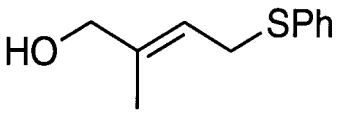
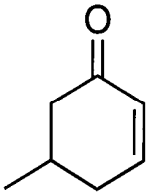
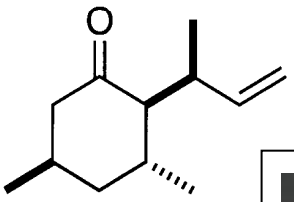


Special Topics in

Organic Synthesis

2018.03





Prepared by Sangho Koo

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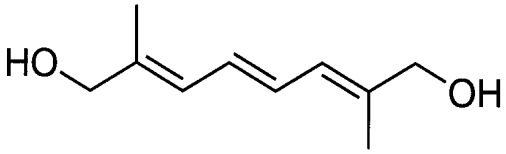
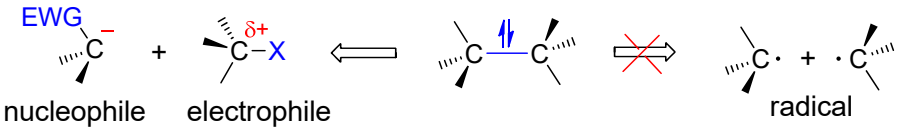
Korea

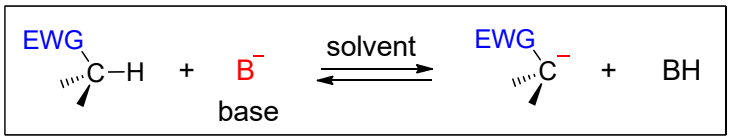


Reference Books: 1. William Carruthers and Iain Coldham, "Modern Methods of Organic Synthesis" 4th Ed; 2004, Cambridge, ISBN 0-521-77830-1

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

Chapter 1. Formation of carbon-carbon single bonds





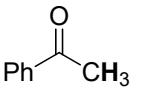
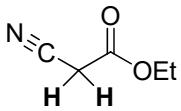
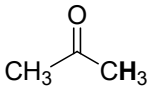
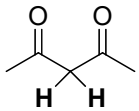
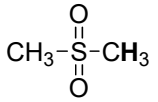
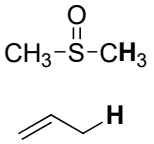
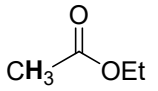
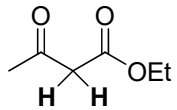
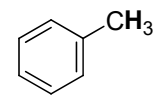
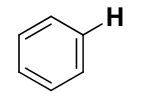
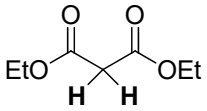
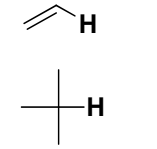
Strength of an acid

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

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

1.1. Alkylation: importance of enolate anions — stability vs reactivity

a. The acidity of the C-H bonds

compound	pK_a	compound	pK_a	compound	pK_a
CH_3CO_2H	5		19	$Ph-NH_2$	~30
	9		20	Ph_3CH	~40
	9		~23		~40
CH_3NO_2	10		~24		40
	11	CH_3CO_2H	~24		41
		$CH_3-C\equiv C-H$	25		43
	13	CH_3CN	~25		44
					52

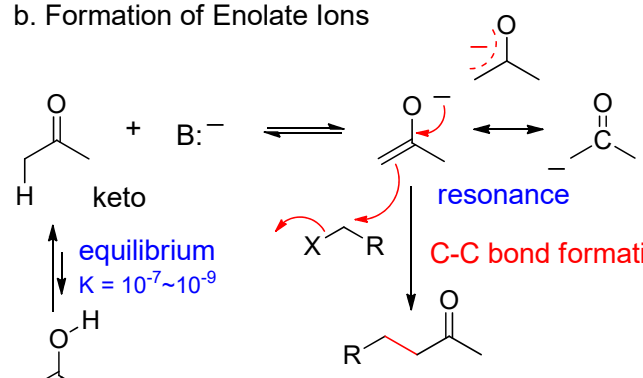
Anion Stabilizing Effect

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

Substituent Effect on pKa

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

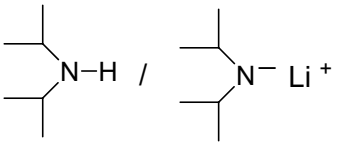
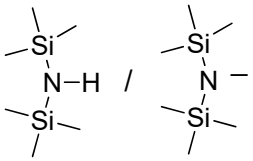
b. Formation of Enolate Ions



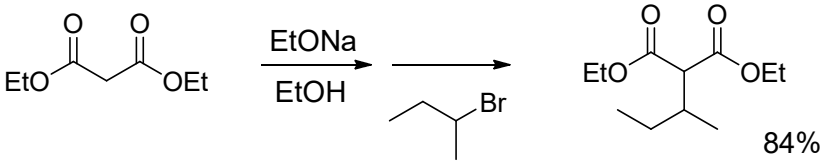
Stability of enolate ion
- resonance stabilization (charge delocalization)
- inductive electron withdrawing effect

X: leaving group (halides, sulfonates)

c. pK_a of the conjugate acid of some bases

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

d. alkylating agents



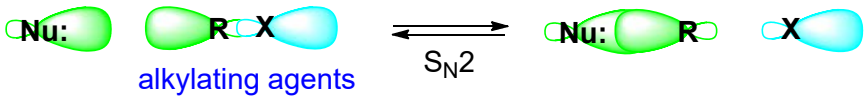
Elecreoegativity Scale

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

Mechanism of alkylation

Stereoelectronic effect (favors trajectory of maximum orbitals overlap)

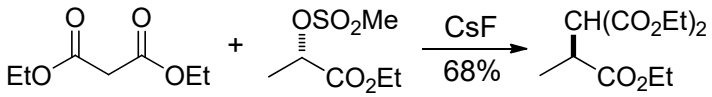
backside attack for S_N2 reaction



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

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

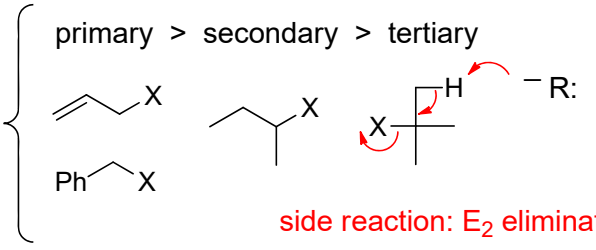
X = I, Br, Cl, OTs, OMs etc.



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

Steric effect (favors small size reactants for alkylation)

primary > secondary > tertiary



side reaction: E_2 elimination

e. Medium Effects in the Alkylation of Enolates

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

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

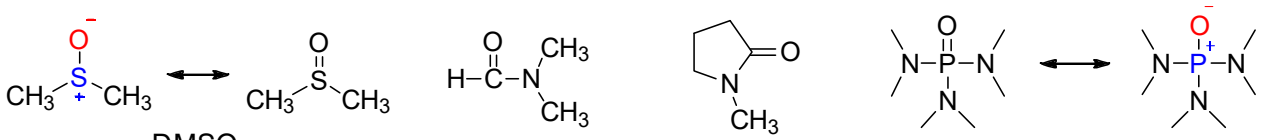
covalently bound enolate anion bare or naked enolate anion

less reactive **more reactive**

M-O bond length in Å

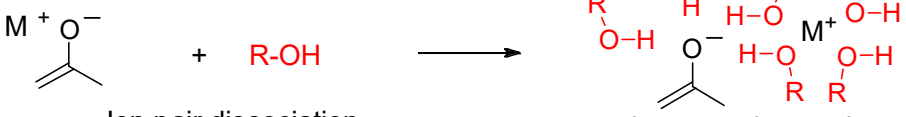
Li: 1.92~2.00, Al: 1.92, Mg: 2.01~2.13, B: 1.36~1.47, Zn: 1.92~2.16, Ti: 1.62~1.73

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



Ion pair dissociation by polar aprotic solvent → naked anion
(effective metal cation solvation only) **more reactive enolate**

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

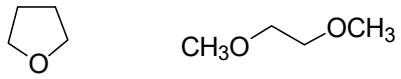


Ion pair dissociation
(cation as well as anion solvation)

less reactive enolate
by hydrogen bonding

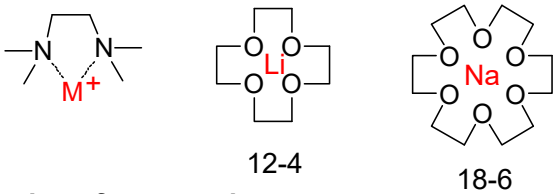
3. **Slightly polar aprotic solvent** - moderately good cation solvator

high aggregation easy workup and purification



kinetic enolate generation

Additives: HMPA, TMEDA, crown ether

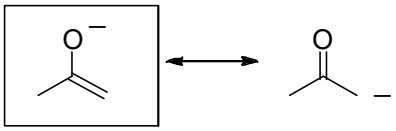


reactive enolate formation
by the selective cation solvation

Properties of some solvents

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

f. O- vs C- alkylation



major contribution

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

Control of O- vs C- alkylation

Free enolates give O- alkylation

1. Counter ion effects

Mg^{++} Li^{+} Na^{+} K^{+} $n\text{-}Bu_4N^{+}$

C- alkyation ← → O- alkylation

2. Solvent effect

polar protic or less polar aprotic ← → polar aprotic

C- alkylation O- alkyation

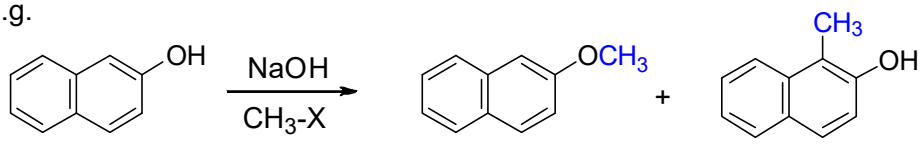
3. Leaving group effect

HSAB theory (hard-soft-acid-base)

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

Soft C- alkylation ← → Hard O- alkylation

e.g.

