

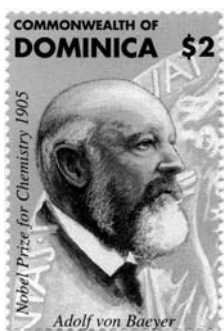
Kurt Alder
1902–1958
Nobel Prize, 1950



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



Name Reactions

Jie Jack Li

Name Reactions

A Collection
of Detailed Reaction Mechanisms

Third Expanded Edition

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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 withstood 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. Furthermore, 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 Woodrooffe 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

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
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Abbreviations and Acronyms

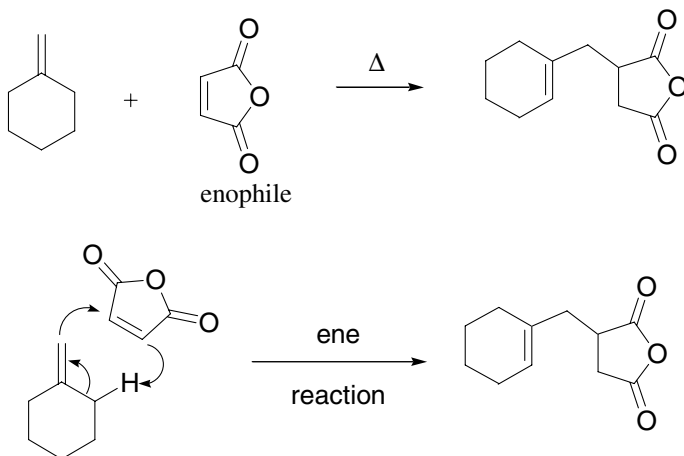
	polymer support
A	adenosine
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alpine-borane [®]	<i>B</i> -isopinocampheyl-9-borabicyclo[3.3.1]-nonane
Ar	aryl
B:	generic base
9-BBN	9-borabicyclo[3.3.1]nonane
[bimim]Cl•2AlCl ₃	1-butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
<i>m</i> -CPBA	<i>m</i> -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- <i>O</i> -dihydroquinine)-phthalazine
(DHQD) ₂ -PHAL	1,4-bis(9- <i>O</i> -dihydroquinidine)-phthalazine
DIAD	diisopropyl azodidicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMFDMA	<i>N,N</i> -dimethylformamide dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
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- <i>tert</i> -butylazodicarbonate
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
E1	unimolecular elimination
E2	bimolecular elimination
E1cB	2-step, base-induced β -elimination <i>via</i> carbanion
EAN	ethylammonium nitrate
EDDA	ethylenediamine diacetate
<i>ee</i>	enantiomeric excess
Ei	two groups leave at about the same time and bond to each other as they are doing so.
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HMTTA	1,1,4,7,10,10-hexamethyltriethylenetetramine
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	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
Nos	nosylate (4-nitrobenzenesulfonyl)
Nu	nucleophile
<i>N</i> -PSP	<i>N</i> -phenylselenophthalimide
<i>N</i> -PSS	<i>N</i> -phenylselenosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
PMB	para-methoxybenzyl
PPA	polyphosphoric acid
PPTS	pyridinium <i>p</i> -toluenesulfonate
PyPh ₂ P	diphenyl 2-pyridylphosphine
Pyr	pyridine
Red-Al	sodium bis(methoxy-ethoxy)aluminum hydride (SMEAH)
Salen	<i>N,N'</i> -disalicylidene-ethylenediamine
SET	single electron transfer
SM	starting material

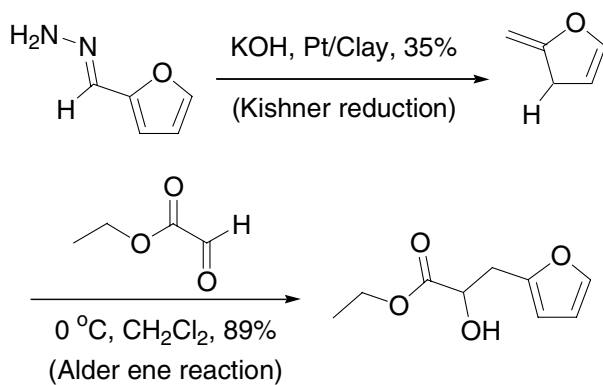
SMEAH	sodium bis(methoxy-ethoxy)aluminum hydride (Red-Al)
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
S _N Ar	nucleophilic substitution on an aromatic ring
TBABB	tetra- <i>n</i> -butylammonium bibenzoate
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TEOC	trimethylsilylethoxycarbonyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tri-2-furylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG	tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2'-bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl
TosMIC	(<i>p</i> -tolylsulfonyl)methyl isocyanide
Ts	tosyl
TsO	tosylate
UHP	urea-hydrogen peroxide

Alder ene reaction

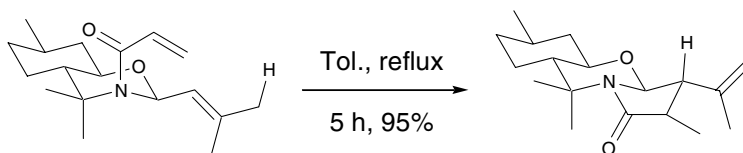
Addition of an enophile to an alkene *via* allylic transposition. Also known as hydroallyl addition.



Example 1¹³



Example 2¹⁴

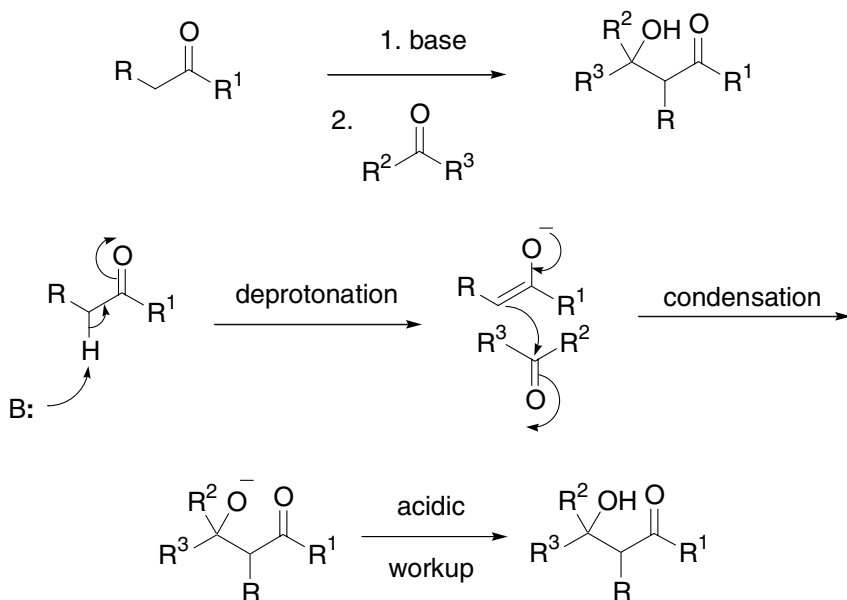


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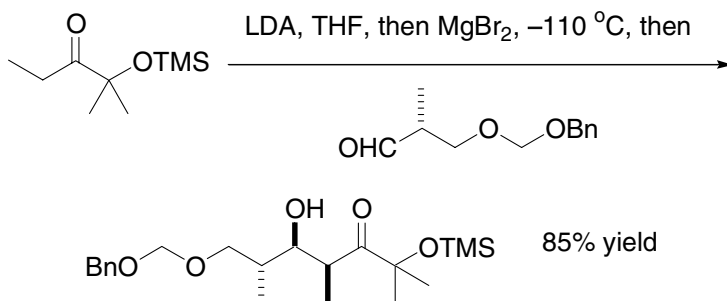
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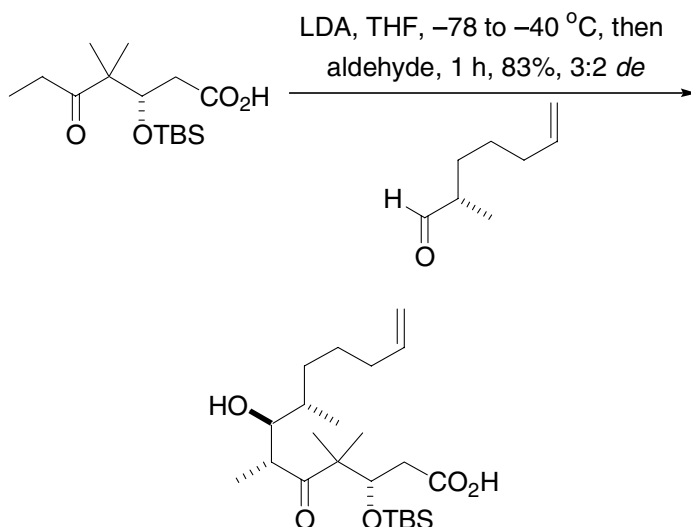
Aldol condensation

Condensation of a carbonyl with an enolate or an enol. A simple case is addition of an enolate to an **aldehyde** to afford an **alcohol**, thus the name **aldol**.



Example 1³



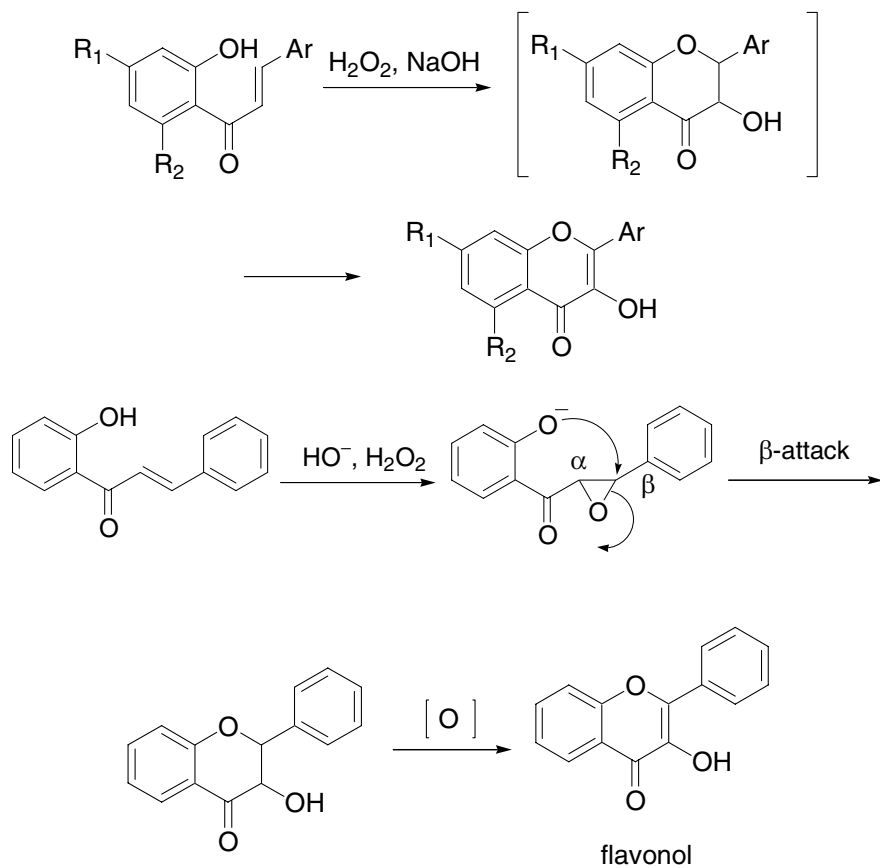
Example 2¹²

References

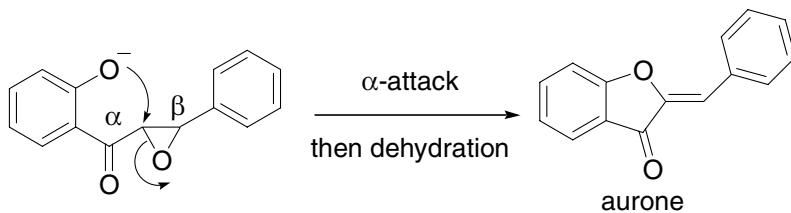
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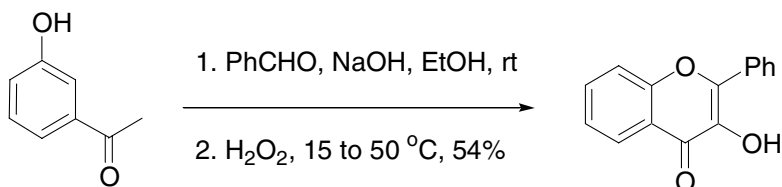
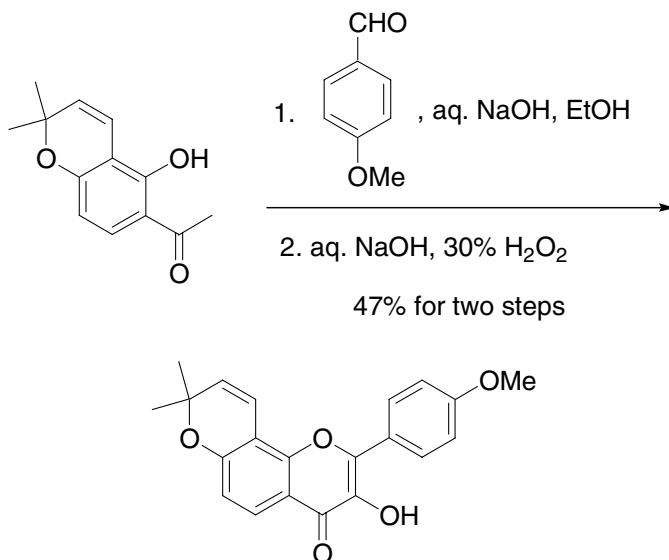
Algar–Flynn–Oyamada Reaction

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



A side reaction:



Example 1⁵Example 2⁵

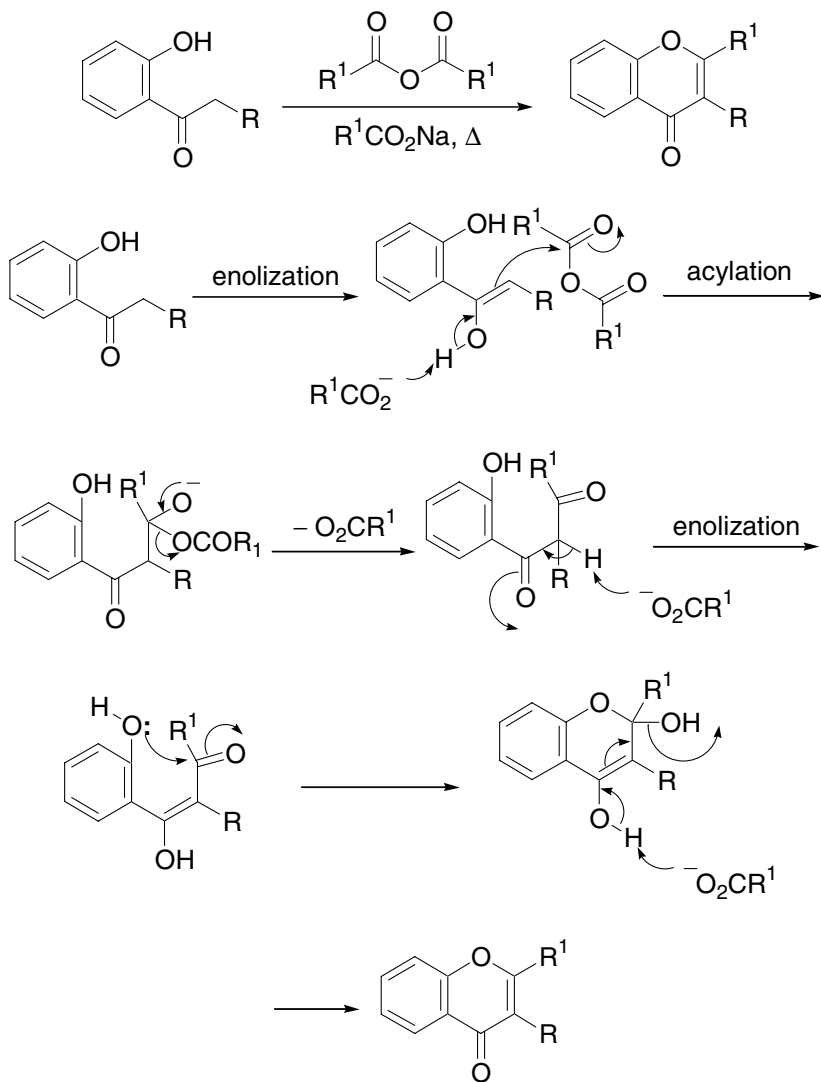
References

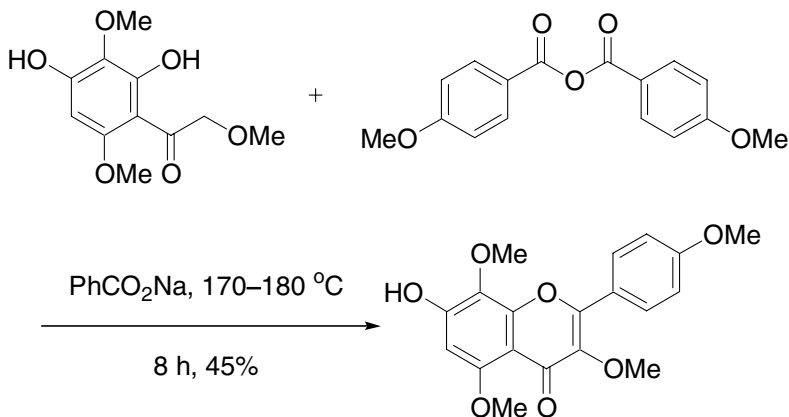
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Allan–Robinson reaction

Synthesis of flavones or isoflavones.



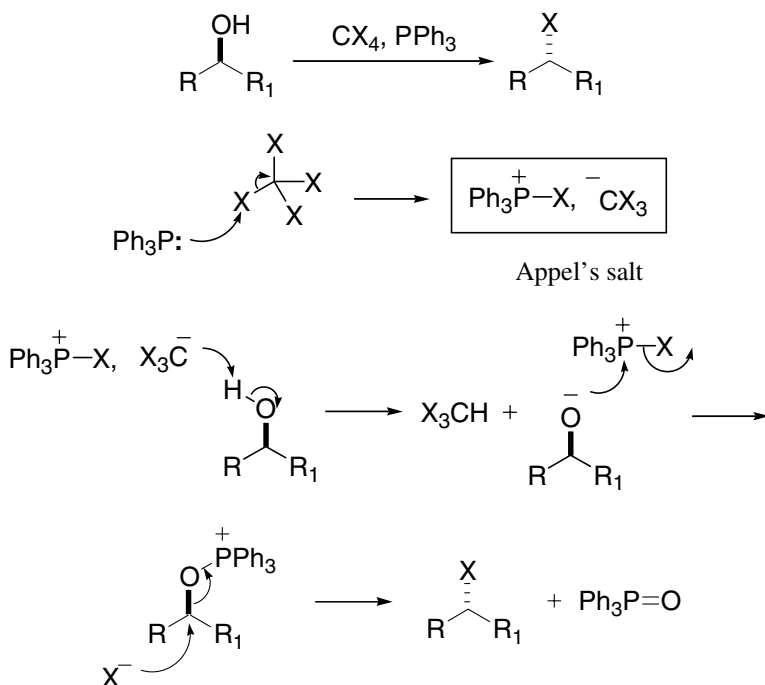
Example 1⁶

References

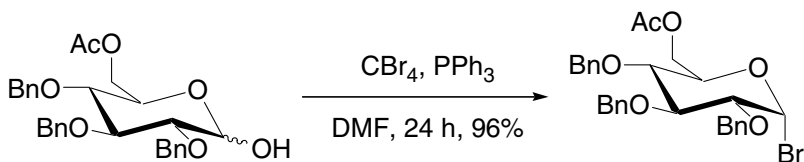
1. Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, 125, 2192. Robert Robinson (United Kingdom, 1886–1975) won the Nobel Prize in Chemistry in 1947 for his studies on alkaloids. However, Robinson himself considered his greatest contribution to science was that he founded the qualitative theory of electronic mechanisms in organic chemistry. Robinson, along with Lapworth (a friend) and Ingold (a rival), pioneered the arrow pushing approach to organic reaction mechanism. Robinson was also an accomplished pianist. J. Allan, his student, also coauthored another important paper with Robinson on the relative directive powers of groups for aromatic substitution.
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Appel reaction

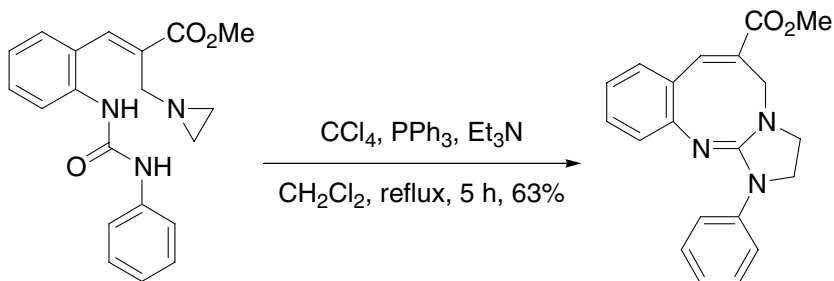
The reaction between triphenylphosphine and tetrahalomethane (CCl_4 , CBr_4) forms a salt known as Appel's salt. Treatment of alcohols with Appel's salt gives rise to the corresponding halides.



Example 1⁷



Example 2, Appel's salt is often used as a dehydrating agent⁸

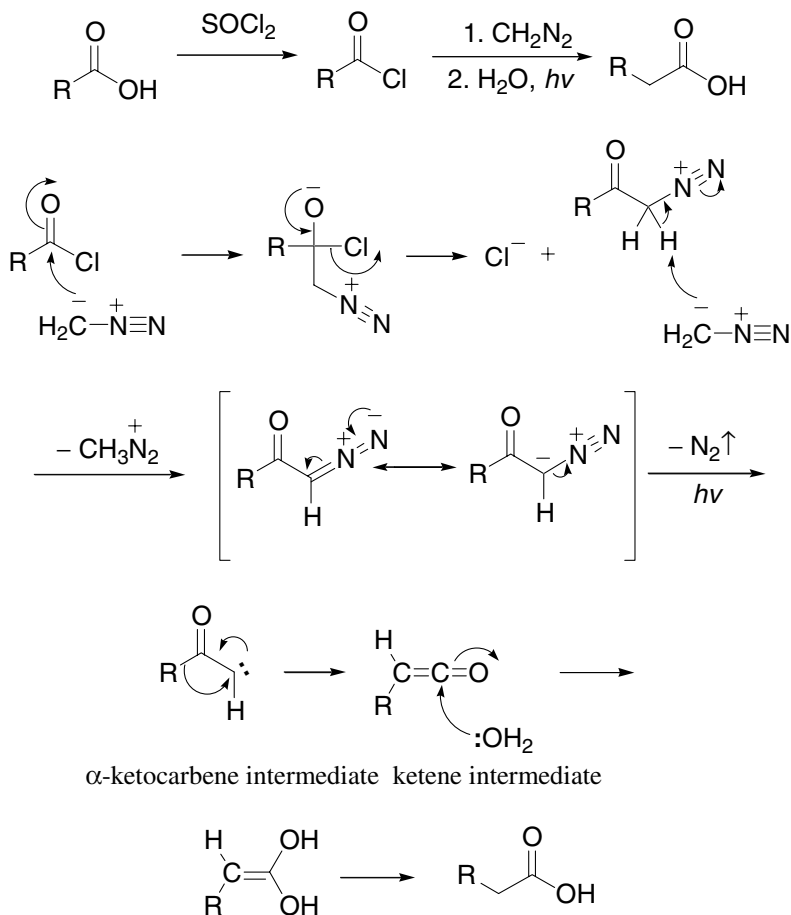


References

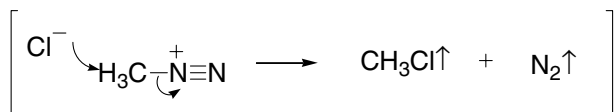
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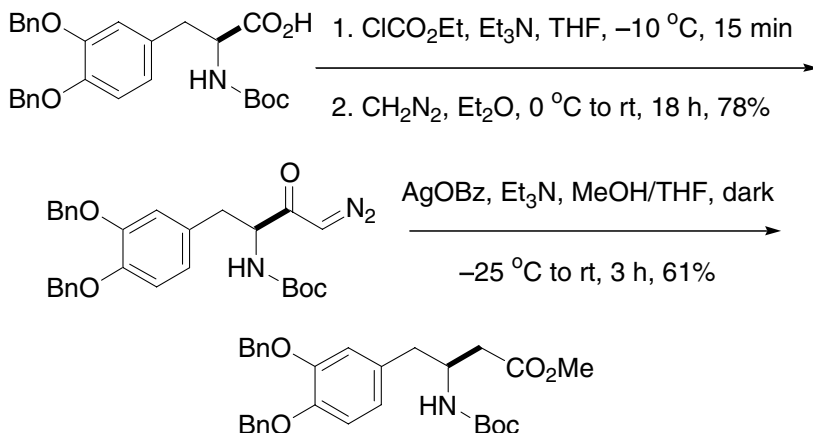
Arndt-Eistert homologation

One carbon homologation of carboxylic acids using diazomethane.



side reaction:



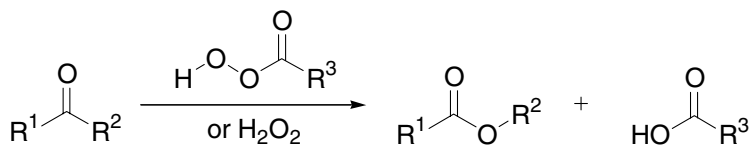
Example 1¹⁰

References

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Baeyer–Villiger oxidation

General scheme:



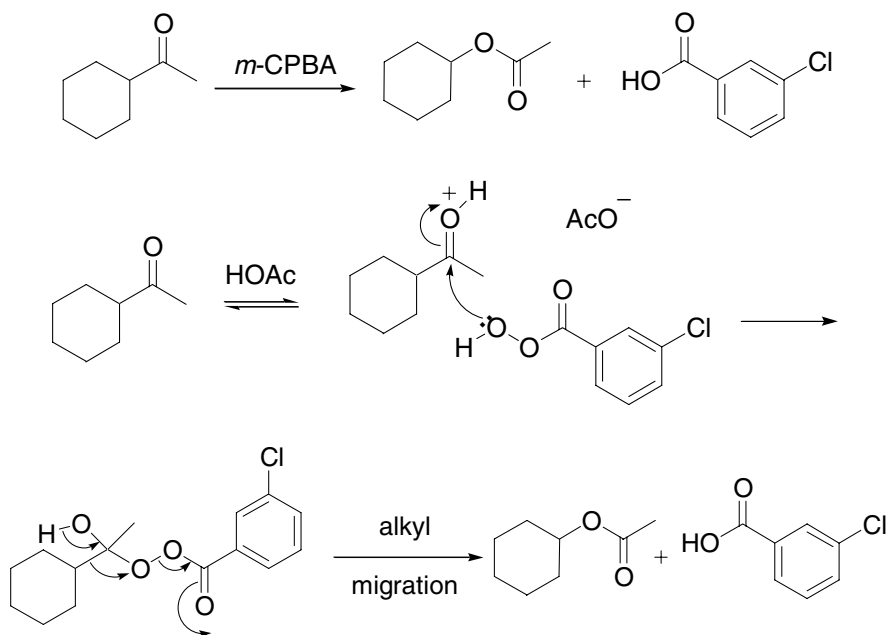
The most electron-rich alkyl group (more substituted carbon) migrates first. The general migration order:

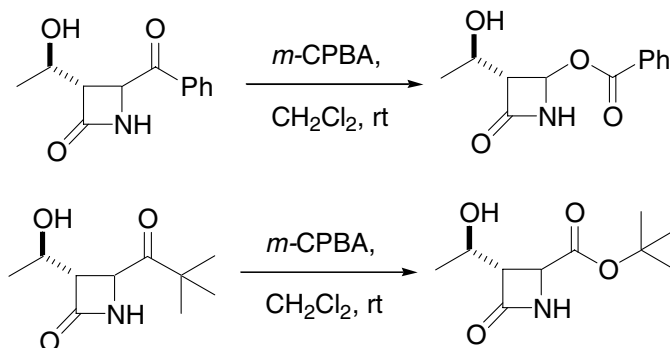
tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > methyl >> H.

For substituted aryls:

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

Example 1:



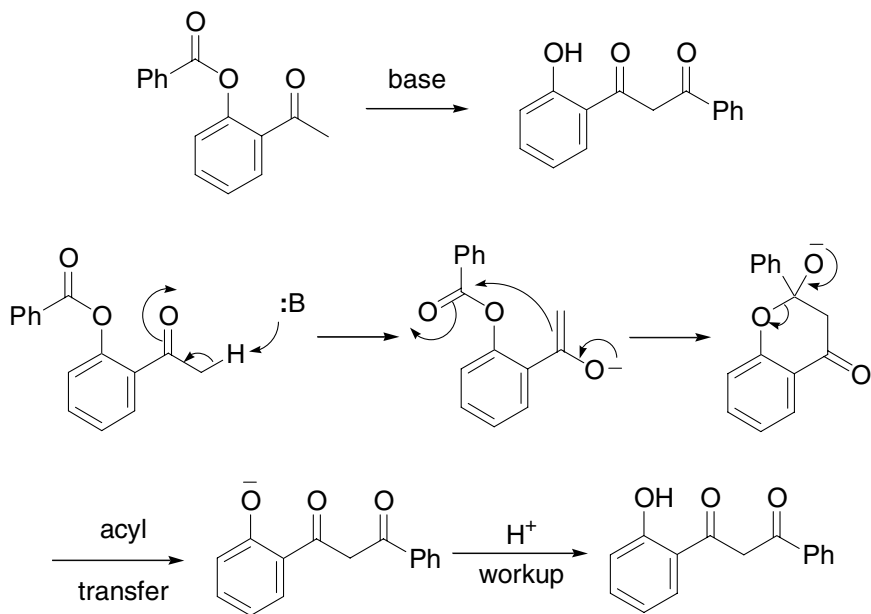
Example 2¹⁰

References

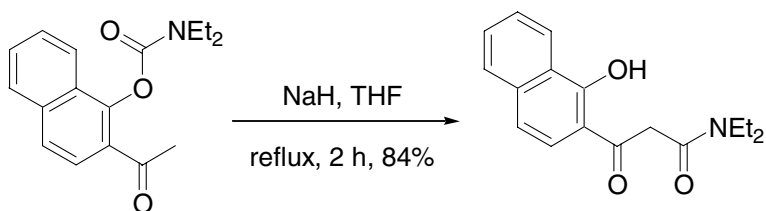
1. v. Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, 32, 3625. Adolf von Baeyer (1835–1917) was one of the most illustrious organic chemists in history. He contributed in many areas of the field. The Baeyer-Drewson indigo synthesis made possible the commercialization of synthetic indigo.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

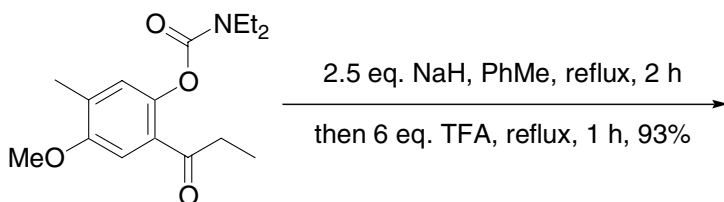
Base-catalyzed acyl transfer reaction that converts α -acyloxyketones to β -diketones.

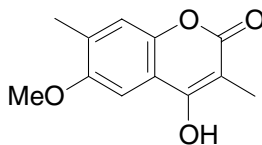


Example 1⁷



Example 2⁸



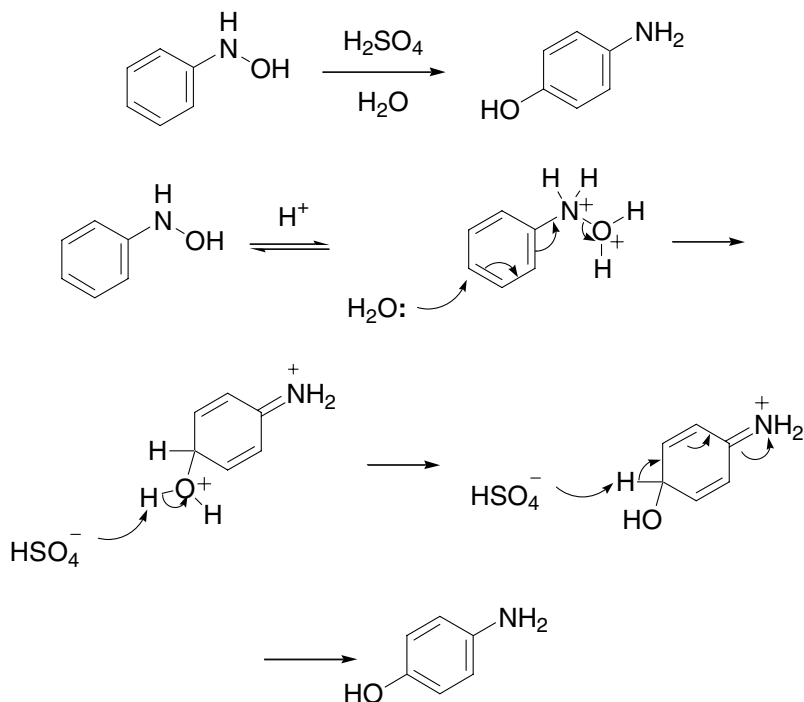


References

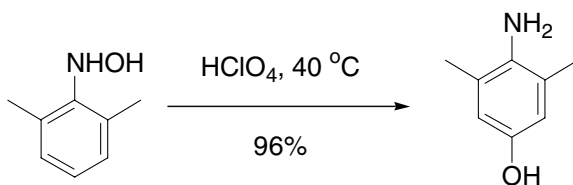
1. Baker, W. J. *Chem. Soc.* **1933**, 1381. Wilson Baker (1900–2002) was born in Run-corn, England. He studied chemistry at Manchester under Arthur Lapworth and at Ox-ford under Robinson. In 1943, Baker was the first one who confirmed that penicillin contained sulfur, of which Robinson commented: “This is a feather in your cap, Baker.” Baker began his independent academic career at University of Bristol. He re-tired in 1965 as the head of the School of Chemistry. Baker was a well-known chem-ist centenarian, spending 47 years in retirement!
2. Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767. K. Venkataraman studied under Robert Robinson Manchester. He returned to India and later arose to be the di-rector of the National Chemical Laboratory at Poona.
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Bamberger rearrangement

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



Example 1⁵



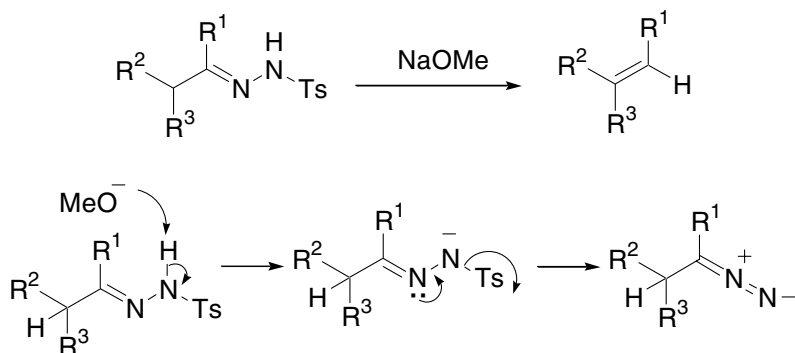
References

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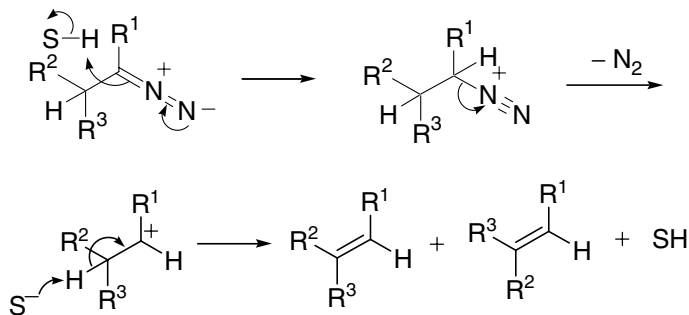
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5. Fishbein, J. C.; McClelland, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 2824.
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Bamford–Stevens reaction

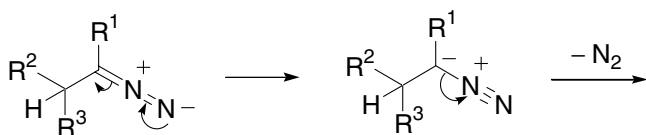
The Bamford–Stevens reaction and the Shapiro reaction share a similar mechanistic pathway. The former uses a base such as Na, NaOMe, LiH, NaH, NaNH₂, heat, *etc.*, whereas the latter employs bases such as alkyllithiums and Grignard reagents. As a result, the Bamford–Stevens reaction furnishes more-substituted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

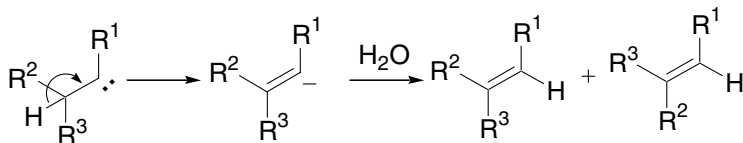


In protic solvent:

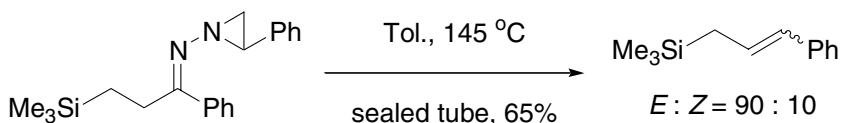


In aprotic solvent:

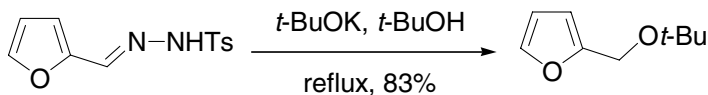




Example 1, thermal Bamford–Stevens⁵



Example 2⁹

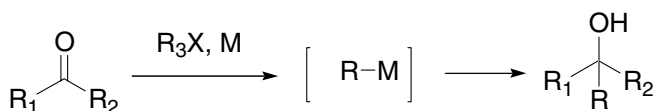


References

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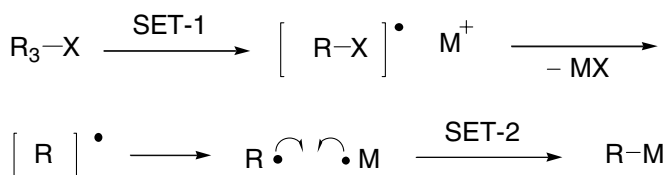
Barbier coupling reaction

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

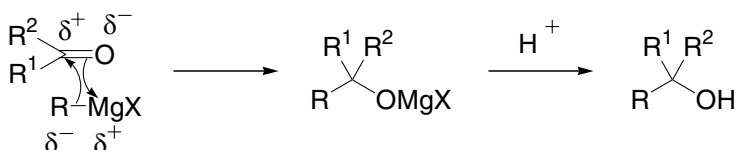


According to conventional wisdom,³ the organometallic intermediate ($\text{M} = \text{Mg}$, Li , Sm , Zn , La , *etc.*) is generated *in situ*, which is intermediately trapped by the carbonyl compound. However, recent experimental and theoretical studies seem to suggest that the Barbier coupling reaction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

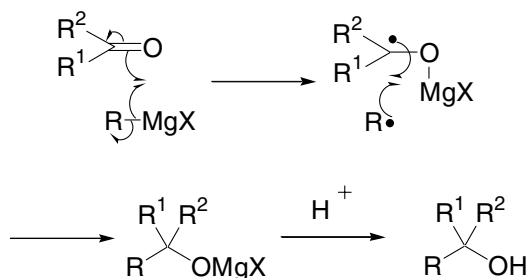
Generation of the Grignard reagent,

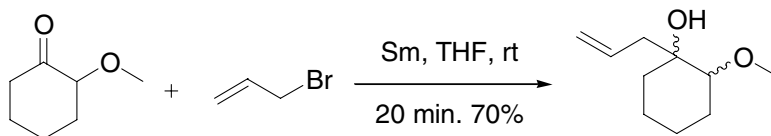
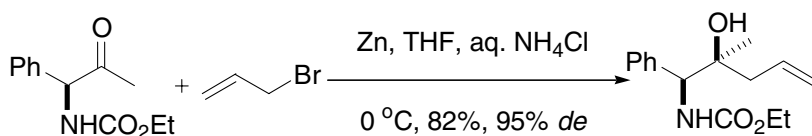


Ionic mechanism,



Single electron transfer mechanism,



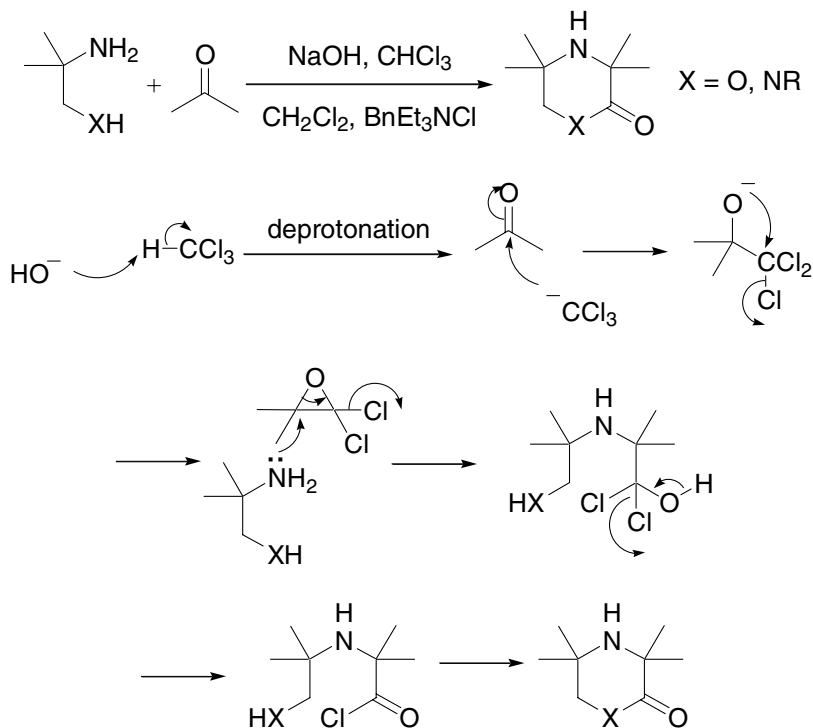
Example 1⁸Example 2¹¹

References

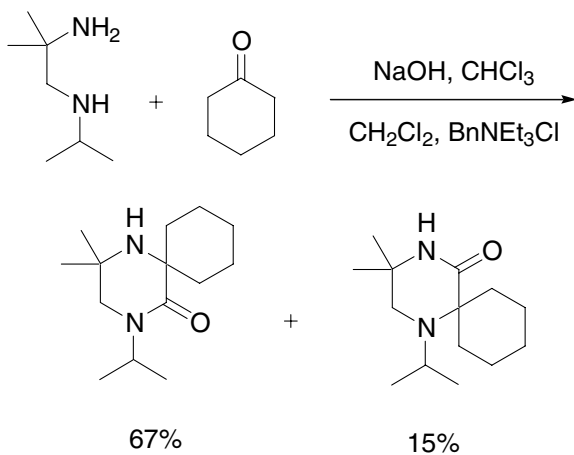
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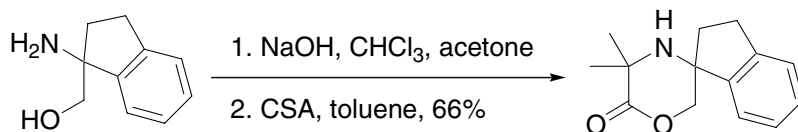
Bargellini reaction

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



Example 1²



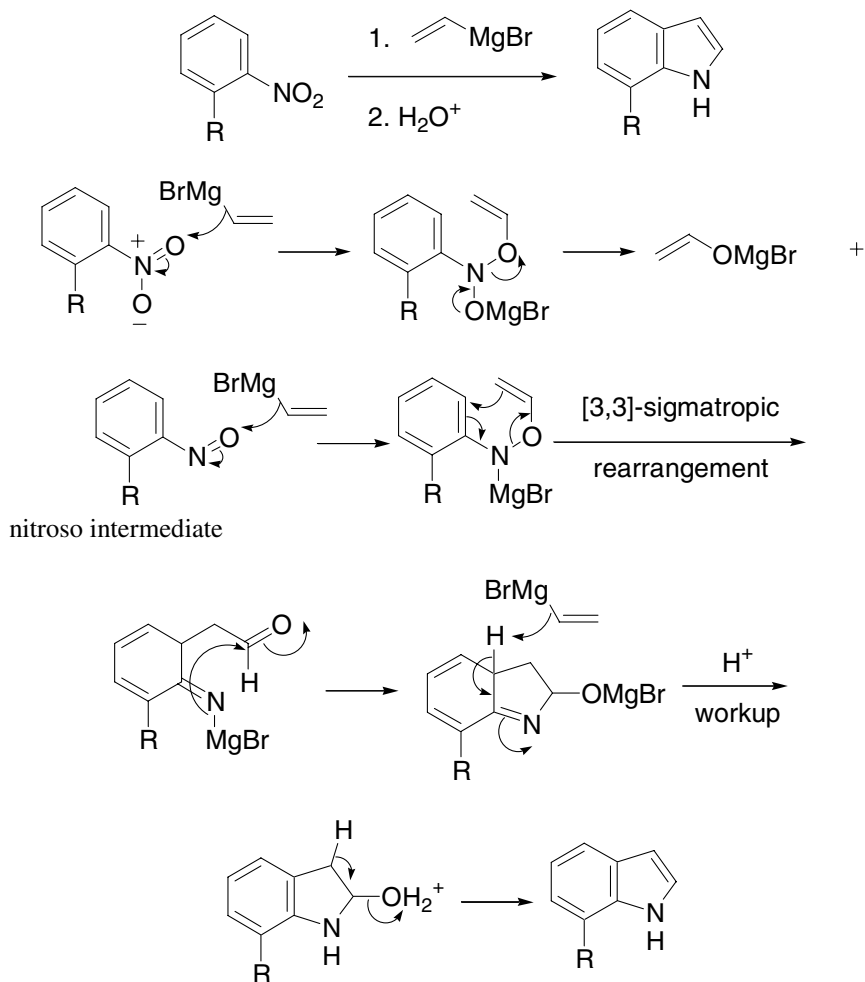
Example 2⁶

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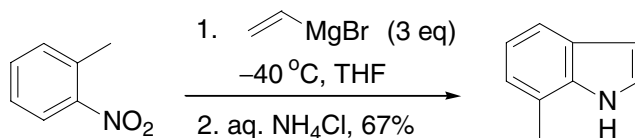
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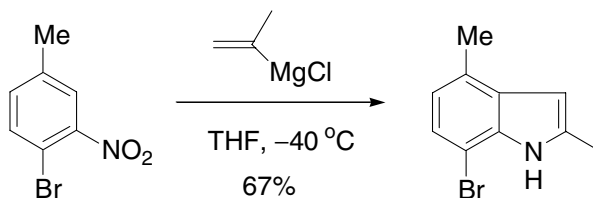
Bartoli indole synthesis

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



Example 1³



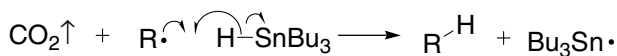
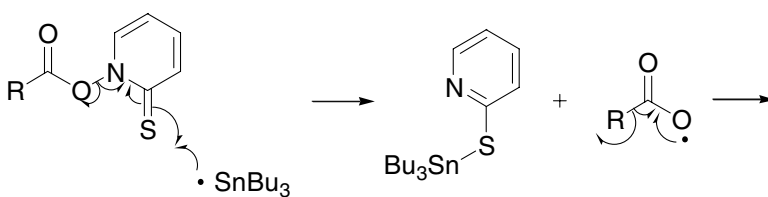
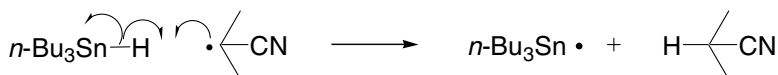
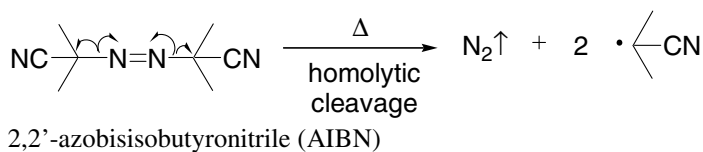
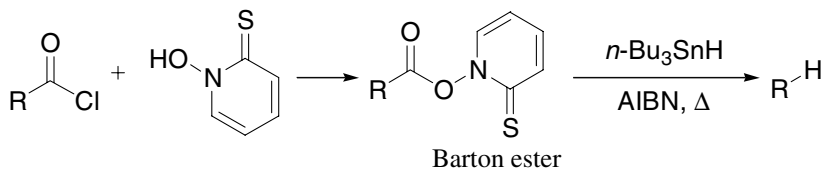
Example 2⁸

References

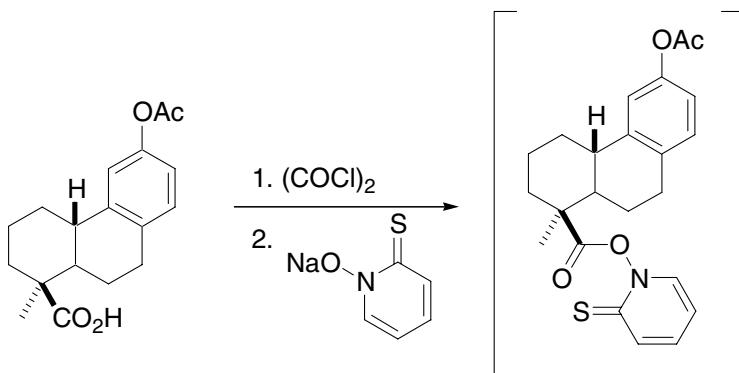
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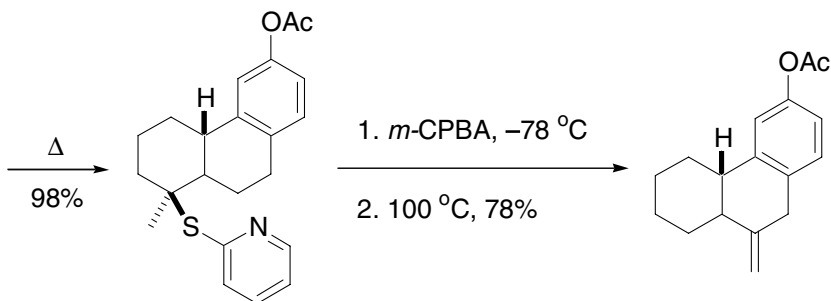
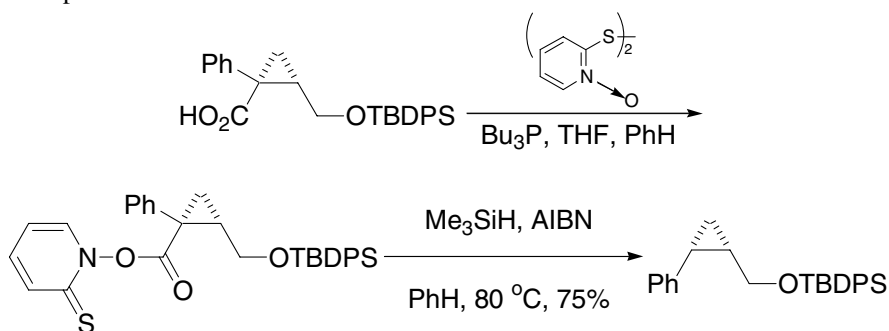
Barton radical decarboxylation

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



Example 1³



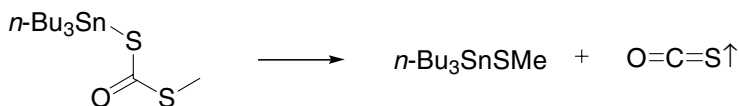
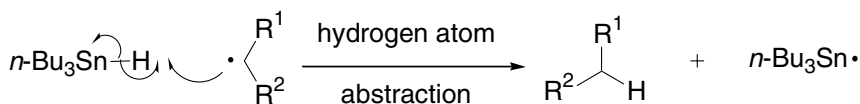
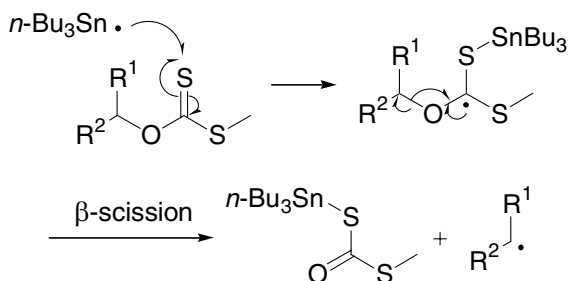
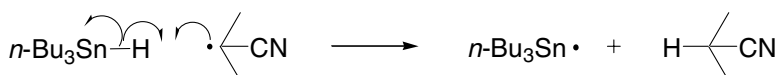
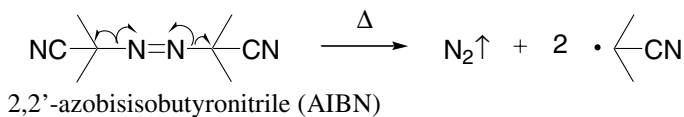
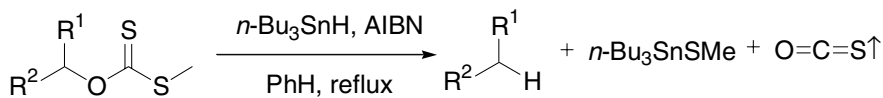
Example 2¹¹

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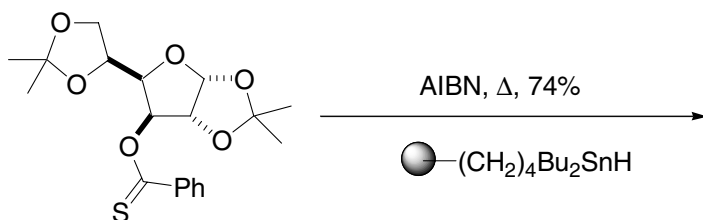
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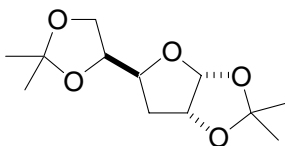
Barton–McCombie deoxygenation

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

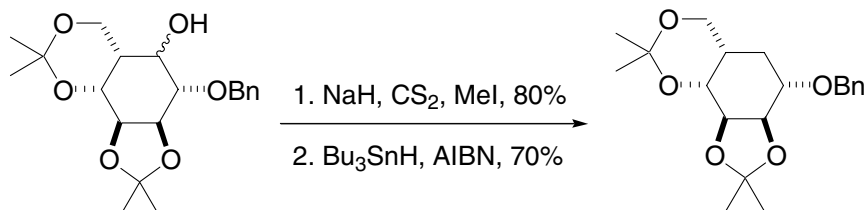


Example 1⁵





Example 2⁹

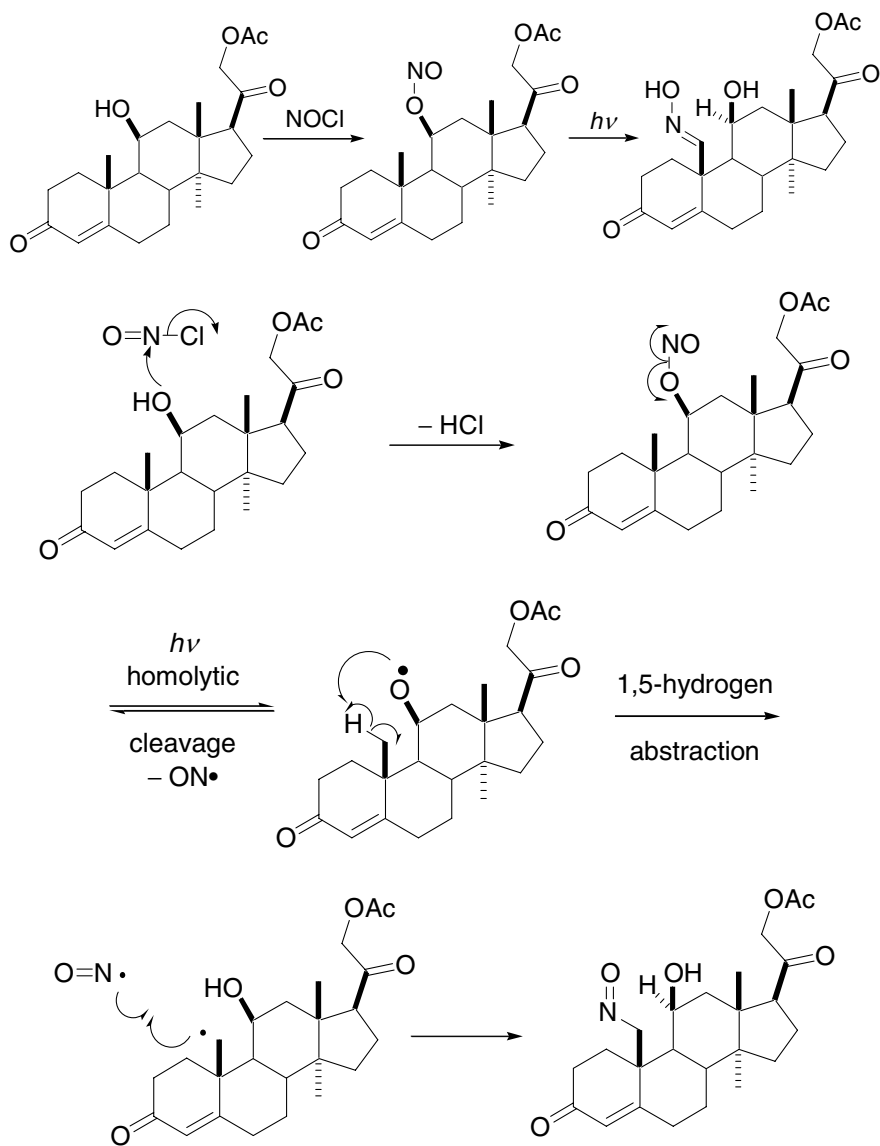


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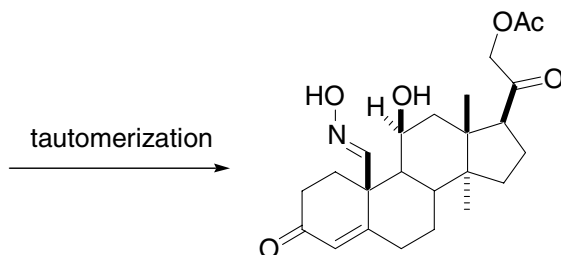
Barton nitrite photolysis

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

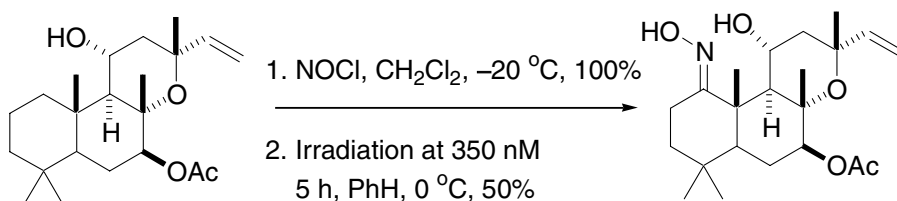


Nitric oxide radical is a stable,
and therefore, long-lived radical

nitroso intermediate



Example¹¹

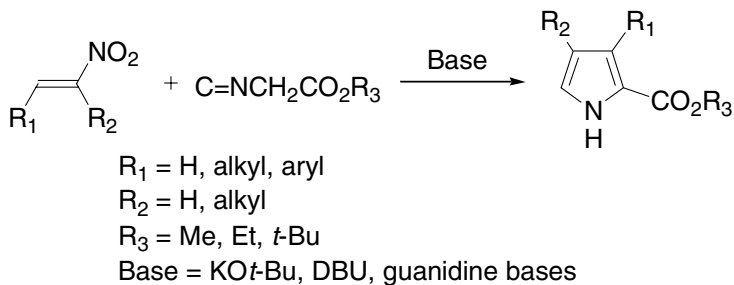


References

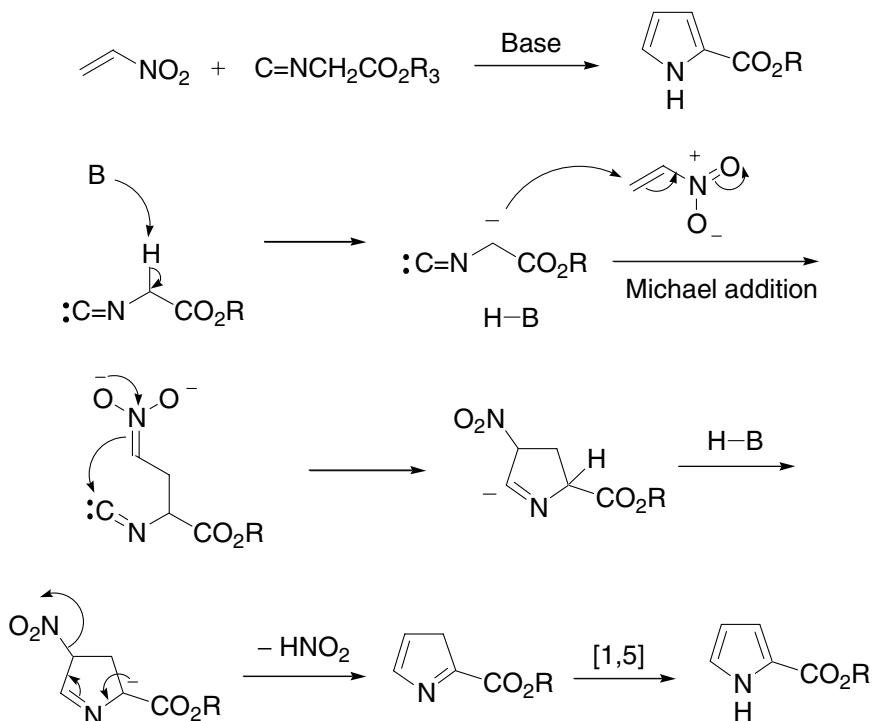
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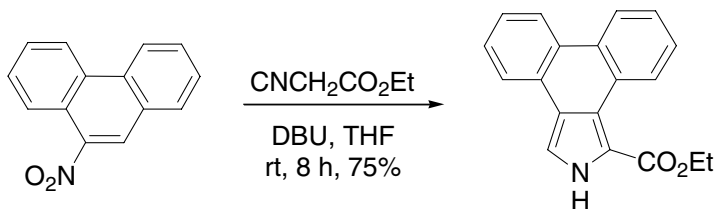
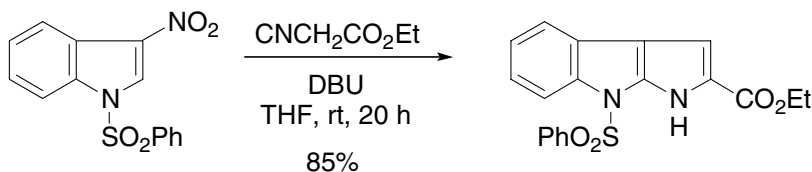
Barton–Zard reaction

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



Example 1



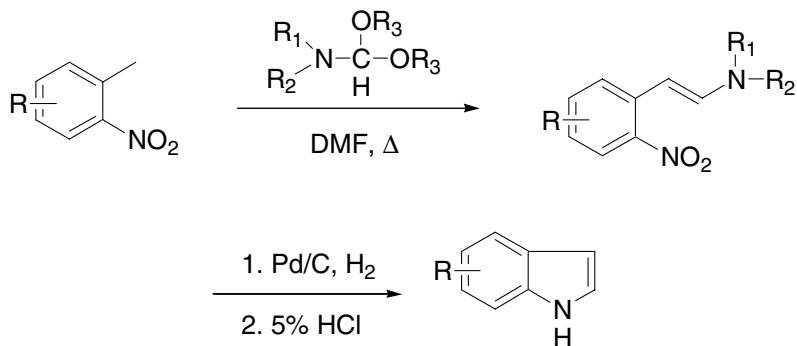
Example 2⁵Example 3⁷

References

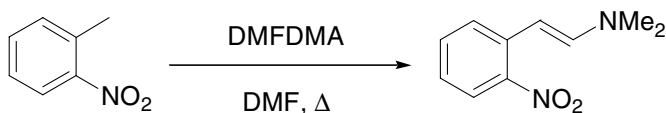
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Batcho–Leimgruber indole synthesis

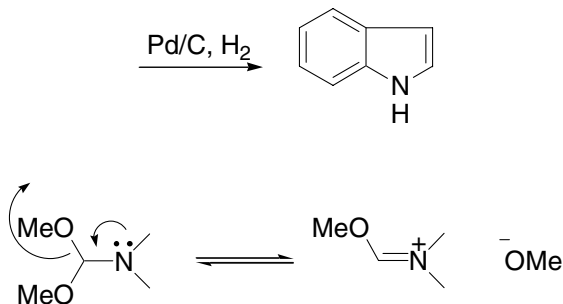
Condensation of *o*-nitrotoluene derivatives with formamide acetals, followed by reduction of the *trans*- β -dimethylamino-2-nitrostyrene to furnish indole derivatives.

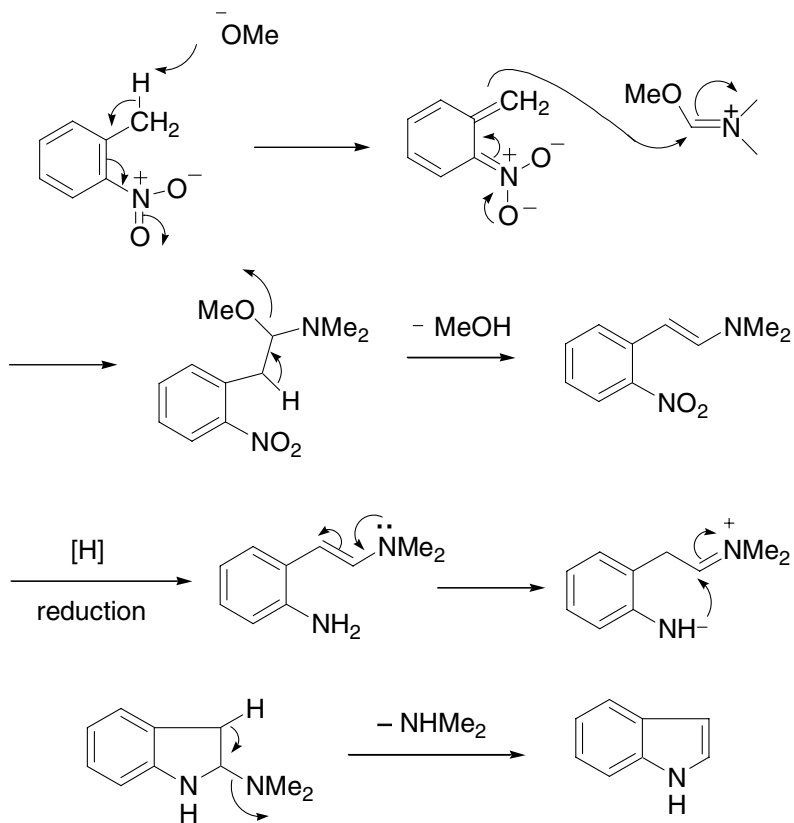


Example 1

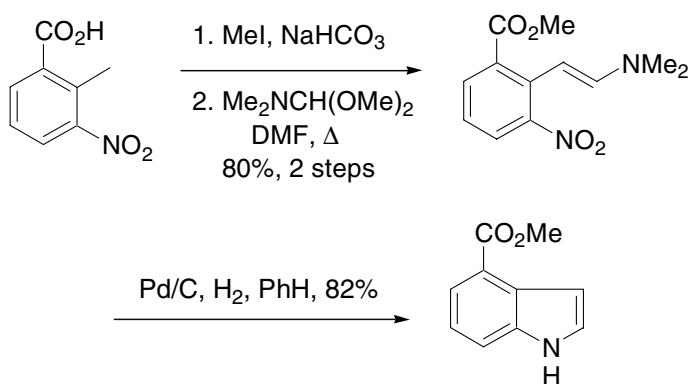


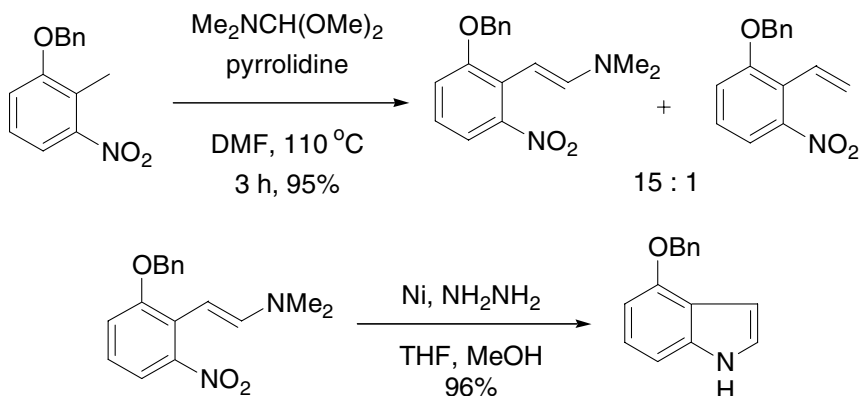
DMFDMA = *N,N*-dimethylformamide dimethyl acetal, $\text{Me}_2\text{NCH(OMe)}_2$





Example 2⁵



Example 3¹⁴

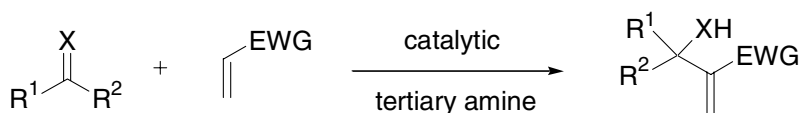
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Baylis–Hillman reaction

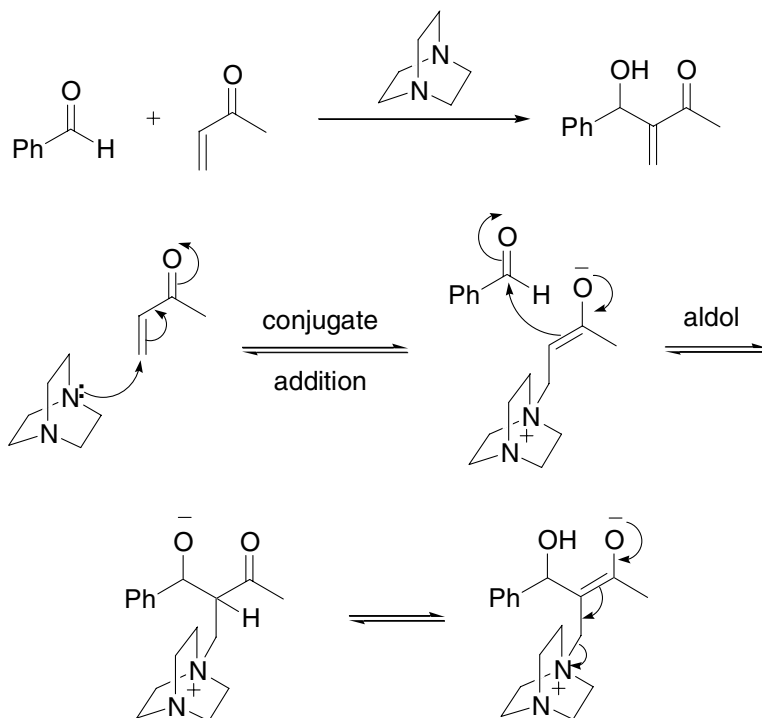
Also known as Morita–Baylis–Hillman reaction, and occasionally known as Rauhut–Currier reaction. It is a carbon–carbon bond-forming transformation of an electron-poor alkene with a carbon electrophile. Electron-poor alkenes include acrylic esters, acrylonitriles, vinyl ketones, vinyl sulfones, and acroleins.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

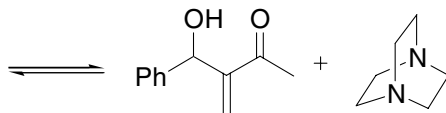
General scheme:



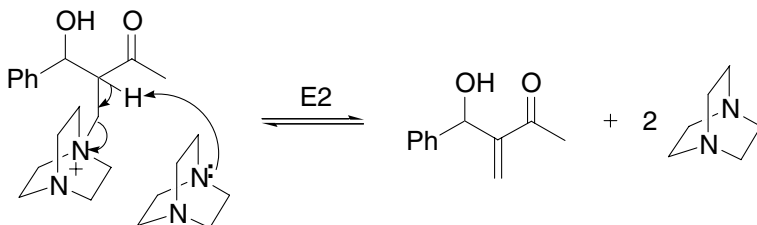
$\text{X} = \text{O}, \text{NR}_2$, $\text{EWG} = \text{CO}_2\text{R}, \text{COR}, \text{CHO}, \text{CN}, \text{SO}_2\text{R}, \text{SO}_3\text{R}, \text{PO}(\text{OEt})_2, \text{CONR}_2, \text{CH}_2=\text{CHCO}_2\text{Me}$

Example 1:

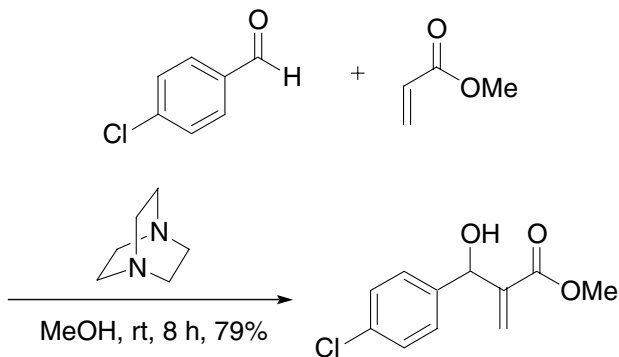




E2 (bimolecular elimination) mechanism is also operative here:



Example 2¹⁰



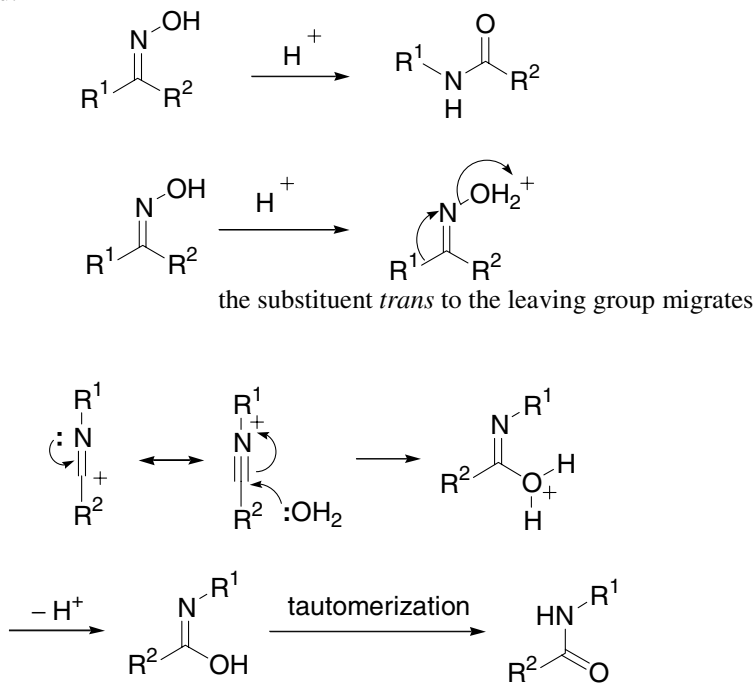
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A novel mechanism involving a hemiacetal intermediate is proposed.

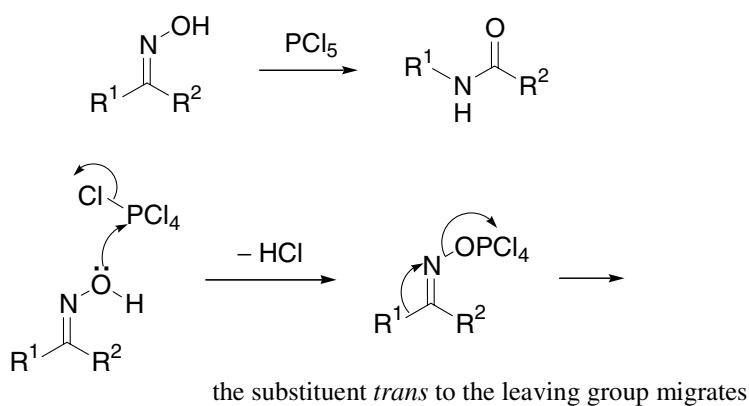
Beckmann rearrangement

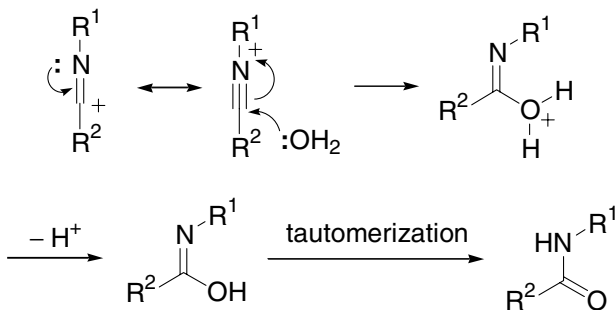
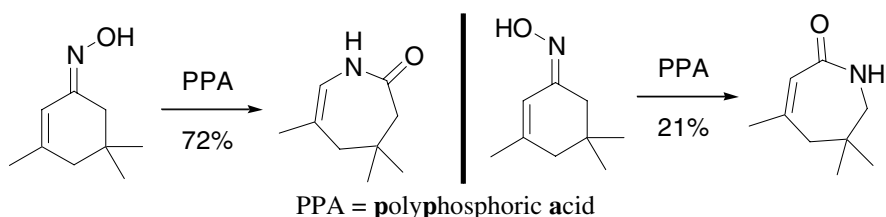
Acid-mediated isomerization of oximes to amides.

In protic acid:



With PCl_5 :



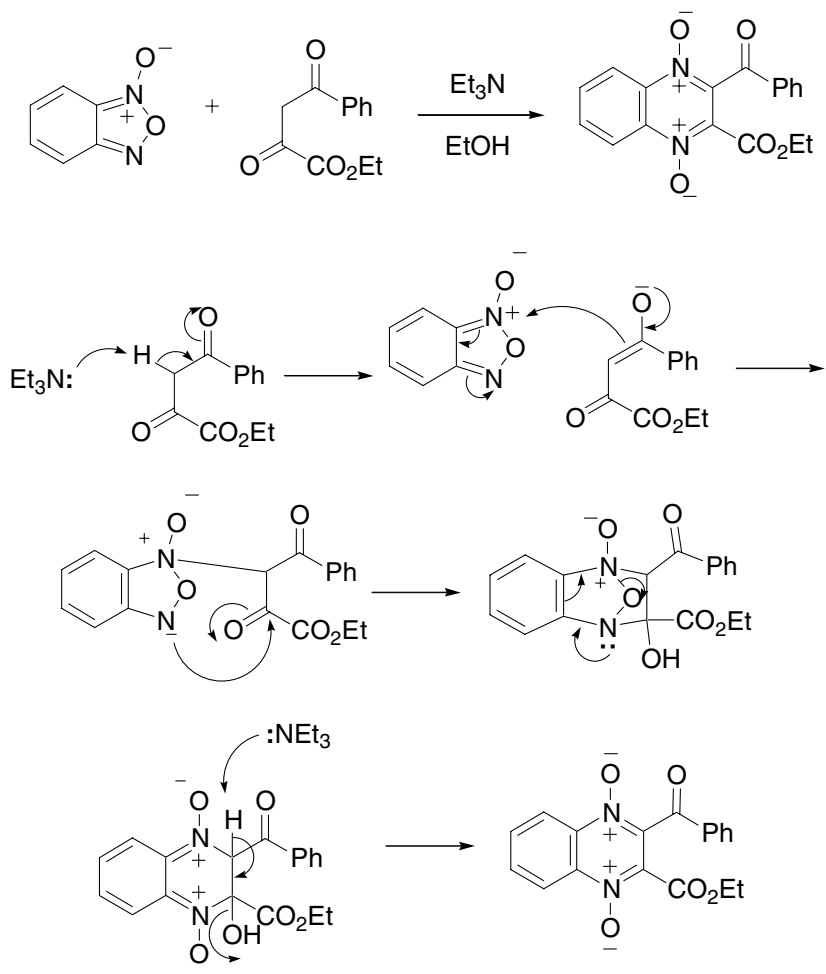
Example 1¹²

References

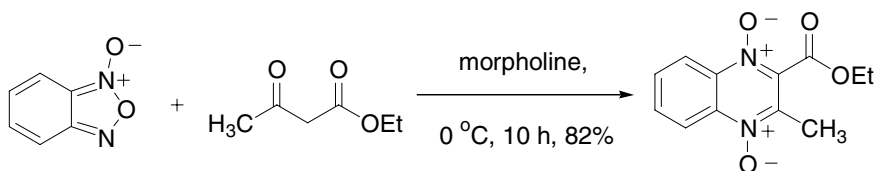
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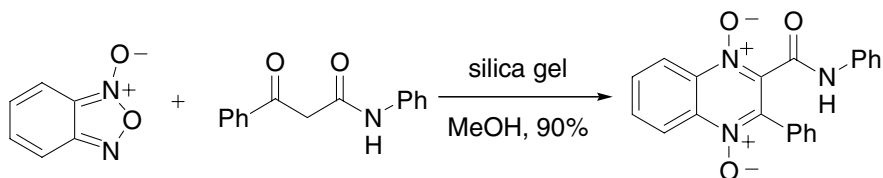
Beirut reaction

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



Example 1³



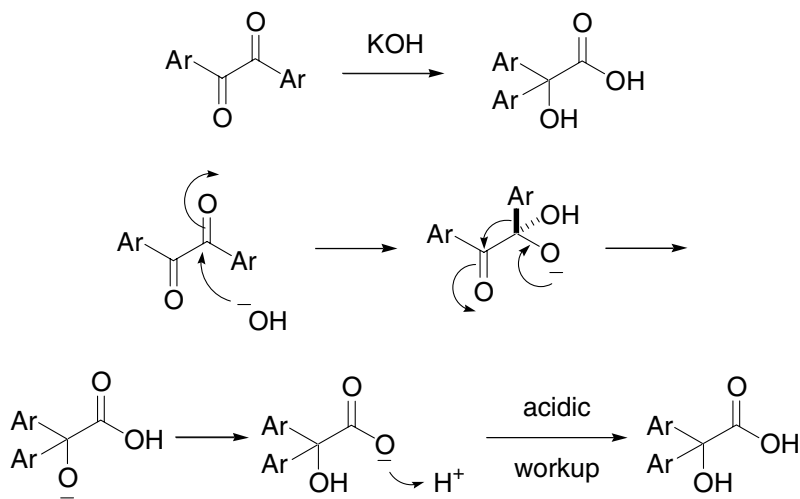
Example 2⁷

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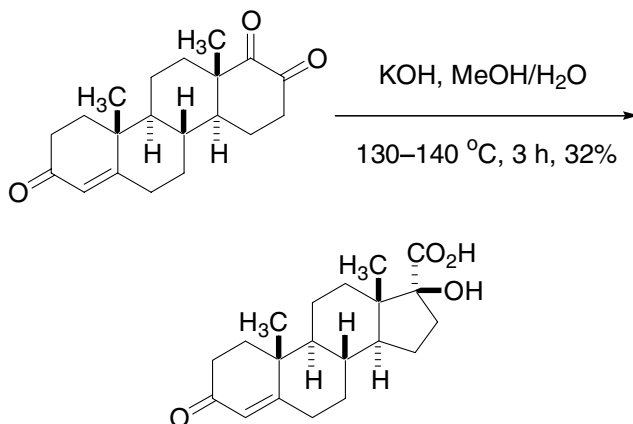
Benzilic acid rearrangement

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



Final deprotonation of the carboxylic acid drives the reaction forward.

Example 1³



References

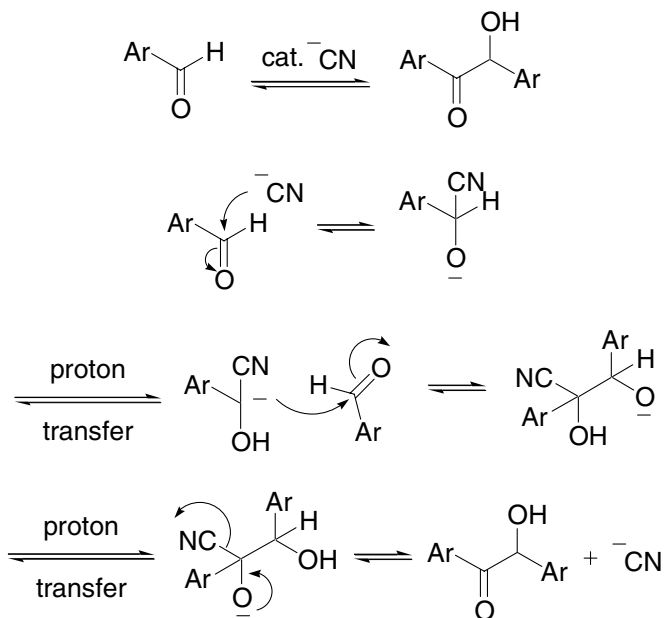
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Liebig would soon transform Giessen from a sleepy university to the Mecca of organic chemistry in Europe. Liebig is now considered the father of organic chemistry. Many classic name reactions were published in the journal that still bears his name,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

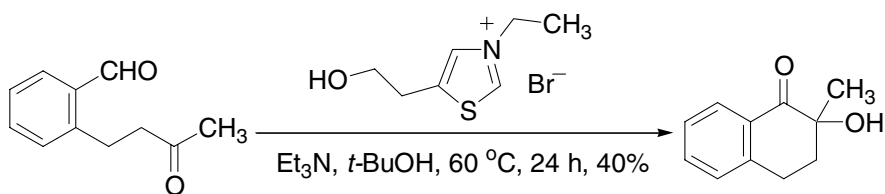
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Benzoin condensation

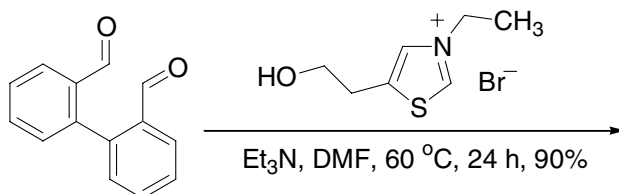
Cyanide-catalyzed condensation of aryl aldehyde to benzoin. Now cyanide is mostly replaced by a thiazolium salt. *Cf.* Stetter reaction.

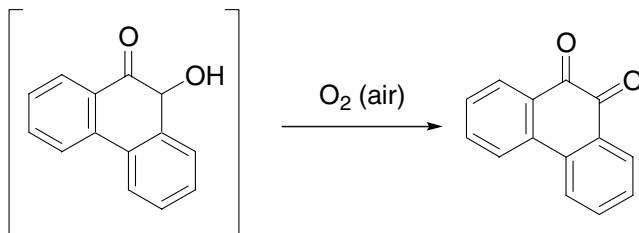


Example 1¹¹



Example 2¹¹



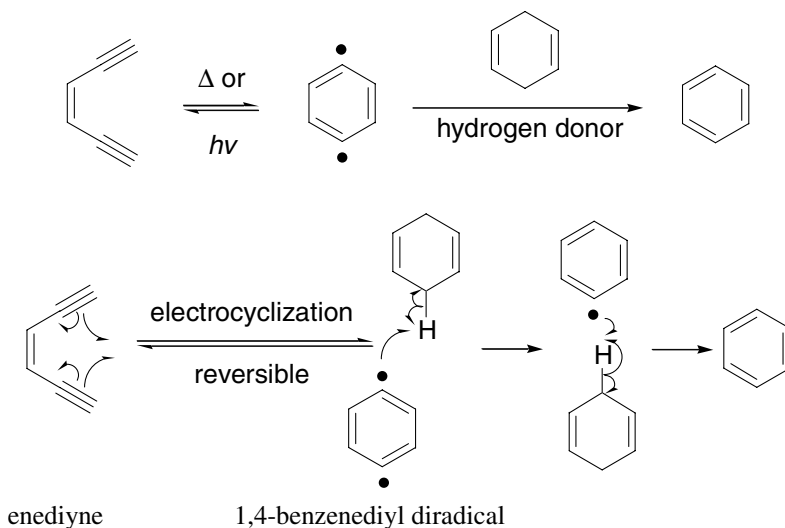


References

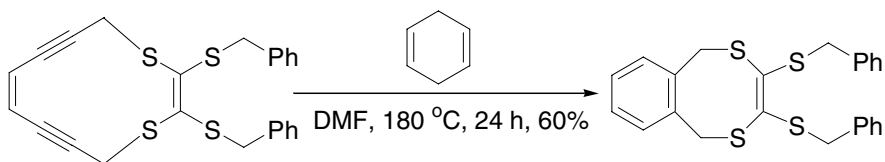
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Bergman cyclization

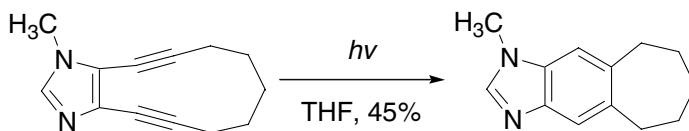
1,4-Benzenediyl diradical formation from enediyne *via* electrocyclization.



Example 1¹⁴



Example 2¹⁵



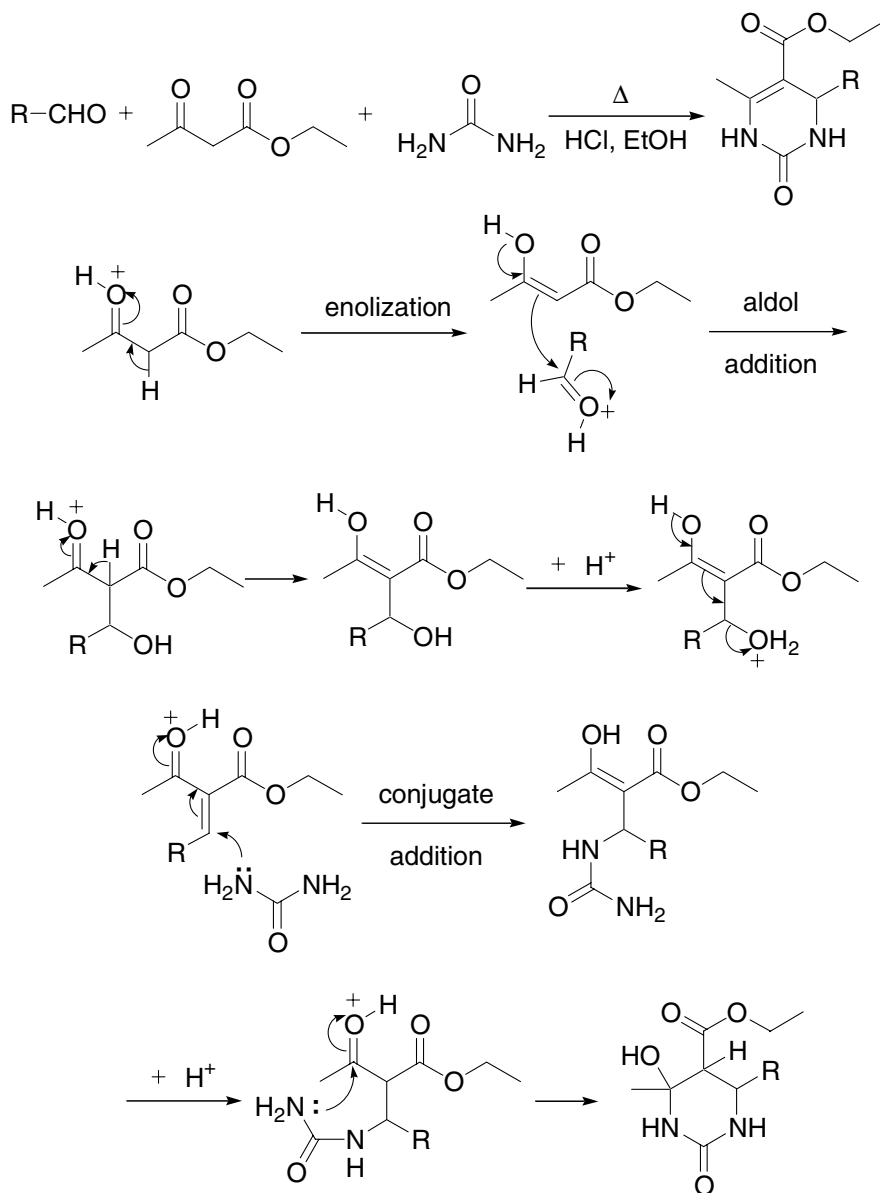
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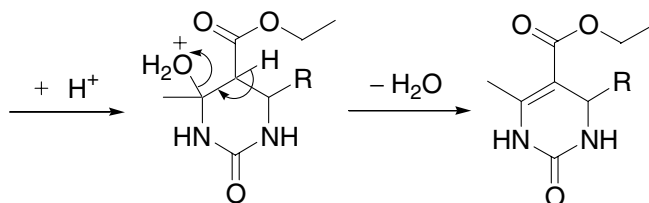
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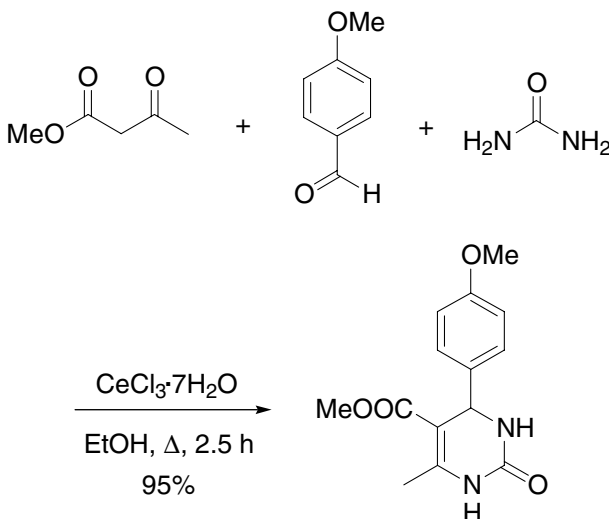
Biginelli pyrimidone synthesis

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).





Example⁹



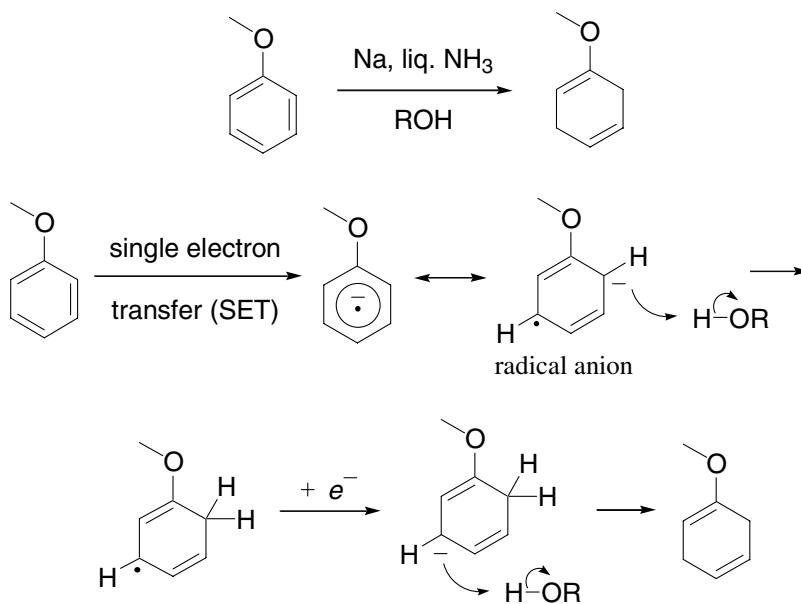
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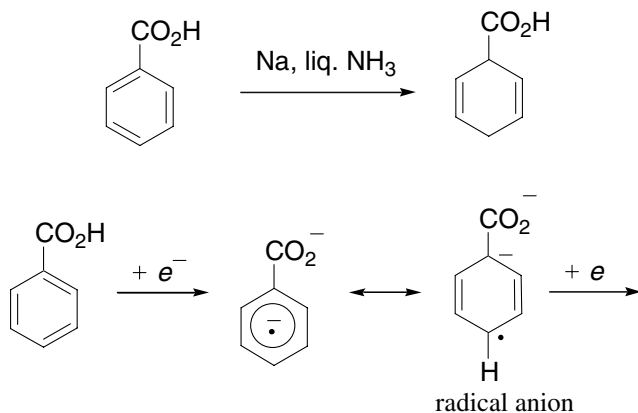
Birch reduction

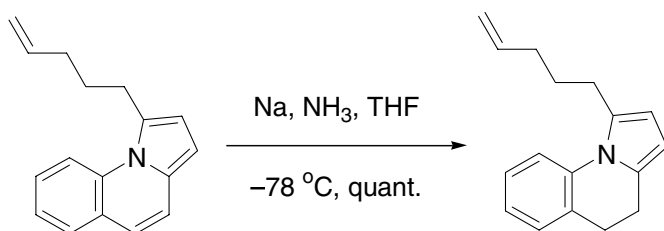
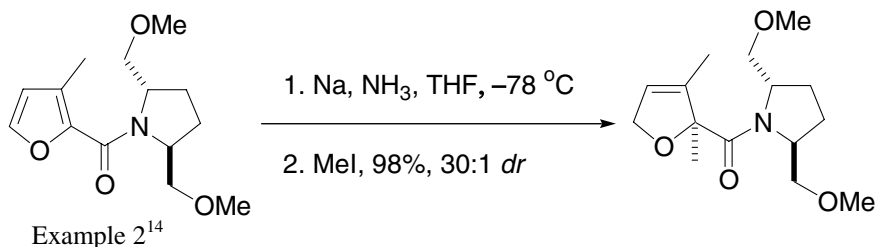
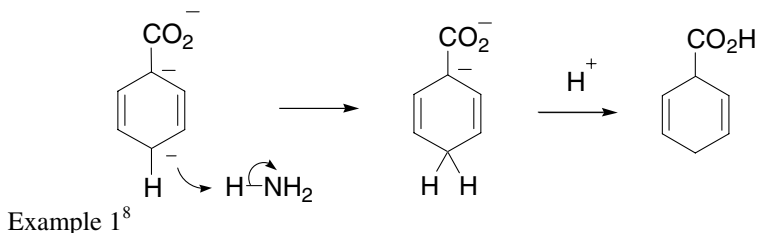
The Birch reduction is the 1,4-reduction of aromatics to their corresponding cyclohexadienes by alkali metals (Li, K, Na) dissolved in liquid ammonia in the presence of an alcohol.

Benzene ring bearing an electron-donating substituent:



Benzene ring with an electron-withdrawing substituent:



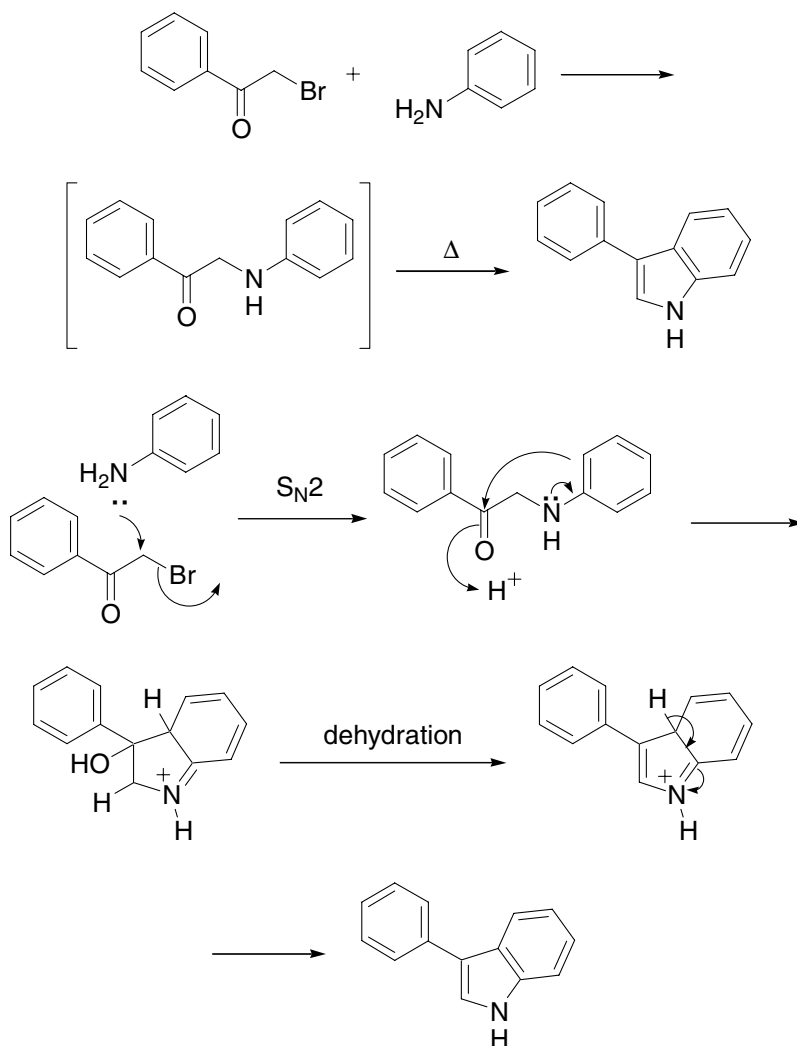


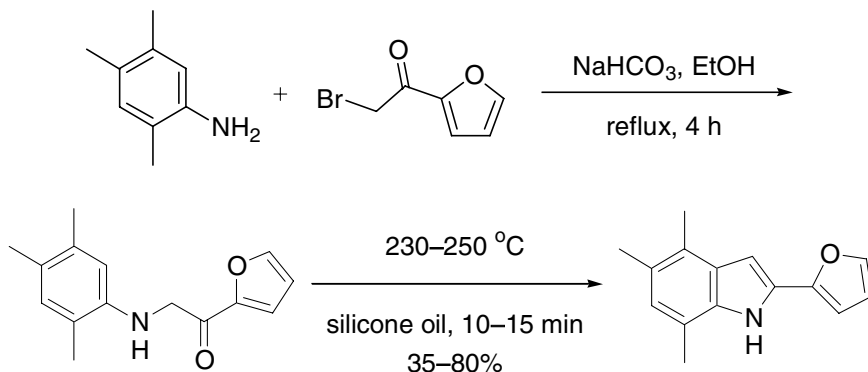
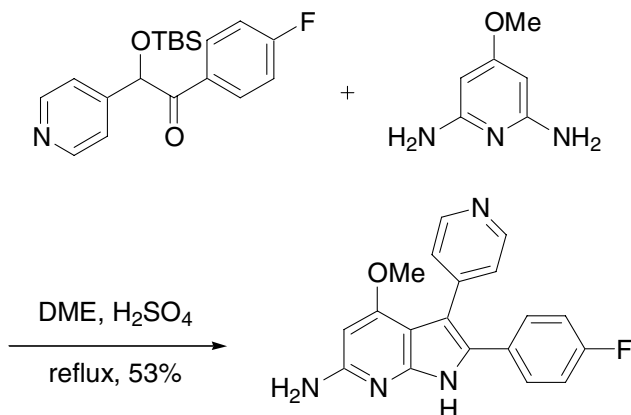
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Bischler–Möhlau indole synthesis

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



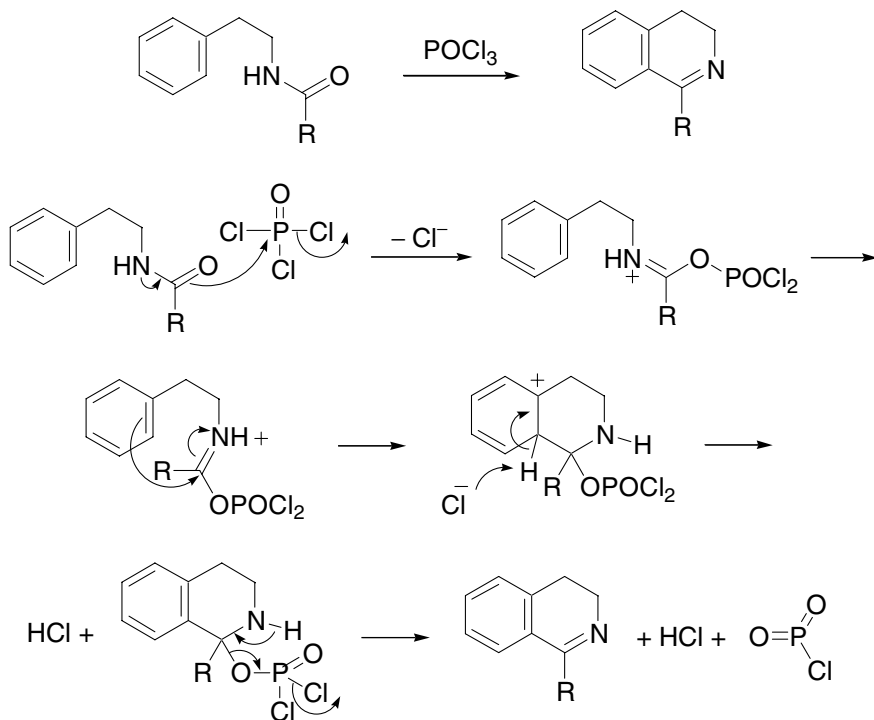
Example 1⁵Example 2⁹

References

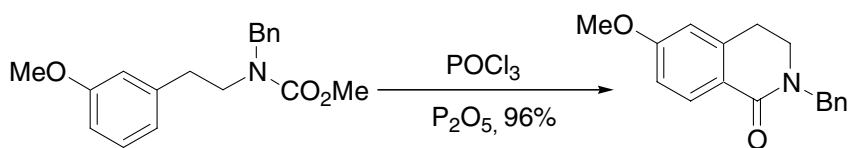
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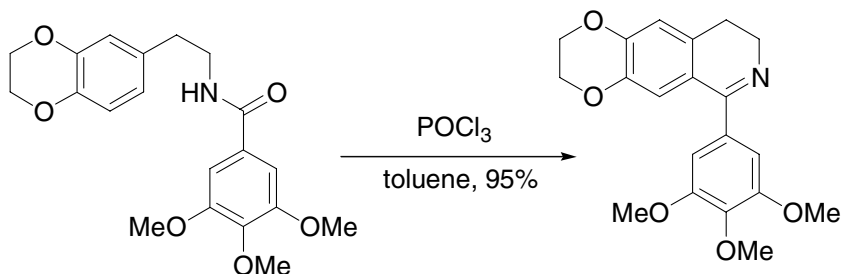
Bischler–Napieralski reaction

Dihydroisoquinolines from β -phenethylamides using phosphorus oxychloride.



Example 1⁶



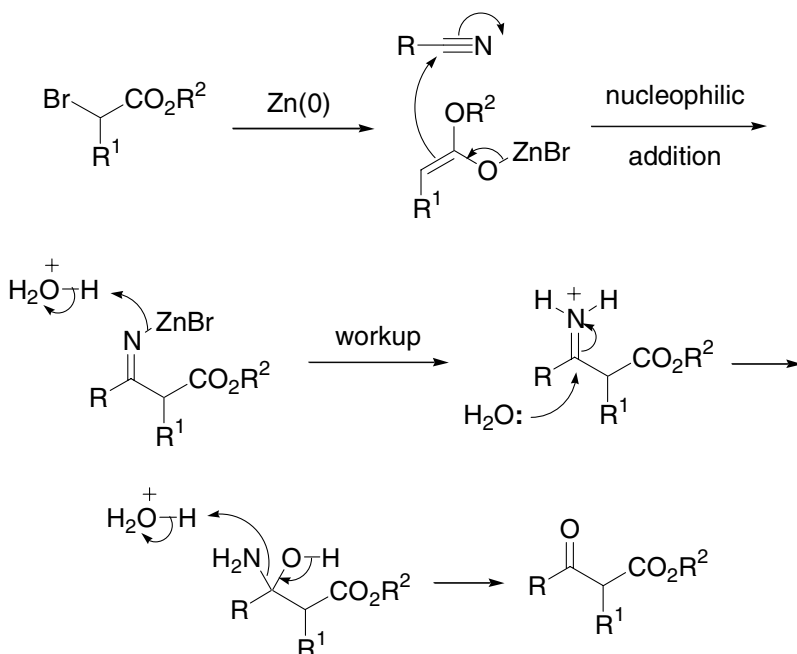
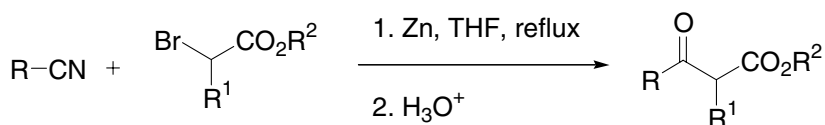
Example 2¹⁰

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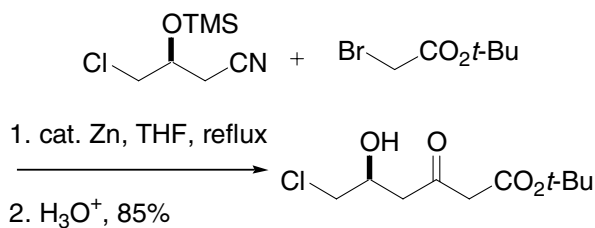
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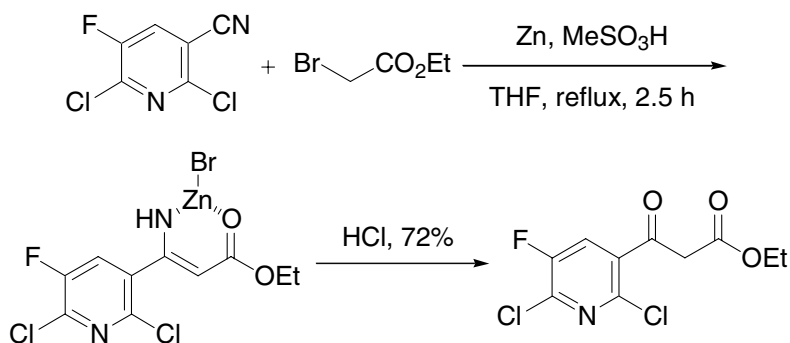
Blaise reaction

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



Example 1, preparation of the statin side chain¹⁰



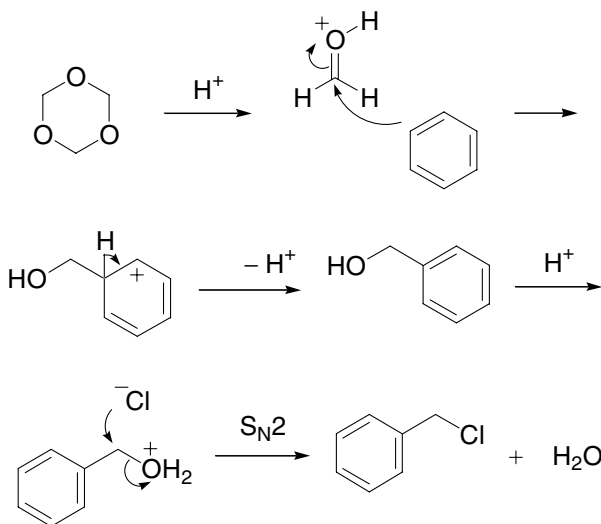
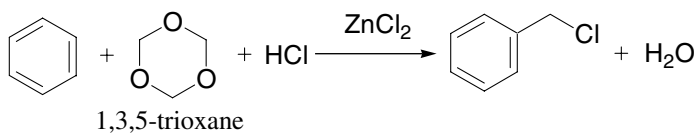
Example 2¹¹

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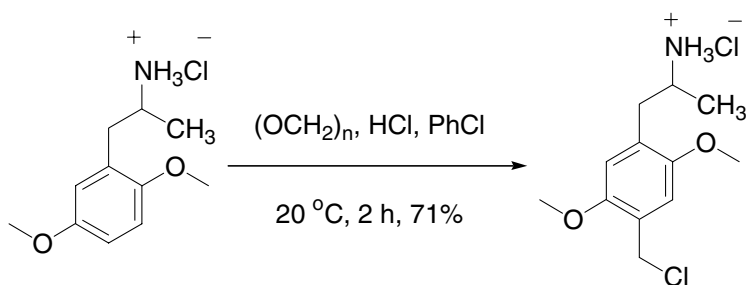
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Blanc chloromethylation

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



Example 1¹²



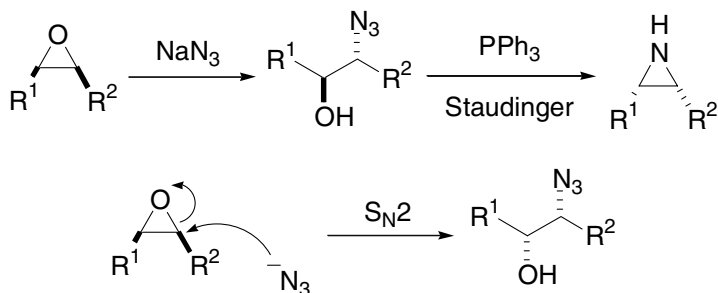
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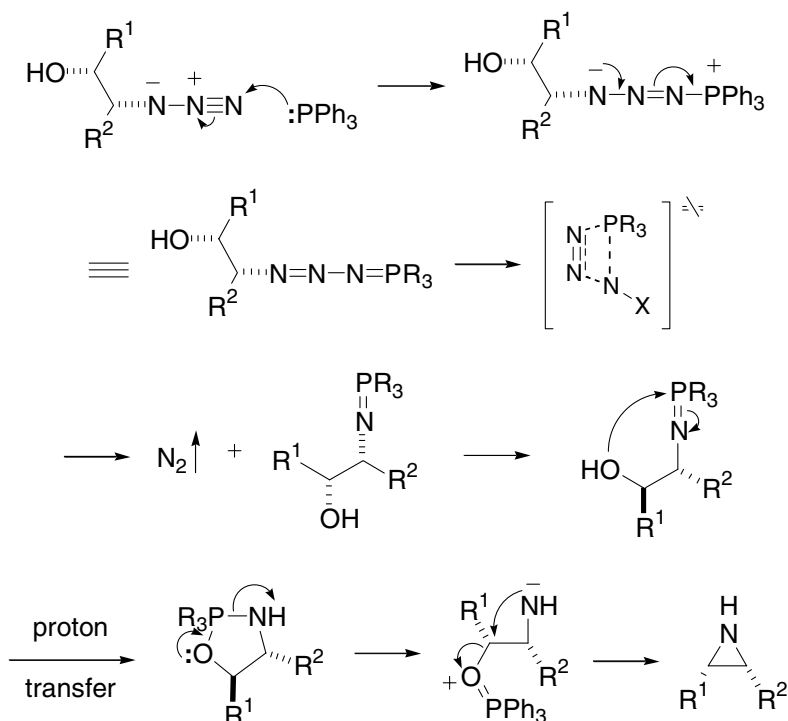
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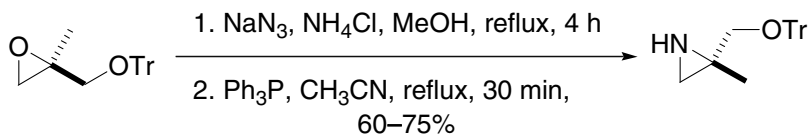
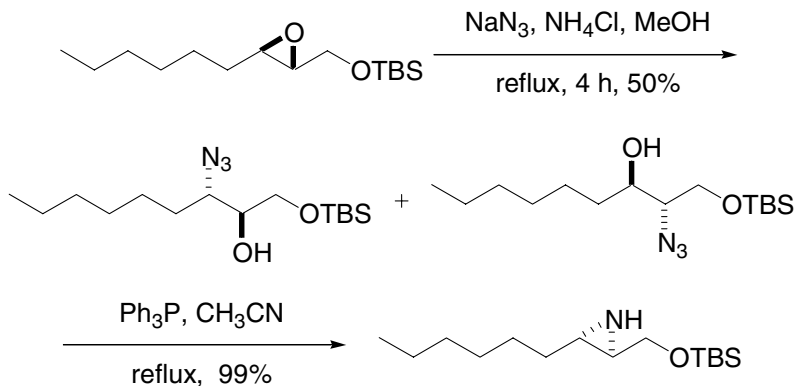
Blum aziridine synthesis

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



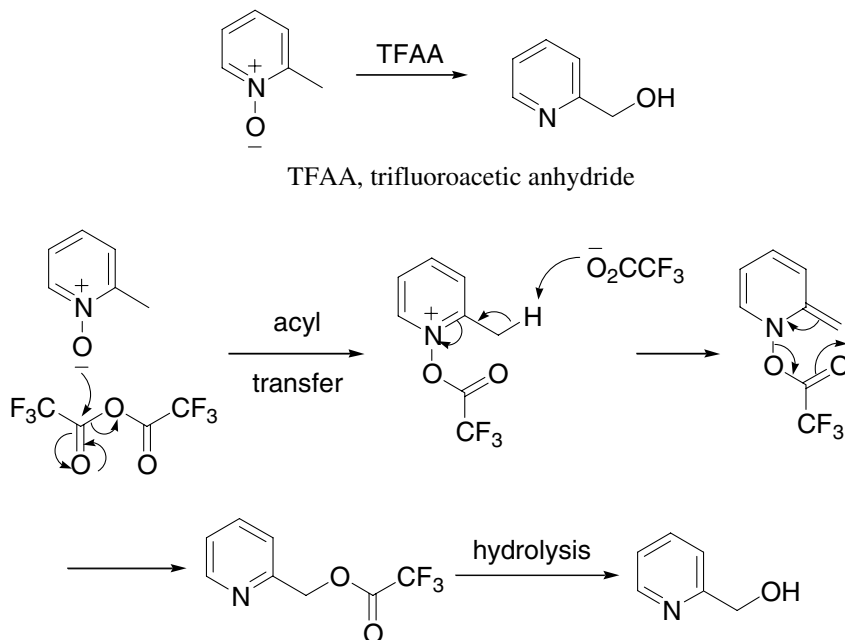
Example 1³Example 2⁵

References

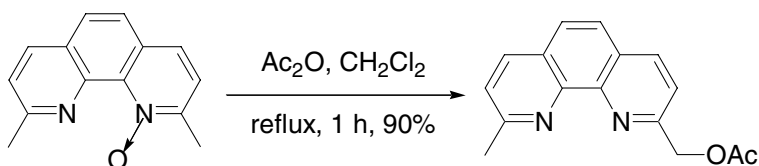
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Boeckelheide reaction

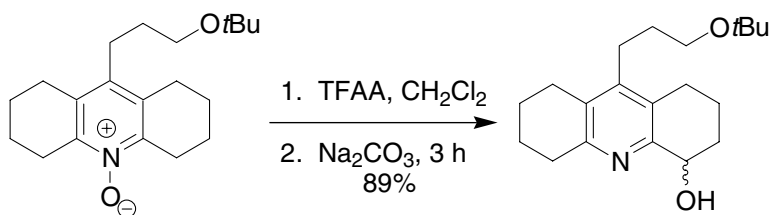
Treatment of 2-methylpyridine *N*-oxide with trifluoroacetic anhydride gives rise to 2-hydroxymethylpyridine.



Example 1⁶



Example 2⁹

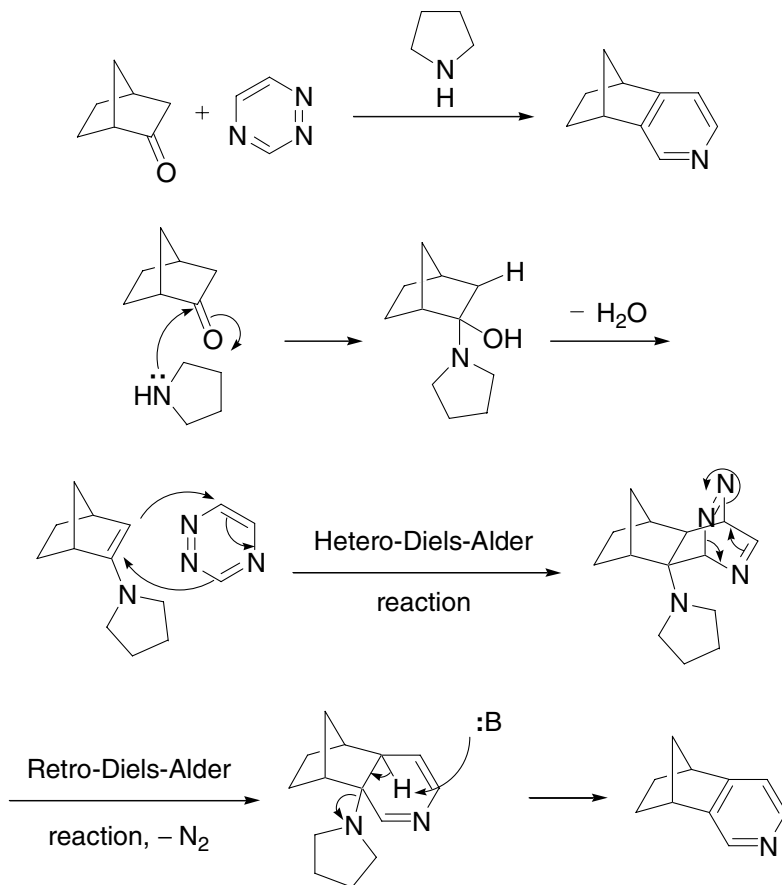


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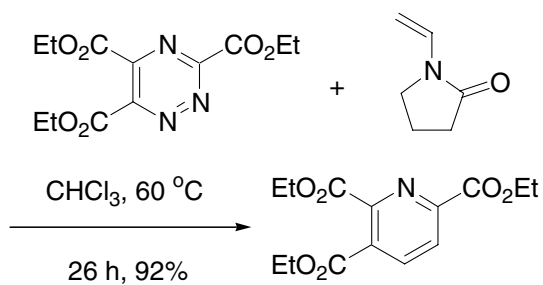
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Boger pyridine synthesis

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



Example 1⁴

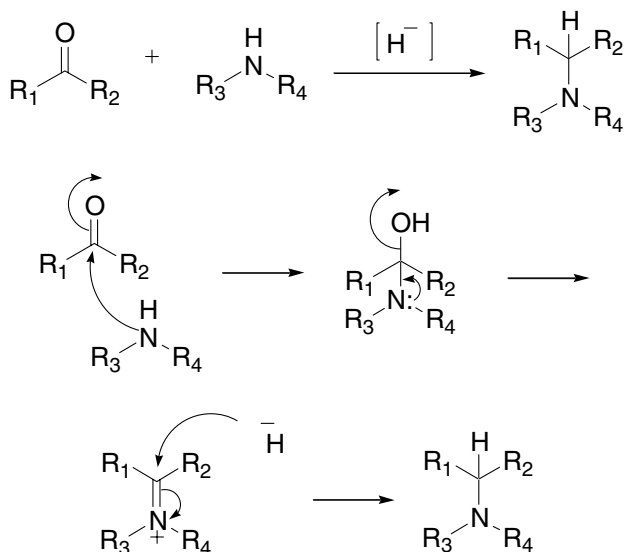


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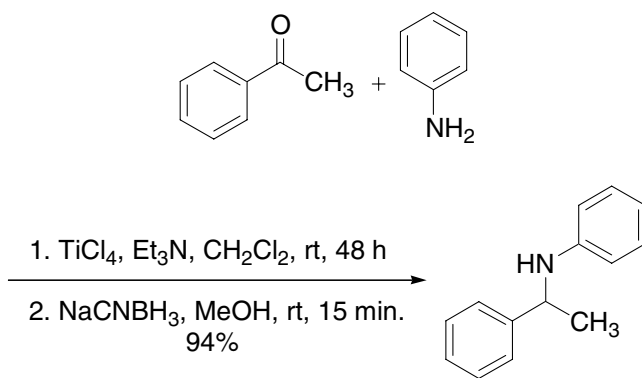
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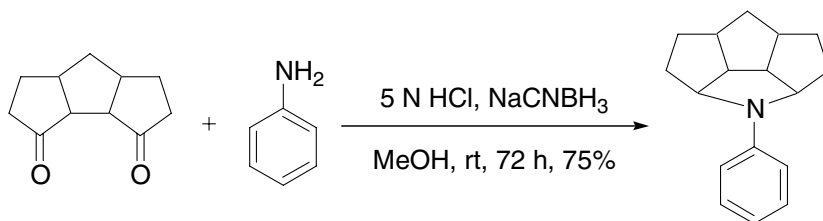
Borch reductive amination

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



Example 1⁴



Example 2⁵

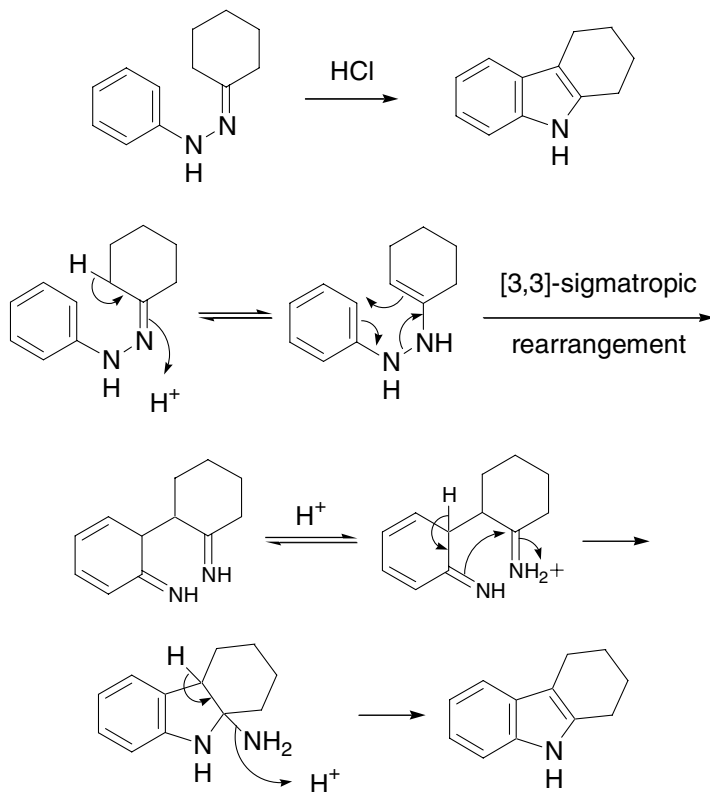
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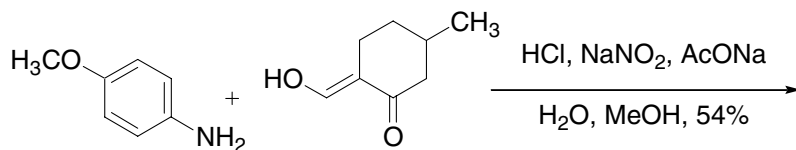
Borsche–Drechsel cyclization

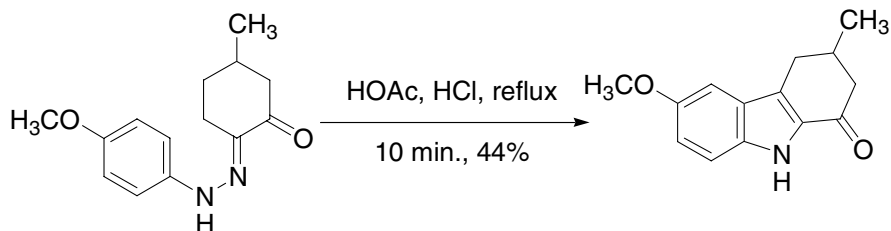
Tetrahydrocarbazole synthesis from cyclohexanone phenylhydrazone.

Cf. Fisher indole synthesis.



Example 1⁸



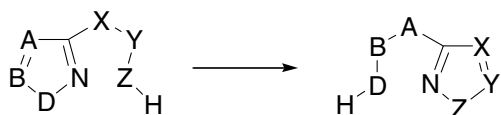


References

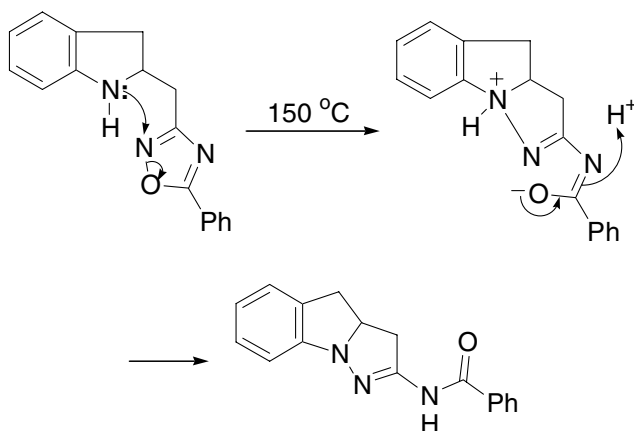
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Boulton–Katritzky rearrangement

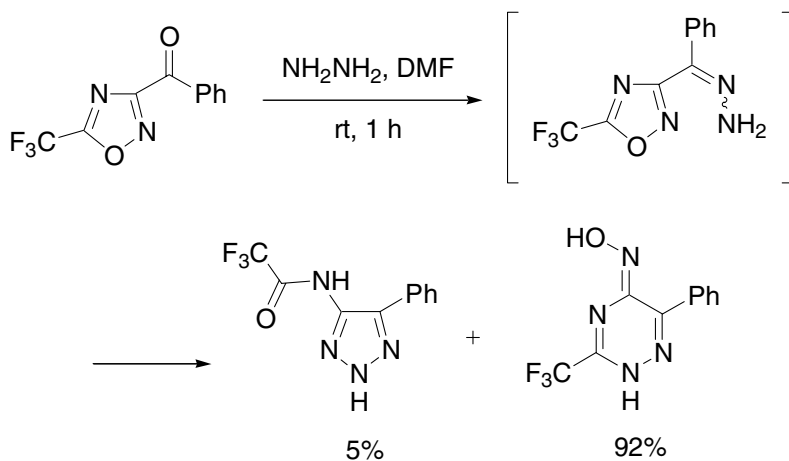
Rearrangement of one five-membered heterocycle into another under thermolysis.

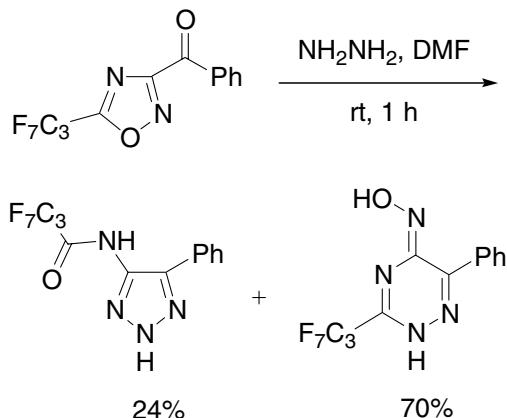


Example 1⁷



Example 2¹¹



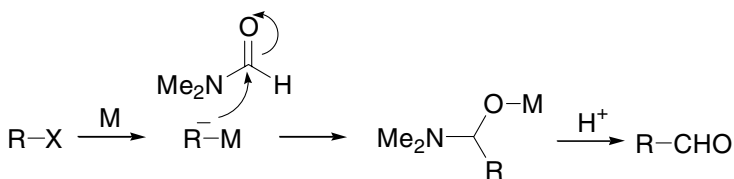


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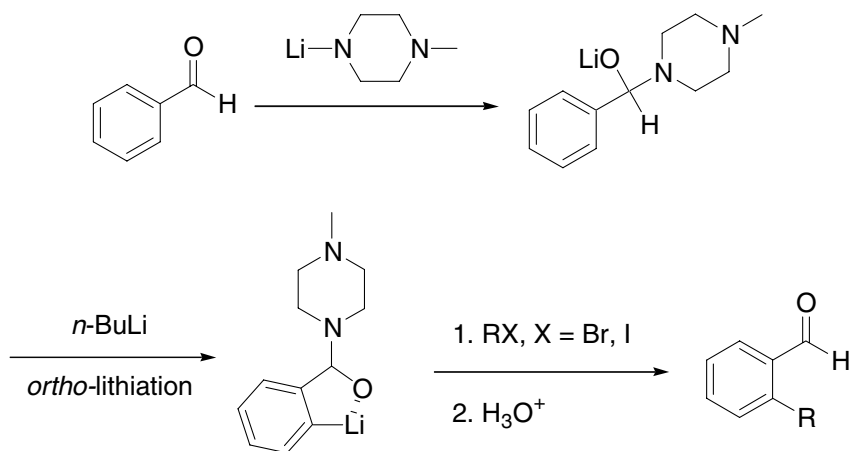
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Bouveault aldehyde synthesis

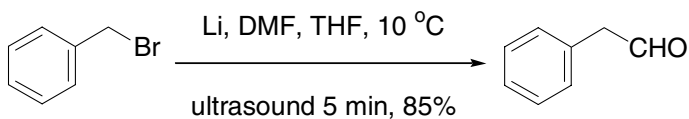
Formylation of an alkyl or aryl halide to the homologous aldehyde by transformation to the corresponding organometallic reagent then addition of DMF (M = Li, Mg, Na, and K).



A modification by Comins:⁷



Example 1⁶

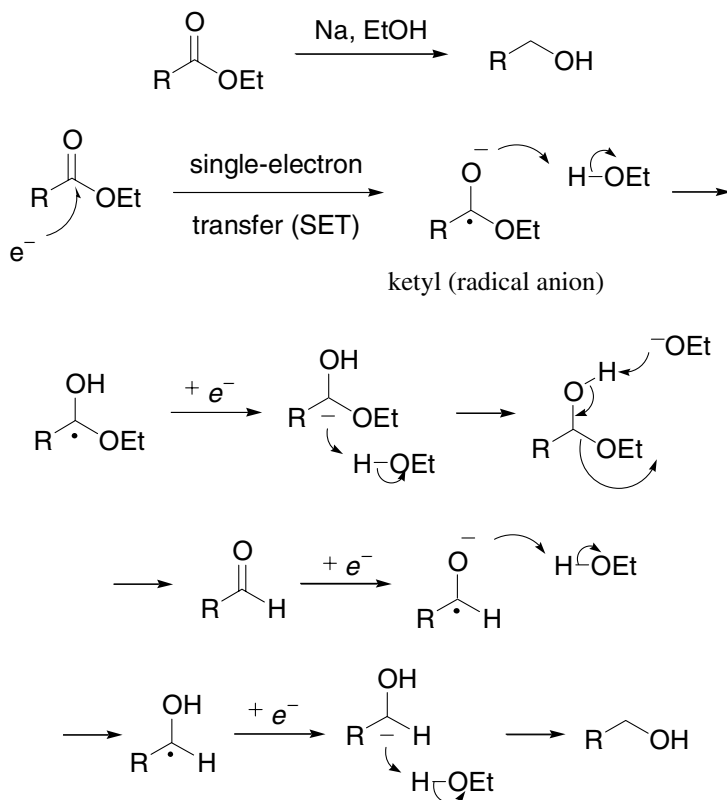


References

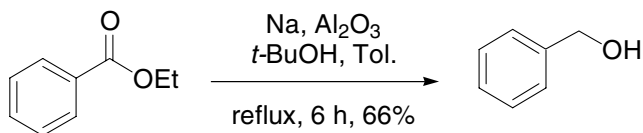
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Bouveault–Blanc reduction

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



Example 1⁸



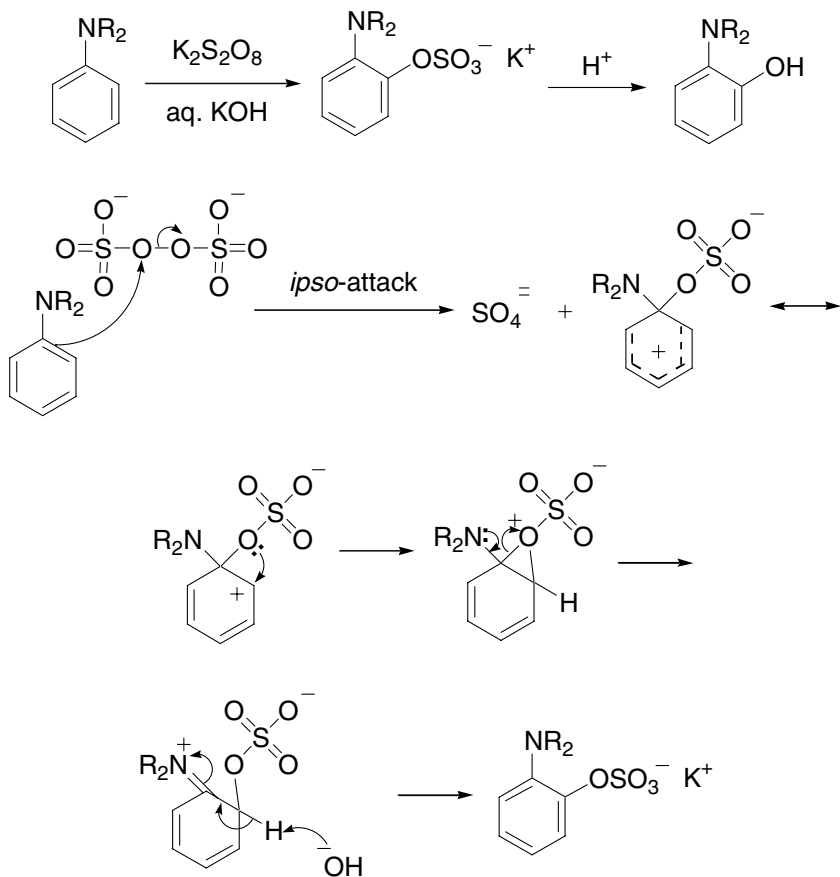
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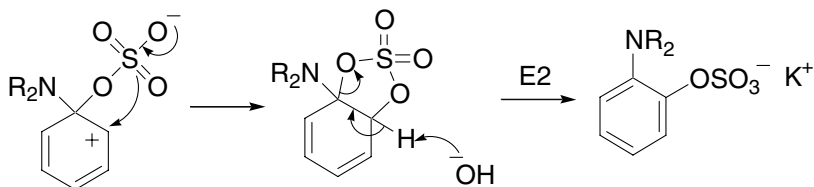
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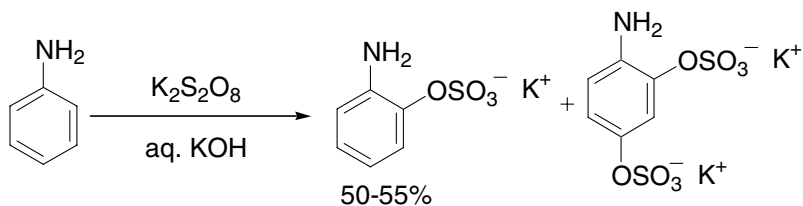
Boydland–Sims oxidation

Oxidation of anilines to phenols using alkaline persulfate.



