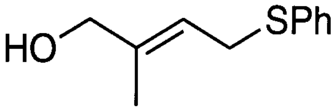
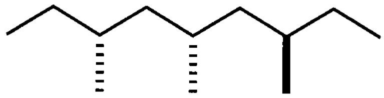
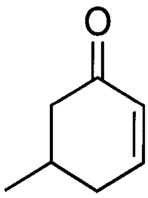


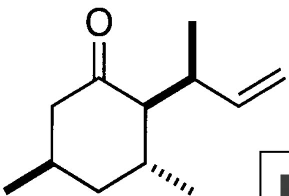


Concise and Comprehensive Course Book of

Organic Synthesis

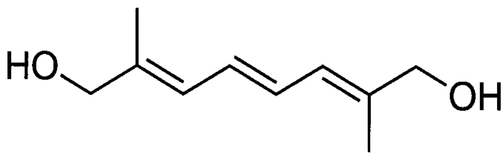
11th Edition (2018.01)





Prepared by Sangho Koo

Dept. of Chemistry, Dept. of Energy Science and Technology, Myongji University, Korea
School of Pharmacy
East China University of Science and Technology, Shanghai, China



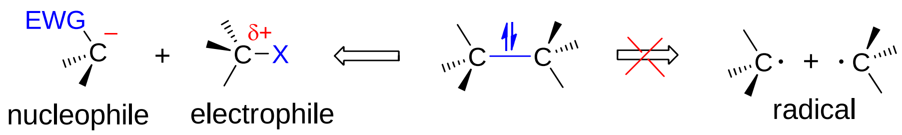
Concise and Comprehensive Course Book of Organic Synthesis

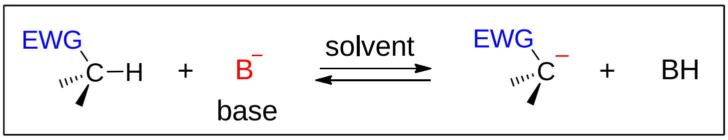
Reference Books

1. William Carruthers and Iain Coldham, “Modern Methods of Organic Synthesis” 4th Ed; 2004, Cambridge, ISBN 0-521-77830-1

2. Francis A. Carey and Richard J. Sundberg, “Advanced Organic Chemistry” 4th Ed, Part B; 2000, Kluwer Academics / Plenum Publisher; New York, ISBN 0-306-46243-5

Chapter 1. Formation of carbon-carbon single bonds





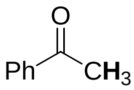
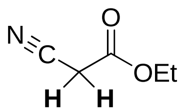
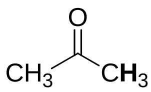
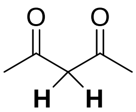
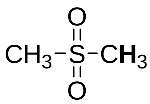
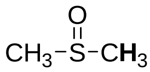
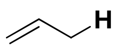
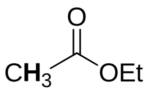
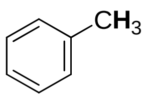
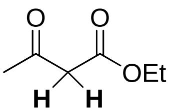
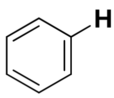
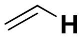
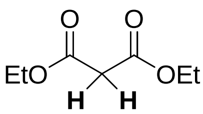
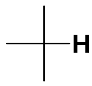
Strength of an acid

$$HA \rightleftharpoons H^+ + A^-$$

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad pK_a = -\log K_a$$

1.1. Alkylation: importance of enolate anions stability vs reactivity

a. The acidity of the C-H bonds

compound	pK_a	compound	pK_a	compound	pK_a
$CH_3CO_2\mathbf{H}$	5		19	Ph–N**H**$_2$	~30
	9		20	$Ph_3C\mathbf{H}$	~40
	9		~23		~40
					40
CH_3NO_2	10		~24		41
	11	$\mathbf{CH_3}CO_2H$	~24		43
		$CH_3-C\equiv C-\mathbf{H}$	25		44
	13	$\mathbf{CH_3}CN$	~25		52

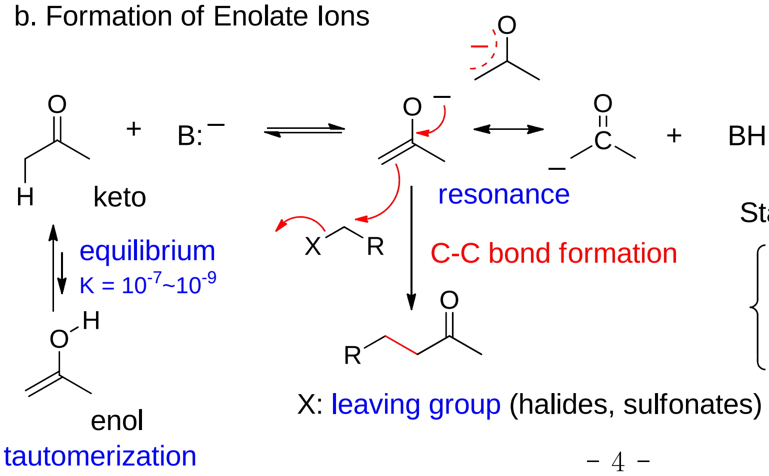
Anion Stabilizing Effect

NO_2 > COR > SO_2R > CO_2R > CN > SOR > Ph, SR >> H > R

Substituent Effect on pKa

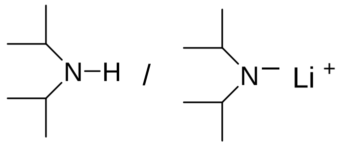
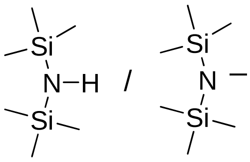
Alkyl (+1~2), Halogen (-1~2), Vinyl (-5~7), Phenyl (-5~7), Sulfide (-3~5)

b. Formation of Enolate Ions

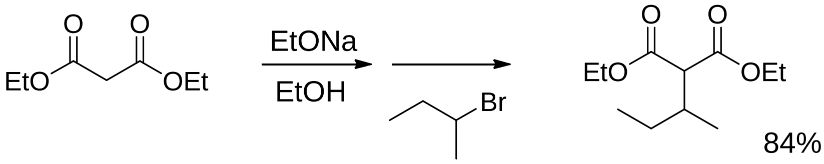


Stability of enolate ion
- resonance stabilization (charge delocalization)
- inductive electron withdrawing effect

c. pK_a of the conjugate acid of some bases

conjugate acid / base	pK_a	conjugate acid / base	pK_a
H_2O / OH^-	15.7	NH_3 / NH_2^-	30
MeOH / MeO^-	16	 Lithium Diisopropylamide (LDA)	33
t-BuOH / *t*-BuO^-	19		
 Hexamethyldisilazide (HMDS)	25	Ph_3CH / Ph_3C^-	33
		RH / R^-	~50
c.f. $Et_3\overset{+}{N}H$ / Et_3N	11	$Ph\text{-}\overset{+}{N}H_3$ / $Ph\text{-}NH_2$	4.6
$Et_2\overset{+}{N}H_2$ / Et_2NH	10.5	$\overset{+}{Py}\text{-}H$ / Pyridine	5.3

d. alkylating agents



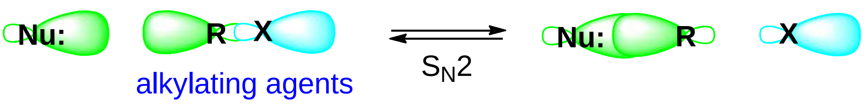
Elecreoegativity Scale

F	4.0
O	3.5
Cl, N	3.0
Br	2.8
C, S, I	2.5
H, P	2.1
B	2.0
Si	1.8

Mechanism of alkylation

Stereoelectronic effect (favors trajectory of maximum orbitals overlap)

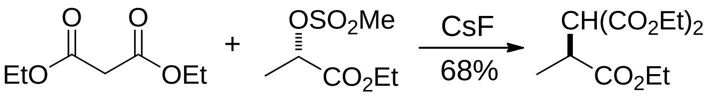
backside attack for S_N2 reaction



the direction of the arrow is decided by the relative stability of Nu^- and X^-

$X:^-$ good leaving group - stabilized anion (resonance or charge delocalized)

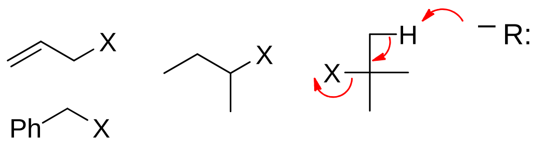
X = I, Br, Cl, OTs, OMs etc.



leaving group	relative rate	conjugate acid	pKa
F^-	10^{-5}	HF	3.1
Cl^-	10^0	HCl	-3.9
Br^-	10^1	HBr	-5.8
I^-	10^2	HI	-10.4
H_2O	10^1	H_3O^+	-1.7
MsO^-	10^4	MsOH	-2.6
TsO^-	10^5	TsOH	-2.8
TfO^-	10^8	TfOH	-6.0

Steric effect (favors small size reactants for alkylation)

primary > secondary > tertiary



side reaction: E_2 elimination

e. Medium Effects in the Alkylation of Enolates

Solvent Effects (classification: polar vs. nonpolar; protic vs. aprotic solvents)

General consideration: **counter ion effect** on the reactivity of enolate

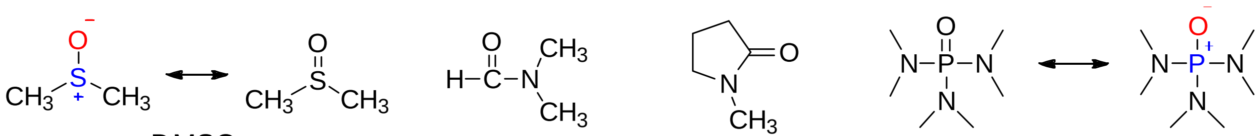
covalently bound enolate anion — bare or naked enolate anion

less reactive — Mg^{2+}, Li^{+}, Na^{+}, K^{+} — **more reactive**

M-O bond length in Å

Li: 1.92~2.00, Al: 1.92, Mg: 2.01~2.13, B: 1.36~1.47, Zn: 1.92~2.16, Ti: 1.62~1.73

1. **polar aprotic** solvent - **fast enolate alkylation**

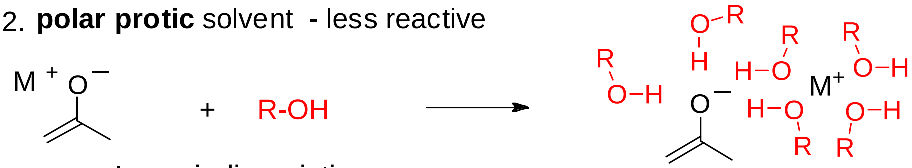


DMSO	DMF	NMP	HMPA
ε = 49	ε = 37	ε = 32	ε = 30
		N-methylpyrrolidone	hexamethylphosphoric triamide

Ion pair dissociation by polar aprotic solvent → naked anion, **more reactive enolate**

(effective metal cation solvation only)

2. **polar protic** solvent - less reactive

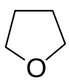


Ion pair dissociation
(cation as well as anion solvation)

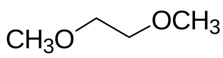
less reactive enolate
by hydrogen bonding

3. **Slightly polar aprotic solvent** - moderately good cation solvator

high aggregation   easy workup and purification



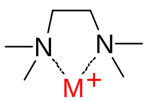
THF

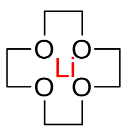


DME

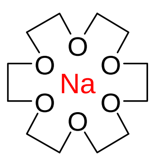
kinetic enolate generation

Additives: HMPA, TMEDA, crown ether





12-4



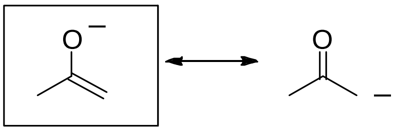
18-6

reactive enolate formation
by the selective cation solvation

Properties of some solvents

solvent	classification	dielectric const	solvent	classification	dielectric const
H_2O	protic	78	DMF	aprotic	37
DMSO	aprotic	49	MeOH	protic	33
MeCN	aprotic	37	AcOH	protic	6

f. O- vs C- alkylation



major contribution

(a negative charge is located on the more electronegative oxygen atom)

Control of O- vs C- alkylation

Free enolates give O- alkylation

1. Counter ion effects

Mg^{++} Li^{+} Na^{+} K^{+} n-Bu_4N^{+}

← C- alkylation → O- alkylation

2. Solvent effect

polar protic or less polar aprotic ← C- alkylation

polar aprotic → O- alkyation

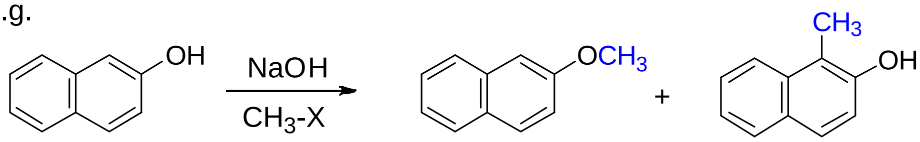
3. Leaving group effect

HSAB theory (hard-soft-acid-base)

I, Br, Cl, OMs, OTs, $R_3O^+BF_4^-$

← Soft C- alkylation → Hard O- alkylation

e.g.

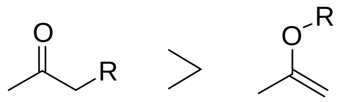


X = I	66	33
X = OTs	100	0

Hammond Postulate (*J. Am. Chem. Soc.* **1955**, *77*, 334)

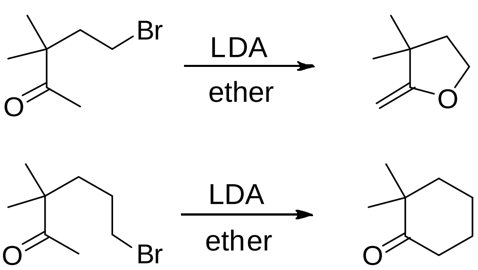
Hard-Hard combination: Early Transition State
Controling factor: Enolate stability

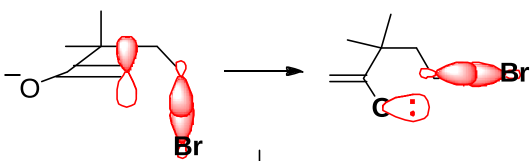
Soft-Soft combination: Late Transition State
Controling factor: Product stability

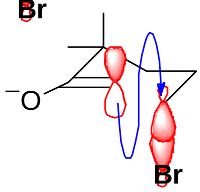


~20 kcal/mole more stable

4. Stereoelectronic effect





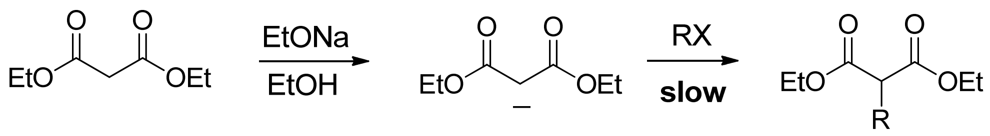


flexible tether

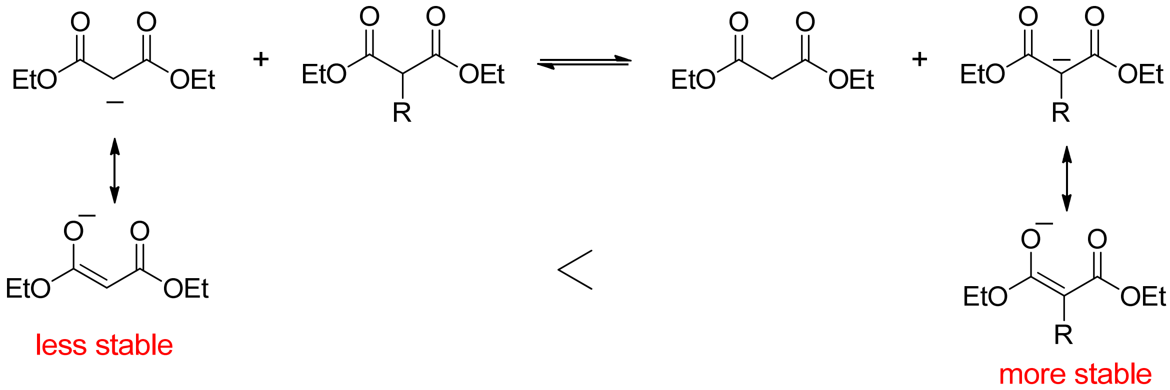
g. dialkylation

Mechanism

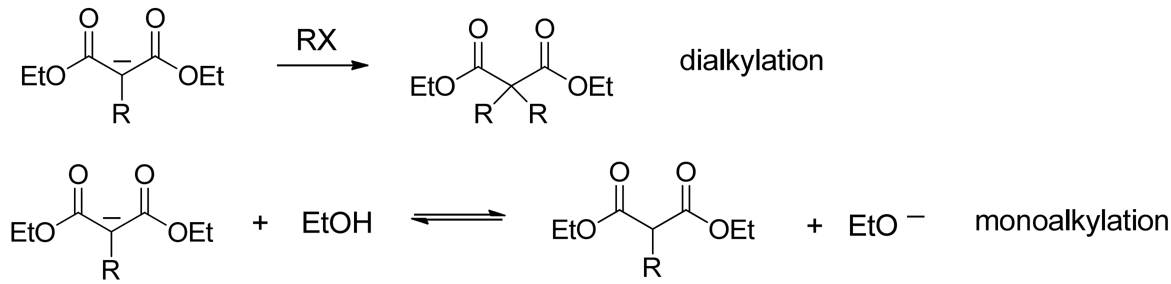
i)



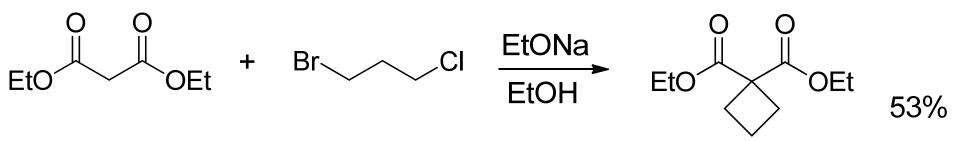
ii)

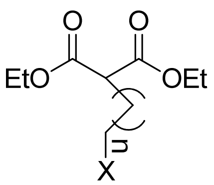


iii)



Cyclization

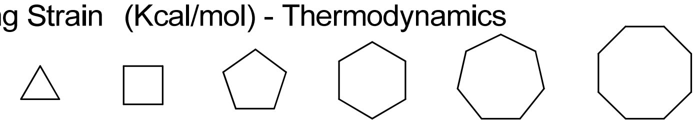




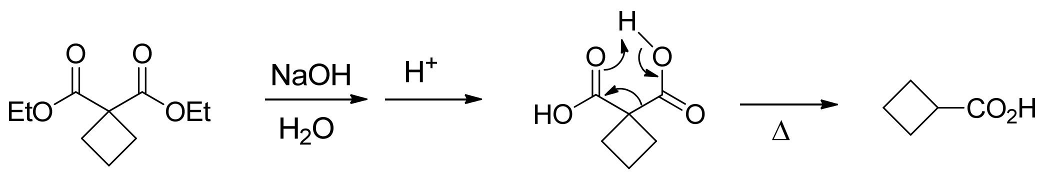
Rate of cyclization - Kinetics

n =	1	2	3	4
	650,000	1	6,500	5

Ring Strain (Kcal/mol) - Thermodynamics

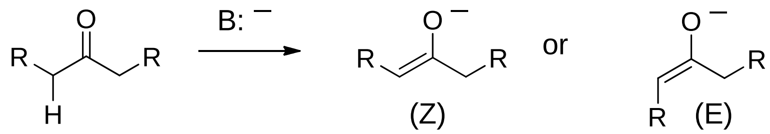


27.6 26.4 6.5 0 6.3 9.6

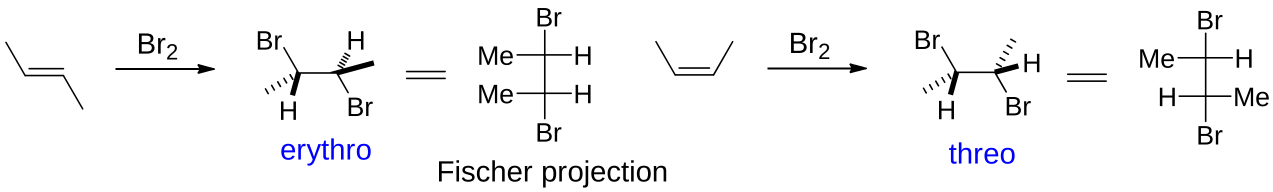


h. Regio- and Stereoselectivity in the Enolate Generation

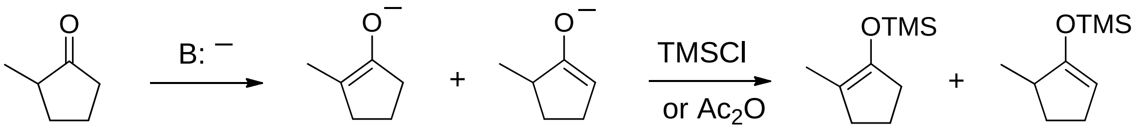
Stereoselectivity



c.f.> **Stereospecific**



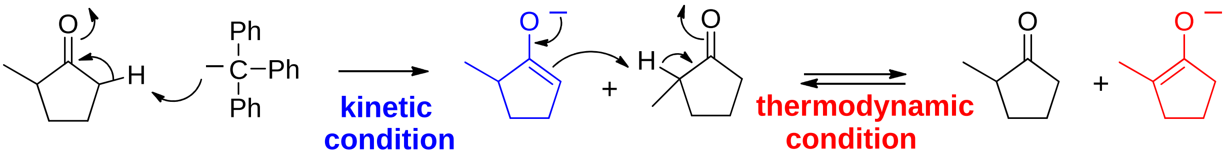
Regioselectivity



Reaction Condition

Base: Ph_3CLi
solvent: DME
room temp.

1. Add ketone to slight excess of base 28% 72%
2. Add base to ketone 94% 6%



1) Control of Regioselectivity

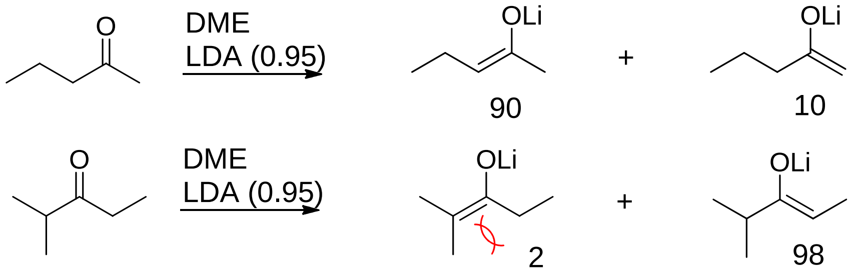
Kinetic Control

1. Product composition is determined by the relative rates of H^+ abstraction
2. Least hindered H^+ is removed
3. Hindered but strong base: LDA, Ph_3CLi
4. No proton sources: H_2O or O_2
5. Low temperature
6. Cation: covalently bonded to oxygen Li > Na > K

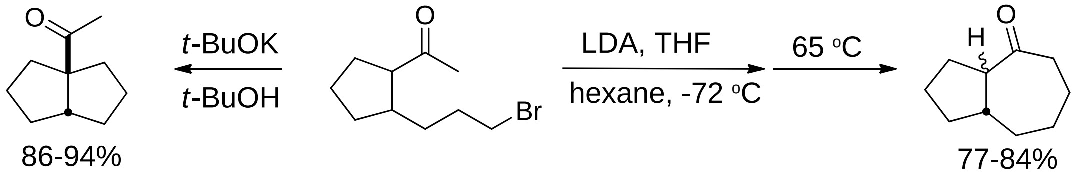
When Ph_3CK was used as a base in the above example the product ratio (28 : 72) changed to 55: 45.

Thermodynamic Control

1. Product distribution is based on their thermodynamic stability (equilibrium condition).
2. Most substituted (most stable) enolate preffered.

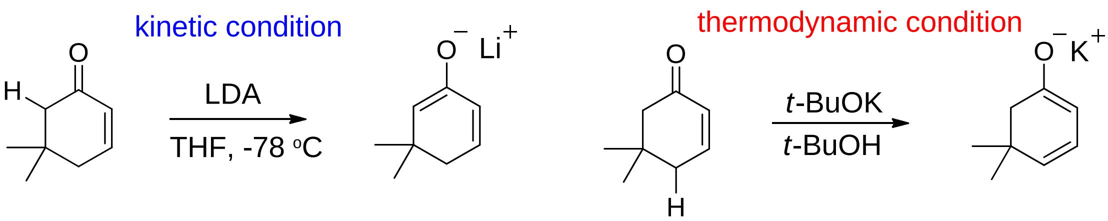


3. Small and weak bases: NaOH, NaOMe, NaH etc.
4. H^+ sources: excess ketone, protic solvent
5. High temperature
6. Ionic counter ion: K, Na

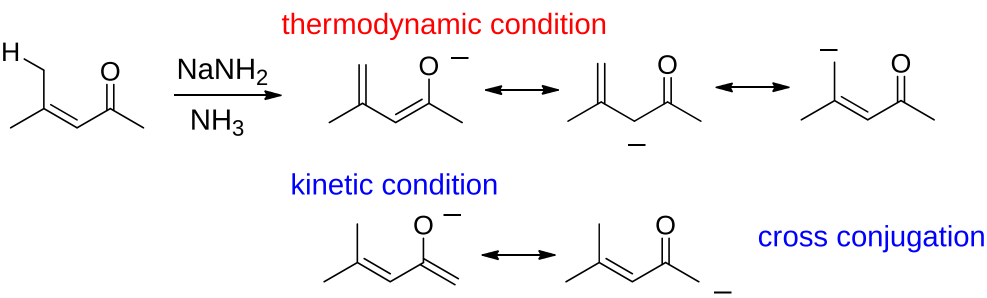


For Conjugate System

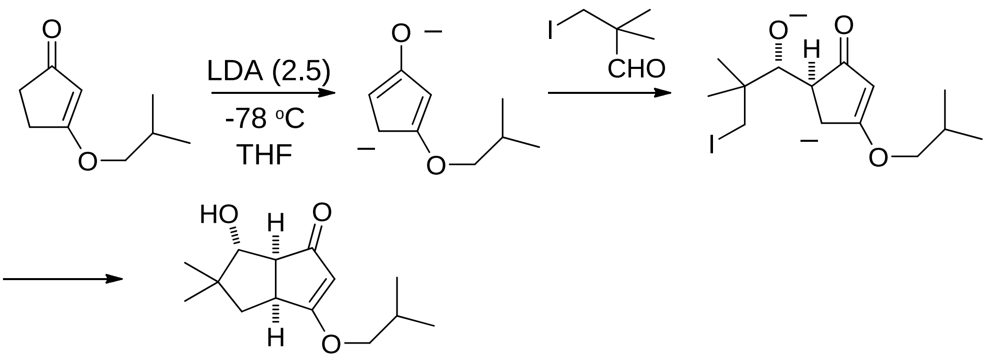
1.



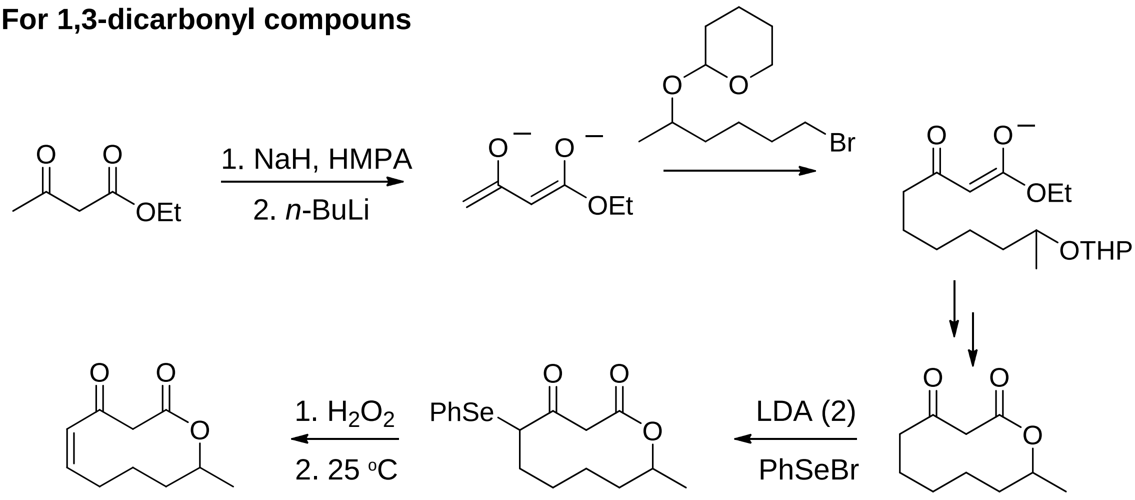
2.



3.

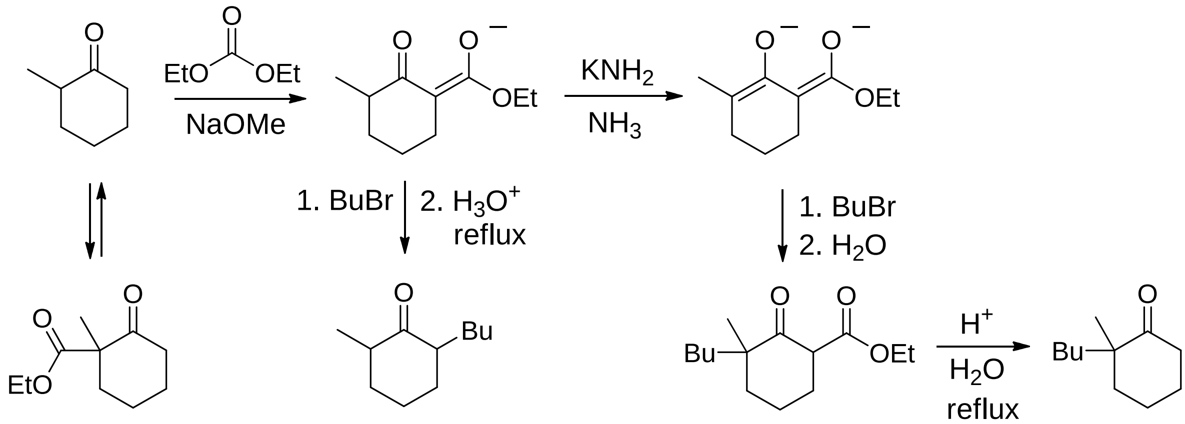


For 1,3-dicarbonyl compouns

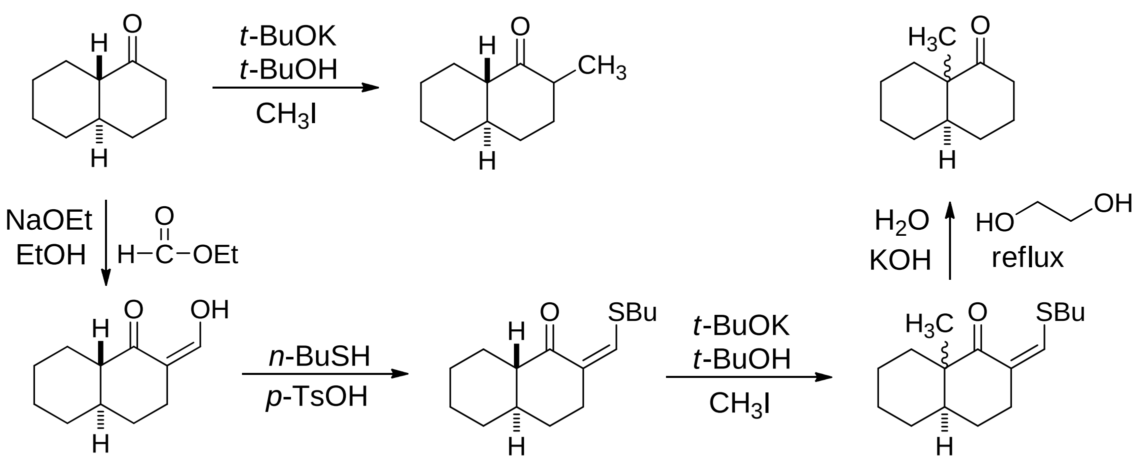


2) Regiospecific Alkylation of Carbonyl Compounds

1. Protection of active methylene site

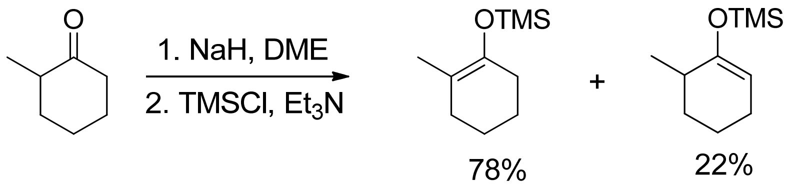


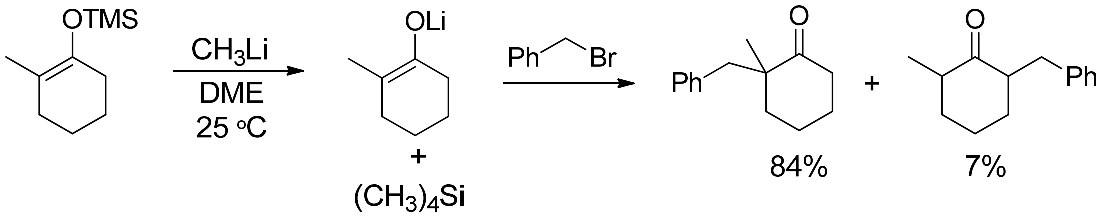
See Claisen Ester Condensation

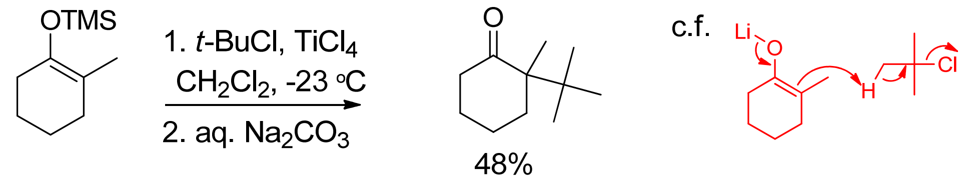


2) Regiospecific Alkylation (continued)

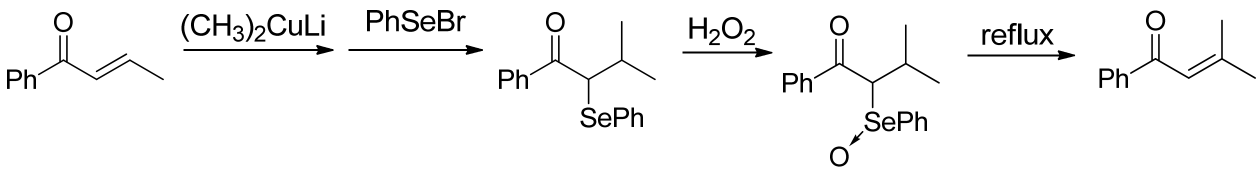
2. Silyl Enol Ether



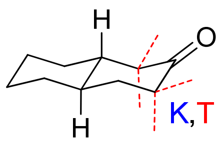


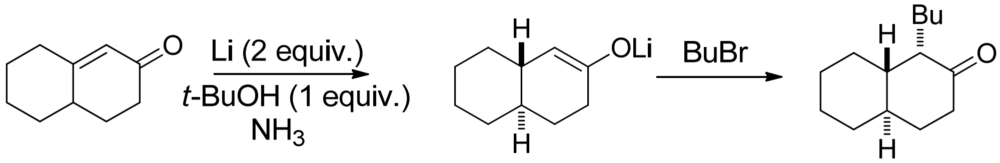


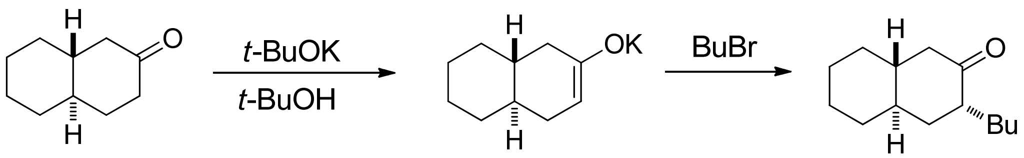
3. Conjugate Addition of Enones

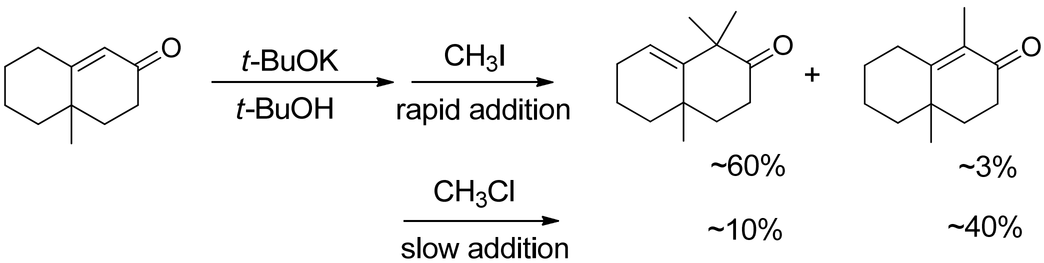


3) Regioselectivity of Decalone System





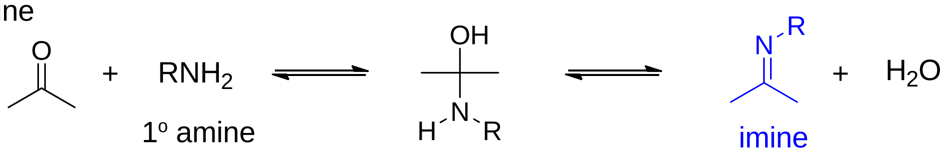




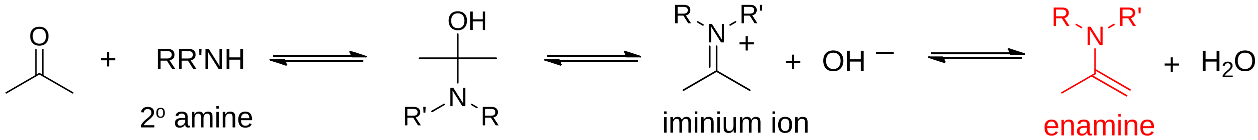
1.2 The Enamine and Related Reactions: Nitrogen Analogues of Enol and Enolate ion

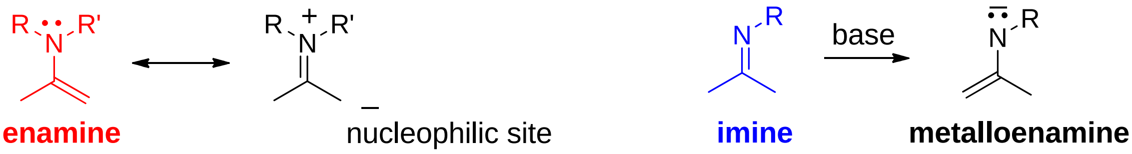
The major problems in enolate alkylation - (i) Aldol reaction; (ii) polyalkylation - can be overcome by the enamine alkylation.