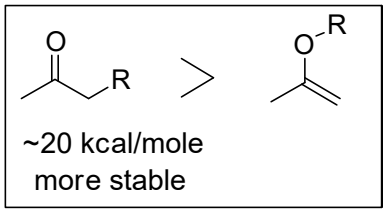


X = I	66	33
X = OTs	100	0

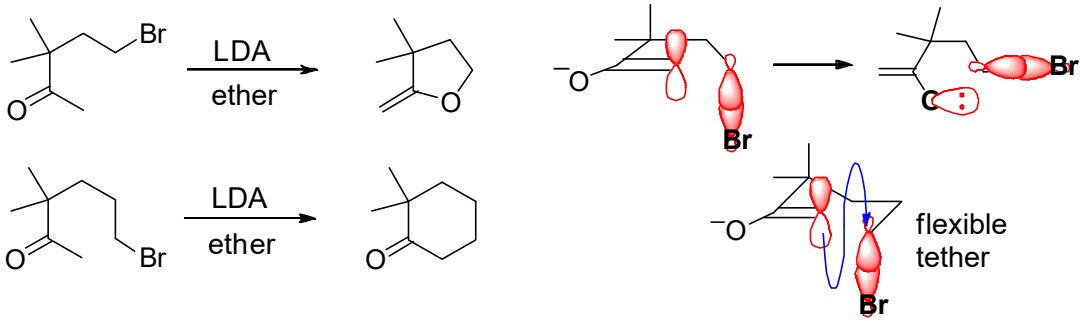
Hammond Postulate (*J. Am. Chem. Soc.* **1955**, *77*, 334)

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

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

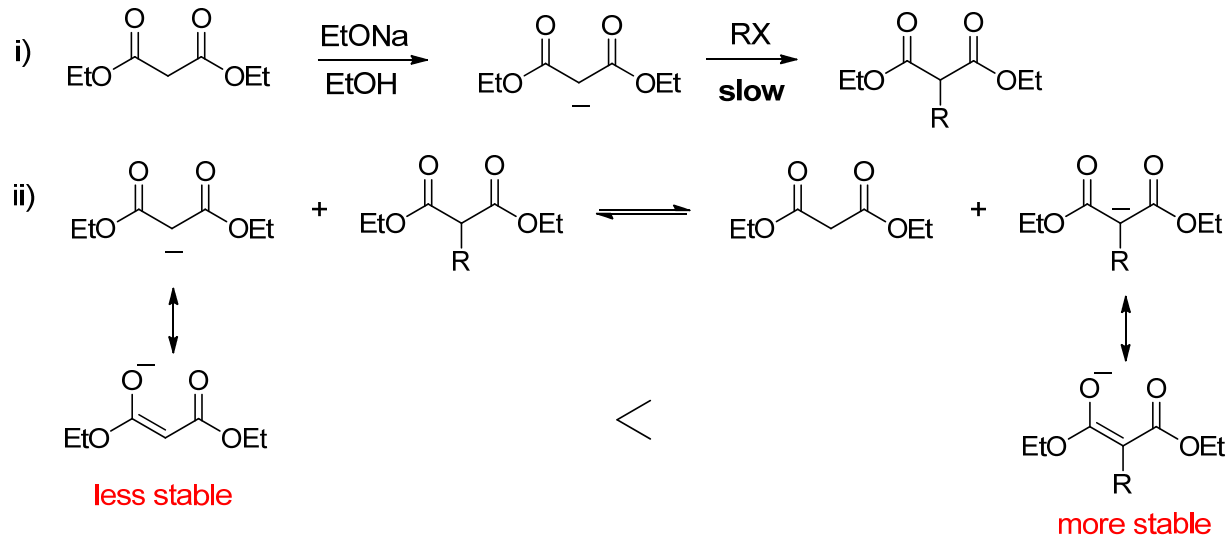


4. Stereoelectronic effect

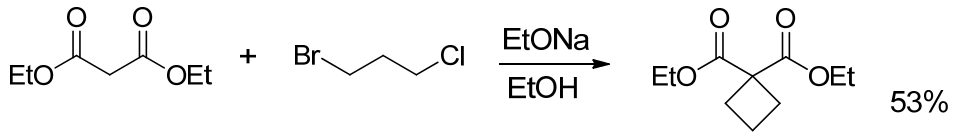


g. dialkylation

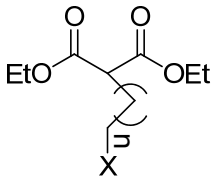
Mechanism



Cyclization

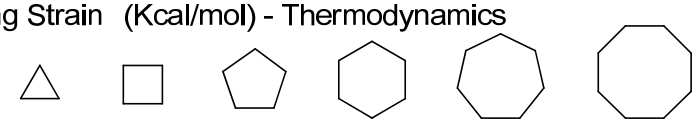


Rate of cyclization - Kinetics

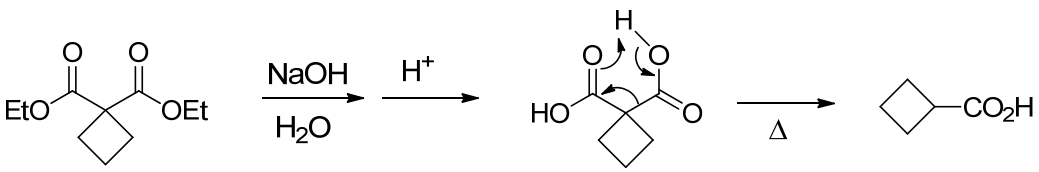


n =	1	2	3	4
	650,000	1	6,500	5

Ring Strain (Kcal/mol) - Thermodynamics

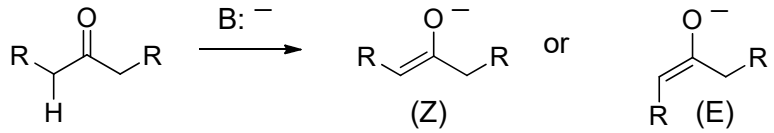


27.6	26.4	6.5	0	6.3	9.6

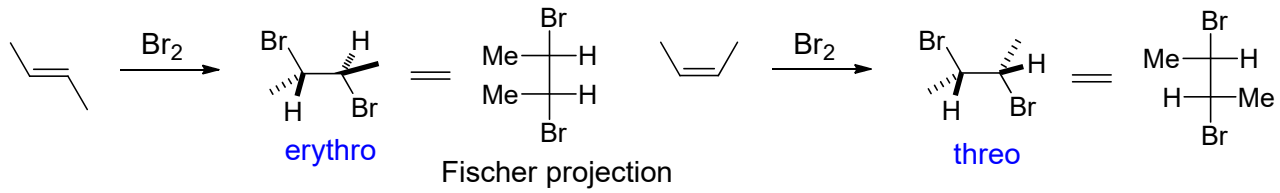


h. Regio- and Stereoselectivity in the Enolate Generation

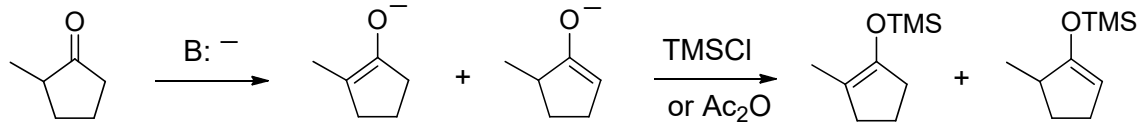
Stereoselectivity



c.f.> **Stereospecific**



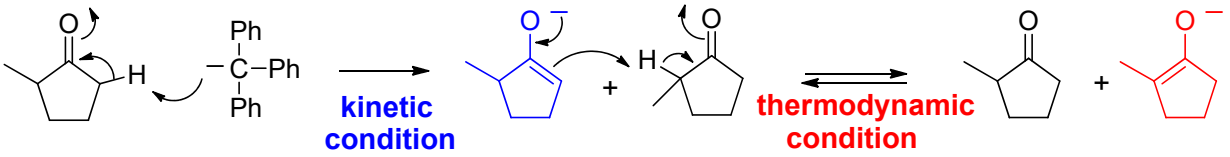
Regioselectivity



Reaction Condition

Base: Ph_3CLi
solvent: DME
room temp.

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



1) Control of Regioselectivity

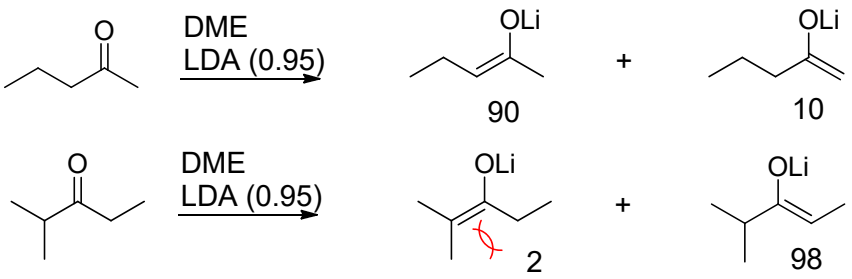
Kinetic Control

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

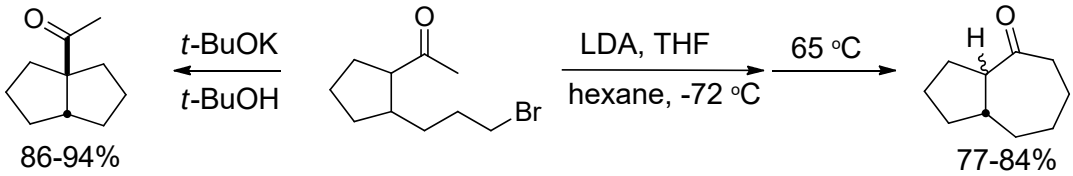
When Ph_3CK was used as a base in the above example the product ratio (28 : 72) changed to 55: 45.

Thermodynamic Control

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

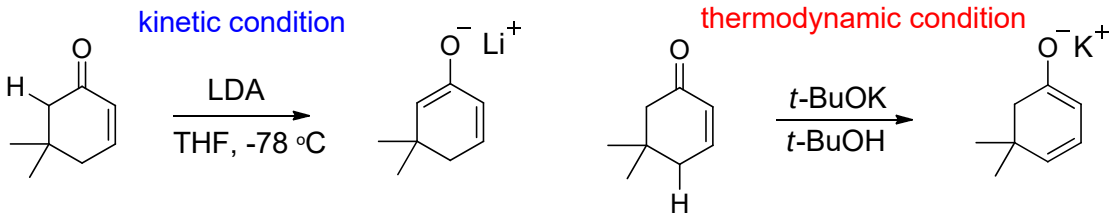


3. Small and weak bases: NaOH, NaOMe, NaH etc.
4. H^+ sources: excess ketone, protic solvent
5. High temperature
6. Ionic counter ion: K, Na

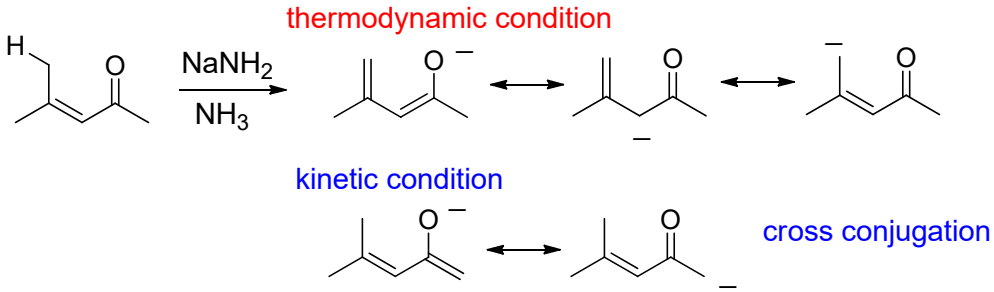


For Conjugate System

1.



2.