Another pathway is also operative:



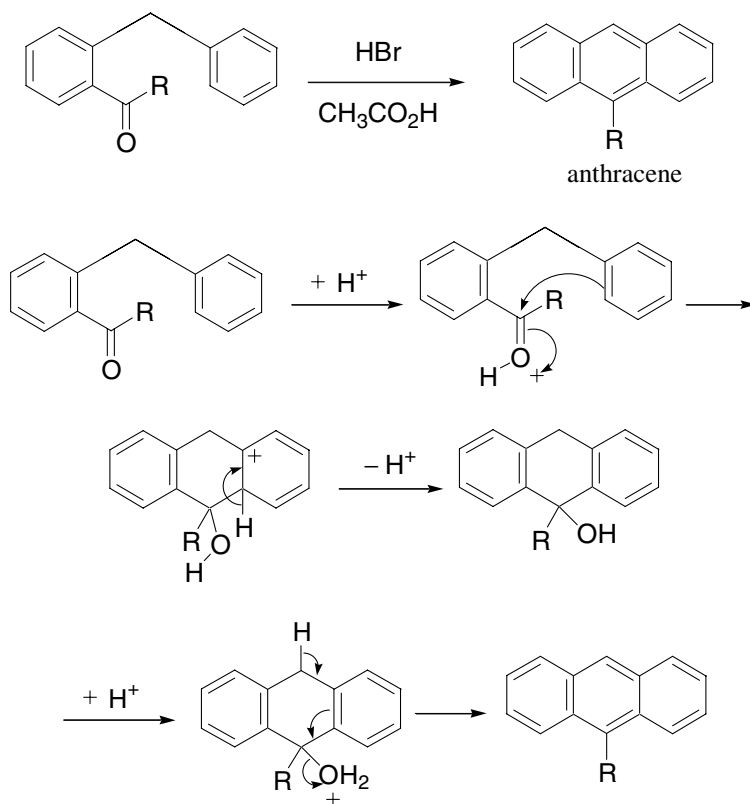
Example 1³

References

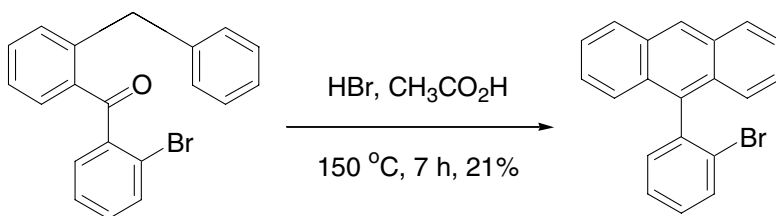
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Bradsher reaction

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



Example⁵



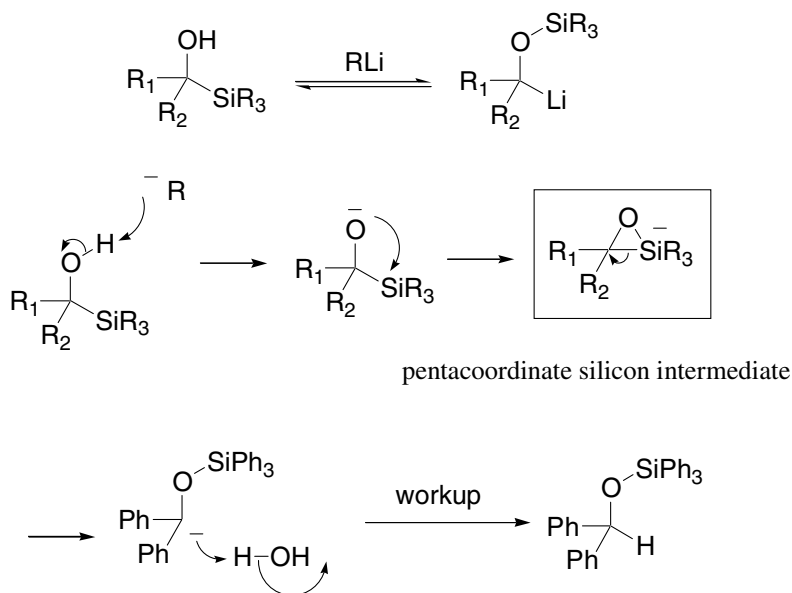
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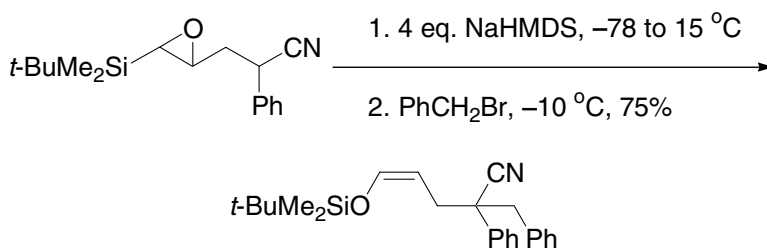
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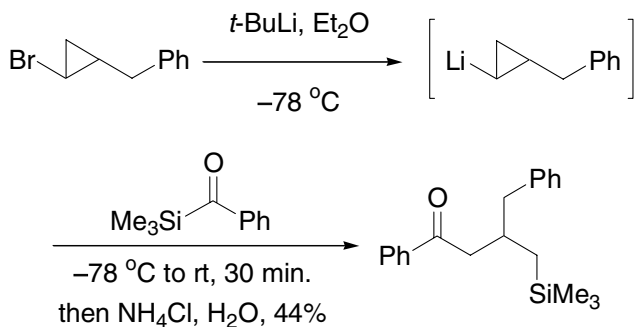
Brook rearrangement

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.



Example 1¹¹



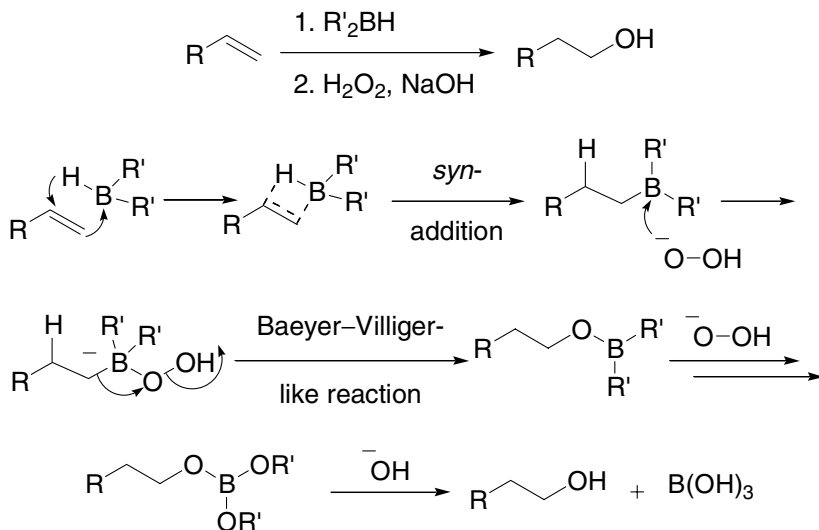
Example 2¹⁴

References

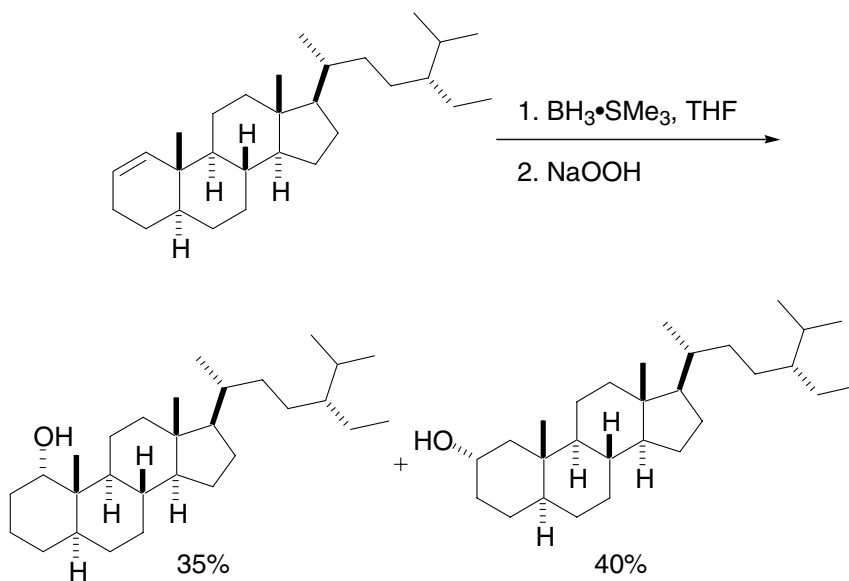
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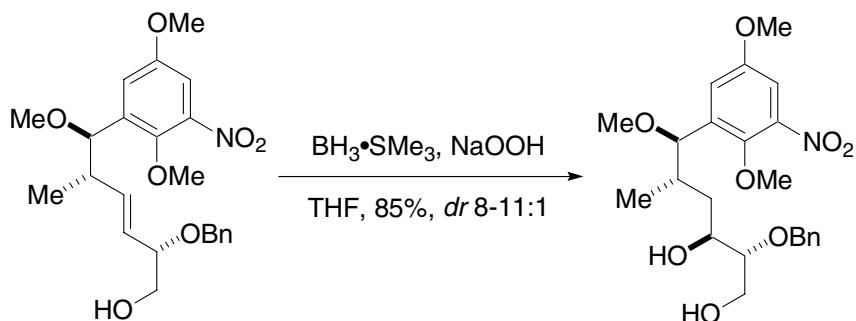
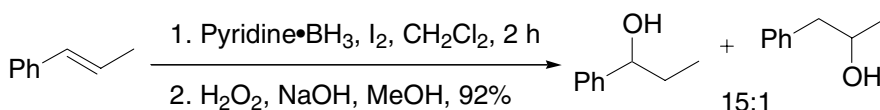
Brown hydroboration

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



Example 1²



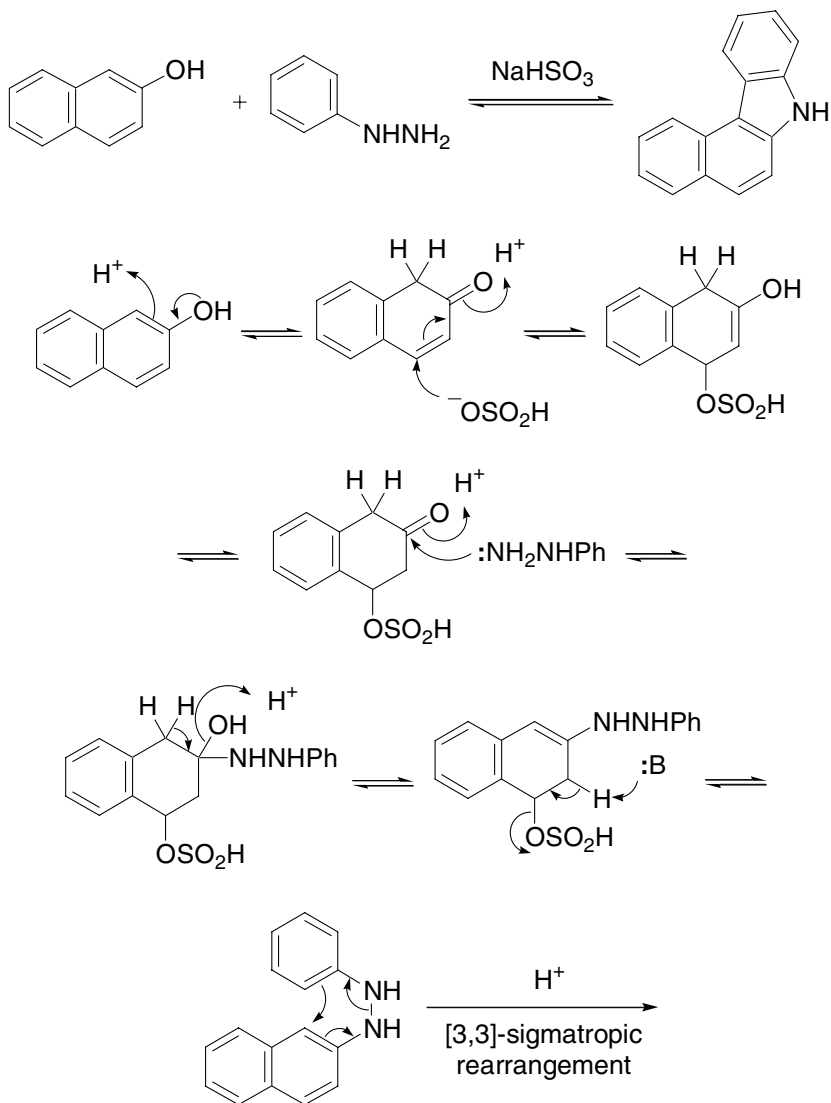
Example 2¹³Example 3¹⁴

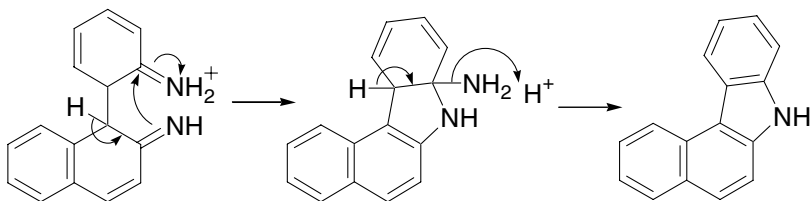
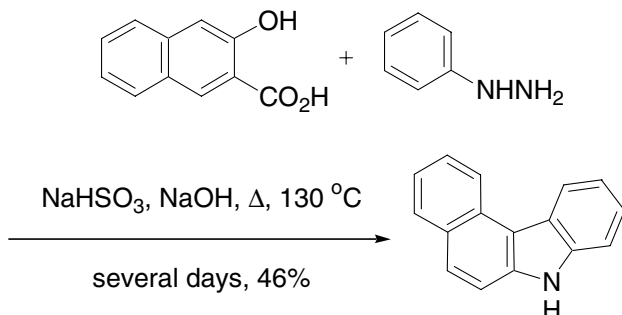
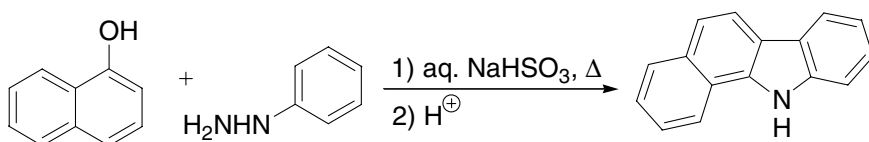
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Bucherer carbazole synthesis

Carbazoles from naphthols and aryl hydrazines promoted by sodium bisulfite.



Example 1³Example 2⁴

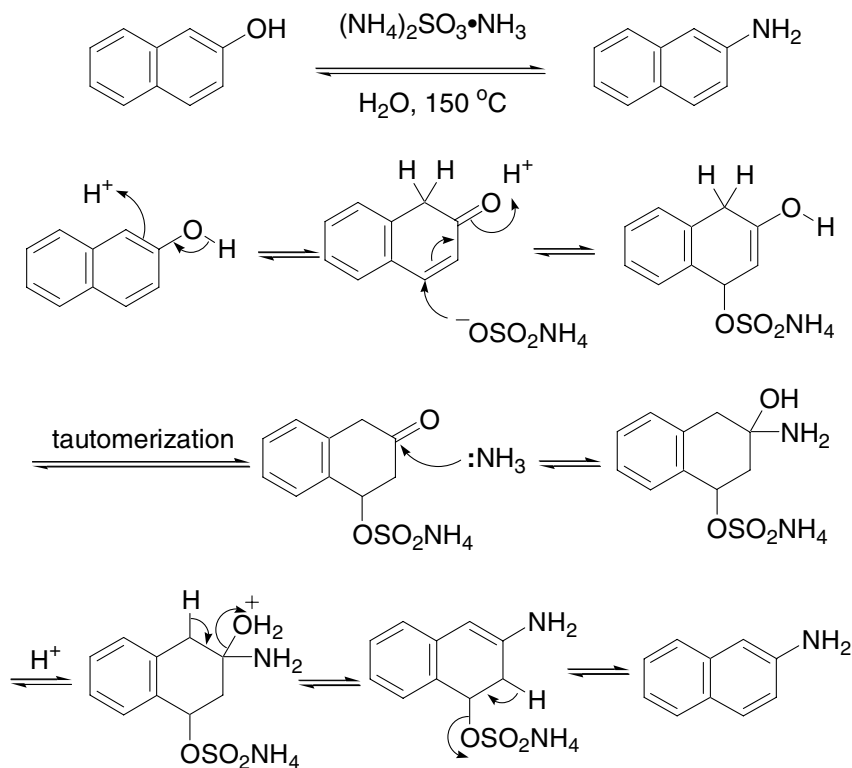
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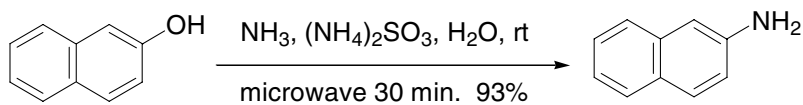
Bucherer reaction

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



Example²

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



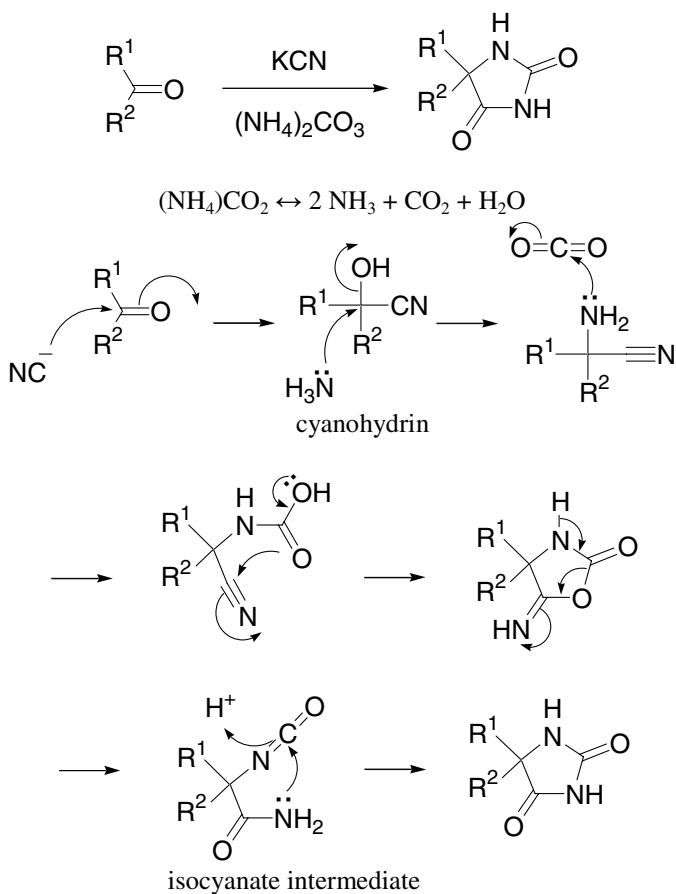
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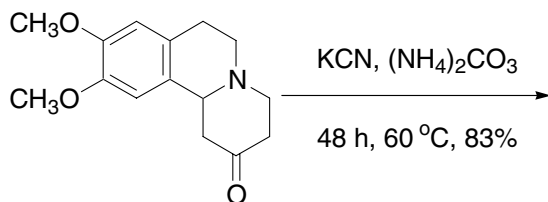
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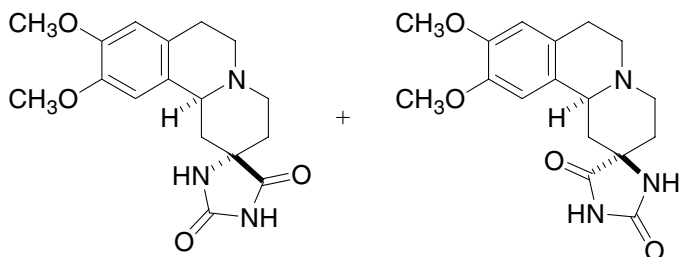
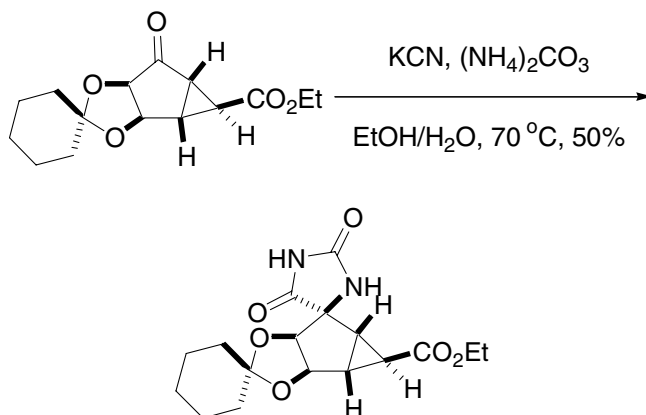
Bucherer–Bergs reaction

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



Example 1¹⁰



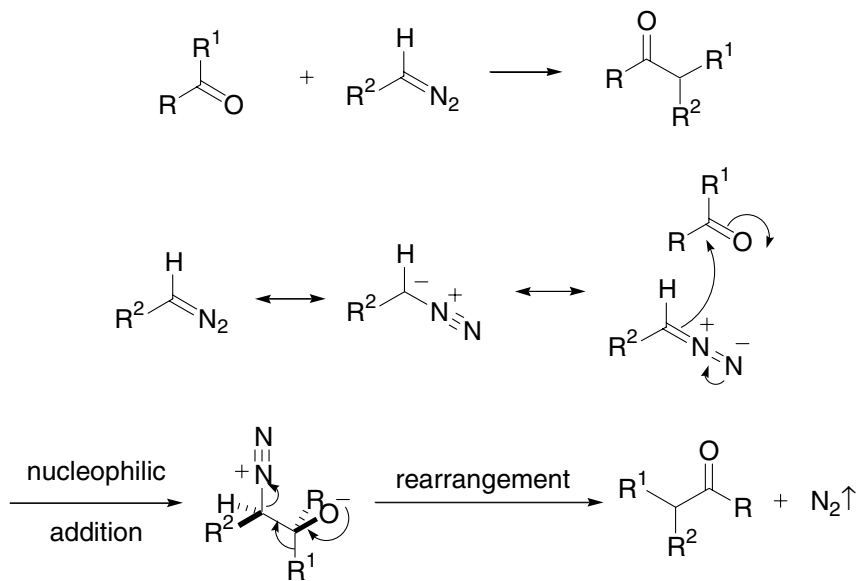
Example 2¹¹

References

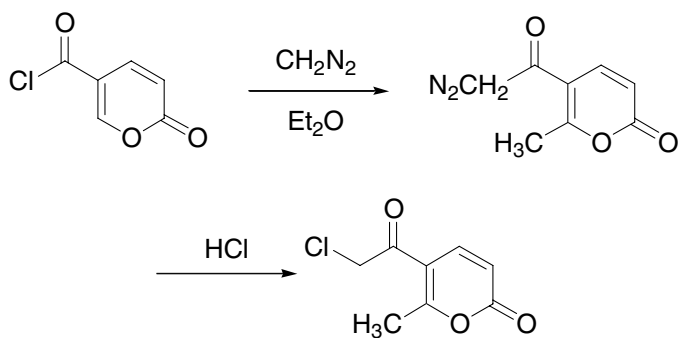
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Büchner–Curtius–Schlotterbeck reaction

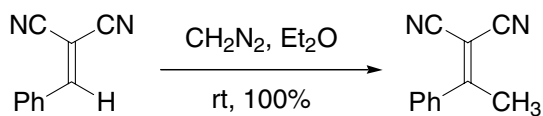
Reaction of carbonyl compounds with aliphatic diazo compounds to deliver homologated ketones.

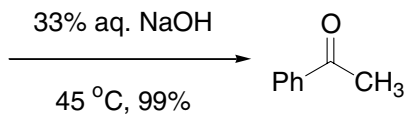


Example 1³



Example 2⁶



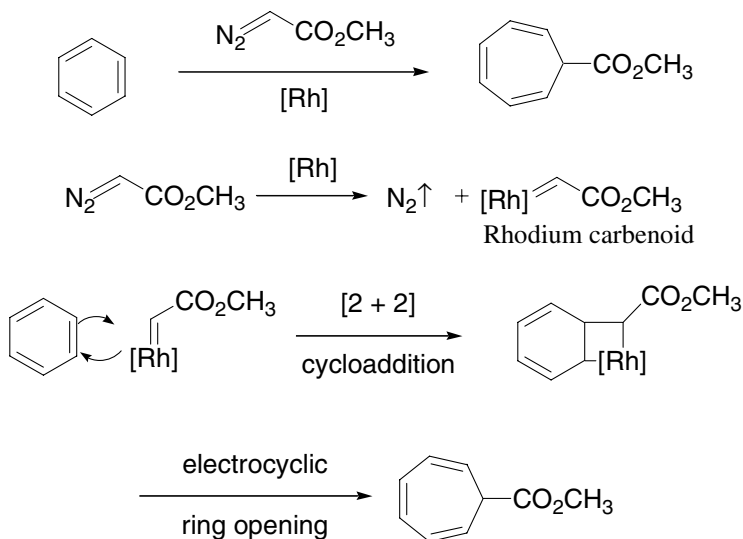


References

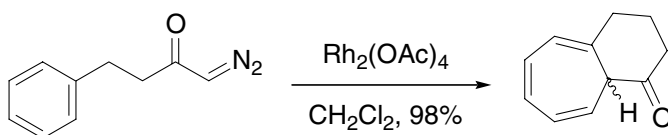
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Büchner method of ring expansion

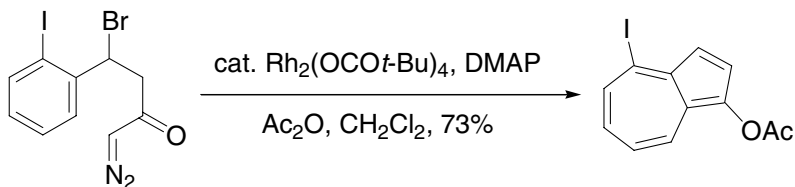
Reaction of benzene with diazoacetic esters to give cyclohepta-2,4,6-trienecarboxylic acid esters. Cf. Pfau–Platter azulene synthesis.



Example 1⁷



Example 2⁸



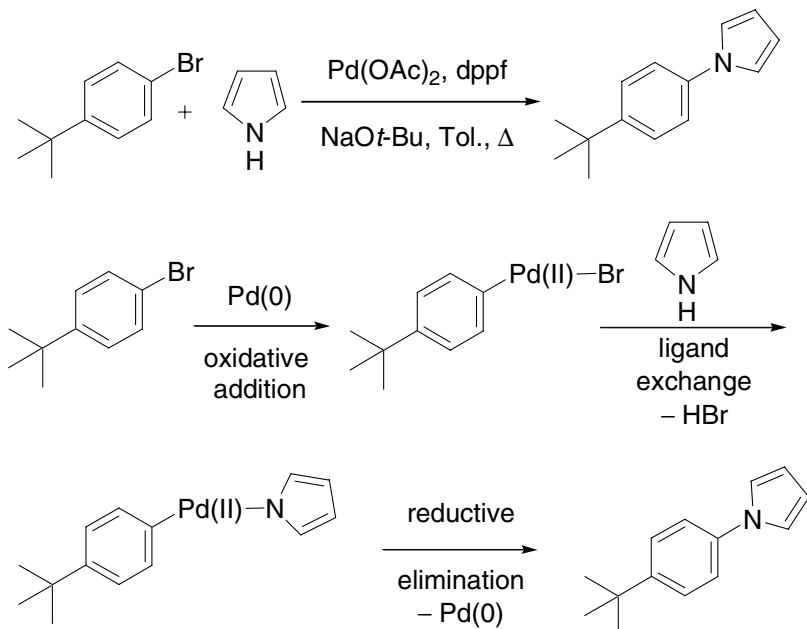
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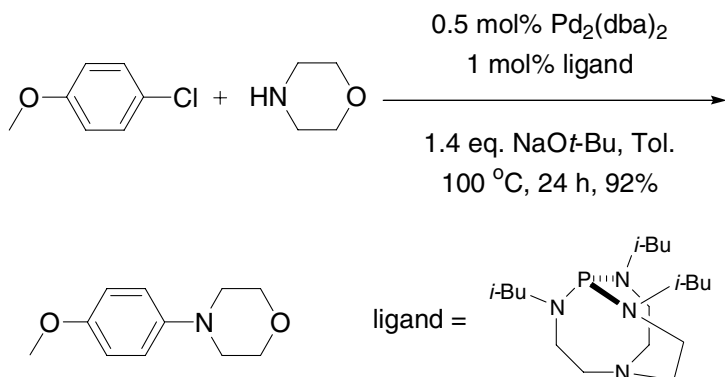
Buchwald–Hartwig C–N and C–O bond formation reactions

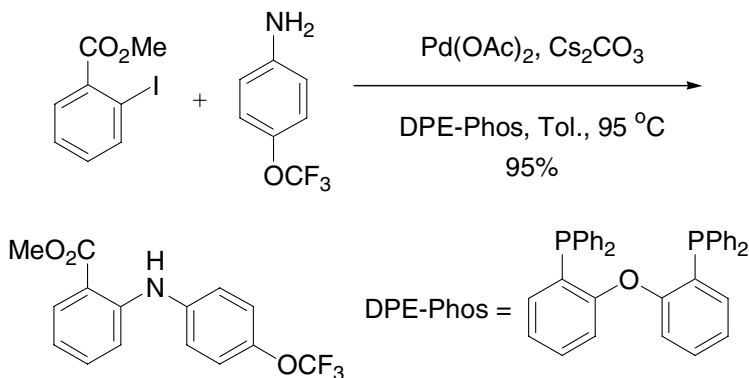
Direct Pd-catalyzed C–N and C–O bond formation from aryl halides and amines in the presence of stoichiometric amount of base.



The C–O bond formation reaction follows a similar mechanistic pathway.^{7–9}

Example 1¹¹



Example 2¹²

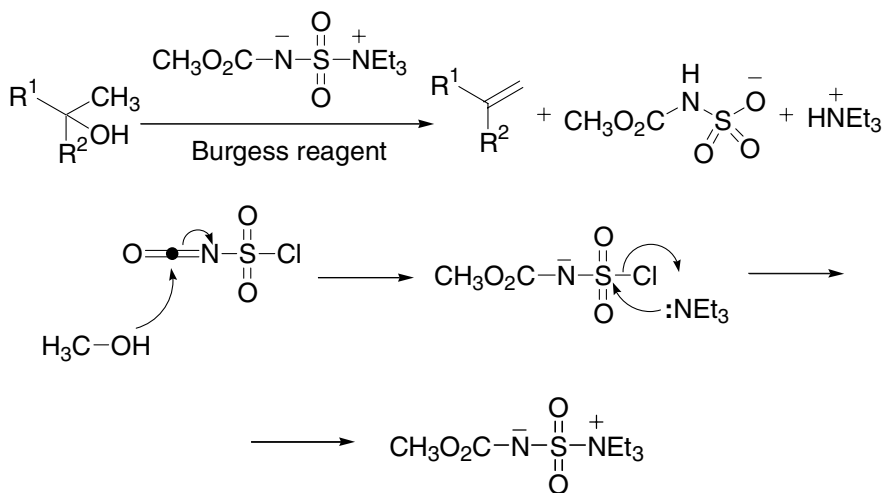
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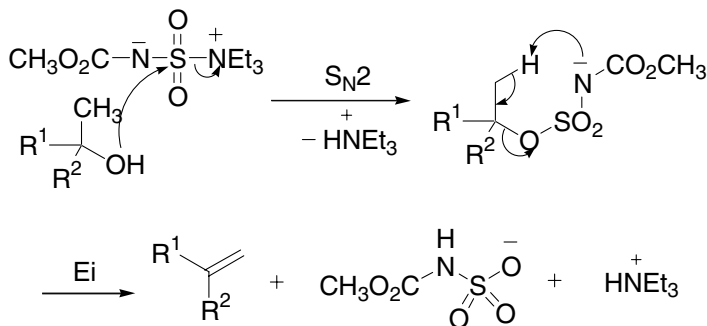
Burgess dehydrating reagent

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.

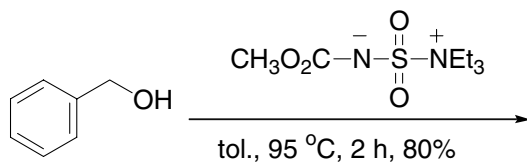
Reagen formation,

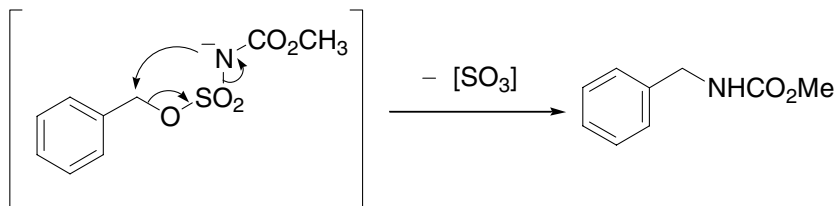
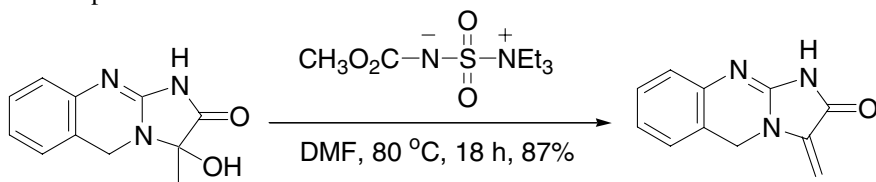
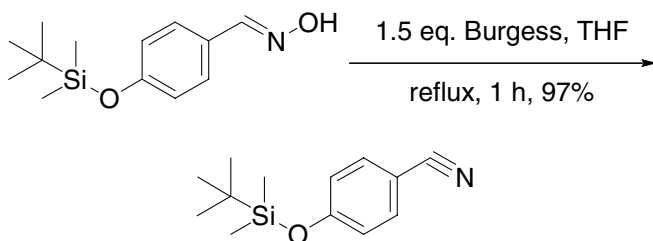


Reaction,



Example 1⁴



Example 2⁵Example 3¹⁰

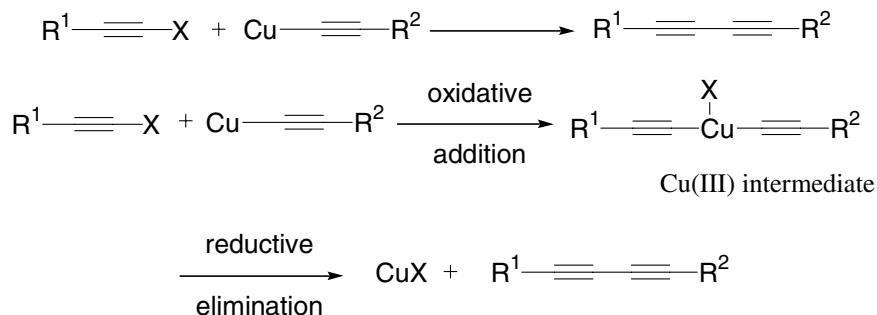
References

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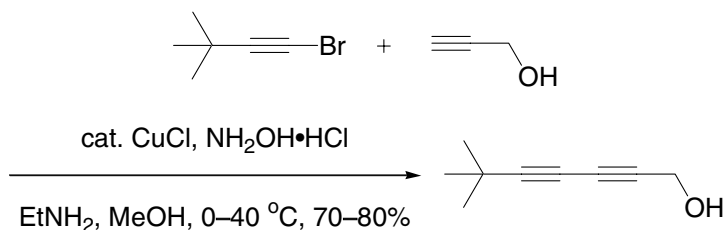
Cadiot–Chodkiewicz coupling

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

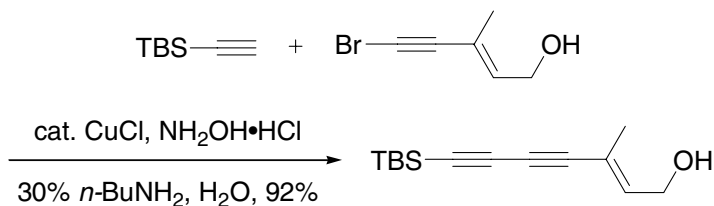
Cf. Castro–Stephens reaction.



Example 1⁶



Example 2¹¹



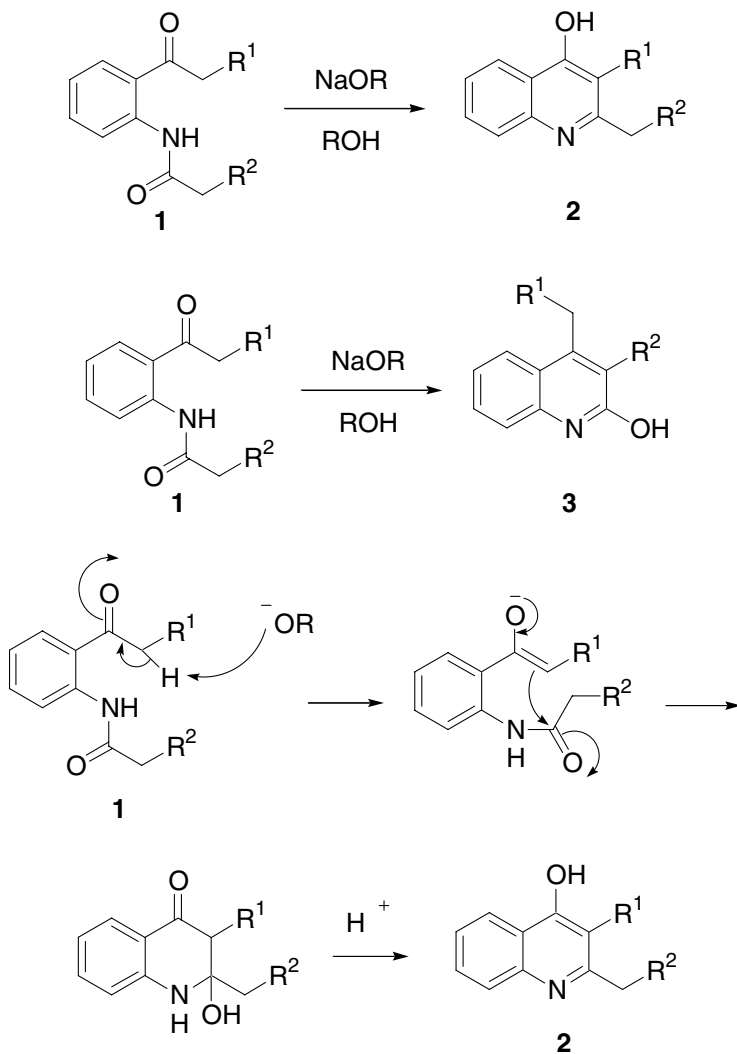
References

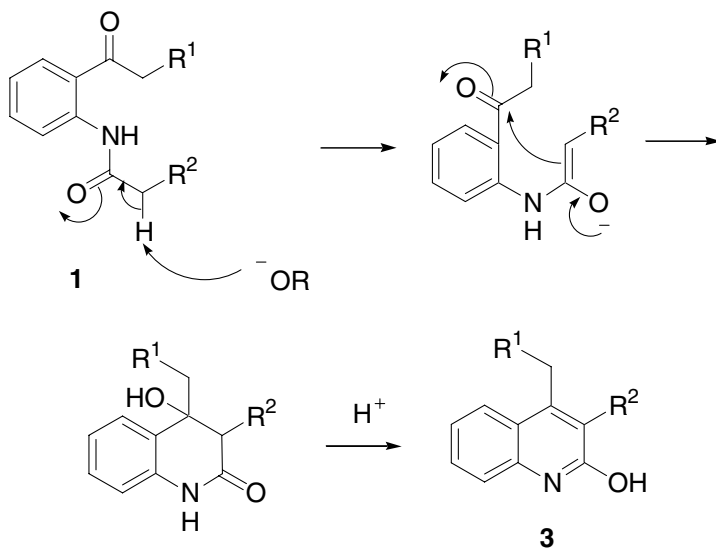
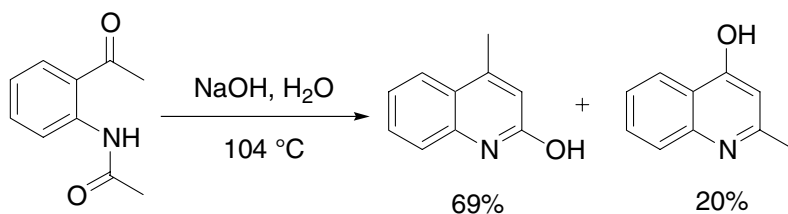
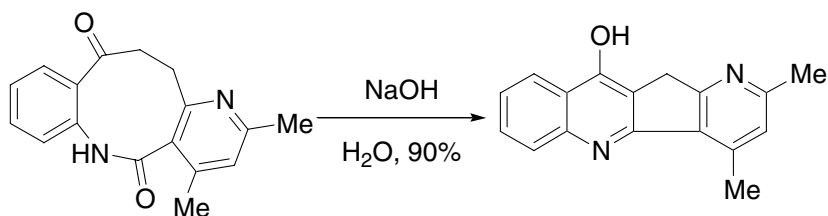
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Camps quinolinol synthesis

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.



Example 1^{1,2}Example 2⁸

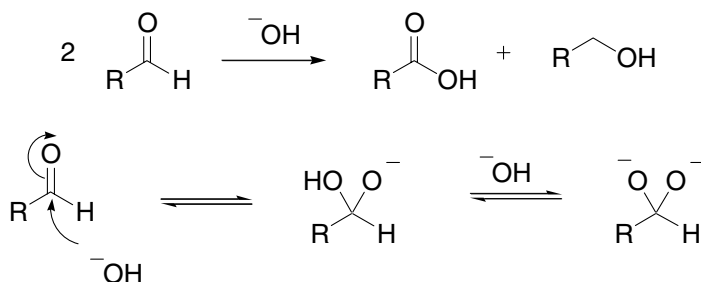
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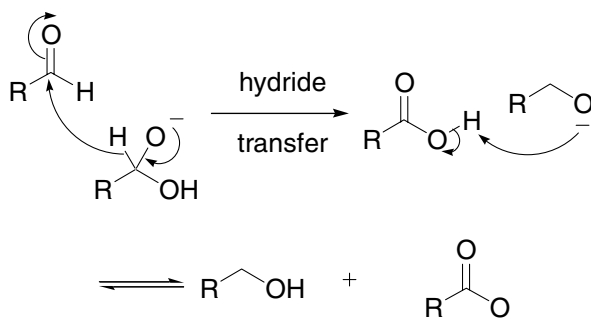
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Cannizzaro disproportionation

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

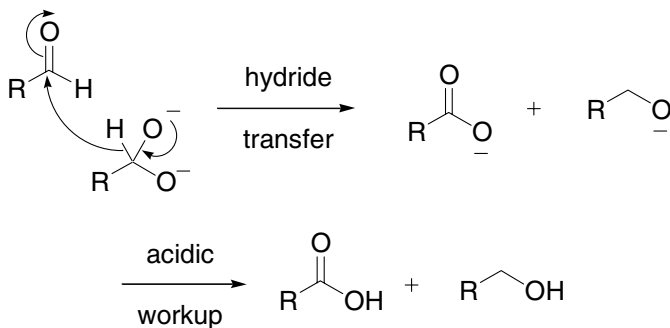


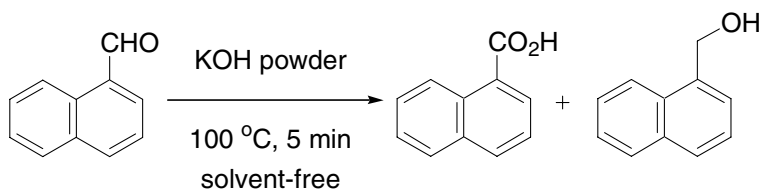
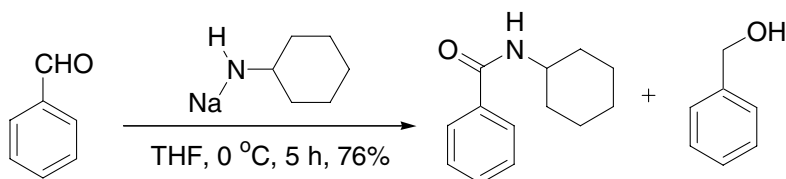
Pathway A:



Final deprotonation of the carboxylic acid drives the reaction forward.

Pathway B:



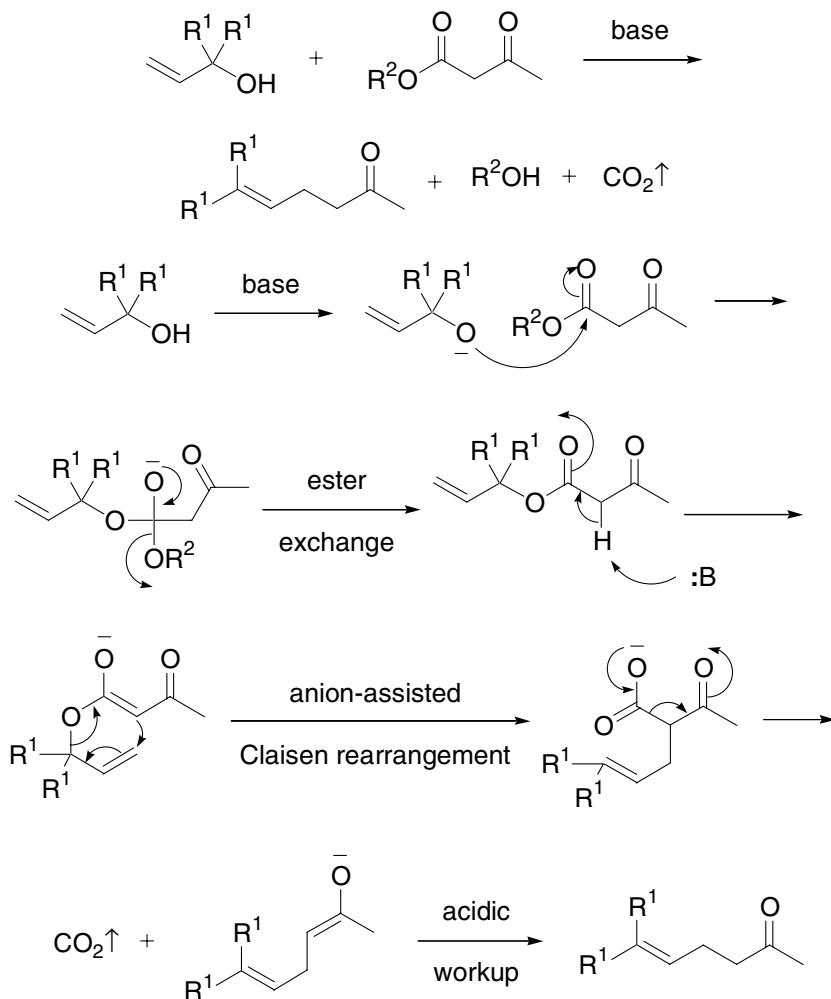
Example 1¹¹Example 2¹³

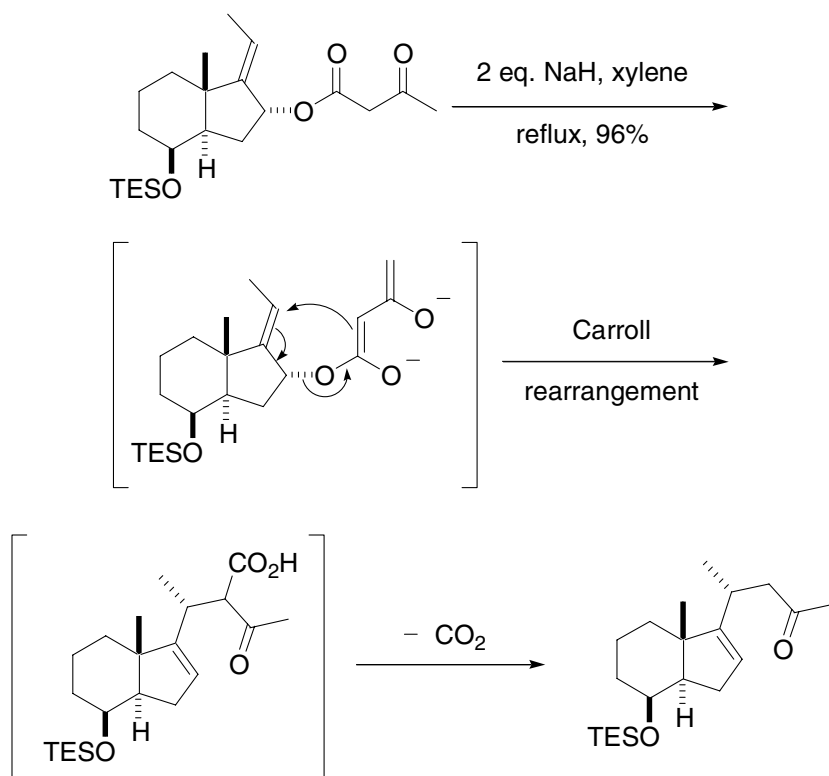
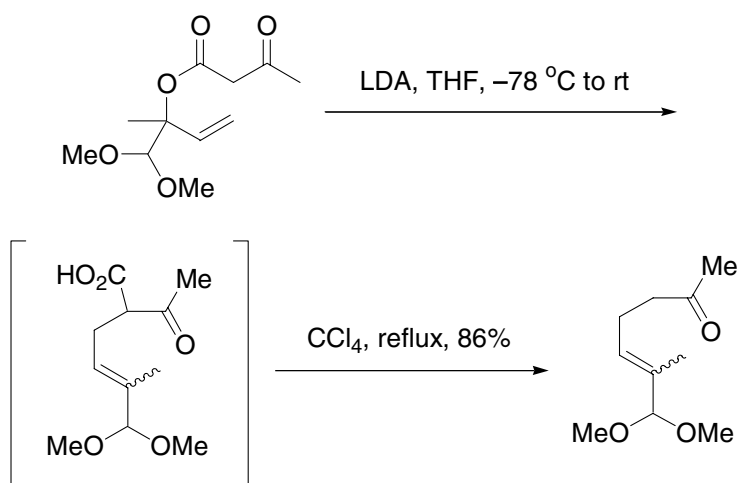
References

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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).



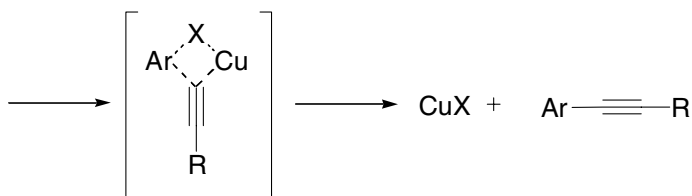
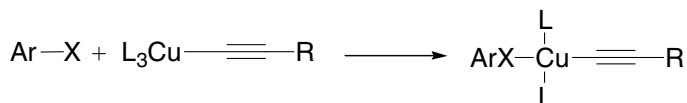
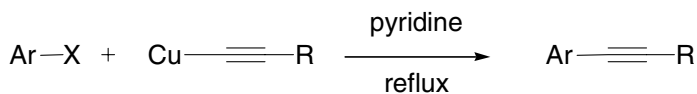
Example 1⁹Example 2¹⁰

References

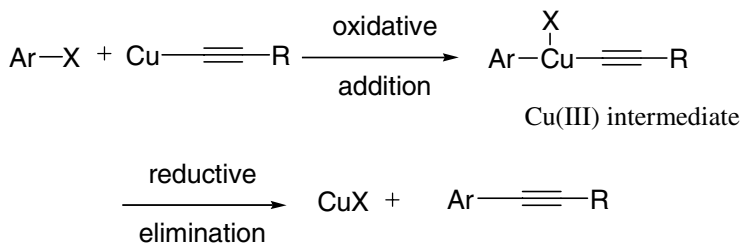
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Castro–Stephens coupling

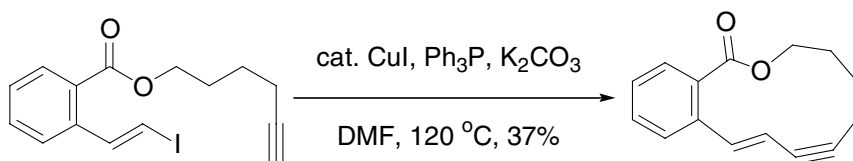
Aryl-acetylene synthesis, *Cf.* Cadiot–Chodkiewicz coupling and Sonogashira coupling. The Castro–Stephens coupling uses stoichiometric copper, whereas the Sonogashira variant uses catalytic palladium and copper.



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



Example⁷

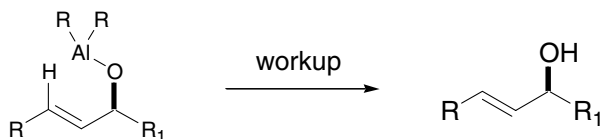
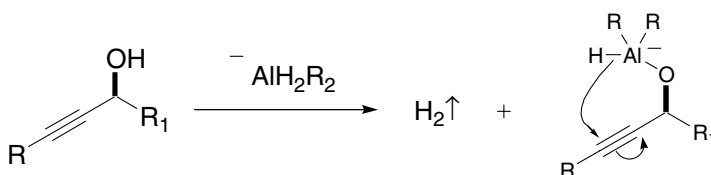
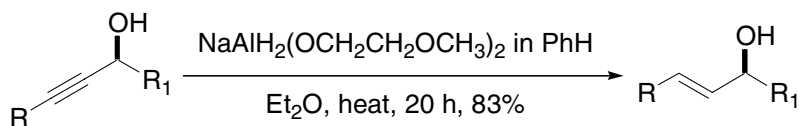


References

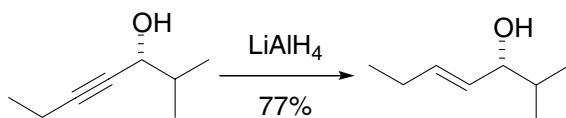
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Chan alkyne reduction

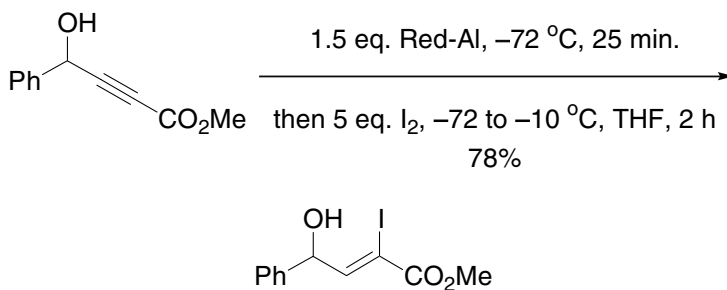
Stereoselective reduction of acetylenic alcohols to *E*-allylic alcohols using sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH, also known as Red-Al) or LiAlH₄.



Example 1³



Example 2⁴

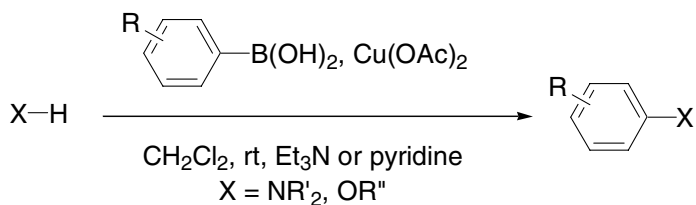


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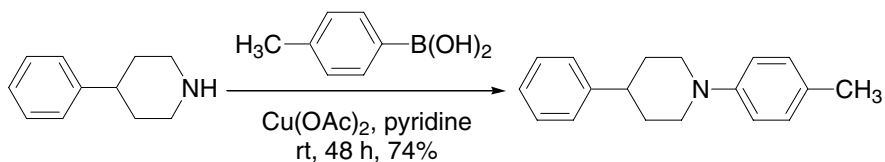
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Chan–Lam coupling reaction

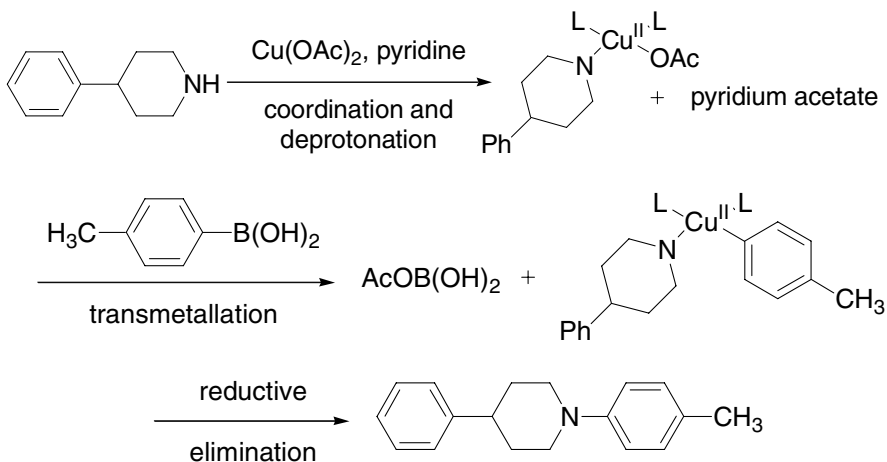
N-Arylation of a wide range of NH substrates by reaction with boronic acid in the presence of cupric acetate and either triethylamine or pyridine at room temperature. The reaction works even for poorly nucleophilic substrates such as arylamide.

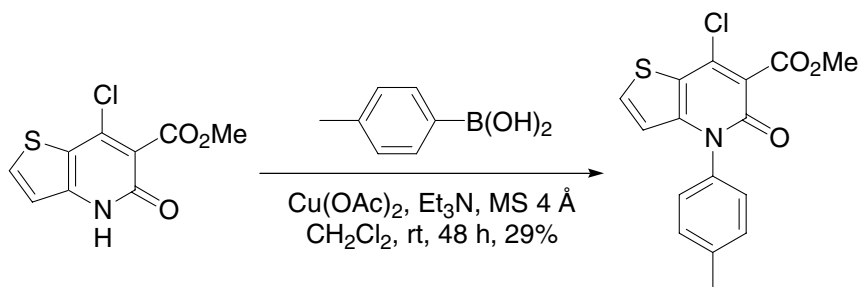


Example 1¹



Mechanism:



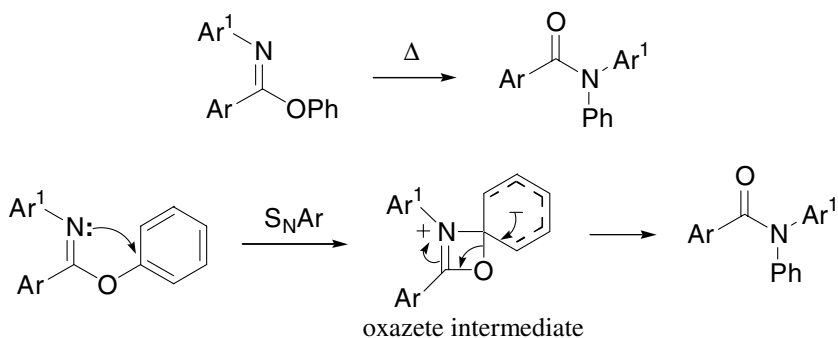
Example 2³

References

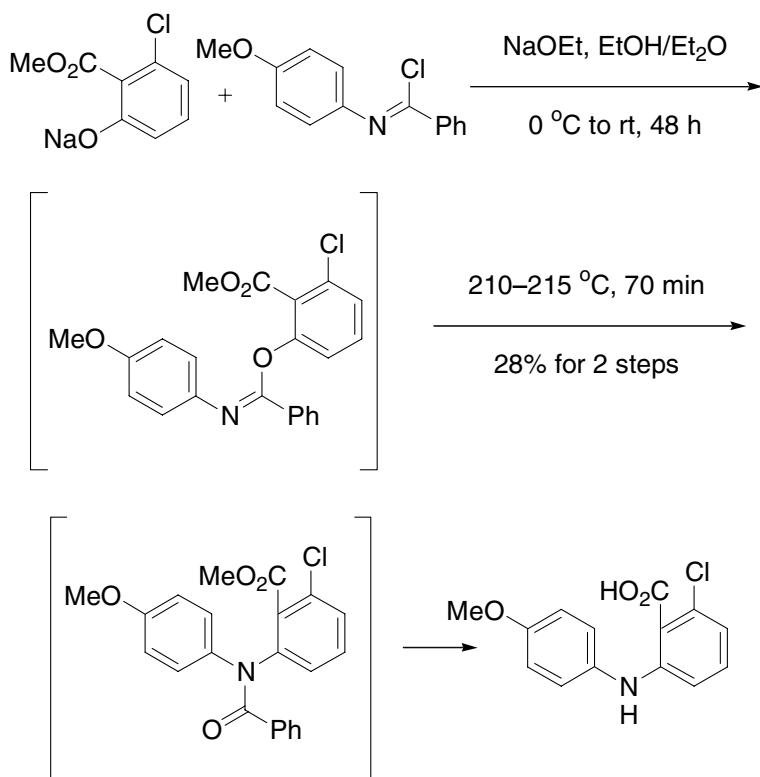
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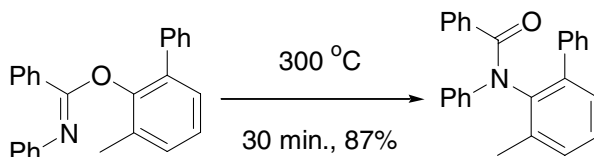
Chapman rearrangement

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



Example 1²



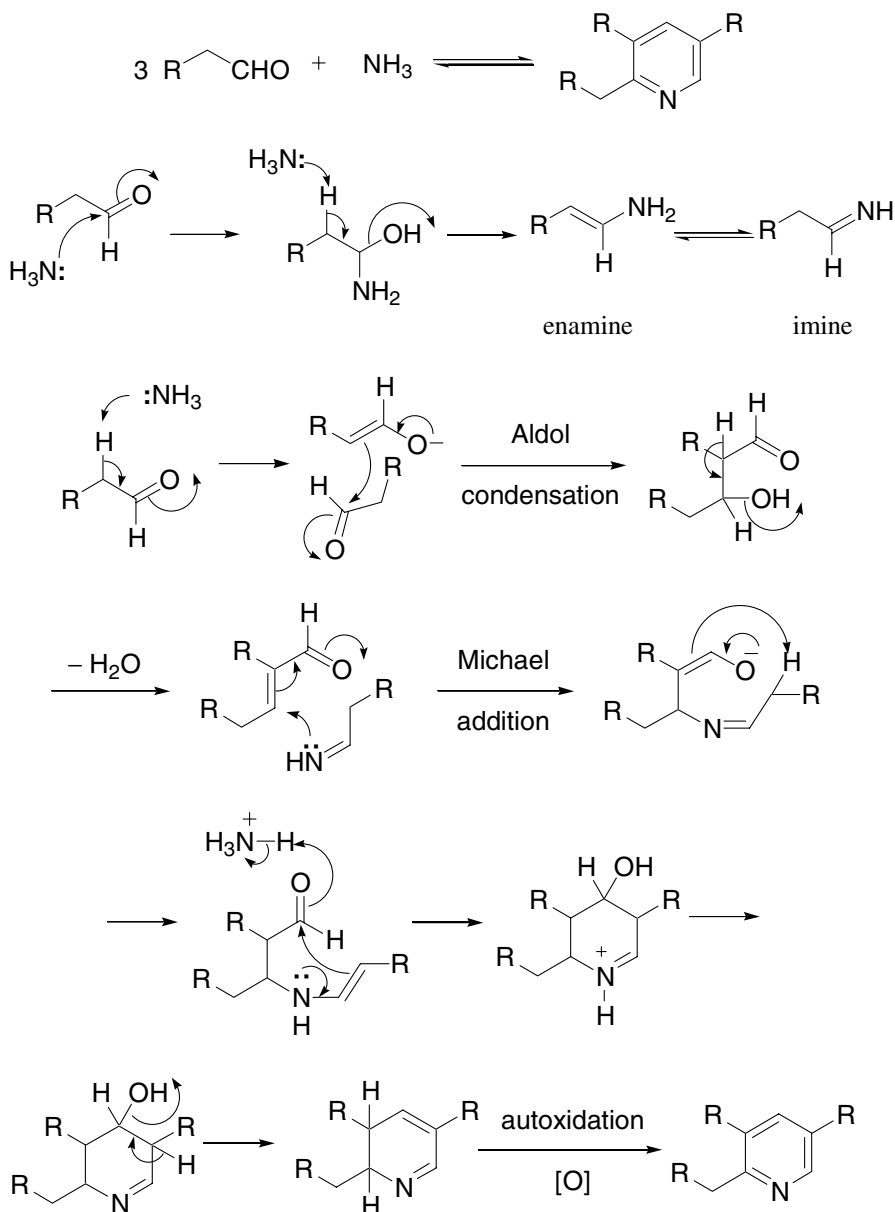
Example 2⁴

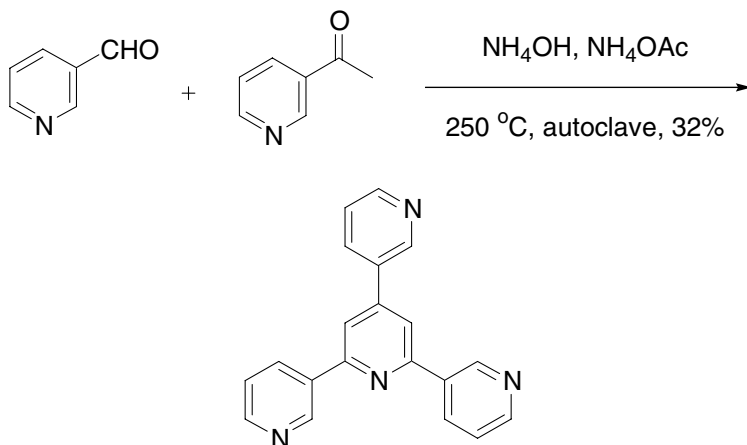
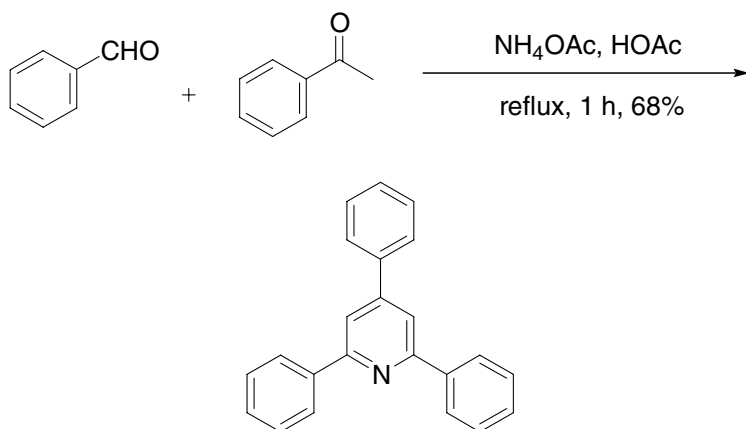
References

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Chichibabin pyridine synthesis

Condensation of aldehydes with ammonia to afford pyridines.



Example 1⁴Example 2⁵

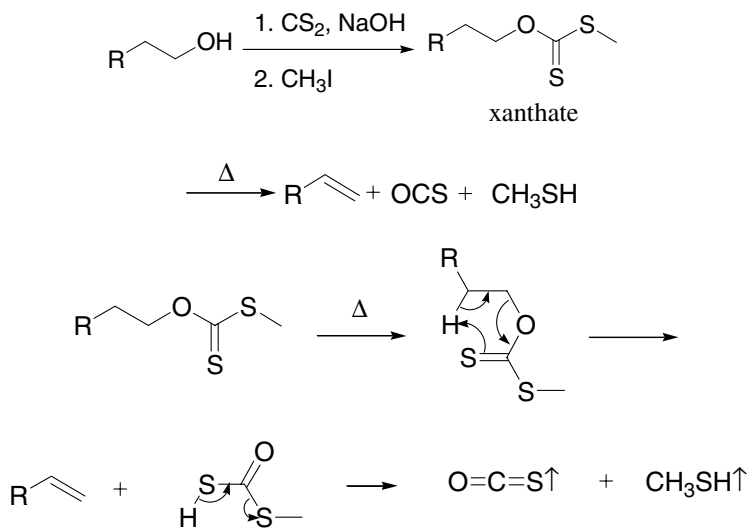
References

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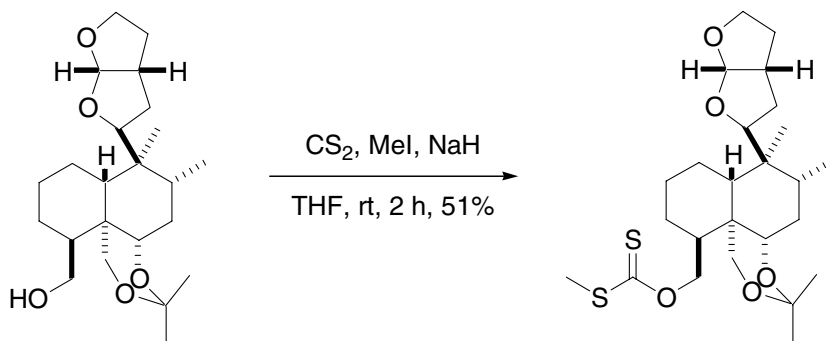
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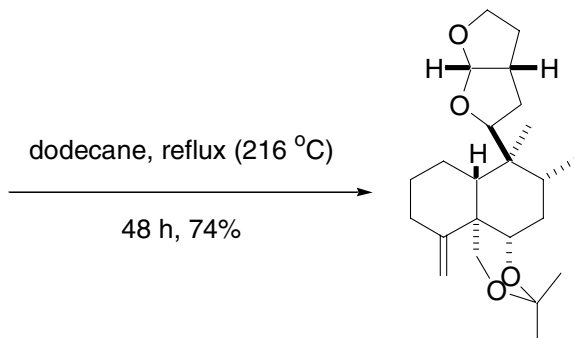
Chugaev elimination

Thermal elimination of xanthates to olefins.

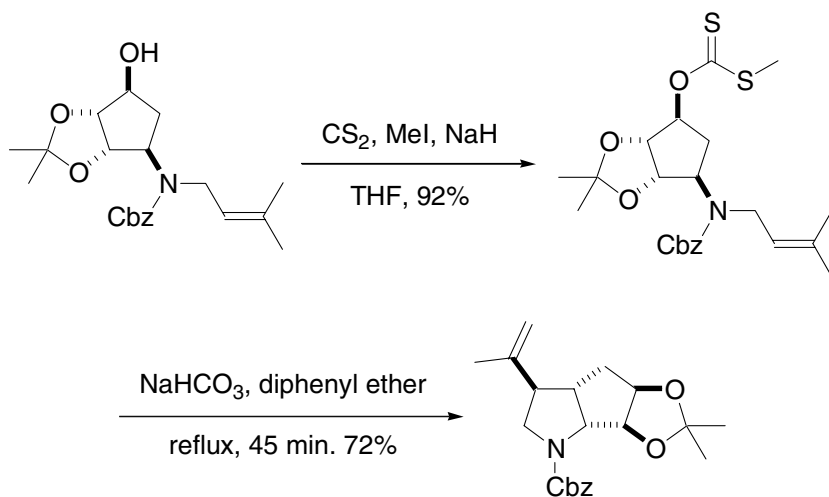


Example 1⁶





Example 2, Chugaev *syn*-elimination is followed by an intramolecular ene reaction⁷

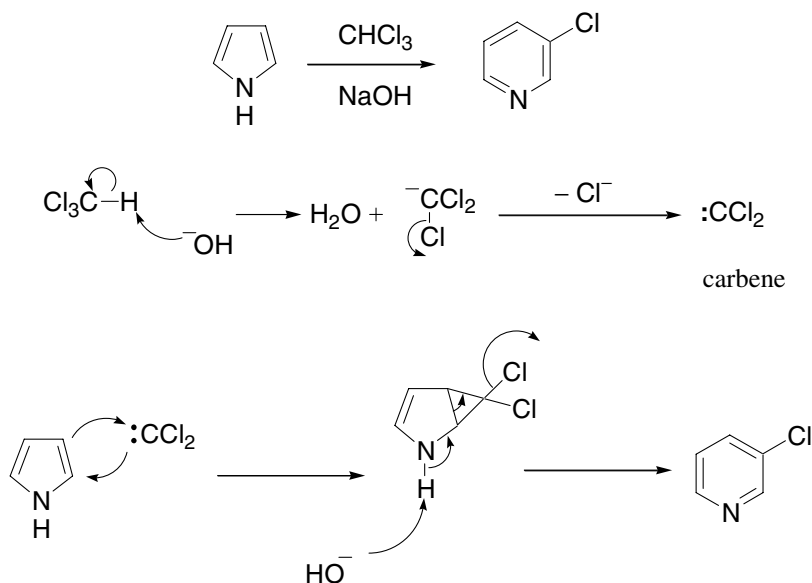


References

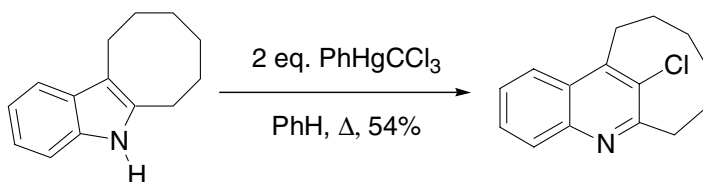
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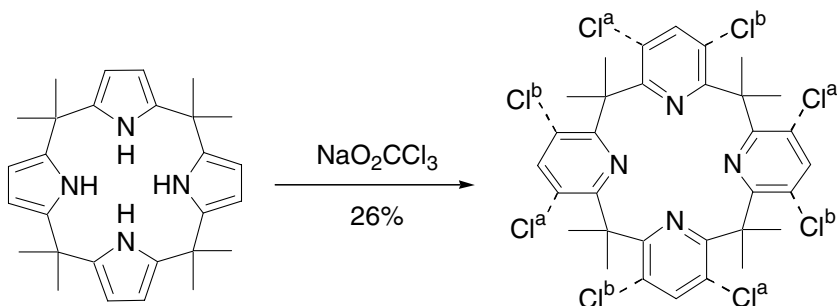
Ciamician–Dennsted rearrangement

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



Example 1⁸



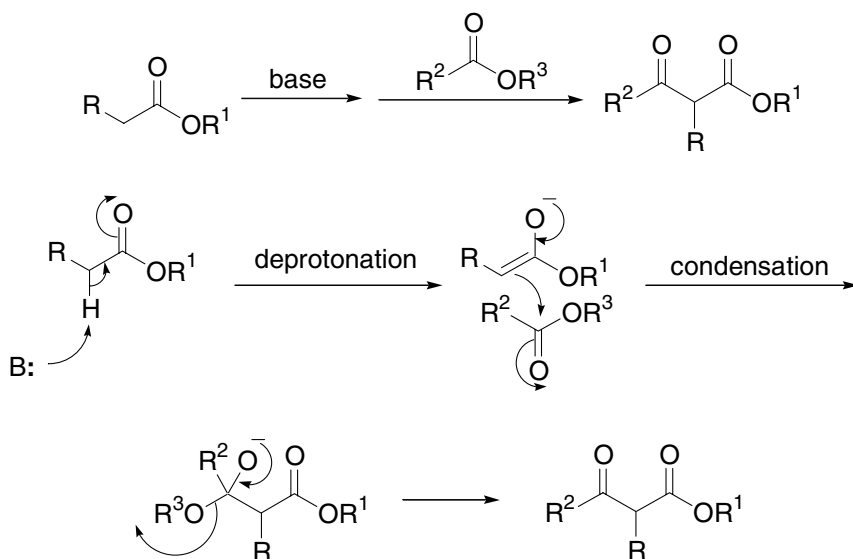
Example 2¹⁰

References

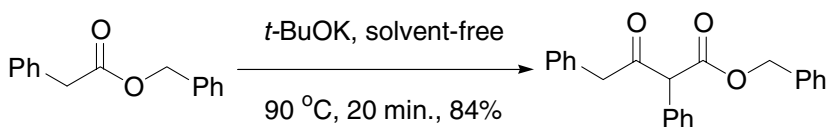
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Claisen condensation

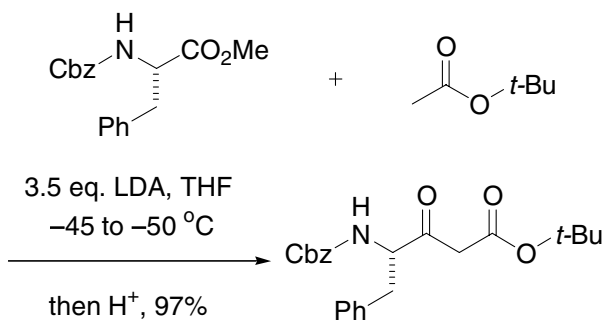
Base-catalyzed condensation of esters to afford β -keto esters.



Example 1⁹



Example 2¹²

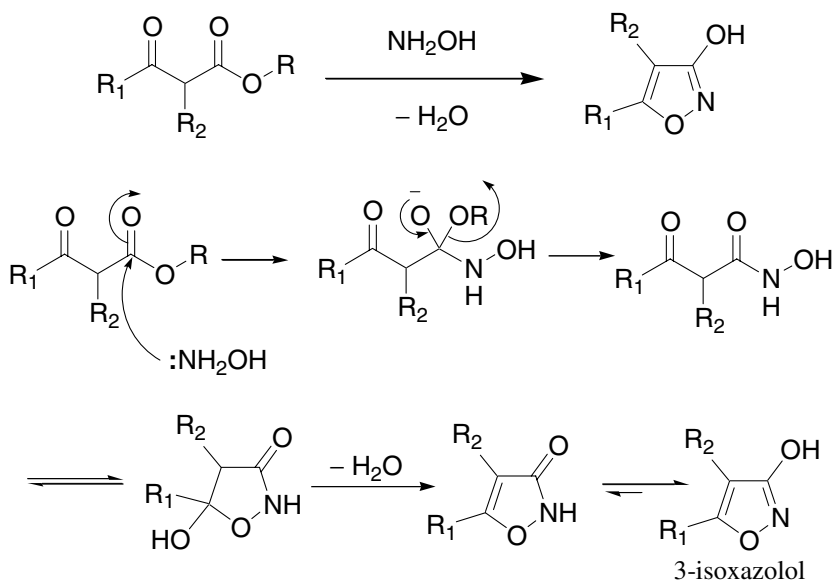


References

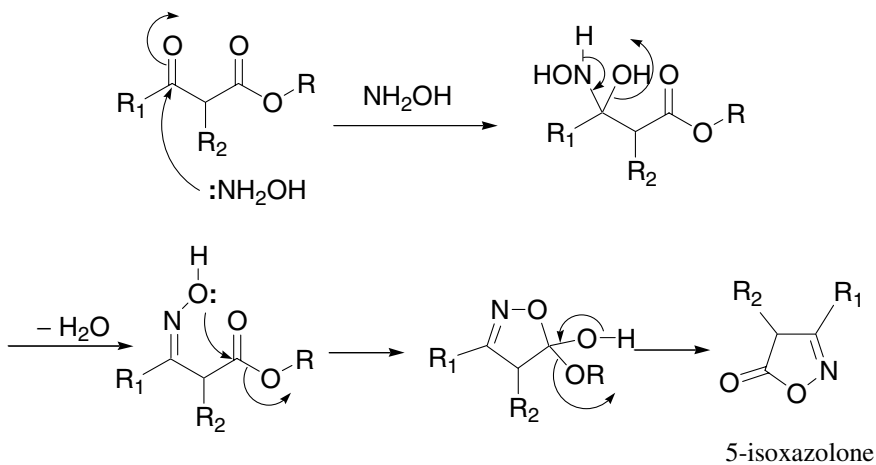
- 1 Claisen, R. L.; Lowman, O. *Ber. Dtsch. Chem. Ges.* **1887**, 20, 651. Rainer Ludwig Claisen (1851–1930), born in Cologne, Germany, probably had the best pedigree in the history of organic chemistry. He apprenticed under Kekulé, Wöhler, von Baeyer, and Fischer before embarking on his own independent research.
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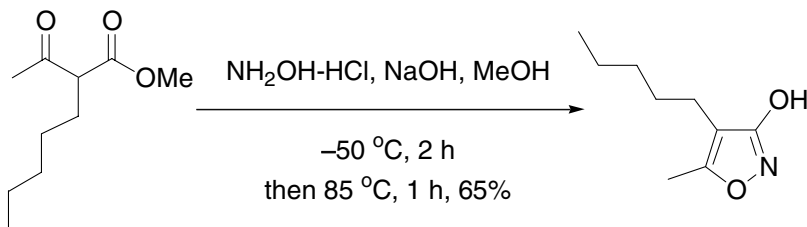
Claisen isoxazole synthesis

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



A side reaction:



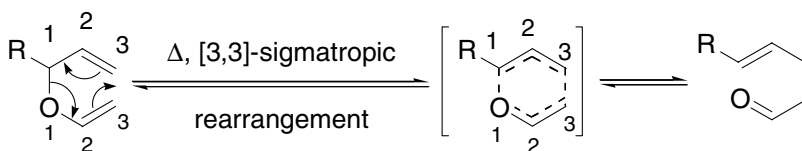
Example²⁰

References

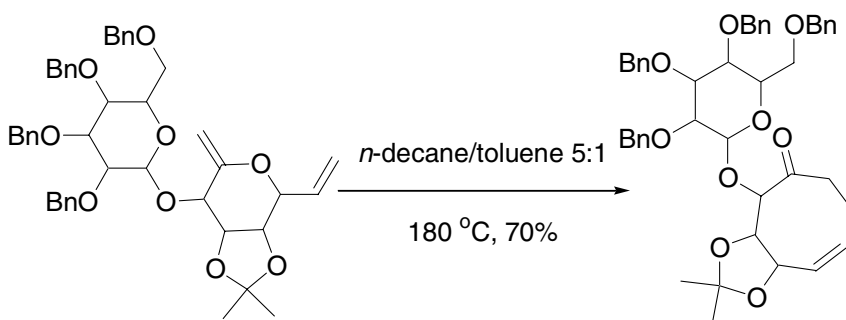
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Claisen rearrangements

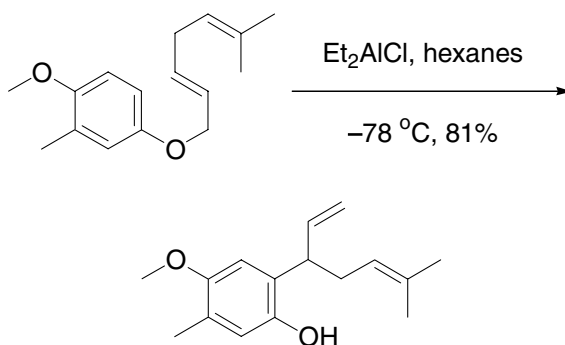
The Claisen, Johnson–Claisen, Ireland–Claisen, *para*-Claisen rearrangements, along with the Carroll rearrangement belong to the category of *[3,3]-sigmatropic rearrangements*. The Claisen rearrangement is a concerted process and the arrow pushing here is merely illustrative.



Example 1⁷



Example 2⁸



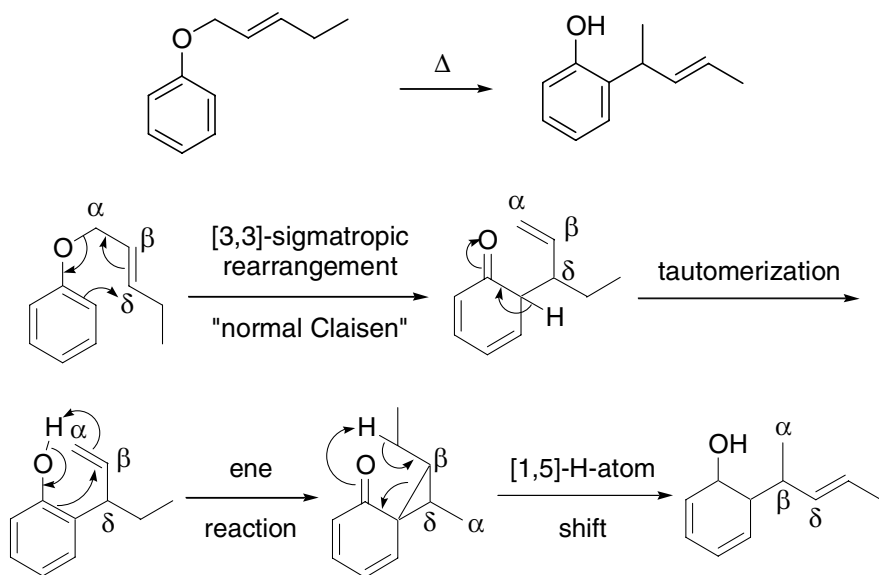
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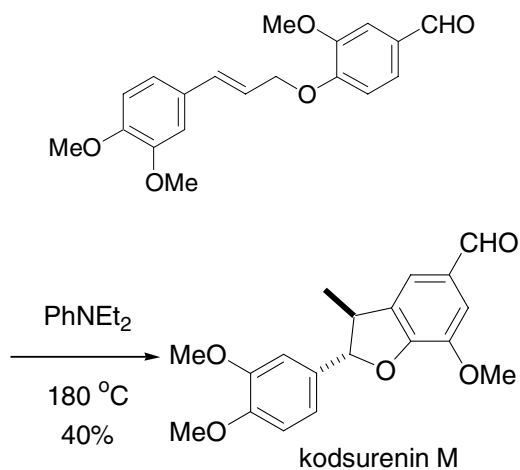
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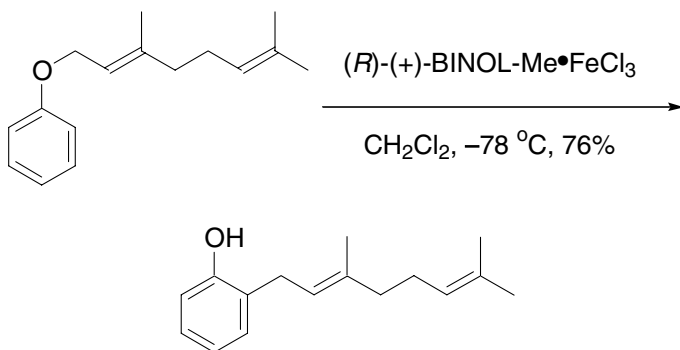
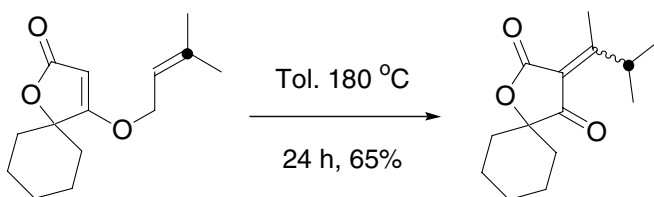
Abnormal Claisen rearrangement

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



Example 1⁴



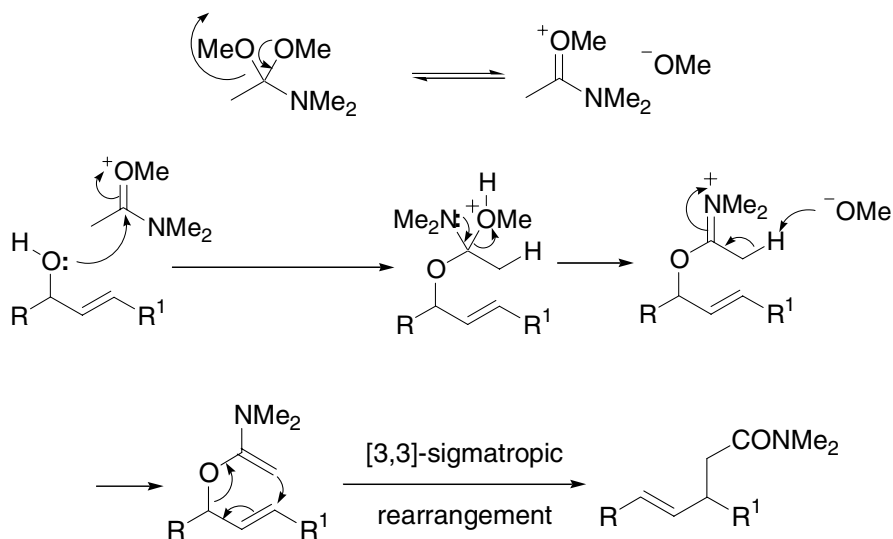
Example 2⁵Example 3⁶

References

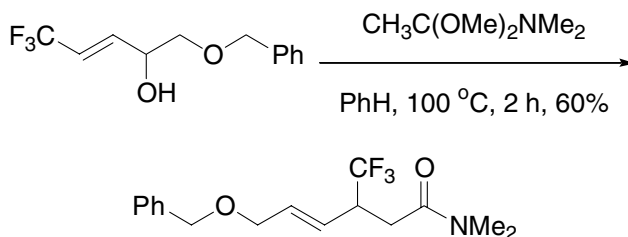
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Eschenmoser–Claisen amide acetal rearrangement

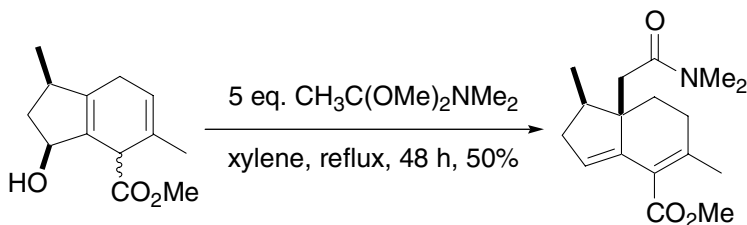
[3,3]-Sigmatropic rearrangement of *N,O*-ketene acetals to yield γ,δ -unsaturated amides. Since Eschenmoser was inspired by Meerwein's observations on the interchange of amide, the Eschenmoser–Claisen rearrangement is sometimes known as the Meerwein–Eschenmoser–Claisen rearrangement.



Example 1⁷



Example 2⁹

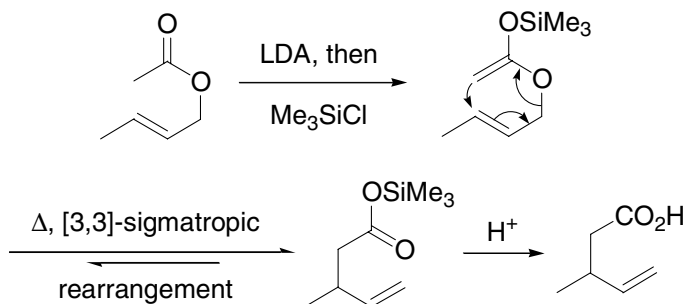


References

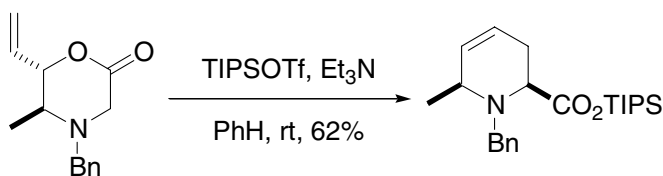
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Ireland–Claisen (silyl ketene acetal) rearrangement

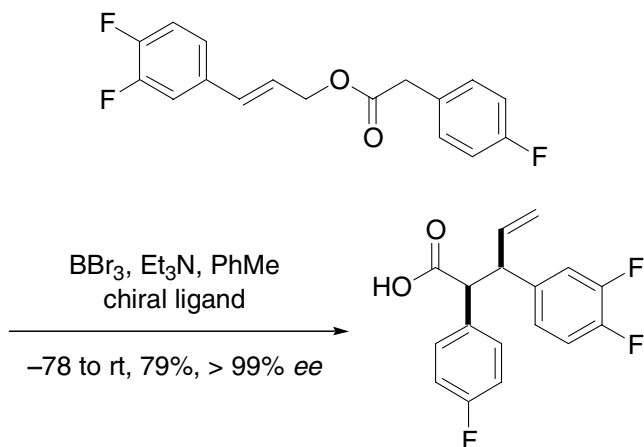
Rearrangement of allyl trimethylsilyl ketene acetal, prepared by reaction of allylic ester enolates with trimethylsilyl chloride, to yield γ,δ -unsaturated carboxylic acids. The Ireland–Claisen rearrangement seems to be advantageous to the other variants of the Claisen rearrangement in terms of *E/Z*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

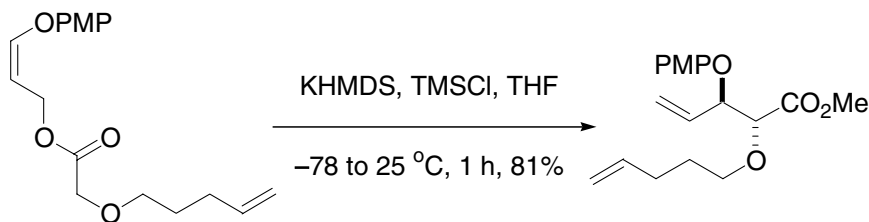


Example 1³



Example 2, a modified Ireland–Claisen rearrangement¹⁰



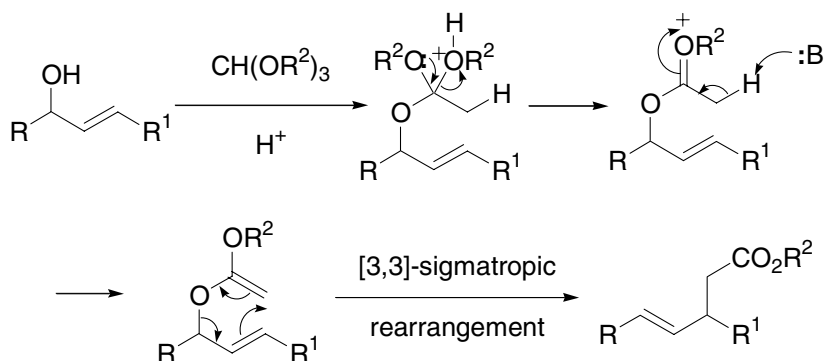
Example 3¹⁴

References

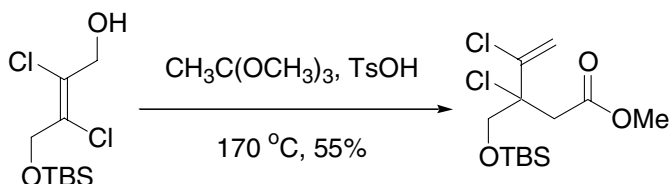
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Johnson–Claisen orthoester rearrangement

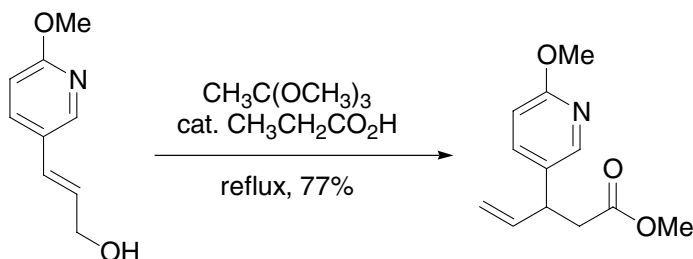
Heating of an allylic alcohol with an excess of trialkyl orthoacetate in the presence of trace amounts of a weak acid to give a mixed orthoester. The orthoester loses ethanol to generate the ketene acetal, which undergoes [3,3]-sigmatropic rearrangement to give a γ,δ -unsaturated ester.



Example 1²



Example 2⁷



References

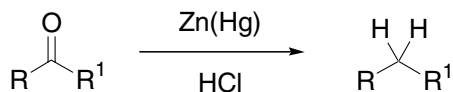
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sin for 20 years before moving to Stanford University, where he was credited with building the modern-day Stanford Chemistry Department.

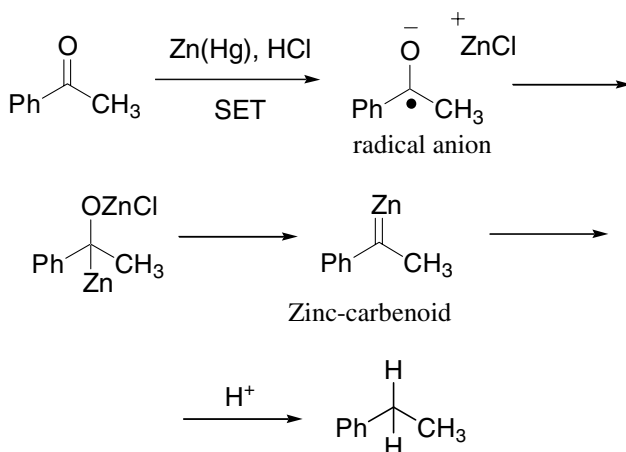
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Clemmensen reduction

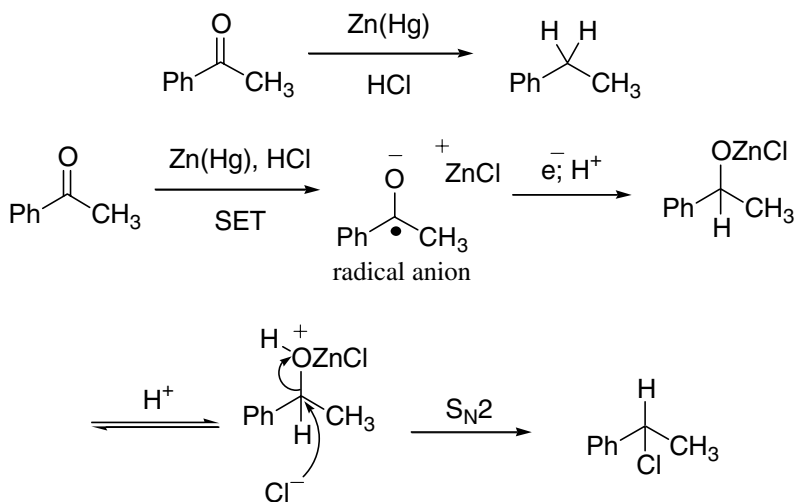
Reduction of aldehydes and ketones to the corresponding methylene compounds using amalgamated zinc and hydrogen chloride.

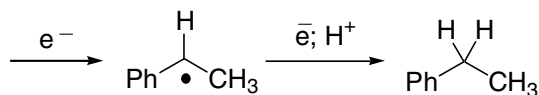
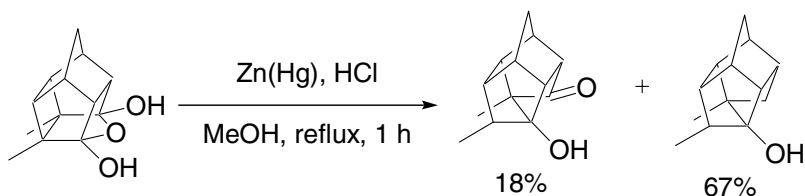
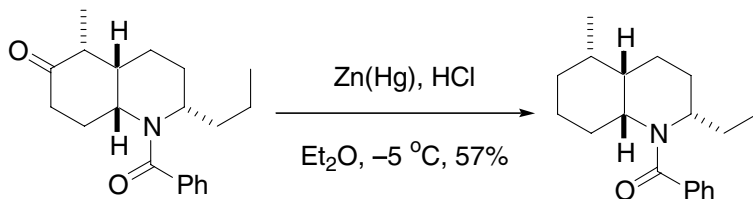


The zinc-carbenoid mechanism:⁶



The radical anion mechanism:



Example 1⁸Example 2¹⁰

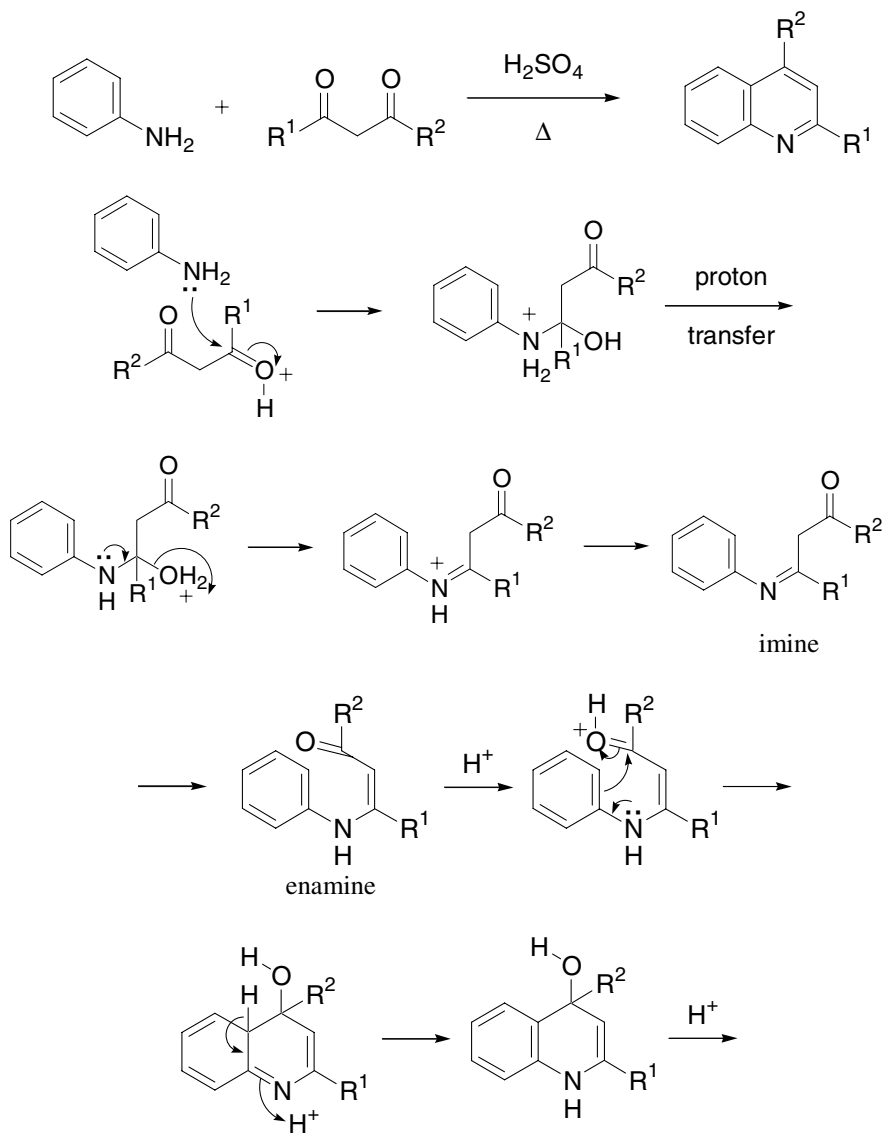
References

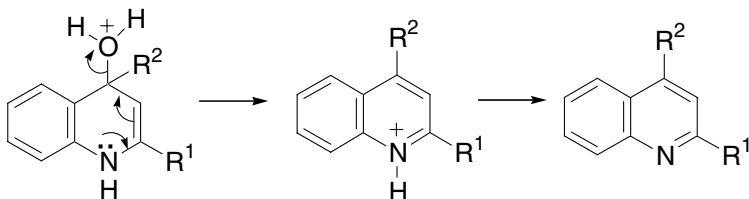
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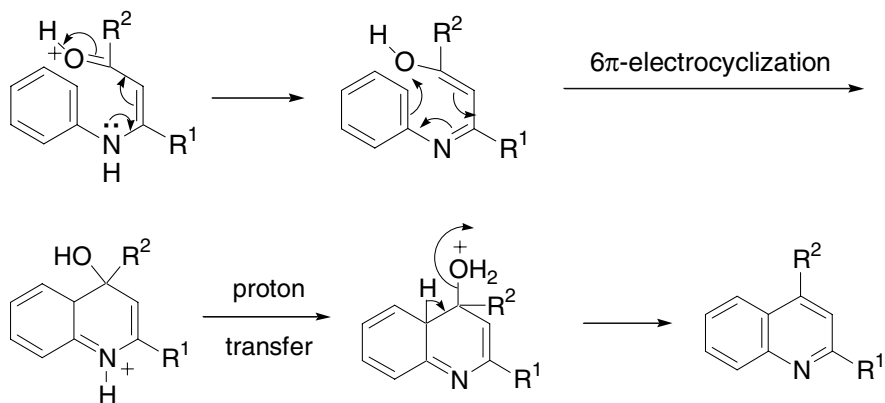
Combes quinoline synthesis

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

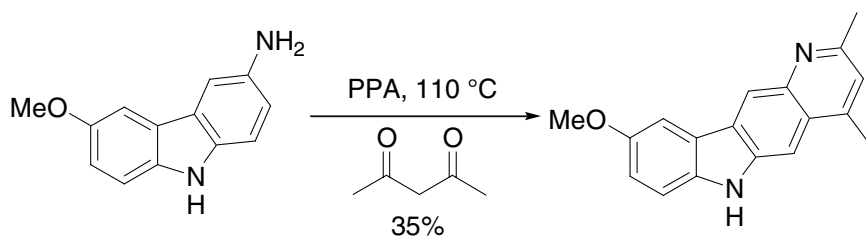




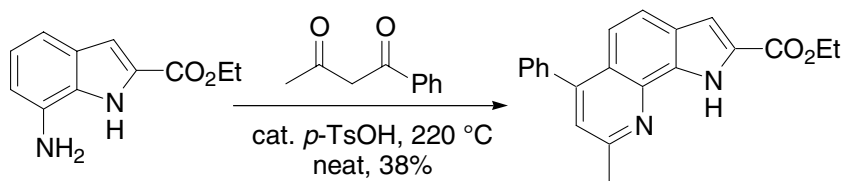
An electrocyclization mechanism is also possible:



Example 1¹⁰



Example 2¹¹

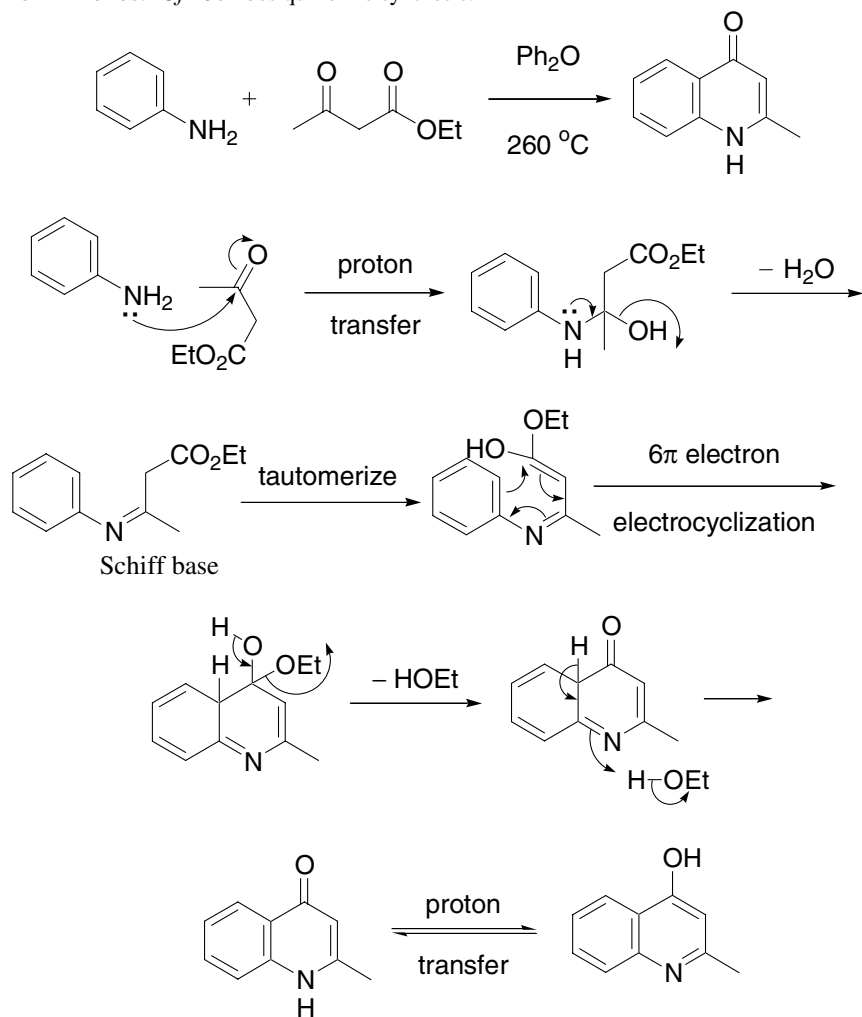


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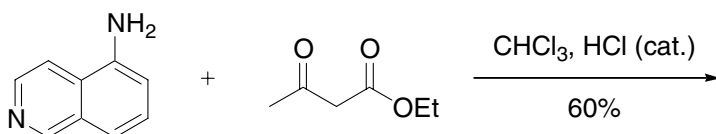
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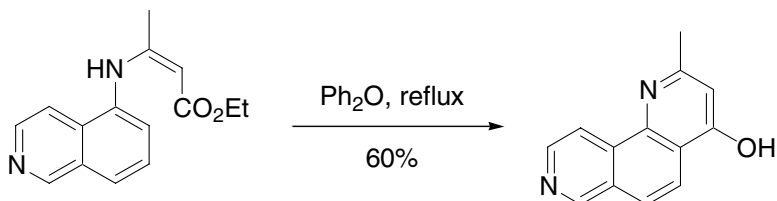
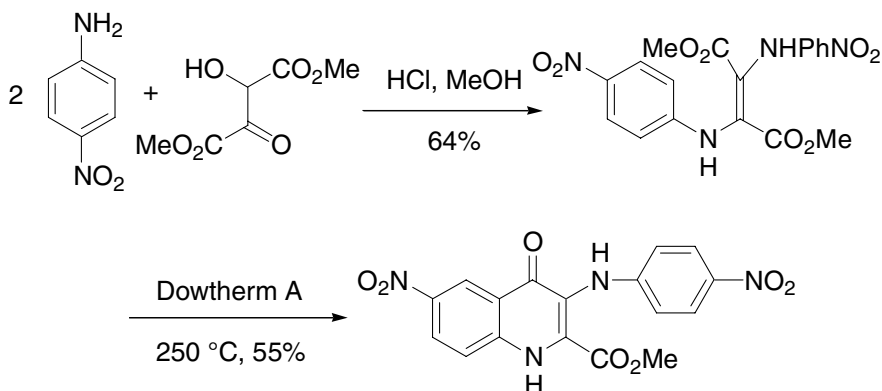
Conrad–Limpach reaction

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



Example 1³



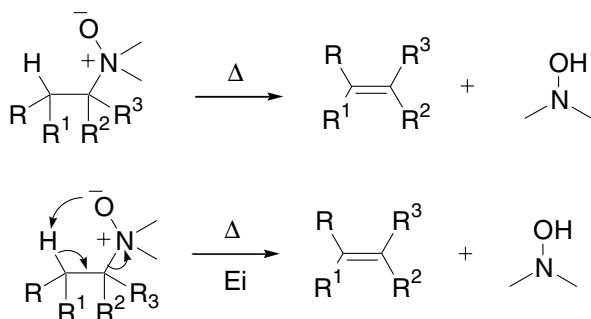
Example 2¹²

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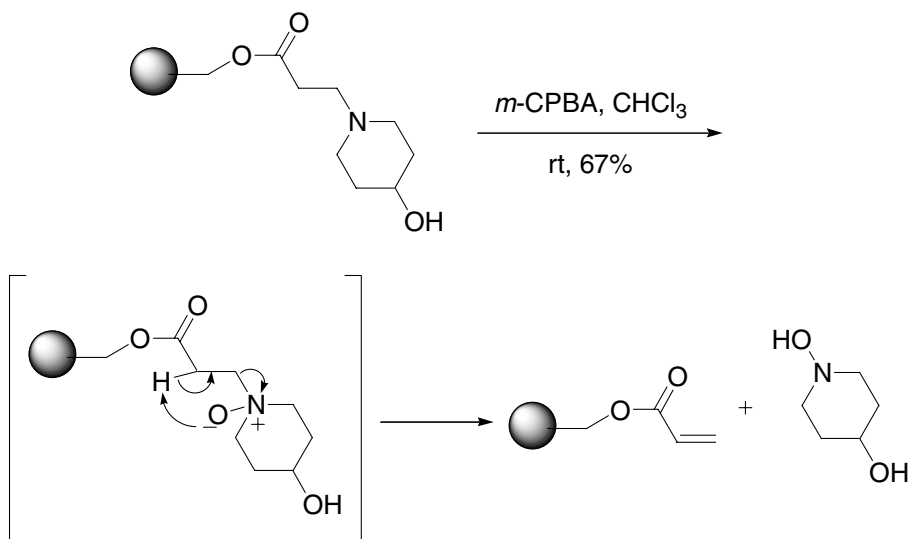
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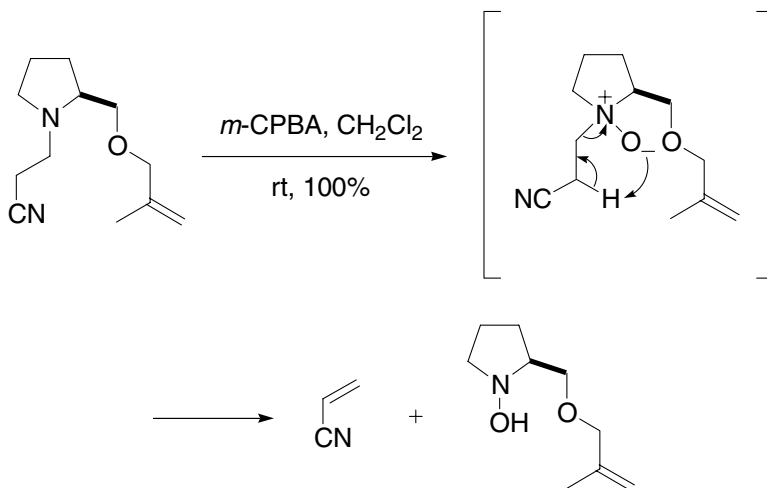
Cope elimination reaction

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



Example 1⁷



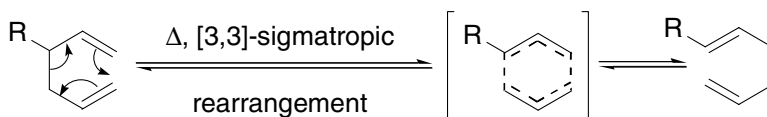
Example 2¹¹

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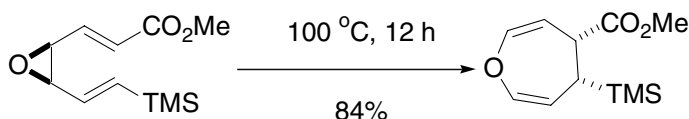
1. Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929. Arthur Clay Cope (1909–1966) was born in Dunreith, Indiana. He was a professor at MIT when he discovered the Cope elimination reaction and the Cope rearrangement. The Arthur Cope Award is a prestigious award in organic chemistry from the American Chemical Society.
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Cope rearrangement

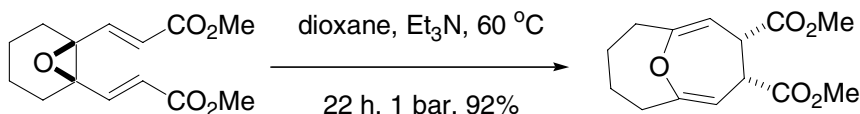
The Cope, oxy-Cope, and anionic oxy-Cope rearrangements belong to the category of *[3,3]-sigmatropic rearrangements*. Since it is a concerted process, the arrow pushing here is only illustrative. Cf. Claisen rearrangement.



Example 1⁵



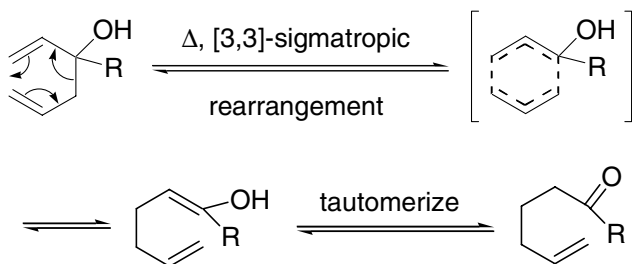
Example 2⁸



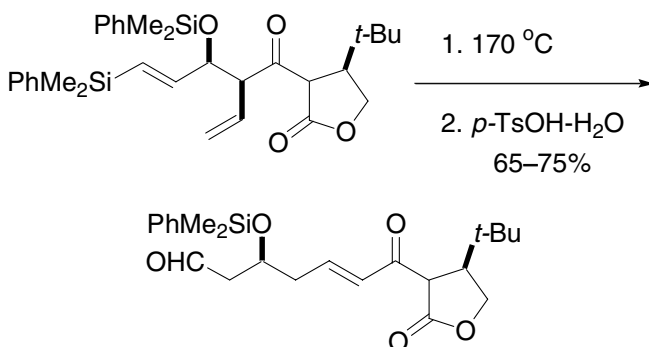
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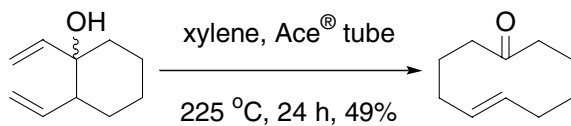
Oxy-Cope rearrangement



Example 1²



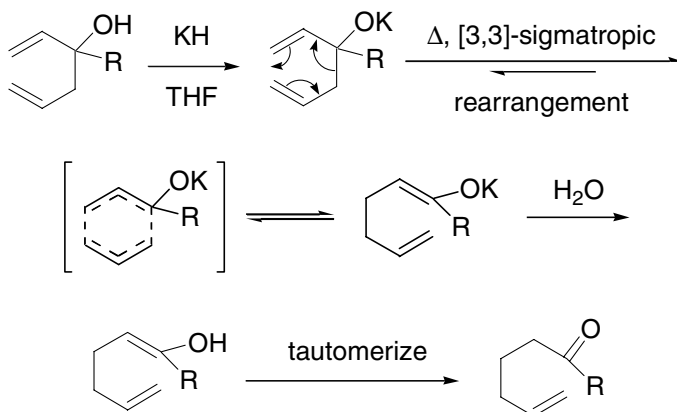
Example 2⁴



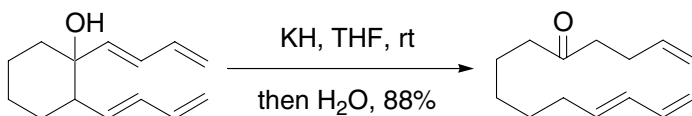
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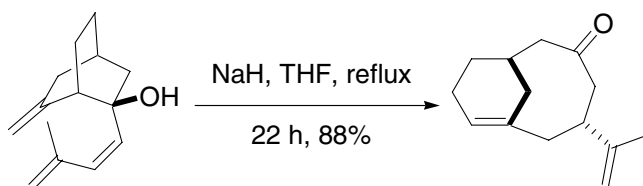
Anionic oxy-Cope rearrangement



Example 1¹



Example 2⁶

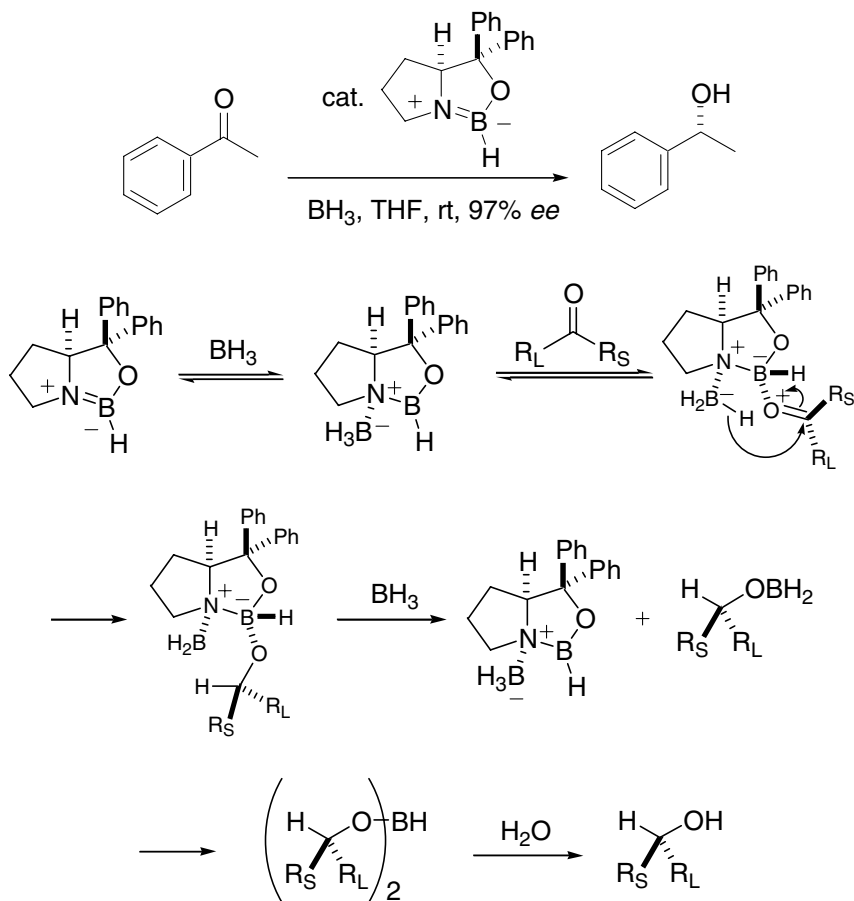


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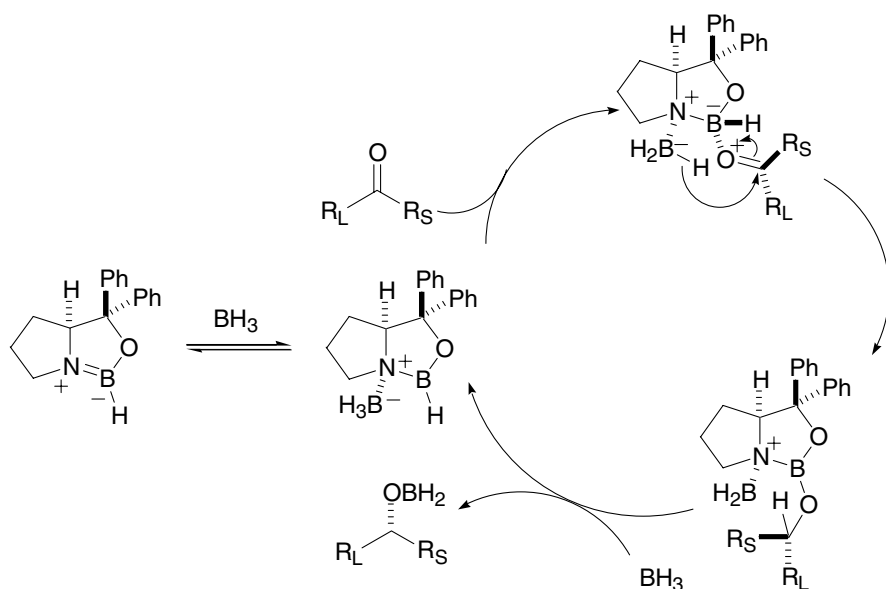
Corey–Bakshi–Shibata (CBS) reduction

Enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines.

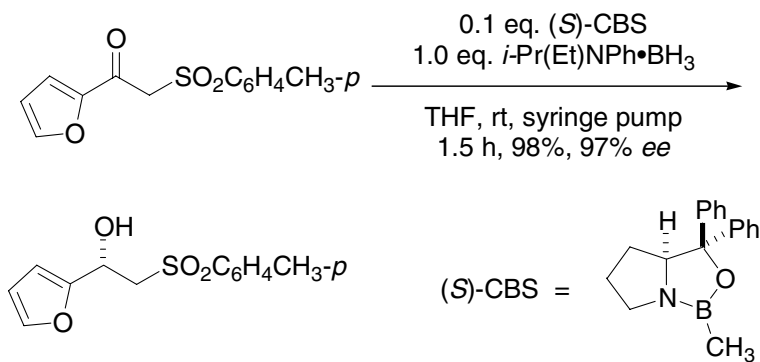


The catalytic cycle is shown on the next page.

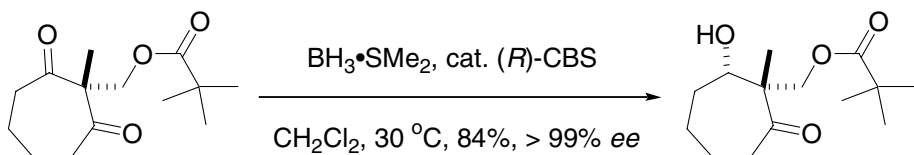
The catalytic cycle:



Example 1⁹



Example 2¹⁴

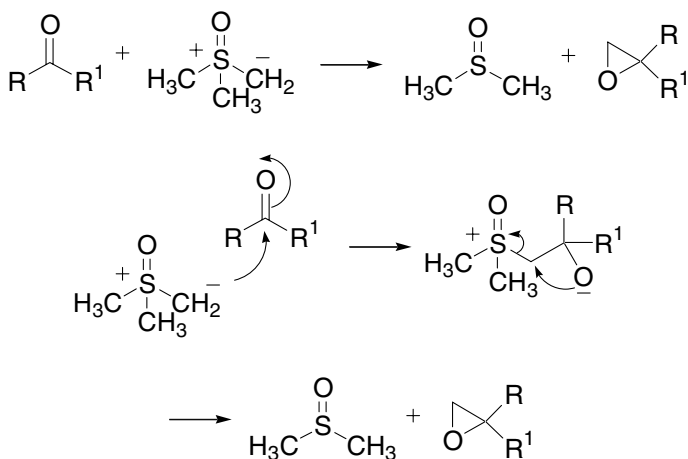
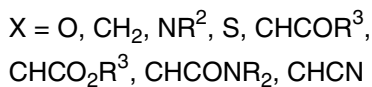
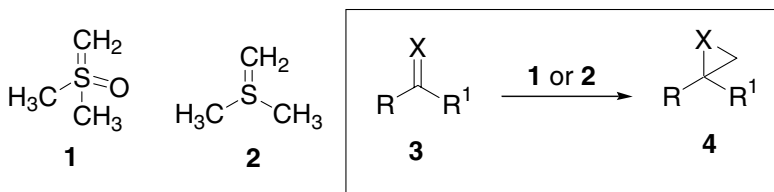


References

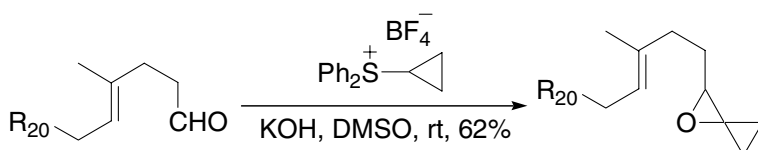
1. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. Elias J. Corey (1928–) was born in Methuen, Massachusetts. After earning his Ph.D. at MIT from John Sheehan at age 22, he began his independent academic career at the University of Illinois in 1950 and moved to Harvard University in 1959. Corey won the Nobel Prize in Chemistry in 1990 for development of novel methods for the synthesis of complex natural compounds and retrosynthetic analysis. He is still carrying out active research at Harvard. Prof. Corey has been a consultant to Pfizer for more than 50 years.
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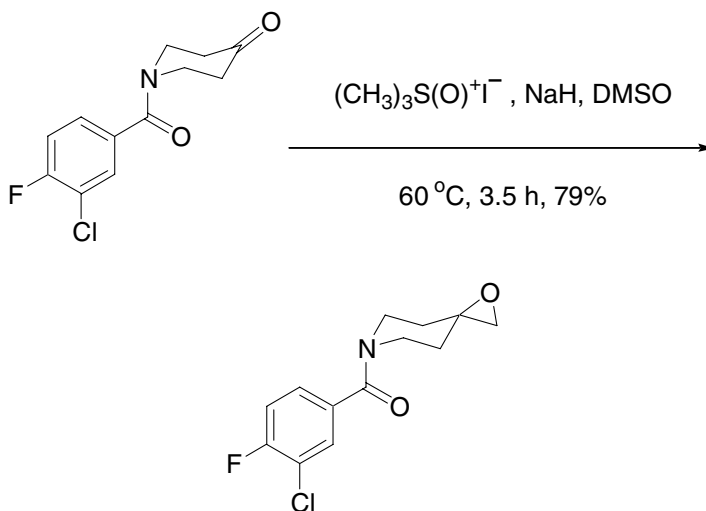
Corey–Chaykovsky reaction

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.



Example 1¹²



Example 2¹⁴

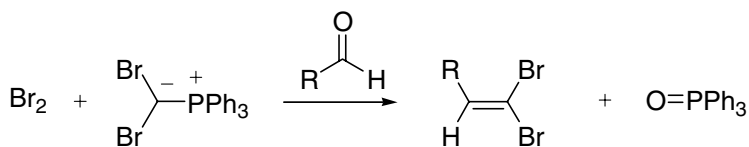
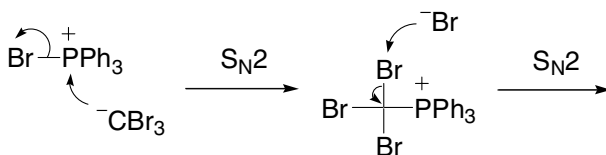
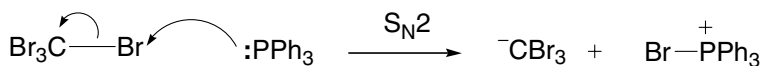
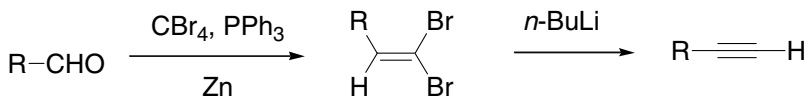
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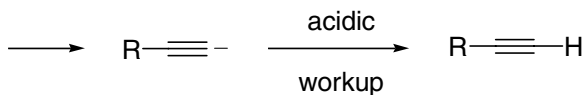
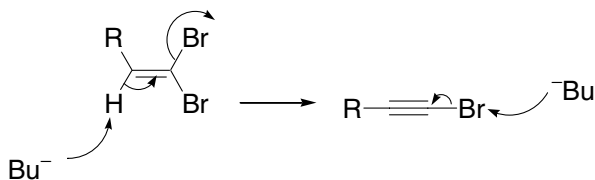
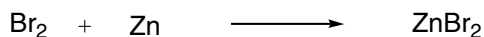
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Corey–Fuchs reaction

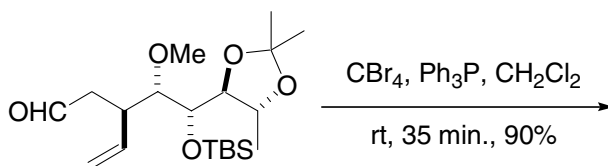
One-carbon homologation of an aldehyde to dibromoolefin, which is then treated with *n*-BuLi to produce a terminal alkyne.

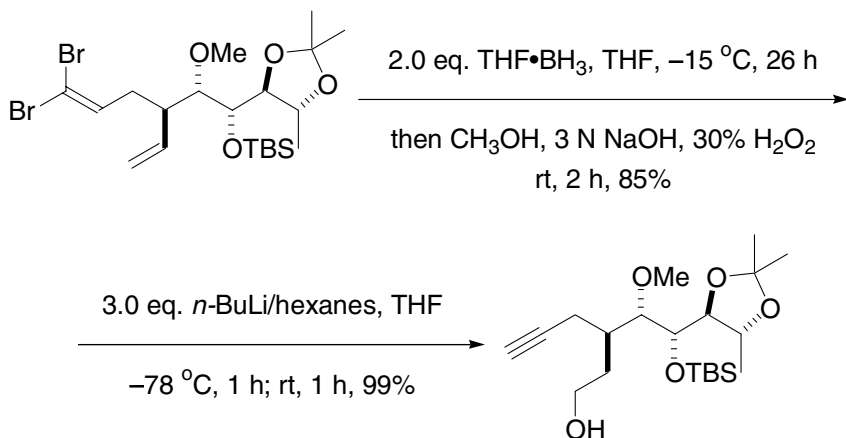
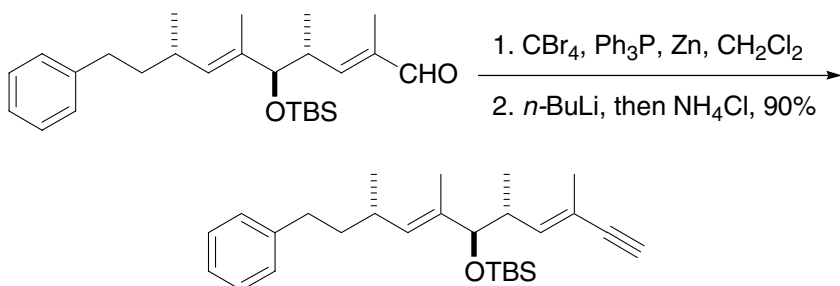


Wittig reaction (see page 621 for the mechanism)



Example 1³



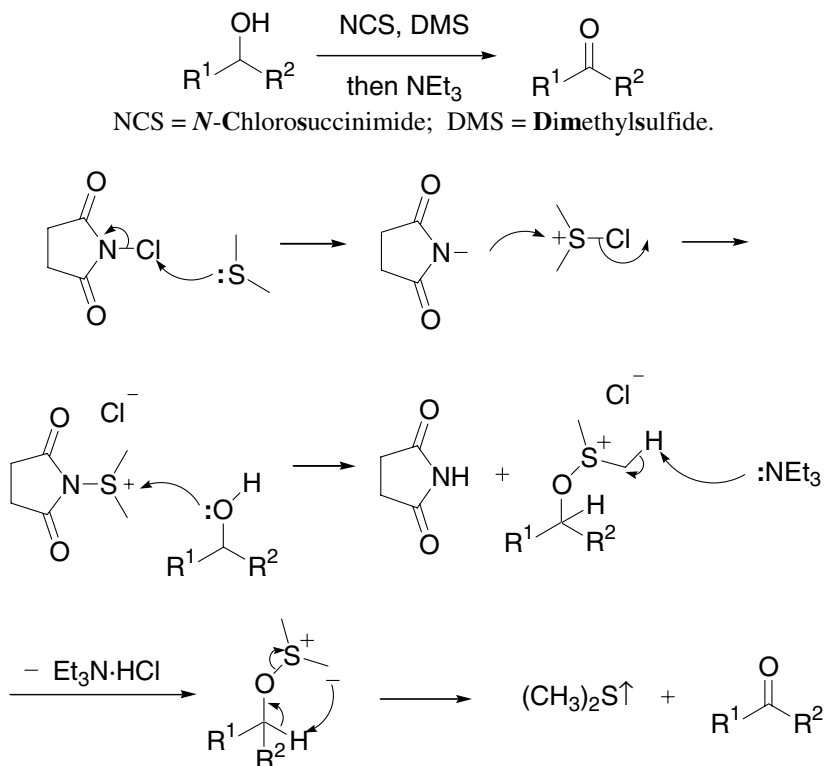
Example 2⁸

References

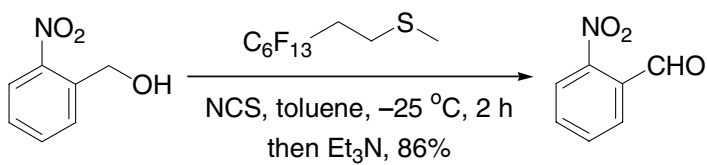
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Corey–Kim oxidation

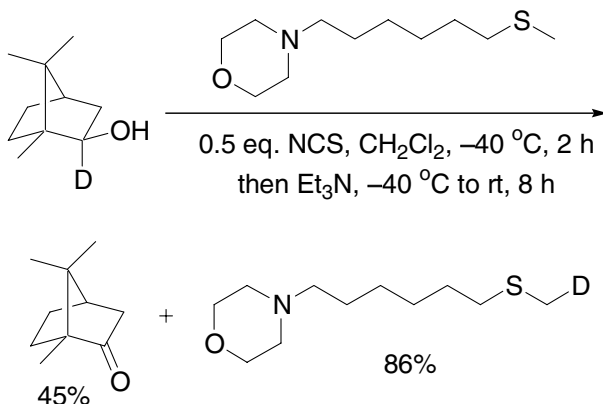
Oxidation of alcohol to the corresponding aldehyde or ketone using NCS/DMS, followed by treatment with a base. *Cf.* Swern oxidation.



