Jie Jack Li

more than 300 reactions!

Name Reactions

A Collection of Detailed Reaction Mechanisms

Third Edition

Danheiser annulation
Buchwald-Hartwig reaction
Corey-Kim oxidation
Mitsunobu reaction
Swern oxidation
Heck reaction
Chan-Lam coupling

Springer

Kurt Alder
1902–1958
Nobel Prize, 1950

Eduard Buchner
1860–1917
Nobel Prize, 1907

Adolf von Baeyer
1835–1917
Nobel Prize, 1905

Elias James Corey
1928–
Nobel Prize, 1990

Derek H. R. Barton
1918–1999
Nobel Prize, 1969

Otto Paul Hermann Diels
1876–1954
Nobel Prize, 1950

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Jie Jack Li

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Third Expanded Edition

Springer

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Dedicated to

Professor E. J. Corey

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
La Jolla, March 2006

Preface

Confucius said: "*Reviewing old knowledge while learning new old knowledge, is that not, after all, a pleasure?*" Indeed, name reactions are not only the fruit of pioneering organic chemists, but also our contemporaries whose combined discoveries have resulted in organic chemistry today. Since publication of this book, Barry Sharpless and Ryoji Noyori, whose name reactions have been included since the first edition, went on to win the Nobel Prizes in 2001. Recently, Richard Schrock, Robert Grubbs, and Yves Chauvin shared the 2005 Nobel Prize in chemistry for their contributions to metathesis, a name reaction that has been also included since the first edition. Therefore, I intend to keep up with the new developments in the field of organic chemistry while retaining the collection of name reactions that have withheld test of time.

The third edition contains major improvements over the previous two editions. I have updated references. Each reaction is now supplemented with two to three representative examples in synthesis to showcase its synthetic utility. As Emil Fischer stated: "*Science is not an abstraction; but as a product of human endeavor it is inseparably bound up in its development with the personalities and fortunes of those who dedicate themselves to it.*" To that end, I added biographical sketches for most of the chemists who discovered or developed those name reactions. Furthemore, I have significantly beefed up the subject index to help the reader navigate the book more easily.

In preparing this manuscript, I have incurred many debts of gratitude to Prof. Reto Mueller of Switzerland, Prof. Robin Ferrier of New Zealand, and Prof. James M. Cook of the University of Wisconsin, Milwaukee; Dr. Yike Ni of California Institute of Technology, and Dr. Shengping Zheng of Columbia University for invaluable suggestions. I also wish to thank Dr. Gilles Chambournier, Prof. Phil S. Baran of Scripps Research Institute and his students, Narendra Ambhaikar, Ben Hafensteiner, Carlos Guerrero, and Dan O'Malley, Prof. Brian M. Stoltz of California Institute of Technology and his students, Kevin Allan, Daniel Caspi, David Ebner, Andrew Harned, Shyam Krishnan, Michael Krout, Qi Charles Liu, Sandy Ma, Justin Mohr, John Phillips, Jennifer Roizen, Brinton Seashore-Ludlow, Nathaniel Sherden, Jennifer Stockdill, and Carolyn Woodroofe 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.

I welcome your critique.

Jack Li
Ann Arbor, Michigan, March 2006

Table of Contents

Abbreviations and Acronyms

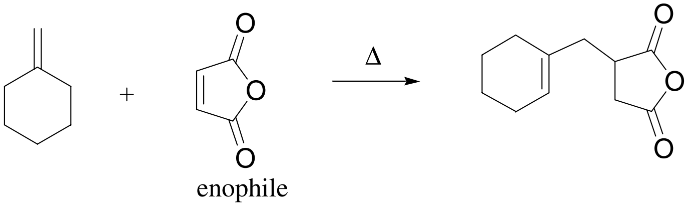
	polymer support
A	adenosine
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alpine-borane®	*B*-isopinocampheyl-9-borabicyclo[3.3.1]-nonane
Ar	aryl
B:	generic base
9-BBN	9-borabicyclo[3.3.1]nonane
[bimim]Cl•2AlCl$_3$	1-butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
t-Bu	*tert*-butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
m-CPBA	*m*-chloroperoxybenzoic acid
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
DEAD	diethyl azodicarboxylate
Δ	solvent heated under reflux
(DHQ)$_2$-PHAL	1,4-bis(9-*O*-dihydroquinine)-phthalazine
(DHQD)$_2$-PHAL	1,4-bis(9-*O*-dihydroquinidine)-phthalazine
DIAD	diisopropyl azodidicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane

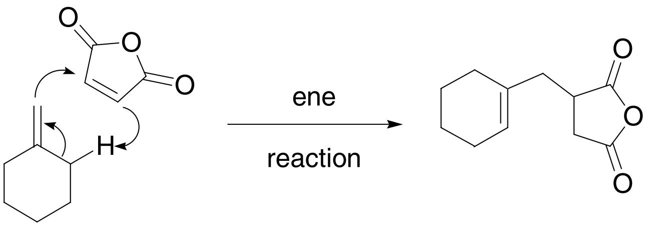
DTBAD	di-*tert*-butylazodicarbonate
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
E1	unimolecular elimination
E2	bimolecular elimination
E1cB	2-step, base-induced β-elimination *via* carbanion
EAN	ethylammonium nitrate
EDDA	ethylenediamine diacetate
ee	enantiomeric excess
Ei	two groups leave at about the 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
Imd	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
M	metal
Mes	mesityl
Ms	methanesulfonyl
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
Nos	nosylate (4-nitrobenzenesulfonyl)
Nu	nucleophile
N-PSP	*N*-phenylselenophthalimide
N-PSS	*N*-phenylselenosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	para-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium *p*-toluenesulfonate
$PyPh_2P$	diphenyl 2-pyridylphosphine
Pyr	pyridine
Red-Al	sodium bis(methoxy-ethoxy)aluminum hydride (SMEAH)
Salen	*N,N´*-disalicylidene-ethylenediamine
SET	single electron transfer
SM	starting material

SMEAH	sodium bis(methoxy-ethoxy)aluminum hydride (Red-Al)
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic substitution on an aromatic ring
TBABB	tetra-*n*-butylammonium bibenzoate
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEOC	trimethysilylethoxycarbonyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMG	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-*p*-tolylphosphino)-1,1'-binaphthyl
TosMIC	(*p*-tolylsulfonyl)methyl isocyanide
Ts	tosyl
TsO	tosylate
UHP	urea-hydrogen peroxide

Alder ene reaction

Addition of an enophile to an alkene *via* allylic transposition. Also known as hydroallyl addition.





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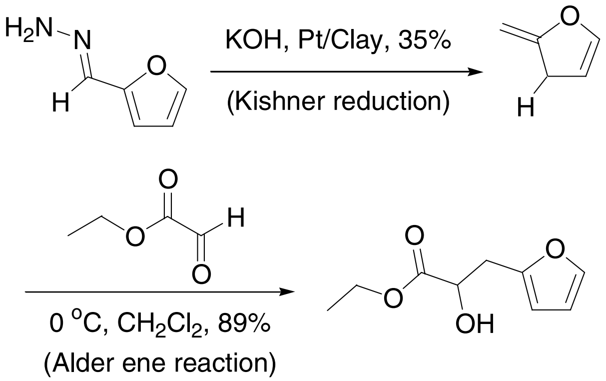

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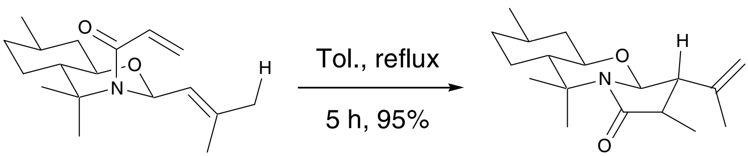

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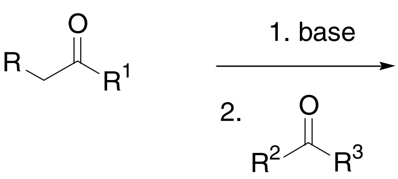
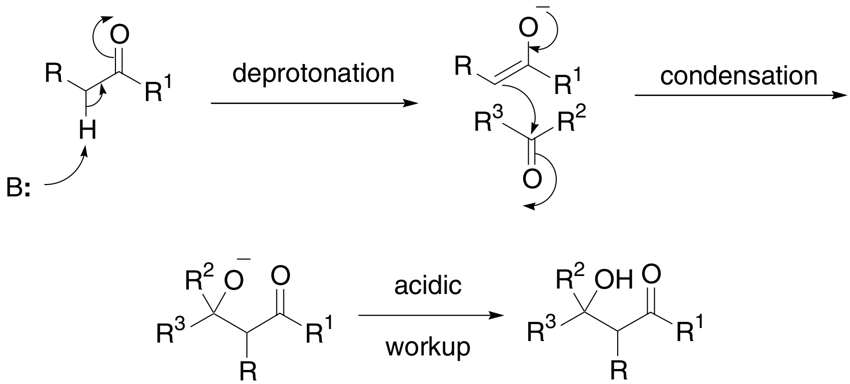
Aldol condensation

Condensation of a carbonyl with an enolate or an enol. A simple case is addition of an enolate to an **ald**ehyde to afford an alcoh**ol**, thus the name **aldol**.





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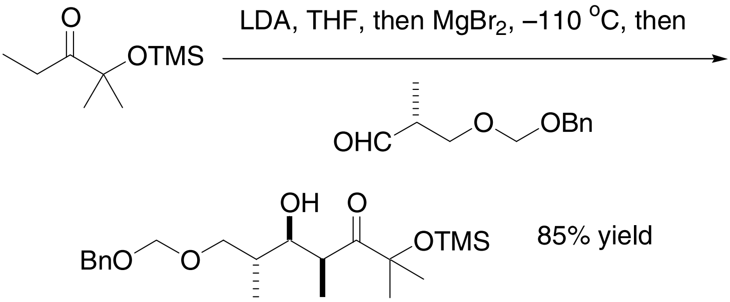

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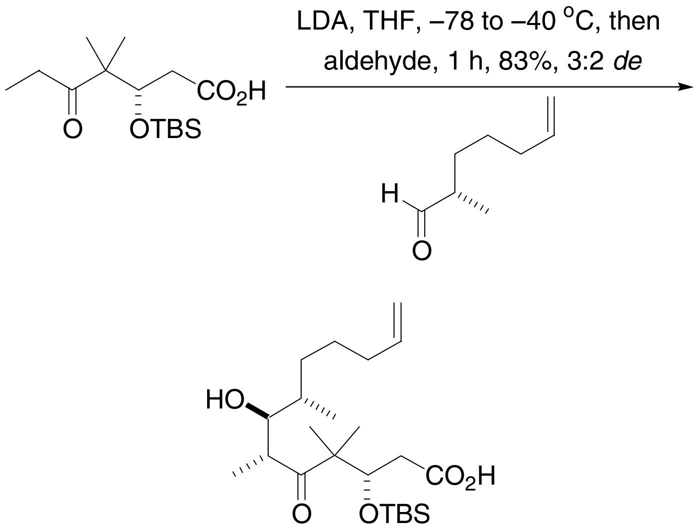

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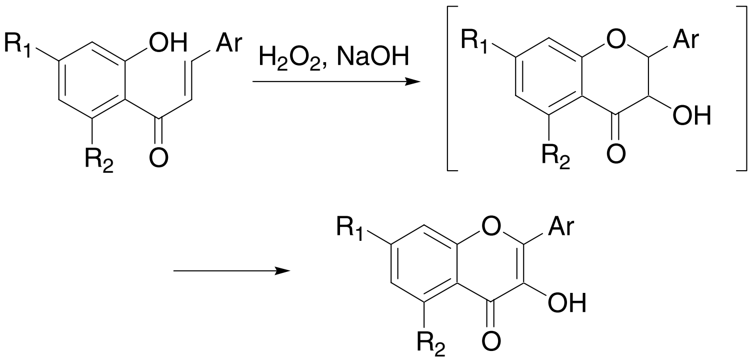
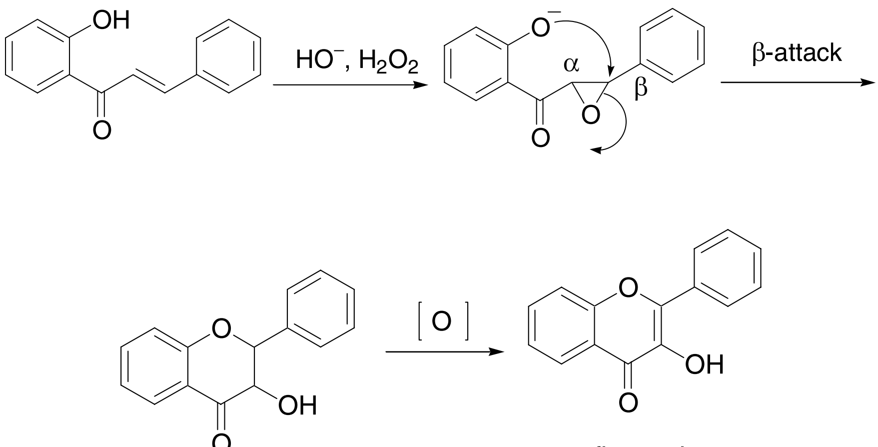
Algar–Flynn–Oyamada Reaction

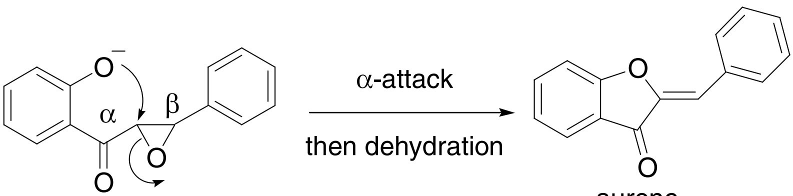
Conversion of 2'-hydroxychalcones to 2-aryl-3-hydroxy-4*H*-1benzopyran-4-ones (flavonols) by alkaline hydrogen peroxide oxidation.





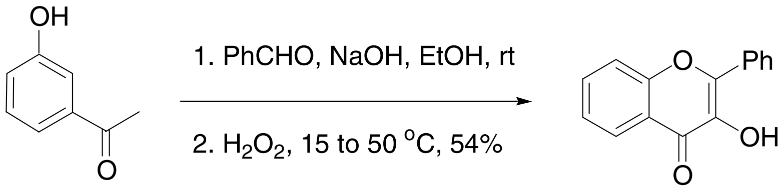
flavonol

A side reaction:



aurone

Example 1[5]



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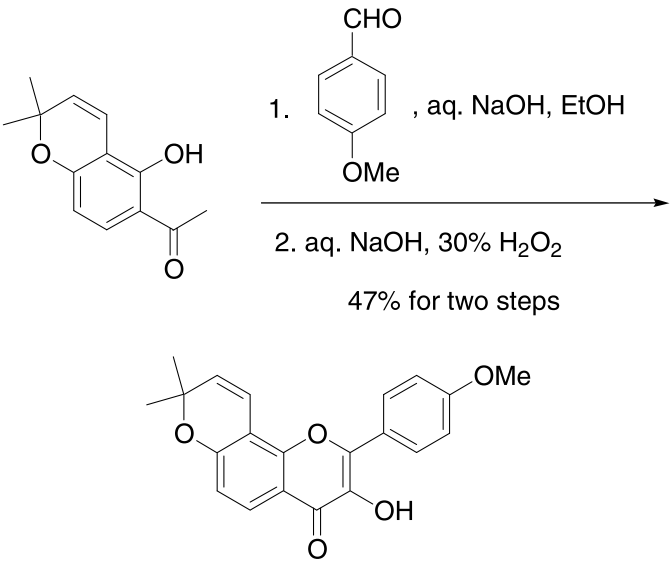

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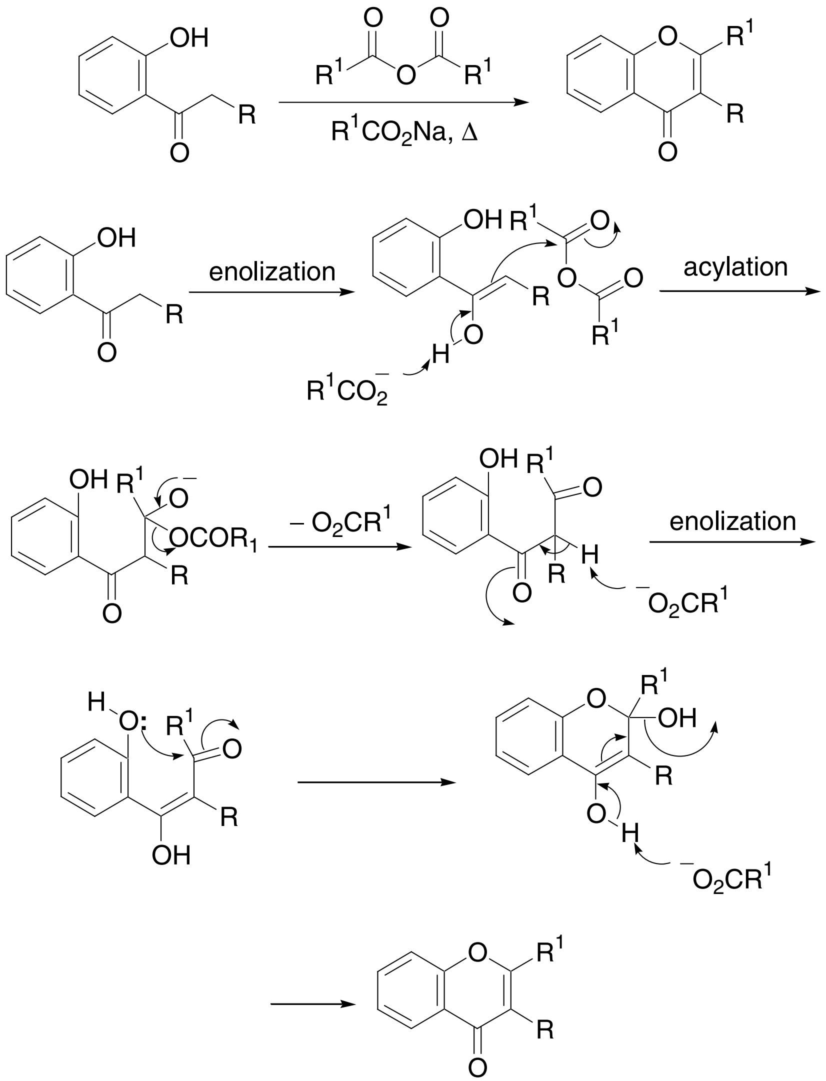
Allan–Robinson reaction

Synthesis of flavones or isoflavones.



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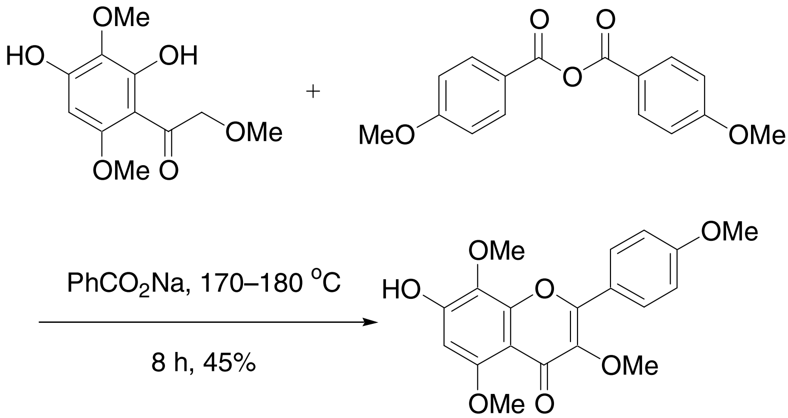

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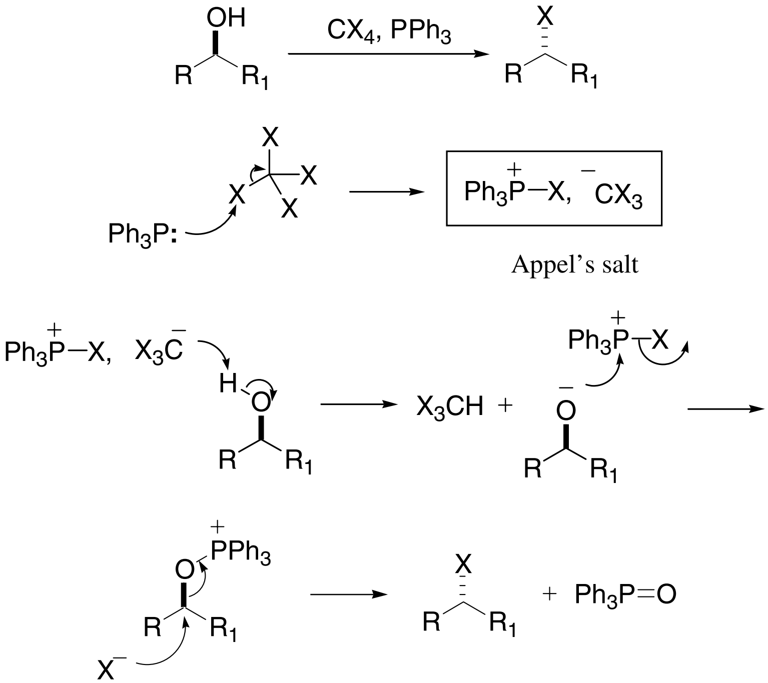
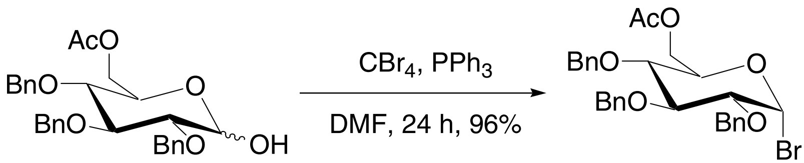
Appel reaction

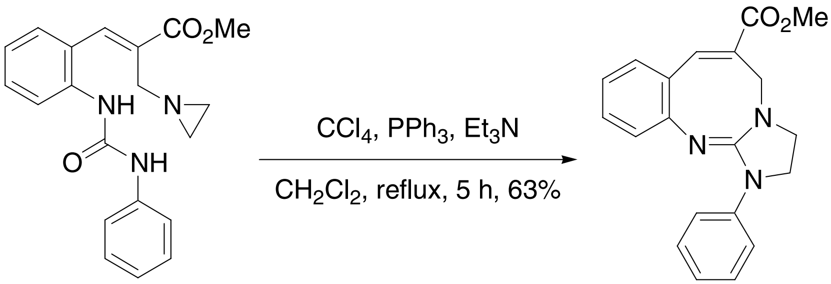
The reaction between triphenylphosphine and tetrahalomethane (CCl_4, CBr_4) forms a salt known as Appel's salt. Treatment of alcohols with Appel's salt gives rise to the corresponding halides.



Example 1[7]



Example 2, Appel's salt is often used as a dehydrating agent[8]



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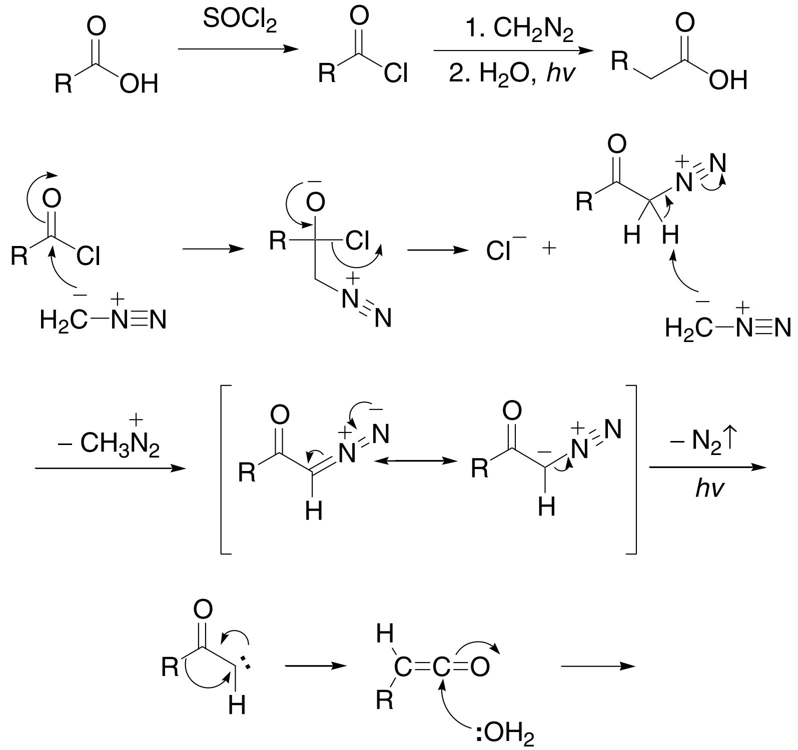
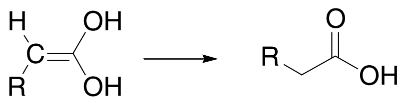
Arndt–Eistert homologation

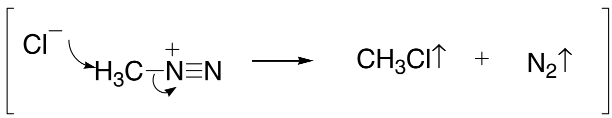
One carbon homologation of carboxylic acids using diazomethane.



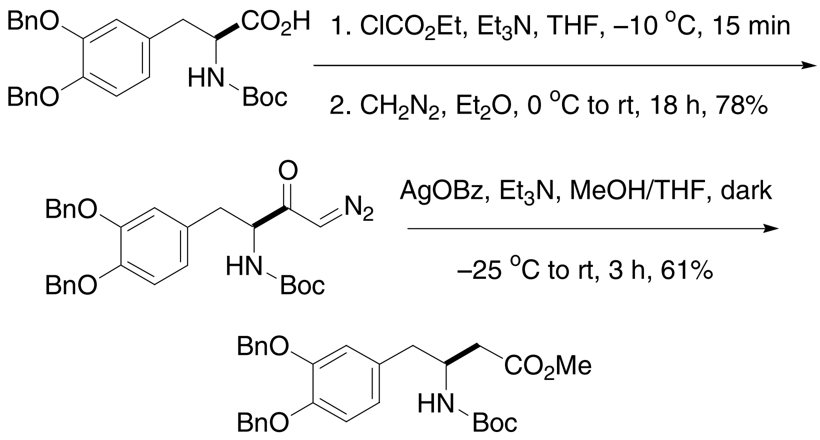
α-ketocarbene intermediate ketene intermediate



side reaction:



Example 1[10]



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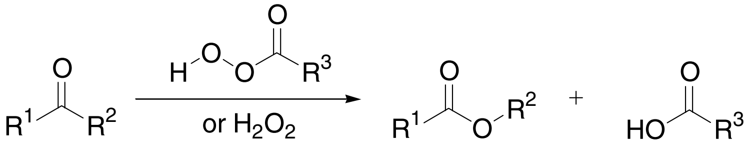
Baeyer–Villiger oxidation

General scheme:



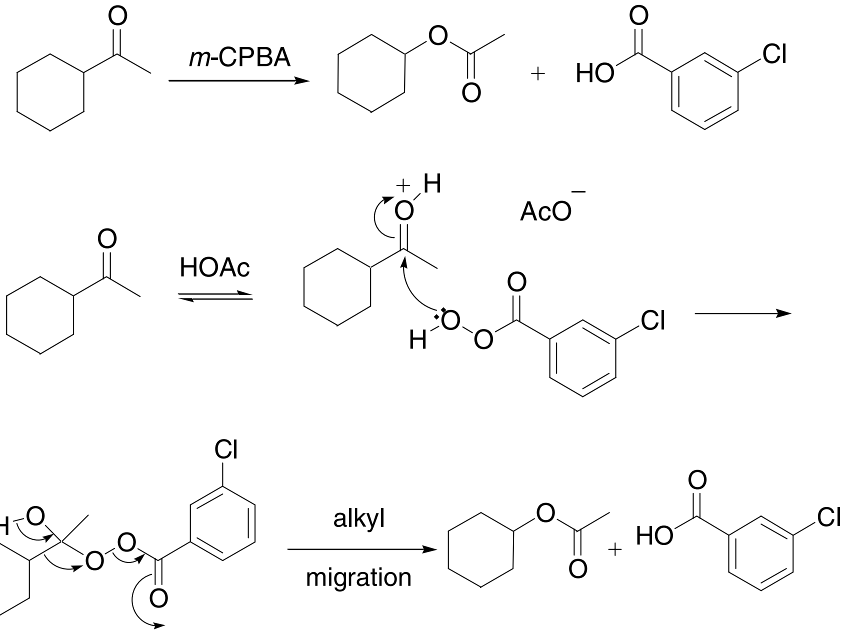
The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order:

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

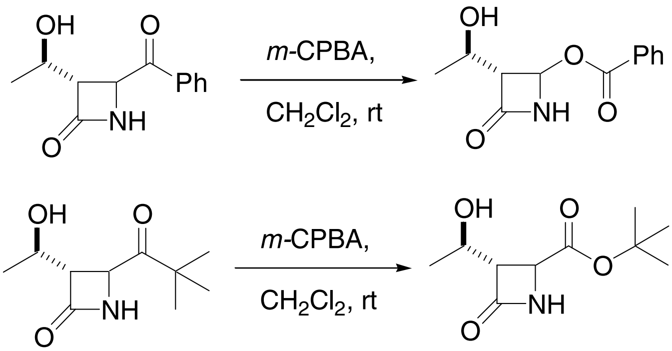
For substituted aryls:

p-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O_2N-Ar

Example 1:



Example 2[10]



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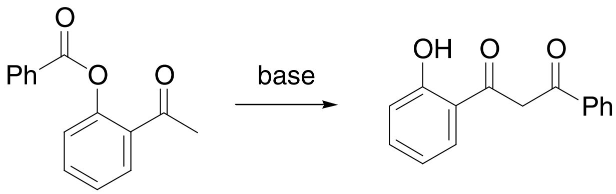
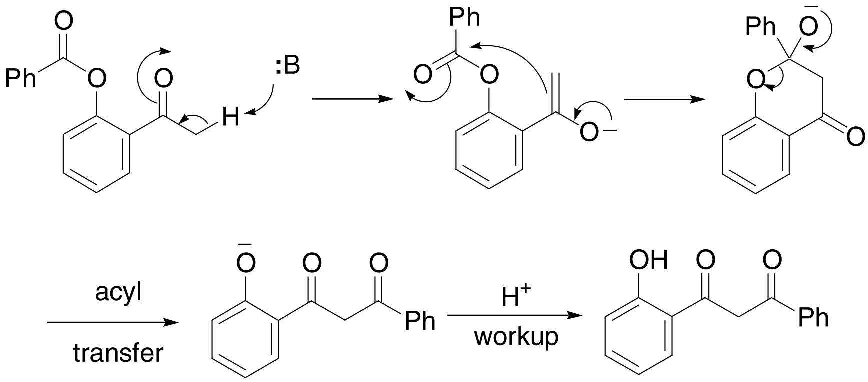
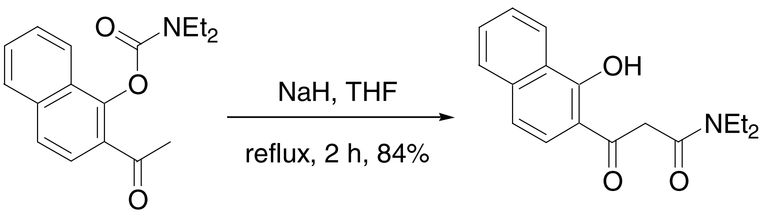
Baker–Venkataraman rearrangement

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

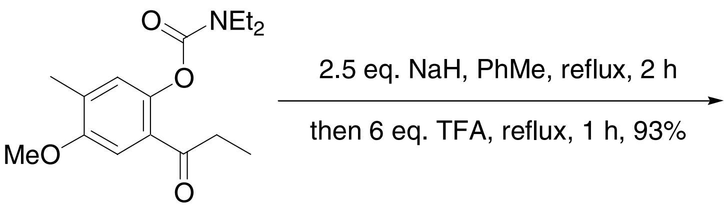


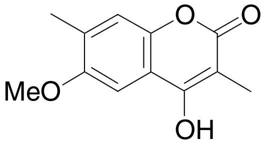


Example 1[7]



Example 2[8]





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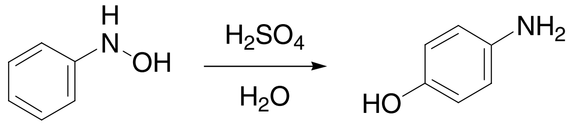
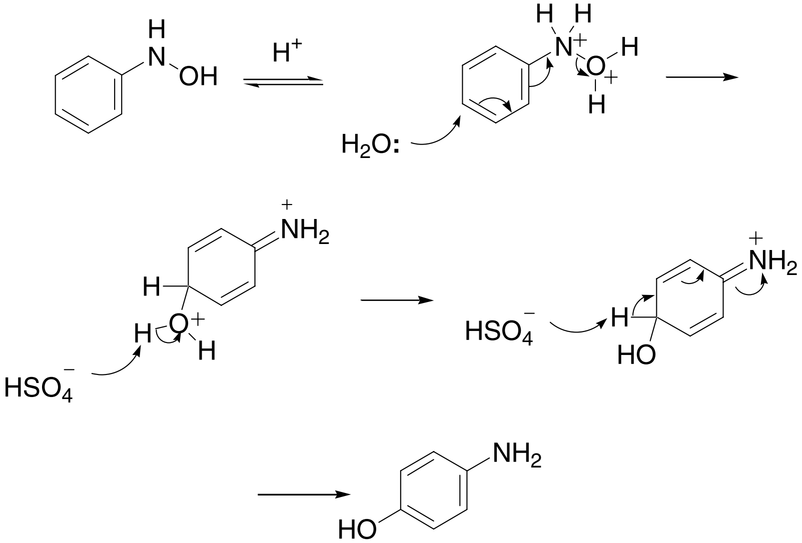
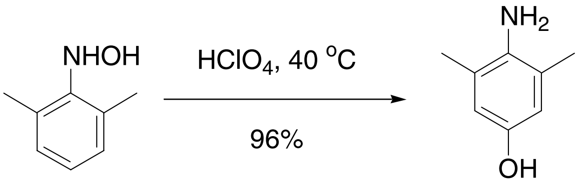
Bamberger rearrangement

Acid-mediated rearrangement of *N*-phenylhydroxylamines to 4-aminophenols.





Example 1[5]



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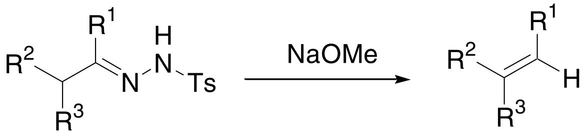
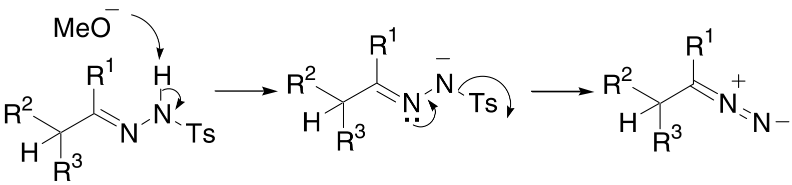
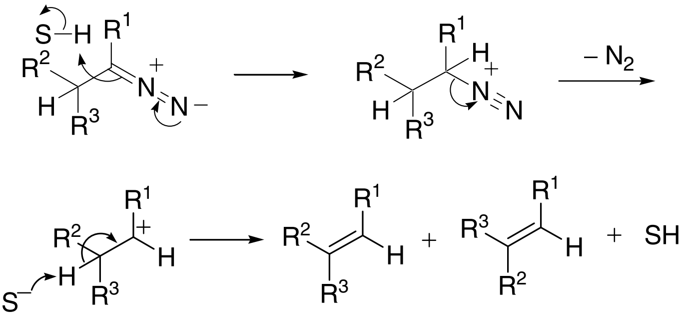
Bamford–Stevens reaction

The Bamford−Stevens reaction and the Shapiro reaction share a similar mechanistic pathway. The former uses a base such as Na, NaOMe, LiH, NaH, $NaNH_2$, 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.

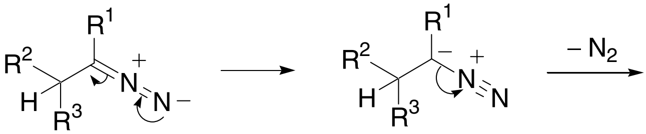


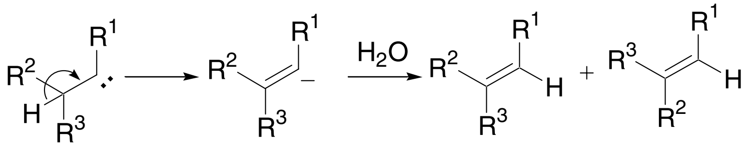


In protic solvent:

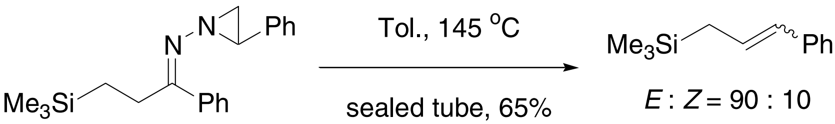


In aprotic solvent:

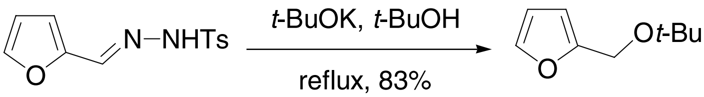




Example 1, thermal Bamford–Stevens[5]



Example 2[9]



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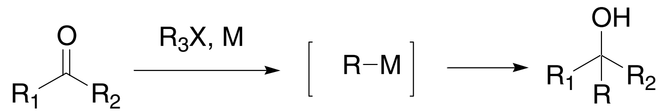
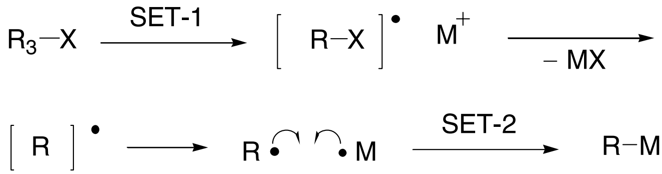
Barbier coupling reaction

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.

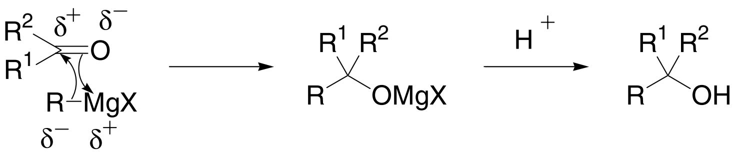


According to conventional wisdom,[3] the organometallic intermediate (M = Mg, Li, Sm, Zn, La, *etc.*) is generated *in situ*, which is intermediately trapped by the carbonyl compound. However, recent experimental and theoretical studies seem to suggest that the Barbier coupling reaction goes through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

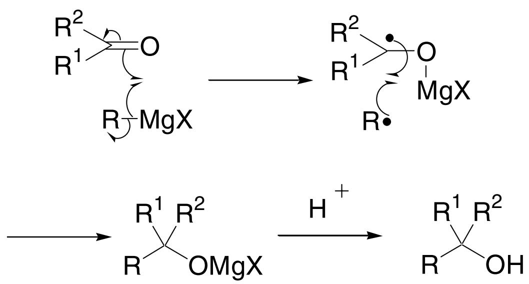
Generation of the Grignard reagent,



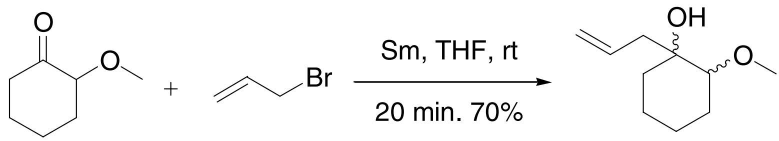
Ionic mechanism,



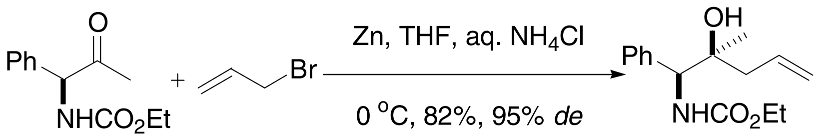
Single electron transfer mechanism,



Example 1[8]



Example 2[11]



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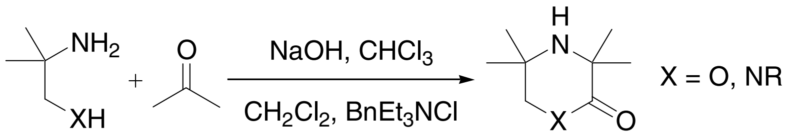
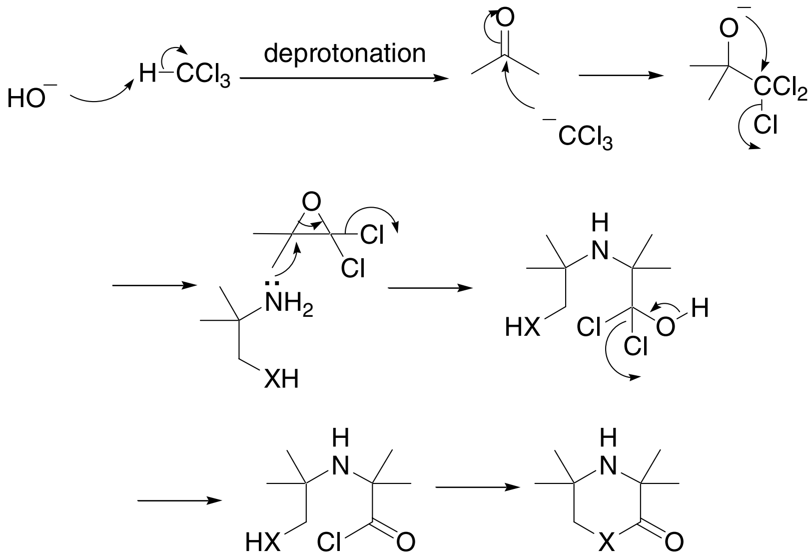
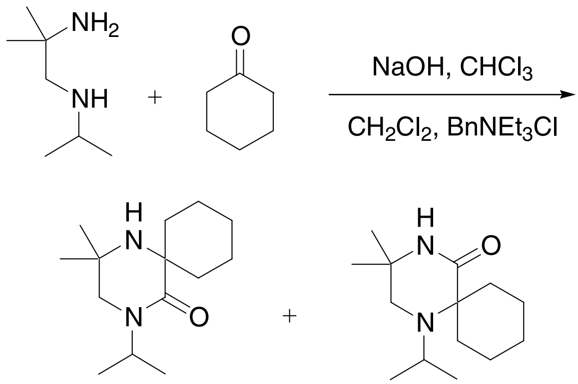
Bargellini reaction

Synthesis of hindered morpholinones or piperazinones from ketones (such as acetone) and 2-amino-2-methyl-1-propanol or 1,2-diaminopropanes.



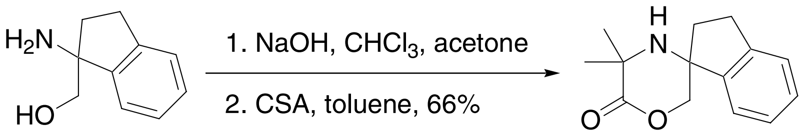


Example 1[2]



67% 15%

Example 2[6]



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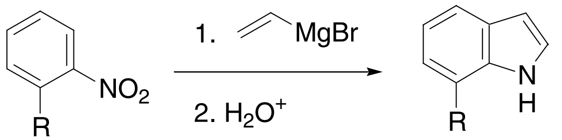
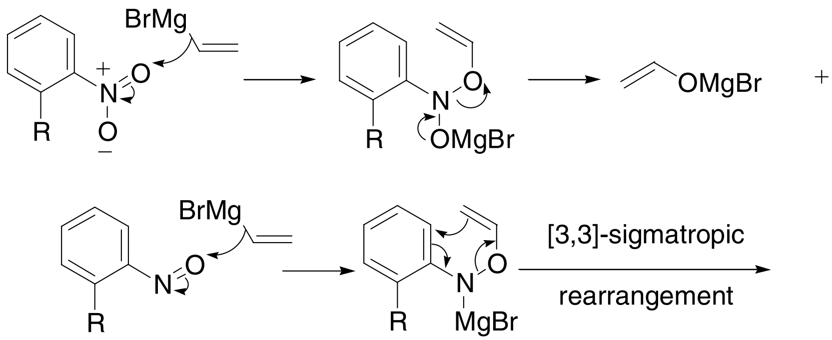
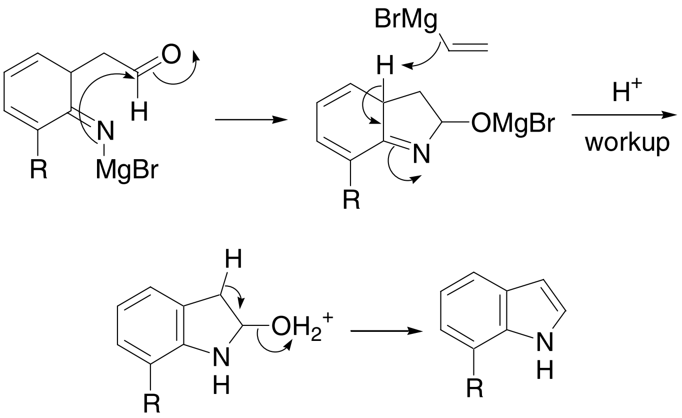
Bartoli indole synthesis

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

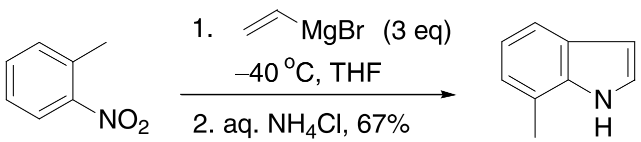




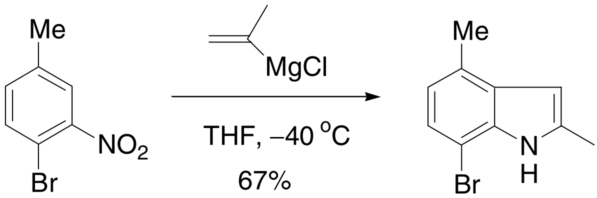
nitroso intermediate



Example 1[3]



Example 2[8]



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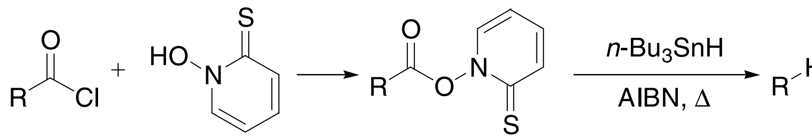
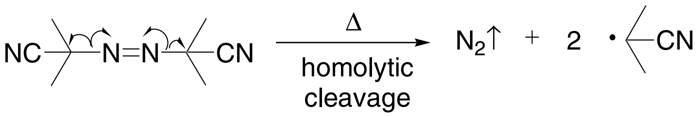
Barton radical decarboxylation

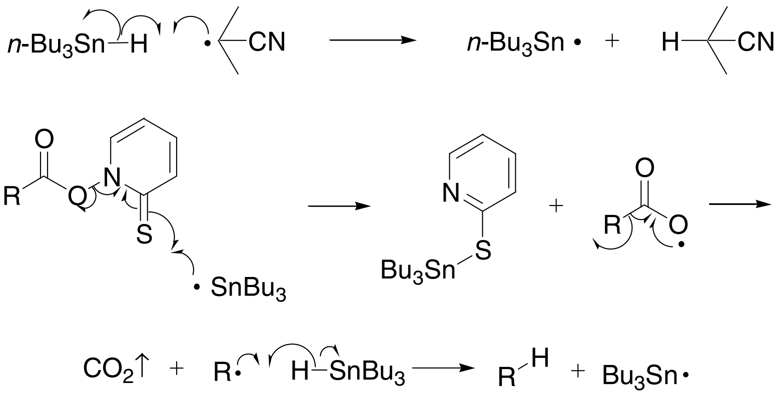
Radical decarboxylation *via* the corresponding thiocarbonyl derivatives of the carboxylic acids.



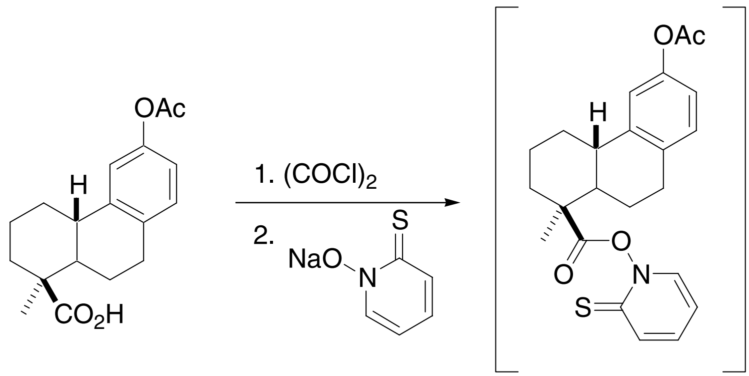
Barton ester

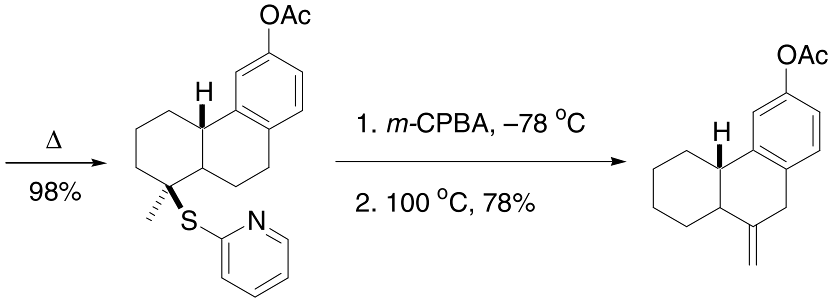


2,2'-azobisisobutyronitrile (AIBN)

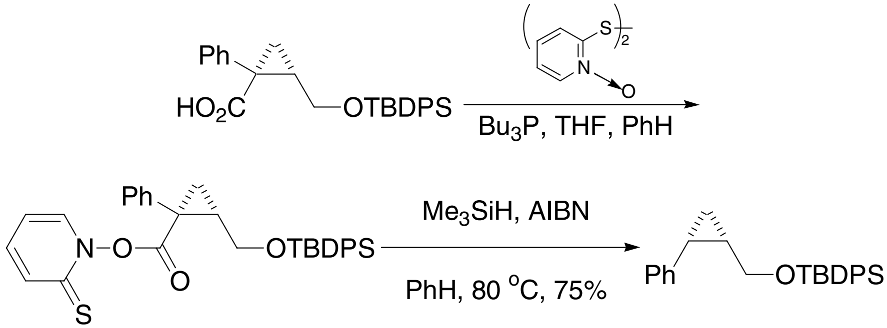


Example 1[3]





Example 2[11]



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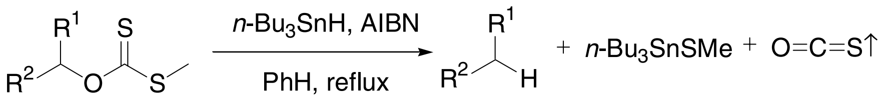
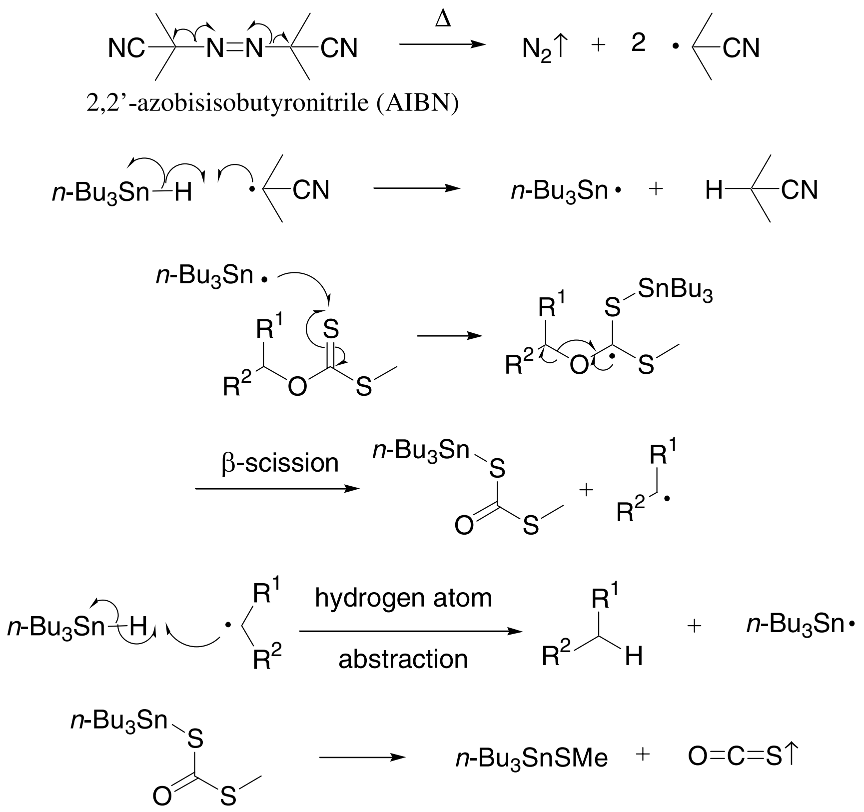
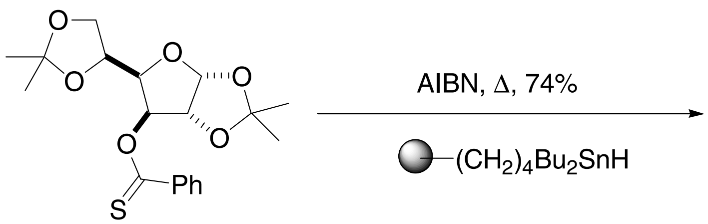
Barton–McCombie deoxygenation

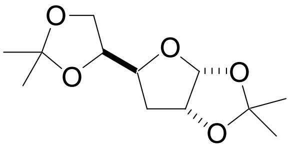
Deoxygenation of alcohols by means of radical scission of their corresponding thiocarbonyl derivatives.



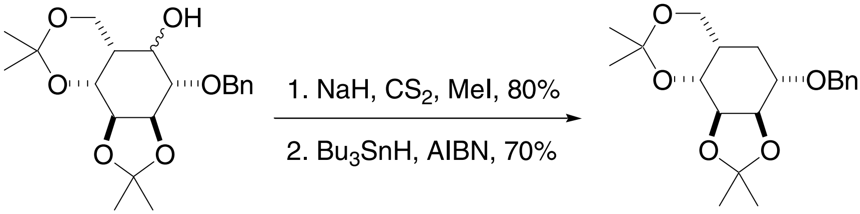


Example 1[5]





Example 2[9]



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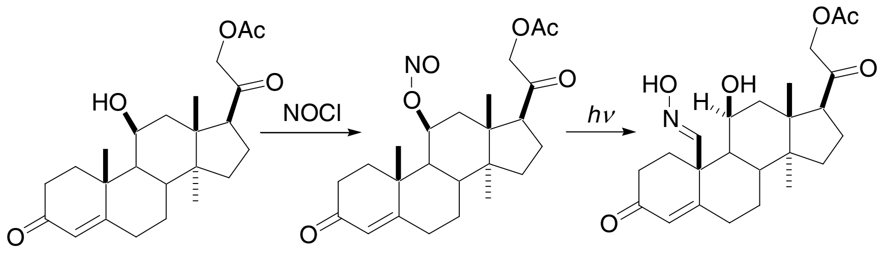
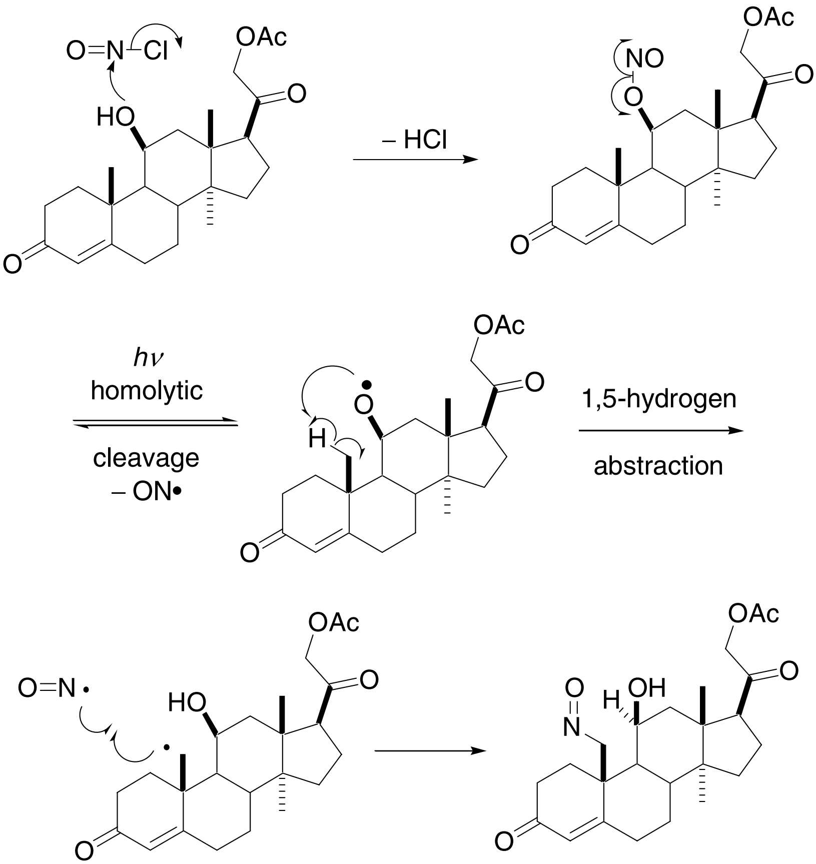
Barton nitrite photolysis

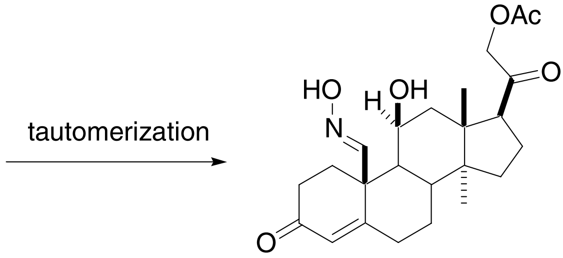
Photolysis of a nitrite ester to a γ-oximino alcohol.



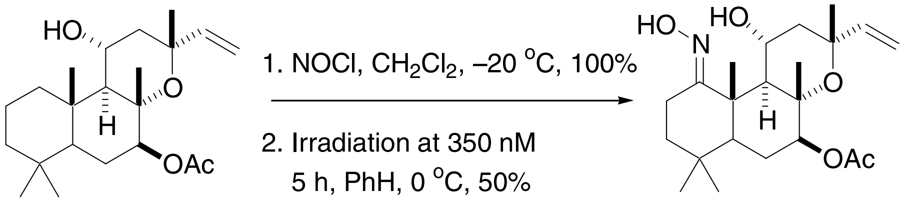


Nitric oxide radical is a stable, and therefore, long-lived radical

nitroso intermediate



Example[11]



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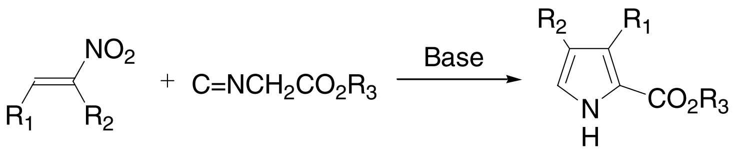
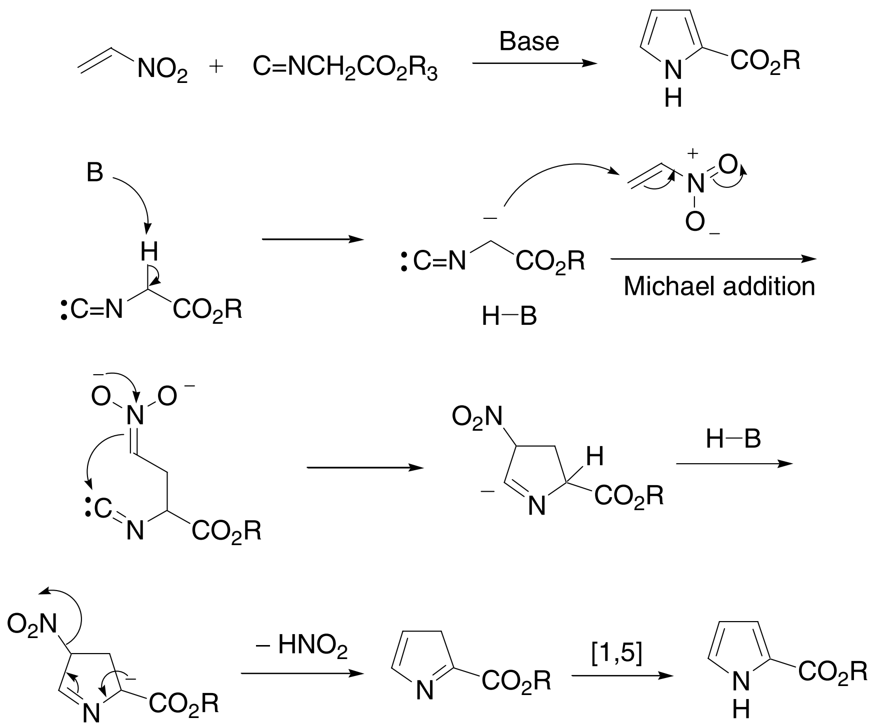
Barton–Zard reaction

Base-induced reaction of nitroalkenes with alkyl α-isocyanoacetates to afford pyrroles.

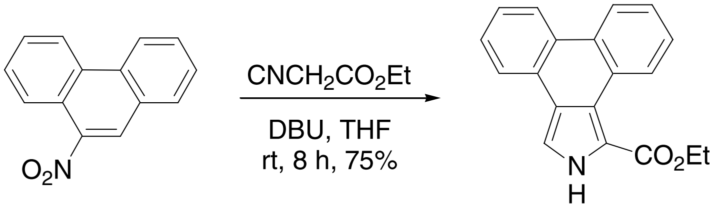


R_1 = H, alkyl, aryl
R_2 = H, alkyl
R_3 = Me, Et, *t*-Bu
Base = KO*t*-Bu, DBU, guanidine bases

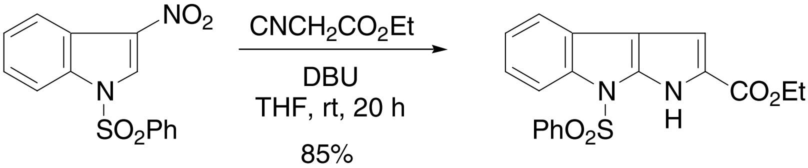
Example 1



Example 2[5]



Example 3[7]



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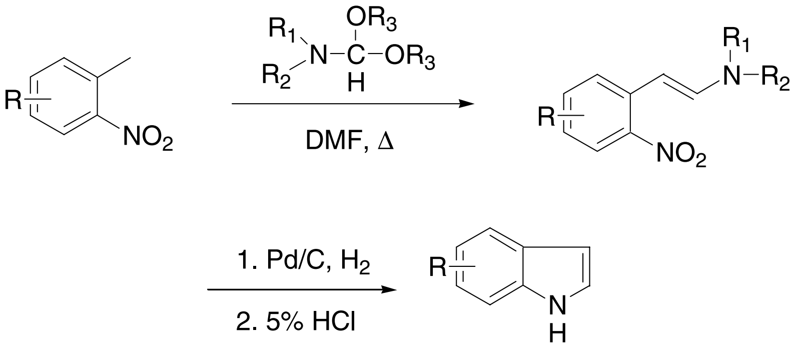
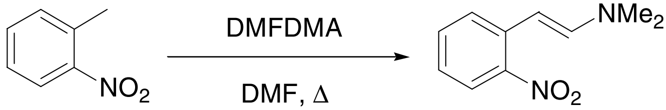
Batcho–Leimgruber indole synthesis

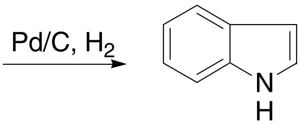
Condensation of *o*-nitrotoluene derivatives with formamide acetals, followed by reduction of the *trans*-β-dimethylamino-2-nitrostyrene to furnish indole derivatives.

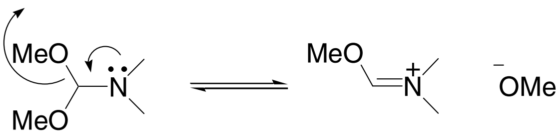


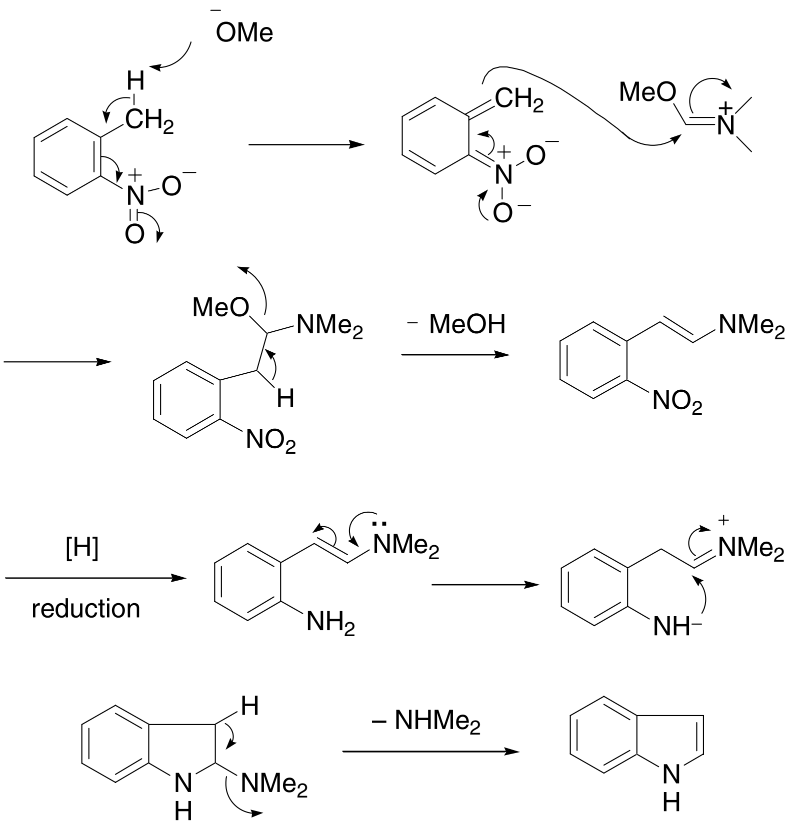
Example 1



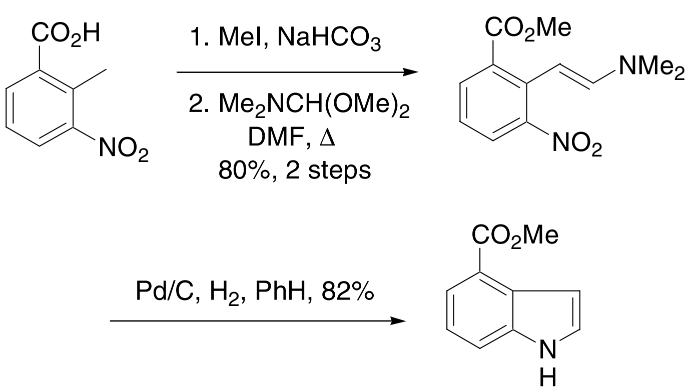
DMFDMA = *N,N*-dimethylformamide dimethyl acetal, $Me_2NCH(OMe)_2$



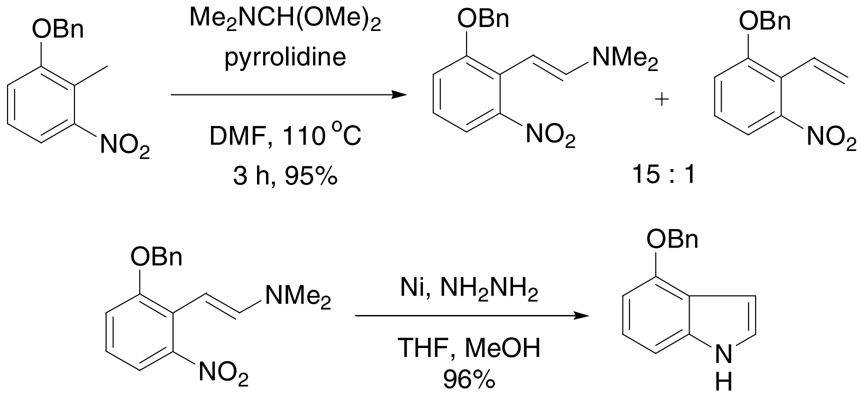



OMe
MeO
− MeOH
[H]
reduction
− NHMe2

Example 2[5]


1. MeI, NaHCO3
2. Me2NCH(OMe)2
DMF, Δ
80%, 2 steps
Pd/C, H2, PhH, 82%

Example 3[14]



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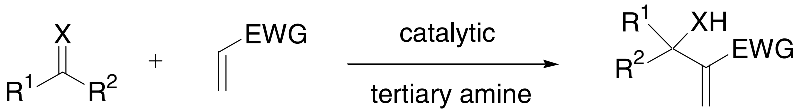
Baylis–Hillman reaction

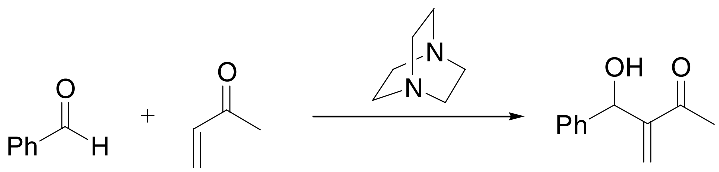
Also known as Morita–Baylis–Hillman reaction, and occasionally known as Rauhut–Currier reaction. It is a carbon–carbon bond-forming transformation of an electron-poor alkene with a carbon electrophile. Electron-poor alkenes include acrylic esters, acrylonitriles, vinyl ketones, vinyl sulfones, and acroleins.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

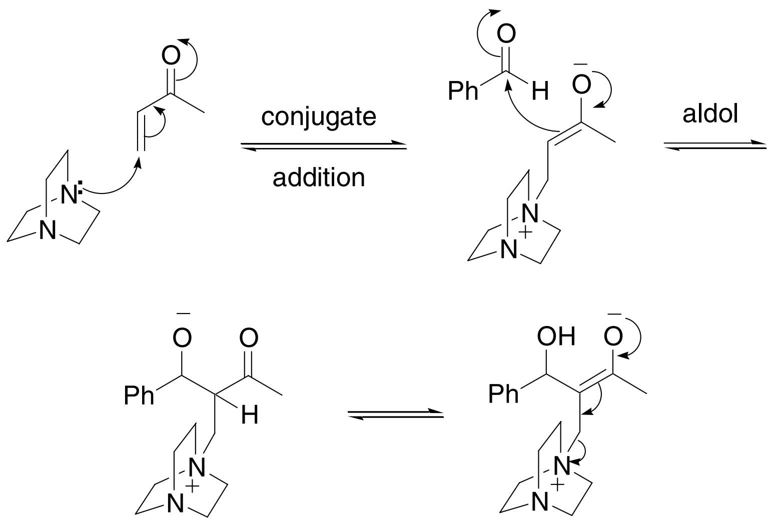
General scheme:

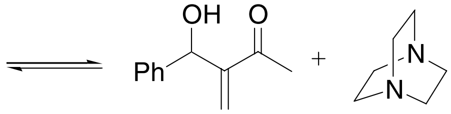


X = O, NR_2, EWG = CO_2R, COR, CHO, CN, SO_2R, SO_3R, $PO(OEt)_2$, $CONR_2$, $CH_2{=}CHCO_2Me$

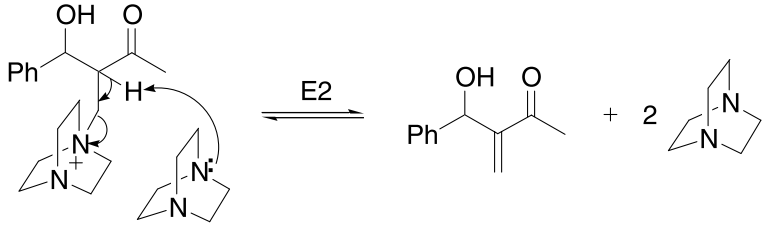
Example 1:



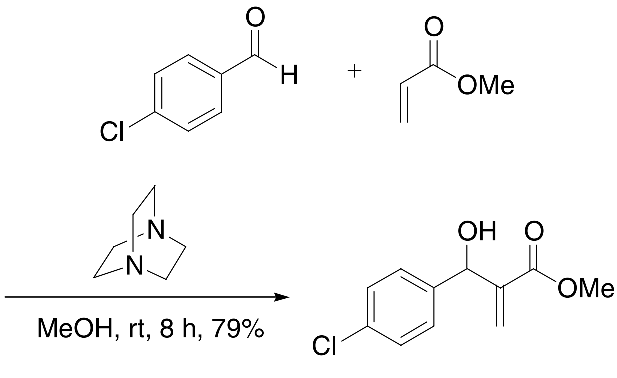




E2 (bimolecular elimination) mechanism is also operative here:



Example 2[10]



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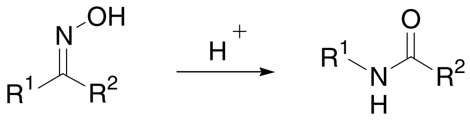
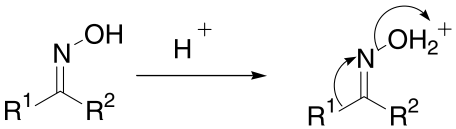
Beckmann rearrangement

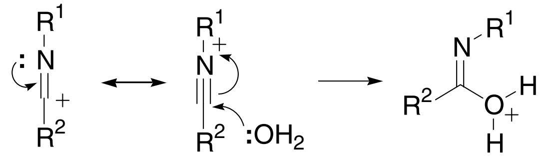
Acid-mediated isomerization of oximes to amides.

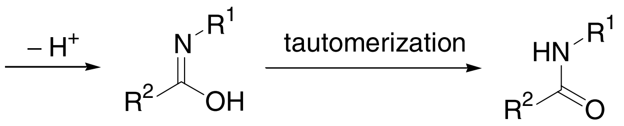
In protic acid:



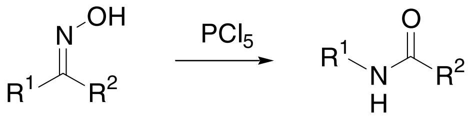


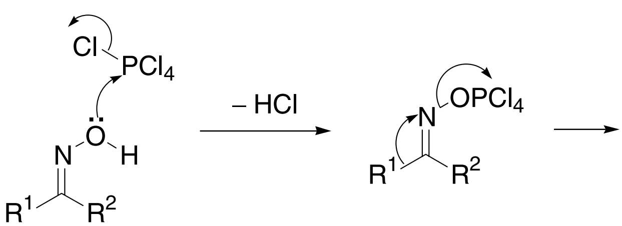
the substituent *trans* to the leaving group migrates



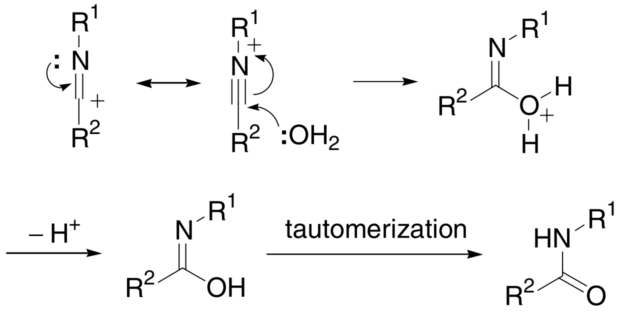


With PCl_5:

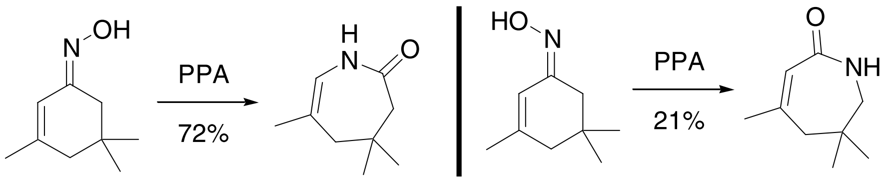




the substituent *trans* to the leaving group migrates



Example 1[12]



PPA = **p**oly**p**hosphoric **a**cid

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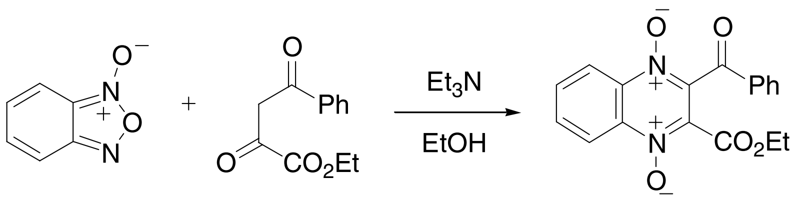
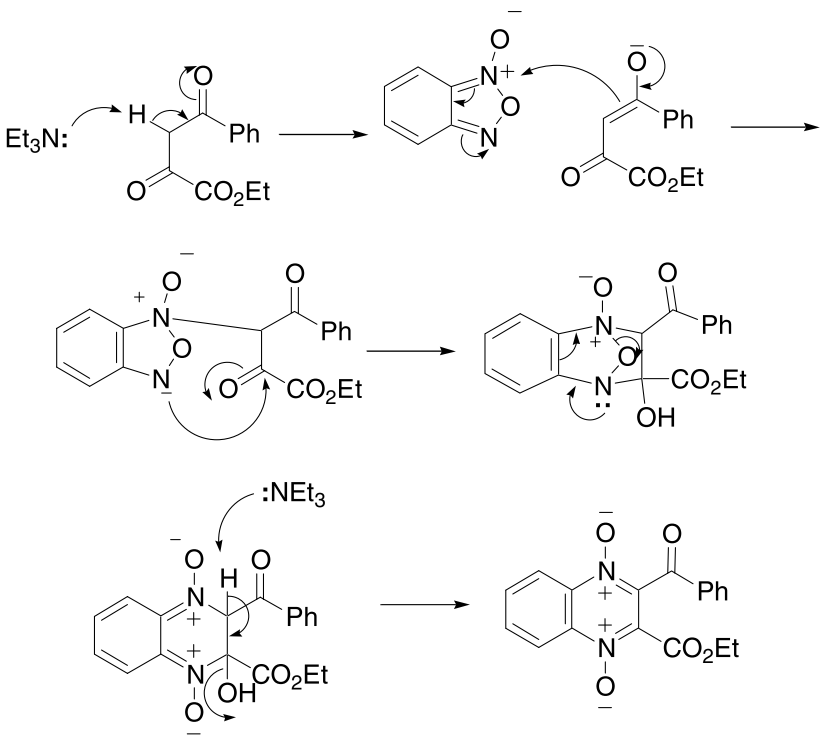
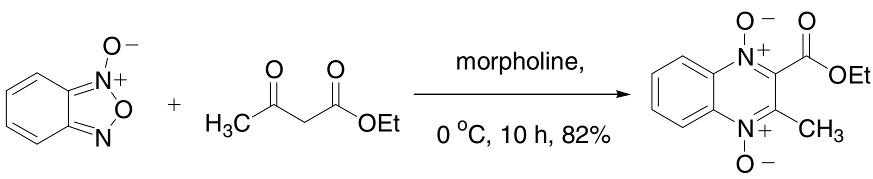
Beirut reaction

Synthesis of quinoxaline-1,4-dioxides from benzofurazan oxide.

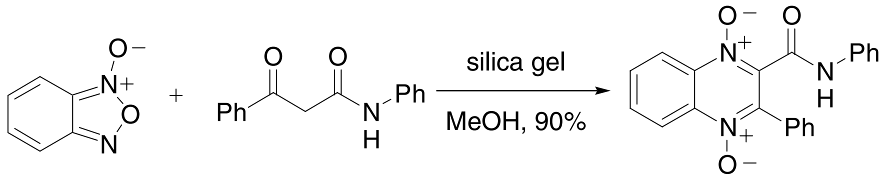




Example 1[3]



Example 2[7]



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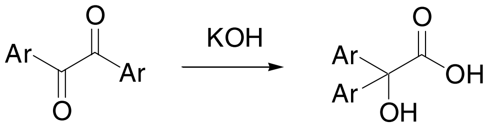
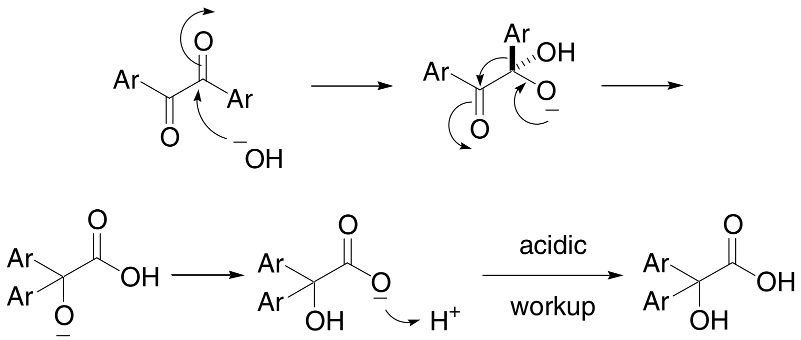
Benzilic acid rearrangement

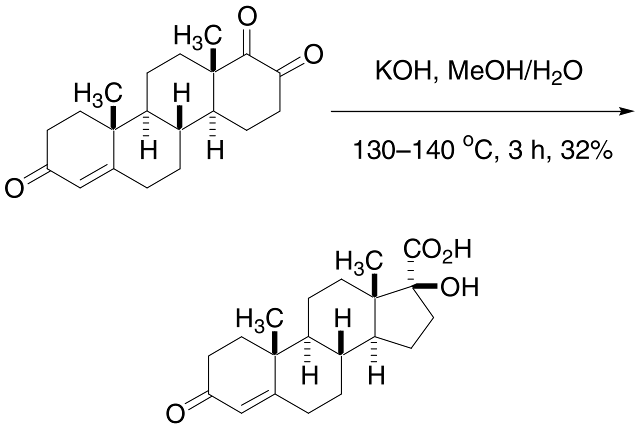
Rearrangement of benzil to benzylic acid *via* aryl migration.





Final deprotonation of the carboxylic acid drives the reaction forward.

Example 1[3]



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Liebig would soon transform Giessen from a sleepy university to the Mecca of organic chemistry in Europe. Liebig is now considered the father of organic chemistry. Many classic name reactions were published in the journal that still bears his name, *Justus Liebigs Annalen der Chemie.*[2]
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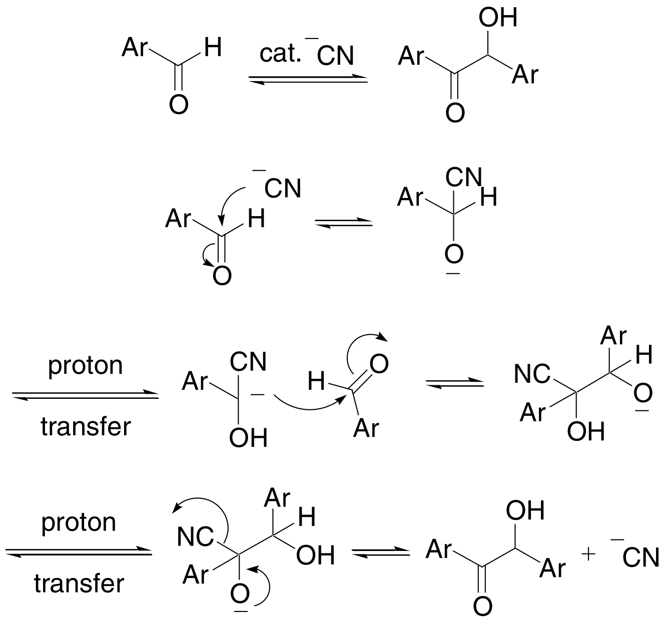
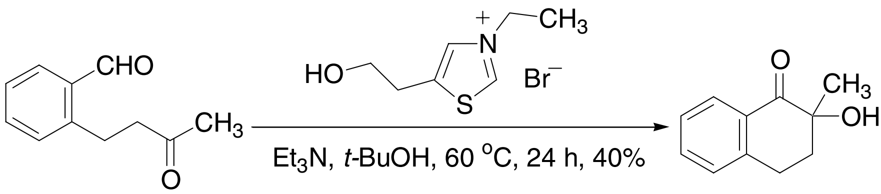
Benzoin condensation

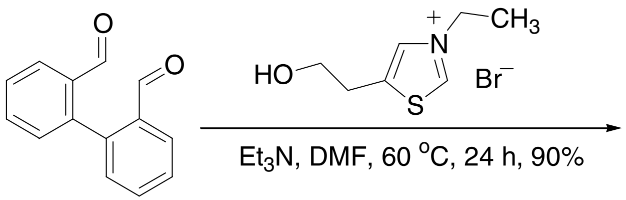
Cyanide-catalyzed condensation of aryl aldehyde to benzoin. Now cyanide is mostly replaced by a thiazolium salt. *Cf.* Stetter reaction.

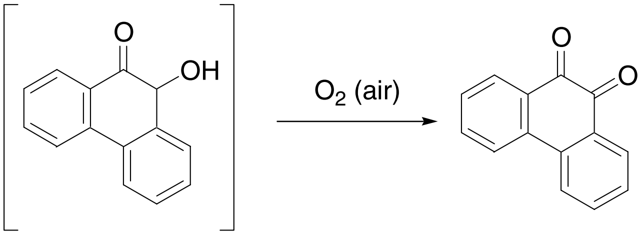


Example 1[11]



Example 2[11]





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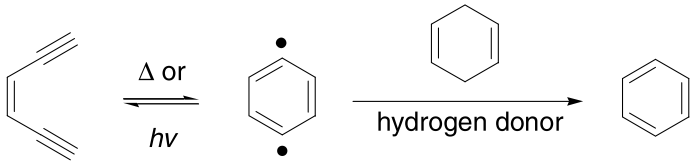
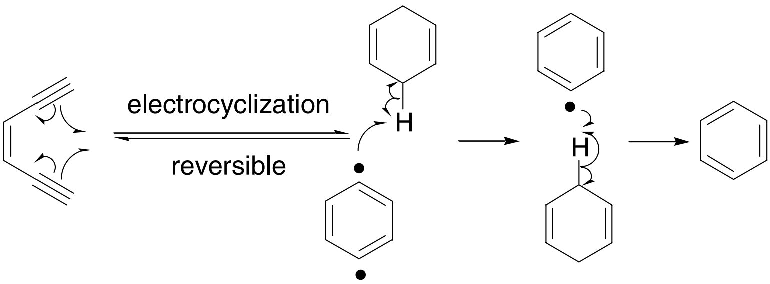
Bergman cyclization

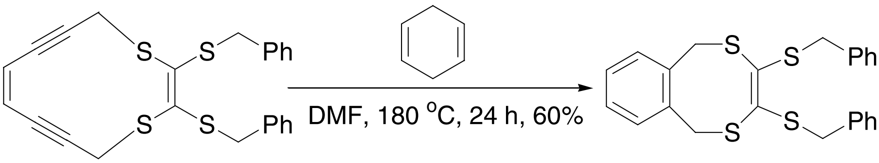
1,4-Benzenediyl diradical formation from enediyne *via* electrocyclization.



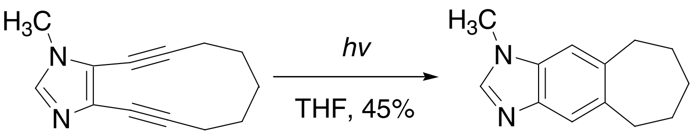


enediyne 1,4-benzenediyl diradical

Example 1[14]



Example 2[15]



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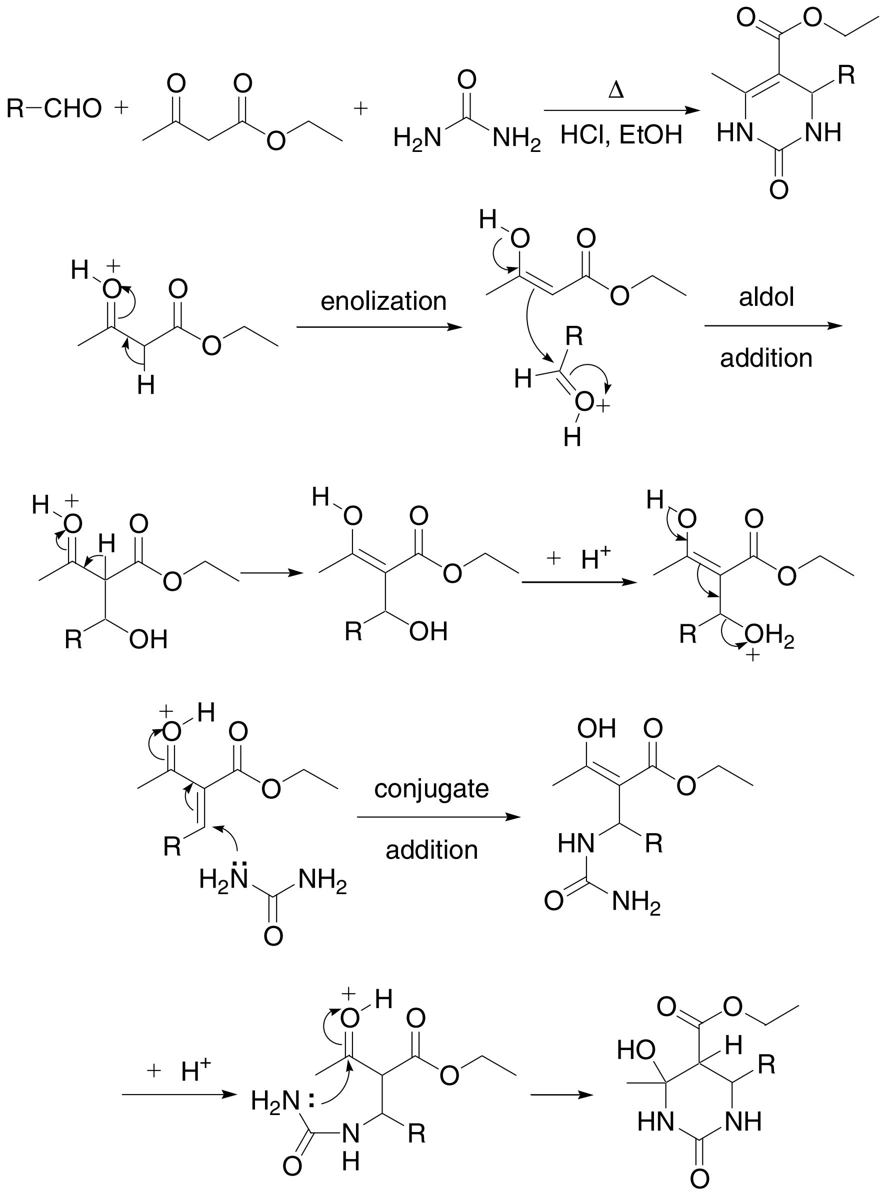
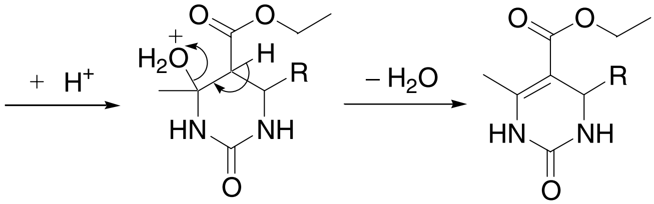
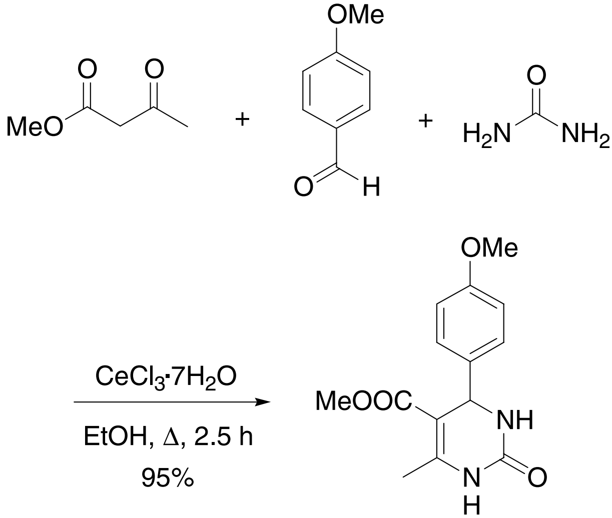
Biginelli pyrimidone synthesis

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





Example[9]



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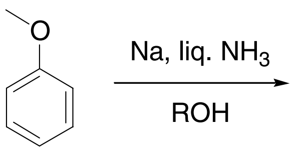
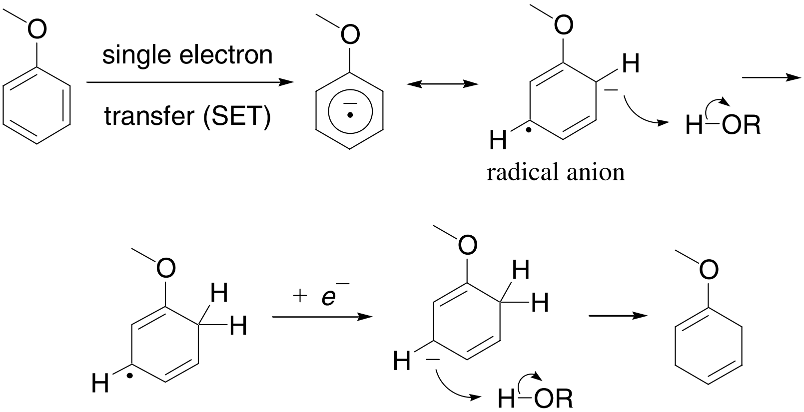
Birch reduction

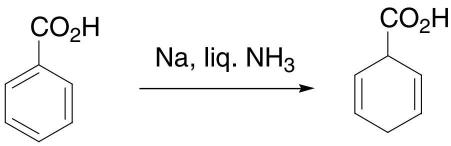
The Birch reduction is the 1,4-reduction of aromatics to their corresponding cyclohexadienes by alkali metals (Li, K, Na) dissolved in liquid ammonia in the presence of an alcohol.

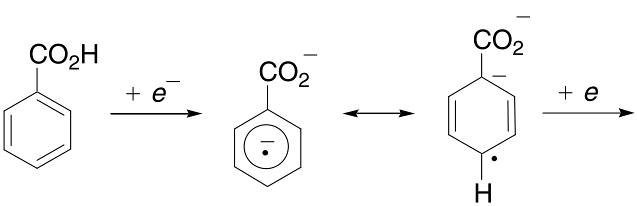
Benzene ring bearing an electron-donating substituent:



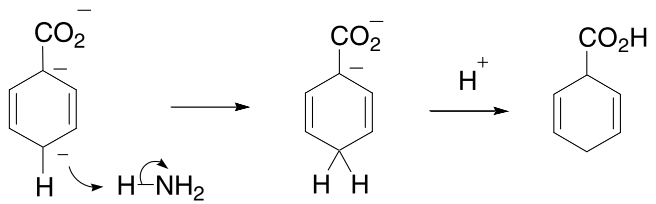


Benzene ring with an electron-withdrawing substituent:

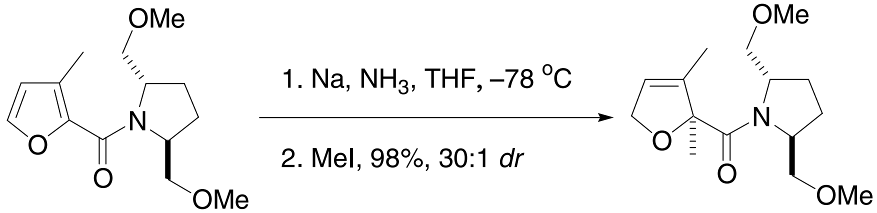




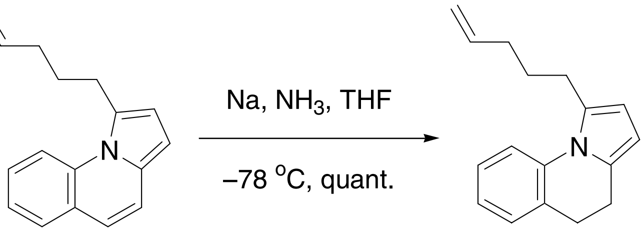
radical anion



Example 1[8]



Example 2[14]



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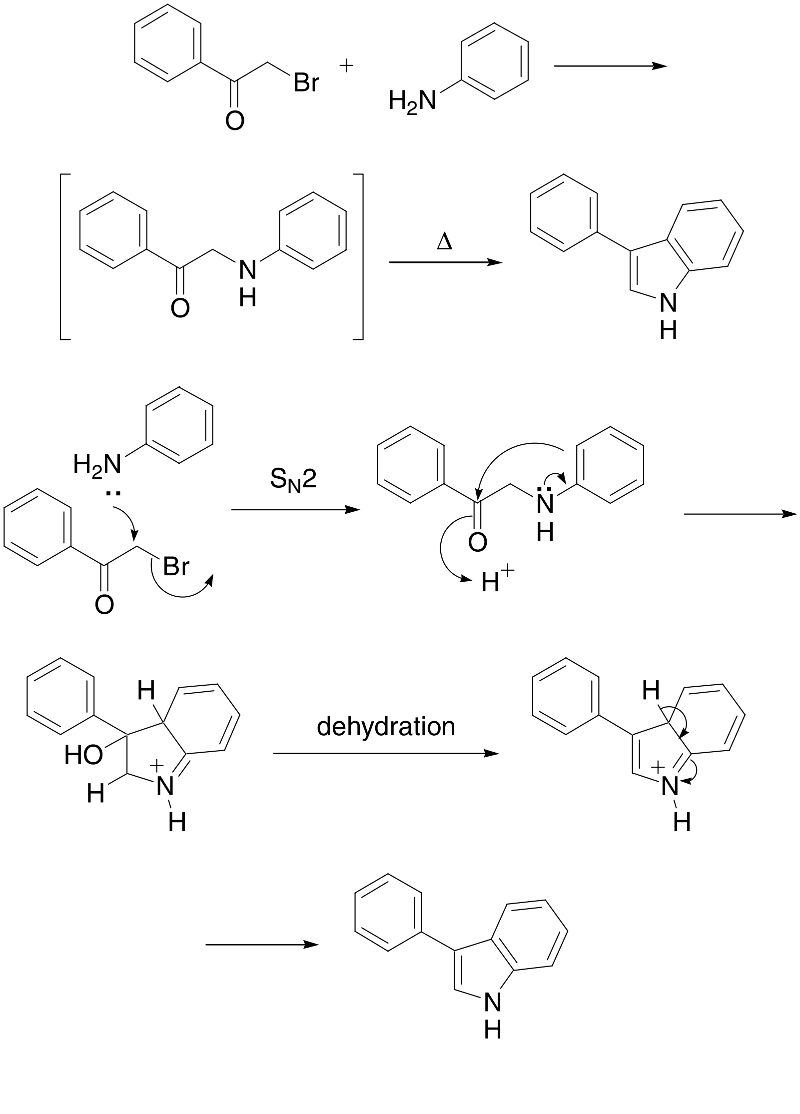
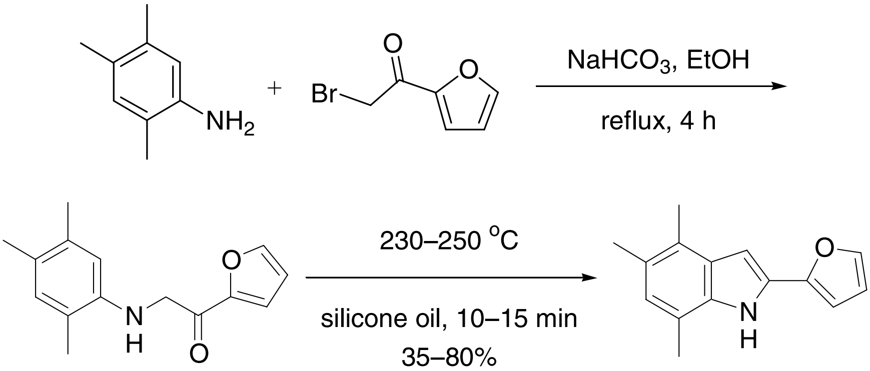
Bischler–Möhlau indole synthesis

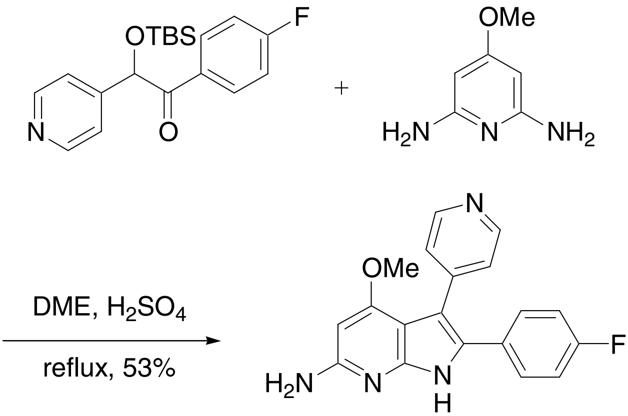
3-Arylindoles from the cyclization of ω-arylamino-ketones and anilines.



Example 1[5]



Example 2[9]



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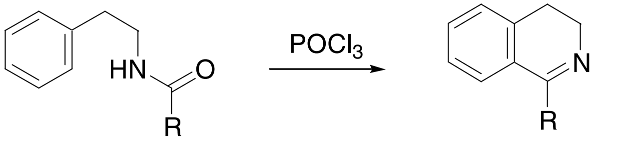
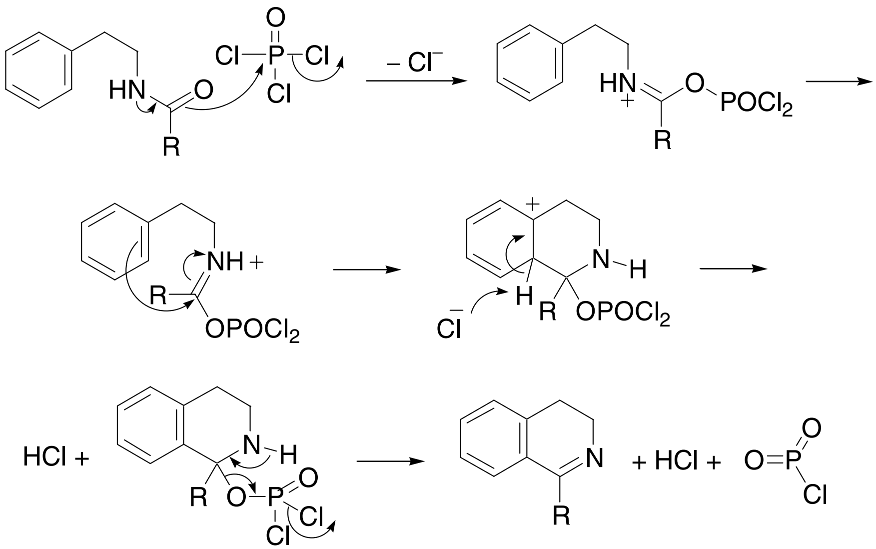
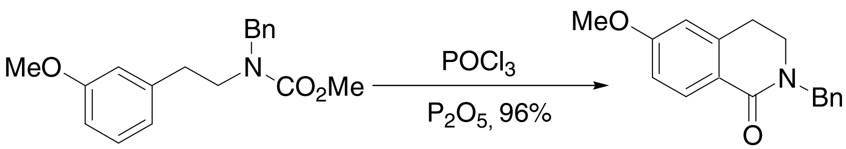
Bischler–Napieralski reaction

Dihydroisoquinolines from β-phenethylamides using phosphorus oxychloride.

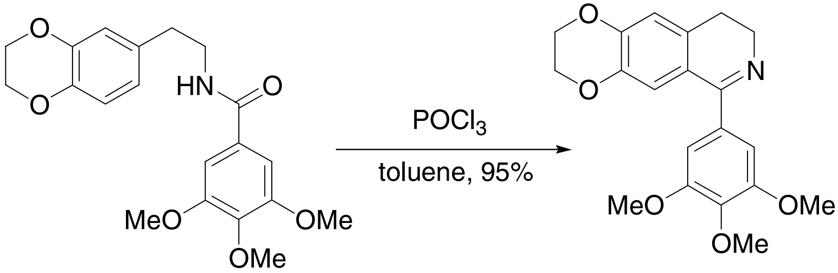




Example 1[6]



Example 2[10]



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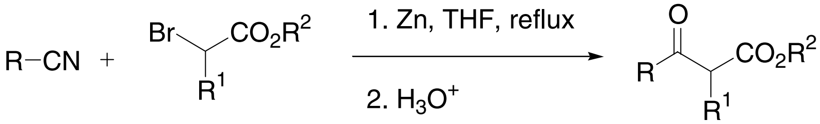
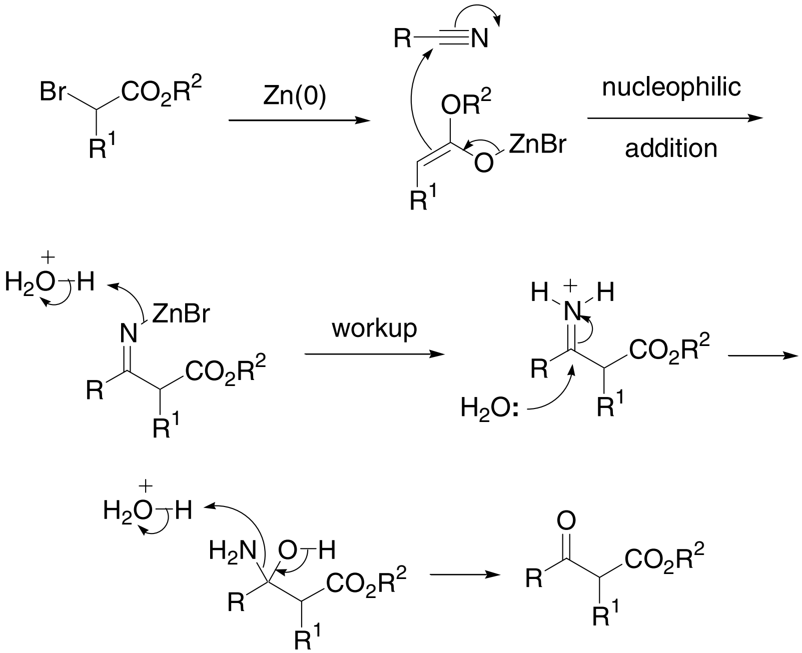
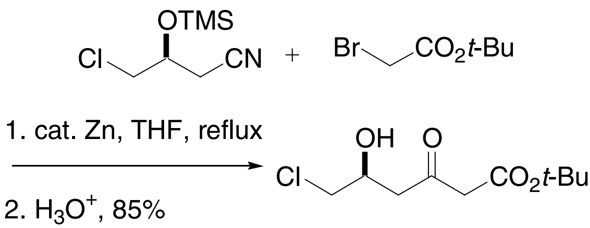
Blaise reaction

β-Ketoesters from nitriles and α-haloesters using Zn.

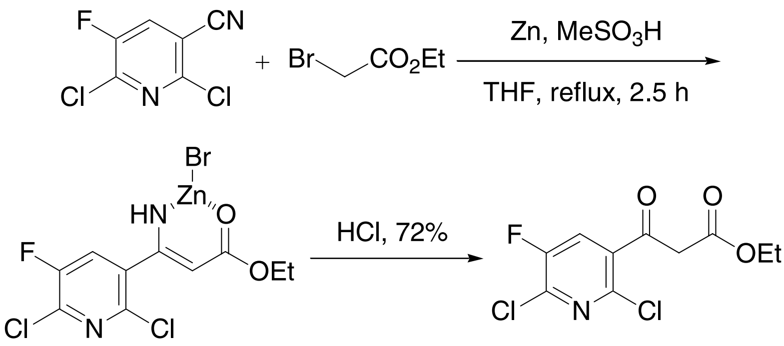




Example 1, preparation of the statin side chain[10]



Example 2[11]



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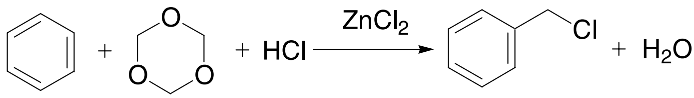
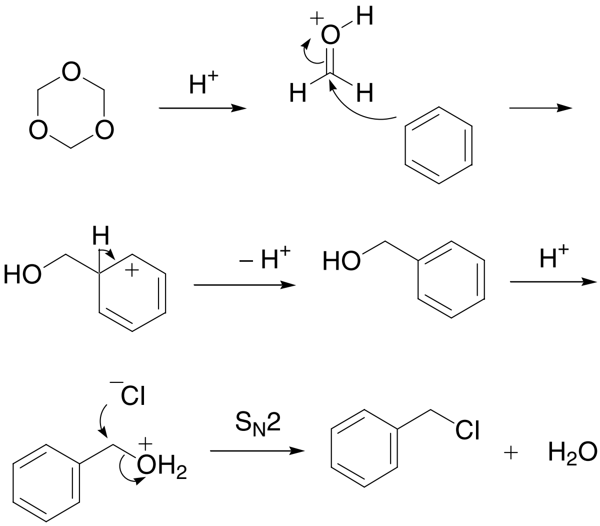
Blanc chloromethylation

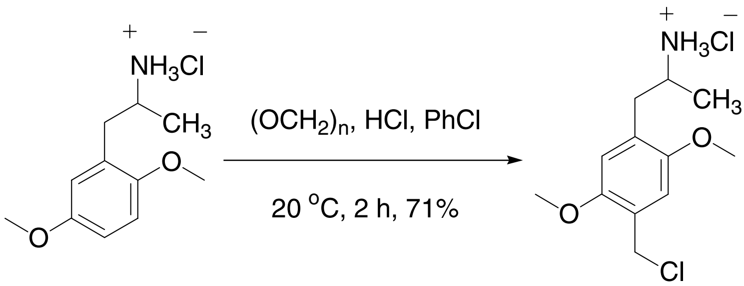
Lewis acid-promoted chloromethyl group installation onto the aromatics rings with 1,3,5-trioxane and HCl.



1,3,5-trioxane



Example 1[12]



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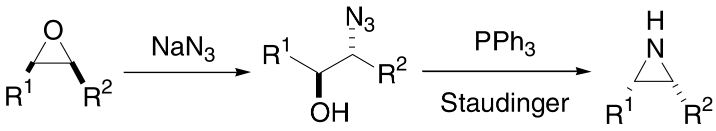
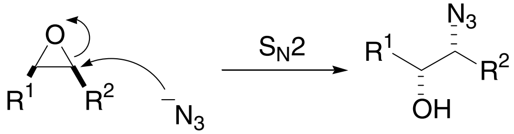
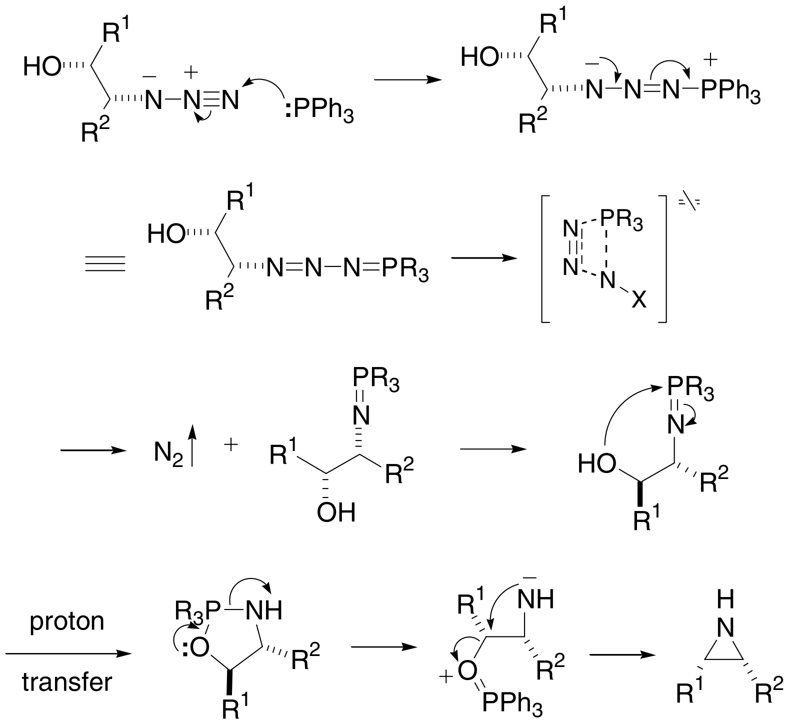
Blum aziridine synthesis

Ring opening of oxiranes using azide is followed by Staudinger reduction of the intermediate azido alcohol to give aziridines.

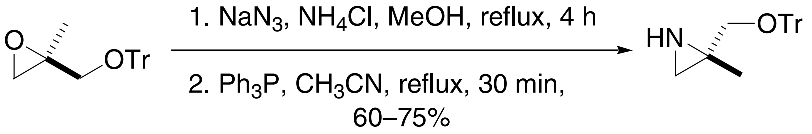




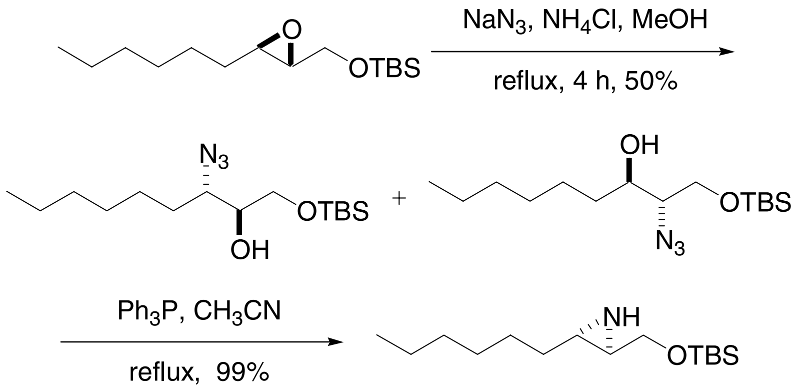
Regardless of the regioselectivity of the S_N2 reaction of the azide, the ultimate stereochemical outcome for the aziridine is the same.



Example 1[3]



Example 2[5]



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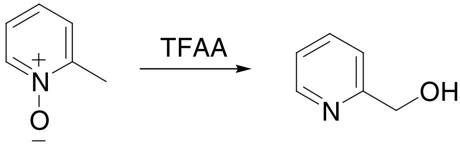
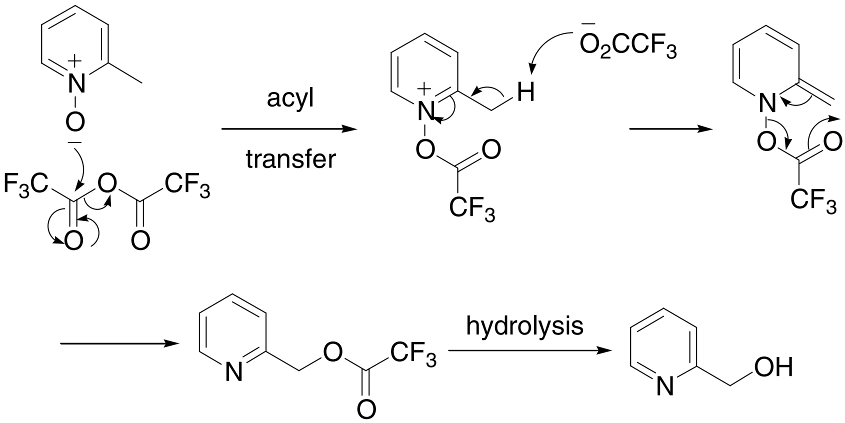
Boekelheide reaction

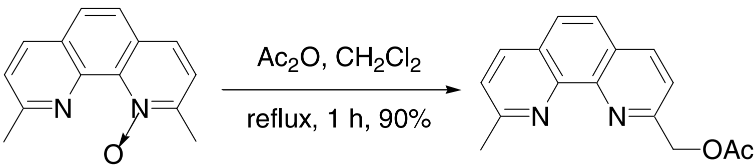
Treatment of 2-methylpyridine *N*-oxide with trifluoroacetic anhydride gives rise to 2-hydroxymethylpyridine.



TFAA, trifluoroacetic anhydride



Example 1[6]



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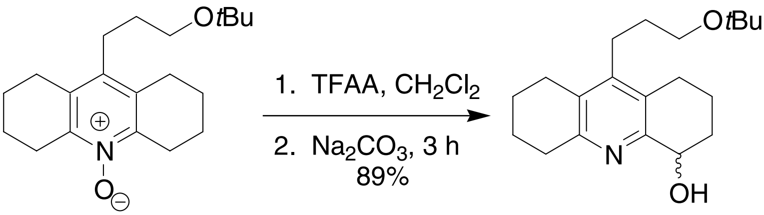

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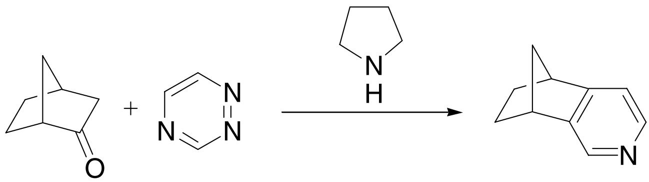
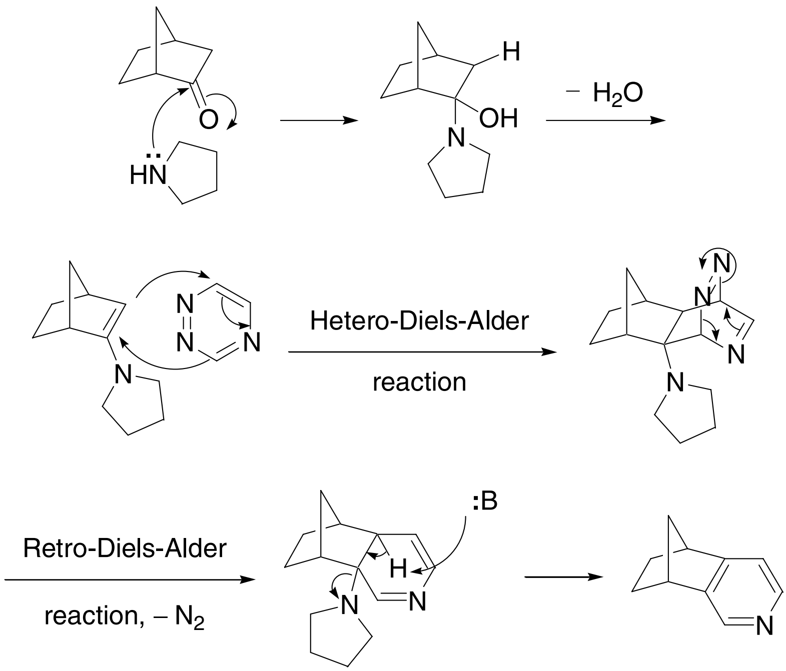
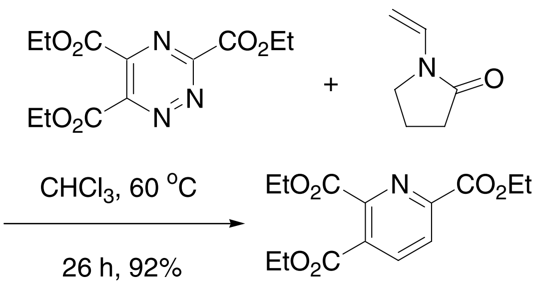
Boger pyridine synthesis

Pyridine synthesis *via* hetero-Diels–Alder reaction of 1,2,4-triazines and dienophiles (e.g. enamine) followed by extrusion of N_2.





Example 1[4]



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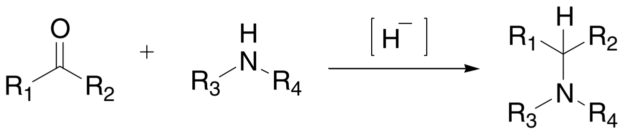
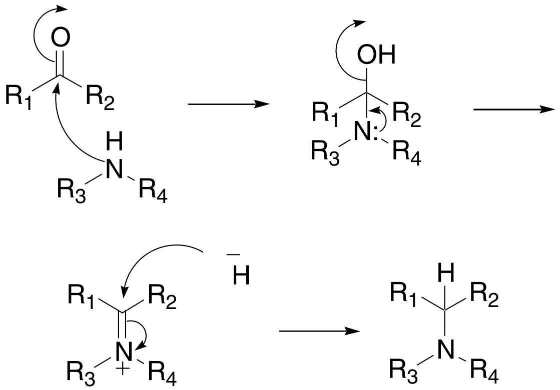
Borch reductive amination

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





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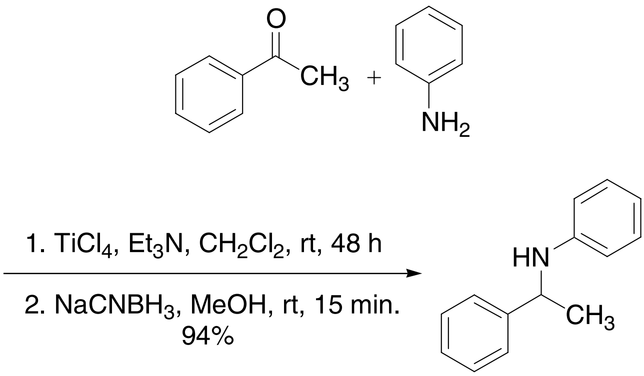

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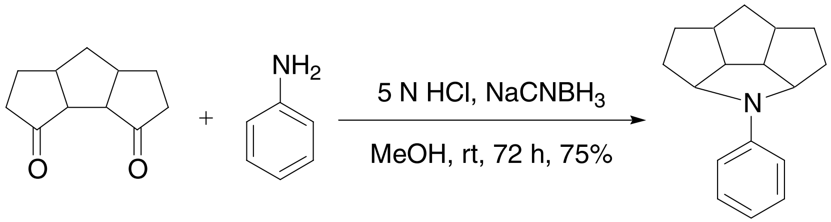

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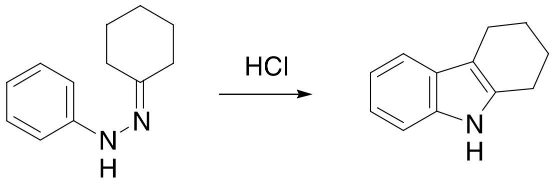
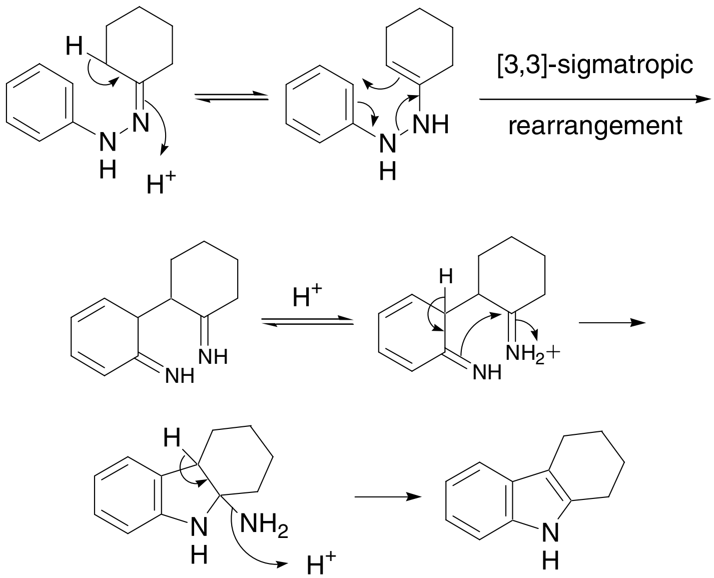
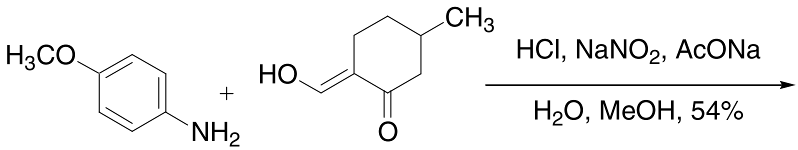
Borsche–Drechsel cyclization

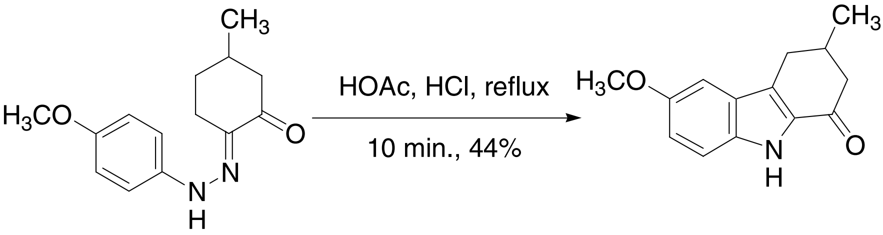
Tetrahydrocarbazole synthesis from cyclohexanone phenylhydrazone.
Cf. Fisher indole synthesis.





Example 1[8]





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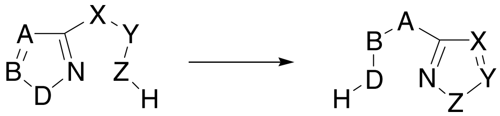
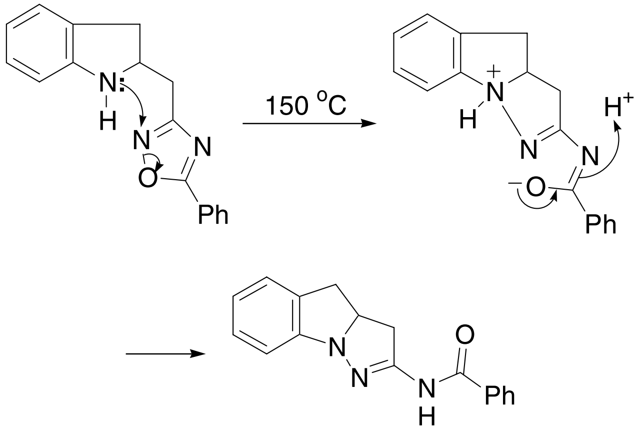
Boulton–Katritzky rearrangement

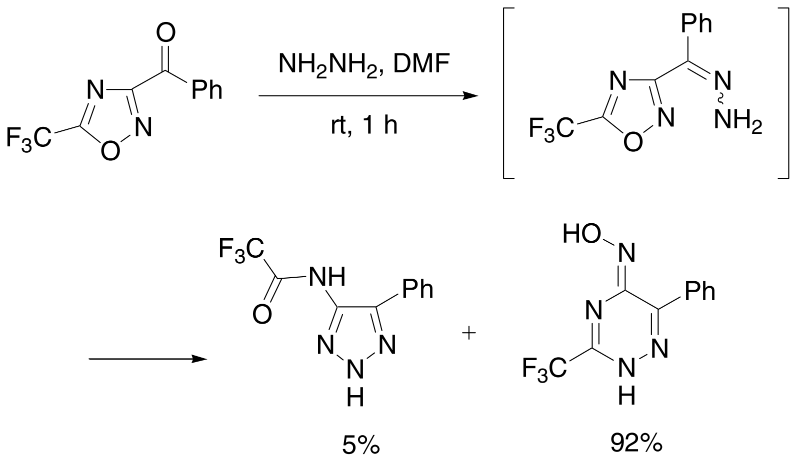
Rearrangement of one five-membered heterocycle into another under thermolysis.

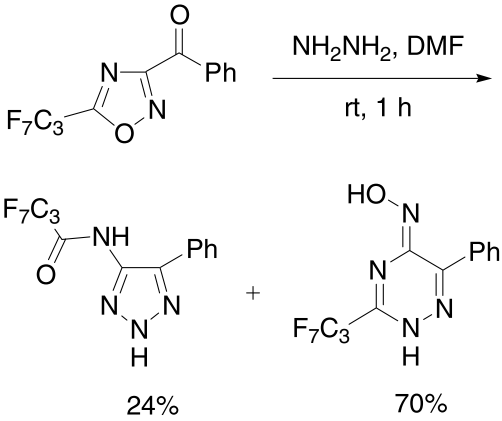


Example 1[7]



Example 2[11]





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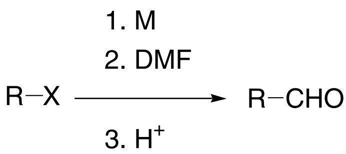
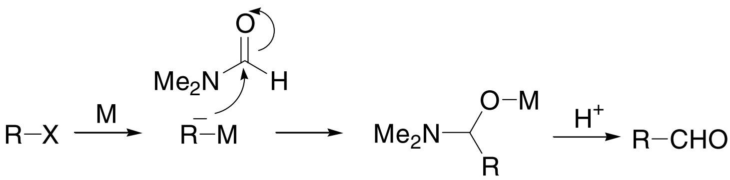
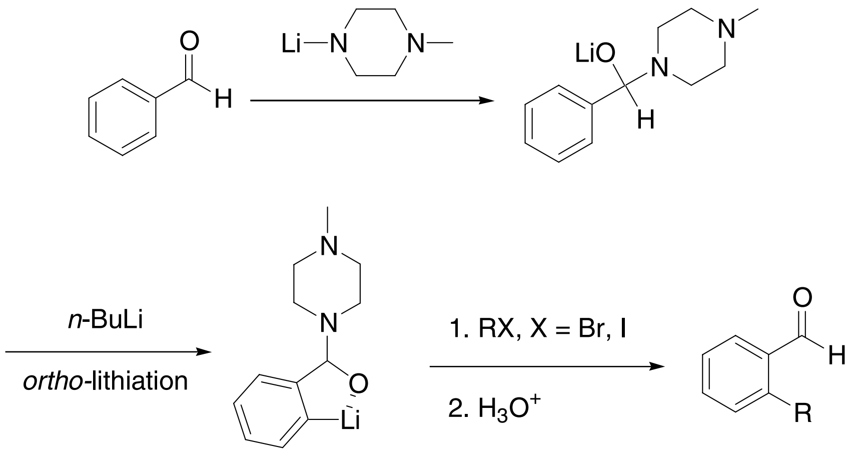
Bouveault aldehyde synthesis

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).

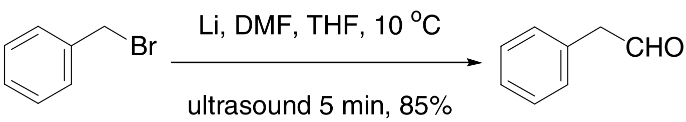




A modification by Comins:[7]



Example 1[6]



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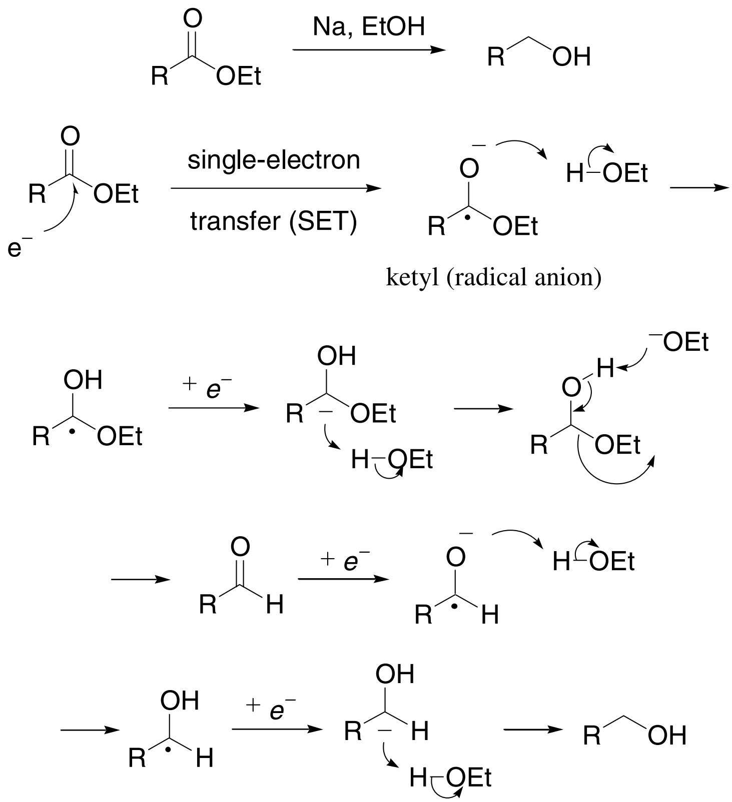
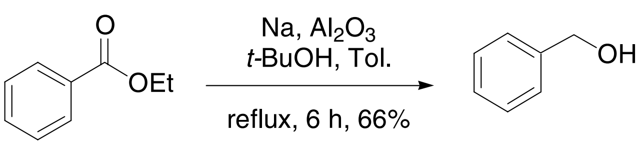
Bouveault–Blanc reduction

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



Example 1[8]



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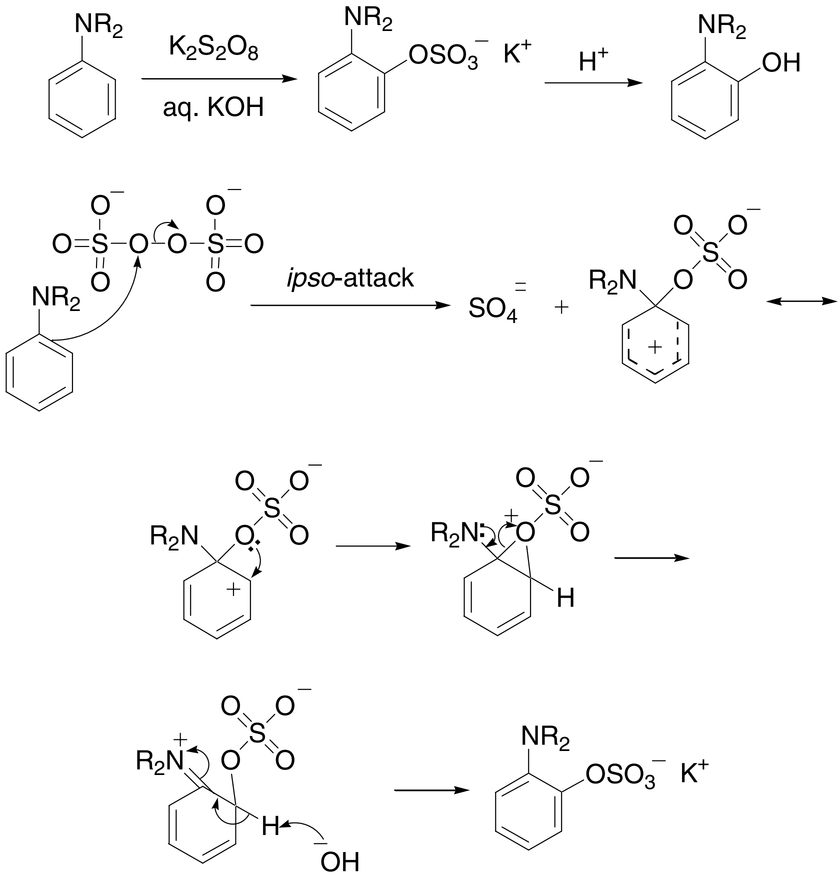
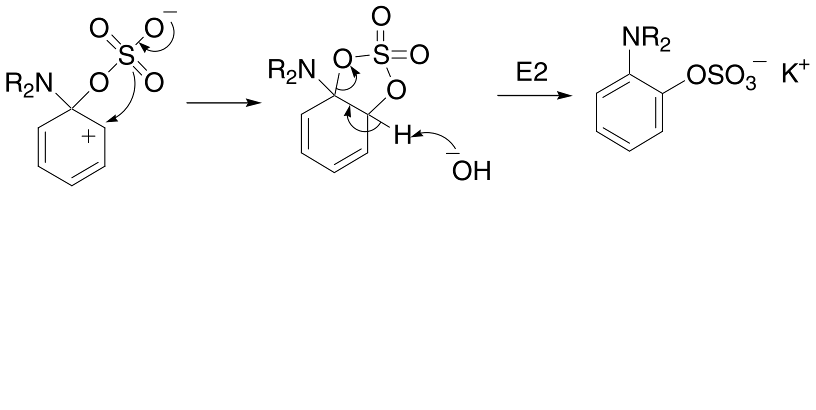
Boyland–Sims oxidation

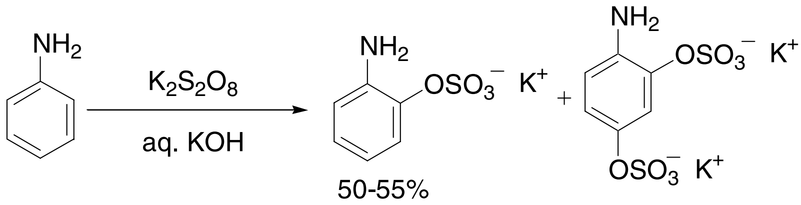
Oxidation of anilines to phenols using alkaline persulfate.