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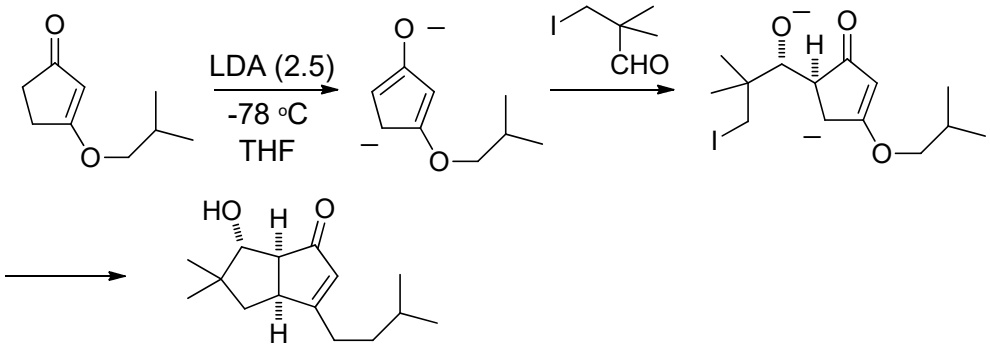
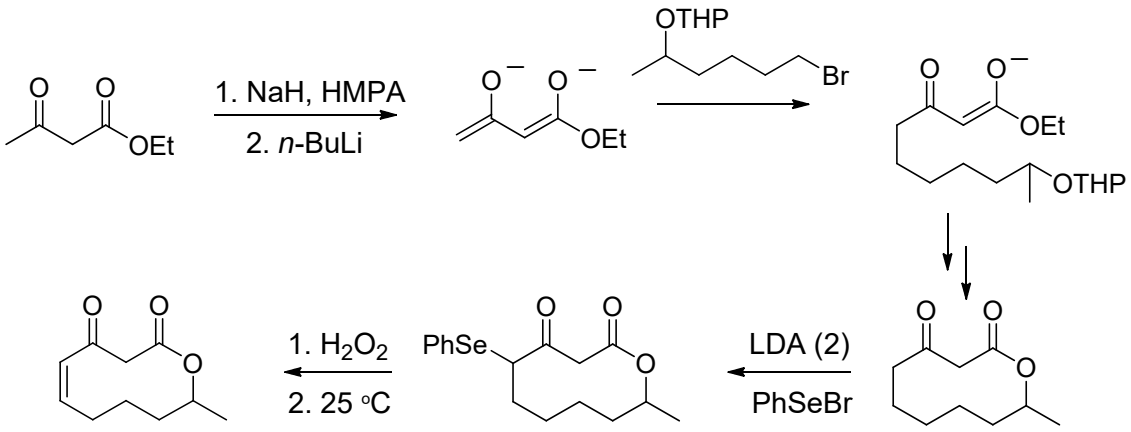
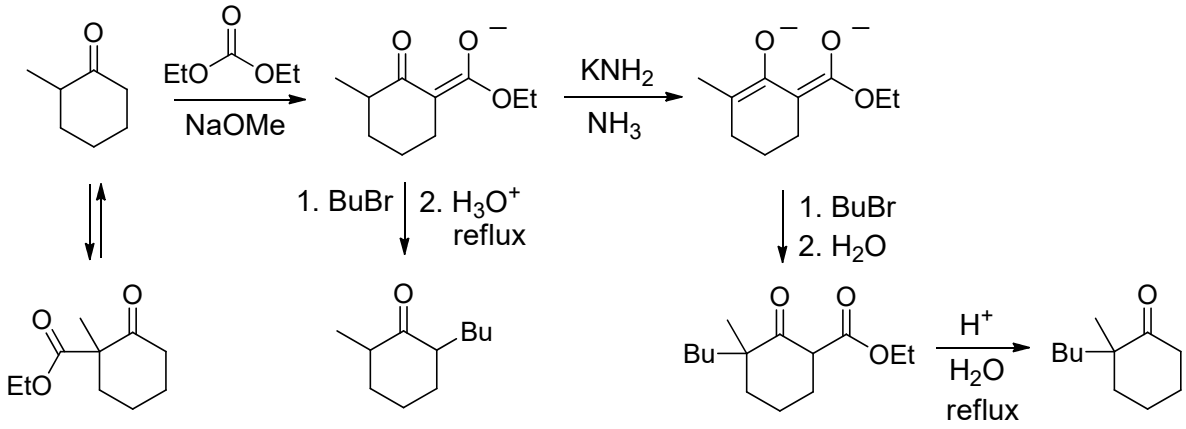


For 1,3-dicarbonyl compouns

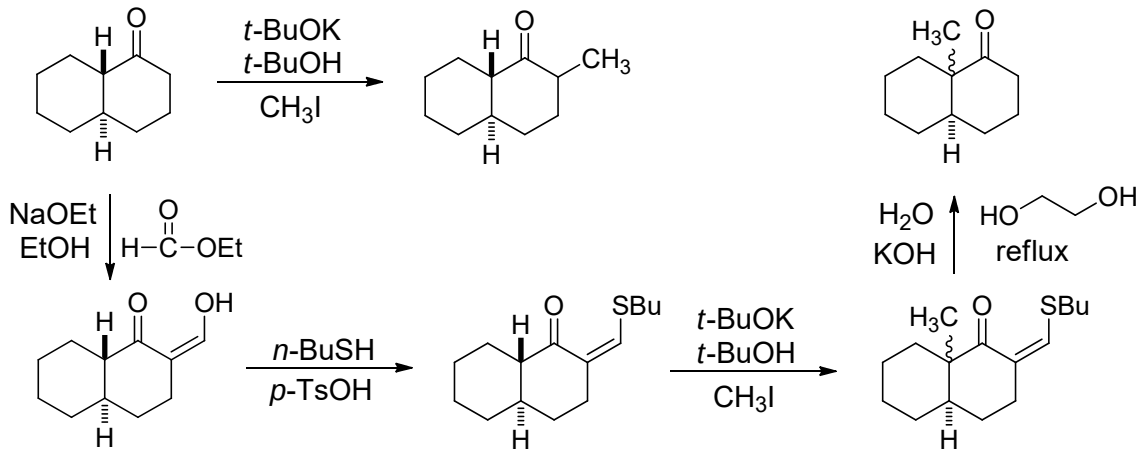


2) Regiospecific Alkylation of Carbonyl Compounds

1. Protection of active methylene site

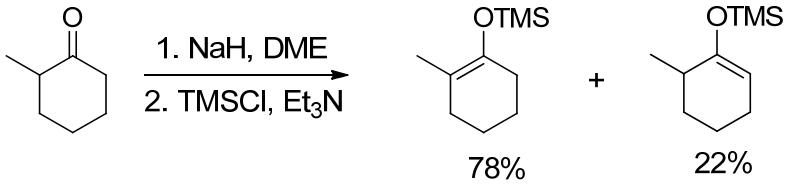


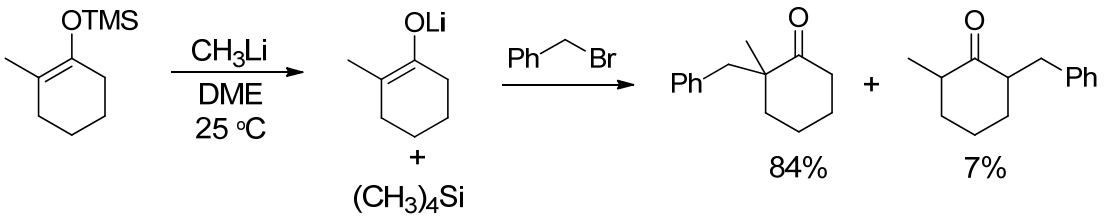
See Claisen Ester Condensation

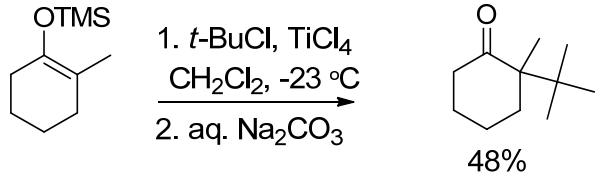


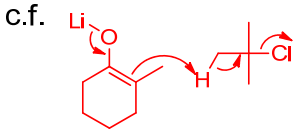
2) Regiospecific Alkylation (continued)

2. Silyl Enol Ether

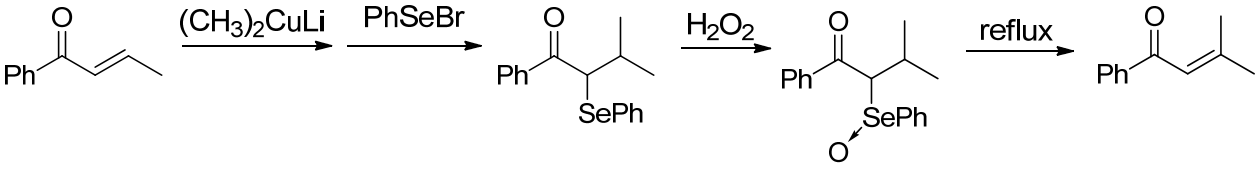




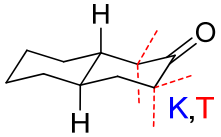


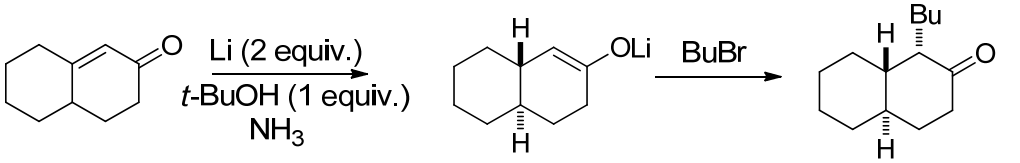


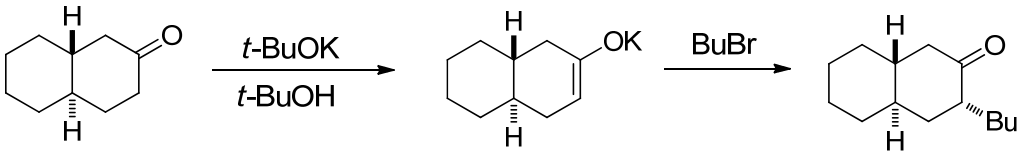
3. Conjugate Addition of Enones

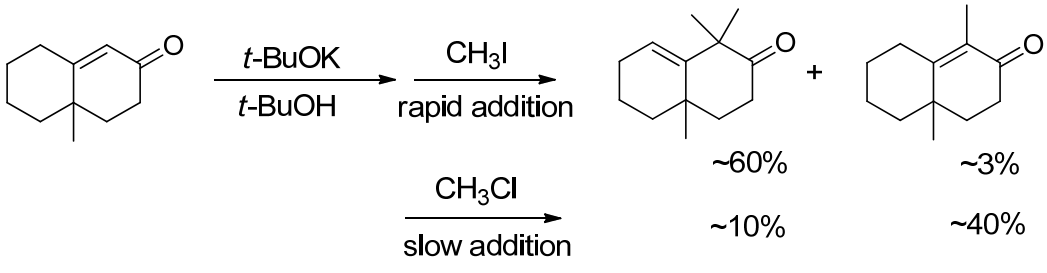


3) Regioselectivity of Decalone System





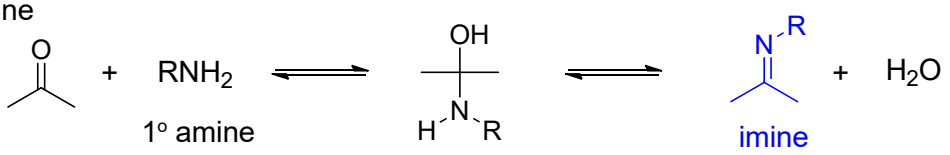




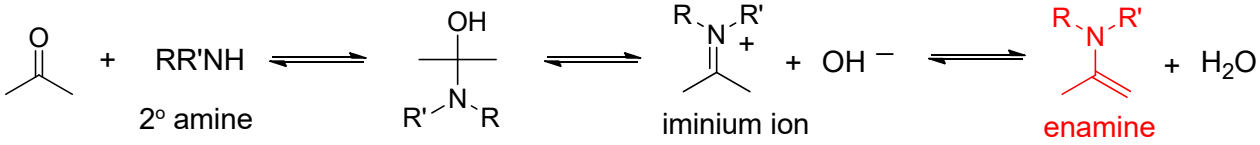
1.2 The Enamine and Related Reactions: Nitrogen Analogues of Enol and Enolate ion