Example 1, fluororous Corey–Kim reaction⁵



Example 2, odorless Corey–Kim reaction⁸

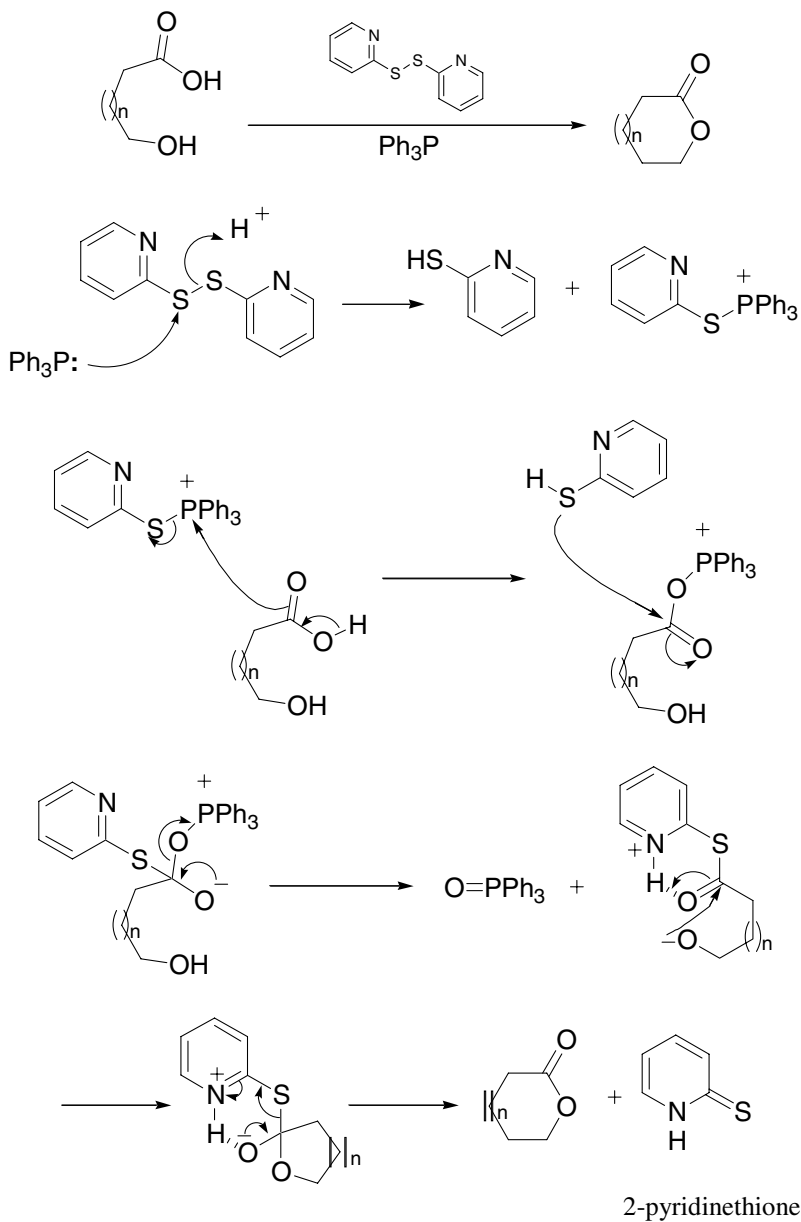


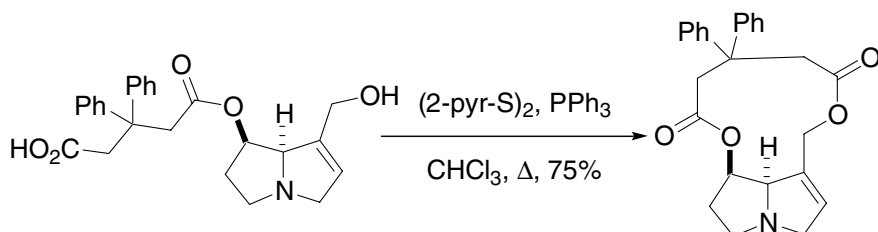
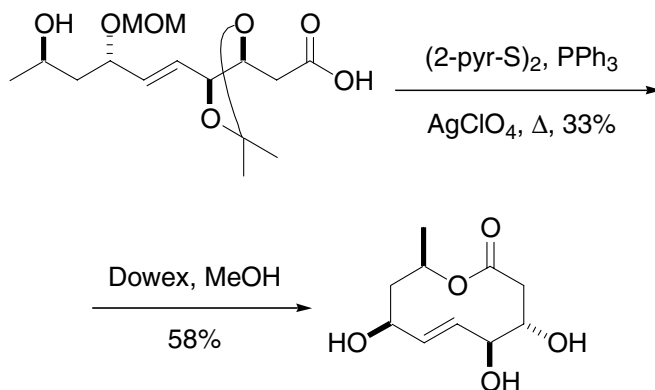
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Corey–Nicolaou macrolactonization

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



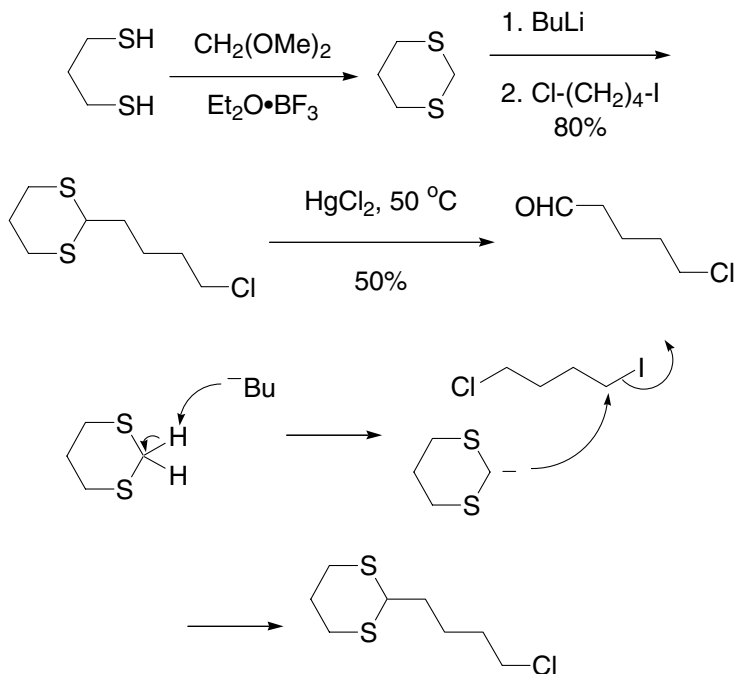
Example 1³Example 2⁶

References

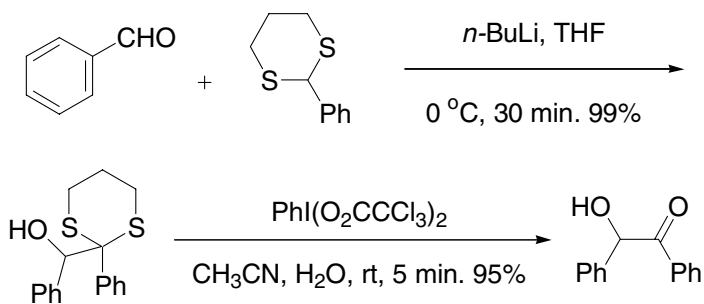
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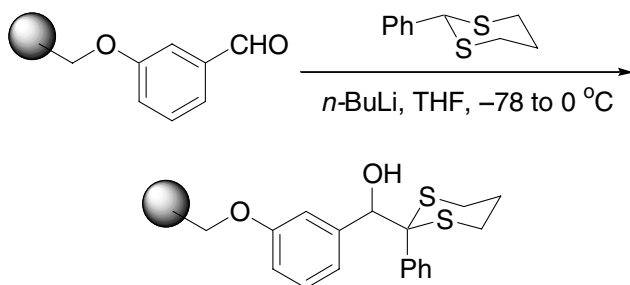
Corey–Seebach reaction

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



Example 1⁶



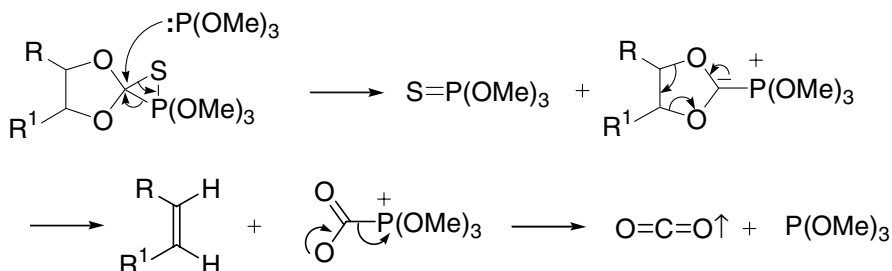
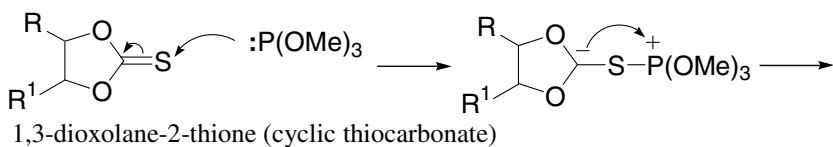
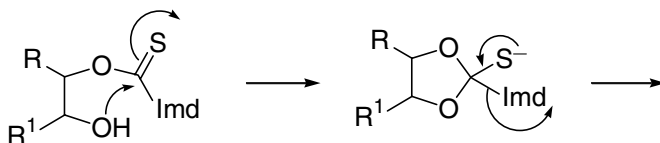
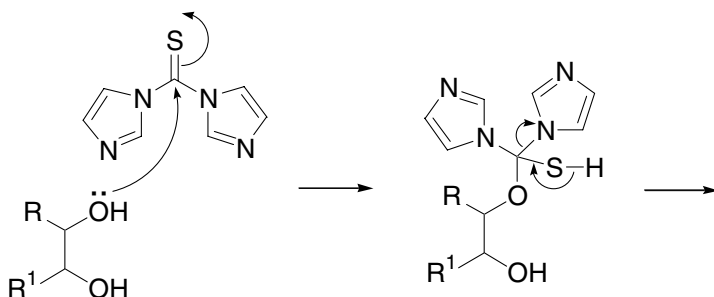
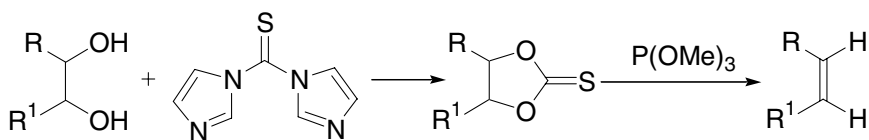
Example 2⁸

References

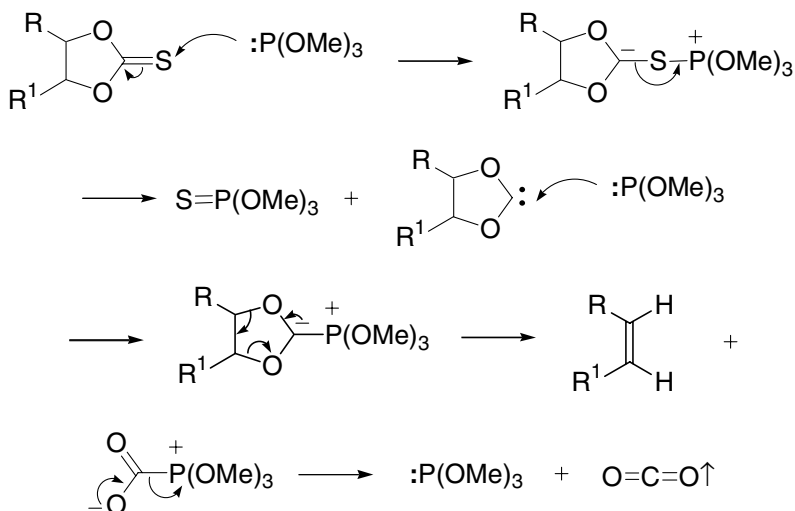
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Corey–Winter olefin synthesis

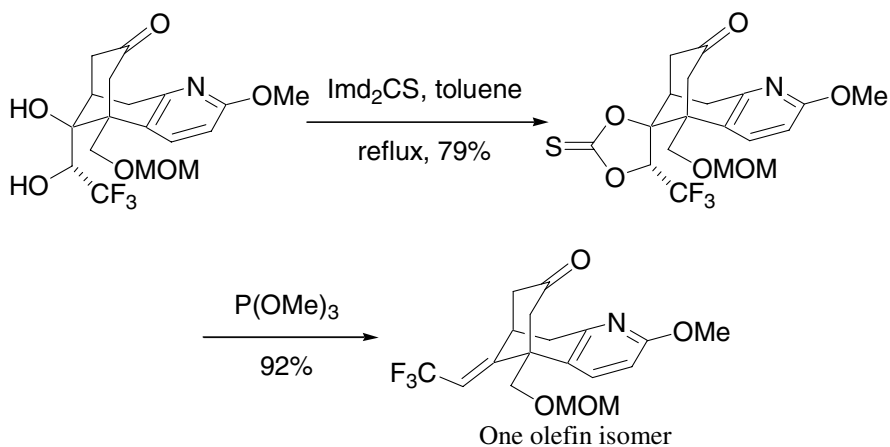
Transformation of diols to the corresponding olefins by sequential treatment with 1,1'-thiocarbonyldiimidazole and trimethylphosphite. Also known as Corey–Winter reductive elimination, or Corey–Winter reductive olefination.



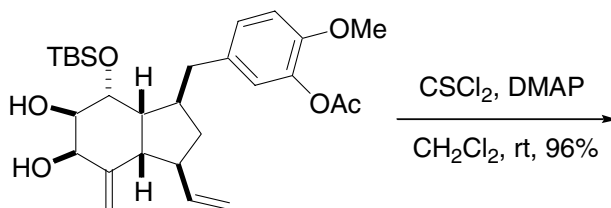
A mechanism involving a carbene intermediate can also be drawn and is supported by pyrolysis studies:

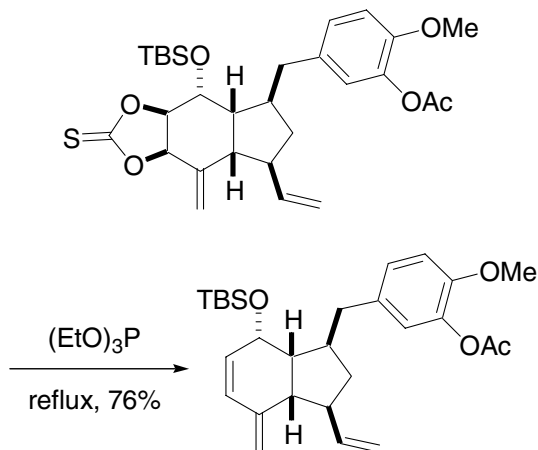


Example 1⁷



Example 2¹¹



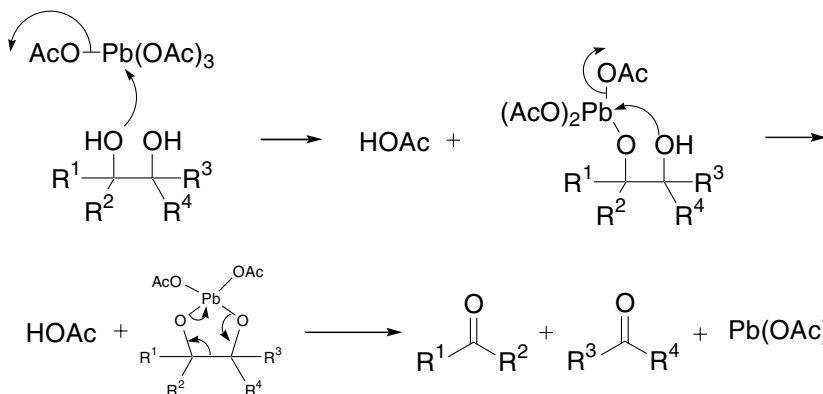
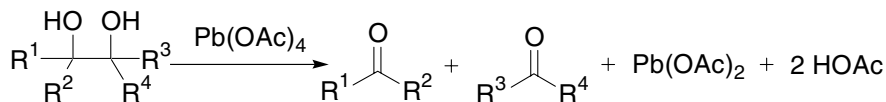


References

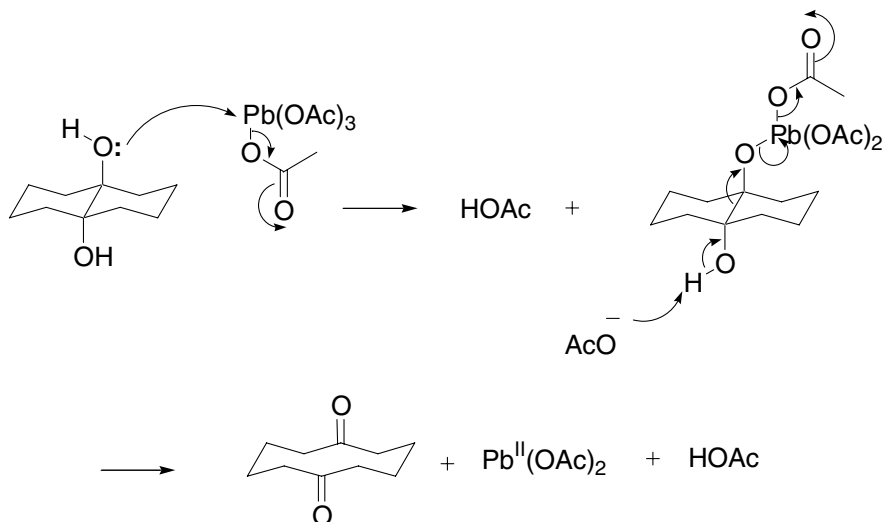
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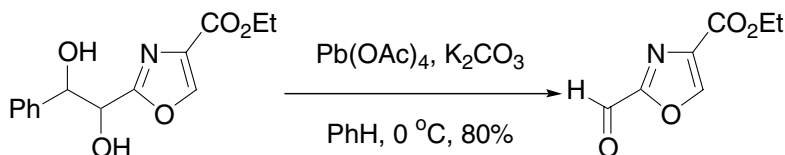
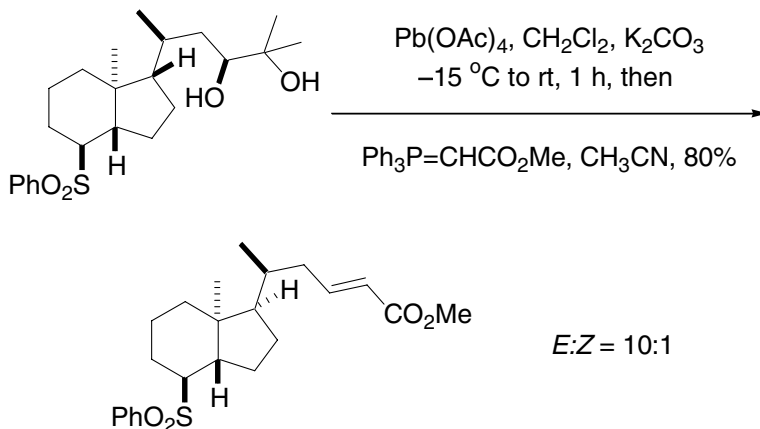
Criegee glycol cleavage

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



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

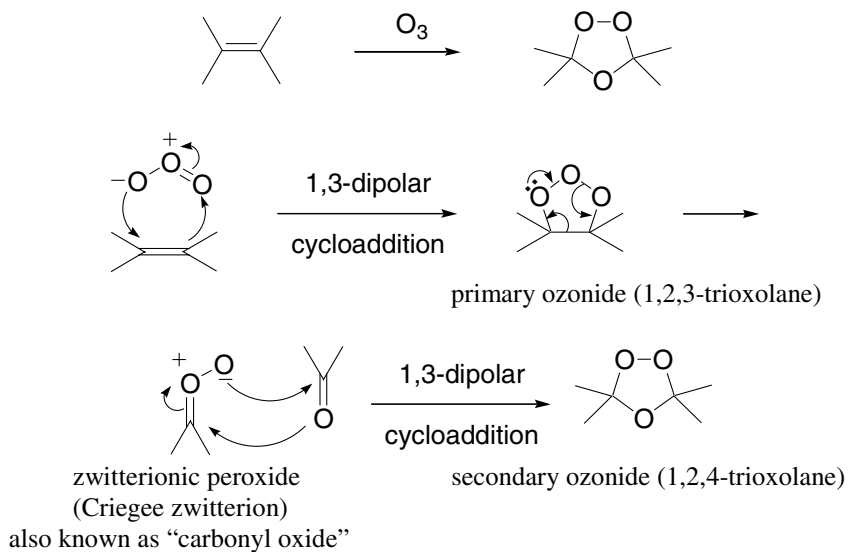


Example 1⁷Example 2⁹

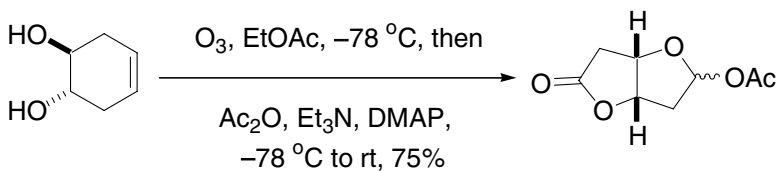
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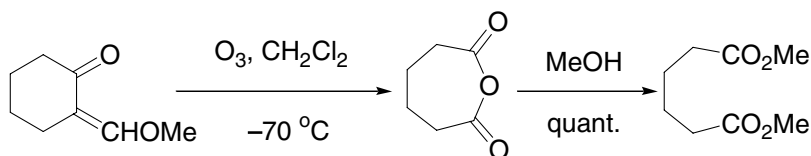
Criegee mechanism of ozonolysis



Example 1¹⁴



Example 2¹⁵



References

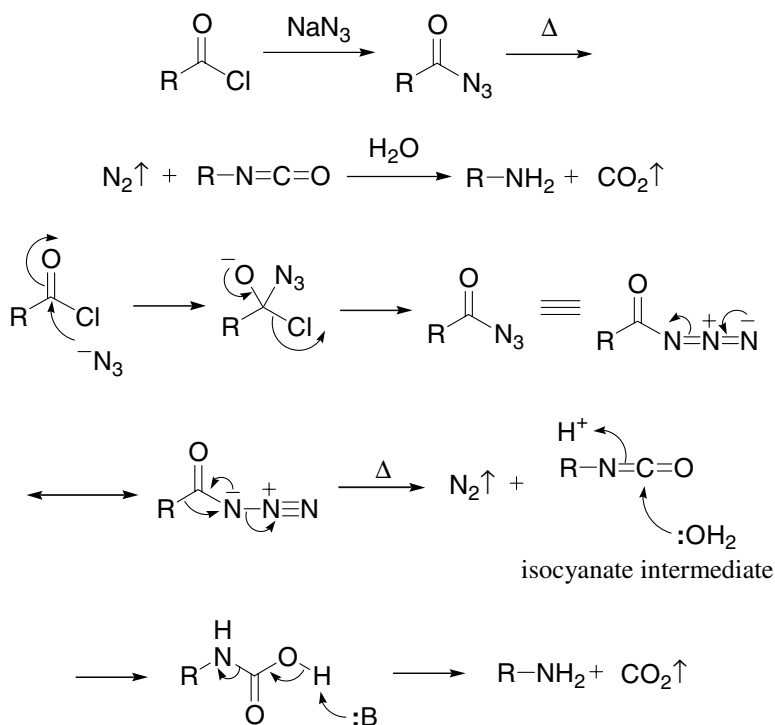
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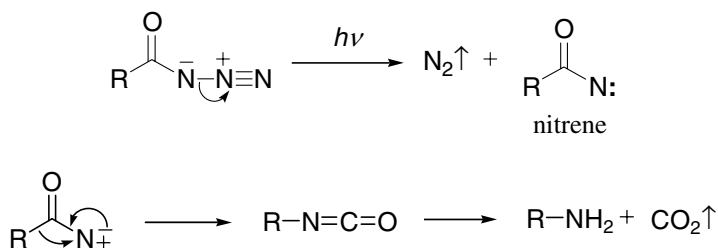
Curtius rearrangement

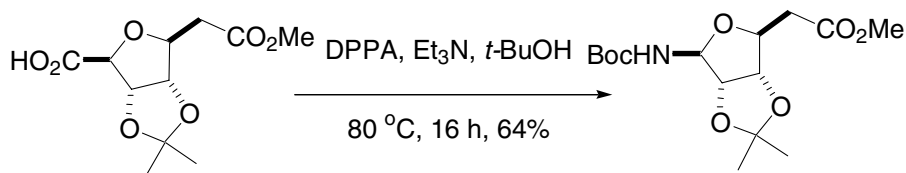
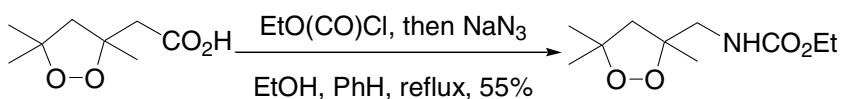
Thermal or photochemical rearrangement of acyl azides into amines *via* isocyanate intermediates. While the thermal rearrangement is a concerted process, the photochemical rearrangement goes through a nitrene intermediate.

The thermal rearrangement:



The photochemical rearrangement:



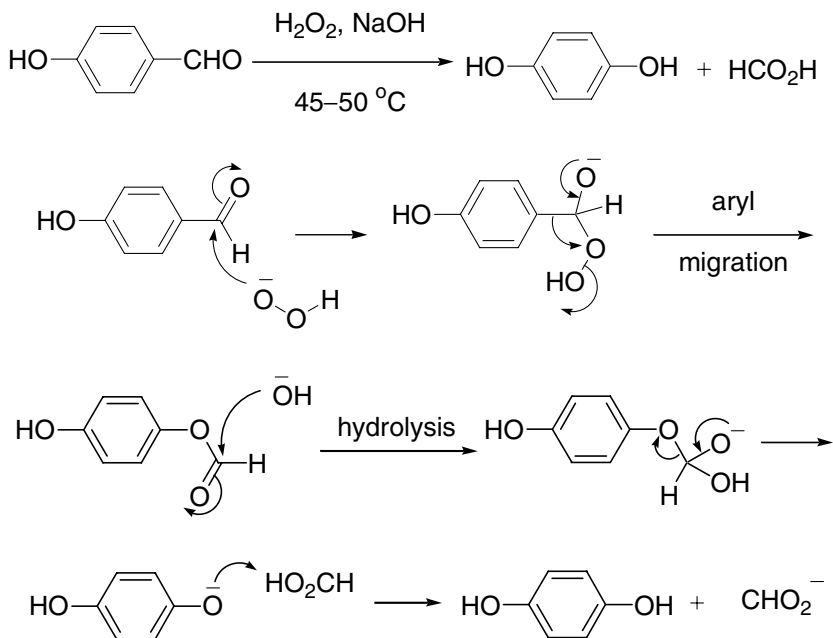
Example 1⁹Example 2¹¹

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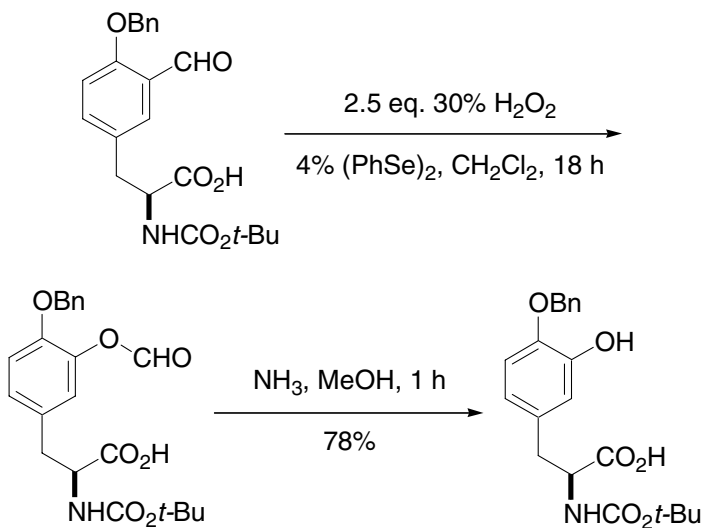
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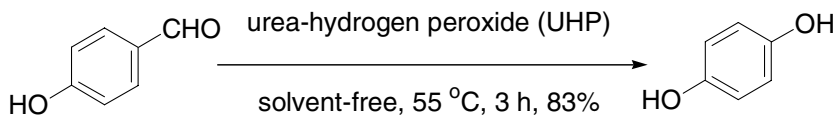
Dakin oxidation

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



Example 1⁶



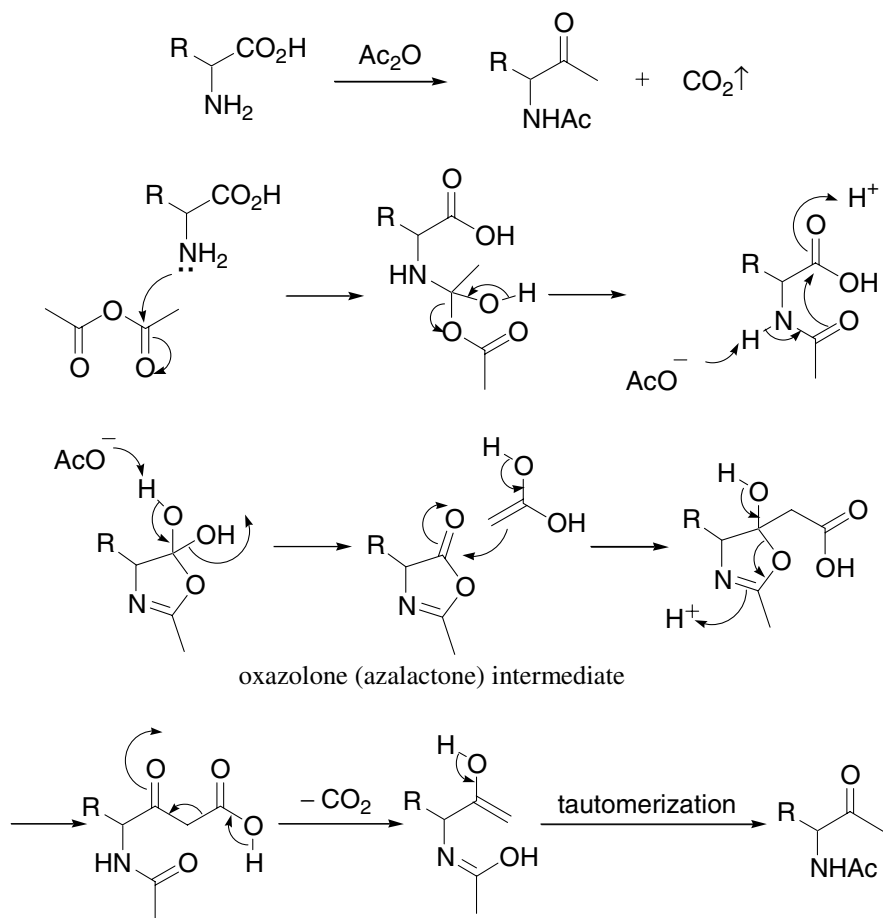
Example 2⁷

References:

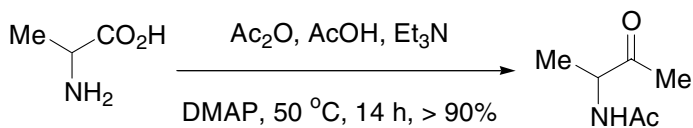
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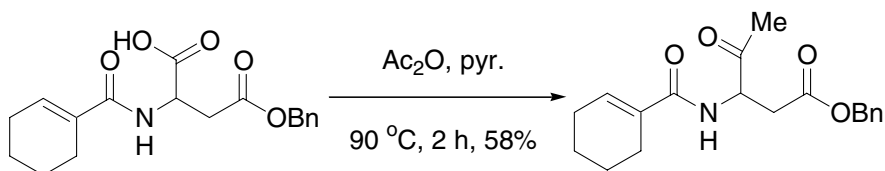
Dakin–West reaction

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



Example 1¹²



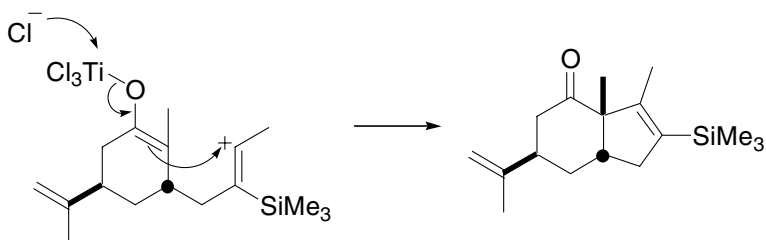
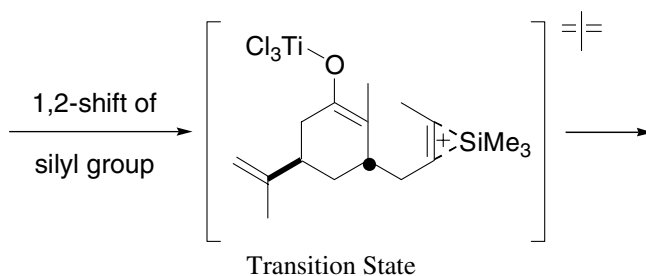
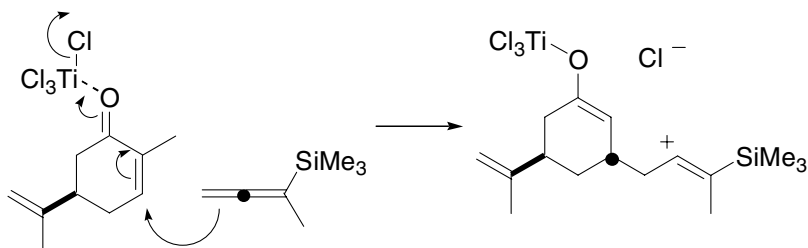
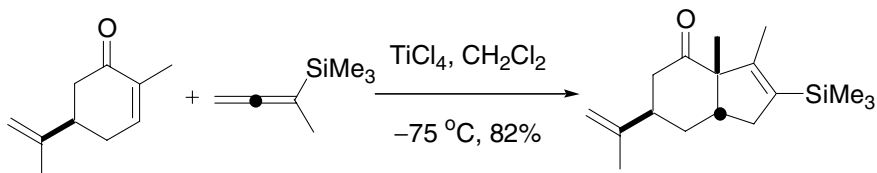
Example 2¹⁴

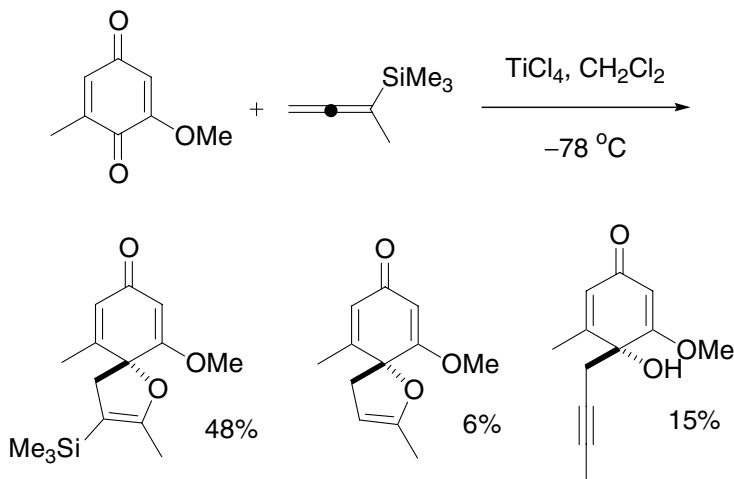
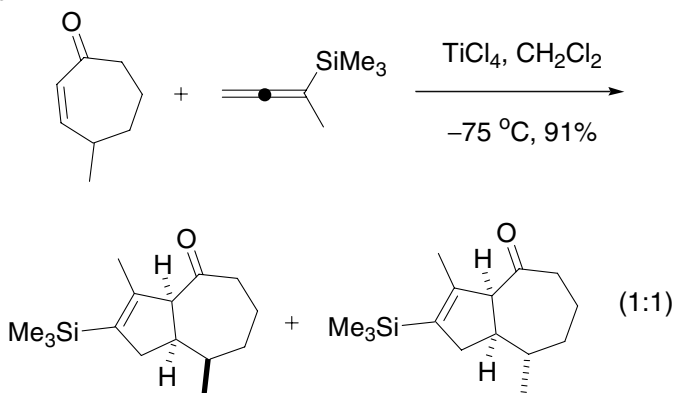
References:

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Danheiser annulation

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



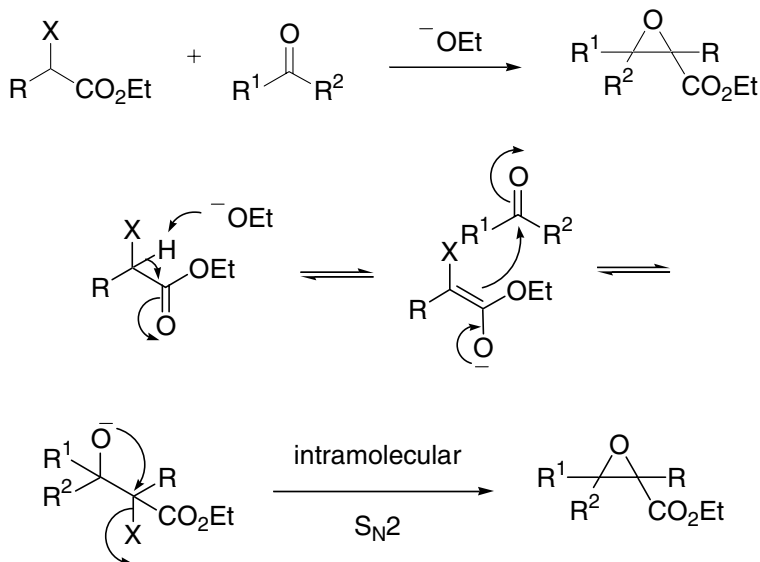
Example 1⁷Example 2⁸

References

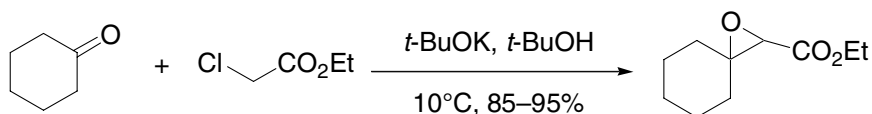
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Darzens glycidic ester condensation

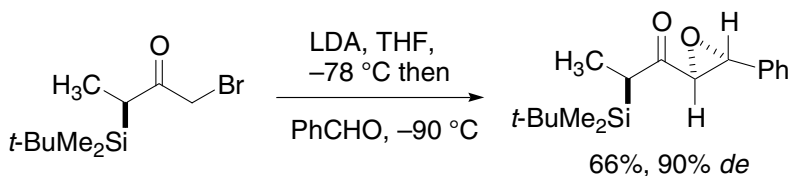
α,β -Epoxy esters (glycidic esters) from base-catalyzed condensation of α -haloesters with carbonyl compounds.



Example 1⁴



Example 2⁹



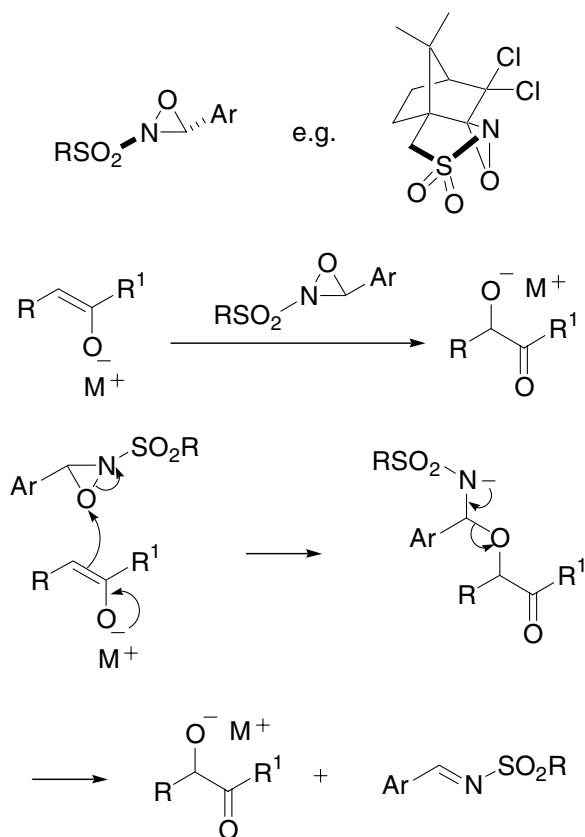
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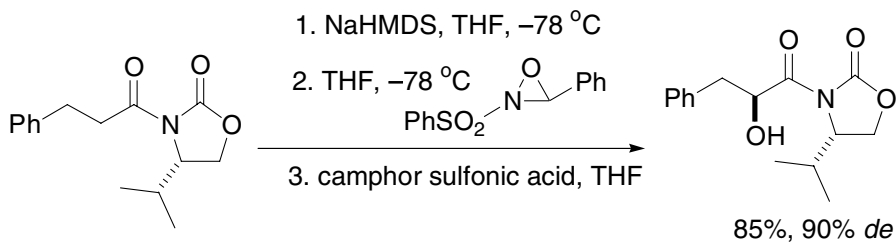
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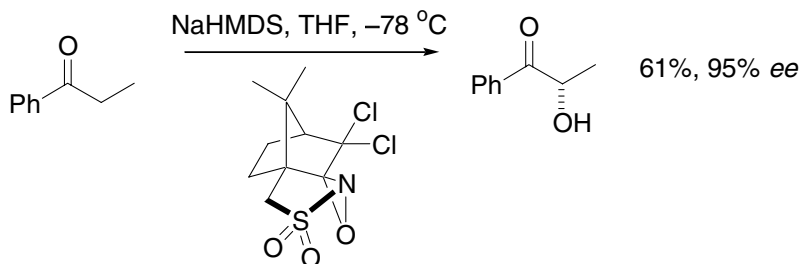
Davis chiral oxaziridine reagents

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



Example 1²



Example 2⁵

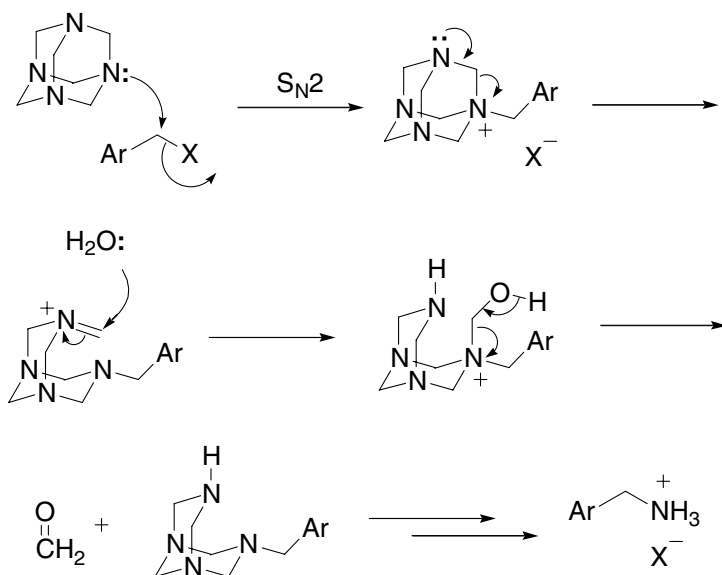
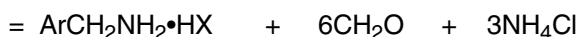
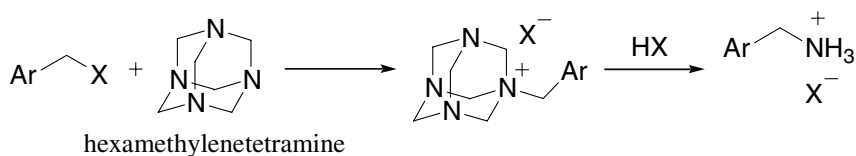
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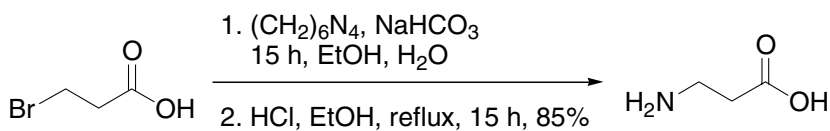
Delépine amine synthesis

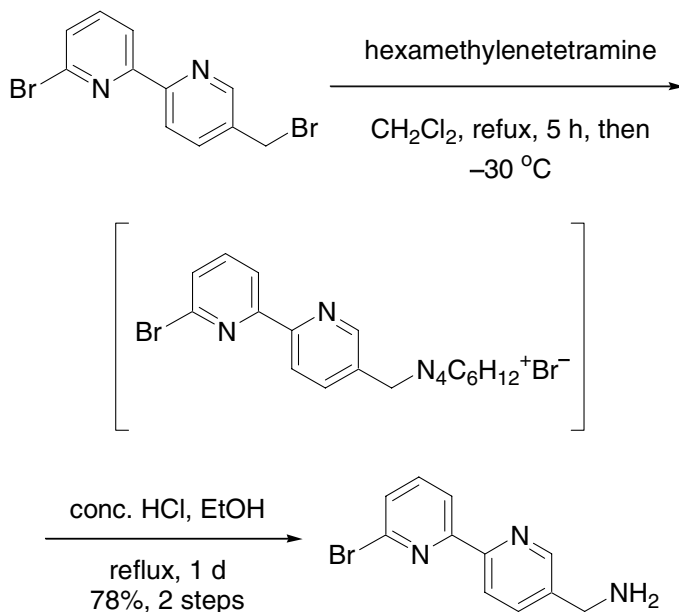
The reaction between alkyl halides and hexamethylenetetramine, followed by cleavage of the resulting salt with ethanolic HCl to yield primary amines.

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.



Example 1⁴



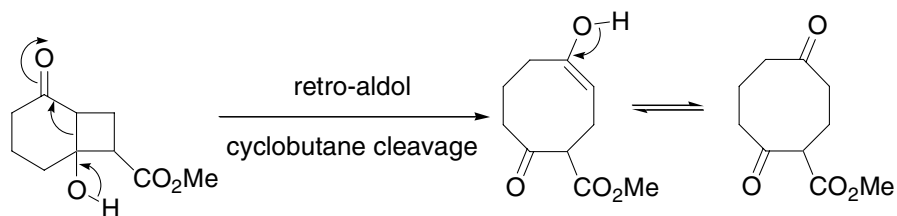
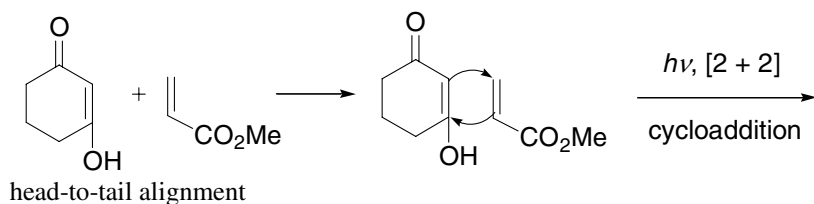
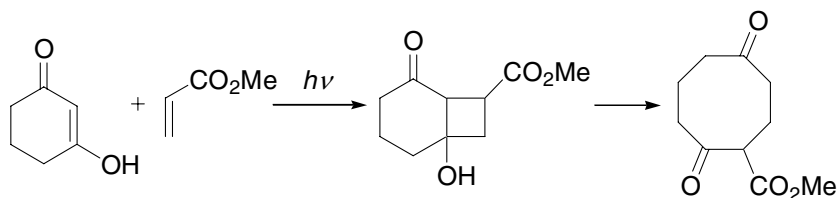
Example 2⁸

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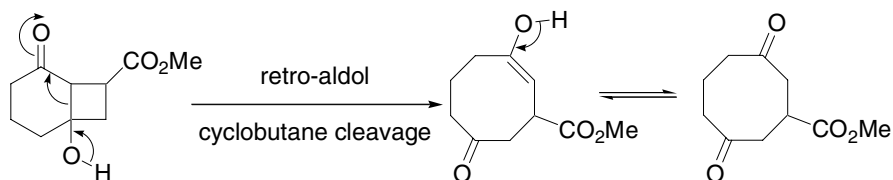
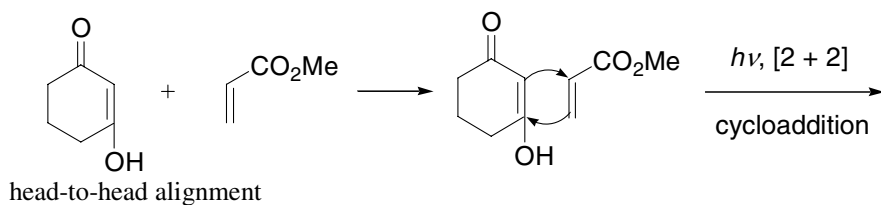
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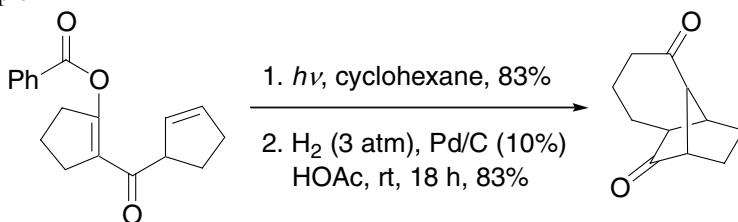
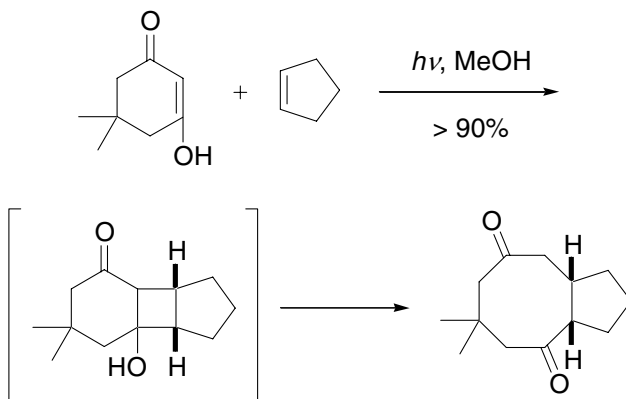
de Mayo reaction

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



Minor regioisomer:



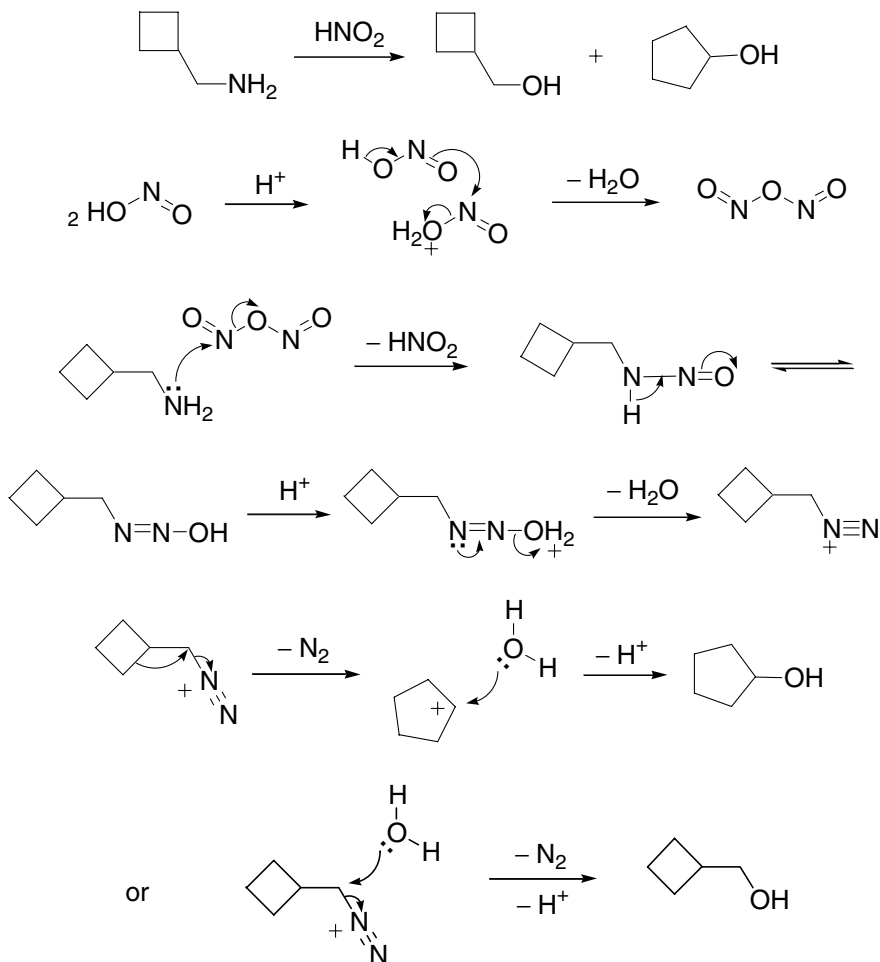
Example 1⁵Example 2⁹

References

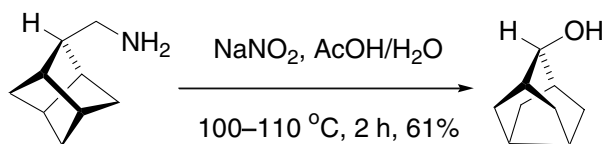
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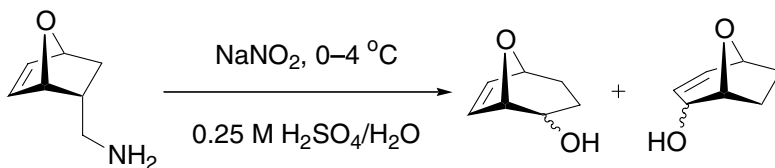
Demjanov rearrangement

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



Example 1⁷



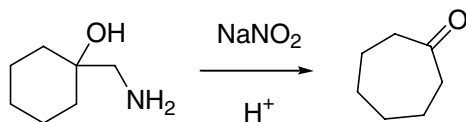
Example 2⁹

References

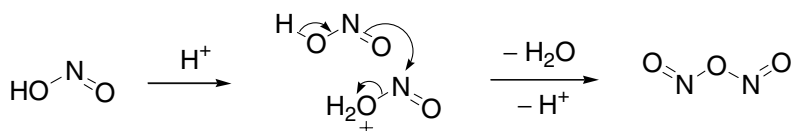
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Tiffeneau–Demjanov rearrangement

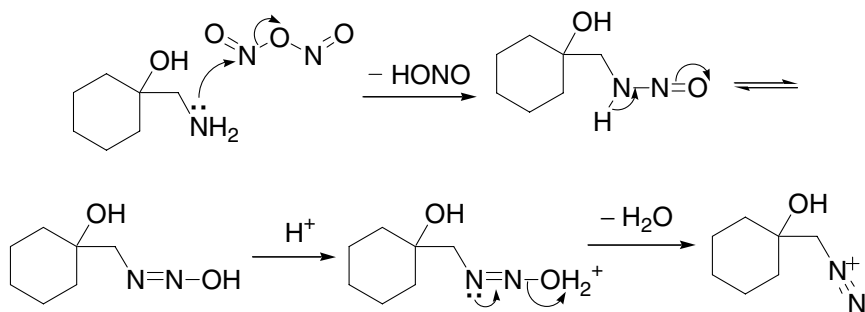
Carbocation rearrangement of β -aminoalcohols *via* diazotization to afford carbonyl compounds through C–C bond migration.



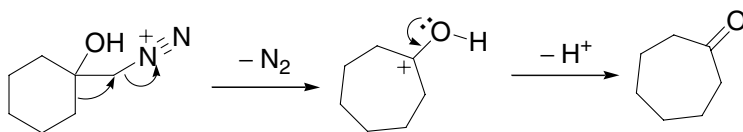
Step 1, Generation of N_2O_3



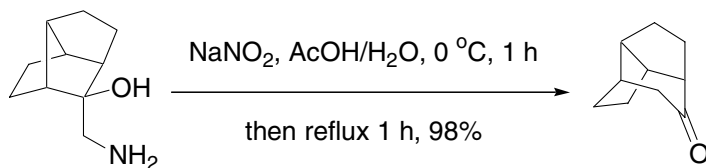
Step 2, Transformation of amine to diazonium salt

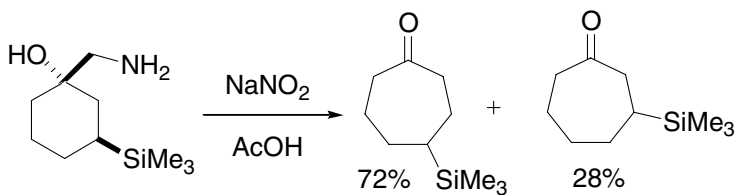


Step 3, Ring-expansion *via* rearrangement



Example 1¹⁰



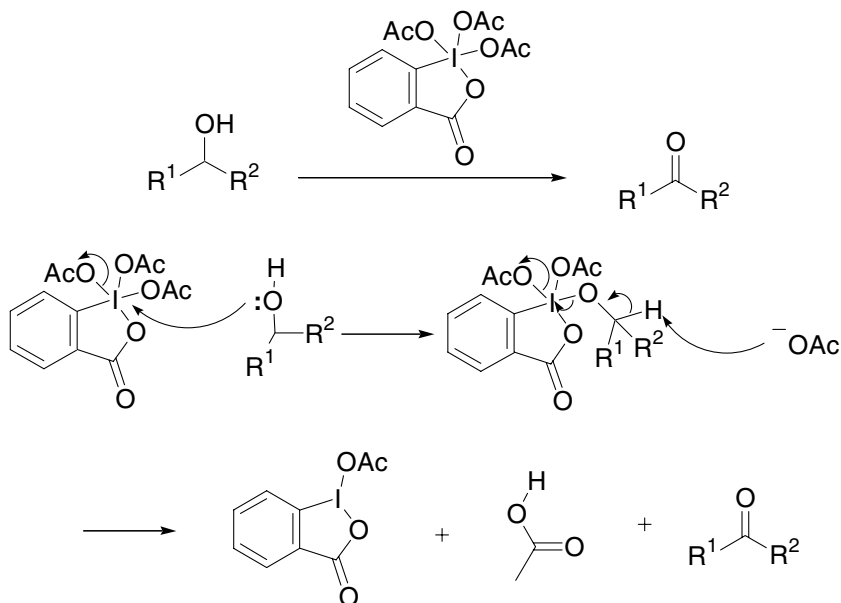
Example 2¹²

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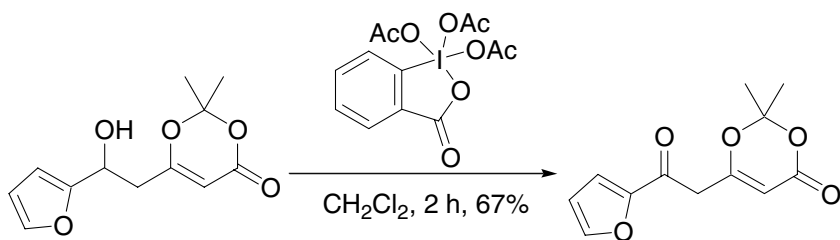
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Dess–Martin periodinane oxidation

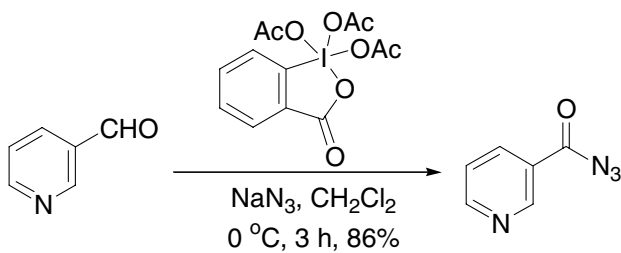
Oxidation of alcohols to the corresponding carbonyl compounds using triacetoxyperiodinane.



Example 1⁹



Example 2¹⁵

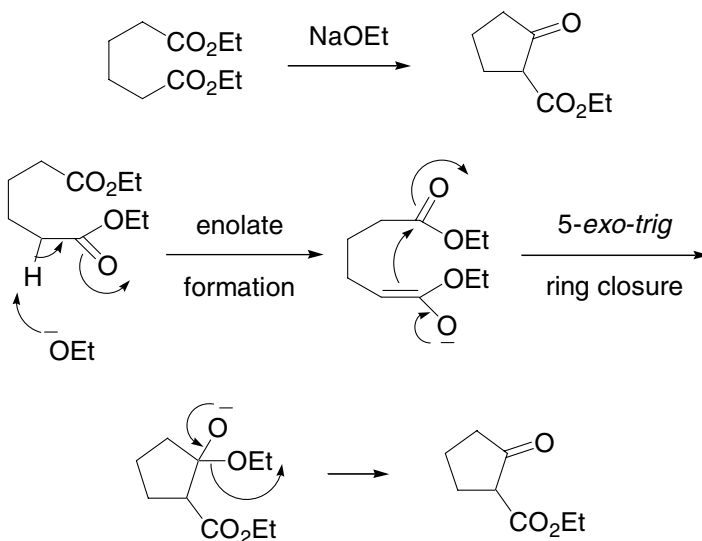


References

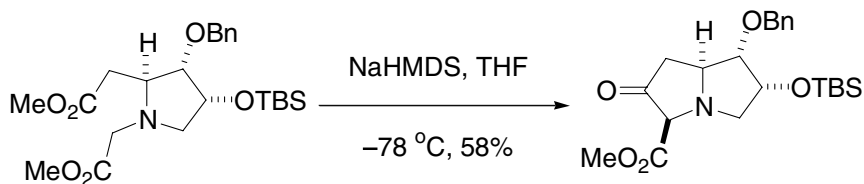
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Dieckmann condensation

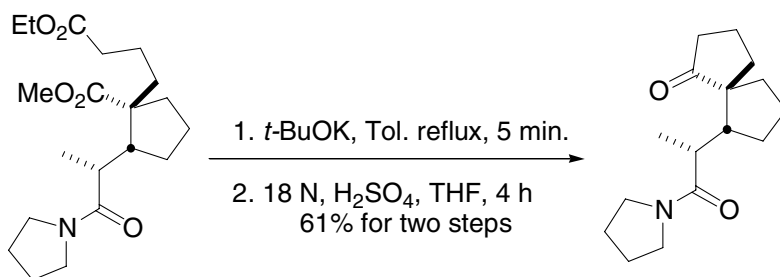
The Dieckmann condensation is the intramolecular version of the Claisen condensation.



Example 1⁷



Example 2⁹



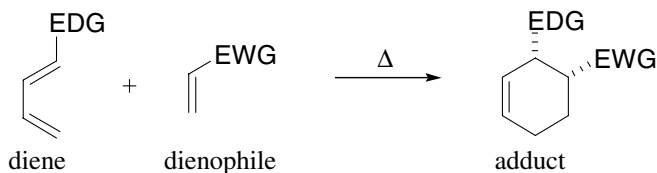
References

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Diels–Alder reaction

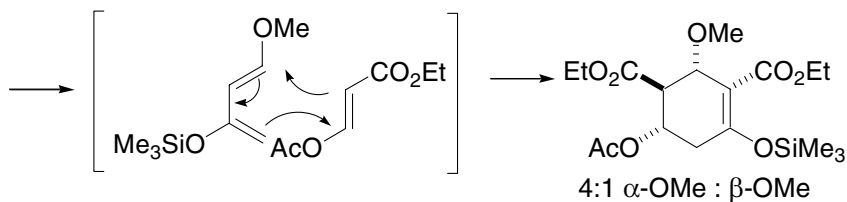
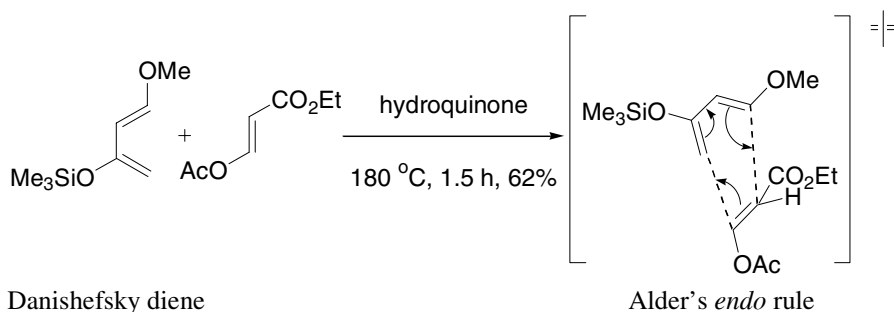
The Diels–Alder reaction, inverse electronic demand Diels–Alder reaction, as well as the hetero-Diels–Alder reaction, belong to the category of *[4+2]-cycloaddition reactions*, which are concerted processes. The arrow pushing here is merely illustrative.

Normal Diels–Alder reaction

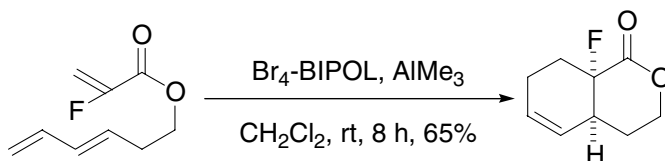


EDG = electron-donating group; EWG = electron-withdrawing group

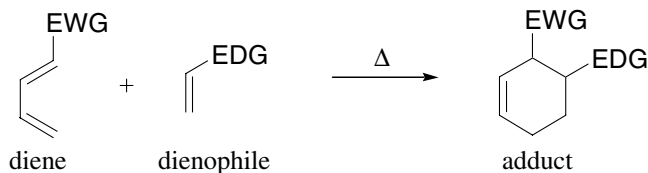
Example 1¹³



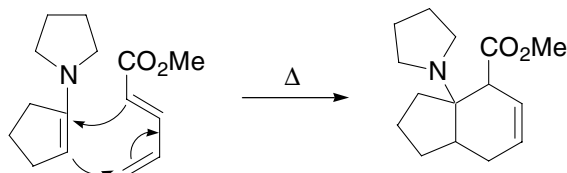
Example 2¹⁷



Inverse electronic demand Diels–Alder reaction

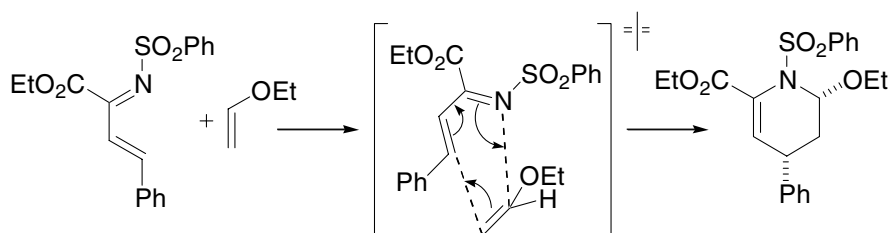


Example 1²

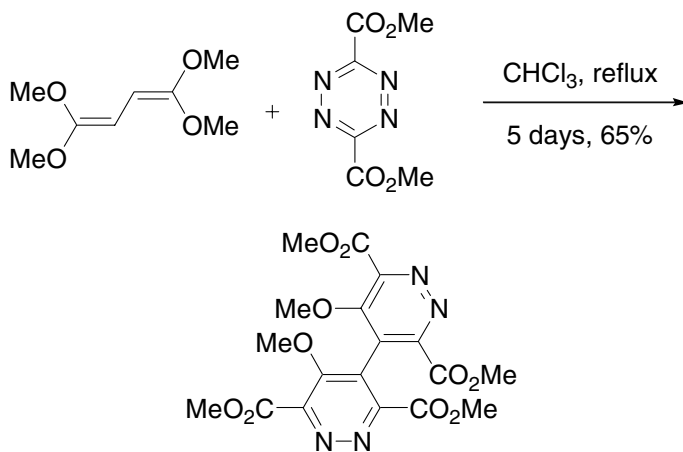


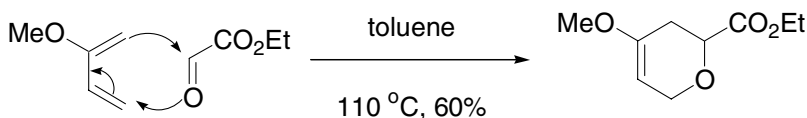
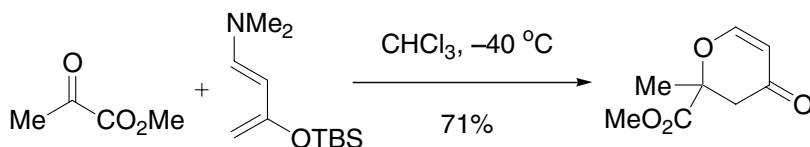
Hetero-Diels–Alder reaction

Heterodiene addition to dienophile



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



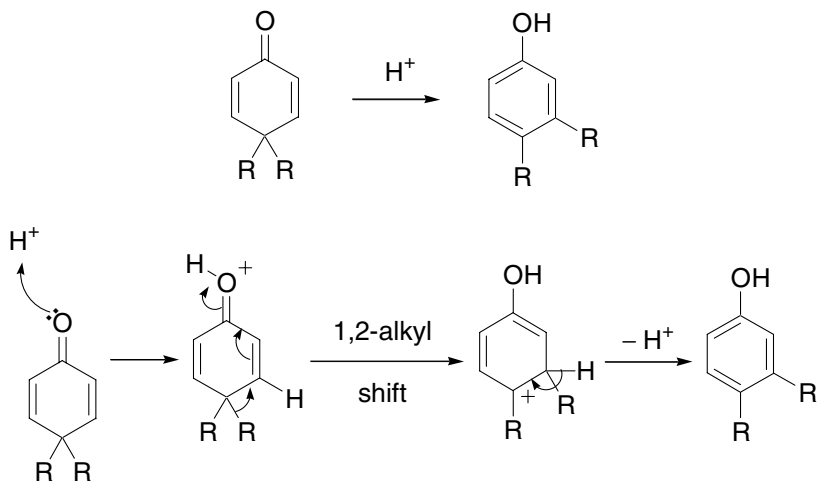
Heterodienophile addition to diene²Example 2, using the Rawal diene⁹

References

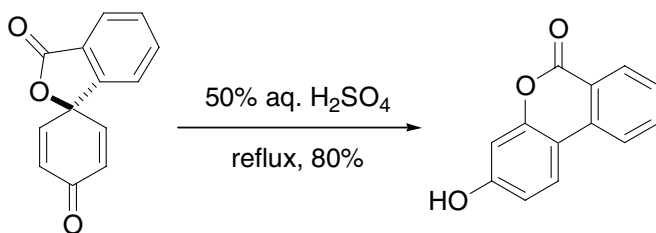
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Dienone-phenol rearrangement

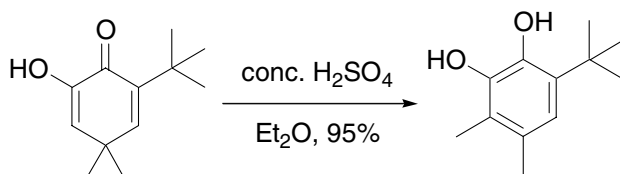
Acid-promoted rearrangement of 4,4-disubstituted cyclohexadienones to 3,4-disubstituted phenols.



Example 1⁴



Example 2⁵



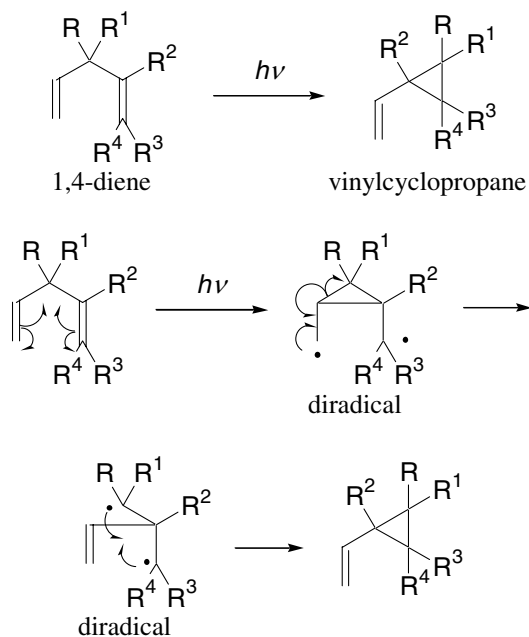
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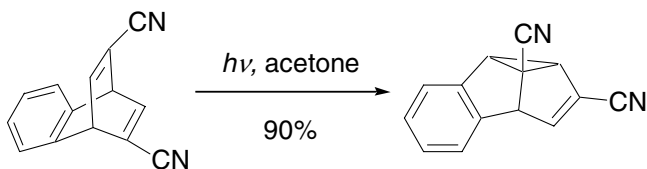
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Di- π -methane rearrangement

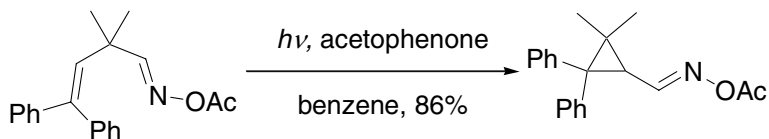
Conversion of 1,4-dienes to vinylcyclopropanes under photolysis. Also known as the Zimmerman rearrangement.



Example 1⁹



Example 2, aza- π -methane rearrangement²

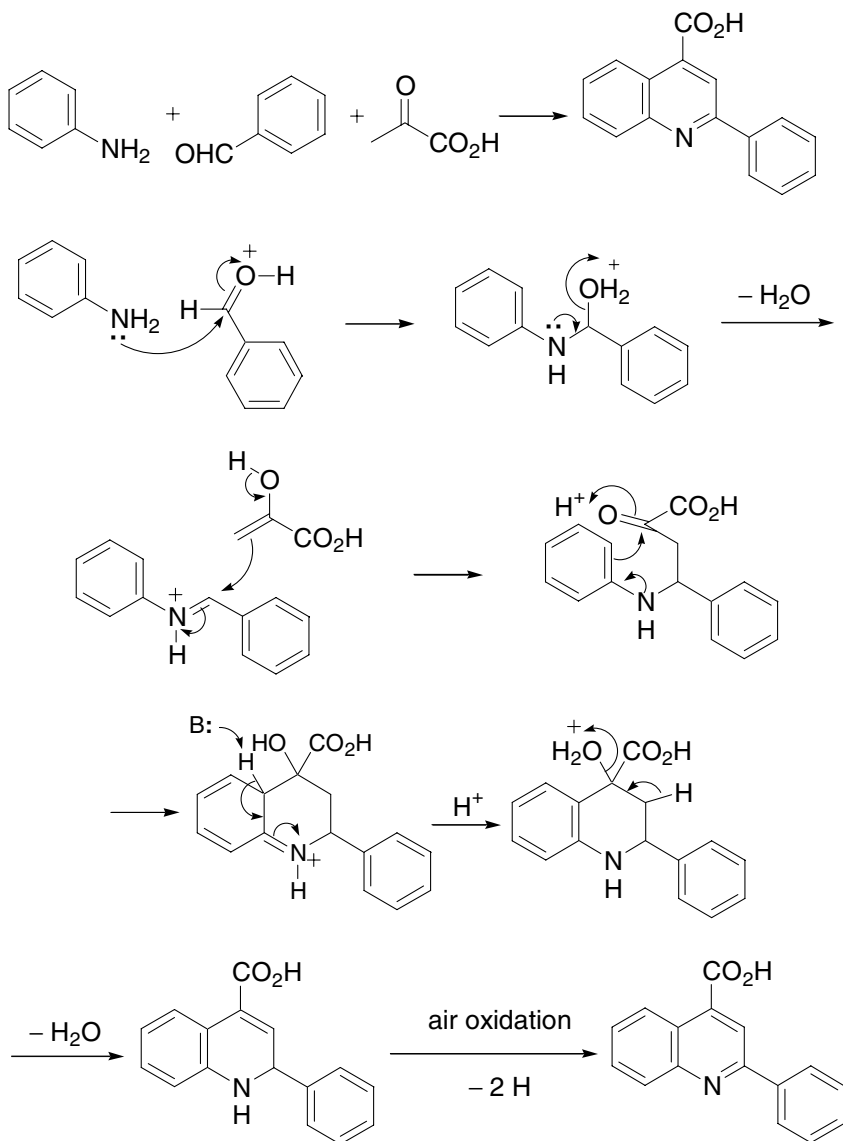


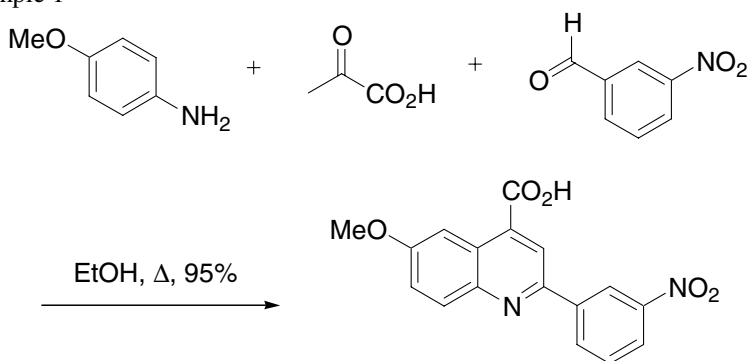
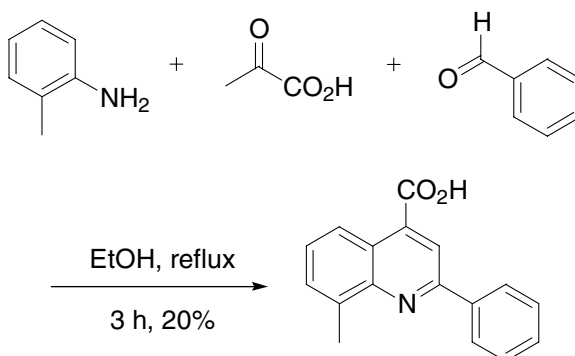
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Doebner quinoline synthesis

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



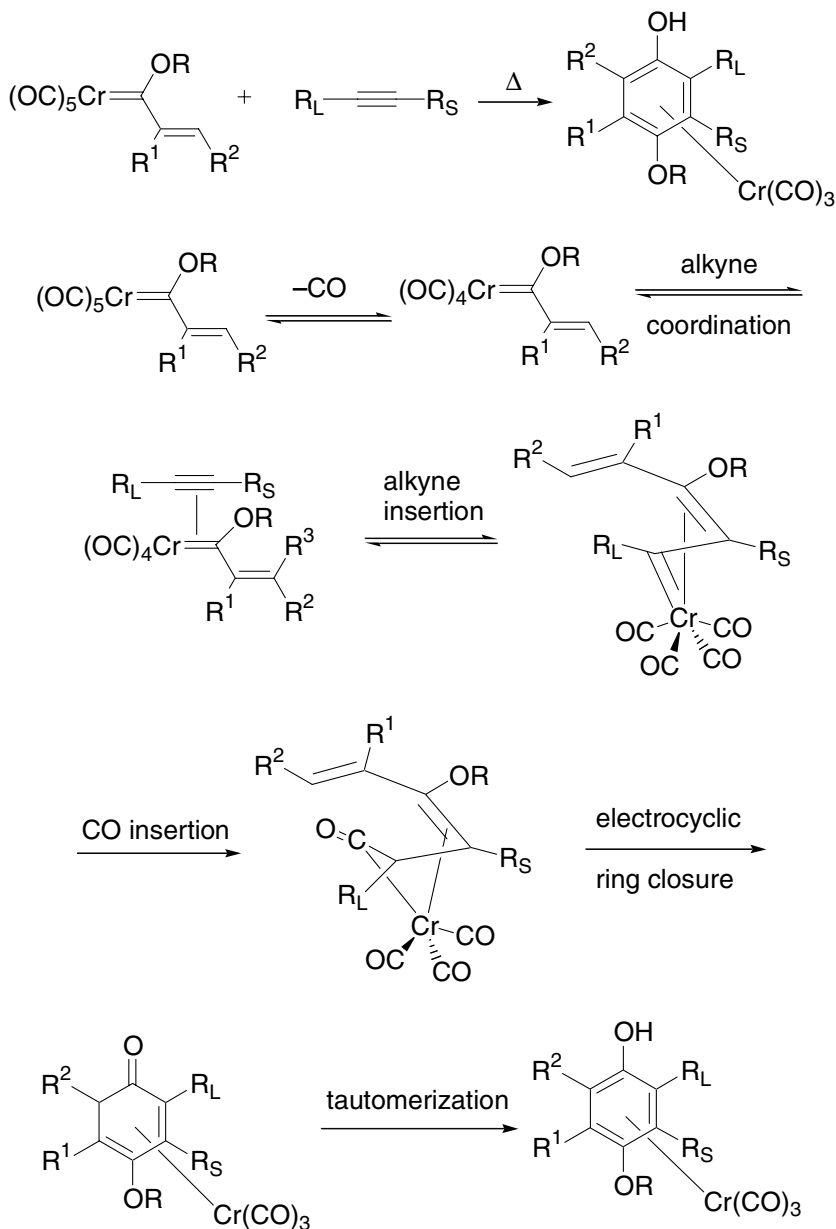
Example 1²Example 2⁶

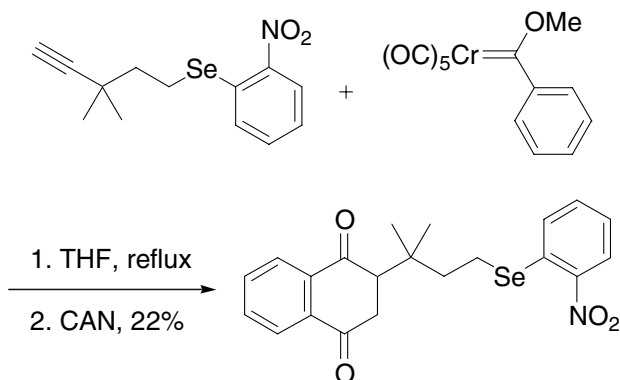
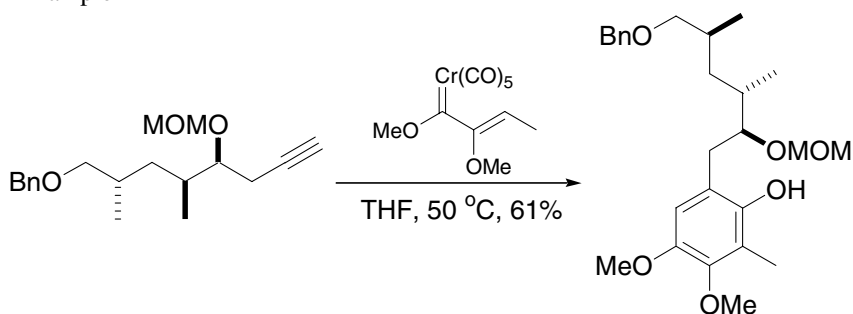
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Dötz reaction

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



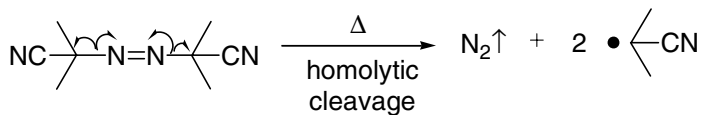
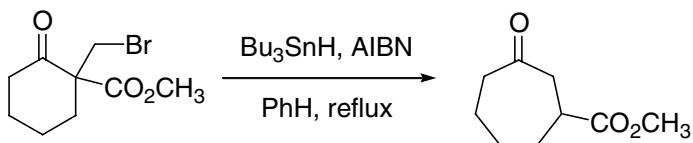
Example 1⁷Example 2¹¹

References

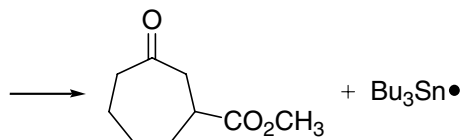
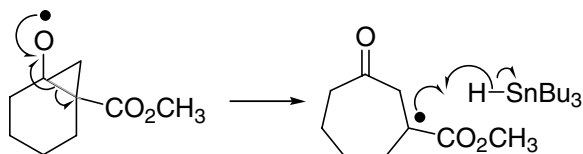
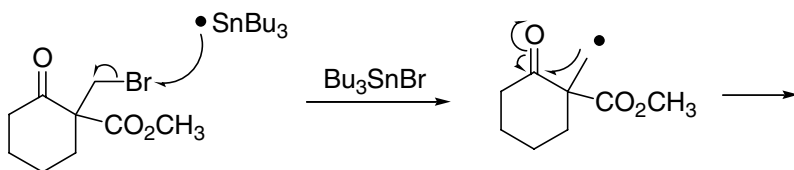
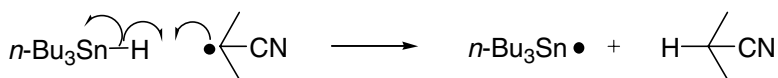
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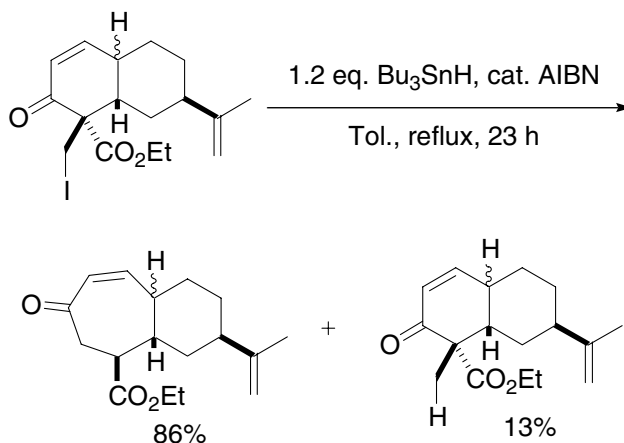
Dowd–Beckwith ring expansion

Radical-mediated ring expansion of 2-halomethyl cycloalkanones.



2,2'-azobisisobutyronitrile (AIBN)



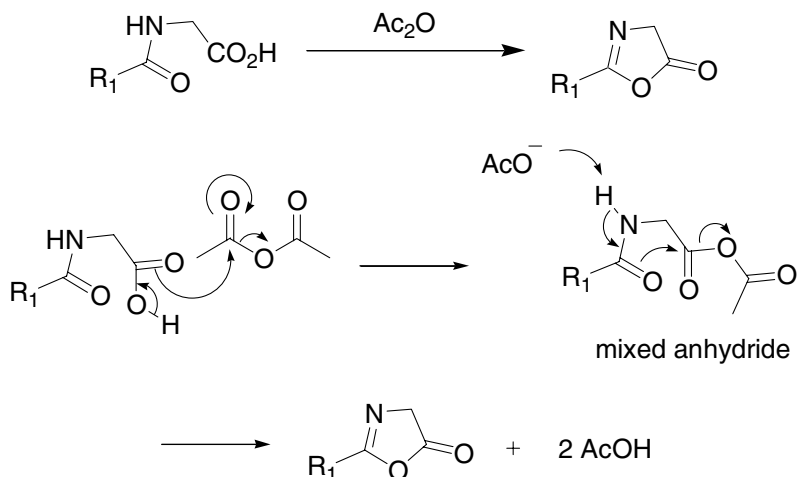
Example 1⁹

References

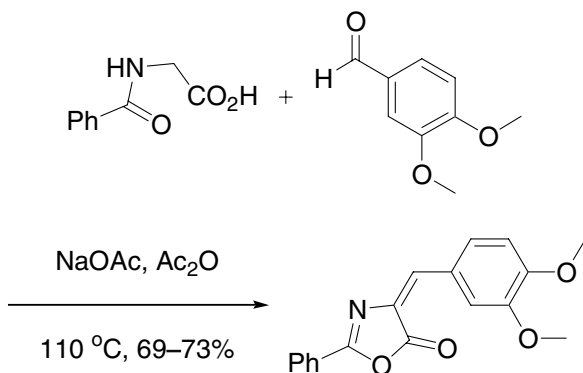
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Erlenmeyer–Plöchl azlactone synthesis

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



Example¹⁴



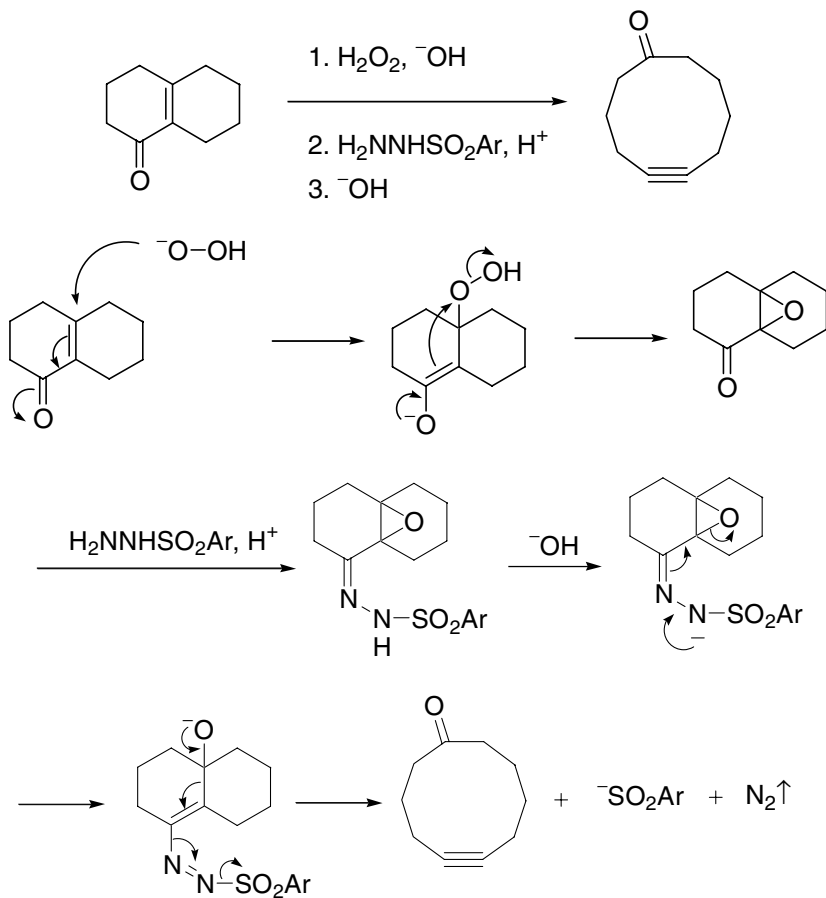
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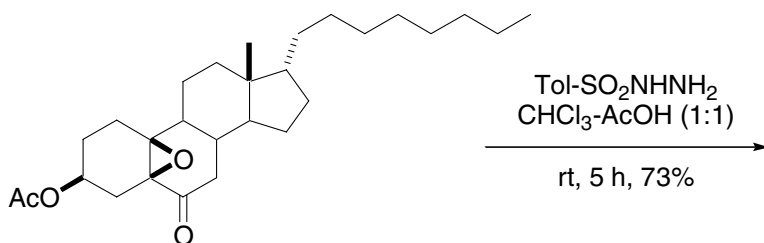
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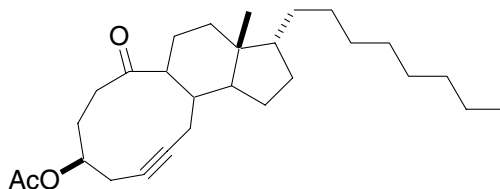
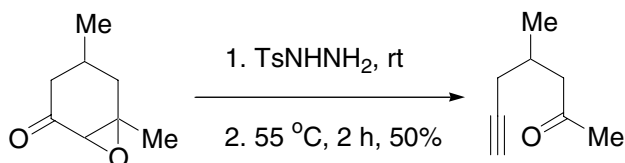
Eschenmoser–Tanabe fragmentation

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



Example 1⁴



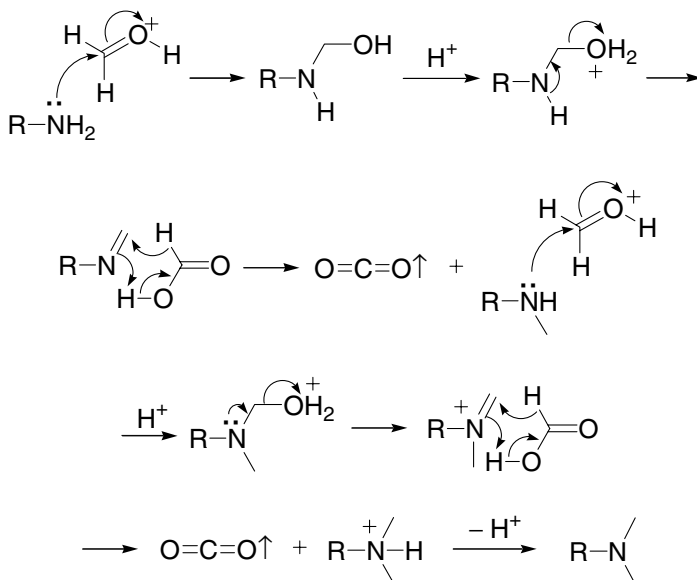
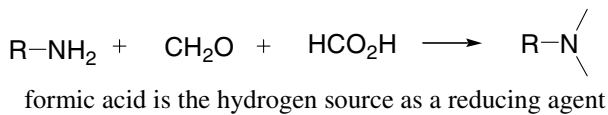
Example 2⁷

References

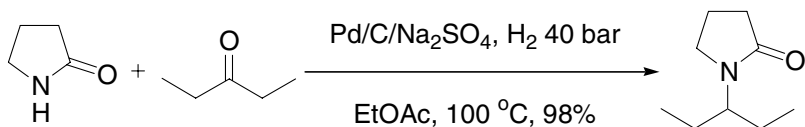
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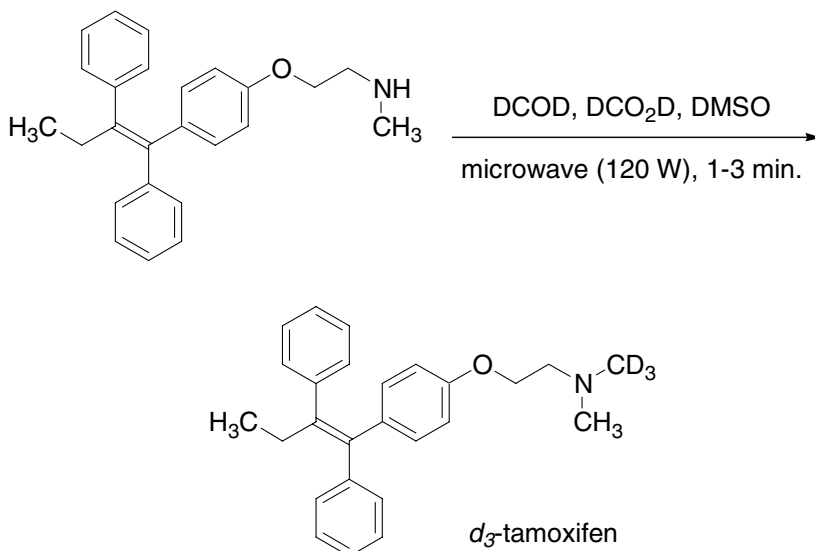
Eschweiler–Clarke reductive alkylation of amines

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



Example 1⁷



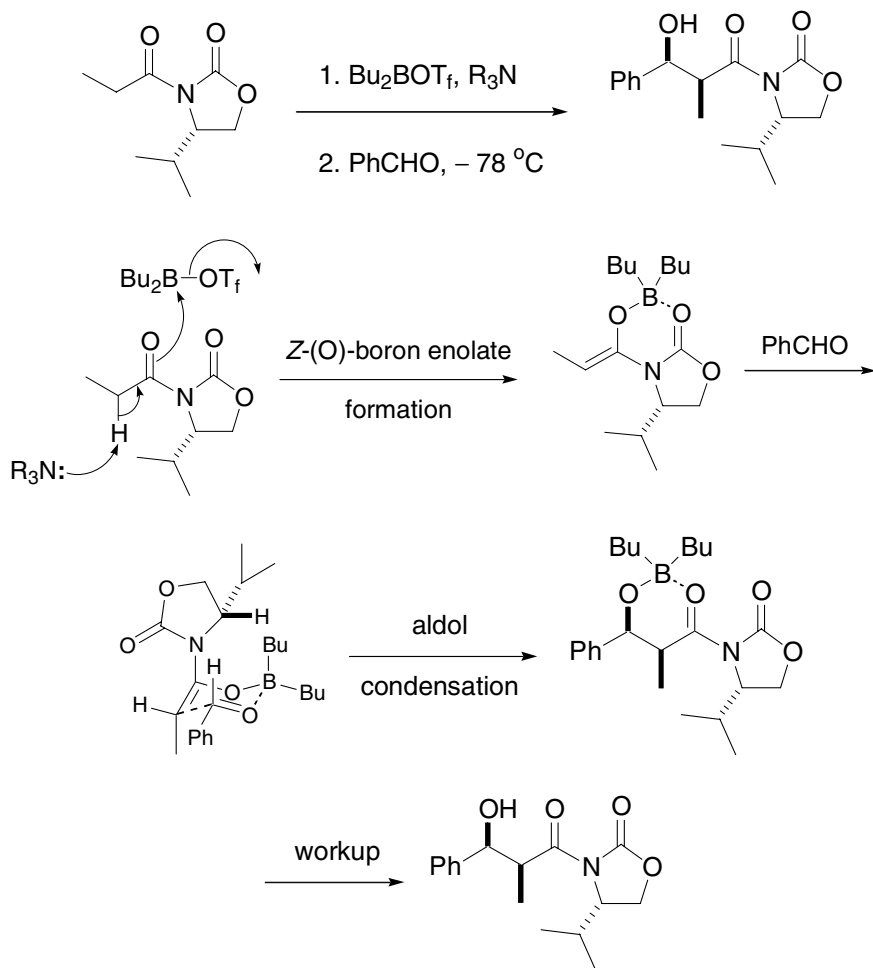
Example 2¹¹

References

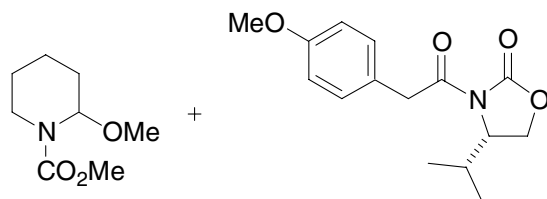
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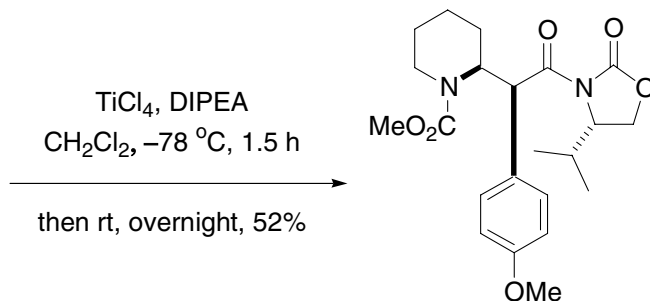
Evans aldol reaction

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

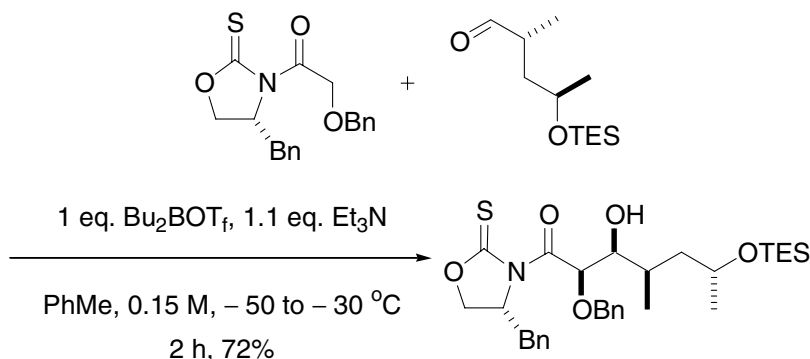


Example 1⁷





Example 2¹³



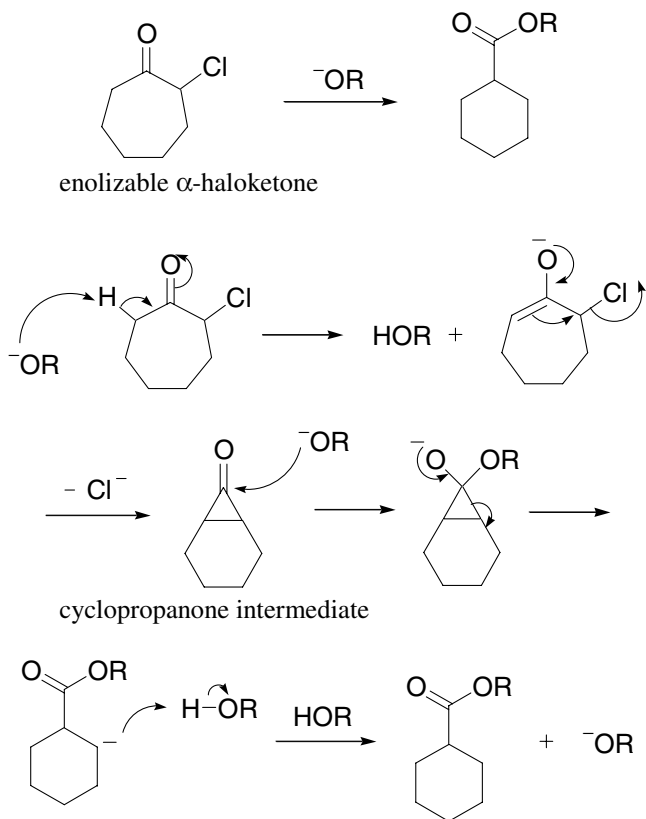
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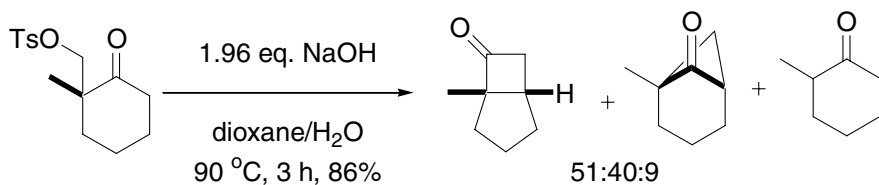
Favorskii rearrangement and quasi-Favorskii rearrangement

Favorskii rearrangement

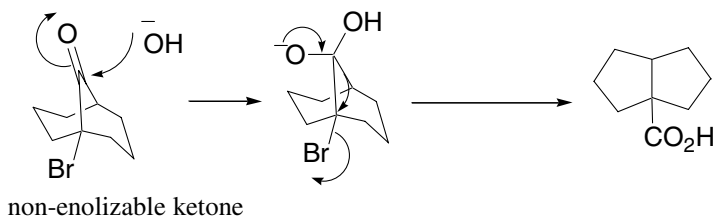
Transformation of enolizable α -haloketones to esters, carboxylic acids, or amides *via* alkoxide-, hydroxide-, or amine-catalyzed rearrangements, respectively.



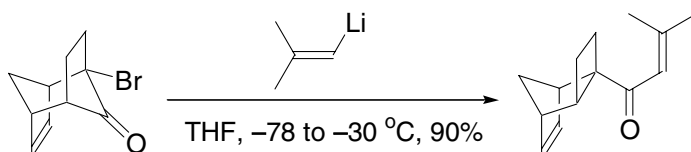
Example 1, homo-Favorskii rearrangement³



Quasi-Favorskii rearrangement



Example 1¹¹

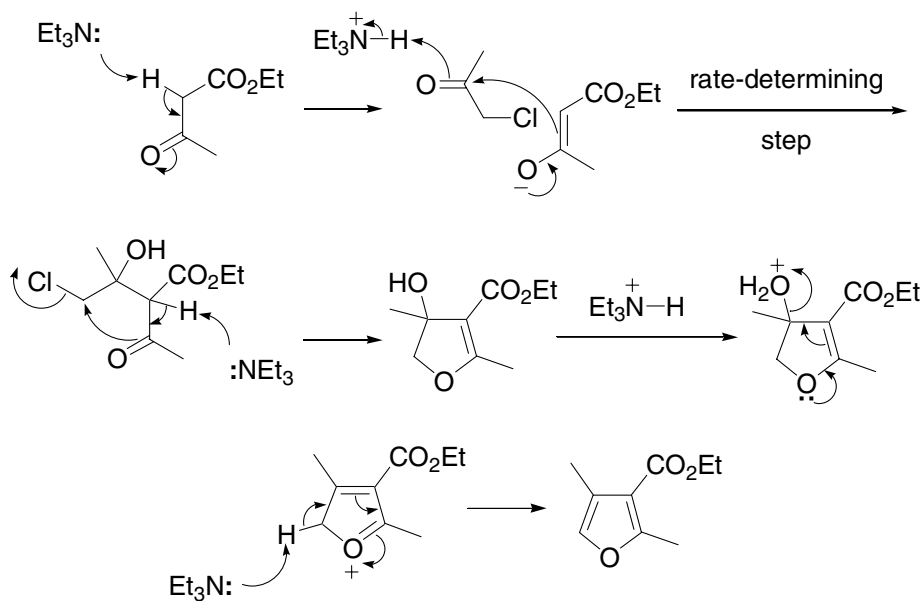
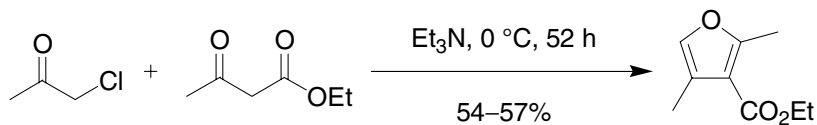


References

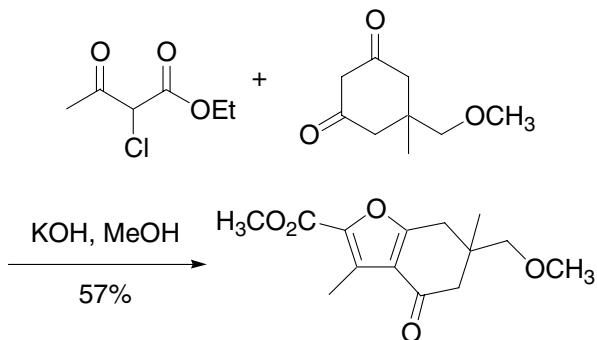
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Feist–Bénary furan synthesis

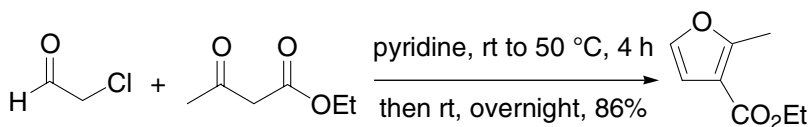
α -Haloketones react with β -ketoesters in the presence of base to fashion furans.



Example 1^{4,5}



Example 2⁶



References

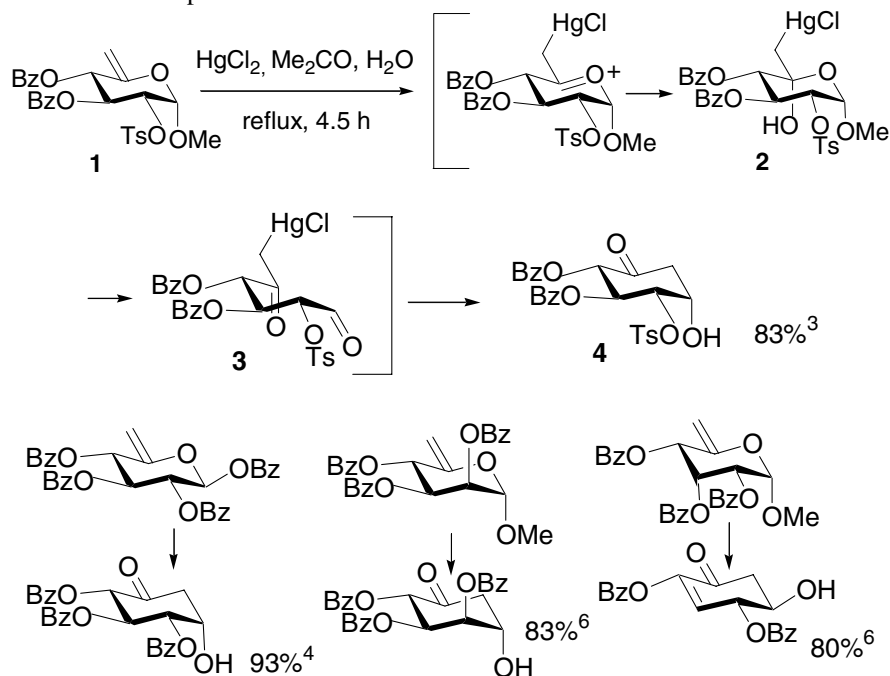
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Ferrier carbocyclization

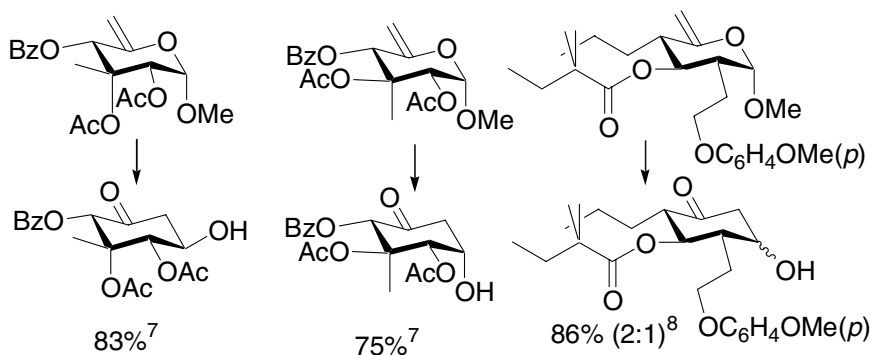
This process (also known as the “Ferrier II Reaction”) has proved to be of considerable value for the efficient, one-step conversion of 5,6-unsaturated hexopyranose derivatives into functionalized cyclohexanones useful for the preparation of such enantiomerically pure compounds as inositols and their 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-mercured 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) trifluoroacetate⁵ and sulfate⁶ 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}

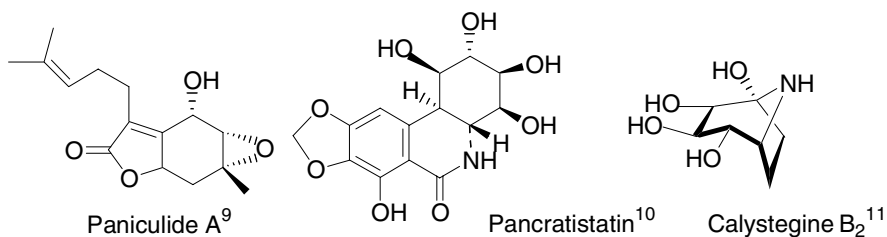
General examples:



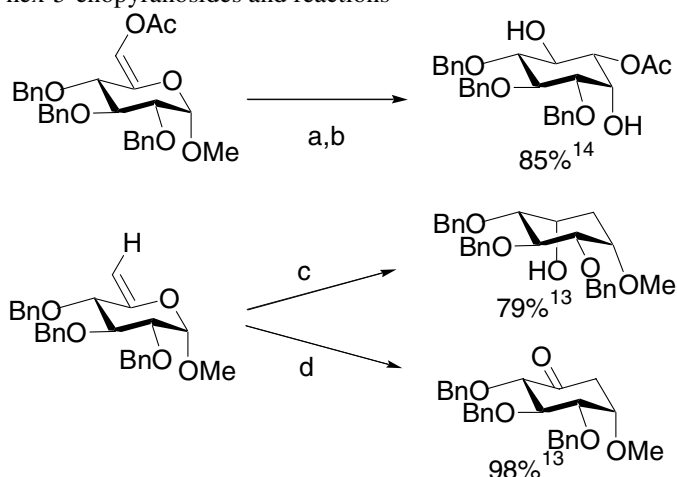
More complex products



Complex bioactive compounds made following the application of the reaction



Modified hex-5-enopyranosides and reactions



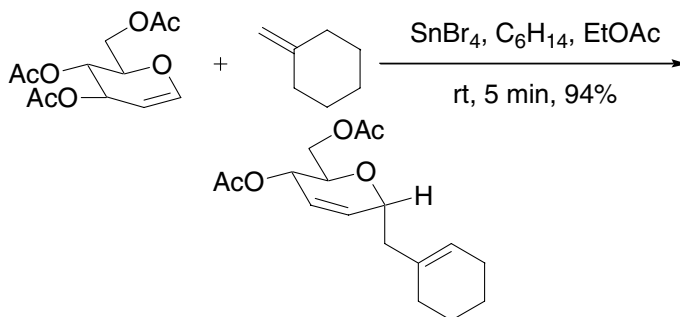
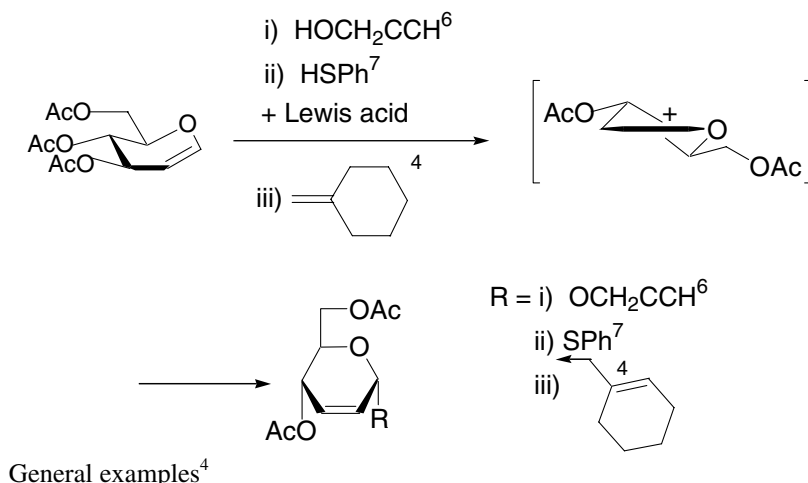
a, $\text{Hg}(\text{OCOCF}_3)_2$, Me_2CO , H_2O , 0 °C; b, $\text{NaBH}(\text{OAc})_3$, AcOH , MeCN , rt; c, *i*- Bu_3Al , PhMe , 40 °C; d, $\text{Ti}(\text{O}i\text{-Pr})\text{Cl}_3$, CH_2Cl_2 , -78 °C, 15 min. (Note: The aglycon is retained in the Al- and Ti-induced reactions).

References

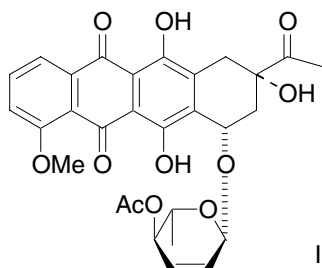
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Ferrier glycal allylic rearrangement

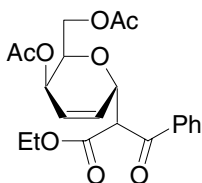
In the presence of Lewis acid catalysts *O*-substituted glycal derivatives can react with *O*-, *S*-, *C*- and, less frequently, *N*-, *P*- and halide nucleophiles to give 2,3-unsaturated glycosyl products.^{1,2} This allylic transformation has been termed the “Ferrier Reaction” or, to avoid complications,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



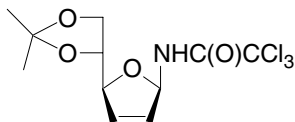
More complex products made directly from the corresponding glycols:



In benzene, $\text{BF}_3 \cdot \text{OEt}_2$,
5 °C, 10 min, (67%,
 α -anomer).⁸

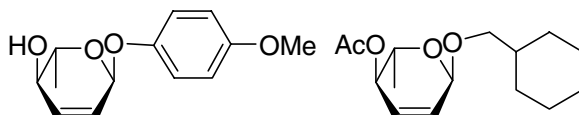


In $\text{PhCOCH}_2\text{CO}_2\text{Et}$,
 $\text{BF}_3 \cdot \text{OEt}_2$,
rt, 15 min,
(81% α -anomer).⁹



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

Products formed without acid catalysts



Promoter:

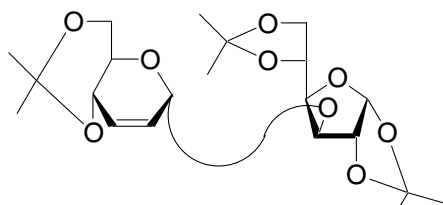
DEAD, Ph_3P
(80%, α -anomer)¹¹

DDQ
(88%, mainly α)¹²

C-3 leaving group of glycol:

hydroxy

acetoxy

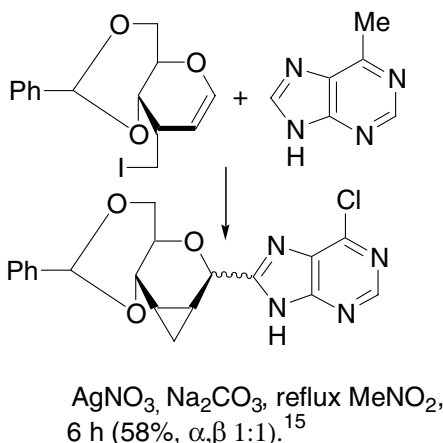
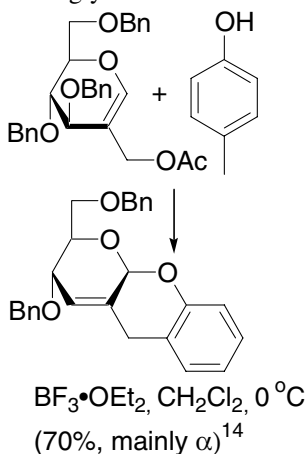


N-iodonium dicollidine perchlorate

(65%, mainly α)¹³

pent-4-enyloxy

Modified glycols and their reactions:

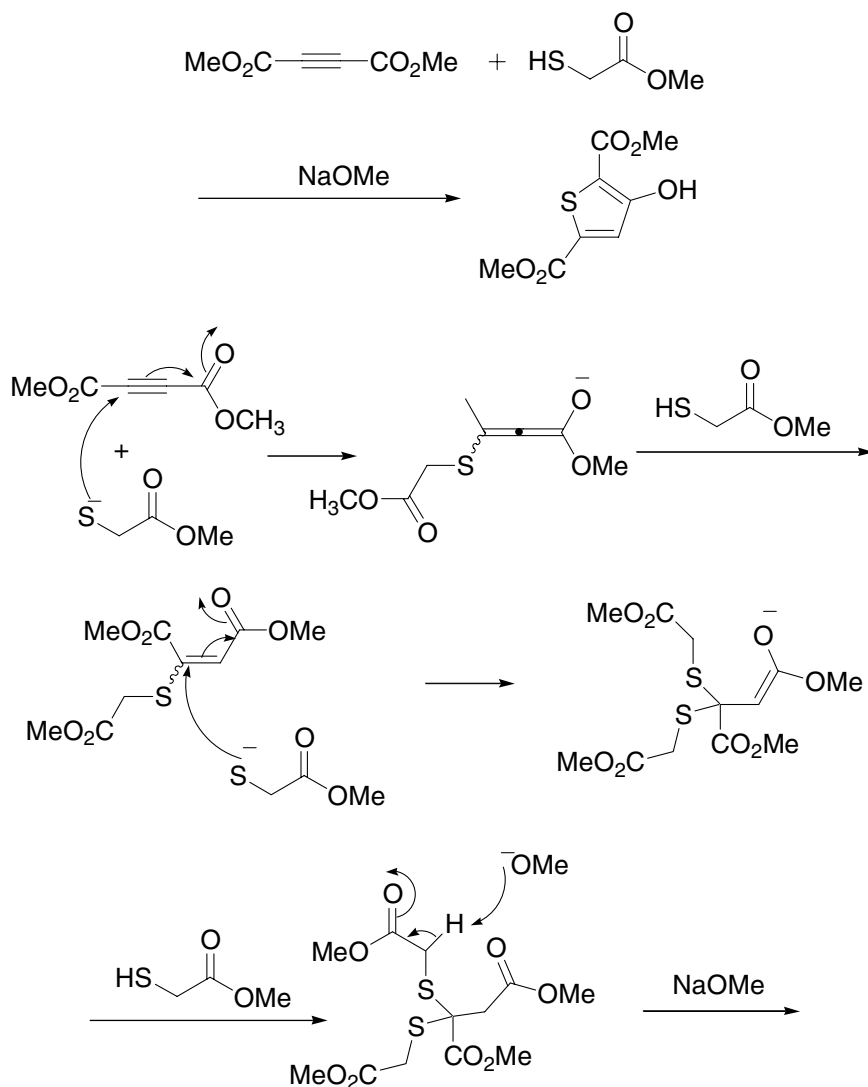


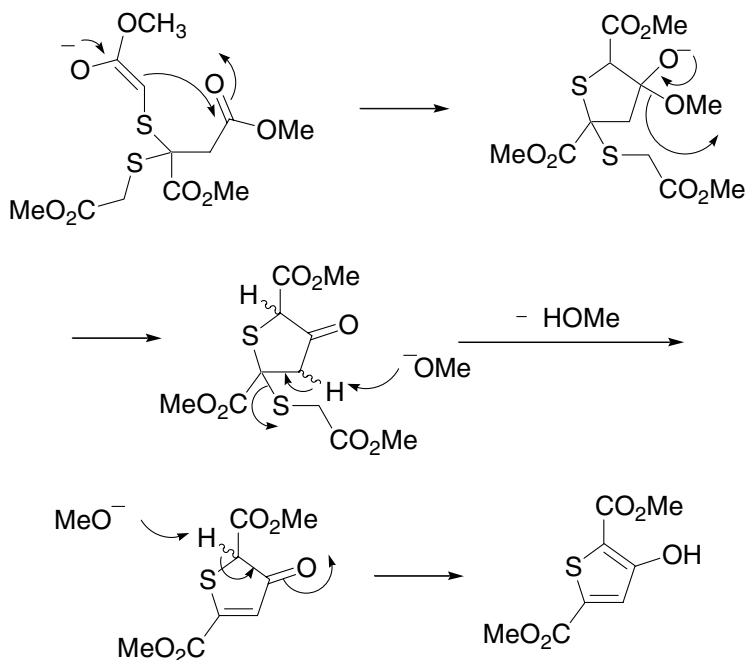
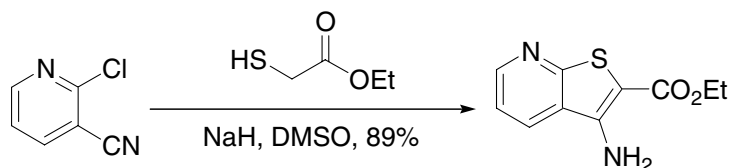
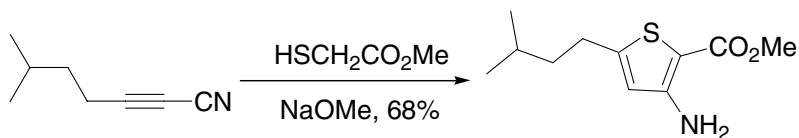
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Fiesselmann thiophene synthesis

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 1⁶Example 2⁸

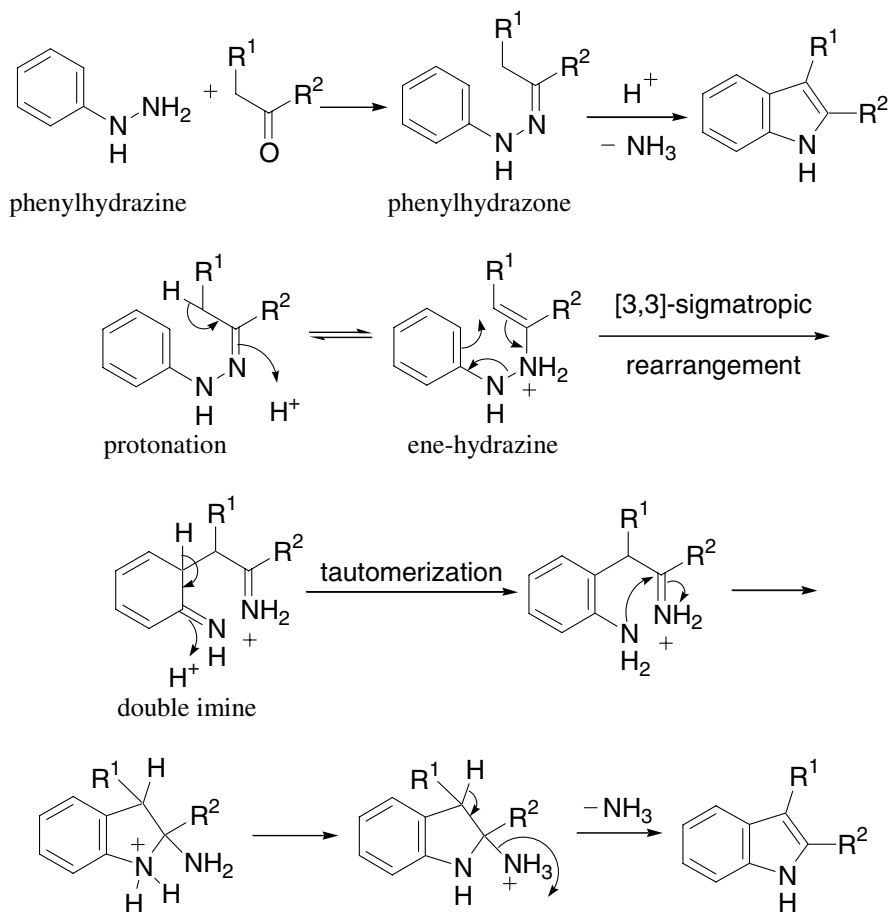
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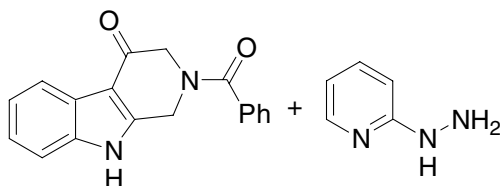
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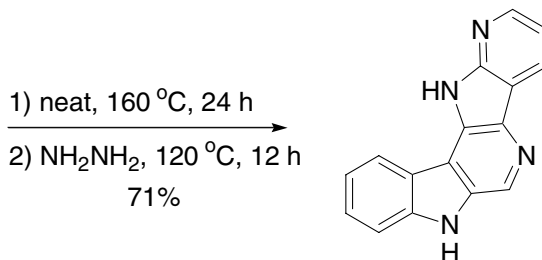
Fischer indole synthesis

Cyclization of arylhydrazones to indoles.

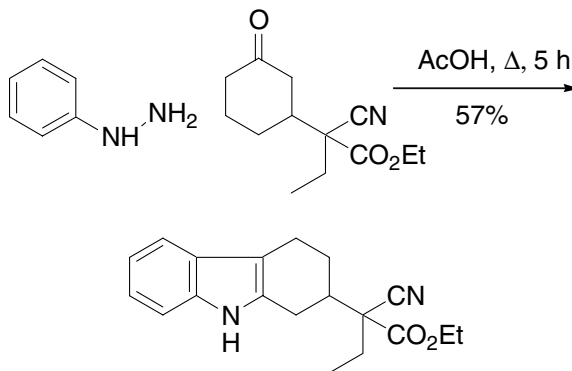


Example 1^{8,12}





Example 2¹³

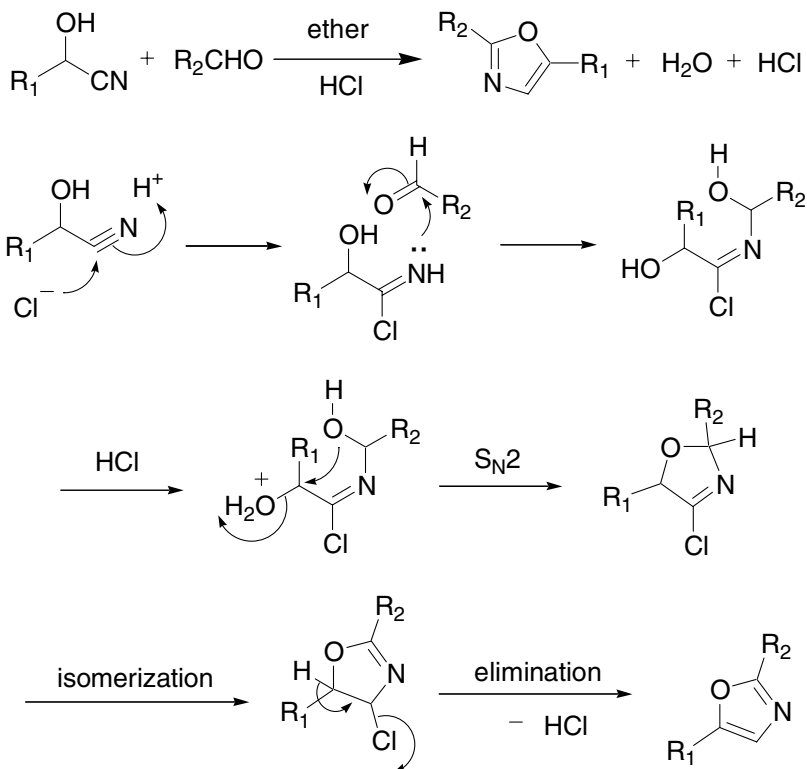


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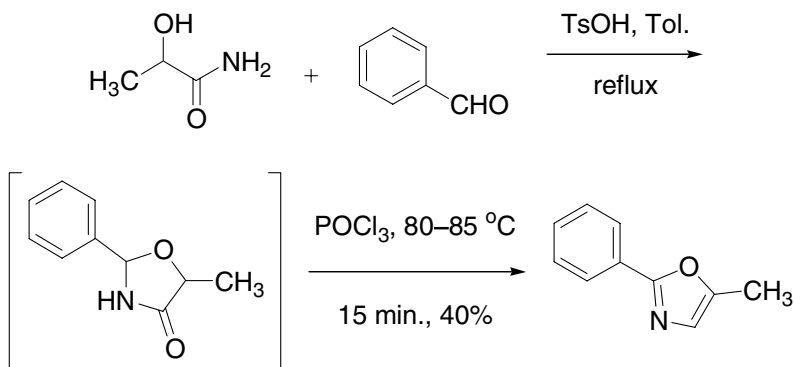
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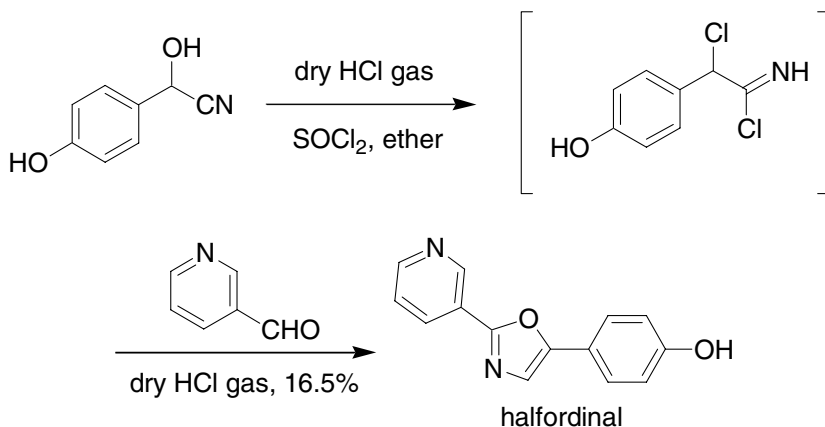
Fischer oxazole synthesis

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



Example 1⁶



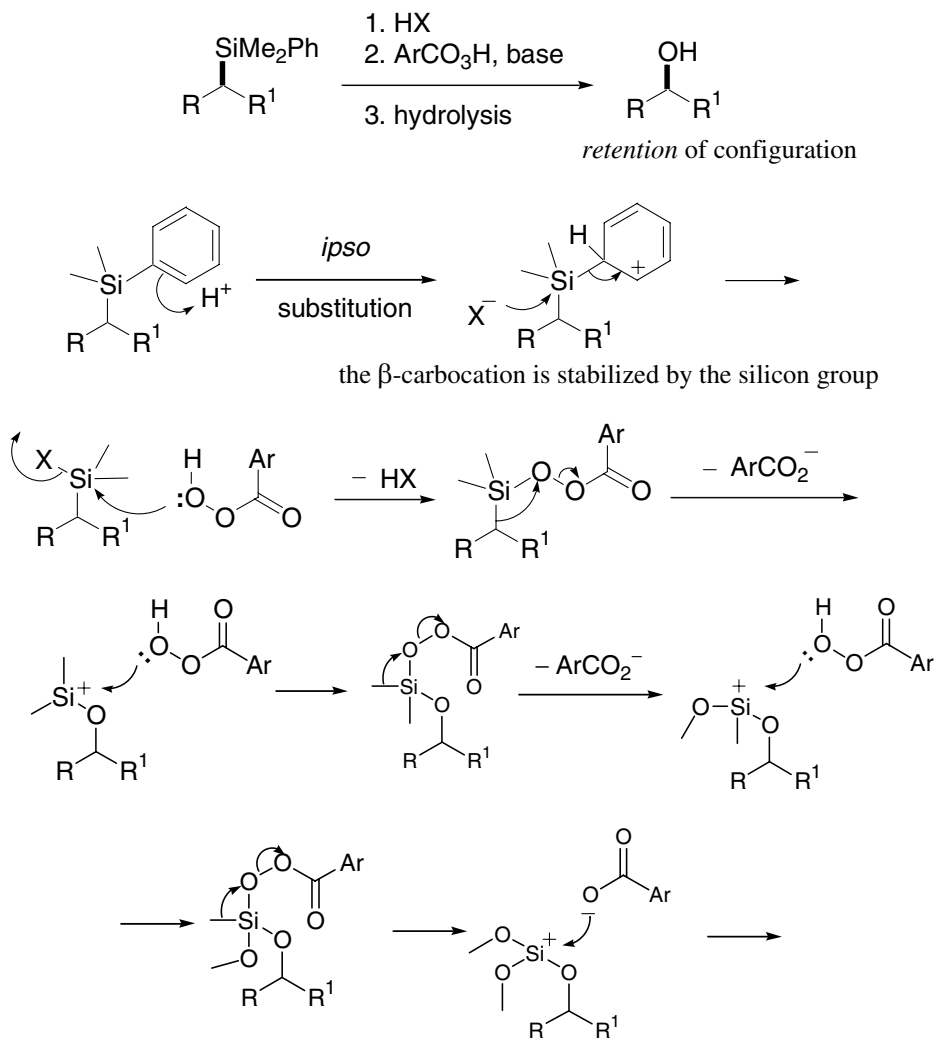
Example 2¹⁰

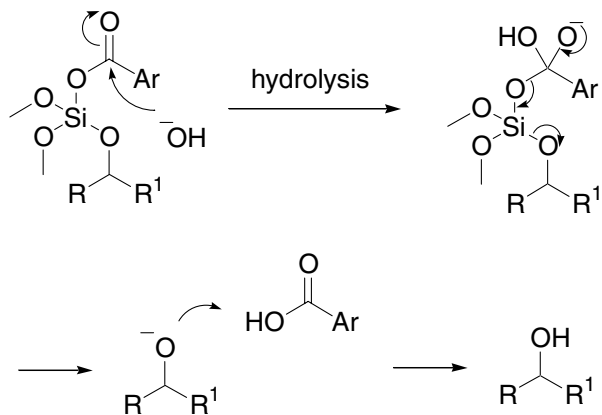
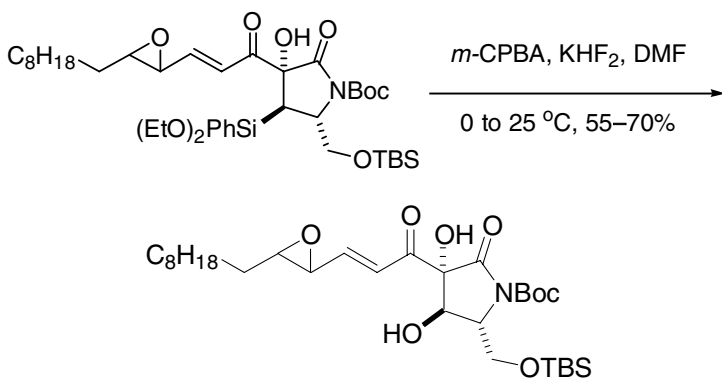
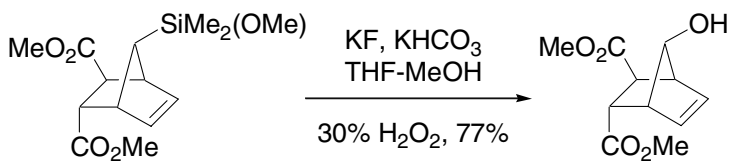
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Fleming–Kumada oxidation

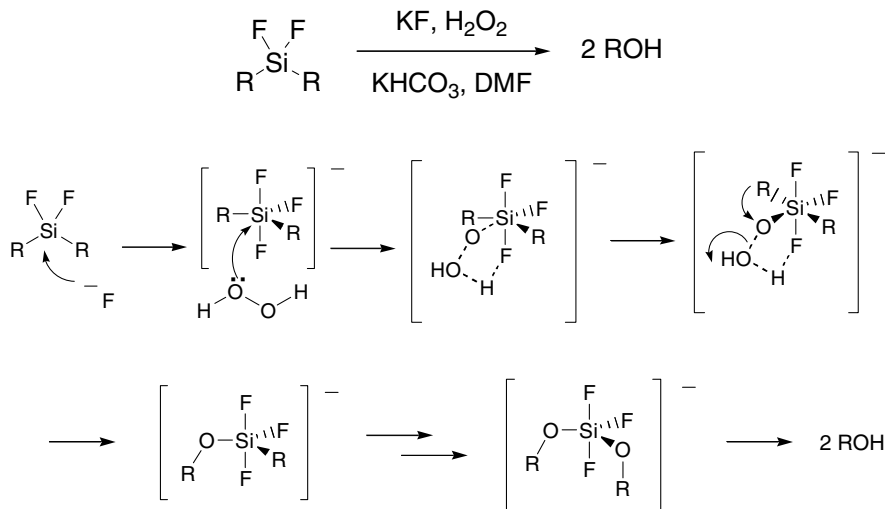
Stereoselective oxidation of alkyl-silanes into the corresponding alkyl-alcohols using peracids.



Example 1⁷Example 2¹²

Tamao–Kumada oxidation¹⁵

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



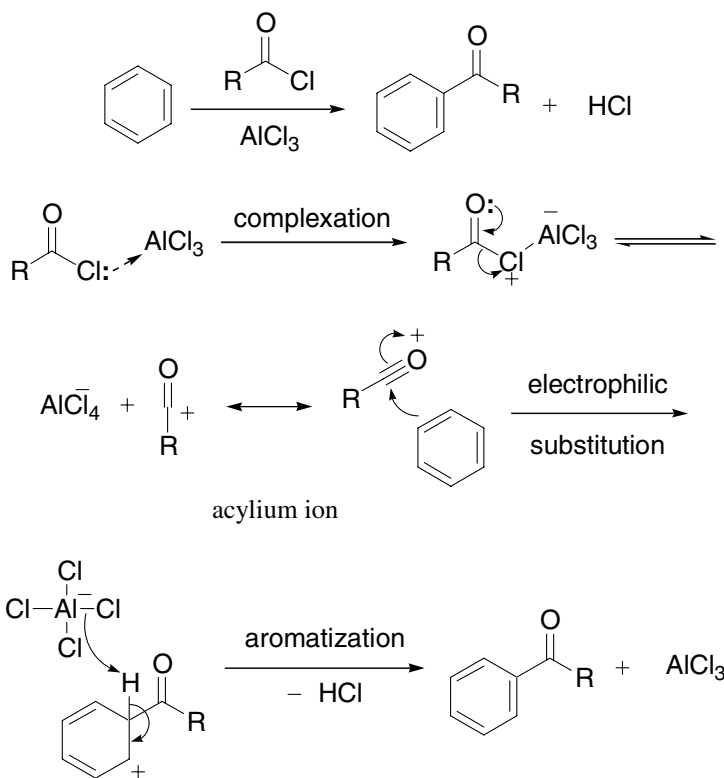
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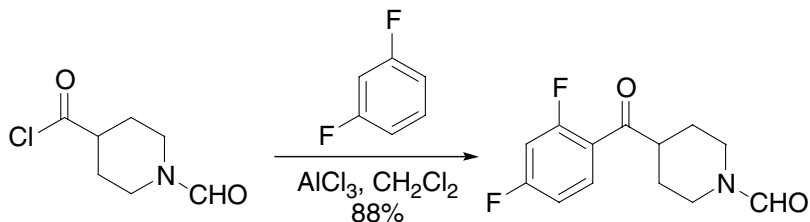
Friedel–Crafts reaction

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.

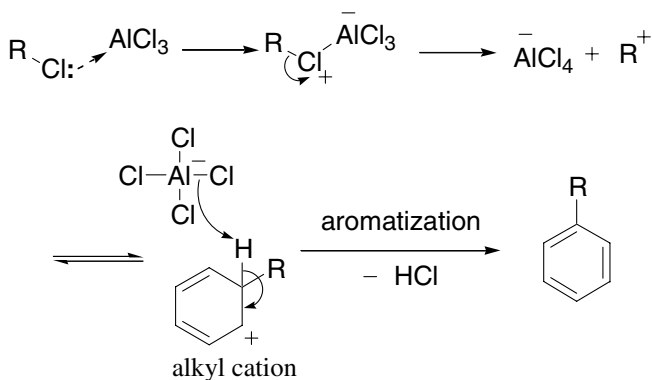


Example 1¹⁶

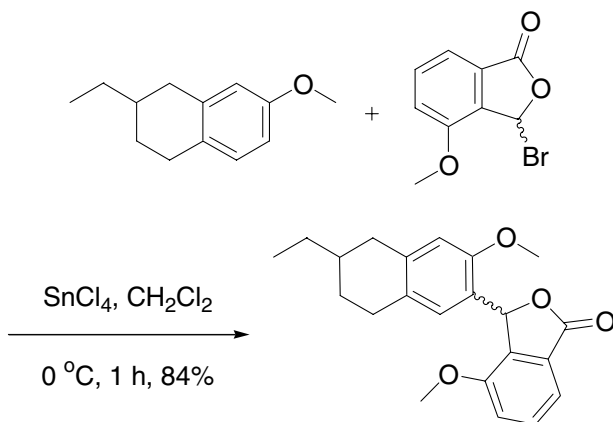


Friedel–Crafts *alkylation* reaction:

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 2⁷



References

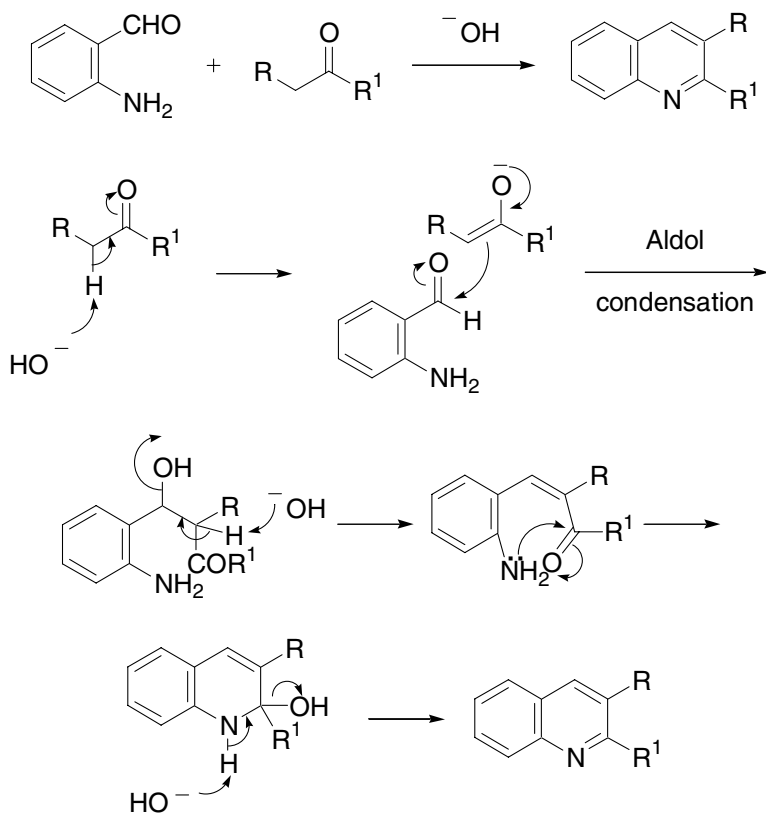
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in 1892 and later served as its president. The discovery of the Friedel–Crafts reaction was the fruit of serendipity and keen observation. In 1877, both Friedel and Crafts were working in Charles A. Wurtz's laboratory. In order to prepare amyl iodide, 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.