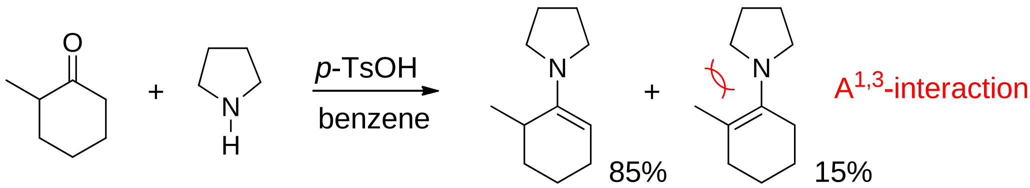
Imine



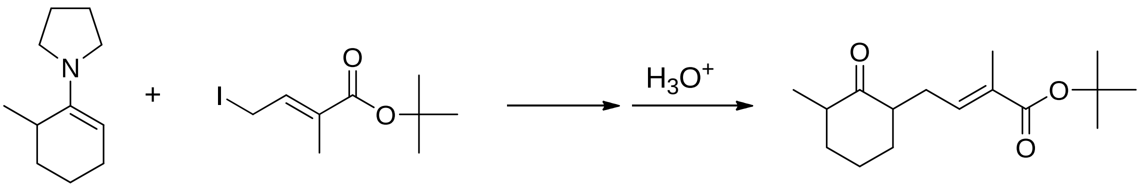
Enamine

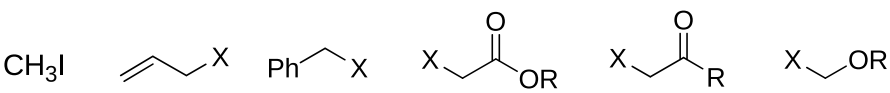




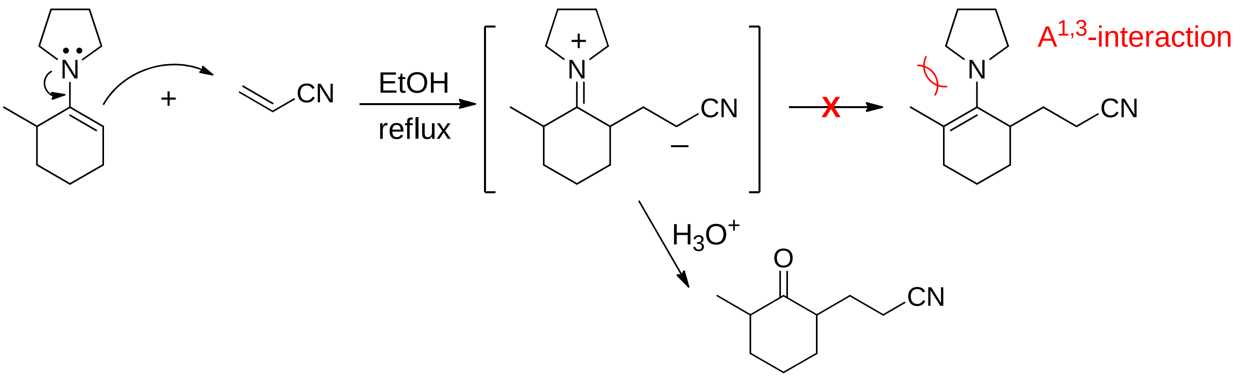


Use reactive electrophiles for alkylation

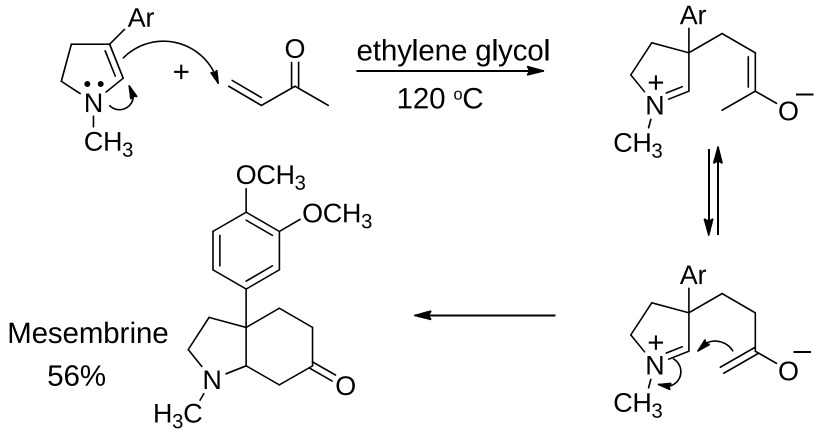




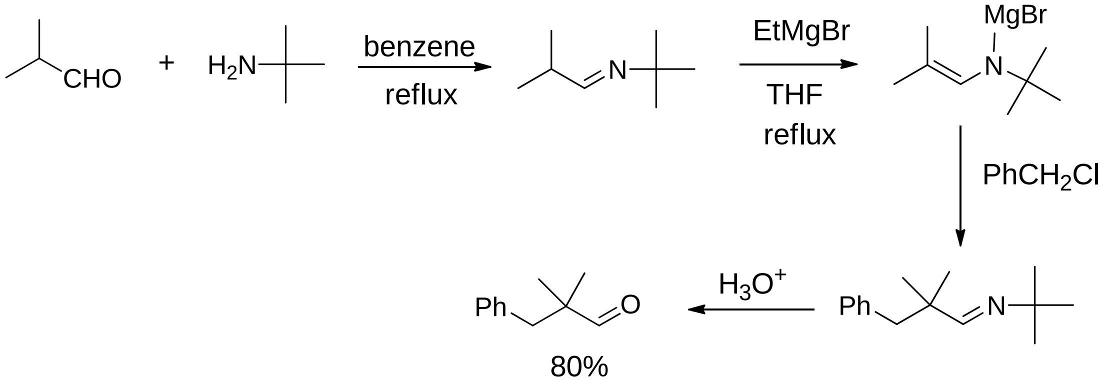
Conjugate addition / mono-alkylation



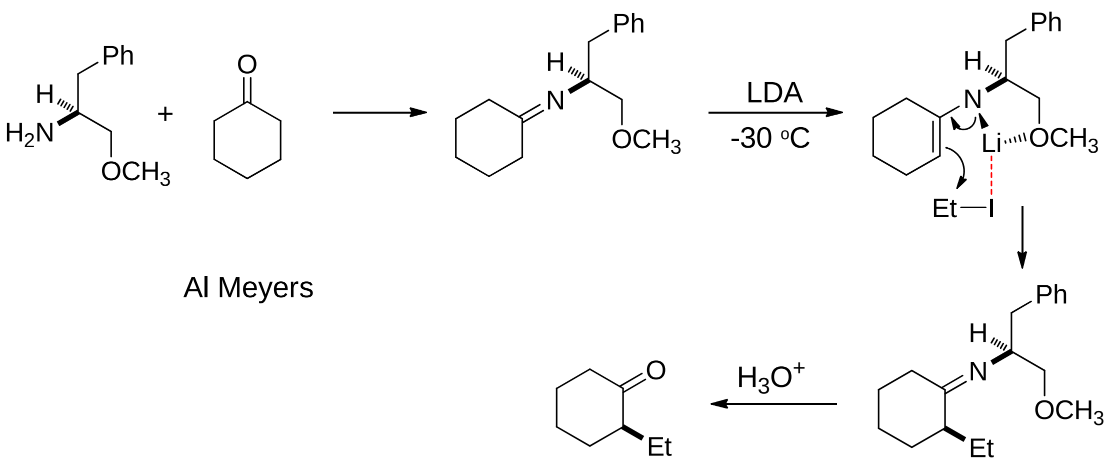
Enamine



Metalloenamines (imine anions)

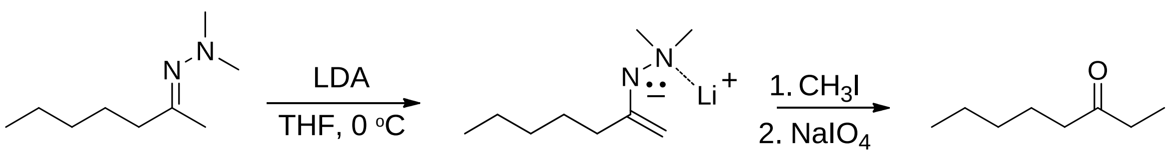


from **Chiral Amine**



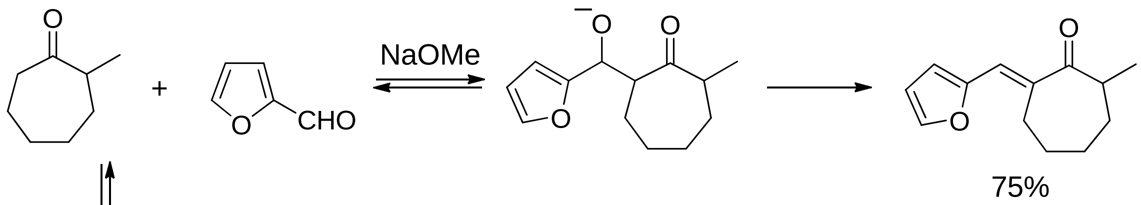
from **Hydrazine**

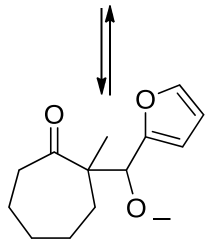
more stable and better stereoselectivity



1.3 Aldol reaction: acid or base-catalyzed self condensation of an aldehyde or a ketone

a. Mixed Aldol Condensation



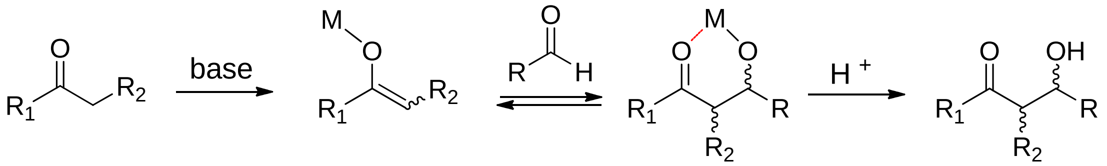


< **Claisen - Schmidt** Condensation >

mixed aldol condensation with aromatic aldehydes

b. DIrected Aldol Condensation

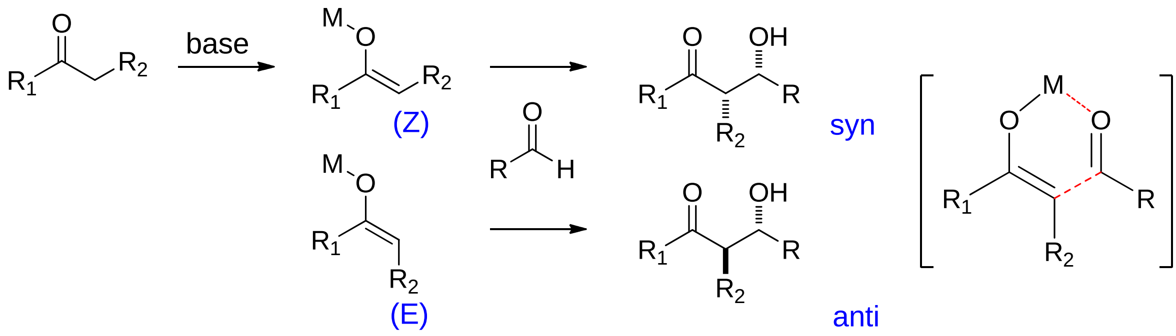
mixed aldol condensation of aliphatic aldehydes and ketones

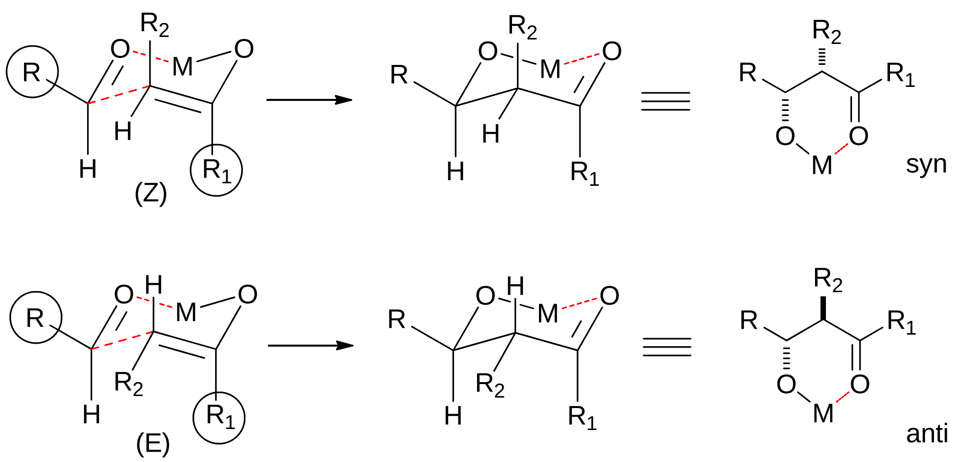


c. Control of Stereochemistry: Kinetic condition

i) Simple Diastereoselectivity

Six-membered ring transition state: Zimmerman / Traxler Transition State

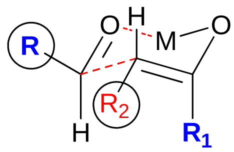




c. Control of Stereochemistry: Kinetic condition (continued)

i) Simple Diastereoselectivity

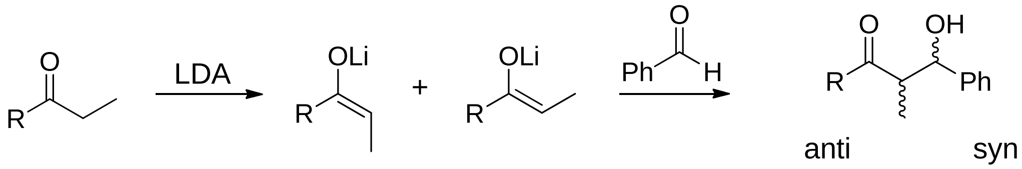
(Z) ⟶ syn, (E) ⟶ anti



(E)

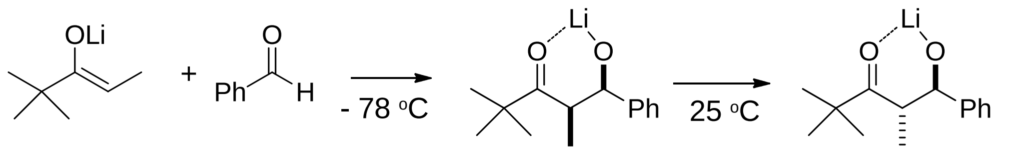
Best correlation

1. R_1, R = large group
2. M = Li, B ⟶ tight transition state
3. (Z) is more selective than (E)

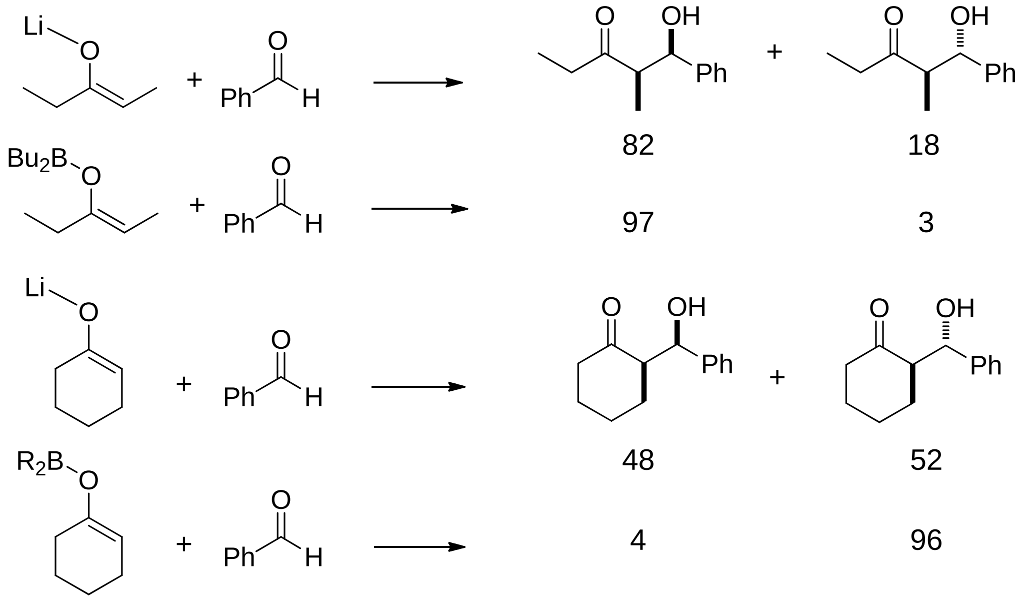


			anti	syn
R = Et	70	30	36	64
i-Pr	40	60	18	82
t-Bu	2	98	2	98

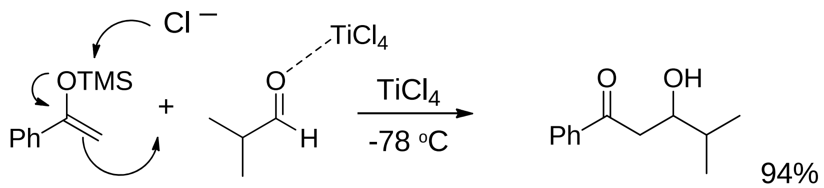
Under Equilibrium Condition (Thermodynamic Condition)



Boron enolates

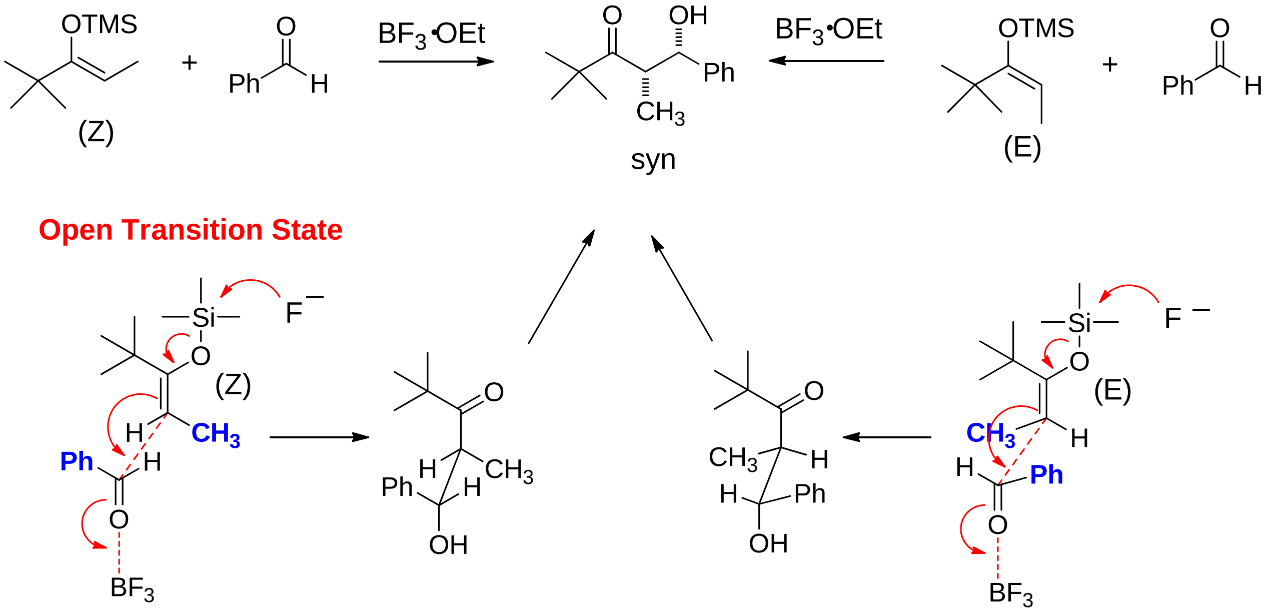


Aldol reaction with **Silyl Enol Ether: Open Transition State**

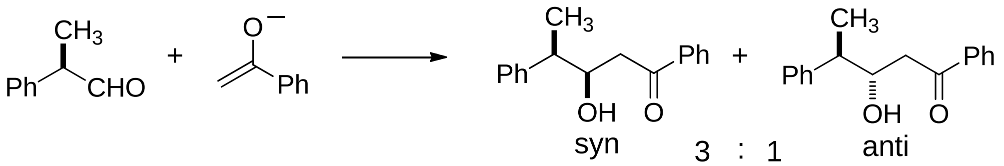


Aldol reaction with **Silyl Enol Ether** (continued)

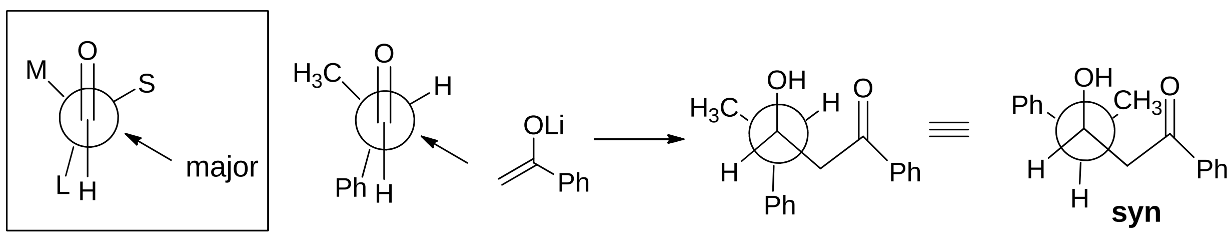
Stereochemistry



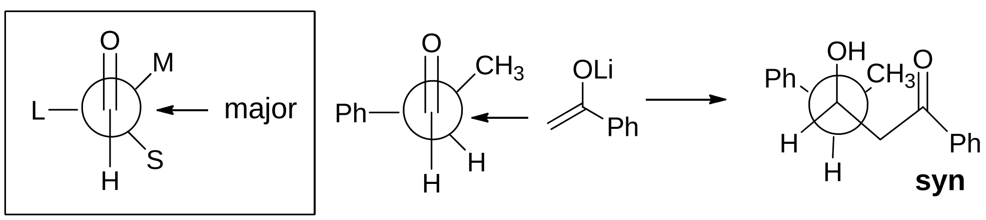
ii) Stereoselectivity between **achiral enolates** and **chiral aldehydes**



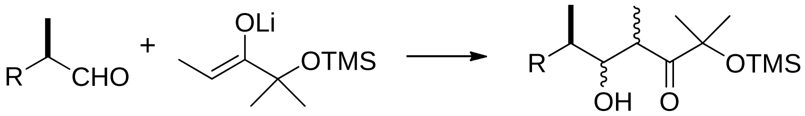
Cram's rule

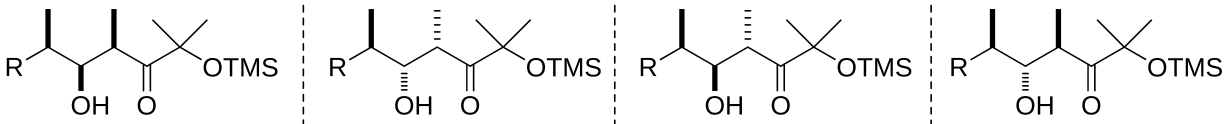


Felkin -Ahn

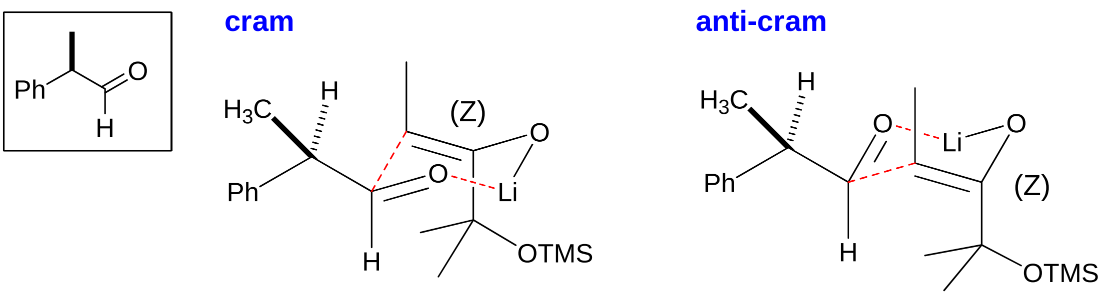


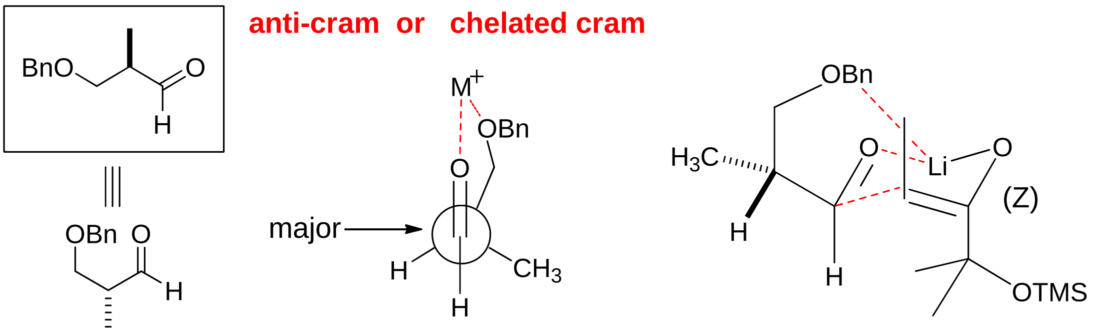
iii) Stereoselectivity between chiral aldehydes and prochiral enolates



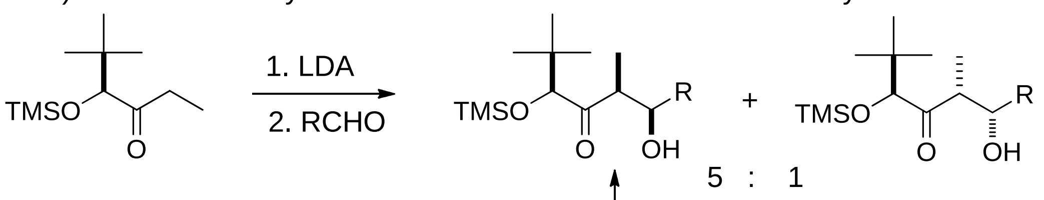


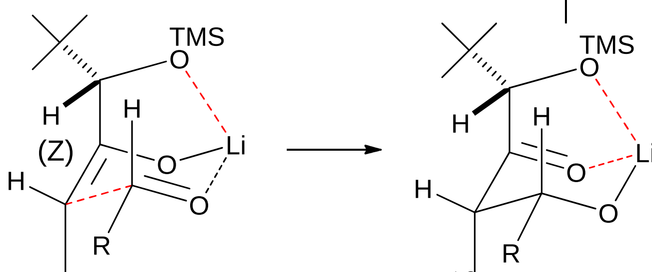
R	syn,syn	anti,syn	syn,anti	anti,anti
R = Ph	81	19	0	0
(alkenyl)	94	6	0	0
OBn	33	67	0	0
OTMS	21	79	0	0



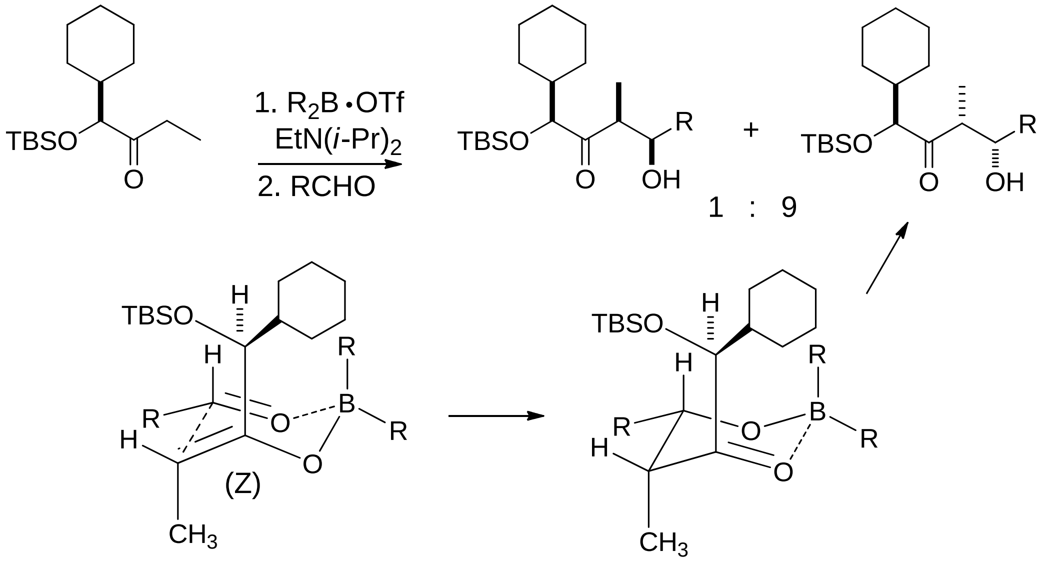


iv) Stereoselectivity between chiral enolates and achiral aldehydes

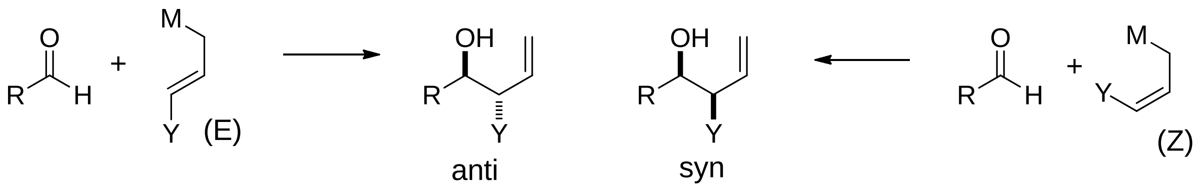


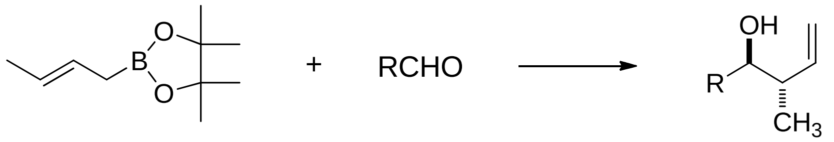


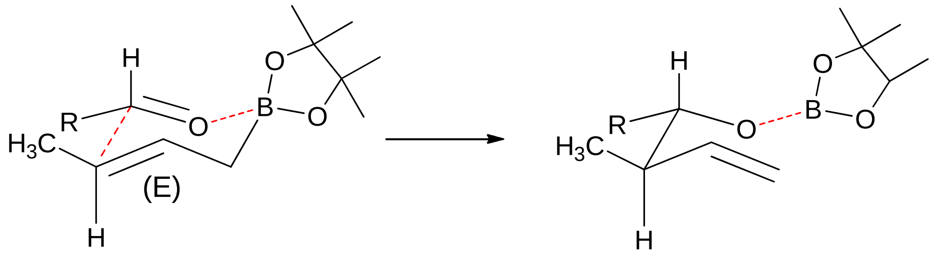
iv) Stereoselectivity between chiral enolates and achiral aldehydes (continued)

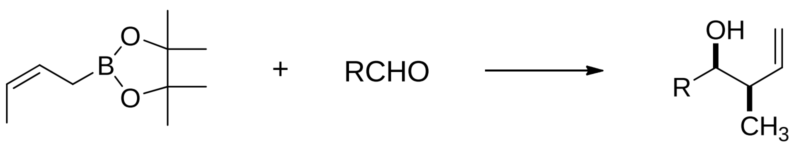


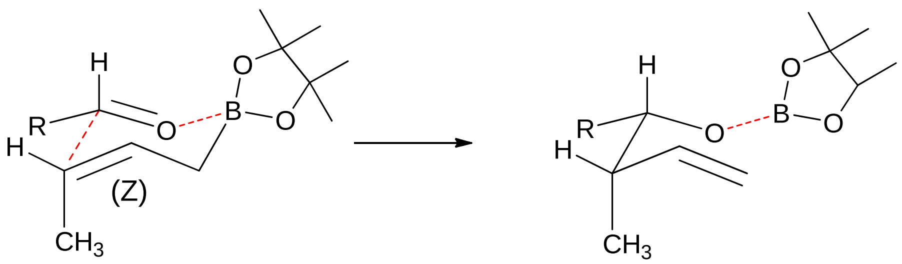
d. Allylmetal compound with aldehydes





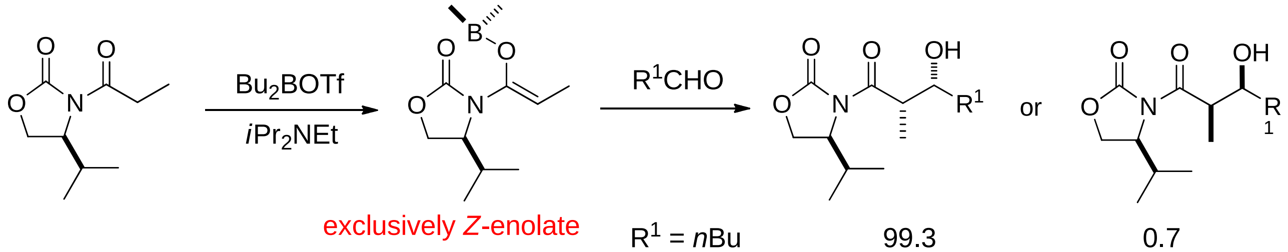






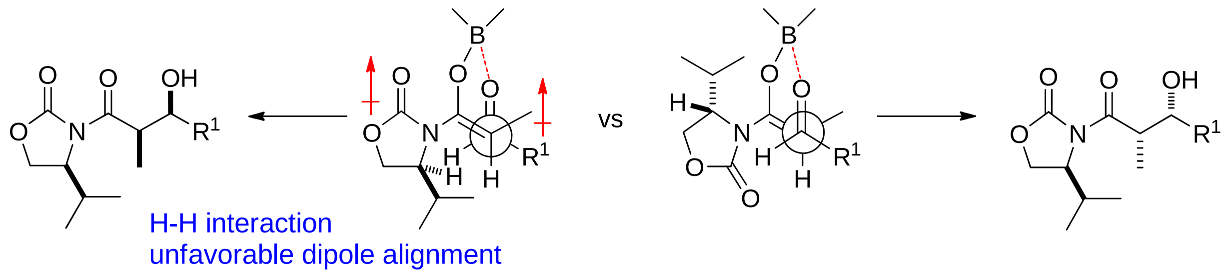
e. Evans' chiral *N*-acyl oxazolidinones

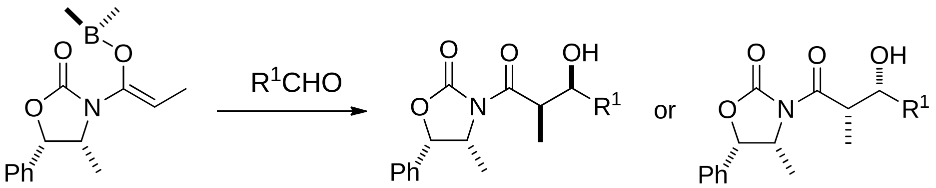
1) Boron enolate



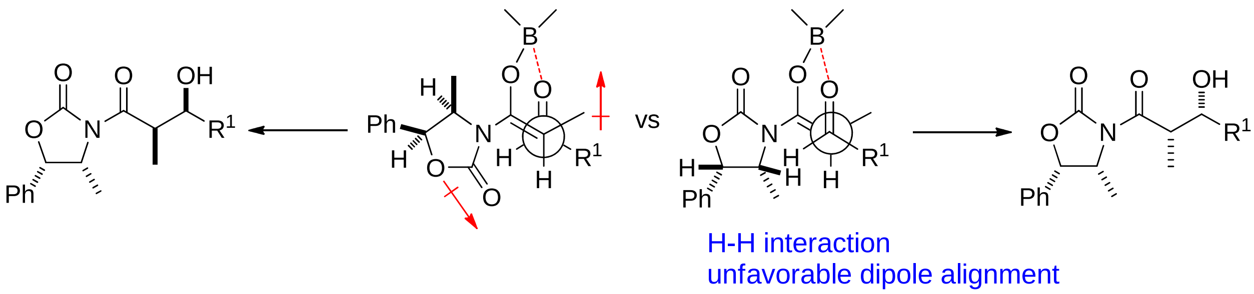
J. Am. Chem. Soc. 1981, 103, 2876
J. Am. Chem. Soc. 1981, 103, 3099

R^1 = *n*Bu	99.3	0.7
R^1 = *i*Pr	99.8	0.2
R^1 = Ph	>99.8	<0.2



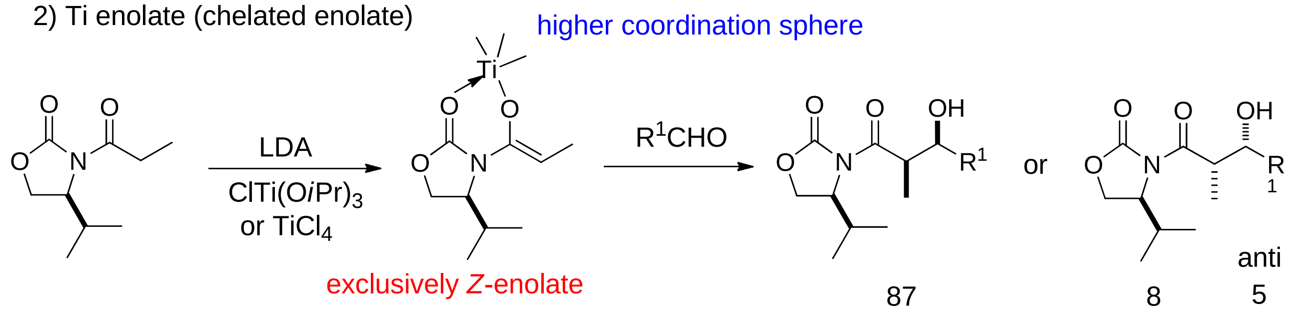


R^1 = *n*Bu	>99.8	<0.2
R^1 = *i*Pr	>99.8	<0.2
R^1 = Ph	>99.8	<0.2

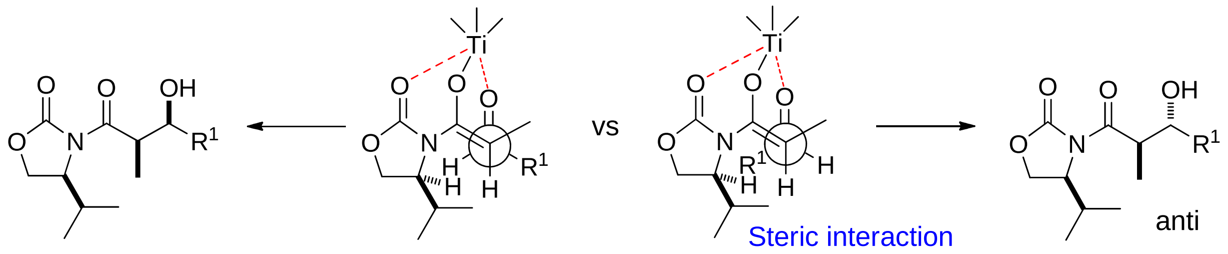


e. Evans' chiral *N*-acyl oxazolidinones

2) Ti enolate (chelated enolate)

