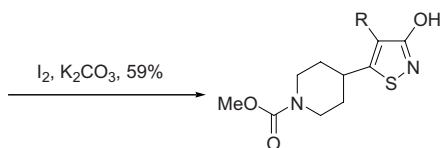
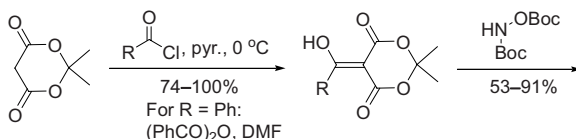


A side reaction:

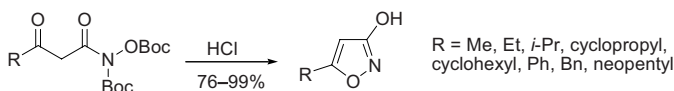
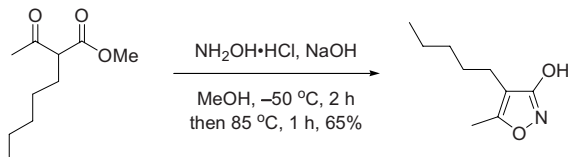


Example 1, A thio-analog⁶



Example 2⁷

Meldrum's acid

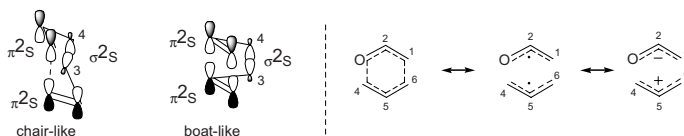
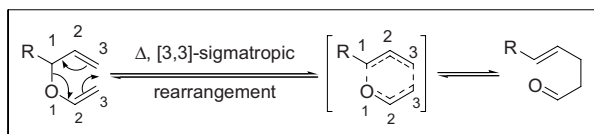
Example 3⁸

References

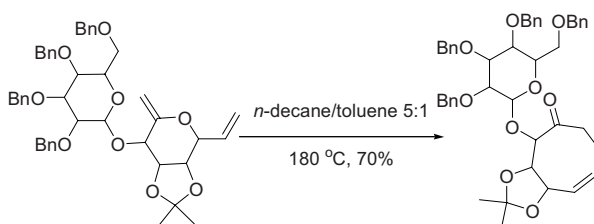
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Claisen rearrangements

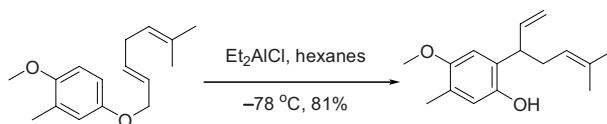
The Claisen, *para*-Claisen rearrangements, Belluś–Claisen rearrangement; Corey–Claisen, Eschenmoser–Claisen rearrangement, Ireland–Claisen, Kazmaier–Claisen, Saucy–Claisen; orthoester Johnson–Claisen, along with the Carroll rearrangement, belong to the category of *[3,3]-sigmatropic rearrangements*. The Claisen rearrangement is a concerted process and the arrow pushing here is merely illustrative.



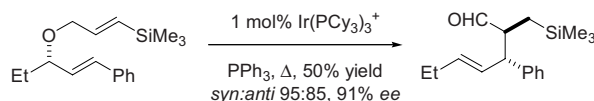
Example 1⁷

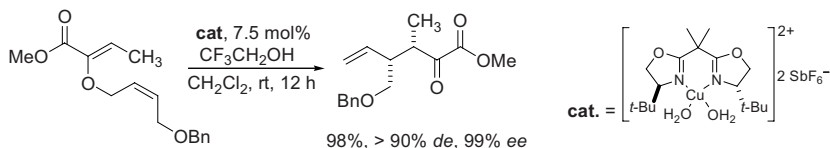
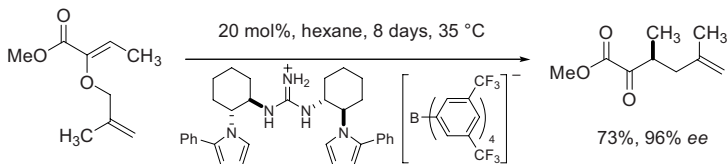


Example 2⁸



Example 3⁹



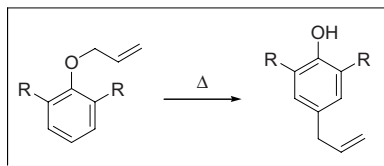
Example 4, Asymmetric Claisen rearrangement¹⁰Example 5, Asymmetric Claisen rearrangement¹¹

References

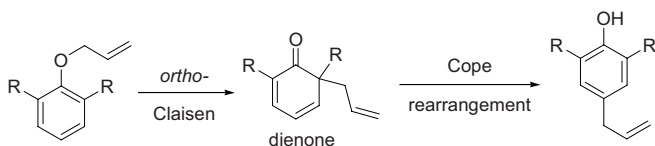
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***para*-Claisen rearrangement**

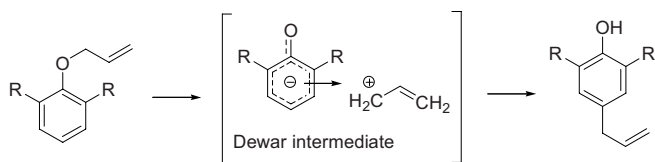
Further rearrangement of the normal *ortho*-Claisen rearrangement product gives the *para*-Claisen rearrangement product.



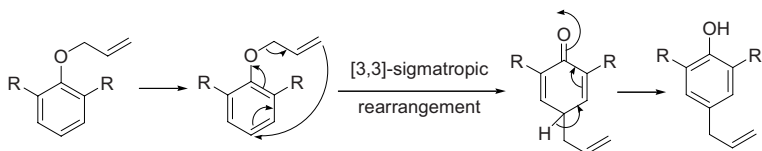
Mechanism 1:

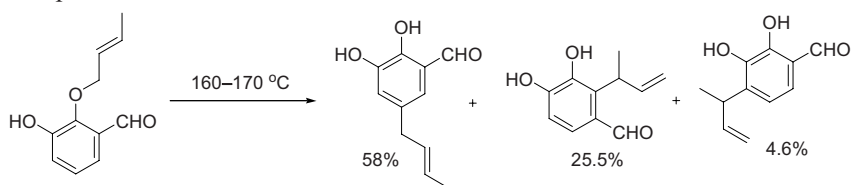
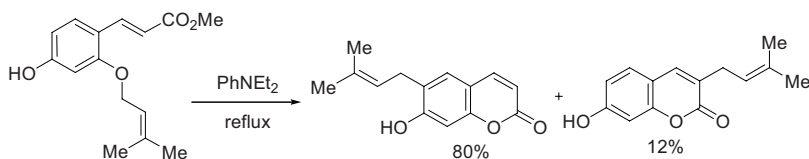
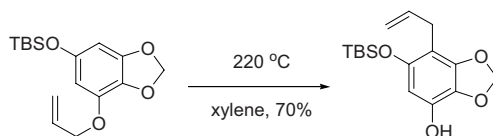
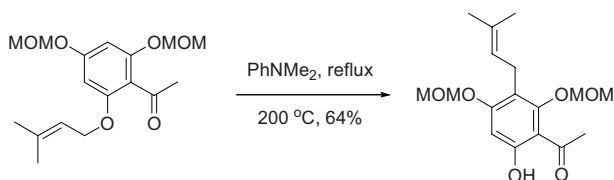


Mechanism 2:



Mechanism 3:



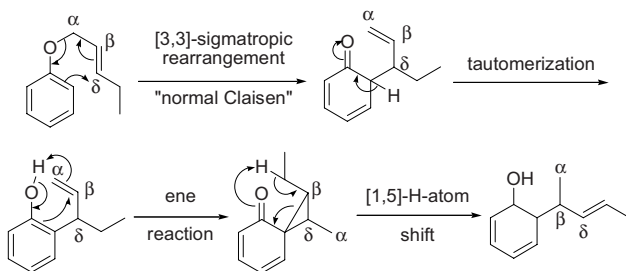
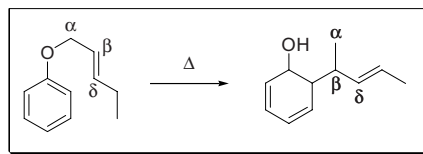
Example 1⁶Example 2⁷Example 3⁸Example 4¹⁰

References

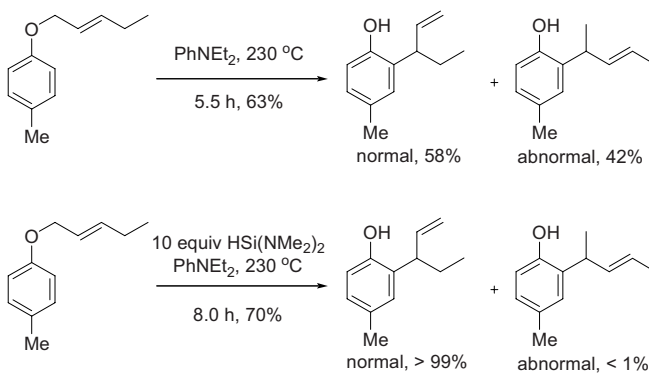
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Abnormal Claisen rearrangement

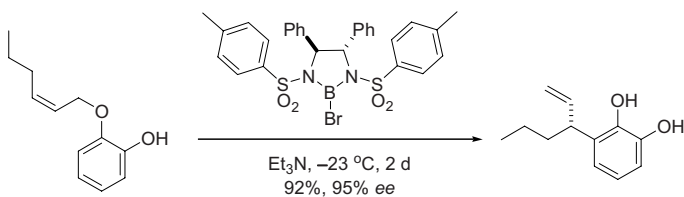
Further rearrangement of the normal Claisen rearrangement product with the β -carbon becoming attached to the ring.

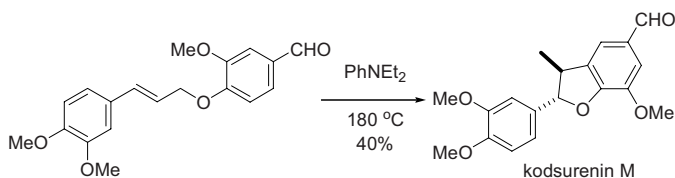
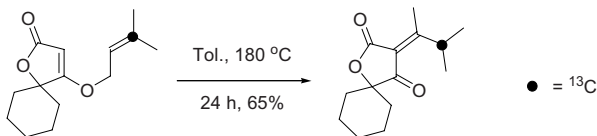
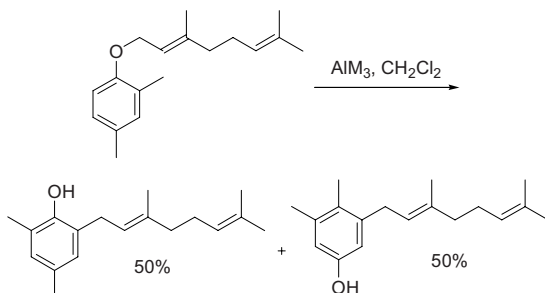


Example 1³



Example 2, Enantioselective aromatic Claisen rearrangement⁴



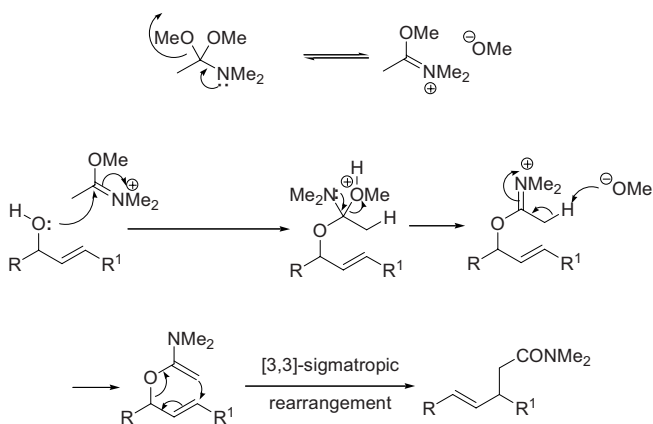
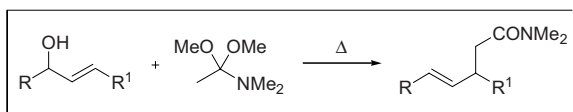
Example 3⁵Example 4⁶Example 5⁷

References

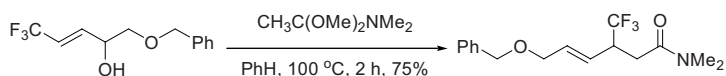
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Eschenmoser–Claisen amide acetal rearrangement

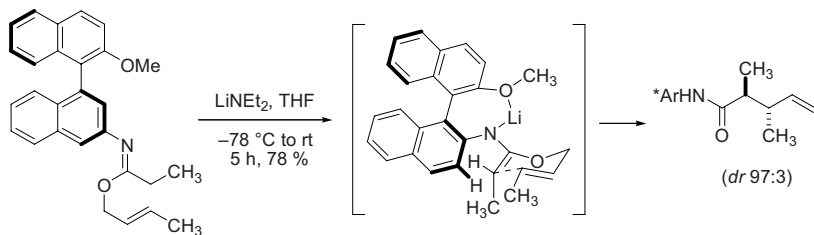
[3,3]-Sigmatropic rearrangement of *N,O*-ketene acetals to yield γ,δ -unsaturated amides. Since Eschenmoser was inspired by Meerwein's observations on the interchange of amide, the Eschenmoser–Claisen rearrangement is sometimes known as the Meerwein–Eschenmoser–Claisen rearrangement.

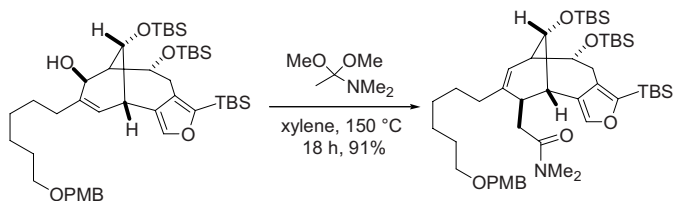
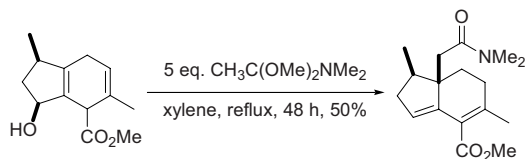


Example 1⁴



Example 2⁵



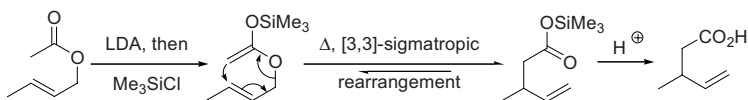
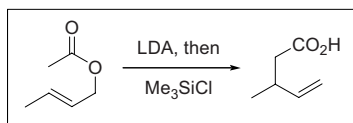
Example 3⁶Example 4⁸

References

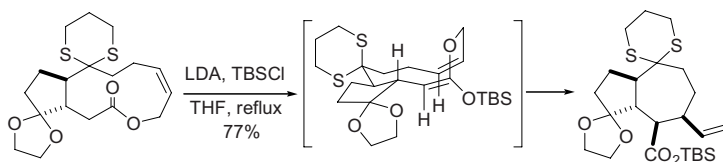
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Ireland–Claisen (silyl ketene acetal) rearrangement

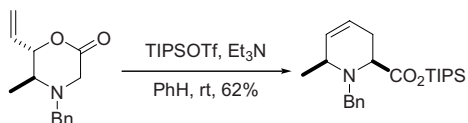
Rearrangement of allyl trimethylsilyl ketene acetal, prepared by reaction of allylic ester enolates with trimethylsilyl chloride, to yield γ,δ -unsaturated carboxylic acids. The Ireland–Claisen rearrangement seems to be advantageous to the other variants of the Claisen rearrangement in terms of *E/Z* geometry control and mild conditions.



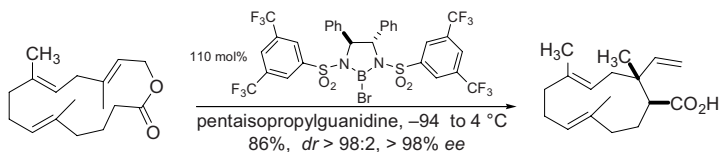
Example 1²

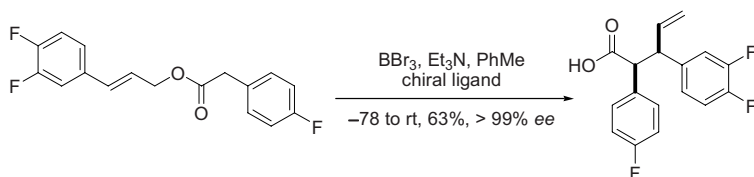
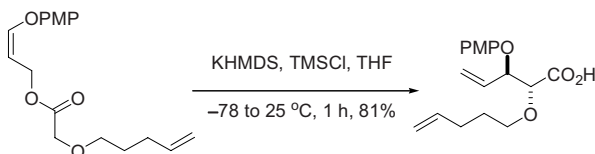


Example 2³



Example 3, Enantioselective ester enolate–Claisen Rearrangement⁶



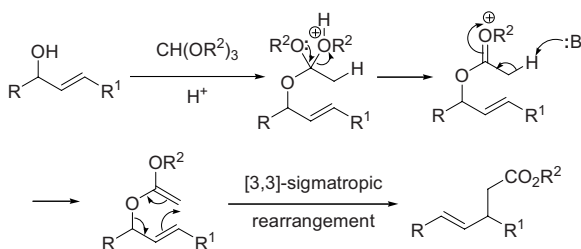
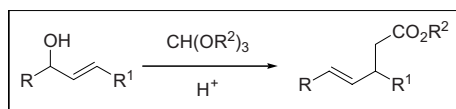
Example 4, A modified Ireland–Claisen rearrangement⁸Example 5⁹

References

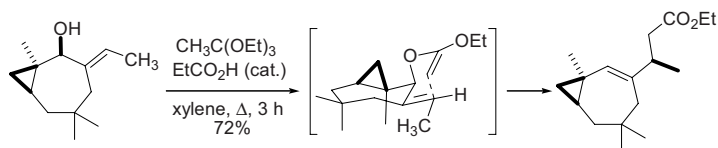
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Johnson–Claisen orthoester rearrangement

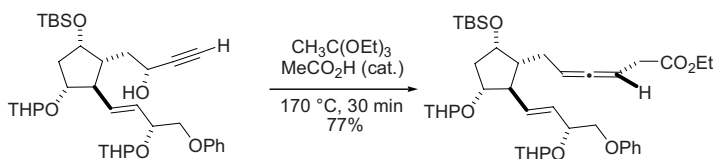
Heating of an allylic alcohol with an excess of trialkyl orthoacetate in the presence of trace amounts of a weak acid gives a mixed orthoester. Mechanistically, the orthoester loses alcohol to generate the ketene acetal, which undergoes [3,3]-sigmatropic rearrangement to give a γ,δ -unsaturated ester.



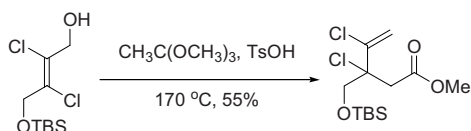
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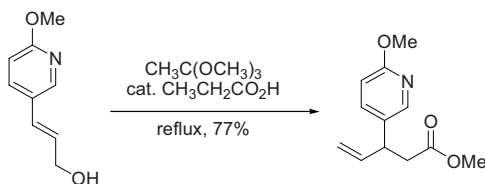
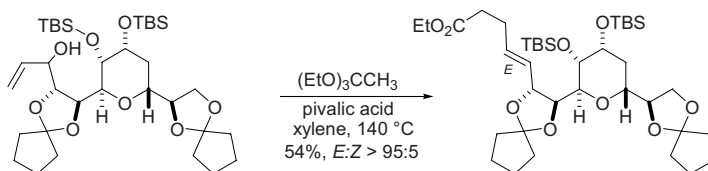


Example 2³



Example 3⁴



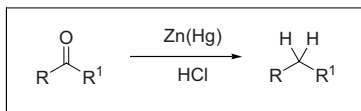
Example 4⁹Example 5¹⁰

References

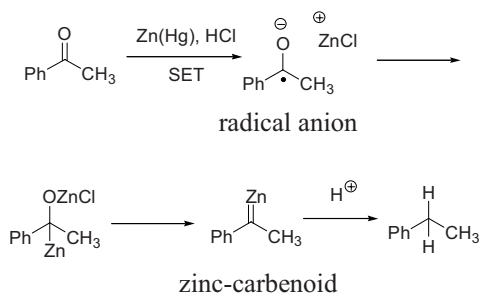
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Clemmensen reduction

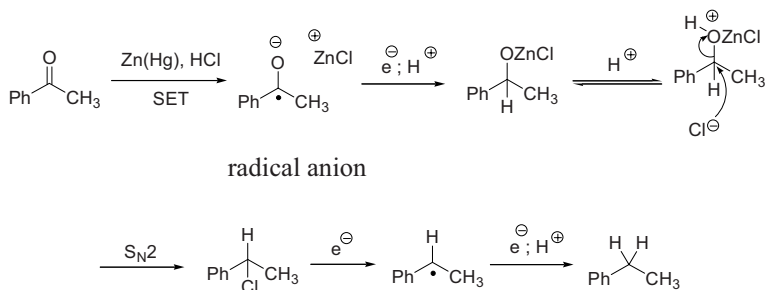
Reduction of aldehydes and ketones to the corresponding methylene compounds using amalgamated zinc in hydrochloric acid.



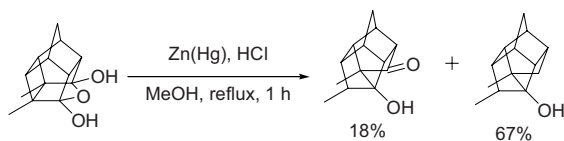
The zinc-carbenoid mechanism:³

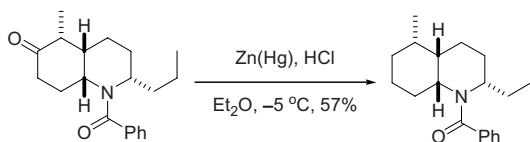
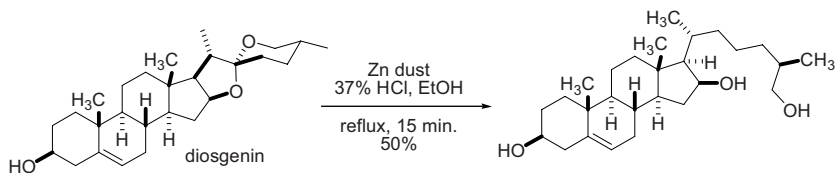


The radical anion mechanism:



Example 1⁵



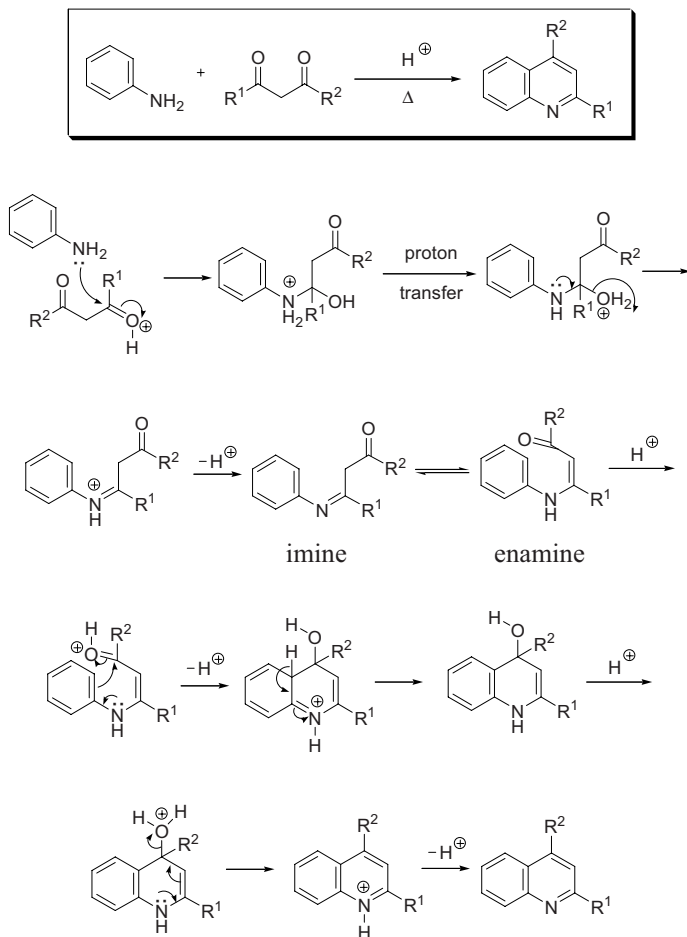
Example 2⁶Example 3⁸

References

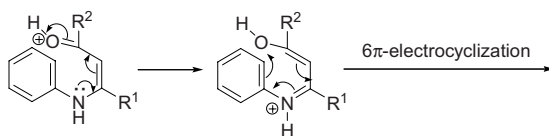
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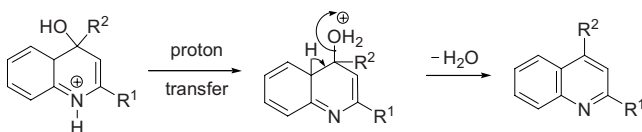
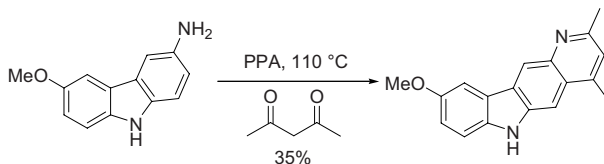
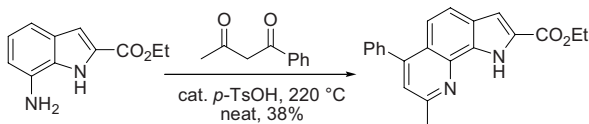
Combes quinoline synthesis

Acid-catalyzed condensation of anilines and β -diketones to assemble quinolines.
Cf. Conrad–Limpach reaction.



An electrocyclization mechanism is also possible:



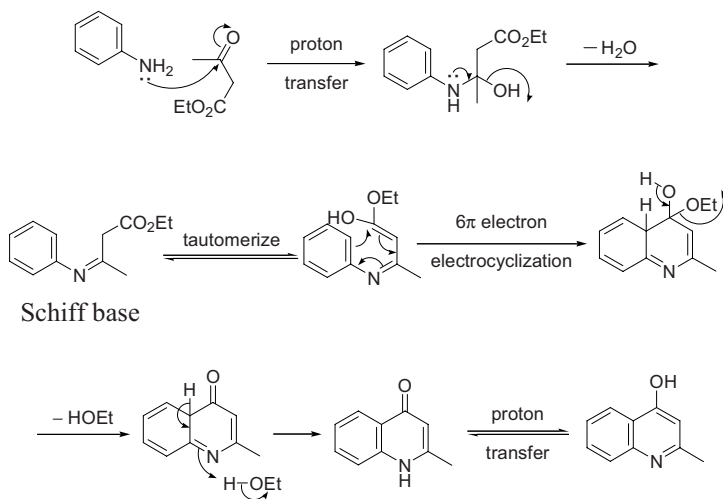
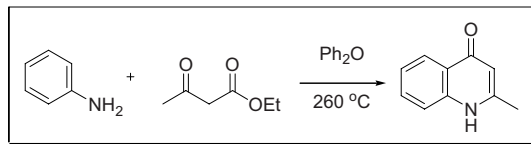
Example 1⁶Example 2⁷

References

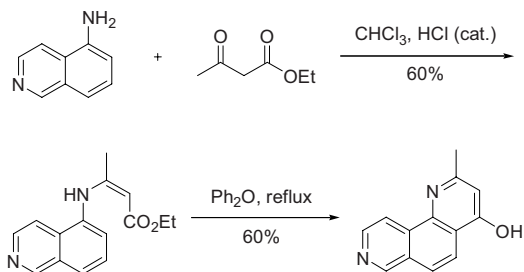
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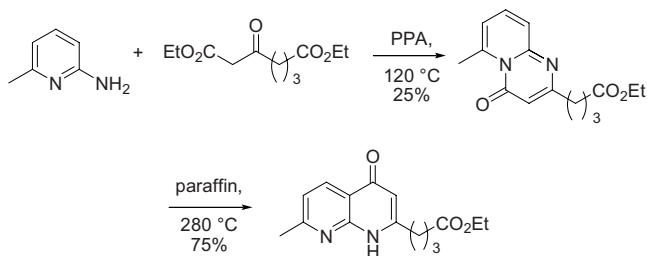
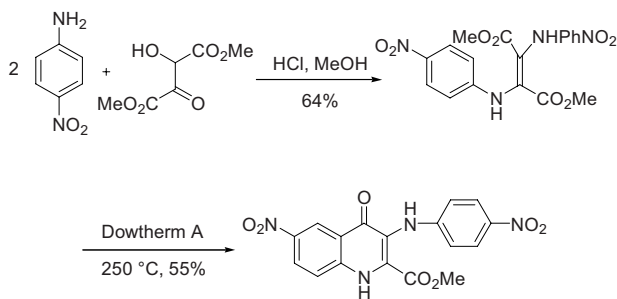
Conrad–Limpach reaction

Thermal or acid-catalyzed condensation of anilines with β -ketoesters leads to quinolin-4-ones. Cf. Combes quinoline synthesis.



Example 1³



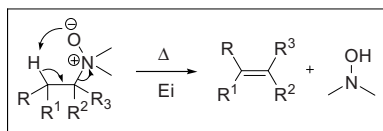
Example 2⁷Example 3⁸

References

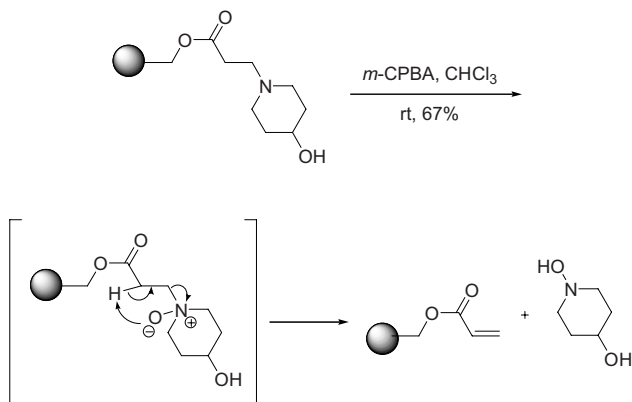
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Cope elimination reaction

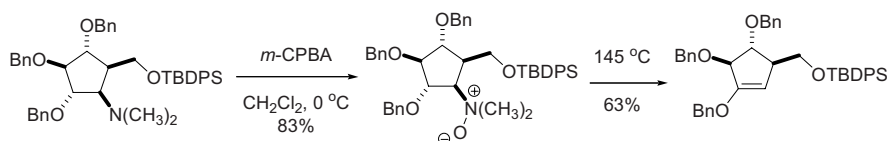
Thermal elimination of *N*-oxides to olefins and *N*-hydroxyl amines.



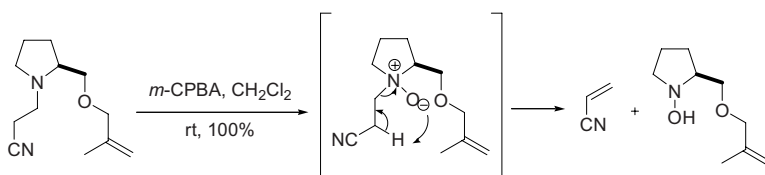
Example 1, Solid-phase Cope elimination⁵

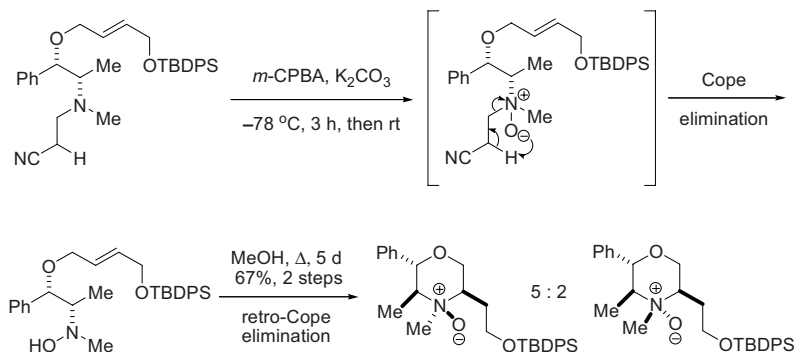


Example 2⁶



Example 3⁸



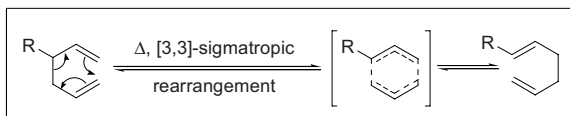
Example 4, Retro-Cope elimination⁹

References

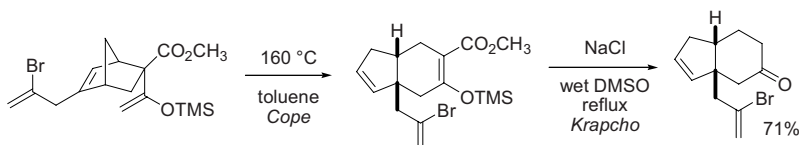
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Cope rearrangement

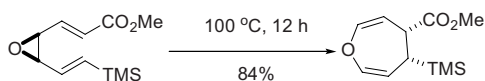
The Cope, oxy-Cope, and anionic oxy-Cope rearrangements belong to the category of *[3,3]-sigmatropic rearrangements*. Since it is a concerted process, the arrow pushing here is only illustrative. This reaction is an equilibrium process. *Cf.* Claisen rearrangement.



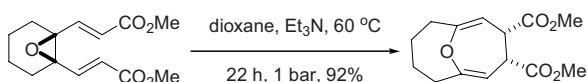
Example 1⁴



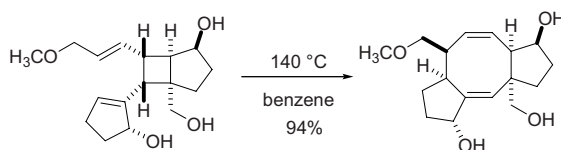
Example 2⁶



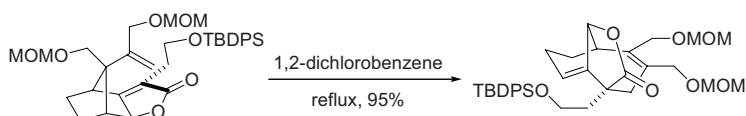
Example 3⁹

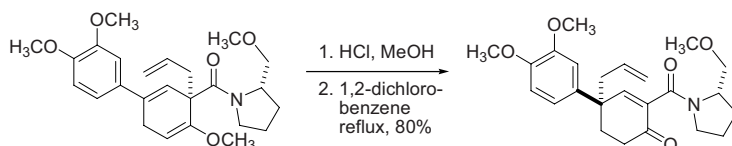


Example 4¹⁰



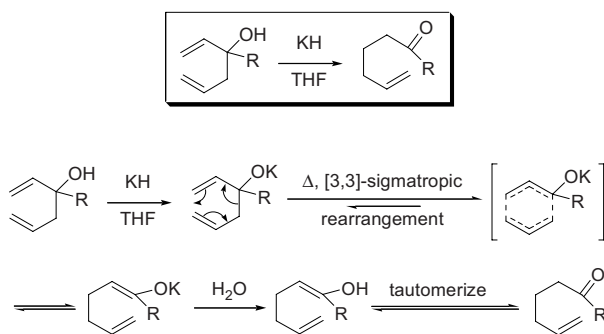
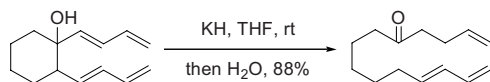
Example 5¹¹

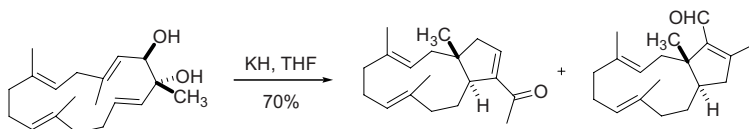
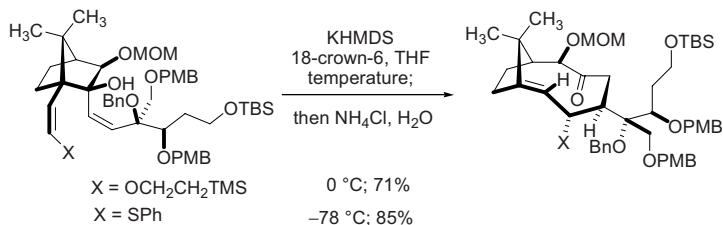
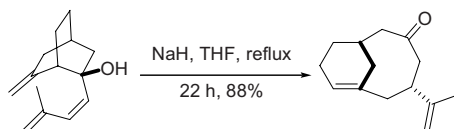
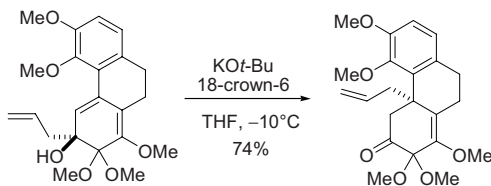


Example 6¹²

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Anionic oxy-Cope rearrangementExample 1¹

Example 2⁴Example 3⁵Example 4⁸Example 5⁹

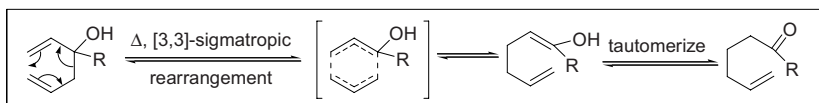
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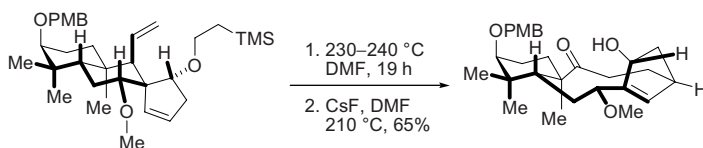
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Oxy-Cope rearrangement

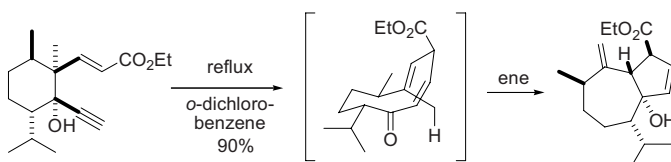
While the anionic oxy-Cope rearrangements work at low temperature, the oxy-Cope rearrangements require high temperature but provide a thermodynamic sink.



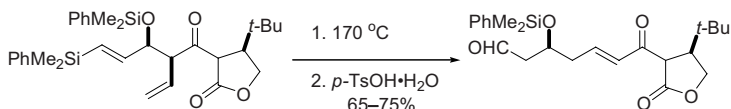
Example 1²



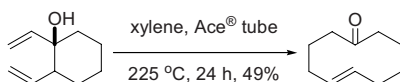
Example 2³



Example 3⁴

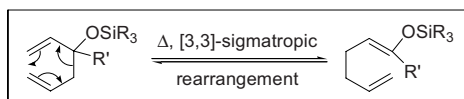
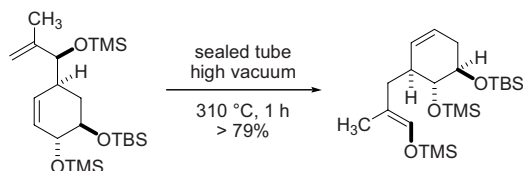
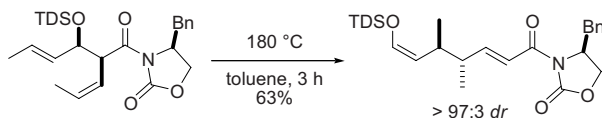


Example 4⁶

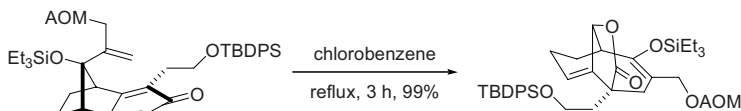


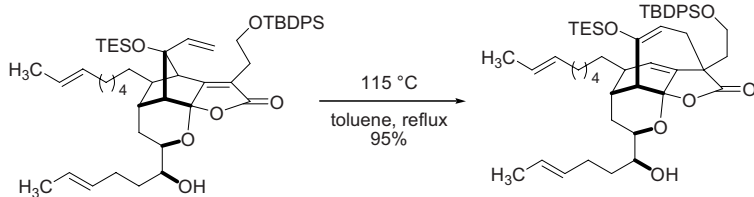
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Siloxy-Cope rearrangementExample 1¹Example 2²

TDS = hexyldimethylsilyl

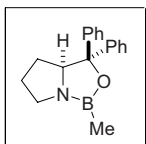
Example 3³AOM = *p*-Anisylloxymethyl = *p*-MeOC₆H₄OCH₂-

Example 4⁴

References

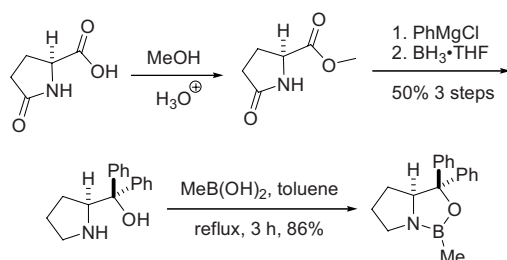
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Corey–Bakshi–Shibata (CBS) reagent

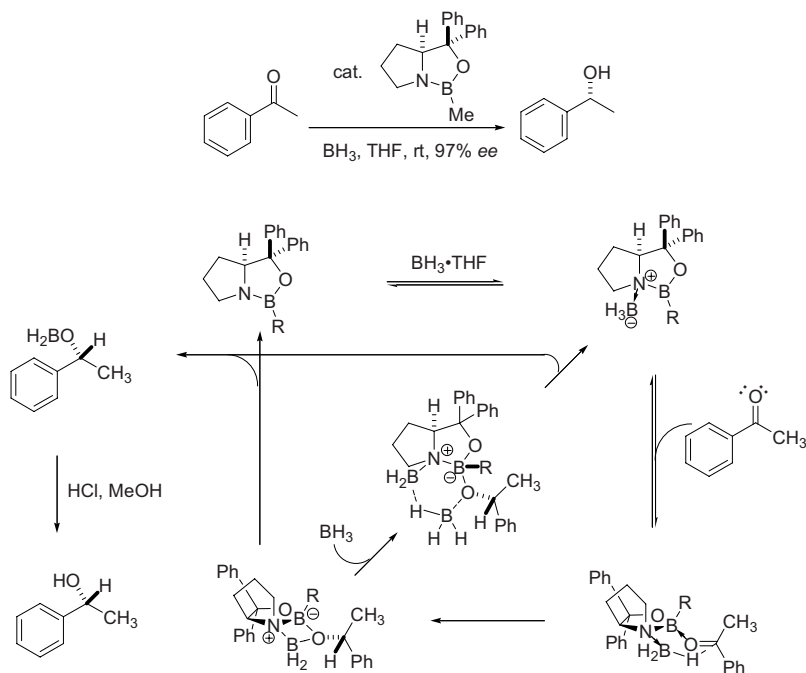


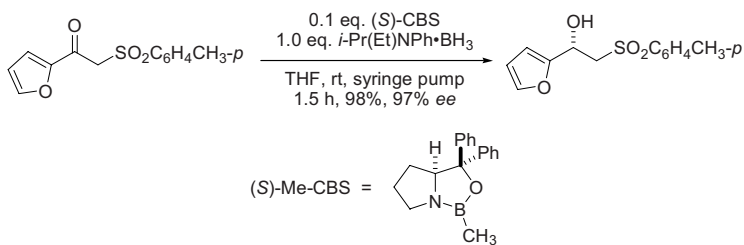
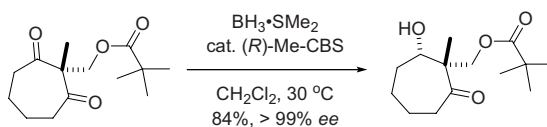
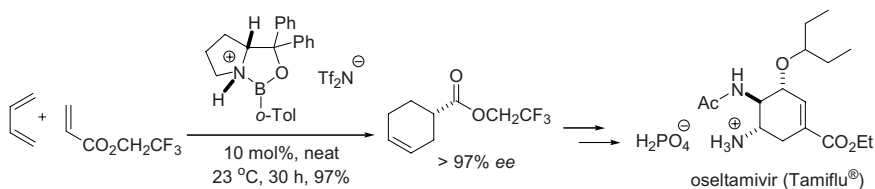
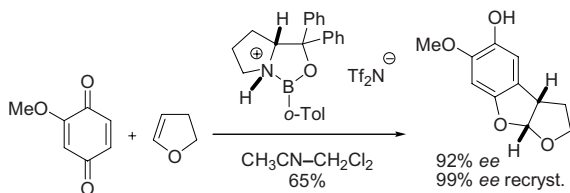
The CBS (Corey–Bakshi–Shibata) reagent is a chiral catalyst derived from proline. Also known as Corey's oxazaborolidine, it is used in enantioselective borane reduction of ketones, asymmetric Diels–Alder reactions and [3 + 2] cycloadditions.

Preparation^{1,3}



The mechanism and catalytic cycle:^{1,3}



Example 1⁶Example 2⁹Example 3¹¹Example 4, Asymmetric [3 + 2]-cycloaddition¹⁰

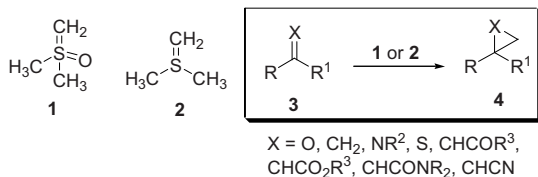
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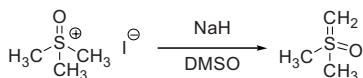
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Corey–Chaykovsky reaction

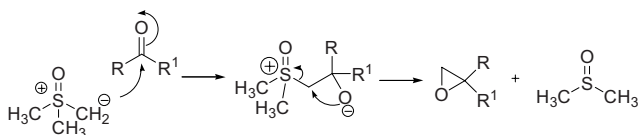
The Corey–Chaykovsky reaction entails the reaction of a sulfur ylide, either dimethylsulfoxonium methylide **1** (Corey's ylide) or dimethylsulfonium methylide **2**, with electrophile **3** such as carbonyl, olefin, imine, or thiocarbonyl, to offer **4** as the corresponding epoxide, cyclopropane, aziridine, or thiirane.



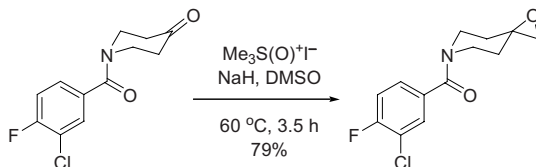
Preparation¹



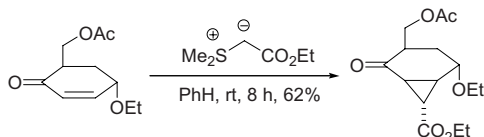
Mechanism¹



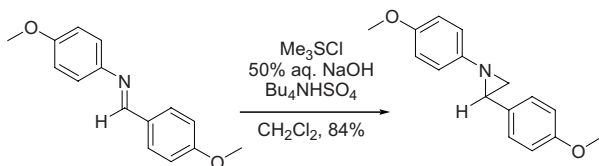
Example 1¹¹

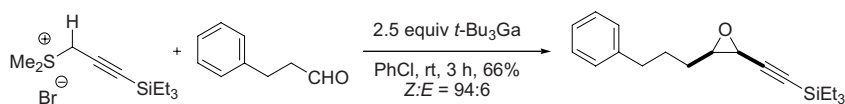
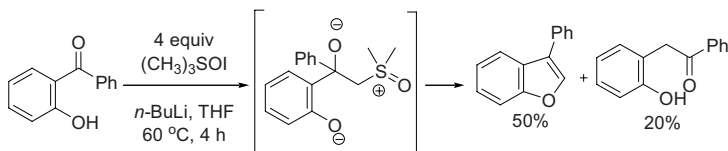


Example 2⁹



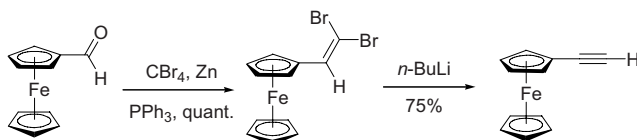
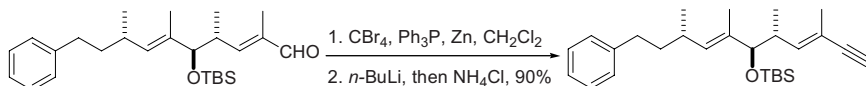
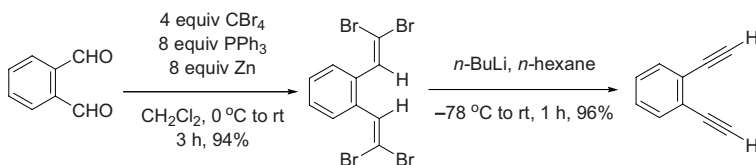
Example 3¹⁰



Example 4¹⁴Example 5¹⁵

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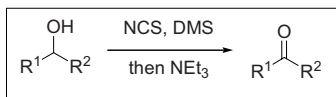
Example 2⁷Example 3⁸Example 4¹⁰

References

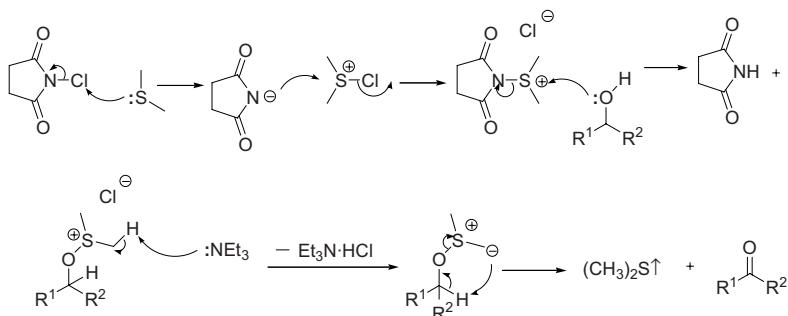
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- 2 For the synthesis of 1-bromalkynes see Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, 35, 3529–3530.
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Corey–Kim oxidation

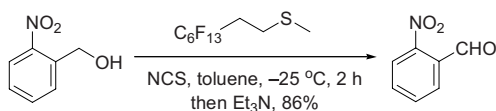
Oxidation of alcohol to the corresponding aldehyde or ketone using NCS/DMS, followed by treatment with a base. *Cf.* Swern oxidation.



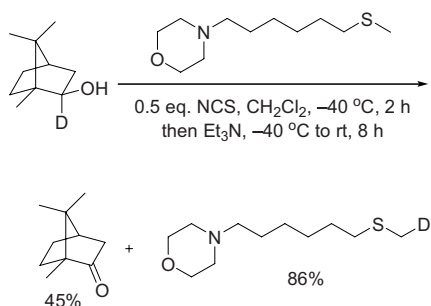
NCS = *N*-Chlorosuccinimide; DMS = Dimethylsulfide.

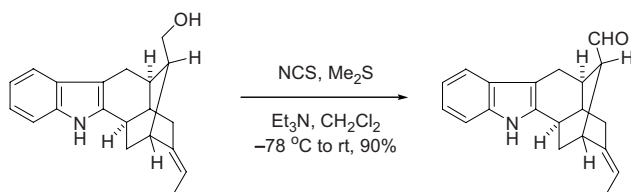
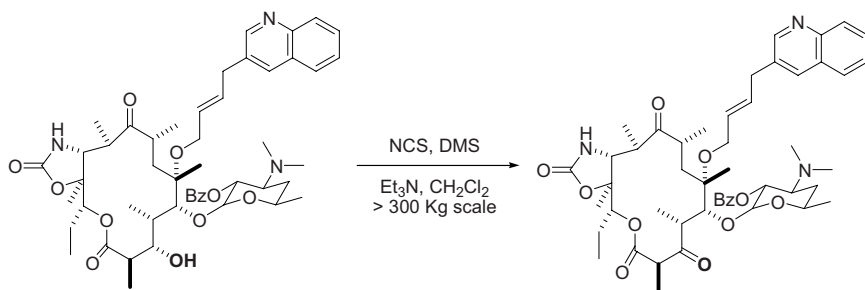


Example 1, Fluorous Corey–Kim reaction⁵



Example 2, Odorless Corey–Kim reaction⁷



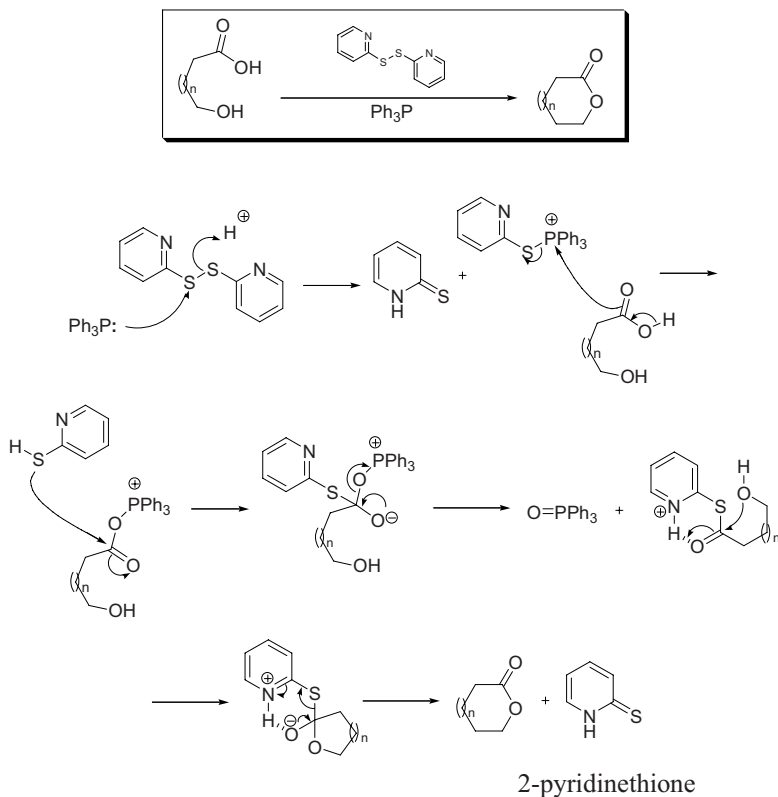
Example 3⁹Example 4¹⁰

References

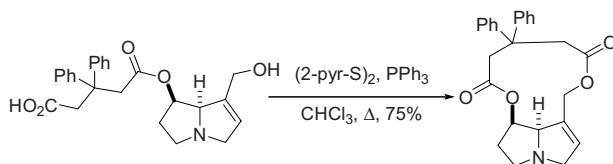
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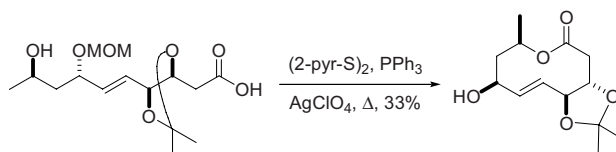
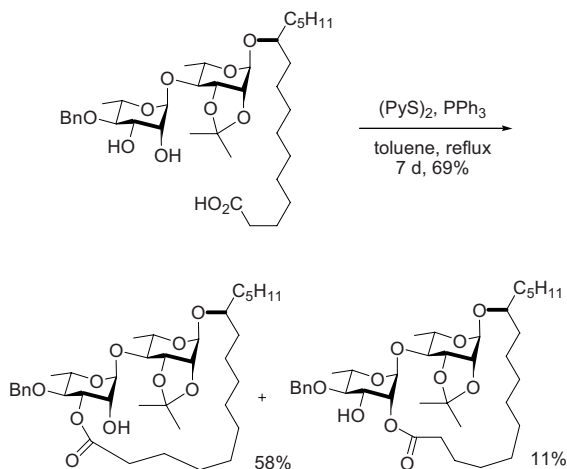
Corey–Nicolaou macrolactonization

Macrolactonization of ω -hydroxyl-acid using 2,2'-dipyridyl disulfide. Also known as the Corey–Nicolaou double activation method.



Example 1³



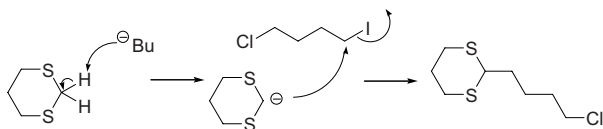
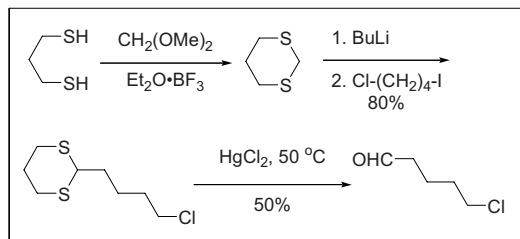
Example 2⁶Example 3⁹

References

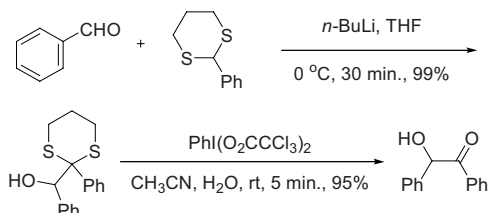
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Corey–Seebach reaction

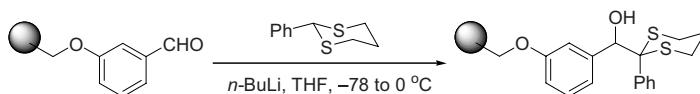
Dithiane as a nucleophile, serving as a masked carbonyl equivalent. This is an example of umpolung.



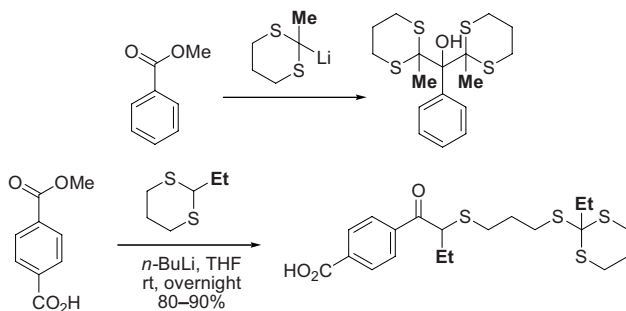
Example 1²

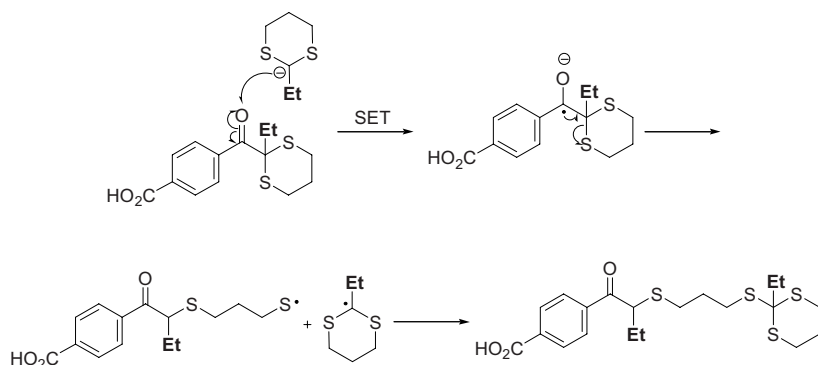
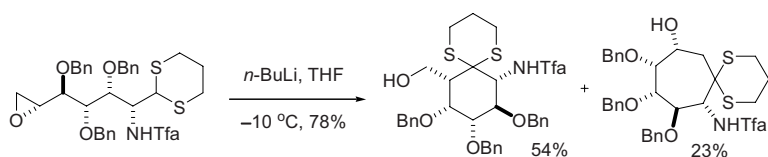


Example 2⁴

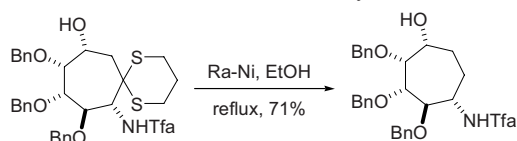


Example 3, Ethyl is infinitely different from methyl⁶



Example 4⁸

Tfa = Trifluoroacetyl

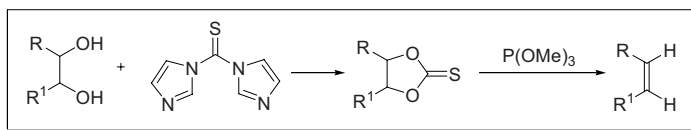


References

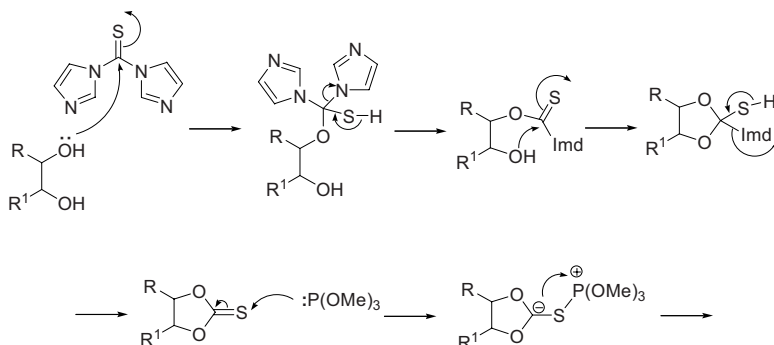
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Corey–Winter olefin synthesis

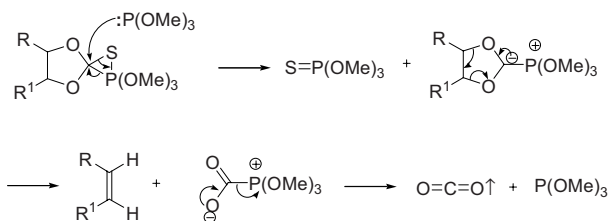
Transformation of diols to the corresponding olefins by sequential treatment with 1,1'-thiocarbonyldiimidazole (TCDI) and trimethylphosphite. Also known as Corey–Winter reductive elimination, or Corey–Winter reductive olefination.



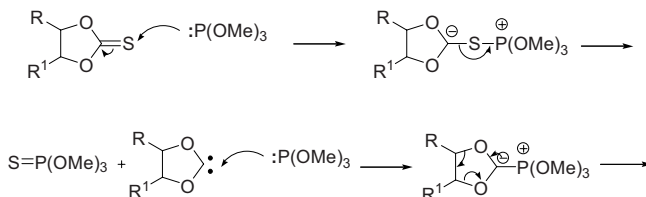
TCDI = Thiocarbonyldiimidazole

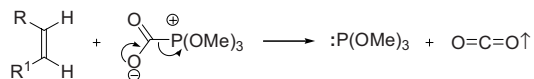
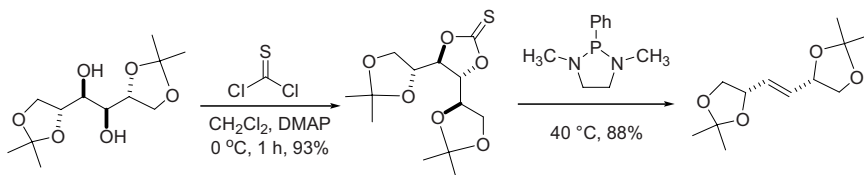
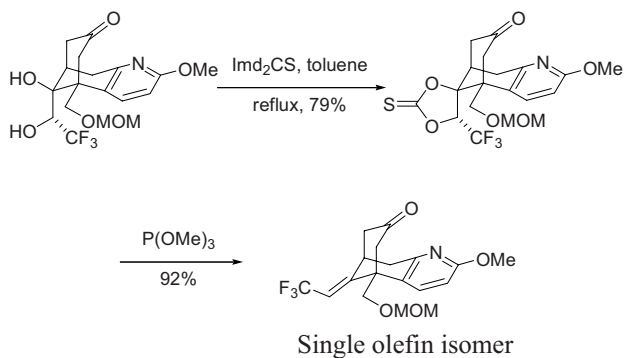
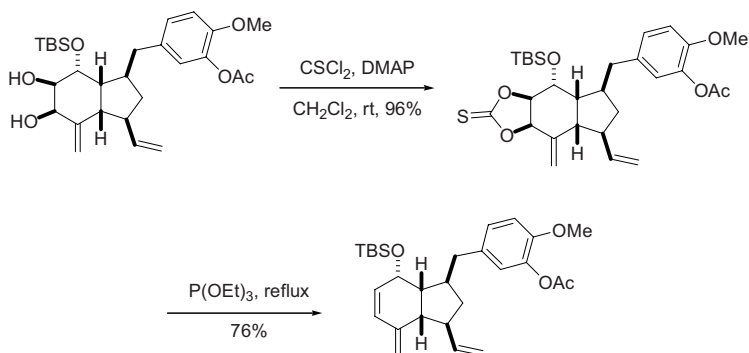


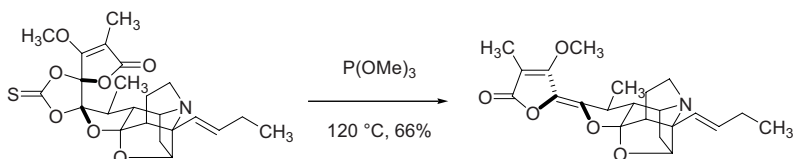
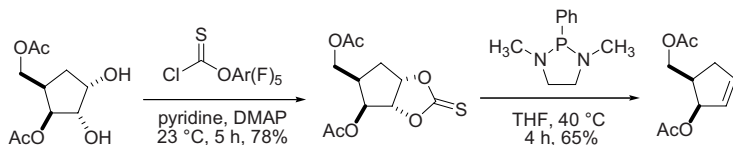
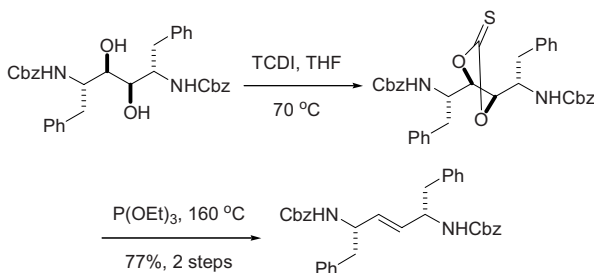
1,3-dioxolane-2-thione (cyclic thiocarbonate)



A mechanism involving a carbene intermediate can also be drawn and is supported by pyrolysis studies:



Example 1²Example 2⁴Example 3⁸

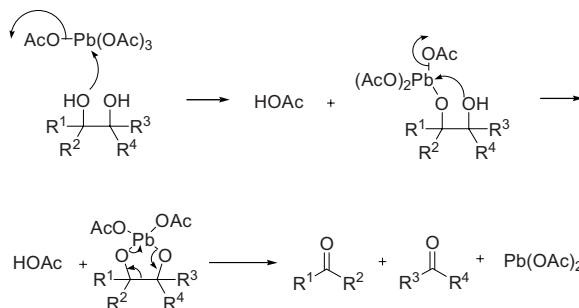
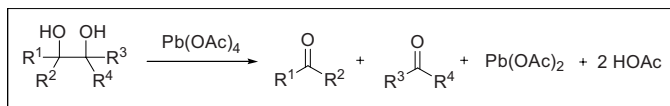
Example 4⁹Example 5¹⁰Example 6¹¹

References

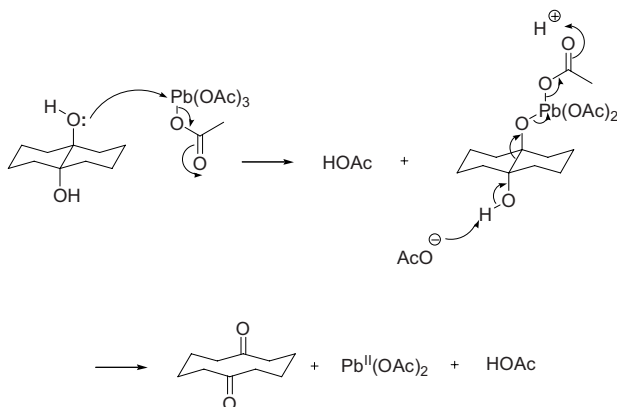
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Criegee glycol cleavage

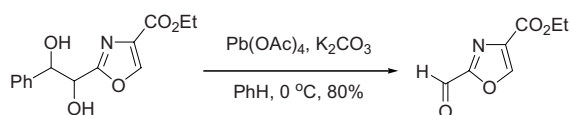
Vicinal diol is oxidized to the two corresponding carbonyl compounds using $\text{Pb}(\text{OAc})_4$ (lead tetraacetate, LTA).

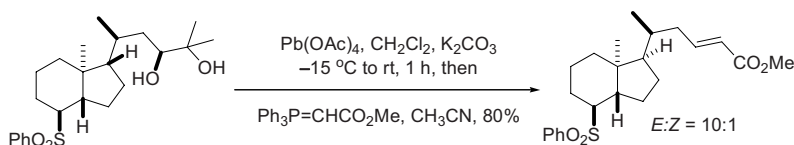
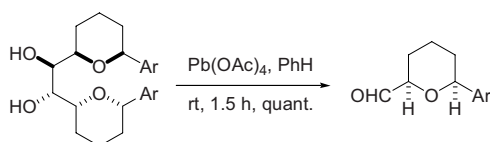
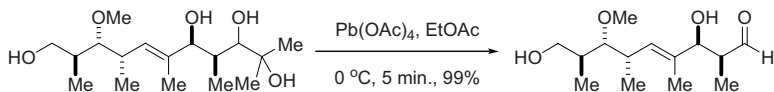


An acyclic mechanism is possible as well. It is much slower than the cyclic mechanism, but is operative when the cyclic intermediate can not form.³



Example 1⁷

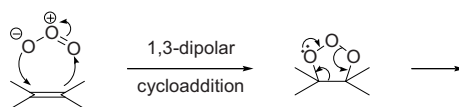
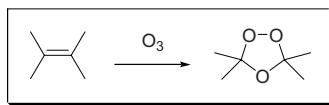


Example 2⁹Example 3¹⁰Example 4¹¹

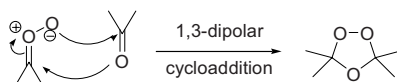
References

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Criegee mechanism of ozonolysis



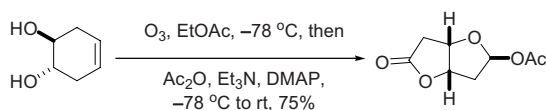
primary ozonide (1,2,3-trioxolane)



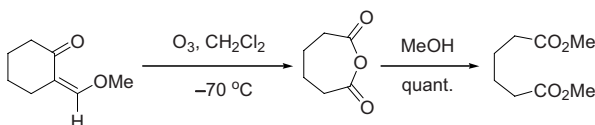
zwitterionic peroxide (Criegee zwitterion)
also known as “carbonyl oxide”

secondary ozonide (1,2,4-trioxolane)

Example 1⁷



Example 2⁸

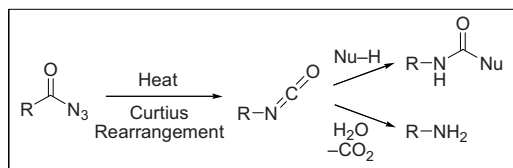


References

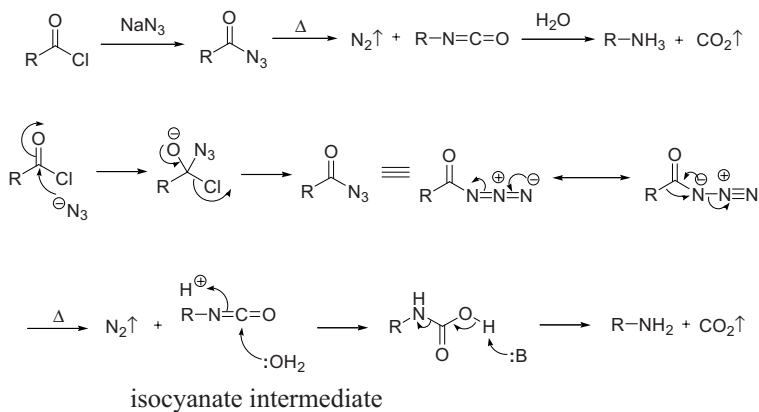
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Curtius rearrangement

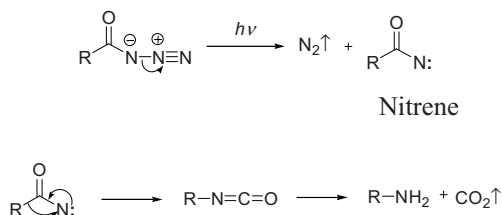
Alkyl-, vinyl-, and aryl-substituted acyl azides undergo thermal 1,2-carbon-to-nitrogen migration with extrusion of dinitrogen — the Curtius rearrangement — producing isocyanates. Reaction of the isocyanate products with nucleophiles, often *in situ*, provides carbamates, ureas, and other *N*-acyl derivatives. Alternatively, hydrolysis of the isocyanates leads to primary amines.

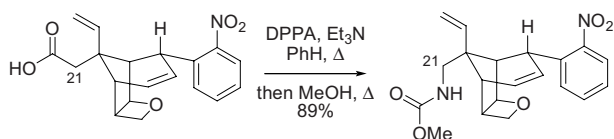


The thermal rearrangement:

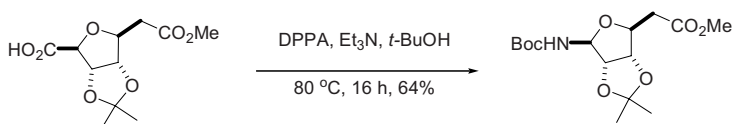
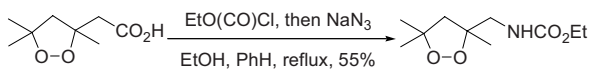
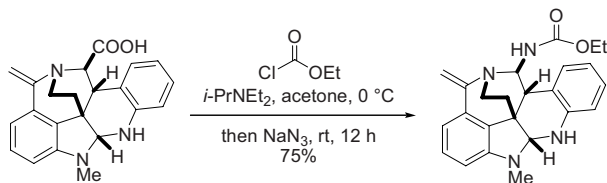
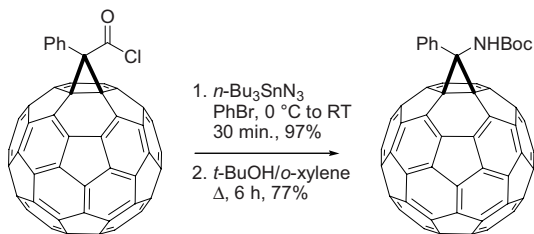


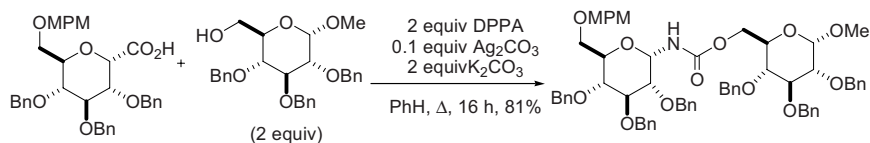
The photochemical rearrangement:



Example 1, The Shioiri–Ninomiya–Yamada modification²

DPPA = diphenylphosphoryl azide

Example 2³Example 3⁴Example 4, The Weinstock variant of the Curtius rearrangement⁶Example 5⁷

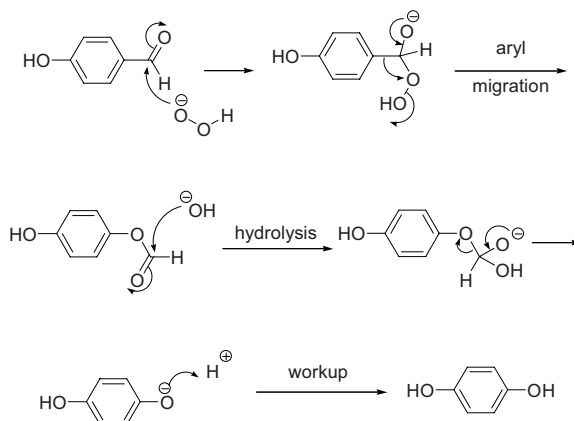
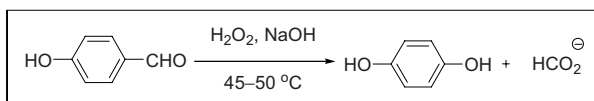
Example 6, The Lebel modification⁸

References

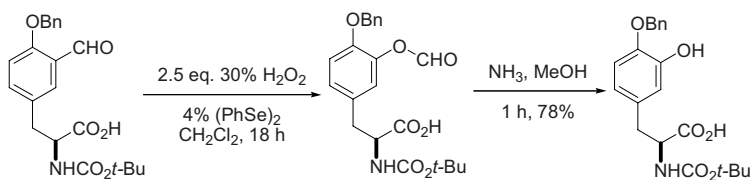
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Dakin oxidation

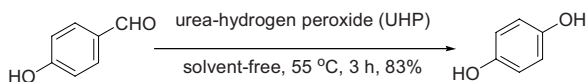
Oxidation of aryl aldehydes or aryl ketones to phenols using basic hydrogen peroxide conditions. *Cf.* A variant of Baeyer–Villiger oxidation.



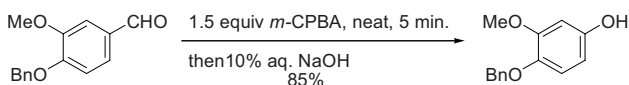
Example 1⁶

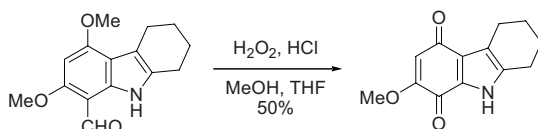


Example 2⁷



Example 3, Improved solvent-free Dakin oxidation protocol⁹



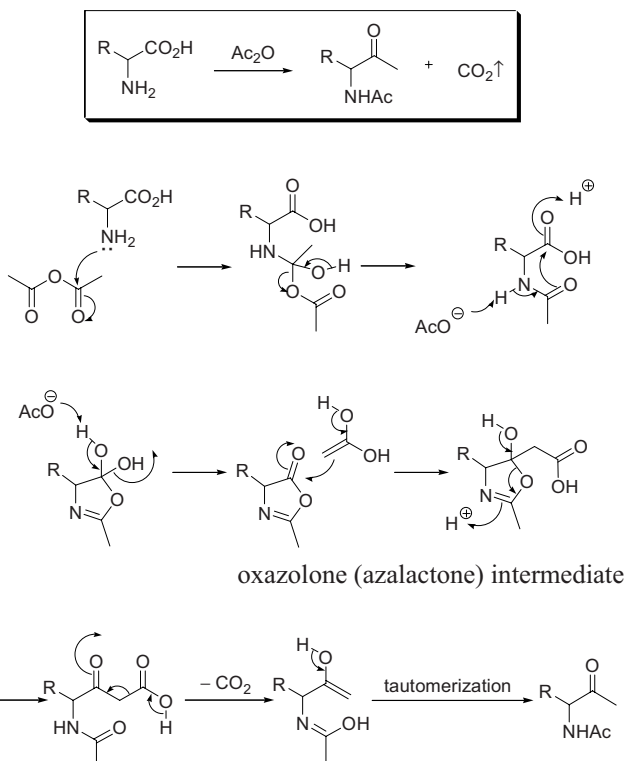
Example 4¹⁰

References:

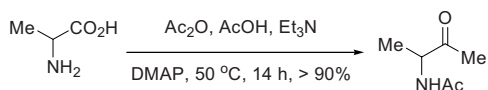
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Dakin–West reaction

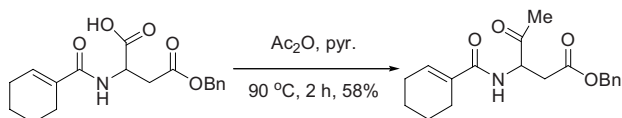
The direct conversion of an α -amino acid into the corresponding α -acetyl-amino-alkyl methyl ketone, *via* oxazoline (azalactone) intermediates. The reaction proceeds in the presence of acetic anhydride and a base, such as pyridine, with the evolution of CO_2 .



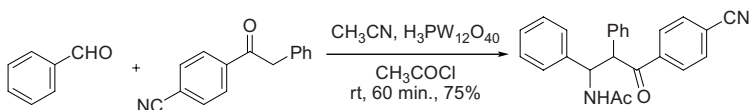
Example 1⁶



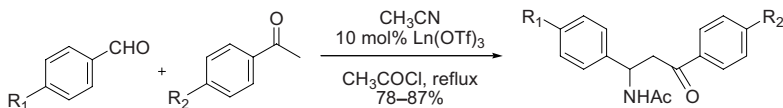
Example 2⁷



Example 3, Green Dakin–West reaction using the heteropoly acid catalyst, acetonitrile is a reactant⁹



Example 4, Acetonitrile is a reactant¹⁰

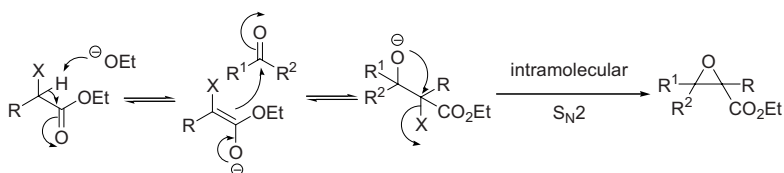
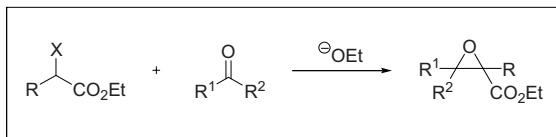


References:

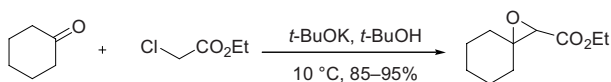
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Darzens condensation

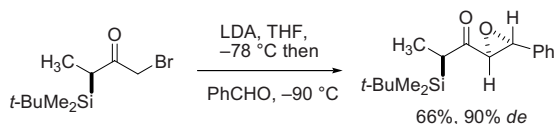
α,β -Epoxy esters (glycidic esters) from base-catalyzed condensation of α -haloesters with carbonyl compounds.



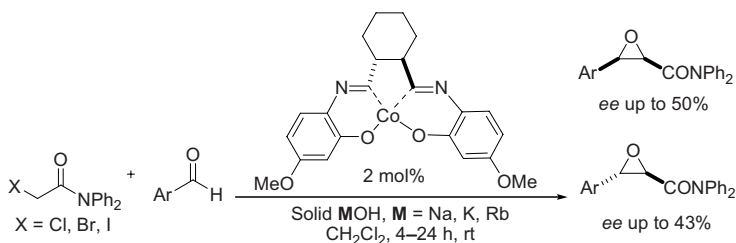
Example 1⁴



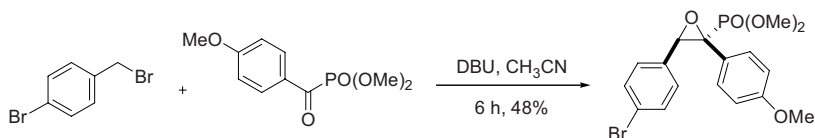
Example 2⁶



Example 3⁹



Example 4, the phenyl ring substituting for the carbonyl to acidify the protons¹⁰



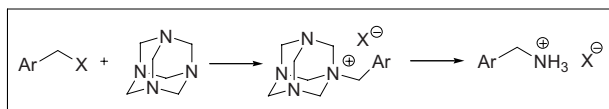
References

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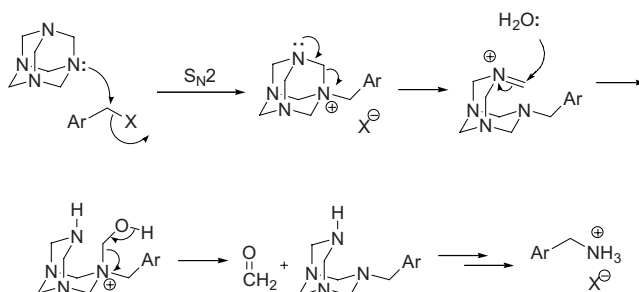
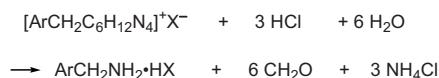
Delépine amine synthesis

The reaction between alkyl halides and hexamethylenetetramine, followed by cleavage of the resulting salt with ethanolic HCl to yield primary amines.

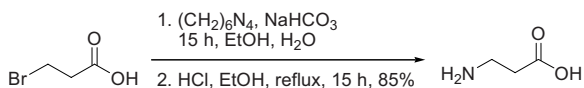
Cf. Gabriel synthesis, where the product is also an amine and Sommelet reaction, where the product is an aldehyde. The Delépine works well for active halides such as benzyl, allyl halides, and α -halo-ketones.



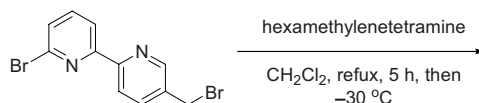
hexamethylenetetramine

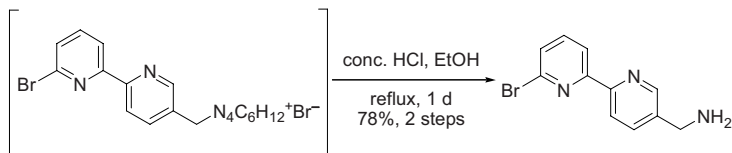
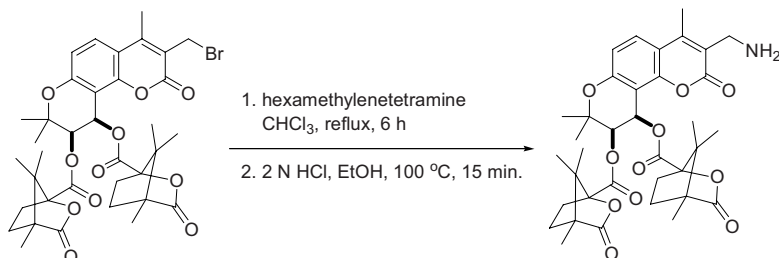
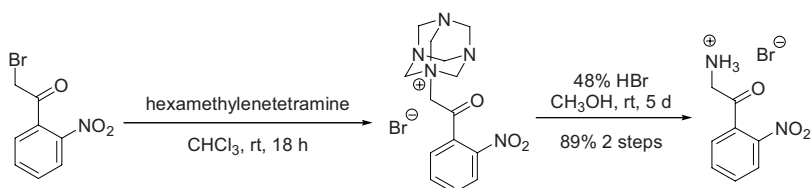


Example 1³



Example 2⁷



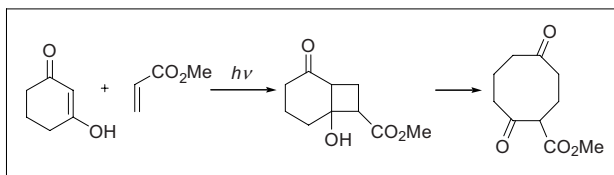
Example 3⁸Example 4⁹

References

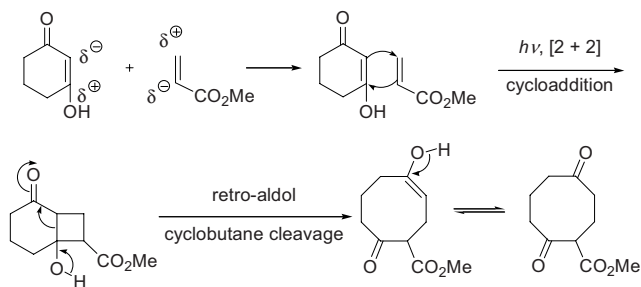
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de Mayo reaction

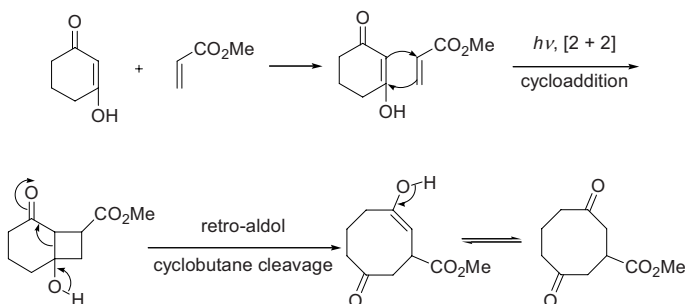
[2 + 2]-Photochemical cyclization of enones with olefins is followed by a retro-aldol reaction to give 1,5-diketones.