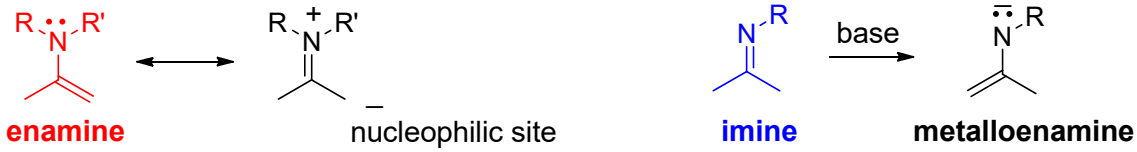
The major problems in enolate alkylation - (i) Aldol reaction; (ii) polyalkylation - can be overcome by the enamine alkylation.

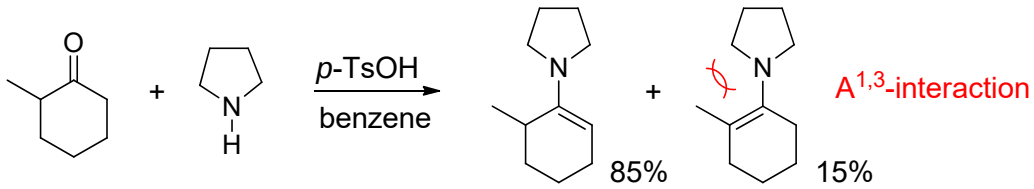
Imine



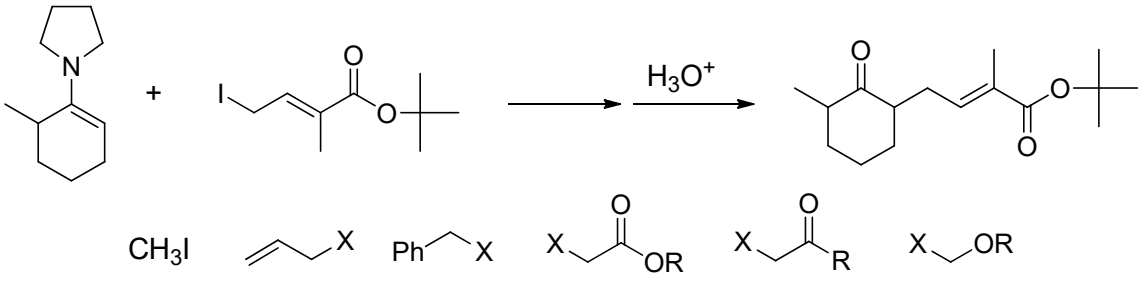
Enamine



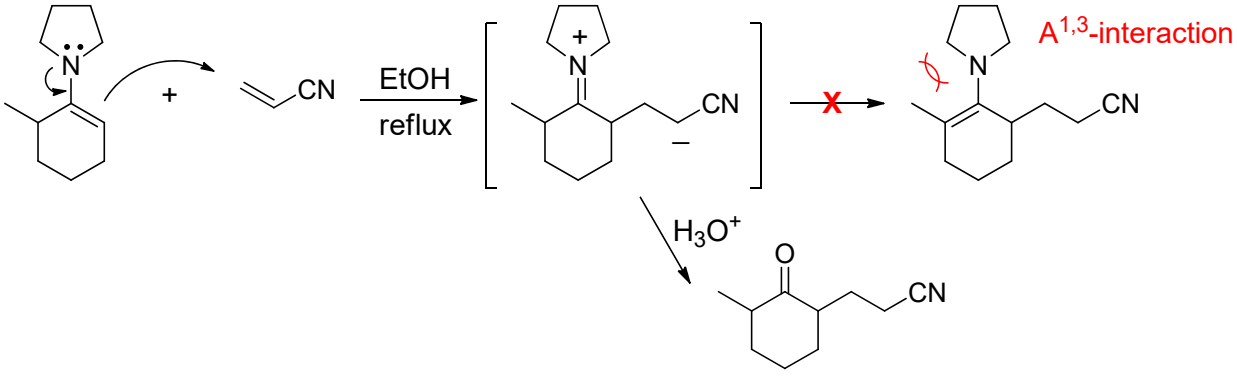




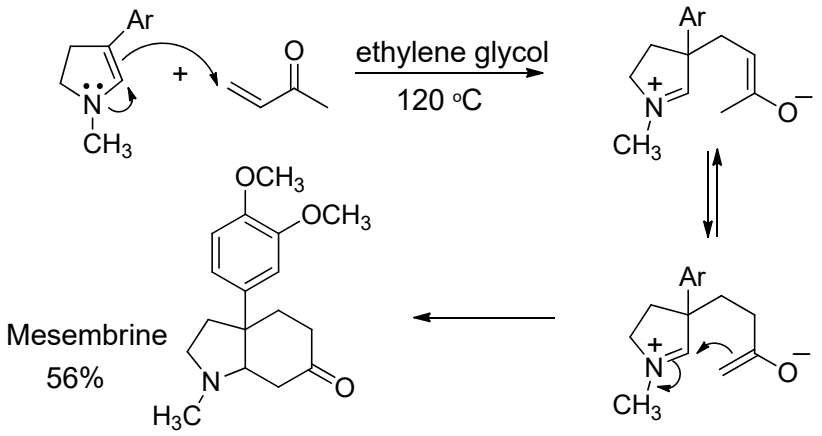
Use reactive electrophiles for alkylation



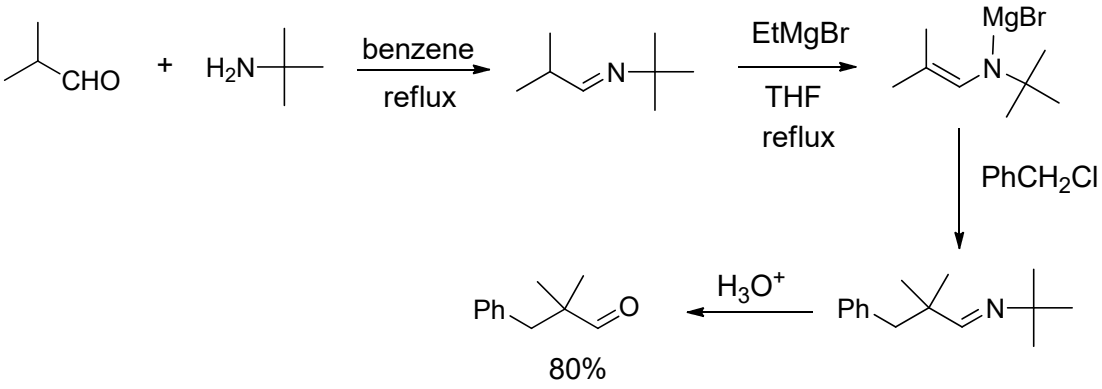
Conjugate addition / mono-alkylation



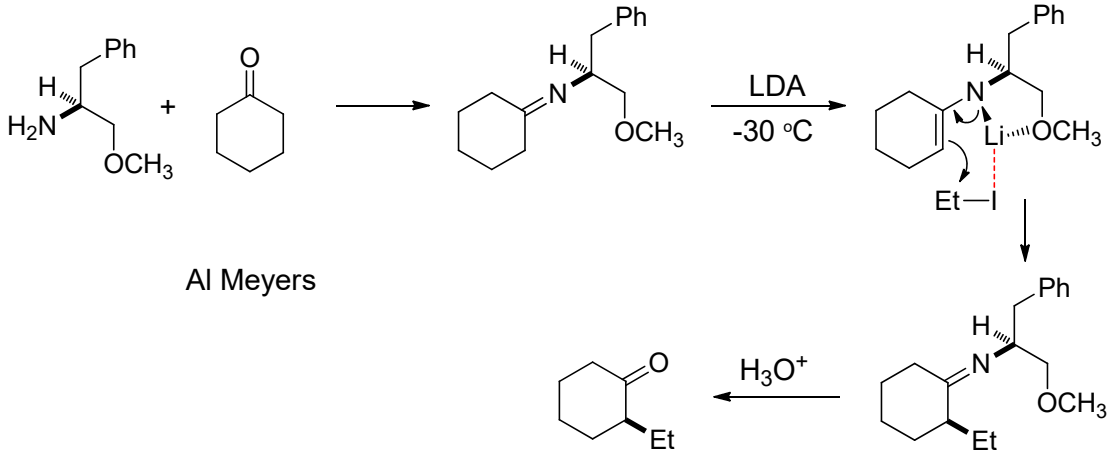
Enamine



Metalloenamines (imine anions)