Another pathway is also operative:



Example 1[3]



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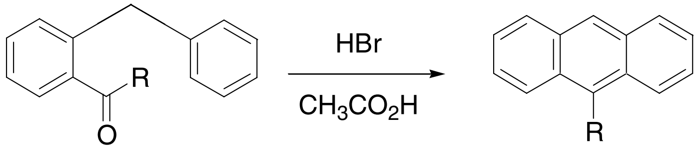
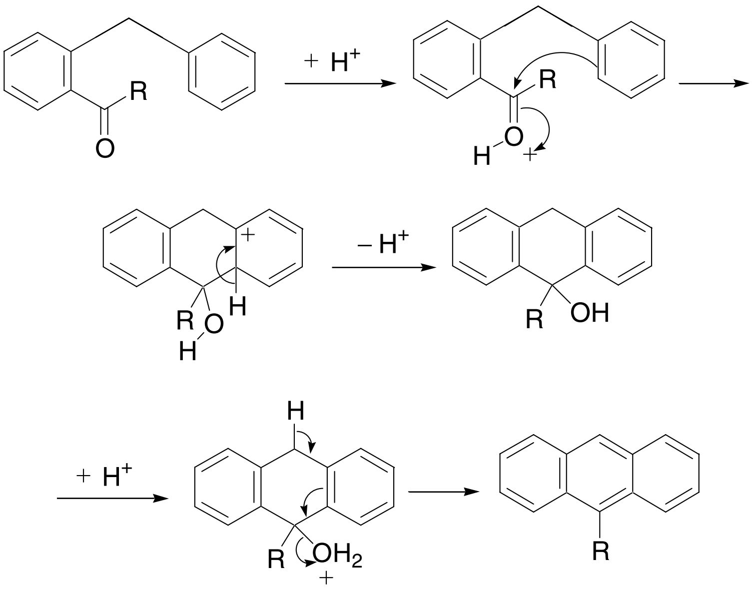
Bradsher reaction

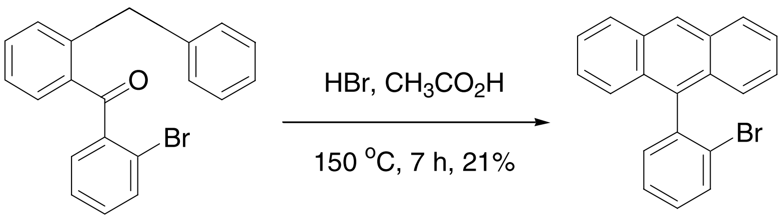
Anthracenes from *ortho*-acyl diarylmethanes *via* acid-catalyzed cyclodehydration.



anthracene



Example[5]



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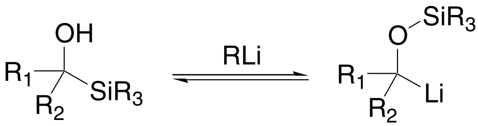
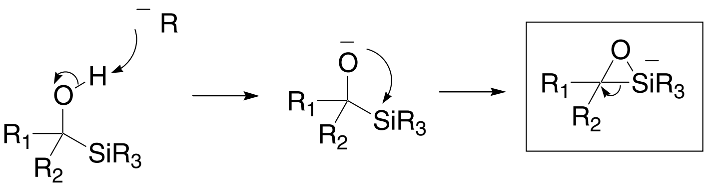
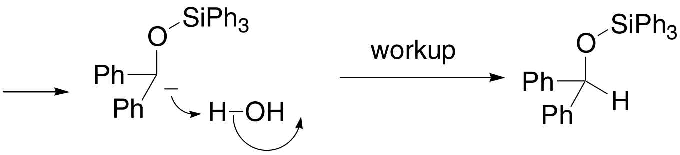
Brook rearrangement

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.

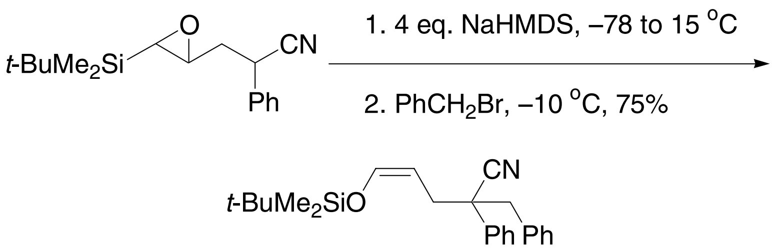




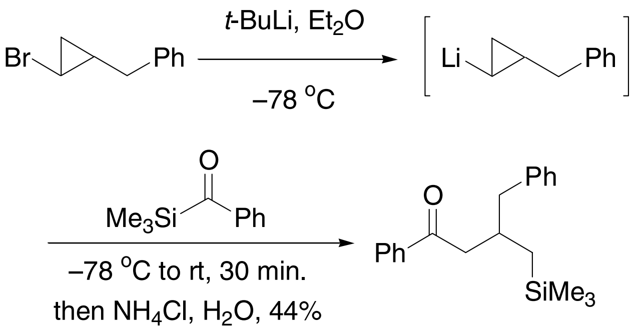
pentacoordinate silicon intermediate



Example 1[11]



Example 2[14]



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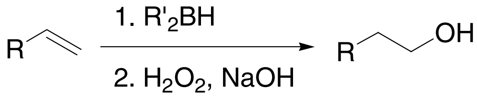
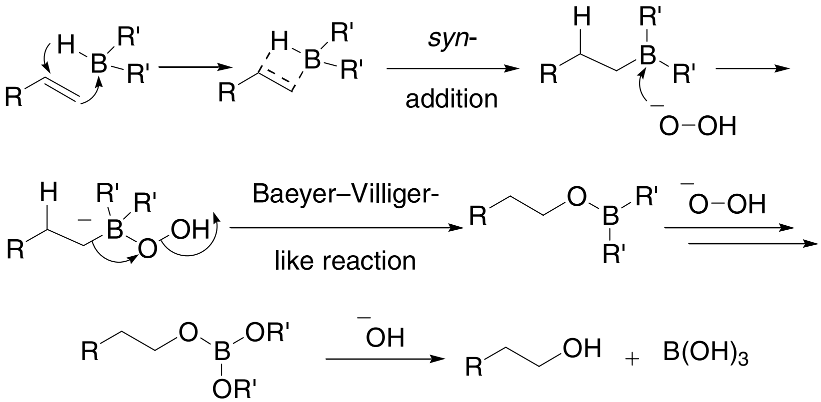
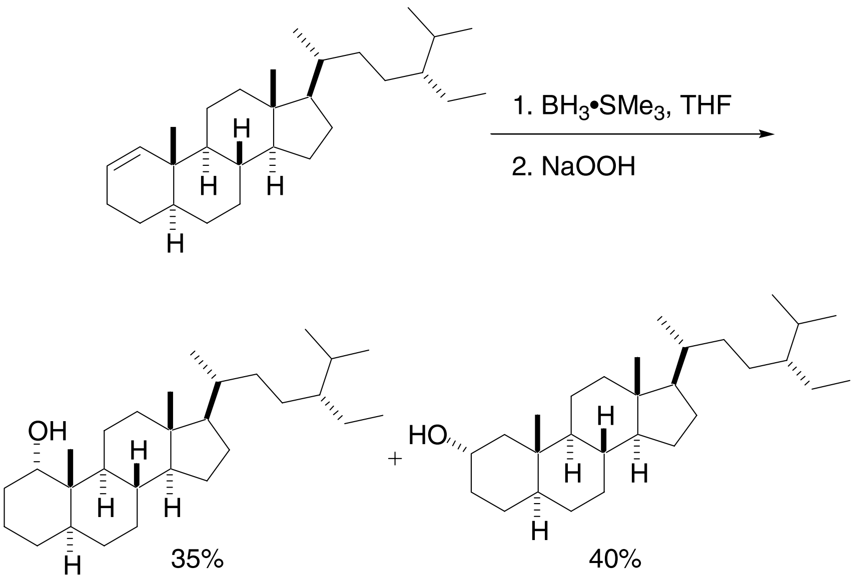
Brown hydroboration

Addition of boranes to olefins, followed by basic oxidation of the organoborane adducts, resulting in alcohols.

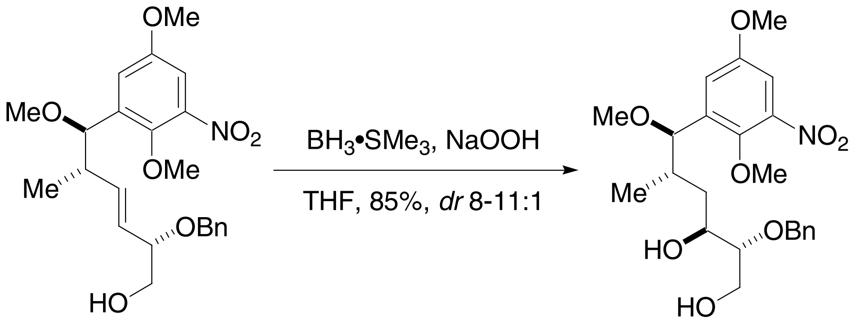




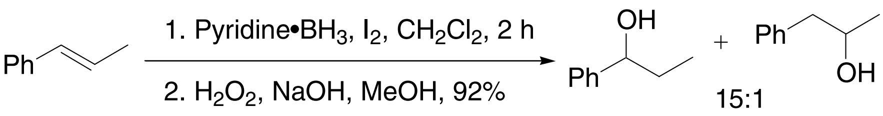
Example 1[2]



Example 2[13]



Example 3[14]



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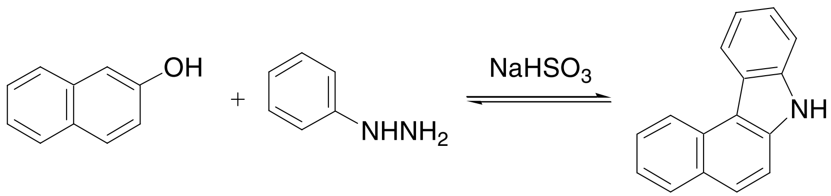
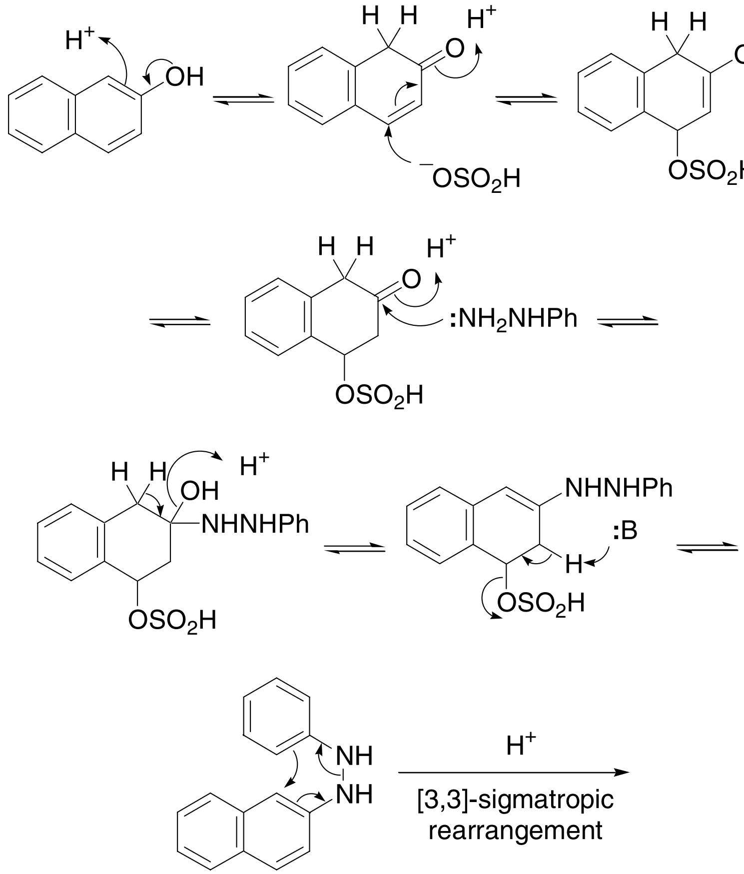
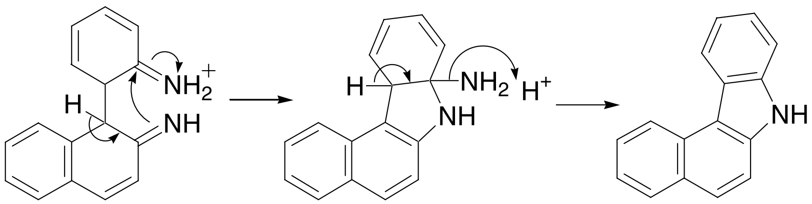
Bucherer carbazole synthesis

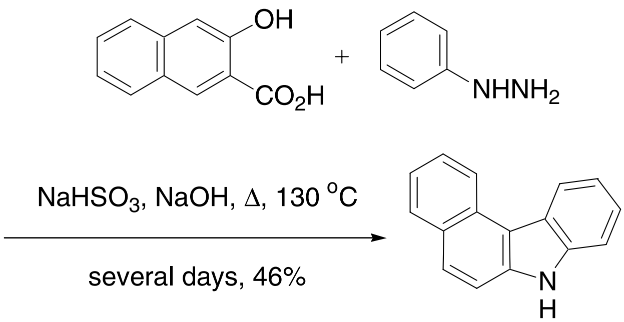
Carbazoles from naphthols and aryl hydrazines promoted by sodium bisulfite.



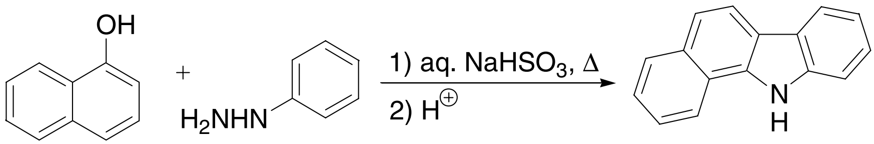




Example 1[3]



Example 2[4]



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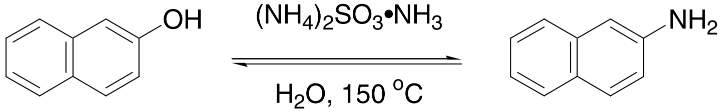
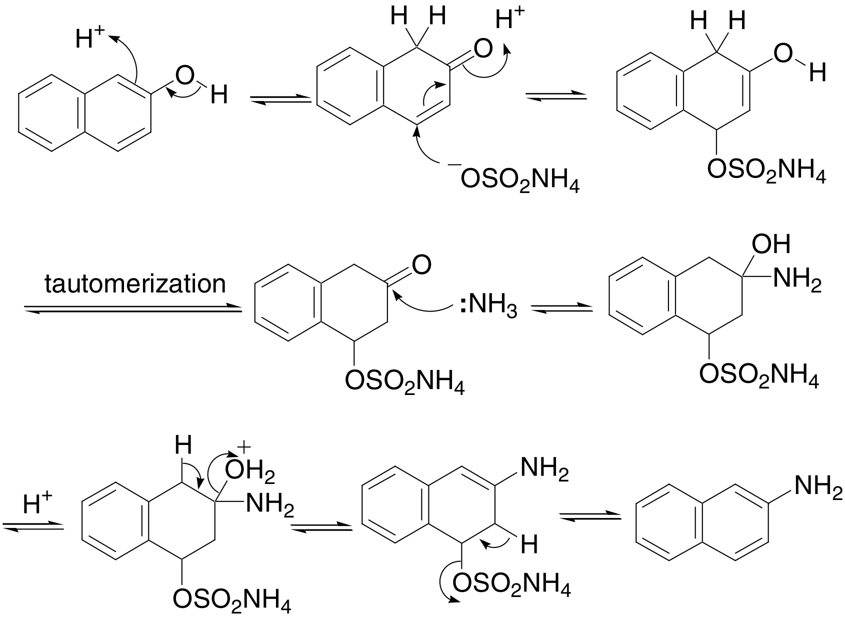
Bucherer reaction

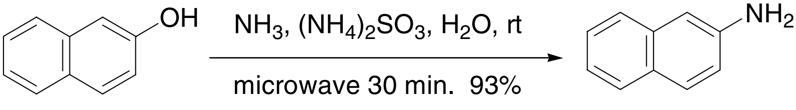
Transformation of β-naphthols to β-naphthylamines using ammonium sulfite.





Example[2]

Although the classic Bucherer reaction requires high temperature, it may be carried out at room temperature with the aid of microwave (150 watts):



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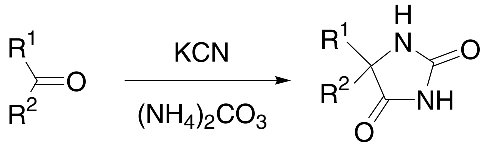
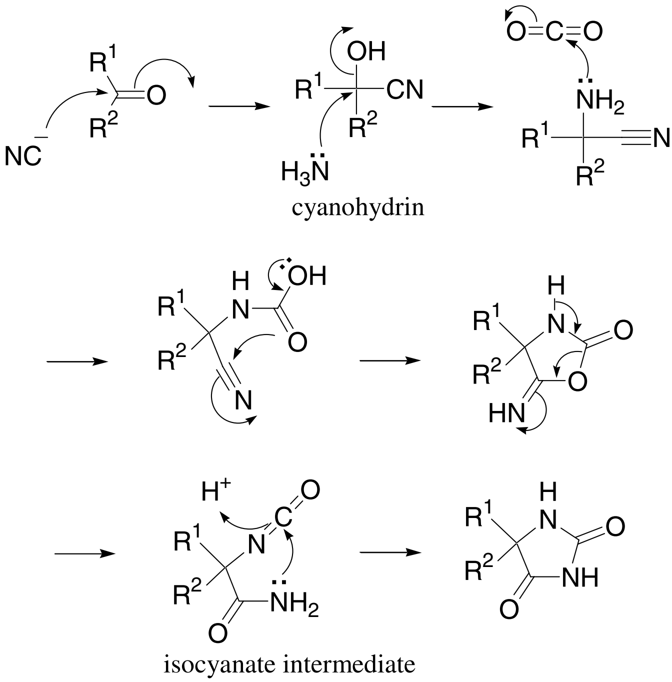
Bucherer–Bergs reaction

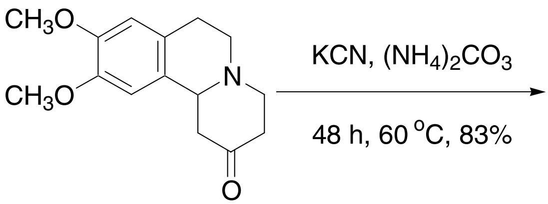
Formation of hydantoins from carbonyl compounds with potassium cyanide (KCN) and ammonium carbonate [$(NH_4)_2CO_3$] or from cyanohydrins and ammonium carbonate. It belongs to the category of multiple component reaction (MCR).

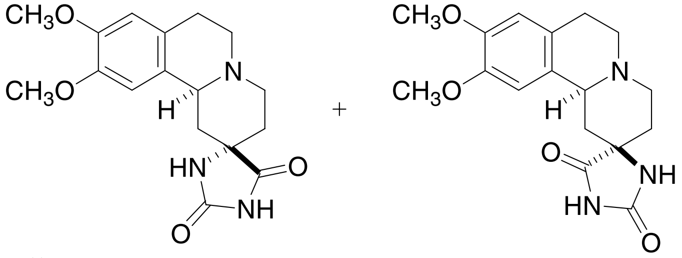


$(NH_4)CO_2 \leftrightarrow 2\ NH_3 + CO_2 + H_2O$

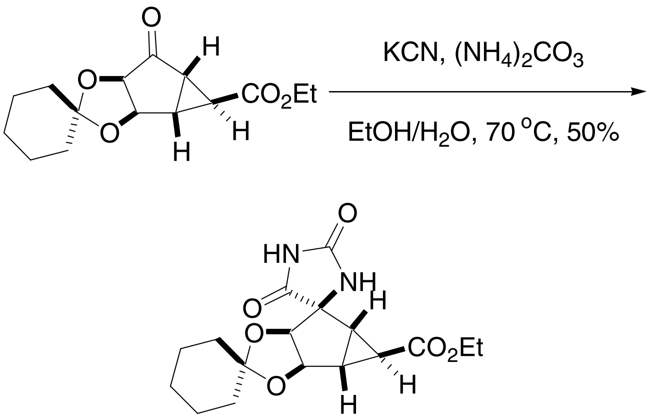


Example 1[10]





Example 2[11]



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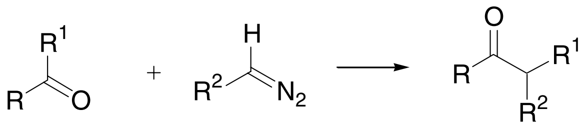
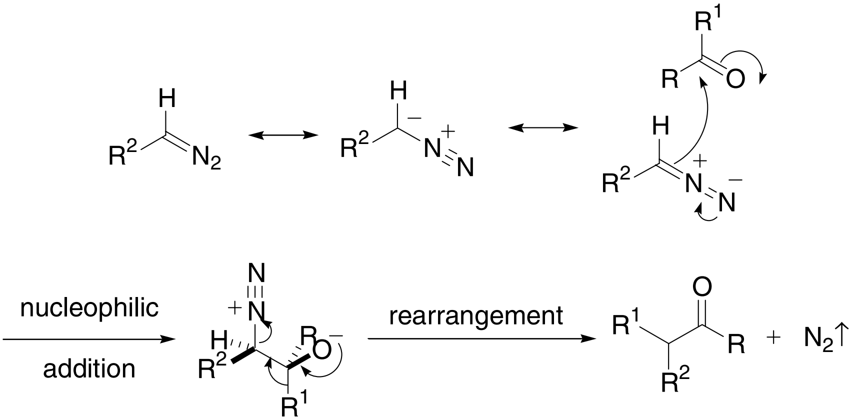
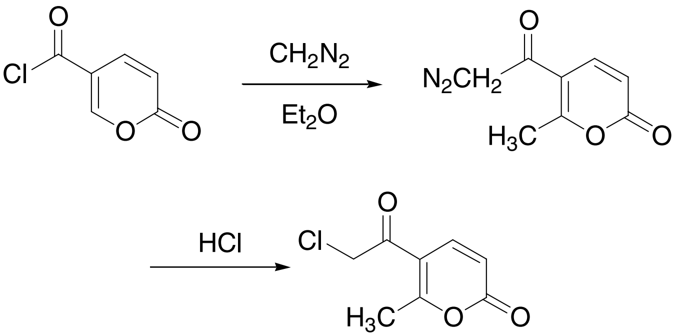
Büchner–Curtius–Schlotterbeck reaction

Reaction of carbonyl compounds with aliphatic diazo compounds to deliver homologated ketones.

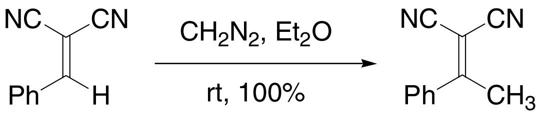


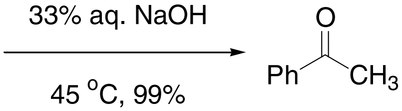


Example 1[3]



Example 2[6]





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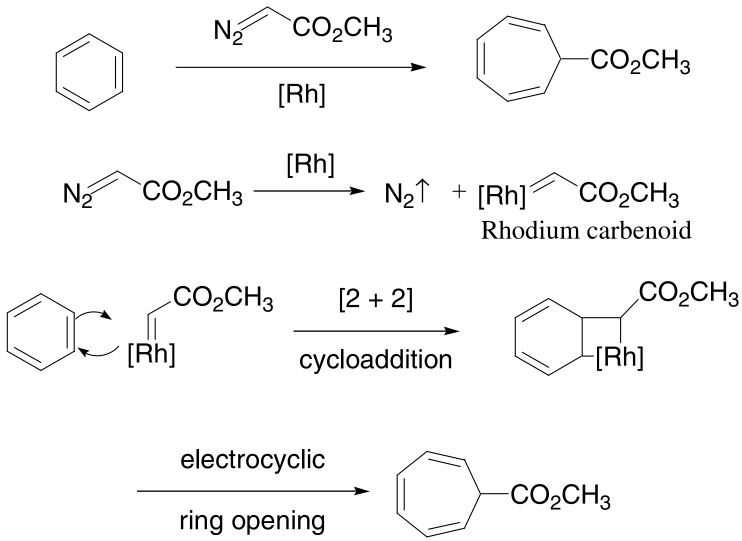
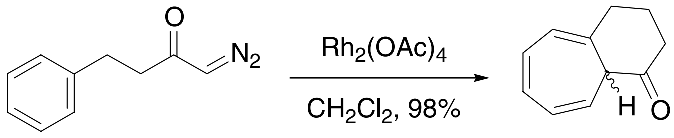
Büchner method of ring expansion

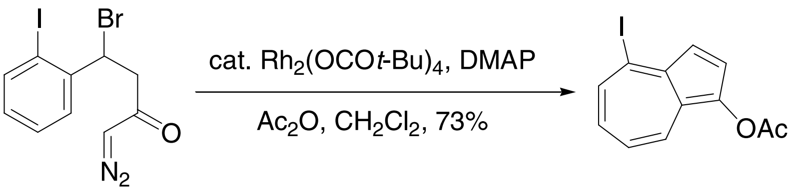
Reaction of benzene with diazoacetic esters to give cyclohepta-2,4,6-trienecarboxylic acid esters. *Cf.* Pfau–Platter azulene synthesis.



Example 1[7]



Example 2[8]



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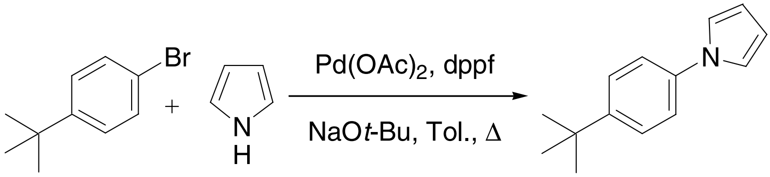
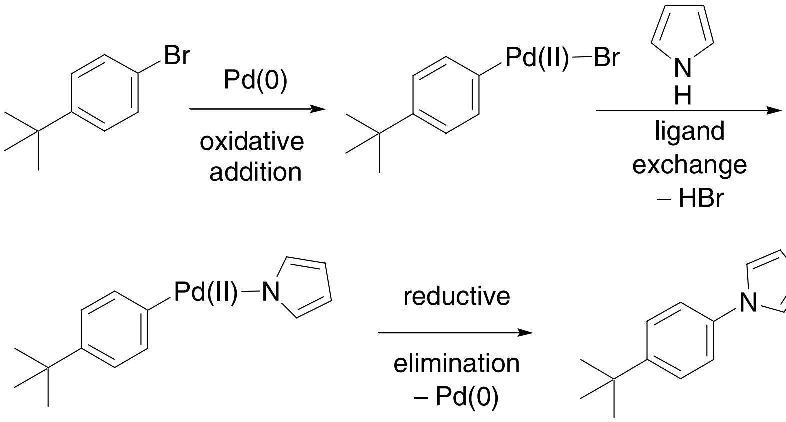
Buchwald–Hartwig C–N and C–O bond formation reactions

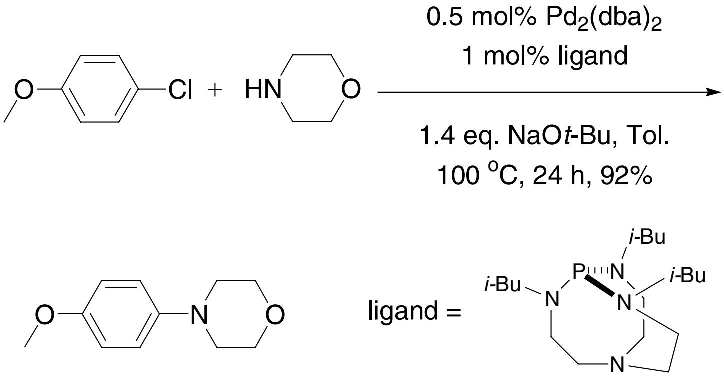
Direct Pd-catalyzed C–N and C–O bond formation from aryl halides and amines in the presence of stoichiometric amount of base.



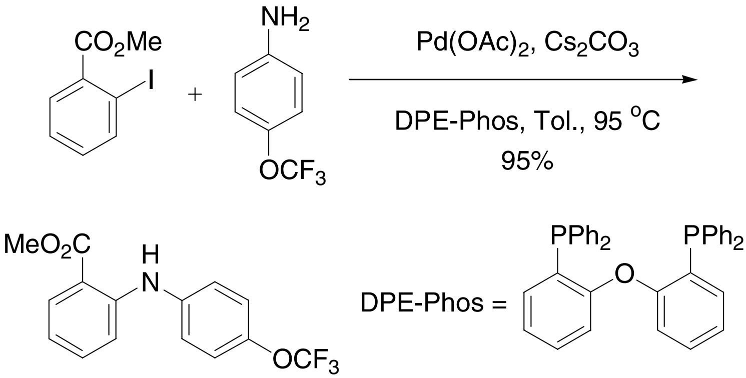


The C–O bond formation reaction follows a similar mechanistic pathway.[7–9]

Example 1[11]



Example 2[12]



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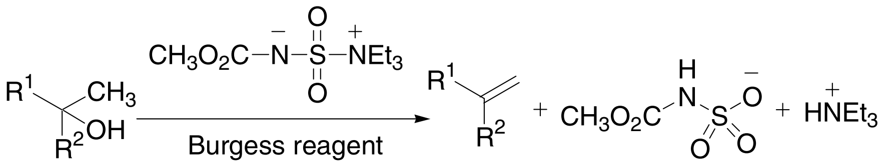
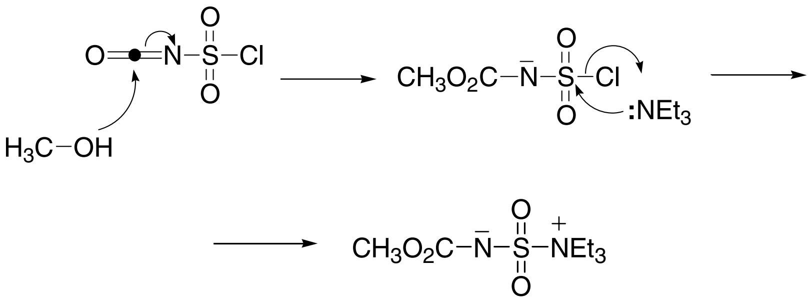
Burgess dehydrating reagent

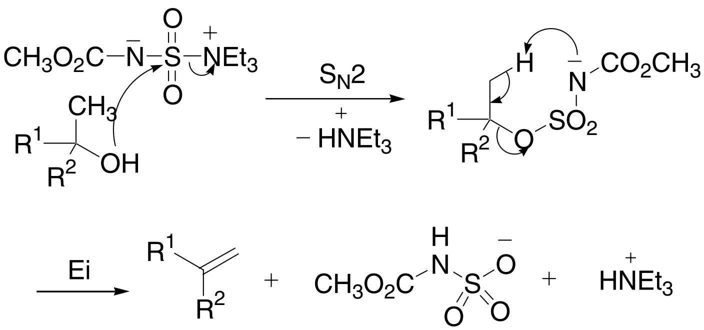
Burgess dehydrating reagent is efficient at generating olefins from secondary and tertiary alcohols where the first-order thermolytic Ei (during the elimination, the two groups leave at about the same time and bond to each other concurrently) mechanism prevails.

Reagen formation,

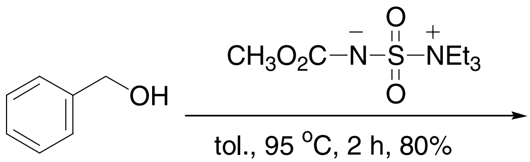


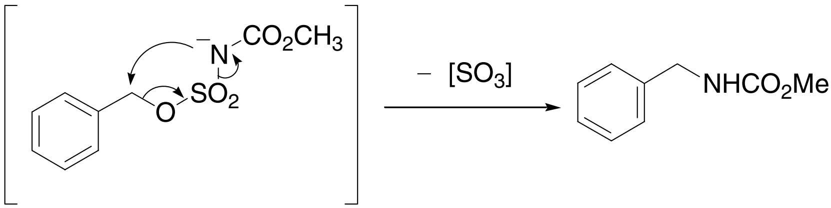


Reaction,

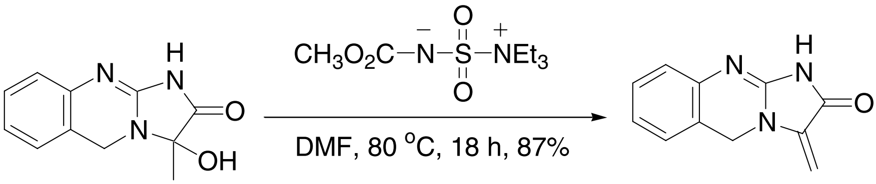


Example 1[4]

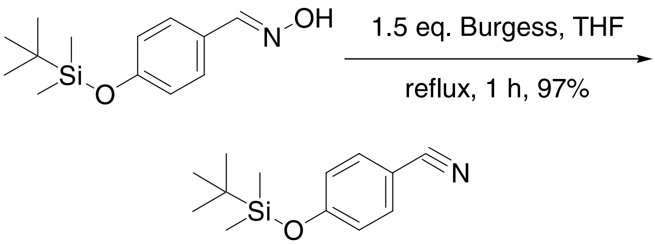




Example 2[5]



Example 3[10]



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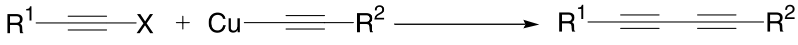
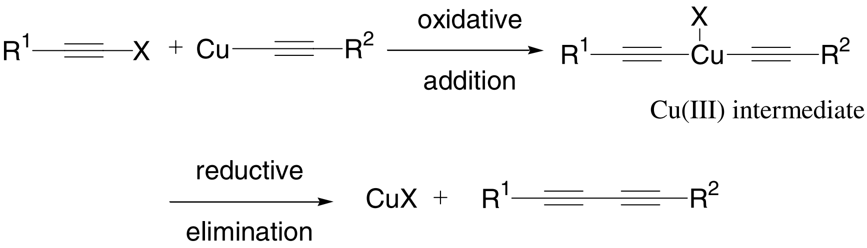
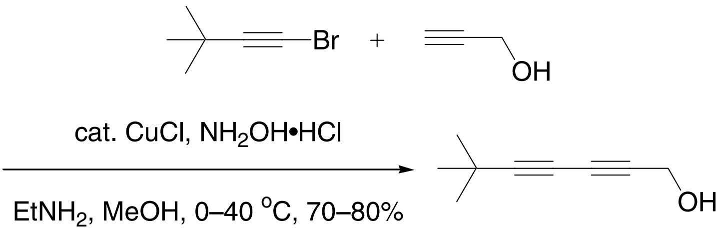
Cadiot–Chodkiewicz coupling

Bis-acetylene synthesis from alkynyl halides and alkynyl copper reagents.
Cf. Castro–Stephens reaction.





Example 1[6]



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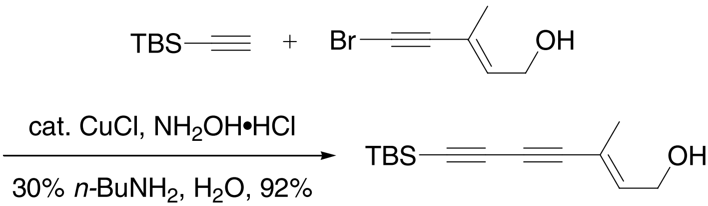

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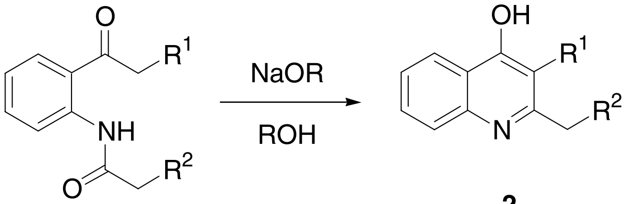
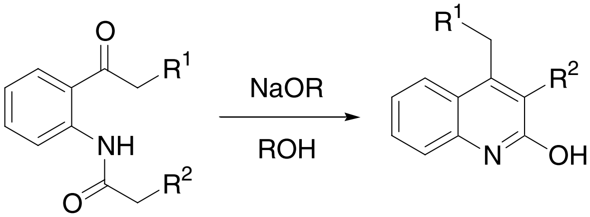
Camps quinolinol synthesis

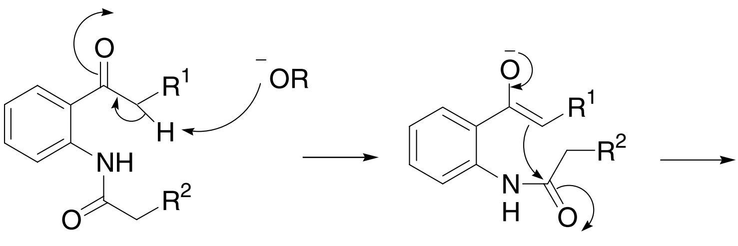
Base-catalyzed intramolecular condensation of a 2-acetamido acetophenone (**1**) to a 2-(and possibly 3)-substituted-quinolin-4-ol (**2**), a 4-(and possibly 3)-substituted-quinolin-2-ol (**3**), or a mixture.



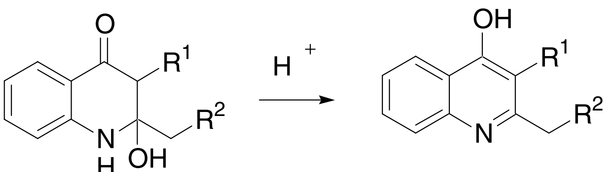
1 **2**



1 **3**



1



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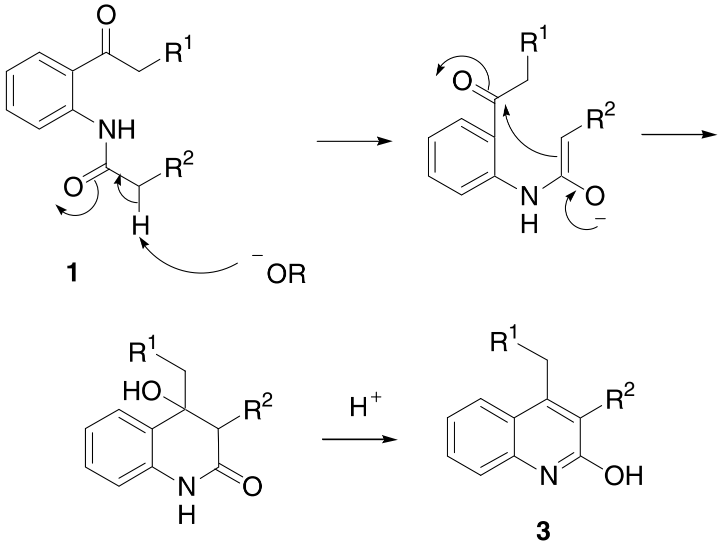
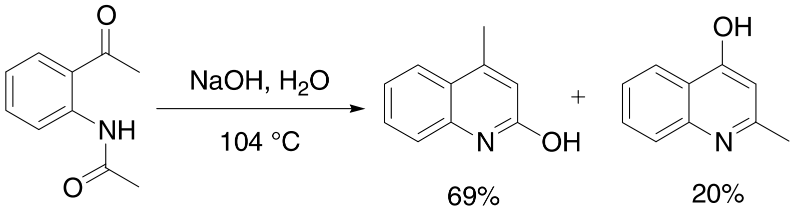
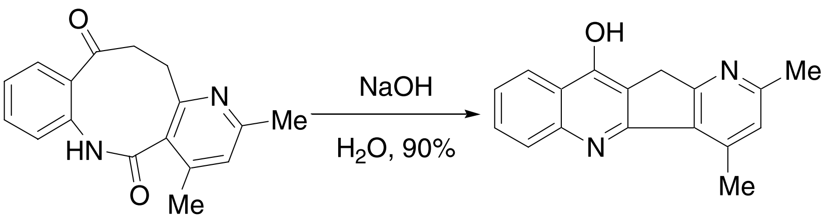


Example 1[1,2]



Example 2[8]



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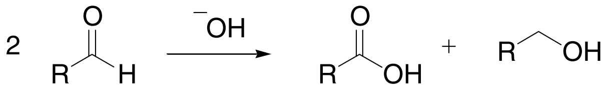
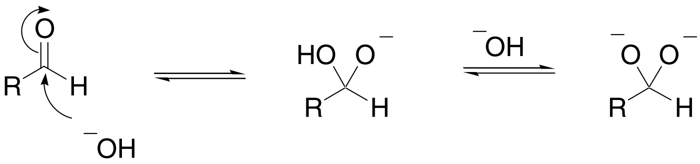
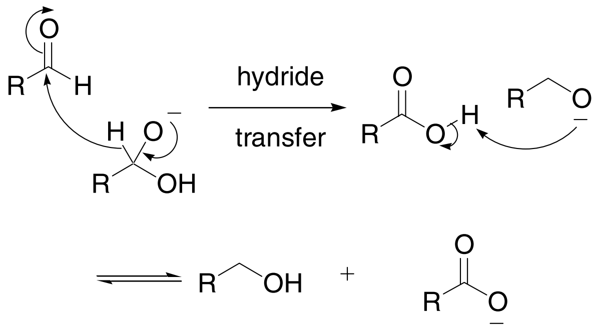
Cannizzaro disproportionation

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



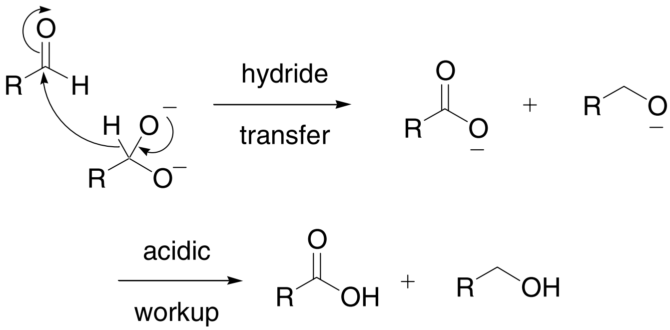


Pathway A:

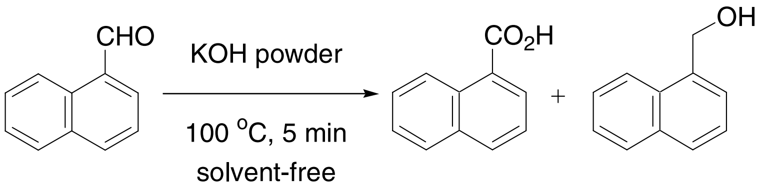


Final deprotonation of the carboxylic acid drives the reaction forward.

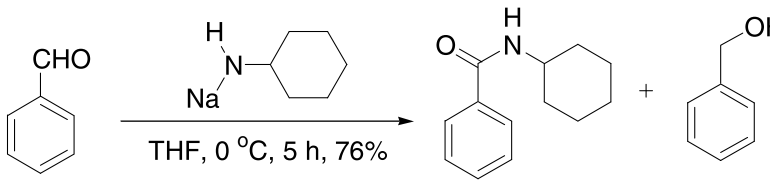
Pathway B:



Example 1[11]



Example 2[13]



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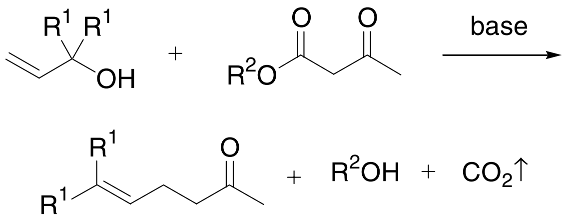
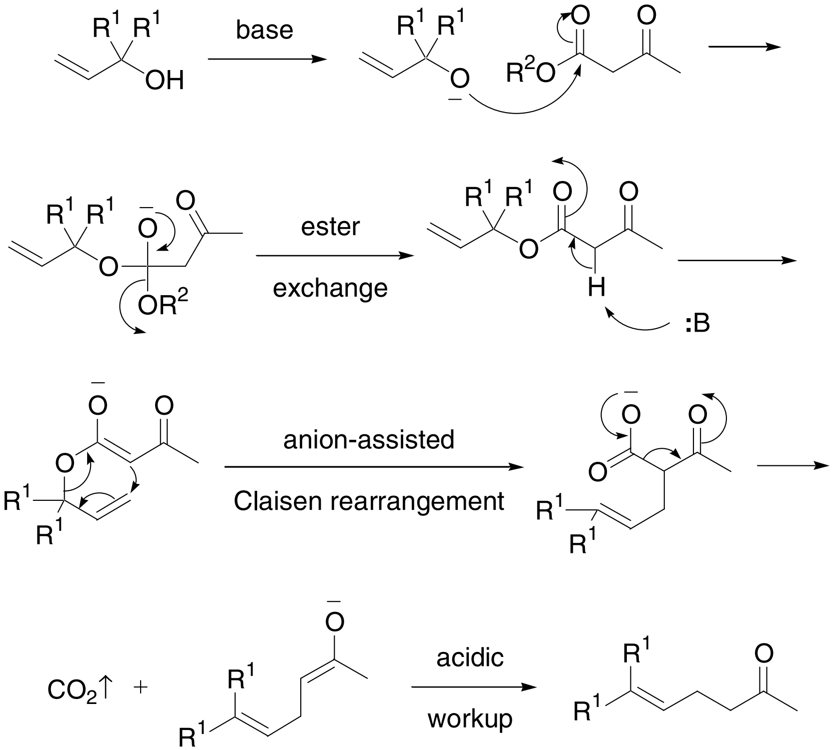
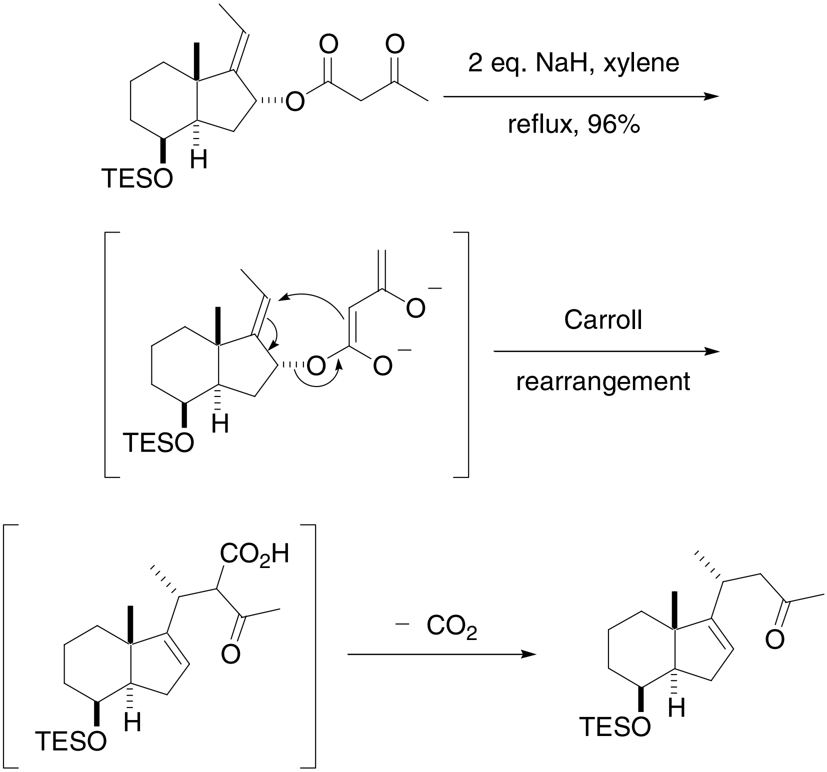
Carroll rearrangement

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 131).

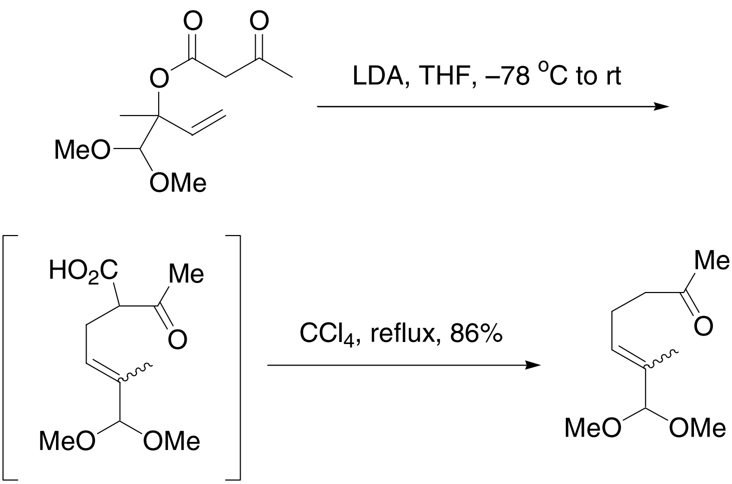




Example 1[9]



Example 2[10]



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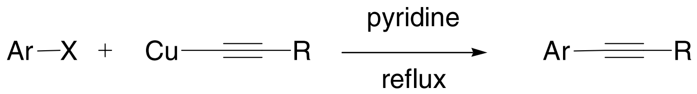
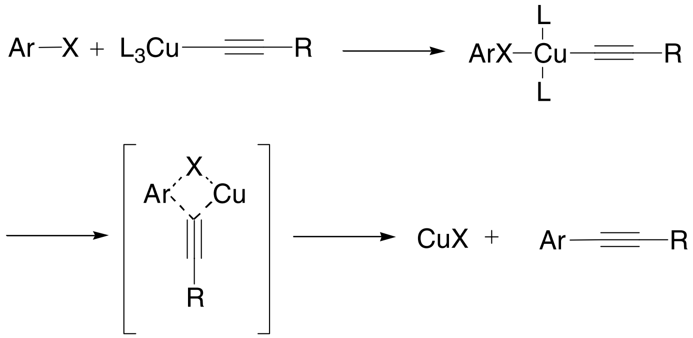
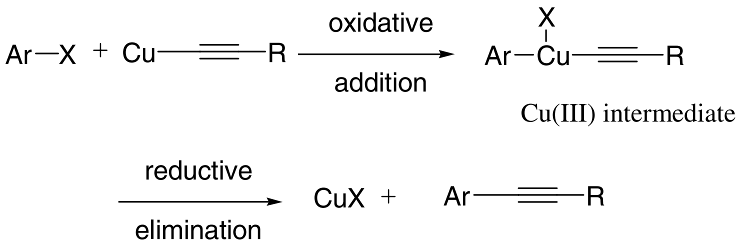
Castro–Stephens coupling

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.

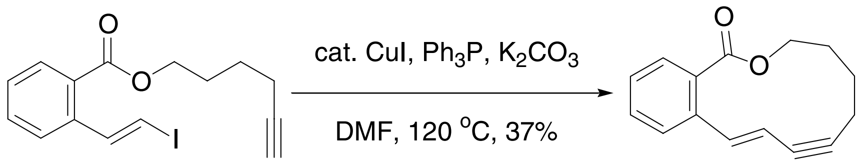




An alternative mechanism similar to that of the Cadiot–Chodkiewicz coupling:



Example[7]



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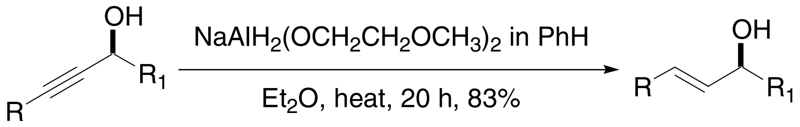
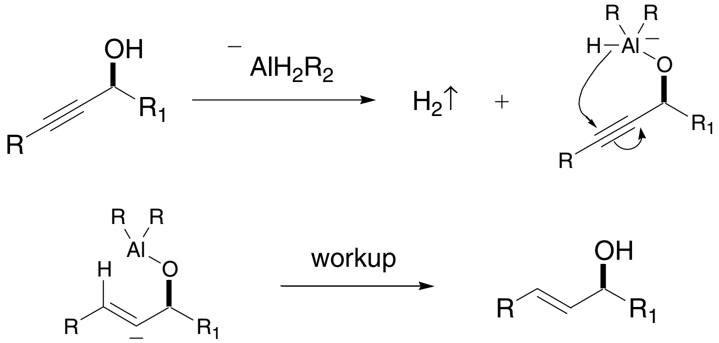
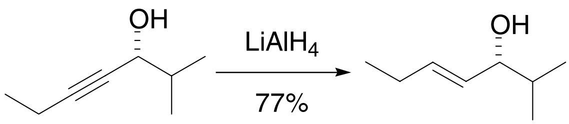
Chan alkyne reduction

Stereoselective reduction of acetylenic alcohols to *E*-allylic alcohols using **s**odium bis(2-**m**ethoxy**e**thoxy)**a**luminum **h**ydride (SMEAH, also known as Red-Al) or Li-AlH_4.

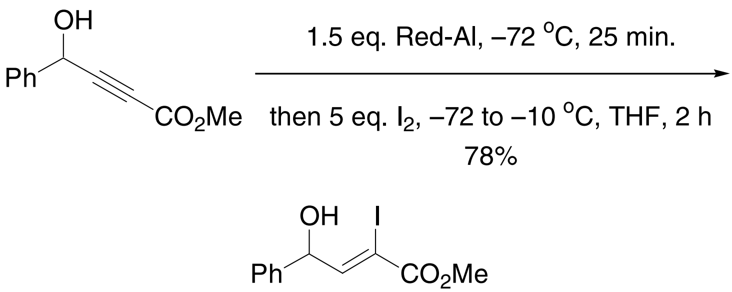




Example 1[3]



Example 2[4]



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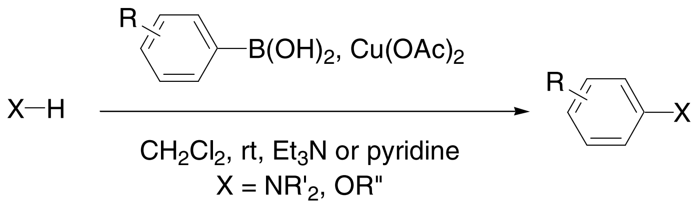
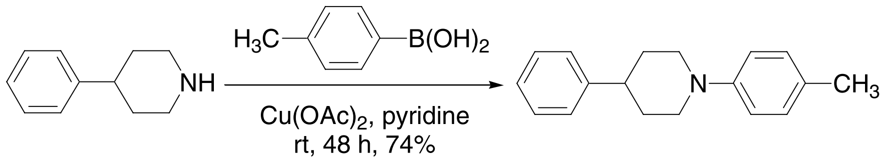
Chan–Lam coupling reaction

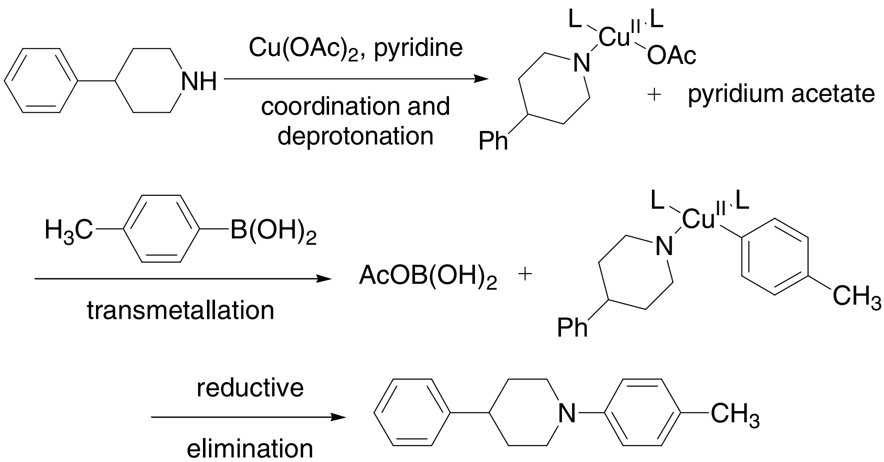
N-Arylation of a wide range of NH substrates by reaction with boronic acid in the presence of cupric acetate and either triethylamine or pyridine at room temperature. The reaction works even for poorly nucleophilic substrates such as arylamide.



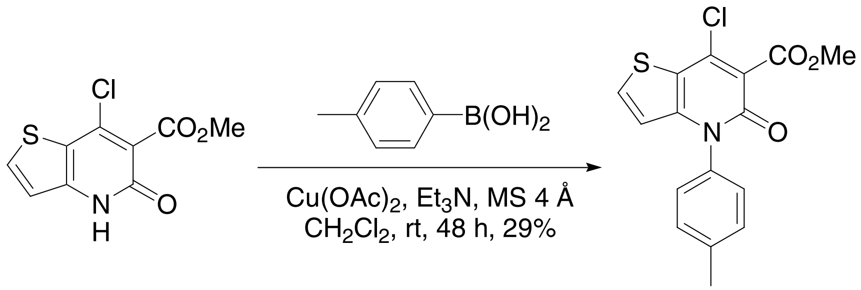
Example 1[1]



Mechanism:



Example 2[3]



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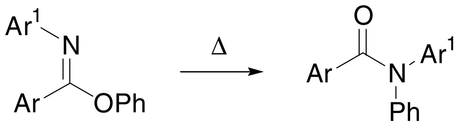
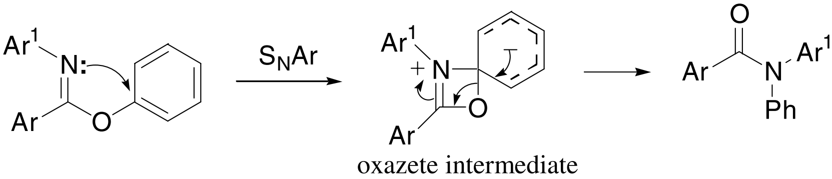
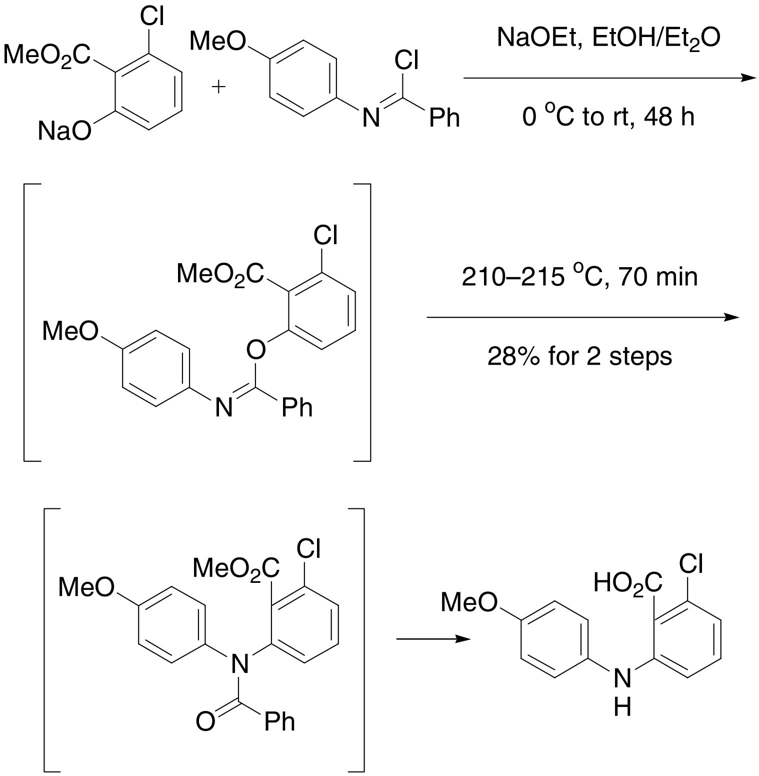
Chapman rearrangement

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

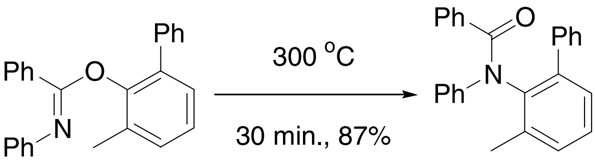




Example 1[2]



Example 2[4]



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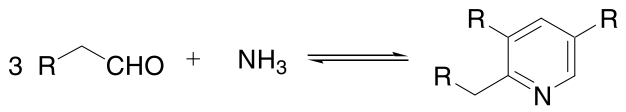
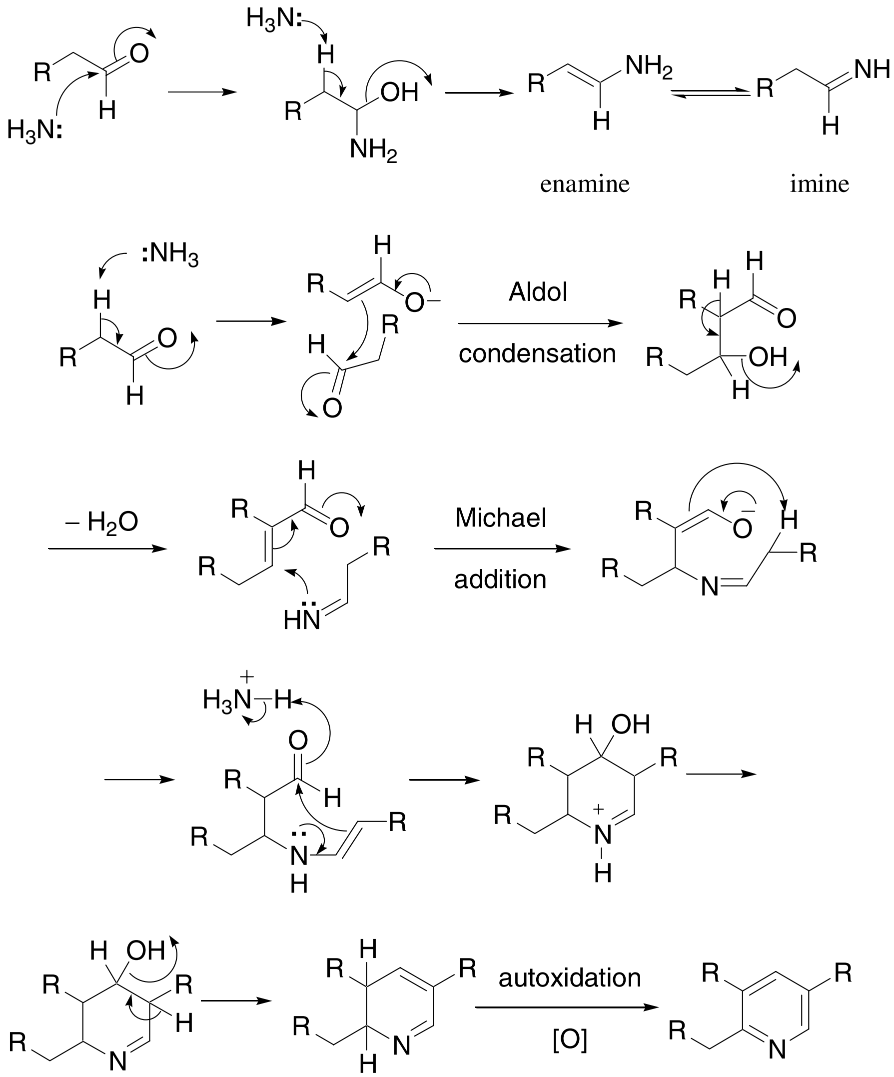
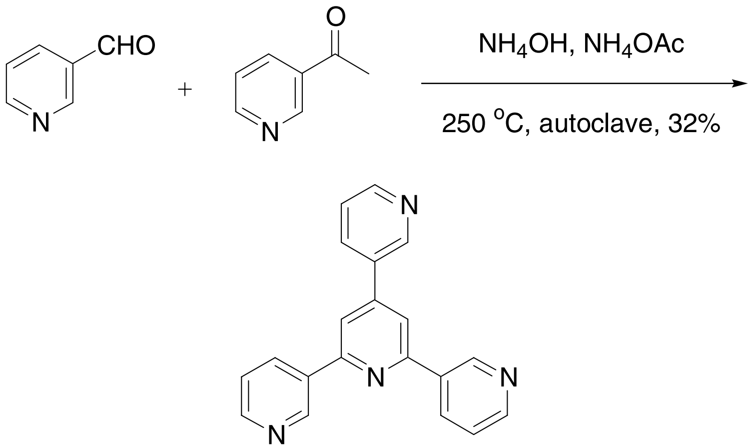
Chichibabin pyridine synthesis

Condensation of aldehydes with ammonia to afford pyridines.

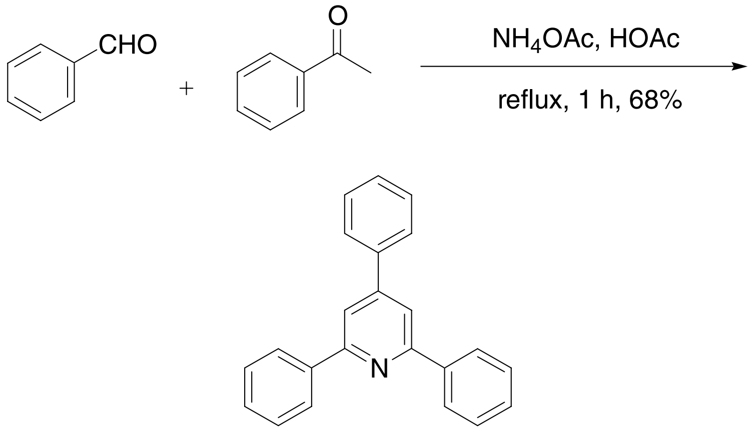




Example 1[4]



Example 2[5]



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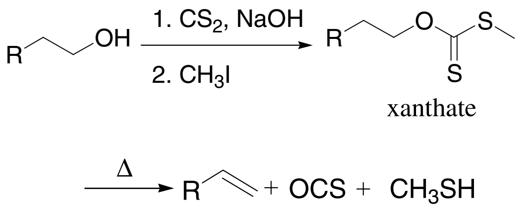
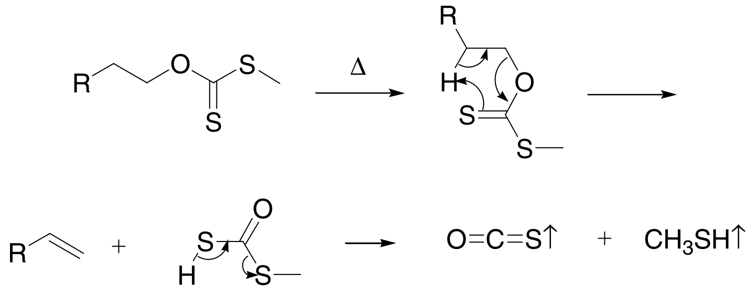
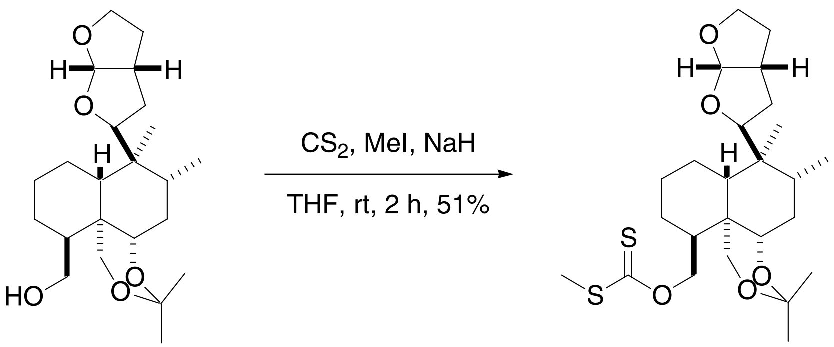
Chugaev elimination

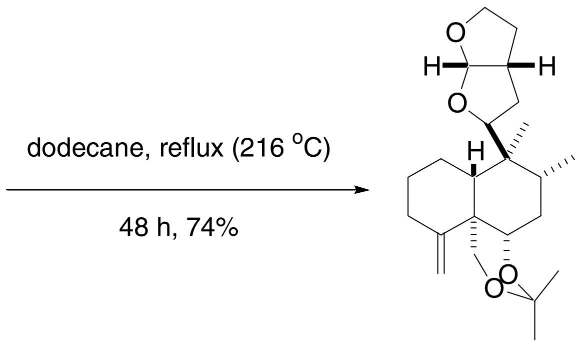
Thermal elimination of xanthates to olefins.



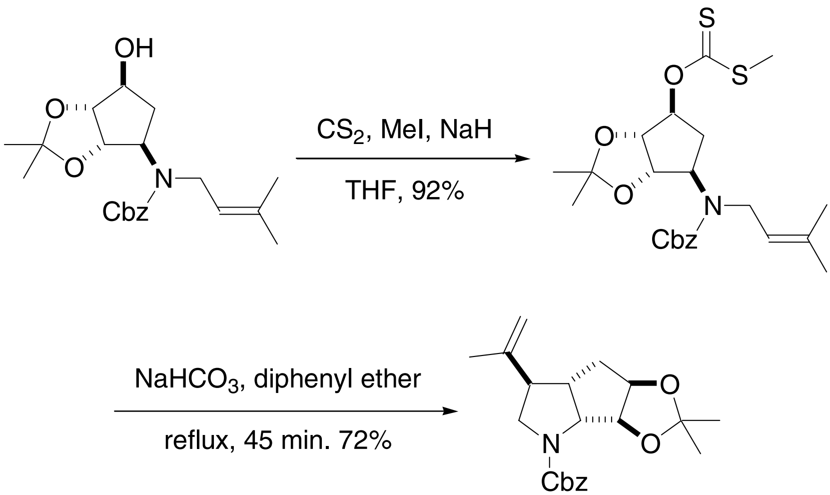


Example 1[6]





Example 2, Chugaev *syn*-elimination is followed by an intramolecular ene reaction[7]



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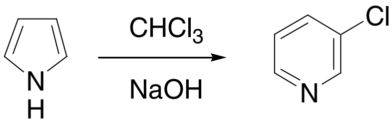
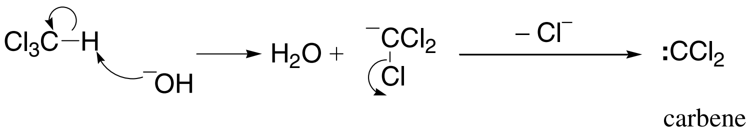
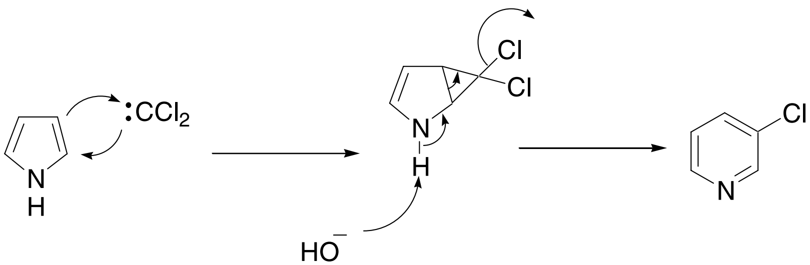
Ciamician–Dennsted rearrangement

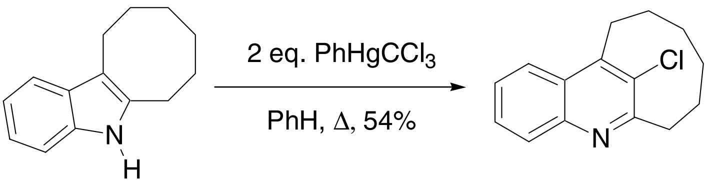
Cyclopropanation of a pyrrole with dichlorocarbene generated from $CHCl_3$ and NaOH. Subsequent rearrangement takes place to give 3-chloropyridine.



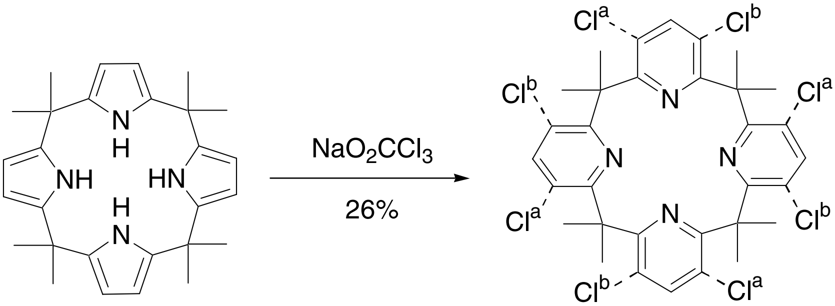




Example 1[8]



Example 2[10]



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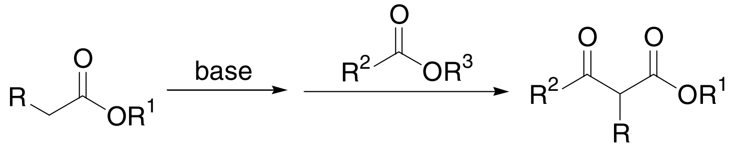
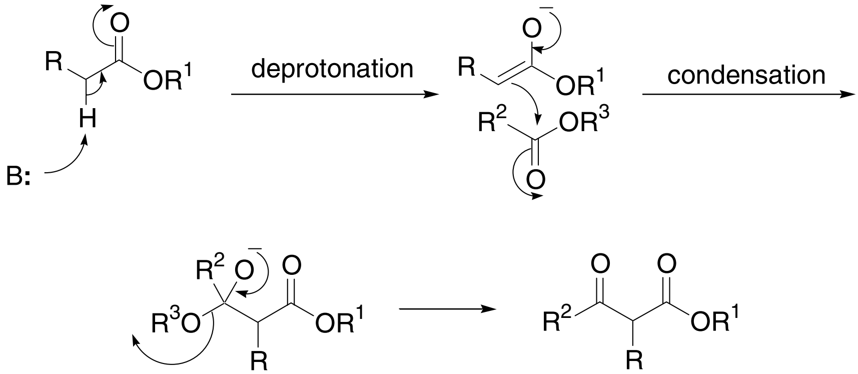
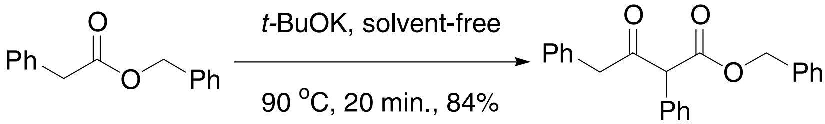
Claisen condensation

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

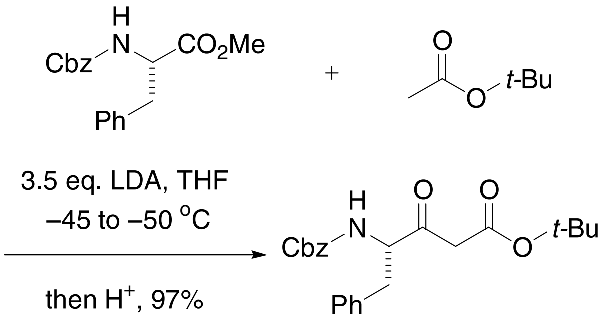




Example 1[9]



Example 2[12]



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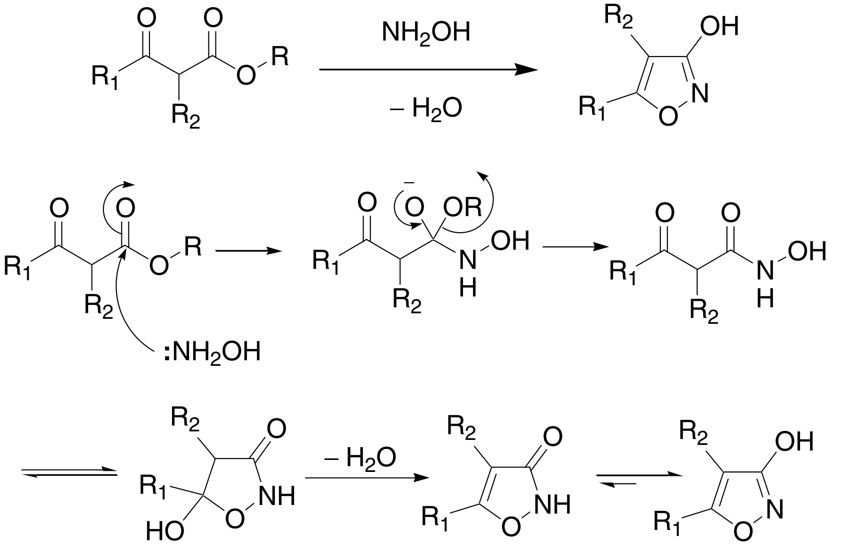
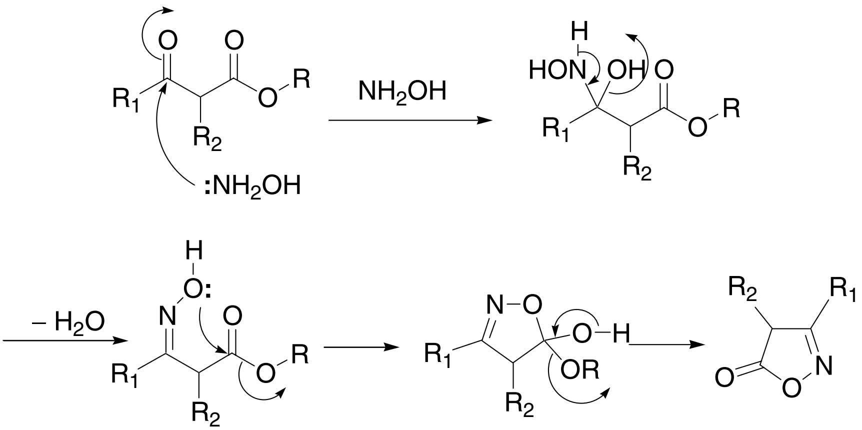
Claisen isoxazole synthesis

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



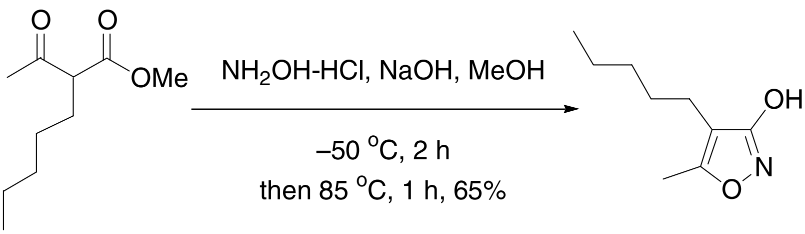
3-isoxazolol

A side reaction:



5-isoxazolone

Example[20]



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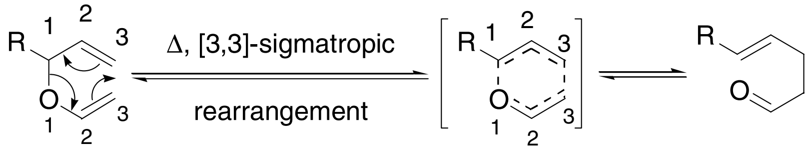
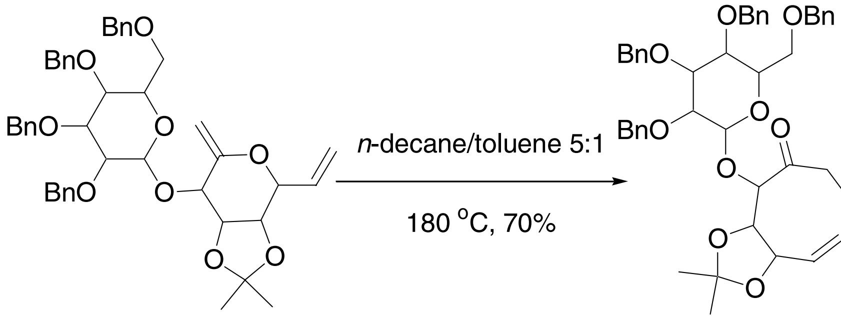
Claisen rearrangements

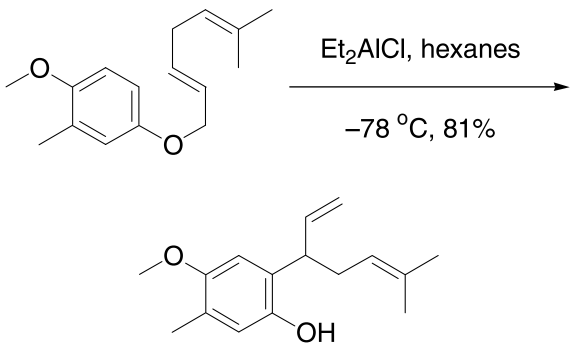
The Claisen, Johnson–Claisen, Ireland–Claisen, *para*-Claisen rearrangements, along with the Carroll rearrangement belong to the category of *[3,3]-sigmatropic rearrangements*. The Claisen rearrangement is a concerted process and the arrow pushing here is merely illustrative.



Example 1[7]



Example 2[8]



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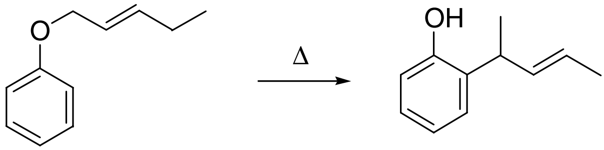
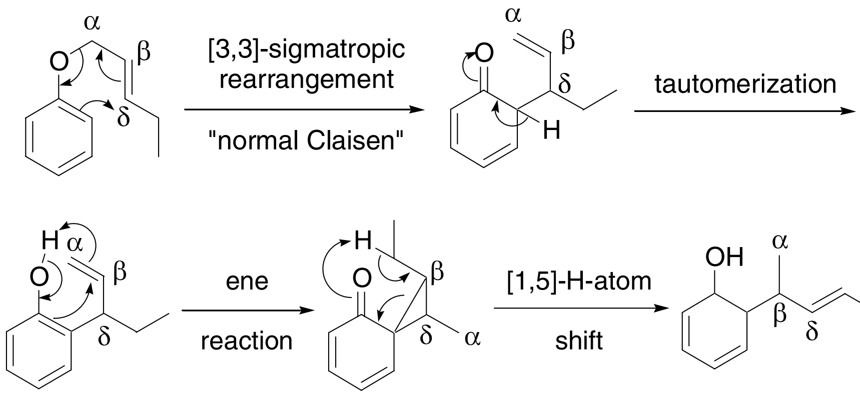
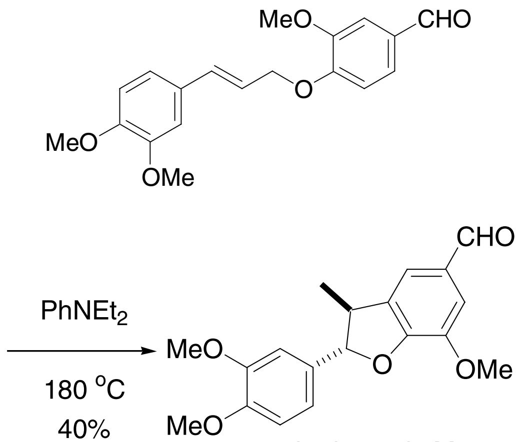
Abnormal Claisen rearrangement

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



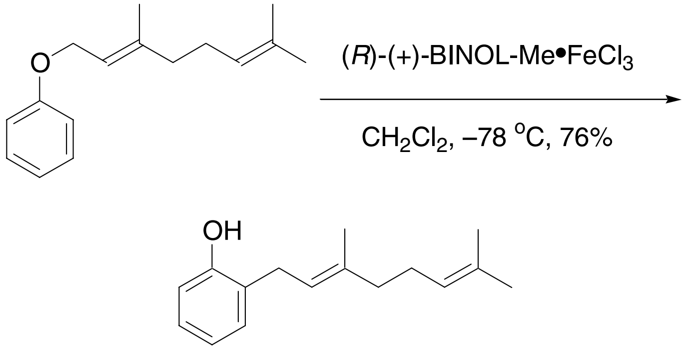


Example 1[4]

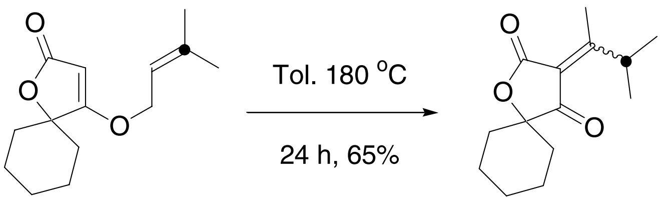


kodsurenin M

Example 2[5]



Example 3[6]



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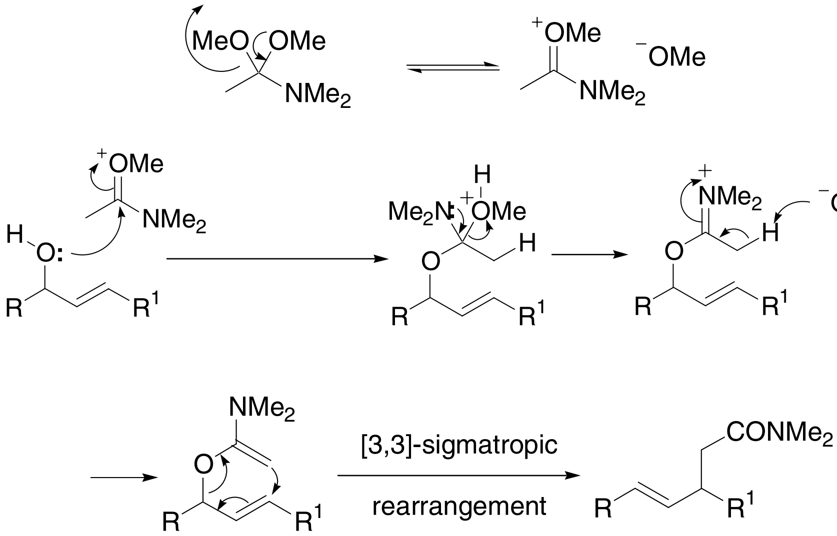
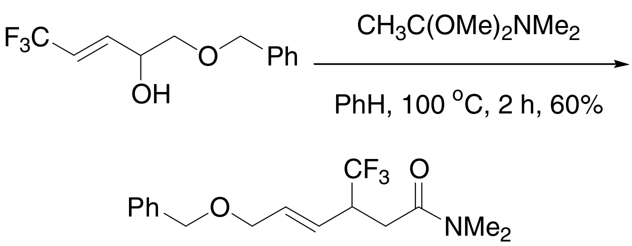
Eschenmoser–Claisen amide acetal rearrangement

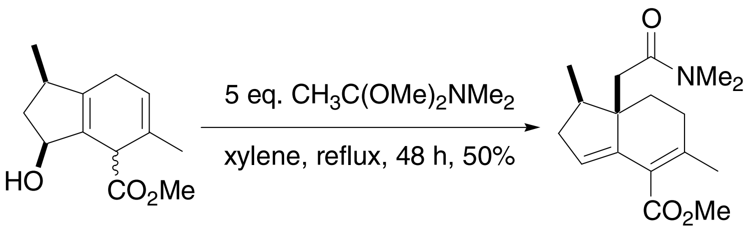
[3,3]-Sigmatropic rearrangement of *N,O*-ketene acetals to yield γ,δ-unsaturated amides. Since Eschenmoser was inspired by Meerwein's observations on the interchange of amide, the Eschenmoser–Claisen rearrangement is sometimes known as the Meerwein–Eschenmoser–Claisen rearrangement.



Example 1[7]



Example 2[9]



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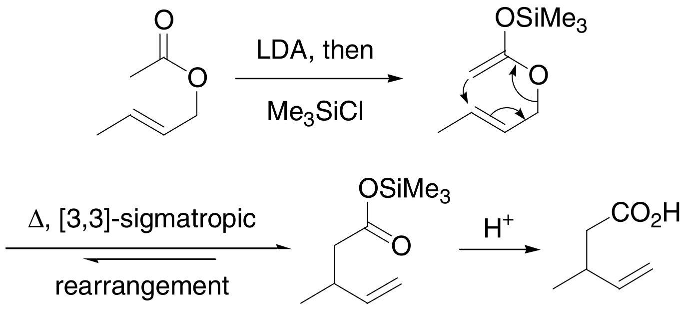
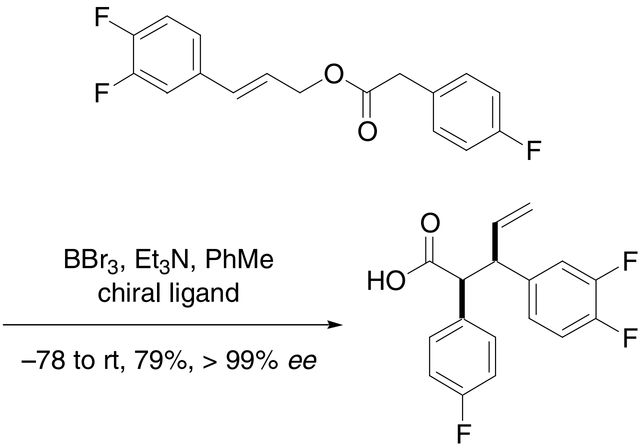
Ireland–Claisen (silyl ketene acetal) rearrangement

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.

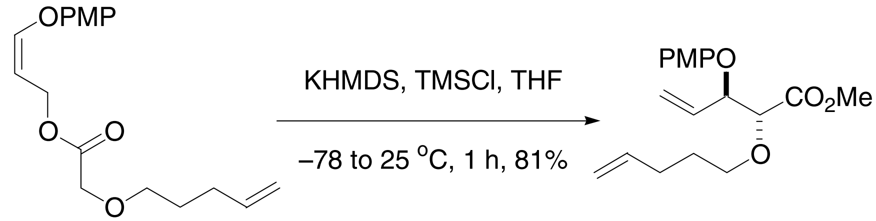


Example 1[3]

Example 2, a modified Ireland–Claisen rearrangement[10]



Example 3[14]



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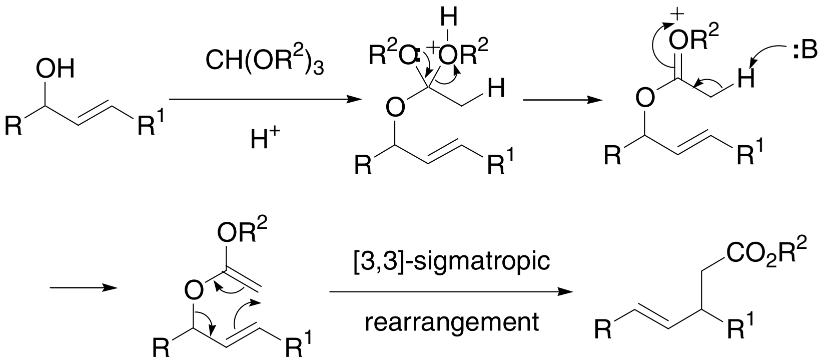
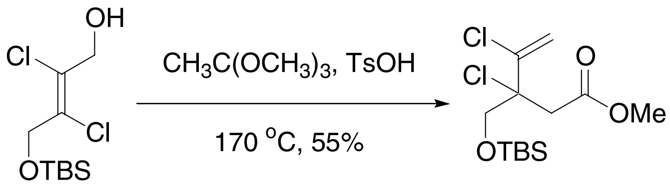
Johnson–Claisen orthoester rearrangement

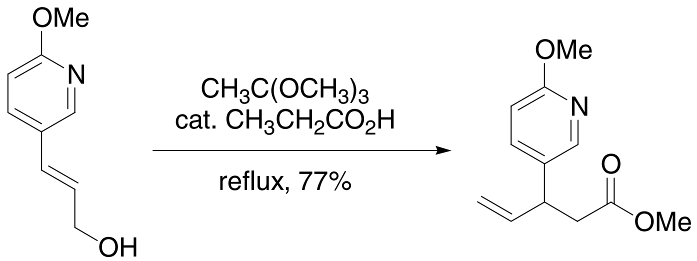
Heating of an allylic alcohol with an excess of trialkyl orthoacetate in the presence of trace amounts of a weak acid to give a mixed orthoester. The orthoester loses ethanol to generate the ketene acetal, which undergoes [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated ester.



Example 1[2]



Example 2[7]



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sin for 20 years before moving to Stanford University, where he was credited with building the modern-day Stanford Chemistry Department.

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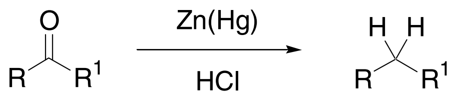
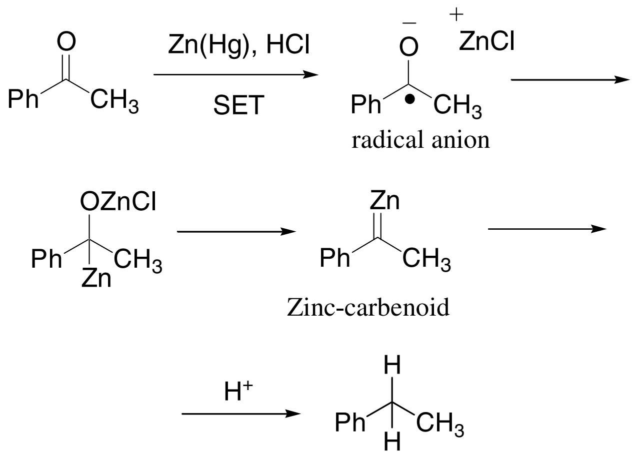
Clemmensen reduction

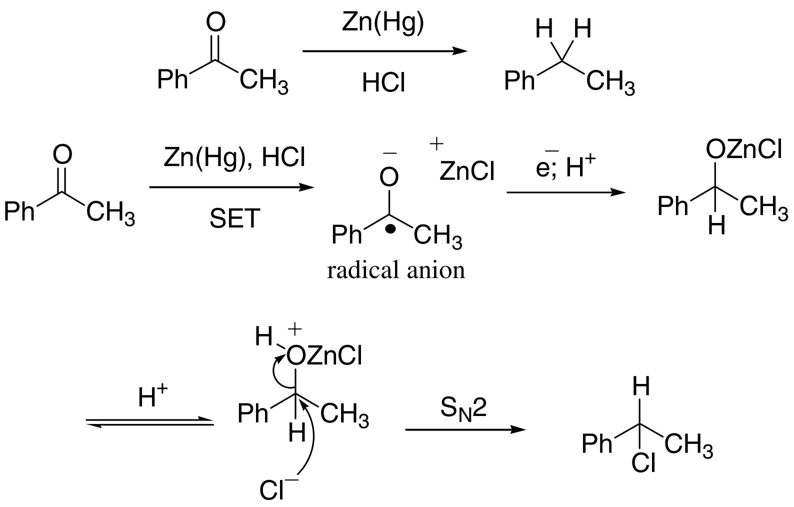
Reduction of aldehydes and ketones to the corresponding methylene compounds using amalgamated zinc and hydrogen chloride.

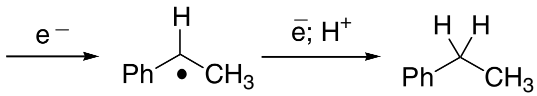


The zinc-carbenoid mechanism:[6]

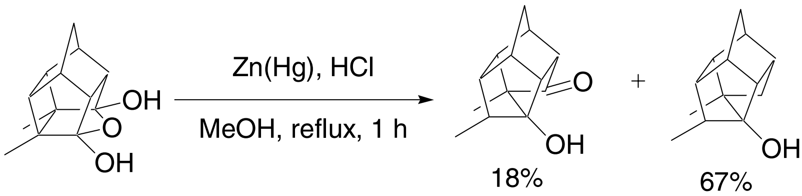


The radical anion mechanism:

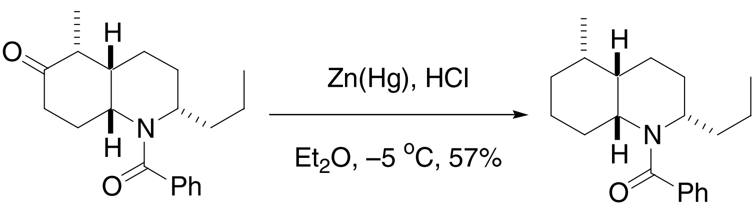




Example 1[8]



Example 2[10]



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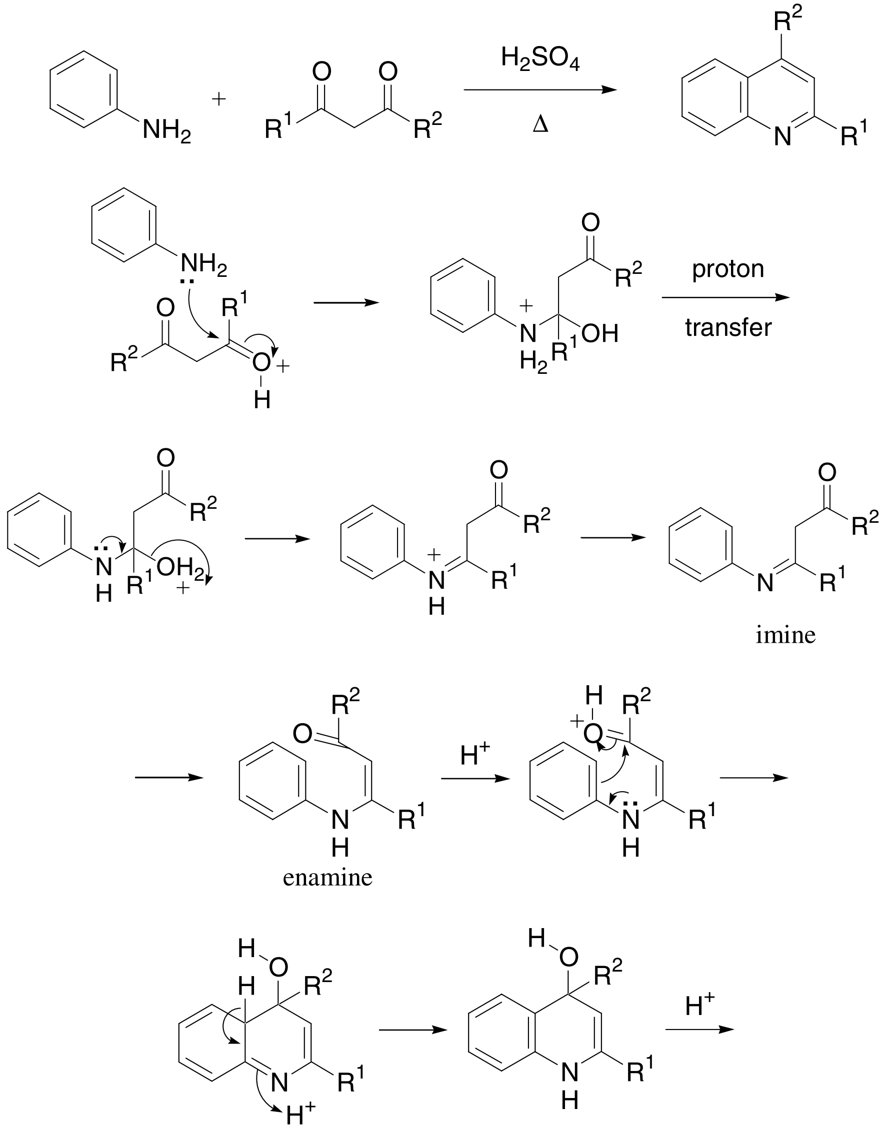
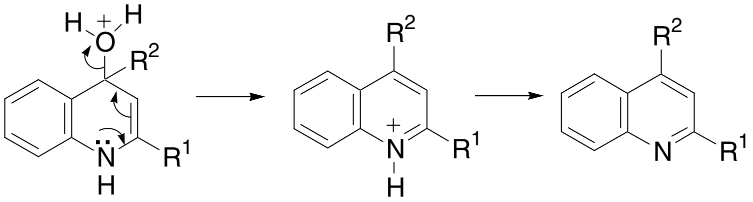
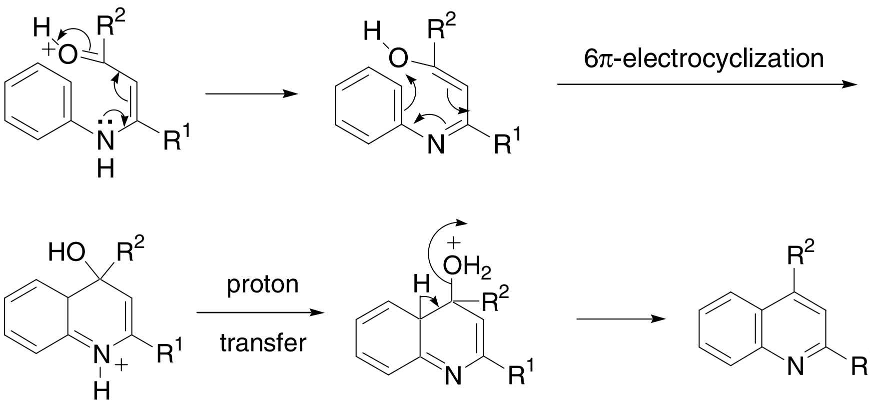
Combes quinoline synthesis

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

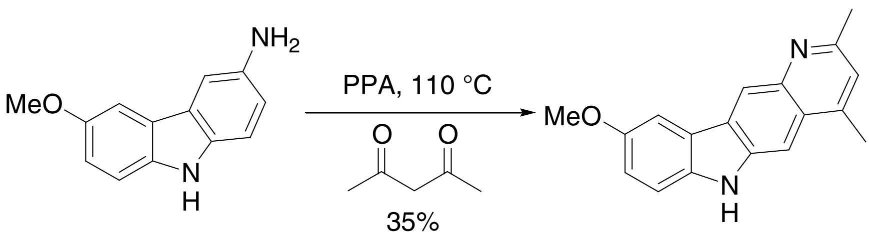




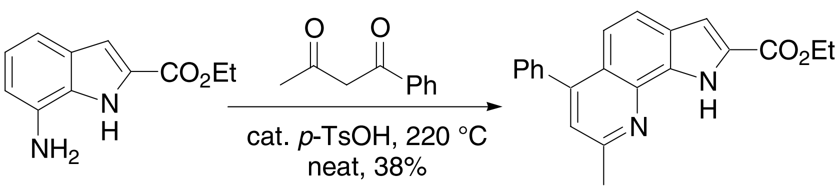
An electrocyclization mechanism is also possible:



Example 1[10]



Example 2[11]



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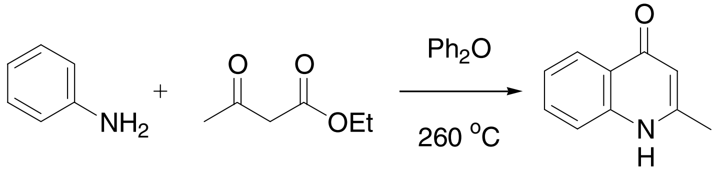
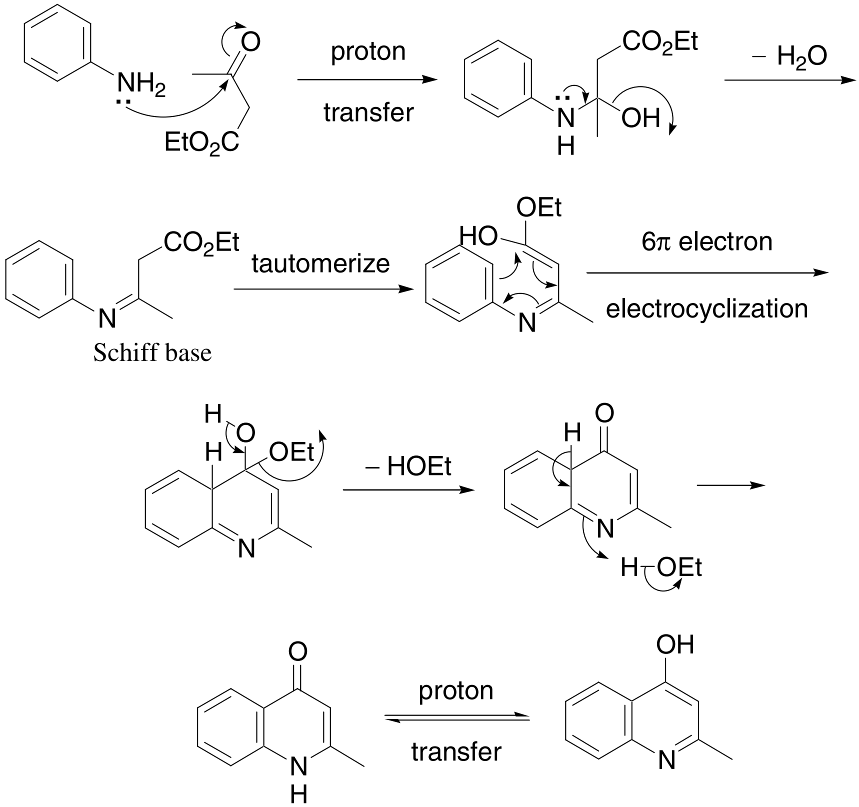
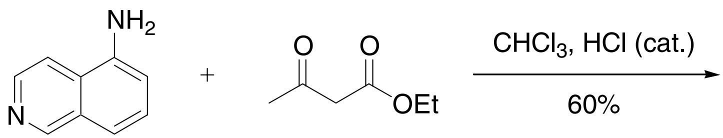
Conrad–Limpach reaction

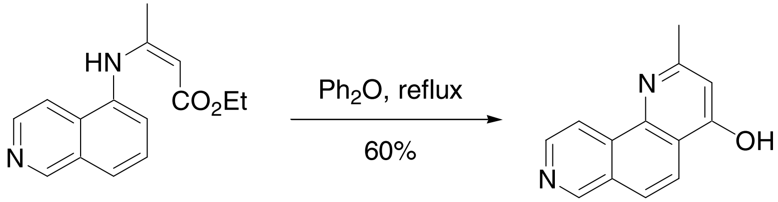
Thermal or acid-catalyzed condensation of anilines with β-ketoesters leads to quinolin-4-ones. *Cf.* Combes quinoline synthesis.



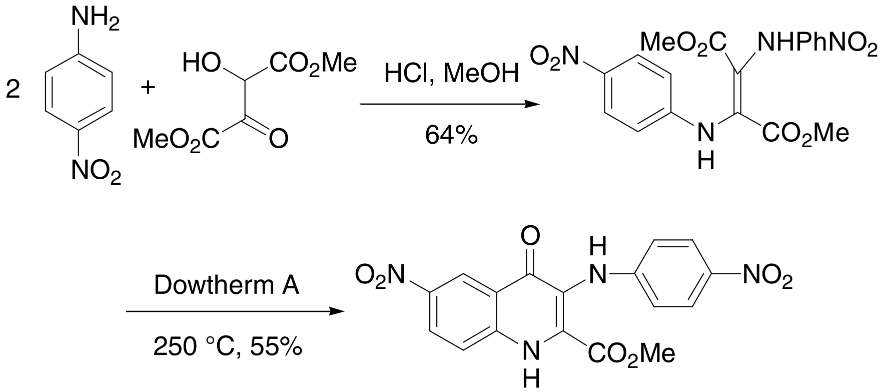


Example 1[3]





Example 2[12]



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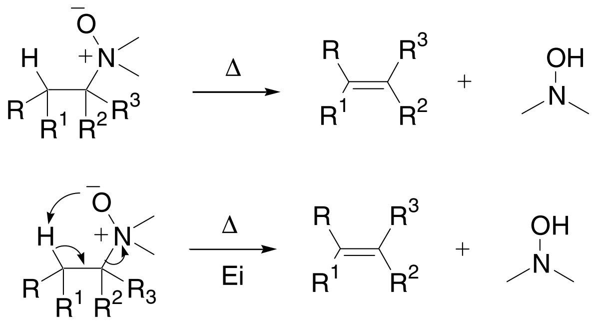
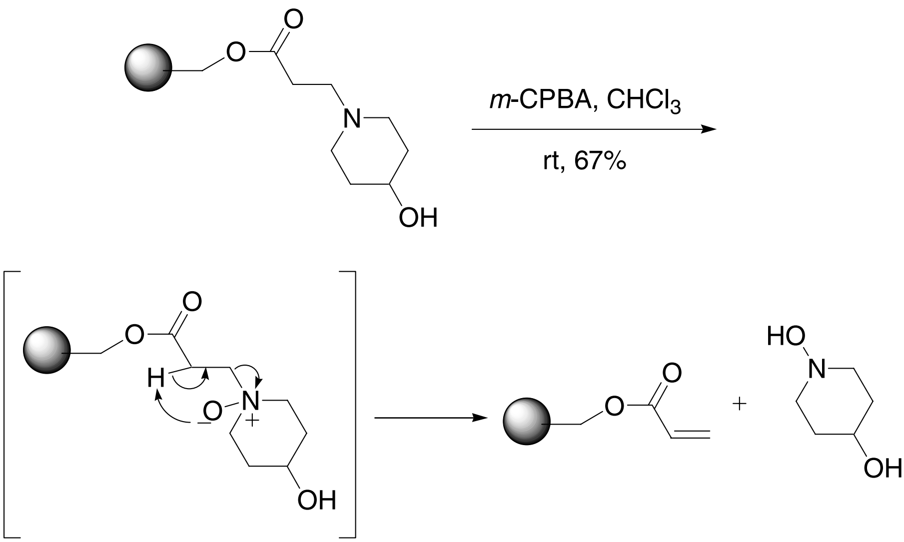
Cope elimination reaction

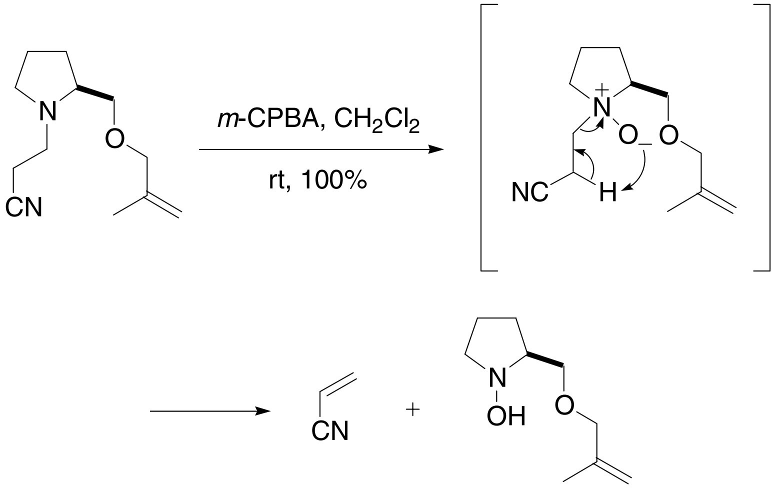
Thermal elimination of *N*-oxides to olefins and *N*-hydroxyl amines.



Example 1[7]



Example 2[11]



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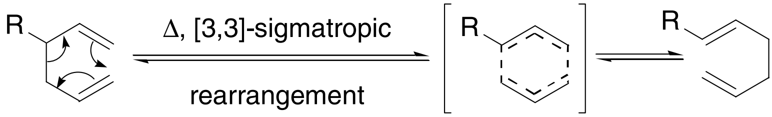
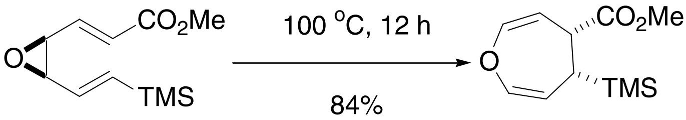
Cope rearrangement

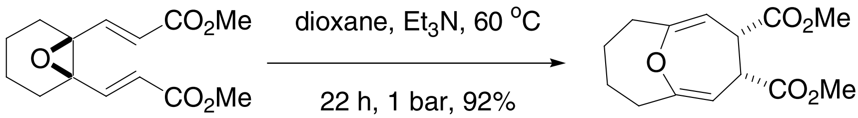
The Cope, oxy-Cope, and anionic oxy-Cope rearrangements belong to the category of *[3,3]-sigmatropic rearrangements*. Since it is a concerted process, the arrow pushing here is only illustrative. *Cf.* Claisen rearrangement.



Example 1[5]



Example 2[8]



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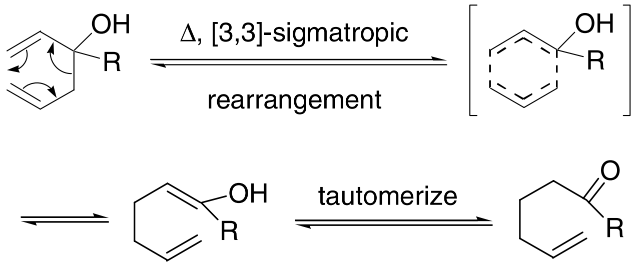
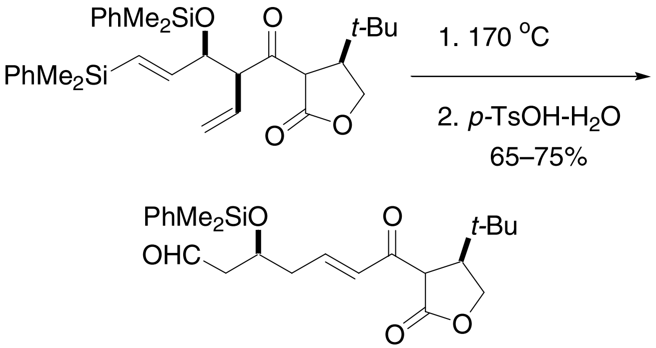
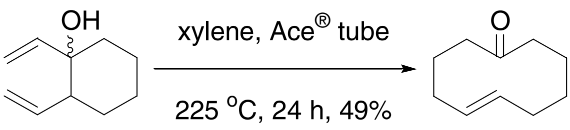
Oxy-Cope rearrangement



Example 1[2]



Example 2[4]



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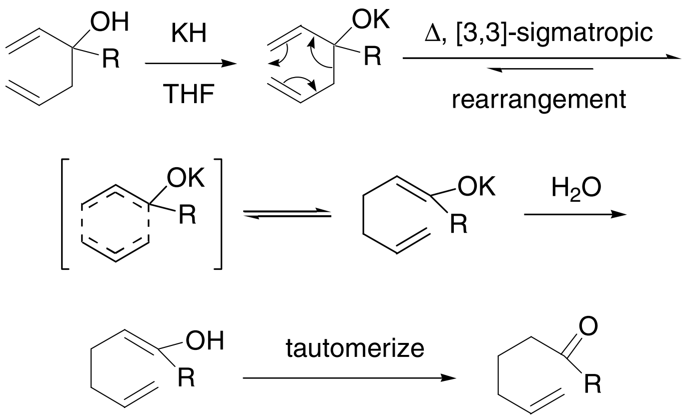
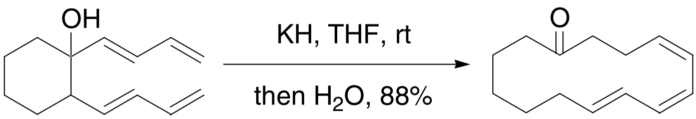
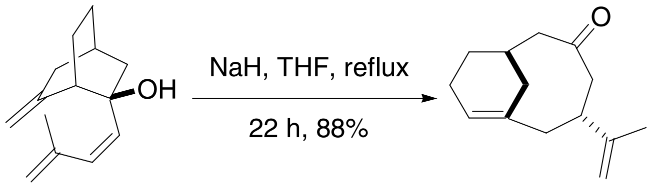
Anionic oxy-Cope rearrangement



Example 1[1]



Example 2[6]



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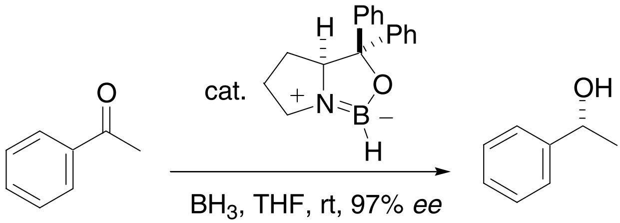
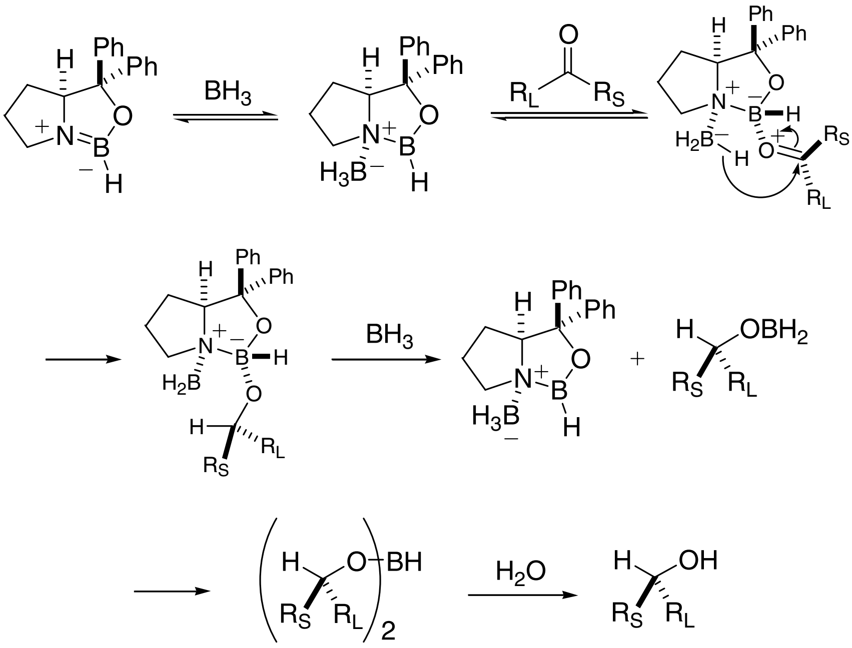
Corey–Bakshi–Shibata (CBS) reduction

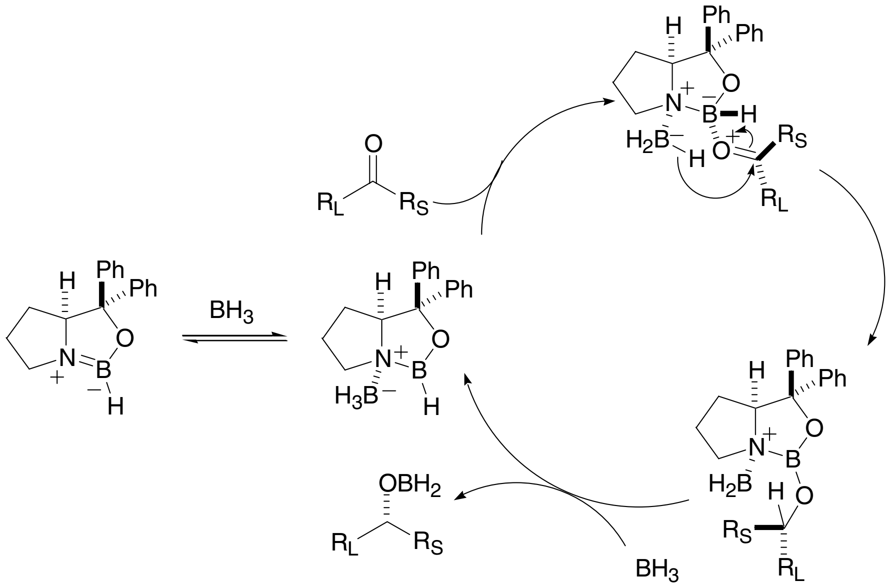
Enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines.



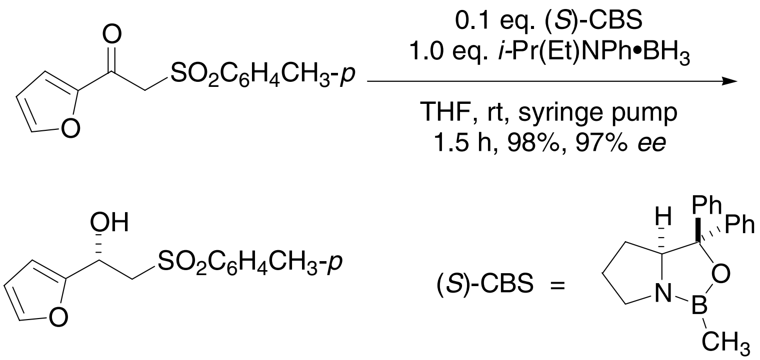


The catalytic cycle is shown on the next page.

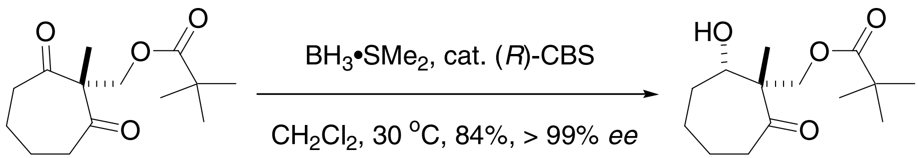
The catalytic cycle:



Example 1[9]



Example 2[14]



References

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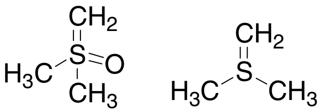
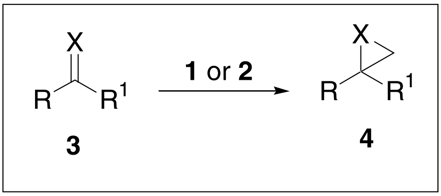
Corey−Chaykovsky reaction

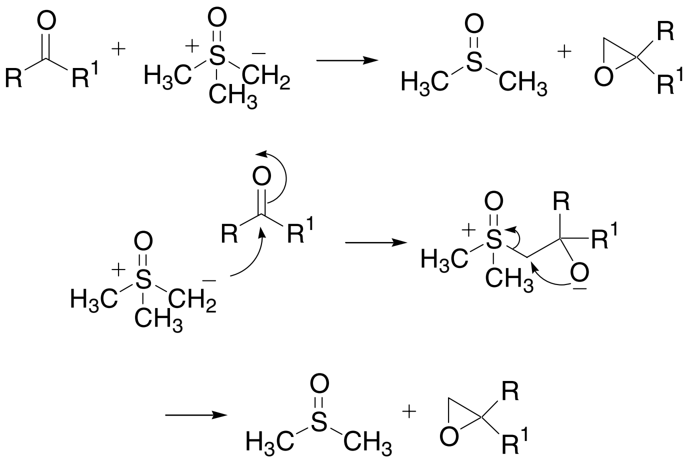
The Corey−Chaykovsky reaction entails the reaction of a sulfur ylide, either dimethylsulfoxonium methylide **1** (Corey's ylide) or dimethylsulfonium methylide **2**, with electrophile **3** such as carbonyl, olefin, imine, or thiocarbonyl, to offer **4** as the corresponding epoxide, cyclopropane, aziridine,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



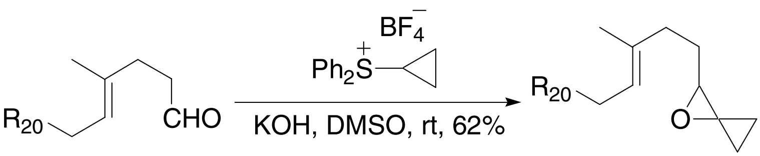
1 **2**



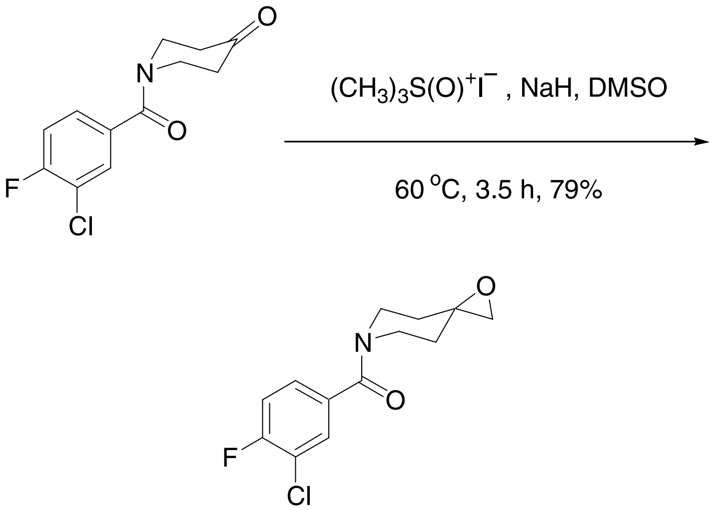
X = O, CH_2, NR^2, S, $CHCOR^3$, $CHCO_2R^3$, $CHCONR_2$, CHCN



Example 1[12]



Example 2[14]



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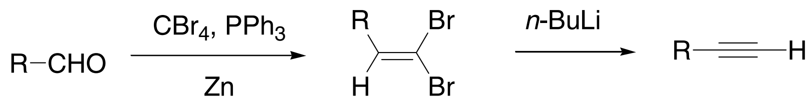
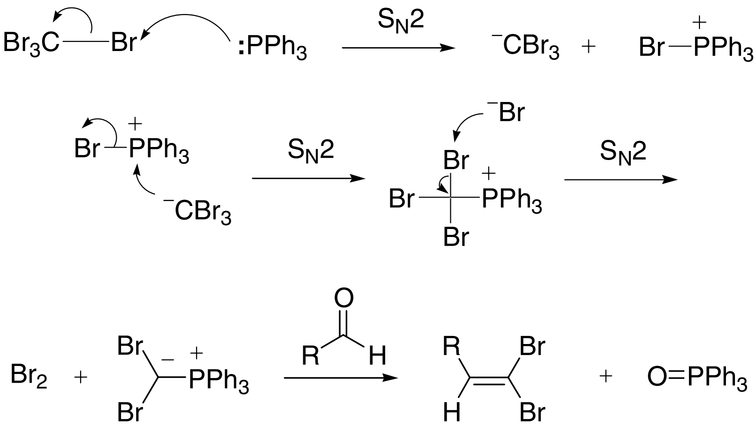
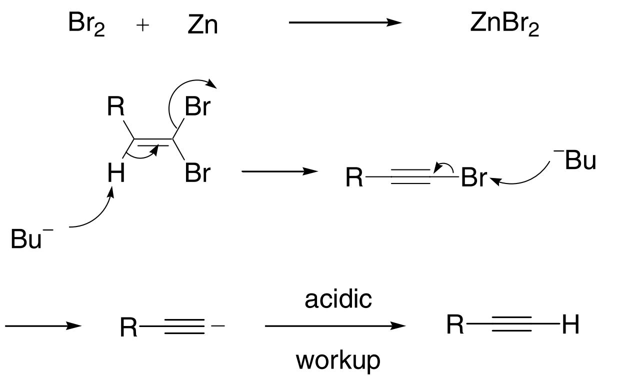
Corey–Fuchs reaction

One-carbon homologation of an aldehyde to dibromoolefin, which is then treated with *n*-BuLi to produce a terminal alkyne.

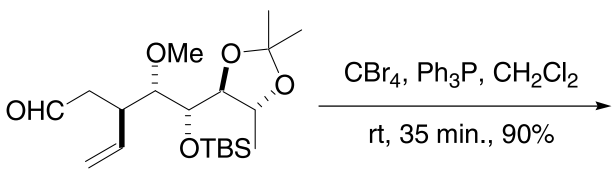


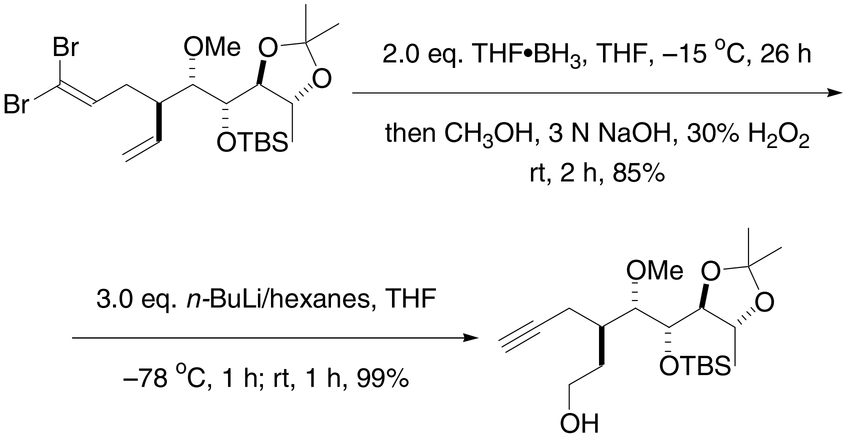


Wittig reaction (see page 621 for the mechanism)

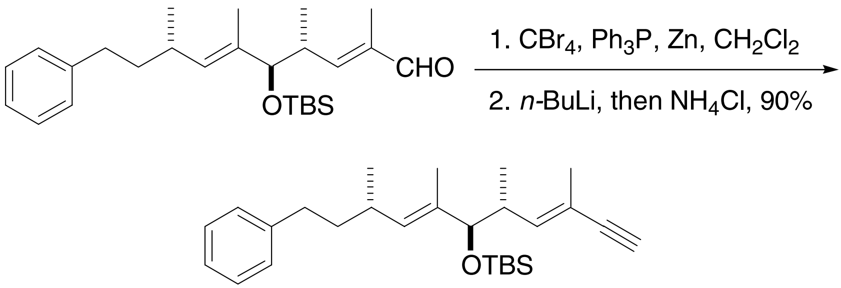


Example 1[3]





Example 2[8]



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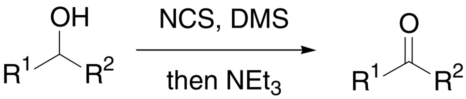
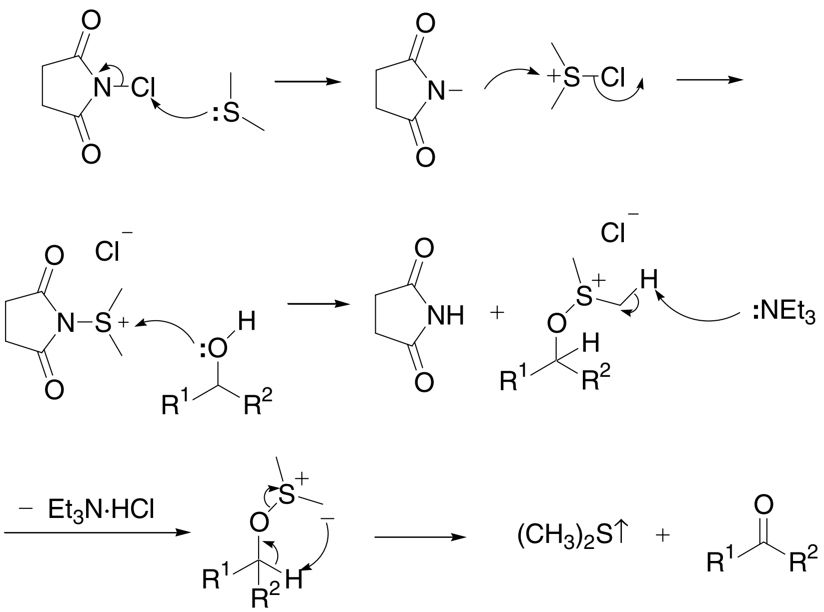
Corey–Kim oxidation

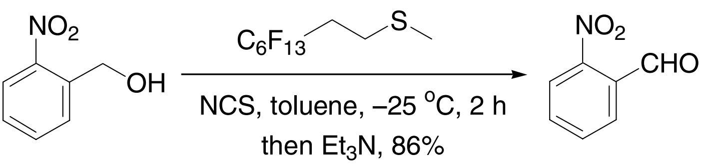
Oxidation of alcohol to the corresponding aldehyde or ketone using NCS/DMS, followed by treatment with a base. *Cf.* Swern oxidation.



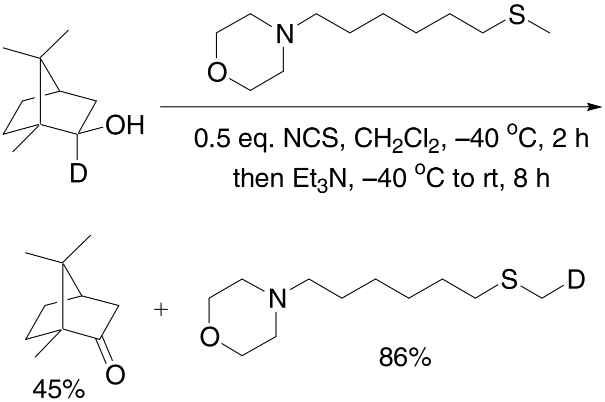
NCS = ***N*****-C**hloro**s**uccinimide; DMS = **Dim**ethyl**s**ulfide.



Example 1, fluorous Corey–Kim reaction[5]



Example 2, odorless Corey–Kim reaction[8]



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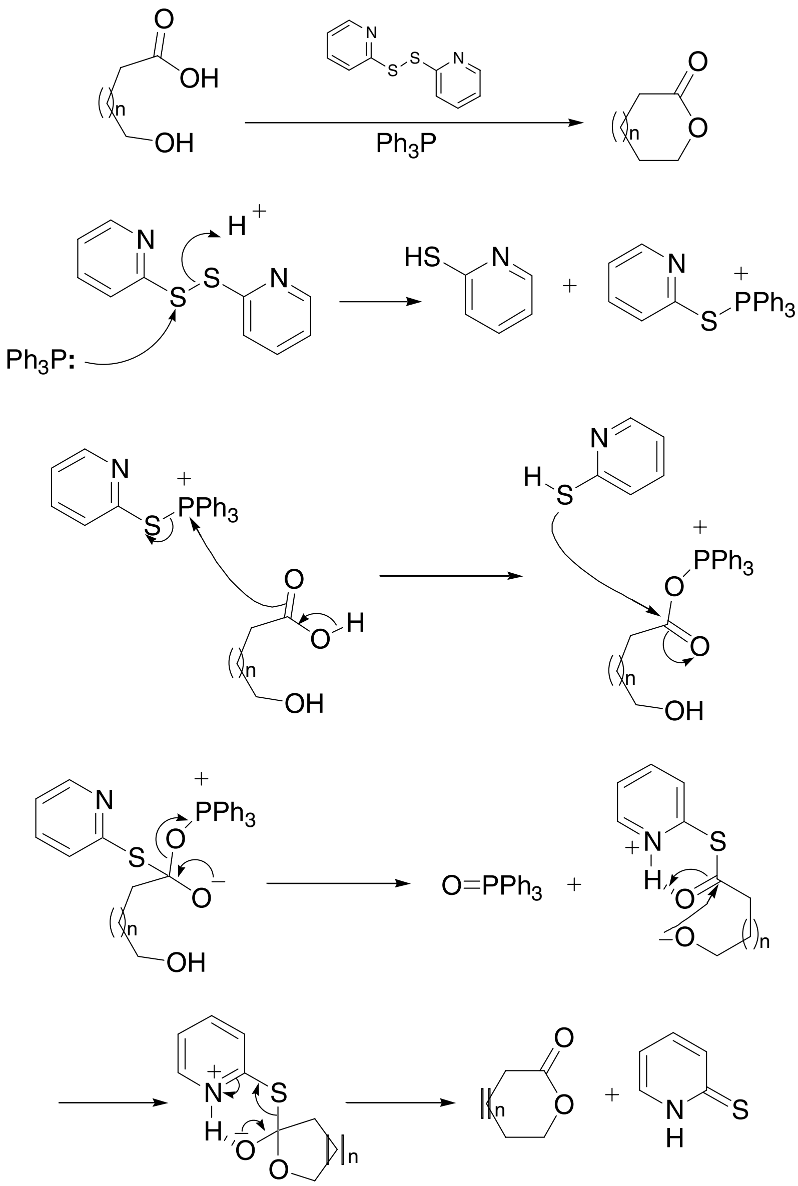
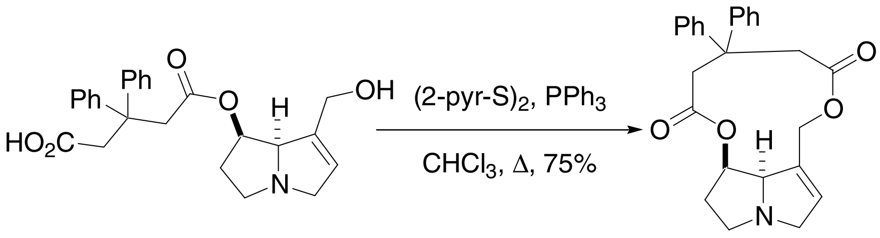
Corey–Nicolaou macrolactonization

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

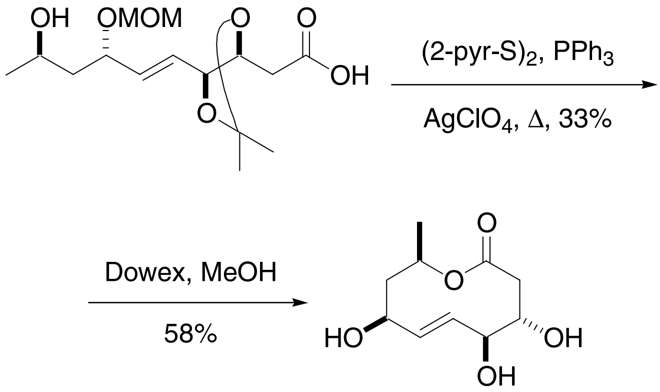


2-pyridinethione

Example 1[3]



Example 2[6]



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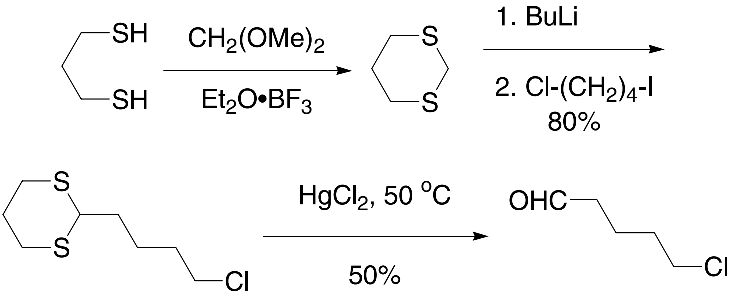
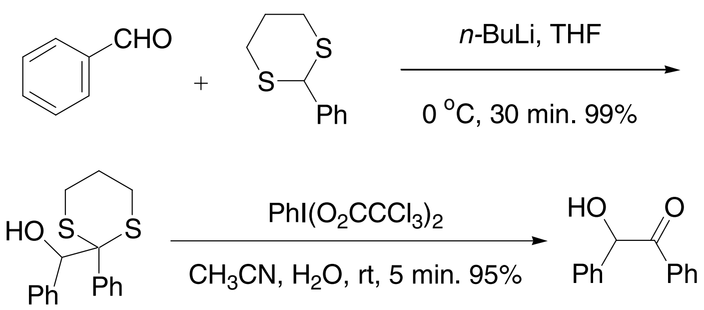
Corey–Seebach reaction

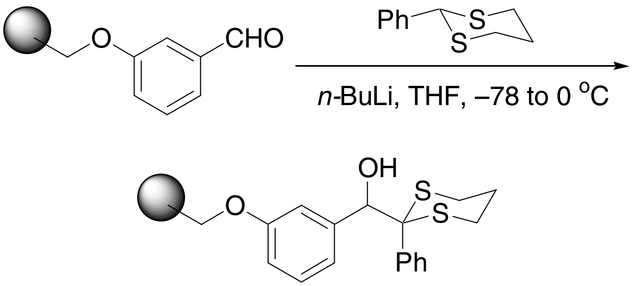
Dithiane as a nucleophile, serving as a masked carbonyl equivalent. This is an example of umpolung.



