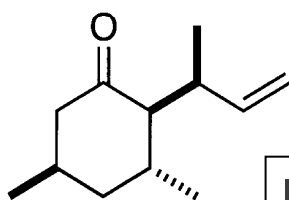
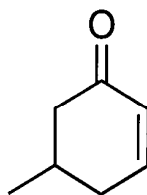


Concise and Comprehensive Course Book of
Organic Synthesis

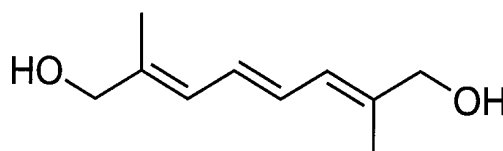
10th Edition (2016.12)



Prepared by Sangho Koo



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East China University of Science and
Technology, Shanghai, China**



Concise and Comprehensive Course Book of Organic Synthesis

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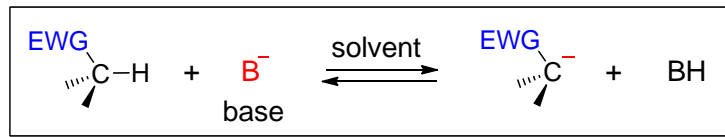
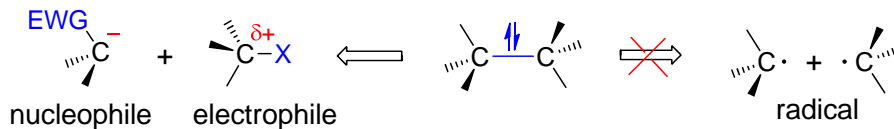
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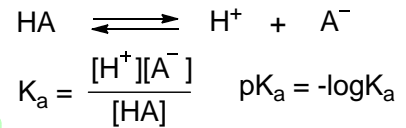
Reference Books

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



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 ₃ CO ₂ H	5	Ph-C(=O)CH ₃	19	Ph-NH ₂	~30
	9	CH ₃ -C(=O)-CH ₃	20	Ph ₃ CH	~40
	9	CH ₃ -S(=O)(=O)-CH ₃	~23	CH ₃ -S(=O)-CH ₃	~40
CH ₃ NO ₂	10	CH ₃ -CO ₂ Et	~24		40
	11	CH ₃ CO ₂ H	~24		41
	13	CH ₃ -C≡C-H	25		43
		CH ₃ CN	~25		44
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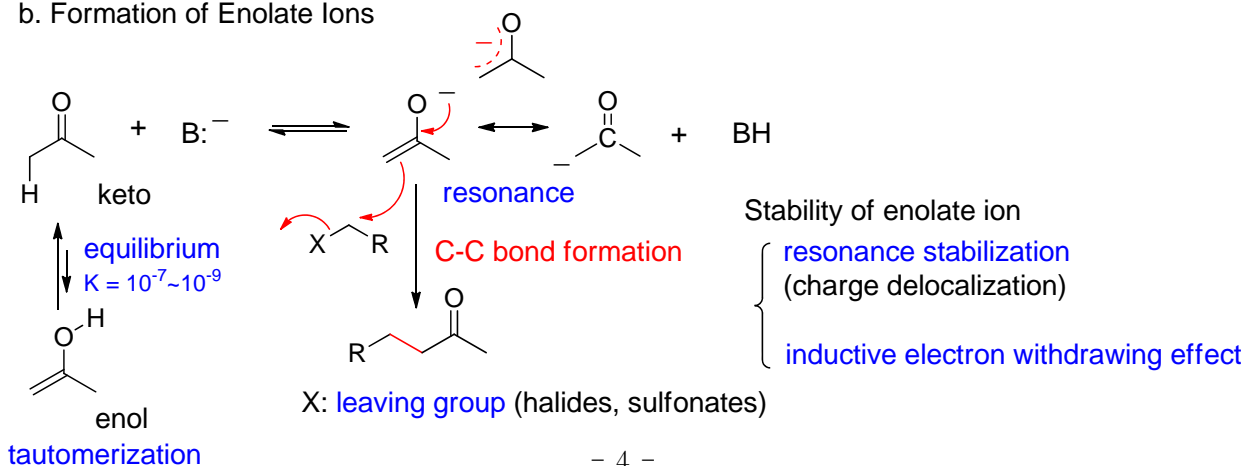
Anion Stabilizing Effect



Substituent Effect on pK_a

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

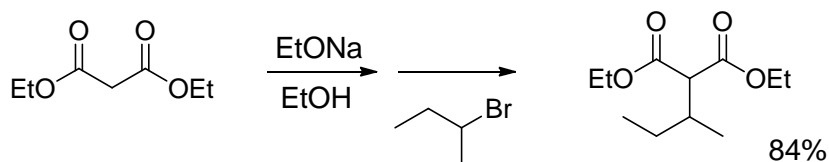
b. Formation of Enolate Ions



c. pK_a of the conjugate acid of some bases

conjugate acid / base	pK _a	conjugate acid / base	pK _a
H ₂ O / OH ⁻	16		33
MeOH / MeO ⁻	16	Lithium Diisopropylamide (LDA)	
<i>t</i> -BuOH / <i>t</i> -BuO ⁻	19	Ph ₃ CH / Ph ₃ C ⁻	33
	25	NH ₃ / NH ₂ ⁻	35
Hexamethyldisilazide (HMDS)		RH / R ⁻	~50
c.f. Et ₃ NH ⁺ / Et ₃ N	11	Ph-NH ₃ ⁺ / Ph-NH ₂	4.6
Et ₂ NH ⁺ / Et ₂ NH	10.5	Py-H ⁺ / Pyridine	5.3

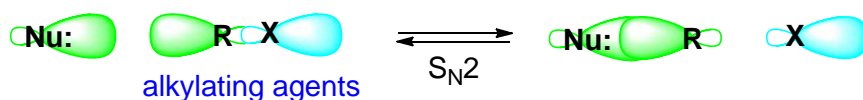
d. alkylating agents



Mechanism of alkylation

Stereoelectronic effect (favors trajectory of maximum orbitals overlap)

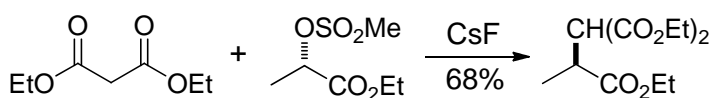
backside attack for S_N2 reaction



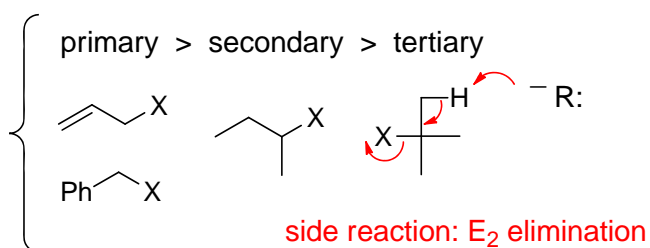
the direction of the arrow is decided by the relative stability of Nu⁻ and X⁻

X⁻ **good leaving group** - stabilized anion (resonance or charge delocalized)

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



Steric effect (favors small size reactants for alkylation)



Electronegativity Scale

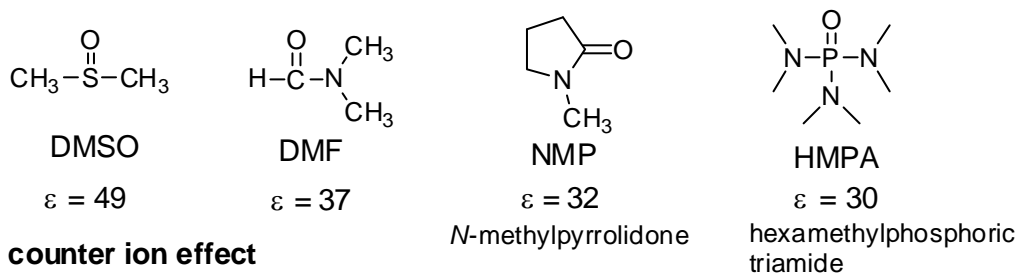
4.0	F
3.5	O
3.0	Cl, N
2.8	Br
2.5	C, S, I
2.1	H, P
2.0	B
1.8	Si

leaving group	relative rate	conjugate acid	pK _a
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 ₂ O	10 ¹	H ₃ O ⁺	-1.7
MsO ⁻	10 ⁴	MsOH	-2.6
TsO ⁻	10 ⁵	TsOH	-2.8
TfO ⁻	10 ⁸	TfOH	-6.0

e. Medium Effects in the Alkylation of Enolates

Solvent Effects (polar-nonpolar, protic-aprotic solvents)

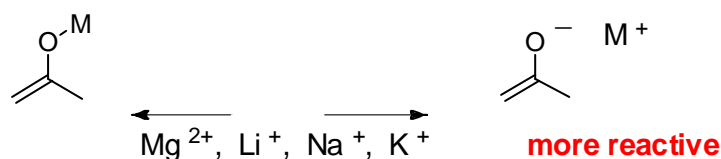
1. **polar aprotic solvent - fast enolate alkylation**



counter ion effect

covalently bound enolate anion

bare or naked enolate anion

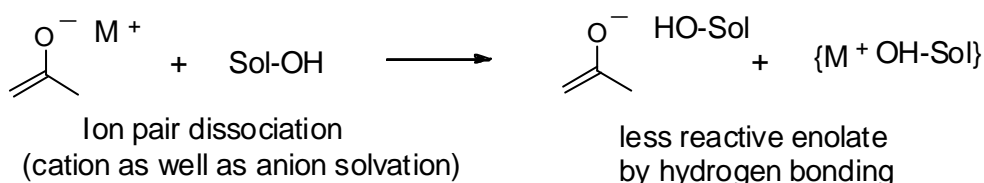


M-O bond length in Å

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

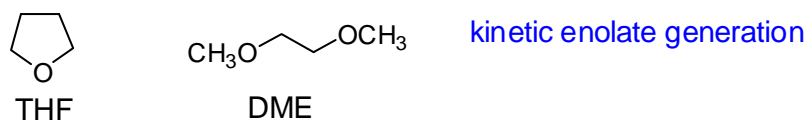
Ion pair dissociation by polar aprotic solvent \longrightarrow **reactive enolate**
(effective cation solvation)

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

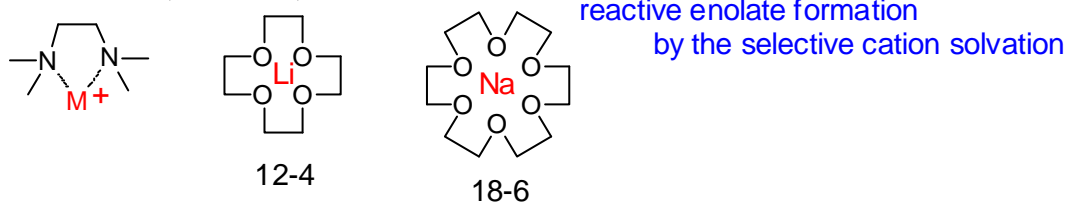


3. **Slightly polar aprotic solvent - moderately good cation solvator**

high aggregation easy workup and purification



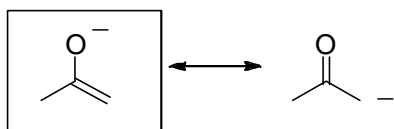
Additives: HMPA, TMEDA, crown ether



Properties of some solvents

solvent	classification	dielectric const	solvent	classification	dielectric const
H ₂ O	protic	78	DMF	aprotic	37
DMSO	aprotic	49	MeOH	protic	33
MeCN	aprotic	37	AcOH	protic	6

f. O- vs C- alkylation



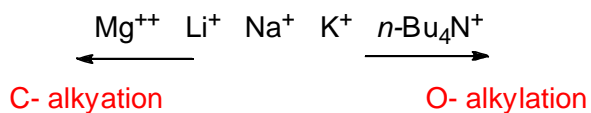
major contribution

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

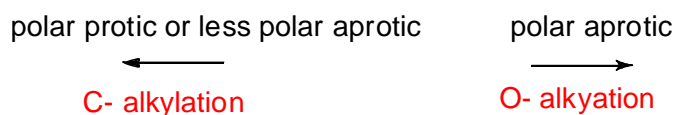
Control of O- vs C- alkylation

Free enolates give O- alkylation

1. Counter ion effects

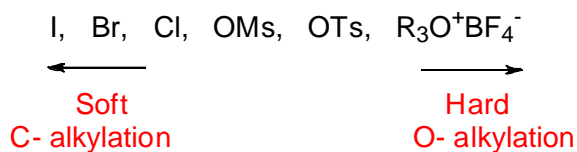


2. Solvent effect

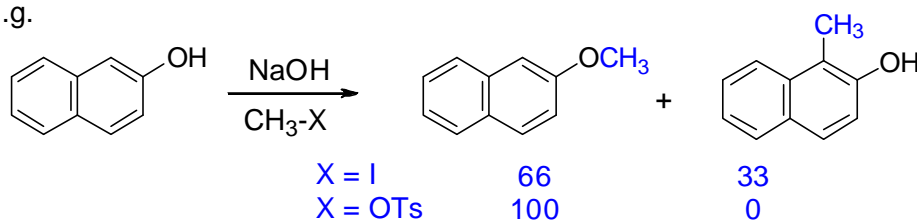


3. Leaving group effect

HSAB theory (hard-soft-acid-base)



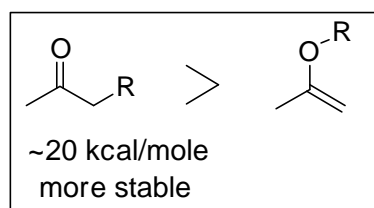
e.g.



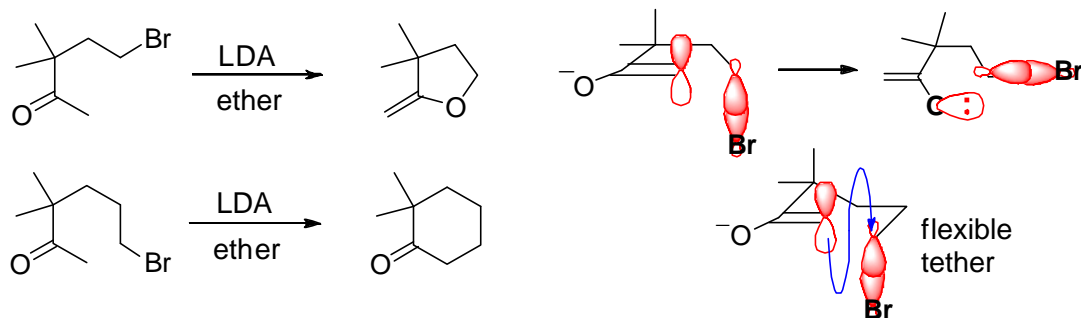
Hammond Postulate (*J. Am. Chem. Soc.* **1955**, *77*, 334)

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

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

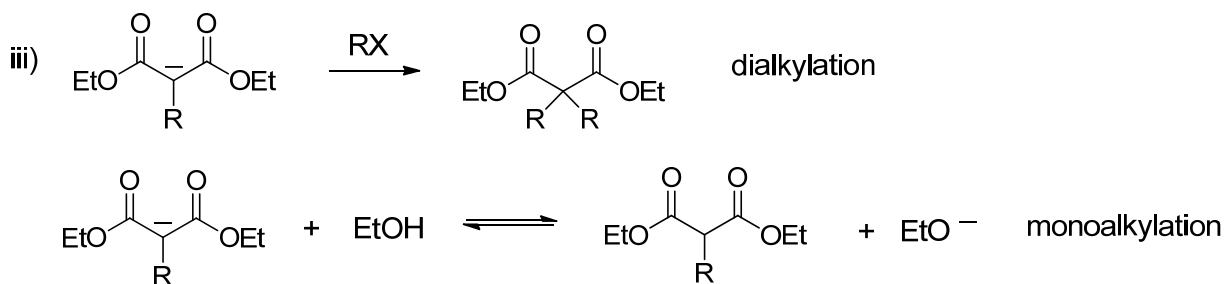
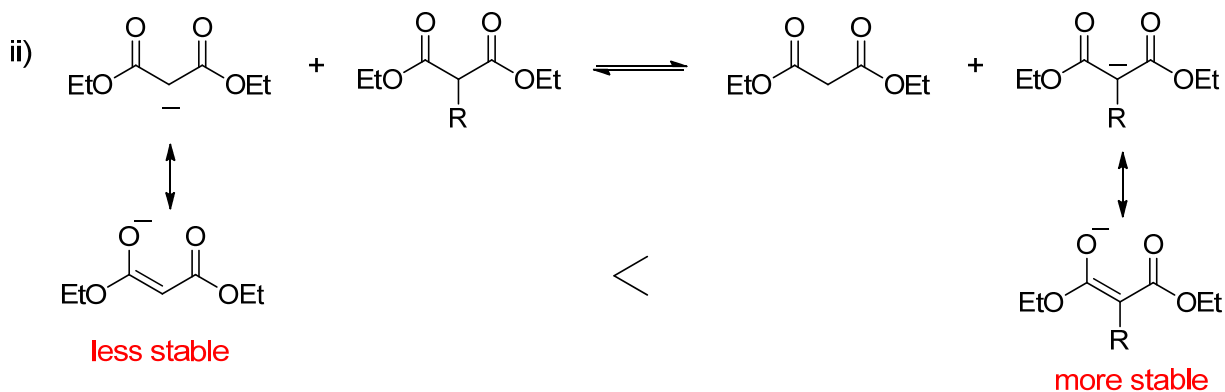
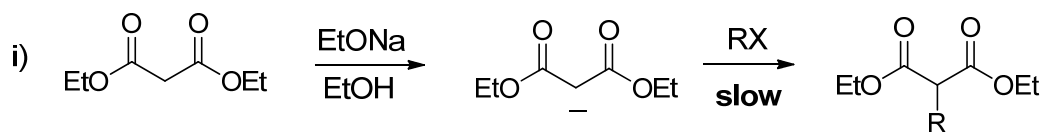


4. Stereoelectronic effect

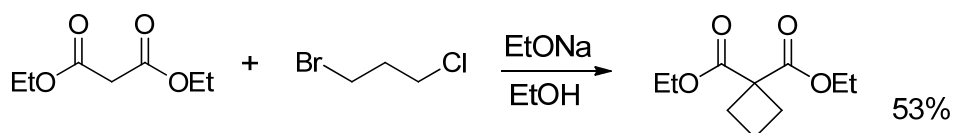


g. dialkylation

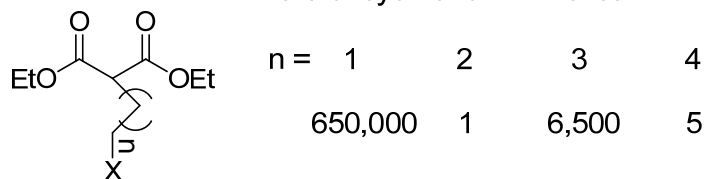
Mechanism



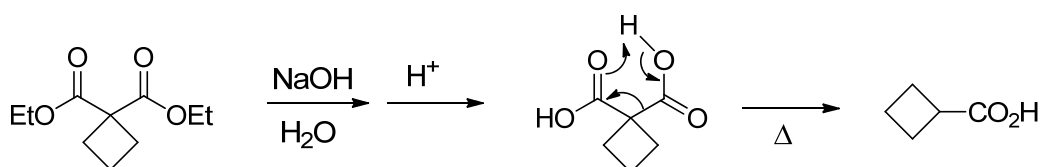
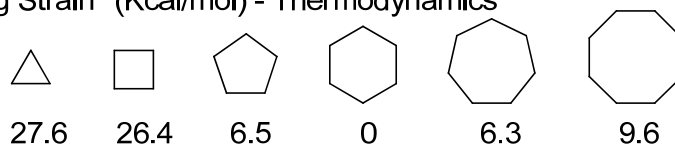
Cyclization



Rate of cyclization - Kinetics

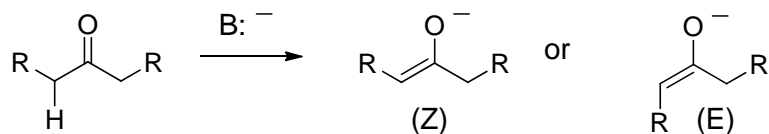


Ring Strain (Kcal/mol) - Thermodynamics

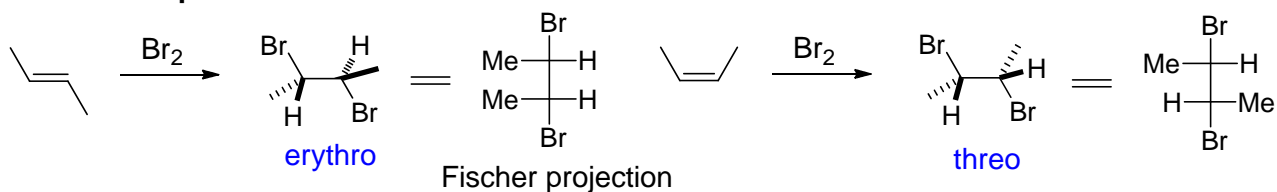


h. Regio- and Stereoselectivity in the Enolate Generation

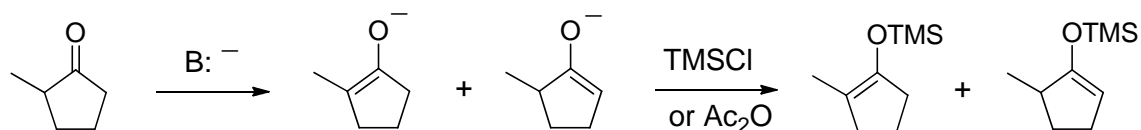
Stereoselectivity



c.f.> Stereospecific



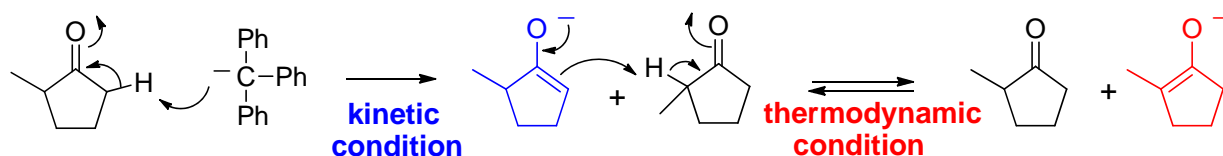
Regioselectivity



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

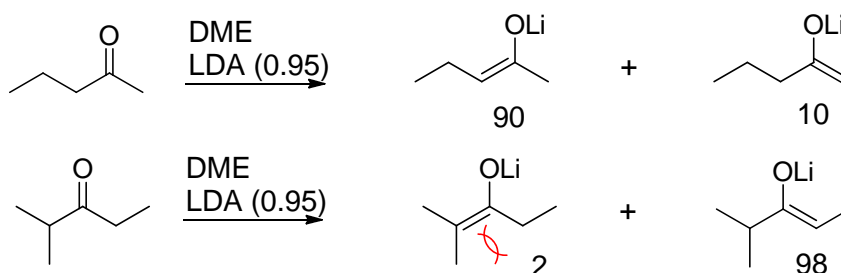
Kinetic Control

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 $Li > Na > K$

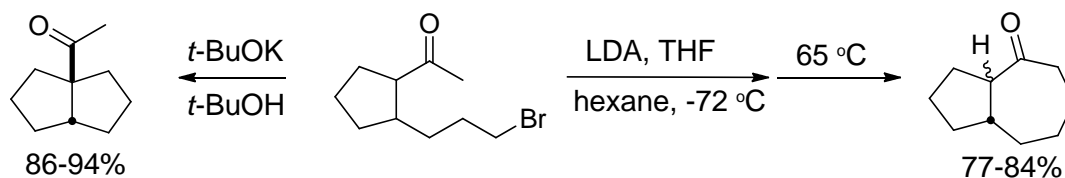
When Ph_3CK was used as a base in the above example the product ratio (28 : 72) changed to 55: 45.

Thermodynamic Control

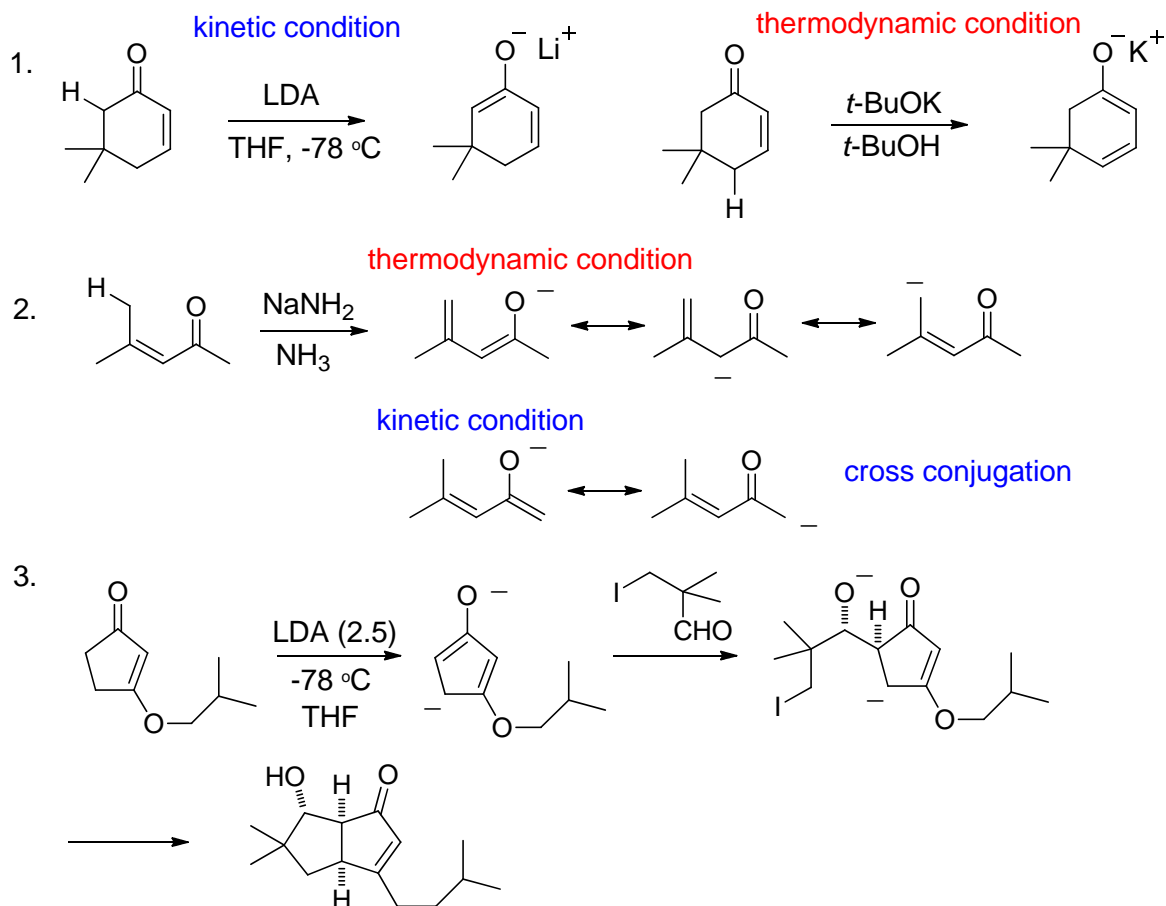
1. Product distribution is based on their thermodynamic stability (equilibrium condition).
2. Most substituted (**most stable**) enolate preferred.



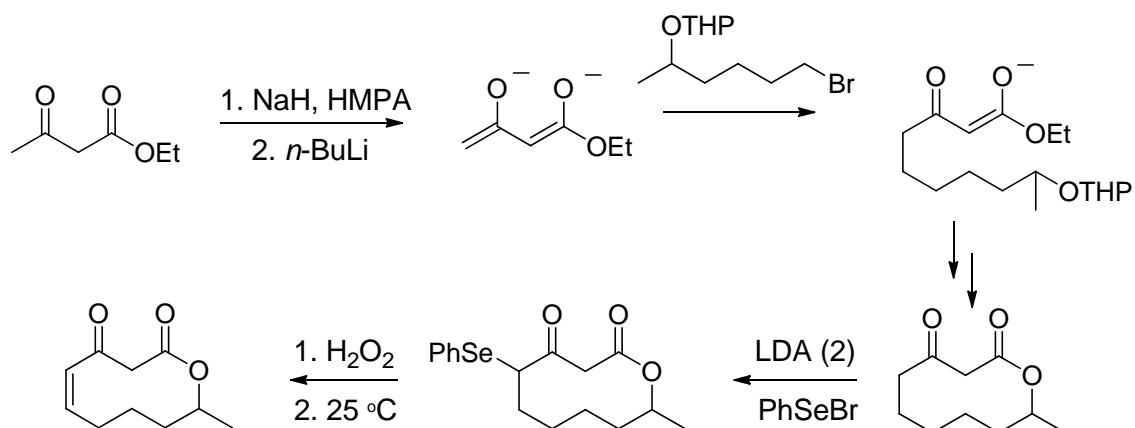
3. Small and weak bases: NaOH, NaOMe, NaH etc.
4. H⁺ sources: excess ketone, protic solvent
5. High temperature
6. Ionic counter ion: K, Na



For Conjugate System

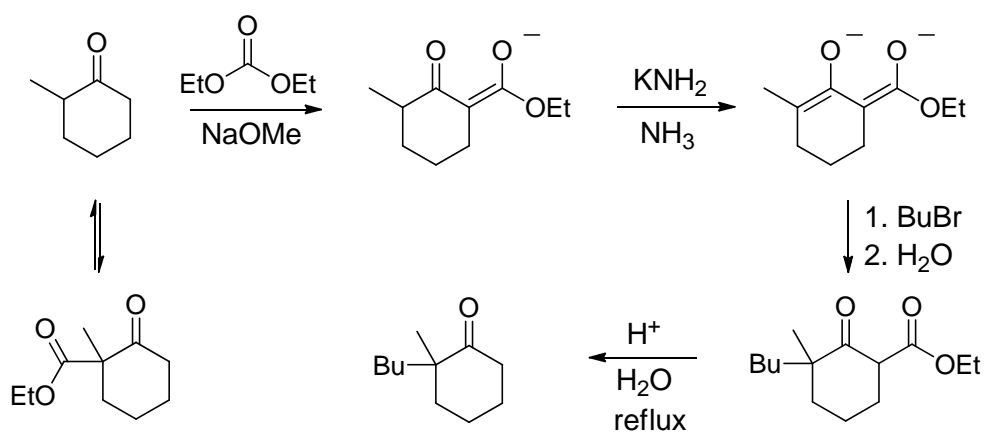


For 1,3-dicarbonyl compounds

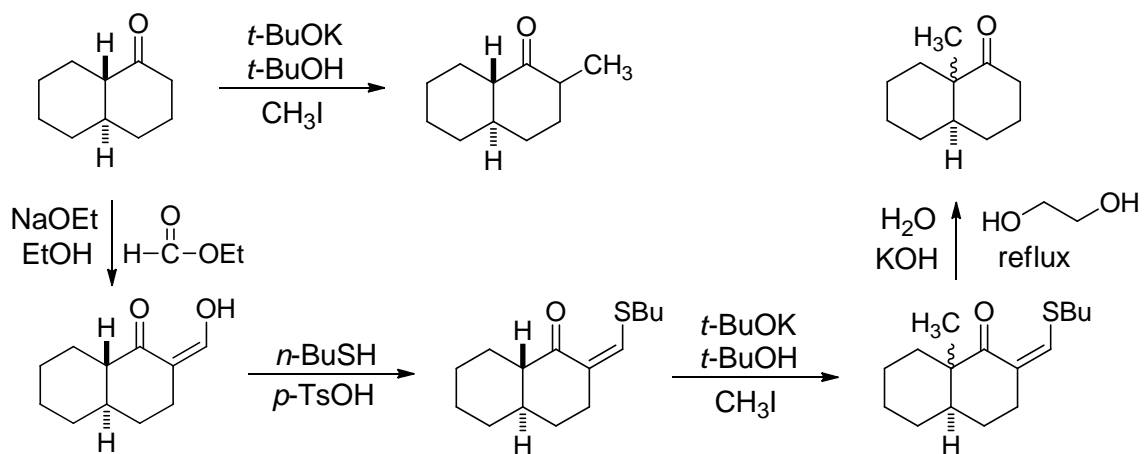


2) Regiospecific Alkylation of Carbonyl Compounds

1. Protection of active methylene site

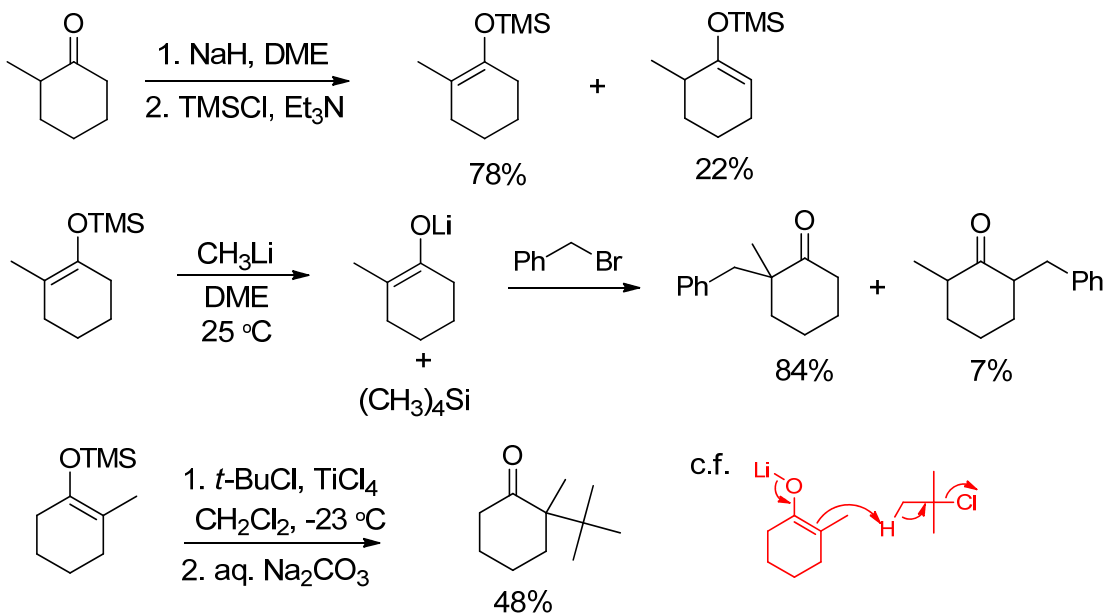


See Claisen Ester Condensation

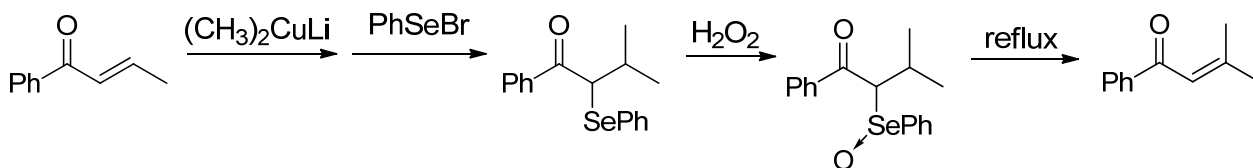


2) Regiospecific Alkylation (continued)

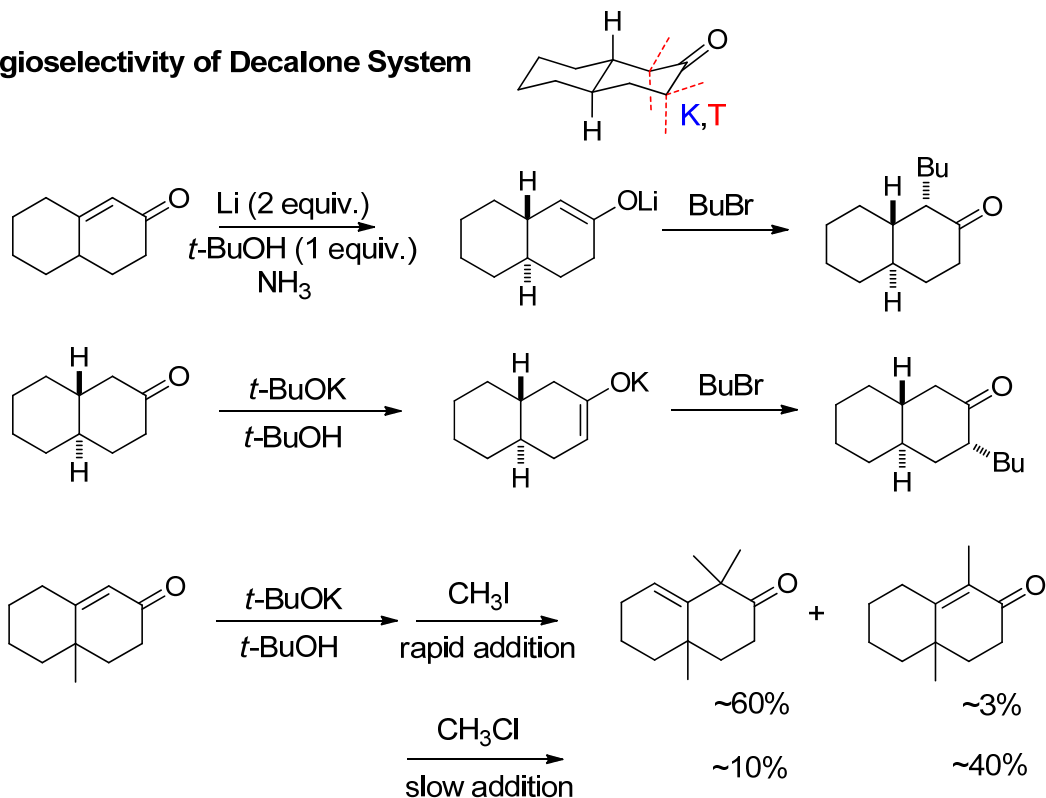
2. Silyl Enol Ether



3. Conjugate Addition of Enones



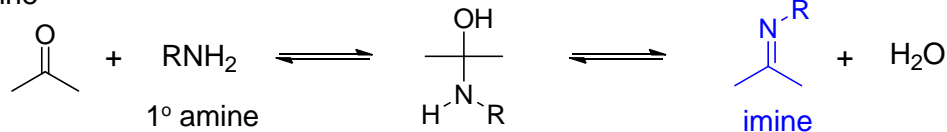
3) Regioselectivity of Decalone System



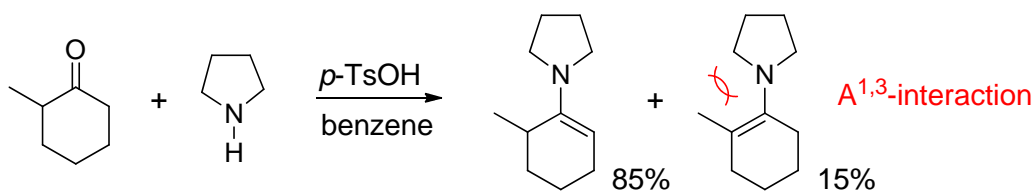
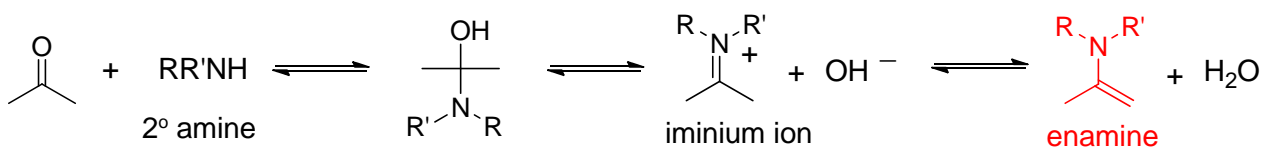
1.2 The Enamine and Related Reactions: Nitrogen Analogues of Enol and Enolate ion