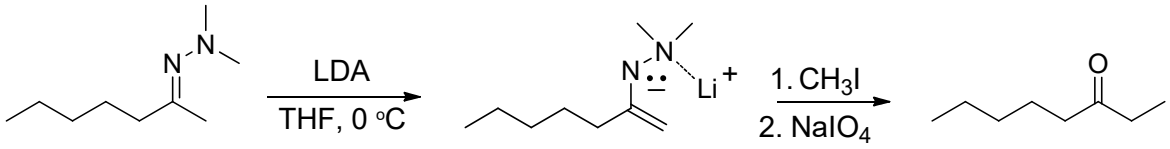
from **Chiral Amine**



Al Meyers

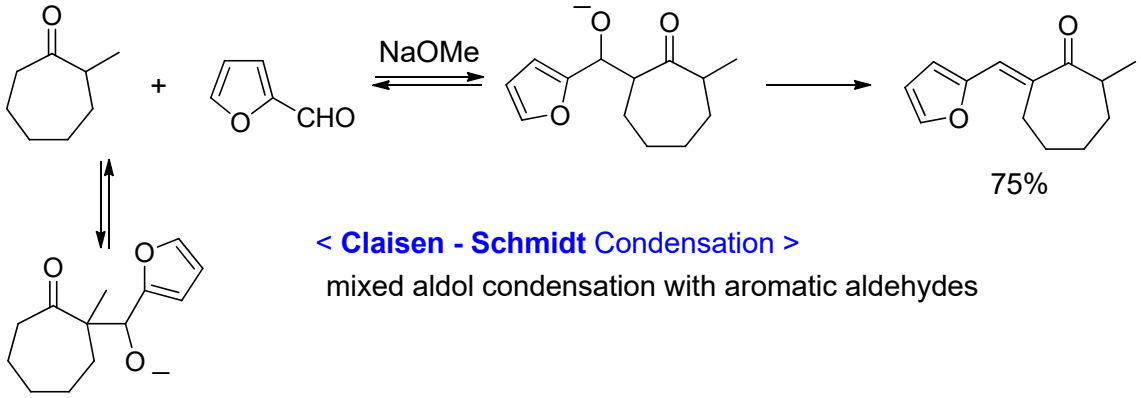
from **Hydrazine**

more stable and better stereoselectivity



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

a. Mixed Aldol Condensation

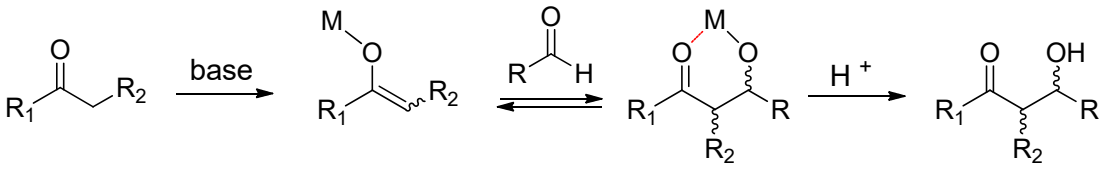


< **Claisen - Schmidt** Condensation >

mixed aldol condensation with aromatic aldehydes

b. DIrected Aldol Condensation

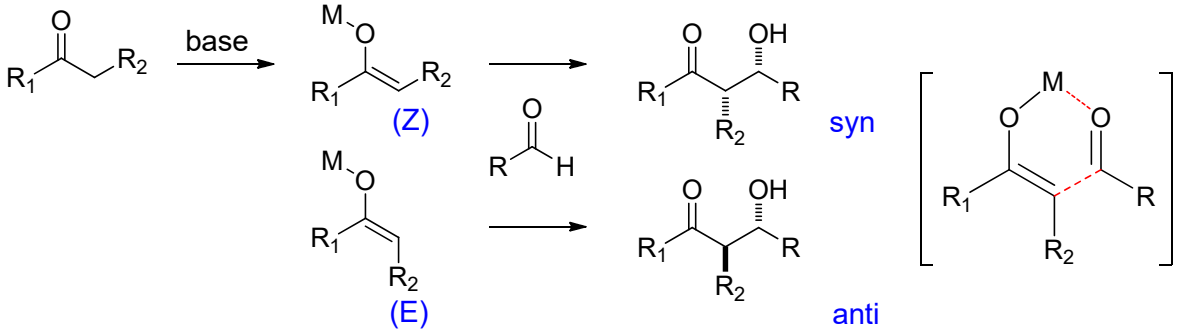
mixed aldol condensation of aliphatic aldehydes and ketones

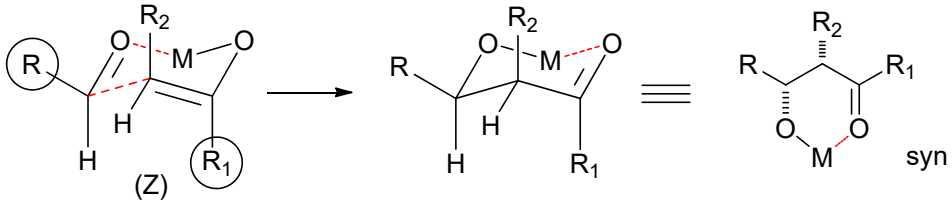


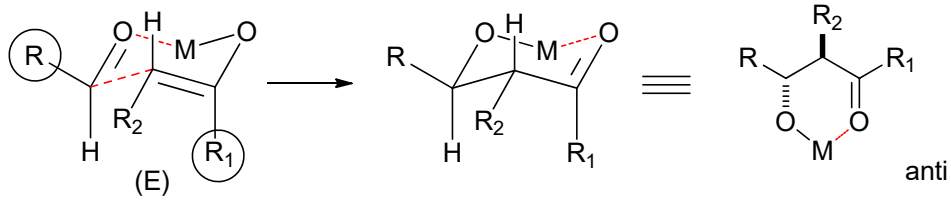
c. Control of Stereochemistry: Kinetic condition

i) Simple Diastereoselectivity

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



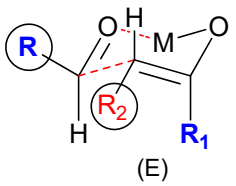




c. Control of Stereochemistry: Kinetic condition (continued)

i) Simple Diastereoselectivity

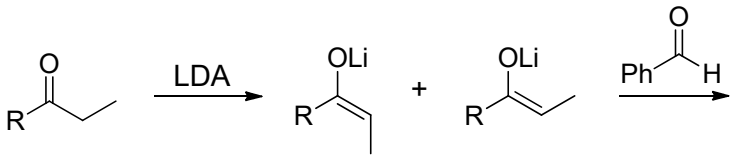
(Z) ⟶ syn, (E) ⟶ anti



(E)

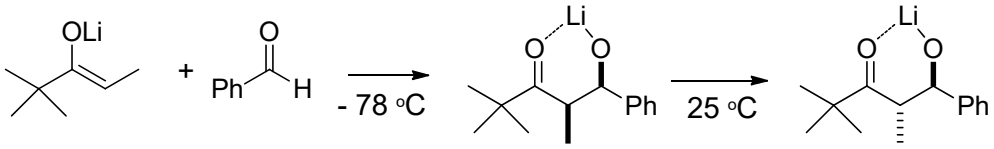
Best correlation

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

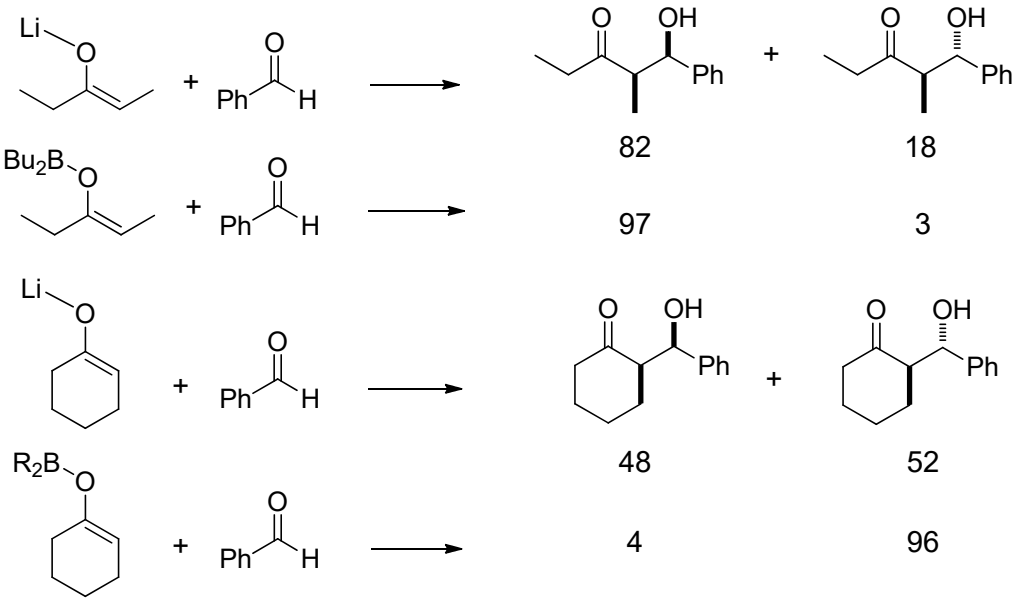


			anti	syn
R = Et	70	30	36	64
i-Pr	40	60	18	82
t-Bu	2	98	2	98

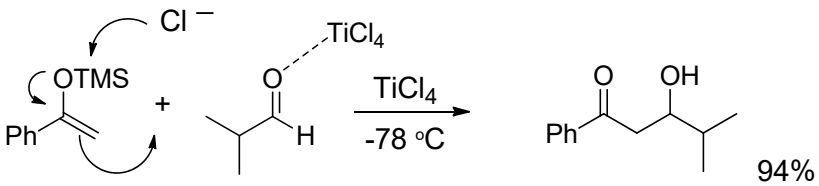
Under Equilibrium Condition (Thermodynamic Condition)



Boron enolates

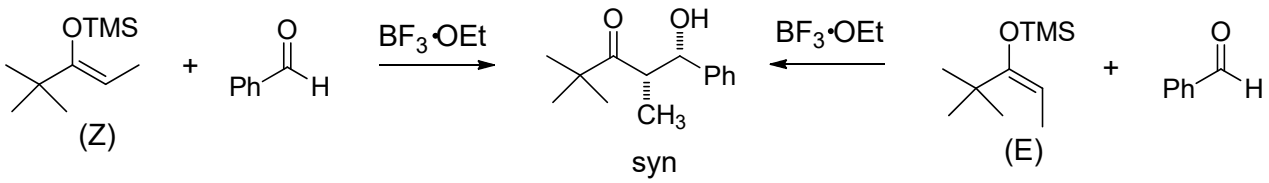


Aldol reaction with **Silyl Enol Ether: Open Transition State**

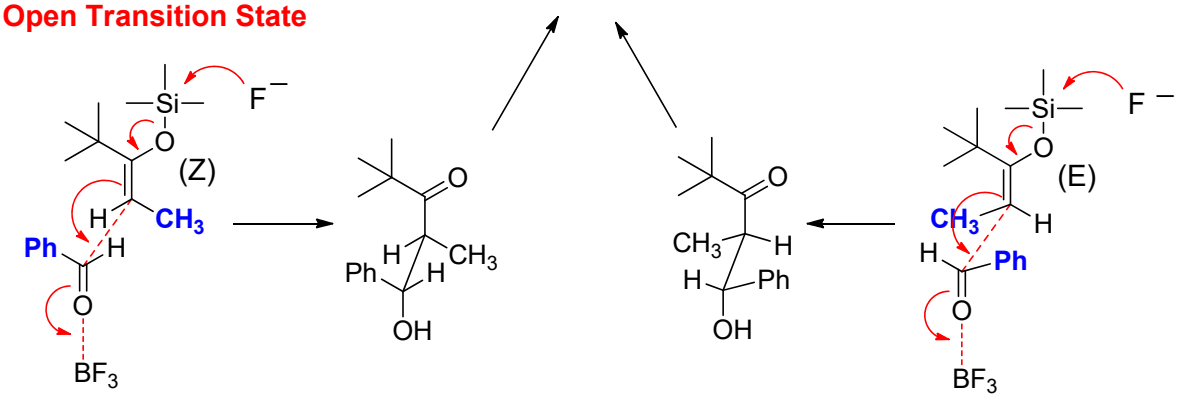


Aldol reaction with **Silyl Enol Ether** (continued)