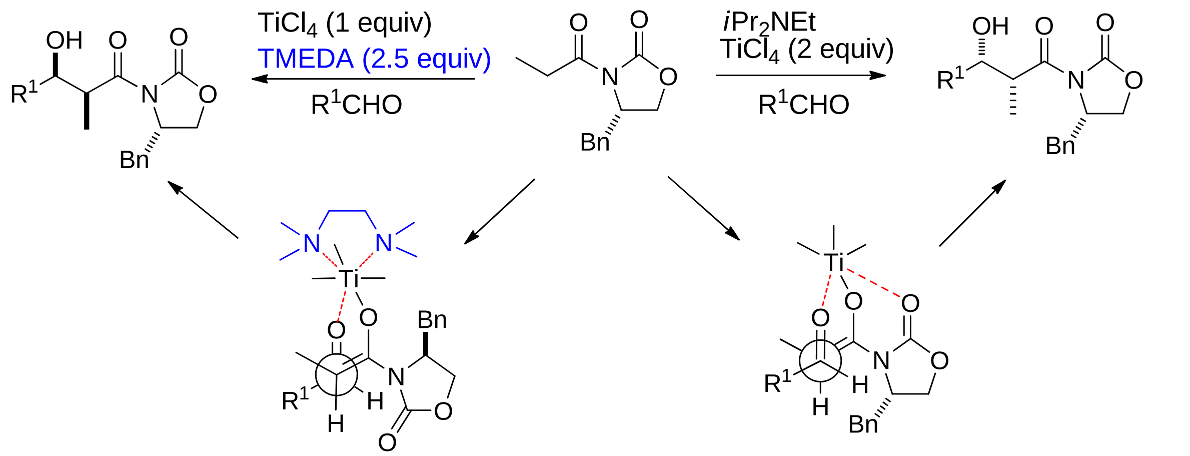


J. Am. Chem. Soc. **1989**, *111*, 5722
J. Am. Chem. Soc. **1991**, *113*, 1047



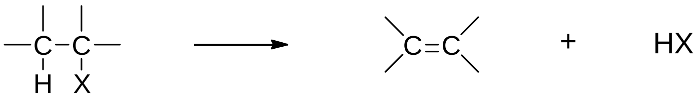
3) Chelated and non-chelated Ti enolates

Crimmins, *J. Am. Chem. Soc.* **1997**, *119*, 7883



Chapter 2. Formation of Carbon-Carbon Double Bonds

2.1 β-Elimination reaction

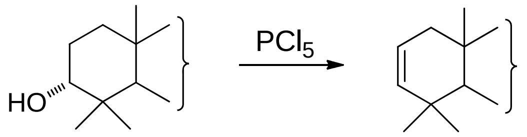


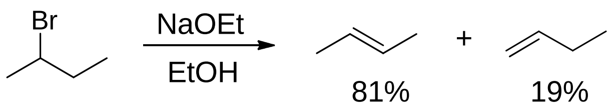
X = OH, OCOR, halogen, OSO_2Ar, $\overset{+}{N}R_3$, $\overset{+}{S}R_2$ E1 or E2 mechanism

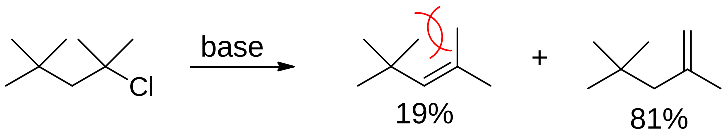
Regioselectivity

Saytzeff rule: more highly substituted (stable) alkene

E1 elimination, base induced elimination of alkyl halides and aryl sulfonates

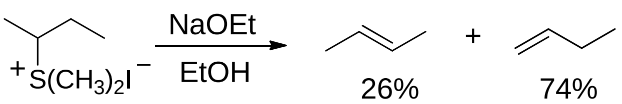


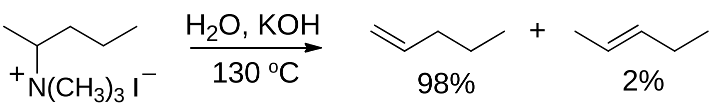




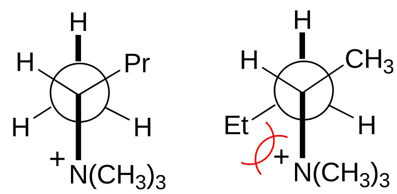
Hofmann rule: less substituted alkene

base induced elimination of quaternary ammonium salts or sulfonium salts



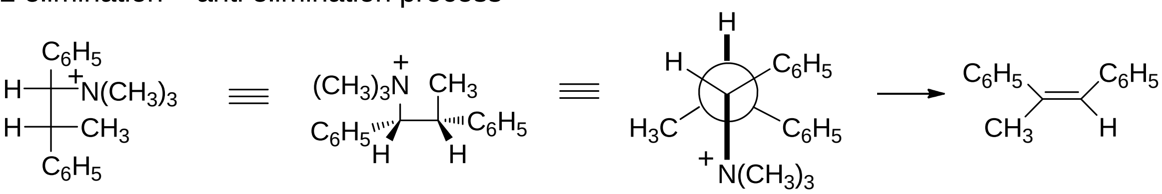


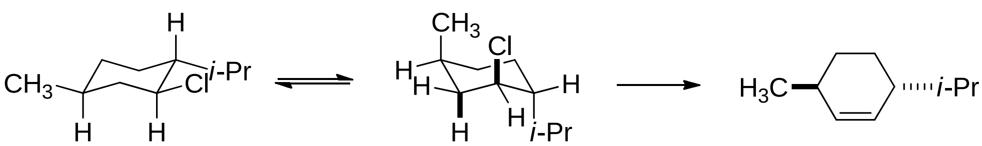
early transition state model

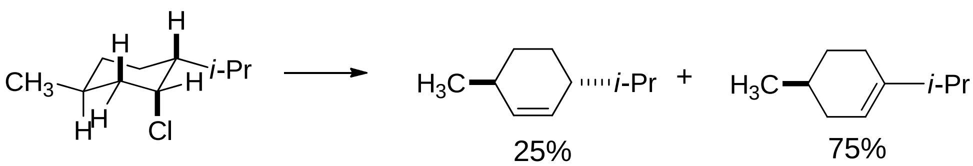


Stereoselectivity

E2 elimination = anti elimination process

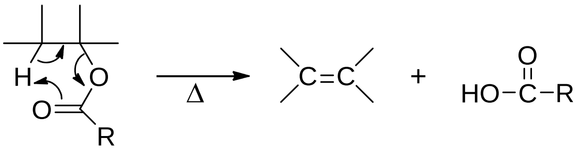




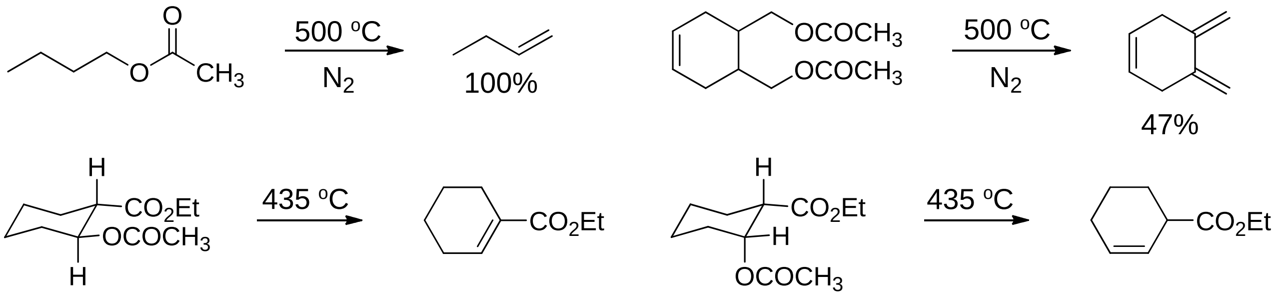


2.2 Pyrolytic **syn** eliminations "concerted cyclic transition state"

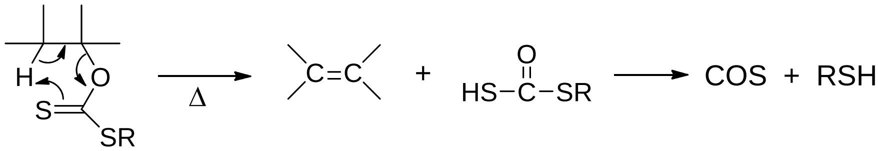
a. carboxylic esters



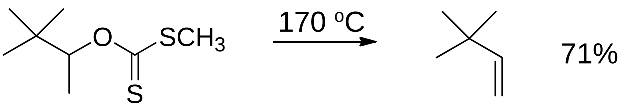
[examples]



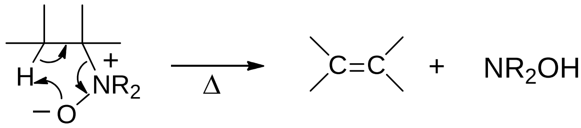
b. xanthate esters - Chugaev reaction



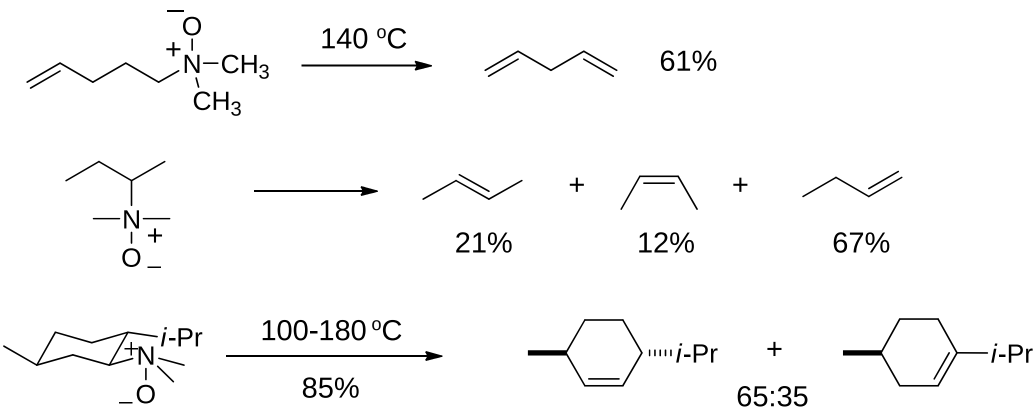
[examples]



c. ammonium oxides - Cope reaction

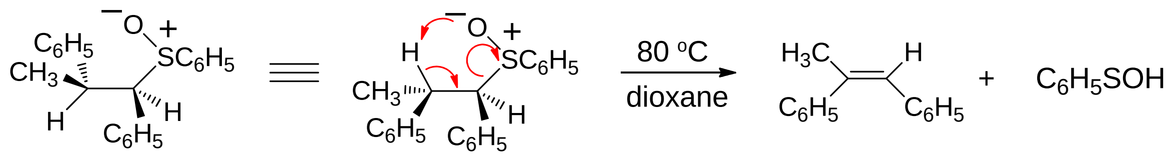


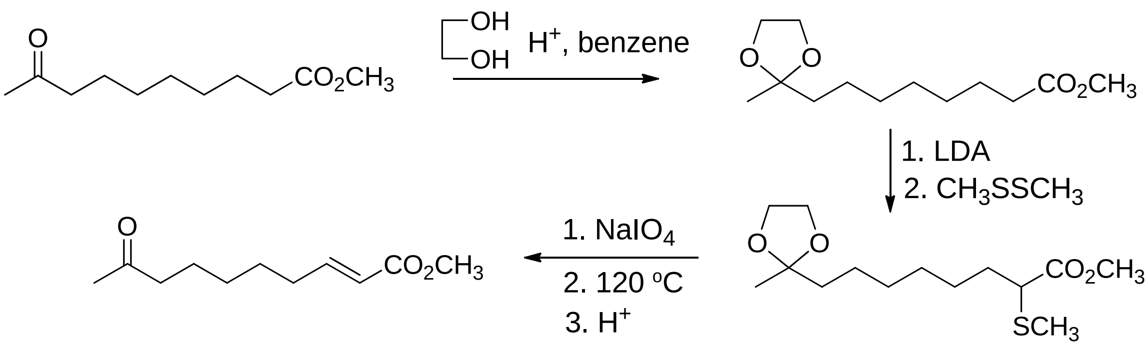
[examples]



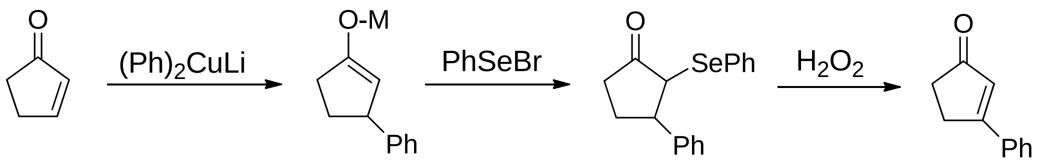
2.2 Pyrolytic **syn** eliminations (continued)

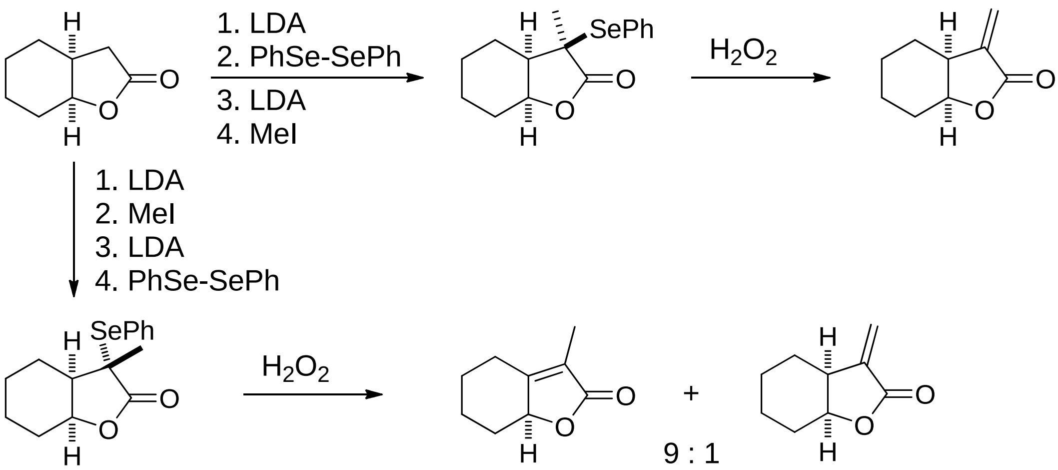
d. Sulfoxides (concerted cyclic pathway)



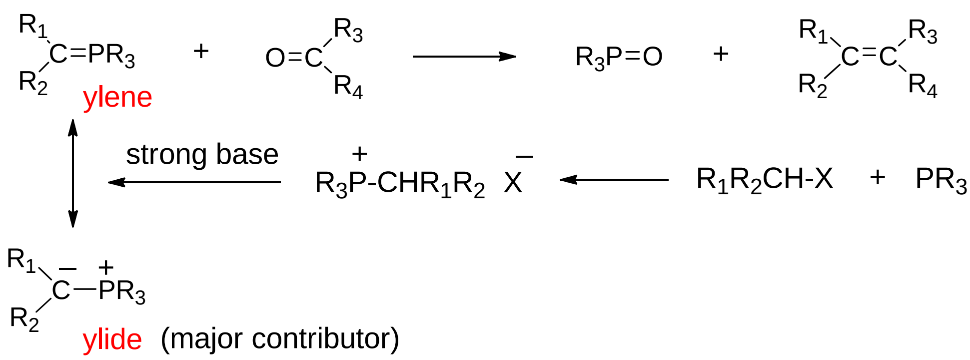


e. Selenoxides: milder conditions (at room temperature or below)

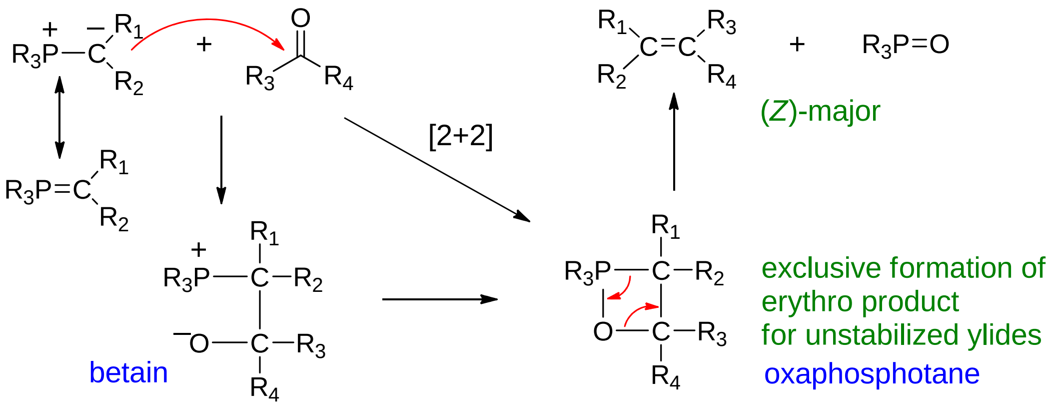




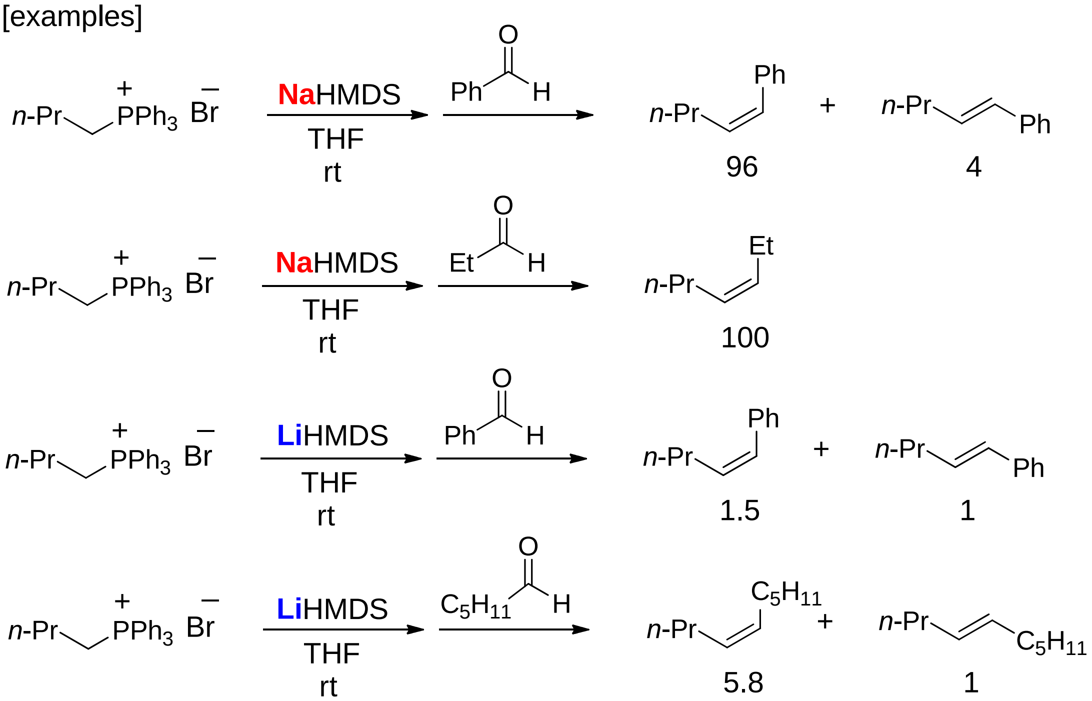
2.3 The Wittig and related reactions



a. The **mechanism** of Wittig reaction

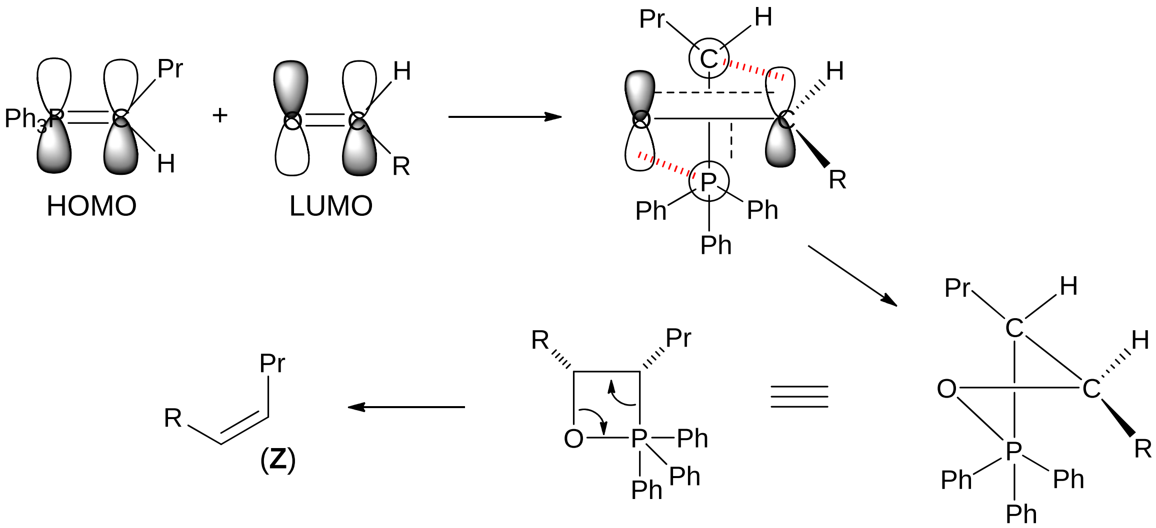


[examples]



Stereoselectivity

Early Transition State, Steric Effect ⟶ (**Z**)-double bonds (major)



Best corelation for **(*Z*)-selectivity**

1. "**Salt-free** " condition

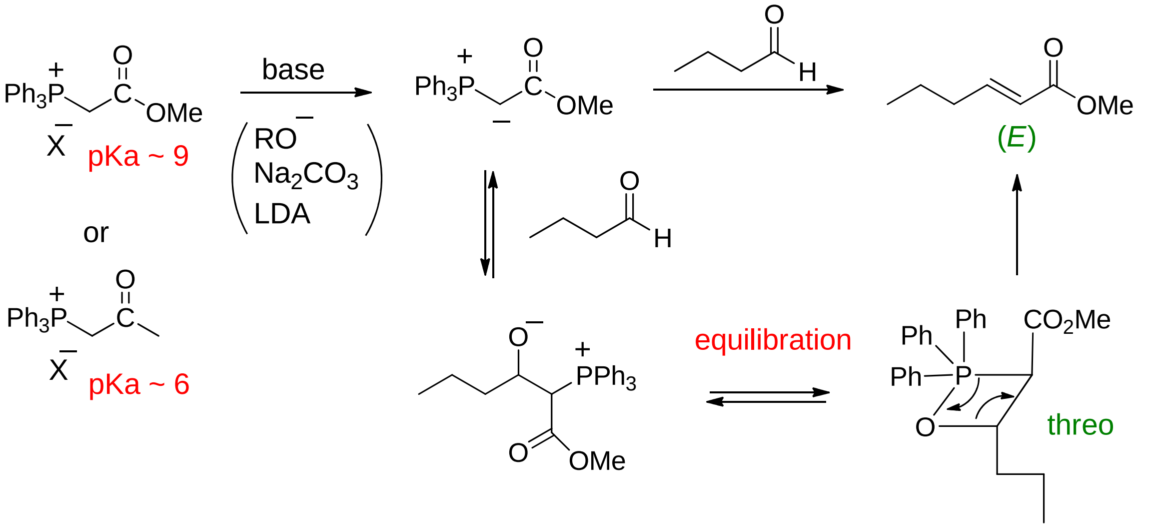
   K, Na as a counter metal ion

   Li-X forms a chelated complex with the reaction intermediate

2. Dipolar aprotic solvents

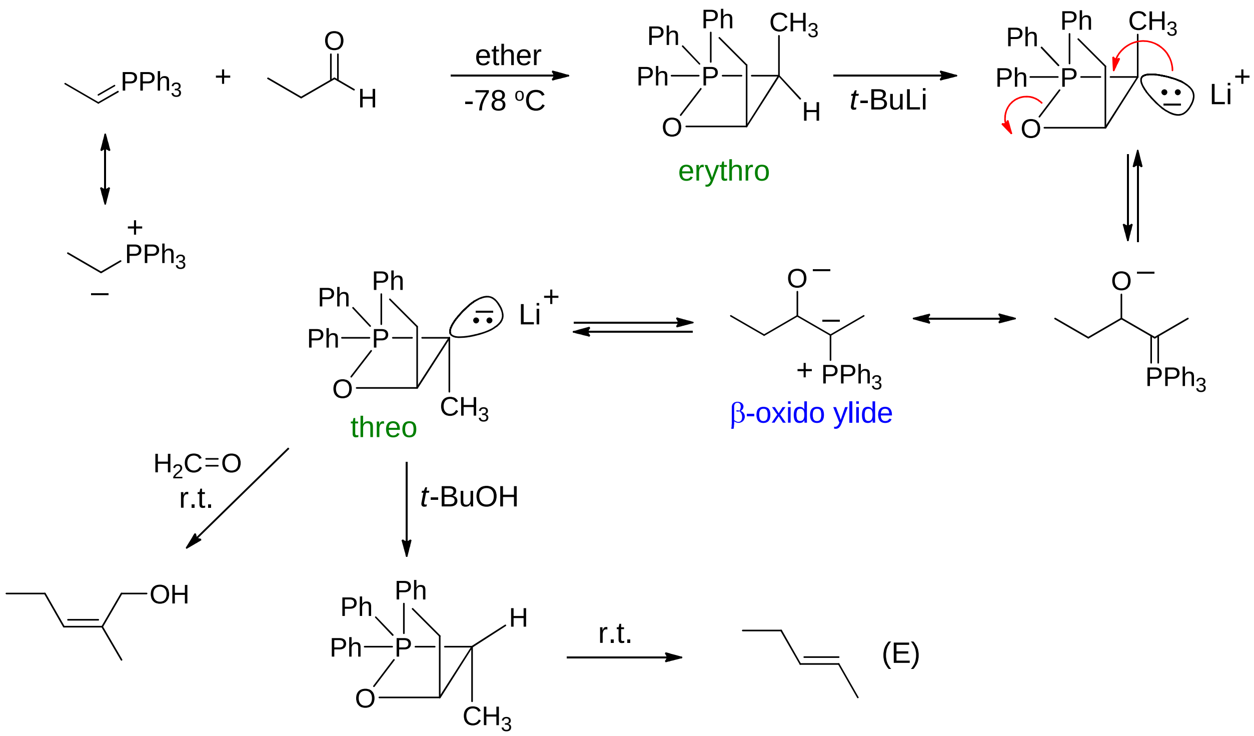
   THF, DMSO, DMF

b. Wittig reaction with **stabilized ylides** ⟶ (*E*)-double bonds (major)



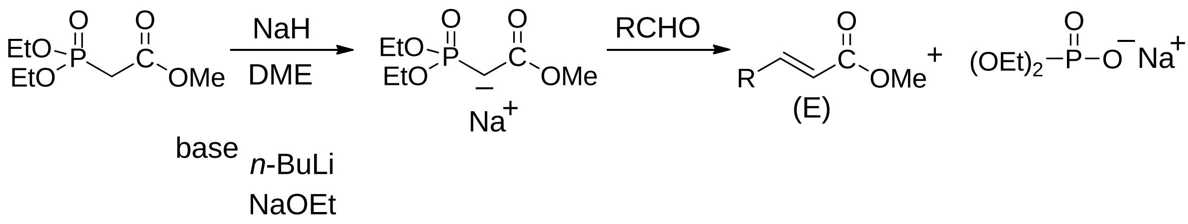
c. **Schlosser Modification** **nonstabilized ylides** ⟶ **(*E*)-alkene**

nonstabilized ylides ⟶	(*Z*)-alkene
stabilized ylides ⟶	(*E*)-alkene



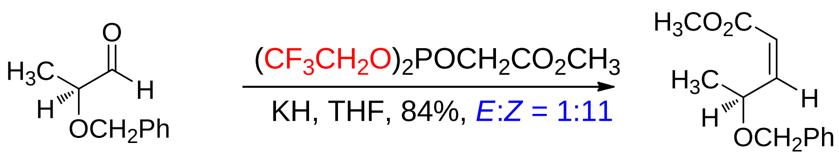
d. Horner - Wadsworth - Emmons Modification

To increase the nucleophilicity of the stabilized ylide: **phosphonate carbanion** is used, which reacts with aldehydes as well as ketones

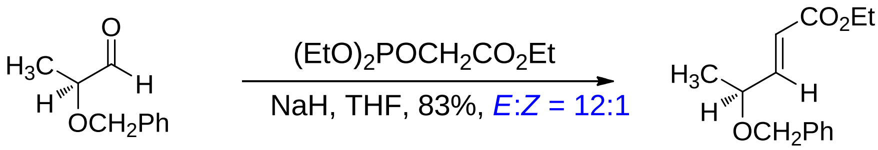


Z-selective HWE reaction

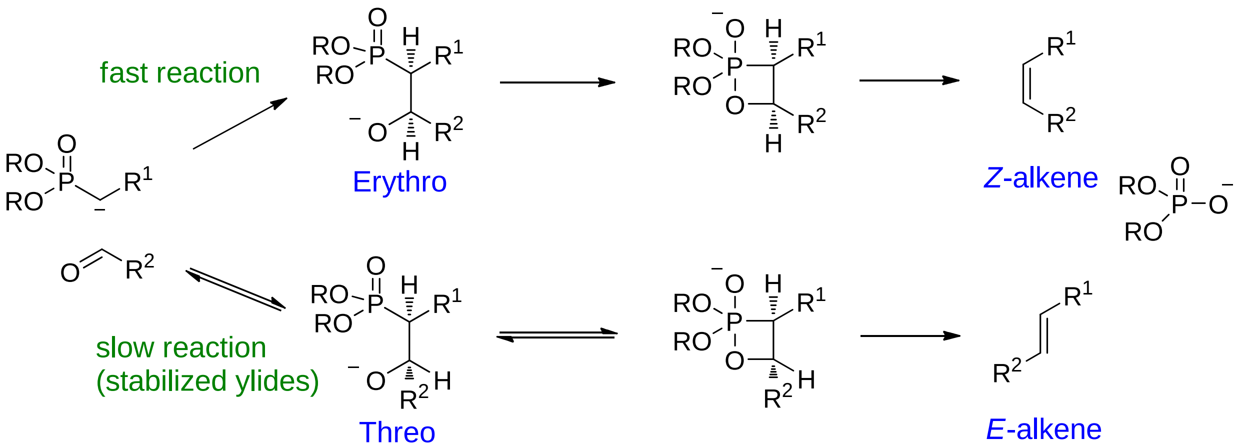
1. Still-Gennari modification: *TL* **1983**, *24*, 4405



c.f.

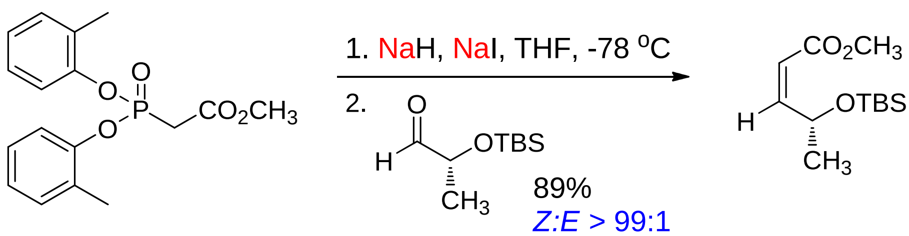


[Mechanism and Origin of Stereoselectivity]

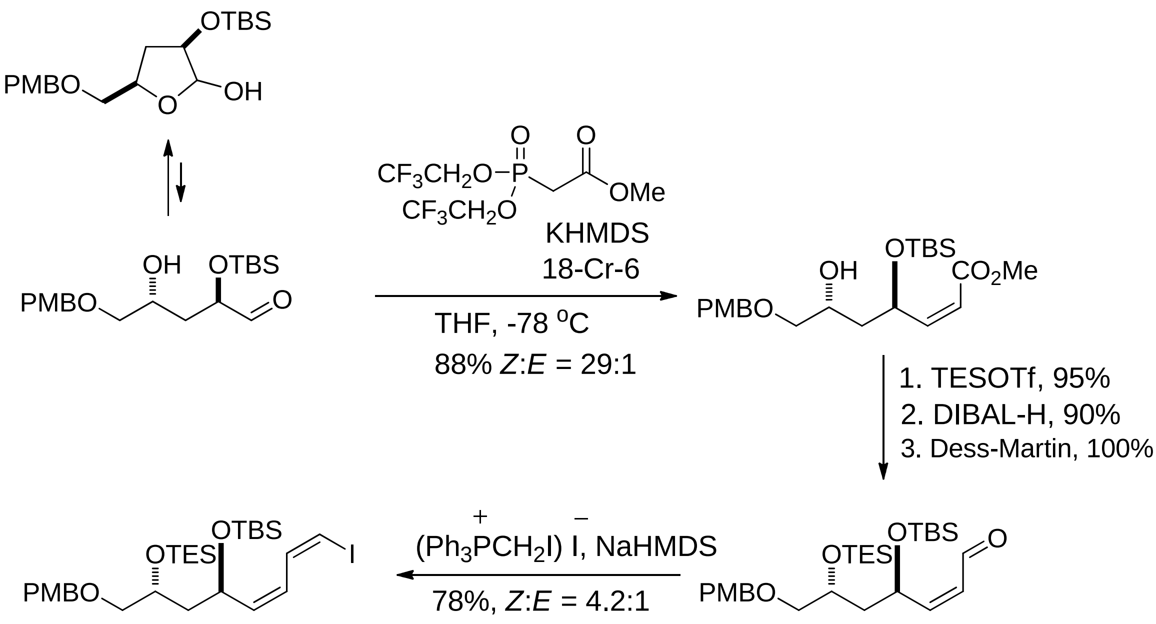


Large R or R^1 groups favor *E* alkene formation.

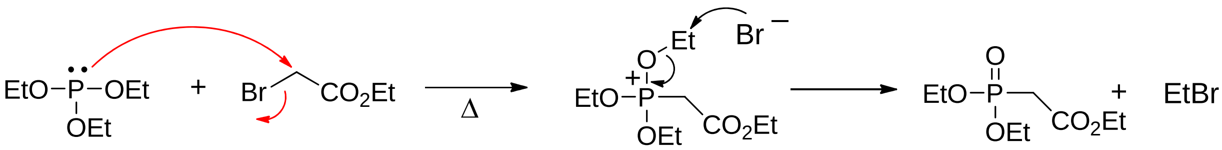
2. Ando method: *TL* **1995**, *36*, 4105; *JOC* **1997**, *62*, 1934.



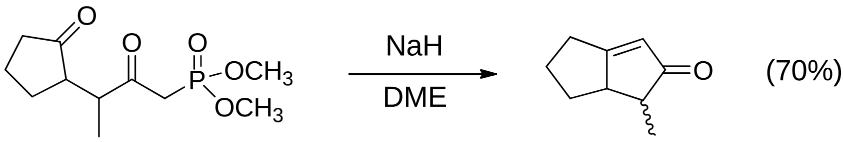
D. L. Boger et. al. *J. Am. Soc. Chem.* **2001**, *123*, 4161.



preparation of phosphonate

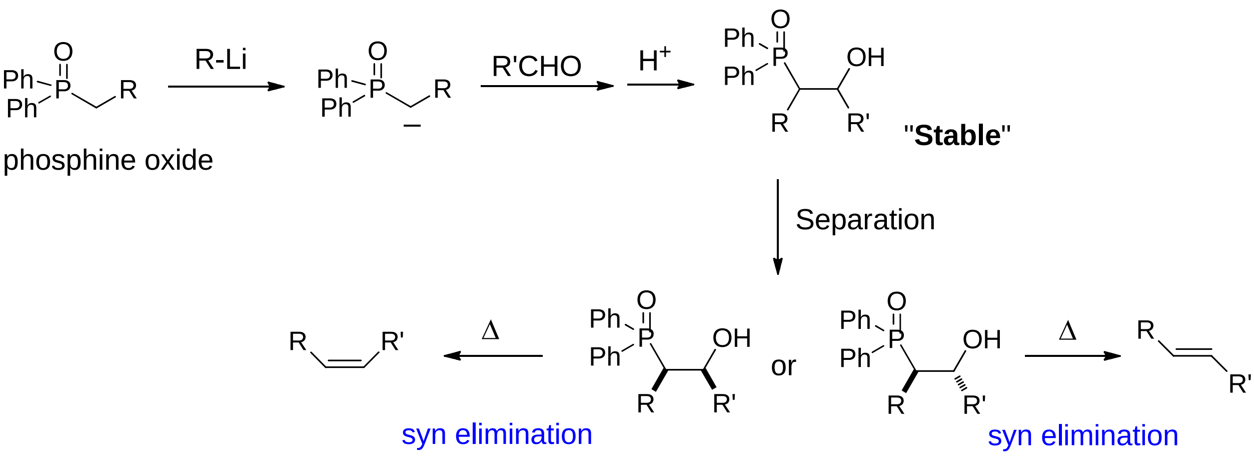


Arbuzov Reaction

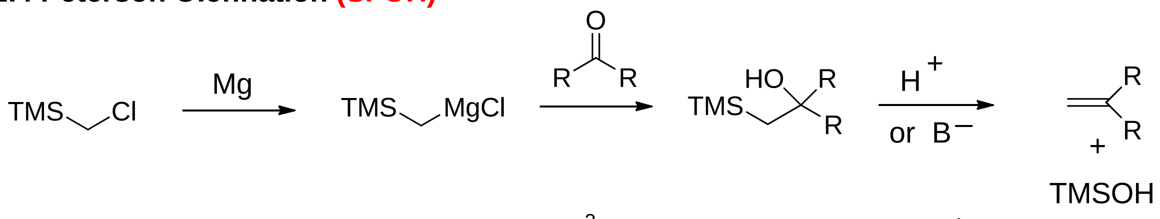


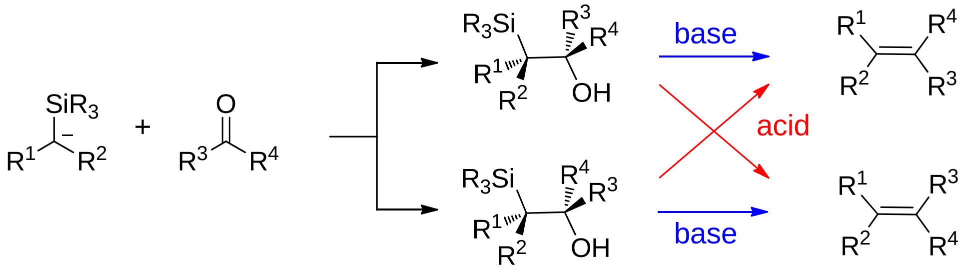
e. Horner - Wittig Reaction

Phosphine oxide carbanion

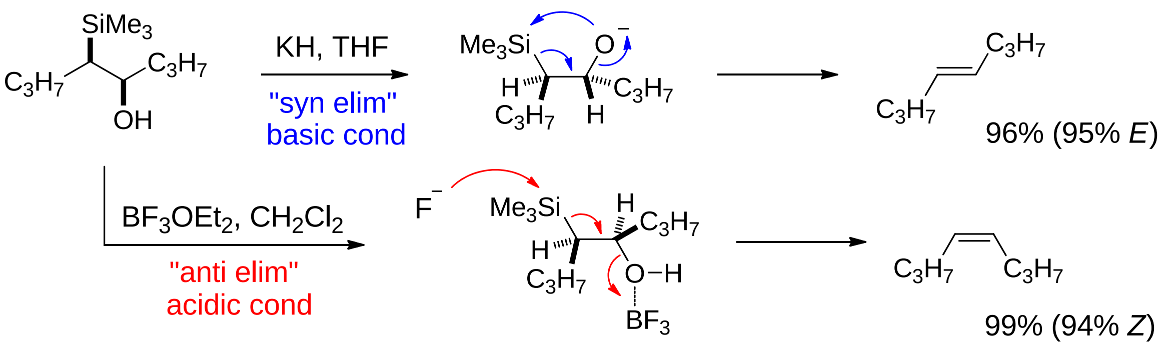


2.4 Peterson Olefination (Si-OH)

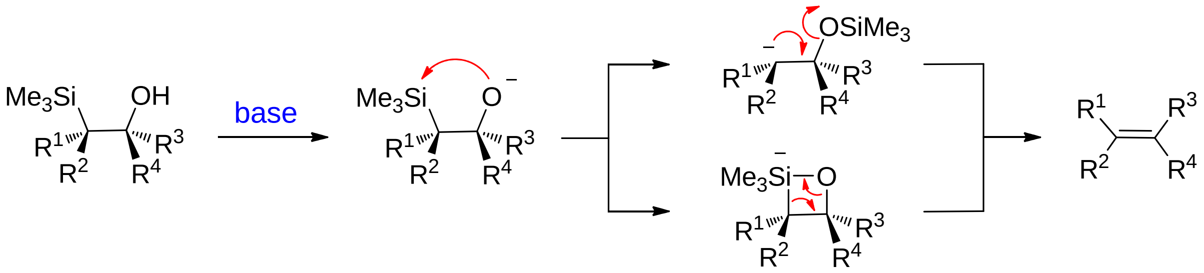




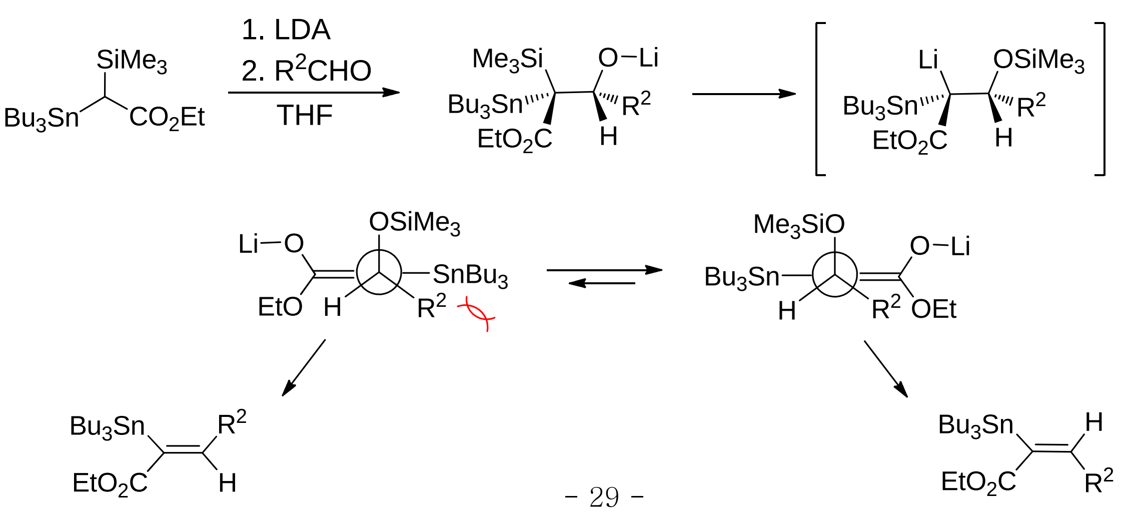
- The addition reaction is generally not stereoselective.
- The elimination is highly stereoselective.