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

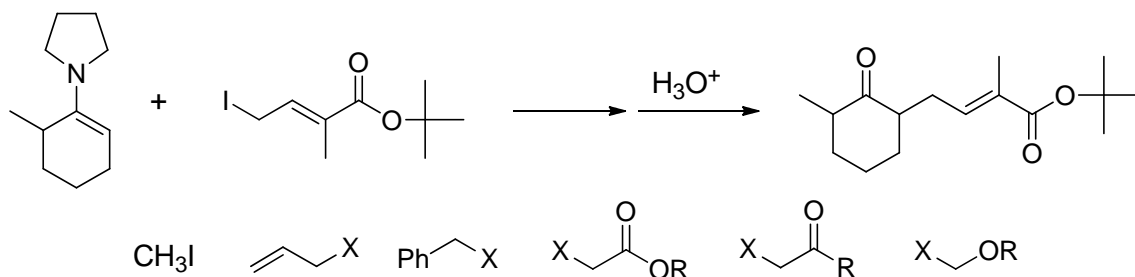
Imine



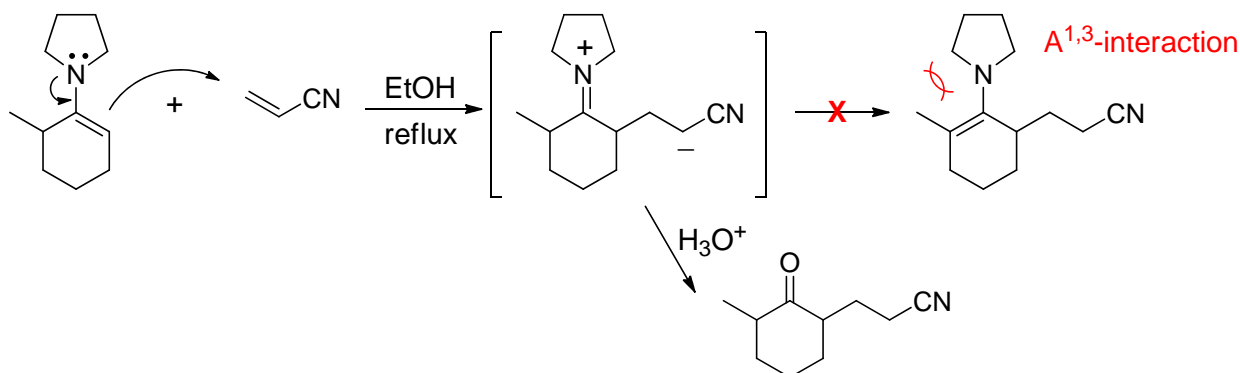
Enamine



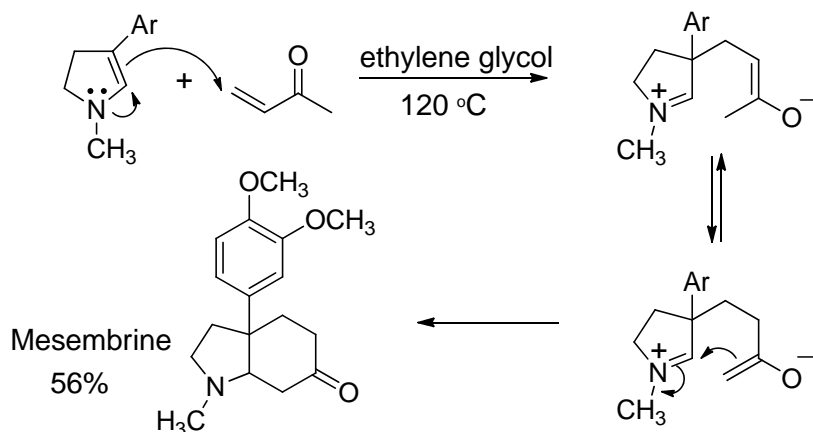
Use reactive electrophiles for alkylation



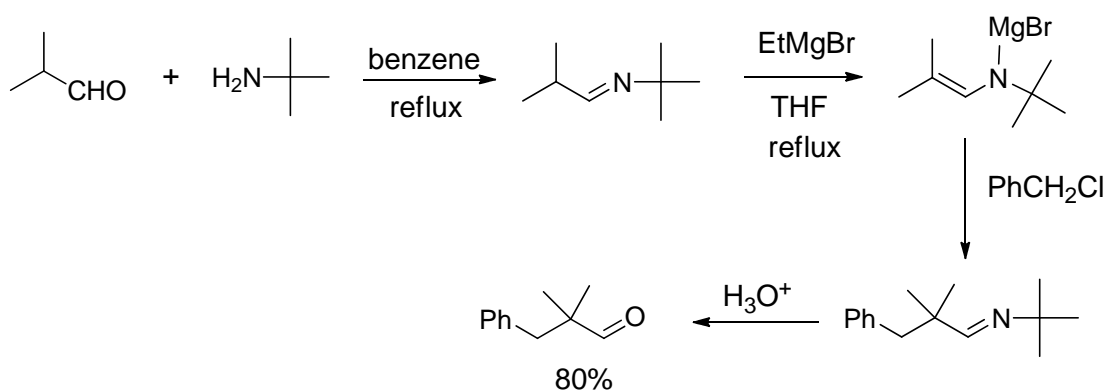
Conjugate addition / mono-alkylation



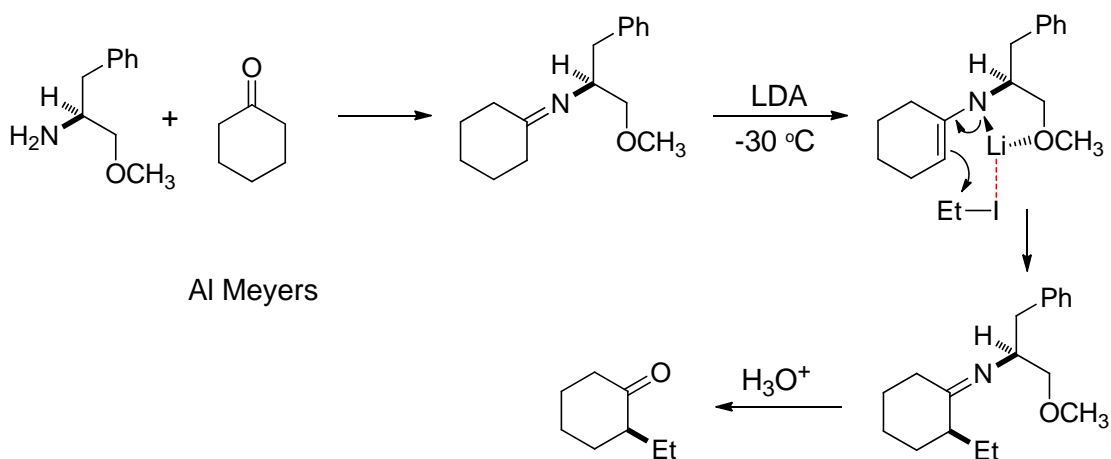
Enamine



Metalloenamines (imine anions)

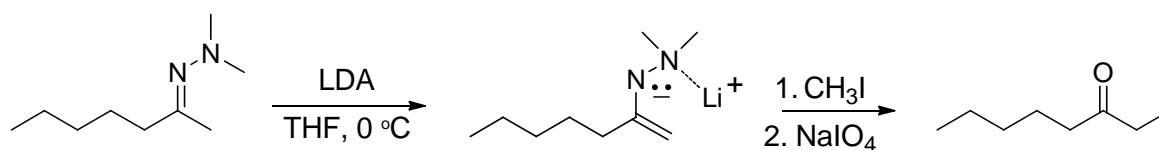


from Chiral Amine



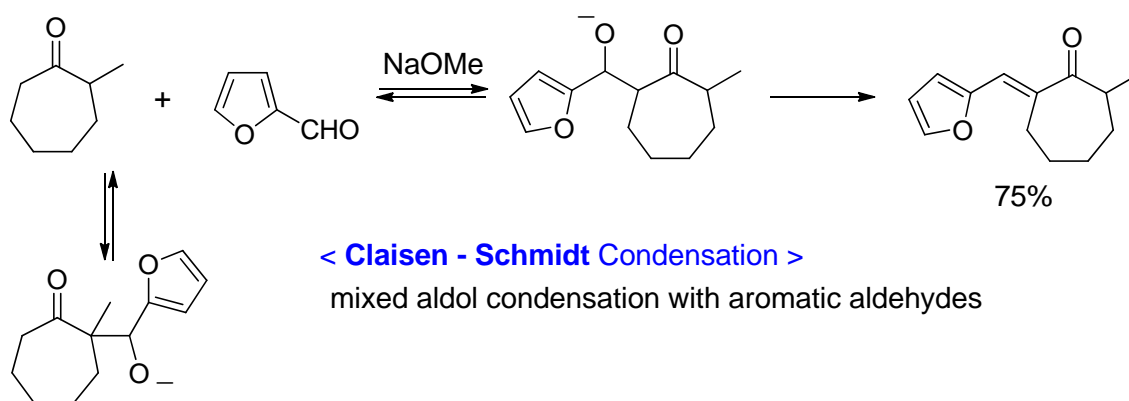
from Hydrazine

more stable and better stereoselectivity



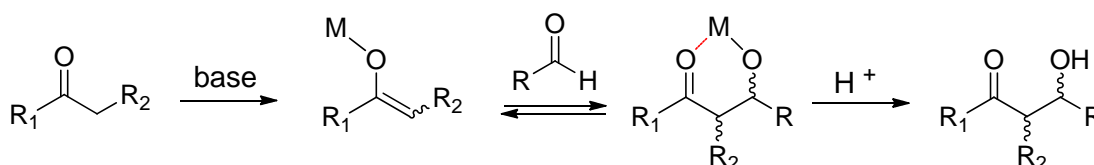
1.3 Aldol reaction: acid or base-catalyzed self condensation of an aldehyde or a ketone

a. Mixed Aldol Condensation



b. Directed Aldol Condensation

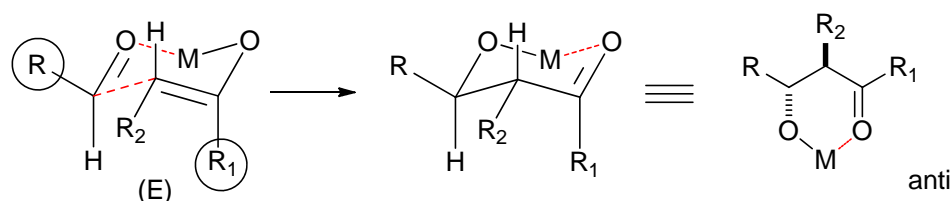
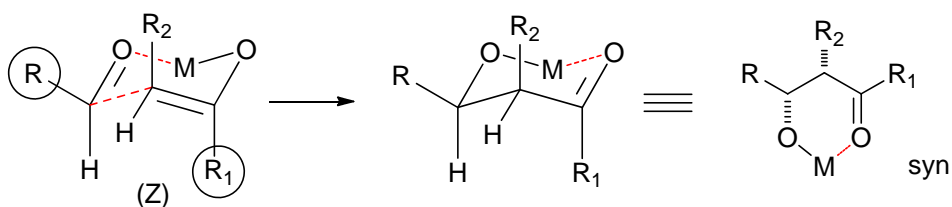
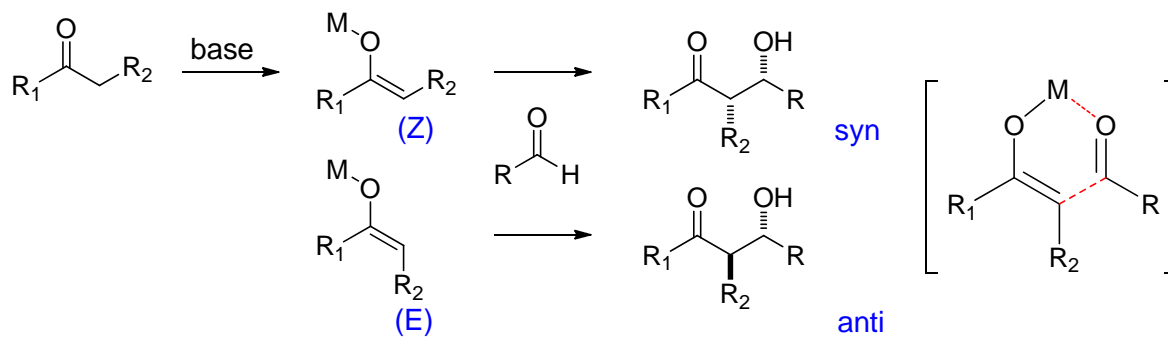
mixed aldol condensation of aliphatic aldehydes and ketones



c. Control of Stereochemistry: Kinetic condition

i) Simple Diastereoselectivity

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



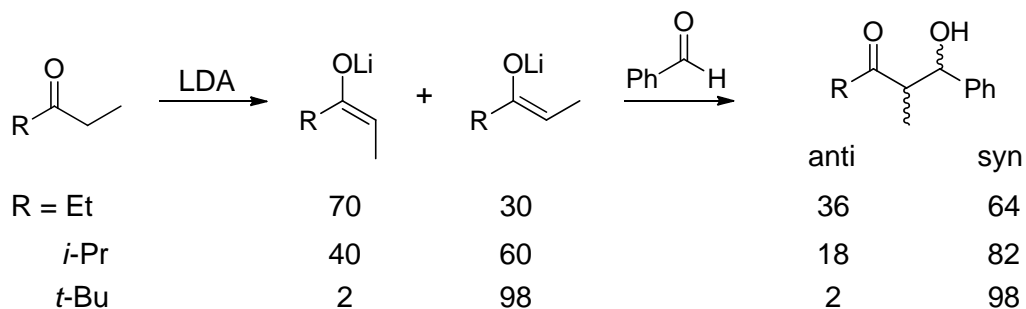
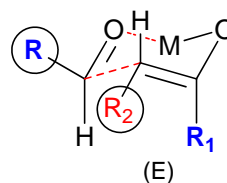
c. Control of Stereochemistry: Kinetic condition (continued)

i) Simple Diastereoselectivity

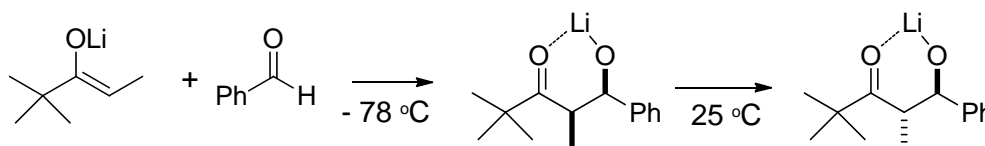


Best correlation

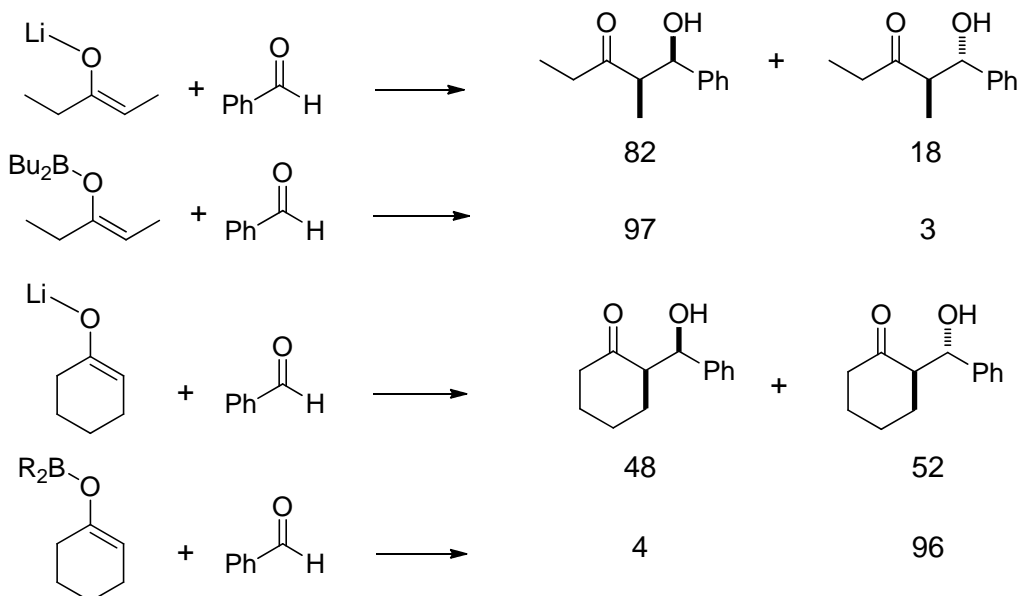
1. R₁, R = large group
2. M = Li, B → tight transition state
3. (Z) is more selective than (E)



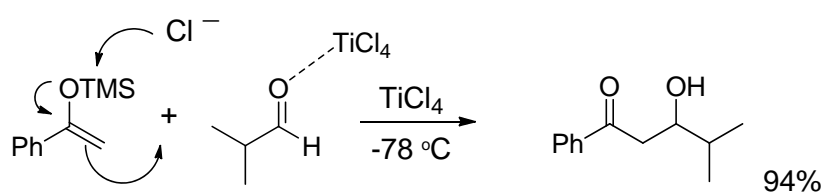
Under Equilibrium Condition (Thermodynamic Condition)



Boron enolates

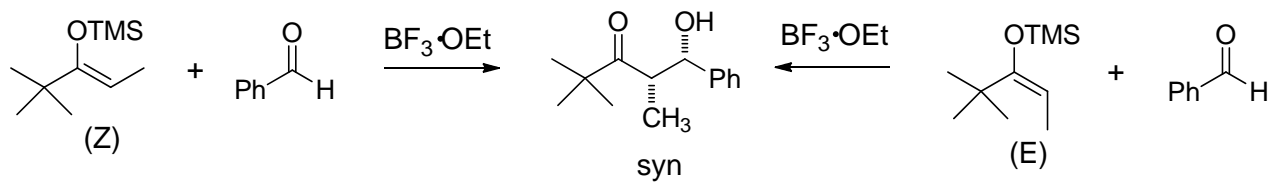


Aldol reaction with Silyl Enol Ether: Open Transition State

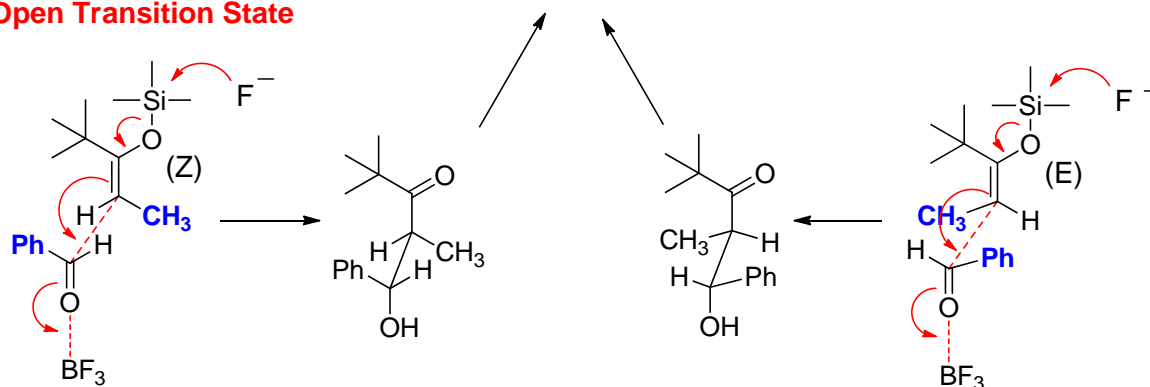


Aldol reaction with **Silyl Enol Ether** (continued)

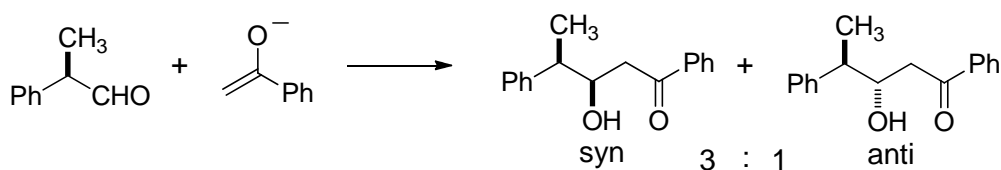
Stereochemistry



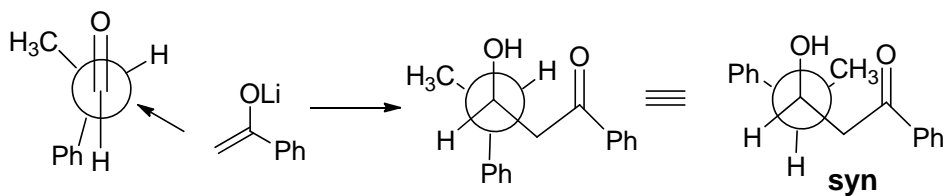
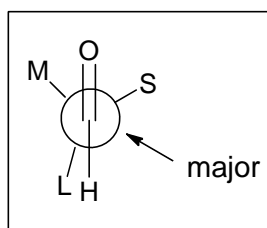
Open Transition State



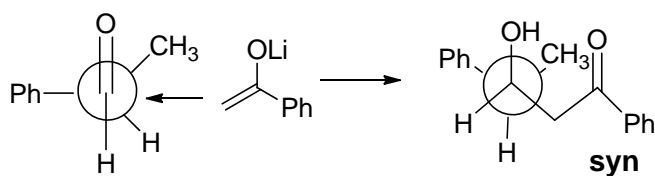
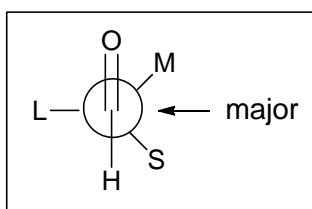
ii) Stereoselectivity between **achiral enolates** and **chiral aldehydes**



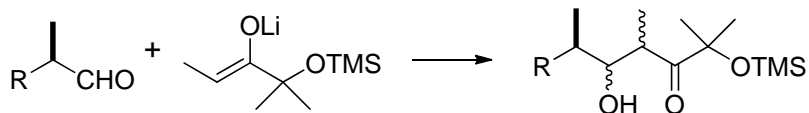
Cram's rule



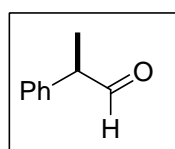
Felkin-Ahn



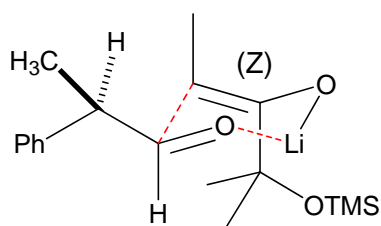
iii) Stereoselectivity between chiral aldehydes and prochiral enolates



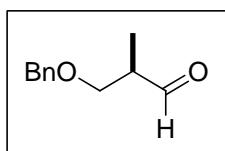
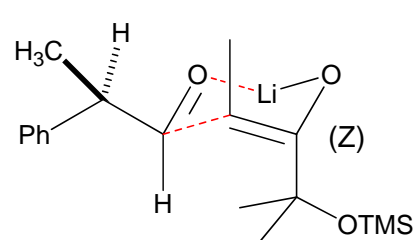
	syn,syn	anti,syn	syn,anti	anti,anti
R = Ph	81	19	0	0
	94	6	0	0
	33	67	0	0
	21	79	0	0



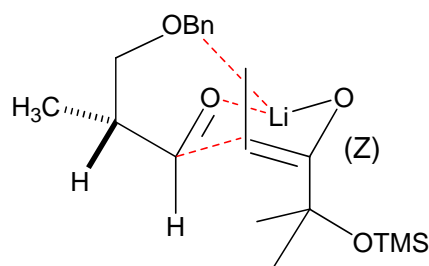
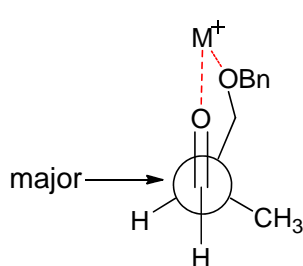
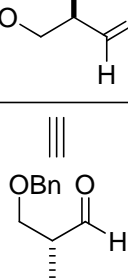
cram



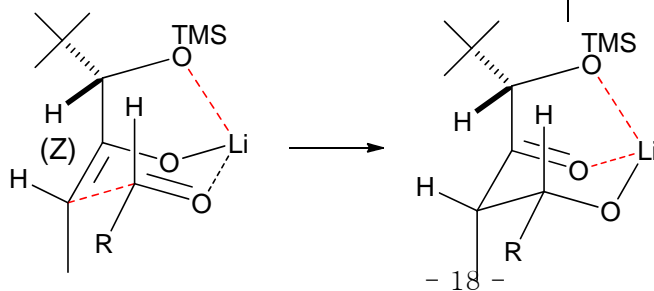
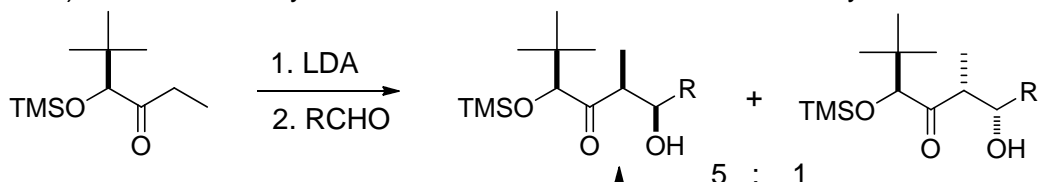
anti-cram



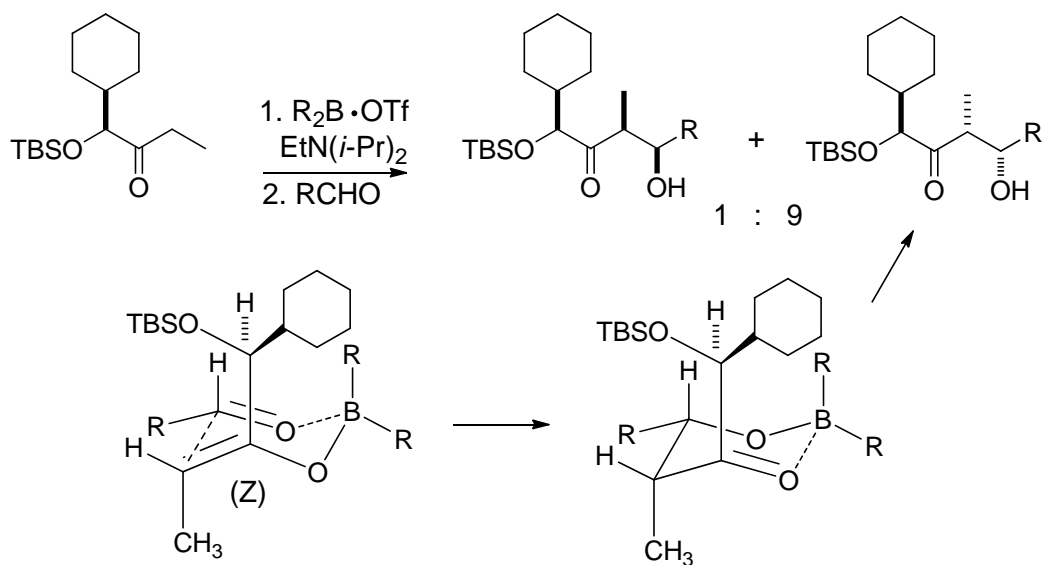
anti-cram or chelated cram



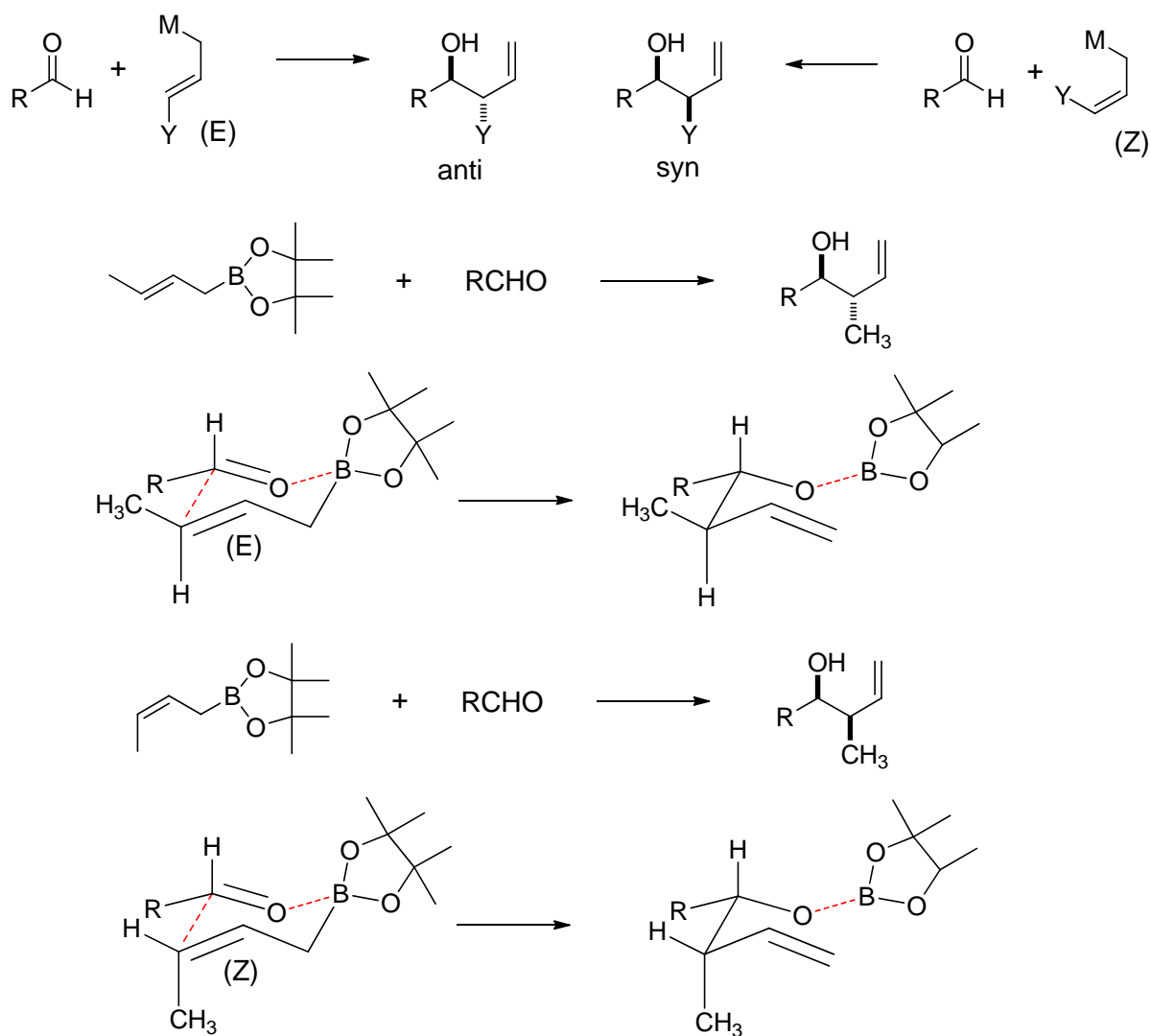
iv) Stereoselectivity between chiral enolates and achiral aldehydes



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

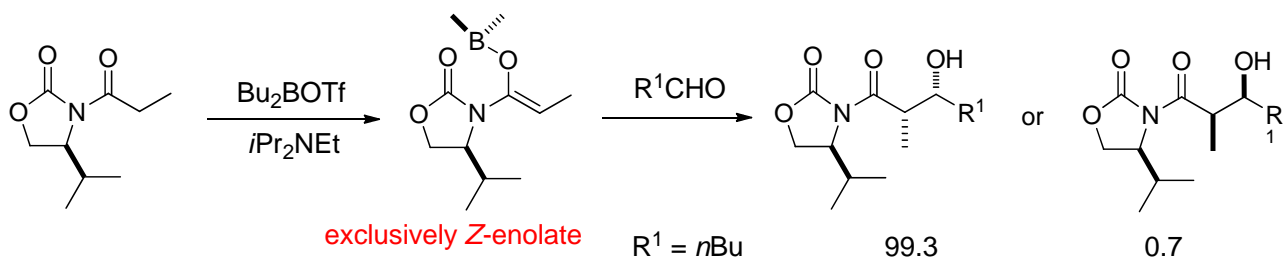


d. Allylmetal compound with aldehydes



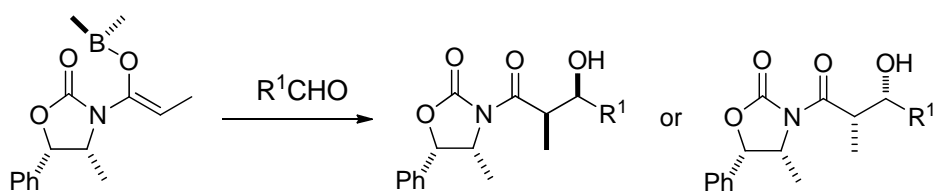
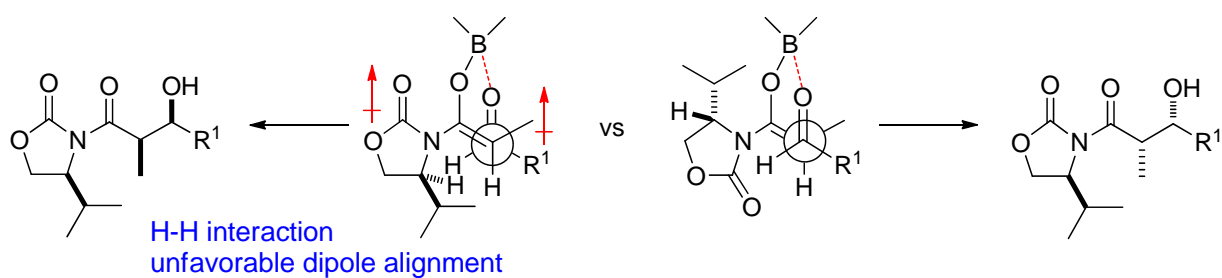
e. Evans' chiral *N*-acyl oxazolidinones

1) Boron enolate



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

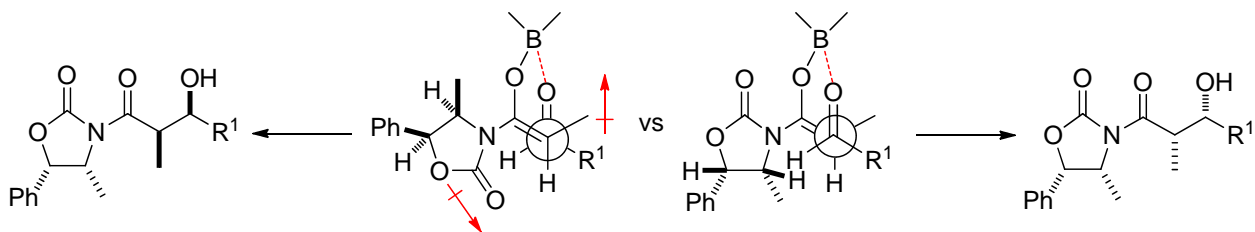
J. Am. Chem. Soc. 1981, 103, 3099



$R^1 = nBu$ >99.8 <0.2

$R^1 = iPr$ >99.8 <0.2

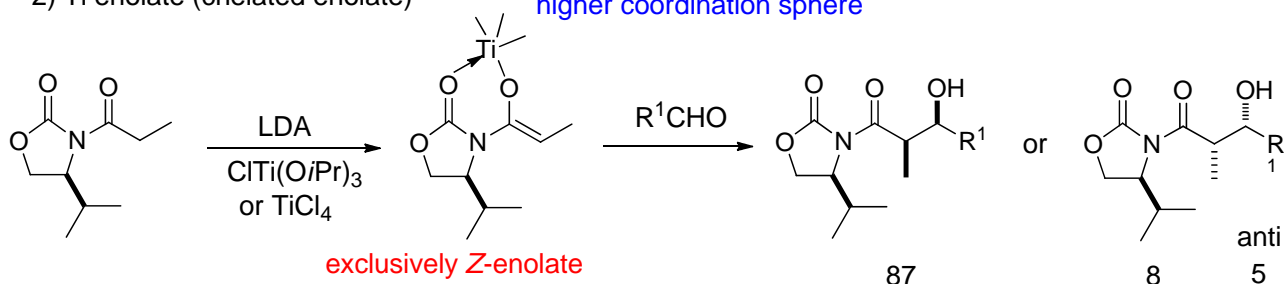
$R^1 = Ph$ >99.8 <0.2



e. Evans' chiral *N*-acyl oxazolidinones

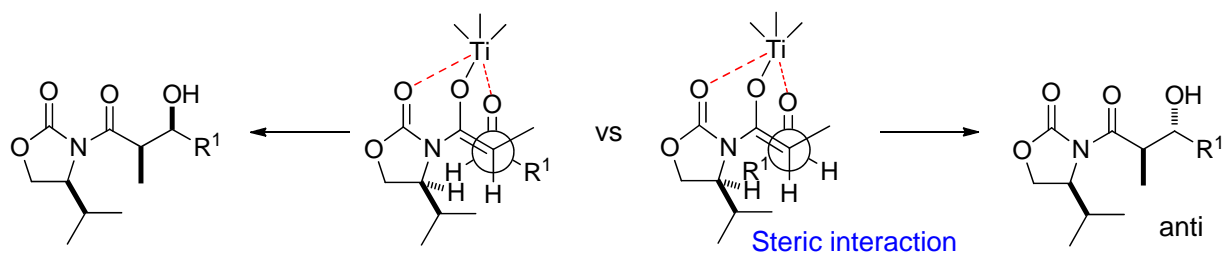
2) Ti enolate (chelated enolate)

higher coordination sphere



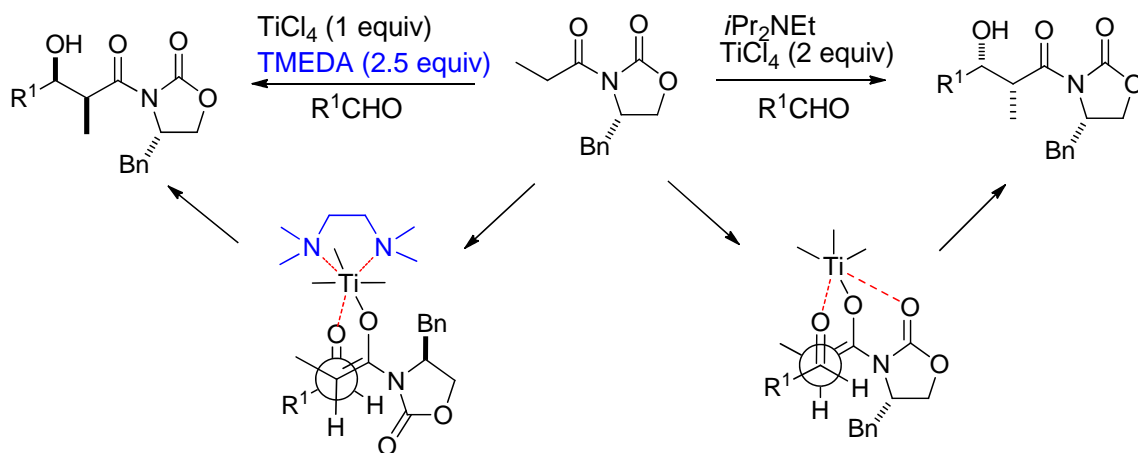
J. Am. Chem. Soc. **1989**, *111*, 5722

J. Am. Chem. Soc. **1991**, *113*, 1047



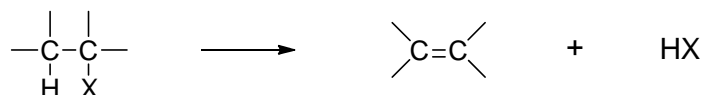
3) Chelated and non-chelated Ti enolates