Example 1[6]



Example 2[8]



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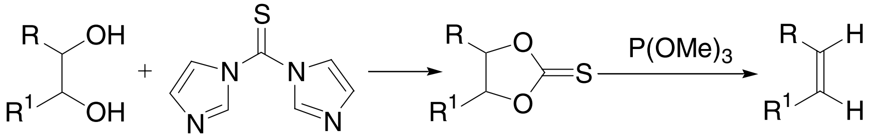
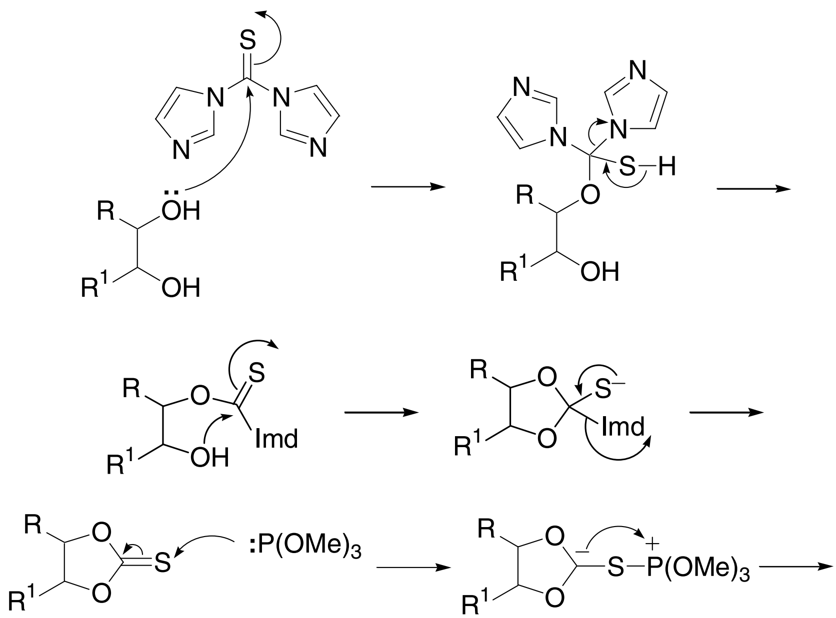
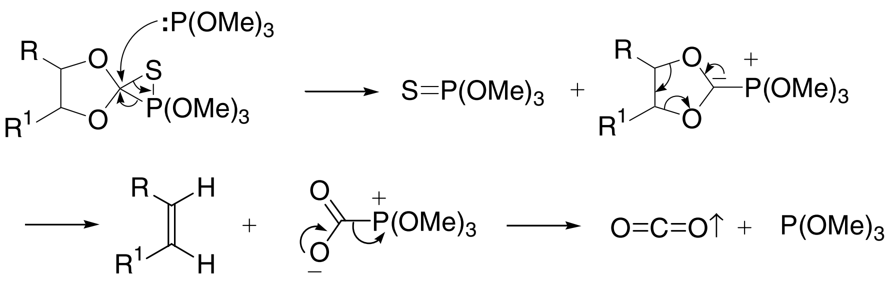
Corey–Winter olefin synthesis

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

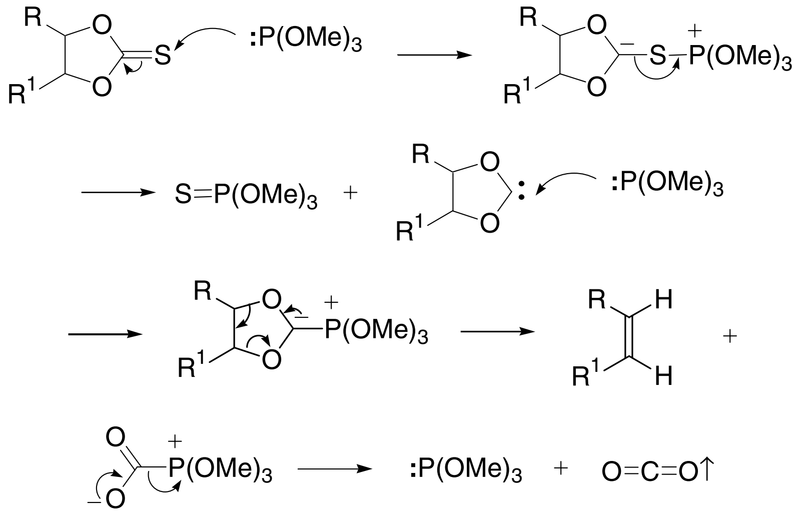




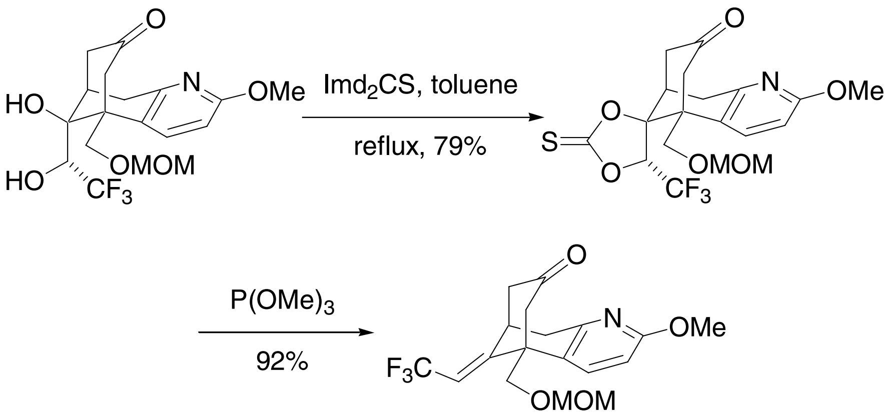
1,3-dioxolane-2-thione (cyclic thiocarbonate)



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

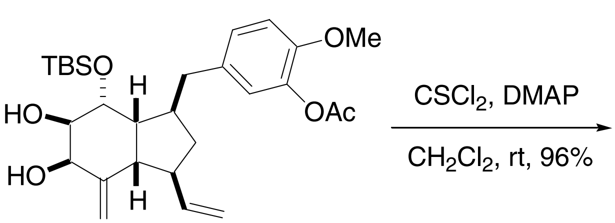


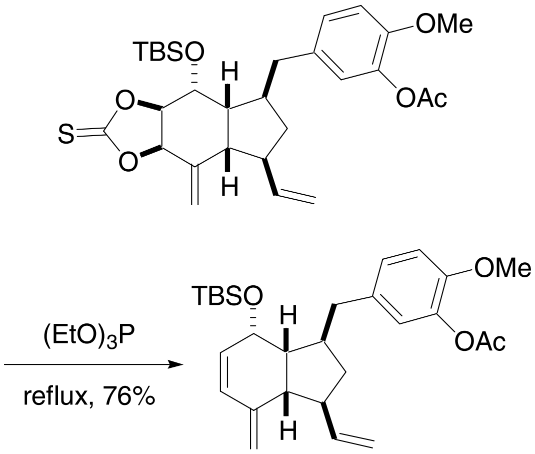
Example 1[7]



One olefin isomer

Example 2[11]





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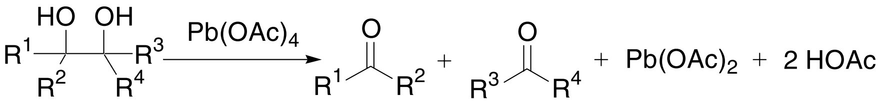
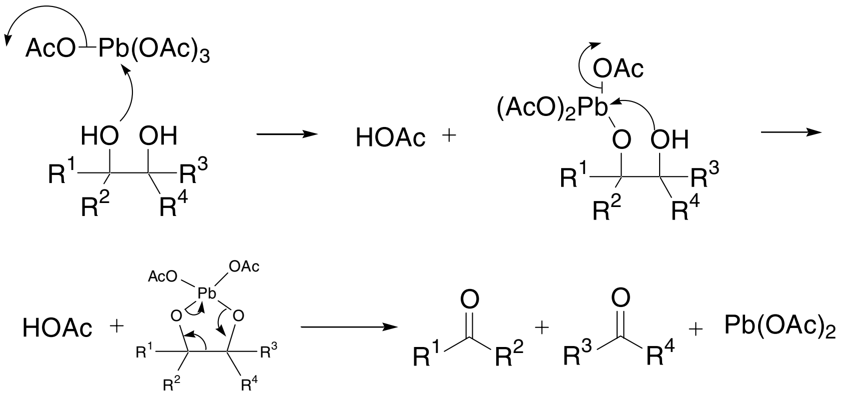
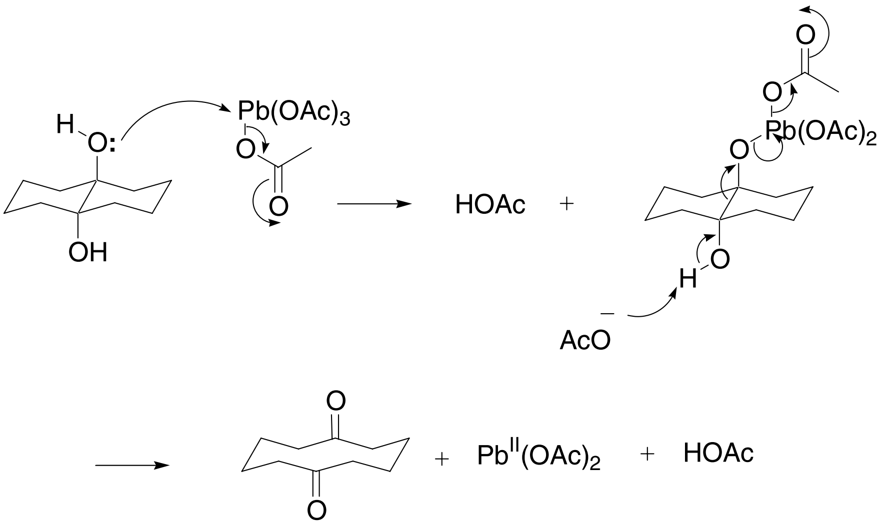
Criegee glycol cleavage

Vicinal diol is oxidized to the two corresponding carbonyl compounds using $Pb(OAc)_4$, **l**ead **t**etra**a**cetate (LTA).

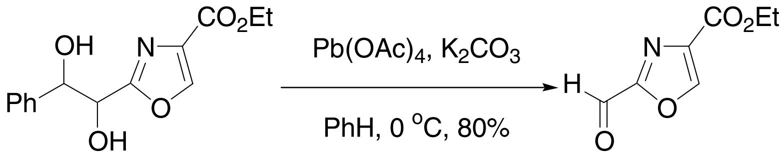




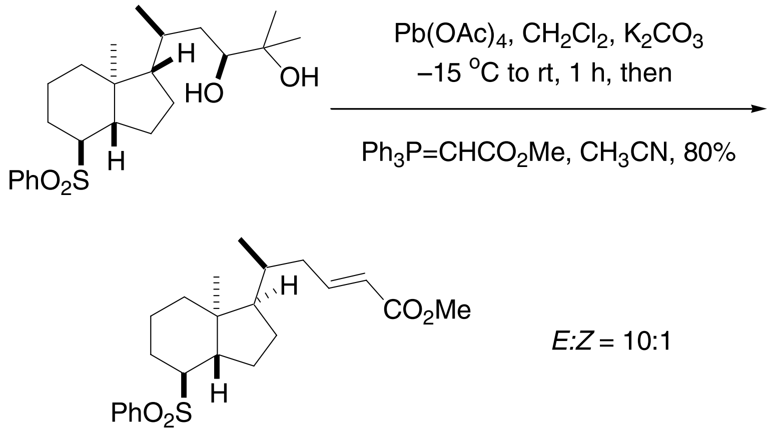
An acyclic mechanism is possible as well. It is much slower than the cyclic mechanism, but is operative when the cyclic intermediate can not form:[3]



Example 1[7]



Example 2[9]



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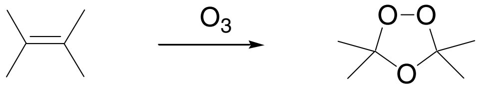
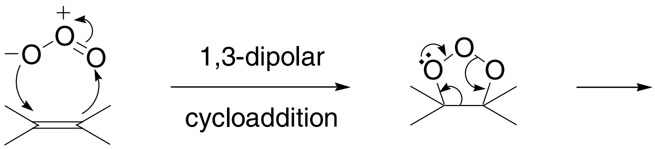
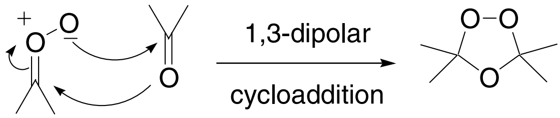
Criegee mechanism of ozonolysis





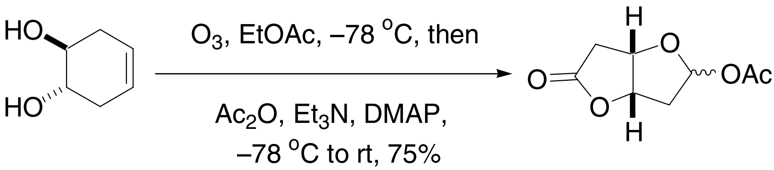
primary ozonide (1,2,3-trioxolane)



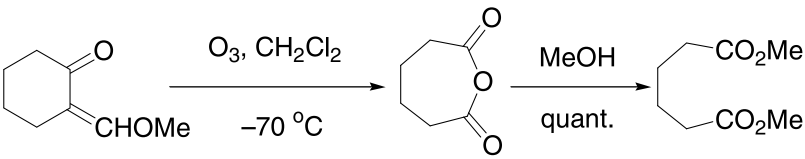
zwitterionic peroxide
(Criegee zwitterion)
also known as "carbonyl oxide"

secondary ozonide (1,2,4-trioxolane)

Example 1[14]



Example 2[15]



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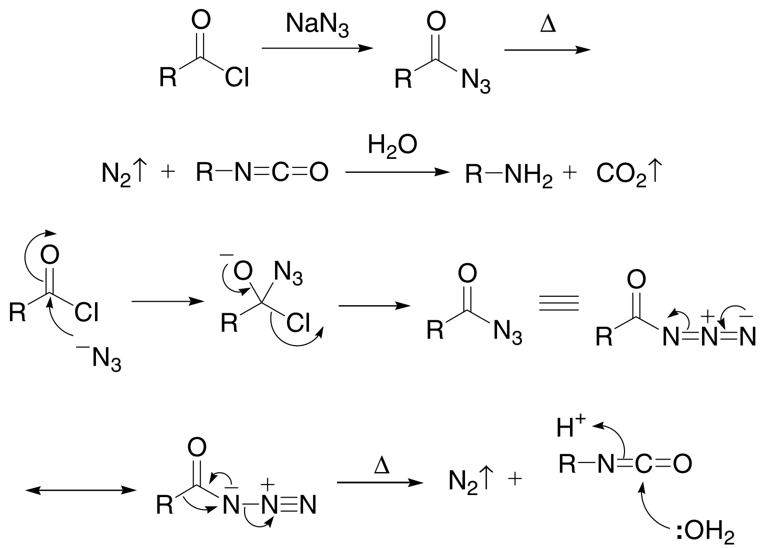
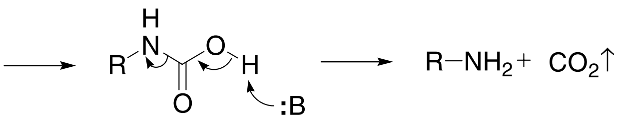
Curtius rearrangement

Thermal or photochemical rearrangement of acyl azides into amines *via* isocyanate intermediates. While the thermal rearrangement is a concerted process, the photochemical rearrangement goes through a nitrene intermediate.

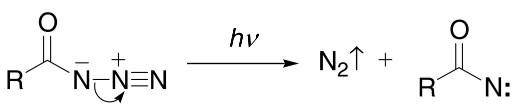
The thermal rearrangement:



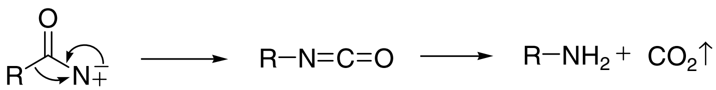
isocyanate intermediate



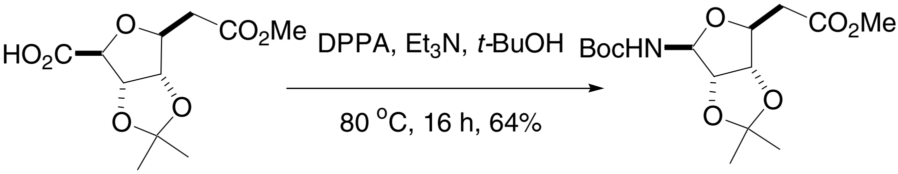
The photochemical rearrangement:



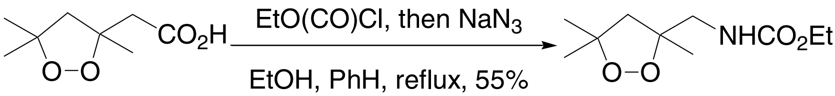
nitrene



Example 1[9]



Example 2[11]



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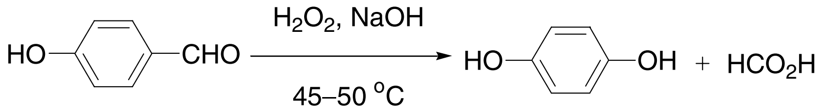
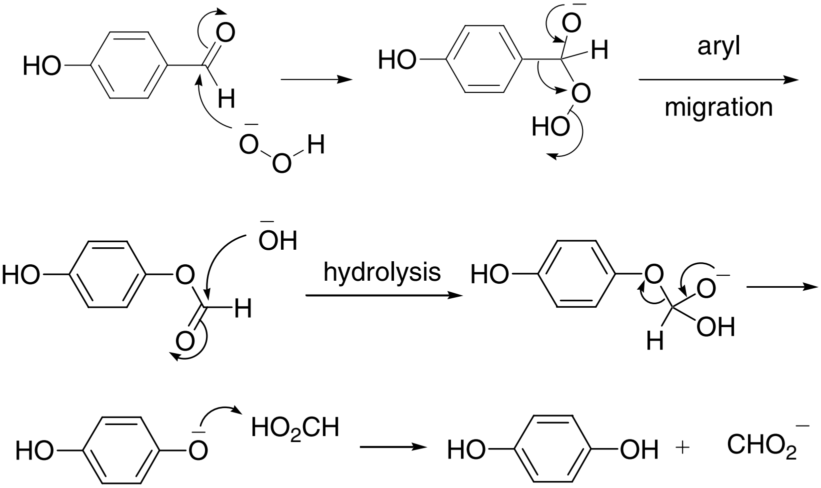
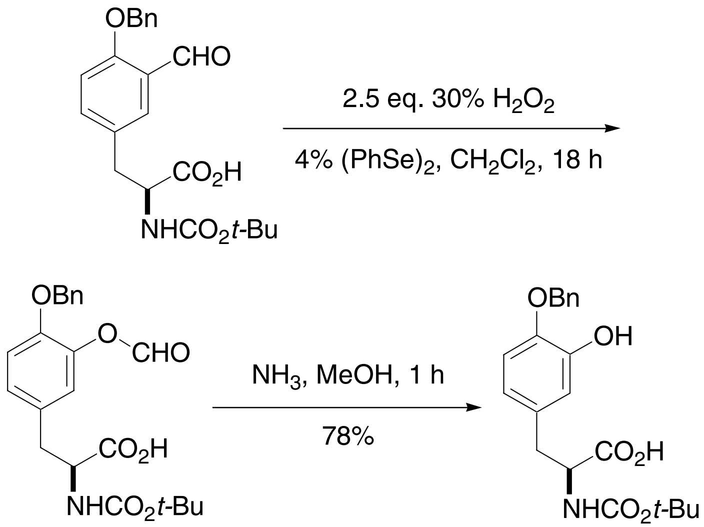
Dakin oxidation

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

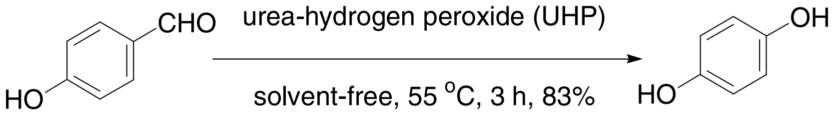




Example 1[6]



Example 2[7]



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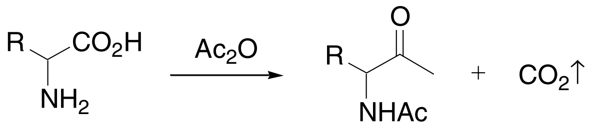
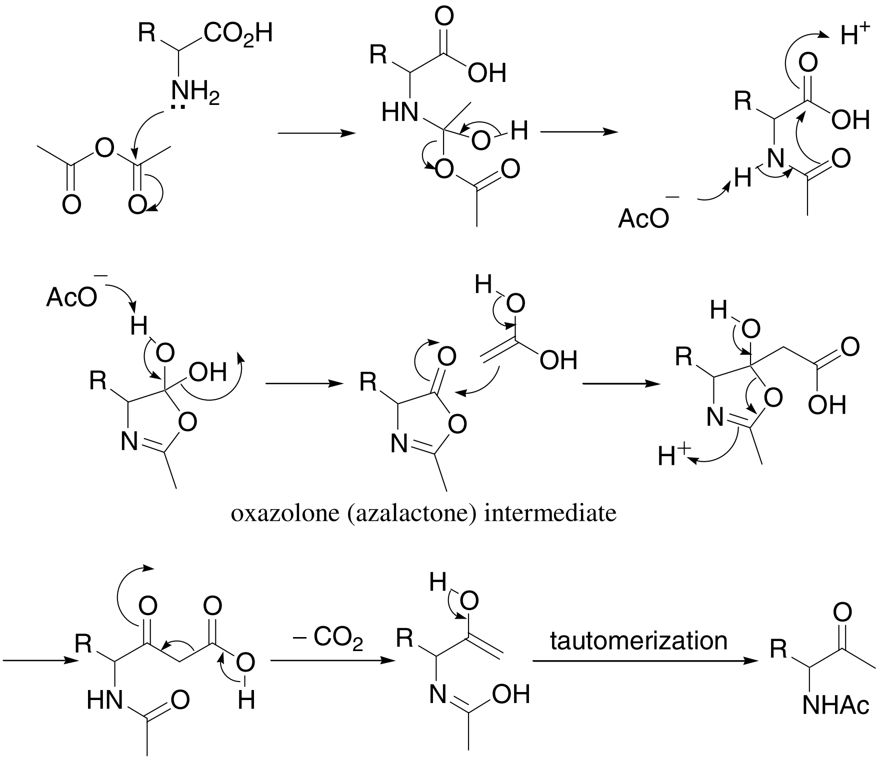
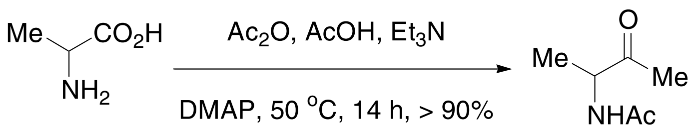
Dakin–West reaction

The direct conversion of an α-amino acid into the corresponding α-acetylamino-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 1[12]



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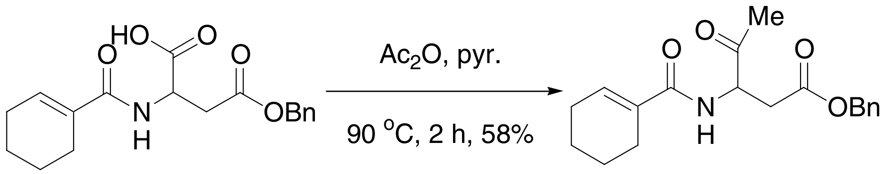

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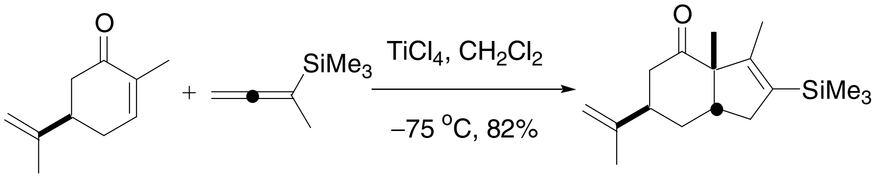
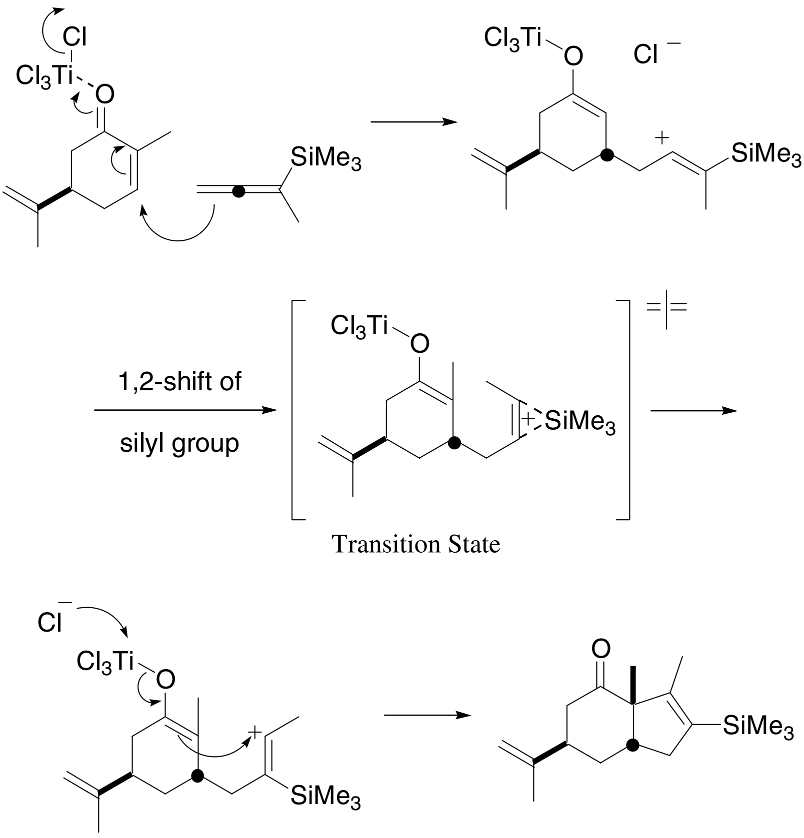
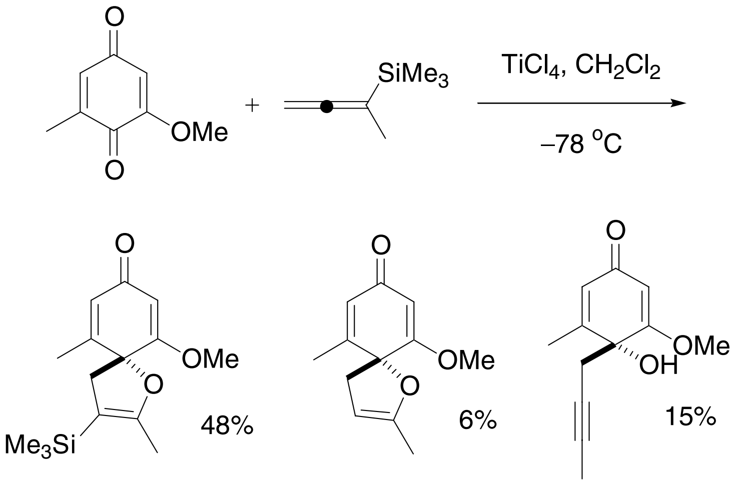
Danheiser annulation

Trimethylsilylcyclopentene annulation from an α,β-unsaturated ketone and trimethylsilylallene in the presence of a Lewis acid.





Example 1[7]



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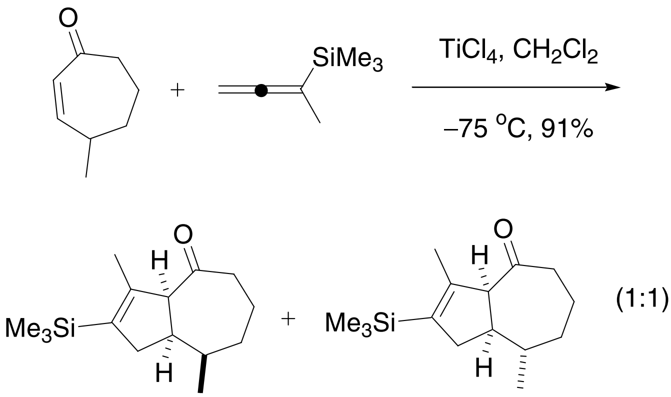

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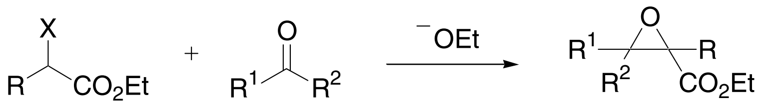
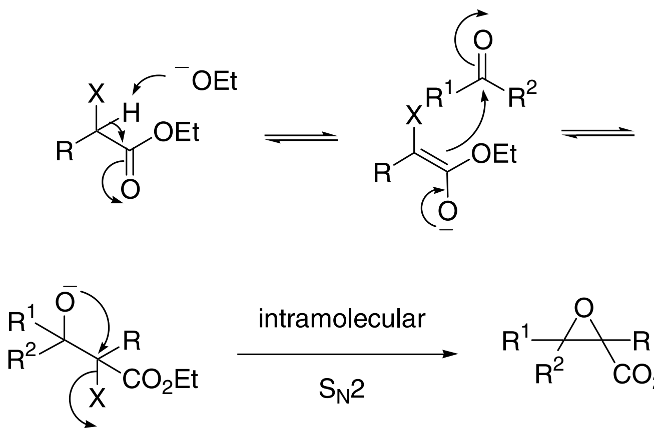
Darzens glycidic ester condensation

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





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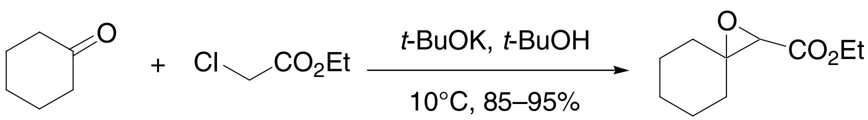

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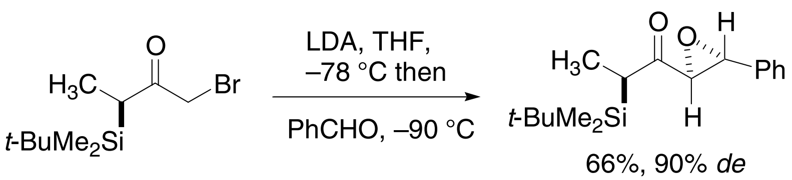

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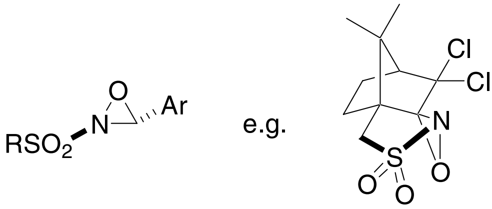
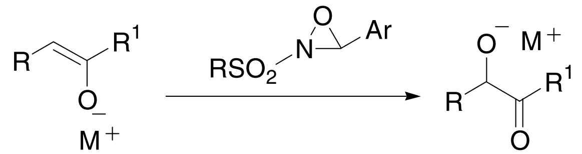
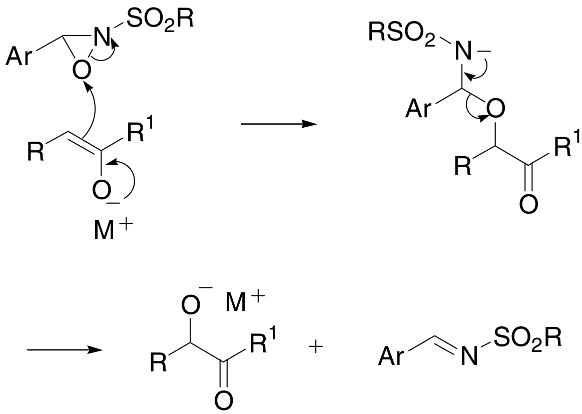
Davis chiral oxaziridine reagents

Chiral *N*-sulfonyloxaziridines employed for asymmetric hydroxylation, *etc.*







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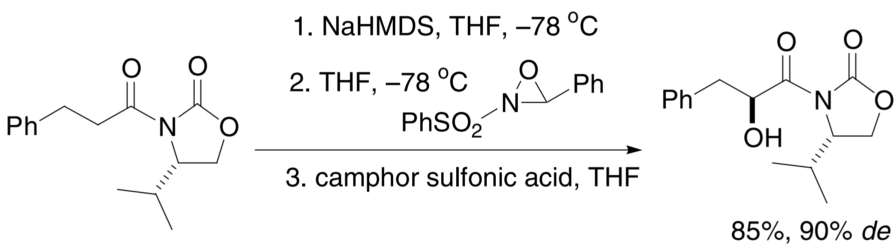
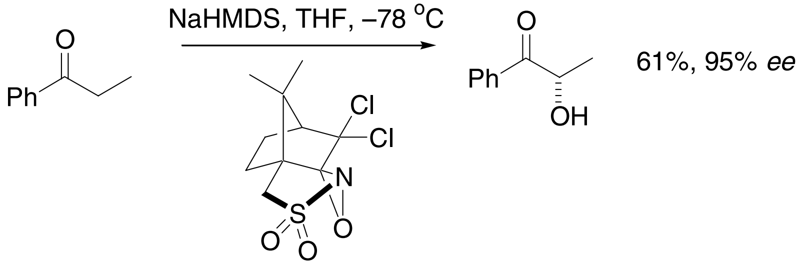


Example 2[5]



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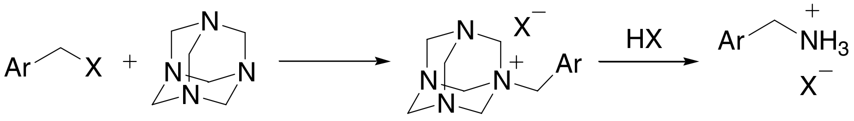
Delépine amine synthesis

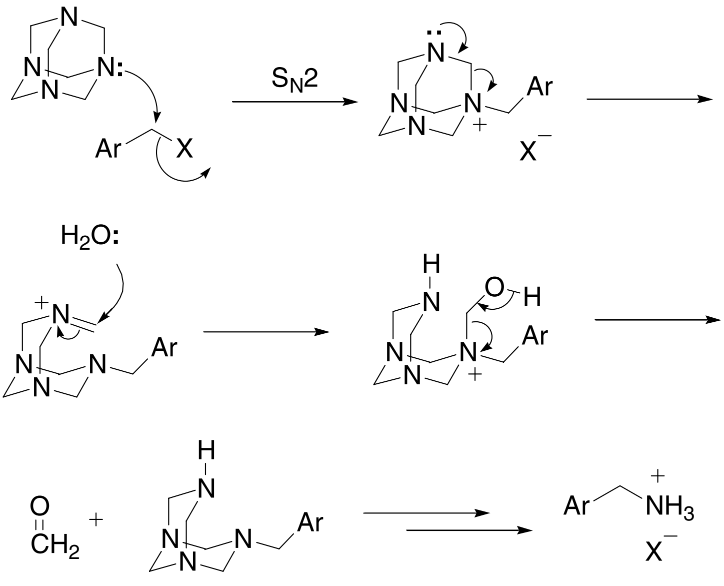
The reaction between alkyl halides and hexamethylenetetramine, followed by cleavage of the resulting salt with ethanolic HCl to yield primary amines.
Cf. Gabriel synthesis, where the product is also amine and Sommelet reaction, where the product is aldehyde. The Delépine works well for active halides such as benzyl, allyl halides, and α-halo-ketones.



hexamethylenetetramine

$$[ArCH_2\text{-}C_6H_{12}N_4]^+X^- \quad + \quad 3HCl \quad + 6H_2O$$

$$= \ ArCH_2NH_2{\bullet}HX \quad + \quad 6CH_2O \quad + \quad 3NH_4Cl$$



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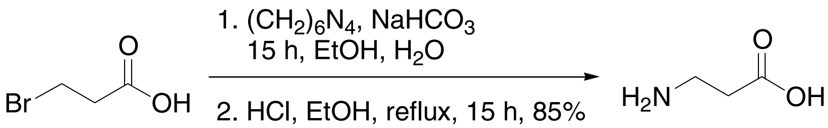

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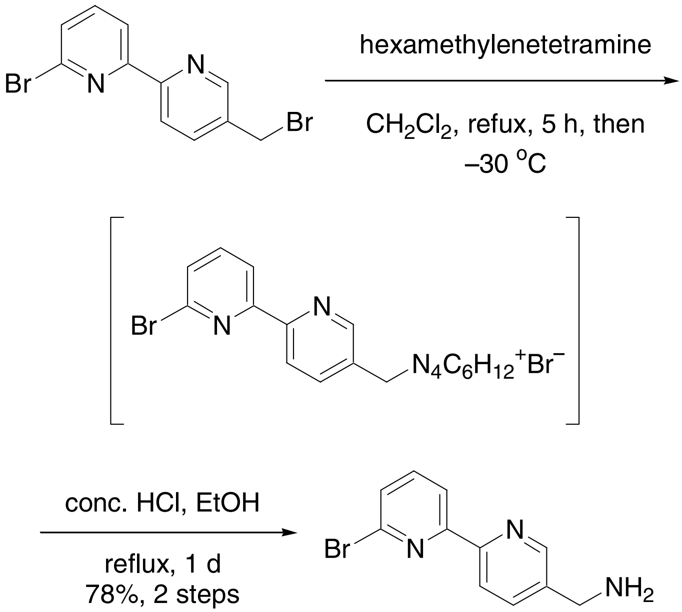

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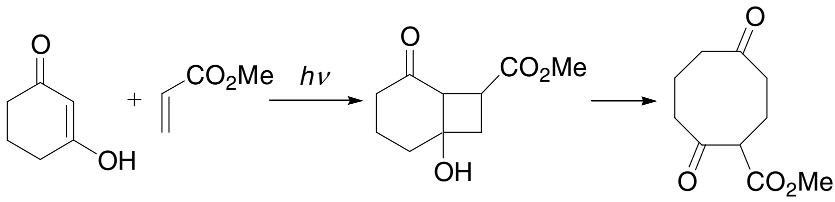
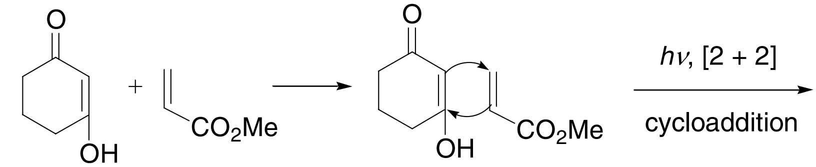
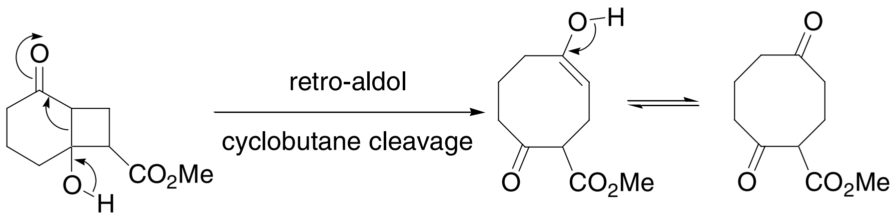
de Mayo reaction

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

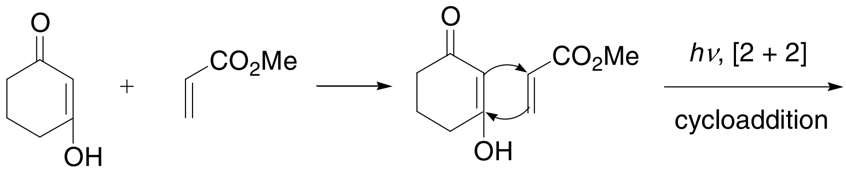




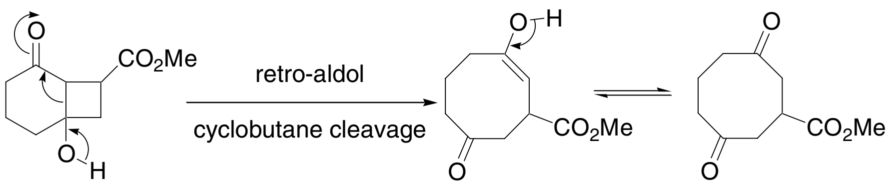
head-to-tail alignment



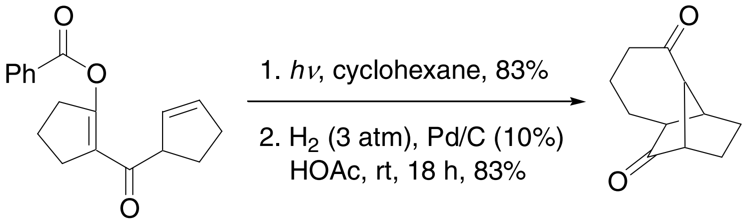
Minor regioisomer:



head-to-head alignment



Example 1[5]



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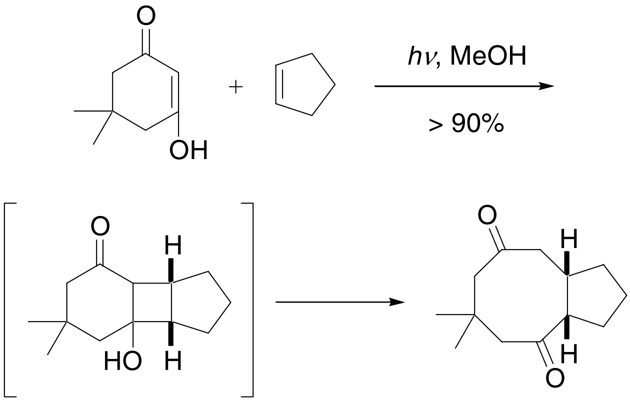

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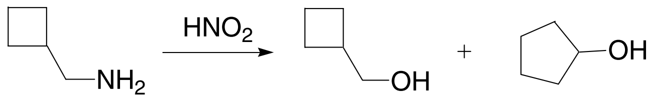
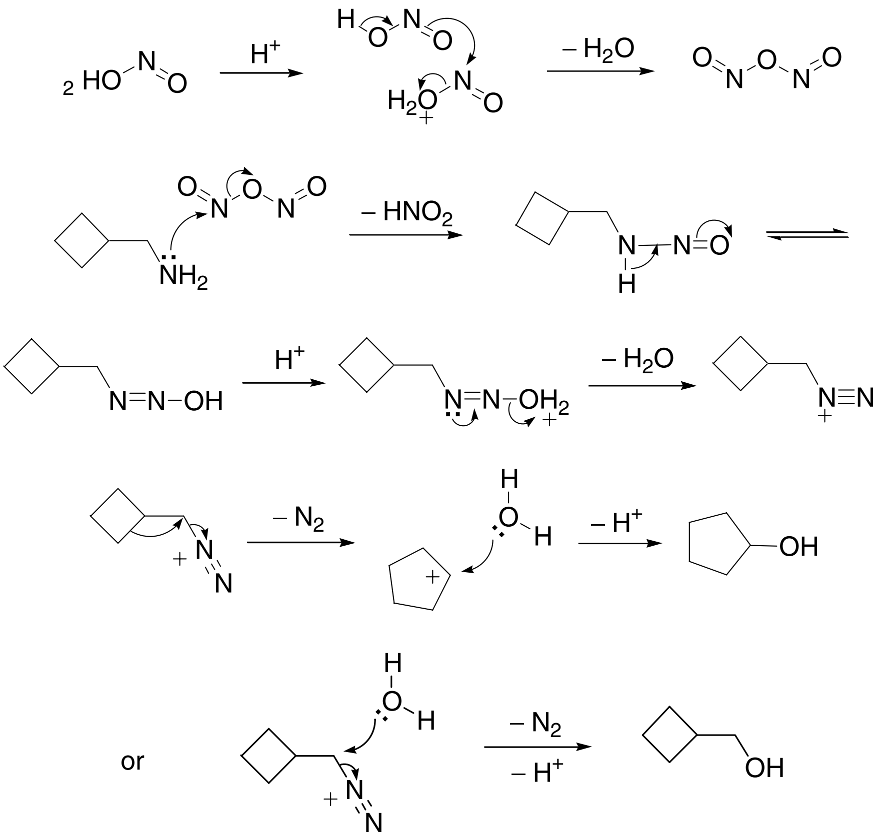
Demjanov rearrangement

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





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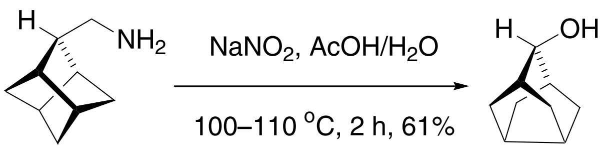
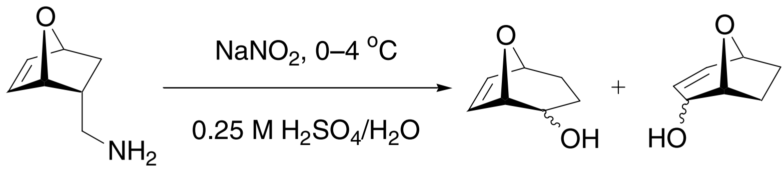


Example 2[9]



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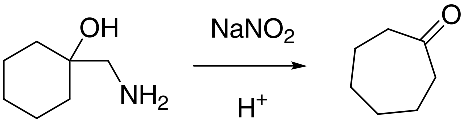
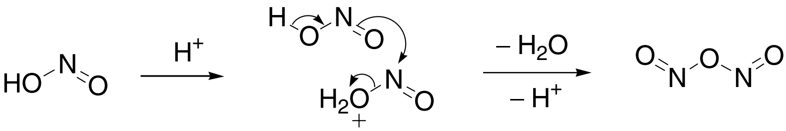
Tiffeneau–Demjanov rearrangement

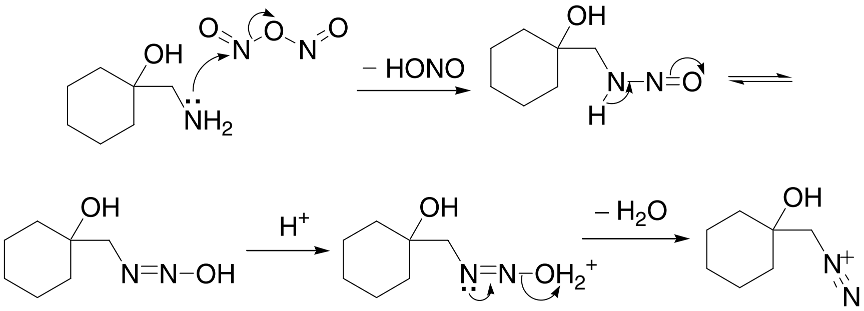
Carbocation rearrangement of β-aminoalcohols *via* diazotization to afford carbonyl compounds through C–C bond migration.



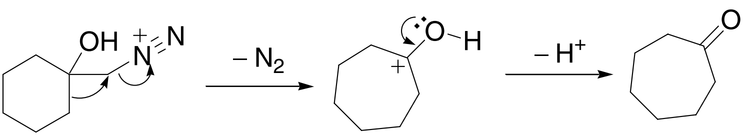
Step 1, Generation of N_2O_3



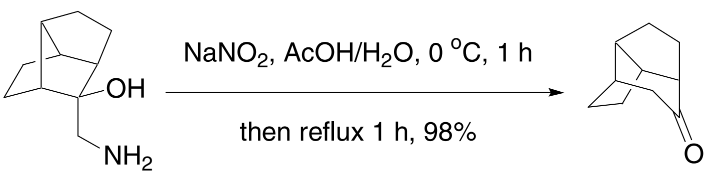
Step 2, Transformation of amine to diazonium salt



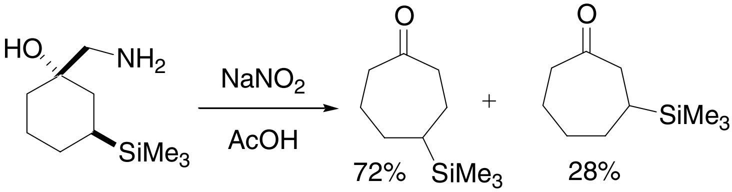
Step 3, Ring-expansion *via* rearrangement



Example 1[10]



Example 2[12]



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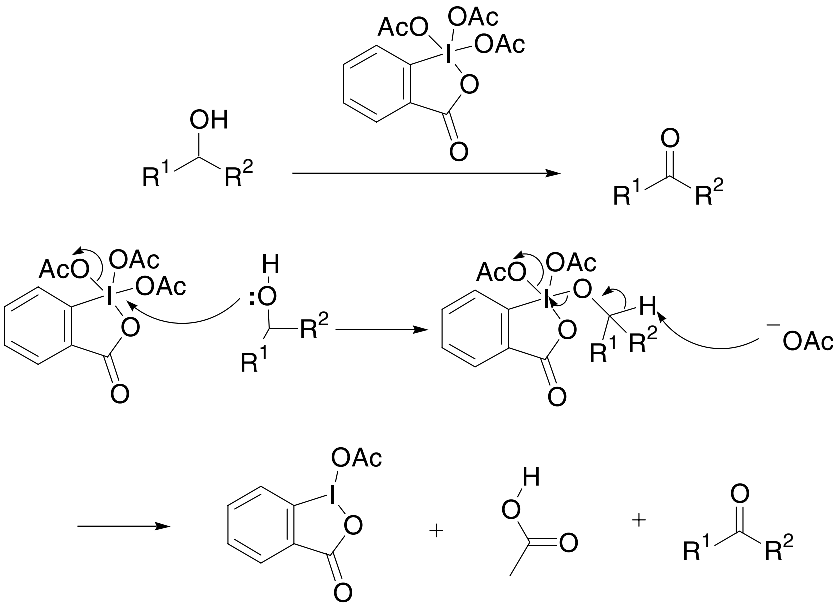
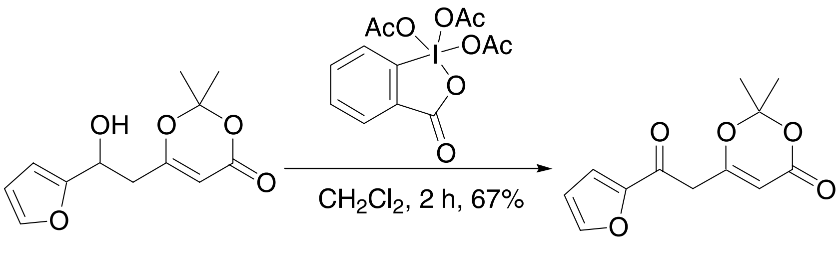
Dess–Martin periodinane oxidation

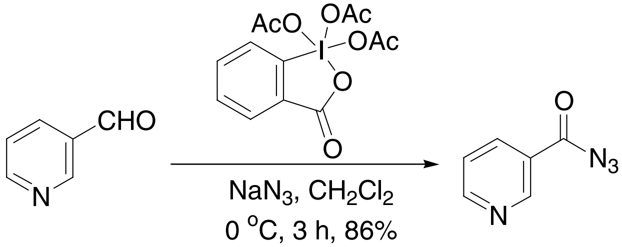
Oxidation of alcohols to the corresponding carbonyl compounds using triacetoxyperiodinane.



Example 1[9]



Example 2[15]



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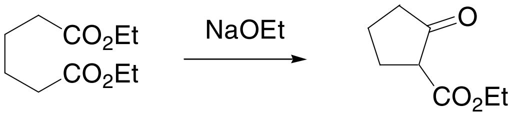
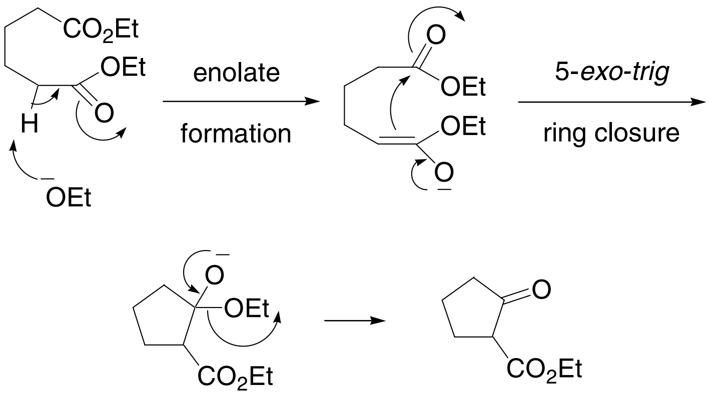
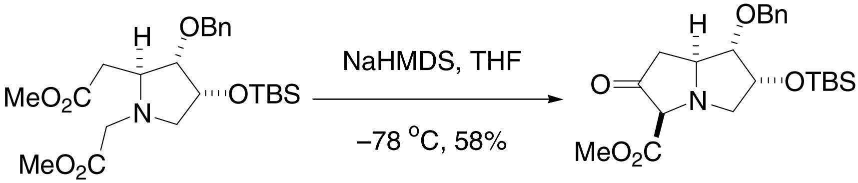
Dieckmann condensation

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

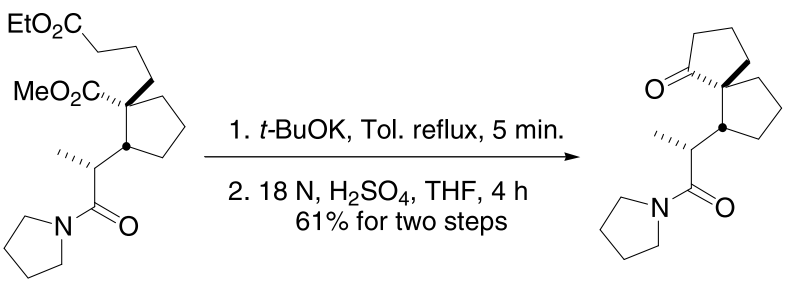




Example 1[7]



Example 2[9]



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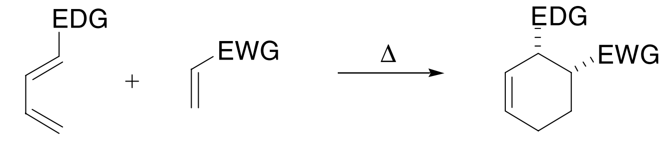
Diels–Alder reaction

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.

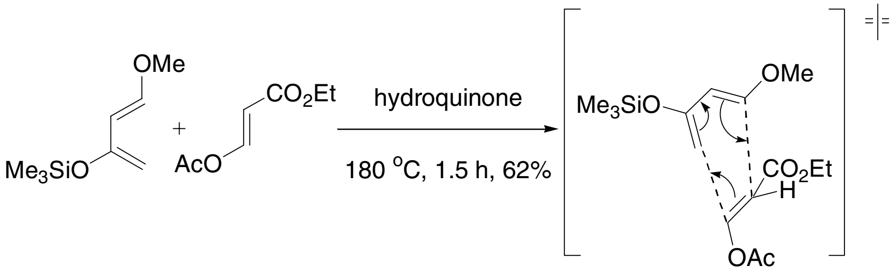
Normal Diels–Alder reaction



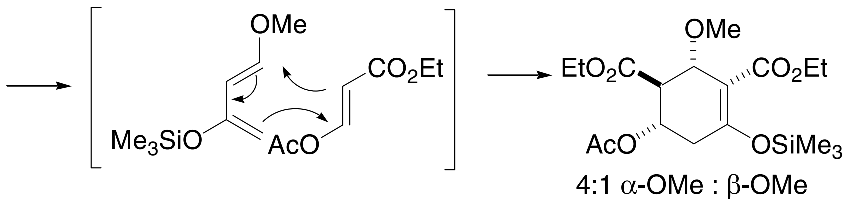
diene dienophile adduct

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

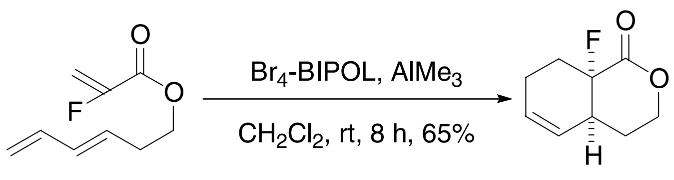
Example 1[13]



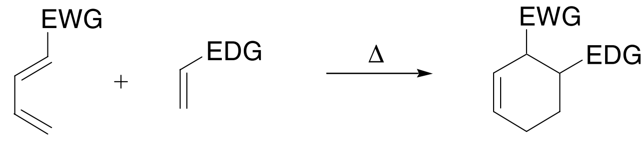
Danishefsky diene Alder's *endo* rule



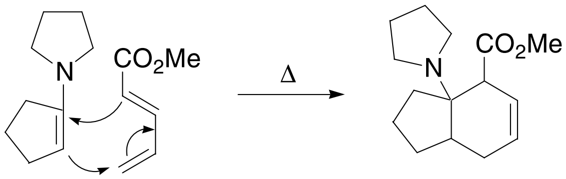
Example 2[17]



Inverse electronic demand Diels–Alder reaction

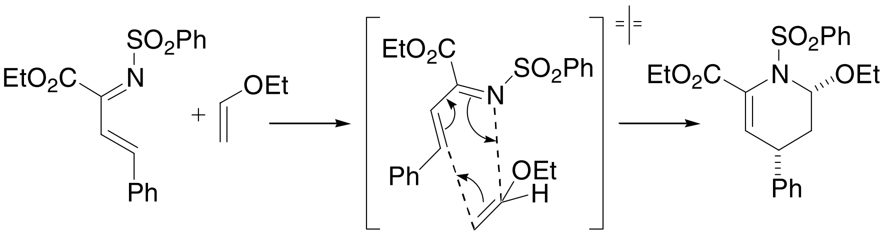


Example 1[2]

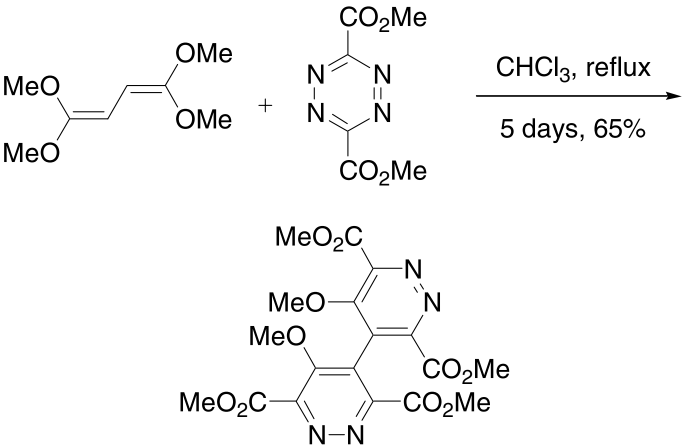


Hetero-Diels–Alder reaction

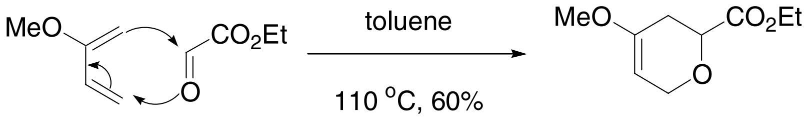
Heterodiene addition to dienophile



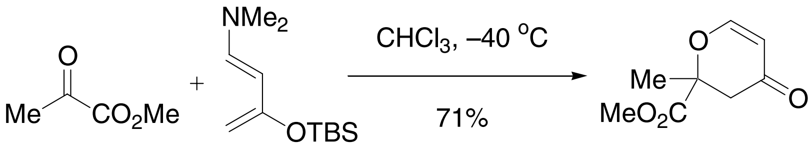
Example 1, the **Boger pyridine synthesis** (see page 67)[8]



Heterodienophile addition to diene[2]



Example 2, using the Rawal diene[9]



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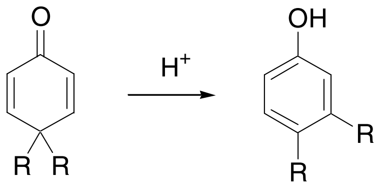
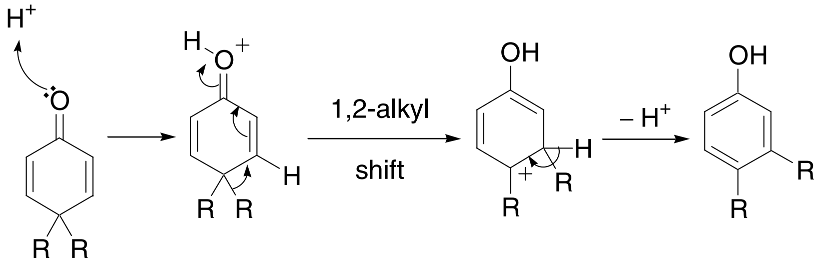
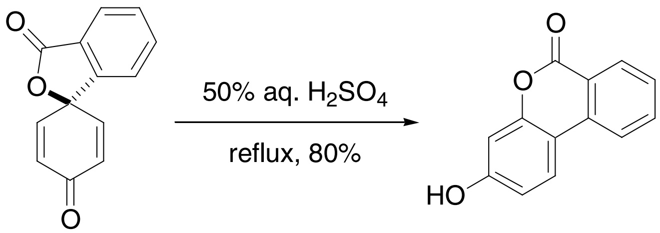
Dienone–phenol rearrangement

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

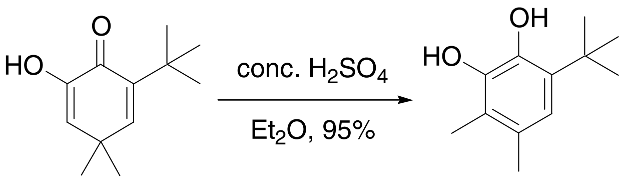




Example 1[4]



Example 2[5]



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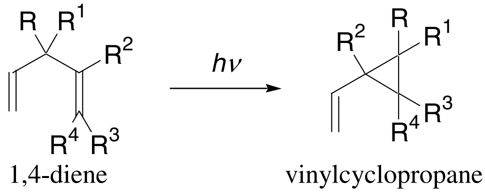
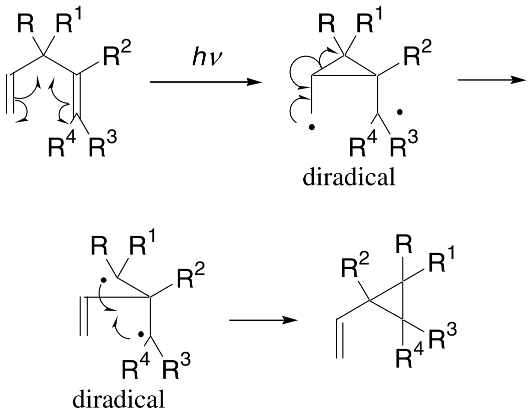
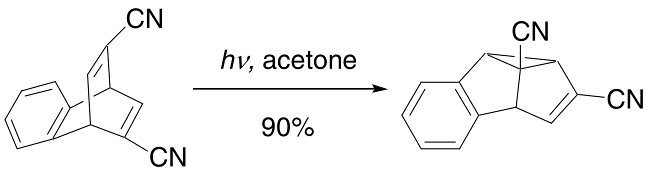
Di-π-methane rearrangement

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

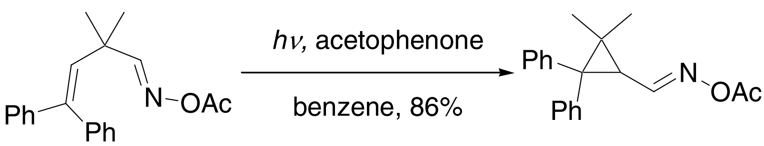




Example 1[9]



Example 2, aza-π-methane rearrangement[2]



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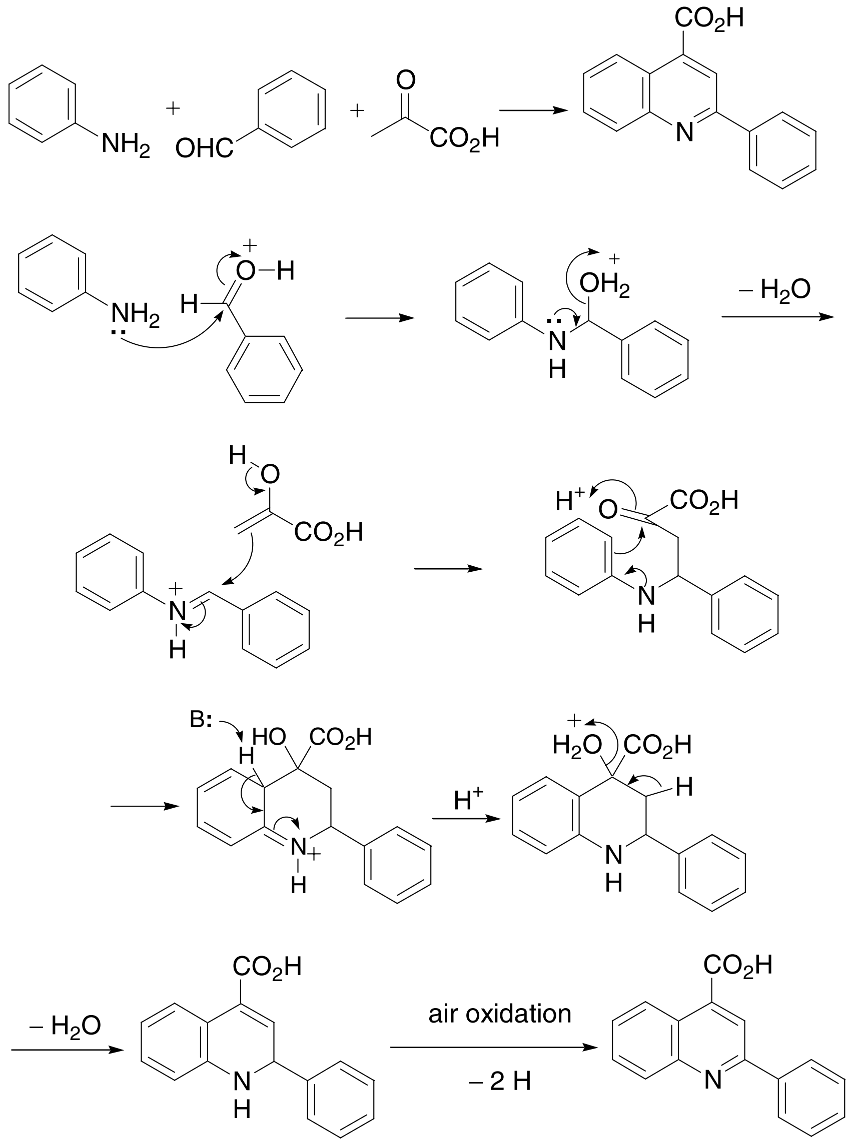
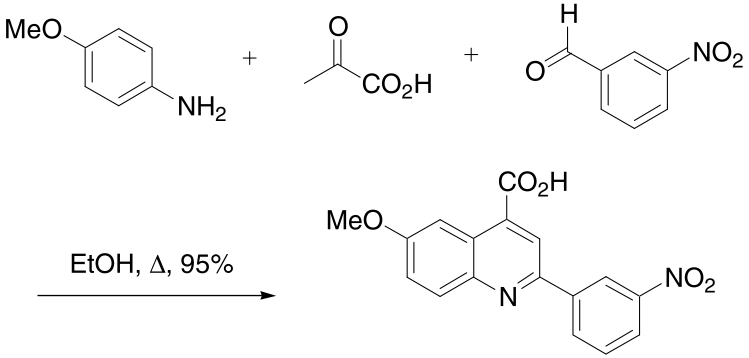
Doebner quinoline synthesis

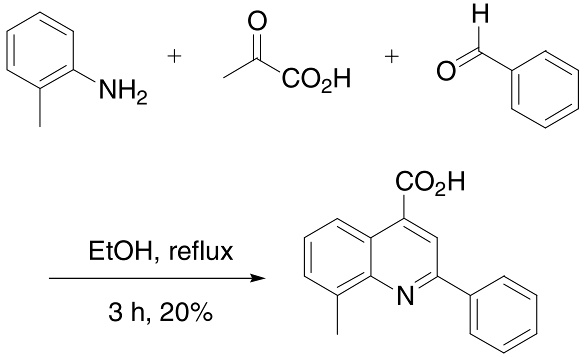
Three-component coupling of an aniline, pyruvic acid, and an aldehyde to provide a quinoline-4-carboxylic acid.



Example 1[2]



Example 2[6]



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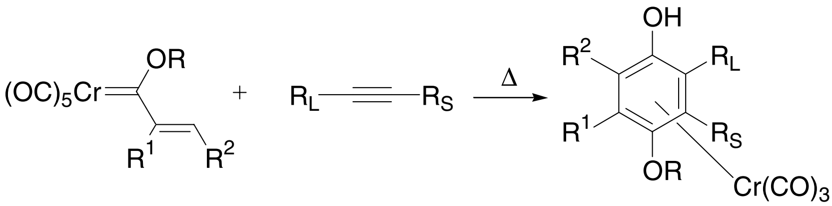
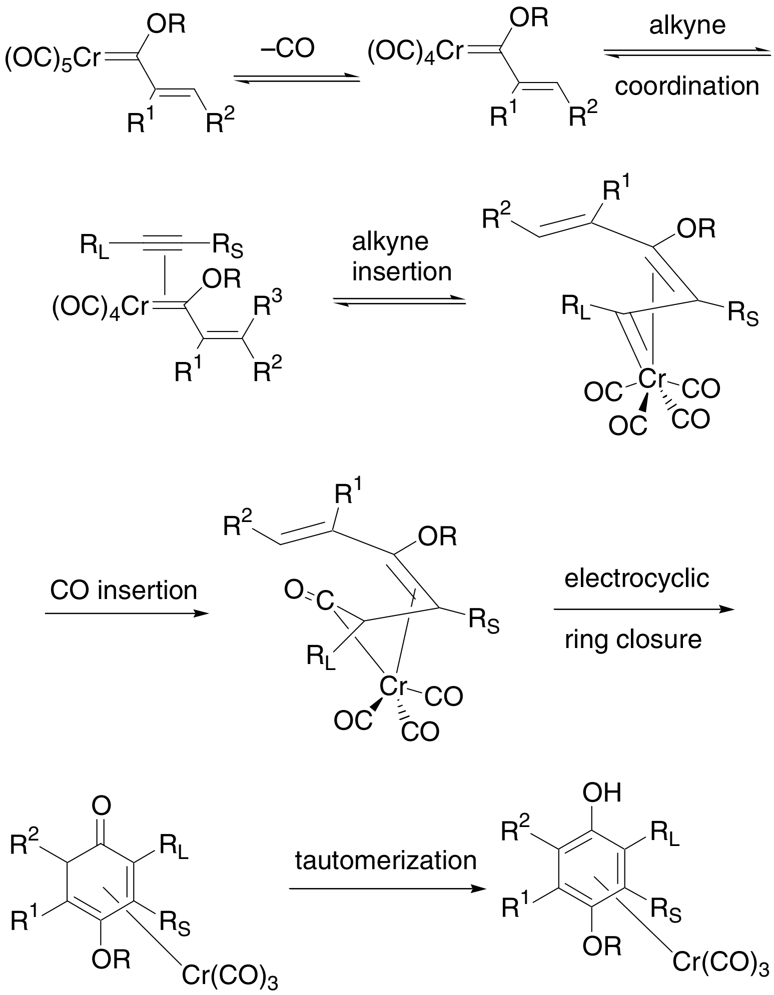
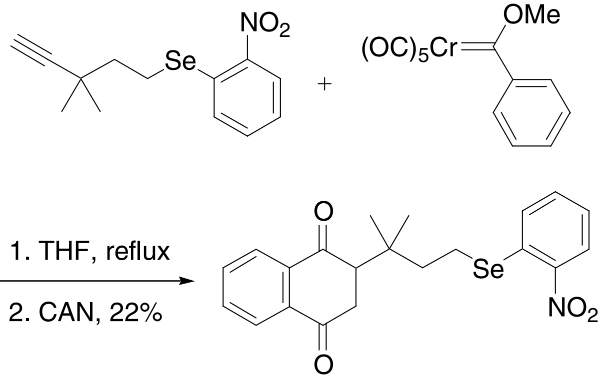
Dötz reaction

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





Example 1[7]



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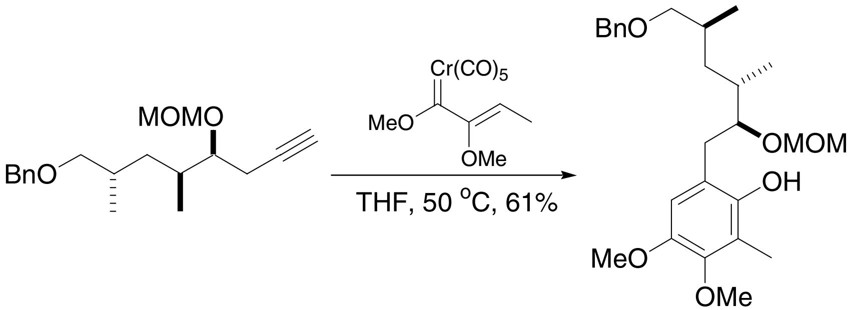

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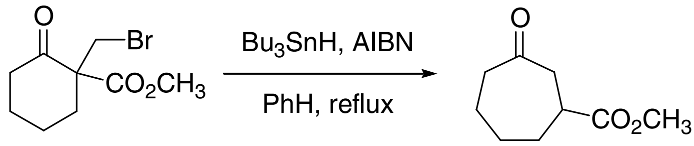
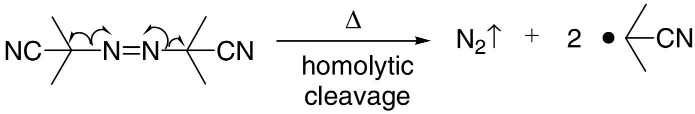
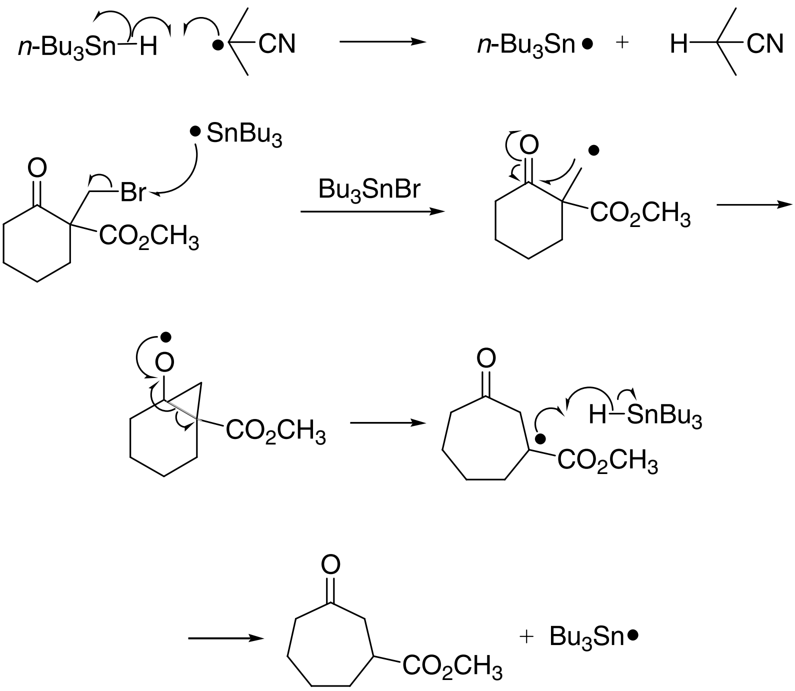
Dowd–Beckwith ring expansion

Radical-mediated ring expansion of 2-halomethyl cycloalkanones.

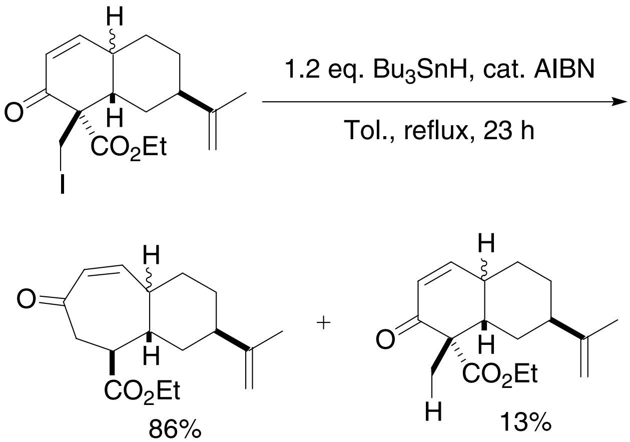




2,2'-azobisisobutyronitrile (AIBN)



Example 1[9]



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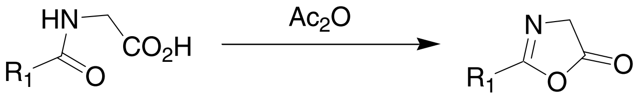
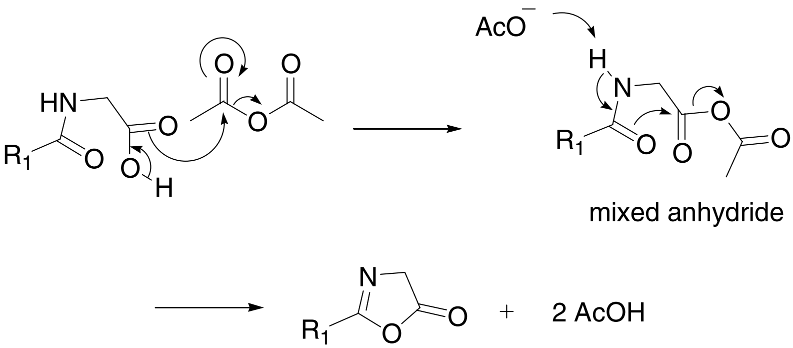
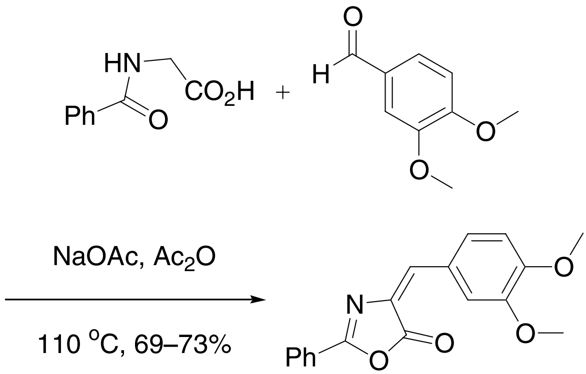
Erlenmeyer−Plöchl azlactone synthesis

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





Example[14]



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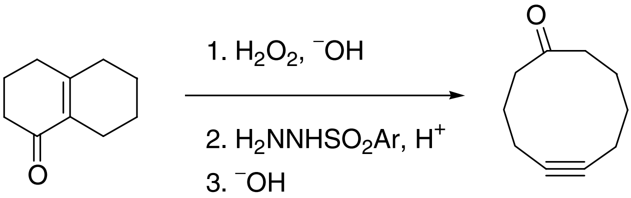
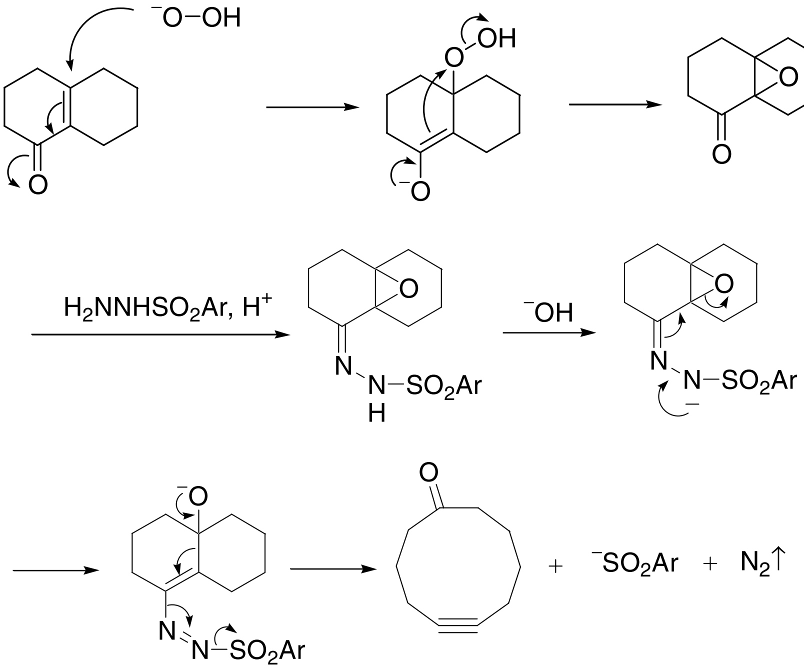
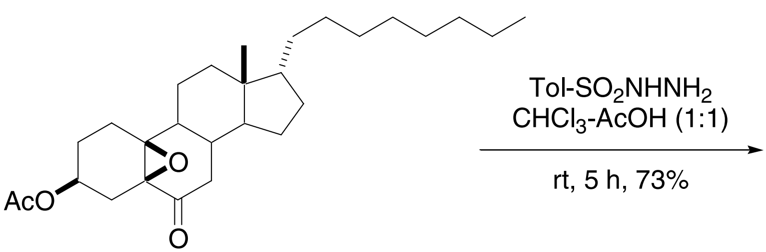
Eschenmoser–Tanabe fragmentation

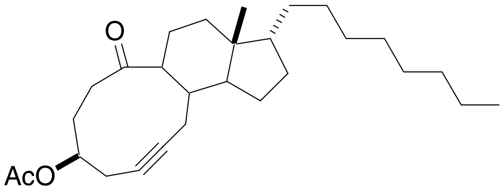
Fragmentation of α,β-epoxyketones *via* the intermediacy of α,β-epoxy sulfonyl-hydrazones.



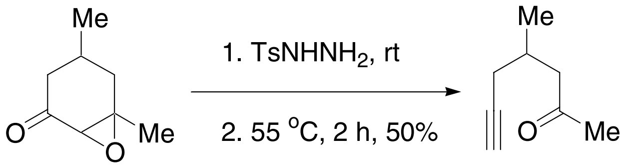


Example 1[4]





Example 2[7]



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2. Eschenmoser (Switzerland, 1925–) is best known for his work on, among many others, the monumental total synthesis of Vitamin B_{12} with R. B. Woodward in 1973. He now holds appointments at ETH Zürich and Scripps Research Institute, La Jolla.
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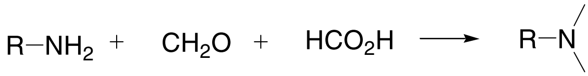
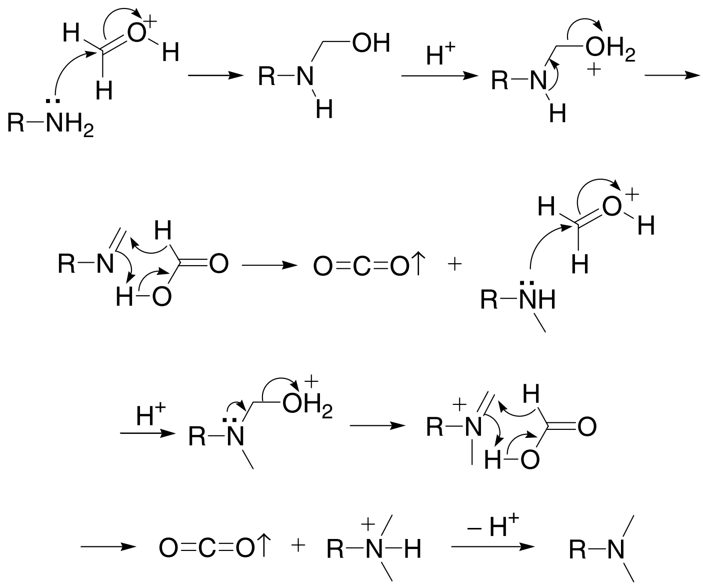
Eschweiler–Clarke reductive alkylation of amines

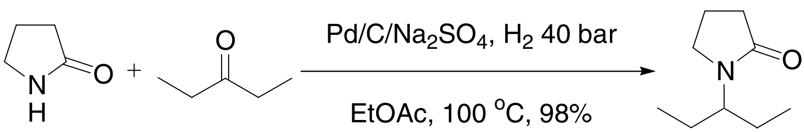
Reductive methylation of primary or secondary amines using formaldehyde and formic acid. *Cf*. Leuckart–Wallach reaction.



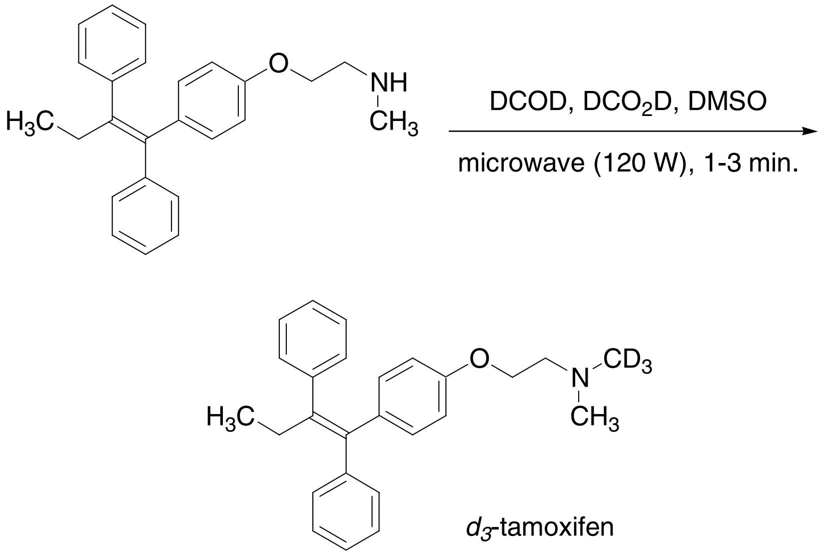
formic acid is the hydrogen source as a reducing agent



Example 1[7]



Example 2[11]



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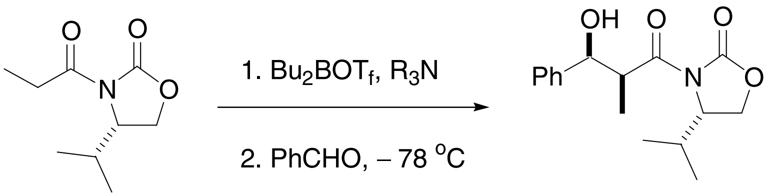
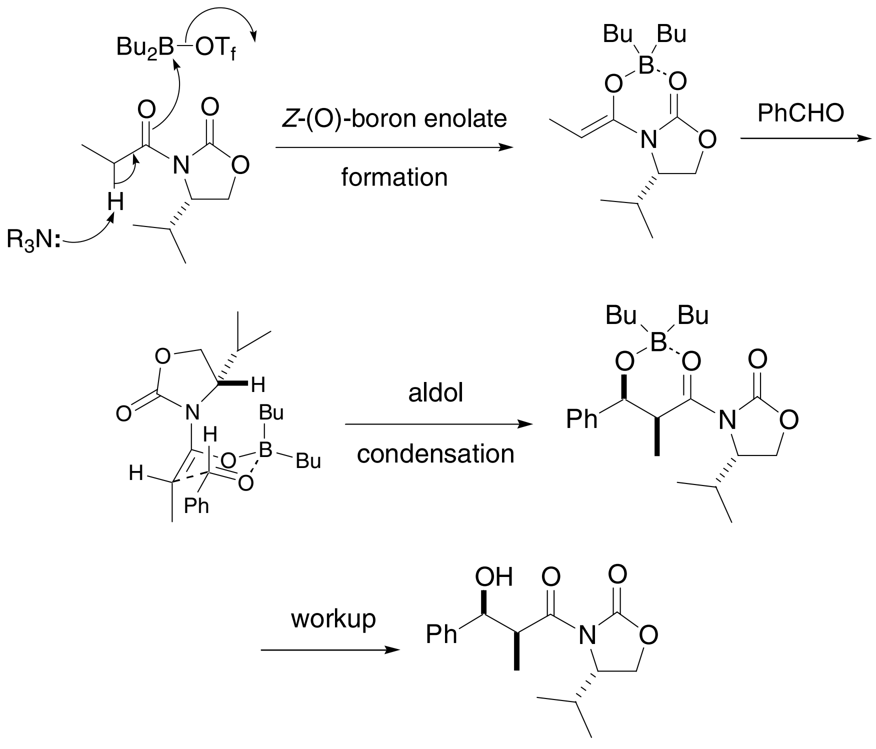
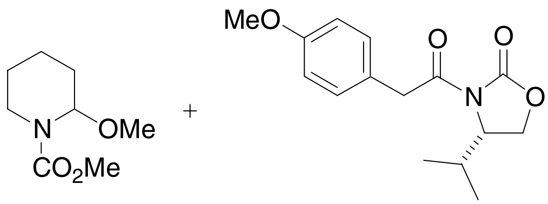
Evans aldol reaction

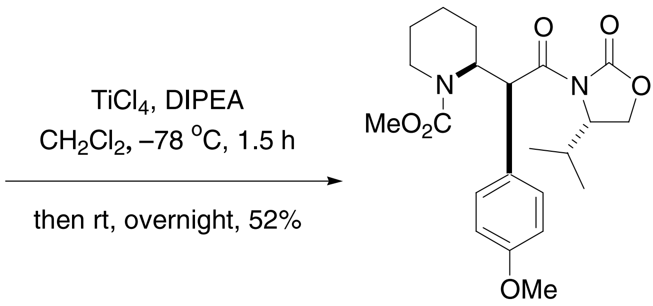
Asymmetric aldol condensation of aldehyde and chiral acyl oxazolidinone, the Evans chiral auxiliary.



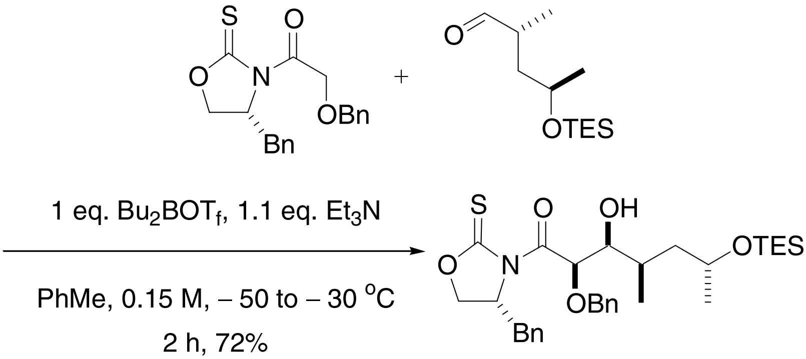


Example 1[7]





Example 2[13]



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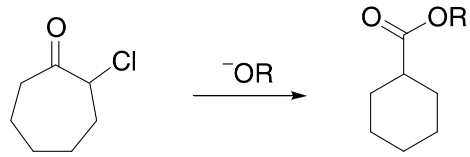
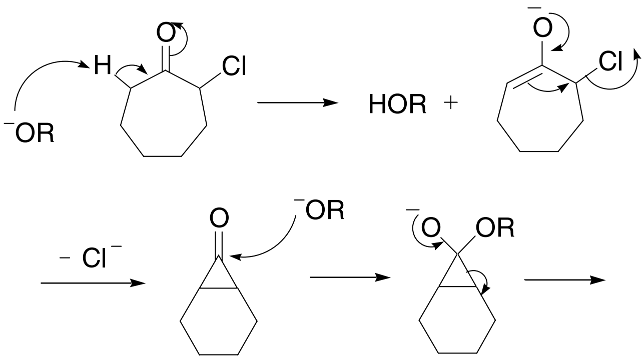
Favorskii rearrangement and quasi-Favorskii rearrangement

Favorskii rearrangement

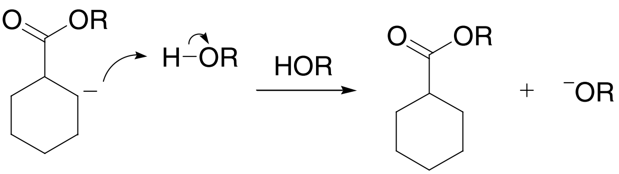
Transformation of enolizable α-haloketones to esters, carboxylic acids, or amides *via* alkoxide-, hydroxide-, or amine-catalyzed rearrangements, respectively.



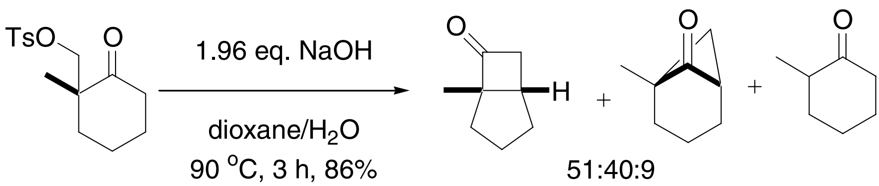
enolizable α-haloketone



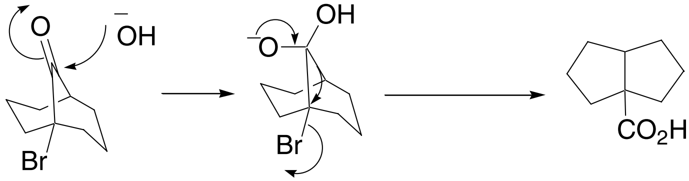
cyclopropanone intermediate



Example 1, homo-Favorskii rearrangement[3]

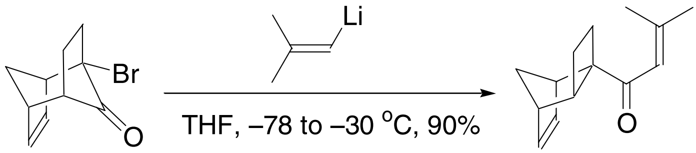


Quasi-Favorskii rearrangement



non-enolizable ketone

Example 1[11]



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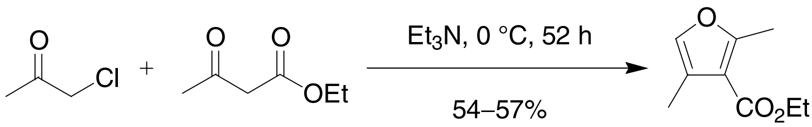
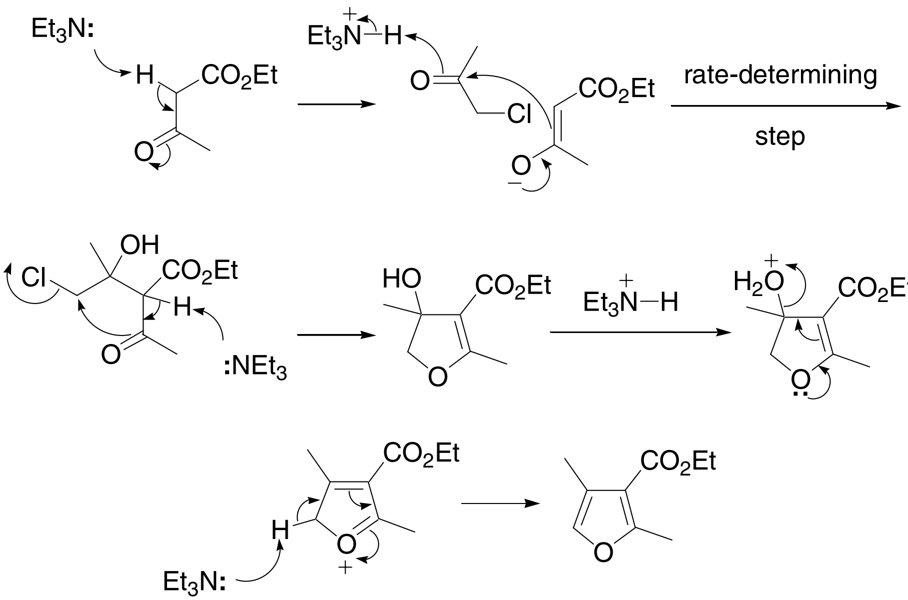
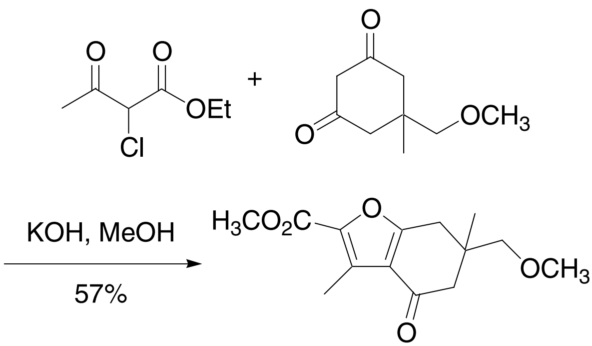
Feist–Bénary furan synthesis

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

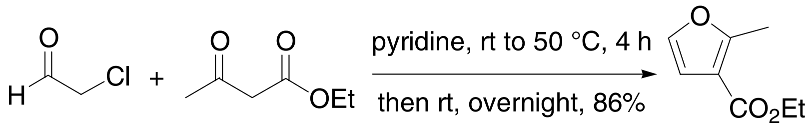




Example 1[4,5]



Example 2[6]



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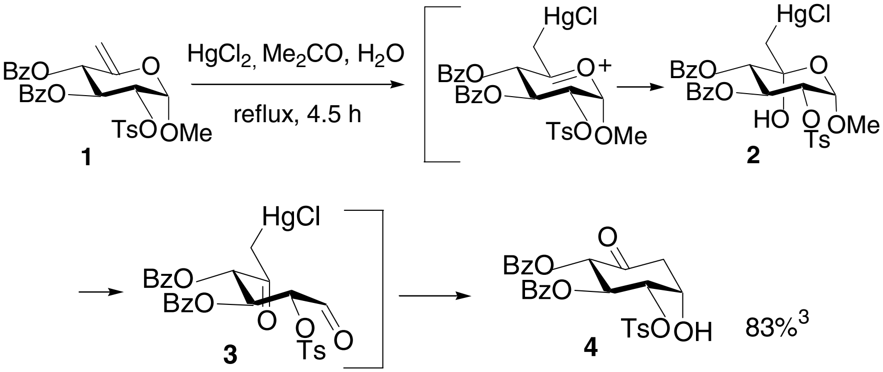
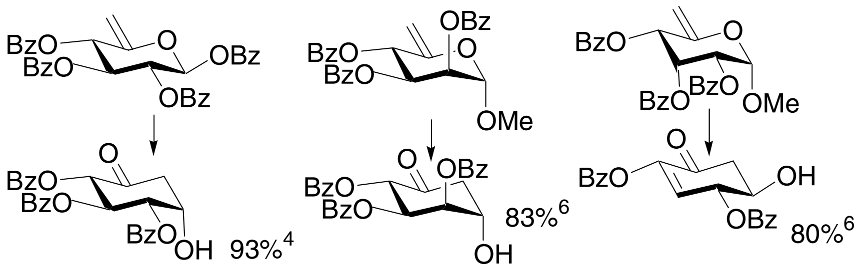
Ferrier carbocyclization

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]

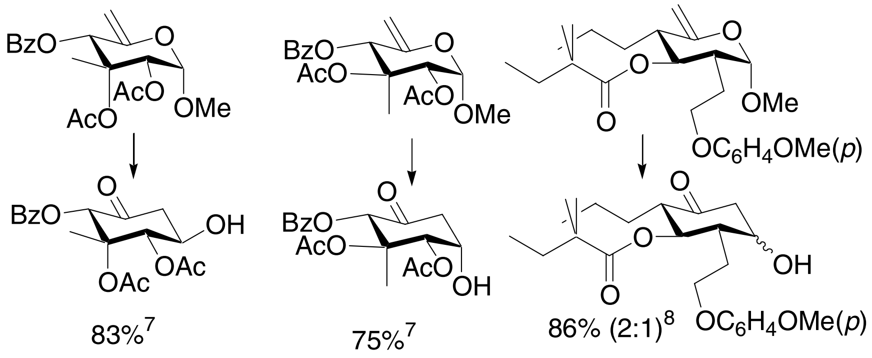
While attempting to find a route from carbohydrates to functionalized cyclopentanes (and hence prostaglandins), Robin Ferrier converted alkene **1** to the standard product of methoxymercuration, but was unable to proceed to cyclopentanes by causing C-6 of the C-6-mercurated product to displace the tosyloxy group from C-2. However, hydroxymercuration of **1** with mercury(II) chloride in refluxing aqueous acetone afforded the unstable hemiacetal **2** from which aldehydoketone **3** and hence the hydroxyketone **4** were formed spontaneously, the latter crystallizing in 83% yield on cooling of the solution.[3] The high yield can be increased to 89% by addition of a trace of acetic acid,[4] and even higher yields have been reported in similar examples. Catalytic amounts of mercury(II) trifluoroacetate[5] and sulfate[6] can promote the reaction, and chelation control has been held responsible for the high stereoselectivity usually observed, the favored epimers having the *trans*-relationship between the hydroxyl groups at the new chiral centers and the substituents at C-3.[1,2]

General examples:

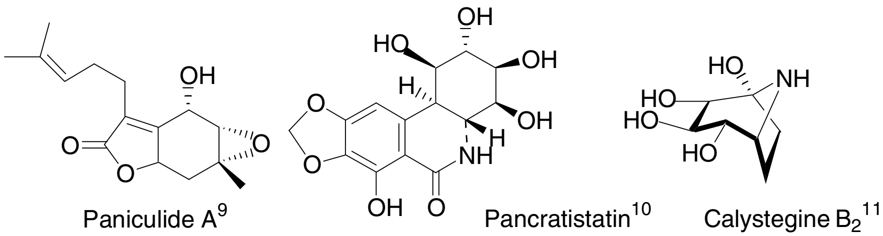




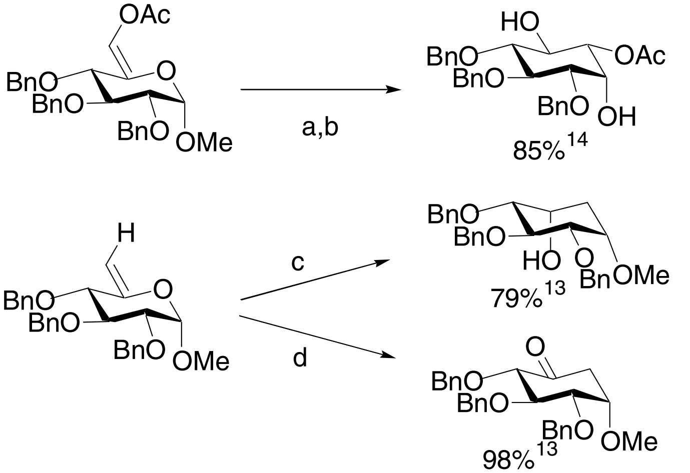
More complex products



Complex bioactive compounds made following the application of the reaction



Modified hex-5-enopyranosides and reactions



a, $Hg(OCOCF_3)_2$, Me_2CO, H_2O, 0 °C; b, $NaBH(OAc)_3$, AcOH, MeCN, rt; c, *i*-Bu_3Al, PhMe, 40 °C; d, Ti(O*i*-Pr)Cl_3, CH_2Cl_2, –78 °C, 15 min. (Note: The aglycon is retained in the Al- and Ti-induced reactions).

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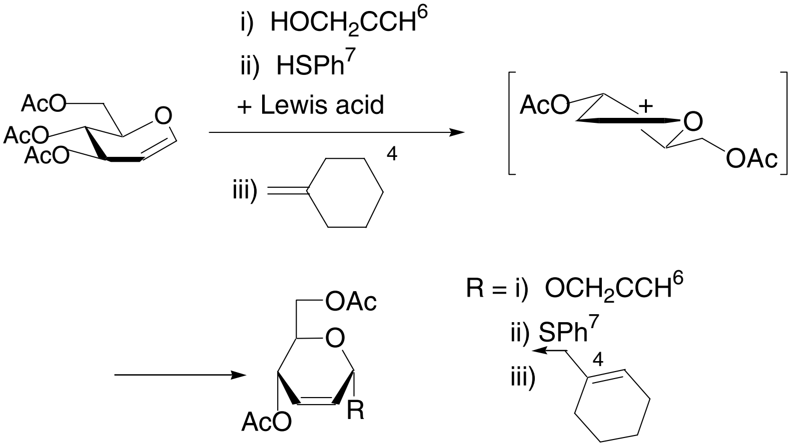
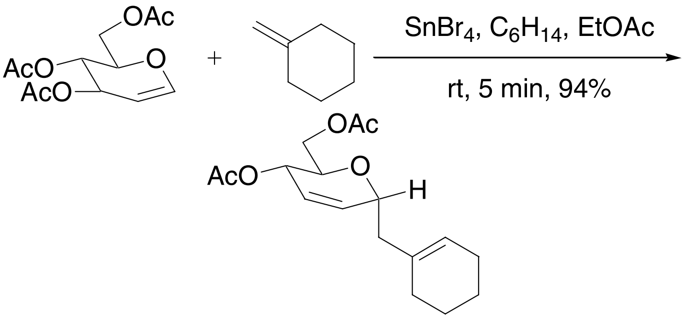
Ferrier glycal allylic rearrangement

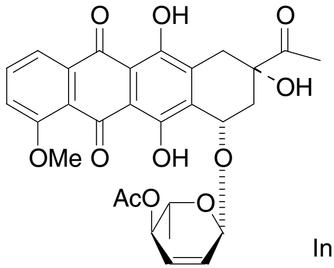
In the presence of Lewis acid catalysts *O*-substituted glycal derivatives can react with *O*-, *S*-, *C*- and, less frequently, *N*-, *P*- and halide nucleophiles to give 2,3-unsaturated glycosyl products.[1,2] This allylic transformation has been termed the "Ferrier Reaction" or, to avoid complications, 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]



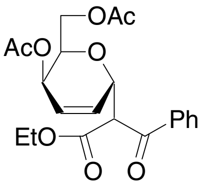
General examples[4]



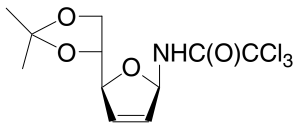
More complex products made directly from the corresponding glycols:



In benzene, $BF_3.OEt_2$, 5 °C, 10 min, (67%, α-anomer).[8]

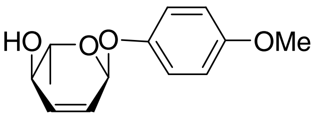


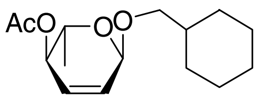
In $PhCOCH_2CO_2Et$, $BF_3.OEt_2$, rt, 15 min, (81% α-anomer).[9]



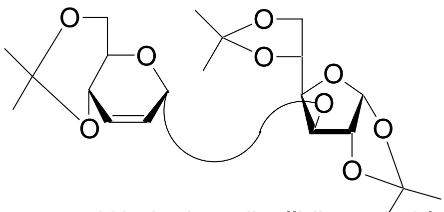
By spontaneous sigmatropic rearrangement of the glycal 3-trichloroacetimidate made with NaH, Cl_3CCN, (78% α–anomer).[10]

Products formed without acid catalysts



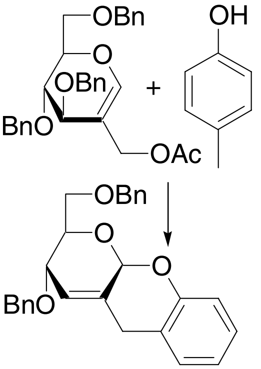


<u>Promoter:</u>	DEAD, Ph_3P (80%, α-anomer)[11]	DDQ (88%, mainly α)[12]
<u>C-3 leaving group of glycal:</u>	hydroxy	acetoxy

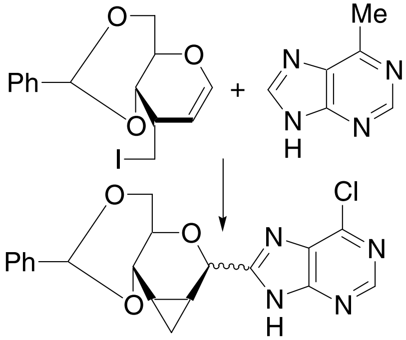


N-iodonium dicollidine perchlorate
(65%, mainly α)[13]
pent-4-enoyloxy

Modified glycals and their reactions:



$BF_3{\bullet}OEt_2$, CH_2Cl_2, 0 °C (70%, mainly α)[14]



$AgNO_3$, Na_2CO_3, reflux $MeNO_2$, 6 h (58%, α,β 1:1).[15]

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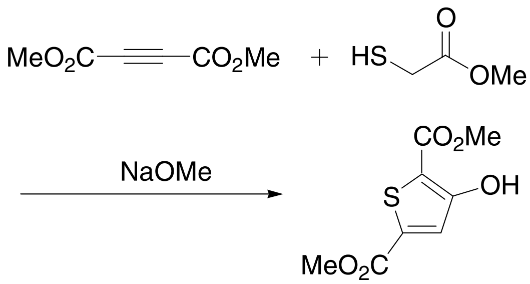
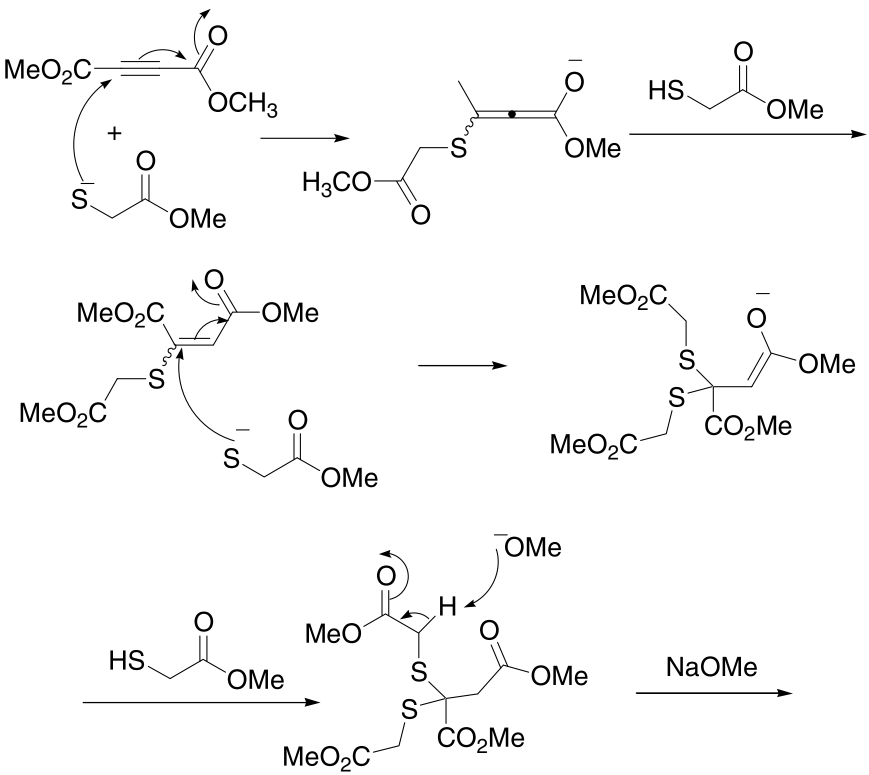
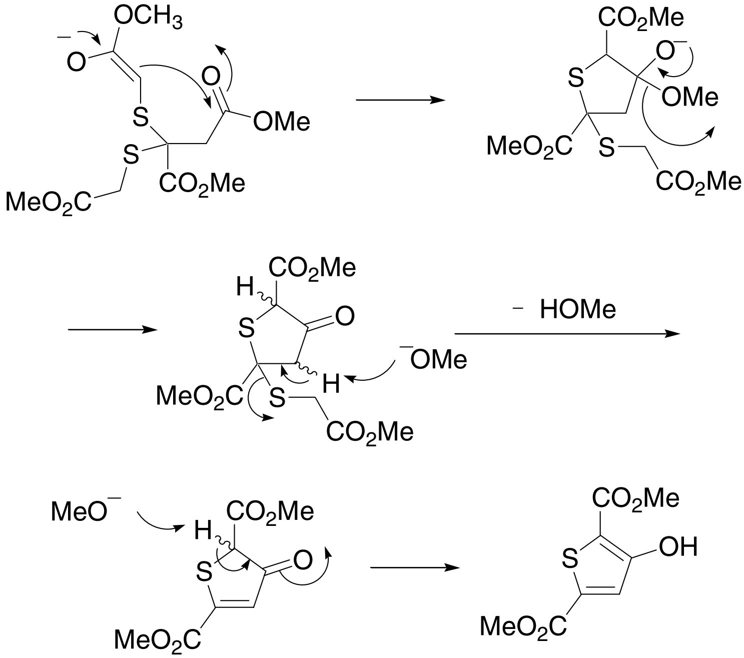
Fiesselmann thiophene synthesis

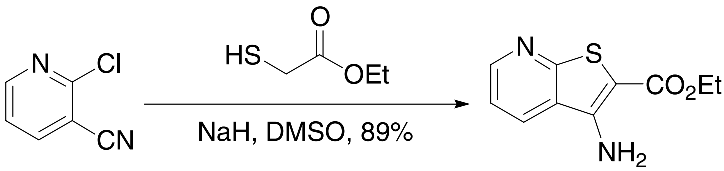
Condensation reaction of thioglycolic acid derivatives with α,β-acetylenic esters, which upon treatment with base result in the formation of 3-hydroxy-2-thiophenecarboxylic acid derivatives.



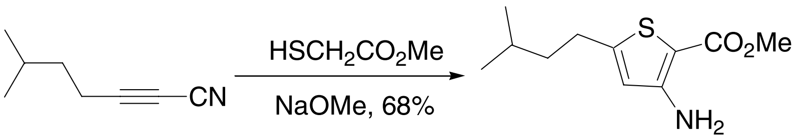




Example 1[6]



Example 2[8]



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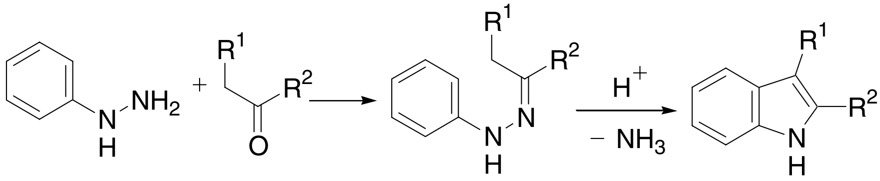
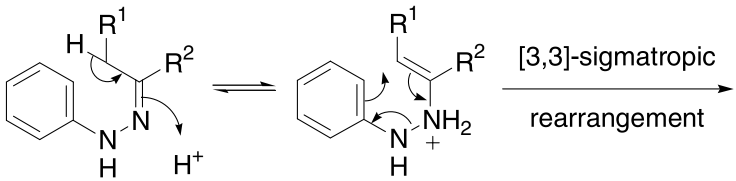
Fischer indole synthesis

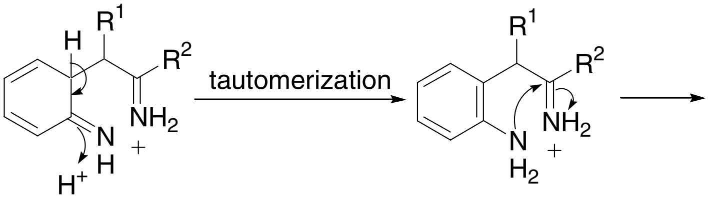
Cyclization of arylhydrazones to indoles.



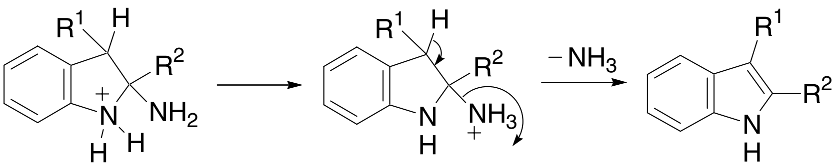
phenylhydrazine phenylhydrazone



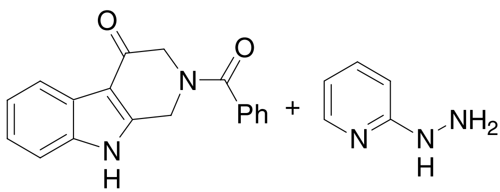
protonation ene-hydrazine

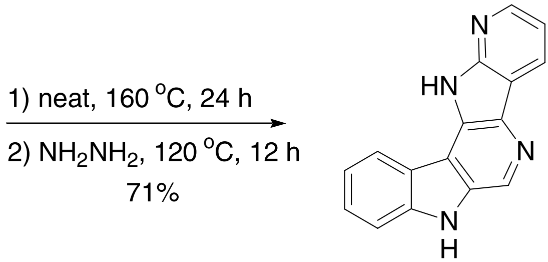


double imine

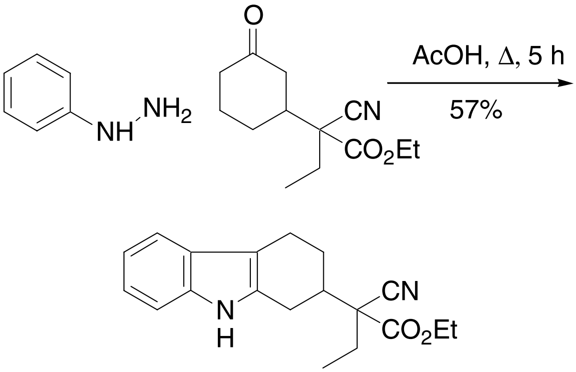


Example 1[8,12]





Example 2[13]



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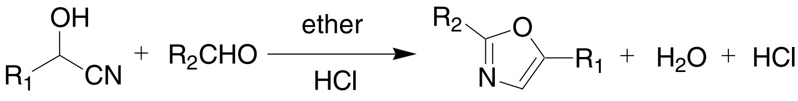
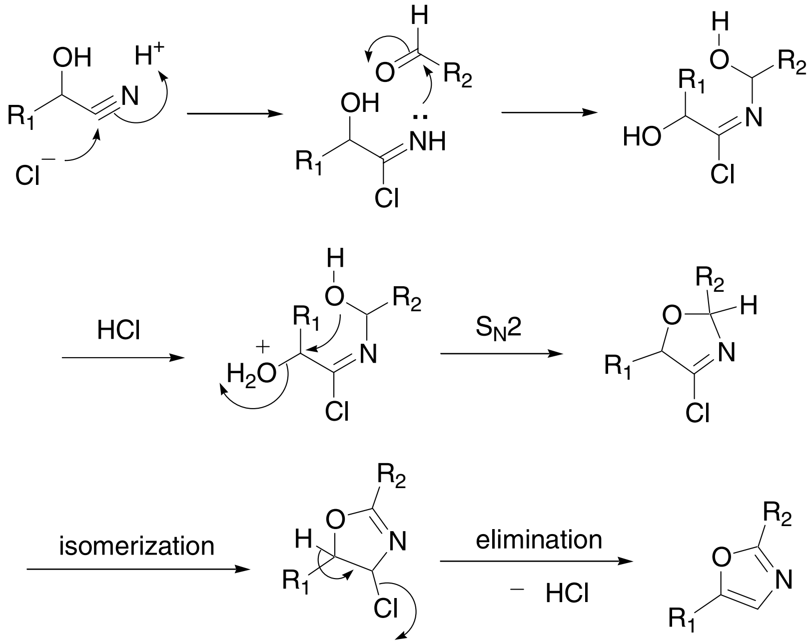
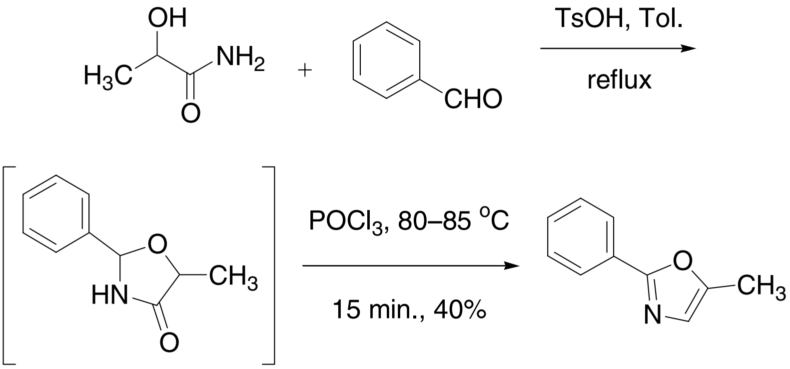
Fischer oxazole synthesis

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

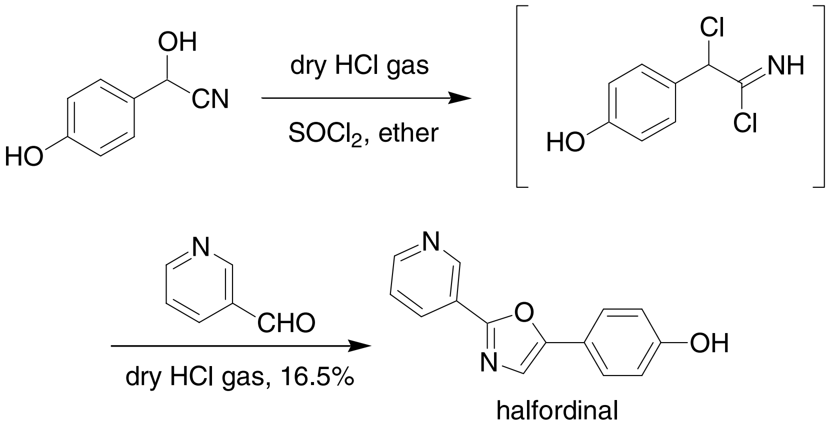




Example 1[6]



Example 2[10]



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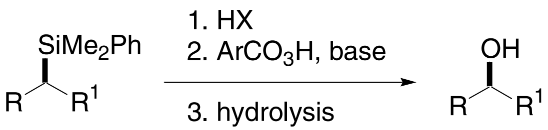
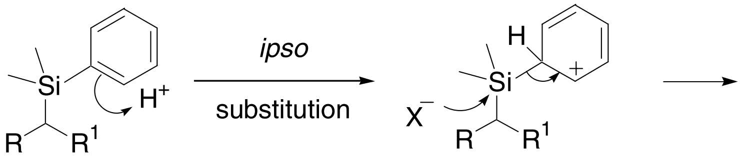
Fleming–Kumada oxidation

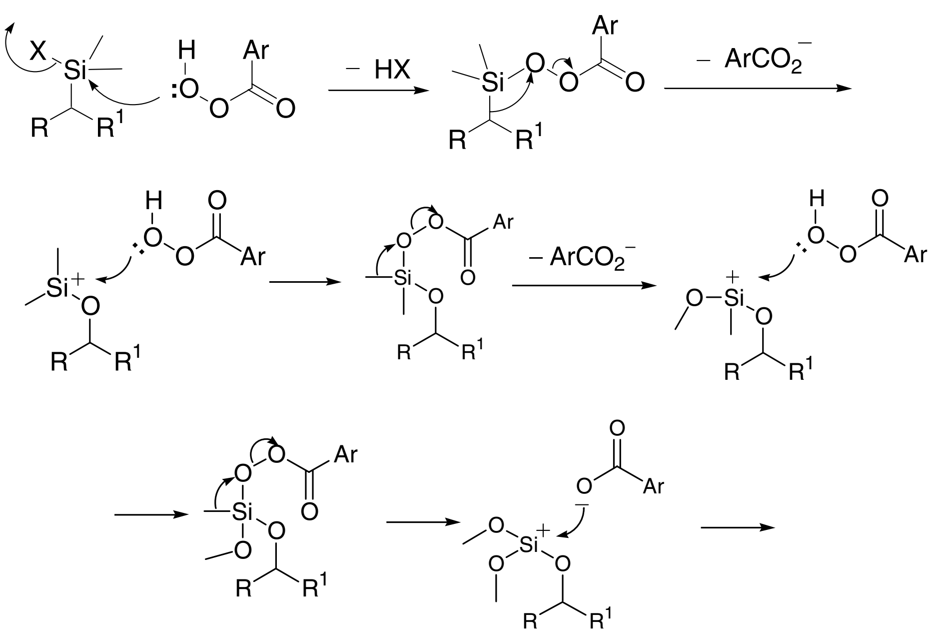
Stereoselective oxidation of alkyl-silanes into the corresponding alkyl-alcohols using peracids.

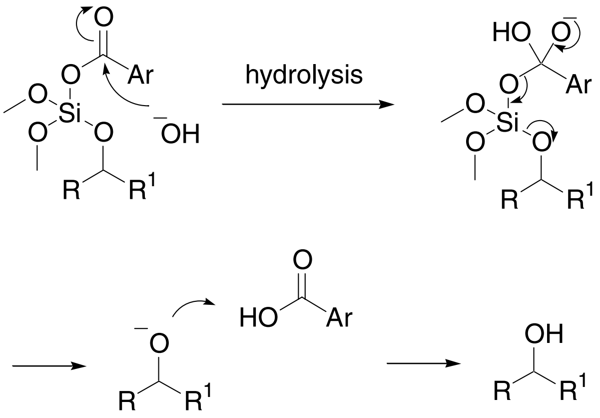


retention of configuration

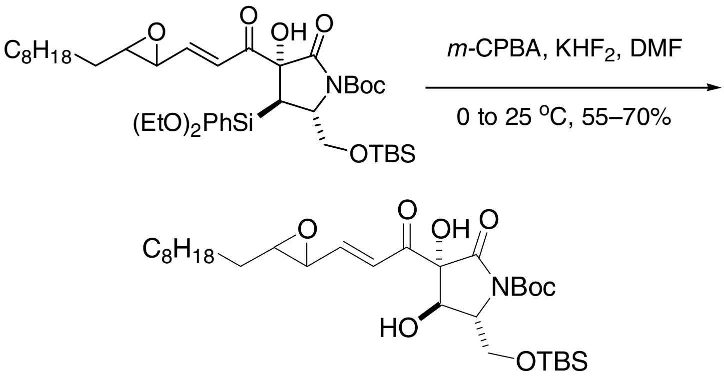


the β-carbocation is stabilized by the silicon group

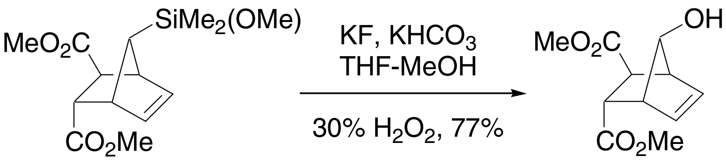




Example 1[7]

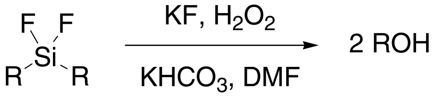


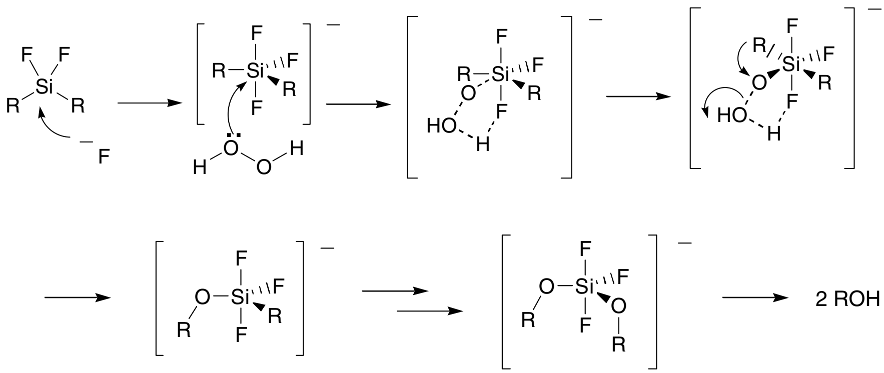
Example 2[12]



Tamao–Kumada oxidation[15]

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





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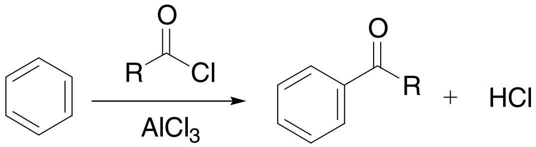
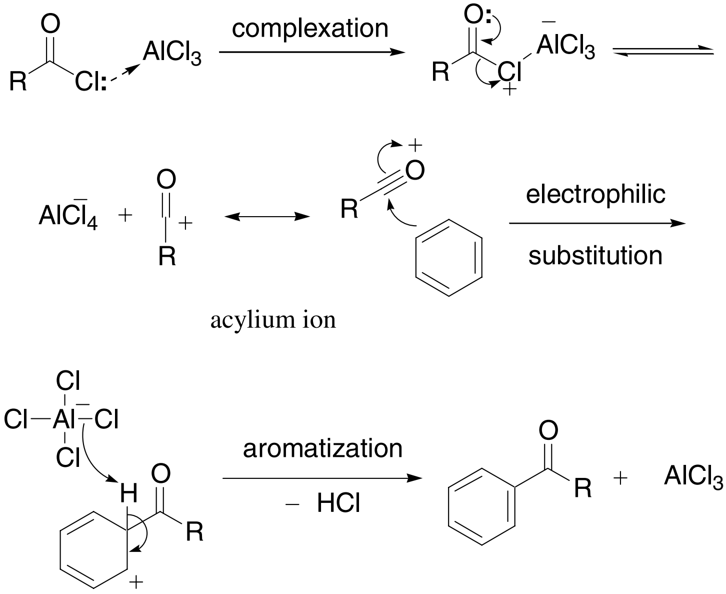
Friedel–Crafts reaction

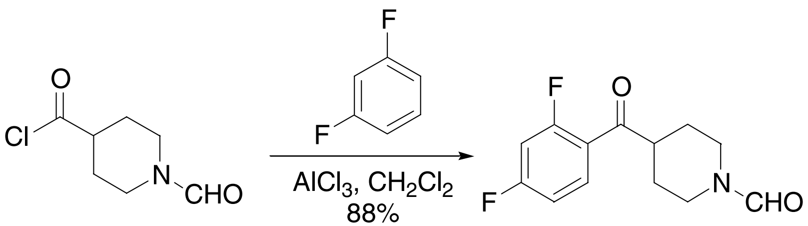
Friedel–Crafts *acylation* reaction:

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.



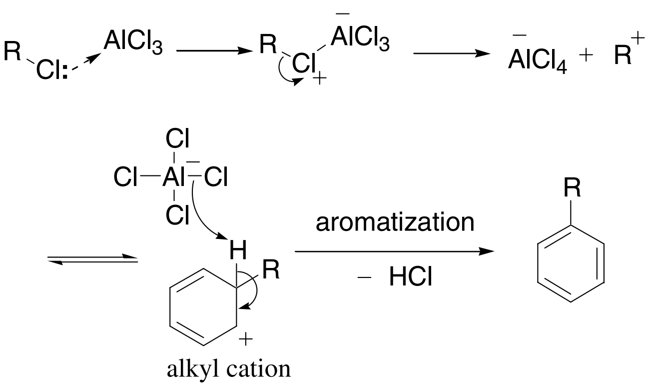


Example 1[16]

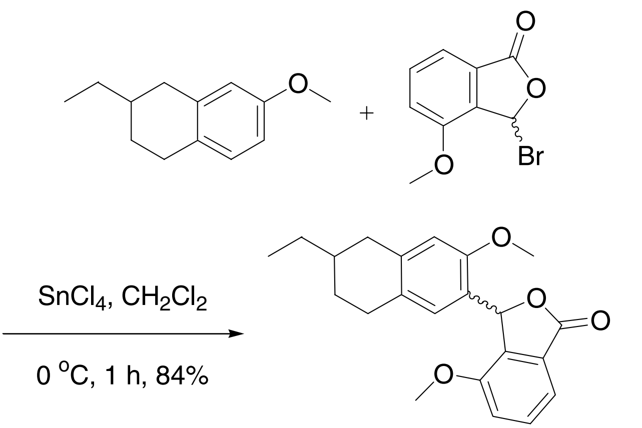


Friedel–Crafts *alkylation* reaction:

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 2[7]



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in 1892 and later served as its president. The discovery of the Friedel–Crafts reaction was the fruit of serendipity and keen observation. In 1877, both Friedel and Crafts were working in Charles A. Wurtz's laboratory. In order to prepare amyl iodide, they treated amyl chloride with aluminum and iodide using benzene as the solvent. Instead of amyl iodide, they ended up with amylbenzene! Unlike others before them who may have simply discarded the reaction, they thoroughly investigated 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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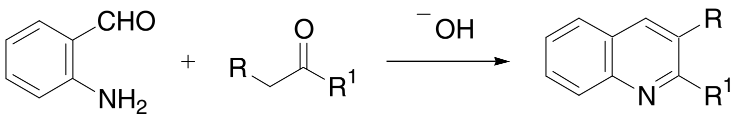
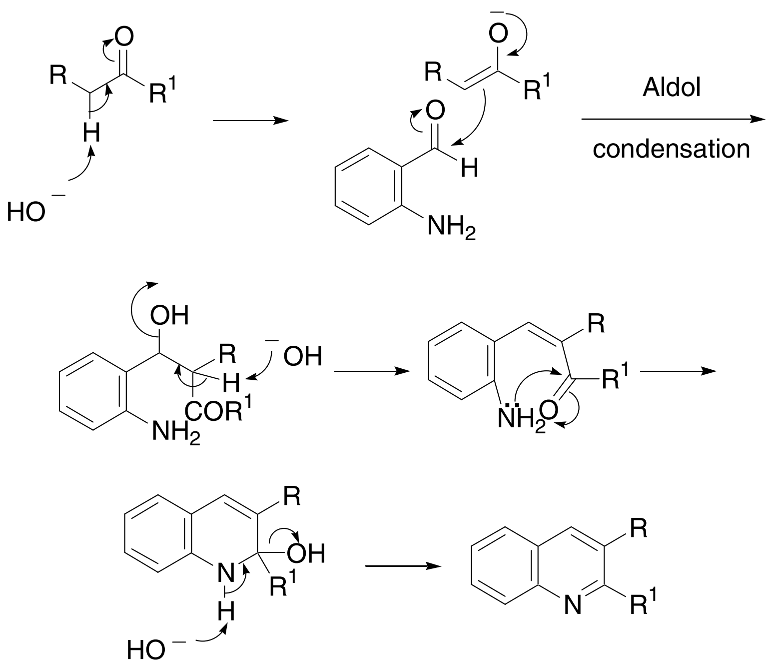
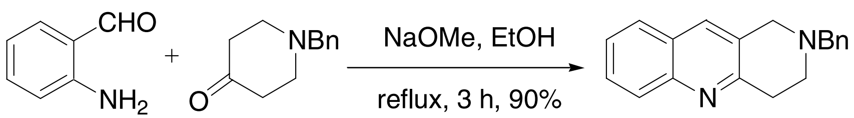
Friedländer quinoline synthesis

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.