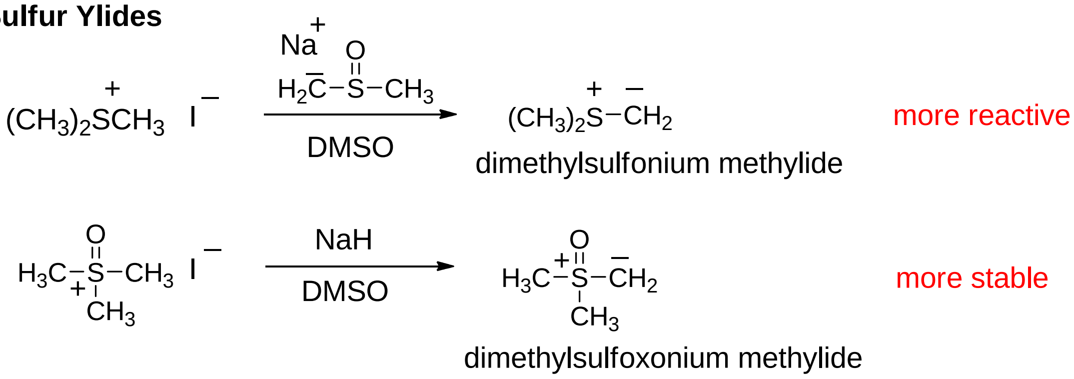
Elimination under basic condition: stepwise vs. concerted mechanism

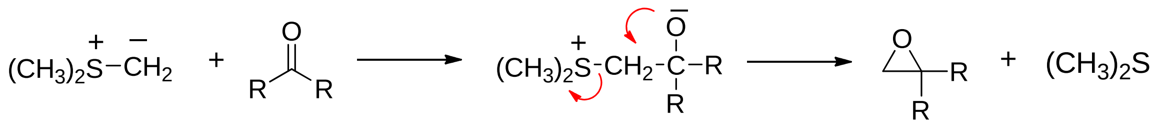


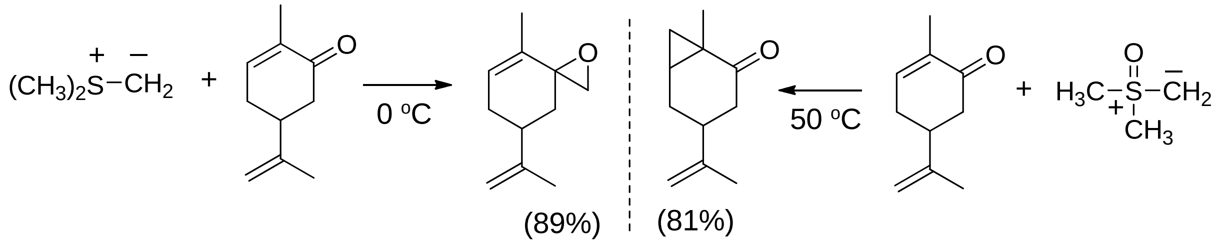
Stepwise mechanism for α-stabilized α-silylcarbanion

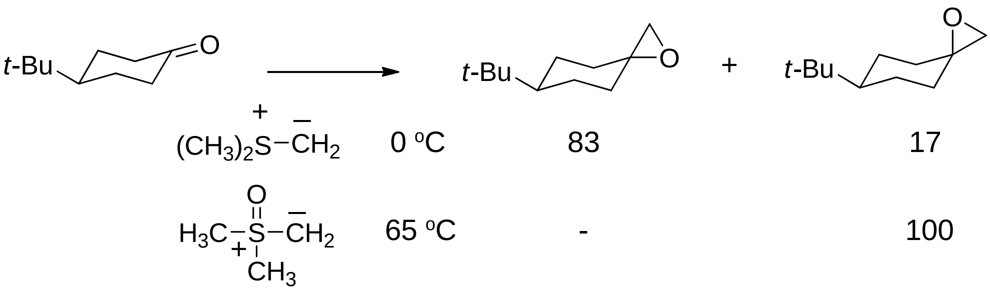


2.5 Sulfur Ylides

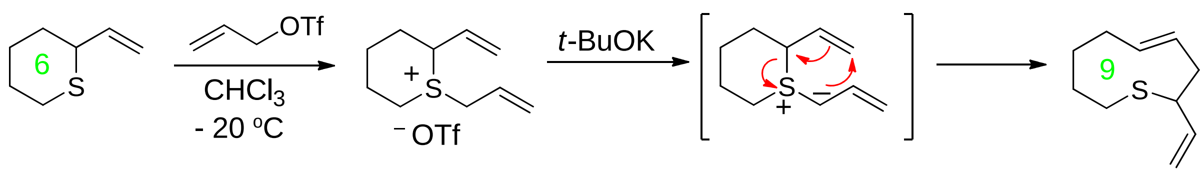


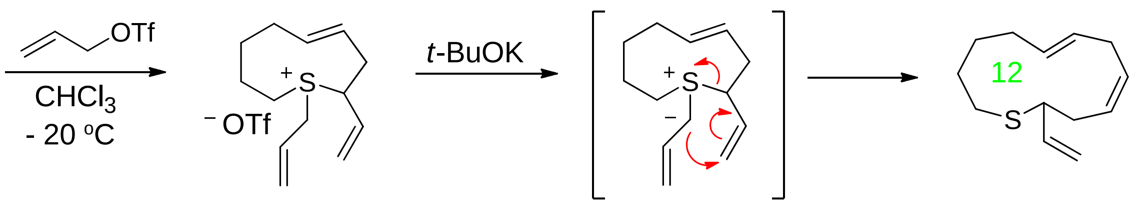






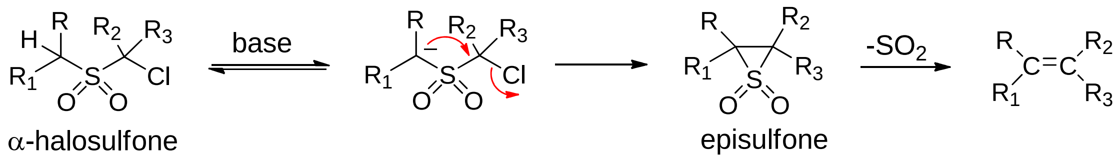
[2.3]-Wittig rearrangement - Ring expansion



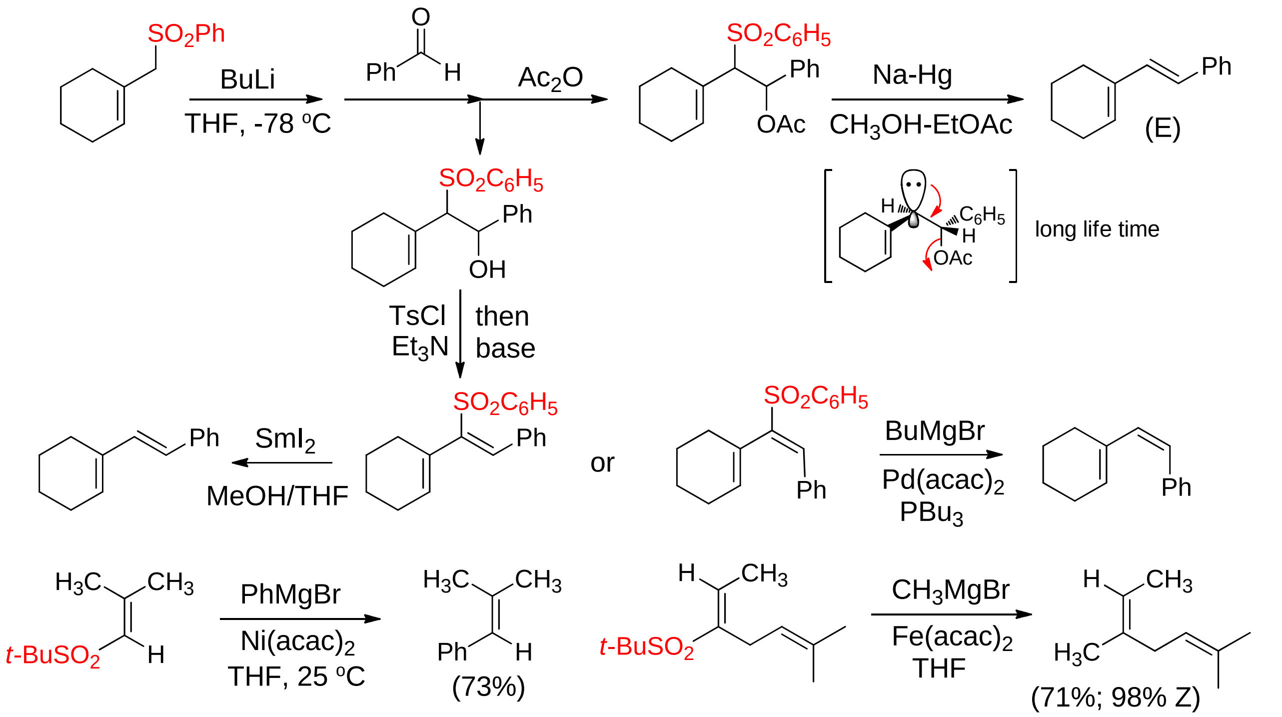


2.6 Alkenes from sulfones

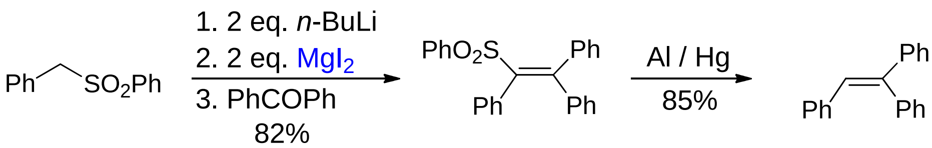
a. Ramberg-Backlund reaction



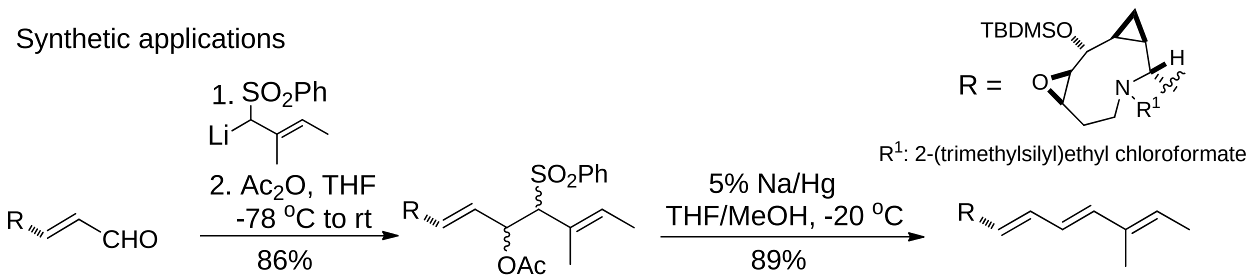
b. Julia olefination

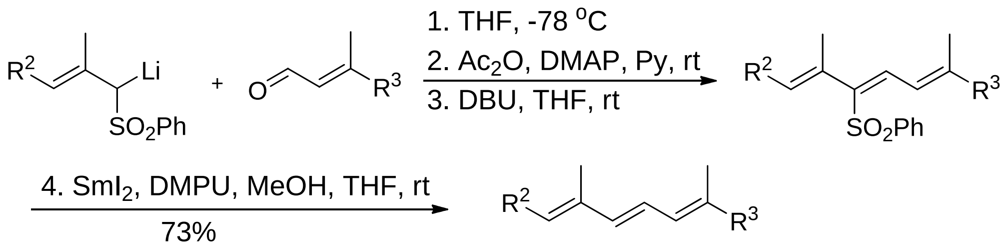


The first report on the sulfone-mediated olefination



Synthetic applications

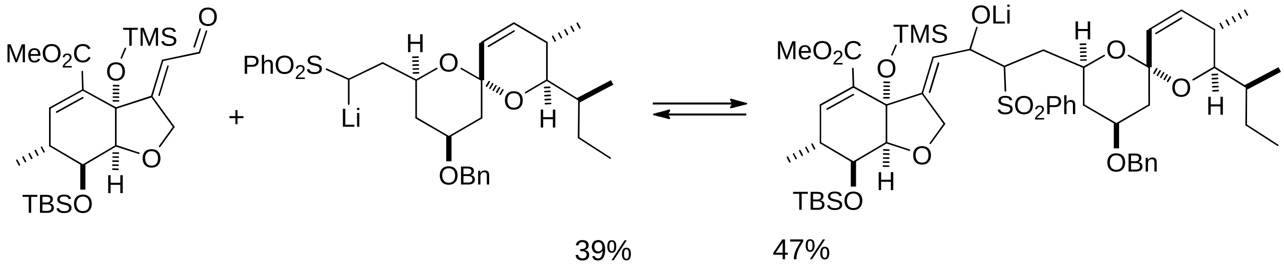


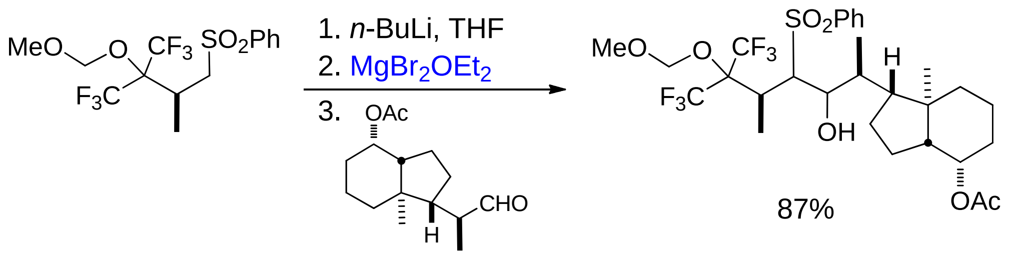


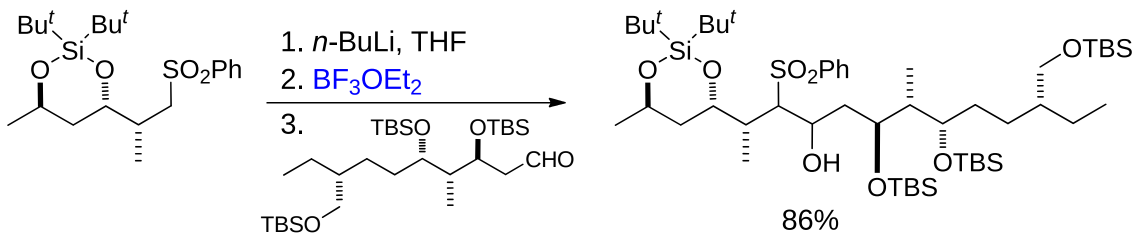
• Sulfone-mediated addition reaction

Different counter metal ions can shift unfavorable equilibrium toward the addition product

Replace lithium with magnesium or use BF_3OEt_2

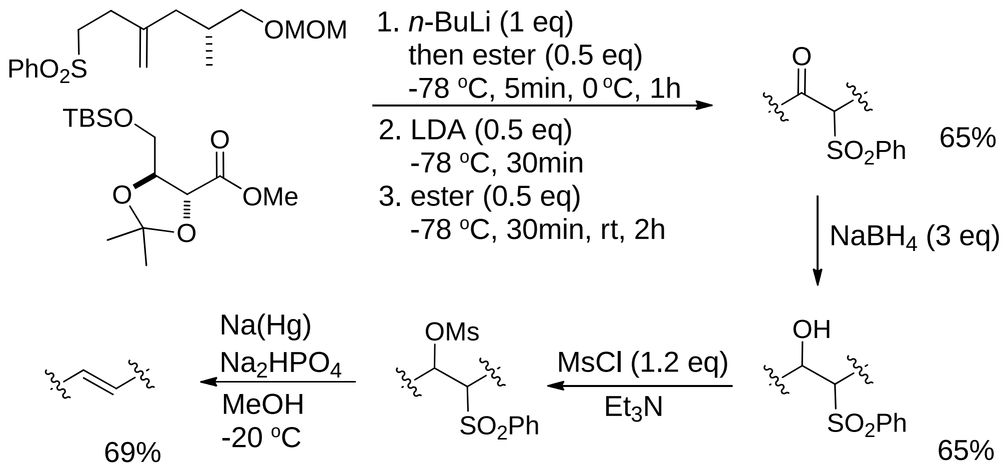






Trapping with Ac_2O, BzCl, MsCl or TMSCl can also shift unfavorable equilibrium toward the addition product

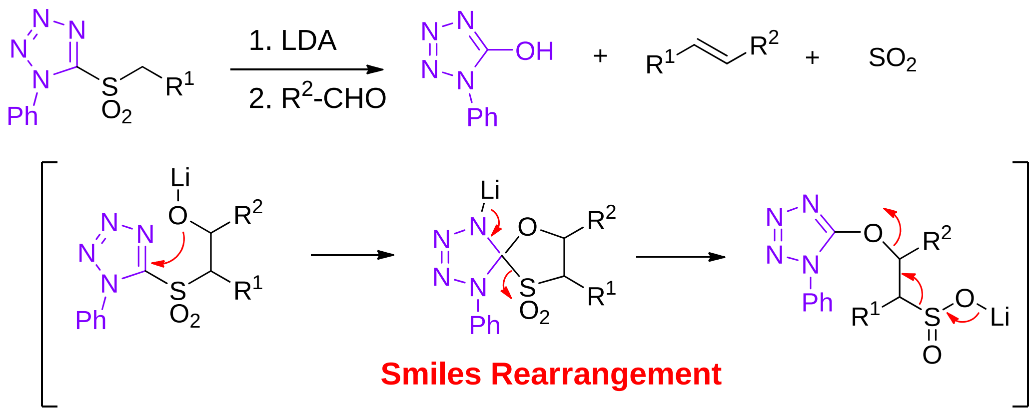
Addition to an ester and reduction of the resulting ketone to β-hydroxysulfone

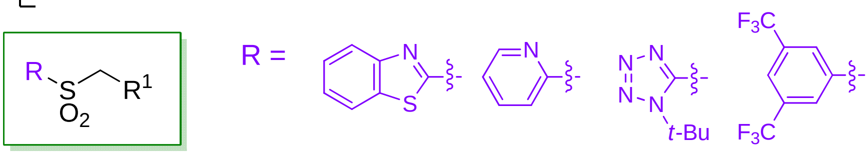


Using DME instead of THF sometimes suppresses the undesirable enolization

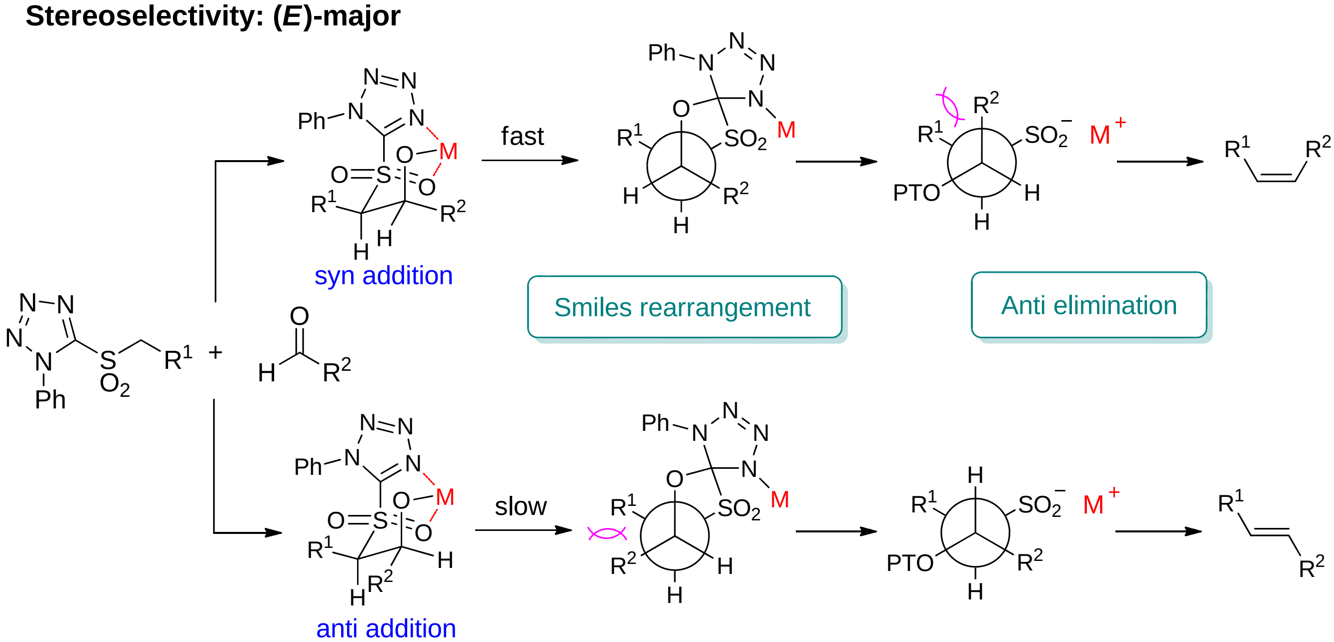
Sulfoxide-mediated addition would lead to improved yields due to the greater reactivity

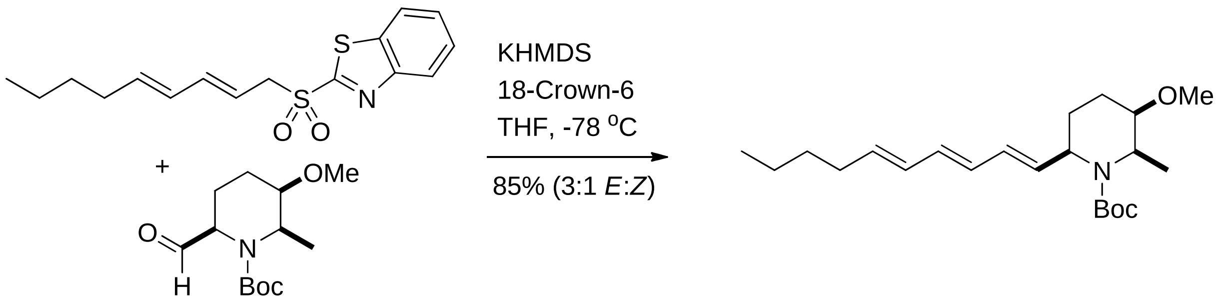
c. Julia-Kocienski olefination

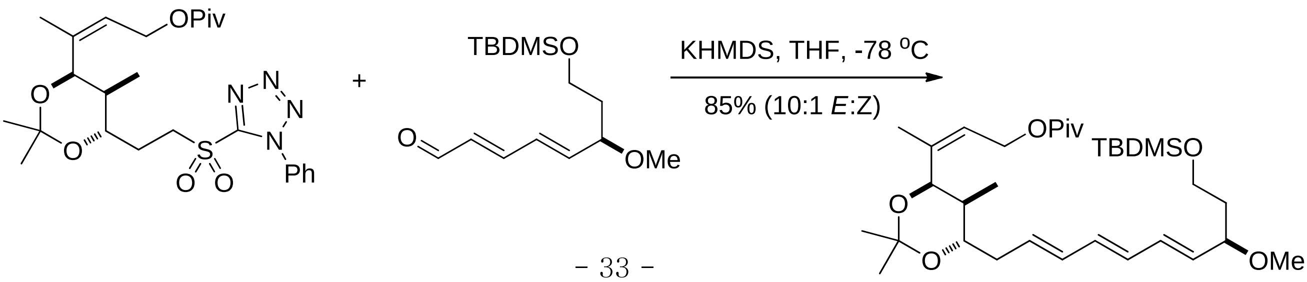




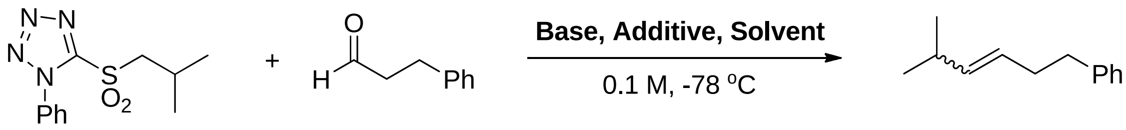
Stereoselectivity: (*E*)-major





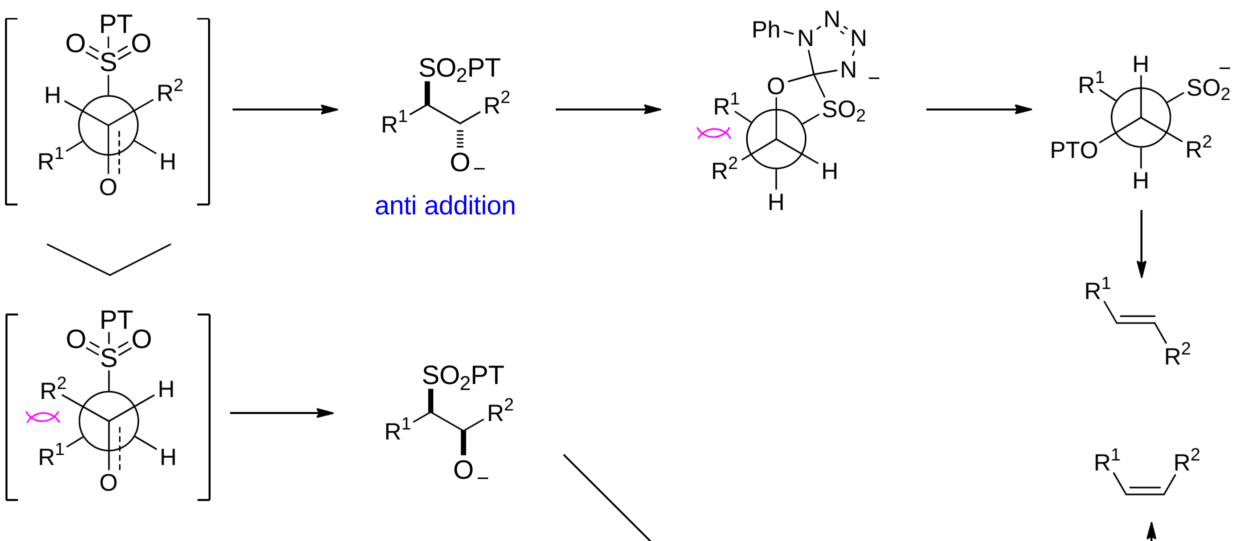


Stereoselectivity

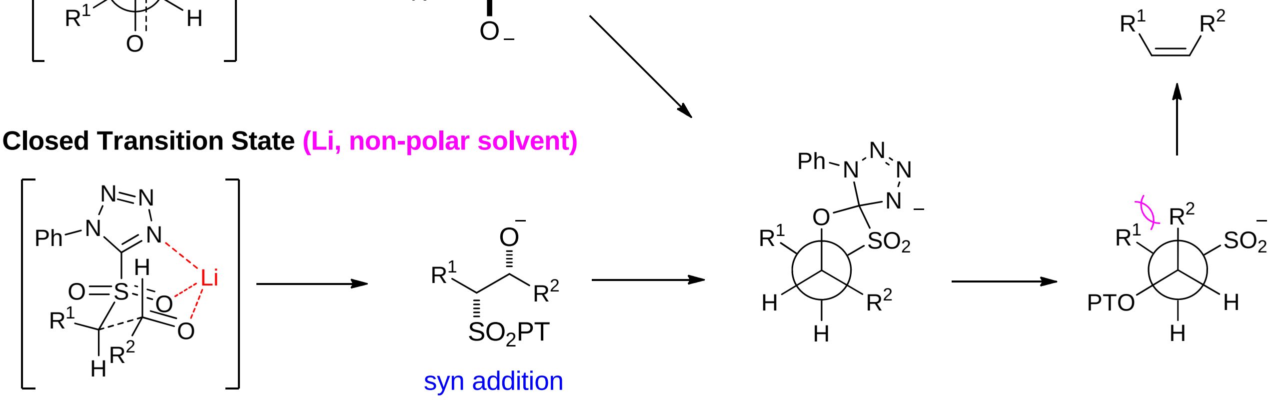


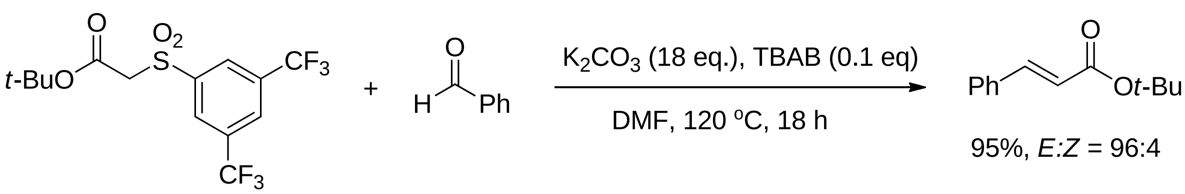
Entry	Base (equiv)	Additive (equiv)	Solvent	Yield	E/Z
1	KHMDS (1.1)		THF	88%	4.3:1
2	KHMDS (1.1)	18-Cr-6 (1.1)	THF	86%	15:1
3	KHMDS (1.1)	18-Cr-6 (2.0)	THF	84%	>50:1
4	KHMDS (1.1)	18-Cr-6 (2.0)	toluene	87%	>50:1
5	KHMDS (1.1)	18-Cr-6 (2.0)	DMF	78%	>50:1
6	NaHMDS (1.1)	18-Cr-6 (2.0)	THF	78%	4:1
7	LiHMDS (1.1)		THF	90%	2.1:1
8	LiHMDS (1.1)	12-Cr-4 (2.0)	THF	79%	3:1

Open Transition State (KHMDS, 18-Cr-6)

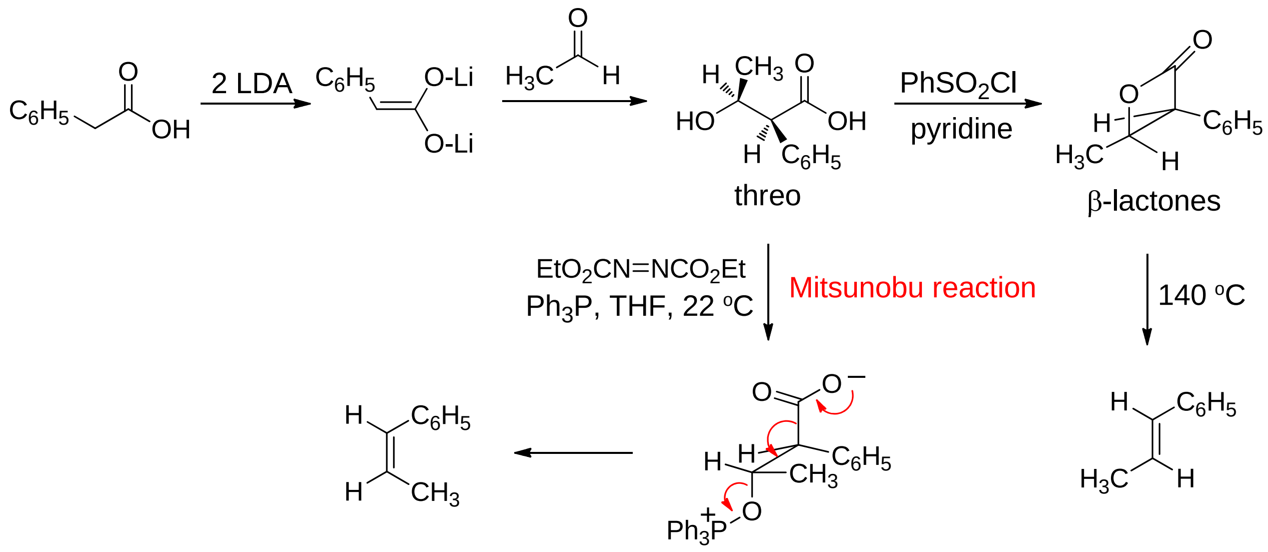


Closed Transition State (Li, non-polar solvent)



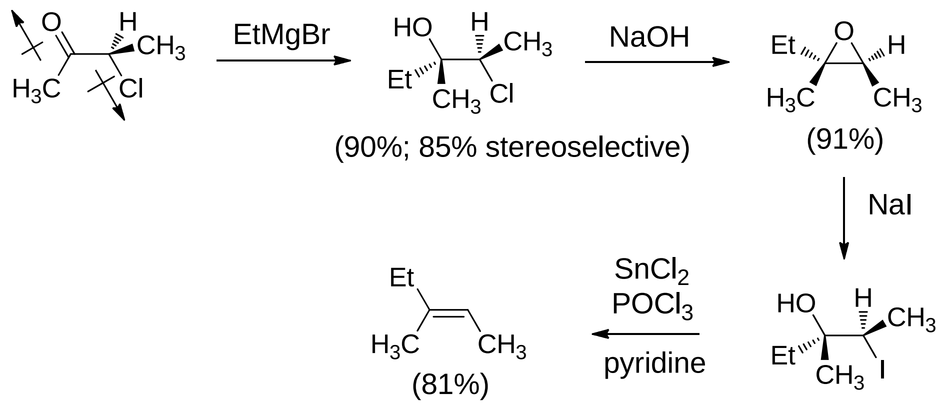


2.7 Decarboxylation of β-lactones

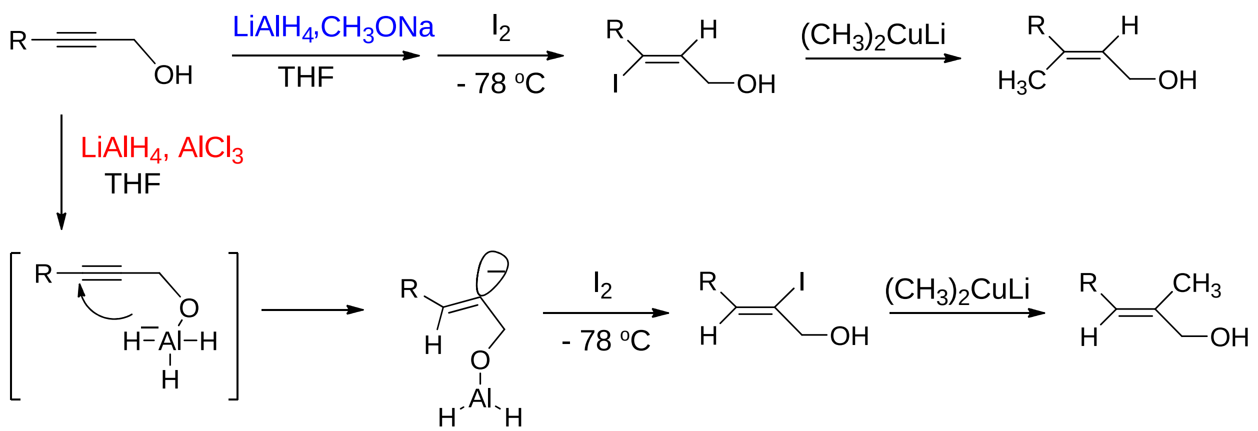


2.8 Stereoselective synthesis of tri- and tetra-substituted alkenes

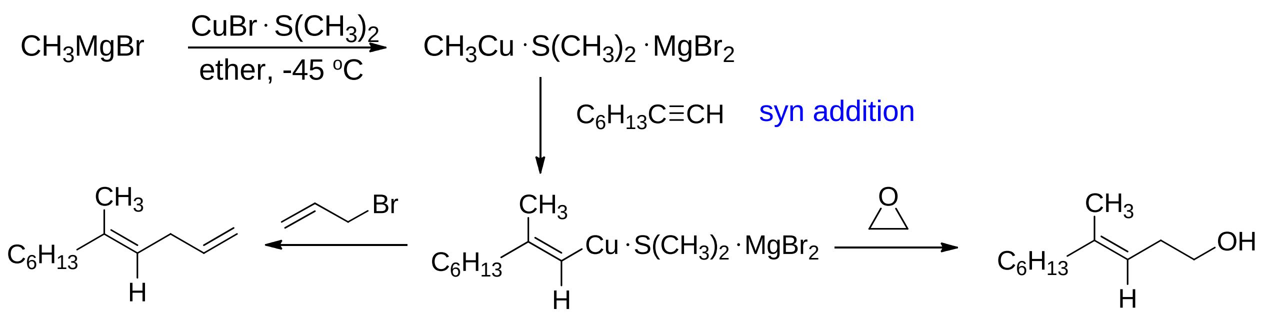
a. Grignard reagent with an α-chloroaldehyde or -ketone