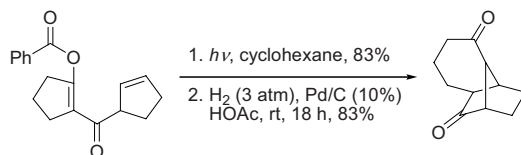
Head-to-tail alignment gives the major product:

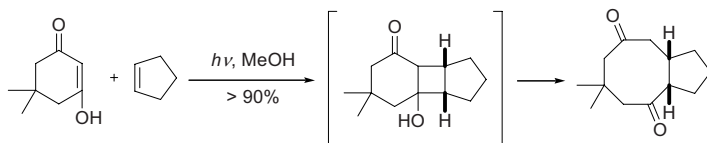
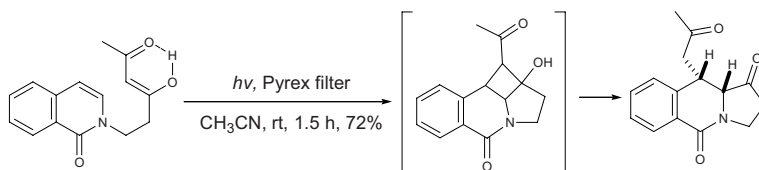
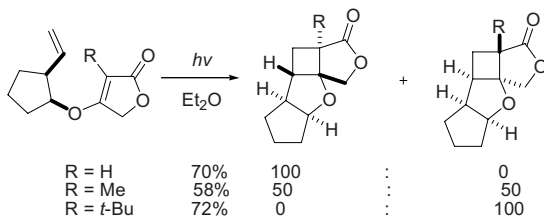


Head-to-head alignment gives the minor regioisomer:



Example 1³



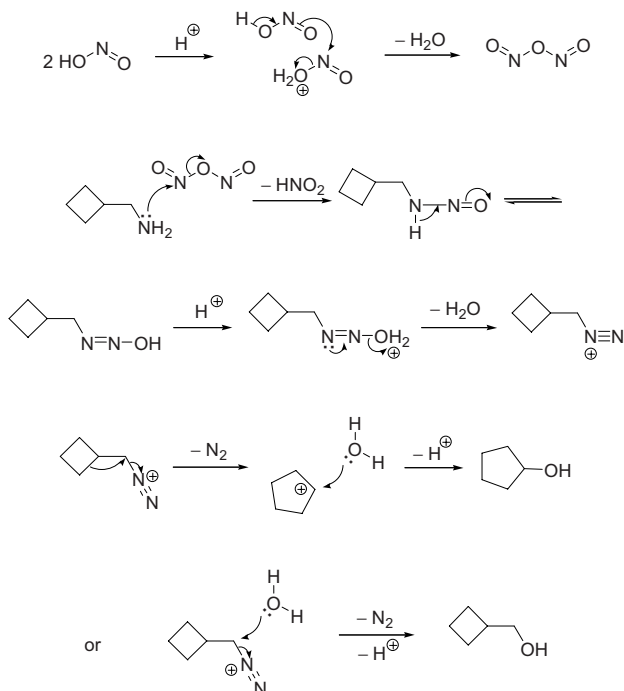
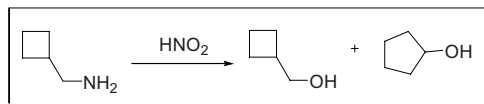
Example 2⁶Example 3⁹Example 4¹⁰

References

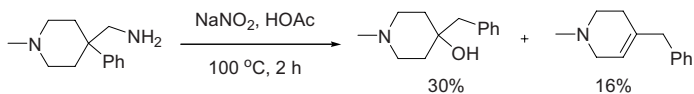
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Demjanov rearrangement

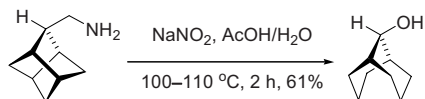
Carbocation rearrangement of primary amines *via* diazotization to give alcohols through C–C bond migration.

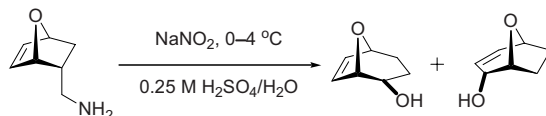
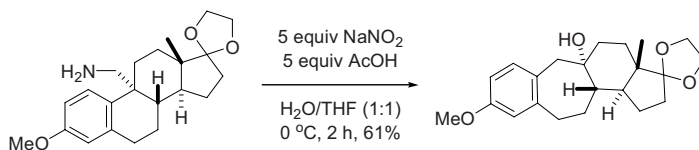


Example 1³



Example 2⁶



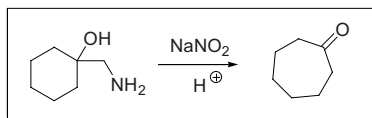
Example 3⁷Example 4⁸

References

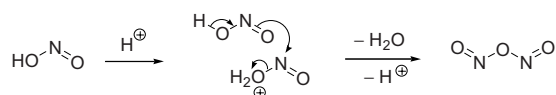
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Tiffeneau–Demjanov rearrangement

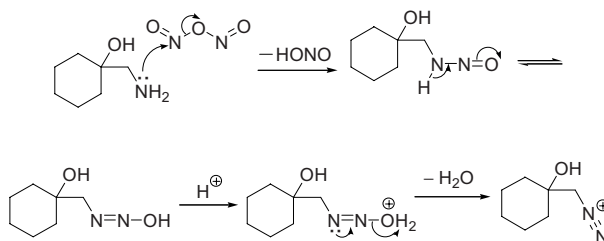
Carbocation rearrangement of β -aminoalcohols *via* diazotization to afford carbonyl compounds through C–C bond migration.



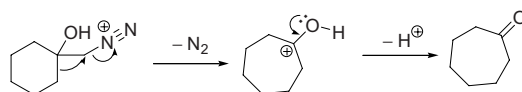
Step 1, Generation of N_2O_3



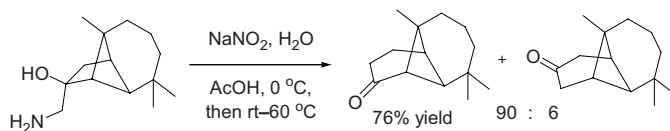
Step 2, Transformation of amine to diazonium salt

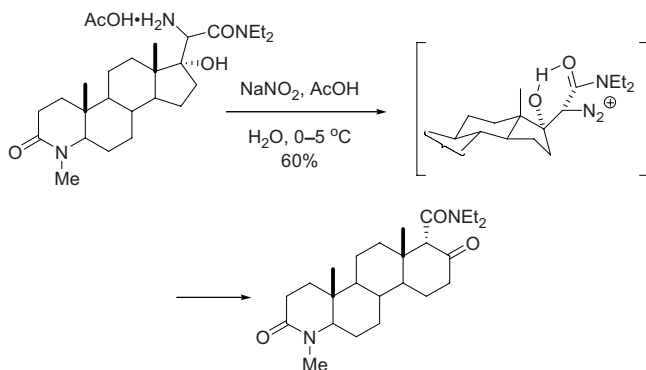
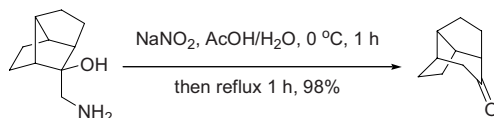
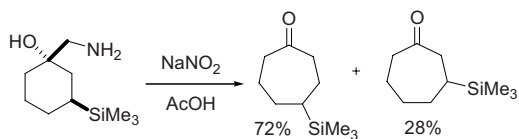


Step 3, Ring-expansion *via* rearrangement



Example 1⁵



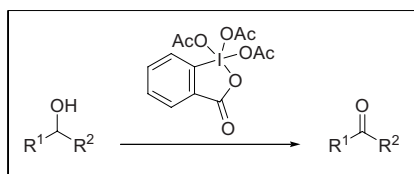
Example 2⁶Example 3⁷Example 4⁹

References

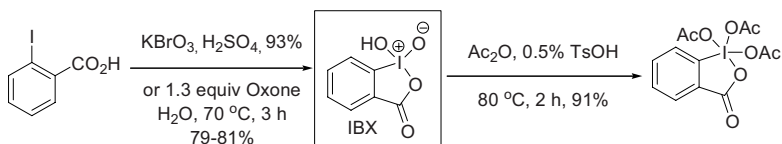
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Dess–Martin periodinane oxidation

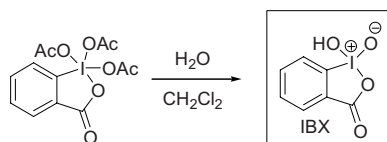
Oxidation of alcohols to the corresponding carbonyl compounds using triacetoxyperiodinane. The Dess–Martin periodinane, 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, is one of the most useful oxidant for the conversion of primary and secondary alcohols to their corresponding aldehyde or ketone products, respectively.



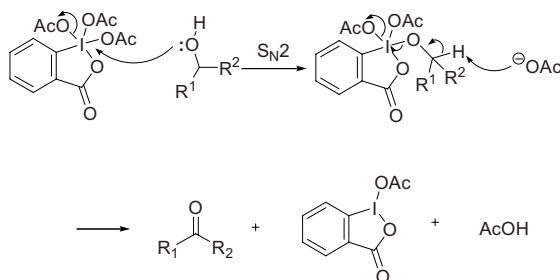
Preparation,^{1,2} The oxone preparation is much safer and easier than KBrO_3 . The IBX intermediate that comes out of it has proven to be far less explosive¹²

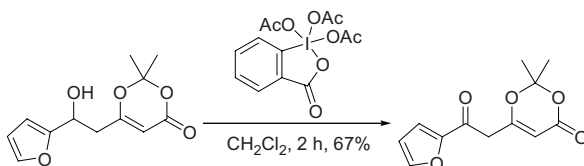
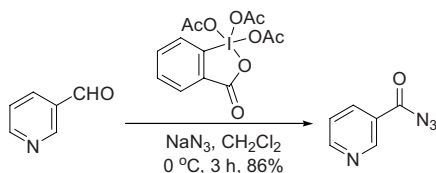
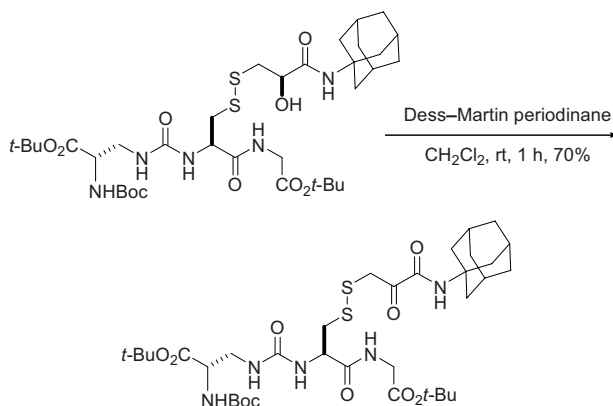
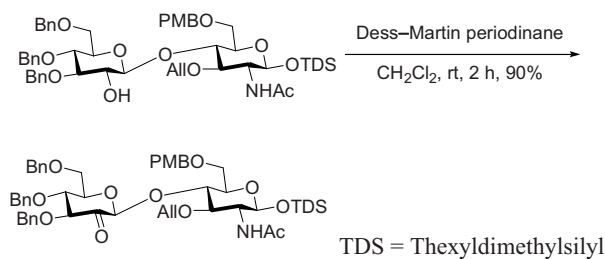


However, The Dess–Martin periodinane is hydrolyzed by moisture to *o*-iodoxybenzoic acid (IBX), which is a more powerful oxidizing agent³



Mechanism¹



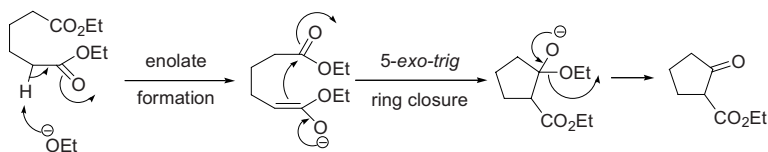
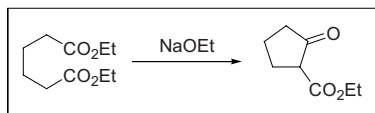
Example 1⁶Example 2, An atypical Dess–Martin periodinane reactivity⁷Example 3¹⁰Example 4¹¹

References

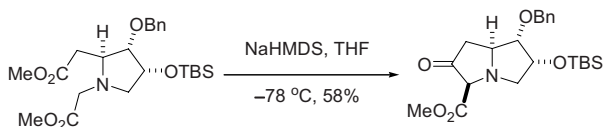
1. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. James Cullen (J. C.) Martin (1928–1999) had a distinguished career spanning 36 years both at the University of Illinois at Urbana-Champaign and Vanderbilt University. J. C.’s formal training in physical organic chemistry with Don Pearson at Vanderbilt and P. D. Bartlett at Harvard prepared him well for his early studies on carbocations and radicals. However, it was his interest in understanding the limits of chemical bonding that led to his landmark investigations into hypervalent compounds of the main group elements. Over a 20-year period the Martin laboratories successfully prepared unprecedented chemical structures from sulfur, phosphorus, silicon and bromine while the ultimate “Holy Grail” of stable pentacoordinate carbon remained elusive. Although most of these studies were driven by J. C.’s fascination with unusual bonding schemes, they were not without practical value. Two hypervalent compounds, Martin’s sulfurane (for dehydration, page 365) and the Dess–Martin periodinane have found widespread application in synthetic organic chemistry. J. C. Martin and his student Daniel Dess developed this methodology at the University of Illinois at Urbana. (Martin’s biography was kindly supplied by Prof. Scott E. Denmark). (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
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Dieckmann condensation

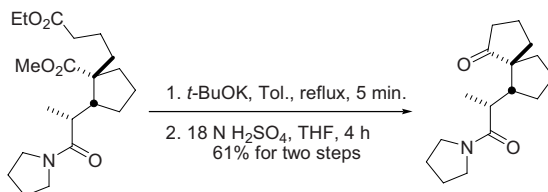
The Dieckmann condensation is the intramolecular version of the Claisen condensation.



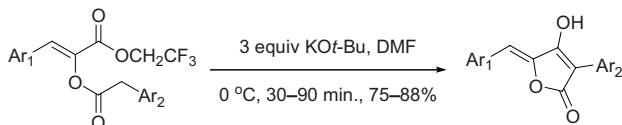
Example 1⁶

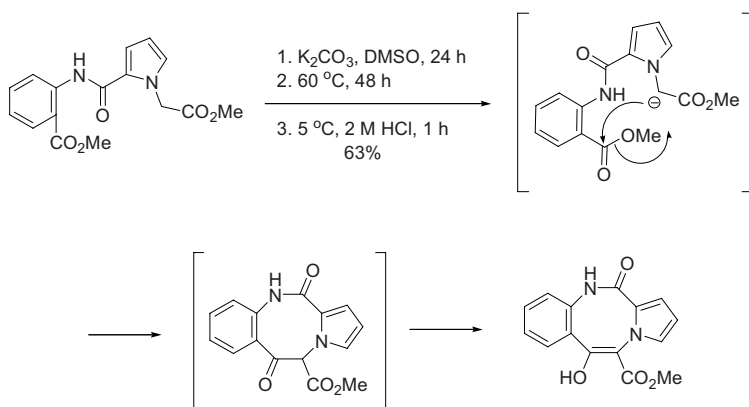


Example 2⁸



Example 3⁹



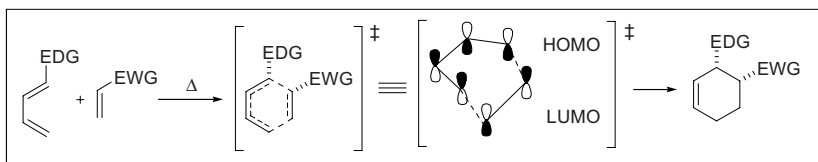
Example 4¹⁰

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Diels–Alder reaction

The Diels–Alder reaction, inverse electronic demand Diels–Alder reaction, as well as the hetero-Diels–Alder reaction, belong to the category of $[4+2]$ -cycloaddition reactions, which are concerted processes. The arrow pushing here is merely illustrative.

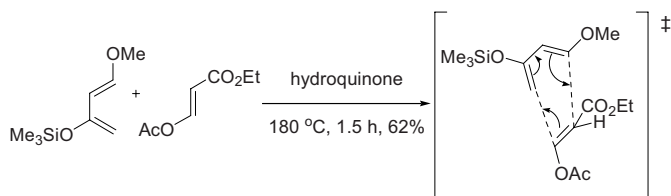


diene dienophile

adduct

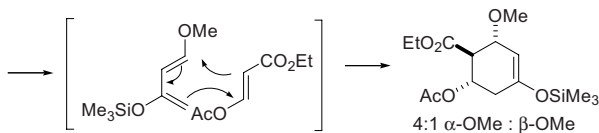
EDG = electron-donating group; EWG = electron-withdrawing group

Example 1⁶

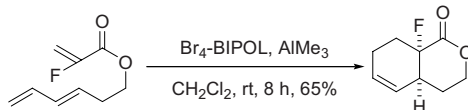


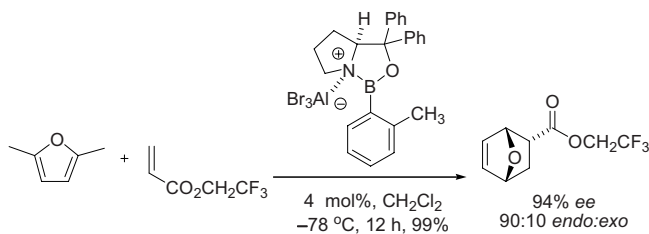
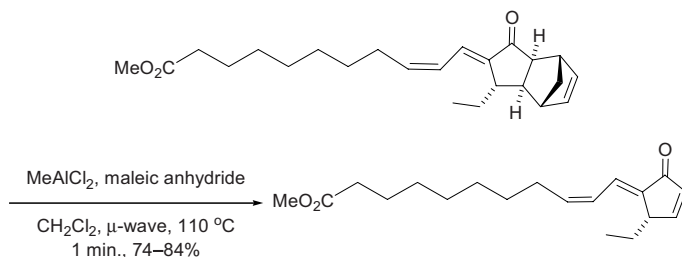
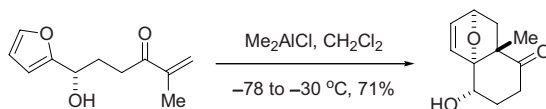
The Danishefsky diene

Alder's *endo* rule



Example 2, Intramolecular Diels–Alder reaction⁷



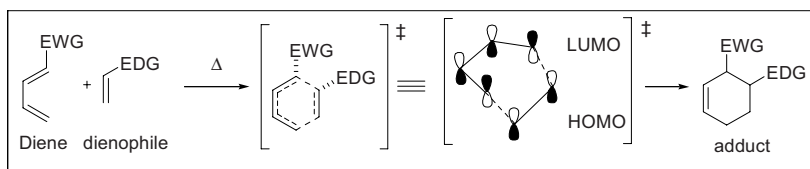
Example 3, Asymmetric Diels–Alder reaction^{5,8}Example 4, Retro-Diels–Alder reaction^{4,9}Example 5, Intramolecular Diels–Alder reaction¹¹

References

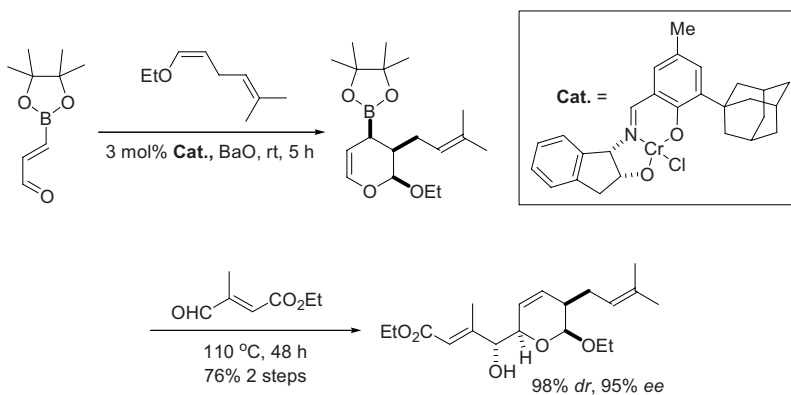
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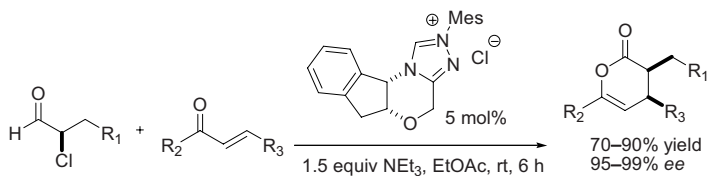
Inverse electronic demand Diels–Alder reaction

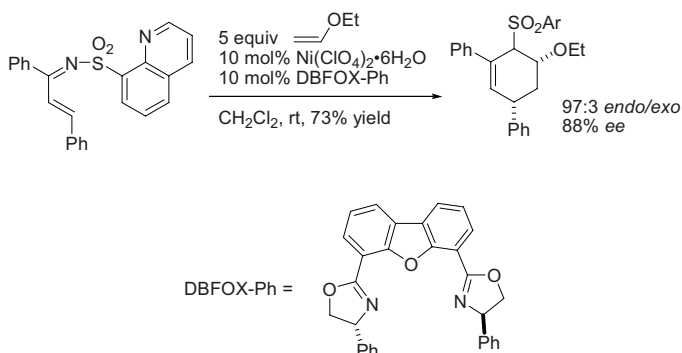
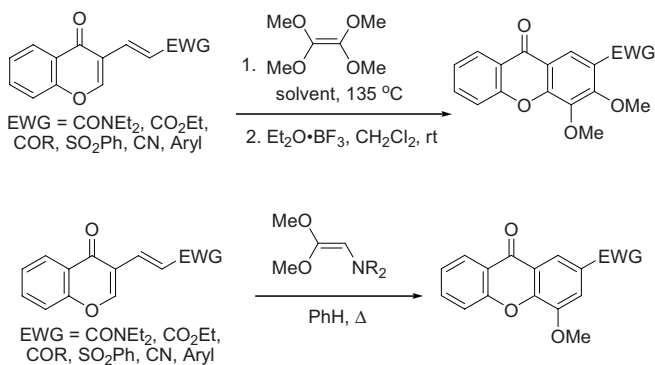


Example 1²



Example 2³



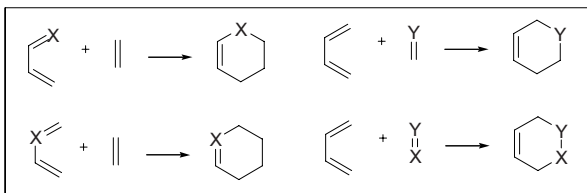
Example 3, Catalytic asymmetric inverse-electron-demand Diels–Alder reaction⁴Example 4⁵

References

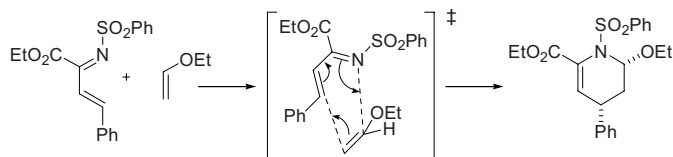
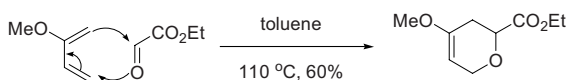
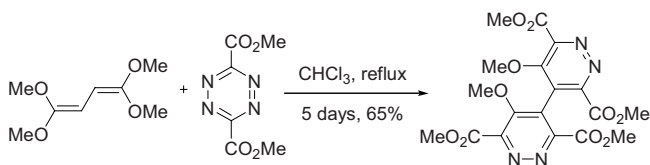
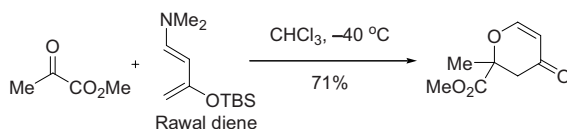
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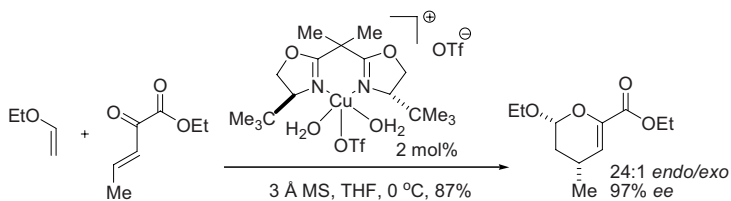
Hetero-Diels–Alder reaction

Heterodiene addition to dienophile or heterodienophile addition to diene. Typical hetero-Diels–Alder reactions are aza-Diels–Alder reaction and oxo-Diels–Alder reaction.



e.g.:

Example 1, Heterodienophile addition to diene¹Example 2, Similar to the **Boger pyridine synthesis** (see page 59)²Example 3, Using **the Rawal diene**⁴Example 4, Also similar to the Boger pyridine synthesis⁶

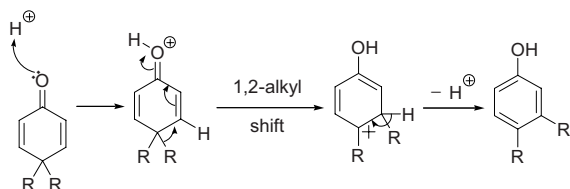
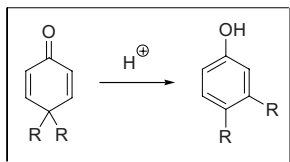
Example 5⁷

References

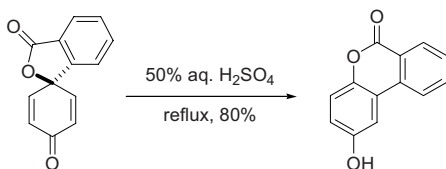
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Dienone–phenol rearrangement

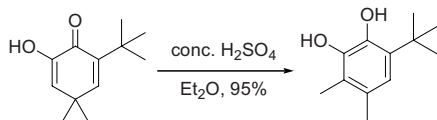
Acid-promoted rearrangement of 4,4-disubstituted cyclohexadienones to 3,4-disubstituted phenols.



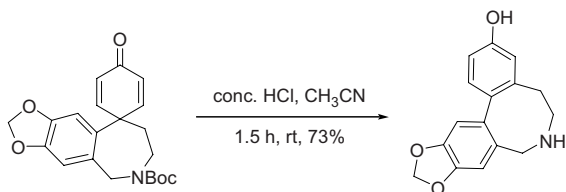
Example 1⁴

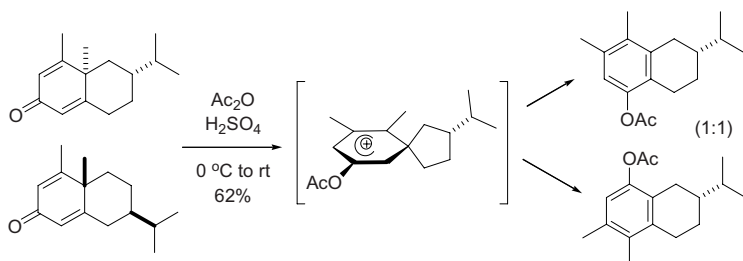


Example 2⁵



Example 3⁹



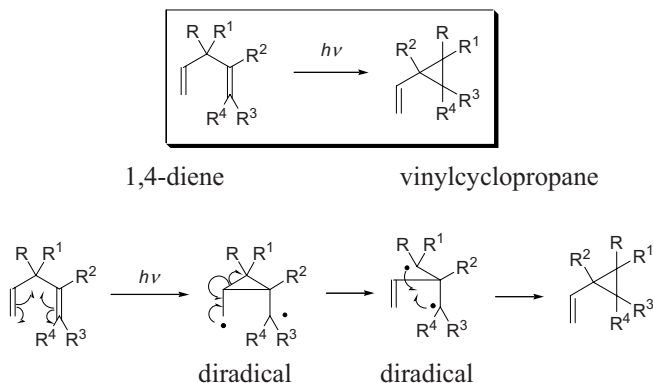
Example 4¹⁰

References

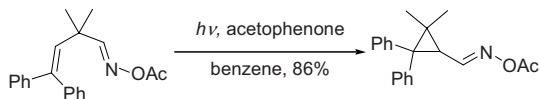
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Di- π -methane rearrangement

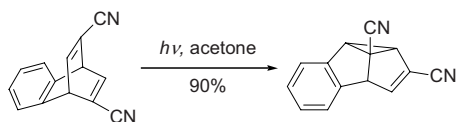
Conversion of 1,4-dienes to vinylcyclopropanes under photolysis. Also known as the **Zimmerman rearrangement**.



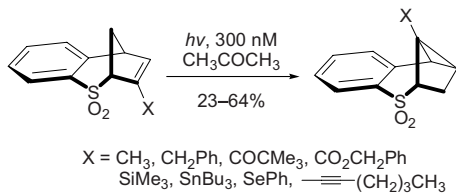
Example 1, Aza- π -methane rearrangement²

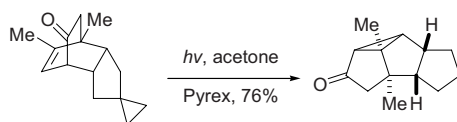


Example 2⁴



Example 3⁸



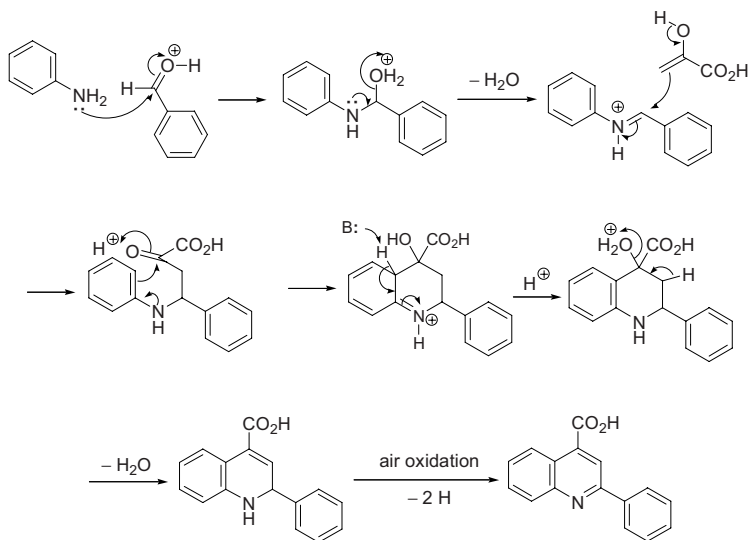
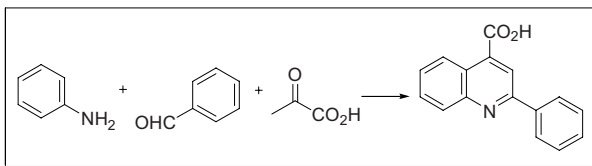
Example 4, Oxa- π -methane rearrangement⁸

References

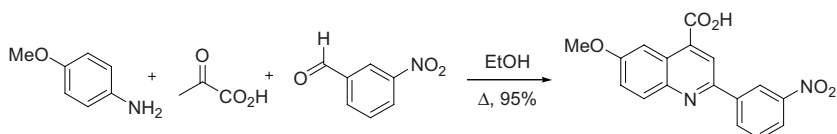
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Doebner quinoline synthesis

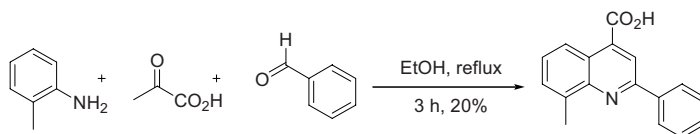
Three-component coupling of an aniline, pyruvic acid, and an aldehyde to provide a quinoline-4-carboxylic acid.

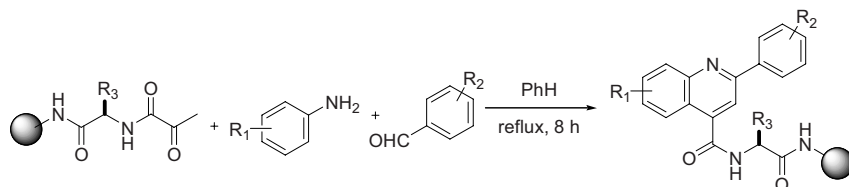


Example 1²



Example 2⁶



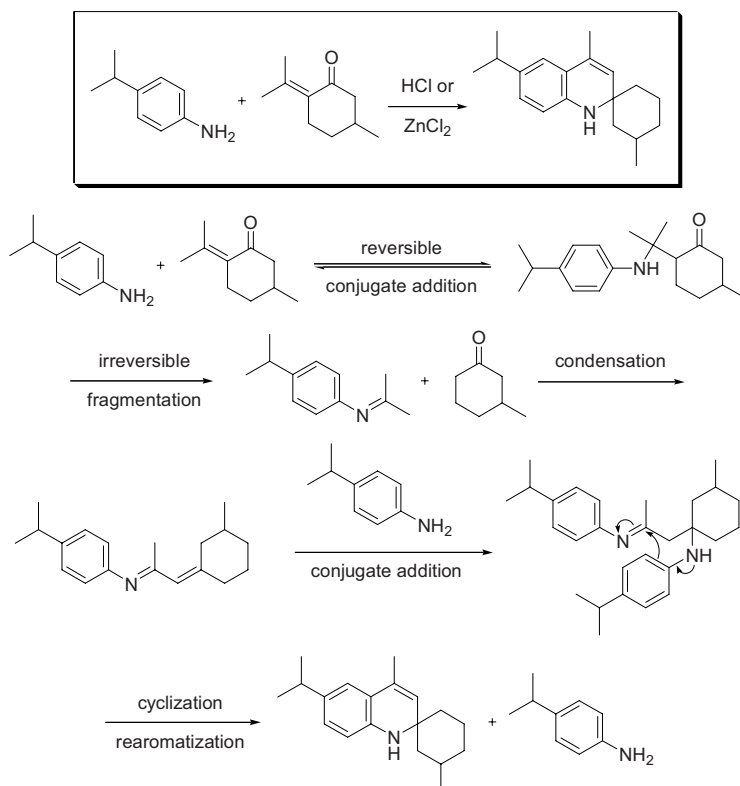
Example 3, Combinatorial Doebner reaction⁷

References

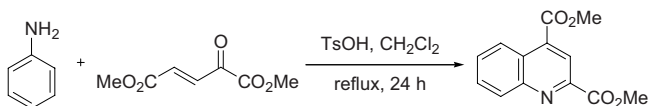
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Doebner–von Miller reaction

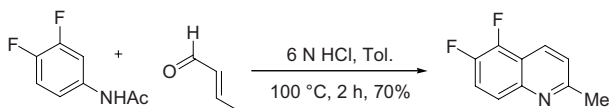
Doebner–von Miller reaction is a variant of the Skraup quinoline synthesis (page 509). Therefore, the mechanism for the Skraup reaction is also operative for the Doebner–von Miller reaction. The following mechanism is favored by Denmark's mechanistic study using ^{13}C -labelled α,β -unsaturated ketones.⁹

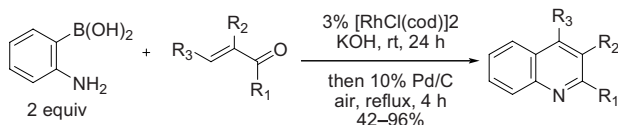


Example 1⁵



Example 2⁶



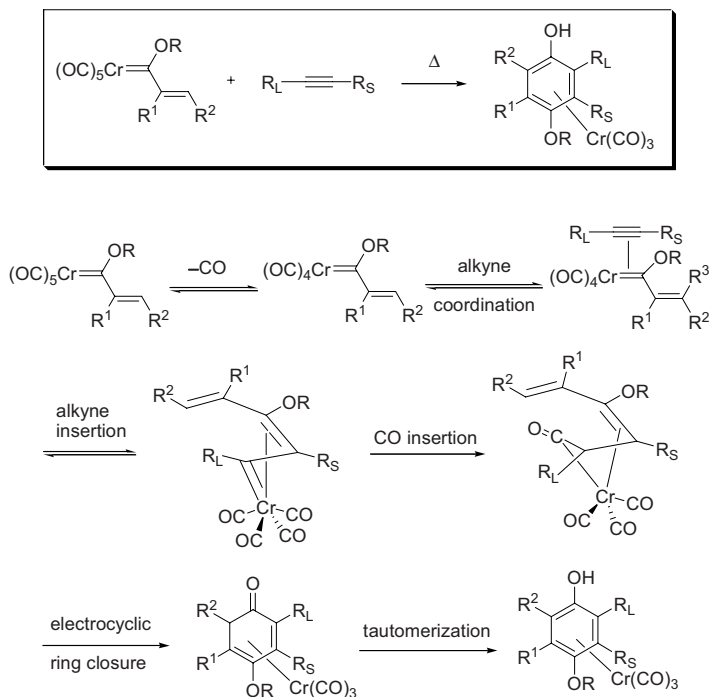
Example 3, A novel variant¹⁰

References

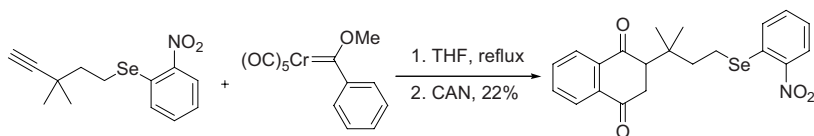
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Dötz reaction

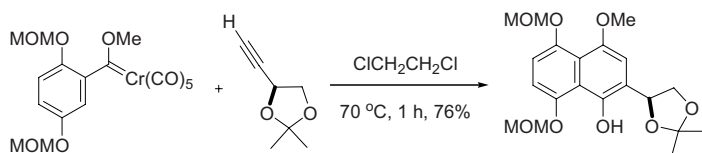
$\text{Cr}(\text{CO})_3$ -coordinated hydroquinone from vinylic alkoxy pentacarbonyl chromium carbene (Fischer carbene) complex and alkynes.

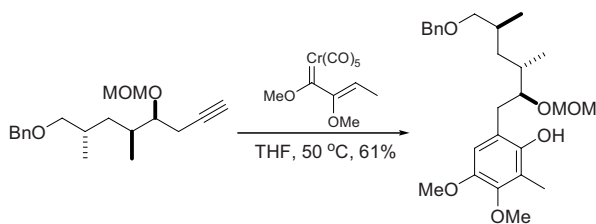
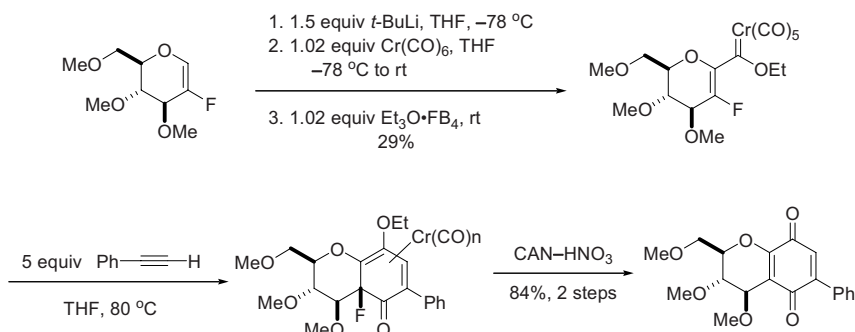


Example 1⁵



Example 3⁸



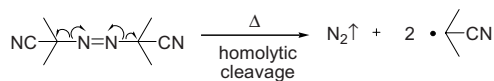
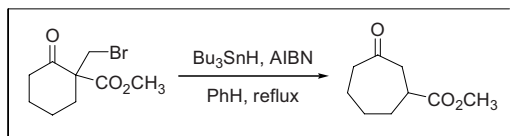
Example 3⁸Example 3⁹

References

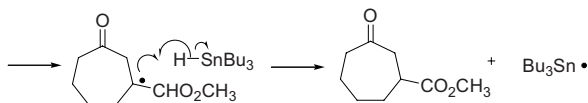
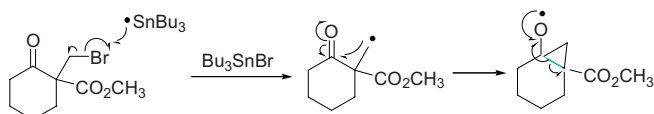
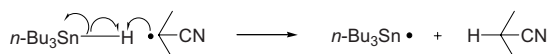
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Dowd–Beckwith ring expansion

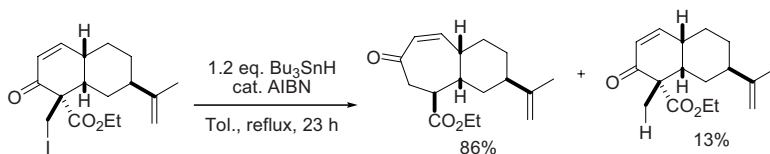
Radical-mediated ring expansion of 2-halomethyl cycloalkanones.



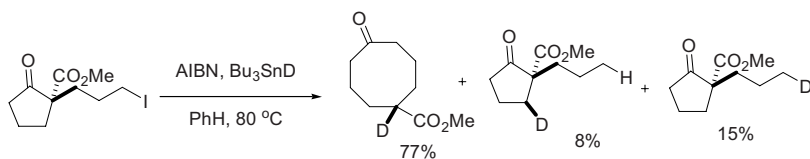
2,2'-azobisisobutyronitrile (AIBN)



Example 1⁴



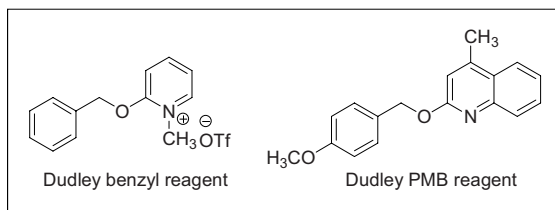
Example 2⁹



References

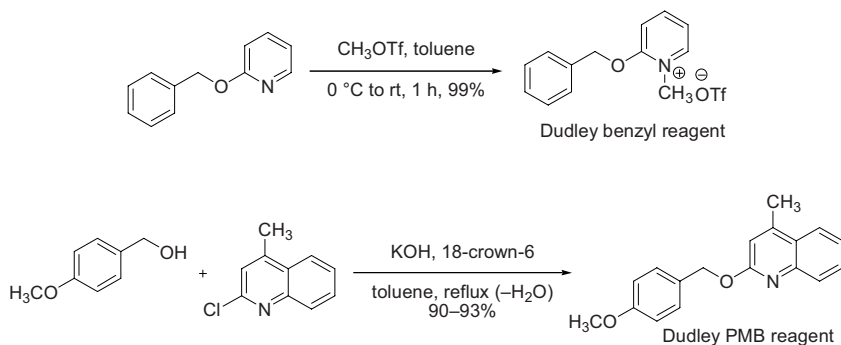
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Dudley reagent



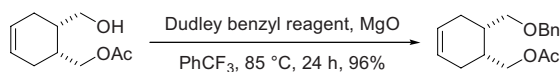
The Dudley reagents are employed for the protection of alcohols as benzyl¹ or PMB² ethers, respectively, under mild conditions. Carboxylic acids are readily protected as well.³ Activation of the appropriate Dudley reagent in the presence of an alcohol furnishes the desired arylmethyl ether. The benzyl reagent is activated upon warming to approximately 80–85 °C, whereas activation of the PMB reagent occurs at room temperature upon treatment with methyl triflate (CH₃OTf) or protic acid.⁴ Aromatic solvents, most commonly trifluorotoluene, often provide the best results. Magnesium oxide (MgO) is typically included in the reaction mixture as an acid scavenger.⁵ For benzylation of carboxylic acids, triethylamine (Et₃N) is used in place of MgO.³

Preparation:^{1–3}



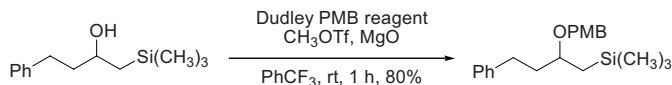
The Dudley reagents are conveniently prepared from readily available starting materials and are indefinitely stable to storage and handling under standard laboratory conditions. Alternatively, both reagents are commercially available.

Example 1⁶



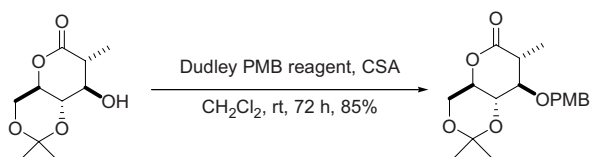
Benzylation of a monoacetylated diol is shown in Example 1.⁶ The Dudley benzyl reagent was uniquely effective for protection of the free alcohol without loss and/or migration of the labile acetyl group.

Example 2²



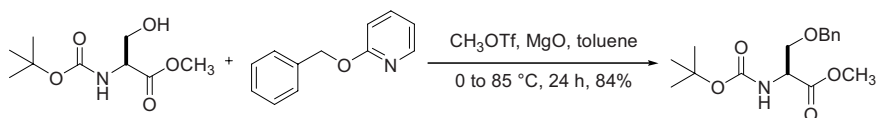
PMB-protection of a β -hydroxysilane can be accomplished without competition from the Peterson elimination (Example 2),² which would occur under the basic or acidic conditions required for many other alkylation reactions.

Example 3⁴



The Dudley PMB reagent can also be activated under mildly acidic conditions using catalytic camphorsulfonic acid (CSA) in lieu of CH_3OTf (Example 3).⁴

Example 4, *In situ*-formation of the Dudley benzyl reagent is achieved by treating a mixture of an alcohol and 2-benzyloxypyridine with CH_3OTf ⁷

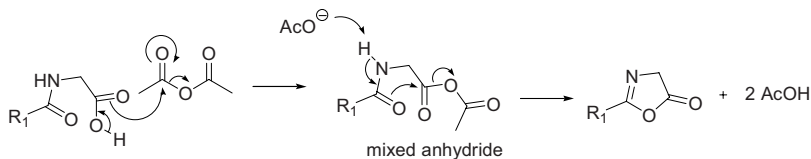
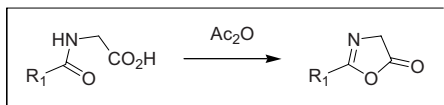


References

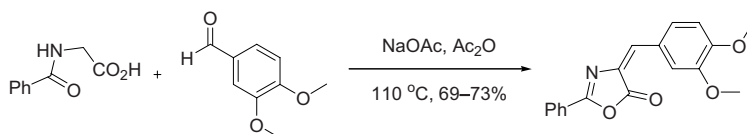
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Δ Erlenmeyer–Plöchl azlactone synthesis

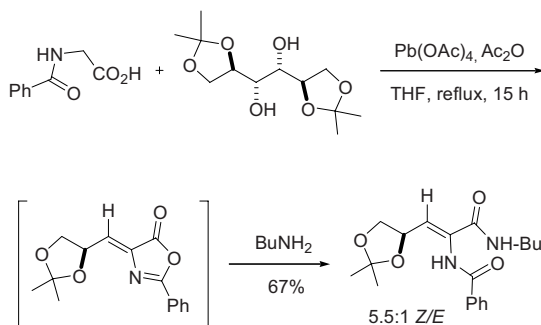
Formation of 5-oxazolones (or “azlactones”) by intramolecular condensation of acylglycines in the presence of acetic anhydride.



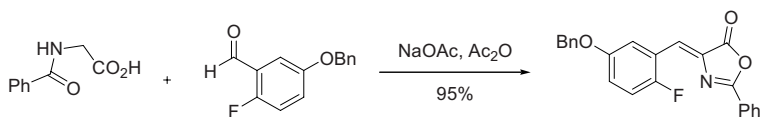
Example 1²



Example 2⁸



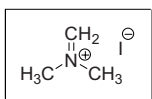
Example 3⁹



References

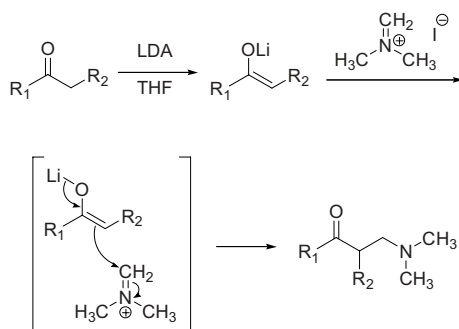
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Eschenmoser's salt



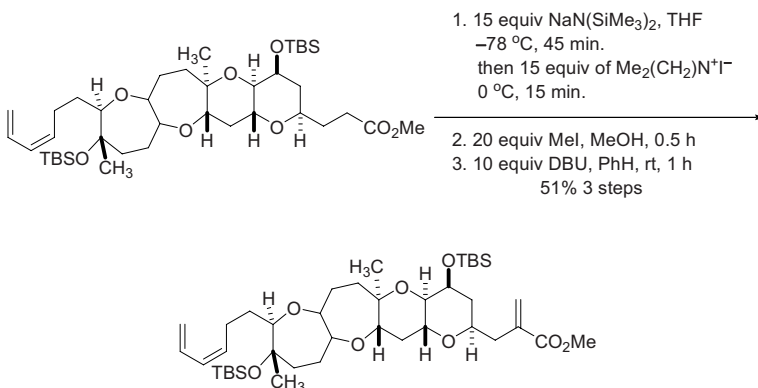
Eschenmoser's salt, dimethylmethylideneammonium iodide, is a strong dimethylaminomethylating agent, used to prepare derivatives of the type $\text{RCH}_2\text{N}(\text{CH}_3)_2$. Enolates, enolsilyl ethers, and even more acidic ketones undergo efficient dimethylaminomethylation—employed in the Mannich reaction.

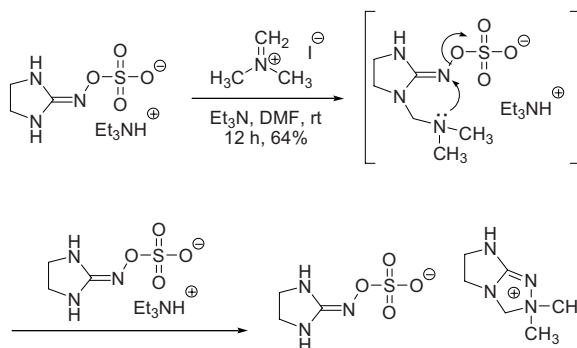
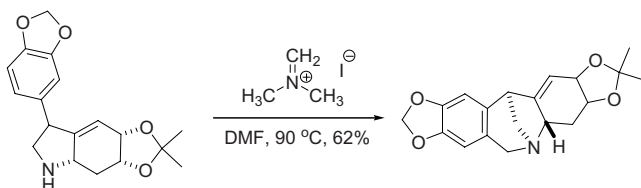
Mechanism



Example 1³

Once prepared, the resulting tertiary amines can be further methylated and then subjected to base-induced elimination to afford methylenated ketones.



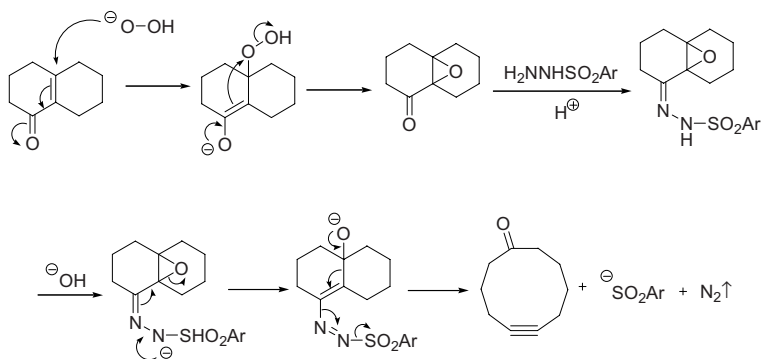
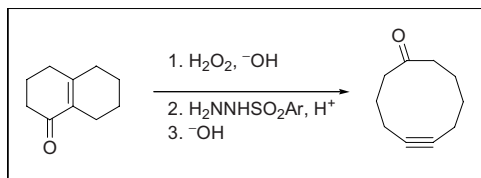
Example 2⁴Example 3⁵

References

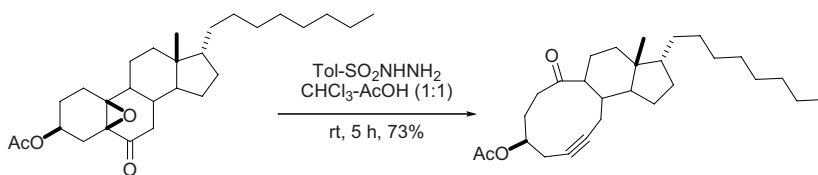
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Eschenmoser–Tanabe fragmentation

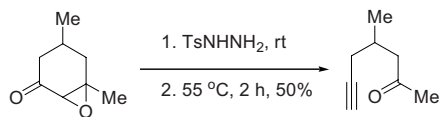
Fragmentation of α,β -epoxyketones *via* the intermediacy of α,β -epoxy sulfonylhydrazones.

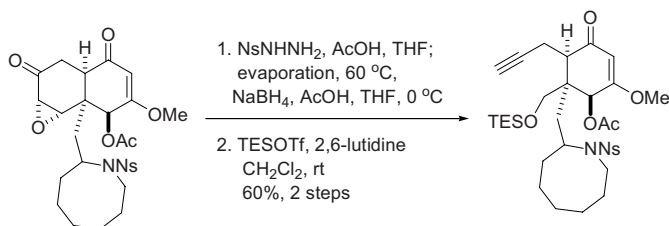


Example 1⁴



Example 2⁷



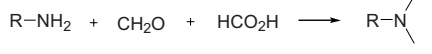
Example 3⁹

References

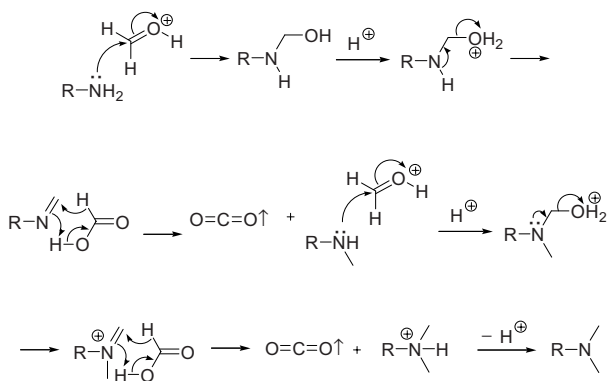
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Eschweiler–Clarke reductive alkylation of amines

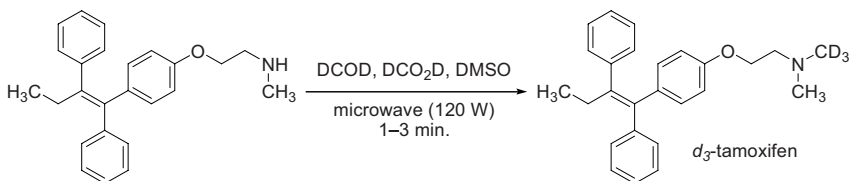
Reductive methylation of primary or secondary amines using formaldehyde and formic acid. *Cf.* Leuckart–Wallach reaction.



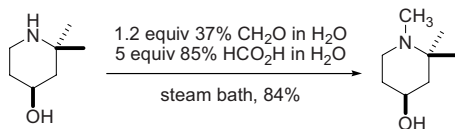
formic acid is the hydride source as a reducing agent

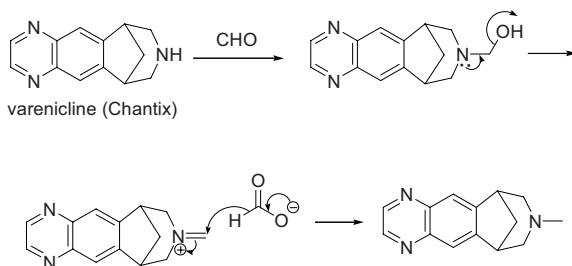


Example 1⁷



Example 2⁹



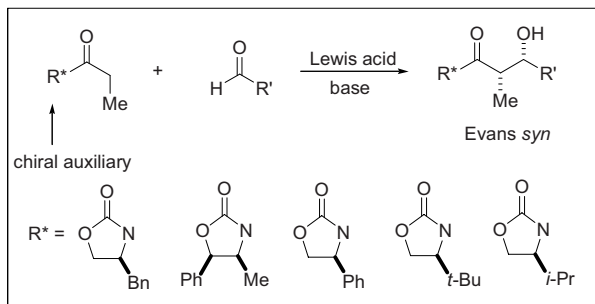
Example 3¹⁰

References

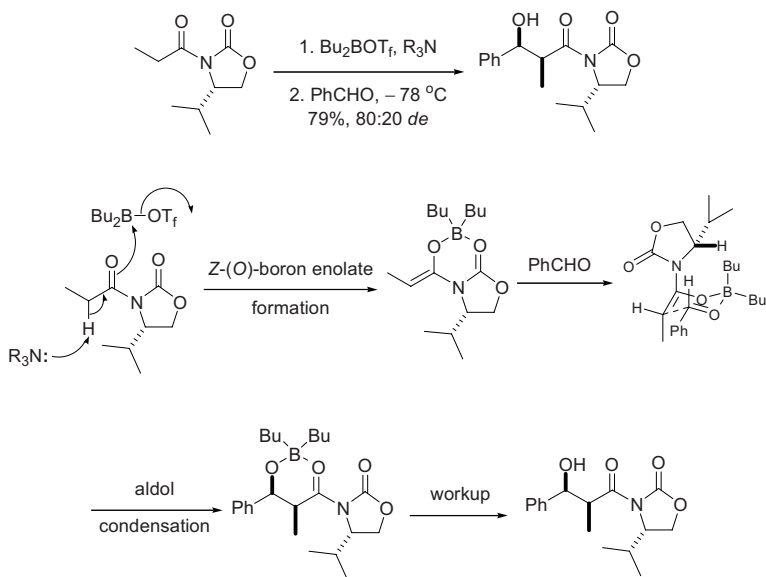
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Evans aldol reaction

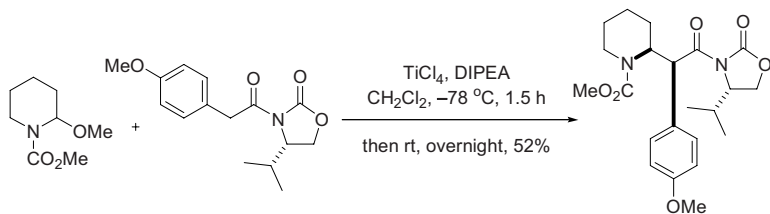
Asymmetric aldol condensation of aldehyde and chiral acyl oxazolidinone, the Evans chiral auxiliary.

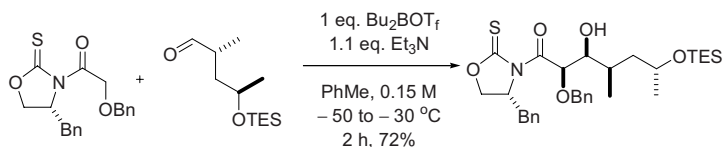
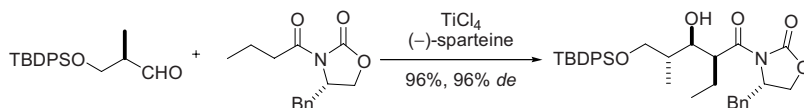


Example 1²



Example 2⁵



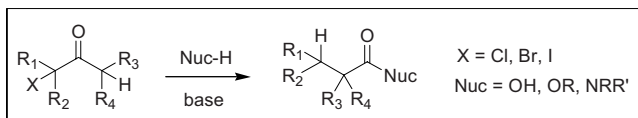
Example 3⁹Example 4, Crimmins procedure¹⁰

References

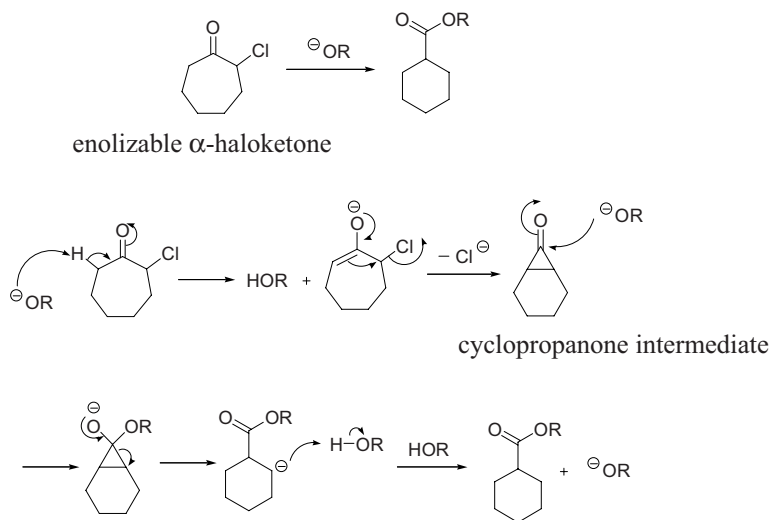
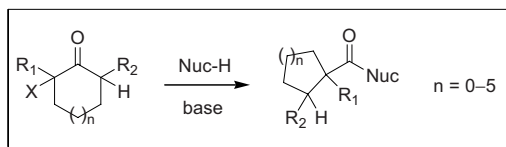
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Favorskii rearrangement

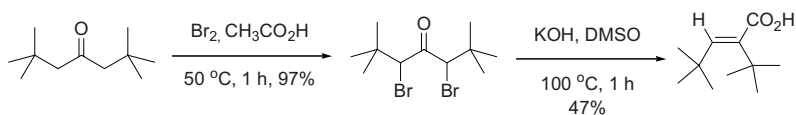
Transformation of enolizable α -haloketones to esters, carboxylic acids, or amides *via* alkoxide-, hydroxide-, or amine-catalyzed rearrangements, respectively.

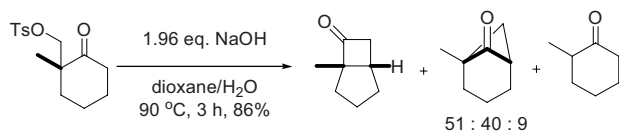
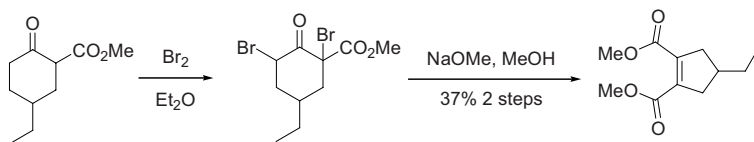
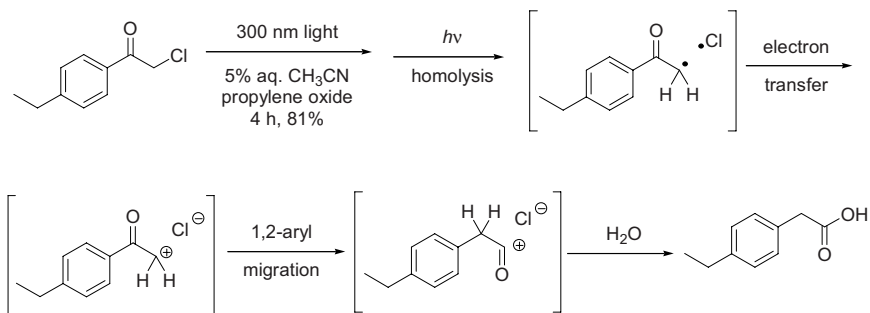
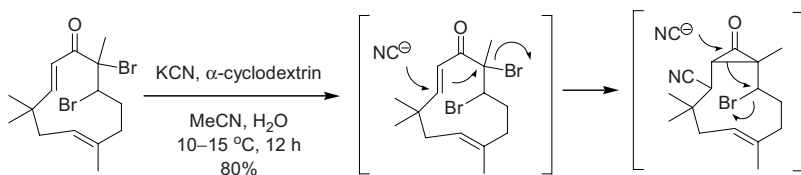


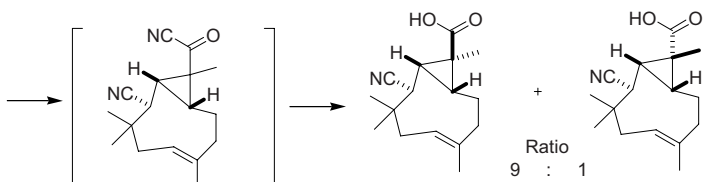
The intramolecular Favorskii Rearrangement:



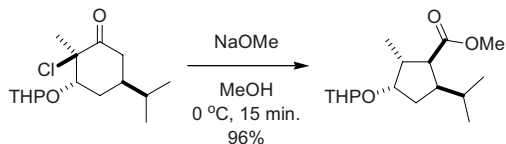
Example 1²



Example 2, Homo-Favorskii rearrangement³Example 3⁶Example 4, Photo-Favorskii Rearrangement⁷Example 5⁸



Example 6¹⁰

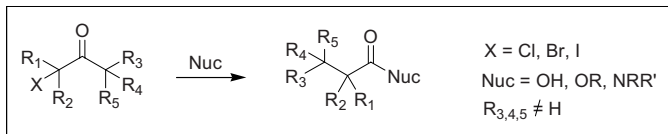


References

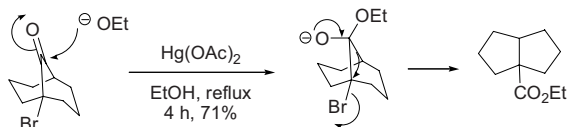
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Quasi-Favorskii rearrangement

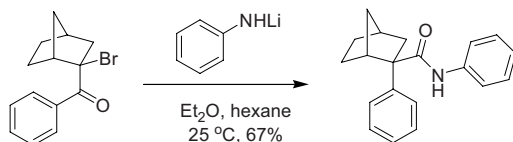
If there are no enolizable hydrogens present, the classical Favorskii rearrangement is not possible. Instead, a semi-benzylic mechanism can lead to a rearrangement referred to as quasi-Favorskii.



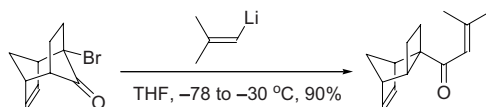
Example 1, Arthur C. Cope's initial discovery¹



Example 2⁵



Example 3⁶

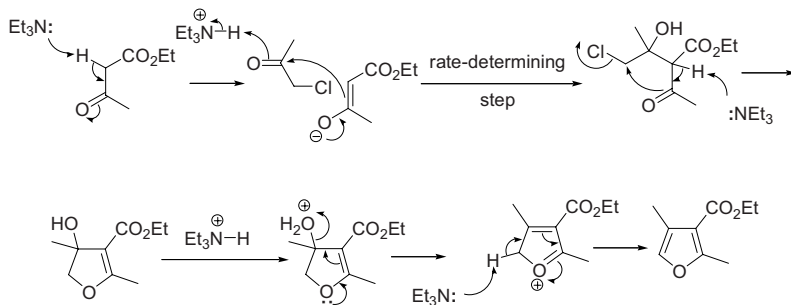
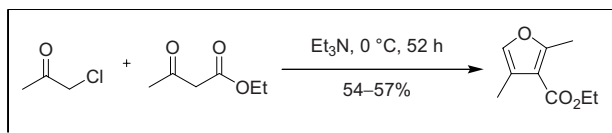


References

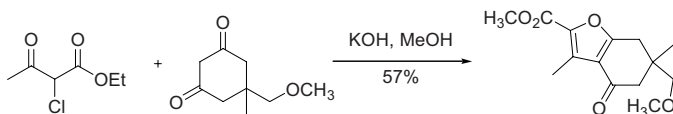
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Feist–Bénary furan synthesis

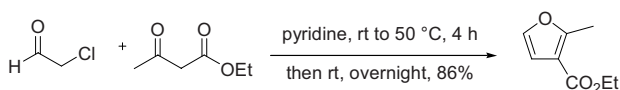
α -Haloketones react with β -ketoesters in the presence of base to fashion furans.



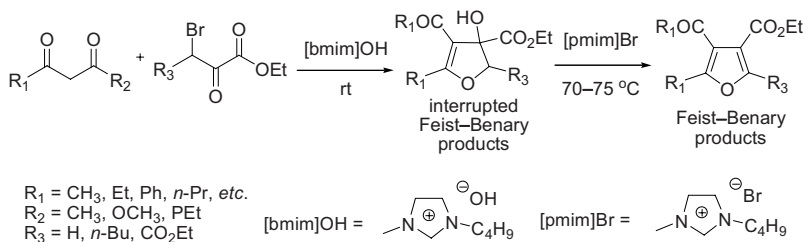
Example 1^{2,3}



Example 2⁴



Example 3, Ionic liquid-promoted interrupted Feist–Bénary reaction¹⁰



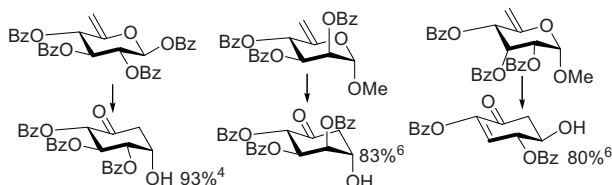
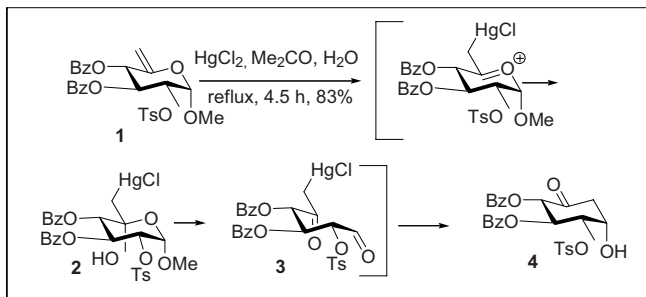
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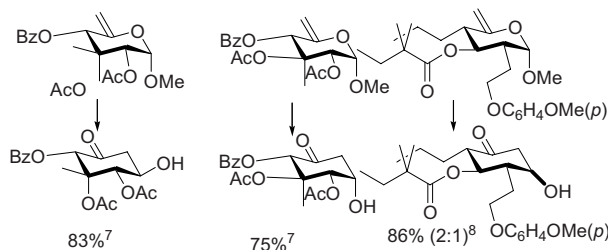
Ferrier carbocyclization

This process (also known as the “Ferrier II Reaction”) has proved to be of considerable value for the efficient, one-step conversion of 5,6-unsaturated hexopyranose derivatives into functionalized cyclohexanones useful for the preparation of such enantiomerically pure compounds as inositols and their amino, deoxy, unsaturated and selectively *O*-substituted derivatives, notably phosphate esters. In addition, the products of the carbocyclization have been incorporated into many complex compounds of interest in biological and medicinal chemistry.^{1,2}

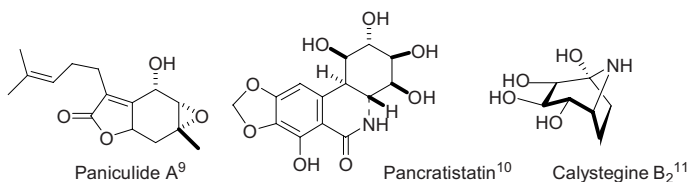
General examples:³



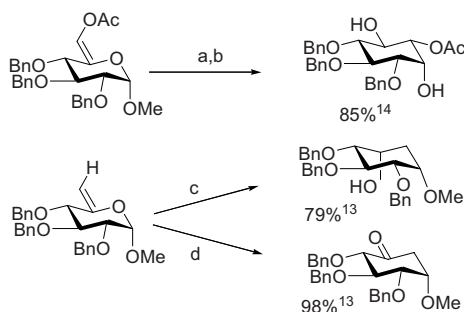
More complex products:



Complex bioactive compounds made following the application of the reaction:



Modified hex-5-enopyranosides and reactions



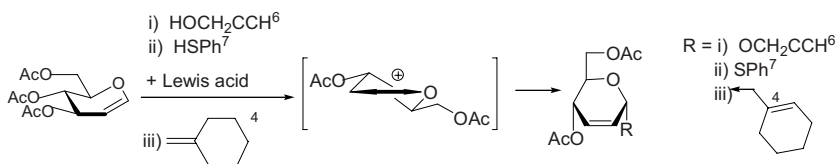
a, $\text{Hg}(\text{OCOCF}_3)_2$, Me_2CO , H_2O , 0°C ; b, $\text{NaBH}(\text{OAc})_3$, AcOH , MeCN , rt; c, $i\text{-Bu}_3\text{Al}$, PhMe , 40°C ; d, $\text{Ti}(\text{O}i\text{-Pr})\text{Cl}_3$, CH_2Cl_2 , -78°C , 15 min. (Note: The aglycon is retained in the Al- and Ti-induced reactions).

References

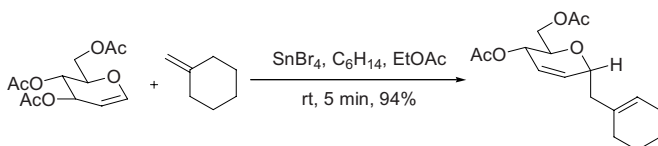
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Ferrier glycol allylic rearrangement

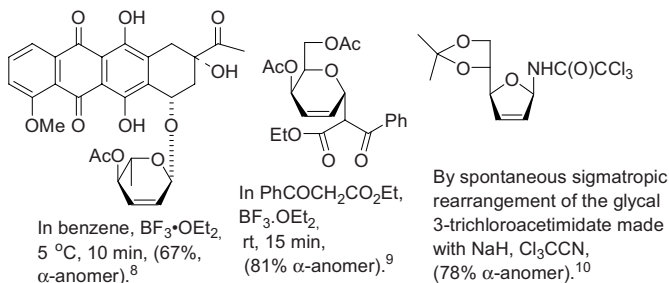
In the presence of Lewis acid catalysts *O*-substituted glycol derivatives can react with *O*-, *S*-, *C*- and, less frequently, *N*-, *P*- and halide nucleophiles to give 2,3-unsaturated glycosyl products.^{1,2} This allylic transformation has been termed the “Ferrier Reaction” or, to avoid complications, the “Ferrier I Reaction” or the “Ferrier Rearrangement”. However, the reaction was first noted by Emil Fischer when he heated tri-*O*-acetyl-*D*-glucal in water.³ When carbon nucleophiles are involved, the term “Carbon Ferrier Reaction” has been used,⁴ although the only contribution the Ferrier group made in this area was to find that tri-*O*-acetyl-*D*-glucal dimerizes under acid catalysis to give a *C*-glycosidic product.⁵ The general reaction is illustrated by the separate conversions of tri-*O*-acetyl-*D*-glucal with *O*-, *S*- and *C*-nucleophiles to the corresponding 2,3-unsaturated glycosyl derivatives. Normally, Lewis acids are used as catalysts, boron trifluoride etherate being the most common. Allyloxycarbenium ions are involved as intermediates, high yields of products are obtained, and glycosidic compounds with quasi-axial bonds (as illustrated) predominate (commonly in the α,β -ratio of about 7:1). The examples illustrated^{4,6,7} are typical of a very large number of literature reports.¹



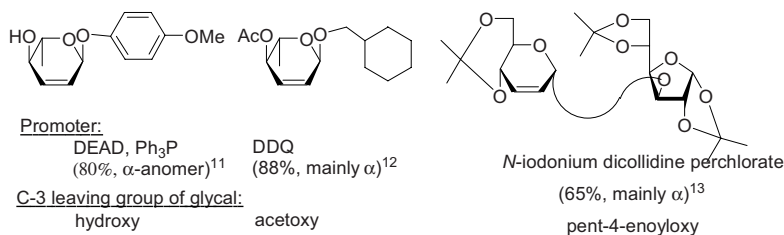
General examples⁴



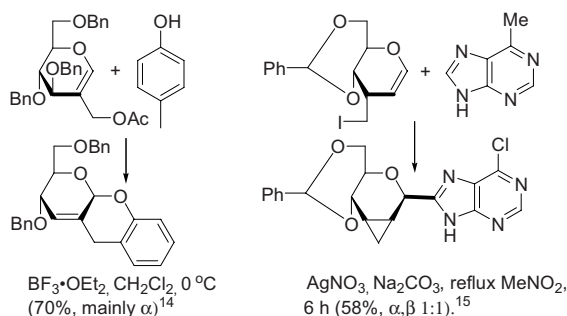
More complex products made directly from the corresponding glycols:



Products formed without acid catalysts



Modified glycals and their reactions:



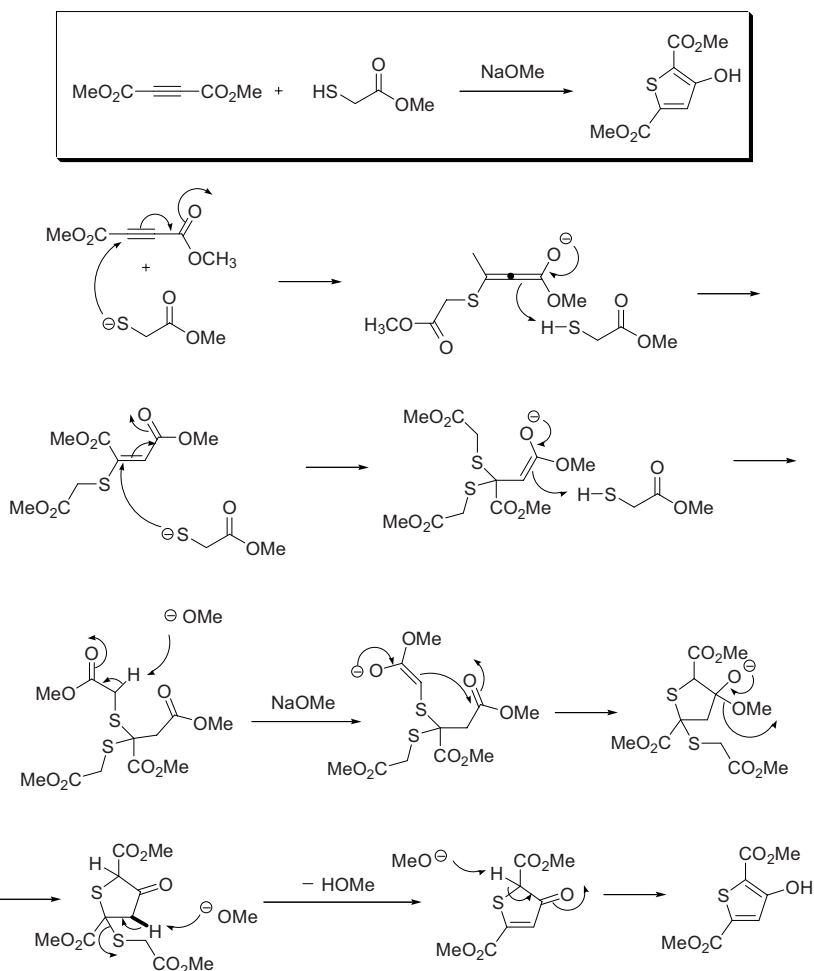
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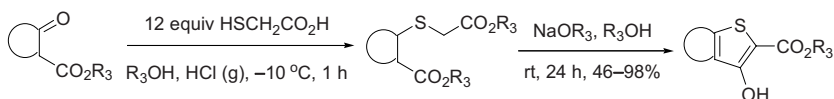
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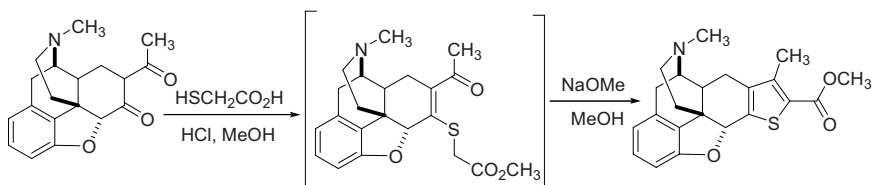
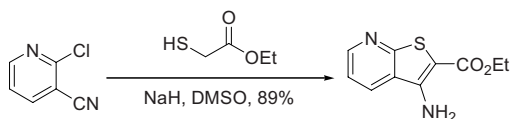
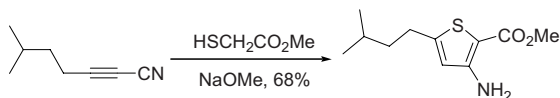
Fiessellmann thiophene synthesis

Condensation reaction of thioglycolic acid derivatives with α,β -acetylenic esters, which upon treatment with base result in the formation of 3-hydroxy-2-thiophenecarboxylic acid derivatives.



Example 1⁵



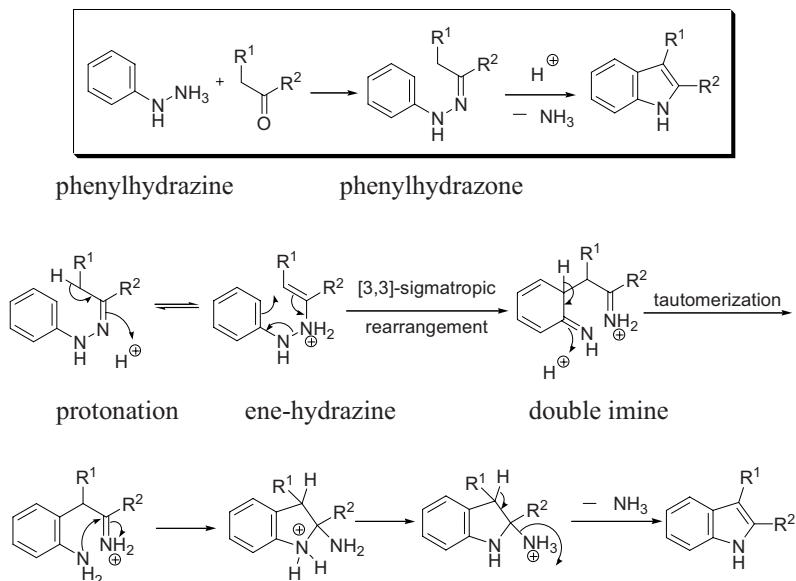
Example 2⁶Example 3⁷Example 4⁹

References

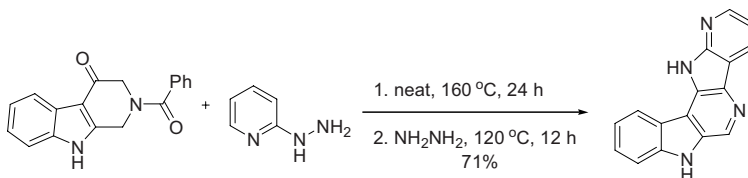
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Fischer indole synthesis

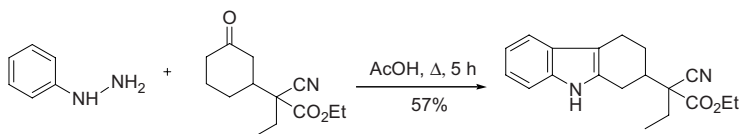
Cyclization of arylhydrazones to indoles.



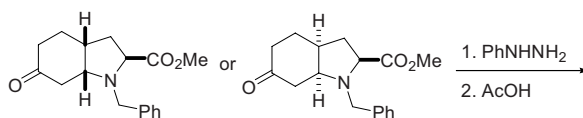
Example 1³

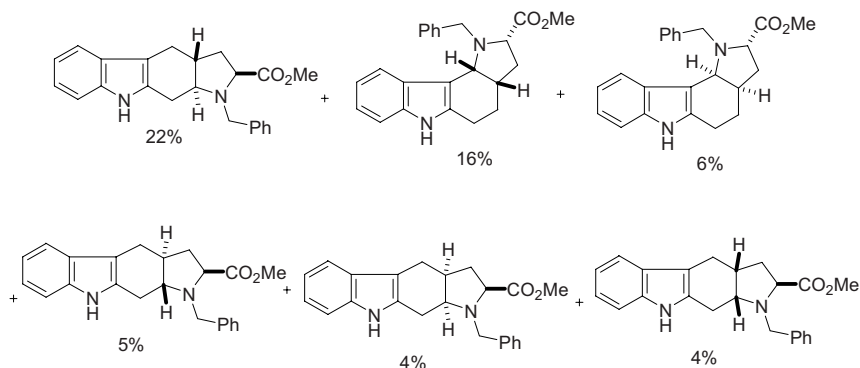


Example 2¹³



Example 4 (Severe racemization)⁹



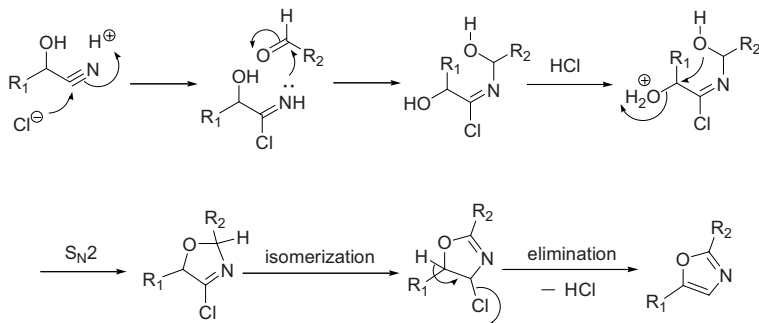


References

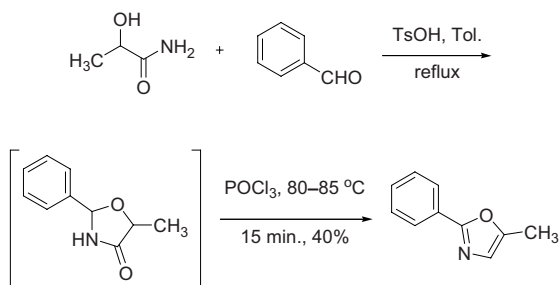
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Fischer oxazole synthesis

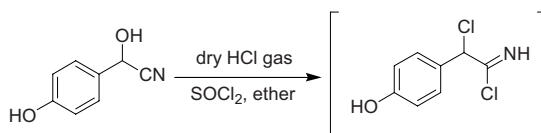
Oxazoles from the condensation of equimolar amounts of aldehyde cyanohydrins and aromatic aldehydes in dry ether in the presence of dry hydrochloric acid.

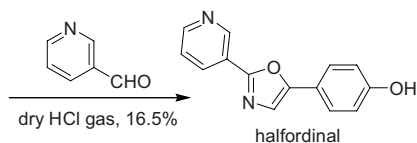


Example 1⁴



Example 2⁸



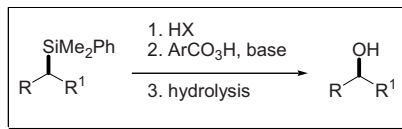


References

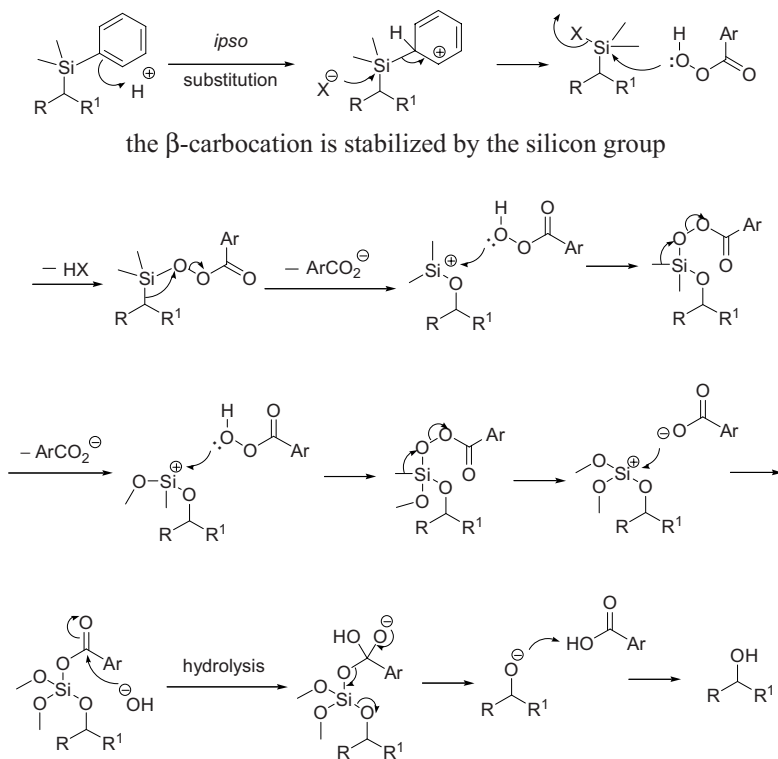
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Fleming–Kumada oxidation

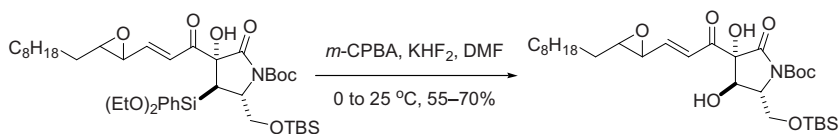
Stereoselective oxidation of alkyl-silanes into the corresponding alkyl-alcohols using peracids.

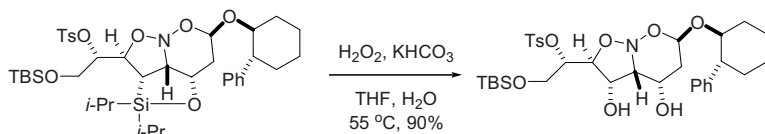
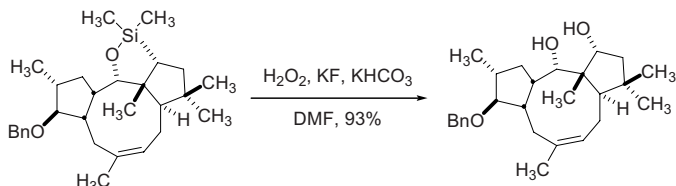
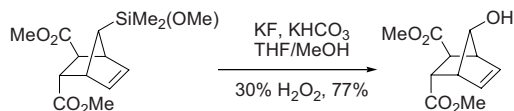


retention of configuration



Example 1⁴



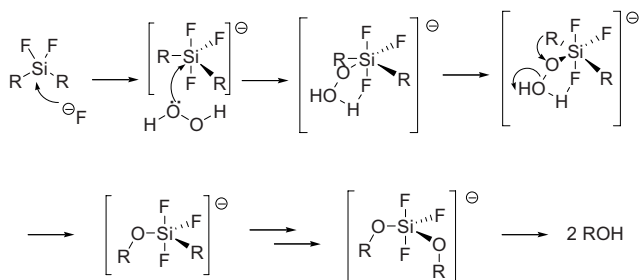
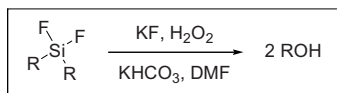
Example 2⁵Example 3⁸Example 4⁹

References

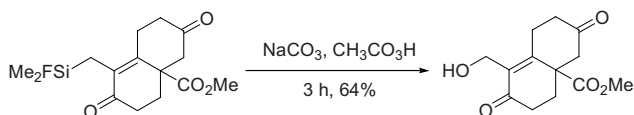
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Tamao–Kumada oxidation

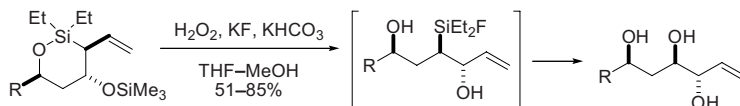
Oxidation of alkyl fluorosilanes to the corresponding alcohols. A variant of the Fleming–Kumada oxidation.