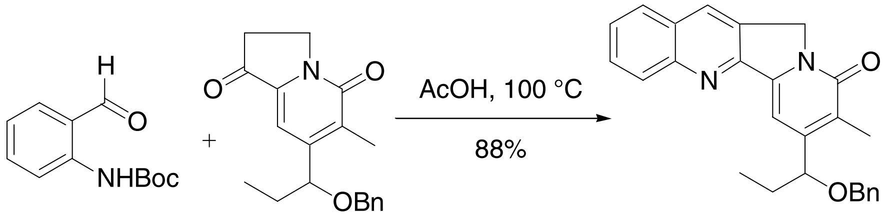




Example 1[5]



Example 2[15]



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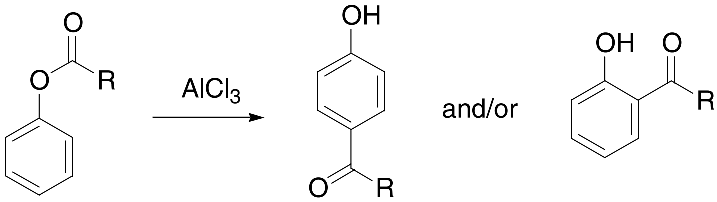
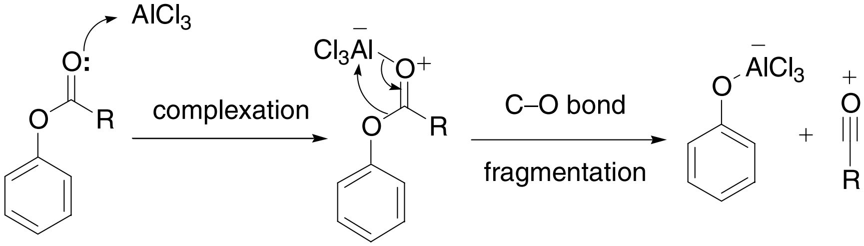
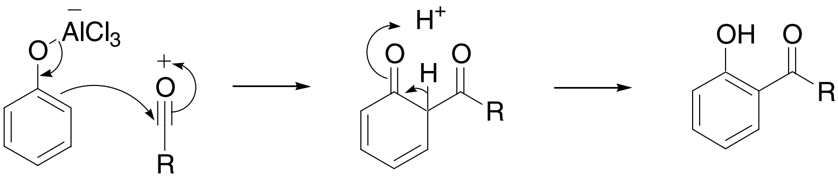
Fries rearrangement

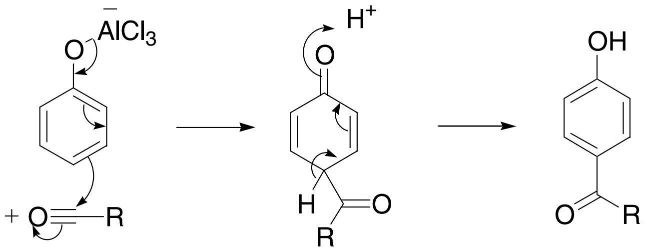
Lewis acid-catalyzed rearrangement of phenol esters and lactams to 2- or 4-ketophenols. Also known as the Fries–Finck rearrangement.



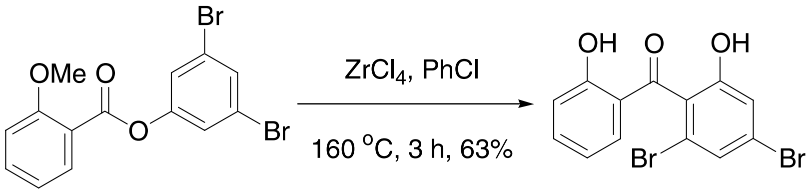


aluminum phenolate, acylium ion

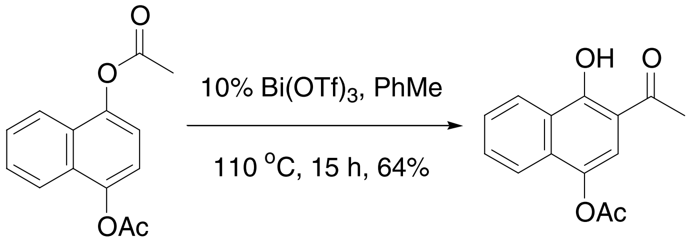




Example 1[11]



Example 2[12]



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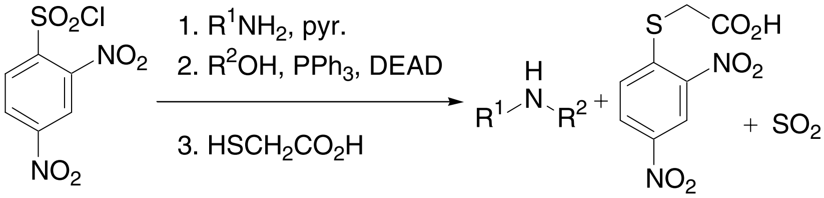
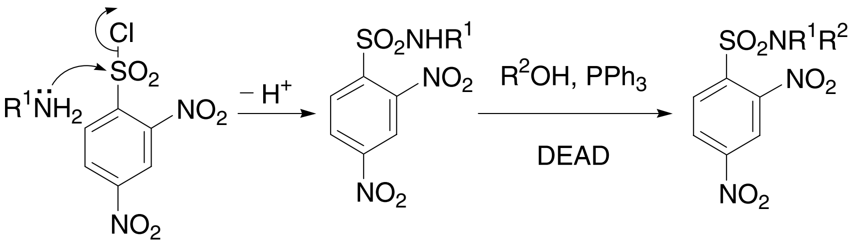
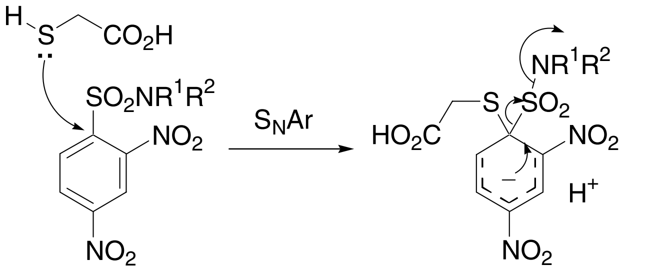
Fukuyama amine synthesis

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

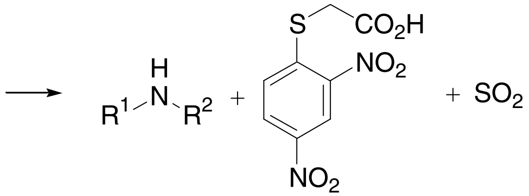




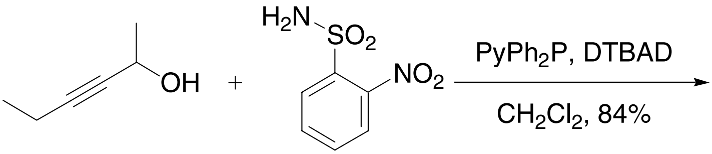
See page 390 for mechanism of the Mitsunobu reaction.



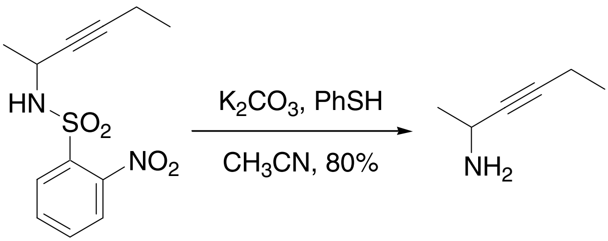
Meisenheimer complex



Example 1[9]



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



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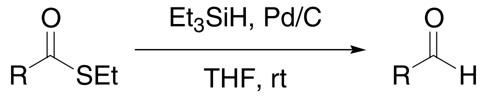
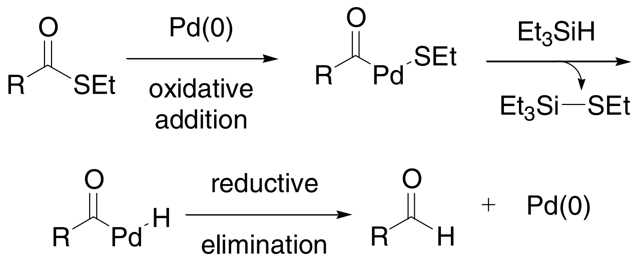
Fukuyama reduction

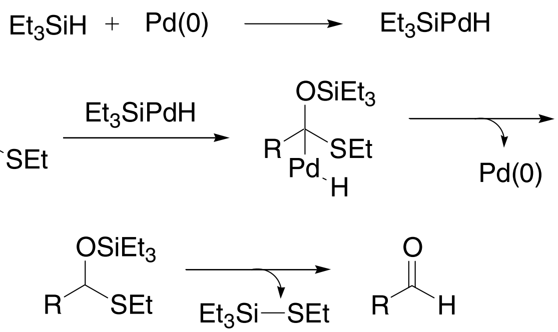
Aldehyde synthesis through reduction of thiol esters with Et_3SiH in the presence of Pd/C catalyst.



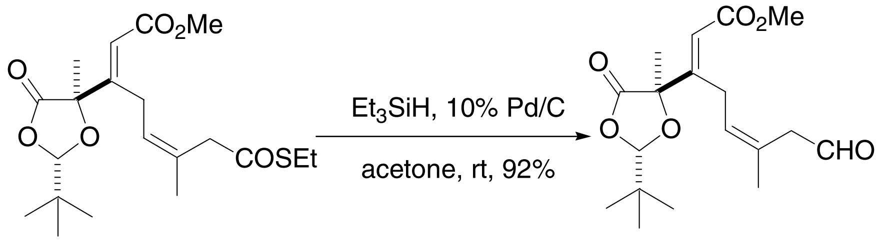
Path A:



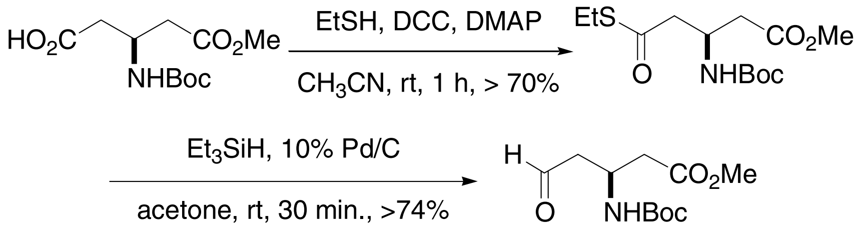
Path B:



Example 1[1]



Example 2[3]



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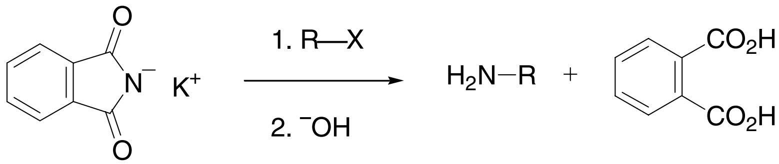
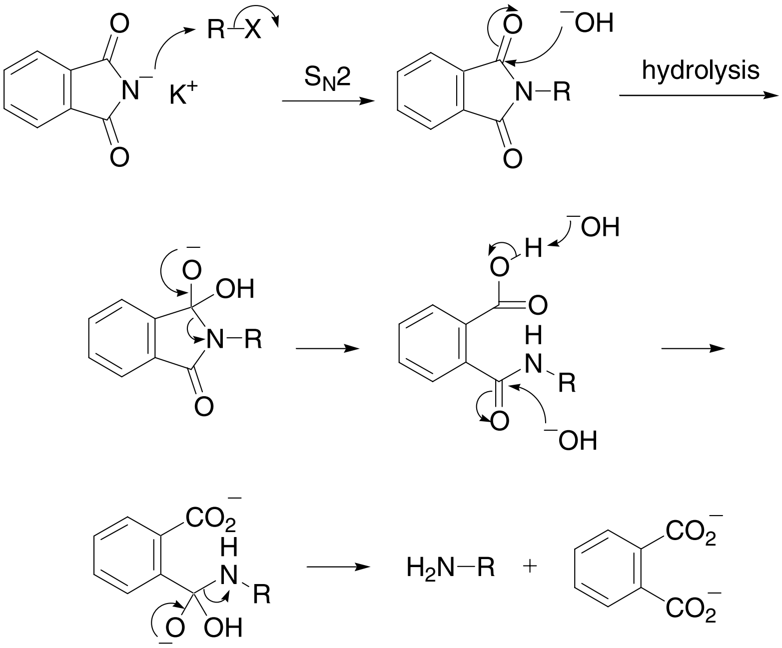
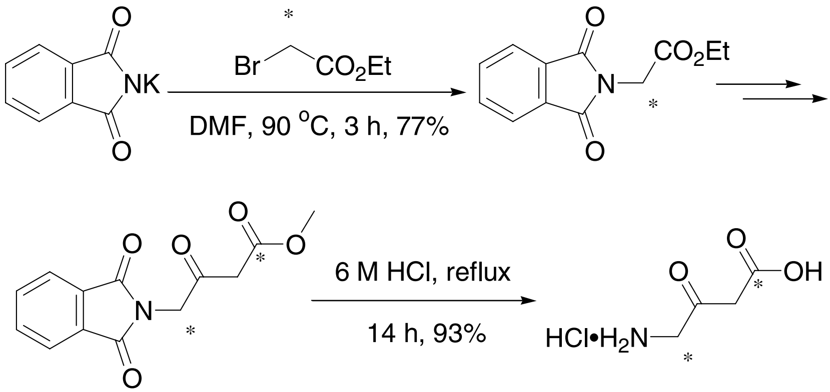
Gabriel synthesis

Synthesis of primary amines using potassium phthalimide and alkyl halides.





Example 1[10]



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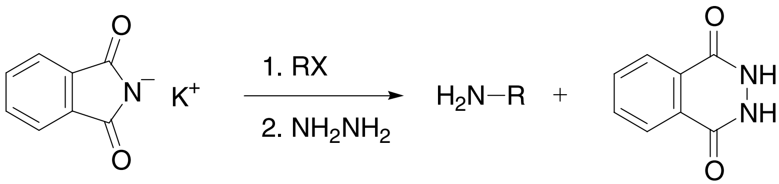
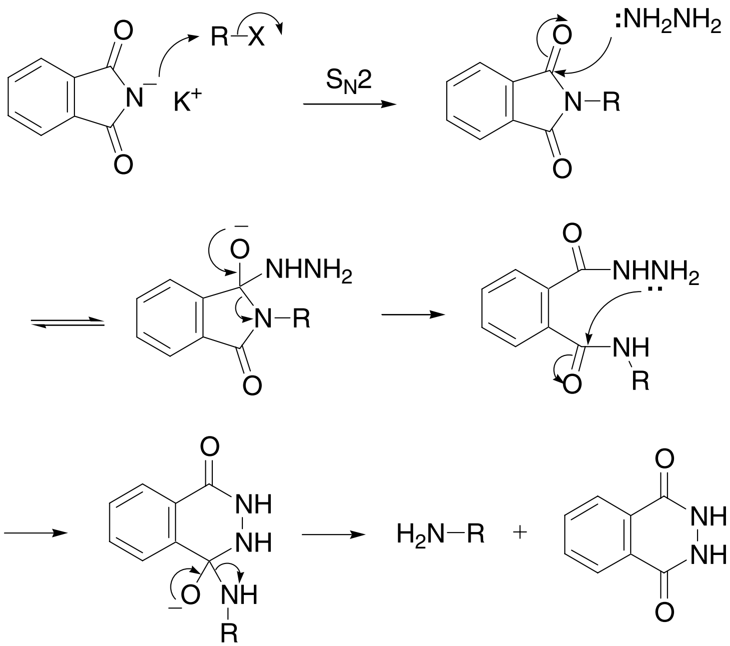
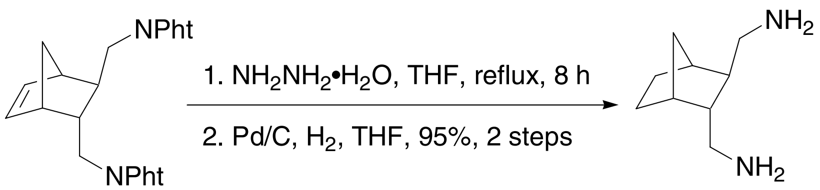
Ing–Manske procedure

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





Example[6]



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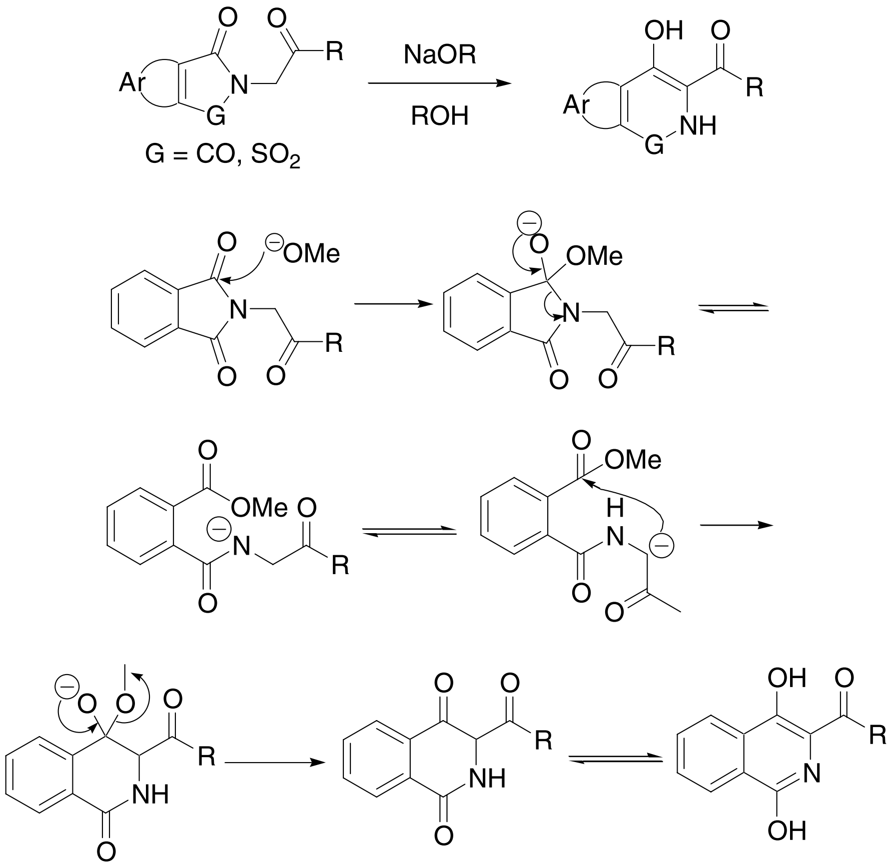
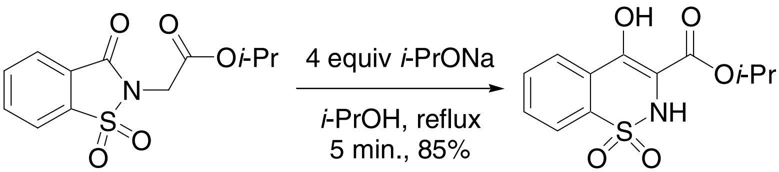
Gabriel–Colman rearrangement

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



Example[11]



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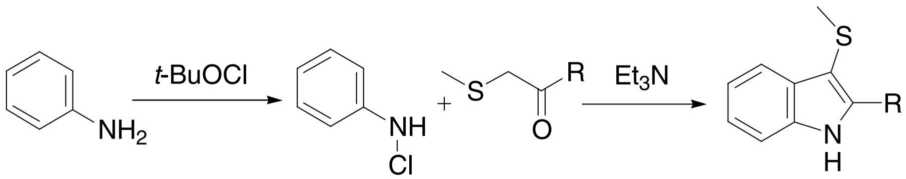
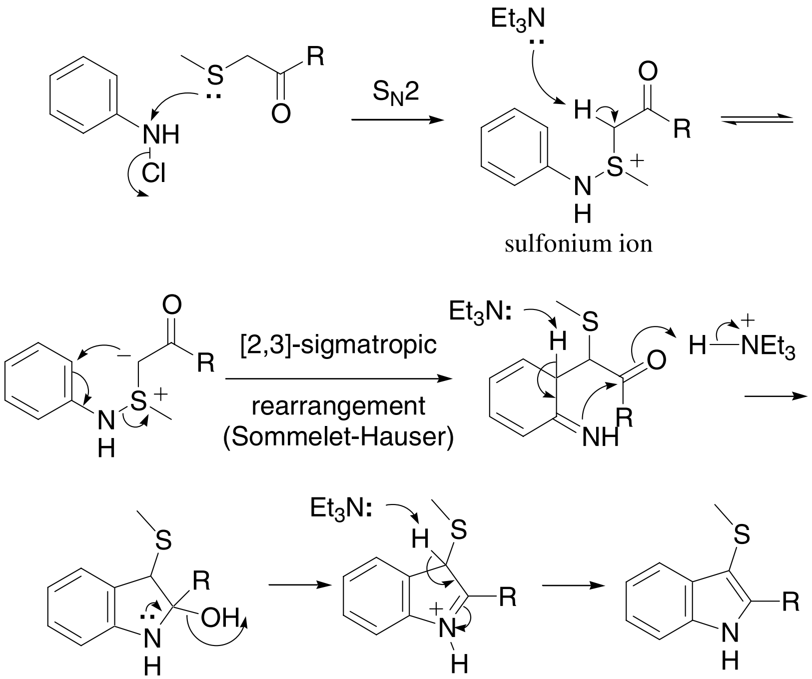
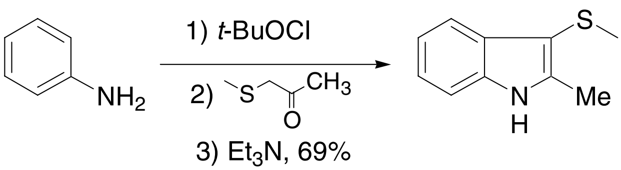
Gassman indole synthesis

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.

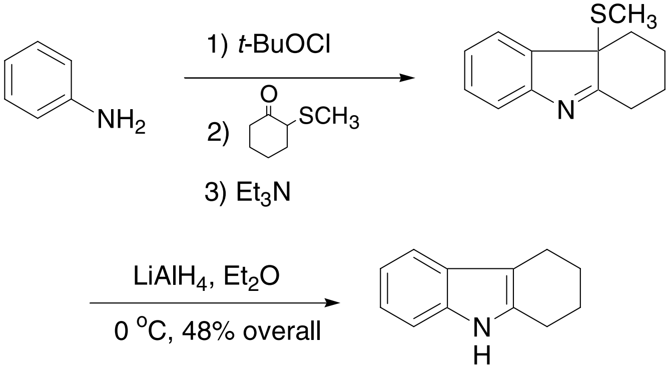




Example 1[1]



Example 2[1]



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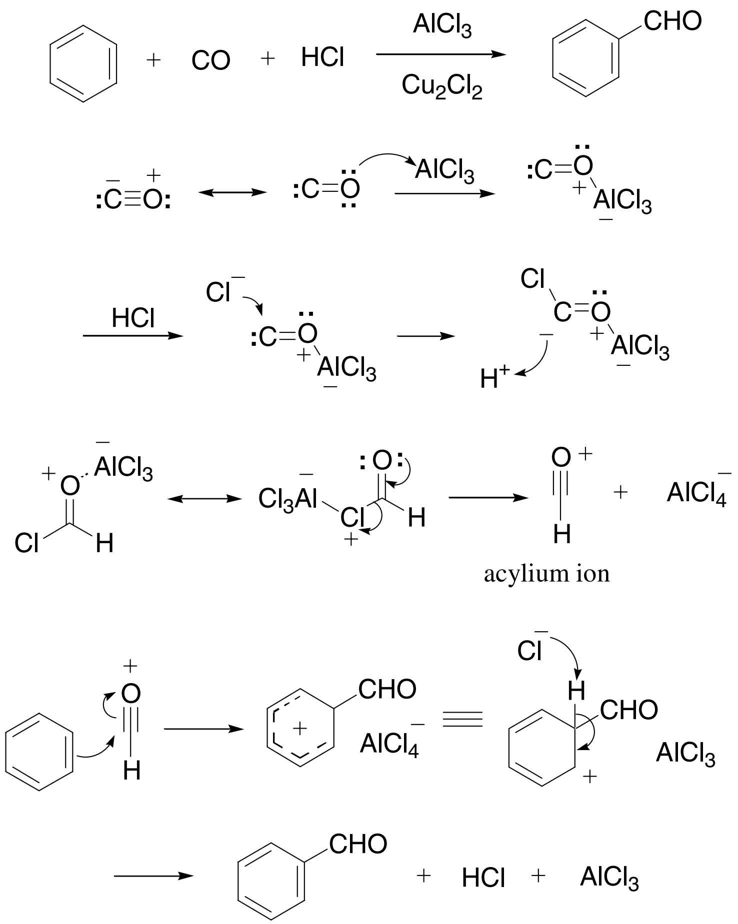
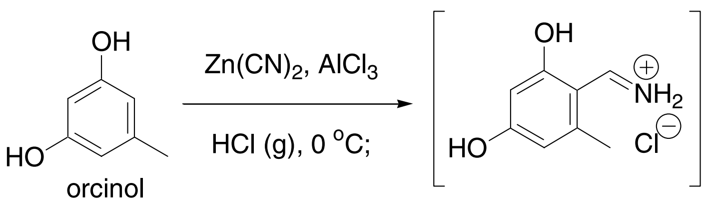
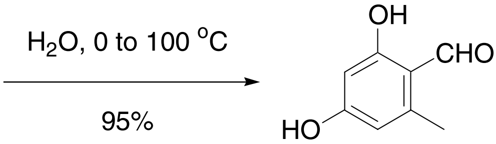
Gattermann–Koch reaction

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



Example, a more practical variant[4]





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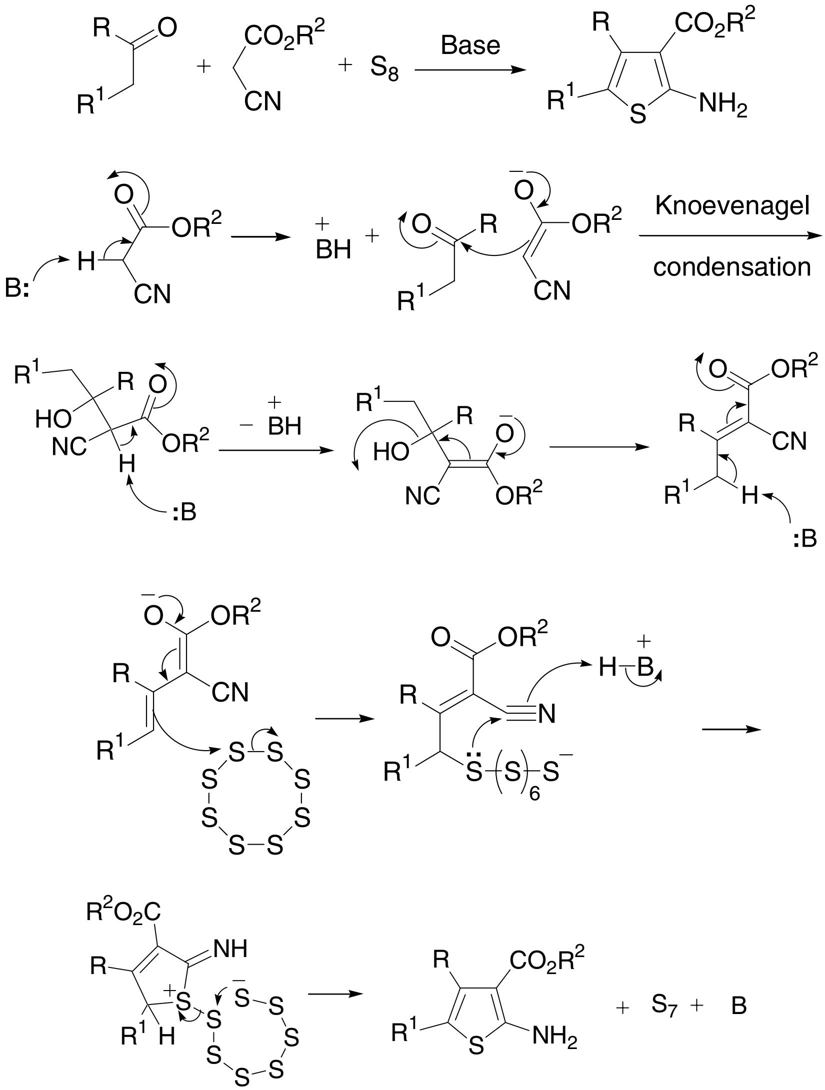
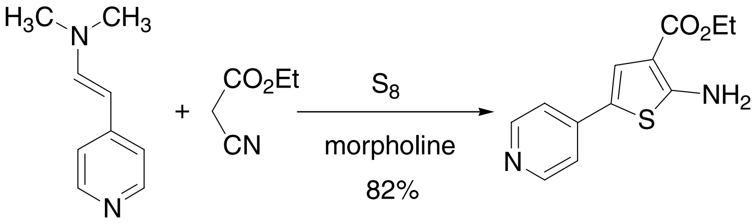
Gewald aminothiophene synthesis

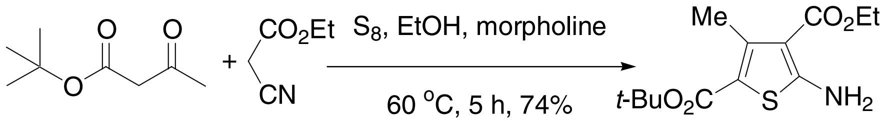
Base-promoted aminothiophene formation from ketone, α-active methylene nitrile and elemental sulfur.



Example 1[8]



Example 2[13]



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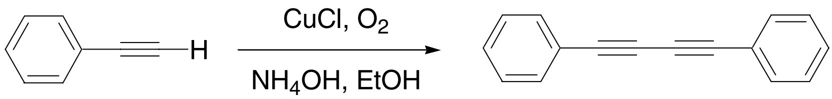
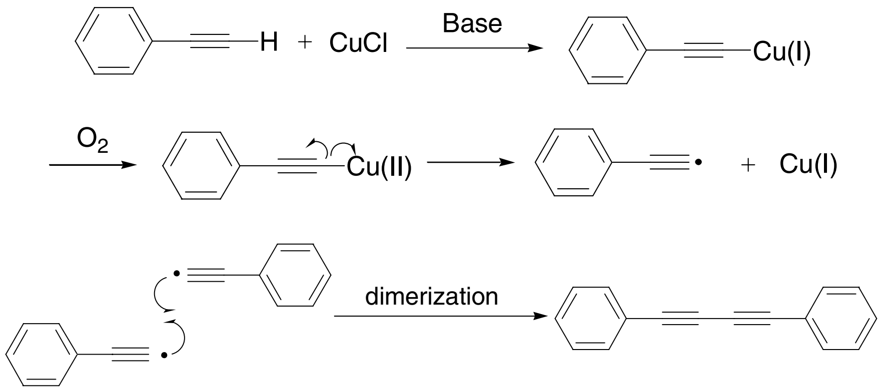
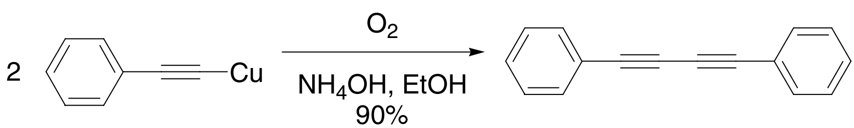
Glaser coupling

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

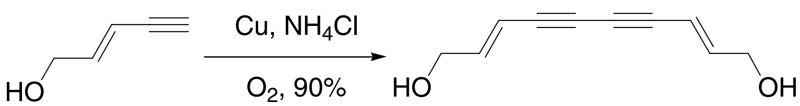




Example 1[1]



Example 2, homo-coupling[2]



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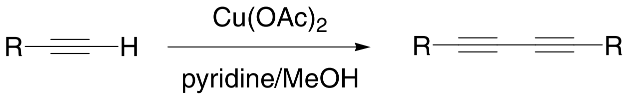
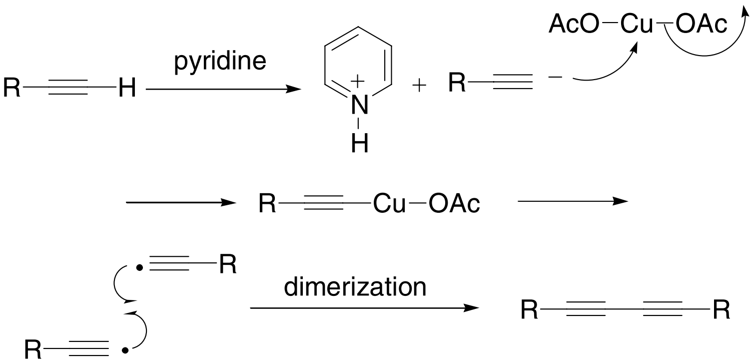
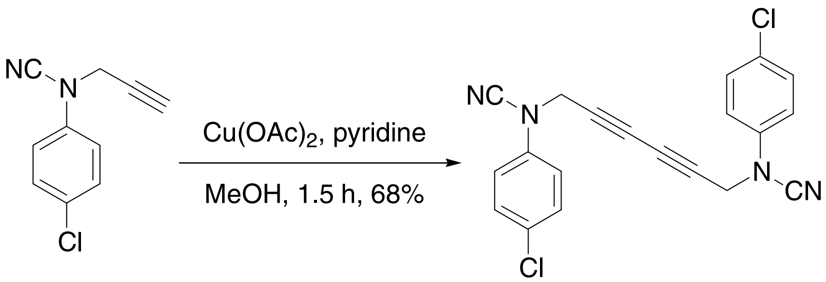
Eglinton coupling

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

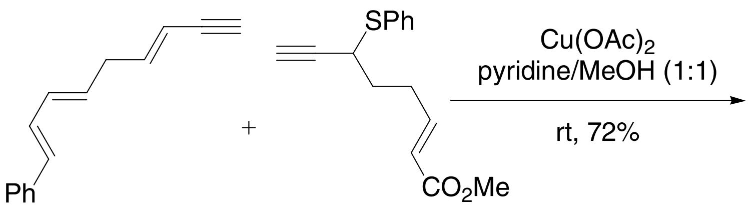


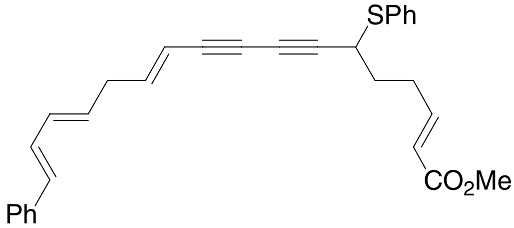


Example 1, homo-coupling[6]



Example 2, cross-coupling[4]





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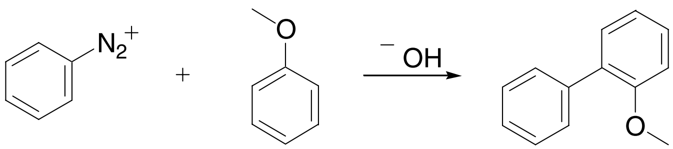
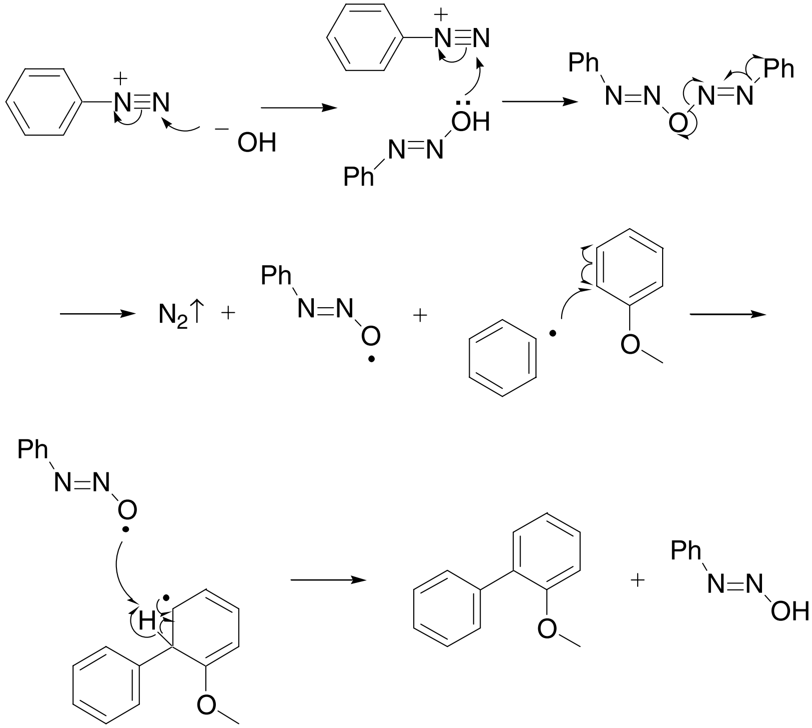
Gomberg–Bachmann reaction

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





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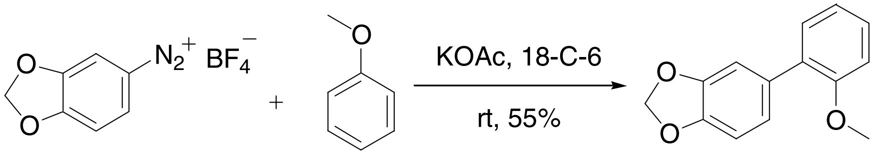
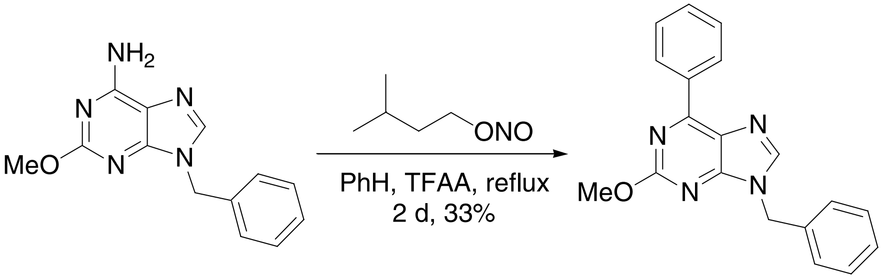


Example 2[5]



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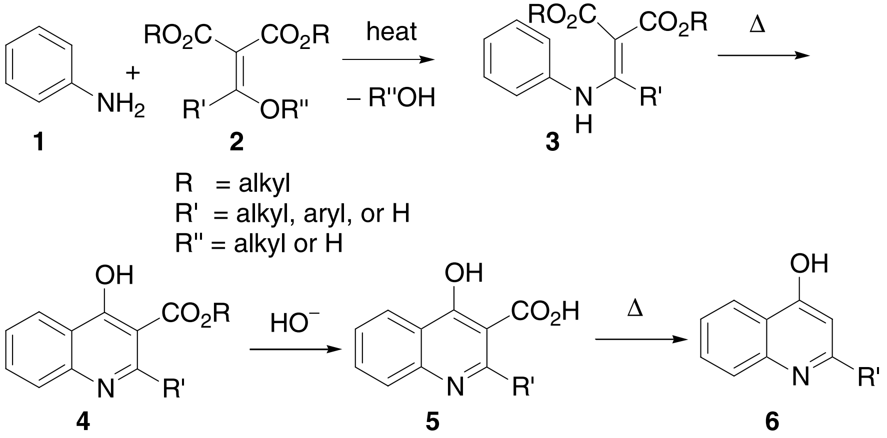
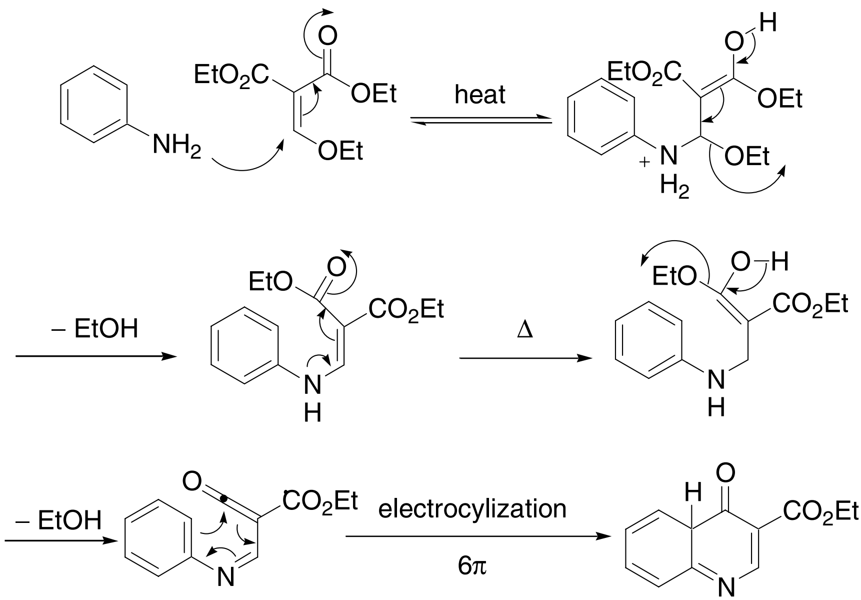
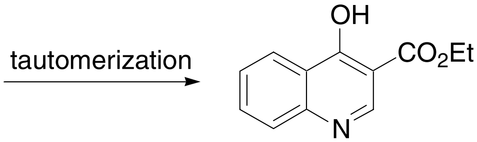
Gould–Jacobs reaction

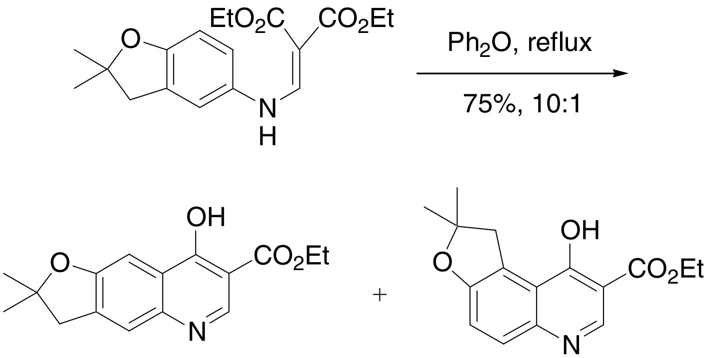
The Gould–Jacobs reaction is a sequence of the following reactions: a. condensation of an aniline **1** with either alkoxy methylenemalonic ester or acyl malonic ester **2** providing the anilidomethylenemalonic ester **3**; b. cyclization of **3** to the 4-hydroxy-3-carboalkoxyquinoline **4**; c. saponification to form acid **5**, and d. decarboxylation to give the 4-hydroxyquinoline **6**.







Example 1[13]



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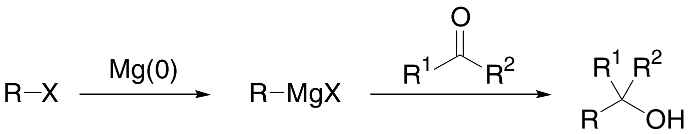
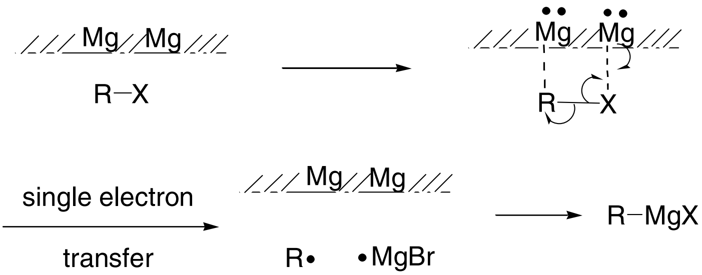
Grignard reaction

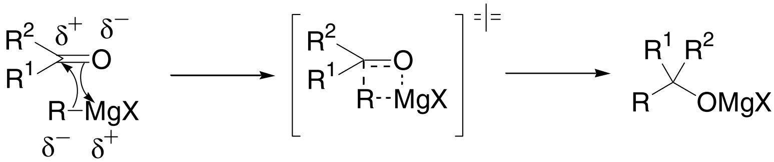
Addition of organomagnesium compounds (Grignard reagents), generated from organohalides and magnesium metal, to electrophiles.



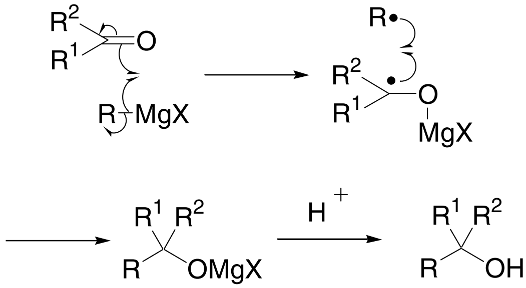
Formation of the Grignard reagent:



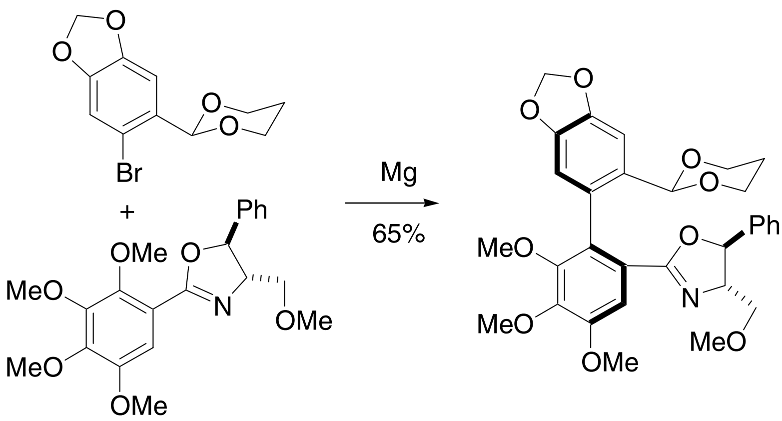
Grignard reaction, ionic mechanism:



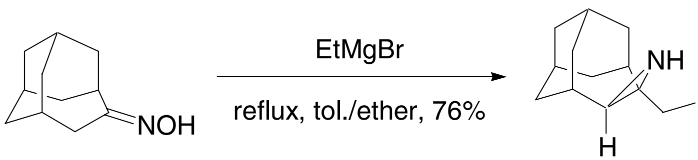
Radical mechanism,



Example 1[6]



Example 2[4]



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.

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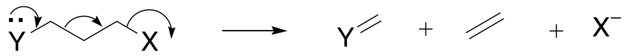
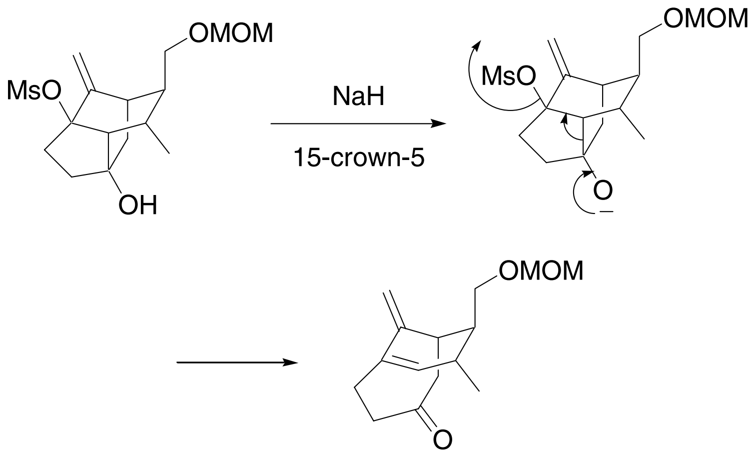
Grob fragmentation

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

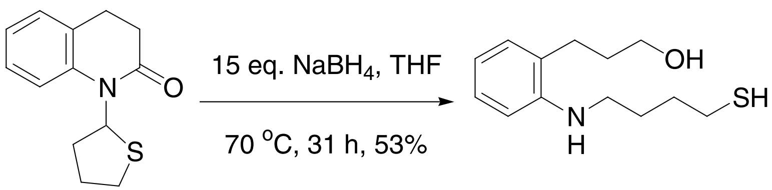


$X = OH_2^+$, OTs, I, Br, Cl; $Y = O^-$, NR_2

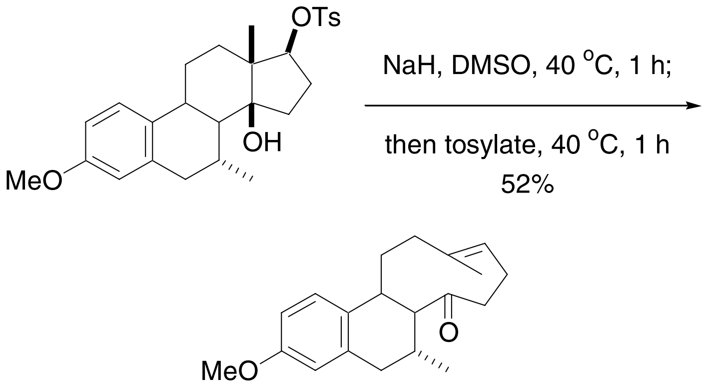
Example 1



Example 2, aza-Grob fragmentation[7]



Example 3[12]



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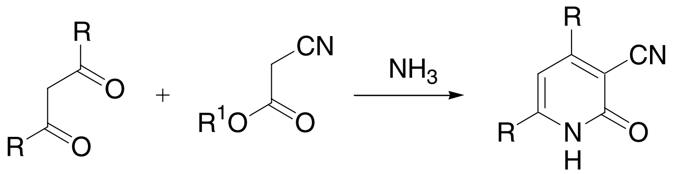
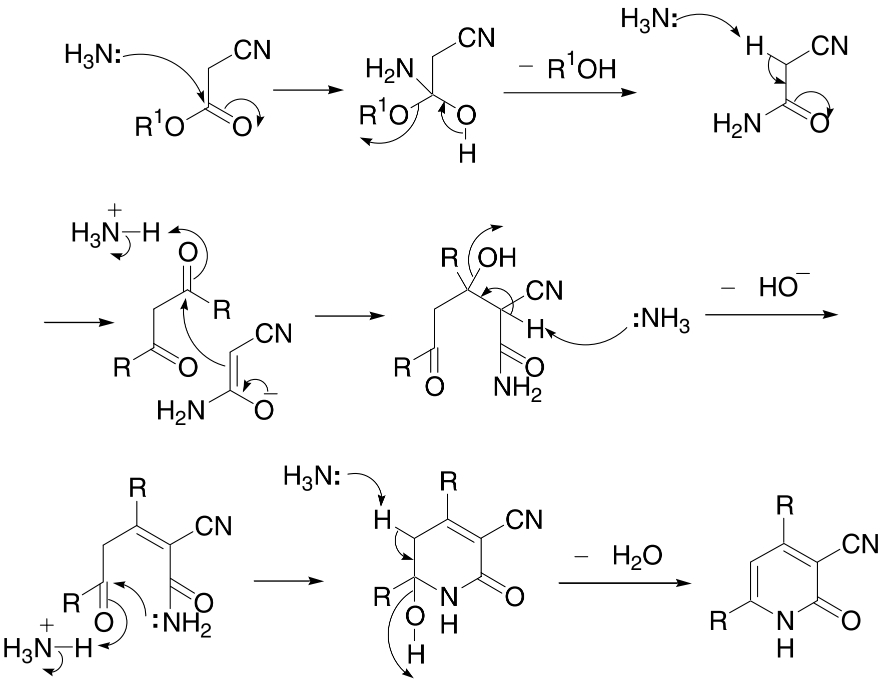
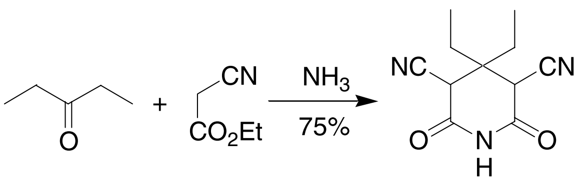
Guareschi–Thorpe condensation

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





Example[7]



Guareschi imide

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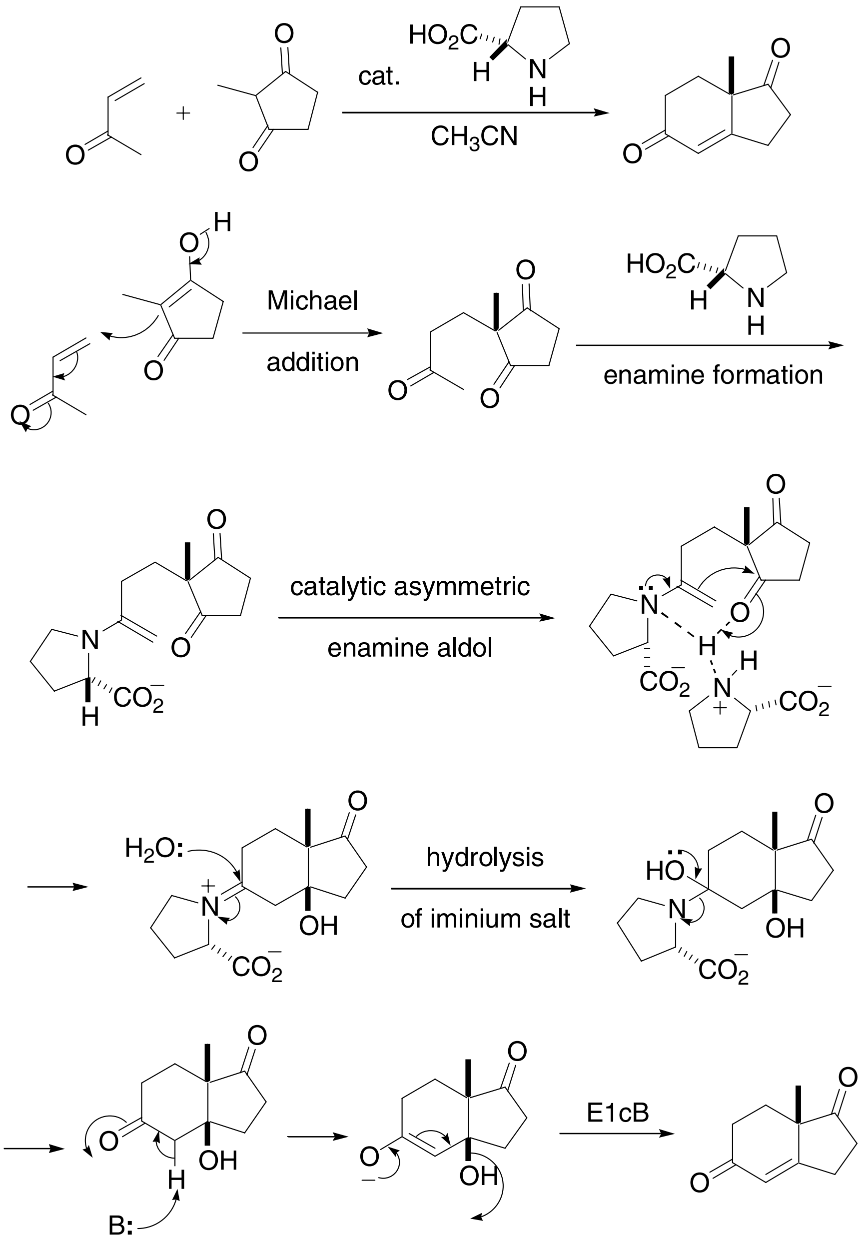
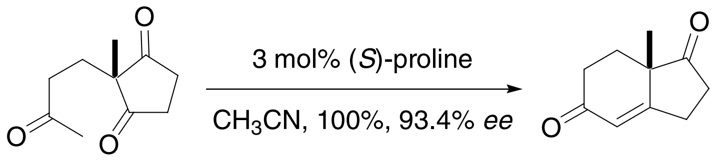
Hajos–Wiechert reaction

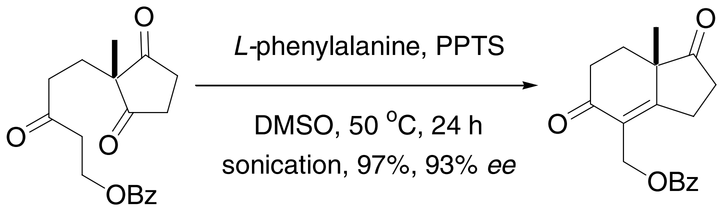
Asymmetric Robinson annulation catalyzed by (*S*)-(−)-proline.



Example 1[1]



Example 2[9]



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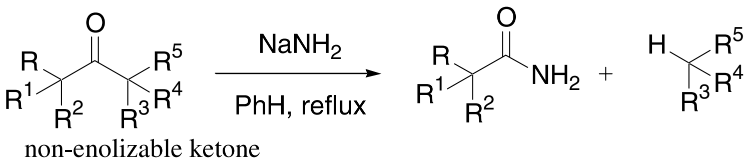
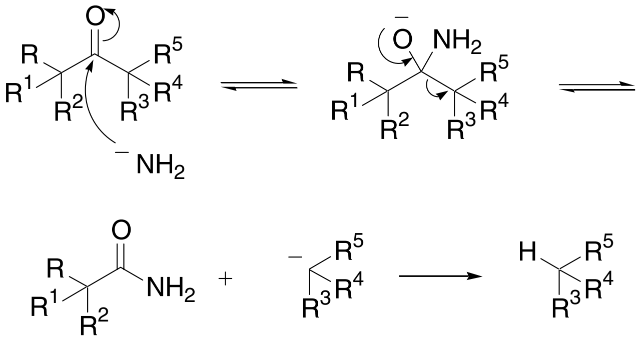
Haller–Bauer reaction

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.





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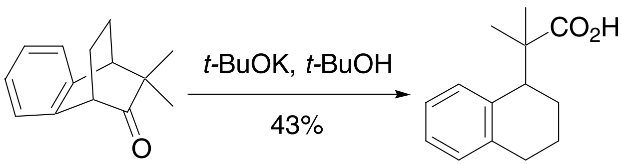
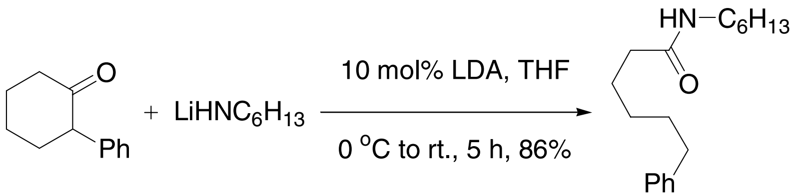


Example 2[12]



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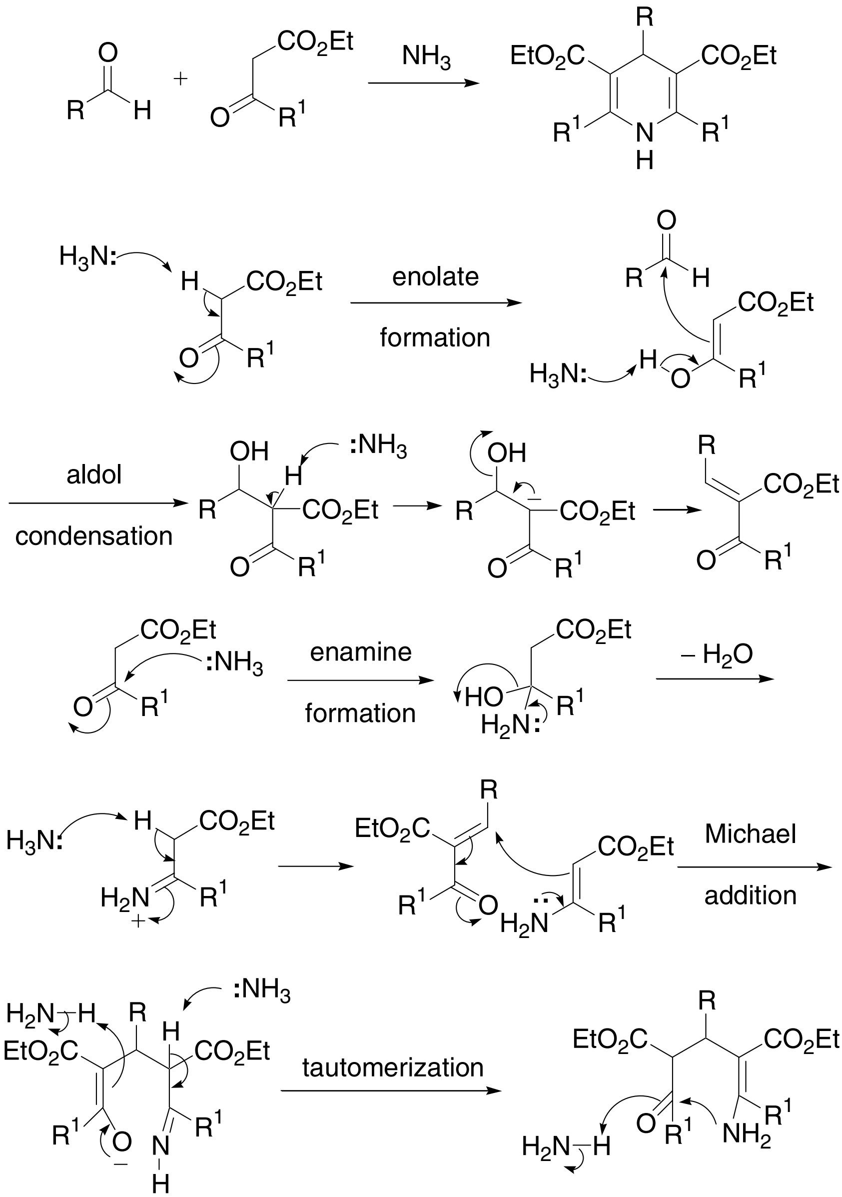
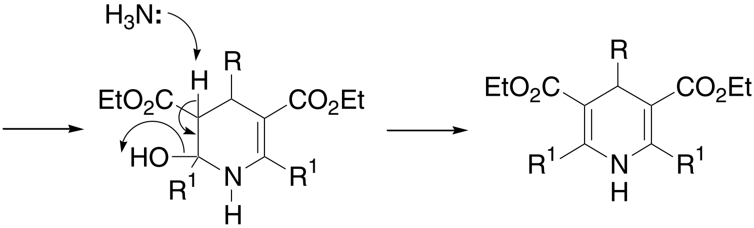
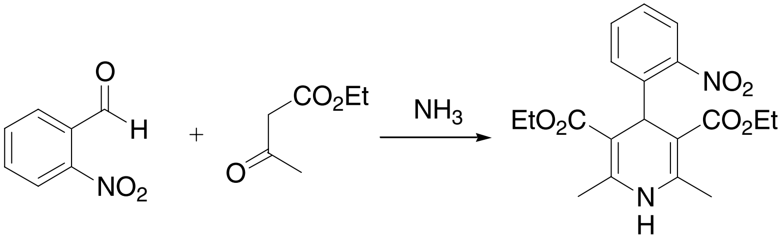
Hantzsch dihydropyridine synthesis

Dihydropyridine from the condensation of aldehyde, β-ketoester and ammonia.





Example 1[6]



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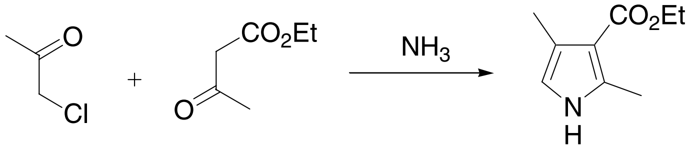
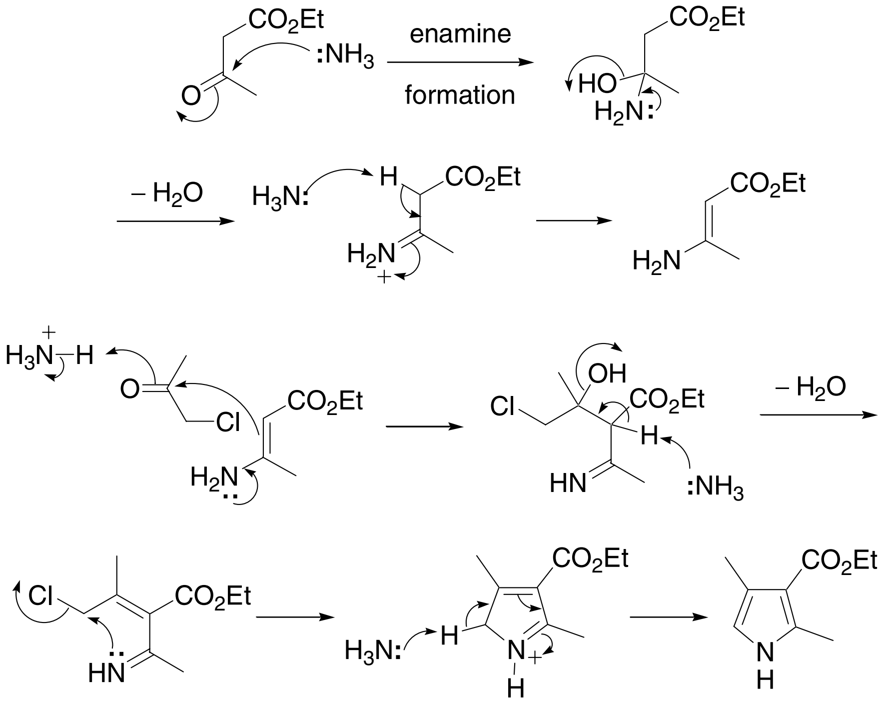
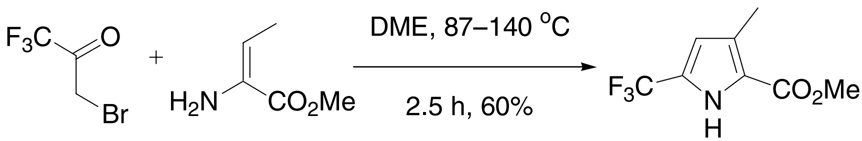
Hantzsch pyrrole synthesis

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

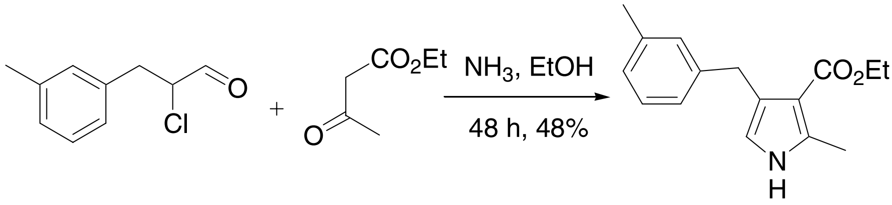




Example 1[5]



Example 2[8]



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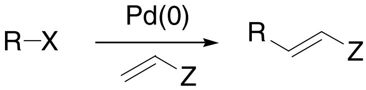
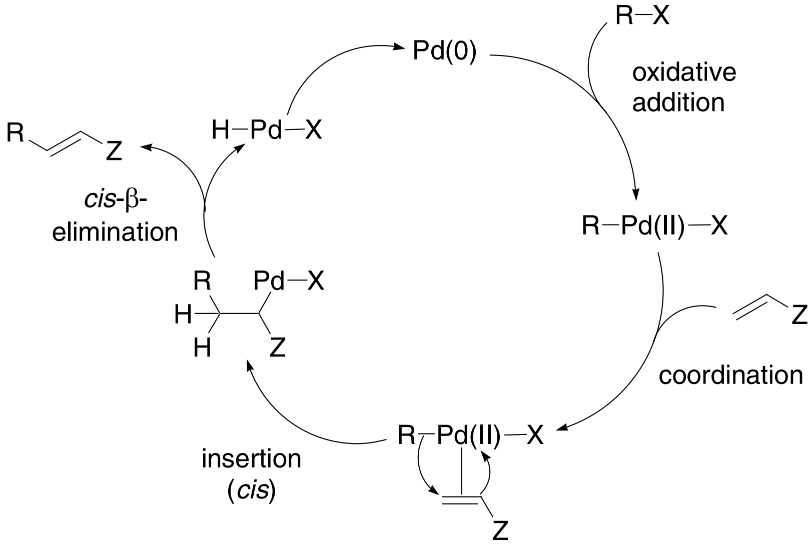
Heck reaction

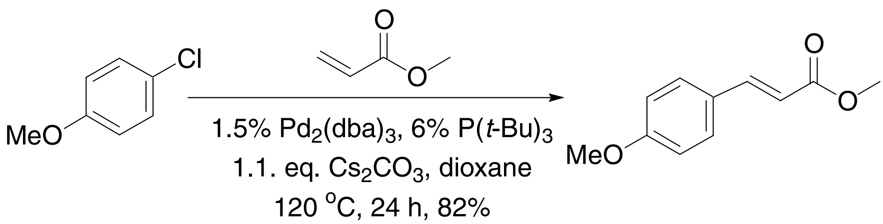
Palladium-catalyzed coupling between organohalides or triflates with olefins.



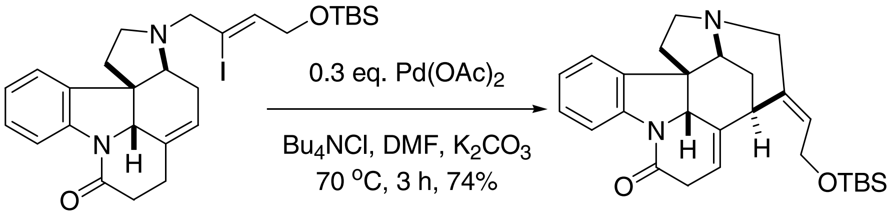
X = I, Br, OTf, Cl, *etc.*
Z = H, R, Ar, CN, CO_2R, OR, OAc, NHAc, *etc.*



Example 1[7]



Example 2[6]



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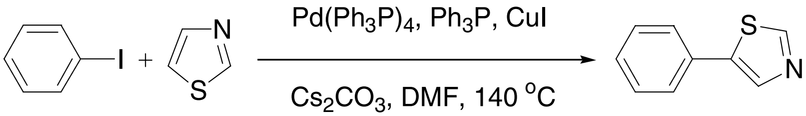
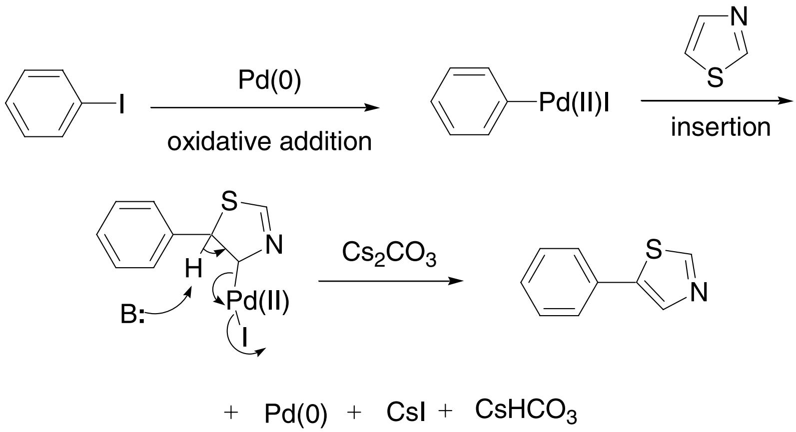
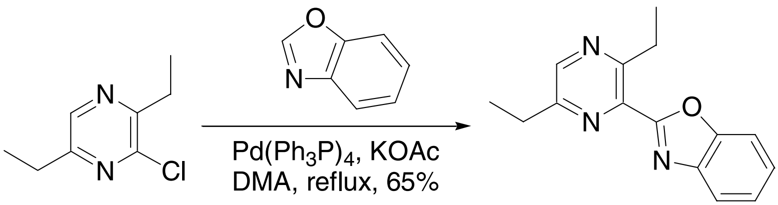
Heteroaryl Heck reaction

Intermolecular or intramolecular Heck reaction that occurs onto a heteroaryl recipient.

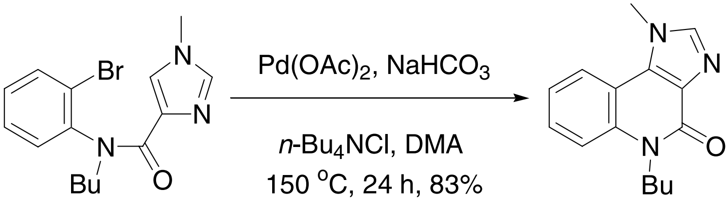




Example 1[3]



Example 2[2]



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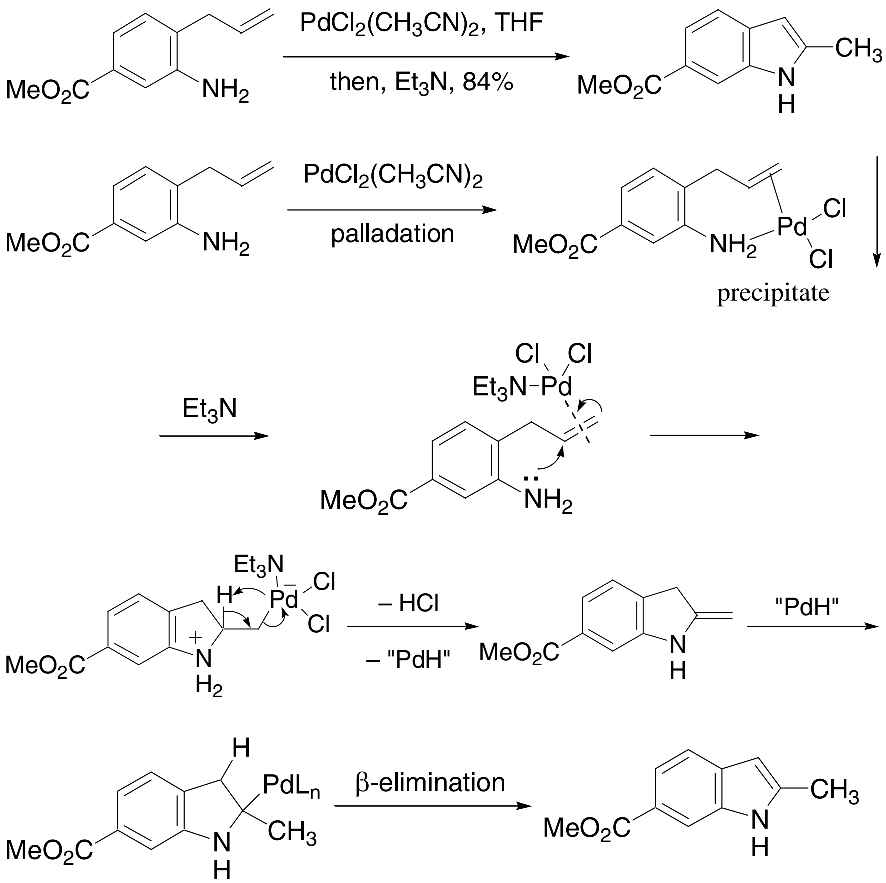
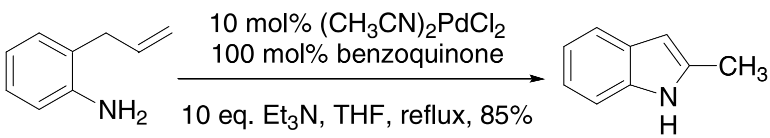
Hegedus indole synthesis

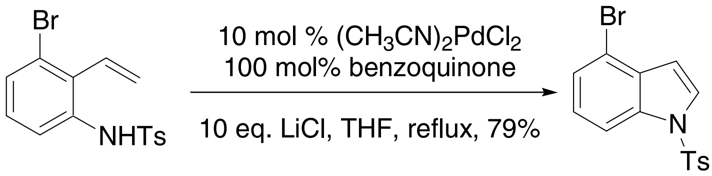
Stoichiometric Pd(II)-mediated oxidative cyclization of alkenyl anilines to indoles. *Cf.* Wacker oxidation.



Example 1[1]



Example 2[4]



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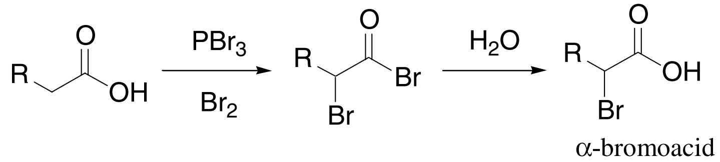
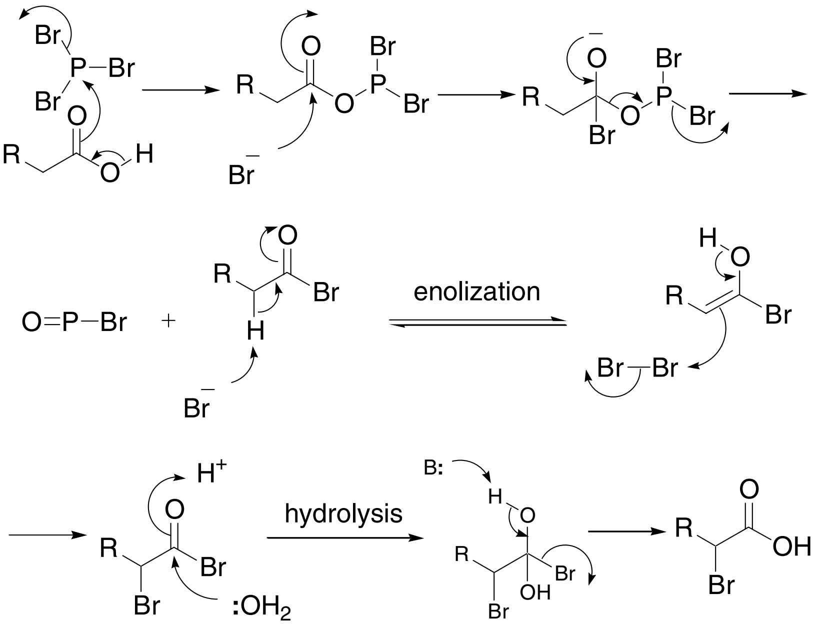
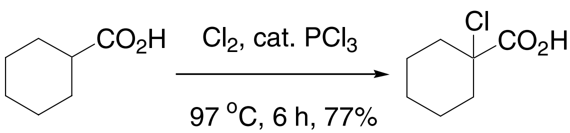
Hell–Volhard–Zelinsky reaction

α-Bromination of carboxylic acids using Br_2/PBr_3.

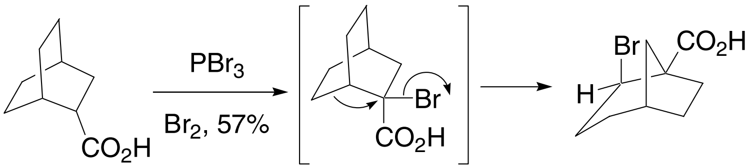




Example 1[7]



Example 2[8]



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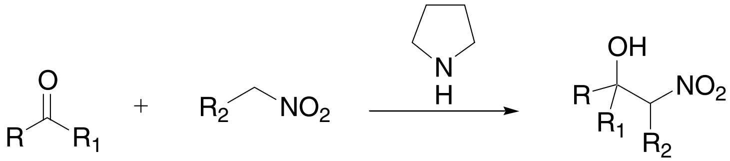
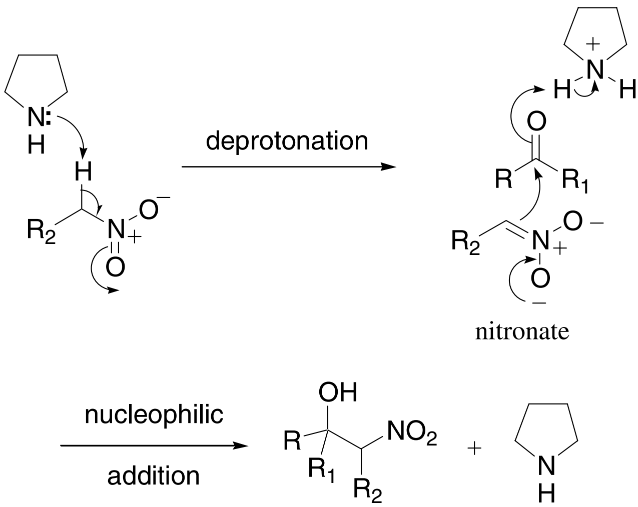
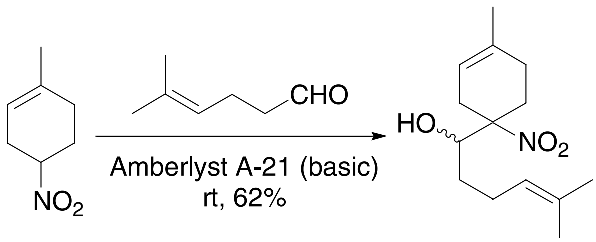
Henry nitroaldol reaction

The nitroaldol condensation reaction involving aldehydes and nitronates, derived from deprotonation of nitroalkanes by bases.

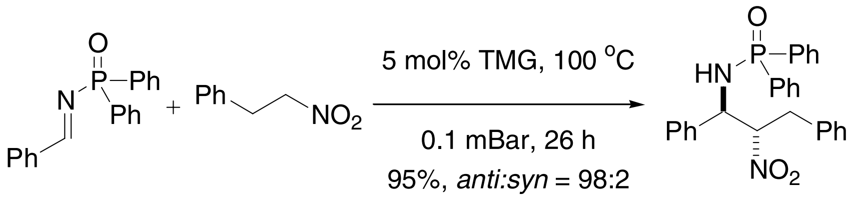




Example 1[6]



Example 2, aza-Henry reaction[14]



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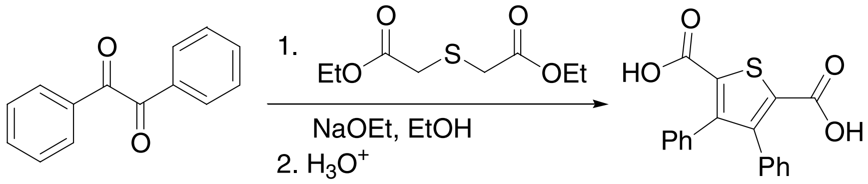
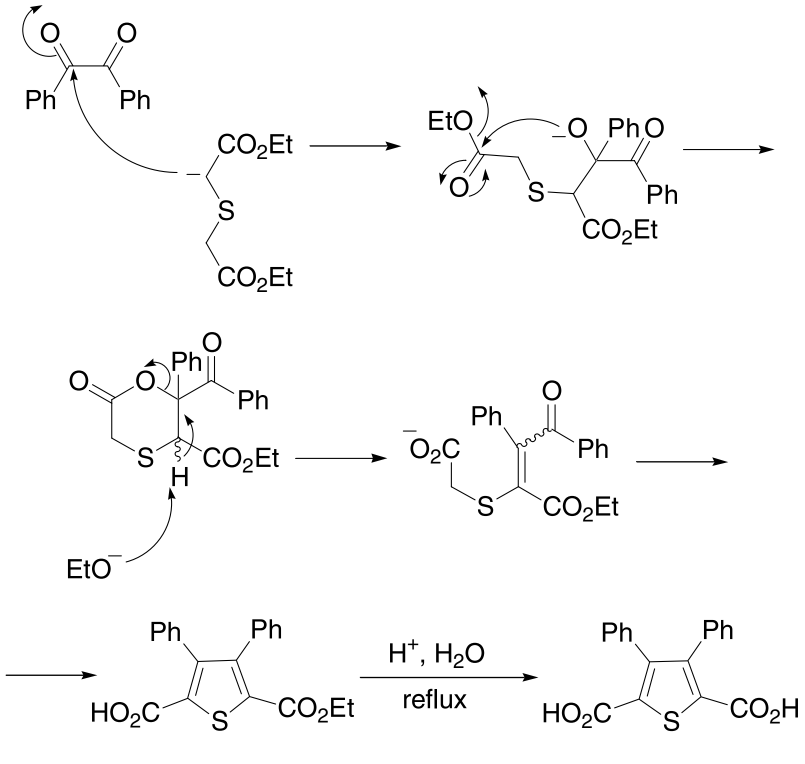
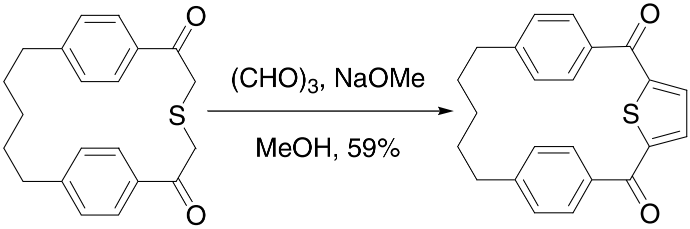
Hinsberg synthesis of thiophene derivatives

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

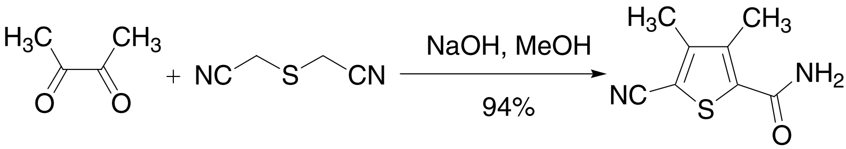




Example 1[11]



Example 2[15]



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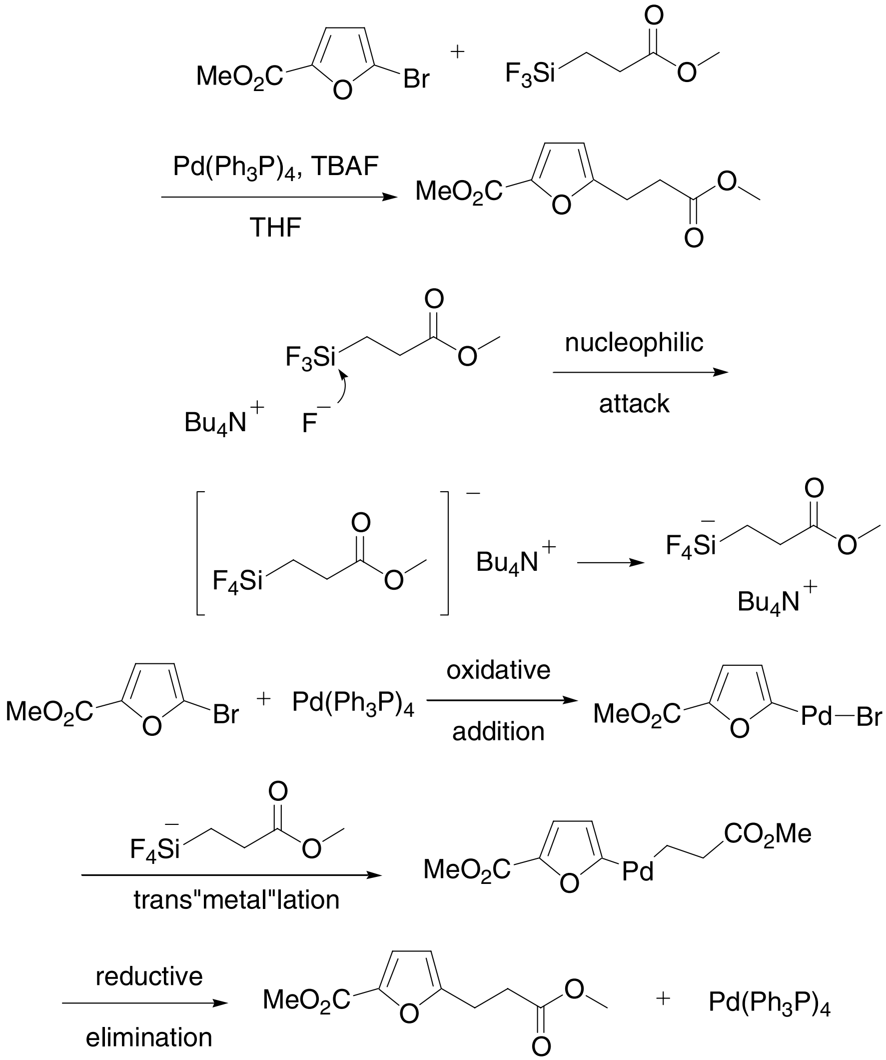
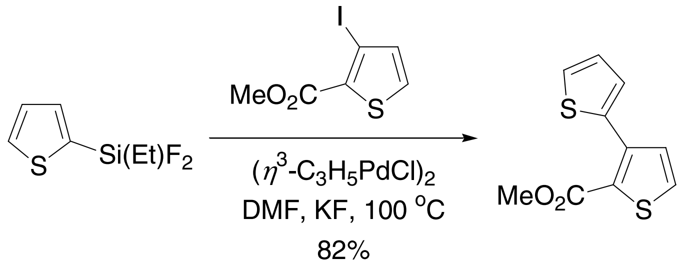
Hiyama cross-coupling reaction

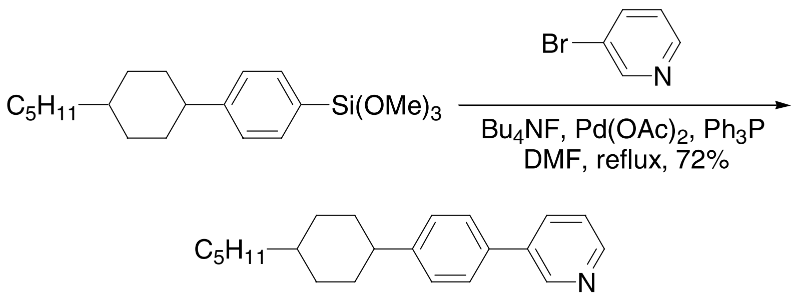
Palladium-catalyzed cross-coupling reaction of organosilicons with organic halides, triflates, *etc*. in the presence of an activating agent such as fluoride or hydroxide (transmetalation is reluctant to occur without the effect of an activating agent). For the catalytic cycle, see the Kumada coupling on page 345.



Example 1[1]



Example 2[5]



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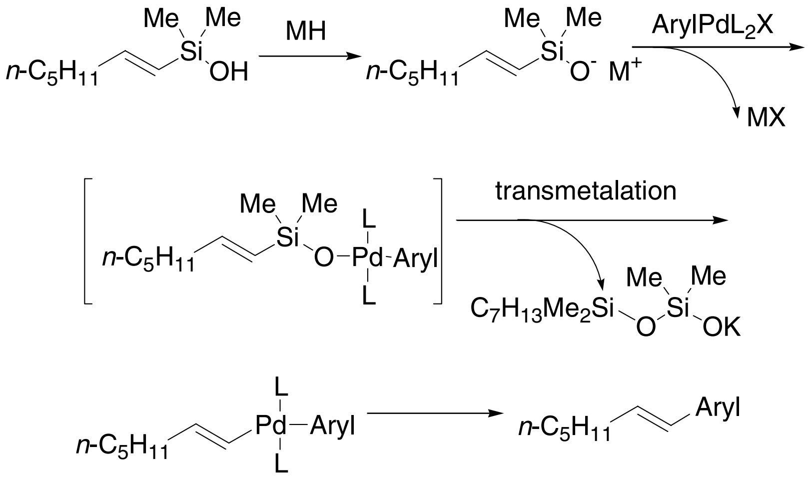
Hiyama–Denmark cross-coupling reaction

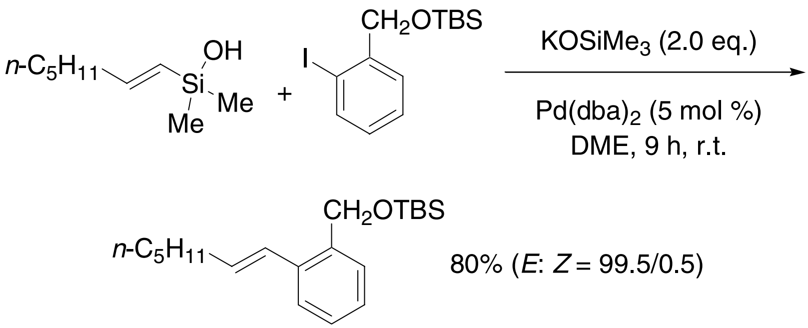
A synthetically important and mechanistically distinct cross-coupling process of organosilanols has been developed. Unlike the Hiyama cross-coupling reaction of polychloro- and fluorosilanes that requires activation by fluoride ion, the Denmark process involves the simple deprotonation of an organosilanol to initiate the coupling. This variant has obvious advantages of avoiding incompatibility with fluoride (silicon protective groups and large-scale reactors).

Mechanistic study[5]

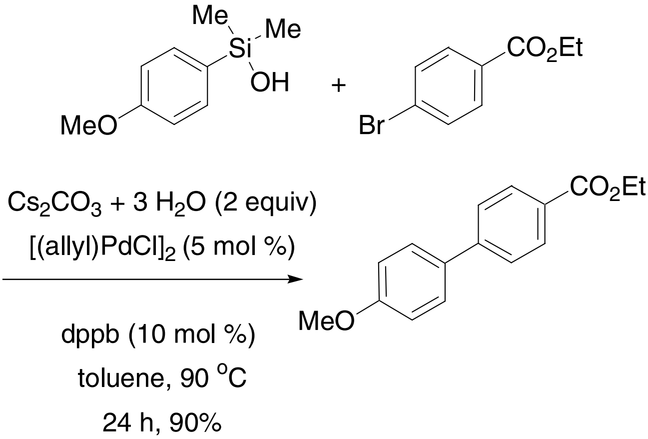


Many organosilanol substrates and different bases have been demonstrated.

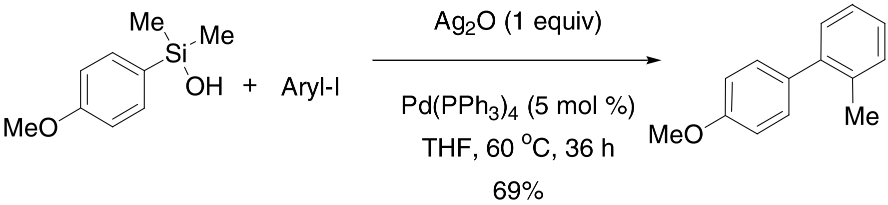
1. Alkenylsilanol ($KOSiMe_3$)[6]



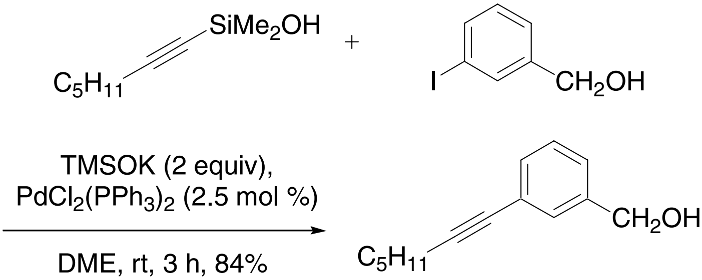
2. Arylsilanol (Cs_2CO_3)[7]



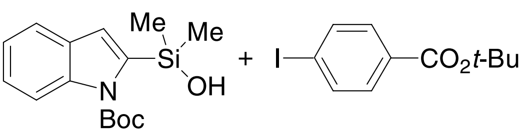
3. Arylsilanol (Ag_2O)[8]

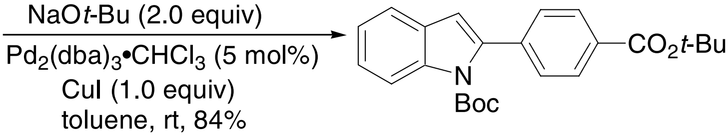


4. Alkynylsilanol ($KOSiMe_3$)[9]

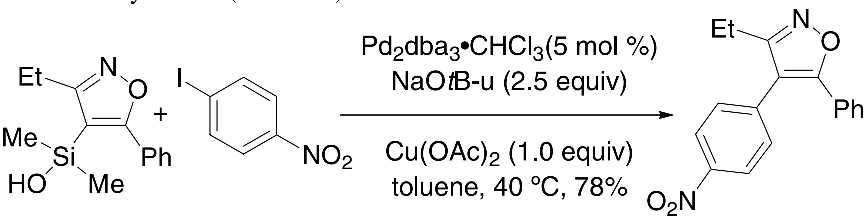


5. 2-Indolylsilanol (KO*t*-Bu)[10]

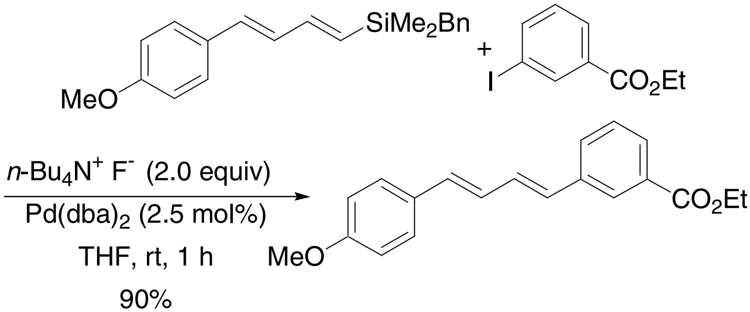




6. 4-Isoxazolylsilanol (NaO*t*-Bu)[11]



7. 1,4-Bis-silyl-1,3-butadienes ($KOSiMe_3$)[12]



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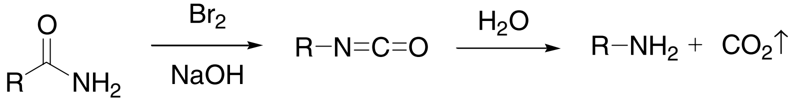
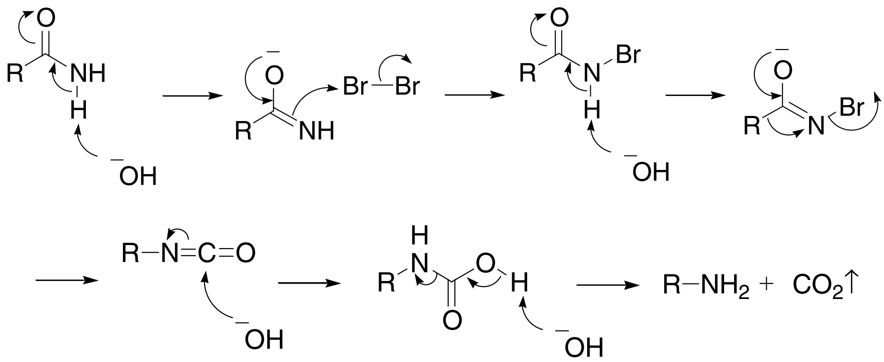
Hofmann rearrangement

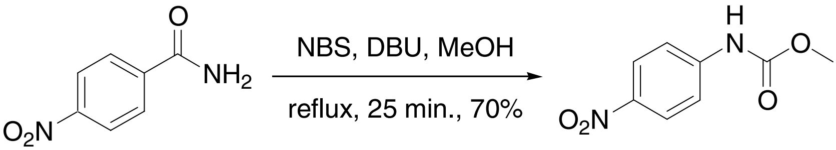
Upon treatment of primary amides with hypohalites, primary amines with one less carbon are obtained *via* the intermediacy of isocyanate. Also know as the Hofmann degradation reaction.



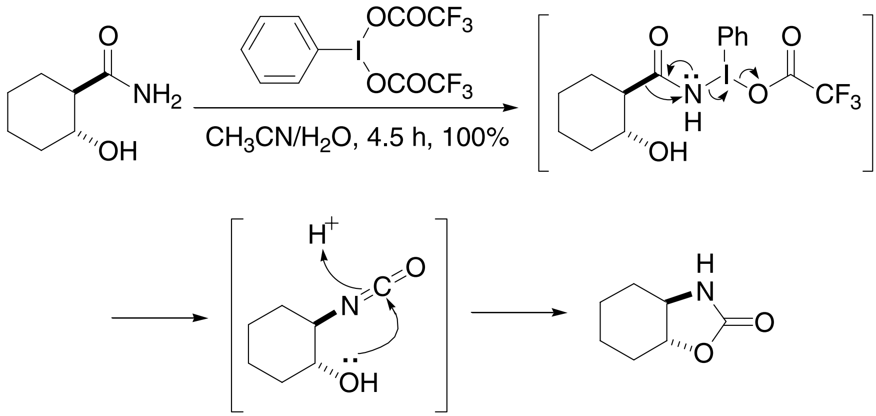


isocyanate intermediate

Example 1[4]



Example 2[9]



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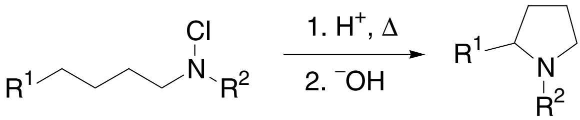
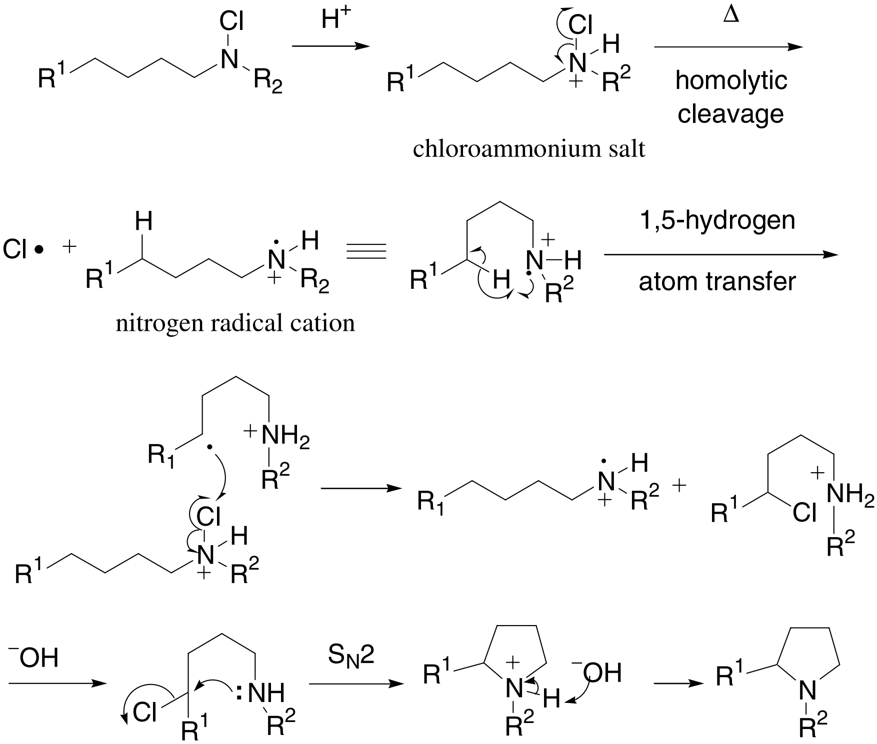
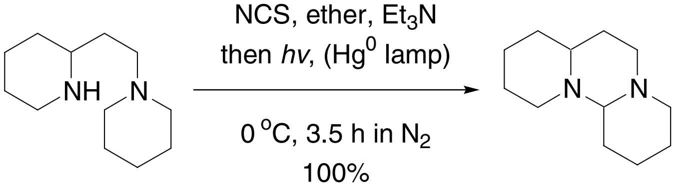
Hofmann–Löffler–Freytag reaction

Formation of pyrrolidines or piperidines by thermal or photochemical decomposition of protonated *N*-haloamines.

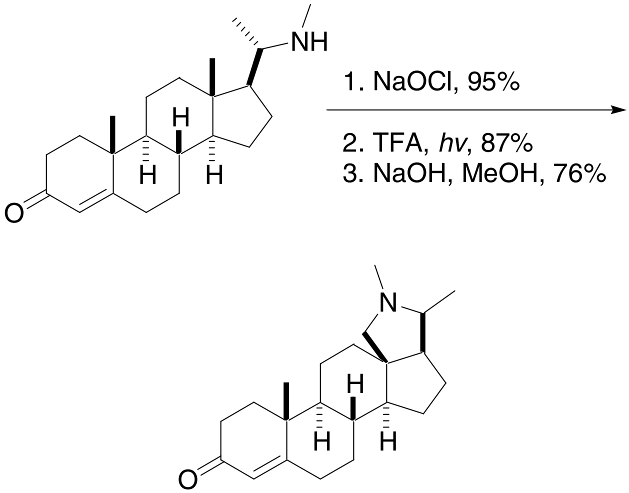




Example 1[6]



Example 2[3]



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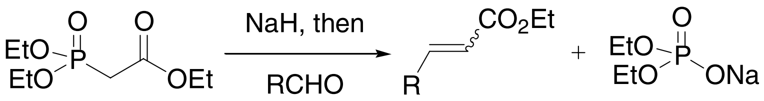
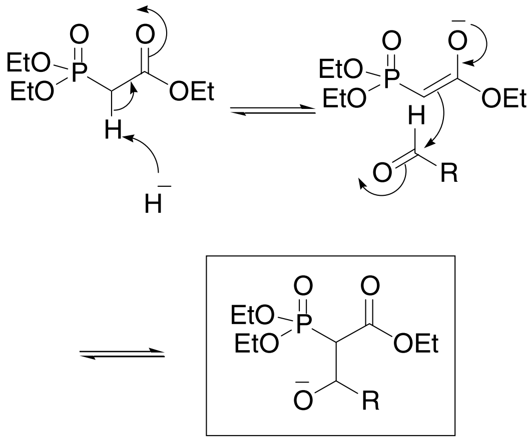
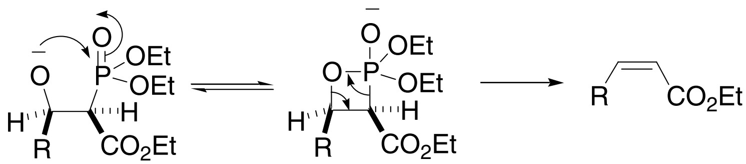
Horner–Wadsworth–Emmons reaction

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.

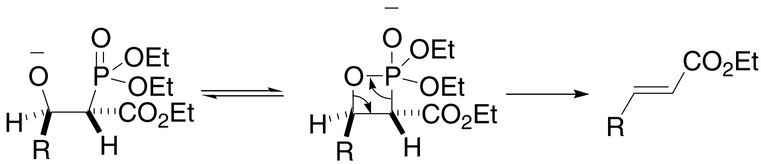




erythro (kinetic) or *threo* (thermodynamic)

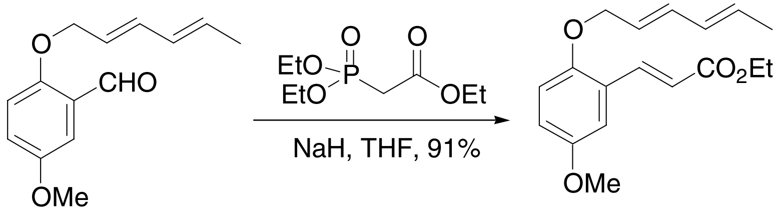


erythro, kinetic adduct

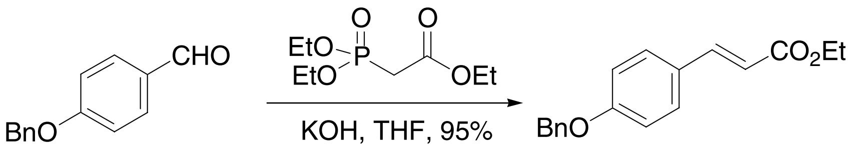


threo, thermodynamic adduct

Example 1[5]



Example 2[8]



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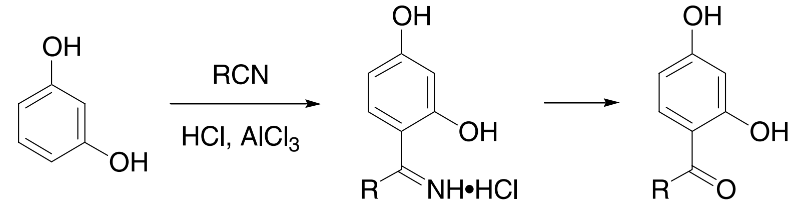
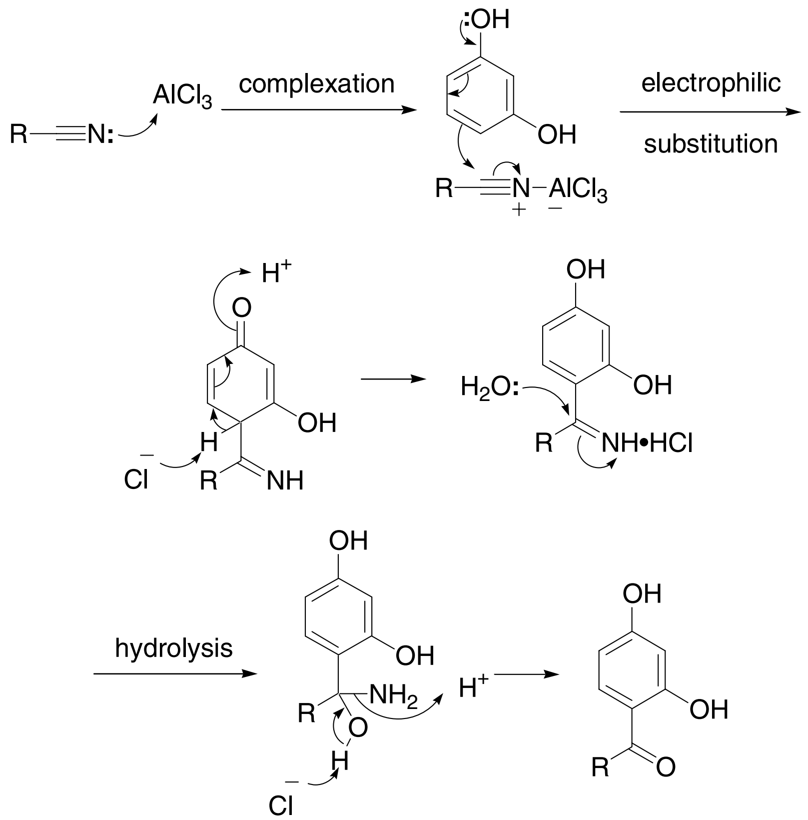
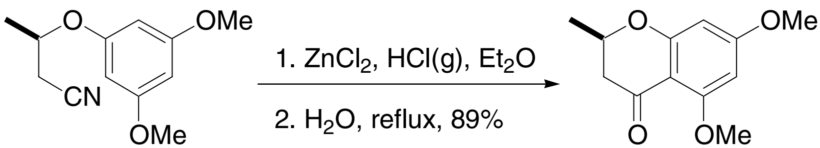
Houben–Hoesch reaction

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

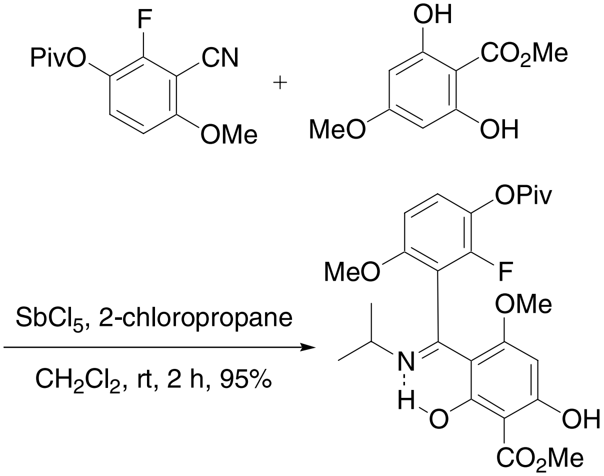




Example 1, intramolecular Houben–Hoesch reaction[5]



Example 2[8]



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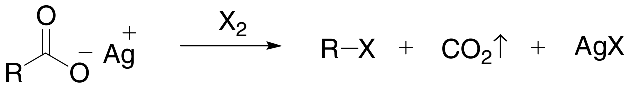
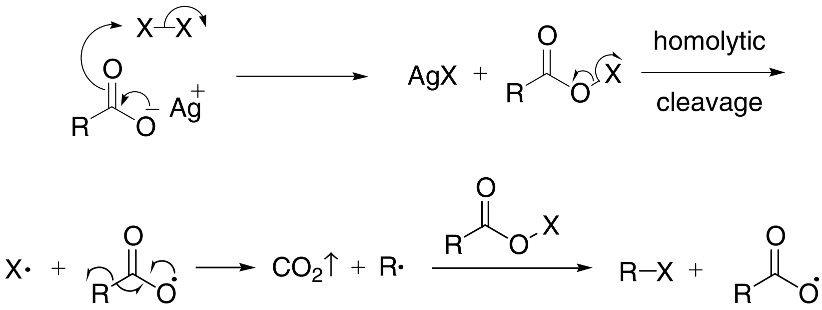
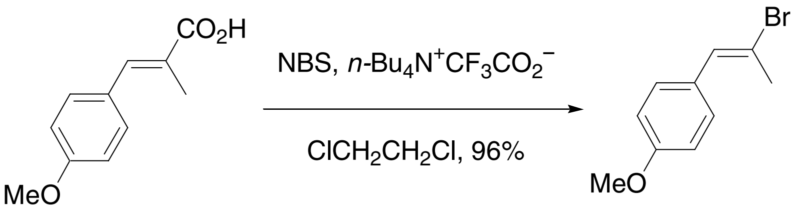
Hunsdiecker–Borodin reaction

Conversion of silver carboxylate to halide by treatment with halogen.

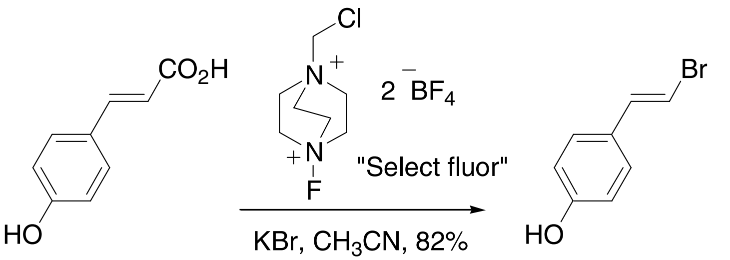




Example 1[6]



Example 2[10]



References

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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.

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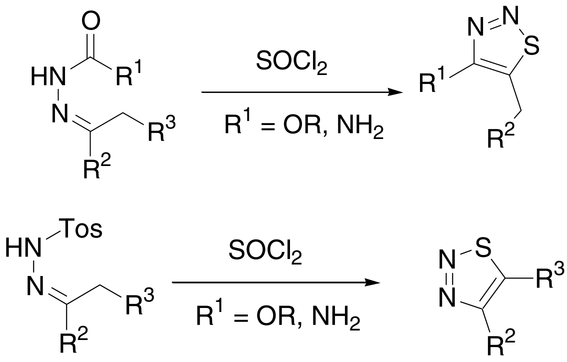
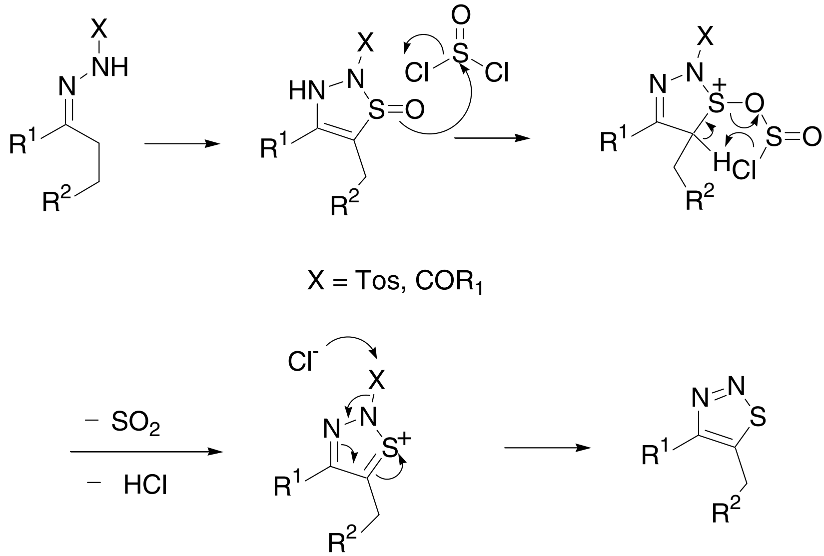
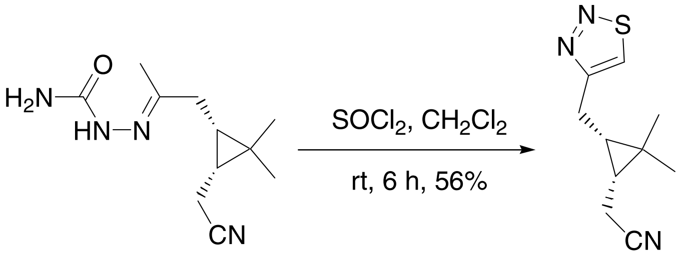
Hurd–Mori 1,2,3-thiadiazole synthesis

Reaction of thionyl chloride with the *N*-acylated or tosyl hydrazone derivatives to provide the 1,2,3-thiadiazole in one step.





Example[17]



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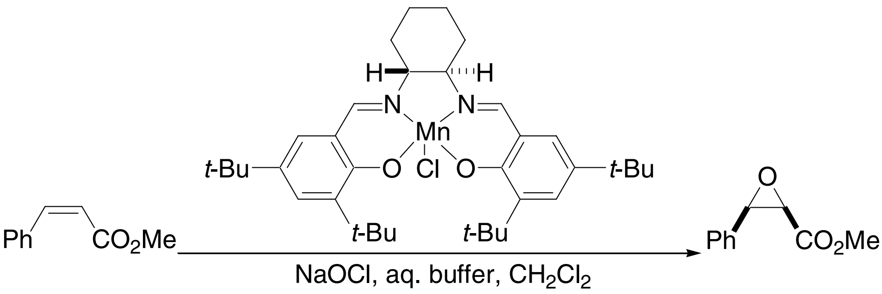
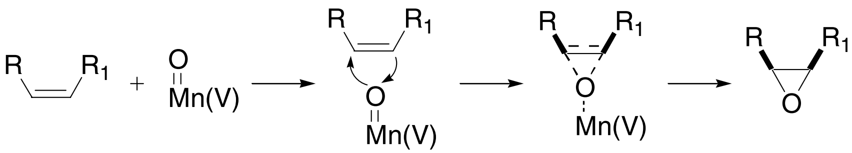
Jacobsen–Katsuki epoxidation

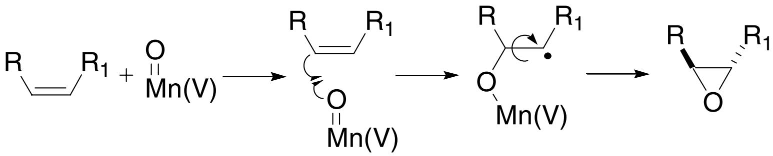
Manganese-catalyzed asymmetric epoxidation of (*Z*)-olefins.



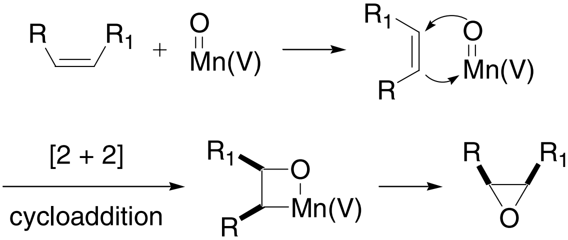
1. Concerted oxygen transfer (*cis*-epoxide):



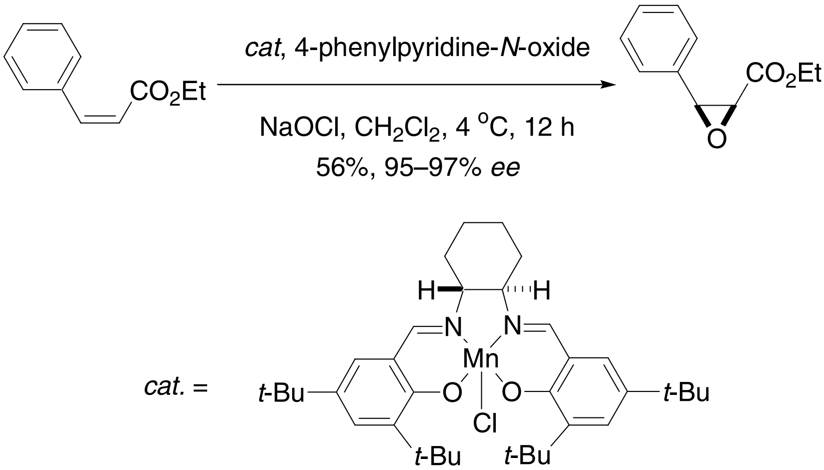
2. Oxygen transfer *via* radical intermediate (*trans*-epoxide):



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



Example[5]



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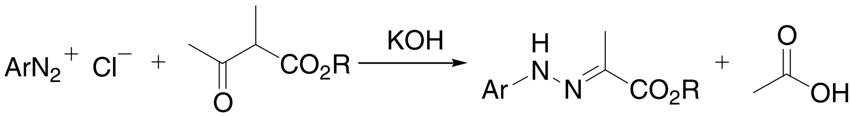
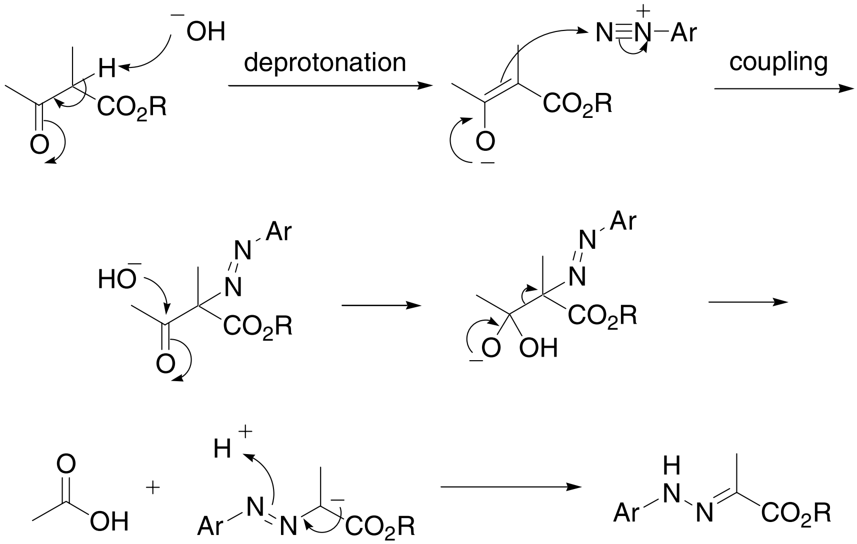
Japp–Klingemann hydrazone synthesis

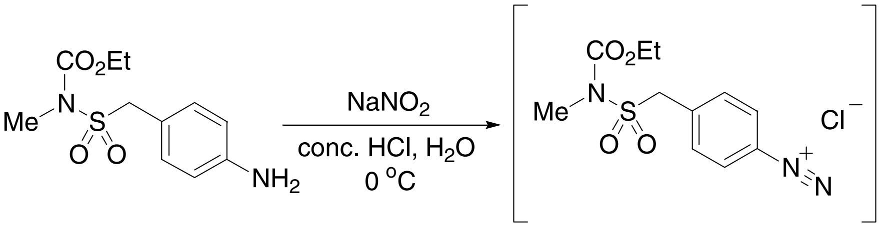
Hydrazones from α-ketoesters and diazonium salts with the acid of base.

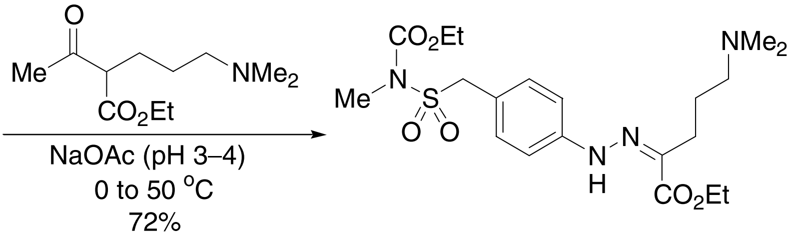


Diazonium salt β-keto-ester hydrazone

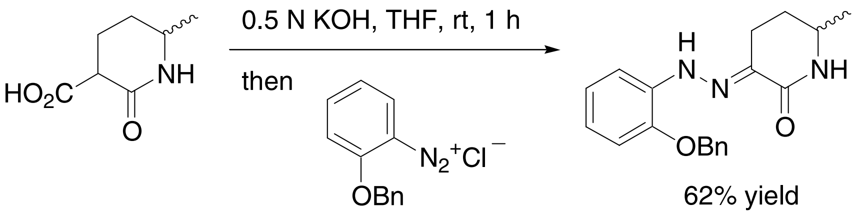


Example 1[6]





Example 2[9]



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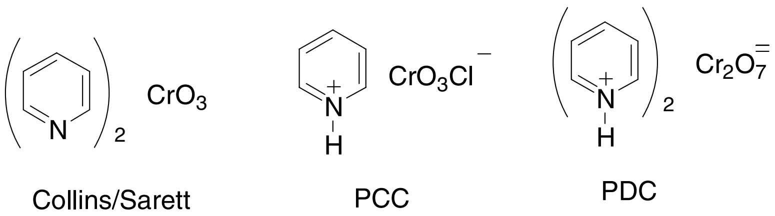
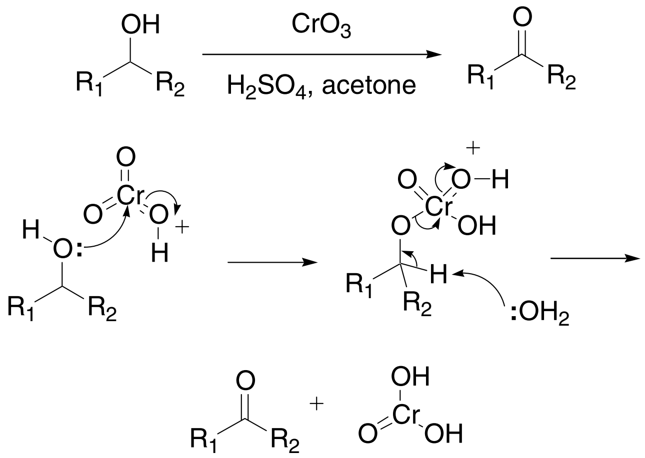
Jones oxidation

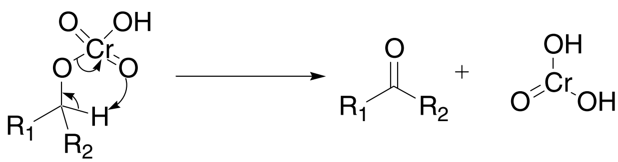
The **Collins/Sarett oxidation** (chromium trioxide-pyridine complex), and **Corey´s PCC** (pyridinium chlorochromate) and **PDC** (pyridinium dichromate) **oxidations** follow a similar pathway as the **Jones oxidation**. All these oxidants have a chromium (VI), normally yellow, which is reduced to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



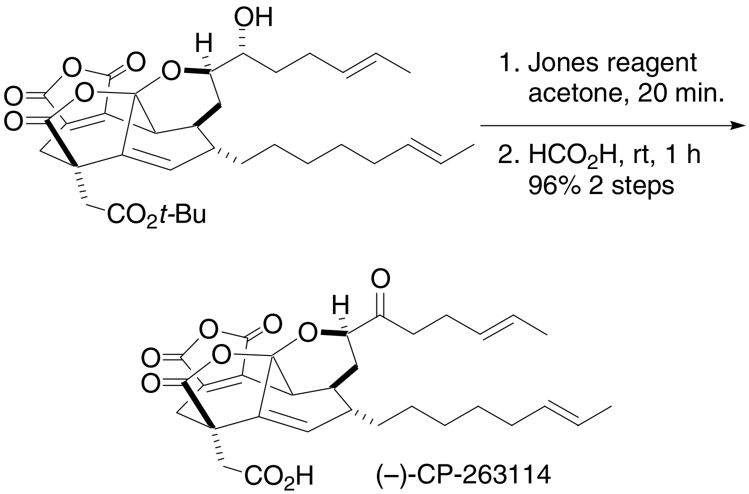
Jones oxidation



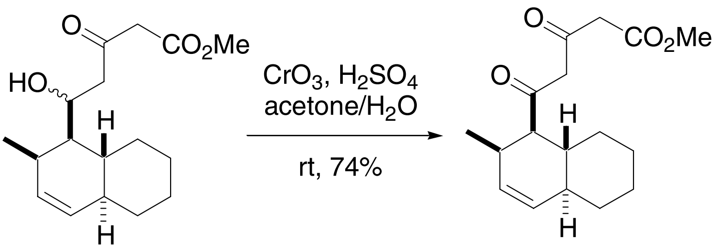
The intramolecular mechanism is also operative:



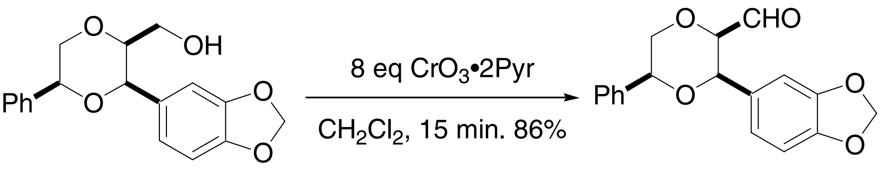
Example 1[14]



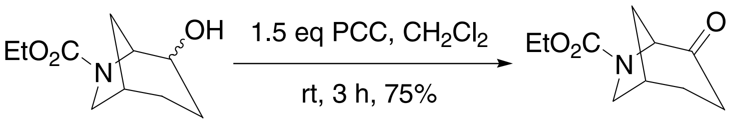
Example 2[15]



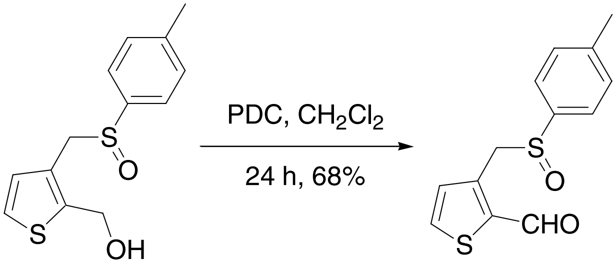
Collins/Sarett oxidation[5]



PCC oxidation[6]



PDC oxidation[7]



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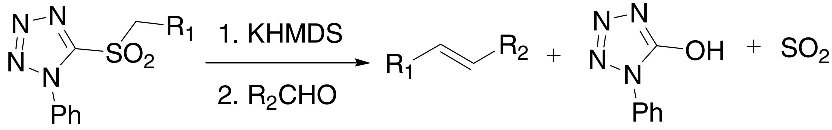
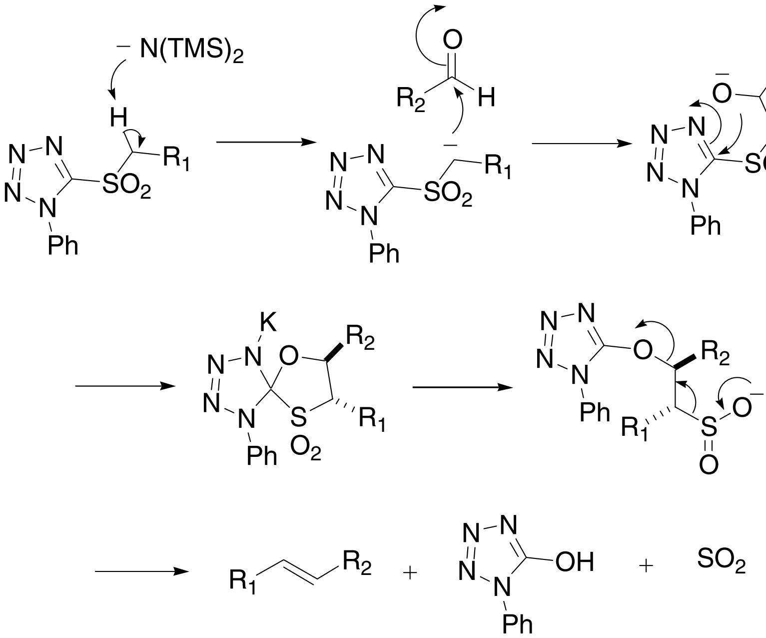
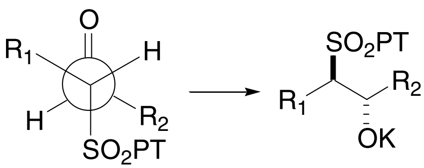
Julia–Kocienski olefination

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

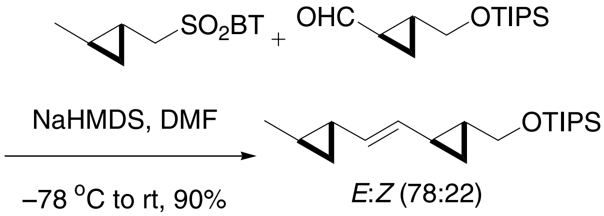




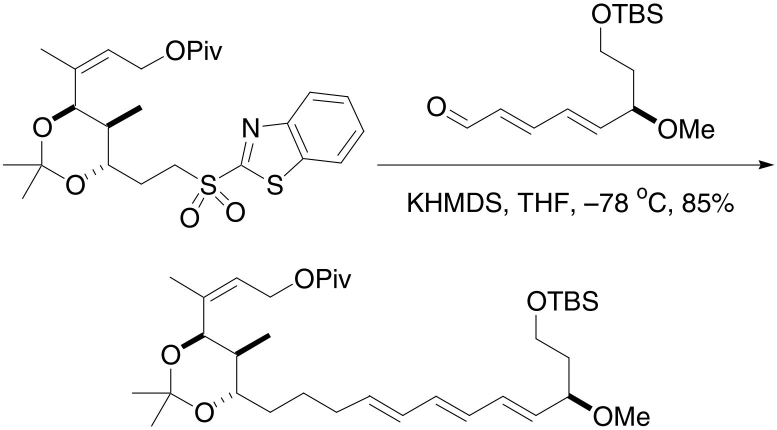
The use of larger counterion (such as K^+) and polar solvents (such as DME) favors an open transition state (PT = phenyltetrazolyl):



Example 1, (BT = benzotriazole)[4]



Example 2[6]



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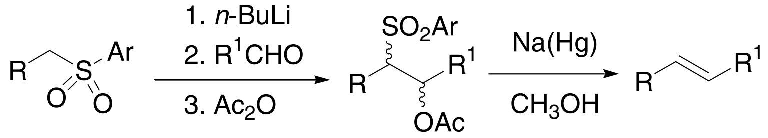
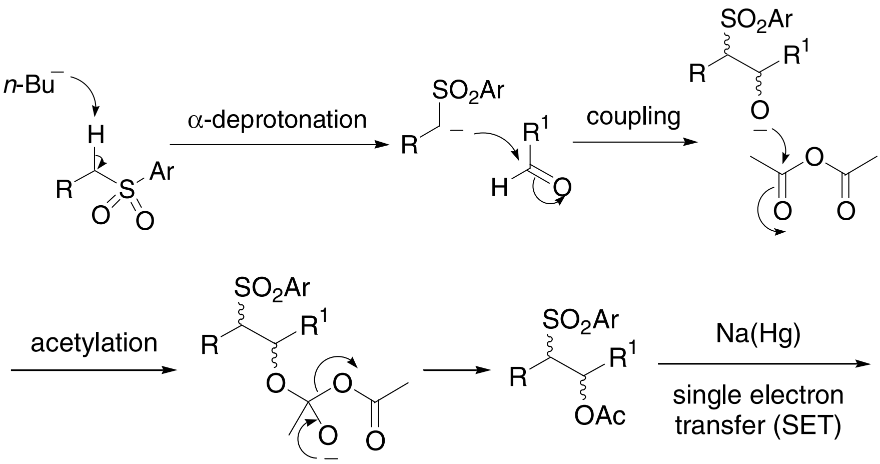
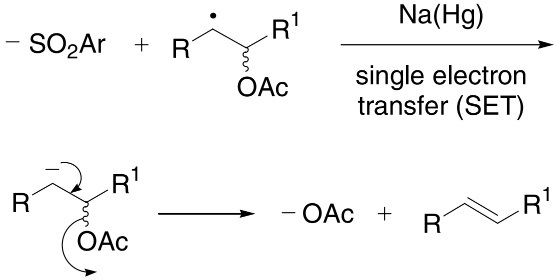
Julia–Lythgoe olefination

(*E*)-Olefins from sulfones and aldehydes.