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



Chapter 2. Formation of Carbon-Carbon Double Bonds

2.1 β -Elimination reaction

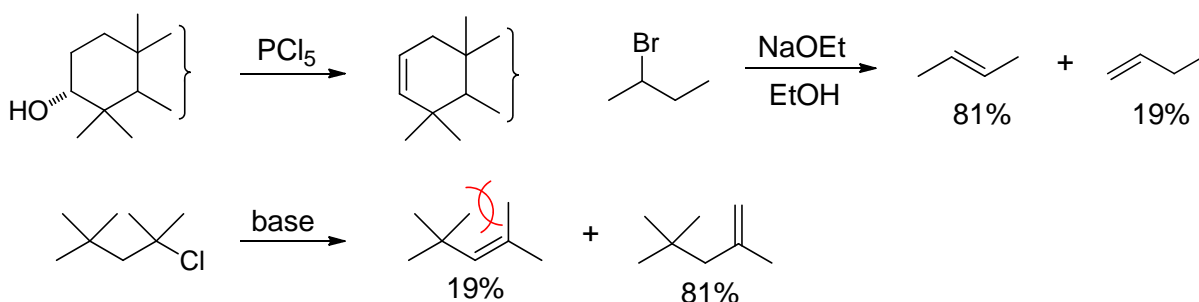


X = OH, OCOR, halogen, OSO₂Ar, NR₃⁺, SR₂⁺ E1 or E2 mechanism

Regioselectivity

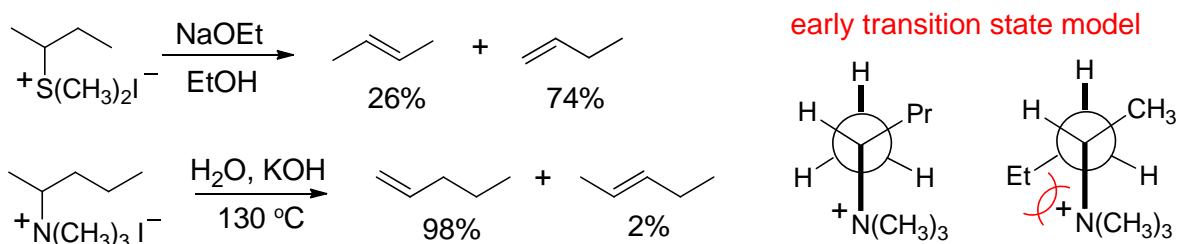
Saytzeff rule: more highly substituted (stable) alkene

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



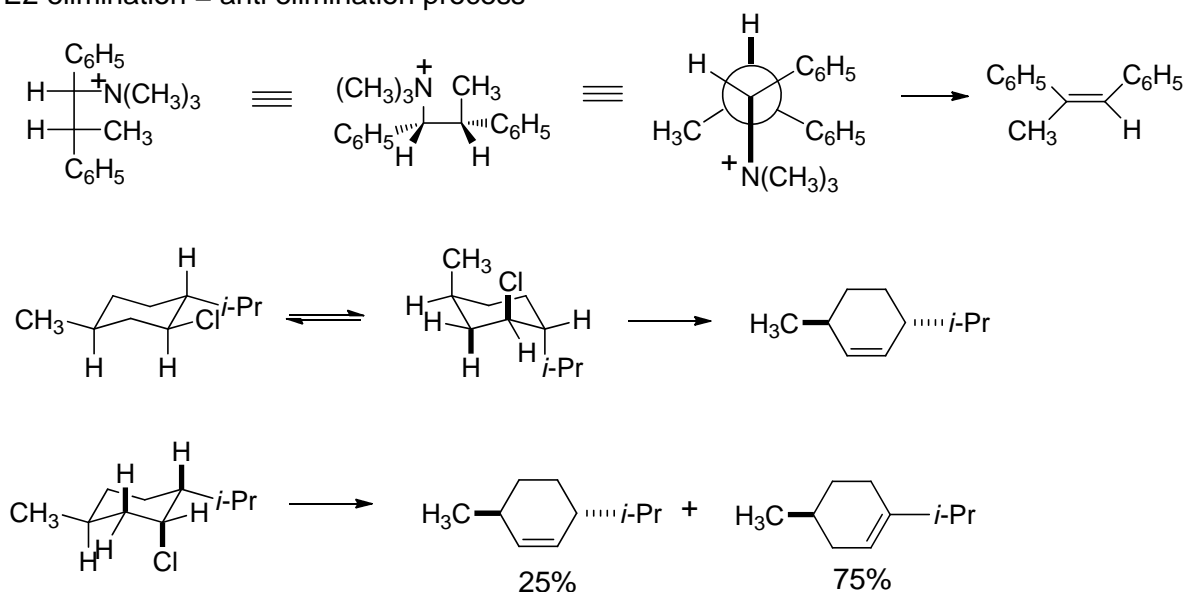
Hofmann rule: less substituted alkene

base induced elimination of **quaternary ammonium salts or sulfonium salts**



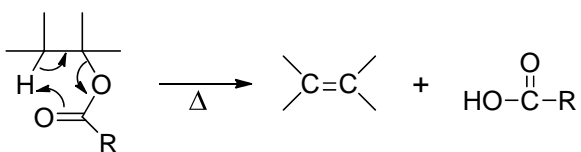
Stereoselectivity

E2 elimination = anti elimination process

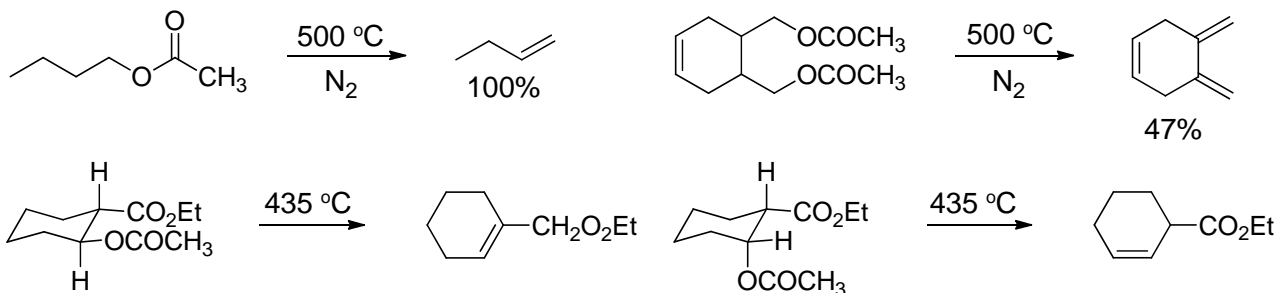


2.2 Pyrolytic **syn** eliminations "concerted cyclic transition state"

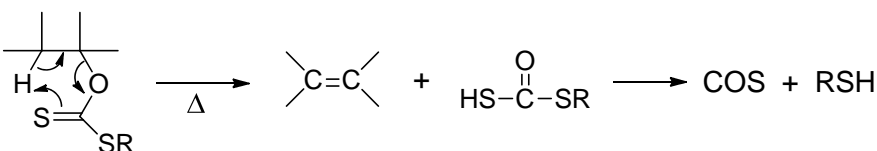
a. carboxylic esters



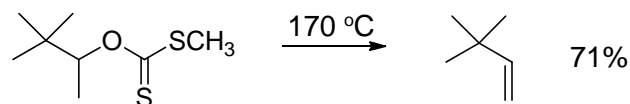
[examples]



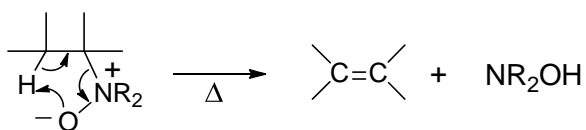
b. xanthate esters - Chugaev reaction



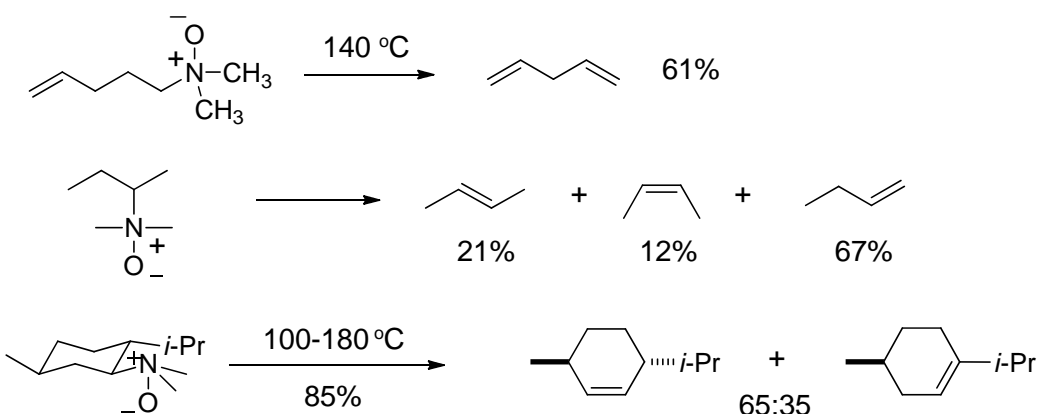
[examples]



c. ammonium oxides - Cope reaction

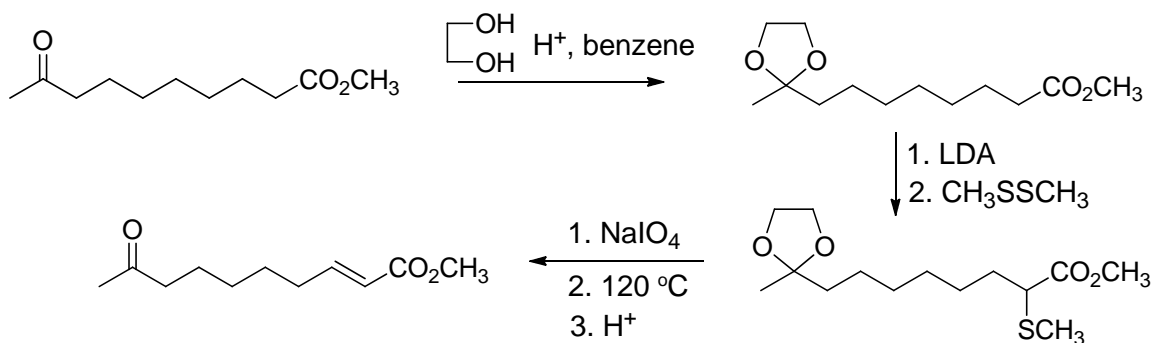
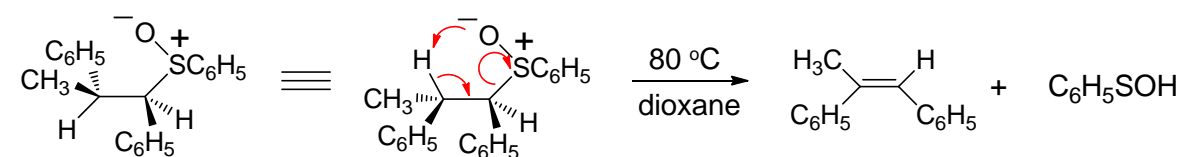


[examples]

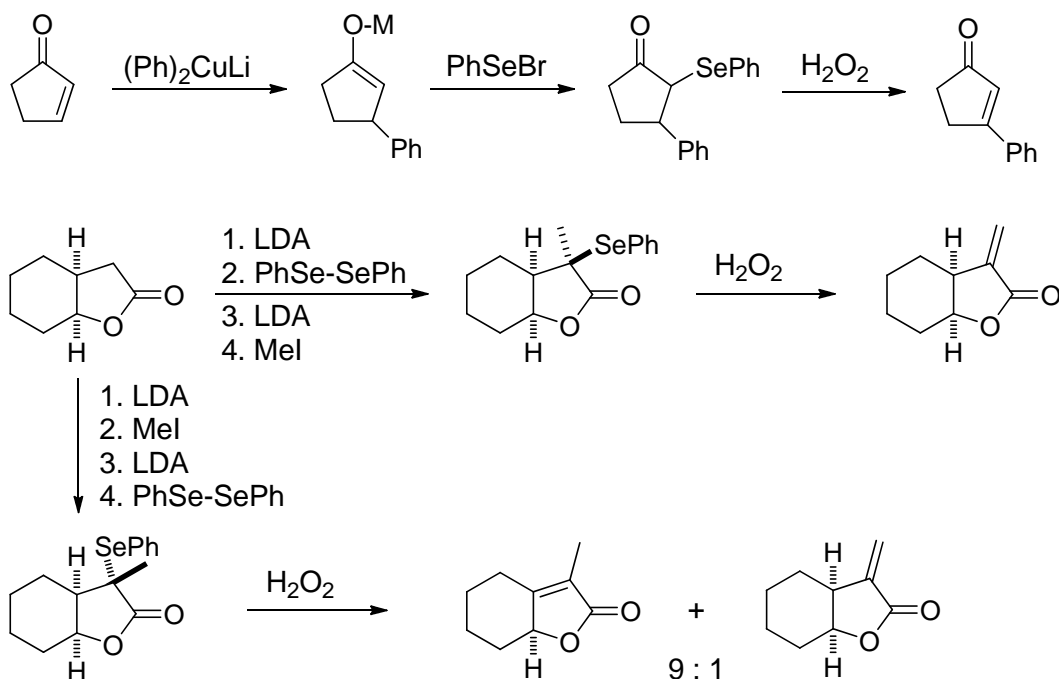


2.2 Pyrolytic **syn** eliminations (continued)

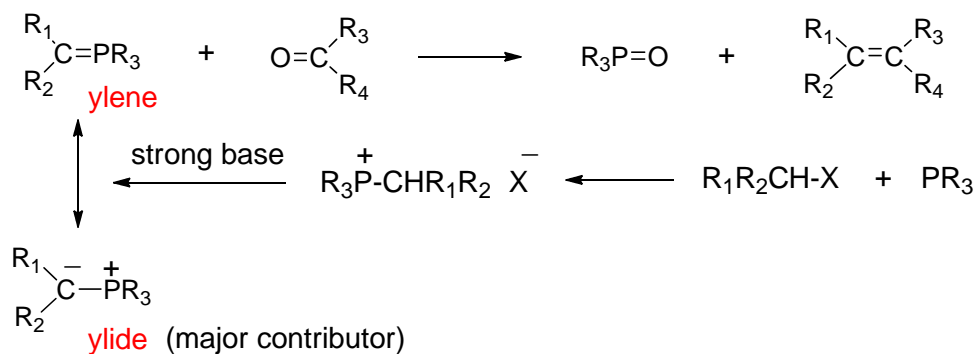
d. Sulfoxides (concerted cyclic pathway)



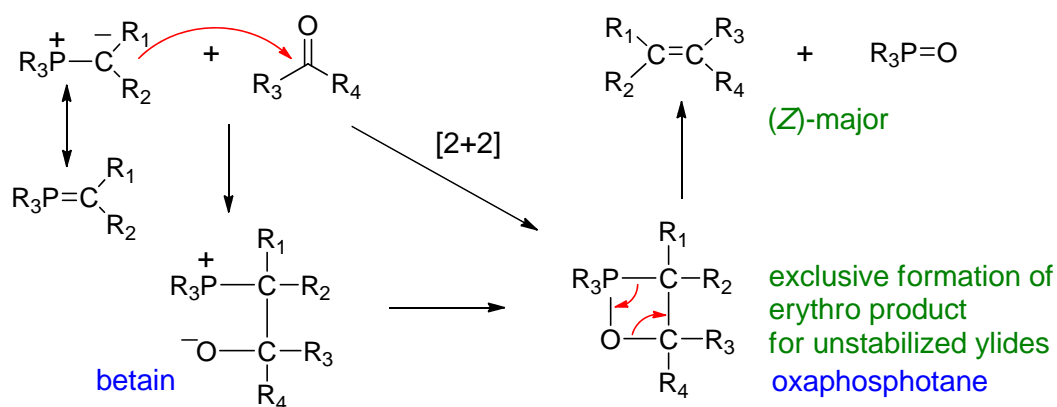
e. Selenoxides: milder conditions (at room temperature or below)



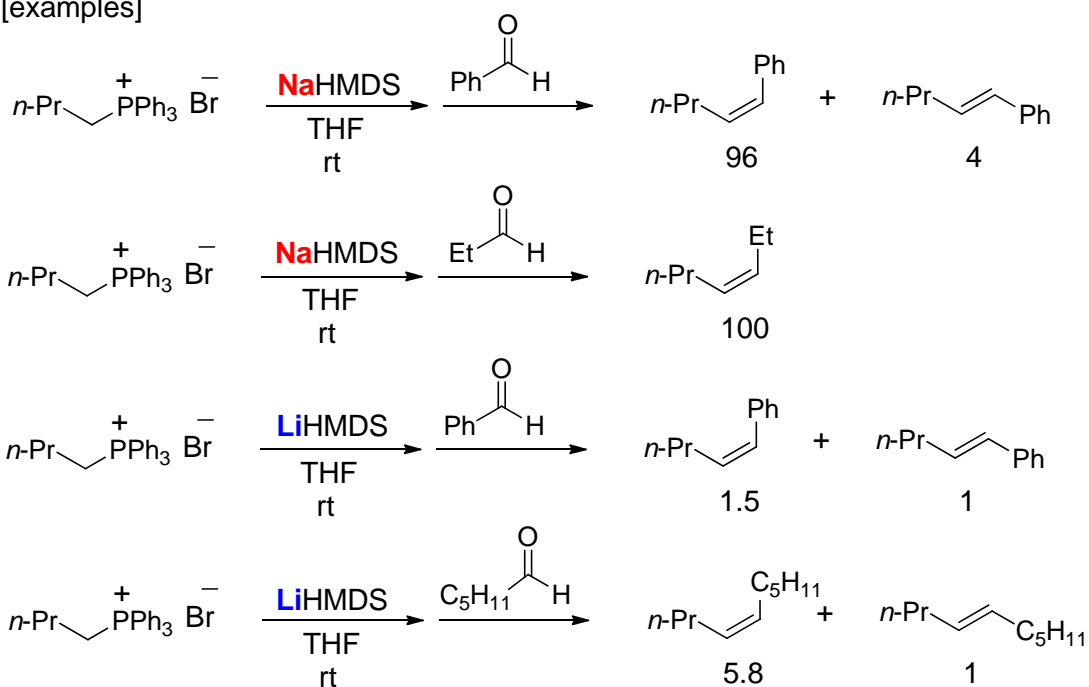
2.3 The Wittig and related reactions



a. The **mechanism** of Wittig reaction

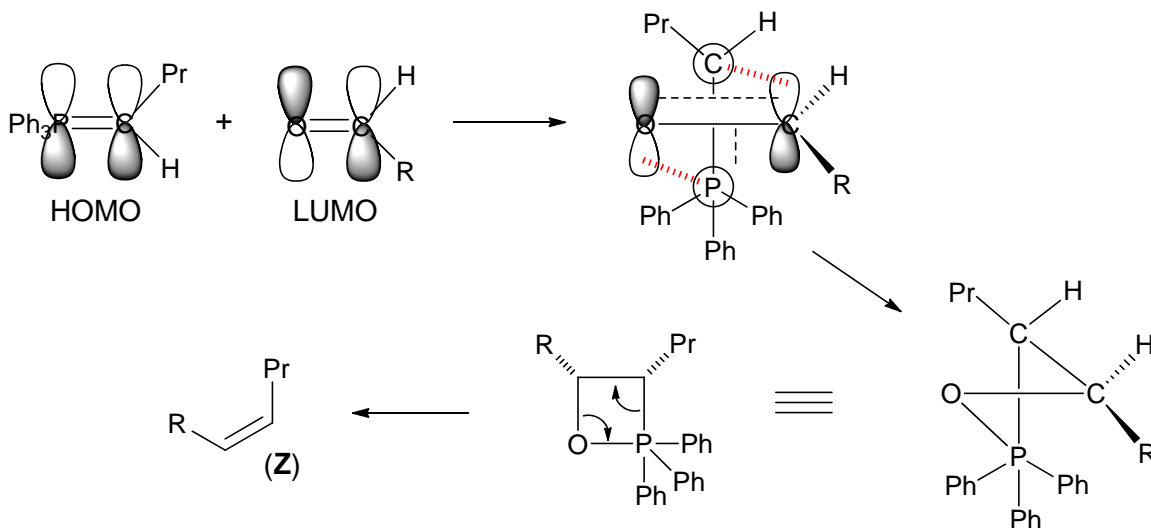


[examples]



Stereoselectivity

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



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

1. "Salt-free" condition

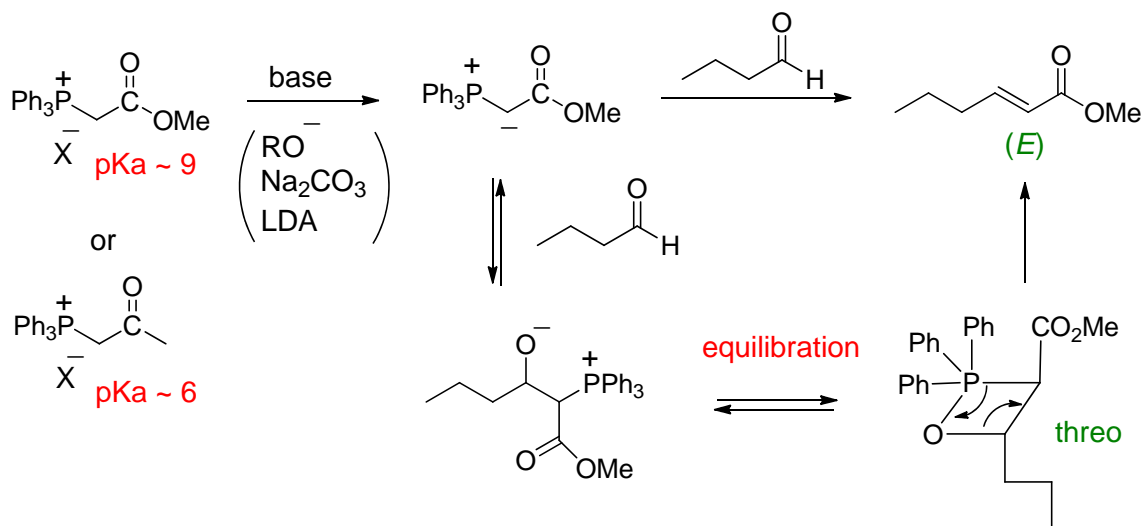
K, Na as a counter metal ion

Li-X forms a chelated complex with the reaction intermediate

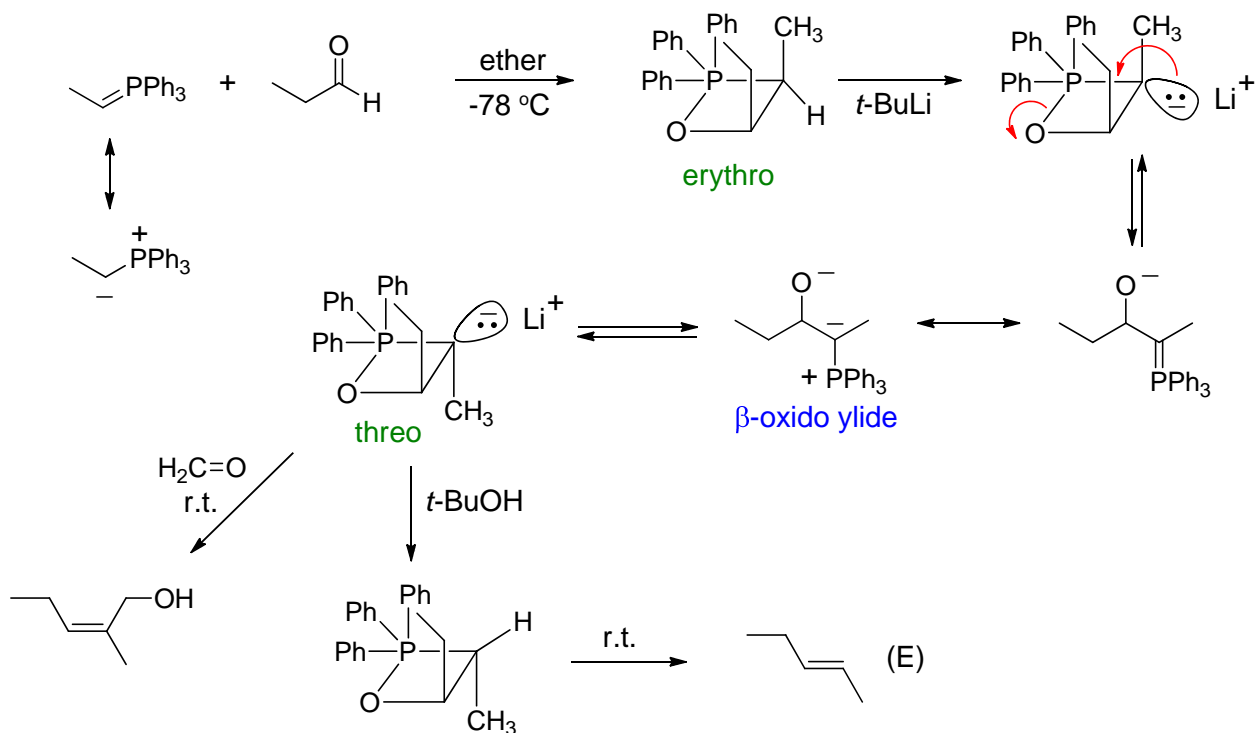
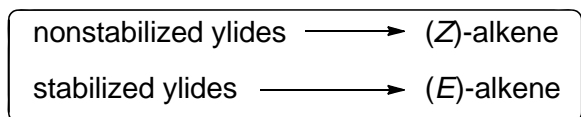
2. Dipolar aprotic solvents

THF, DMSO, DMF

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

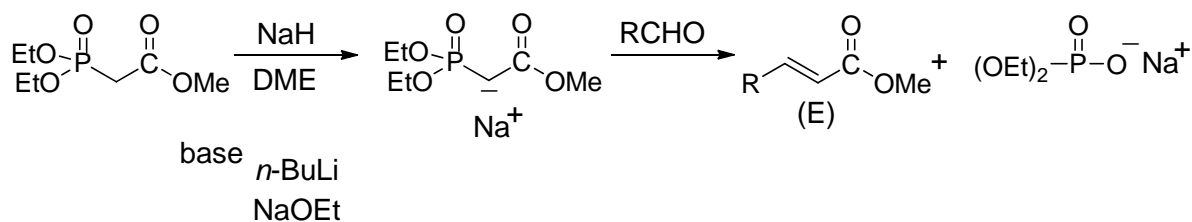


c. **Schlosser Modification** **nonstabilized ylides** \longrightarrow **(E)**-alkene



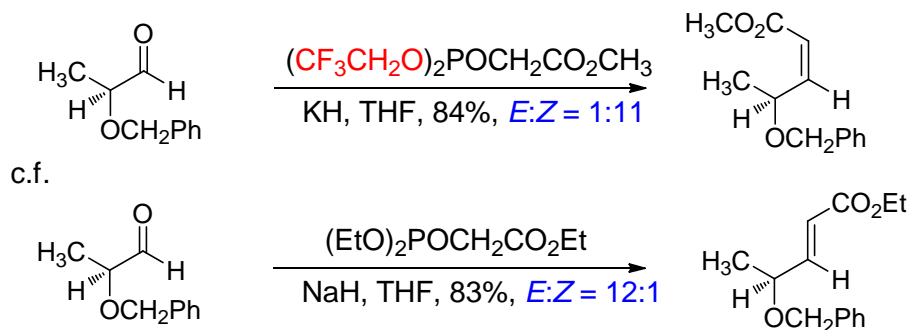
d. Horner - Wadsworth - Emmons Modification

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

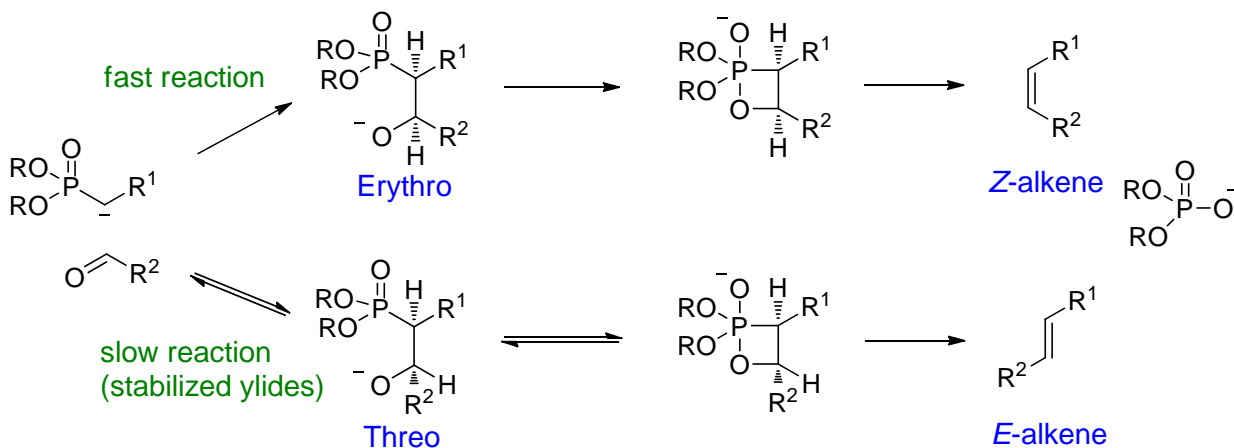


Z-selective HWE reaction

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

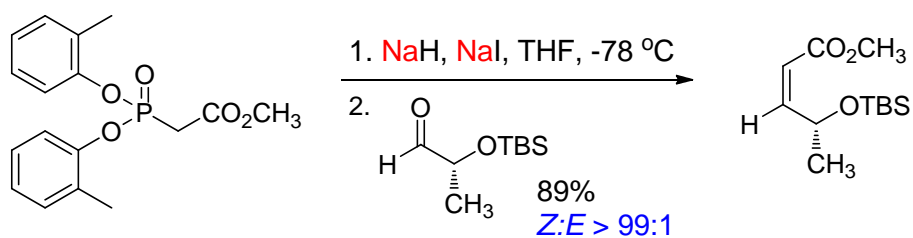


[Mechanism and Origin of Stereoselectivity]

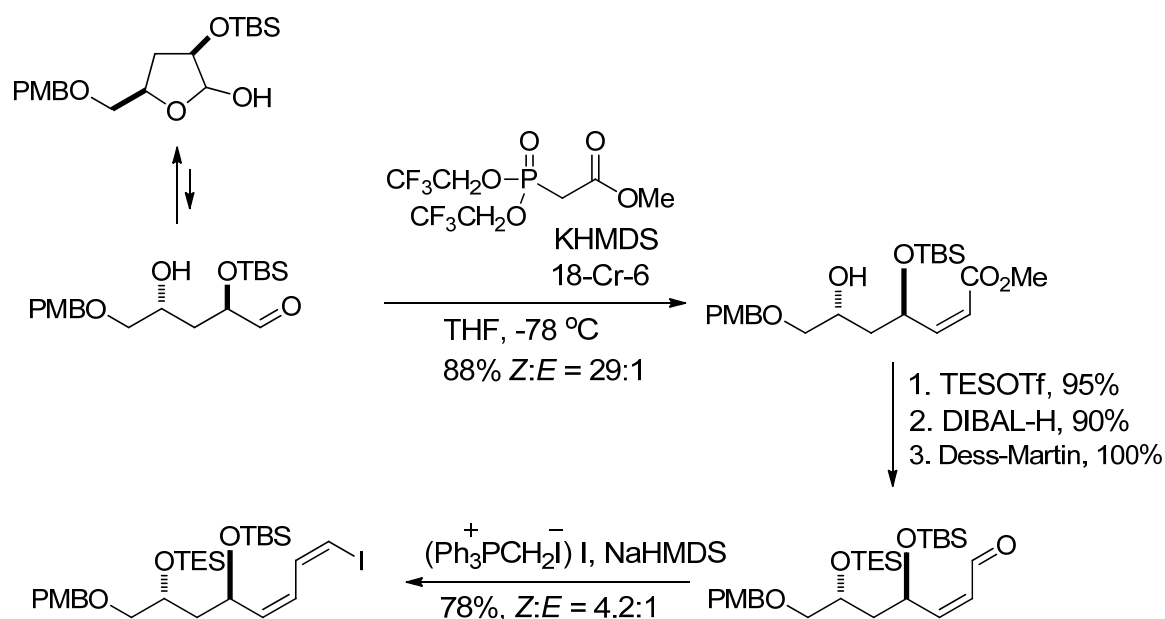


Large R or R¹ groups favor E alkene formation.

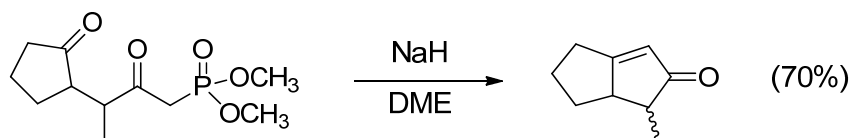
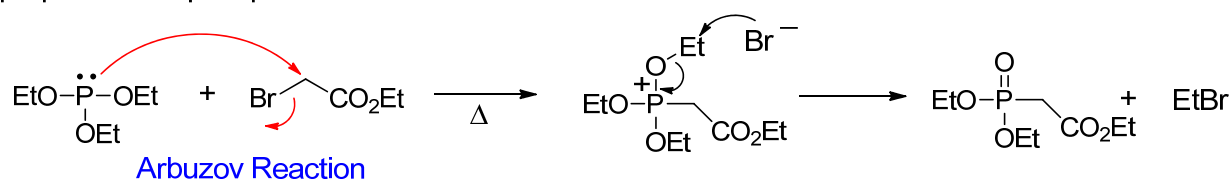
2. Ando method: *TL* **1995**, 36, 4105; *JOC* **1997**, 62, 1934.



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

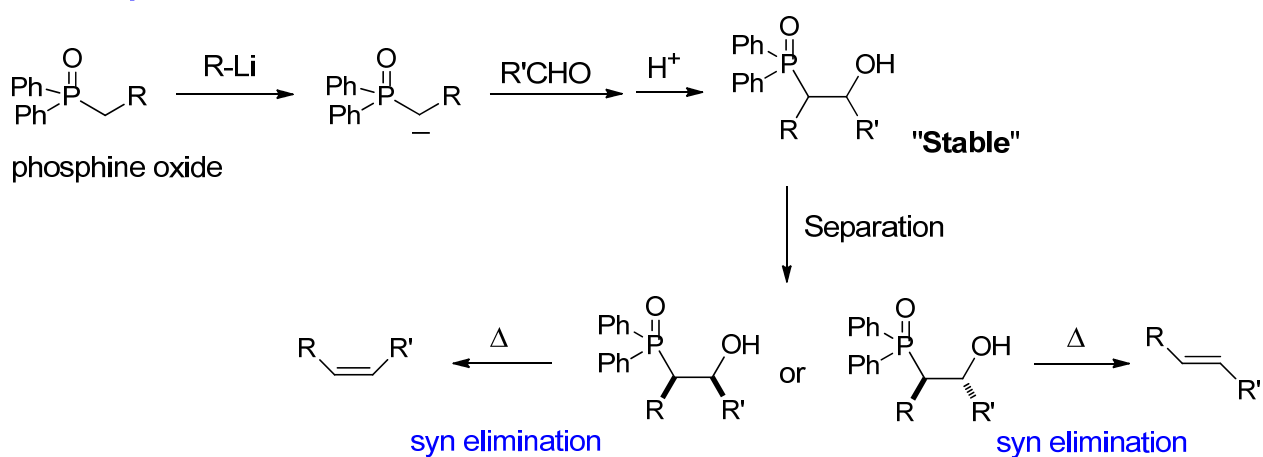


preparation of phosphonate

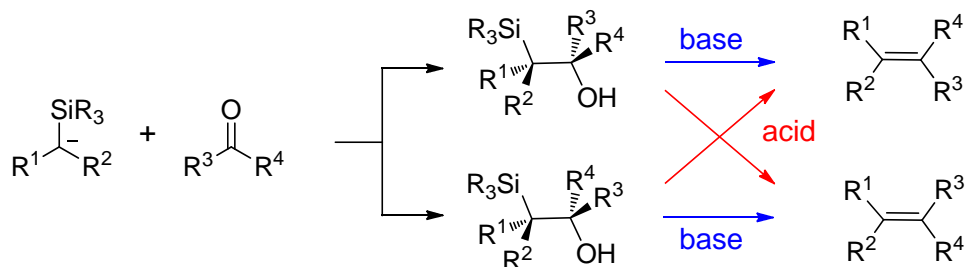
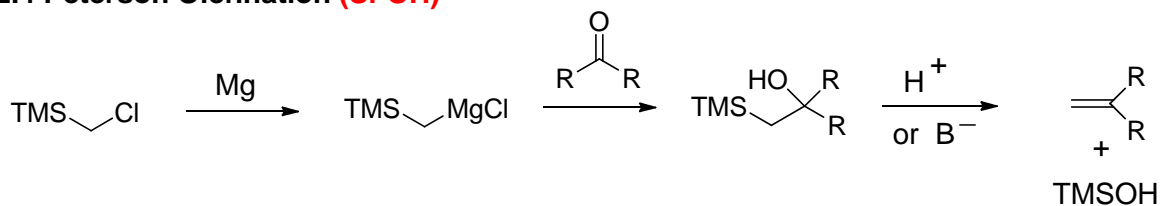


e. Horner - Wittig Reaction

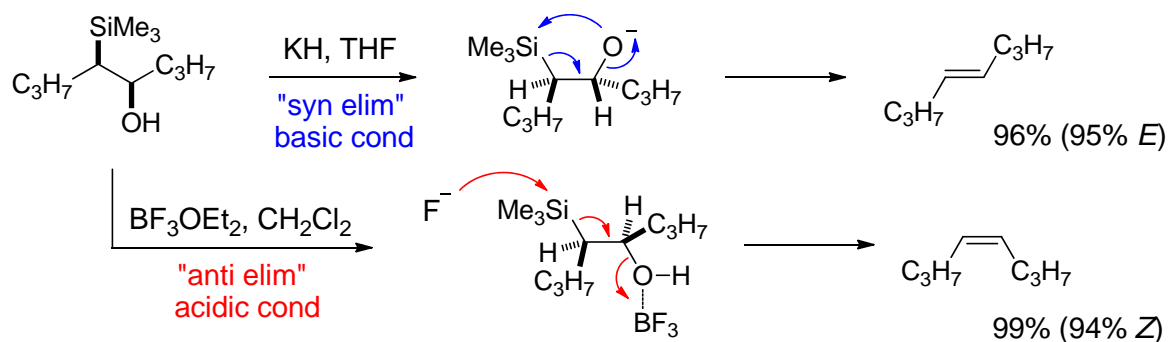
Phosphine oxide carbanion



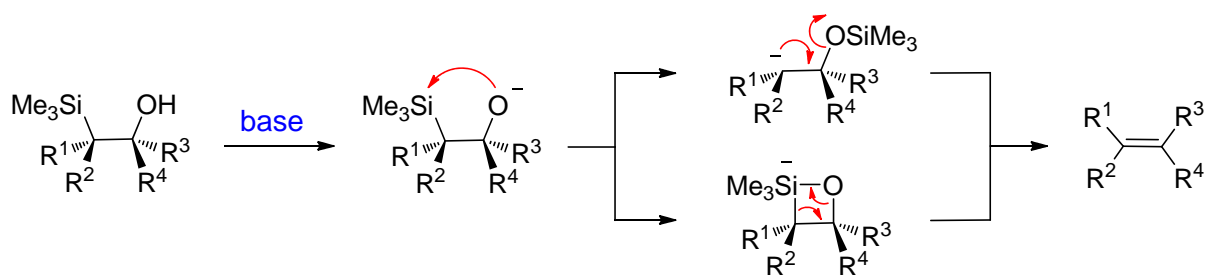
2.4 Peterson Olefination (Si-OH)



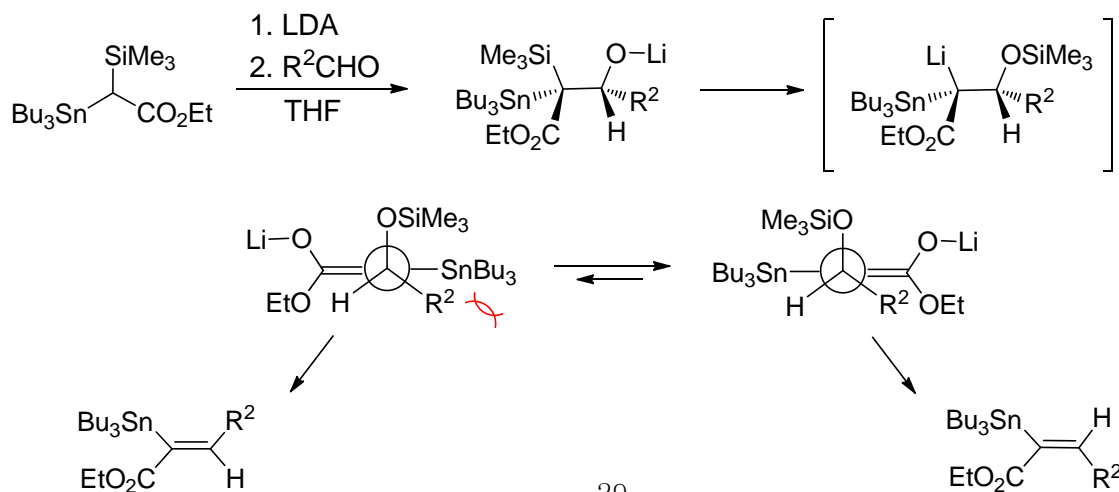
- The addition reaction is generally not stereoselective.
- The elimination is highly stereoselective.