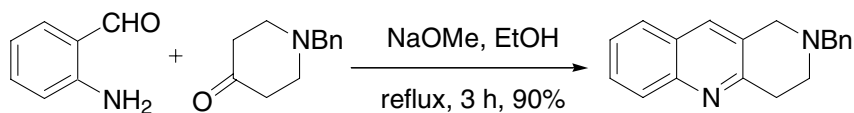
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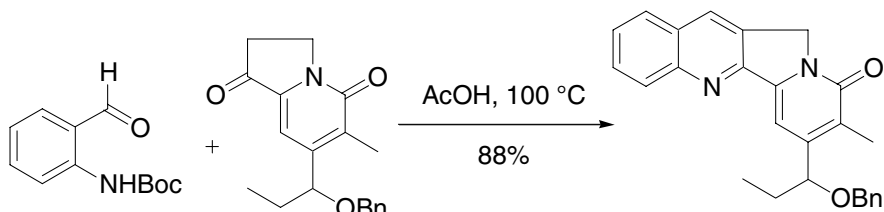
Friedländer quinoline synthesis

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 1⁵



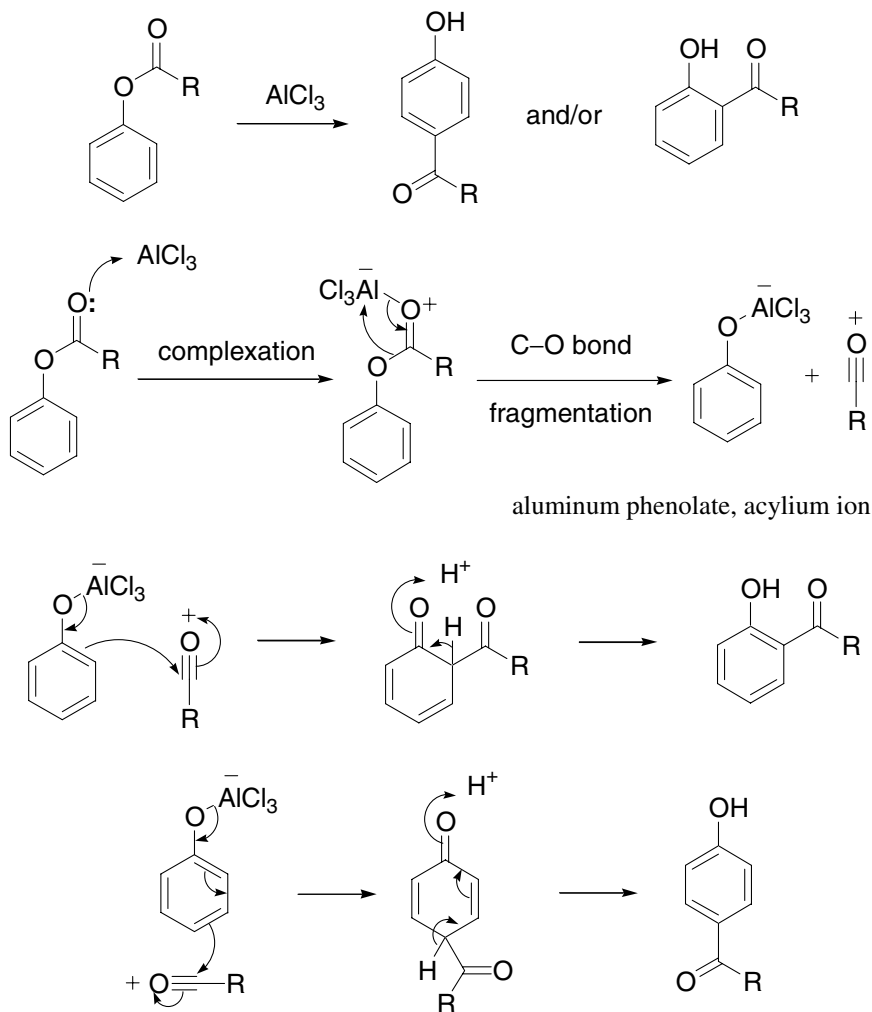
Example 2¹⁵

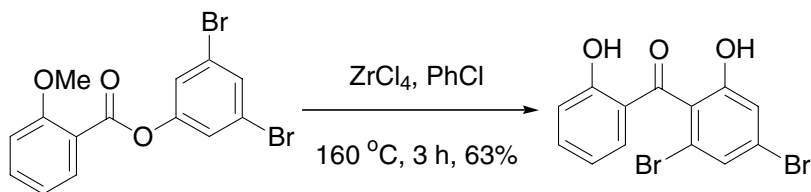
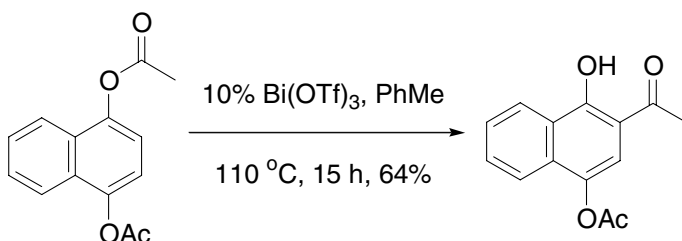
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Fries rearrangement

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



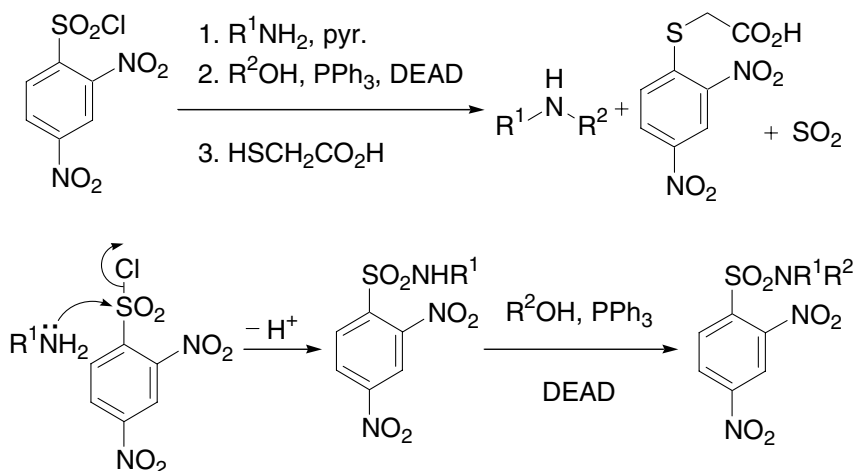
Example 1¹¹Example 2¹²

References

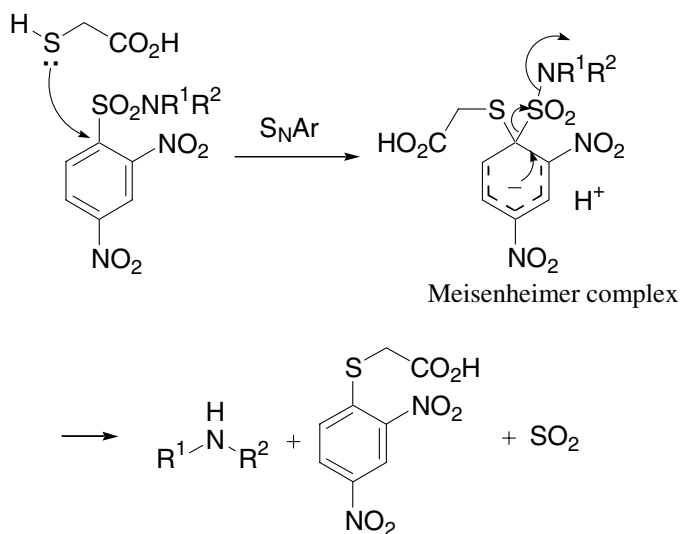
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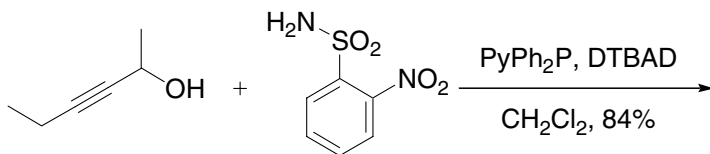
Fukuyama amine synthesis

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

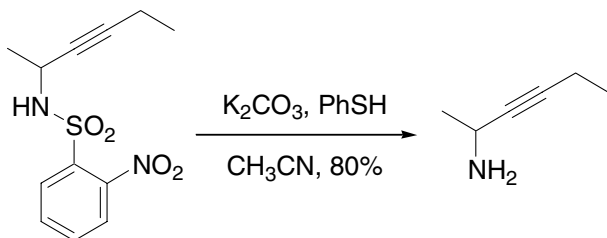


See page 390 for mechanism of the Mitsunobu reaction.



Example 1⁹

PyPh₂P = diphenyl 2-pyridylphosphine; DTBAD = di-*tert*-butylazodicarbonate

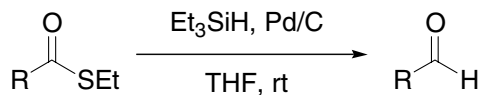


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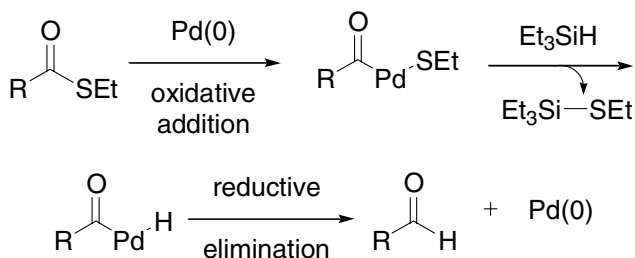
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Fukuyama reduction

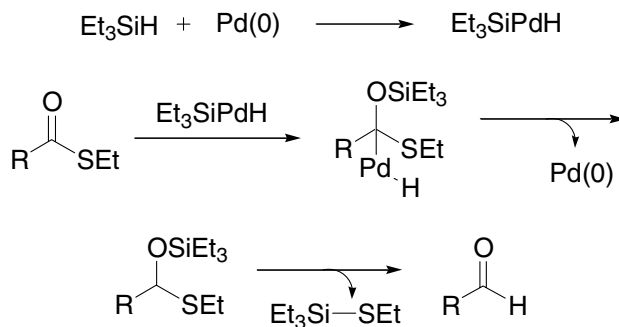
Aldehyde synthesis through reduction of thiol esters with Et_3SiH in the presence of Pd/C catalyst.



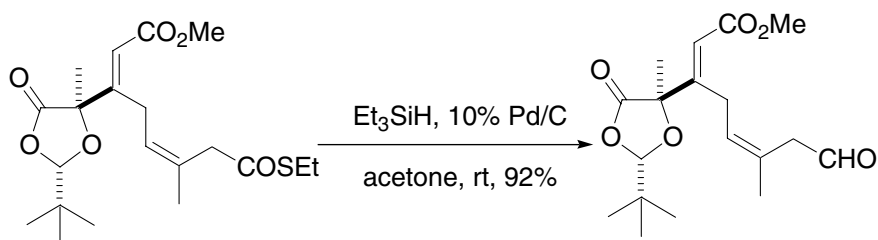
Path A:

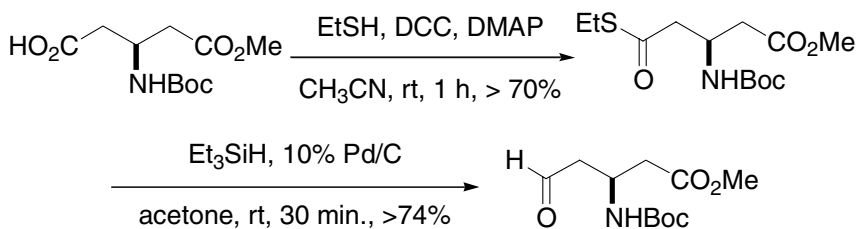


Path B:



Example 1¹



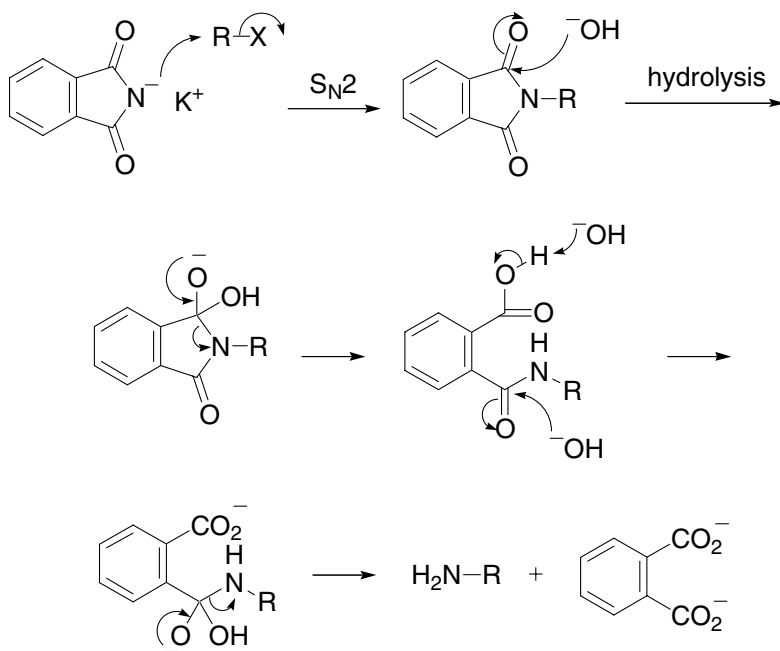
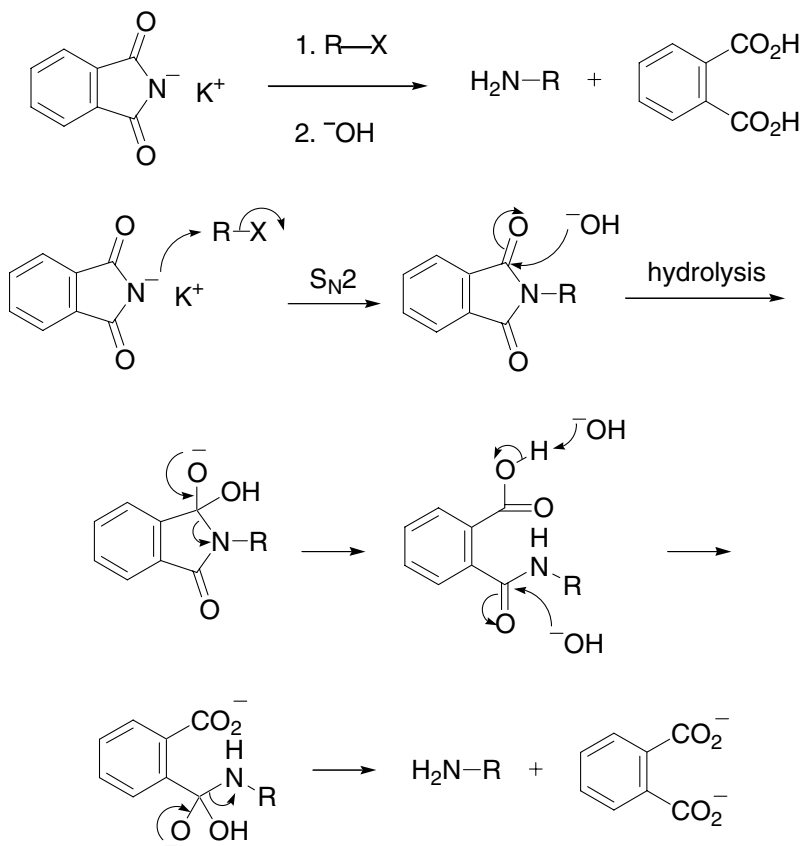
Example 2³

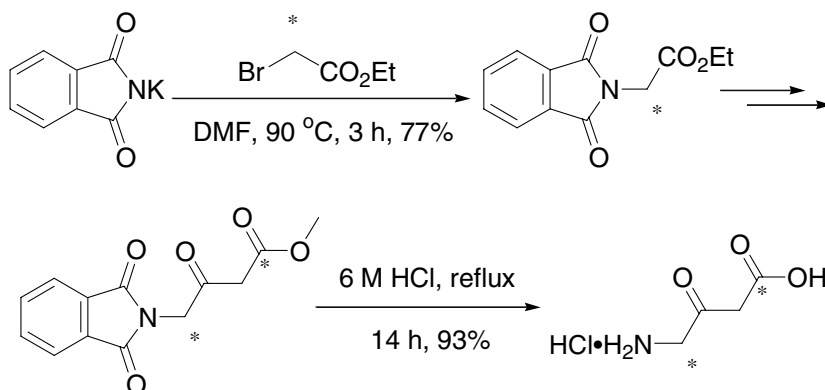
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Gabriel synthesis

Synthesis of primary amines using potassium phthalimide and alkyl halides.



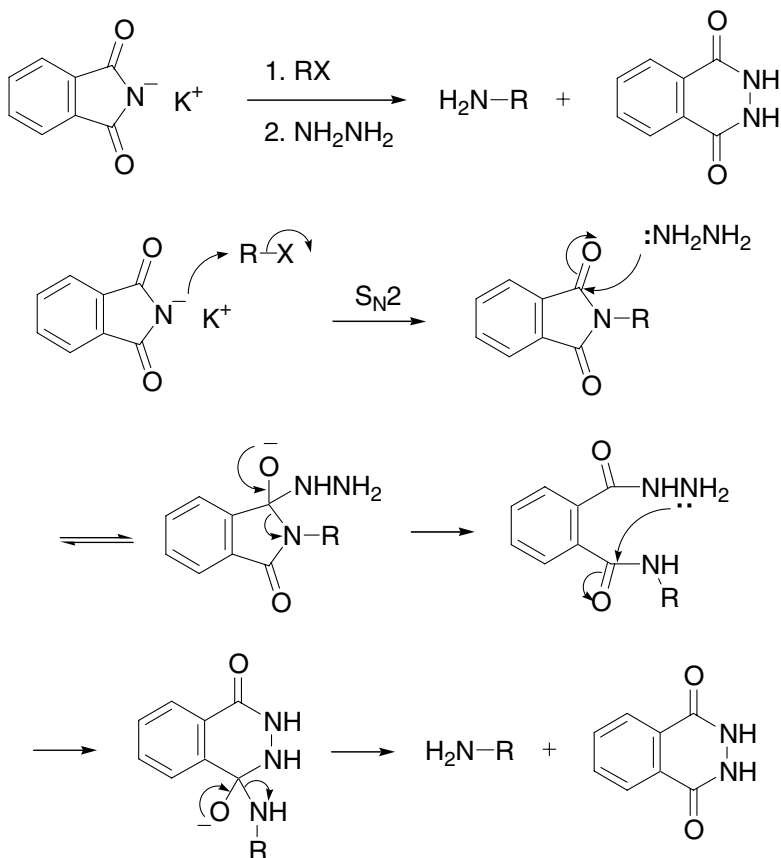
Example 1¹⁰

References

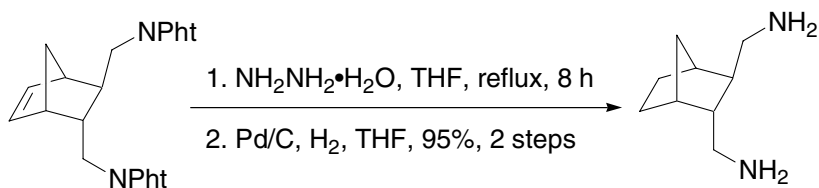
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Ing-Manske procedure

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



Example⁶

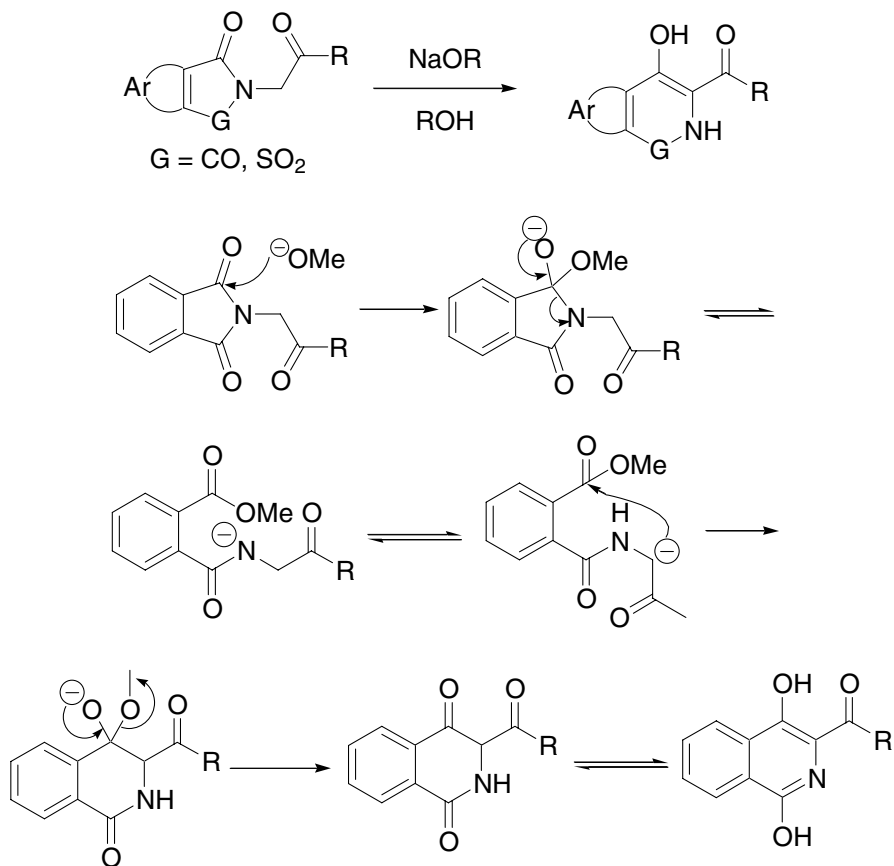


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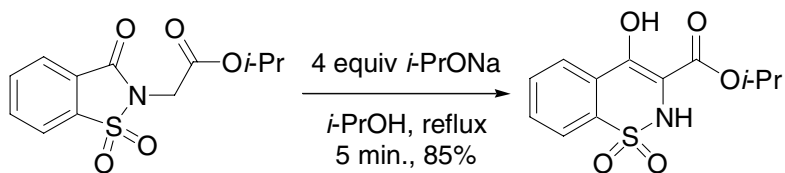
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Gabriel–Colman rearrangement

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



Example¹¹

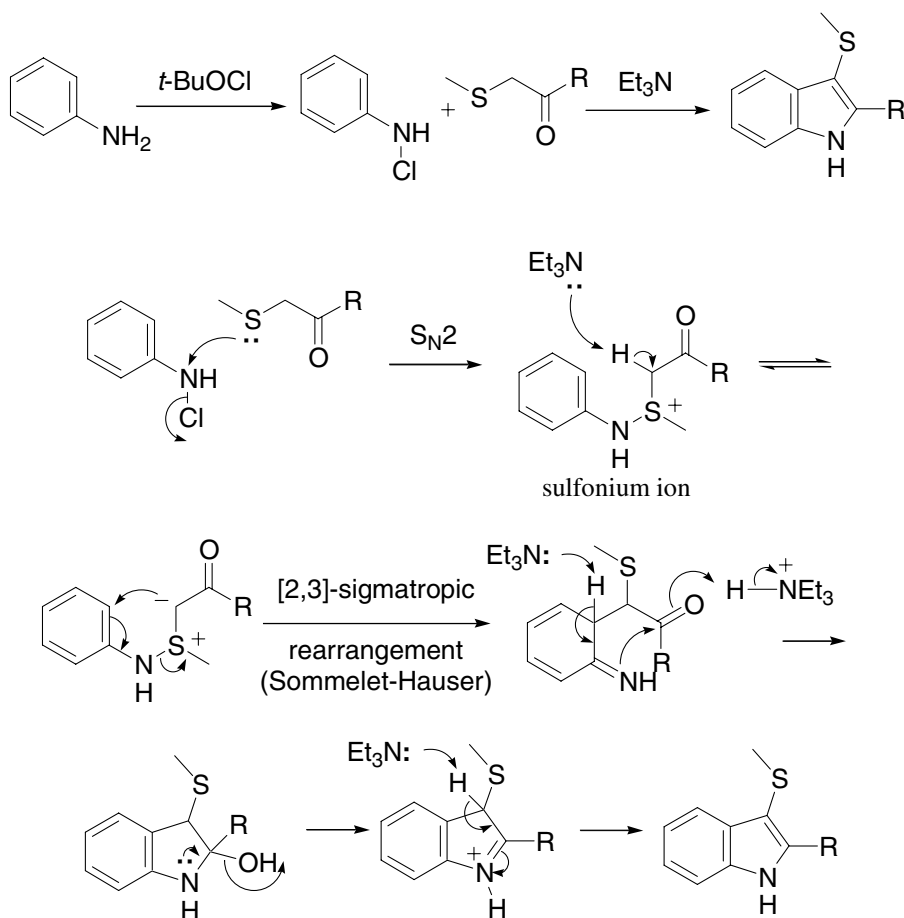


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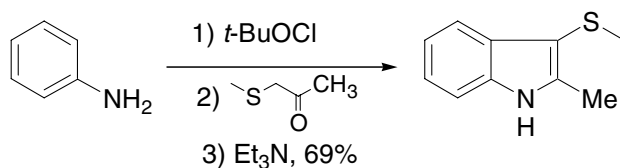
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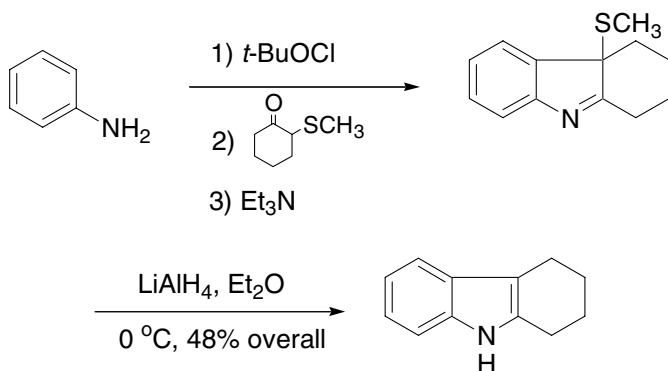
Gassman indole synthesis

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



Example 1¹



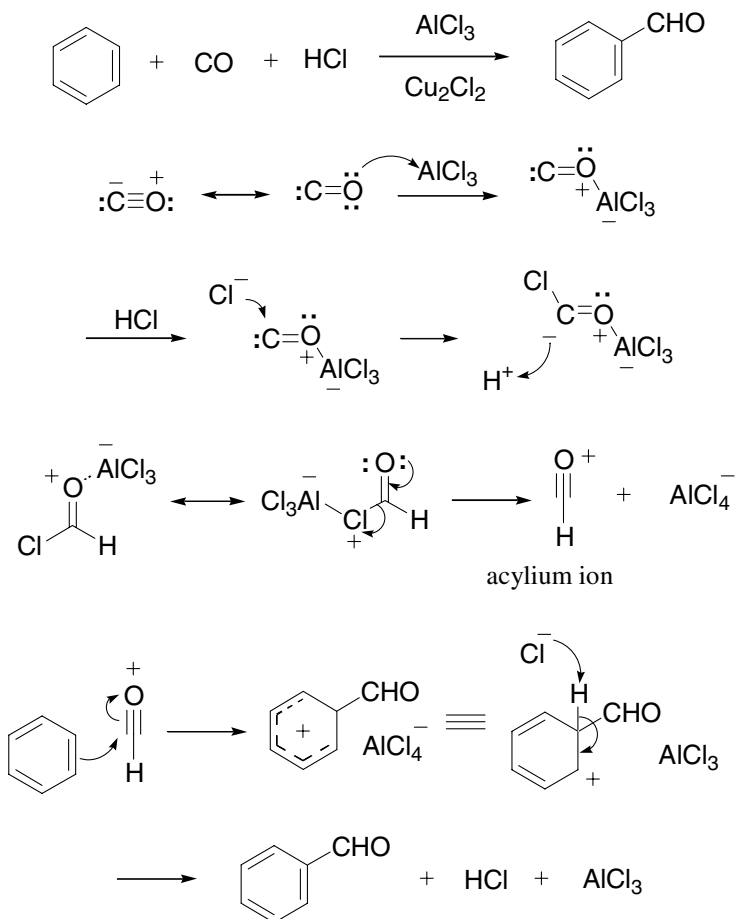
Example 2¹

References

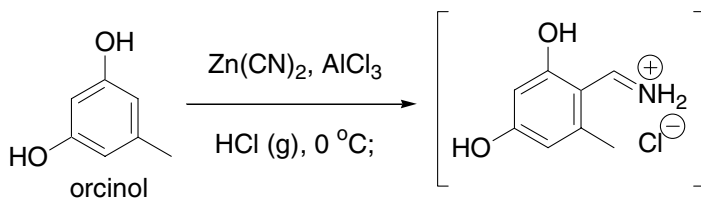
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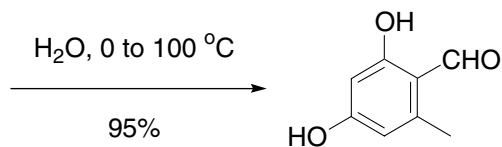
Gattermann–Koch reaction

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



Example, a more practical variant⁴



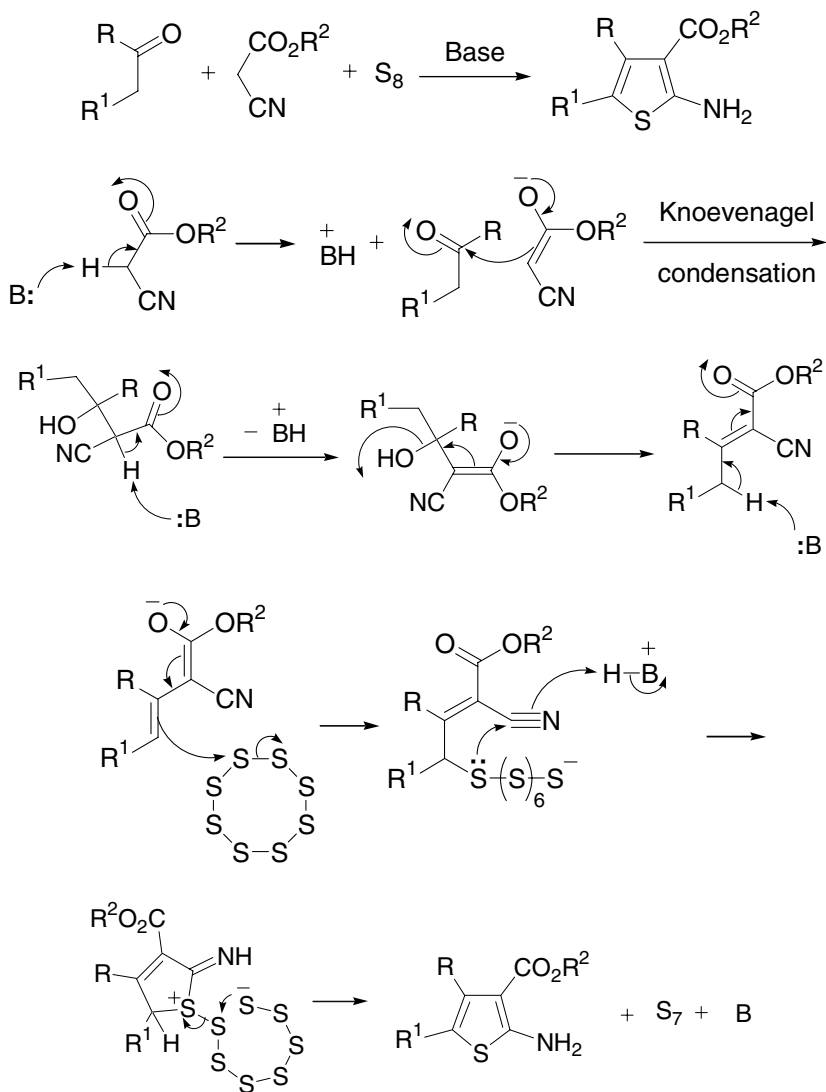


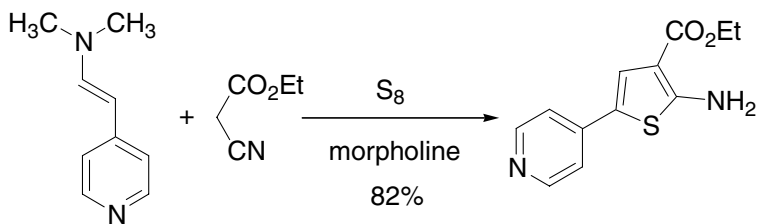
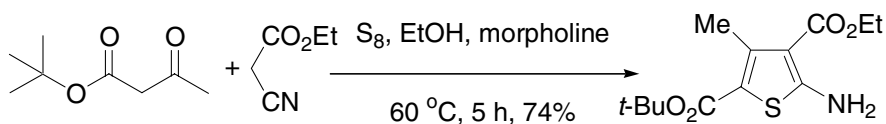
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Gewald aminothiophene synthesis

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



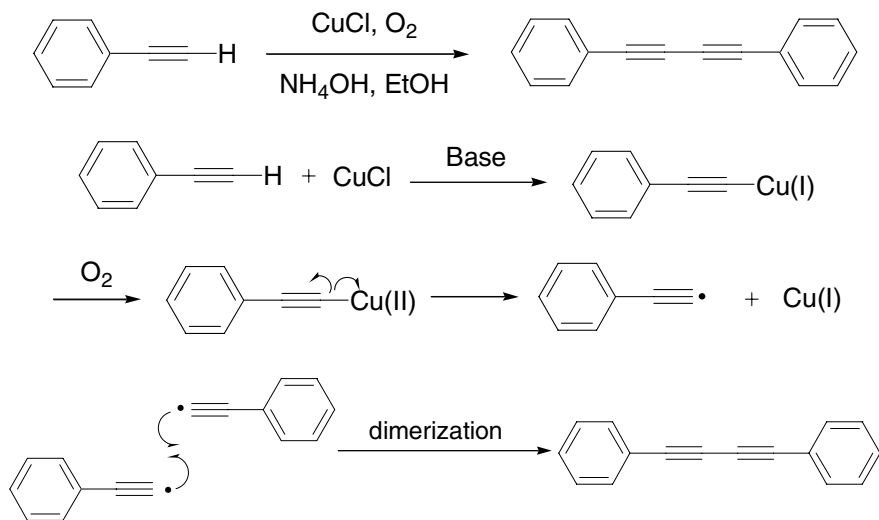
Example 1⁸Example 2¹³

References

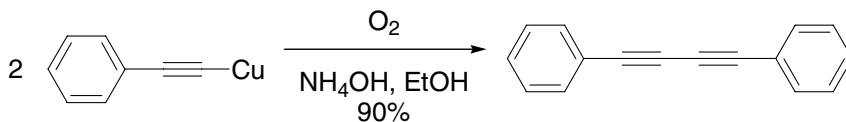
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Glaser coupling

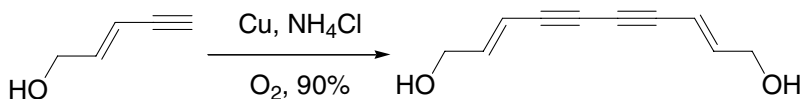
Oxidative homo-coupling of terminal alkynes using copper catalyst in the presence of oxygen.



Example 1¹



Example 2, homo-coupling²



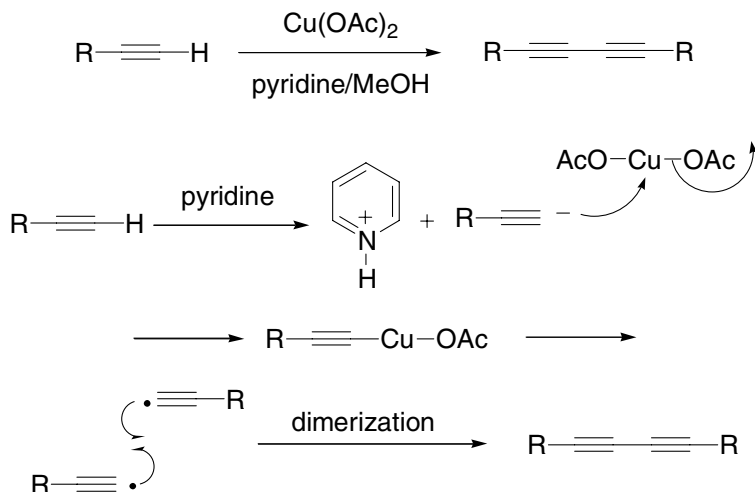
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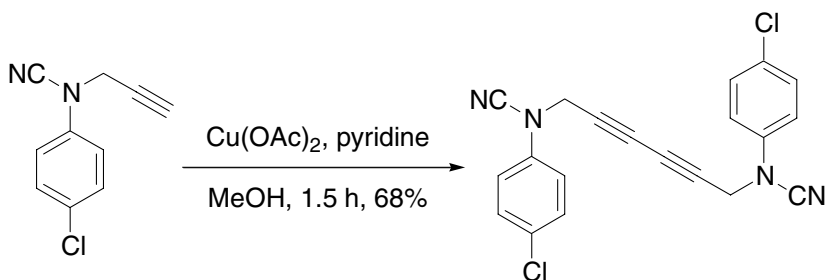
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Eglinton coupling

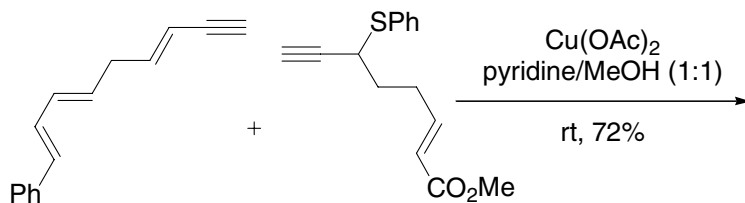
Oxidative homo-coupling of terminal alkynes mediated by stoichiometric (or often excess) $\text{Cu}(\text{OAc})_2$. A variant of the Glaser coupling reaction.

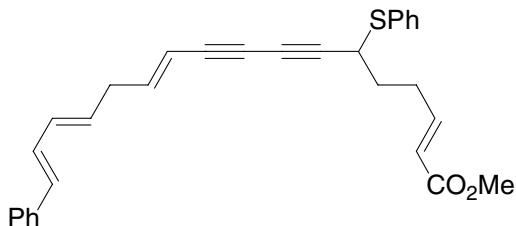


Example 1, homo-coupling⁶



Example 2, cross-coupling⁴



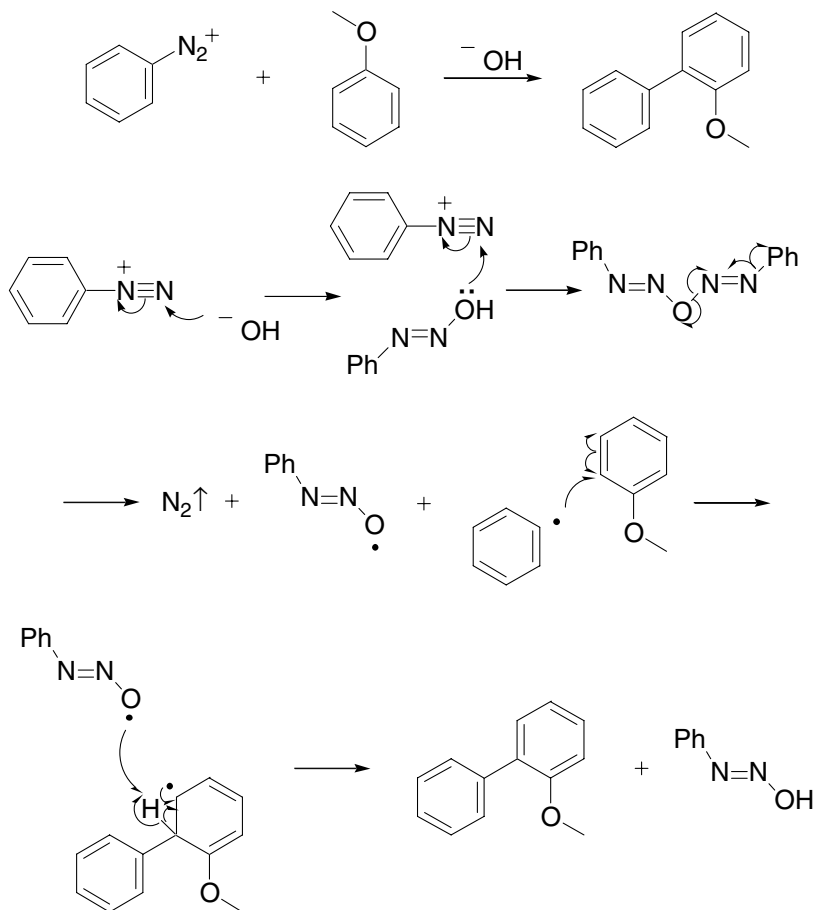


References

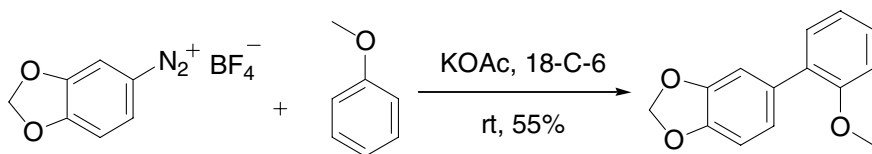
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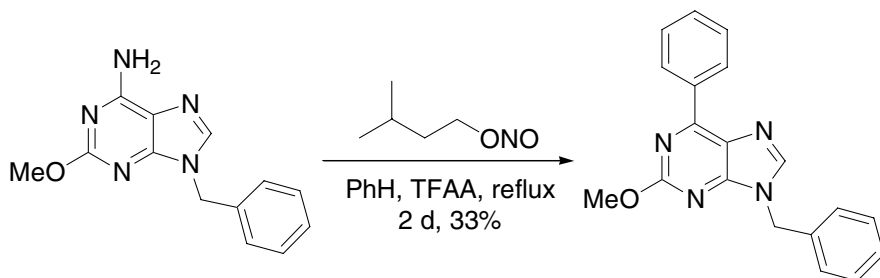
Gomberg–Bachmann reaction

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



Example 1⁴



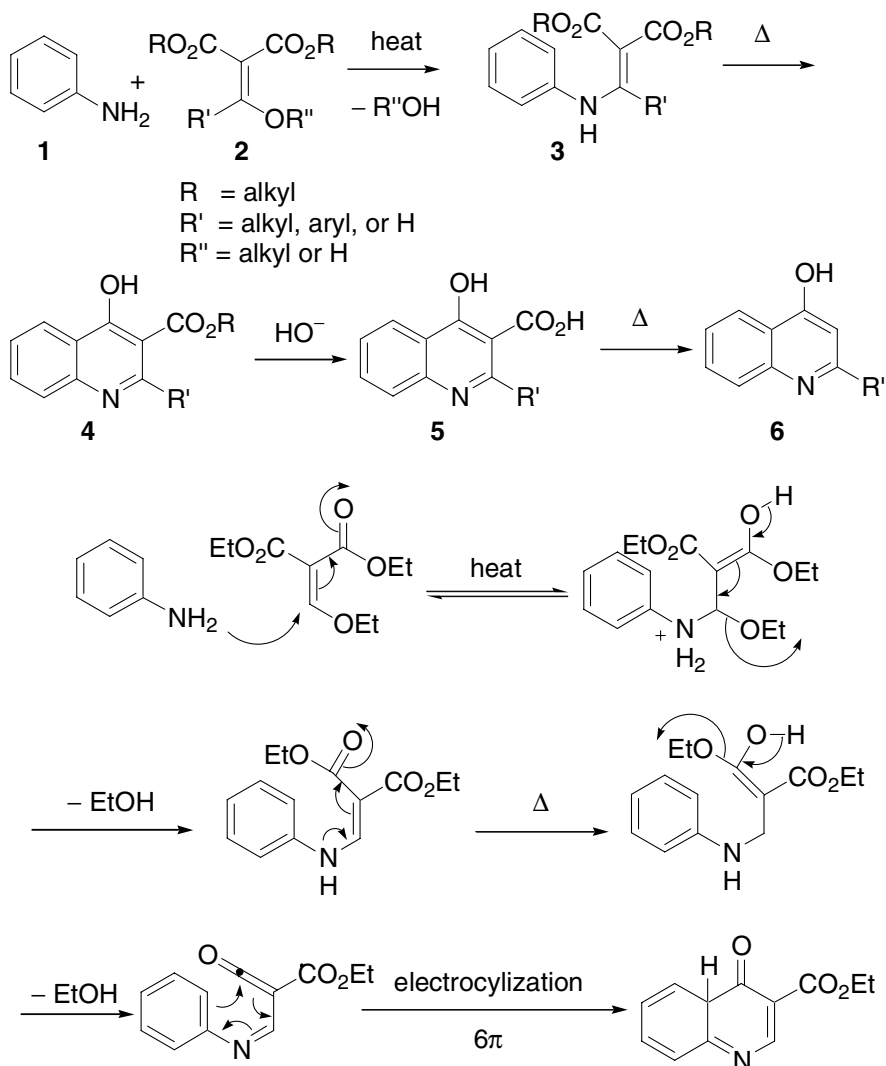
Example 2⁵

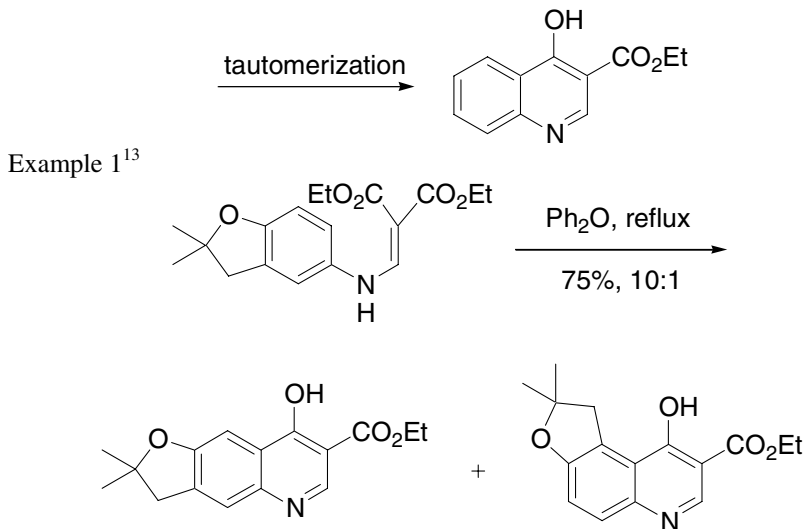
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Gould–Jacobs reaction

The Gould–Jacobs reaction is a sequence of the following reactions: a. condensation of an aniline **1** with either alkoxy methylenemalononic ester or acyl malonic ester **2** providing the anilidomethylenemalononic 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**.



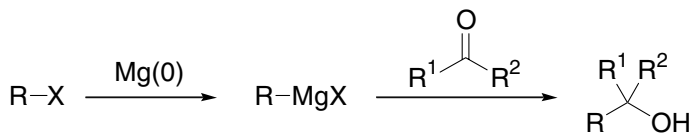


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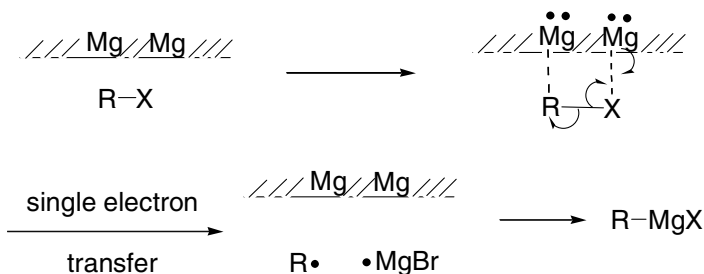
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Grignard reaction

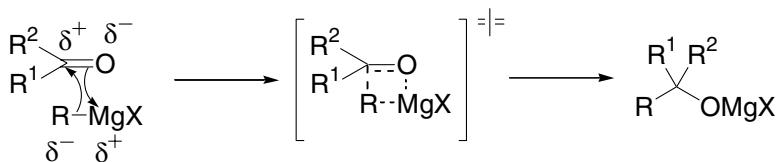
Addition of organomagnesium compounds (Grignard reagents), generated from organohalides and magnesium metal, to electrophiles.



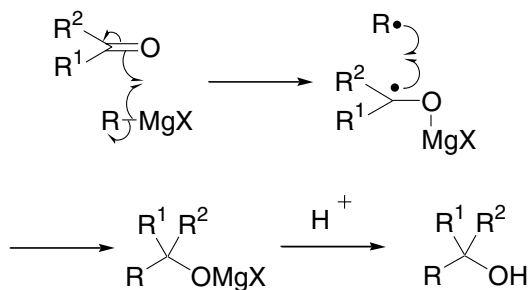
Formation of the Grignard reagent:

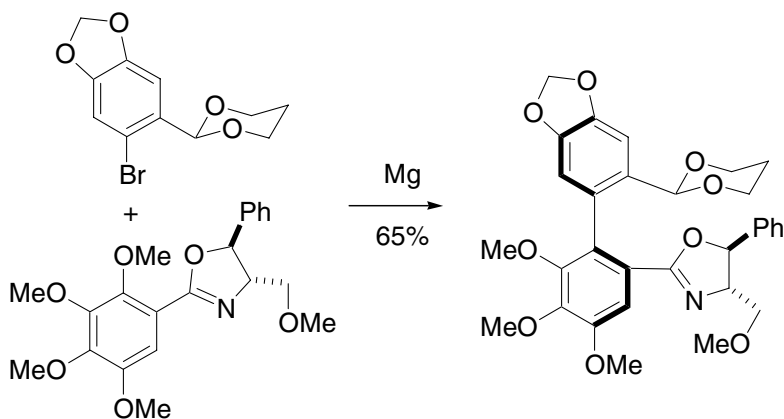
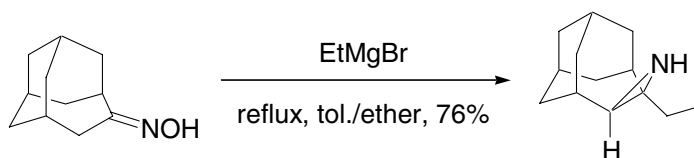


Grignard reaction, ionic mechanism:



Radical mechanism,



Example 1⁶Example 2⁴

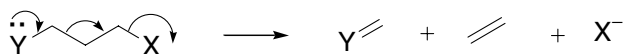
This reaction is known as the **Hoch–Campbell aziridine synthesis**, which entails treatment of ketoximes with excess Grignard reagents and subsequent hydrolysis of the organometallic complex to produce aziridines.

References

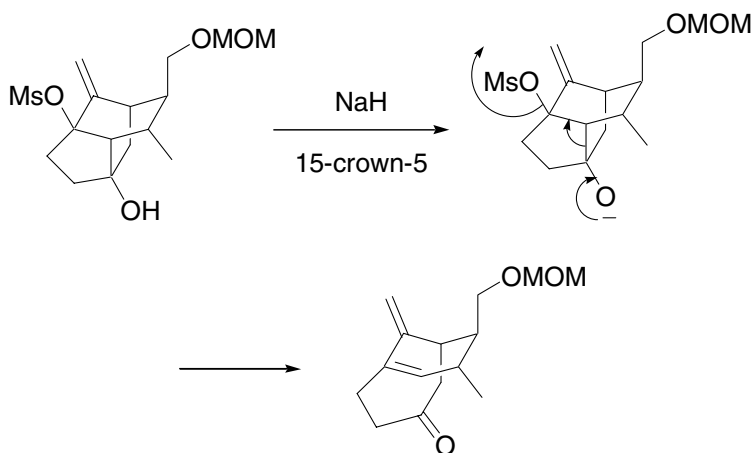
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Grob fragmentation

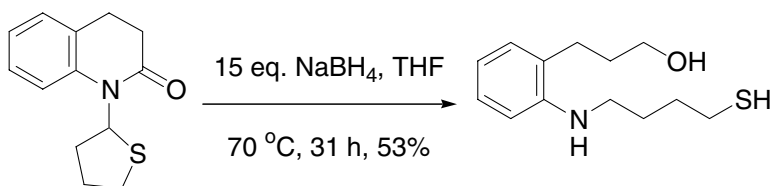
C—C bond cleavage primarily via a concerted process involving a five atom system. General scheme:

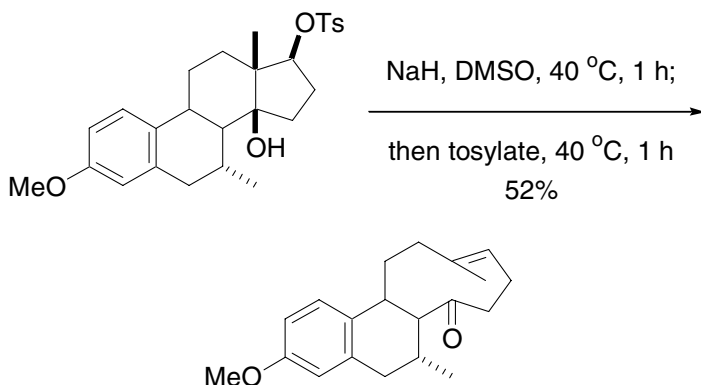


Example 1



Example 2, aza-Grob fragmentation⁷



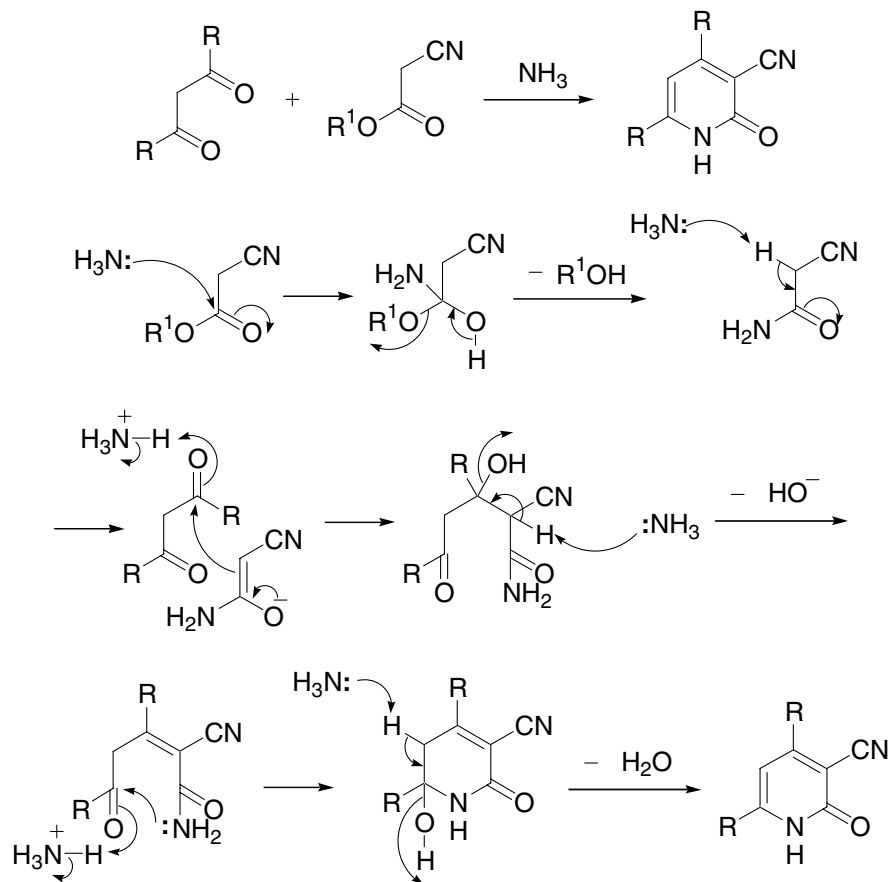
Example 3¹²

References

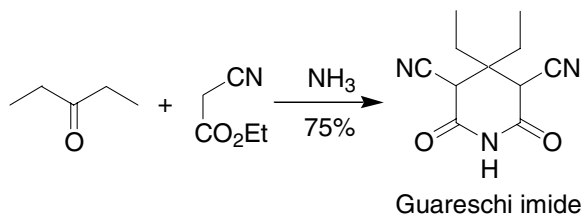
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Guareschi–Thorpe condensation

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



Example⁷

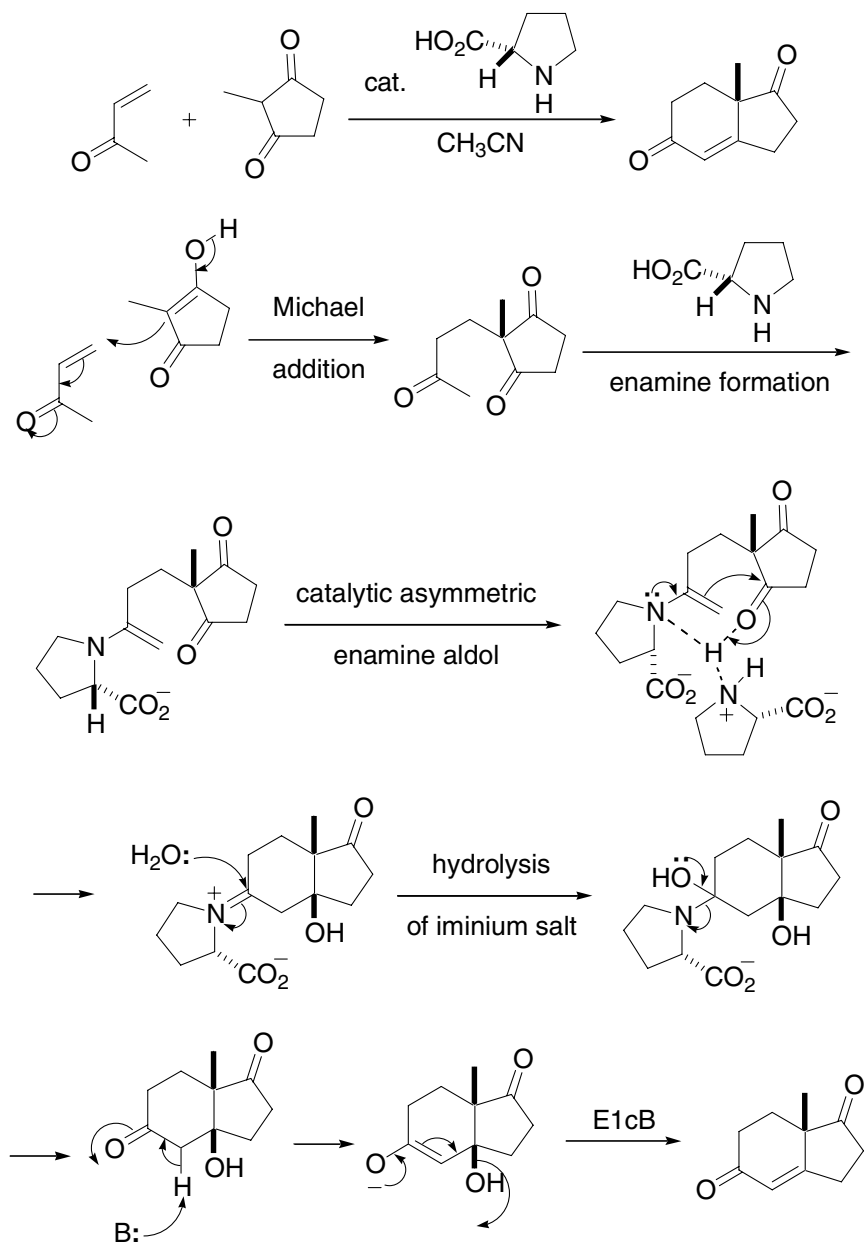


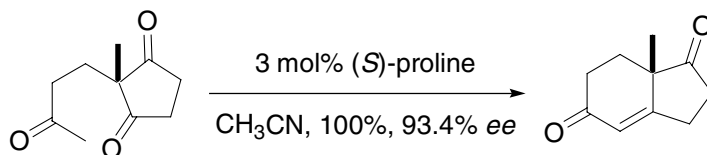
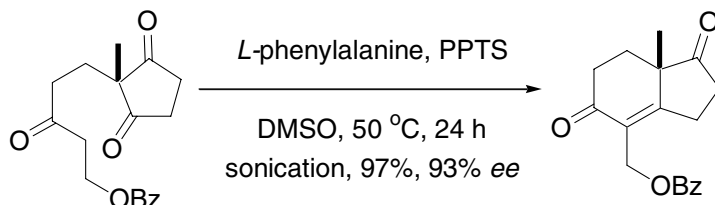
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Hajos–Wiechert reaction

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



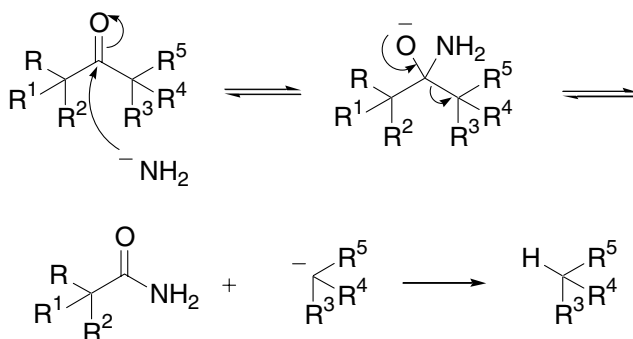
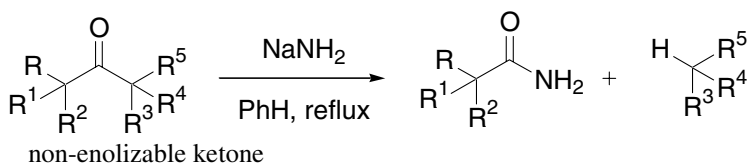
Example 1¹Example 2⁹

References

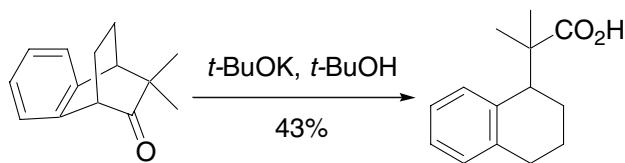
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Haller–Bauer reaction

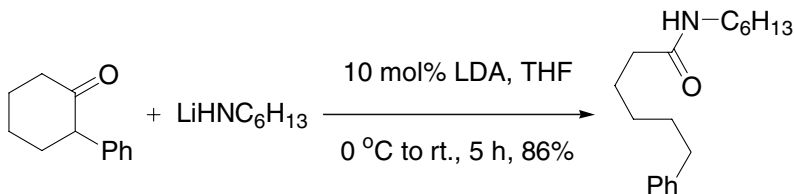
Base-induced cleavage of non-enolizable ketones leading to carboxylic amide derivative and a neutral fragment in which the carbonyl group is replaced by a hydrogen.



Example 1⁴



Example 2¹²

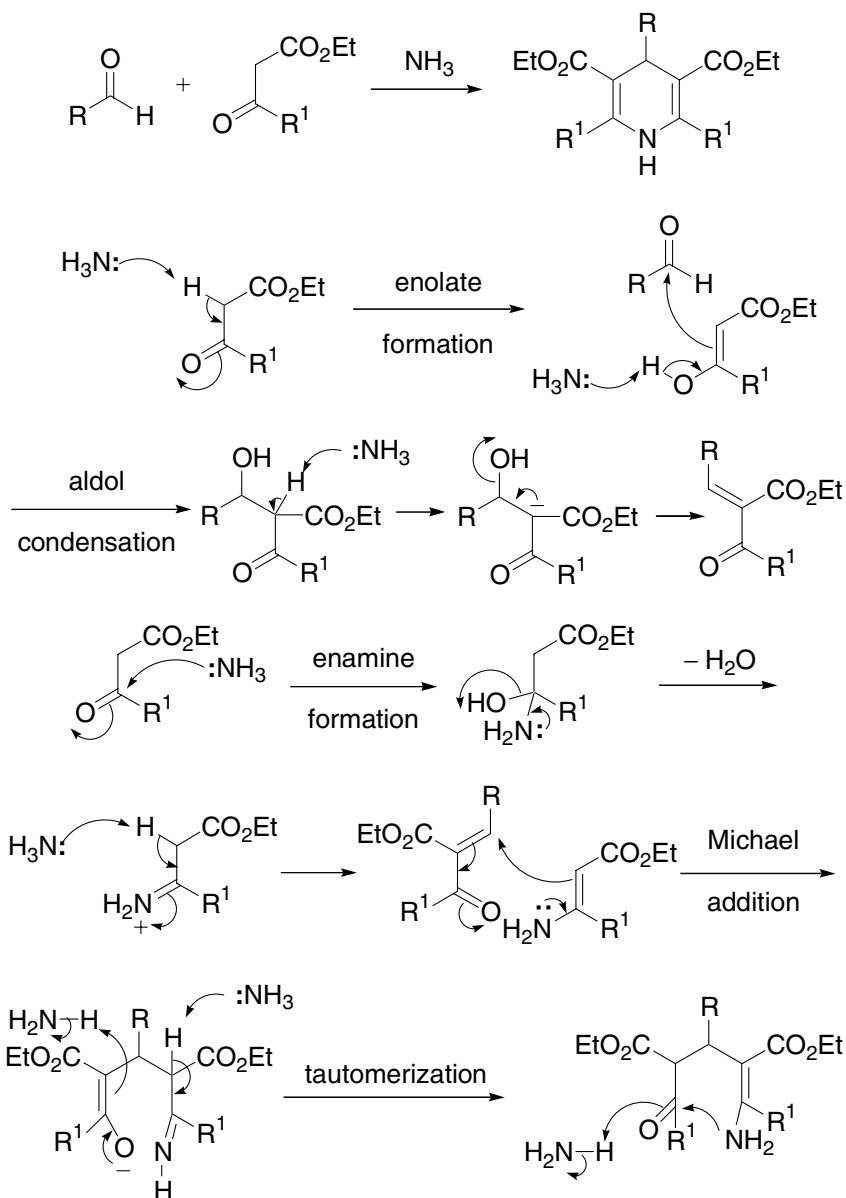


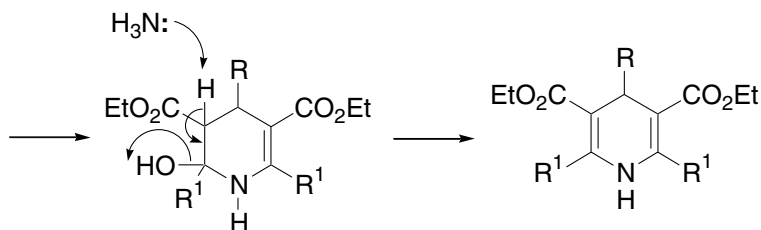
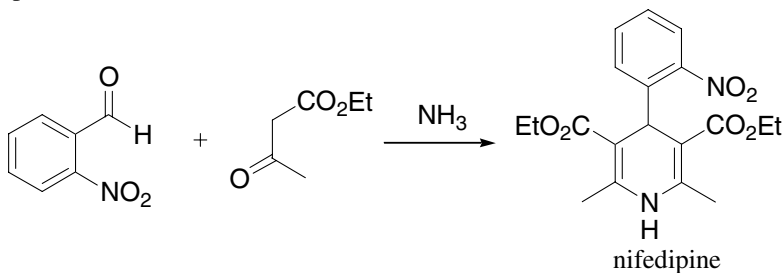
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Hantzsch dihydropyridine synthesis

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



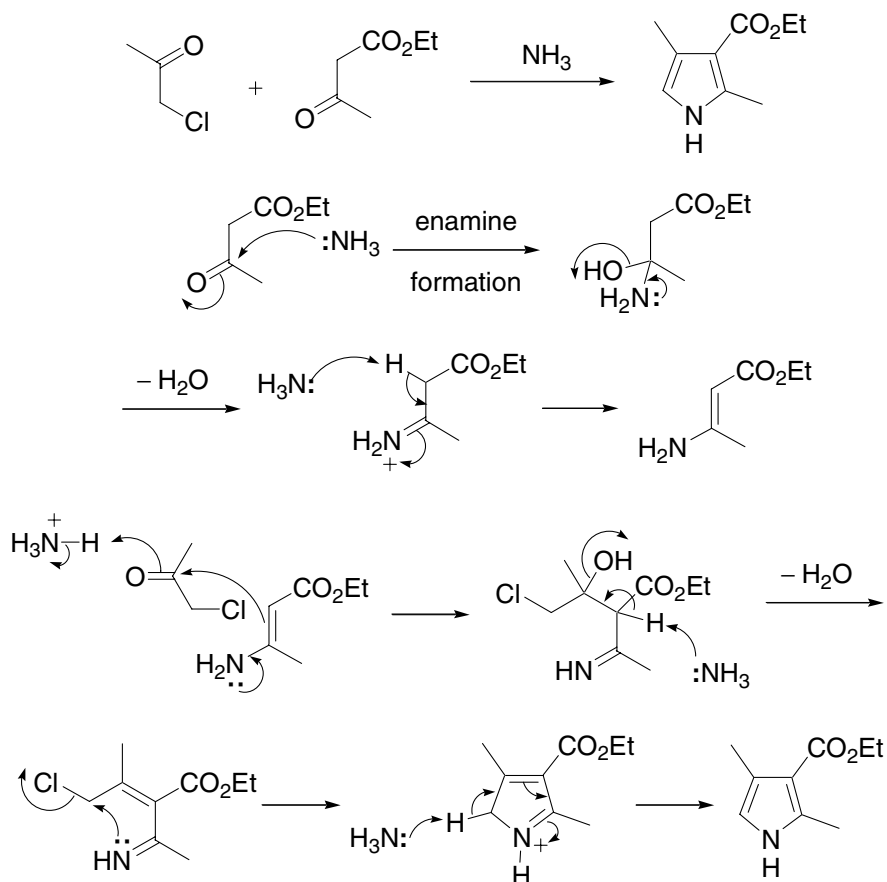
Example 1⁶

References

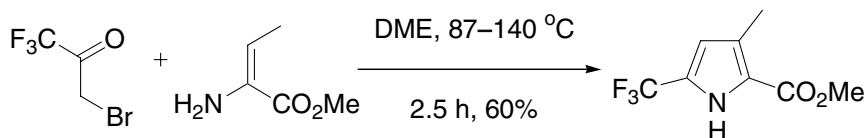
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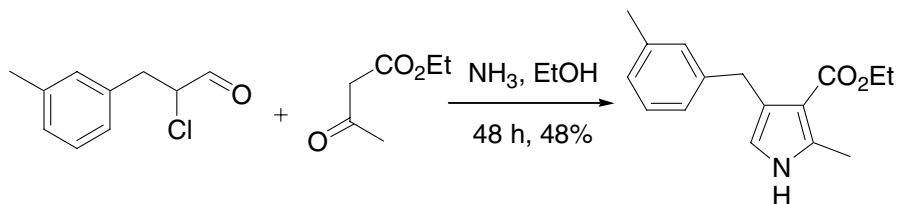
Hantzsch pyrrole synthesis

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



Example 1⁵



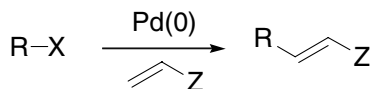
Example 2⁸

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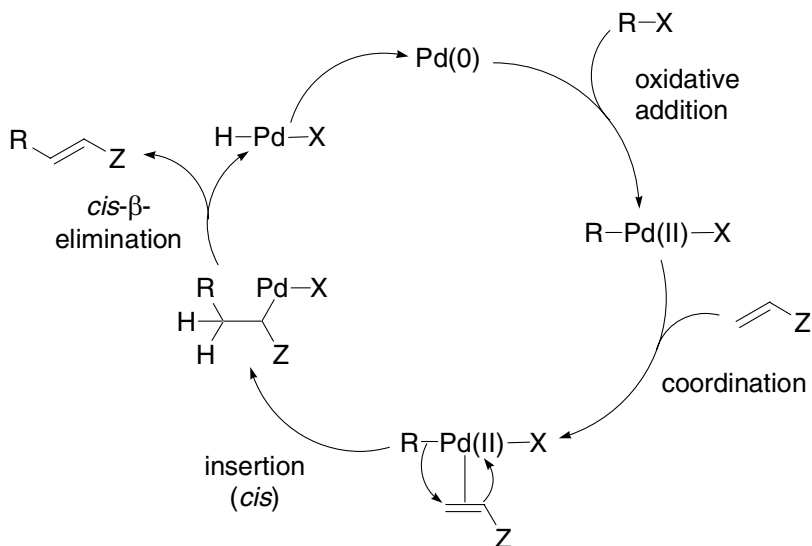
Heck reaction

Palladium-catalyzed coupling between organohalides or triflates with olefins.

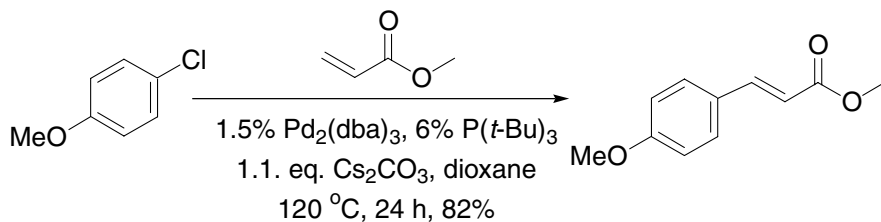


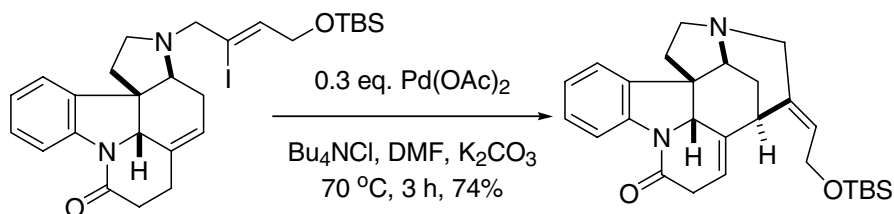
$\text{X} = \text{I}, \text{Br}, \text{OTf}, \text{Cl}, \text{etc.}$

$\text{Z} = \text{H}, \text{R}, \text{Ar}, \text{CN}, \text{CO}_2\text{R}, \text{OR}, \text{OAc}, \text{NHAc}, \text{etc.}$



Example 1⁷



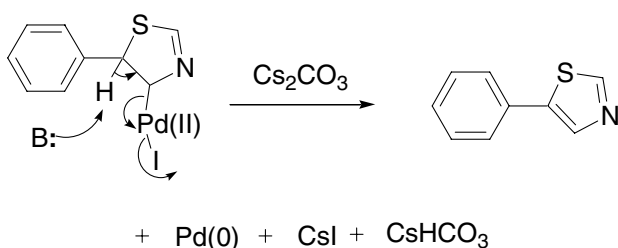
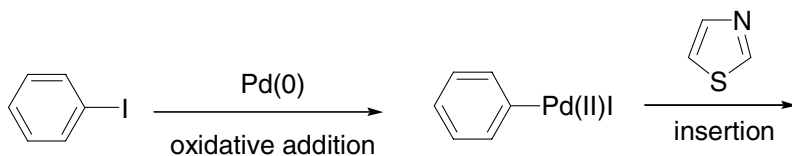
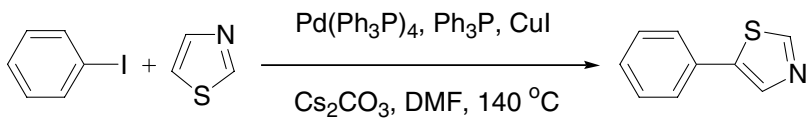
Example 2⁶

References

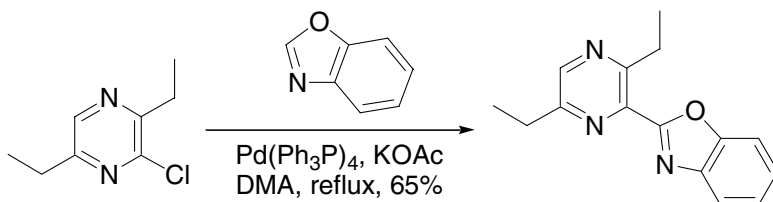
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Heteroaryl Heck reaction

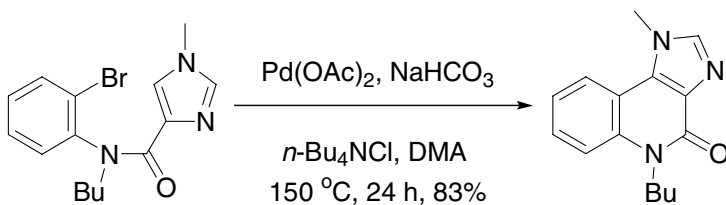
Intermolecular or intramolecular Heck reaction that occurs onto a heteroaryl recipient.



Example 1³



Example 2²

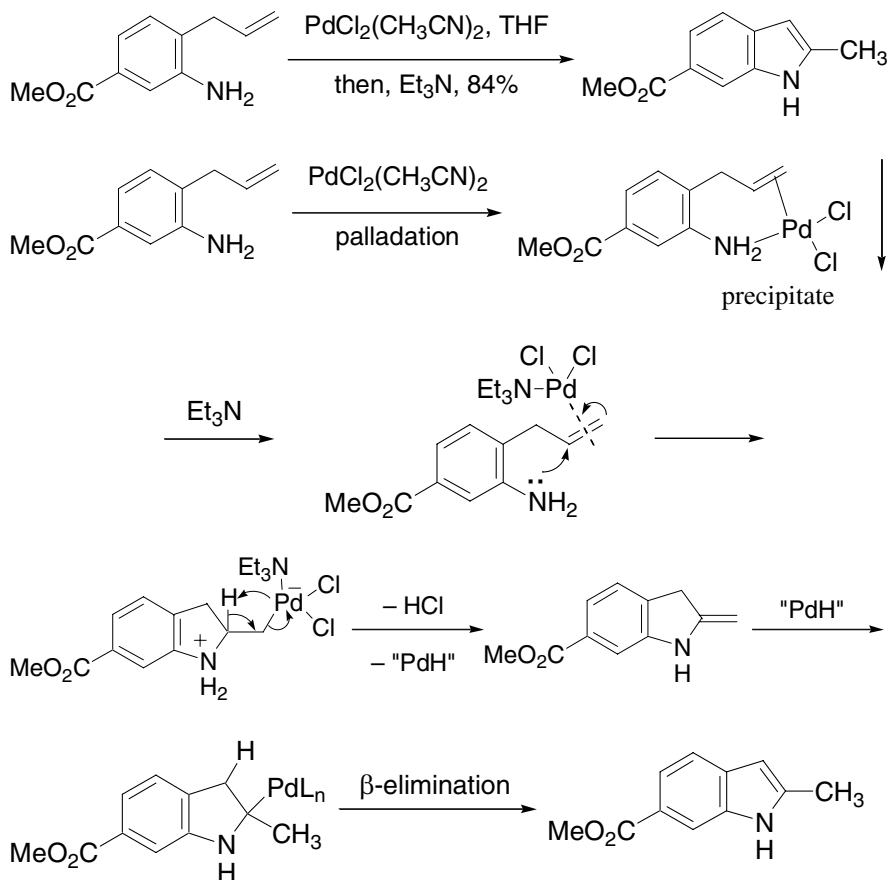


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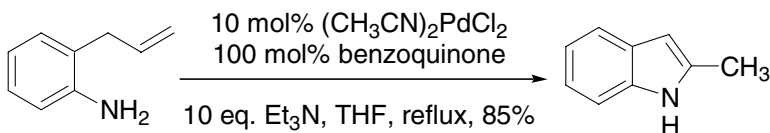
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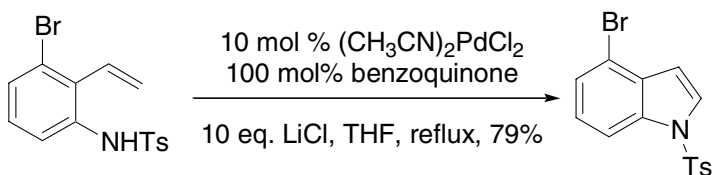
Hegedus indole synthesis

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



Example 1¹



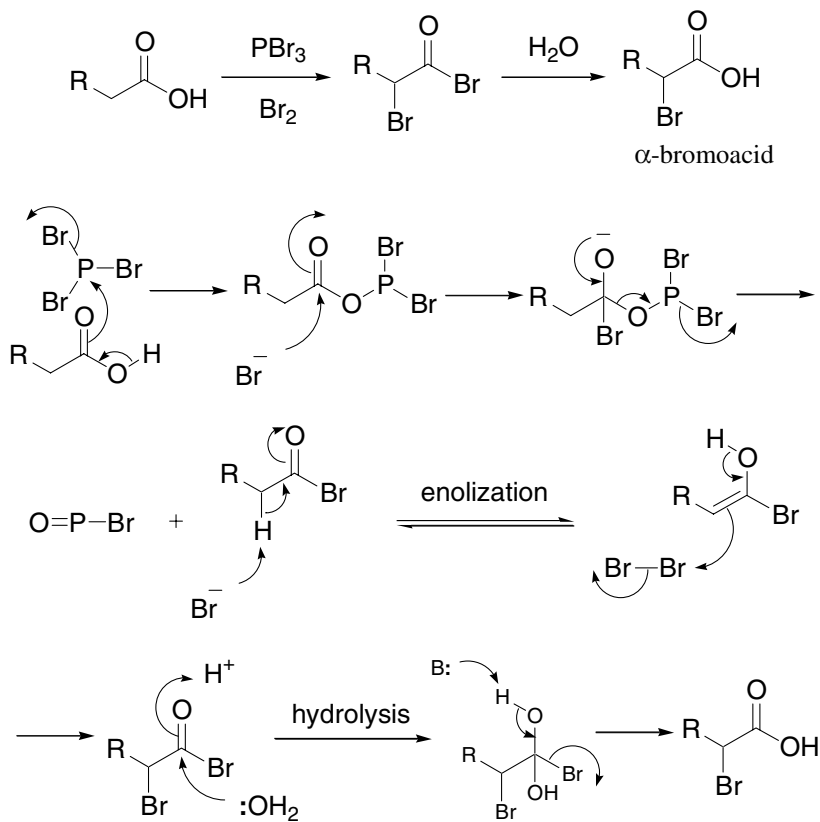
Example 2⁴

References

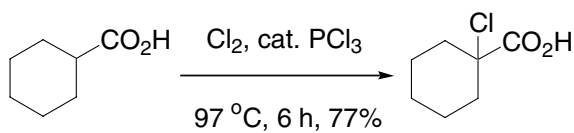
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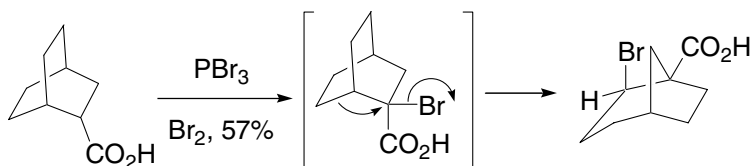
Hell-Volhard-Zelinsky reaction

α -Bromination of carboxylic acids using Br_2/PBr_3 .



Example 1⁷



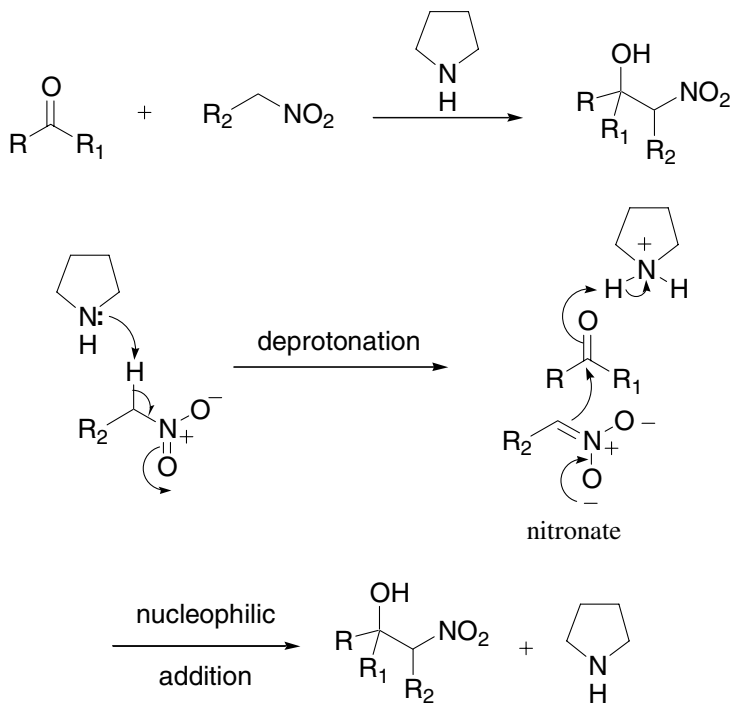
Example 2⁸

References

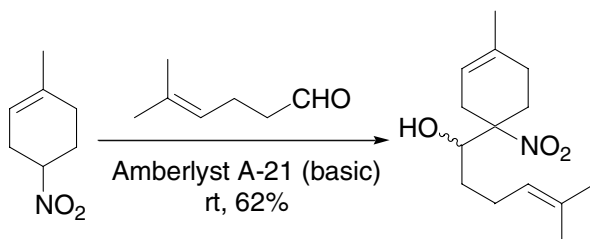
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Henry nitroaldol reaction

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



Example 1⁶



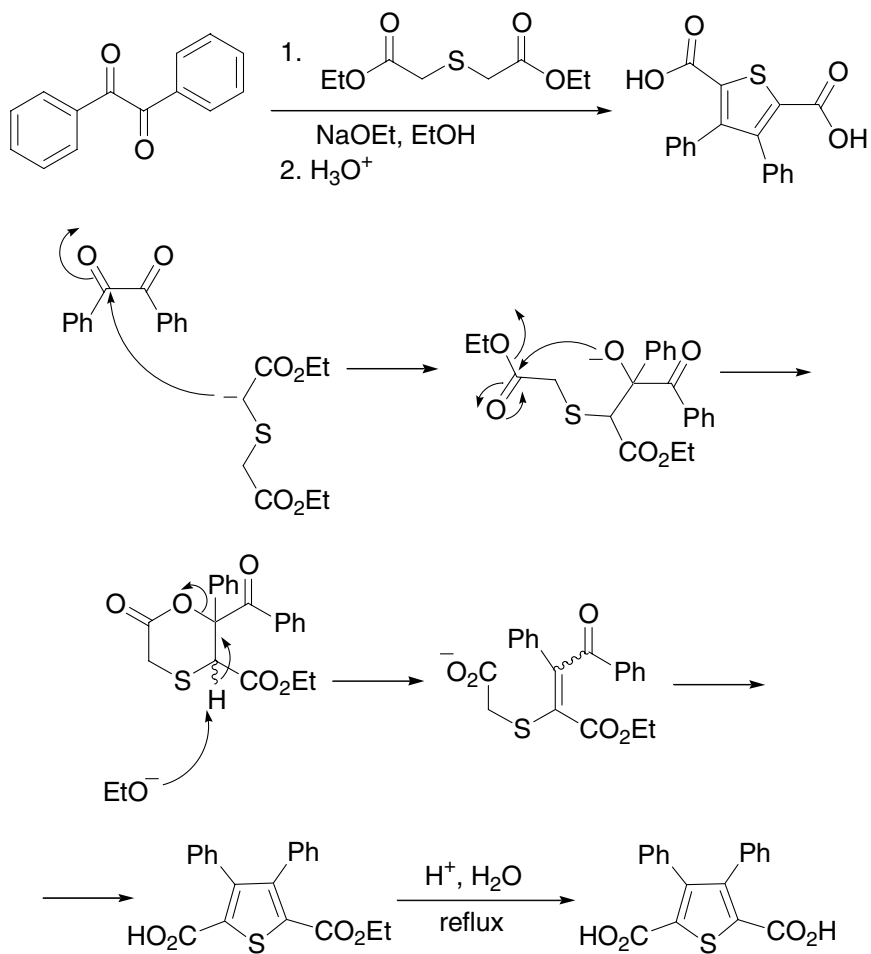
Example 2, aza-Henry reaction¹⁴

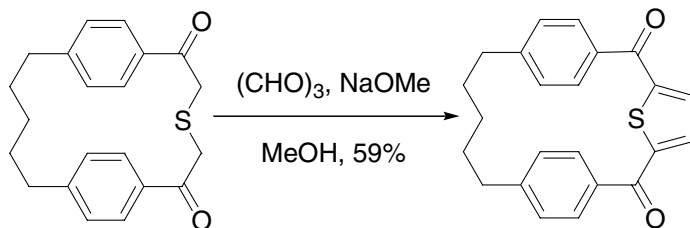
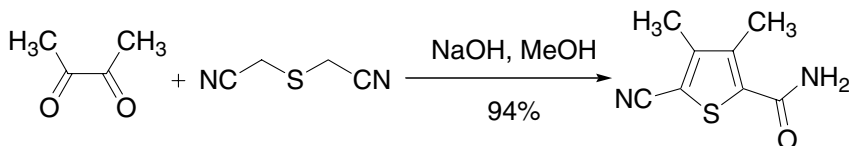
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Hinsberg synthesis of thiophene derivatives

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.



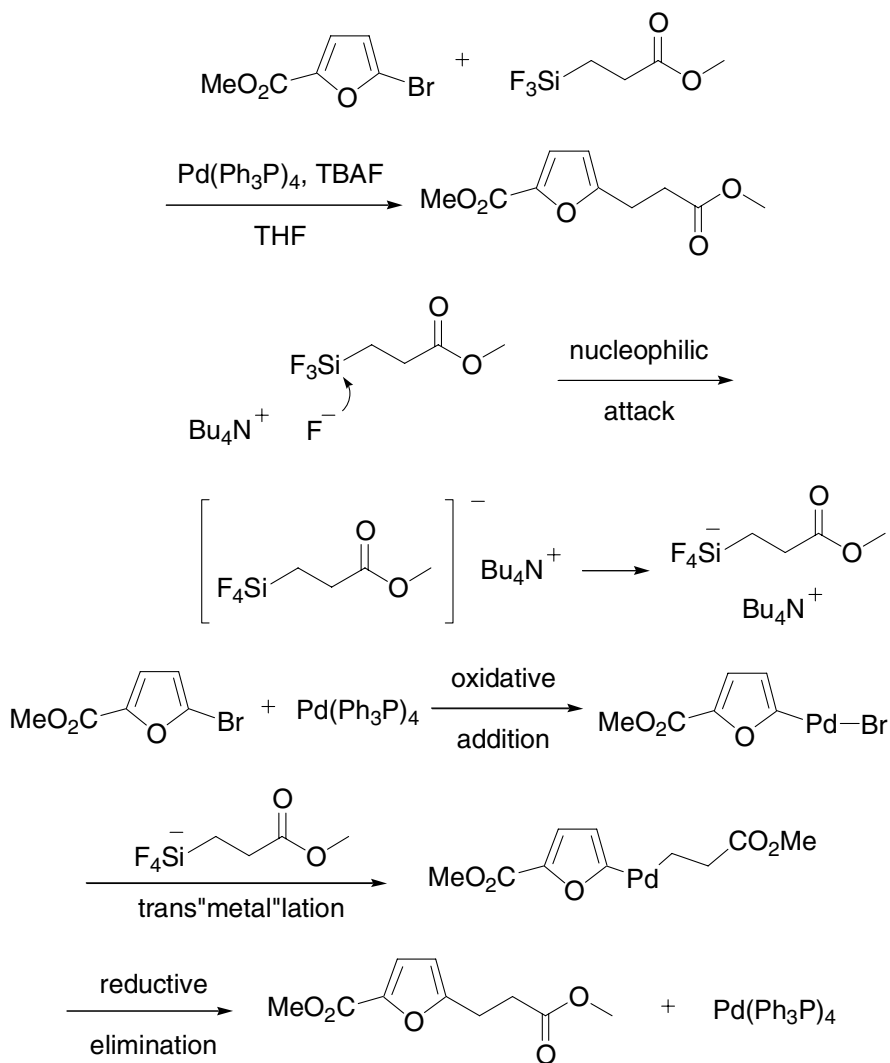
Example 1¹¹Example 2¹⁵

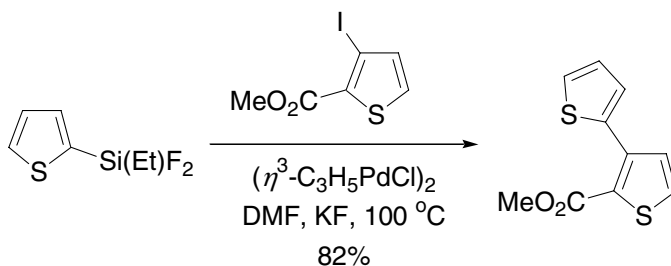
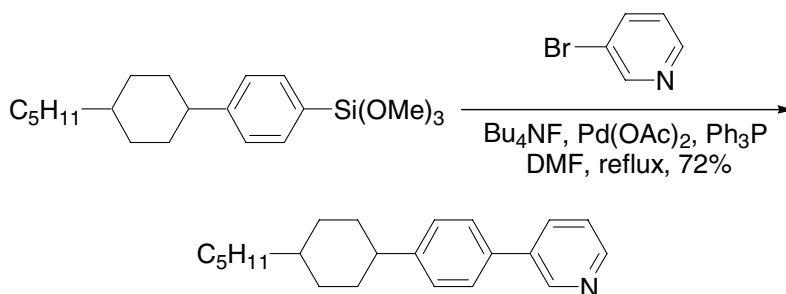
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Hiyama cross-coupling reaction

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 1¹Example 2⁵

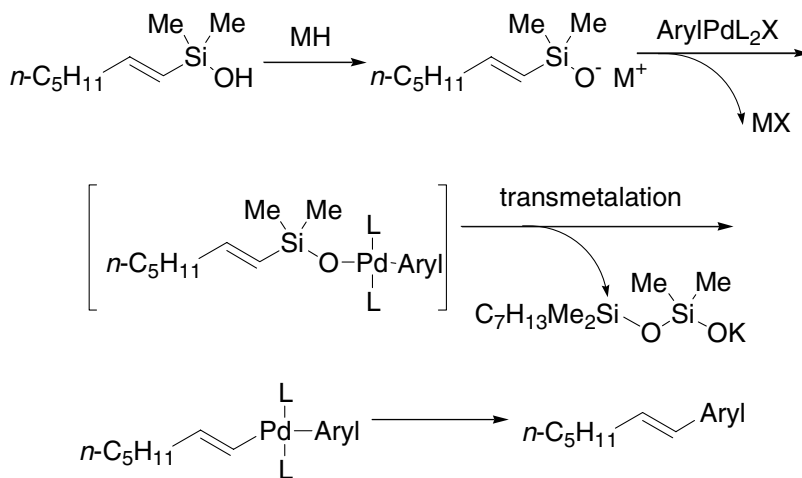
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Hiyama–Denmark cross-coupling reaction

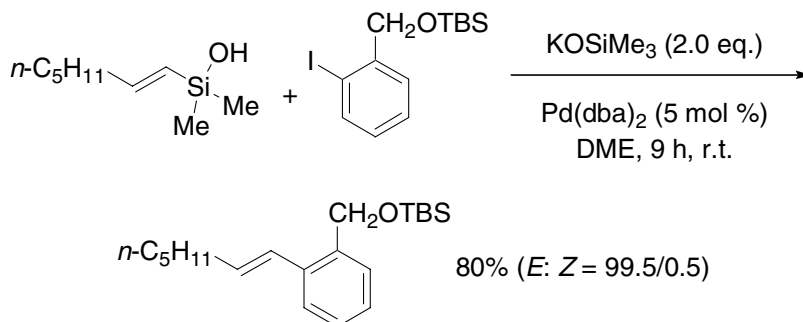
A synthetically important and mechanistically distinct cross-coupling process of organosilanols has been developed. Unlike the Hiyama cross-coupling reaction of polychloro- and fluorosilanes that requires activation by fluoride ion, the Denmark process involves the simple deprotonation of an organosilanol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

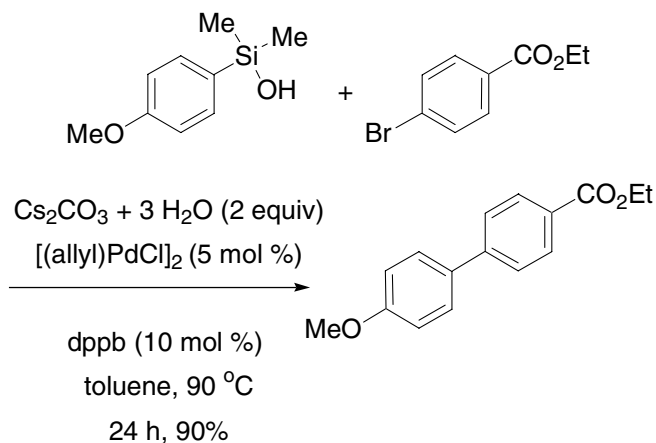
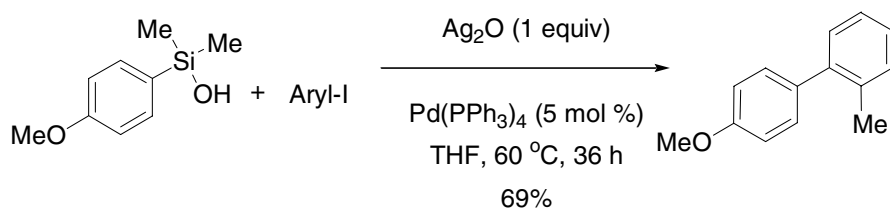
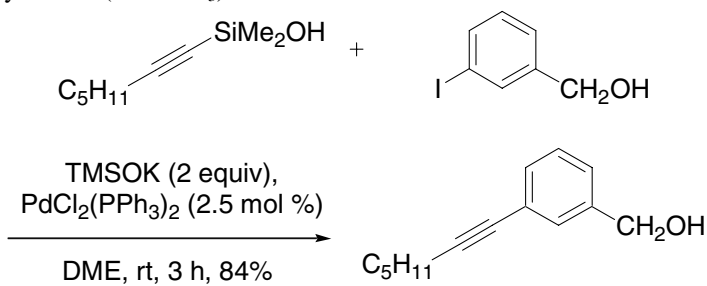
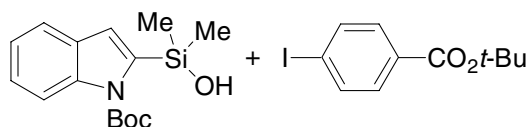
Mechanistic study⁵

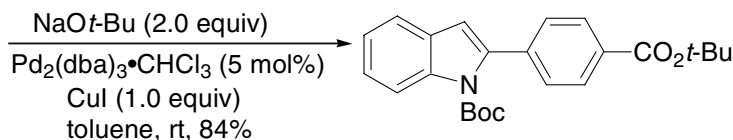


Many organosilanol substrates and different bases have been demonstrated.

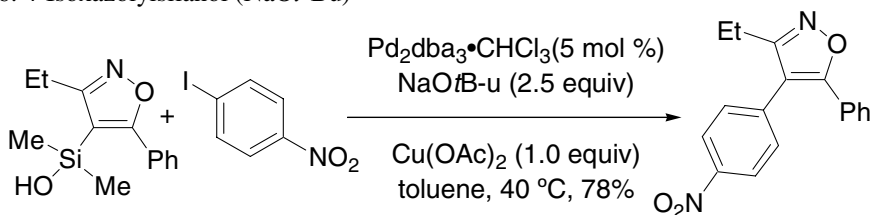
1. Alkenylsilanol (KOSiMe₃)⁶



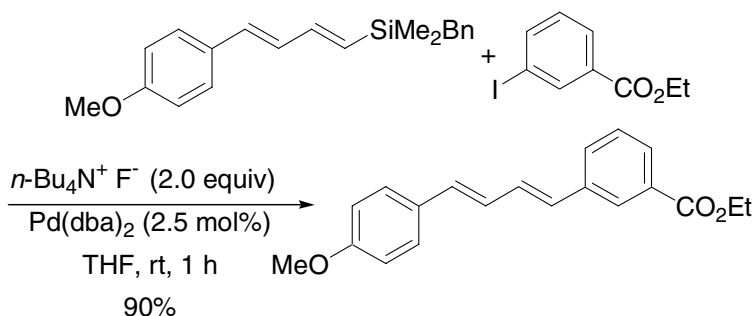
2. Arylsilanol (Cs_2CO_3)⁷3. Arylsilanol (Ag_2O)⁸4. Alkynylsilanol (KOSiMe_3)⁹5. 2-Indolylsilanol (KOt-Bu)¹⁰



6. 4-Isoxazolylsilanol (NaOt-Bu)¹¹



7. 1,4-Bis-silyl-1,3-butadienes (KOSiMe₃)¹²

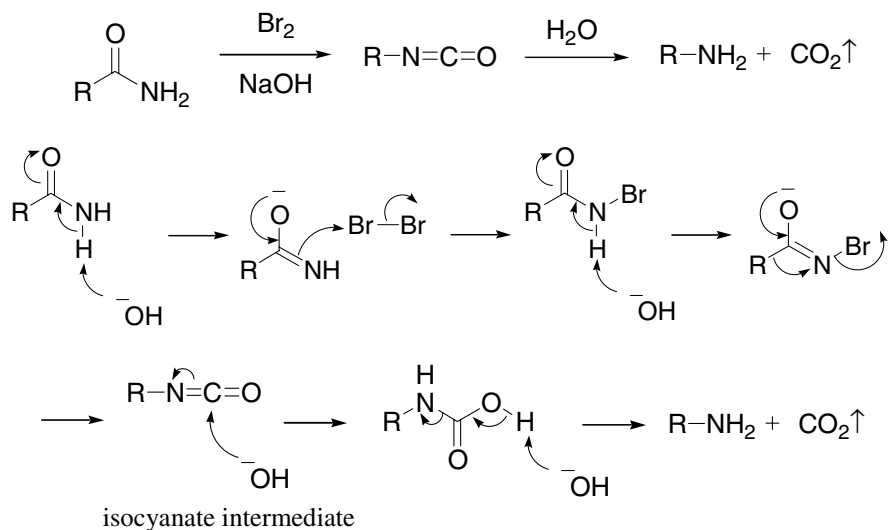


References

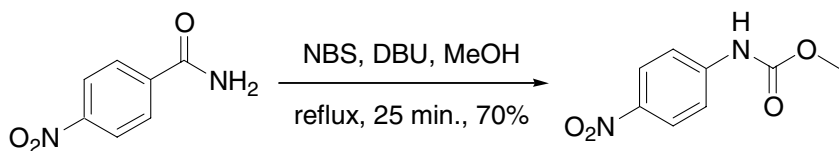
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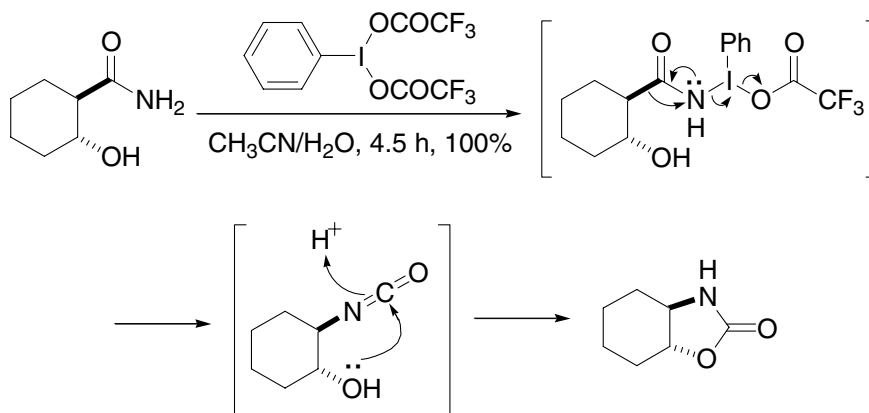
Hofmann rearrangement

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



Example 1⁴



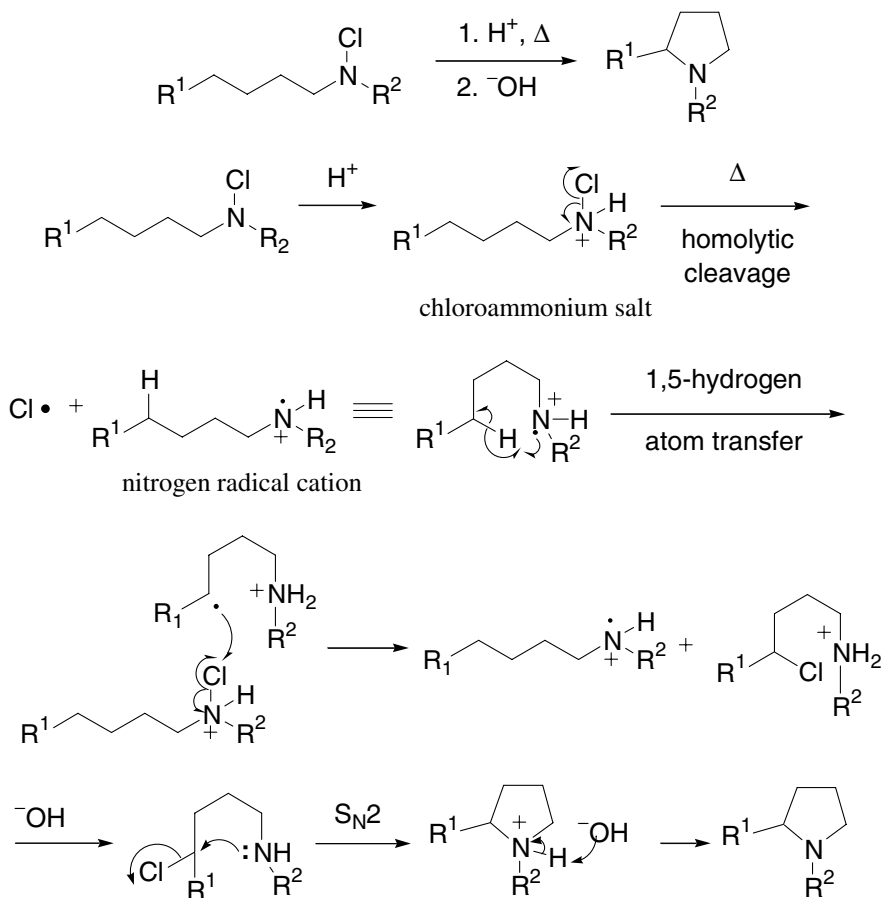
Example 2⁹

References

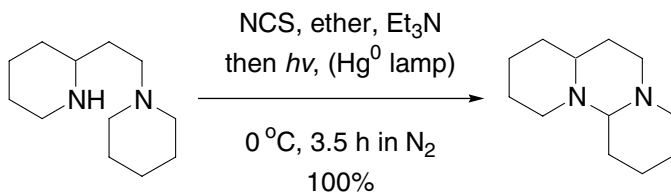
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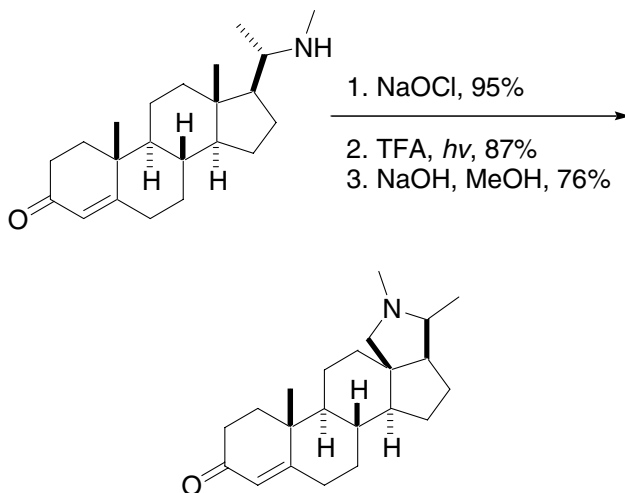
Hofmann–Löffler–Freitag reaction

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



Example 1⁶



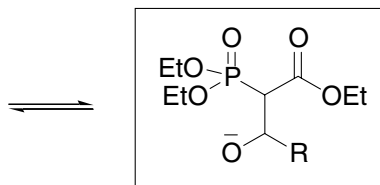
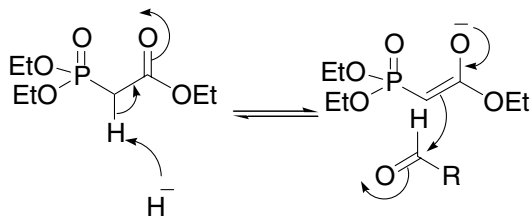
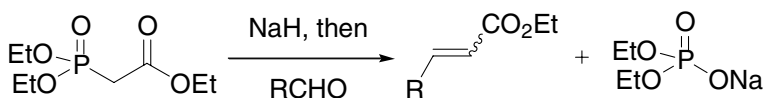
Example 2³

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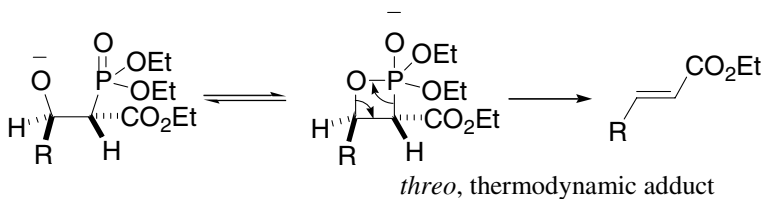
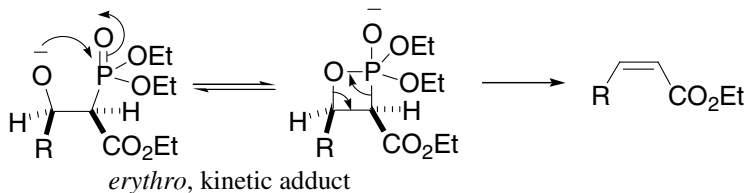
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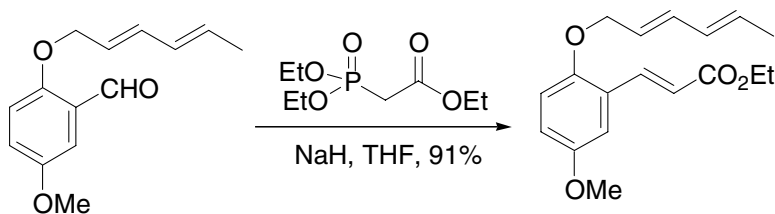
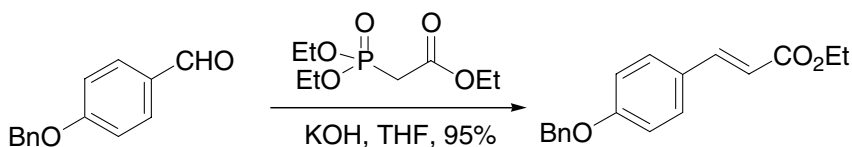
Horner–Wadsworth–Emmons reaction

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)



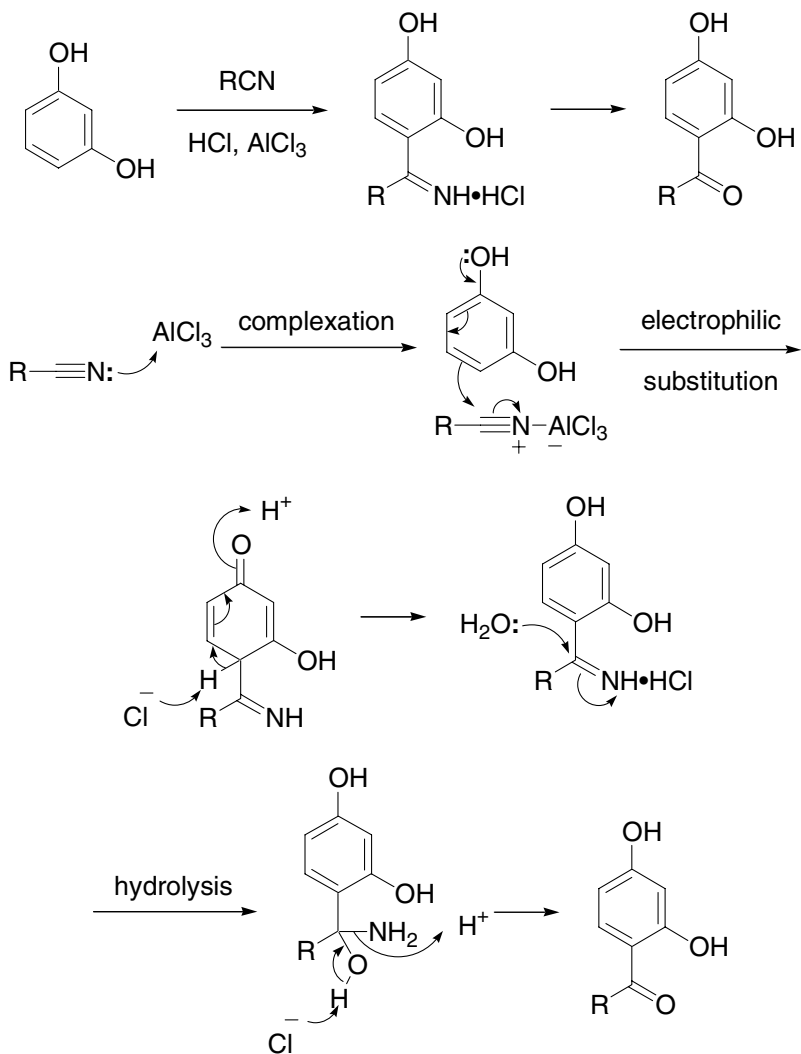
Example 1⁵Example 2⁸

References

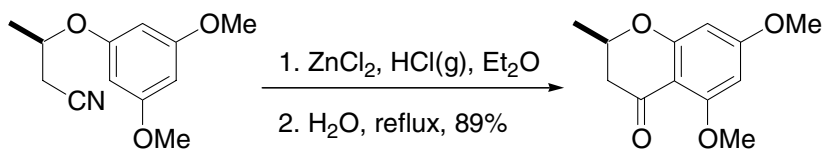
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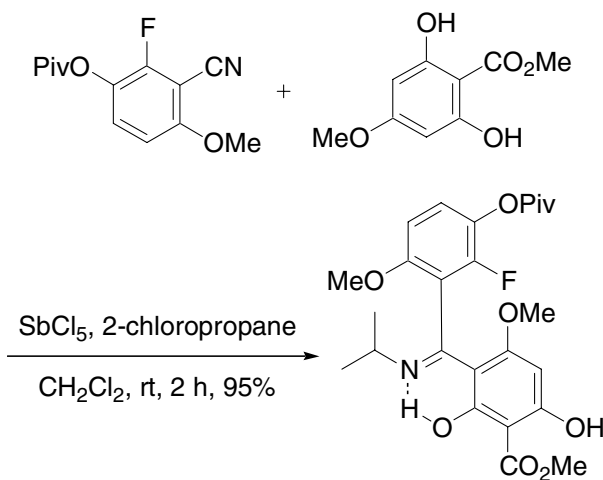
Houben–Hoesch reaction

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



Example 1, intramolecular Houben–Hoesch reaction⁵



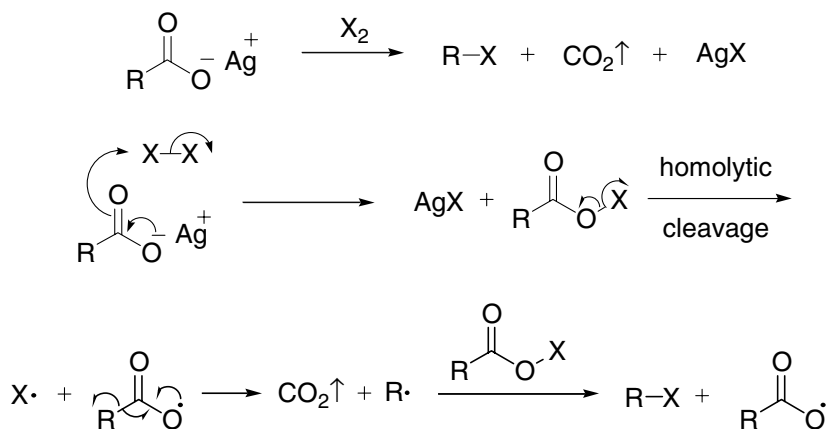
Example 2⁸

References

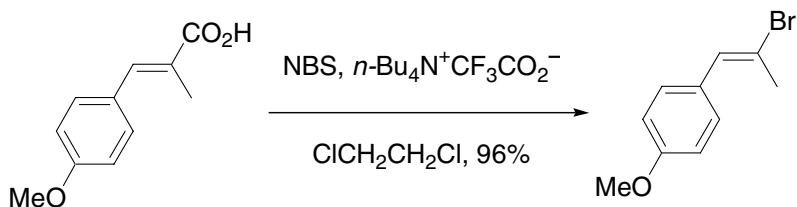
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Hunsdiecker–Borodin reaction

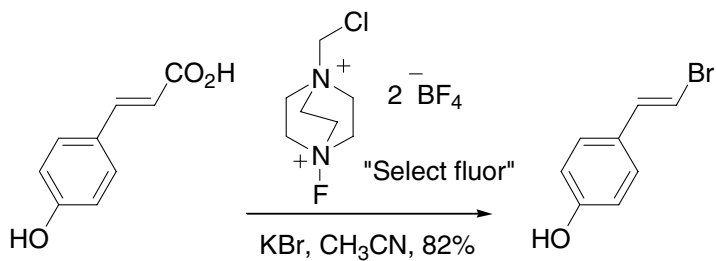
Conversion of silver carboxylate to halide by treatment with halogen.



Example 1⁶



Example 2¹⁰



References

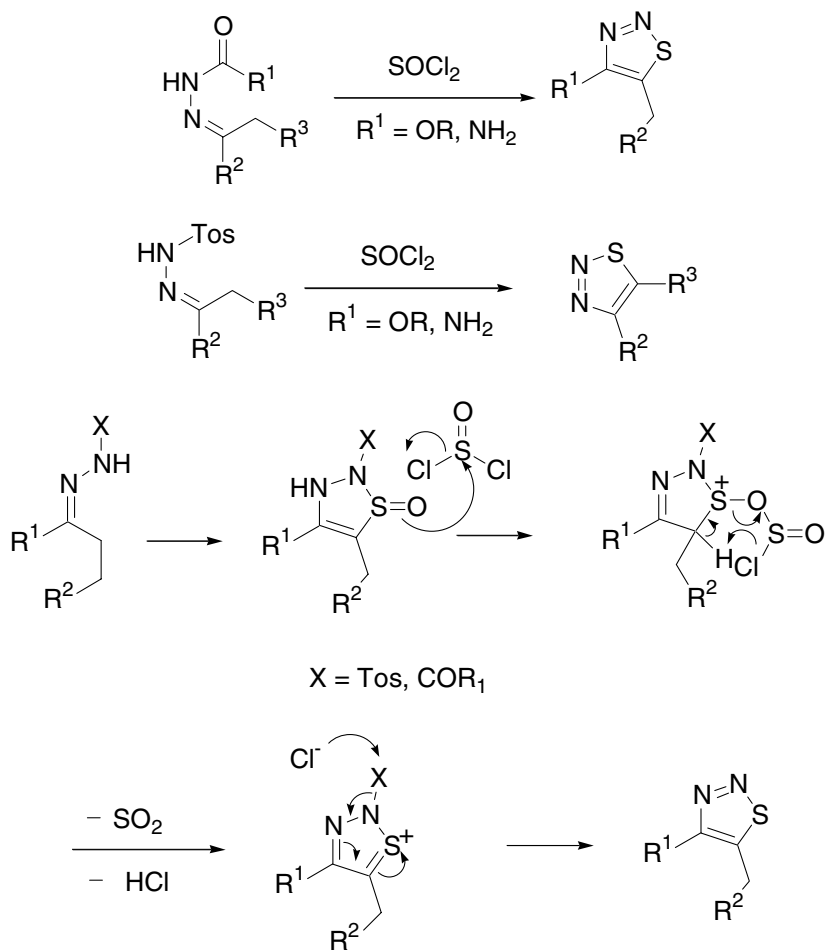
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Heinz and Cläre Hunsdiecker converted Borodin's synthesis into a general method, the Hunsdiecker or Hunsdiecker–Borodin reaction. Borodin was also an accomplished composer and is now best known for his musical masterpiece, opera Prince Egor. He kept a piano outside his laboratory.

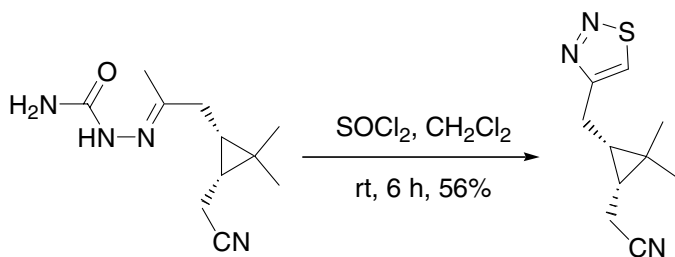
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Hurd–Mori 1,2,3-thiadiazole synthesis

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



Example¹⁷

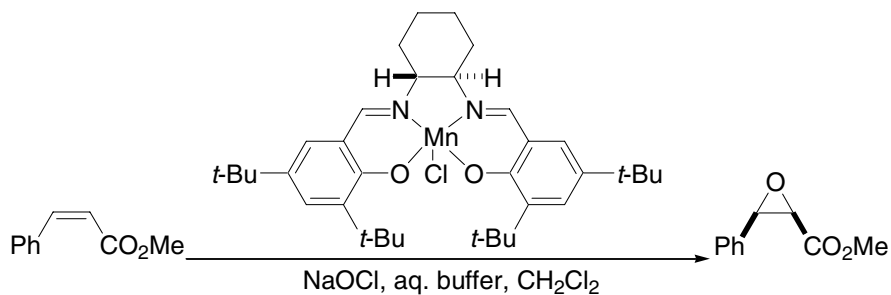


References

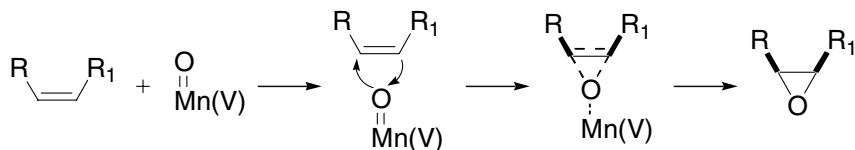
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Jacobsen–Katsuki epoxidation

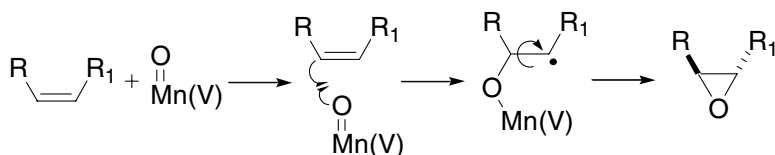
Manganese-catalyzed asymmetric epoxidation of (*Z*)-olefins.



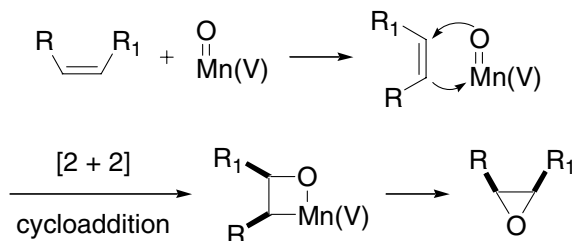
1. Concerted oxygen transfer (*cis*-epoxide):

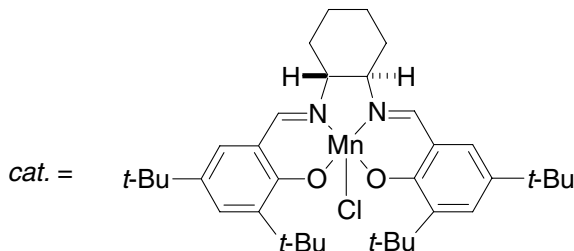
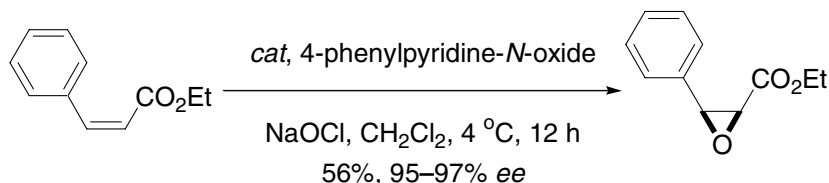


2. Oxygen transfer *via* radical intermediate (*trans*-epoxide):



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



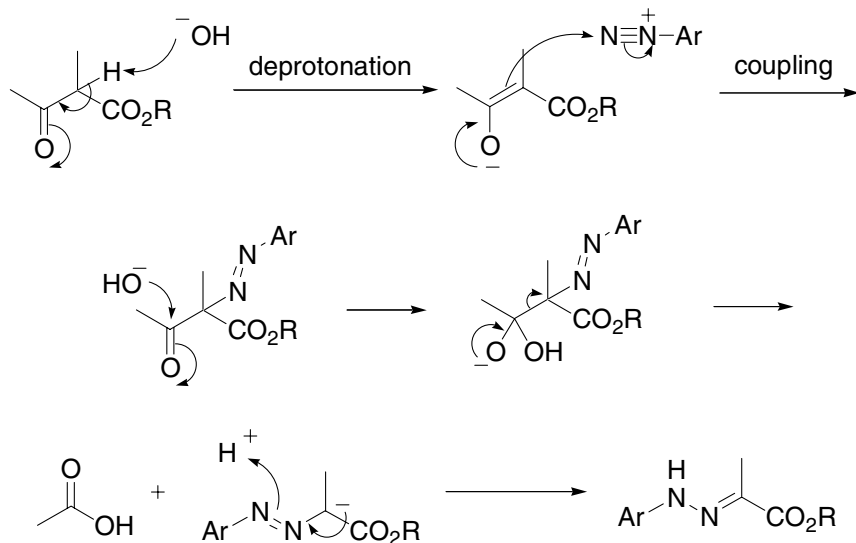
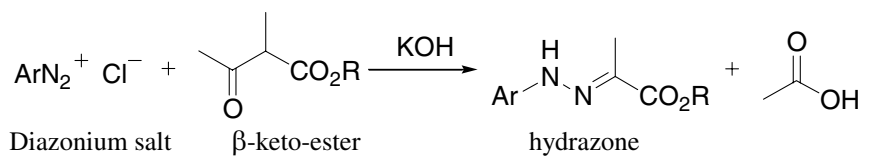
Example⁵

References

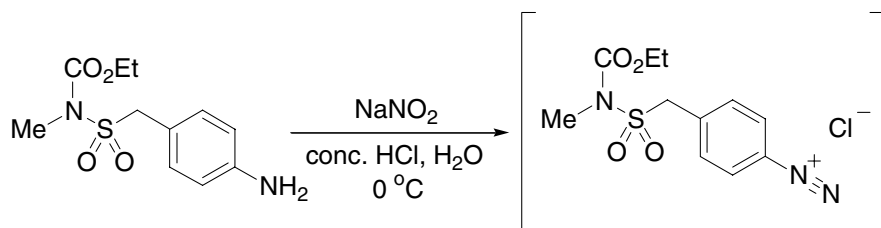
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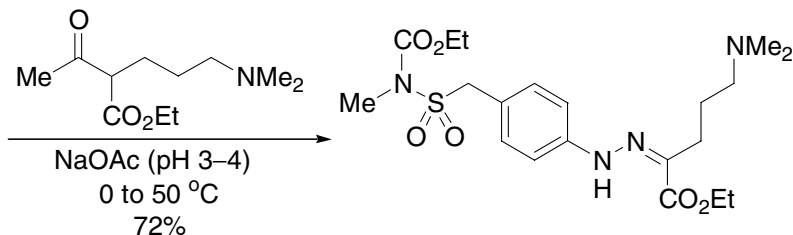
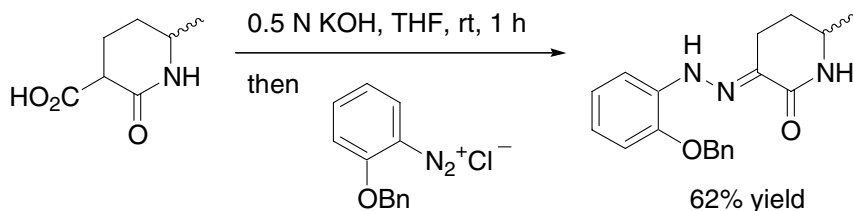
Japp–Klingemann hydrazone synthesis

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



Example 1⁶



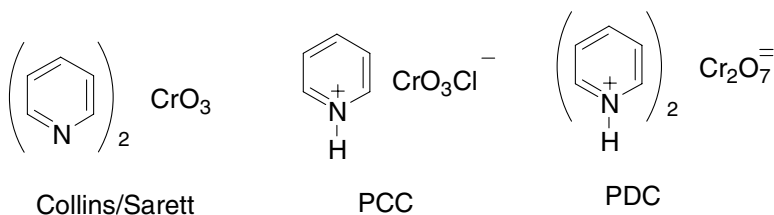
Example 2⁹

References

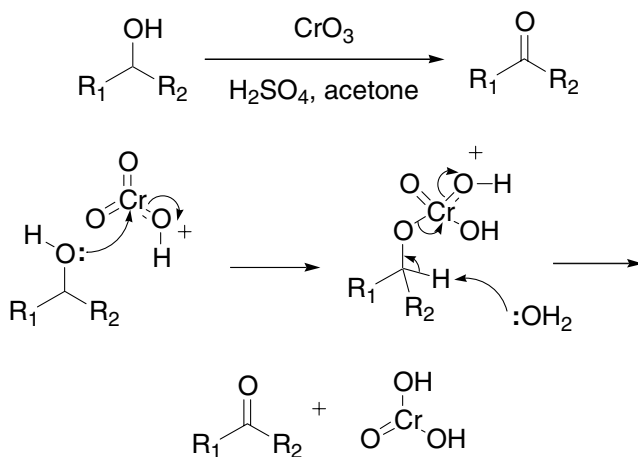
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Jones oxidation

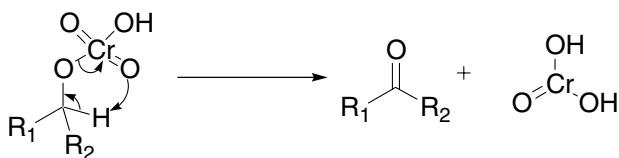
The **Collins/Sarett oxidation** (chromium trioxide-pyridine complex), and **C Corey's PCC** (pyridinium chlorochromate) and **PDC** (pyridinium dichromate) **oxidations** follow a similar pathway as the **Jones oxidation**. All these oxidants have a chromium (VI), normally yellow, which is reduced to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

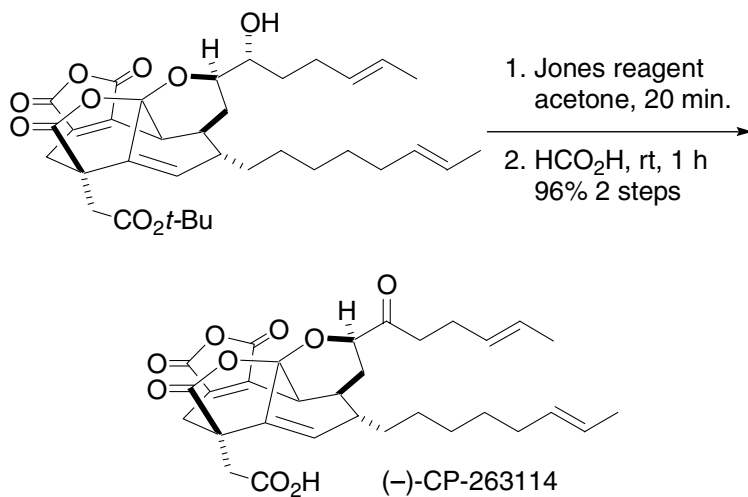
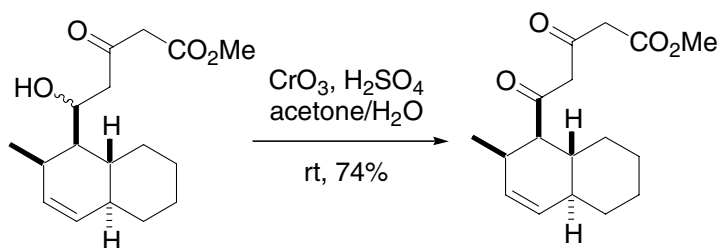
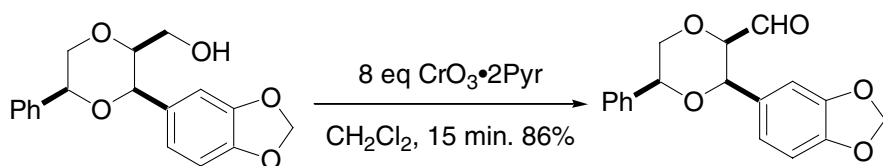
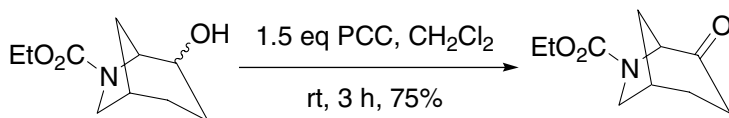


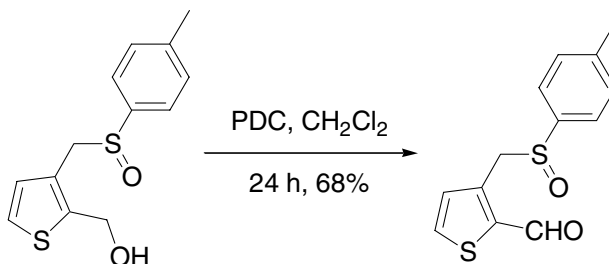
Jones oxidation



The intramolecular mechanism is also operative:



Example 1¹⁴Example 2¹⁵Collins/Sarett oxidation⁵PCC oxidation⁶

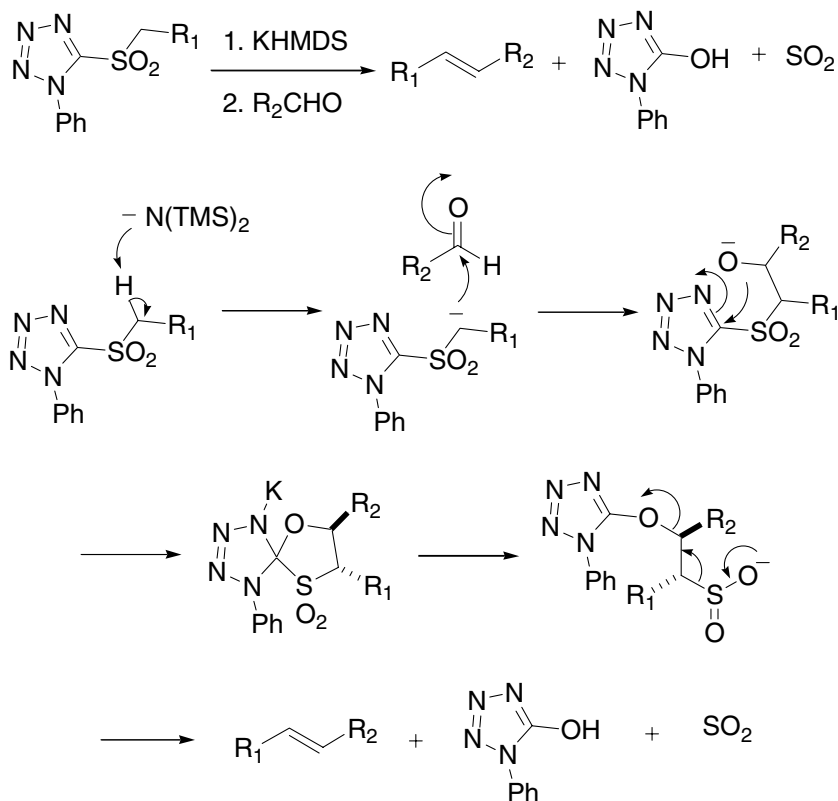
PDC oxidation⁷

References

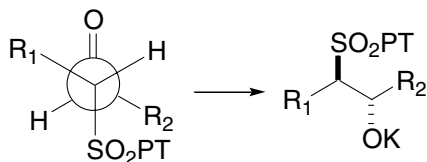
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Julia–Kocienski olefination

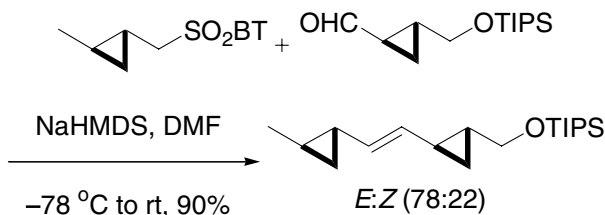
Modified one-pot Julia olefination to give predominantly (*E*)-olefins from heteroarylsulfones and aldehydes. A sulfone reduction step is *not* required.