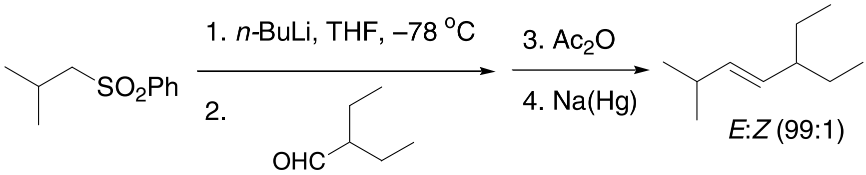




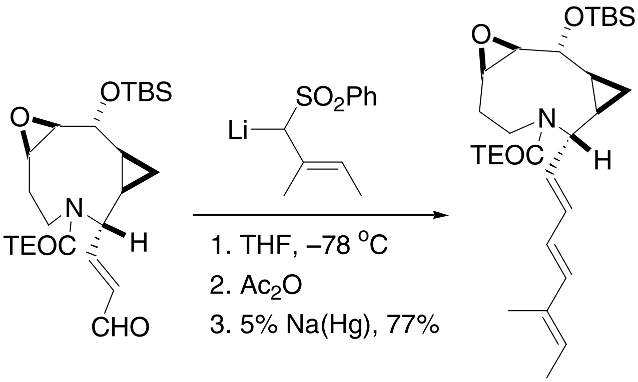
4 possible diastereomers



Example 1[3]



Example 2[4]



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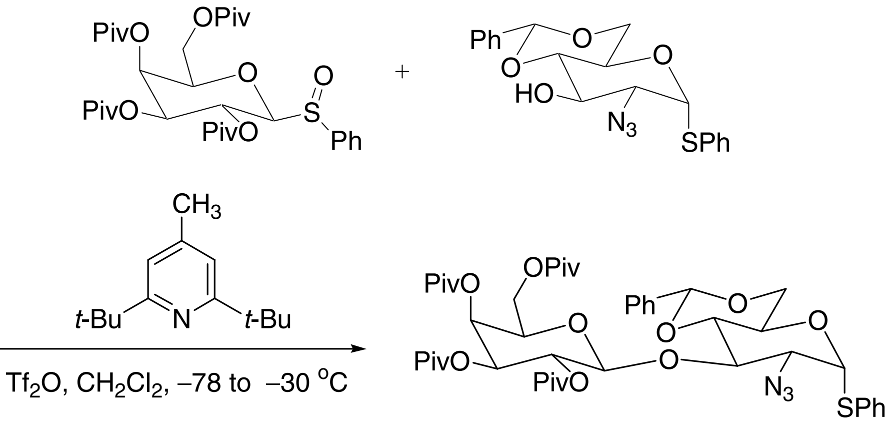
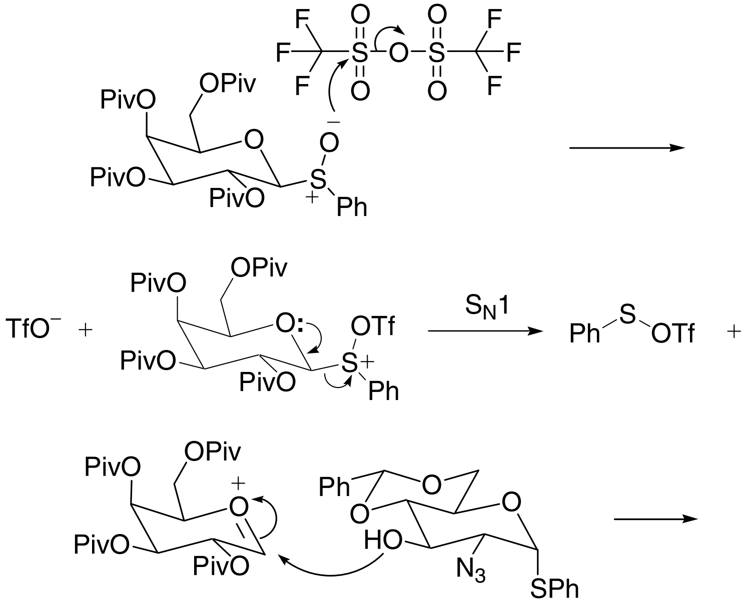
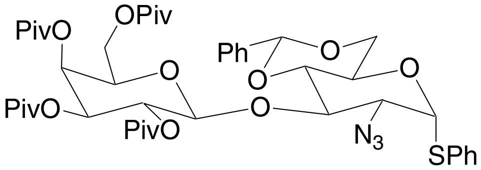
Kahne–Crich glycosidation

Diastereoselective glycosidation of a sulfoxide at the anomeric center as the glycosyl acceptor. The sulfoxide activation is achieved using Tf_2O.

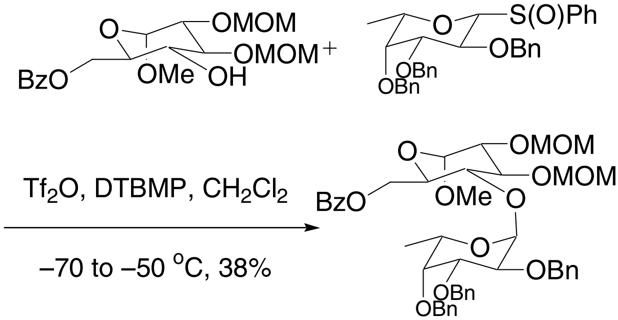




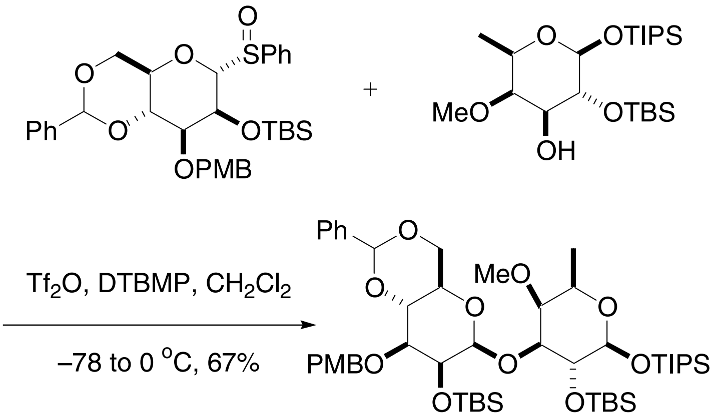
oxonium ion



Example 1[2]



Example 2[6]



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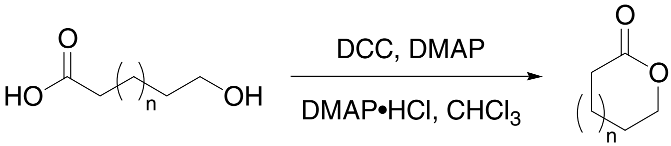
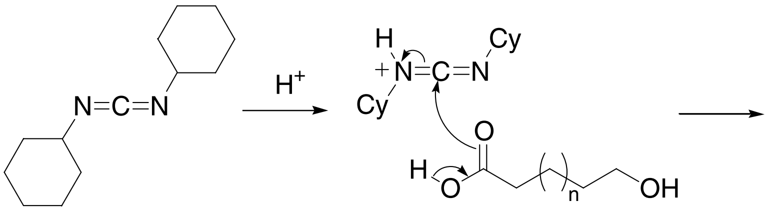
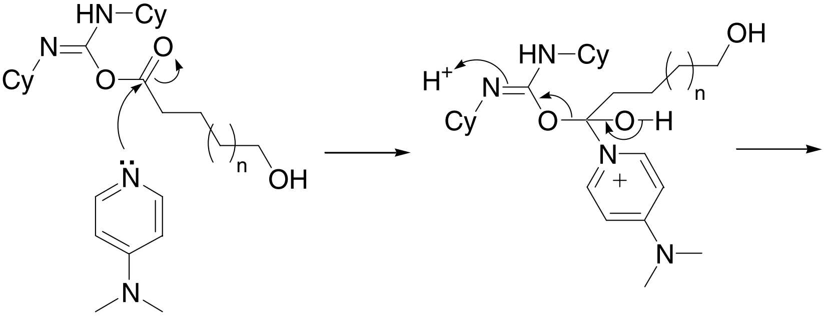
Keck macrolactonization

Macrolactonization of ω-hydroxyl acids using a combination of DCC, DMAP and DMAP•HCl.

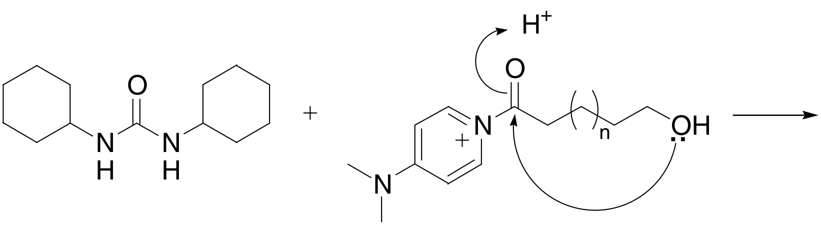




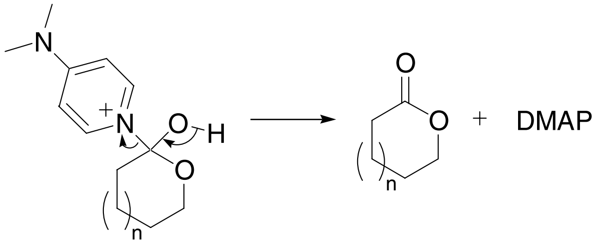
1,3-dicyclohexylcarbodiimide (DCC)



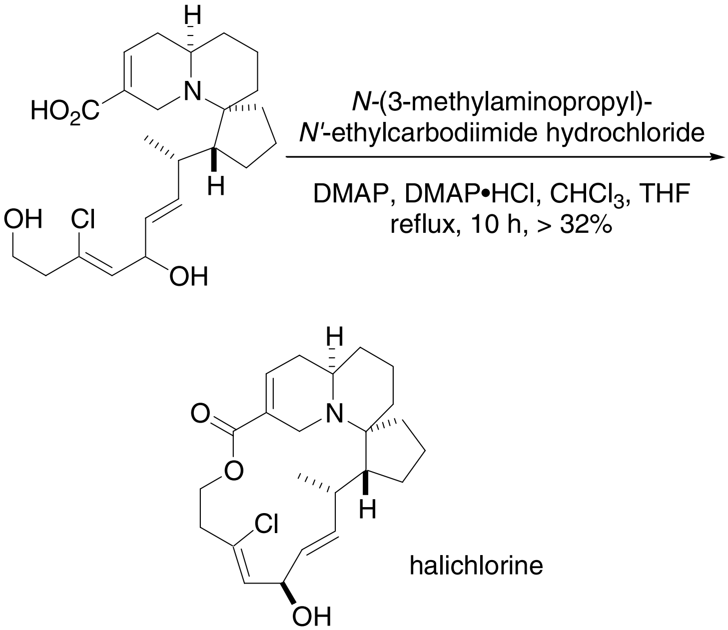
dimethylaminopyridine (DMAP)



1,3-dicyclohexylurea



Example 1[7]



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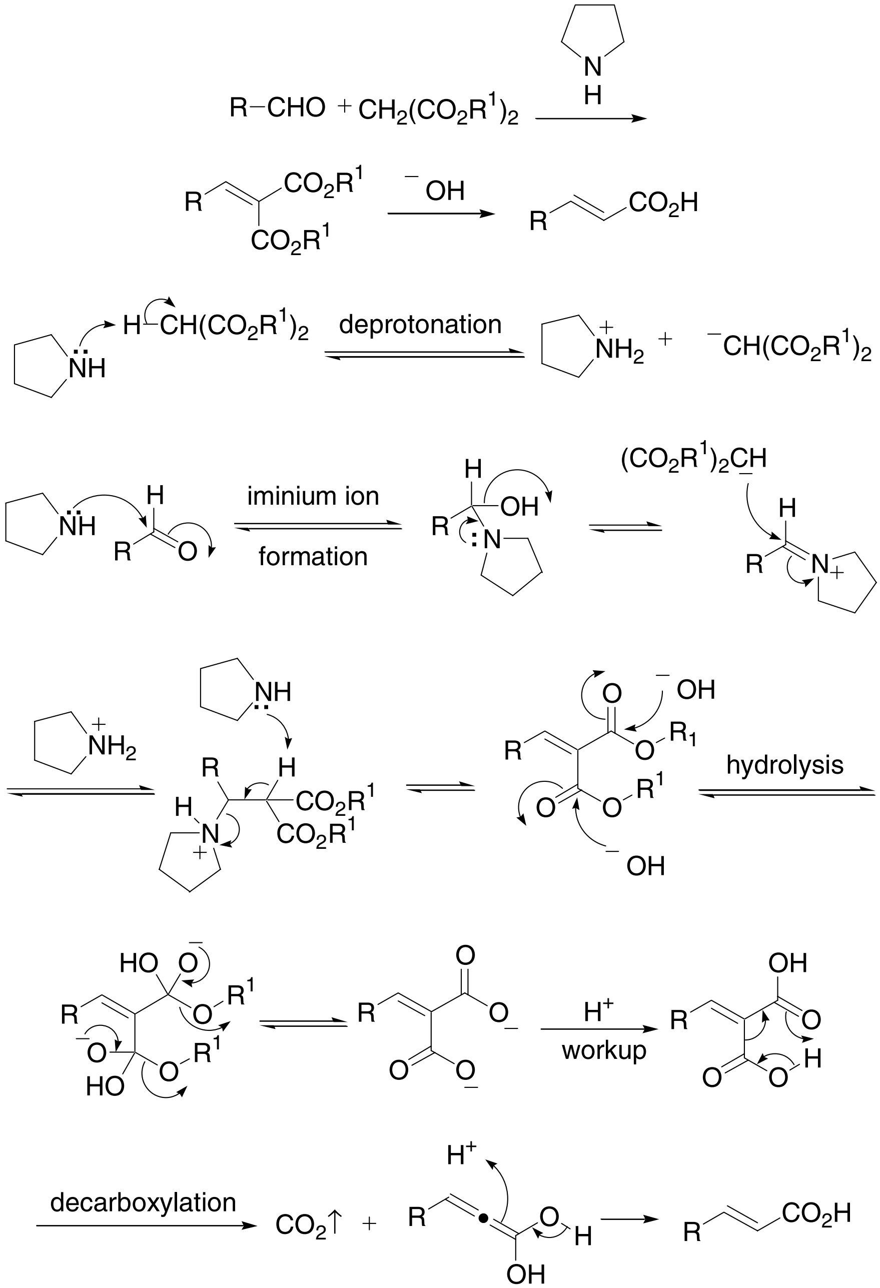
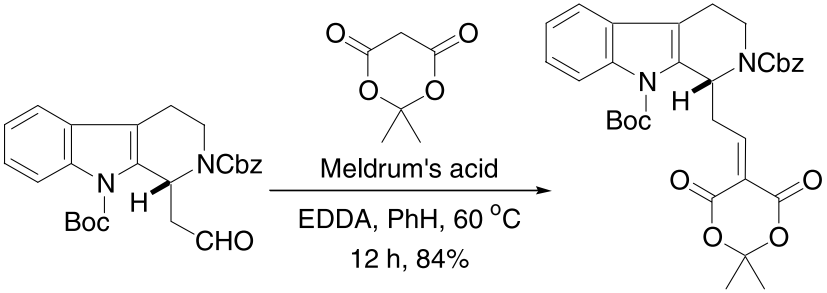
Knoevenagel condensation

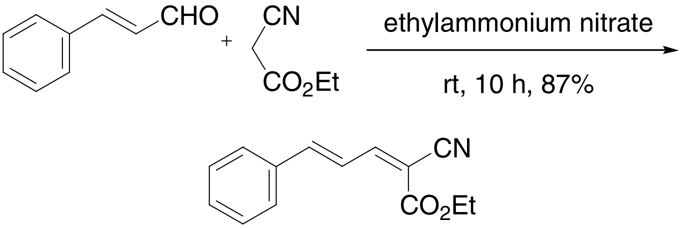
Condensation between carbonyl compounds and activated methylene compounds catalyzed by amines.



Example 1[7]



Example 2, using ionic liquid ethylammonium nitrate (EAN) as solvent[13]



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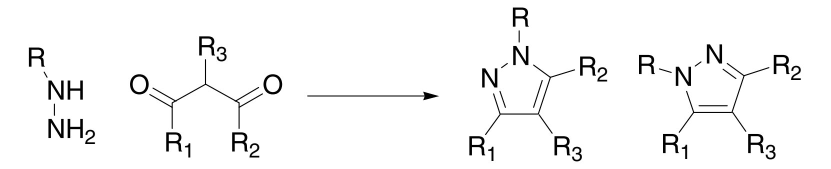
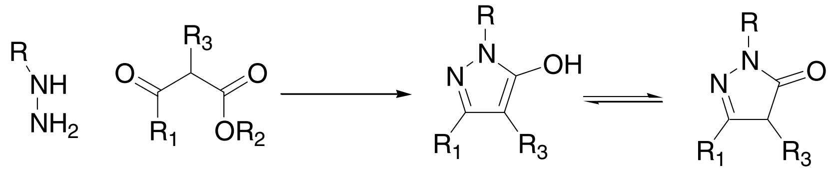
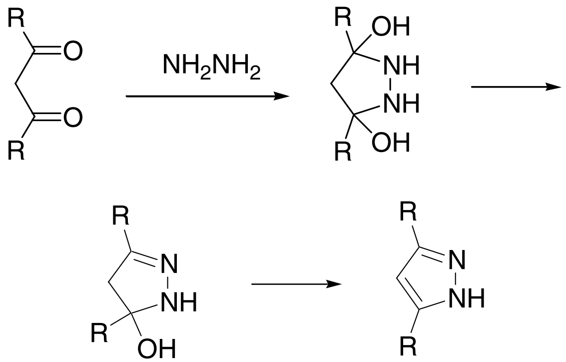
Knorr pyrazole synthesis

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 333).

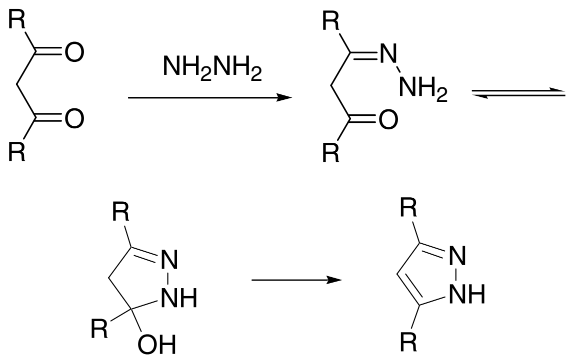


R = H, Alkyl, Aryl, Het-aryl, Acyl, *etc*.

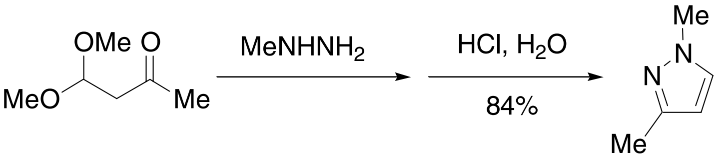




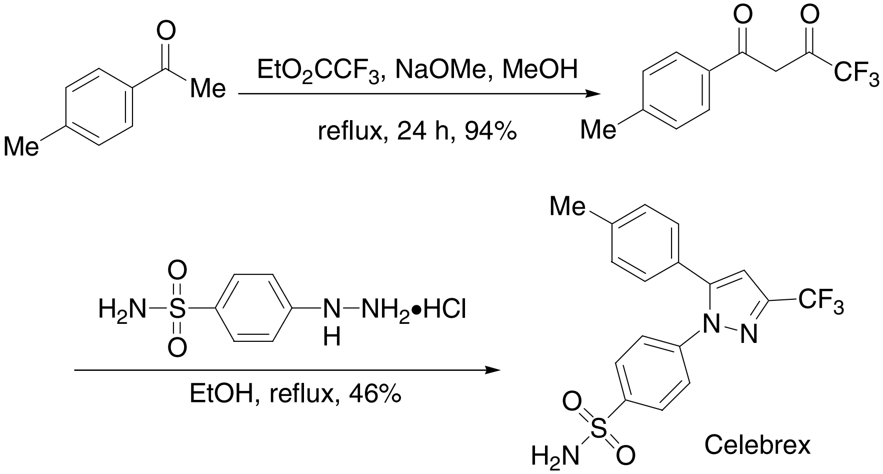
Alternatively,



Example 1[5]



Example 2[13]



Celebrex

References

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2 Knorr, L. *Ber Dtsch. Chem. Ges.* **1884**, *17*, 546, 2032.

3 Knorr, L. *Ber Dtsch. Chem. Ges.* **1885**, *18*, 311.

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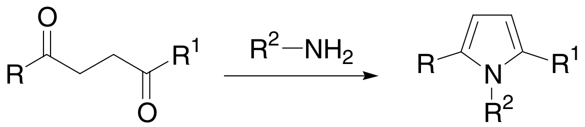
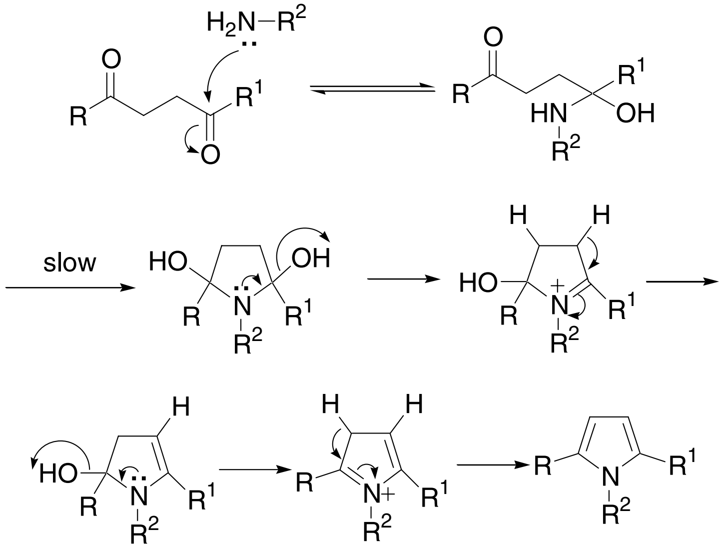
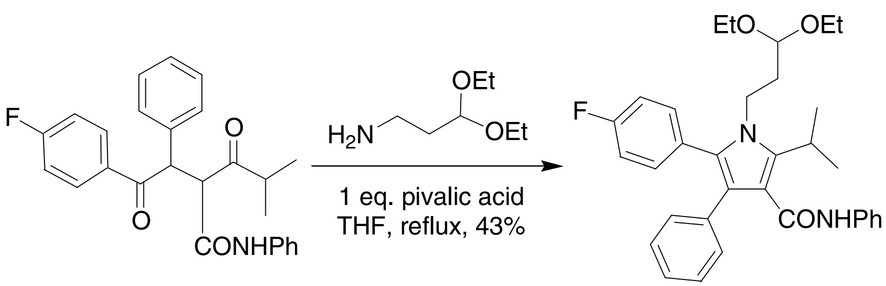
Paal–Knorr pyrrole synthesis

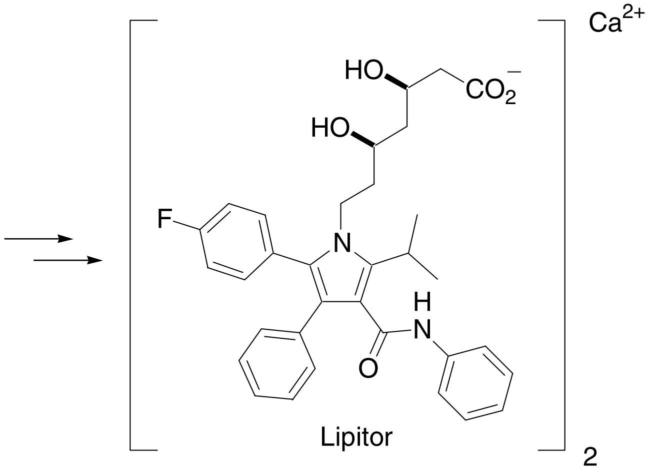
Reaction between 1,4-ketones and primary amines (or ammonia) to give pyrroles. A variation of the Knorr pyrazole synthesis (page 331).



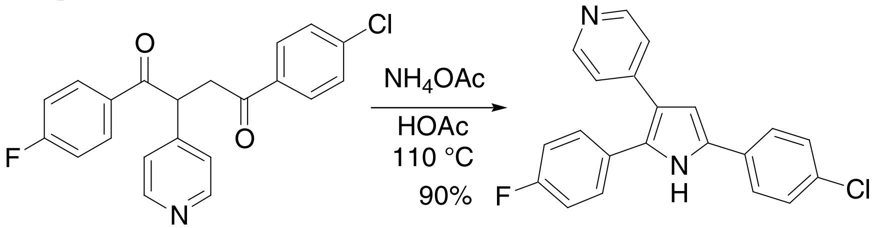


Example 1[5]





Example 2[7]



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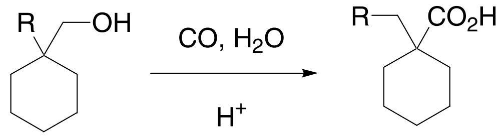
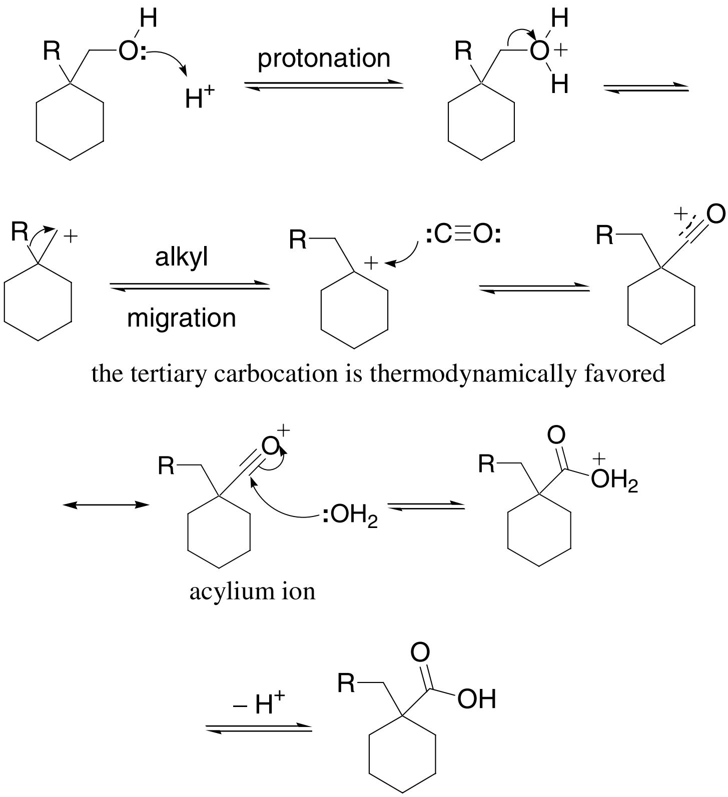
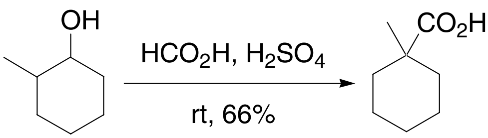
Koch–Haaf carbonylation

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

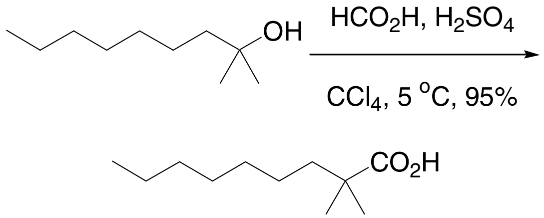




Example 1[5]



Example 2[7]



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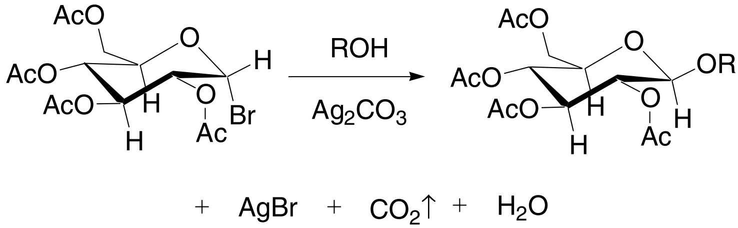
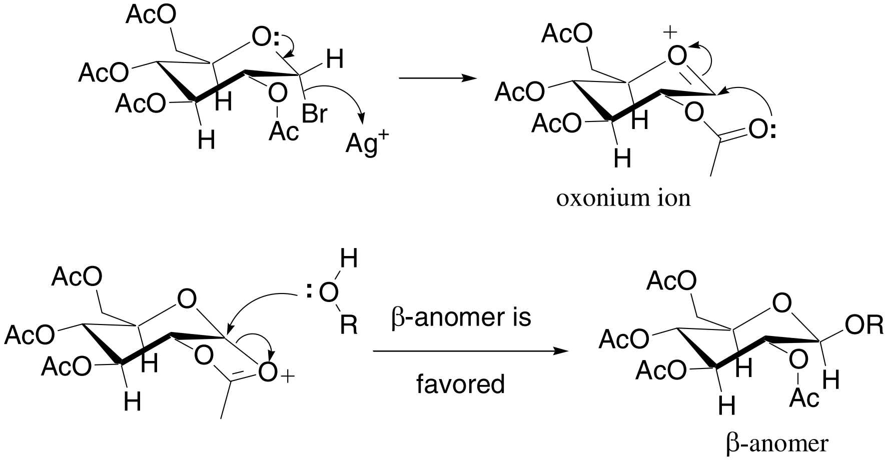
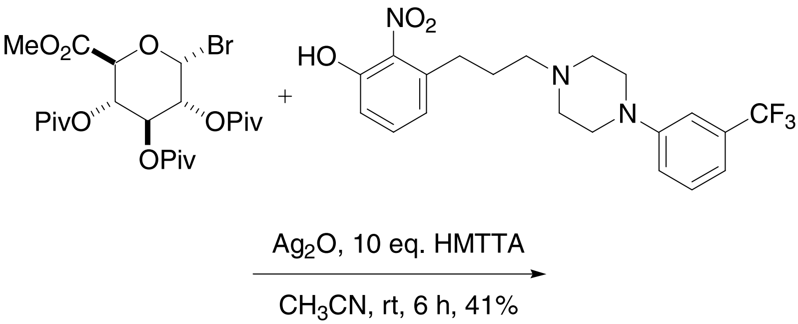
Koenig–Knorr glycosidation

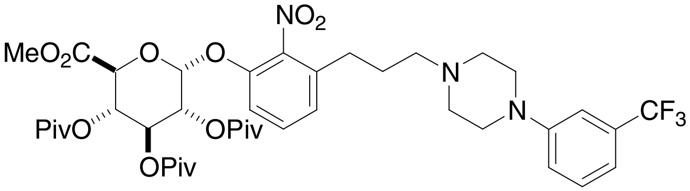
Formation of the β-glycoside from α-halocarbohydrate under the influence of silver salt.



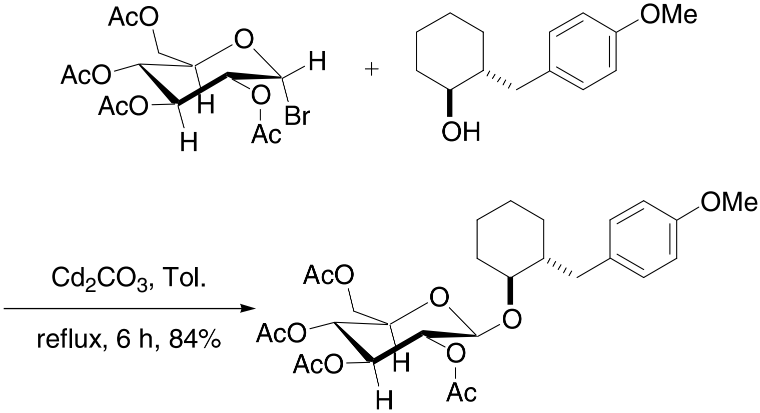


Example 1[13]





Example 2[15]



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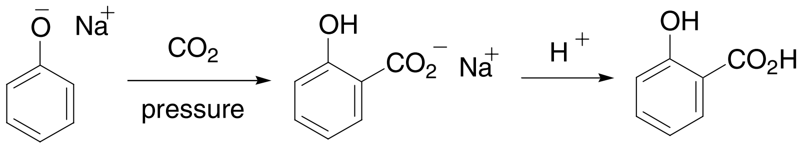
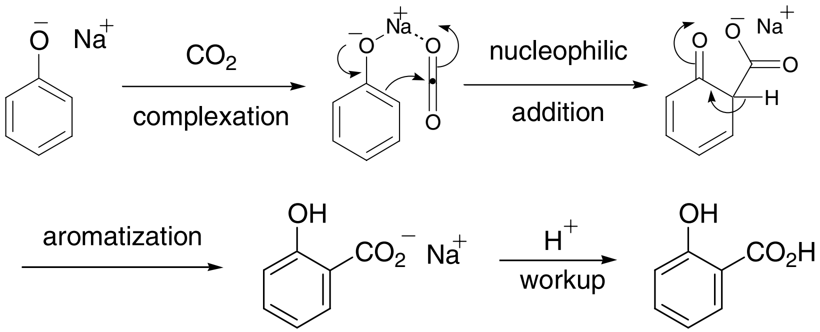
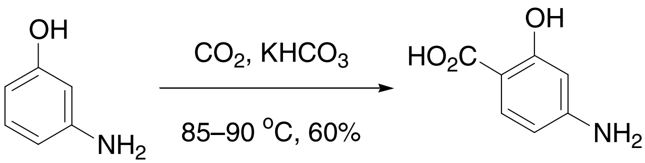
Kolbe–Schmitt reaction

Carboxylation of sodium phenoxides with carbon dioxide, to give salicylic acid, the precursor to the synthesis of aspirin.

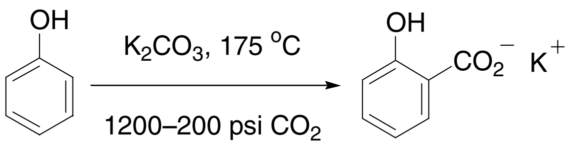




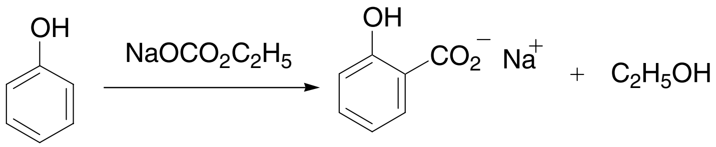
Example 1[3]



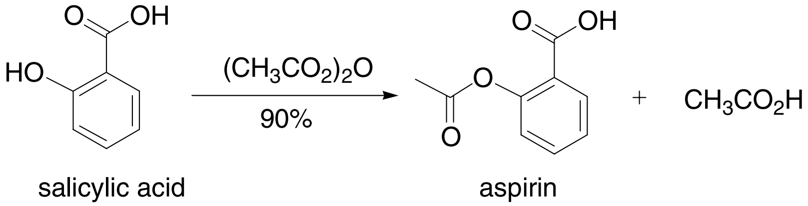
Example 2, the **Marasse modification** of the Kolbe–Schmitt reaction uses excess of anhydrous potassium carbonate in place of carbon dioxide[4]



Example 3, the Jones modification of the Kolbe–Schmitt reaction employs sodium ethyl carbonate[5]



Salicylic acid is the precursor to the synthesis of aspirin:



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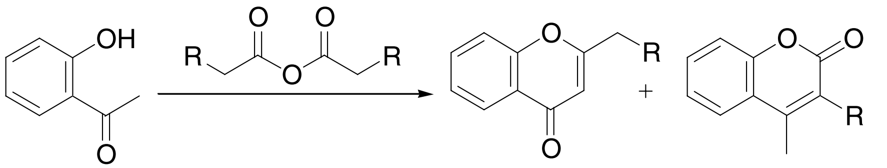
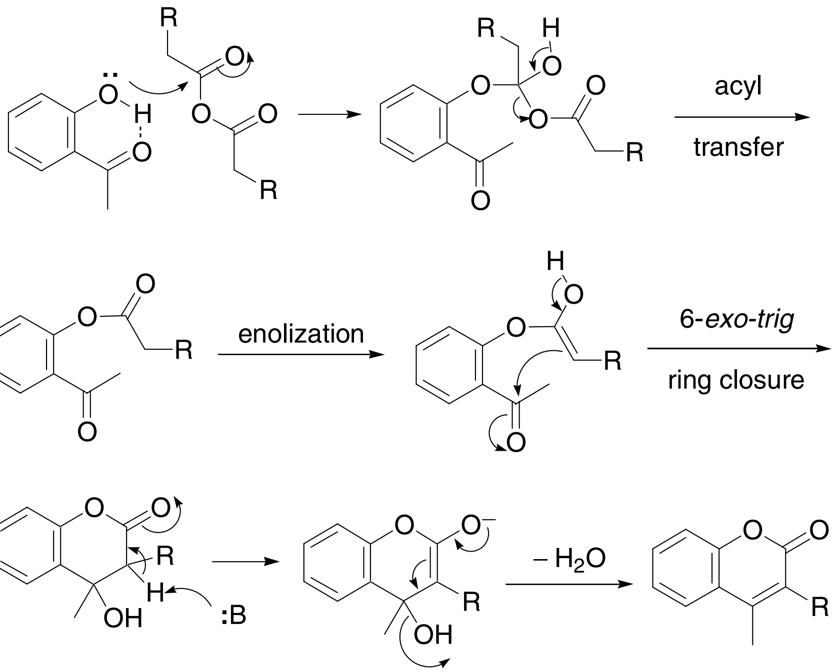
Kostanecki reaction

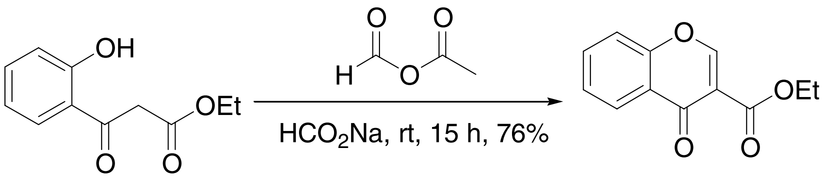
Also known as **Kostanecki–Robinson reaction**. Transformation **1**→**2** represents an **Allan–Robinson reaction** (see page 8), whereas **1**→**3** is a **Kostanecki (acylation) reaction**:



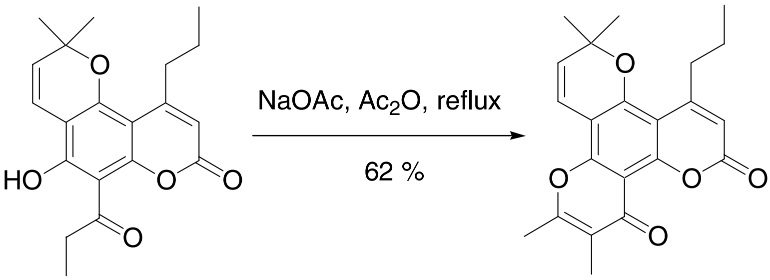
1 **2** **3**



Example 1[5]



Example 2[13]



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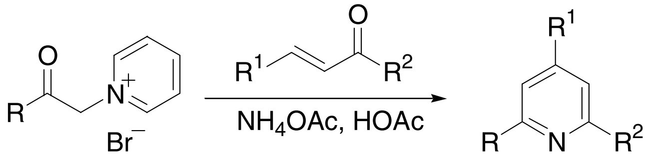
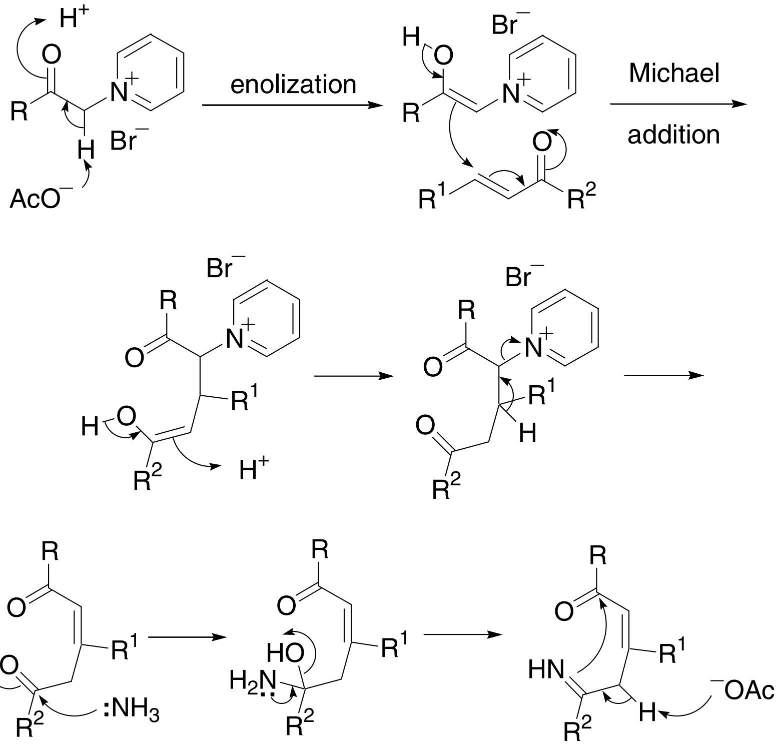
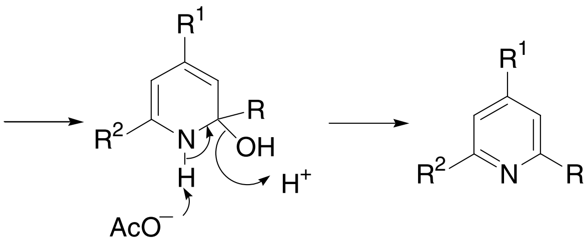
Kröhnke pyridine synthesis

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

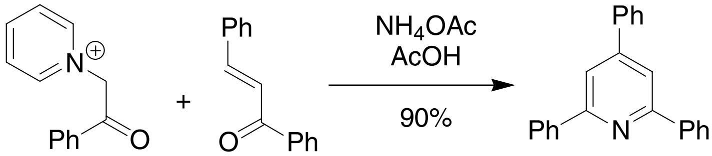




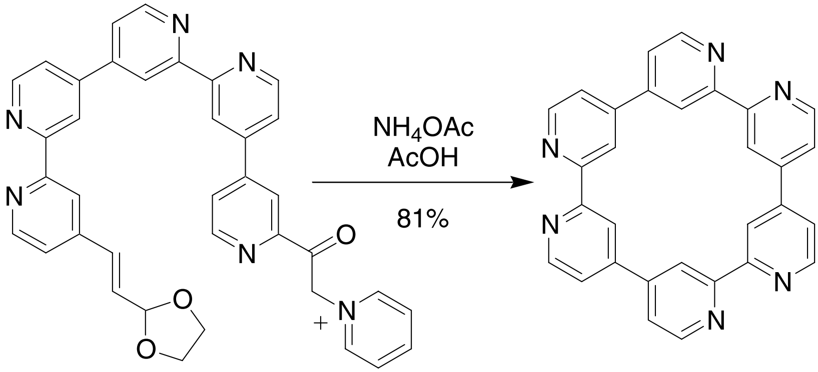
The ketone is more reactive than the enone



Example 1[2]



Example 2[10]



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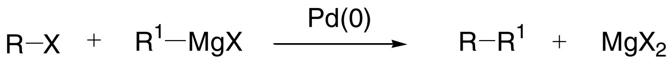
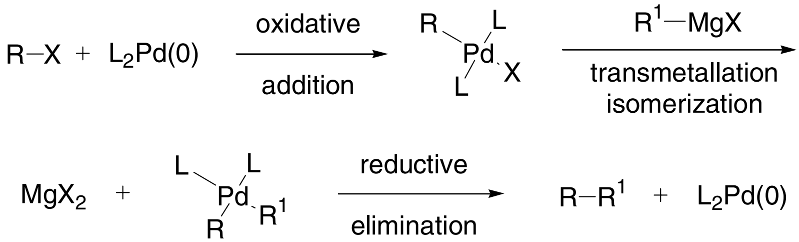
Kumada cross-coupling reaction

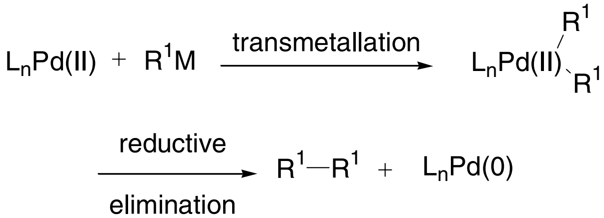
The Kumada cross-coupling reaction (also occasionally known as the Kharasch cross-coupling reaction) is a nickel- or palladium-catalyzed cross-coupling reaction of a Grignard reagent with an organic halide, triflate, *etc*.

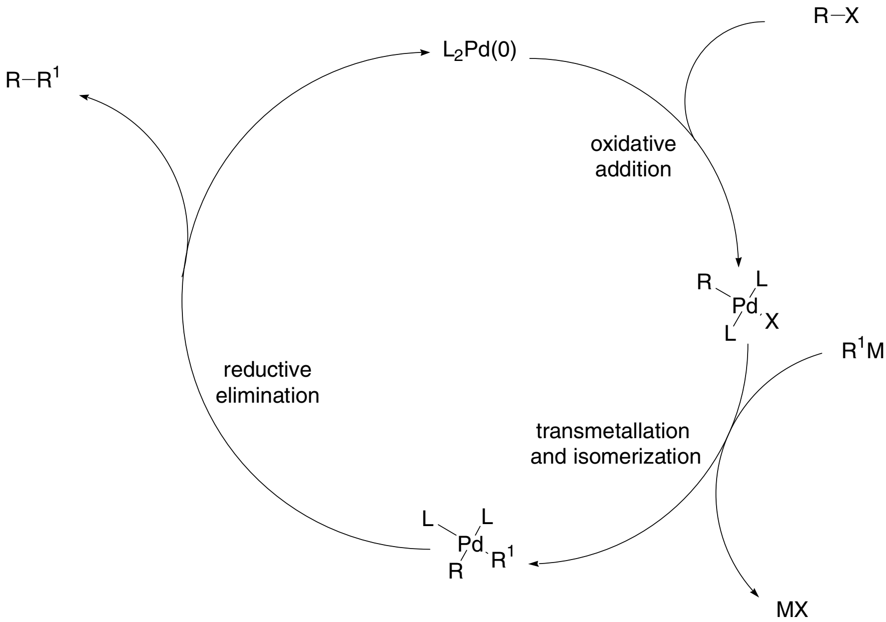




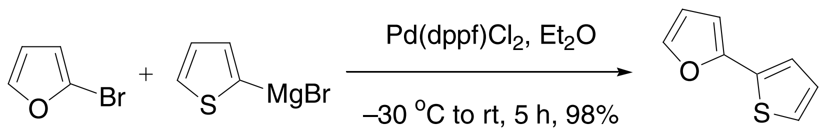
The Kumada cross-coupling reaction, as well as the Negishi, Stille, Hiyama, and Suzuki cross-coupling reactions, belong to the same category of Pd-catalyzed cross-coupling reactions of organic halides, triflates and other electrophiles with organometallic reagents. These reactions follow a general mechanistic cycle as shown on the next page. 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:

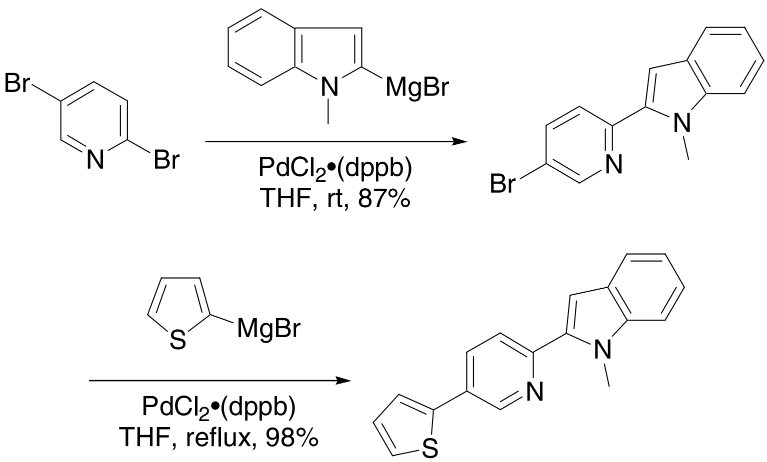




Example 1[2]



Example 2[4]



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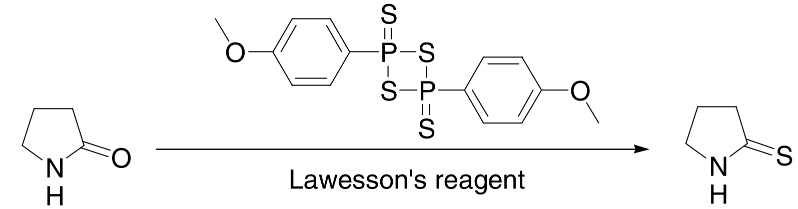
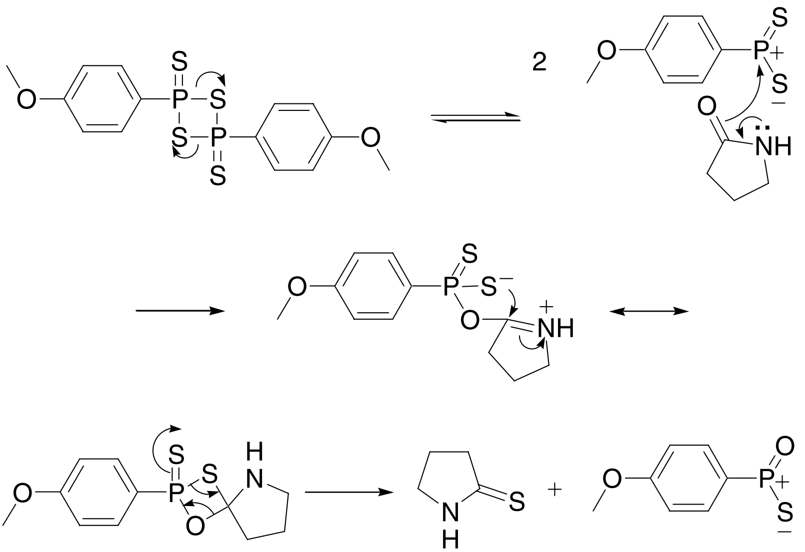
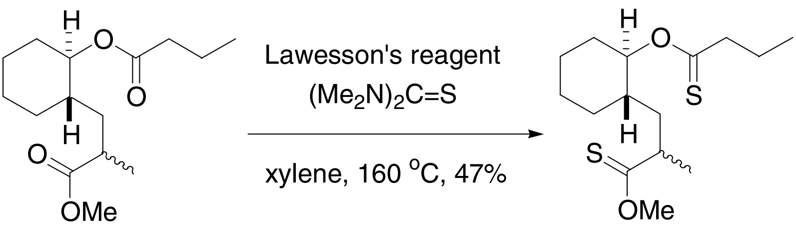
Lawesson's reagent

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

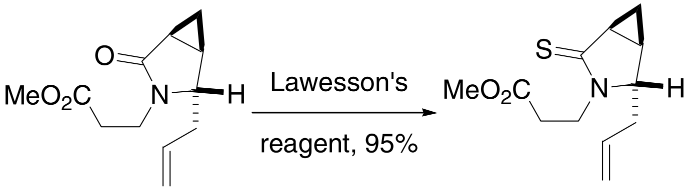




Example 1[4]



Example 2[4]



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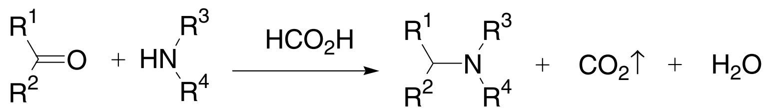
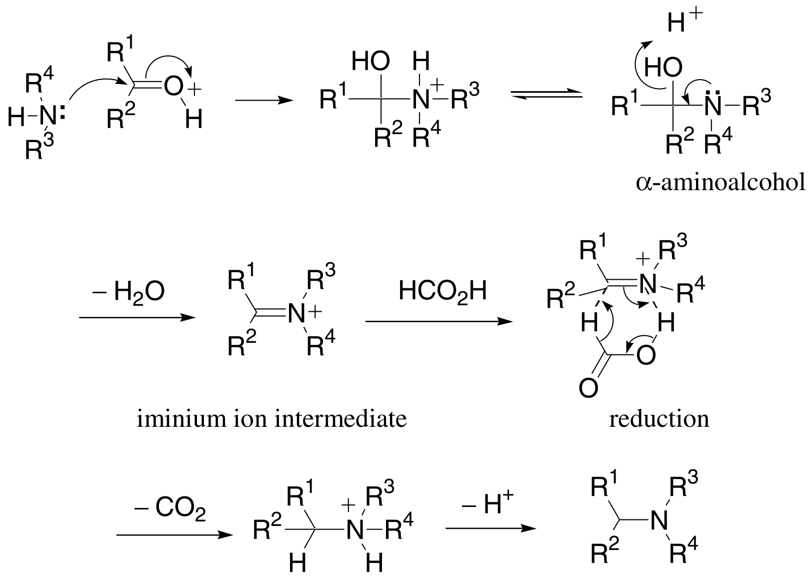
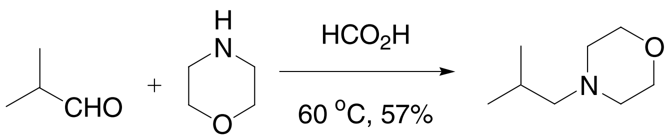
Leuckart–Wallach reaction

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 Eschweiler–Clarke reductive alkylation of amines.

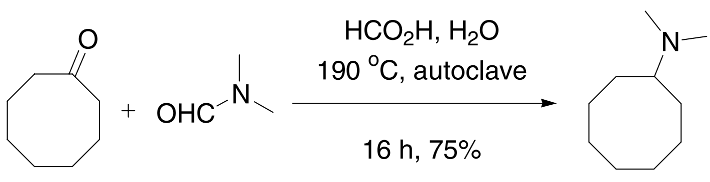




Example 1[5]



Example 2[7]



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2. Wallach, O. *Justus Liebigs Ann. Chem.* **1892**, *272*, 99. Otto Wallach (1847–1931), born in Königsberg, Prussia, studied under Wöhler and Hofmann. He was the director of the Chemical Institute at Göttingen from 1889 to 1915. His book "Terpene und Kampfer" served as the foundation for future work in terpene chemistry. Wallach was awarded the Nobel Prize in Chemistry in 1910 for his work on alicyclic compounds.
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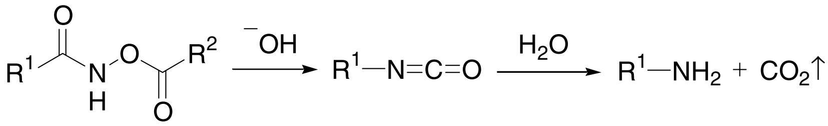
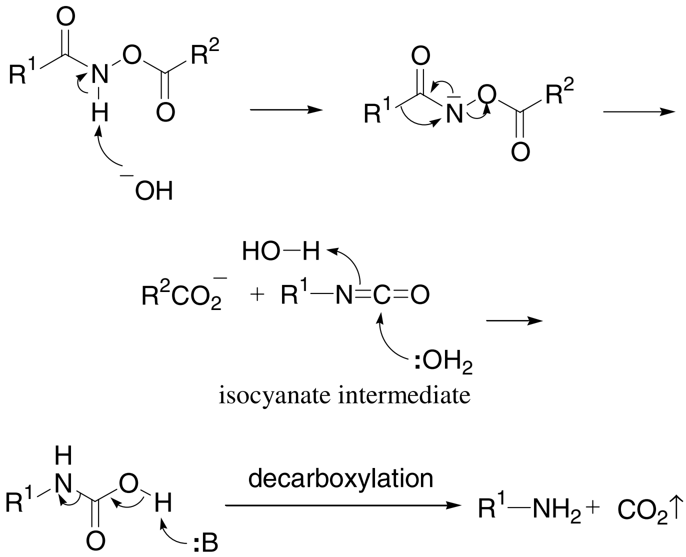
Lossen rearrangement

Treatment of *O*-acylated hydroxamic acids with base provides isocyanates.





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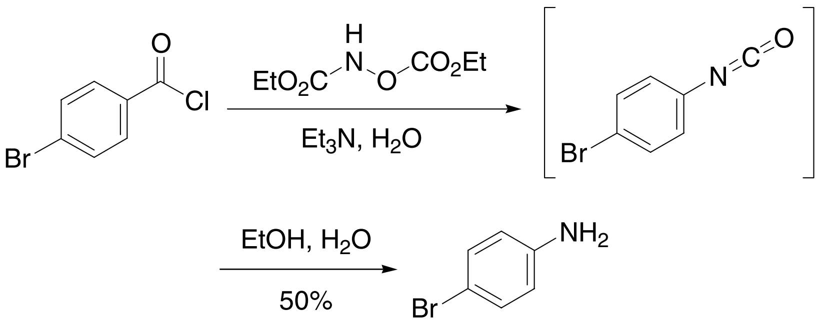
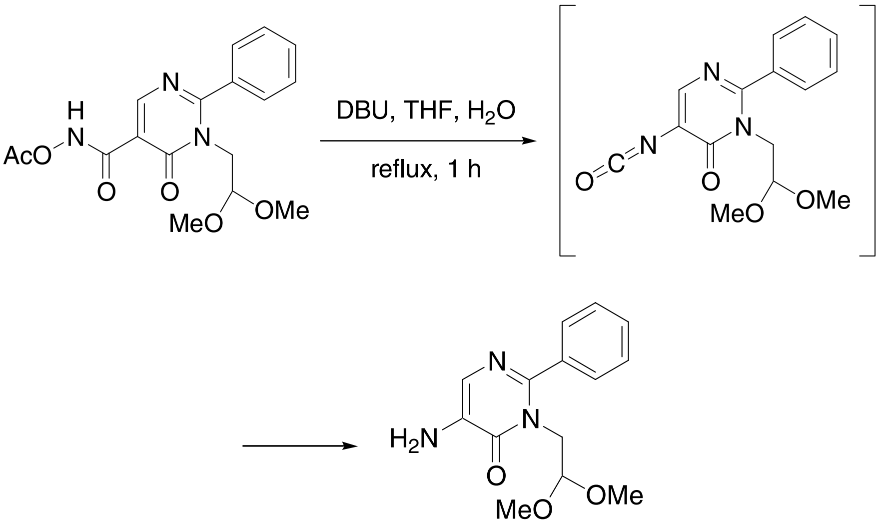


Example 2[8]



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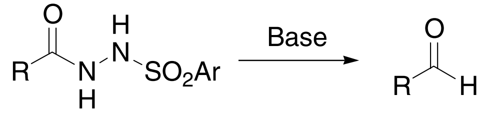
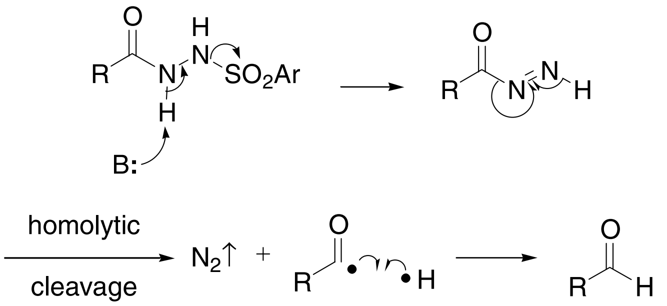
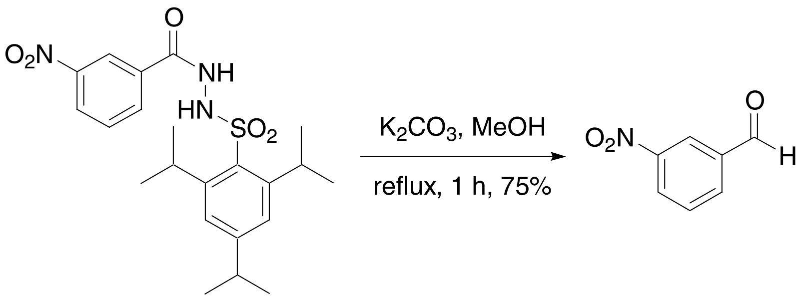
McFadyen–Stevens reduction

Treatment of acylbenzenesulfonylhydrazines with base delivers the corresponding aldehydes.

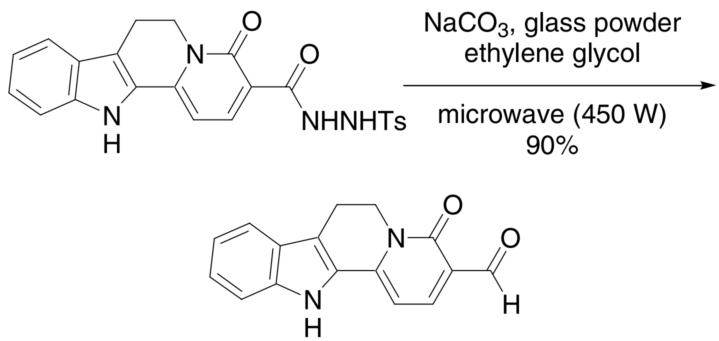




Example 1[9]



Example 2[11]



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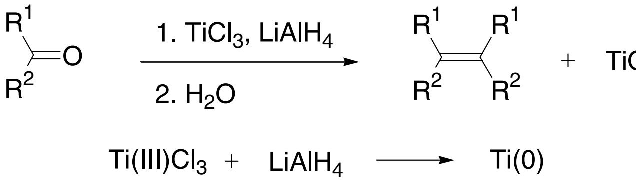
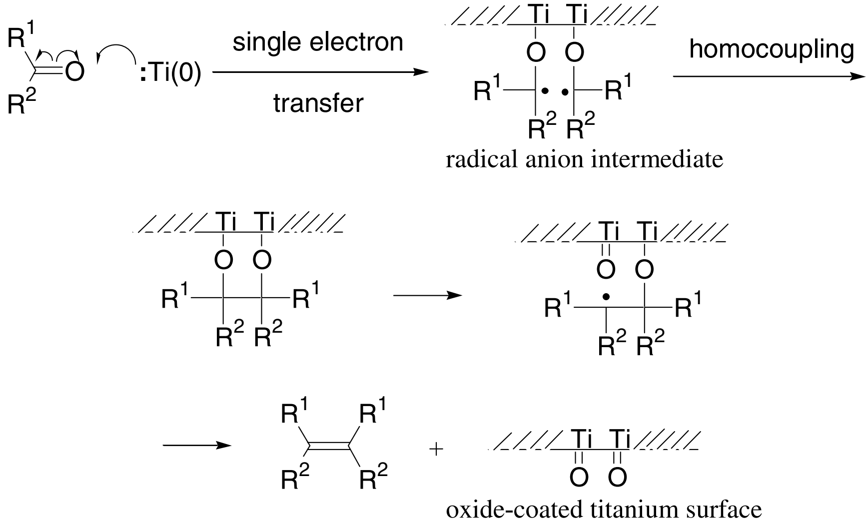
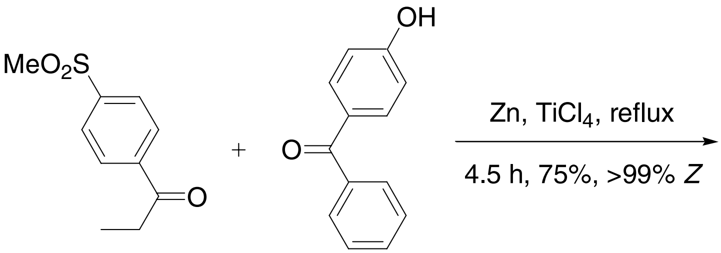
McMurry coupling

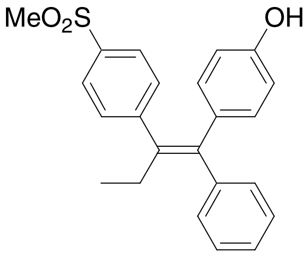
Olefination of carbonyls with low-valent titanium such as Ti(0) derived from $TiCl_3/LiAlH_4$. Single-electron process.



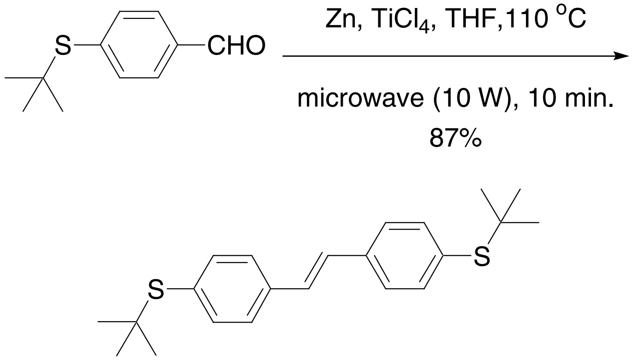


Example 1[12]





Example 2[13]



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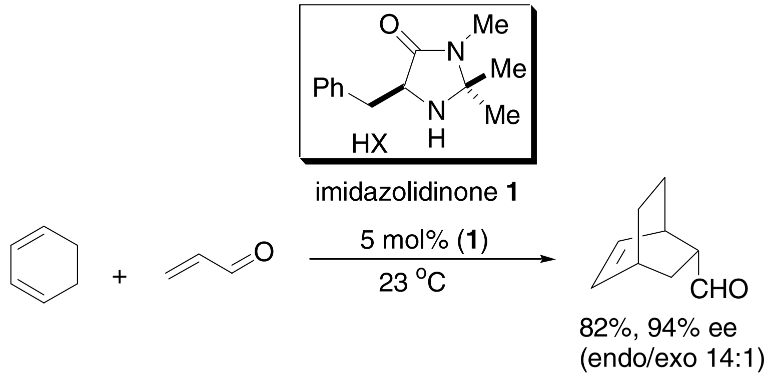
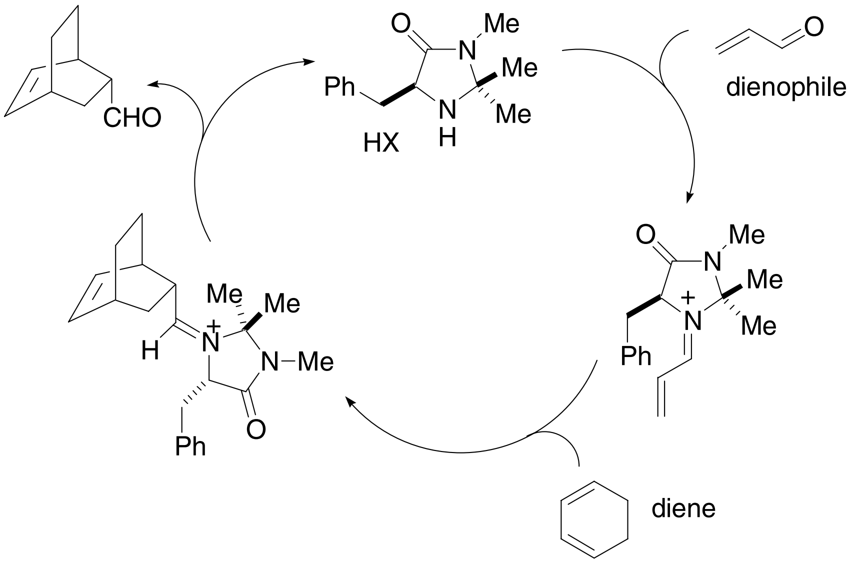
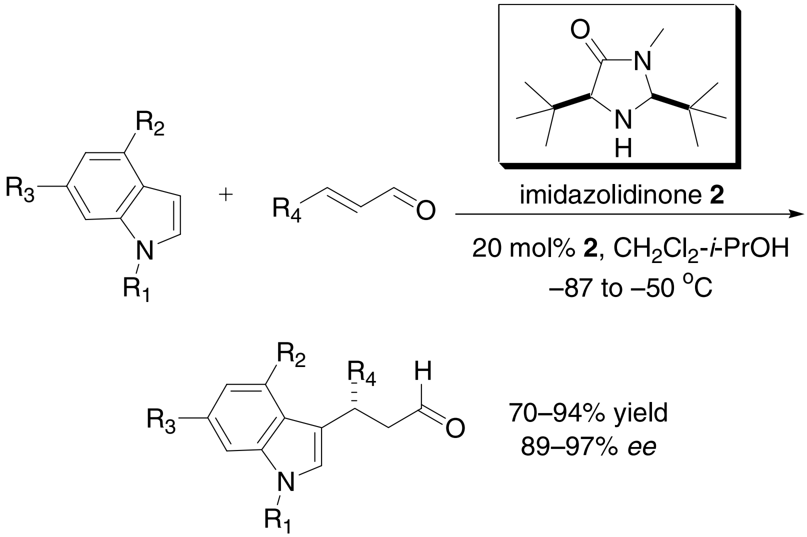
MacMillan catalyst

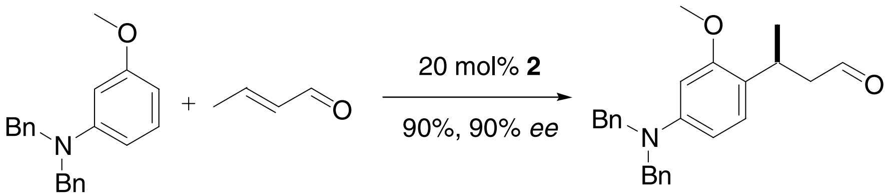
Highly enantioselective and general asymmetric organocatalytic Diels-Alder reaction using α-amino acid-derived imidazolidinones (of type **1**) as catalysts. The first generation of MacMillan catalyst (**1**) has been employed in a variety of organocatalytic enantioselective reactions. Typical examples are: Diels-Alder reaction;[1] nitrone cycloaddition,[2] pyrrole Friedel–Crafts reaction,[3] indole addition,[4] vinylogous Michael addition;[5] α-chlorination;[6] hydride addition;[7] cyclopropanation;[8] α-fluorination.[9] The second generation of MacMillan catalyst (**2**) was used to catalyze 1,4-addition of *C*-nucleophiles employing various indoles.



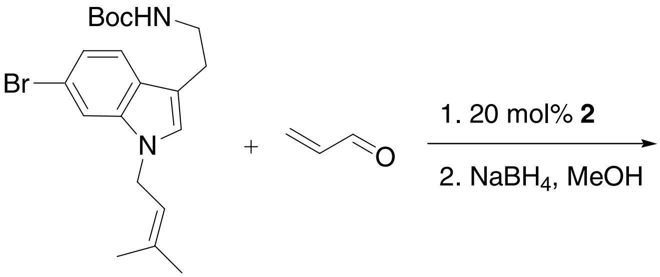


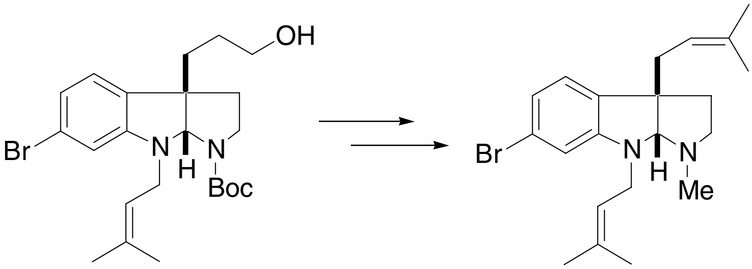


Example 1[11]



Example 2[10]





78% yield
90% ee

(–)-flustramine B

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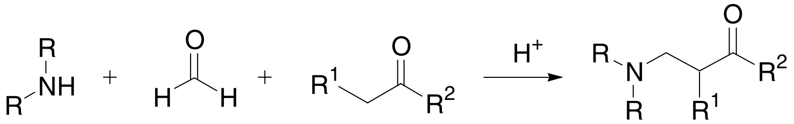
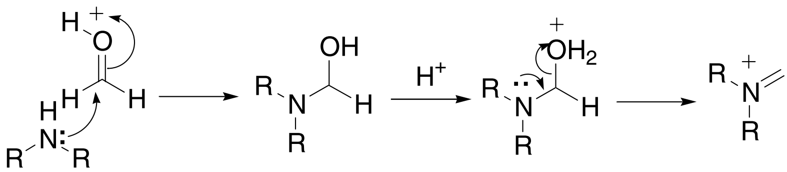
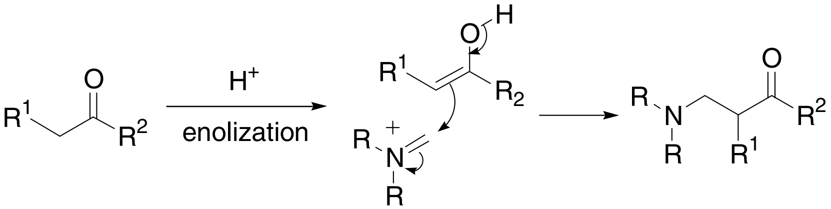
Mannich reaction

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

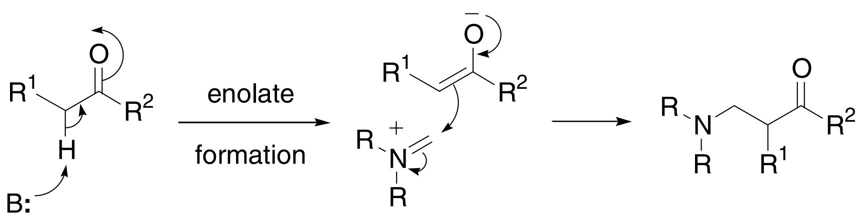




When R = H, the $^{+}Me_2N{=}CH_2$ salt is known as **Eschenmoser's salt**

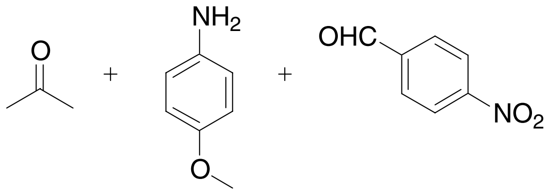


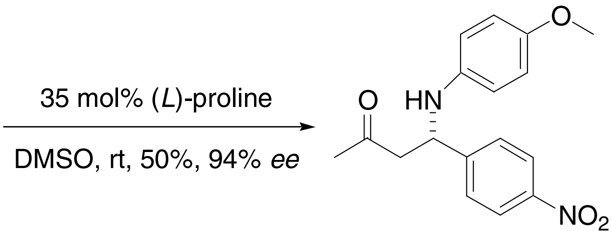
The Mannich reaction can also operate under basic conditions:



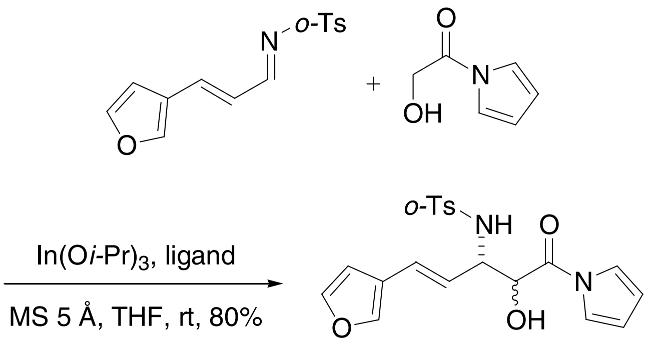
Mannich Base

Example 1, asymmetric Mannich reaction[4]





Example 2, asymmetric aza-Mannich reaction[13]



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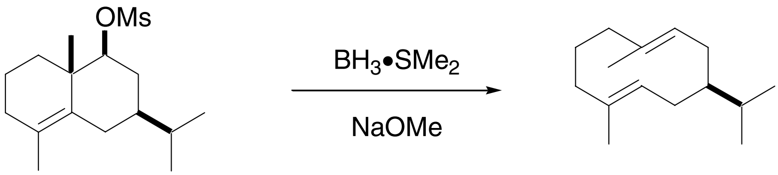
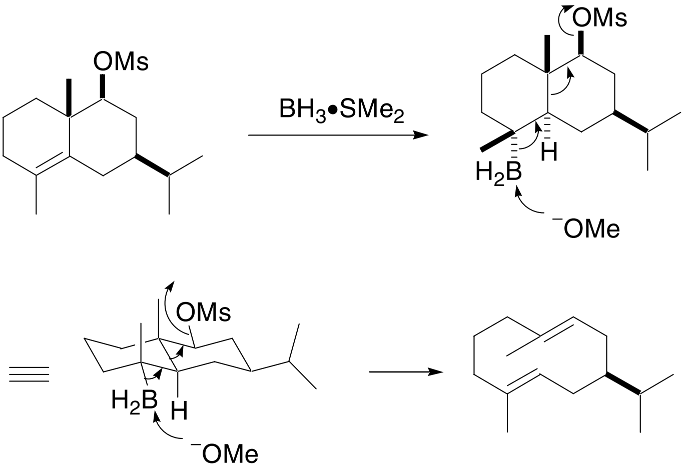
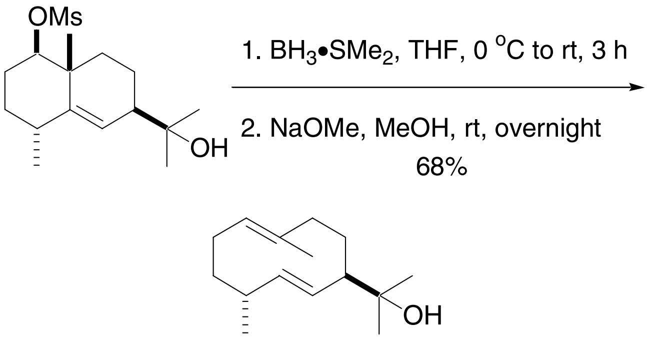
Marshall boronate fragmentation

Marshall boronate fragmentation is a variation of the Grob fragmentation (page 273) category.

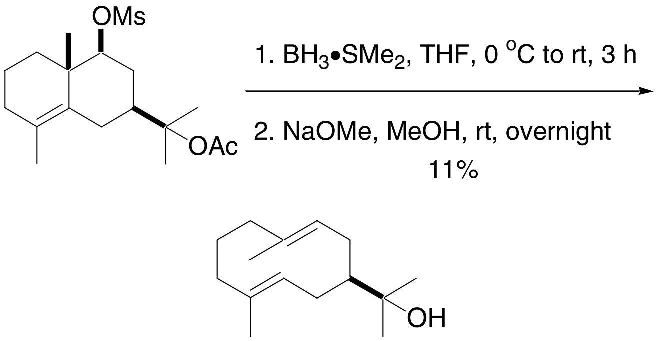




Example 1[5]



Example 2[6]



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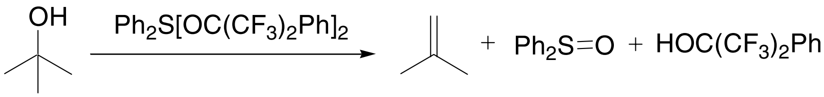
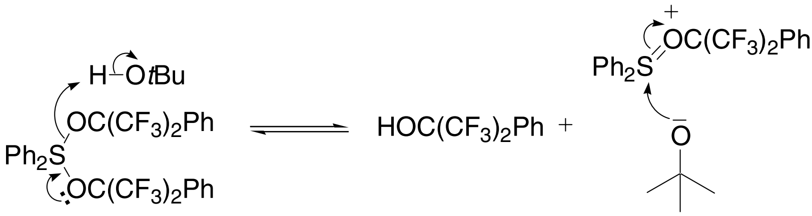
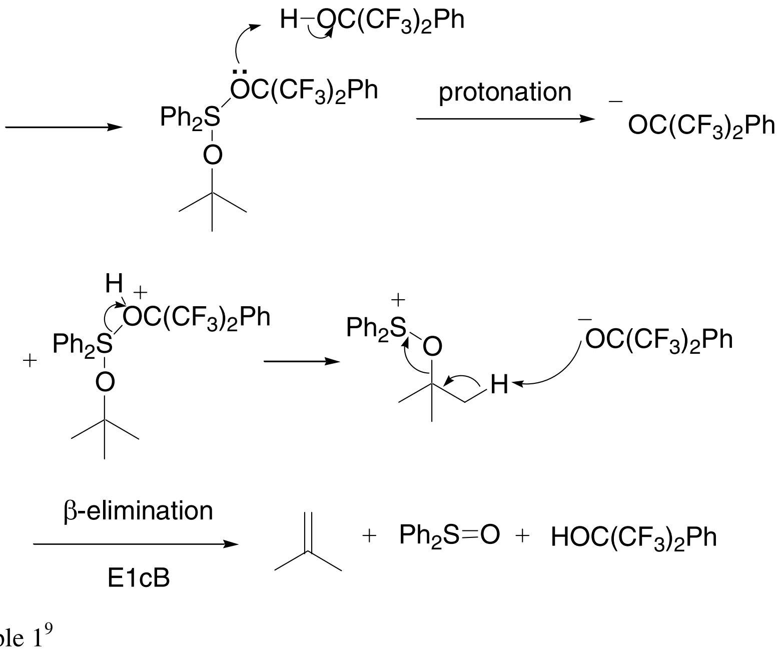
Martin's sulfurane dehydrating reagent

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

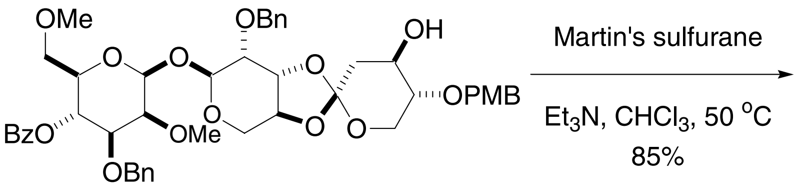


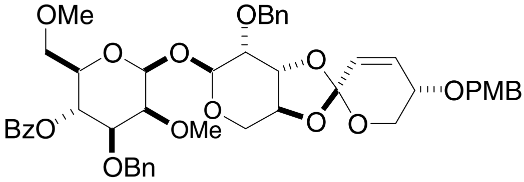


The alcohol is acidic

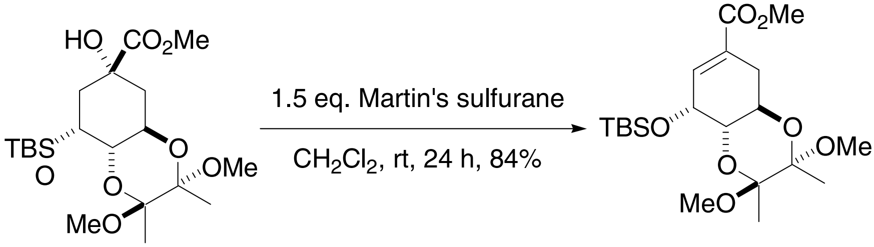


Example 1[9]





Example 2[10]



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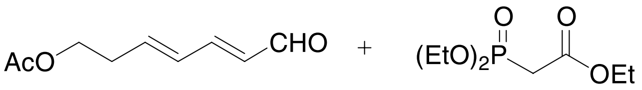
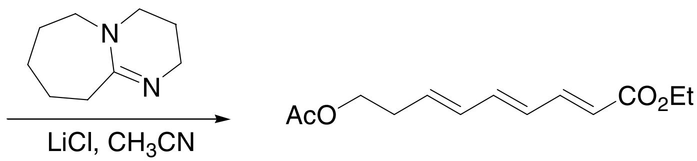
Masamune–Roush conditions

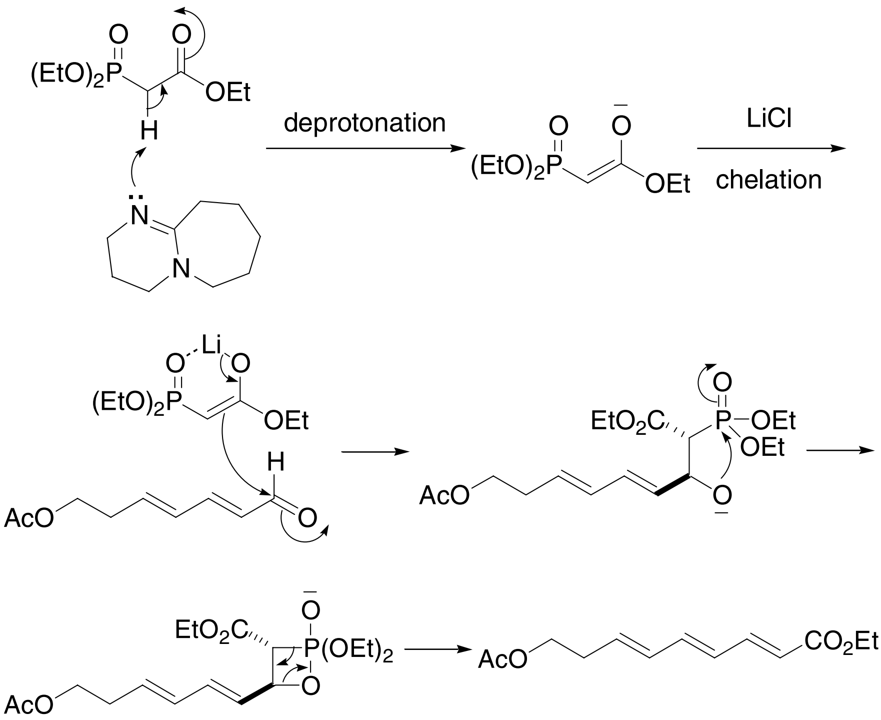
Applicable to base-sensitive aldehydes and phosphonates for the Horner–Wadsworth–Emmons reaction



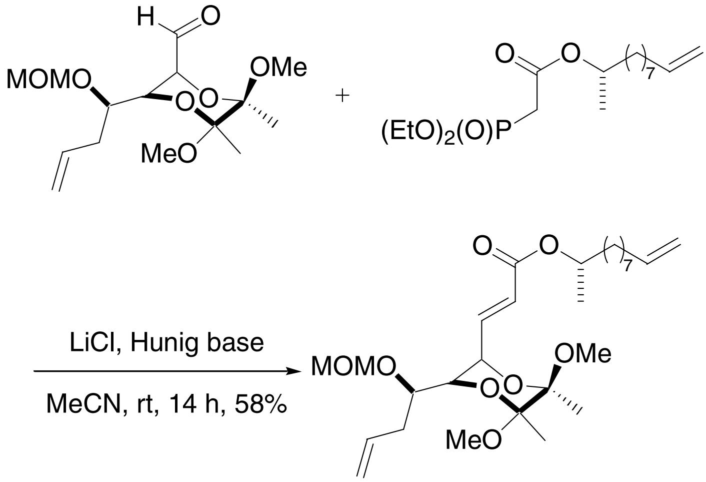
α-keto or α-alkoxycarbonyl phosphonate required



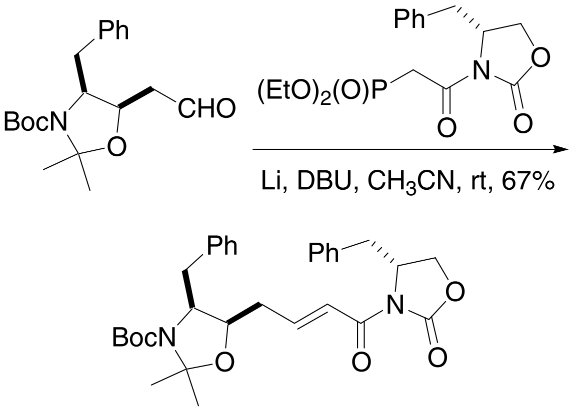
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)



Example 1[6]



Example 2[7]



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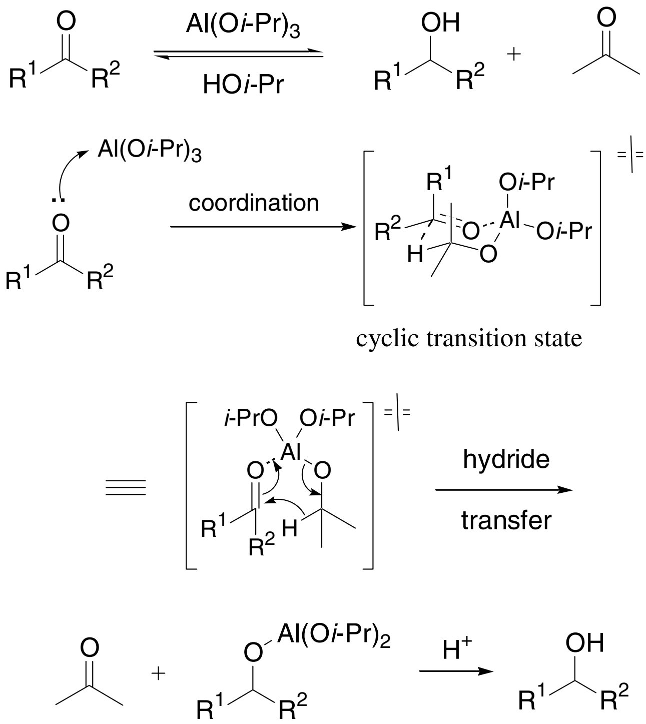
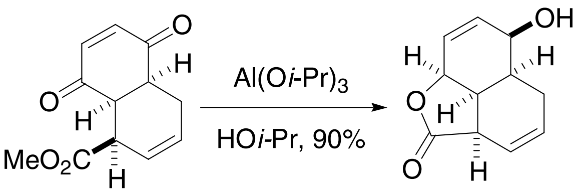
Meerwein–Ponndorf–Verley reduction

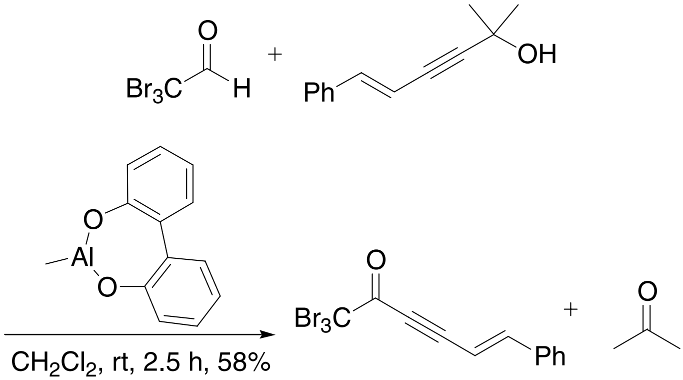
Reduction of ketones to the corresponding alcohols using Al(O*i*-Pr)$_3$ in isopropanol.



Example 1[2]



Example 2[12]



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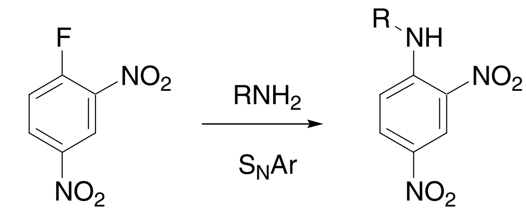
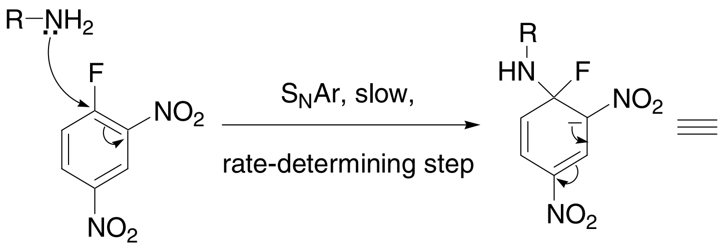
Meisenheimer complex

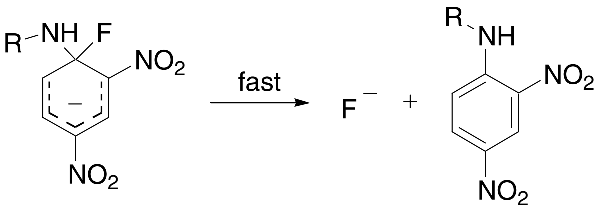
Also known as Meisenheimer–Jackson salt, the stable intermediate for certain S_NAr reactions.



Sanger's reagent

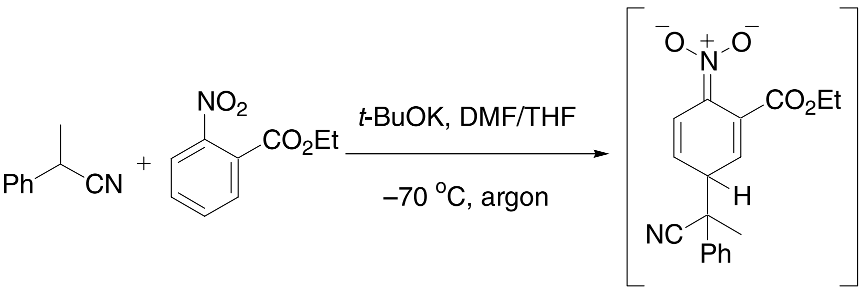


ipso attack *ipso* substitution

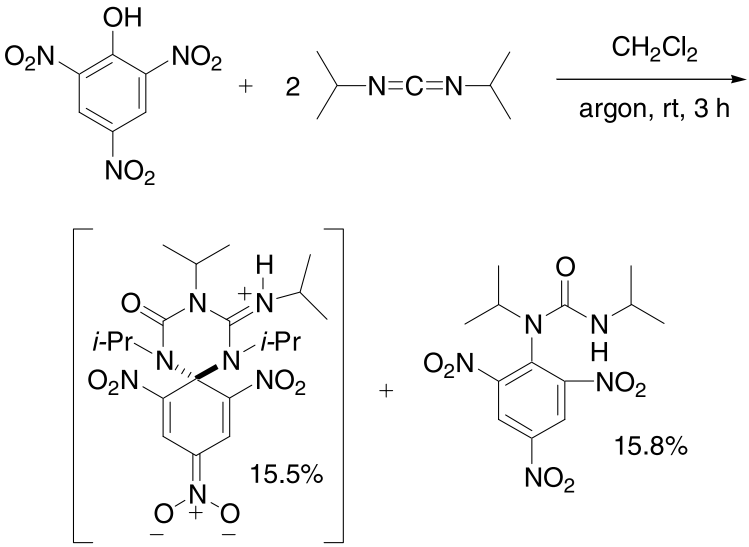


Meisenheimer complex (**Meisenheimer–Jackson salt**)

Example 1[10]



Example 2[13]



The reaction using Sanger's reagent is faster than using the corresponding chloro-, bromo-, and iodo-dinitrobenzene—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.

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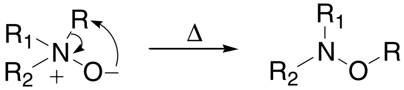
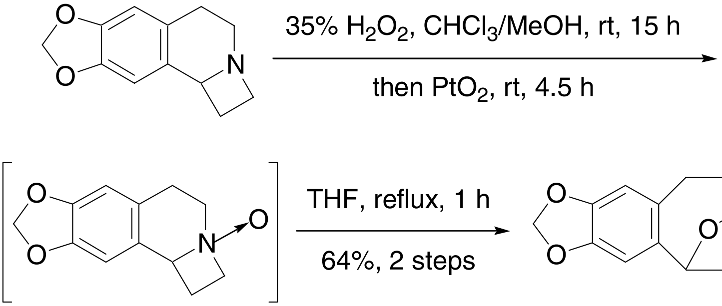
[1,2]-Meisenheimer rearrangement

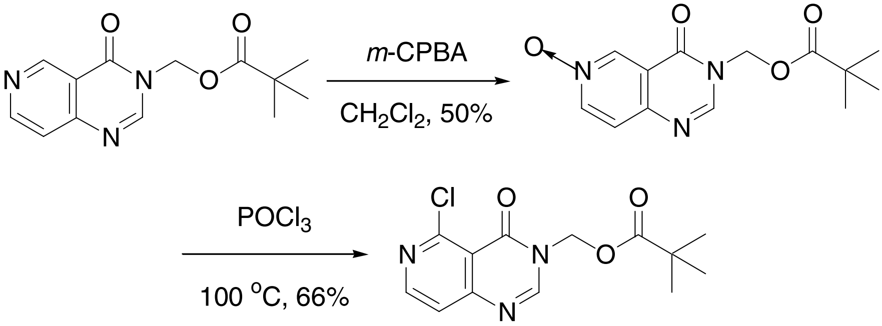
[1,2]-Sigmatropic rearrangement of tertiary amine *N*-oxides to hydroxylamines:



Example 1[5]



Example 2[6]



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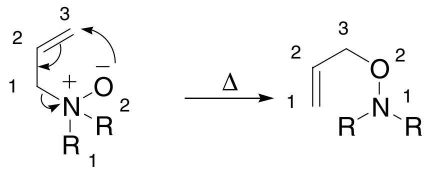
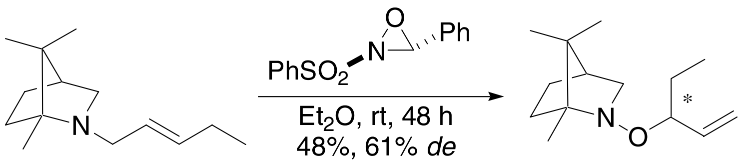
[2,3]-Meisenheimer rearrangement

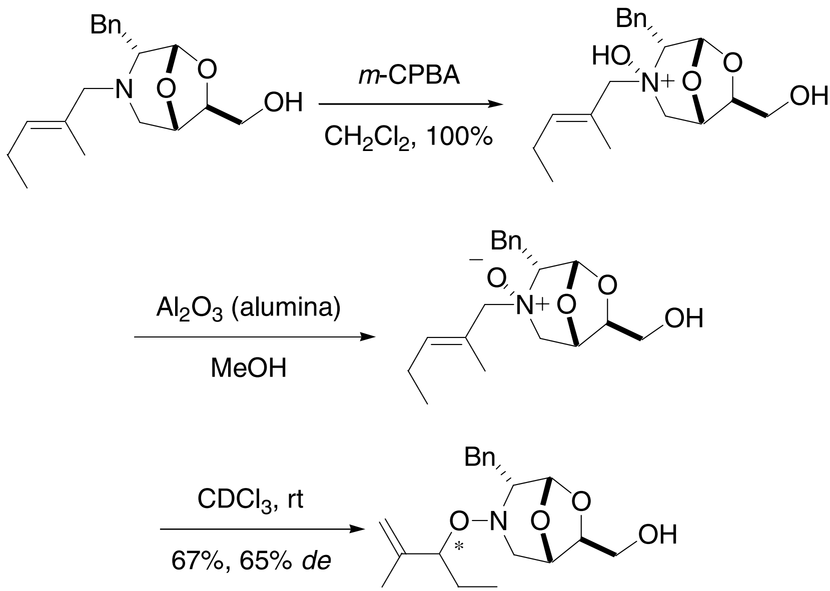
[2,3]-Sigmatropic rearrangement of allylic tertiary amine-*N*-oxides to give *O*-allyl hydroxylamines:



Example 1[7]



Example 2[8]



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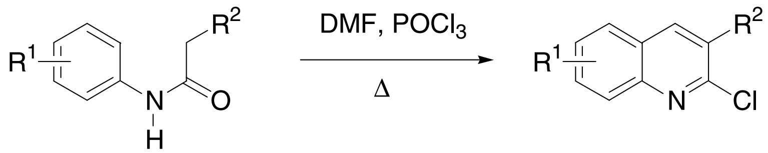
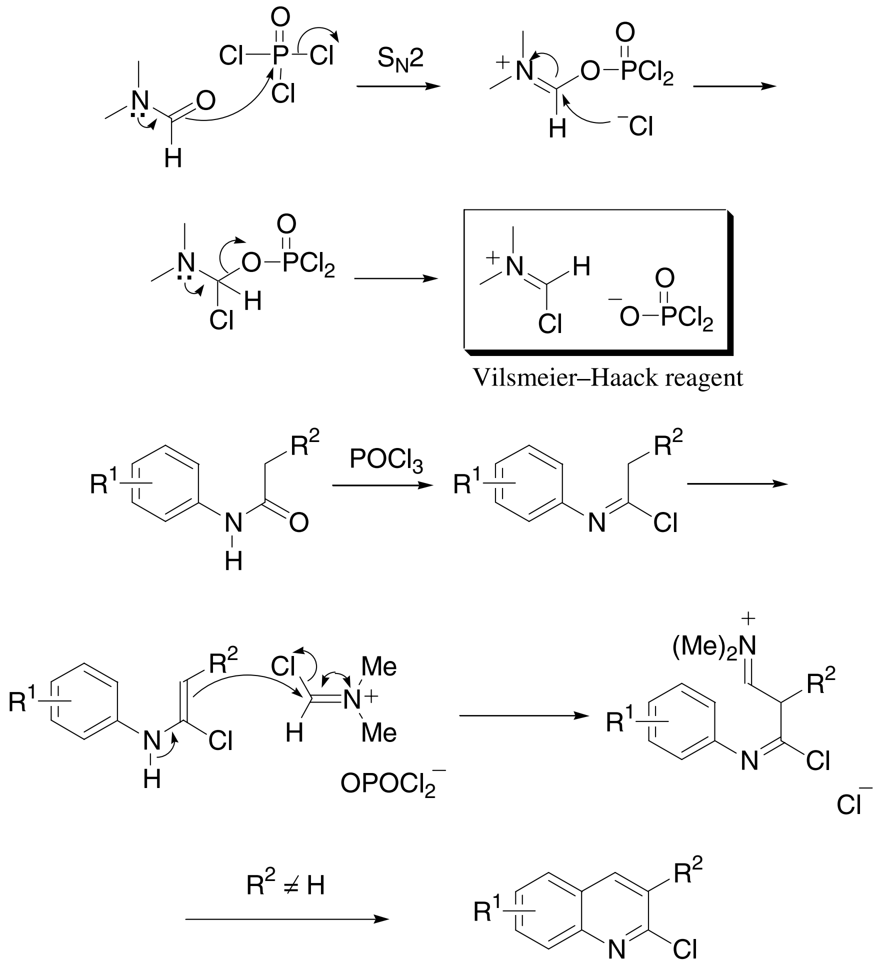
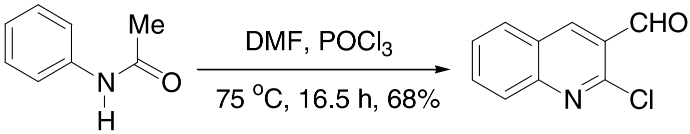
Meth–Cohn quinoline synthesis

Conversion of acylanilides into 2-chloro-3-substituted quinolines by the action of Vilsmeier's reagent in warmed phosphorus oxychloride ($POCl_3$) as solvent.

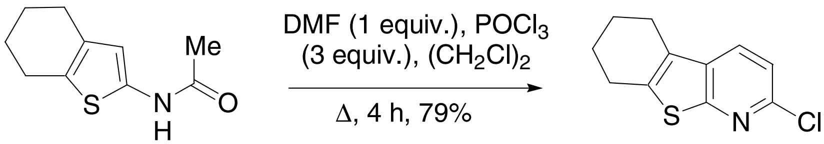




Example 1[5]



Example 2[5]



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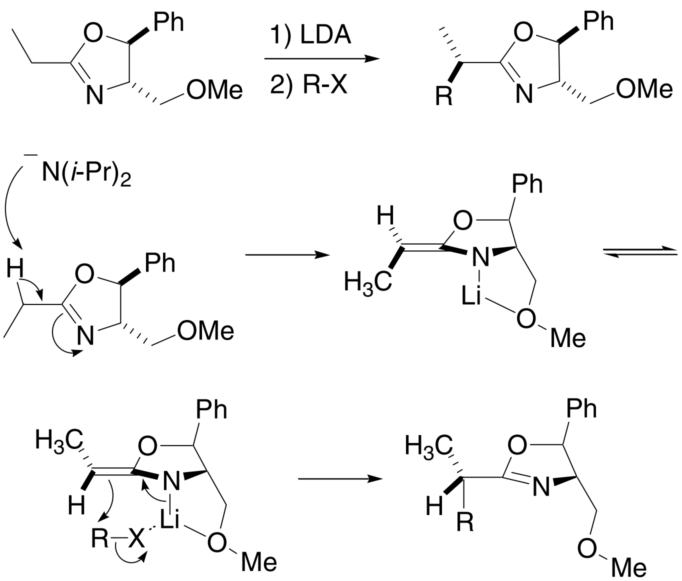
Meyers oxazoline method

Chiral oxazolines employed as activating groups and/or chiral auxiliaries in nucleophilic addition and substitution reactions that lead to the asymmetric construction of carbon-carbon bonds.



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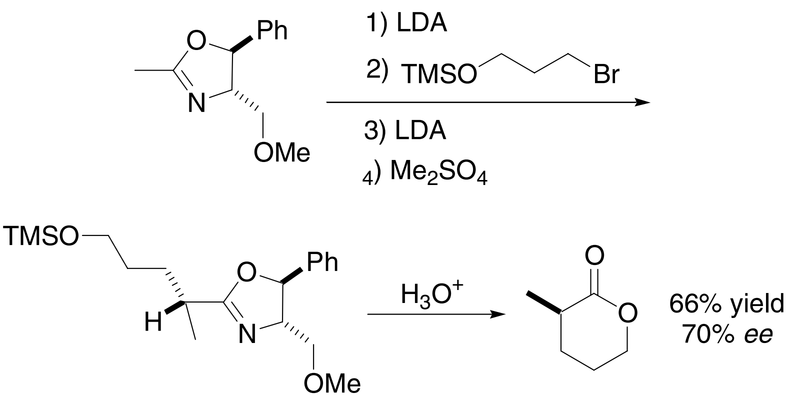
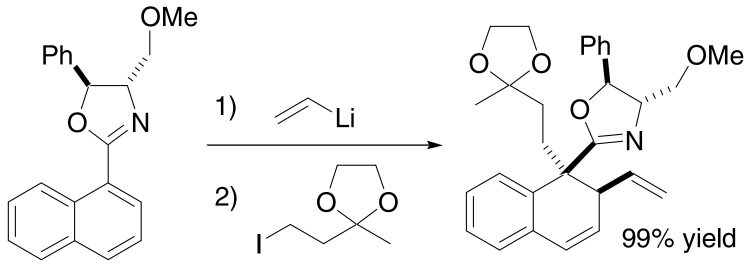


Example 2[12]



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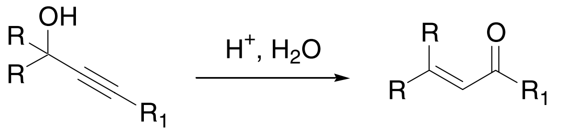
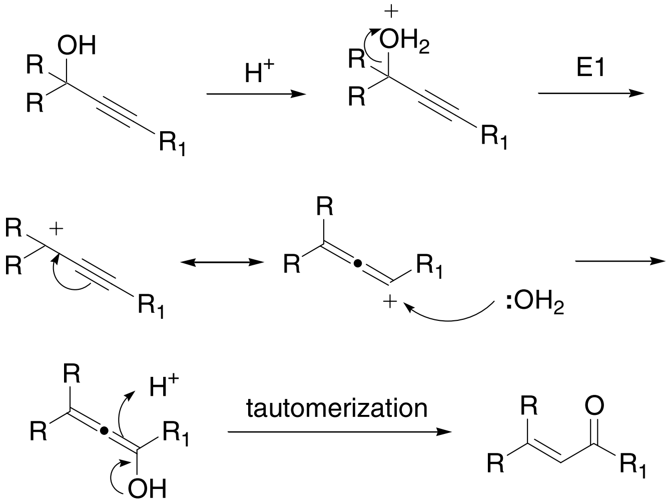
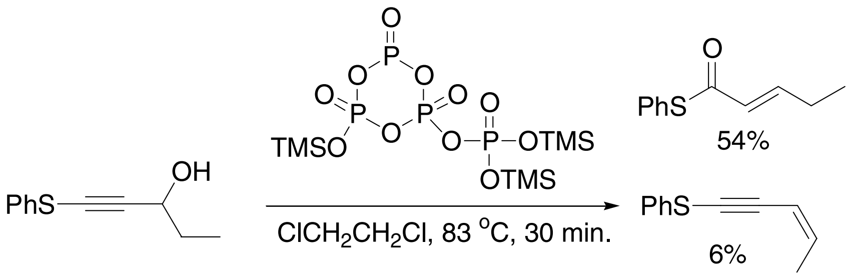
Meyer–Schuster rearrangement

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.

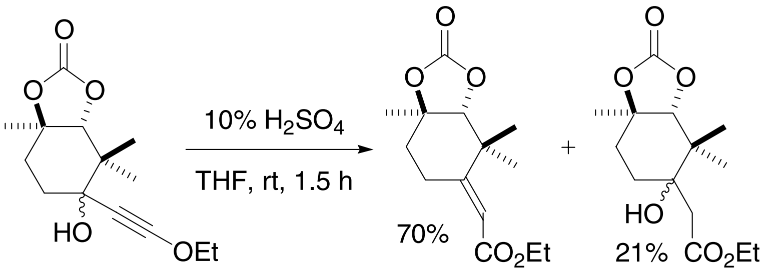




Example 1[8]



Example 2[10]



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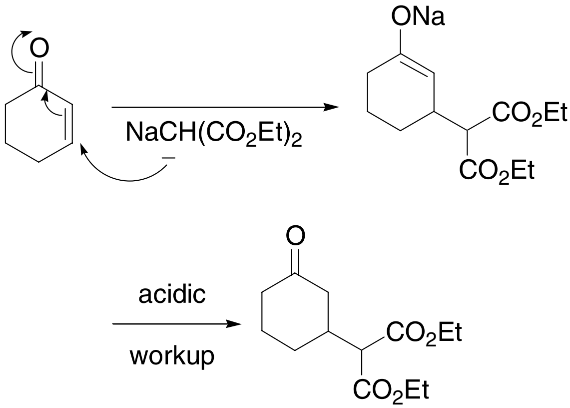
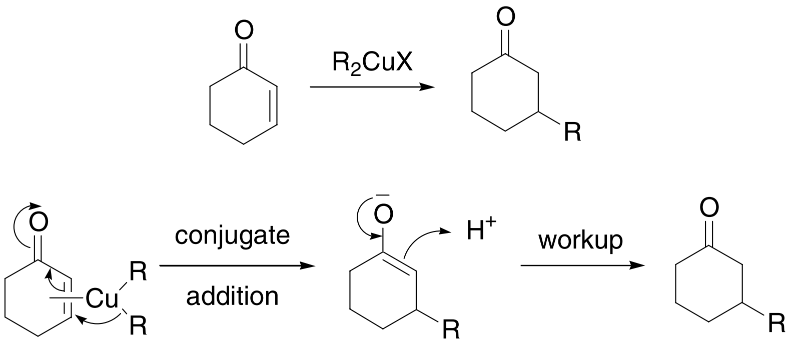
Michael addition

Conjugate addition of a carbon-nucleophile to an α,β-unsaturated system.

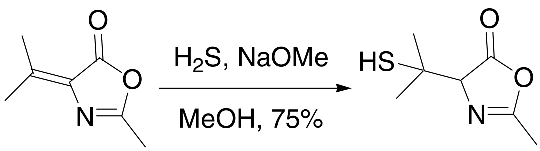
Example 1



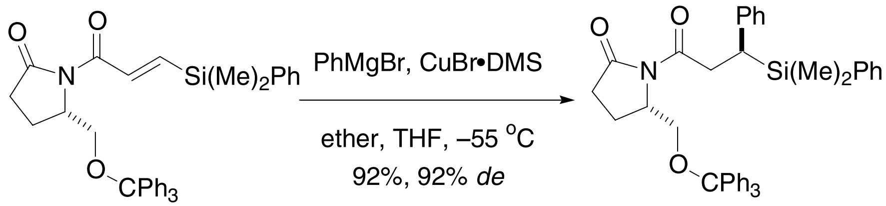
Example 2



Example 3[4]



Example 4[3]



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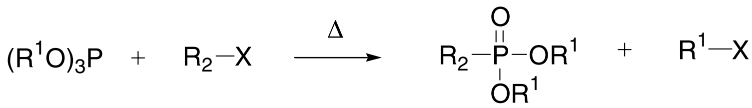
Michaelis–Arbuzov phosphonate synthesis

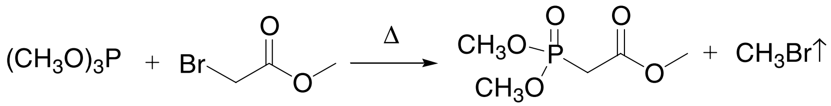
Phosphonate synthesis from the reaction of alkyl halides with phosphites.

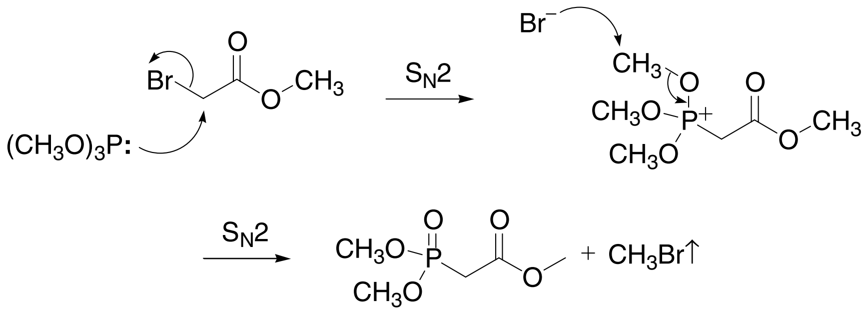
General scheme:



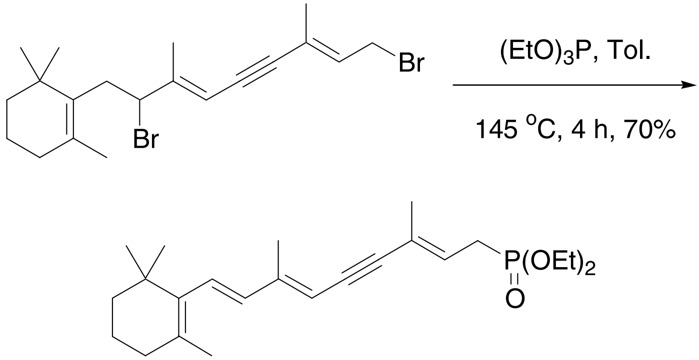
R^1 = alkyl, *etc*.; R_2 = alkyl, acyl, *etc*.; X = Cl, Br, I

For instance:

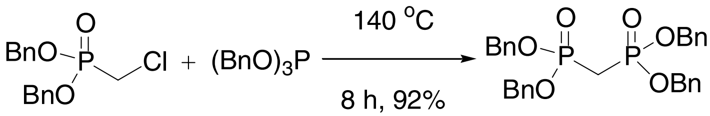




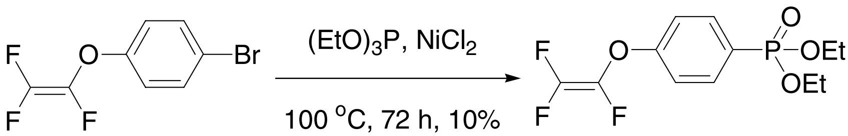
Example 1[3]



Example 2[13]



Example 3[14]



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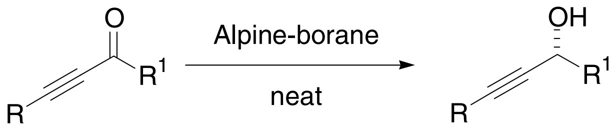
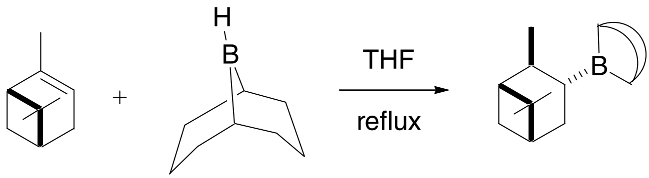
Midland reduction

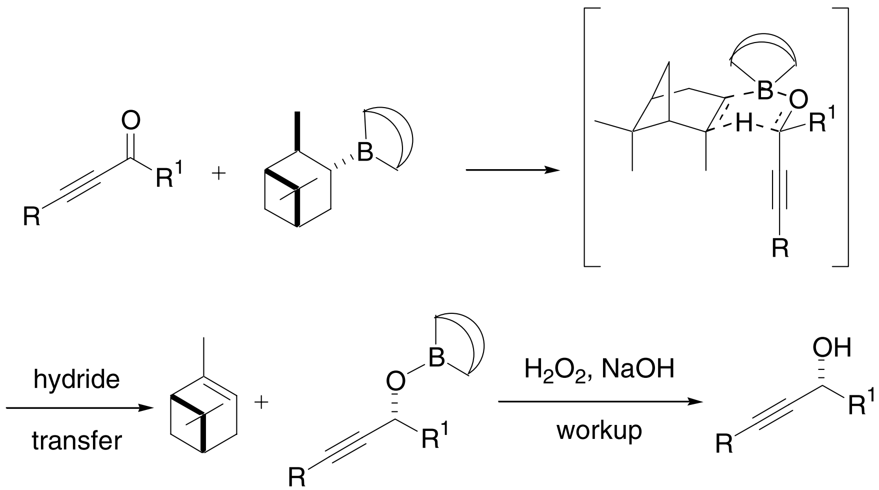
Asymmetric reduction of ketones using Alpine-borane®.
Alpine-borane® = *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane.



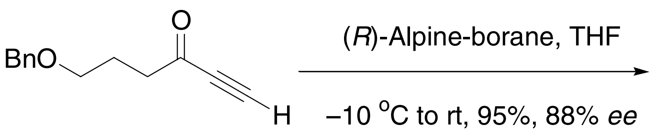


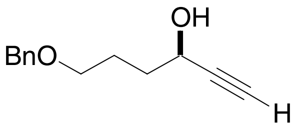
(1*R*)-(+)-α-pinene 9-BBN (*R*)-Alpine-borane

9-BBN = 9-borabicyclo[3.3.1]nonane

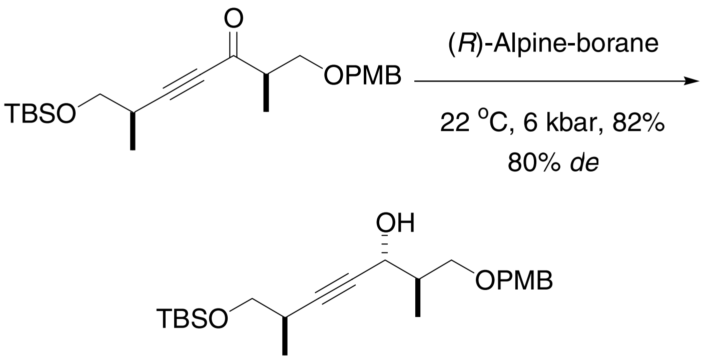


Example 1[6]





Example 2[7]



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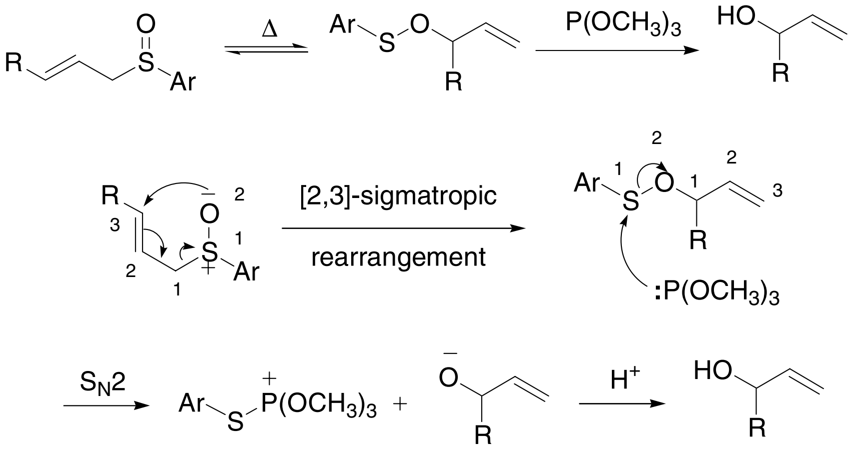
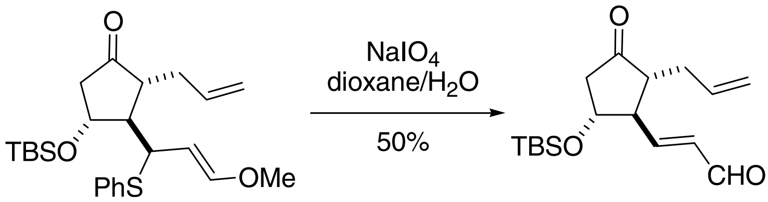
Mislow–Evans rearrangement

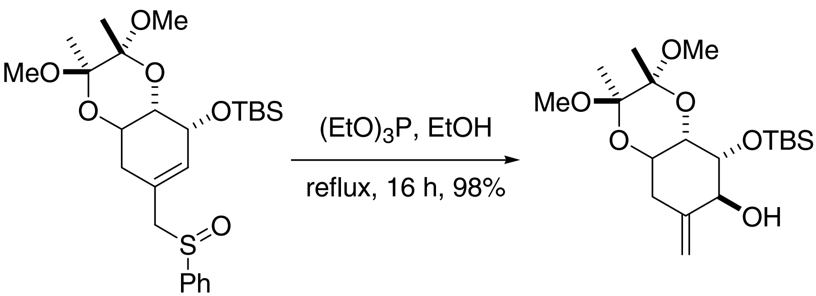
[2,3]-Sigmatropic rearrangement of allylic sulfoxide to allylic alcohol.



Example 1[6]



Example 2[11]



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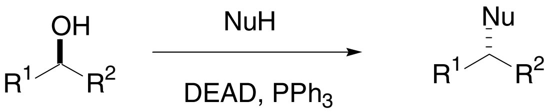
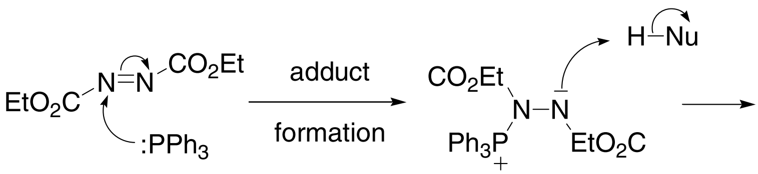
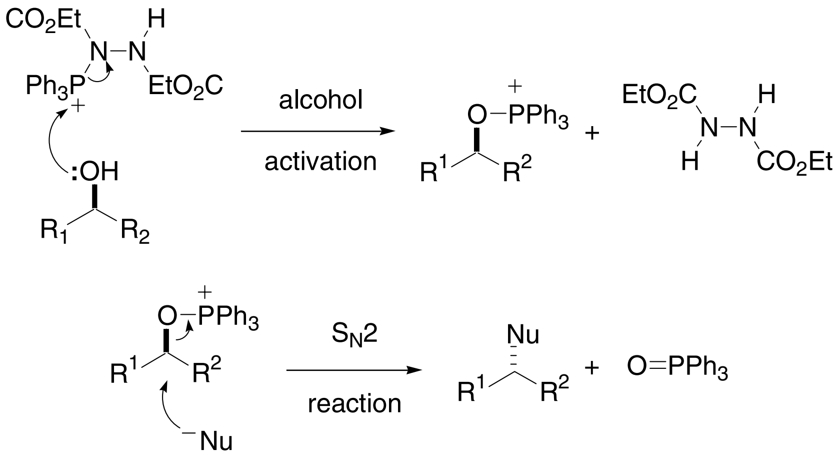
Mitsunobu reaction

S_N2 inversion of an alcohol by a nucleophile using diethyl azodicarboxylate (DEAD) and triphenylphosphine.

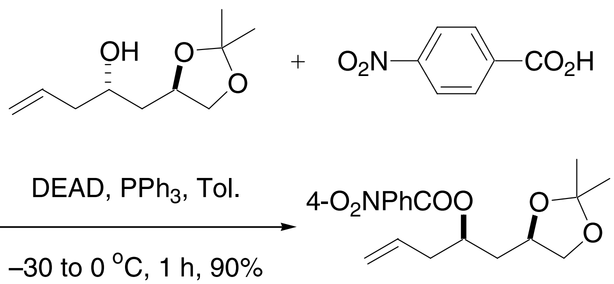




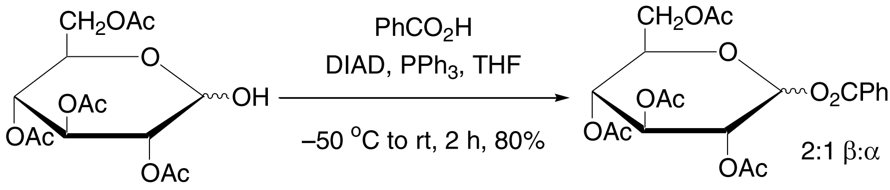
Diethyl azodicarboxylate (DEAD)



Example 1[4]



Example 2[3]



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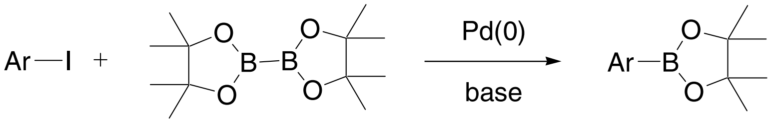
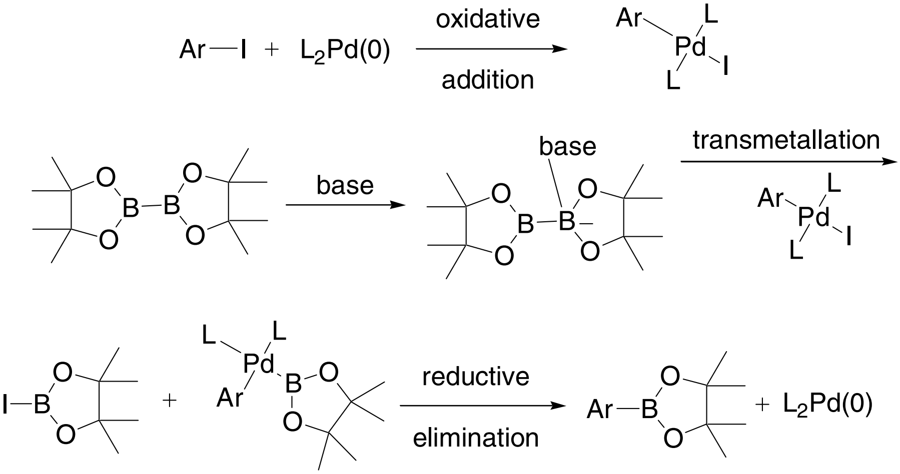
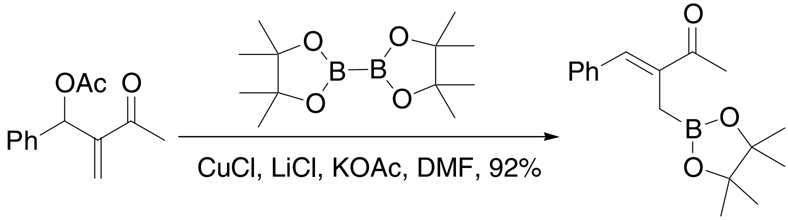
Miyaura borylation

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

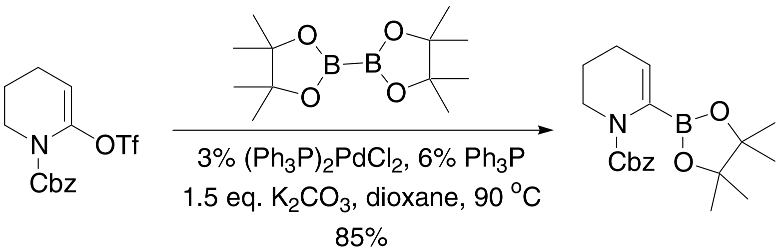




Example 1[11]



Example 2[12]



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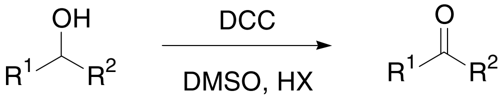
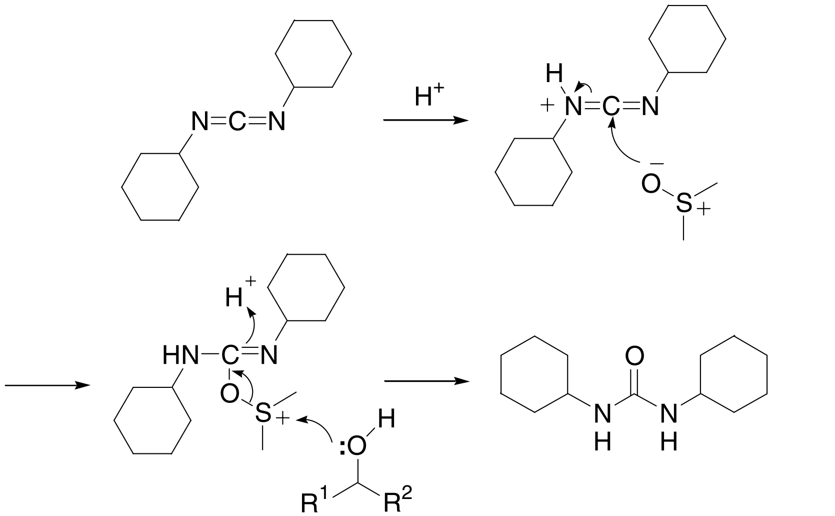
Moffatt oxidation

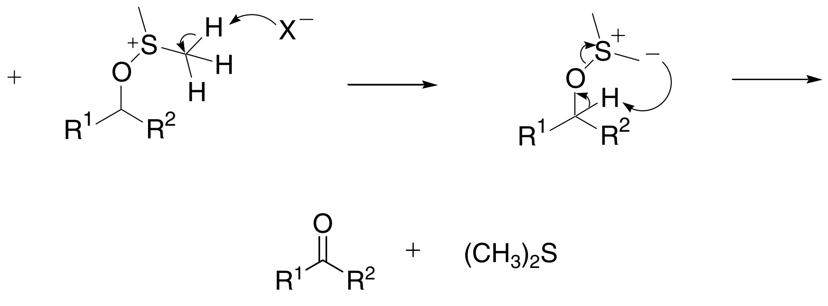
Oxidation of alcohols using DCC and DMSO, also known as “Pfitzner–Moffatt oxidation”.



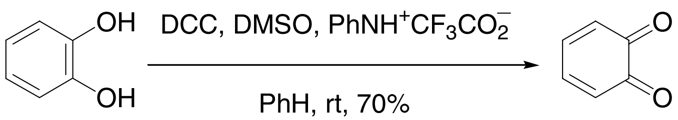
DCC, 1,3-dicyclohexylcarbodiimide



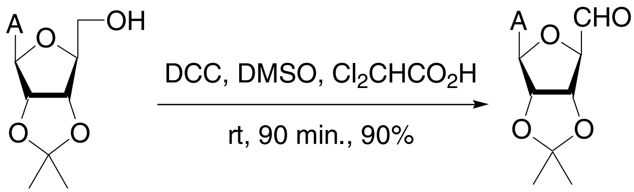
1,3-dicyclohexylurea



Example 1[3]



Example 2[10]



A = adenosine

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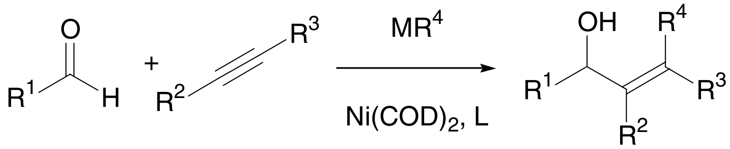
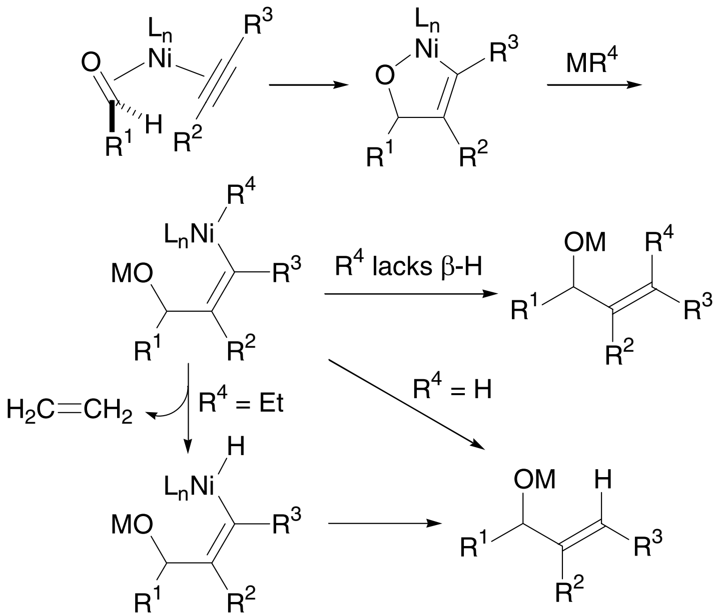
Montgomery coupling

Oxidative nickel-catalyzed coupling of aldehydes and alkynes to generate allylic alcohols. Intermolecular and intramolecular examples are both effective, and the transmetalating agent (MR^4) may be an organosilane, organoborane, organozinc, or alkenylzirconium.[1–5]

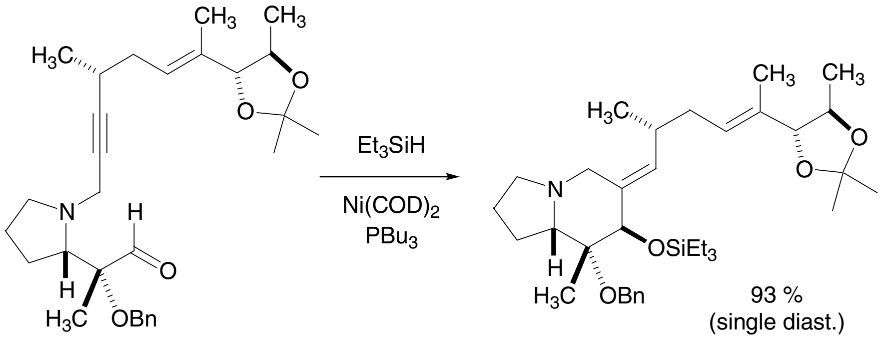


R^1, R^3 = alkyl or aryl
R^2, R^4 = alkyl, aryl, or H

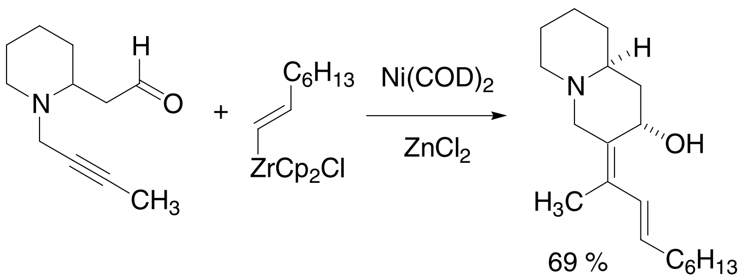
The mechanism was proposed to involve the formation of a nickel metallacycle by the oxidative cyclization of Ni(0) with the aldehyde and alkyne, followed by conversion of the metallacycle to product by a transmetalation/reductive elimination sequence. If R^4 possesses a β-hydrogen, then β-hydride elimination after the transmetalation step generates the product with R^4 = H in some instances. The mechanism was shown to be ligand dependent, and the mechanism depicted below is undoubtedly oversimplified.[4]



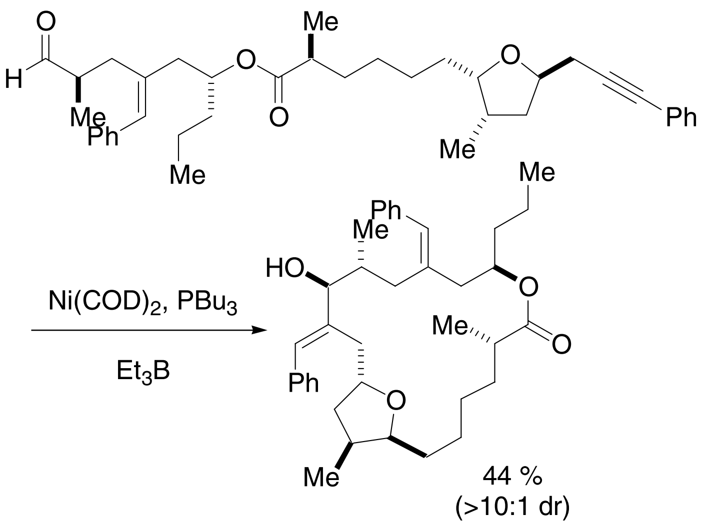
Example 1[6]



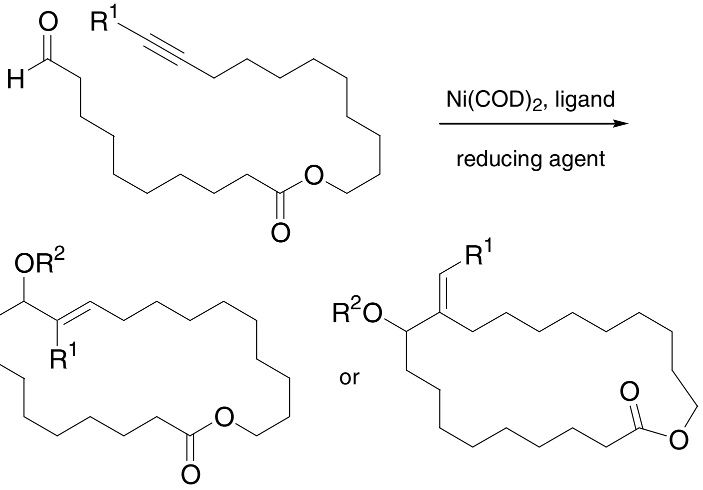
Example 2[7]

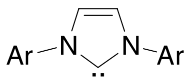


Example 3[8]



Example 4[9]



ligand	reducing agent	yield (ratio)
PMe_3	Et_3B	89 % (4.5:1)
	Et_3SiH	93 % (1:5)

Ar = 2,6 di-isopropylphenyl

A number of related processes involving alternate π-systems including enones, dienes, and allenes have been reported.[10]

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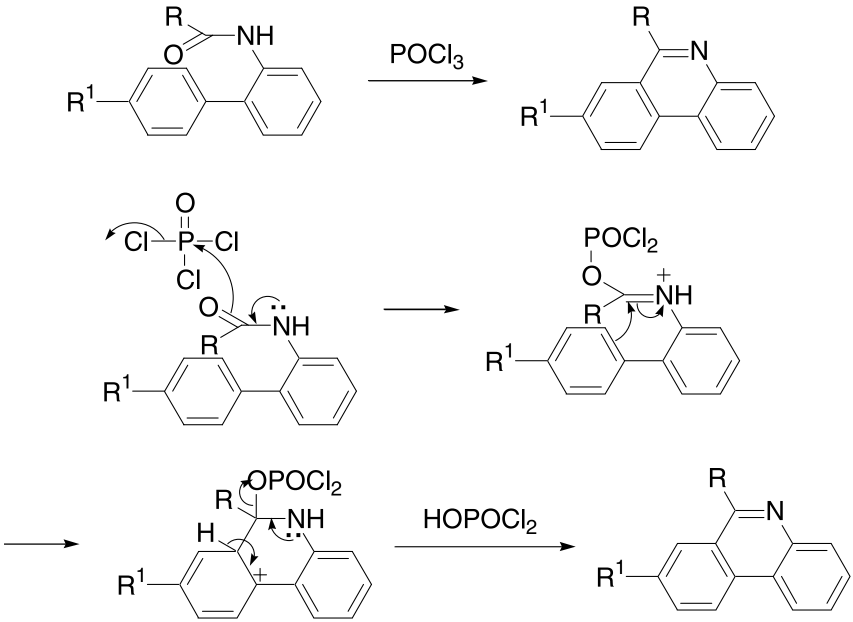
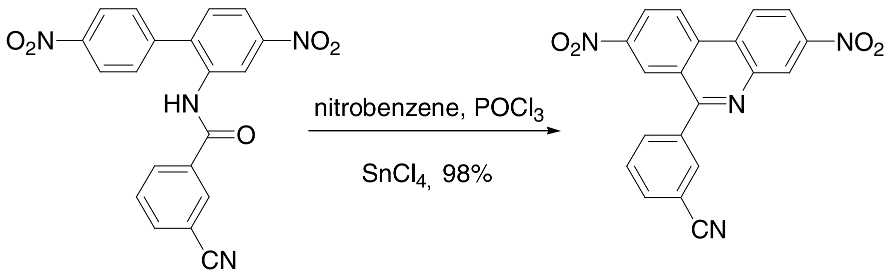
Morgan–Walls reaction

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

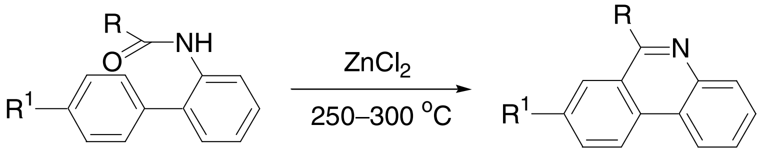


Example 1[10]

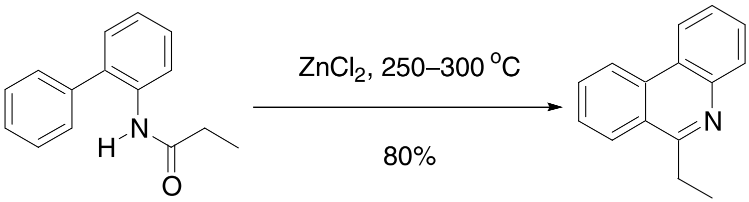


Pictet–Hubert reaction

Phenanthridine cyclization by dehydrative ring closure of acyl-*o*-aminobiphenyls on heating with zinc chloride at 250–300 °C.