Example 1³



Example 2⁴



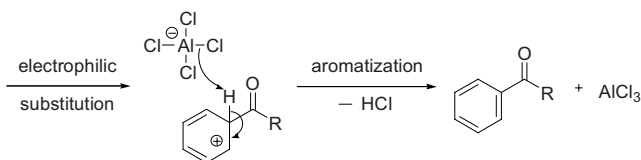
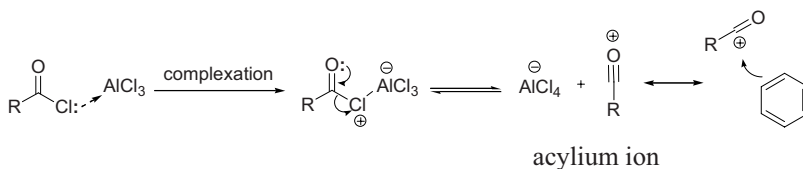
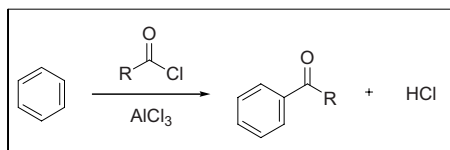
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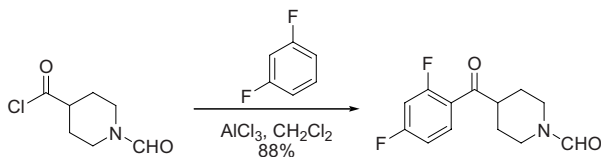
Friedel–Crafts reaction

Friedel–Crafts acylation reaction

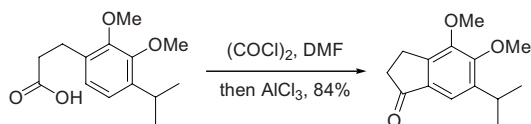
Introduction of an acyl group onto an aromatic substrate by treating the substrate with an acyl halide or anhydride in the presence of a Lewis acid.



Example 1, Intermolecular Friedel–Crafts acylation⁶



Example 2, Intramolecular Friedel–Crafts acylation⁷

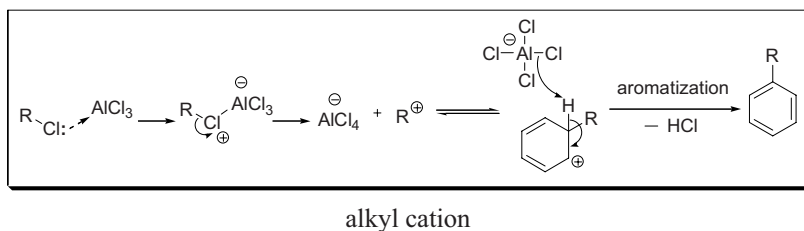


the Lewis acid-catalyzed alkylations and acylations and published more than 50 papers and patents on the Friedel–Crafts reaction, which has become one of the most useful organic reactions.

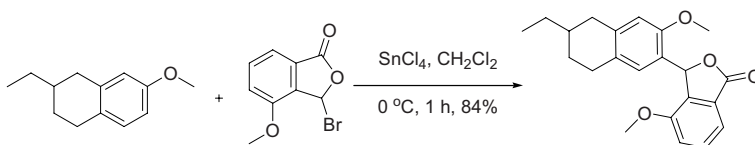
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Friedel–Crafts alkylation reaction

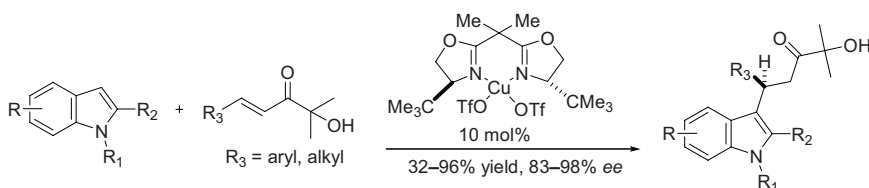
Introduction of an alkyl group onto an aromatic substrate by treating the substrate with an alkylating agent such as alkyl halide, alkene, alkyne and alcohol in the presence of a Lewis acid.

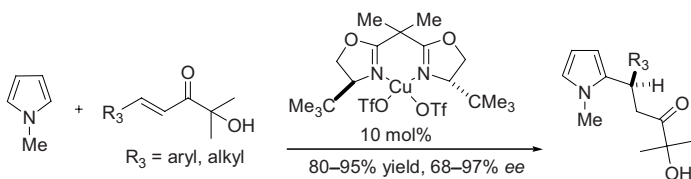
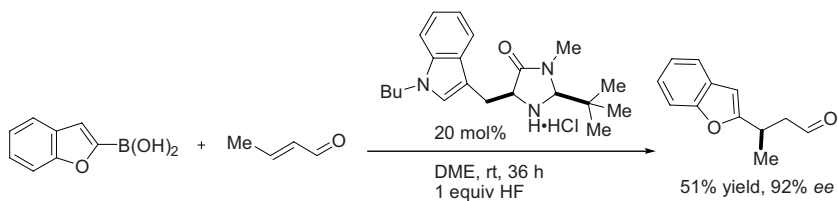


Example 1¹



Example 2⁴



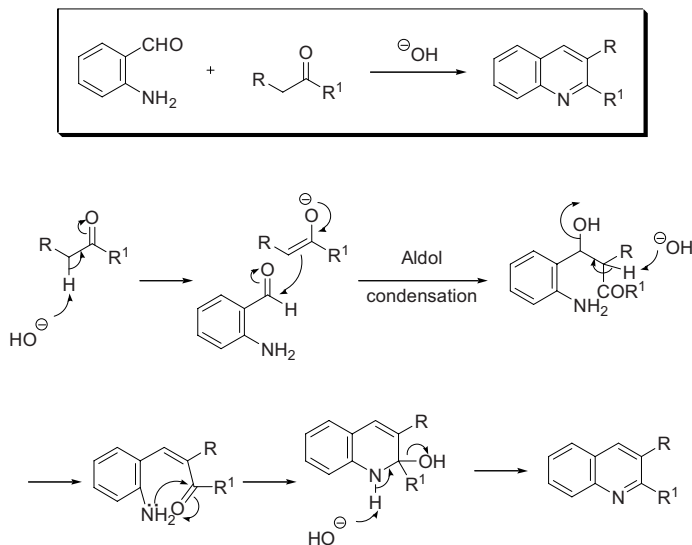
Example 3⁵

References

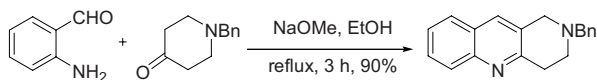
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Friedländer quinoline synthesis

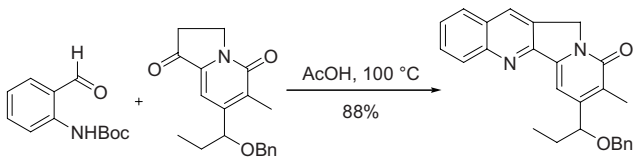
The Friedländer quinoline synthesis combines an α -amino aldehyde or ketone with another aldehyde or ketone with at least one methylene α adjacent to the carbonyl to furnish a substituted quinoline. The reaction can be promoted by acid, base, or heat.

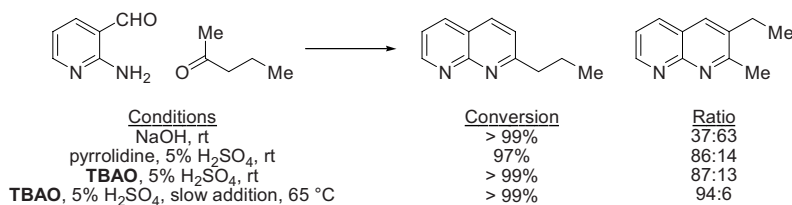


Example 1⁵

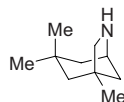
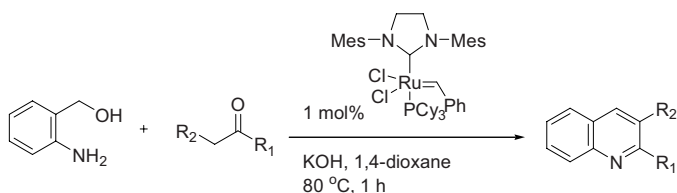


Example 2⁷



Example 3⁸

TBAO = 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane

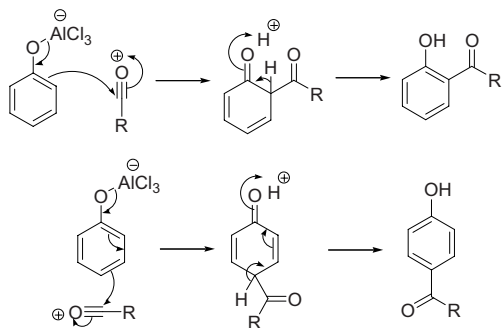
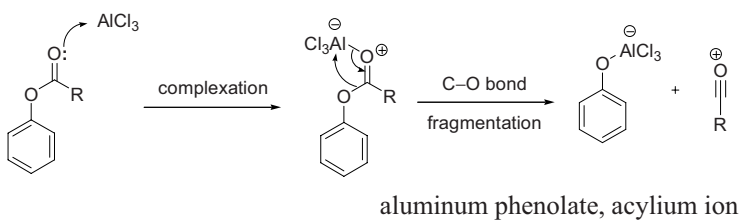
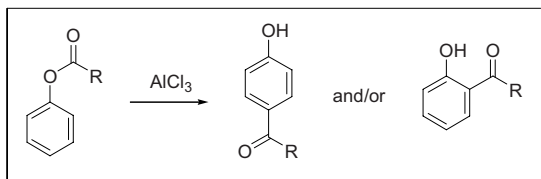
Example 4¹⁰

References

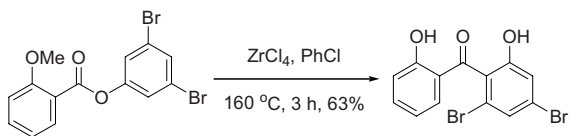
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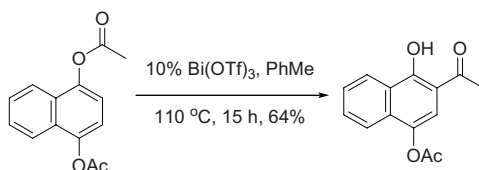
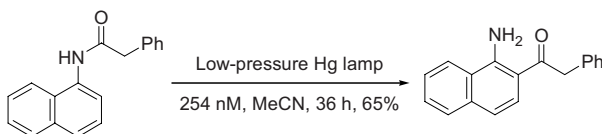
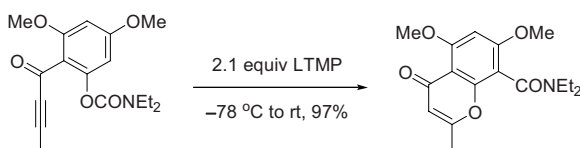
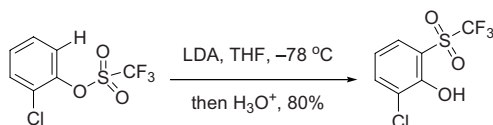
Fries rearrangement

Lewis acid-catalyzed rearrangement of phenol esters and lactams to 2- or 4-ketophenols. Also known as the Fries–Finck rearrangement.



Example 1⁵



Example 2⁶Example 3, Photo-Fries rearrangement⁷Example 4, *ortho*-Fries rearrangement⁸Example 5, Thia-Fries rearrangement⁹

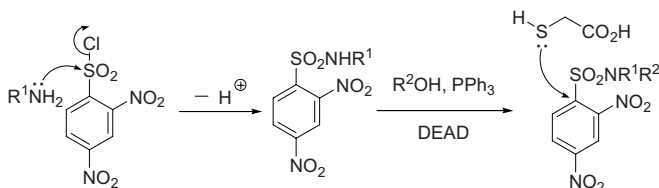
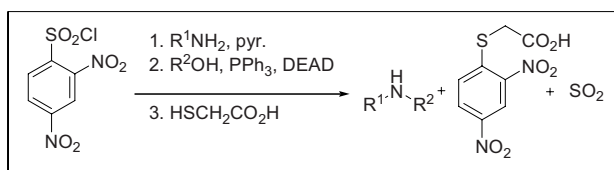
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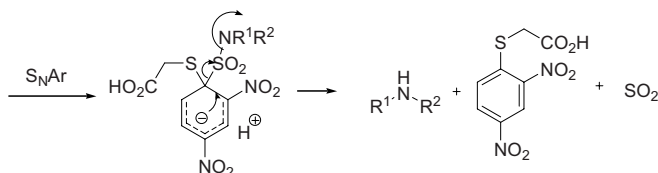
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Fukuyama amine synthesis

Transformation of a primary amine to a secondary amine using 2,4-dinitrobenzenesulfonyl chloride and an alcohol. Also known as the Fukuyama–Mitsunobu procedure.

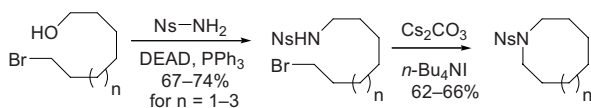


See page 365 for mechanism of the Mitsunobu reaction.

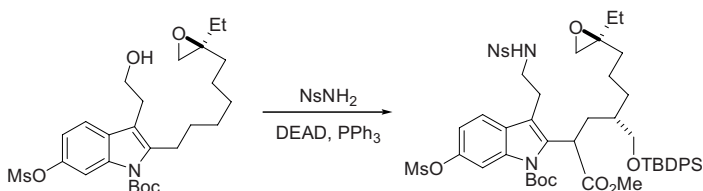


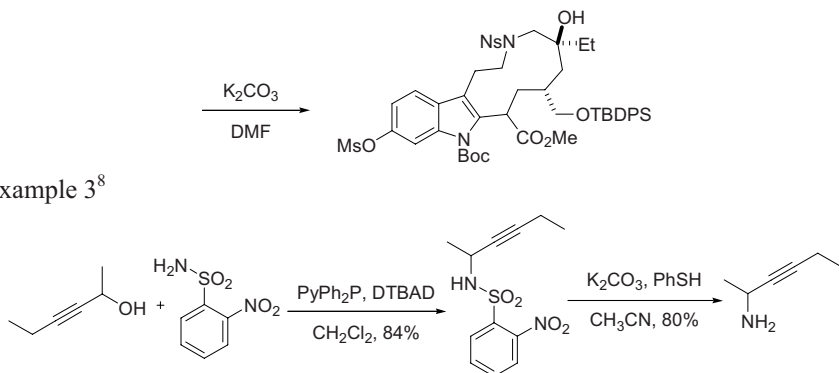
Meisenheimer complex

Example 1⁶



Example 2⁷



Example 3⁸

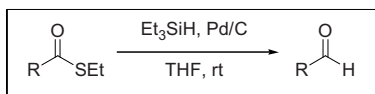
$PyPh_2P$ = diphenyl 2-pyridylphosphine; DTBAD = di-*tert*-butylazodicarbonate

References

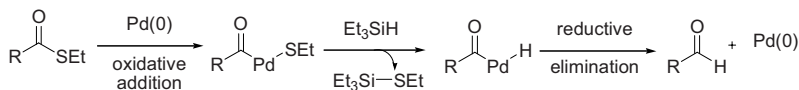
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Fukuyama reduction

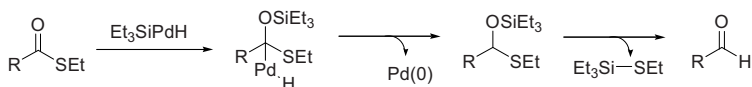
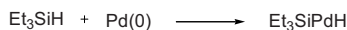
Aldehyde synthesis through reduction of thiol esters with Et_3SiH in the presence of Pd/C catalyst.



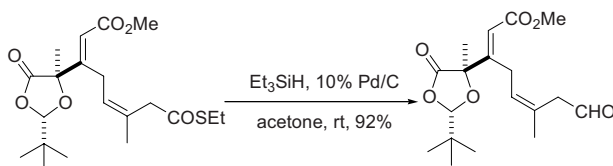
Path A:



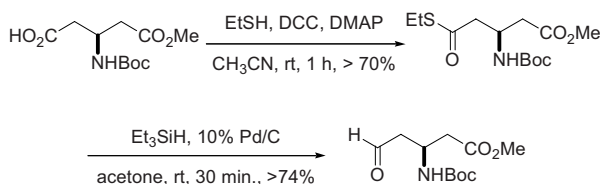
Path B:



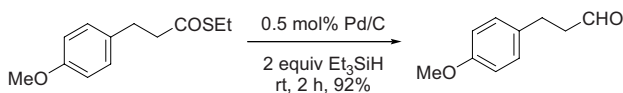
Example 1¹



Example 2³



Example 3⁸

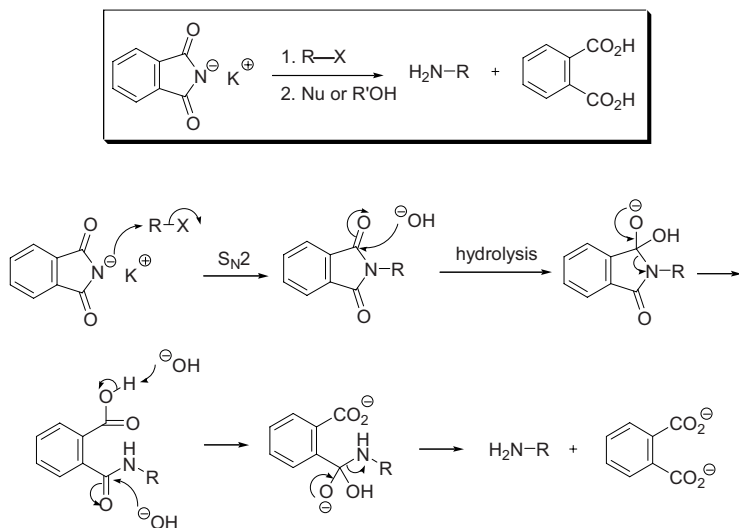


References

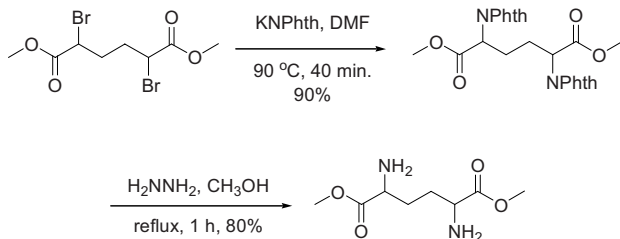
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Gabriel synthesis

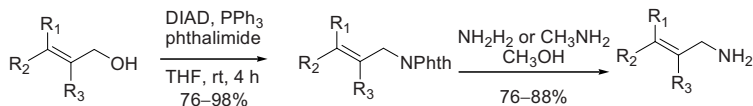
Synthesis of primary amines using potassium phthalimide and alkyl halides.

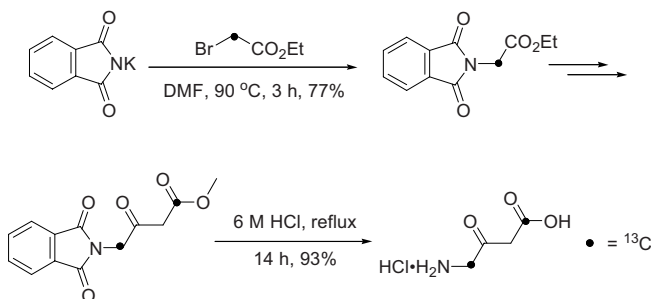
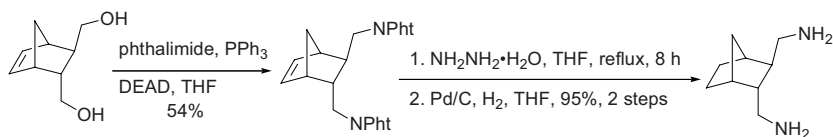


Example 1²



Example 2⁶



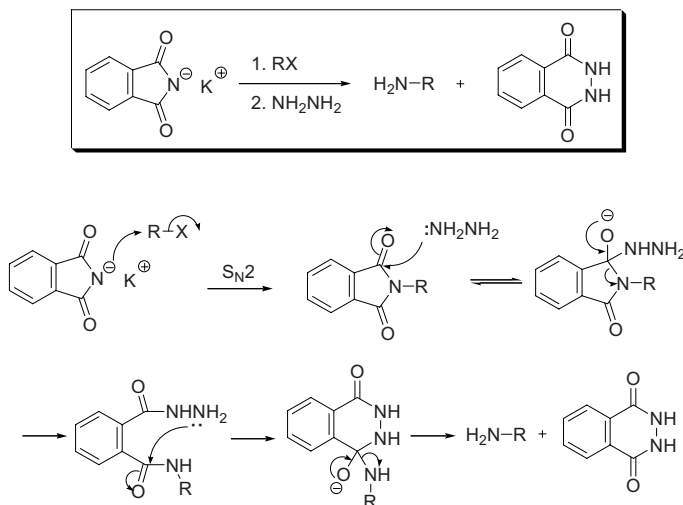
Example 3⁸Example 4⁹

References

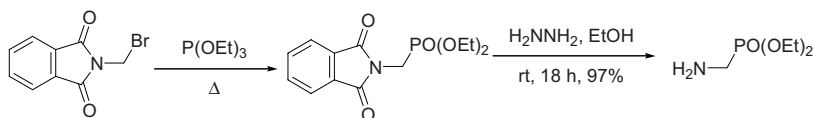
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Ing–Manske procedure

A variant of Gabriel amine synthesis where hydrazine is used to release the amine from the corresponding phthalimide:



Example 1⁶

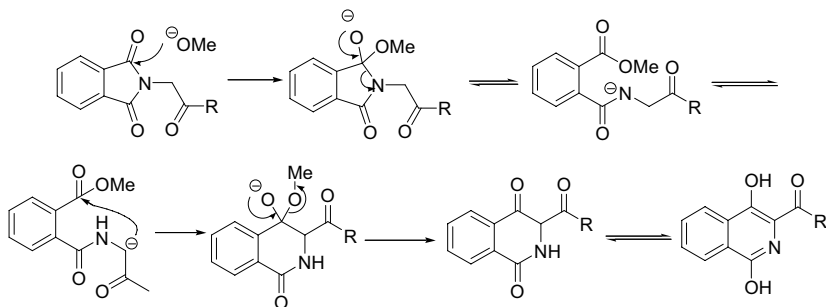
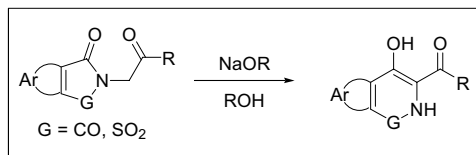


References

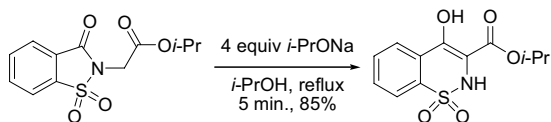
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Gabriel–Colman rearrangement

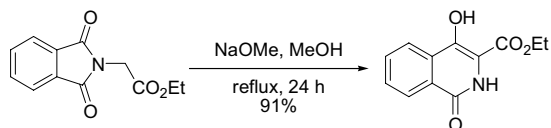
Reaction of the enolate of a maleimidyl acetate to provide isoquinoline 1,4-diol.



Example 1⁶



Example 2⁹

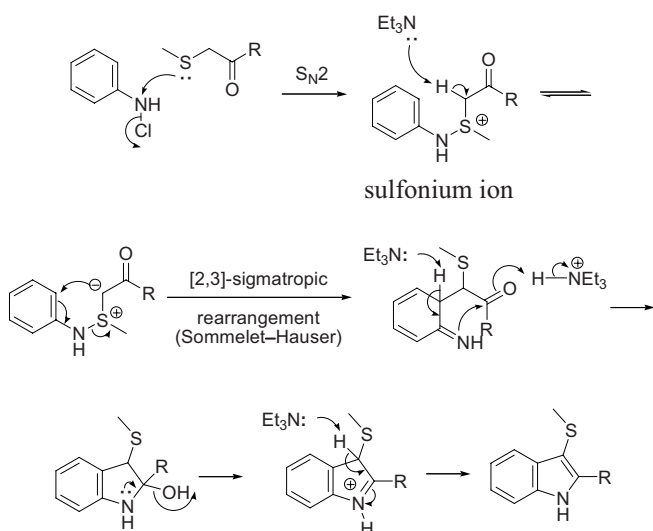
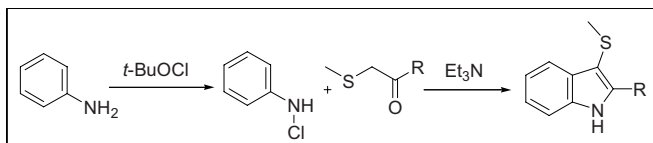


References

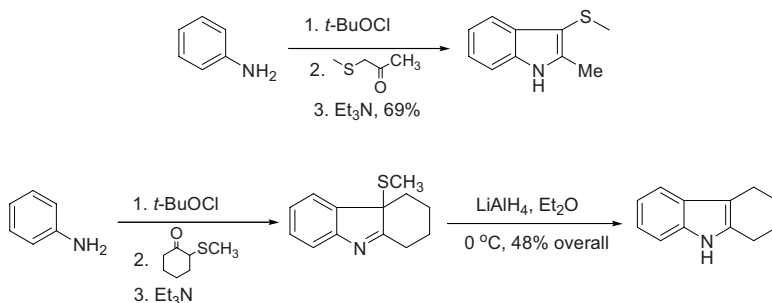
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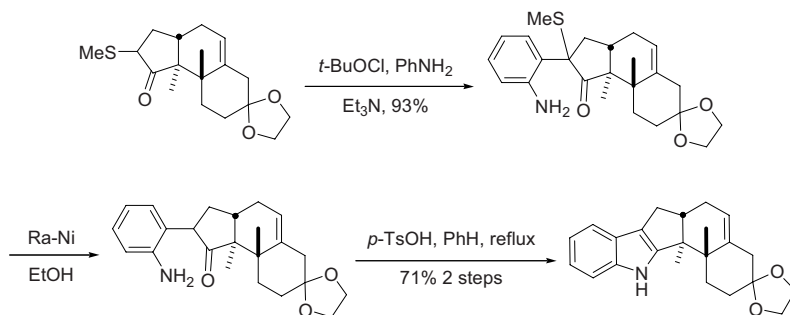
Gassman indole synthesis

The Gassman indole synthesis involves a one-pot process in which a hypohalite, a β -carbonyl sulfide derivative, and a base are added sequentially to an aniline or a substituted aniline to provide 3-thioalkoxyindoles. The sulfur can be easily removed by hydrogenolysis or Raney nickel.



Example 1¹



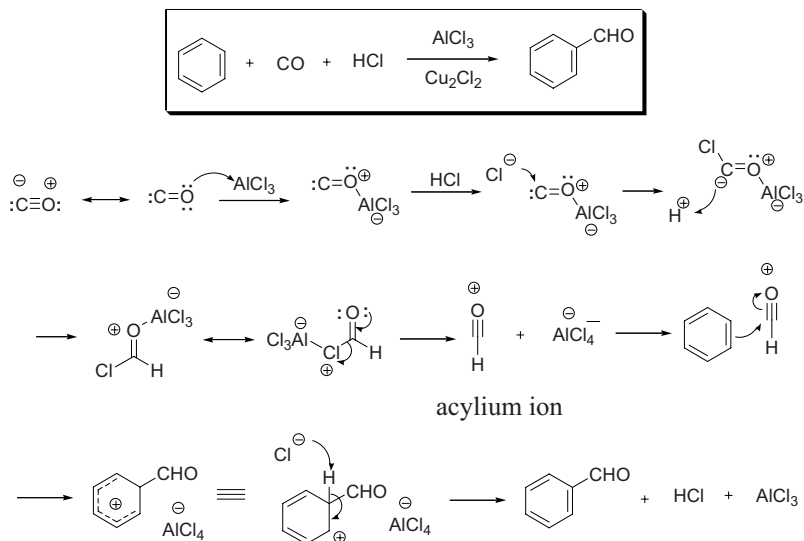
Example 2²

References

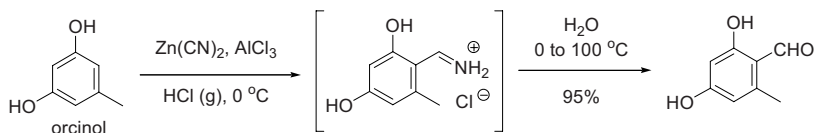
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Gattermann–Koch reaction

Formylation of arenes using carbon monoxide and hydrogen chloride in the presence of aluminum chloride under high pressure.



Example, A more practical variant⁴

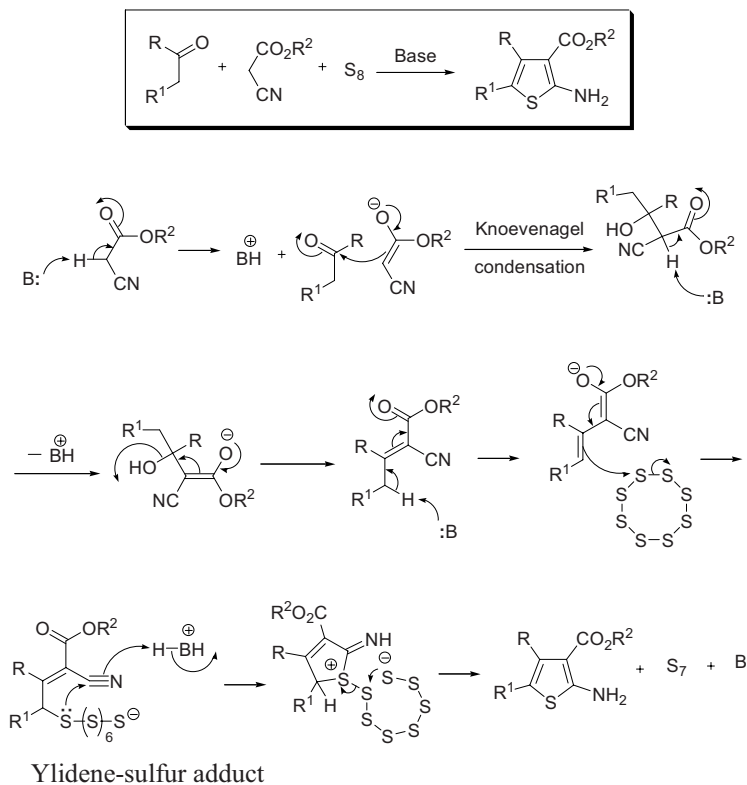


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Gewald aminothiophene synthesis

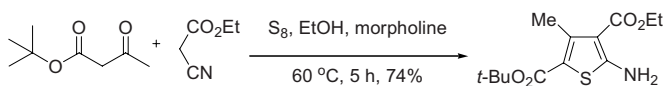
Base-promoted aminothiophene formation from ketone, α -active methylene nitrile and elemental sulfur.

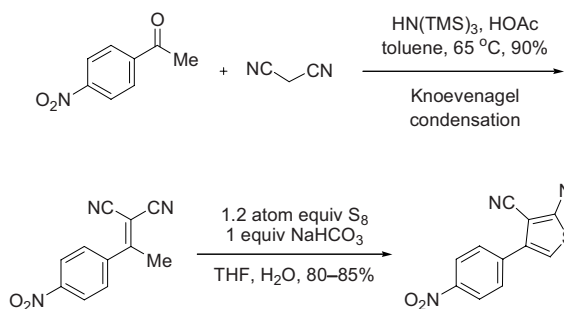
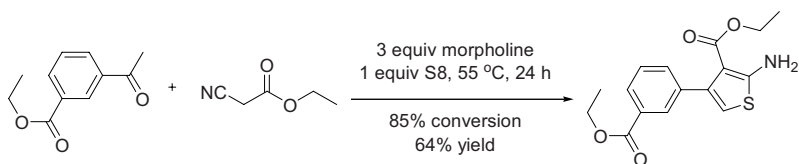
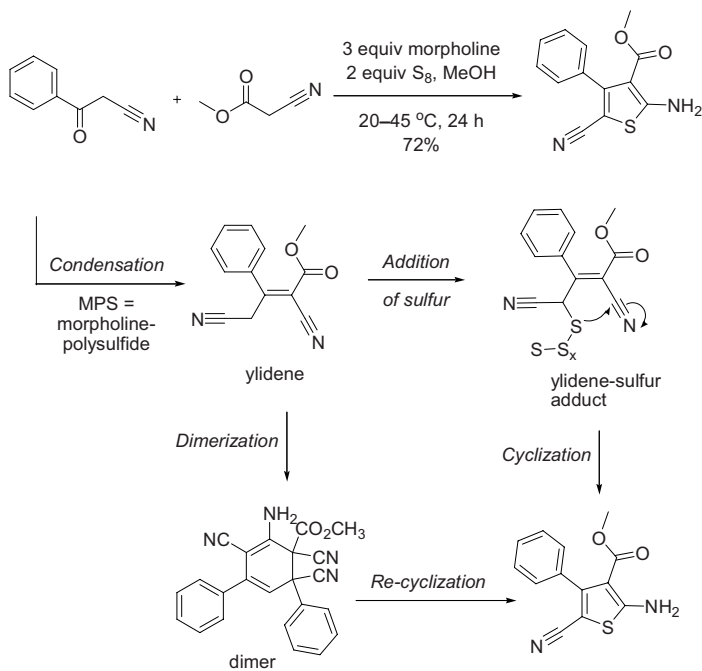


Example 1⁴



Example 2⁷



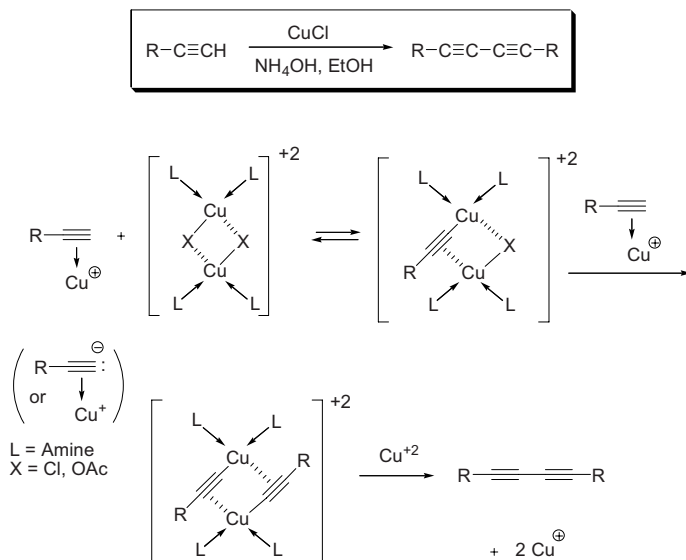
Example 3⁹Example 4¹⁰Example 5¹¹

References

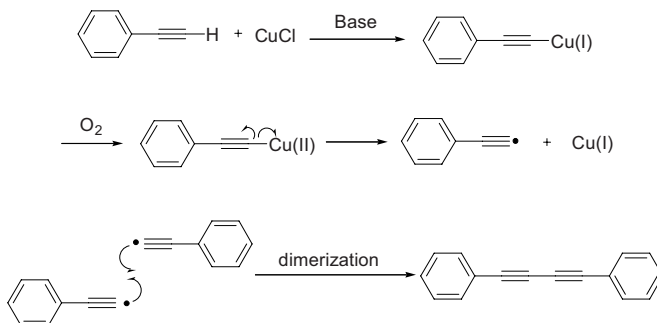
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Glaser coupling

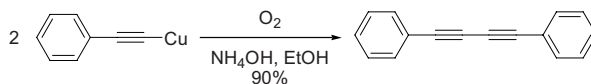
Oxidative homo-coupling of terminal alkynes using copper catalyst in the presence of oxygen.

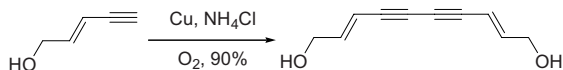
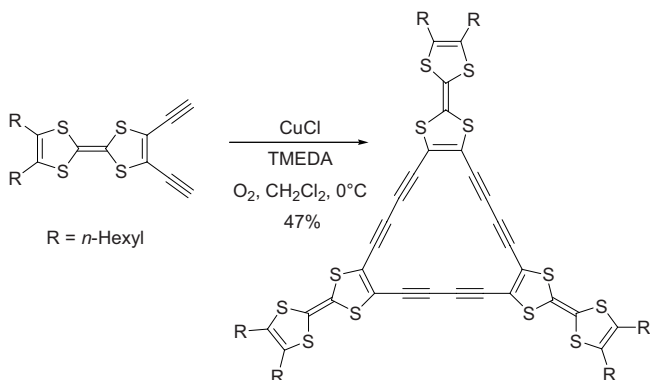


Alternatively, the radical mechanism is also operative:



Example 1¹



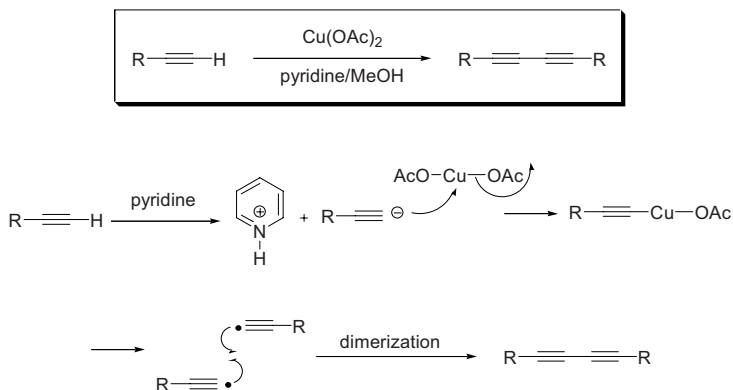
Example 2, Homo-coupling²Example 3⁷

References

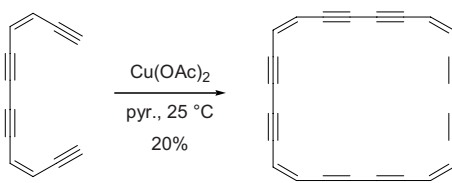
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Eglinton coupling

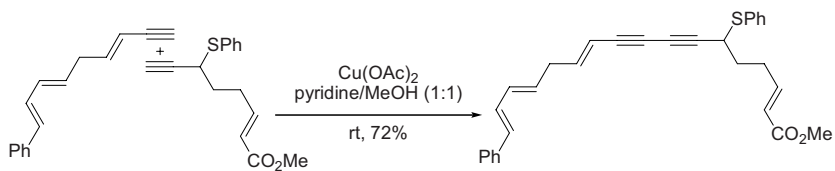
Oxidative homo-coupling of terminal alkynes mediated by stoichiometric (or often excess) $\text{Cu}(\text{OAc})_2$. A variant of the Glaser coupling reaction.



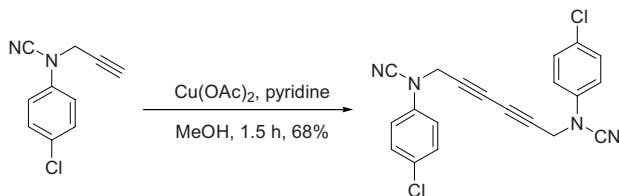
Example 1²

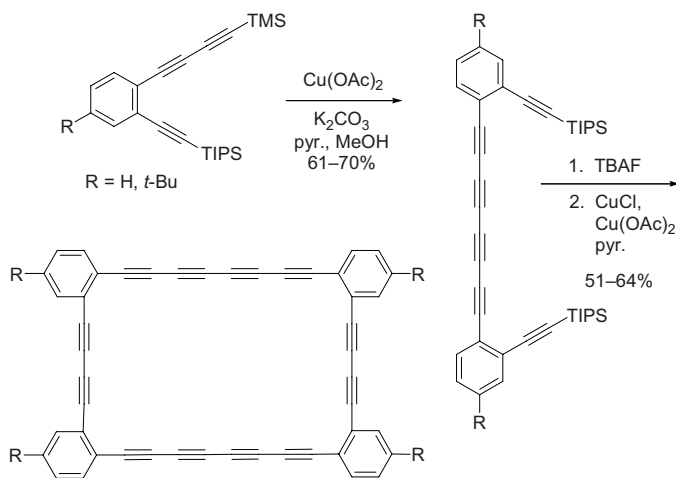
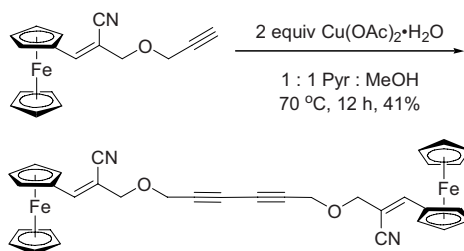
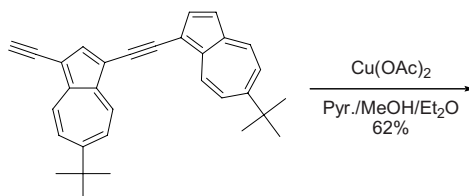


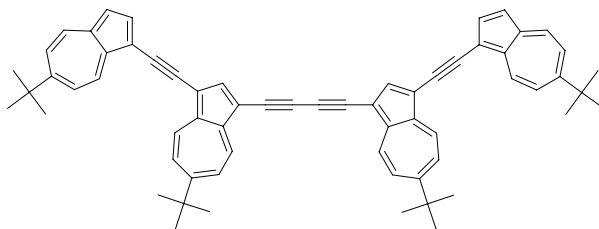
Example 2, Cross-coupling³



Example 3, Homo-coupling⁴



Example 4⁵Example 5¹¹Example 6¹²

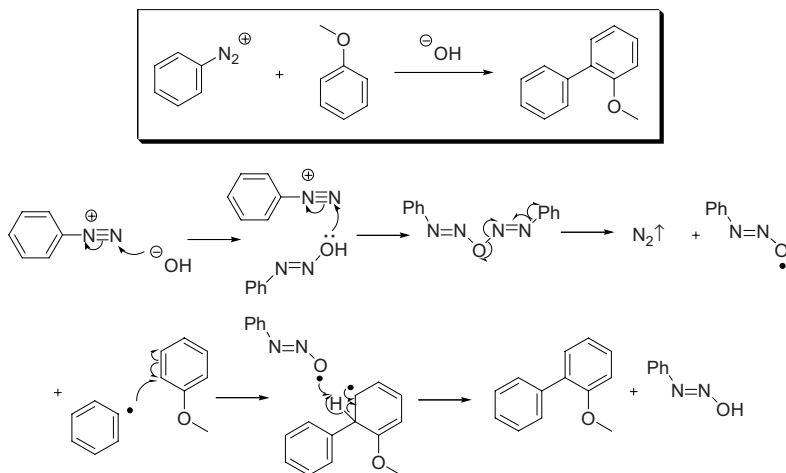


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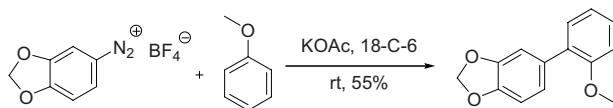
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Gomberg–Bachmann reaction

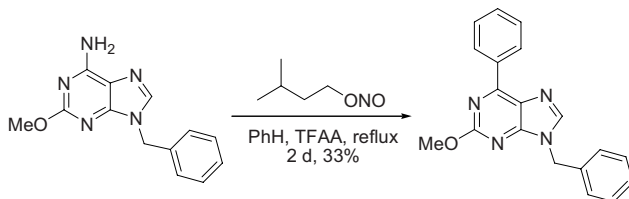
Base-promoted radical coupling between an aryl diazonium salt and an arene to form a diaryl compound.



Example 1⁴



Example 2⁵



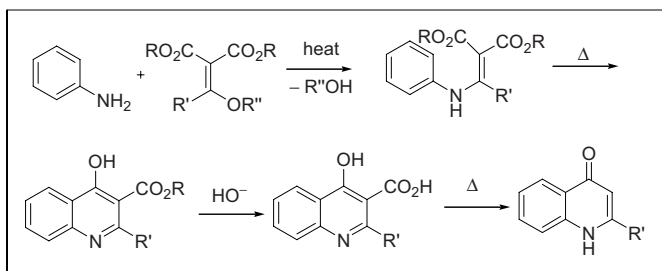
References

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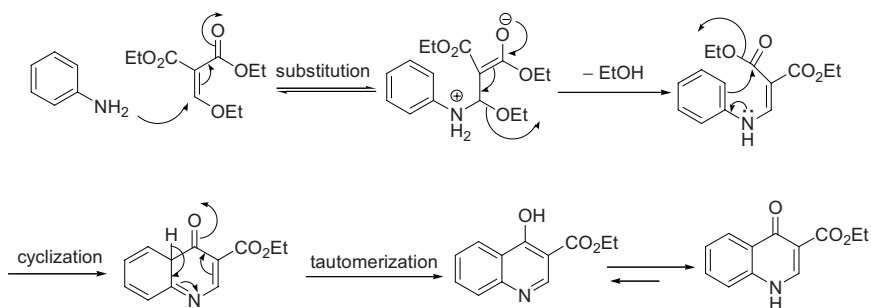
Gould–Jacobs reaction

The Gould–Jacobs reaction is a sequence of the following reactions:

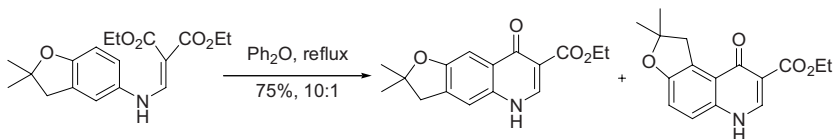
- Substitution of an aniline with either alkoxy methylenemalononic ester or acyl malonic ester providing the anilinomethylenemalononic ester;
- Cyclization of to the 4-hydroxy-3-carboalkoxyquinoline (4-hydroxyquinolines exist predominantly in 4-oxoform);
- Saponification to form acid;
- Decarboxylation to give the 4-hydroxyquinoline. Extension could lead to unsubstituted parent heterocycles with fused pyridine ring of Skraup type.

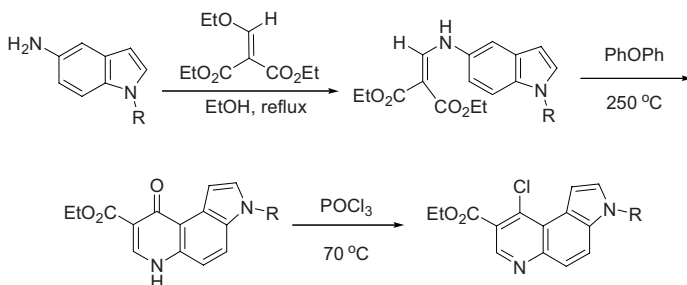
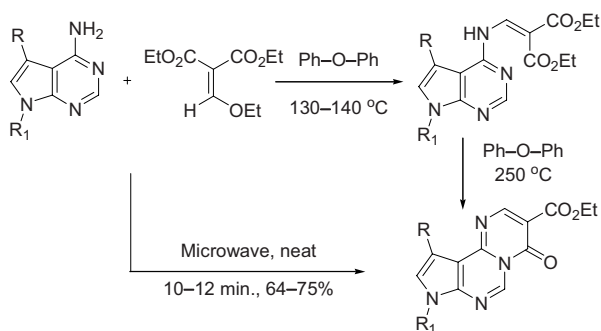
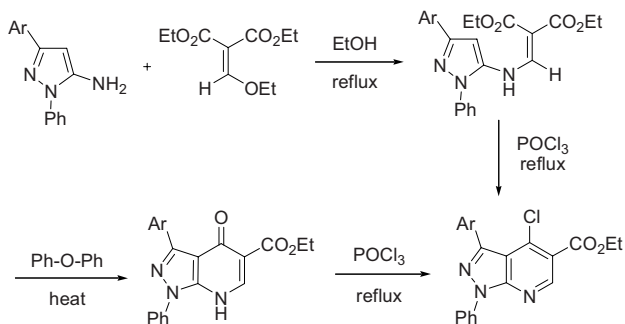


R = alkyl; R' = alkyl, aryl, or H; R'' = alkyl or H



Example 1³



Example 2⁸Example 3, Microwave-assisted Gould–Jacobs reaction⁹Example 4¹⁰

References

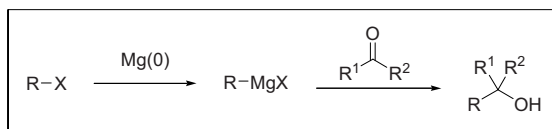
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ler Institute for Medical Research where he discovered the Gould–Jacobs reaction with his colleague Walter A. Jacobs.

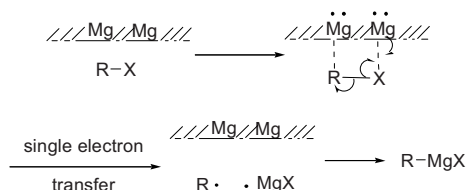
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Grignard reaction

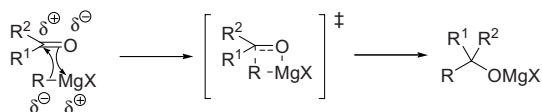
Addition of organomagnesium compounds (Grignard reagents), generated from organohalides and magnesium metal, to electrophiles.



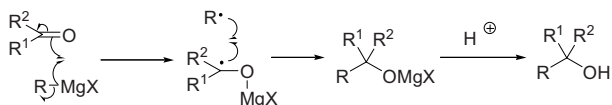
Formation of the Grignard reagent:



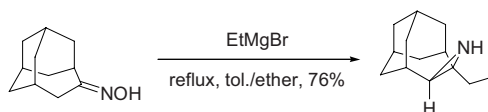
Grignard reaction, ionic mechanism:



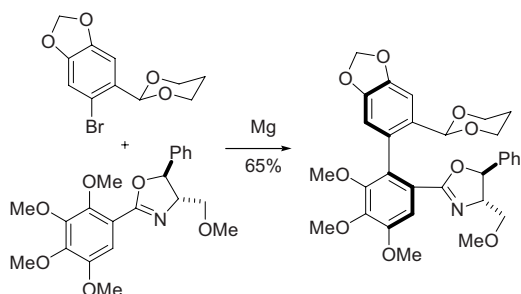
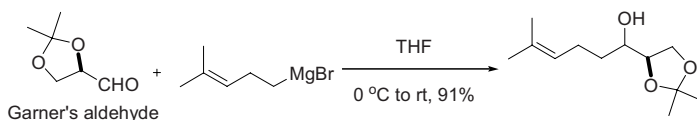
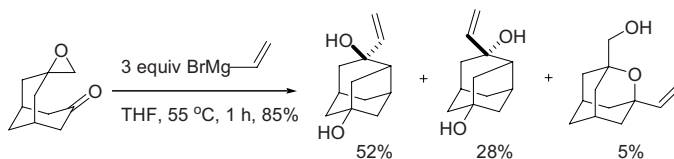
Radical mechanism,



Example 1⁴



This reaction is known as the *Hoch–Campbell aziridine synthesis*, which entails treatment of ketoximes with excess Grignard reagents and subsequent hydrolysis of the organometallic complex to produce aziridines.

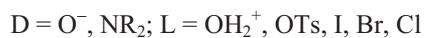
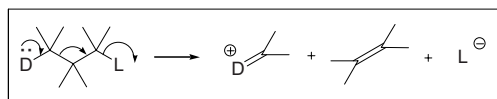
Example 2⁵Example 5¹⁰Example 6¹¹

References

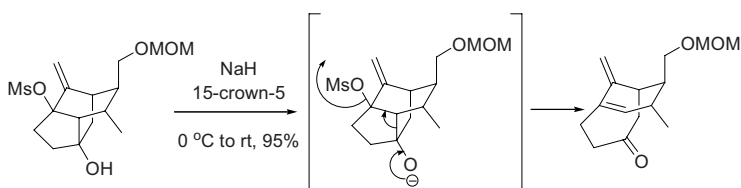
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Grob fragmentation

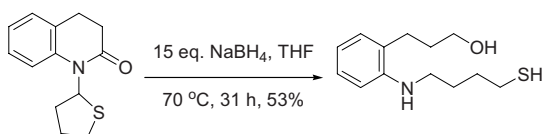
The C–C bond cleavage primarily via a concerted process involving a five atom system. General scheme:



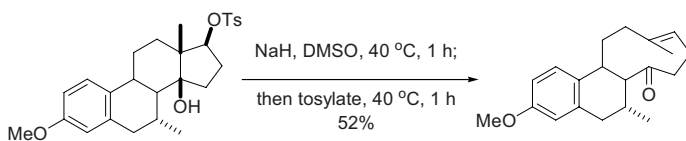
Example 1²



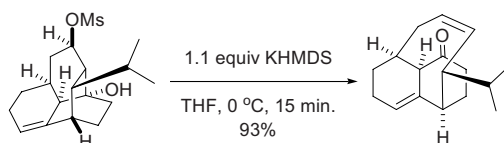
Example 2, Aza-Grob fragmentation³



Example 3⁷



Example 4⁸

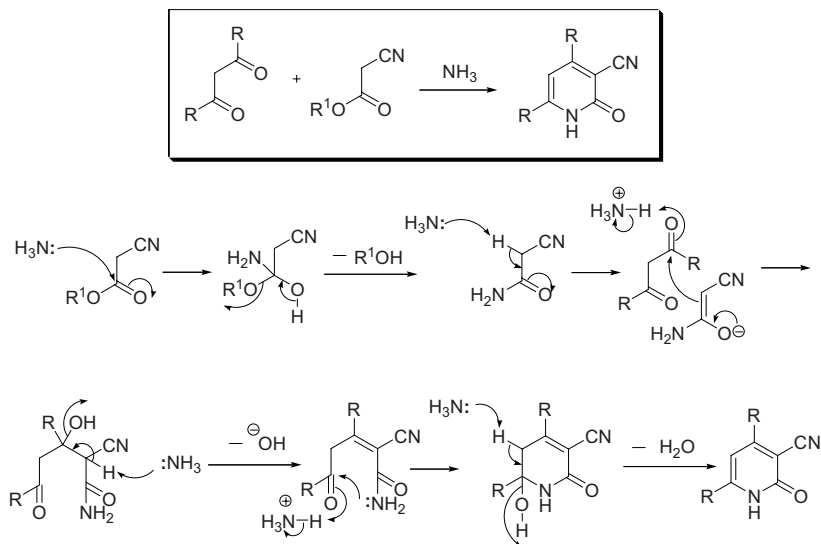


References

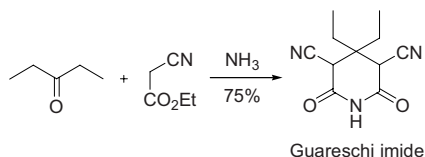
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Guareschi–Thorpe condensation

2-Pyridone formation from the condensation of cyanoacetic ester with diketone in the presence of ammonia.



Example⁶

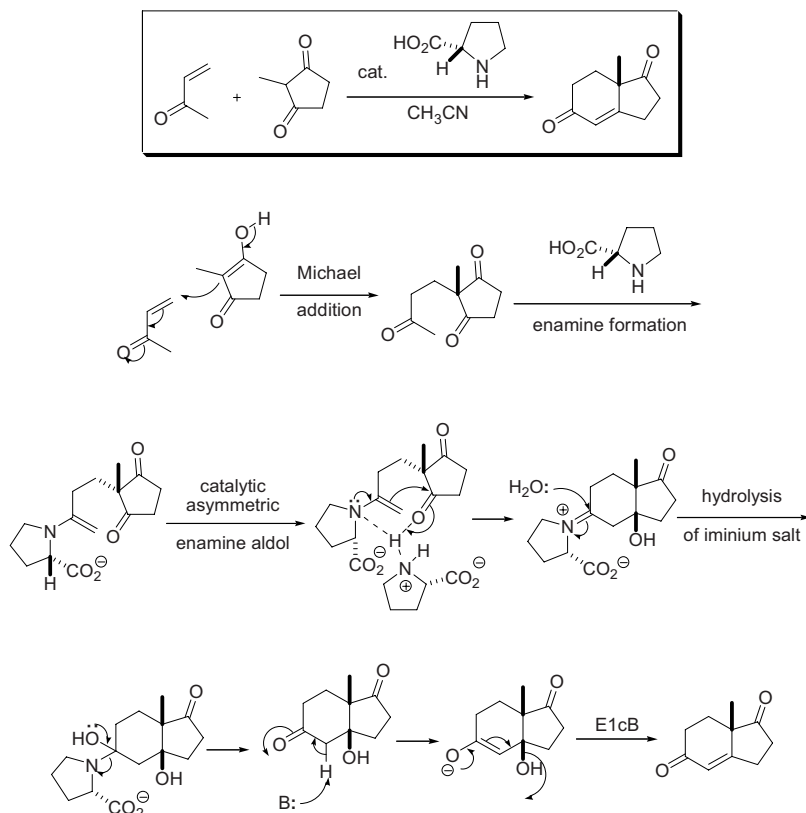


References

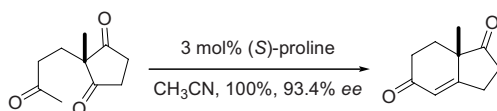
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Hajos–Wiechert reaction

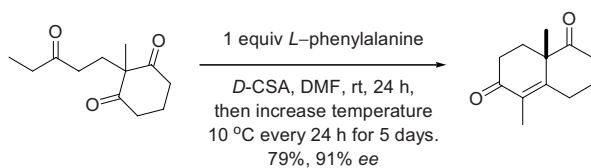
Asymmetric Robinson annulation catalyzed by (*S*)-(-)-proline.

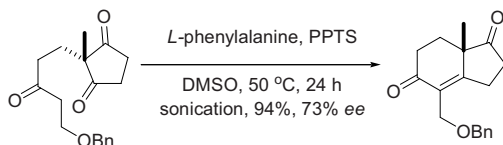
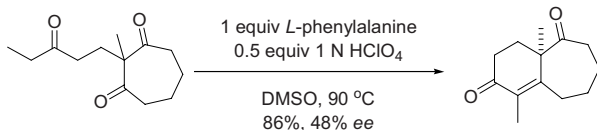


Example 1^{1a}



Example 2³



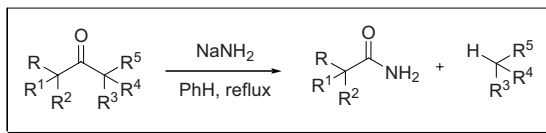
Example 3⁸Example 4⁹

References

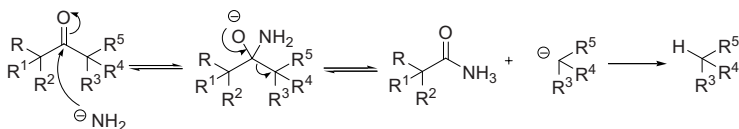
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Haller–Bauer reaction

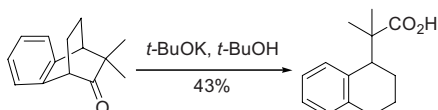
Base-induced cleavage of non-enolizable ketones leading to carboxylic amide derivative and a neutral fragment in which the carbonyl group is replaced by a hydrogen.



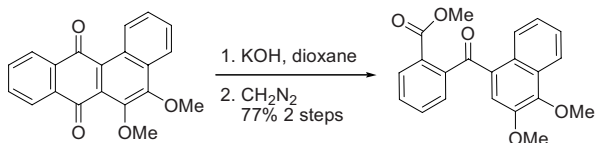
non-enolizable ketone



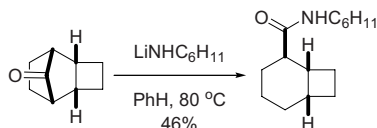
Example 1⁴



Example 2⁹



Example 3, Racemization¹⁰

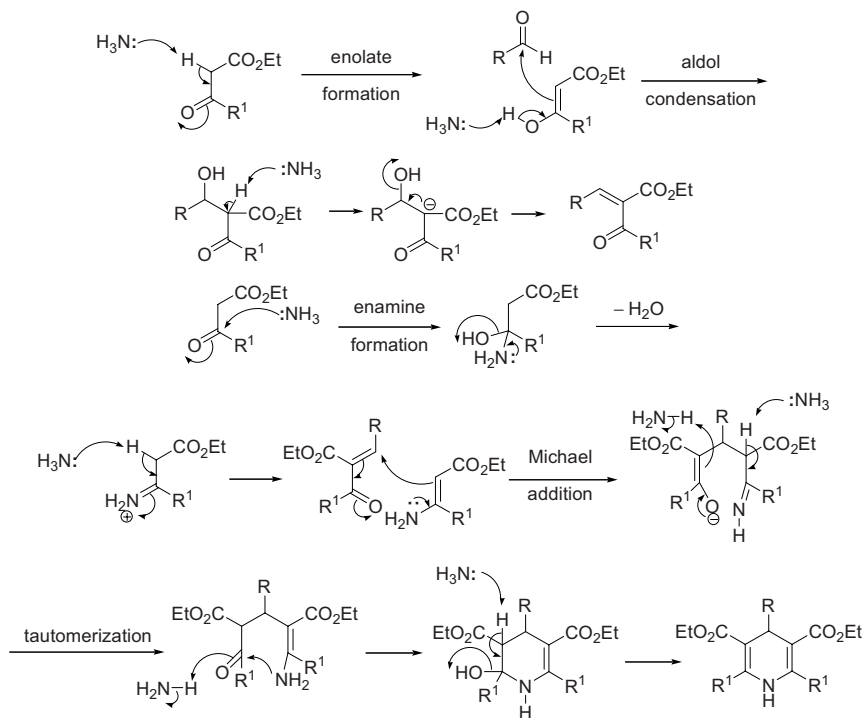
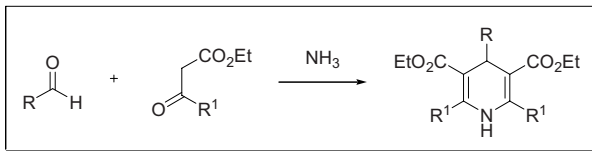


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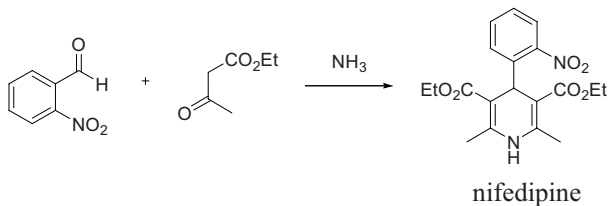
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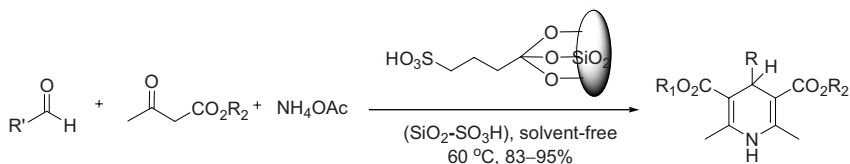
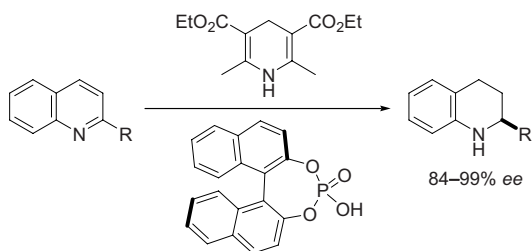
Hantzsch dihydropyridine synthesis

1,4-Dihydropyridine from the condensation of aldehyde, β -ketoester and ammonia. Hantzsch 1,4-dihydropyridines are popular reducing reagents in organocatalysis.



Example 1²



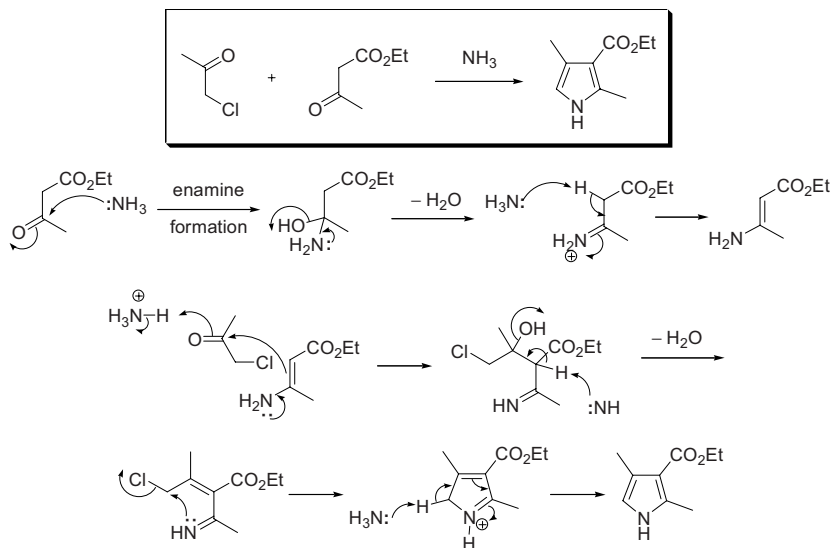
Example 2⁹Example 3, Hantzsch 1,4-dihydropyridine as a hydrogen donor¹⁰

References

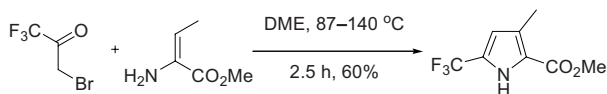
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Hantzsch pyrrole synthesis

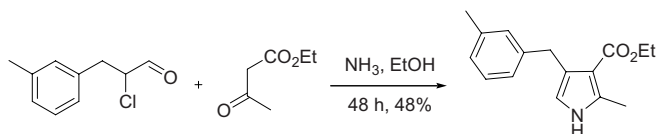
Reaction of α -chloromethyl ketones with β -ketoesters and ammonia to assemble pyrroles.



Example 1⁴



Example 2⁷

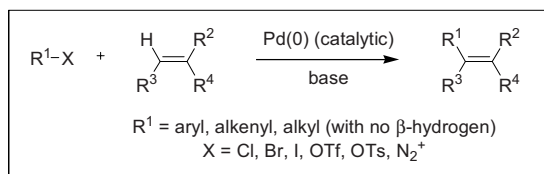


References

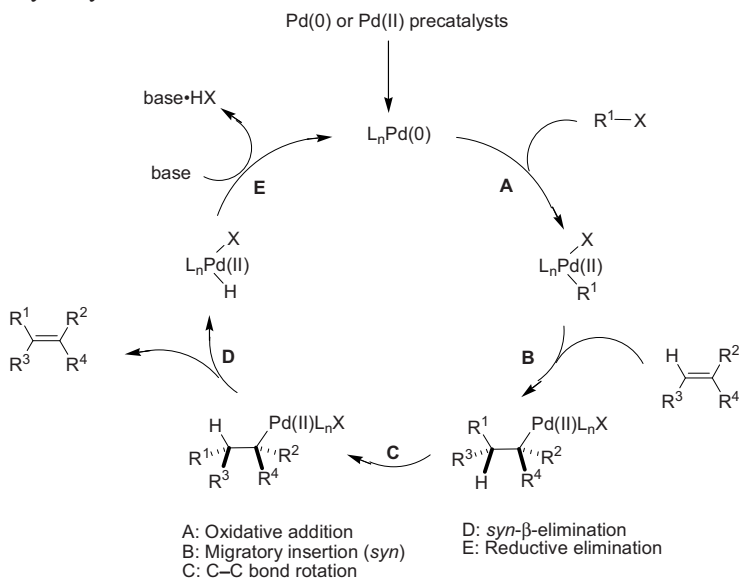
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Heck reaction

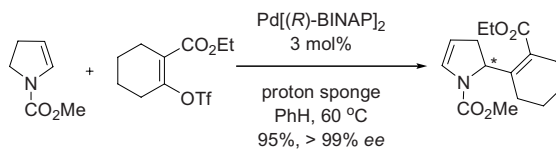
The palladium-catalyzed alkenylation or arylation of olefins.

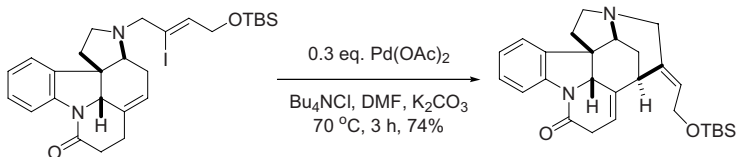
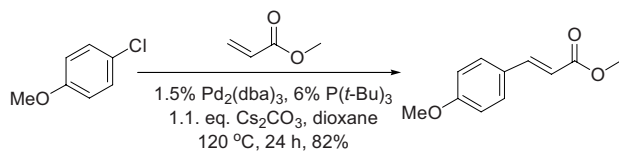
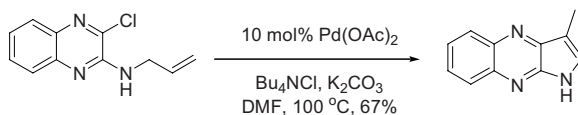
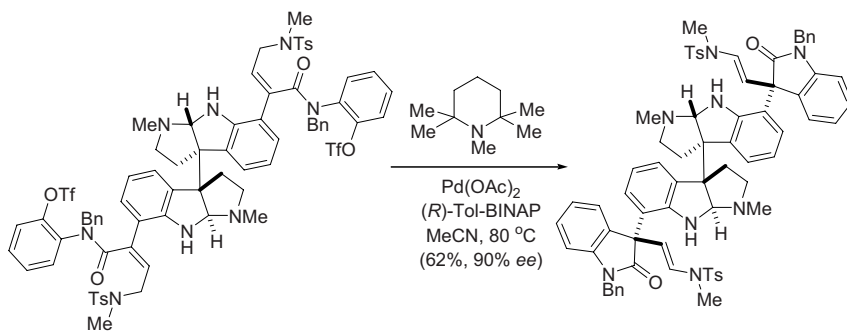
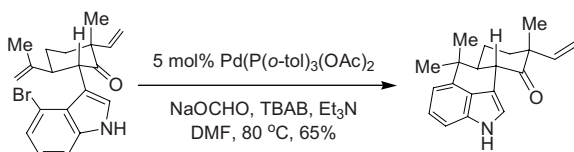


The catalytic cycle:



Example 1, Asymmetric intermolecular Heck reaction⁶



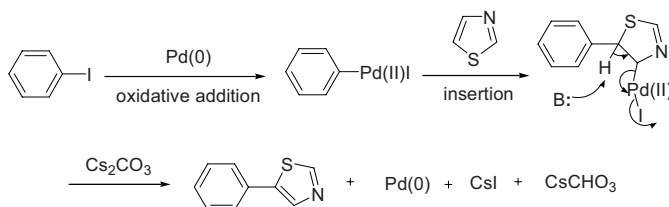
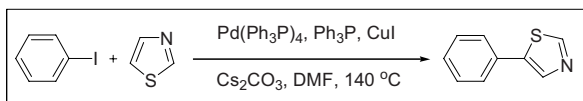
Example 2, Intramolecular Heck⁷Example 3⁸Example 4, Intramolecular Heck⁹Example 5, Intramolecular Heck¹³Example 6, Reductive Heck reaction¹⁷

References

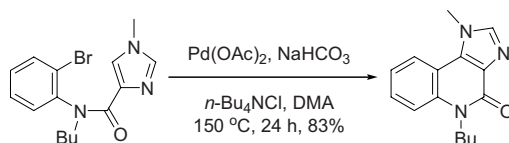
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Heteroaryl Heck reaction

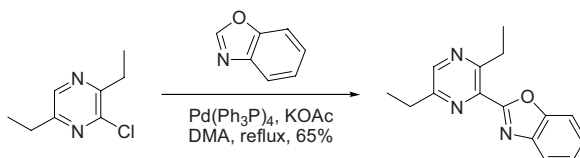
Intermolecular or intramolecular Heck reaction that occurs onto a heteroaryl re-cipient.



Example 1²



Example 2³

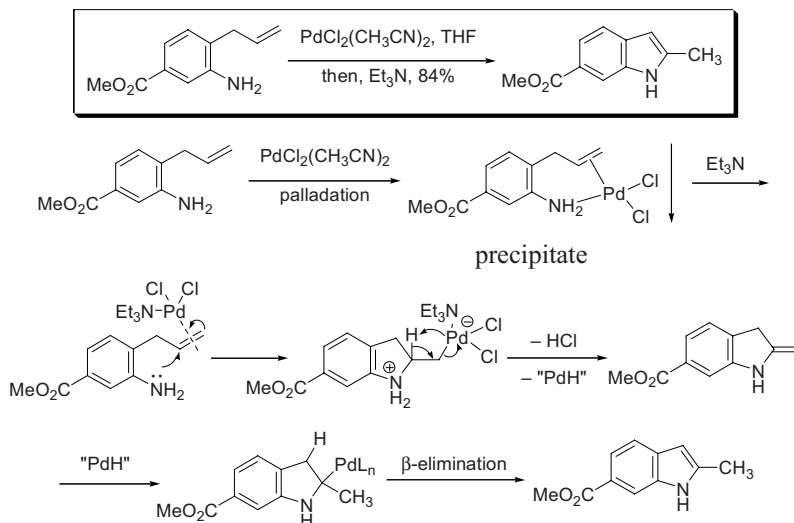


References

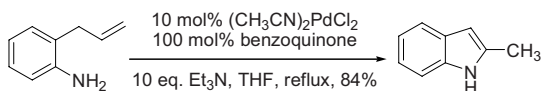
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Hegedus indole synthesis

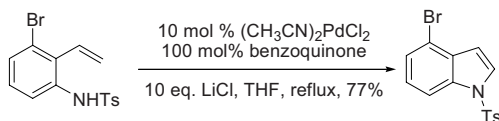
Stoichiometric Pd(II)-mediated oxidative cyclization of alkenyl anilines to indoles. Cf. Wacker oxidation.



Example 1^{1a}



Example 2^{1d}

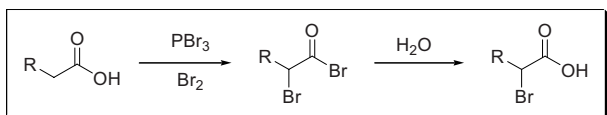


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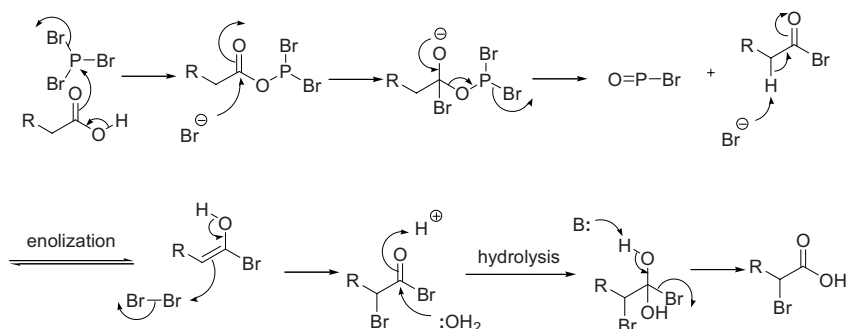
- (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674–2676. Lou Hegedus is a professor at Colorado State University. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (c) Hegedus, L. S.; Winton, P. M.; Varaprath, S. *J. Org. Chem.* **1981**, *46*, 2215–2221. (d) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657–2662. (e) Hegedus, L. S. *Angew. Chem., Int. Ed.* **1988**, *27*, 1113–1126. (Review).
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Hell–Volhard–Zelinsky reaction

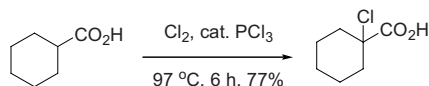
α -Halogenation of carboxylic acids using X_2/PBr_3 .



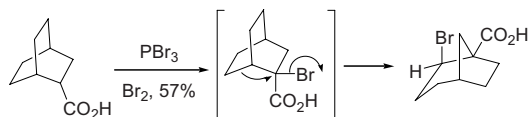
α -bromoacid



Example 1⁵



Example 2⁶

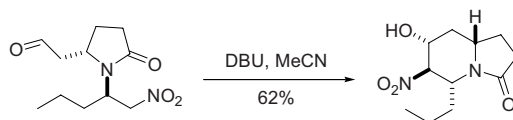


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Tyaspol, Russia. He studied at Göttingen under Victor Meyer, receiving his Ph.D. in 1889. Zelinsky returned to Russia and became a professor at the University of Moscow. On his ninetieth birthday in 1951, he was awarded the Order of Lenin.

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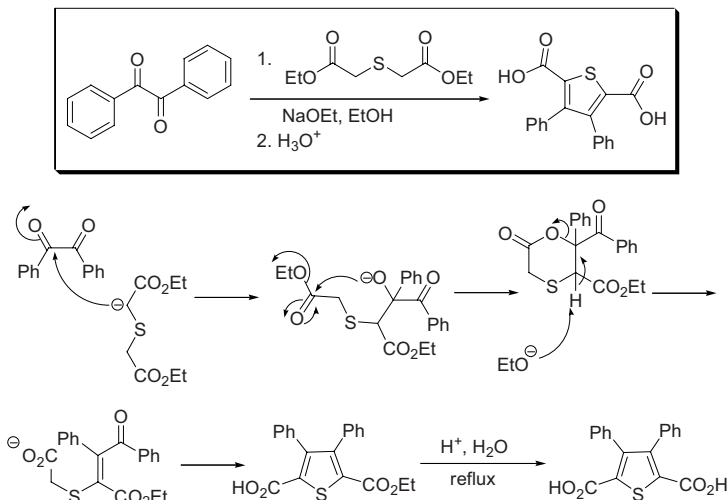
Example 4, Intramolecular Henry reaction¹⁰

References

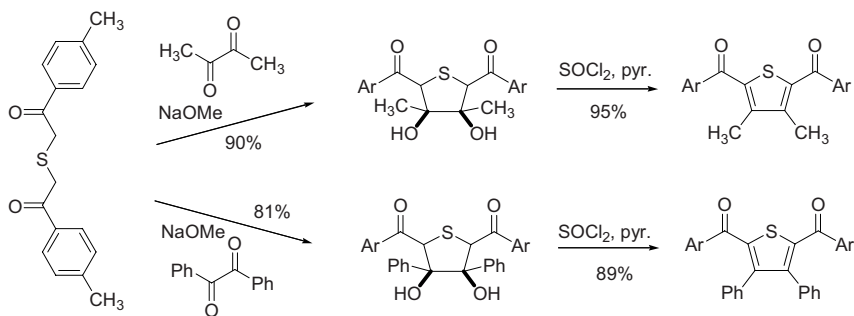
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Hinsberg synthesis of thiophene derivatives

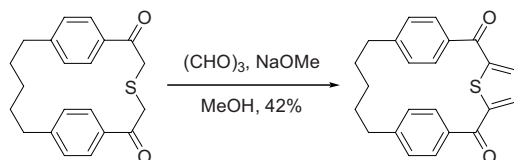
Condensation of diethyl thiodiglycolate and α -diketones under basic conditions, which provides 3,4-disubstituted thiophene-2,5-dicarbonyls upon hydrolysis of the crude ester product with aqueous acid.

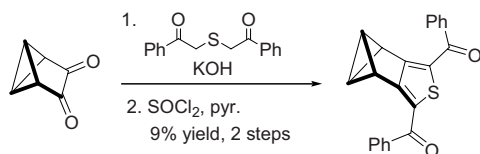
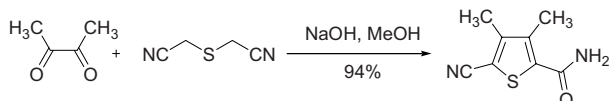
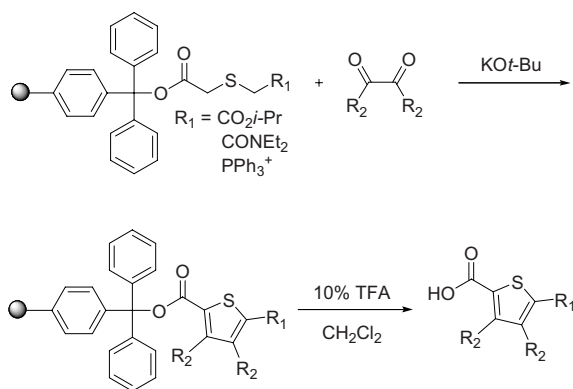


Example 1²



Example 2⁴



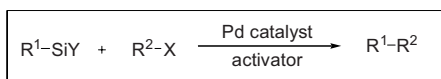
Example 3⁵Example 4⁶Example 5, Polymer-support Hinsberg thiophene synthesis⁹

References

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Hiyama cross-coupling reaction

Palladium-catalyzed cross-coupling reaction of organosilicons with organic halides, triflates, *etc.* In the presence of an activating agent such as fluoride or hydroxide (transmetalation is reluctant to occur without the effect of an activating agent). For the catalytic cycle, see the Kumada coupling on page 325.



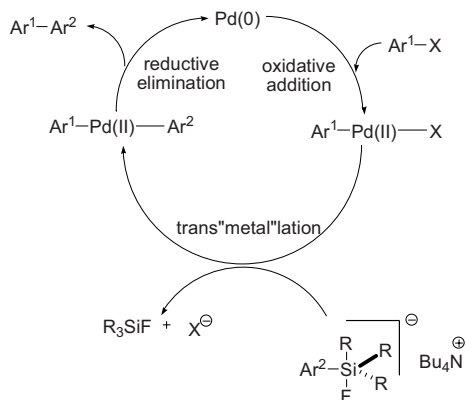
R^1 = alkenyl, aryl, alkynyl, alkyl

R^2 = aryl, alkyl, alkenyl

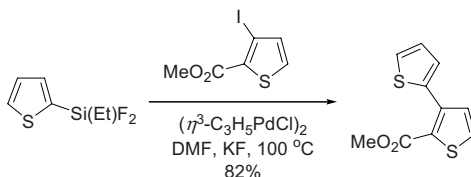
Y = (OR)₃, Me₃, Me₂OH, Me_(3-n)F_(n+3)

X = Cl, Br, I, OTf

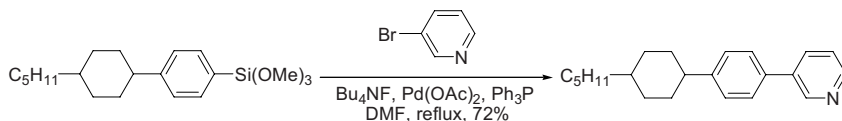
activator = TBAF, base

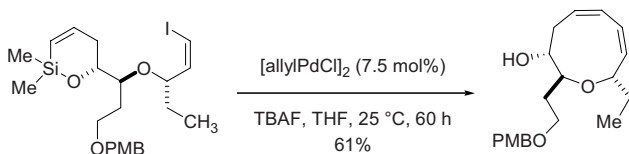
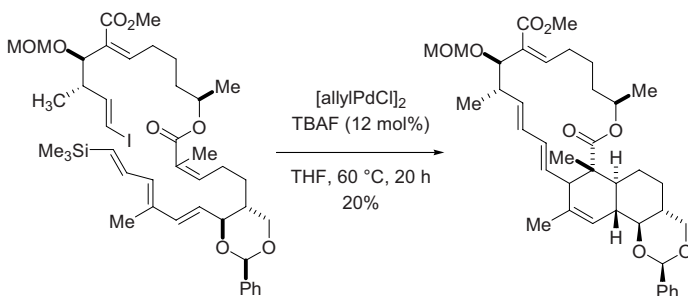


Example 1^{1a}



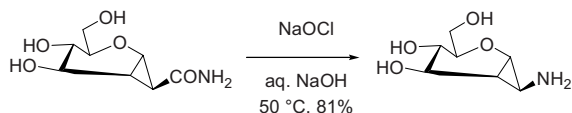
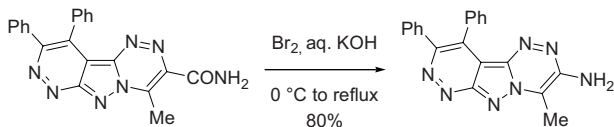
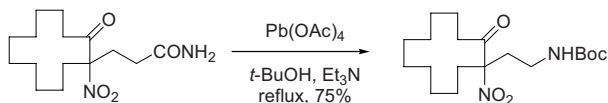
Example 2²



Example 3⁷Example 4⁹

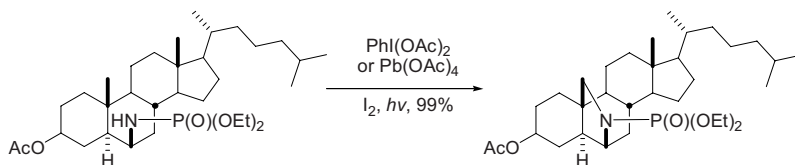
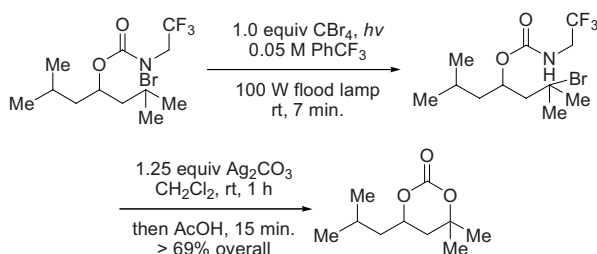
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Example 4, Sodium hypochlorite⁷Example 5, The original conditions, bromine and hydroxide⁹Example 6, Lead tetraacetate¹⁰

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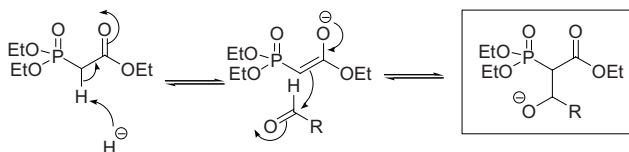
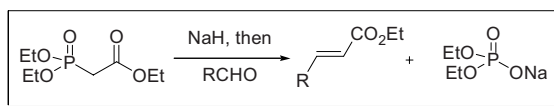
Example 4⁷Example 5¹²

References

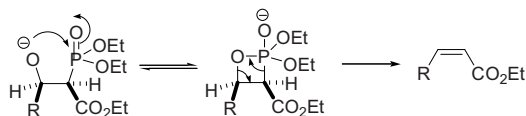
- (a) Hofmann, A. W. *Ber.* **1883**, *16*, 558–560. (b) Löffler, K.; Freytag, C. *Ber.* **1909**, *42*, 3727.
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Horner–Wadsworth–Emmons reaction

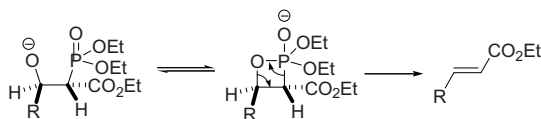
Olefin formation from aldehydes and phosphonates. Workup is more advantageous than the corresponding Wittig reaction because the phosphate by-product can be washed away with water. Typically gives the *trans*- rather than the *cis*-olefins.