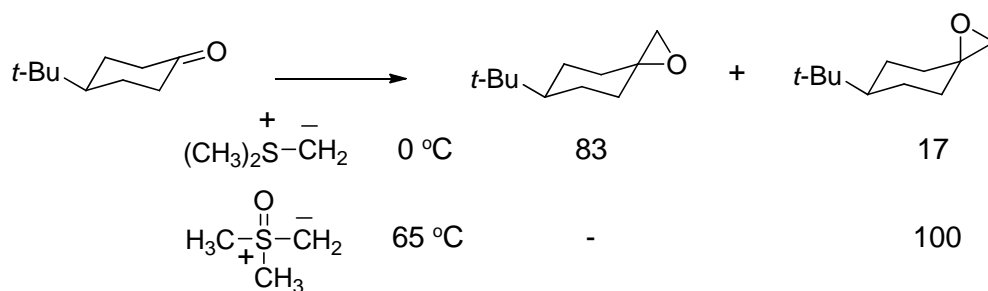
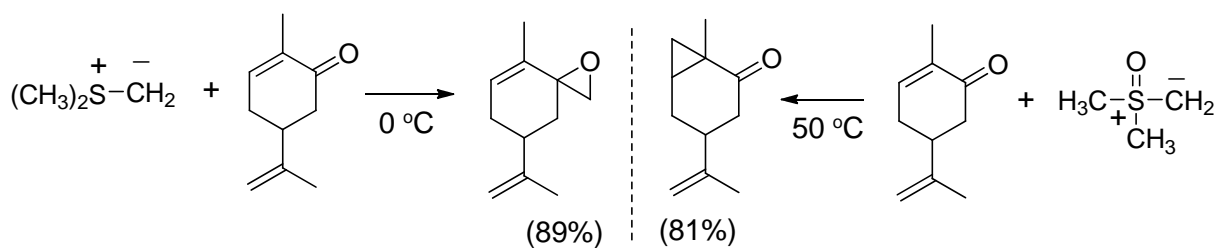
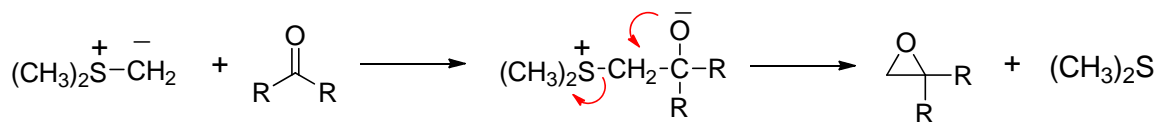
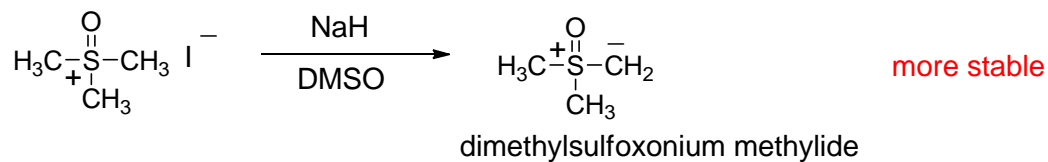
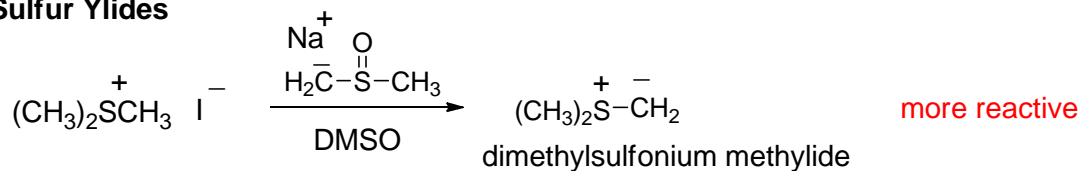
Elimination under **basic condition**: stepwise vs. concerted mechanism



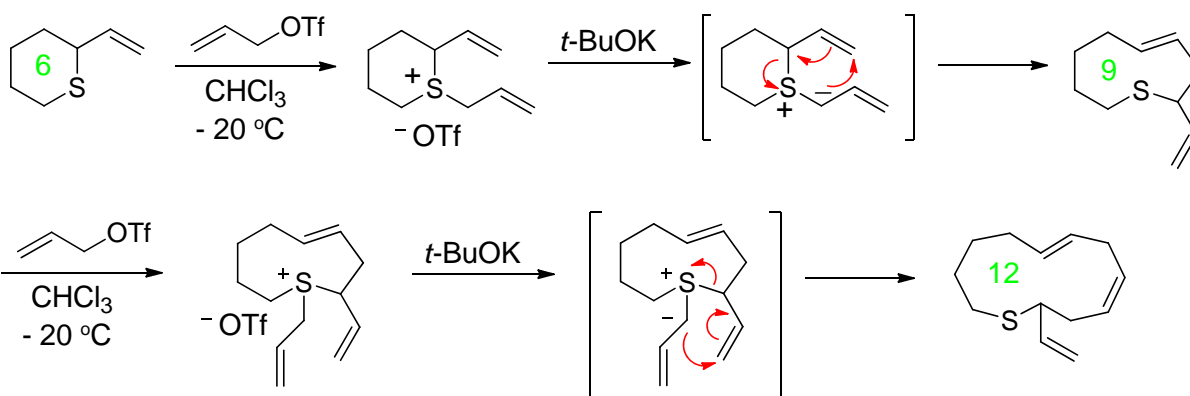
Stepwise mechanism for α -stabilized α -silylcarbanion



2.5 Sulfur Ylides

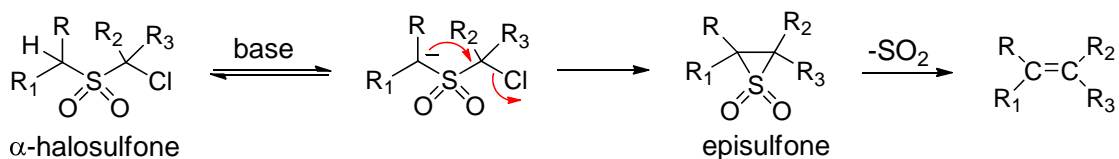


[2.3]-Wittig rearrangement - Ring expansion

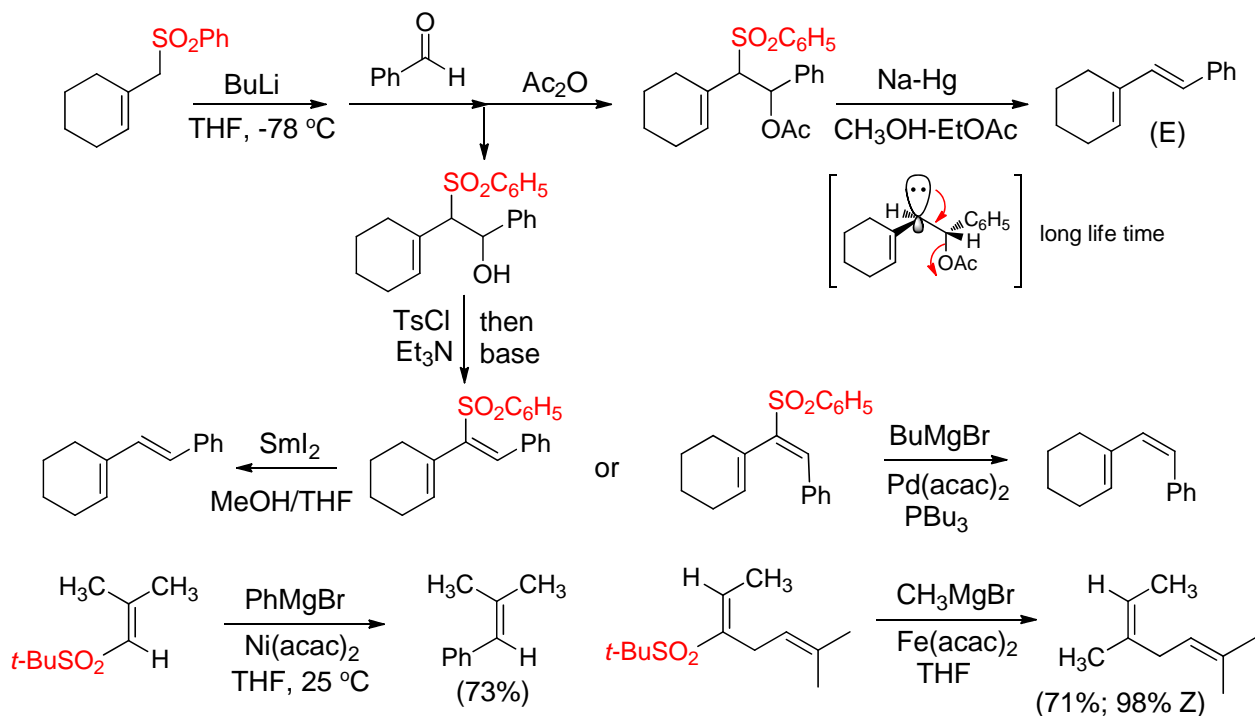


2.6 Alkenes from sulfones

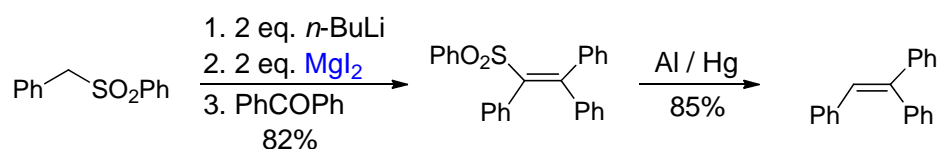
a. Ramberg-Bäcklund reaction



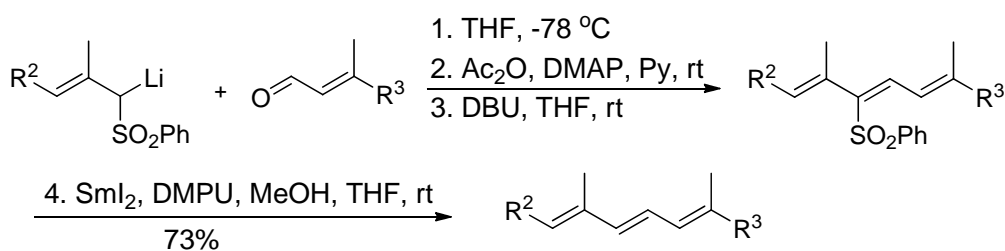
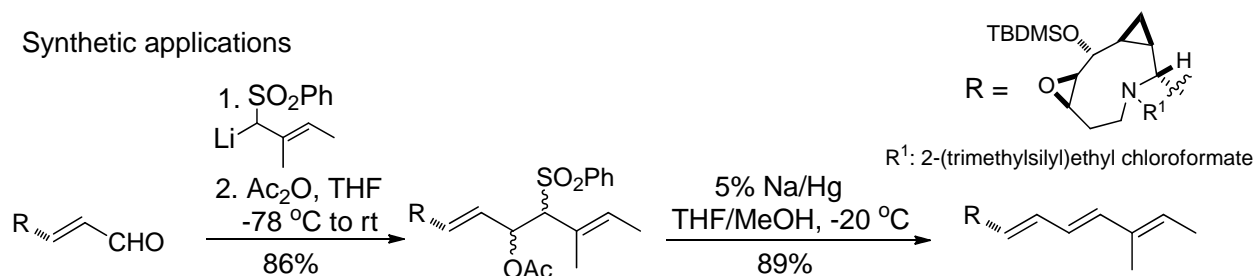
b. Julia olefination



The first report on the sulfone-mediated olefination



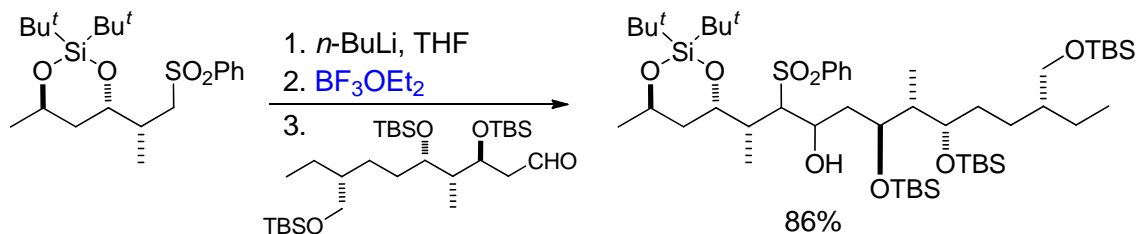
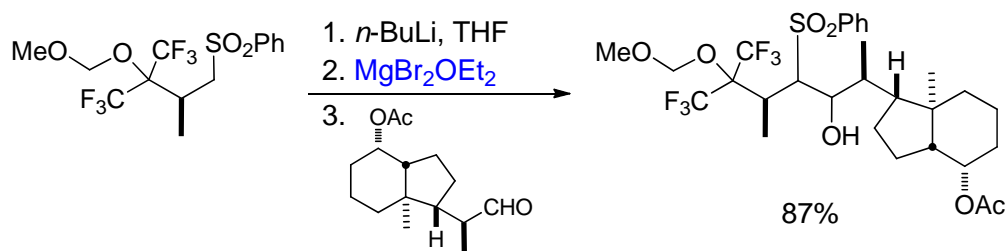
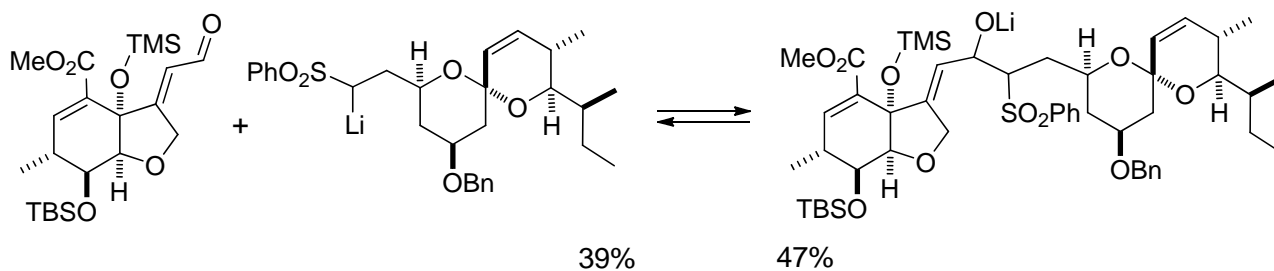
Synthetic applications



• Sulfone-mediated addition reaction

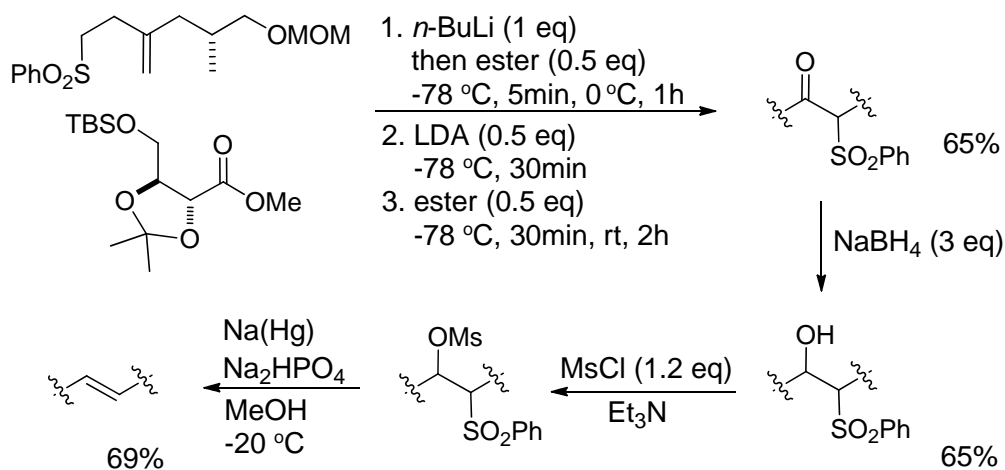
Different counter metal ions can shift unfavorable equilibrium toward the addition product

Replace **lithium** with **magnesium** or use **BF₃OEt₂**



Trapping with Ac₂O, BzCl, MsCl or TMSCl can also shift unfavorable equilibrium toward the addition product

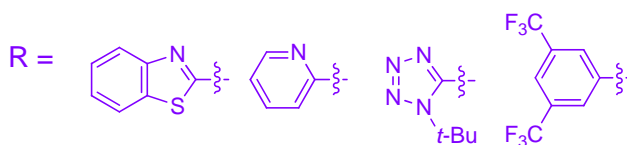
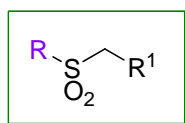
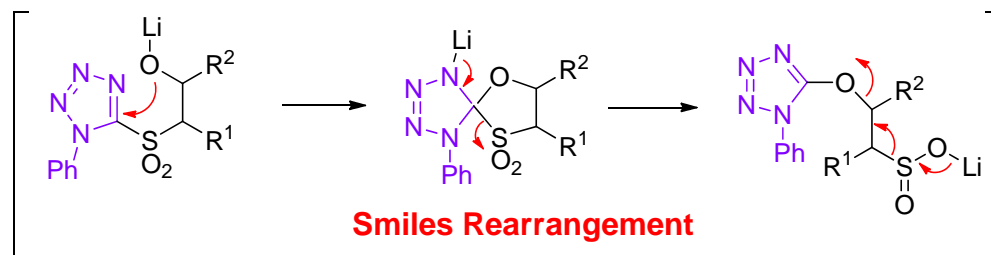
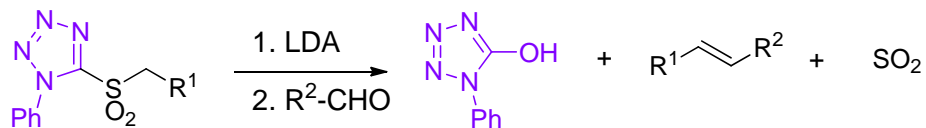
Addition to an ester and reduction of the resulting ketone to β-hydroxysulfone



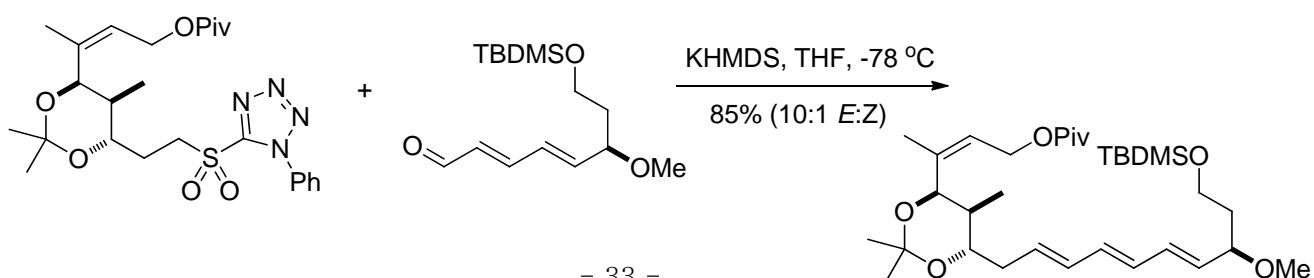
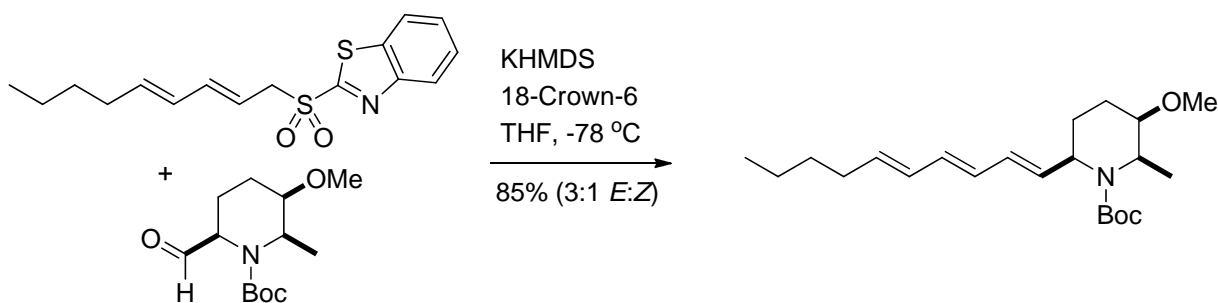
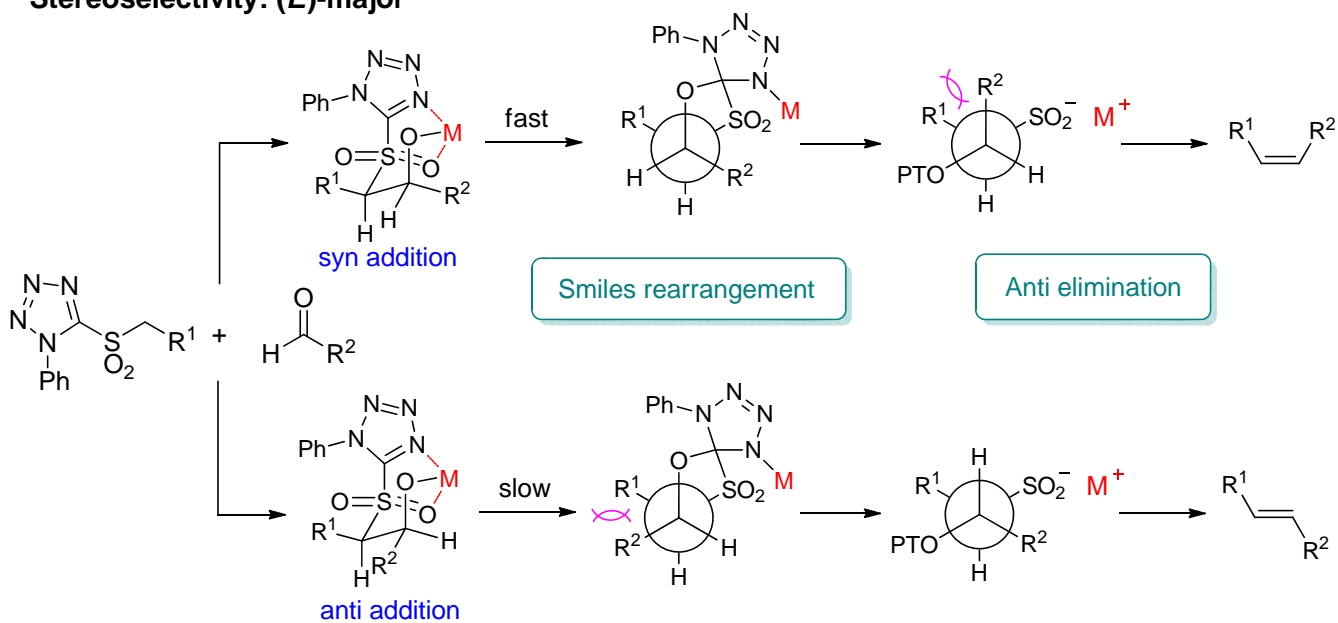
Using DME instead of THF sometimes suppresses the undesirable enolization

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

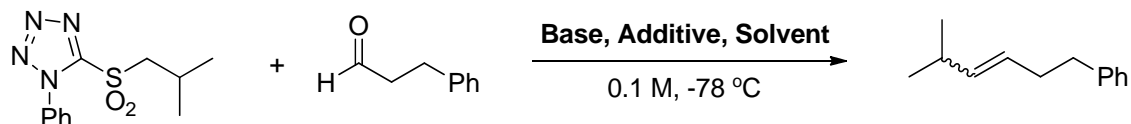
c. Julia-Kocienski olefination



Stereoselectivity: (E)-major

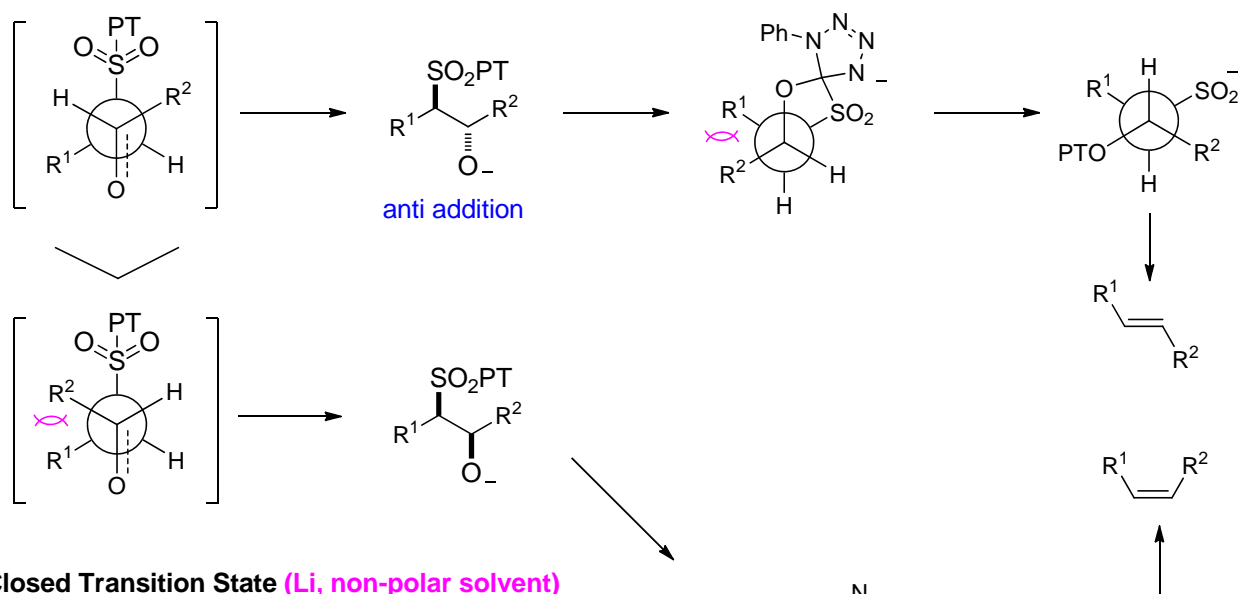


Stereoselectivity

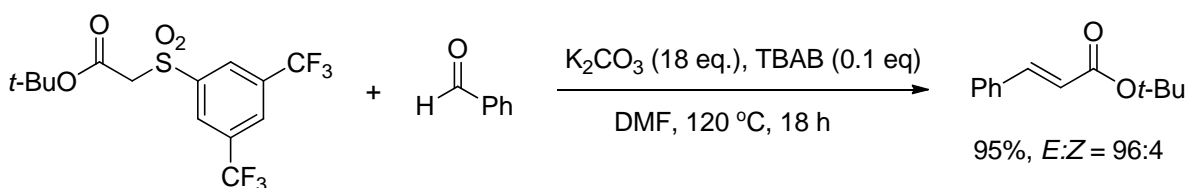
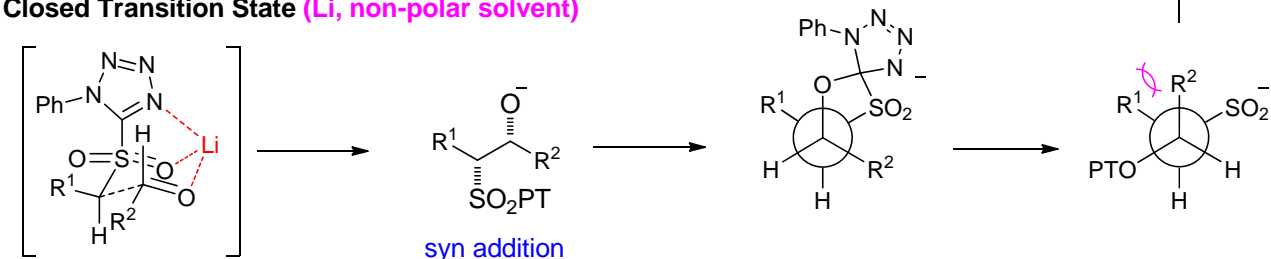


Entry	Base (equiv)	Additive (equiv)	Solvent	Yield	E/Z
1	KHMDS (1.1)		THF	88%	4.3:1
2	KHMDS (1.1)	18-Cr-6 (1.1)	THF	86%	15:1
3	KHMDS (1.1)	18-Cr-6 (2.0)	THF	84%	>50:1
4	KHMDS (1.1)	18-Cr-6 (2.0)	toluene	87%	>50:1
5	KHMDS (1.1)	18-Cr-6 (2.0)	DMF	78%	>50:1
6	NaHMDS (1.1)	18-Cr-6 (2.0)	THF	78%	4:1
7	LiHMDS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

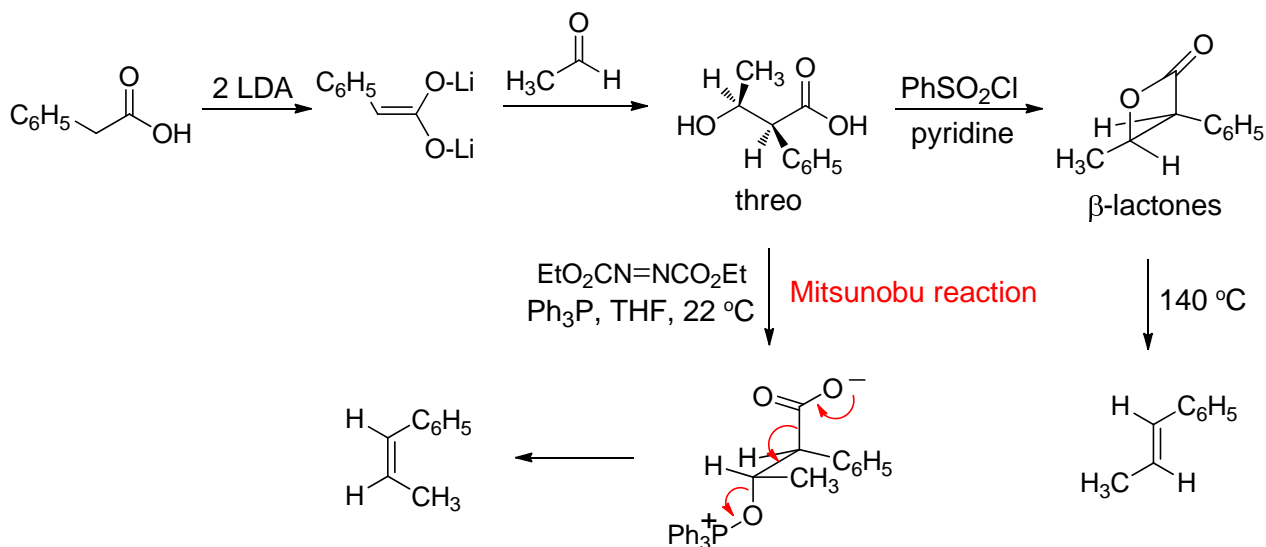
Open Transition State (KHMDS, 18-Cr-6)



Closed Transition State (Li, non-polar solvent)

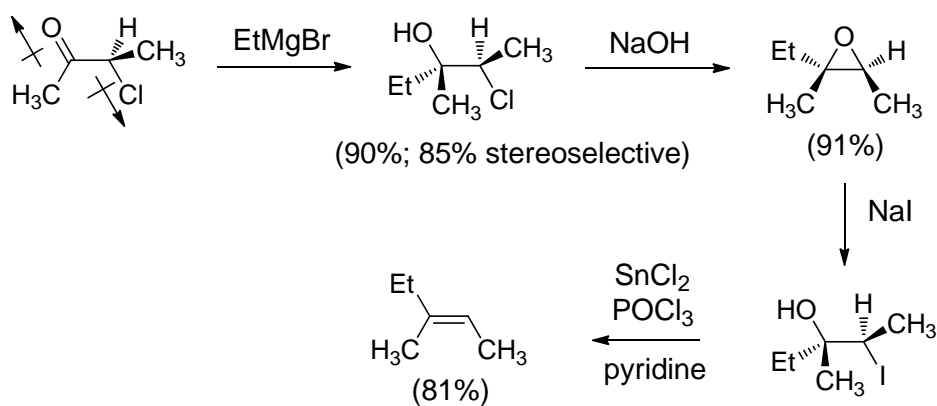


2.7 Decarboxylation of β -lactones

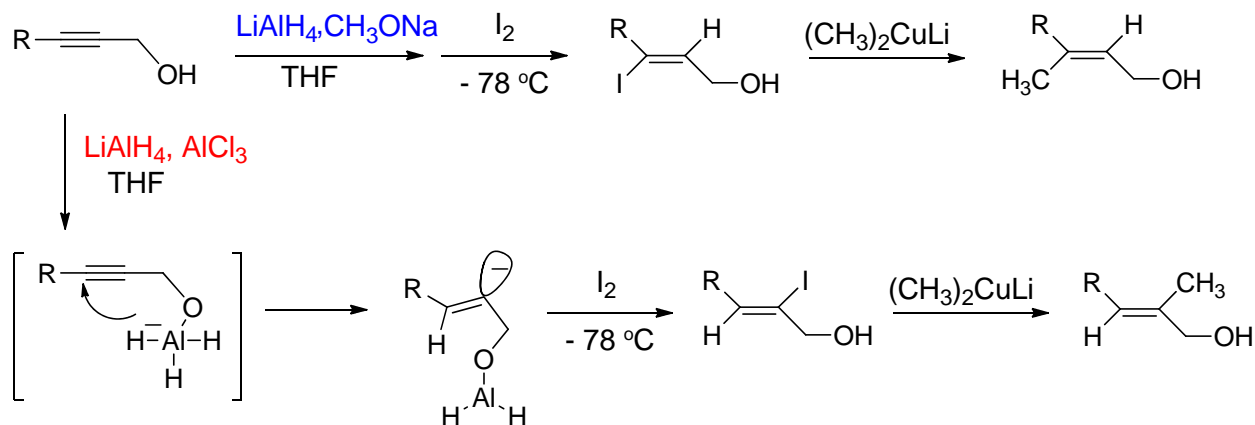


2.8 Stereoselective synthesis of tri- and tetra-substituted alkenes

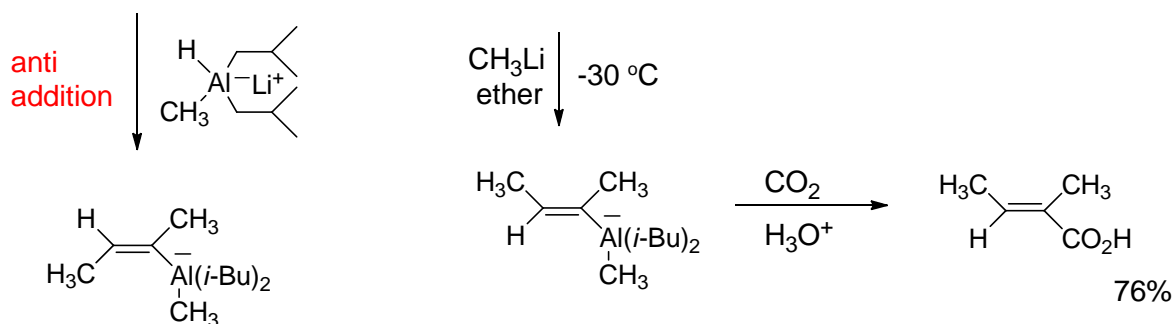
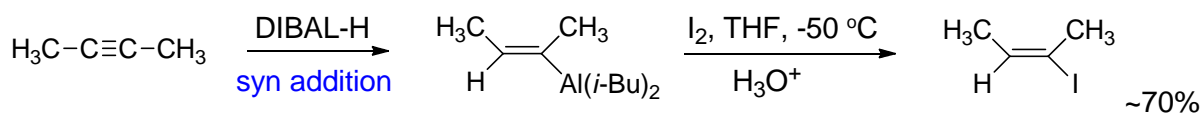
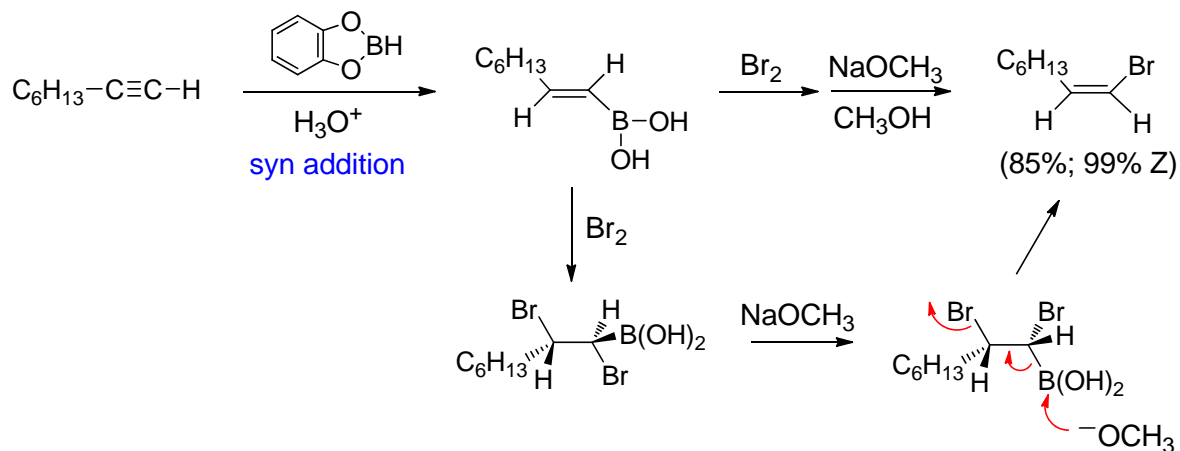
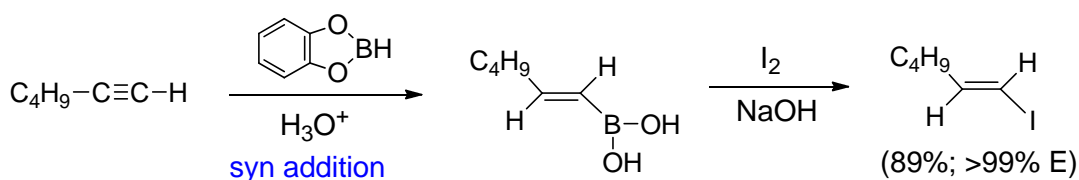
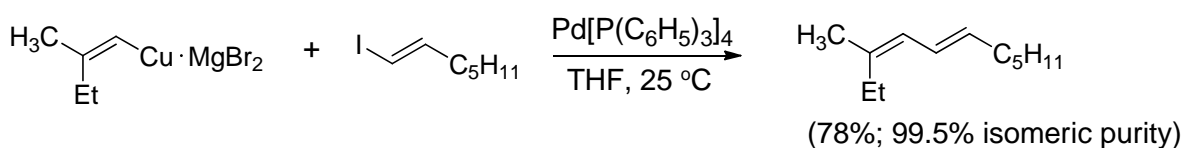
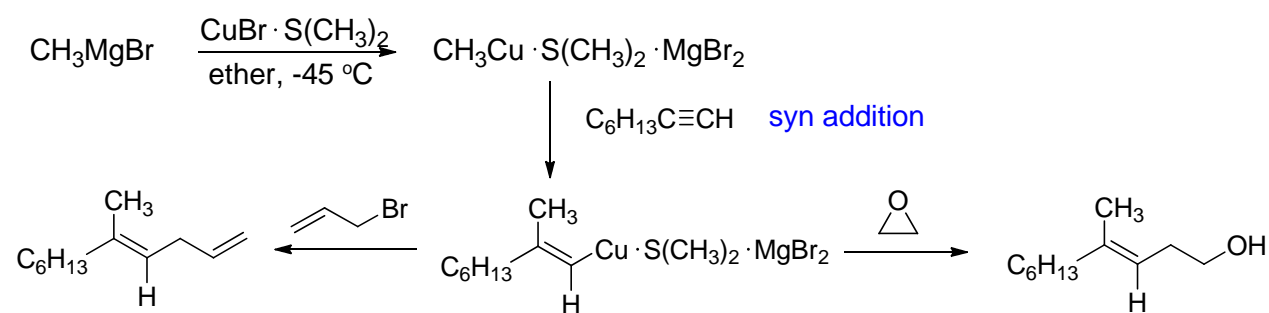
a. Grignard reagent with an α -chloroaldehyde or -ketone