Example 2[7]



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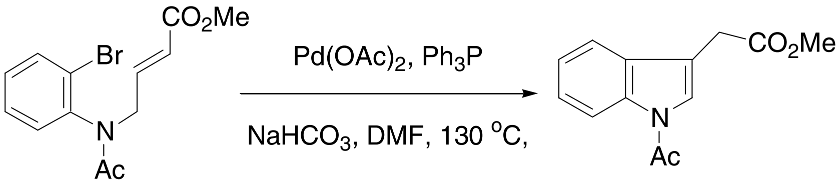
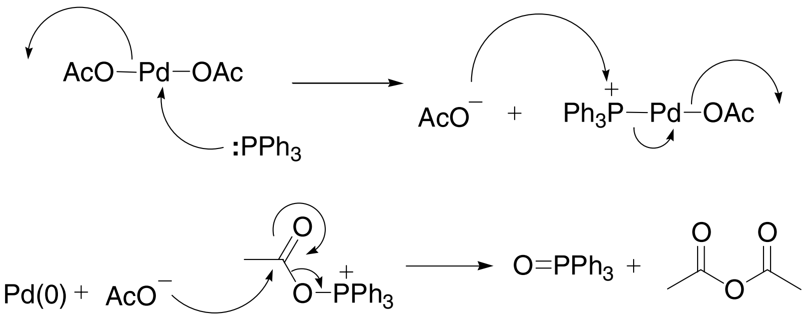
Mori−Ban indole synthesis

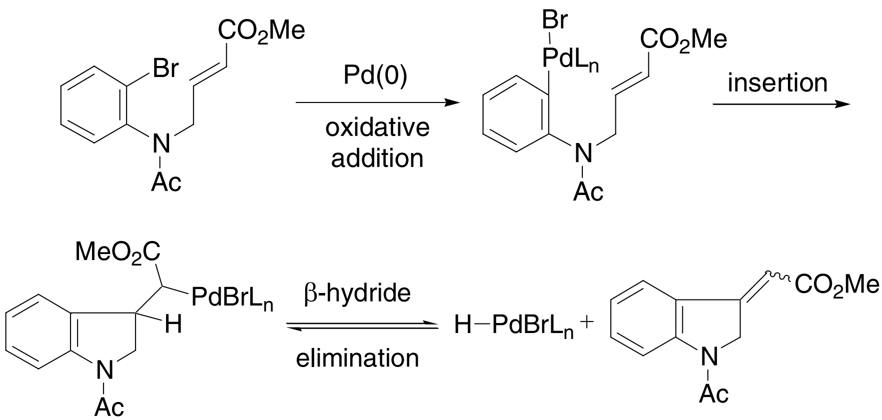
Intramolecular Heck reaction of *o*-halo-aniline with pendant olefin to prepare indole.

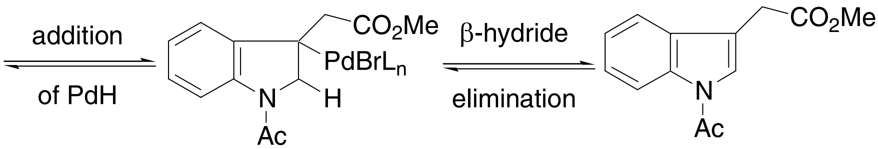


Reduction of $Pd(OAc)_2$ to Pd(0) using Ph_3P:



Mori−Ban indole synthesis:

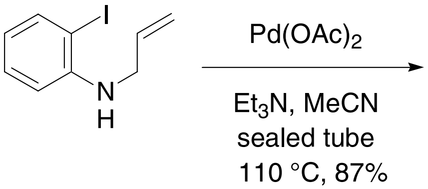




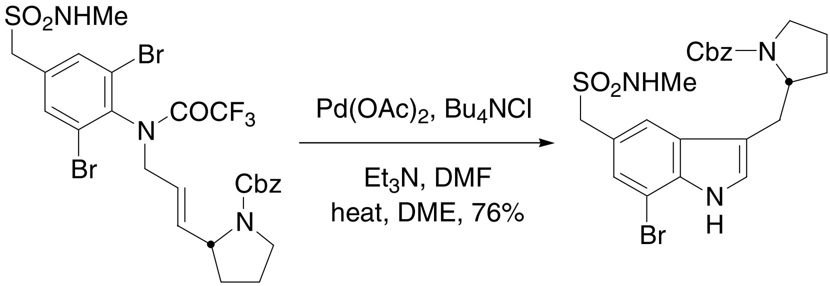
Regeneration of Pd(0):

$$H{-}PdBrL_n + NaHCO_3 \longrightarrow Pd(0) + NaBr + H_2O + CO_2\uparrow$$

Example 1[1]



Example 2[12]



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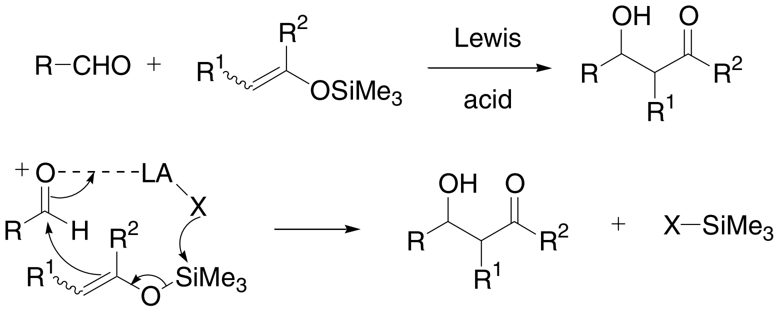
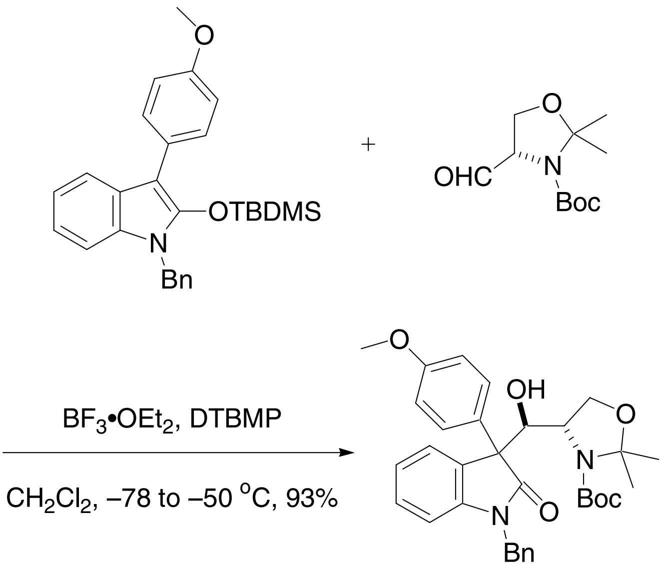
Mukaiyama aldol reaction

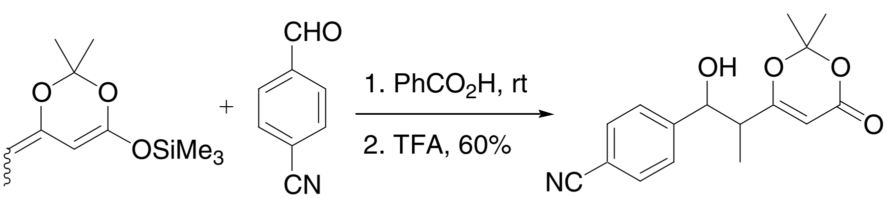
Lewis acid-catalyzed aldol condensation of aldehyde and silyl enol ether.



Example 1[14]



Example 2[15]



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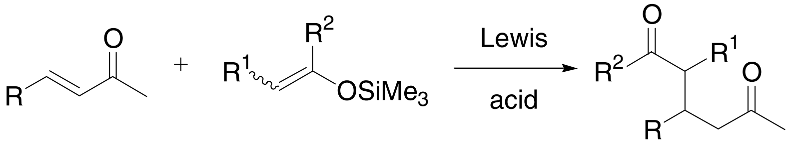
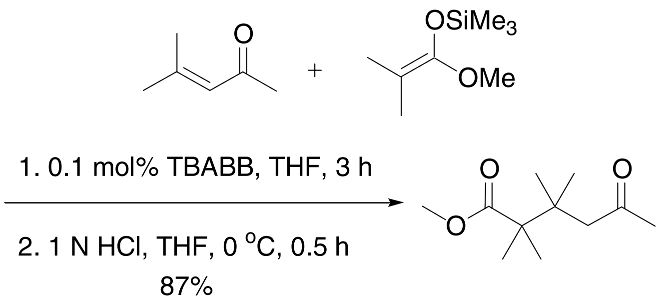
Mukaiyama Michael addition

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

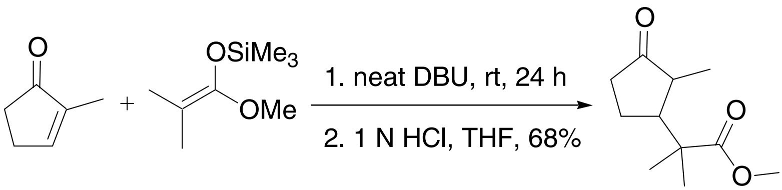


Example 1[4]



TBABB = tetra-*n*-butylammonium bibenzoate

Example 2[7]



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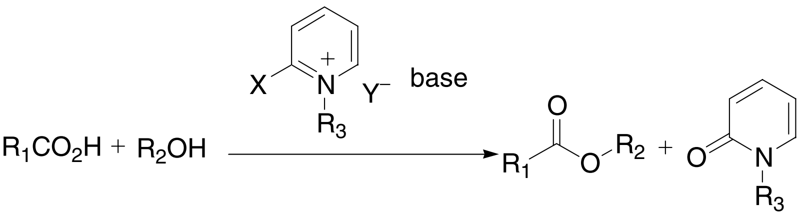
Mukaiyama reagent

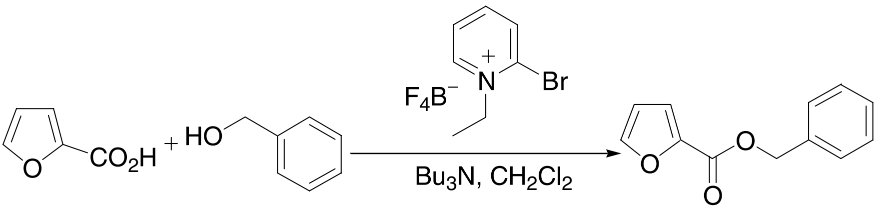
Mukaiyama reagent such as 2-chloro-1-methyl-pyridinium iodide for esterification or amide formation.

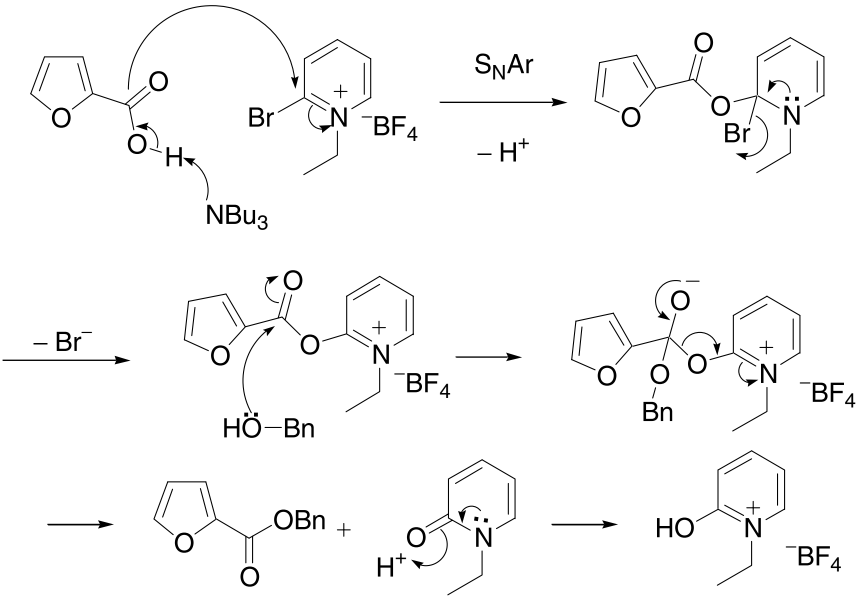
General scheme:



X = F, Cl, Br

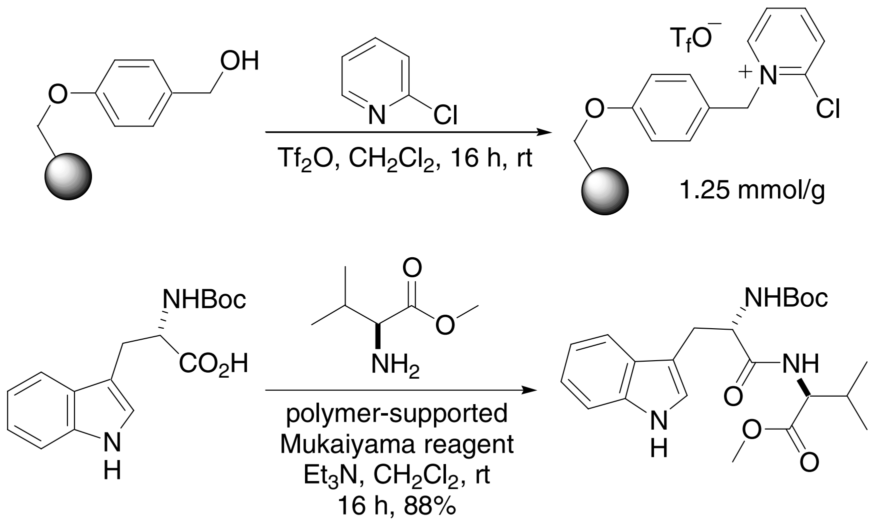
Example 1[3]





Amide formation using the Mukaiyama reagent follows a similar mechanistic pathway.[4]

Example 2, polymer-supported Mukaiyama reagent[8]



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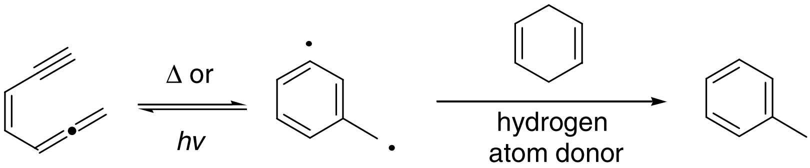
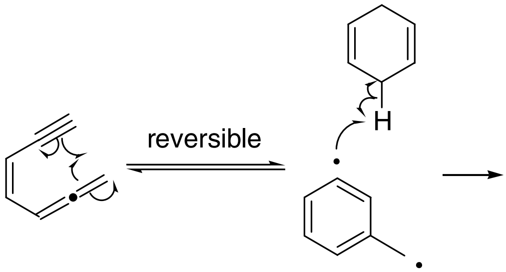
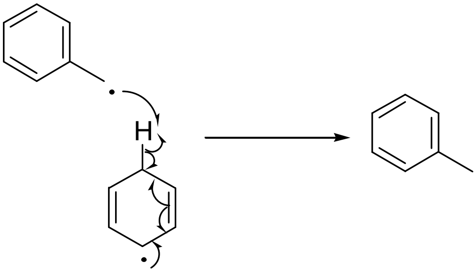
Myers–Saito cyclization

Cf. Bergman cyclization and Schmittel cyclization.

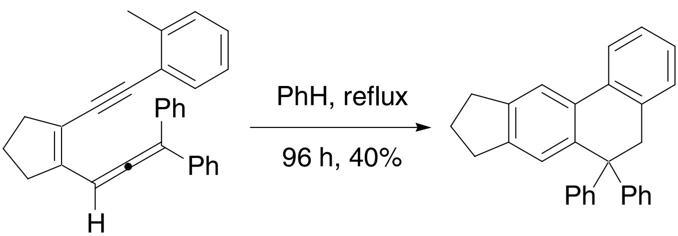




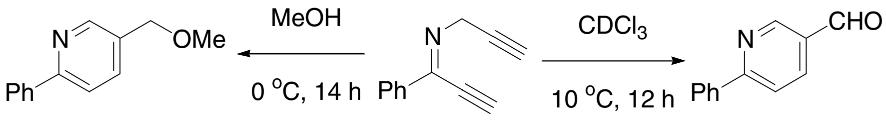
allenyl enyne diradical



Example 1[6]



Example 2, aza-Myers–Saito reaction[16]



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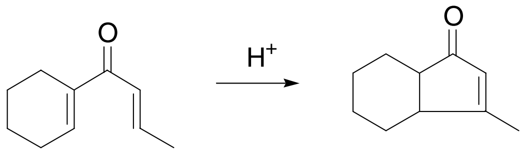
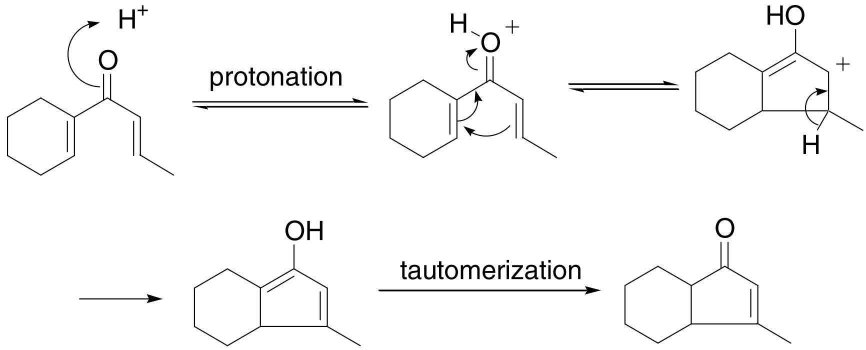
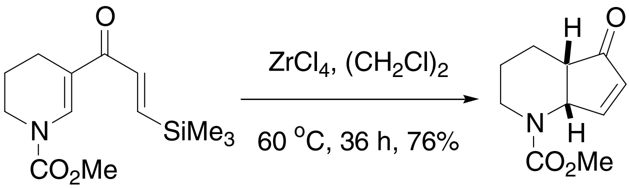
Nazarov cyclization

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

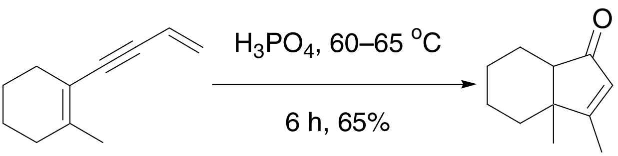




Example 1[2]



Example 2, cyclization of *in situ* generated di-vinyl ketone[12]



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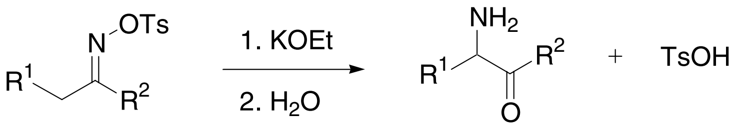
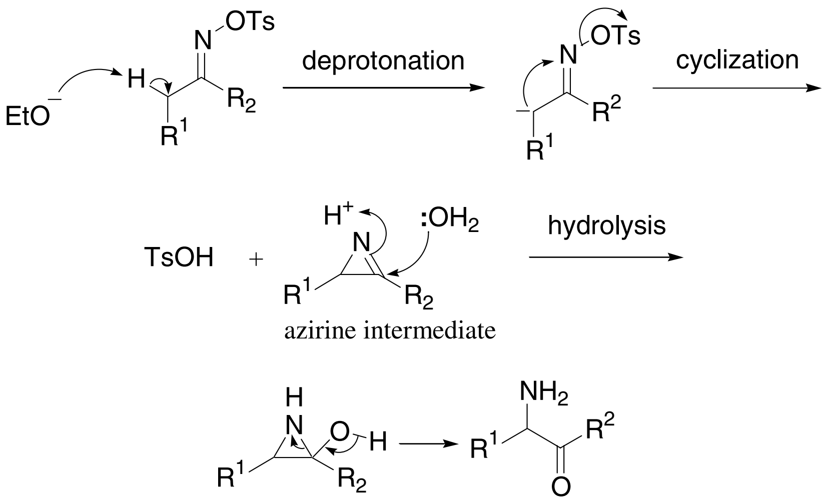
Neber rearrangement

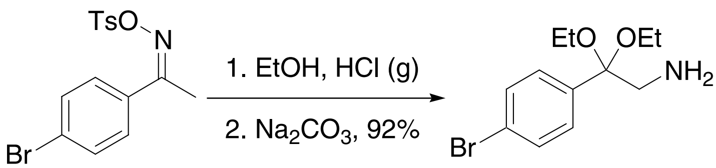
α-Aminoketone from tosyl ketoxime and base.



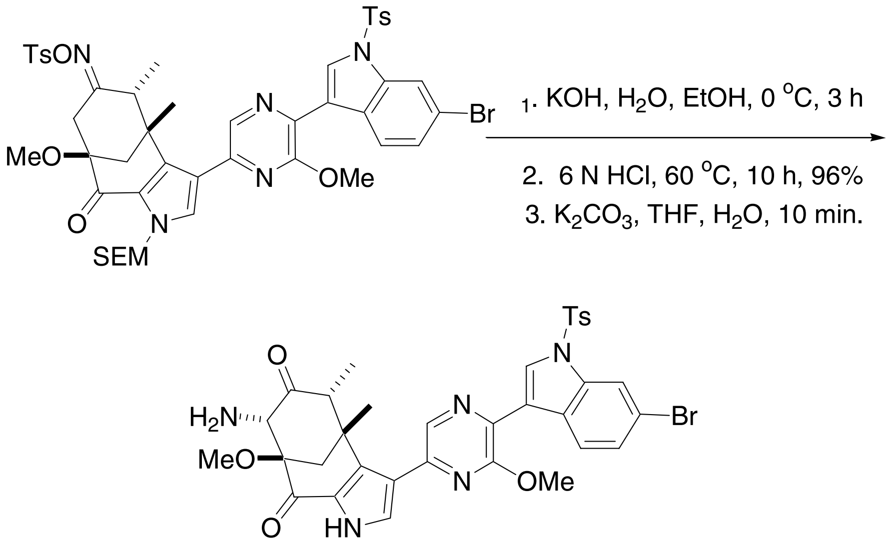
ketoxime α-aminoketone



Example 1[5]



Example 2[15]



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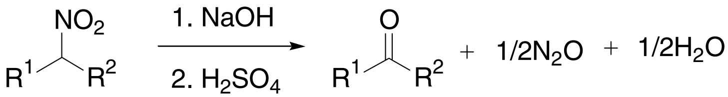
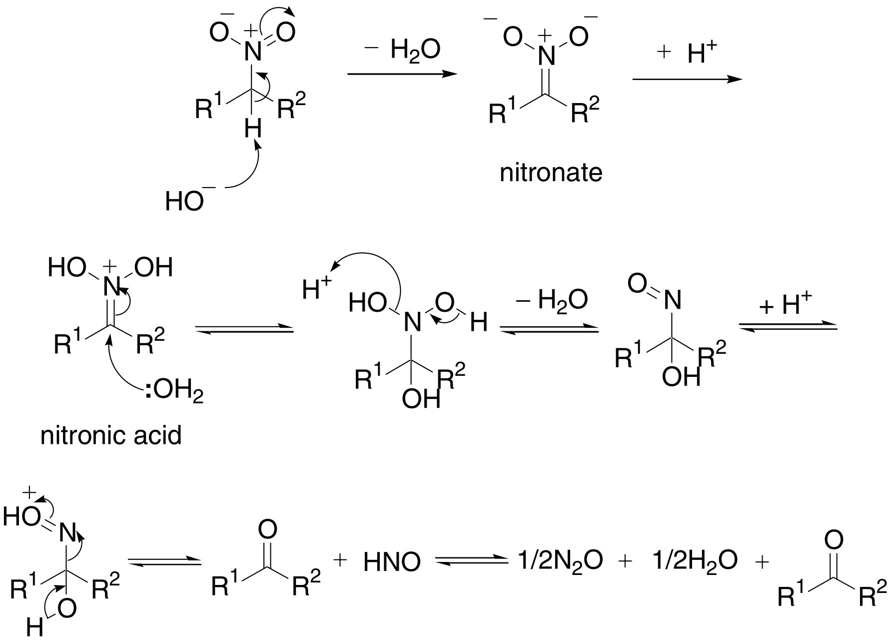
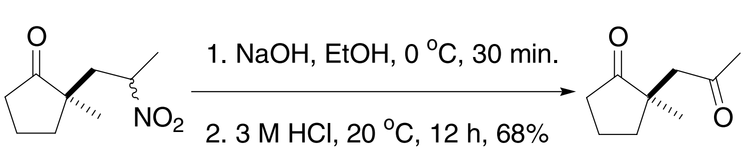
Nef reaction

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

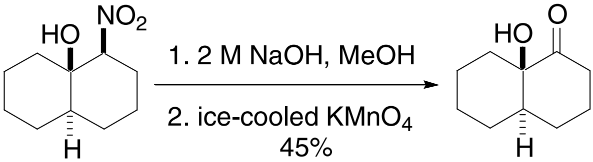




Example 1[7]



Example 2[11]



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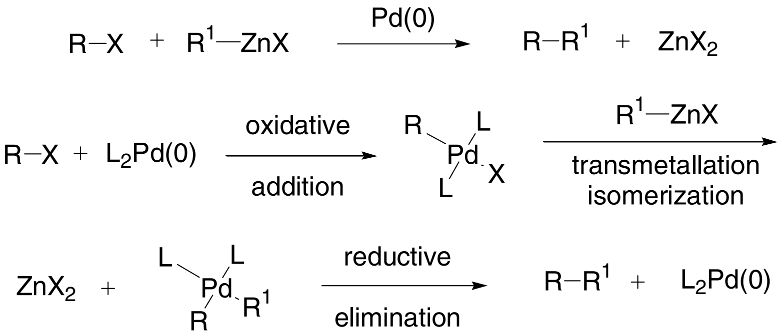
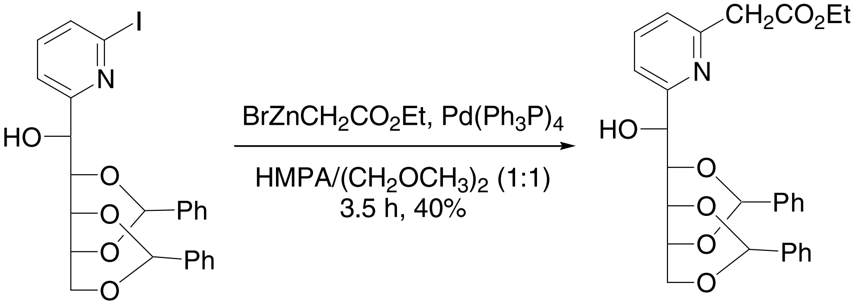
Negishi cross-coupling reaction

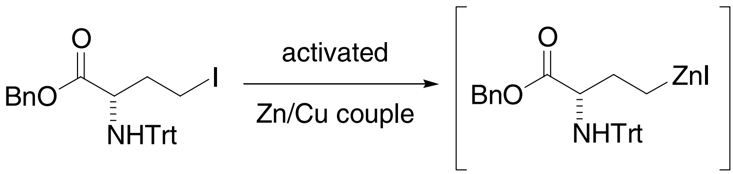
Palladium-catalyzed cross-coupling reaction of organozinc reagents with organic halides, triflates, *etc*. It is compatible with many functional groups including ketones, esters, amines, and nitriles. For the catalytic cycle, see the Kumada coupling on page 345.

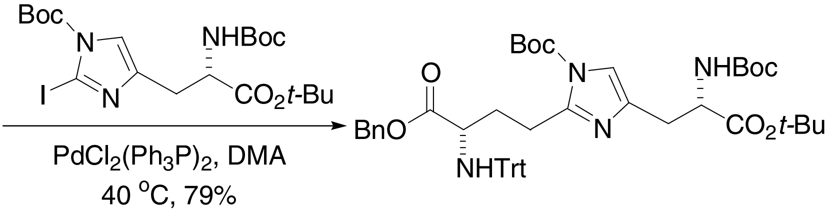


Example 1[5]



Example 2[6]





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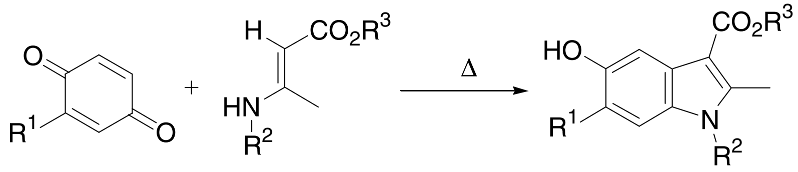
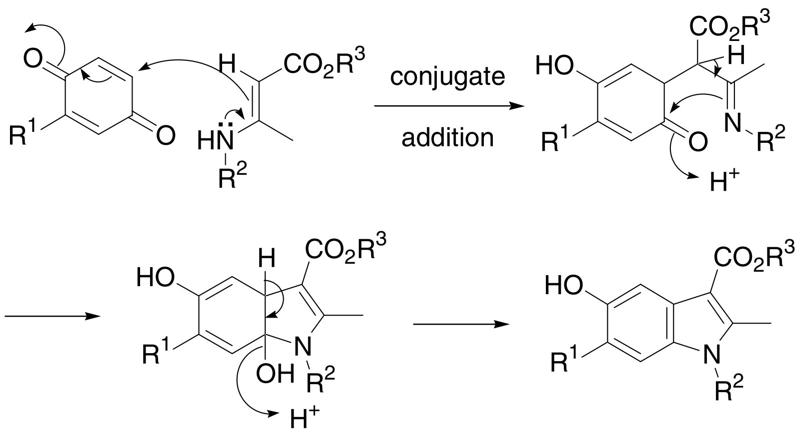
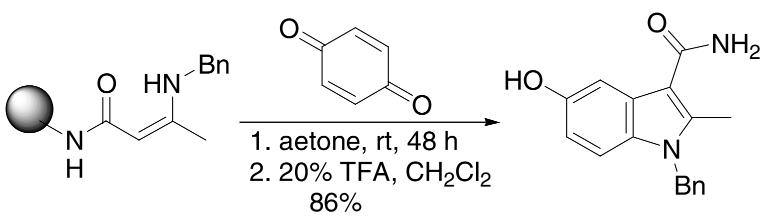
Nenitzescu indole synthesis

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

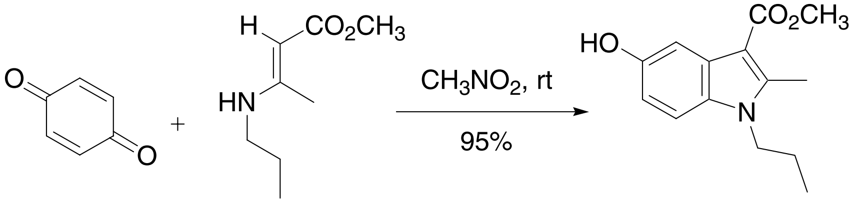




Example 1[7]



Example 2[8]



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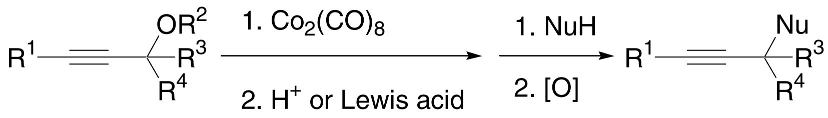
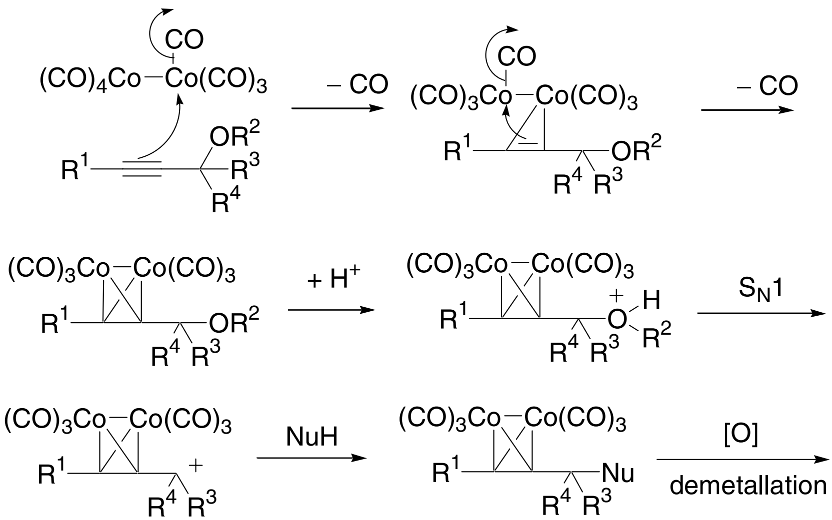
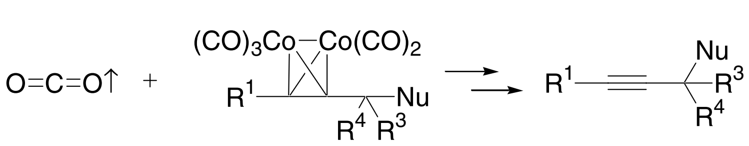
Nicholas reaction

Hexacarbonyldicobalt-stabilized propargyl cation is captured by a nucleophile. Subsequent oxidative demetallation then gives propargylated product.

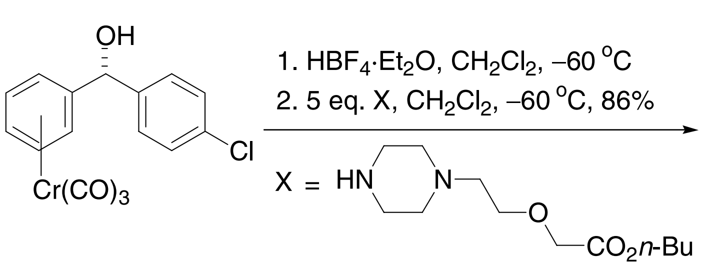


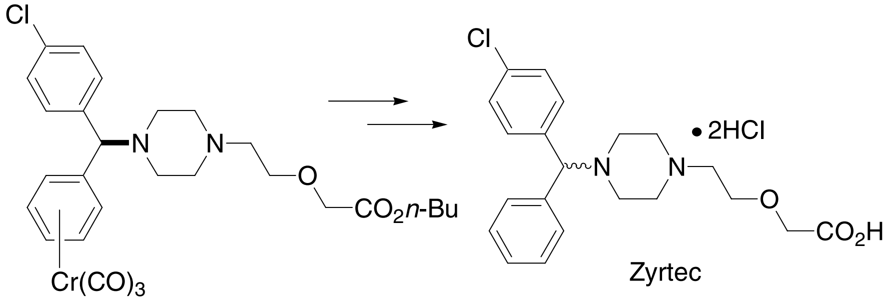


propargyl cation intermediate (stabilized by the hexacarbonyldicobalt complex).

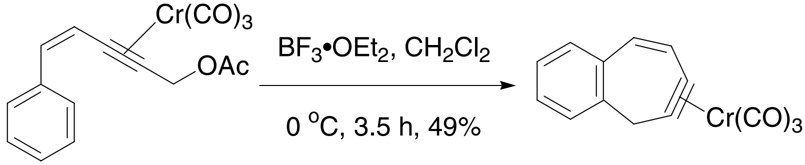


Example 1, chromium variant of the Nicholas reaction[5]





Example 2, intramolecular Nicholas reaction using chromium[11]



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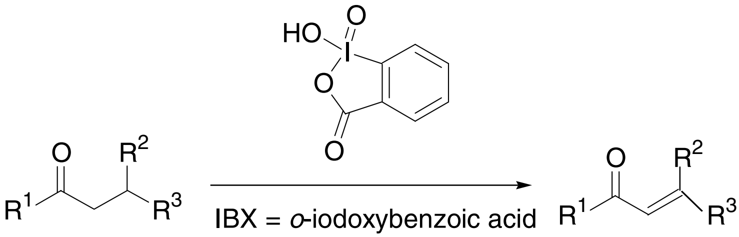
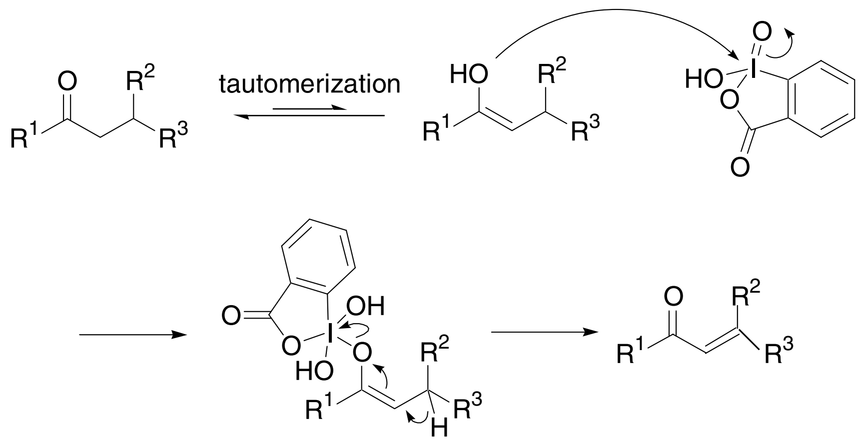
Nicolaou dehydrogenation

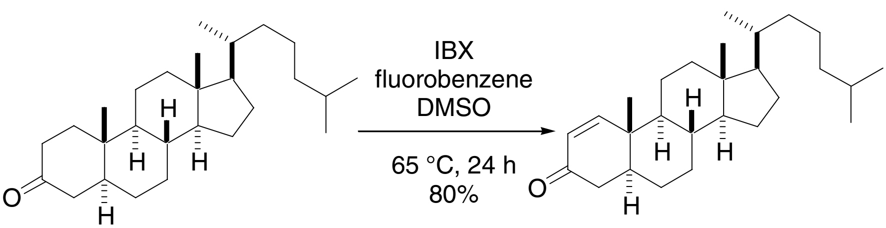
α,β-Unsaturation of aldehydes and ketones mediated by stoichiometric amounts of IBX (*o*-iodoxybenzoic acid), alternative to Saegusa oxidation (page 515).[1]



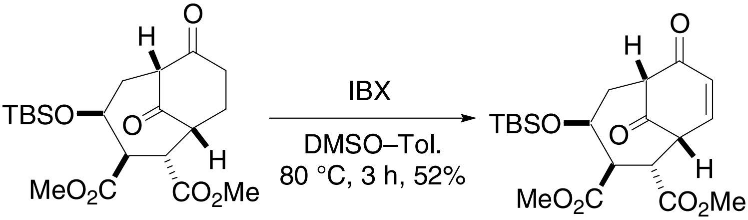
A SET mechanism has also been proposed.[2] Additionally, silyl enol ethers are also viable substrates.[3]



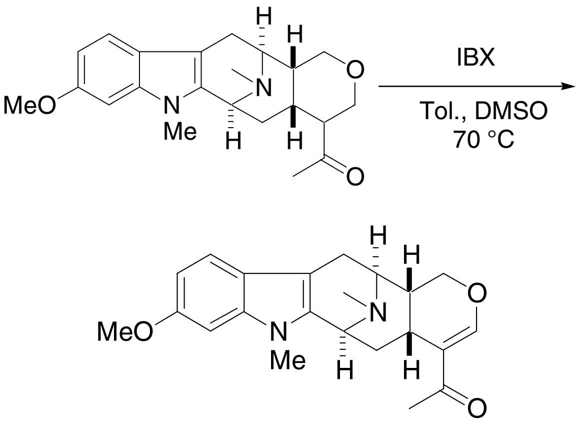
Example 1[1]



Example 2[4]



e. g.3[10]



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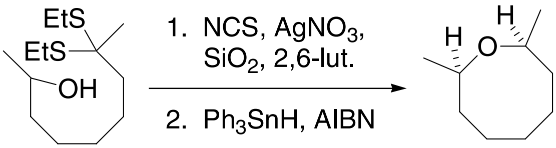
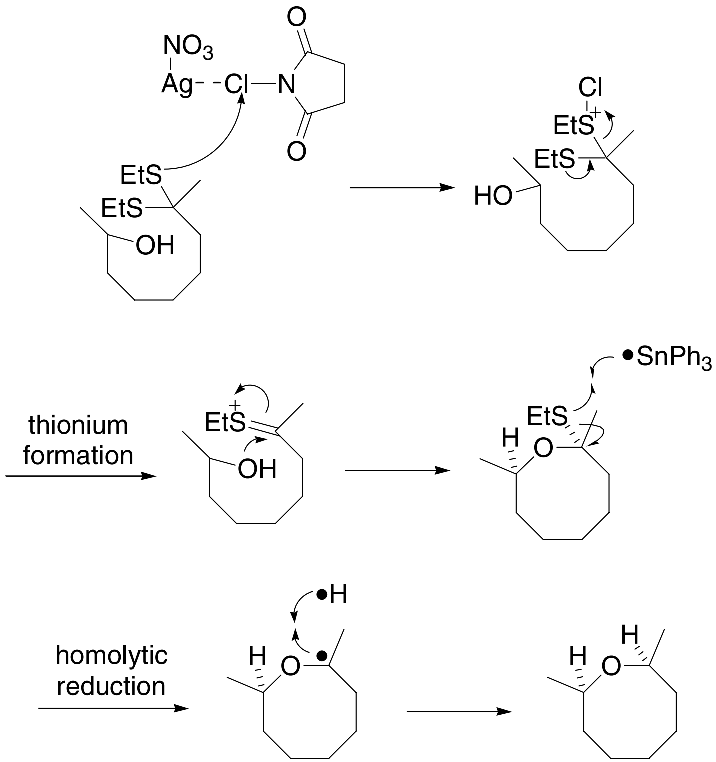
Nicolaou hydroxy-dithioketal cyclization

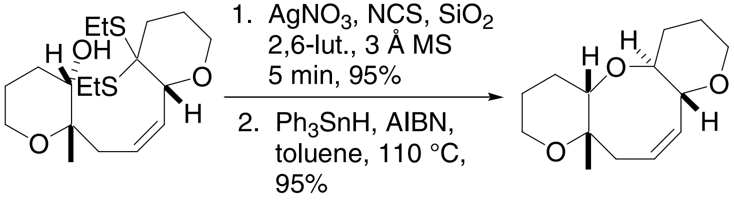
Two step synthesis of medium-ring ethers through the intermediacy of thionium ions followed by sulfide reduction.



The mechanism is analogous to the hydroxy-ketone cyclization except that the mixed ketal is isolable. It can be reductively cleaved using Ph_3SnH/AIBN:

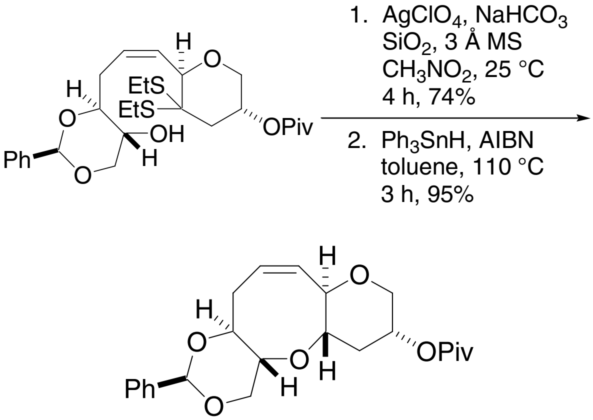


e. g. 1[1]



Example 2, carbocyclization is also possible[3]:

Example 3, the cyclizations tolerate ordinary acetals[5]:



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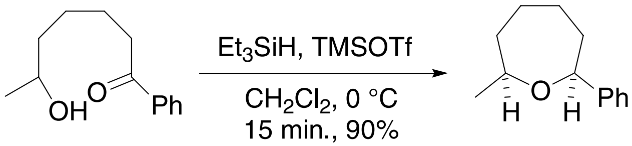
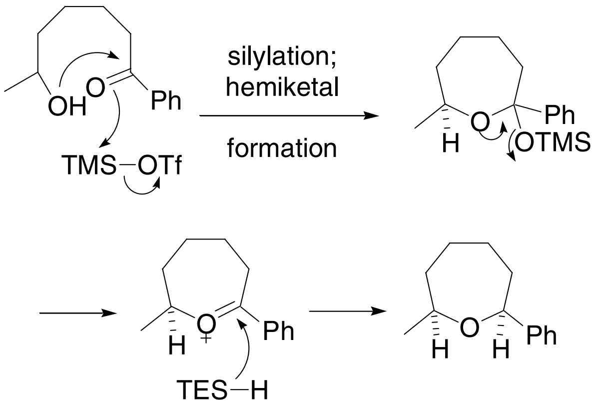
Nicolaou hydroxy-ketone reductive cyclic ether formation

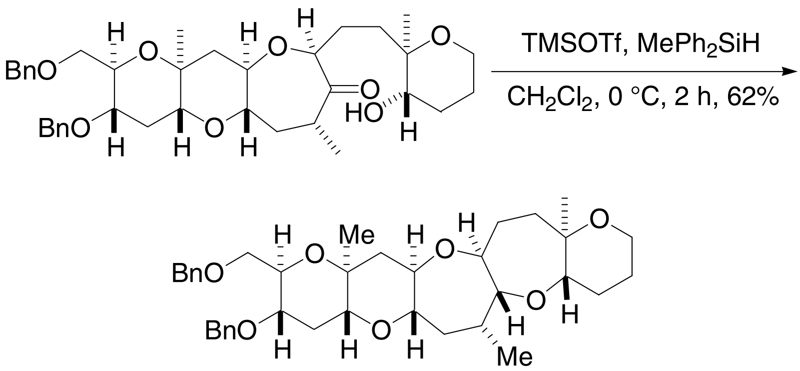
Acid-catalyzed conversion of a ketone with a pendant hydroxyl group into a cyclic ether with net reduction of the carbonyl.



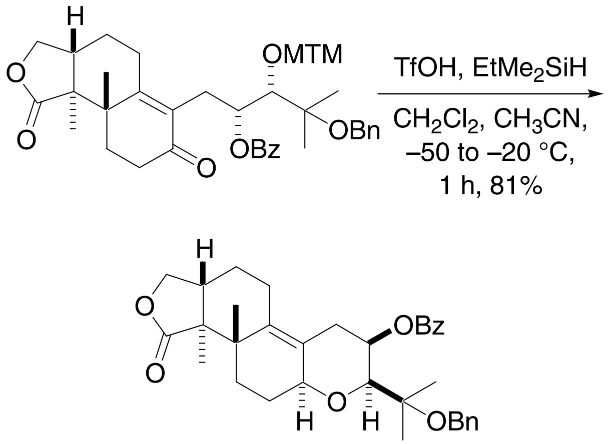
The mechanism involves hemiketal formation followed by reduction of the oxocarbonium group:



Example 1[1]



e. g. 2[2]



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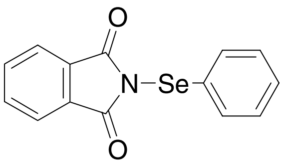
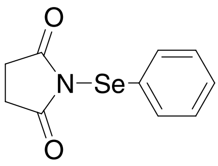
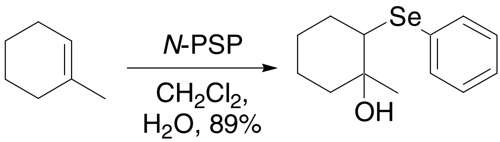
Nicolaou oxyselenation

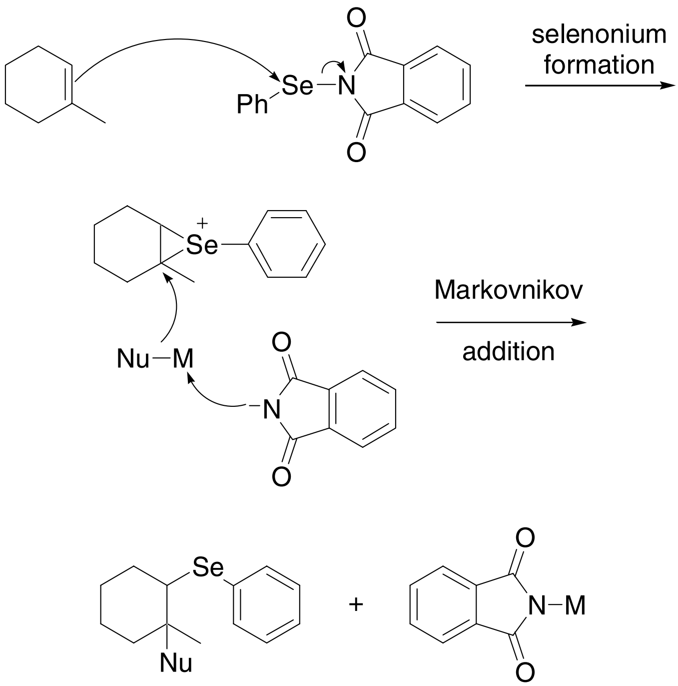
Activation of alkenes towards nucleophilic attack by a variety of nucleophiles employing *N*-phenylselenophthalimide or *N*-phenylselenosuccinimide as an electrophilic source of the phenylseleno group.

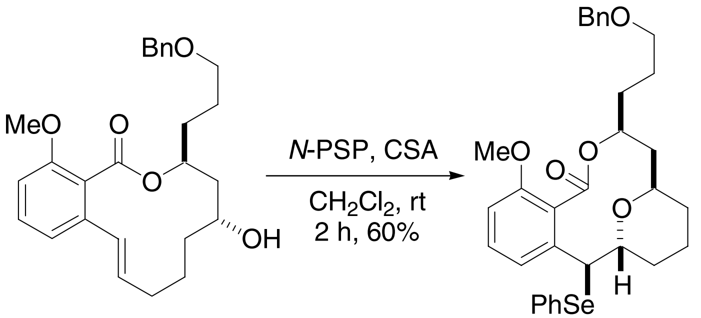
N-PSP = *N*-phenylselenophthalimide   *N*-PSS = *N*-phenylselenosuccinimide



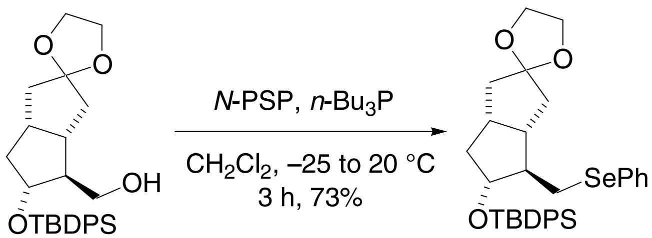
The reagent may require acid activation depending on the type of transformation being attempted. The mechanism parallels that of halohydrin formation using an electrophilic source of halide in an aqueous medium:



Example 1[3]



Example 2, in addition to oxyselenide formation, carbo- and heteroseleno cyclization, *N*-PSP can be used to generate selenides from alcohols and selenol esters from carboxylic acids, respectively, in the presence of a stoichiometric amount of *n*-Bu_3P.[6]



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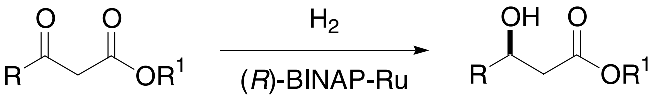
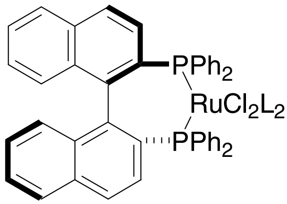
Noyori asymmetric hydrogenation

Asymmetric reduction of carbonyl *via* hydrogenation catalyzed by ruthenium(II) BINAP complex.

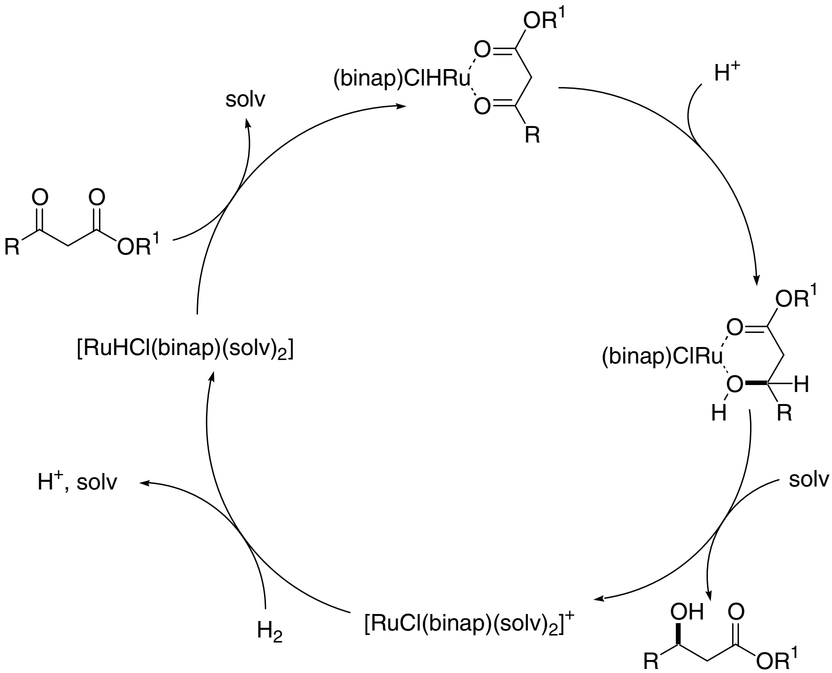


(*R*)-BINAP-Ru =

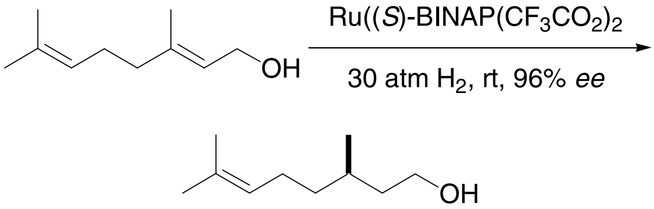


$$[\mathrm{RuCl_2(binap)(solv)_2}] \xrightarrow[-\,\mathrm{HCl}]{\mathrm{H_2}} [\mathrm{RuHCl(binap)(solv)_2}]$$

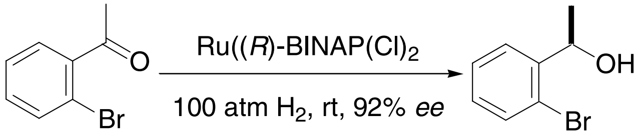
The catalytic cycle:



Example 1[2]



Example 2[3]



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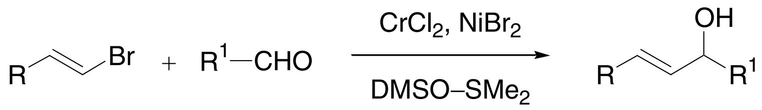
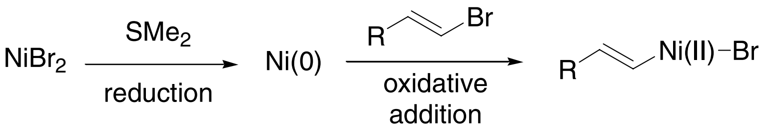
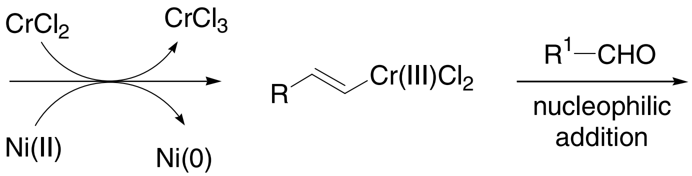
Nozaki–Hiyama–Kishi reaction

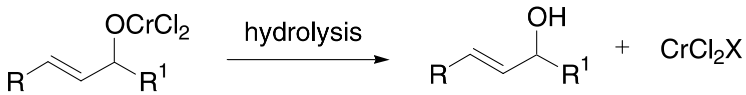
Cr−Ni bimetallic catalyst-promoted redox addition of vinyl halides to aldehydes.



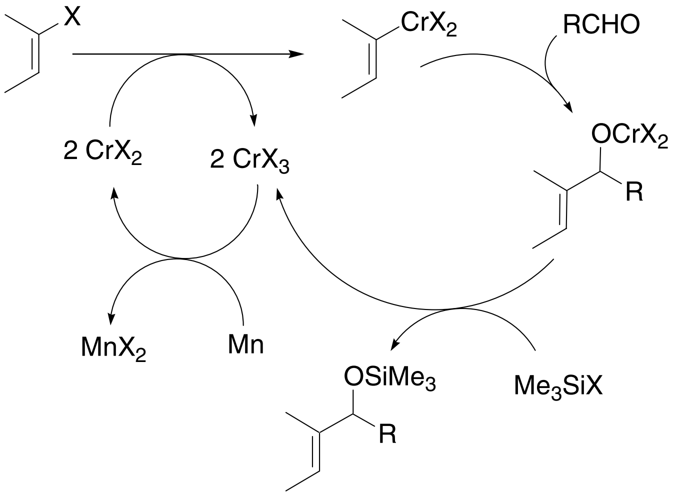




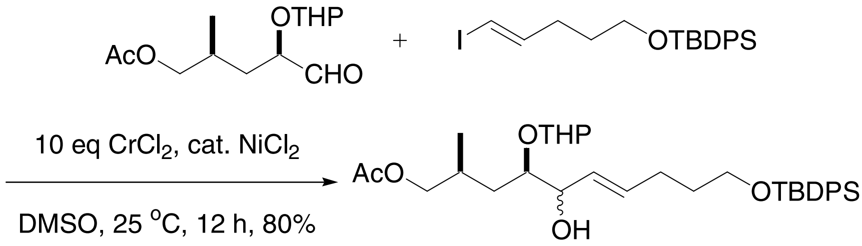
Transmetalation and then reduction by Me_2S



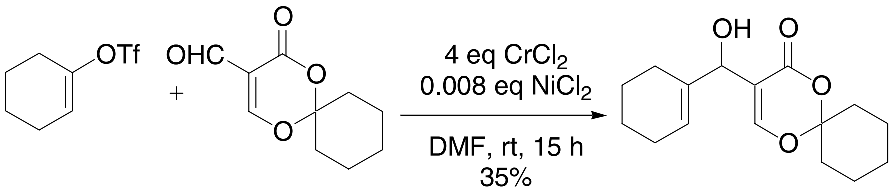
The catalytic cycle:[7]



Example 1[8]



Example 2[12]



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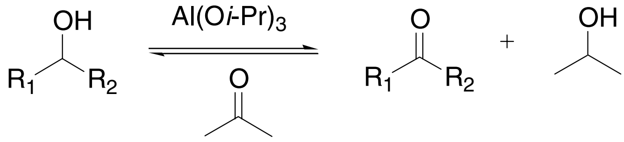
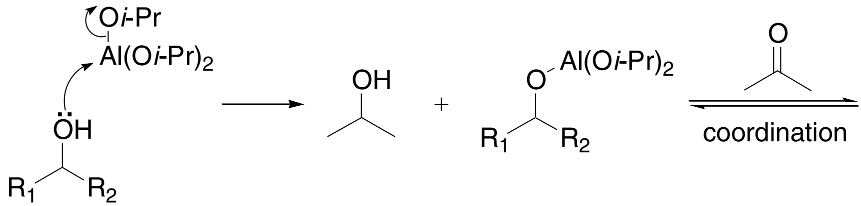
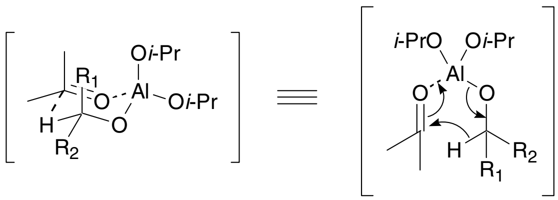
Oppenauer oxidation

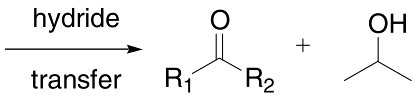
Alkoxide-catalyzed oxidation of secondary alcohols.



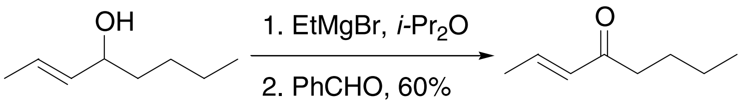




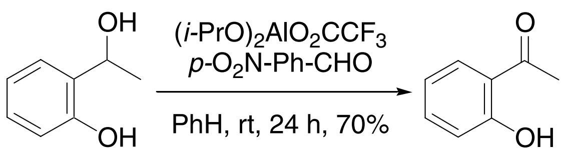
cyclic transition state



Example 1, magnesium Oppenauer oxidation[3]



Example 2[12]



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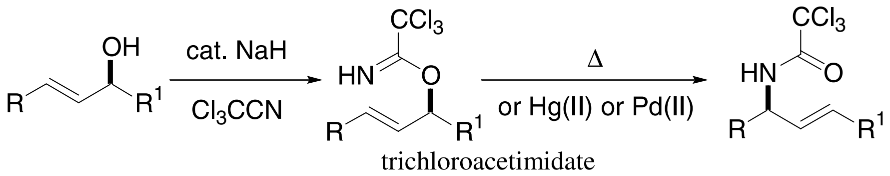
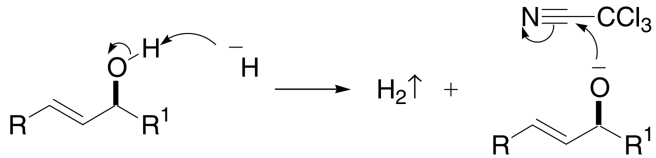
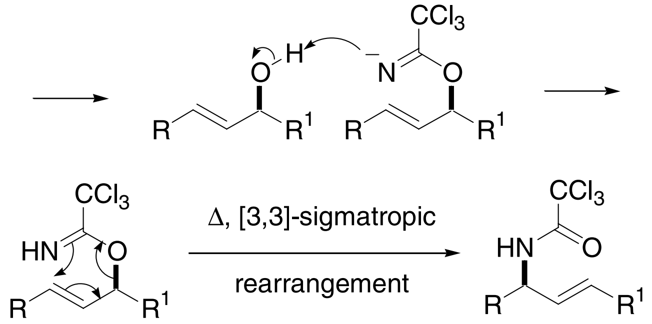
Overman rearrangement

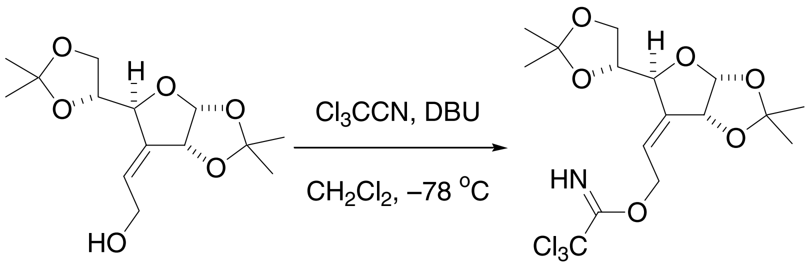
Stereoselective transformation of allylic alcohol to allylic trichloroacetamide *via* trichloroacetimidate intermediate.

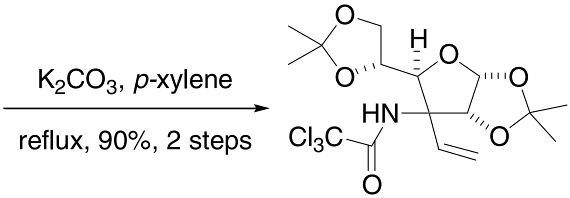




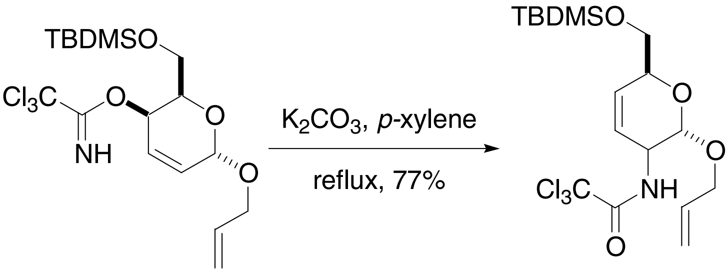


Example 1[13]





Example 2[14]



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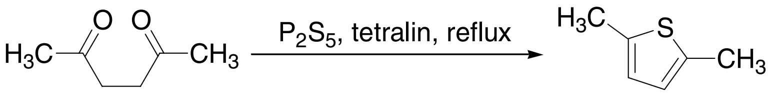
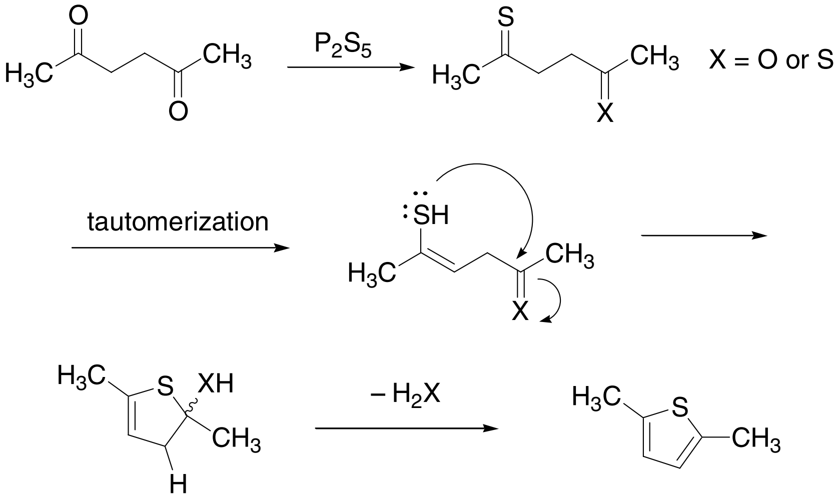
Paal thiophene synthesis

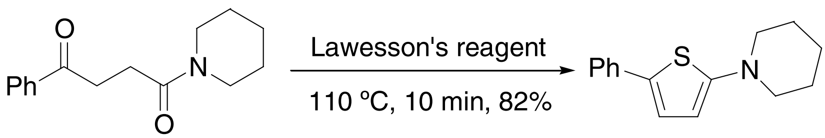
Thiophene synthesis from addition of a sulfur atom to 1,4-dicarbonyl compounds and subsequent dehydration.



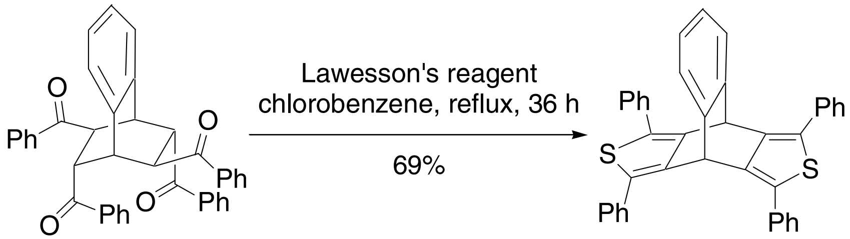
The reaction now is frequently carried out using the Lawesson's reagent. For the mechanism of carbonyl to thiocarbonyl transformation, see Lawesson's reagent on page 348.



Example 1[4]



Example 2[8]



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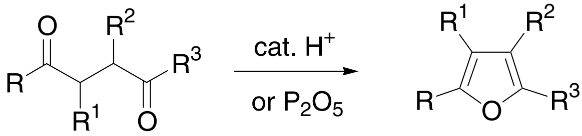
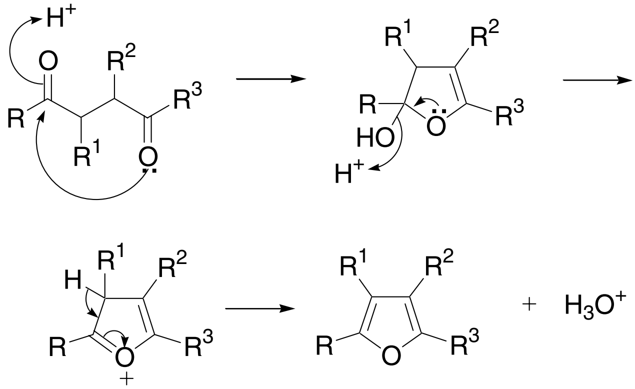
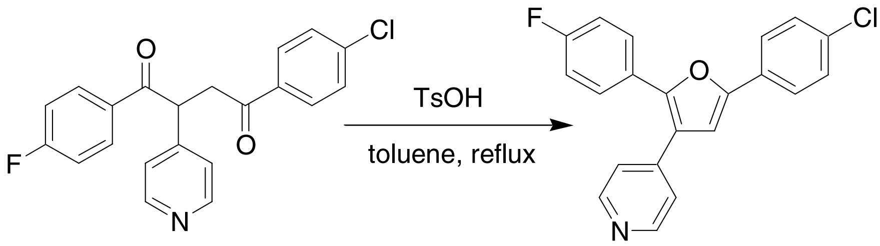
Paal–Knorr furan synthesis

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

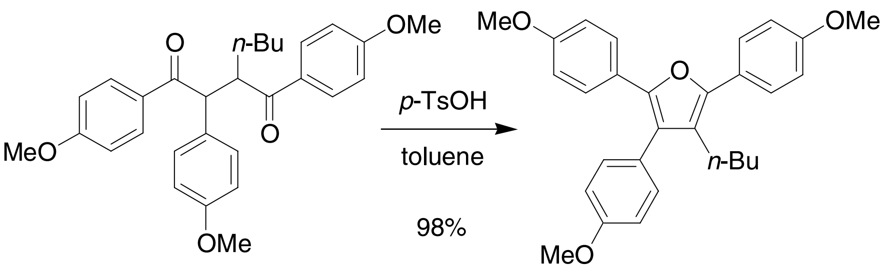




Example 1[10]



Example 2[14]



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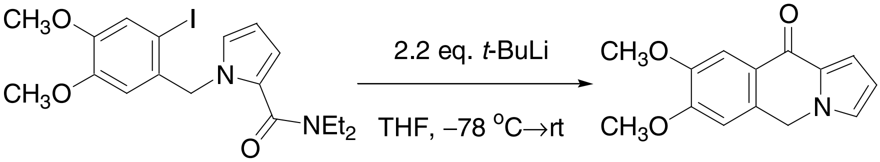
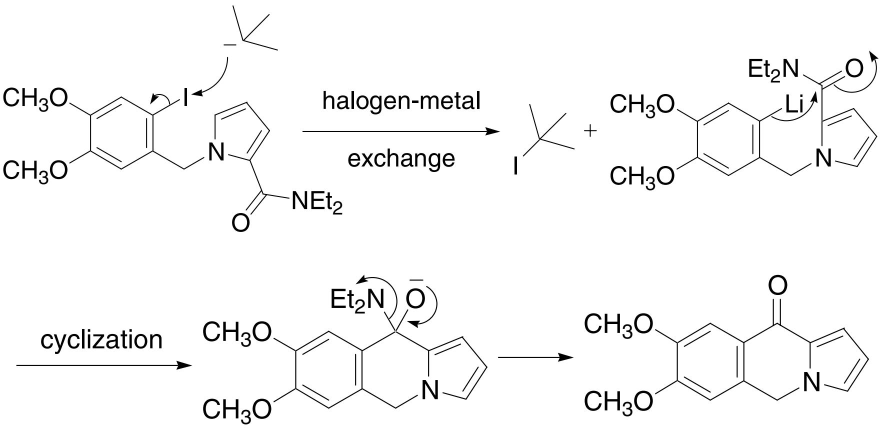
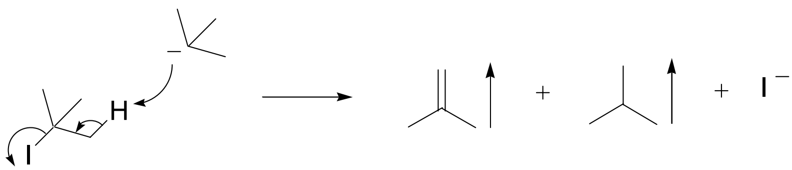
Parham cyclization

Annulation of aryl halides with *ortho* side chains bearing a pendant electrophilic moiety *via* treatment with an organolithium reagent, involving halogen-metal exchange and subsequent nucleophilic cyclization to form 4- to 7-membered rings.

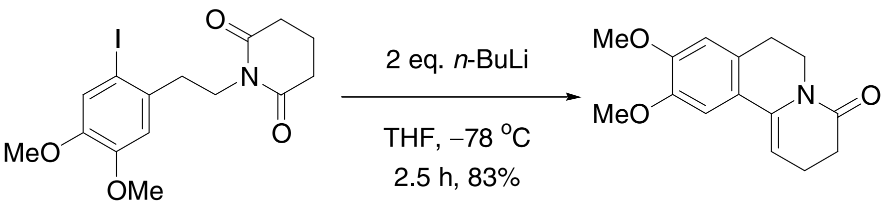




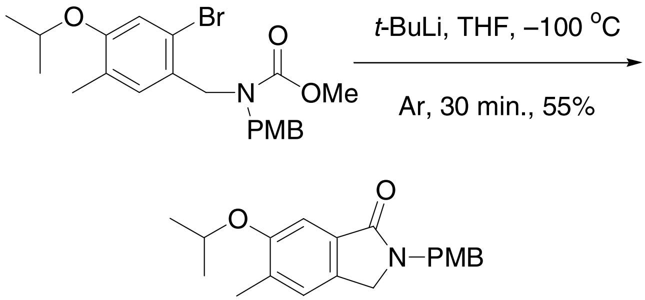
The fate of the second equivalent of *t*-BuLi:



Example 1[9]



Example 2[16]



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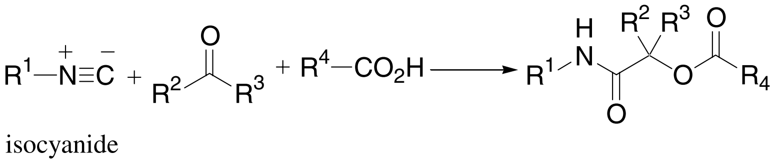
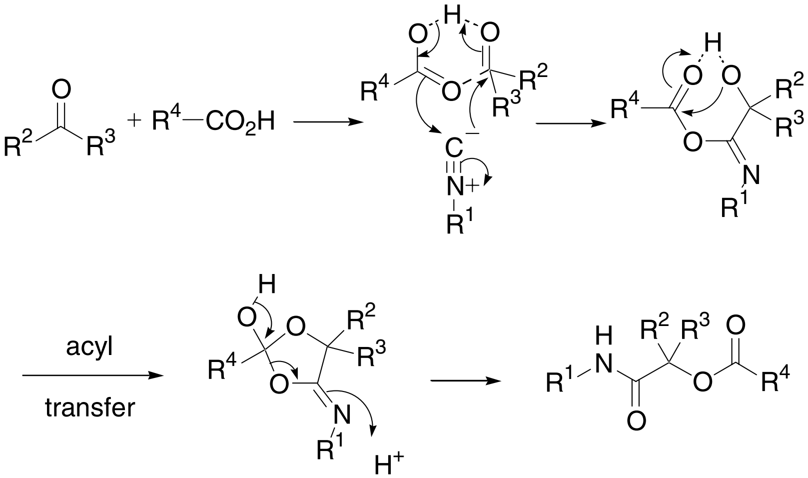
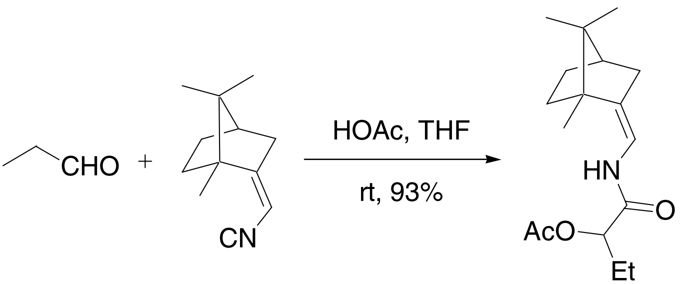
Passerini reaction

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

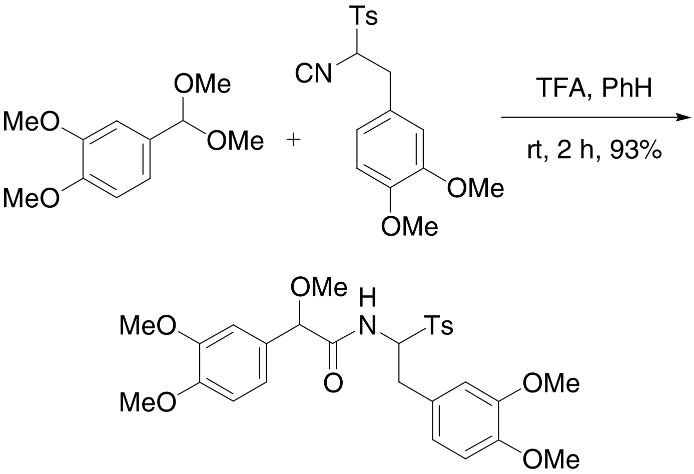




Example 1[5]



Example 2[3]



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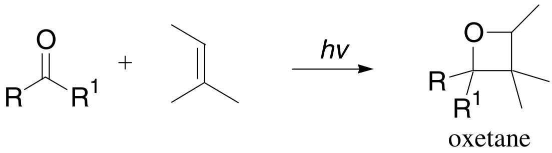
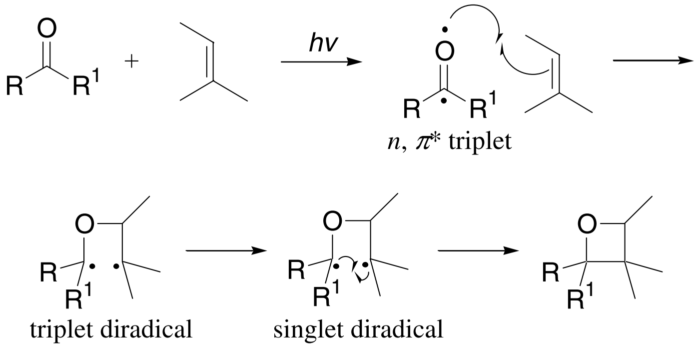
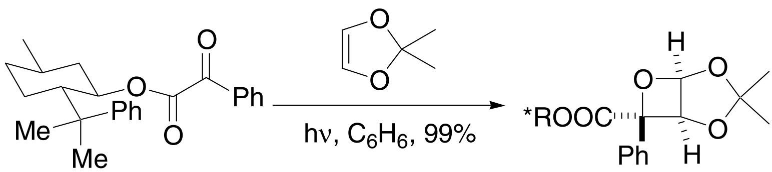
Paternó–Büchi reaction

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

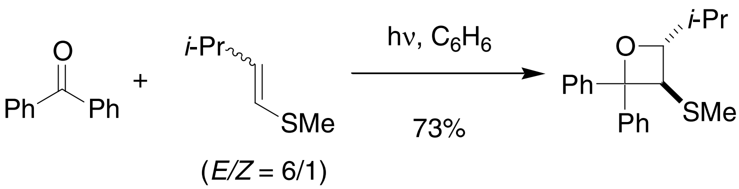




Example 1[4]



Example 2[6]



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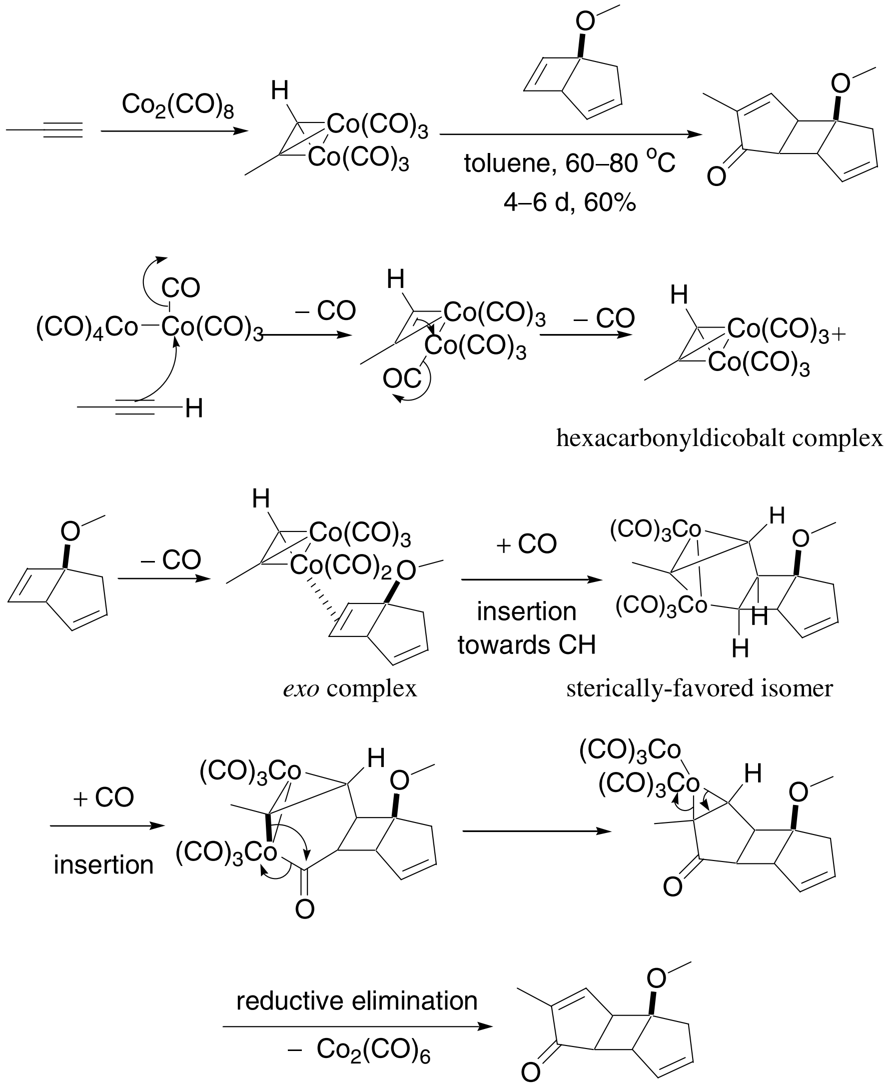
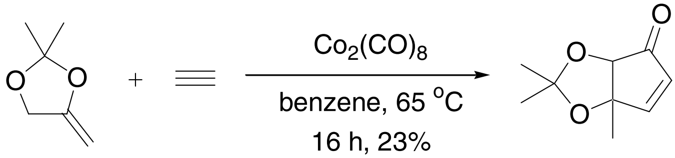
Pauson−Khand cyclopentenone synthesis

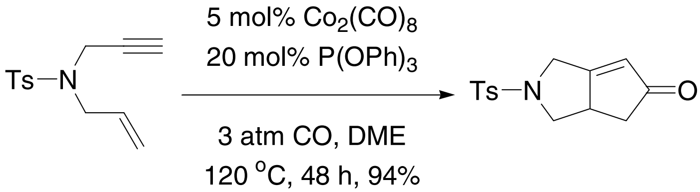
Formal [2 + 2 +1] cycloaddition of an alkene, alkyne, and carbon monoxide mediated by octacarbonyl dicobalt.



Example 1[6]



Example 2, a catalytic version[9]



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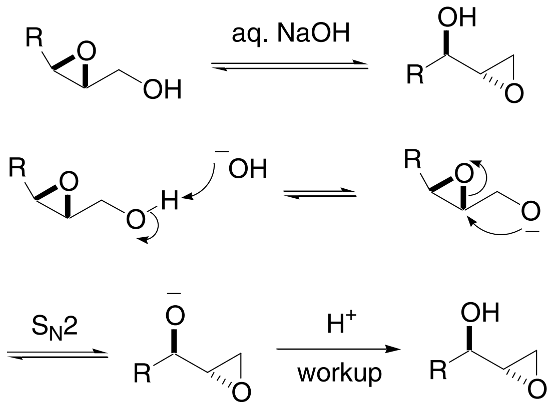
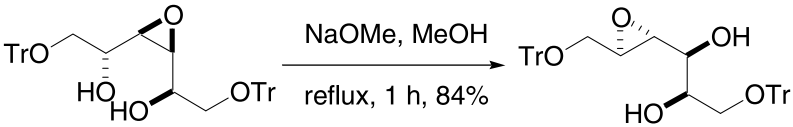
Payne rearrangement

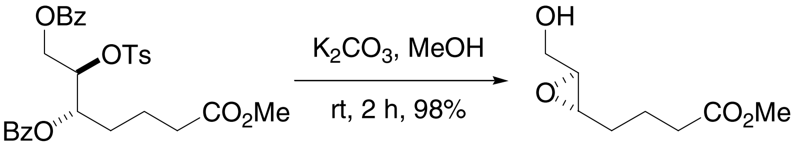
Base-promoted isomerization of 2,3-epoxy alcohols. Also known as epoxide migration.



Example 1[2]



Example 2[3]



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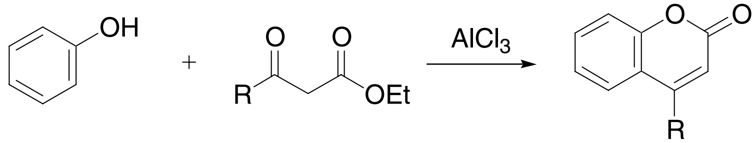
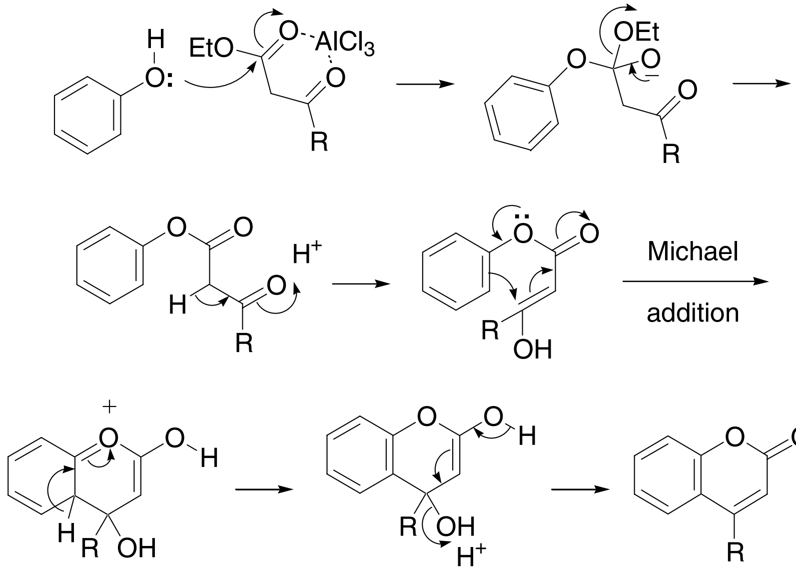
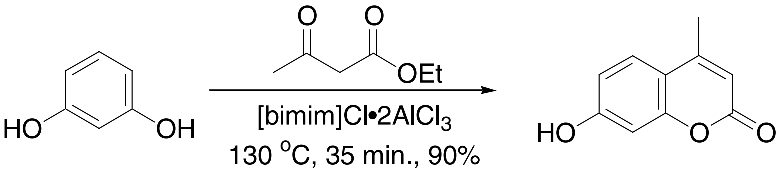
Pechmann coumarin synthesis

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



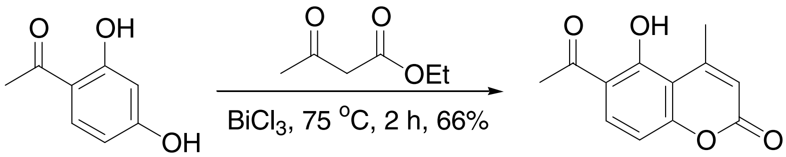


Example 1[11]



$[bimim]Cl•2AlCl_3$ = 1-Butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)

Example 2[14]



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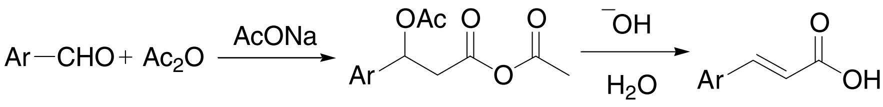
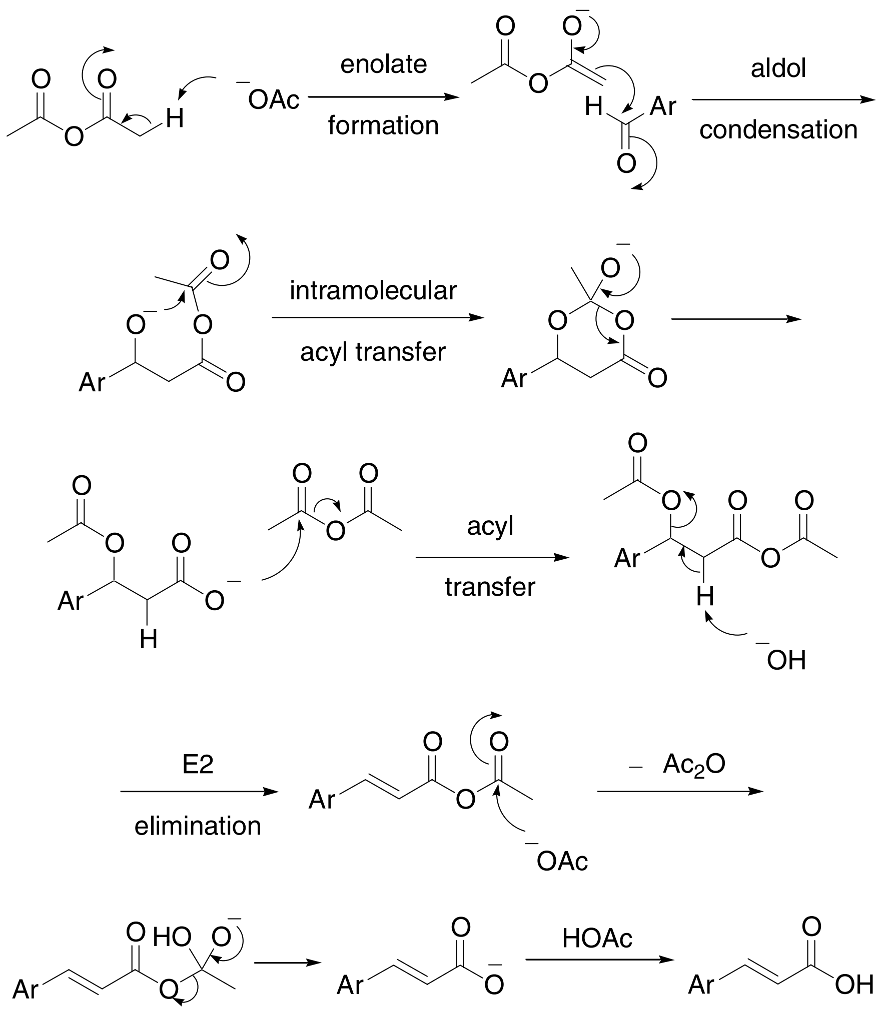
Perkin reaction

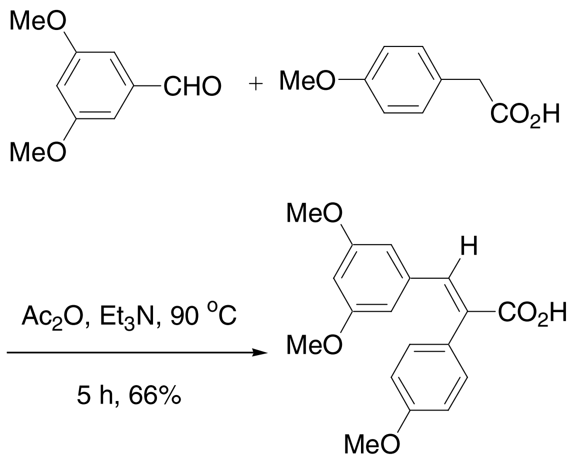
Cinnamic acid synthesis from aryl aldehyde and acetic anhydride.



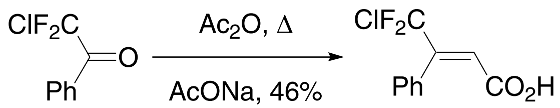
cinnamic acid



Example 1[9]



Example 2[10]



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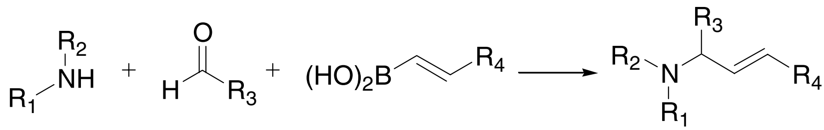
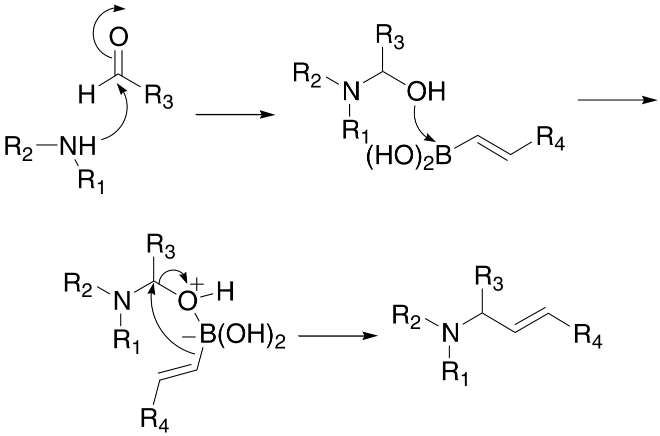
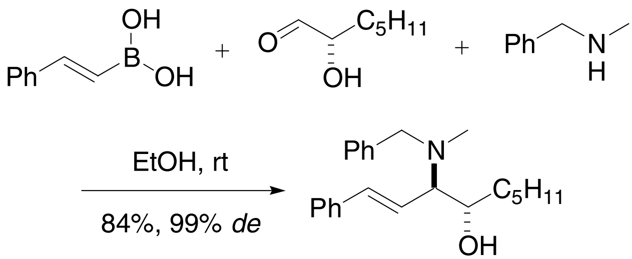
Petasis reaction

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.

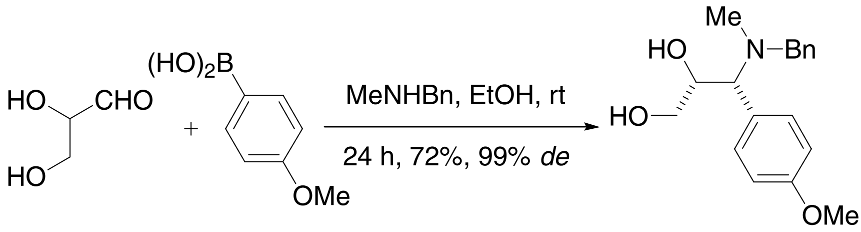




Example 1[5]



Example 2[7]



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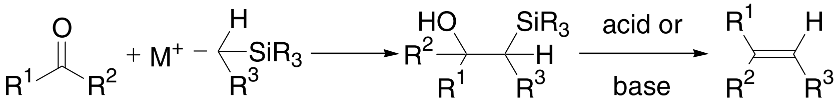
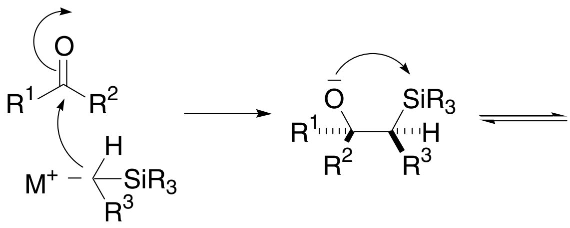
Peterson olefination

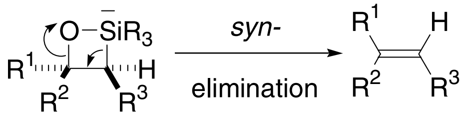
Alkenes from α-silyl carbanion and carbonyl compounds. Also known as sila-Wittig reaction.



Basic conditions:



β-silylalkoxide intermediate



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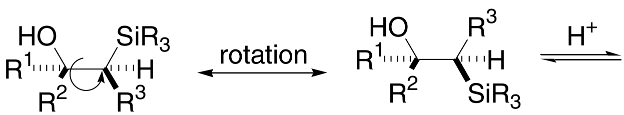
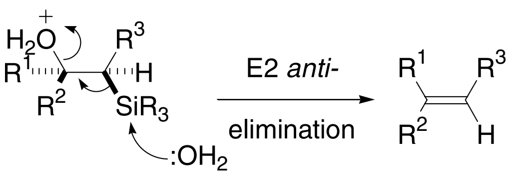
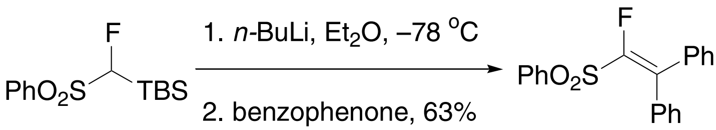


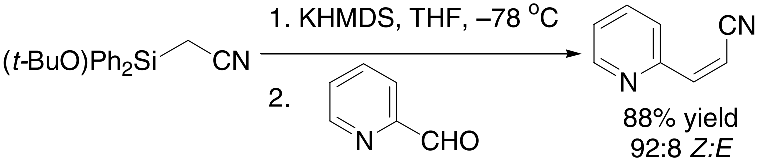
β-hydroxysilane



Example 1[10]



Example 2[12]



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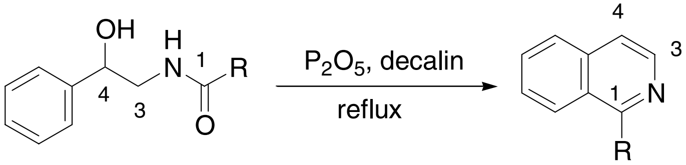
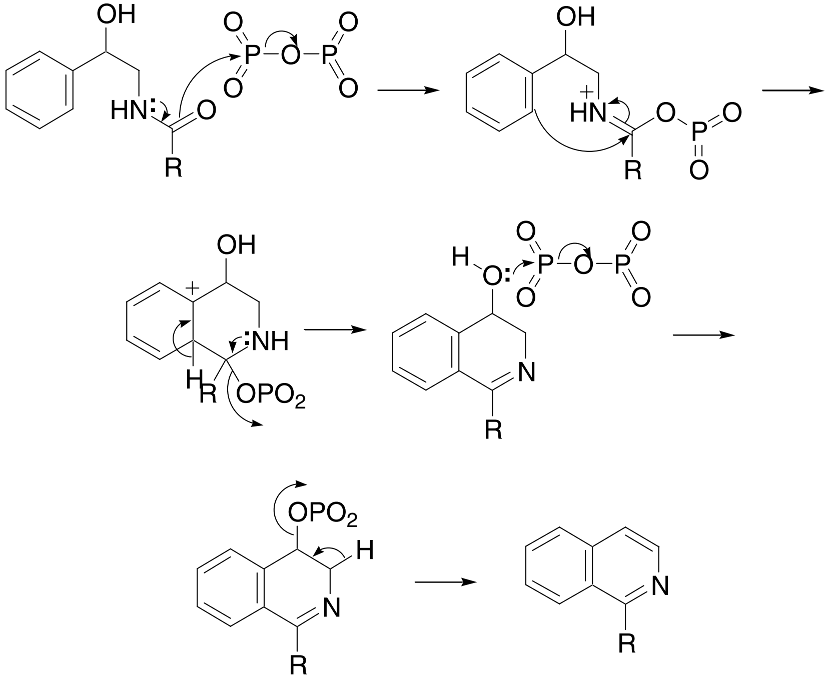
Pictet–Gams isoquinoline synthesis

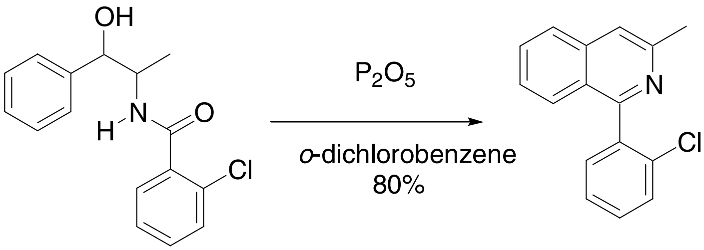
The isoquinoline framework is derived from the corresponding acyl derivatives of β-hydroxy-β-phenylethylamines. Upon exposure to a dehydrating agent such as phosphorus pentaoxide, or phosphorus oxychloride, under reflux conditions and in an inert solvent such as decalin, isoquinoline frameworks are formed.



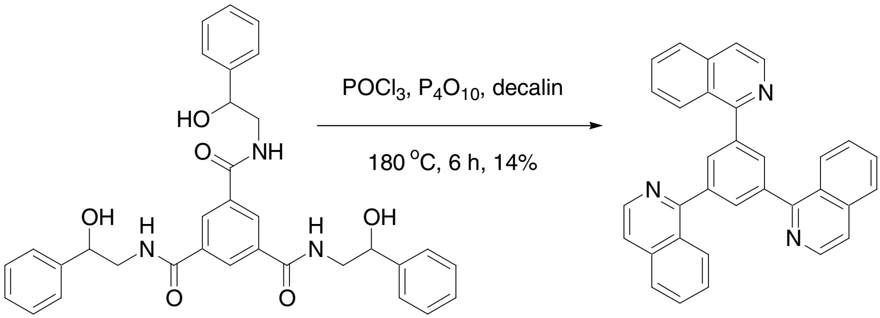
P_2O_5 actually exists as P_4O_{10}, an adamantane-like structure.



Example 1[10]



Example 2[7]



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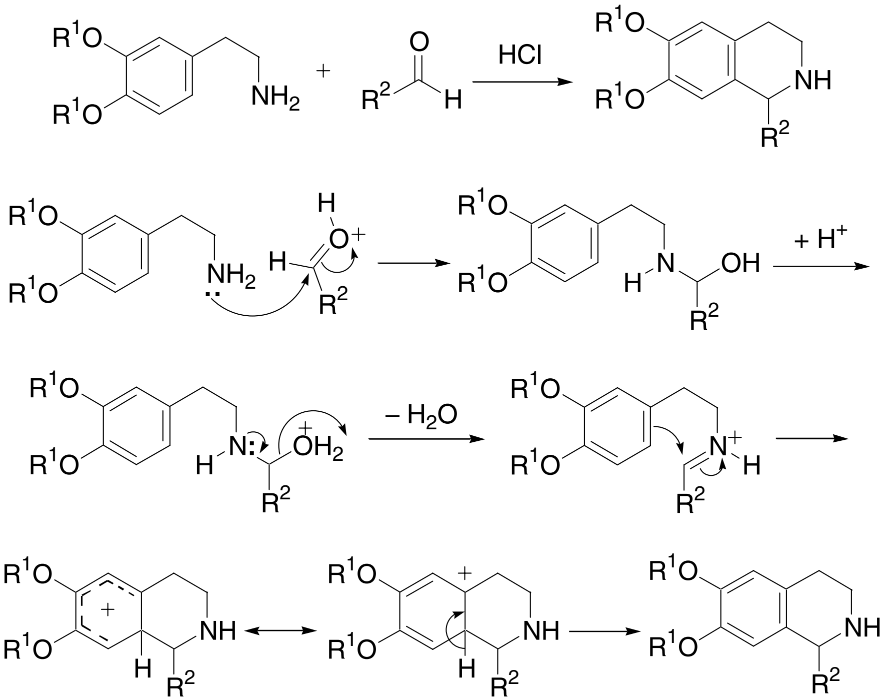
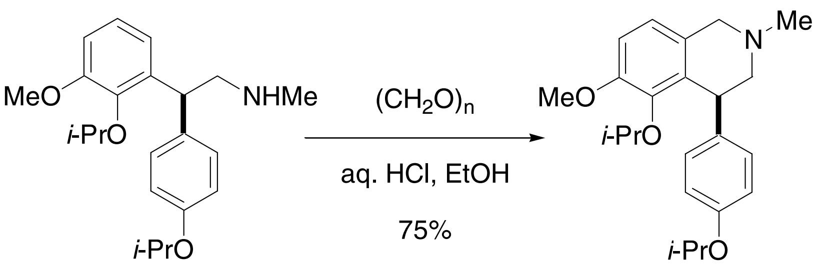
Pictet–Spengler tetrahydroisoquinoline synthesis

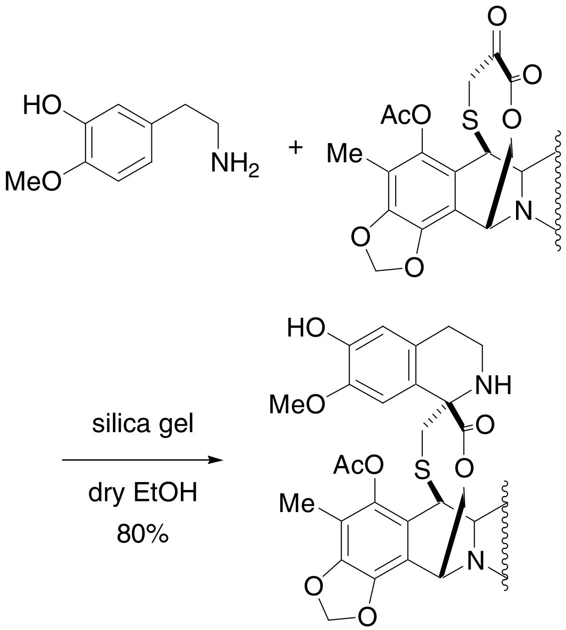
Tetrahydroisoquinolines from condensation of β-arylethylamines and carbonyl compounds followed by cyclization.



Example 1[12]



Example 2[9]



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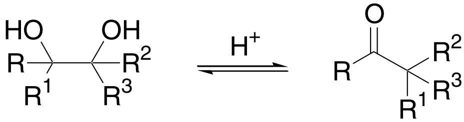
Pinacol rearrangement

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

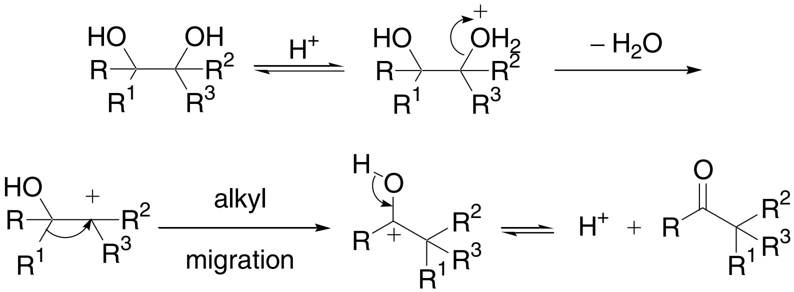


The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order:

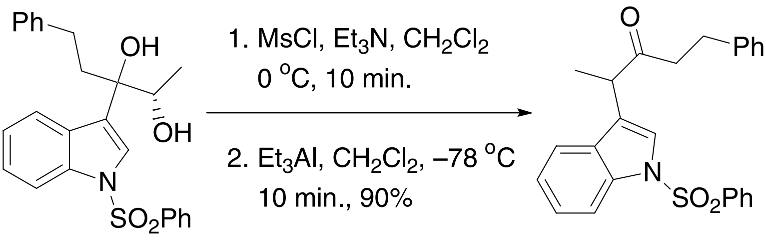
tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > methyl >> H.

For substituted aryls:

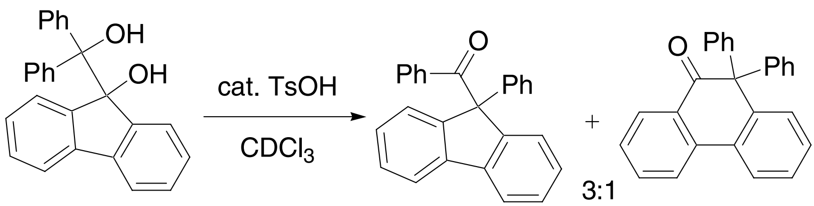
p-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O_2N-Ar



Example 1[12]



Example 2[14]



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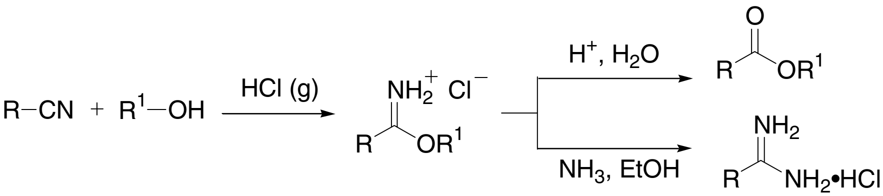
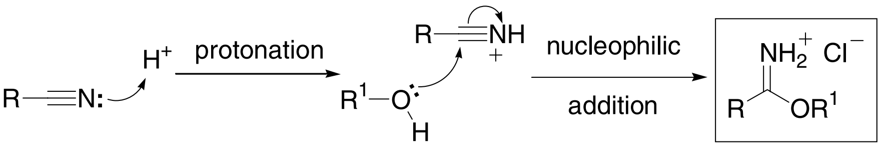
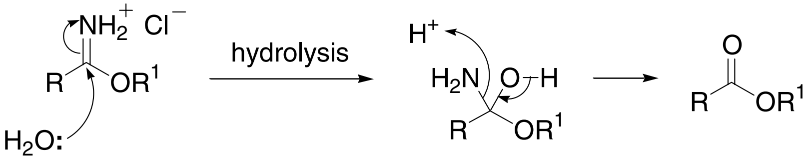
Pinner reaction

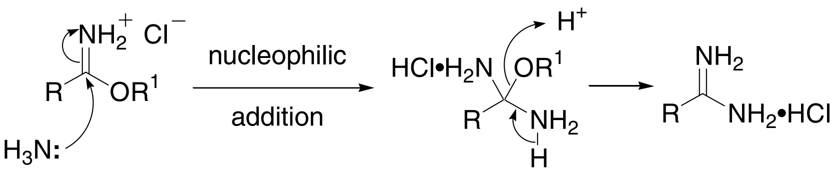
Transformation of a nitrile into an imino ether, which can be converted to either an ester or an amidine.



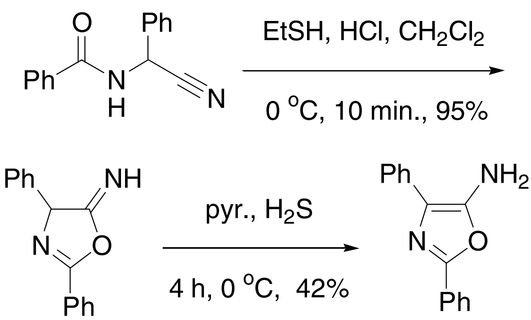


common intermediate

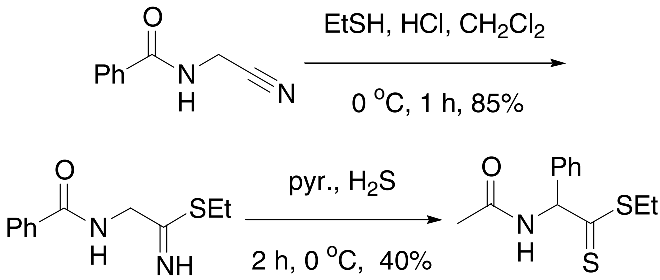




Example 1[3]



Example 2[3]



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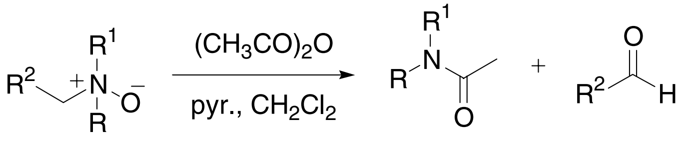
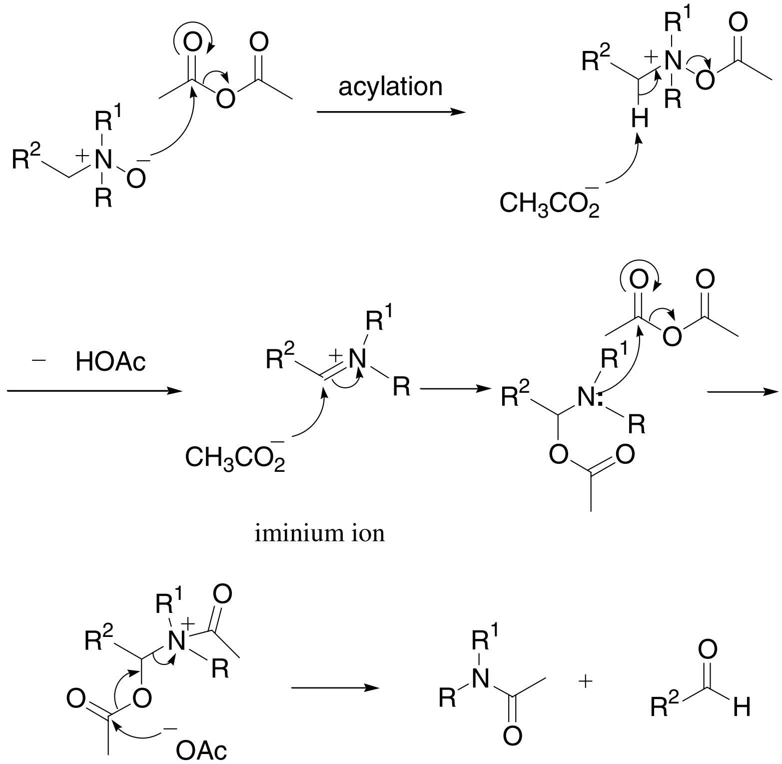
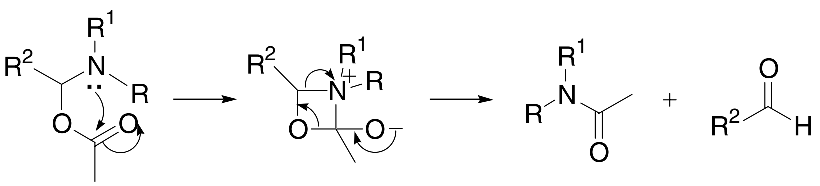
Polonovski reaction

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.

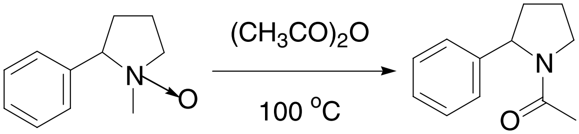




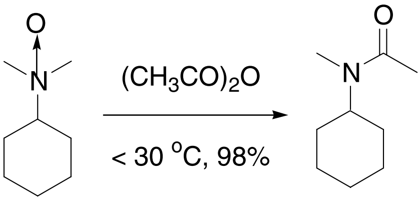
The intramolecular pathway is also possible:



Example 1[1]



Example 2[2]



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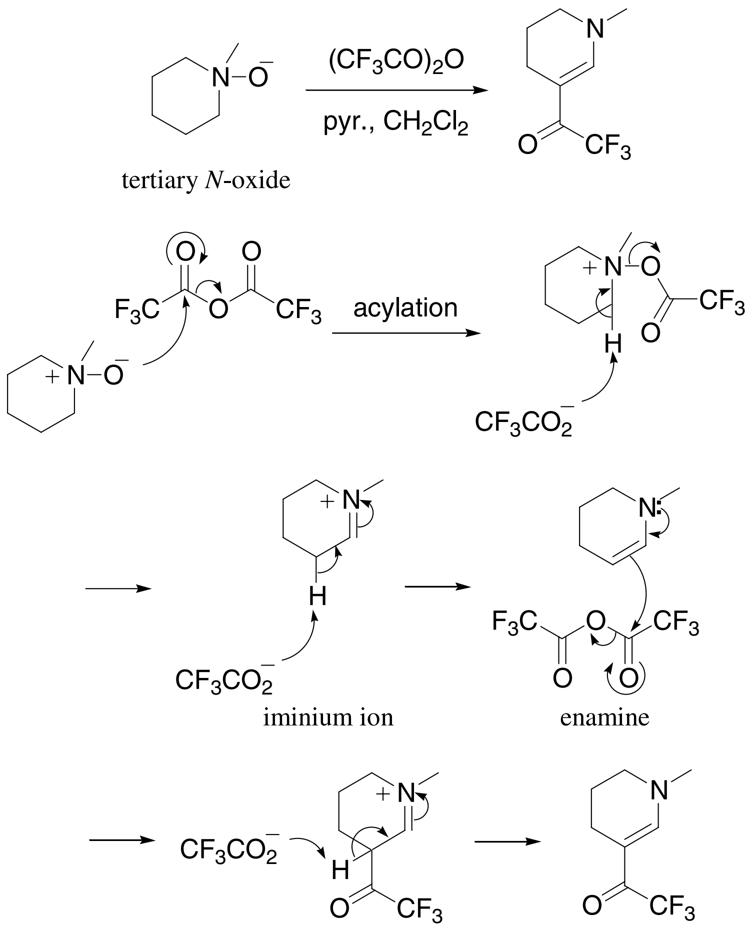
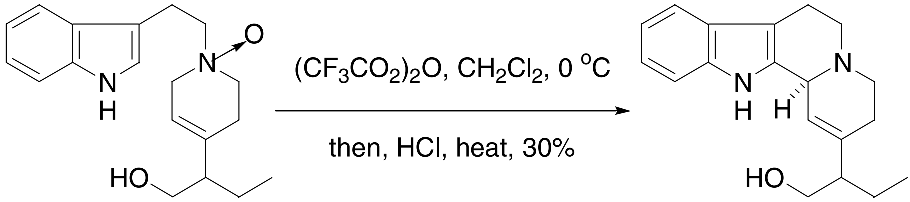
Polonovski–Potier reaction

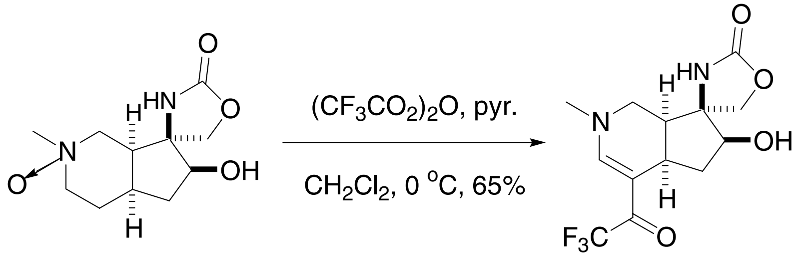
A modification of the Polonovski reaction where trifluoroacetic anhydride is used in place of acetic anhydride. Because the reaction conditions for the Polonovski–Potier reaction are mild, it has largely replaced the Polonovski reaction.



Example 1[2]



Example 2[5]



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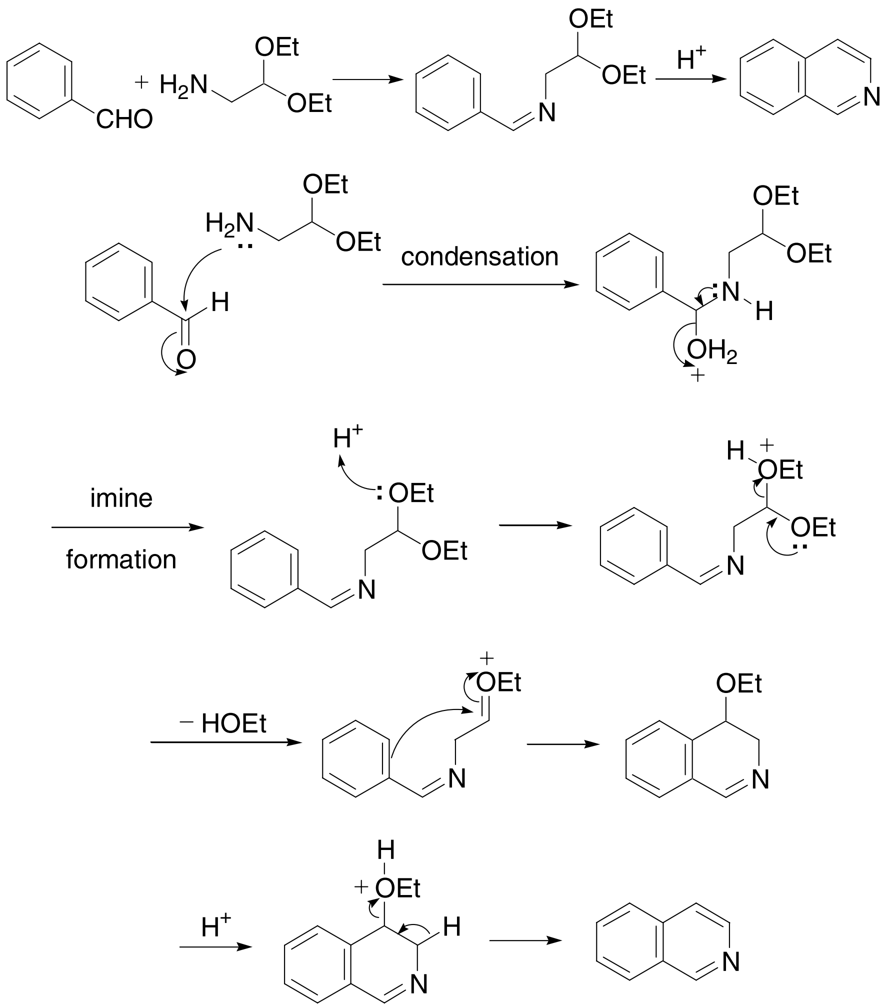
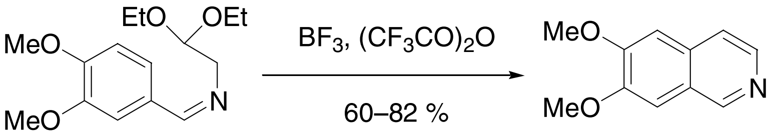
Pomeranz–Fritsch reaction

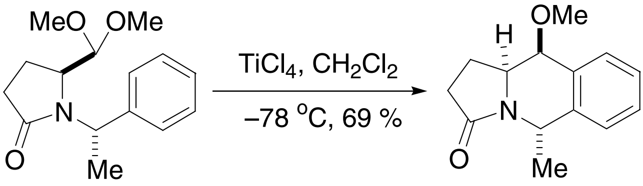
Isoquinoline synthesis *via* acid-mediated cyclization of the appropriate aminoacetal intermediate.



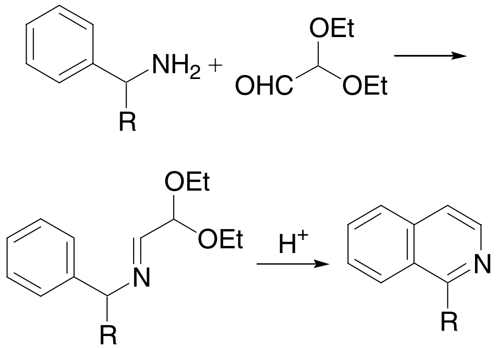
Example 1[5]



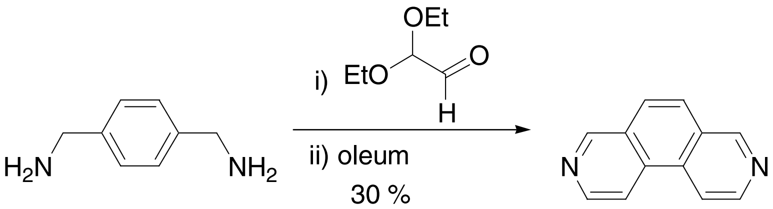
Example 2[12]



Schlittler–Müller modification



Example 3[7]



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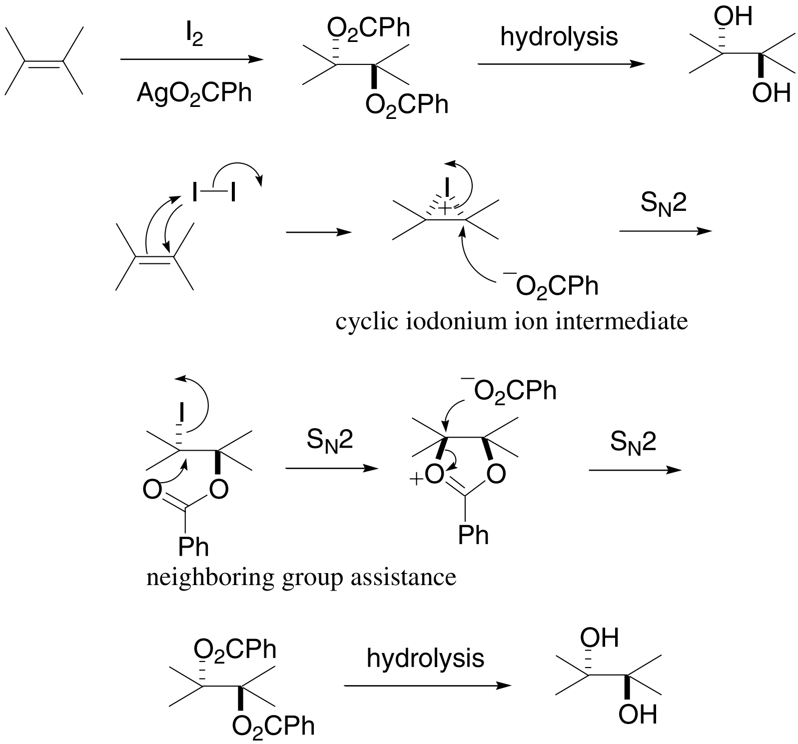
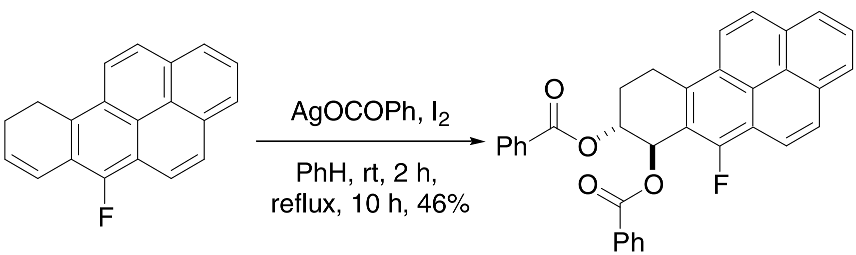
Prévost *trans*-dihydroxylation

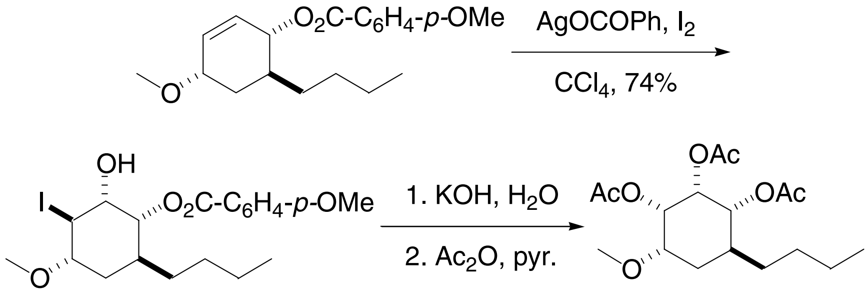
Cf. Woodward *cis*-dihydroxylation.



Example 1[8]

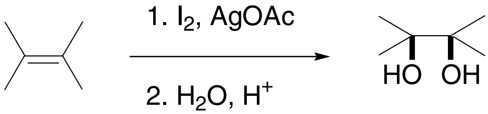


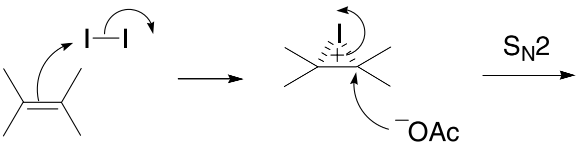
Example 2[12]



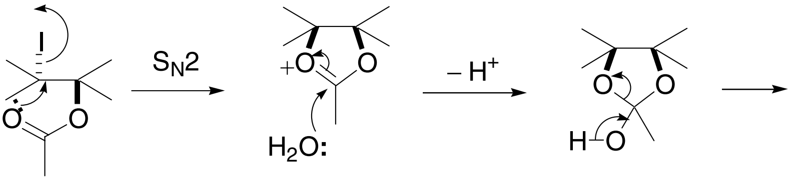
Woodward *cis*-dihydroxylation[13]

Cf. Prévost *trans*-dihydroxylation.

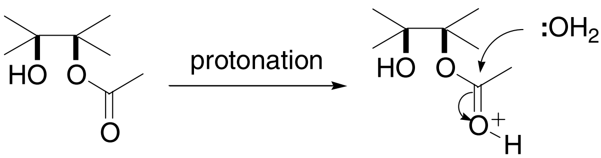


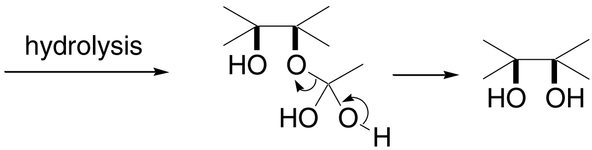


cyclic iodonium ion intermediate



neighboring group assistance





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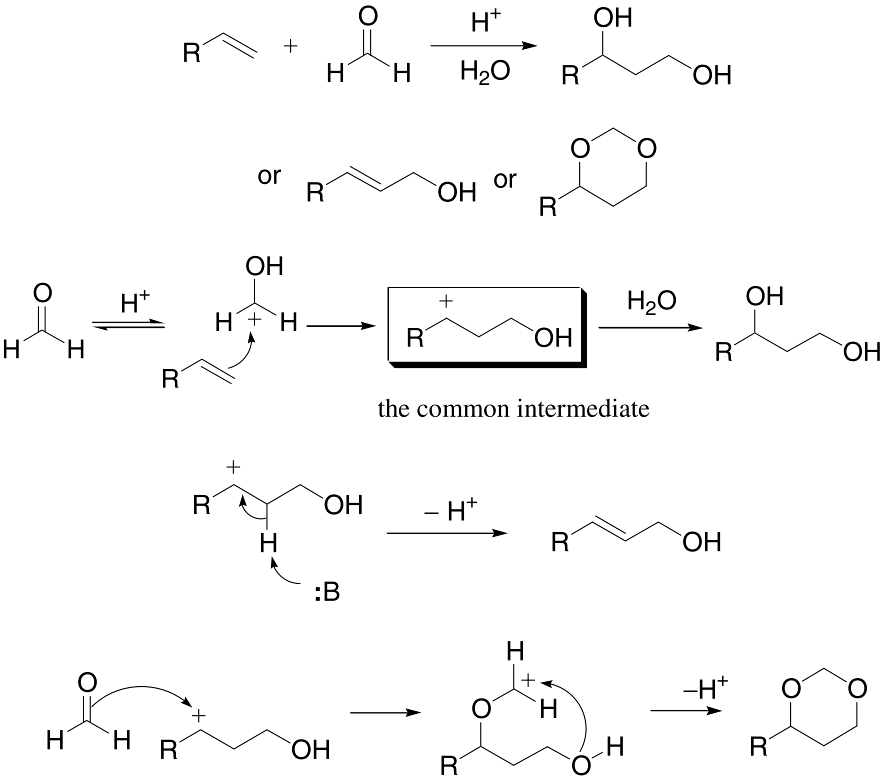
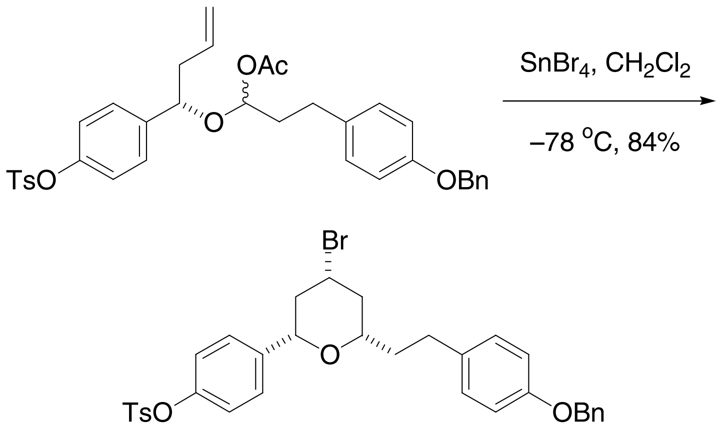
Prins reaction

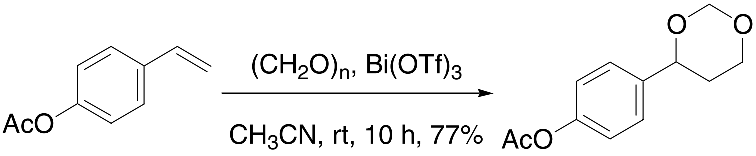
Addition of alkene to formaldehyde.



Example 1[8]



Example 2[10]



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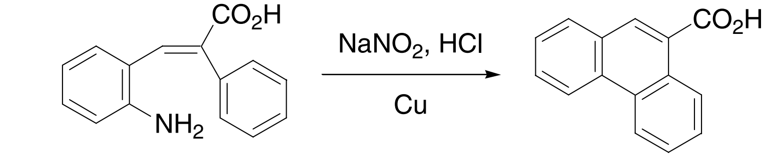
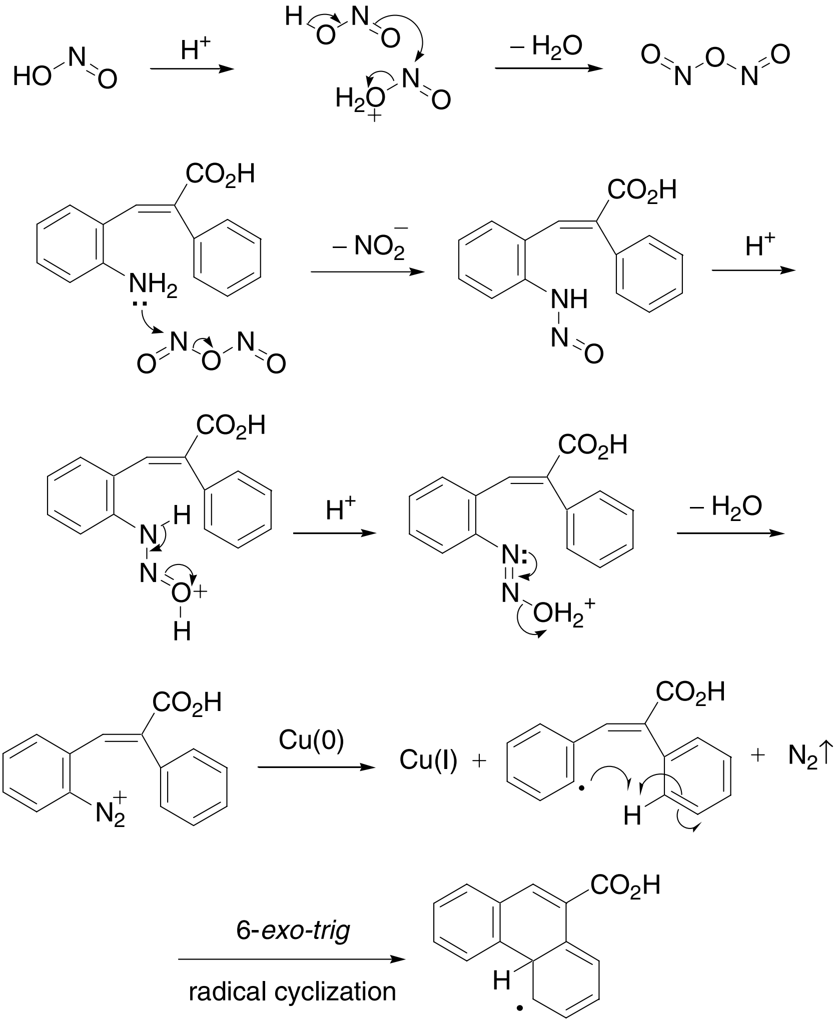
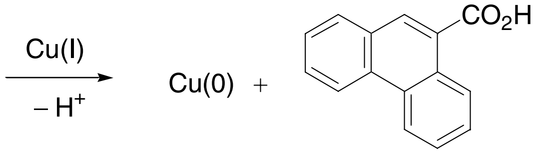
Pschorr cyclization

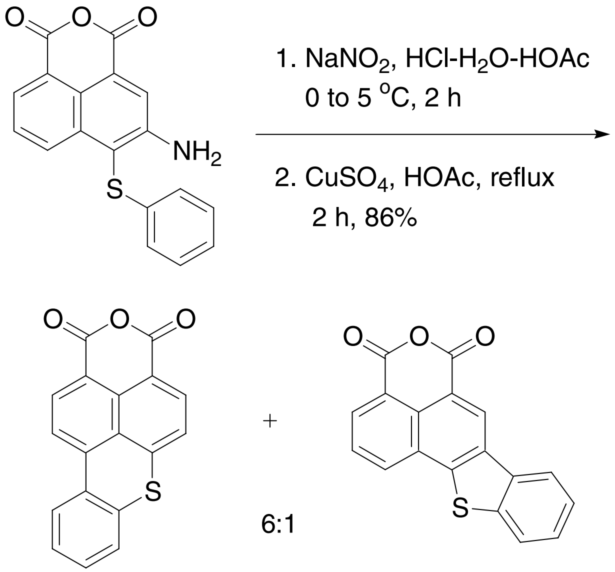
The intramolecular version of the Gomberg–Bachmann reaction.