The stereochemical outcome: *erythro* (kinetic) or *threo* (thermodynamic)

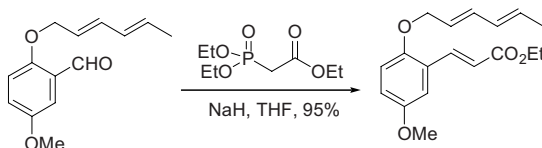


erythro, kinetic adduct

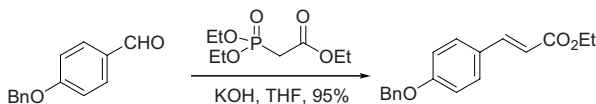


threo, thermodynamic adduct

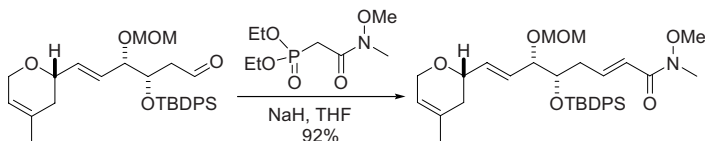
Example 1³

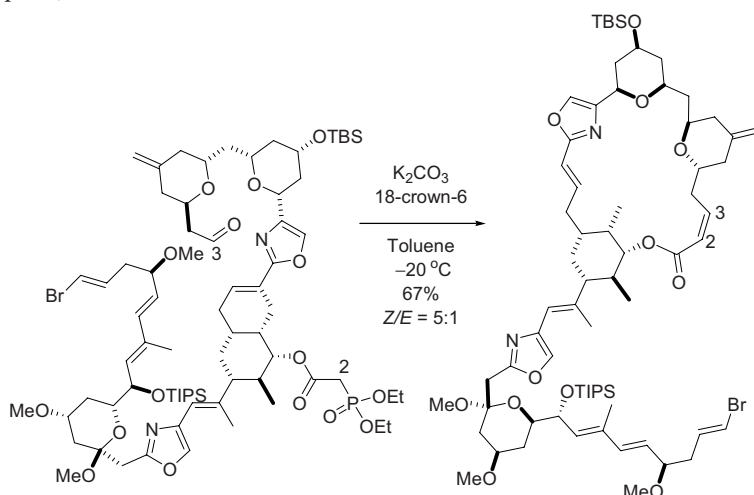


Example 2⁴



Example 3⁷



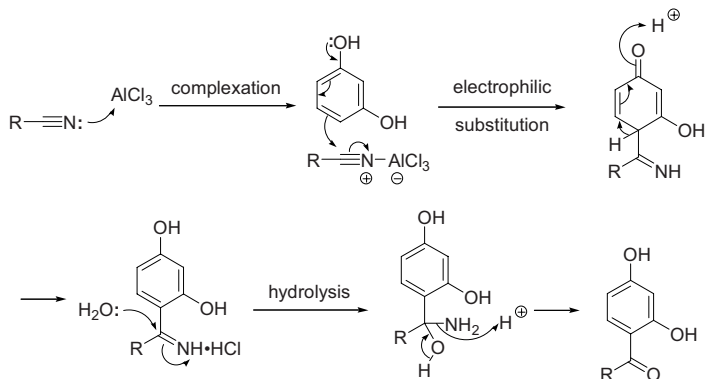
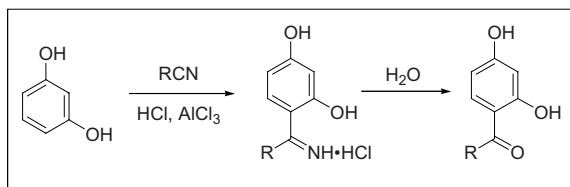
Example 4, Intramolecular Horner–Wadsworth–Emmons⁹

References

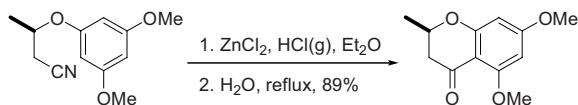
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Houben–Hoesch reaction

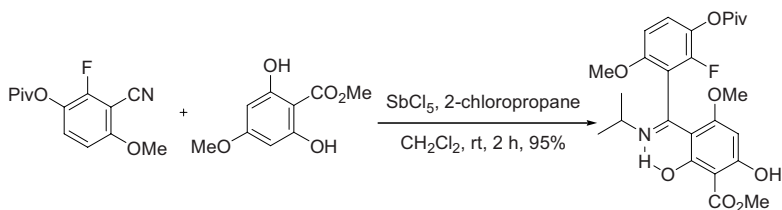
Acid-catalyzed acylation of phenols as well as phenolic ethers using nitriles.



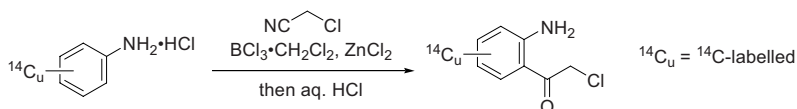
Example 1, Intramolecular Houben–Hoesch reaction³

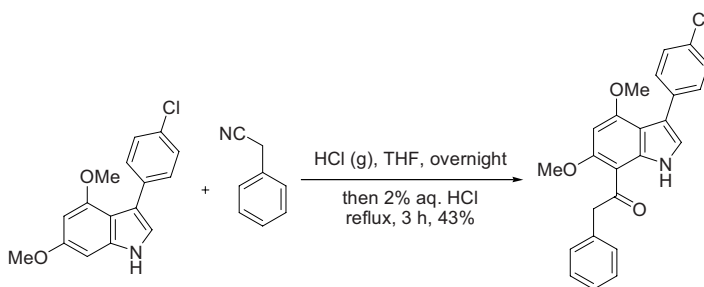


Example 2⁶



Example 3⁸



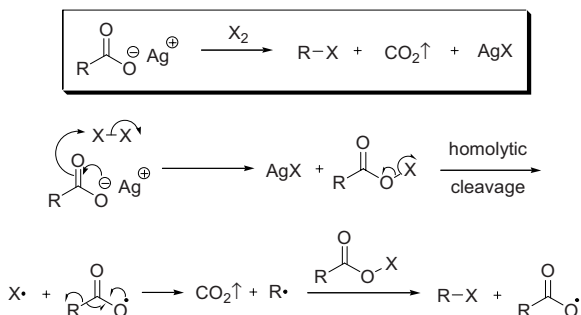
Example 4⁹

References

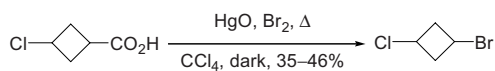
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Hunsdiecker–Borodin reaction

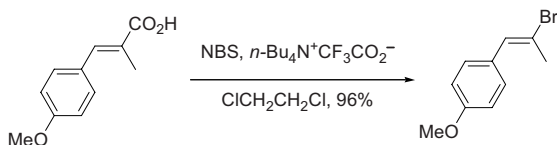
Conversion of silver carboxylate to halide by treatment with halogen.



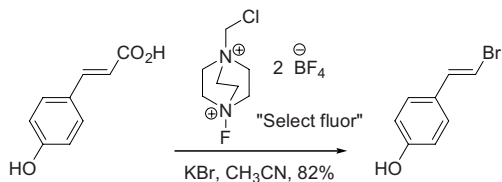
Example 1⁵



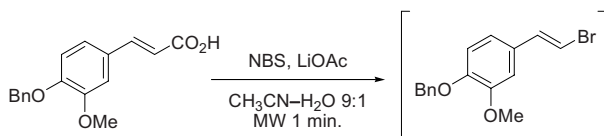
Example 2⁶

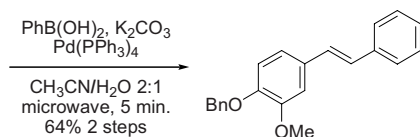


Example 3⁸



Example 4, One-pot microwave-Hunsdiecker–Borodin followed by Suzuki¹⁰



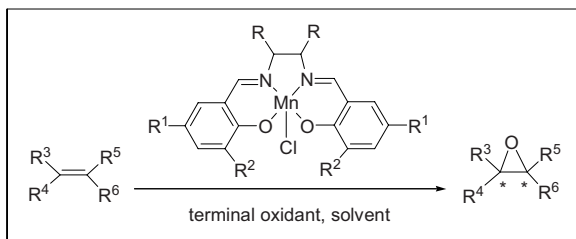


References

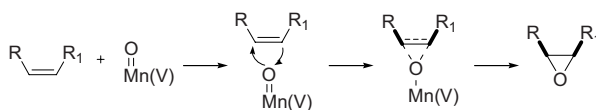
1. (a) Borodin, A. *Ann.* **1861**, *119*, 121–123. Aleksandr Porfirevič Borodin (1833–1887) was born in St Petersburg, the illegitimate son of a prince. He prepared methyl bromide from silver acetate in 1861, but another eighty years elapsed before Heinz and Cläre Hunsdiecker converted Borodin's synthesis into a general method, the Hunsdiecker or Hunsdiecker–Borodin reaction. Borodin was also an accomplished composer and is now best known for his musical masterpiece, opera Prince Egor. He kept a piano outside his laboratory. (b) Hunsdiecker, H.; Hunsdiecker, C. *Ber.* **1942**, *75*, 291–297. Cläre Hunsdiecker was born in 1903 and educated in Cologne. She developed the bromination of silver carboxylate alongside her husband, Heinz.
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Jacobsen–Katsuki epoxidation

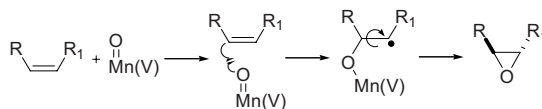
Mn(III)salen-catalyzed asymmetric epoxidation of (*Z*)-olefins.



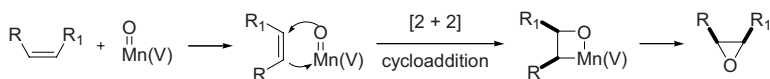
1. Concerted oxygen transfer (*cis*-epoxide):



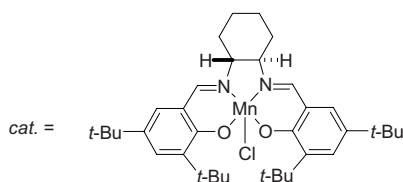
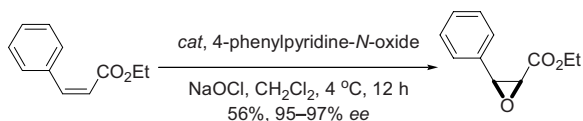
2. Oxygen transfer *via* radical intermediate (*trans*-epoxide):

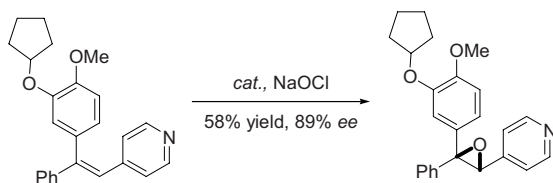
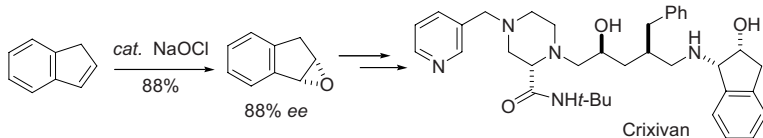


3. Oxygen transfer *via* manganaoxetane intermediate (*cis*-epoxide):



Example 1²



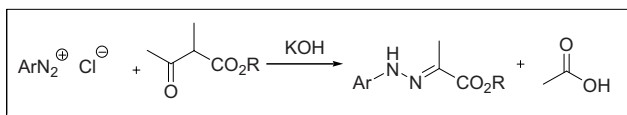
Example 2⁵Example 2⁶

References

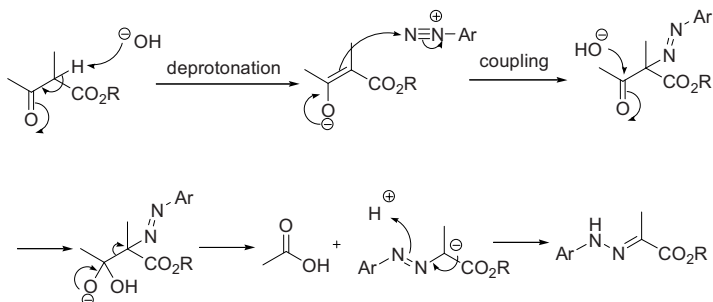
- (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2903. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345–7348. (c) Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055–1058. (d) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320–4323. (e) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457–5460.
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Japp–Klingemann hydrazone synthesis

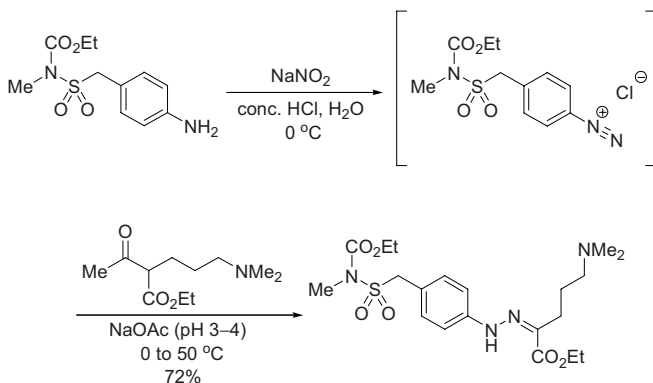
Hydrazones from β -ketoesters and diazonium salts with the acid or base.



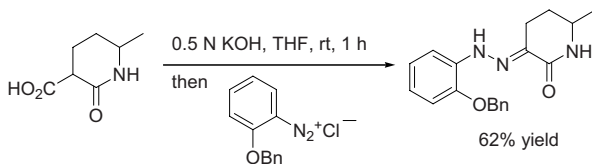
Diazonium salt β -keto-ester hydrazone

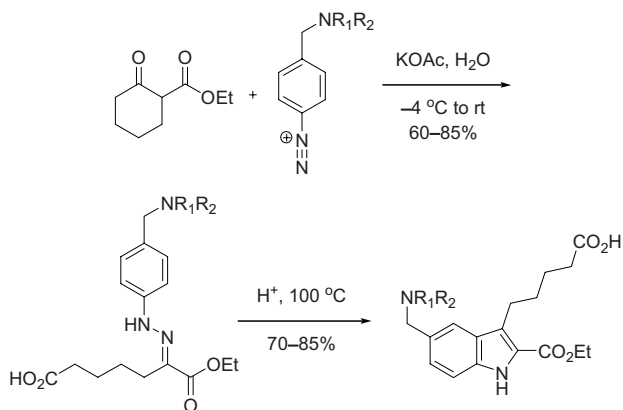


Example 1⁴



Example 2⁶



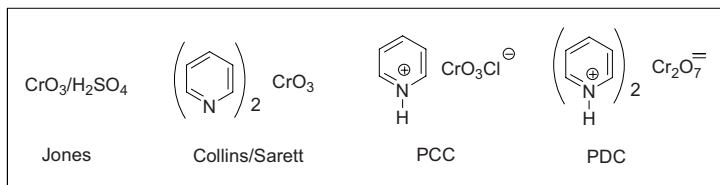
Example 3¹⁰

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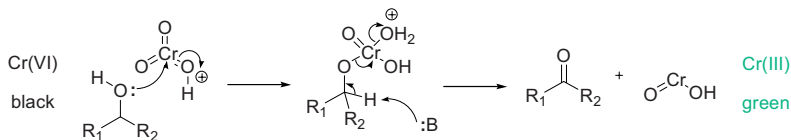
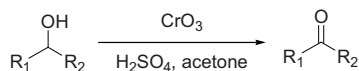
Jones oxidation

The **Collins/Sarett oxidation** (chromium trioxide-pyridine complex), and **Corey's PCC** (pyridinium chlorochromate) and **PDC** (pyridinium dichromate) **oxidations** follow a similar pathway as the **Jones oxidation** (chromium trioxide and sulfuric acid in acetone). All these oxidants have a chromium (VI), normally black or yellow, which is reduced to Cr(IV), often green.

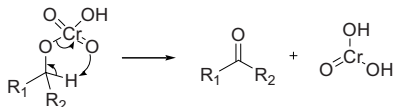


Jones oxidation

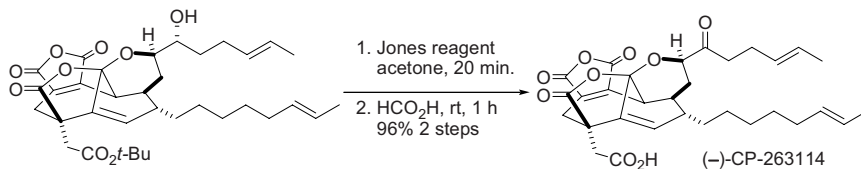
By the Jones oxidation, the primary alcohols are oxidized to the corresponding aldehyde or carboxylic acids, whereas the secondary alcohols are oxidized to the corresponding ketones.

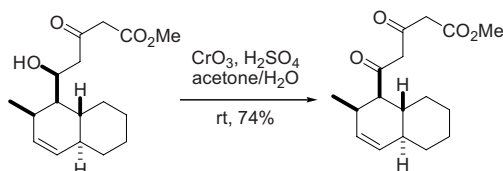
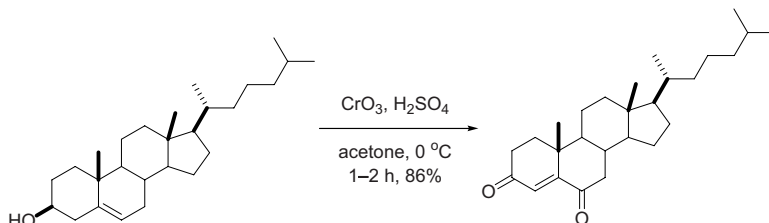


The intramolecular mechanism is also operative:



Example 1⁶



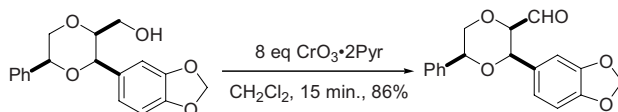
Example 2⁷Example 3¹⁹

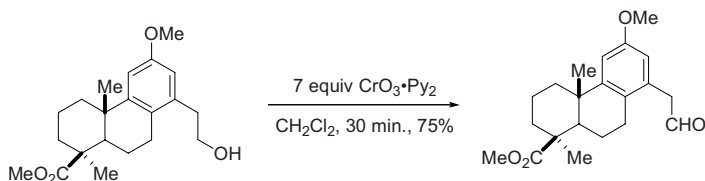
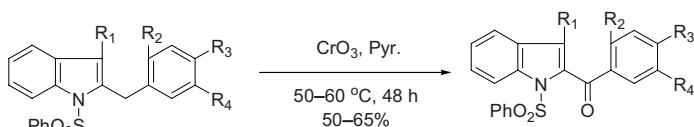
References

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Collins–Sarett oxidation

Different from the Jones oxidation, the Collins–Sarett oxidation converts primary alcohols to the corresponding aldehydes.

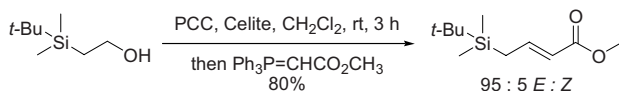
Example 1⁵

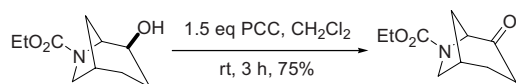
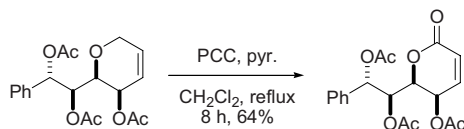
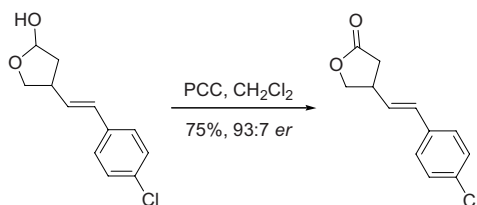
Example 2⁷Example 3⁹

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PCC oxidation

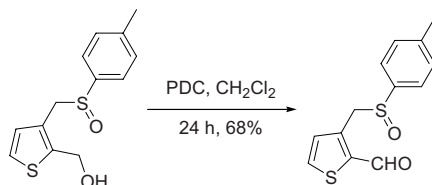
Example 1, One-pot PCC–Wittig reactions²

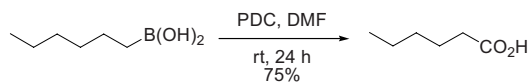
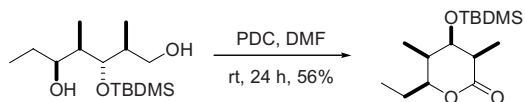
Example 2³Example 3⁴Example 4⁵

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PDC oxidation

Example 1²

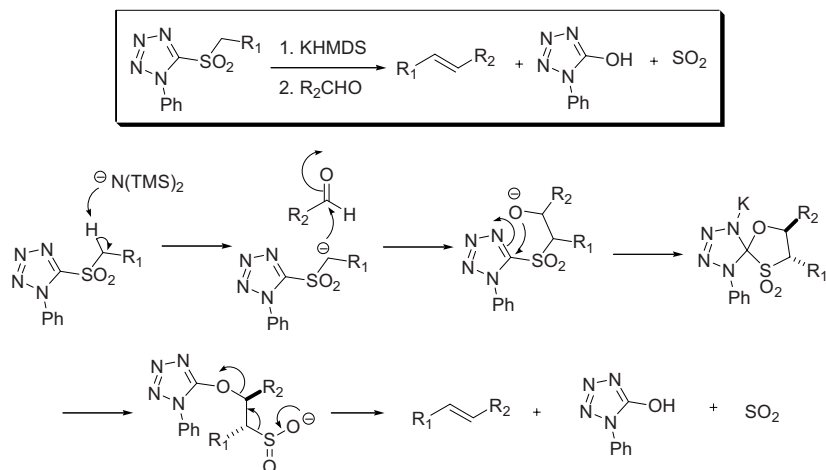
Example 2, Cleavage of primary carbon–boron bond³Example 3⁴

References

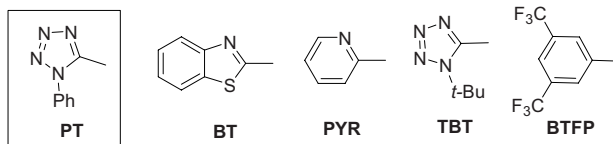
- 1 Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
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Julia–Kocienski olefination

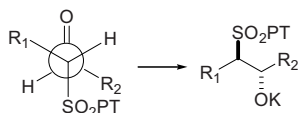
Modified one-pot Julia olefination to give predominantly (*E*)-olefins from heteroarylsulfones and aldehydes. A sulfone reduction step is *not* required.



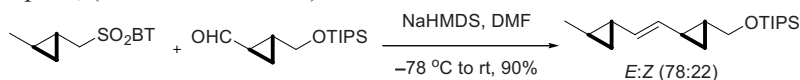
Alternatives to tetrazole:



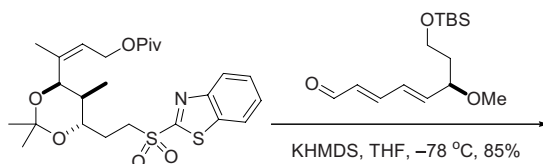
The use of larger counterion (such as K^+) and polar solvents (such as DME) favors an open transition state (PT = phenyltetrazolyl):

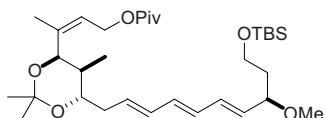
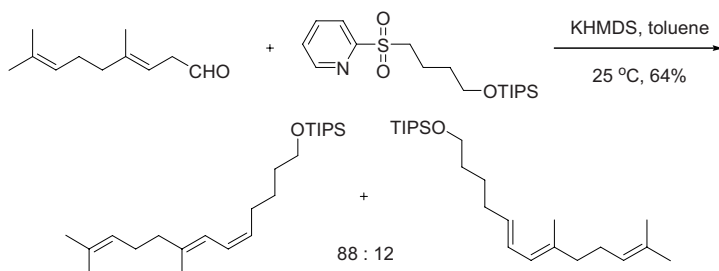
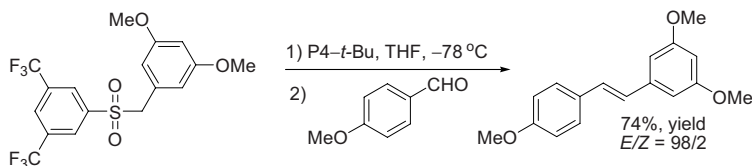


Example 1, (BT = benzothiazole)²



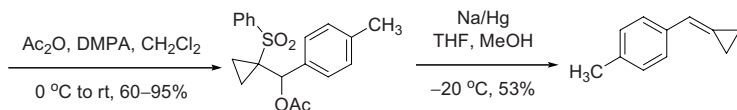
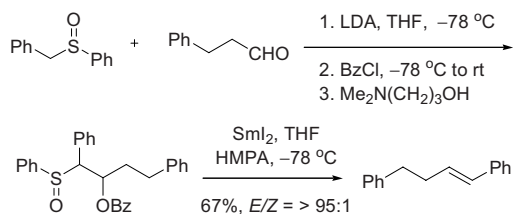
Example 2³



Example 3⁷Example 4⁸

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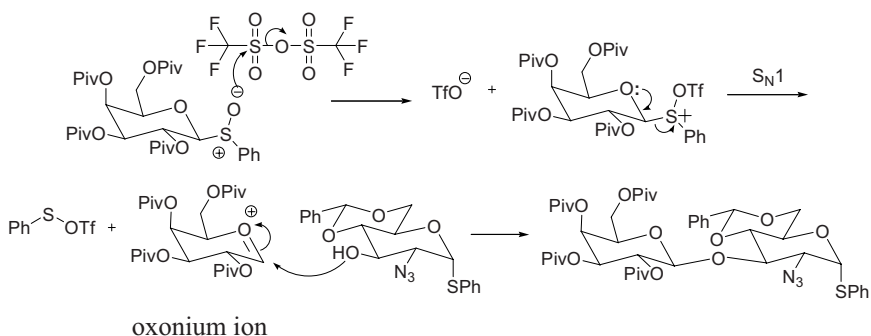
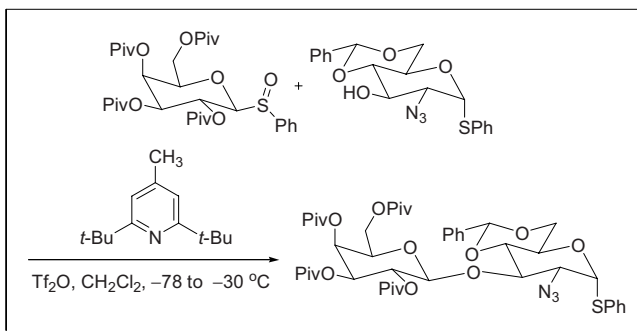
Example 4⁸

References

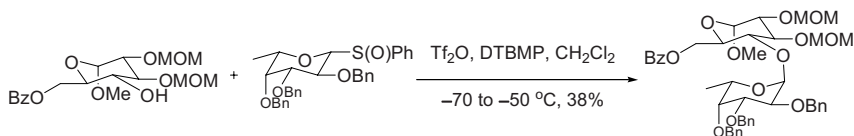
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Kahne glycosidation

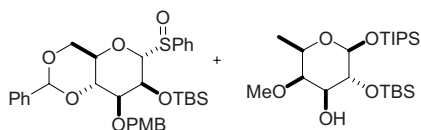
Diastereoselective glycosidation of a sulfoxide at the anomeric center as the glycosyl acceptor. The sulfoxide activation is achieved using $\text{ Tf}_2\text{O}$.

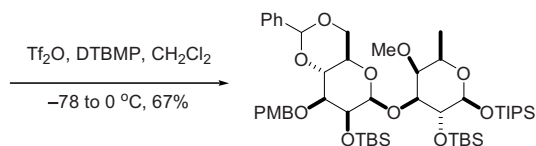


Example 1^d

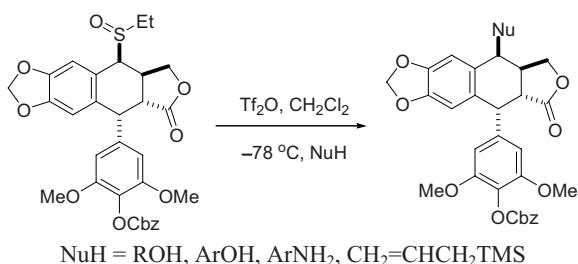


Example 2⁴





Example 3, Reverse Kahne-type glycosylation⁶

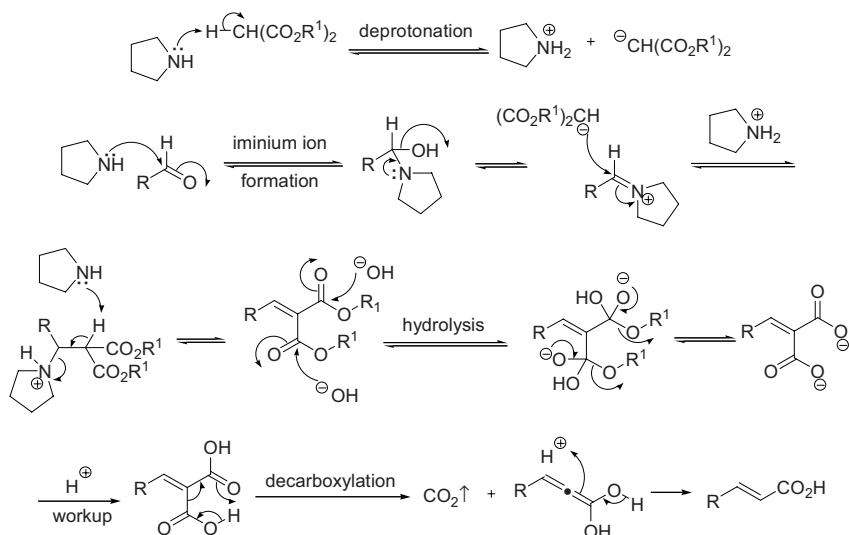
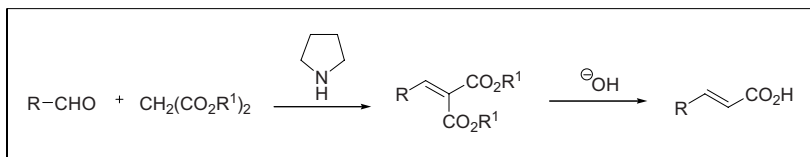


References

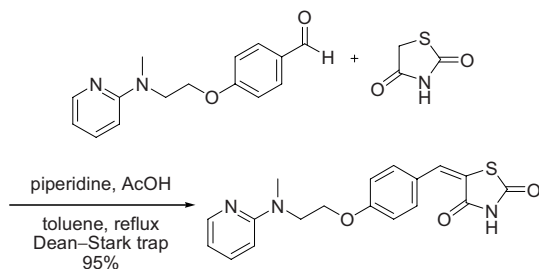
1. (a) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882. (b) Yan, L.; Taylor, C. M.; Goodnow, R., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6953–6954. (c) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239–9248. (d) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961–5969. Daniel Kahne now teaches at Harvard University.
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Knoevenagel condensation

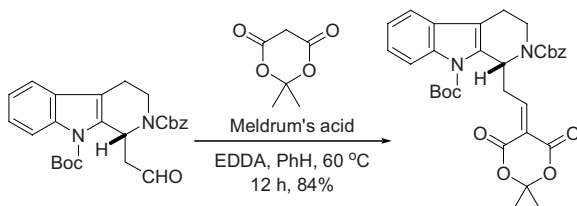
Condensation between carbonyl compounds and activated methylene compounds catalyzed by amines.



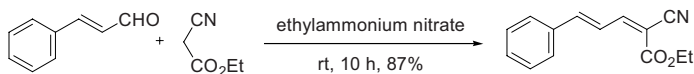
Example 1³



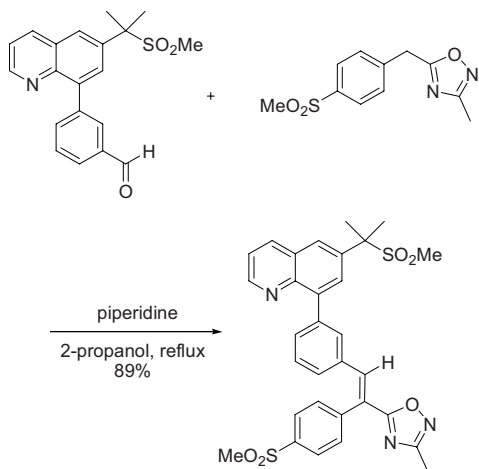
Example 2, EDDA = Ethylenediamine diacetate⁵



Example 3, Using ionic liquid ethylammonium nitrate (EAN) as solvent⁸



Example 4⁹

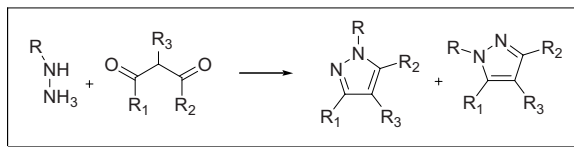


References

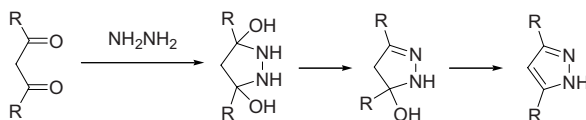
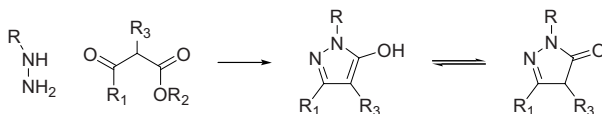
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Knorr pyrazole synthesis

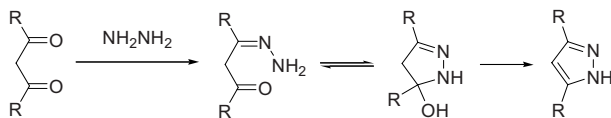
Reaction of hydrazine or substituted hydrazine with 1,3-dicarbonyl compounds to provide the pyrazole or pyrazolone ring system. *Cf.* Paal–Knorr pyrrole synthesis (page 411).



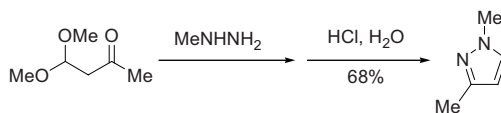
R = H, Alkyl, Aryl, Het-aryl, Acyl, *etc.*



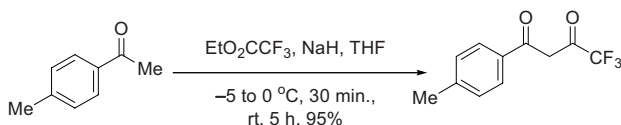
Alternatively,

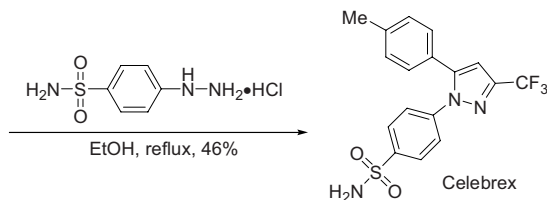


Example 1²



Example 2⁸



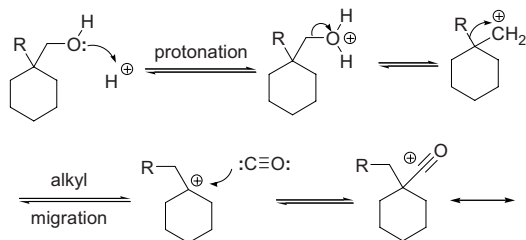
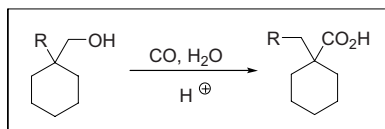


References

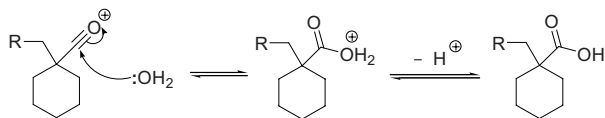
- 1 (a) Knorr, L. *Ber* **1883**, *16*, 2597. Ludwig Knorr (1859–1921) was born near Munich, Germany. After studying under Volhard, Emil Fischer, and Bunsen, he was appointed professor of chemistry at Jena. Knorr made tremendous contributions in the synthesis of heterocycles in addition to discovering the important pyrazolone drug, pyrine. (b) Knorr, L. *Ber* **1884**, *17*, 546, 2032. (c) Knorr, L. *Ber.* **1885**, *18*, 311. (d) Knorr, L. *Ann.* **1887**, 238, 137.
- 2 Burness, D. M. *J. Org. Chem.* **1956**, *21*, 97–101.
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Koch–Haaf carbonylation

Strong acid-catalyzed tertiary carboxylic acid formation from alcohols or olefins and CO.

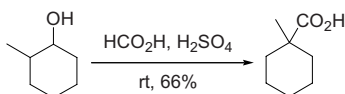


The tertiary carbocation is thermodynamically favored

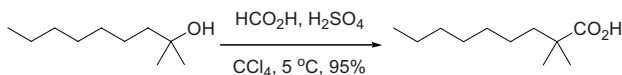


acylium ion

Example 1³



Example 2⁵

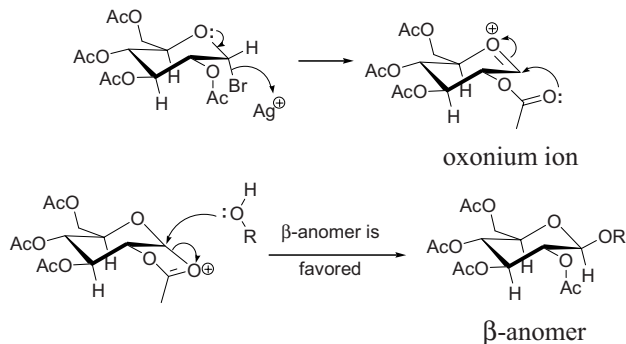
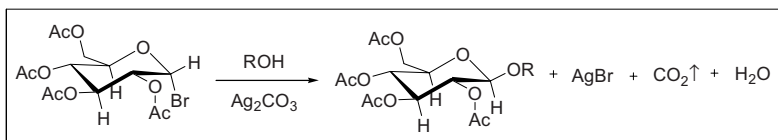


References

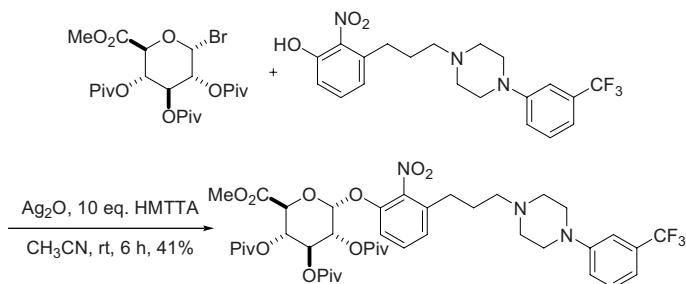
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Koenig–Knorr glycosidation

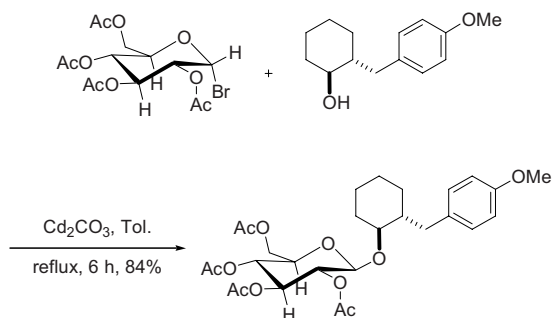
Formation of the β -glycoside from α -halocarbohydrate under the influence of silver salt.

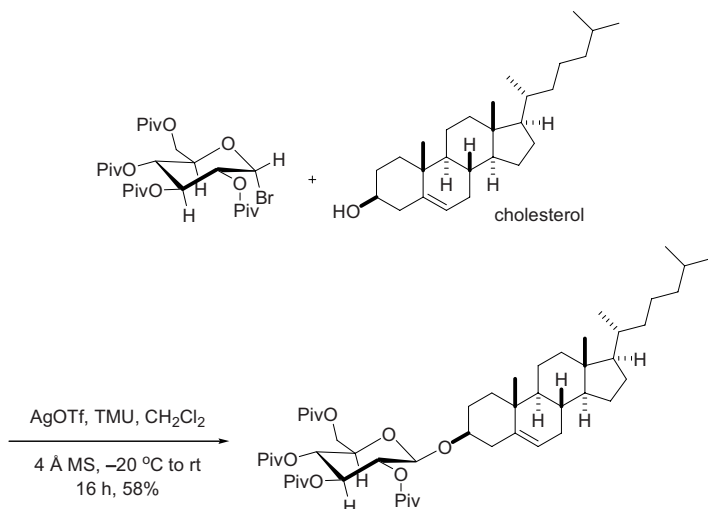


Example 1⁷



Example 2⁸



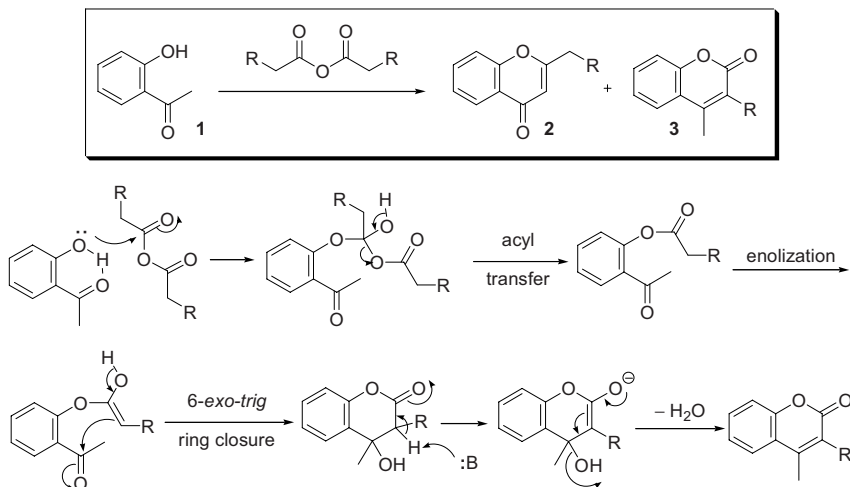
Example 3⁹

References

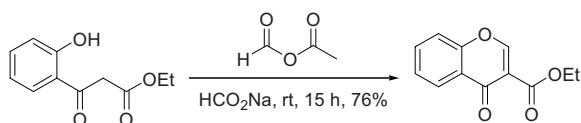
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Kostanecki reaction

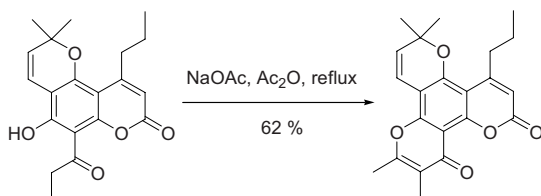
Also known as **Kostanecki–Robinson reaction**. Transformation **1**→**2** represents an **Allan–Robinson reaction** (see page 8), whereas **1**→**3** is a **Kostanecki (acylation) reaction**:



Example 1²



Example 2³

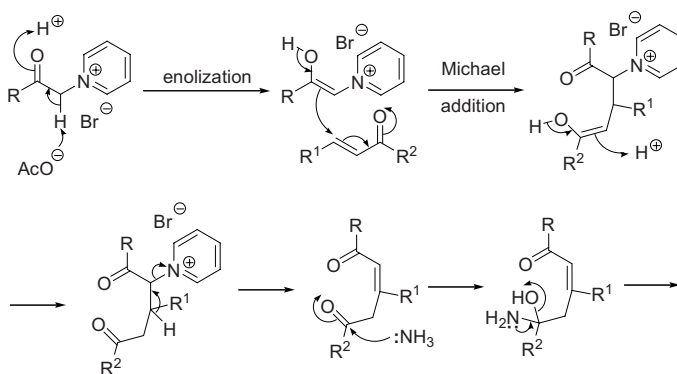
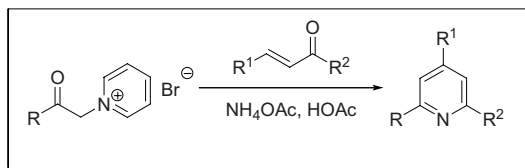


References

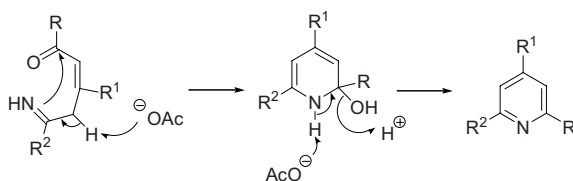
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Kröhnke pyridine synthesis

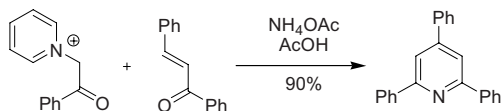
Pyridines from α -pyridinium methyl ketone salts and α,β -unsaturated ketones.



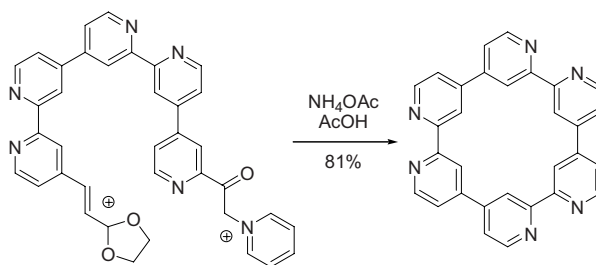
The ketone is more reactive than the enone

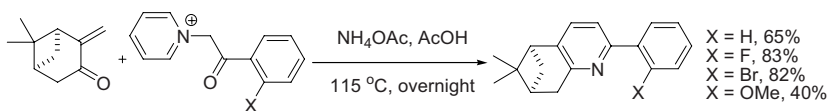


Example 1^b



Example 2⁴



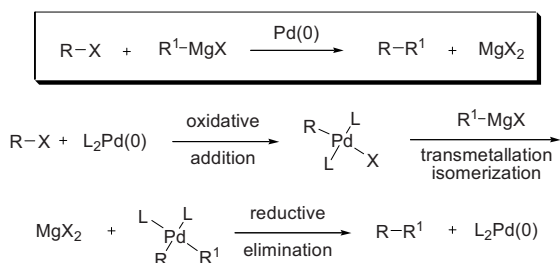
Example 3⁶

References

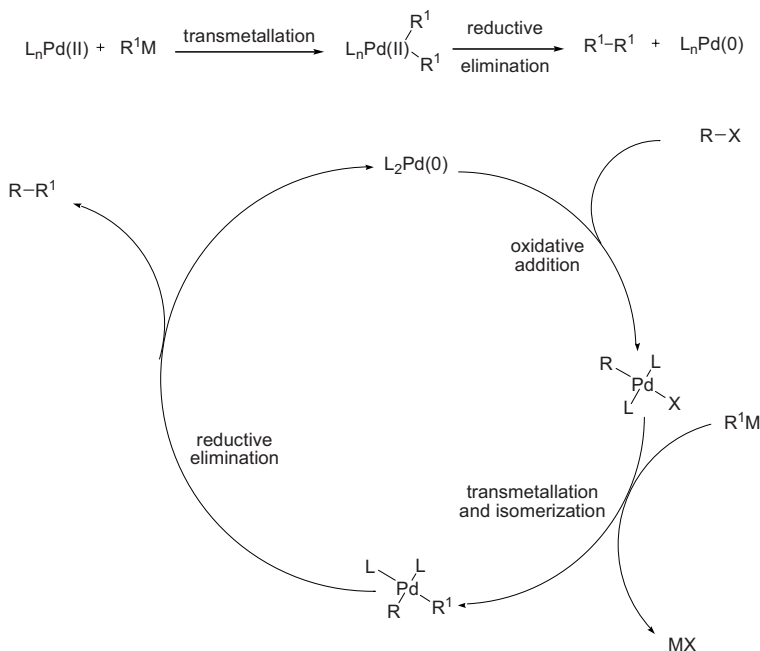
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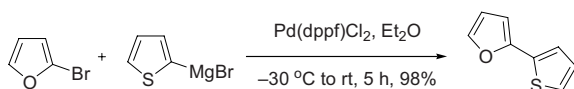
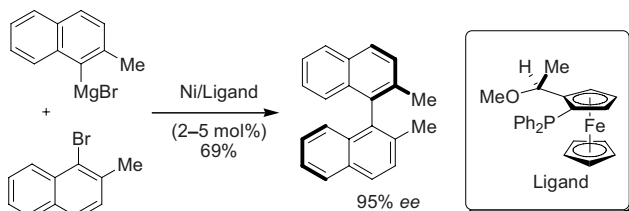
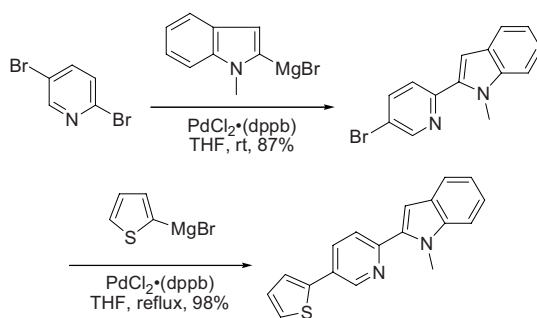
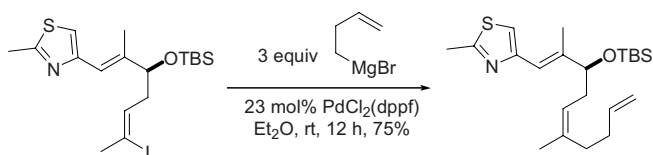
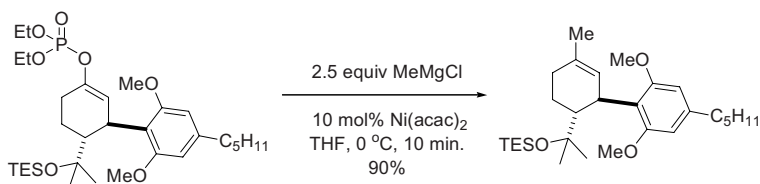
Kumada cross-coupling reaction

The Kumada cross-coupling reaction (also occasionally known as the Kharasch cross-coupling reaction) was originally reported as the nickel-catalyzed cross-coupling of Grignard reagents with aryl- or alkenyl halides. It has subsequently been developed to encompass the coupling of organolithium or organomagnesium compounds with aryl-, alkenyl or alkyl halides, catalyzed by nickel or palladium. The Kumada cross-coupling reaction, as well as the Negishi, Stille, Hiyama, and Suzuki cross-coupling reactions, belong to the same category of Pd-catalyzed cross-coupling reactions of organic halides, triflates and other electrophiles with organometallic reagents. These reactions follow a general mechanistic catalytic cycle as shown below. There are slight variations for the Hiyama and Suzuki reactions, for which an additional activation step is required for the transmetalation to occur.



The catalytic cycle:



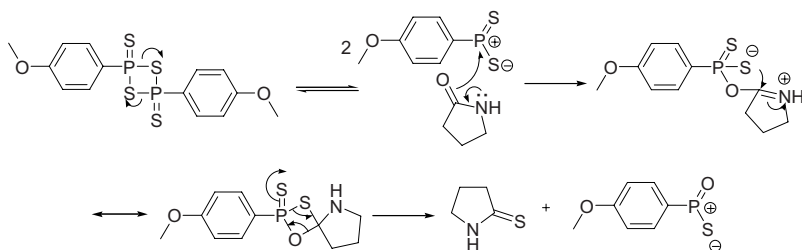
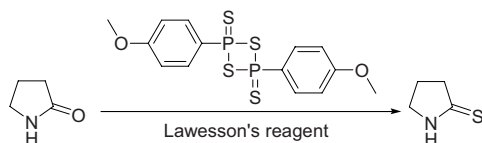
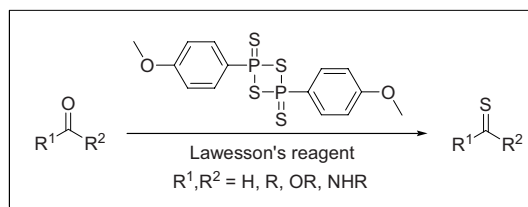
Example 1²Example 2³Example 3⁵Example 4⁸Example 5⁹

References

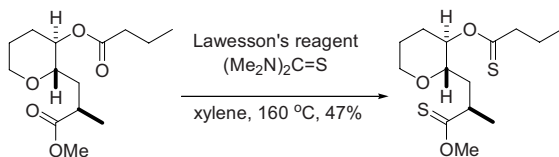
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Lawesson's reagent

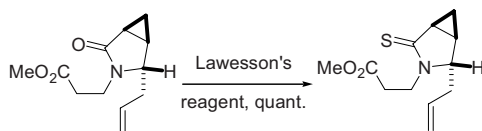
2,4-Bis(4-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide transforms the carbonyl groups of aldehydes, ketones, amides, lactams, esters and lactones into the corresponding thiocarbonyl compounds. *Cf.* Knorr thiophene synthesis.

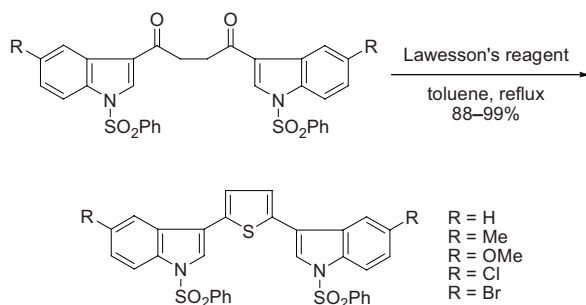
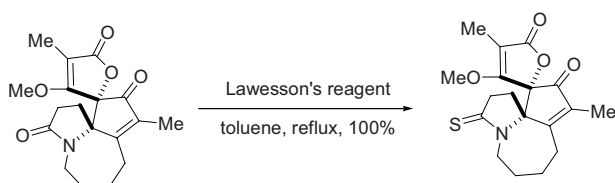


Example 1⁴



Example 2⁵



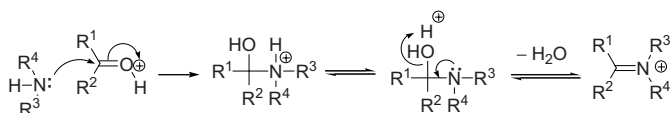
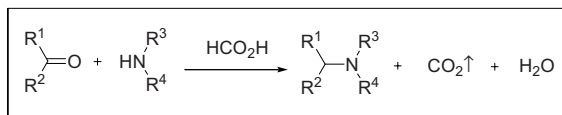
Example 3, Thiophene from dione⁸Example 4¹⁰

References

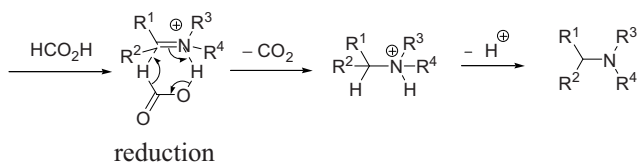
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Leuckart–Wallach reaction

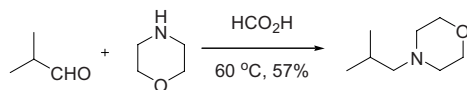
Amine synthesis from reductive amination of a ketone and an amine in the presence of excess formic acid, which serves as the reducing reagent by delivering a hydride. When the ketone is replaced by formaldehyde, it becomes the Eschweiler–Clarke reductive alkylation of amines on page 210.



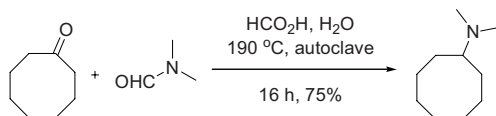
gem-aminoalcohol; iminium ion intermediate



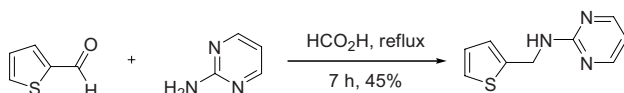
Example 1⁴

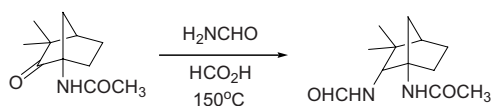


Example 2⁶

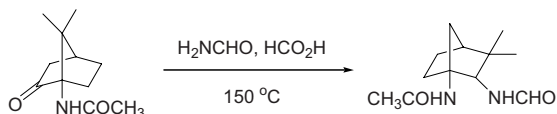


Example 3⁷



Example 4⁸

An unexpected intramolecular transamidation *via* a Wagner–Meerwein shift after the Leuckart–Wallach reaction

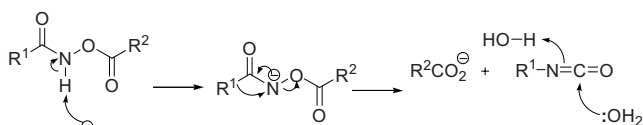
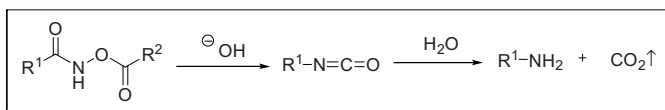


References

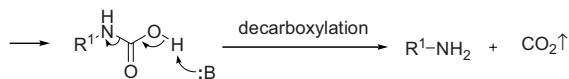
1. Leuckart, R. *Ber.* **1885**, *18*, 2341–2344. Carl L. R. A. Leuckart (1854–1889) was born in Giessen, Germany. After studying under Bunsen, Kolbe, and von Baeyer, he became an assistant professor at Göttingen. Unfortunately, chemistry lost a brilliant contributor by his sudden death at age 35 as a result of a fall in his parent's house.
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Lossen rearrangement

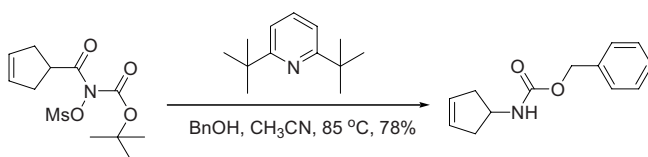
The Lossen rearrangement involves the generation of an isocyanate via thermal or base-mediated rearrangement of an activated hydroxamate which can be generated from the corresponding hydroxamic acid. Activation of the hydroxamic acid can be achieved through *O*-acylation, *O*-arylation, chlorination, or *O*-sulfonylation. Such hydroxamic acids can also be activated using polyphosphoric acid, carbodiimide, Mitsunobu conditions, or silylation. The product of the Lossen rearrangement, an isocyanate can be subsequently converted to an urea or an amine acid resulting in the net loss of one carbon atom relative to the starting hydroxamic acid.



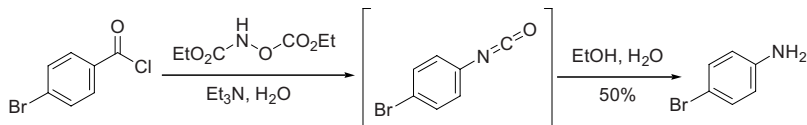
isocyanate intermediate

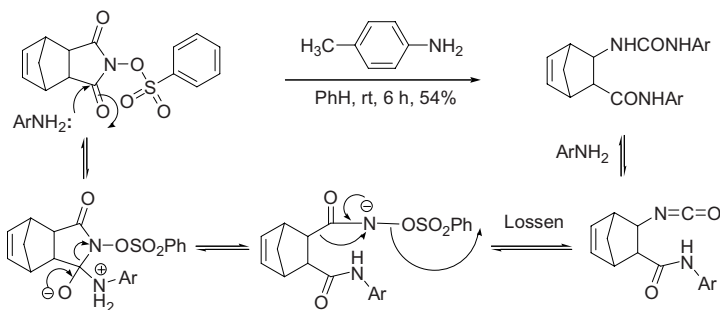
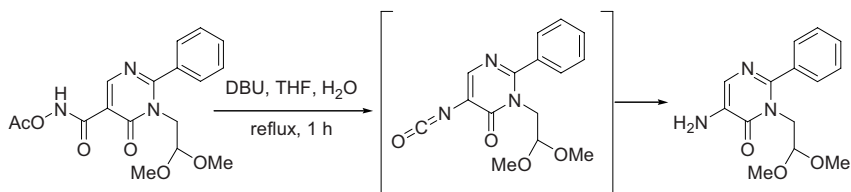


Example 1⁶



Example 2⁷



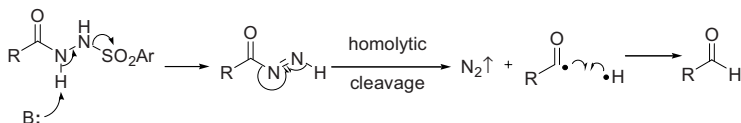
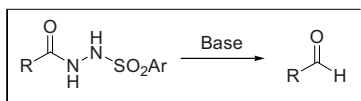
Example 3⁸Example 4⁹

References

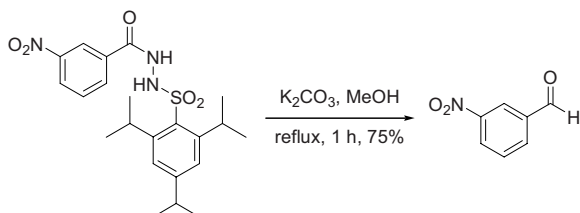
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McFadyen–Stevens reduction

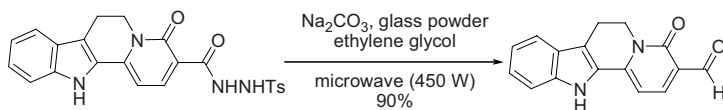
Treatment of acylbenzenesulfonylhydrazines with base delivers the corresponding aldehydes.



Example 1⁸



Example 2¹⁰

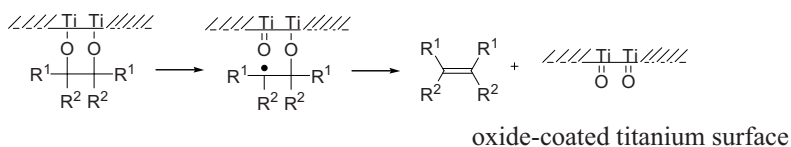
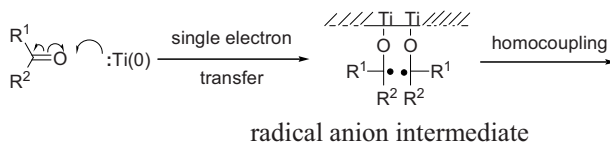
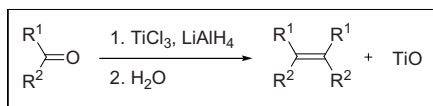


References

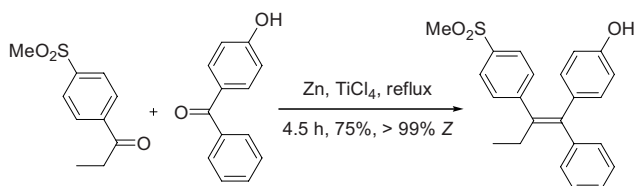
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McMurry coupling

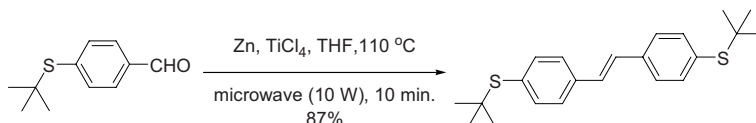
Olefination of carbonyls with low-valent titanium such as Ti(0) derived from $\text{TiCl}_3/\text{LiAlH}_4$. A single-electron process.

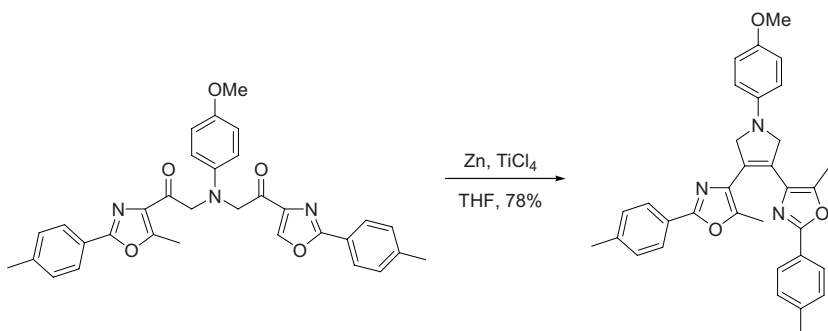
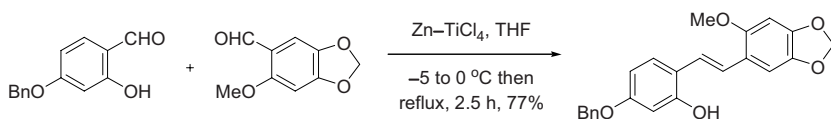


Example 1, Cross-McMurry coupling⁷



Example 2, Homo-McMurry coupling⁸



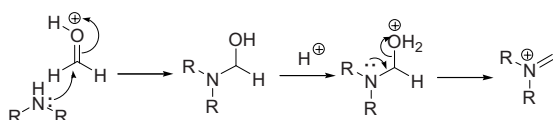
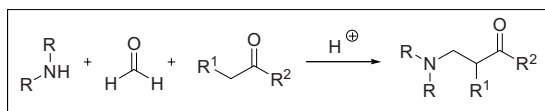
Example 3, Cross-McMurry coupling⁹Example 4, Cross-McMurry coupling¹⁰

References

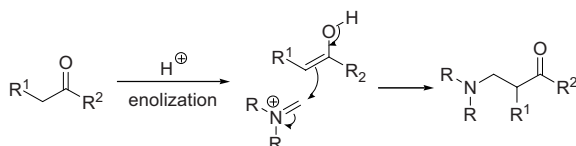
1. (a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4712. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524. (Review).
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Mannich reaction

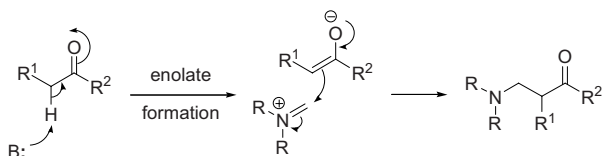
Three-component aminomethylation from amine, aldehyde and a compound with an acidic methylene moiety.



When R = Me, the $^+\text{Me}_2\text{N=CH}_2$ salt is known as *Eschenmoser's salt* (page 206)

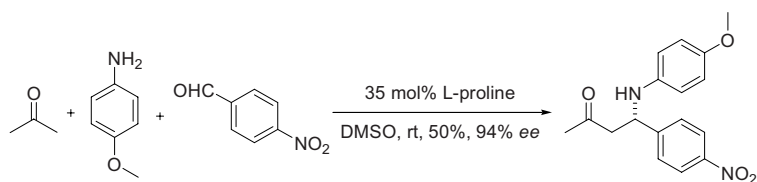


The Mannich reaction can also operate under basic conditions:

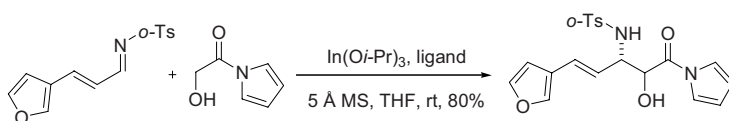


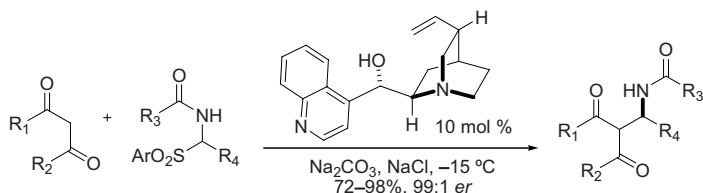
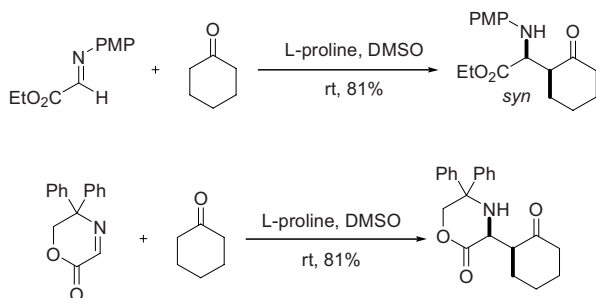
Mannich Base

Example 1, Asymmetric Mannich reaction²



Example 2, Asymmetric Mannich-type reaction⁹



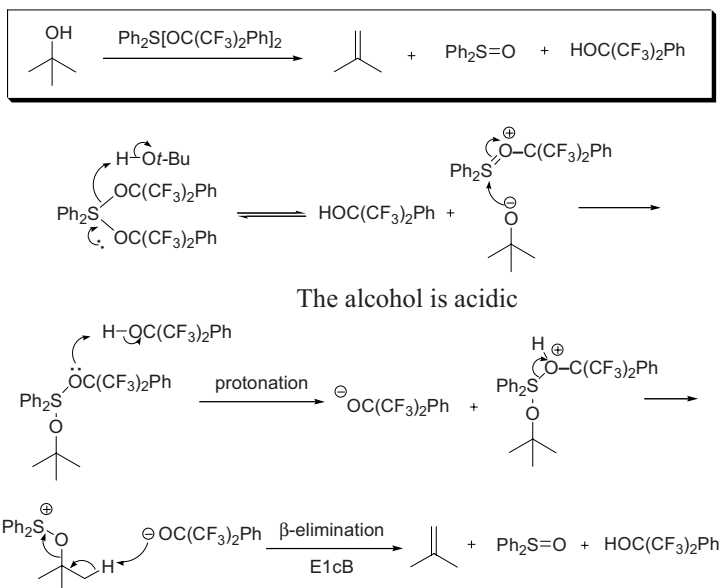
Example 3, Asymmetric Mannich reaction¹⁰Example 4¹¹

References

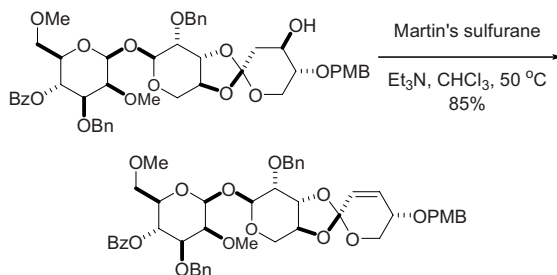
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Martin's sulfurane dehydrating reagent

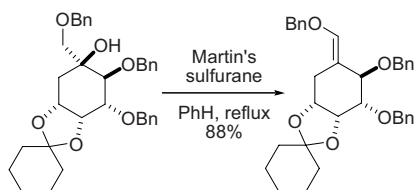
Dehydrates secondary and tertiary alcohols to give olefins, but forms ethers with primary alcohols. *Cf.* Burgess dehydrating reagent.

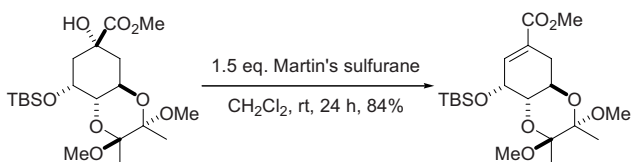
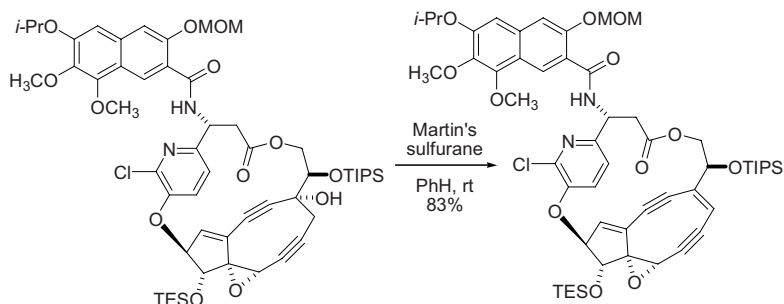


Example 1⁵



Example 2⁶



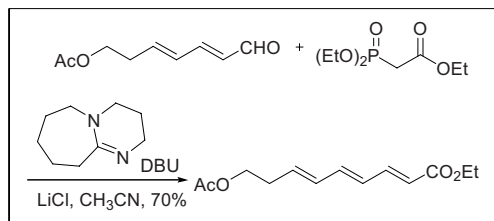
Example 3⁷Example 4⁹

References

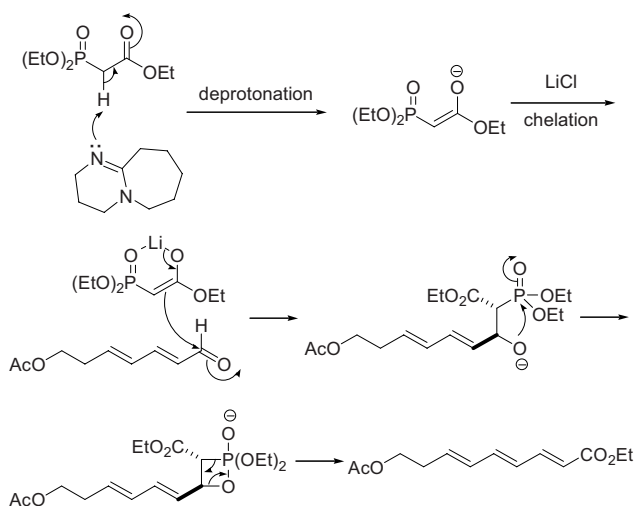
- (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2339–2341; (b) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2341–2342; (c) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329. (d) Martin, J. C.; Arhart, R. J.; Franz, J. A.; Perozzi, E. F.; Kaplan, L. J. *Org. Synth.* **1977**, *57*, 22–26.
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Masamune–Roush conditions for the Horner–Emmons reaction

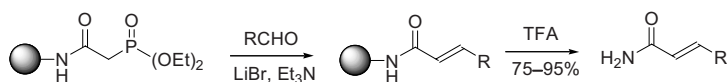
Applicable to base-sensitive aldehydes and phosphonates for the Horner–Wadsworth–Emmons reaction. α -Keto or α -alkoxycarbonyl phosphonate required.



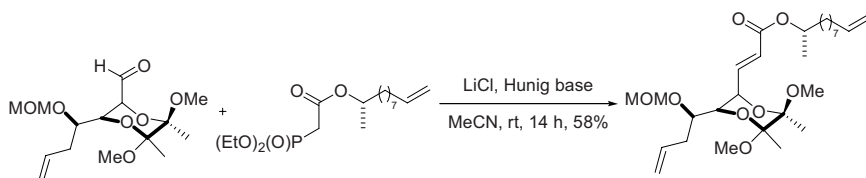
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

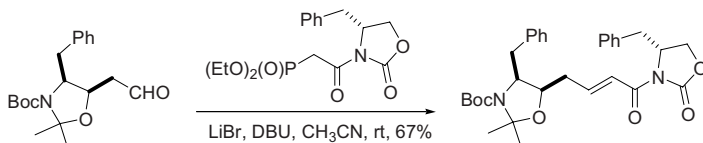
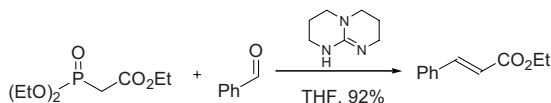
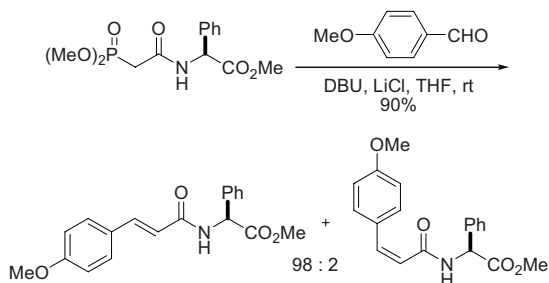


Example 1⁵



Example 2⁶



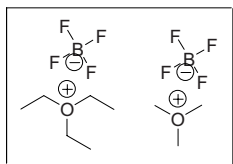
Example 3⁷Example 4⁸Example 5¹⁰

References

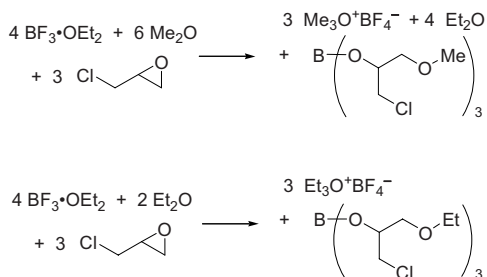
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Meerwein's salt

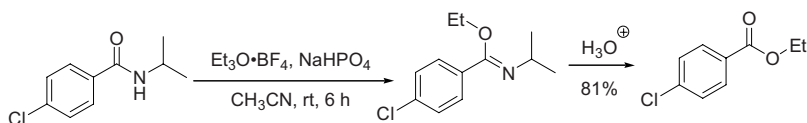
Meerwein's salts, also known as the Meerwein reagent, refer to trimethyloxonium tetrafluoroborate ($\text{Me}_3\text{O}^+\text{BF}_4^-$) and triethyloxonium tetrafluoroborate ($\text{Et}_3\text{O}^+\text{BF}_4^-$). Named after the inventor Hans Meerwein,¹ these trialkyloxonium salts are powerful alkylating agents.



Preparation:²

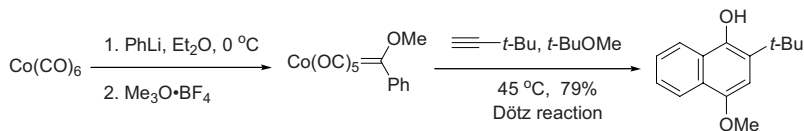


Example 1, The Meerwein reagent is an excellent *O*-alkylating agent:⁵

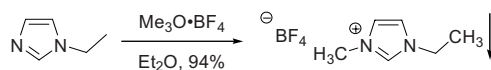


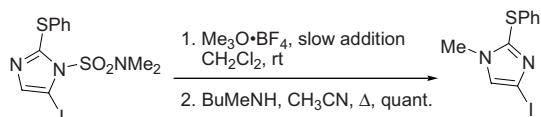
Transforming an amide into its corresponding ethyl or methyl esters

Example 2, *Metal*-methylation⁴



Example 3, *N*-Alkylation, the product is an ionic liquid⁸



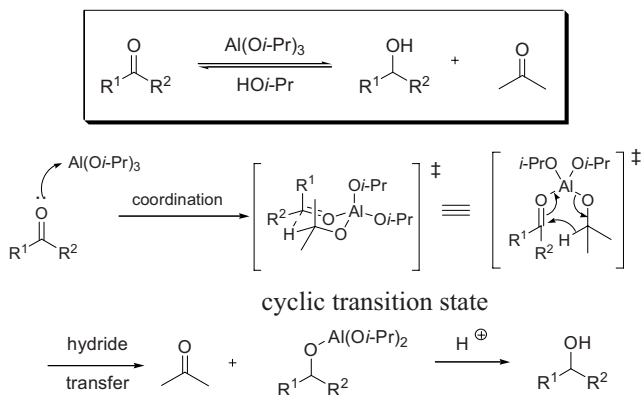
Example 4, *N*-Methylation⁹

References

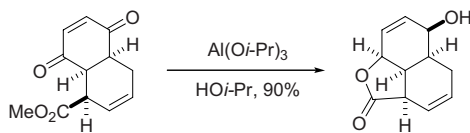
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Meerwein–Ponndorf–Verley reduction

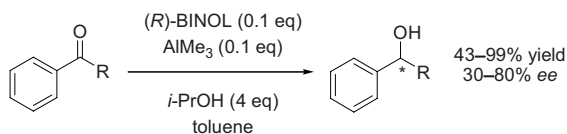
Reduction of ketones to the corresponding alcohols using $\text{Al}(\text{O}i\text{-Pr})_3$ in isopropanol. Reverse of the Oppenauer oxidation.



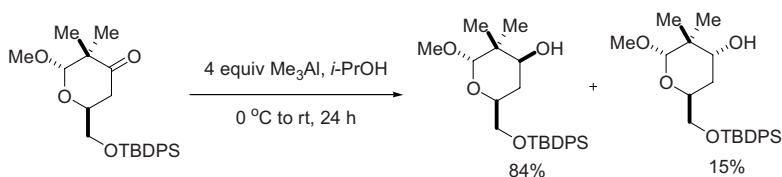
Example 1²

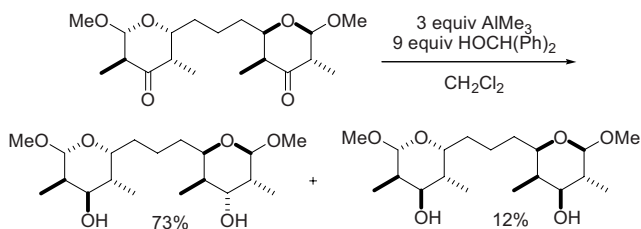


Example 2⁴



Example 3⁷



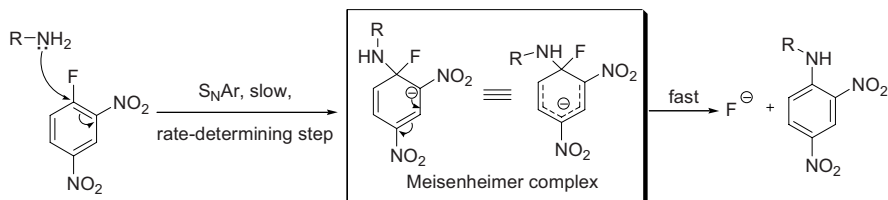
Example 4⁹

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Meisenheimer complex

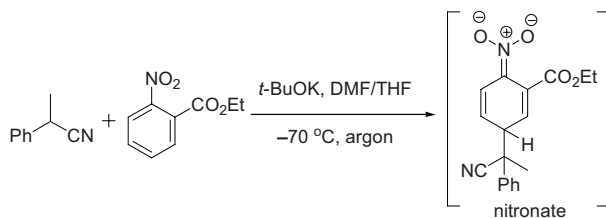
Also known as **the Meisenheimer–Jackson salt**, the stable intermediate for certain S_NAr reactions.



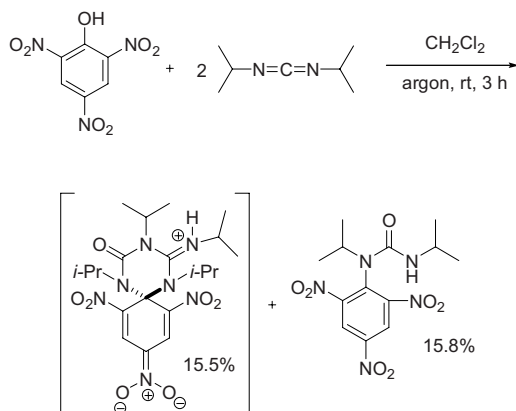
Sanger's reagent, *ipso* attack

ipso substitution

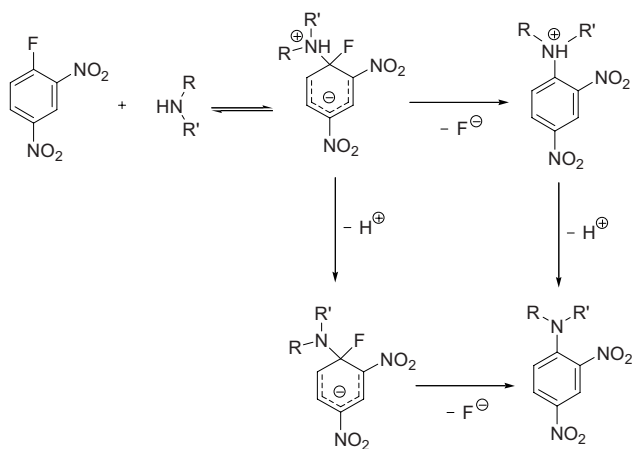
Example 1⁷



Example 2⁹



The reaction using Sanger's reagent is faster than using the corresponding chloro-, bromo-, and iododinitrobenzene—the fluoro-Meisenheimer complex is the most stabilized because F is the most electron-withdrawing. The reaction rate does not depend upon the capacity of the leaving group.

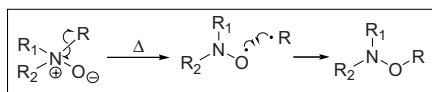
Example 3¹⁰

References

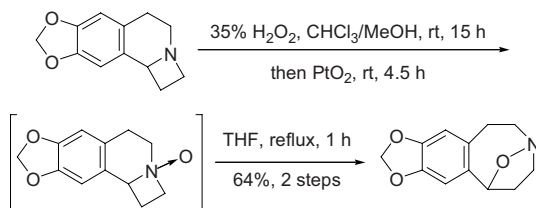
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[1,2]-Meisenheimer rearrangement

[1,2]-Sigmatropic rearrangement of tertiary amine *N*-oxides to substituted hydroxylamines.



Example 1⁷

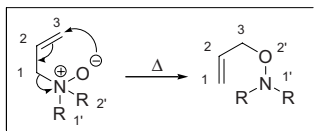


References

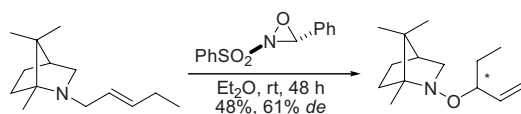
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[2,3]-Meisenheimer rearrangement

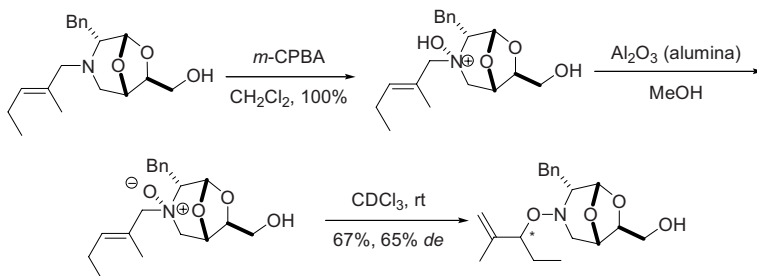
[2,3]-Sigmatropic rearrangement of allylic tertiary amine-*N*-oxides to give *O*-allyl hydroxylamines:



Example 1⁷



Example 2⁸



References

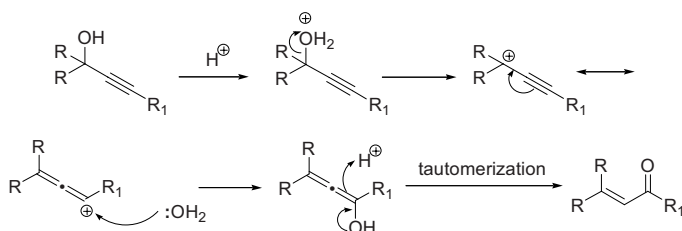
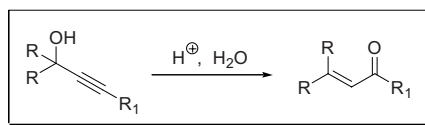
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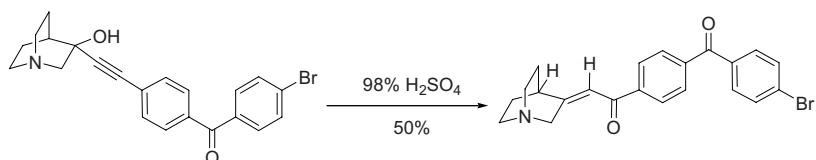
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Meyer–Schuster rearrangement

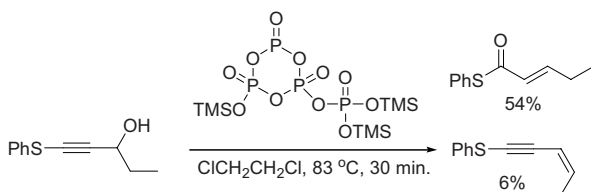
The isomerization of secondary and tertiary α -acetylenic alcohols to α,β -unsaturated carbonyl compounds *via* 1,3-shift. When the acetylenic group is terminal, the products are aldehydes, whereas the internal acetylenes give ketones. *Cf.* Rupe rearrangement.



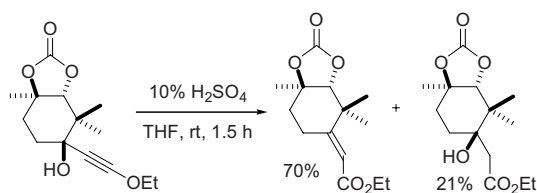
Example 1⁶

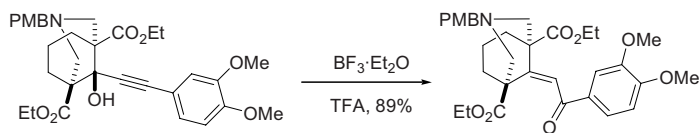


Example 2⁷



Example 3⁸



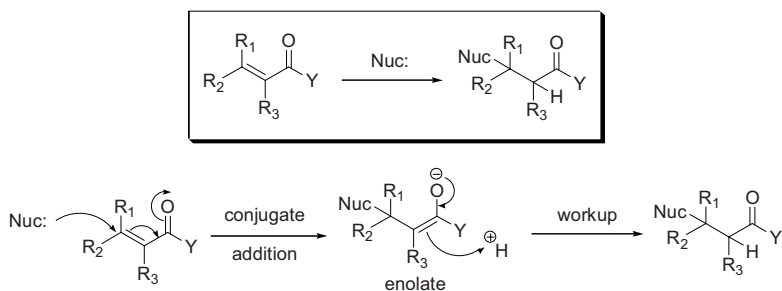
Example 4⁹

References

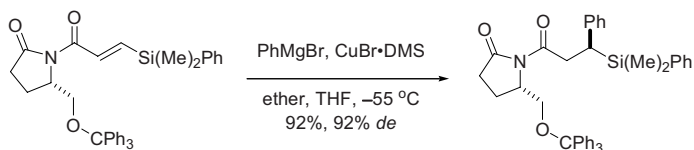
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Michael addition

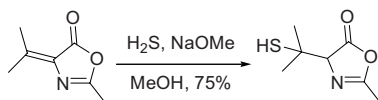
Also known as conjugate addition, Michael addition is the 1,4-addition of a nucleophile to an α,β -unsaturated system.