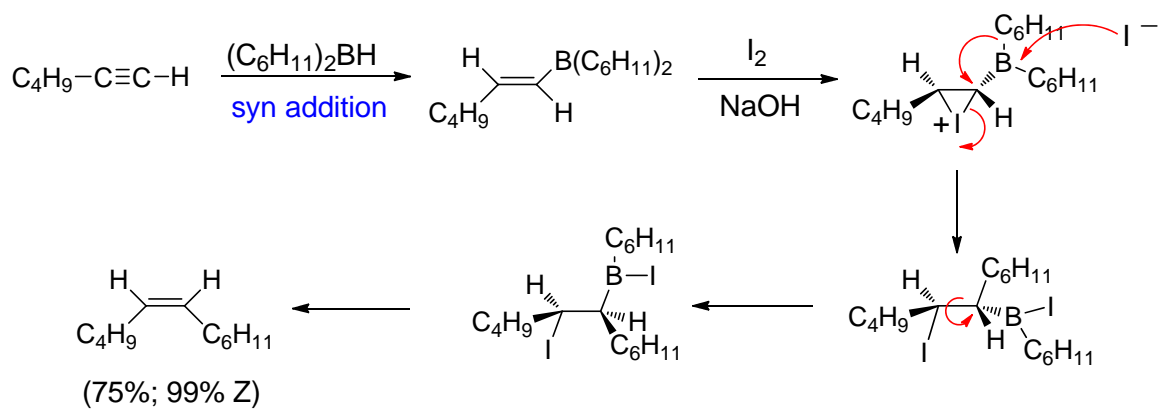


b. Reduction of propargylic alcohol with LiAlH_4

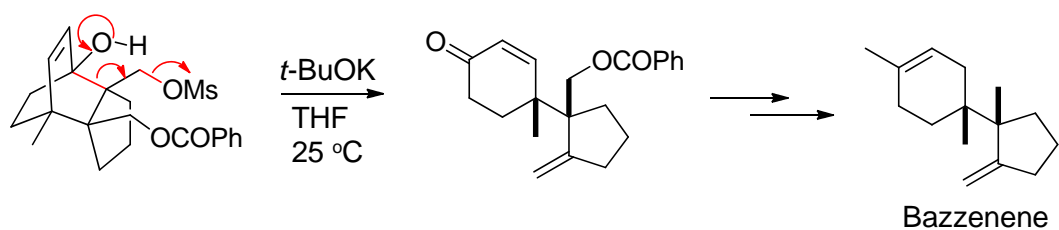
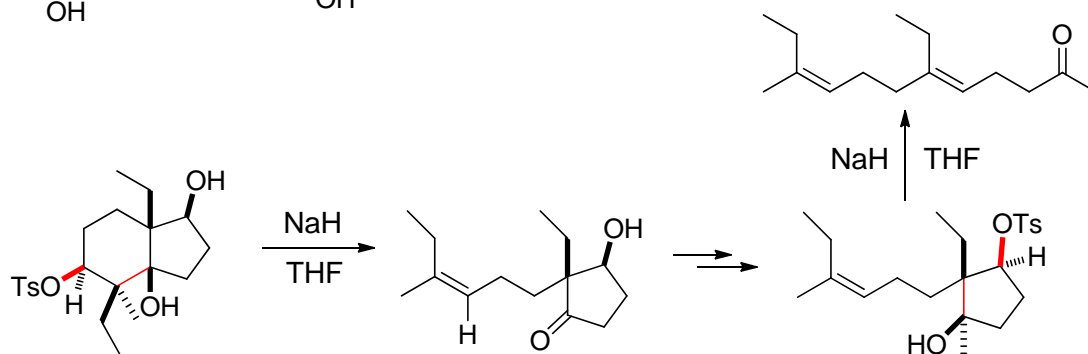
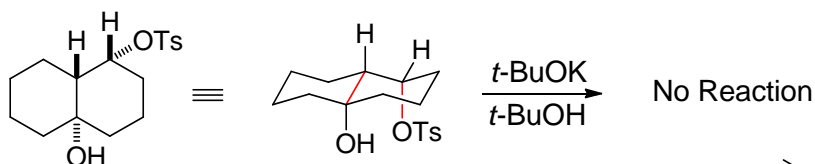
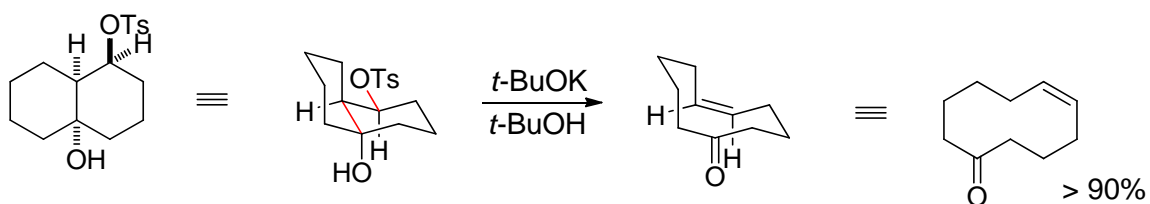
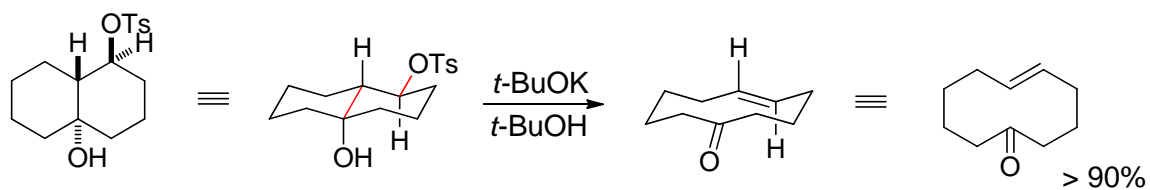
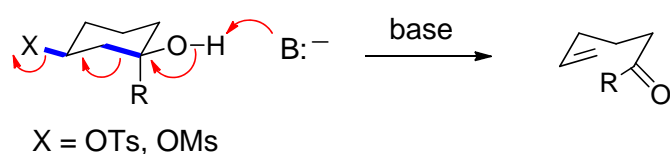


c. Reaction of organocopper or organoborane with alkynes

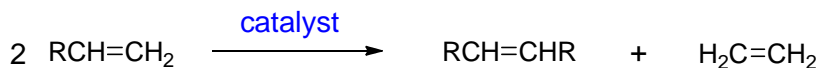




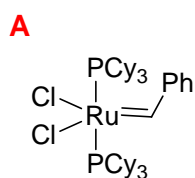
2.9 Fragmentation reactions



2.10 Olefin Metathesis



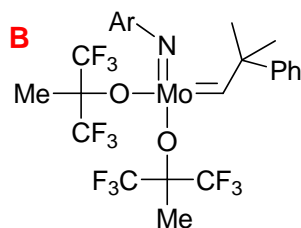
ruthenium or molybdenum alkylidene (carbene) complex



Cy: Cyclohexyl

Grubbs I

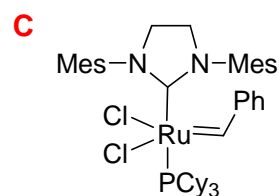
(stable but less reactive)



Ar: 2,6-diisopropylphenyl

Schrock

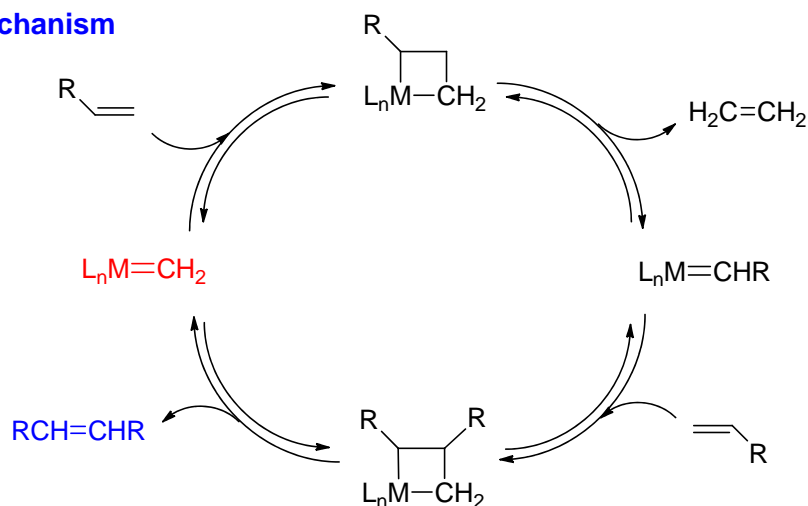
(useful for tri- or tetra-substituted alkenes)



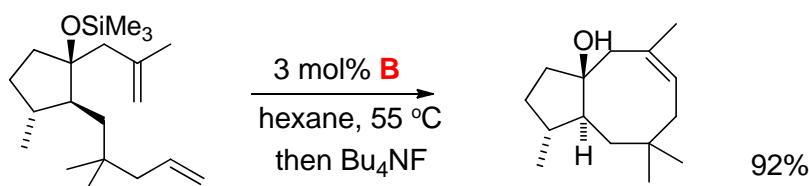
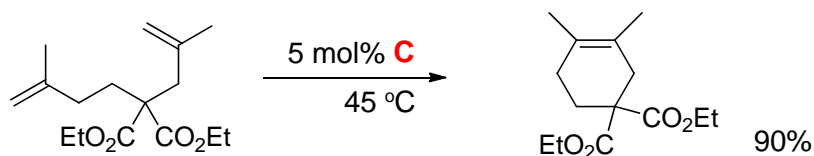
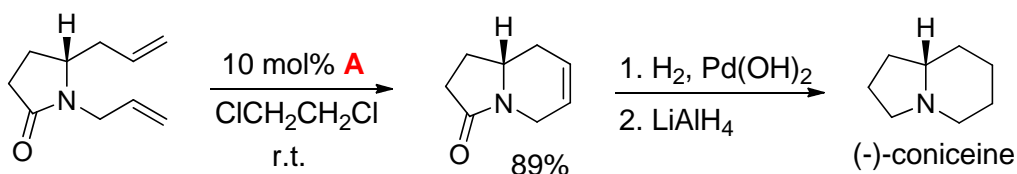
Mes: 2,4,6-trimethylphenyl

Grubbs II

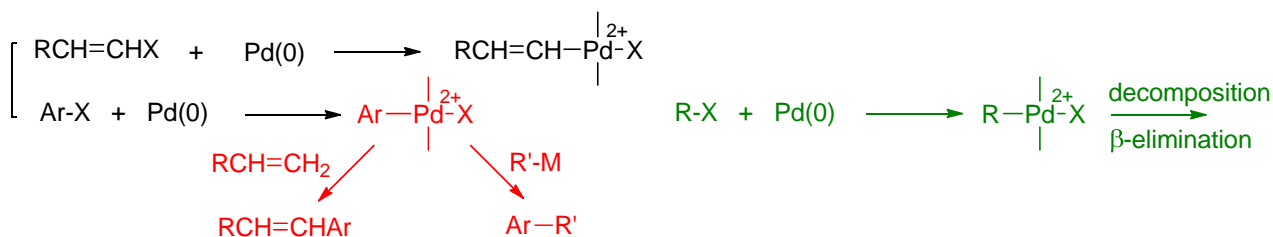
Mechanism



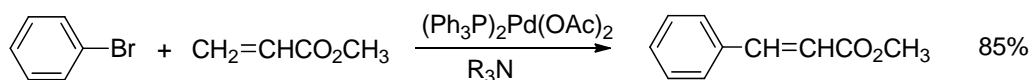
RCM (Ring Closing Metathesis)



2.11 Pd - Catalyzed Reaction

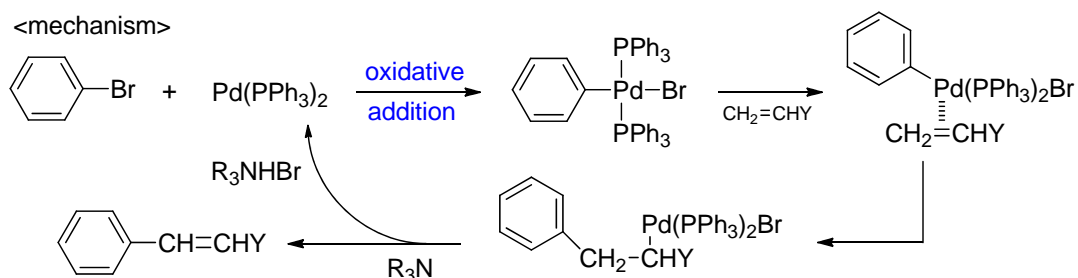


a. Heck reaction (reaction with alkenes)



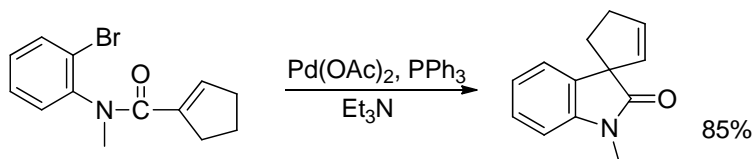
in situ reduction of Pd(II) to Pd(0): Pd(OAc)₂ + 2PPh₃

<mechanism>

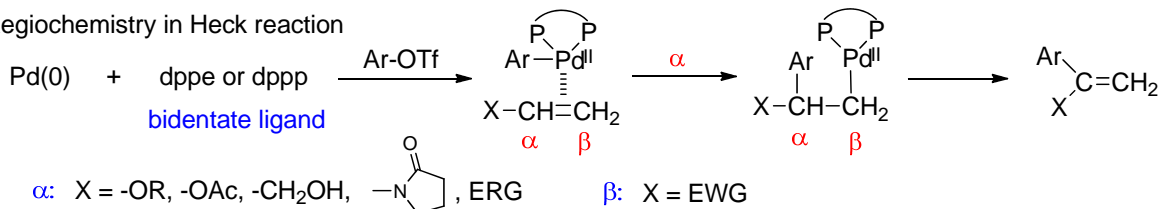


* High halide concentration promote formation of [PdL₂X]⁻, which retards coordination to double bonds.

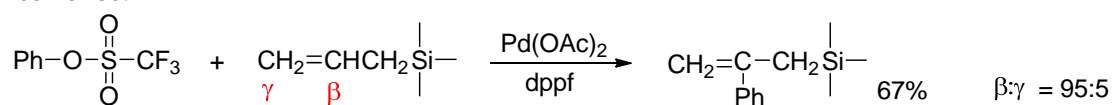
Use -OTf instead of -X to accelerate complexation with alkenes.



Regiochemistry in Heck reaction

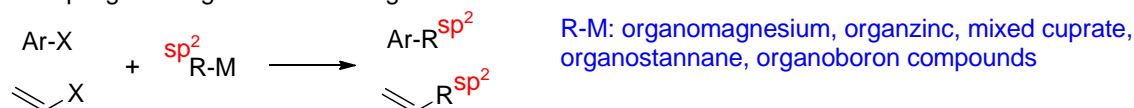


Silicon effect



b. Palladium-catalyzed cross coupling reaction

b-1. Coupling with organometallic reagents

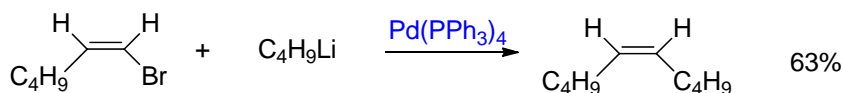
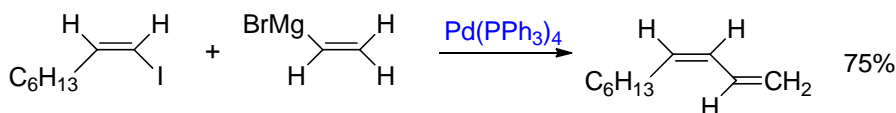


X: halides, sulfonates biaryls, dienes, polyenes, enynes

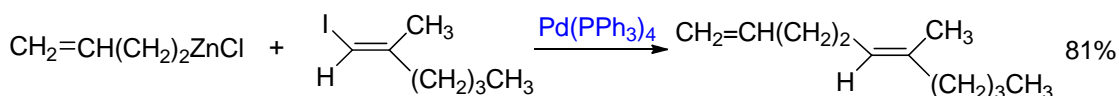
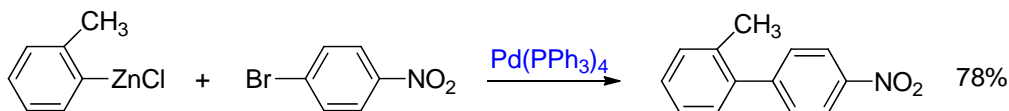
Steps in cross-coupling reaction:

oxidative addition - transmetalation - reductive elimination

b-1-1. Grignard and organolithium reagents with Alkenyl halides

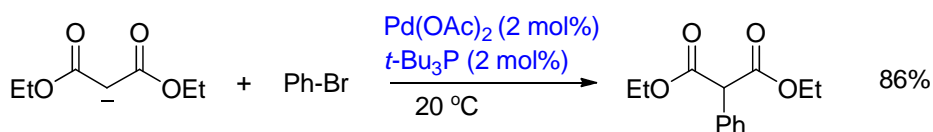
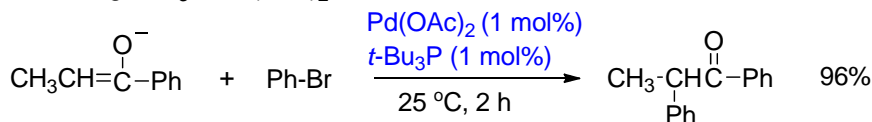


b-1-2. Organozinc reagents

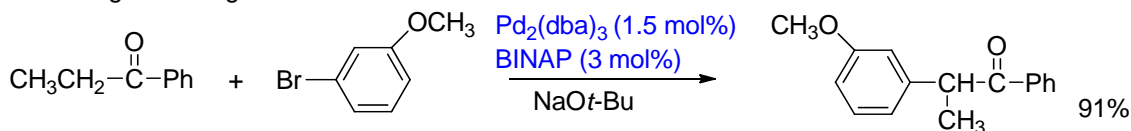


b-1-3. Arylation of enolates

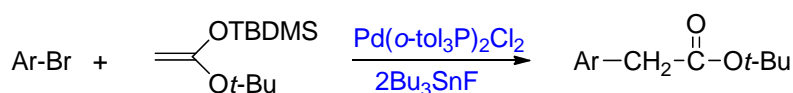
a. using *t*-Bu₃P, Pd(OAc)₂



b. using BINAP ligand

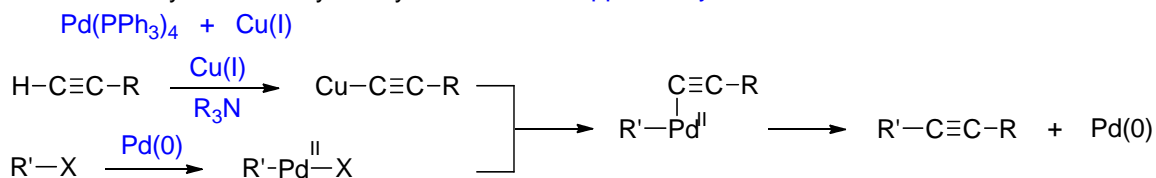


c. O-silyl ketene acetals with Bu₃Sn-F

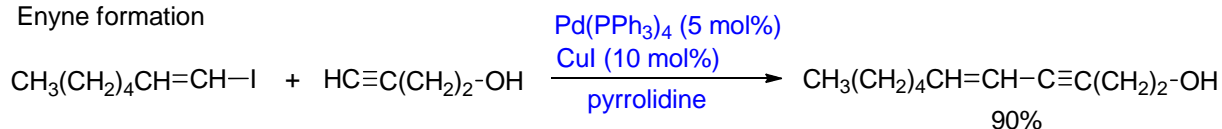


b-1-4. Terminal alkynes with vinyl or aryl halides

"copper acetylide"



Enyne formation



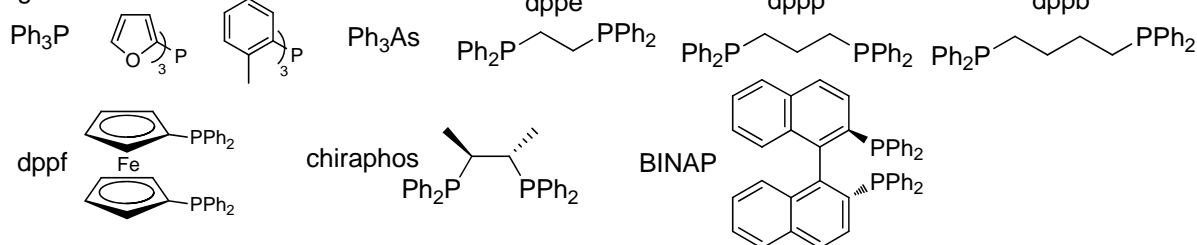
b-1-5. Coupling with stannanes

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

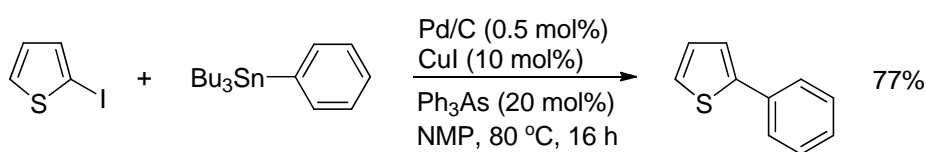
Group that can be transferred from tin:

alkynyl > alkenyl > aryl > methyl > alkyl

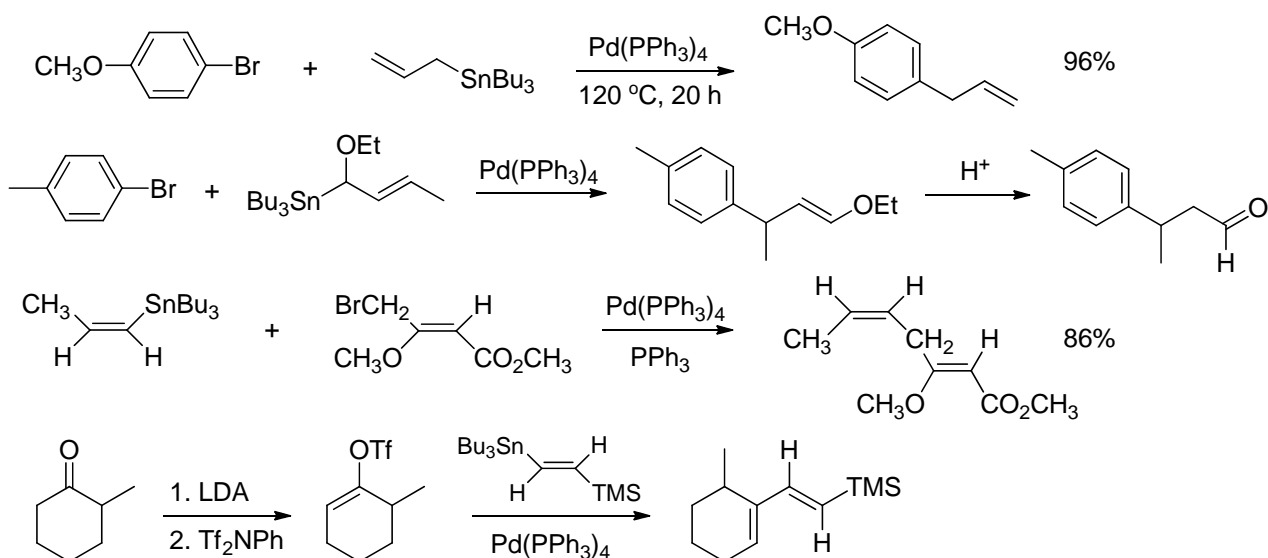
Ligand



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



Examples

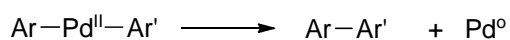
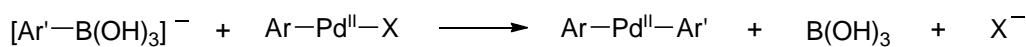
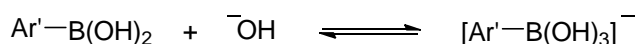
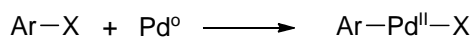


b-1-6. Coupling with organoboranes

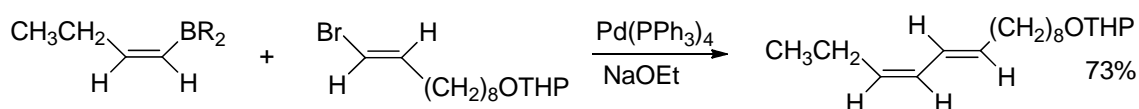
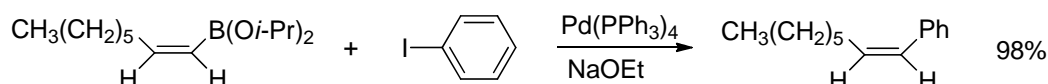
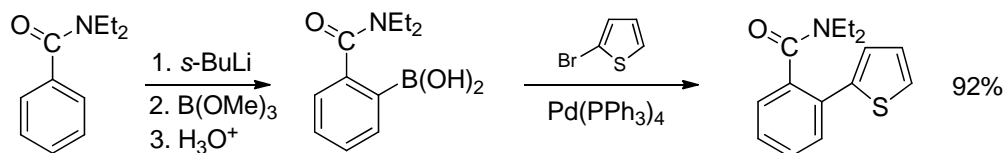
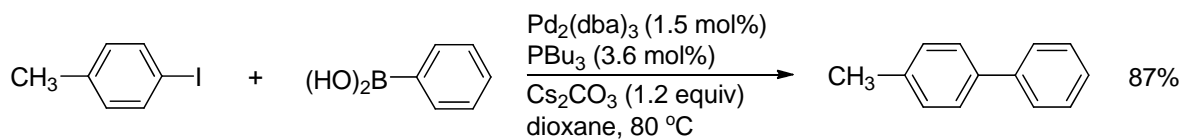
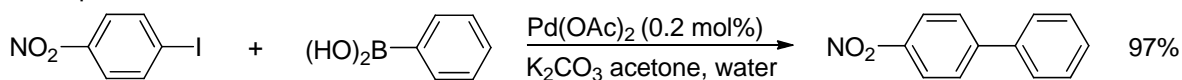
Cross-coupling reaction of aryl or vinyl boron compound (boronic acids, boronate esters, boranes)
 "Suzuki reaction" boric acid as a byproduct

Rate-determining step: oxidative addition or transmetallation

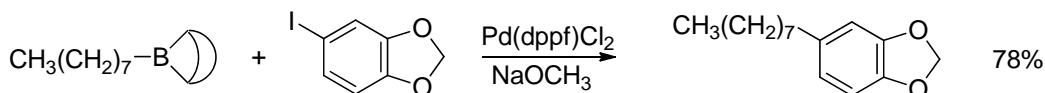
Base catalysis is required for boronic acids to generate more reactive boronate anion.



Examples



Alkyl-aryl coupling using 9-BBN

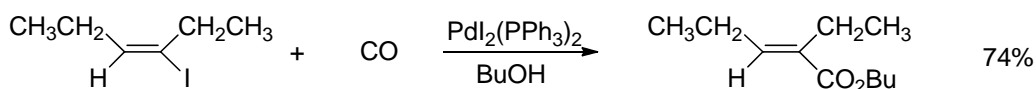


Bases

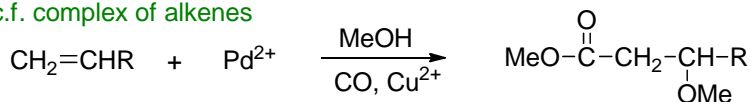
Cs_2CO_3 or $\text{TIOH} > \text{NaOH}$

b-2. Reaction with carbon monoxide (CO)

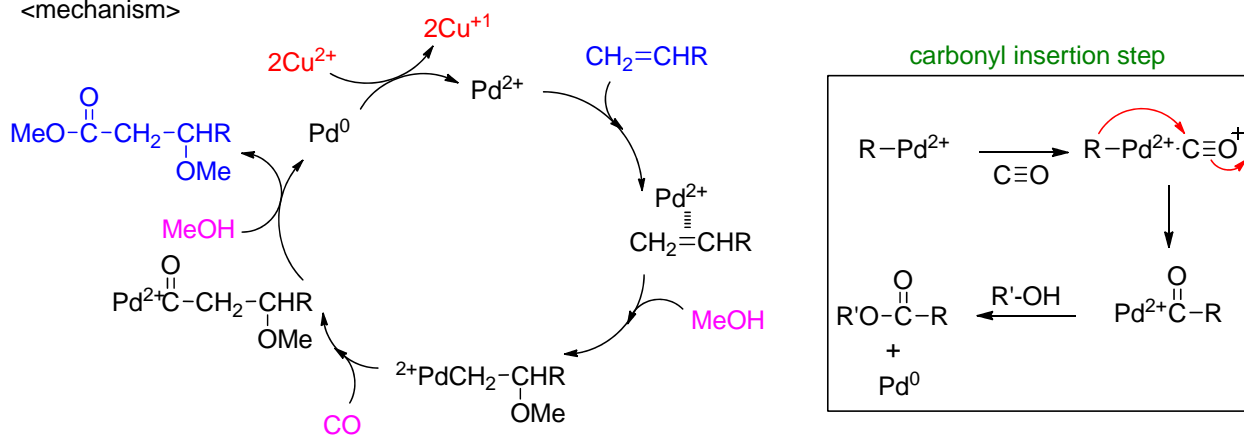
b-2-1. Reaction in ROH



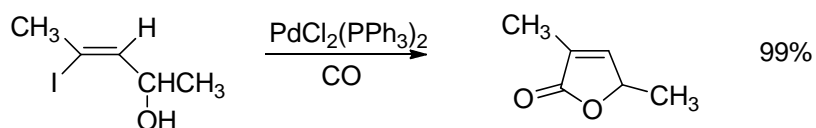
c.f. complex of alkenes



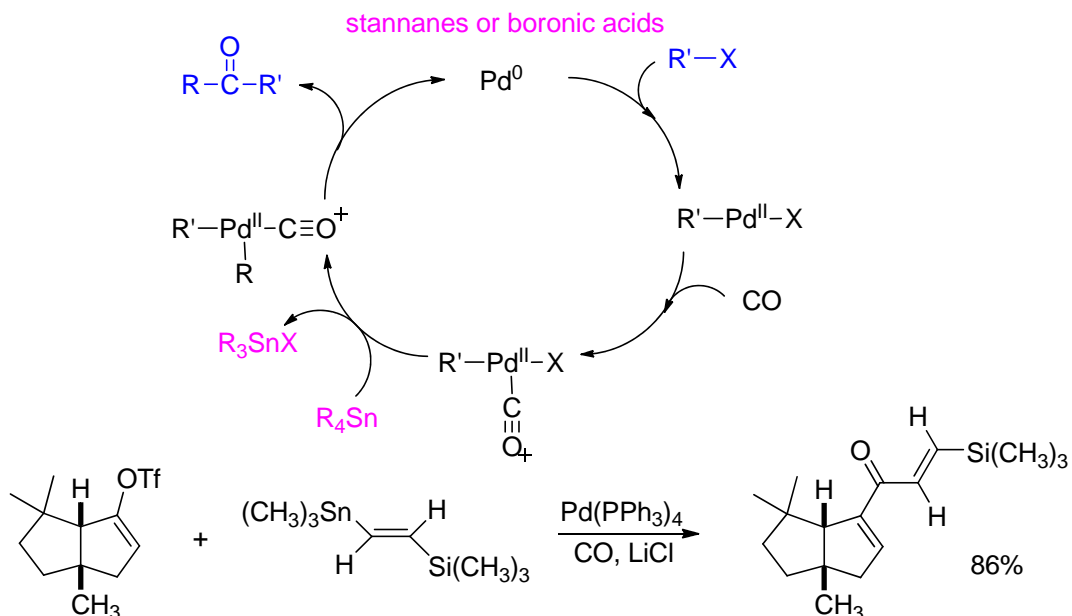
<mechanism>



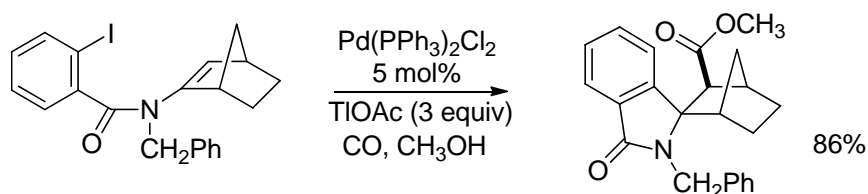
Intramolecular Palladium-catalyzed cross coupling reaction



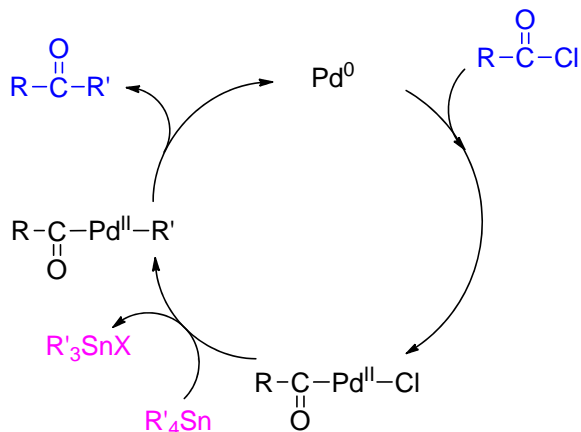
b-2-2. Coupling of organometallic reagents with aryl or vinyl halides