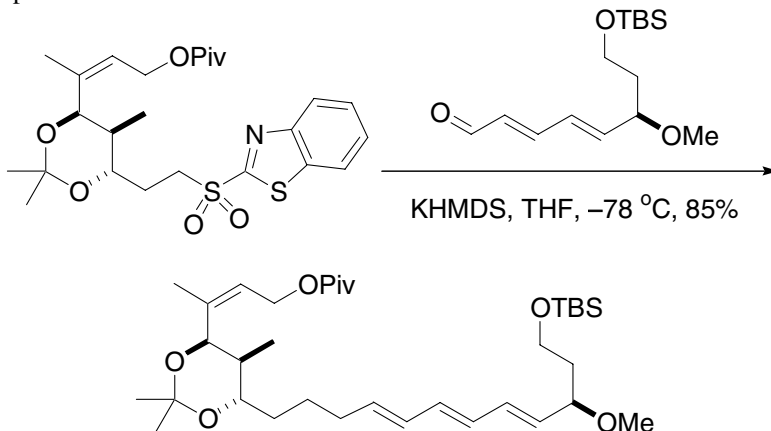
The use of larger counterion (such as K^+) and polar solvents (such as DME) favors an open transition state (PT = phenyltetrazolyl):



Example 1, (BT = benzotriazole)⁴



Example 2⁶

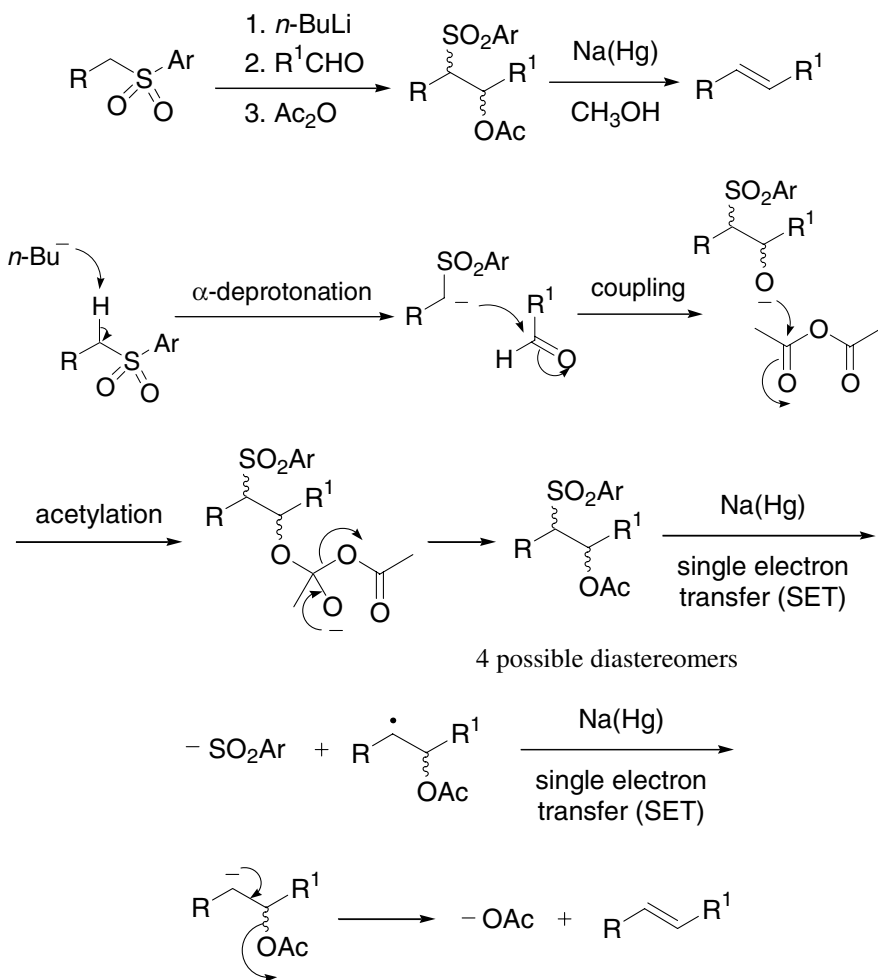


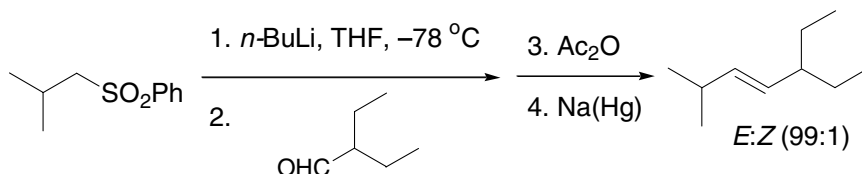
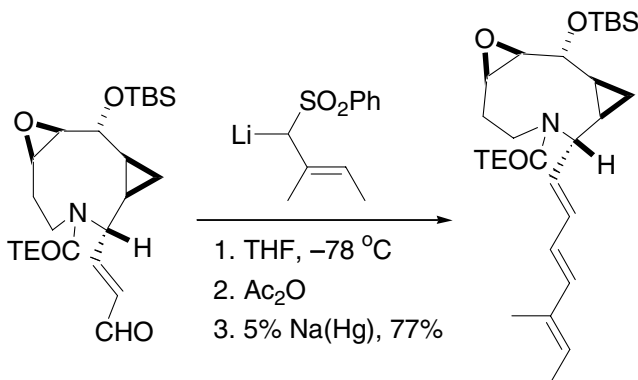
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Julia–Lythgoe olefination

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



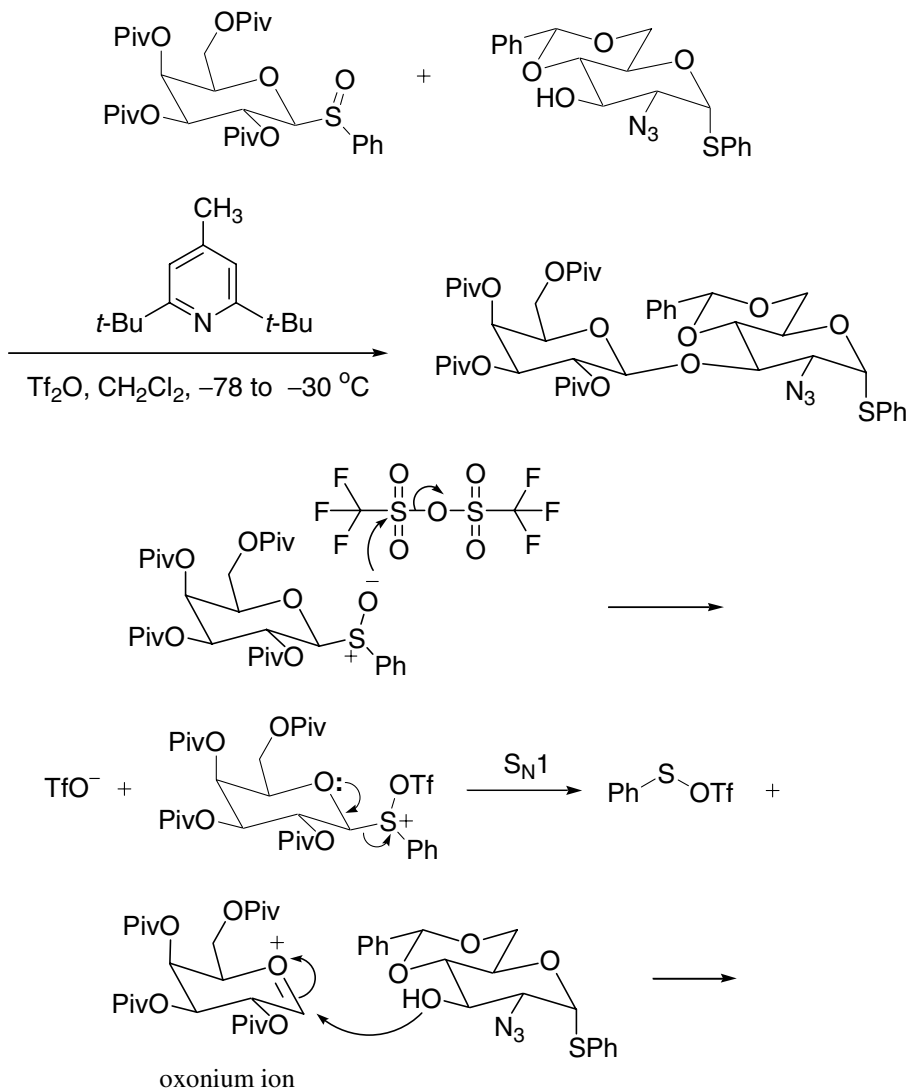
Example 1³Example 2⁴

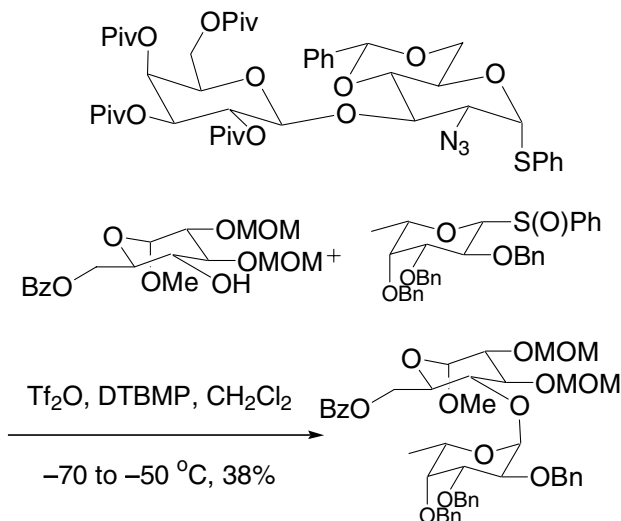
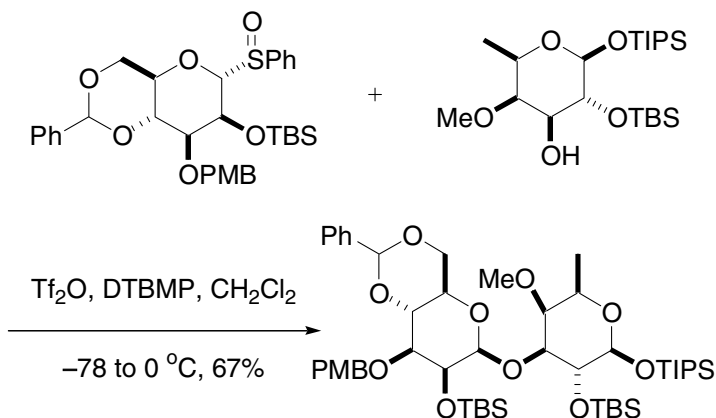
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Kahne–Crich glycosidation

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



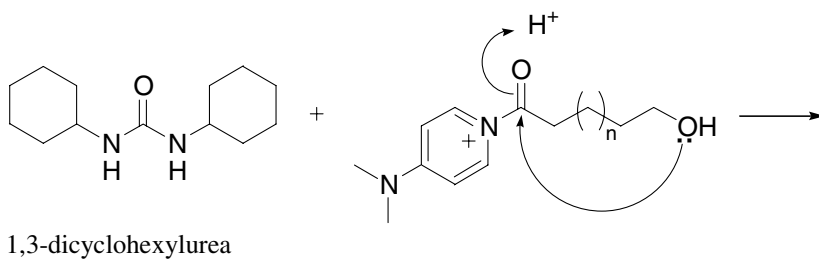
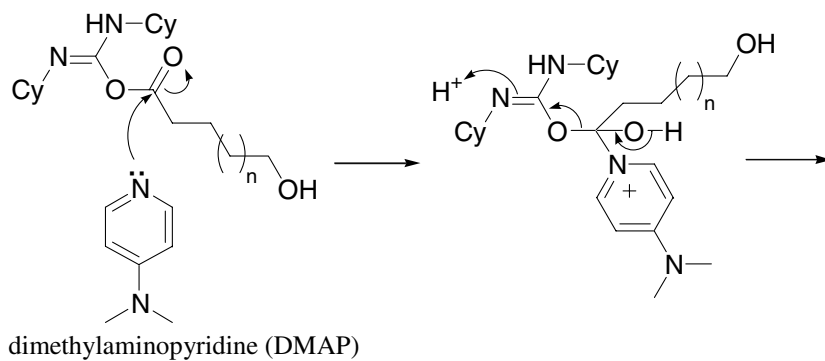
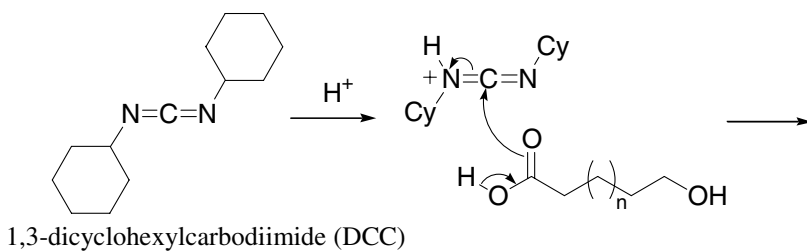
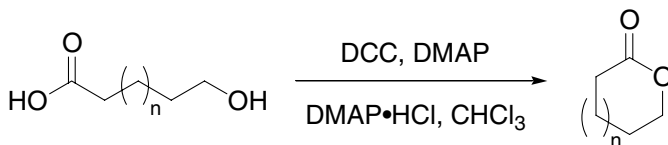
Example 1²Example 2⁶

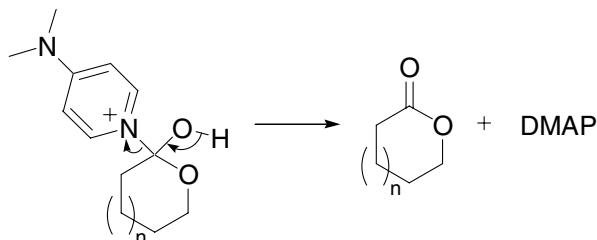
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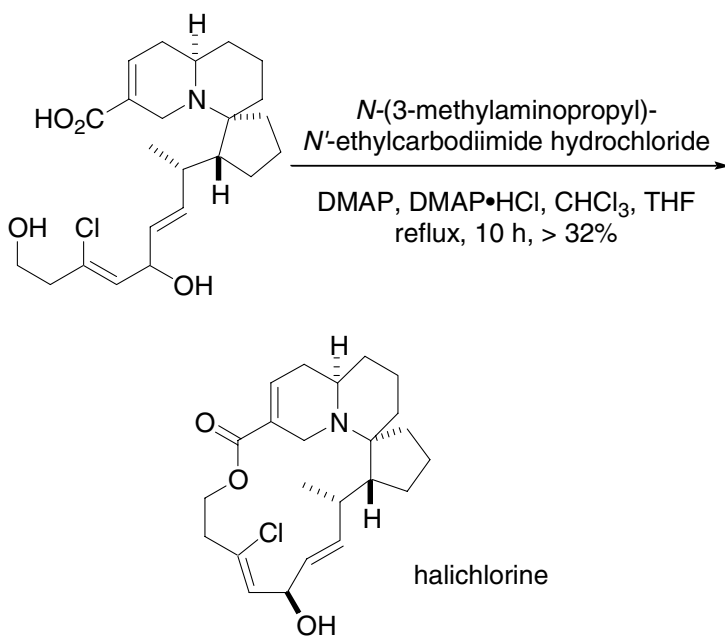
Keck macrolactonization

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





Example 1⁷

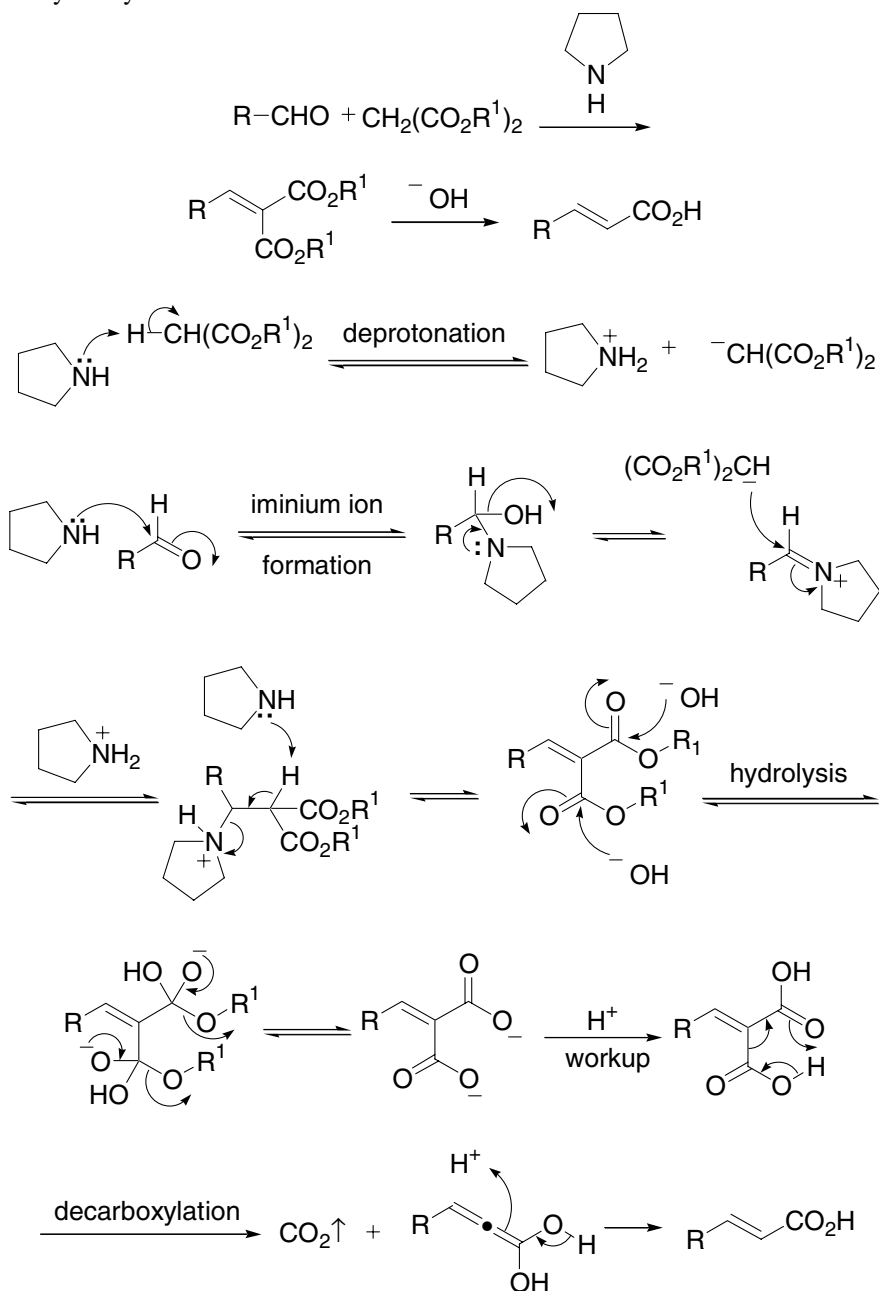


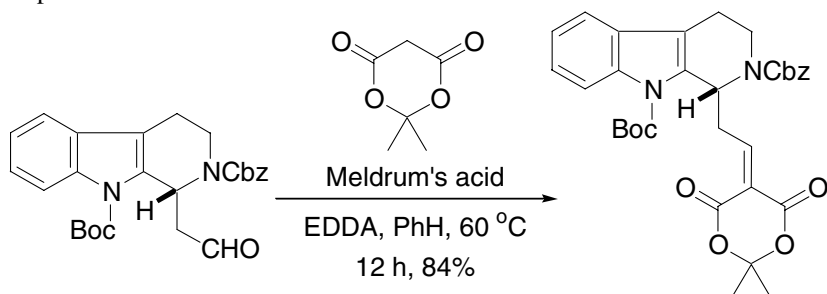
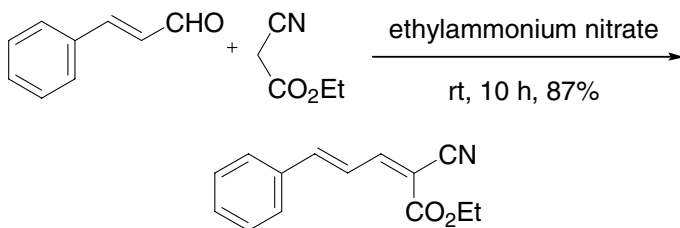
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Knoevenagel condensation

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



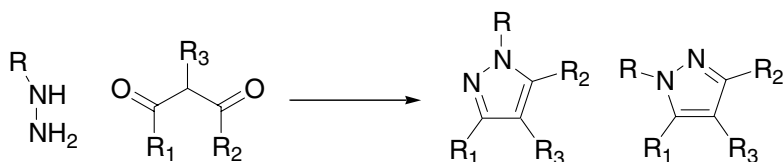
Example 1⁷Example 2, using ionic liquid ethylammonium nitrate (EAN) as solvent¹³

References

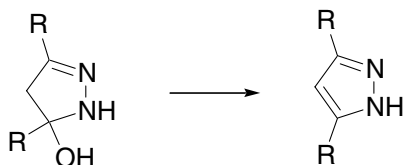
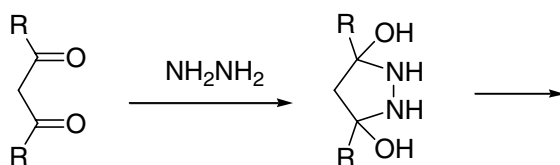
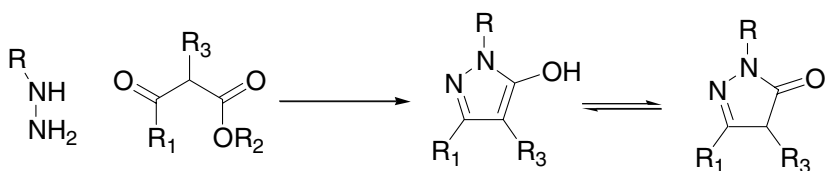
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Knorr pyrazole synthesis

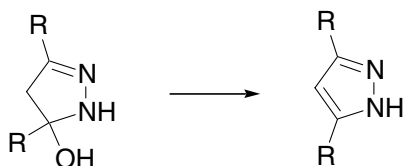
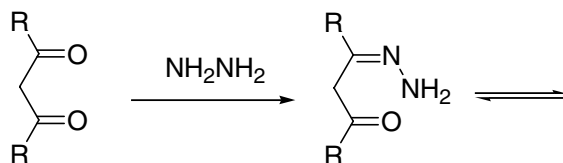
Reaction of hydrazine or substituted hydrazine with 1,3-dicarbonyl compounds to provide the pyrazole or pyrazolone ring system. Cf. Paal–Knorr pyrrole synthesis (page 333).

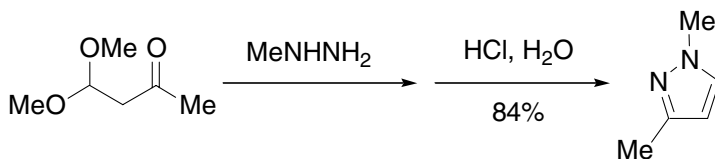
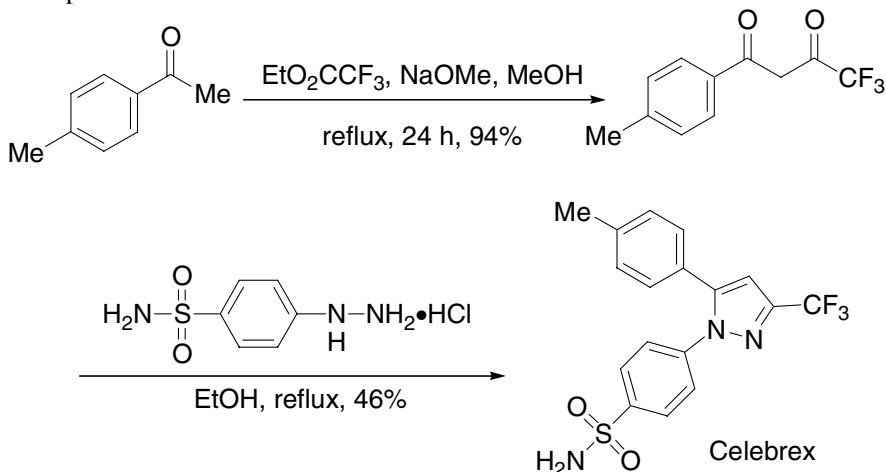


$R = H, \text{ Alkyl, Aryl, Het-aryl, Acyl, etc.}$



Alternatively,



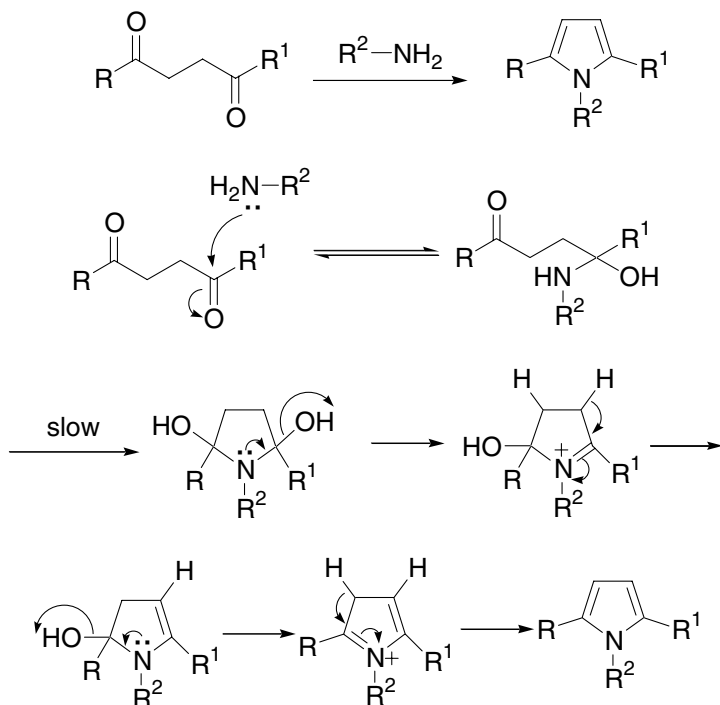
Example 1⁵Example 2¹³

References

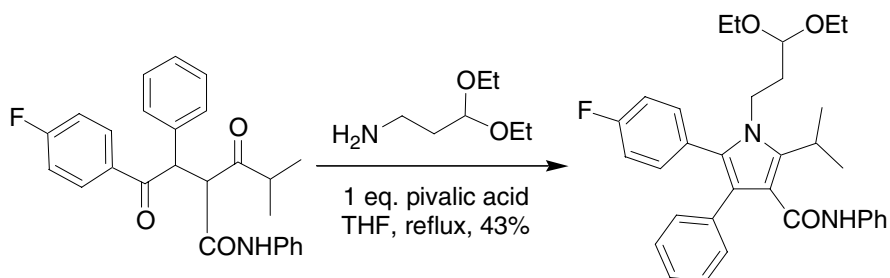
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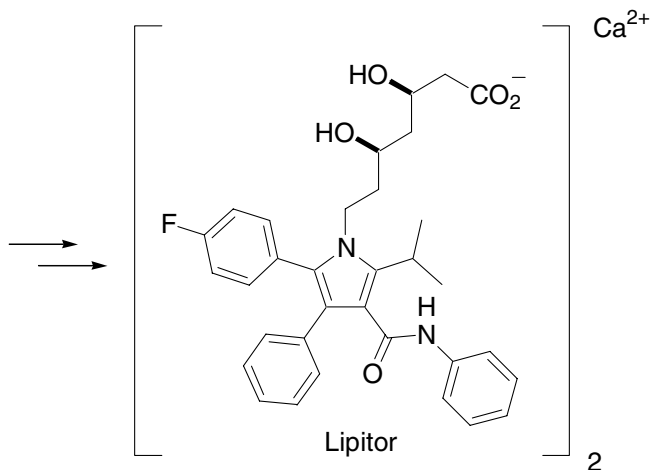
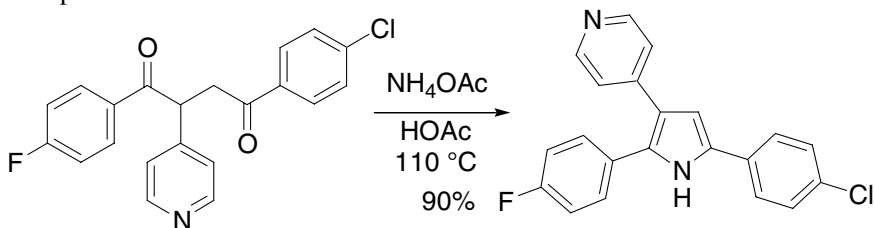
Paal–Knorr pyrrole synthesis

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



Example 1⁵



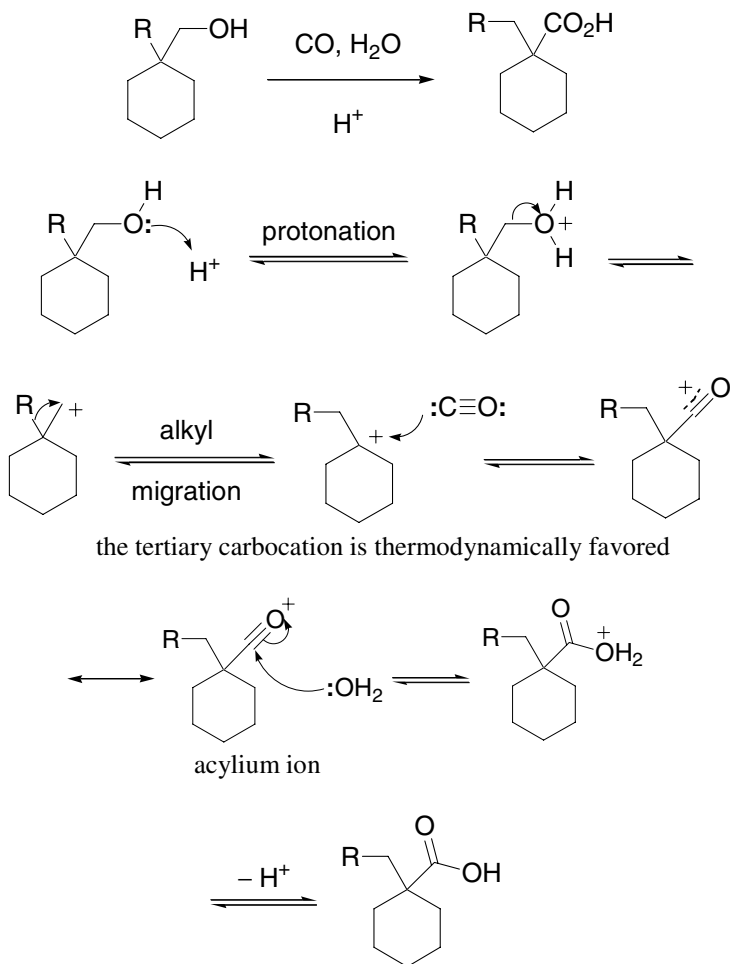
Example 2⁷

References

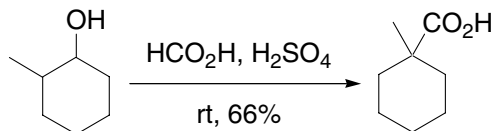
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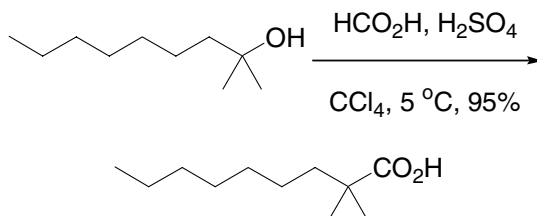
Koch–Haaf carbonylation

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



Example 1⁵



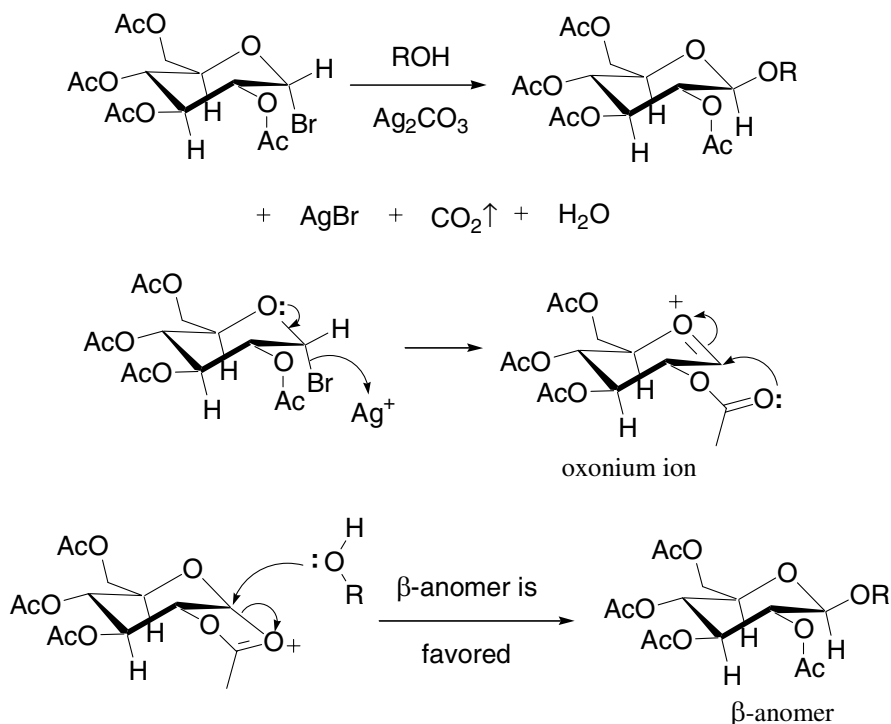
Example 2⁷

References

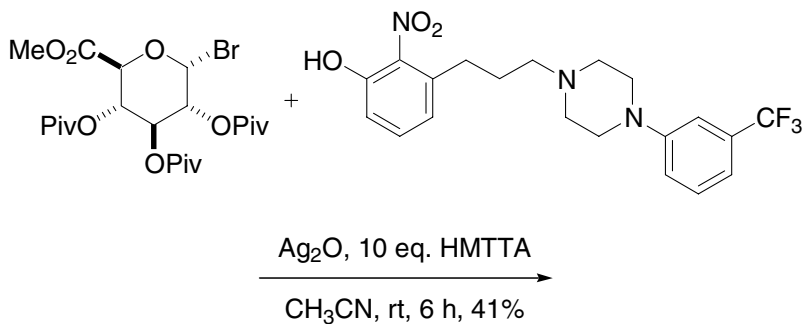
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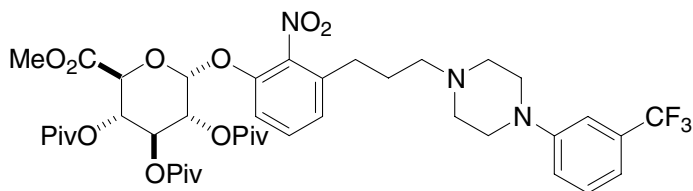
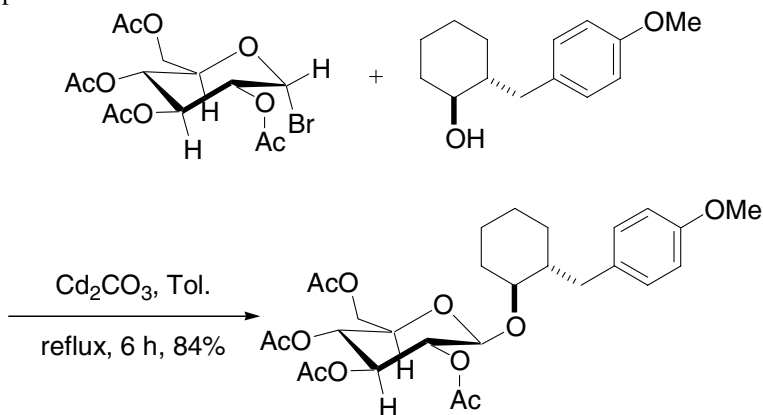
Koenig–Knorr glycosidation

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



Example 1¹³



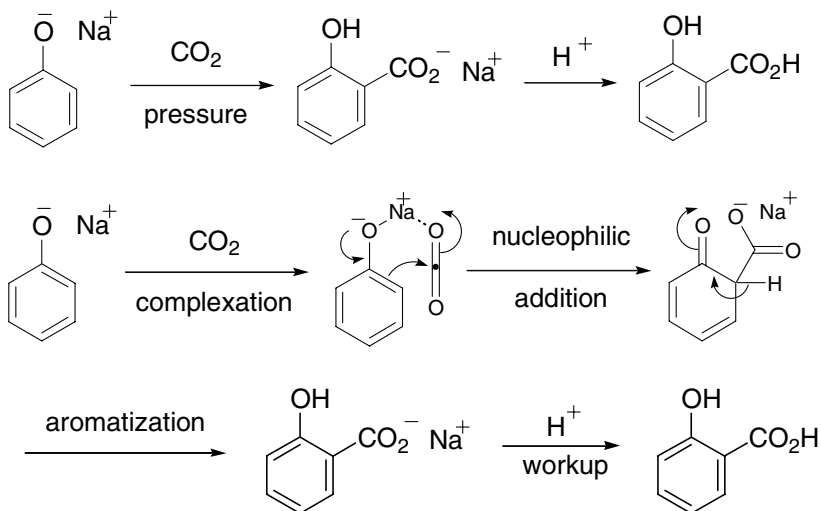
Example 2¹⁵

References

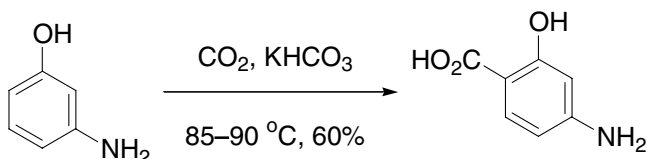
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Kolbe–Schmitt reaction

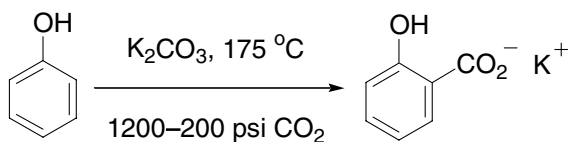
Carboxylation of sodium phenoxides with carbon dioxide, to give salicylic acid, the precursor to the synthesis of aspirin.



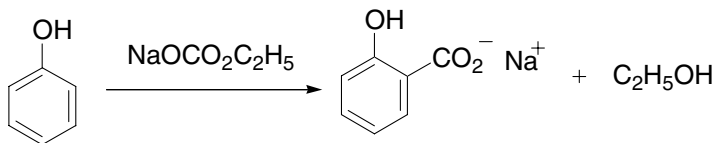
Example 1³



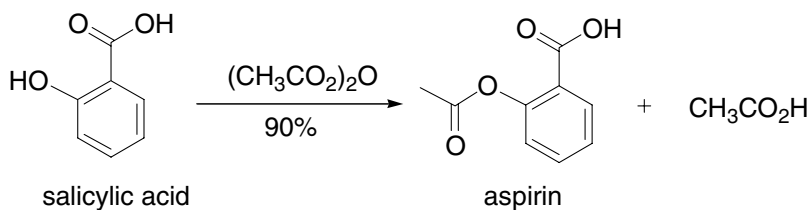
Example 2, the **Marasse modification** of the Kolbe–Schmitt reaction uses excess of anhydrous potassium carbonate in place of carbon dioxide⁴



Example 3, the Jones modification of the Kolbe–Schmitt reaction employs sodium ethyl carbonate⁵



Salicylic acid is the precursor to the synthesis of aspirin:

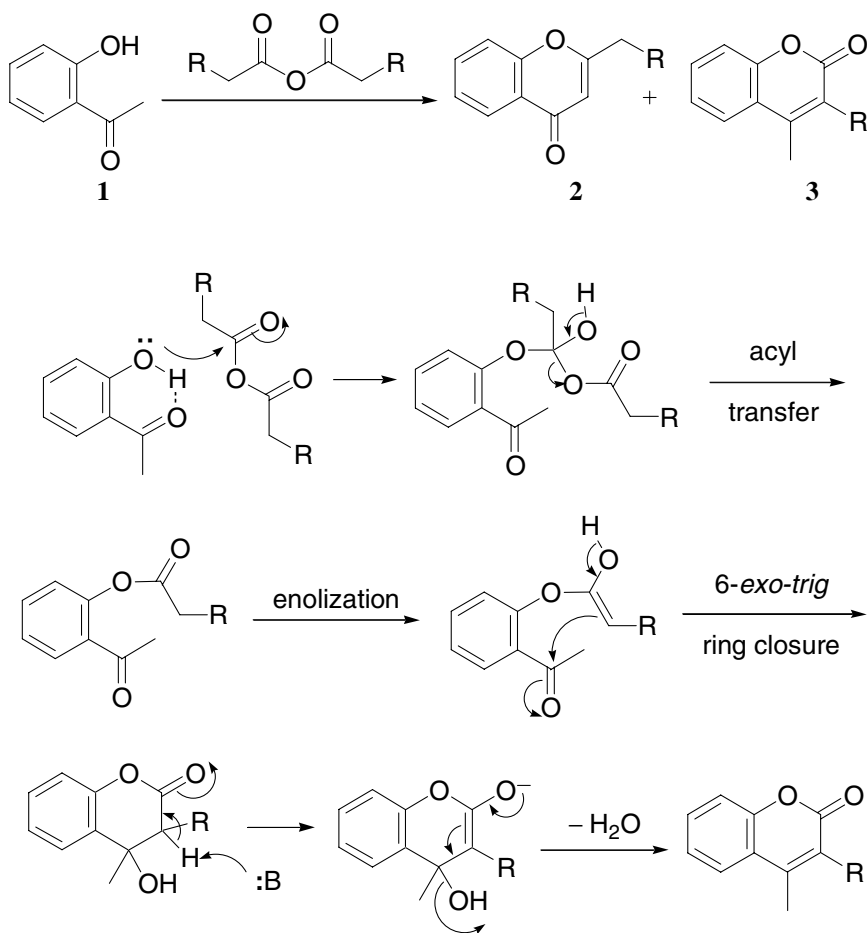


References

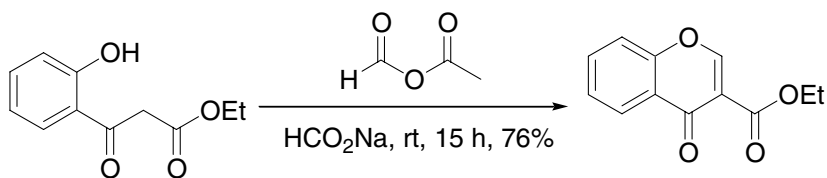
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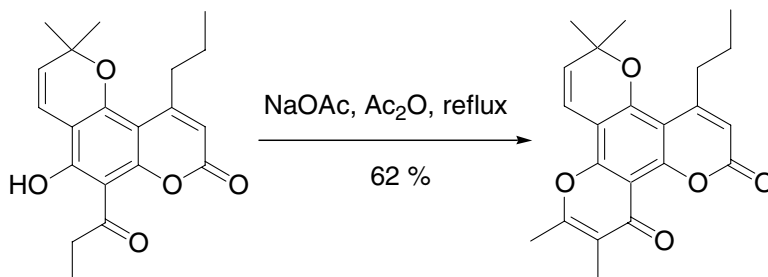
Kostanecki reaction

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



Example 1⁵



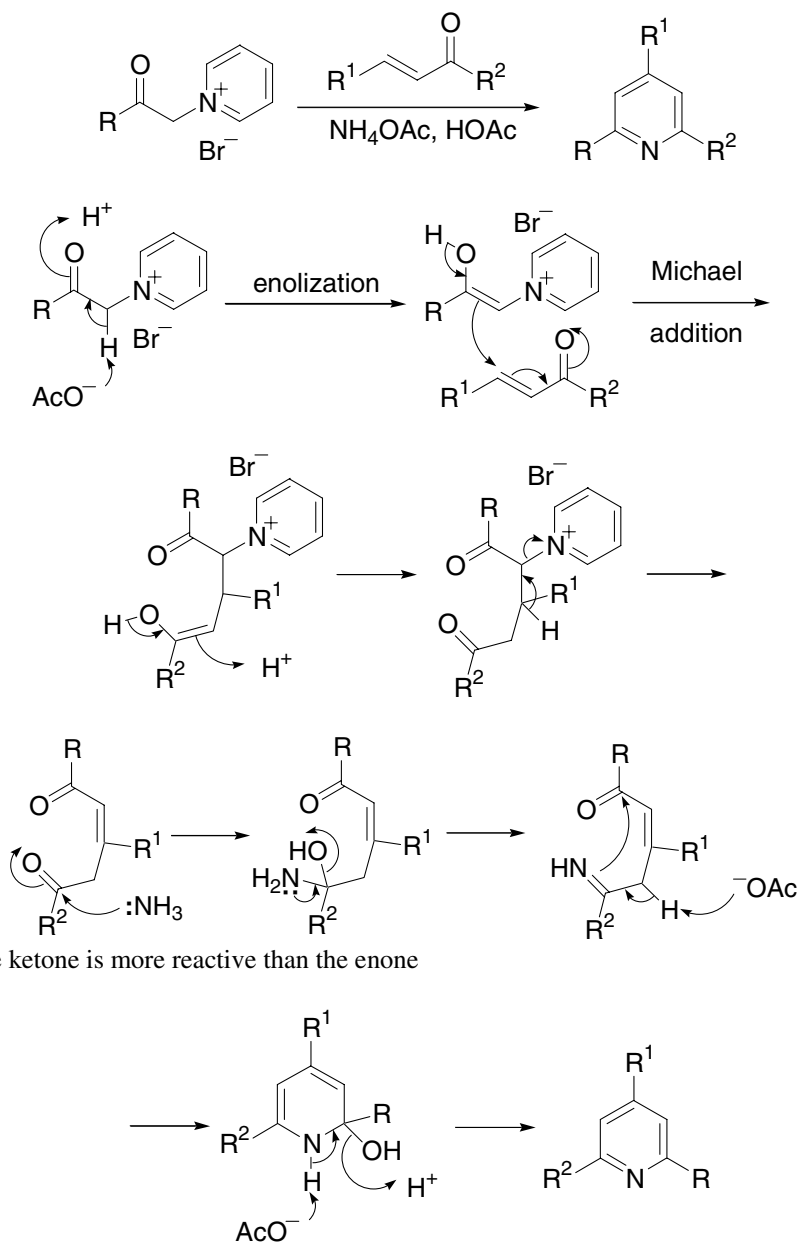
Example 2¹³

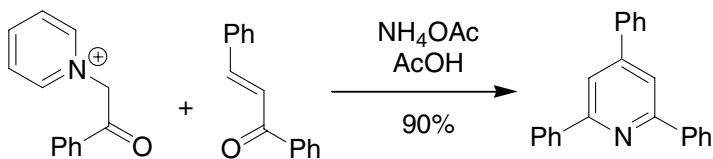
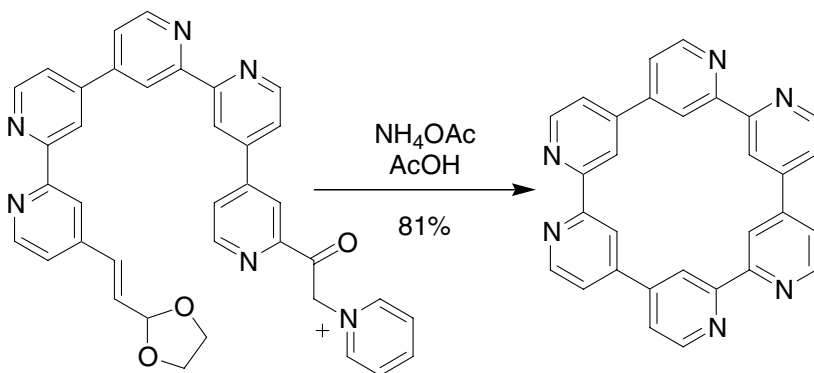
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Kröhnke pyridine synthesis

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



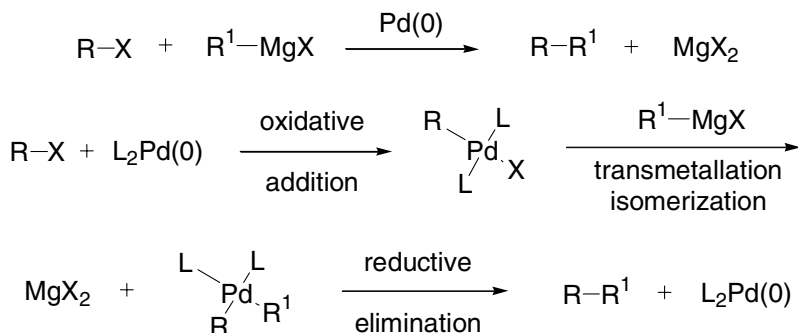
Example 1²Example 2¹⁰

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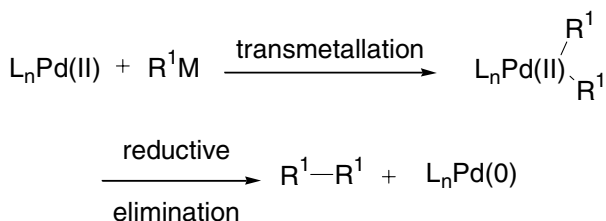
Kumada cross-coupling reaction

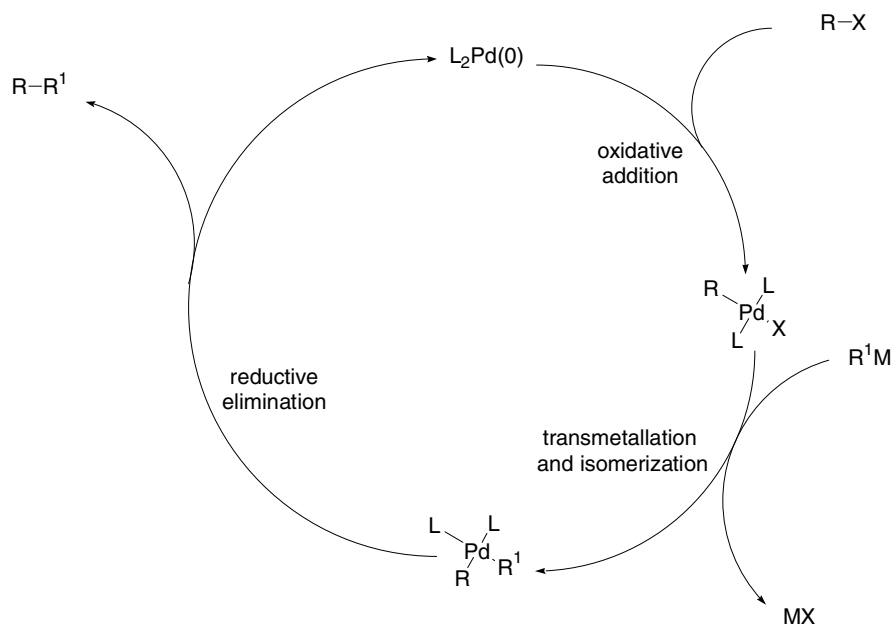
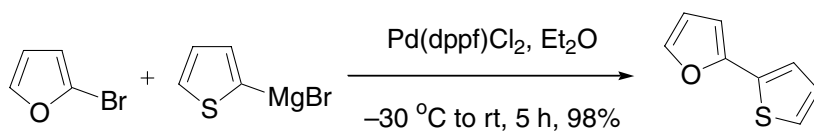
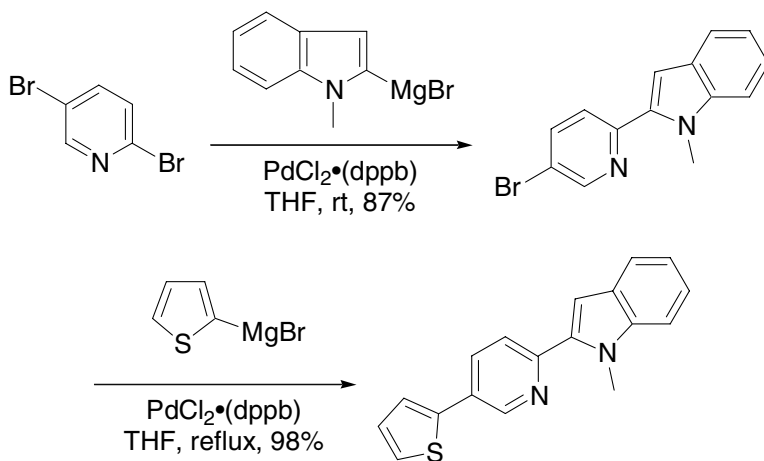
The Kumada cross-coupling reaction (also occasionally known as the Kharasch cross-coupling reaction) is a nickel- or palladium-catalyzed cross-coupling reaction of a Grignard reagent with an organic halide, triflate, *etc.*



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:



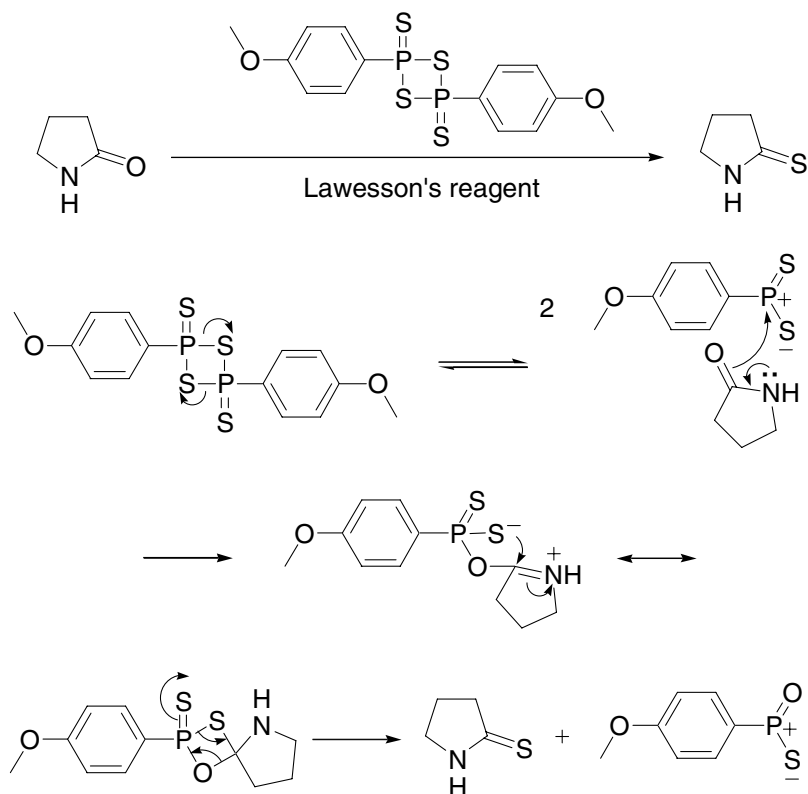
Example 1²Example 2⁴

References

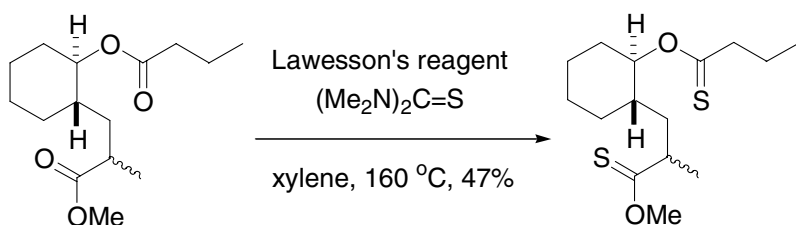
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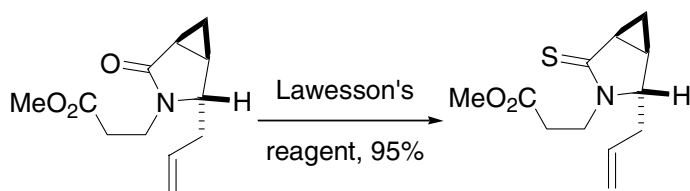
Lawesson's reagent

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 1⁴



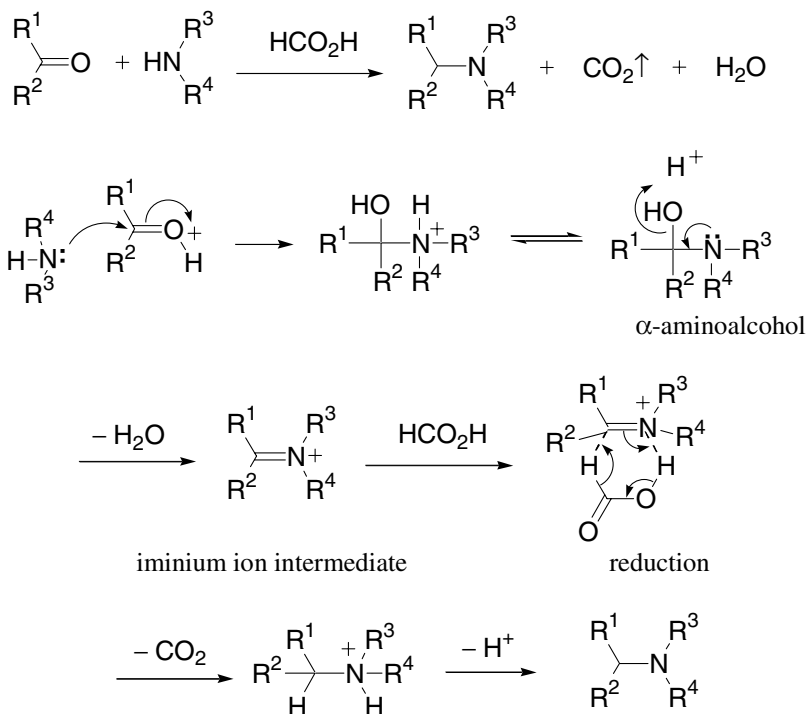
Example 2⁴

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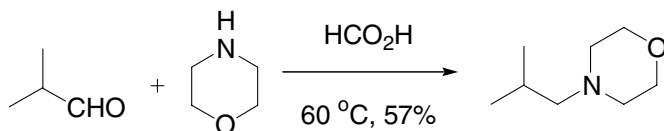
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Leuckart–Wallach reaction

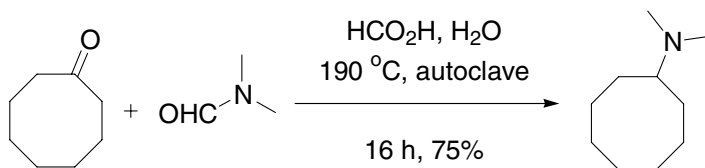
Amine synthesis from reductive amination of a ketone and an amine in the presence of excess formic acid, which serves as the reducing reagent by delivering a hydride. When the ketone is replaced by formaldehyde, it becomes Eschweiler–Clarke reductive alkylation of amines.



Example 1⁵



Example 2⁷

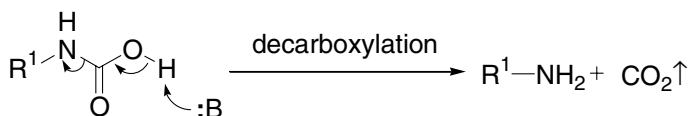
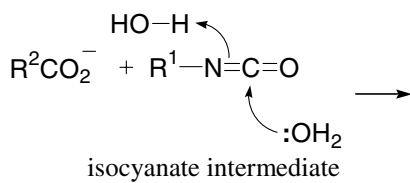
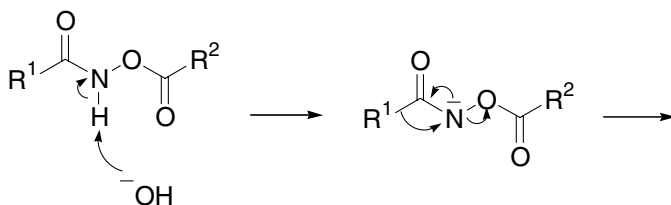
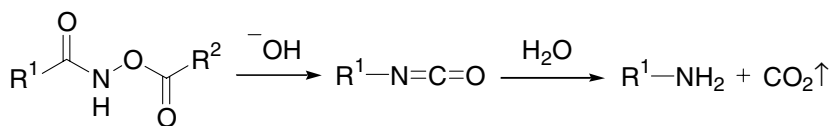


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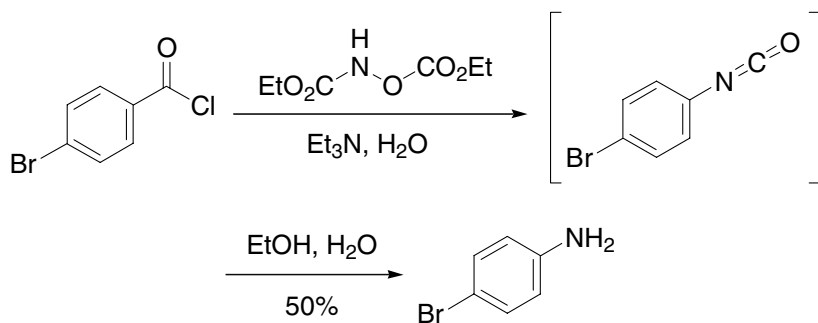
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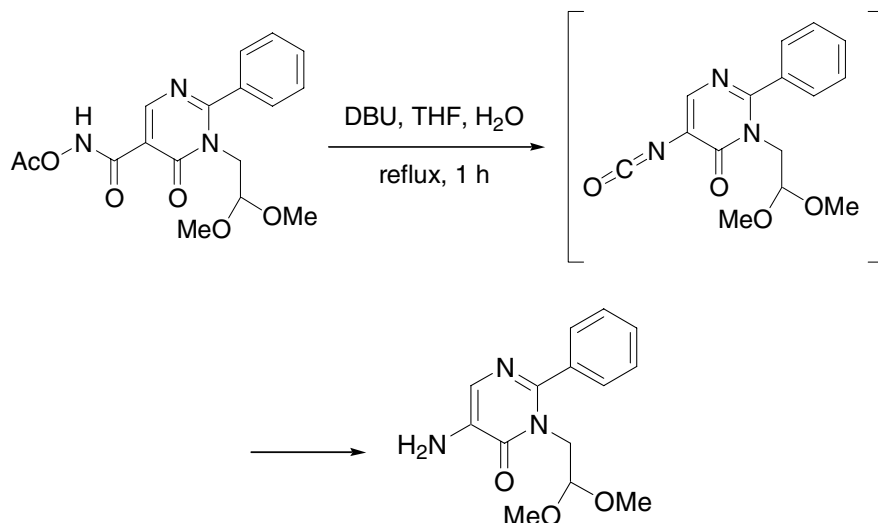
Lossen rearrangement

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



Example 1⁶



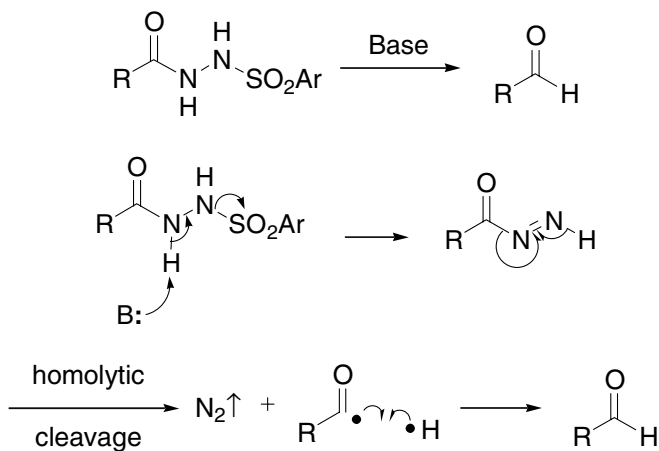
Example 2⁸

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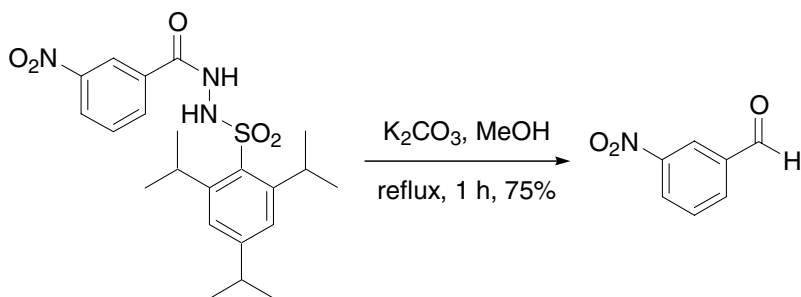
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McFadyen–Stevens reduction

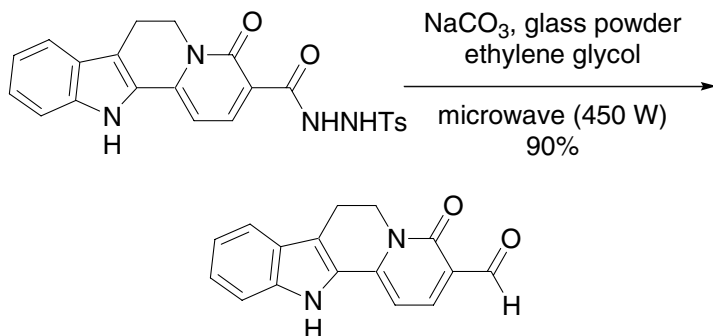
Treatment of acylbenzenesulfonylhydrazines with base delivers the corresponding aldehydes.



Example 1⁹



Example 2¹¹

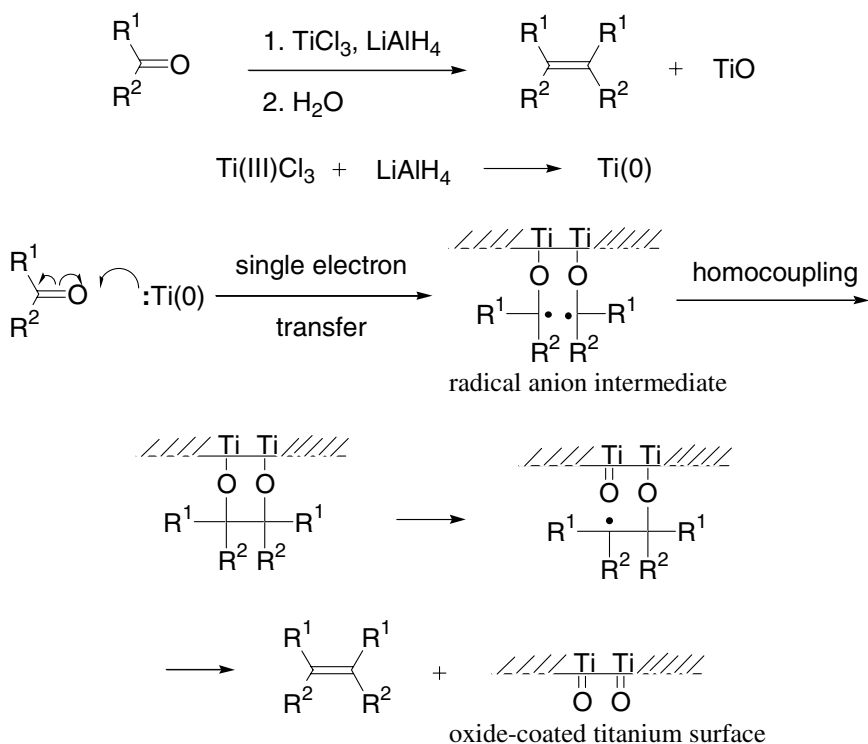


References

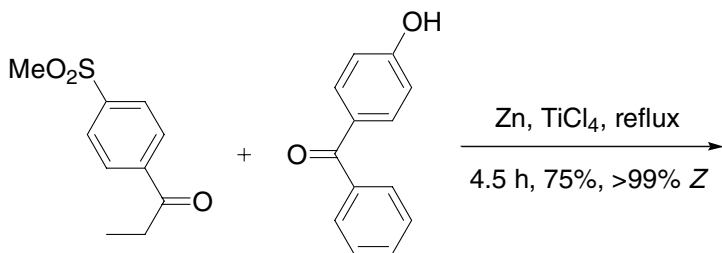
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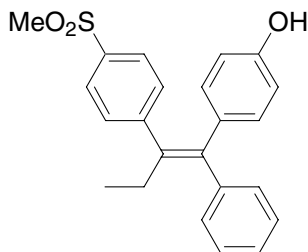
McMurry coupling

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

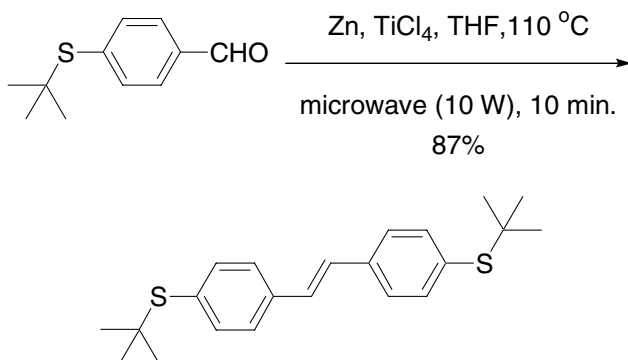


Example 1¹²





Example 2¹³

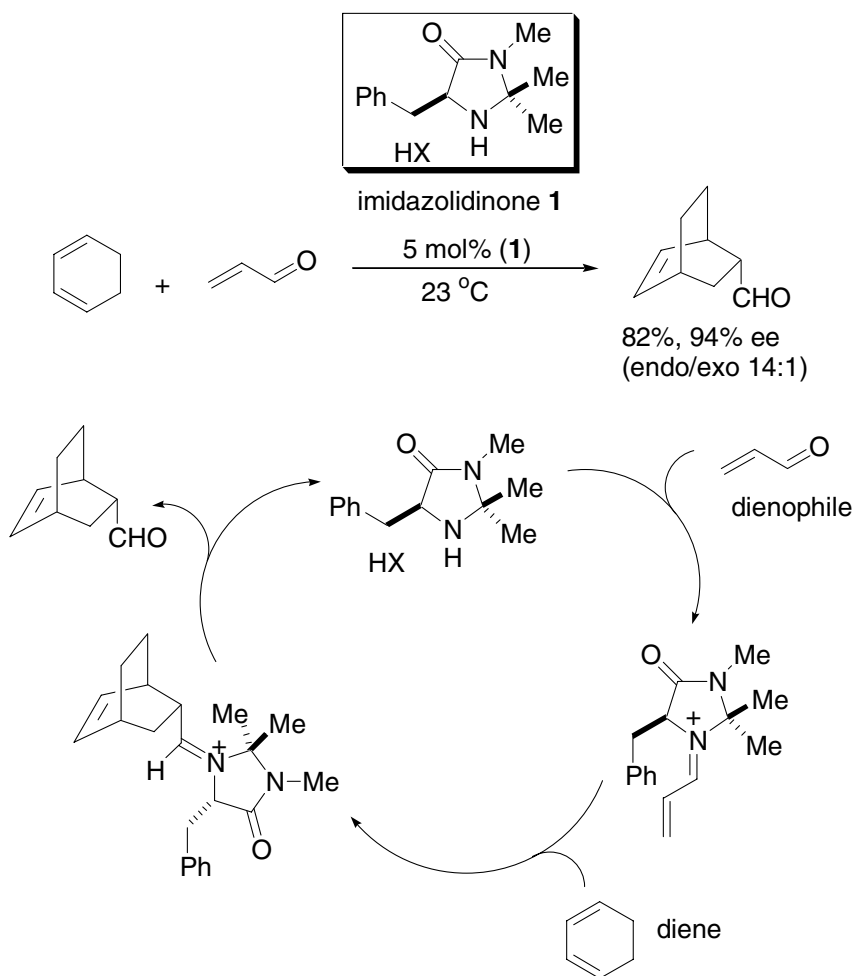


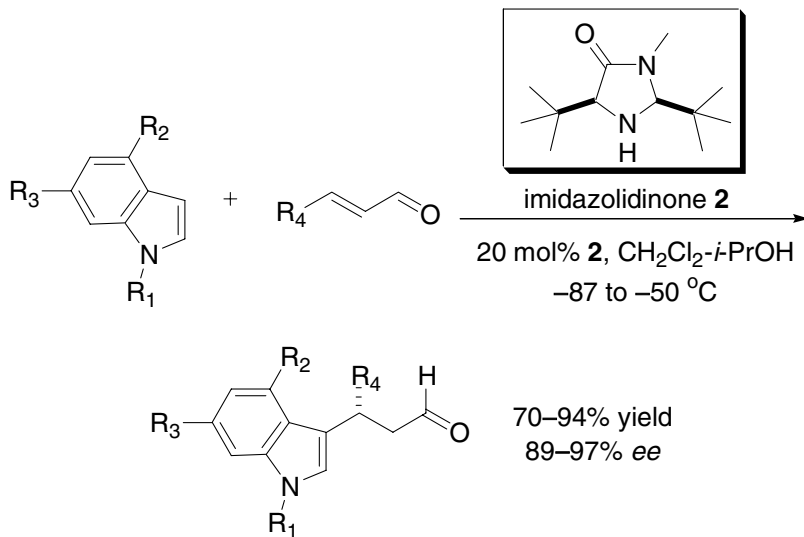
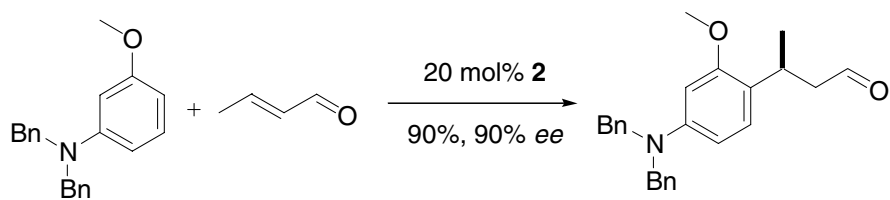
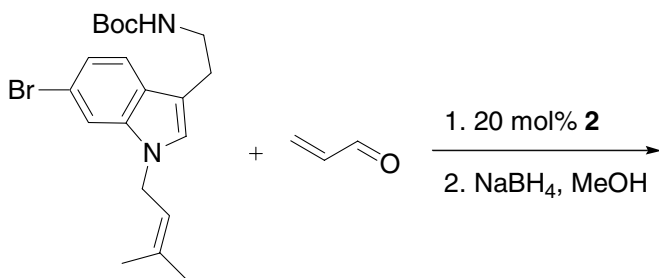
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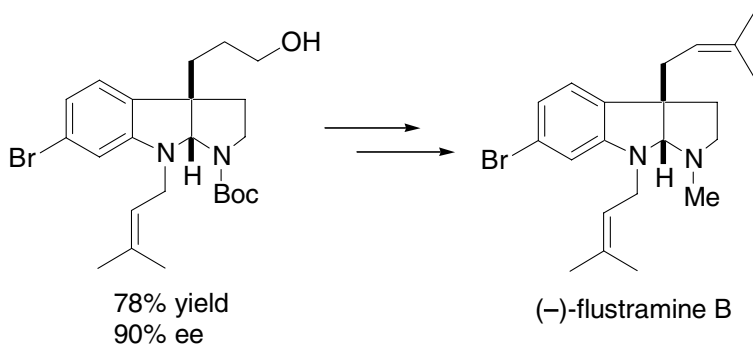
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MacMillan catalyst

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 nitronc 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 1¹¹Example 2¹⁰

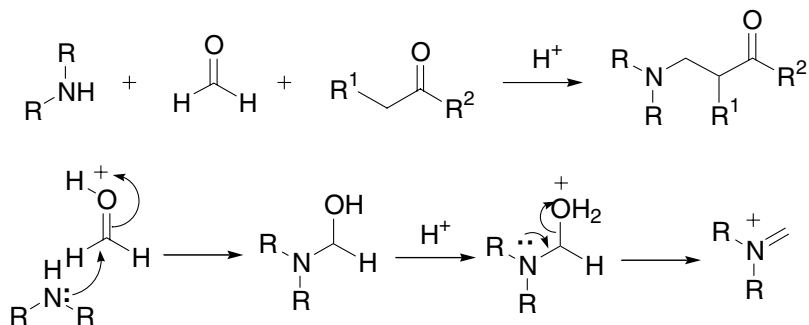


References

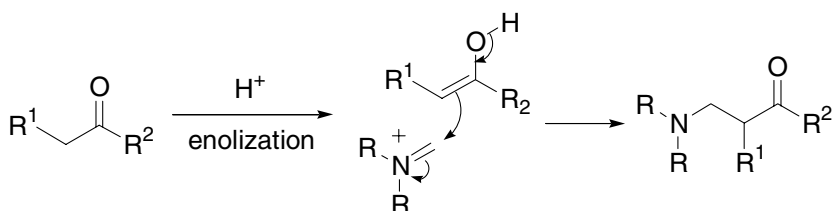
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Mannich reaction

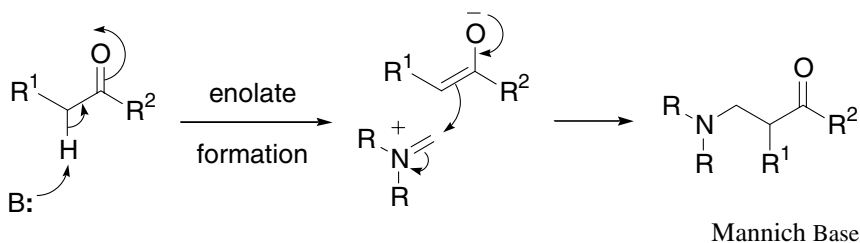
Three-component aminomethylation from amine, formaldehyde and a compound with an acidic methylene moiety.



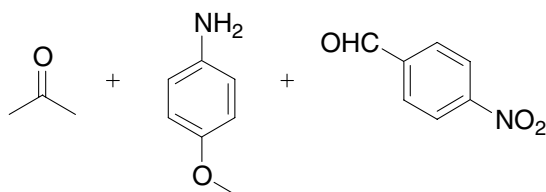
When $\text{R} = \text{H}$, the $^+\text{Me}_2\text{N}=\text{CH}_2$ salt is known as **Eschenmoser's salt**

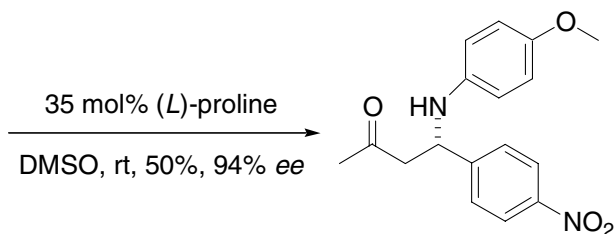


The Mannich reaction can also operate under basic conditions:

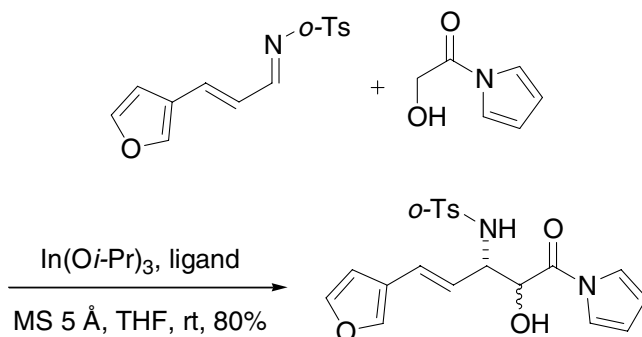


Example 1, asymmetric Mannich reaction⁴





Example 2, asymmetric aza-Mannich reaction¹³

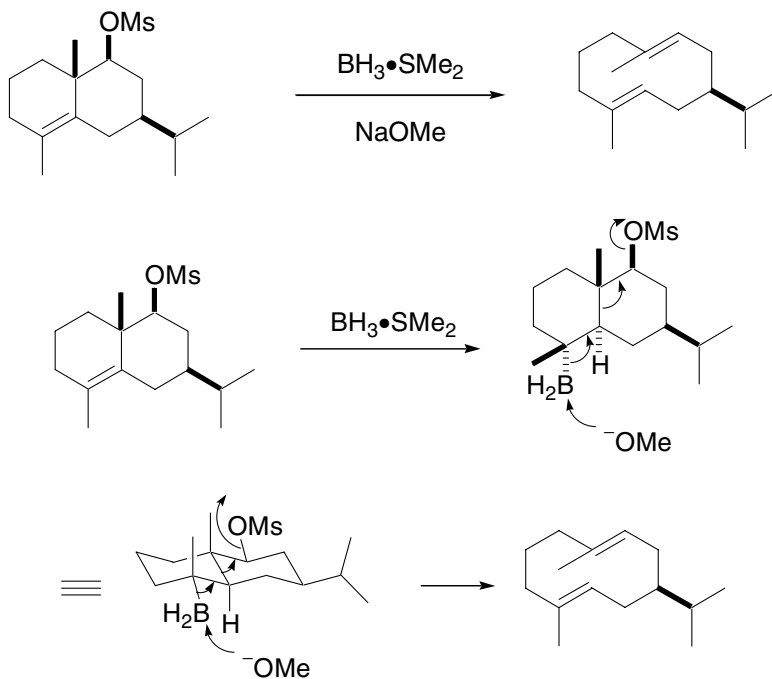


References

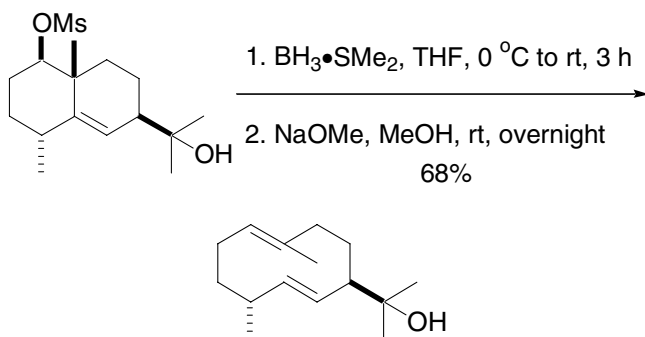
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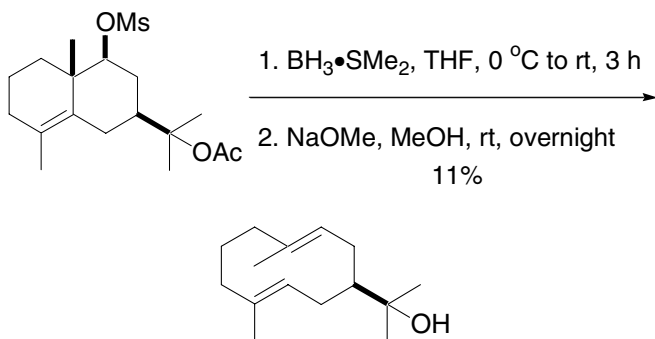
Marshall boronate fragmentation

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



Example 1⁵



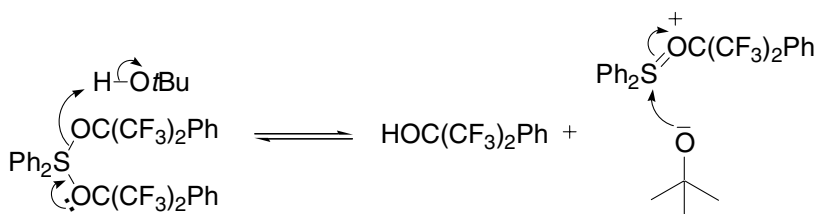
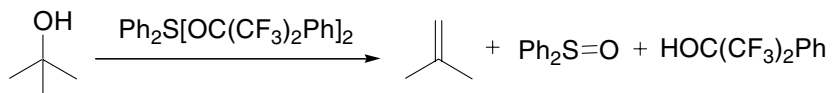
Example 2⁶

References

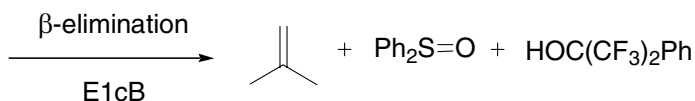
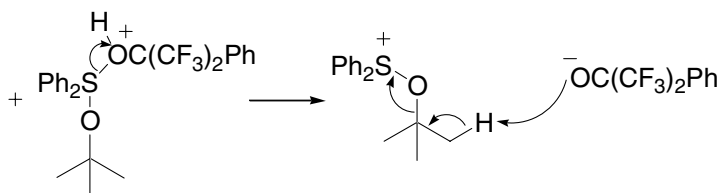
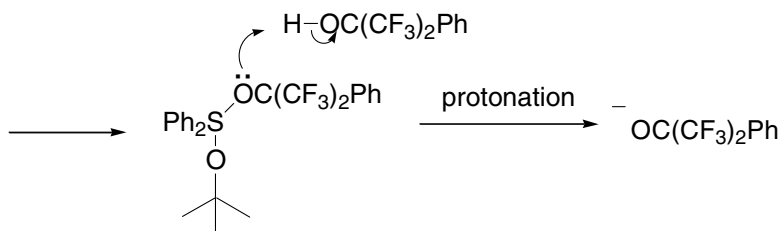
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Martin's sulfurane dehydrating reagent

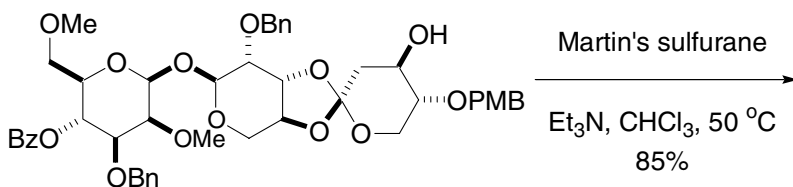
Dehydrates secondary and tertiary alcohols to give olefins, but forms ethers with primary alcohols. *Cf.* Burgess dehydrating reagent.

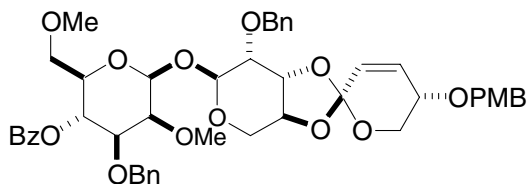
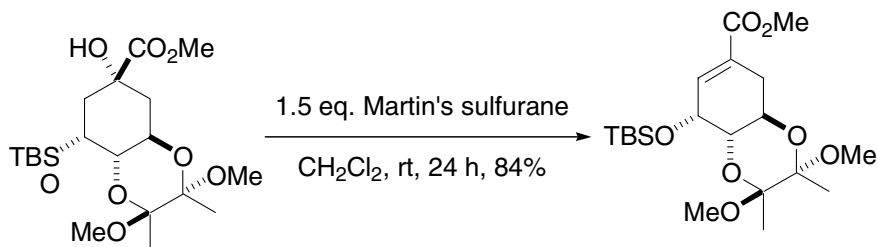


The alcohol is acidic



Example 1⁹



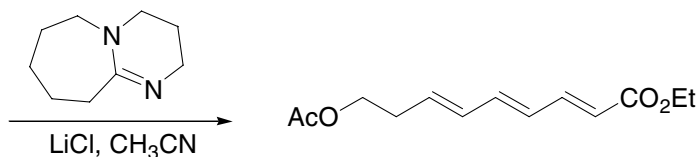
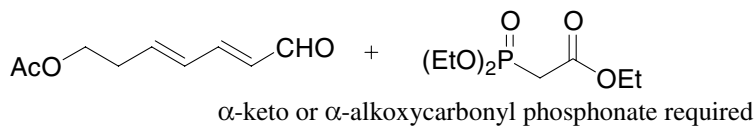
Example 2¹⁰

References

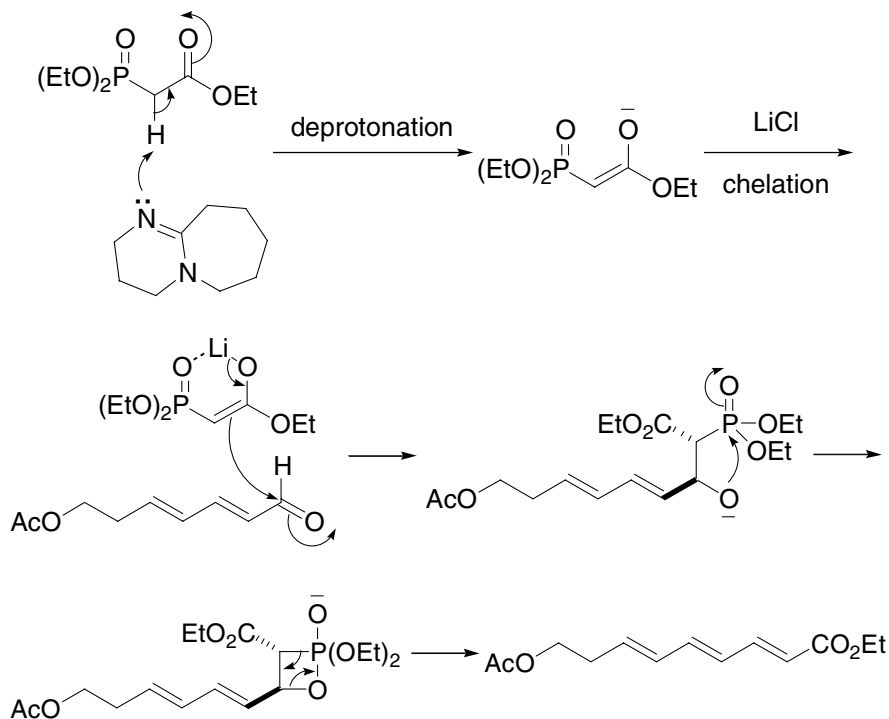
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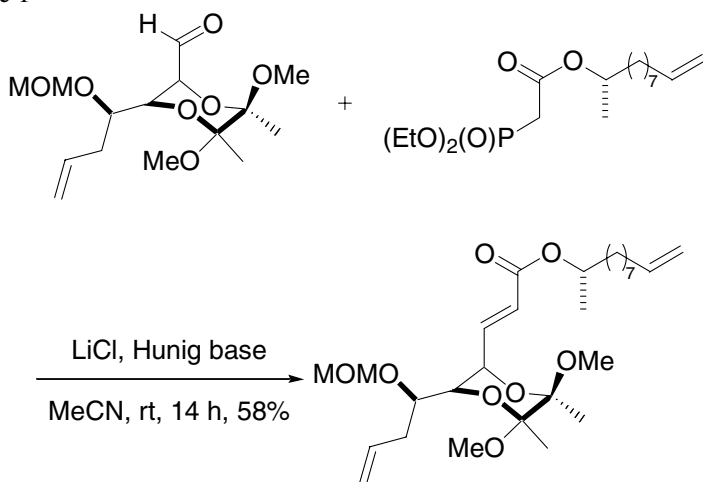
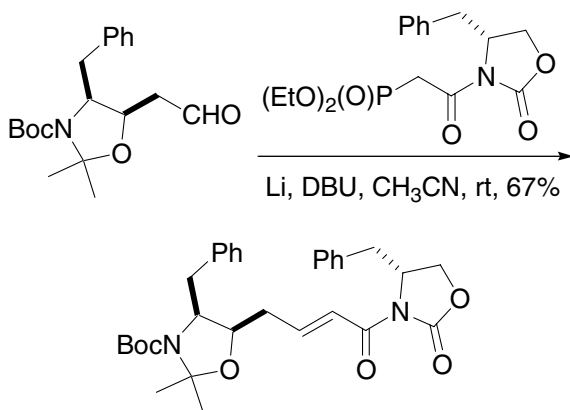
Masamune–Roush conditions

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



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



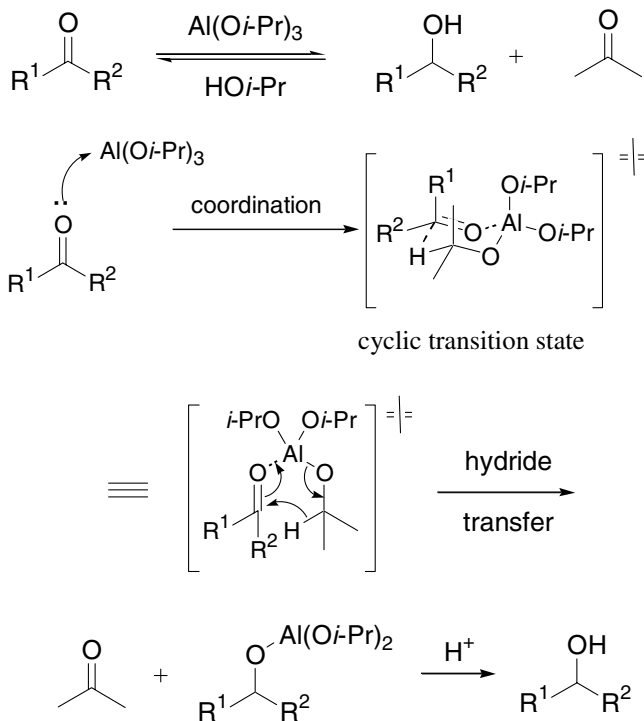
Example 1⁶Example 2⁷

References

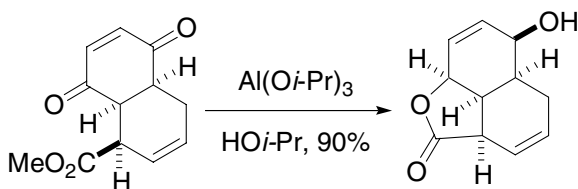
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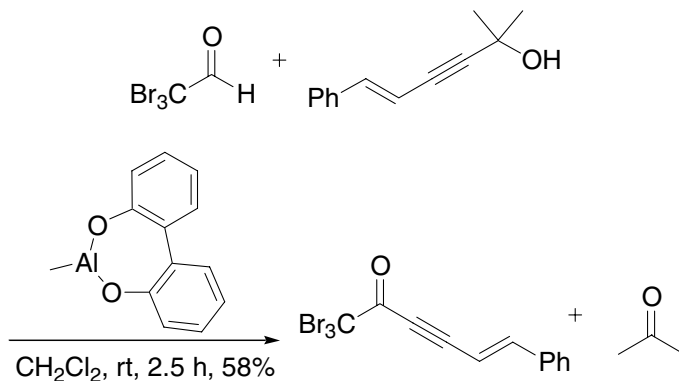
Meerwein–Ponndorf–Verley reduction

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



Example 1²



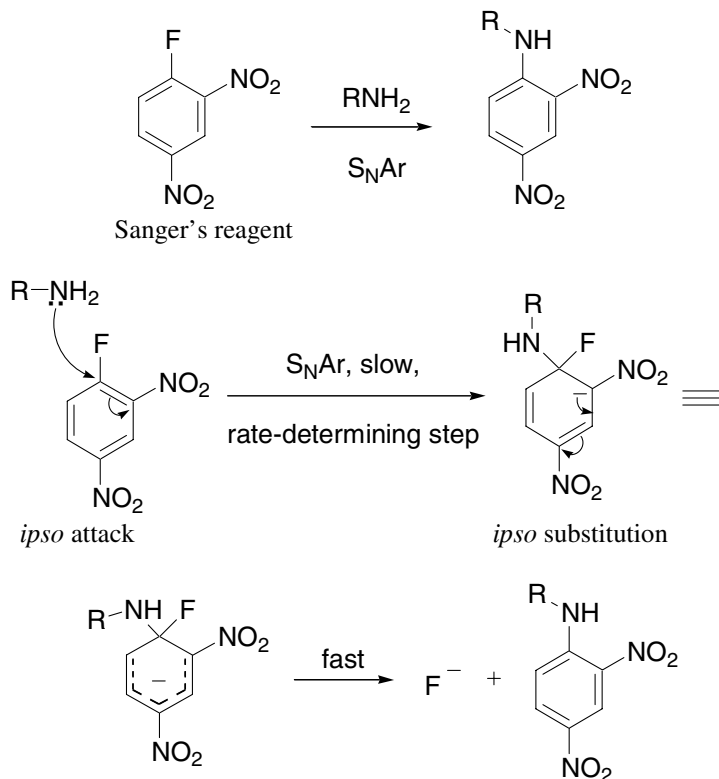
Example 2¹²

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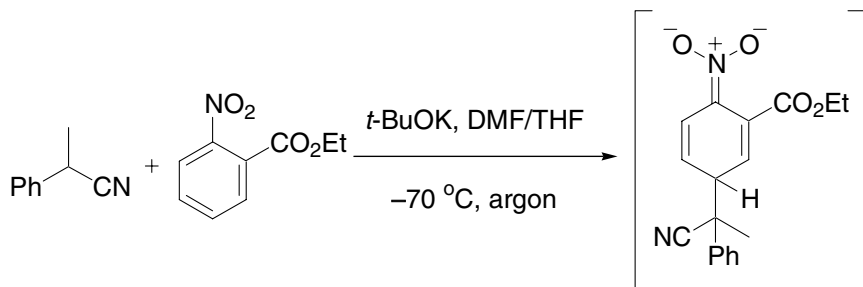
Meisenheimer complex

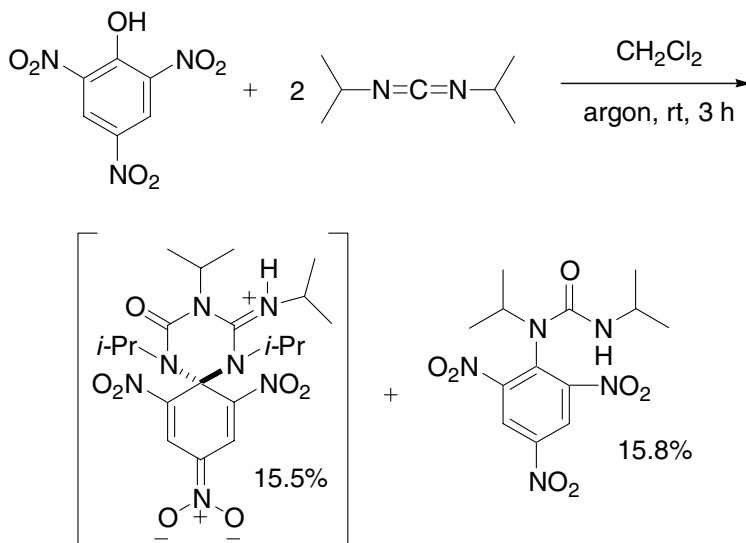
Also known as Meisenheimer–Jackson salt, the stable intermediate for certain S_NAr reactions.



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

Example 1¹⁰



Example 2¹³

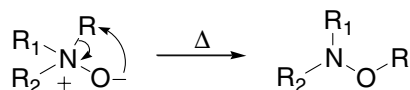
The reaction using Sanger's reagent is faster than using the corresponding chloro-, bromo-, and iodo-dinitrobenzene—the fluoro-Meisenheimer complex is the most stabilized because F is the most electron-withdrawing. The reaction rate does not depend upon the capacity of the leaving group.

References

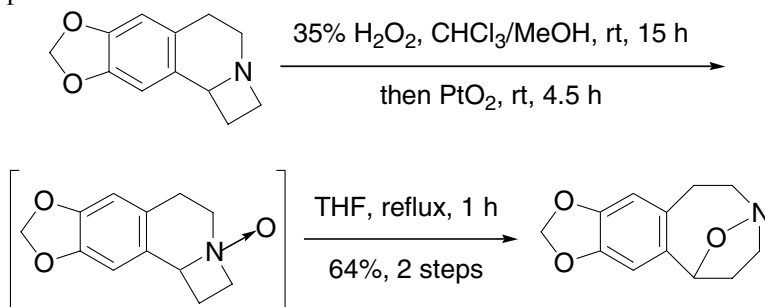
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[1,2]-Meisenheimer rearrangement

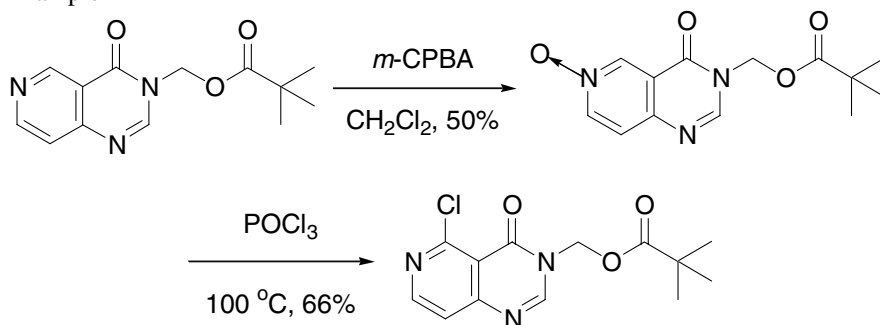
[1,2]-Sigmatropic rearrangement of tertiary amine *N*-oxides to hydroxylamines:



Example 1⁵



Example 2⁶

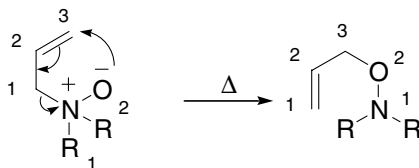


References

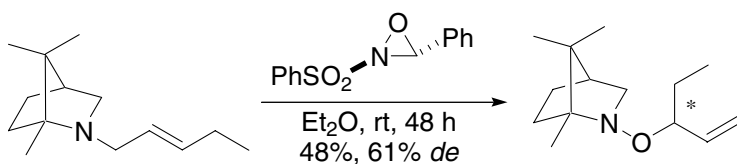
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[2,3]-Meisenheimer rearrangement

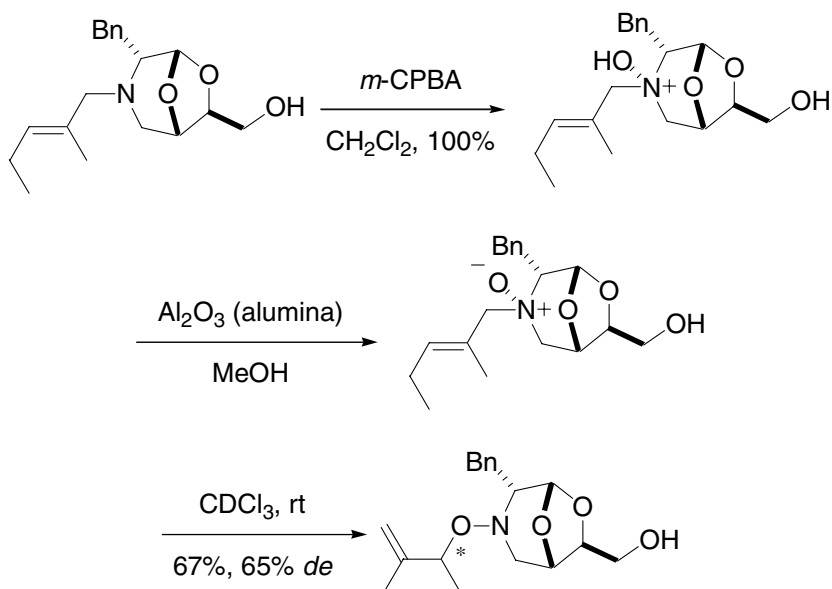
[2,3]-Sigmatropic rearrangement of allylic tertiary amine-*N*-oxides to give *O*-allyl hydroxylamines:



Example 1⁷



Example 2⁸

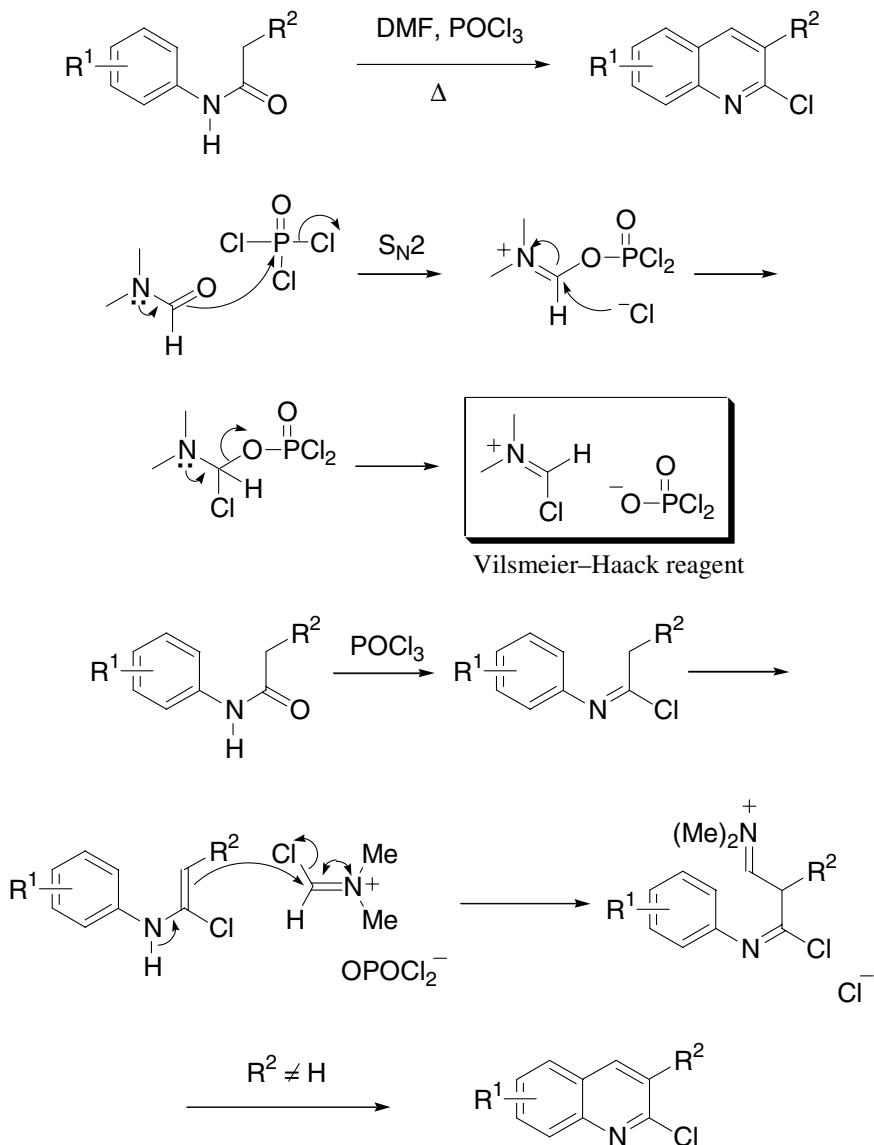


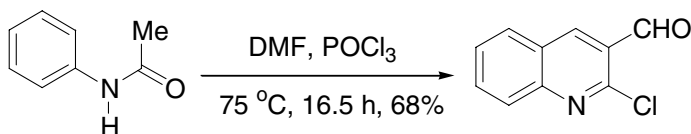
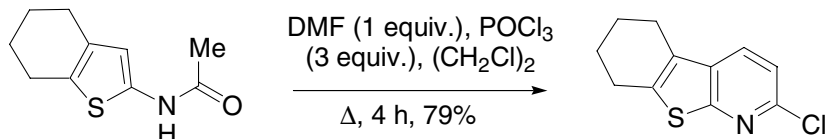
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Meth-Cohn quinoline synthesis

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



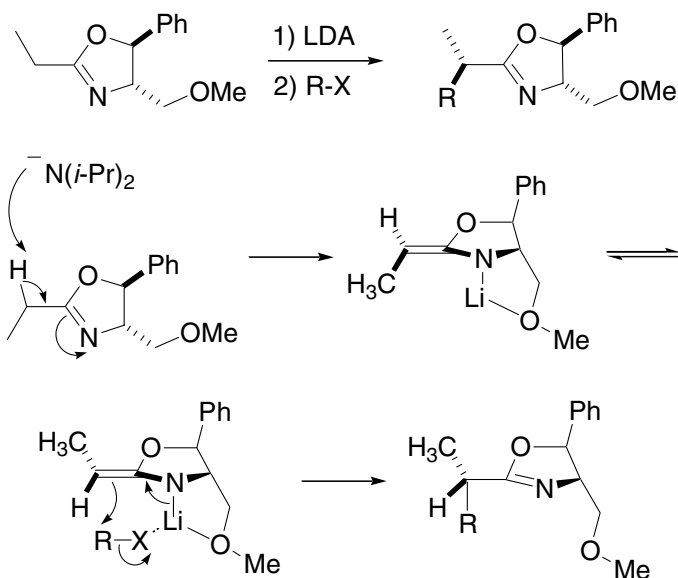
Example 1⁵Example 2⁵

References

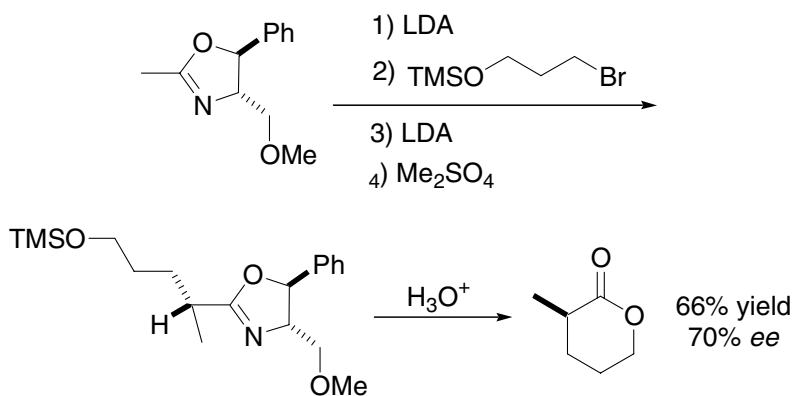
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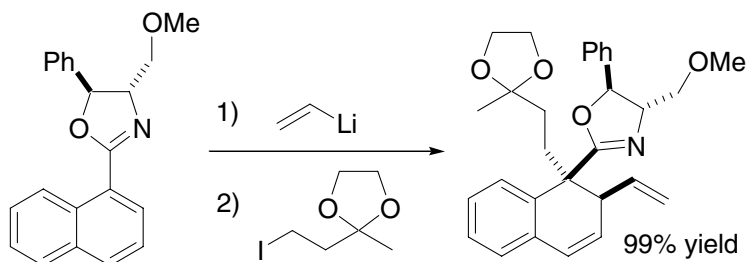
Meyers oxazoline method

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.



Example 1⁸



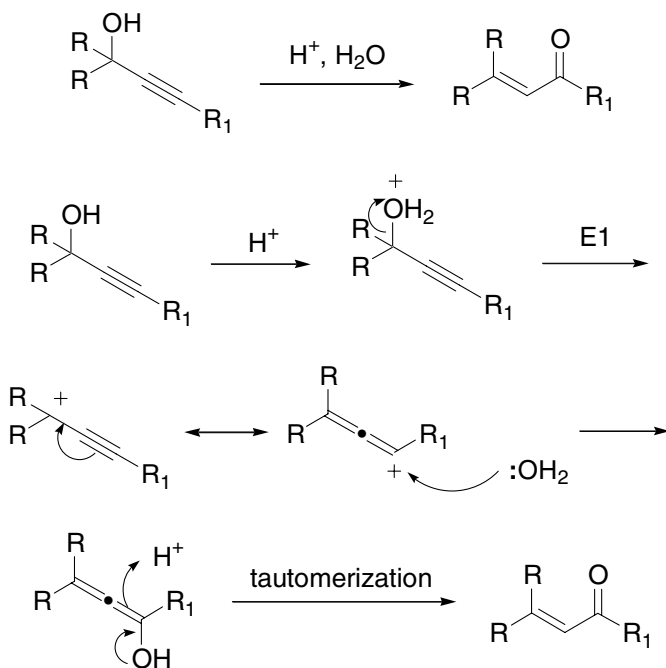
Example 2¹²

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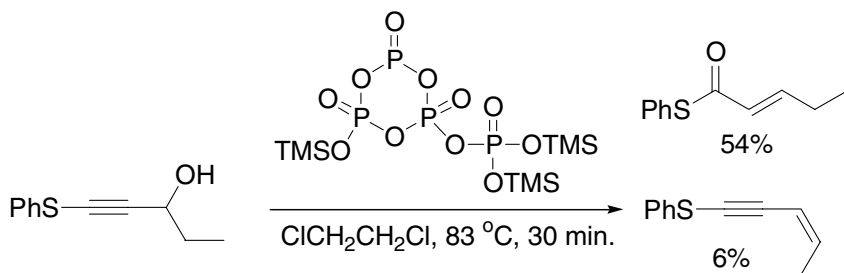
1. Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268. While Albert I. Meyers was an assistant professor at Wayne State University, neighboring pharmaceutical firm Parke-Davis (Drs. George Moersch and Harry Crooks) donated several kilograms of (1*S*, 2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (Meyers referred to it as the Parke-Davis diol), from which his chemistry with chiral oxazolines began. Meyers is currently Professor Emeritus at Colorado State University.
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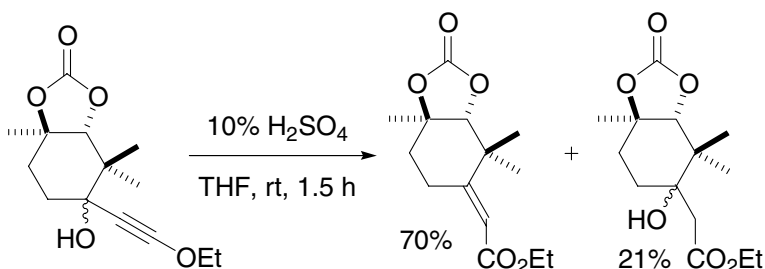
Meyer–Schuster rearrangement

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 1⁸



Example 2¹⁰

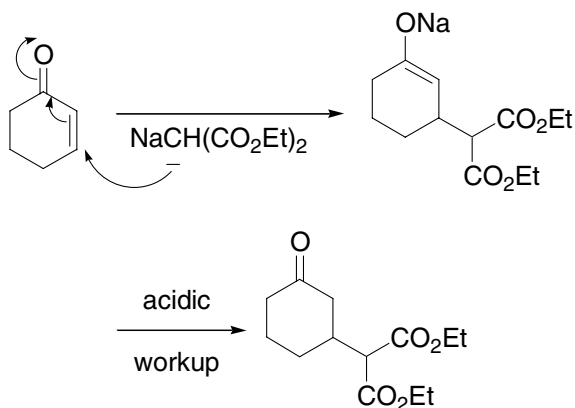
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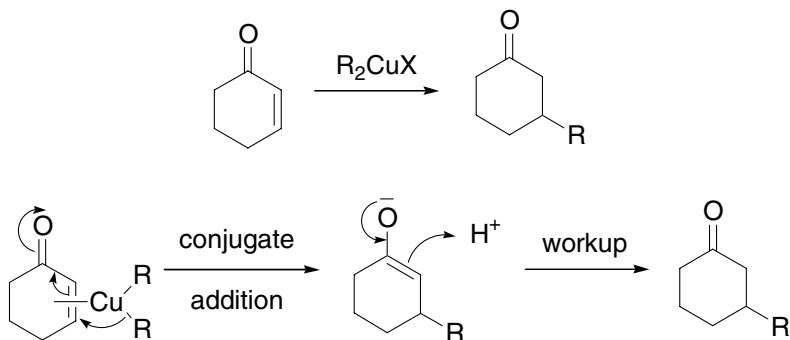
Michael addition

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

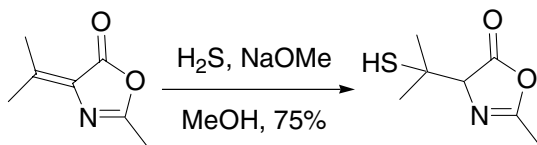
Example 1

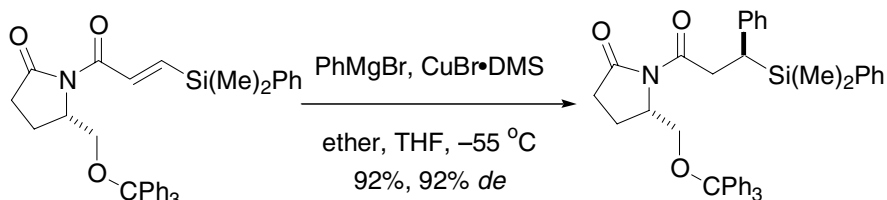


Example 2



Example 3⁴



Example 4³

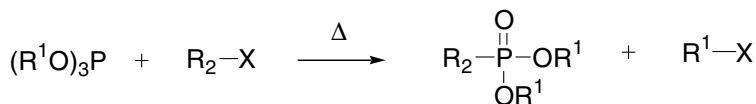
References

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Michaelis–Arbuzov phosphonate synthesis

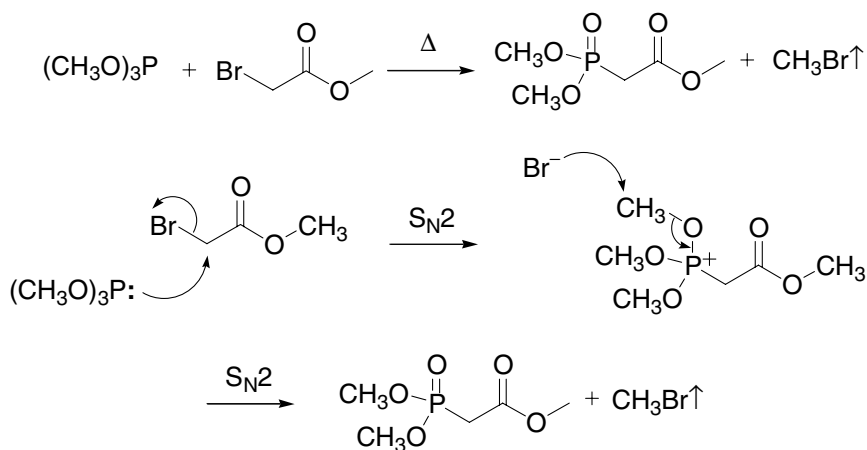
Phosphonate synthesis from the reaction of alkyl halides with phosphites.

General scheme:

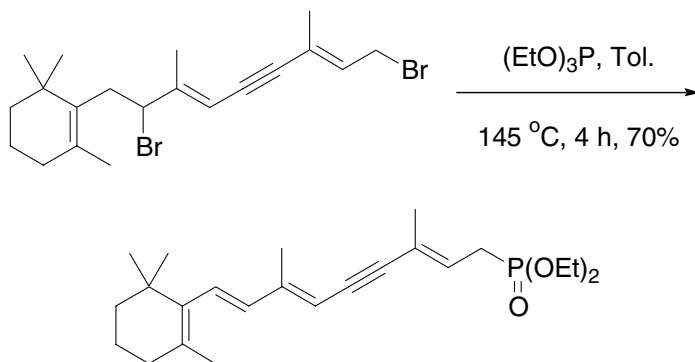


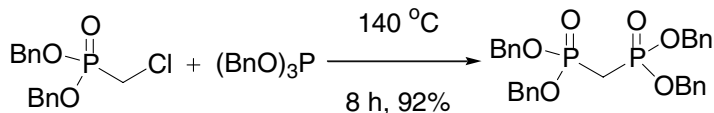
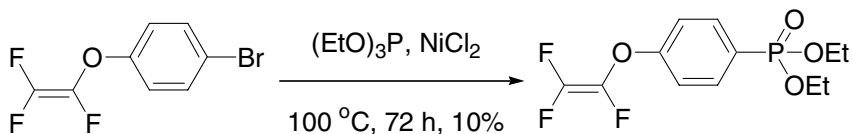
$\text{R}^1 = \text{alkyl, etc.}; \text{R}_2 = \text{alkyl, acyl, etc.}; \text{X} = \text{Cl, Br, I}$

For instance:



Example 1³



Example 2¹³Example 3¹⁴

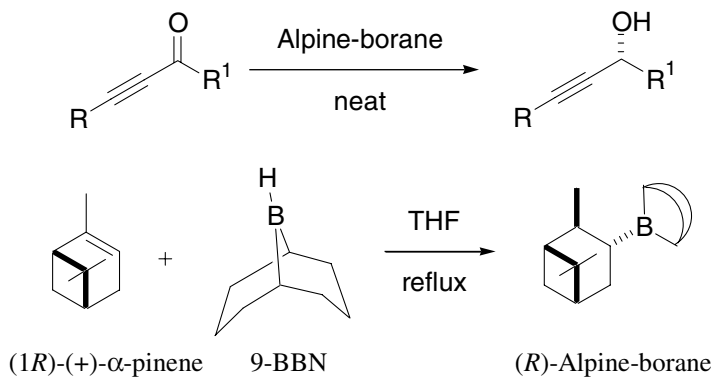
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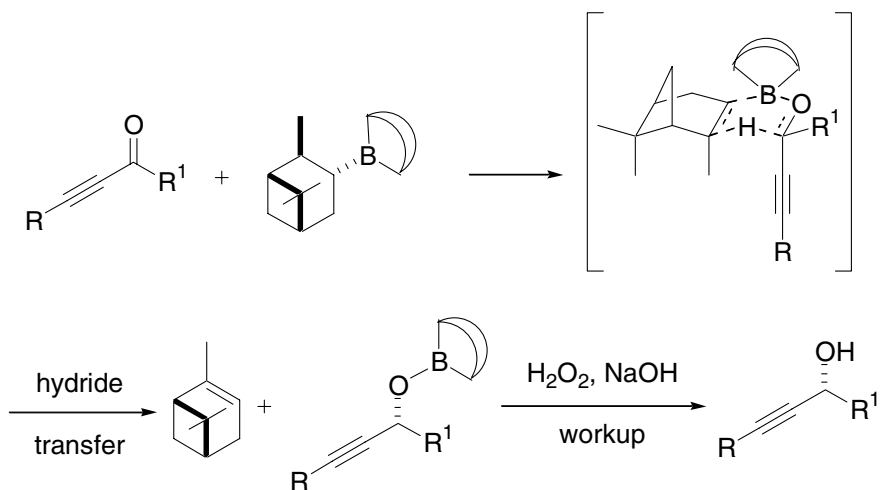
Midland reduction

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

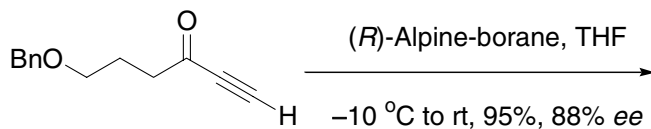
Alpine-borane[®] = *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane.

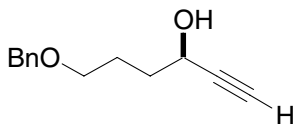
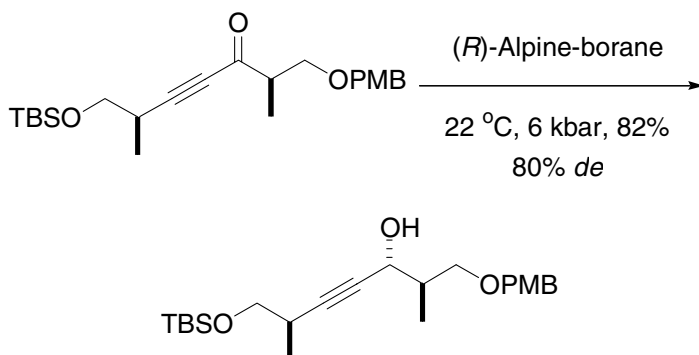


9-BBN = 9-borabicyclo[3.3.1]nonane



Example 1⁶



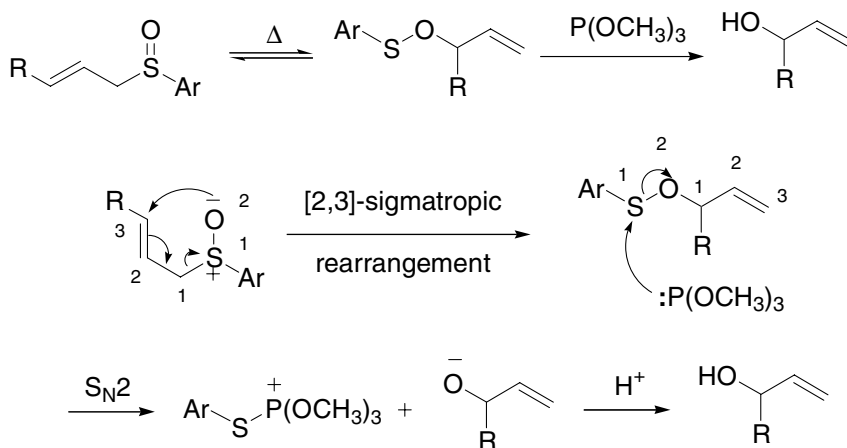
Example 2⁷

References

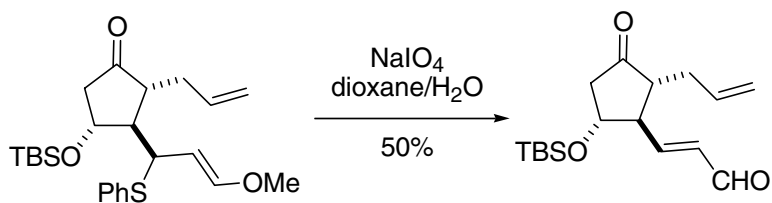
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Mislow–Evans rearrangement

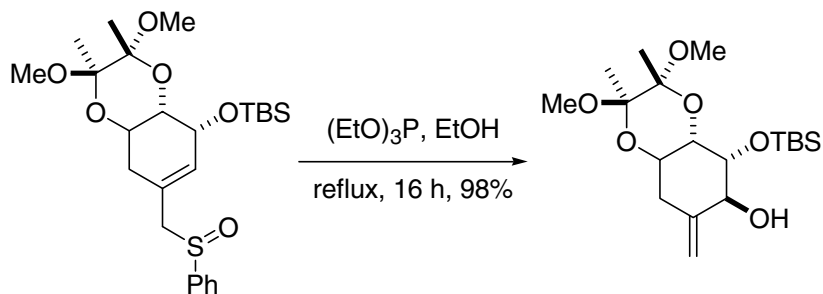
[2,3]-Sigmatropic rearrangement of allylic sulfoxide to allylic alcohol.



Example 1⁶



Example 2¹¹



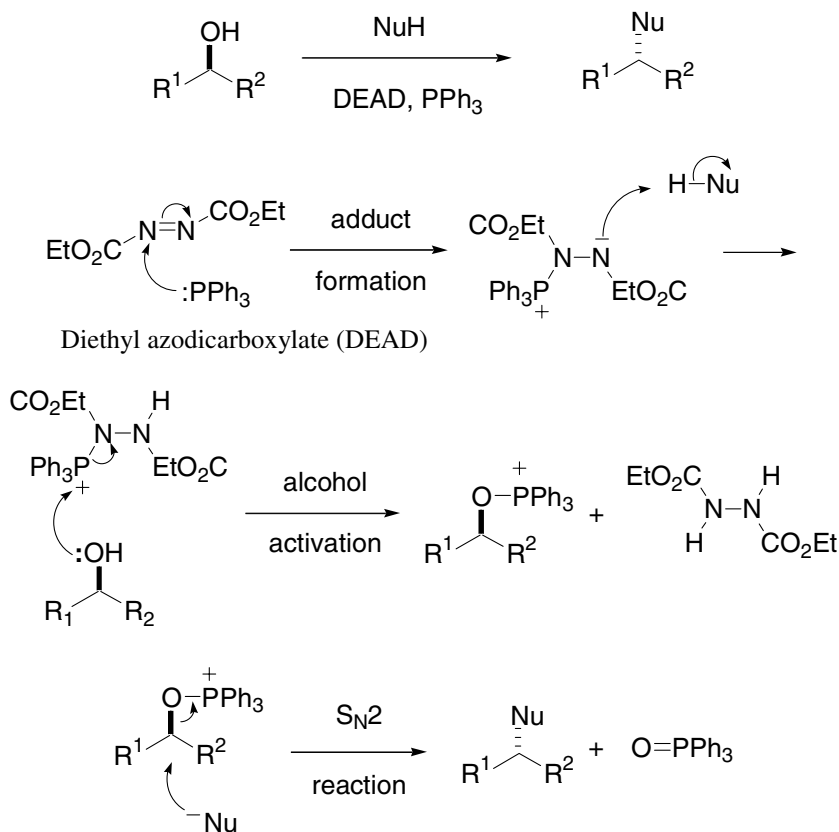
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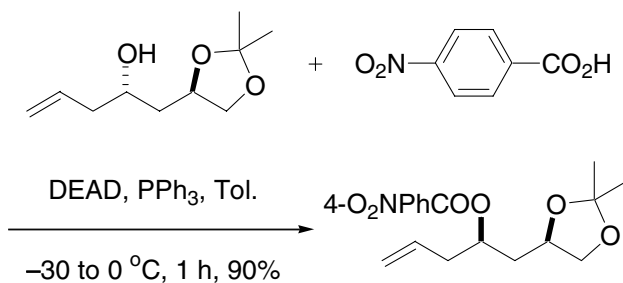
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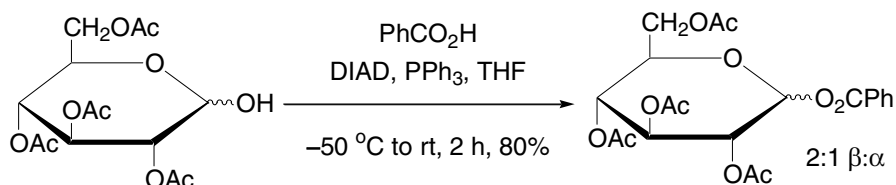
Mitsunobu reaction

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



Example 1⁴



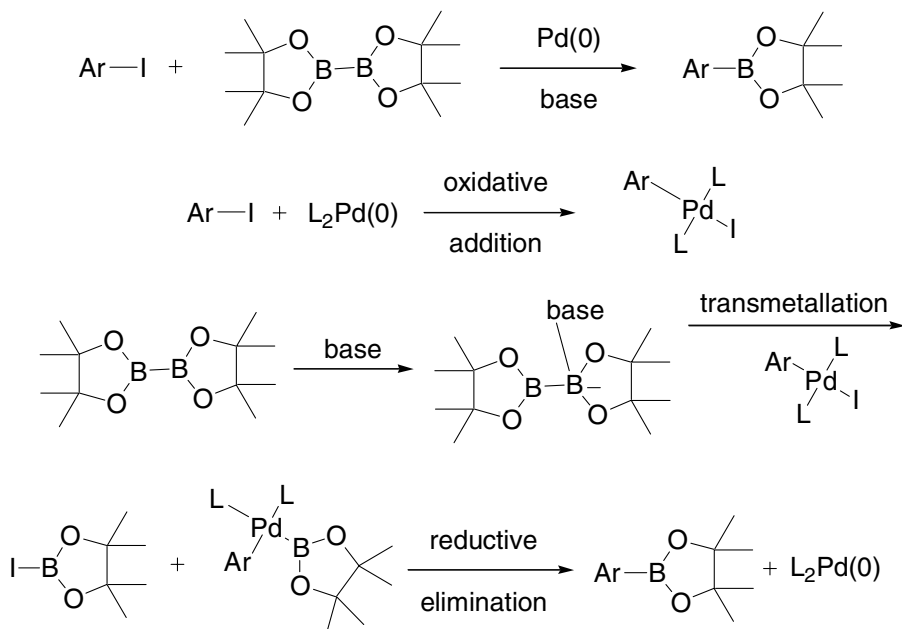
Example 2³

References

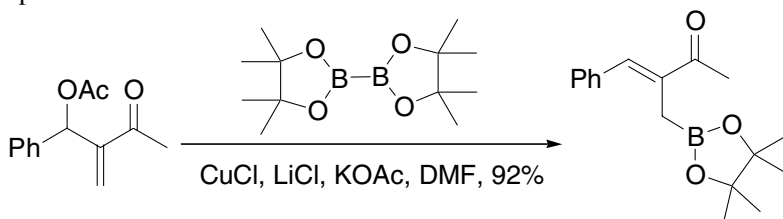
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Miyaura borylation

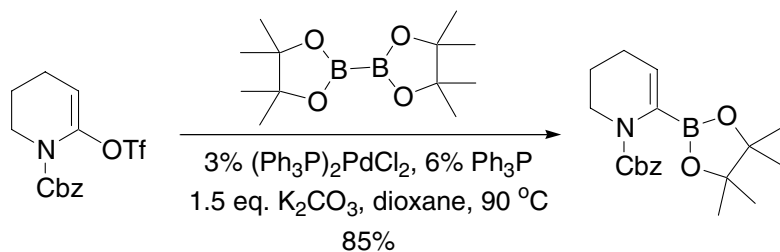
Palladium-catalyzed reaction of aryl halides with diboron reagent to produce arylboronates. Also known as Hosomi–Miyaura borylation.



Example 1¹¹



Example 2¹²

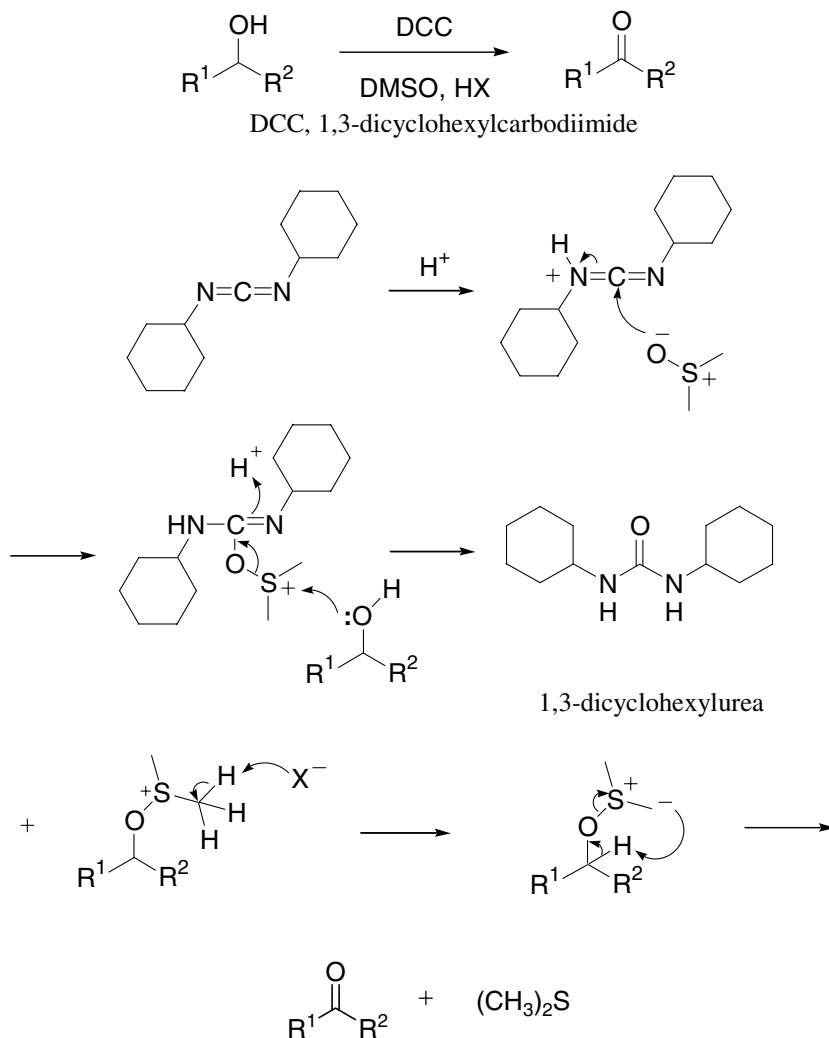


References

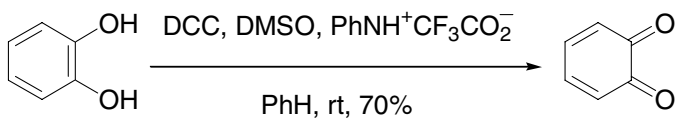
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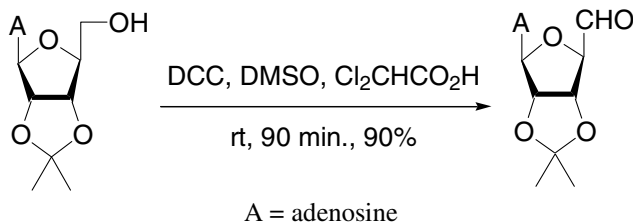
Moffatt oxidation

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



Example 1³



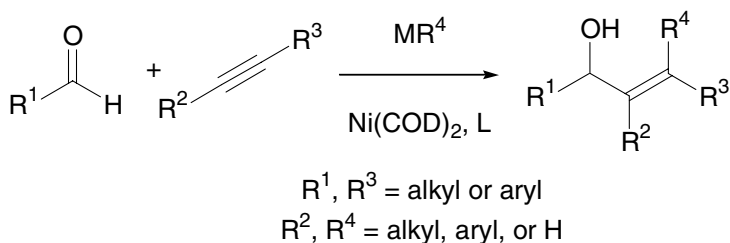
Example 2¹⁰

References

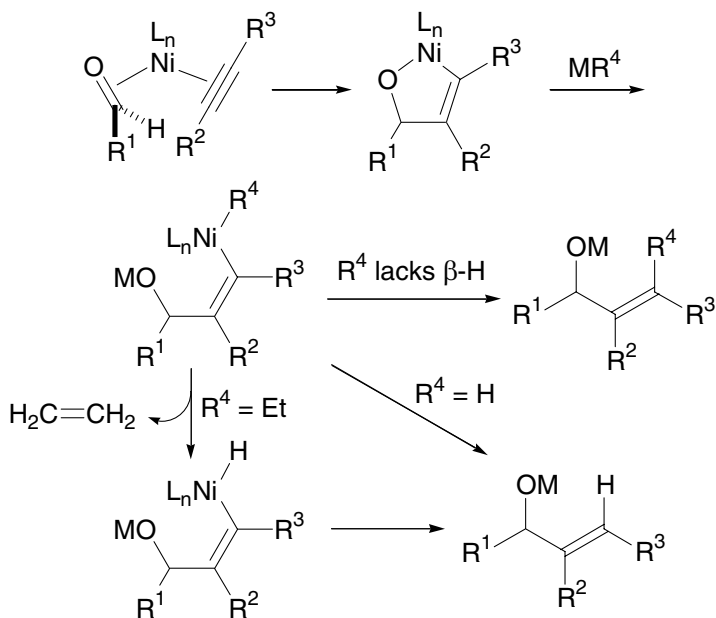
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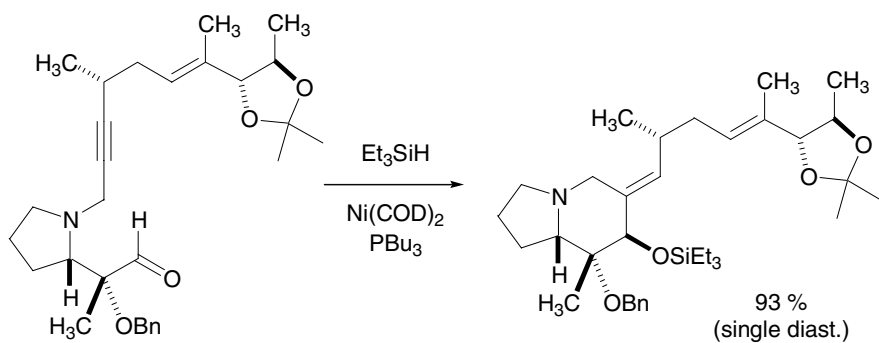
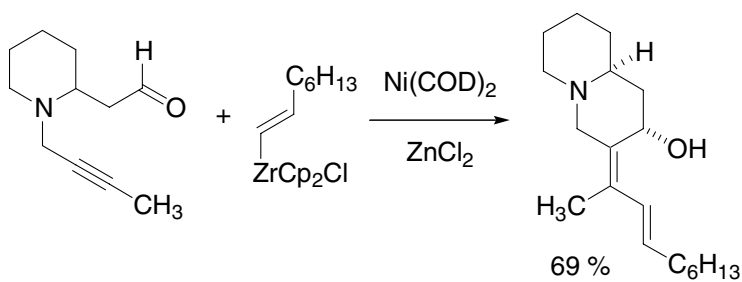
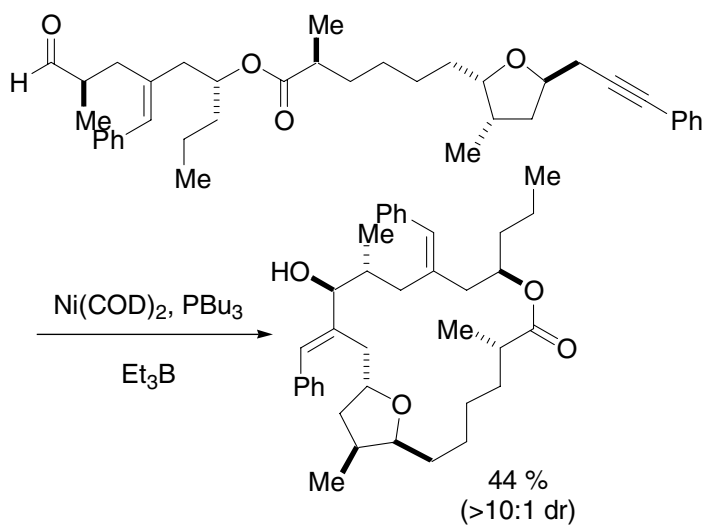
Montgomery coupling

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



The mechanism was proposed to involve the formation of a nickel metallacycle by the oxidative cyclization of $\text{Ni}(0)$ 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 $\text{R}^4 = \text{H}$ in some instances. The mechanism was shown to be ligand dependent, and the mechanism depicted below is undoubtedly oversimplified.⁴



Example 1⁶Example 2⁷Example 3⁸

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Reaction scheme showing the synthesis of macrocyclic enones and enol ethers from a long-chain alkyne-alkenal derivative.

Starting material: A long-chain molecule containing an alkyne and an alkenal moiety.

Reaction conditions: Ni(COD)_2 , ligand, reducing agent.

Products:

- Macrocyclic enone (left): A large ring containing an enone and an ester group.
- Macrocyclic enol ether (right): A large ring containing an enol ether and an ester group.