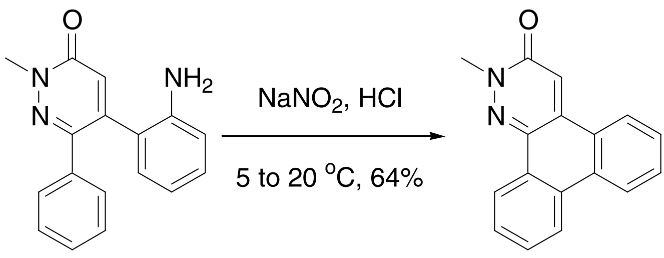




Example 1[10]



Example 2[11]



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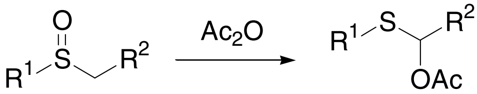
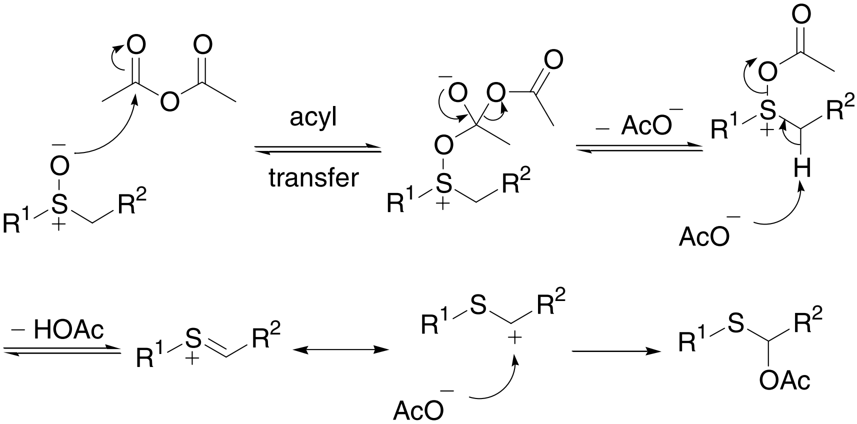
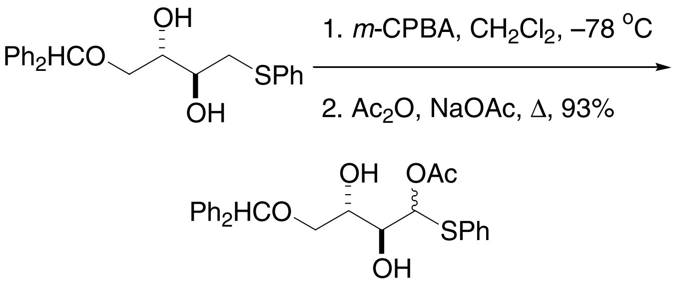
Pummerer rearrangement

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

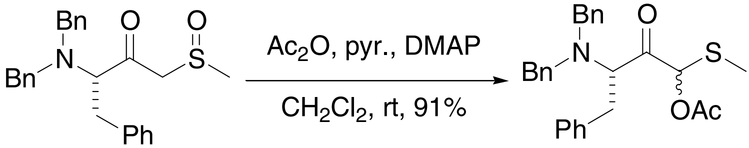




Example 1[2]



Example 2[13]



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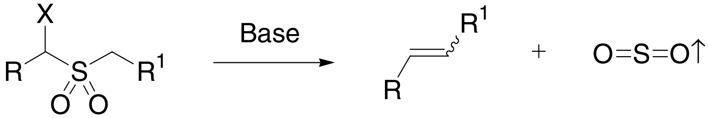
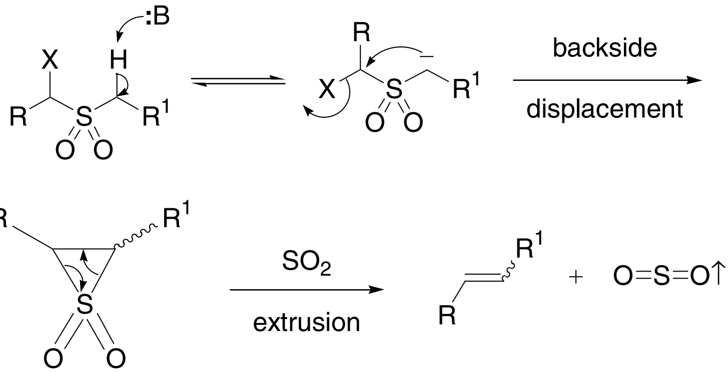
Ramberg–Bäcklund reaction

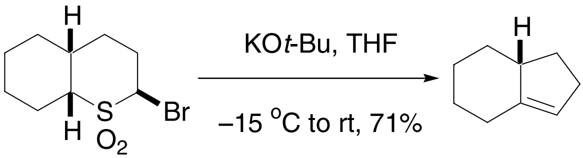
Olefin synthesis *via* α-halosulfone extrusion.



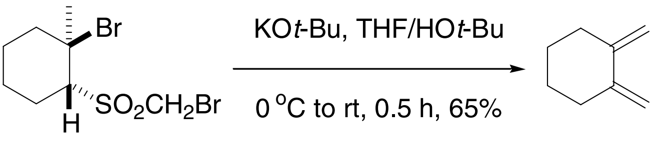


episulfone intermediate

Example 1[4]



Example 2[5]



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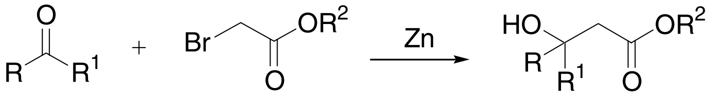
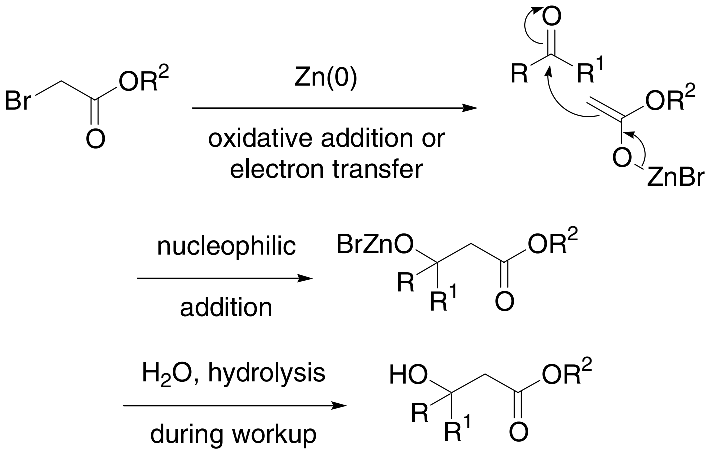
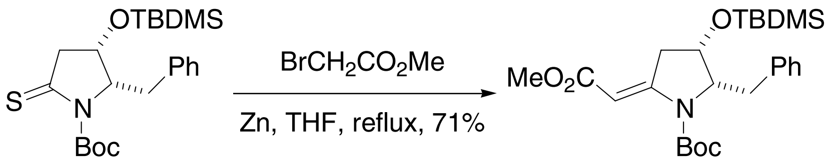
Reformatsky reaction

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

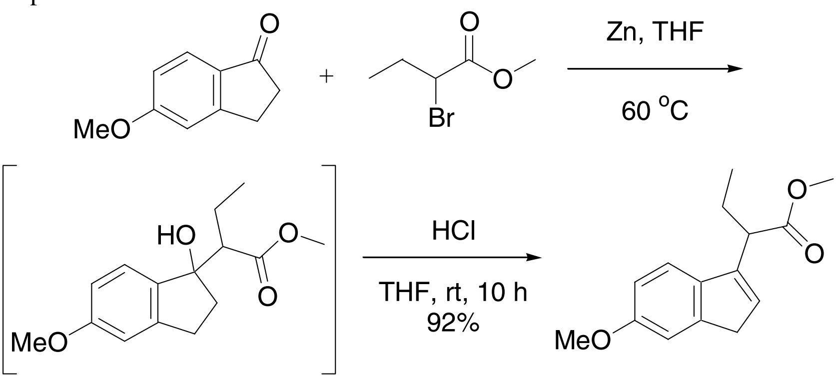




Example 1[5]



Example 2[11]



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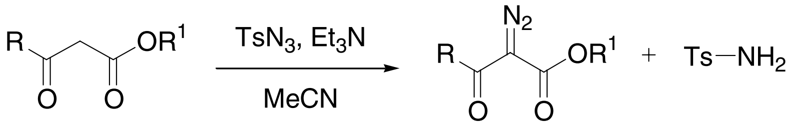
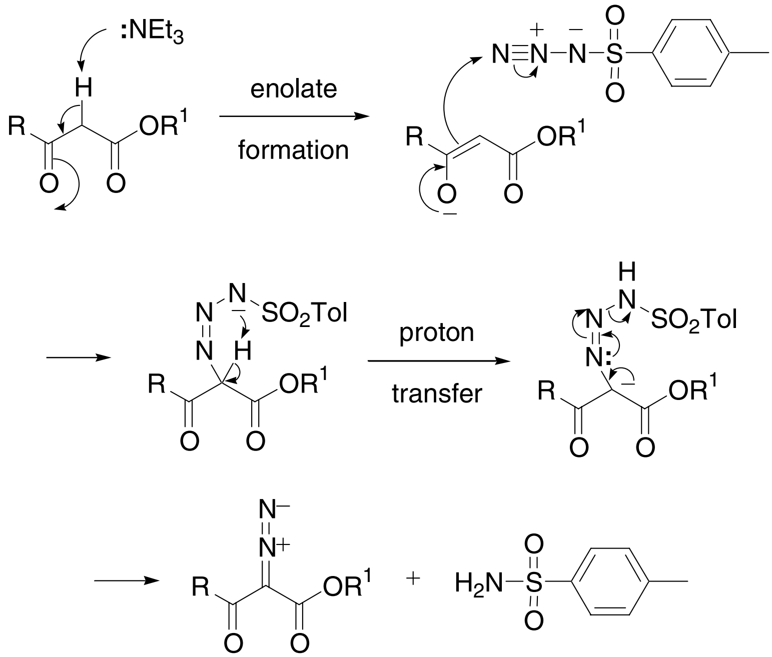
Regitz diazo synthesis

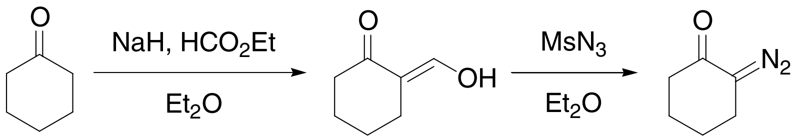
Synthesis of 2-diazo-1,3-dicarbonyl or 2-diazo-3-ketoesters using sulfonyl azide.

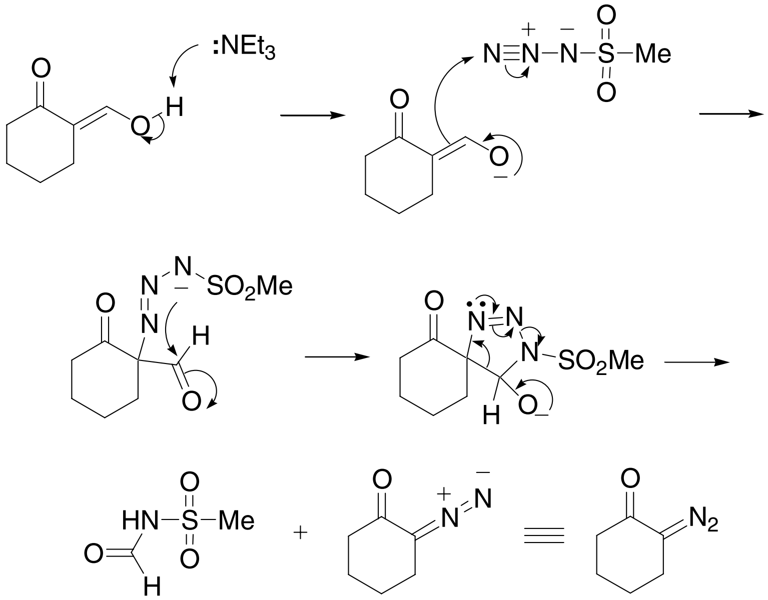




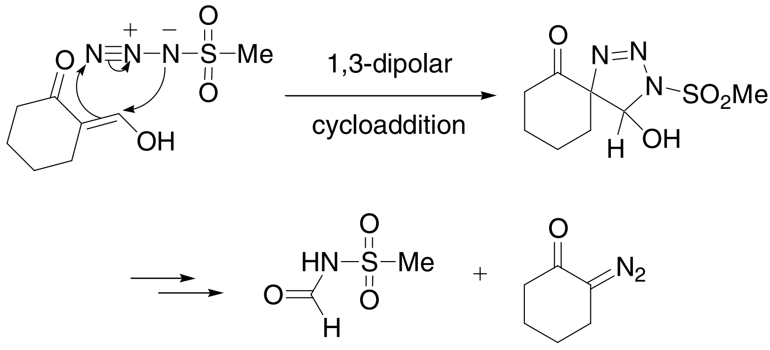
tosyl amide is the by-product

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

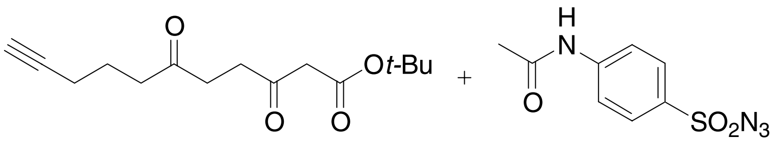


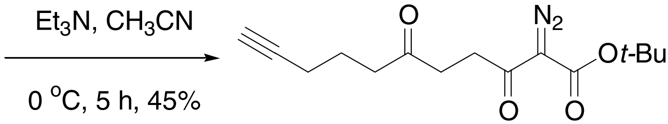


Alternatively, the triazole intermediate may be assembled *via* a 1,3-dipolar cycloaddition of the enol and mesyl azide:

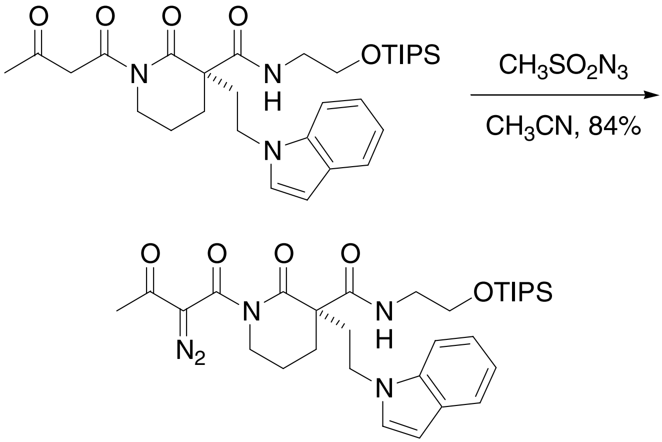


Example 1[10]





Example 2[6]



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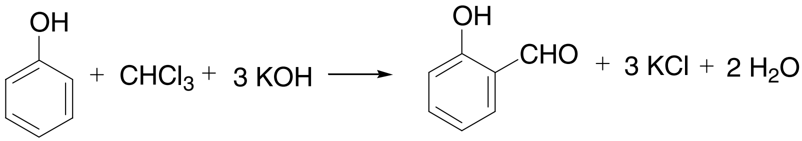
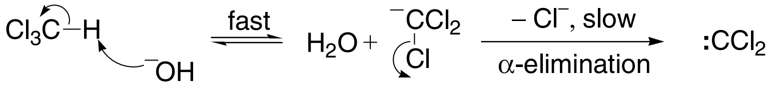
Reimer–Tiemann reaction

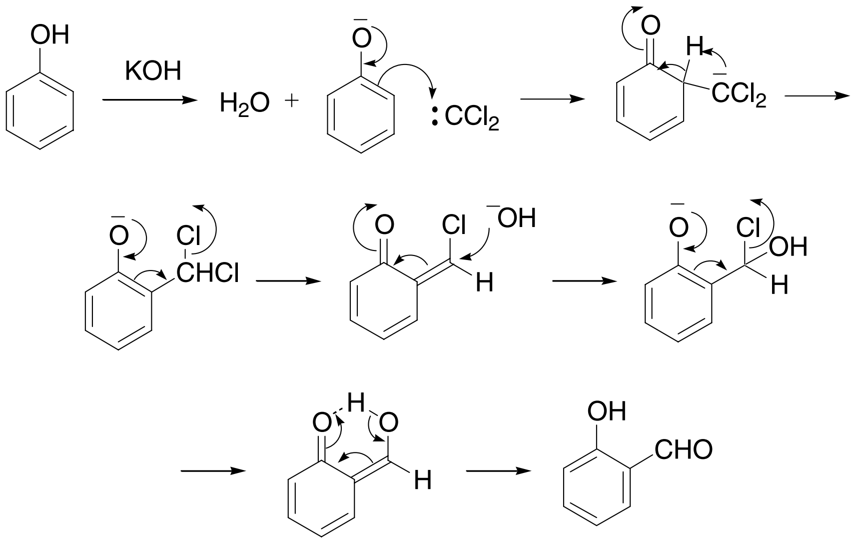
Synthesis of *o*-formylphenol from phenols and chloroform in alkaline medium.



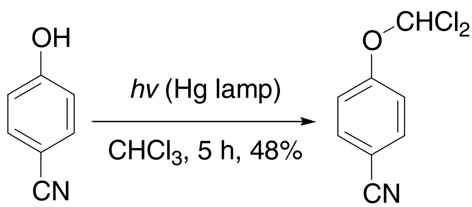
a. Carbene generation:



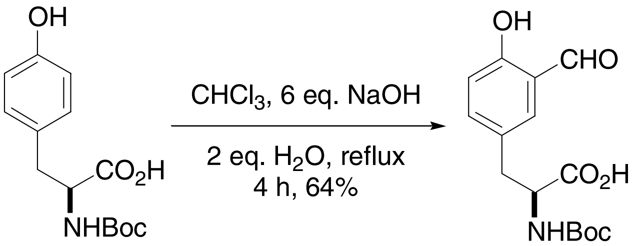
b. Addition of dichlorocarbene and hydrolysis:



Example 1, photo Reimer–Tiemann reaction without base[8]



Example 2[9]



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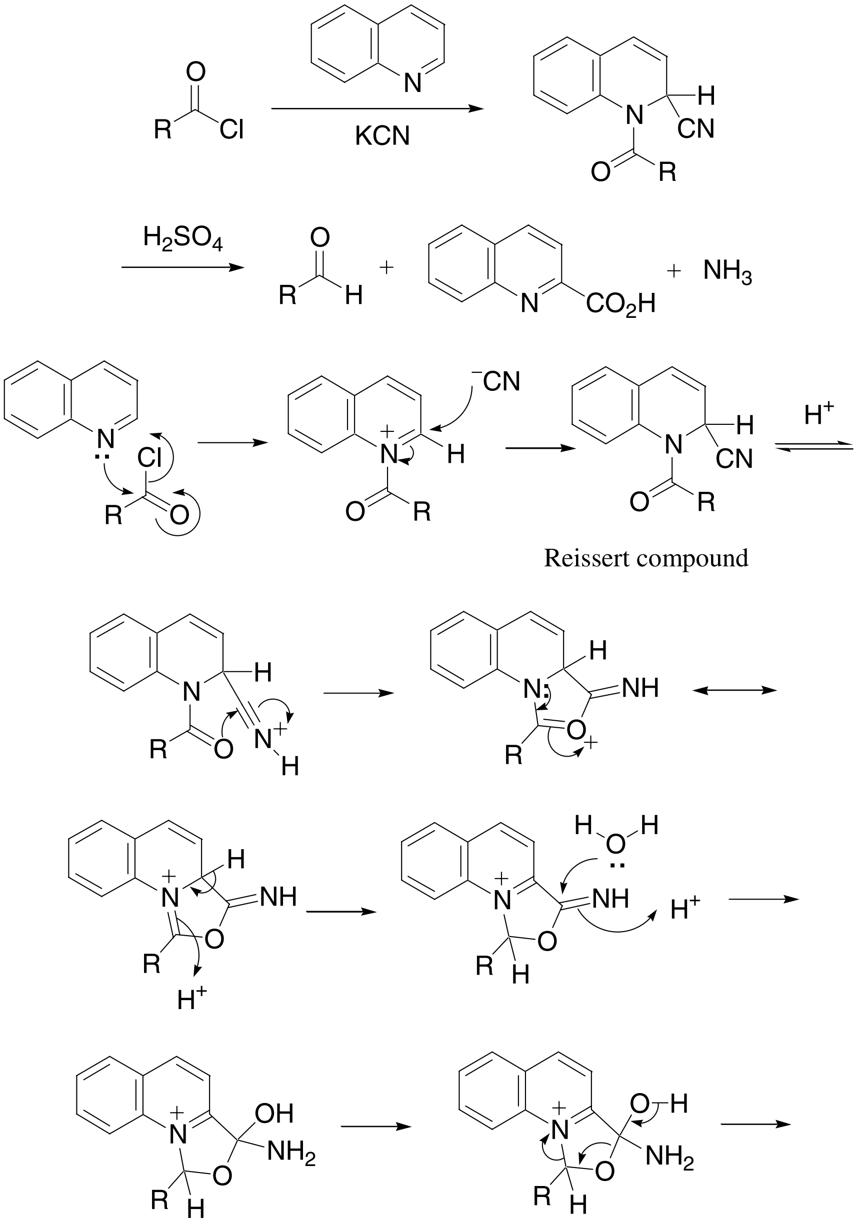
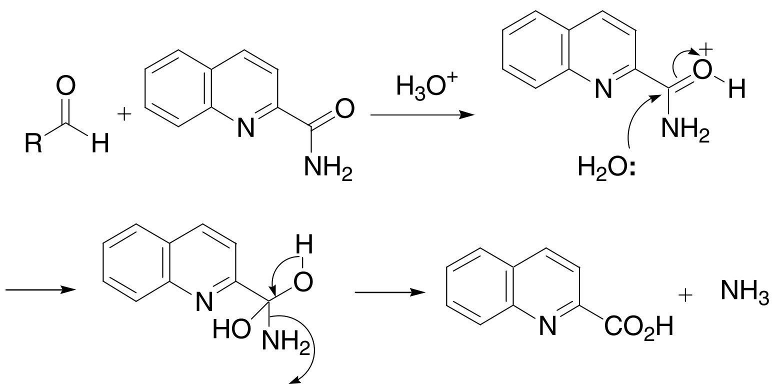
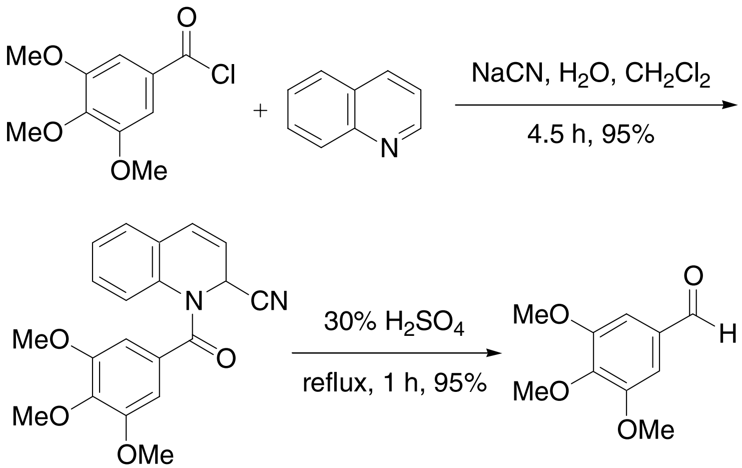
Reissert aldehyde synthesis

Aldehyde synthesis from the corresponding acid chloride, quinoline, and KCN.

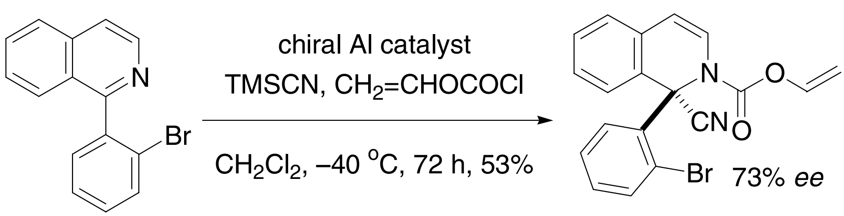




Example 1[4]



Example 2[10]



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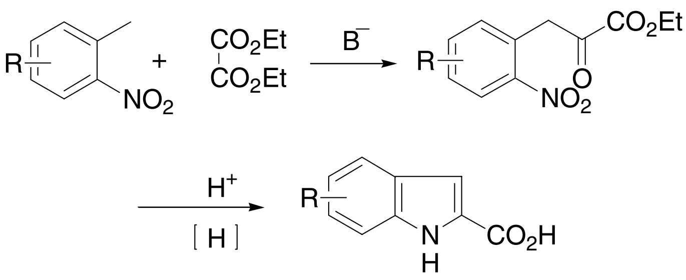
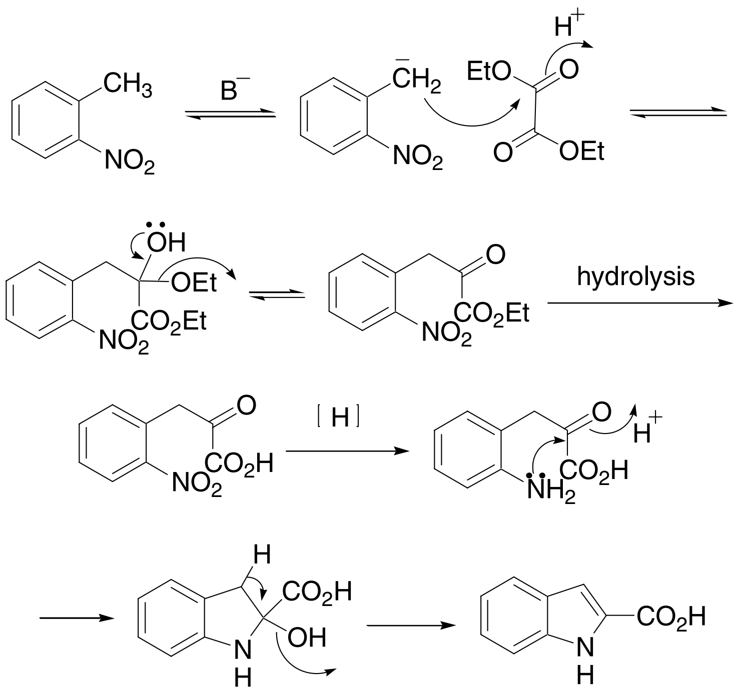
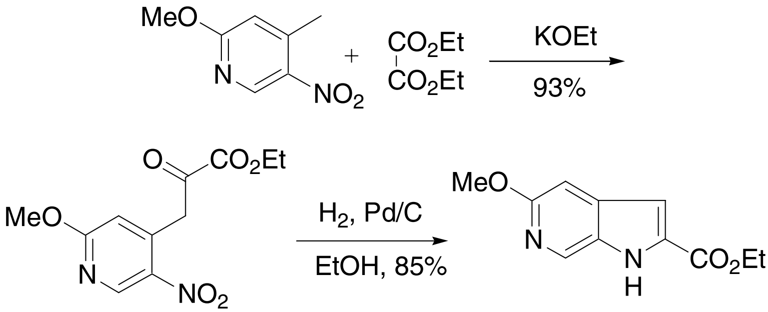
Reissert indole synthesis

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.

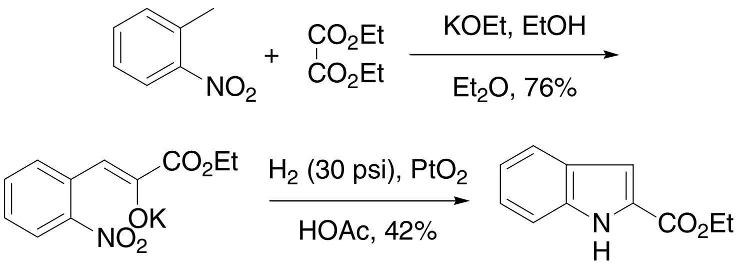




Example 1[3]



Example 2[5]



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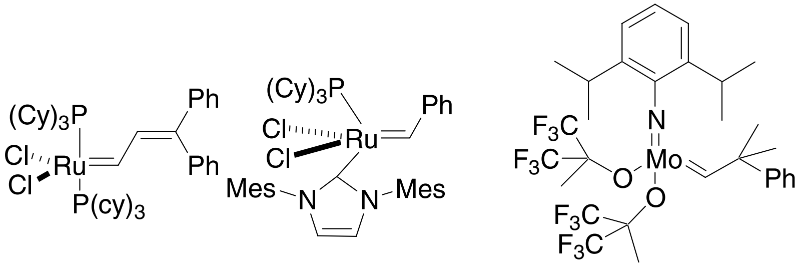
Ring-closing metathesis (RCM)

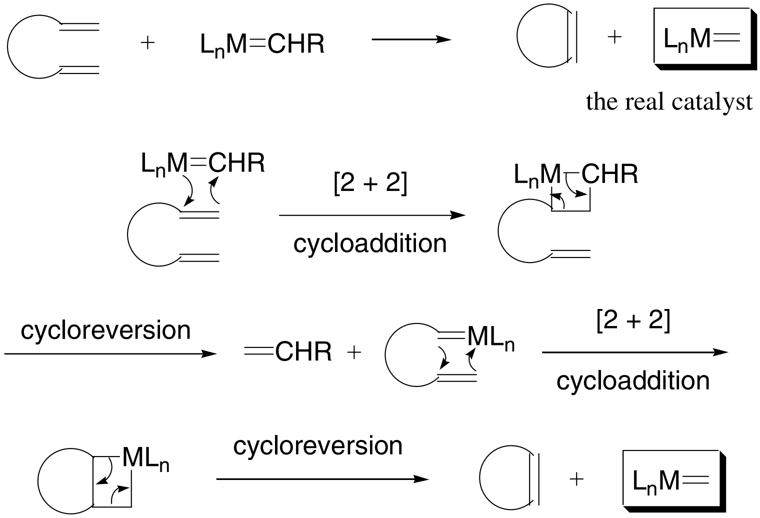


Grubbs' reagents
Mes = mesityl

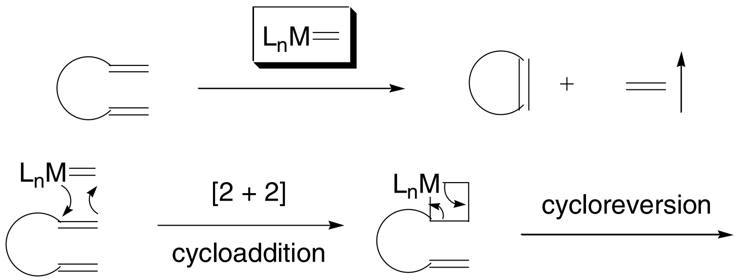
Schrock's reagent

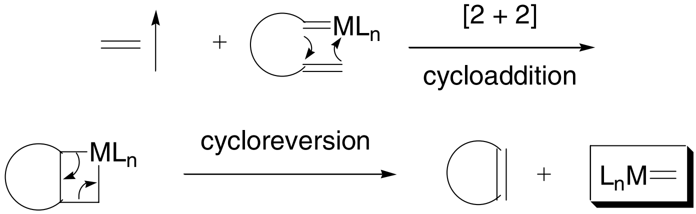
All three catalysts are illustrated as "L_nM=CHR" in the mechanism below.

Generation of the catalyst from the precatalysts:

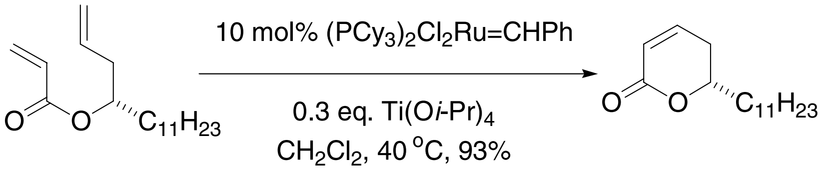


Catalytic cycle:

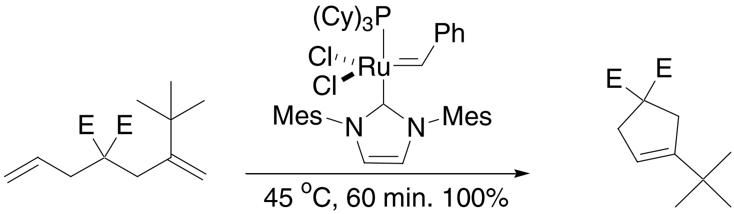




Example 1[4]



Example 2[9]



$E = CO_2Et$

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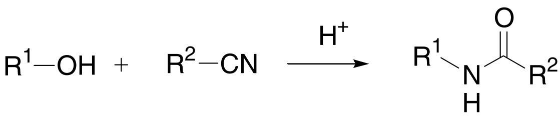
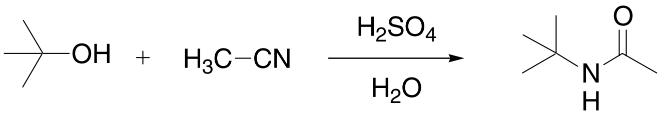
Ritter reaction

Amides from nitriles and alcohols in strong acids.

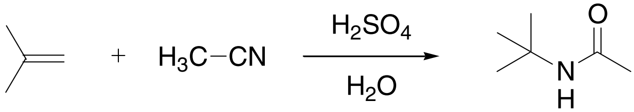
General scheme:

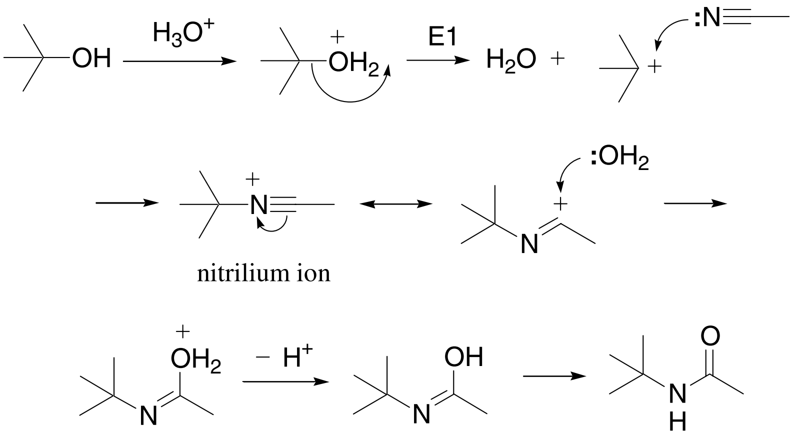


e.g.:

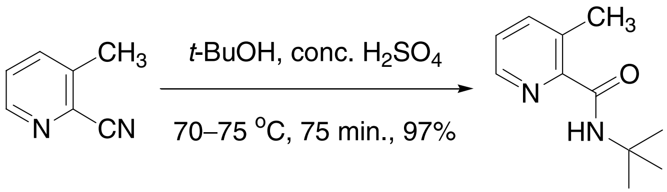


Similarly:

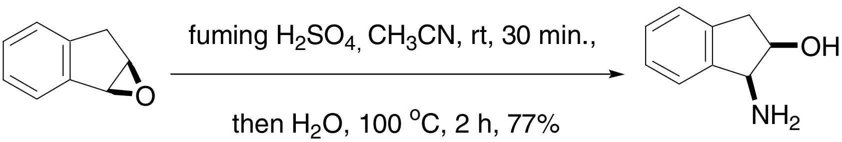




Example 1[4]



Example 2[8]



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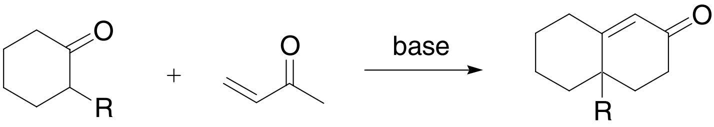
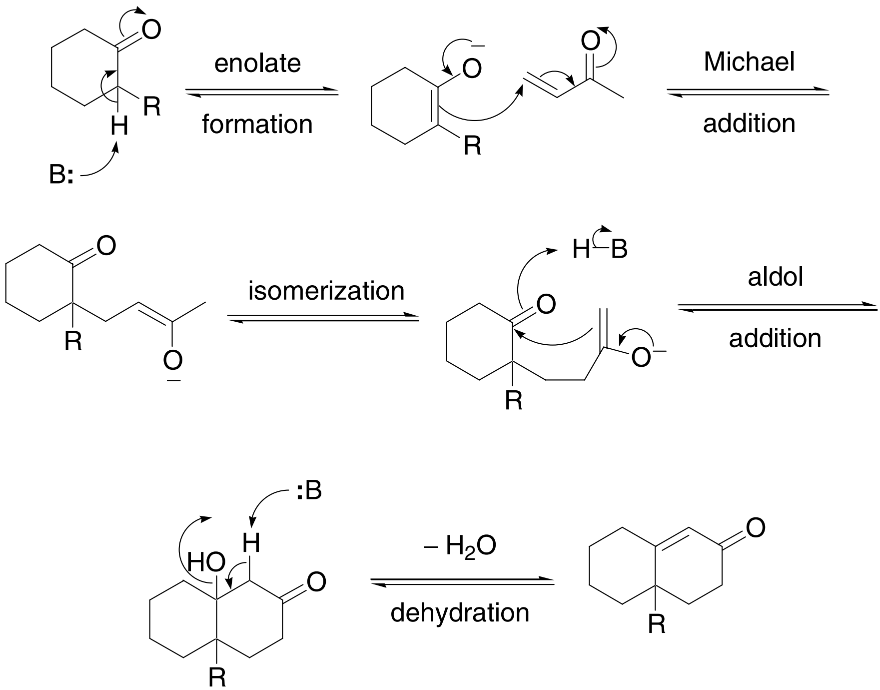
Robinson annulation

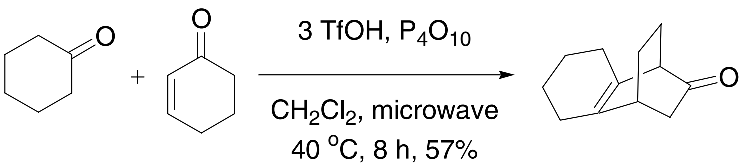
Michael addition of cyclohexanones to methyl vinyl ketone followed by intramolecular aldol condensation to afford six-membered α,β-unsaturated ketones.



methyl vinyl ketone (MVK)



Example[11]



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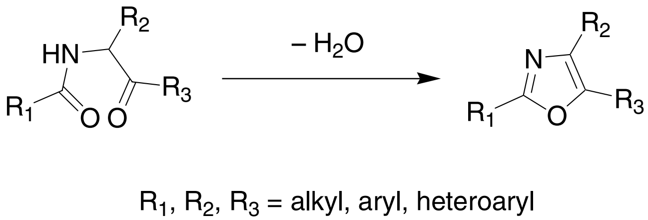
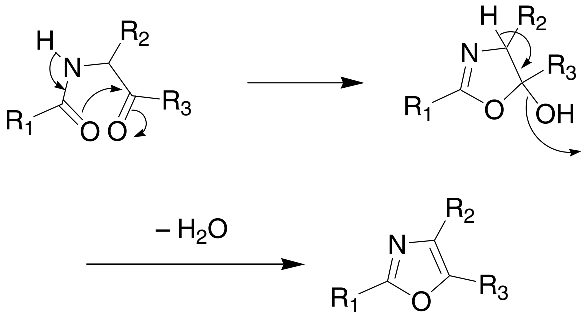
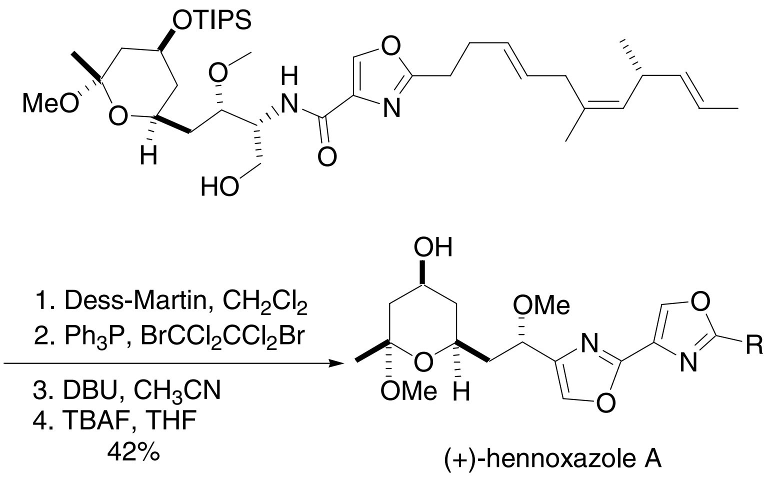
Robinson–Gabriel synthesis

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

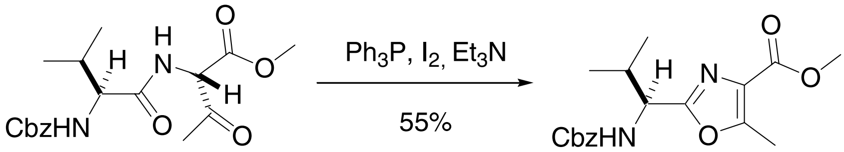




Example 1[9]



Example 2[8]



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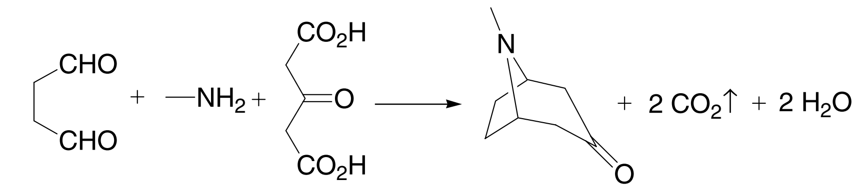
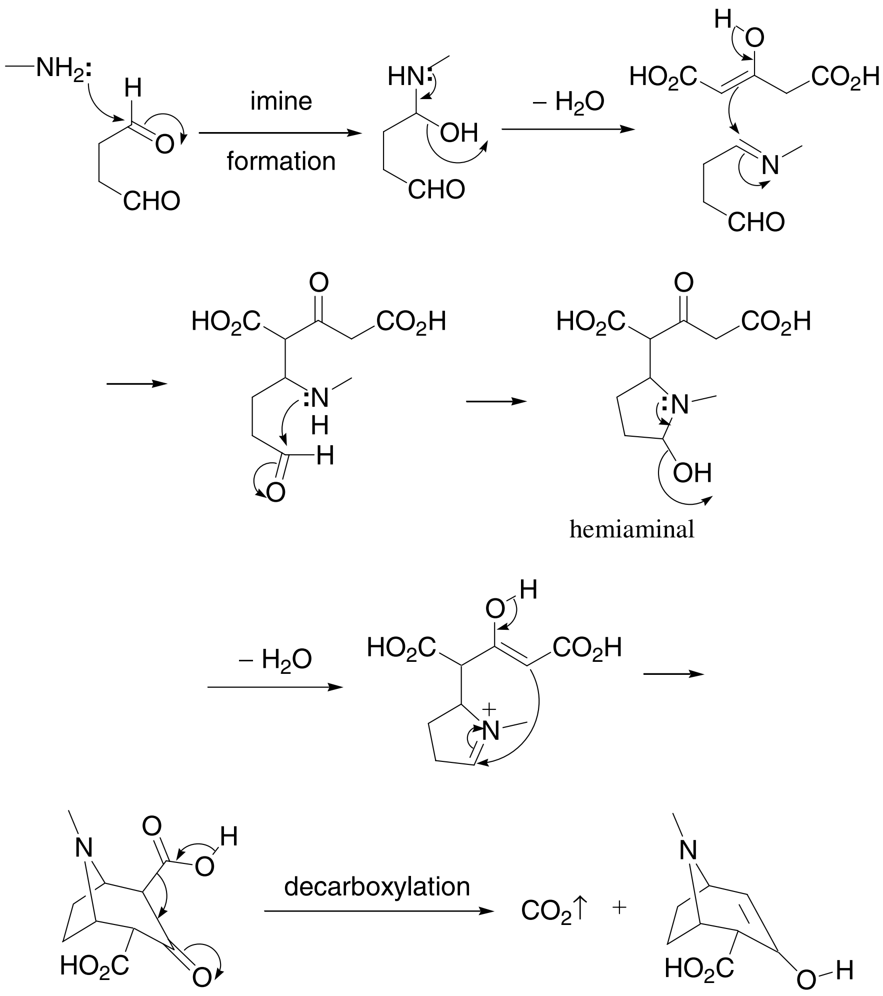
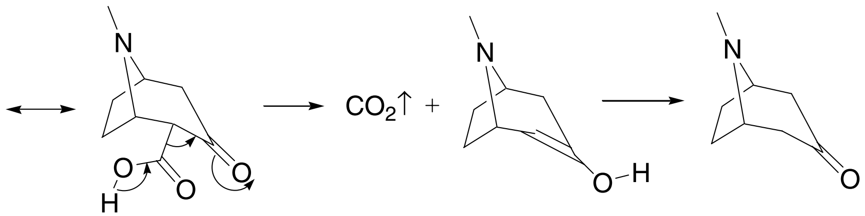
Robinson–Schöpf reaction

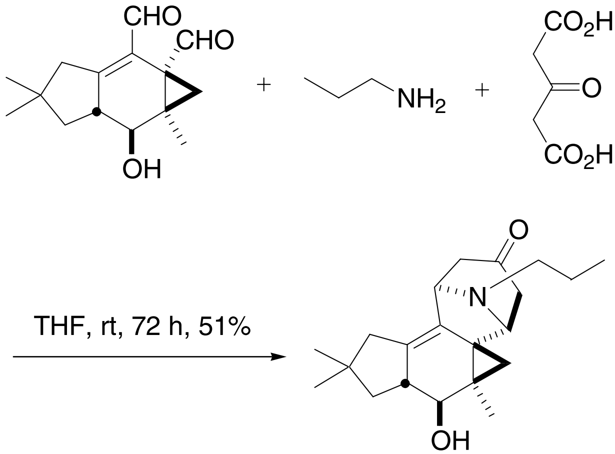
Tropinone synthesis.







Example[7]



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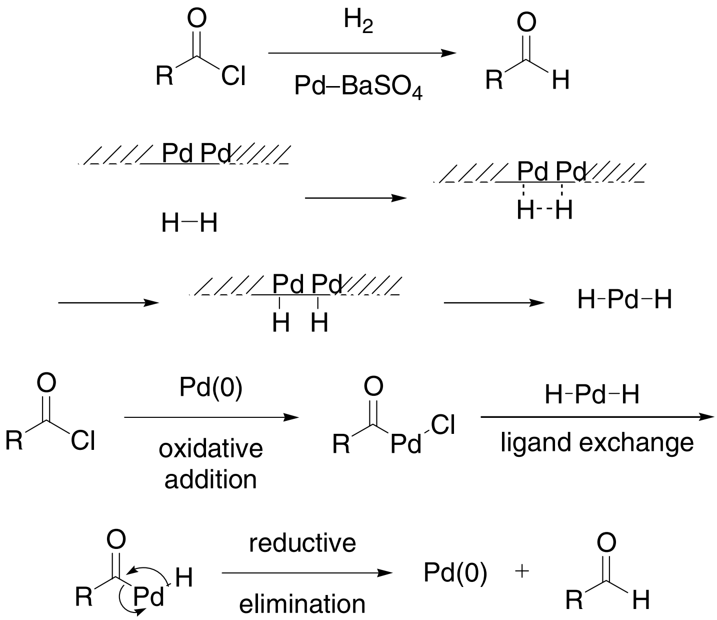
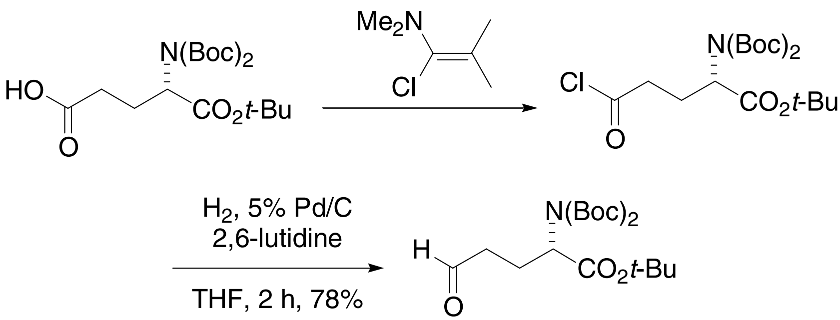
Rosenmund reduction

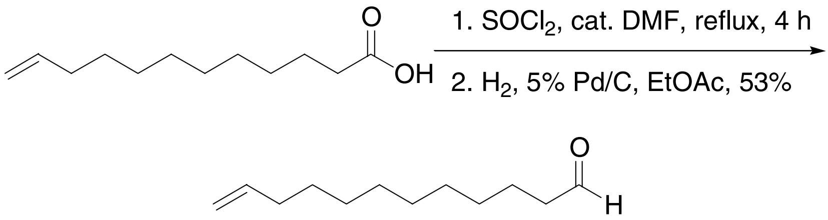
Hydrogenation reduction of acid chloride to aldehyde using $BaSO_4$-poisoned palladium catalyst. Without poison, the resulting aldehyde may be further reduced to alcohol.



Example 1[6]



Example 2[9]



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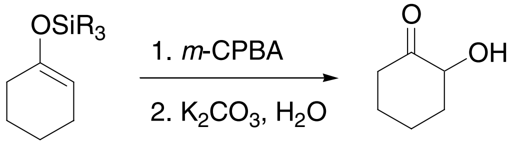
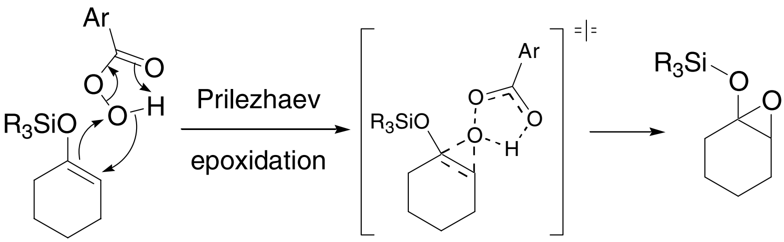
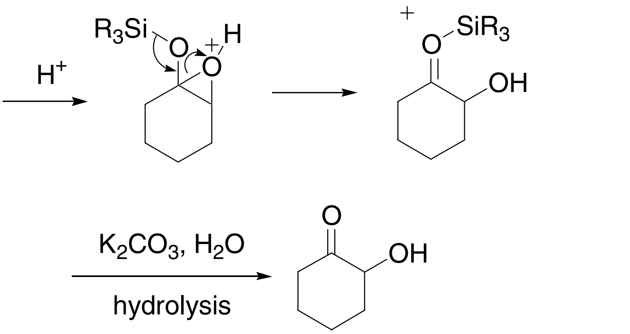
Rubottom oxidation

α-Hydroxylation of enolsilanes.

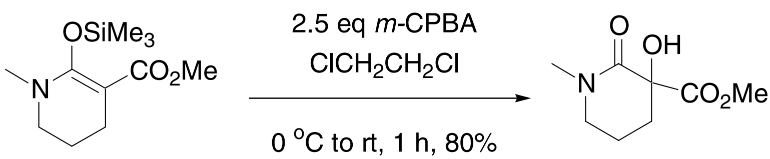




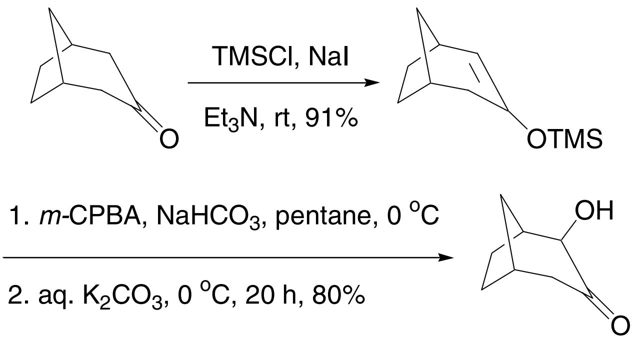
The "butterfly" transition state



Example 1[5]



Example 2[10]



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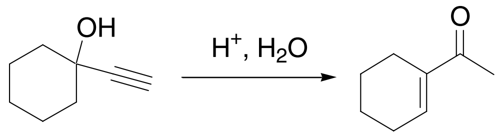
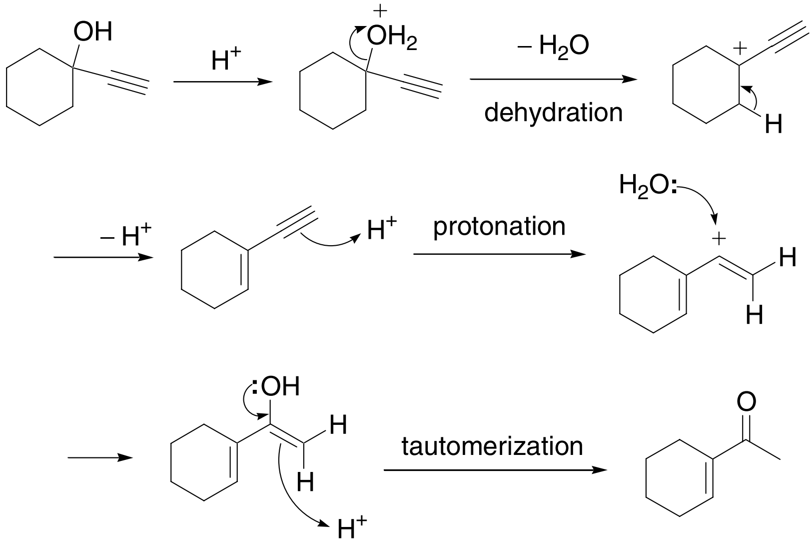
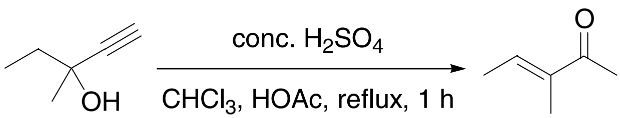
Rupe rearrangement

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.

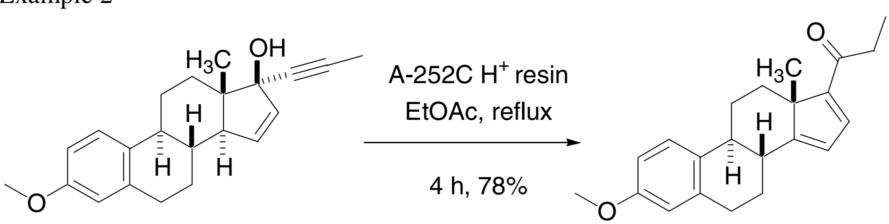




Example 1[6]



Example 2[10]



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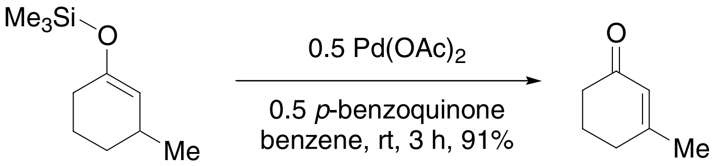
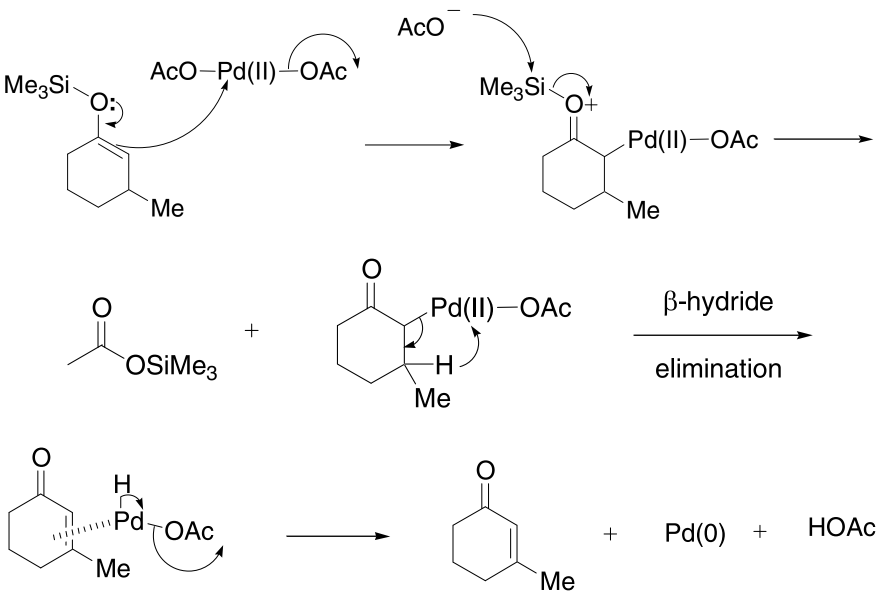
Saegusa oxidation

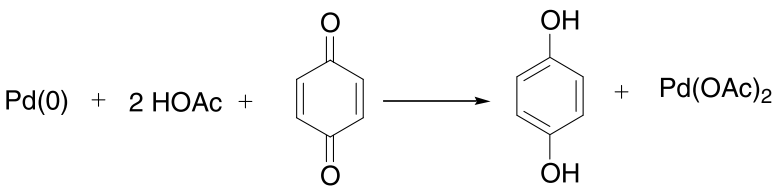
Palladium-catalyzed conversion of enol silanes to enones, also known as the Saegusa enone synthesis.



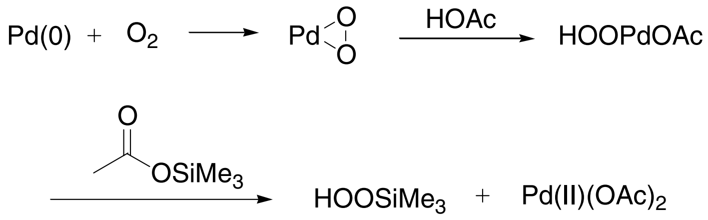
The mechanism is similar to that of the Wacker oxidation (page 610).



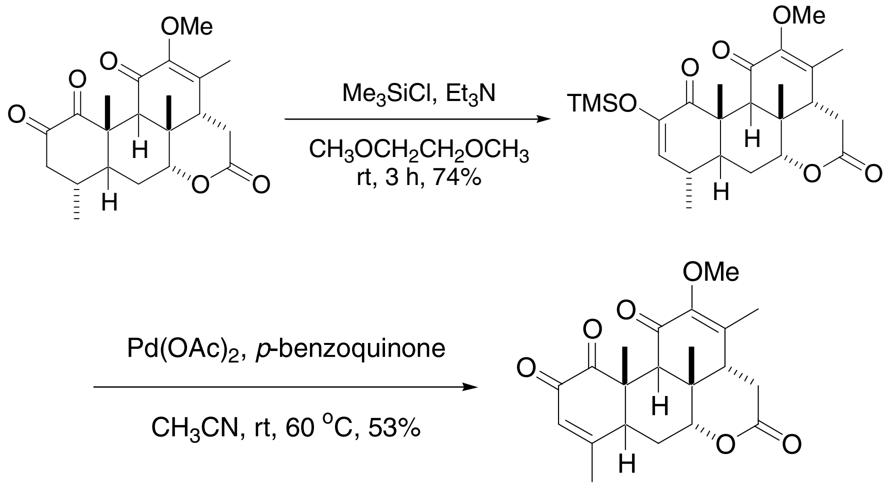
Regenerating the Pd(II) oxidant:



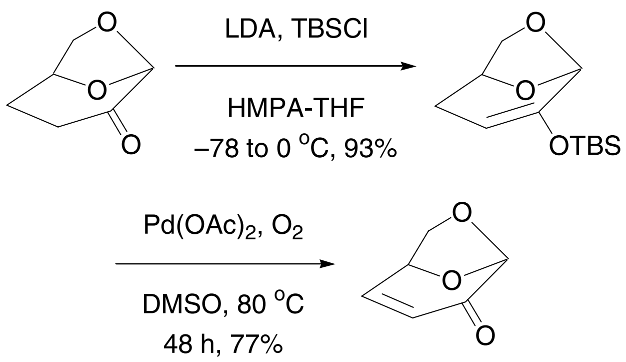
Larock reported regeneration of the Pd(II) oxidant using oxygen:[4]



Example 1[3]



Example 2[8]



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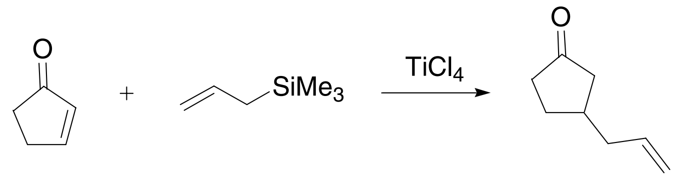
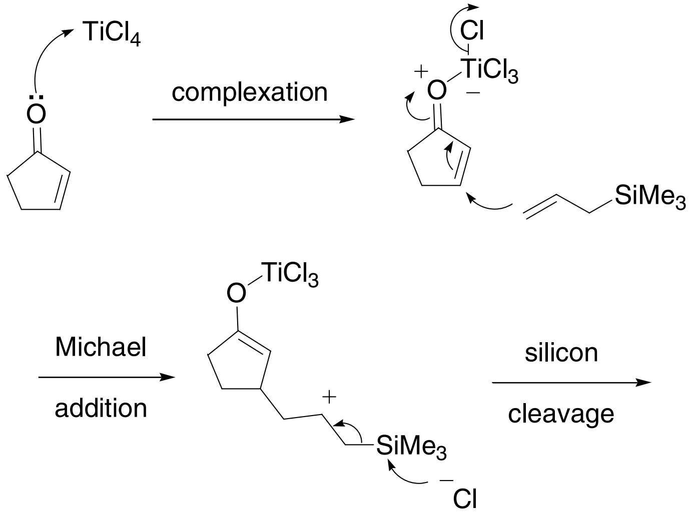
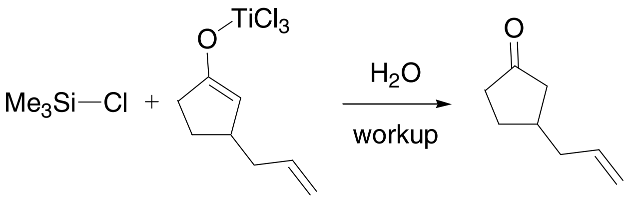
Sakurai allylation reaction

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 it is not part of an α,β-unsaturated system (Example 2), giving rise to an alcohol.

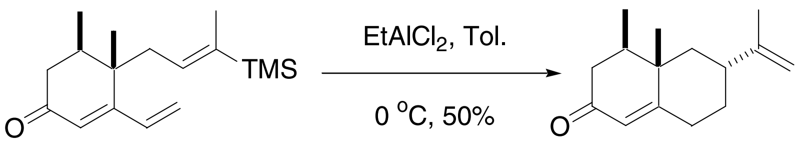




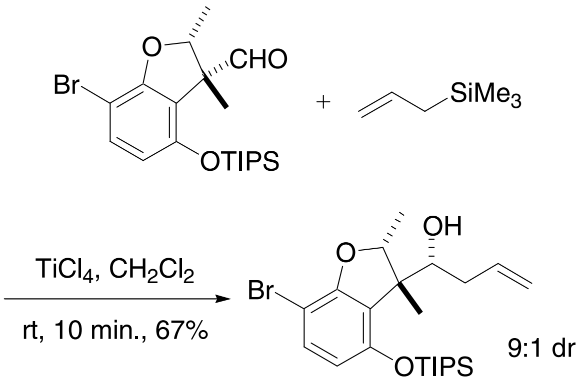
The β-carbocation is stabilized by the silicon atom



Example 1[2]



Example 2[14]



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Sandmeyer reaction

Haloarenes from the reaction of a diazonium salt with CuX.

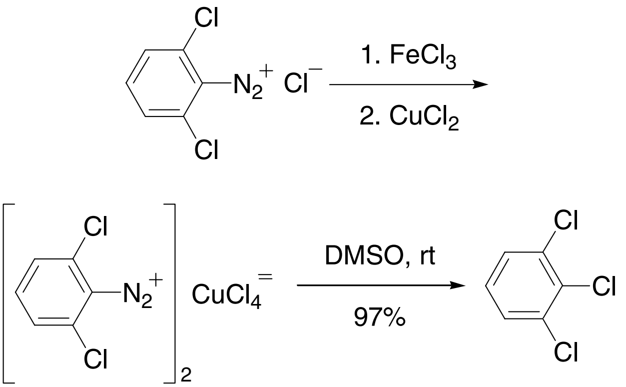
$$ArN_2^+\ Y^- \xrightarrow{CuX} Ar{-}X \qquad X = Cl, Br, CN$$

e.g.:

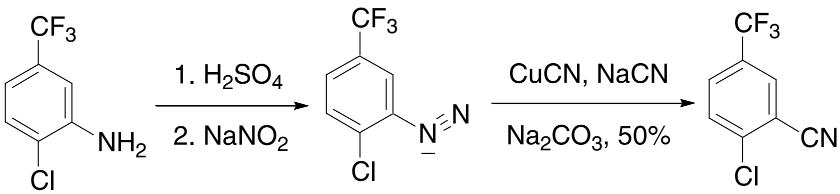
$$ArN_2^+\ Cl^- \xrightarrow{CuCl} Ar{-}Cl$$

$$ArN_2^+\ Cl^- \xrightarrow{CuCl} N_2\uparrow + Ar\bullet + CuCl_2 \longrightarrow Ar{-}Cl + CuCl$$

Example 1[5]



Example 2[11]



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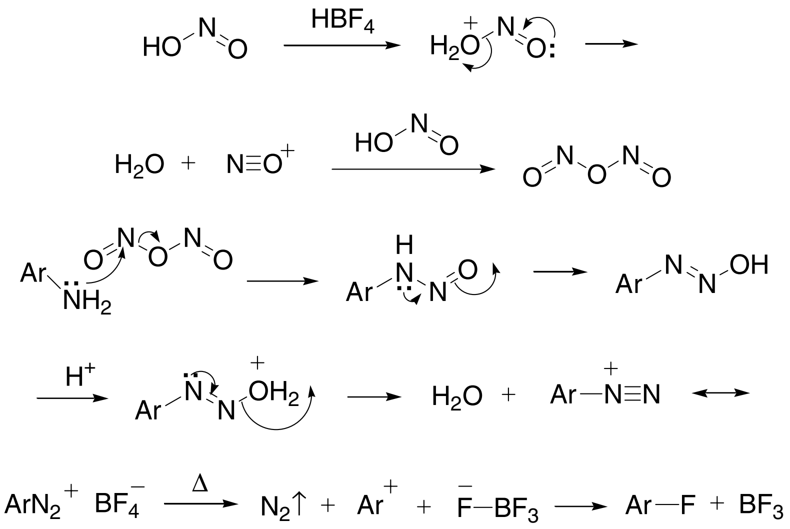
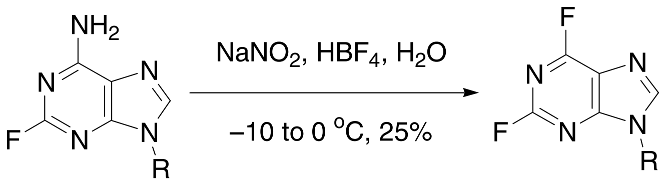
Schiemann reaction

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

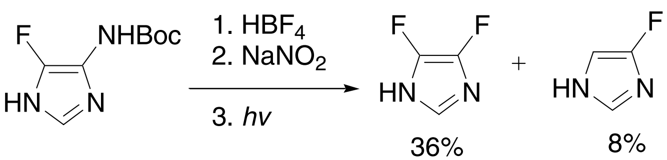
$$Ar{-}NH_2 + HNO_2 + HBF_4 \longrightarrow ArN_2^+\ BF_4^- \xrightarrow{\Delta} Ar{-}F + N_2\uparrow + BF_3$$



Example 1[4]



Example 2[10]



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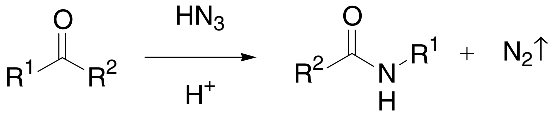
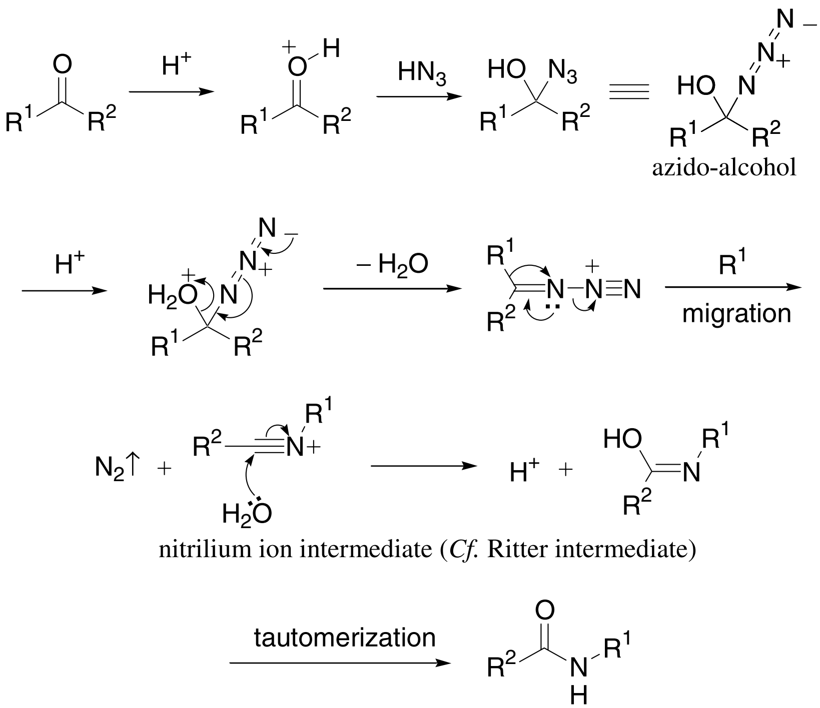
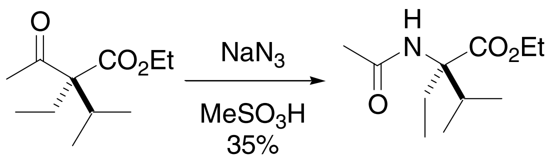
Schmidt reaction

Conversion of ketones to amides using HN_3 (hydrazoic acid).

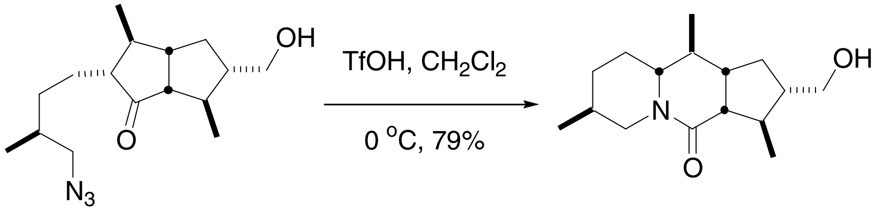




Example 1, a classic example[11]



Example 2, a variant[15]



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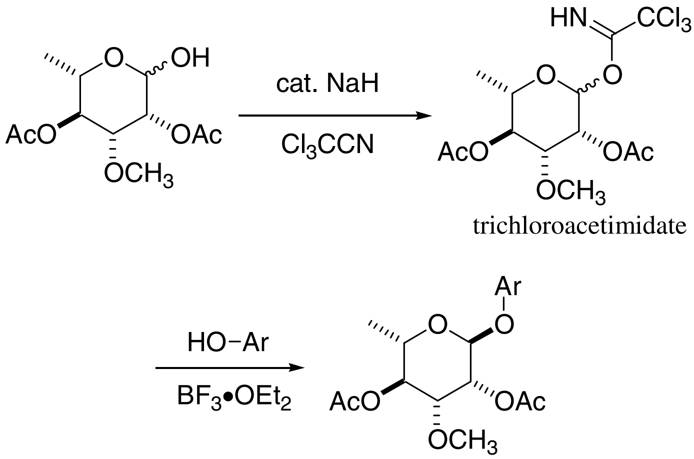
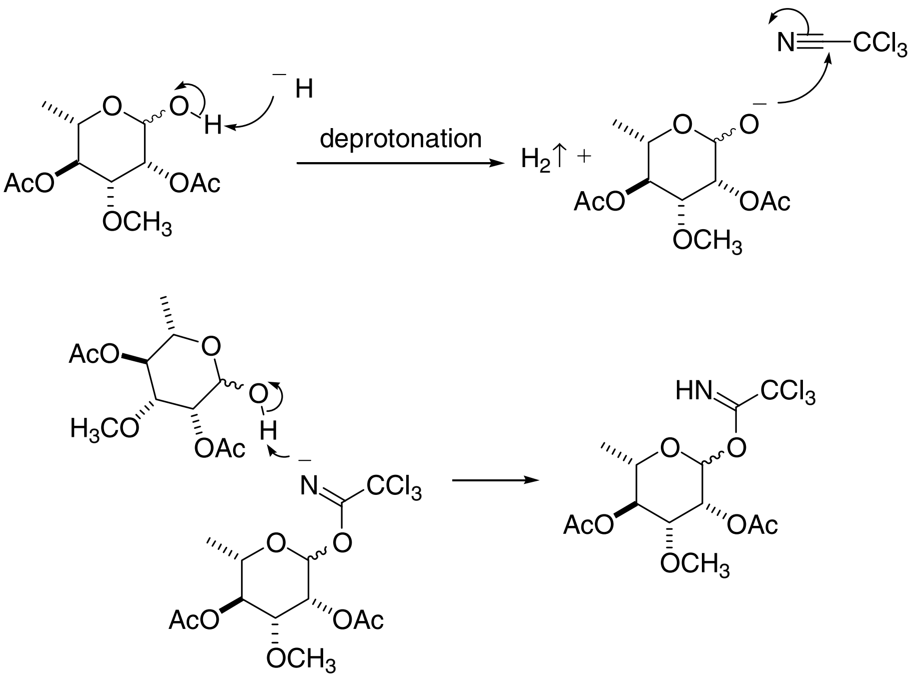
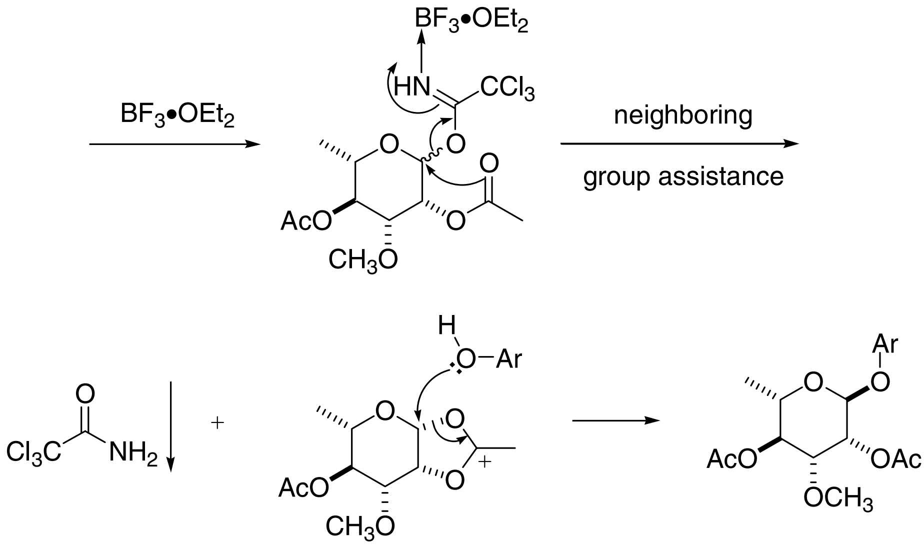
Schmidt's trichloroacetimidate glycosidation reaction

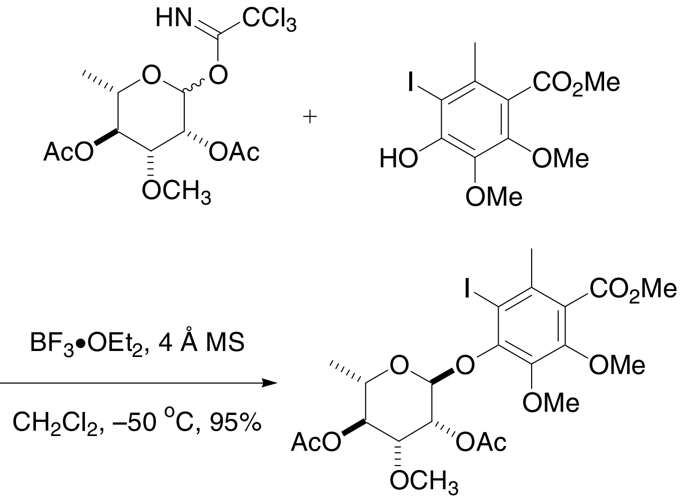
Lewis acid-promoted glycosidation of trichloroacetimidates with alcohols or phenols.



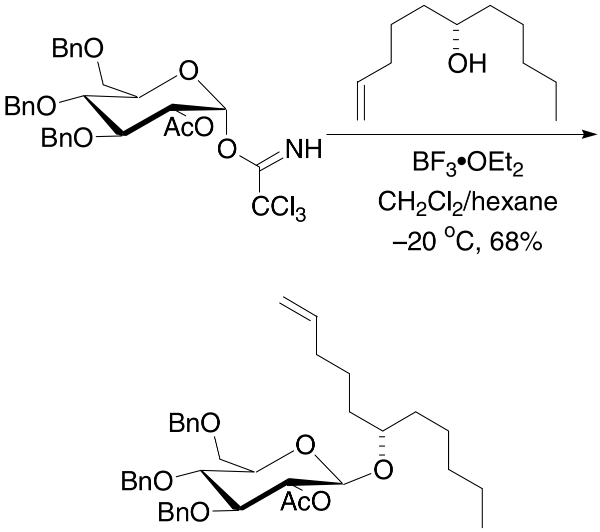



BF3•OEt2
BF3•OEt2
HN
CCl3
O
O
O
AcO
CH3O
neighboring
group assistance
O
Cl3C
NH2
+
H
O–Ar
O
O
O
+
AcO
CH3O
Ar
O
O
AcO
OAc
OCH3

Example 1[5]


HN
CCl3
O
O
AcO
OAc
OCH3
+
I
CO2Me
HO
OMe
OMe
BF3•OEt2, 4 Å MS
CH2Cl2, –50 °C, 95%
I
CO2Me
O
O
OMe
OMe
AcO
OAc
OCH3

Example 2[7]



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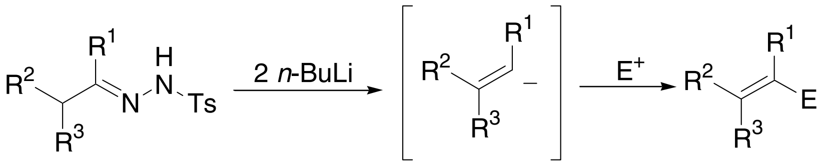
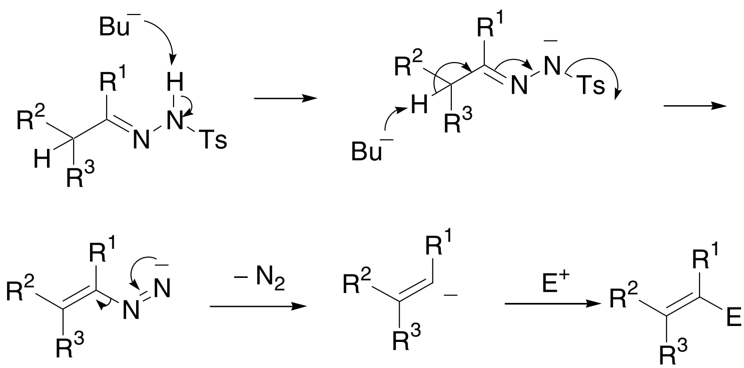
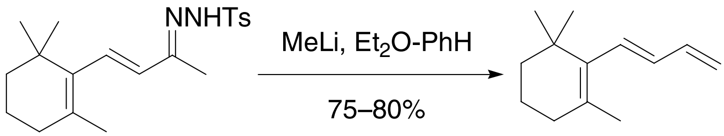
Shapiro reaction

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, $NaNH_2$, *etc*. Consequently, the Shapiro reaction generally affords the less-substituted olefins as the kinetic products, while the Bamford–Stevens reaction delivers the more-substituted olefins as the thermodynamic products.

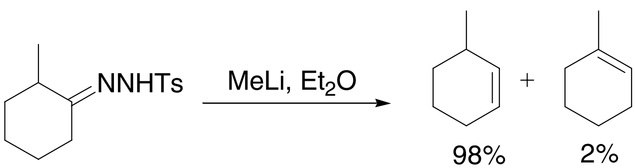




Example 1[3]



Example 2[2]



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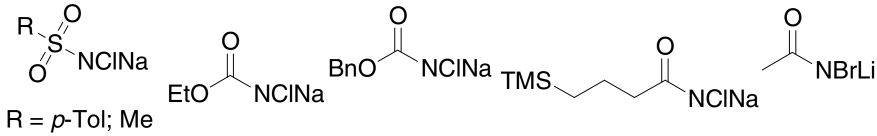
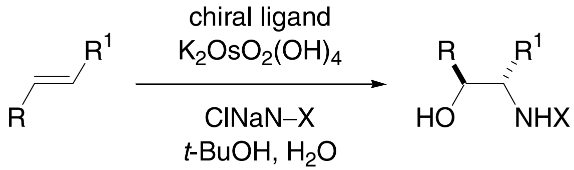
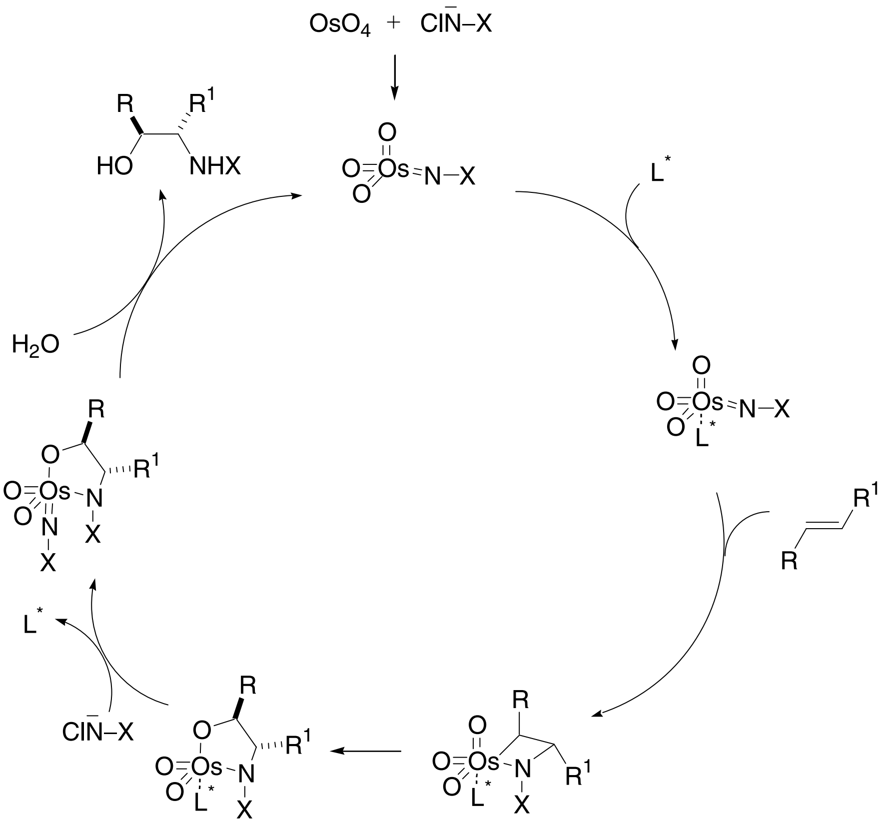
Sharpless asymmetric amino hydroxylation

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

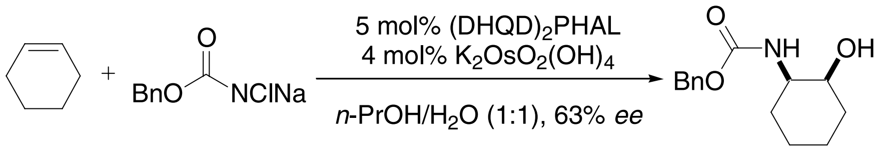




The catalytic cycle:

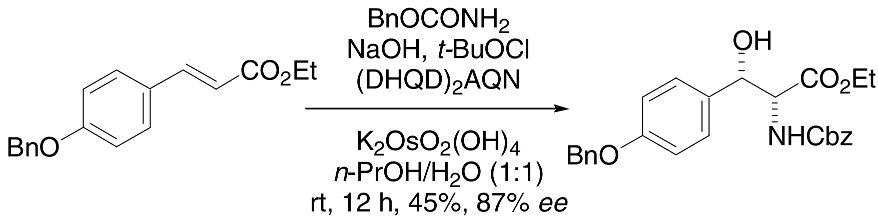


Example 1[4]



$(DHQD)_2$-PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine (page 536).

Example 2[9]



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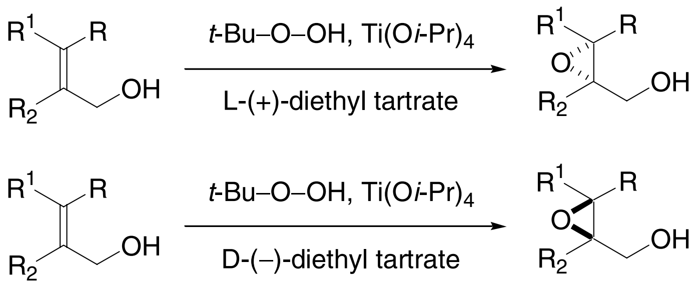
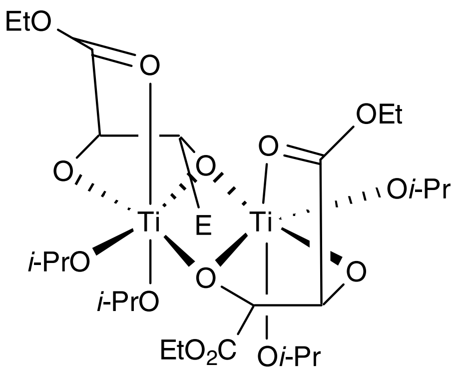
Sharpless asymmetric epoxidation

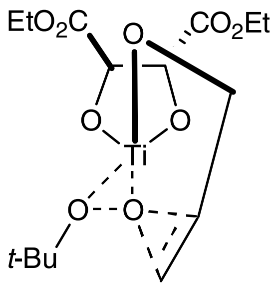
Enantioselective epoxidation of allylic alcohols using *t*-butyl peroxide, titanium tetra-*iso*-propoxide, and optically pure diethyl tartrate.



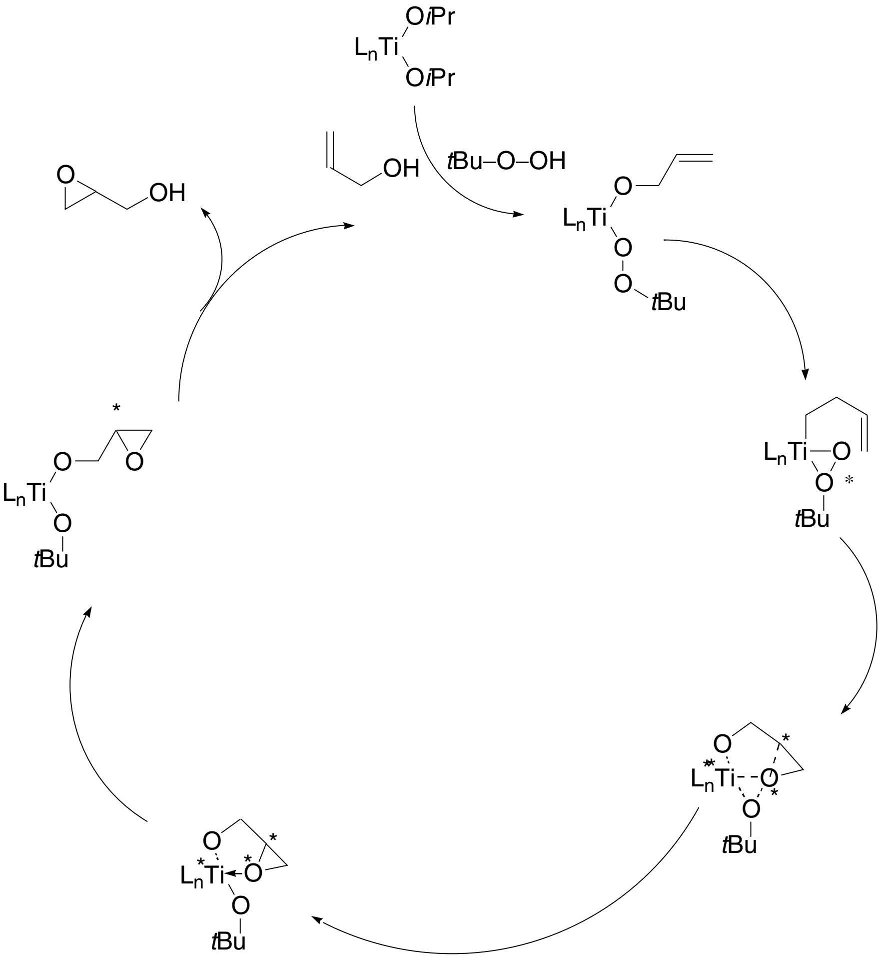
The putative active catalyst, E = CO_2Et:[2]



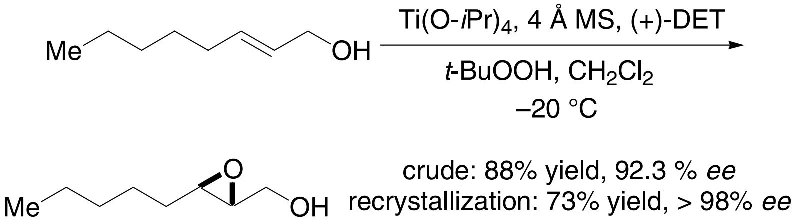
The transition state:



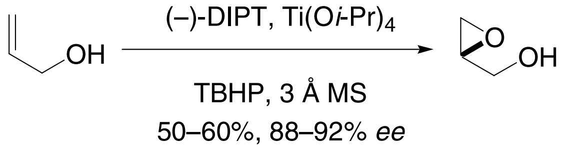
The catalytic cycle:



Example 1[5]



Example 2[5]



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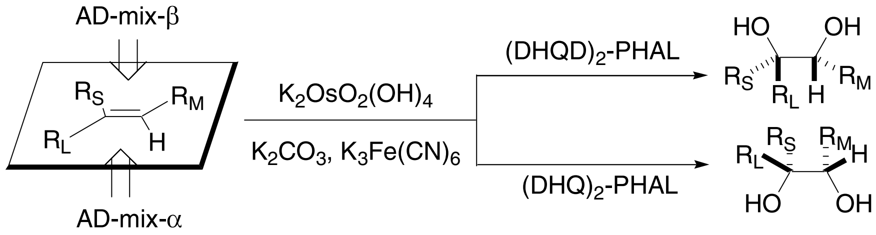
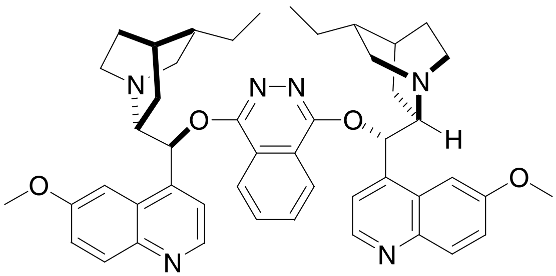
Sharpless asymmetric dihydroxylation

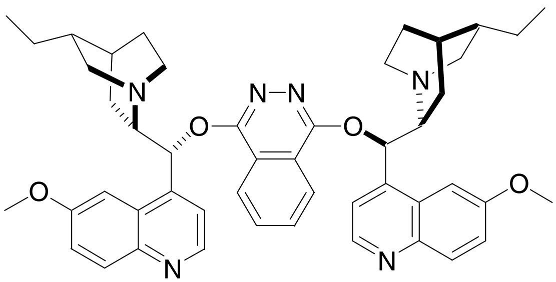
Enantioselective *cis*-dihydroxylation of olefins using osmium catalyst in the presence of cinchona alkaloid ligands.



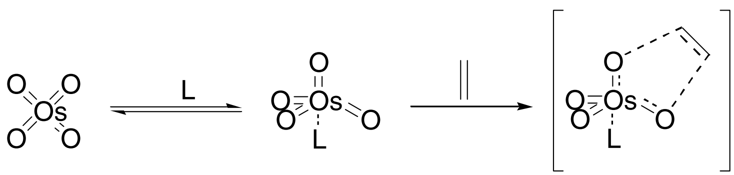
$(DHQD)_2$-PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine:

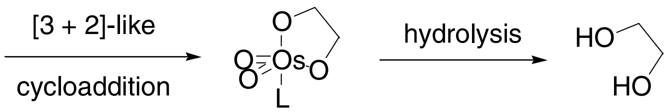


$(DHQ)_2$-PHAL = 1,4-bis(9-*O*-dihydroquinine)phthalazine:



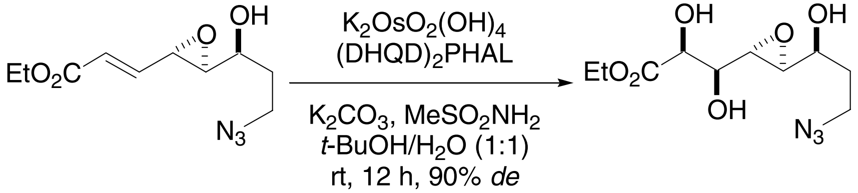
The concerted [3 + 2] cycloaddition mechanism:



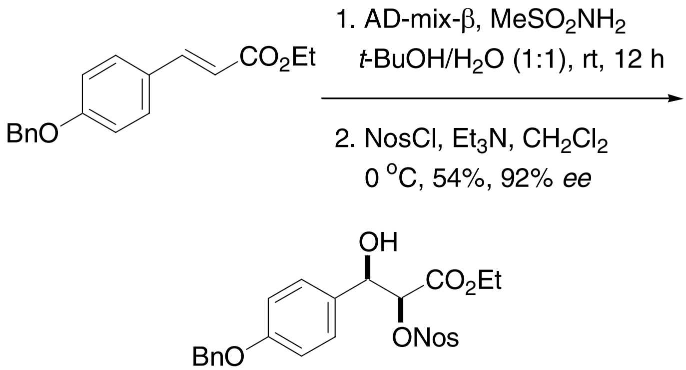


The catalytic cycle is shown on page 539 (the secondary cycle is shut off by maintaining a low concentration of olefin):

Example 1[3]



Example 2[9]



Nos = nosylate = 4-nitrobenzenesulfonyl

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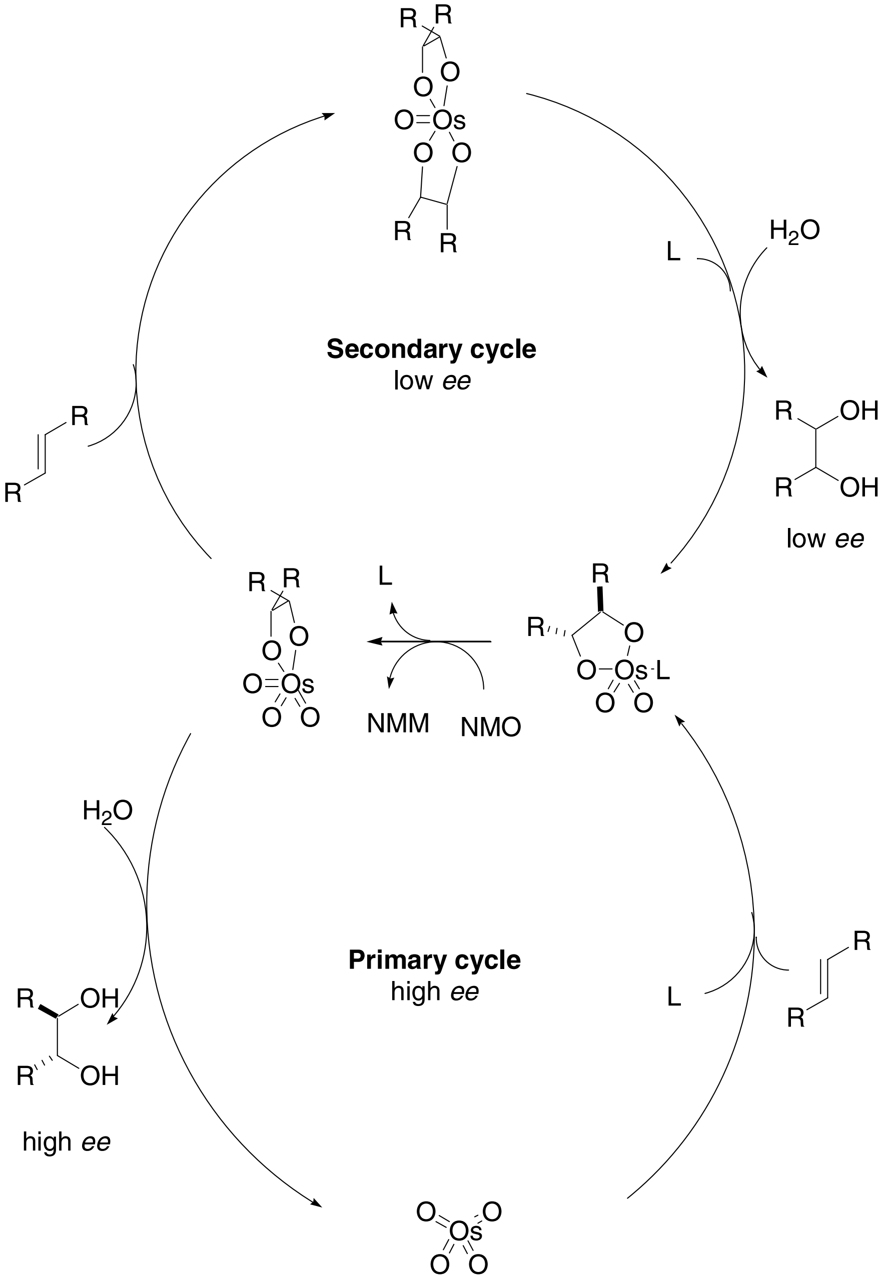
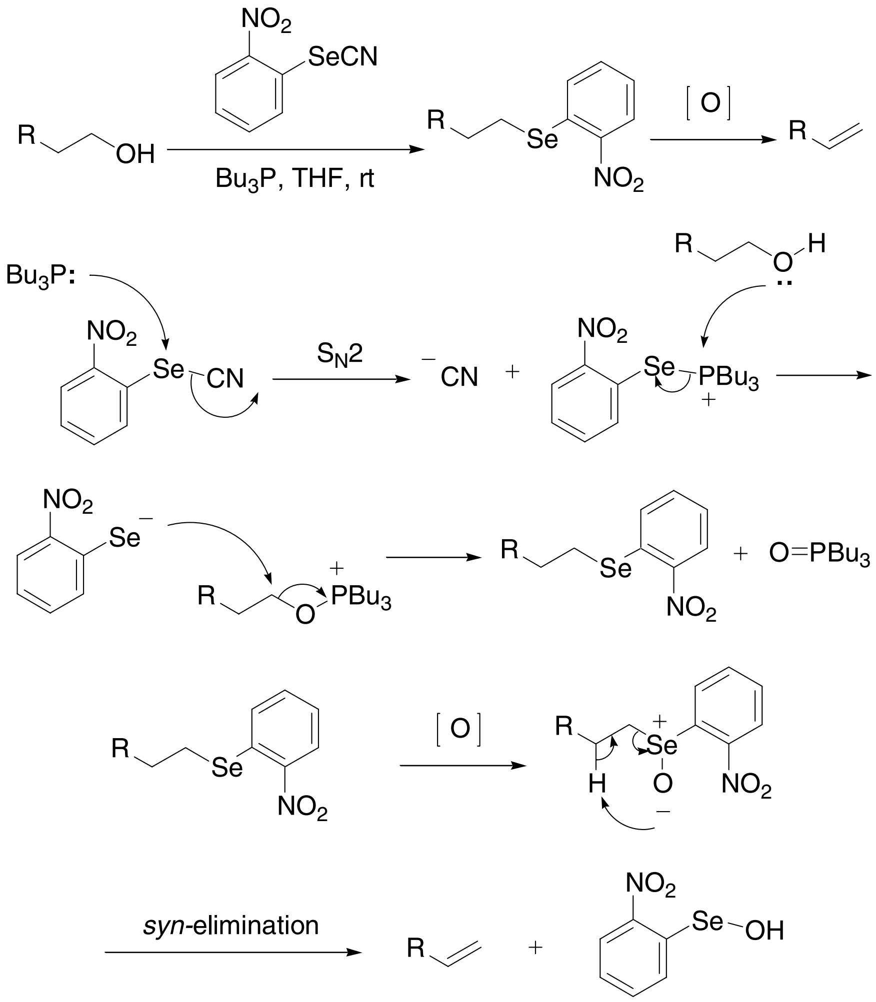


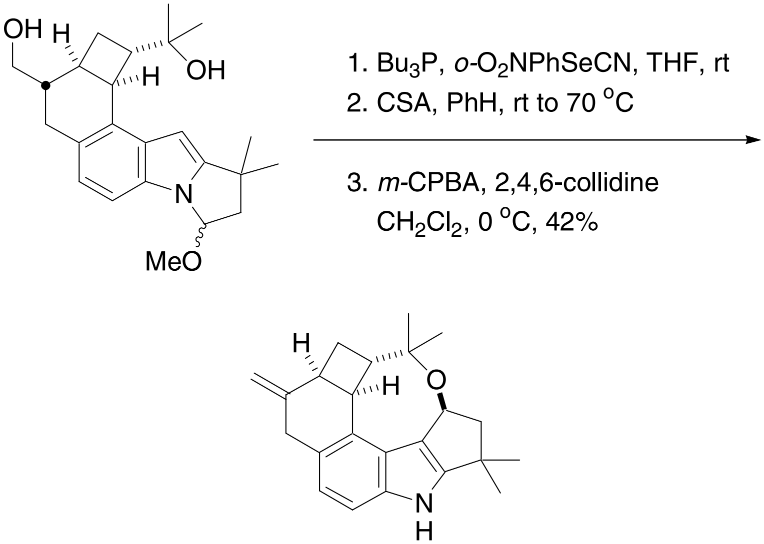
The catalytic cycle of the Sharpless dihydroxylation

Sharpless olefin synthesis

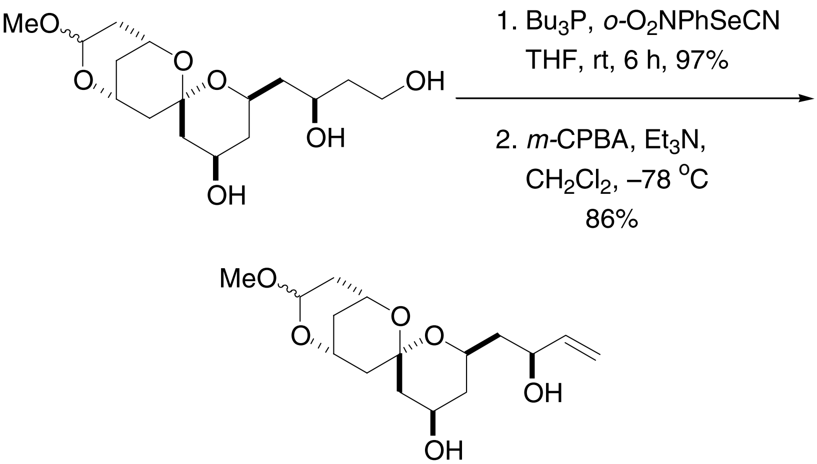
Olefin synthesis from the *syn*-oxidative elimination of *o*-nitrophenyl selenides, which may be prepared using *o*-nitrophenyl selenocyanate and Bu_3P, among other methods.



Example 1[9]



Example 2[13]



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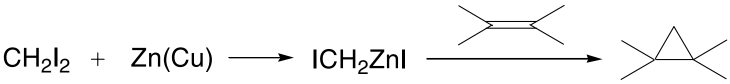
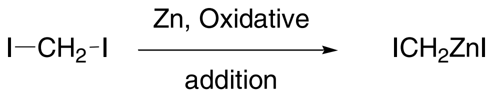
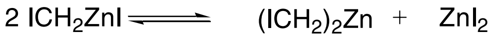
Simmons–Smith reaction

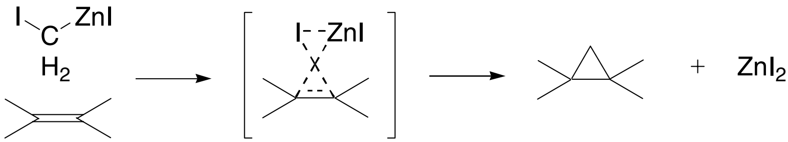
Cyclopropanation of olefins using CH_2I_2 and Zn(Cu).



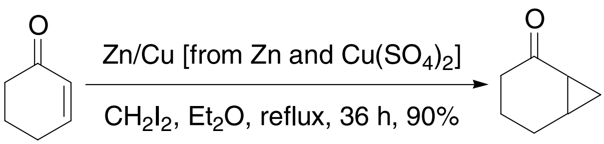


Simmons–Smith reagent

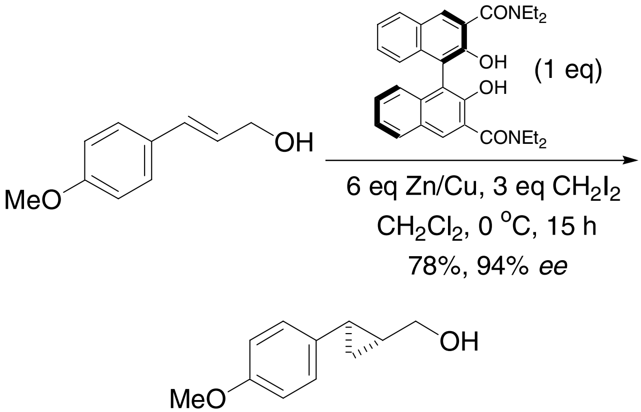




Example 1[2]



Example 2, asymmetric version[13]



References

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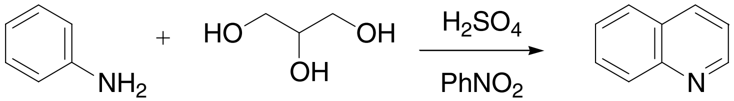
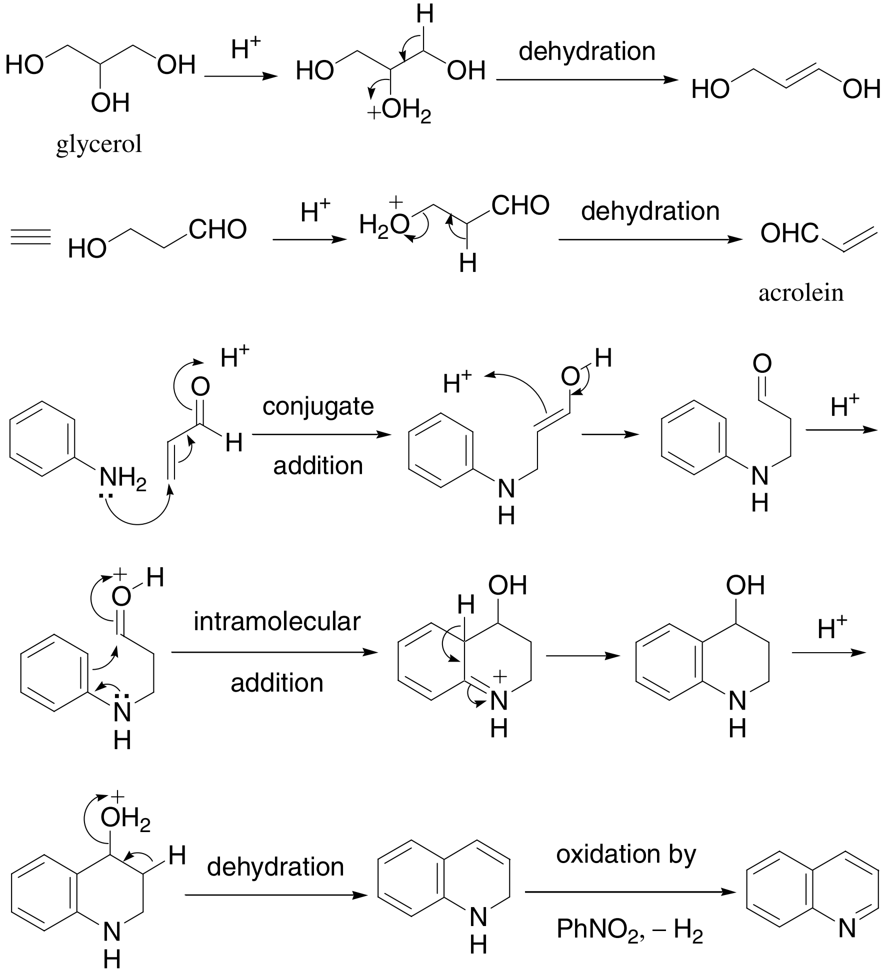
Skraup quinoline synthesis

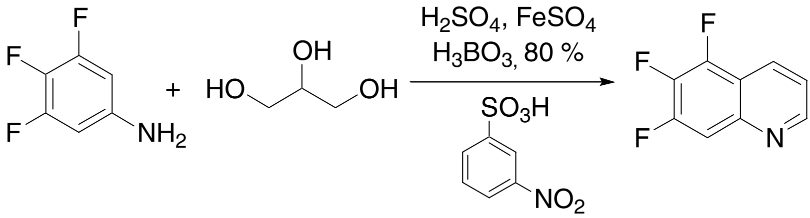
Quinoline from aniline, glycerol, sulfuric acid and oxidizing agent (e.g. $PhNO_2$).



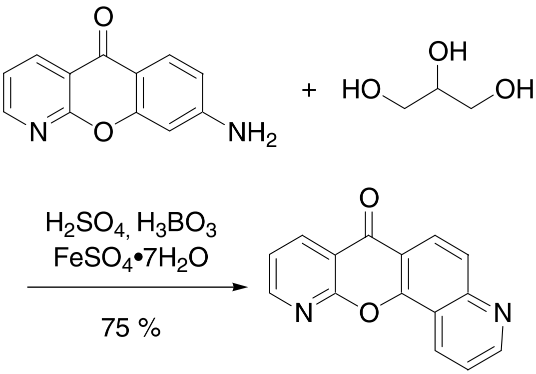


For an alternative mechanism, see that of the Doebner–von Miller reaction (page 547).

Example 1[9]



Example 2[10]



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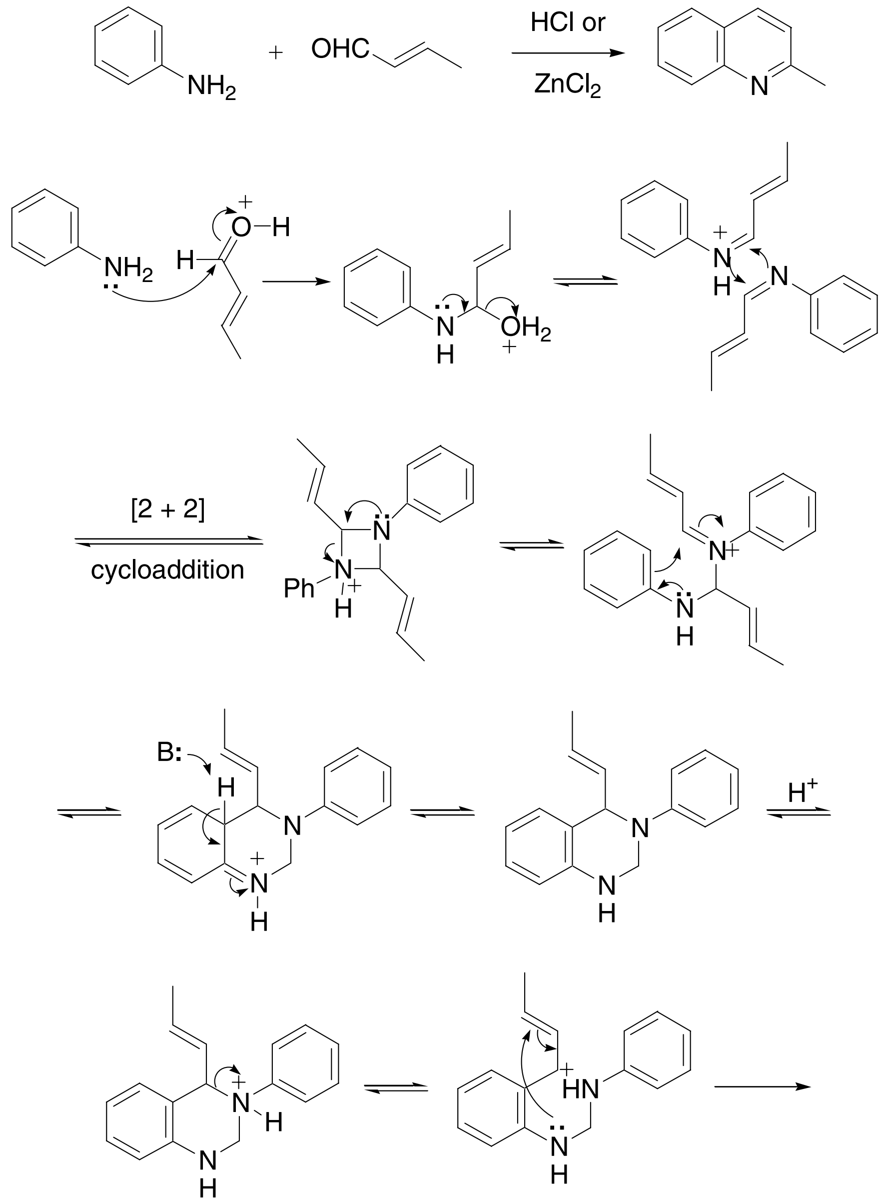
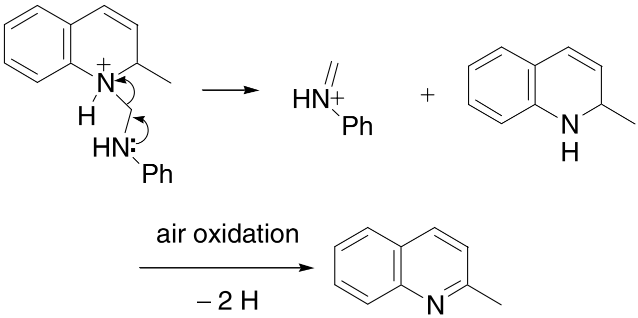
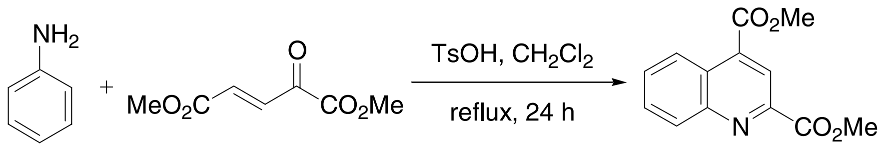
Doebner–von Miller reaction

Doebner–von Miller reaction is a variant of the Skraup quinoline synthesis (page 545). Therefore, the mechanism for the Skraup reaction is also operative for the Doebner–von Miller reaction. An alternative mechanism shown below is based on the fact that the preformed imine (Schiff base) also gives 2-methylquinoline:

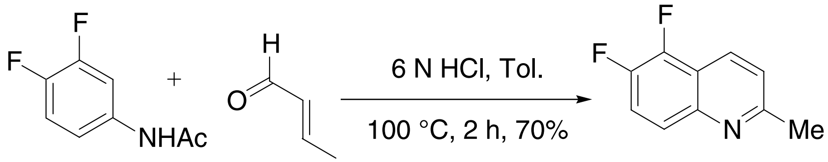




Example 1[7]



Example 2[8]



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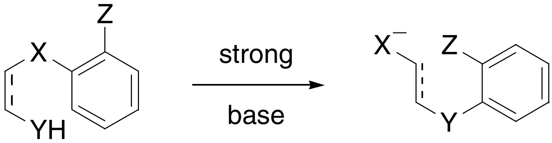
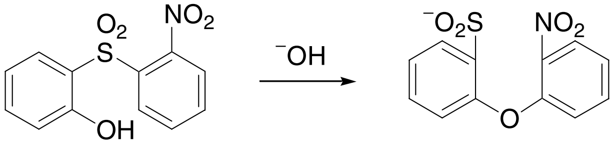
Smiles rearrangement

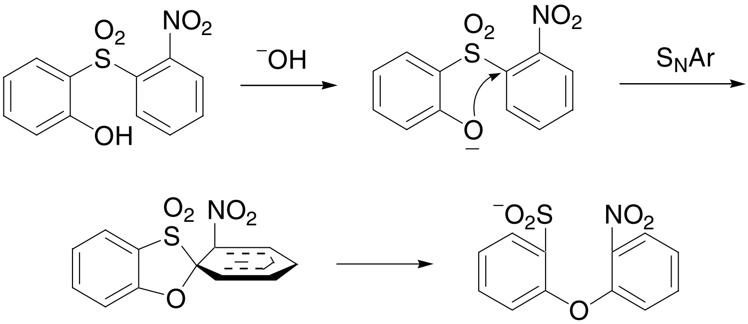
Intramolecular nucleophilic aromatic rearrangement. General scheme:



X = S, SO, SO_2, O, CO_2
YH = OH, NHR, SH, CH_2R, CONHR
Z = NO_2, SO_2R

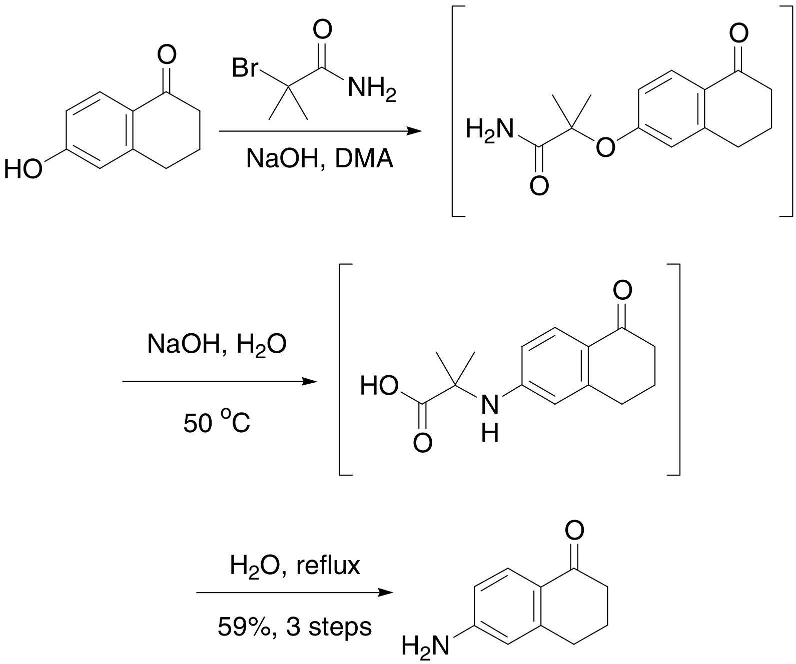
e.g.:





spirocyclic anion intermediate
(Meisenheimer complex)

Example[8]



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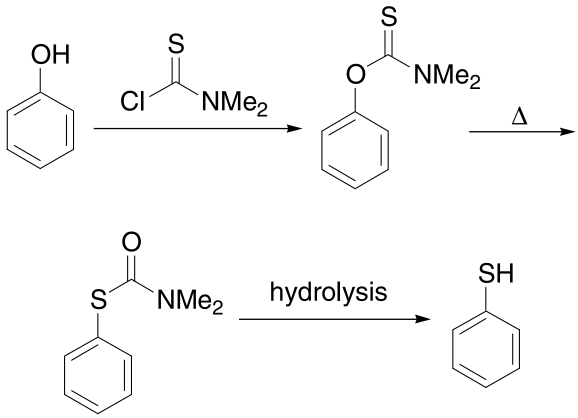
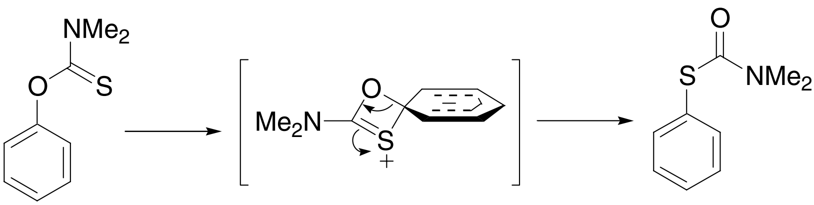
Newman–Kwart reaction

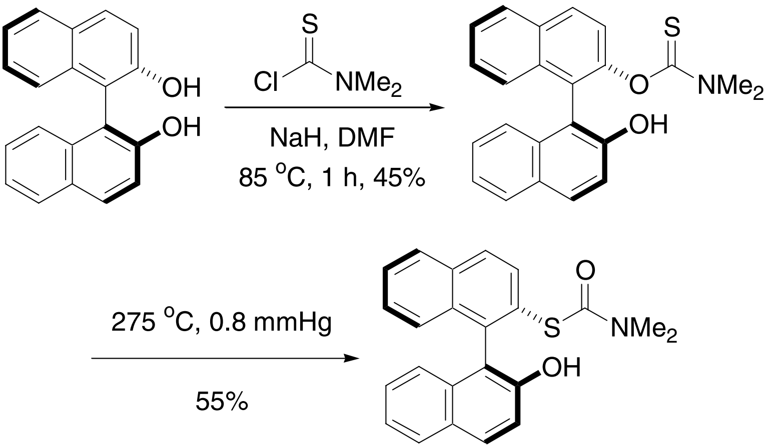
Transformation of phenol to the corresponding thiophenol, a variant of the Smile reaction (page 549).



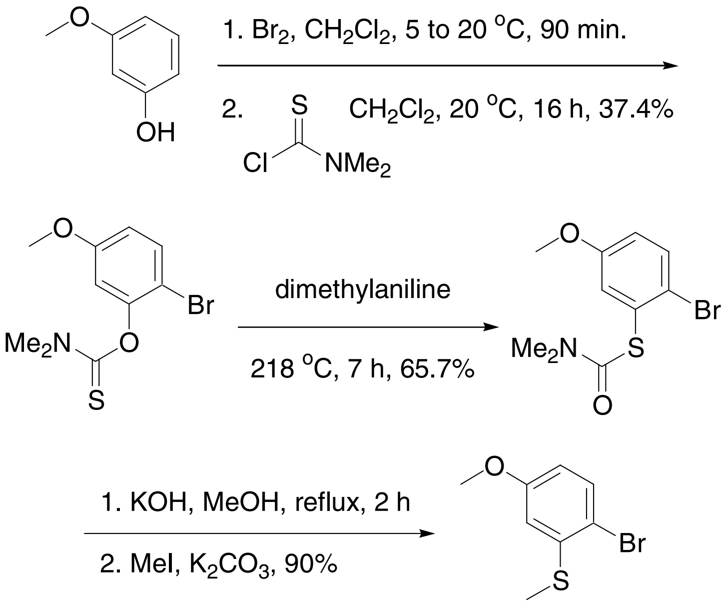
Mechanism:



Example 1[8]



Example 2[9]



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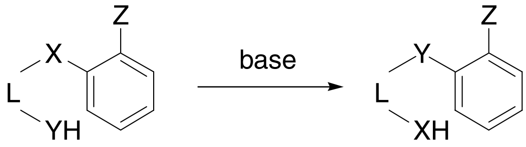
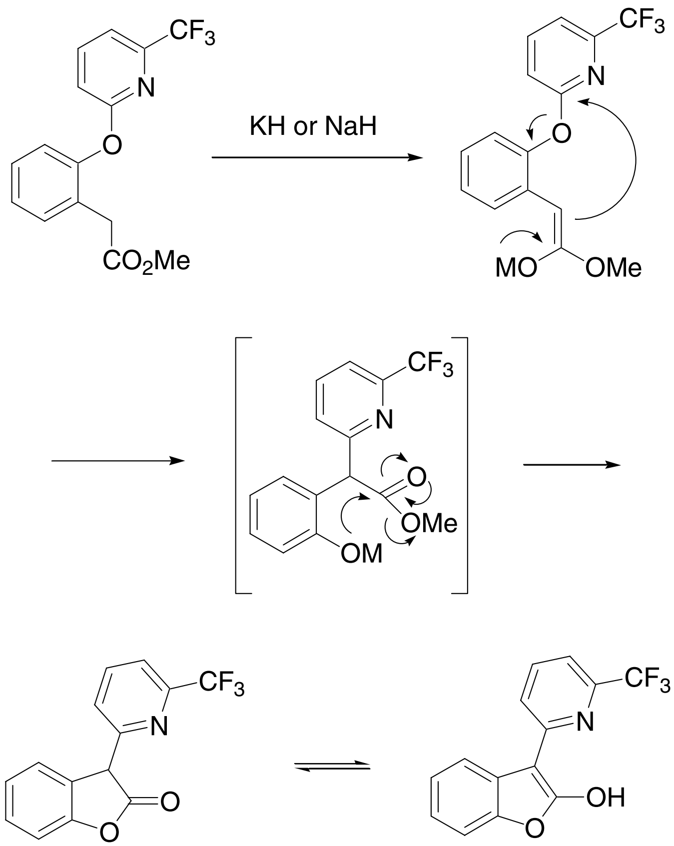
Truce–Smile rearrangement

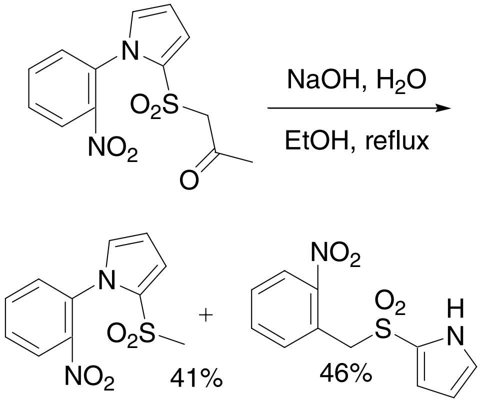
Smiles rearrangement where Y is carbon:



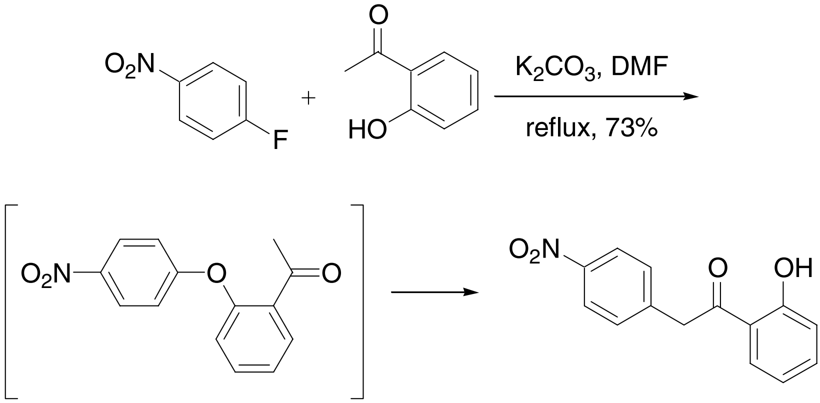
Example 1[6]



Example 2[8]



Example 3[9]



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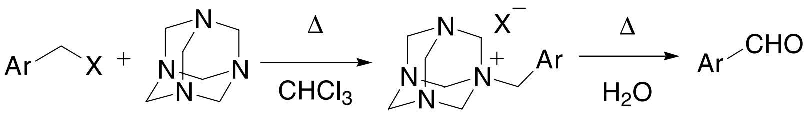
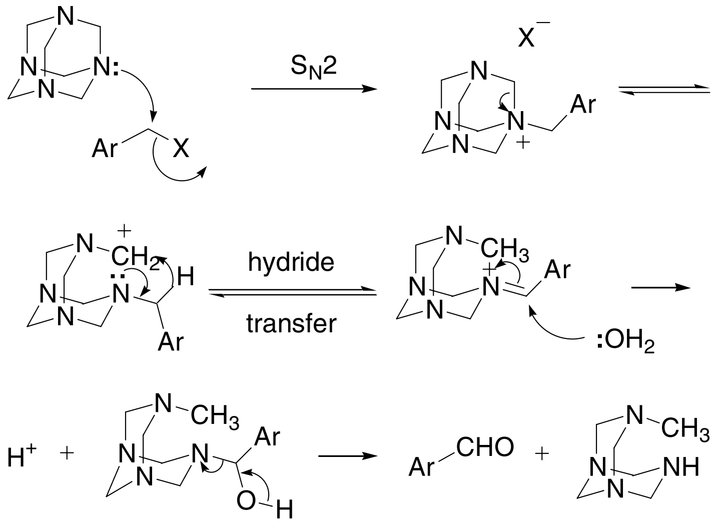
Sommelet reaction

Transformation of benzyl halides to the corresponding benzaldehydes with the aide of hexamethylenetetramine.

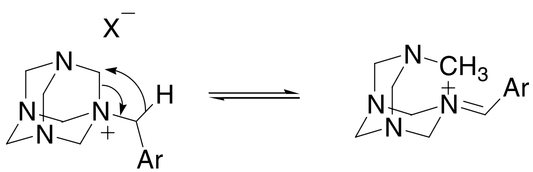


hexamethylenetetramine

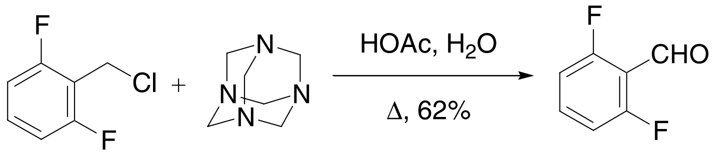


hemiaminal

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



Example[9]



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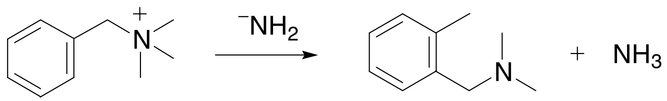
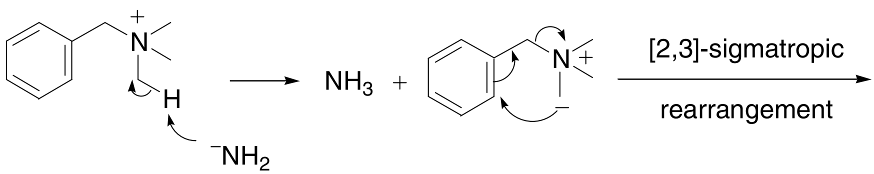
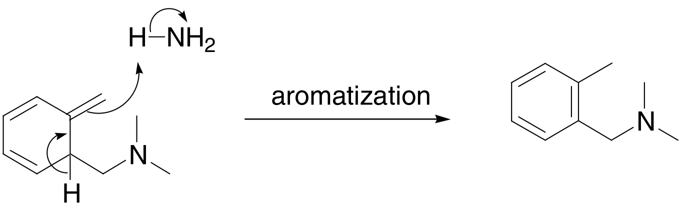
Sommelet–Hauser rearrangement

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

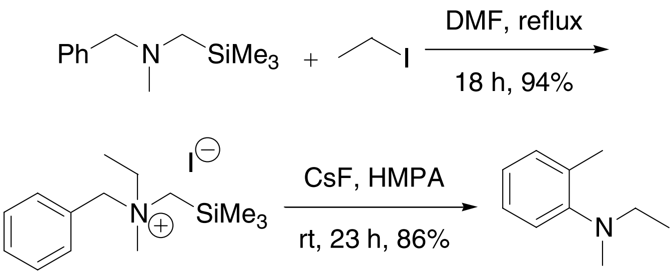




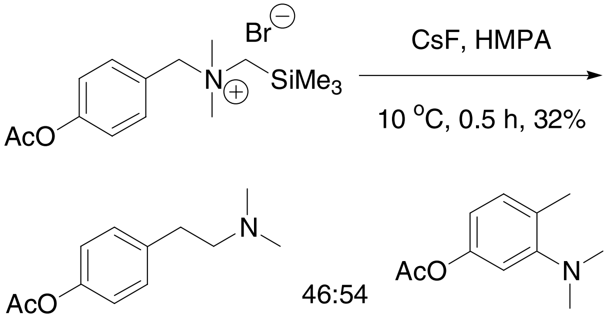
ammonium ylide



Example 1[5]



Example 2[6]



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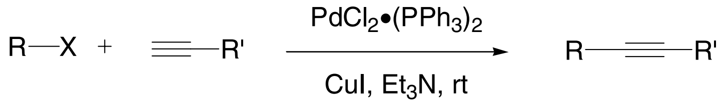
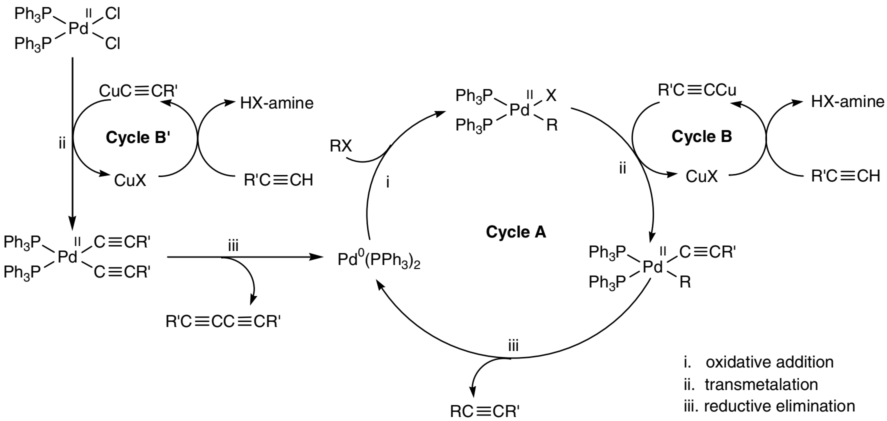
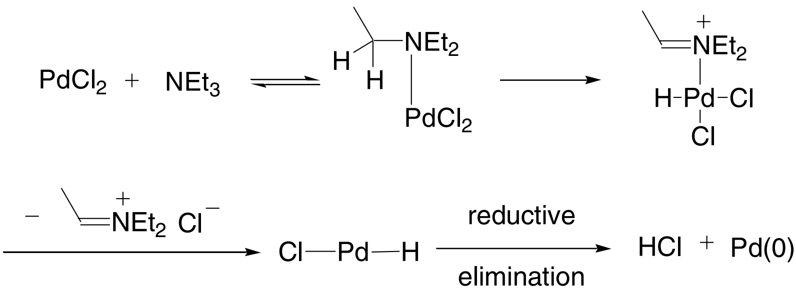
Sonogashira reaction

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.