Tandem intramolecular Heck-carbonylation reaction



Coupling of organostannane with acyl chlorides

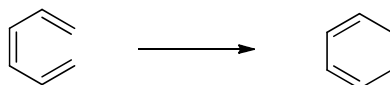


Chapter 3. Pericyclic Reaction

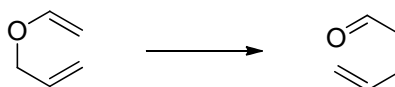
Introduction

Pericyclic Reaction: Concerted Process; Cyclic Transition State

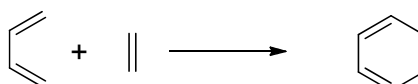
1. Electrocyclic Reaction



2. Sigmatropic Rearrangement

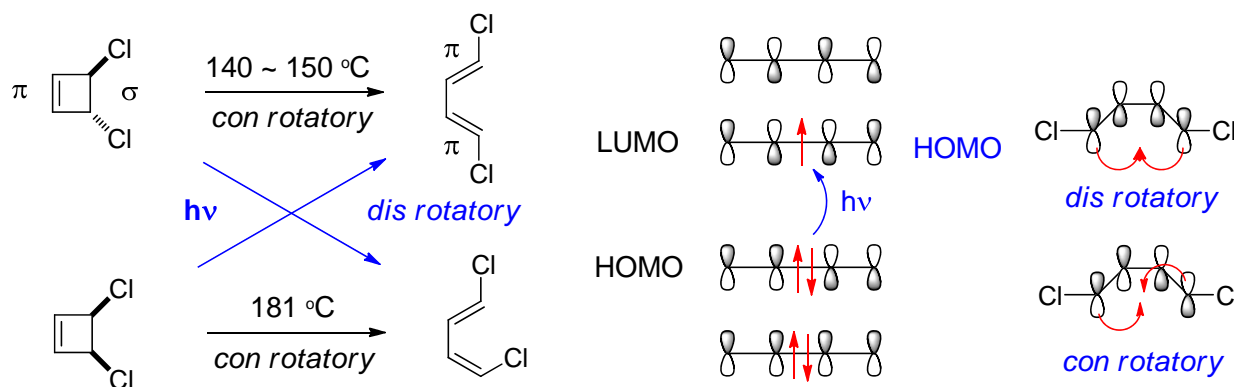


3. Cycloaddition

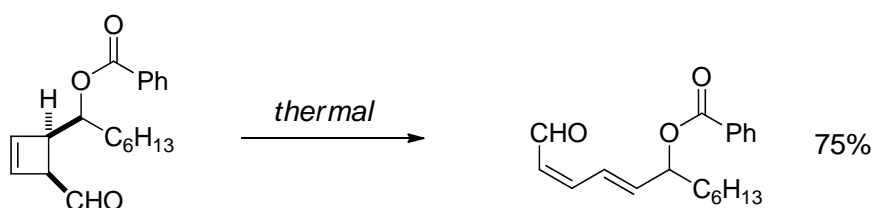
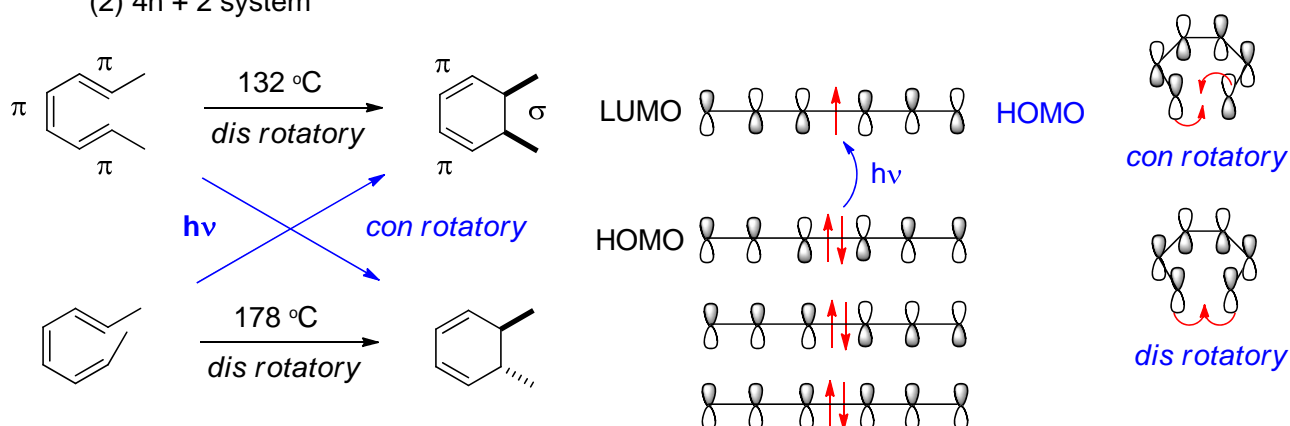


Woodward-Hoffmann Rules

(1) $4n$ system

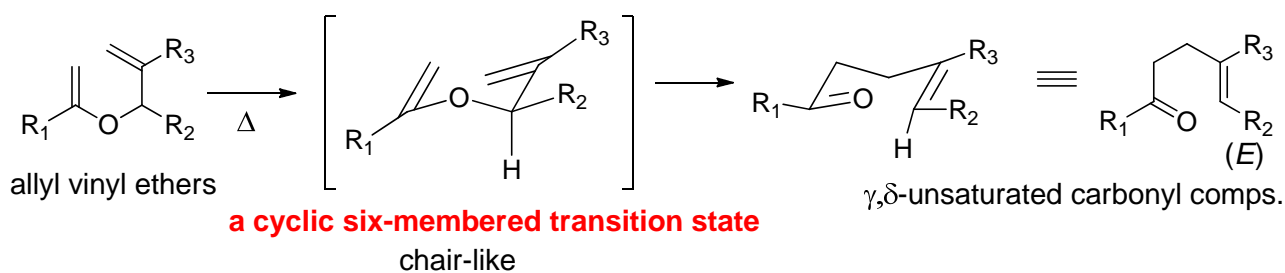


(2) $4n + 2$ system

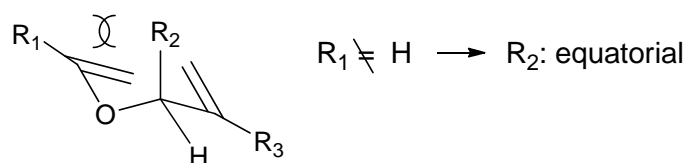


3-1 Claisen Rearrangement of Allyl Vinyl Ethers

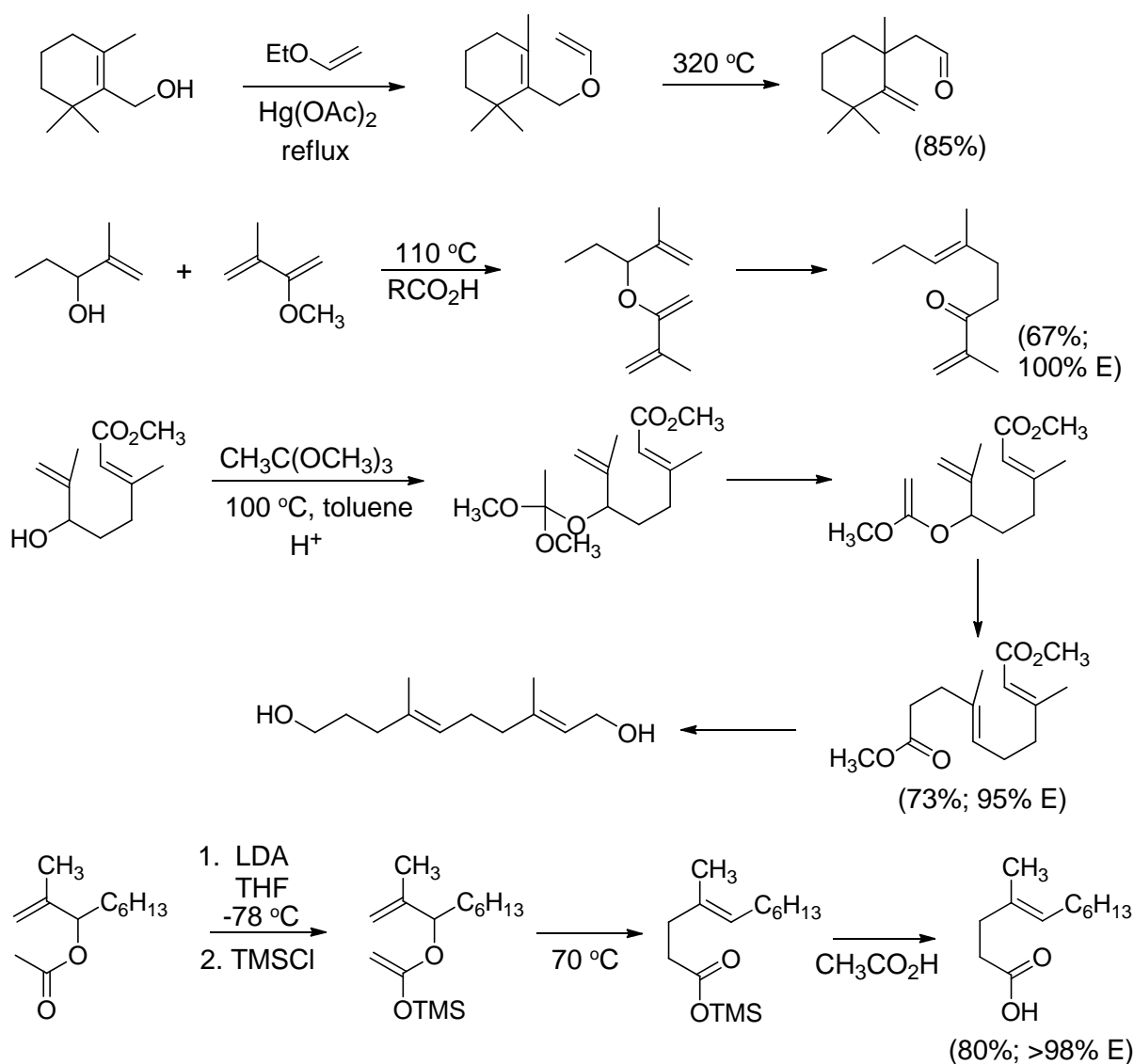
[3,3]-sigmatropic Rearrangement - Concerted Mechanism



c.f.

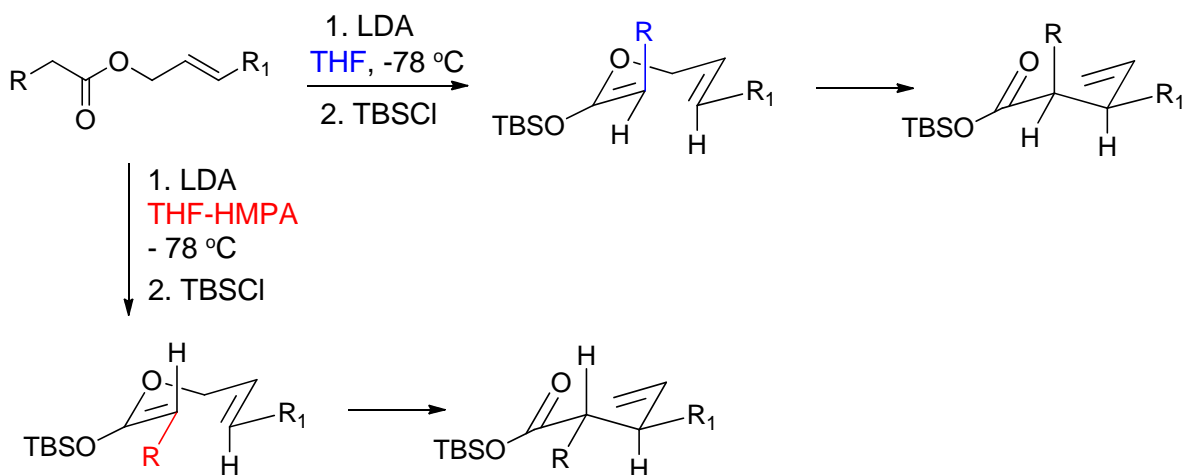
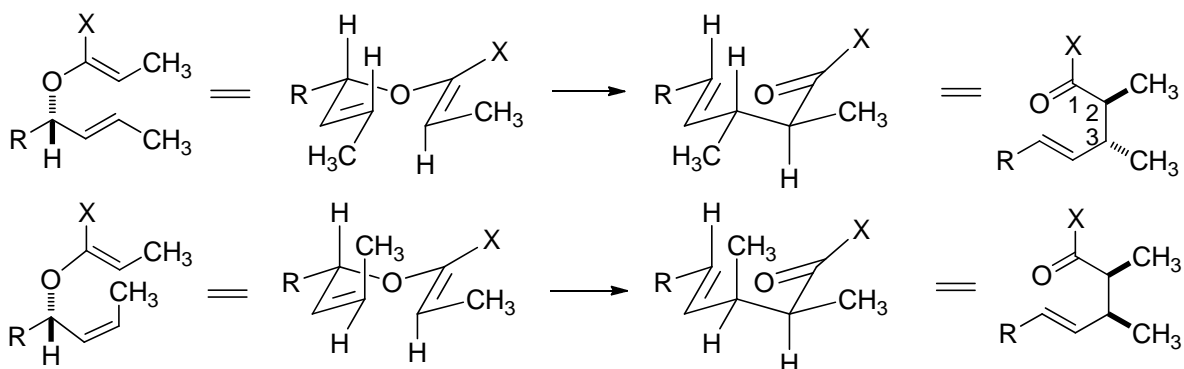
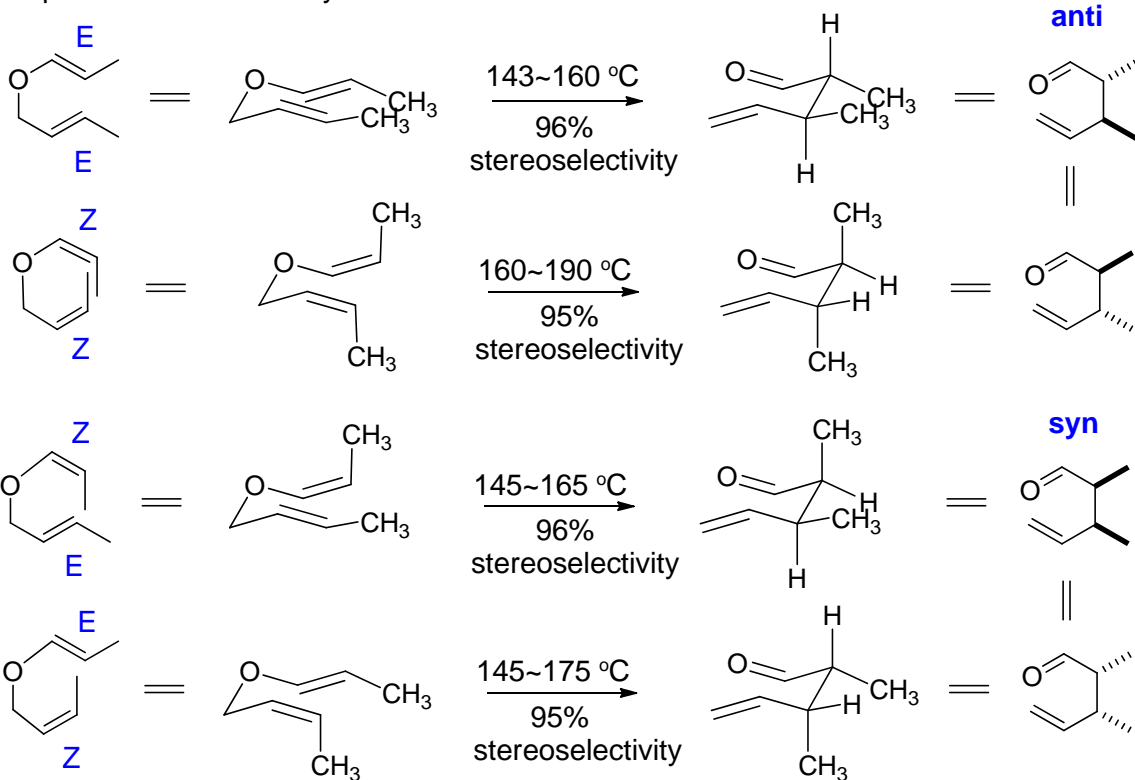


a. Preparation of Allyl Vinyl Ethers



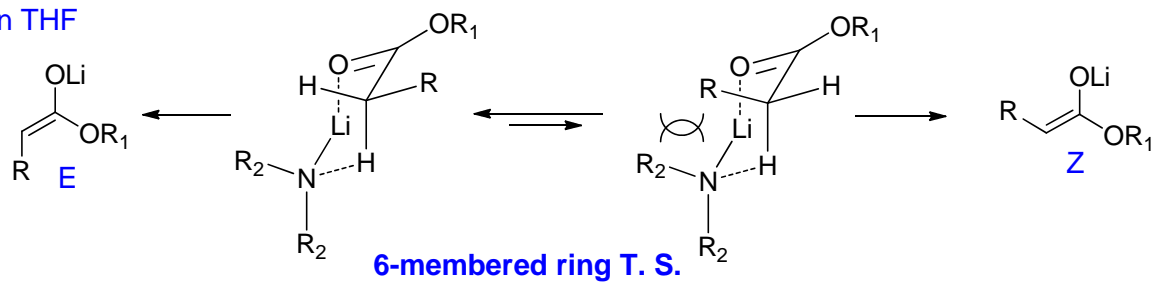
b. Stereochemical Control

simple diastereoselectivity

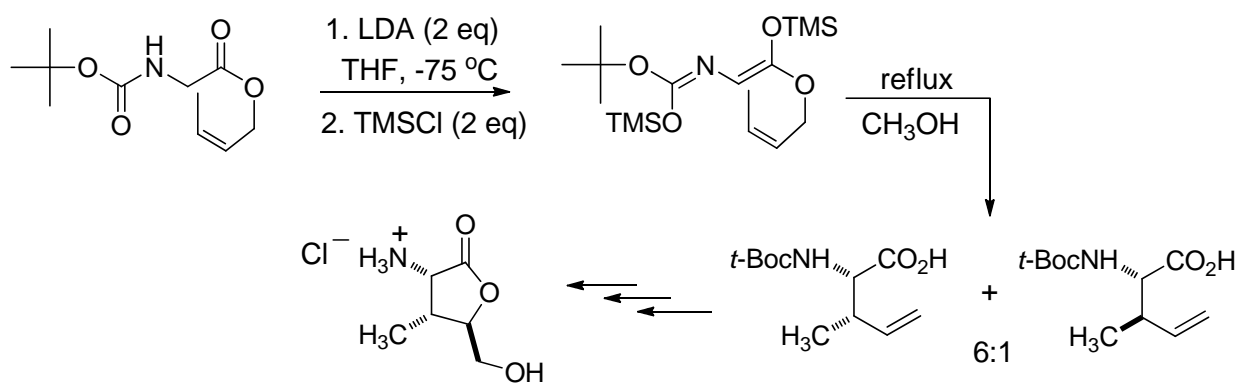
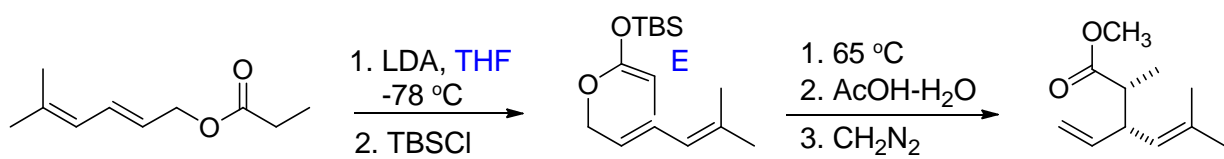
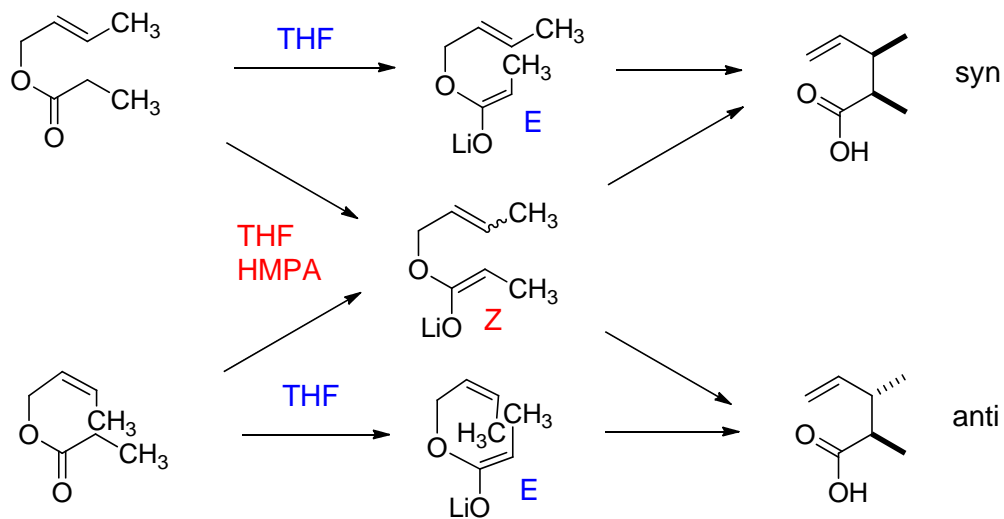
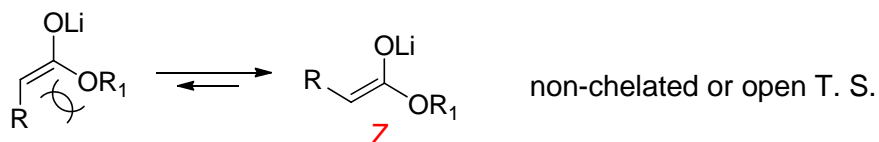


Formation of (Z)- or (E)-enolate

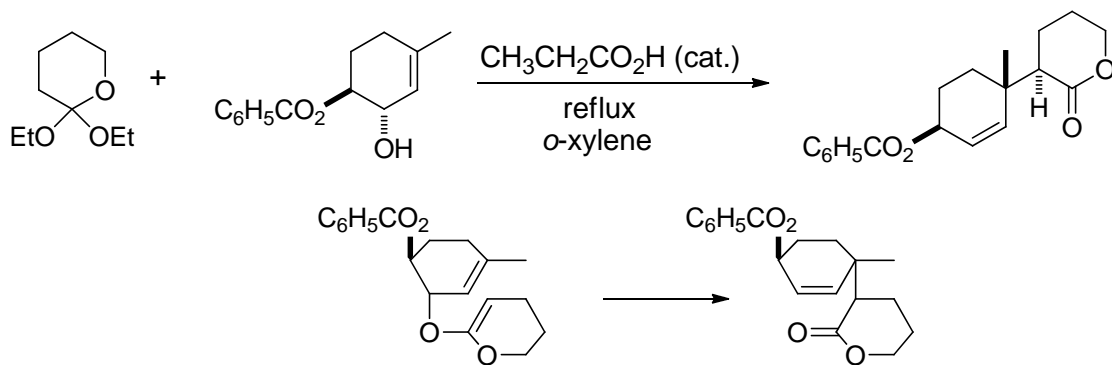
In THF



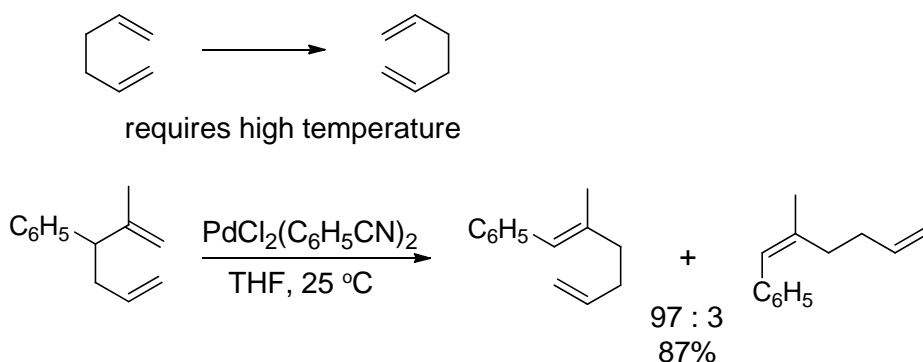
In THF-HMPA



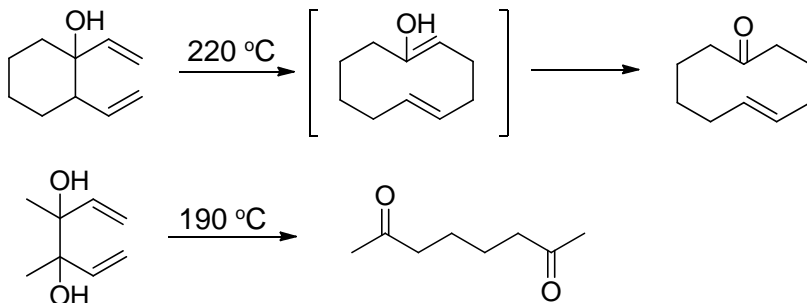
Boat-like Transition State - when double bond forms part of a ring



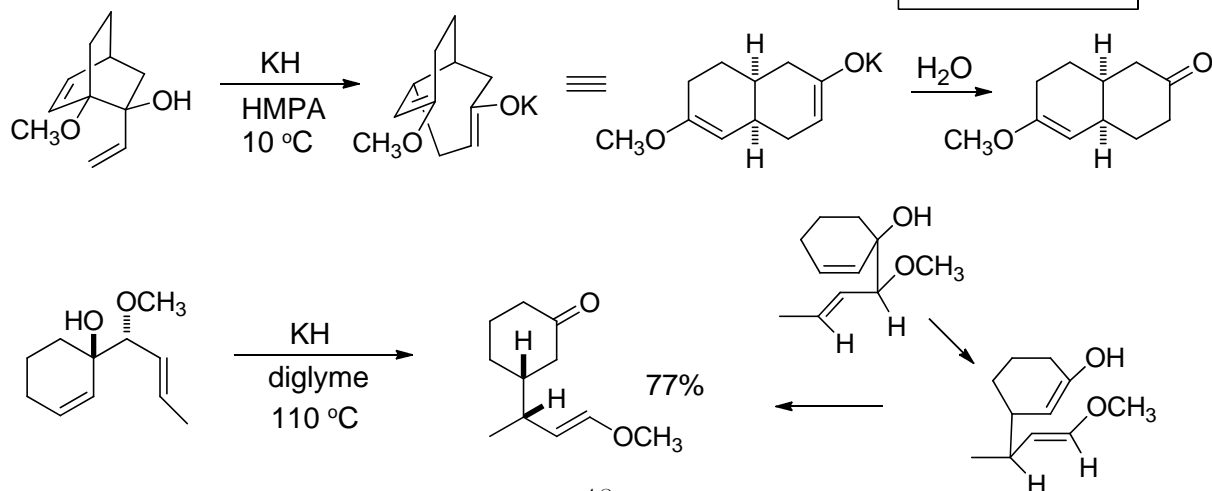
3-2 Cope rearrangement - [3,3]-sigmatropic rearrangement



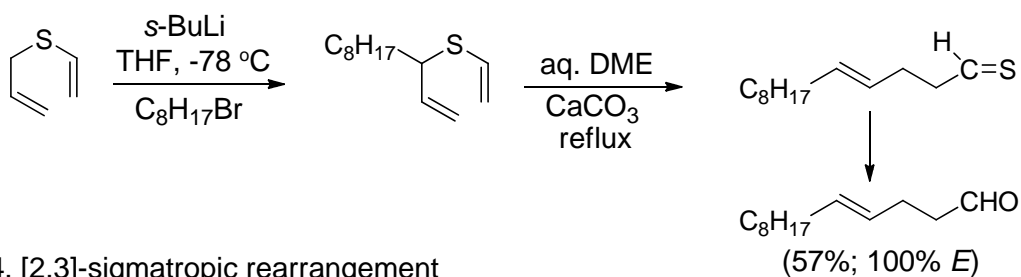
Oxy-Cope rearrangement



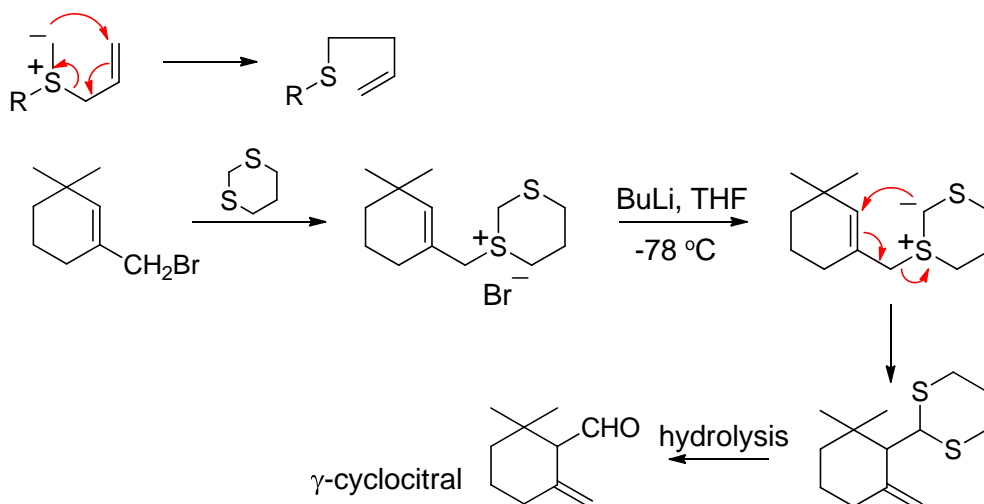
Anionic Oxy-Cope rearrangement



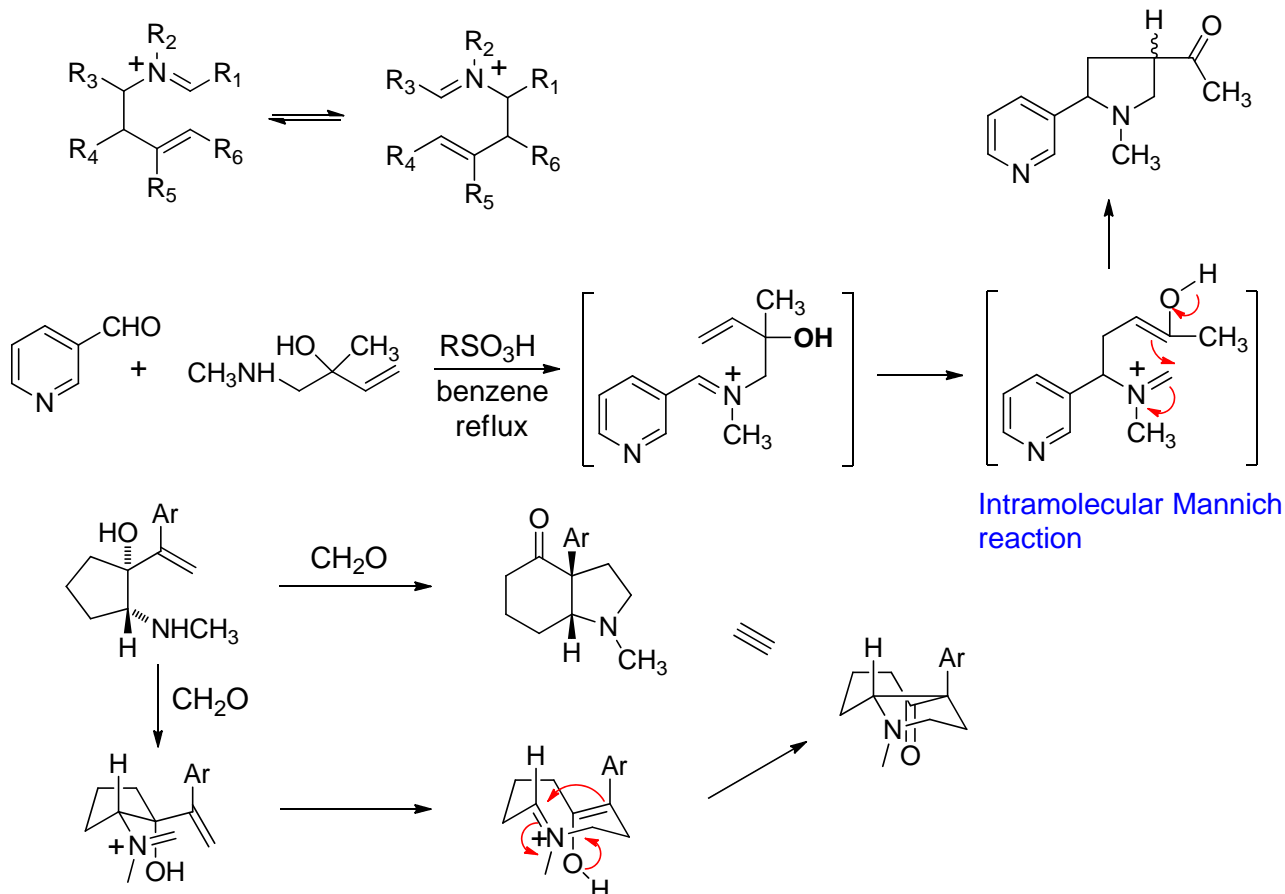
3-3. Thio Claisen Rearrangement



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



3-5. aza-Cope rearrangement

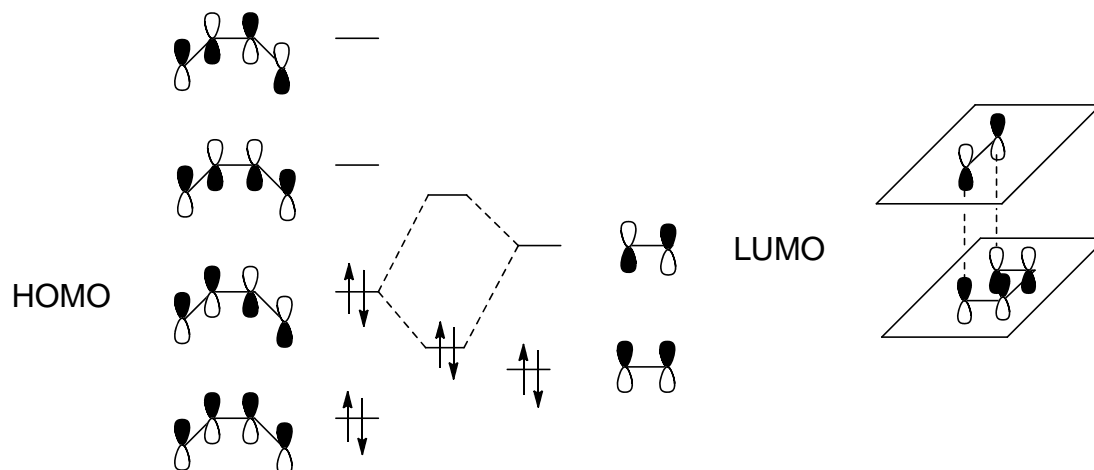


3-6 Diels-Alder reaction

Cycloaddition of dienes and alkenes \longrightarrow Synthesis of substituted cyclohexenes

Orbital symmetry $[\pi4s + \pi2s]$ — Allowed process

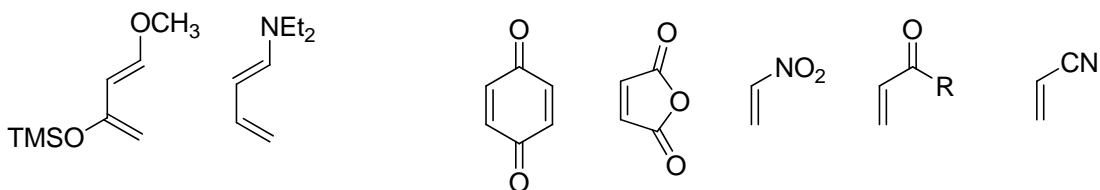
Concerted mechanism — stereospecificity



Electron donating group increase the HOMO energy level

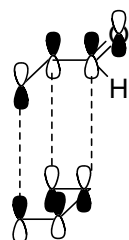
Electron withdrawing group decrease the LUMO energy level

↓
Electron releasing diene + Electron withdrawing dienophile

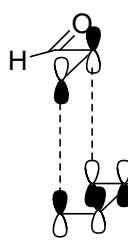


Alder Rule (Endo Rule)