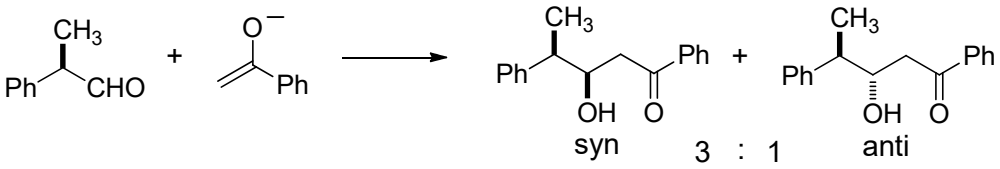
Stereochemistry



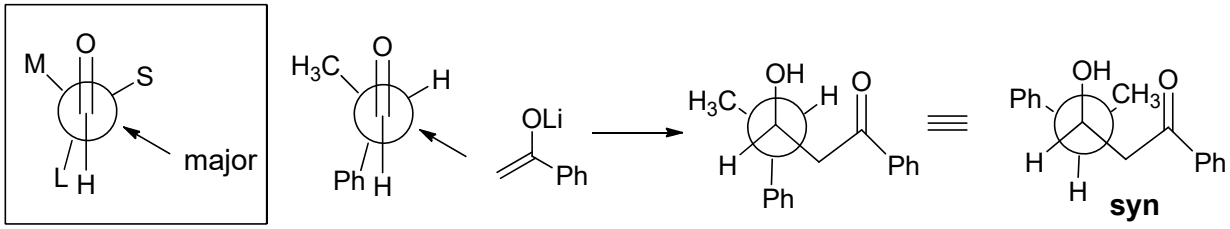
Open Transition State



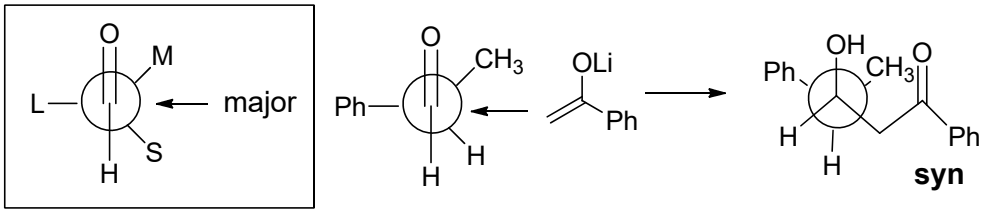
ii) Stereoselectivity between **achiral enolates** and **chiral aldehydes**



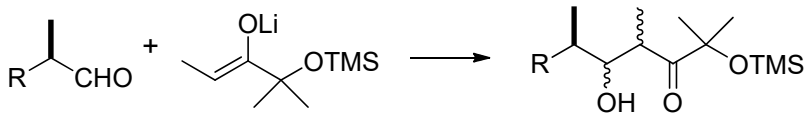
Cram's rule

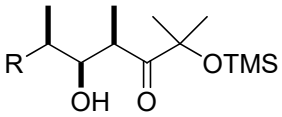
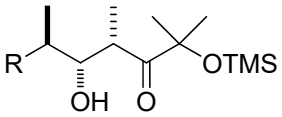
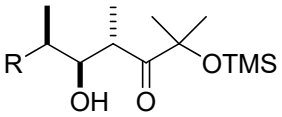
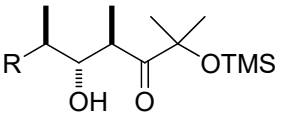
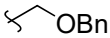


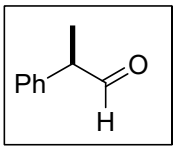
Felkin -Ahn



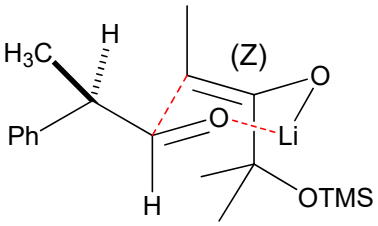
iii) Stereoselectivity between chiral aldehydes and prochiral enolates



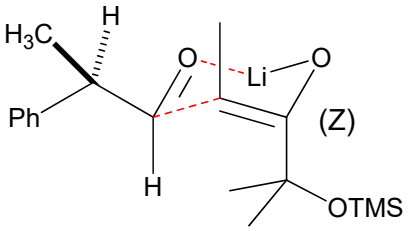
 syn,syn	 anti,syn	 syn,anti	 anti,anti
R = Ph 81	19	0	0
 94	6	0	0
 33	67	0	0
 21	79	0	0