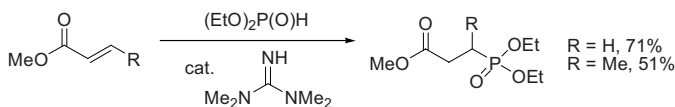
Example 1, Asymmetric Michael addition²



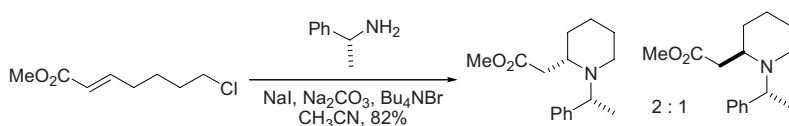
Example 2, Thia-Michael addition³

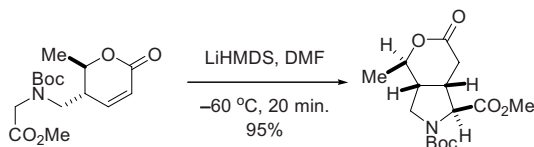


Example 3, Phospha-Michael addition⁷



Example 4, Asymmetric aza-Michael addition⁹



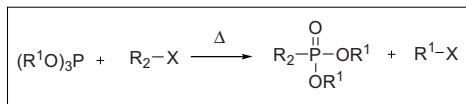
Example 5, Intramolecular Michael addition¹⁰

References

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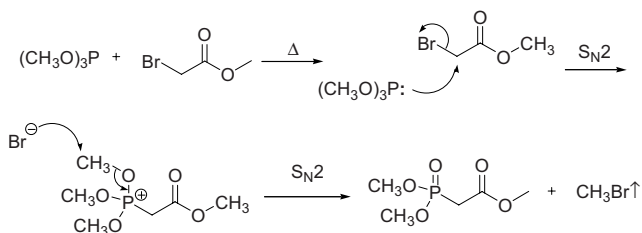
Michaelis–Arbuzov phosphonate synthesis

Phosphonate synthesis from the reaction of alkyl halides with phosphites.
General scheme:

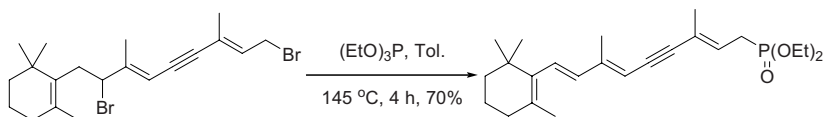


R^1 = alkyl, *etc.*; R_2 = alkyl, acyl, *etc.*; X = Cl, Br, I

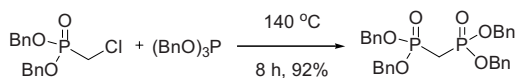
For instance:



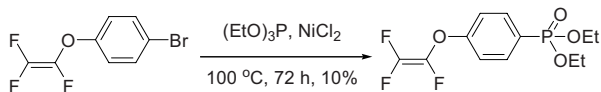
Example 1²



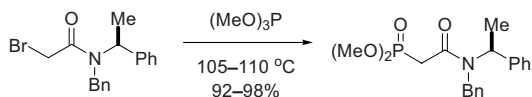
Example 2⁶

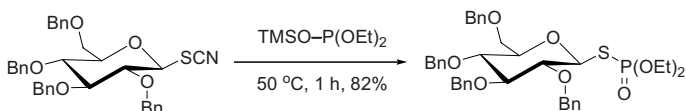


Example 3⁷



Example 4⁹



Example 5¹⁰

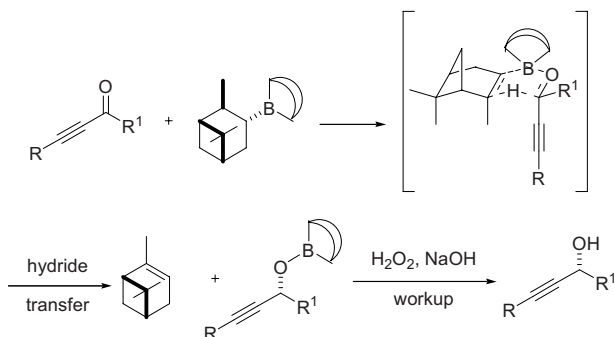
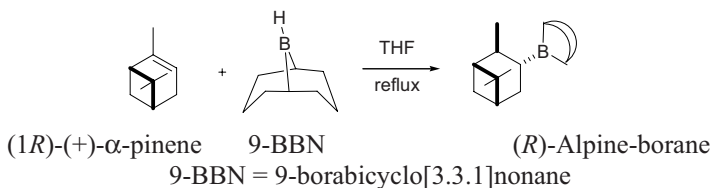
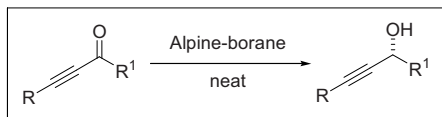
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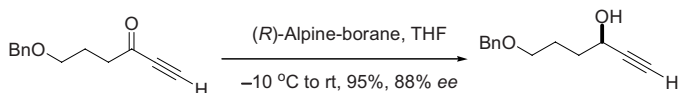
Midland reduction

Asymmetric reduction of ketones using Alpine-borane[®].

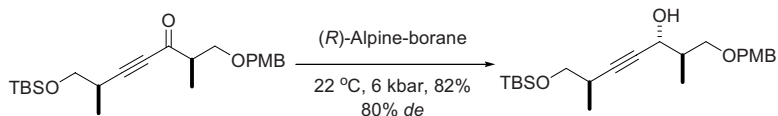
Alpine-borane[®] = *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane.

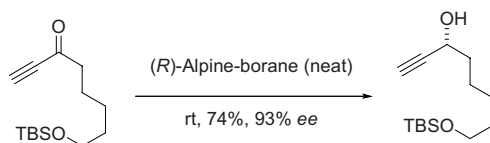


Example 1⁶



Example 2⁷



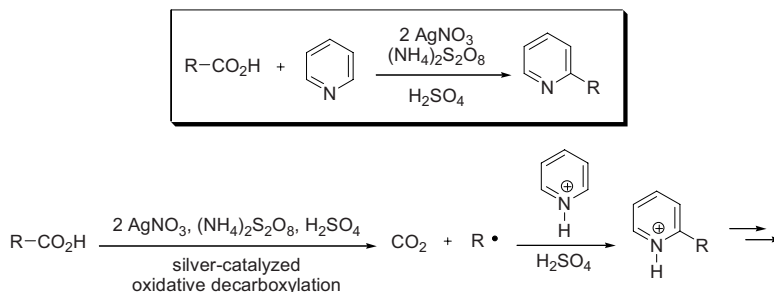
Example 3⁸

References

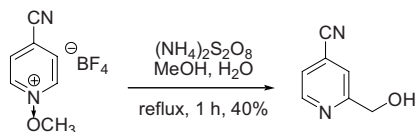
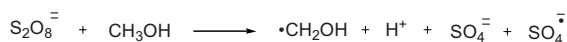
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Minisci reaction

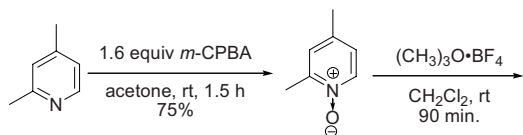
Radical-based carbon–carbon bond formation with electron-deficient heteroaromatics. The reaction entails an intermolecular addition of a nucleophilic radical to protonated heteroaromatic nucleus.



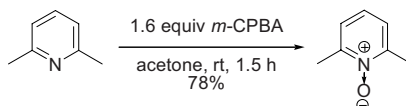
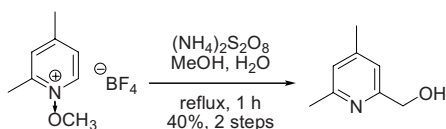
Example 1⁴

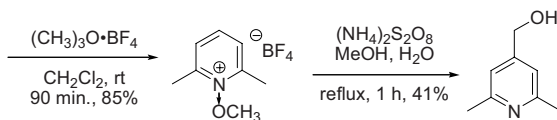


Example 2⁵

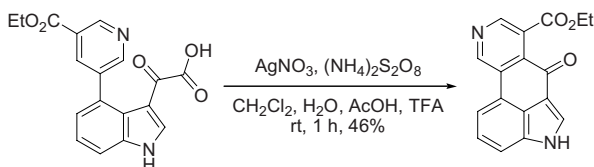


Meerwein's reagent

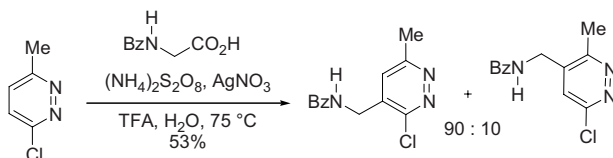




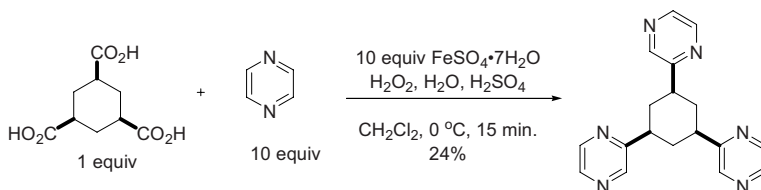
Example 3, Intramolecular Minisci reaction⁶



Example 4⁷



Example 5¹⁰

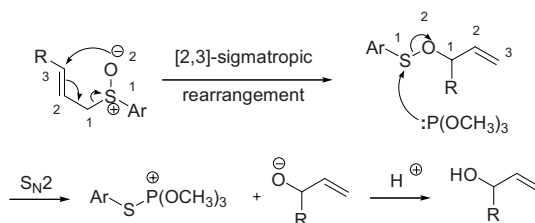
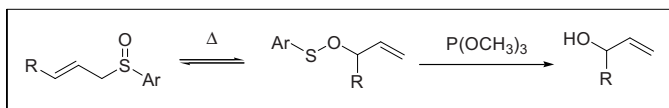


References

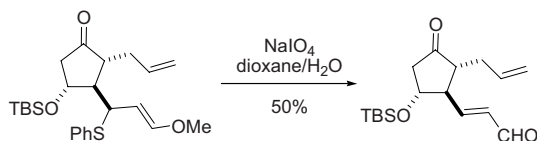
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Mislow–Evans rearrangement

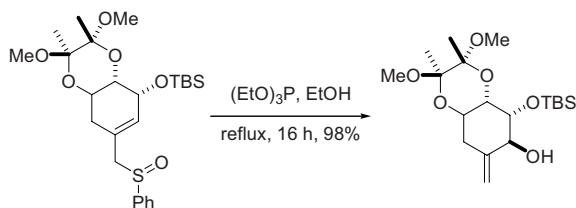
[2,3]-Sigmatropic rearrangement of allylic sulfoxide to allylic alcohol.



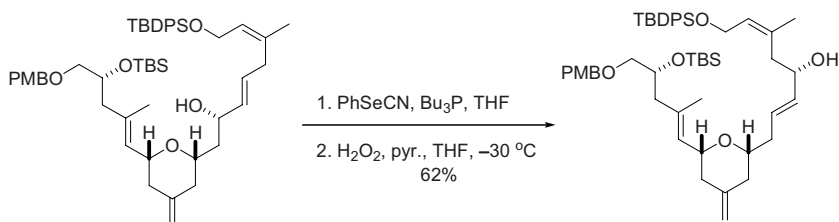
Example 1²



Example 2⁷



Example 3, Seleno-Mislow–Evans⁸

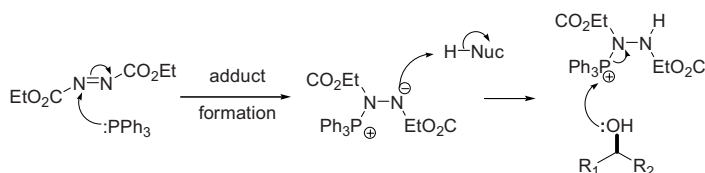
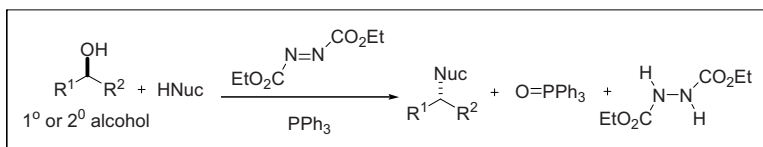


References

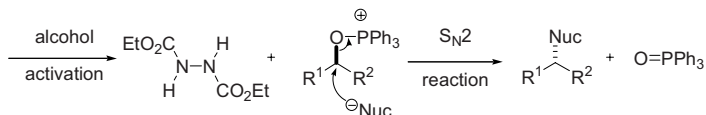
1. (a) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100–2104. (b) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956–4957. (c) Evans, D. A.; Andrews, G. C. *J. Am. Chem. Soc.* **1972**, *94*, 3672–3674. (d) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155. (Review).
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Mitsunobu reaction

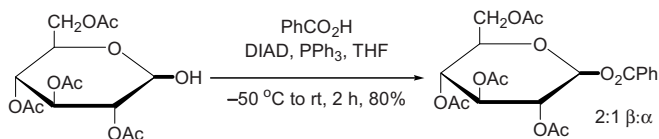
S_N2 inversion of an alcohol by a nucleophile using disubstituted azodicarboxylates (originally, diethyl diazodicarboxylate, or DEAD) and trisubstituted phosphines (originally, triphenylphosphine).



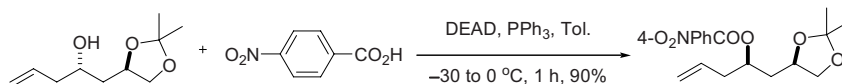
Diethyl azodicarboxylate (DEAD)

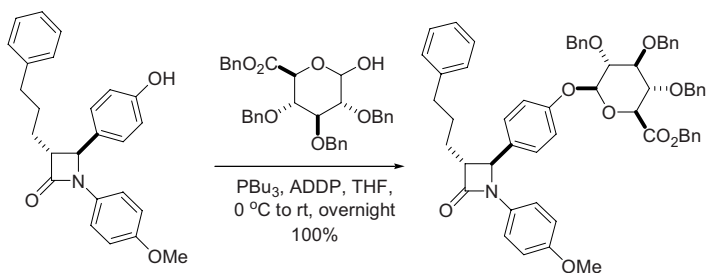


Example 1²

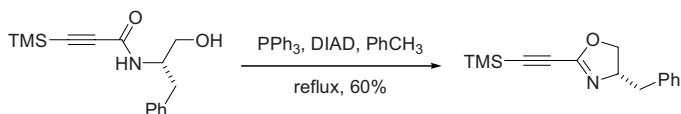
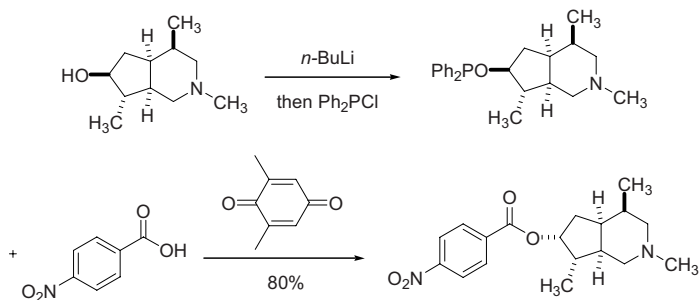
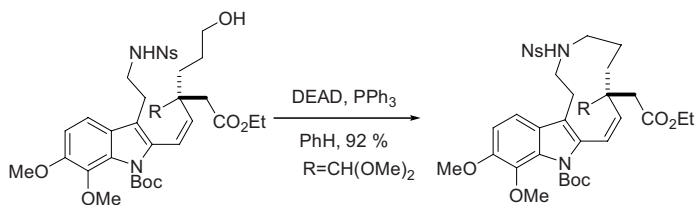


Example 2³



Example 3, Ether formation⁶

ADDP = 1,1'-(azodicarbonyl)dipiperidine

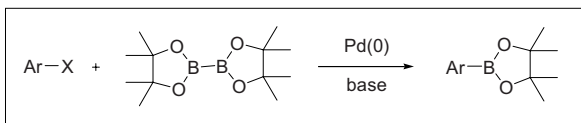
Example 4⁷Example 5⁸Example 6, Intramolecular Mitsunobu reaction⁹

References

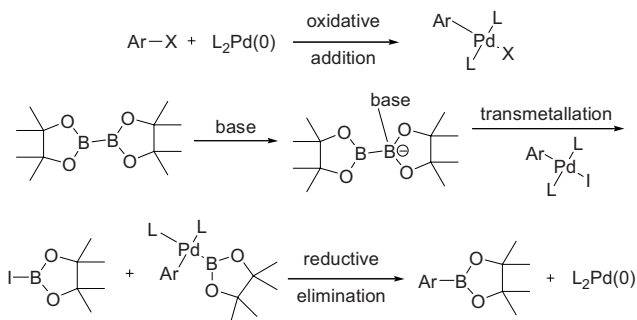
1. (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28. (Review).
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Miyaura borylation

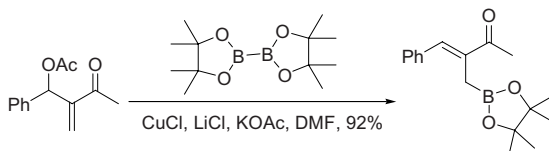
Palladium-catalyzed reaction of aryl halides with diboron reagents to produce arylboronates. Also known as Hosomi–Miyaura borylation.



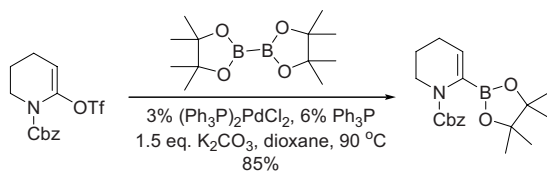
X = I, Br, Cl, OTf.

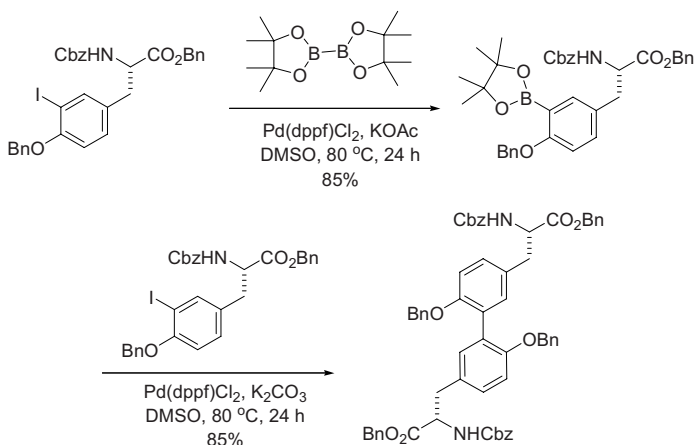
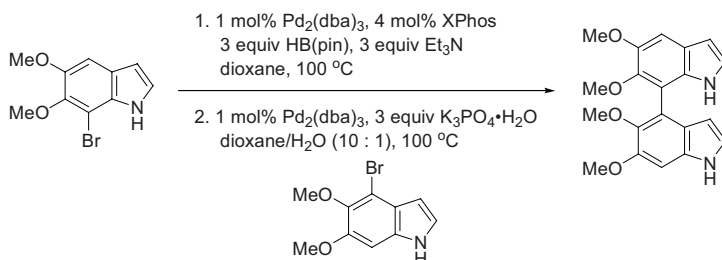


Example 1⁷



Example 2⁸



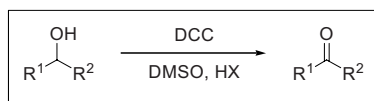
Example 3⁹Example 4, One-pot synthesis of biindolyl¹⁰

References

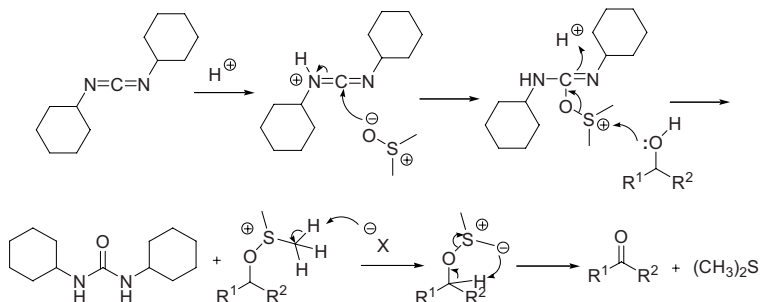
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Moffatt oxidation

Oxidation of alcohols using DCC and DMSO, aka “Pfitzner–Moffatt oxidation”.

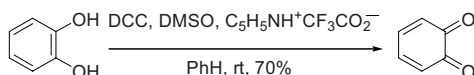


DCC, 1,3-dicyclohexylcarbodiimide

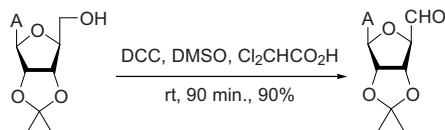


1,3-dicyclohexylurea

Example 1²



Example 2⁸



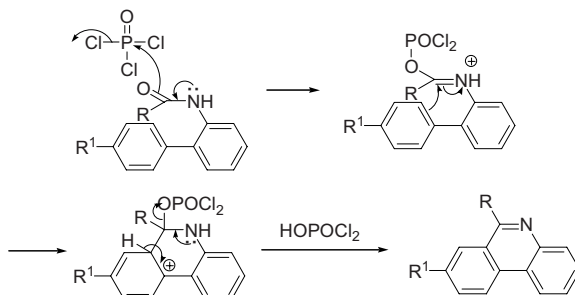
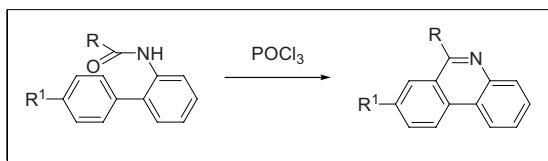
A = adenosine

References

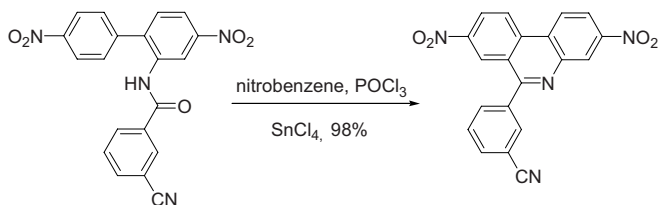
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Morgan–Walls reaction

Phenanthridine cyclization by dehydrative ring closure of acyl-*o*-aminobiphenyls with phosphorus oxychloride in boiling nitrobenzene.

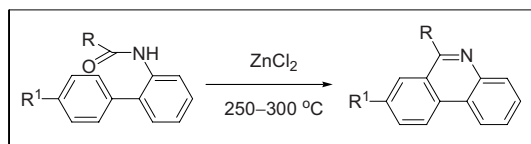


Example 1⁶

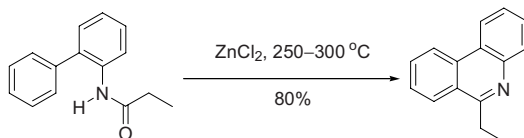


Pictet–Hubert reaction

The Morgan–Walls reaction is a variant of the Pictet–Hubert reaction where the phenanthridine cyclization was accomplished by dehydrative ring closure of acyl-*o*-aminobiphenyls on heating with zinc chloride at 250–300 °C.



Example 2⁴

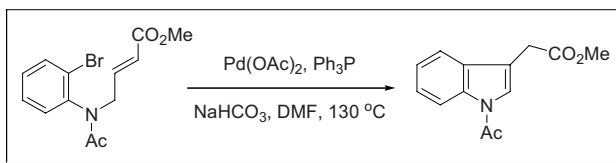


References

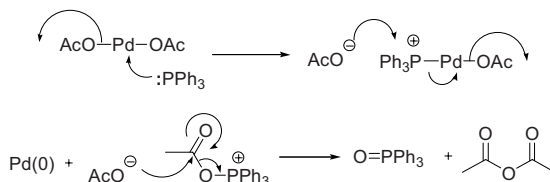
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Mori–Ban indole synthesis

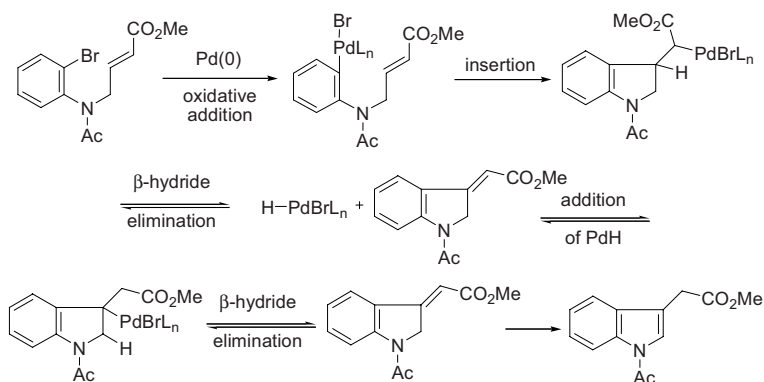
Intramolecular Heck reaction of *o*-halo-aniline with pendant olefin to prepare indole.



Reduction of $\text{Pd}(\text{OAc})_2$ to $\text{Pd}(0)$ using Ph_3P :



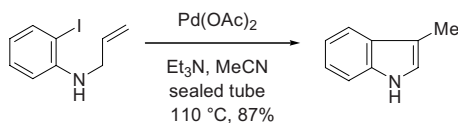
Mori–Ban indole synthesis:

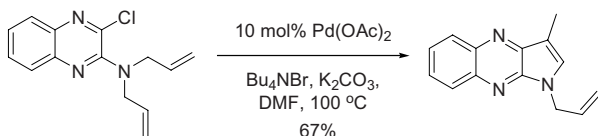
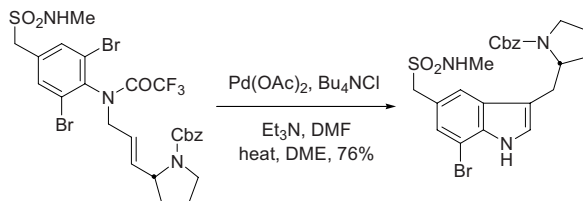


Regeneration of $\text{Pd}(0)$:



Example 1^{1a}



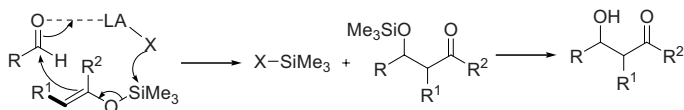
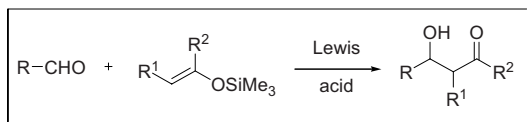
Example 2⁴Example 3⁷

References

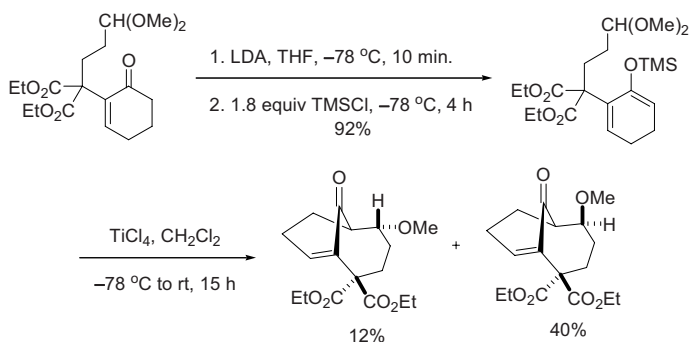
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Mukaiyama aldol reaction

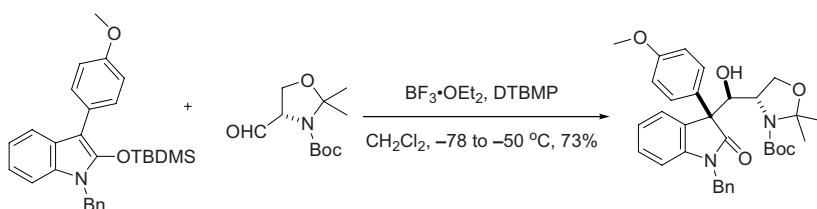
Lewis acid-catalyzed aldol condensation of aldehyde and silyl enol ether.



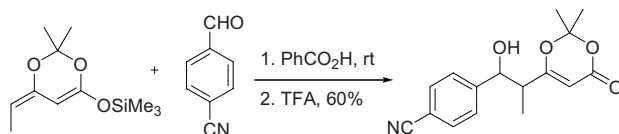
Example 1, Intramolecular Mukaiyama aldol reaction³

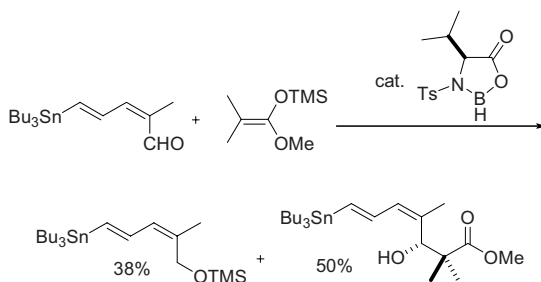
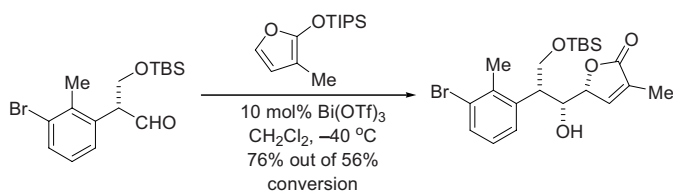


Example 2, Mukaiyama aldol reaction⁷



Example 3, Vinylogous Mukaiyama aldol reaction⁸



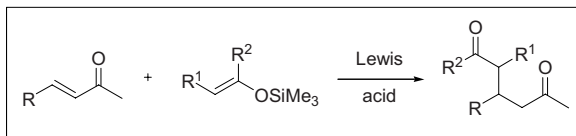
Example 4, Asymmetric Mukaiyama aldol reaction¹⁰Example 5, Mukaiyama aldol reaction¹²

References

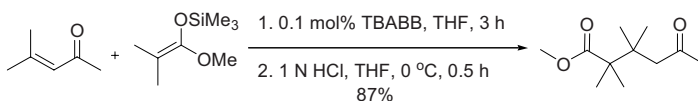
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Mukaiyama Michael addition

Lewis acid-catalyzed Michael addition of silyl enol ether to an α,β -unsaturated system.

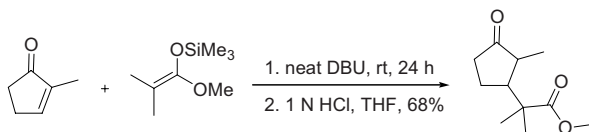


Example 1²

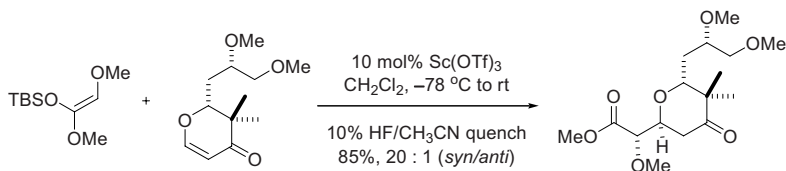


TBABB = tetra-*n*-butylammonium bibenzoate

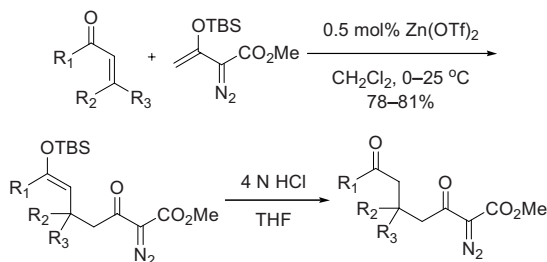
Example 2⁵



Example 3⁸



Example 4⁹



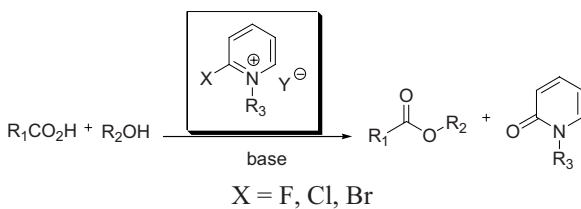
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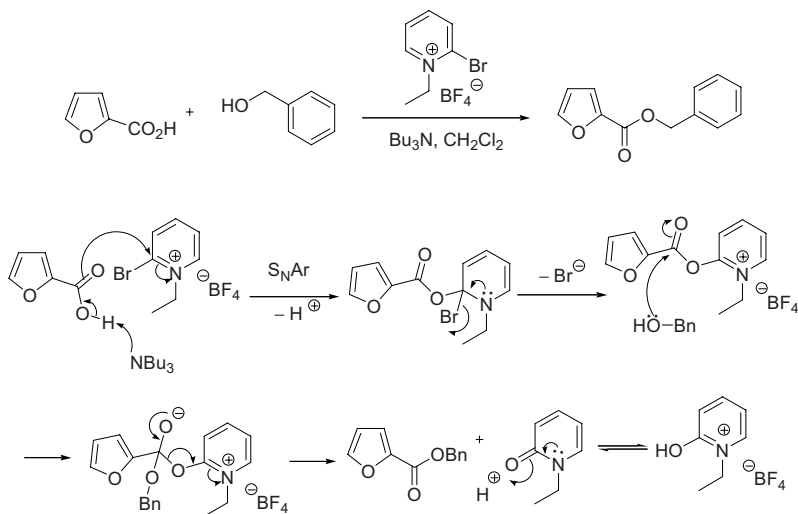
Mukaiyama reagent

Mukaiyama reagent such as 2-chloro-1-methyl-pyridinium iodide for esterification or amide formation.

General scheme:

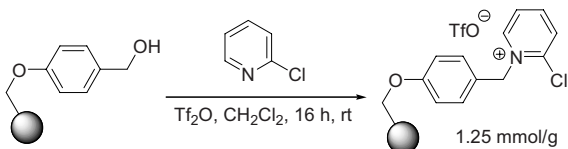


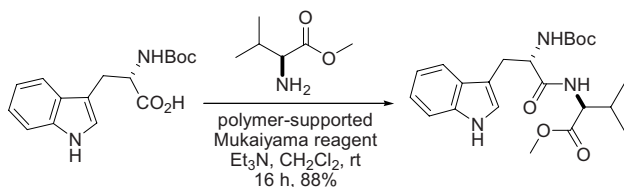
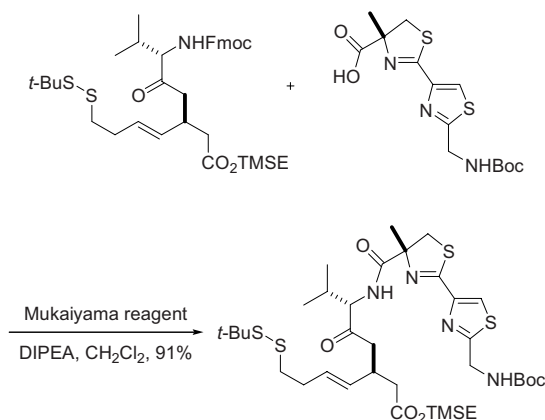
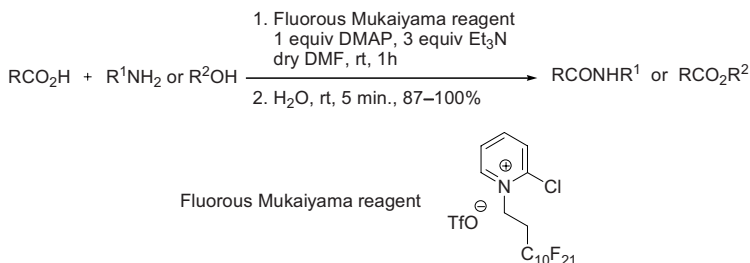
Example 1^{1c}



Amide formation using the Mukaiyama reagent follows a similar mechanistic pathway.^{1d}

Example 2, Polymer-supported Mukaiyama reagent⁵



Example 3⁹Example 4, Fluorous Mukaiyama reagent¹⁰

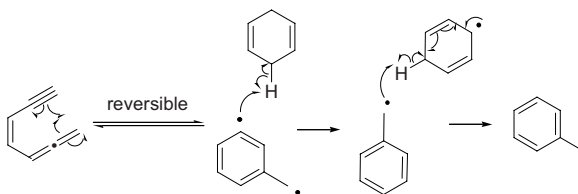
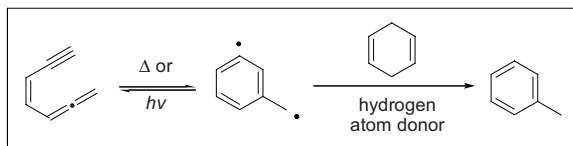
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Myers–Saito cyclization

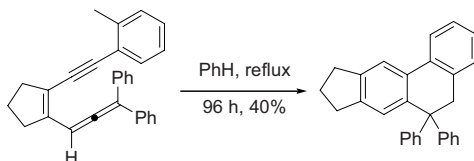
Cf. Bergman cyclization and Schmittel cyclization.



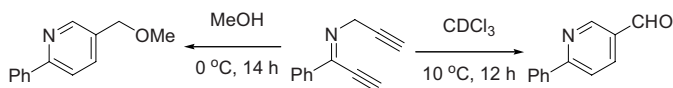
allenyl enyne

diradical

Example 1³



Example 2, Aza-Myers–Saito reaction⁸

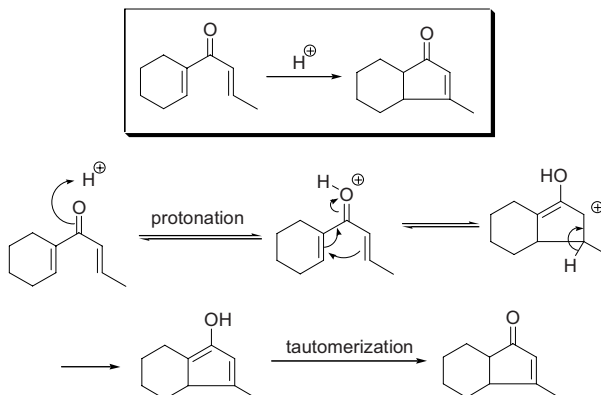


References

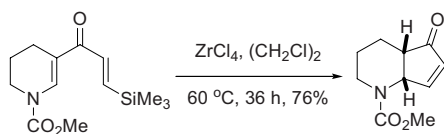
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Nazarov cyclization

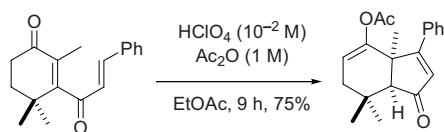
Acid-catalyzed electrocyclic formation of cyclopentenone from di-vinyl ketone.



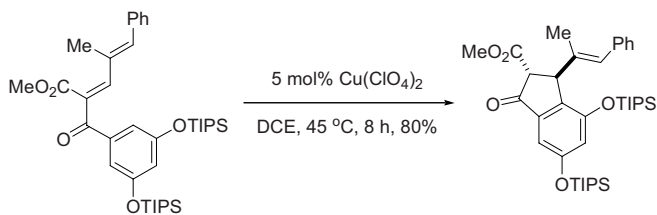
Example 1²

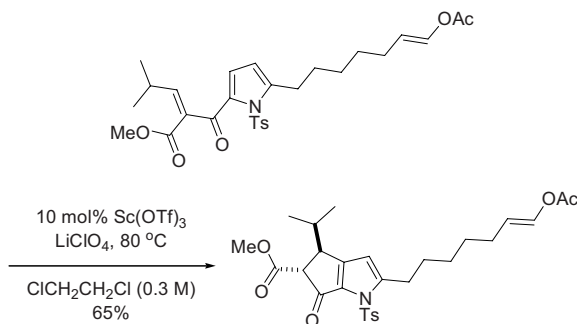
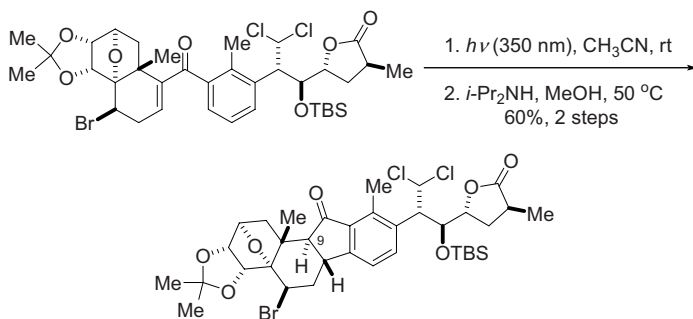


Example 2⁶



Example 3⁹



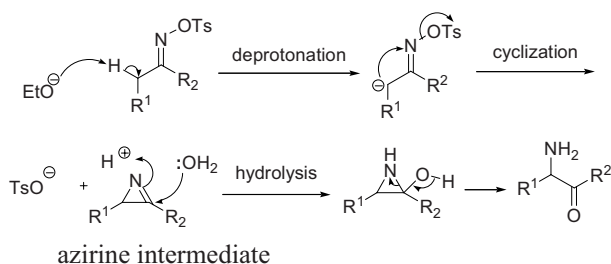
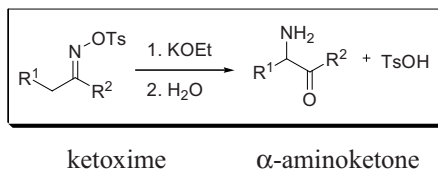
Example 4¹⁰Example 5¹¹

References

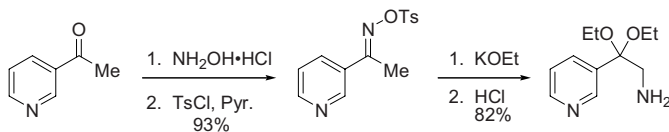
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Neber rearrangement

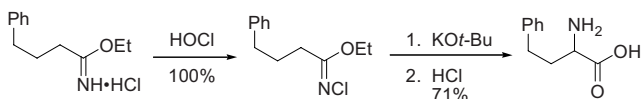
α -Aminoketone from tosyl ketoxime and base. The net conversion of a ketone into an α -aminoketone *via* the oxime.



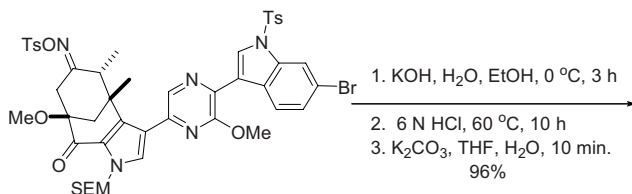
Example 1³

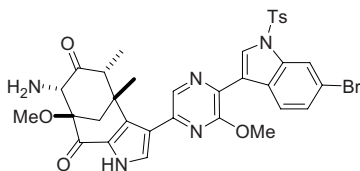
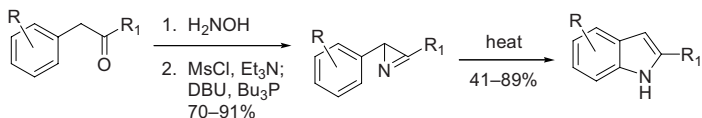


Example 2, A variant using iminochloride⁵



Example 3⁸



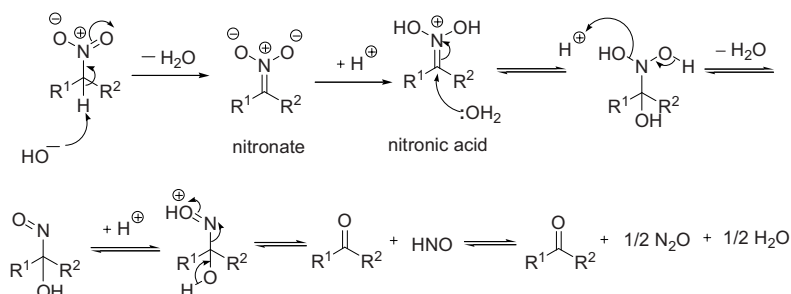
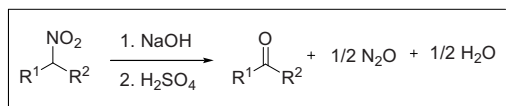
Example 4⁹

References

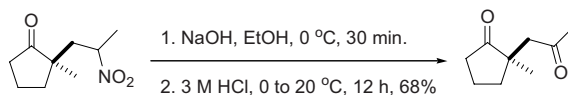
1. Neber, P. W.; v. Friedolsheim, A. *Ann.* **1926**, *449*, 109–134.
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Nef reaction

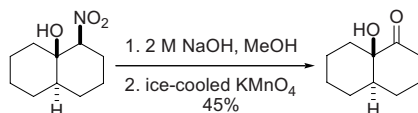
Conversion of a primary or secondary nitroalkane into the corresponding carbonyl compound.



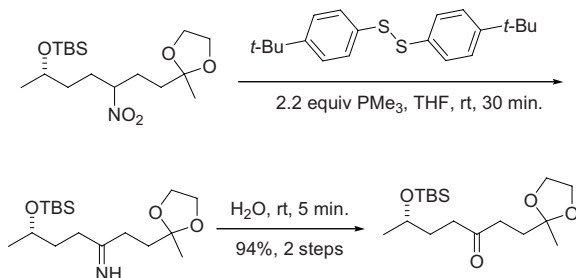
Example 1⁴

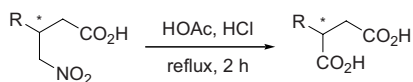


Example 2⁷



Example 3⁹



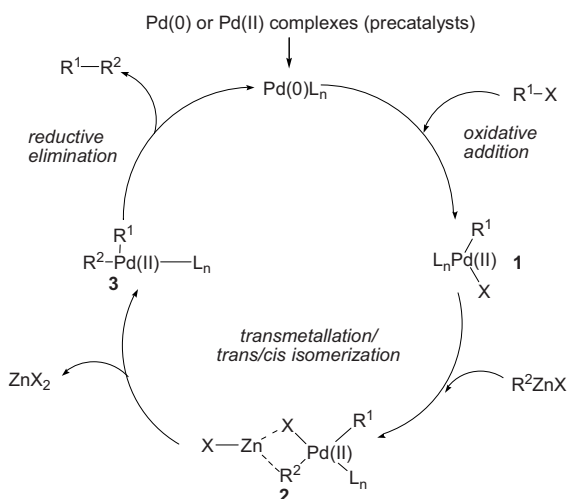
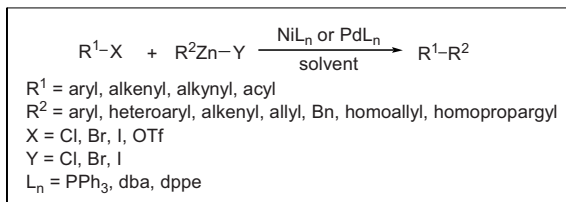
Example 4¹⁰

References

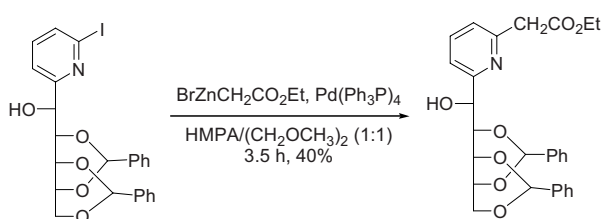
1. Nef, J. U. *Ann.* **1894**, 280, 263–342. John Ulrich Nef (1862–1915) was born in Switzerland and emigrated to the US at the age of four with his parents. He went to Munich, Germany to study with Adolf von Baeyer, earning a Ph.D. In 1886. Back to the States, he served as a professor at Purdue University, Clark University, and the University of Chicago. The Nef reaction was discovered at Clark University in Worcester, Massachusetts. Nef was temperamental and impulsive, suffering from a couple of mental breakdowns. He was also highly individualistic, and had never published with a coworker save for three early articles.
2. Pinnick, H. W. *Org. React.* **1990**, 38, 655–792. (Review).
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Negishi cross-coupling reaction

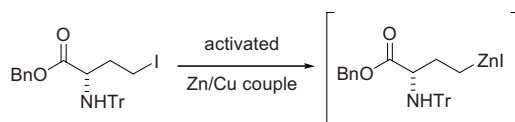
The Negishi cross-coupling reaction is the nickel- or palladium-catalyzed coupling of organozinc compounds with various halides or triflates (aryl, alkenyl, alkynyl, and acyl).

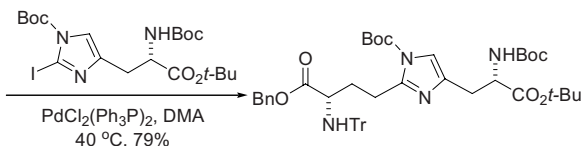
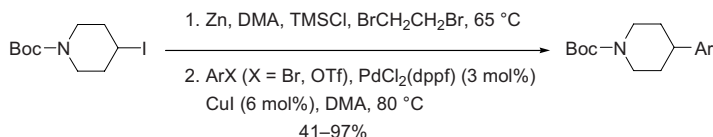
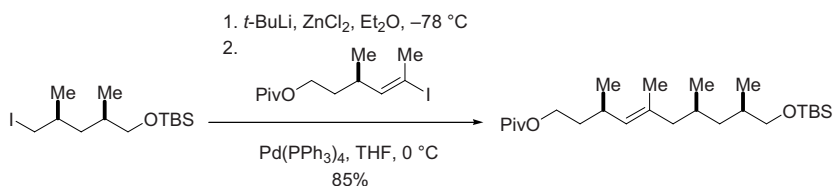


Example 1³



Example 2⁴



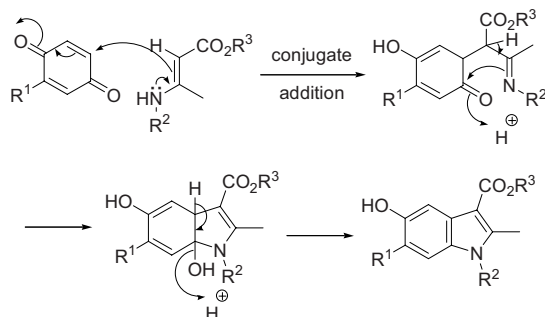
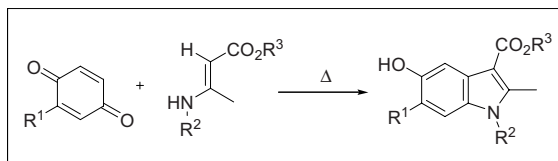
Example 3⁸Example 4⁹

References

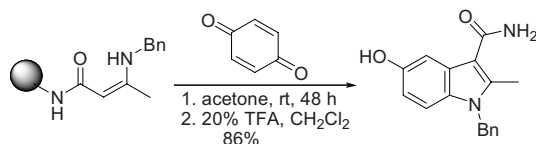
1. (a) Negishi, E.-I.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, 596–597. (b) Negishi, E.-I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821–1823. (c) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340–348. (Review).
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Nenitzescu indole synthesis

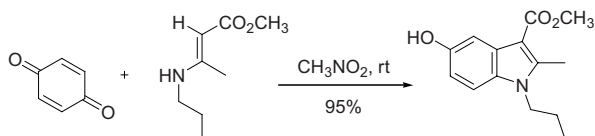
5-Hydroxyindole from condensation of *p*-benzoquinone and β -aminocrotonate.



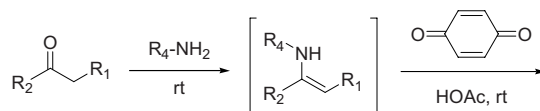
Example 1⁵

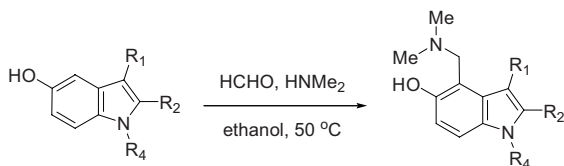
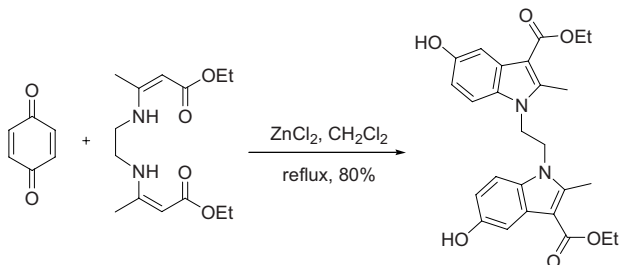


Example 2⁶



Example 3⁷



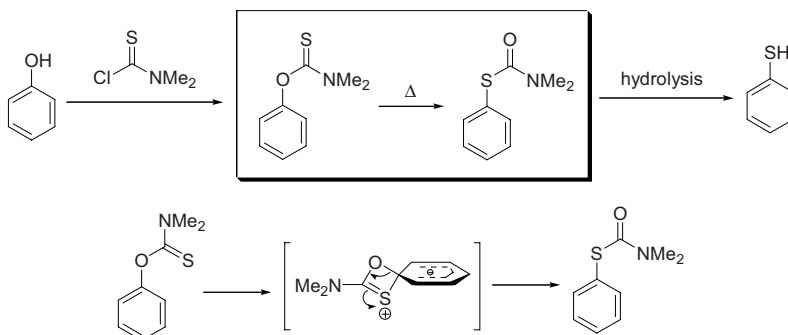
Example 4¹⁰

References

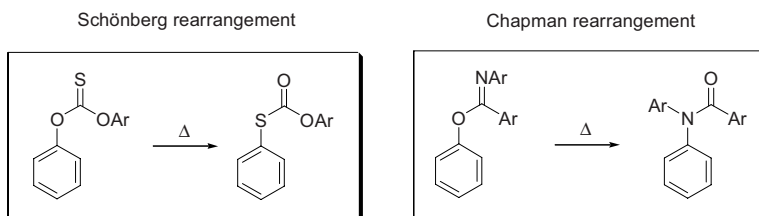
1. Nenitzescu, C. D. *Bull. Soc. Chim. Romania* **1929**, *11*, 37–43.
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Newman–Kwart rearrangement

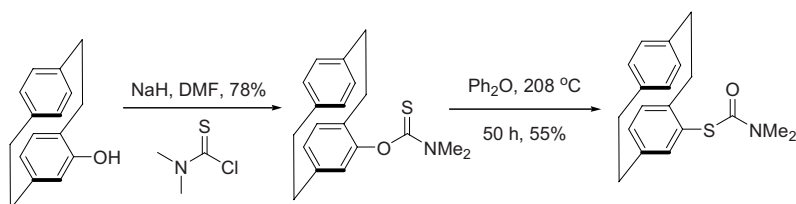
Transformation of phenol to the corresponding thiophenol, a variant of the *Smile* reaction (page 513).

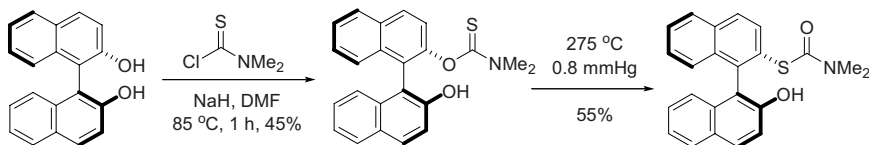
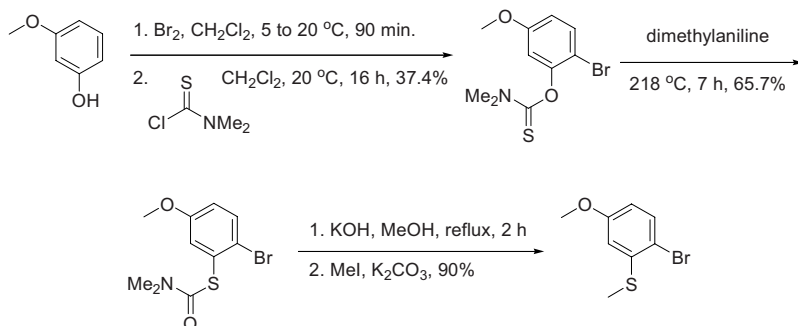


The Newman–Kwart rearrangement is a member of a series of related rearrangements, such as the **Schönberg rearrangement** and the **Chapman rearrangement** (page 105), in which aryl groups migrate intramolecularly between nonadjacent atoms. The Schönberg rearrangement is the most similar and involves the 1,3-migration of an aryl group from oxygen to sulfur in a diarylthioncarbonate. The Chapman rearrangement involves an analogous migration but to nitrogen.



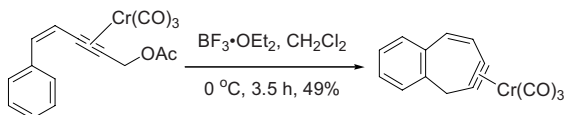
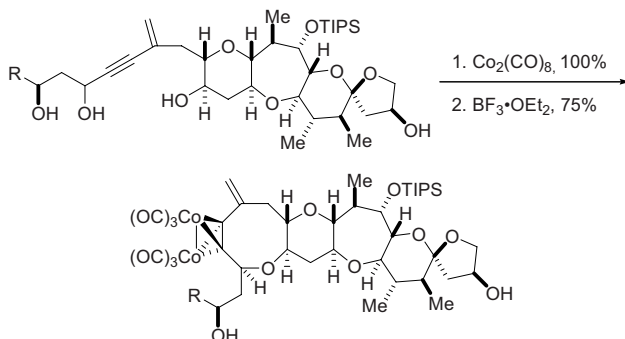
Example 1⁵



Example 2⁶Example 3⁷

References

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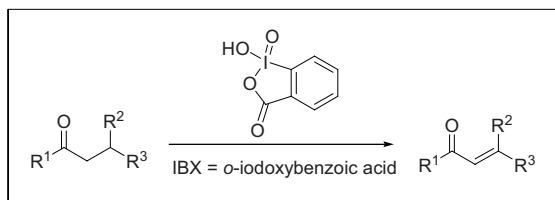
Example 3, Intramolecular Nicholas reaction using chromium⁷Example 4⁹

References

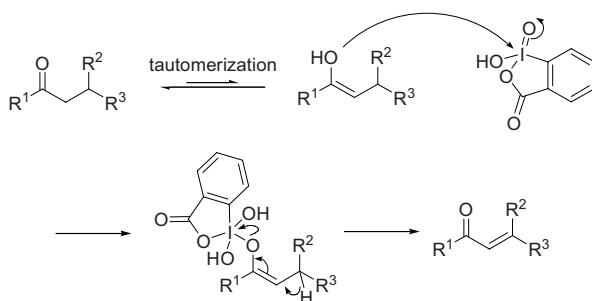
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Nicolaou IBX dehydrogenation

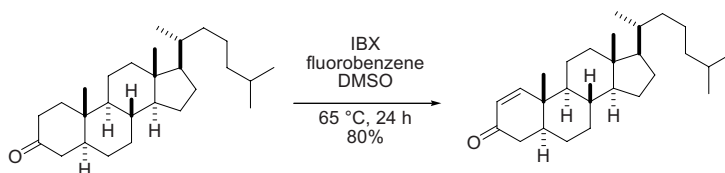
α,β -Unsaturation of aldehydes and ketones mediated by stoichiometric amounts of *o*-iodoxybenzoic acid (IBX), alternative to the Saegusa oxidation (page 482).



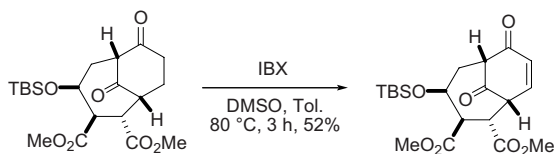
A SET mechanism has also been proposed. Additionally, silyl enol ethers are also viable substrates.

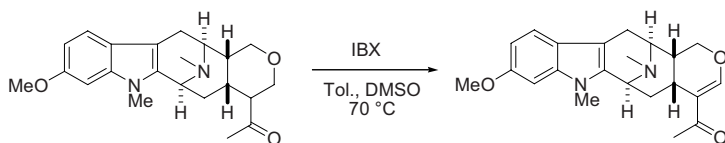
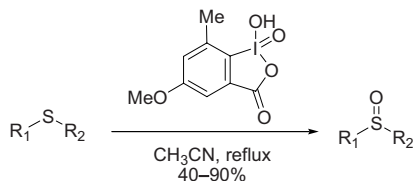
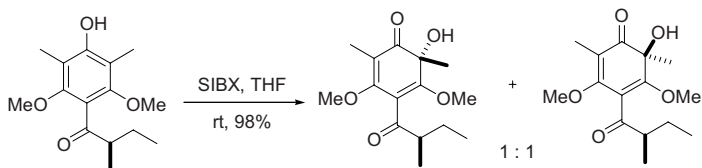


Example 1^{1a}



Example 2³



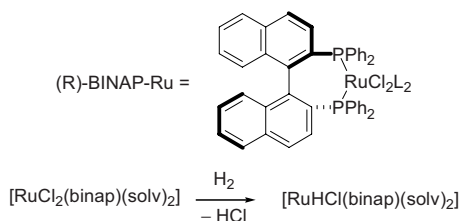
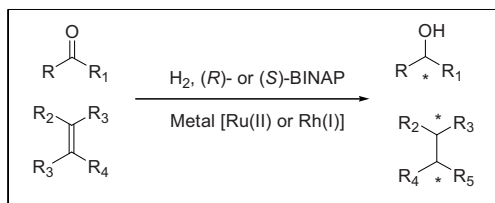
Example 3⁷Example 4, *o*-Methyl-IBX (Me-IBX)⁹Example 5, Stabilized IBX (SIBX)¹⁰

References

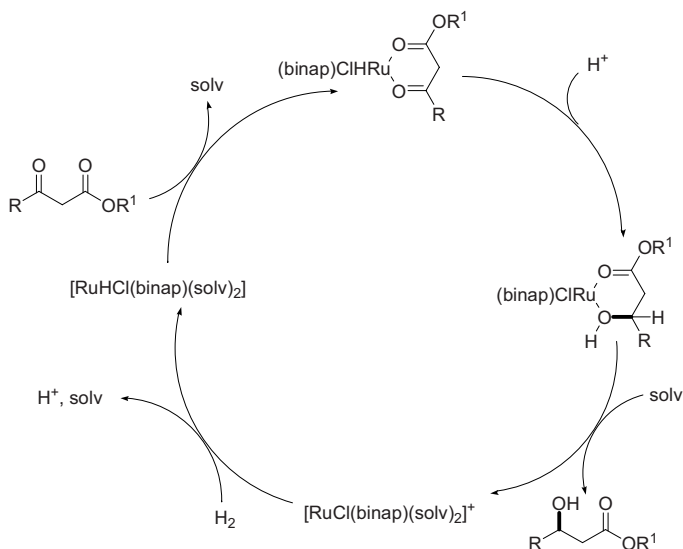
1. (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993–996. (c) Nicolaou, K. C.; Gray, D. L.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996–1000.
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Noyori asymmetric hydrogenation

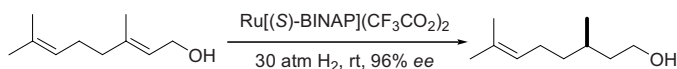
Asymmetric reduction of carbonyls and alkenes *via* hydrogenation, catalyzed by a ruthenium(II) BINAP complex.

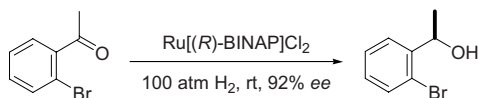
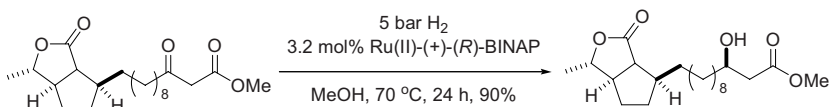
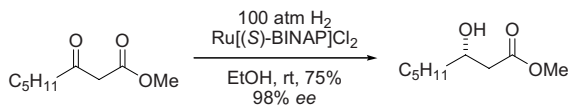


The catalytic cycle:



Example 1^{1b}



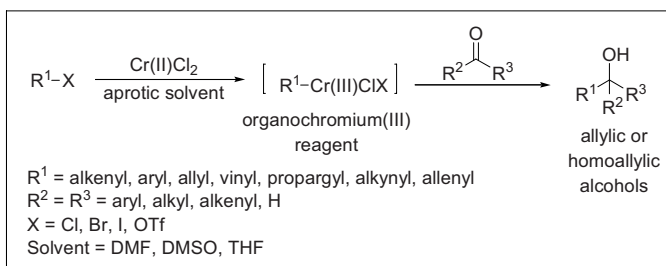
Example 2^{1c}Example 3⁹Example 4¹⁰

References

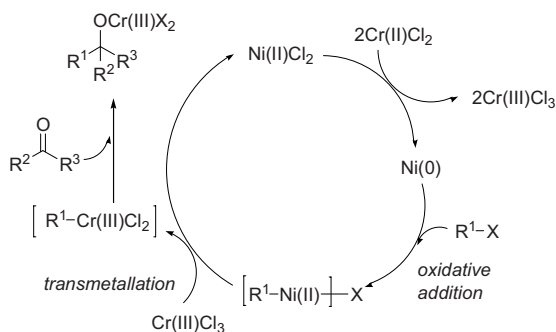
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Nozaki–Hiyama–Kishi reaction

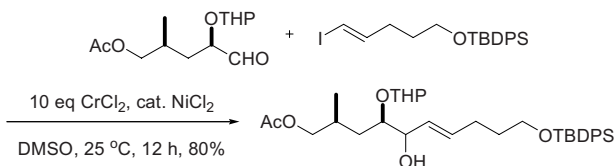
Cr–Ni bimetallic catalyst-promoted redox addition of vinyl halides to aldehydes.



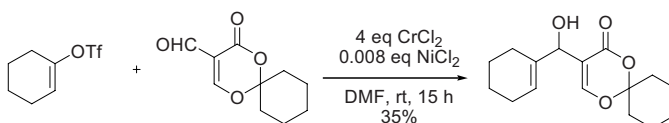
The catalytic cycle:²

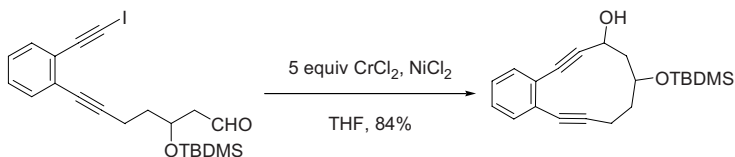
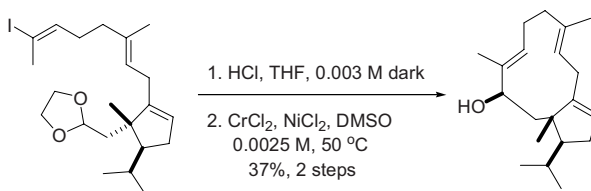


Example 1³



Example 2⁵



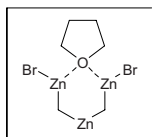
Example 3, Intramolecular Nozaki–Hiyama–Kishi reaction⁸Example 4, Intramolecular Nozaki–Hiyama–Kishi reaction⁹

References

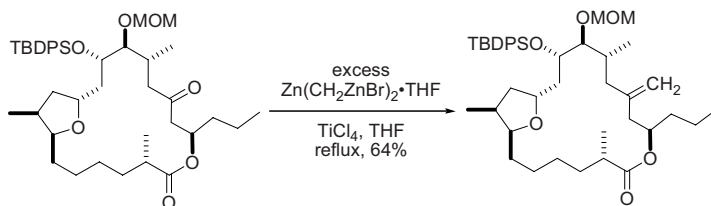
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Nysted reagent

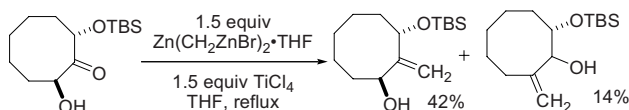
The Nysted reagent, cyclo-dibromodi- μ -methylene(μ -tetrahydrofuran)trizinc, is used for the olefination of ketones and aldehydes.



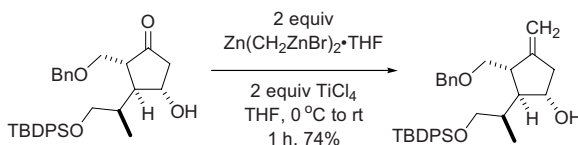
Example 1, The Wittig reagent opened the lactone:⁶



Example 2⁸



Example 3⁹

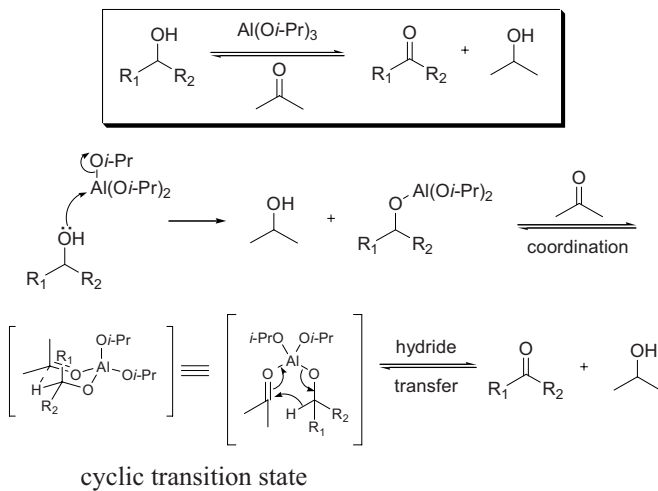


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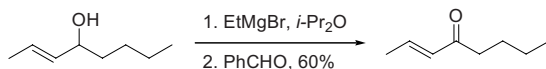
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Oppenauer oxidation

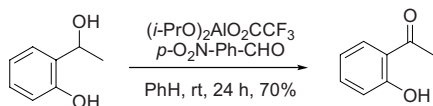
Alkoxide-catalyzed oxidation of secondary alcohols. Reverse of the Meerwein–Ponndorf–Verley reduction.



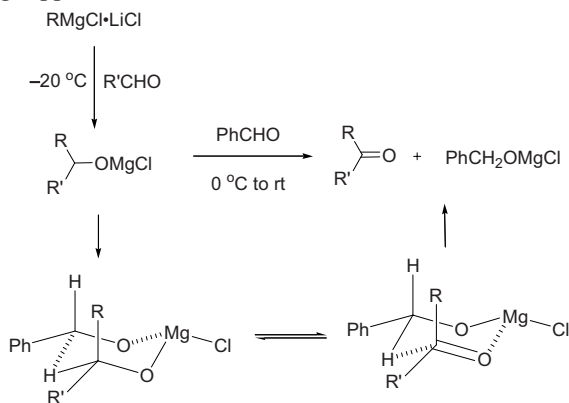
Example 1, Mg-Oppenauer oxidation³

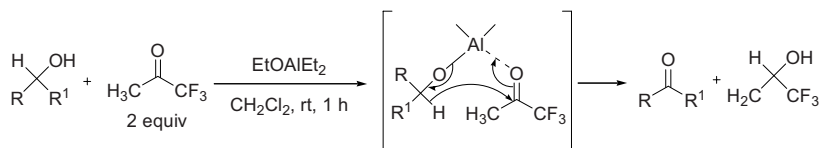


Example 2⁶



Example 3, Mg-Oppenauer oxidation⁸



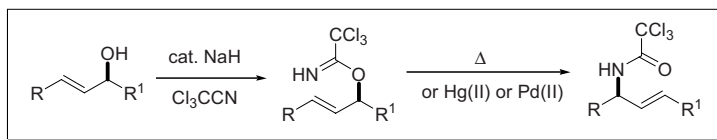
Example 4¹⁰

References

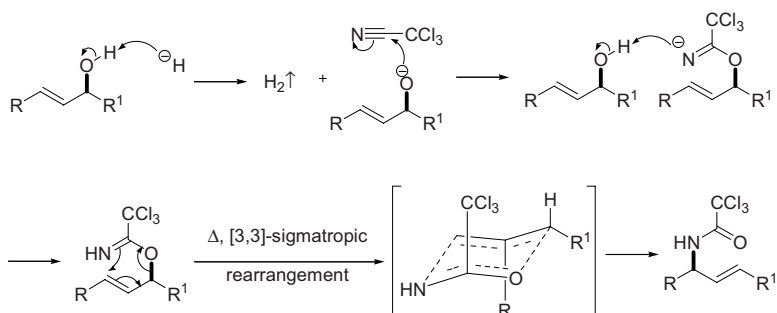
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Overman rearrangement

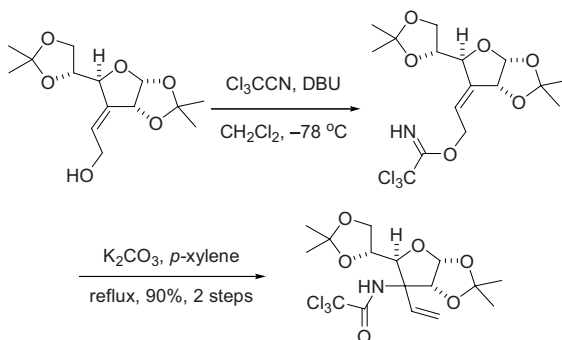
Stereoselective transformation of allylic alcohol to allylic trichloroacetamide *via* trichloroacetimidate intermediate.



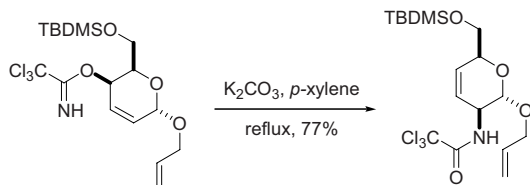
trichloroacetimidate

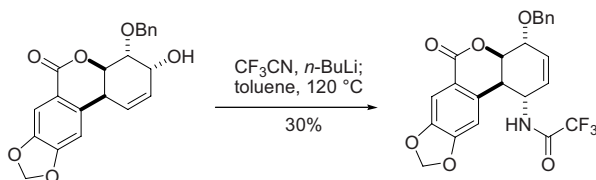
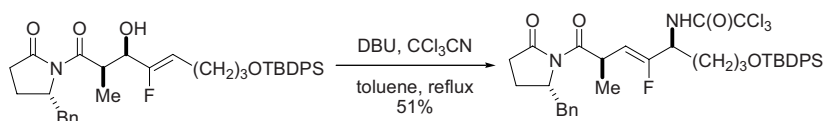


Example 1⁵



Example 2⁶



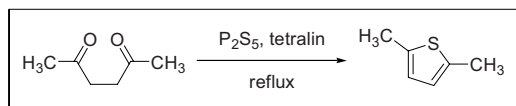
Example 3⁷Example 4⁹

References

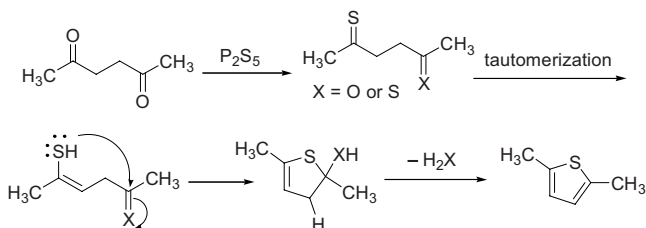
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Paal thiophene synthesis

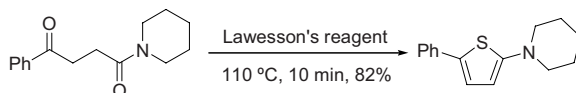
Thiophene synthesis from addition of a sulfur atom to 1,4-diketones and subsequent dehydration.



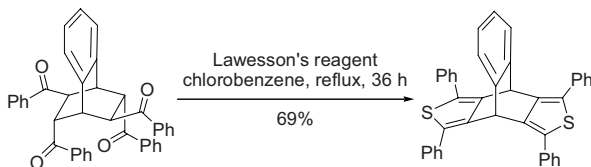
The reaction now is frequently carried out using the Lawesson's reagent. For the mechanism of carbonyl to thiocarbonyl transformation, see Lawesson's reagent on page 328.



Example 1²



Example 2³

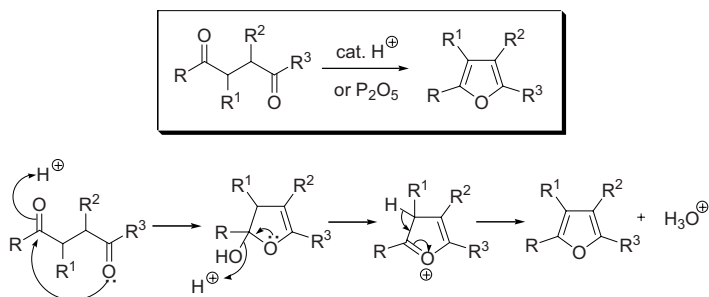


References

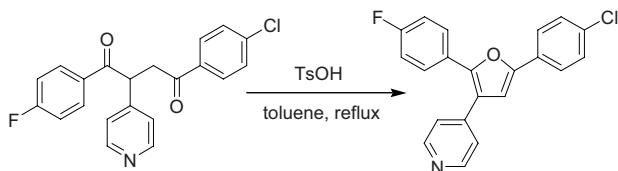
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Paal–Knorr furan synthesis

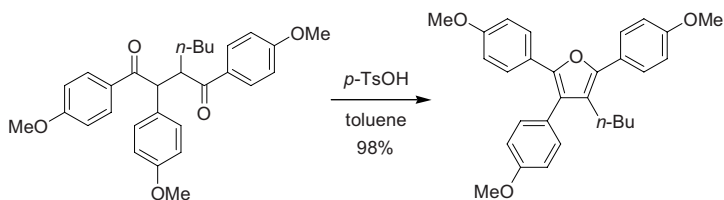
Acid-catalyzed cyclization of 1,4-diketones to form furans.



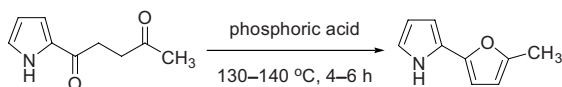
Example 1³

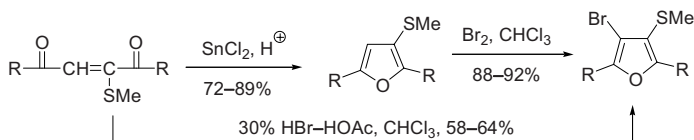


Example 2⁶



Example 3⁹



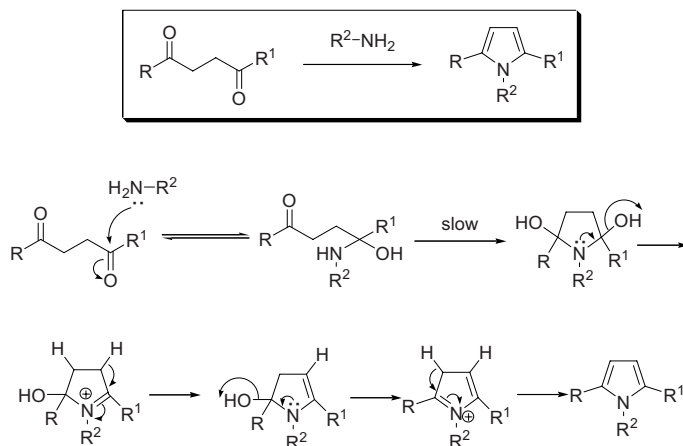
Example 4¹⁰

References

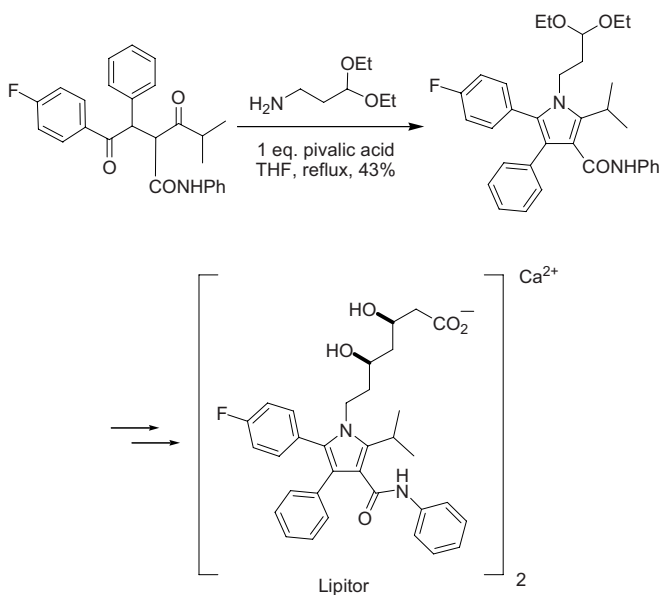
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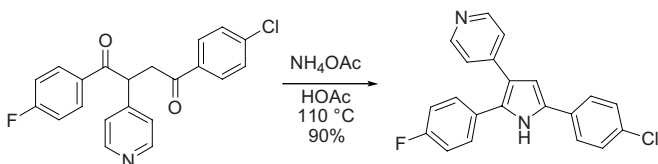
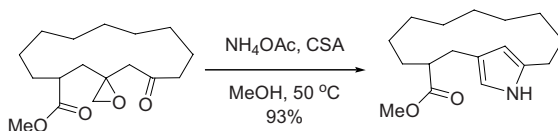
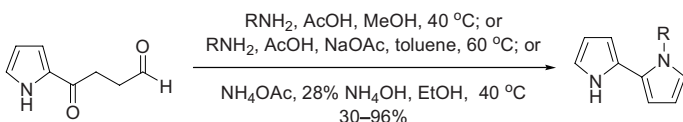
Paal–Knorr pyrrole synthesis

Reaction between 1,4-diketones and primary amines (or ammonia) to give pyrroles. A variation of the Knorr pyrazole synthesis (page 317).



Example 1⁴



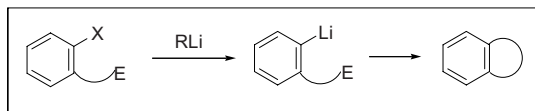
Example 2⁵Example 3⁹Example 4¹⁰

References

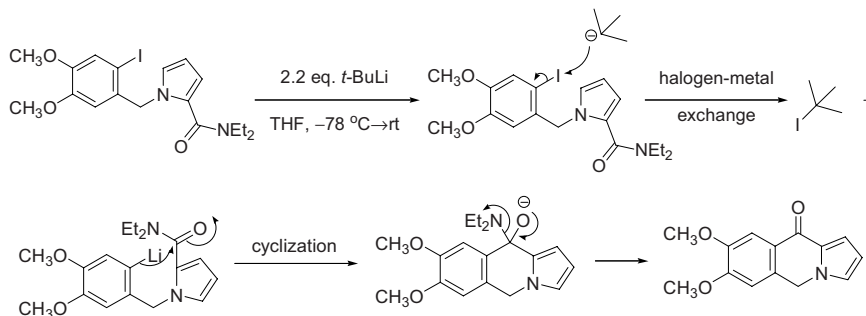
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Parham cyclization

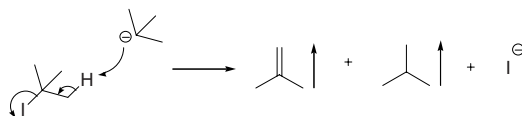
The Parham cyclization is the generation by halogen–lithium exchange of aryllithiums and heteroaryllithiums, and their subsequent intramolecular cyclization onto an electrophilic site.



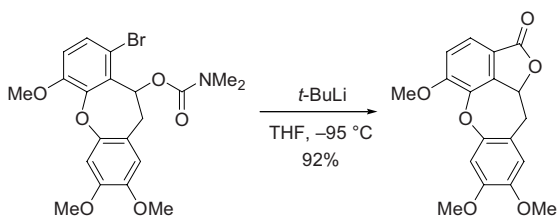
E.g.



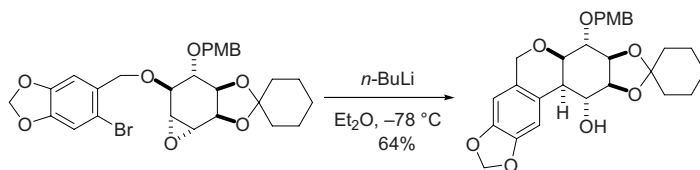
The fate of the second equivalent of *t*-BuLi:

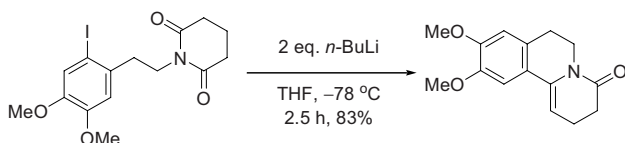
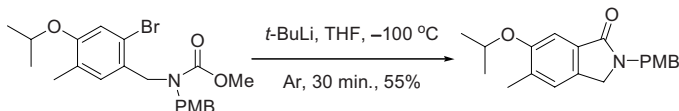


Example 1²



Example 2⁴



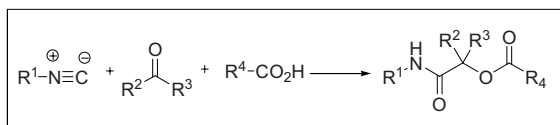
Example 3⁵Example 4⁹

References

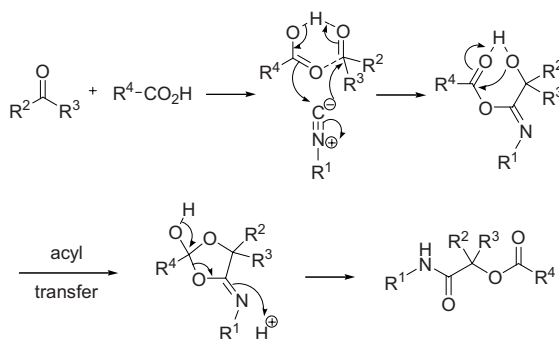
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Passerini reaction

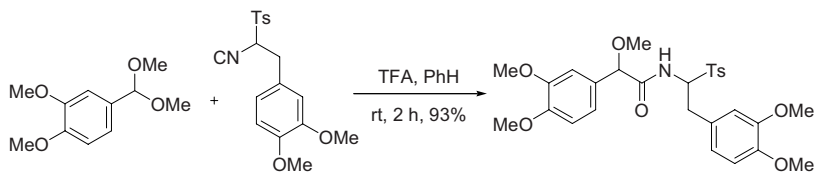
Three-component condensation (3CC) of carboxylic acids, *C*-isocyanides, and carbonyl compounds to afford α -acyloxycarboxamides. *Cf.* Ugi reaction.



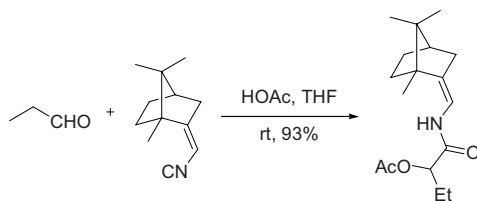
isocyanide



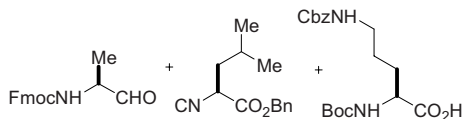
Example 1³

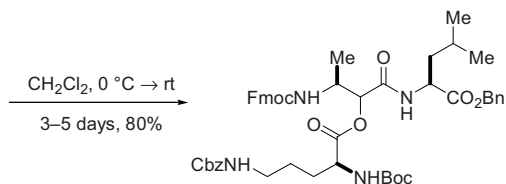
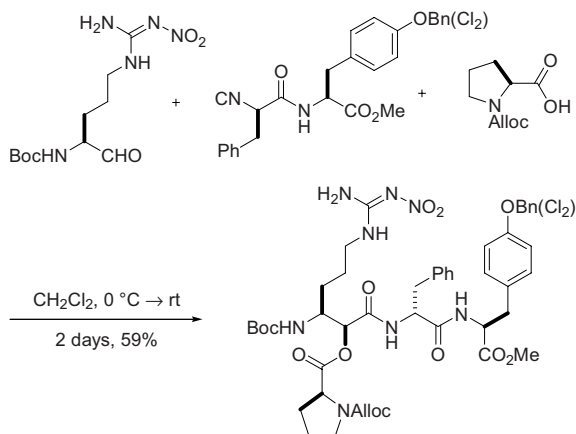


Example 2⁵



Example 3⁶



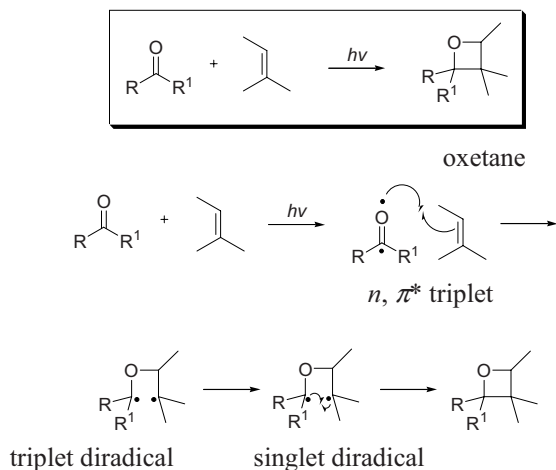
Example 4⁷

References

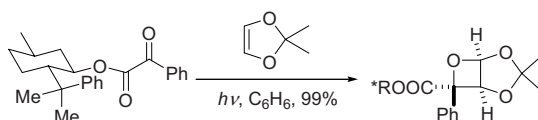
1. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126–129. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181–188. Mario Passerini (b, 1891) was born in Scandicci, Italy. He obtained his Ph.D. in chemistry and pharmacy at the University of Florence, where he was a professor for most of his career.
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Paternó–Büchi reaction

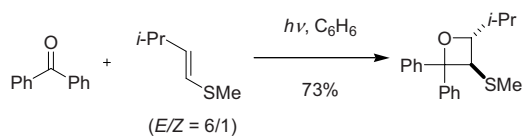
Photoinduced electrocyclicization of a carbonyl with an alkene to form polysubstituted oxetane ring systems



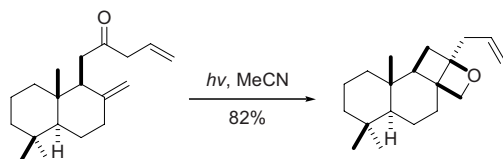
Example 1²

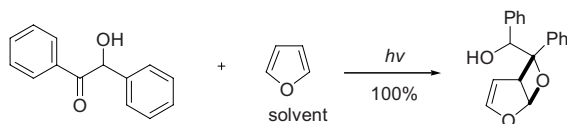


Example 2⁴



Example 3⁶



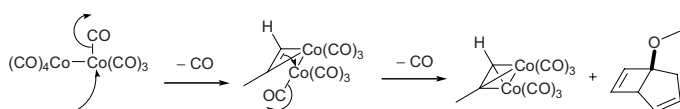
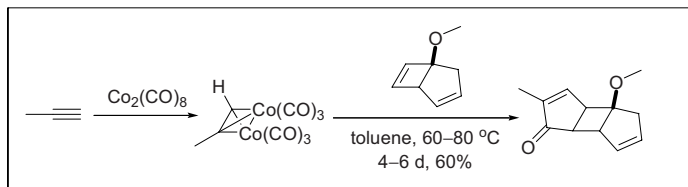
Example 4⁸

References

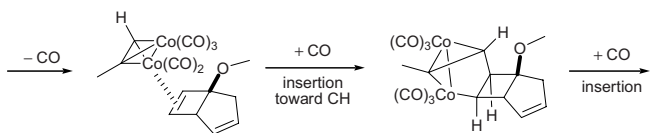
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Pauson–Khand reaction

Formal $[2 + 2 + 1]$ cycloaddition of an alkyne, alkyne, and carbon monoxide mediated by octacarbonyl dicobalt to form cyclopentenones.