Endo

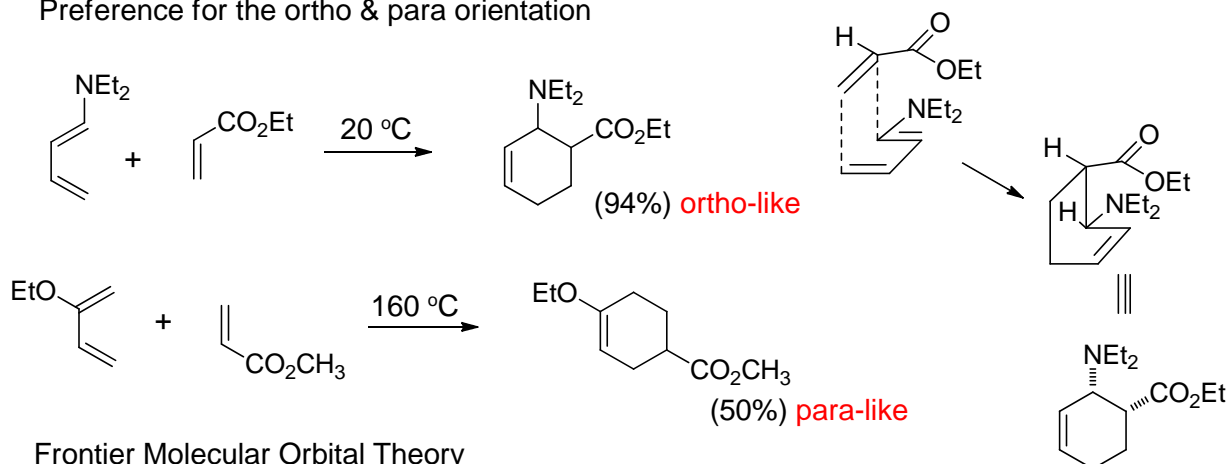


Exo



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



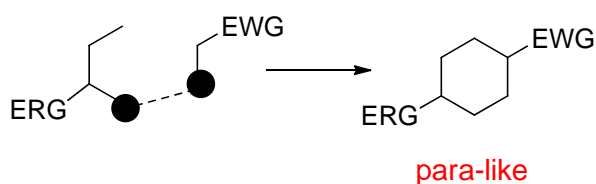
III. Diene with ERG @ C-2



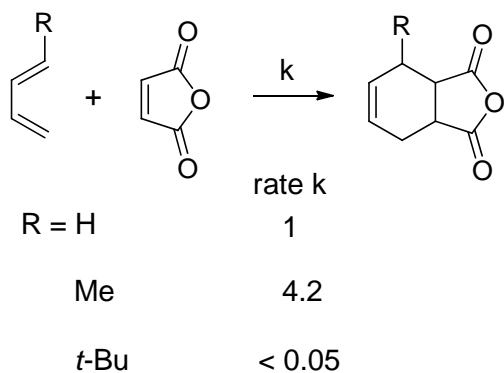
case 1: I + II



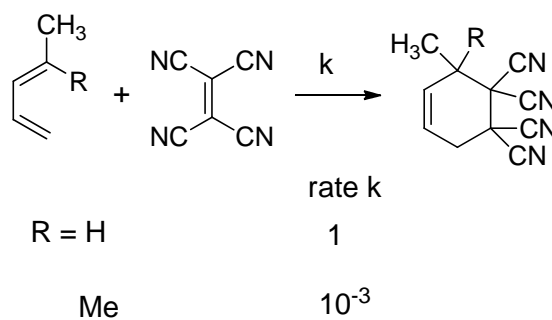
case 2: I + III

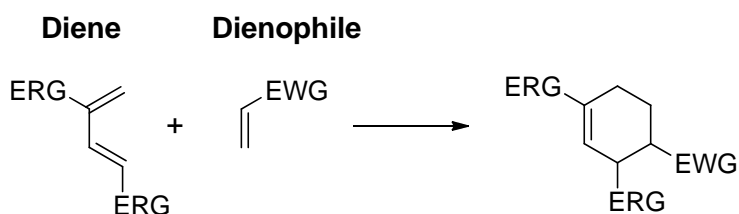


Steric Effects



S-Cis Conformation



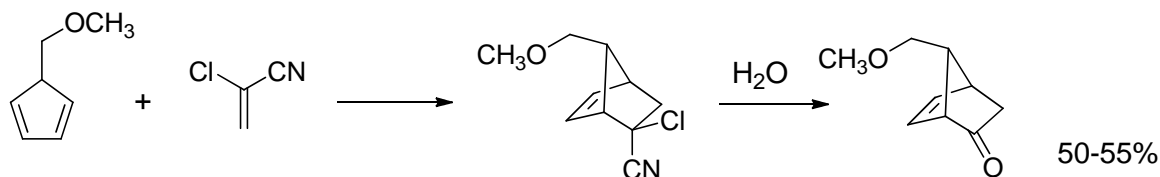


Dienophile

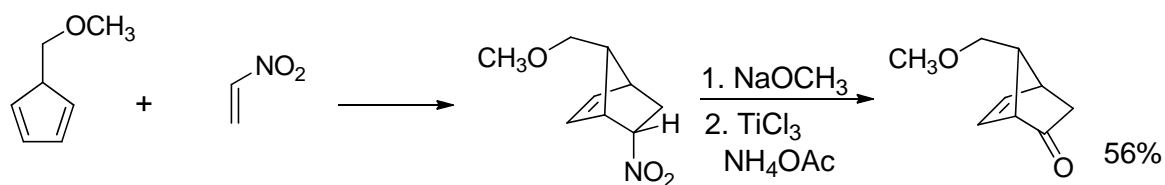
a. ketene equivalent



1. α -chloroacrylonitrile



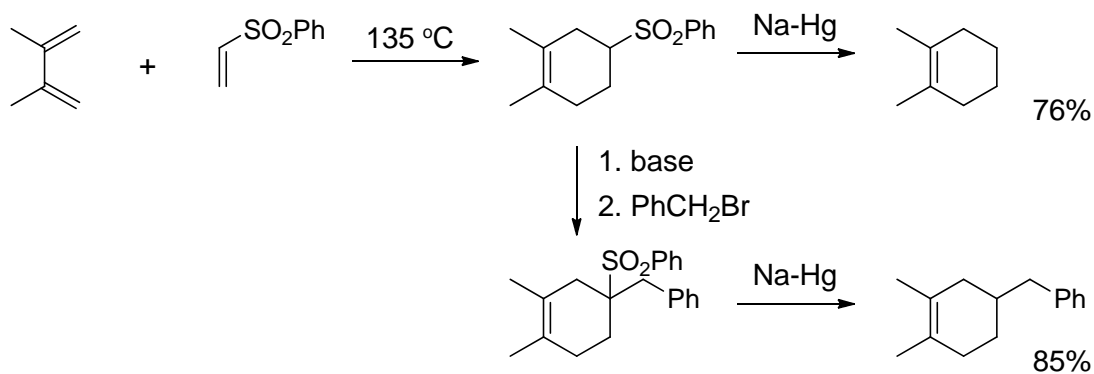
2. nitroalkane



b. ethylene equivalent



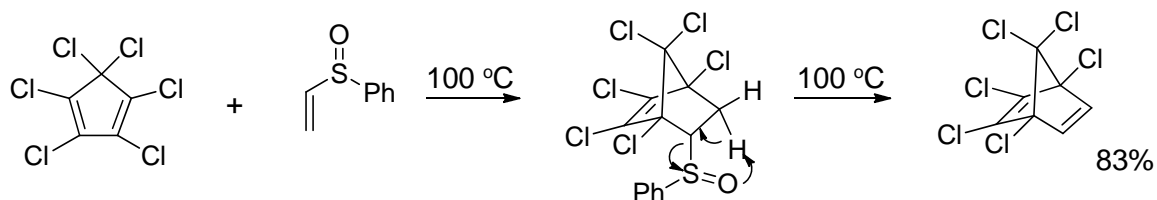
vinyl sulfone



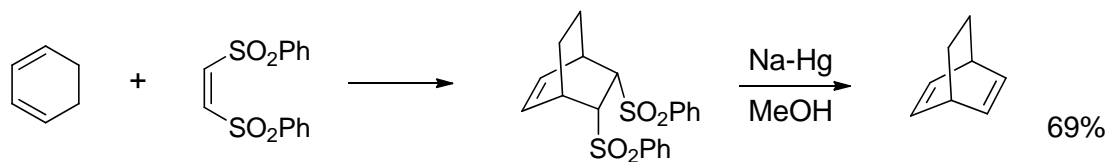
c. acetylene equivalent



1. phenyl vinyl sulfoxide

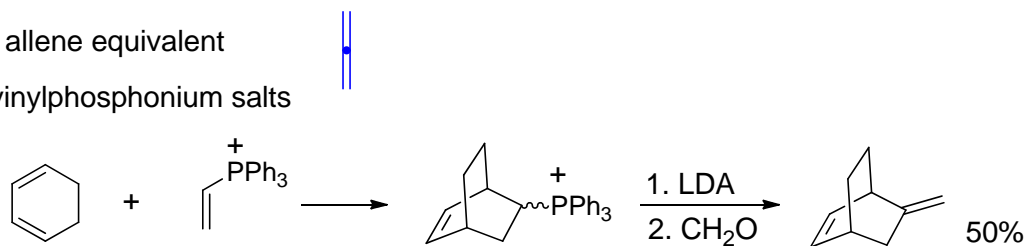


2. bis(benzenesulfonyl)ethene



d. allene equivalent

vinylphosphonium salts

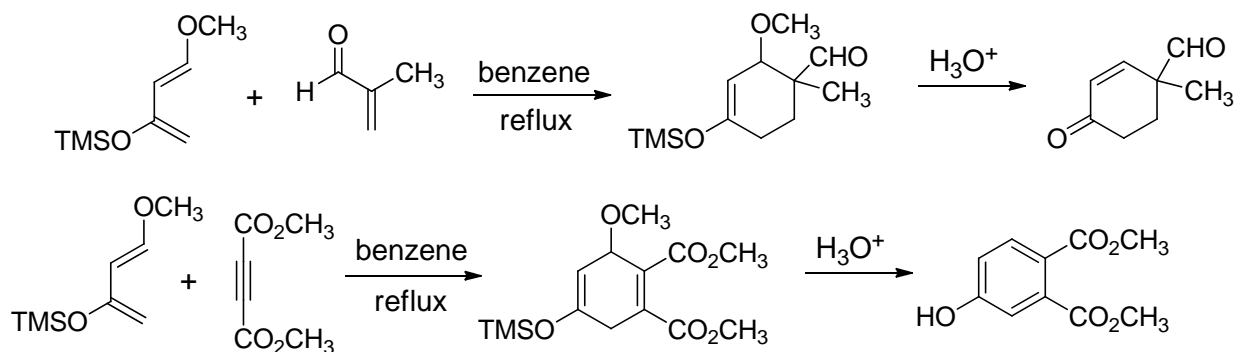


Diene

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

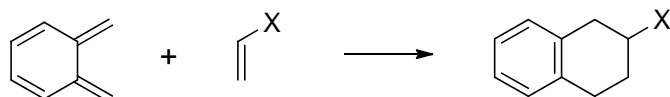
a. Functionalized diene

Danishefsky's diene



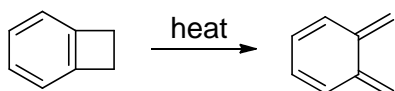
b. Unstable diene : highly reactive - in situ generation

Quinodimethanes

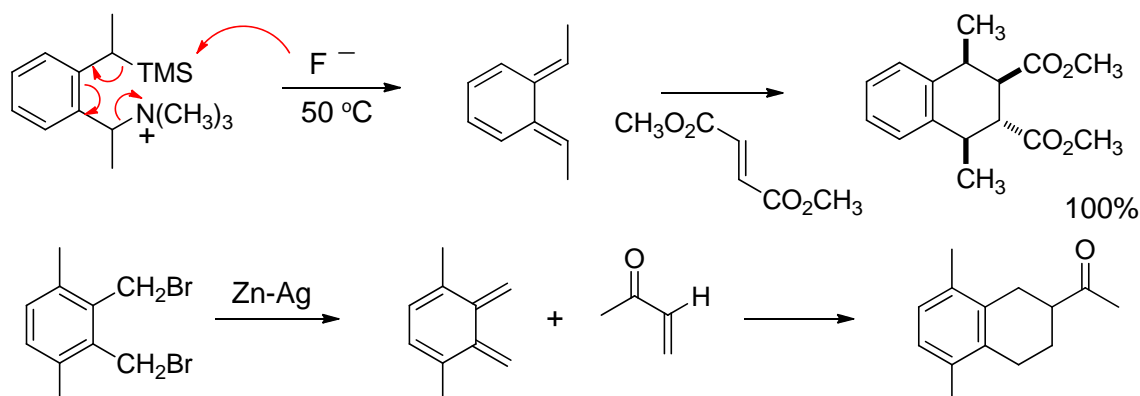


Generation of quinodimethanes

1. pyrolysis of benzocyclobutenes

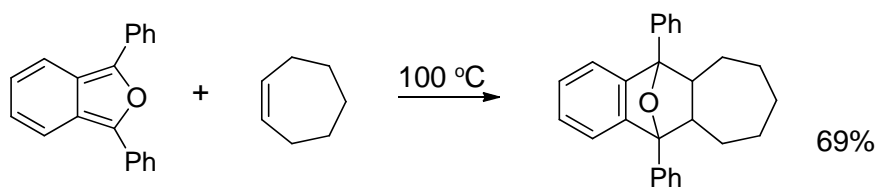


2. elimination from α,α -ortho-disubstituted benzenes



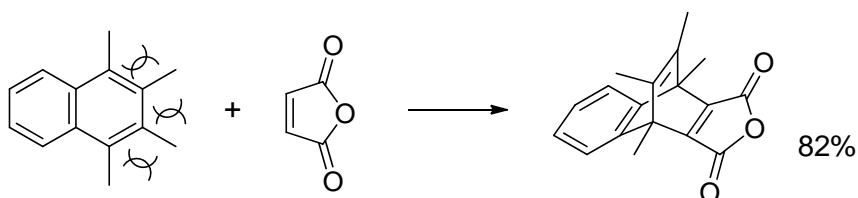
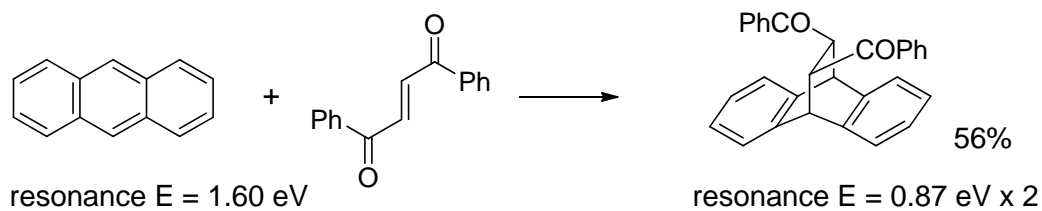
c. Highly reactive dienes

Benzo[C]furan (isobenzofuran)



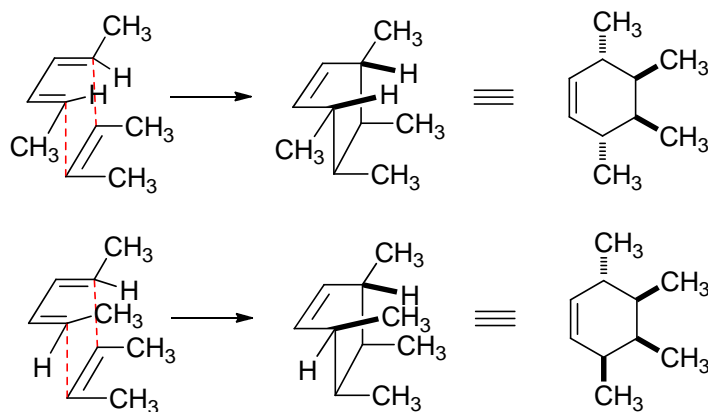
d. Moderately reactive dienes

Polycyclic aromatic hydrocarbons



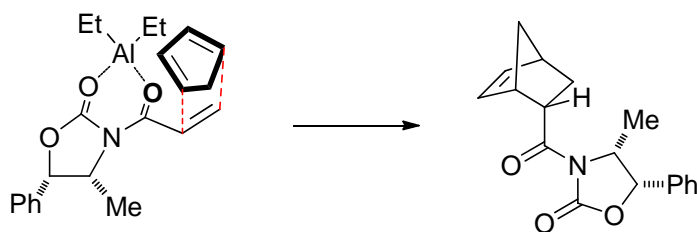
Stereochemistry

diastereoselectivity

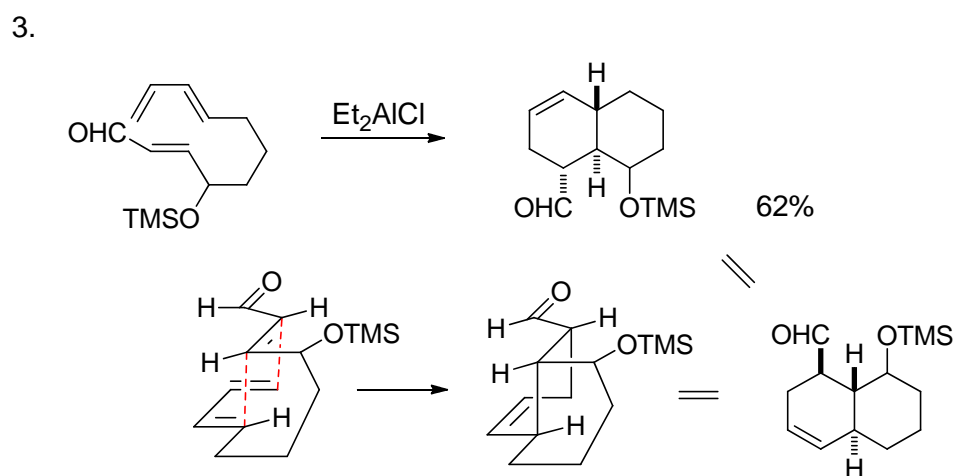
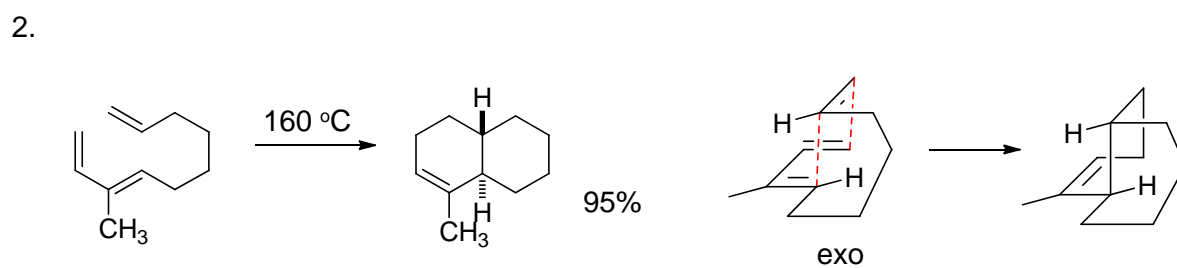
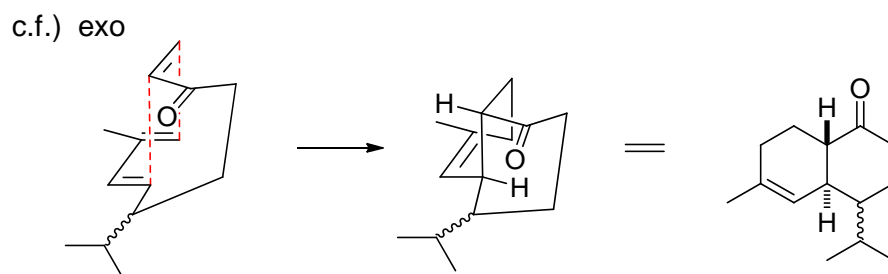
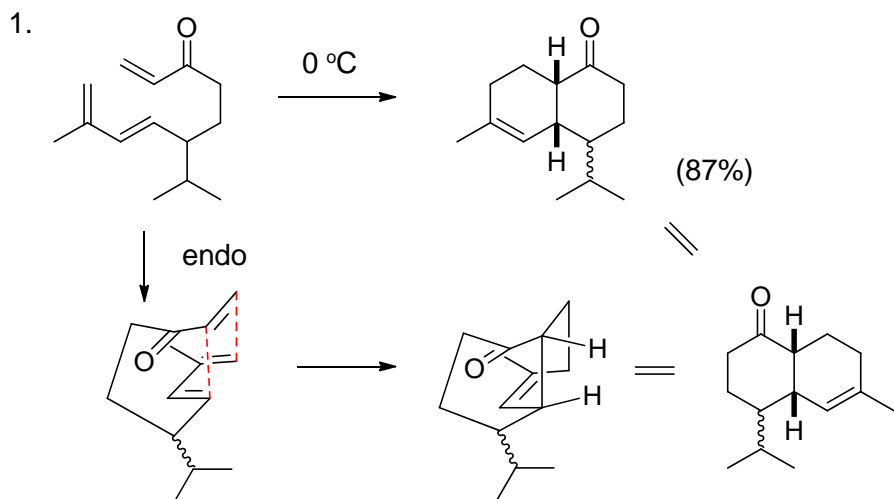


enantioselectivity

endo selectivity



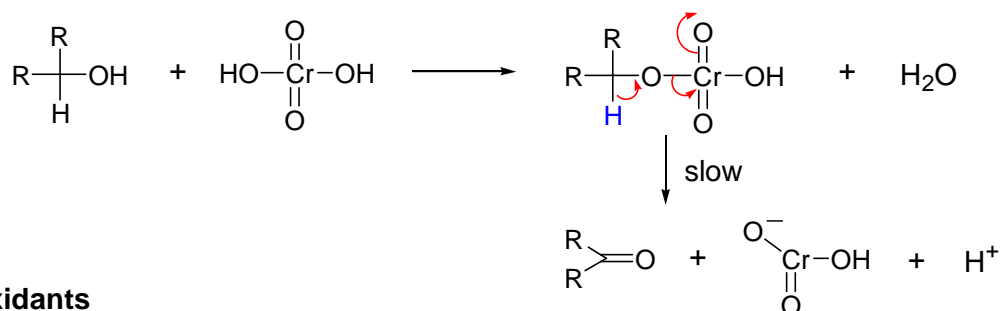
Intramolecular Diels-Alder Reaction



Chapter 4. Oxidation

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

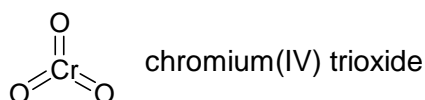
General Mechanism of Alcohol Oxidation



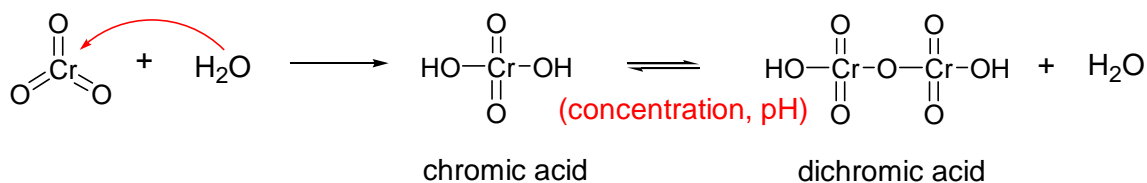
Oxidants

a. Transition metal oxidants

1) Cr(VI) - based reagents

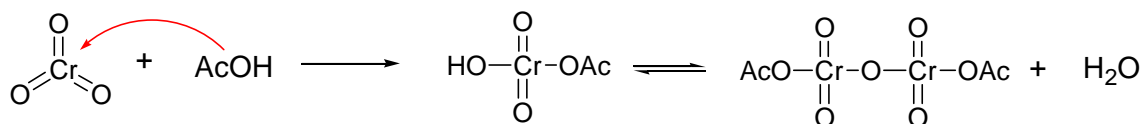


Jones' reagent

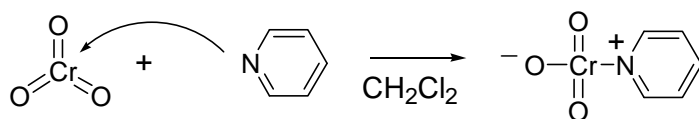
 acidic aqueous solution of chromic acid $\text{CrO}_3 + \text{aq. H}_2\text{SO}_4$ 

Dropwise addition of the reagent to an acetone solution of alcohols at 0 °C

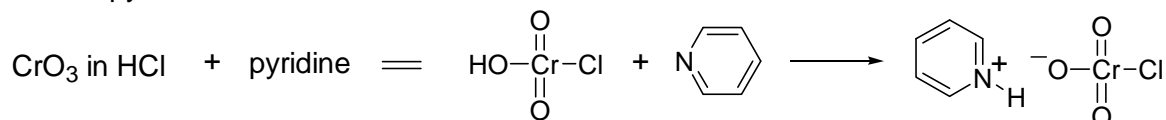
CrO₃ in AcOH



Collin's reagent: CrO₃ in pyridine

 good for acid sensitive substrates

PCC

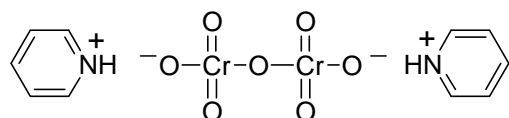
 pyridinium chlorochromate

PDC

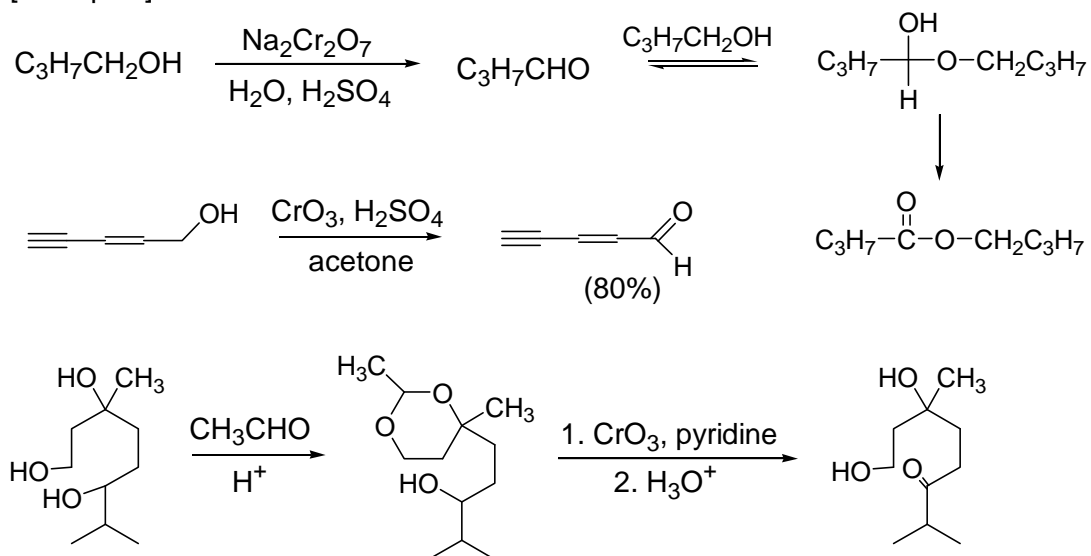
 pyridinium dichromate

solvent: DMF or CH₂Cl₂

CrO₃ in H₂O (small amount) + pyridine oxidation of 2° alcohols or allylic alcohols



[examples]



2) Mn(VII), Mn(IV)

Potassium permanganate **KMnO₄**

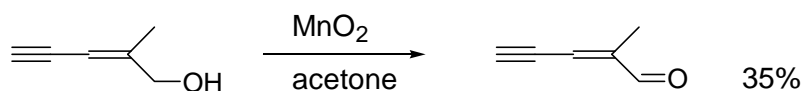
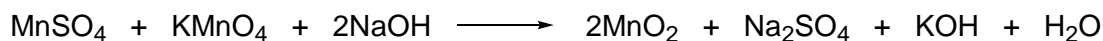
Very strong oxidant - overoxidation problem

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

Manganese dioxide **MnO₂**

selective for allylic and benzylic alcohol

preparation

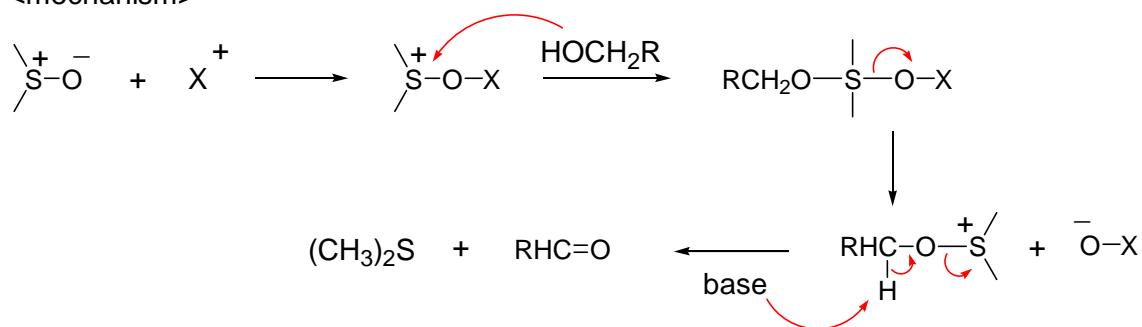


b. Other Oxidant

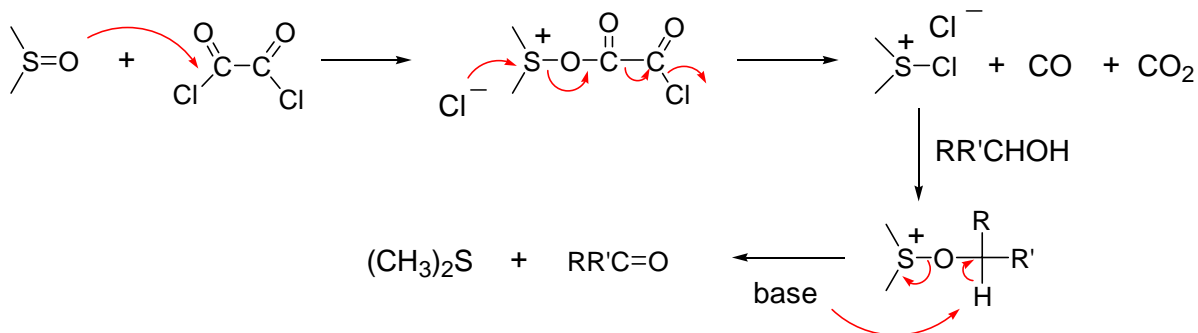
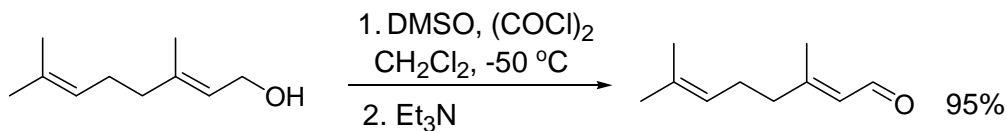
1) DMSO + electrophile (X⁺)

DCC, Ac₂O, Tf₂O, Oxalic chloride

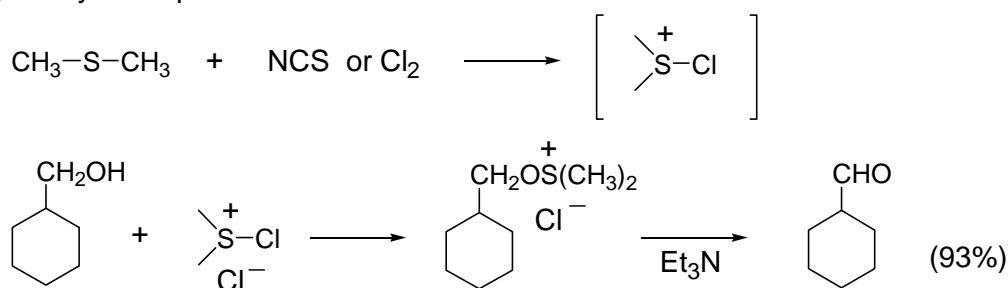
<mechanism>



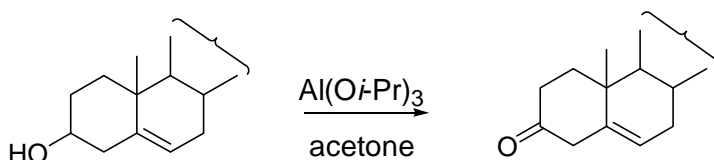
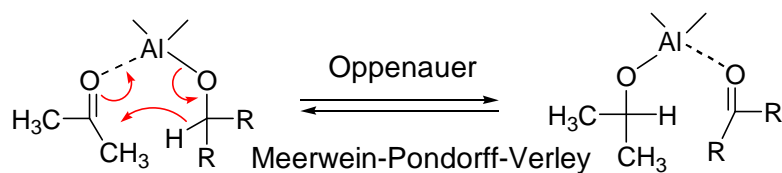
Swern Oxidation



2) Corey - Kim procedure

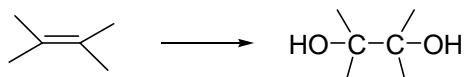


3) Oppenauer oxidation



4-2. Oxidation of carbon - carbon double bonds

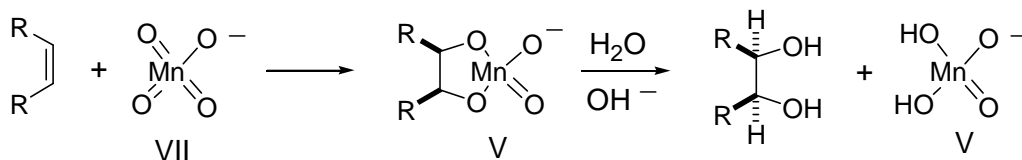
4-2-1. Perhydroxylation



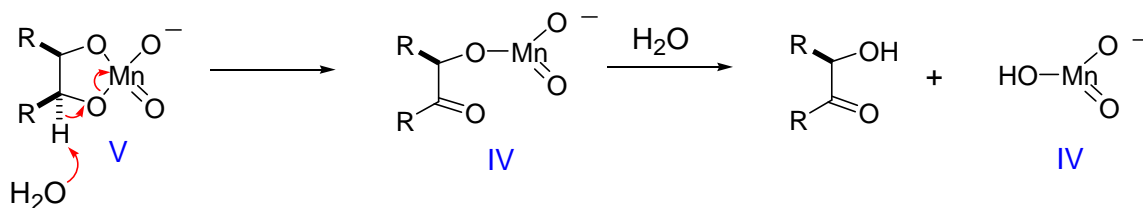
a) KMnO_4 potassium permanganate

syn - perhydroxylation \leftarrow cyclic intermediate

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



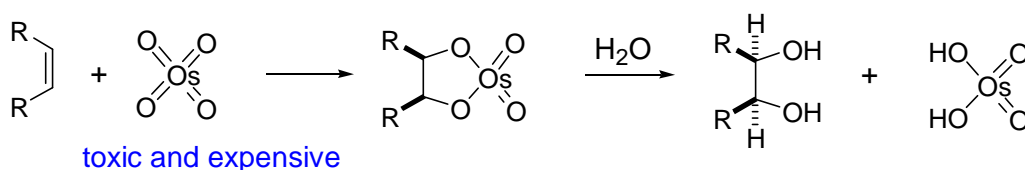
ketol formation



b) Osmium tetroxide

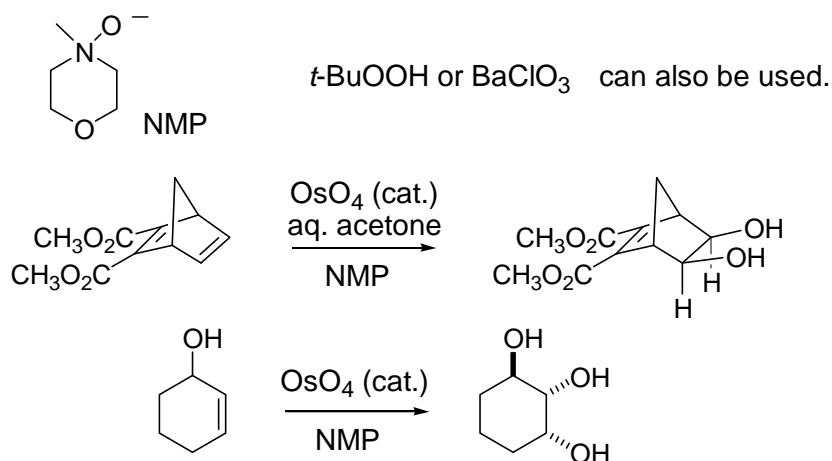
Selective and mild glycol formation

Stereospecific syn addition through cyclic osmate ester



Upjohn Process

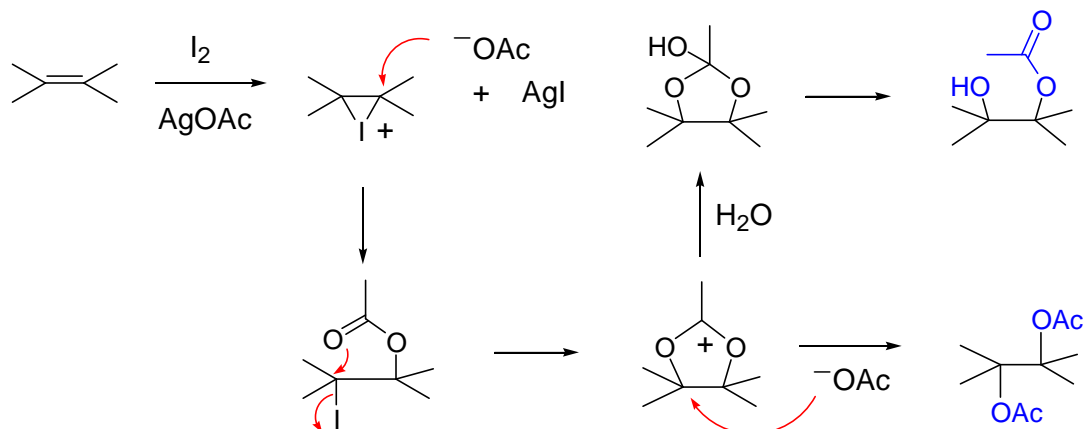
Use amine oxide as a stoichiometric oxidant: *N*-methylmorpholine-*N*-oxide



c) Iodine and silvercarbonate

Prevost condition (anhydrous condition) \longrightarrow trans-glycol derivative

Woodward condition (aqueous condition) \longrightarrow cis-glycol derivatives

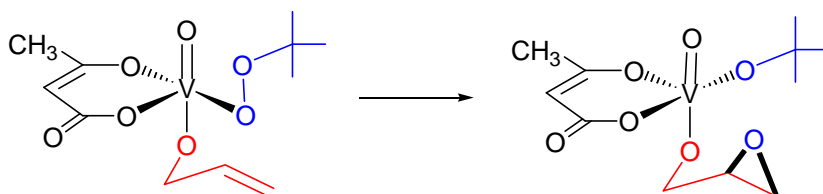
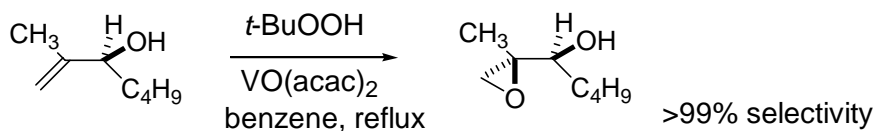


4-2-2 Epoxidation

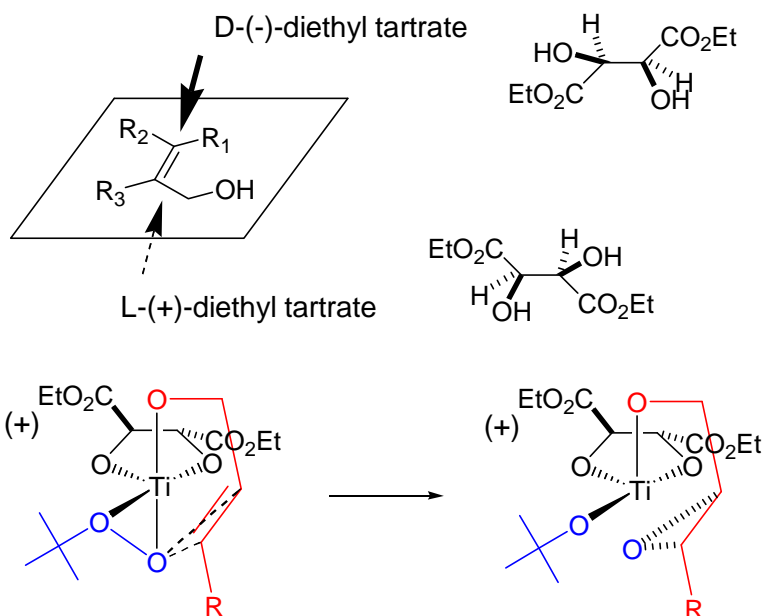
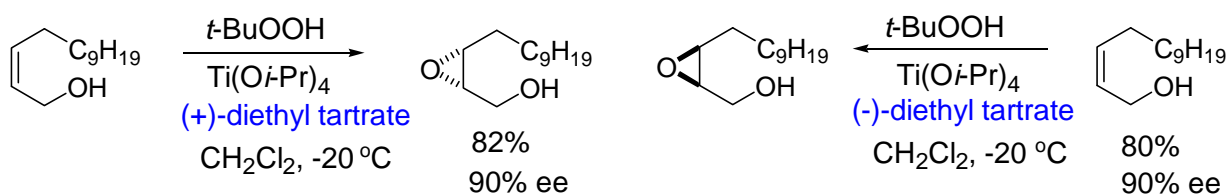
a) Transition metal oxidants

Epoxidation of allylic alcohol

$\left\{ \begin{array}{l} \text{V, Mo, Ti as a catalyst} \\ t\text{-BuOOH as a stoichiometric oxidant} \end{array} \right.$

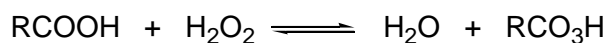


Asymmetric epoxidation of allylic alcohol - Sharpless epoxidation



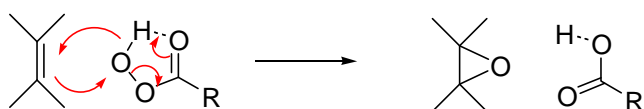
b) Peroxidic reagents

MCPBA, peracetic acid perbenzoic acid etc.