Reaction conditions table:

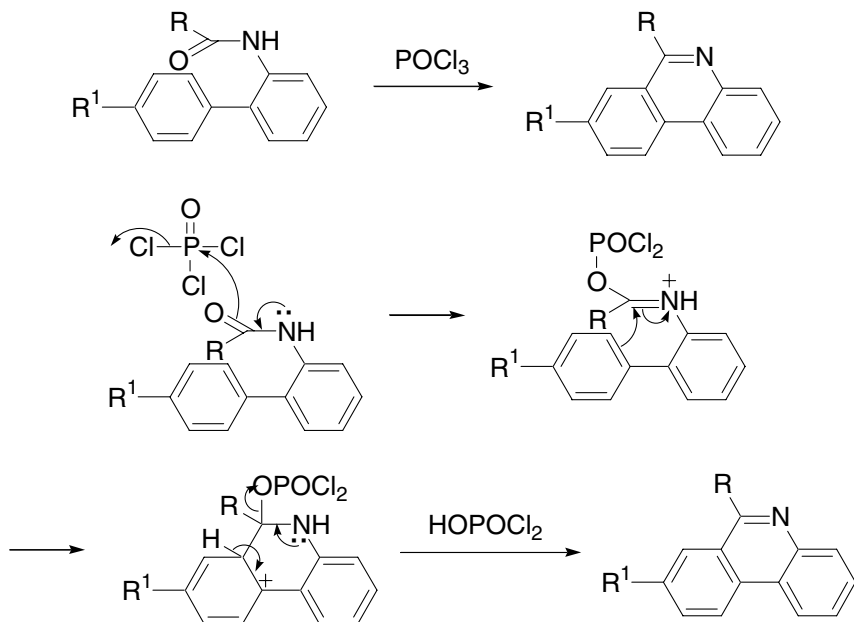
ligand	reducing agent	yield (ratio)
PMe_3	Et_3B	89 % (4.5:1)
$\text{Ar-N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{N-Ar}$	Et_3SiH	93 % (1:5)

Ar = 2,6 di-isopropylphenyl

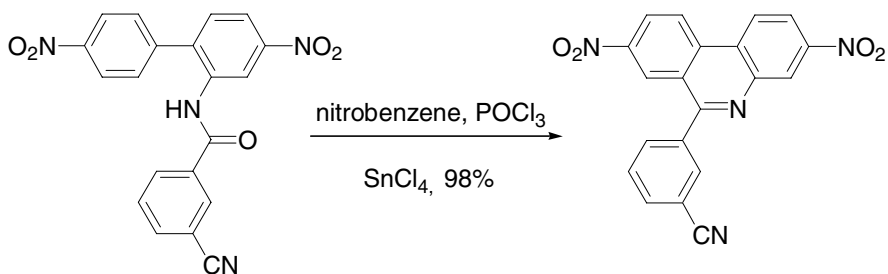
A number of related processes involving alternate π -systems including enones, dienes, and allenes have been reported.¹⁰

Morgan–Walls reaction

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

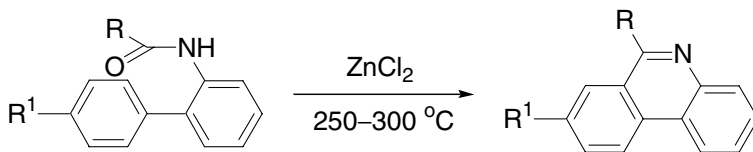


Example 1¹⁰

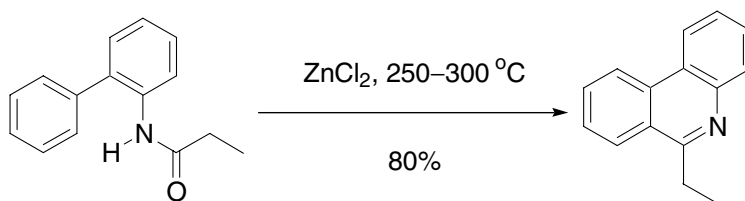


Pictet–Hubert reaction

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



Example 2⁷

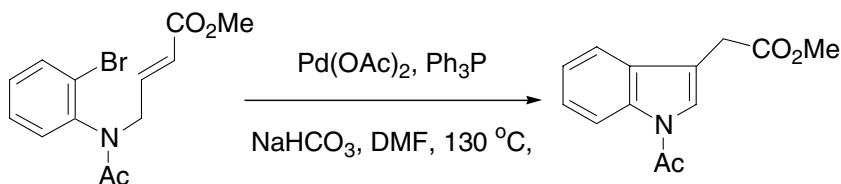


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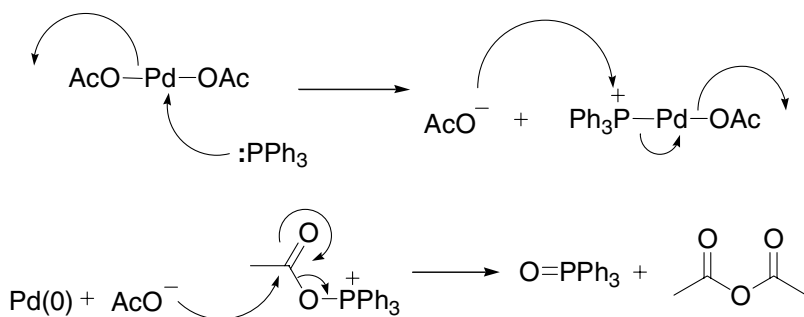
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Mori–Ban indole synthesis

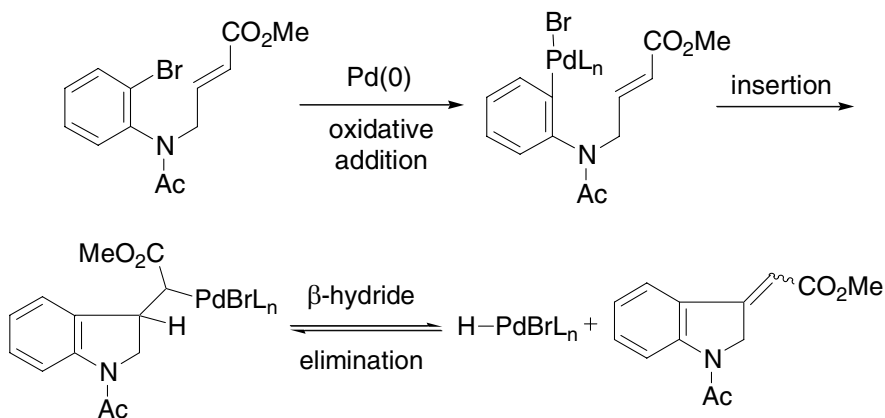
Intramolecular Heck reaction of *o*-halo-aniline with pendant olefin to prepare indole.

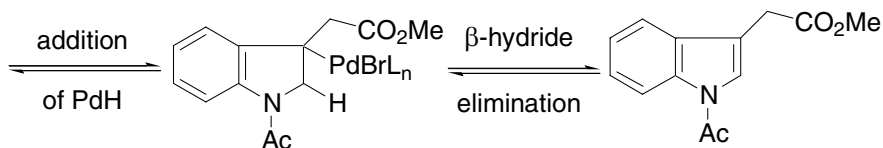


Reduction of $\text{Pd}(\text{OAc})_2$ to $\text{Pd}(0)$ using Ph_3P :



Mori–Ban indole synthesis:

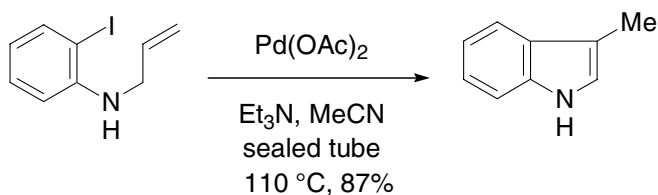




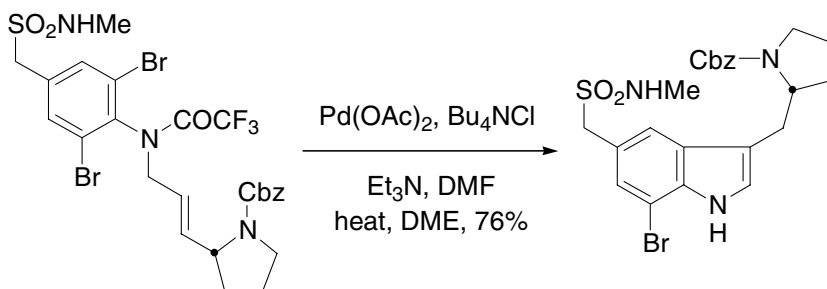
Regeneration of Pd(0):



Example 1¹



Example 2¹²

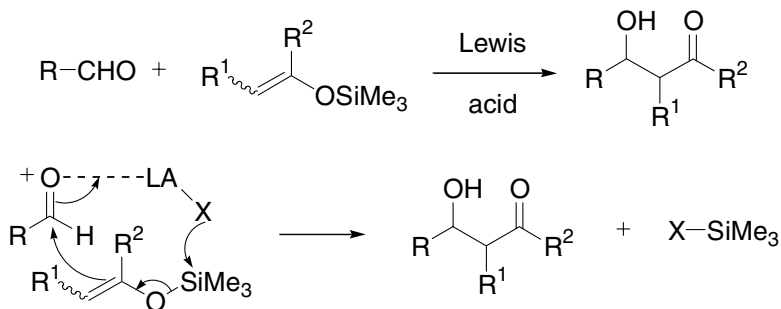


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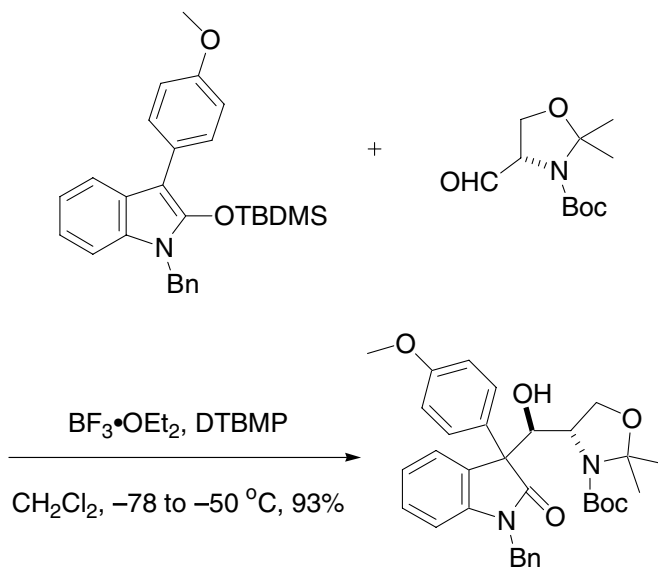
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Mukaiyama aldol reaction

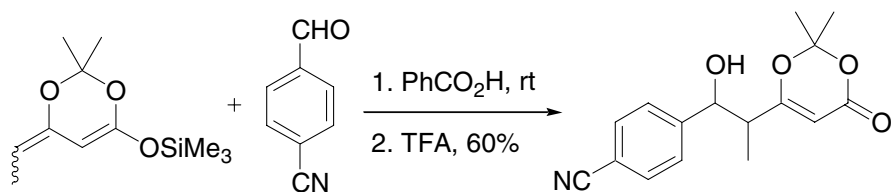
Lewis acid-catalyzed aldol condensation of aldehyde and silyl enol ether.



Example 1¹⁴



Example 2¹⁵

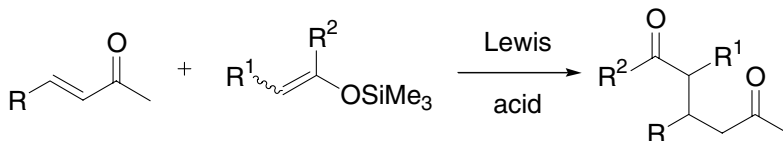


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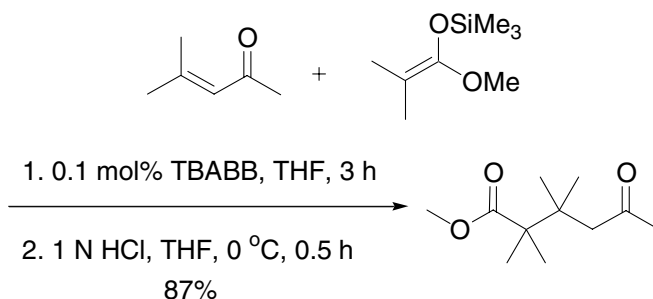
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Mukaiyama Michael addition

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

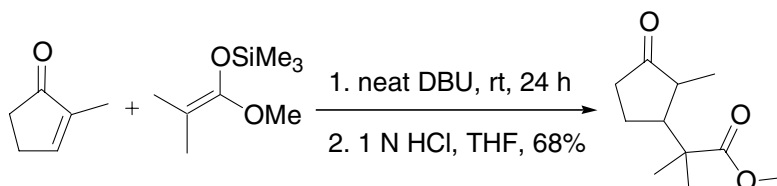


Example 1⁴



TBABB = tetra-*n*-butylammonium bibenzoate

Example 2⁷



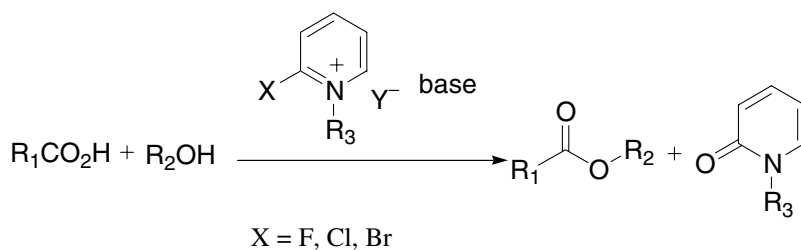
References

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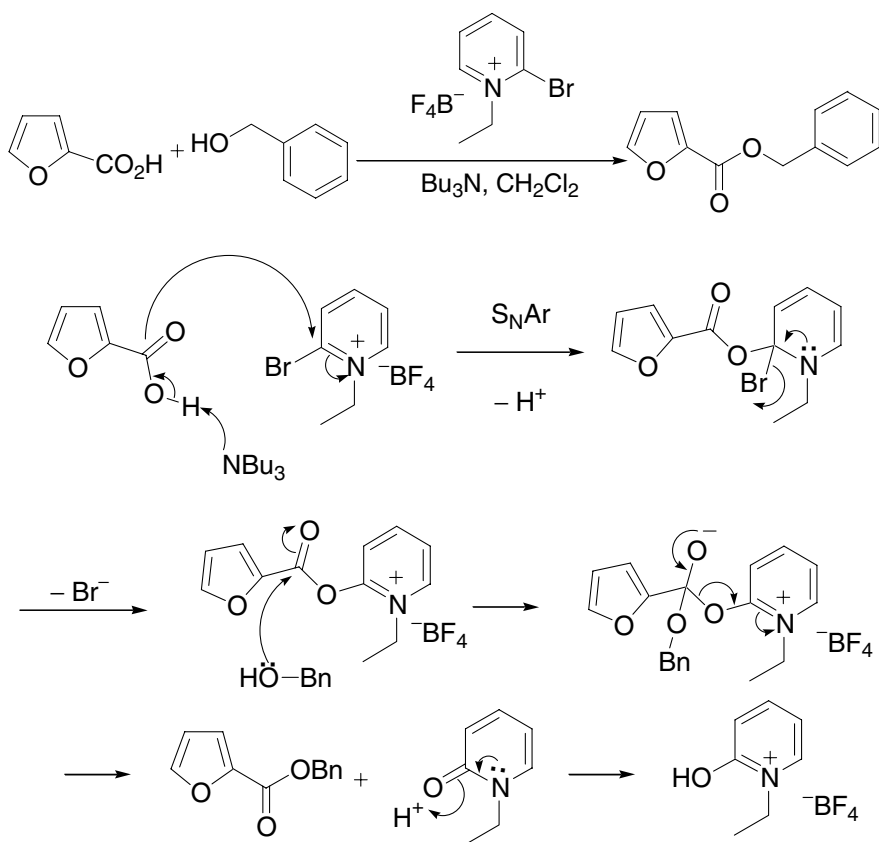
Mukaiyama reagent

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

General scheme:

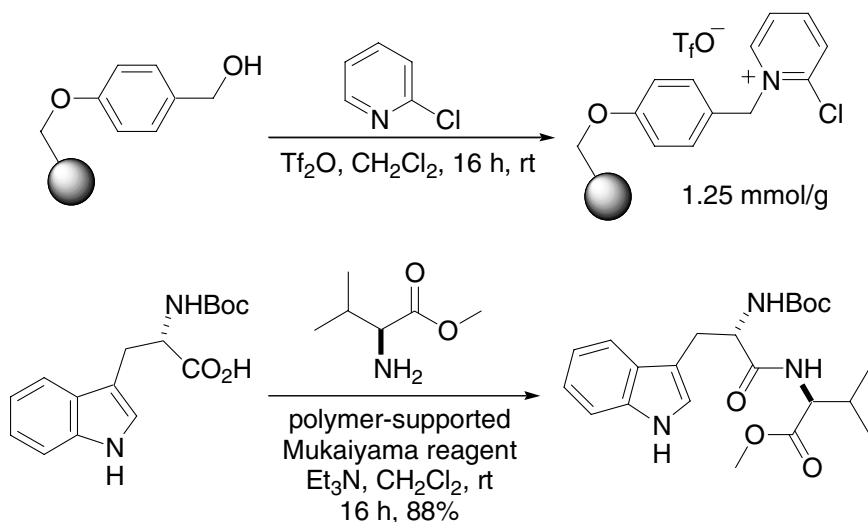


Example 1³



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

Example 2, polymer-supported Mukaiyama reagent⁸

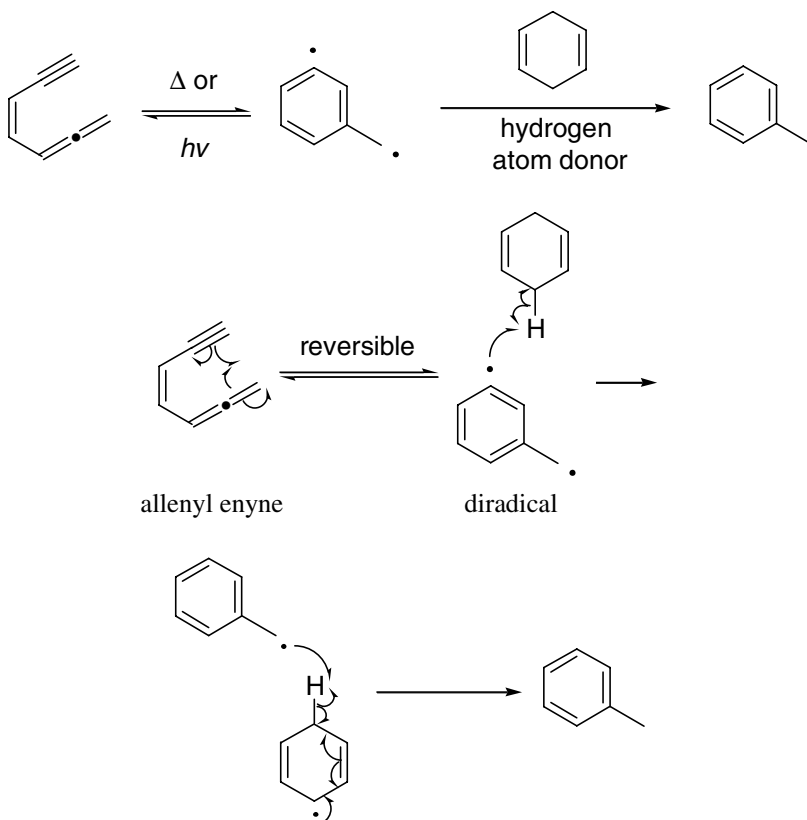


References

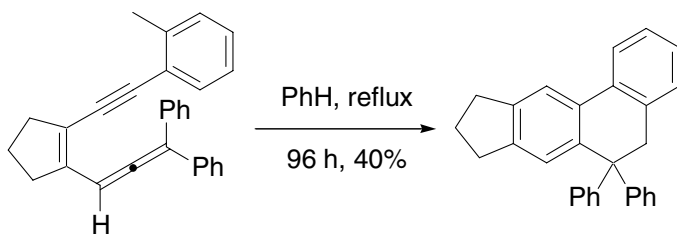
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Myers–Saito cyclization

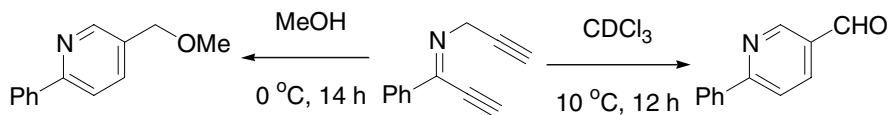
Cf. Bergman cyclization and Schmittel cyclization.



Example 1⁶



Example 2, aza-Myers–Saito reaction¹⁶

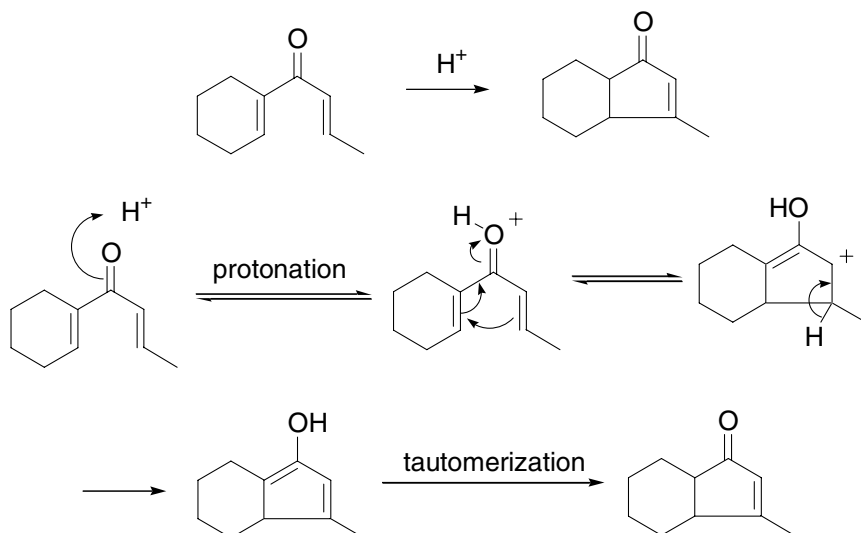


References

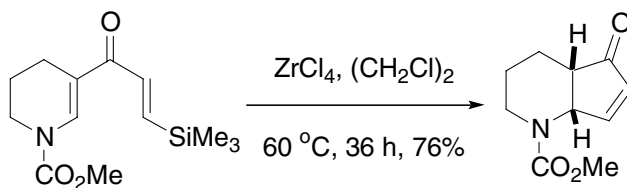
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Nazarov cyclization

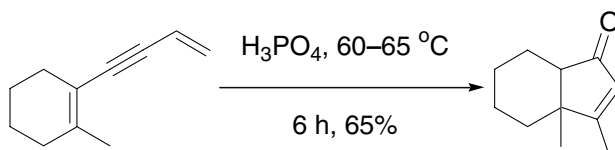
Acid-catalyzed electrocyclic formation of cyclopentenone from di-vinyl ketone.



Example 1²



Example 2, cyclization of *in situ* generated di-vinyl ketone¹²



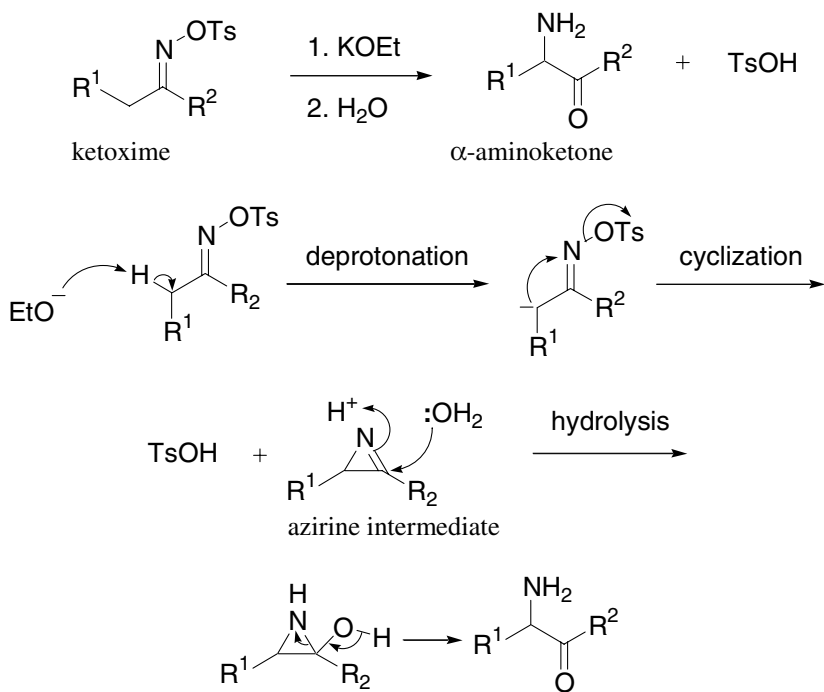
References

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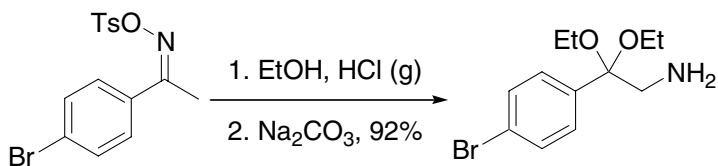
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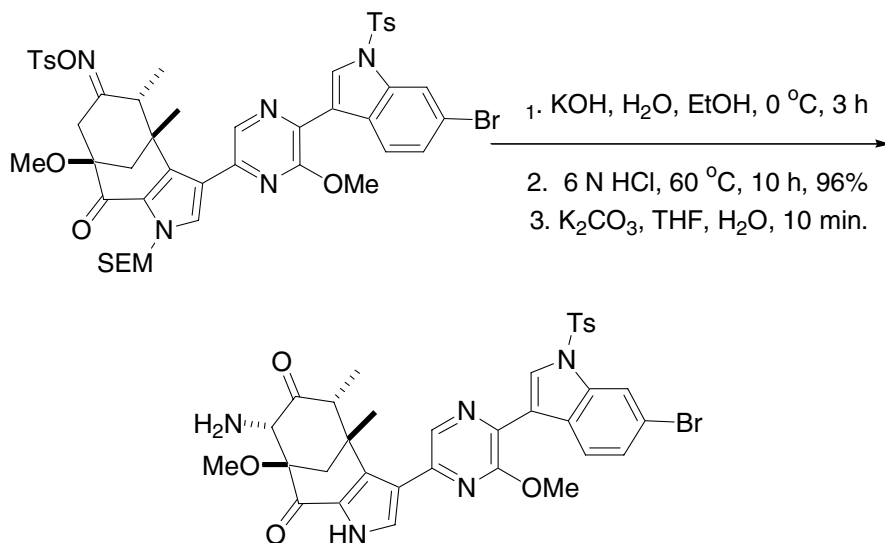
Neber rearrangement

α -Aminoketone from tosyl ketoxime and base.



Example 1⁵



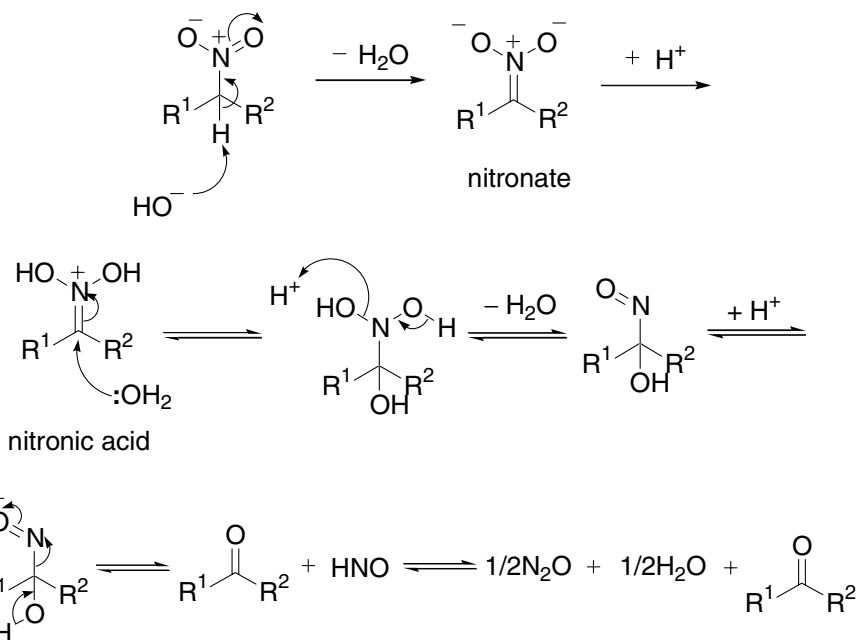
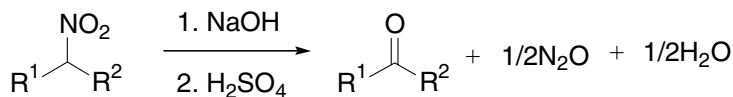
Example 2¹⁵

References

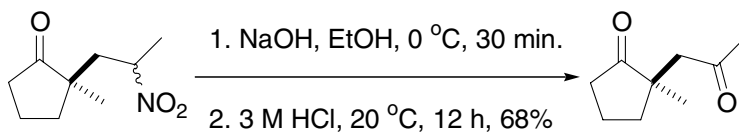
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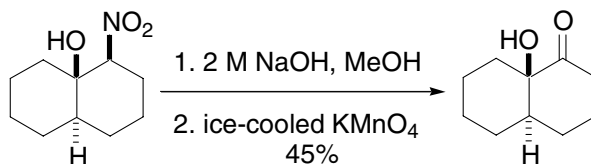
Nef reaction

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



Example 1⁷



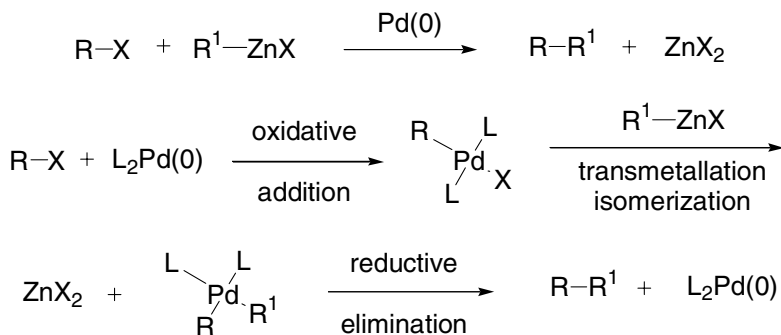
Example 2¹¹

References

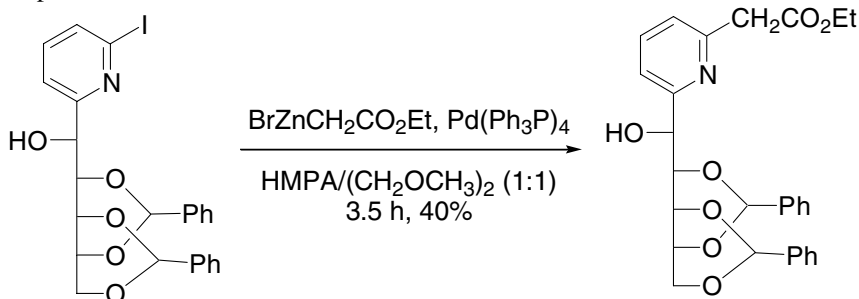
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Negishi cross-coupling reaction

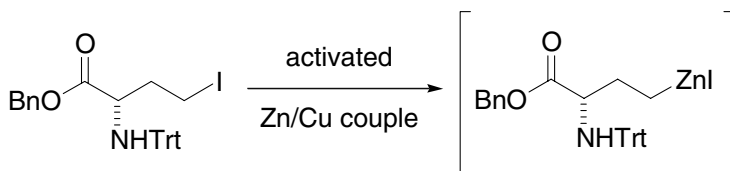
Palladium-catalyzed cross-coupling reaction of organozinc reagents with organic halides, triflates, *etc.* It is compatible with many functional groups including ketones, esters, amines, and nitriles. For the catalytic cycle, see the Kumada coupling on page 345.

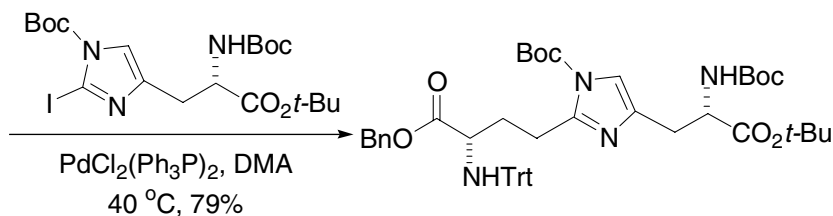


Example 1⁵



Example 2⁶



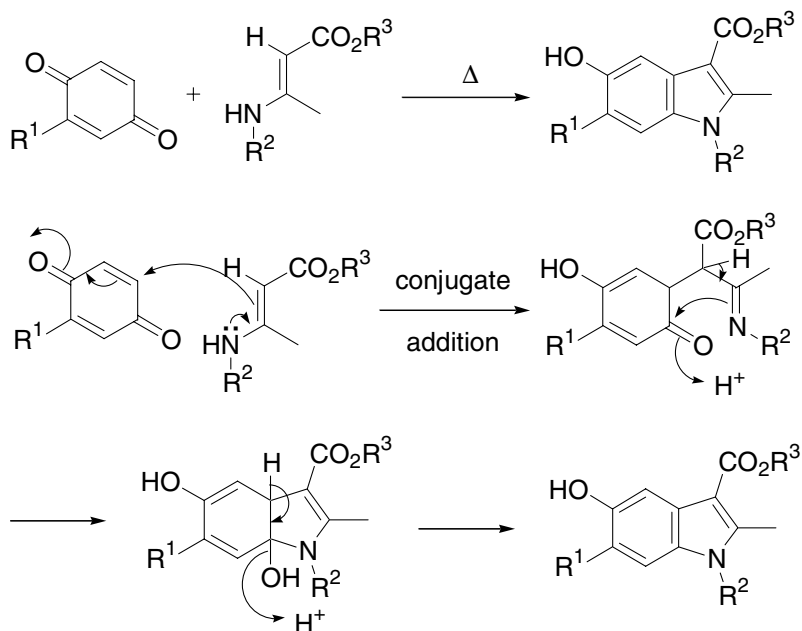


References

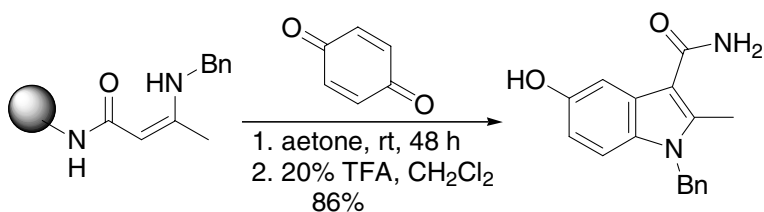
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Nenitzescu indole synthesis

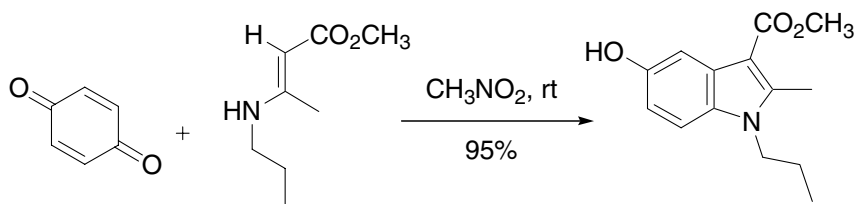
5-Hydroxyindole from condensation of *p*-benzoquinone and β -aminocrotonate.



Example 1⁷



Example 2⁸

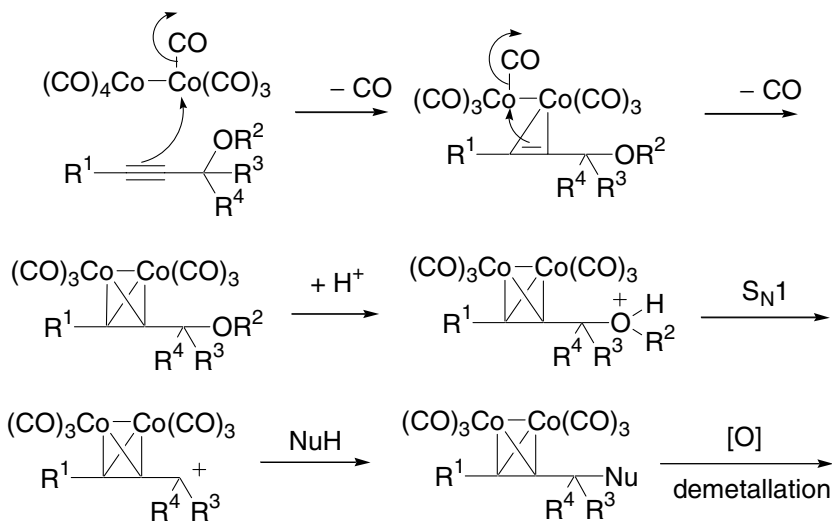
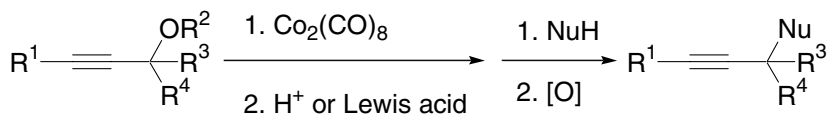


References

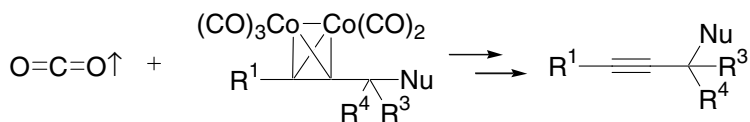
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Nicholas reaction

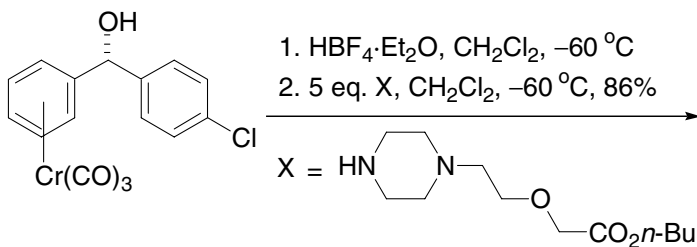
Hexacarbonyldicobalt-stabilized propargyl cation is captured by a nucleophile. Subsequent oxidative demetallation then gives propargylated product.

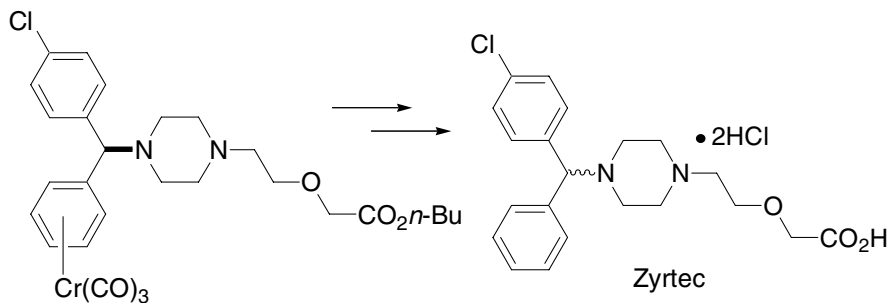


propargyl cation intermediate (stabilized by the hexacarbonyldicobalt complex).

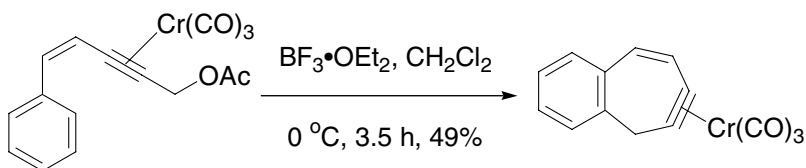


Example 1, chromium variant of the Nicholas reaction⁵





Example 2, intramolecular Nicholas reaction using chromium¹¹

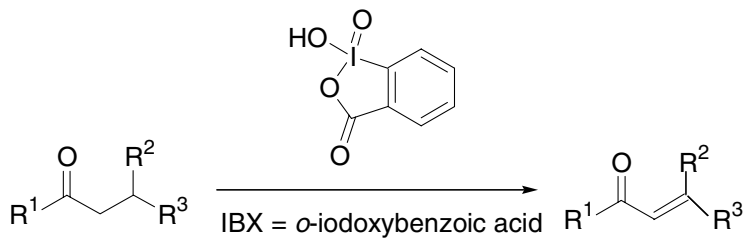


References

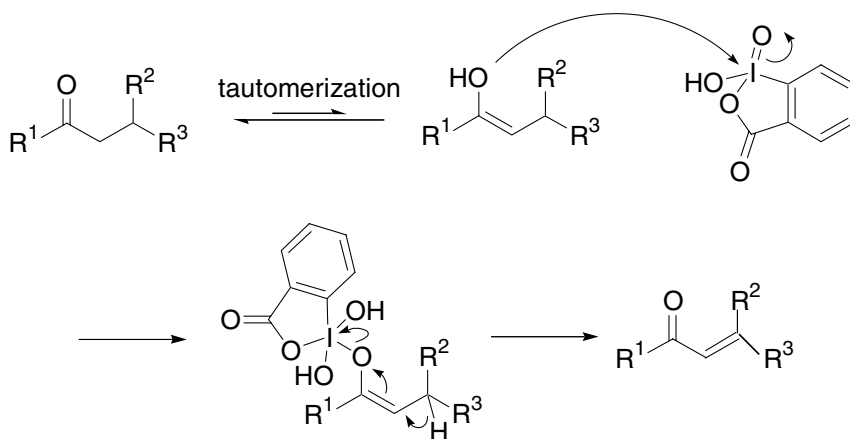
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Nicolaou dehydrogenation

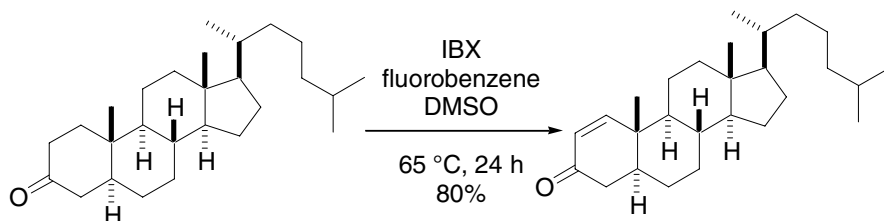
α,β -Unsaturation of aldehydes and ketones mediated by stoichiometric amounts of IBX (*o*-iodoxybenzoic acid), alternative to Saegusa oxidation (page 515).¹

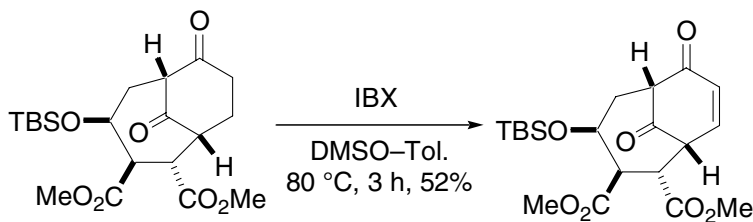
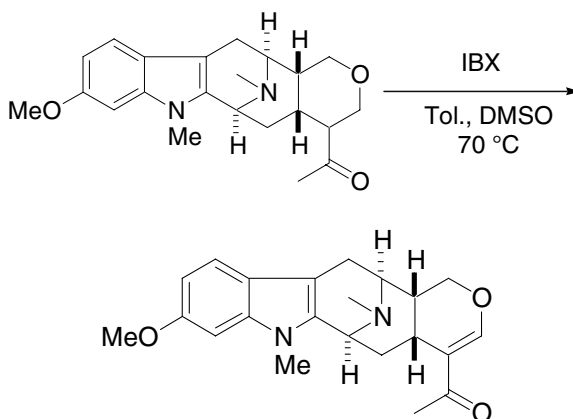


A SET mechanism has also been proposed.² Additionally, silyl enol ethers are also viable substrates.³



Example 1¹



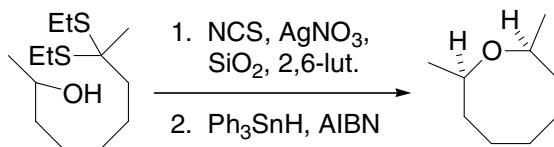
Example 2⁴e. g. 3¹⁰

References

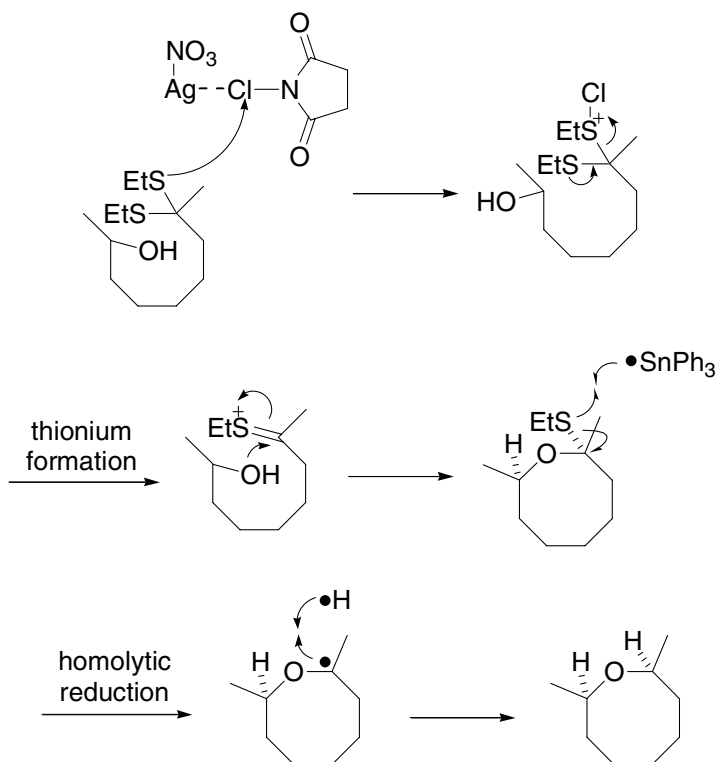
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Nicolaou hydroxy-dithioketal cyclization

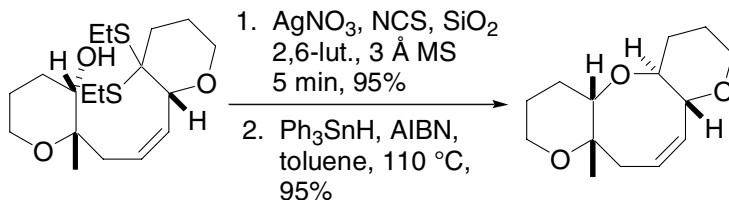
Two step synthesis of medium-ring ethers through the intermediacy of thionium ions followed by sulfide reduction.



The mechanism is analogous to the hydroxy-ketone cyclization except that the mixed ketal is isolable. It can be reductively cleaved using Ph₃SnH/AIBN:



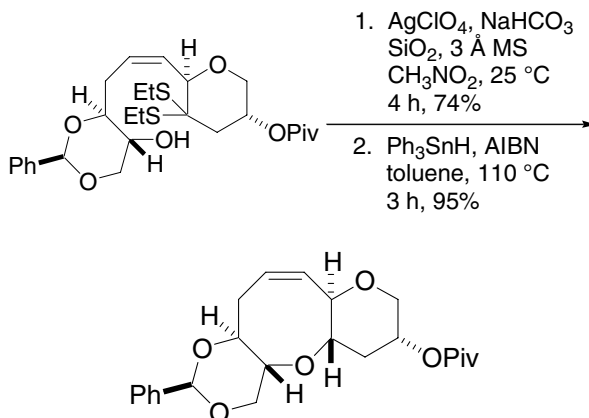
e. g. 1¹



Example 2, carbocyclization is also possible³:



Example 3, the cyclizations tolerate ordinary acetals⁵:

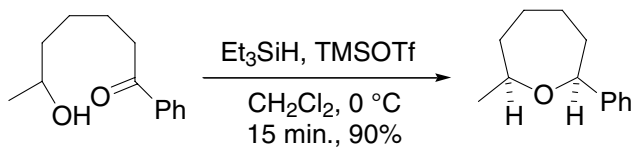


References

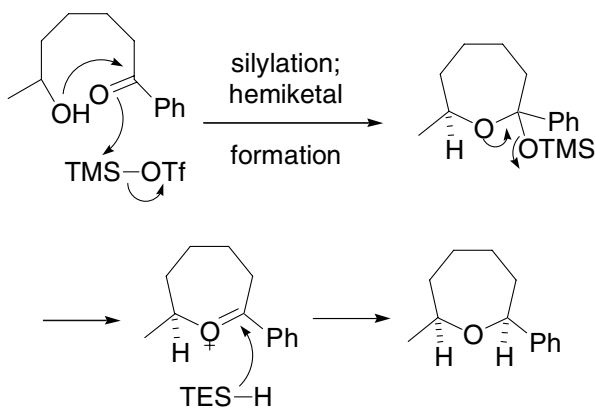
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Nicolaou hydroxy-ketone reductive cyclic ether formation

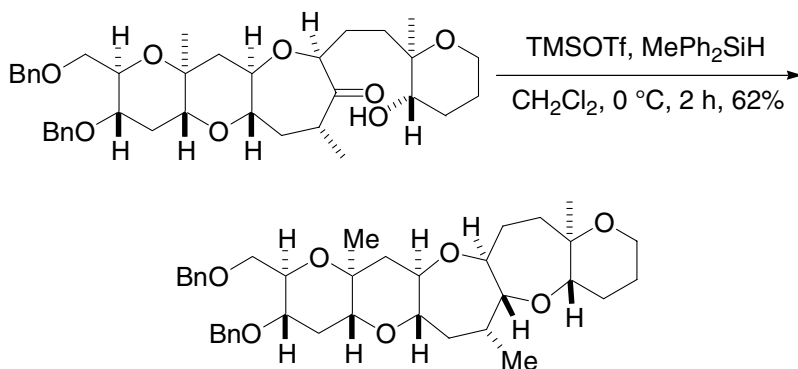
Acid-catalyzed conversion of a ketone with a pendant hydroxyl group into a cyclic ether with net reduction of the carbonyl.



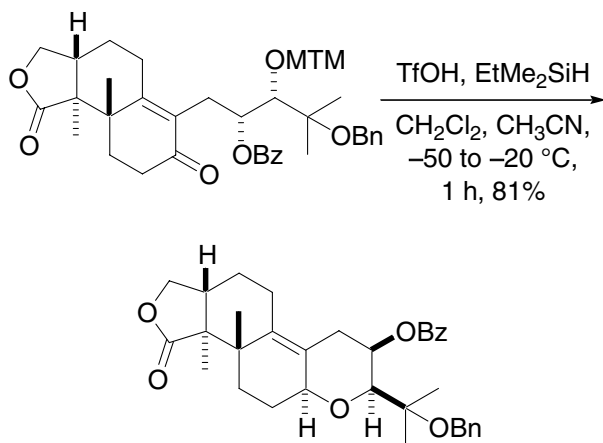
The mechanism involves hemiketal formation followed by reduction of the oxocarbenium group:



Example 1¹



e. g. 2²

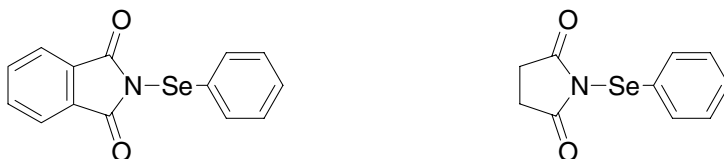


References

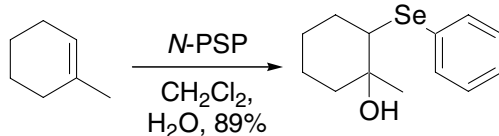
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Nicolaou oxyselenation

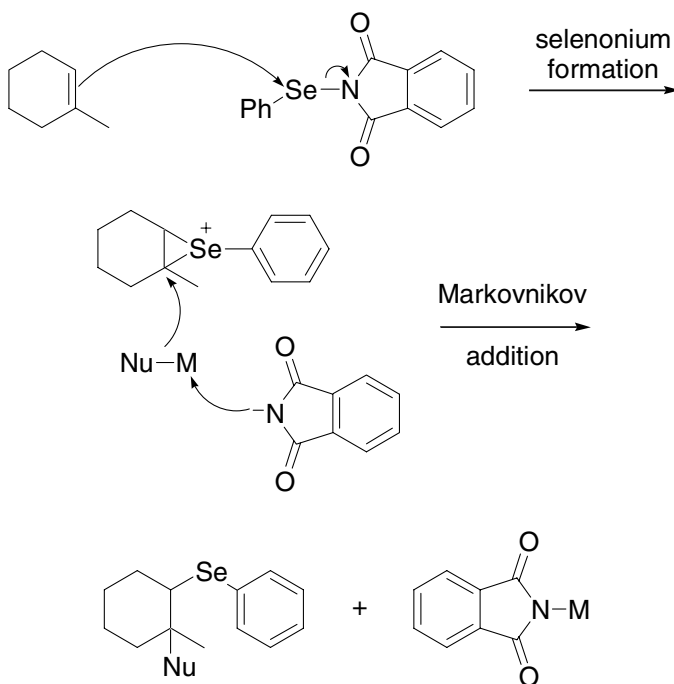
Activation of alkenes towards nucleophilic attack by a variety of nucleophiles employing *N*-phenylselenophthalimide or *N*-phenylselenosuccinimide as an electrophilic source of the phenylseleno group.

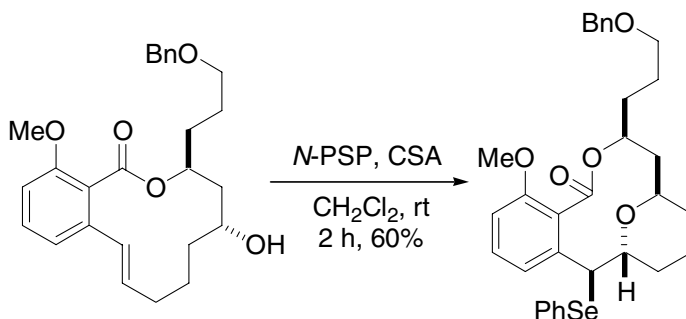


N-PSP = *N*-phenylselenophthalimide *N*-PSS = *N*-phenylselenosuccinimide

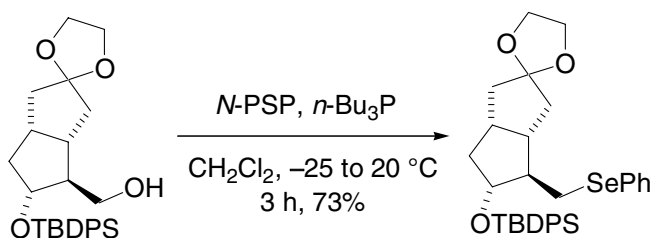


The reagent may require acid activation depending on the type of transformation being attempted. The mechanism parallels that of halohydrin formation using an electrophilic source of halide in an aqueous medium:



Example 1³

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*-Bu₃P.⁶

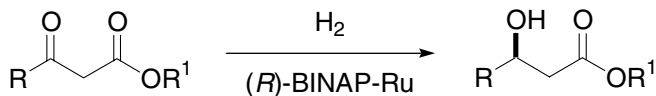


References

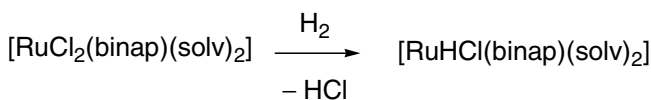
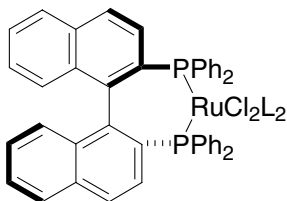
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Noyori asymmetric hydrogenation

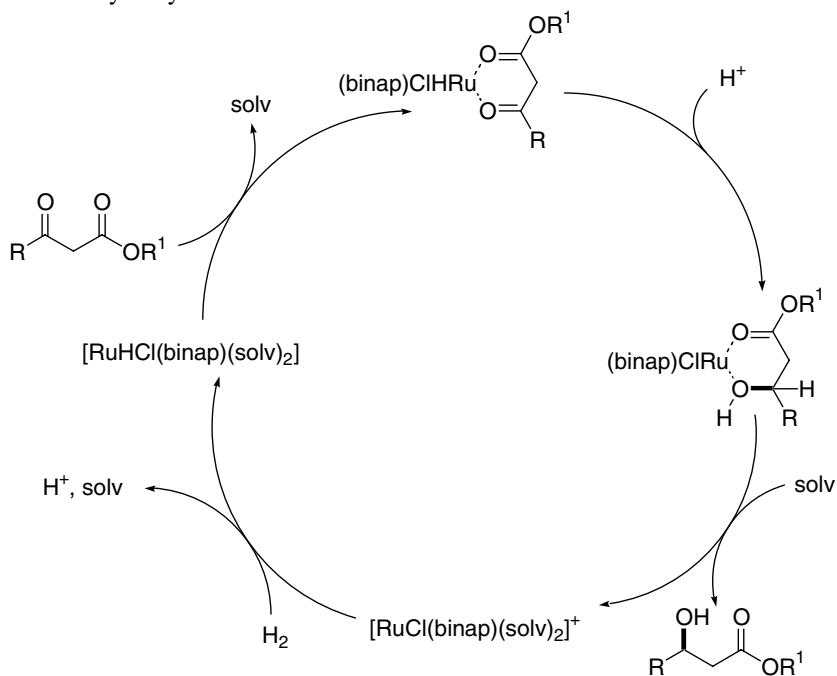
Asymmetric reduction of carbonyl *via* hydrogenation catalyzed by ruthenium(II) BINAP complex.

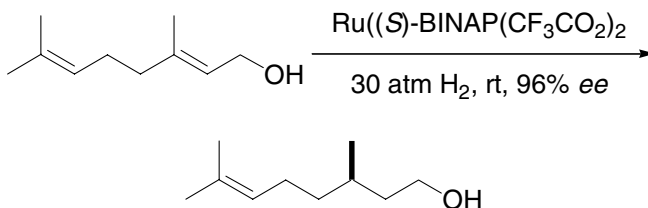
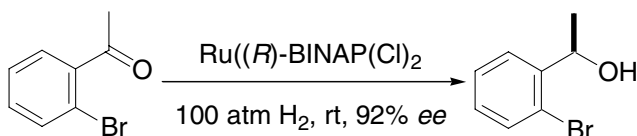


(R)-BINAP-Ru =



The catalytic cycle:



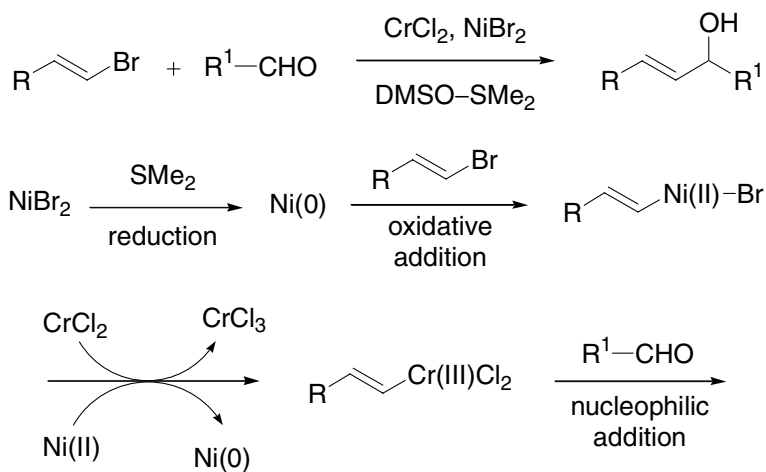
Example 1²Example 2³

References

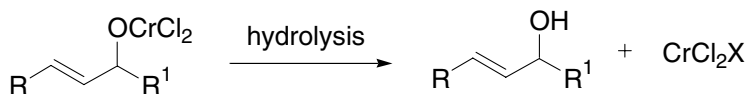
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Nozaki–Hiyama–Kishi reaction

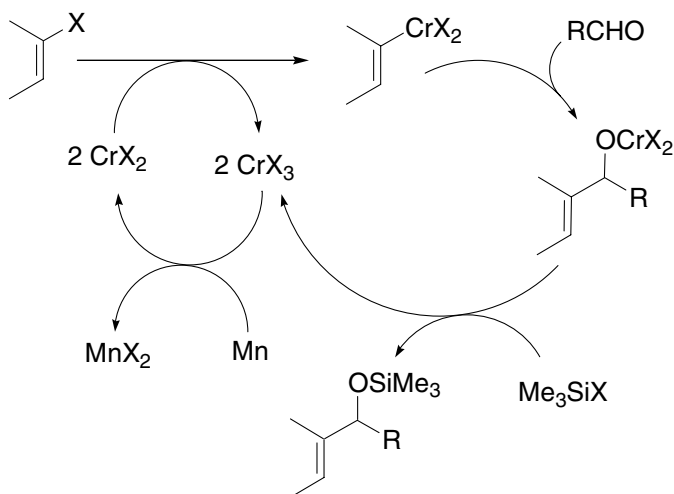
Cr–Ni bimetallic catalyst-promoted redox addition of vinyl halides to aldehydes.

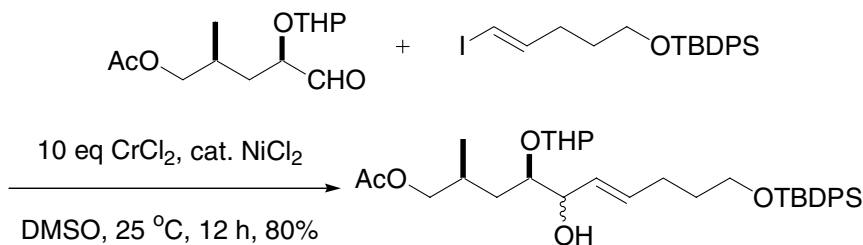
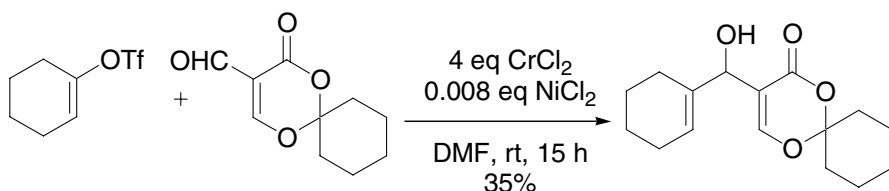


Transmetalation and then reduction by Me_2S



The catalytic cycle:⁷



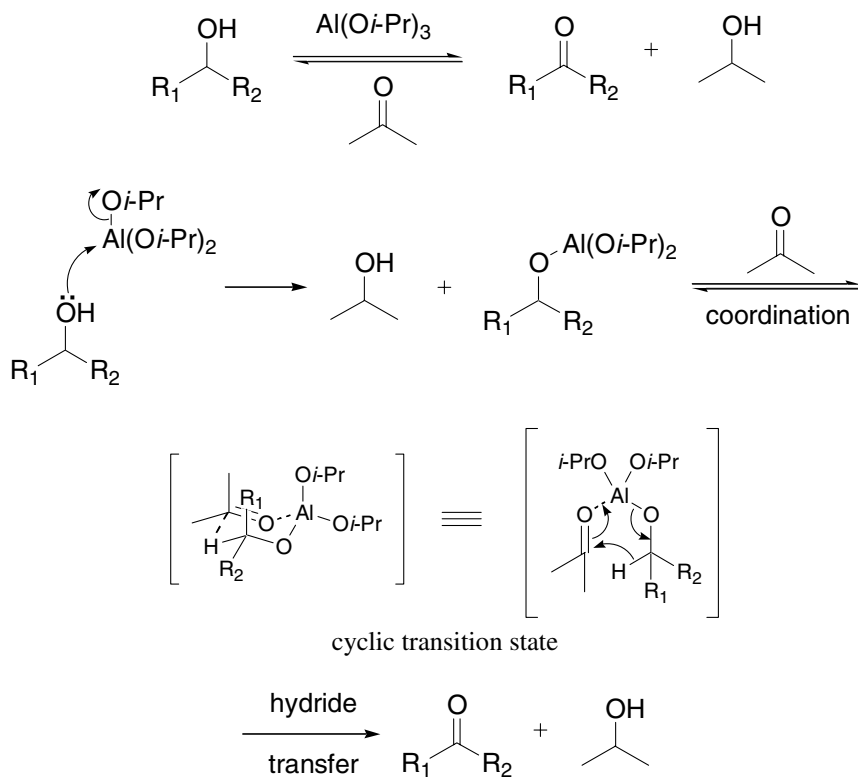
Example 1⁸Example 2¹²

References

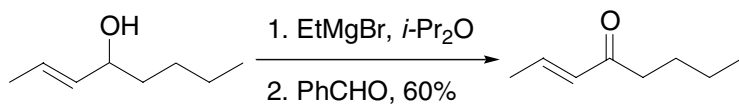
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Oppenauer oxidation

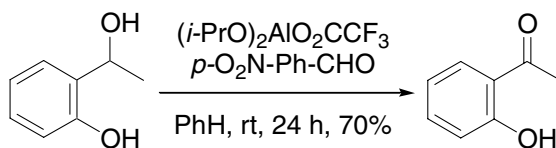
Alkoxide-catalyzed oxidation of secondary alcohols.



Example 1, magnesium Oppenauer oxidation³



Example 2¹²

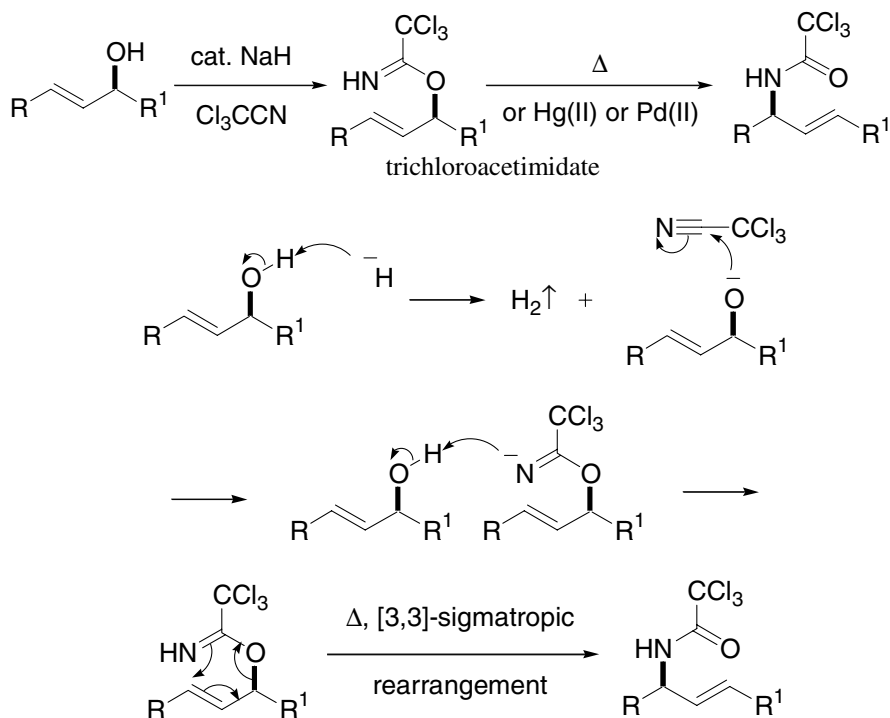


References

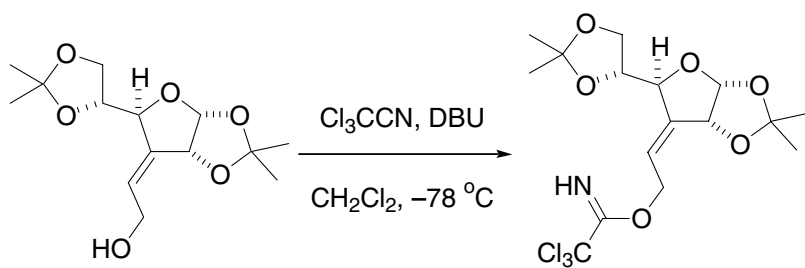
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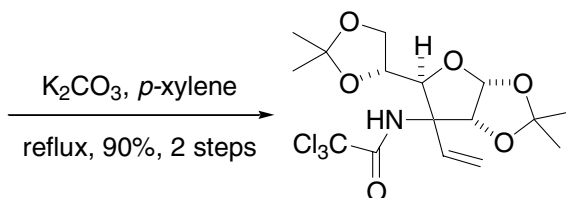
Overman rearrangement

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

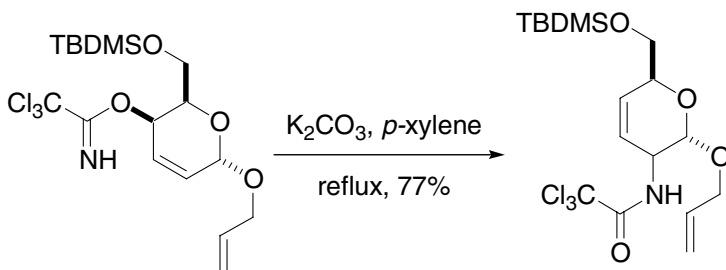


Example 1¹³





Example 2¹⁴

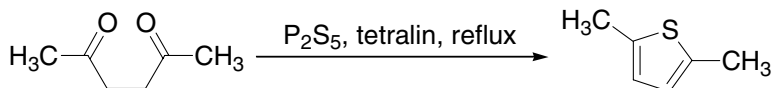


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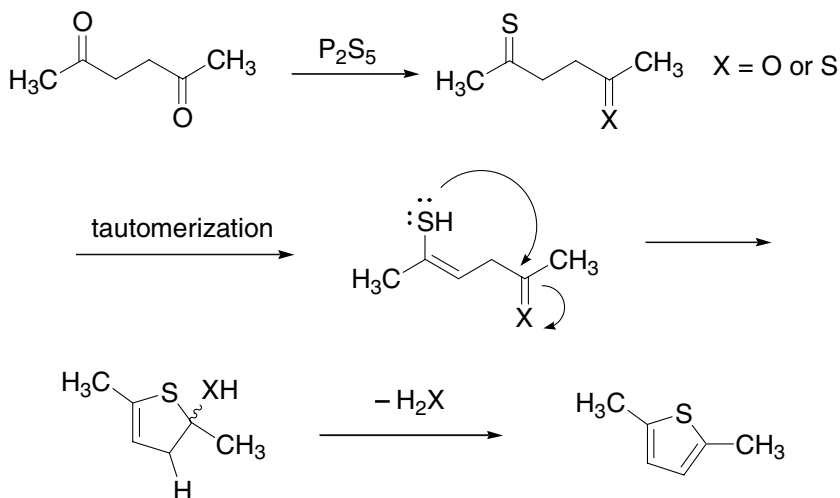
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Paal thiophene synthesis

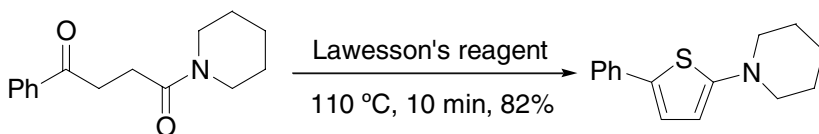
Thiophene synthesis from addition of a sulfur atom to 1,4-dicarbonyl compounds and subsequent dehydration.

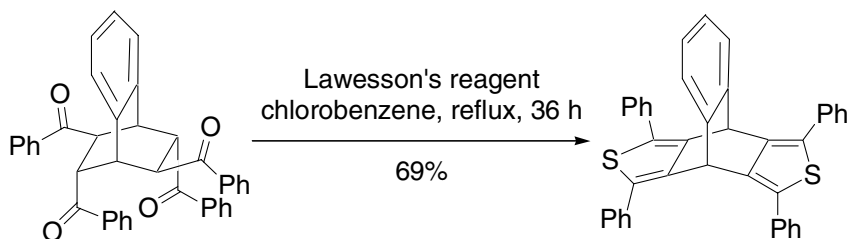


The reaction now is frequently carried out using the Lawesson's reagent. For the mechanism of carbonyl to thiocarbonyl transformation, see Lawesson's reagent on page 348.



Example 1⁴



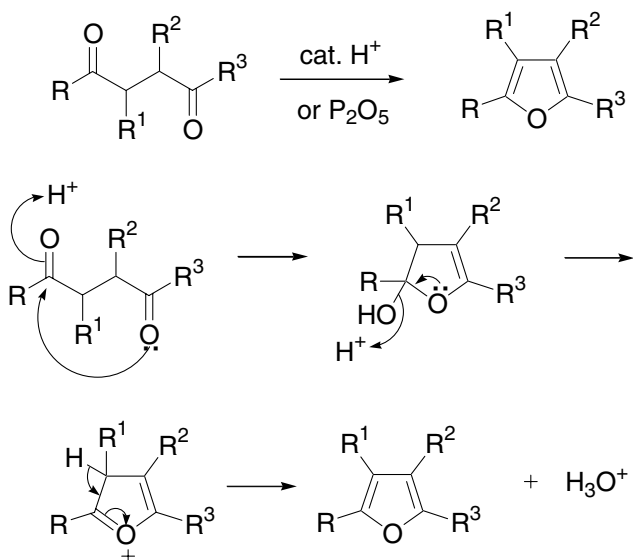
Example 2⁸

References

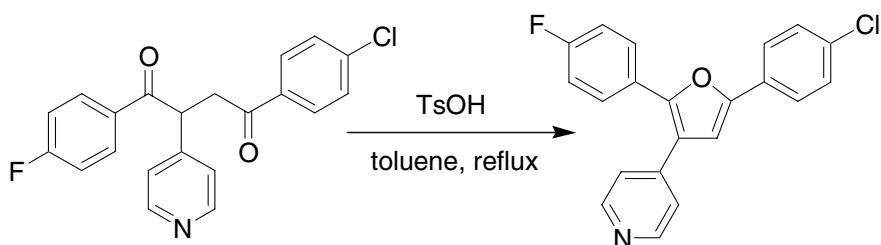
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Paal–Knorr furan synthesis

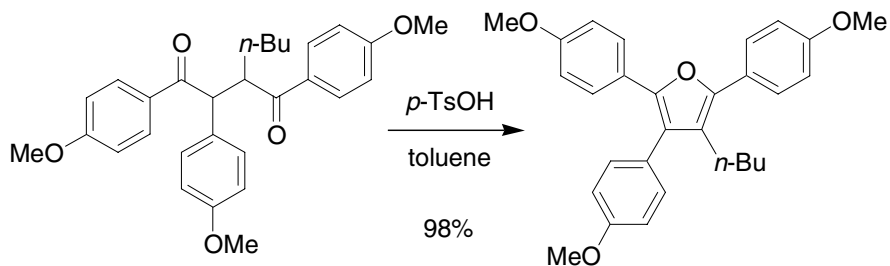
Acid-catalyzed cyclization of 1,4-ketones to form furans.



Example 1¹⁰



Example 2¹⁴

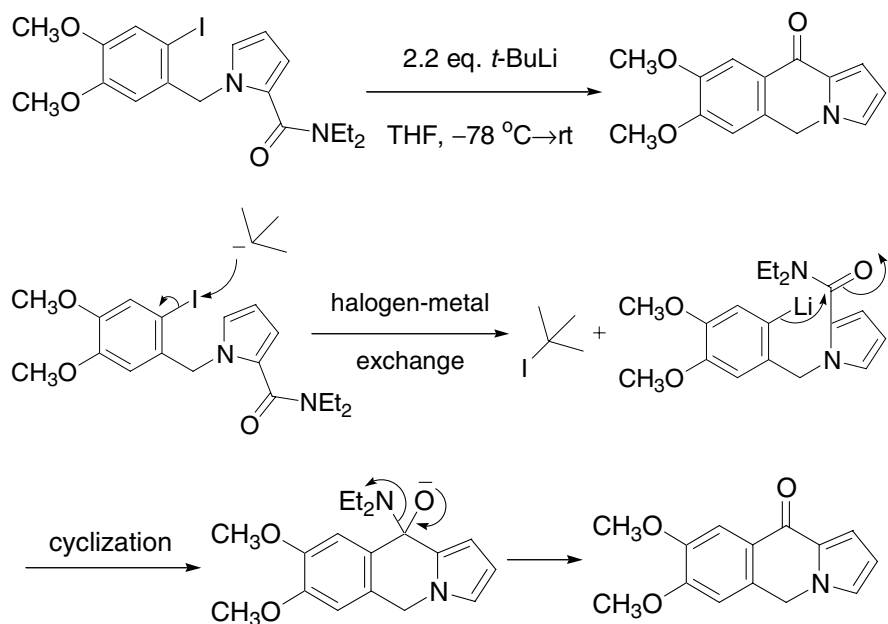


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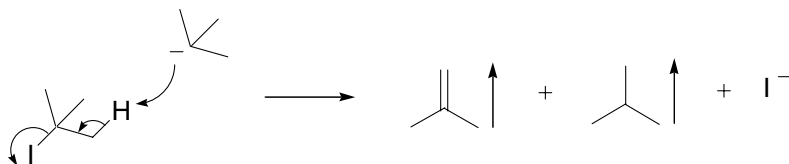
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Parham cyclization

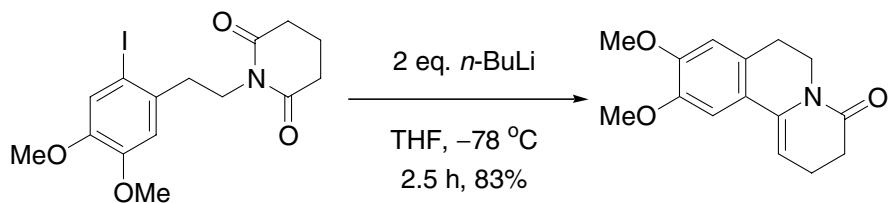
Annulation of aryl halides with *ortho* side chains bearing a pendant electrophilic moiety *via* treatment with an organolithium reagent, involving halogen-metal exchange and subsequent nucleophilic cyclization to form 4- to 7-membered rings.

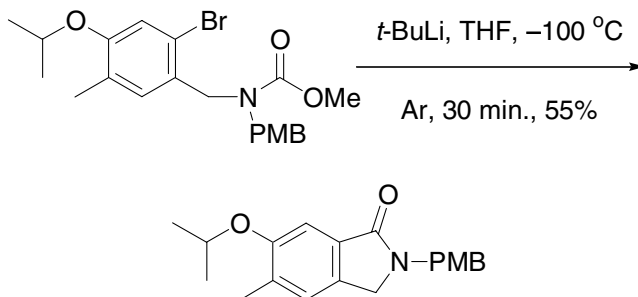


The fate of the second equivalent of *t*-BuLi:



Example 1⁹



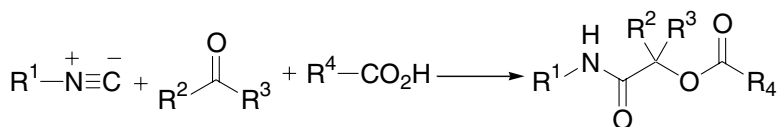
Example 2¹⁶

References

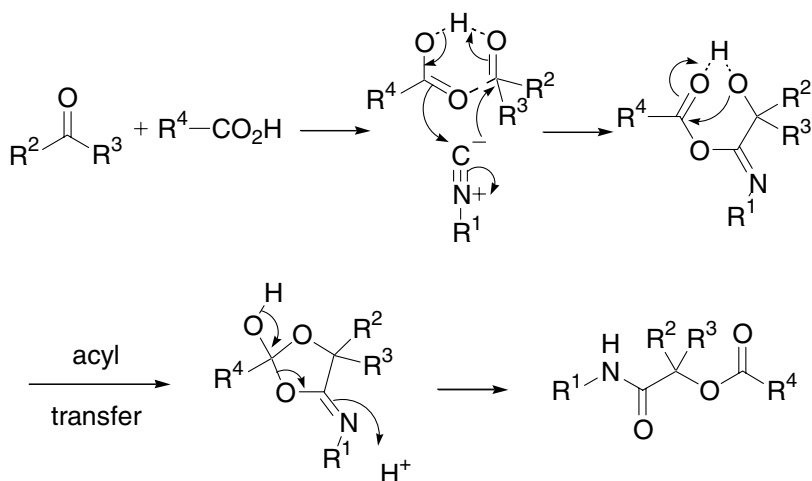
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Passerini reaction

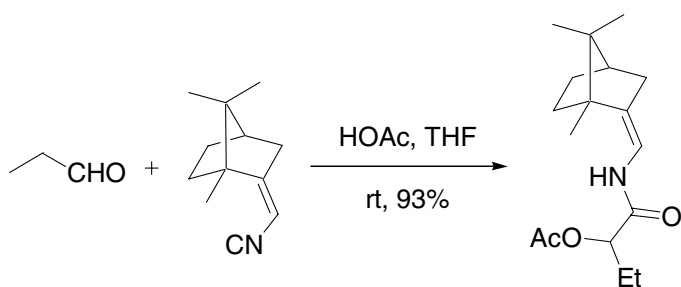
Three-component condensation (3CC) of carboxylic acids, *C*-isocyanides, and carbonyl compounds to afford α -acyloxycarboxamides. Cf. Ugi reaction.

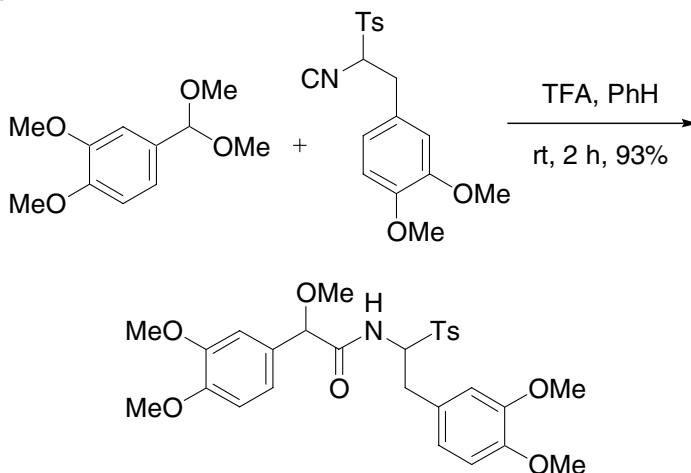


isocyanide



Example 1⁵



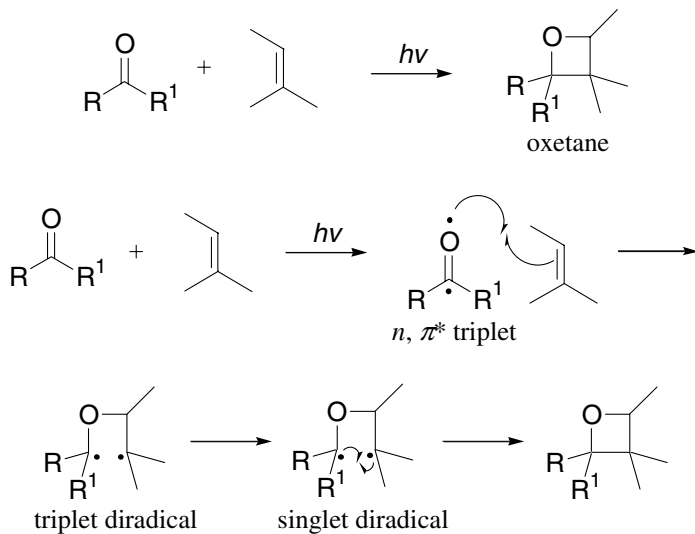
Example 2³

References

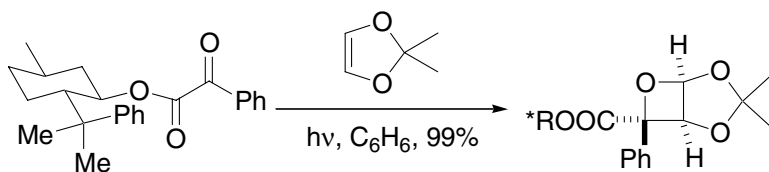
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Paternó-Büchi reaction

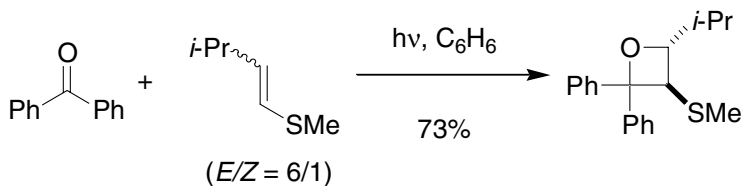
Photoinduced electrocycloization of a carbonyl with an alkene to form polysubstituted oxetane ring systems



Example 1⁴



Example 2⁶

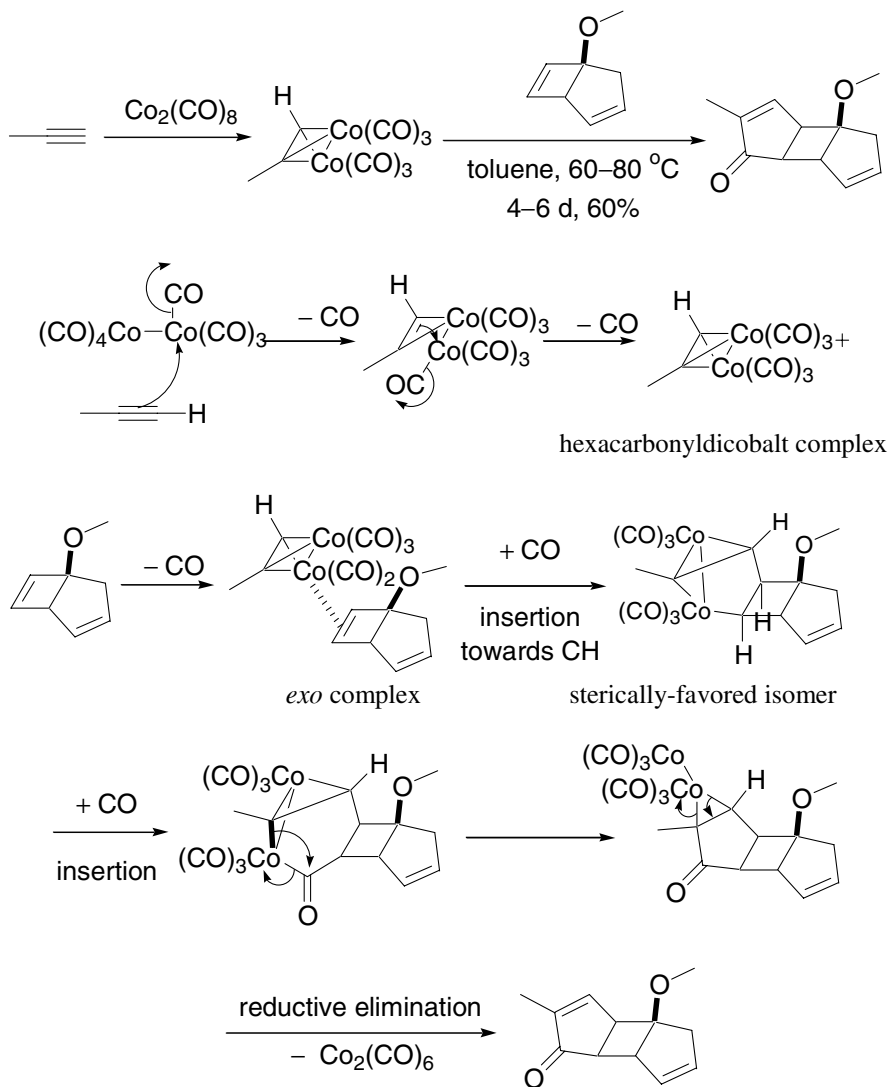


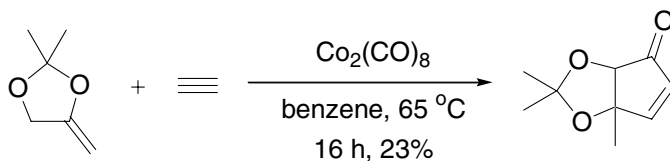
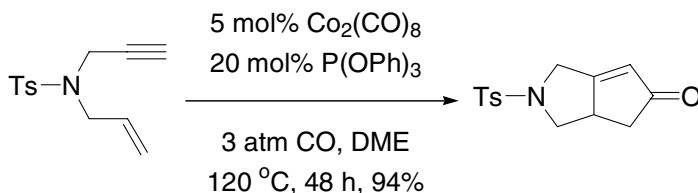
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Pauson–Khand cyclopentenone synthesis

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



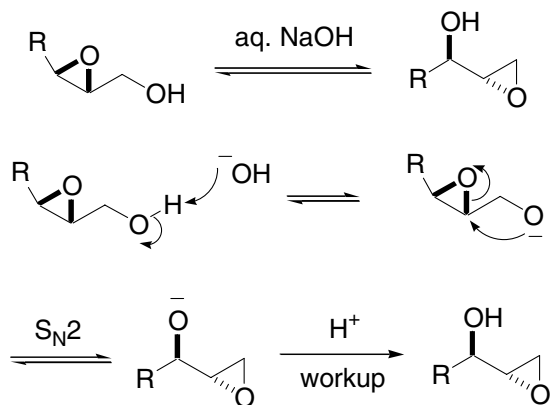
Example 1⁶Example 2, a catalytic version⁹

References

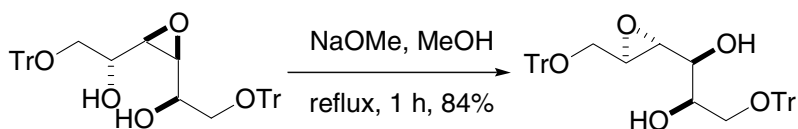
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Payne rearrangement

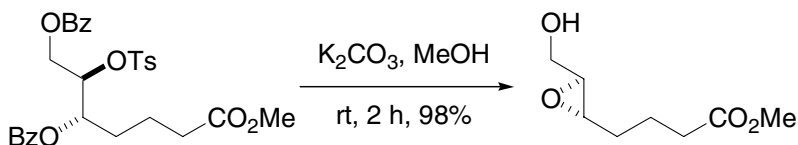
Base-promoted isomerization of 2,3-epoxy alcohols. Also known as epoxide migration.



Example 1²



Example 2³



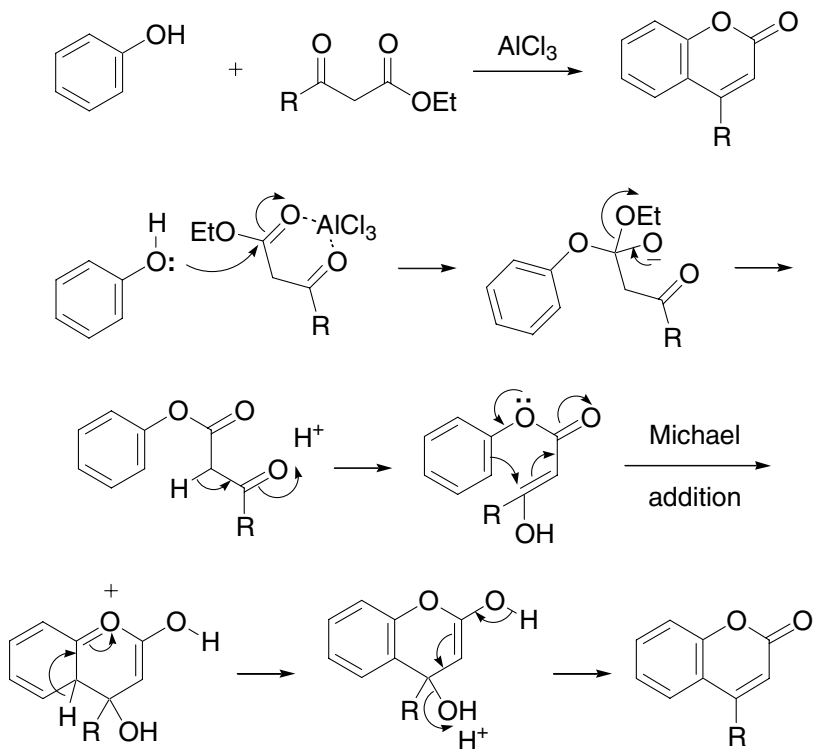
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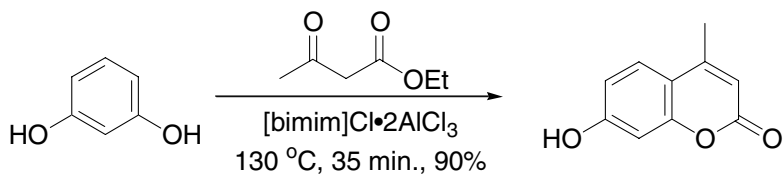
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Pechmann coumarin synthesis

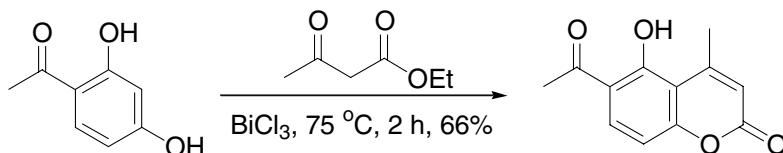
Lewis acid-mediated condensation of phenol with β -ketoester to produce coumarin.



Example 1¹¹



[bimim]Cl•2AlCl₃ = 1-Butyl-3-methylimidazolium chloroaluminuminate (a Lewis acid ionic liquid)

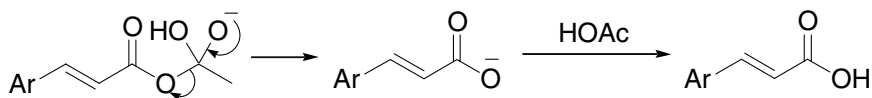
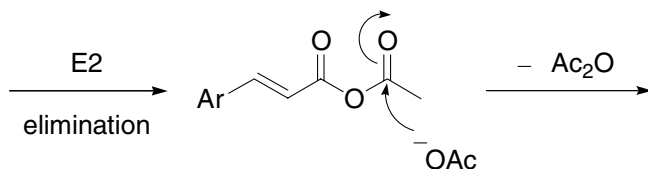
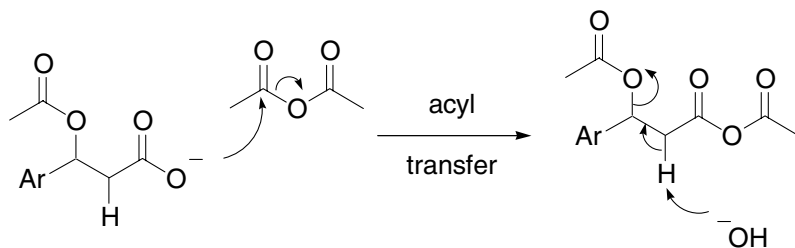
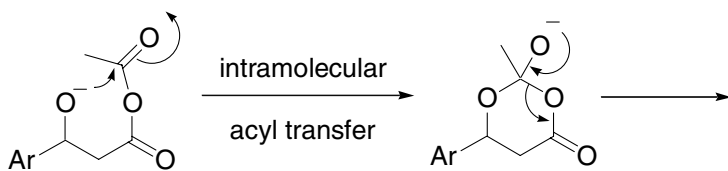
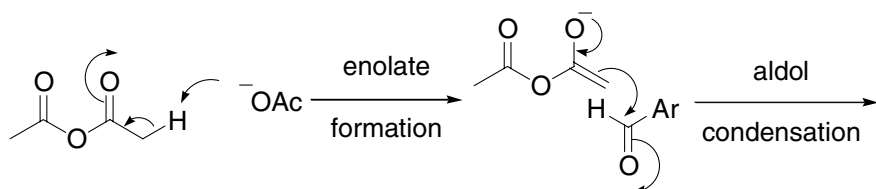
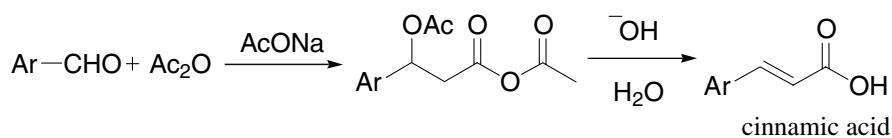
Example 2¹⁴

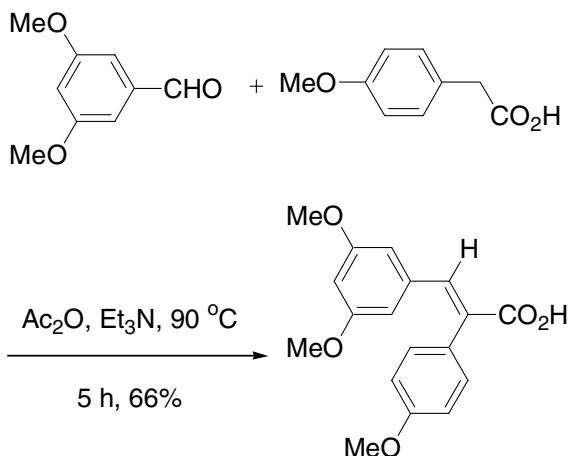
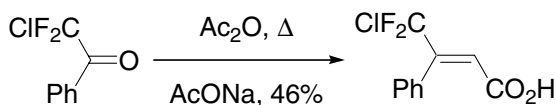
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Perkin reaction

Cinnamic acid synthesis from aryl aldehyde and acetic anhydride.



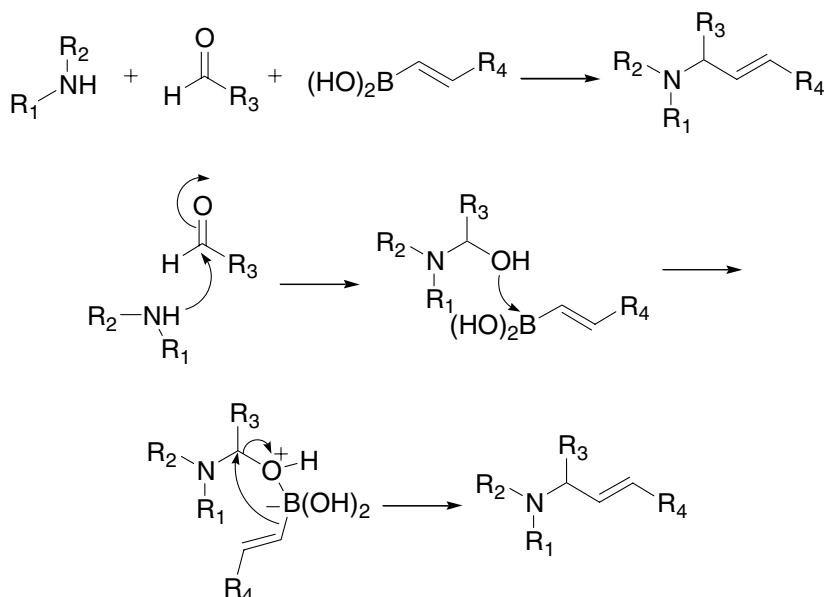
Example 1⁹Example 2¹⁰

References

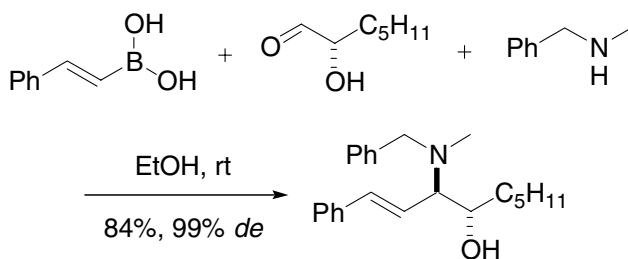
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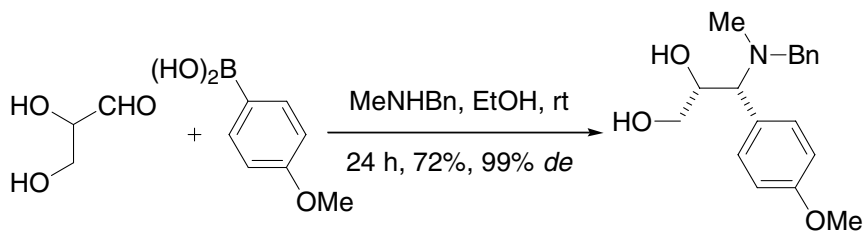
Petasis reaction

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



Example 1⁵



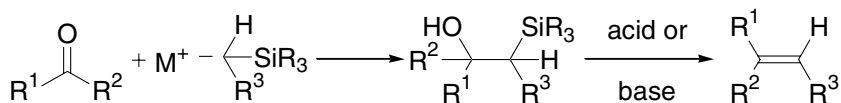
Example 2⁷

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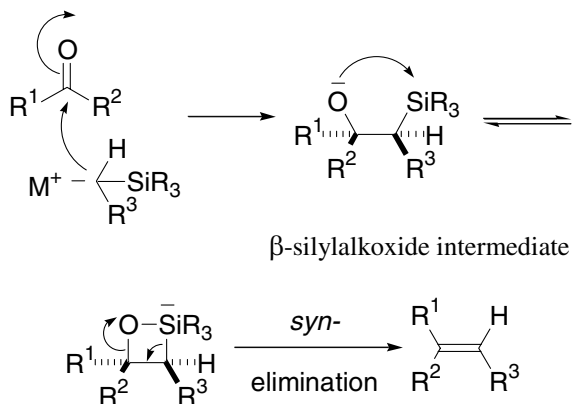
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Peterson olefination

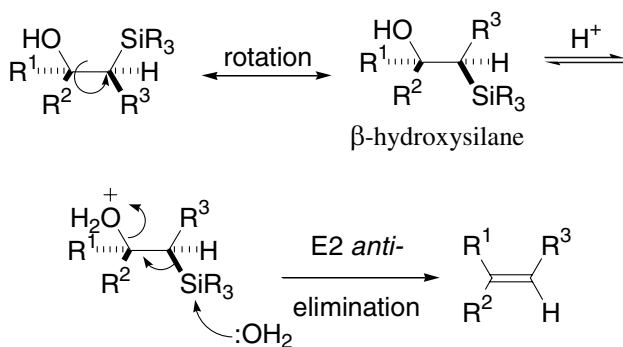
Alkenes from α -silyl carbanion and carbonyl compounds. Also known as sila-Wittig reaction.



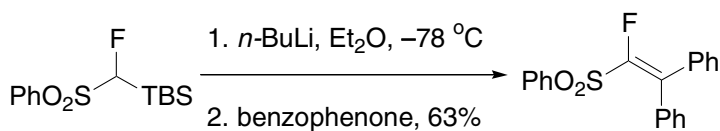
Basic conditions:

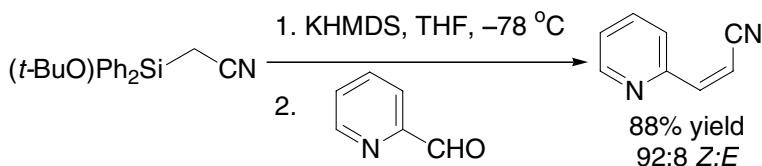


Acidic conditions:



Example 1¹⁰



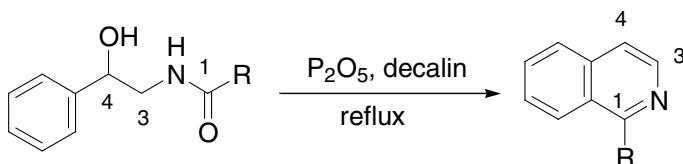
Example 2¹²

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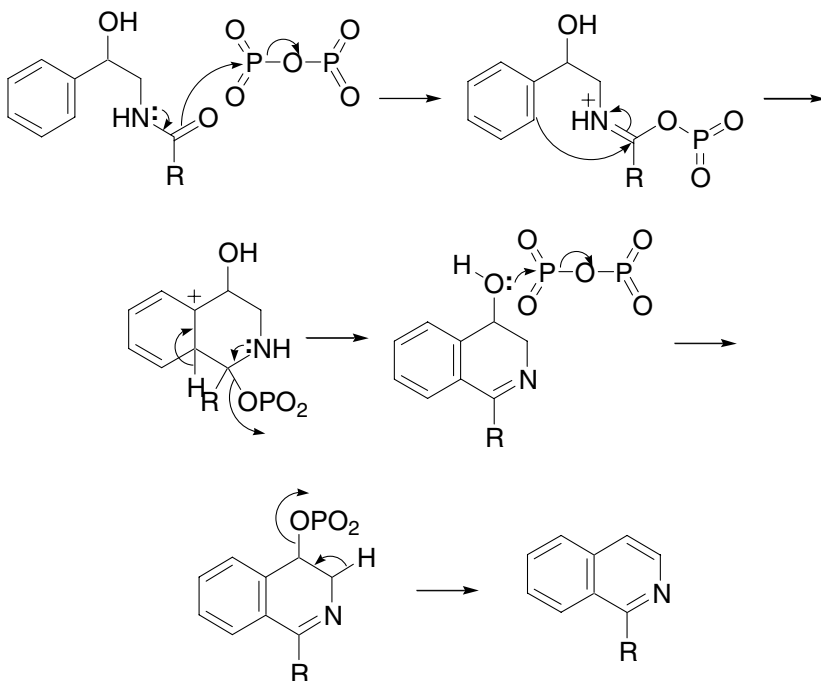
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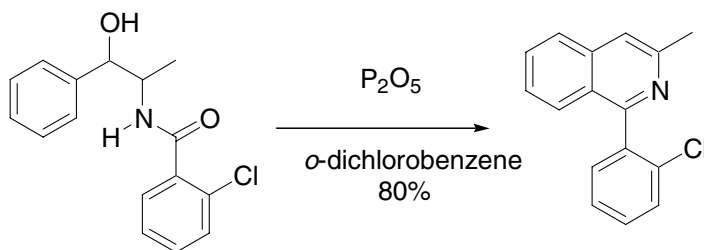
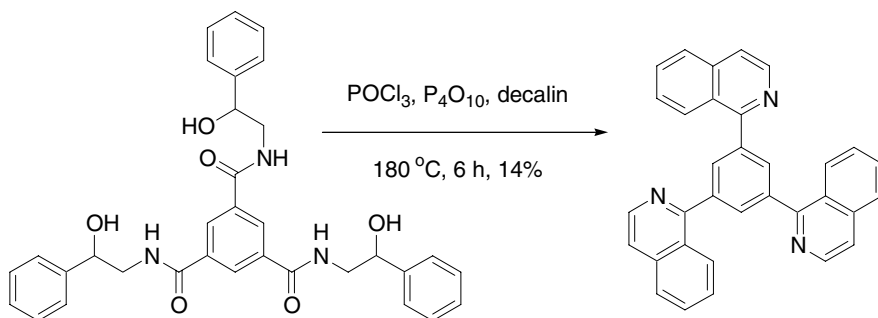
Pictet–Gams isoquinoline synthesis

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.



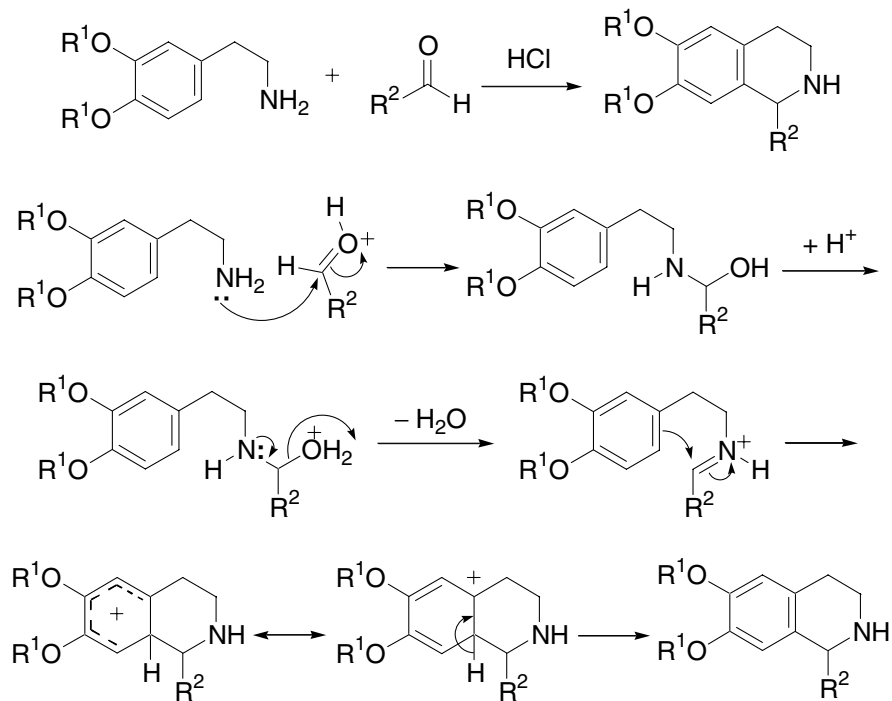
Example 1¹⁰Example 2⁷

Reference

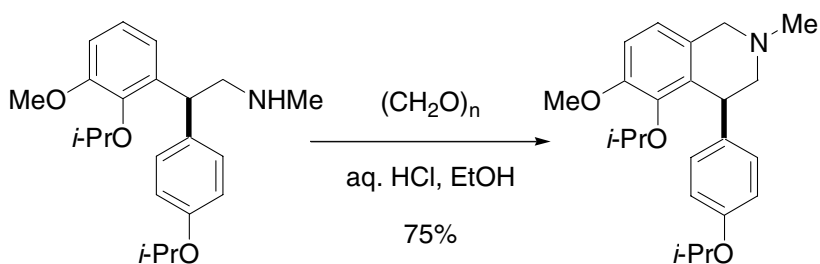
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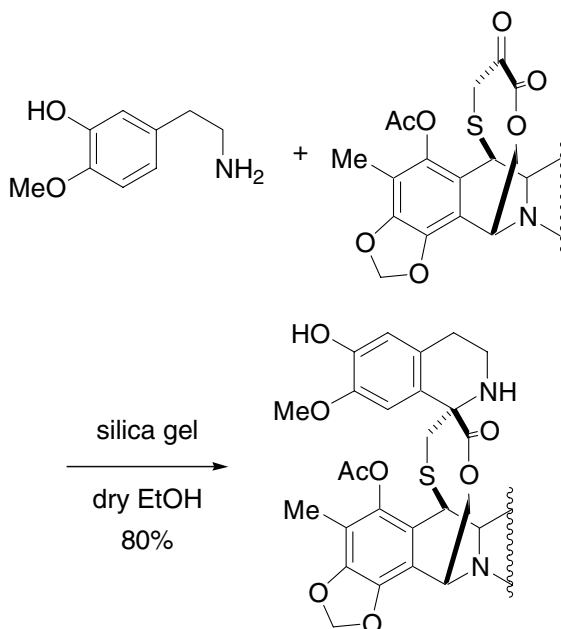
Pictet–Spengler tetrahydroisoquinoline synthesis

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



Example 1¹²



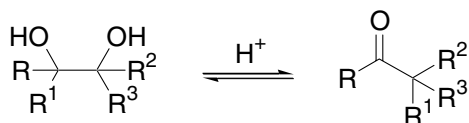
Example 2⁹

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Pinacol rearrangement

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

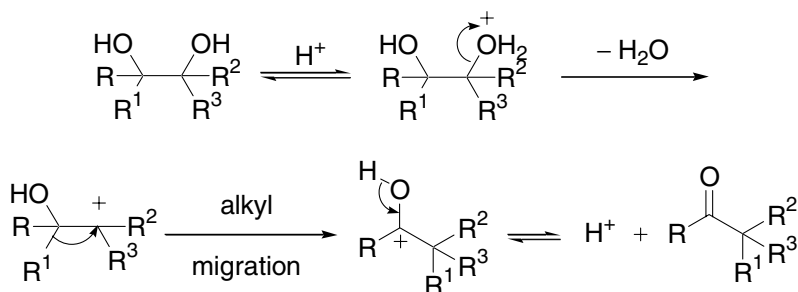


The most electron-rich alkyl group (more substituted carbon) migrates first.
The general migration order:

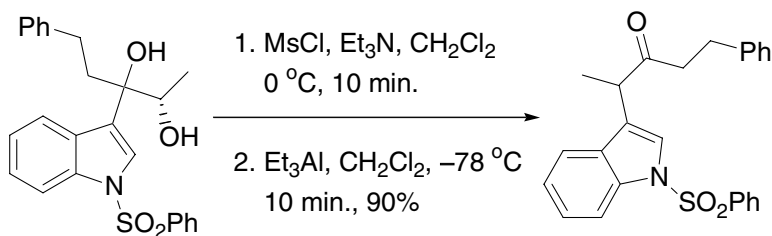
tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl >
primary alkyl > methyl >> H.

For substituted aryls:

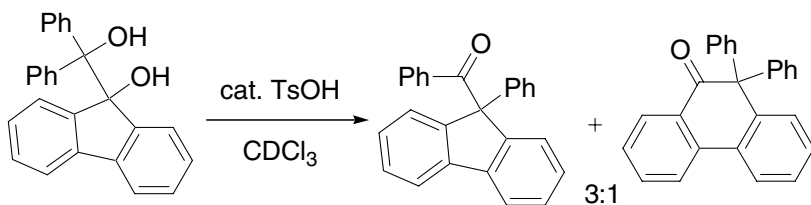
p-MeO-Ar > *p*-Me-Ar > *p*-Cl-Ar > *p*-Br-Ar > *p*-MeOAr > *p*-O₂N-Ar



Example 1¹²



Example 2¹⁴

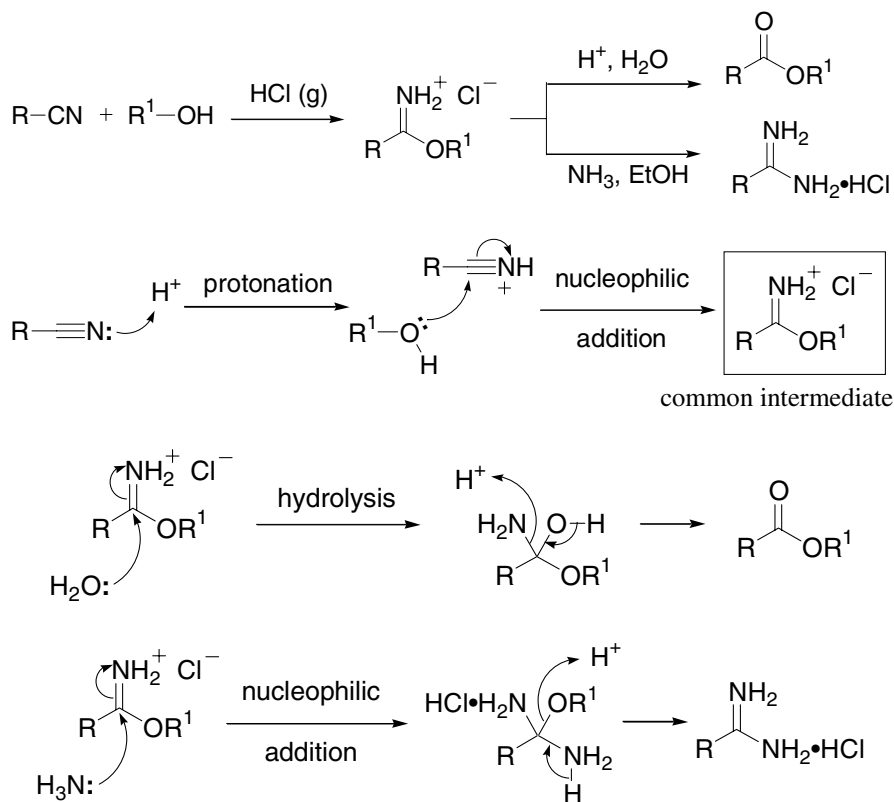


References

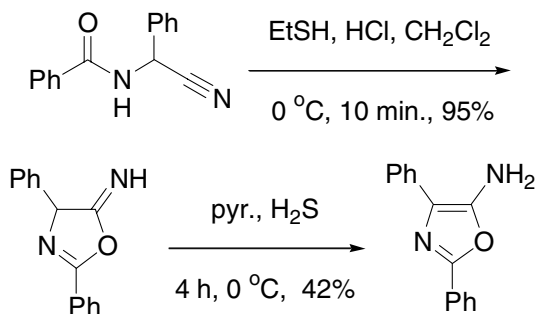
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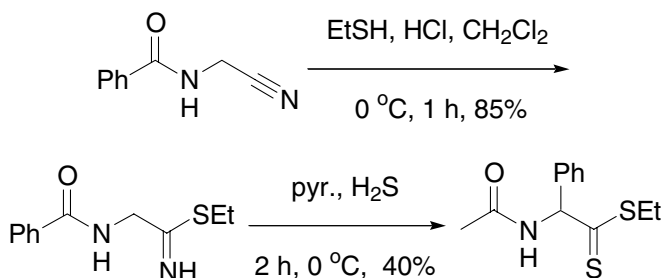
Pinner reaction

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



Example 1³



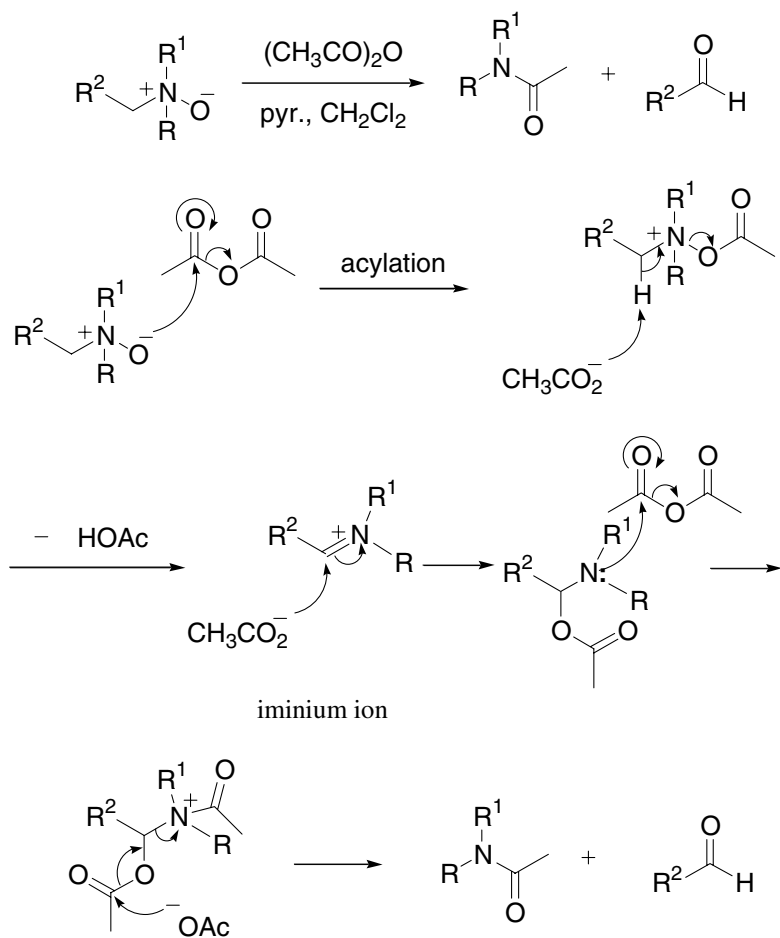
Example 2³

References

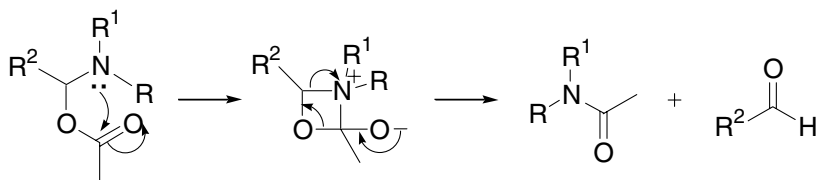
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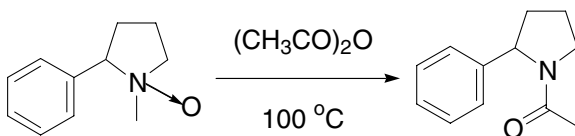
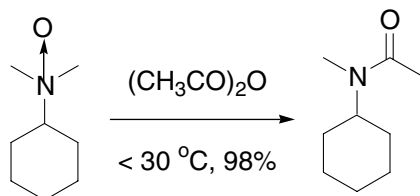
Polonovski reaction

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



The intramolecular pathway is also possible:



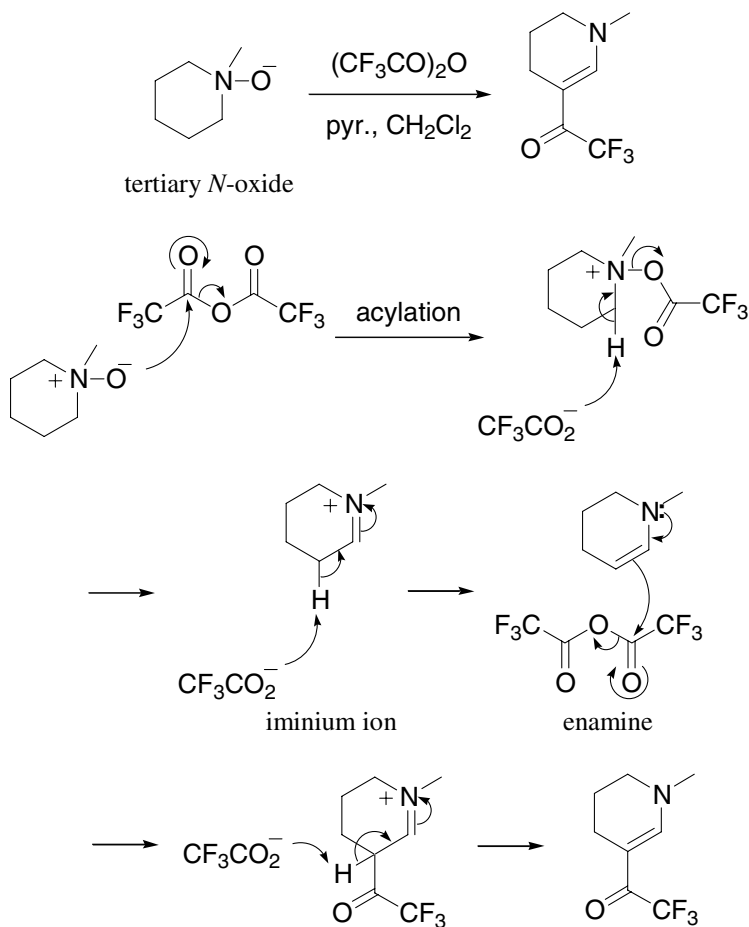
Example 1¹Example 2²

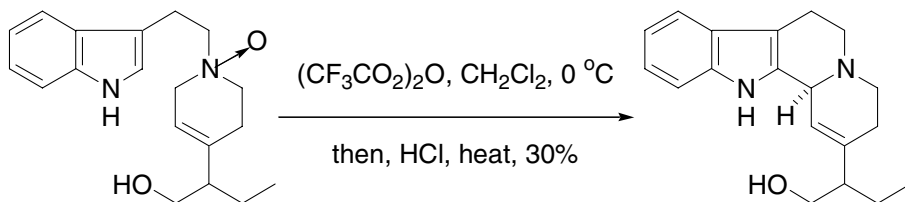
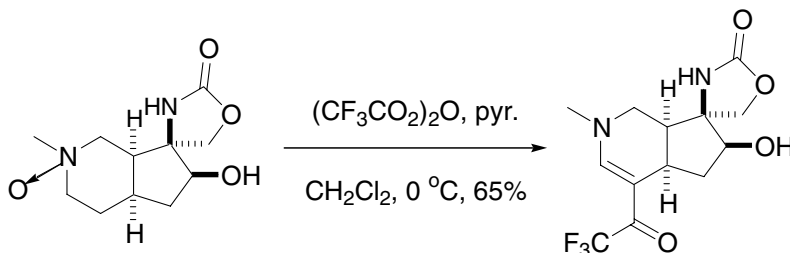
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Polonovski–Potier reaction

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.



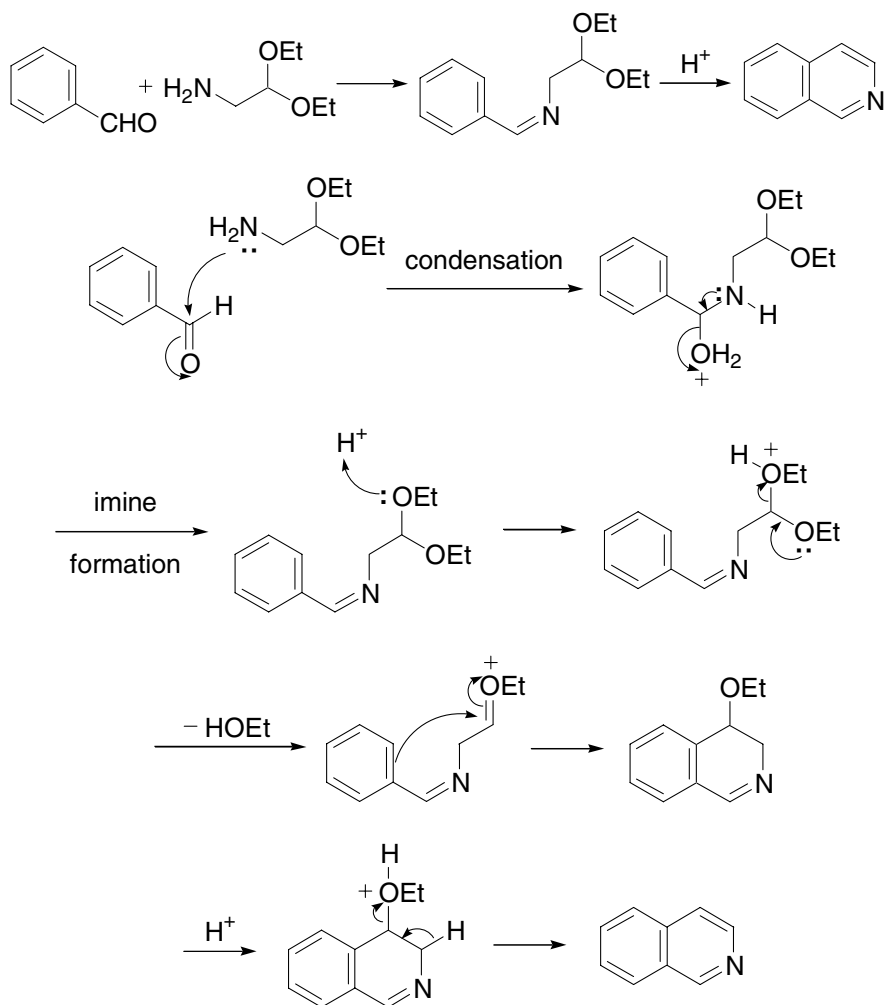
Example 1²Example 2⁵

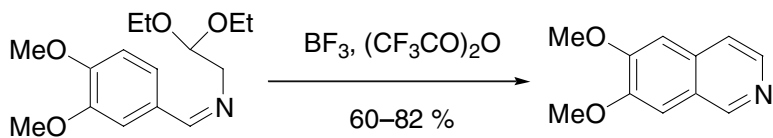
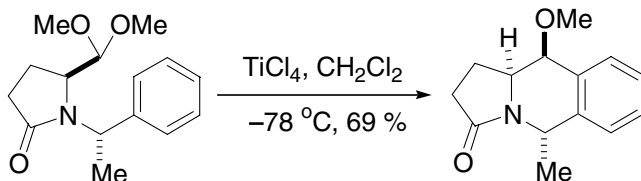
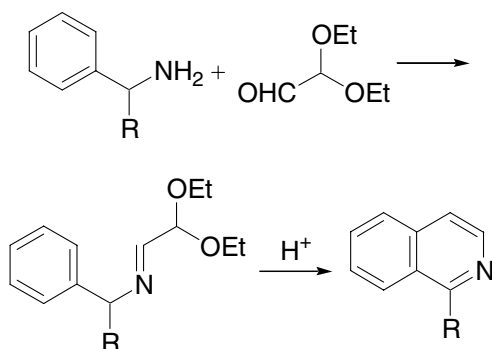
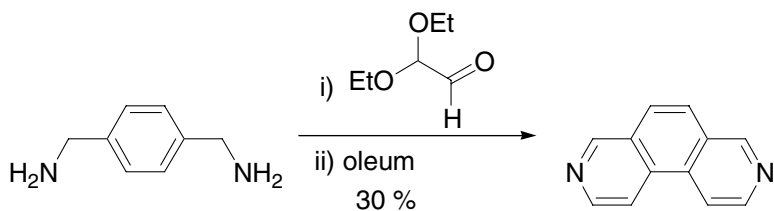
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Pomeranz–Fritsch reaction

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



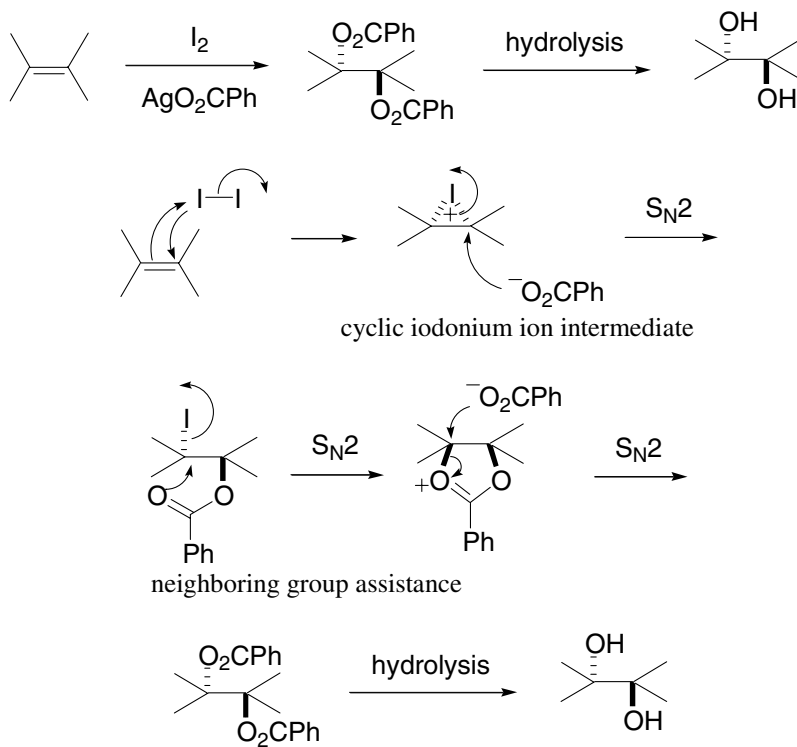
Example 1⁵Example 2¹²**Schlittler–Müller modification**Example 3⁷

References

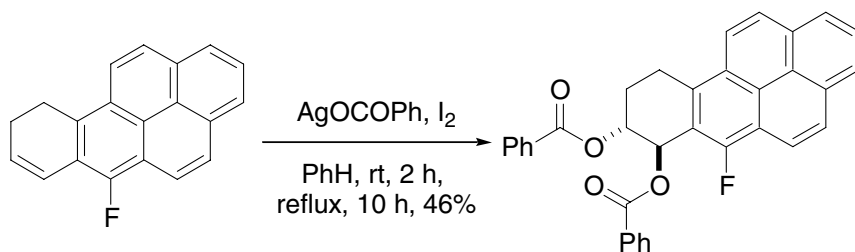
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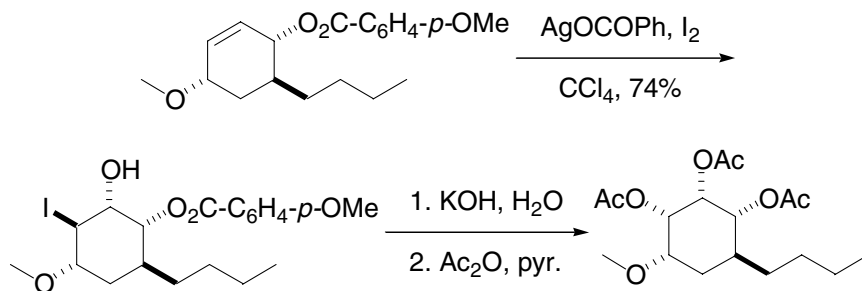
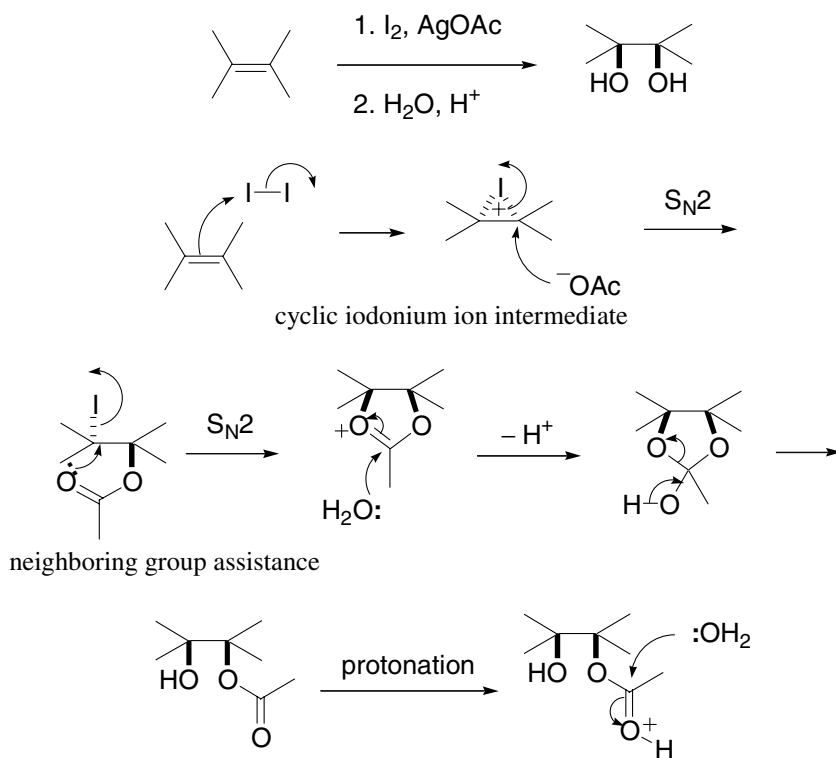
Prévost *trans*-dihydroxylation

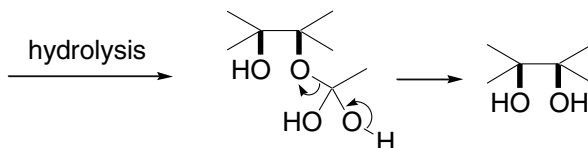
Cf. Woodward *cis*-dihydroxylation.



Example 1⁸



Example 2¹²**Woodward *cis*-dihydroxylation**¹³Cf. Prévost *trans*-dihydroxylation.

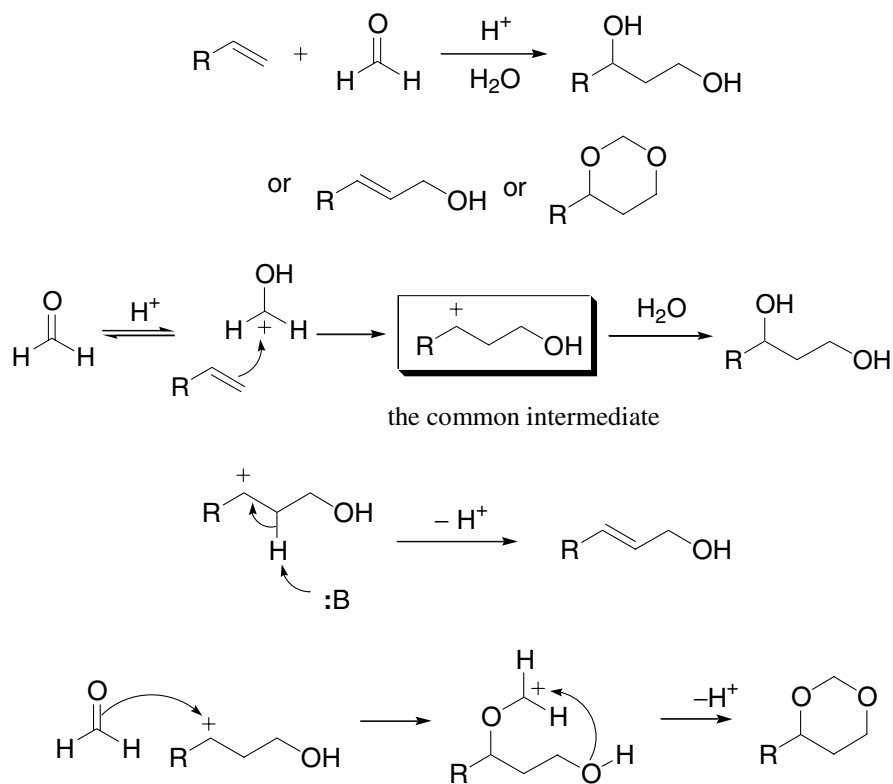


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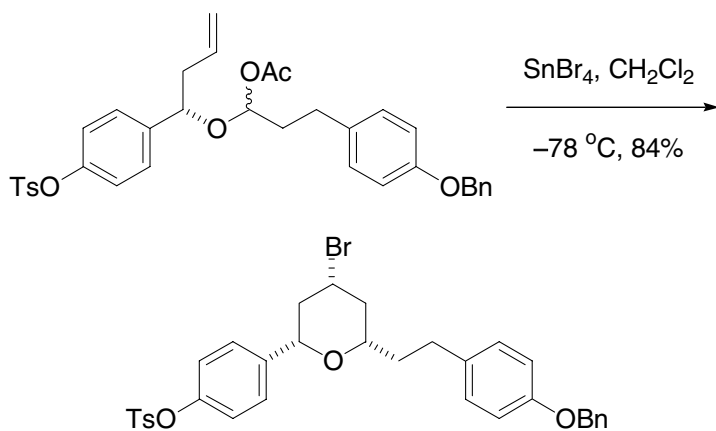
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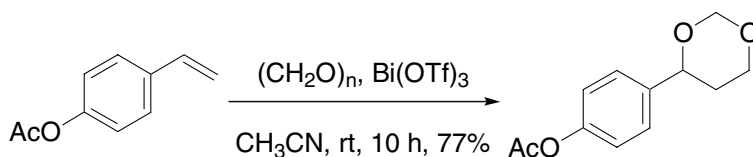
Prins reaction

Addition of alkene to formaldehyde.