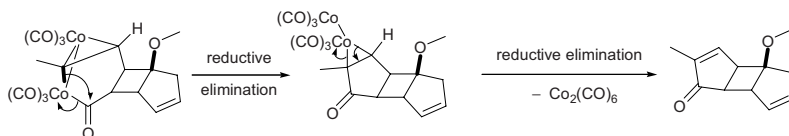


hexacarbonyldicobalt complex

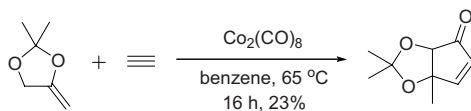


exo complex

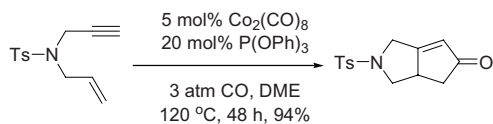
sterically-favored isomer

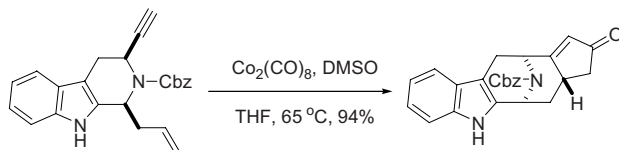
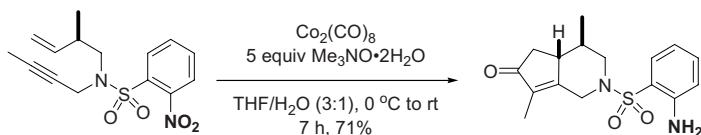


Example 1³



Example 2, A catalytic version⁶



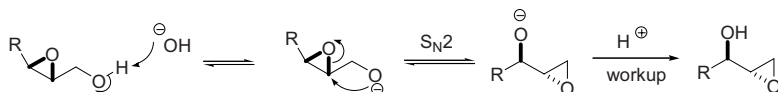
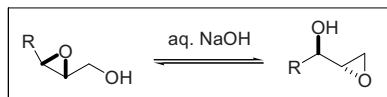
Example 3, Intramolecular Pauson–Khand reaction⁹Example 4, Intramolecular Pauson–Khand reaction¹⁰

References

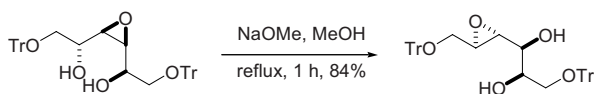
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Payne rearrangement

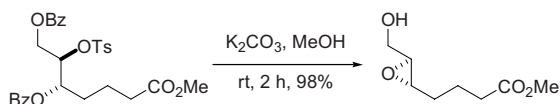
The isomerization of 2,3-epoxy alcohol under the influence of a base to 1,2-epoxy-3-ol is referred to as the Payne rearrangement. Also known as epoxide migration.



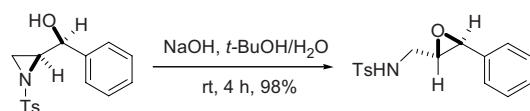
Example 1²



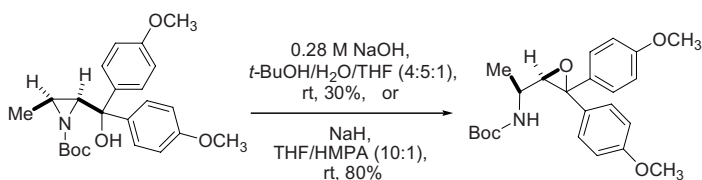
Example 2³



Example 3, Aza-Payne rearrangement⁸



Example 4, Aza-Payne rearrangement⁹

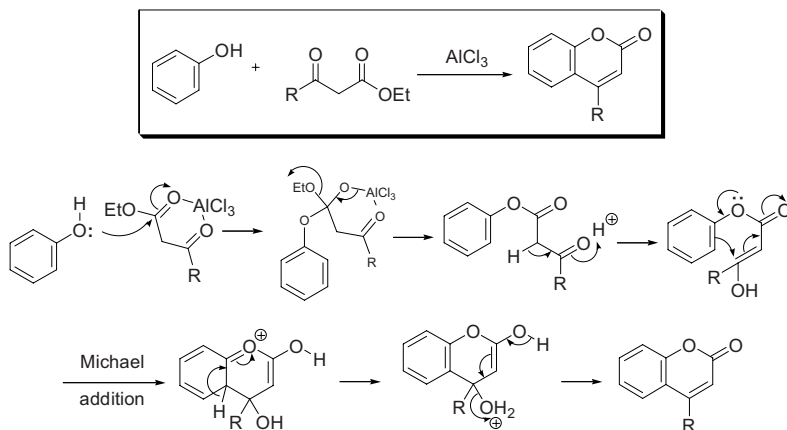


References

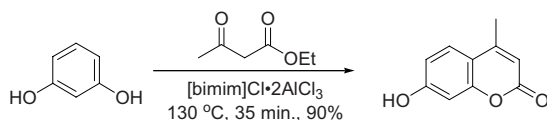
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Pechmann coumarin synthesis

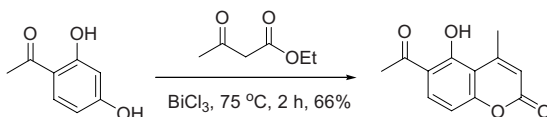
Lewis acid-mediated condensation of phenol with β -ketoester to produce coumarin.



Example 1⁶



Example 2⁸

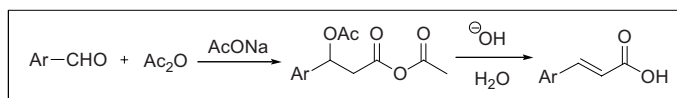


References

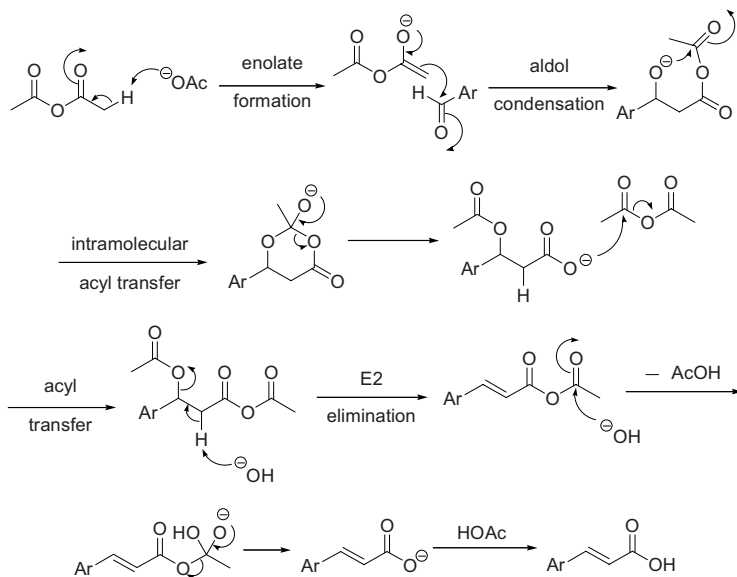
1. von Pechmann, H.; Duisberg, C. *Ber.* **1883**, *16*, 2119. Hans von Pechmann (1850–1902) was born in Nürnberg, Germany. After his doctorate, he worked with Frankland and von Baeyer. Pechmann taught at Munich and Tübingen. He committed suicide by taking cyanide.
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Perkin reaction

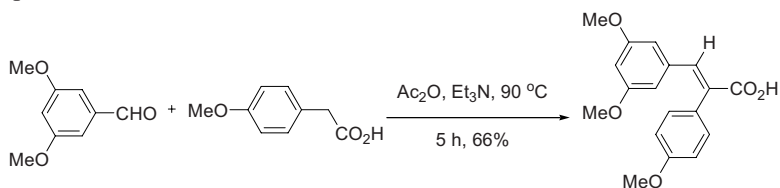
Cinnamic acid synthesis from aryl aldehyde and acetic anhydride.



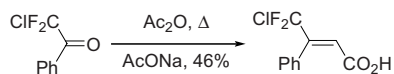
cinnamic acid



Example 1⁷



Example 2⁹

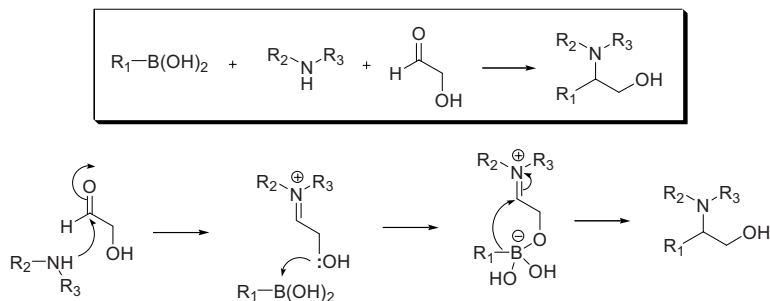


References

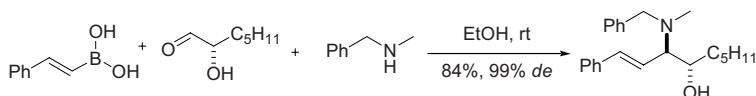
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Petasis reaction

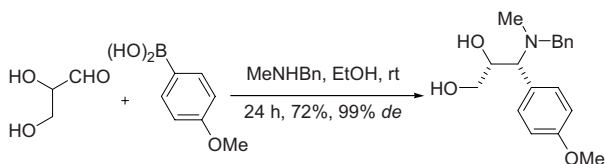
Allylic amine from the three-component reaction of a vinyl boronic acid, a carbonyl and an amine. Also known as boronic acid-Mannich or Petasis boronic acid-Mannich reaction. Cf. Mannich reaction.



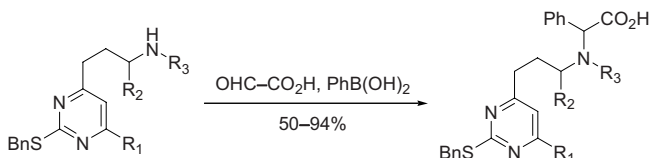
Example 1²



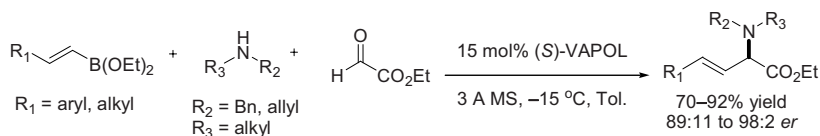
Example 2⁴



Example 3⁹



Example 4, Asymmetric Petasis reaction¹⁰

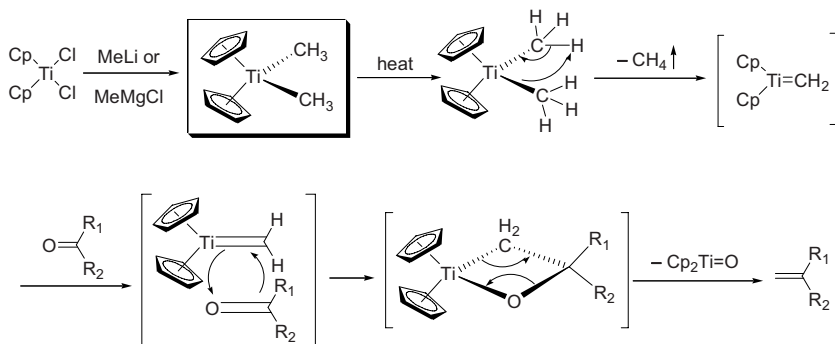


References

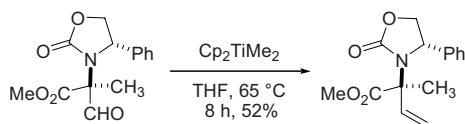
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Petasis reagent

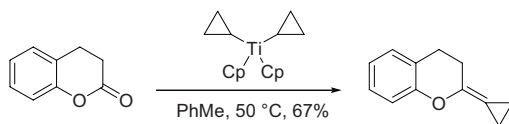
The Petasis reagent (Cp_2TiMe_2 , dimethyltitanocene) undergoes similar olefination reactions with ketones and aldehydes as does the Tebbe's reagent. The originally proposed mechanism⁵ was very different from that of Tebbe olefination. However, later experimental data seem to suggest that both Petasis and Tebbe olefination share the same mechanism, i.e., the carbene mechanism involving a four-membered titanium oxide ring intermediate.⁹ Petasis reagent is easier to make than the Tebbe reagent.



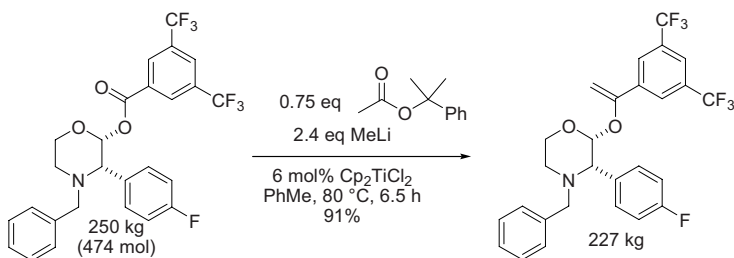
Example 1²

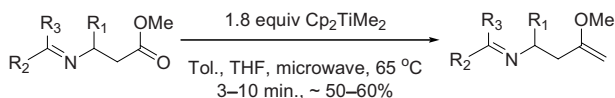


Example 2³



Example 3⁵



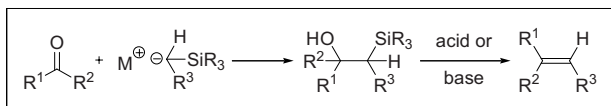
Example 4⁸

References

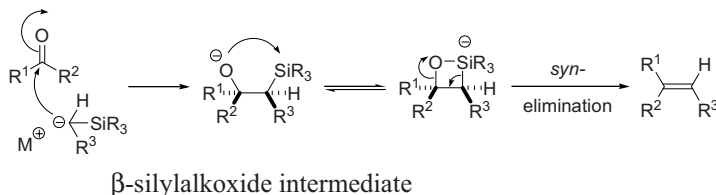
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Peterson olefination

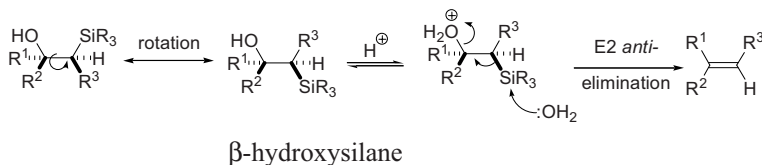
Alkenes from α -silyl carbanions and carbonyl compounds. Also known as the sila-Wittig reaction.



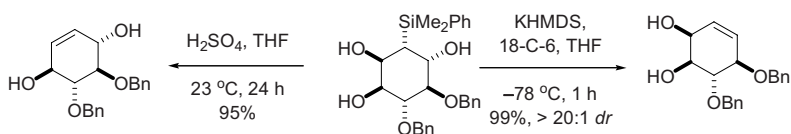
Basic conditions:



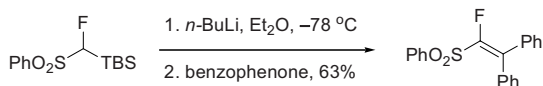
Acidic conditions:



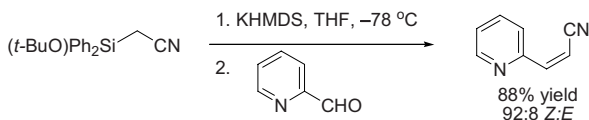
Example 1⁶

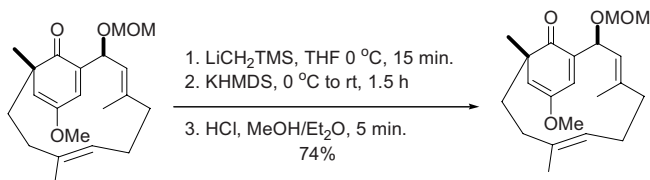


Example 2⁷



Example 3⁸



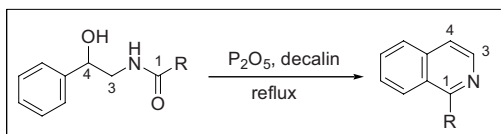
Example 4¹⁰

References

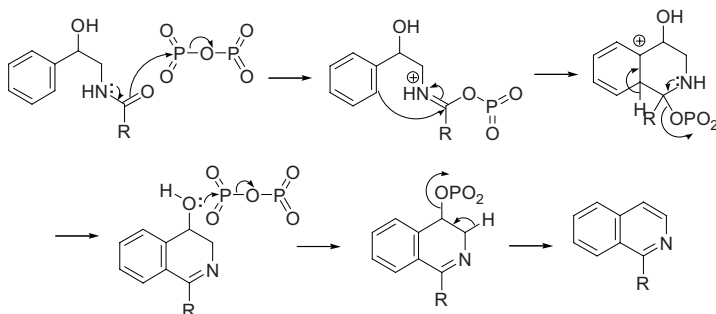
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Pictet–Gams isoquinoline synthesis

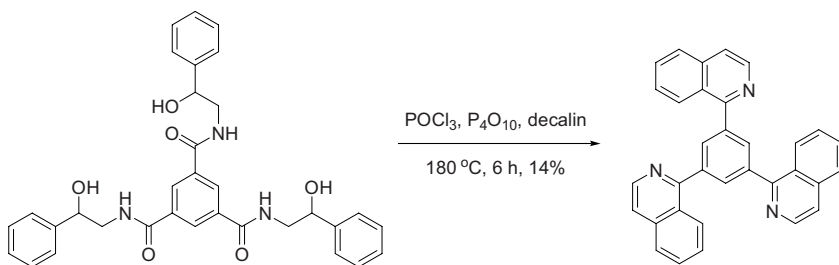
The isoquinoline framework is derived from the corresponding acyl derivatives of β -hydroxy- β -phenylethylamines. Upon exposure to a dehydrating agent such as phosphorus pentoxide, or phosphorus oxychloride, under reflux and in an inert solvent such as decalin, isoquinoline frameworks are formed.



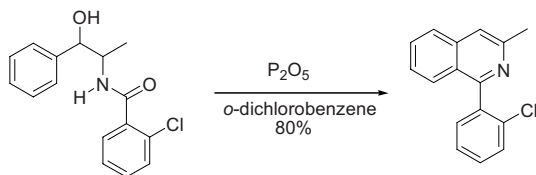
P_2O_5 actually exists as P_4O_{10} , an adamantane-like structure.



Example 1⁴



Example 2⁷

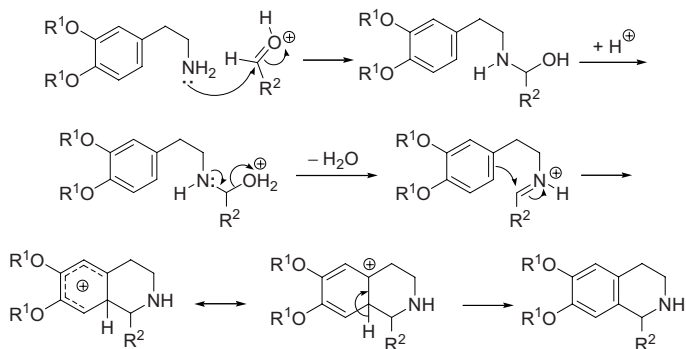
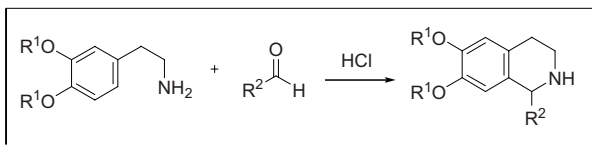


Reference

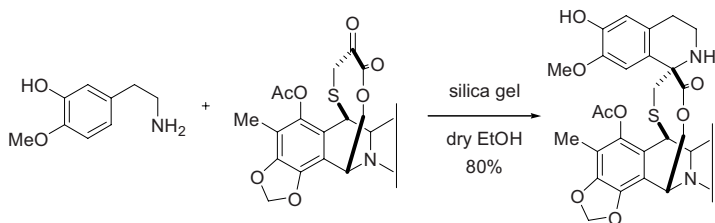
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Pictet–Spengler tetrahydroisoquinoline synthesis

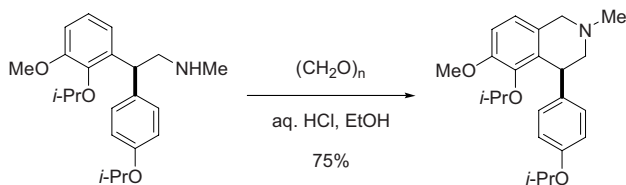
Tetrahydroisoquinolines from condensation of β -arylethylamines and carbonyl compounds followed by cyclization.

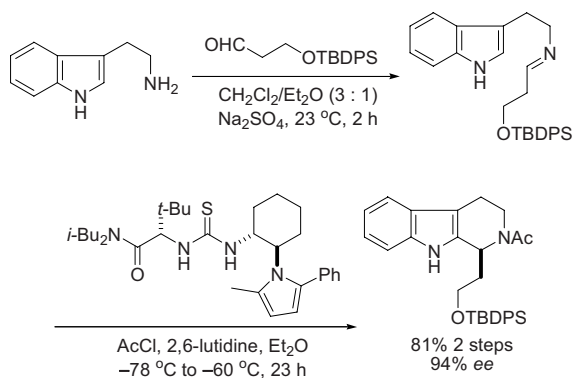
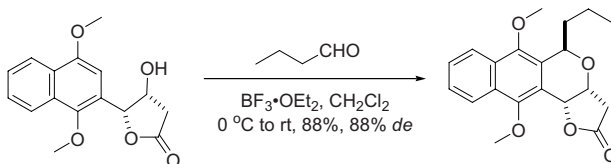


Example 1⁴



Example 2⁷



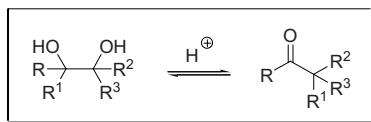
Example 3, Asymmetric acyl Pictet–Spengler⁹Example 4, Oxa-Pictet–Spengler¹⁰

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Pinacol rearrangement

Acid-catalyzed rearrangement of vicinal diols (pinacols) to carbonyl compounds.

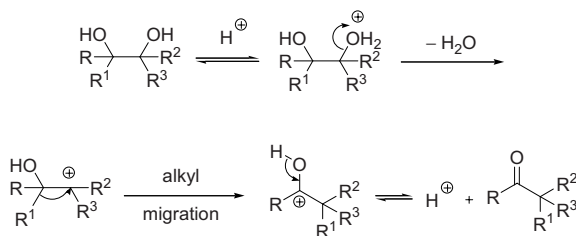


The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order:

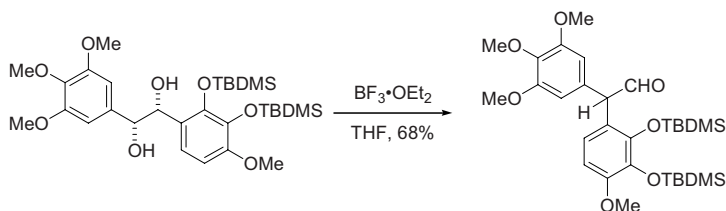
tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl >
primary alkyl > methyl >> H.

For substituted aryls:

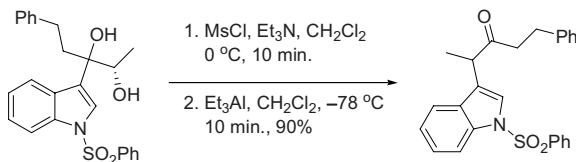
p-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O₂N-Ar

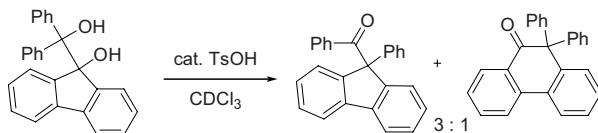
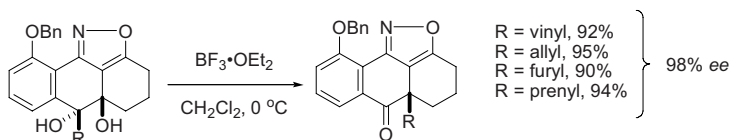


Example 1⁴



Example 2⁵



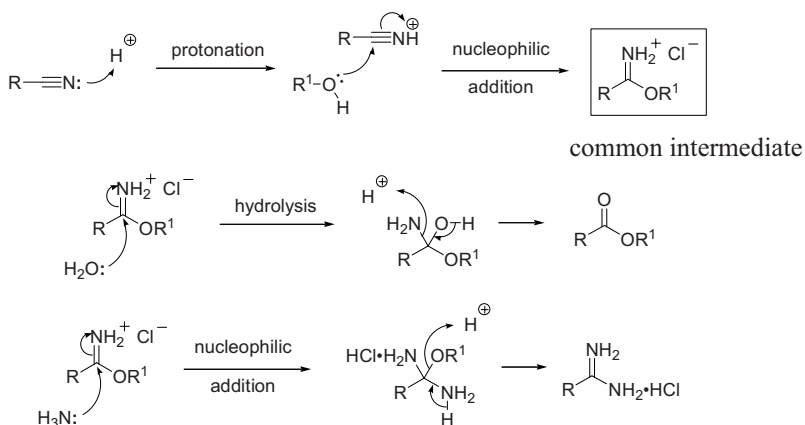
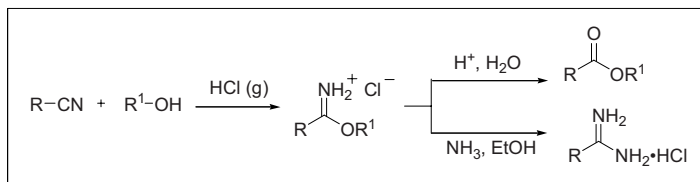
Example 3⁷Example 4⁹

References

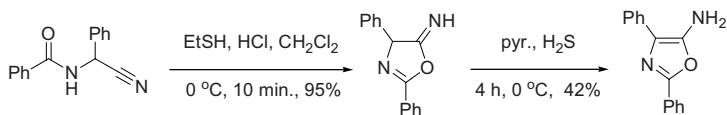
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Pinner reaction

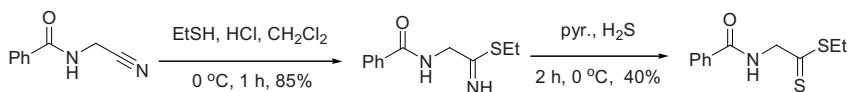
Transformation of a nitrile into an imino ether, which can be converted to either an ester or an amidine.



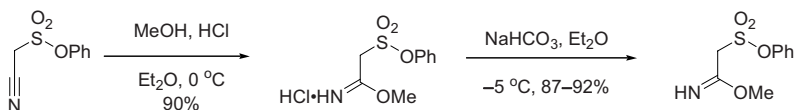
Example 1²

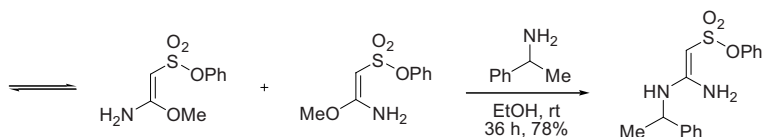
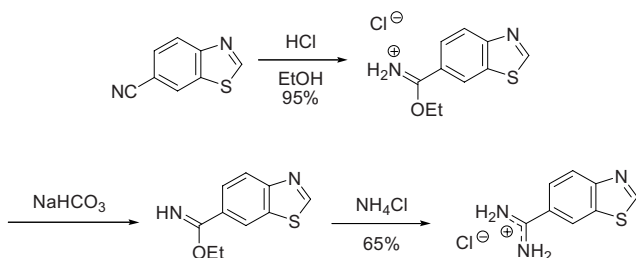


Example 2²



Example 3⁶



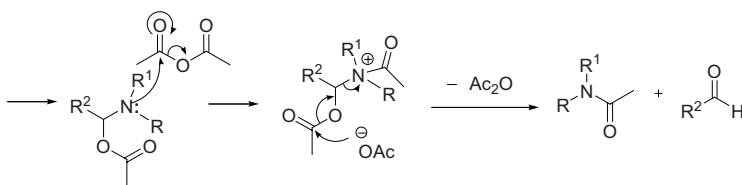
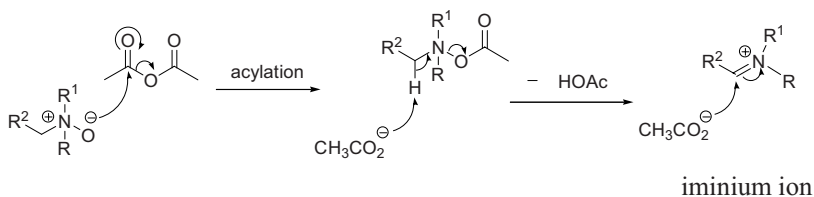
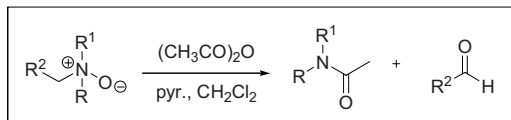
Example 4¹⁰

References

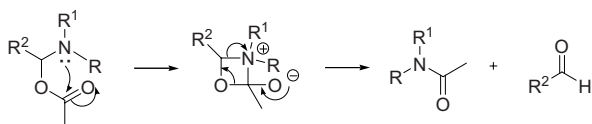
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Polonovski reaction

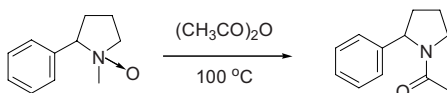
Treatment of a tertiary *N*-oxide with an activating agent such as acetic anhydride, resulting in rearrangement where an *N,N*-disubstituted acetamide and an aldehyde are generated.



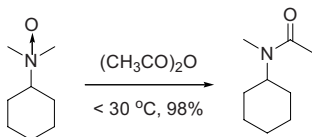
The intramolecular pathway is also operative:

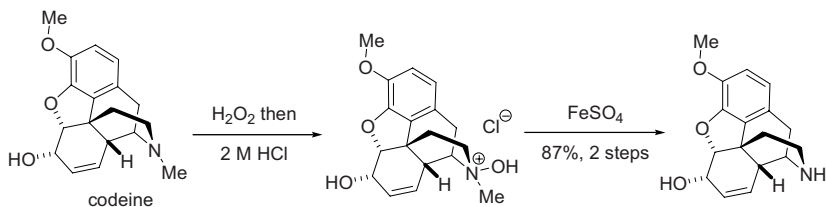


Example 1¹



Example 2²



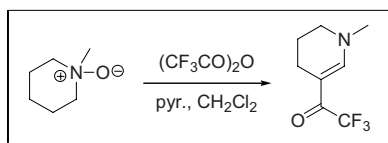
Example 3, Iron salt-mediated Polonovski reaction⁹

References

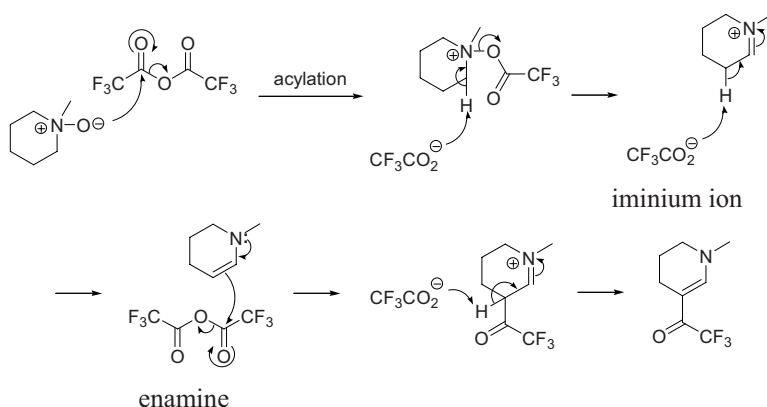
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Polonovski–Potier reaction

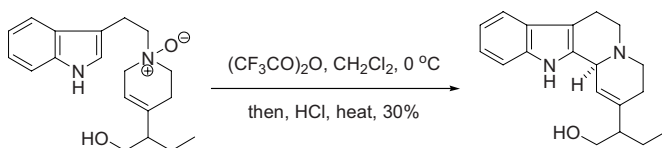
A modification of the Polonovski reaction where trifluoroacetic anhydride is used in place of acetic anhydride. Because the reaction conditions for the Polonovski–Potier reaction are mild, it has largely replaced the Polonovski reaction.



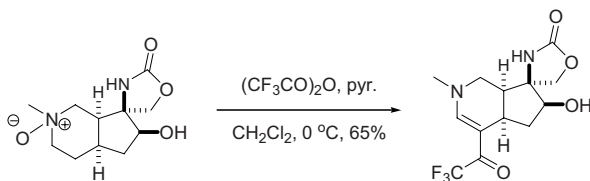
tertiary *N*-oxide

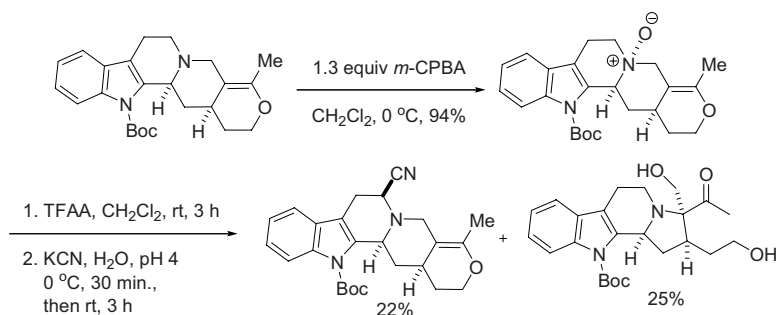
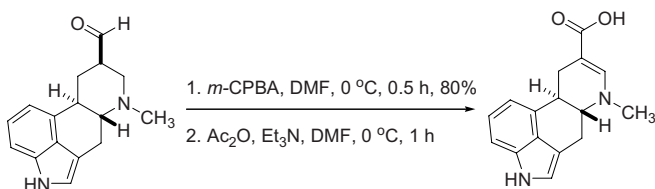


Example 1²



Example 2⁵



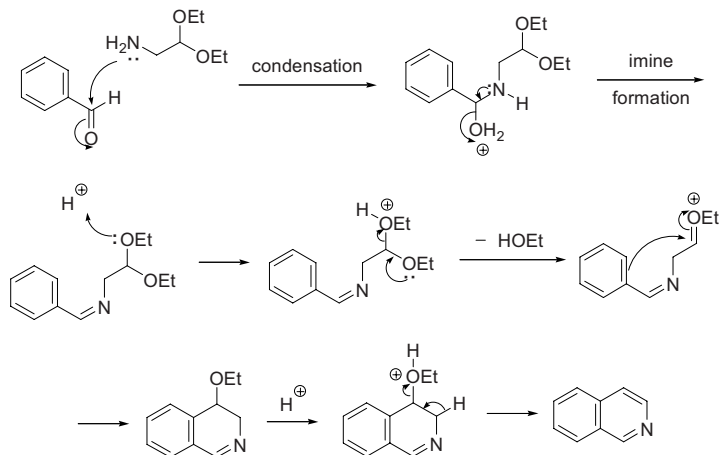
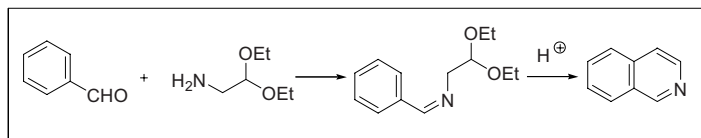
Example 3⁸Example 4¹⁰

References

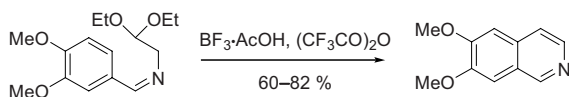
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Pomeranz–Fritsch reaction

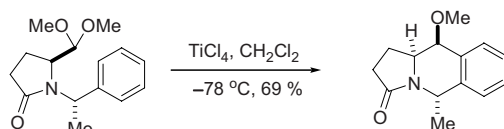
Isoquinoline synthesis *via* acid-mediated cyclization of the appropriate aminoacetal intermediate.

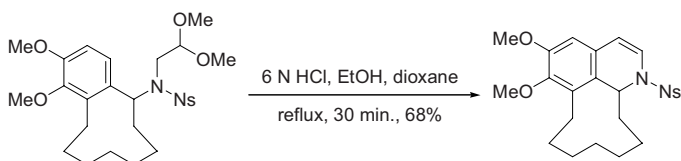
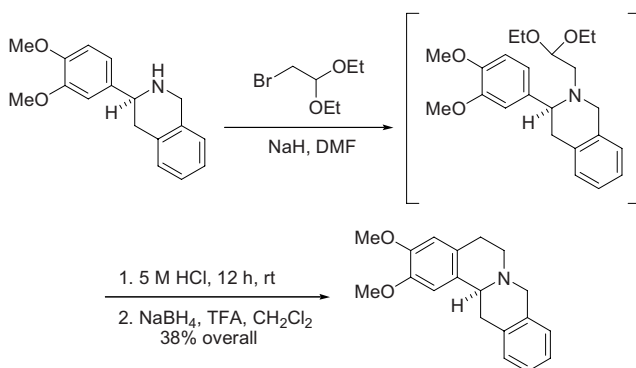


Example 1³



Example 2⁴



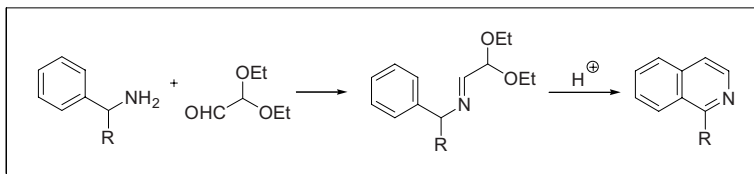
Example 3⁹Example 4, **Bobbitt modification**¹⁰

References

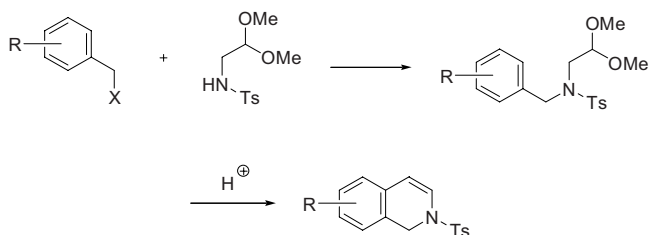
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Schlittler–Müller modification

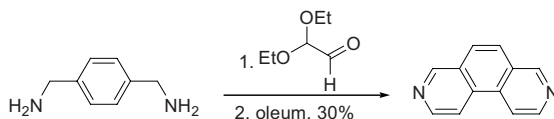
Simple permutation where the amine and the aldehyde switch places for the two reactants in comparison to the Pomeranz–Fritsch reaction.



Example 1³



Example 2⁴

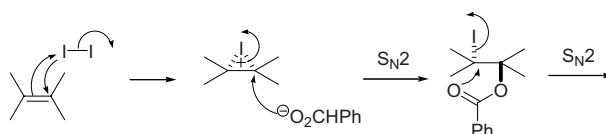
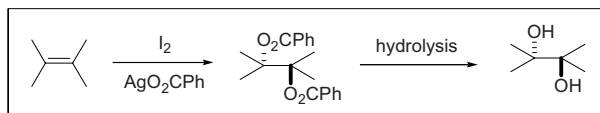


References

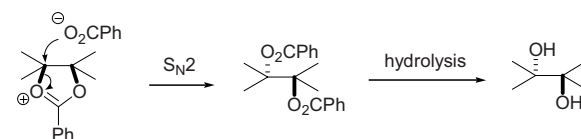
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Prévost *trans*-dihydroxylation

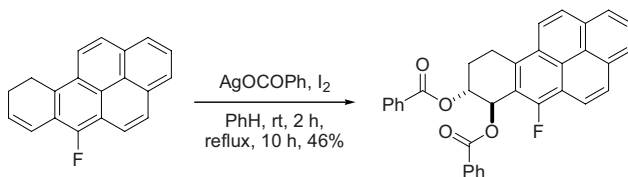
Cf. Woodward *cis*-dihydroxylation.



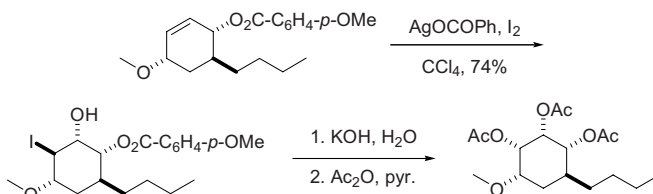
cyclic iodonium ion intermediate neighboring group assistance



Example 1⁵



Example 2⁹

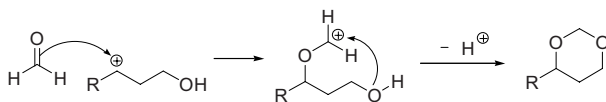
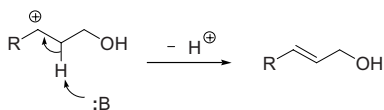
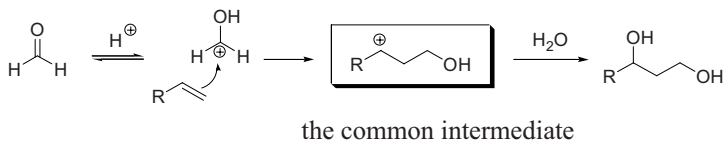
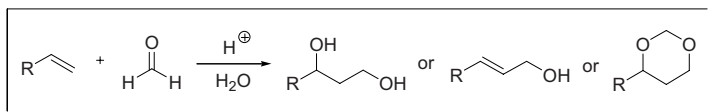


References

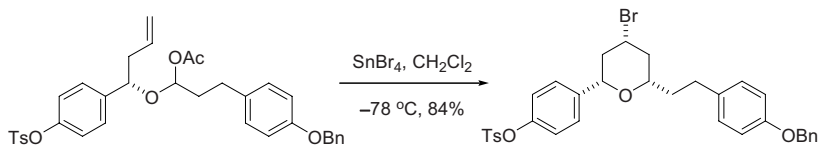
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Prins reaction

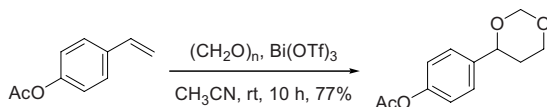
The Prins reaction is the acid-catalyzed addition of aldehydes to alkenes and gives different products depending on the reaction conditions.

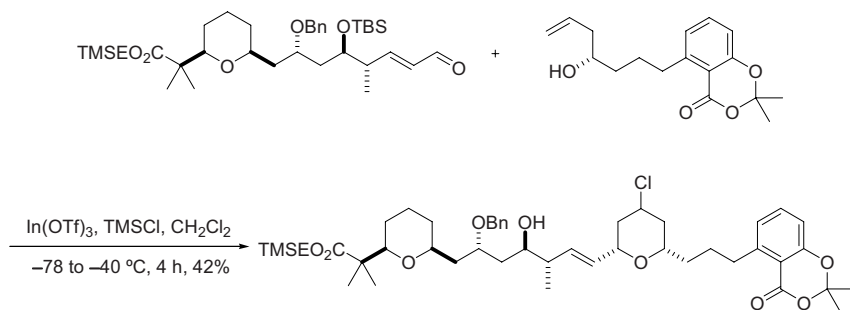
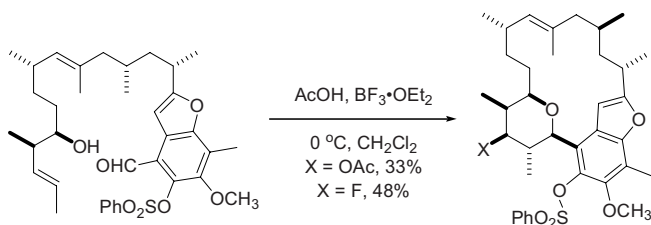


Example 1⁵



Example 2⁷



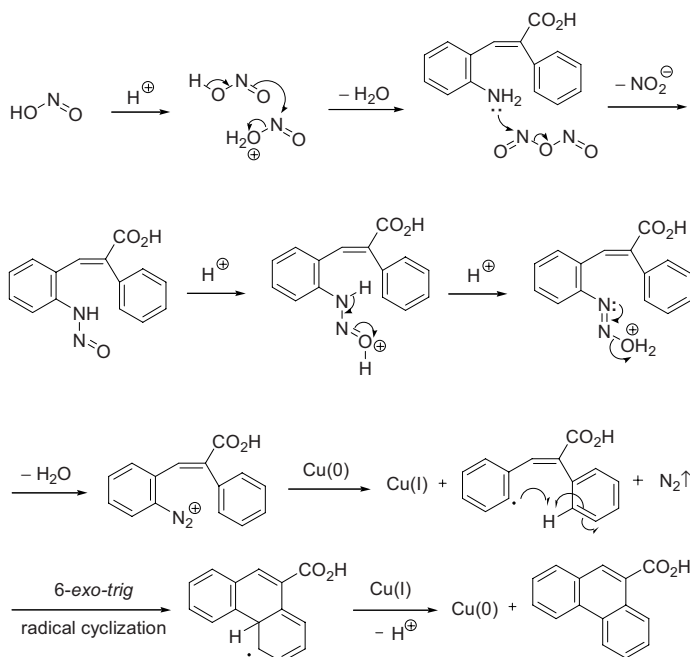
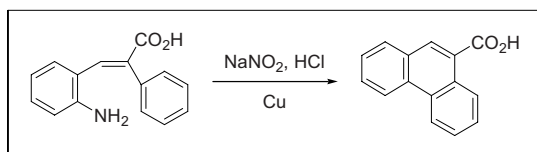
Example 3⁹Example 4¹⁰

References

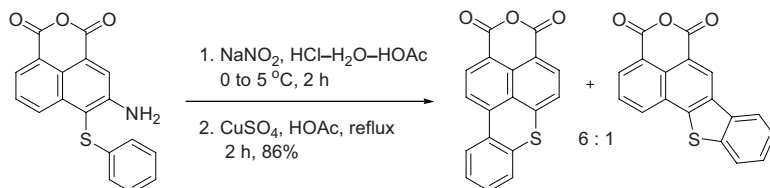
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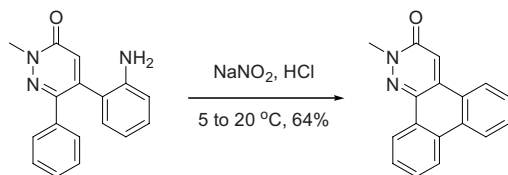
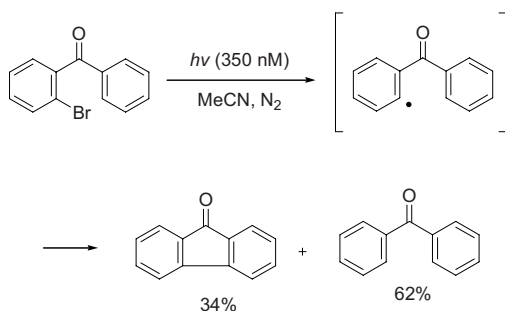
Pschorr cyclization

The intramolecular version of the Gomberg–Bachmann reaction.



Example 1⁷



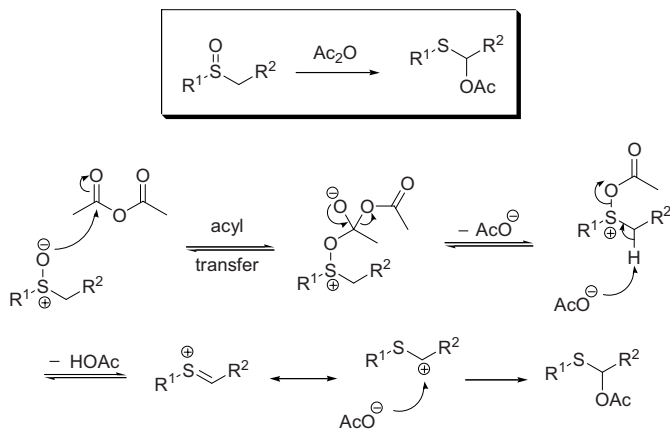
Example 2⁸Example 3¹⁰

References

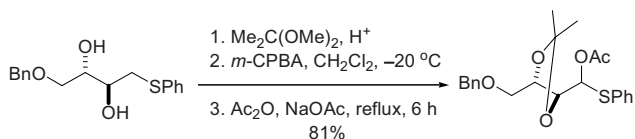
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Pummerer rearrangement

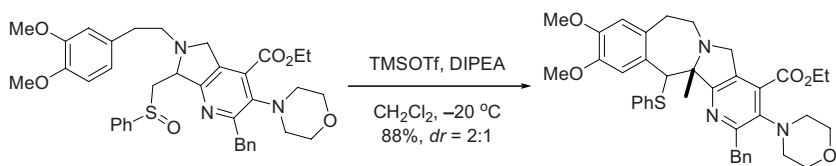
The transformation of sulfoxides into α -acyloxythioethers using acetic anhydride.



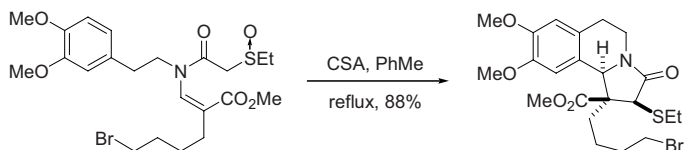
Example 1²

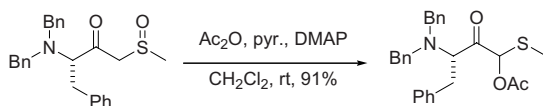


Example 2⁷



Example 3⁸



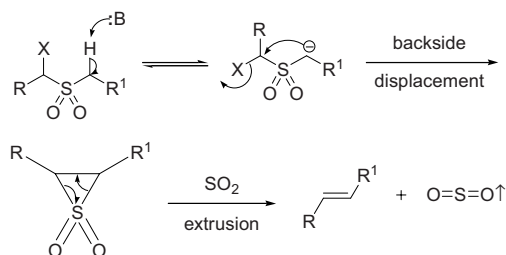
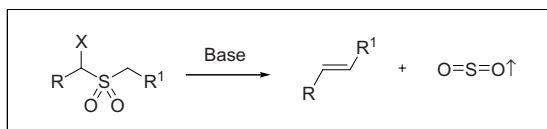
Example 4⁹

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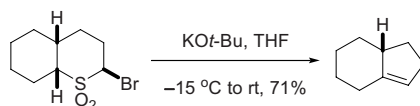
Ramberg–Bäcklund reaction

Olefin synthesis *via* α -halosulfone extrusion.

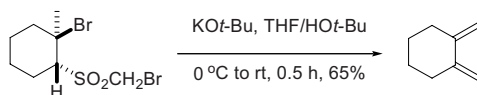


episulfone intermediate

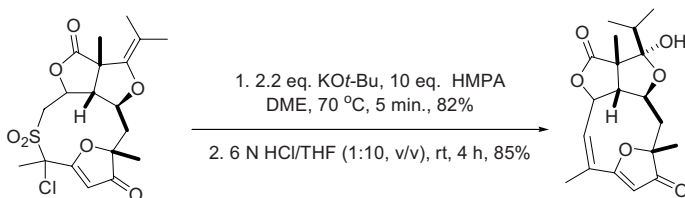
Example 1⁴

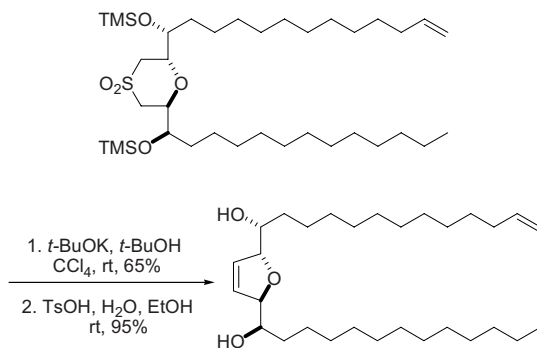


Example 2⁵



Example 3⁶



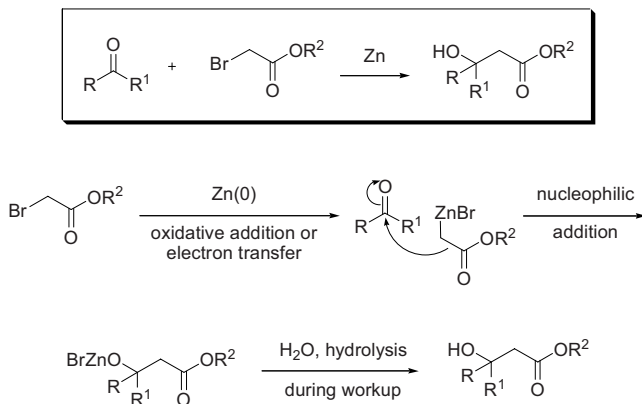
Example 4, *in situ* chlorination⁷

References

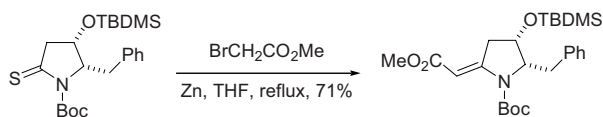
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Reformatsky reaction

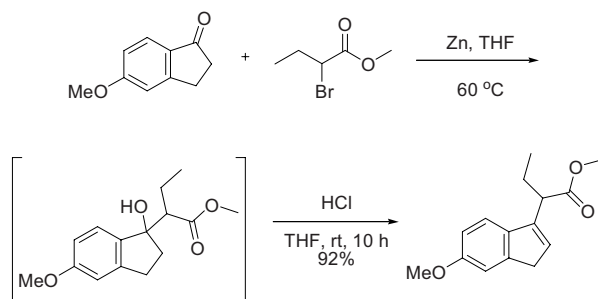
Nucleophilic addition of organozinc reagents generated from α -haloesters to carbonyls.

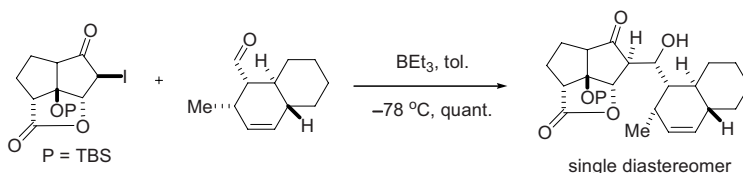
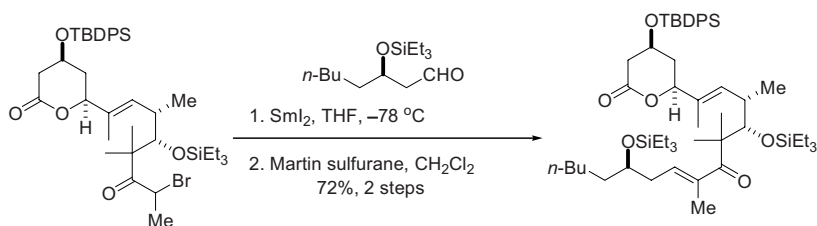


Example 1⁴



Example 2⁶



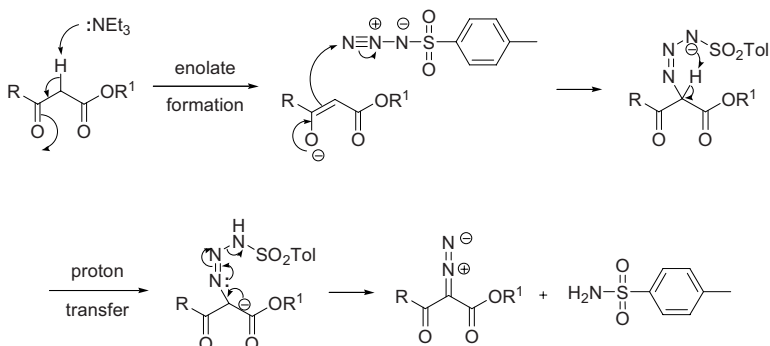
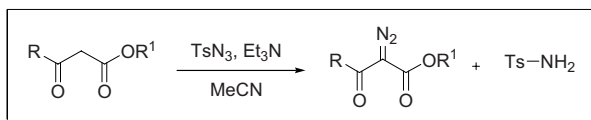
Example 3, Boron-mediated Reformatsky reaction⁸Example 4, SmI_2 -mediated Reformatsky reaction⁹

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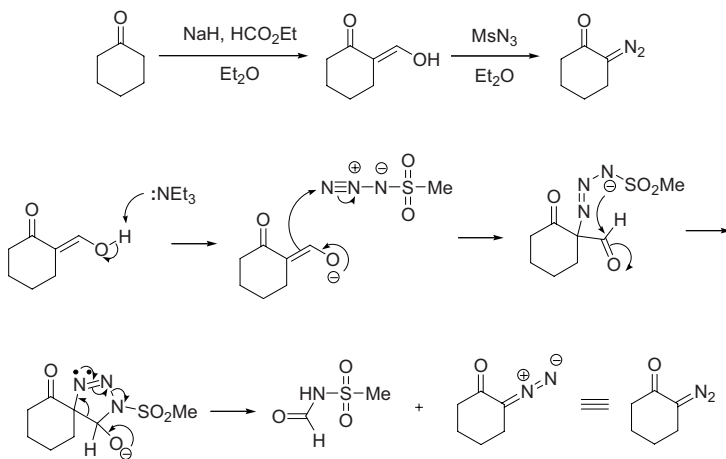
Regitz diazo synthesis

Synthesis of 2-diazo-1,3-diketones or 2-diazo-3-oxoesters using sulfonyl azides.

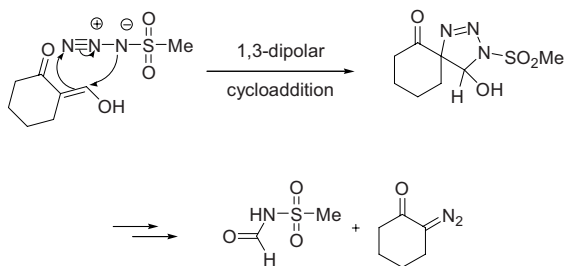
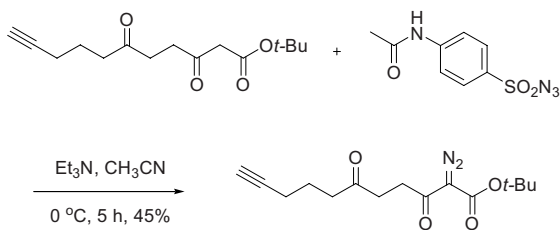
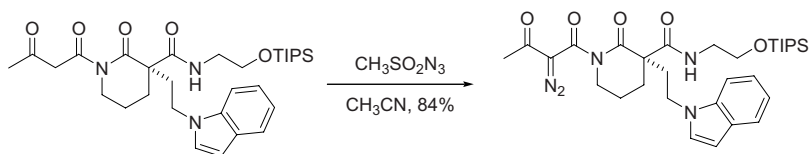


tosyl amide is the by-product

When only one carbonyl is present, ethylformate can be used as an activating auxiliary:⁶⁻⁹



Alternatively, the triazole intermediate may be assembled *via* a 1,3-dipolar cycloaddition of the enol and mesyl azide:

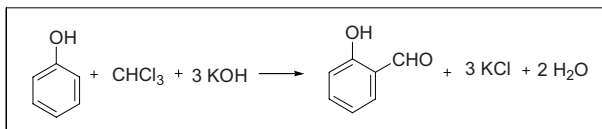
Example 1⁵Example 2¹⁰

References

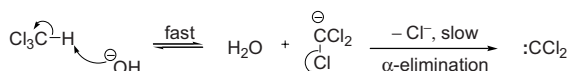
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Reimer–Tiemann reaction

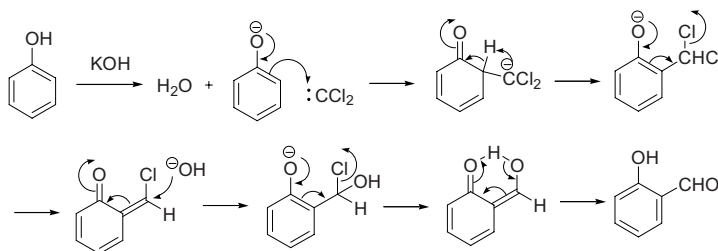
Synthesis of *o*-formylphenol from phenols and chloroform in alkaline medium.



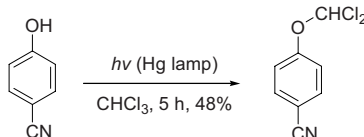
a. Carbene generation:



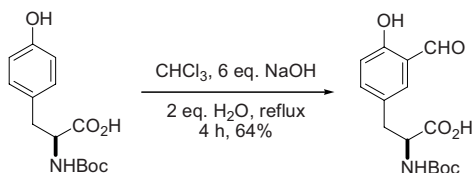
b. Addition of dichlorocarbene and hydrolysis:



Example 1, Photo-Reimer–Tiemann reaction without base⁷



Example 2⁸

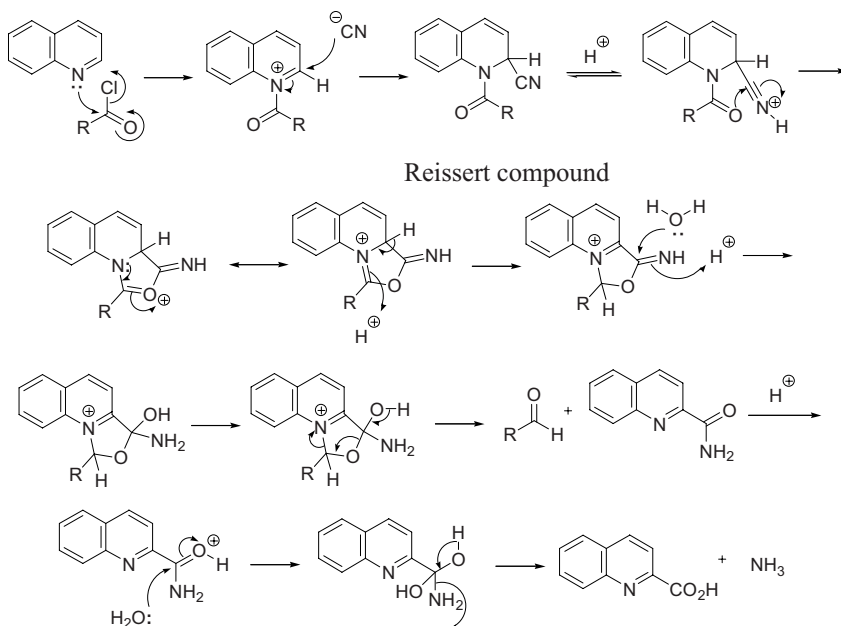
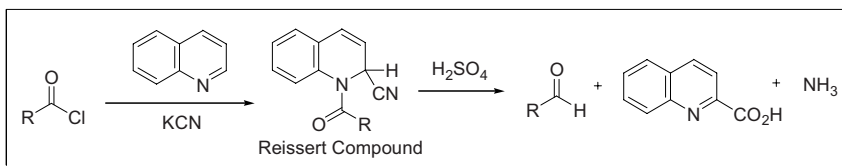


References

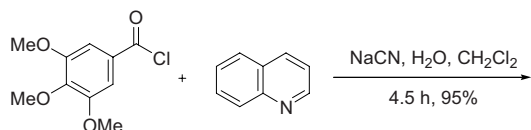
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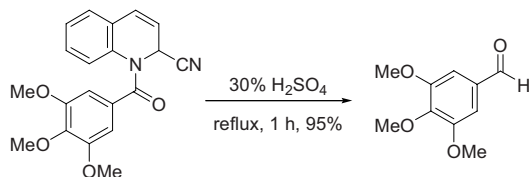
Reissert reaction

Treatment of quinoline or isoquinoline with acid chloride and KCN gives quinaldic acid, aldehyde, and KCN.

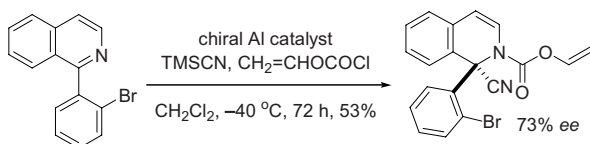


Example 1³

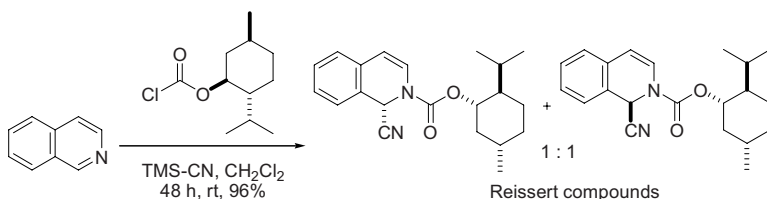




Example 2, Reissert compound from isoquinoline⁷



Example 3, Reissert compound from isoquinoline¹⁰

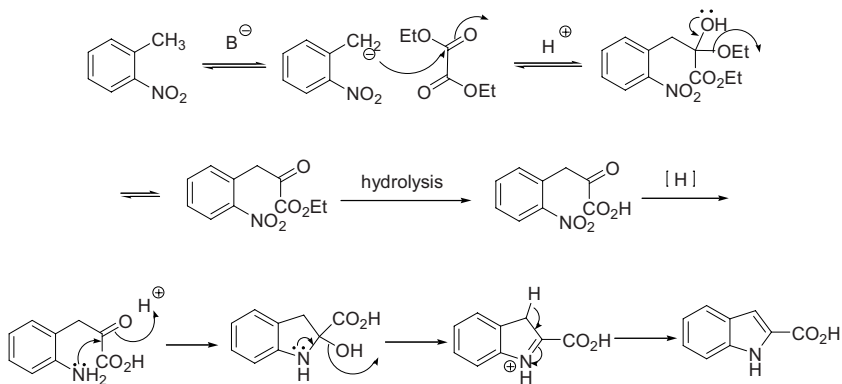
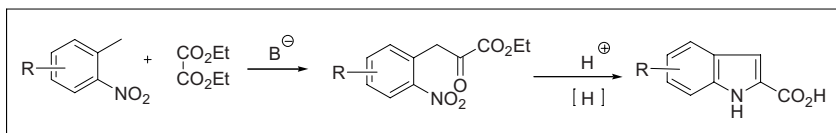


References

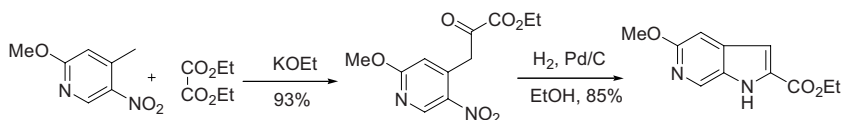
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Reissert indole synthesis

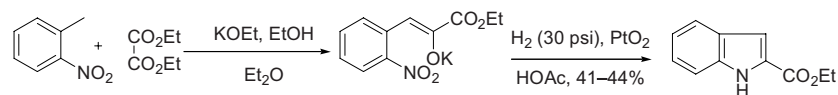
The Reissert indole synthesis involves base-catalyzed condensation of an *o*-nitrotoluene derivative with an ethyl oxalate, which is followed by reductive cyclization to an indole-2-carboxylic acid derivative.

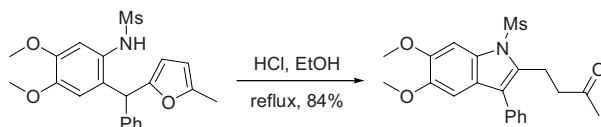


Example 1²



Example 2³

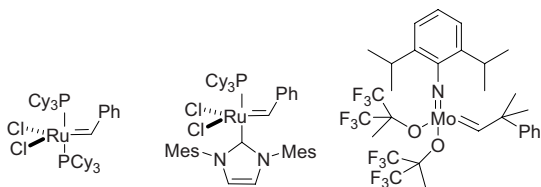


Example 3, Furan ring as the masked carbonyl¹⁰

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Ring-closing metathesis (RCM)



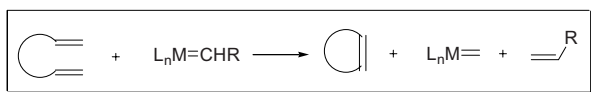
Grubbs' catalysts

Schrock's catalyst

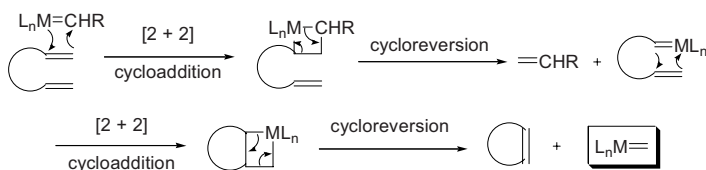
Mes = mesityl

All three catalysts are illustrated as " $L_nM=CHR$ " in the mechanism below.

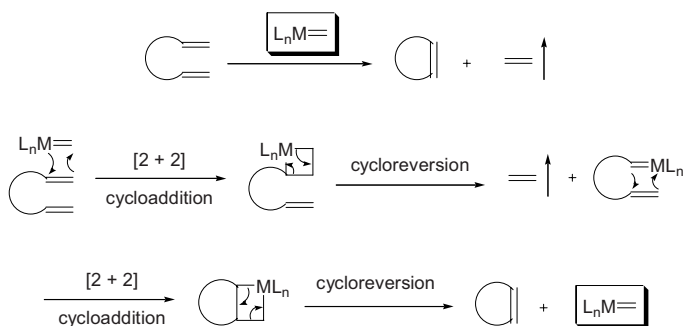
Generation of the real catalyst from the precatalysts:

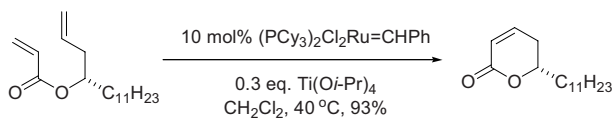
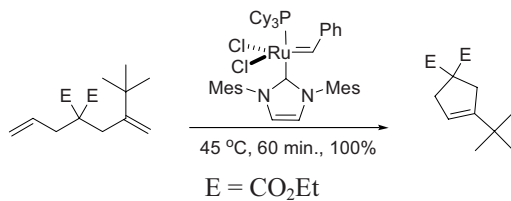
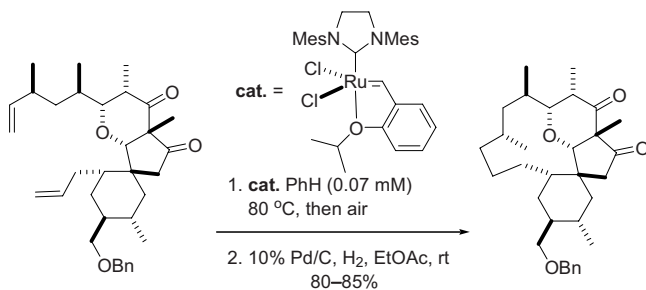
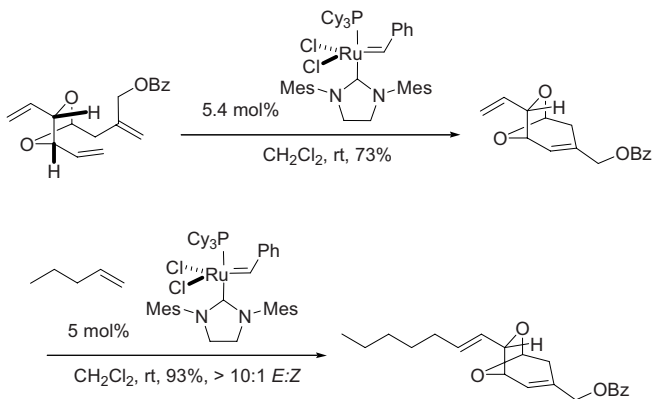


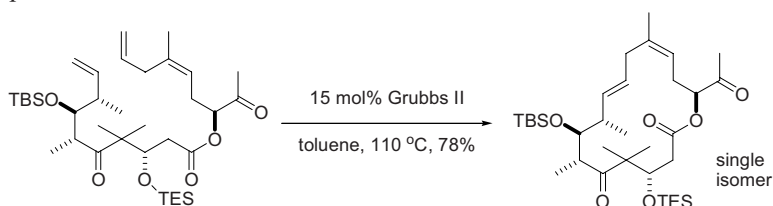
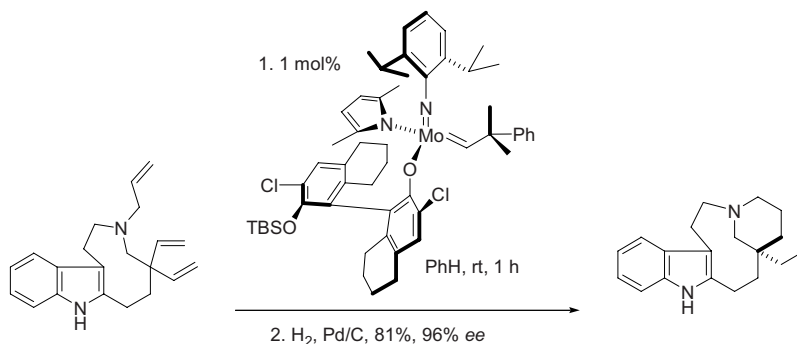
the active catalyst



Catalytic cycle:

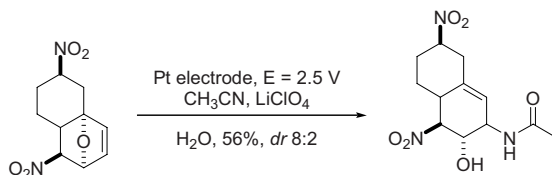
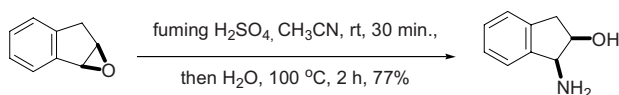


Example 1³Example 2⁵Example 3⁷Example 4⁹

Example 5¹⁰Example 6¹²

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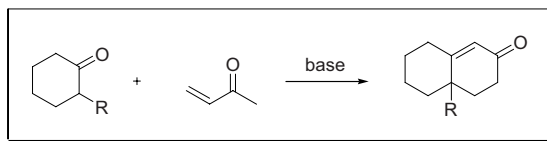
Example 3⁵Example 4⁶

References

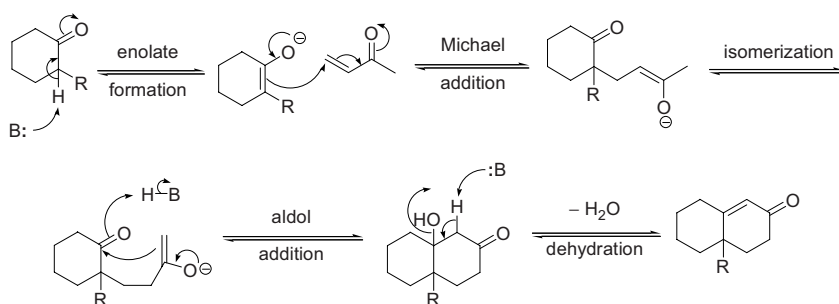
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Robinson annulation

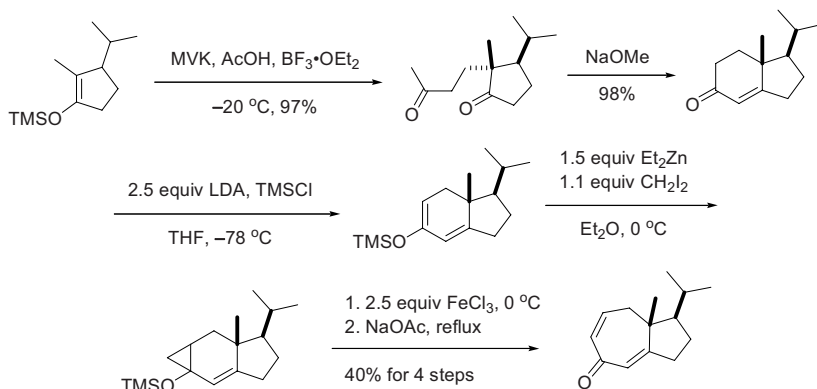
Michael addition of cyclohexanones to methyl vinyl ketone followed by intramolecular aldol condensation to afford six-membered α,β -unsaturated ketones.



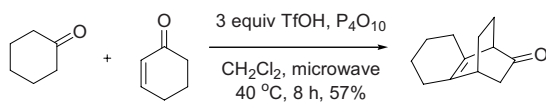
methyl vinyl ketone (MVK)

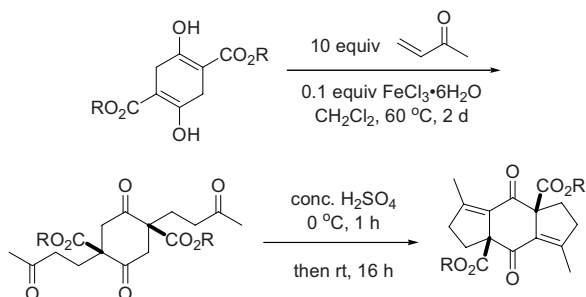
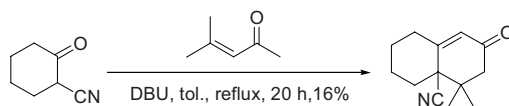


Example 1, Homo-Robinson⁷



Example 2⁸



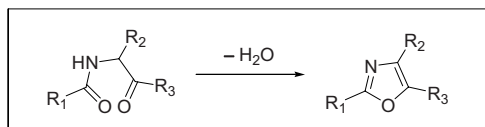
Example 3, Double Robinson-type cyclopentene annulation⁹Example 4¹⁰

References

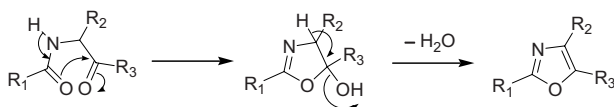
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Robinson–Gabriel synthesis

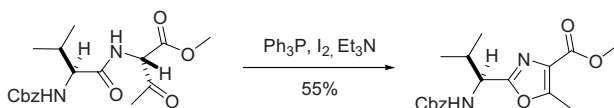
Cyclodehydration of 2-acylamidoketones to give 2,5-di- and 2,4,5-trialkyl, aryl, heteroaryl-, and aralkyloxazoles.



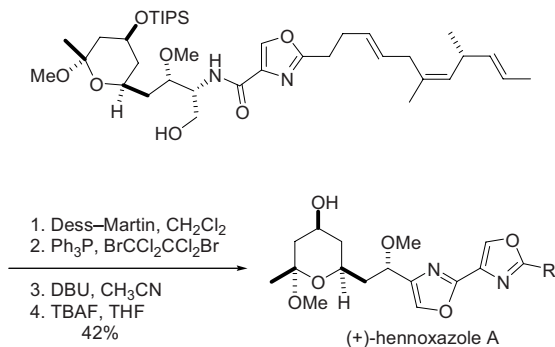
$R_1, R_2, R_3 = \text{alkyl, aryl, heteroaryl}$



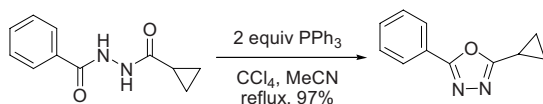
Example 1³

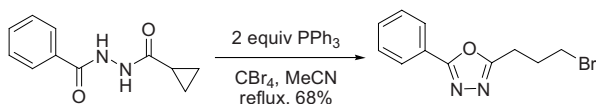
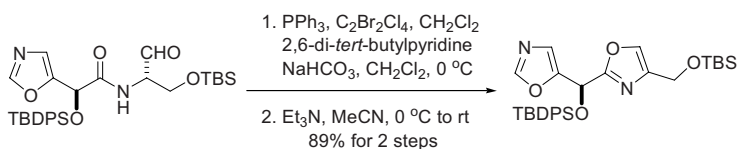


Example 2⁴



Example 3, Halogen effect⁹



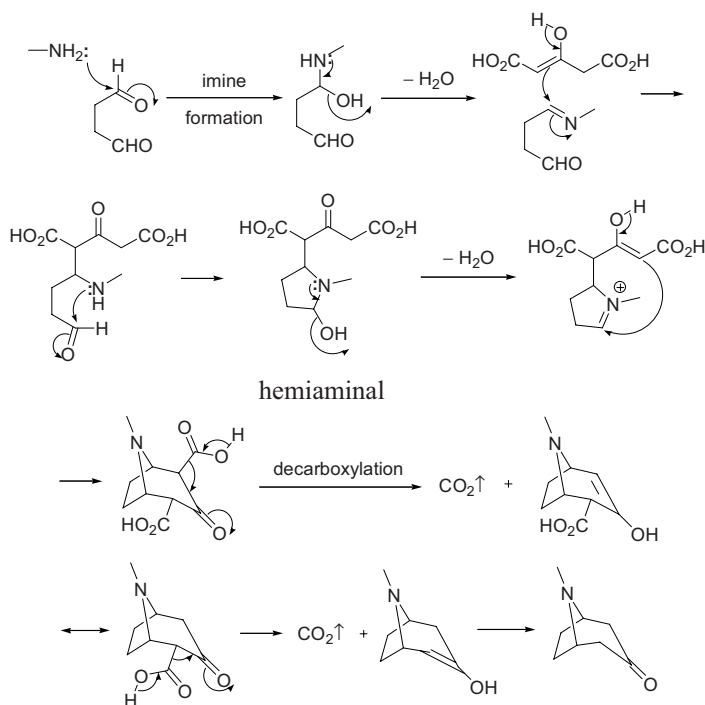
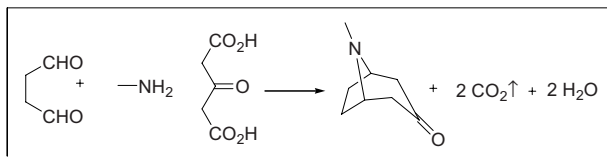
Example 4¹⁰

References

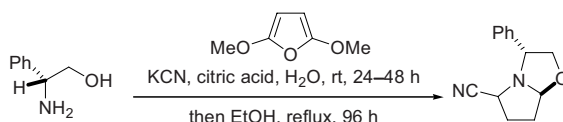
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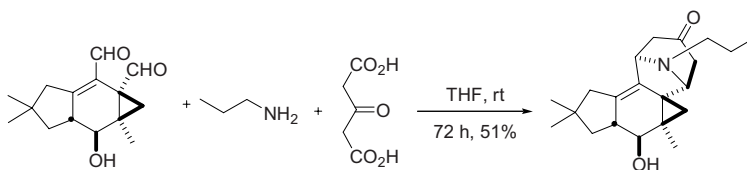
Robinson–Schöpf reaction

1,4-Diketone condensations with primary amines to give tropinones.



Example 1⁵



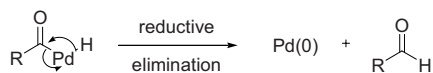
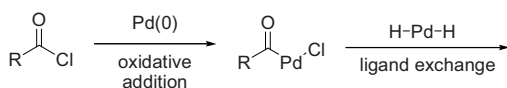
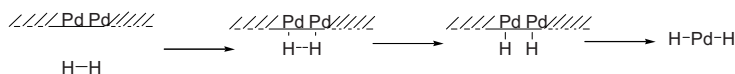
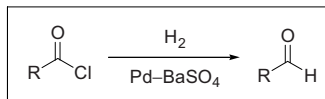
Example 2⁹

References

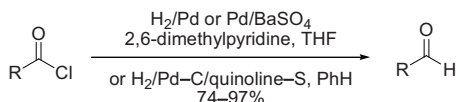
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Rosenmund reduction

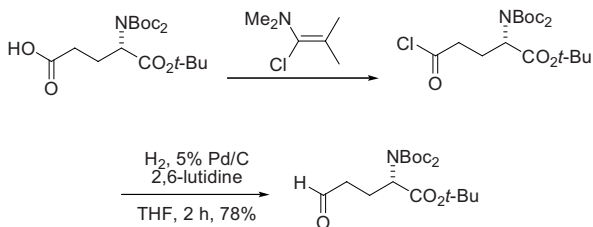
Hydrogenation reduction of acid chloride to aldehyde using BaSO₄-poisoned palladium catalyst. Without this poisoning, the resulting aldehyde may be further reduced to the corresponding alcohol.



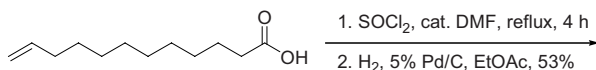
Example 1⁴

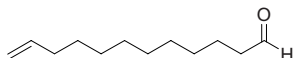


Example 2⁶



Example 3⁹



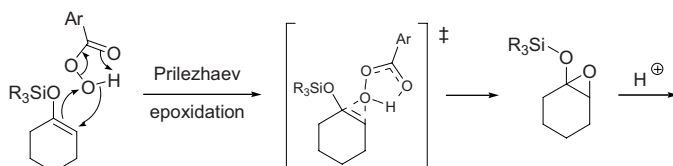
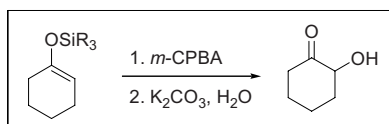


References

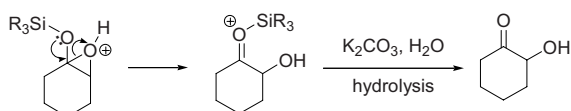
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Rubottom oxidation

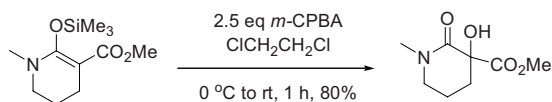
α -Hydroxylation of enolsilanes.



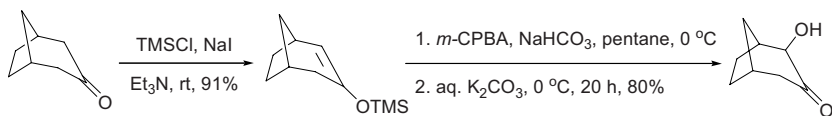
The “butterfly” transition state



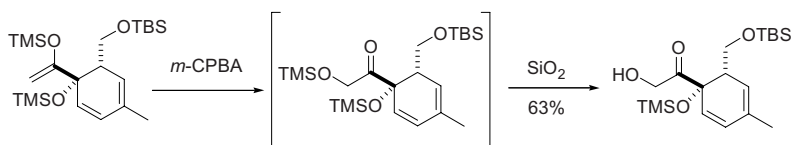
Example 1²

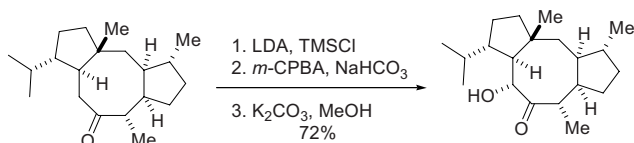


Example 2³



Example 3⁴



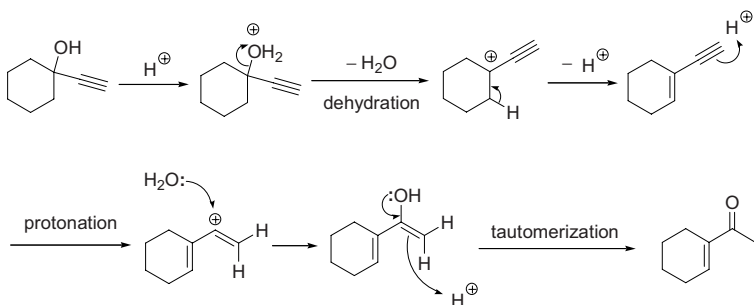
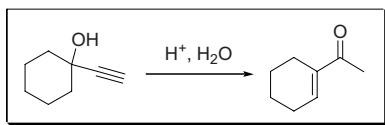
Example 4⁵

References

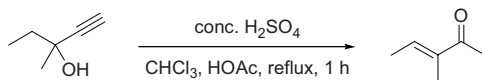
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Rupe rearrangement

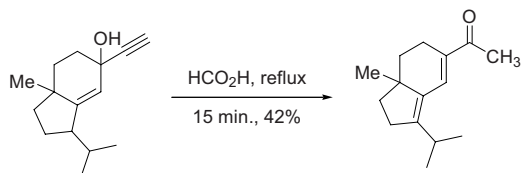
Acid-catalyzed rearrangement of tertiary α -acetylenic (terminal) alcohols, leading to the formation of α,β -unsaturated ketones rather than the corresponding α,β -unsaturated aldehydes. *Cf.* Meyer–Schuster rearrangement.