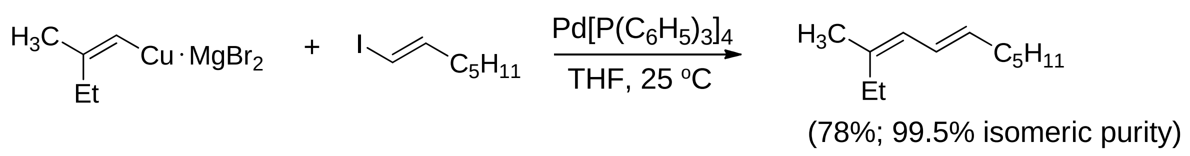


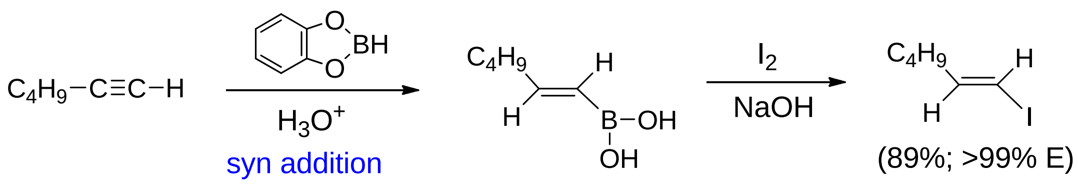
b. Reduction of propargylic alcohol with $LiAlH_4$

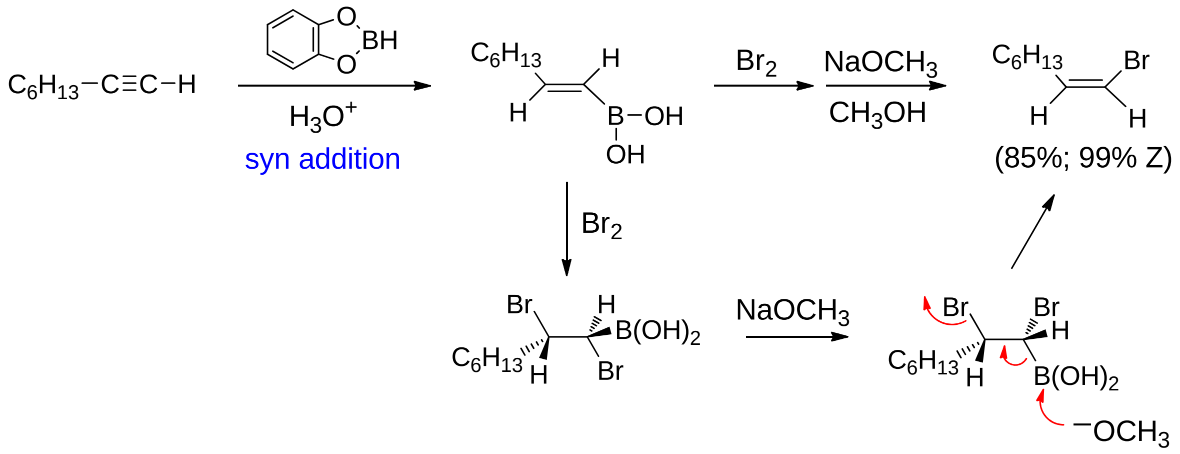


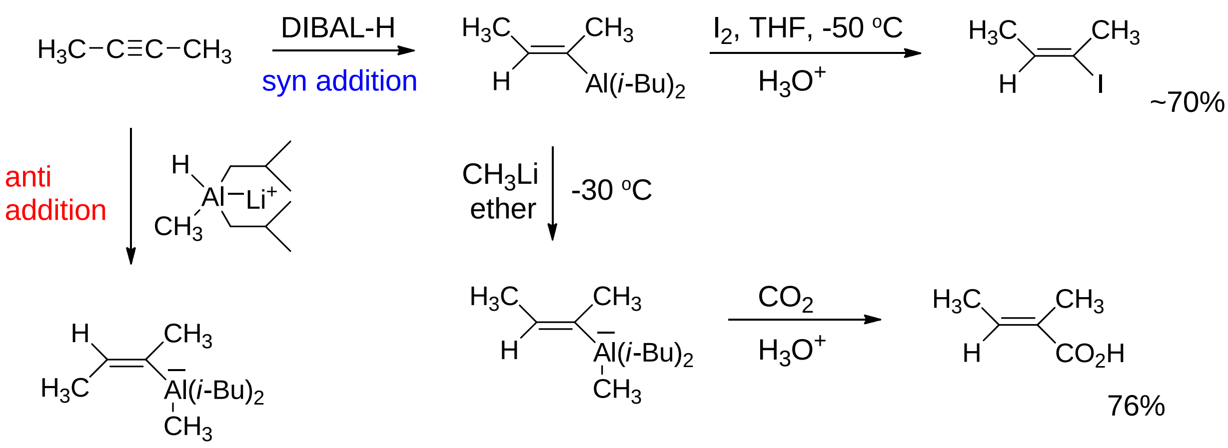
c. Reaction of organocopper or organoborane with alkynes

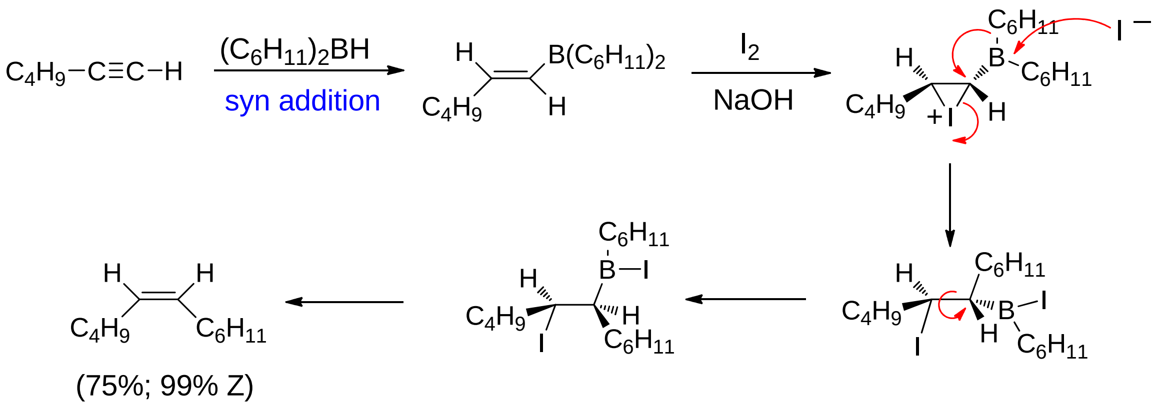




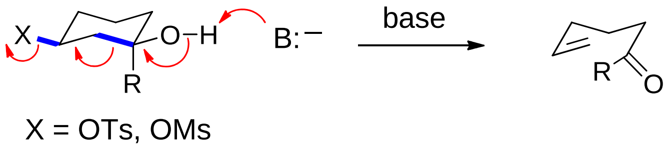


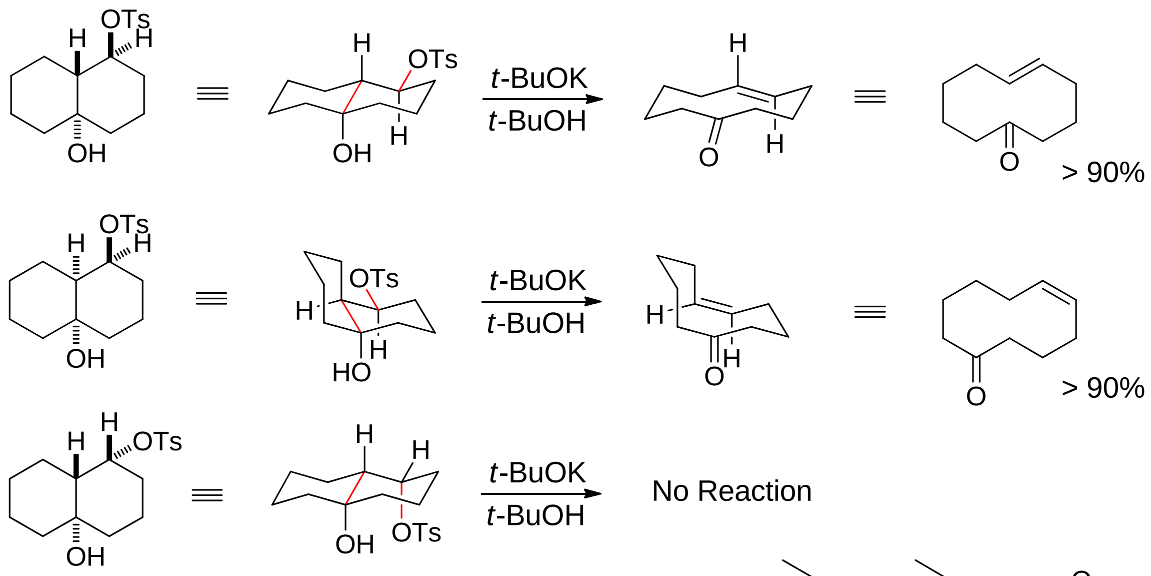


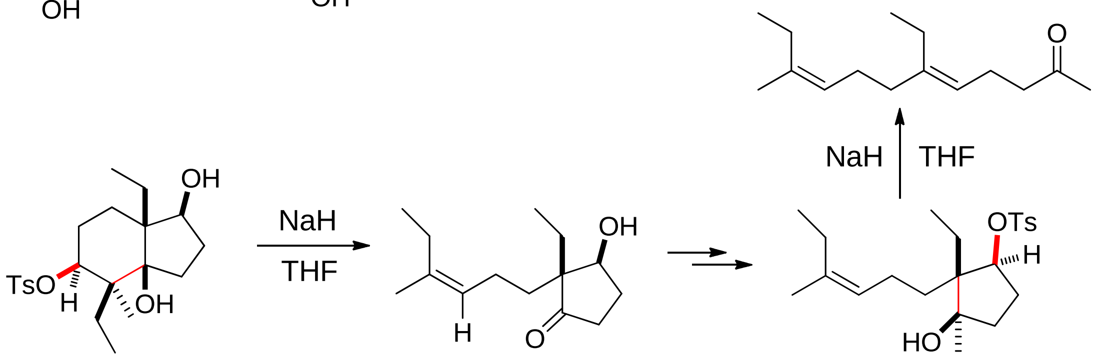


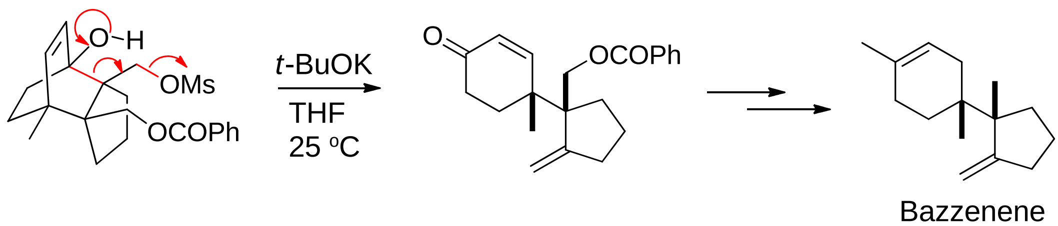


2.9 Fragmentation reactions







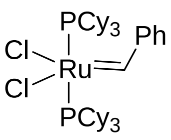


2.10 Olefin Metathesis

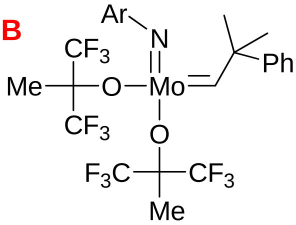
$$2\ RCH{=}CH_2 \xrightarrow{\text{catalyst}} RCH{=}CHR + H_2C{=}CH_2$$

ruthenium or molybdenum alkylidene (carbene) complex

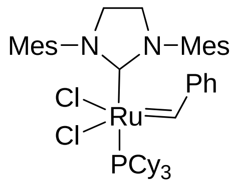
A



B



C



Cy: Cyclohexyl

Grubbs I

(stable but less reactive)

Ar: 2,6-diisopropylphenyl

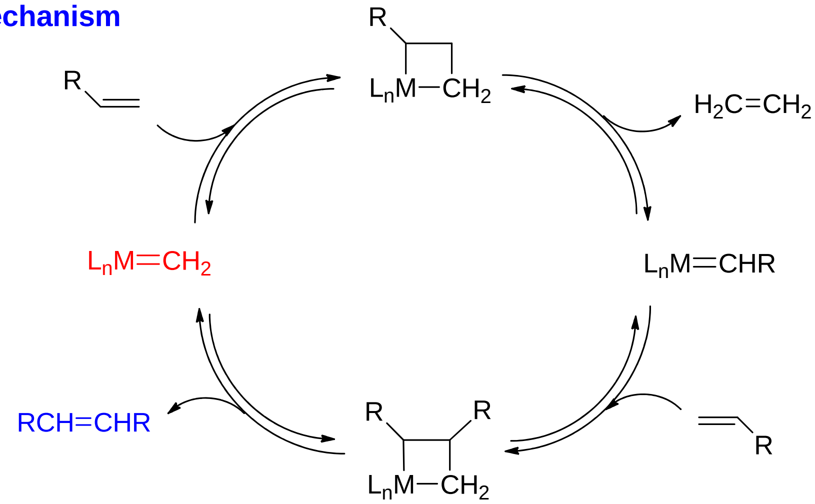
Schrock

Mes: 2,4,6-trimethylphenyl

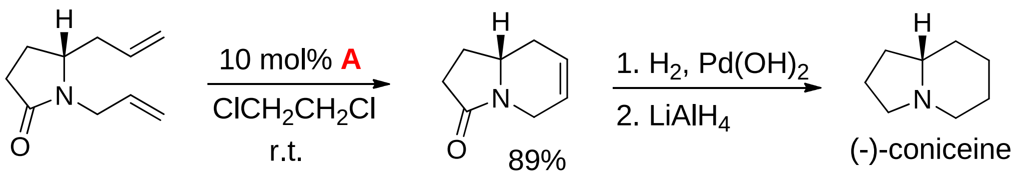
Grubbs II

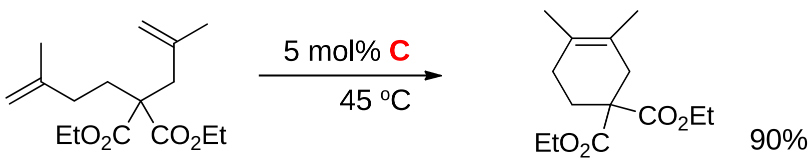
(useful for tri- or tetra-substituted alkenes)

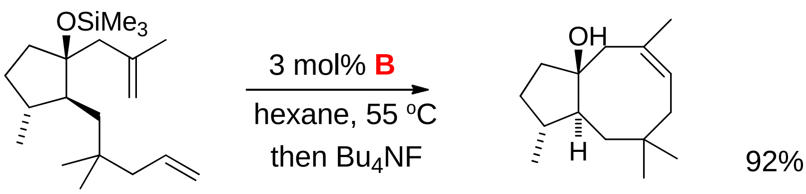
Mechanism



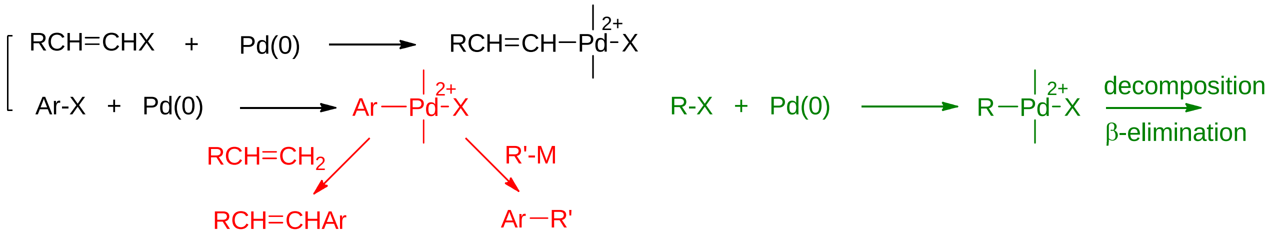
RCM (Ring Closing Metathesis)



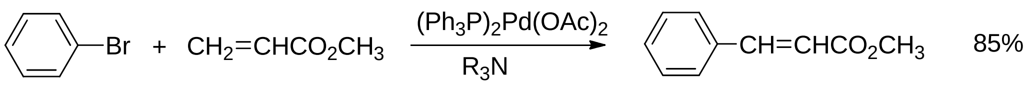




2.11 Pd - Catalyzed Reaction

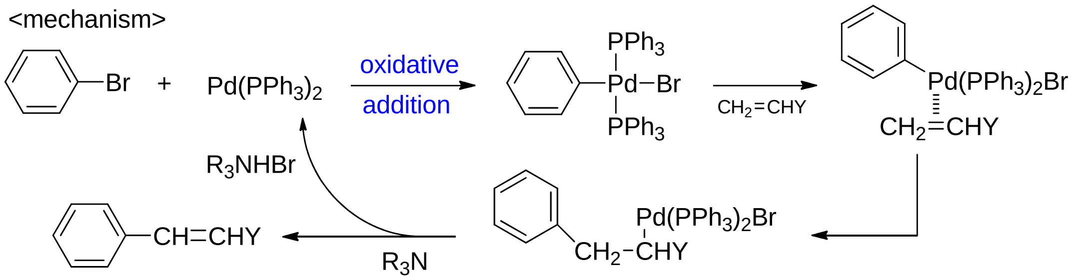


a. Heck reaction (reaction with alkenes)



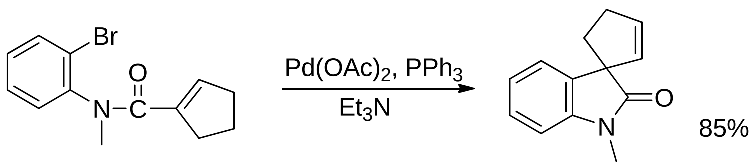
in situ reduction of Pd(II) to Pd(0): $Pd(OAc)_2$ + $2PPh_3$

<mechanism>

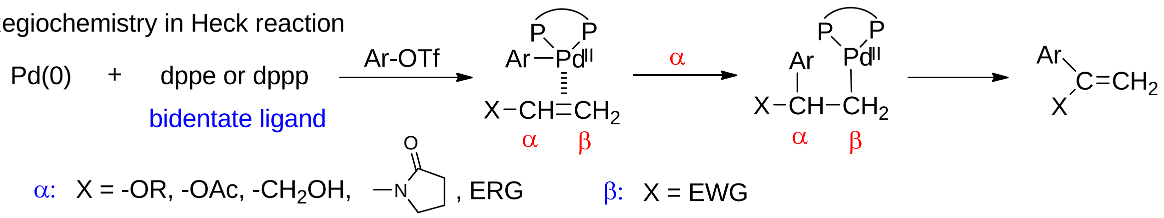


* High halide concentration promote formation of $[PdL_2X]^-$, which retards coordination to double bonds.

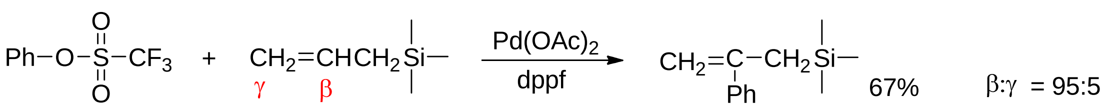
Use -OTf instead of -X to accelerate complexation with alkenes.



Regiochemistry in Heck reaction

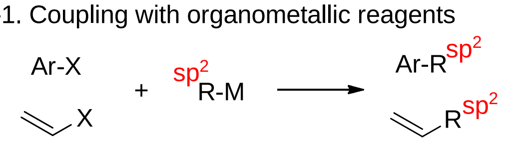


Silicon effect



b. Palladium-catalyzed cross coupling reaction

b-1. Coupling with organometallic reagents



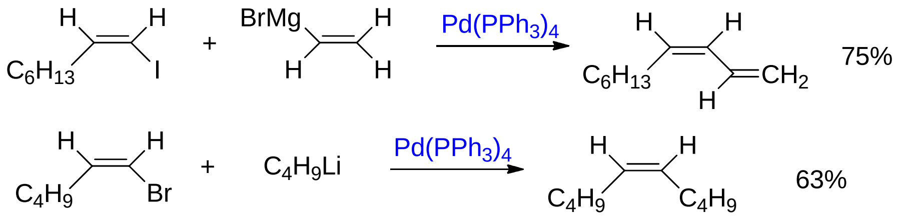
R-M: organomagnesium, organzinc, mixed cuprate, organostannane, organoboron compounds

X: halides, sulfonates

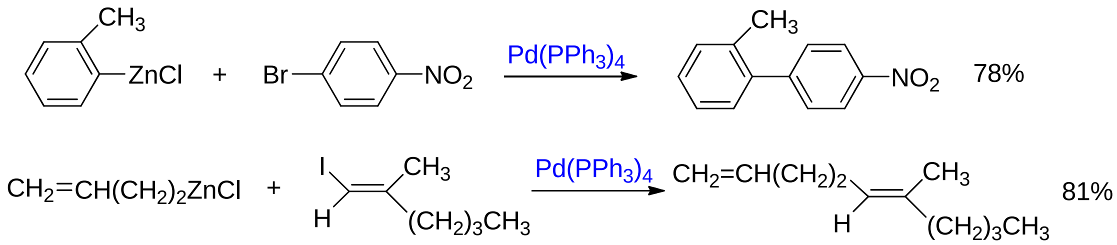
biaryls, dienes, polyenes, enynes

Steps in cross-coupling reaction:

oxidative addition - transmetallation - reductive elimination b-1-1. Grignard and organolithium reagents with Alkenyl halides

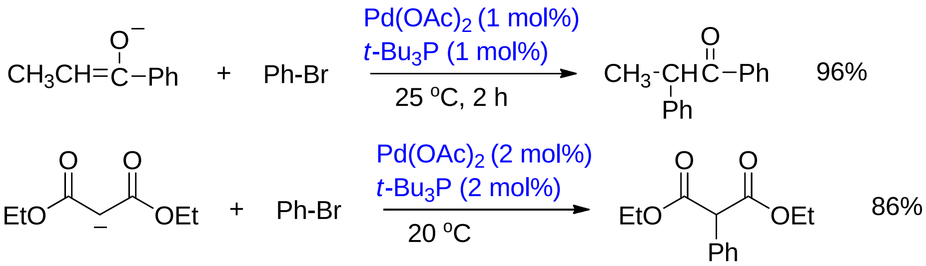


b-1-2. Organozinc reagents

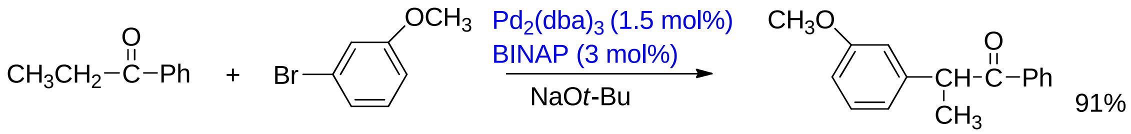


b-1-3. Arylation of enolates

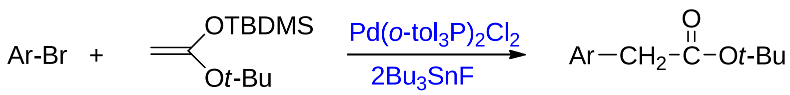
a. using t-Bu_3P, $Pd(OAc)_2$



b. using BINAP ligand

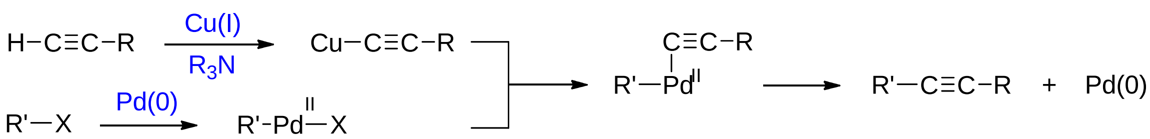


c. O-silyl ketene acetals with Bu_3Sn-F

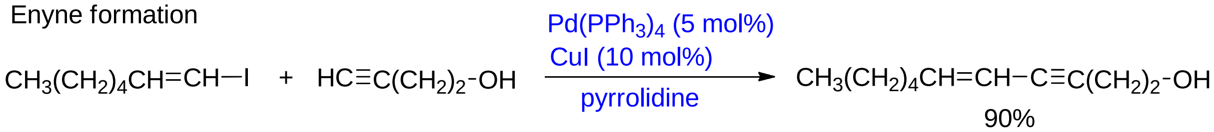


b-1-.4. Terminal alkynes with vinyl or aryl halides "copper acetylide"

$Pd(PPh_3)_4$ + Cu(I)



Enyne formation



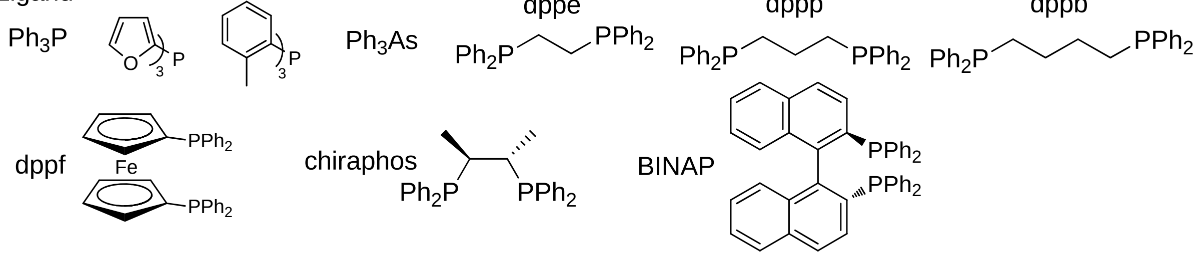
b-1-5. Coupling with stannanes

Cross-coupling reactions of aryl and alkenyl stannanes with benzylic, aryl, alkenyl, allylic halides
"Stille reactions"

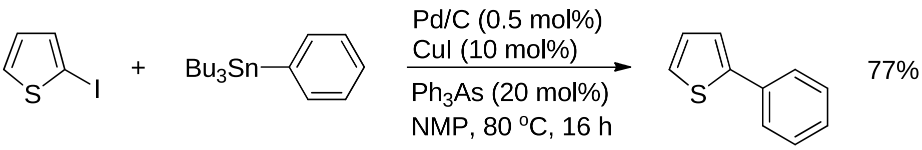
Group that can be transferred from tin:

alkynyl > alkenyl > aryl > methyl > alkyl

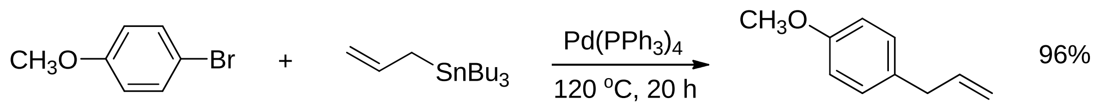
Ligand

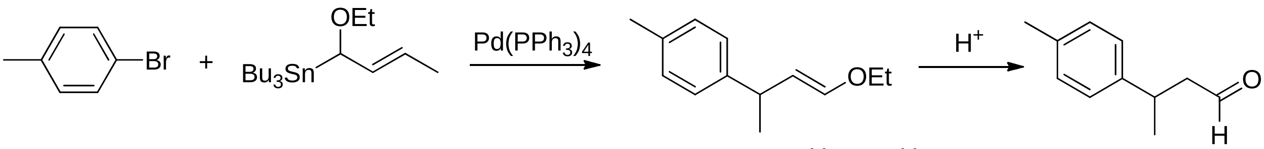


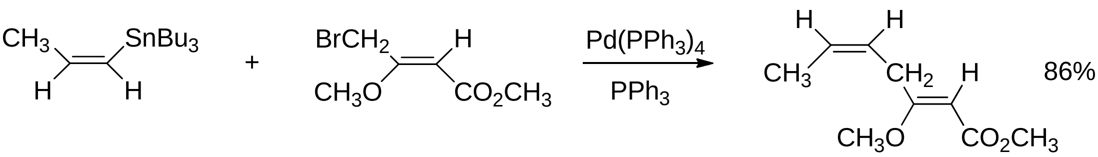
Ar-Ar coupling rates are increased by Cu(I) co-catalyst

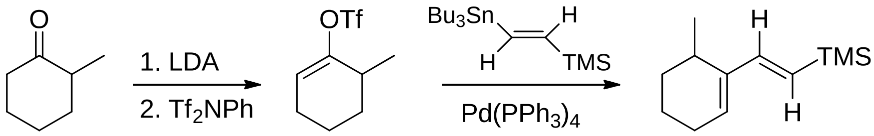


Eaxamples









b-1-6. Coupling with organoboranes

Cross-coupling reaction of aryl or vinyl boron compound (boronic acids, boronate esters, boranes)
"Suzuki reaction"

boric acid as a biproduct

Rate-determining step: oxidative addition or transmetallation

Base catalysis is required for boronic acids to generate more reactive boronate anion.

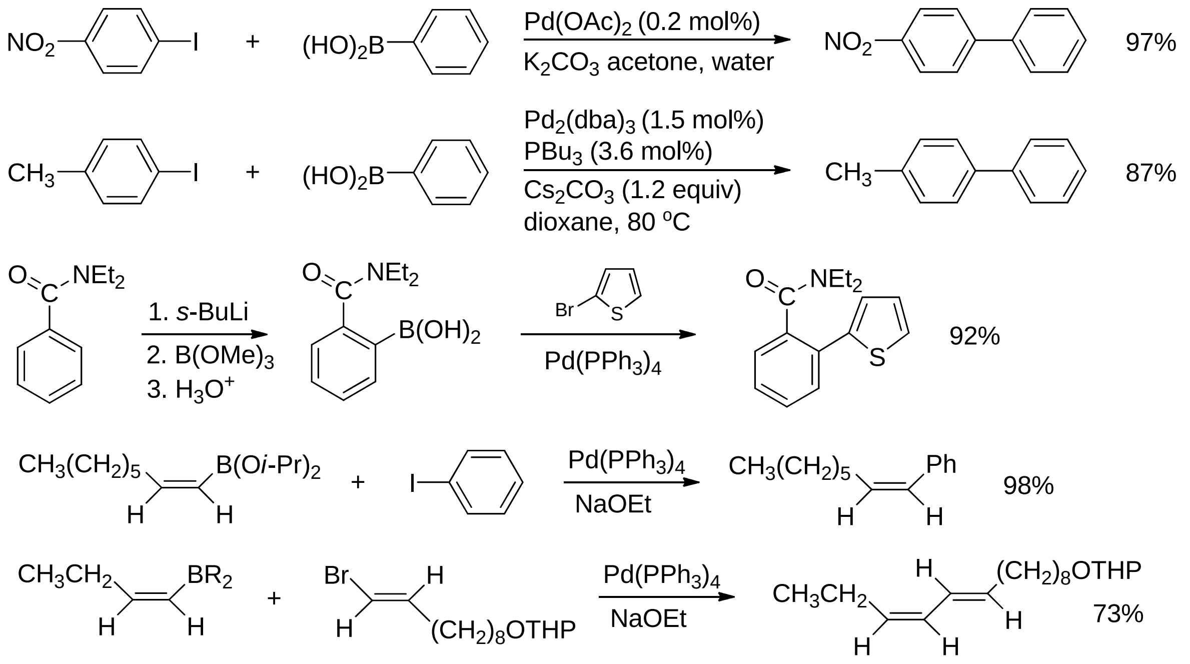
$$\mathrm{Ar{-}X} + \mathrm{Pd^o} \longrightarrow \mathrm{Ar{-}Pd^{II}{-}X}$$

$$\mathrm{Ar'{-}B(OH)_2} + {}^{-}\mathrm{OH} \rightleftharpoons [\mathrm{Ar'{-}B(OH)_3}]^{-}$$

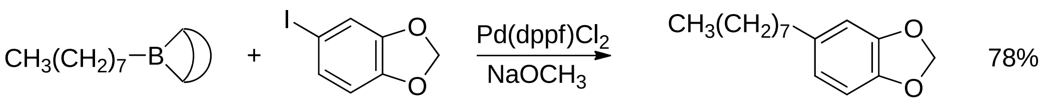
$$[\mathrm{Ar'{-}B(OH)_3}]^{-} + \mathrm{Ar{-}Pd^{II}{-}X} \longrightarrow \mathrm{Ar{-}Pd^{II}{-}Ar'} + \mathrm{B(OH)_3} + \mathrm{X^{-}}$$

$$\mathrm{Ar{-}Pd^{II}{-}Ar'} \longrightarrow \mathrm{Ar{-}Ar'} + \mathrm{Pd^o}$$

Eaxamples



Alkyl-aryl coupling using 9-BBN

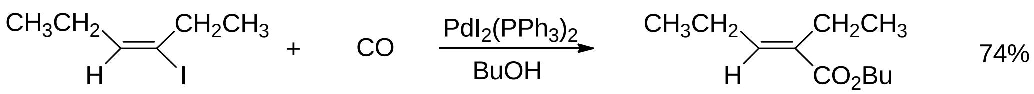


Bases

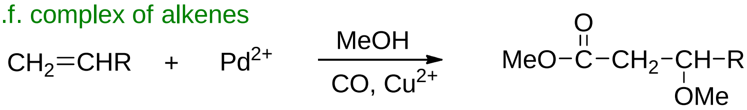
Cs_2CO_3 or TlOH > NaOH

b-2. Reaction with carbon monoxide (CO)