Example 1⁸



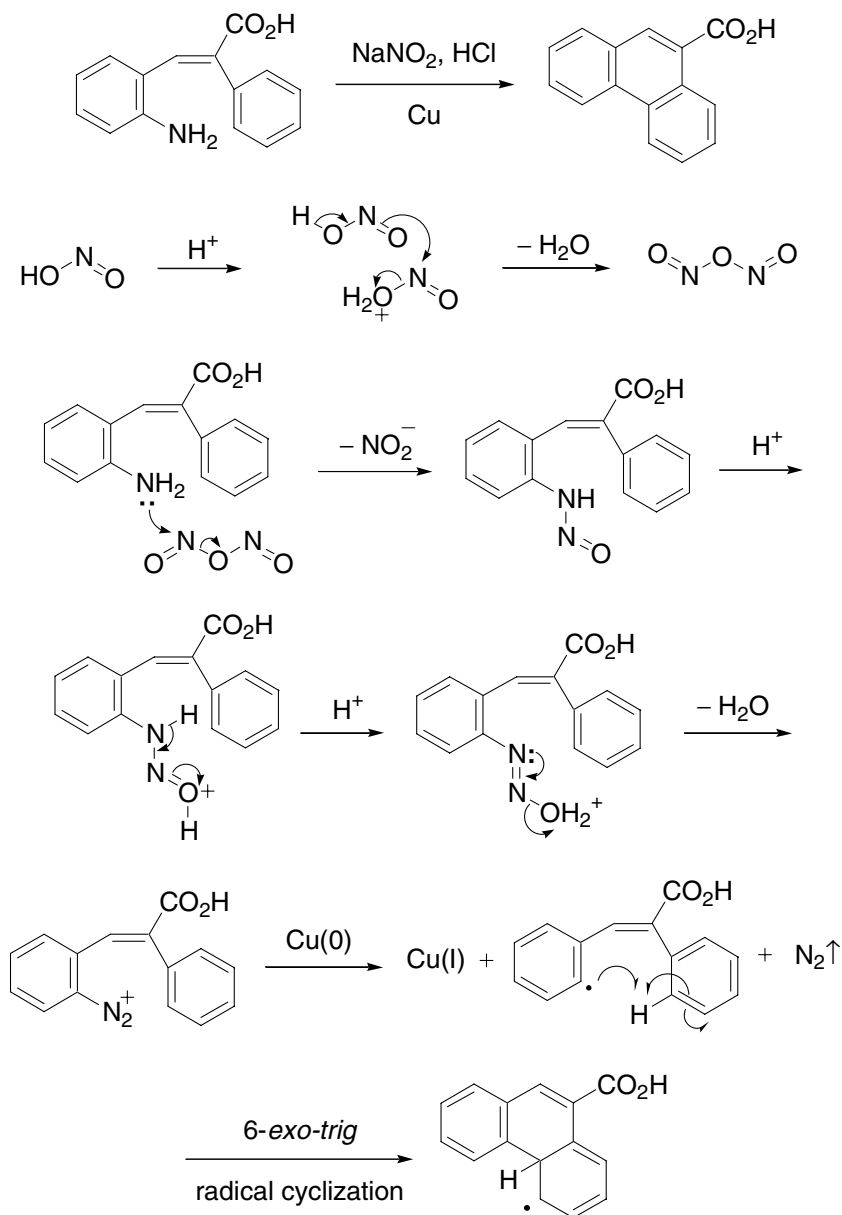
Example 2¹⁰

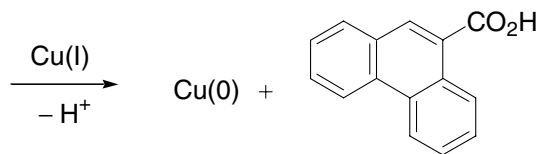
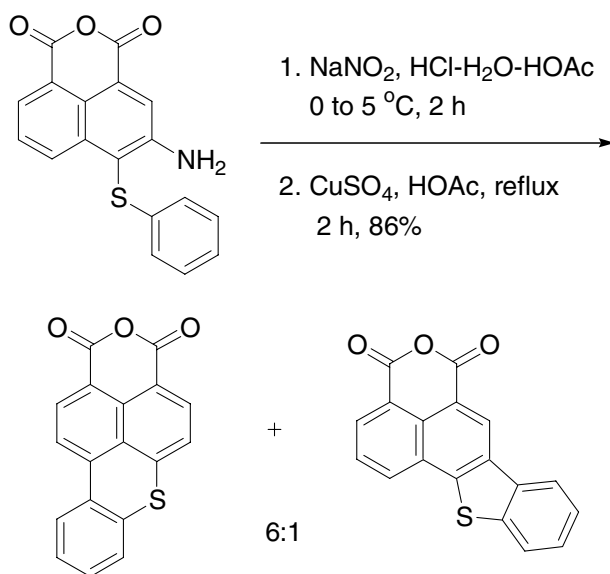
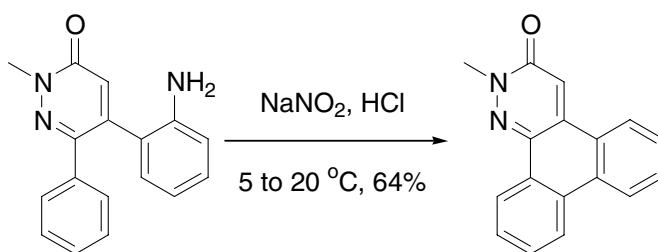
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Pschorr cyclization

The intramolecular version of the Gomberg–Bachmann reaction.



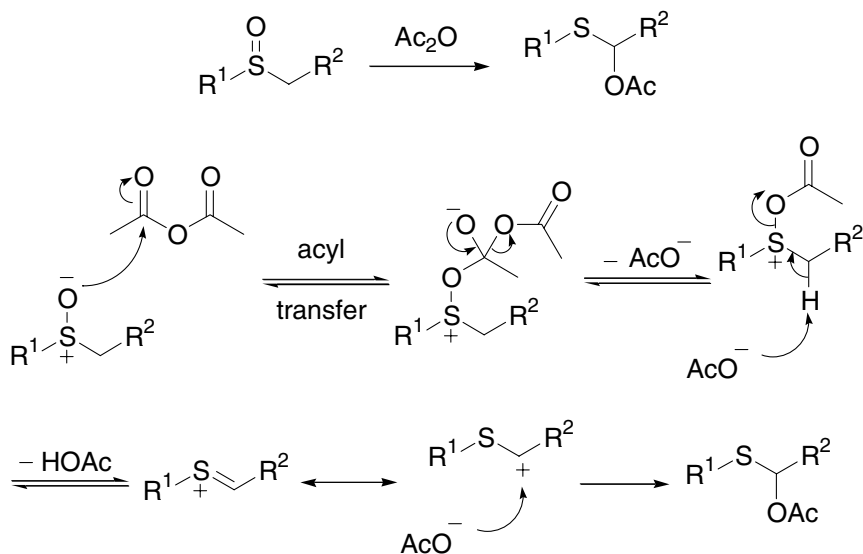
Example 1¹⁰Example 2¹¹

References

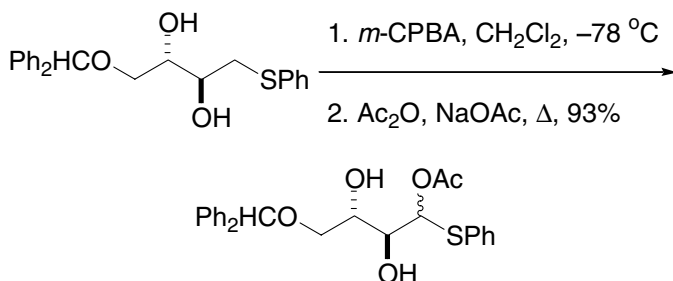
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Pummerer rearrangement

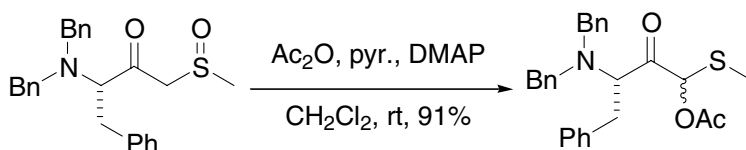
The transformation of sulfoxides into α -acyloxythioethers using acetic anhydride.



Example 1²



Example 2¹³

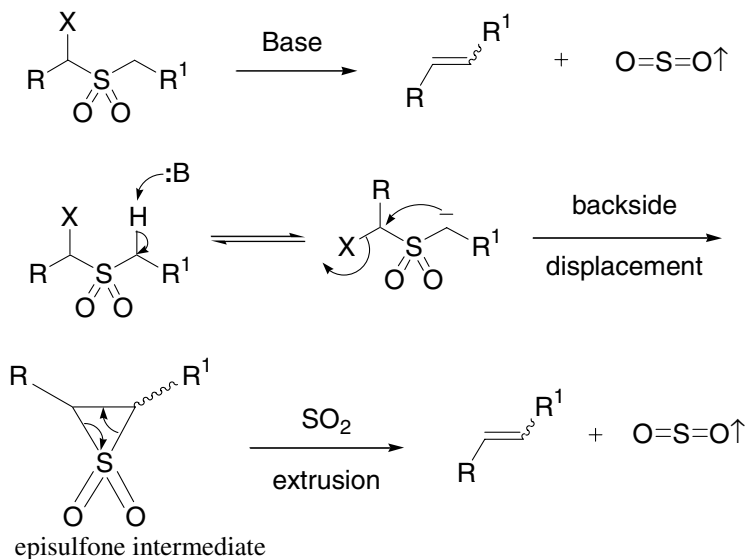


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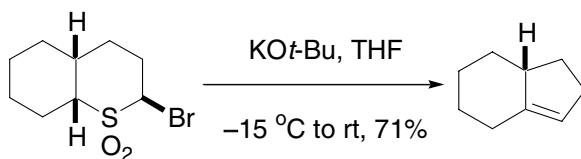
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Ramberg–Bäcklund reaction

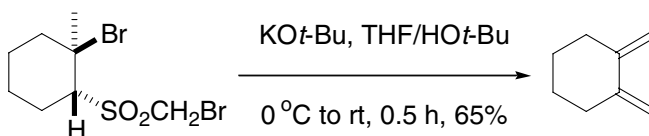
Olefin synthesis *via* α -halosulfone extrusion.



Example 1⁴



Example 2⁵

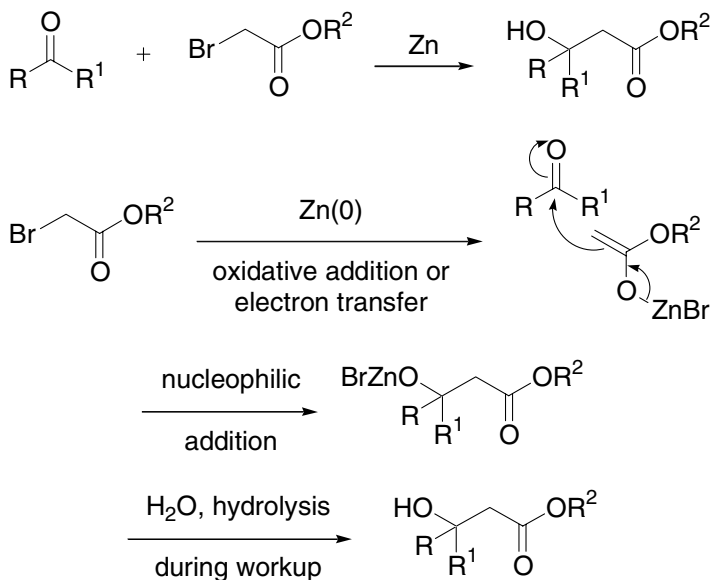


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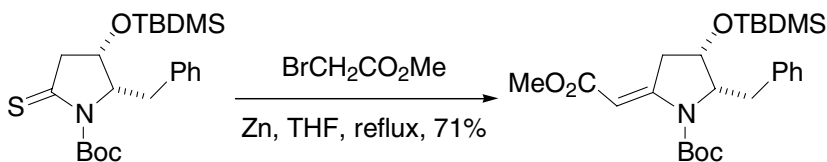
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Reformatsky reaction

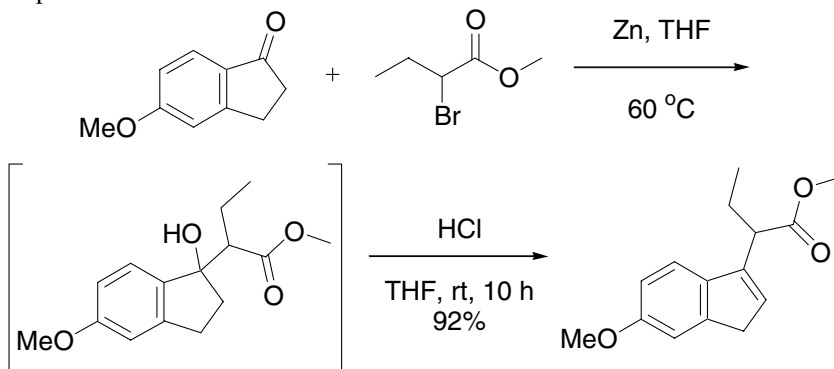
Nucleophilic addition of organozinc reagents generated from α -haloesters to carbonyls.



Example 1⁵



Example 2¹¹

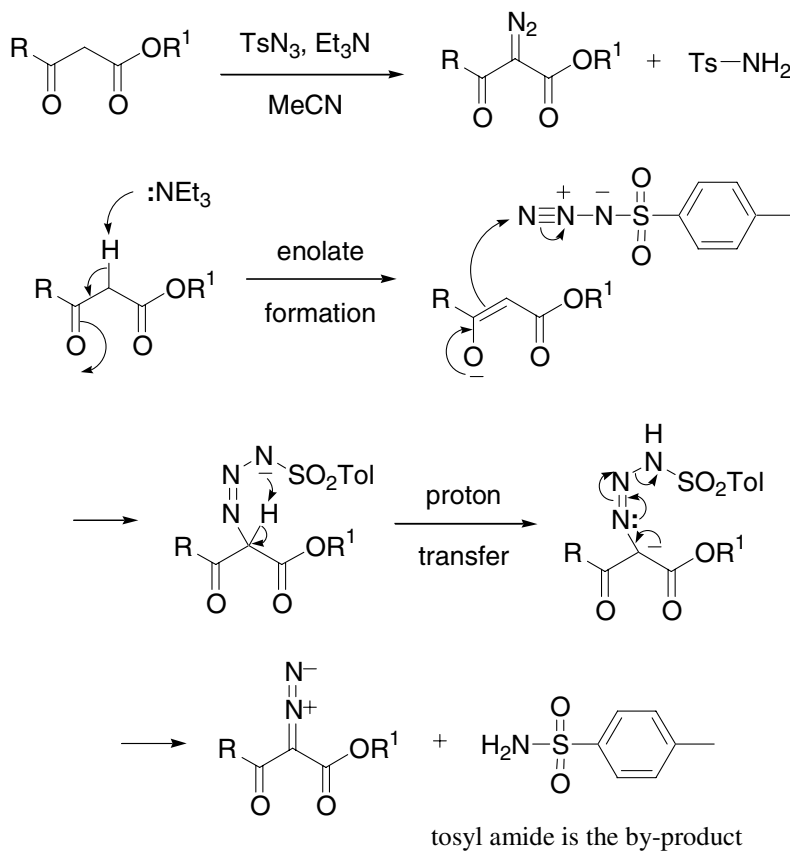


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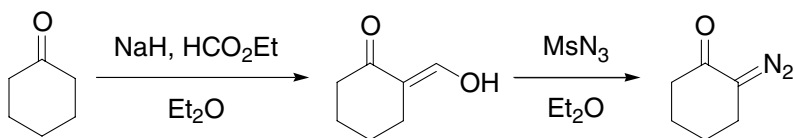
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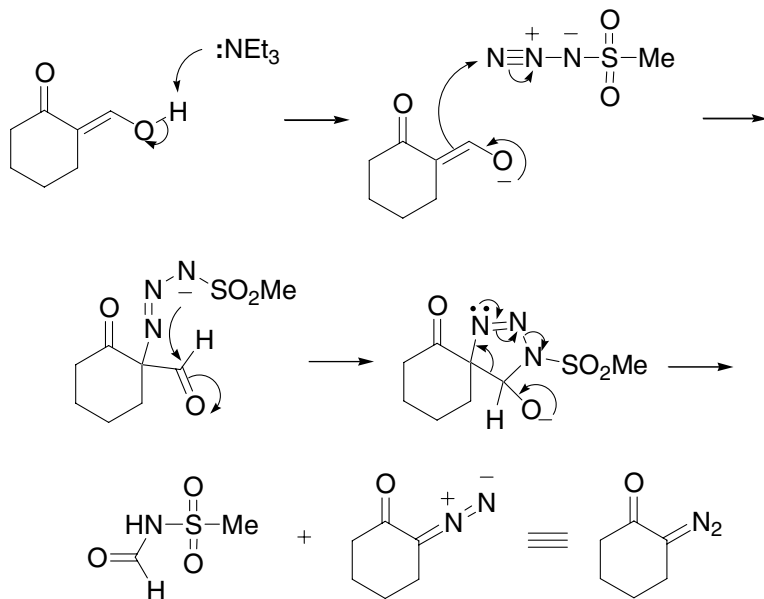
Regitz diazo synthesis

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

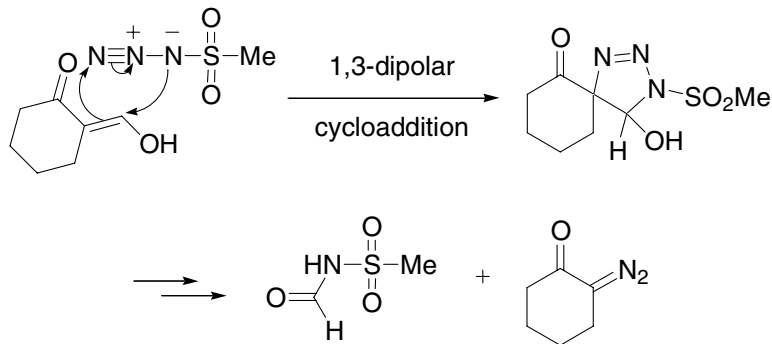


When only one carbonyl is present, ethylformate can be used as an activating auxiliary:⁶⁻⁹

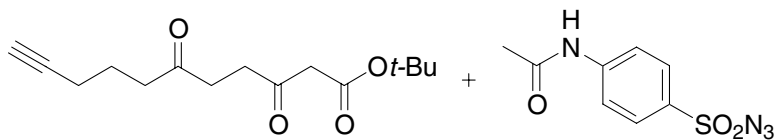


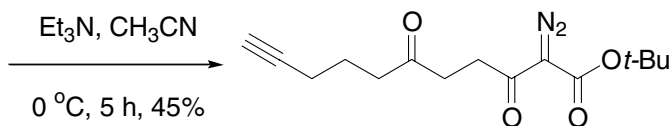
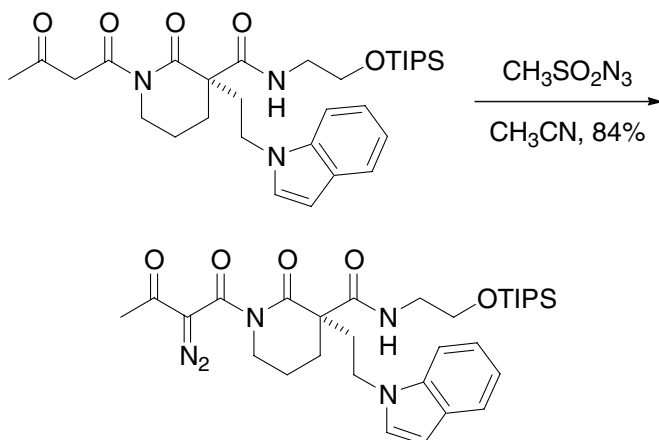


Alternatively, the triazole intermediate may be assembled *via* a 1,3-dipolar cycloaddition of the enol and mesyl azide:



Example 1¹⁰



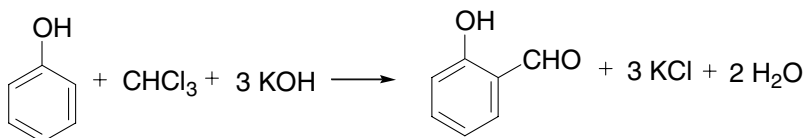
Example 2⁶

References

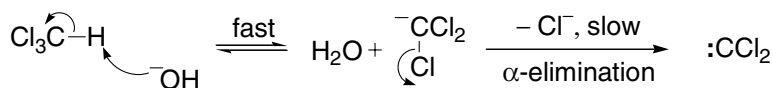
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Reimer–Tiemann reaction

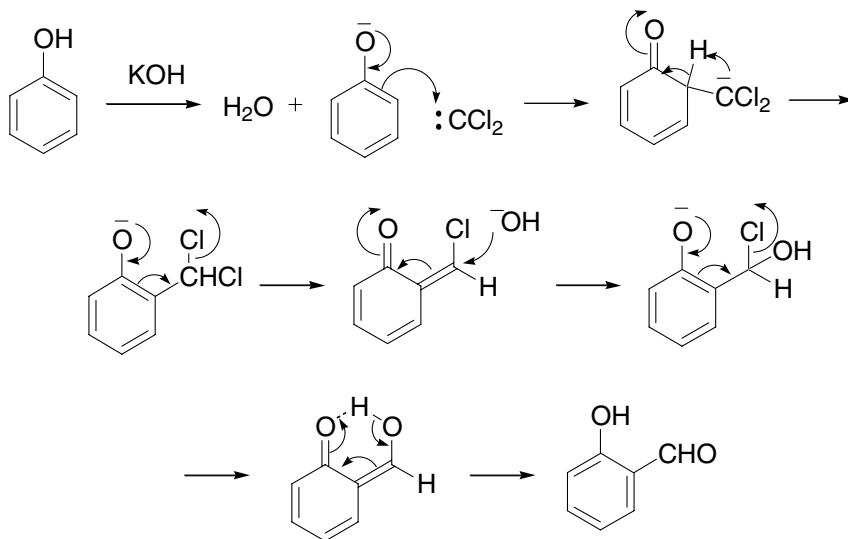
Synthesis of *o*-formylphenol from phenols and chloroform in alkaline medium.



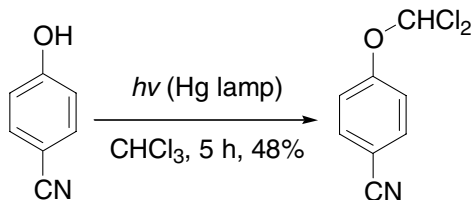
a. Carbene generation:

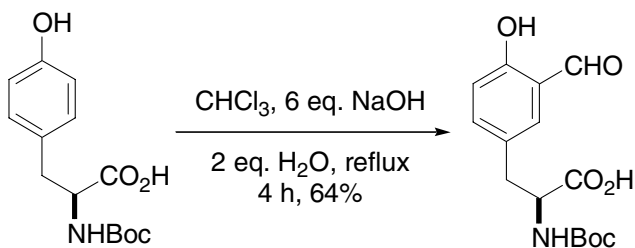


b. Addition of dichlorocarbene and hydrolysis:



Example 1, photo Reimer–Tiemann reaction without base⁸



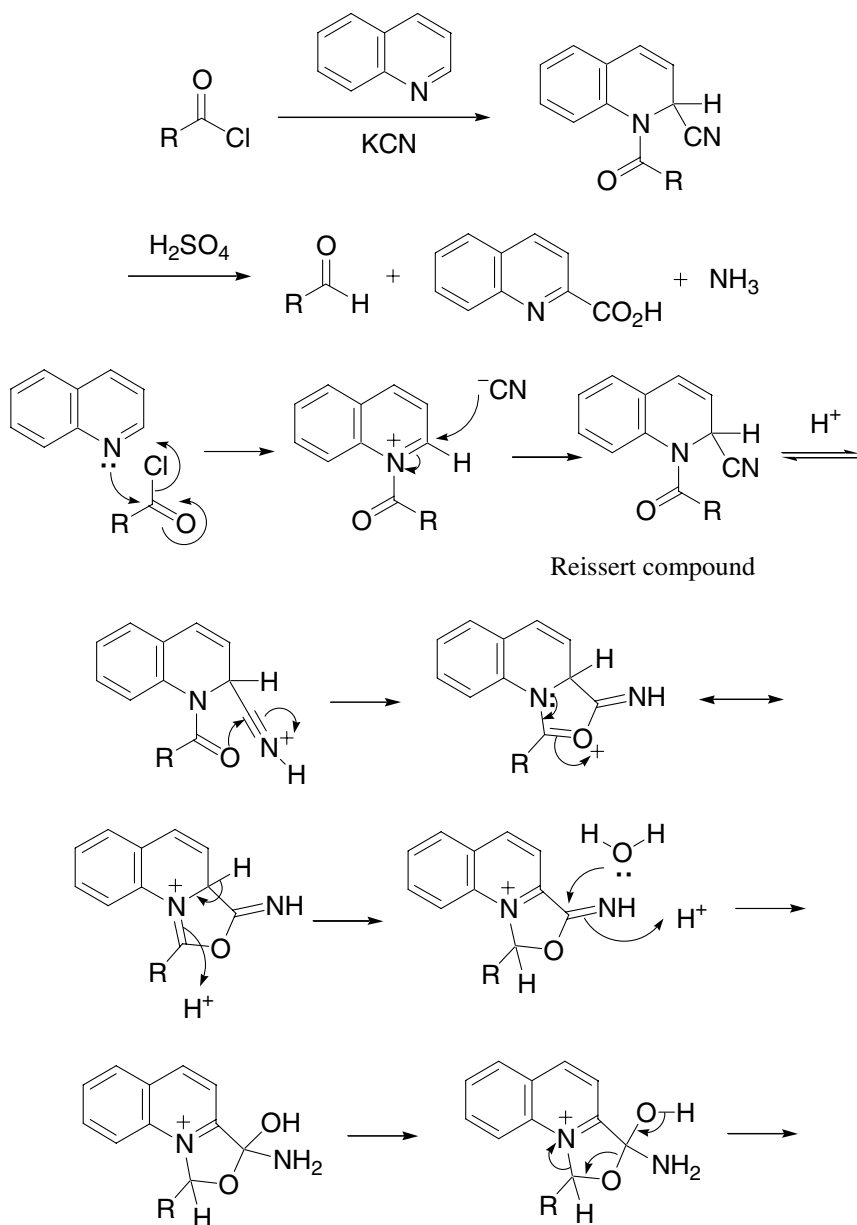
Example 2⁹

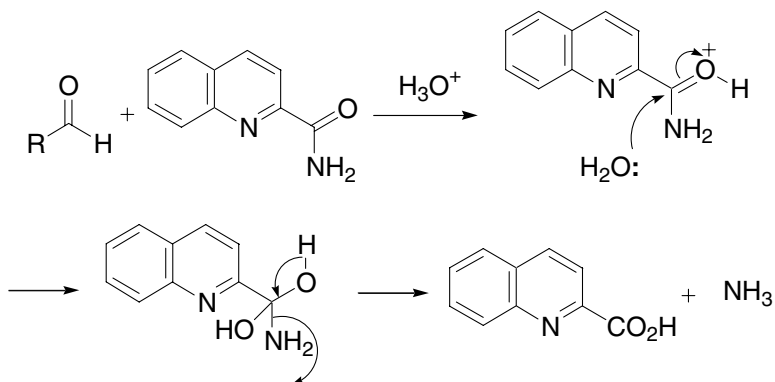
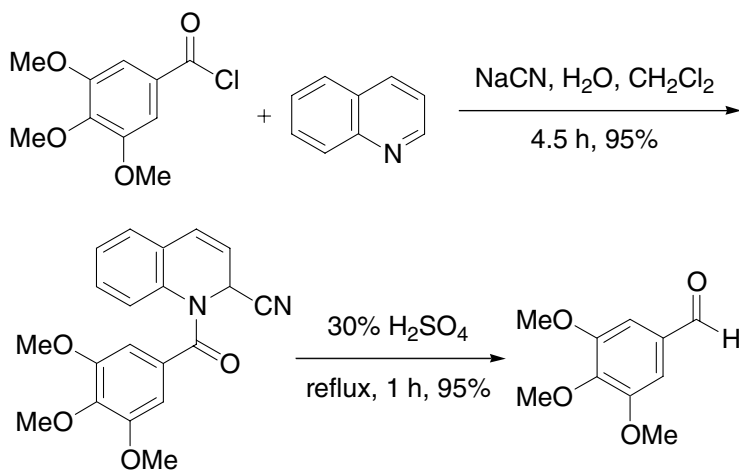
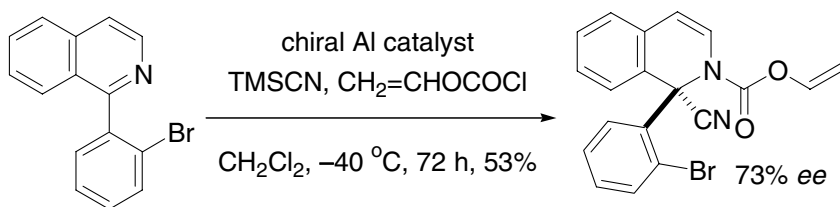
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Reissert aldehyde synthesis

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



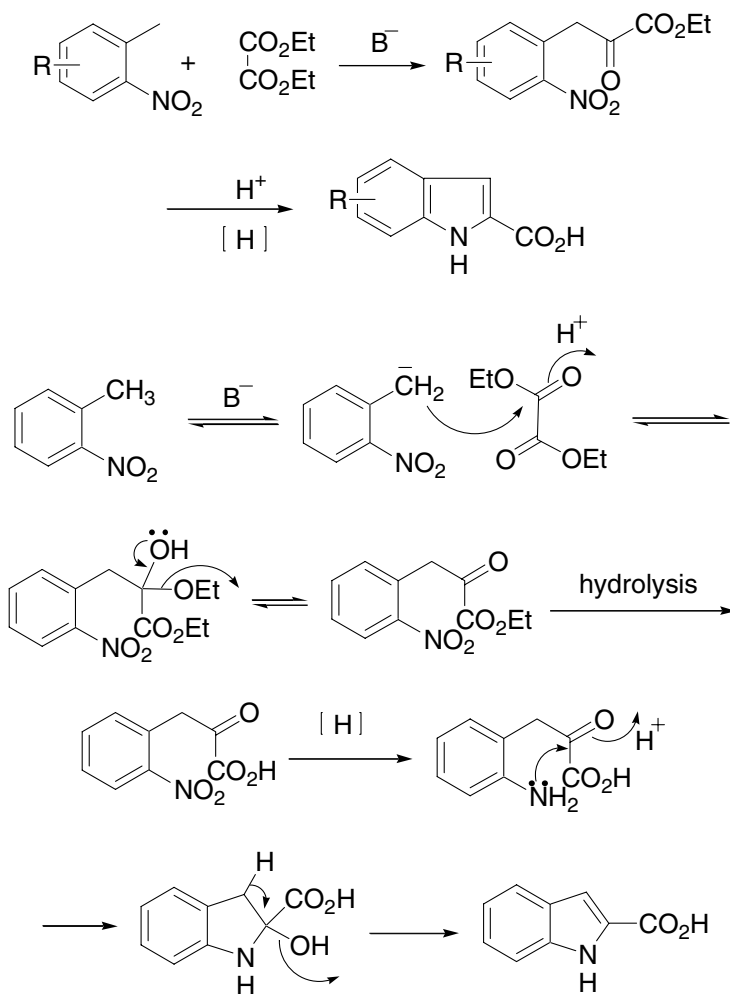
Example 1⁴Example 2¹⁰

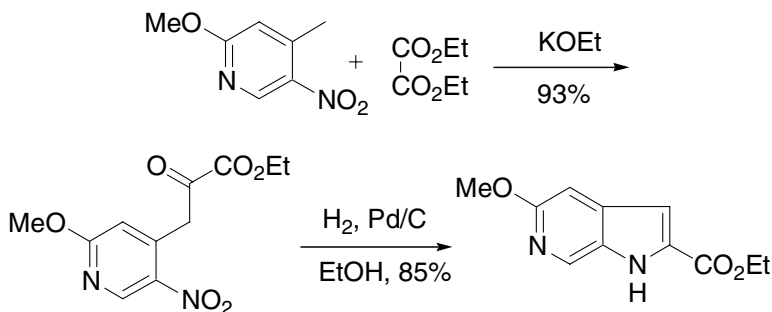
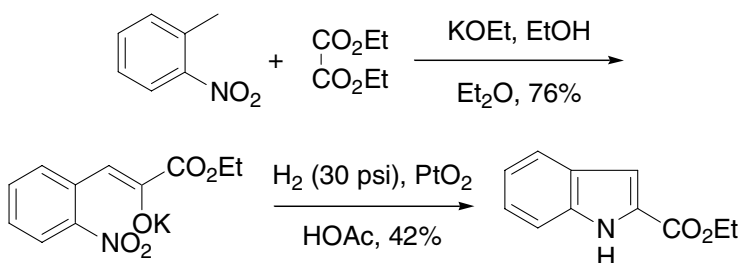
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Reissert indole synthesis

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.

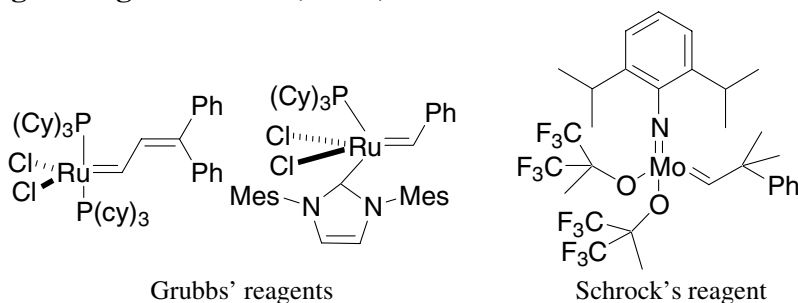


Example 1³Example 2⁵

References

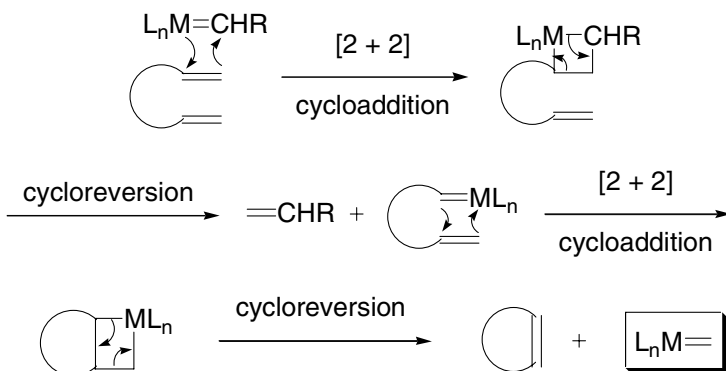
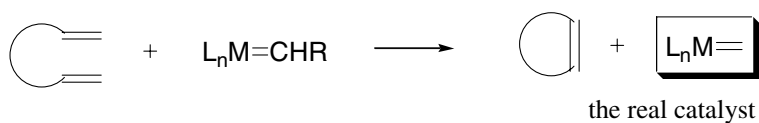
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Ring-closing metathesis (RCM)

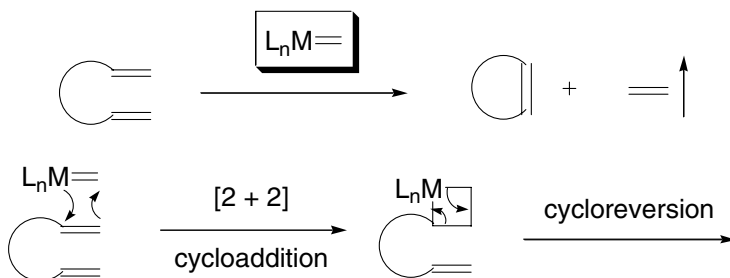


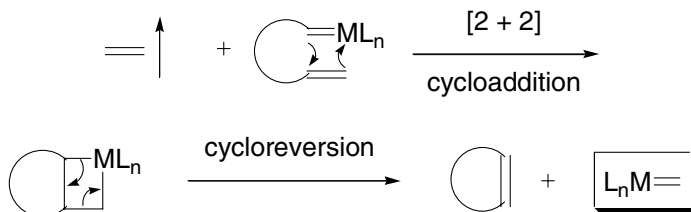
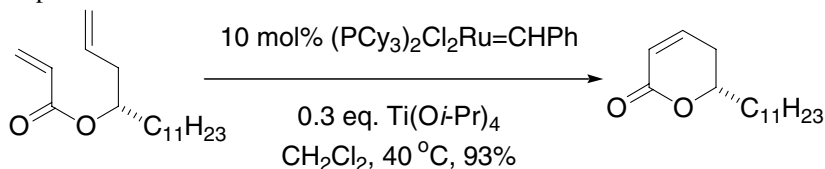
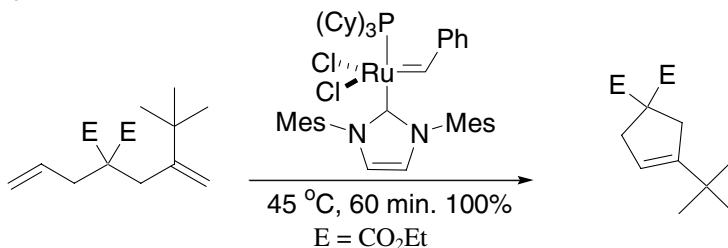
All three catalysts are illustrated as “ $L_nM=CHR$ ” in the mechanism below.

Generation of the catalyst from the precatalysts:



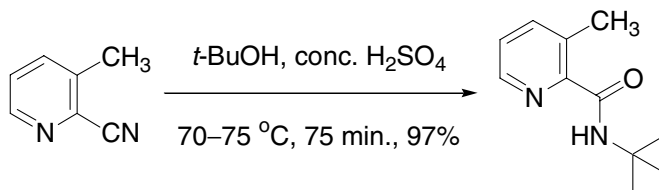
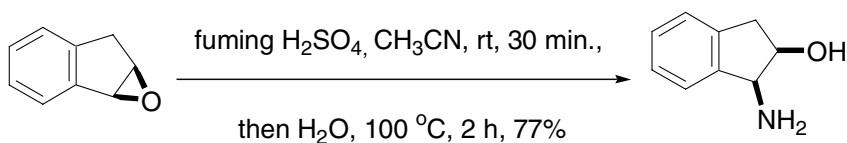
Catalytic cycle:



Example 1⁴Example 2⁹

References

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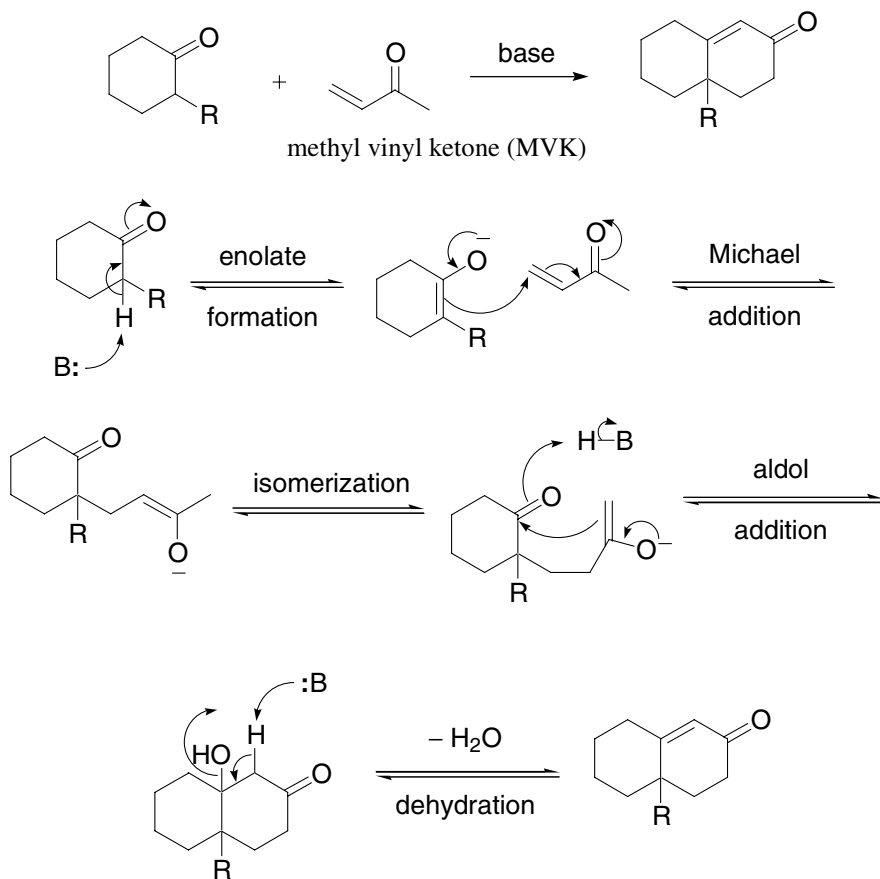
Example 1⁴Example 2⁸

References

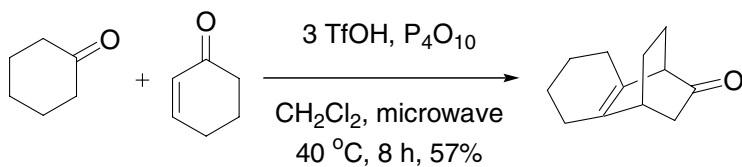
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Robinson annulation

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



Example¹¹

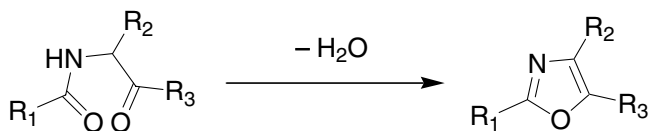


References

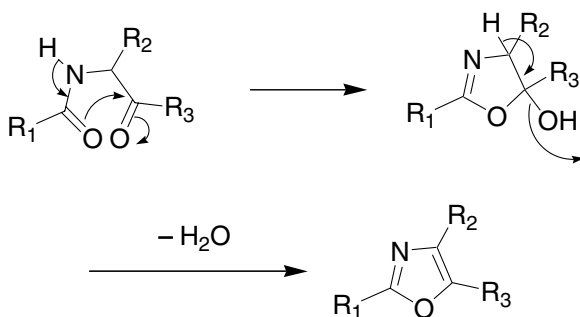
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Robinson–Gabriel synthesis

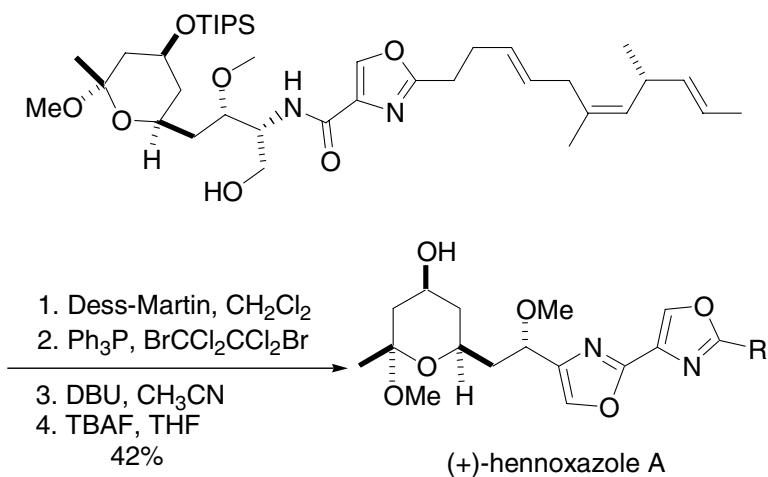
Cyclodehydration of 2-acylamidoketones to give 2,5-di- and 2,4,5-trialkyl, aryl, heteroaryl-, and aralkyloxazoles.



$\text{R}_1, \text{R}_2, \text{R}_3 = \text{alkyl, aryl, heteroaryl}$

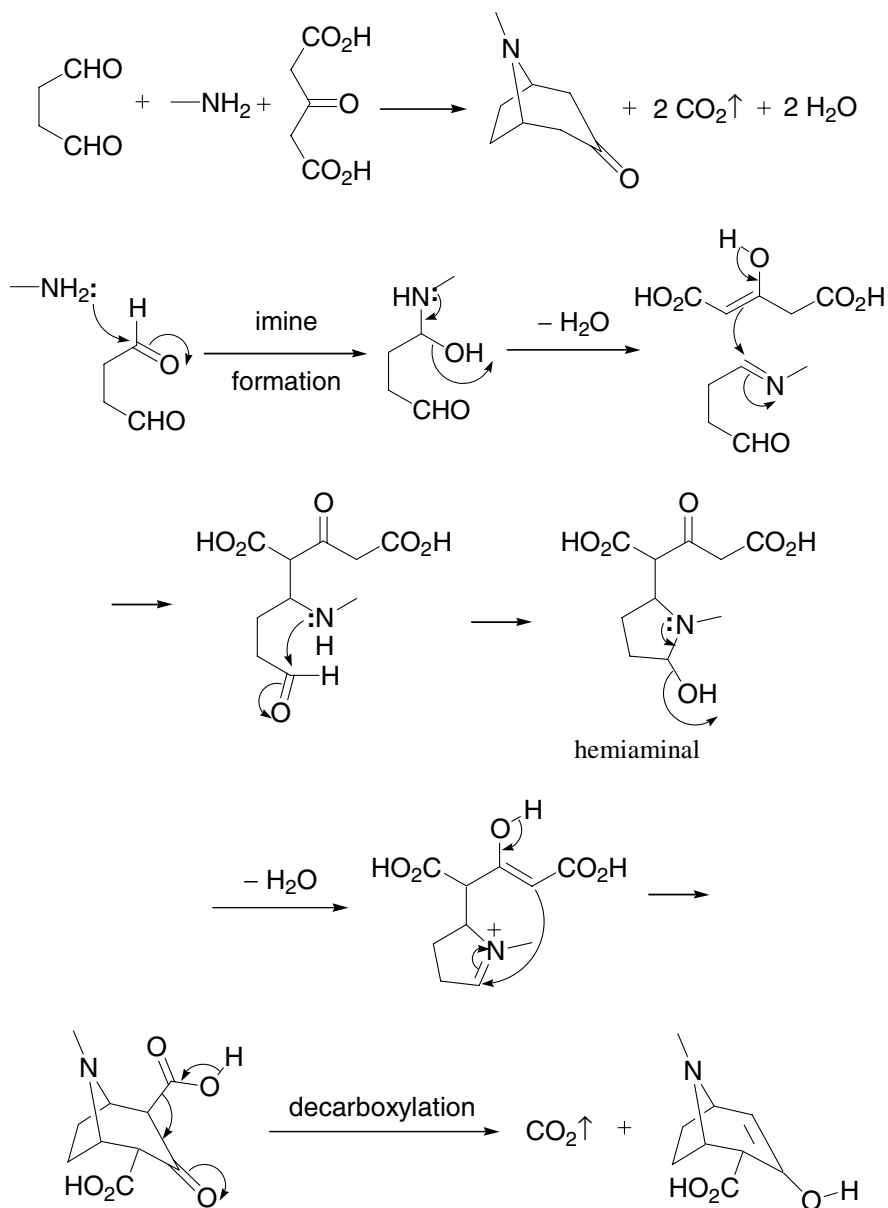


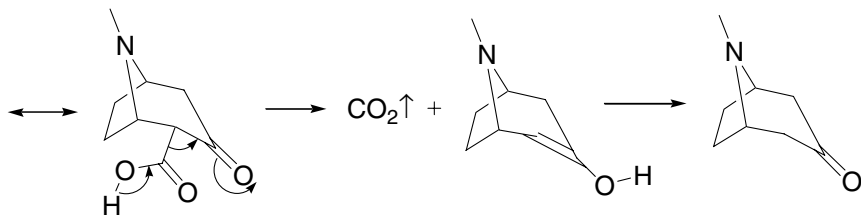
Example 1⁹



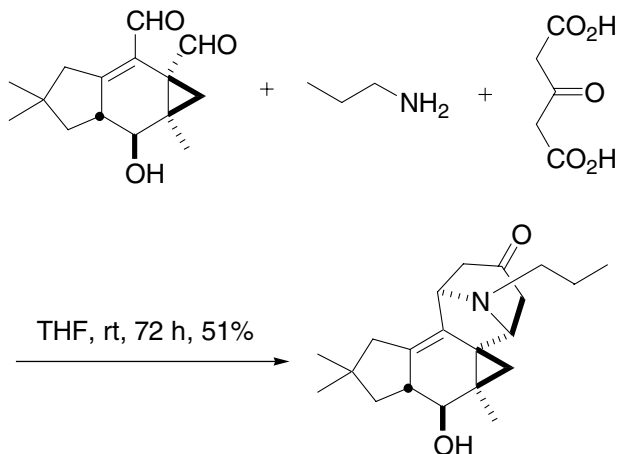
Robinson–Schöpf reaction

Tropinone synthesis.





Example⁷

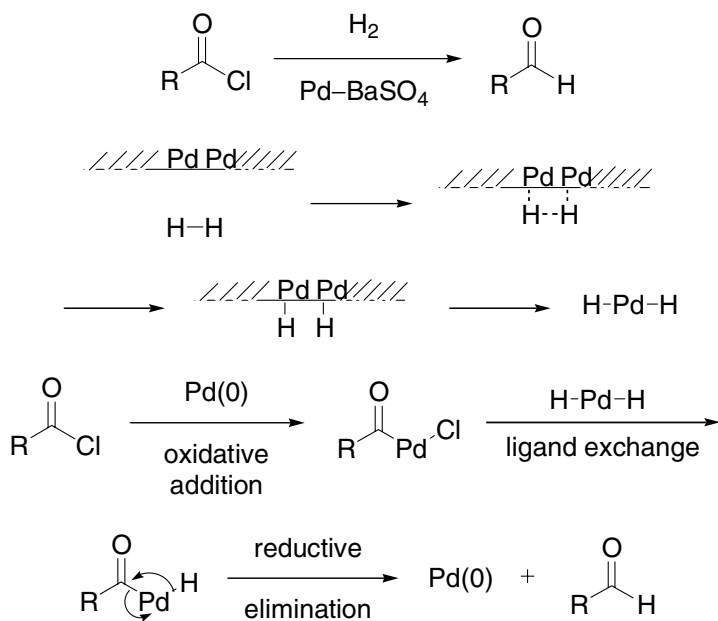


References

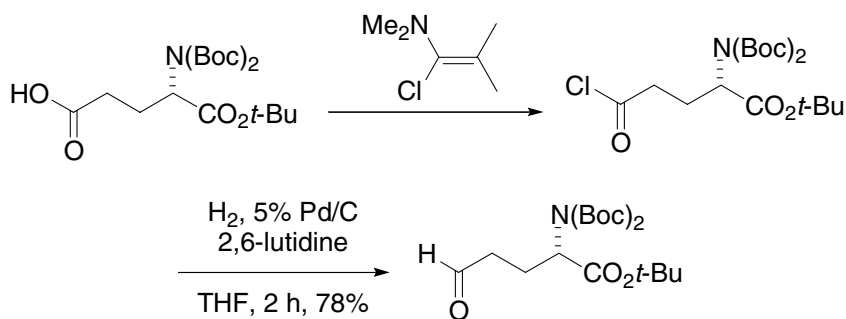
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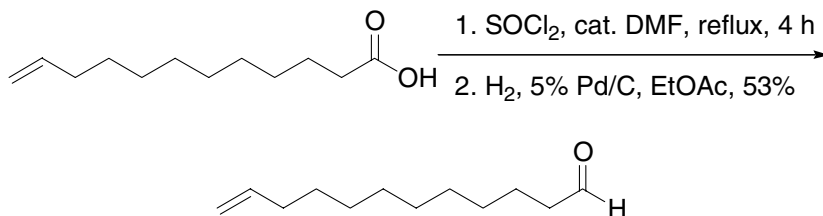
Rosenmund reduction

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



Example 1⁶



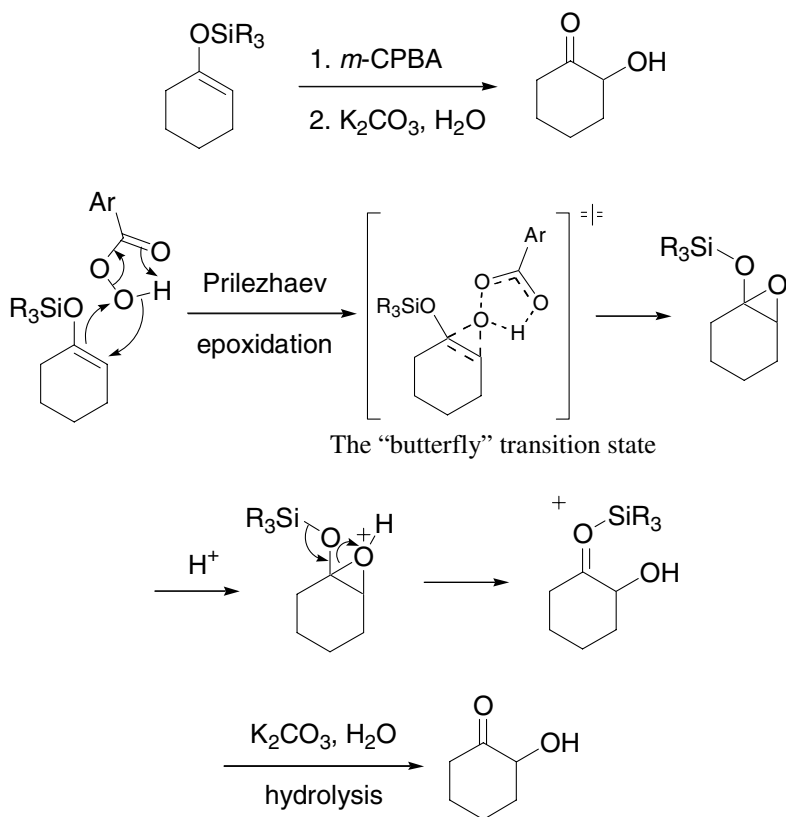
Example 2⁹

References

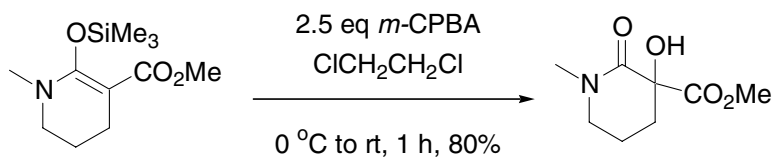
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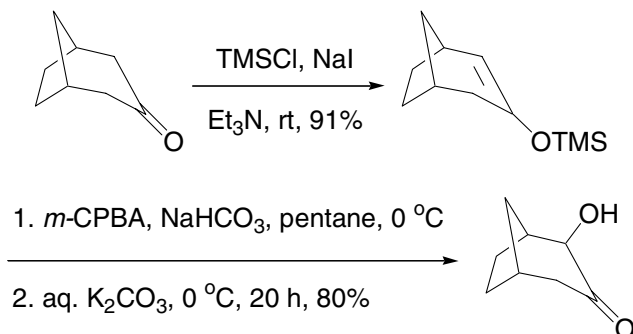
Rubottom oxidation

α -Hydroxylation of enolsilanes.



Example 1⁵



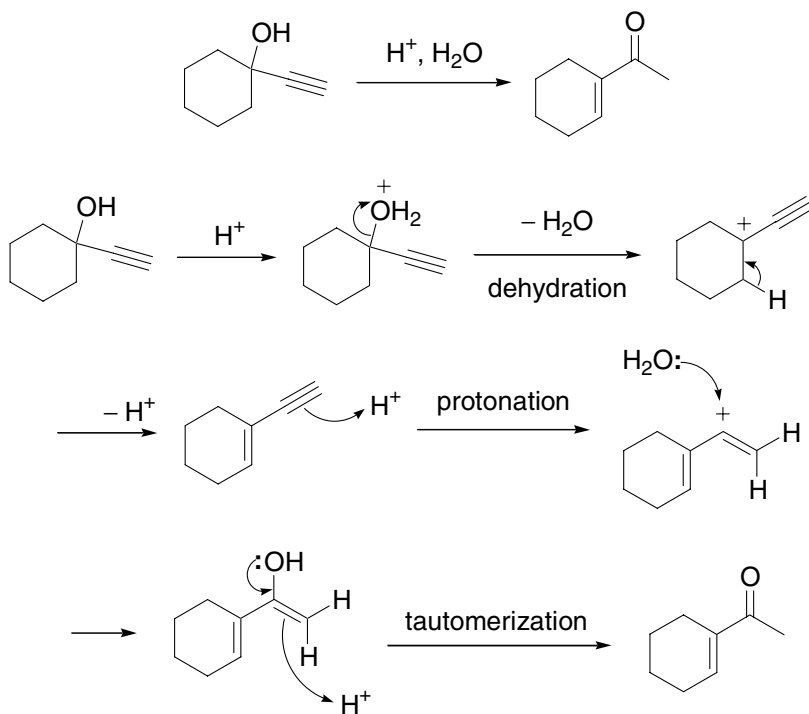
Example 2¹⁰

References

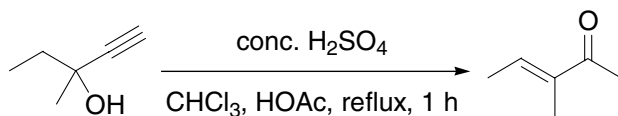
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Rupe rearrangement

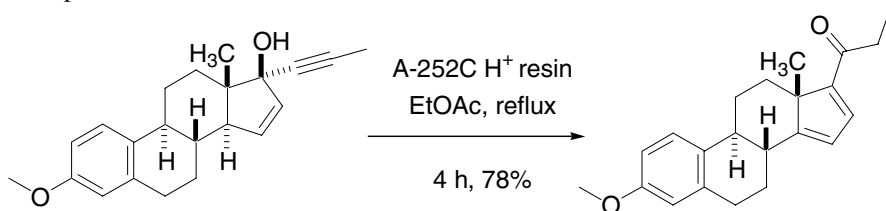
Acid-catalyzed rearrangement of tertiary α -acetylenic (terminal) alcohols, leading to the formation of α,β -unsaturated ketones rather than the corresponding α,β -unsaturated aldehydes. Cf. Meyer–Schuster rearrangement.



Example 1⁶



Example 2¹⁰

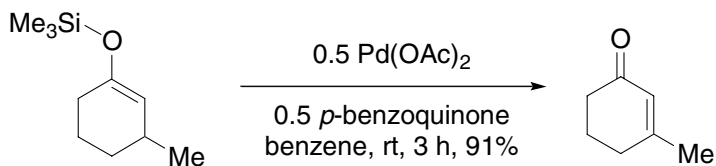


References

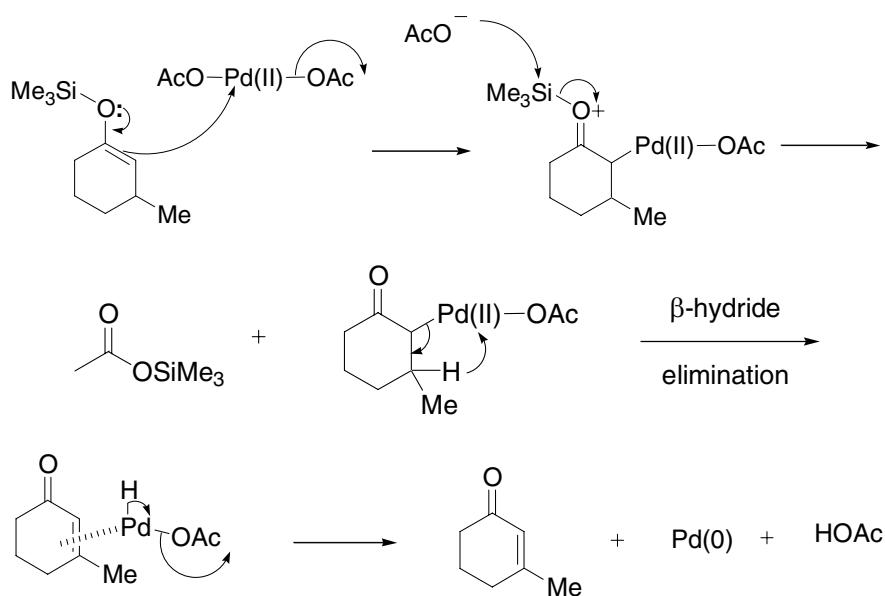
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Saegusa oxidation

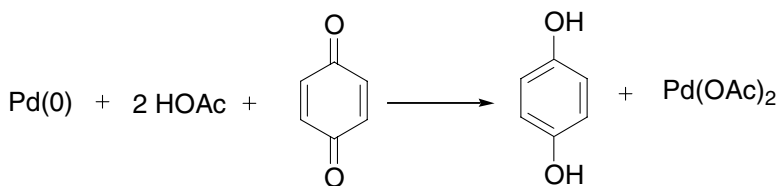
Palladium-catalyzed conversion of enol silanes to enones, also known as the Saegusa enone synthesis.



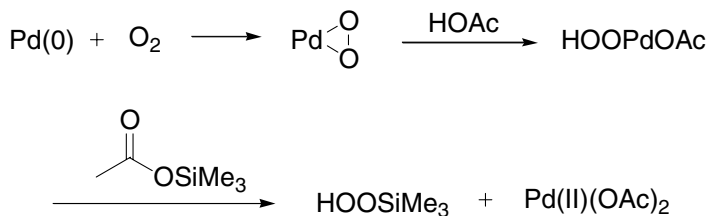
The mechanism is similar to that of the Wacker oxidation (page 610).



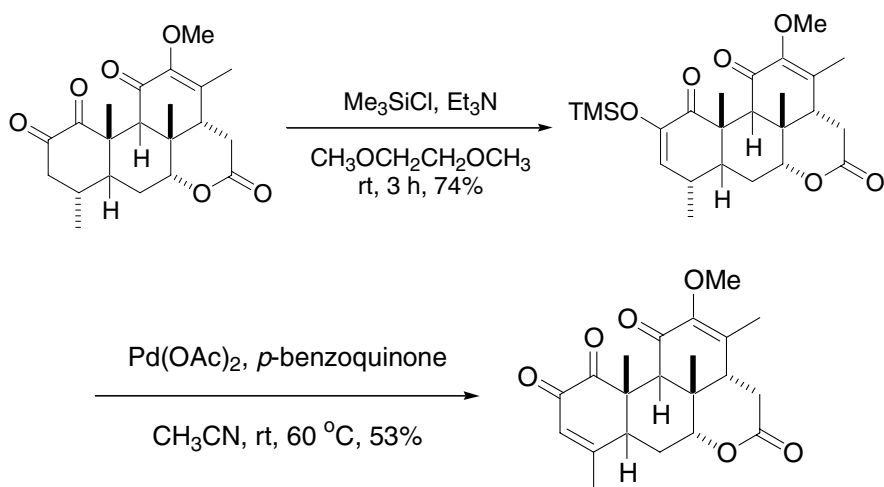
Regenerating the Pd(II) oxidant:



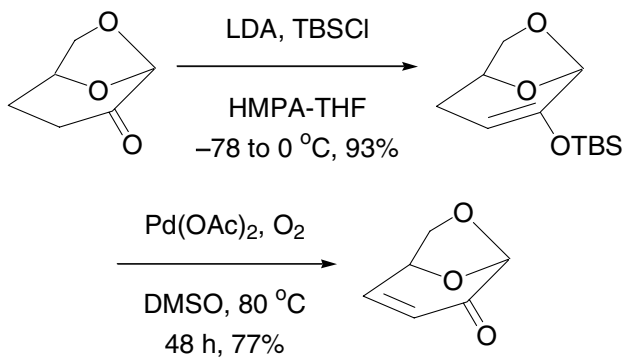
Larock reported regeneration of the Pd(II) oxidant using oxygen:⁴



Example 1³



Example 2⁸

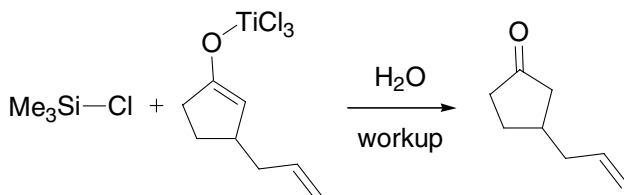
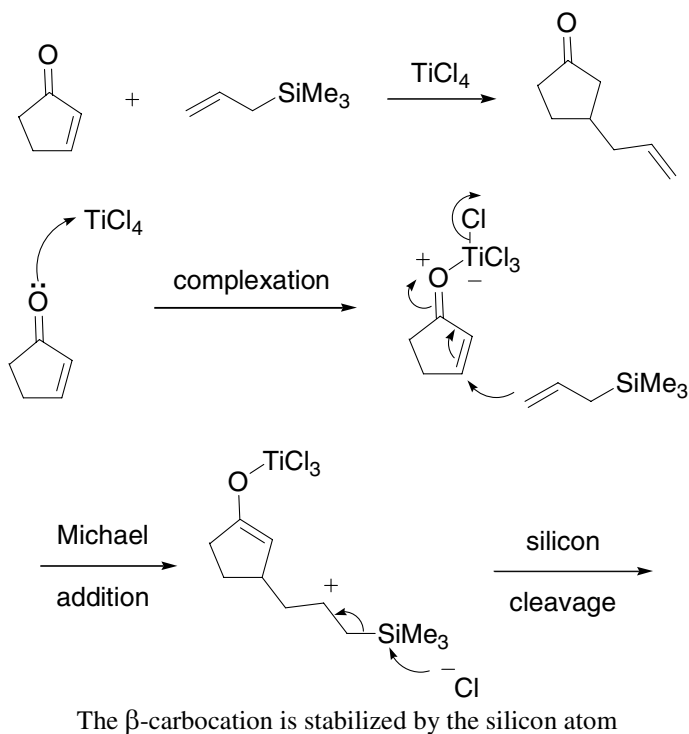


References

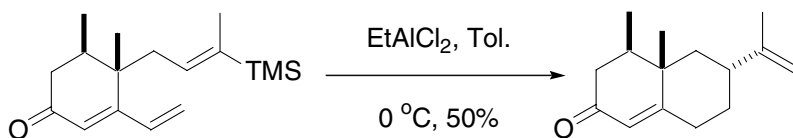
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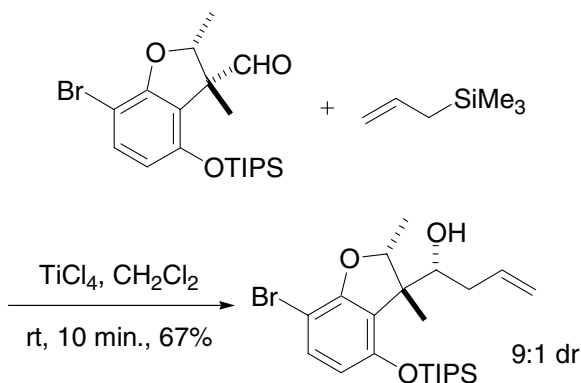
Sakurai allylation reaction

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



Example 1²



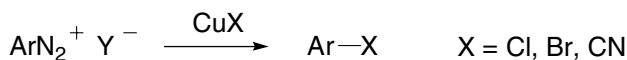
Example 2¹⁴

References

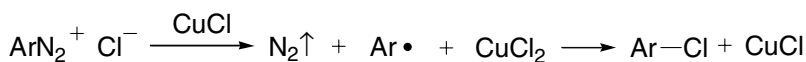
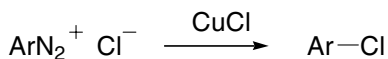
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Sandmeyer reaction

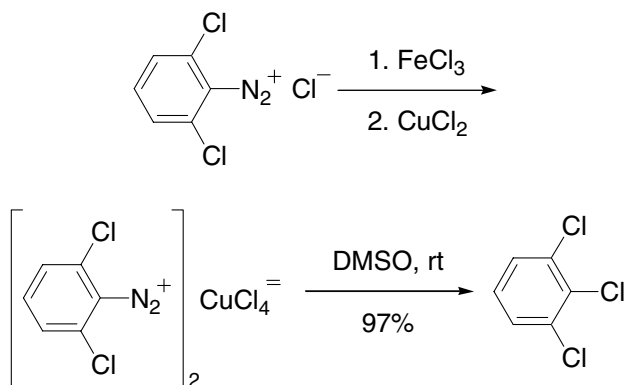
Haloarenes from the reaction of a diazonium salt with CuX.



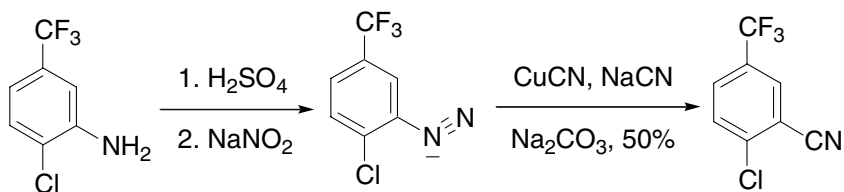
e.g.:



Example 1⁵



Example 2¹¹



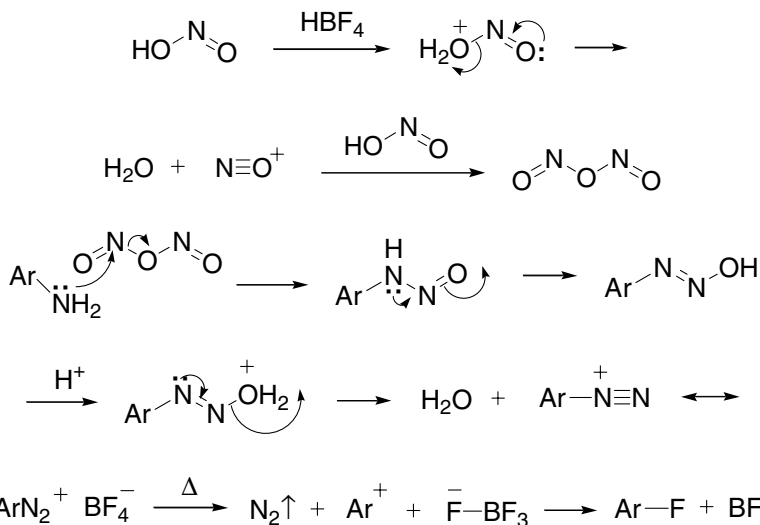
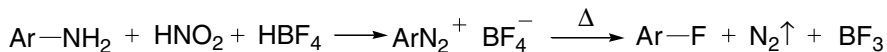
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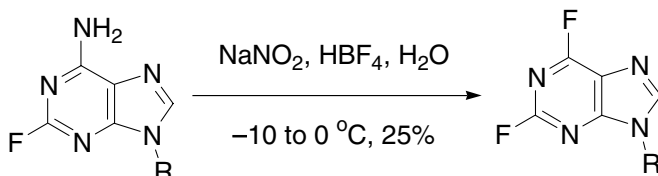
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Schiemann reaction

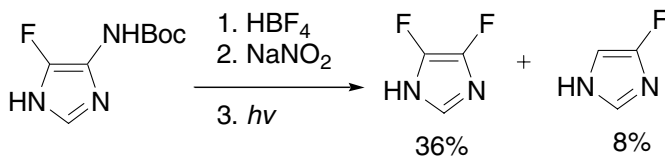
Fluoroarene formation from arylamines. Also known as the Balz–Schiemann reaction.



Example 1⁴



Example 2¹⁰

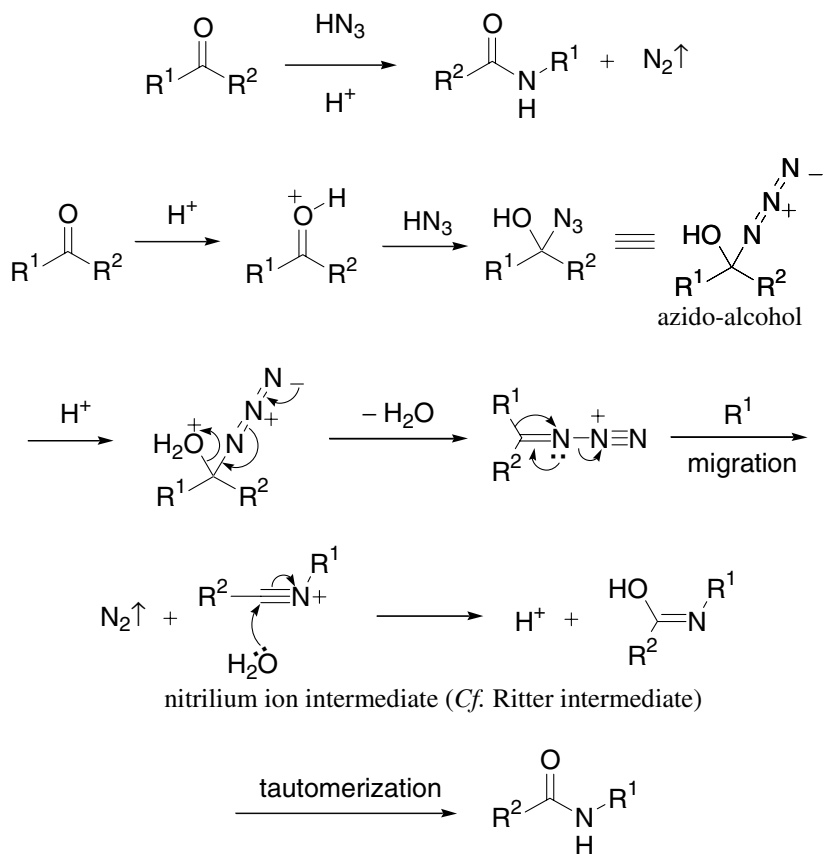


References

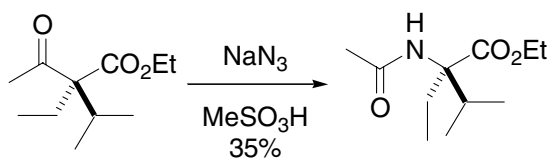
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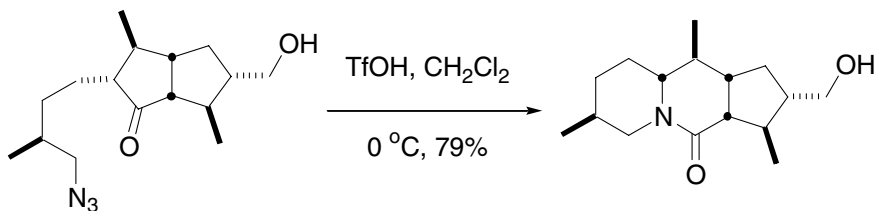
Schmidt reaction

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



Example 1, a classic example¹¹



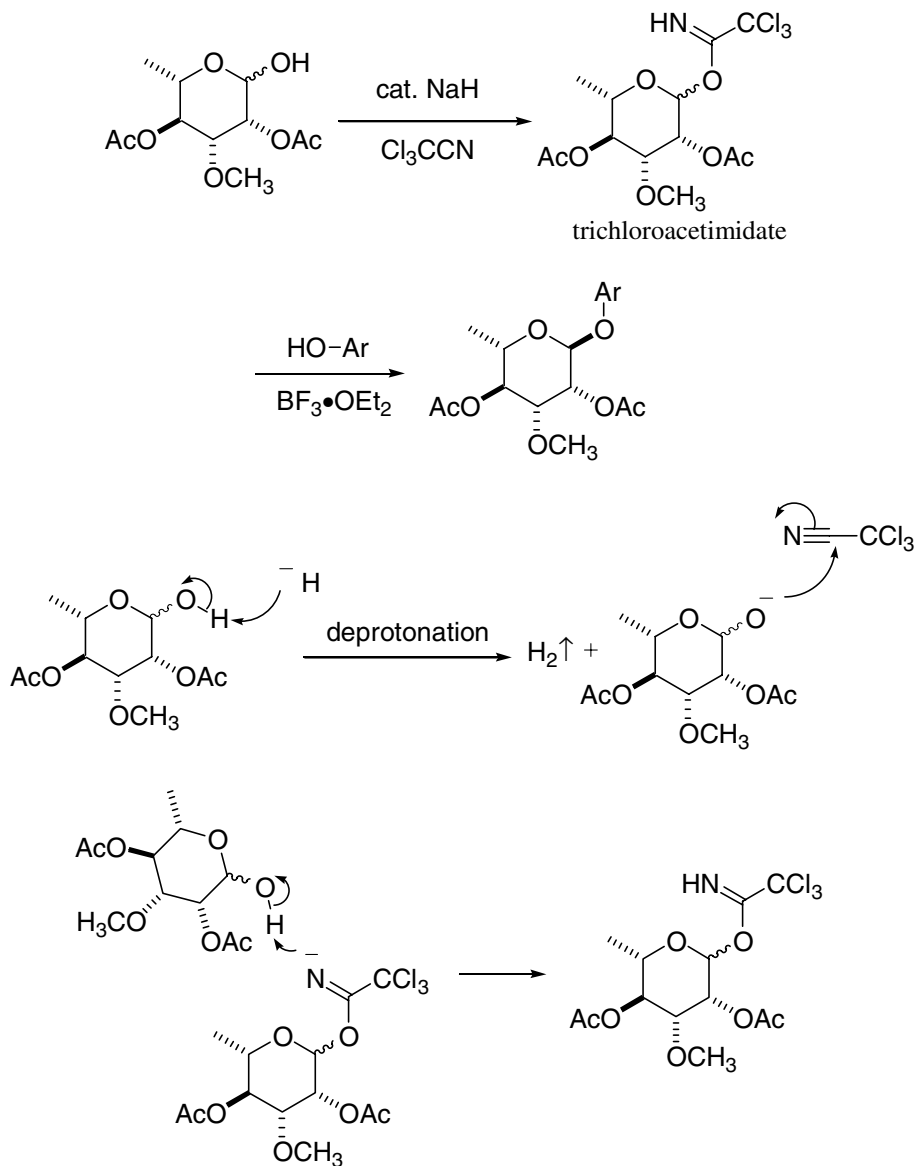
Example 2, a variant¹⁵

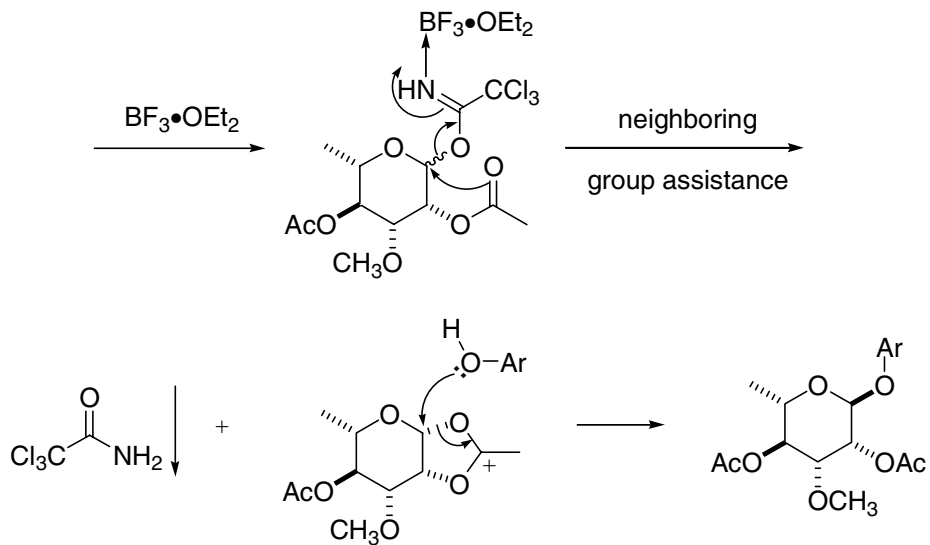
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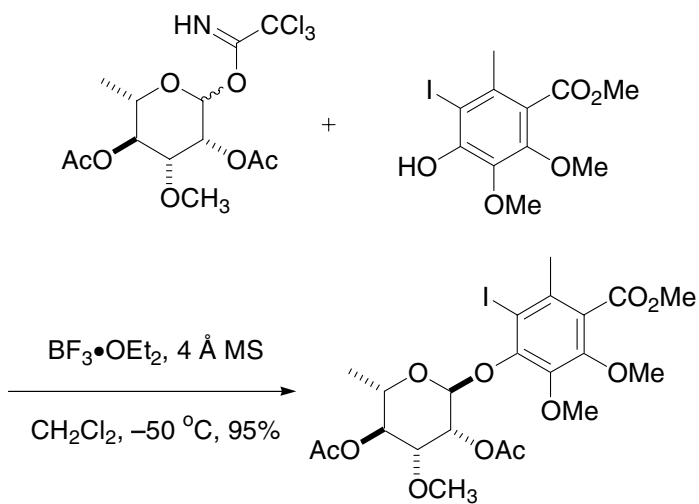
Schmidt's trichloroacetimidate glycosidation reaction

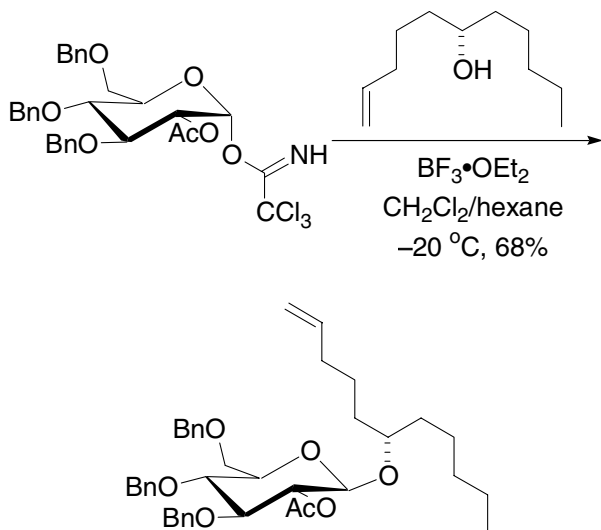
Lewis acid-promoted glycosidation of trichloroacetimidates with alcohols or phenols.





Example 1⁵



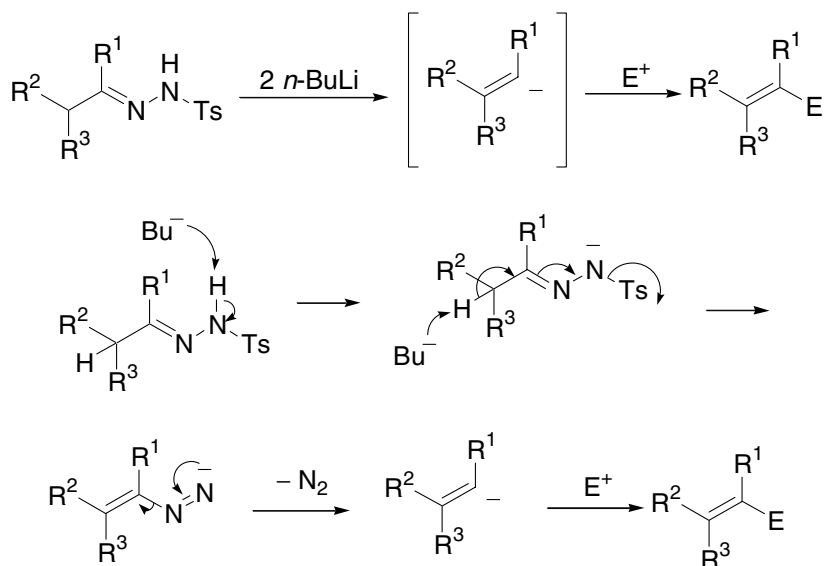
Example 2⁷

References

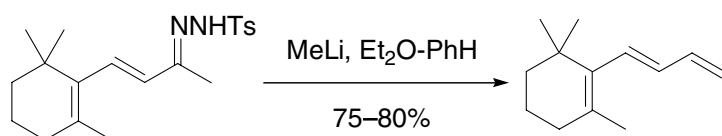
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Shapiro reaction

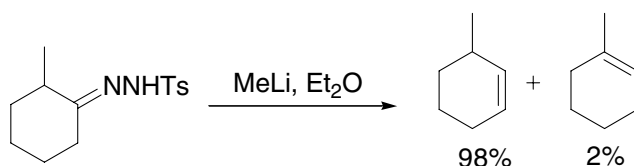
The Shapiro reaction is a variant of the Bamford–Stevens reaction. The former uses bases such as alkyl lithium and Grignard reagents whereas the latter employs bases such as Na, NaOMe, LiH, NaH, NaNH₂, *etc.* Consequently, the Shapiro reaction generally affords the less-substituted olefins as the kinetic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



Example 1³



Example 2²

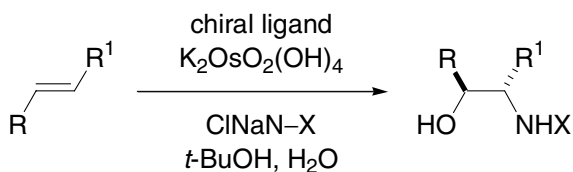
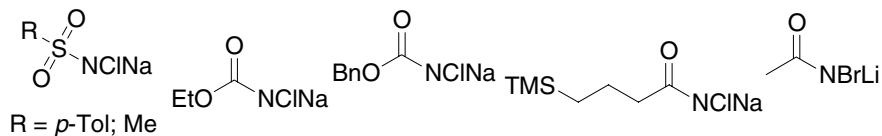


References

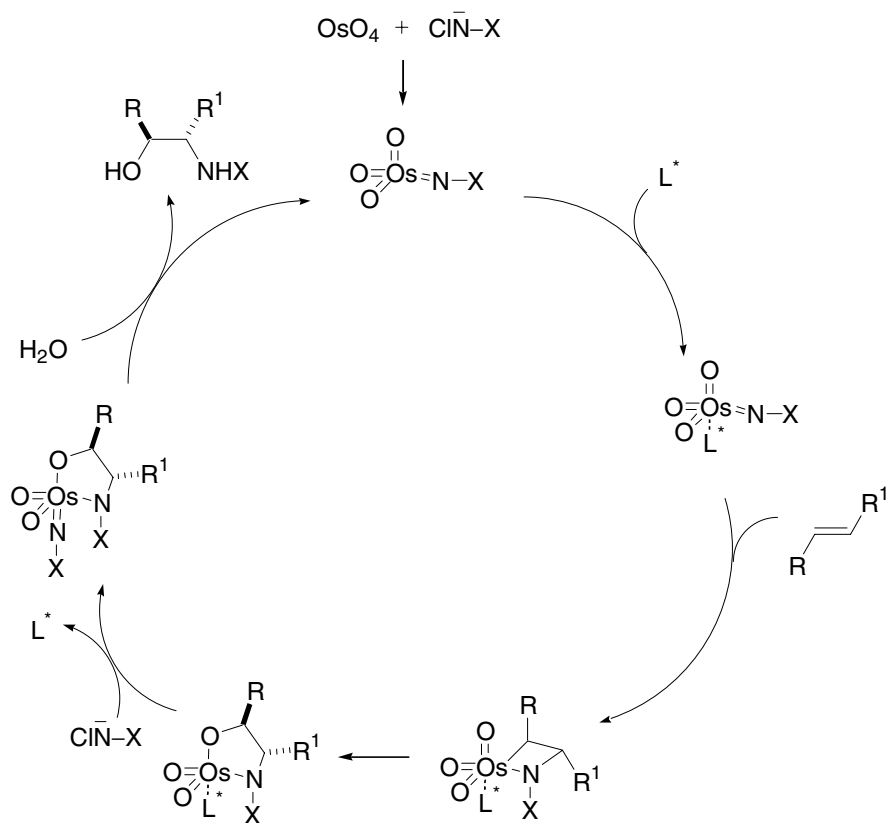
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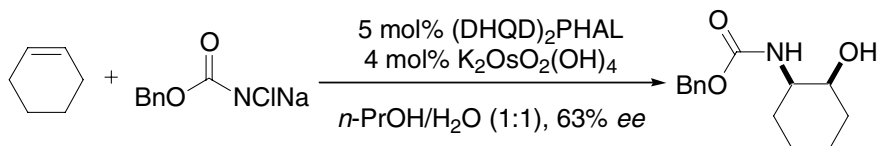
Sharpless asymmetric amino hydroxylation

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

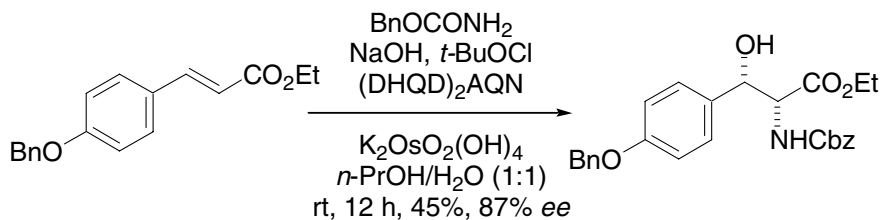


The catalytic cycle:



Example 1⁴

(DHQD)₂-PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine (page 536).

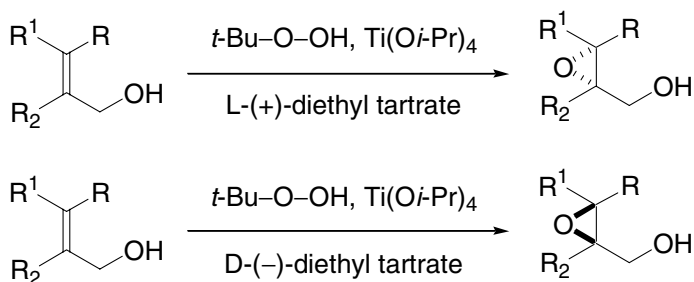
Example 2⁹

References

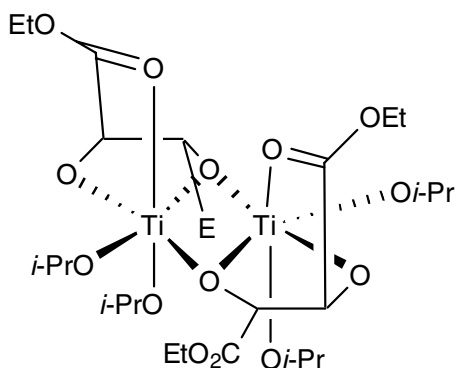
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Sharpless asymmetric epoxidation

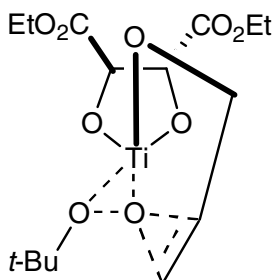
Enantioselective epoxidation of allylic alcohols using *t*-butyl peroxide, titanium tetra-*iso*-propoxide, and optically pure diethyl tartrate.



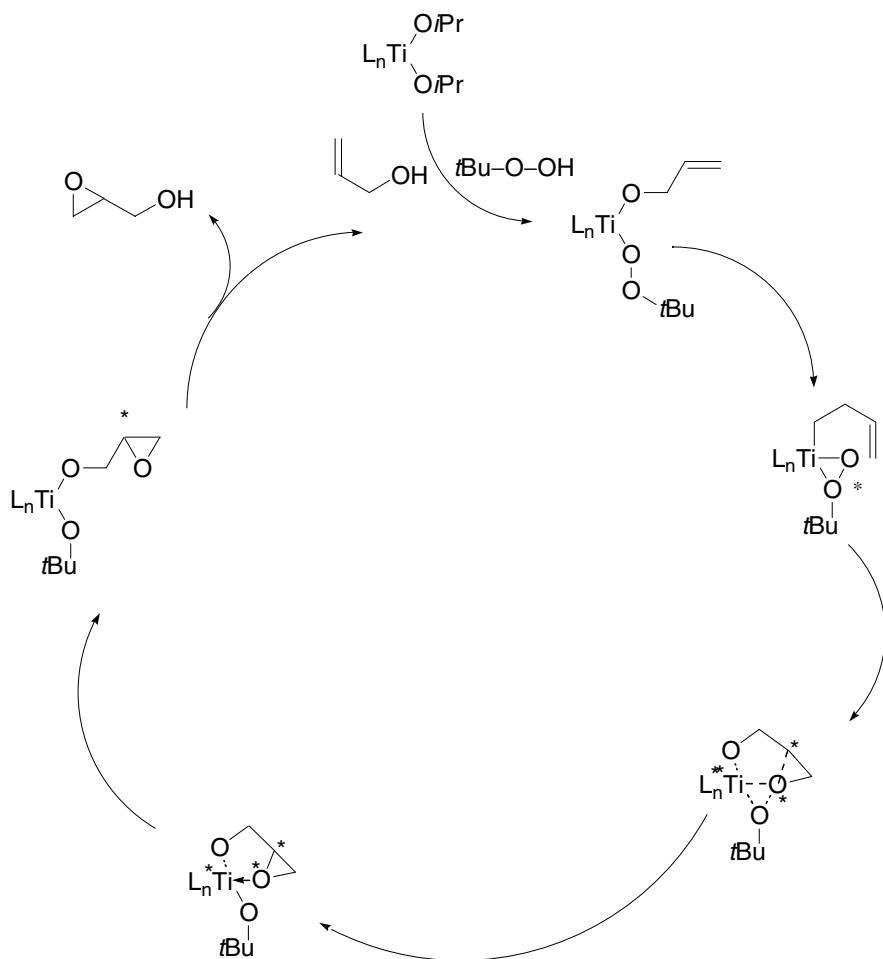
The putative active catalyst, E = CO₂Et:²



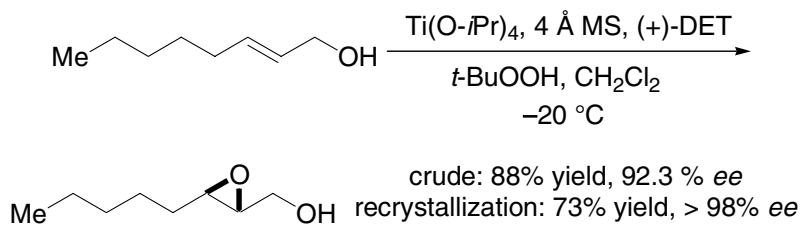
The transition state:

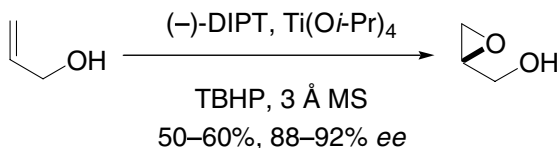


The catalytic cycle:



Example 1⁵



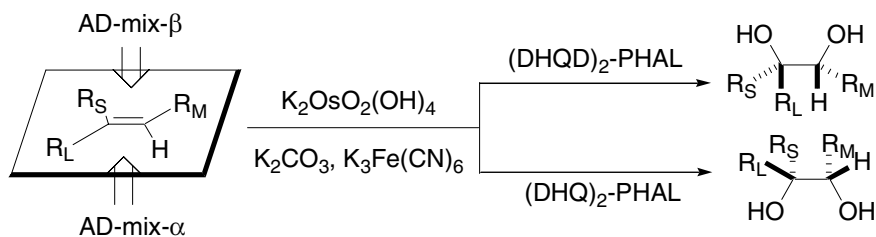
Example 2⁵

References

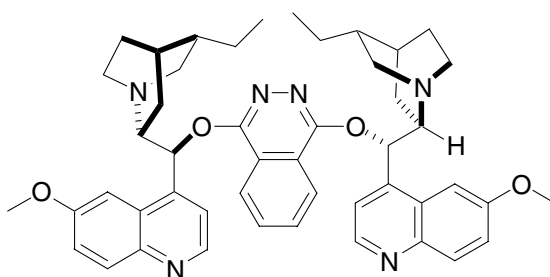
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Sharpless asymmetric dihydroxylation

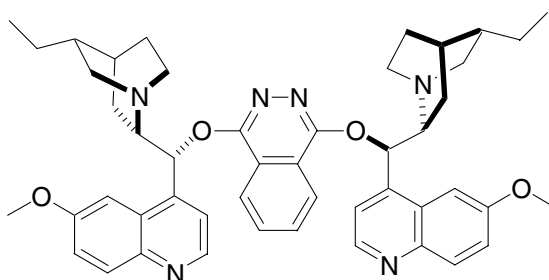
Enantioselective *cis*-dihydroxylation of olefins using osmium catalyst in the presence of cinchona alkaloid ligands.



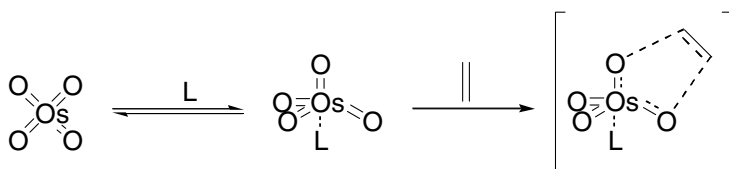
$(\text{DHQD})_2\text{-PHAL}$ = 1,4-bis(9-*O*-dihydroquinidine)phthalazine:

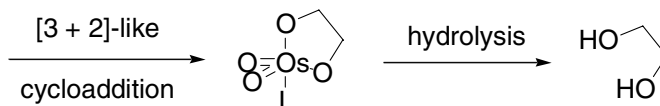


$(\text{DHQ})_2\text{-PHAL}$ = 1,4-bis(9-*O*-dihydroquinine)phthalazine:



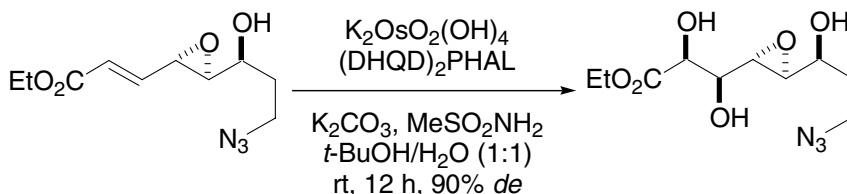
The concerted [3 + 2] cycloaddition mechanism:



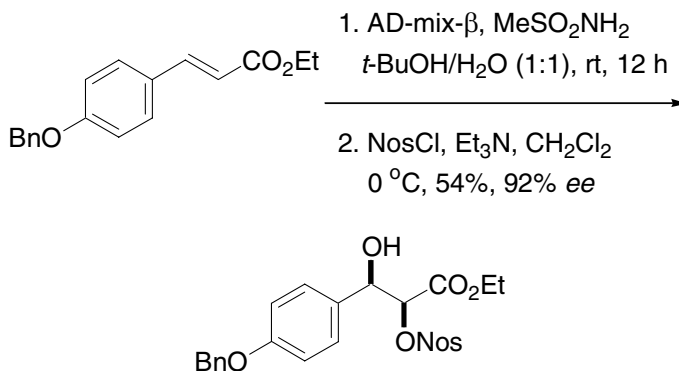


The catalytic cycle is shown on page 539 (the secondary cycle is shut off by maintaining a low concentration of olefin):

Example 1³



Example 2⁹

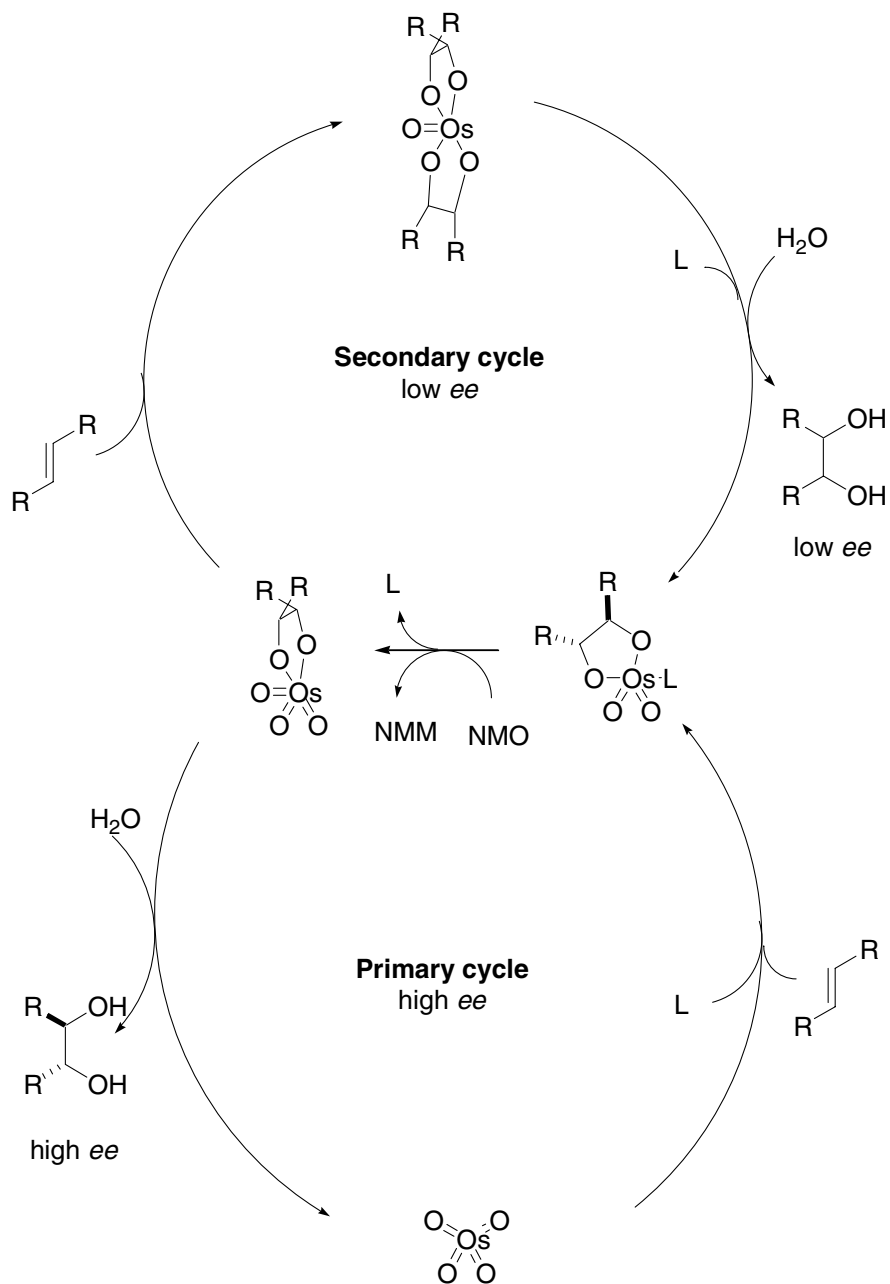


Nos = nosylate = 4-nitrobenzenesulfonyl

References

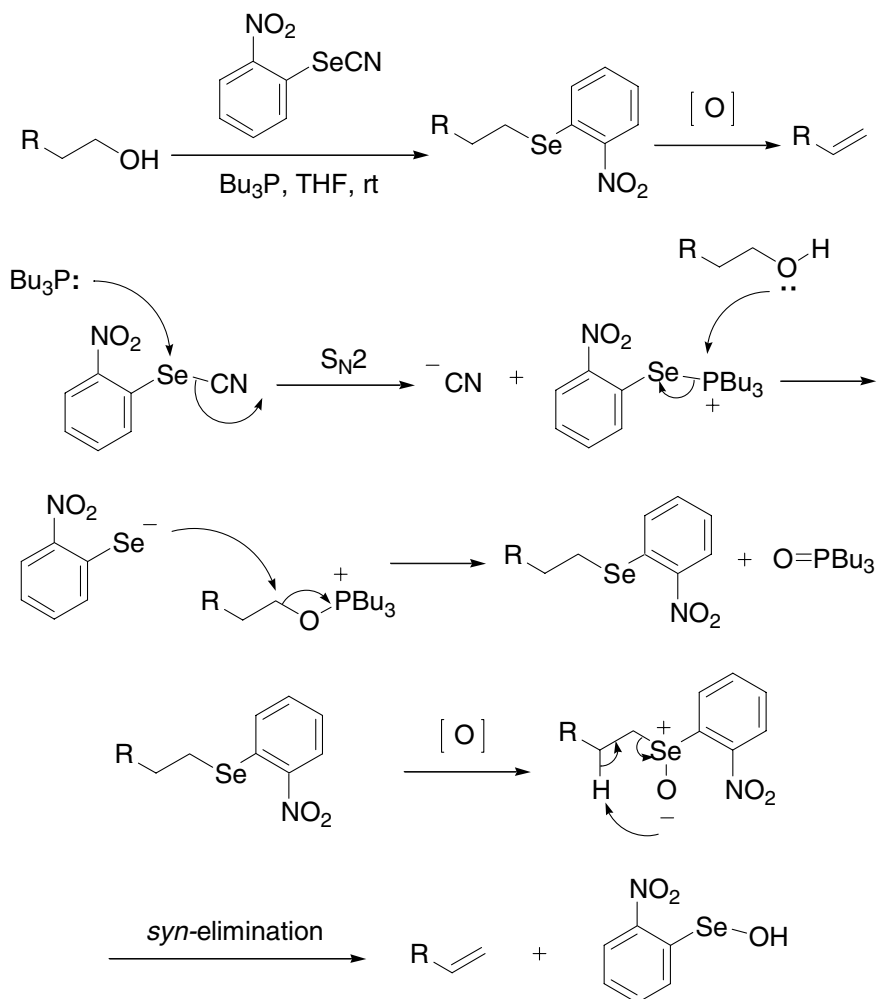
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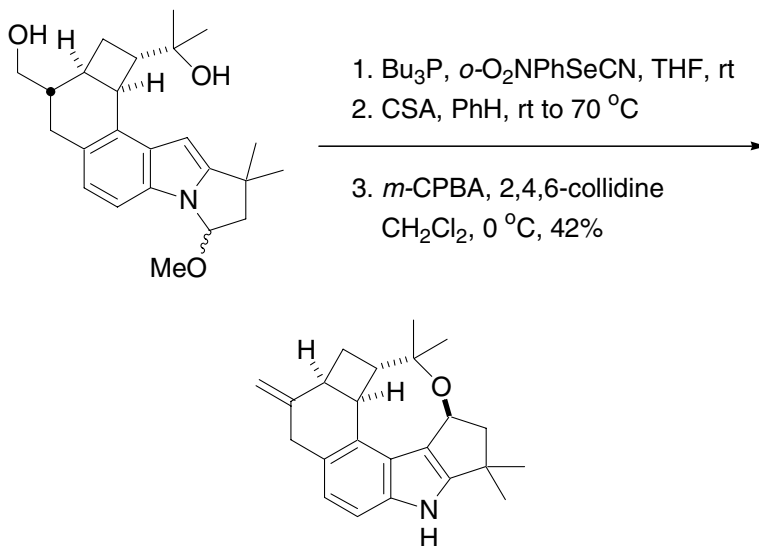
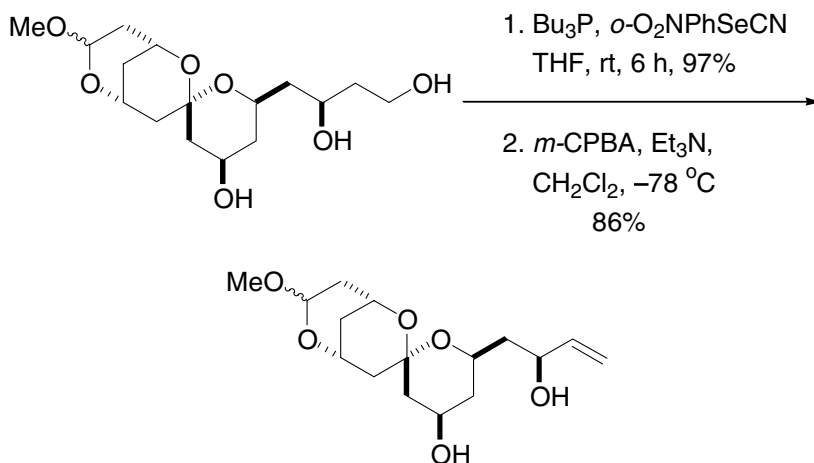
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Sharpless olefin synthesis

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



Example 1⁹Example 2¹³

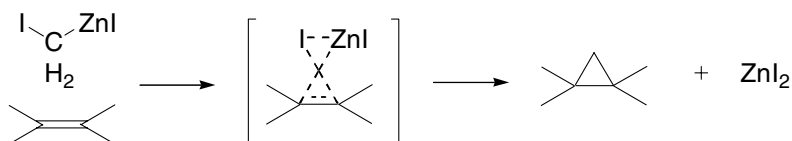
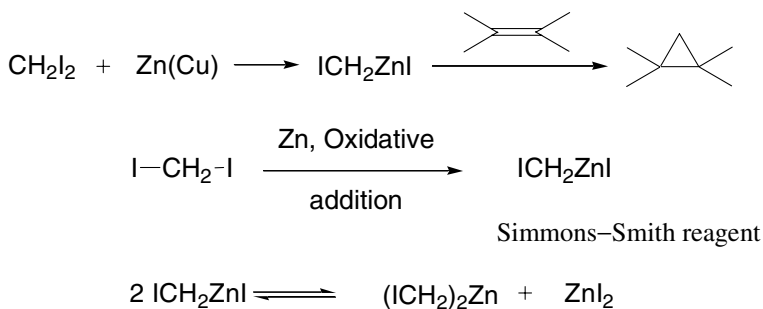
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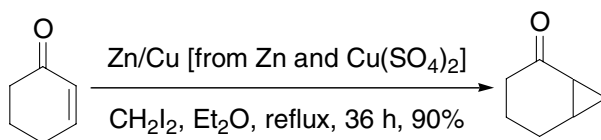
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Simmons–Smith reaction

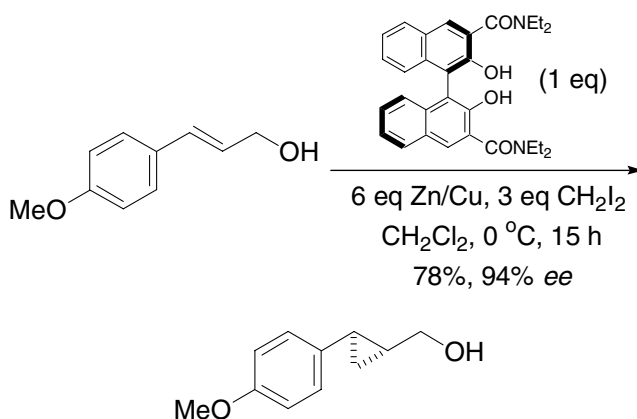
Cyclopropanation of olefins using CH_2I_2 and $\text{Zn}(\text{Cu})$.



Example 1²



Example 2, asymmetric version¹³

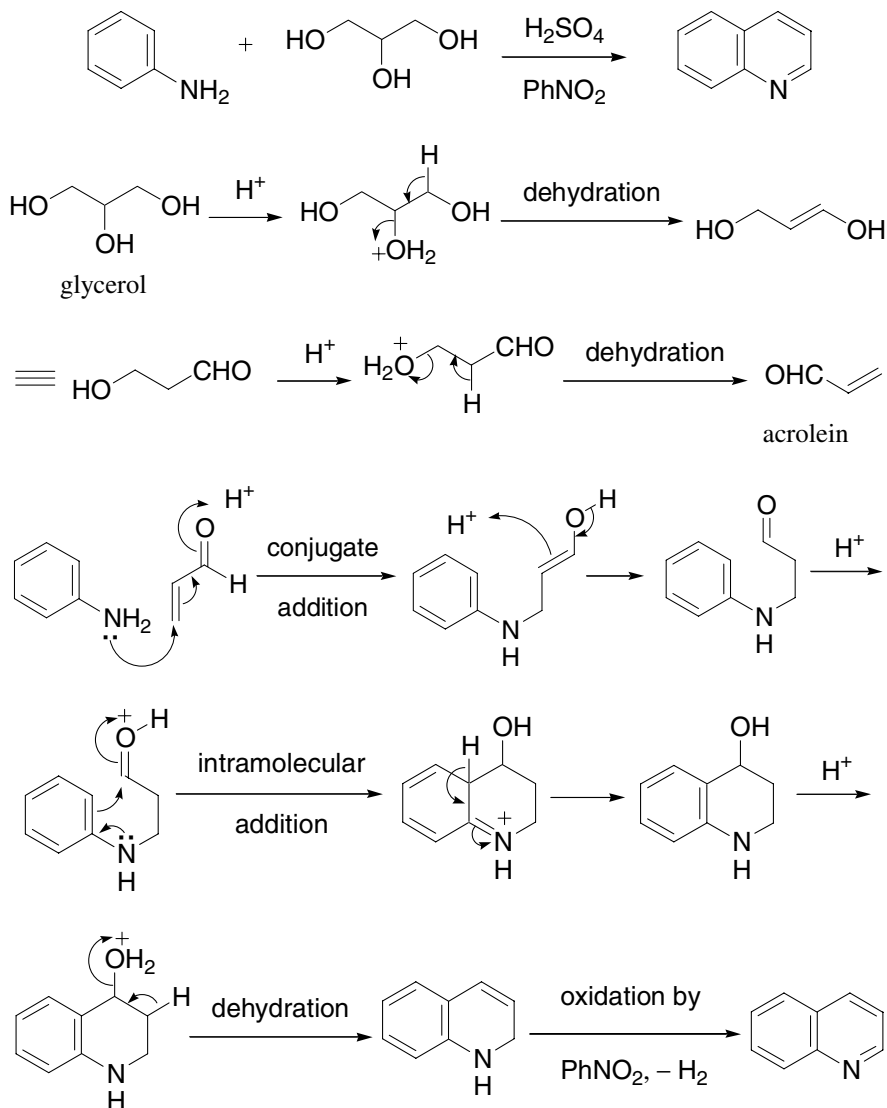


References

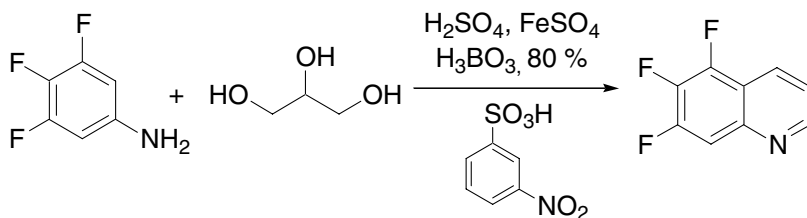
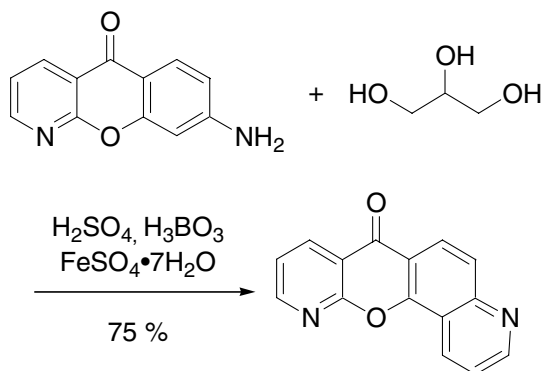
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Skraup quinoline synthesis

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).

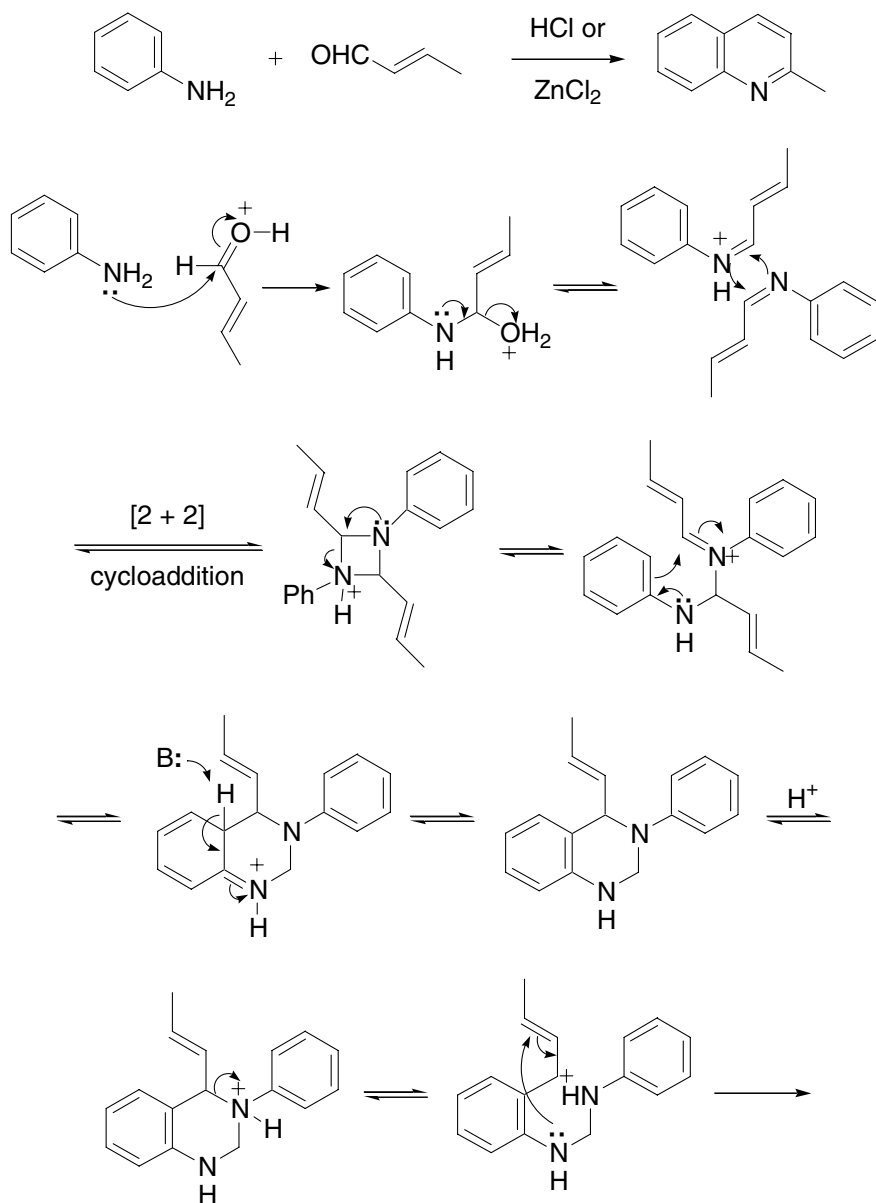
Example 1⁹Example 2¹⁰

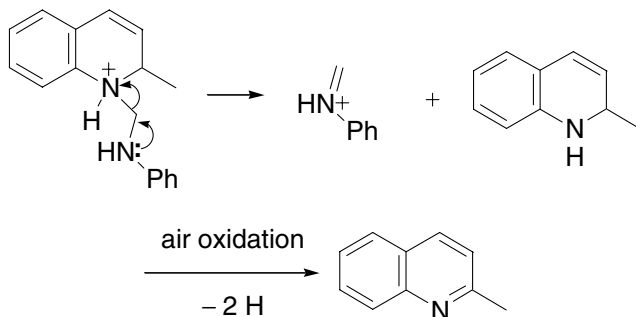
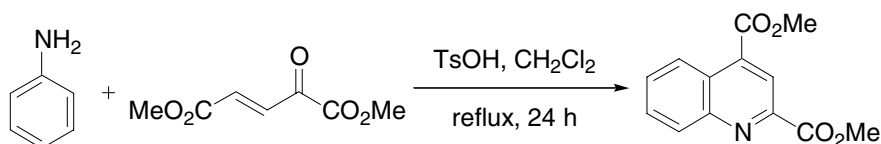
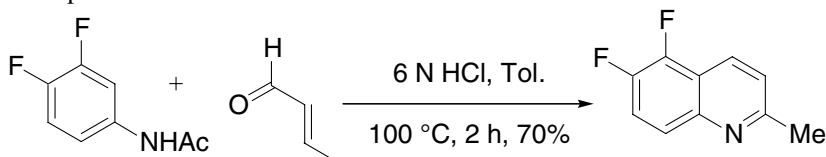
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Doebner–von Miller reaction

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:



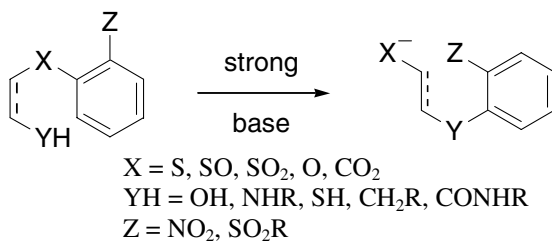
Example 1⁷Example 2⁸

References

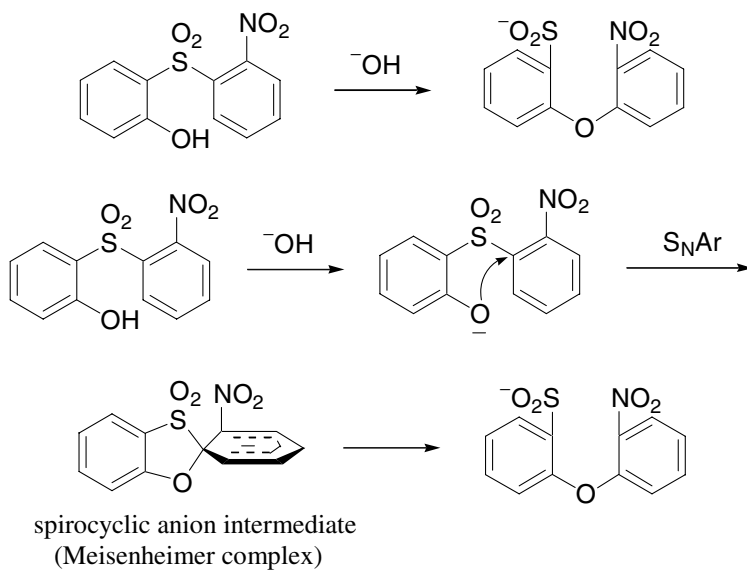
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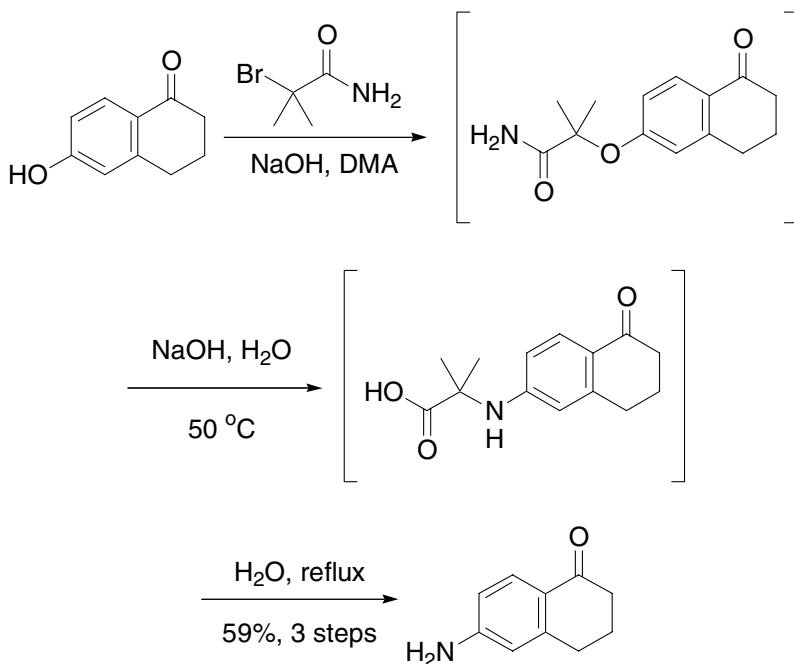
Smiles rearrangement

Intramolecular nucleophilic aromatic rearrangement. General scheme:



e.g.:



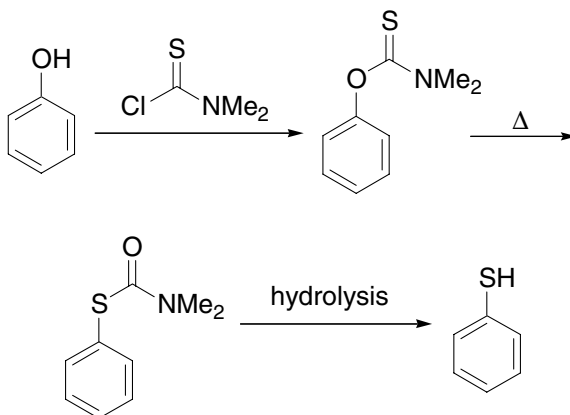
Example⁸

References

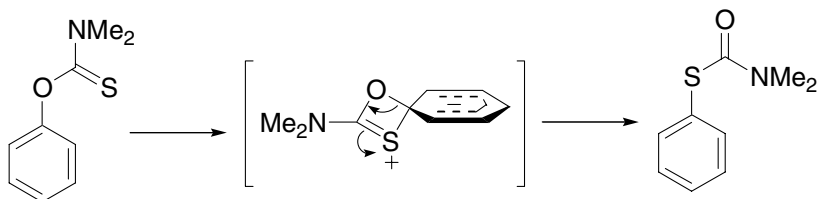
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Newman-Kwart reaction

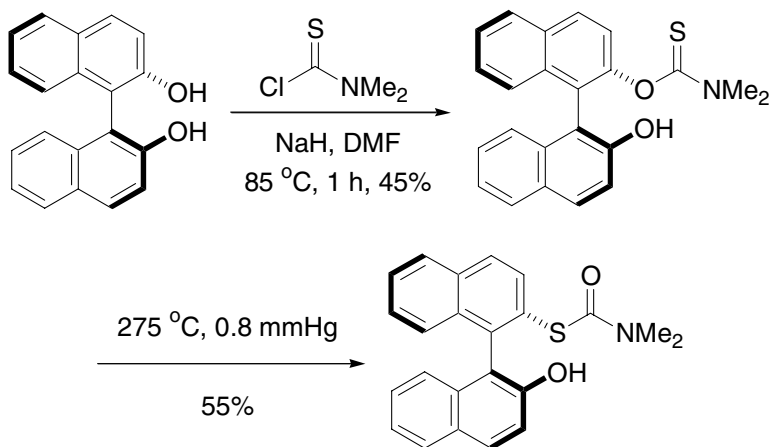
Transformation of phenol to the corresponding thiophenol, a variant of the Smile reaction (page 549).

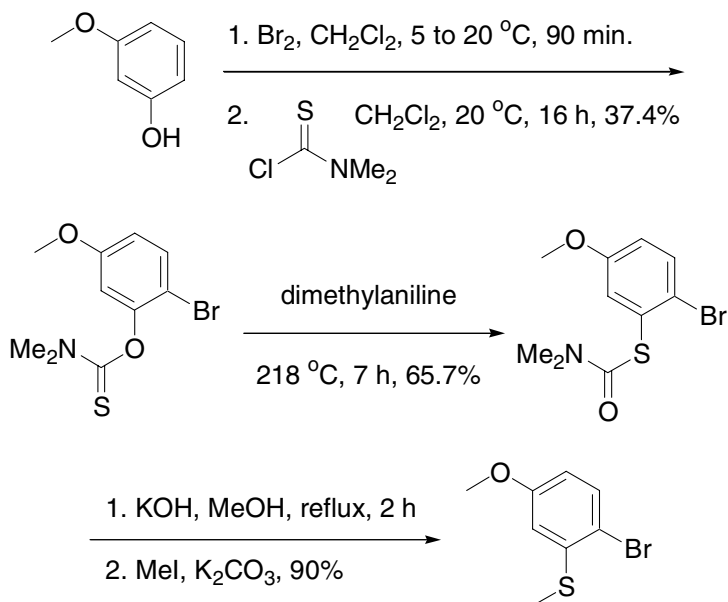


Mechanism:



Example 1⁸



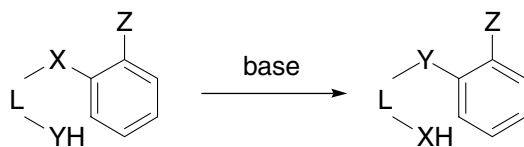
Example 2⁹

References

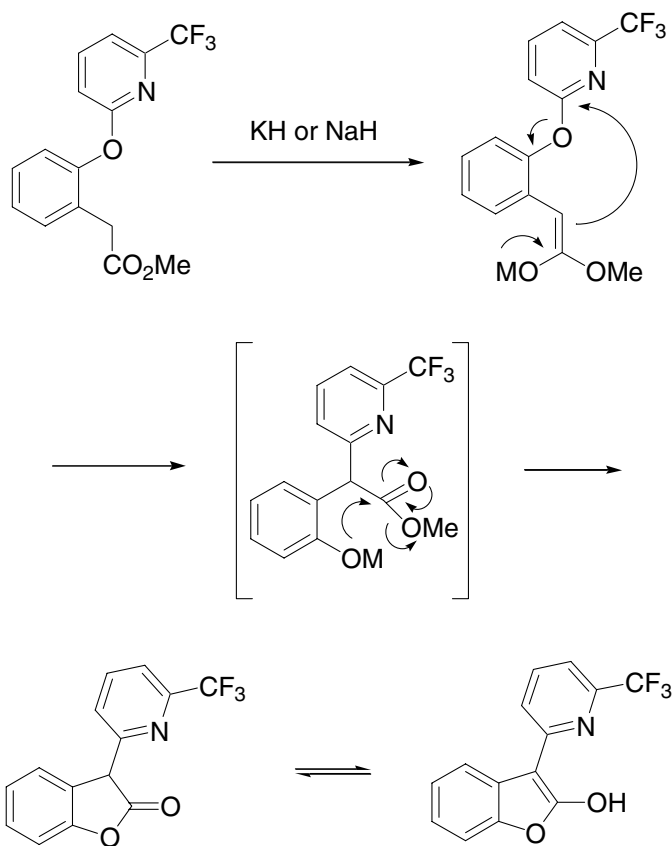
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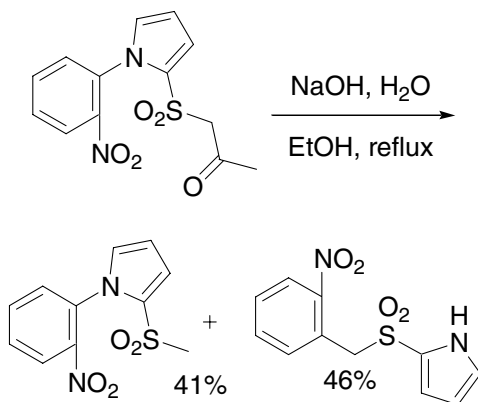
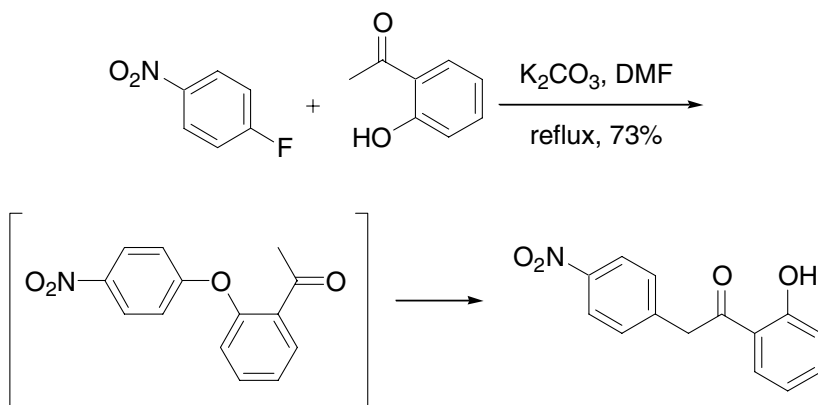
Truce–Smile rearrangement

Smiles rearrangement where Y is carbon:



Example 1⁶



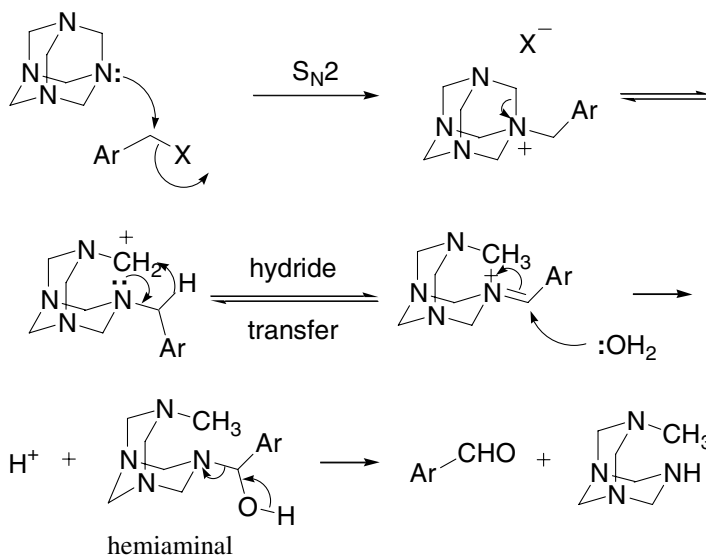
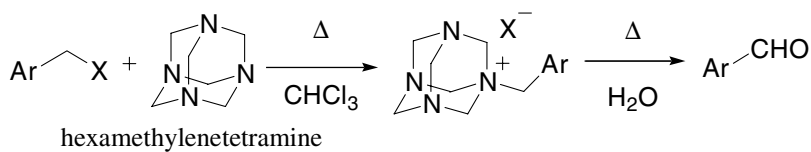
Example 2⁸Example 3⁹

References

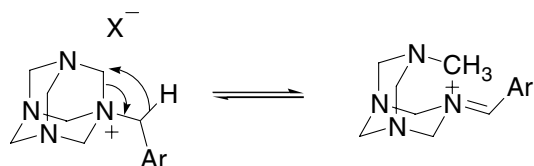
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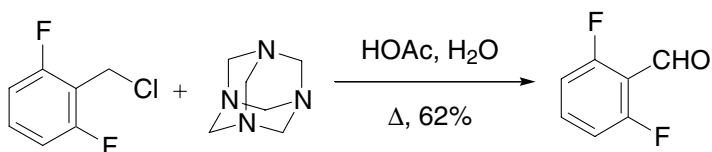
Sommelet reaction

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



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



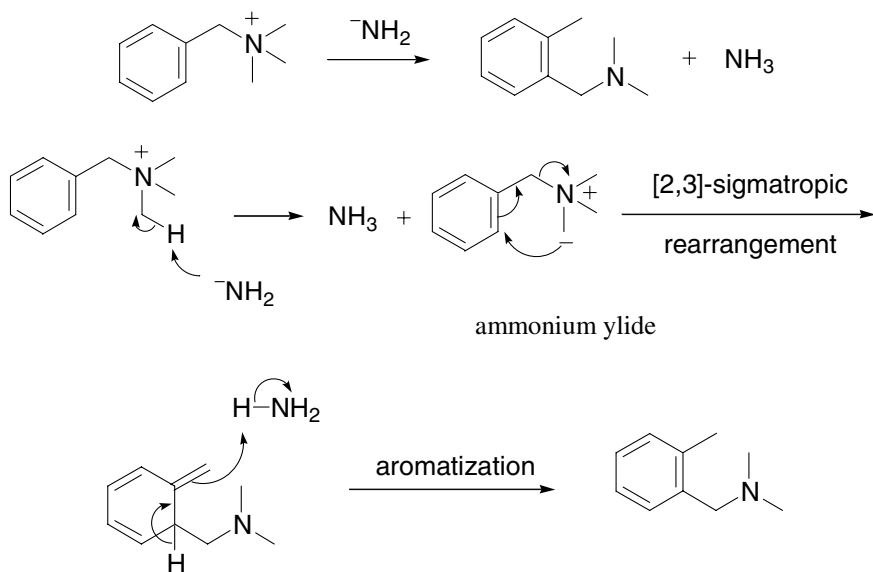
Example⁹

References

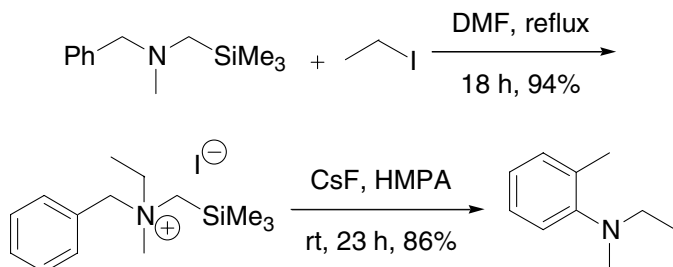
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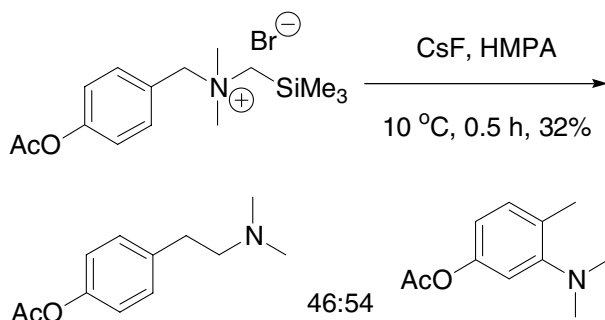
Sommelet–Hauser rearrangement

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



Example 1⁵



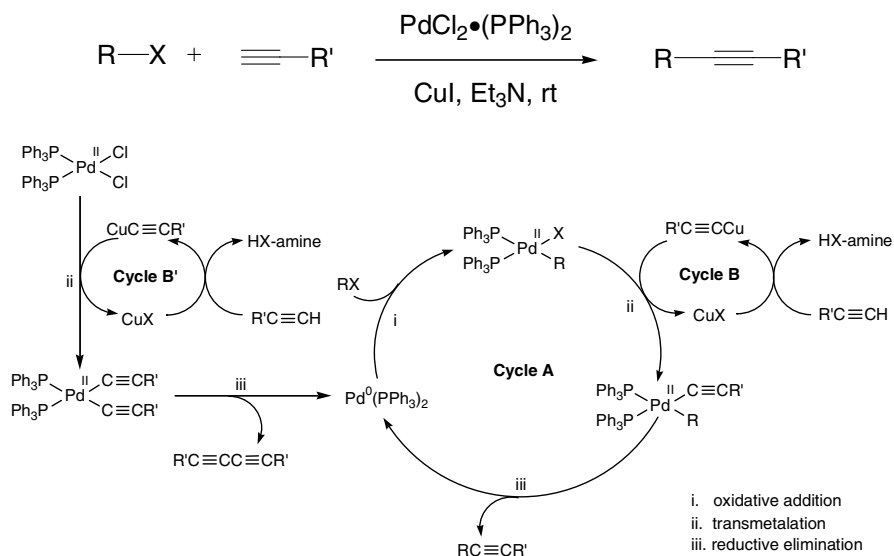
Example 2⁶

References

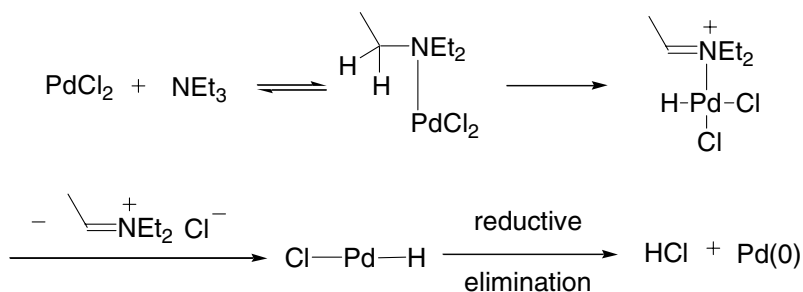
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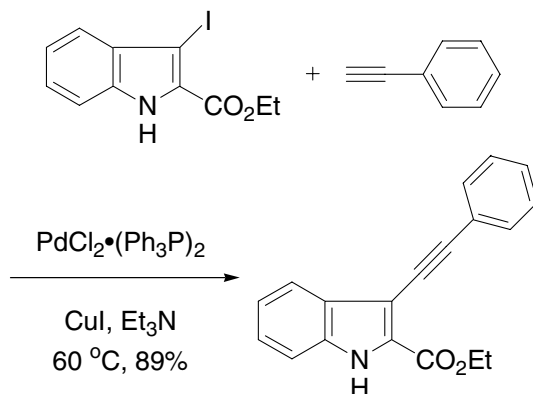
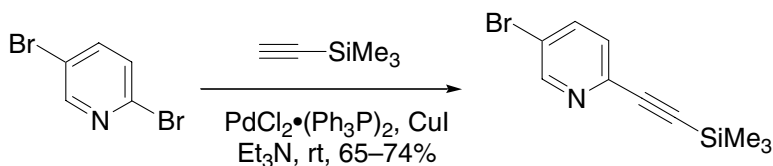
Sonogashira reaction

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



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



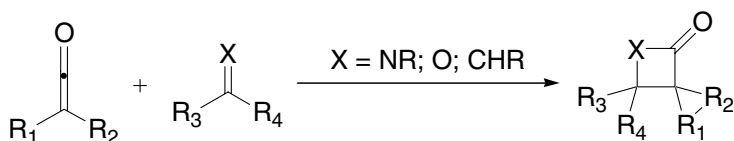
Example 1³Example 2⁵

References

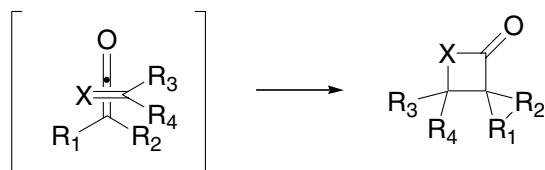
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Staudinger ketene cycloaddition

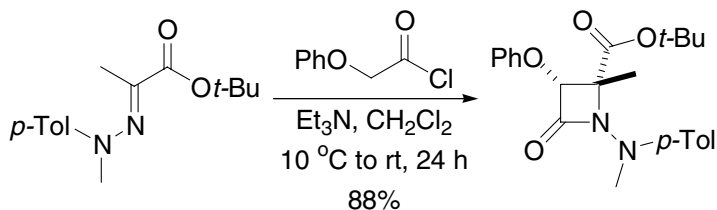
[2 + 2] Cycloaddition of ketene and imine to form β -lactam. Other coupling partners for ketene also include: olefin to give cyclobutanone and carbonyl to give β -lactone.