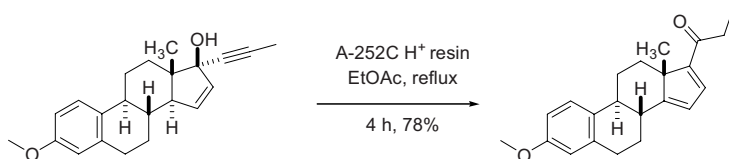
Example 1⁴



Example 2⁸



Example 3⁹

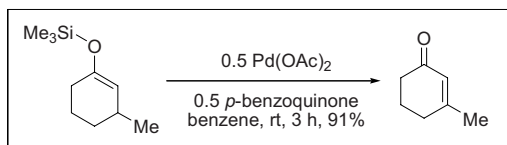


References

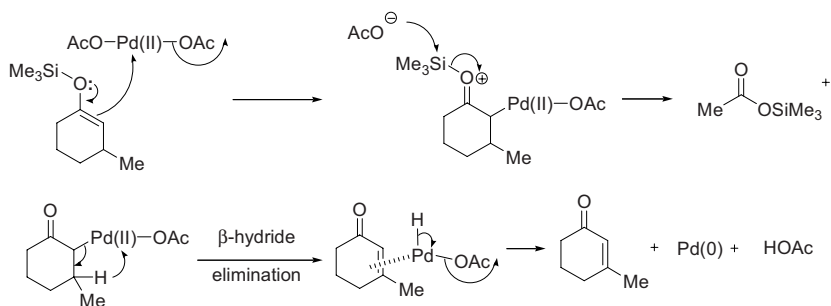
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Saegusa oxidation

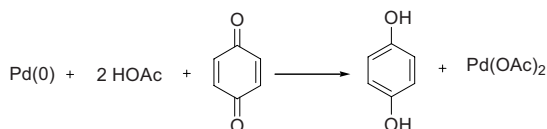
Palladium-catalyzed conversion of enol silanes to enones, also known as the Saegusa enone synthesis.



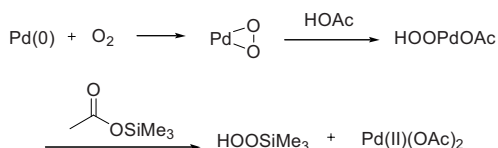
The mechanism is similar to that of the Wacker oxidation (page 564).



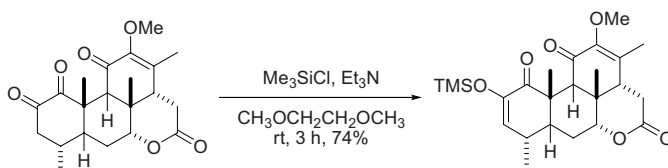
Regenerating the Pd(II) oxidant:

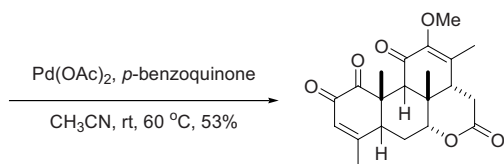
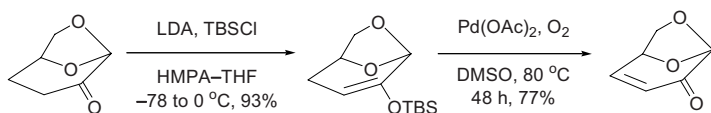
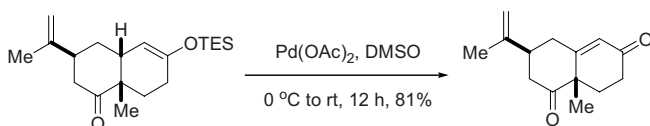


Larock reported regeneration of the Pd(II) oxidant using oxygen:⁴



Example 1³



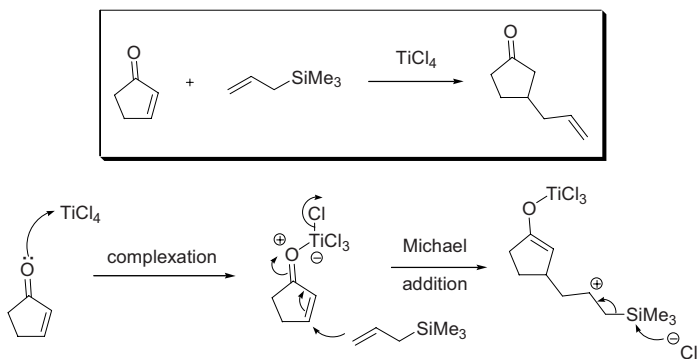
Example 2⁸Example 3¹⁰

References

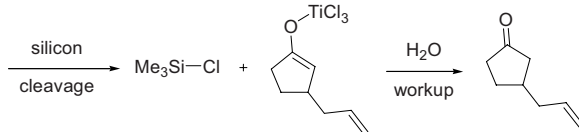
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Sakurai allylation reaction

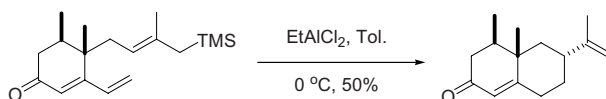
Lewis acid-mediated addition of allylsilanes to carbon nucleophiles. Also known as the Hosomi–Sakurai reaction. The allylsilane will add to the carbonyl compound directly if the electrophile (carbonyl group) is not part of an α,β -unsaturated system (Example 2), giving rise to an alcohol.



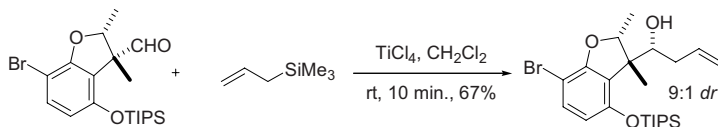
The β -carbocation is stabilized by the β -silicon effect



Example 1²

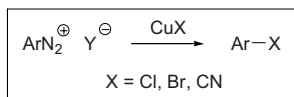


Example 2⁶



Sandmeyer reaction

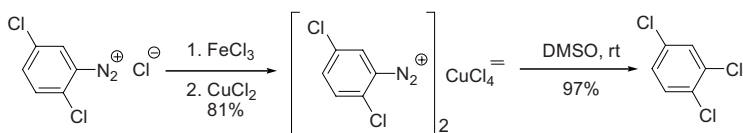
Haloarenes from the reaction of a diazonium salt with CuX.



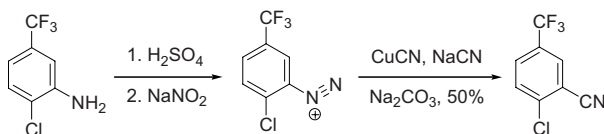
e.g.:



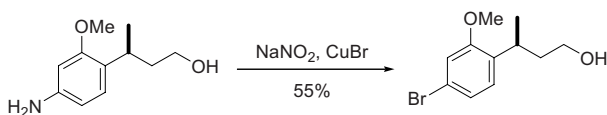
Example 1⁴



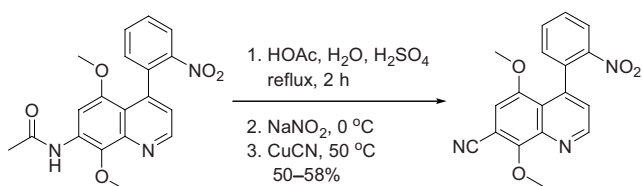
Example 2⁷



Example 3⁸



Example 4⁹

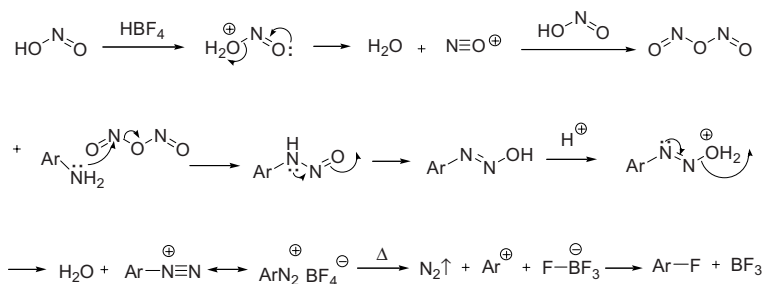
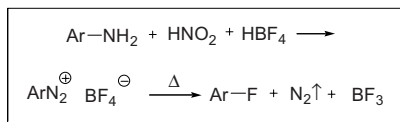


References

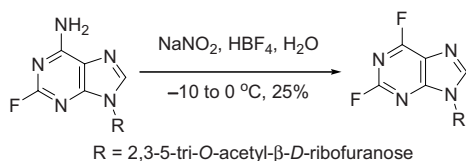
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Schiemann reaction

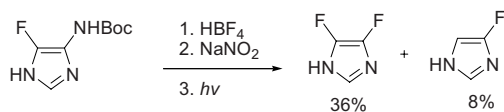
Fluoroarene formation from arylamines. Also known as the Balz–Schiemann reaction.



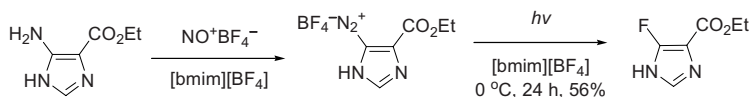
Example 1⁴

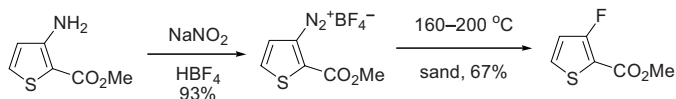


Example 2, Photo-Schiemann reaction⁶



Example 3, Photo-Schiemann reaction⁸



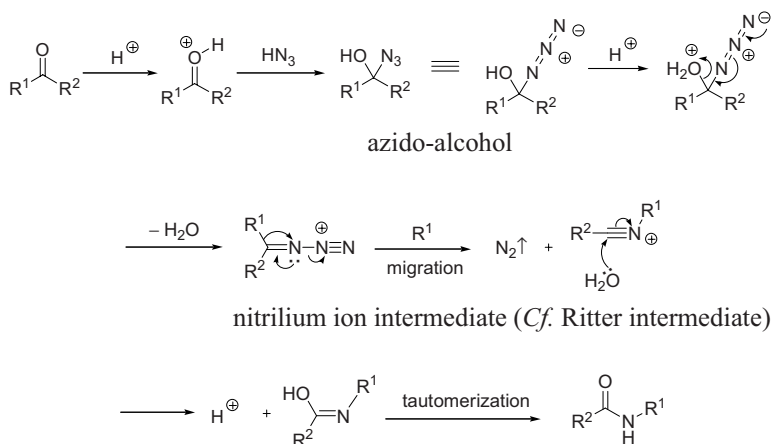
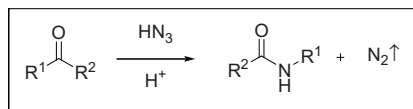
Example 4¹⁰

References

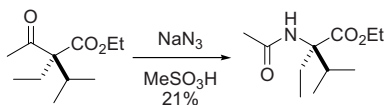
1. Balz, G.; Schiemann, G. *Ber.* **1927**, *60*, 1186–1190. Günther Schiemann was born in Breslau, Germany in 1899. In 1925, he received his doctorate at Breslau, where he became an assistant professor. In 1950, he became the Chair of Technical Chemistry at Istanbul, where he extensively studied aromatic fluorine compounds.
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Schmidt rearrangement

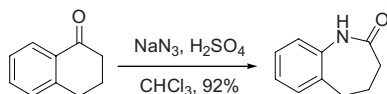
The Schmidt reactions refer to the acid-catalyzed reactions of hydrazoic acid with electrophiles, such as carbonyl compounds, tertiary alcohols and alkenes. These substrates undergo rearrangement and extrusion of nitrogen to furnish amines, nitriles, amides or imines.

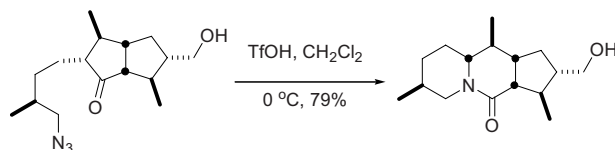
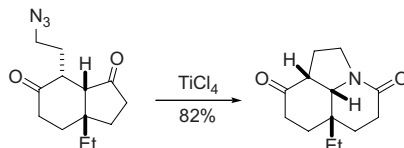
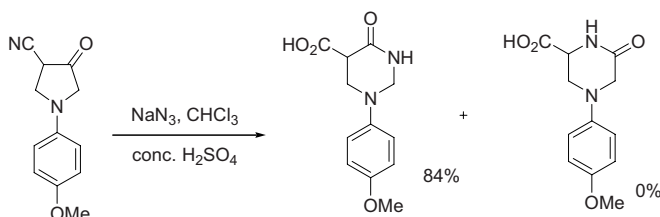


Example 1, A classic example³



Example 2⁵



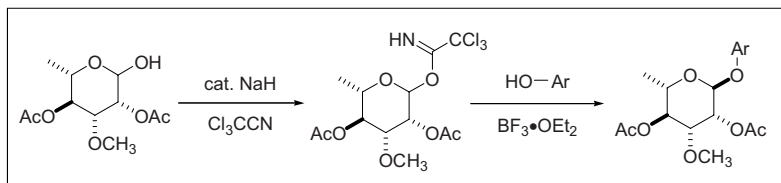
Example 3, Intramolecular Schmidt rearrangement⁶Example 4, Intramolecular Schmidt rearrangement⁸Example 5, Intermolecular Schmidt rearrangement⁹

References

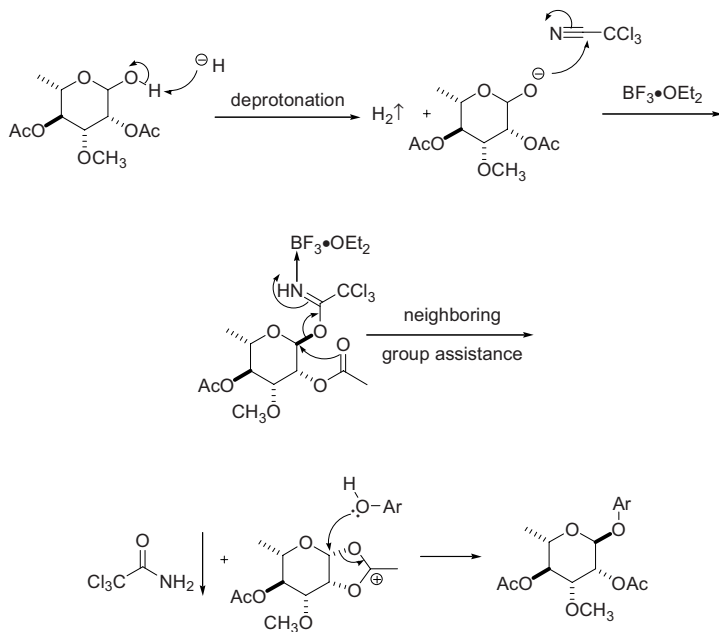
1. (a) Schmidt, K. F. *Angew. Chem.* **1923**, 36, 511. Karl Friedrich Schmidt (1887–1971) collaborated with Curtius at the University of Heidelberg, where Schmidt became a Professor of Chemistry after 1923. (b) Schmidt, K. F. *Ber.* **1924**, 57, 704–706.
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Schmidt's trichloroacetimidate glycosidation reaction

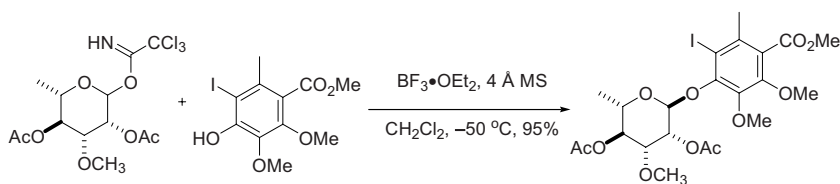
Lewis acid-promoted glycosidation of trichloroacetimidates with alcohols or phenols.

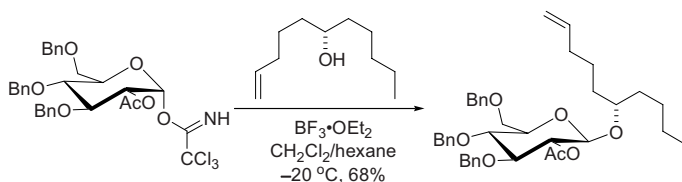
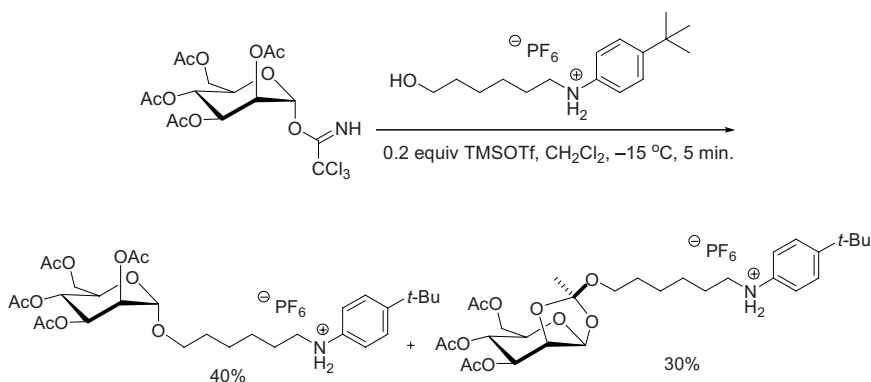


trichloroacetimidate



Example 1⁵



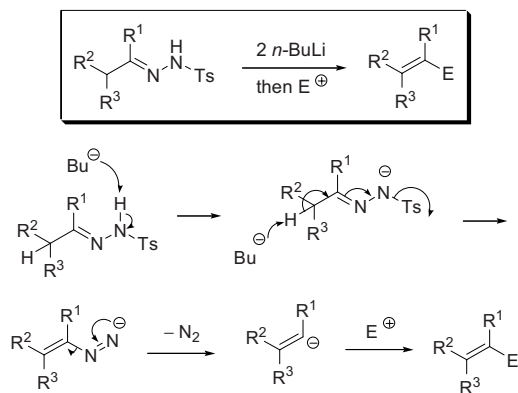
Example 2⁷Example 3⁹

References

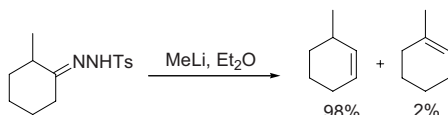
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Shapiro reaction

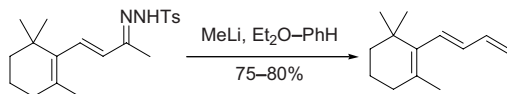
The Shapiro reaction is a variant of the Bamford–Stevens reaction. The former uses bases such as alkyl lithium and Grignard reagents whereas the latter employs bases such as Na, NaOMe, LiH, NaH, NaNH₂, *etc.* Consequently, the Shapiro reaction generally affords the less-substituted olefins (the kinetic products), while the Bamford–Stevens reaction delivers the more-substituted olefins (the thermodynamic products).



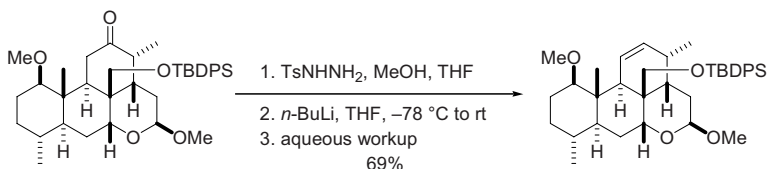
Example 1²

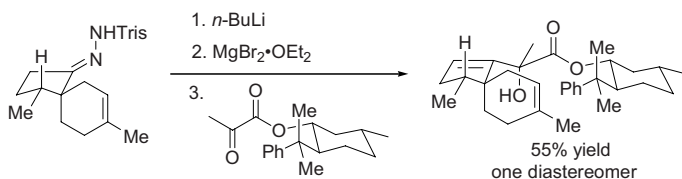


Example 2³



Example 3⁷



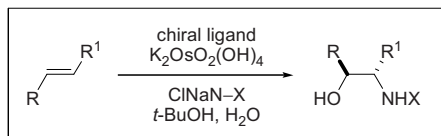
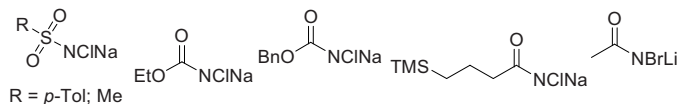
Example 4⁸

References

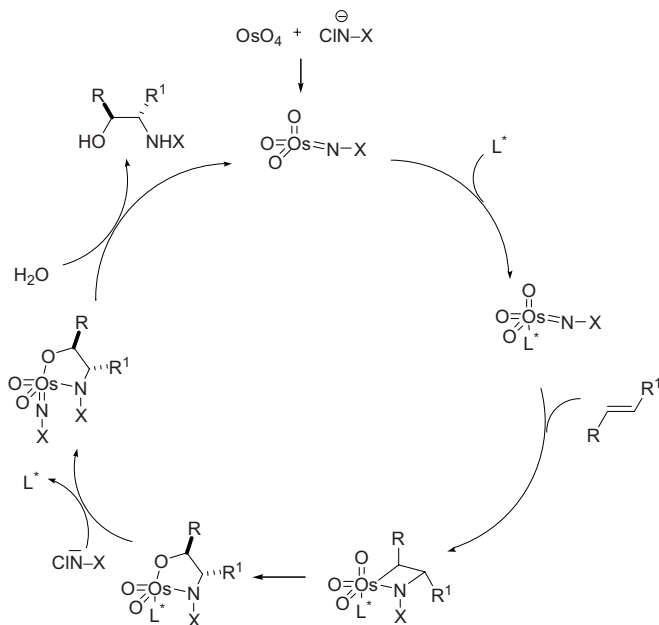
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Sharpless asymmetric amino-hydroxylation

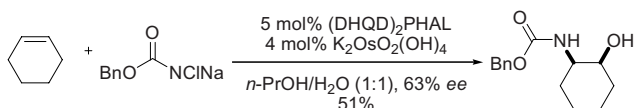
Osmium-mediated *cis*-addition of nitrogen and oxygen to olefins. Regioselectivity may be controlled by ligand. Nitrogen sources (X–NCINa) include:



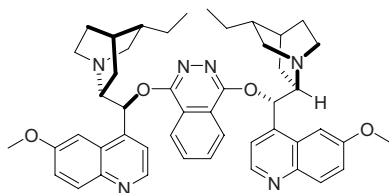
The catalytic cycle:



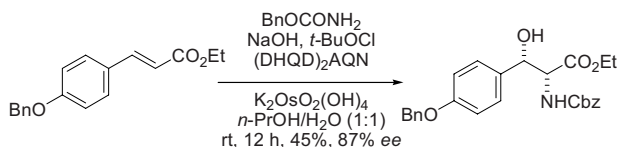
Example 1^{1b}



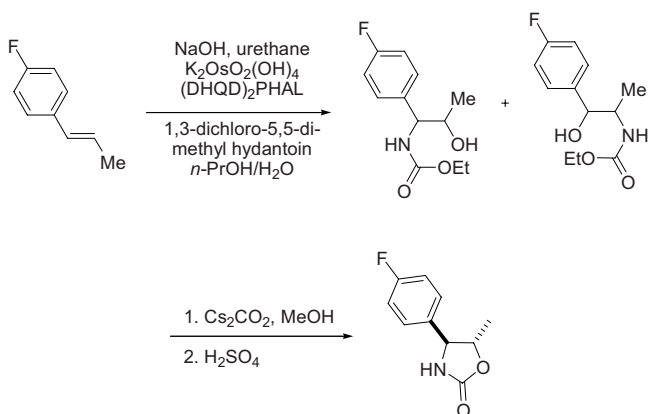
(DHQD)₂-PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine:



Example 2²



Example 3⁶



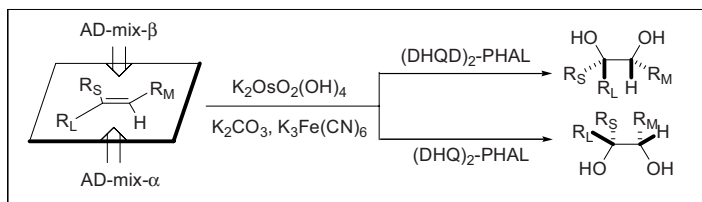
References

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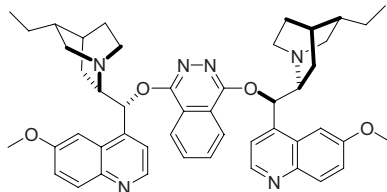
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Sharpless asymmetric dihydroxylation

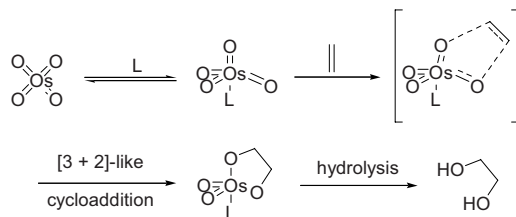
Enantioselective *cis*-dihydroxylation of olefins using osmium catalyst in the presence of cinchona alkaloid ligands.



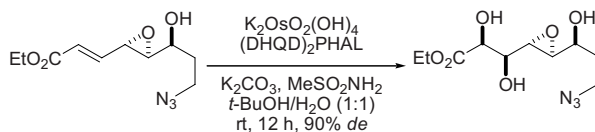
(DHQ)₂-PHAL = 1,4-bis(9-*O*-dihydroquinine)phthalazine:



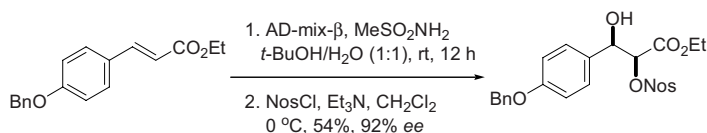
The concerted [3 + 2] cycloaddition mechanism:⁵



Example 1²

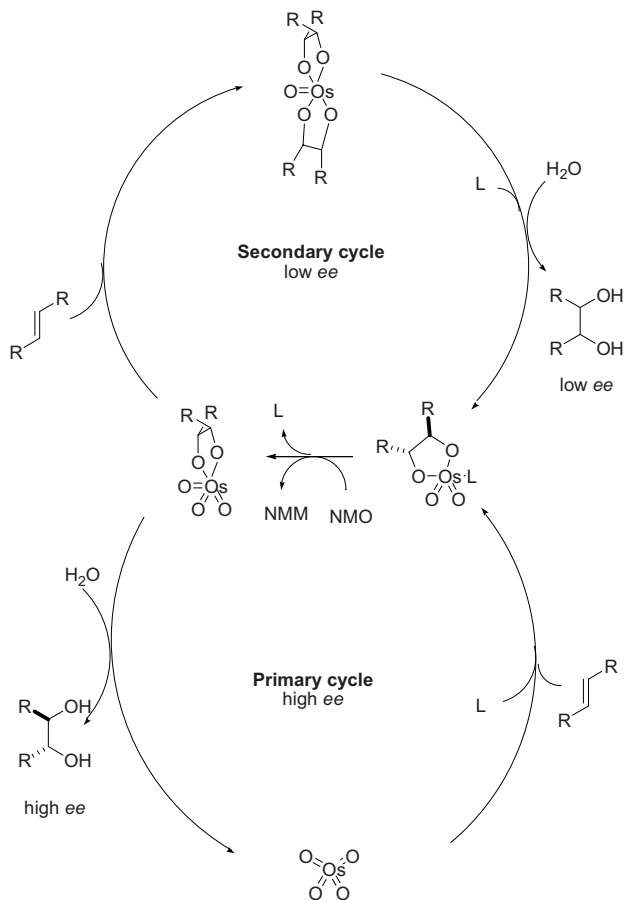


Example 2⁴

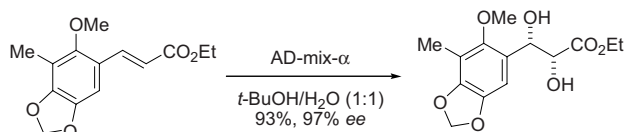


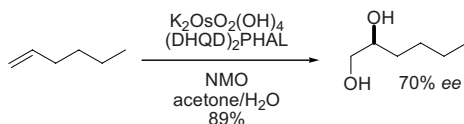
Nos = nosylate = 4-nitrobenzenesulfonyl

The catalytic cycle: (the secondary cycle is shut off by maintaining a low concentration of olefin):



Example 3⁹



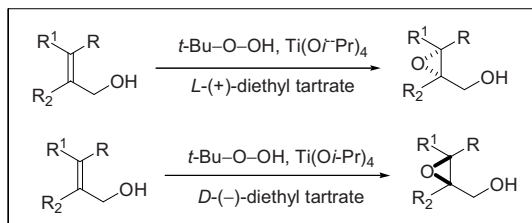
Example 4¹⁰

References

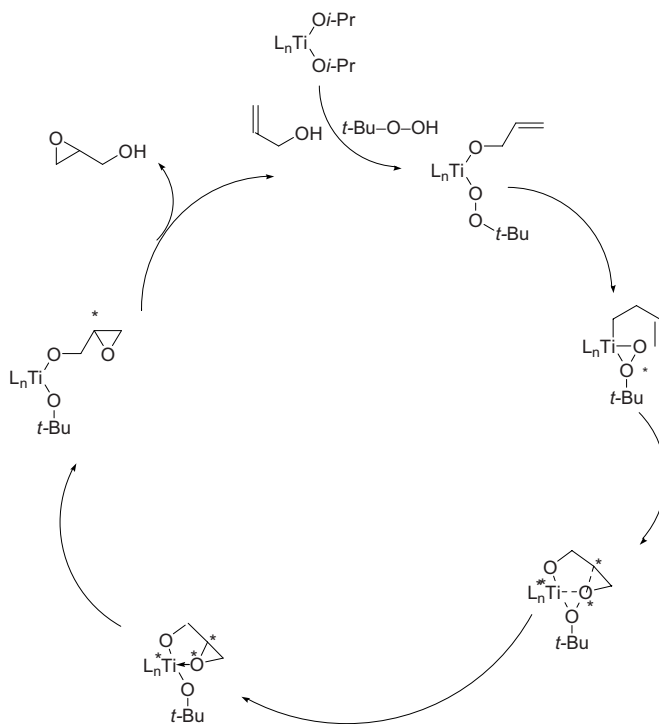
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Sharpless asymmetric epoxidation

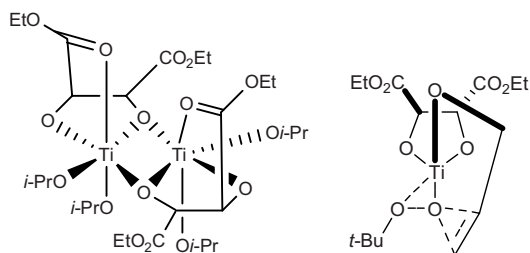
Enantioselective epoxidation of allylic alcohols using *t*-butyl peroxide, titanium tetra-*iso*-propoxide, and optically pure diethyl tartrate.



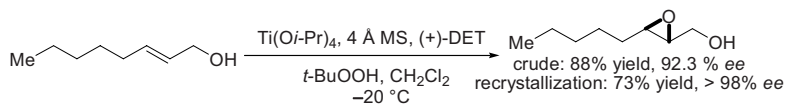
The catalytic cycle:



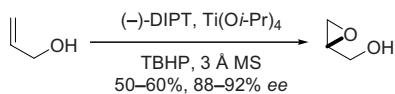
The putative active catalyst and the transition state:



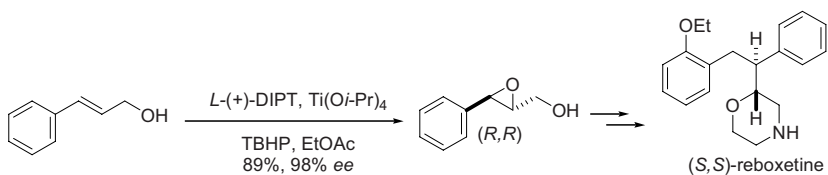
Example 1³



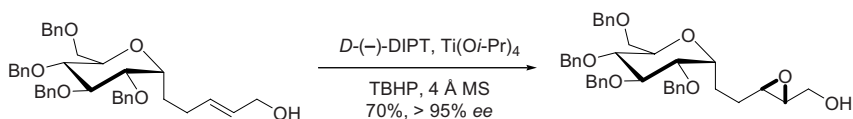
Example 2³



Example 3¹¹



Example 4¹²

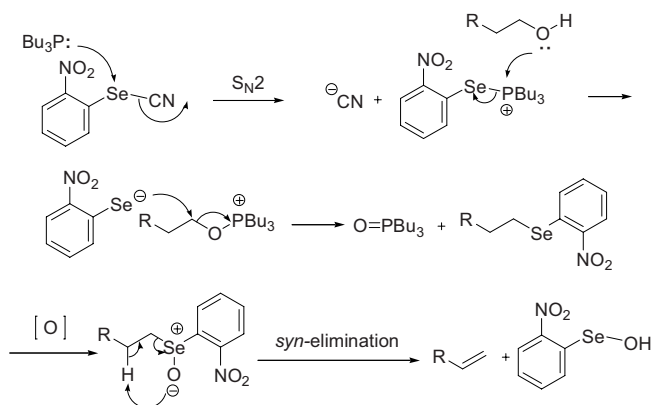
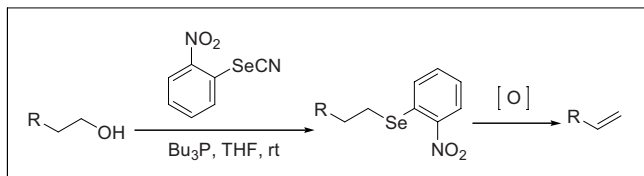


References

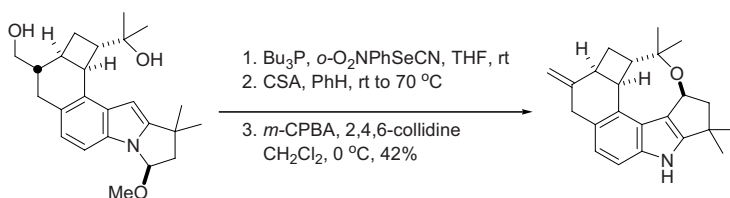
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Sharpless olefin synthesis

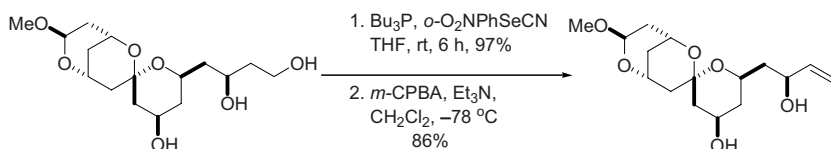
Olefin synthesis from the *syn*-oxidative elimination of *o*-nitrophenyl selenides, which may be prepared using *o*-nitrophenyl selenocyanate and Bu₃P, among other methods.

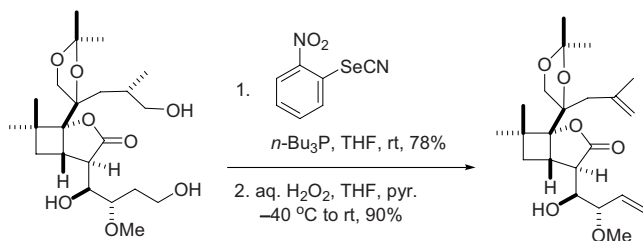
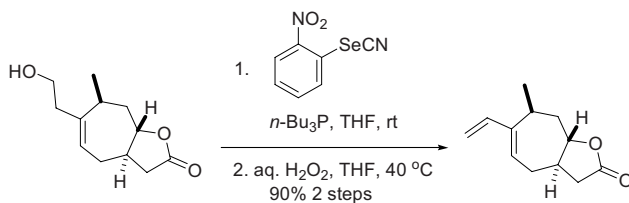


Example 1³



Example 2⁶



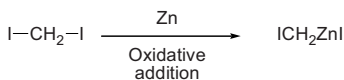
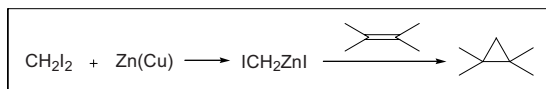
Example 3⁹Example 4¹⁰

References

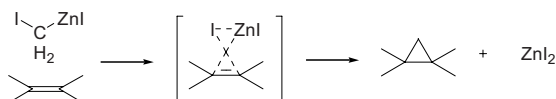
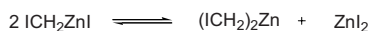
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Simmons–Smith reaction

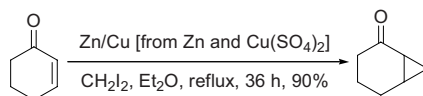
Cyclopropanation of olefins using CH_2I_2 and $\text{Zn}(\text{Cu})$.



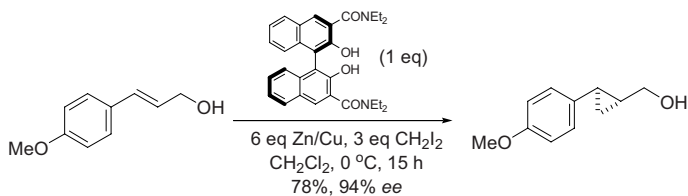
Simmons–Smith reagent



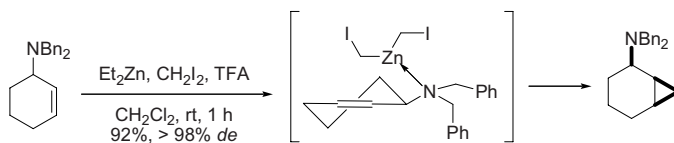
Example 1²

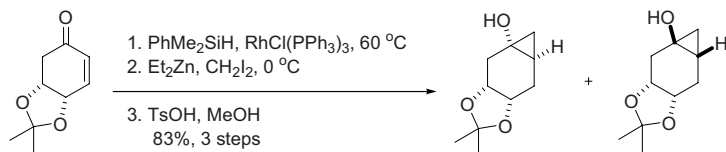


Example 2, An asymmetric version³



Example 3, Diastereoselective Simmons–Smith cyclopropanations of allylic amines and carbamates⁹



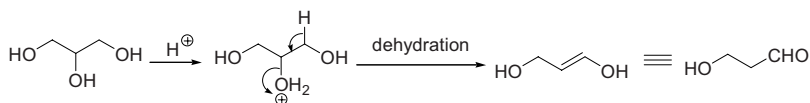
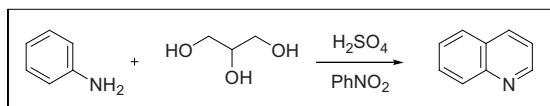
Example 4¹⁰

References

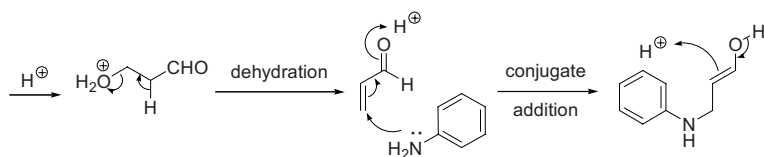
1. Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324. Howard E. Simmons (1929–1997) was born in Norfolk, Virginia. He carried out his graduate studies at MIT under John D. Roberts and Arthur Cope. After obtaining his Ph.D. In 1954, he joined the Chemical Department of the DuPont Company, where he discovered the Simmons–Smith reaction with his colleague, R. D. Smith. Simmons rose to be the vice president of the Central Research at DuPont in 1979. His views on physical exercise were the same as those of Alexander Woollcot’s: “If I think about exercise, I know if I wait long enough, the thought will go away.”
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Skraup quinoline synthesis

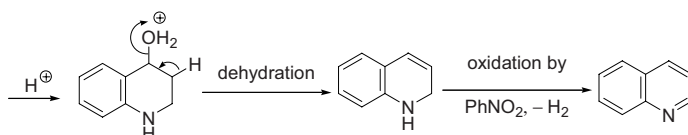
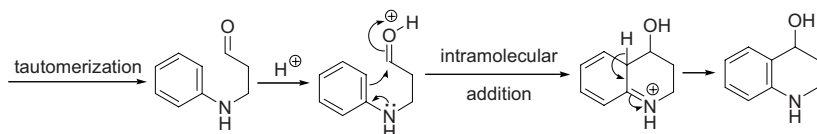
Quinoline from aniline, glycerol, sulfuric acid and oxidizing agent (e.g. PhNO_2).



glycerol

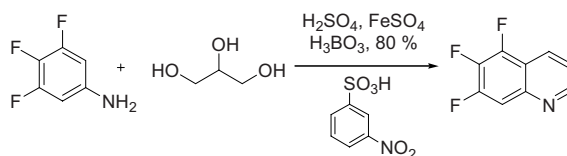


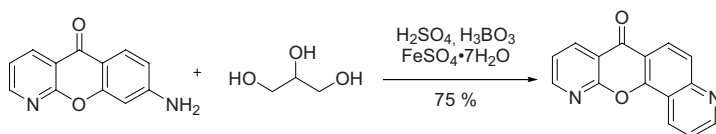
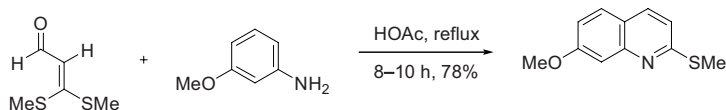
acrolein



For an alternative mechanism, see that of the Doebner–von Miller reaction (page 196).

Example 1⁵



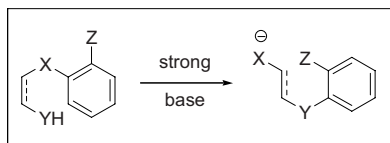
Example 2⁶Example 3, A modified Skraup quinoline synthesis⁸

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Smiles rearrangement

Intramolecular nucleophilic aromatic rearrangement. General scheme:

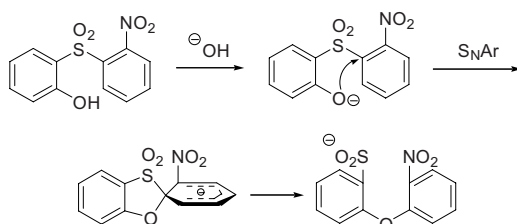


X = S, SO, SO₂, O, CO₂

YH = OH, NHR, SH, CH₂R, CONHR

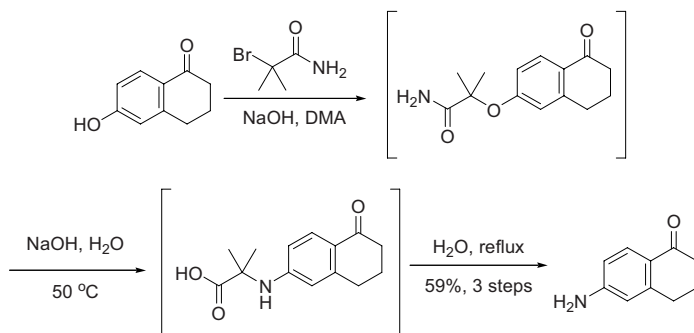
Z = NO₂, SO₂R

e.g.:

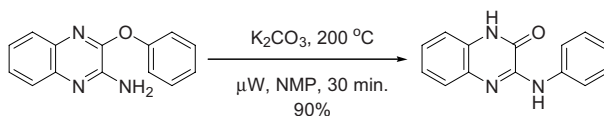


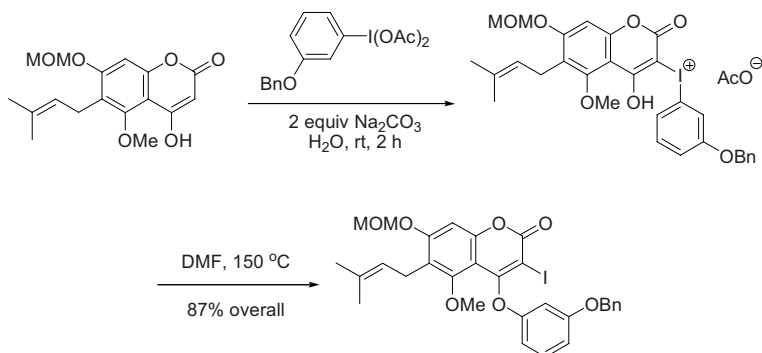
spirocyclic anion intermediate (Meisenheimer complex)

Example 1⁷



Example 2, Microwave Smiles rearrangement⁹



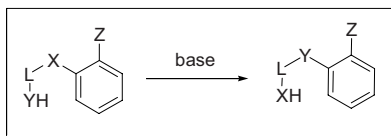
Example 3¹⁰

References

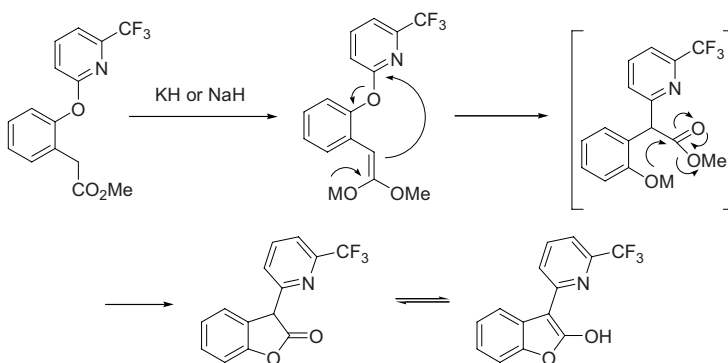
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Truce–Smile rearrangement

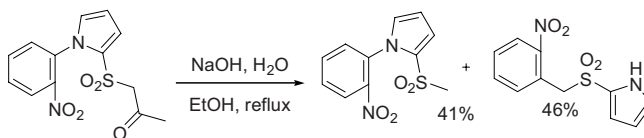
A variant of the Smiles rearrangement where Y is carbon:



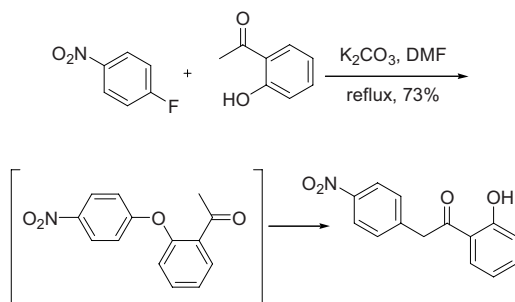
Example 1⁶

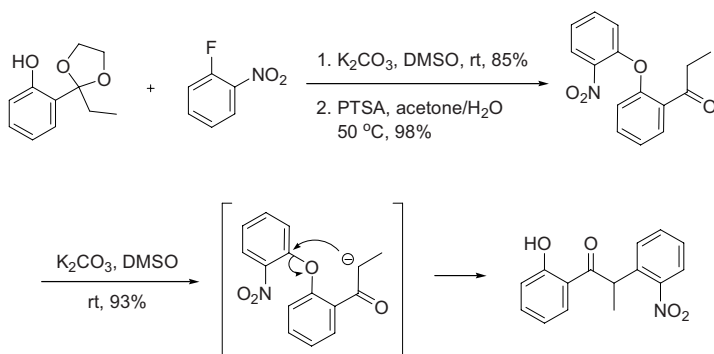


Example 2⁷



Example 3⁸



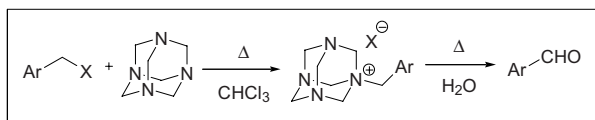
Example 4¹⁰

References

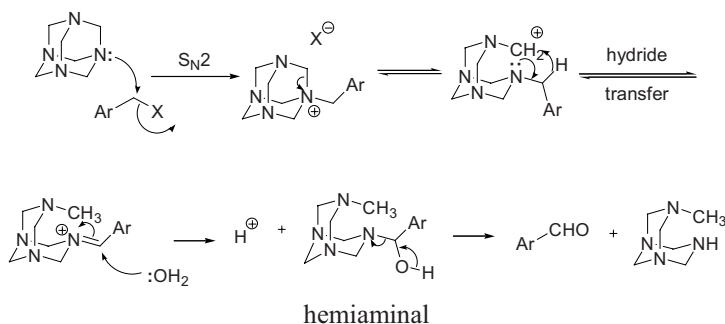
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Sommelet reaction

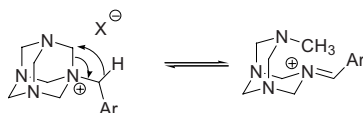
Transformation of benzyl halides to the corresponding benzaldehydes with the aide of hexamethylenetetramine. *Cf.* Delépine amine synthesis (page 171).



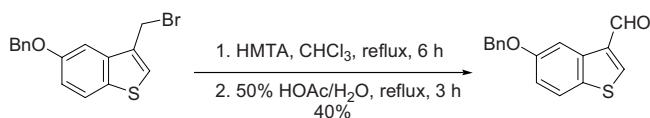
hexamethylenetetramine



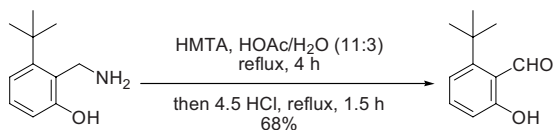
The hydride transfer and the ring-opening of hexamethylenetetramine may occur in a synchronized fashion:

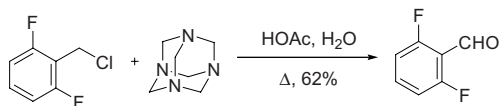
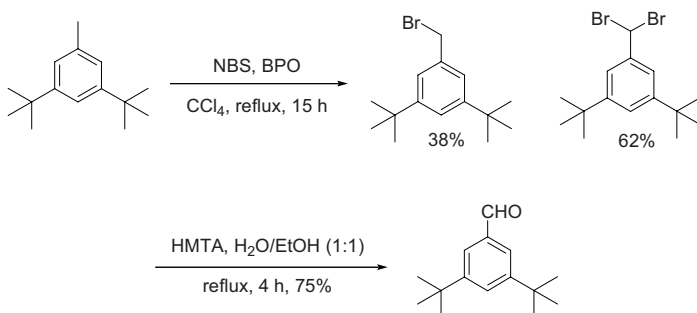


Example 1³



Example 2⁴



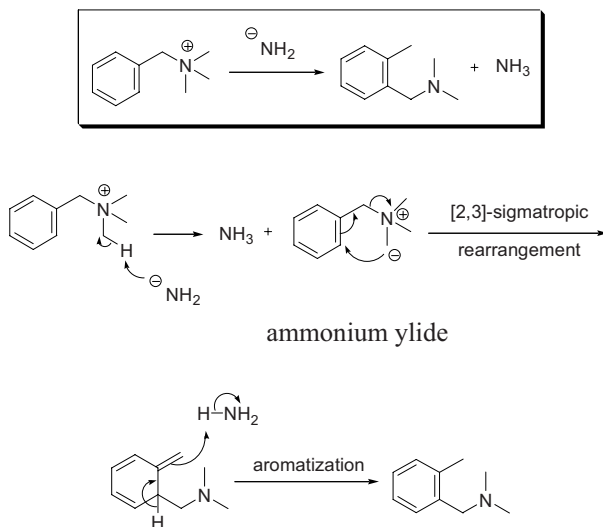
Example 3⁷Example 4⁸

References

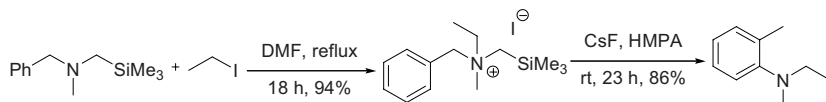
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Sommelet–Hauser rearrangement

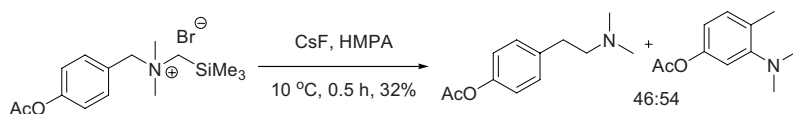
[2,3]-Wittig rearrangement of benzylic quaternary ammonium salts upon treatment with alkali metal amides *via* the ammonium ylide intermediates.



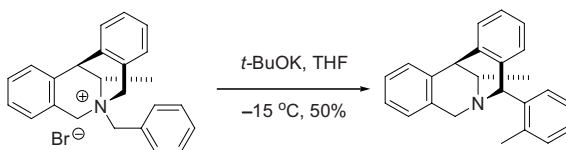
Example 1³

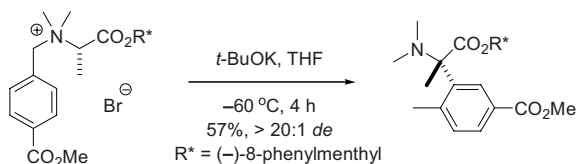


Example 2⁴



Example 3⁸



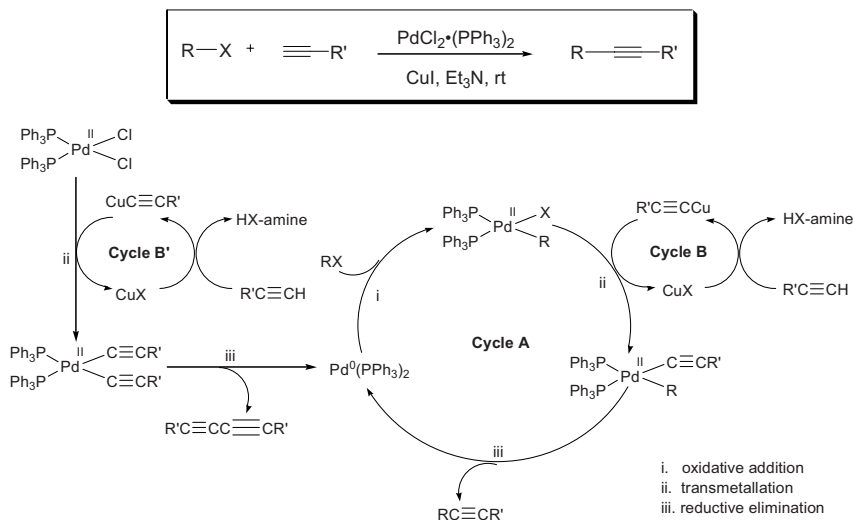
Example 4¹⁰

References

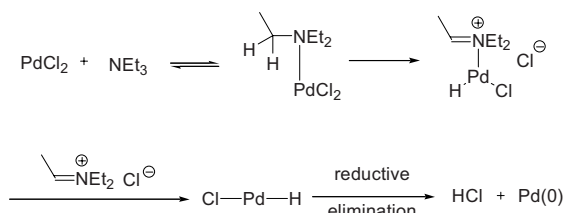
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Sonogashira reaction

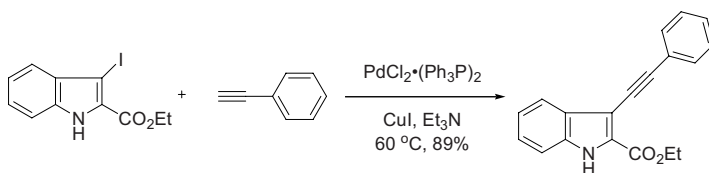
Pd/Cu-catalyzed cross-coupling of organohalides with terminal alkynes. Cf. Cadiot–Chodkiewicz coupling and Castro–Stephens reaction. The Castro–Stephens coupling uses stoichiometric copper, whereas the Sonogashira variant uses catalytic palladium and copper.

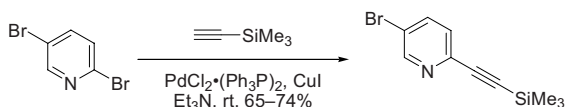
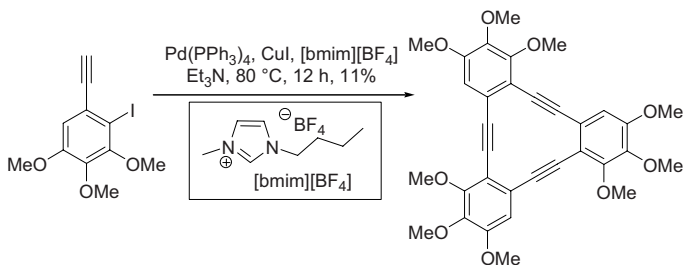
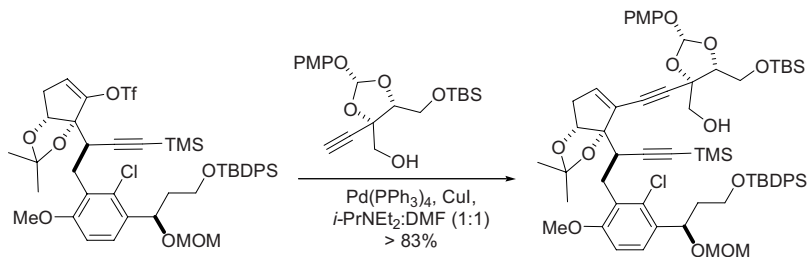


Note that Et_3N may reduce Pd(II) to Pd(0) as well, where Et_3N is oxidized to the iminium ion at the same time:



Example 1²



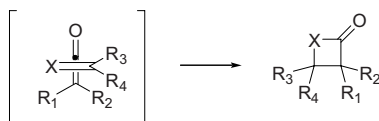
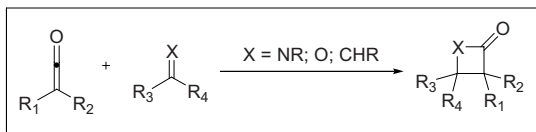
Example 2³Example 3⁸Example 4⁹

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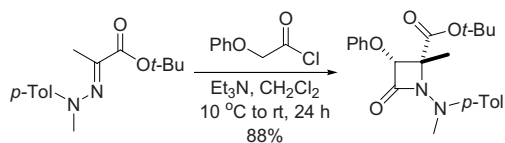
Staudinger ketene cycloaddition

[2 + 2]-Cycloaddition of ketene and imine to form β -lactam. Other coupling partners for ketenes include: olefin to give cyclobutanone and carbonyl to give β -lactone.

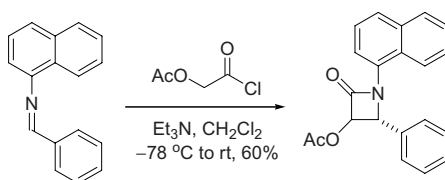


puckered transition state:

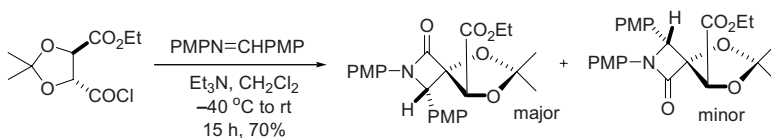
Example 1⁶

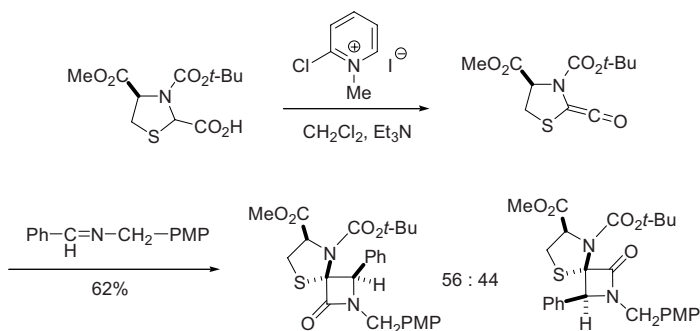


Example 2⁷



Example 3⁹



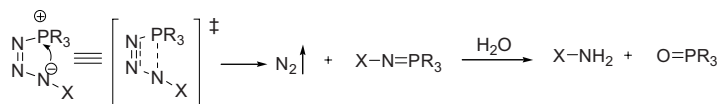
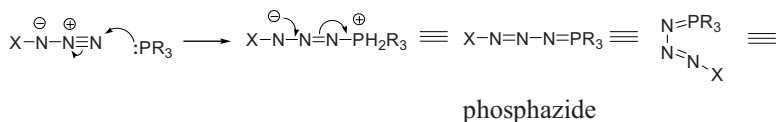
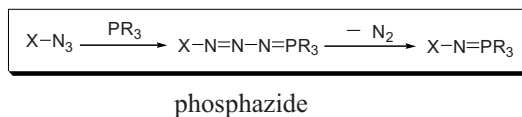
Example 4¹⁰

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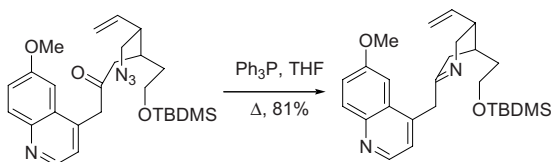
Staudinger reduction

Phosphazo compounds (e.g., iminophosphoranes) from the reaction of tertiary phosphine (e.g., Ph_3P) with organic azides.

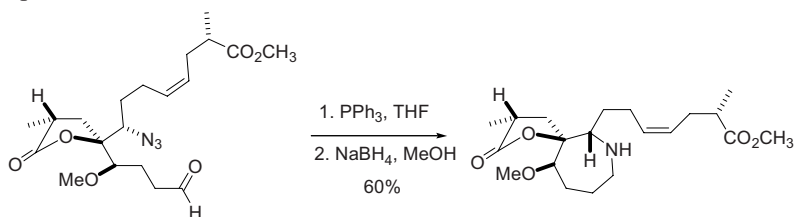


4-membered ring transition state

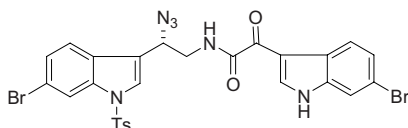
Example 1²

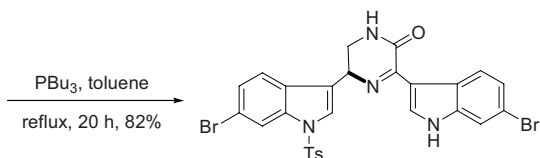
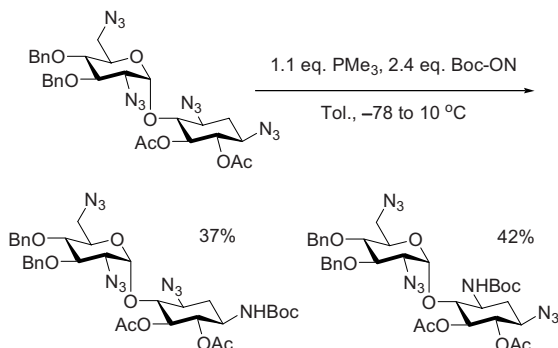
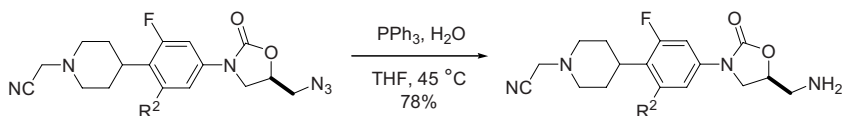


Example 2³



Example 3⁴



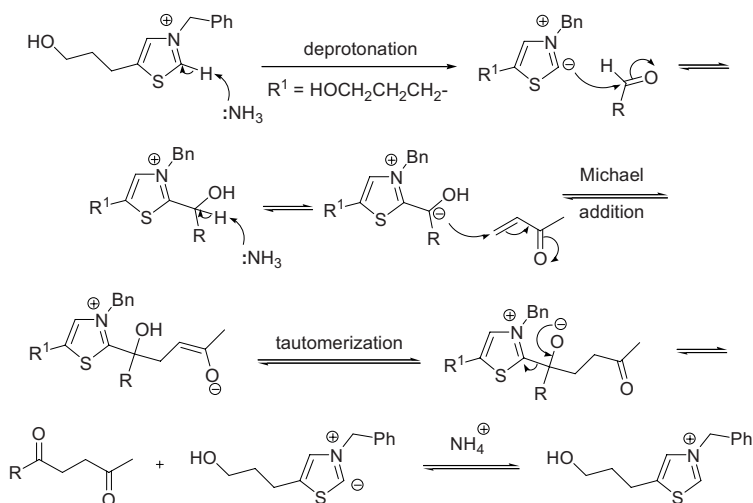
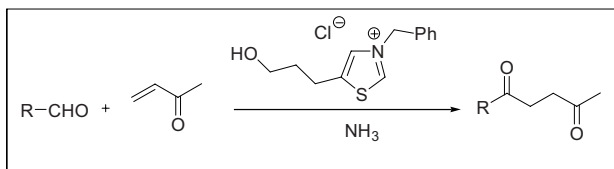
Example 4⁸Example 5⁹

References

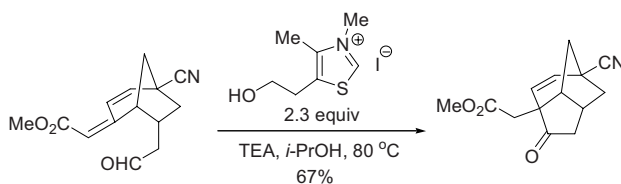
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Stetter reaction

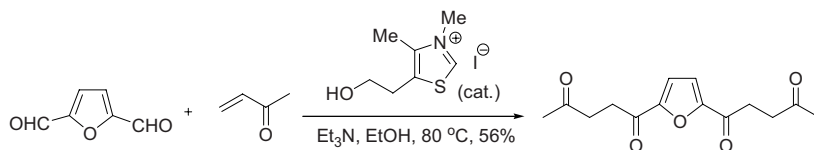
1,4-Dicarbonyl derivatives from aldehydes and α,β -unsaturated ketones and esters. The thiazolium catalyst serves as a safe surrogate for ^-CN . Also known as the Michael–Stetter reaction. *Cf.* Benzoin condensation.

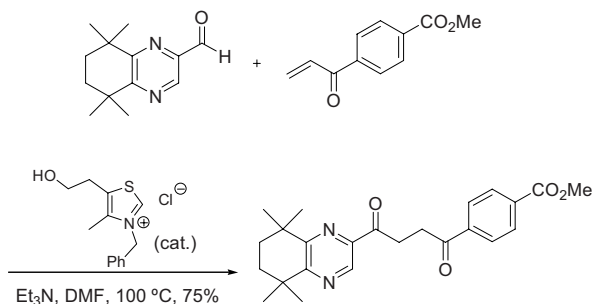
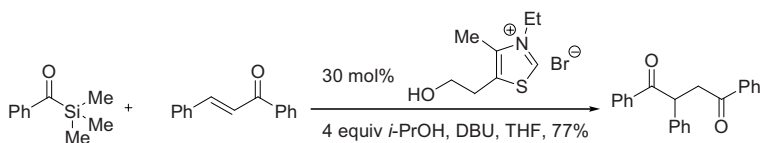


Example 1, Intramolecular Stetter reaction²



Example 2³



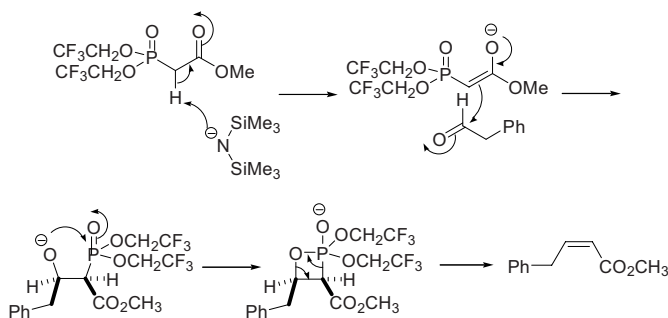
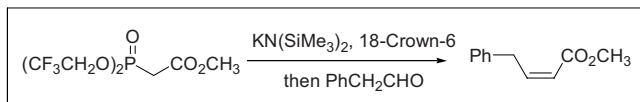
Example 3⁵Example 4, Sila-Stetter reaction⁹

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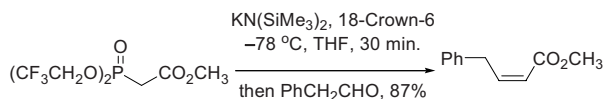
Still–Gennari phosphonate reaction

A variant of the Horner–Emmons reaction using bis(trifluoroethyl)phosphonate to give *Z*-olefins.

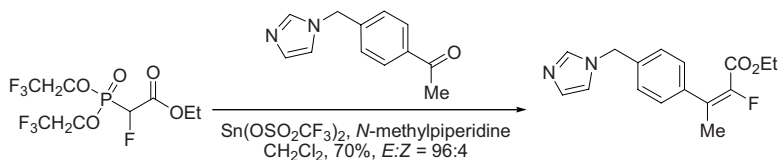


erythro isomer, kinetic adduct

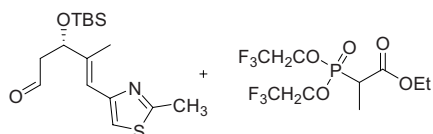
Example 1²

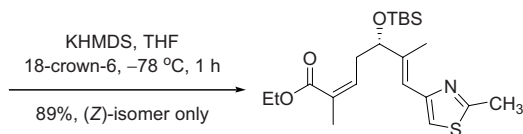


Example 2³

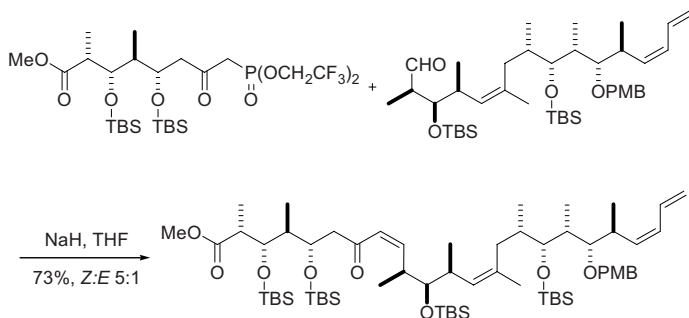


Example 3⁴





Example 4⁹

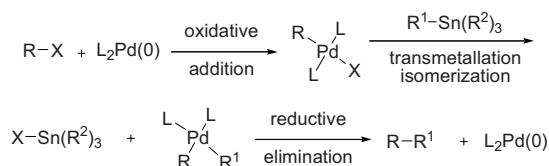
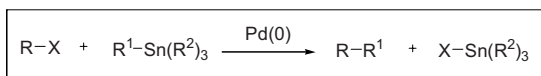


References

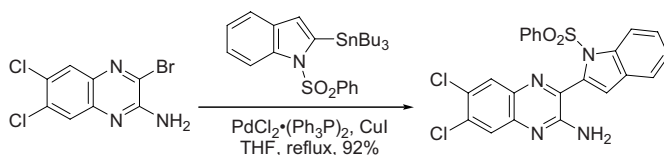
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Stille coupling

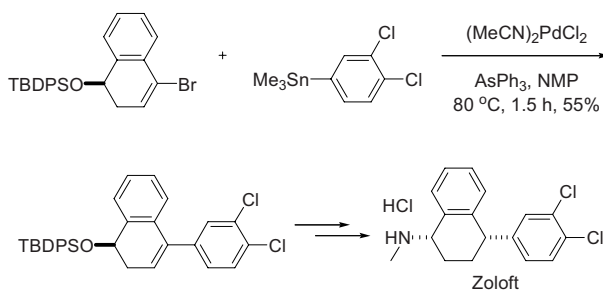
Palladium-catalyzed cross-coupling reaction of organostannanes with organic halides, triflates, *etc.* For the catalytic cycle, see Kumada coupling on page 325.



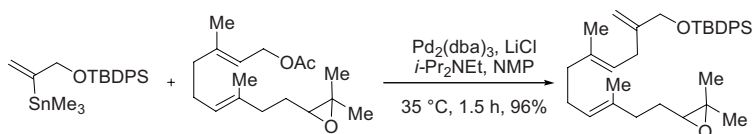
Example 1⁴

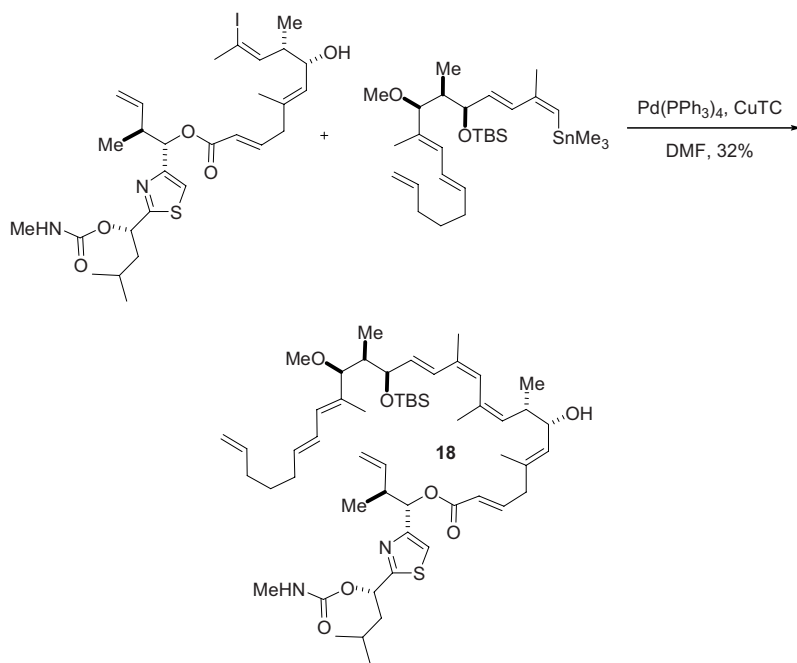


Example 2⁵



Example 3, π -Allyl Stille coupling⁸



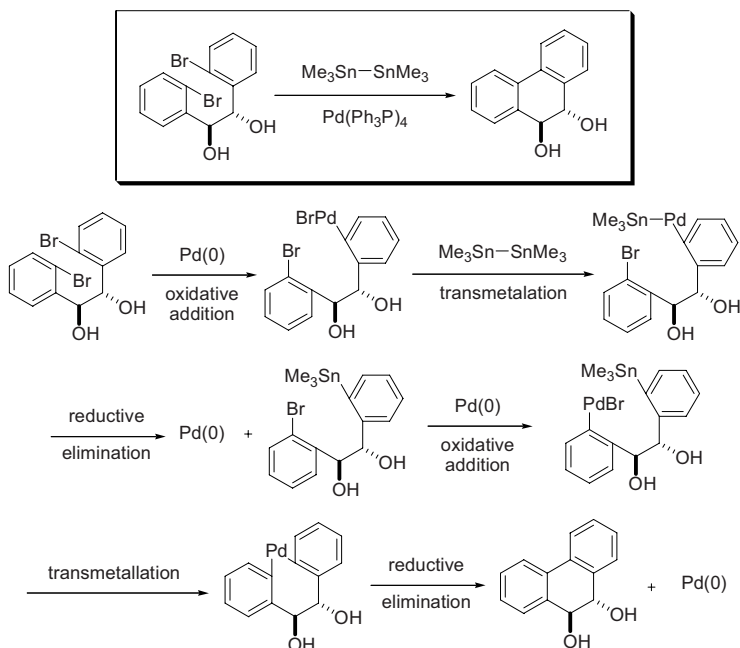
Example 4⁹

References

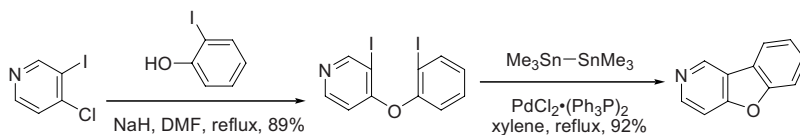
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Stille–Kelly reaction

Palladium-catalyzed intramolecular cross-coupling reaction of bis-aryl halides using ditin reagents.



Example 1⁶

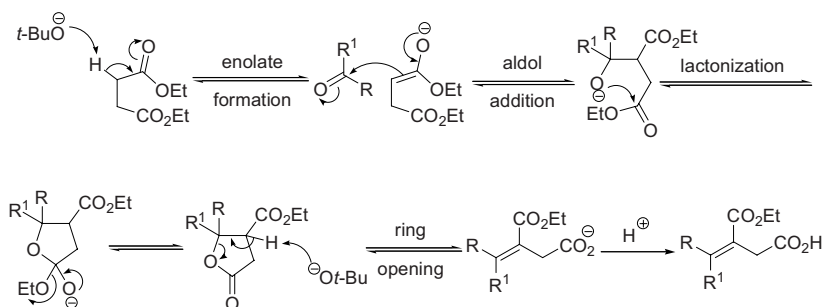
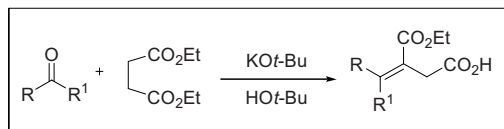


References

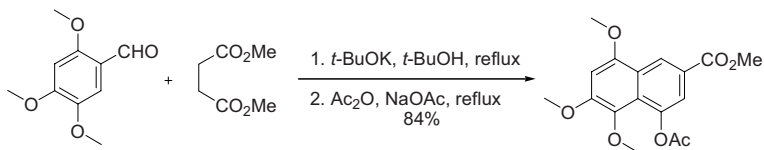
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Stobbe condensation

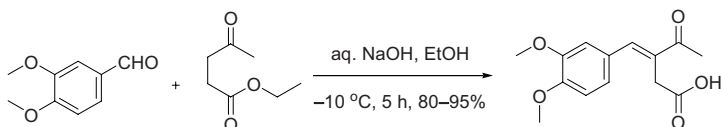
Condensation of diethyl succinate and its derivatives with carbonyl compounds in the presence of bases.



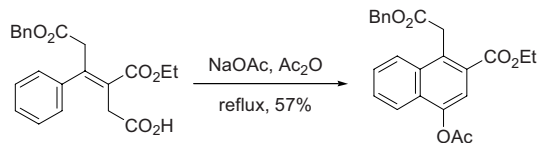
Example 1, Stobbe condensation and cyclization⁵

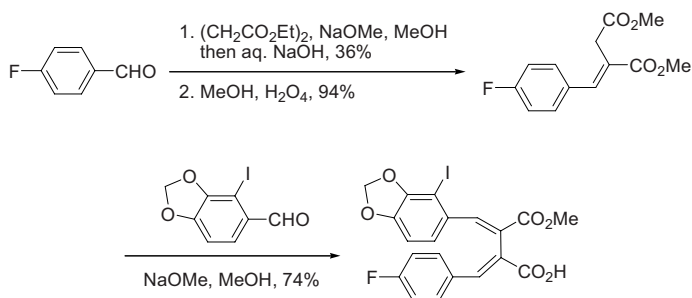


Example 2, Stobbe condensation⁶



Example 3, Cyclization of the Stobbe product⁷



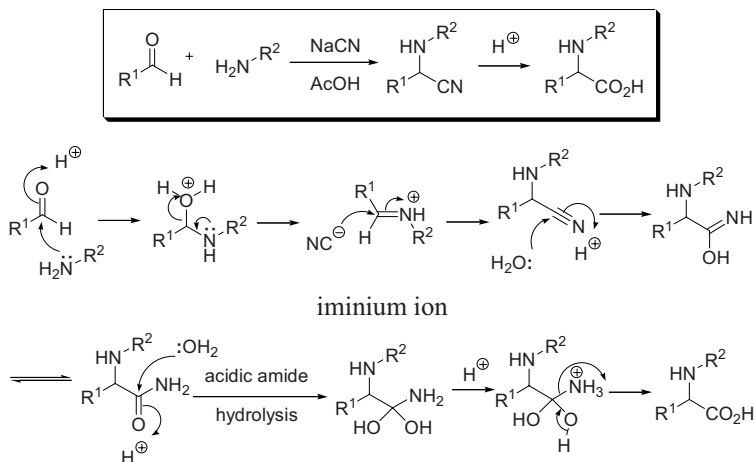
Example 4, Two sequential Stobbe condensations⁹

References

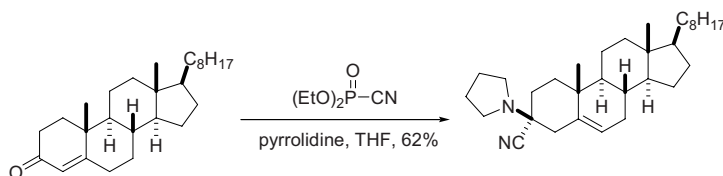
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Strecker amino acid synthesis

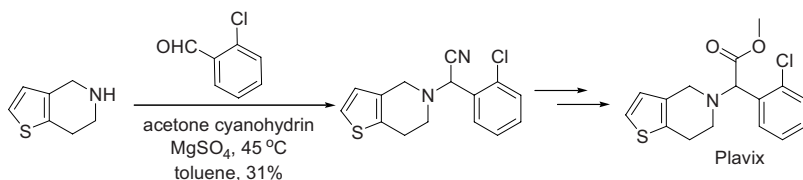
Sodium cyanide-promoted condensation of aldehyde, or ketone, with amine to afford α -amino nitrile, which may be hydrolyzed to α -amino acid.



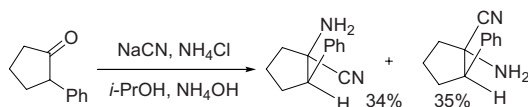
Example 1, Soluble cyanide source²

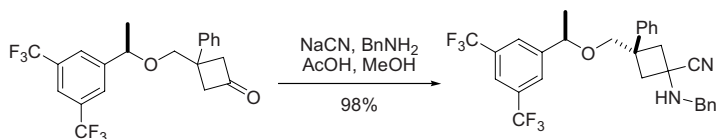


Example 2³



Example 3⁸



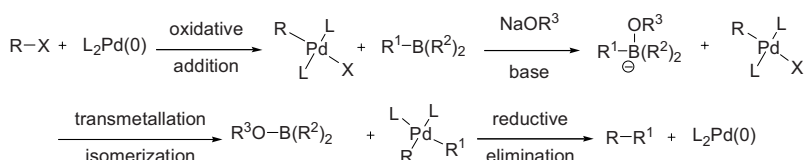
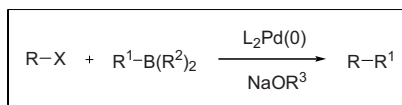
Example 4⁹

References

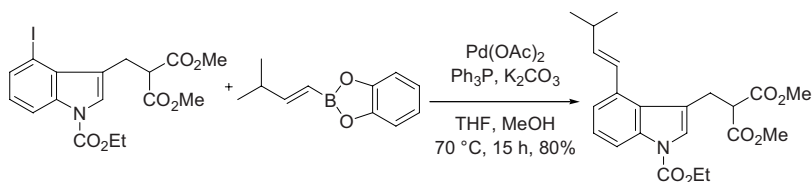
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Suzuki–Miyaura coupling

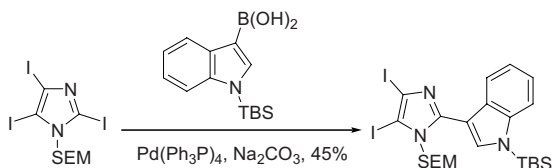
Palladium-catalyzed cross-coupling reaction of organoboranes with organic halides, triflates, *etc.* In the presence of a base (transmetalation is reluctant to occur without the activating effect of a base). For the catalytic cycle, see Kumada coupling on page 325.



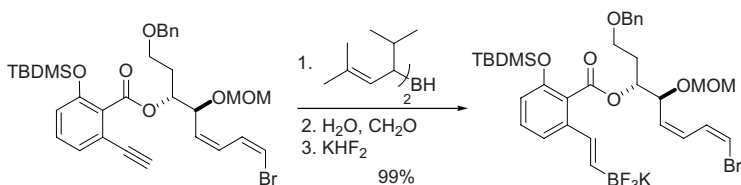
Example 1²

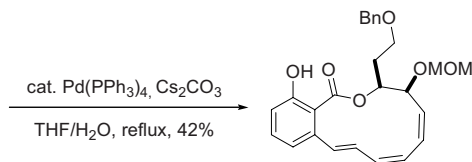
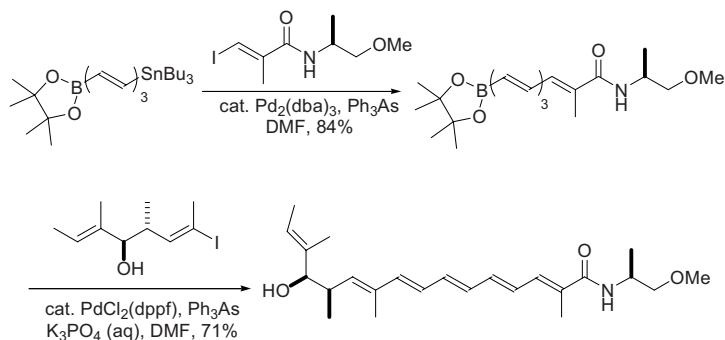


Example 2⁴



Example 3, Intramolecular Suzuki–Miyaura coupling⁸



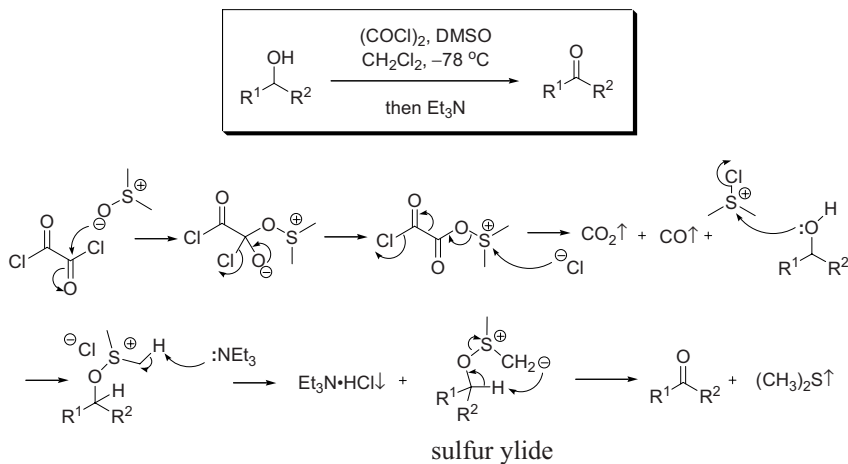
Example 4⁹

References

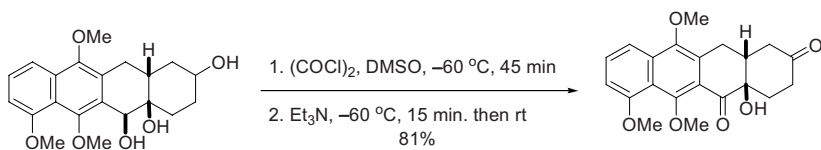
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Swern oxidation

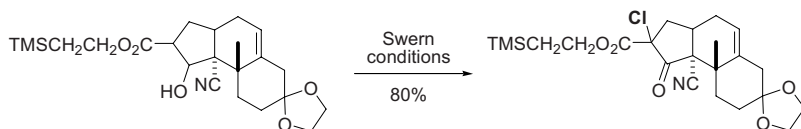
Oxidation of alcohols to the corresponding carbonyl compounds using $(\text{COCl})_2$, DMSO, and quenching with Et_3N .



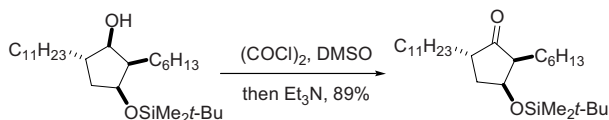
Example 1²

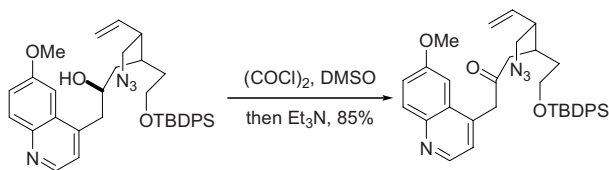


Example 2³



Example 3⁵



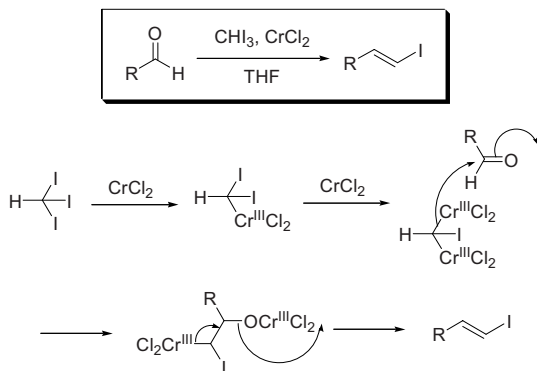
Example 4⁷

References

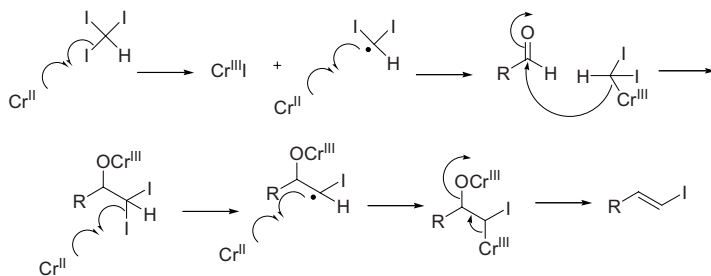
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Takai reaction

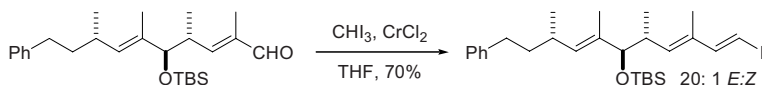
Stereoselective conversion of an aldehyde to the corresponding *E*-vinyl iodide using CHI_3 and CrCl_2 .