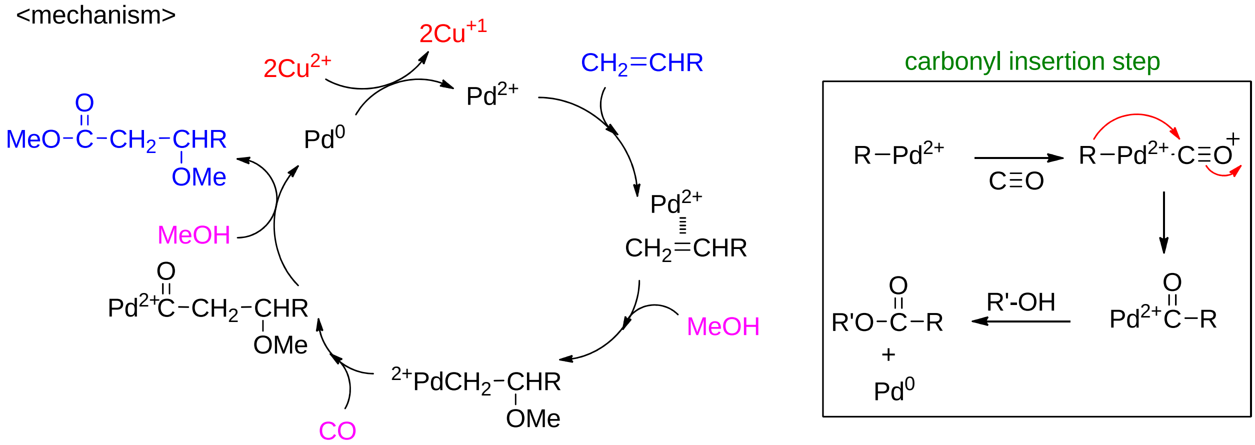
b-2-1. Reaction in ROH



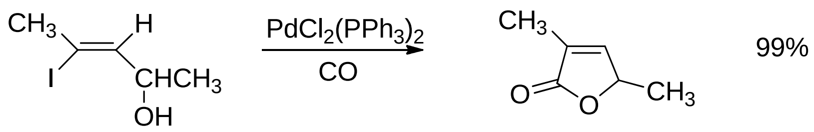
c.f. complex of alkenes



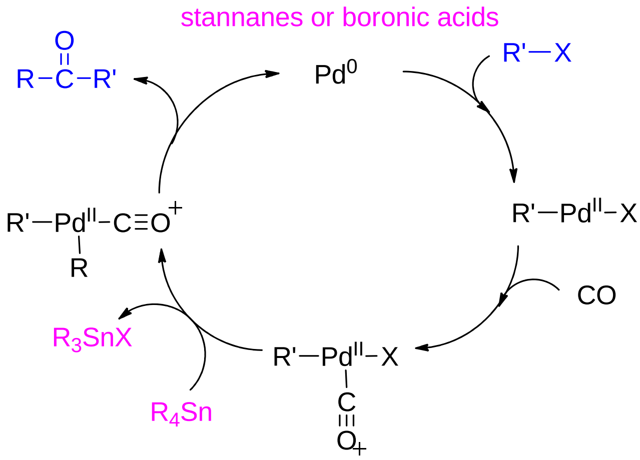
<mechanism>

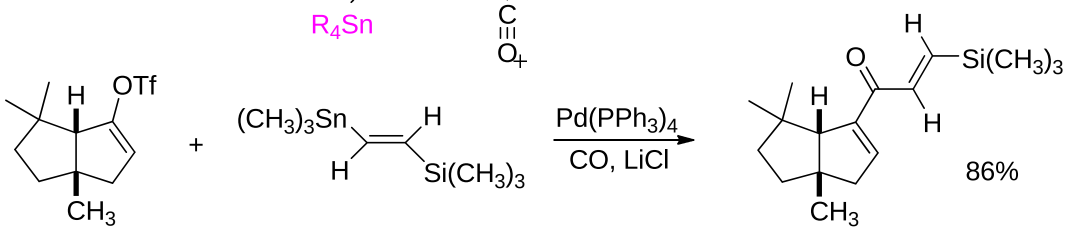


Intramolecular Palladium-catalyzed cross coupling reaction

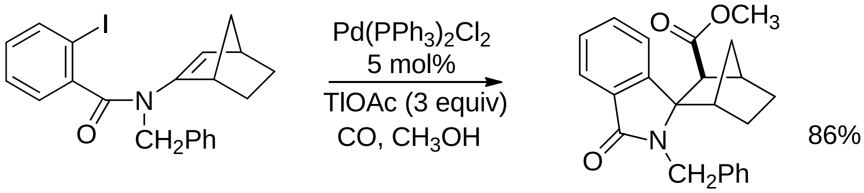


b-2-2. Coupling of organometallic reagents with aryl or vinyl halides

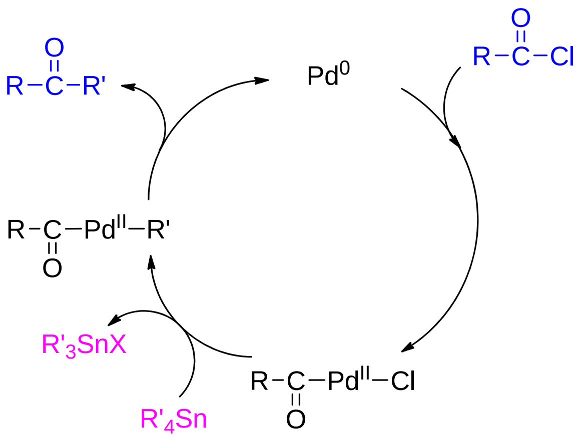




Tandem intramolecular Heck-carbonylation reaction



Coupling of organostannane with acyl chlorides

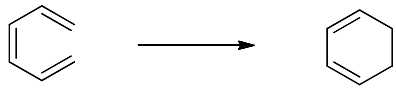


Chapter 3. Pericyclic Reaction

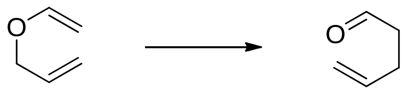
Introduction

Pericyclic Reaction: Concerted Process; Cyclic Transition State

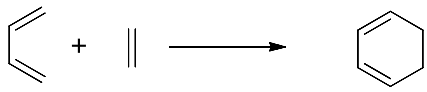
1. Electrocyclic Reaction



2. Sigmatropic Rearrangement

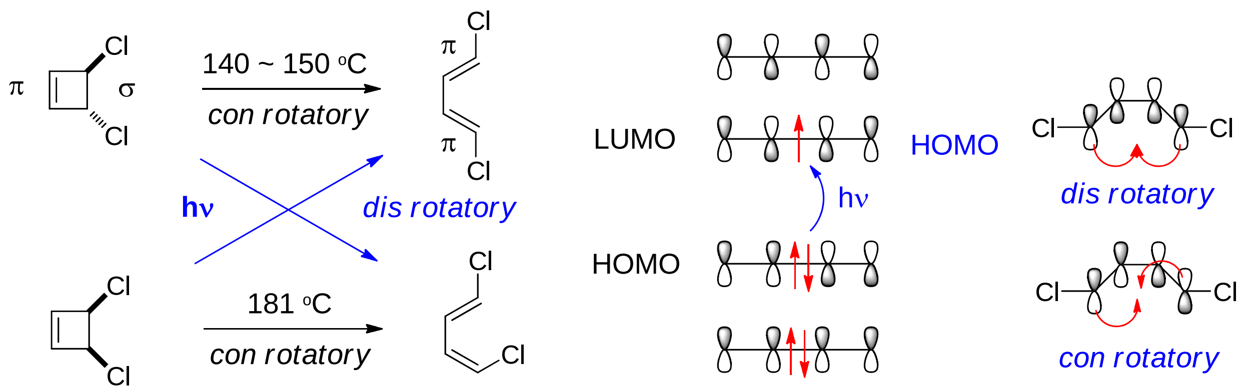


3. Cycloaddition

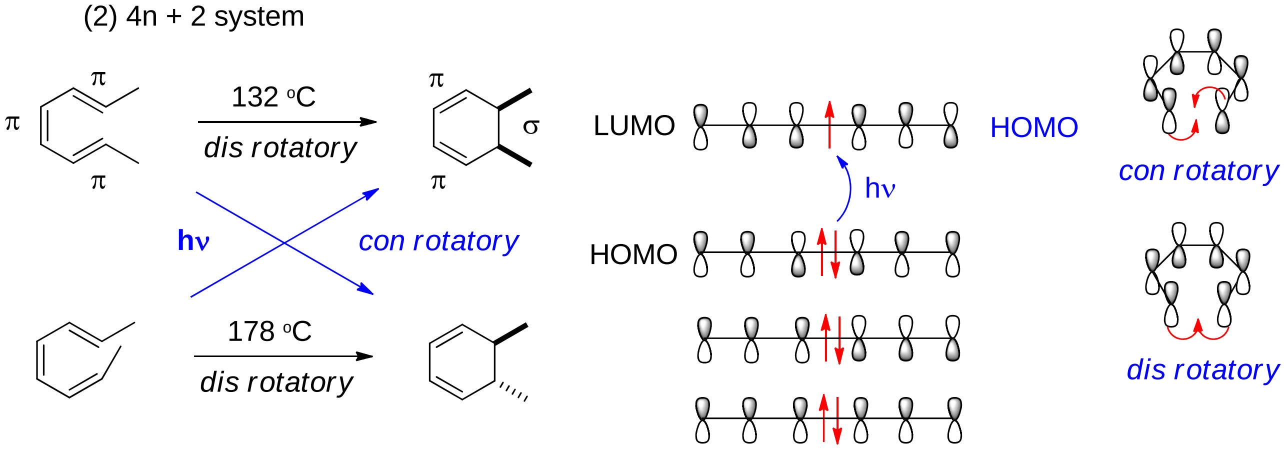


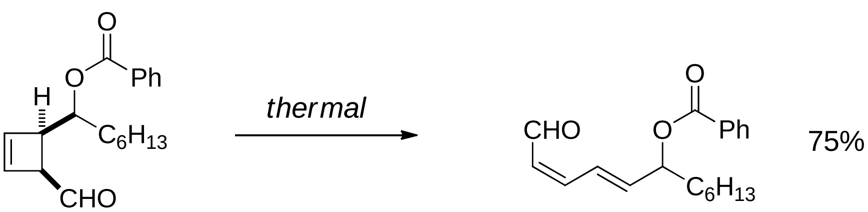
Woodward-Hoffmann Rules

(1) 4n system



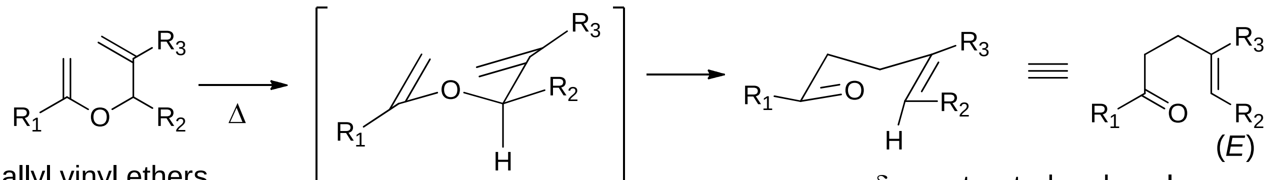
(2) 4n + 2 system





3-1 Claisen Rearrangement of Allyl Vinyl Ethers

[3,3]-sigmatropic Rearrangement - Concerted Mechanism



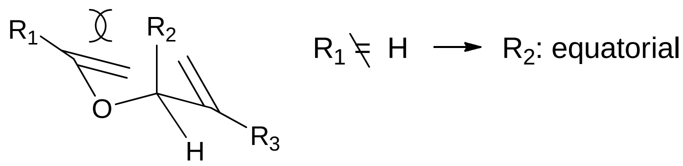
allyl vinyl ethers

a cyclic six-membered transition state

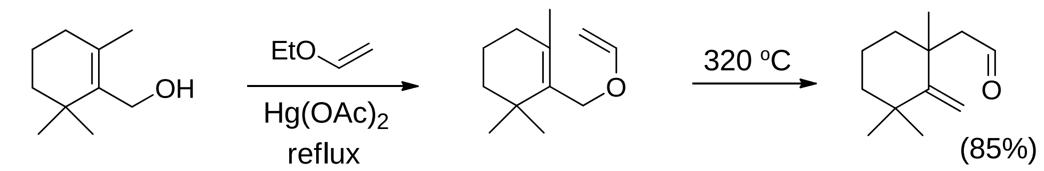
chair-like

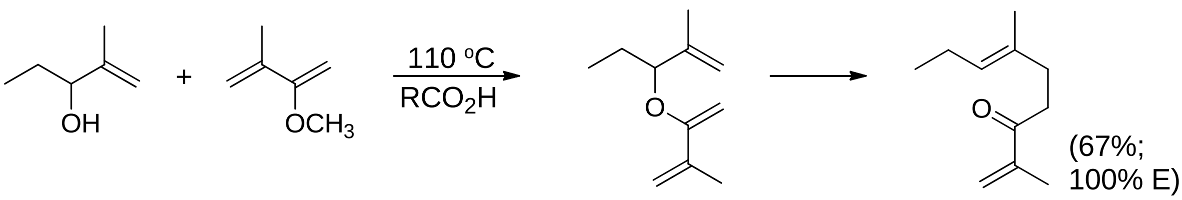
γ,δ-unsaturated carbonyl comps.

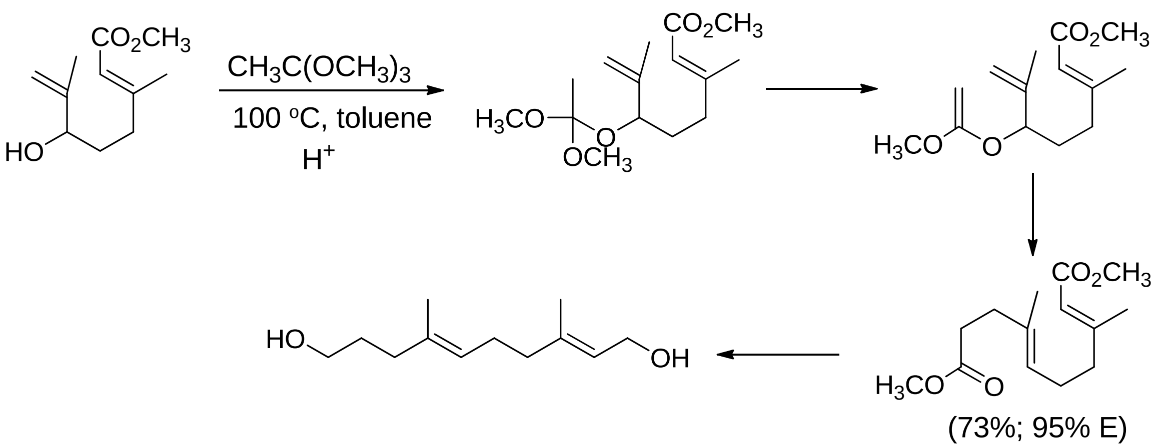
c.f.

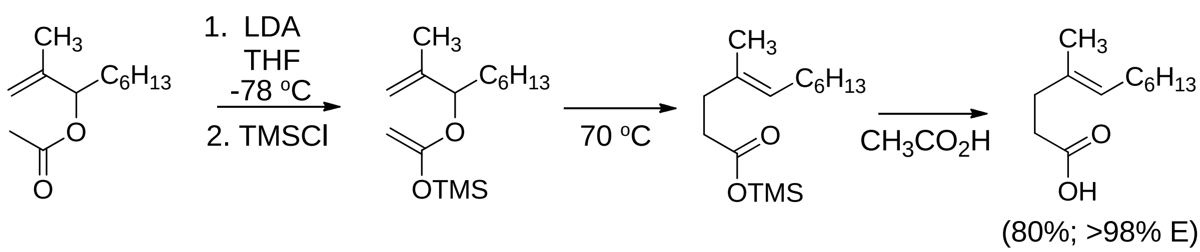


a. Preparation of Allyl Vinyl Ethers



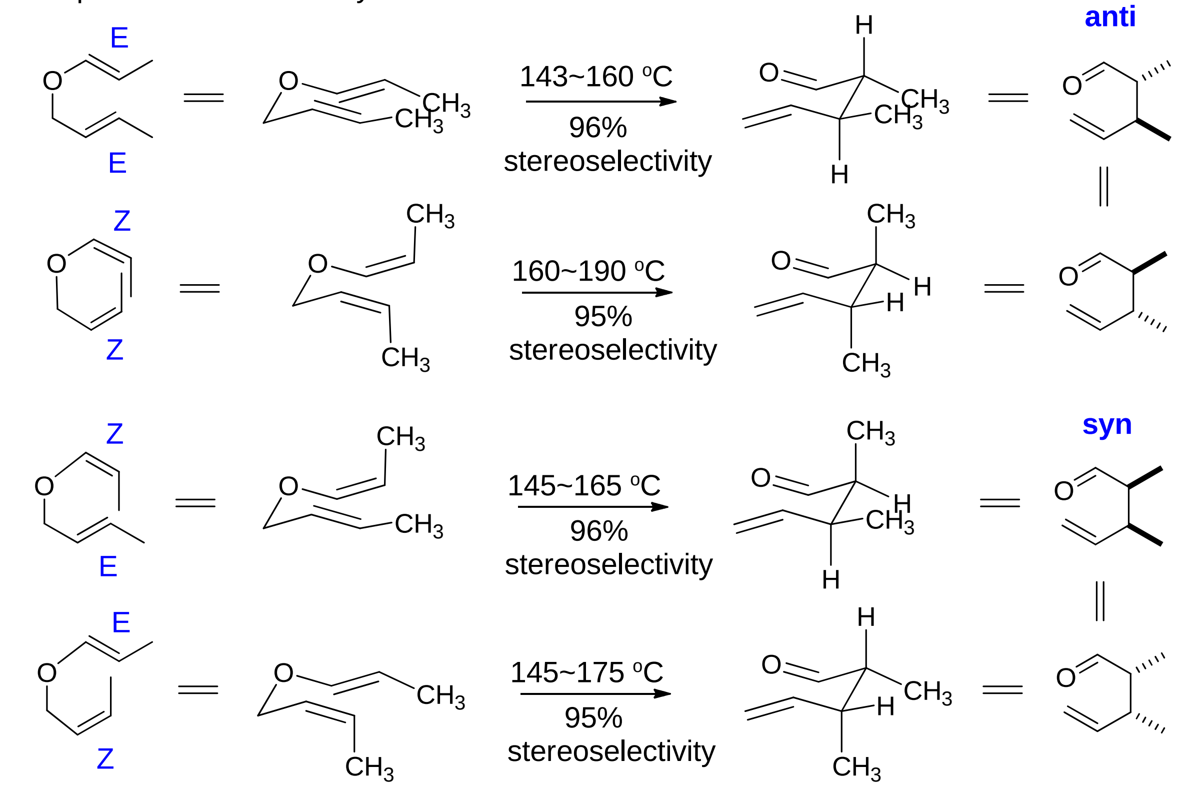


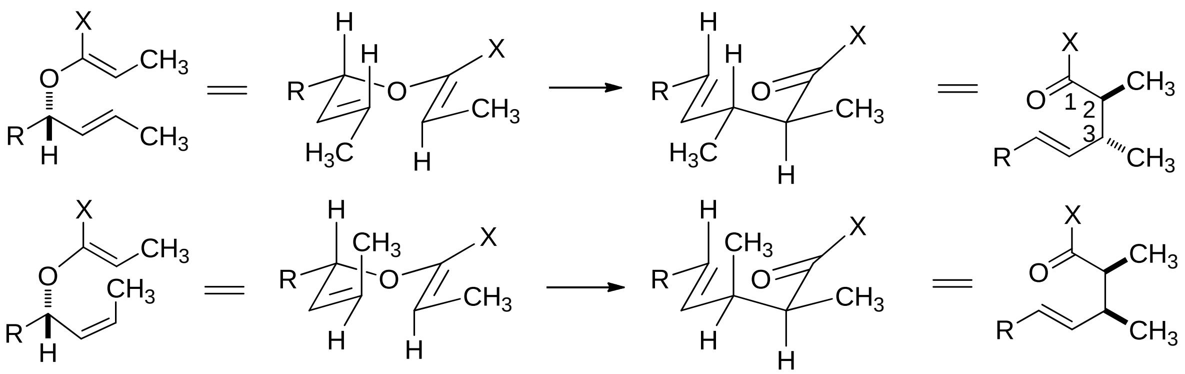


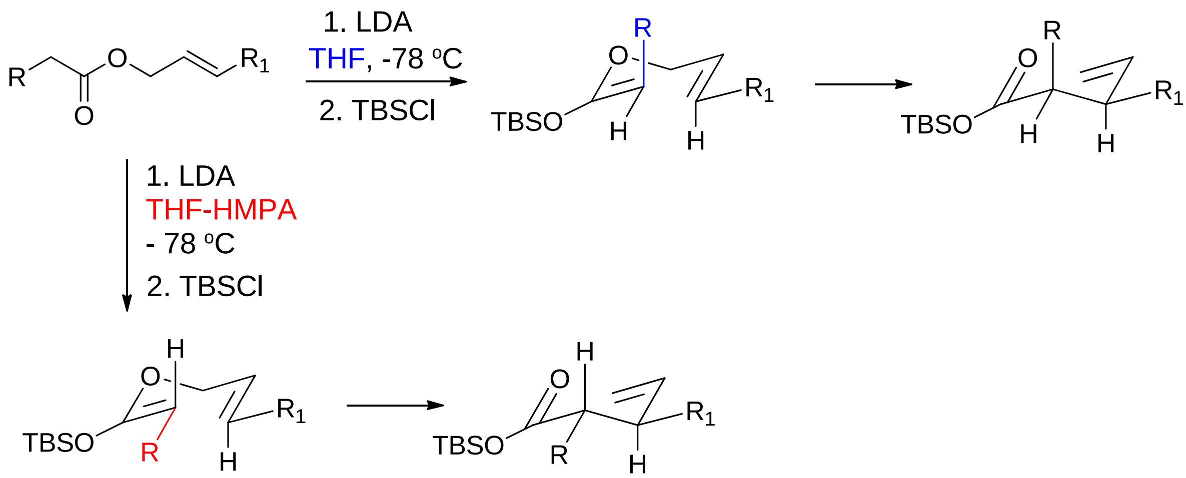


b. Stereochemical Control

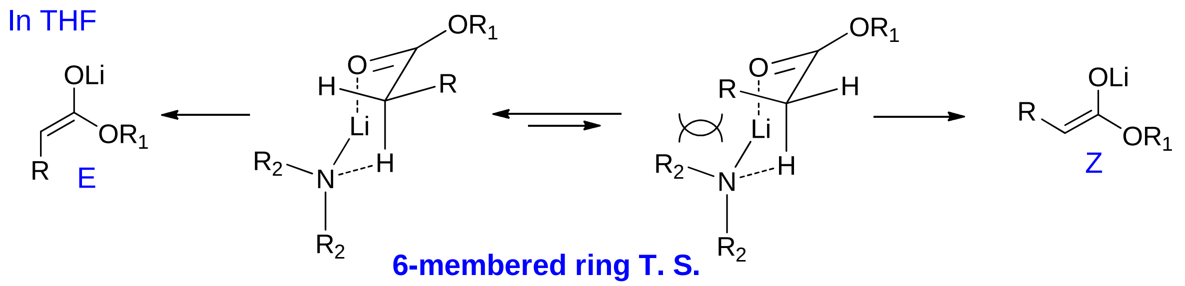
simple diastereoselectivity

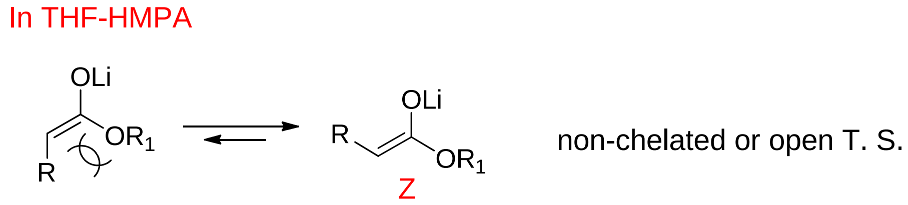


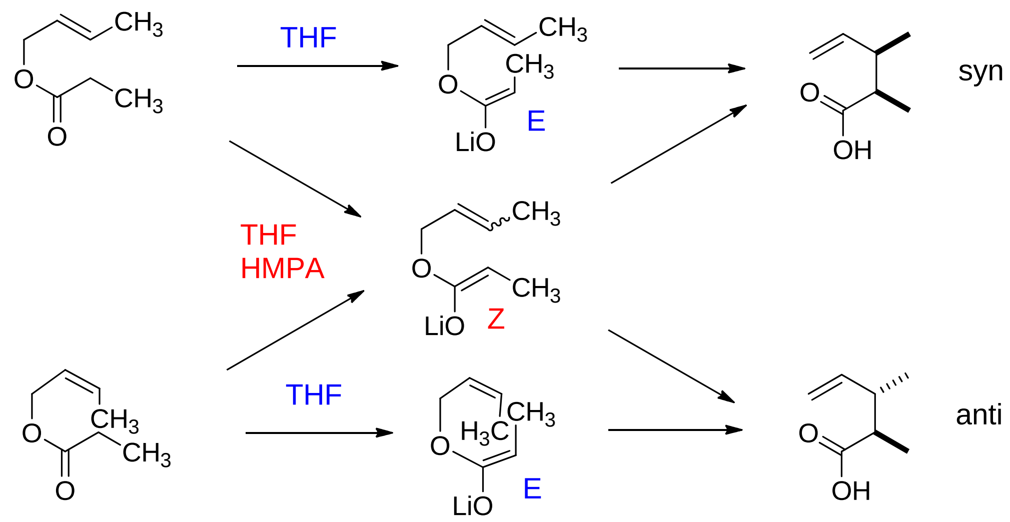


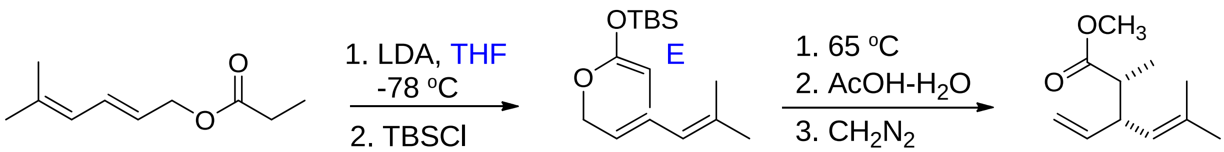


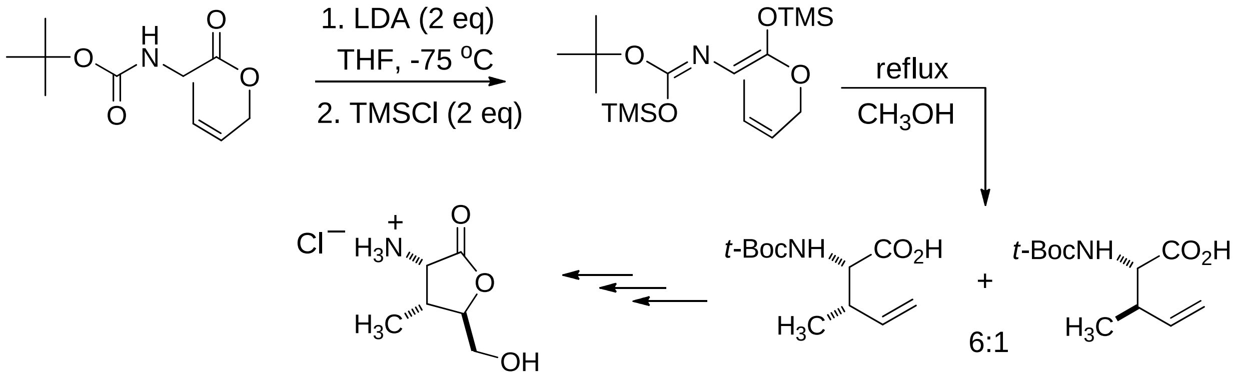
Formation of (Z)- or (E)-enolate



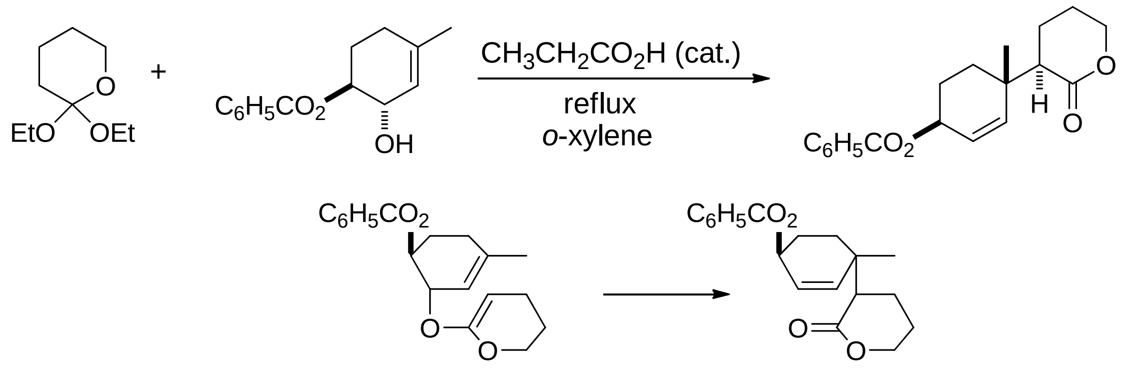




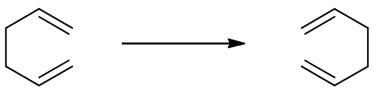




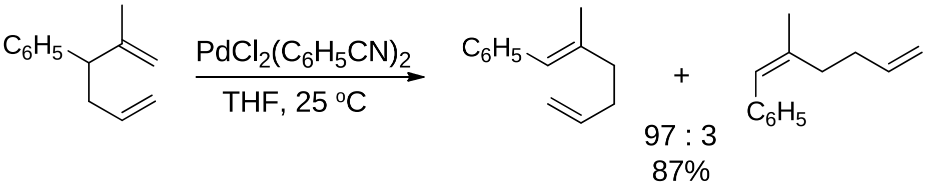
Boat-like Transition State - when double bond forms part of a ring



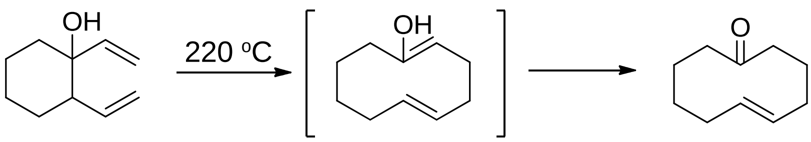
3-2 Cope rearrangement - [3,3]-sigmatropic rearrangement

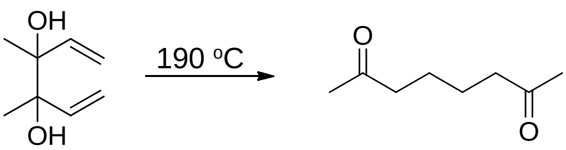


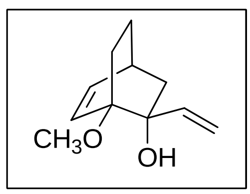
requires high temperature



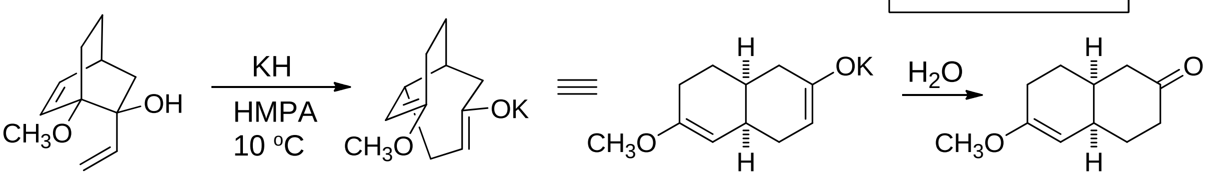
Oxy-Cope rearrangement

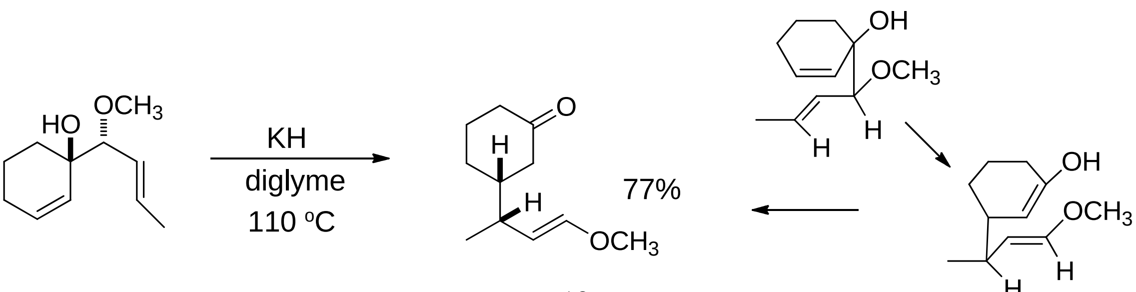




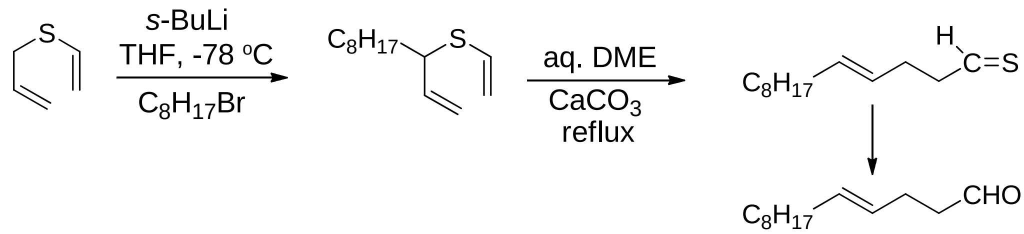


Anionic Oxy-Cope rearrangement



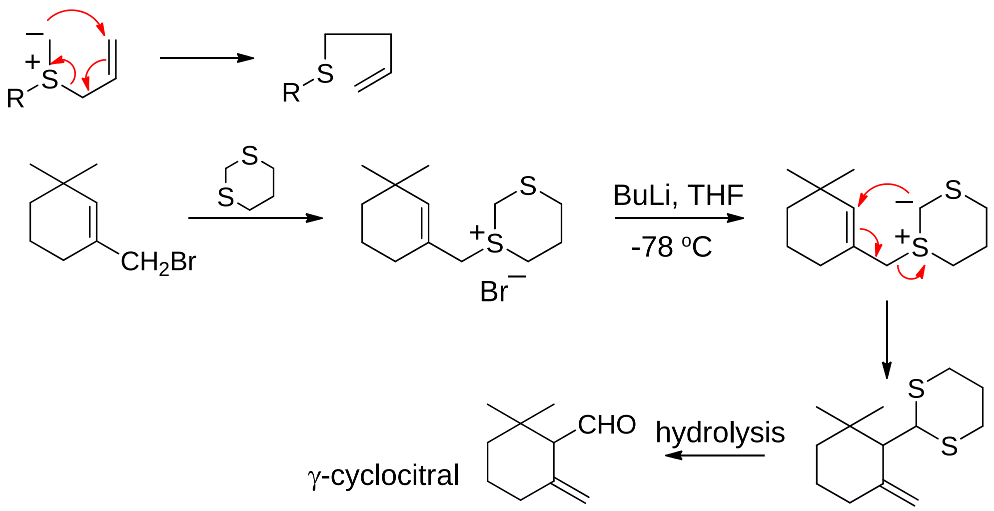


3-3. Thio Claisen Rearrangement

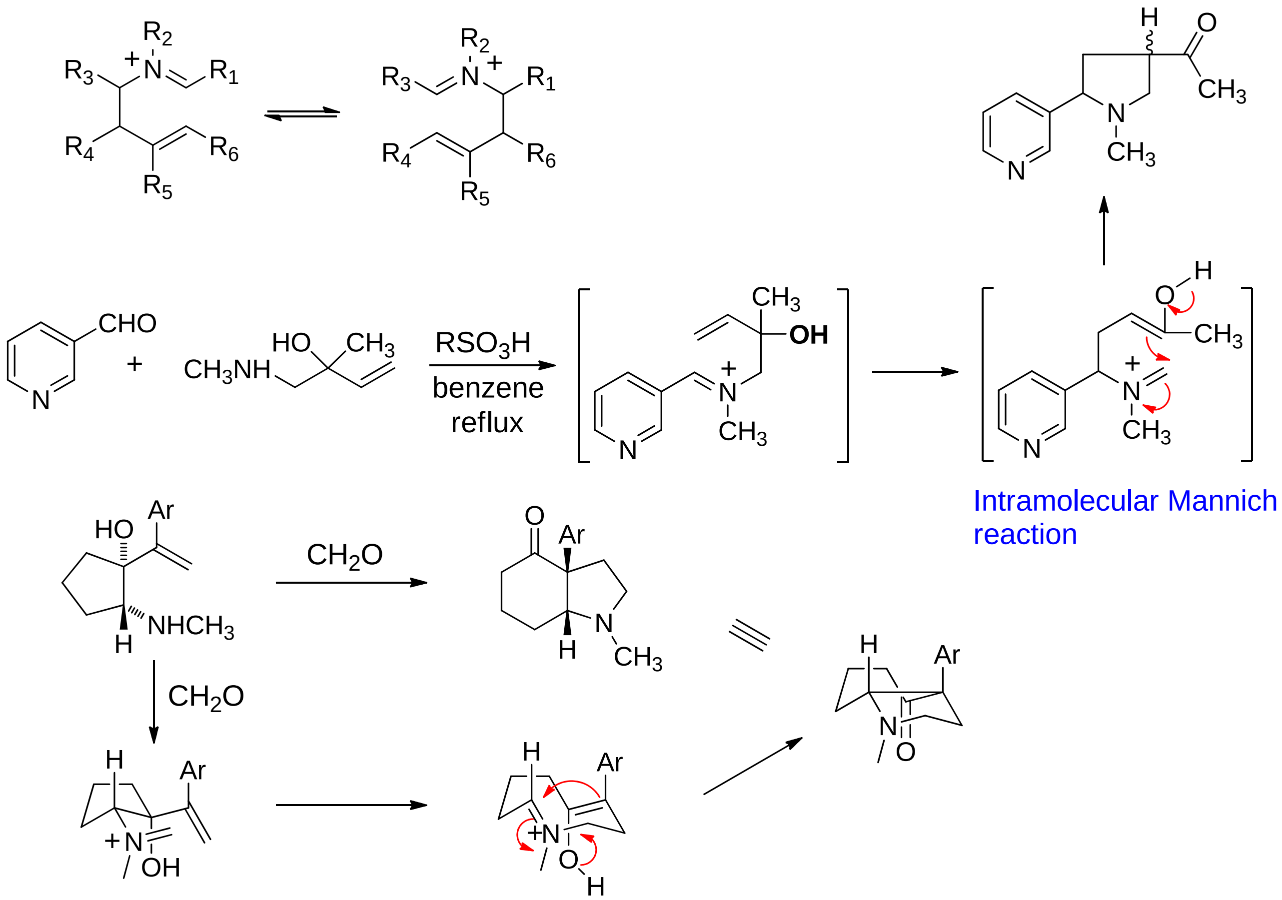


(57%; 100% *E*)

3-4. [2,3]-sigmatropic rearrangement



3-5. aza-Cope rearrangement

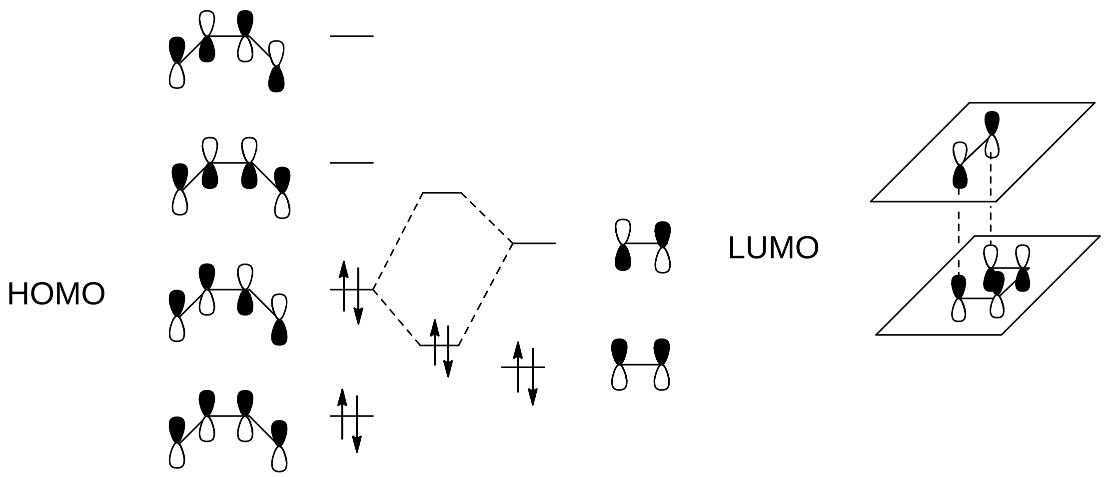


3-6 Diels-Alder reaction

Cycloaddition of dienes and alkenes ⟶ Synthesis of substituted cyclohexenes

Orbital symmetry [π4s + π2s] — Allowed process

Concerted mechanism — stereospecificity

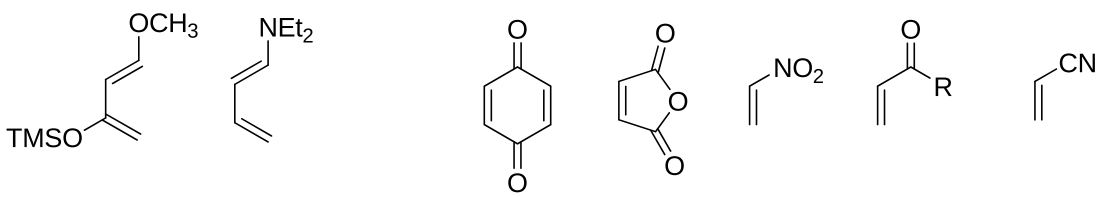


Electron donating group increase the HOMO energy level

Electron withdrawing group decrease the LUMO energy level

↓

Electron releasing diene + Electron withdrawing dienophile

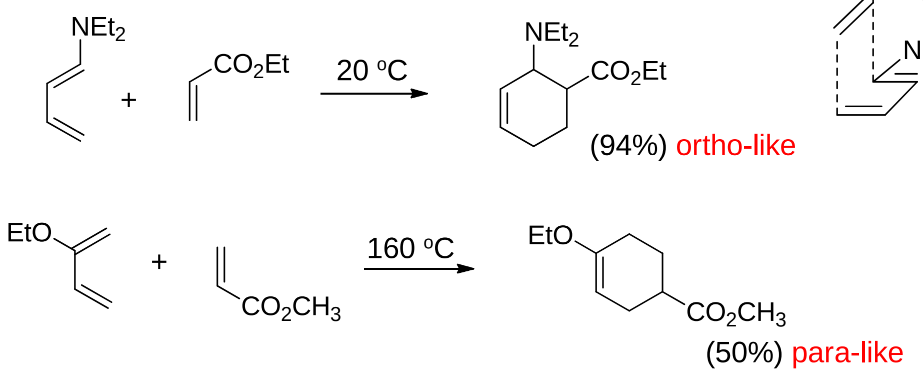


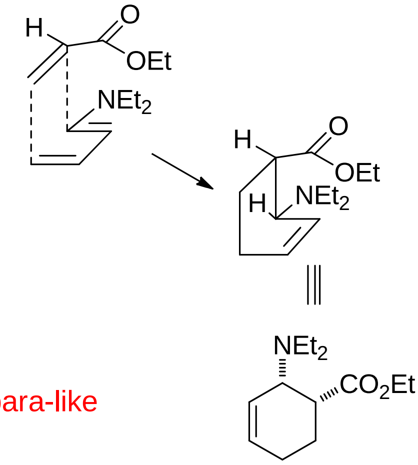
Alder Rule (Endo Rule)

Endo Exo

Regioselectivity

Preference for the ortho & para orientation





Frontier Molecular Orbital Theory

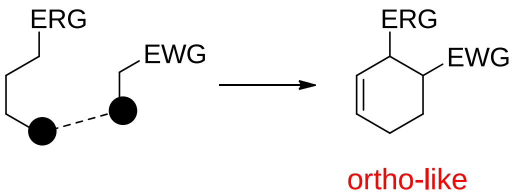
Bonding between carbons with **highest orbital coefficients**