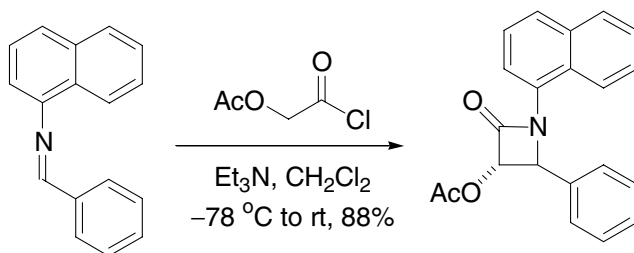
puckered transition state:



Example 1⁸



Example 2⁹

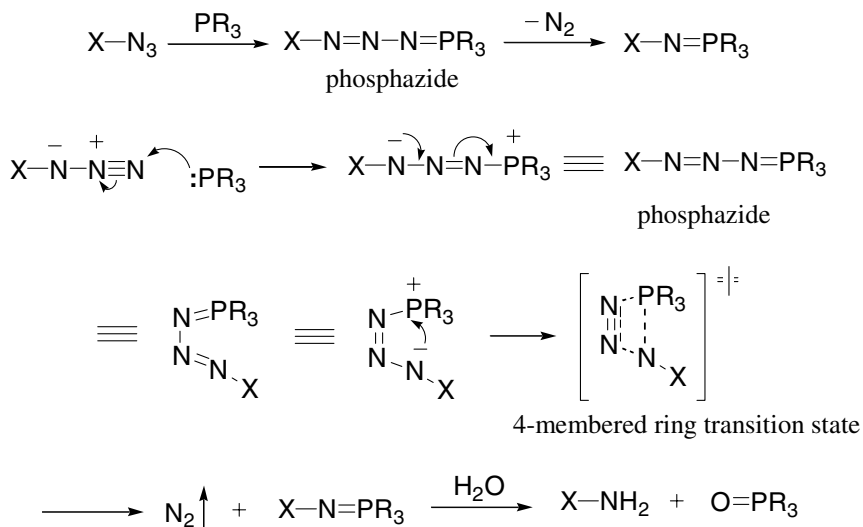


References

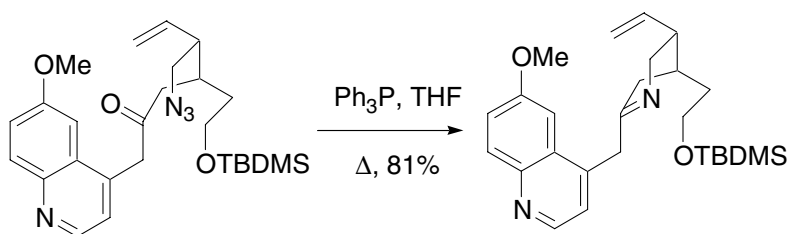
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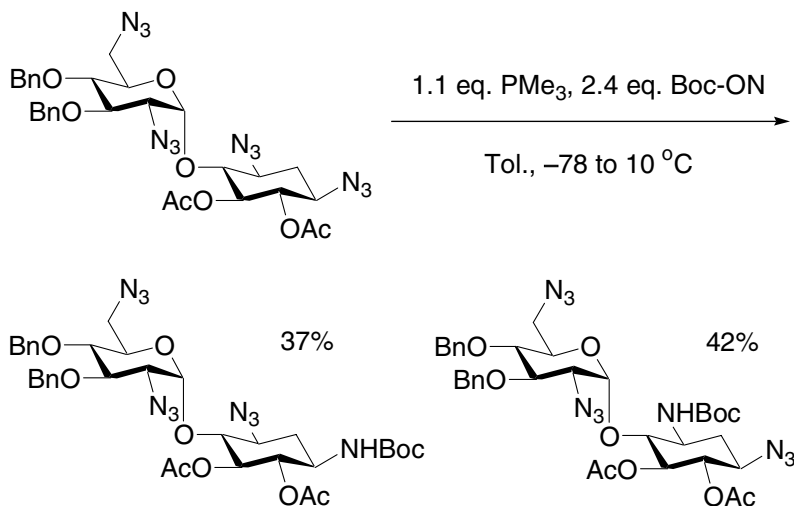
Staudinger reduction

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



Example 1⁷



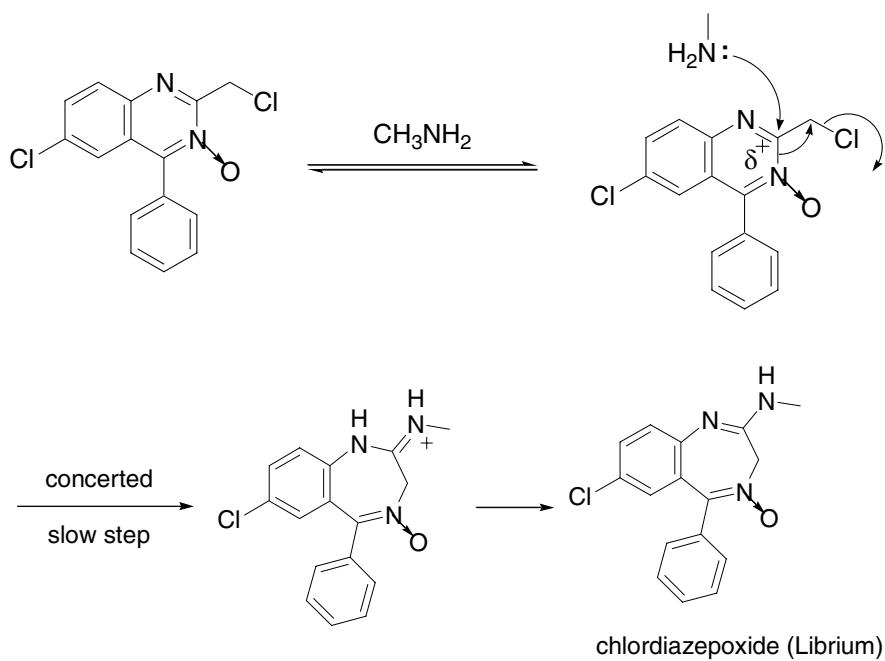
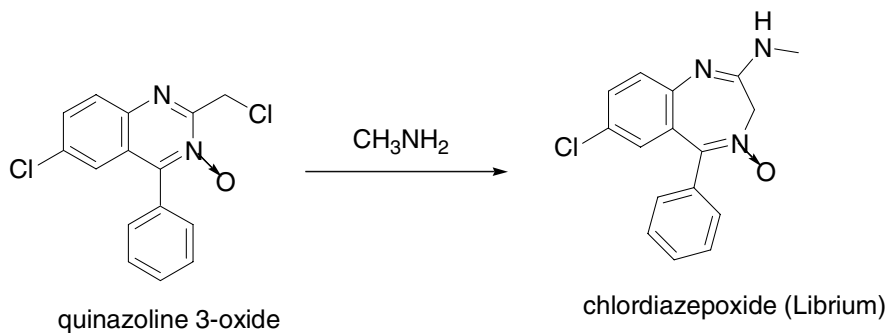
Example 2¹²

References

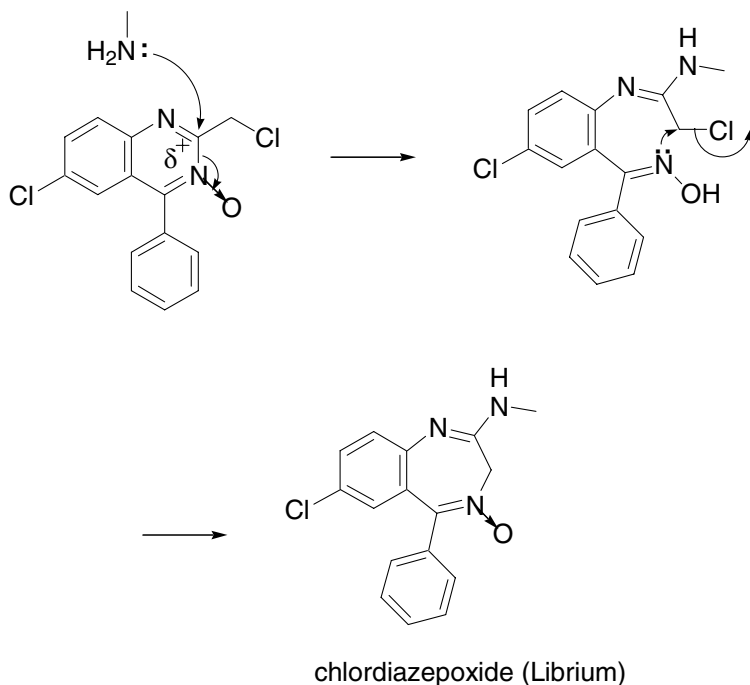
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Sternbach benzodiazepine synthesis

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



A step-wise mechanism is also possible:

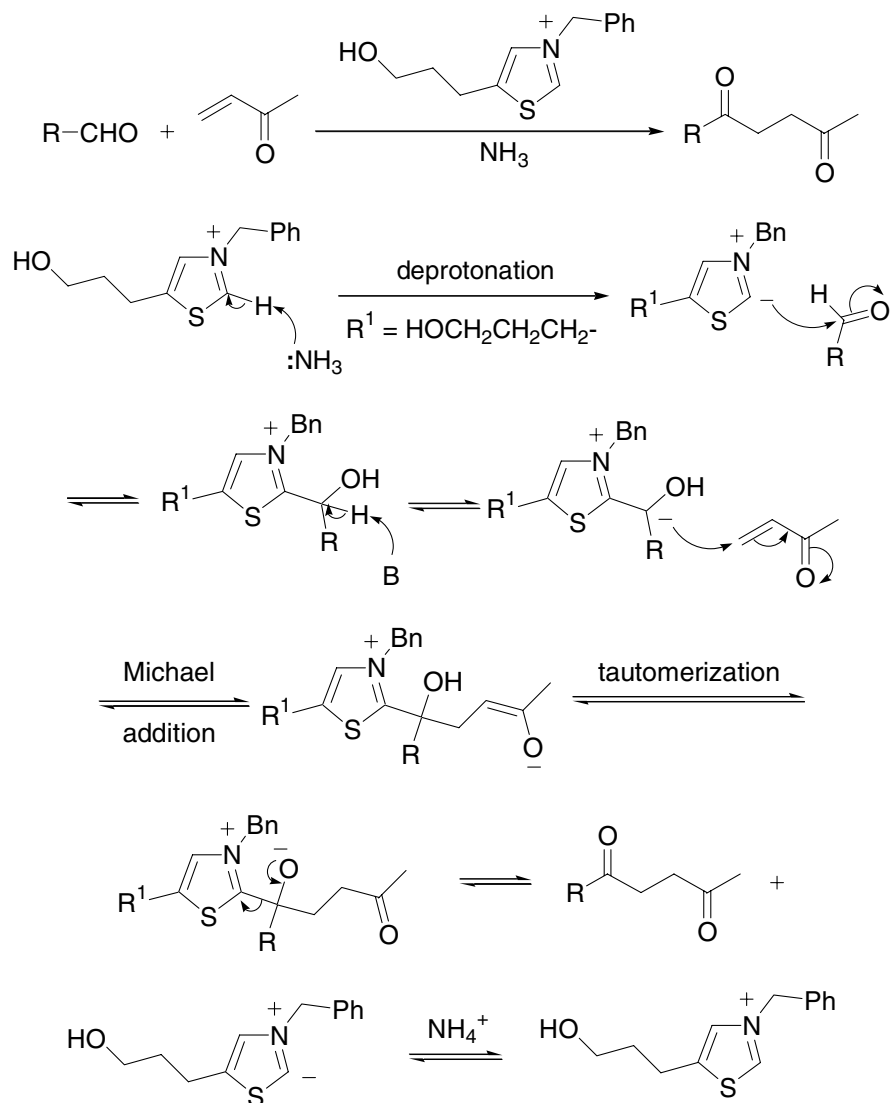


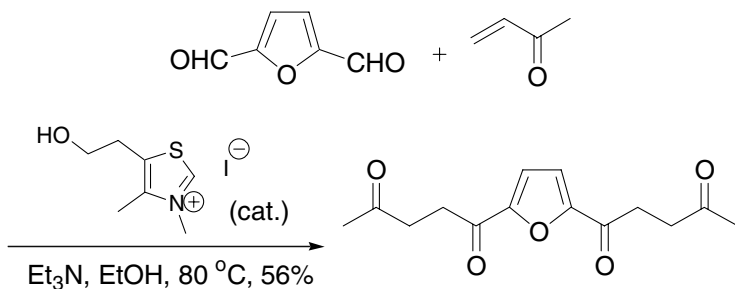
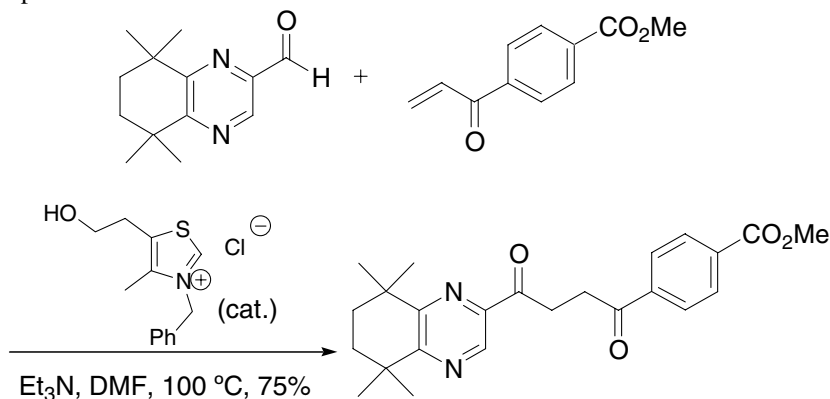
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Stetter reaction

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.



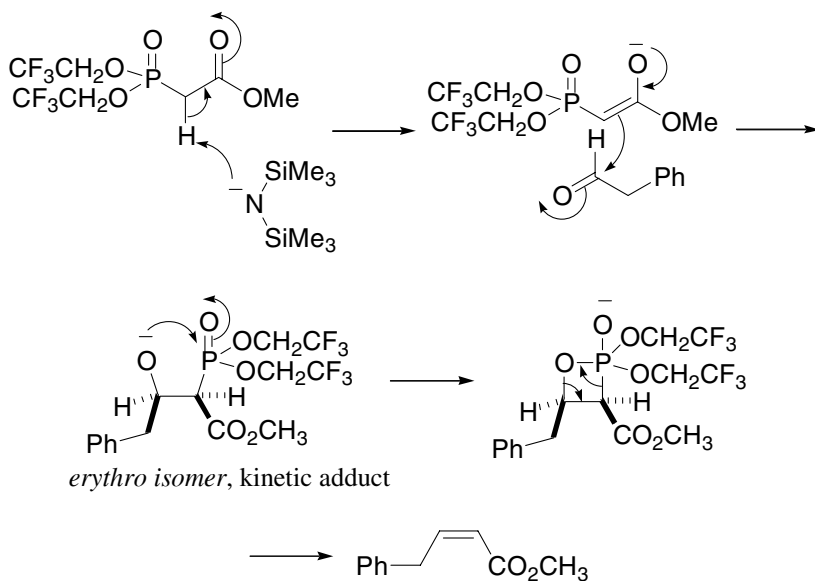
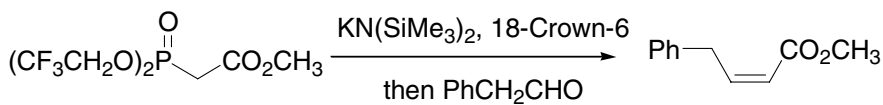
Example 1⁴Example 2¹¹

References

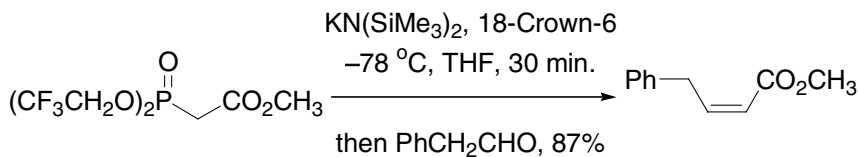
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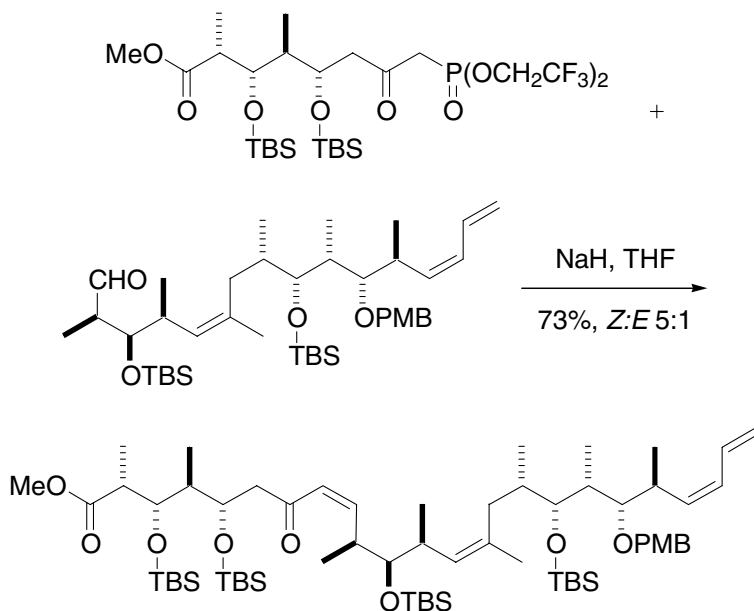
Still–Gennari phosphonate reaction

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



Example 1³



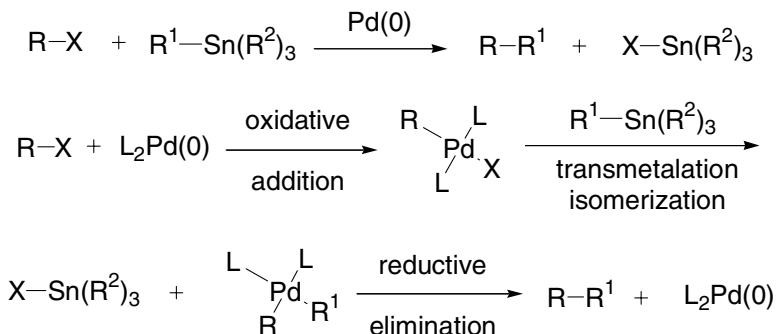
Example 2¹²

References

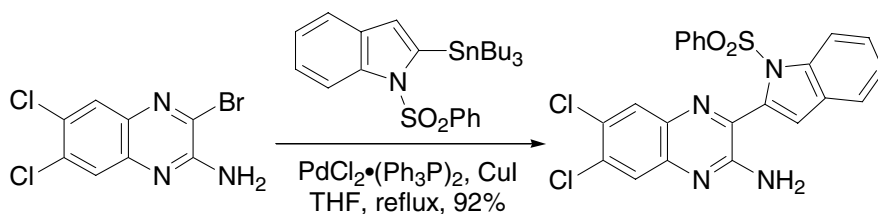
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Stille coupling

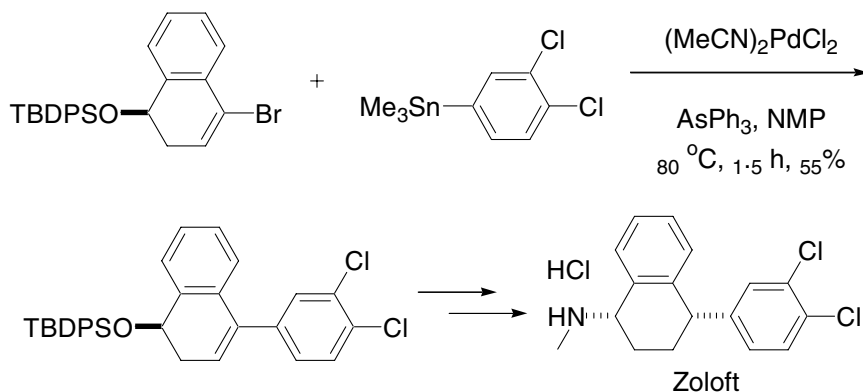
Palladium-catalyzed cross-coupling reaction of organostannanes with organic halides, triflates, *etc.* For the catalytic cycle, see Kumada coupling on page 345.



Example 1⁶



Example 2⁷

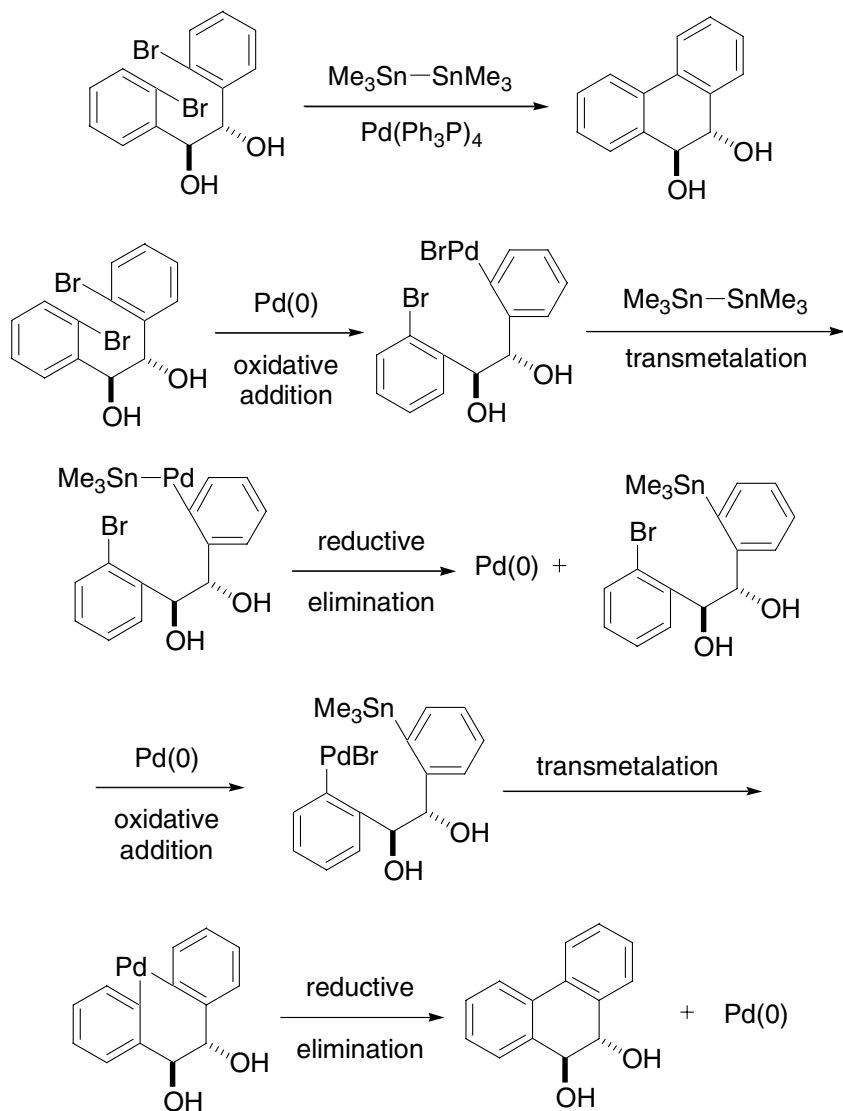


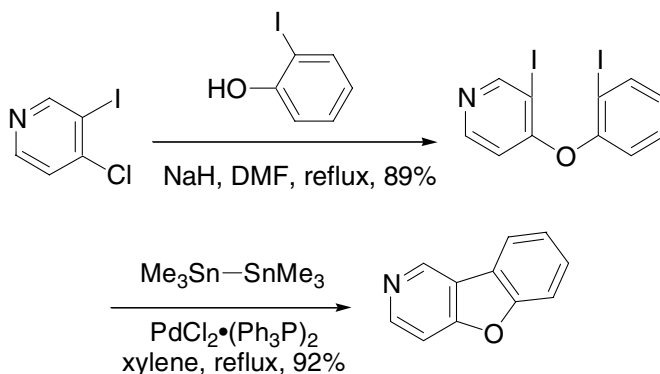
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Stille–Kelly reaction

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



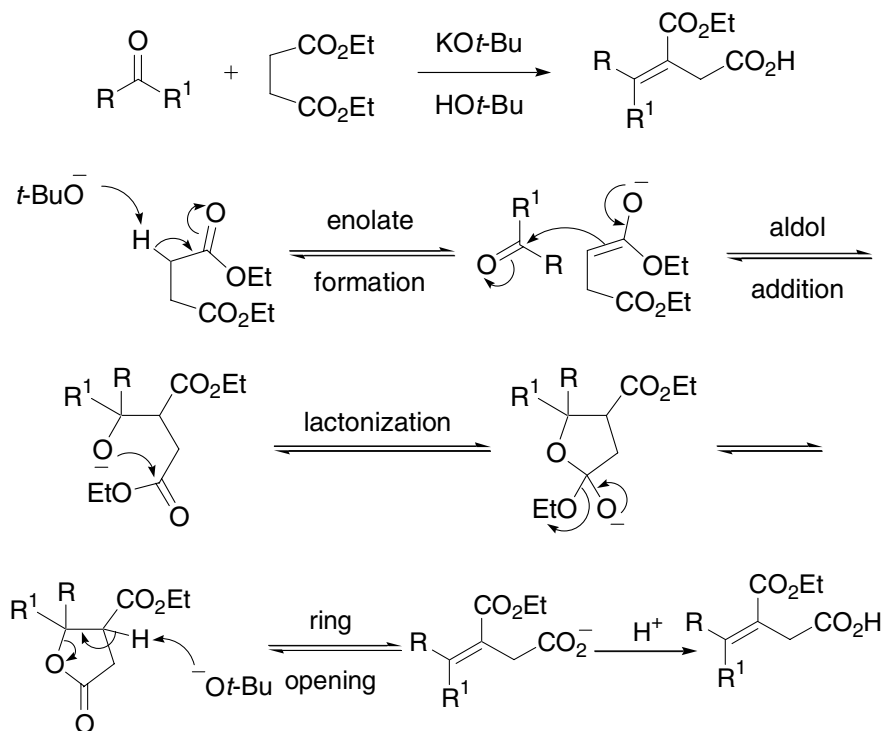
Example⁸

References

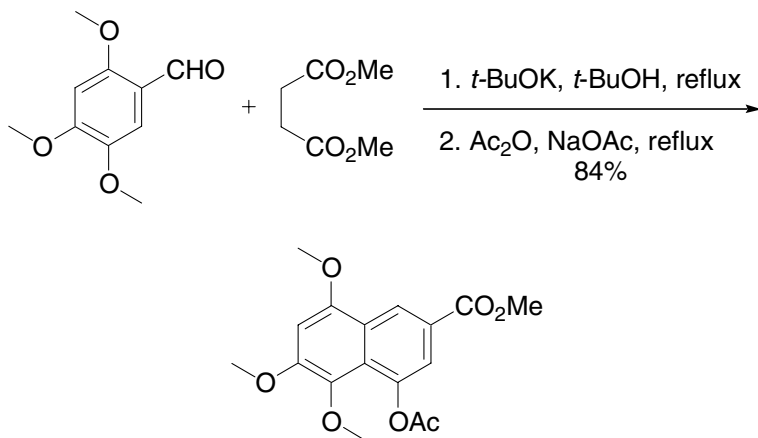
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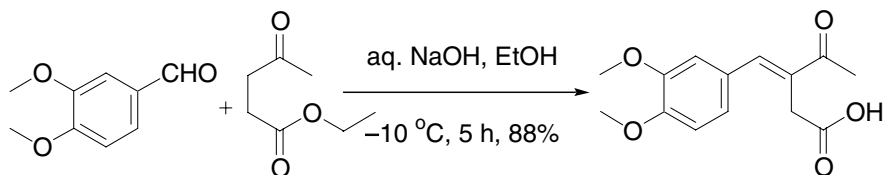
Stobbe condensation

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



Example 1¹²



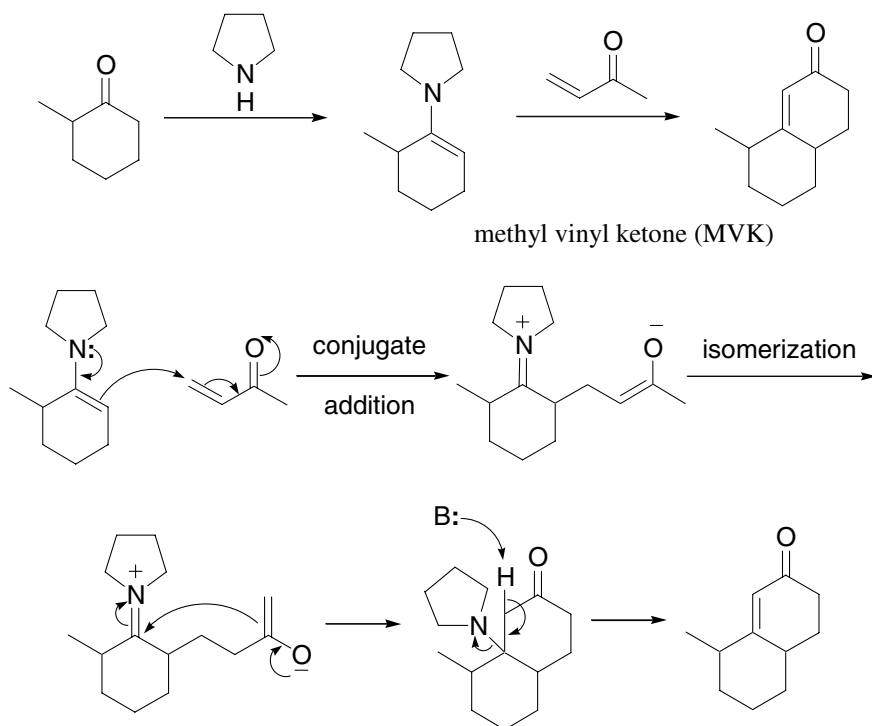
Example 2¹³

References

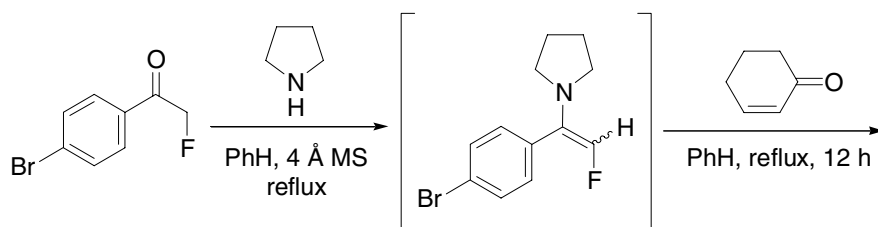
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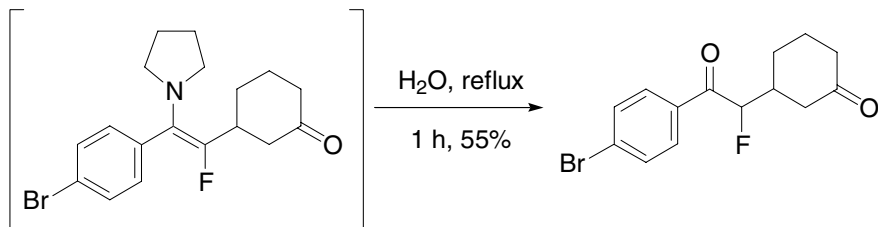
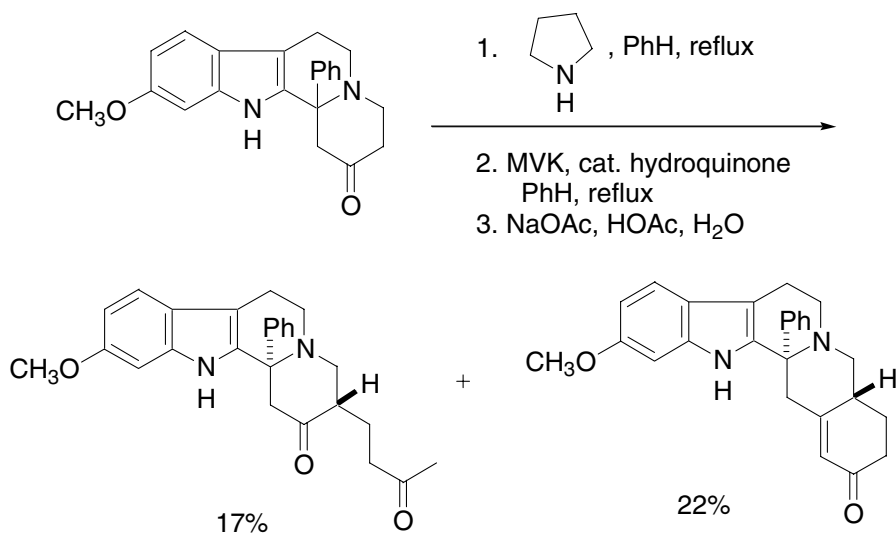
Stork enamine reaction

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 1⁷



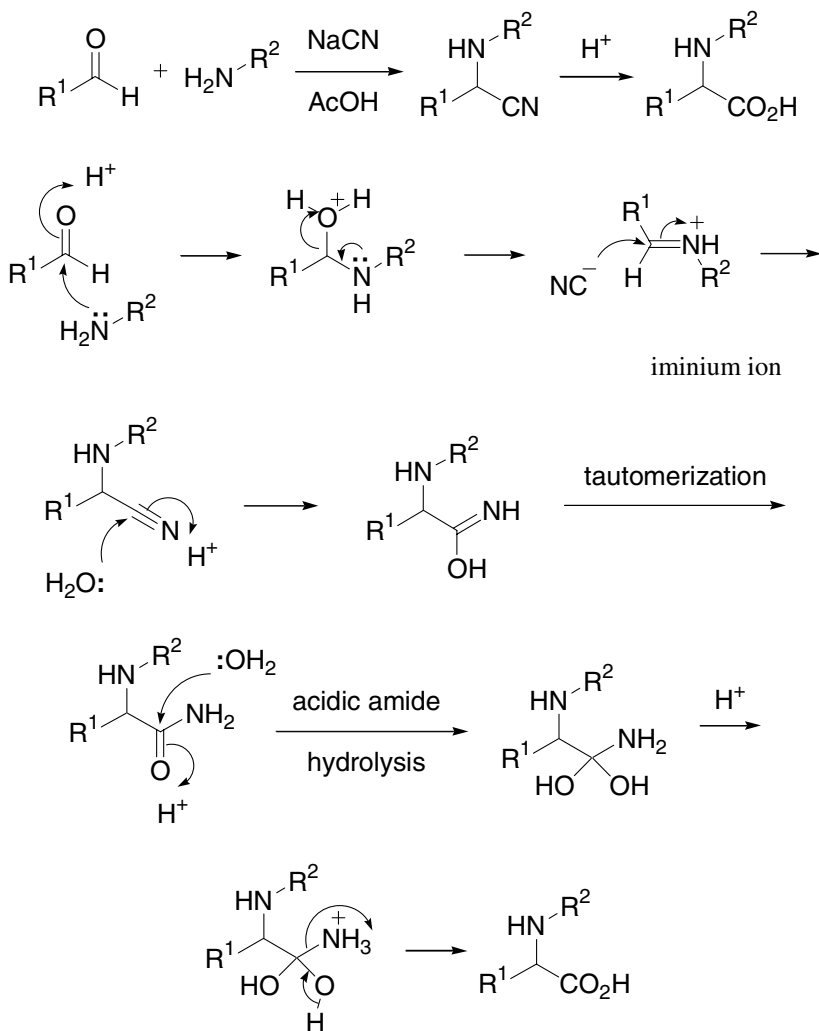
Example 2⁸

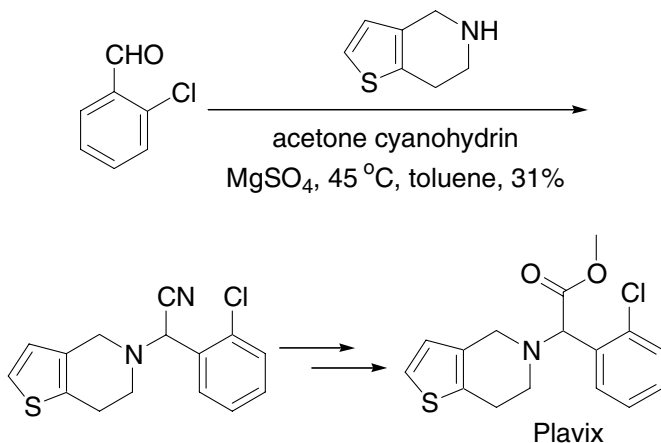
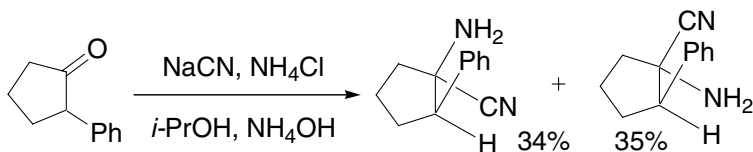
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Strecker amino acid synthesis

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



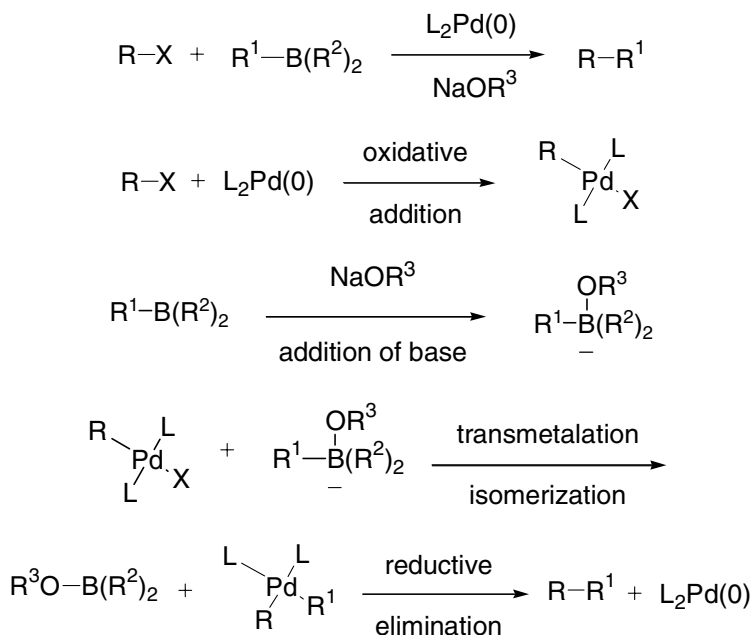
Example 1⁶Example 2¹³

References

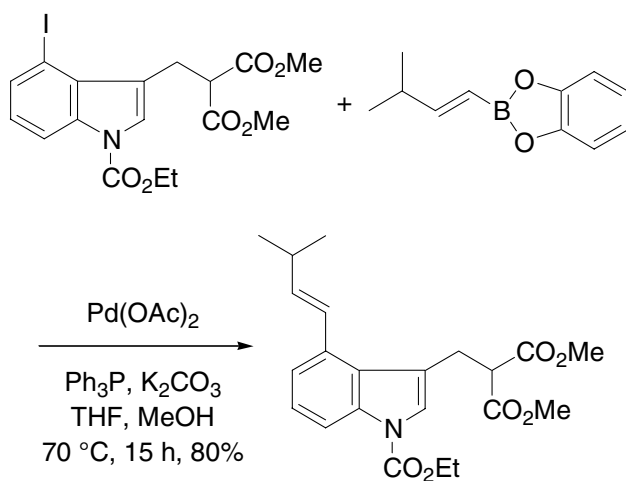
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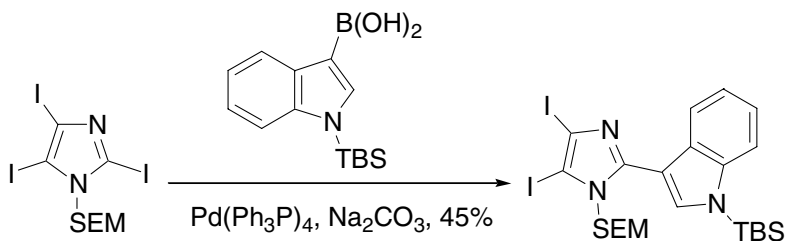
Suzuki coupling

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 1¹



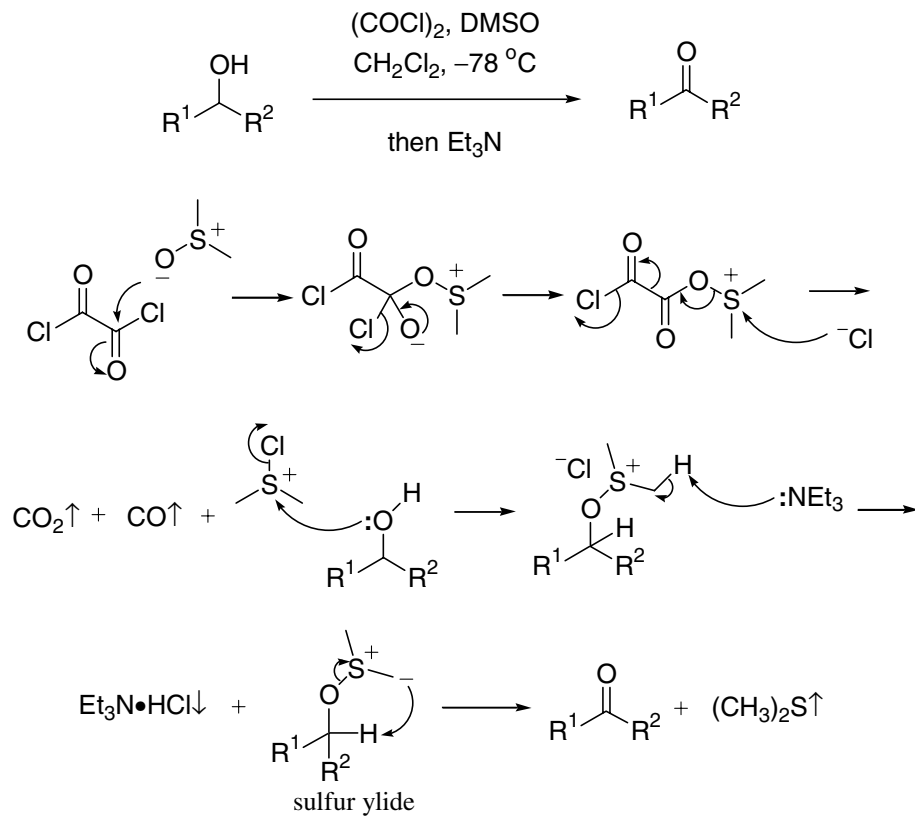
Example 2⁴

References

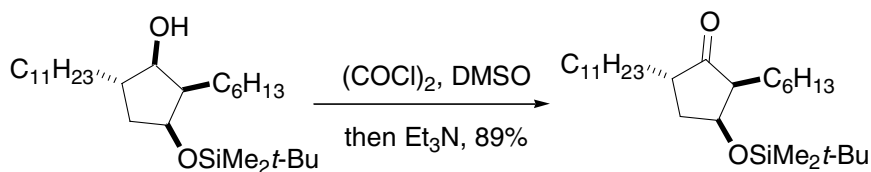
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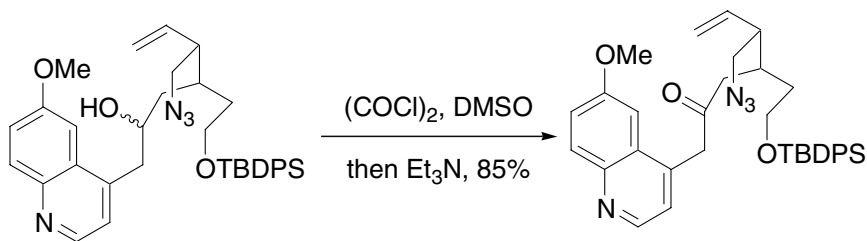
Swern oxidation

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



Example 1⁵



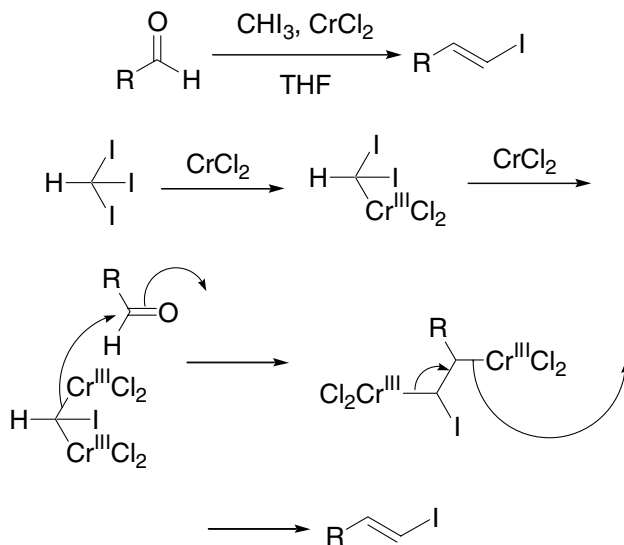
Example 2¹¹

References

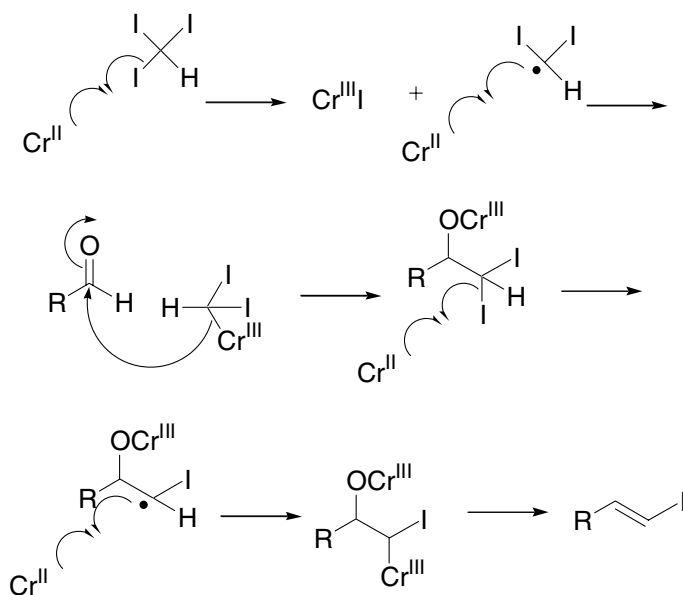
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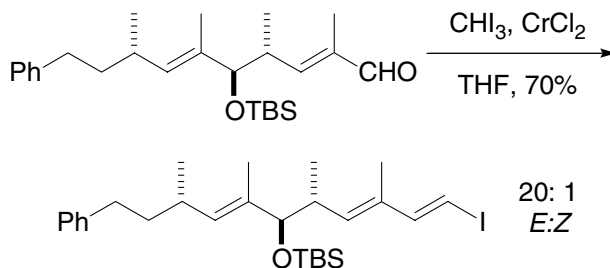
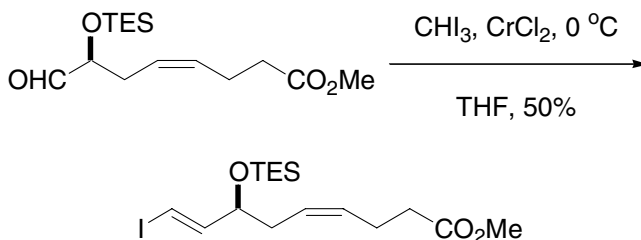
Takai iodoalkene synthesis

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



A radical mechanism is recently proposed¹⁰



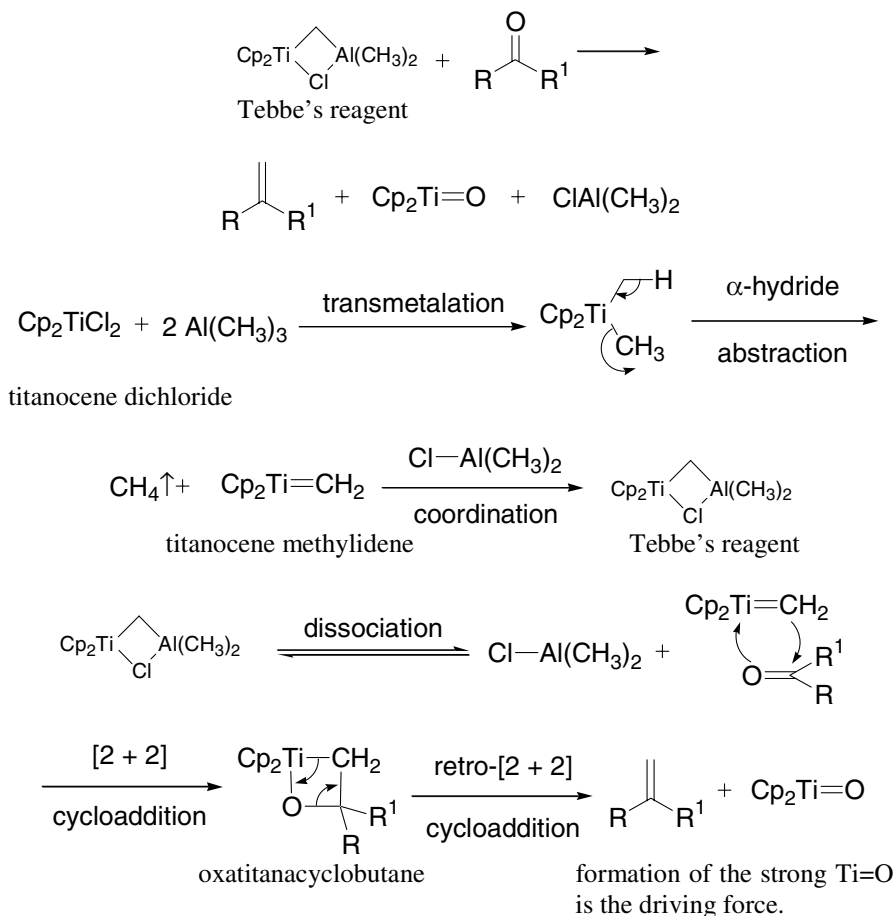
Example 1²Example 2⁵

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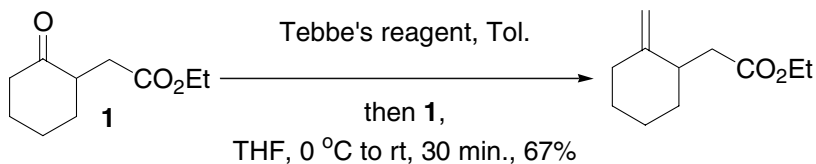
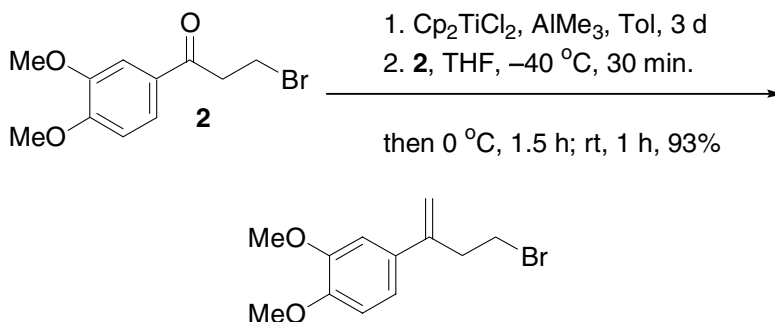
Tebbe olefination

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



Petasis alkenylation

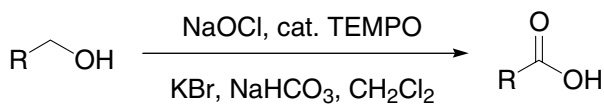
The Petasis reagent (Me_2TiCp_2 , dimethyltitanocene) undergoes similar olefination reactions with ketones and aldehydes. The originally proposed mechanism⁵ was very different from that of Tebbe olefination. However, later experimental data seem to suggest that both Petasis and Tebbe olefination share the same mechanism, i.e., the carbene mechanism involving a four-membered titanium oxide ring intermediate.⁹

Example 1³Example 2⁴

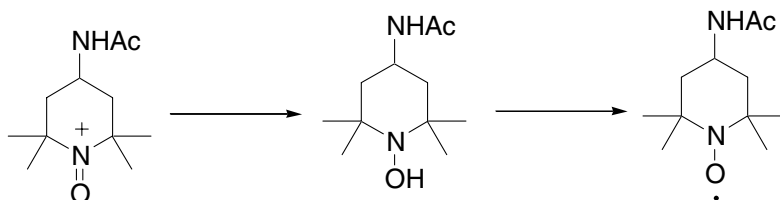
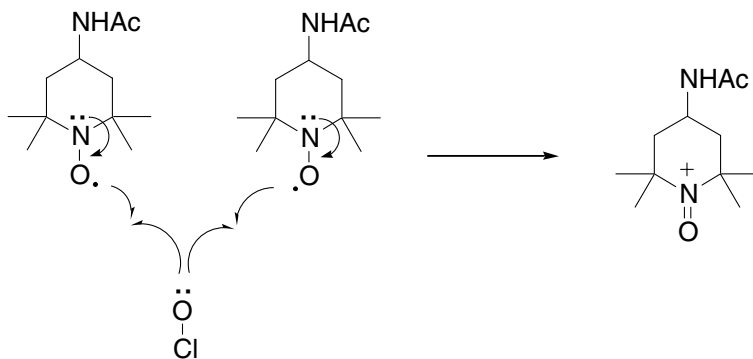
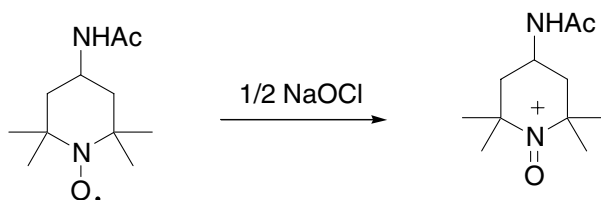
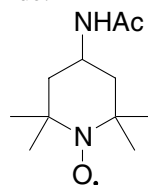
References

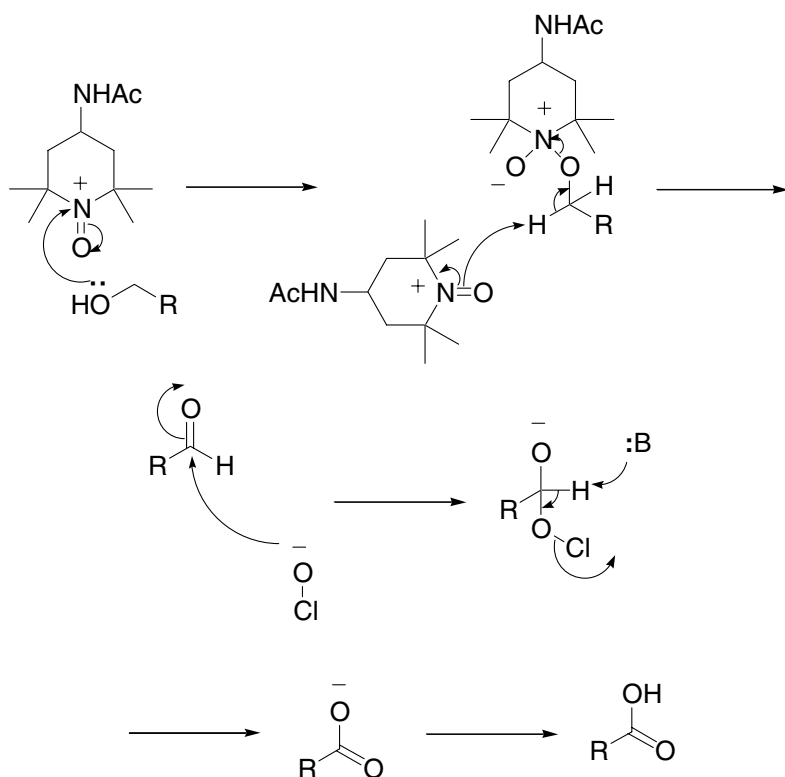
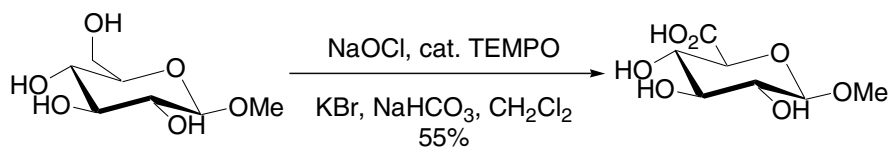
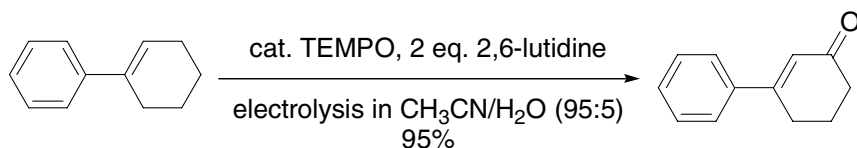
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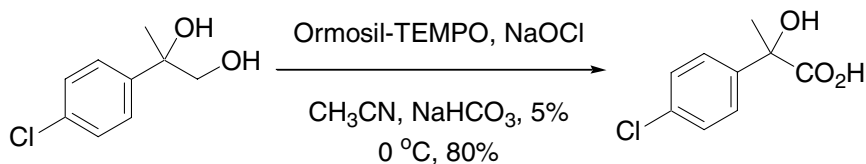
TEMPO-mediated oxidation



TEMPO = **t**etramethyl **p**entahydropyridine **o**xide:



Example 1⁷Example 2¹⁰

Example 3¹²

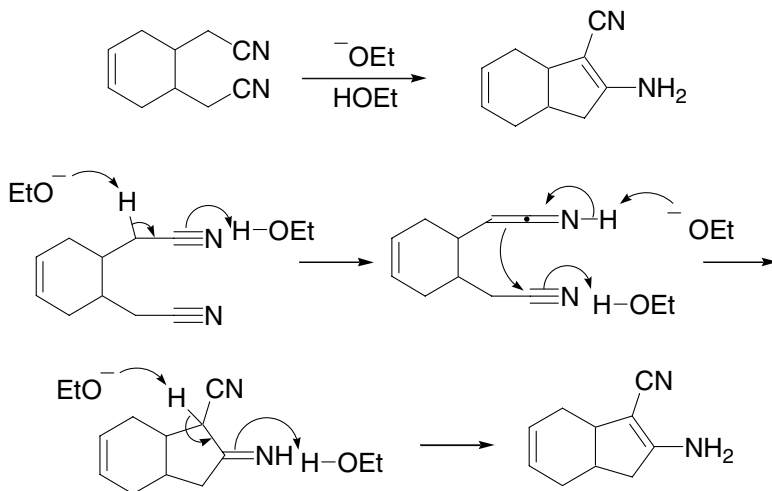
“Ormosil-TEMPO” is a sol-gel hydrophobized nanostructured silica matrix doped with TEMPO

References

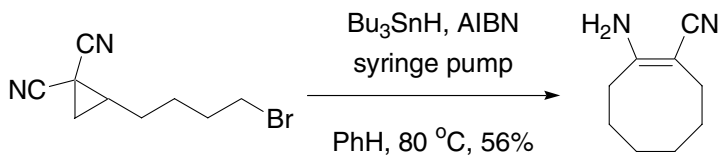
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Thorpe–Ziegler reaction

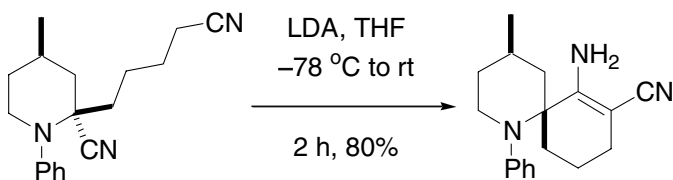
The intramolecular version of the Thorpe reaction, which is base-catalyzed self-condensation of nitriles to yield imines that tautomerize to enamine.



Example 1, a radical Thorpe–Ziegler reaction⁵



Example 2¹⁰

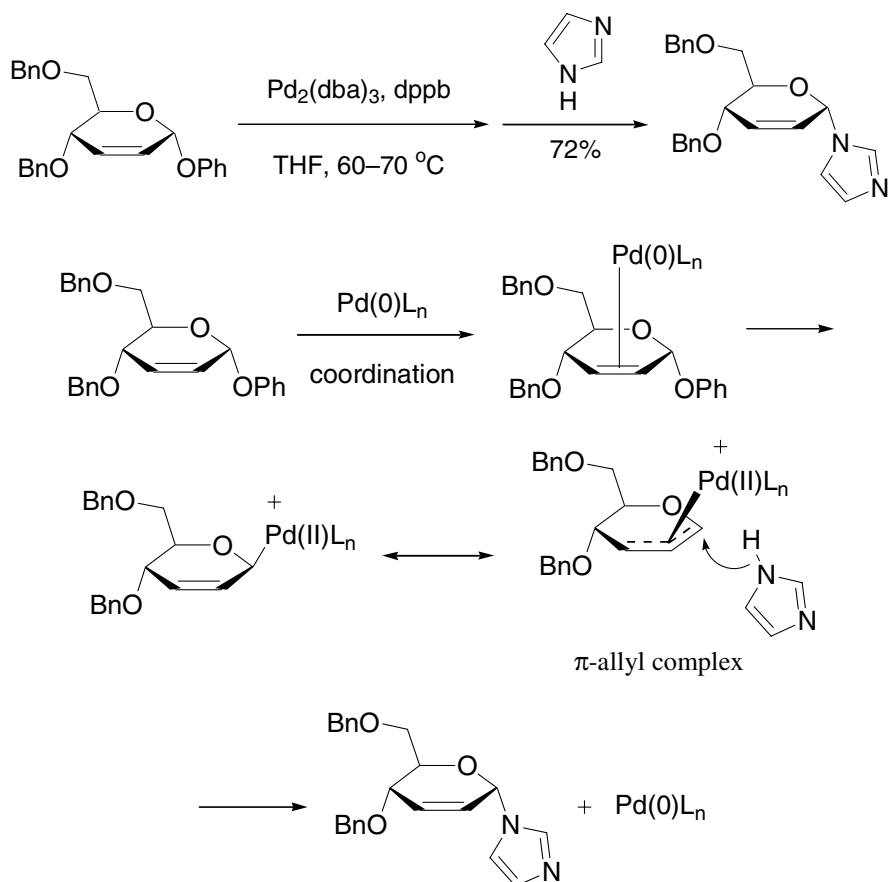


References

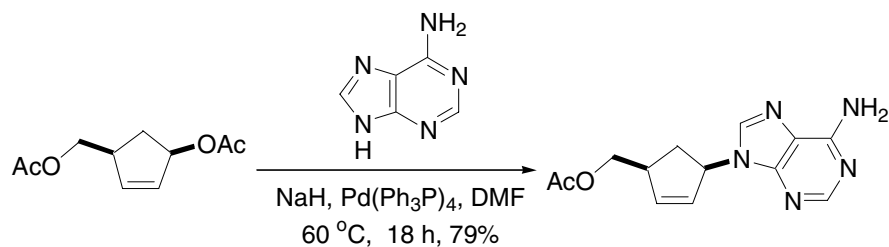
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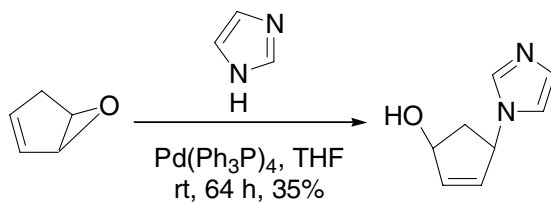
Tsuji–Trost reaction

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



Example 1⁴



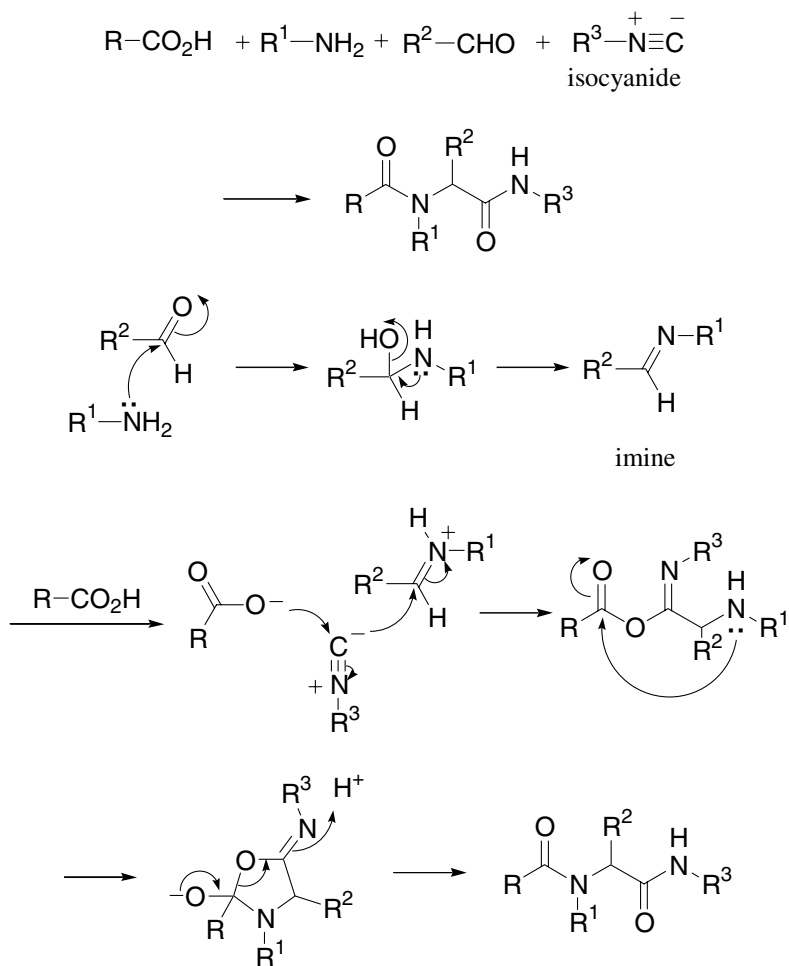
Example 2⁷

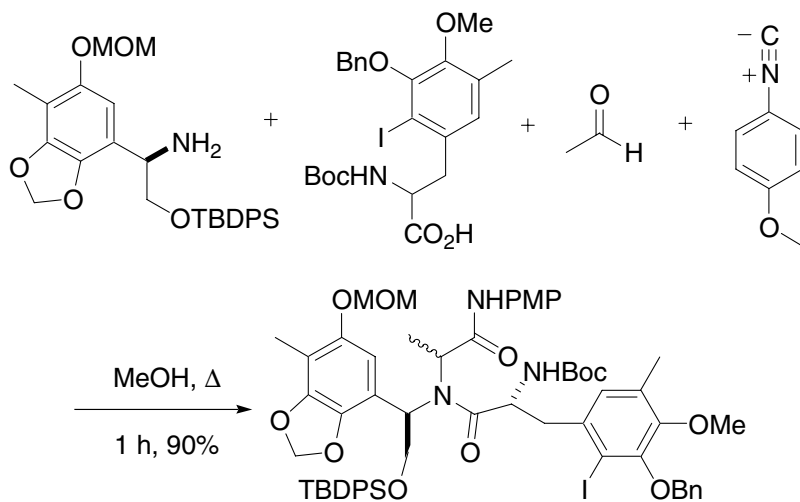
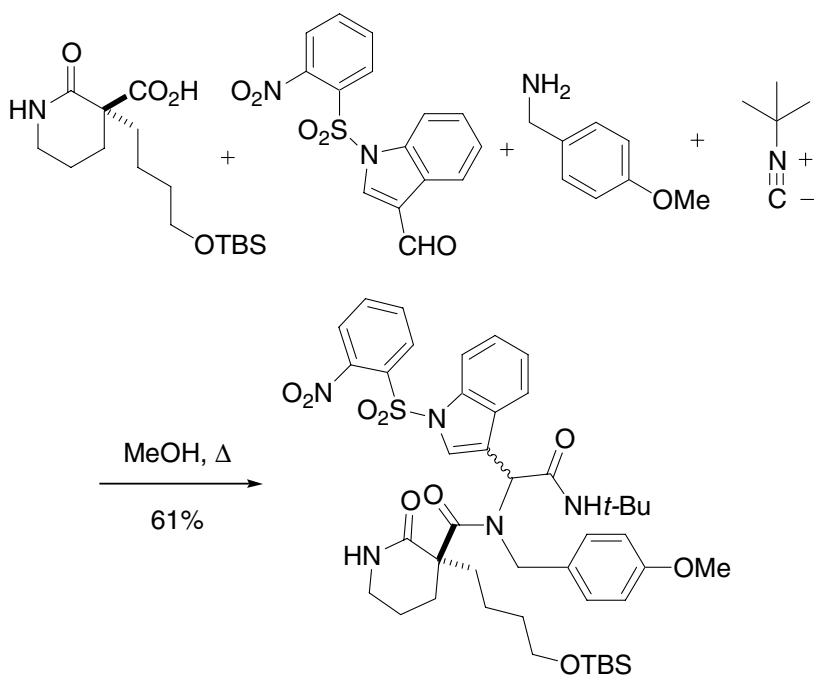
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Ugi reaction

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



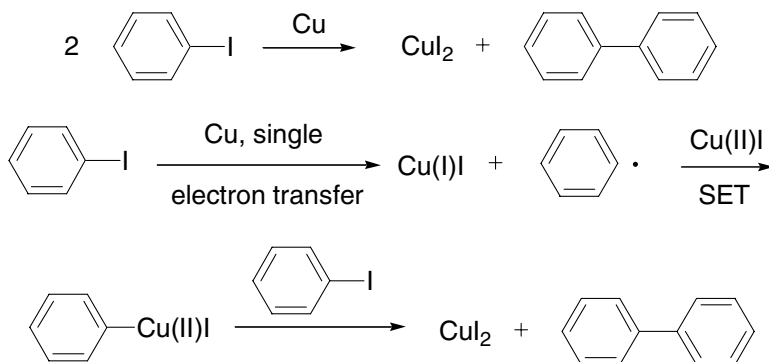
Example 1¹⁰Example 2¹³

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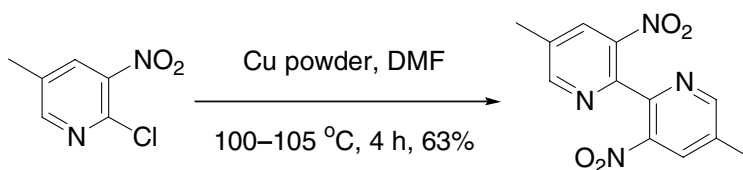
Ullmann reaction

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

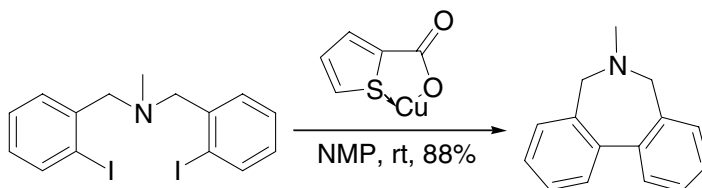


The overall transformation of PhI to PhCuI is an oxidative addition process.

Example 1⁵



Example 2⁶



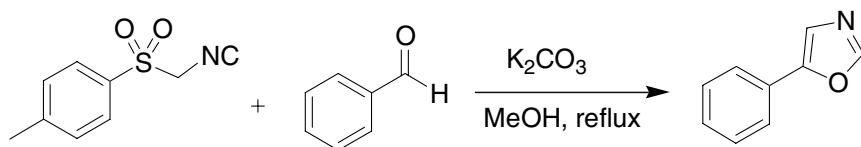
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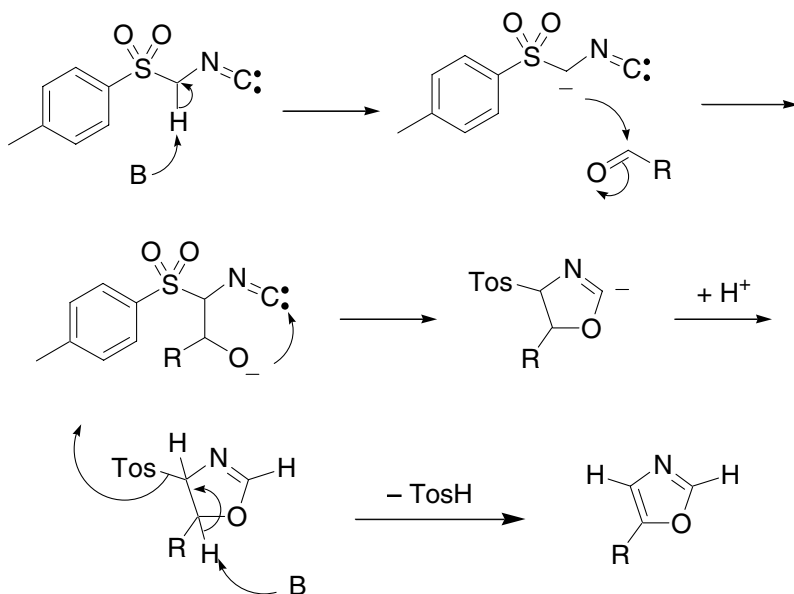
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van Leusen oxazole synthesis

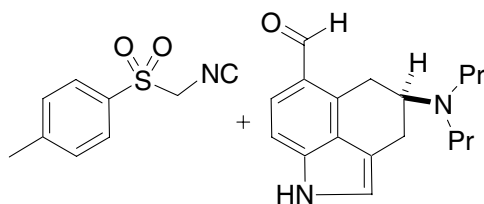
5-Substituted oxazoles through the reaction of *p*-tolylsulfonylmethyl isocyanide (TosMIC) with aldehydes in protic solvents at refluxing temperatures.

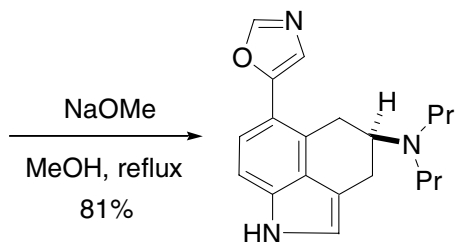


p-tolylsulfonylmethyl isocyanide (TosMIC)

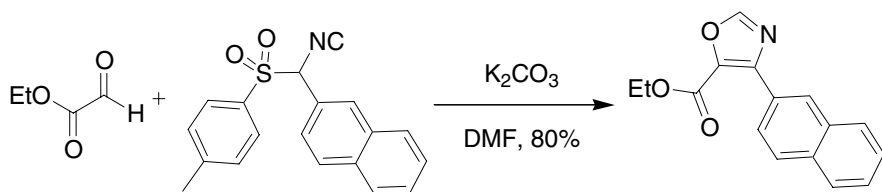


Example 1⁷





Example 2¹⁰

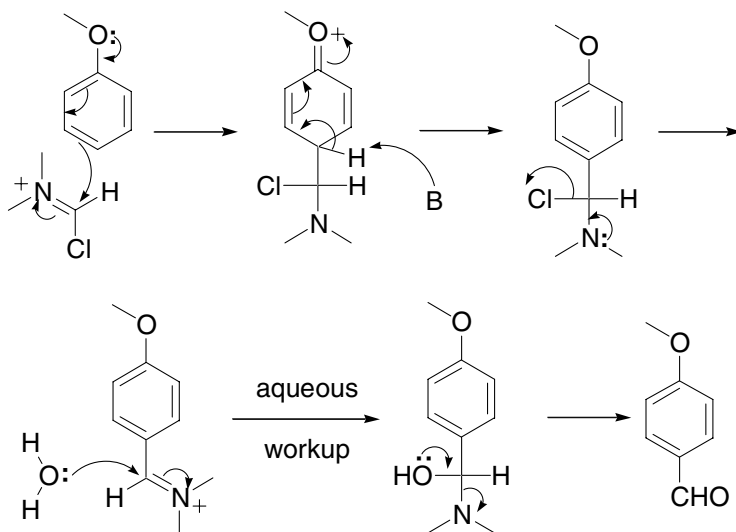
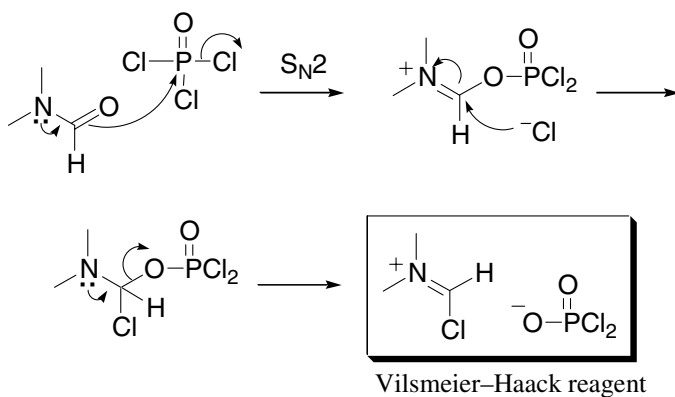
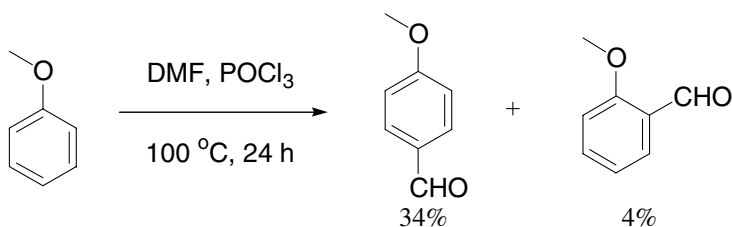


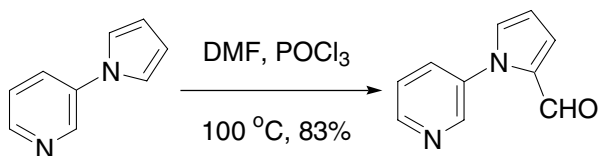
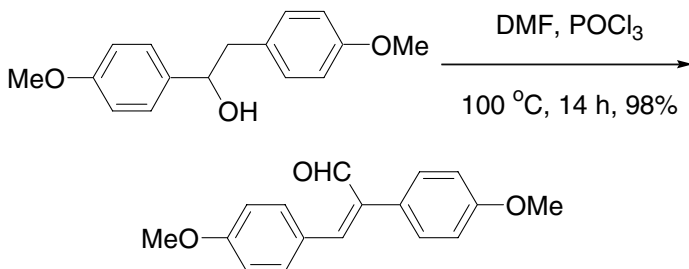
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Vilsmeier–Haack reaction

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



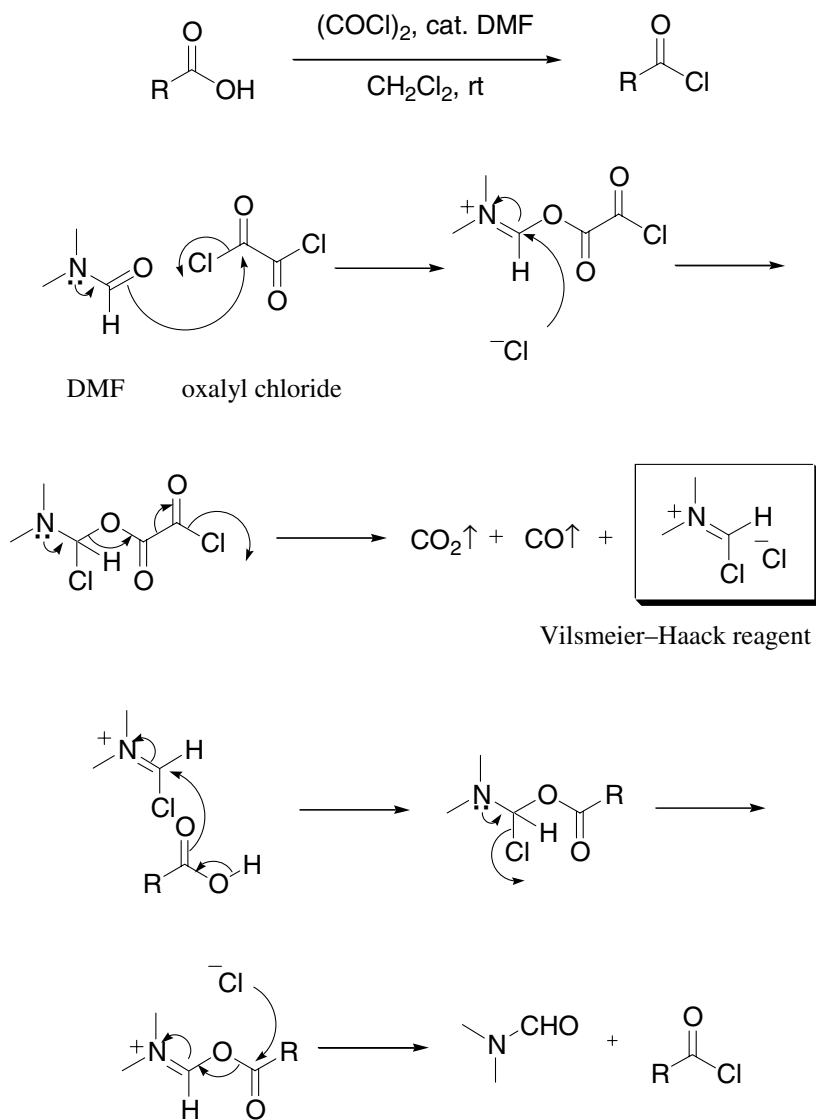
Example 1³Example 2²

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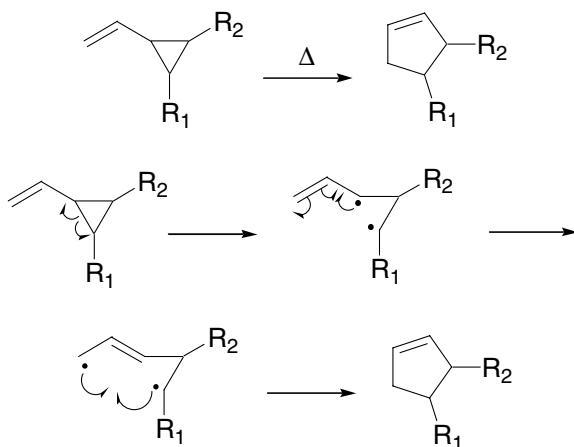
Vilsmeier mechanism for acid chloride formation

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.

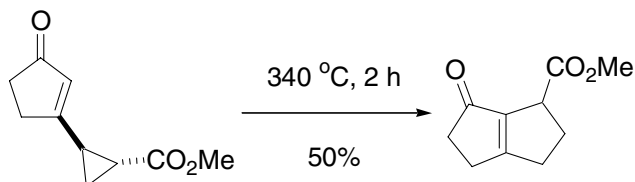


Vinylcyclopropane–cyclopentene rearrangement

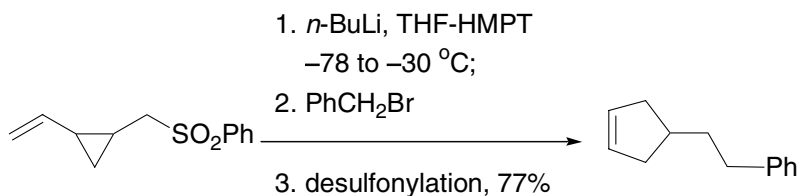
Transformation of vinylcyclopropane to cyclopentene *via* a diradical intermediate.



Example 1⁵



Example 2⁶



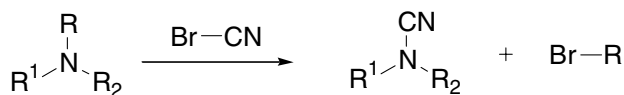
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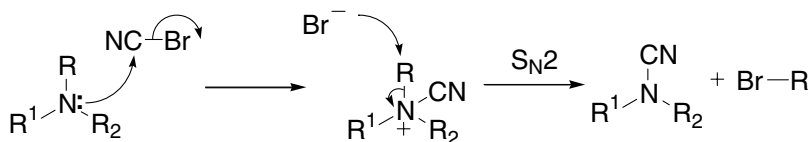
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von Braun reaction

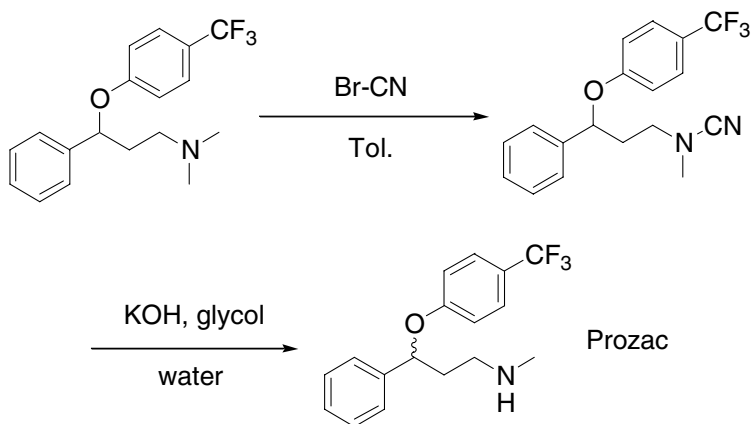
Treatment of tertiary amines with cyanogen bromide, resulting in a substituted cyanamide and alkyl halides.



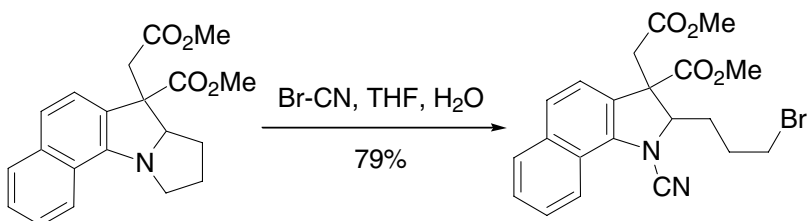
Cyanogen bromide (BrCN) is a *counterattack reagent*.



Example 1⁶



Example 2⁷

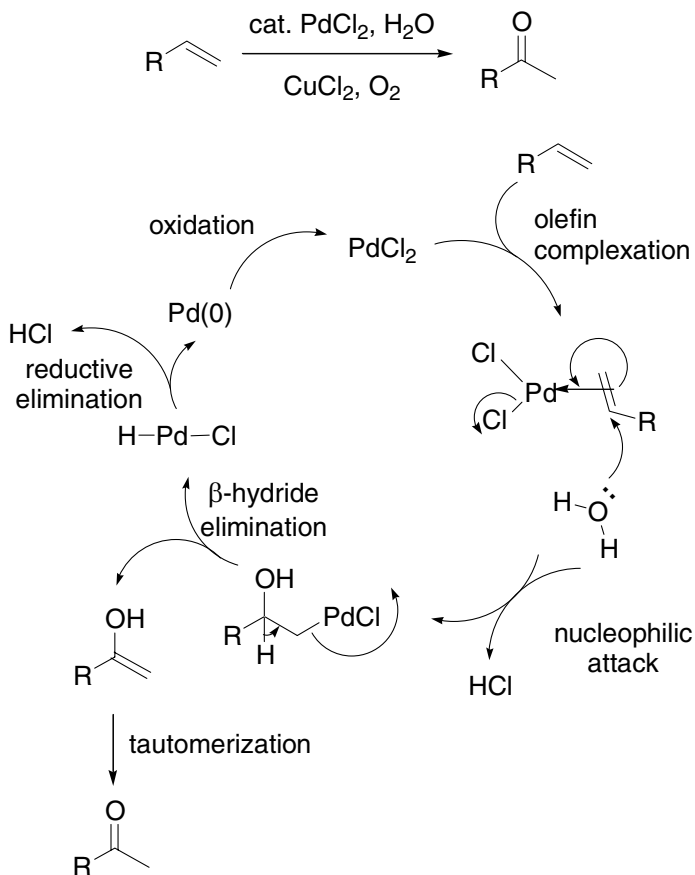


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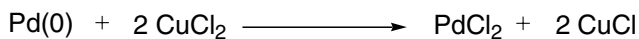
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Wacker oxidation

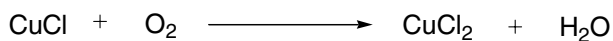
Palladium-catalyzed oxidation of olefins to ketones.

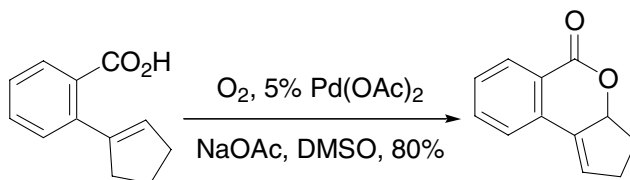
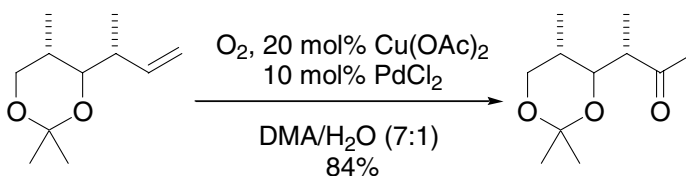


Regeneration of $\text{Pd}(\text{II})$:



Regeneration of $\text{Cu}(\text{II})$:



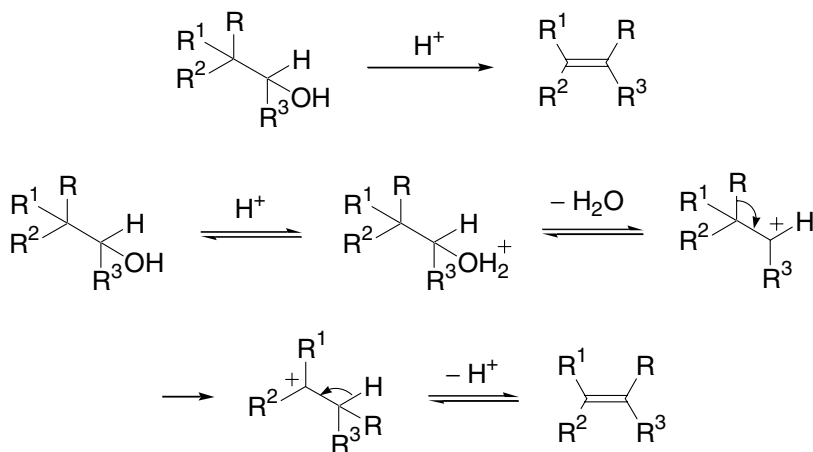
Example 1⁶Example 2¹⁰

References

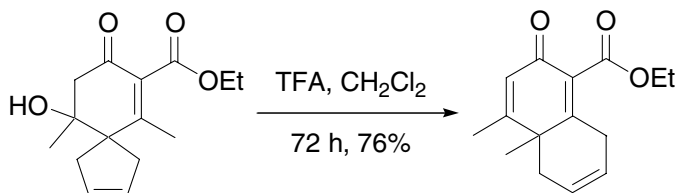
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Wagner–Meerwein rearrangement

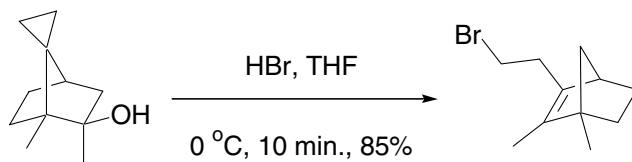
Acid-catalyzed alkyl group migration of alcohols to give more substituted olefins.



Example 1¹³



Example 2¹⁴



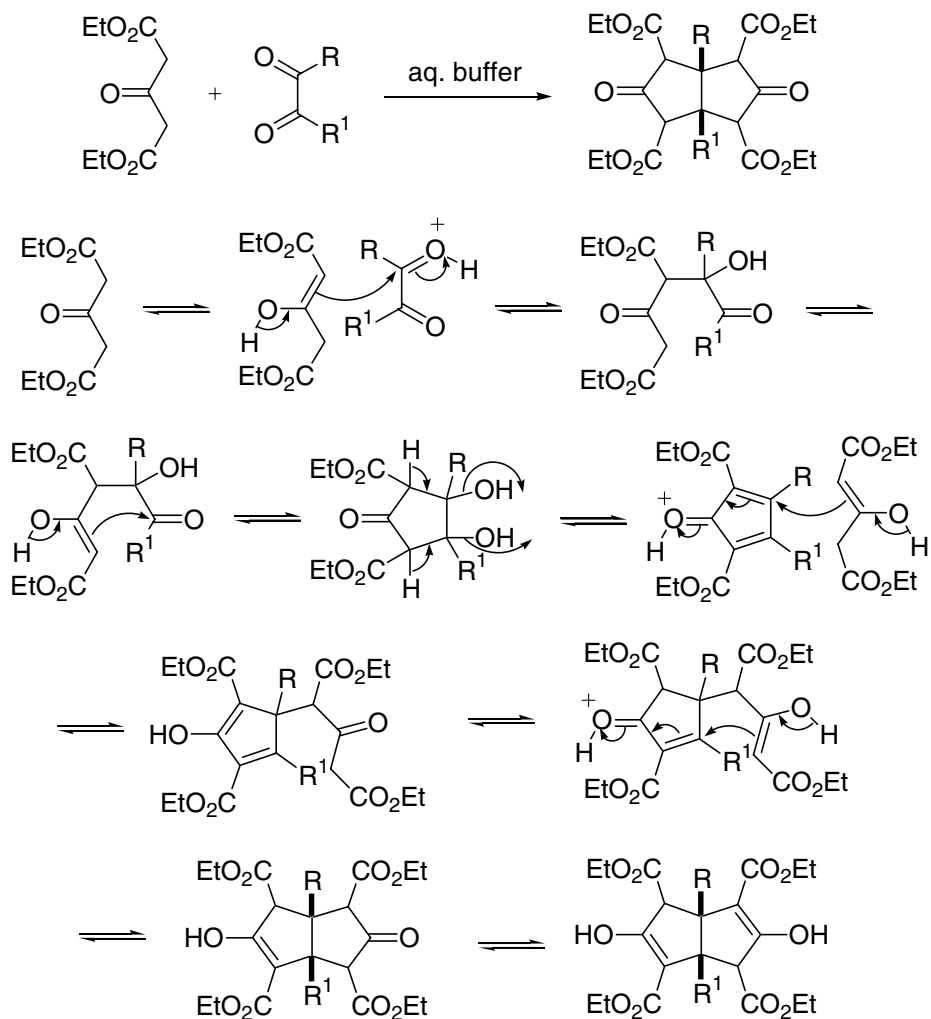
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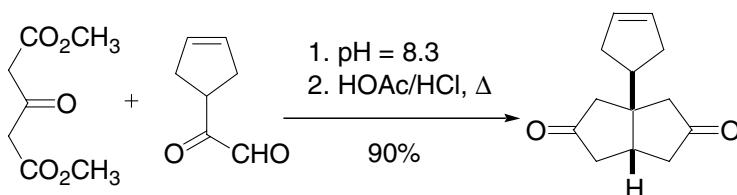
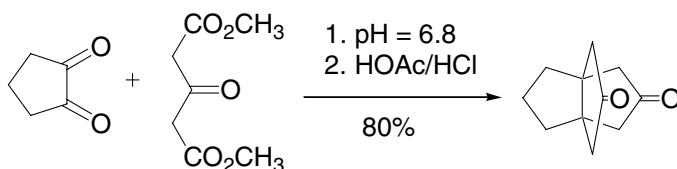
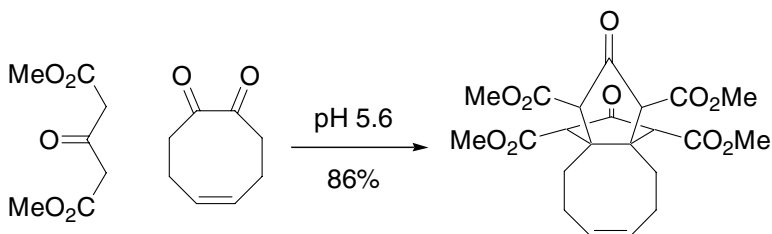
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Weiss–Cook reaction

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



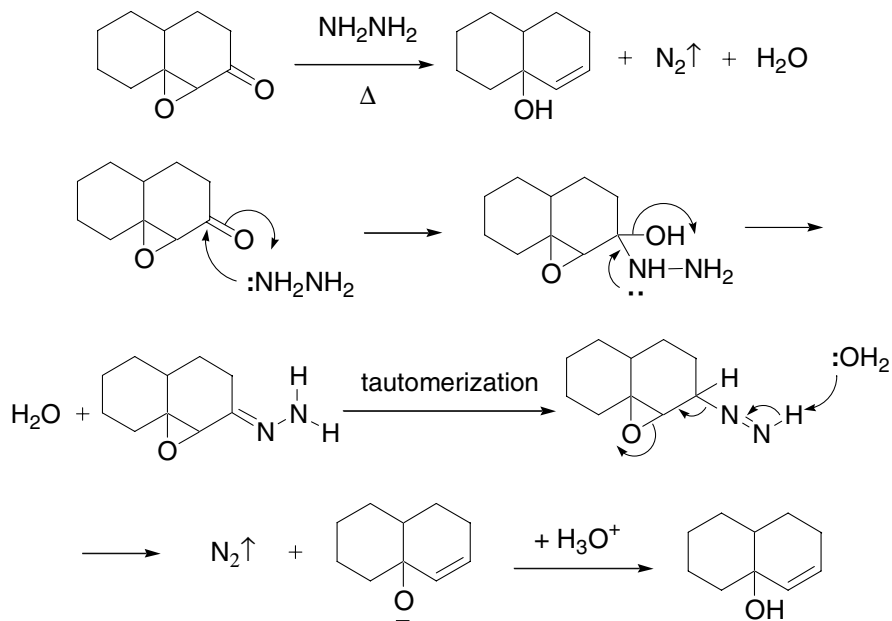
Example 1²Example 2³Example 3⁶

References

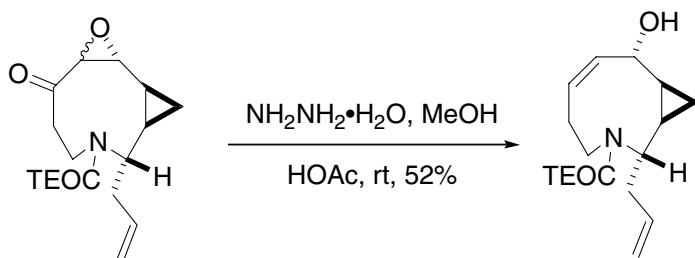
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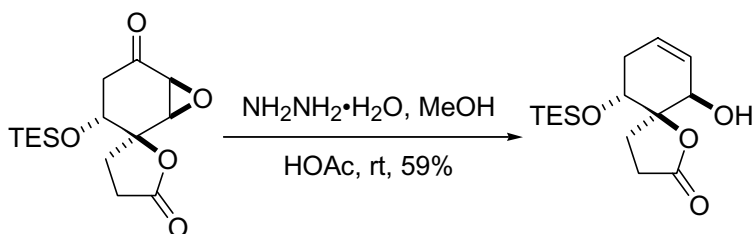
Wharton oxygen transposition reaction

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



Example 1⁵



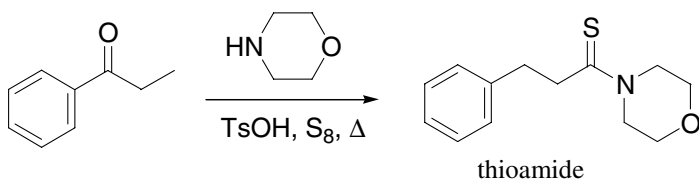
Example 2⁷

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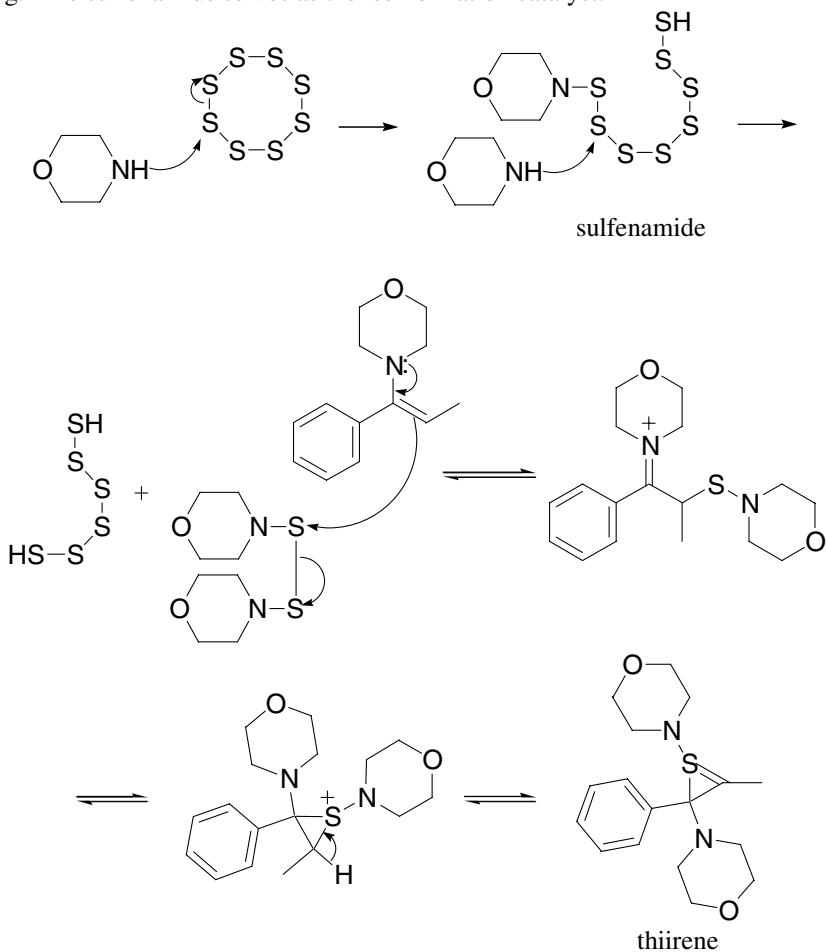
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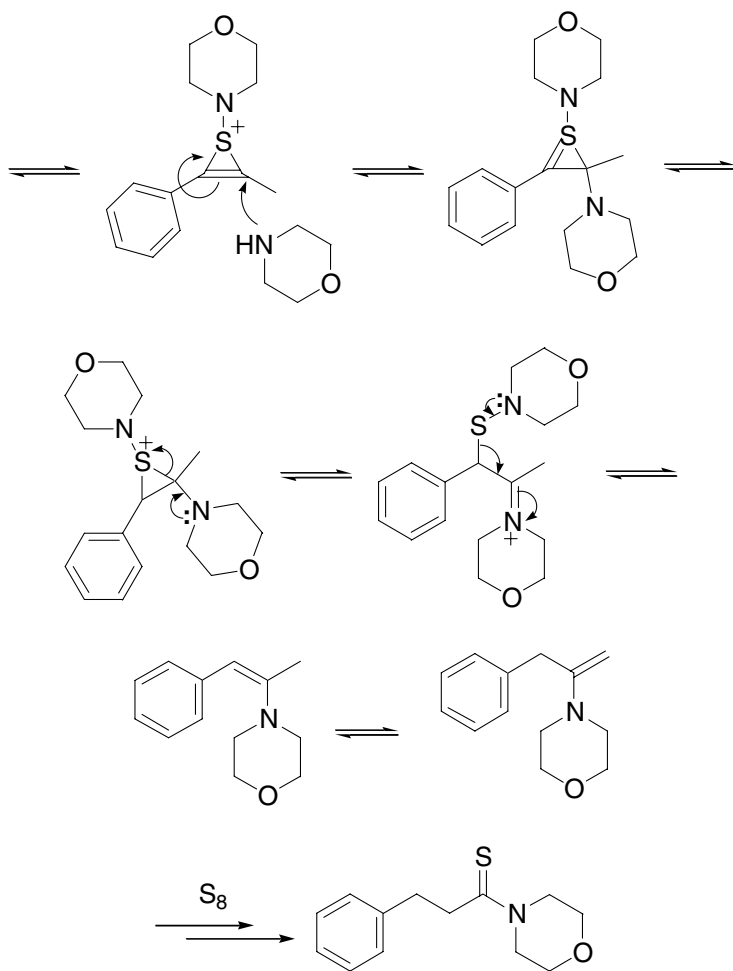
Willgerodt–Kindler reaction

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

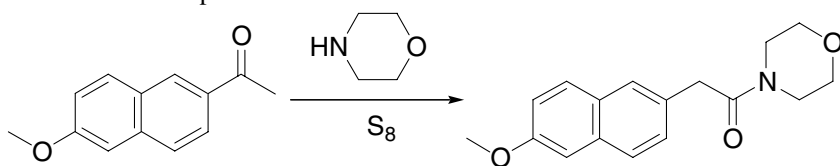


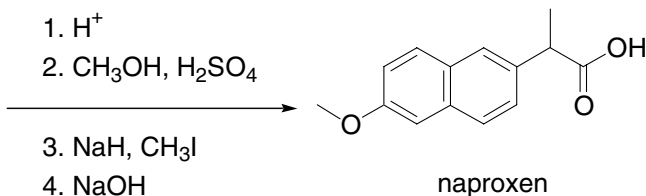
In Carmack's mechanism,⁸ the most unusual movement of a carbonyl group from methylene carbon to methylene carbon was proposed to go through an intricate pathway *via* a highly reactive intermediate with a sulfur-containing heterocyclic ring. The sulfenamide serves as the isomerization catalyst:



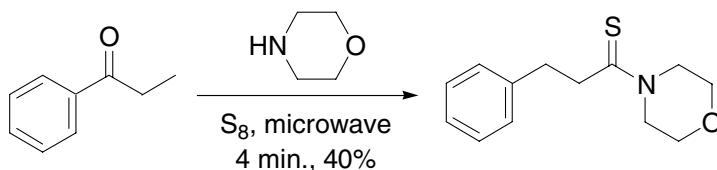


Example 1, the Willgerød–Kindler reaction was a key operation in the initial synthesis of racemic Naproxen:⁶





Example 2¹¹

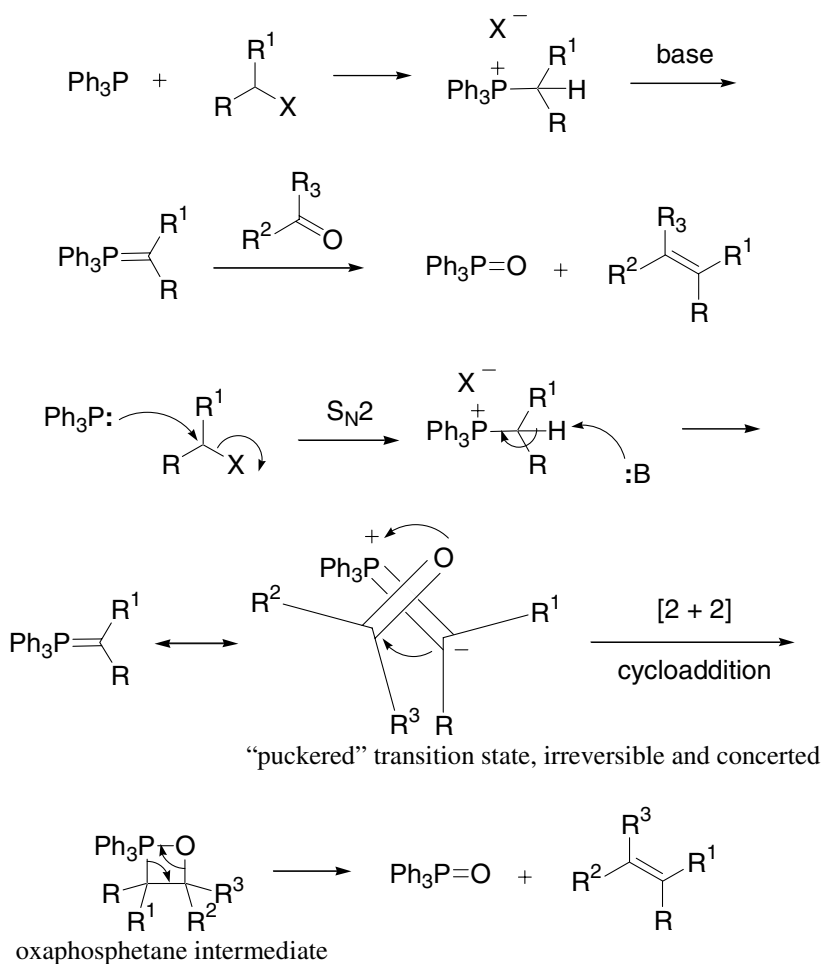


References

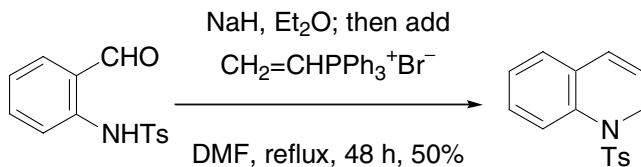
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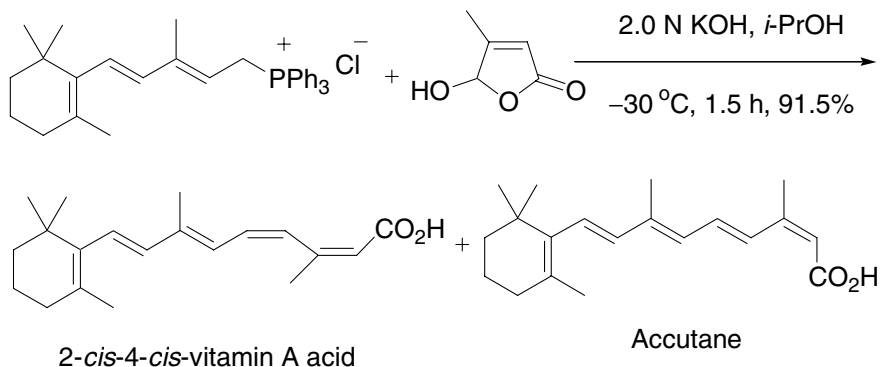
Wittig reaction

Olefination of carbonyls using phosphorus ylides.

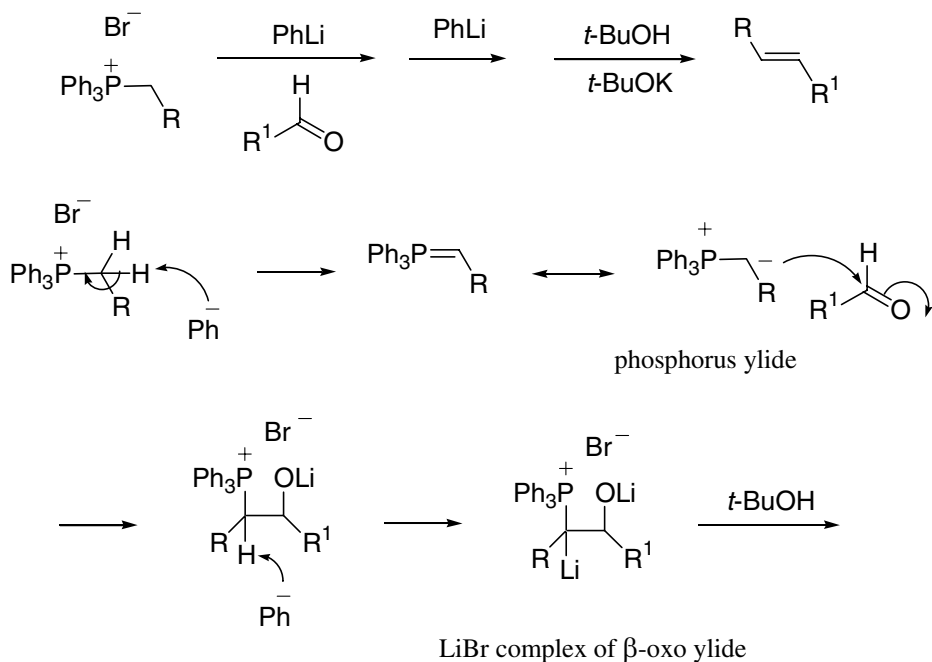


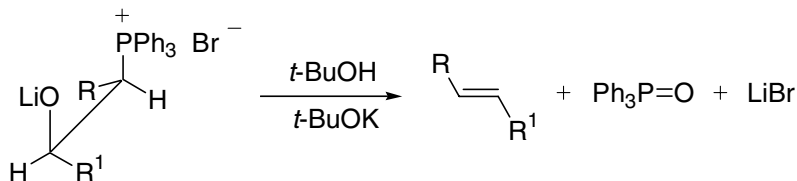
Example 1³



Example 2⁴**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.





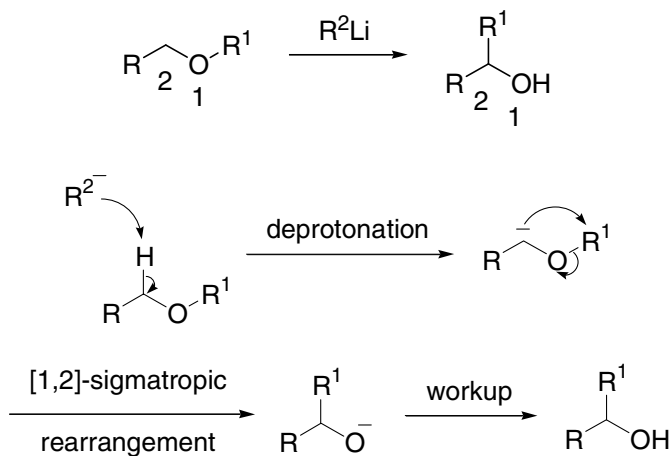
LiBr complex of *threo*-betaine

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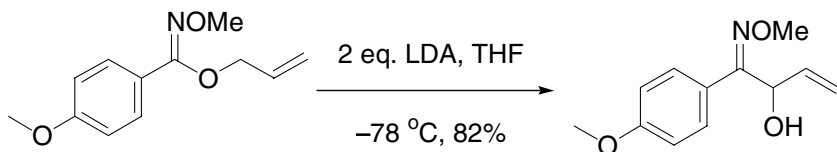
[1,2]-Wittig rearrangement

Treatment of ethers with alkyl lithium results in alcohols.

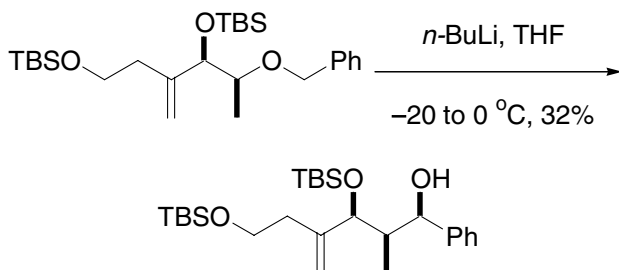


The radical mechanism is also possible as radical intermediates have been identified.

Example 1⁴



Example 2⁵

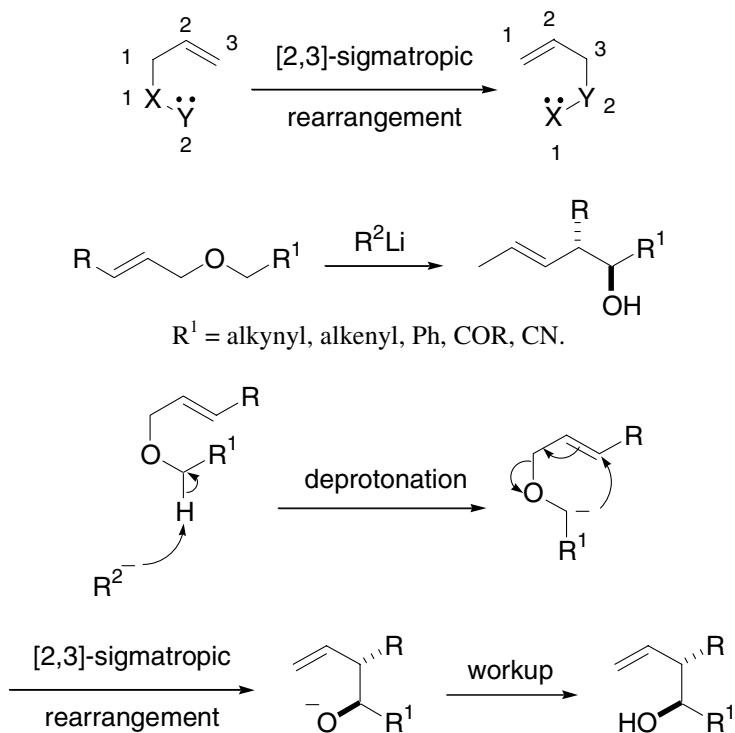


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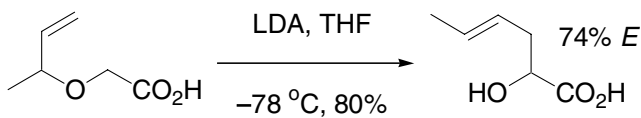
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[2,3]-Wittig rearrangement

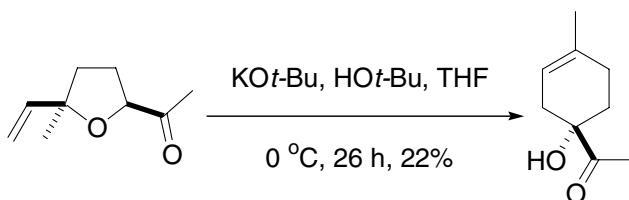
Transformation of allyl ethers into homoallylic alcohols by treatment with base. Also known as Still–Wittig rearrangement. *Cf.* Sommelet–Hauser rearrangement



Example 1³



Example 2²

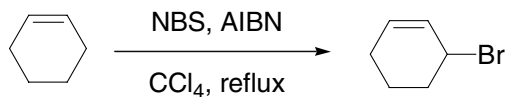


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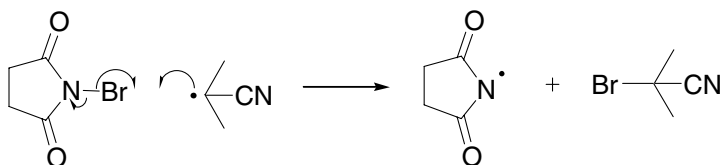
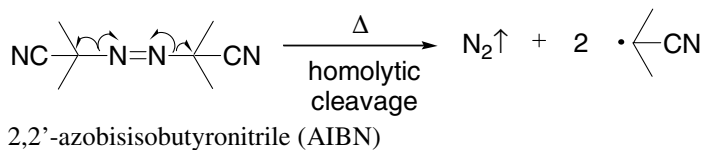
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Wohl-Ziegler reaction

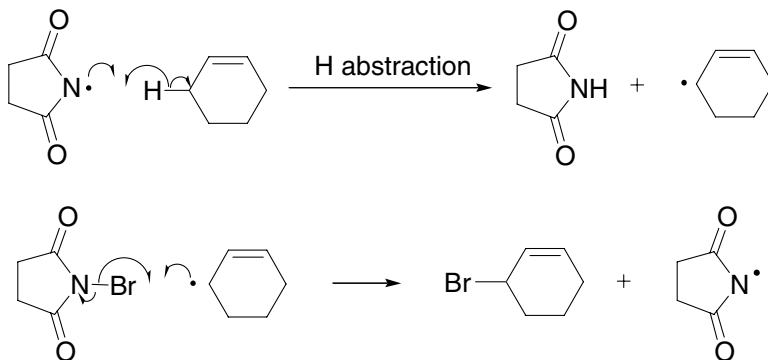
Radical-initiated allylic bromination using NBS, and catalytic AIBN as initiator or NBS under photolysis.



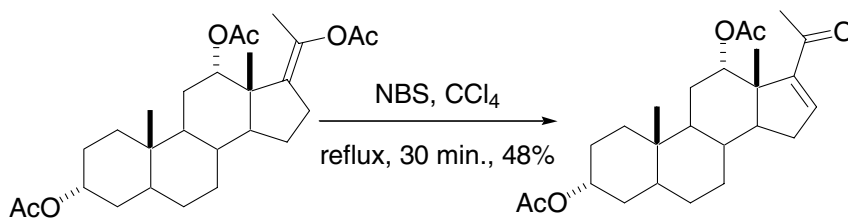
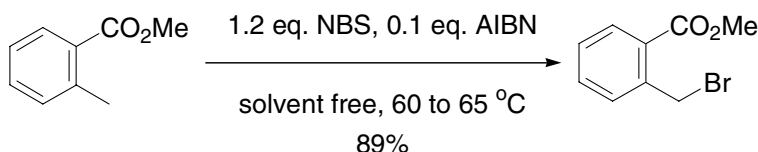
Initiation:



Propagation:



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

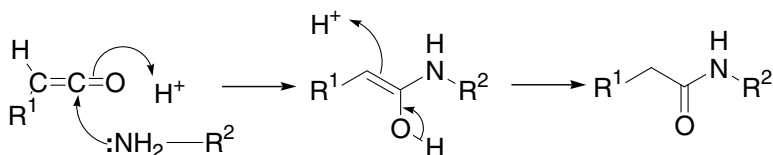
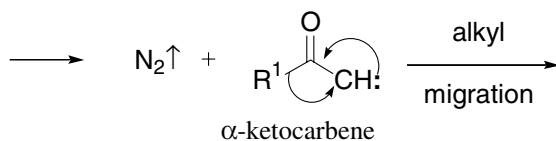
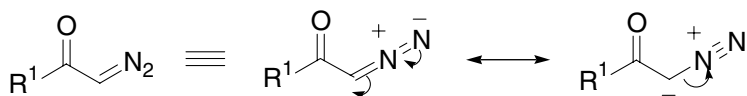
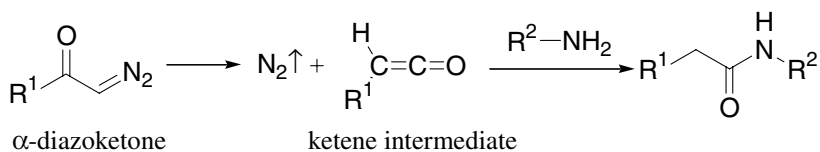
Example 1³Example 2¹³

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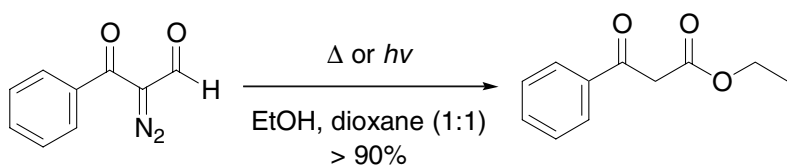
Wolff rearrangement

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

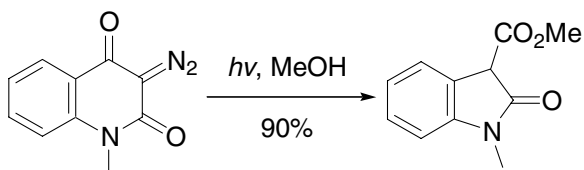


Treatment of the ketene with water would give the corresponding homologated carboxylic acid.

Example 1²



Example 2⁴

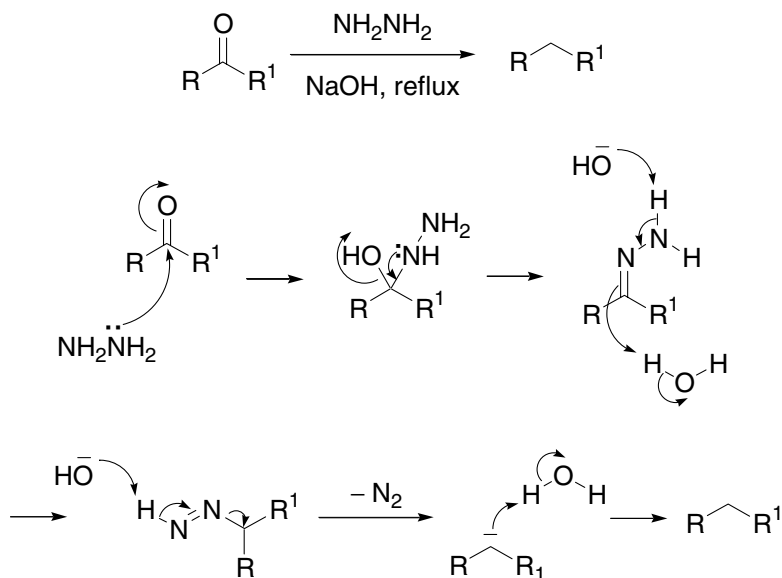


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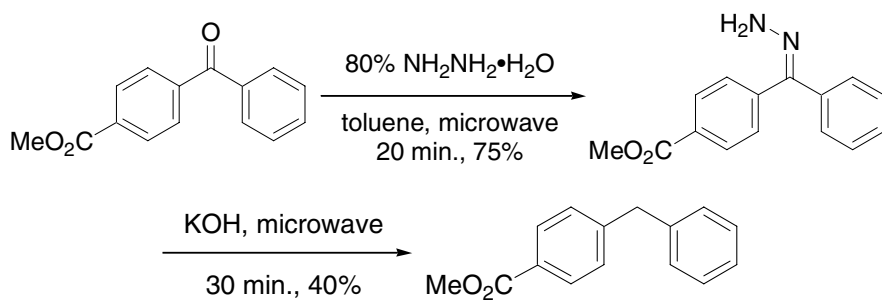
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Wolff–Kishner reduction

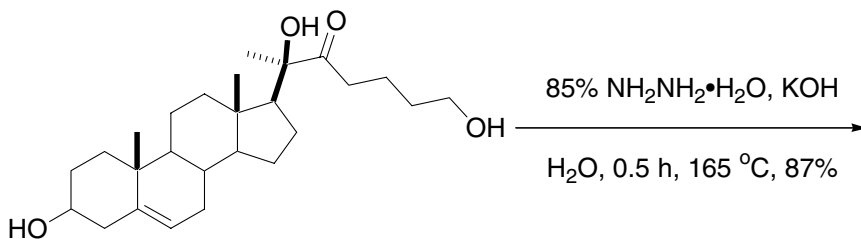
Carbonyl reduction to methylene using basic hydrazine.

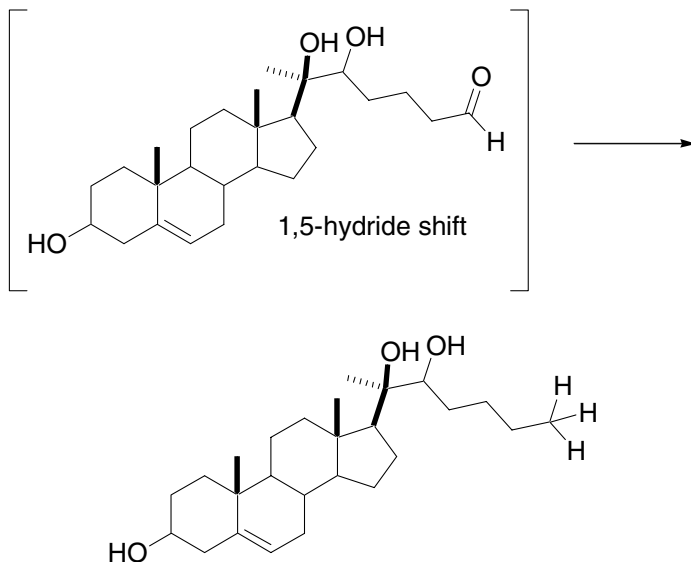


Example 1¹¹



Example 2¹²



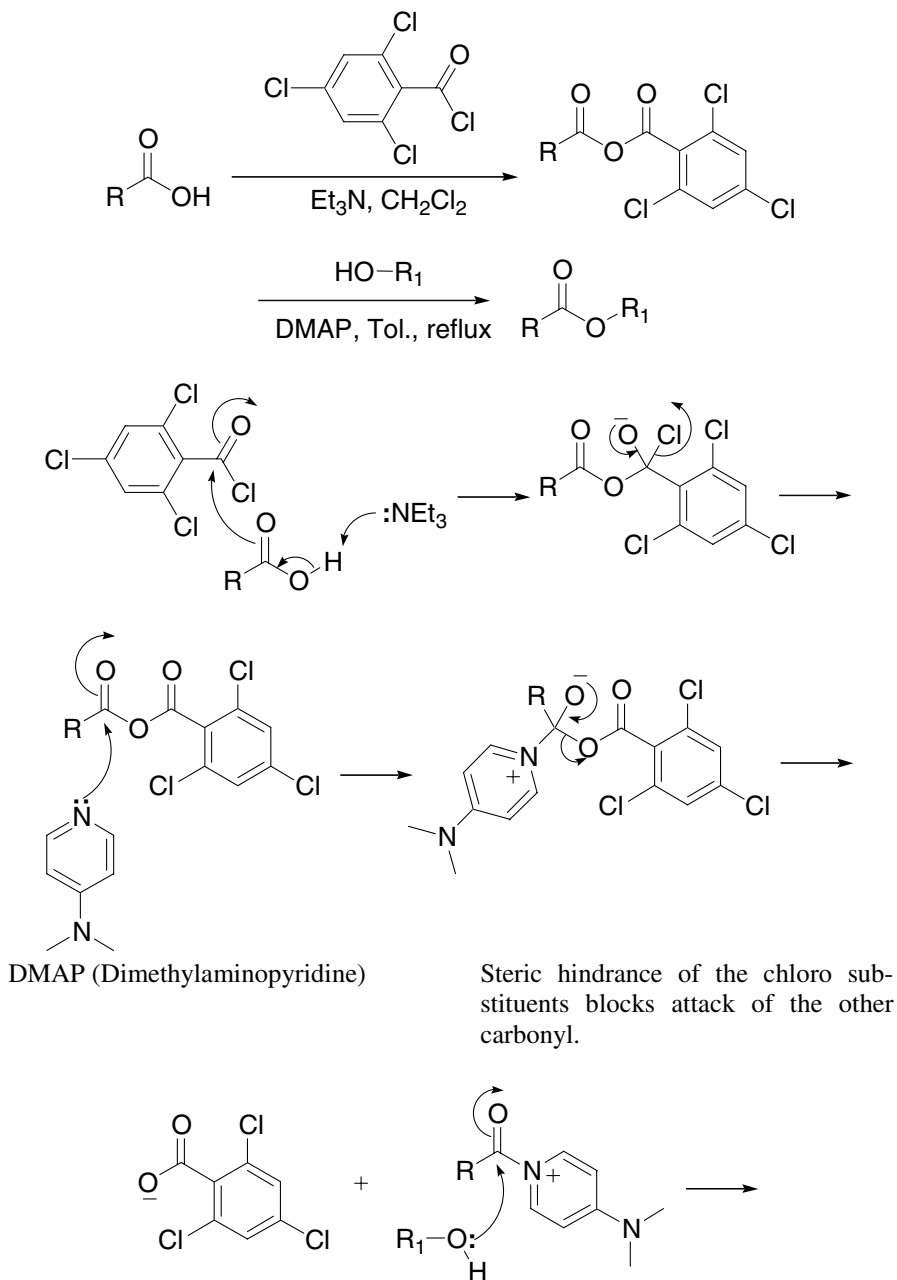


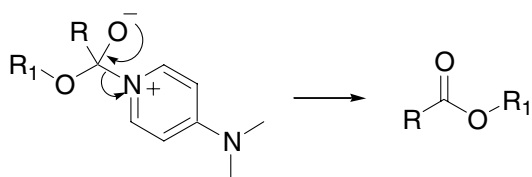
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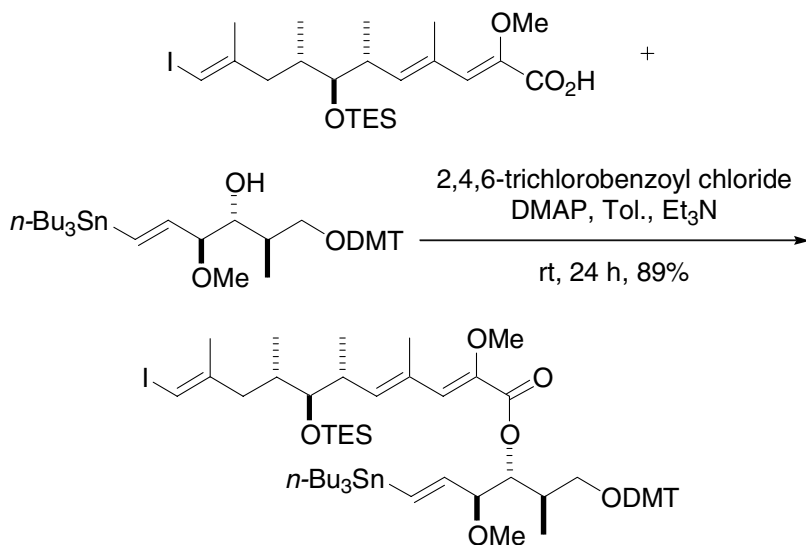
Yamaguchi esterification

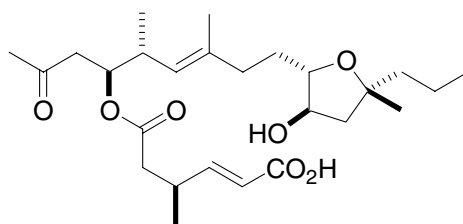
Esterification using 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent).





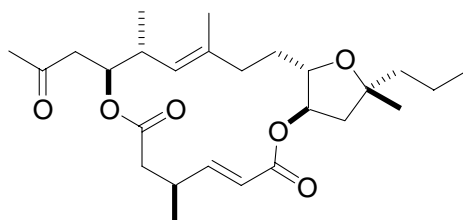
Example 1⁹



Example 2¹¹

2,4,6-trichlorobenzoyl chloride
Et₃N, THF

then DMAP, toluene, 62%

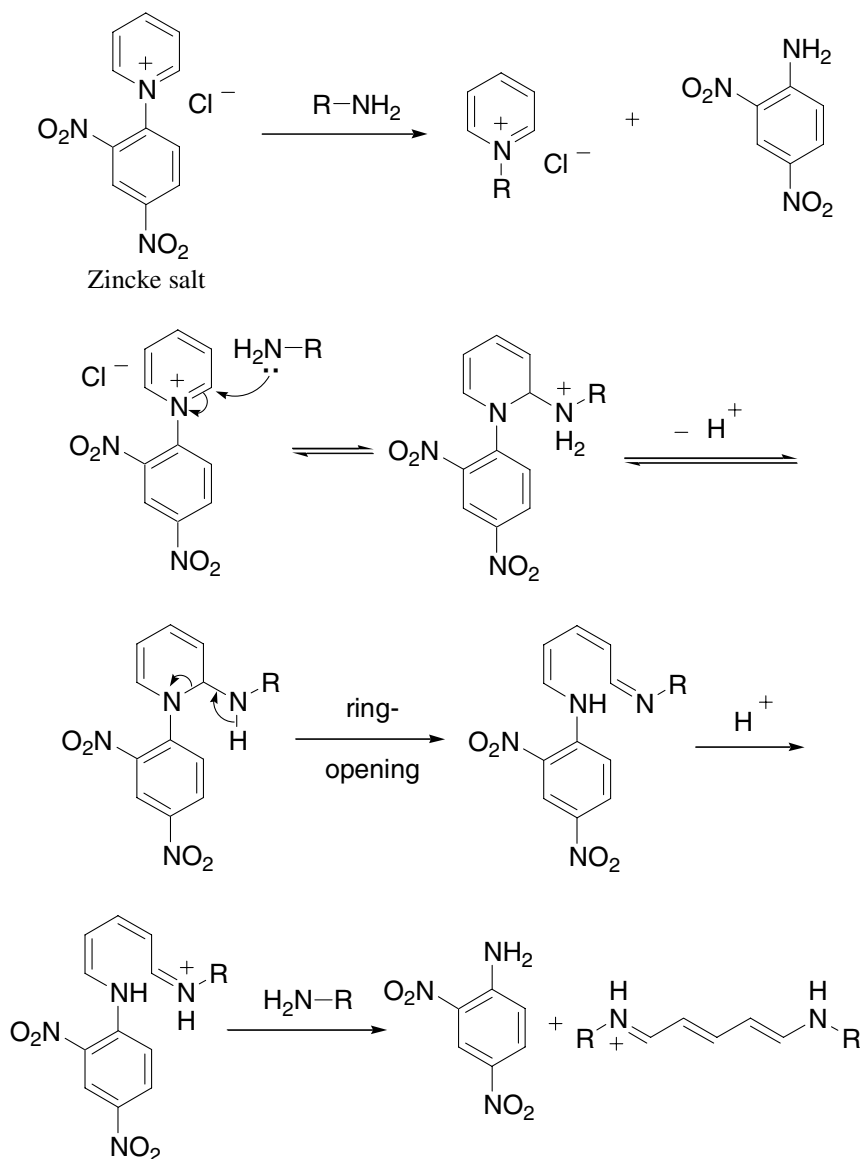


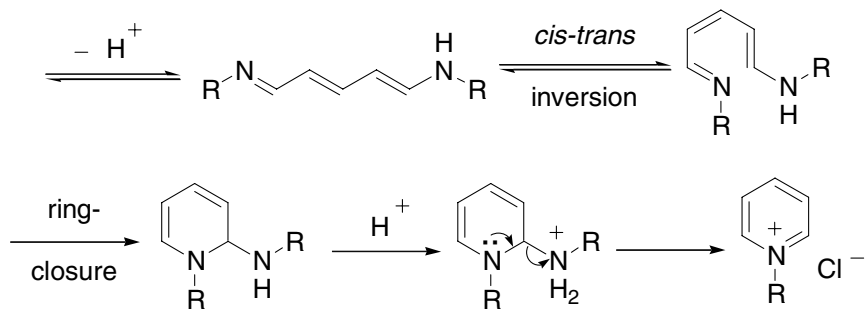
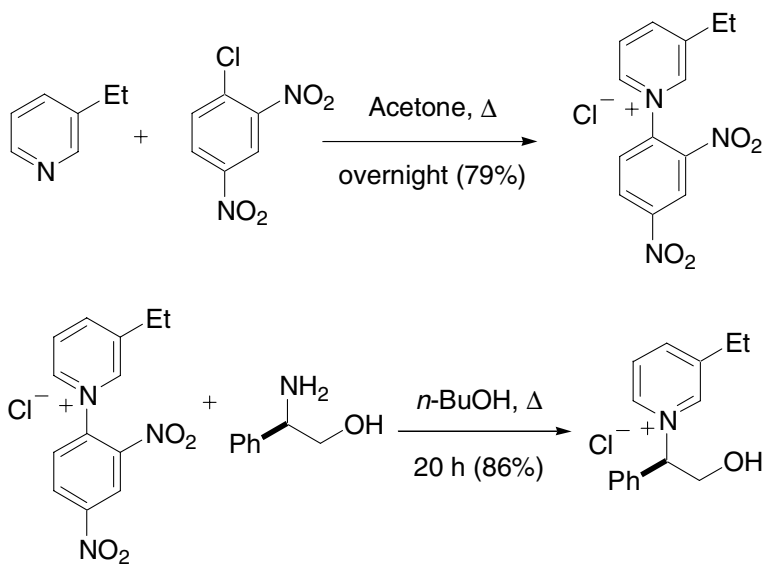
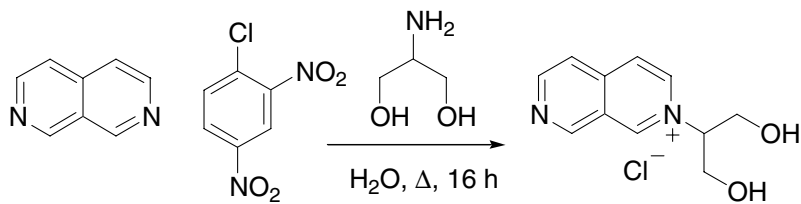
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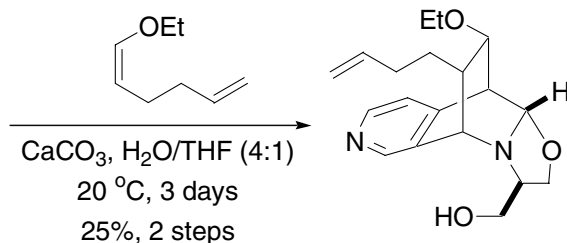
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Zincke reaction

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



Example 1¹³Example 2¹⁶



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Emil Fischer
1852–1919
Nobel Prize, 1902



Victor Grignard
1871–1935
Nobel Prize, 1912



Hermann Staudinger
1881–1965
Nobel Prize, 1953



Robert Robinson
1886–1975
Nobel Prize, 1947



Georg Wittig
1897–1987
Nobel Prize, 1979



Otto Wallach
1847–1931
Nobel Prize, 1910



Karl Ziegler
1898–1973
Nobel Prize, 1963