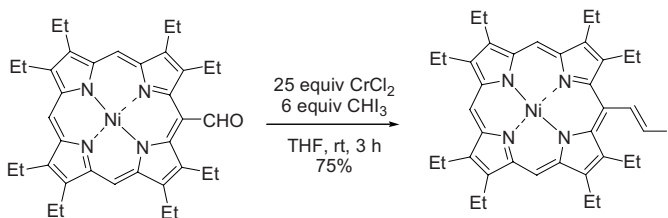
A radical mechanism was recently proposed¹⁰

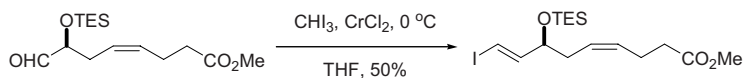
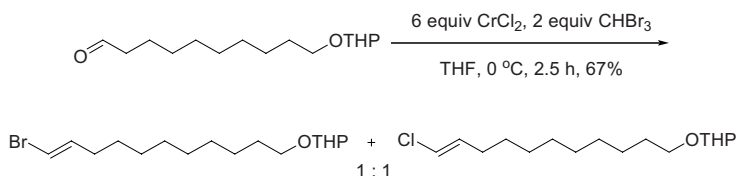
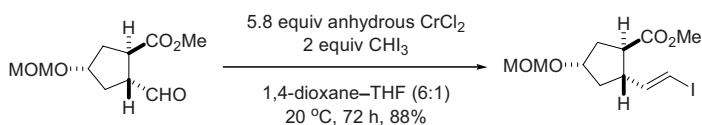


Example 1²



Example 2³



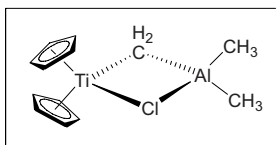
Example 3⁴Example 4, A Br/Cl variant⁹Example 5¹⁰

References

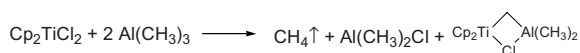
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Tebbe's reagent

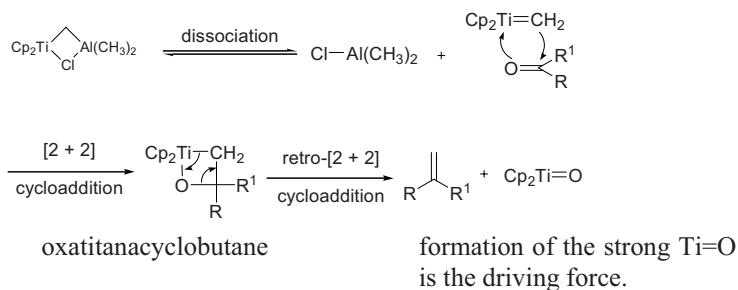
The Tebbe's reagent, μ -chlorobis(cyclopentadienyl)(dimethylaluminium)- μ -methylenetitanium, transforms a carbonyl compound to the corresponding *exo*-olefin.



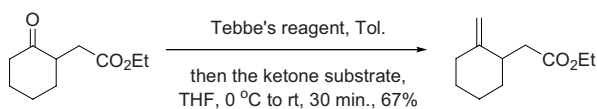
Preparation:^{2,6}



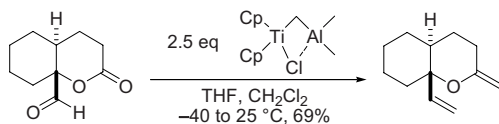
Mechanism:³

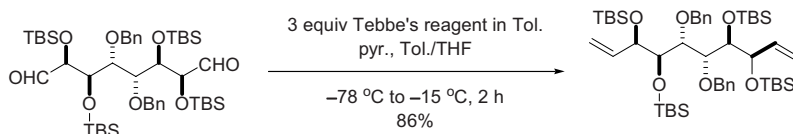
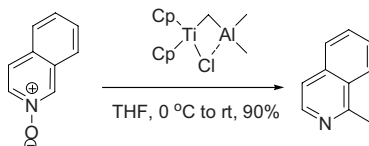
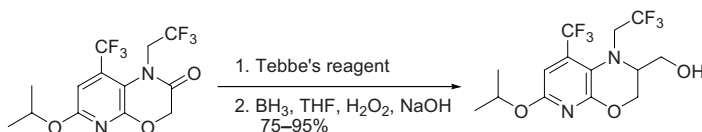


Example 1, Ketone²



Example 2, Double Tebbe⁴



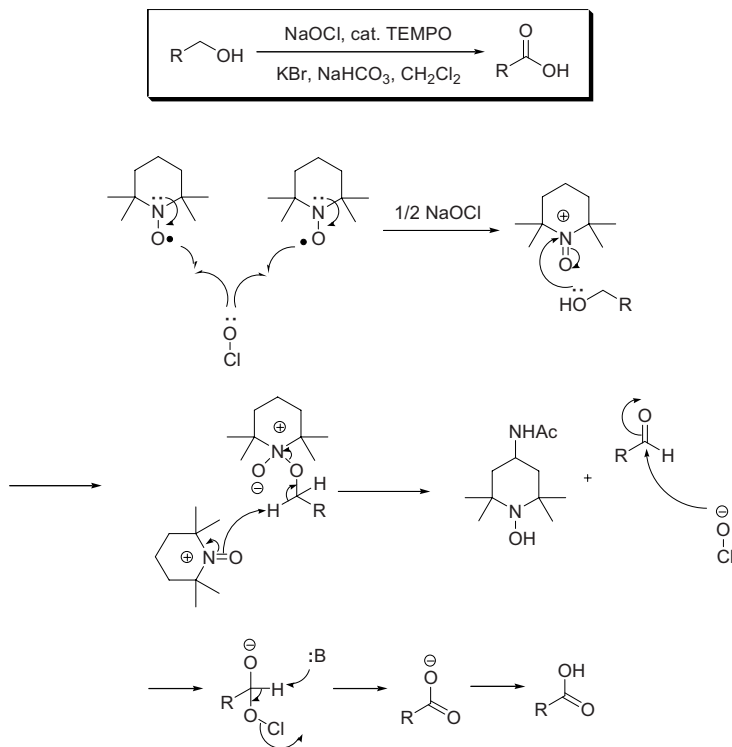
Example 3, Double Tebbe⁵Example 4, *N*-Oxide⁶Example 5, Amide¹¹

References

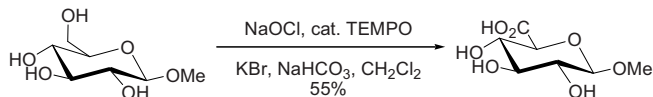
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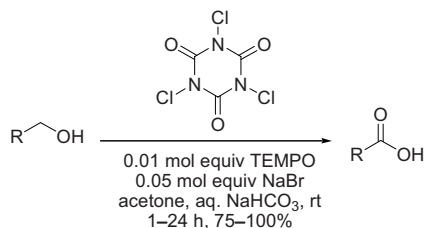
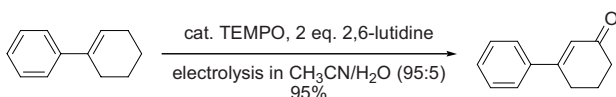
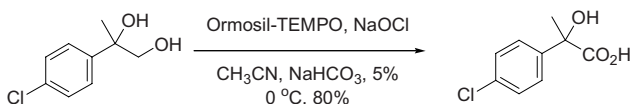
TEMPO oxidation

TEMPO = **T**etramethyl **p**entahydropyridine **o**xide. 2,2,6,6-Tetramethylpiperidinyloxy is a stable nitroxyl radical, which serves in oxidations as catalyst



Example 1⁴



Example 2, Trichloroisocyanuric/TEMPO Oxidation⁵Example 3⁸Example 4¹⁰

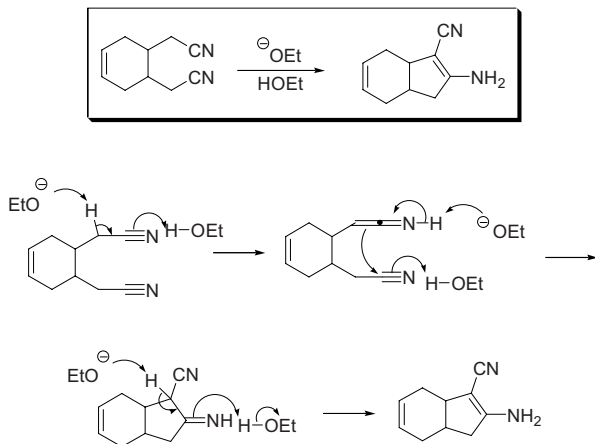
“Ormosil-TEMPO” is a sol-gel hydrophobized nanostructured silica matrix doped with TEMPO

References

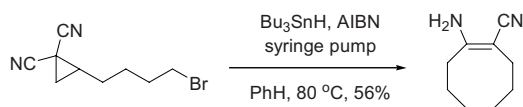
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Thorpe–Ziegler reaction

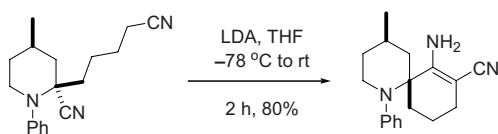
The intramolecular version of the Thorpe reaction, which is base-catalyzed self-condensation of nitriles to yield imines that tautomerize to enamine.



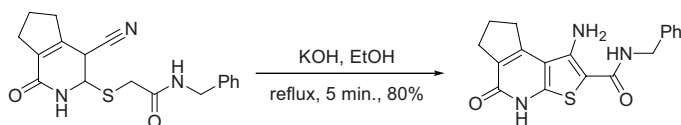
Example 1, A radical Thorpe–Ziegler reaction²

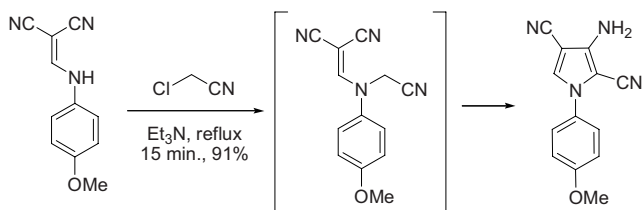


Example 2⁵



Example 3⁸



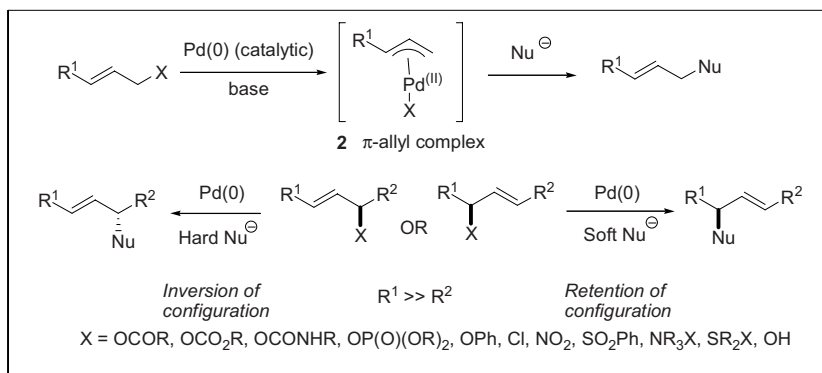
Example 4⁹

References

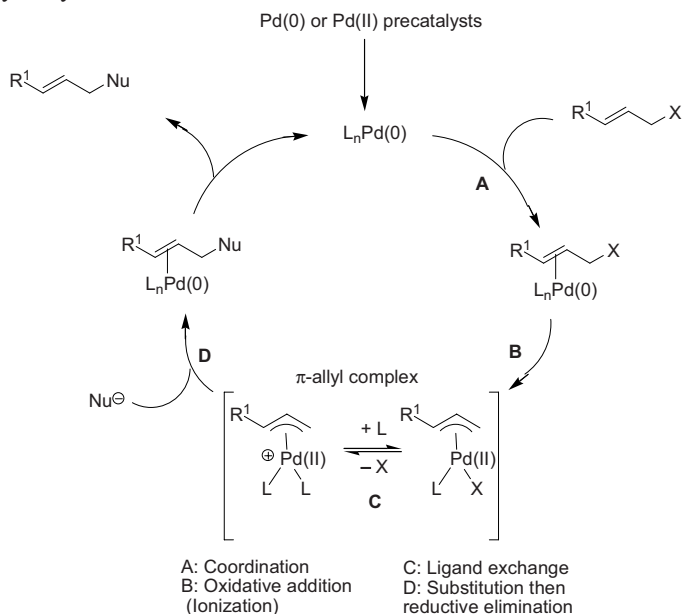
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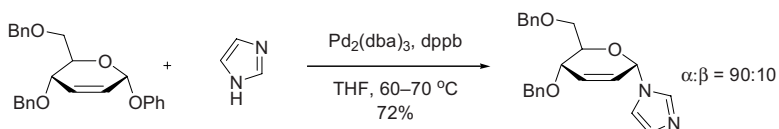
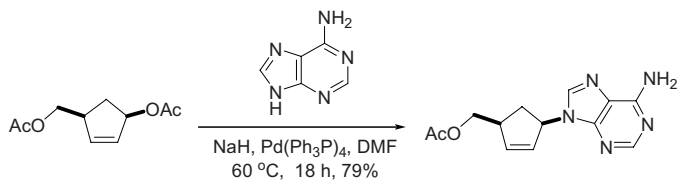
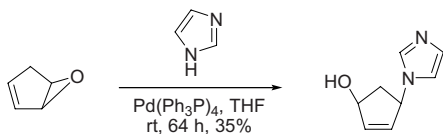
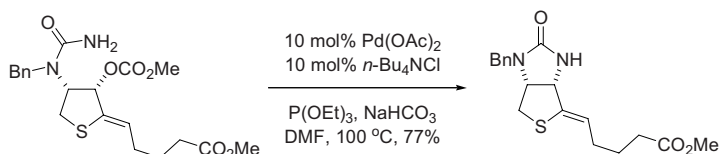
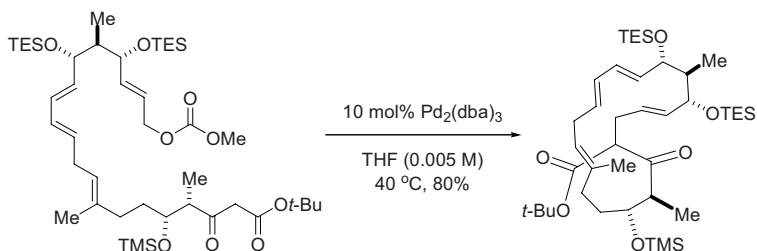
Tsuji–Trost reaction

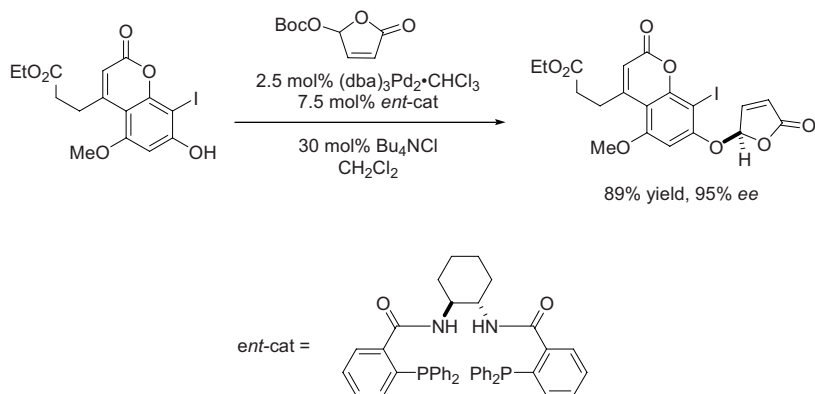
The Tsuji–Trost reaction is the palladium-catalyzed substitution of allylic leaving groups by carbon nucleophiles. These reactions proceed via π -allylpalladium intermediates.



The catalytic cycle:



Example 1, Allylic ether³Example 2, Allylic acetate³Example 3, Allylic epoxide⁵Example 4, Intramolecular Tsuji–Trost reaction⁶Example 5, Intramolecular Tsuji–Trost reaction⁷

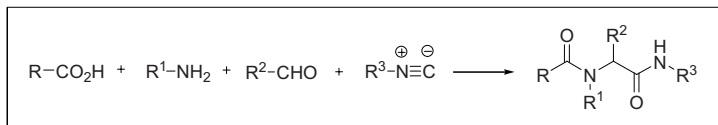
Example 6, Asymmetric Tsuji–Trost reaction⁸

References

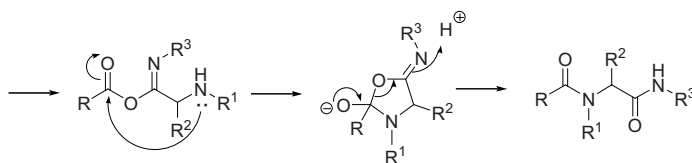
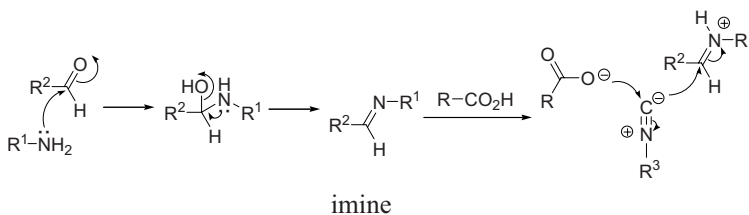
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Ugi reaction

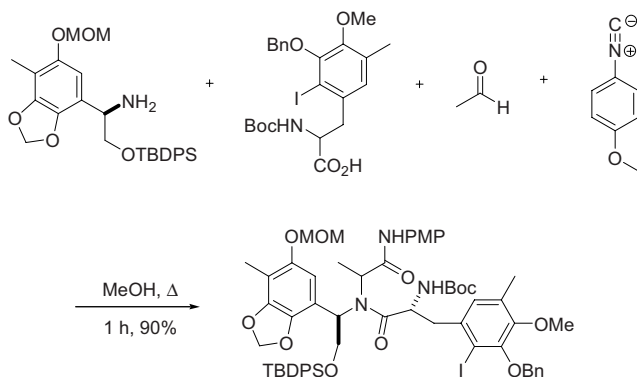
Four-component condensation (4CC) of carboxylic acids, *C*-isocyanides, amines, and carbonyl compounds to afford diamides. *Cf.* Passerini reaction.

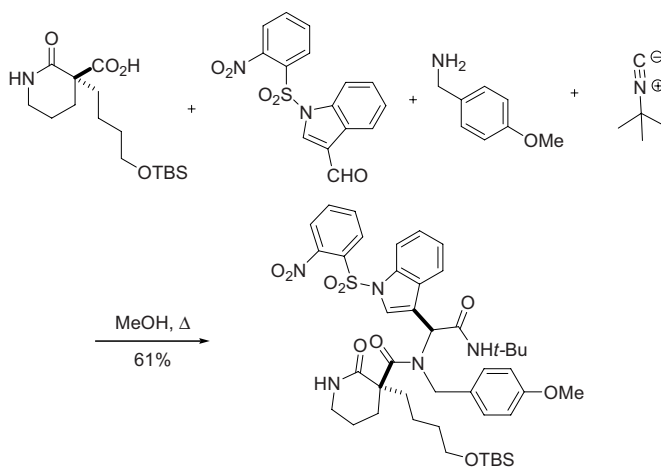
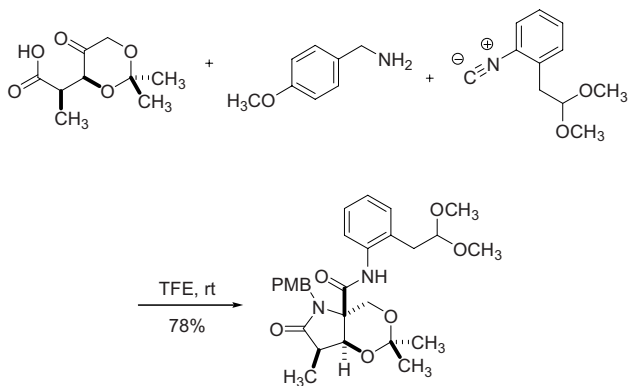
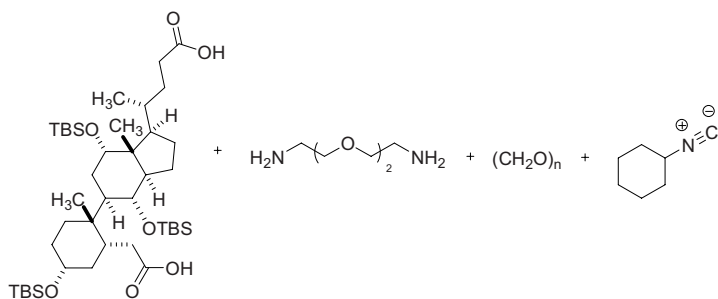


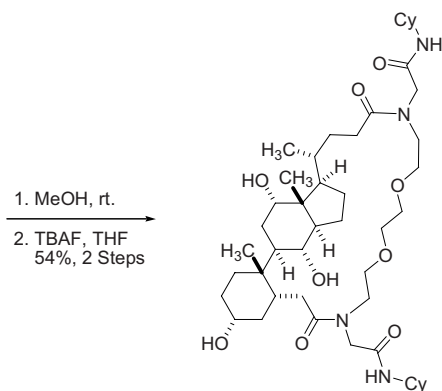
isocyanide



Example 1²



Example 2⁵Example 3⁷Example 4⁸

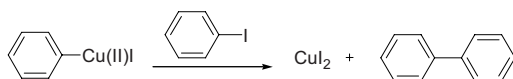
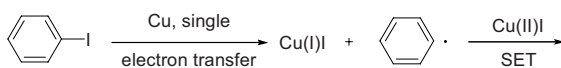
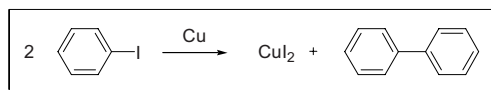


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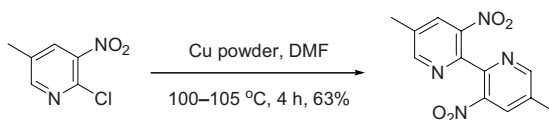
Ullmann coupling

Homocoupling of aryl halides in the presence of Cu or Ni or Pd to afford biaryls.

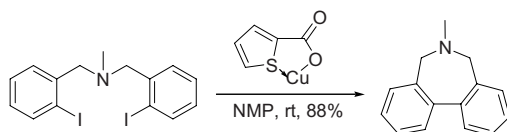


The overall transformation of PhI to PhCuI is an oxidative addition process.

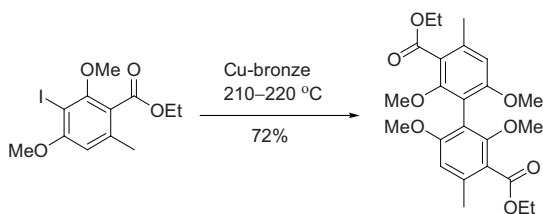
Example 1³

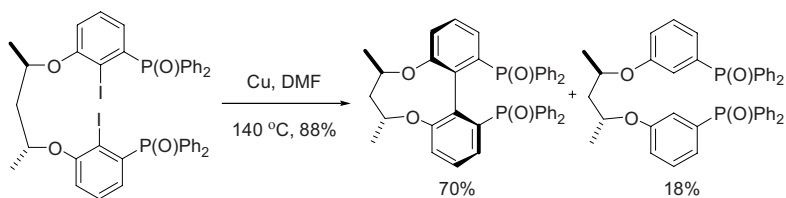
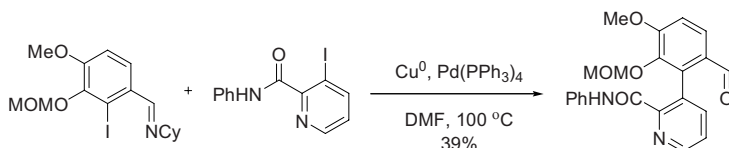


Example 2, CuTC-catalyzed Ullmann coupling⁴



Example 3⁵



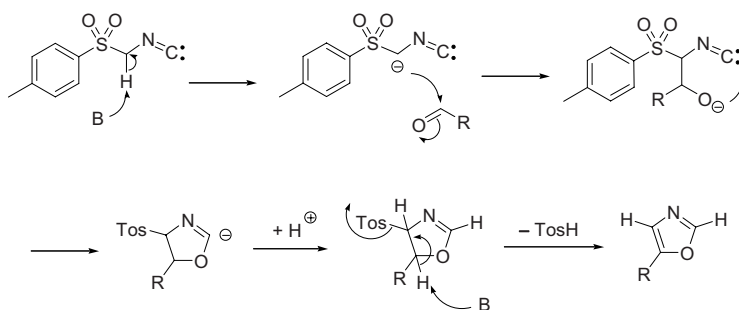
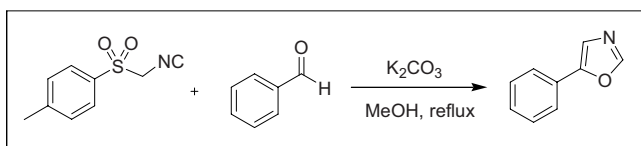
Example 4⁸Example 5⁹

References

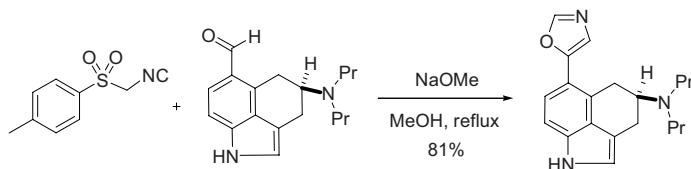
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van Leusen oxazole synthesis

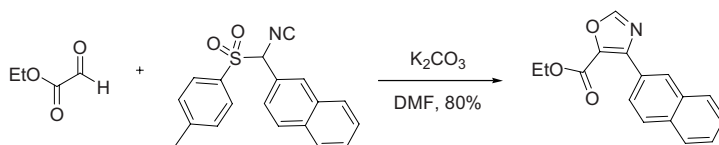
5-Substituted oxazoles through the reaction of *p*-tolylsulfonylmethyl isocyanide (TosMIC, also known as the van Leusen reagent) with aldehydes in protic solvents at refluxing temperatures.

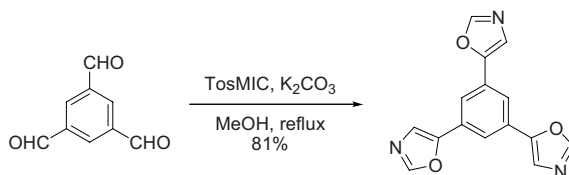
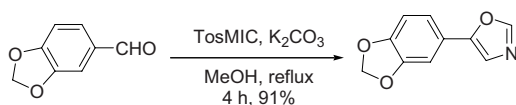


Example 1³



Example 2⁵



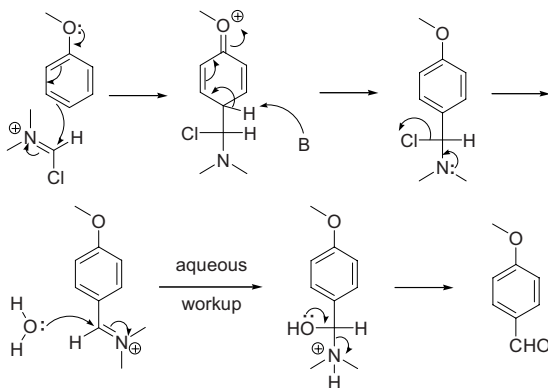
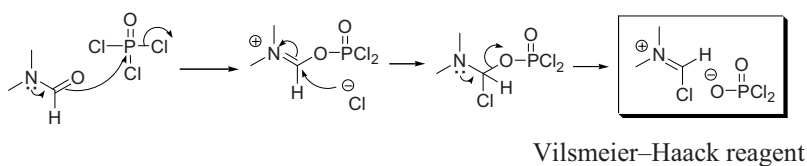
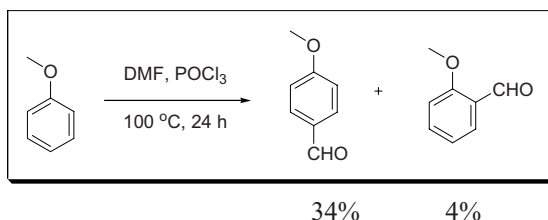
Example 3⁹Example 4¹⁰

References

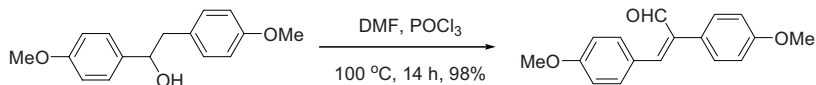
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Vilsmeier–Haack reaction

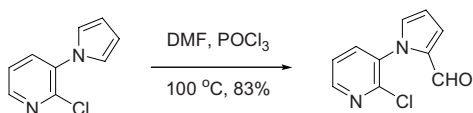
The Vilsmeier–Haack reagent, a chloroiminium salt, is a weak electrophile. Therefore, the Vilsmeier–Haack reaction works better with electron-rich carbocycles and heterocycles.

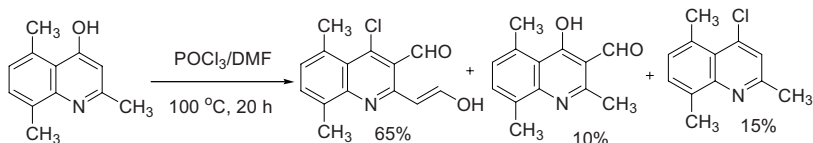
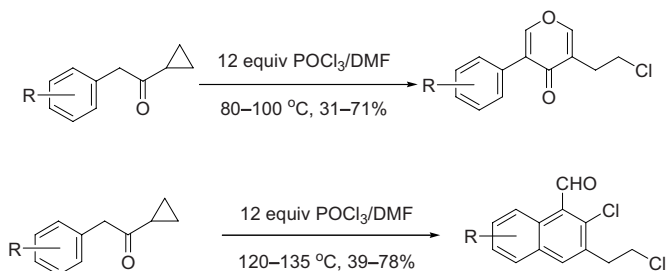


Example 1²



Example 2³



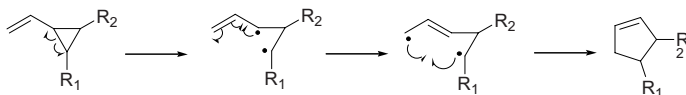
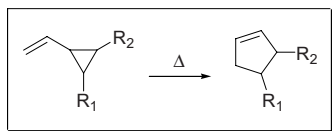
Example 3⁹Example 4¹⁰

References

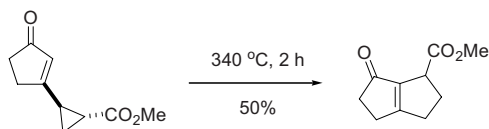
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Vinylcyclopropane–cyclopentene rearrangement

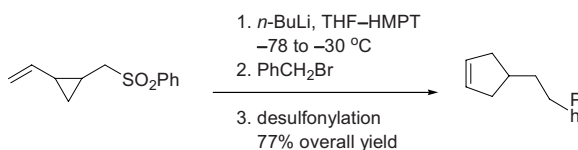
Transformation of vinylcyclopropane to cyclopentene *via* a diradical intermediate.



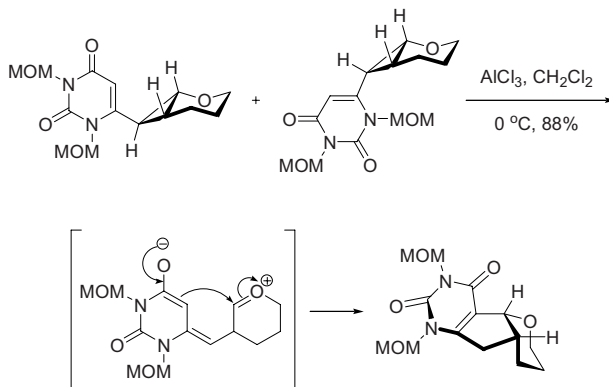
Example 1¹

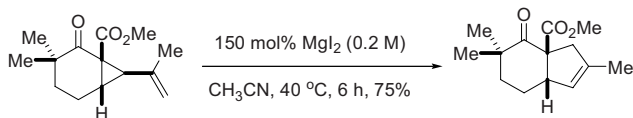


Example 2²



Example 3⁹



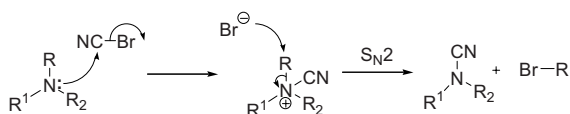
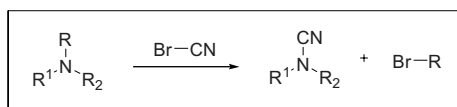
Example 4¹⁰

References

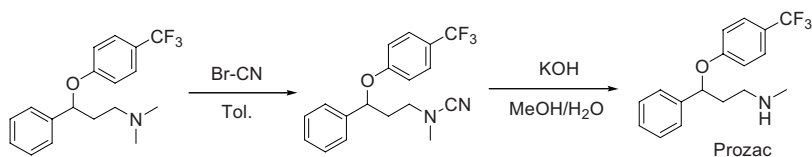
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von Braun reaction

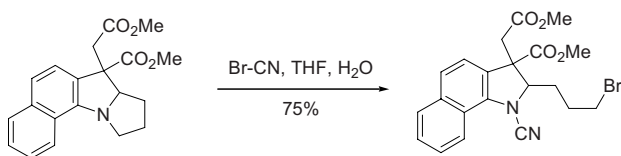
Different from the von Braun degradation reaction (amide to nitrile), the von Braun reaction refers to the treatment of tertiary amines with cyanogen bromide, resulting in a substituted cyanamide.



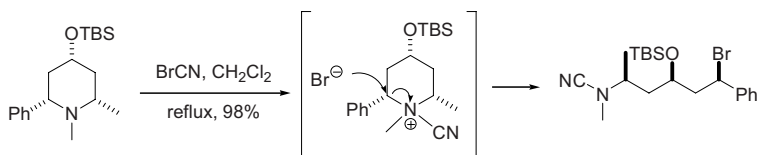
Example 1⁴



Example 2⁵



Example 3⁹



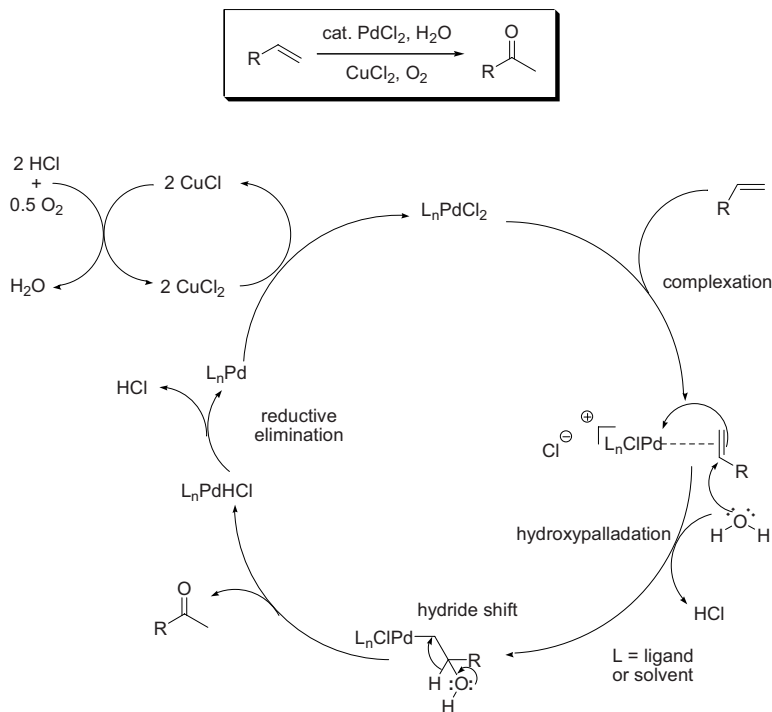
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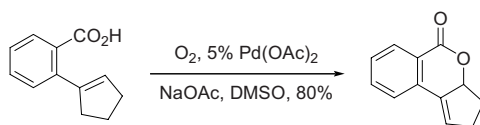
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Wacker oxidation

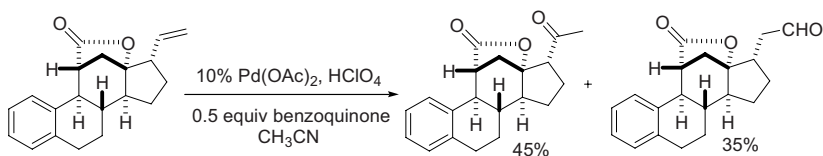
Palladium-catalyzed oxidation of olefins to ketones, and aldehydes in certain cases.

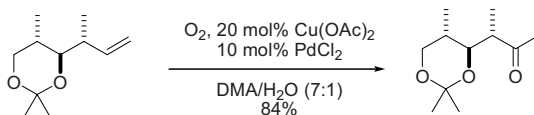
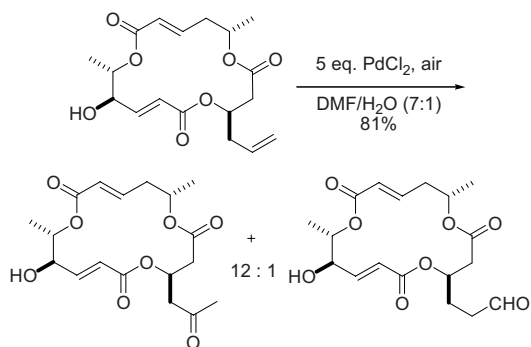


Example 1⁵



Example 2⁷



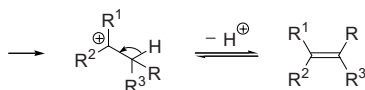
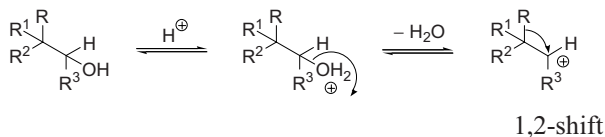
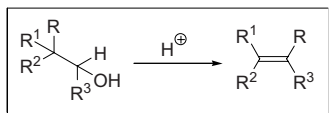
Example 3⁹Example 4¹⁰

References

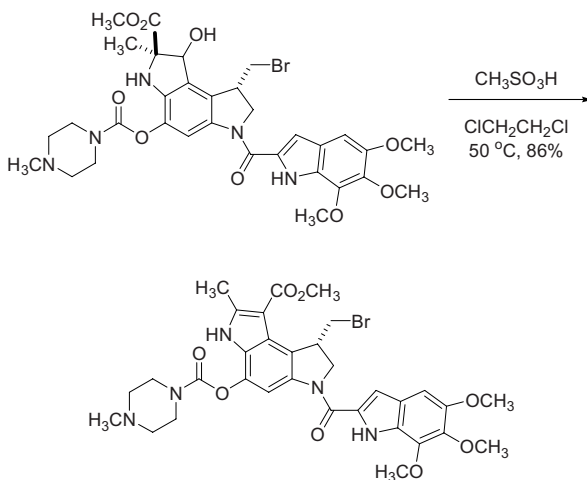
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Wagner–Meerwein rearrangement

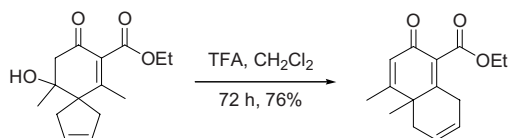
Acid-catalyzed alkyl group migration of alcohols to give more substituted olefins.

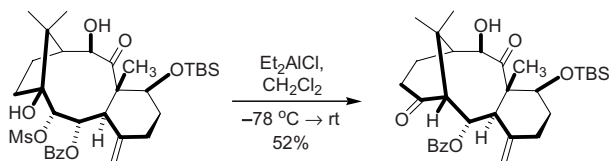
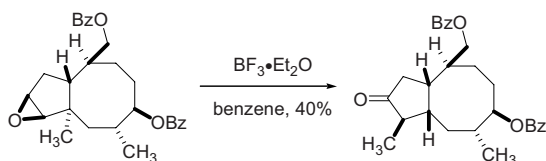


Example 1³



Example 2, Double Wagner–Meerwein rearrangement⁶



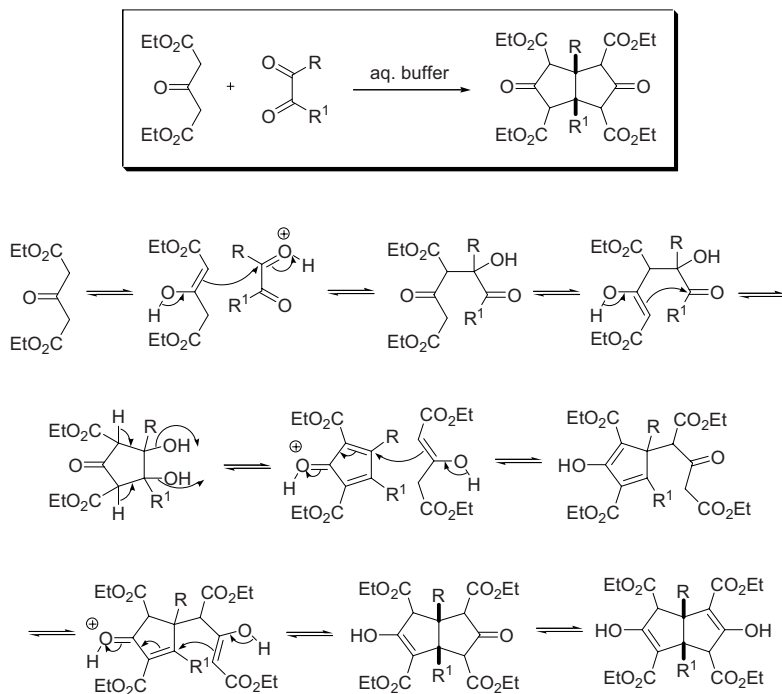
Example 3⁷Example 4⁹

References

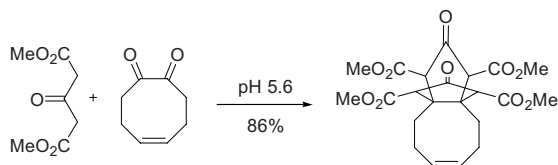
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Weiss–Cook reaction

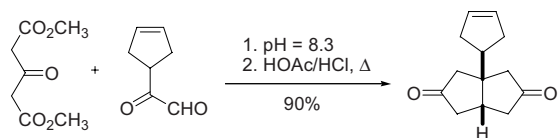
Synthesis of *cis*-bicyclo[3.3.0]octane-3,7-dione. The product is frequently decarboxylated.

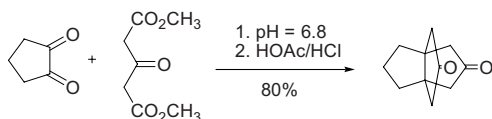
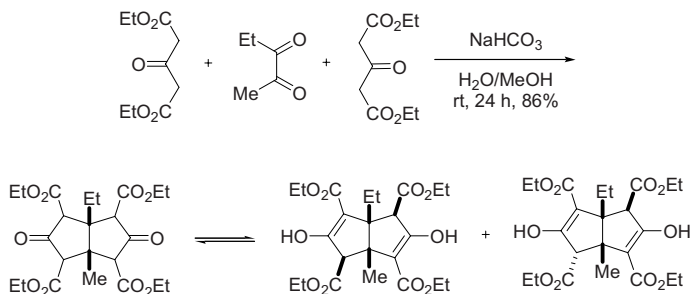


Example 1²



Example 2³



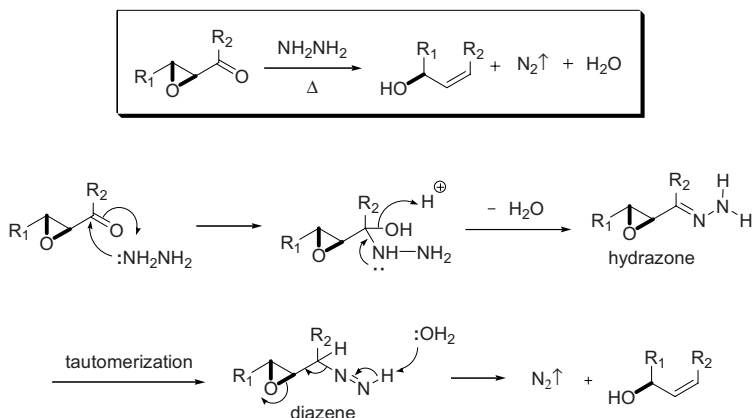
Example 3⁴Example 4⁹

References

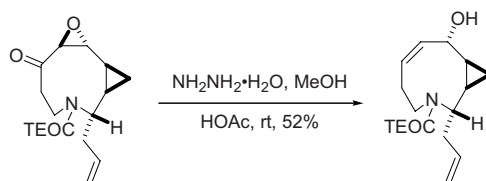
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Wharton reaction

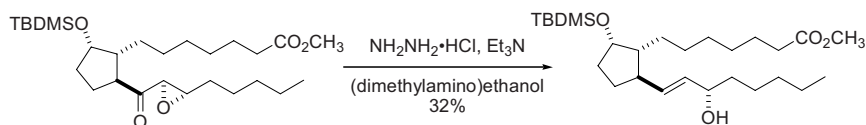
Reduction of α,β -epoxy ketones by hydrazine to allylic alcohols.



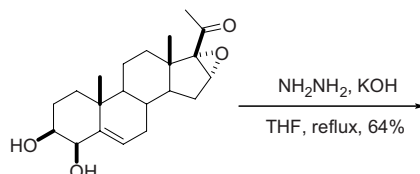
Example 1⁵

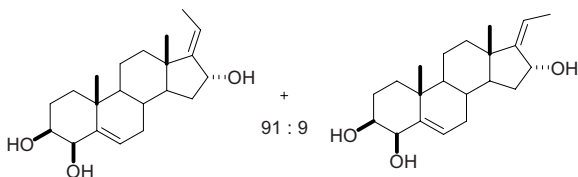
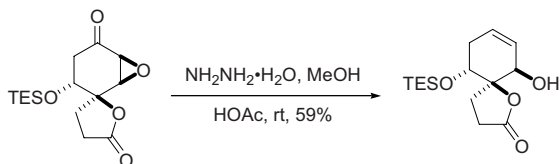


Example 2⁶



Example 3⁷

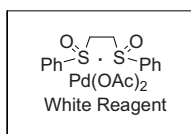


Example 4⁸

References

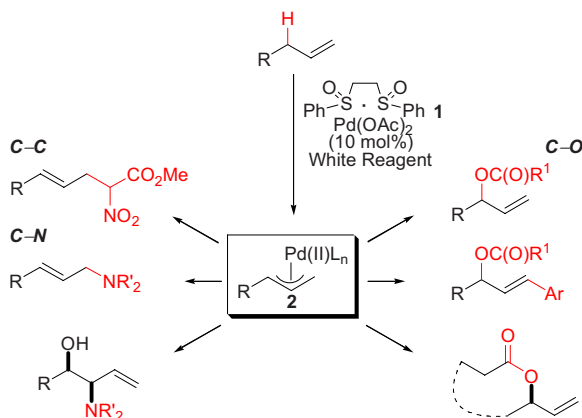
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White Reagent



The White Reagent **1** is a highly versatile, commercially-available catalyst for allylic C–H oxidation which allows for the construction of useful C–O, C–N, and C–C bonds directly from relatively inert allylic C–H bonds (Figure 1).^{1–11} The White Reagent enables novel and predictable disconnections for the synthesis of complex molecules which can streamline their synthesis.^{2,4,7,8} Widely available α -olefins undergo intra- and intermolecular C–H oxidation with remarkably high levels of chemo-, regio-, and stereoselectivity. Mechanistic studies provide evidence that the White Reagent promotes allylic C–H cleavage to generate π -allylpalladium intermediate **2** which can then be functionalized with an oxygen, nitrogen or carbon nucleophile (Figure 1).³

Figure 1



Common organic functionality such as Lewis basic phenol **3**,³ acid-labile acetal **4**,⁸ highly reactive aryl triflate **6**,¹¹ and depsipeptide **5**⁵ are well-tolerated under the mild reaction conditions (Figure 2). In all cases the products are isolated as one regioisomer and olefin isomer after column purification.

Current state-of-the-art methods for constructing C–N bonds rely on functional group interconversions or C–C bond forming reactions using preoxidized materials. Allylic amination using the White Reagent can streamline the synthesis of nitrogen-containing molecules by reducing the functional group manipulations necessary for working with oxygenated intermediates. Allylic C–H amination was used to synthesize (–)-**8**, an intermediate in the synthesis of *L*-acosamine derivative **9** (Figure 3A).⁷ The C–H amination route to (–)-**8** proceeded in half the total number of steps, no functional group manipulations, and

comparable overall yield to the alternative C–O to C–N bond-forming route. Intermolecular C–H amination has also led to the construction of (+)-deoxynegamycin analogue **12** in five less steps and improved overall yield compared to the alternative route relying on C–O substitution (Figure 3B).⁸

Figure 2

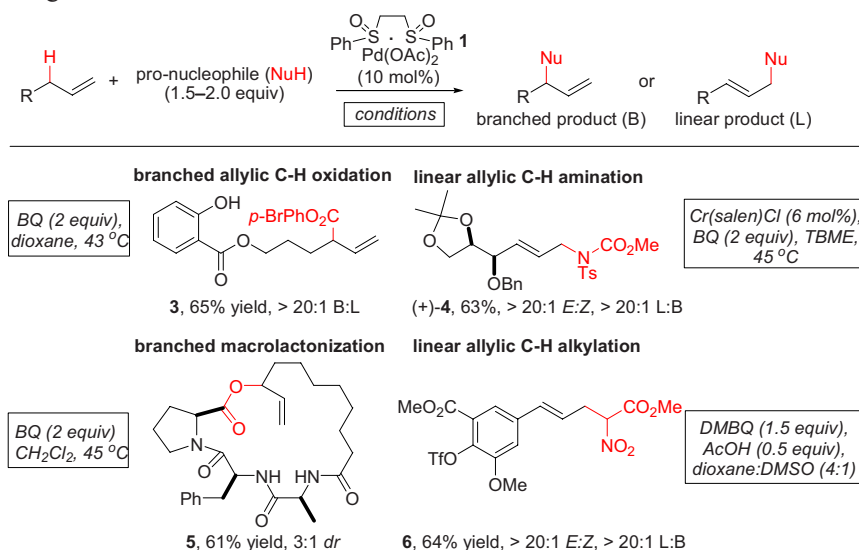
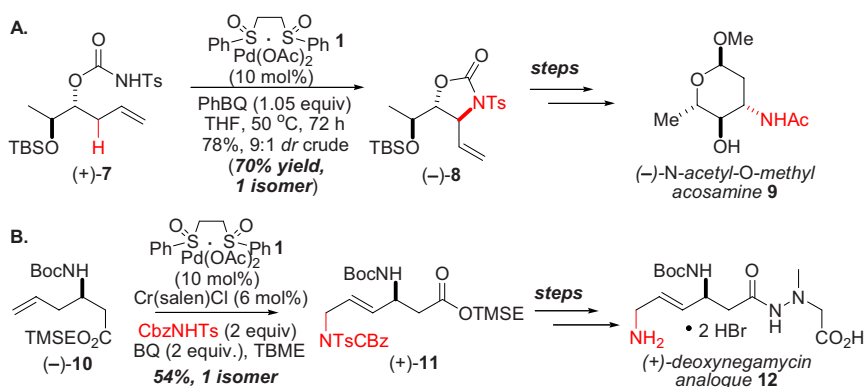


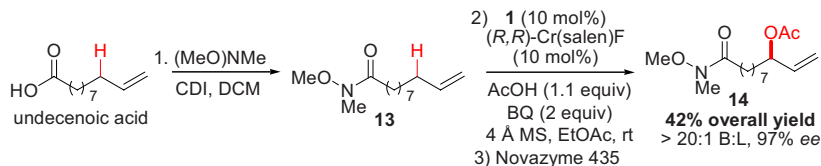
Figure 3



Similarly, allylic C–H oxidation can streamline the construction of oxygenated compounds by reducing functional group manipulations necessary for working with bisoxygenated intermediates. For example, a chiral allylic C–H oxidation/enzymatic resolution sequence furnished bisoxygenated compound **14** in 97% ee and in 42% overall yield in just 3 steps from a commercially available

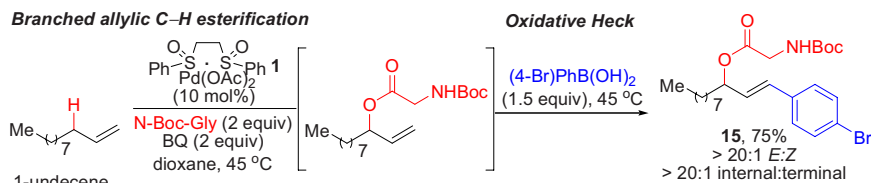
monooxygenated precursor, 11-undecenoic acid (Figure 4).¹⁰ Alternative routes to similar molecules require protection/deprotection sequences and use a kinetic resolution giving a maximum of 50% yield.

Figure 4



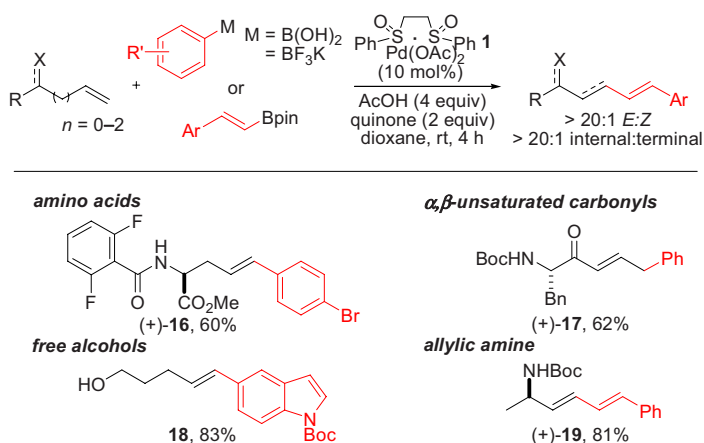
In addition to allylic C–H oxidation, the White Reagent also catalyzes intermolecular Heck arylations.⁶ Notably, the arylation uses electronically *unbiased* α -olefins and aryl boronic acids and occurs under acidic, oxidative conditions. A one-pot allylic C–H oxidation/vinylic C–H arylation reaction furnishes *E*-arylated allylic esters with high regio- and stereoselectivities (Figure 5). This three-component coupling can be used to rapidly synthesize densely functionalized products from inexpensive hydrocarbon feedstocks. *N*-Boc glycine allylic ester **9** was synthesized in one step using commercially available olefin, amino acid, and boronic acid reagents. Compounds similar to **15** have been transformed into medicinally relevant dipeptidyl peptidase IV inhibitors.⁶

Figure 5



Besides the one-pot process described above, the White Reagent catalyzes a chelate-controlled oxidative Heck arylation between a wide range of α -olefins and organoborane compounds in good yields and with excellent regio- and stereoselectivities (Figure 6).⁹ Unlike other Heck arylation methods, no Pd–H isomerization is observed under the mild reaction conditions. Aryl boronic acids, styrenylpinacol boronic esters, and aryl potassium trifluoroborates (activated with boric acid) are all compatible with the general reaction conditions.

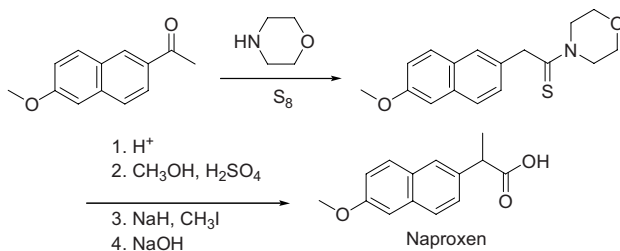
Figure 6



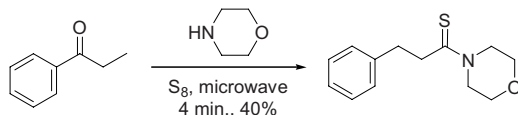
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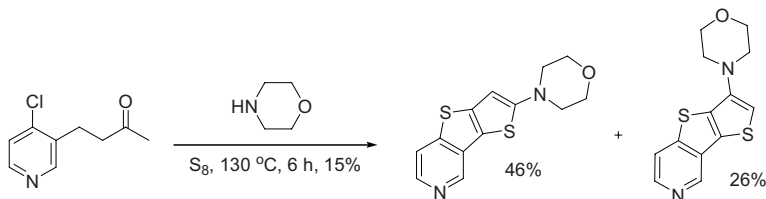
Example 1, The Willgerdt–Kindler reaction was a key operation in the initial synthesis of racemic Naproxen:³



Example 2⁵



Example 3, A domino annulation reaction under Willgerdt–Kindler conditions:¹⁰

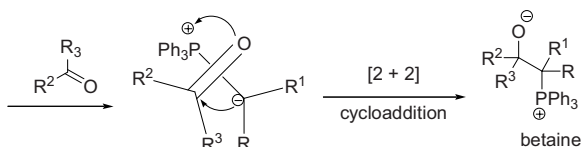
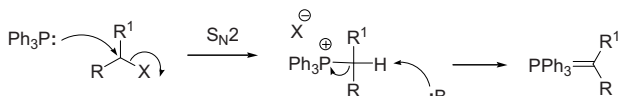
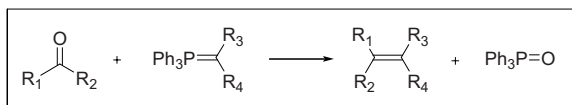


References

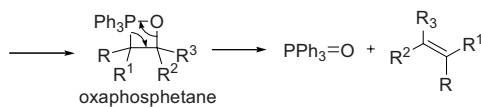
- (a) Willgerodt, C. *Ber.* **1887**, 20, 2467–2470. Conrad Willgerodt (1841–1930), born in Harlingerode, Germany, was a son of a farmer. He worked to accumulate enough money to support his study toward his doctorate, which he received from Claus. He became a professor at Freiburg, where he taught for 37 years. (b) Kindler, K. *Arch. Pharm.* **1927**, 265, 389–415.
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Wittig reaction

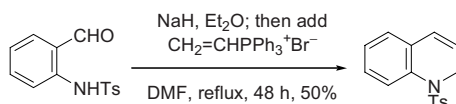
Olefination of carbonyls using phosphorus ylides, typically the *Z*-olefin is obtained.



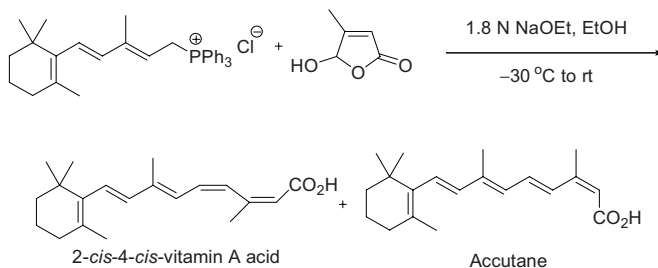
“puckered” transition state, irreversible and concerted

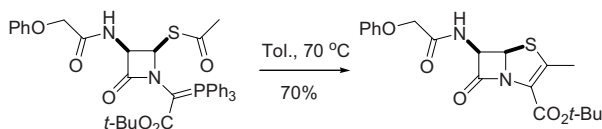
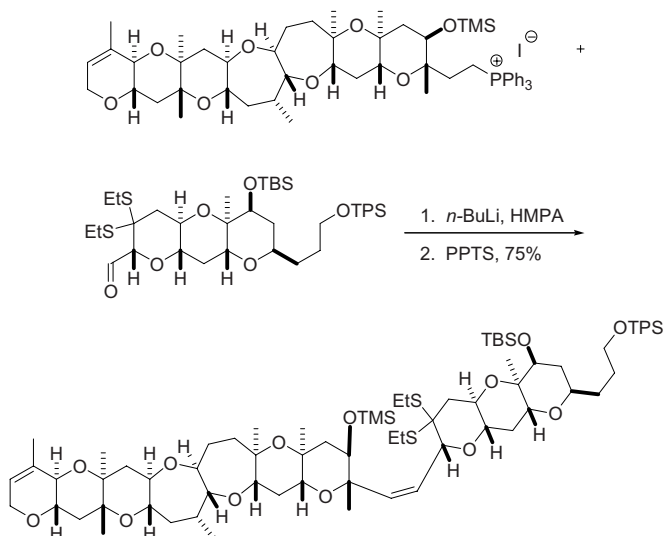


Example 1³



Example 2⁴



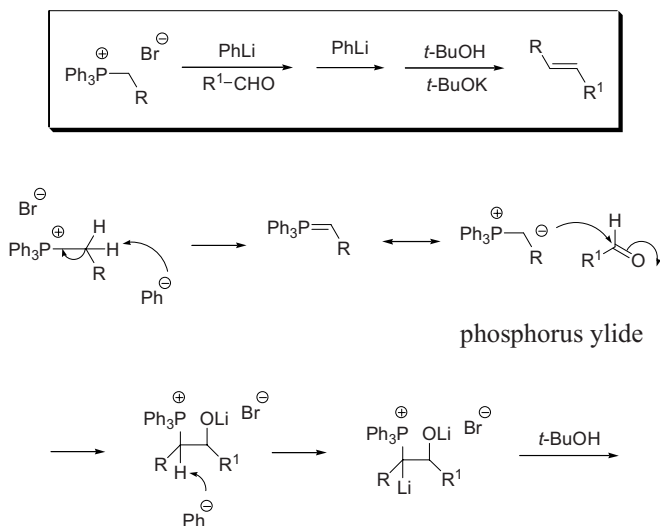
Example 3⁵Example 4⁹

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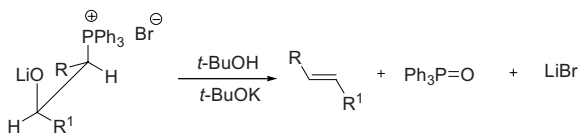
Schlosser modification of the Wittig reaction

The normal Wittig reaction of nonstabilized ylides with aldehydes gives *Z*-olefins. The Schlosser modification of the Wittig reaction of nonstabilized ylides furnishes *E*-olefins instead.



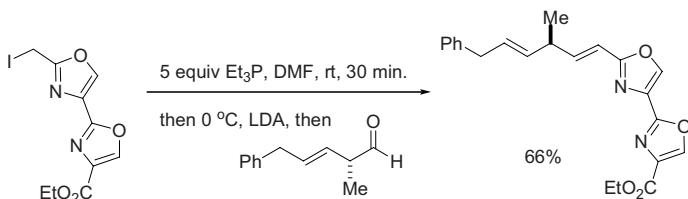
LiBr complex of β -oxo ylide

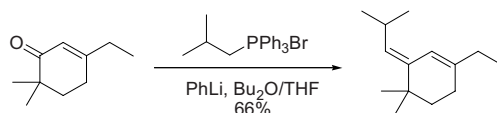
These conditions allow for the *erythro* betaine to interconvert to the *threo* betaine



LiBr complex of *threo* betaine

Example 1⁶



Example 2¹⁰

References

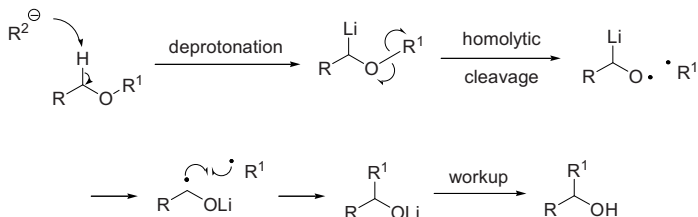
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[1,2]-Wittig rearrangement

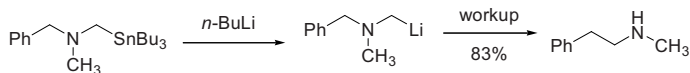
Treatment of ethers with bases, such as alkyl lithium, results in alcohols.



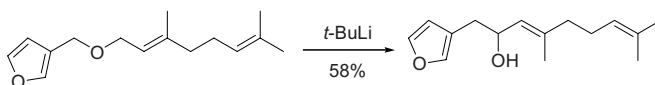
The [1,2]-Wittig rearrangement is believed to proceed via a radical mechanism:



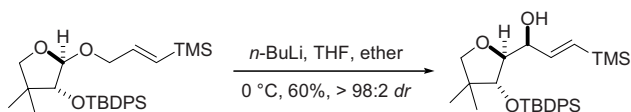
Example 1, Aza [1,2]-Wittig rearrangement²



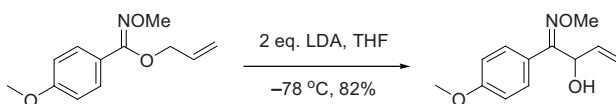
Example 2³



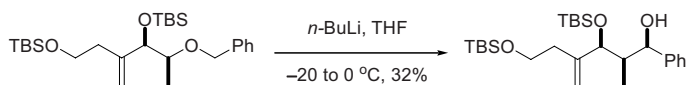
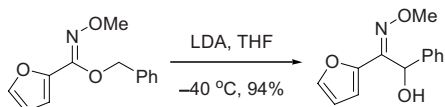
Example 3⁴



Example 4⁶



Example 5⁸

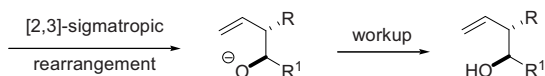
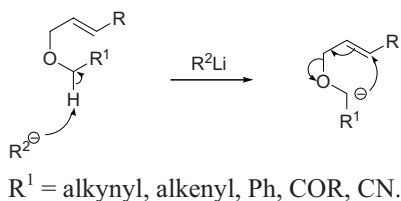
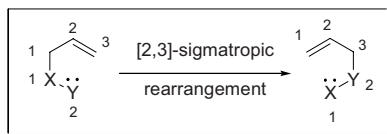
Example 6⁹

References

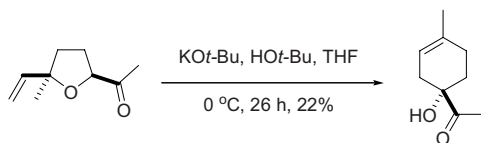
- 1 Wittig, G.; Löhmman, L. *Ann.* **1942**, 550, 260–268.
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[2,3]-Wittig rearrangement

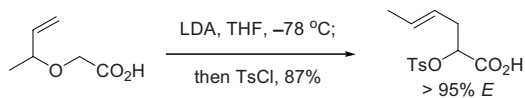
Transformation of allyl ethers into homoallylic alcohols by treatment with base. Also known as the Still–Wittig rearrangement. Cf. Sommelet–Hauser rearrangement.



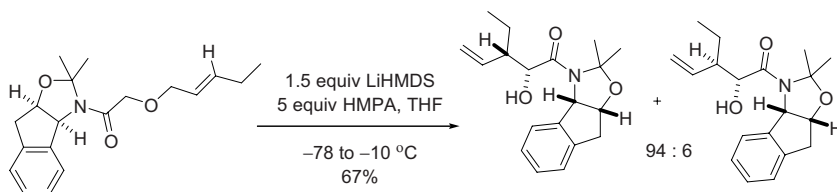
Example 1²

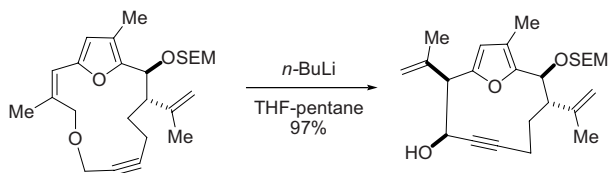


Example 2³



Example 3⁵



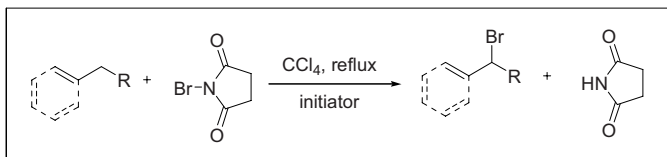
Example 4⁶

References

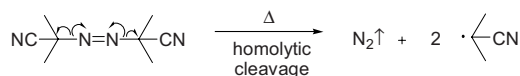
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Wohl–Ziegler reaction

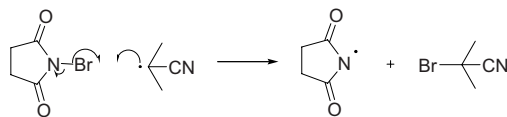
The Wohl–Ziegler reaction is the reaction of an allylic or benzylic substrate with *N*-bromosuccinimide (NBS) under radical initiating conditions to provide the corresponding allylic or benzylic bromide. Conditions used to promote the radical reaction are typically radical initiators, light and/or heat; carbon tetrachloride (CCl₄) is typically utilized as the solvent.



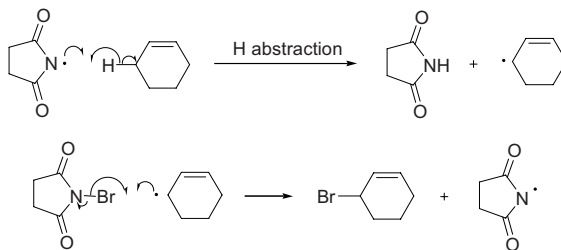
Initiation:



2,2'-azobisisobutyronitrile (AIBN)

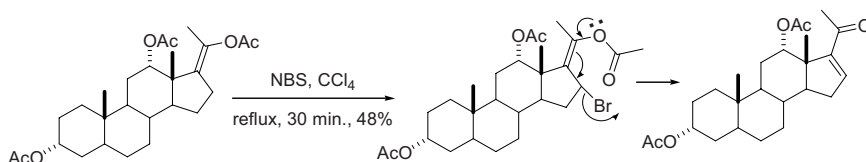


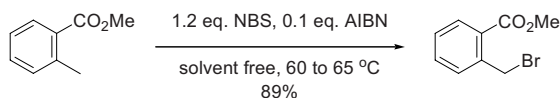
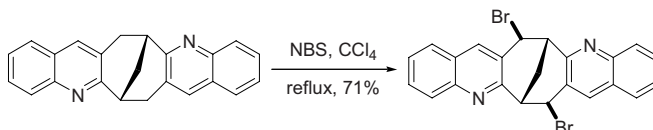
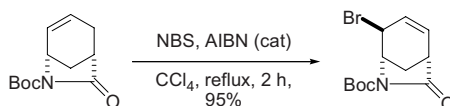
Propagation:



The succinimidyl radical is now available for the next cycle of the radical chain reaction.

Example 1³



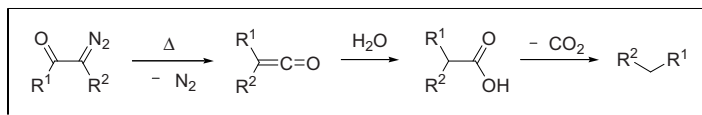
Example 2⁷Example 3⁸Example 4⁹

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Wolff rearrangement

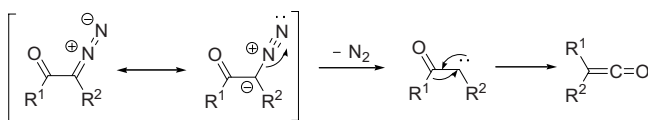
Conversion of an α -diazoketone into a ketene.



α -diazoketone

ketene intermediate

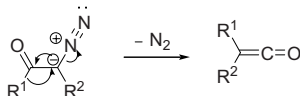
Step-wise mechanism:



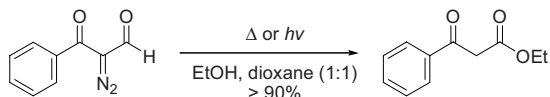
α -ketocarbene

Treatment of the ketene with water would give the corresponding homologated carboxylic acid.

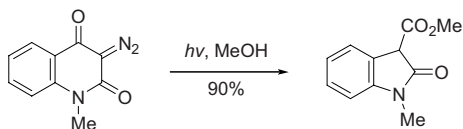
Concerted mechanism:

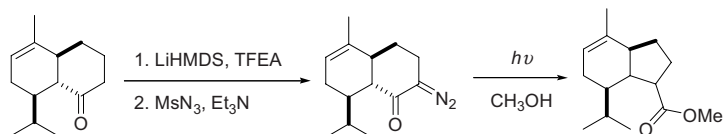
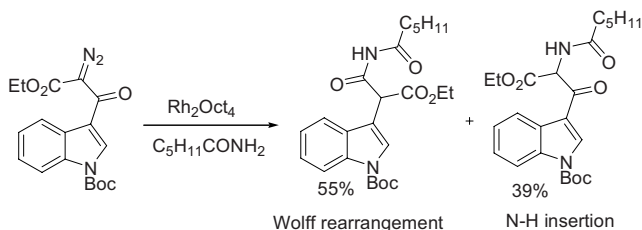


Example 1²



Example 2³



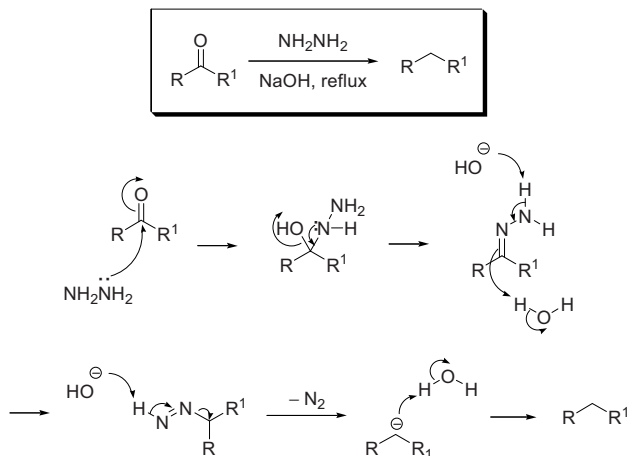
Example 3⁴Example 4⁹

References

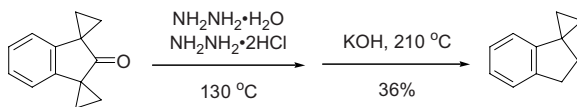
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Wolff–Kishner reduction

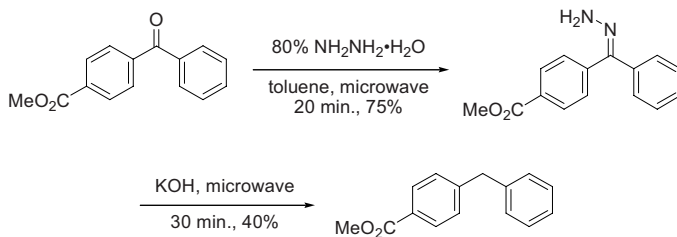
Carbonyl reduction to methylene using basic hydrazine.



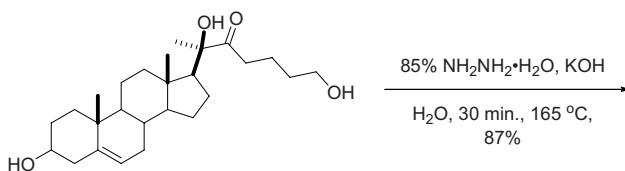
Example 1, Huang Minlon modification, with loss of ethylene here⁵

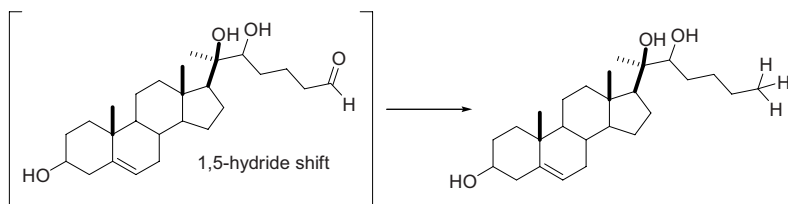


Example 2⁷

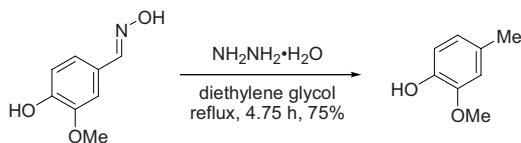


Example 3⁸





Example 4, Huang Minlon modification¹⁰

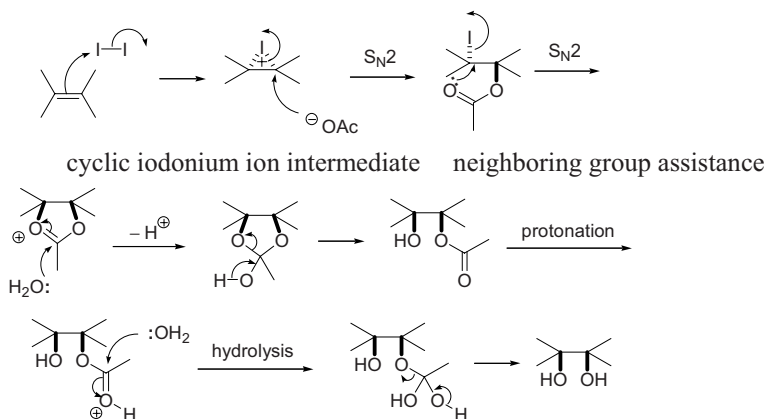
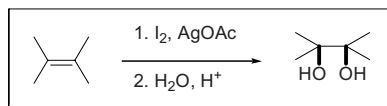


References

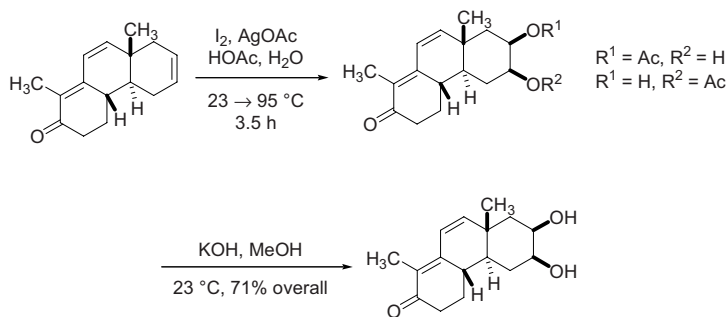
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Woodward *cis*-dihydroxylation

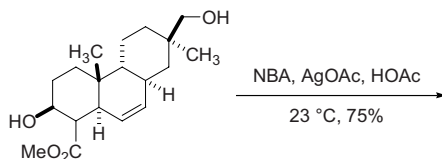
Cf. Prévost *trans*-dihydroxylation.

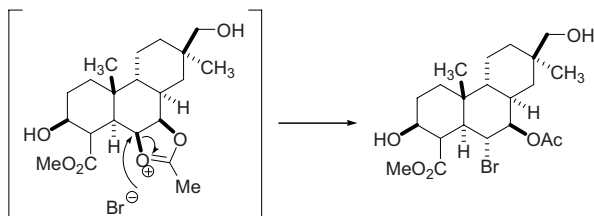


Example 1¹



Example 2⁶



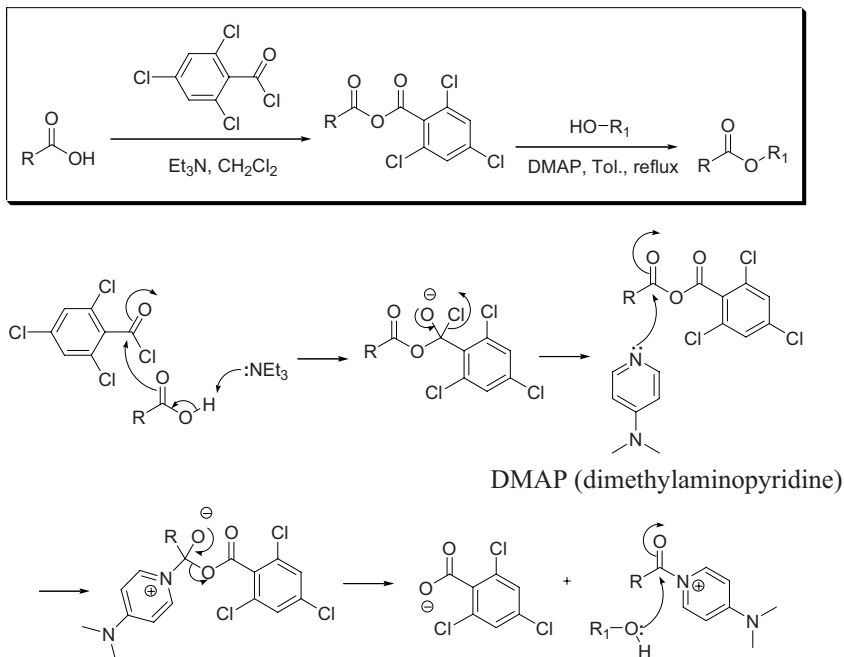


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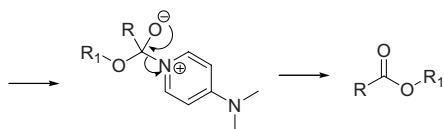
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Yamaguchi esterification

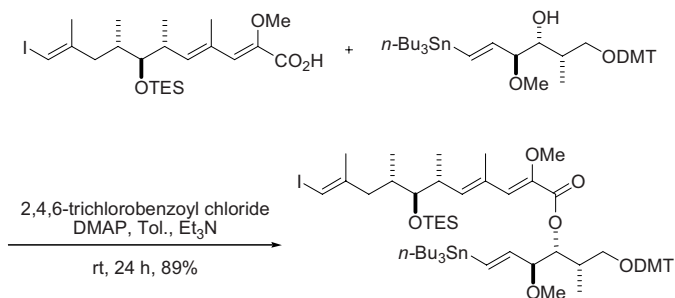
Esterification using 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent).

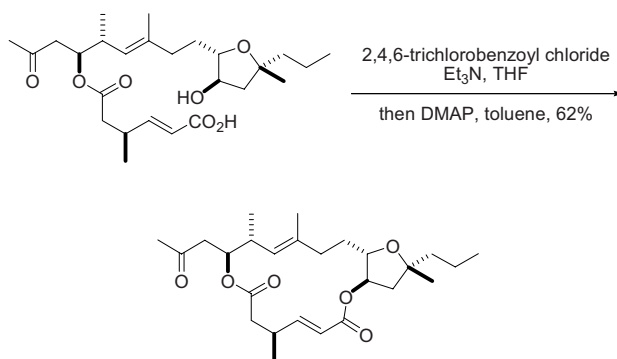
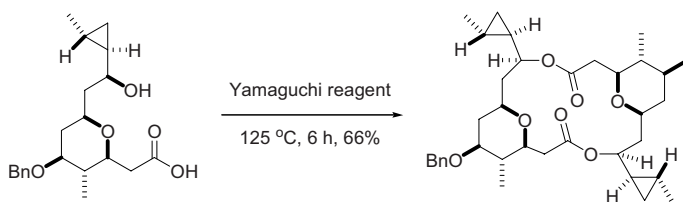


Steric hindrance of the chloro substituents blocks attack of the other carbonyl of the mixed anhydride intermediate.



Example 1, Intermolecular coupling⁵



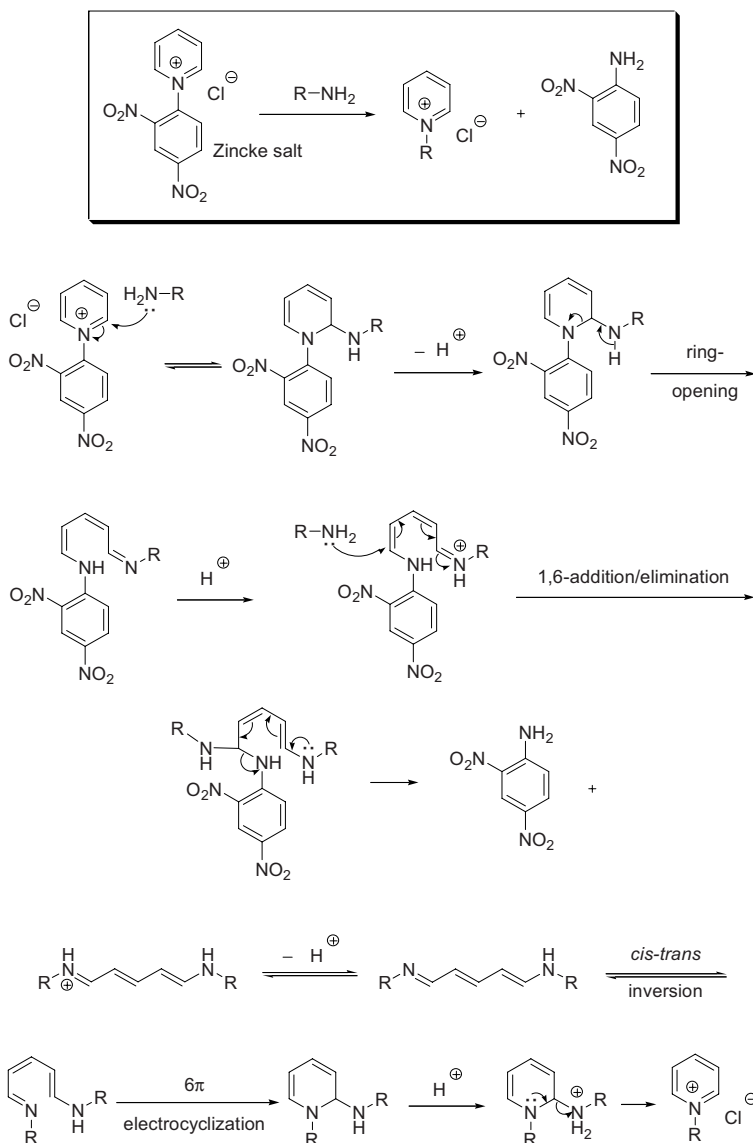
Example 2, Intramolecular coupling⁷Example 3, Dimerization⁸

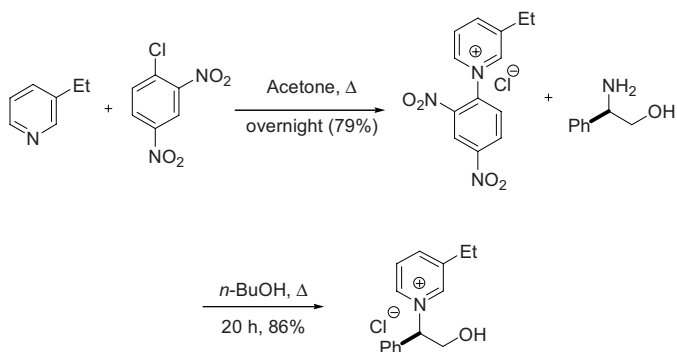
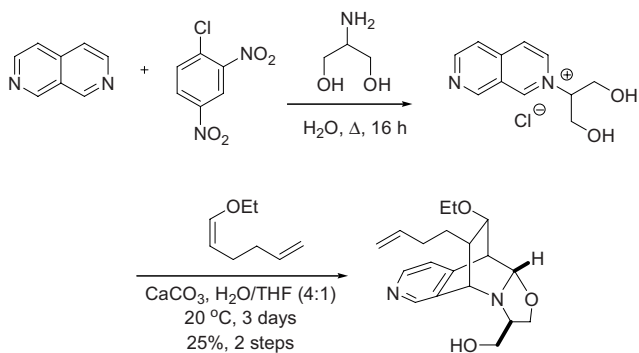
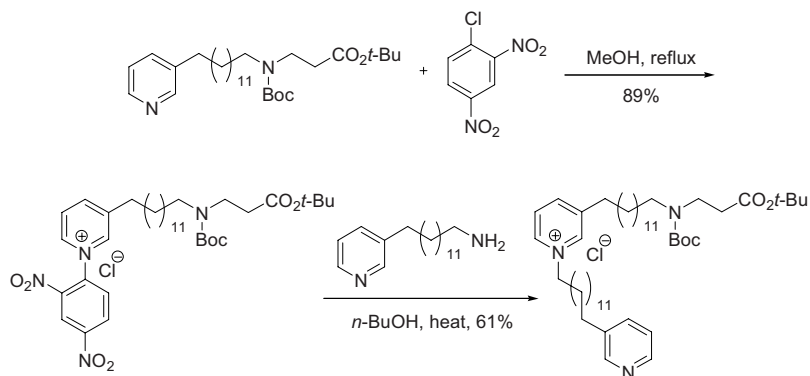
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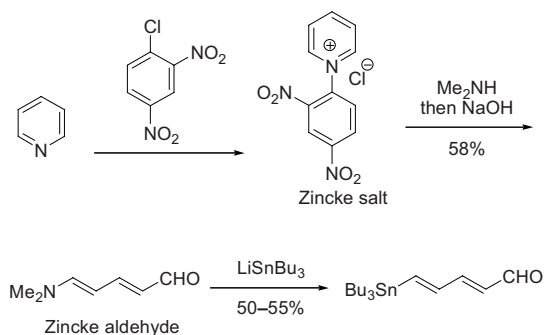
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Zincke reaction

The Zincke reaction is an overall amine exchange process that converts *N*-(2,4-dinitrophenyl)pyridinium salts, known as Zincke salts, to *N*-aryl or *N*-alkyl pyridiniums upon treatment with the appropriate aniline or alkyl amine.



Example 1⁵Example 2⁶Example 3⁹

Example 4¹⁰

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