I. Dienophile with EWG

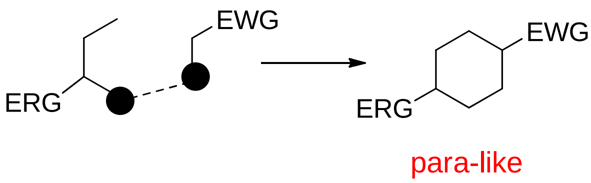
II. Diene with ERG @ C-1

III. Diene with ERG @ C-2

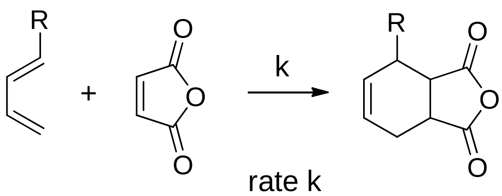
case 1: I+ II



case 2: I + III

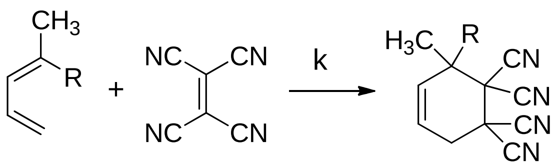


Steric Effects

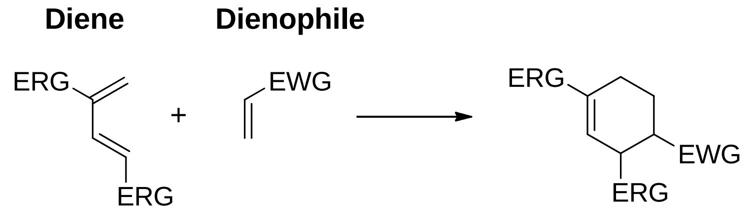


	rate k
R = H	1
Me	4.2
t-Bu	< 0.05

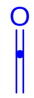
S-Cis Conformation



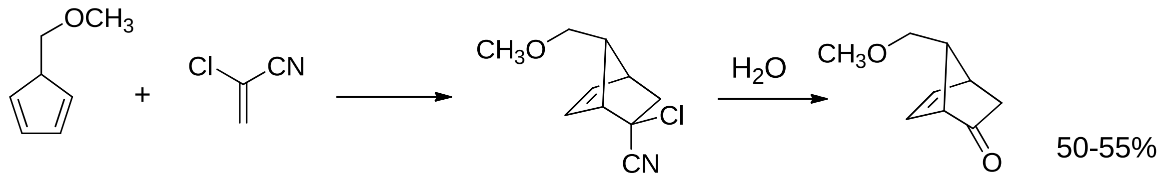
	rate k
R = H	1
Me	10^{-3}



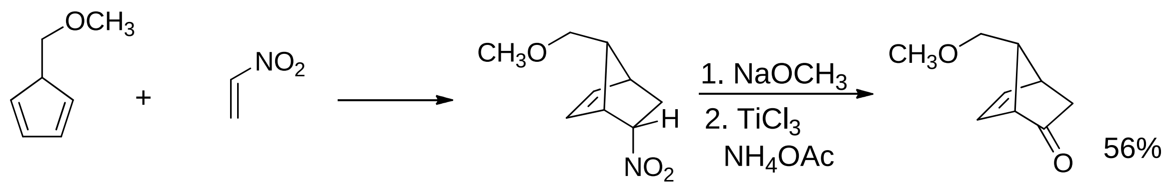
Dienophile

a. ketene equivalent 

1. α-chloroacrylonitrile

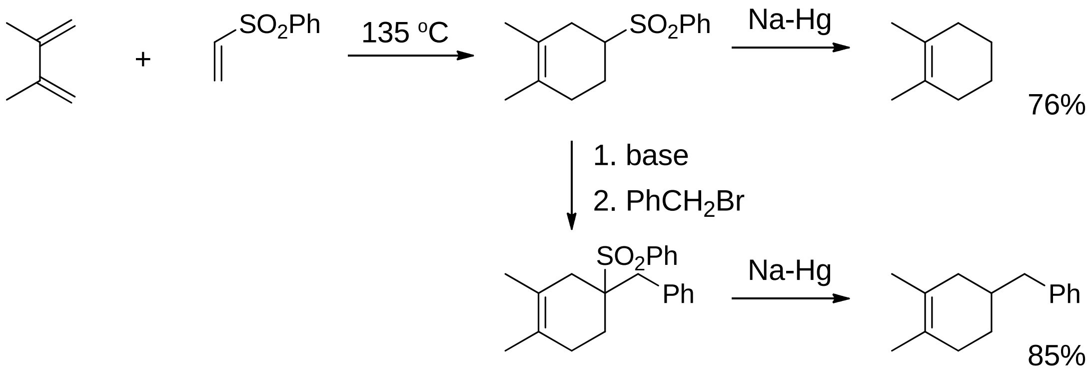


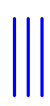
2. nitroalkane



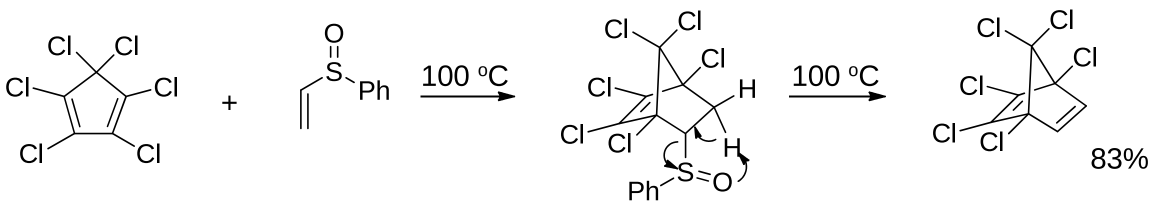
b. ethylene equivalent

vinyl sulfone

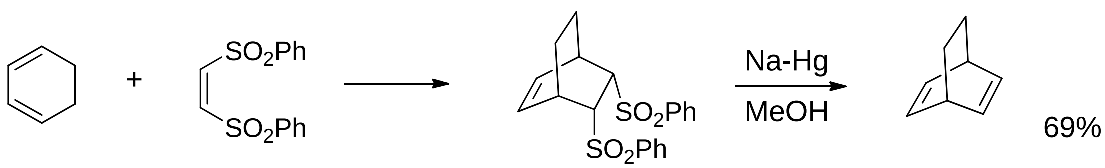


c. acetylene equivalent 

1. phenyl vinyl sulfoxide

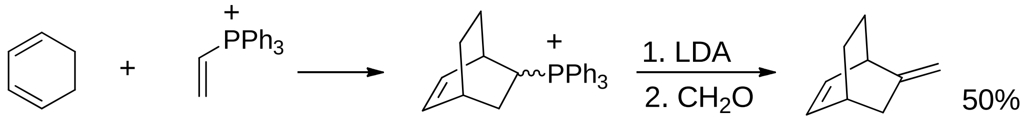


2. bis(benzenesulfonyl)ethene



d. allene equivalent

vinylphosphonium salts

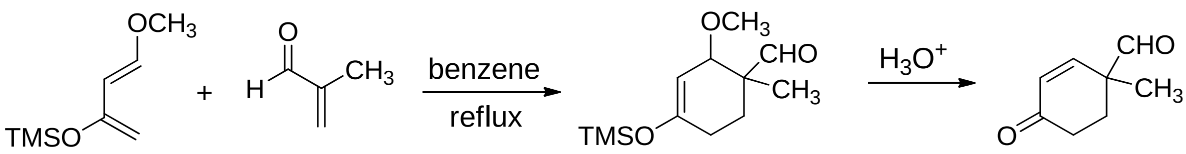


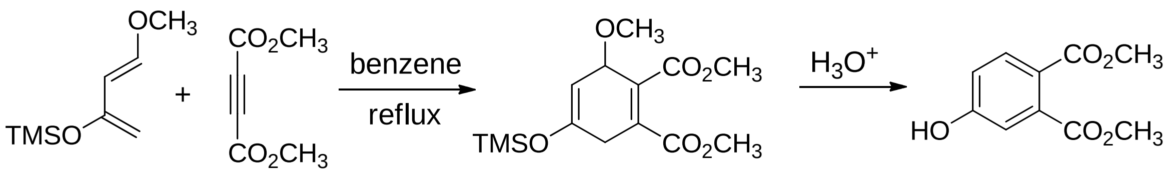
Diene

Simple dienes are good enough to react with "good" dienophile. Steric effect may be important.

a. Functionalized diene

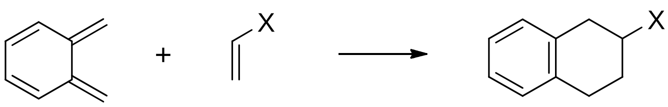
Danishefsky's diene





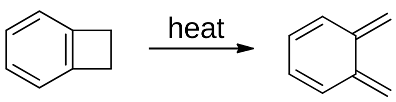
b. Unstable diene : highly reactive - in situ generation

Quinodimethanes

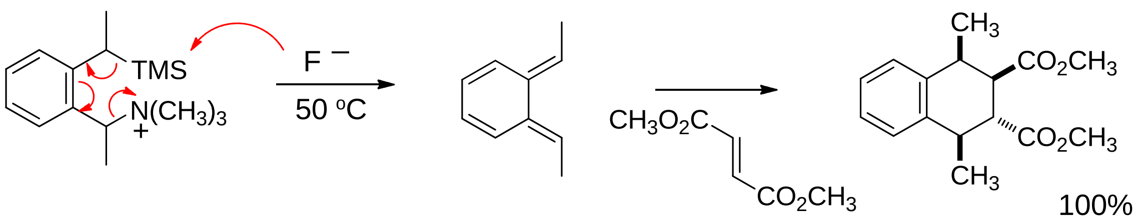


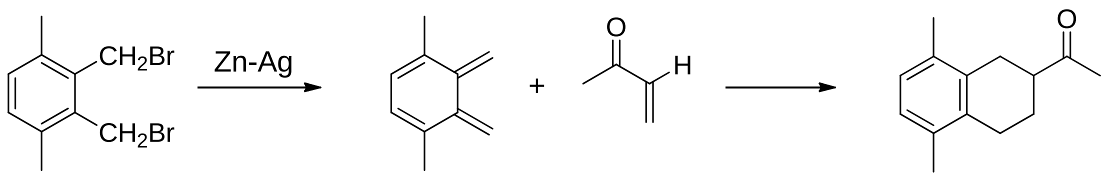
Generation of quinodimethanes

1. pyrolysis of benzocyclobutenes



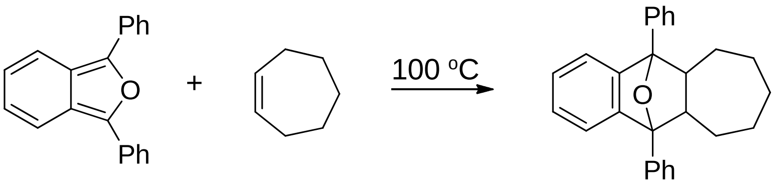
2. elimination from α,α-ortho-disubstituted benzenes





c. Highly reactive dienes

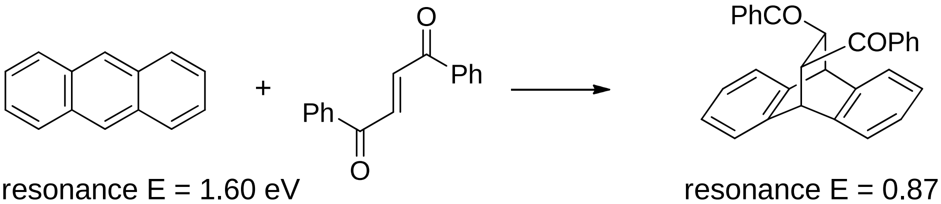
Benzo[C]furan (isobenzofuran)



69%

d. Moderately reactive dienes

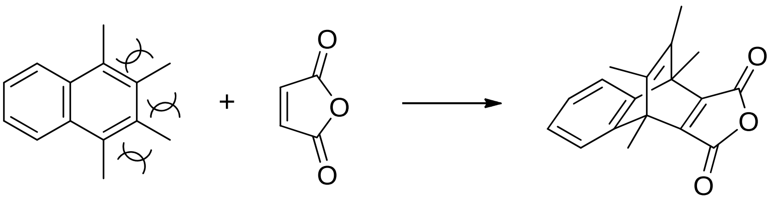
Polycyclic aromatic hydrocarbons



56%

resonance E = 1.60 eV

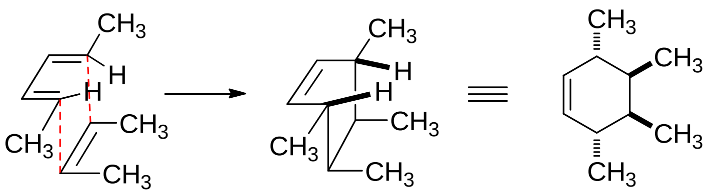
resonance E = 0.87 eV x 2

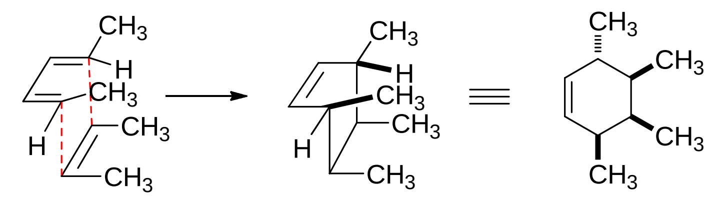


82%

Stereochemistry

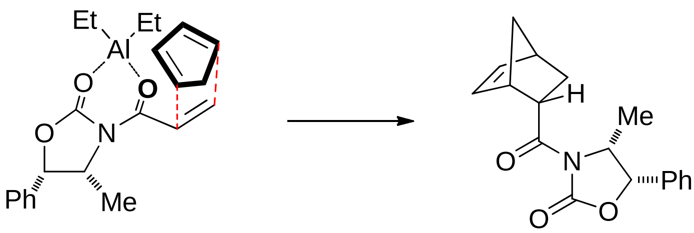
diastereoselectivity





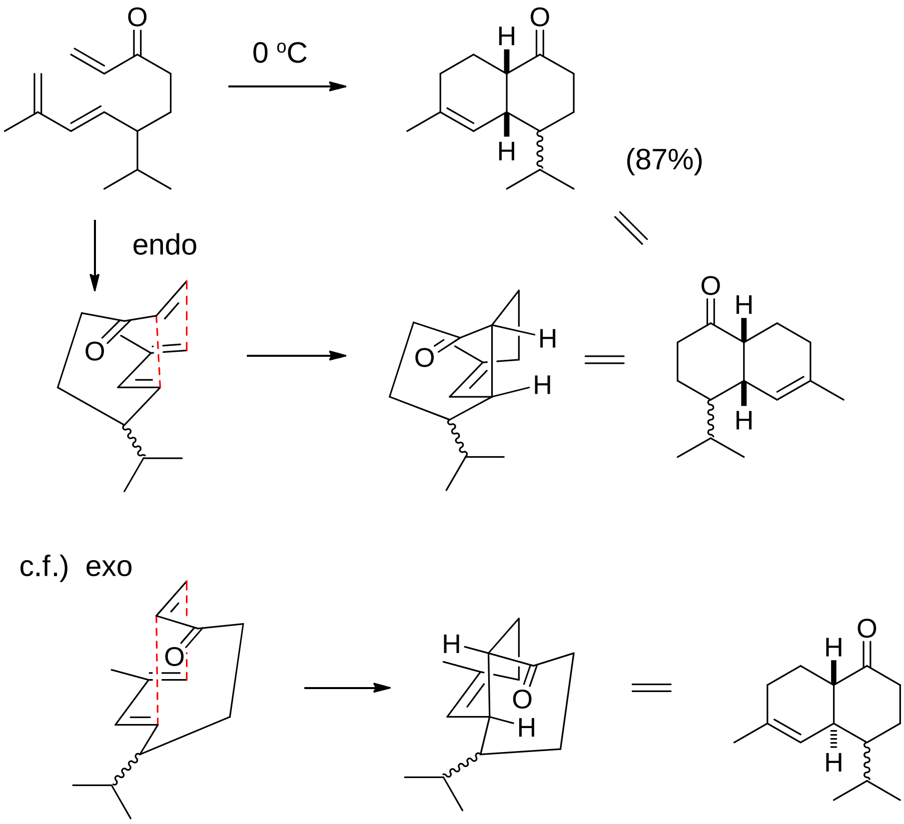
enantioselectivity

endo selectivity

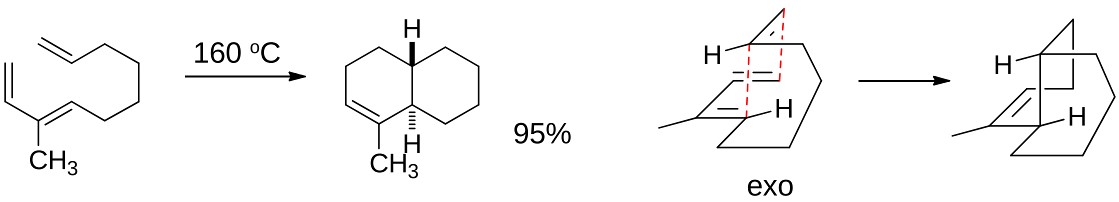


Intramolecular Diels-Alder Reaction

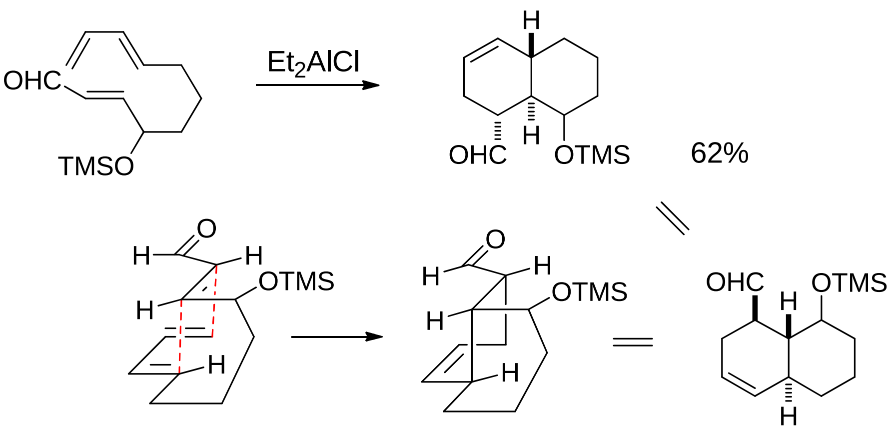
1.



2.



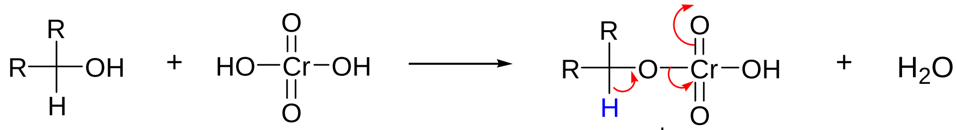
3.

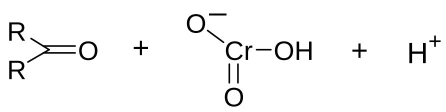


Chapter 4. Oxidation

4-1. Oxidation of alcohols to aldehydes, ketones or carboxylic acids

General Mechanism of Alcohol Oxidation

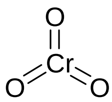




Oxidants

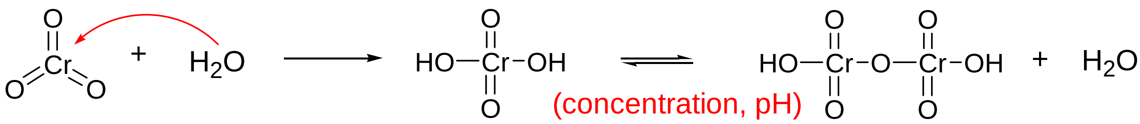
a. Transition metal oxidants

1) Cr(VI) - based reagents



chromium(IV) trioxide

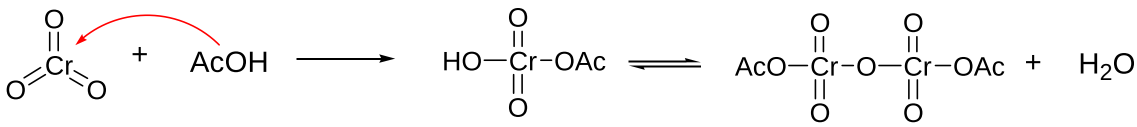
Jones' reagent aicdic aqueous solution of chromic acid CrO_3 + aq. H_2SO_4



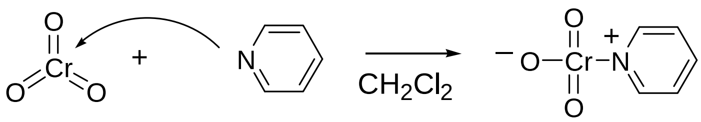
chromic acid dichromic acid

Dropwise addition of the reagent to an acetone solution of alcohols at 0 ^oC

CrO_3 in AcOH

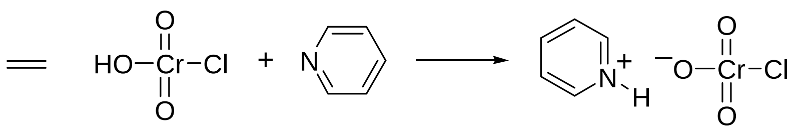


Collin's reagent: CrO_3 in pyridine good for acid sensitive substrates



PCC pyridinium chlorochromate

CrO_3 in HCl + pyridine

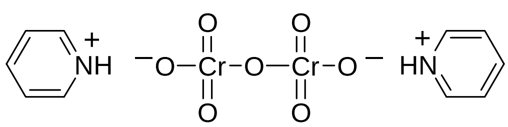


PDC pyridinium dichromate

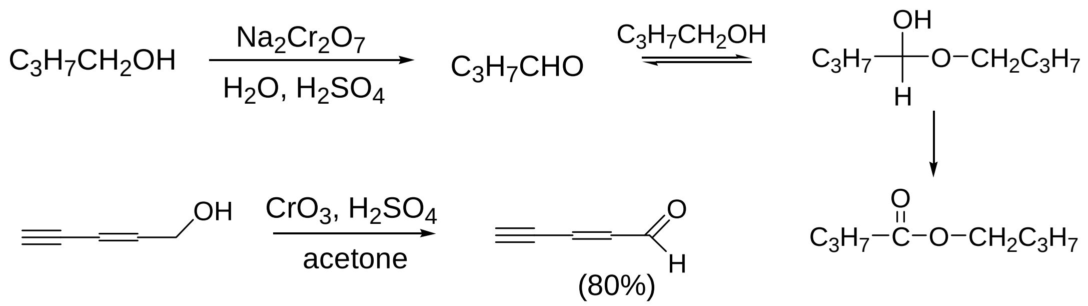
solvent: DMF or CH_2Cl_2

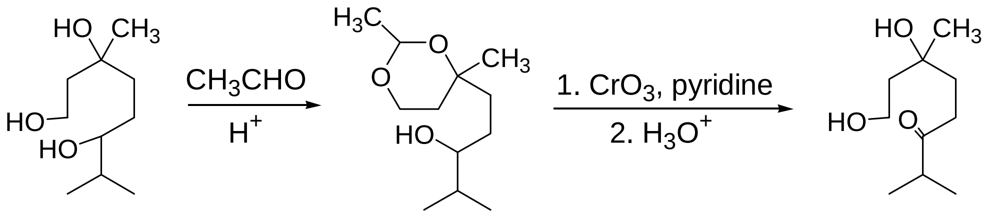
CrO_3 in H_2O (small amount) + pyridine

oxidation of 2^0 alcohols or allylic alcohols



[examples]





2) Mn(VII), Mn(IV)

Potassium permanganate **$KMnO_4$**

Very strong oxidant - overoxidation problem

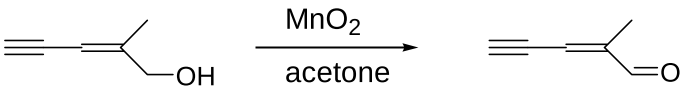
insoluble in most organic solvents ⟶ Use 18-Cr-6 or PTCatalyst

Manganese dioxide **MnO_2**

selective for allylic and benzylic alcohol

preparation

$$MnSO_4 + KMnO_4 + 2NaOH \longrightarrow 2MnO_2 + Na_2SO_4 + KOH + H_2O$$



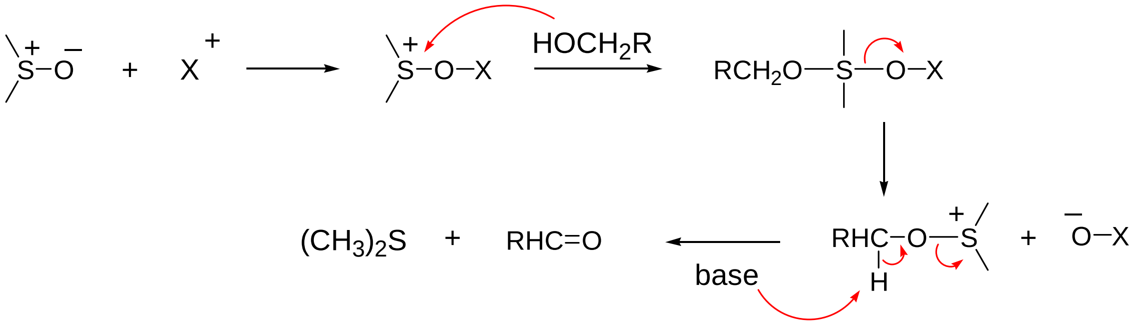
35%

b. Other Oxidant

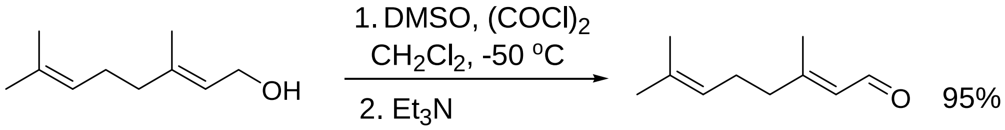
1) DMSO + electrophile (X^+)

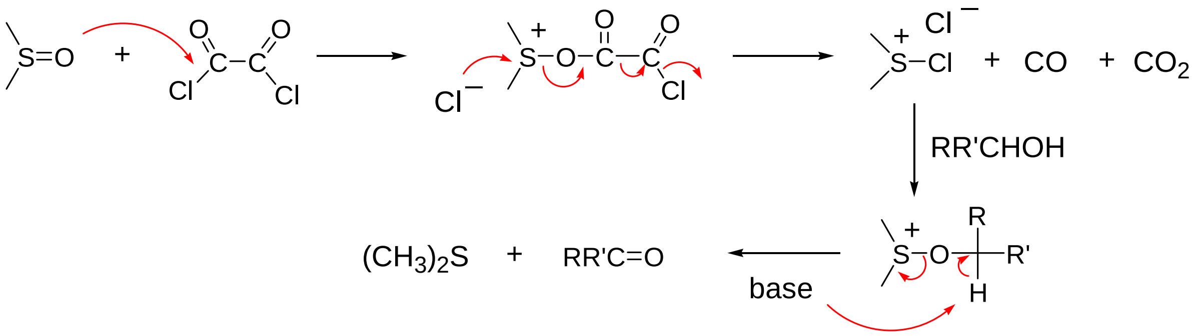
DCC, Ac_2O, Tf_2O, Oxalic chloride

<mechanism>

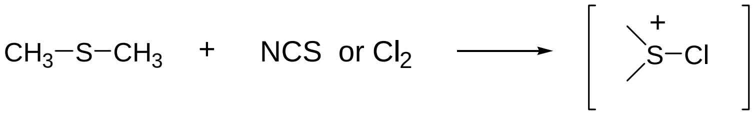


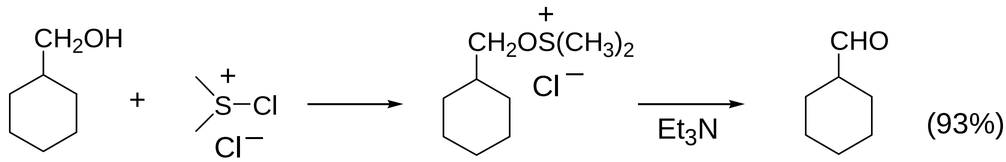
Swern Oxidation



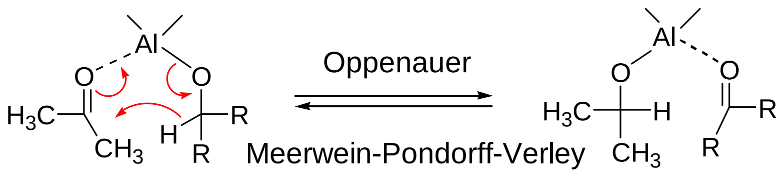


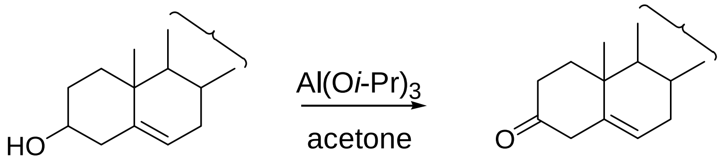
2) Corey - Kim procedure





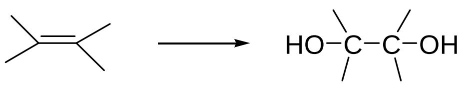
3) Oppenauer oxidation





4-2. Oxidation of carbon - carbon double bonds

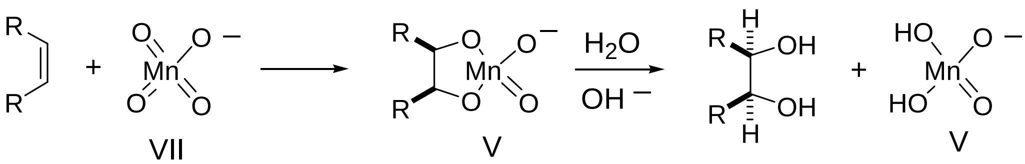
4-2-1. Perhydroxylation



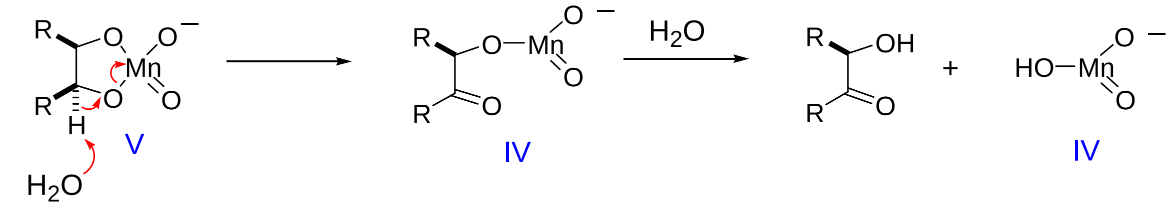
a) $KMnO_4$ potassium permanganate

syn - perhydroxylation ← cyclic intermediate

control further oxidation (ketol formation) : glycol formation in **alkaline solution**



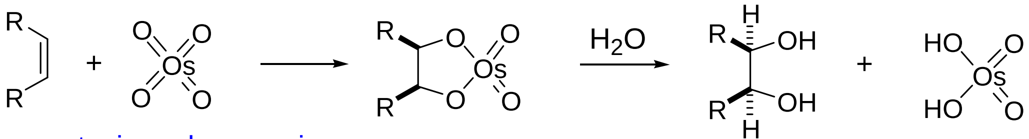
ketol formation



b) Osmium tetroxide

Selective and mild glycol formation

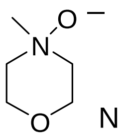
Stereospecific syn addition through cyclic osmate ester



toxic and expensive

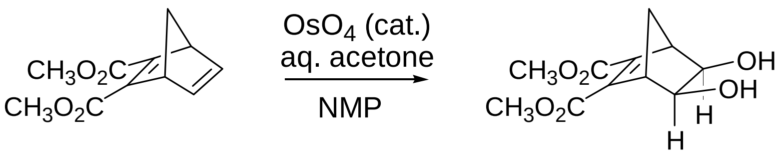
Upjohn Process

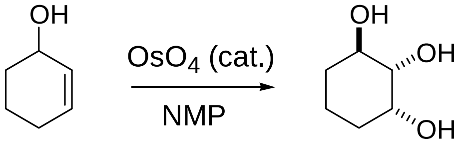
Use amine oxide as a stoichiometric oxidant: *N*-methylmorpholine-*N*-oxide



NMP

t-BuOOH or $BaClO_3$ can also be used.

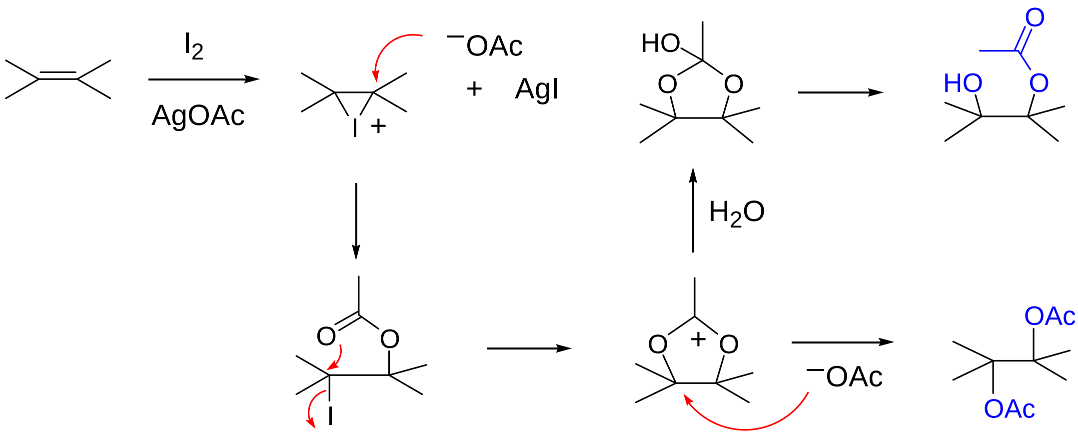




c) Iodine and silvercarbonate

Prevost condition (anhydrous condition) ⟶ trans-glycol derivative

Woodward condition (aqueous condition) ⟶ cis-glycol derivatives

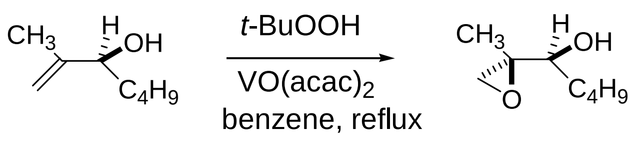


4-2-2 Epoxidation

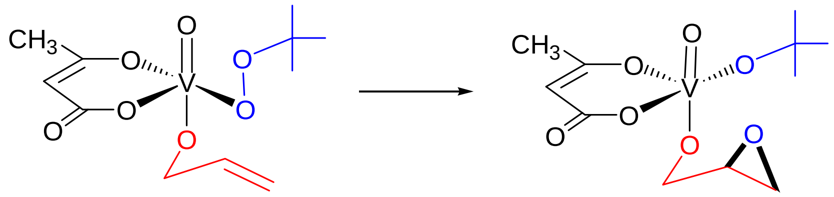
a) Transition metal oxidants

Epoxidation of allylic alcohol

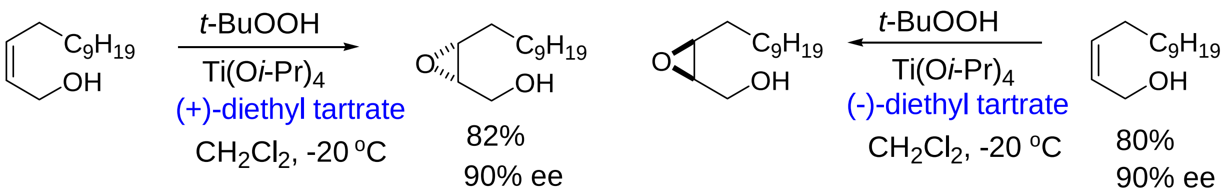
- V, Mo, Ti as a catalyst
- *t*-BuOOH as a stoichiometric oxidant

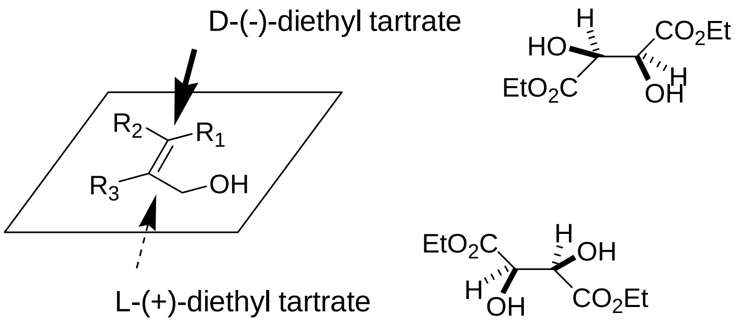


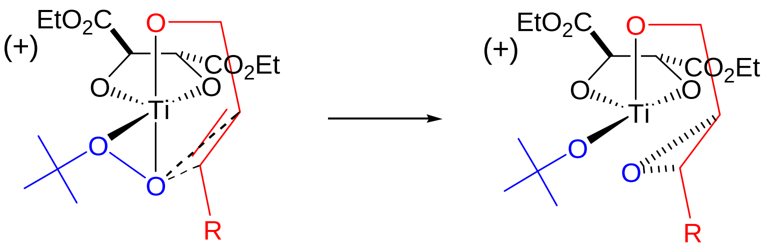
>99% selectivity



Asymmetric epoxidation of allylic alcohol - Sharpless epoxidation





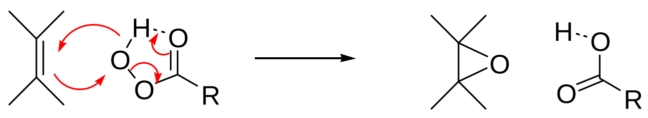


b) Peroxidic reagents

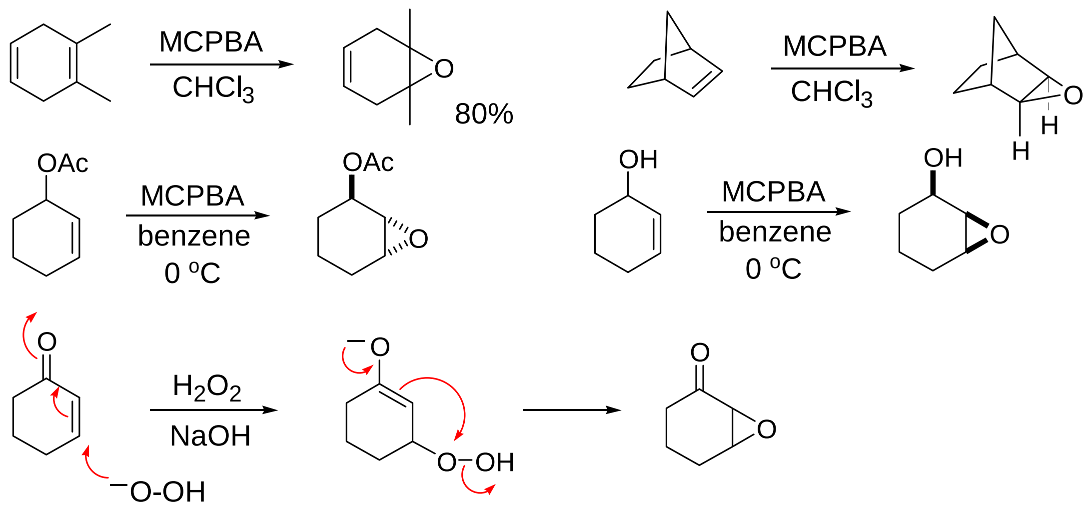
MCPBA, peracetic acid perbenzoic acid etc.