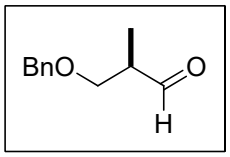


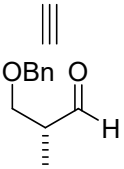
cram



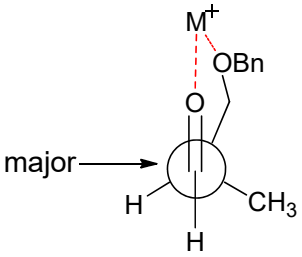
anti-cram

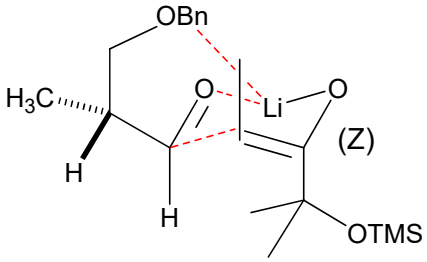




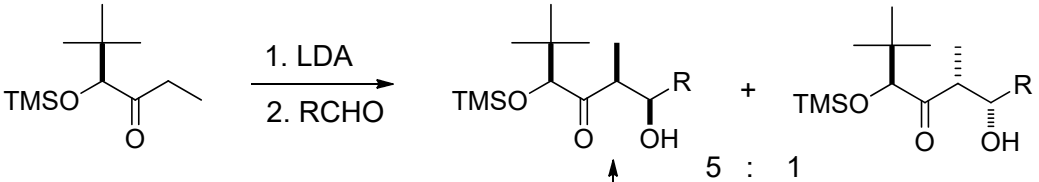


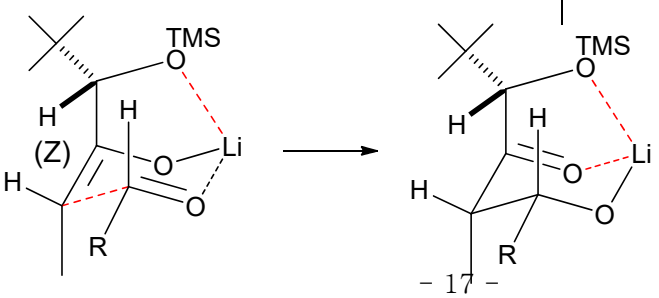
anti-cram or chelated cram



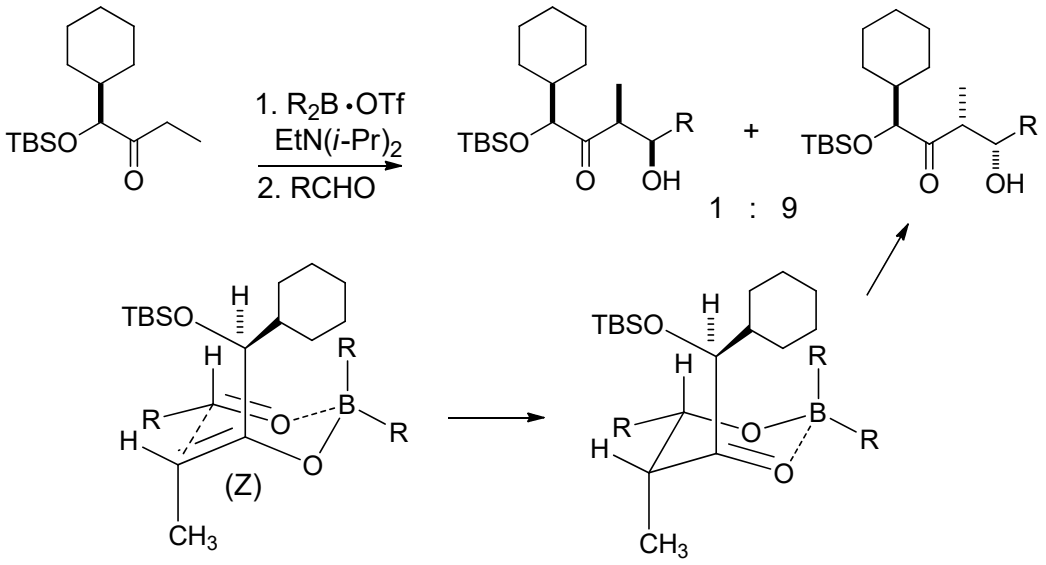


iv) Stereoselectivity between chiral enolates and achiral aldehydes

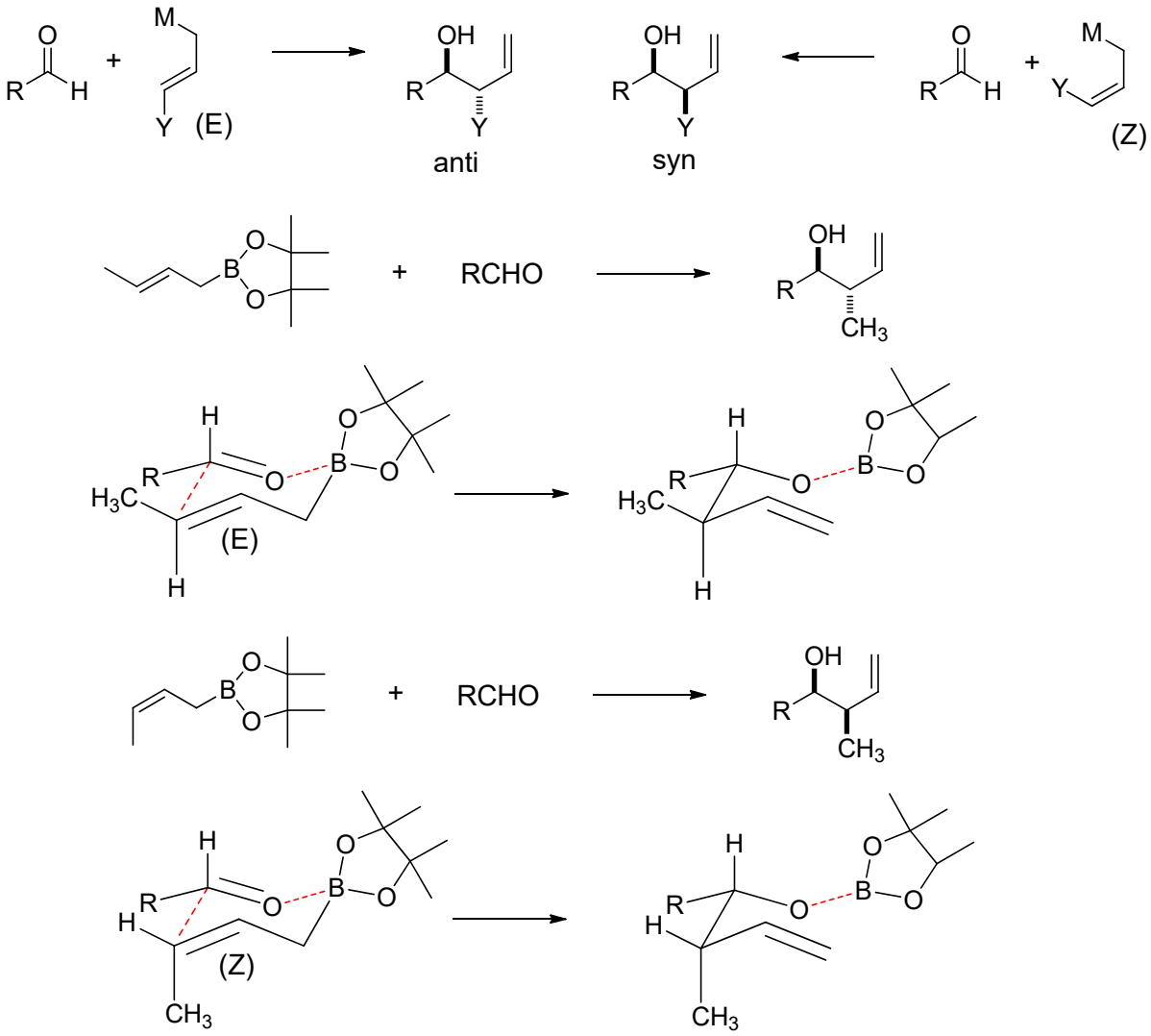




iv) Stereoselectivity between chiral enolates and achiral aldehydes (continued)

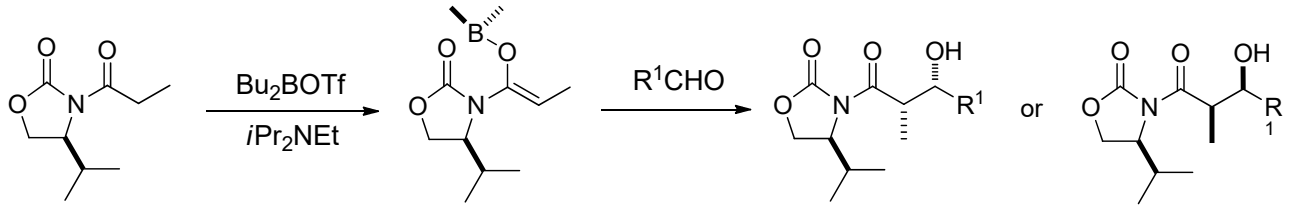


d. Allylmetal compound with aldehydes



e. Evans' chiral *N*-acyl oxazolidinones

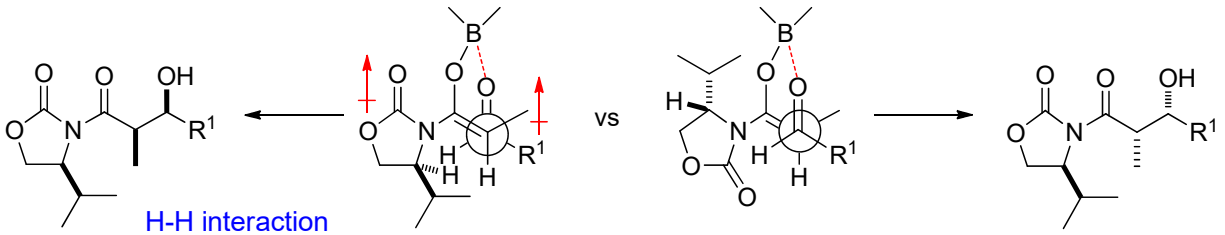
1) Boron enolate



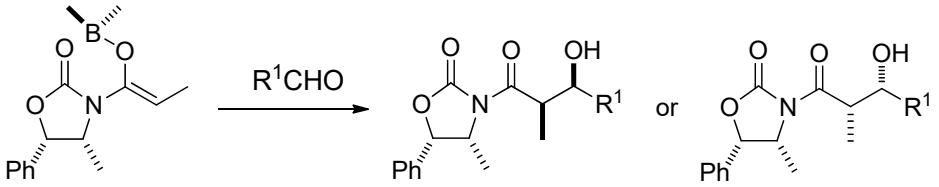
exclusively *Z*-enolate

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

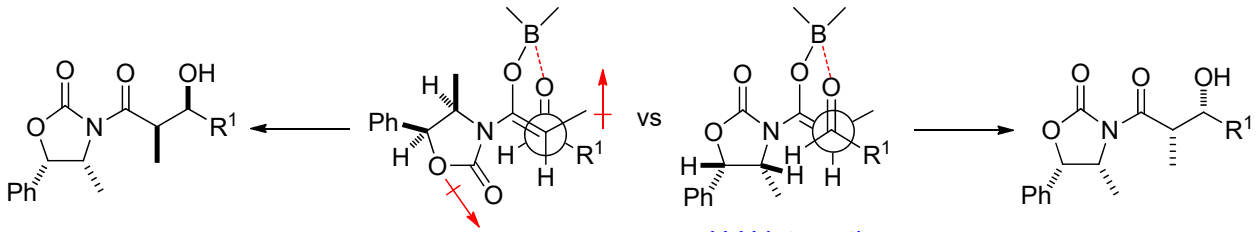
J. Am. Chem. Soc. 1981, 103, 2876
J. Am. Chem. Soc. 1981, 103, 3099



H-H interaction
unfavorable dipole alignment



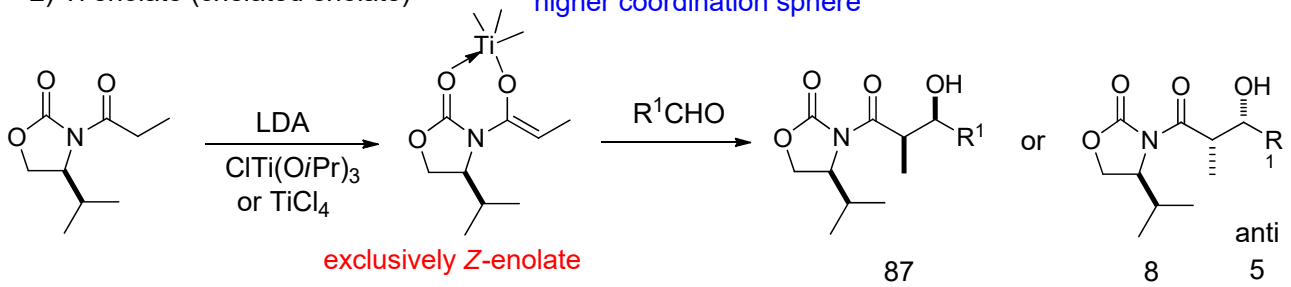
R^1 = *n*Bu	>99.8	<0.2
R^1 = *i*Pr	>99.8	<0.2
R^1 = Ph	>99.8	<0.2



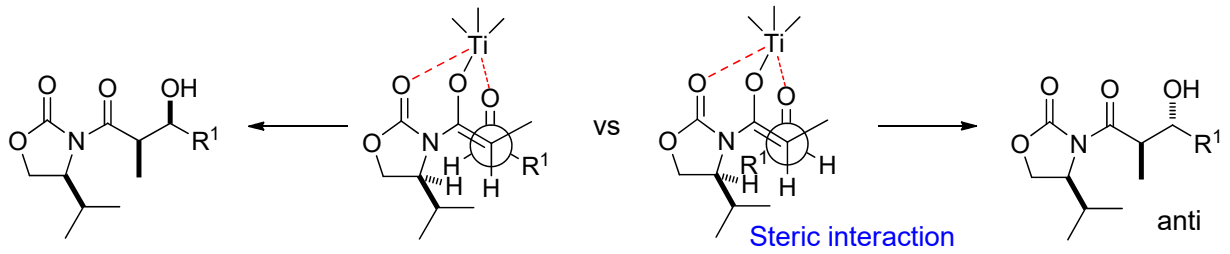
H-H interaction
unfavorable dipole alignment

e. Evans' chiral *N*-acyl oxazolidinones

2) Ti enolate (chelated enolate)

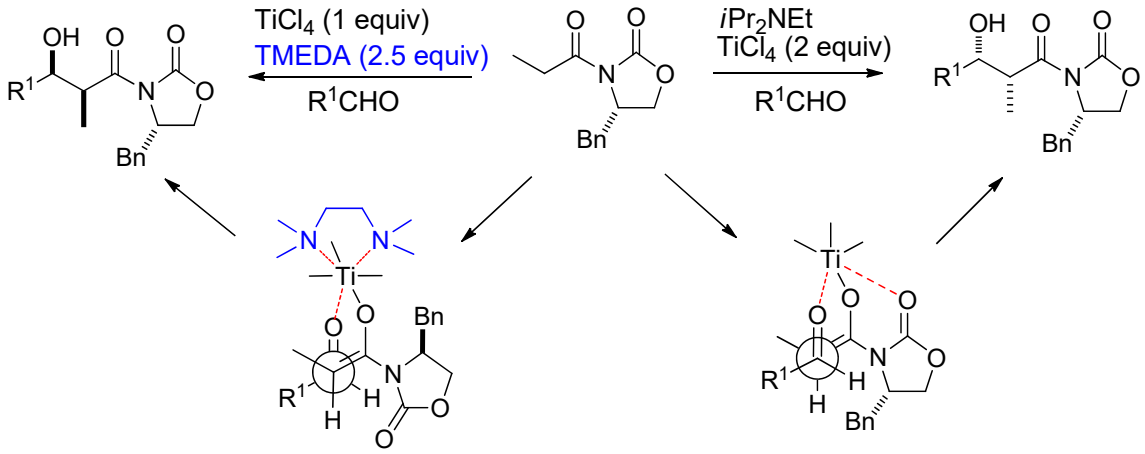


J. Am. Chem. Soc. **1989**, *111*, 5722
J. Am. Chem. Soc. **1991**, *113*, 1047



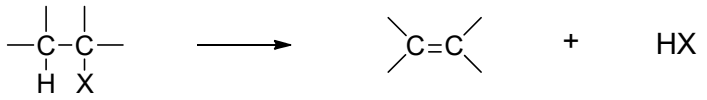
3) Chelated and non-chelated Ti enolates