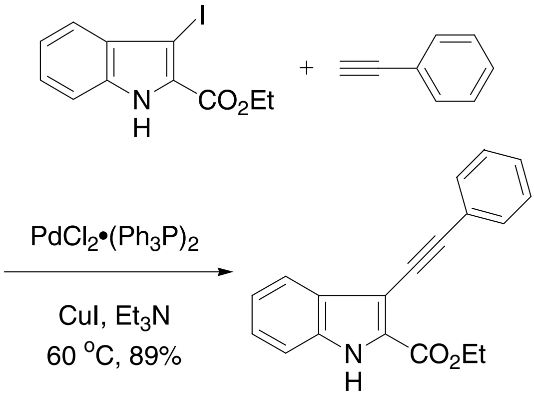




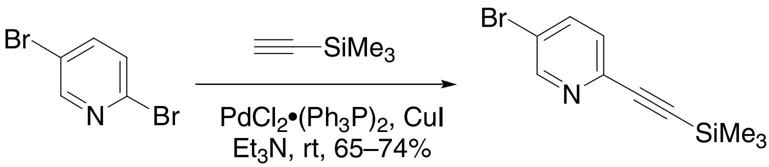
Note that Et_3N may reduce Pd(II) to Pd(0) as well, where Et_3N is oxidized to iminium ion at the same time:



Example 1[3]



Example 2[5]



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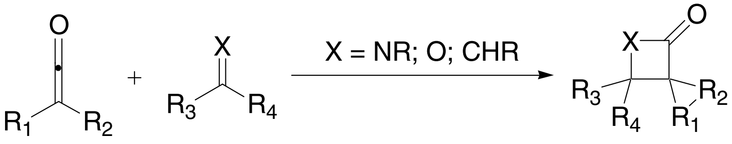
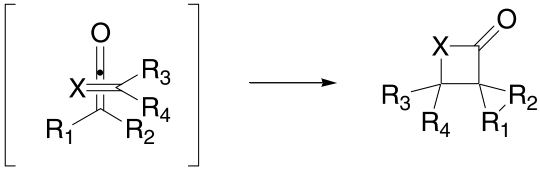
Staudinger ketene cycloaddition

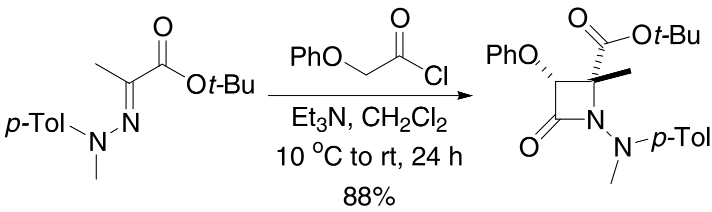
[2 + 2] Cycloaddition of ketene and imine to form β-lactam. Other coupling partners for ketene also include: olefin to give cyclobutanone and carbonyl to give β-lactone.



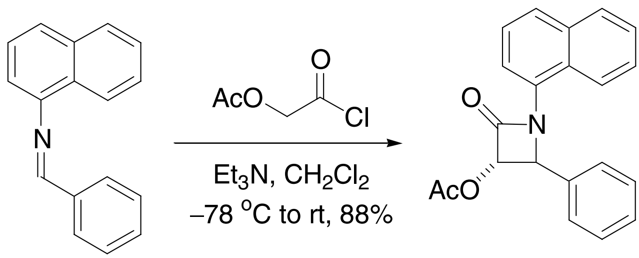
puckered transition state:



Example 1[8]



Example 2[9]



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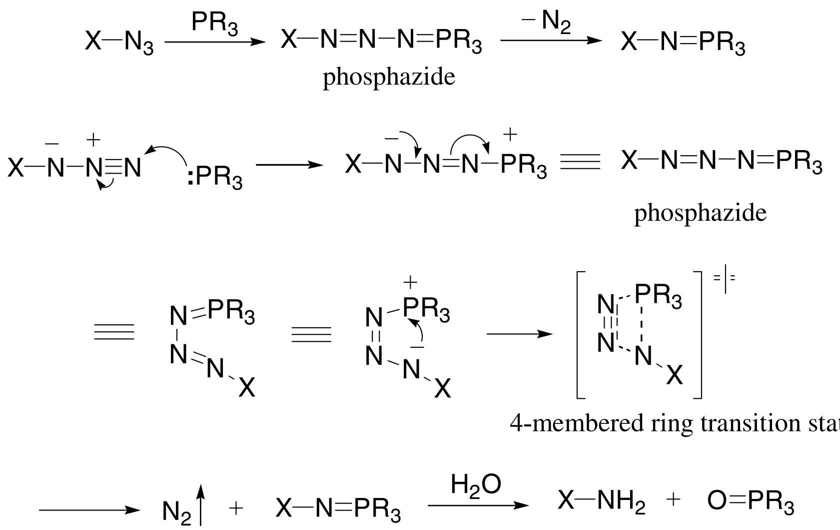
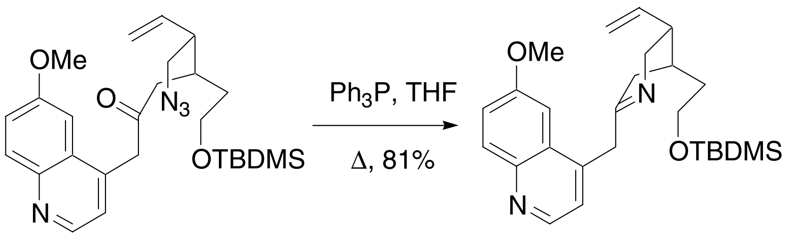
Staudinger reduction

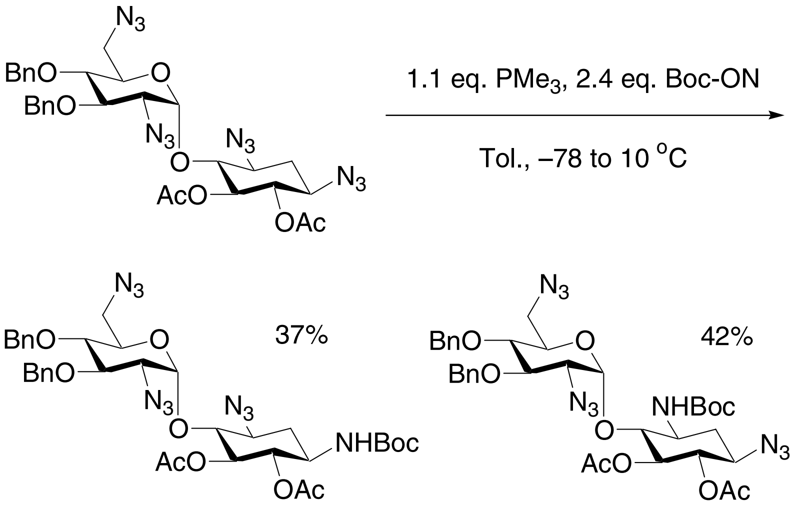
Phosphazo compounds (e.g. iminophosphoranes) from the reaction of tertiary phosphine (Example Ph_3P) with organic azides.



Example 1[7]



Example 2[12]



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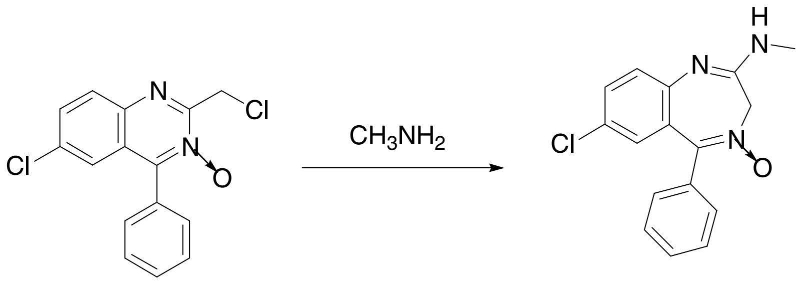
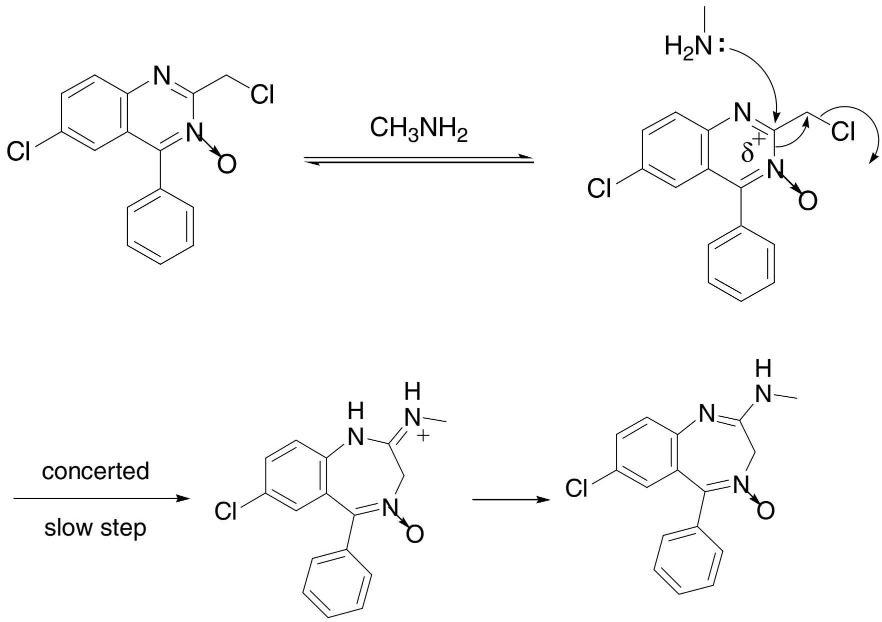
Sternbach benzodiazepine synthesis

Treatment of quinazoline 3-oxide with amines gives the rearrangement product, 1,4-benzodiazepine.



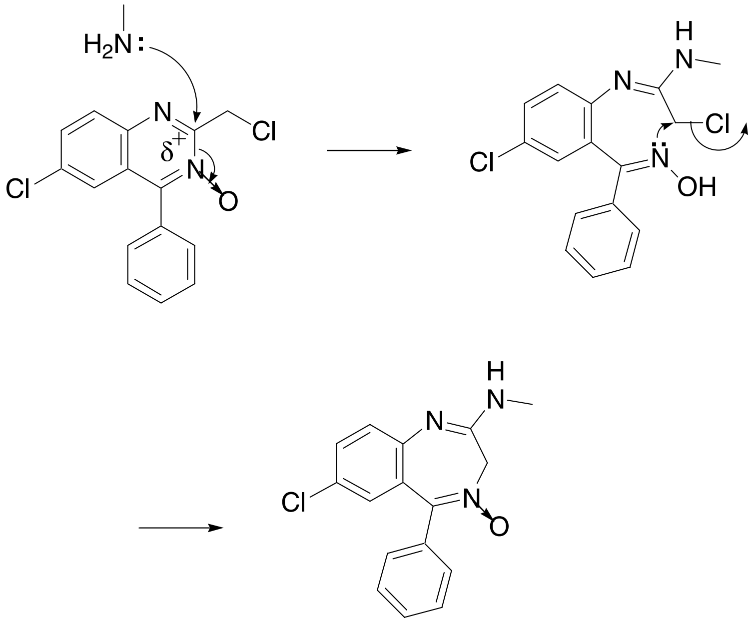
quinazoline 3-oxide

chlordiazepoxide (Librium)



chlordiazepoxide (Librium)

A step-wise mechanism is also possible:



chlordiazepoxide (Librium)

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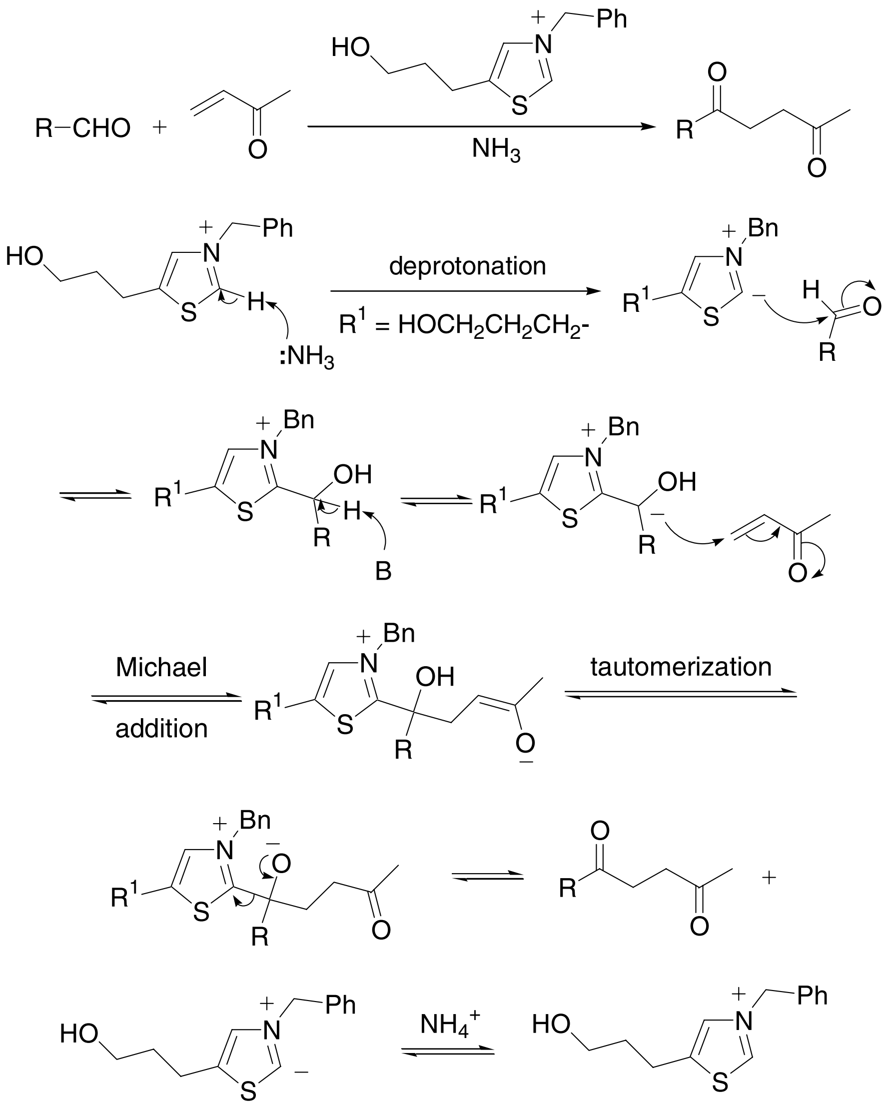
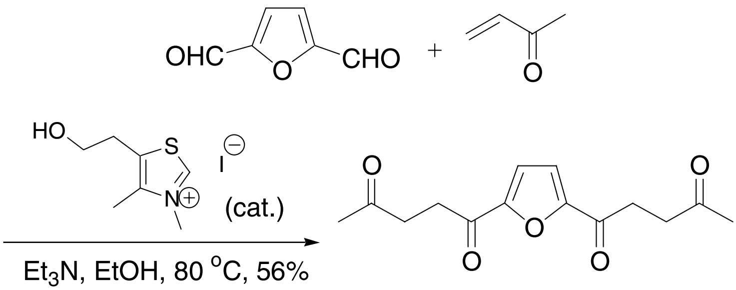
Stetter reaction

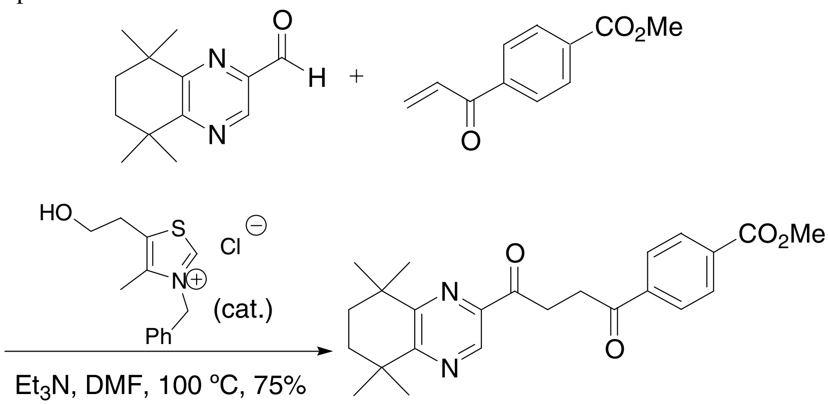
1,4-Dicarbonyl derivatives from aldehydes and α,β-unsaturated ketones. The thiazolium catalyst serves as a safe surrogate for $^{-}$CN. Also known as the Michael–Stetter reaction. *Cf*. Benzoin condensation.



Example 1[4]



Example 2[11]



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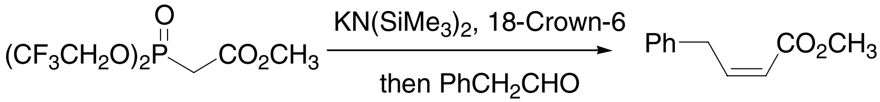
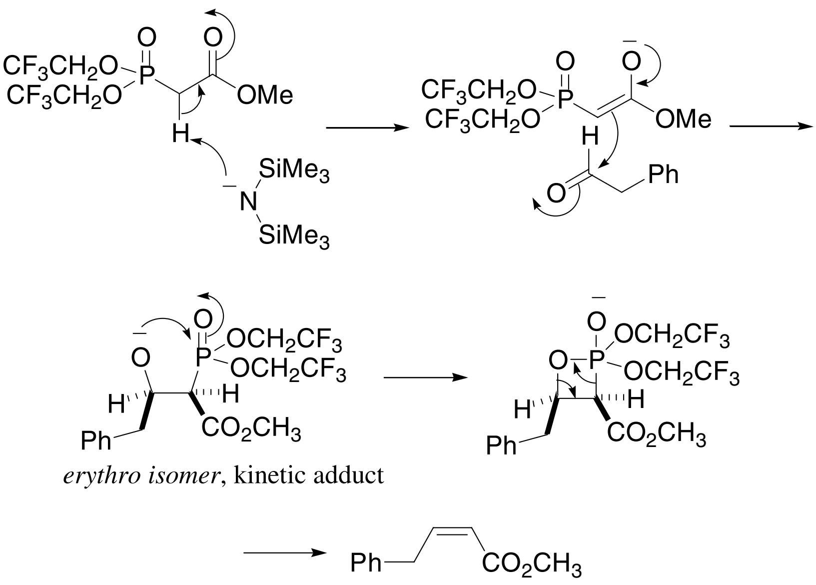
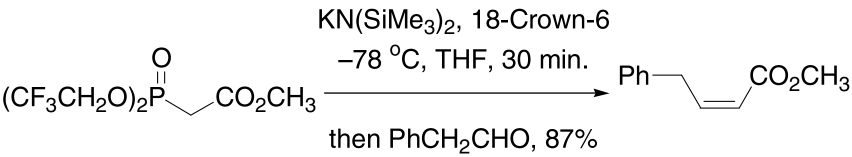
Still–Gennari phosphonate reaction

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

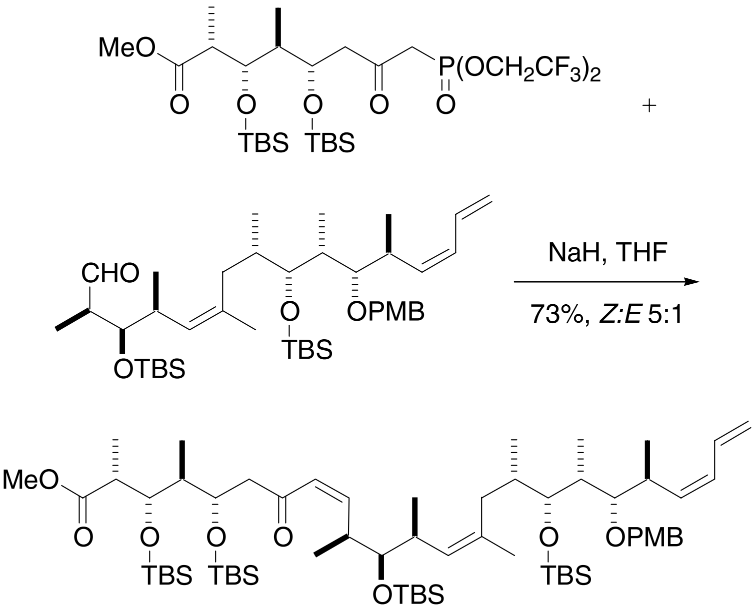




Example 1[3]



Example 2[12]



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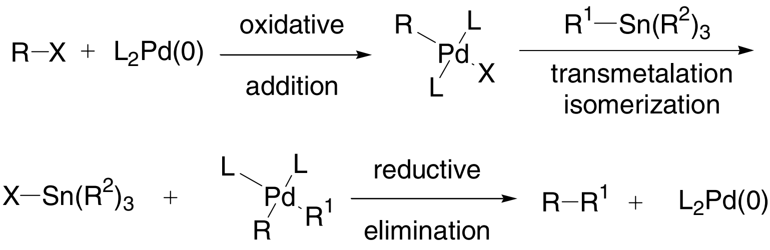
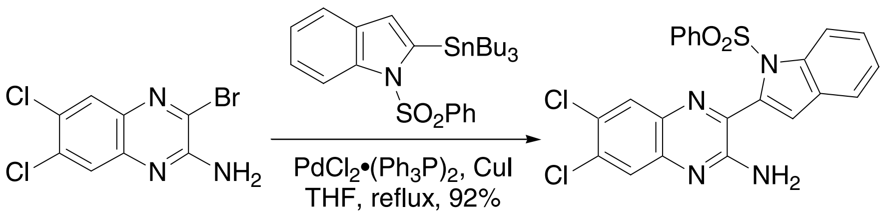
Stille coupling

Palladium-catalyzed cross-coupling reaction of organostannanes with organic halides, triflates, *etc*. For the catalytic cycle, see Kumada coupling on page 345.

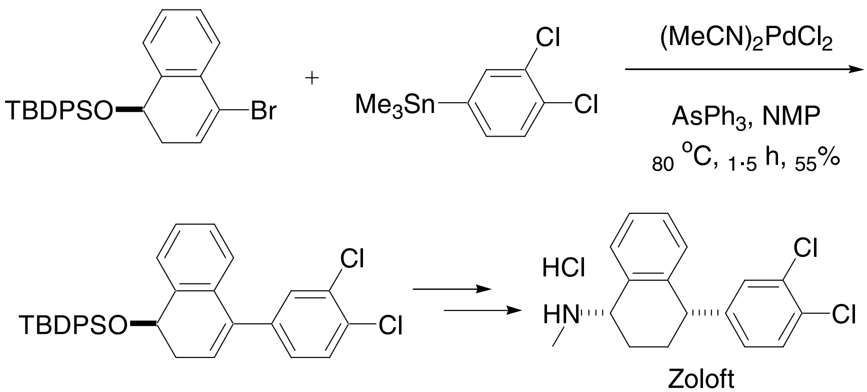
$$R{-}X \;+\; R^1{-}Sn(R^2)_3 \xrightarrow{Pd(0)} R{-}R^1 \;+\; X{-}Sn(R^2)_3$$



Example 1[6]



Example 2[7]



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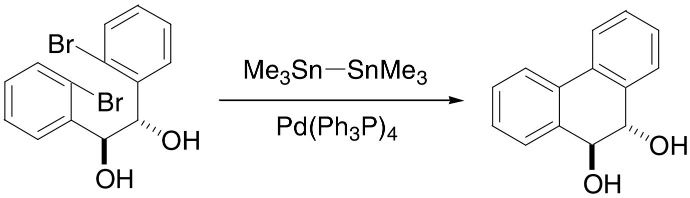
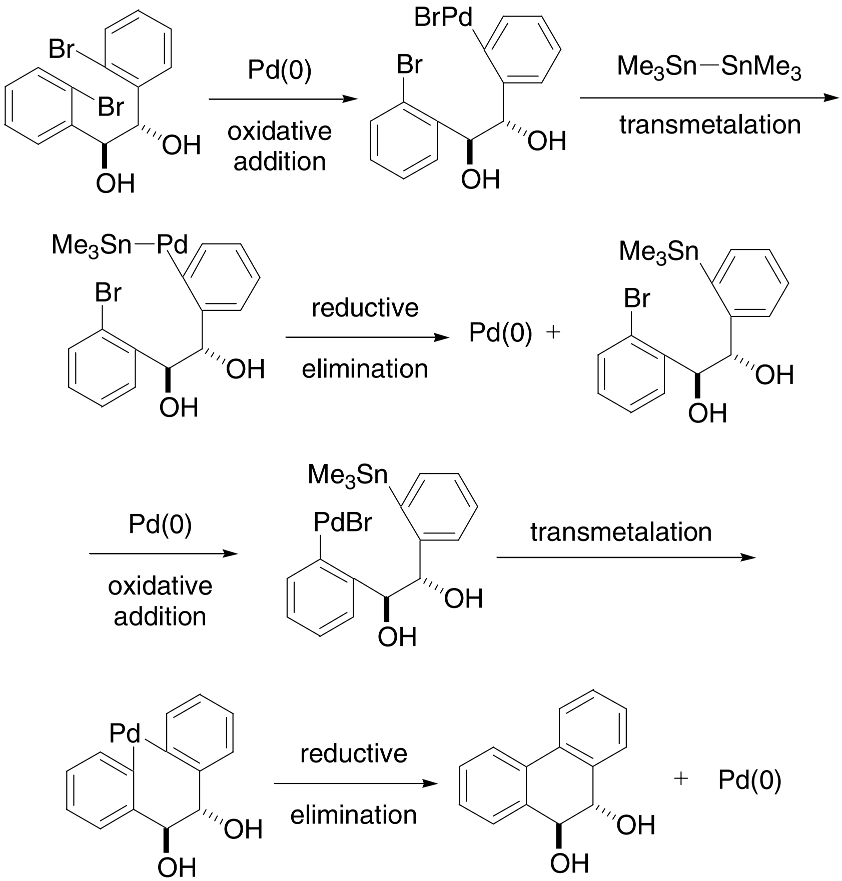
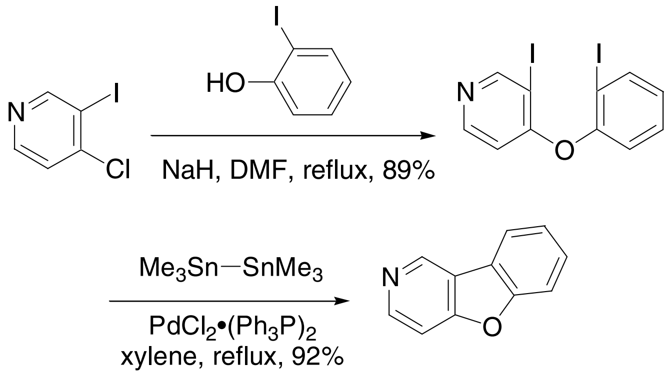
Stille–Kelly reaction

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





Example[8]



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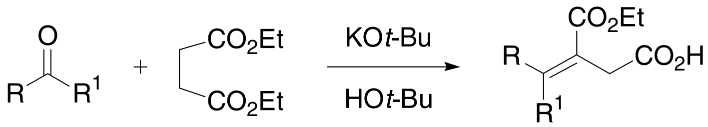
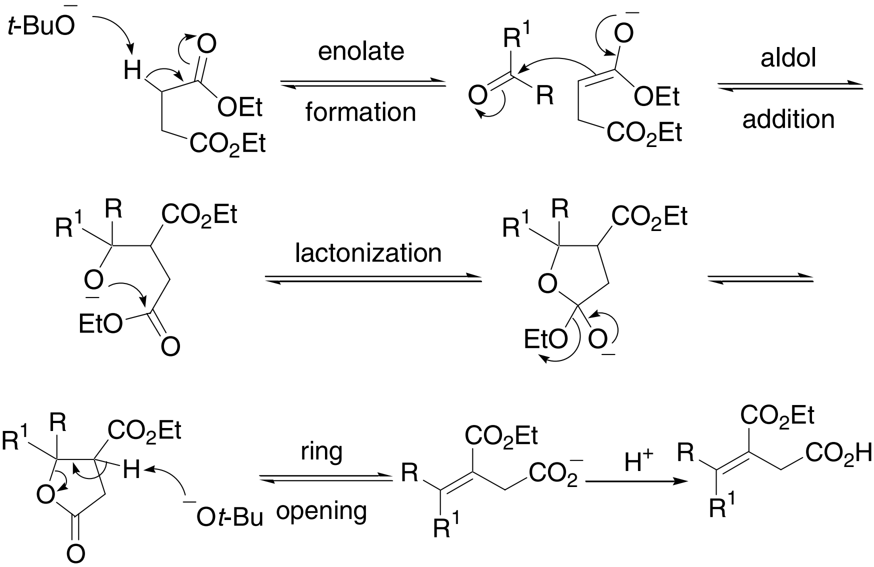
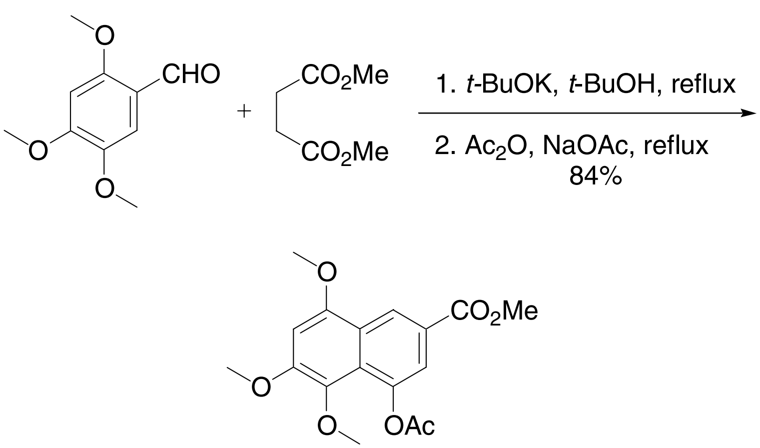
Stobbe condensation

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

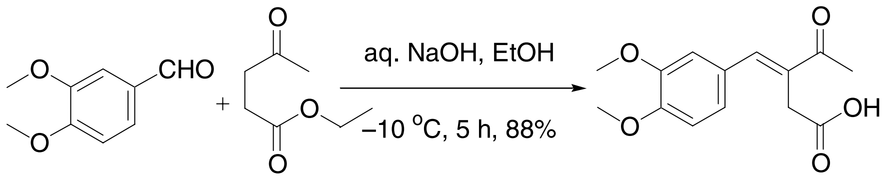




Example 1[12]



Example 2[13]



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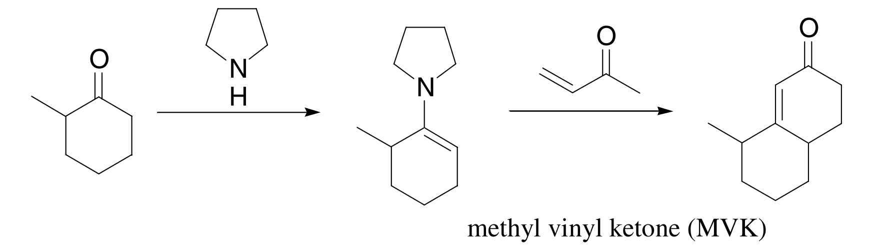
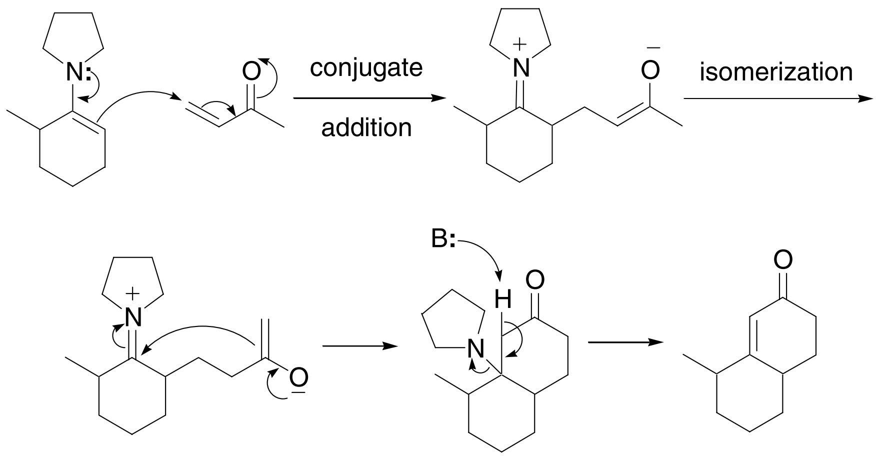
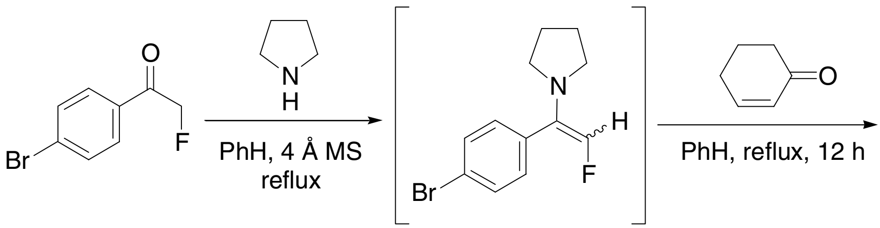
Stork enamine reaction

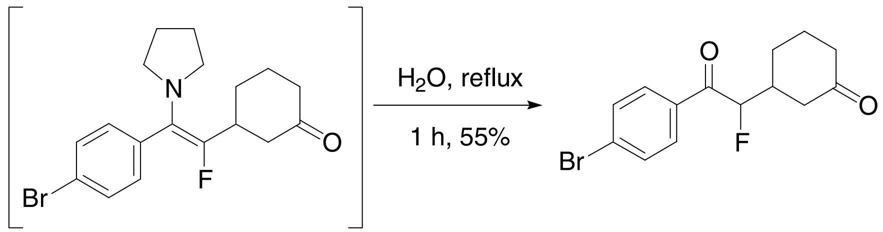
A variant of the Robinson annulation, where bulky amines such as pyrrolidine are used, making the conjugate addition to methyl vinyl ketone (MVK) take place at the less hindered side of two possible enamines.



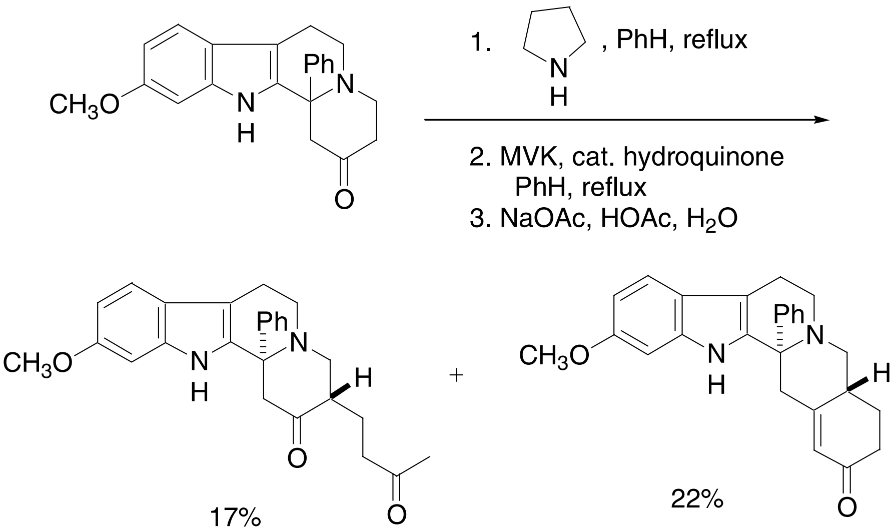


Example 1[7]





Example 2[8]



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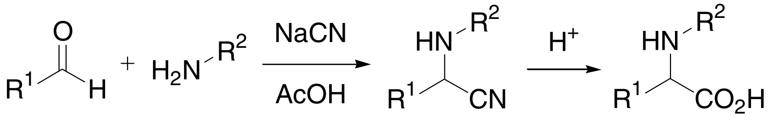
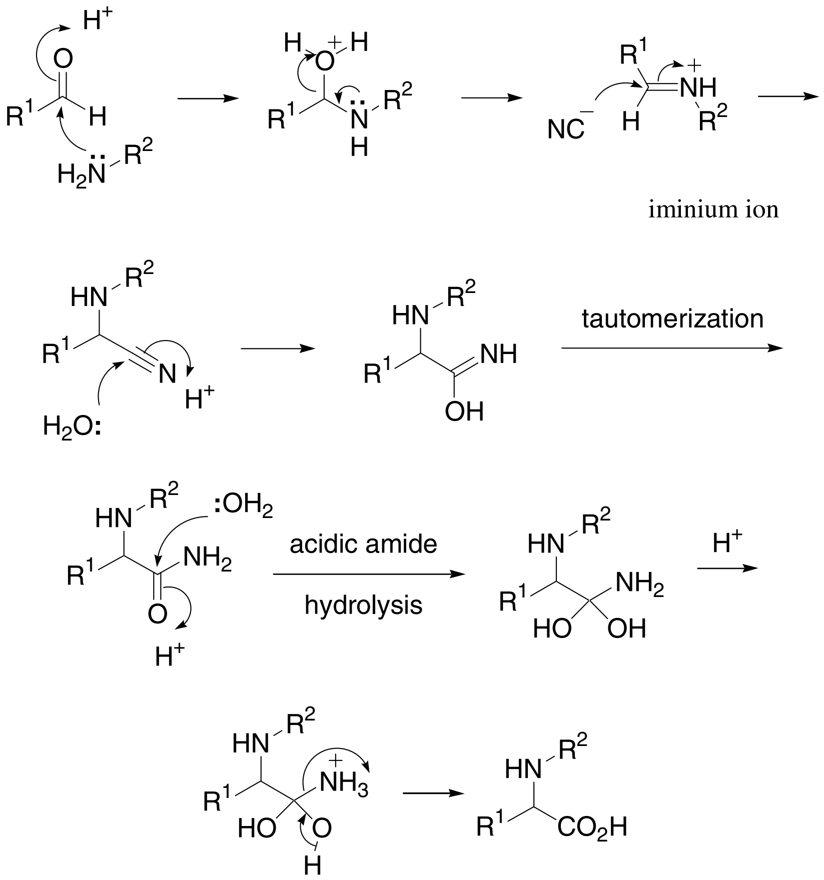
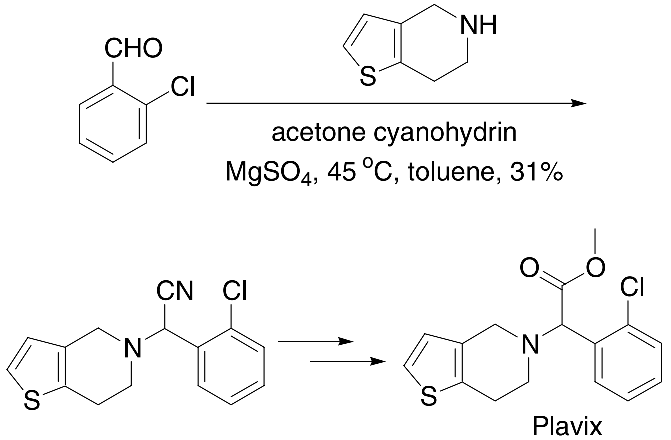
Strecker amino acid synthesis

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

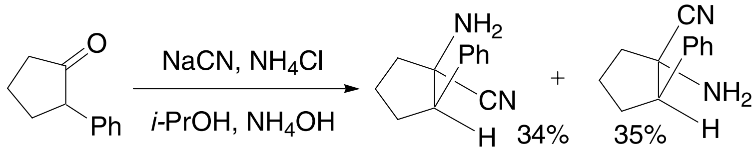




Example 1[6]



Example 2[13]



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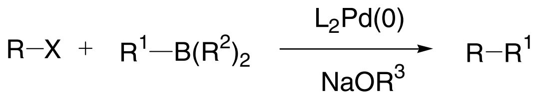
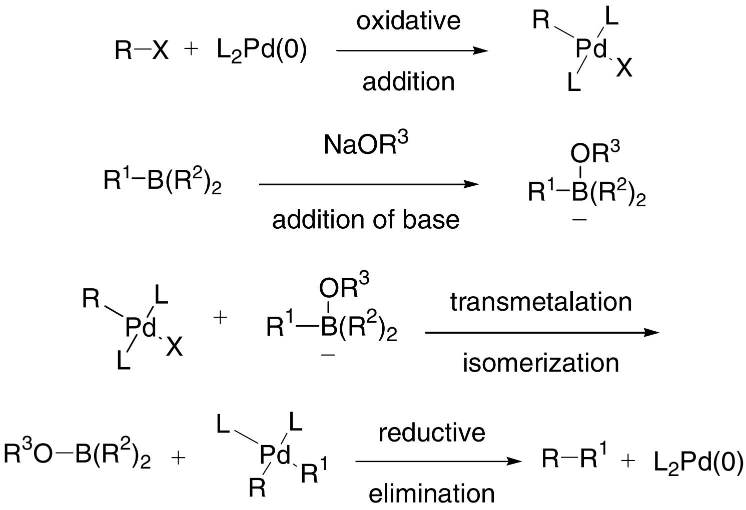
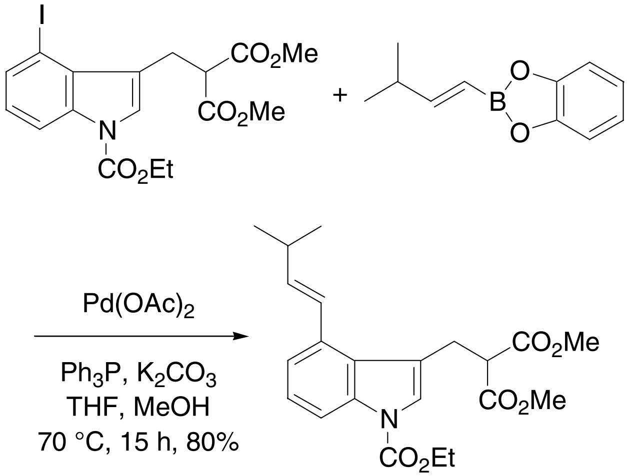
Suzuki coupling

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 345.

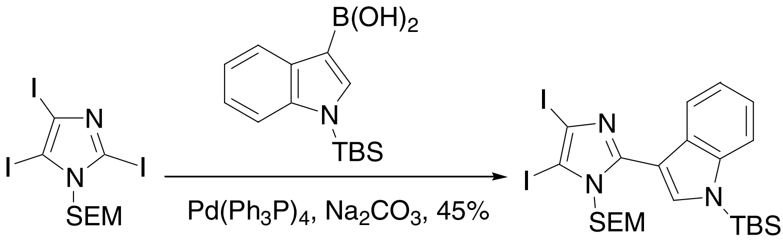




Example 1[1]



Example 2[4]



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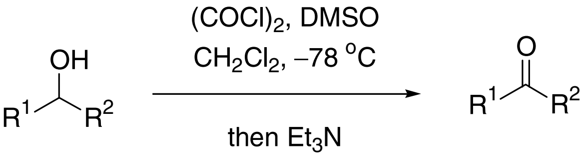
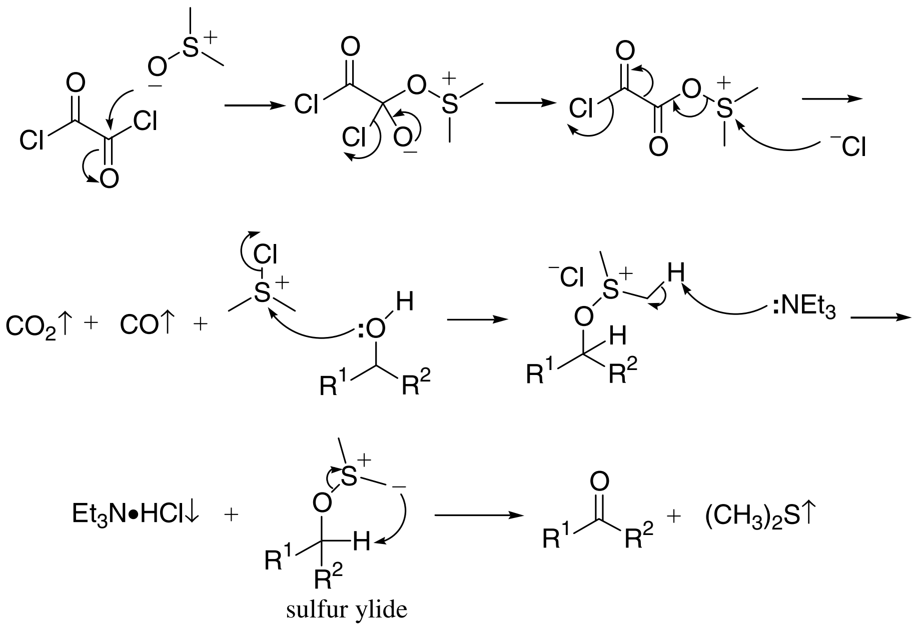
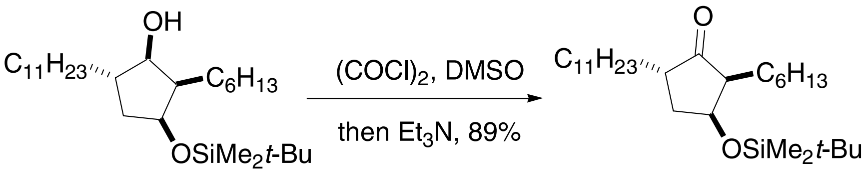
Swern oxidation

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

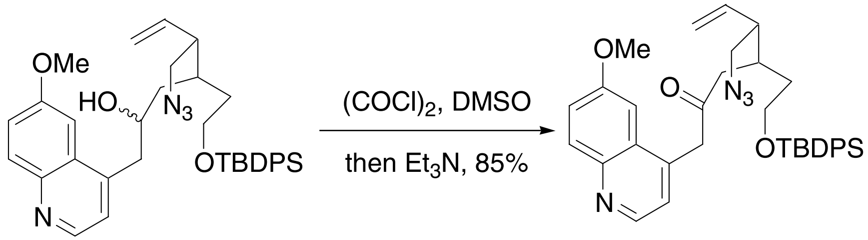




Example 1[5]



Example 2[11]



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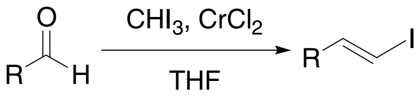
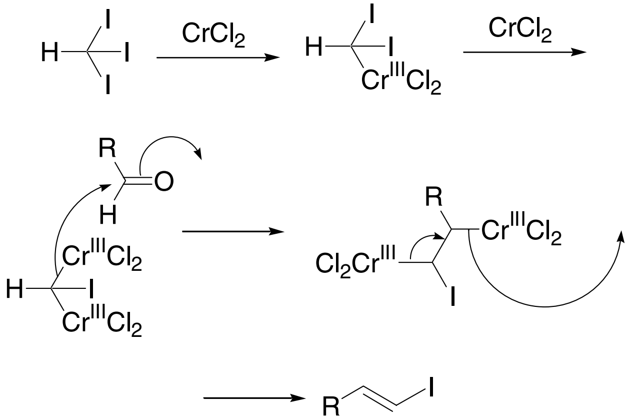
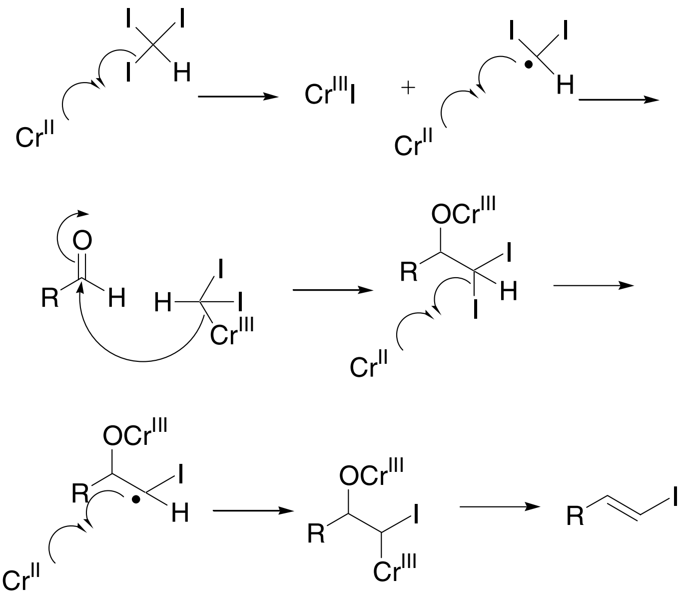
Takai iodoalkene synthesis

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

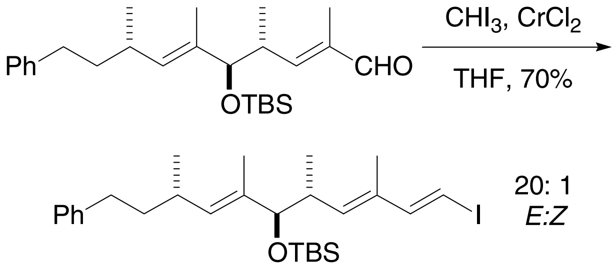




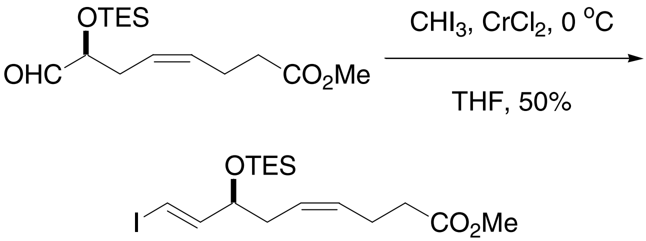
A radical mechanism is recently proposed[10]



Example 1[2]



Example 2[5]



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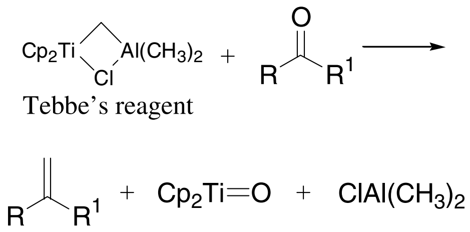
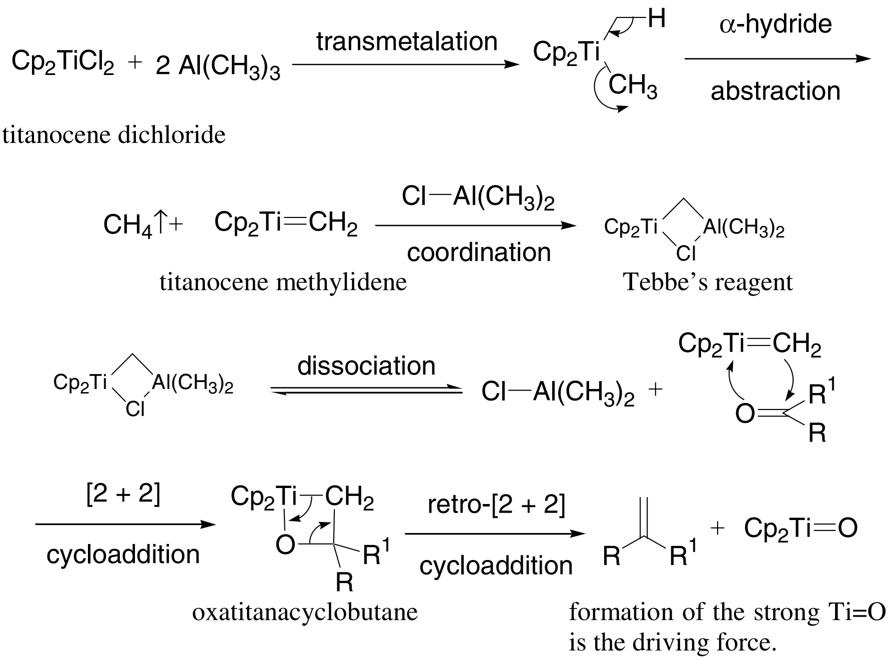
Tebbe olefination

Transformation of a carbonyl compound to the corresponding *exo*-olefin using Tebbe's reagent.

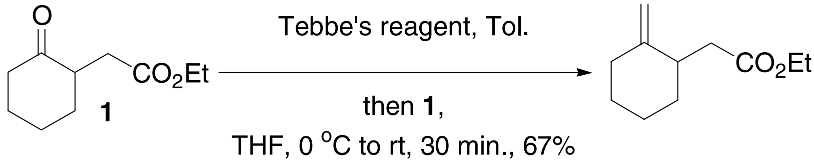




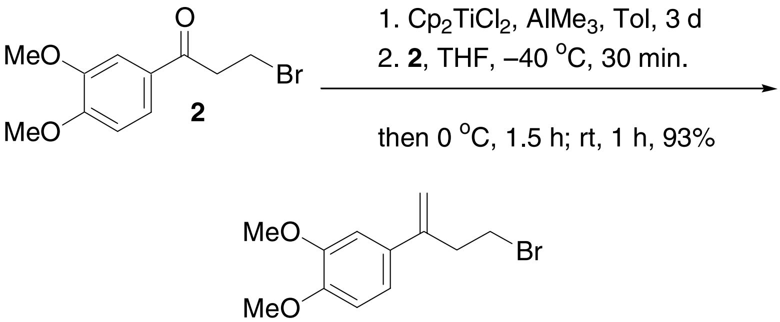
Petasis alkenylation

The Petasis reagent (Me_2TiCp_2, dimethyltitanocene) undergoes similar olefination reactions with ketones and aldehydes. The originally proposed mechanism[5] 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]

Example 1[3]



Example 2[4]



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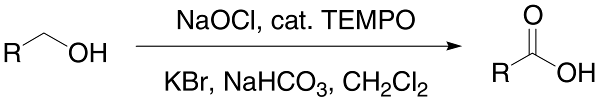
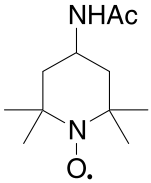
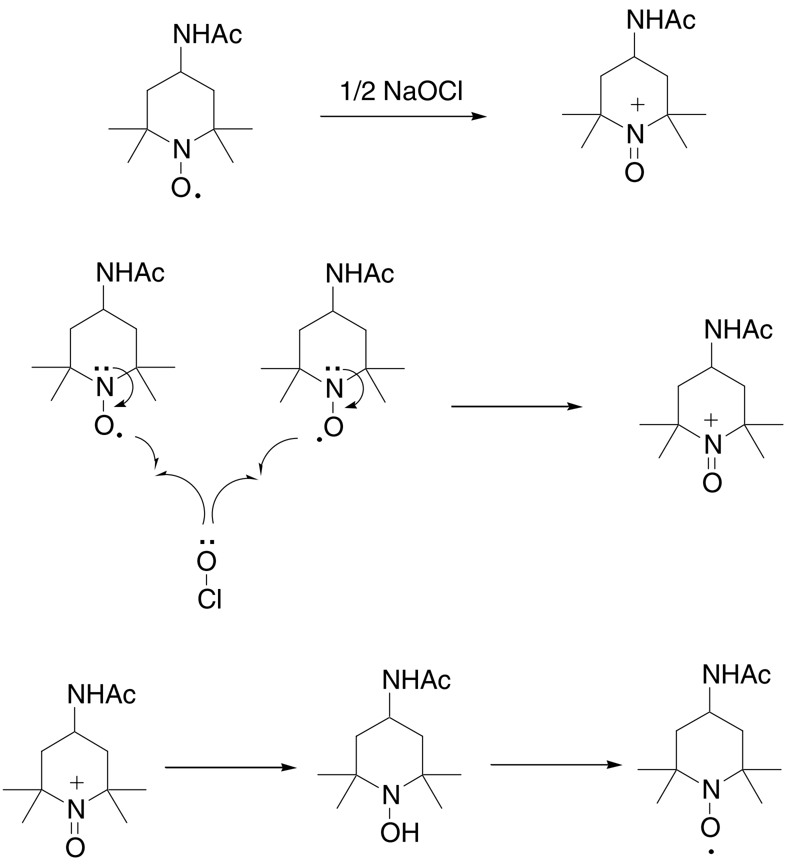
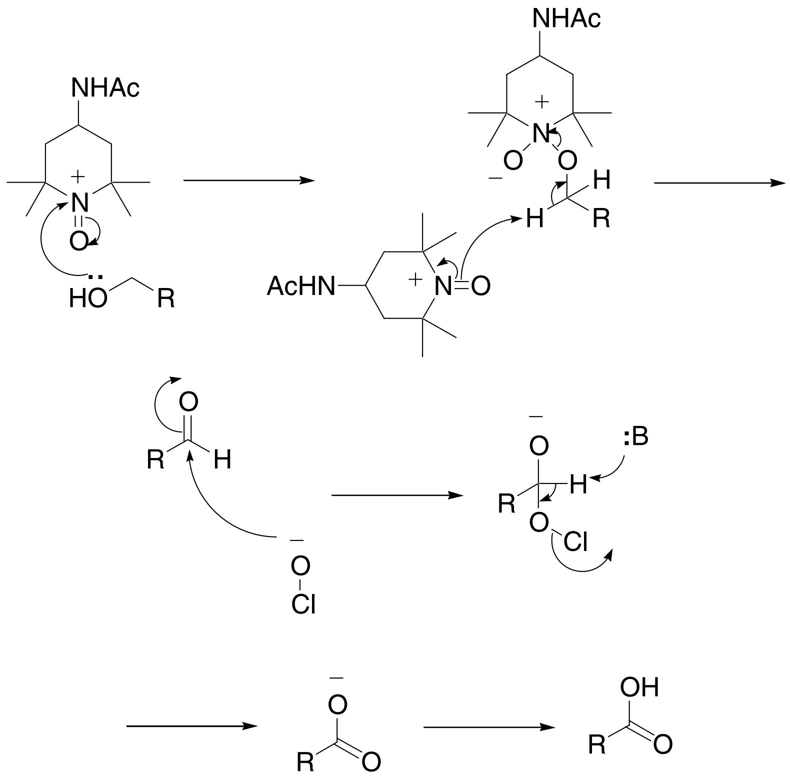
TEMPO-mediated oxidation



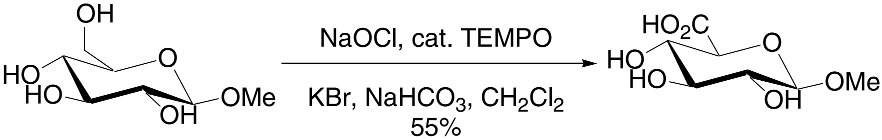
TEMPO = **te**tra**m**ethyl **p**entahydropyridine **o**xide:



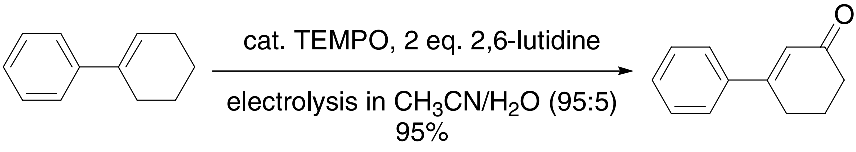




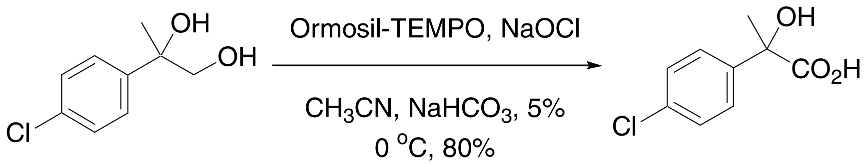
Example 1[7]



Example 2[10]



Example 3[12]



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

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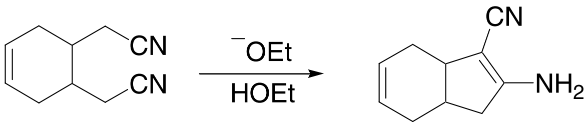
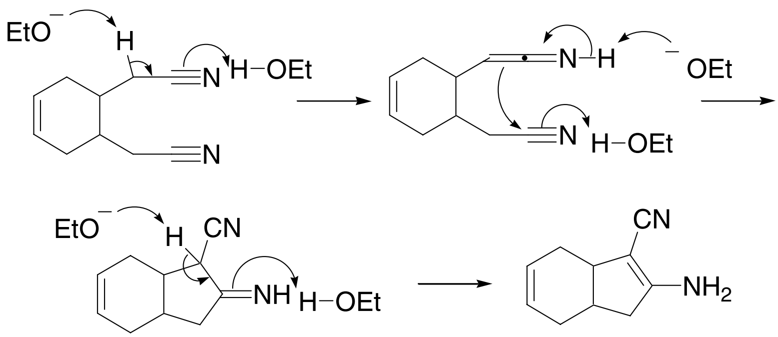
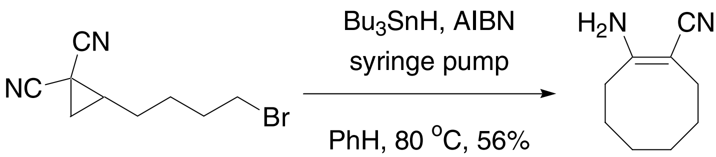
Thorpe–Ziegler reaction

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

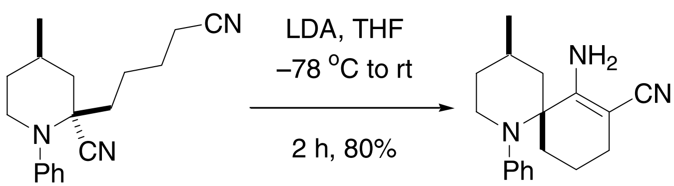




Example 1, a radical Thorpe–Ziegler reaction[5]



Example 2[10]



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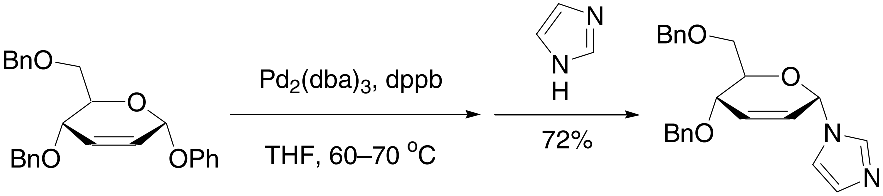
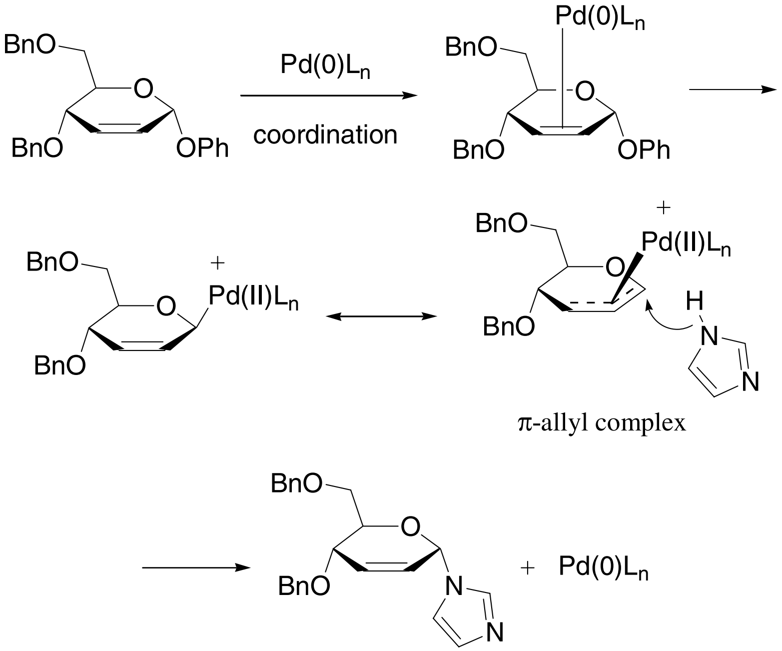
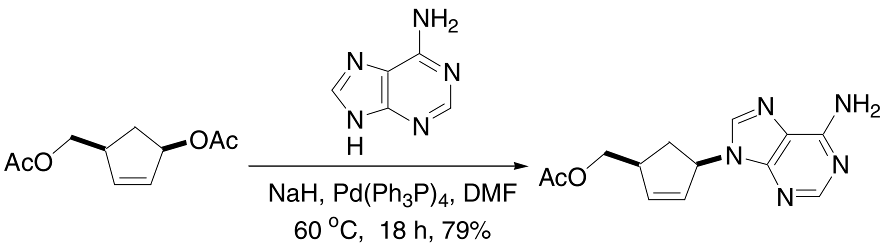
Tsuji–Trost reaction

Palladium-catalyzed allylation using nucleophiles with allylic halides, acetates, carbonates, *etc*. via intermediate allylpalladium complexes, and typically with overall retention of stereochemistry.

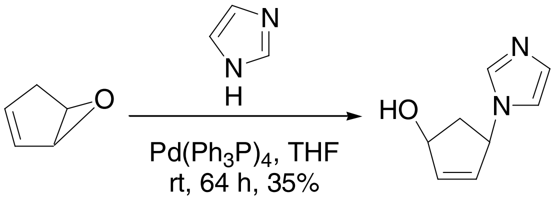




Example 1[4]



Example 2[7]



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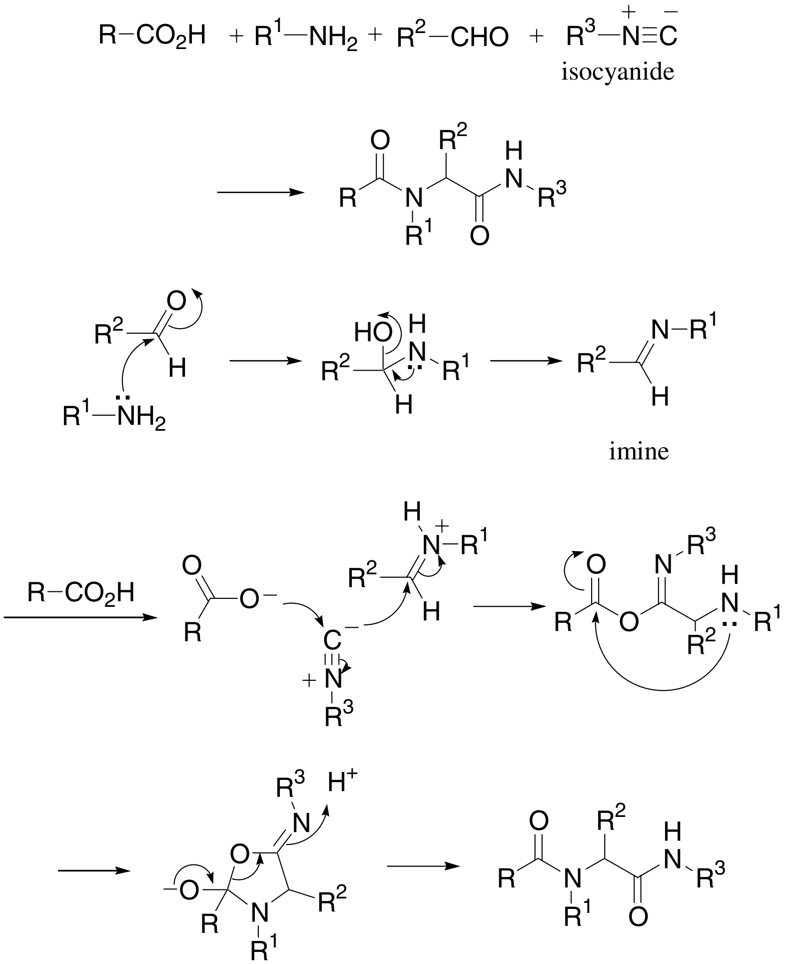
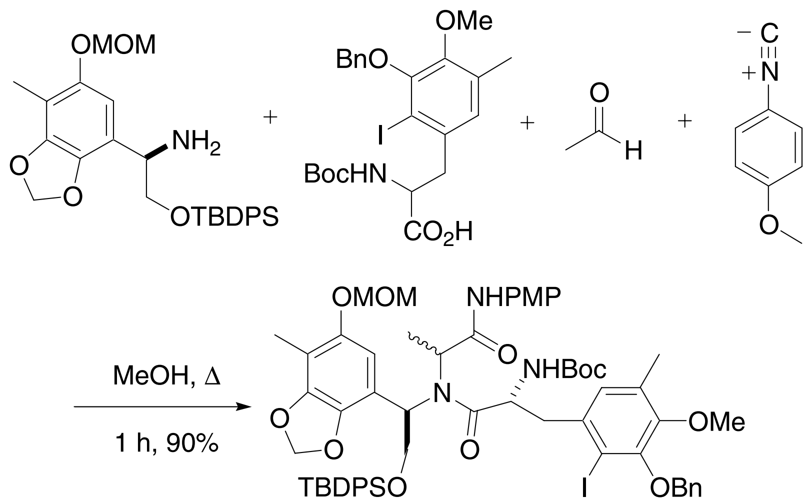
Ugi reaction

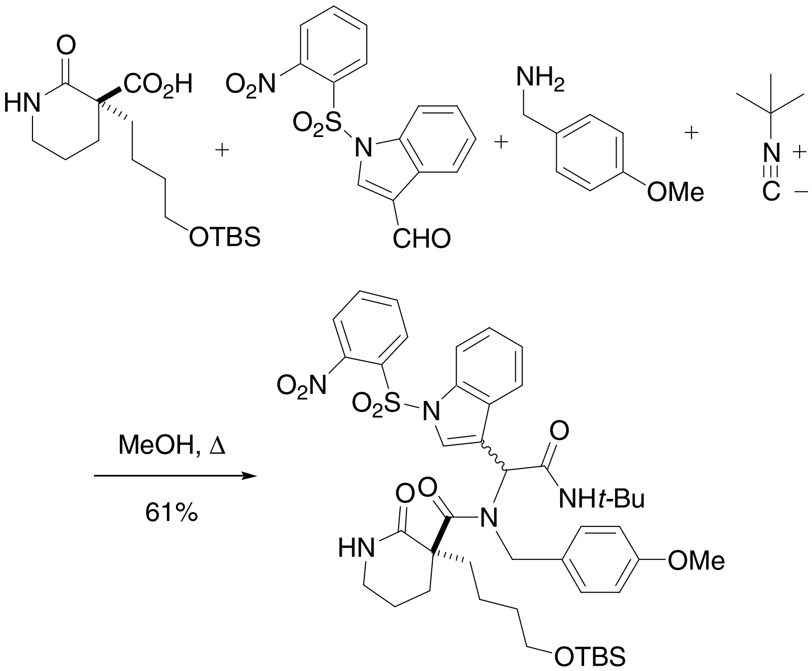
Four-component condensation (4CC) of carboxylic acids, *C*-isocyanides, amines, and carbonyl compounds to afford diamides. *Cf*. Passerini reaction.



Example 1[10]



Example 2[13]



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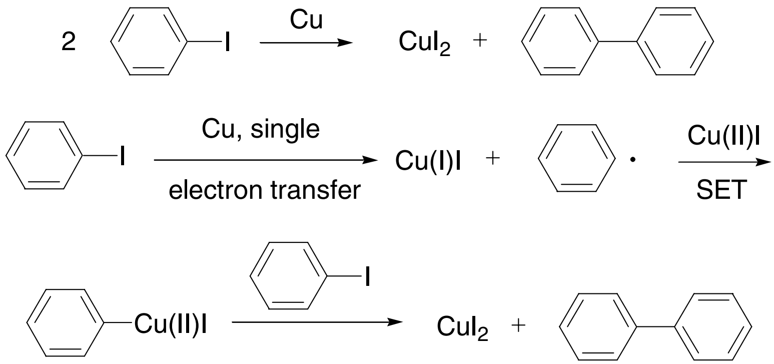
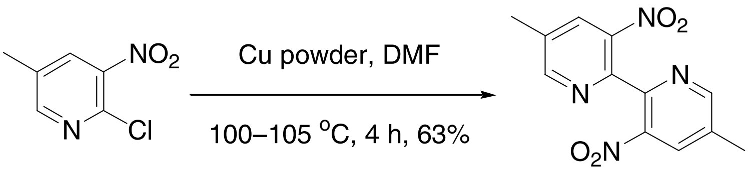
Ullmann reaction

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

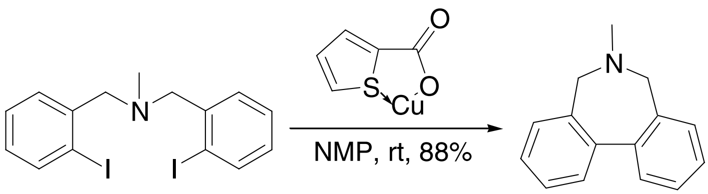


The overall transformation of PhI to PhCuI is an oxidative addition process.

Example 1[5]



Example 2[6]



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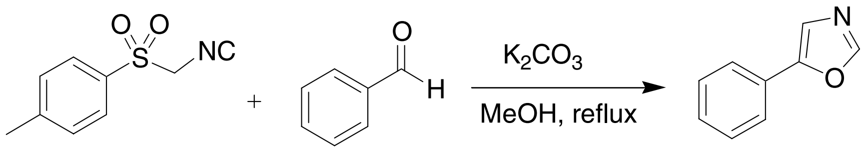
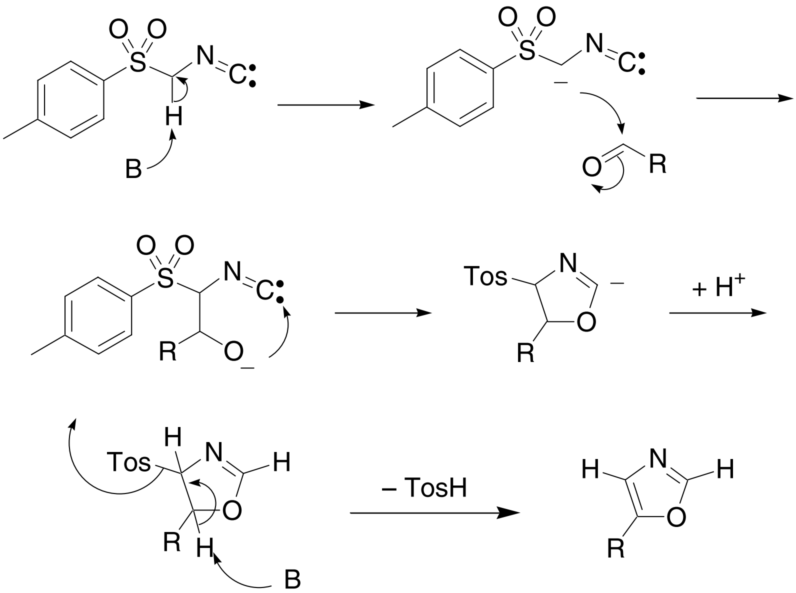
van Leusen oxazole synthesis

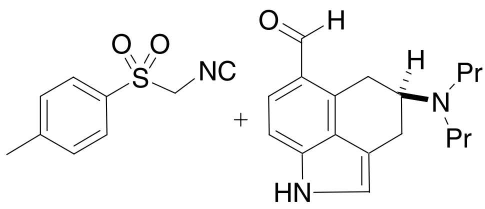
5-Substituted oxazoles through the reaction of *p*-tolylsulfonylmethyl isocyanide (TosMIC) with aldehydes in protic solvents at refluxing temperatures.

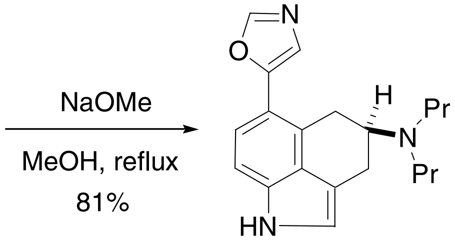


p-tolylsulfonylmethyl isocyanide (TosMIC)

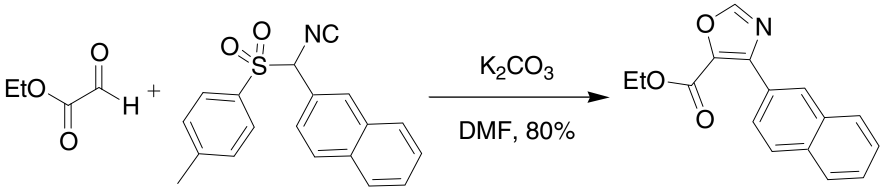


Example 1[7]





Example 2[10]



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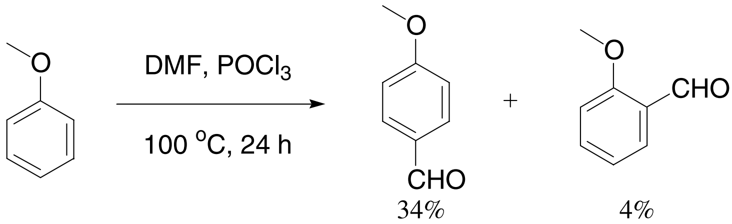
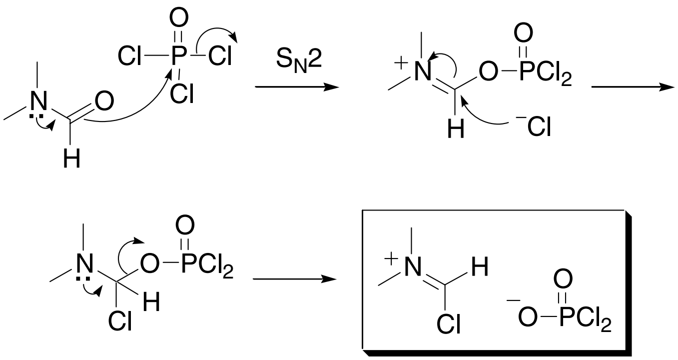
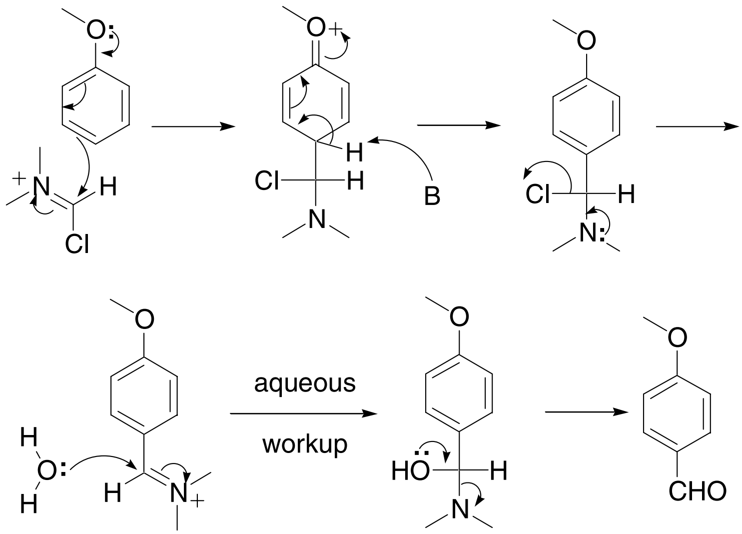
Vilsmeier–Haack reaction

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

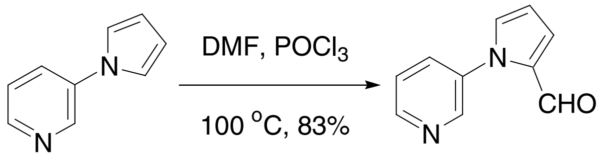




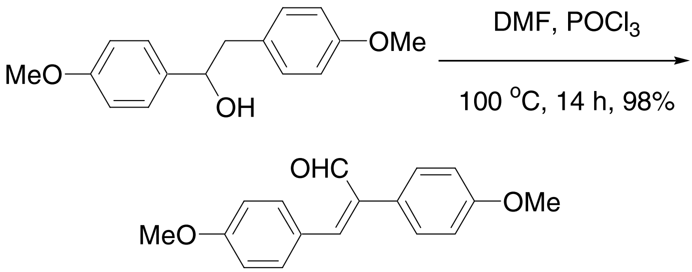
Vilsmeier–Haack reagent



Example 1[3]



Example 2[2]



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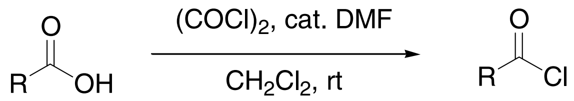
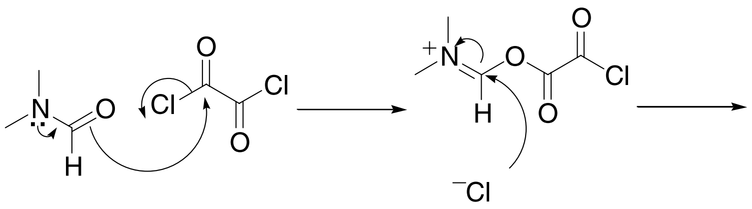
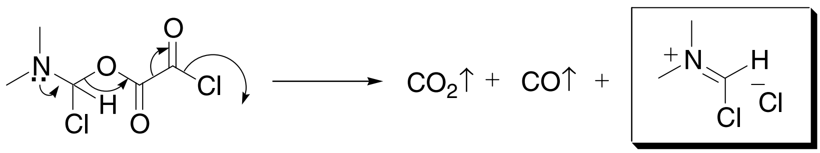
Vilsmeier mechanism for acid chloride formation

Transformation of a carboxylic acid to the corresponding acid chloride using oxalyl chloride and catalytic amount of dimethyl formamide (DMF). It is a lot faster than without DMF, which generally needs reflux.

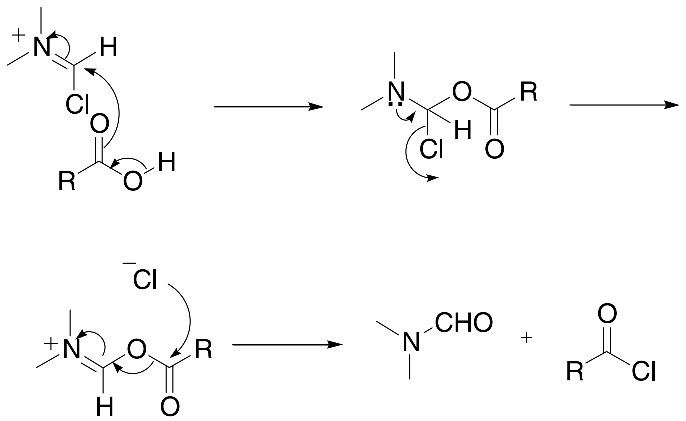




DMF oxalyl chloride



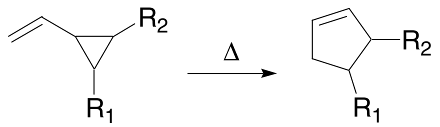
Vilsmeier–Haack reagent

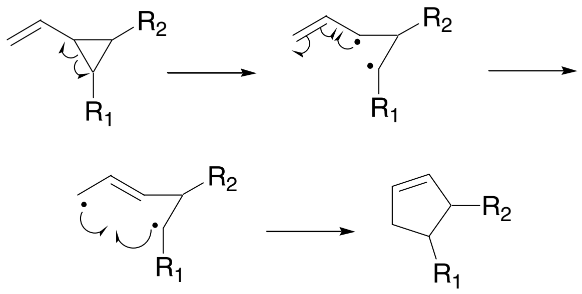


DMF recovered, therefore only catalytic amount is required

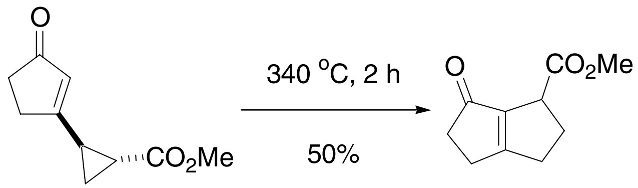
Vinylcyclopropane−cyclopentene rearrangement

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

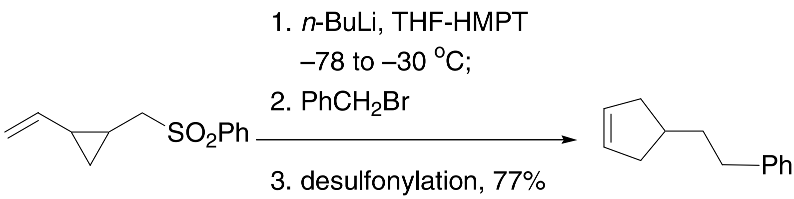




Example 1[5]



Example 2[6]



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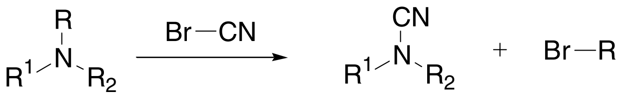
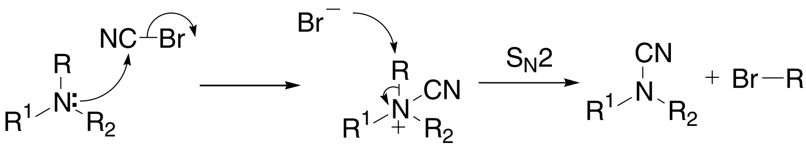
von Braun reaction

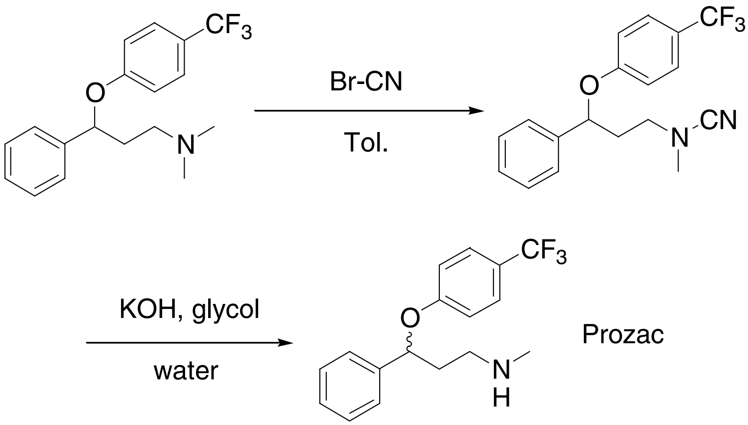
Treatment of tertiary amines with cyanogen bromide, resulting in a substituted cyanamide and alkyl halides.



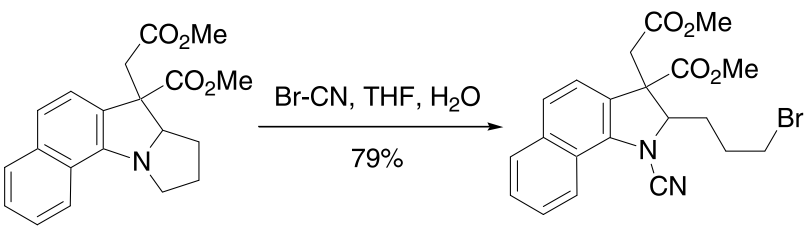
Cyanogen bromide (BrCN) is a *counterattack reagent*.



Example 1[6]



Example 2[7]



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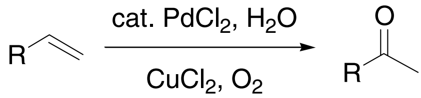
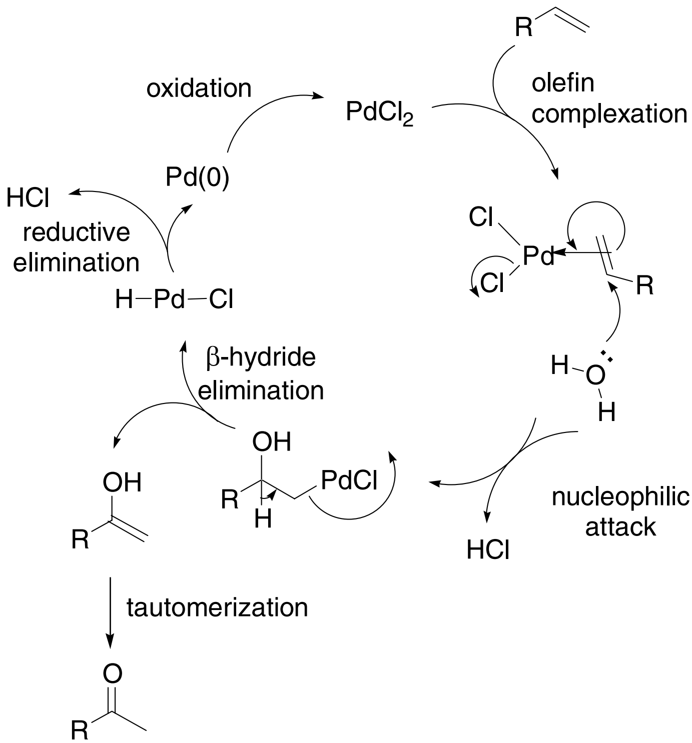
Wacker oxidation

Palladium-catalyzed oxidation of olefins to ketones.





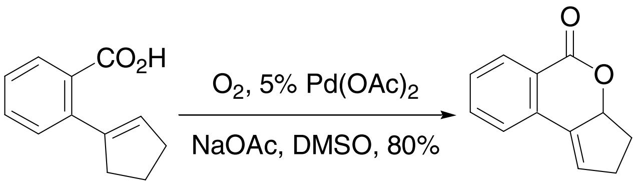
Regeneration of Pd(II):

$$Pd(0) + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl$$

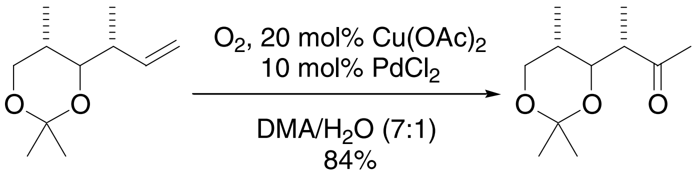
Regeneration of Cu(II):

$$CuCl + O_2 \longrightarrow CuCl_2 + H_2O$$

Example 1[6]



Example 2[10]



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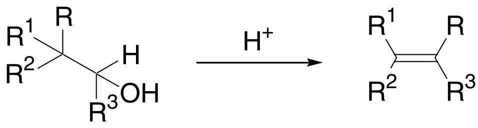
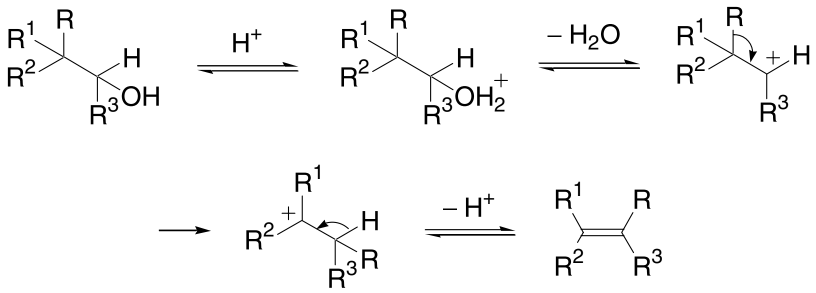
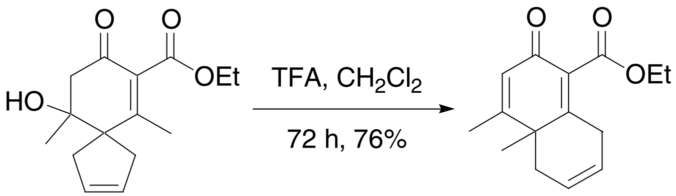
Wagner–Meerwein rearrangement

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

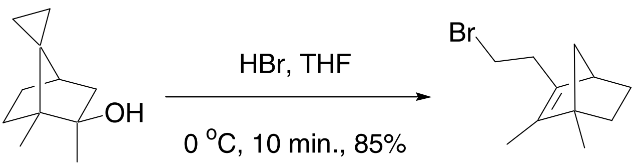




Example 1[13]



Example 2[14]



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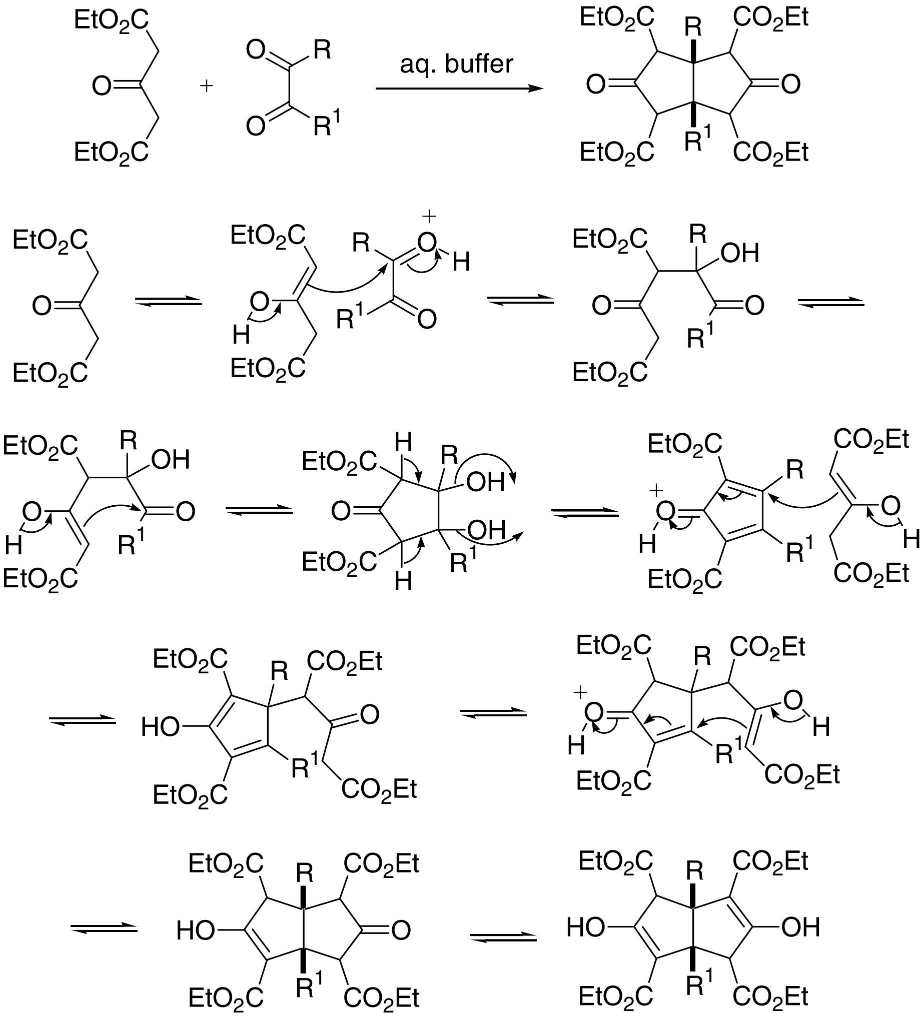
Weiss–Cook reaction

Synthesis of *cis*-bicyclo[3.3.0]octane-3,7-dione.



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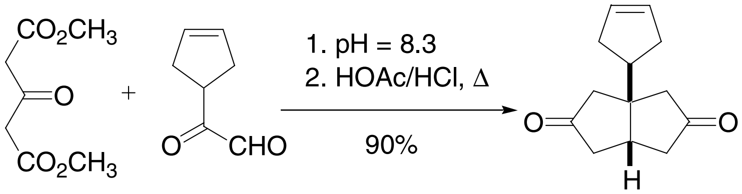

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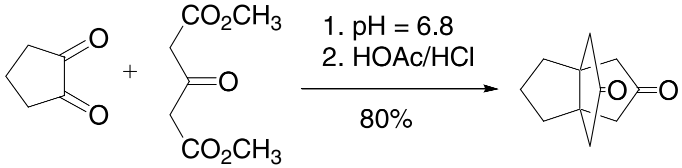

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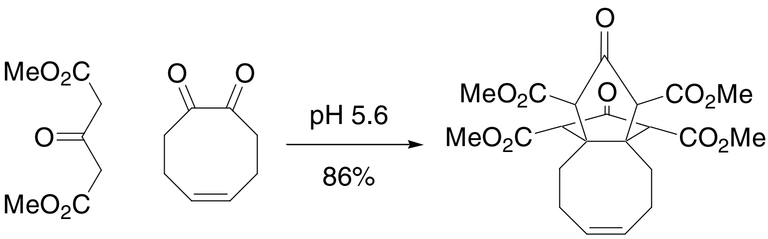

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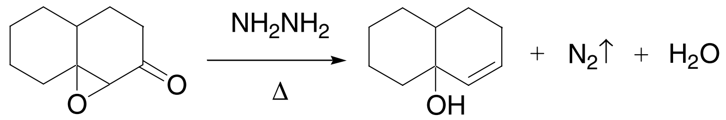
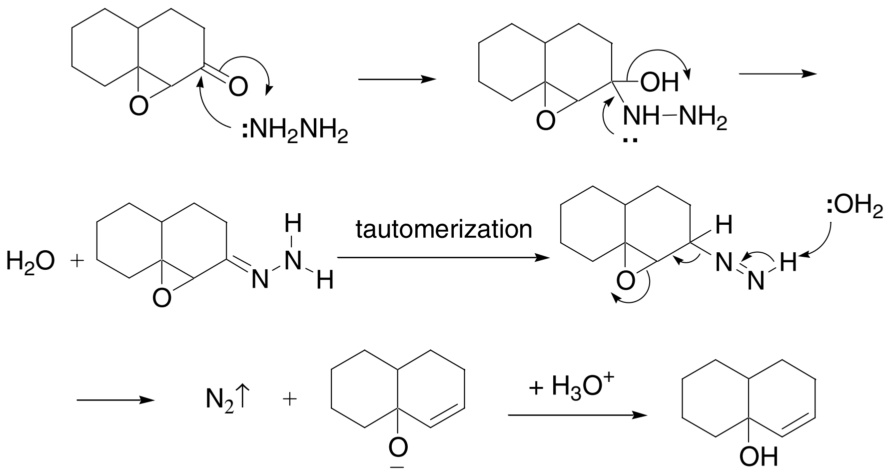
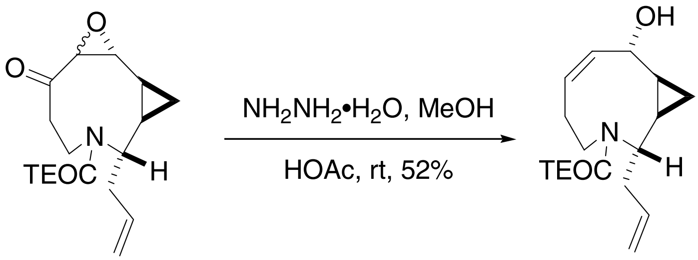
Wharton oxygen transposition reaction

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

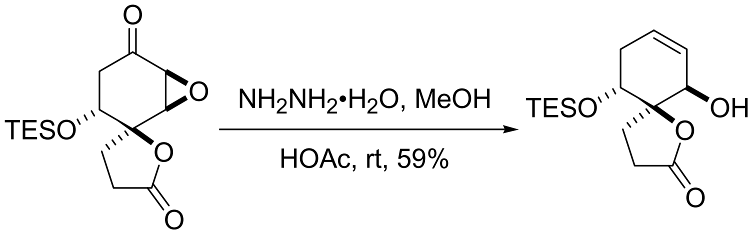




Example 1[5]



Example 2[7]



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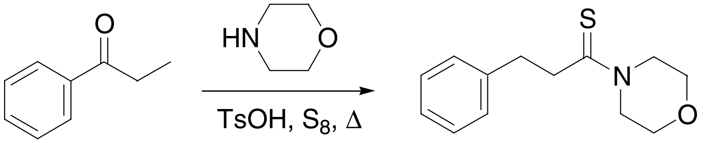
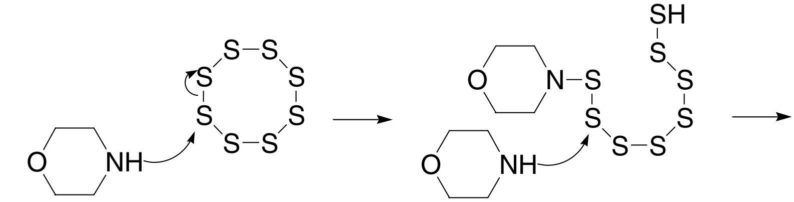
Willgerodt–Kindler reaction

Conversion of ketones to the corresponding thioamide and/or ammonium salt.

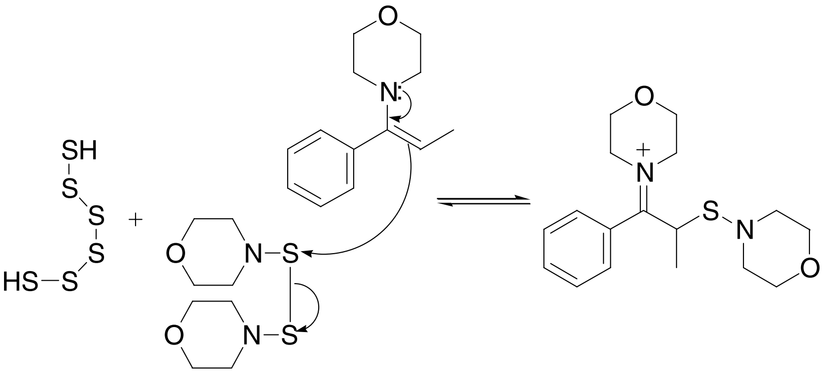


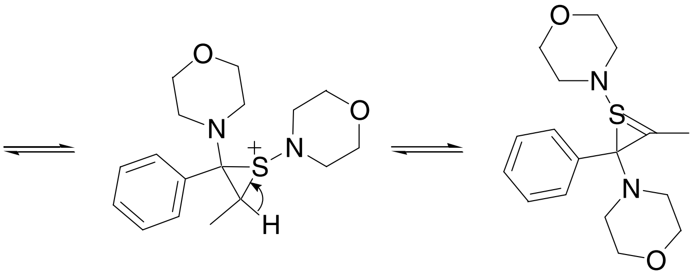
thioamide

In Carmack's mechanism,[8] the most unusual movement of a carbonyl group from methylene carbon to methylene carbon was proposed to go through an intricate pathway *via* a highly reactive intermediate with a sulfur-containing heterocyclic ring. The sulfenamide serves as the isomerization catalyst:

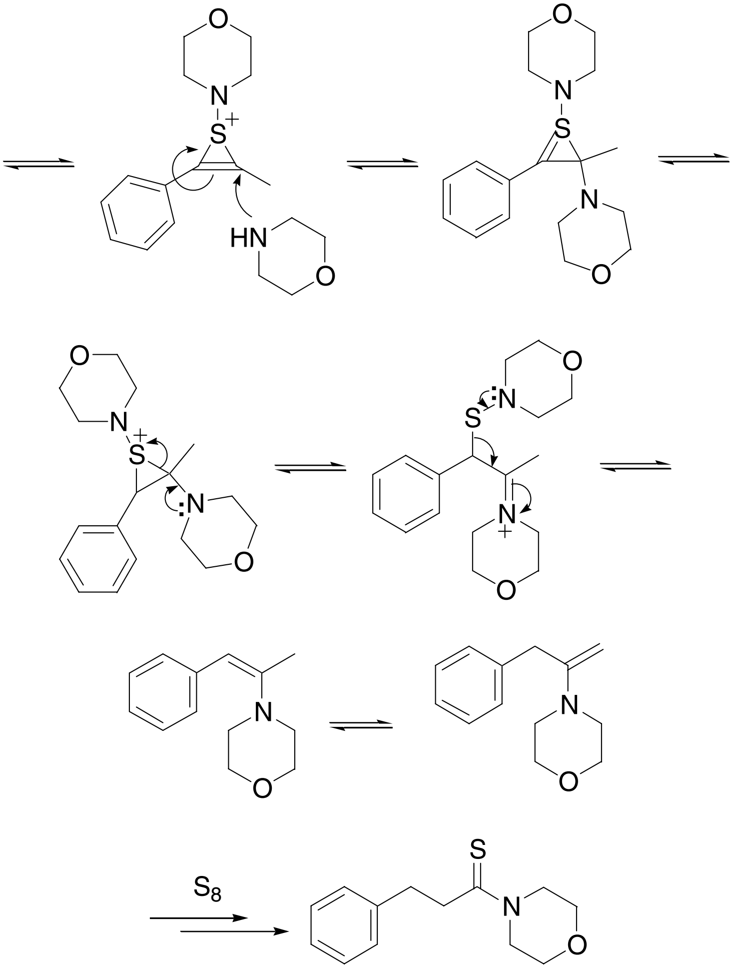


sulfenamide

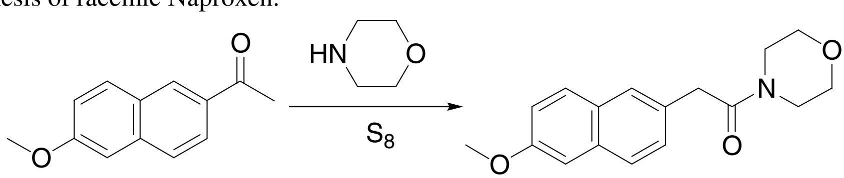


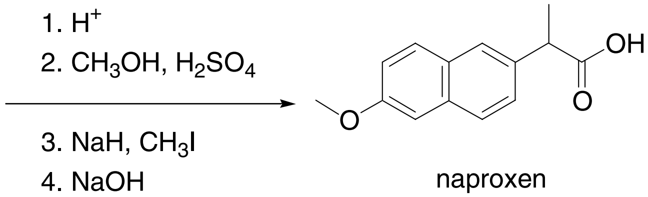


thiirene

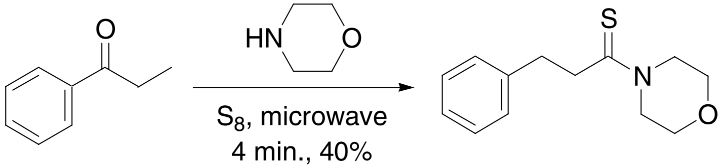


Example 1, the Willgerodt–Kindler reaction was a key operation in the initial synthesis of racemic Naproxen:[6]





Example 2[11]



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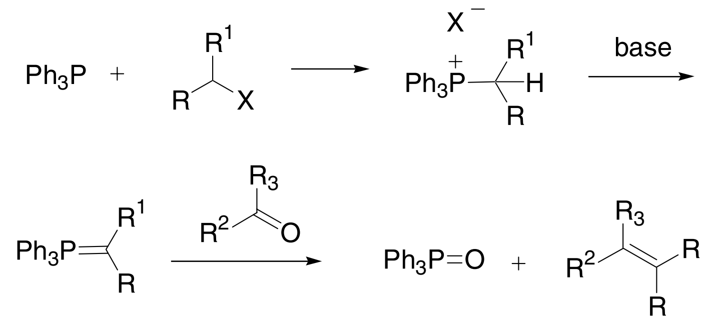
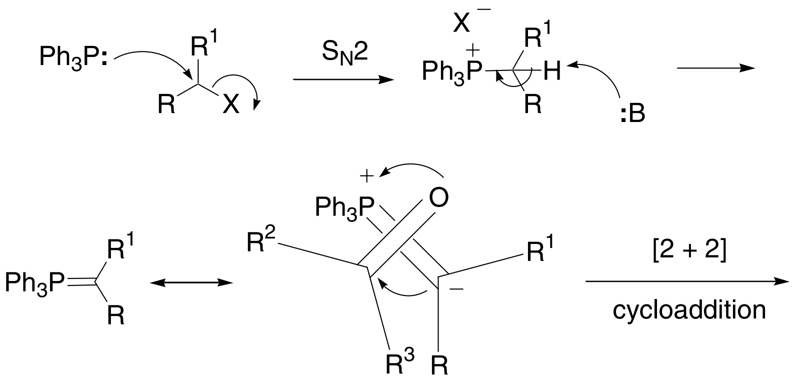
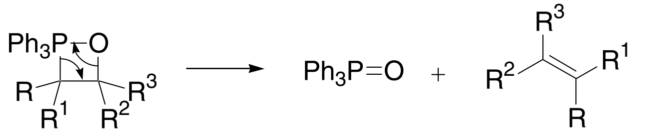
Wittig reaction

Olefination of carbonyls using phosphorus ylides.



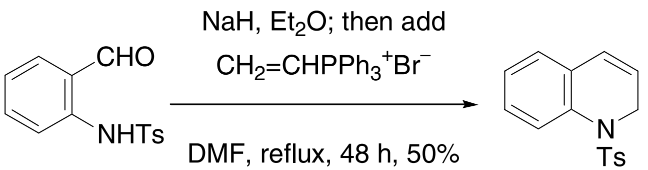


“puckered” transition state, irreversible and concerted

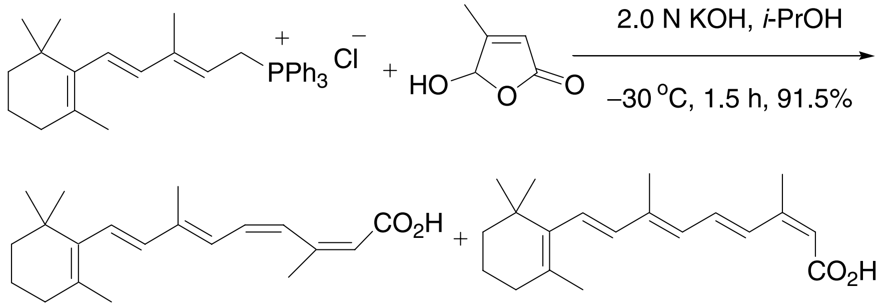


oxaphosphetane intermediate

Example 1[3]



Example 2[4]

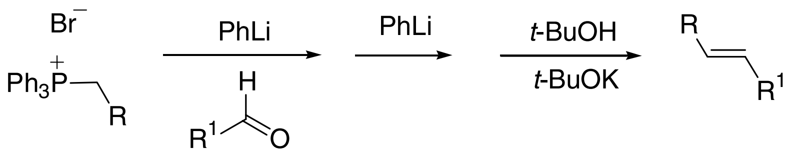


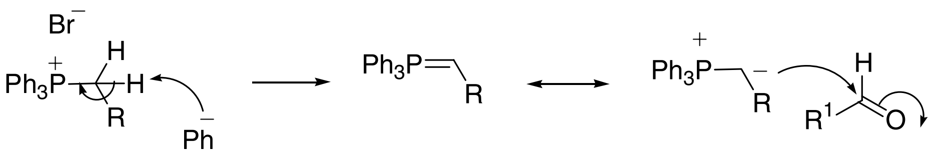
2-*cis*-4-*cis*-vitamin A acid

Accutane

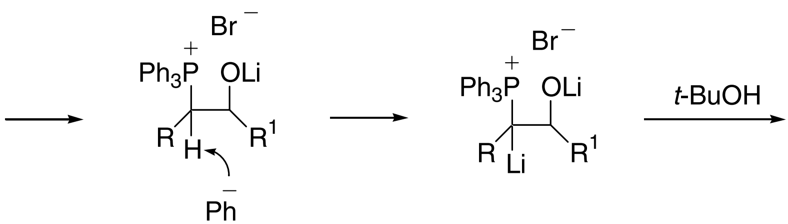
Schlosser modification of the Wittig reaction[11–17]

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.

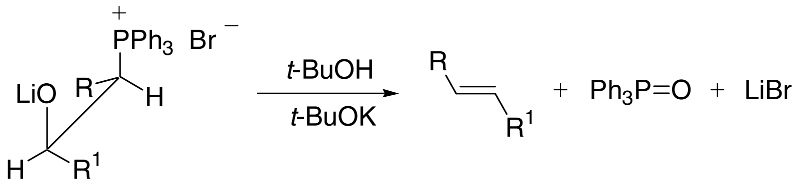




phosphorus ylide



LiBr complex of β-oxo ylide



LiBr complex of *threo*-betaine

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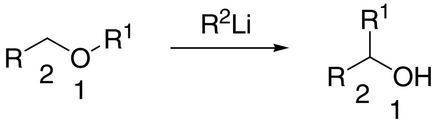
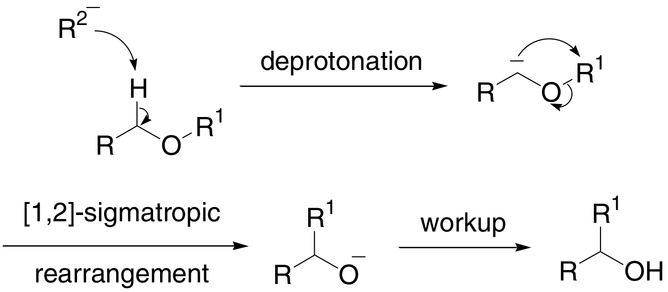
[1,2]-Wittig rearrangement

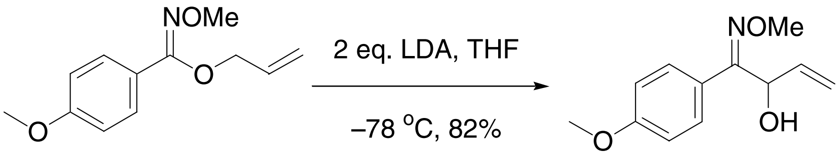
Treatment of ethers with alkyl lithium results in alcohols.



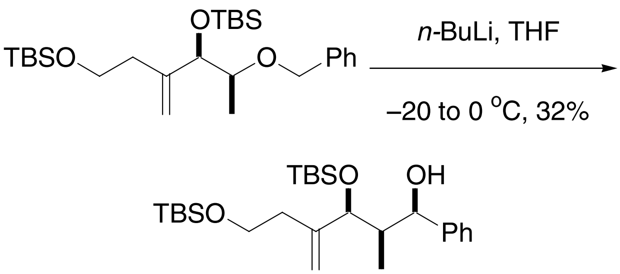


The radical mechanism is also possible as radical intermediates have been identified.

Example 1[4]



Example 2[5]



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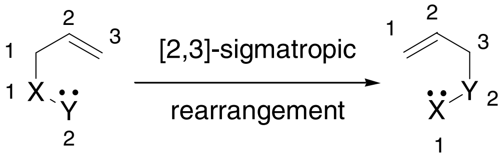
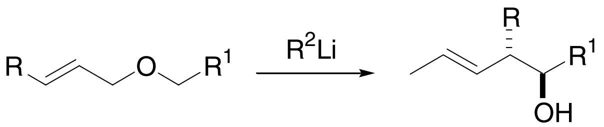
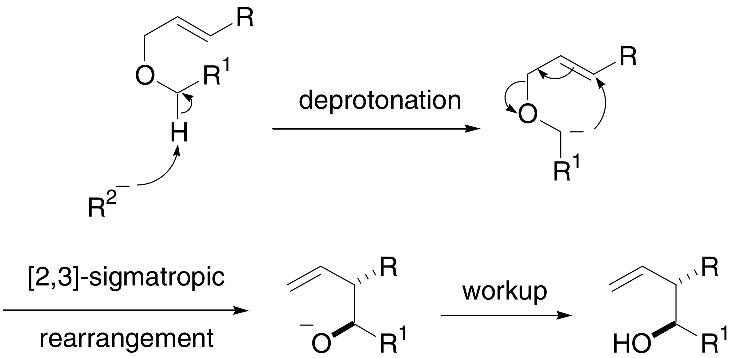
[2,3]-Wittig rearrangement

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

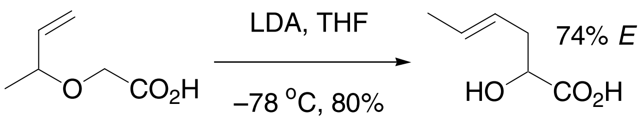




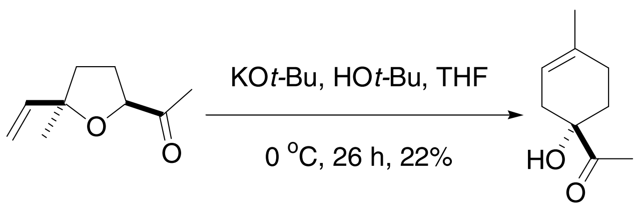
R^1 = alkynyl, alkenyl, Ph, COR, CN.



Example 1[3]



Example 2[2]



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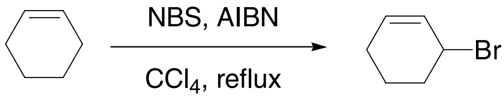
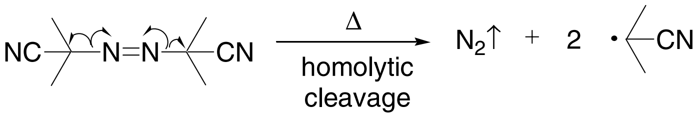
Wohl–Ziegler reaction

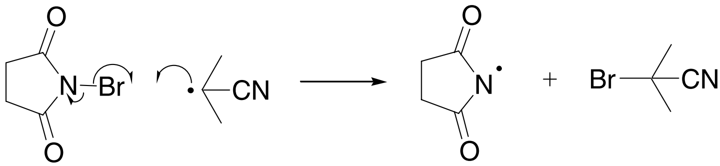
Radical-initiated allylic bromination using NBS, and catalytic AIBN as initiator or NBS under photolysis.



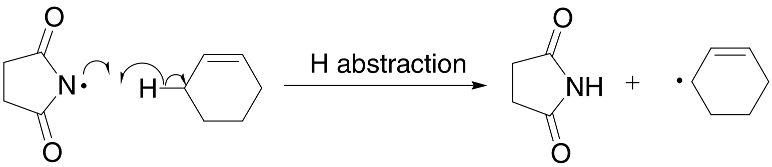
Initiation:

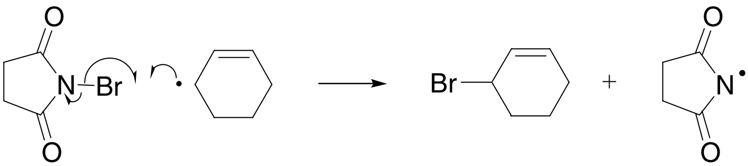


2,2'-azobisisobutyronitrile (AIBN)



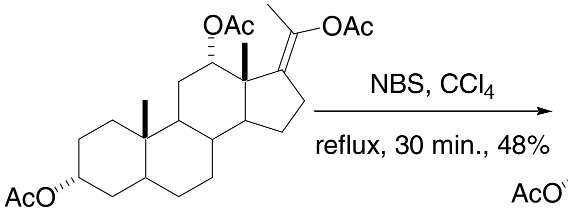
Propagation:



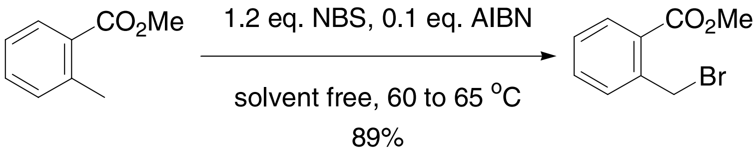


The succinimidyl radical is now available for the next cycle of the radical chain reaction.

Example 1[3]



Example 2[13]



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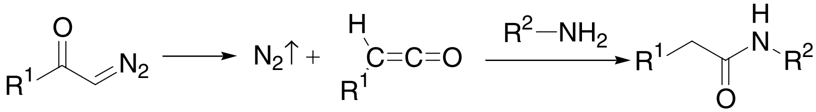
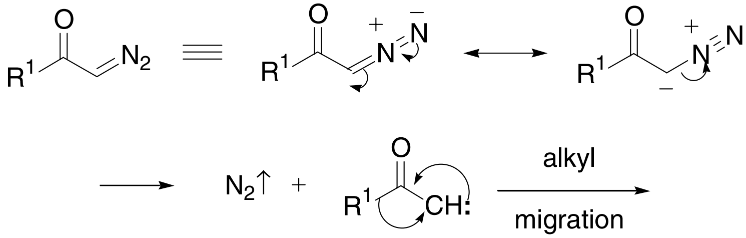
Wolff rearrangement

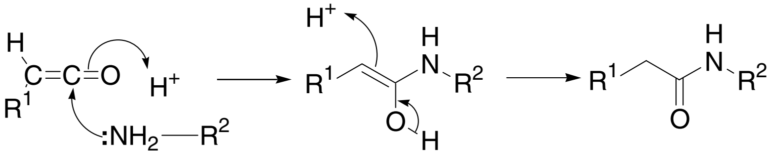
One-carbon homologation *via* the intermediacy of α-diazoketone and ketene.



α-diazoketone ketene intermediate

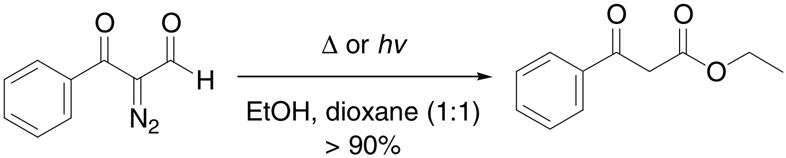


α-ketocarbene

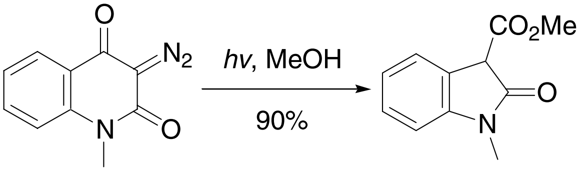


Treatment of the ketene with water would give the corresponding homologated carboxylic acid.

Example 1[2]



Example 2[4]



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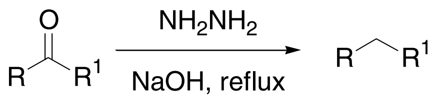
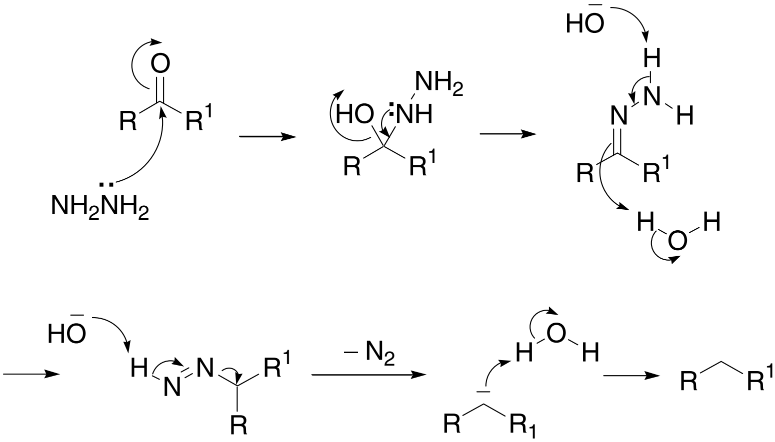
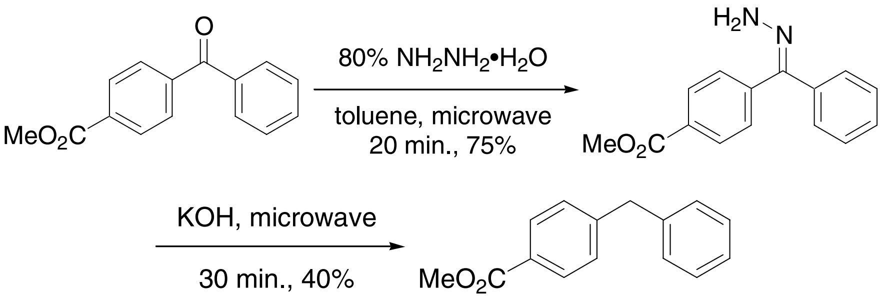
Wolff–Kishner reduction

Carbonyl reduction to methylene using basic hydrazine.





Example 1[11]



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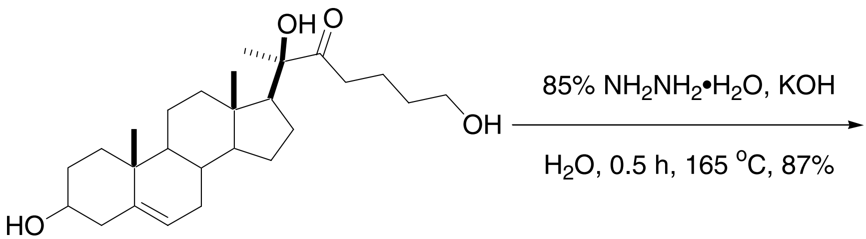

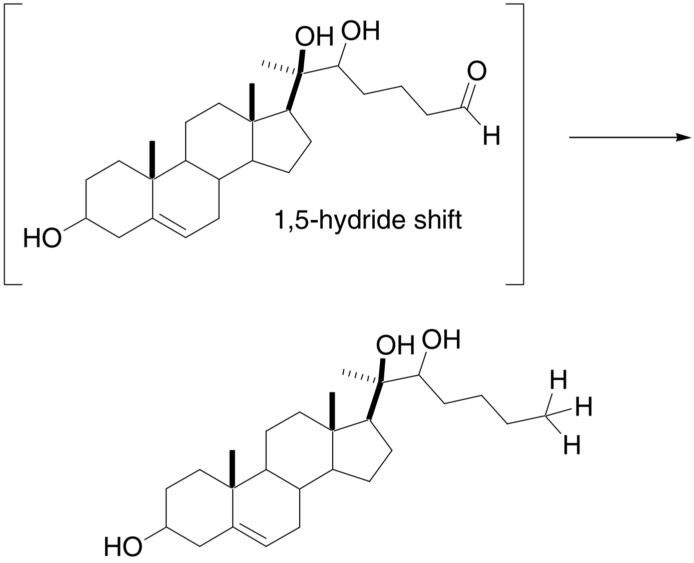

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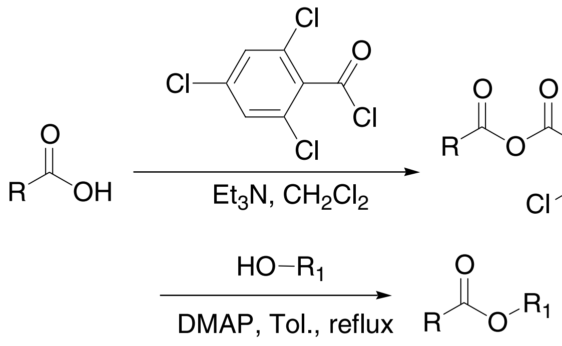
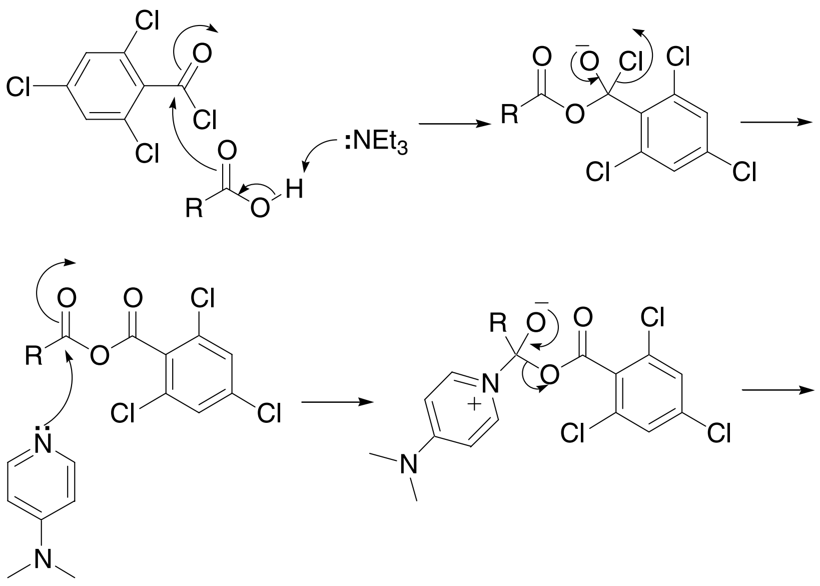
Yamaguchi esterification

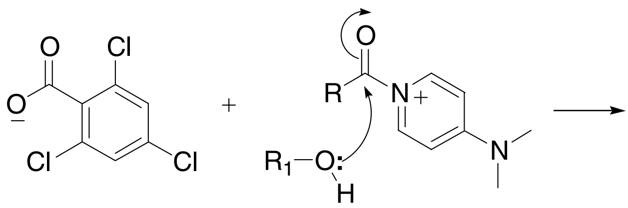
Esterification using 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent).

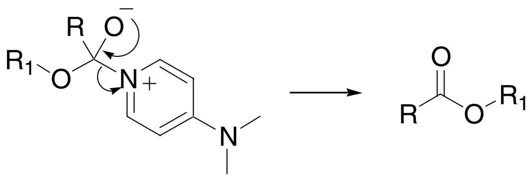




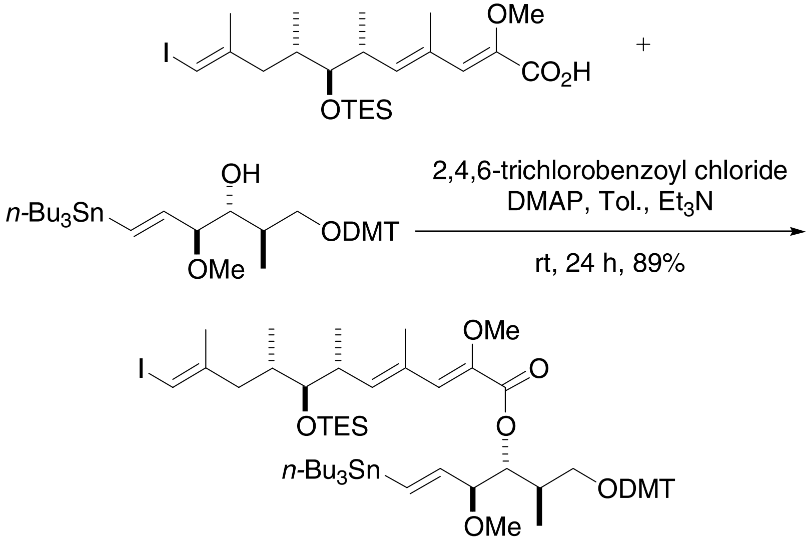
DMAP (Dimethylaminopyridine)

Steric hindrance of the chloro substituents blocks attack of the other carbonyl.

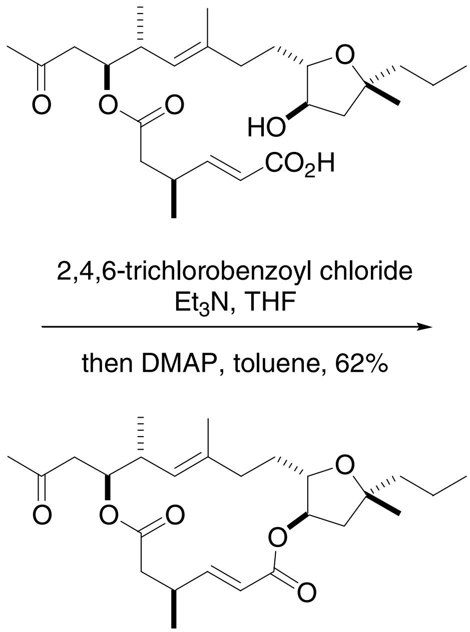



R
O
R1
O
N+
N
O
R
O
R1

Example 1[9]


I
OMe
CO2H
OTES
+
n-Bu3Sn
OH
OMe
ODMT
2,4,6-trichlorobenzoyl chloride
DMAP, Tol., Et3N
rt, 24 h, 89%
I
OMe
O
OTES
O
n-Bu3Sn
OMe
ODMT

Example 2[11]



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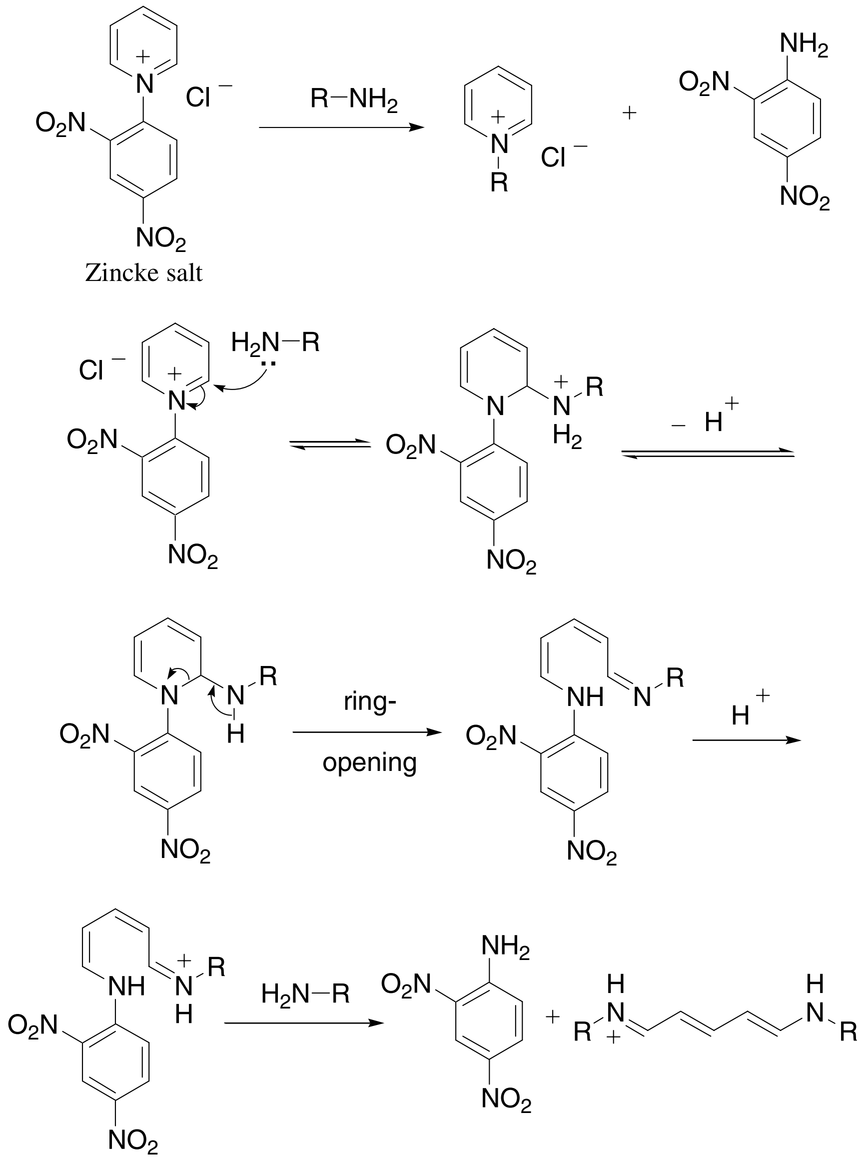
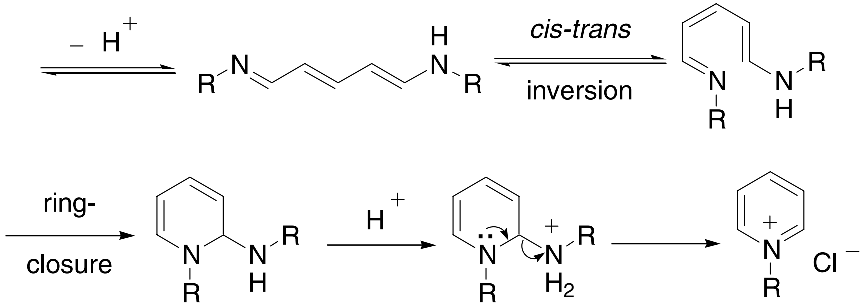
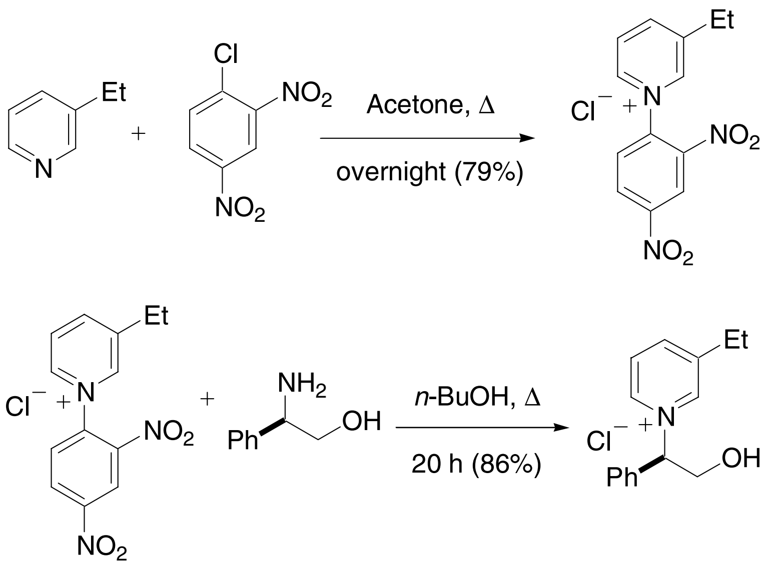
Zincke reaction

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.

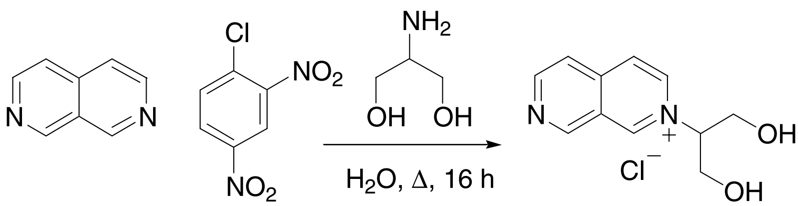


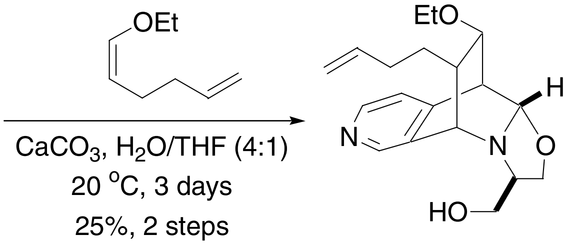


Example 1[13]



Example 2[16]





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Subject index

D

E

O

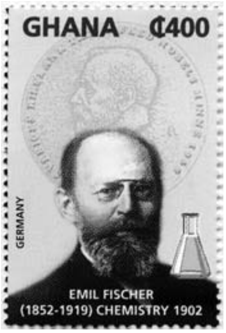
P

Q

R

T

Emil Fischer
1852–1919
Nobel Prize, 1902



Robert Robinson
1886–1975
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