$$RCOOH + H_2O_2 \rightleftharpoons H_2O + RCO_3H$$

Stereospecific syn addition　　　concerted process

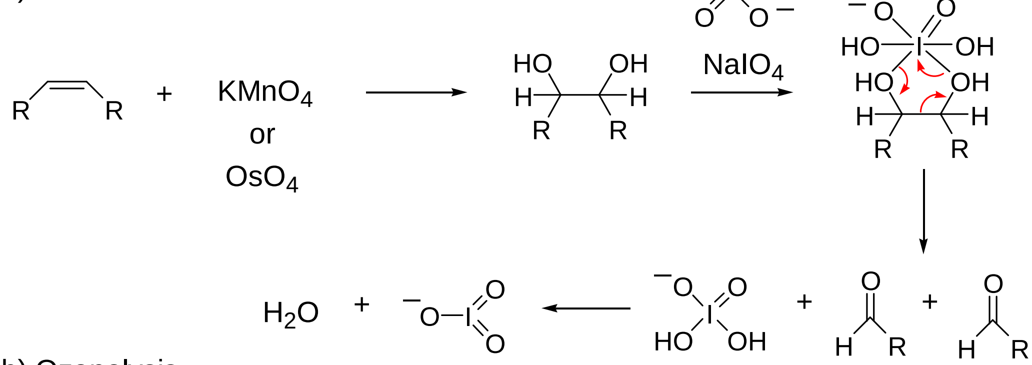


rate increased by electron donating substituents on alkenes and electron withdrawing substituents on peroxy-acid

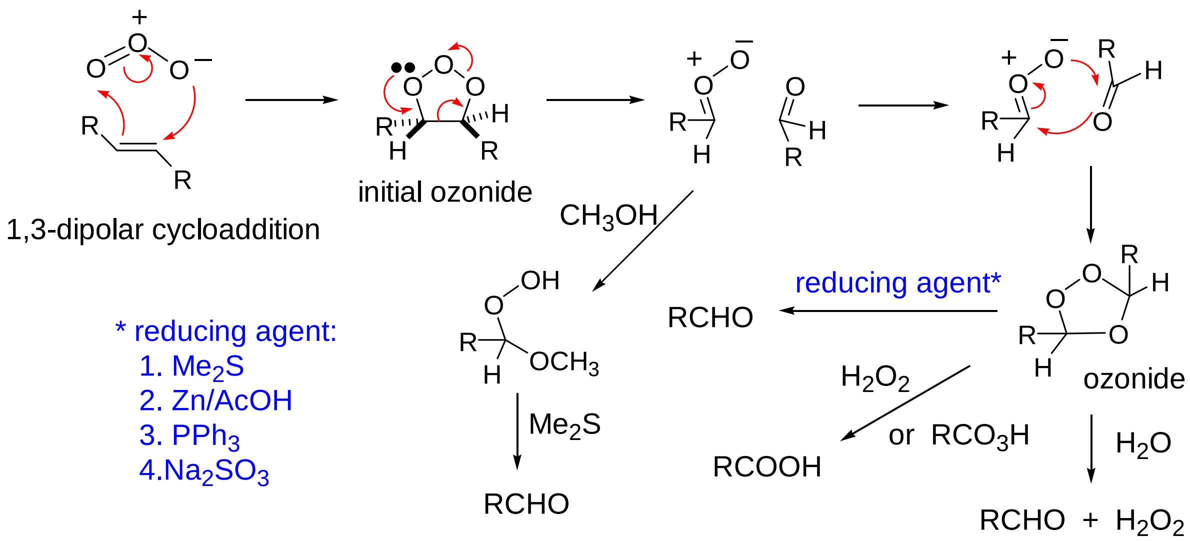


4-2-3 Cleavage of double bonds

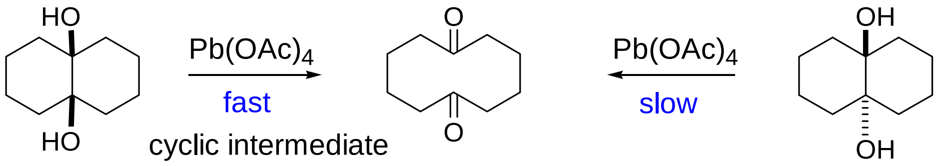
a) Transition metal oxidants



b) Ozonolysis

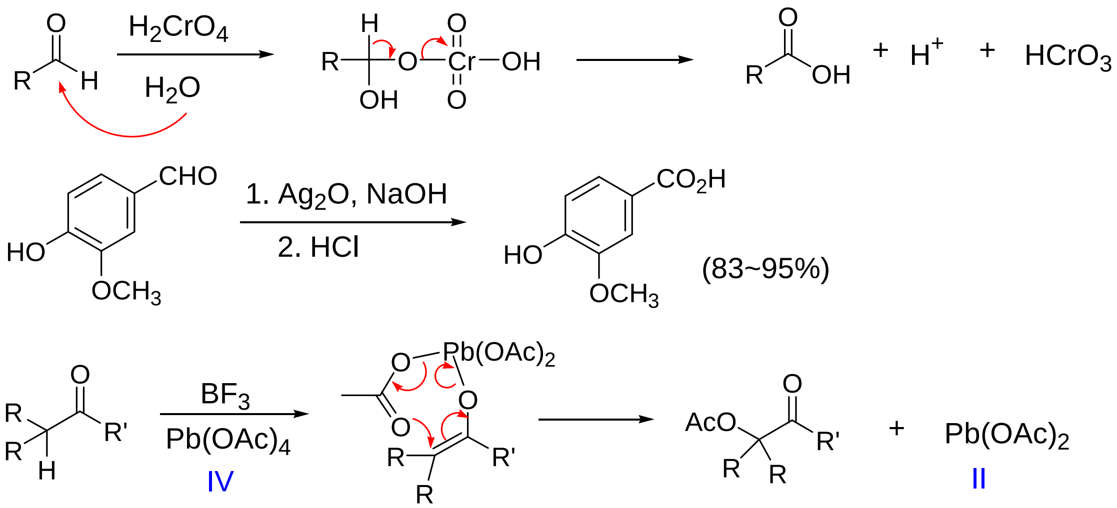


c) $Pb(OAc)_4$

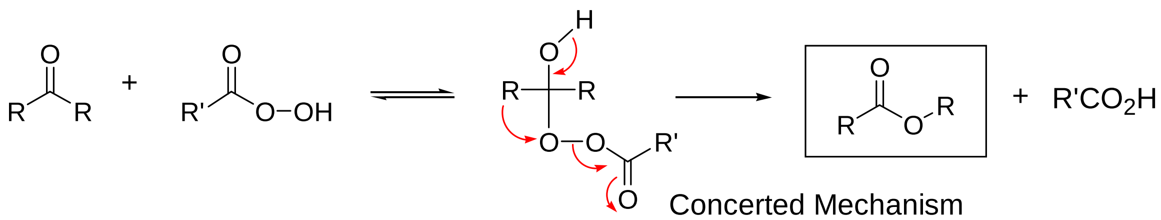


4-3 Oxidation of Ketones and Aldehydes

a) Transition Metal Oxidant

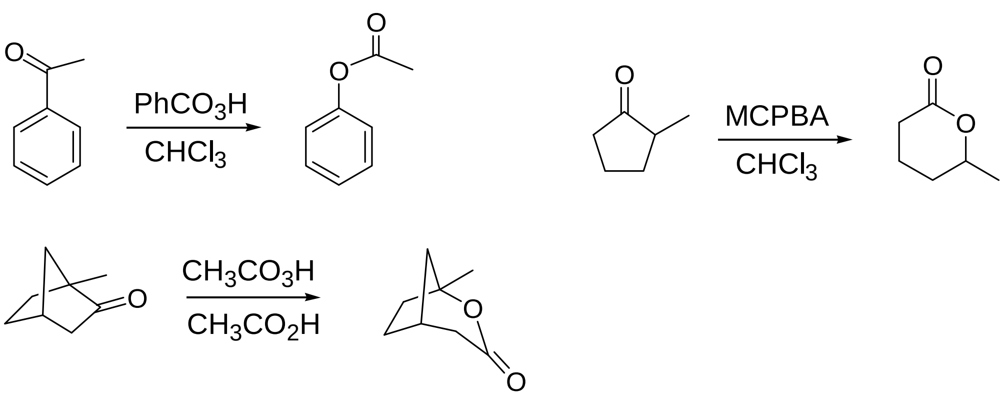


b) Peroxy-acid Oxidants: Baeyer - Villiger oxidation



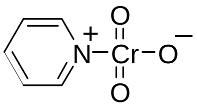
Migratory Aptitude

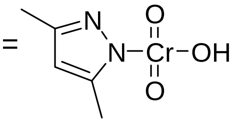
t-alkyl, s-alkyl > benzyl, phenyl > primary-alkyl > cyclopropyl > methyl

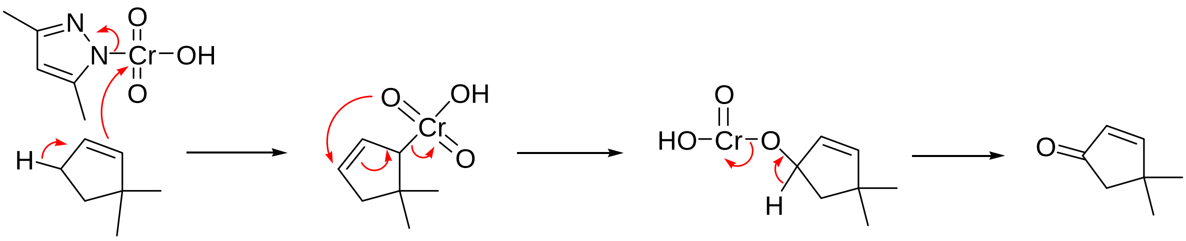


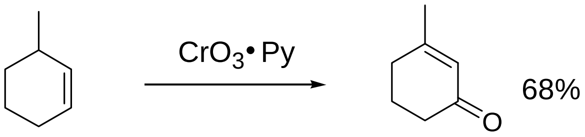
4-4 Allylic Oxidation

a) Transition Metal Oxidants

CrO_3• Py = 

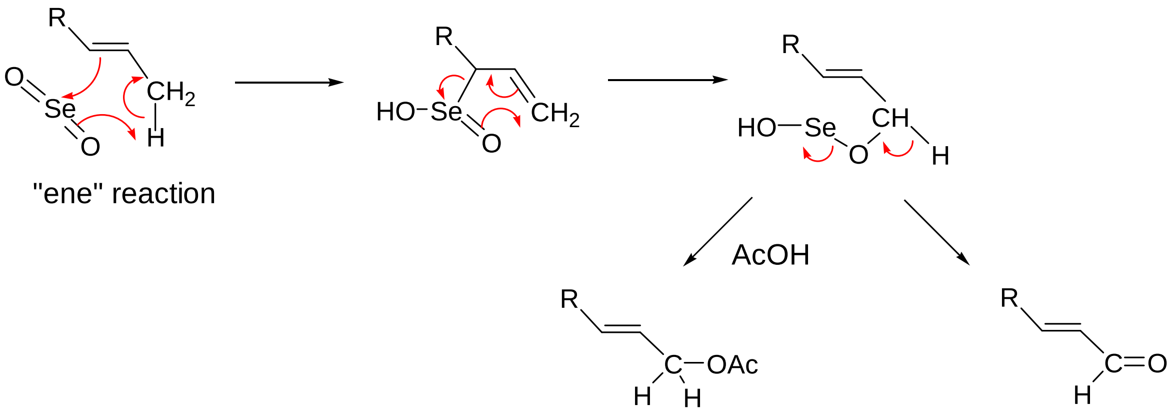
CrO_3•3,5-dimethylpyrazole = 





b) SeO_2

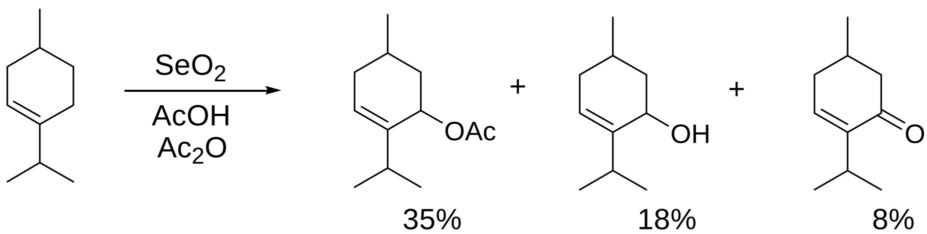
Alkenes ⟶ α,β-unsaturated carbonyl compounds (major product)
allylic alcohols or esters



Catalytic process

1.5-2 mol% SeO_2 / *t*-BuOOH (stoichiometric reagent)

allylic alcohol is the major product



Chapter 5. Reduction

5.1 Catalytic Hydrogenation

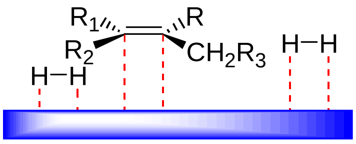
$$RHC{=}CHR' + H_2 \xrightarrow[\text{catalyst}]{\text{transition metal}} RH_2C\text{-}CH_2R'$$

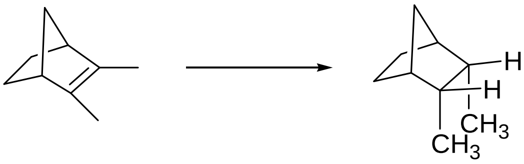
"Pt, Pd, Rh, Ru, Ni"

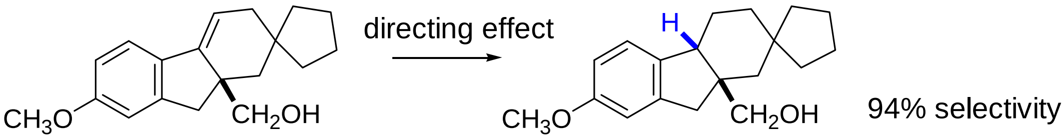
<mechanism>

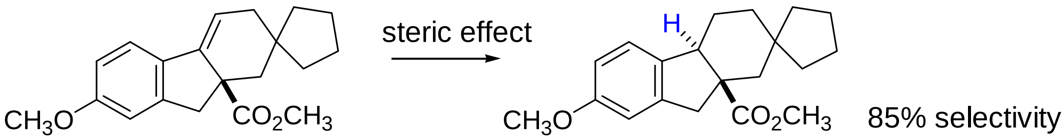
Stereoselective syn addition from the less hindered side of double bond

Heterogeneous (may cause double bond migration)

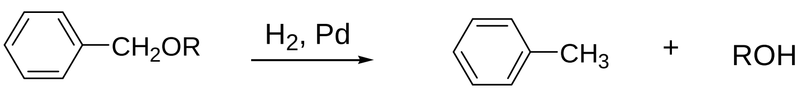






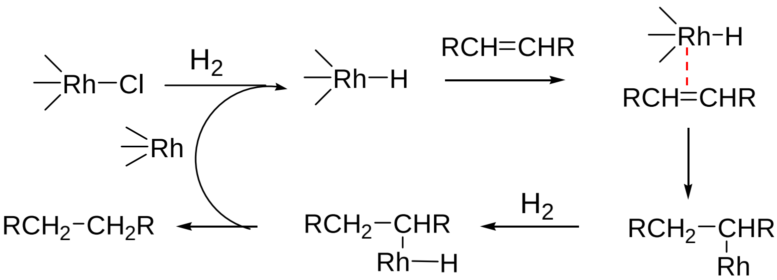


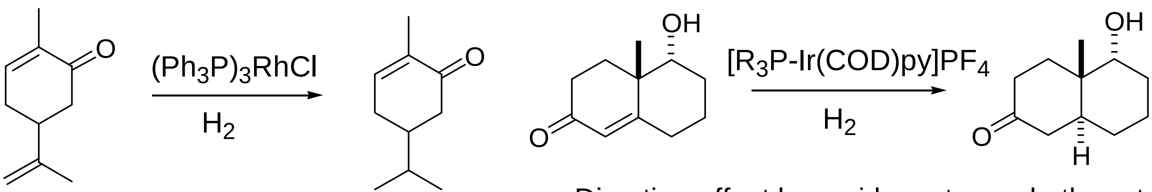
Hydrogenolysis



Homogeneous catalysts (soluble complex)

Wilkinson's catalyst : $(PPh_3)_3RhCl$ minimize the migration process

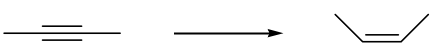




Directing effect by amide, ester and ether etc.

Lindlar's catalyst: partial reduction of alkynes to (*Z*)-alkenes

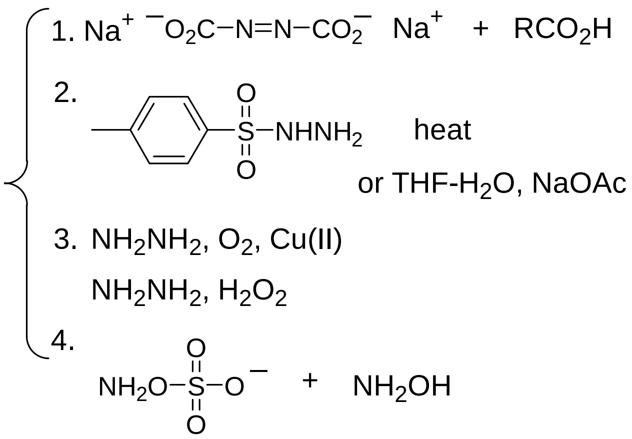
Pd-$CaCO_3$ (Lead) or quinoline : heterogeneous cat.

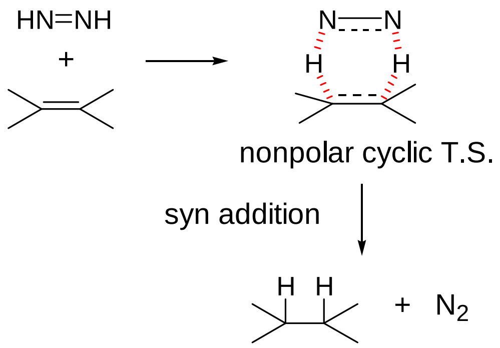


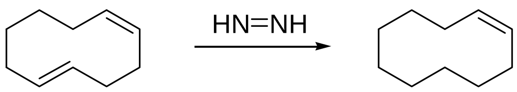
5-2 Diimide

HN=NH

unstable in situ generation







5-3 Group III Hydride-donor Reagents

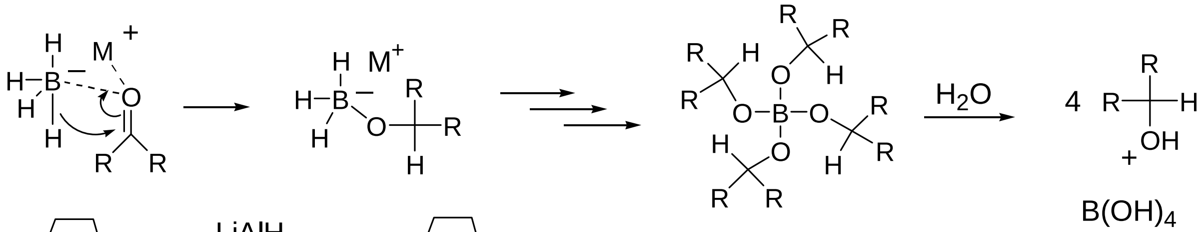
B, Al

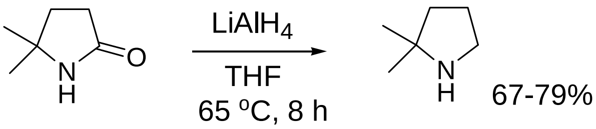
5-3-1 Reduction of Carbonyl Compounds

$NaBH_4$	$LiAlH_4$
Mild reducing agent Reacts rapidly with aldehydes and ketones Reacts slowly with esters Solvents: EtOH, H_2O	Powerful hydride donor reagent Reacts rapidly with esters, nitriles and amides as well as aldehydes and ketones Solvents: THF or ether

<No Reaction with Isolated Double Bonds !!!>

<Mechanism of reduction>





Selectivity or Reactivity of B/Al hydrides

1. Nature of the metal cation

Li, Ca > Na ⟶ $LiBH_4$, $Ca(BH_4)_2$ > $NaBH_4$

Lewis acid strength
or hardness

Selectivity or Reactivity of B/Al hydrides

2. Effect of Ligands

a. Alkoxy ligand: Increase solubility of the reagent
selective reduction @ low temperature

$LiAlH(Ot\text{-}Bu)_3$ $NaAlH_2(OCH_2CH_2OCH_3)_2$ = Red-Al™

b. Nitrile ligand: Electron withdrawing group

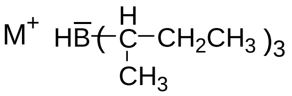
reduced reactivity Iminium ion ⟶ amine

$NaBH_3CN$

c. Alkyl ligand

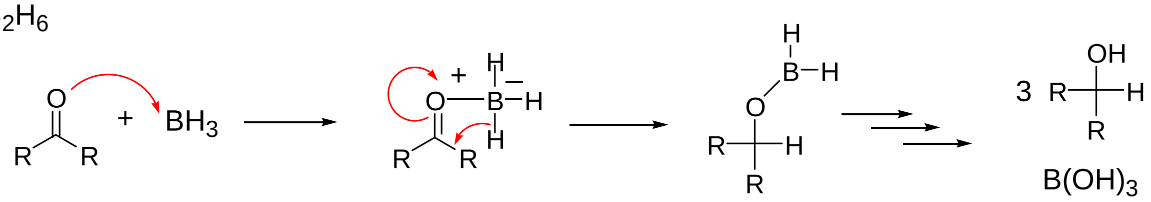
Size effect ⟶ Selective reduction

Selectrides™ (stereoselective reduction)



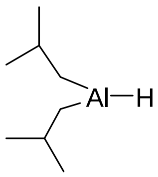
Neutral Boron and Aluminum Hydrides

BH_3 : Borane AlH_3 : Alane
B_2H_6



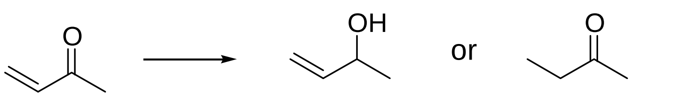
Carboxylic acid ⟶ primary alcohol
Amide ⟶ Amine
Do not react with esters, nitro, and cyano

DIBAL



Selective reduction of esters to aldehydes at low temperature

Reduction of a,β–unsaturated carbonyl compounds



1,2-reduction 1,4-reduction

1,2-reduction

Luche condition: $NaBH_4$ + $CeCl_3$
DIBAL
9-BBN

1,4-reduction

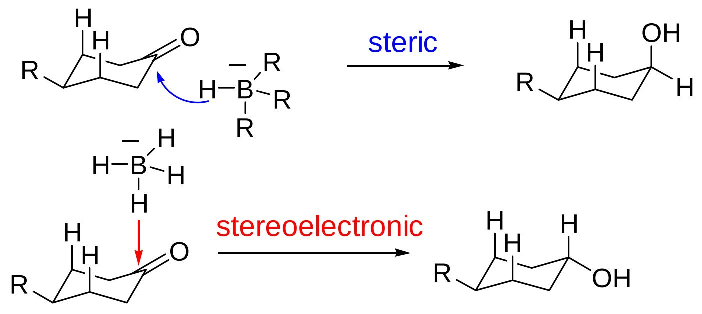
Catalytic hydrogenation
"H^-" + Copper salt : Cu-H
Wilkinson's catalyst + Et_3SiH

Stereoselectivity

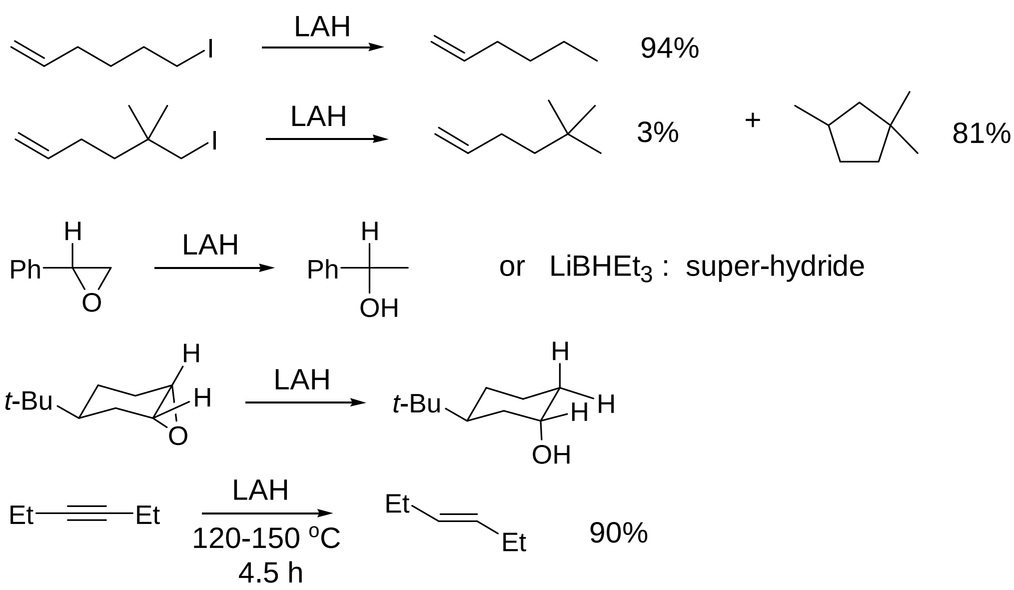
Cyclohexanone derivatives

Steric approach control vs Stereoelectronic control

sterically hindered hydride donor approaches to the equatorial position to give axial alcohol



5-3-2 Reduction of Other Functional Groups



5-4 Hydrogen Atom Donors

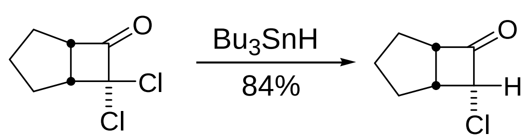
***n*-Bu$_3$SnH**

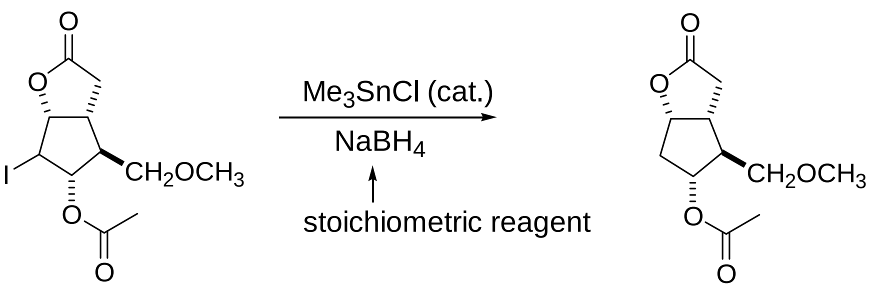
1. Replace halogen by H <Free Radical Chain Mechanism>

In• + Bu_3SnH ⟶ In-H + Bu_3Sn•

Bu_3Sn• + R-X ⟶ R• + Bu_3S_nX

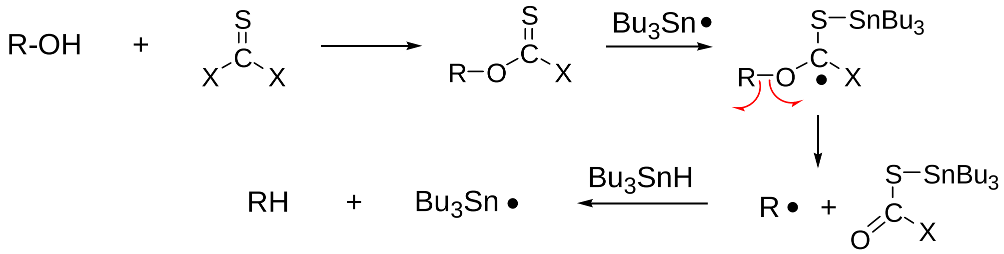
R• + Bu_3SnH ⟶ RH + Bu_3Sn•

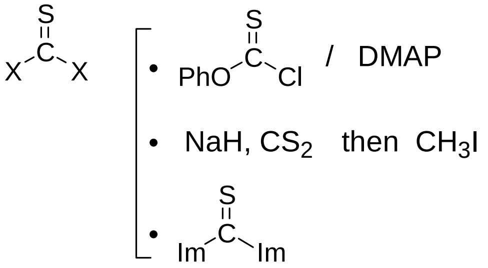




n-Bu_3SnH

2. Reductive deoxygenation of alcohols

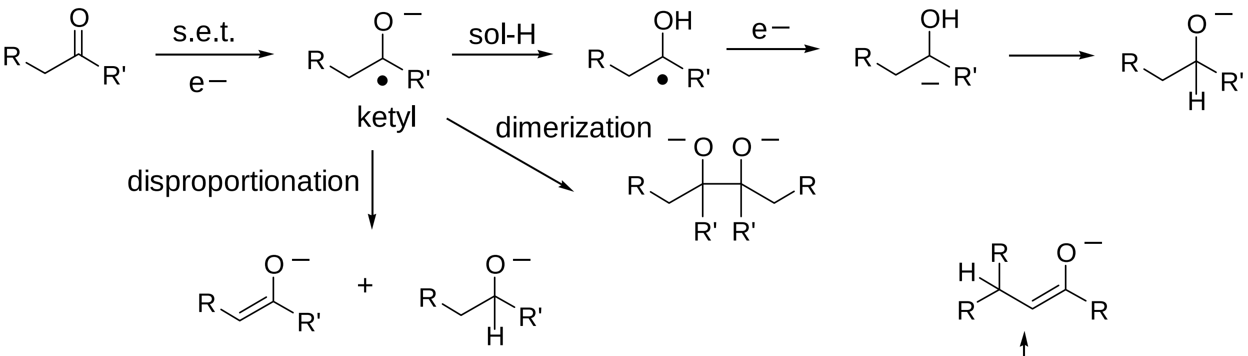




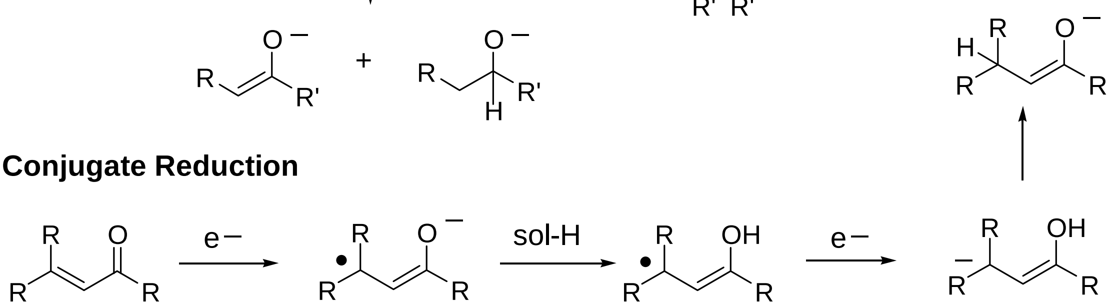
5-5 Dissolving - Metal Reduction

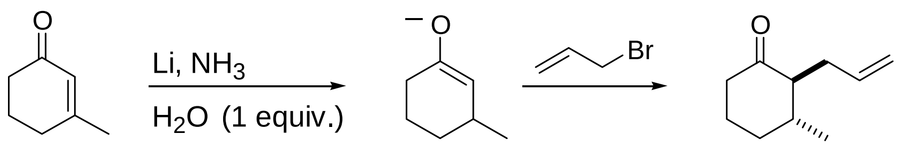
5-5-1 Addition of hydrogen

<mechanism> single electron transfer



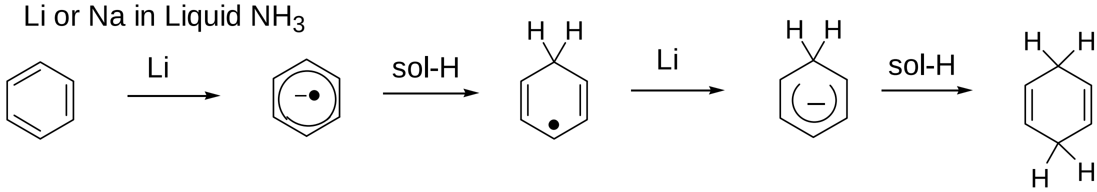
Conjugate Reduction





Birch Reduction partial reduction of aromatic ring

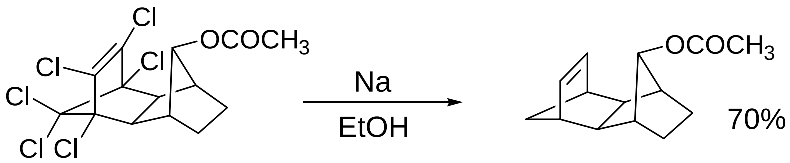
Li or Na in Liquid NH_3



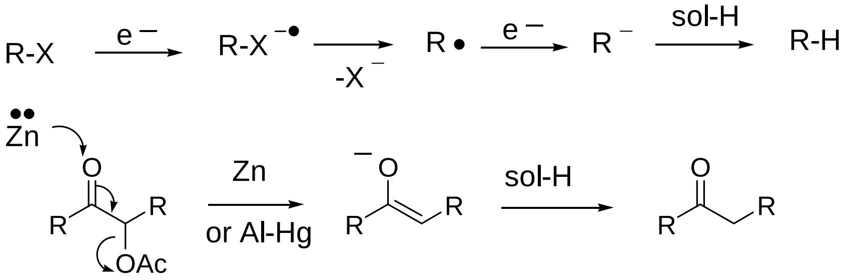
*Benzene ring with electron-withdrawing substituents reacts too fast !!!

Regiochemisty for protonation

5-5-2 Reductive removal of functional group

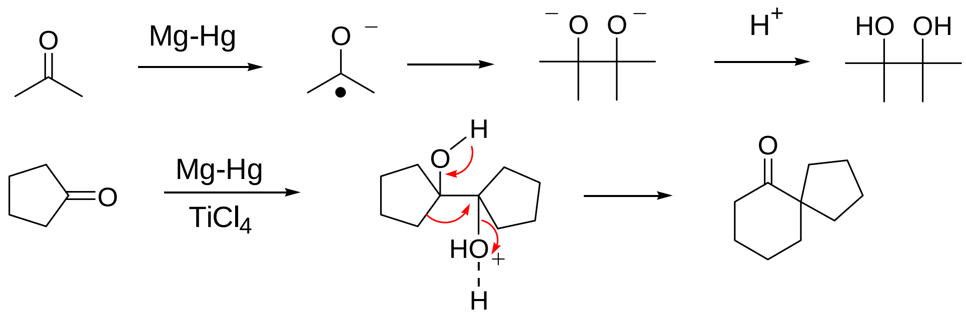


<Mechanism>



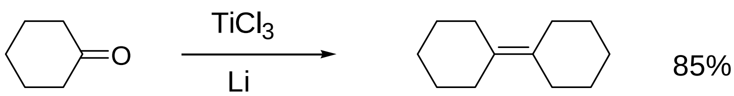
5-5-3 Reductive carbon-carbon bond formation

Pinacol coupling

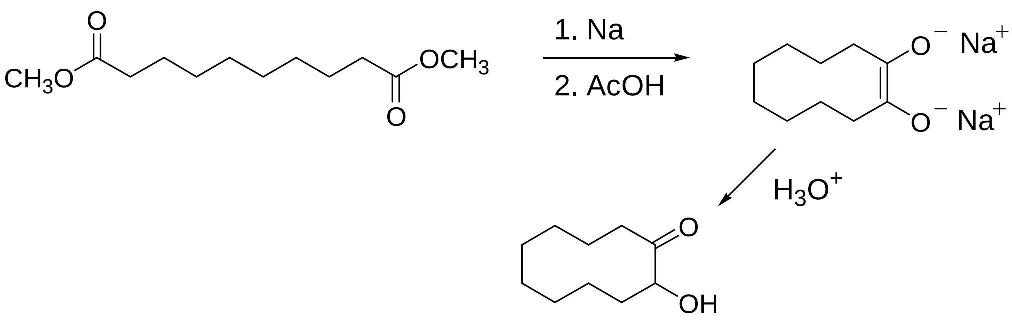


pinacol

$TiCl_3$ and Li or K or Zn-Cu or LAH

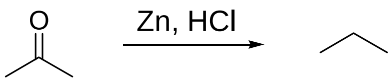


Acyloin condensation Esters ⟶ α-hydroxyketone (acyloin)

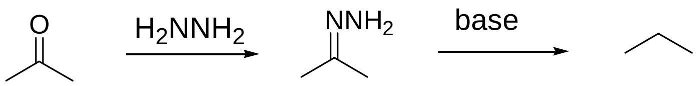


5-6 Reductive Deoxygenation of Carbonyl Group

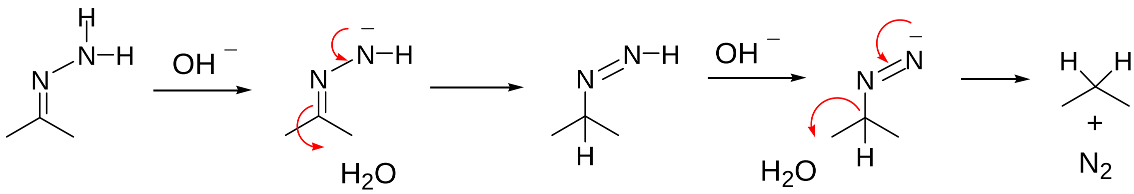
Clemmensen reduction Strongly acidic condition



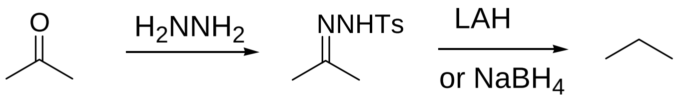
Wolff-Kishner reduction base-catalyzed decomposition of hydrazone



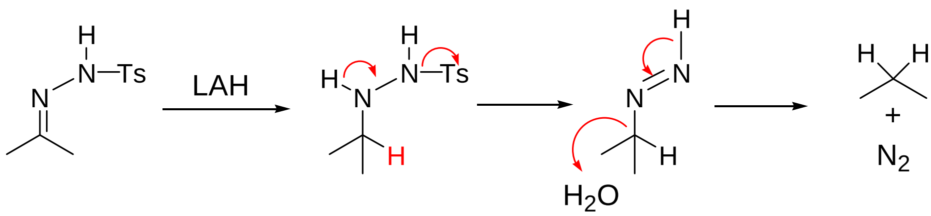
<mechanism>



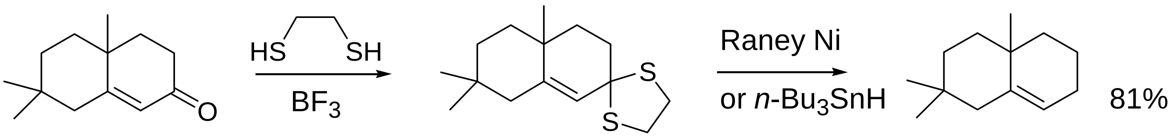
Tosylhydrazone reduction



<mechanism>

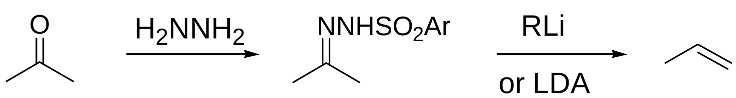


Thioketal Desulfurization



Shapiro reaction

Carbonyl group ⟶ Alkene



<mechanism>