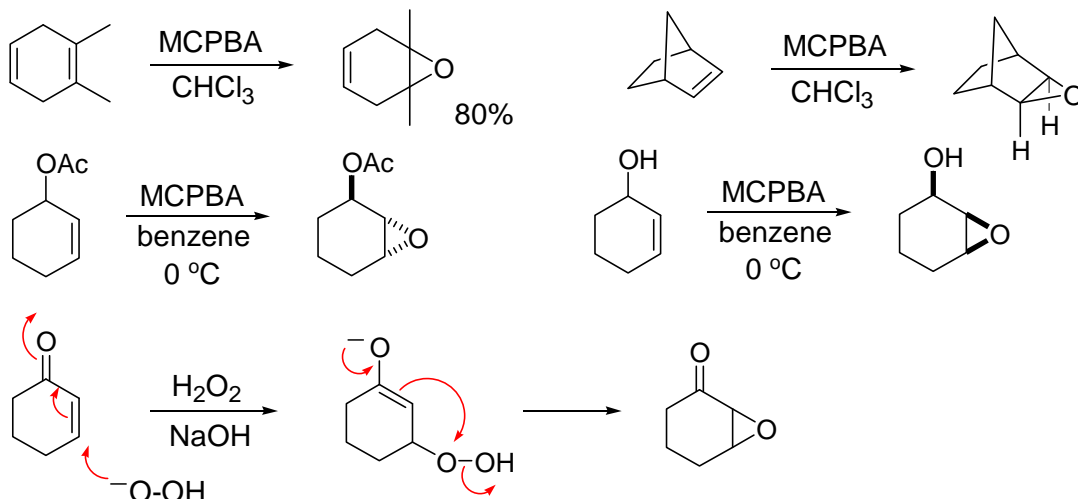


Stereospecific syn addition

concerted process

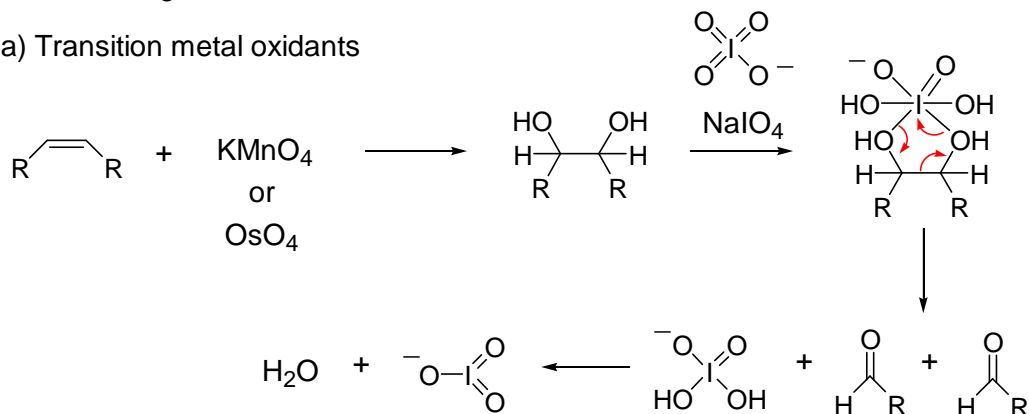


rate increased by electron donating substituents on alkenes and electron withdrawing substituents on peroxy-acid

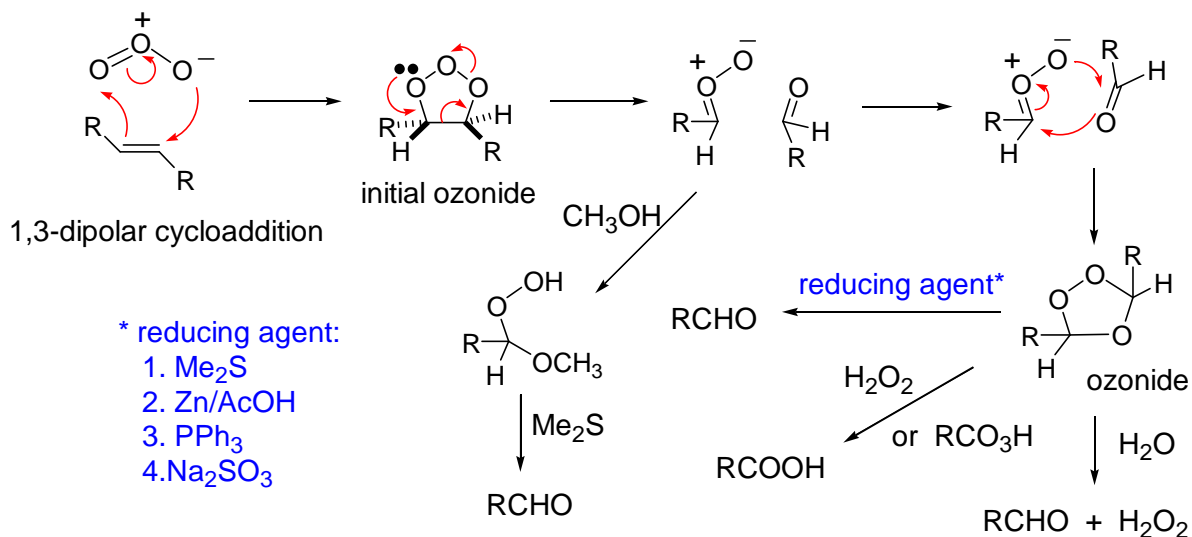


4-2-3 Cleavage of double bonds

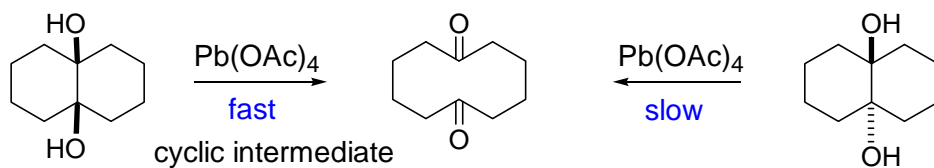
a) Transition metal oxidants



b) Ozonolysis

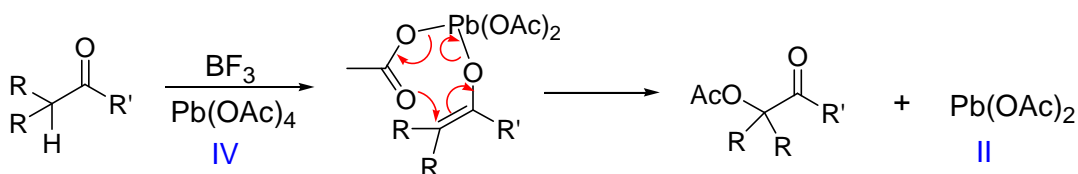
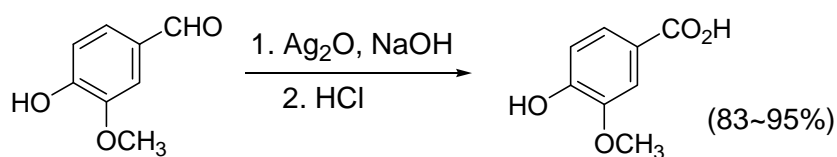
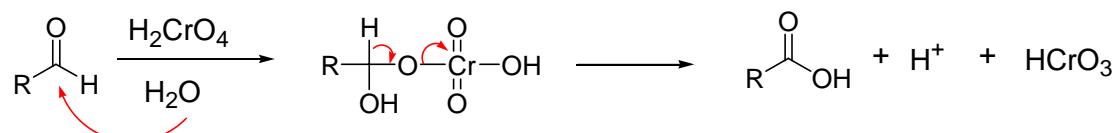


c) $\text{Pb}(\text{OAc})_4$

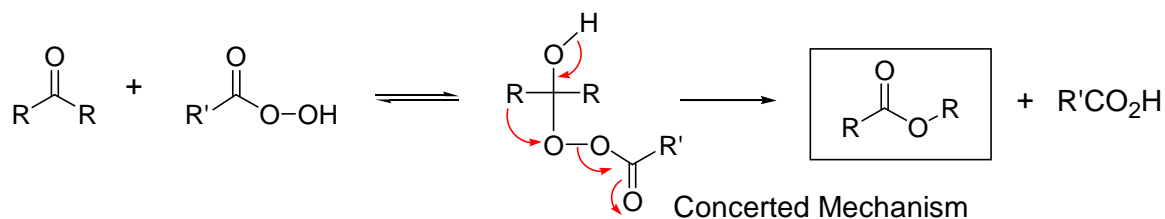


4-3 Oxidation of Ketones and Aldehydes

a) Transition Metal Oxidant

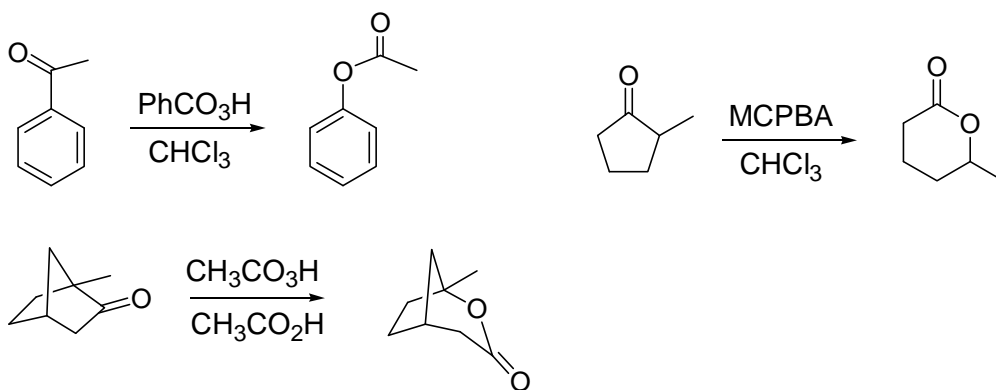


b) Peroxy-acid Oxidants: Baeyer - Villiger oxidation



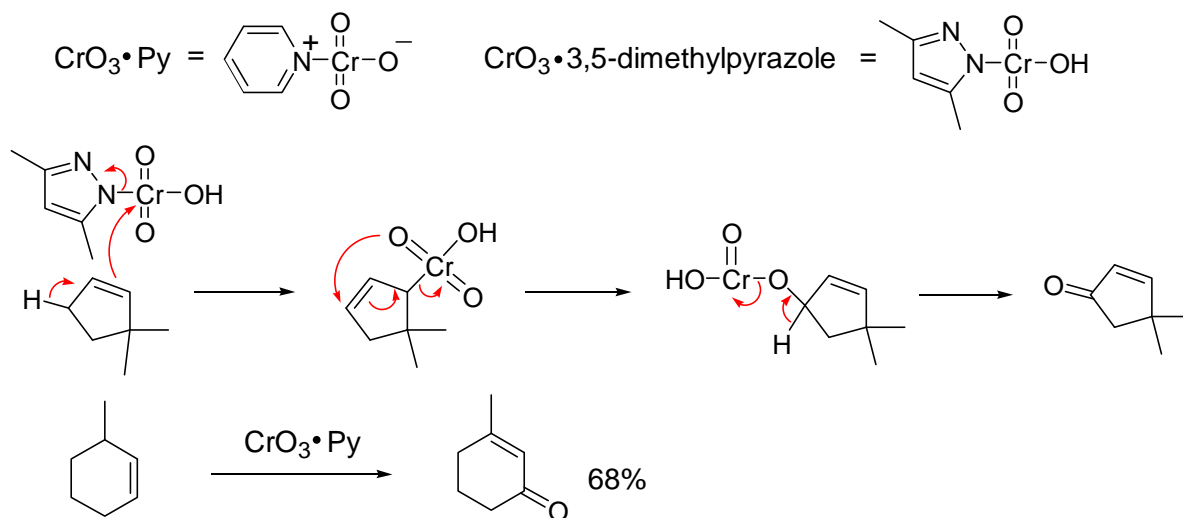
Migratory Aptitude

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



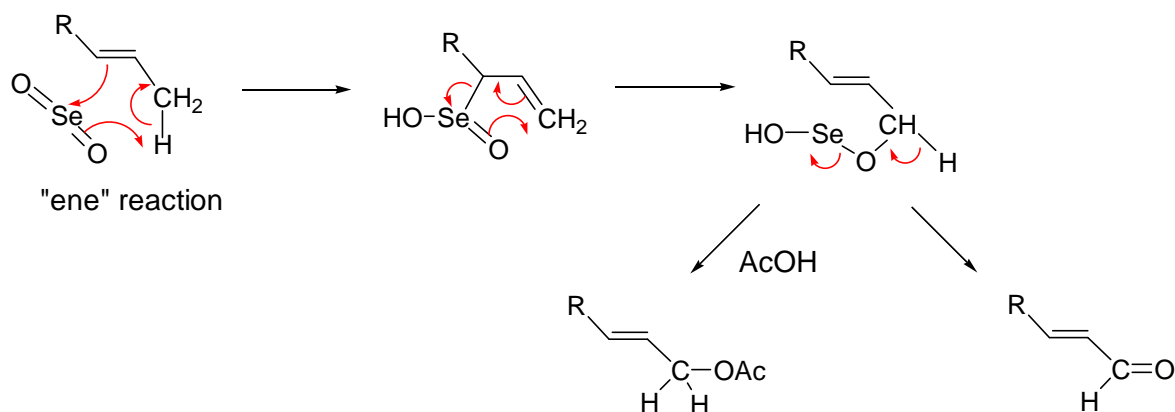
4-4 Allylic Oxidation

a) Transition Metal Oxidants



b) SeO_2

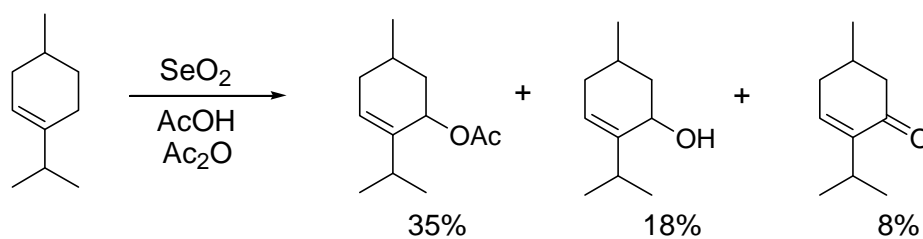
Alkenes \longrightarrow α,β -unsaturated carbonyl compounds (major product)
allylic alcohols or esters



Catalytic process

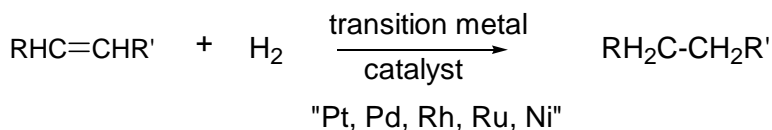
1.5-2 mol% SeO_2 / $t\text{-BuOOH}$ (stoichiometric reagent)

allylic alcohol is the major product



Chapter 5. Reduction

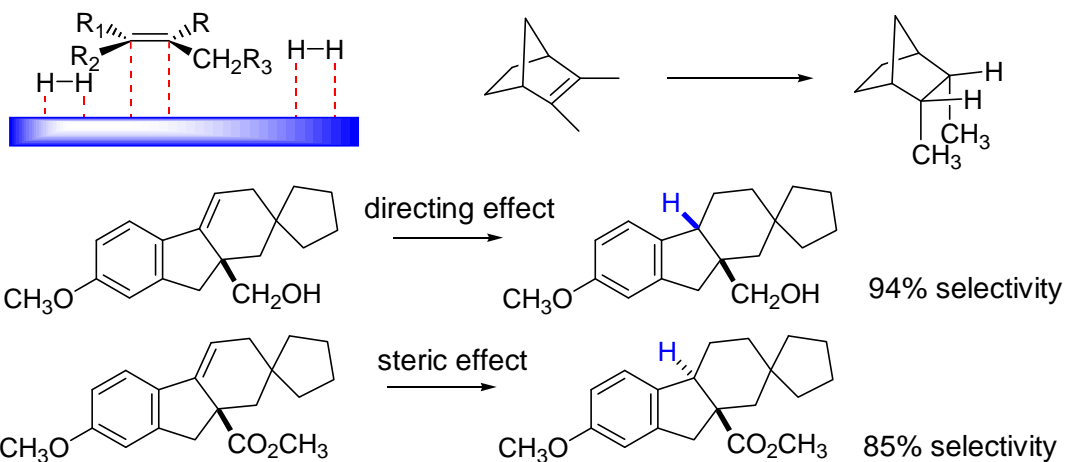
5.1 Catalytic Hydrogenation



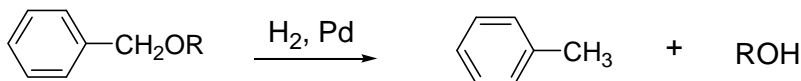
<mechanism>

Stereoselective syn addition from the less hindered side of double bond

Heterogeneous (may cause double bond migration)

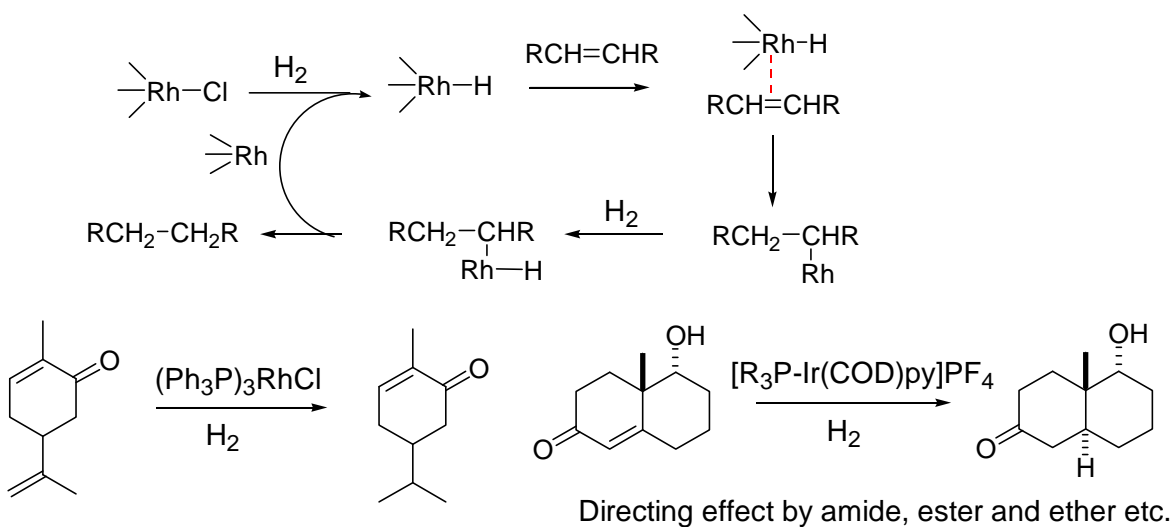


Hydrogenolysis



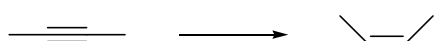
Homogeneous catalysts (soluble complex)

Wilkinson's catalyst: $(\text{PPh}_3)_3\text{RhCl}$ minimize the migration process



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

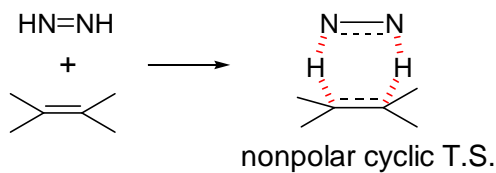
Pd-CaCO_3 (Lead) or quinoline : heterogeneous cat.



5-2 Diimide

HN=NH
unstable

in situ generation



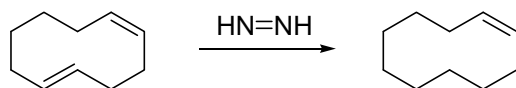
1. $\text{Na}^+ \text{ } ^-\text{O}_2\text{C}-\text{N}=\text{N}-\text{CO}_2^- \text{Na}^+ + \text{RCO}_2\text{H}$

2. heat
or THF-H₂O, NaOAc

3. $\text{NH}_2\text{NH}_2, \text{O}_2, \text{Cu(II)}$

$\text{NH}_2\text{NH}_2, \text{H}_2\text{O}_2$

4. + NH_2OH



5-3 Group III Hydride-donor Reagents

B, Al

5-3-1 Reduction of Carbonyl Compounds

NaBH_4

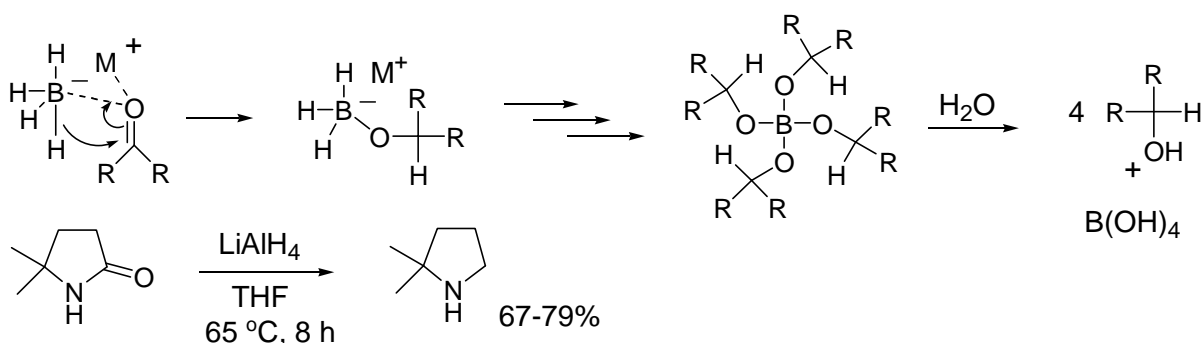
Mild reducing agent
Reacts rapidly with aldehydes and ketones
Reacts slowly with esters
Solvents: EtOH, H₂O

LiAlH_4

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

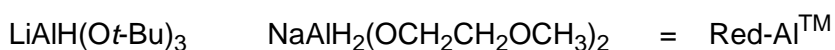
$\text{Li, Ca} > \text{Na} \longrightarrow \text{LiBH}_4, \text{Ca(BH}_4)_2 > \text{NaBH}_4$

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

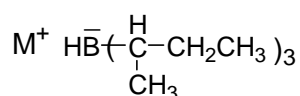


- b. Nitrile ligand: Electron withdrawing group
reduced reactivity Iminium ion \longrightarrow amine
 NaBH_3CN

- c. Alkyl ligand

Size effect \longrightarrow Selective reduction

SelectridesTM (stereoselective reduction)

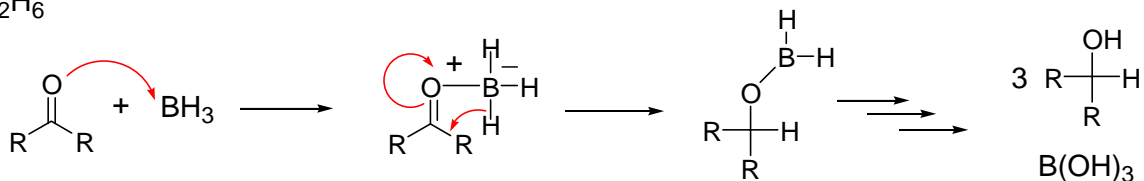


Neutral Boron and Aluminum Hydrides

BH_3 : Borane

AlH_3 : Alane

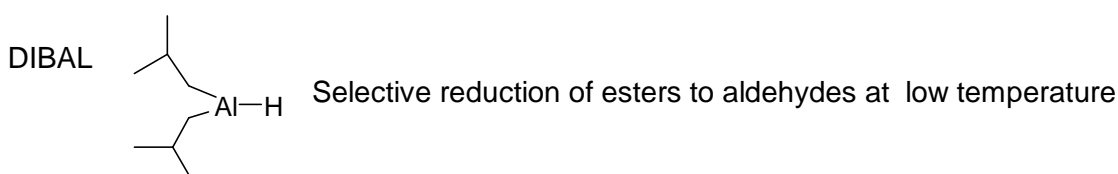
B_2H_6



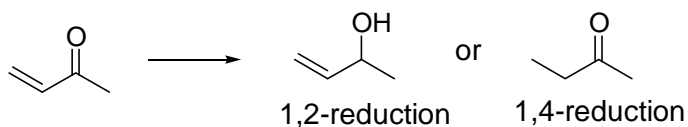
Carboxylic acid \longrightarrow primary alcohol

Amide \longrightarrow Amine

Do not react with esters, nitro, and cyano



Reduction of α,β -unsaturated carbonyl compounds



1,2-reduction

Luiche condition: $\text{NaBH}_4 + \text{CeCl}_3$

DIBAL

9-BBN

1,4-reduction

Catalytic hydrogenation

"H⁻" + Copper salt : Cu-H

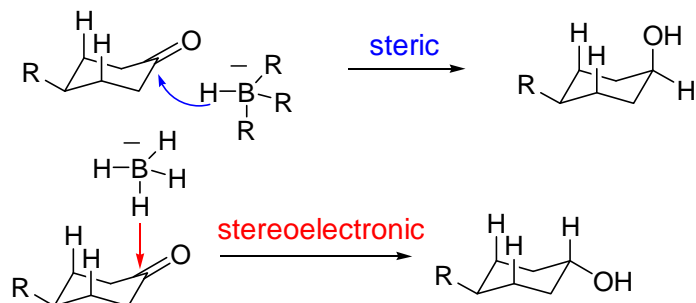
Wilkinson's catalyst + Et_3SiH

Stereoselectivity

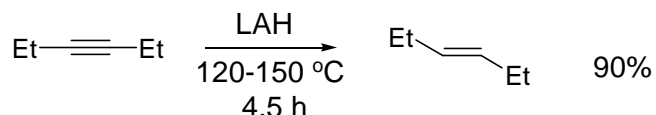
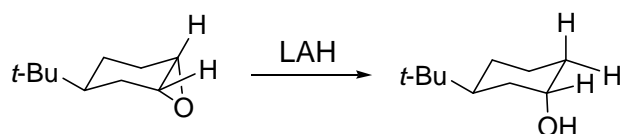
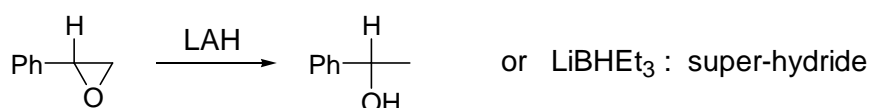
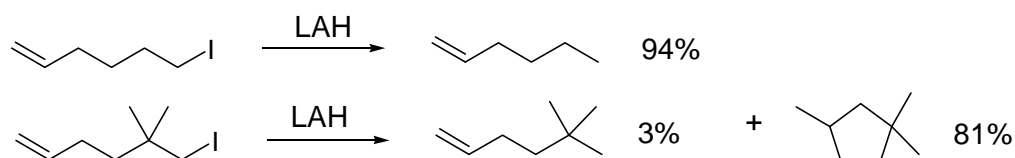
Cyclohexanone derivatives

Steric approach control vs Stereoelectronic control

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



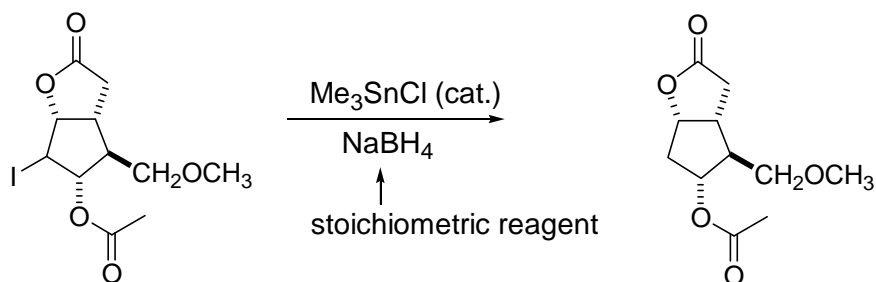
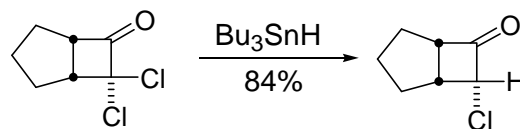
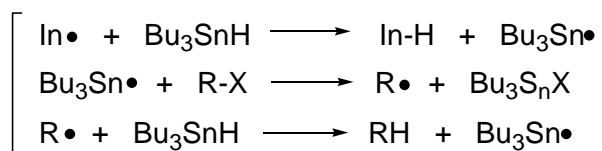
5-3-2 Reduction of Other Functional Groups



5-4 Hydrogen Atom Donors

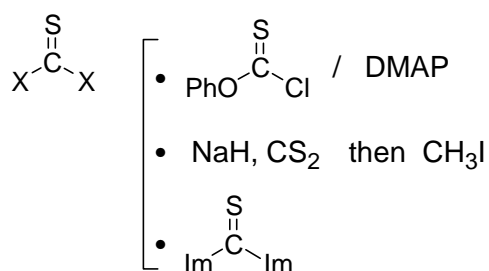
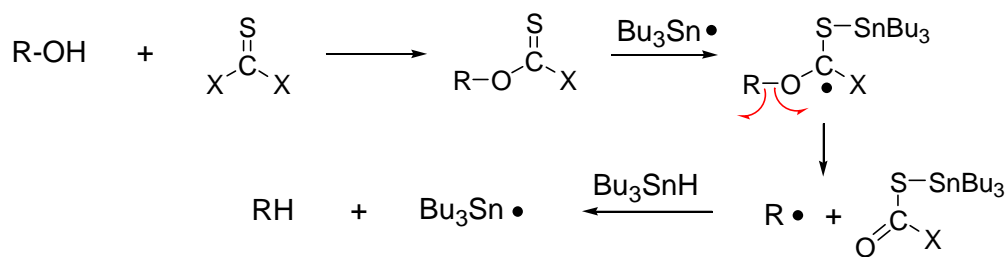
n-Bu₃SnH

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



n-Bu₃SnH

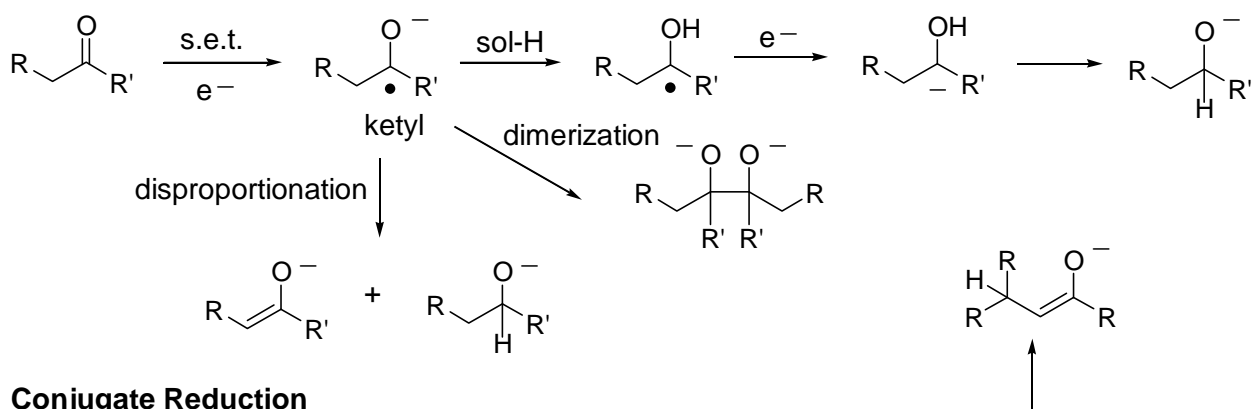
2. Reductive deoxygenation of alcohols



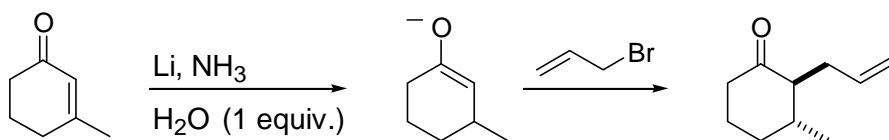
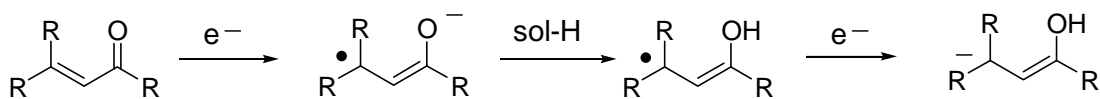
5-5 Dissolving - Metal Reduction

5-5-1 Addition of hydrogen

<mechanism> single electron transfer

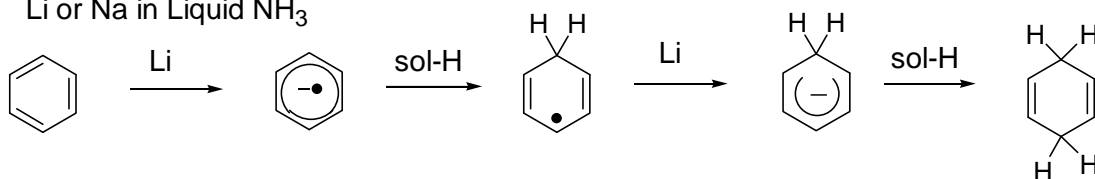


Conjugate Reduction



Birch Reduction partial reduction of aromatic ring

Li or Na in Liquid NH₃

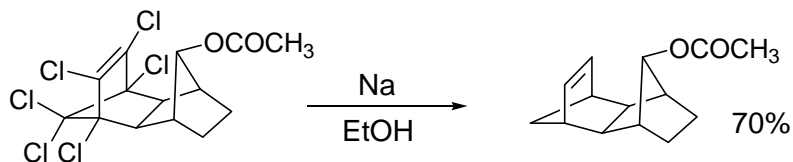


*Benzene ring with electron-withdrawing substituents reacts too fast !!!

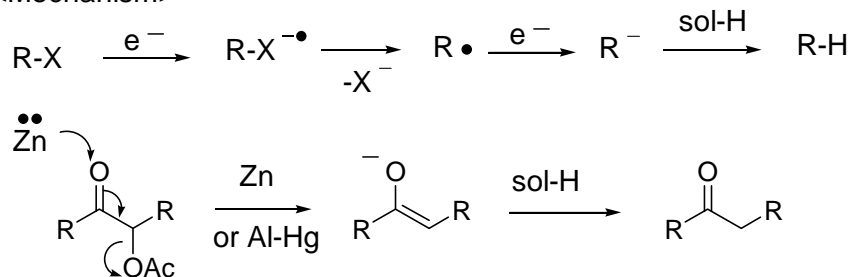
Regiochemistry for protonation



5-5-2 Reductive removal of functional group

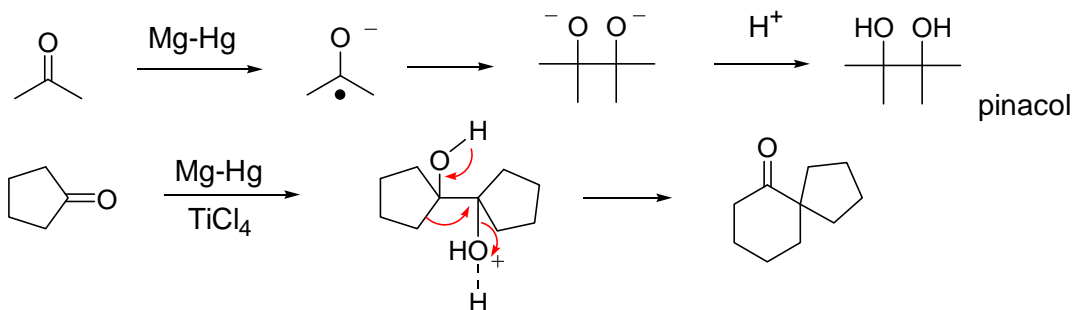


<Mechanism>

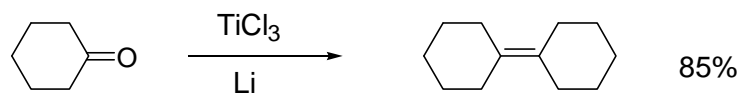


5-5-3 Reductive carbon-carbon bond formation

Pinacol coupling

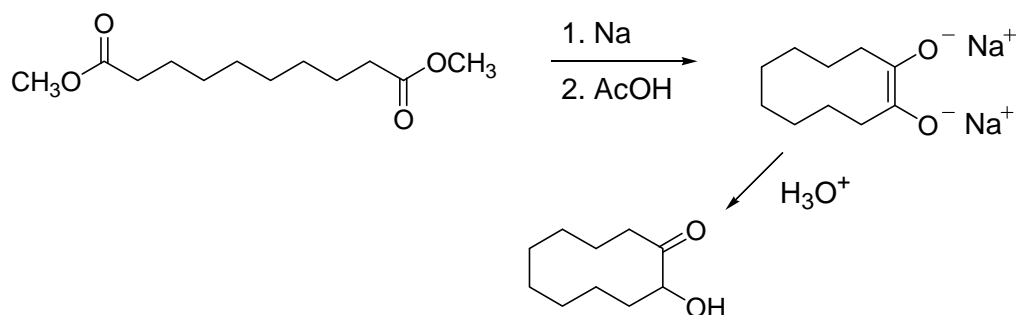


TiCl₃ and Li or K or Zn-Cu or LAH



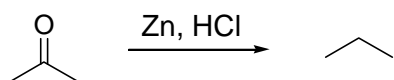
Acyloin condensation

Esters \longrightarrow α -hydroxyketone (acyloin)

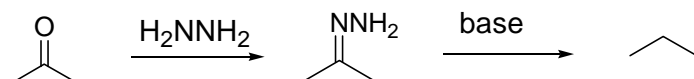


5-6 Reductive Deoxygenation of Carbonyl Group

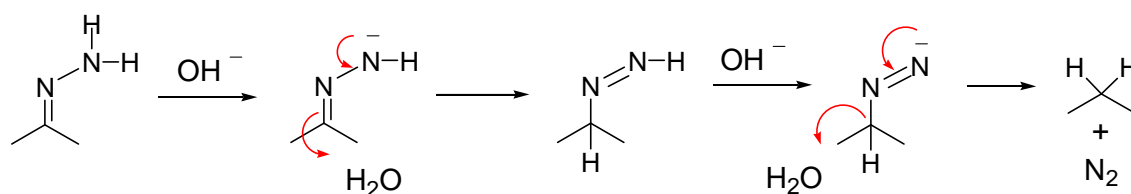
Clemmensen reduction Strongly acidic condition



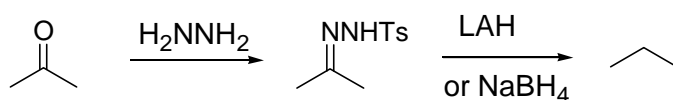
Wolff-Kishner reduction base-catalyzed decomposition of hydrazone



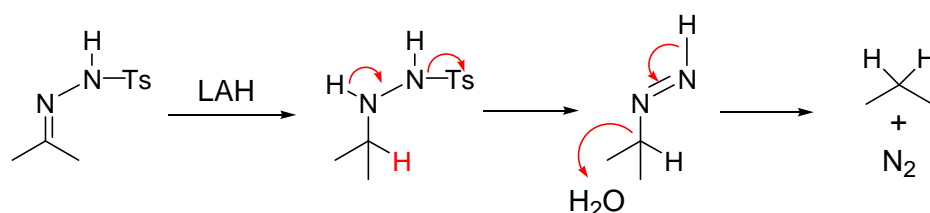
<mechanism>



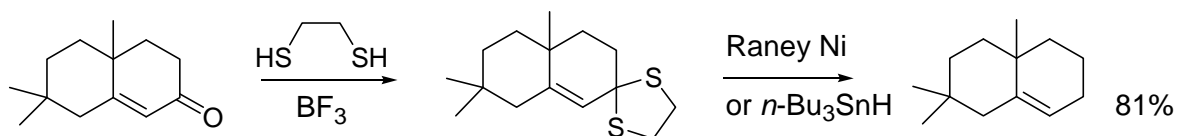
Tosylhydrazone reduction



<mechanism>

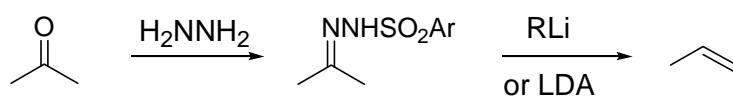


Thioketal Desulfurization



Shapiro reaction

Carbonyl group \longrightarrow Alkene



<mechanism>