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



Chapter 2. Formation of Carbon-Carbon Double Bonds

2.1 β-Elimination reaction

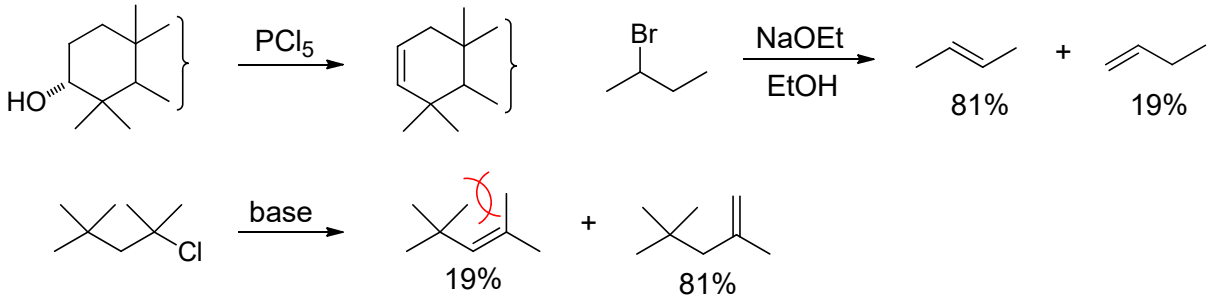


X = OH, OCOR, halogen, OSO_2Ar, $N\overset{+}{R}_3$, $S\overset{+}{R}_2$ E1 or E2 mechanism

Regioselectivity

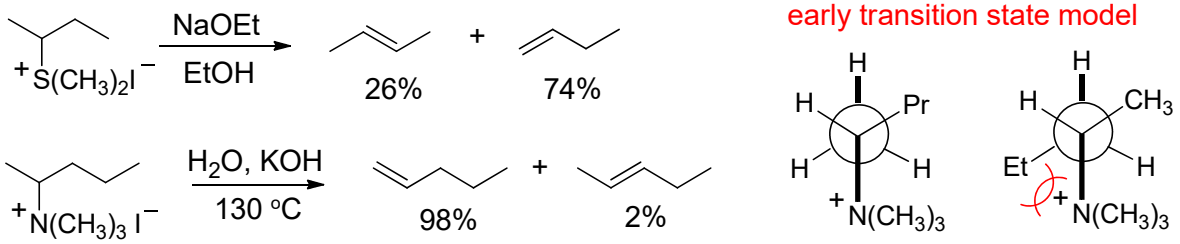
Saytzeff rule: more highly substituted (stable) alkene

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



Hofmann rule: less substituted alkene

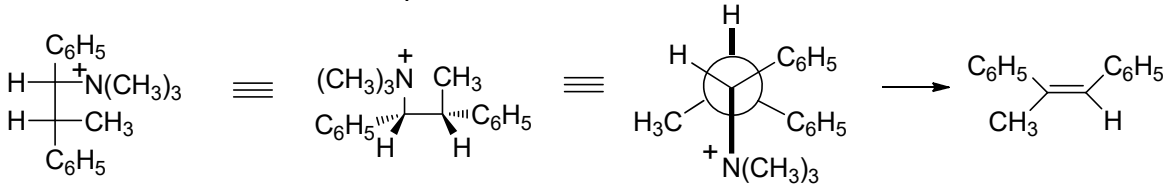
base induced elimination of quaternary ammonium salts or sulfonium salts

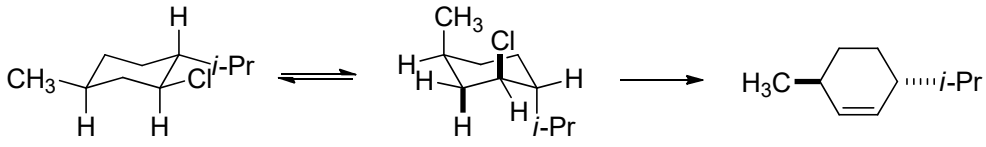


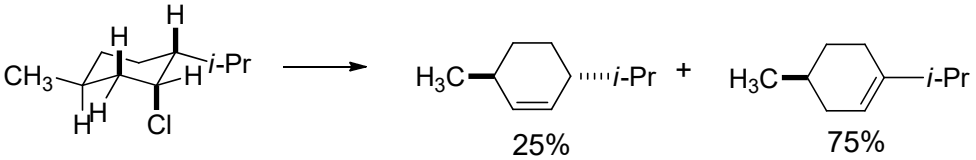
early transition state model

Stereoselectivity

E2 elimination = anti elimination process

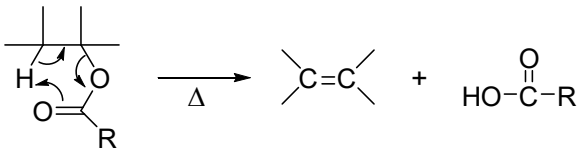




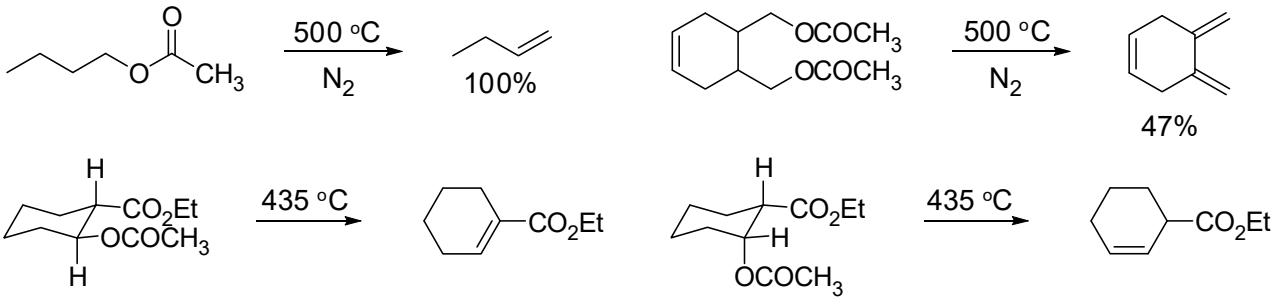


2.2 Pyrolytic **syn** eliminations "concerted cyclic transition state"

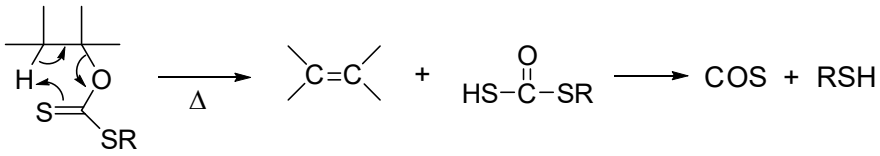
a. carboxylic esters



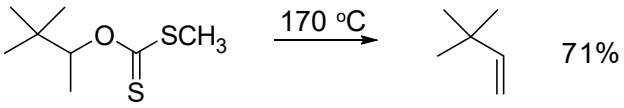
[examples]



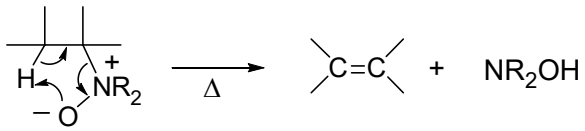
b. xanthate esters - Chugaev reaction



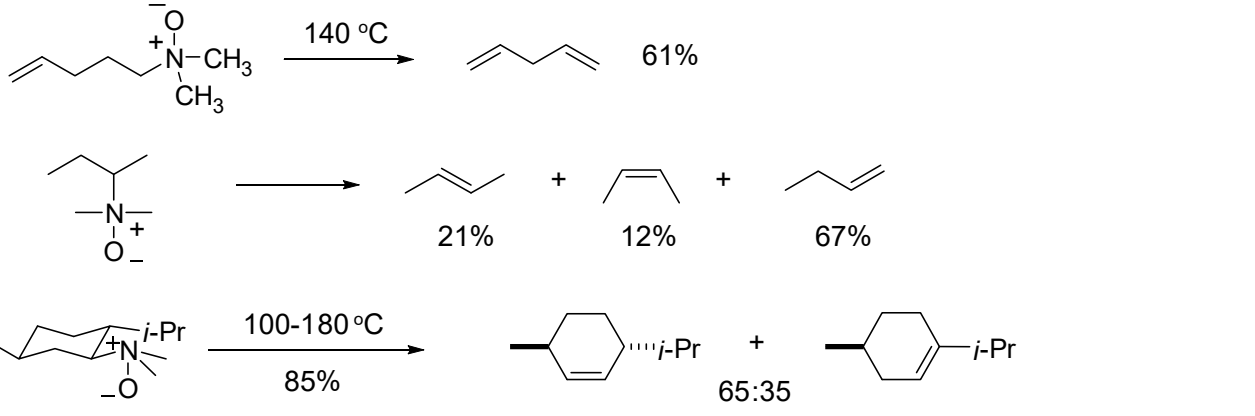
[examples]



c. ammonium oxides - Cope reaction

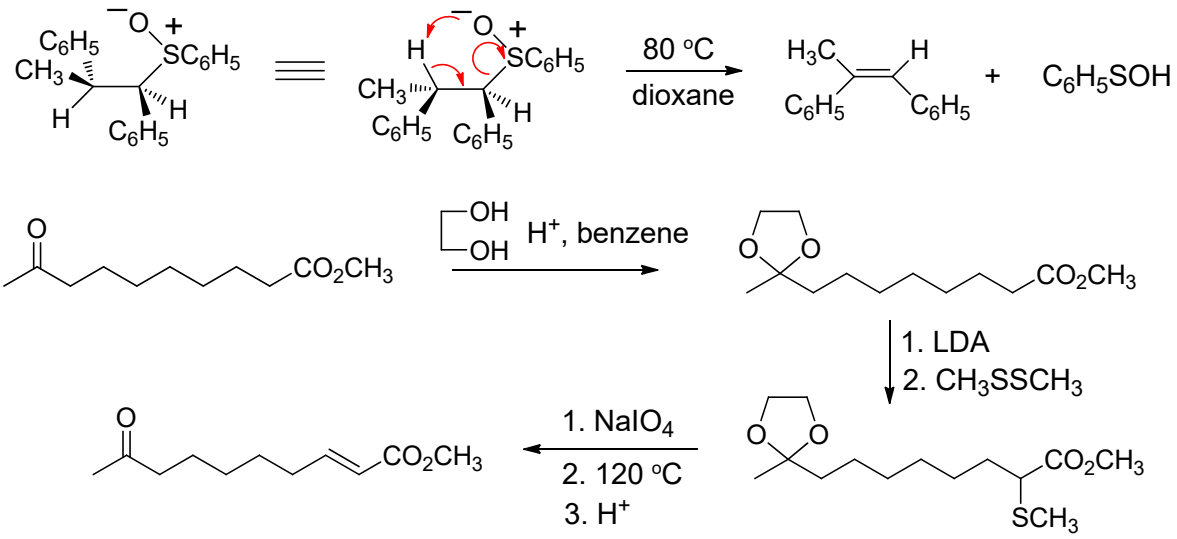


[examples]

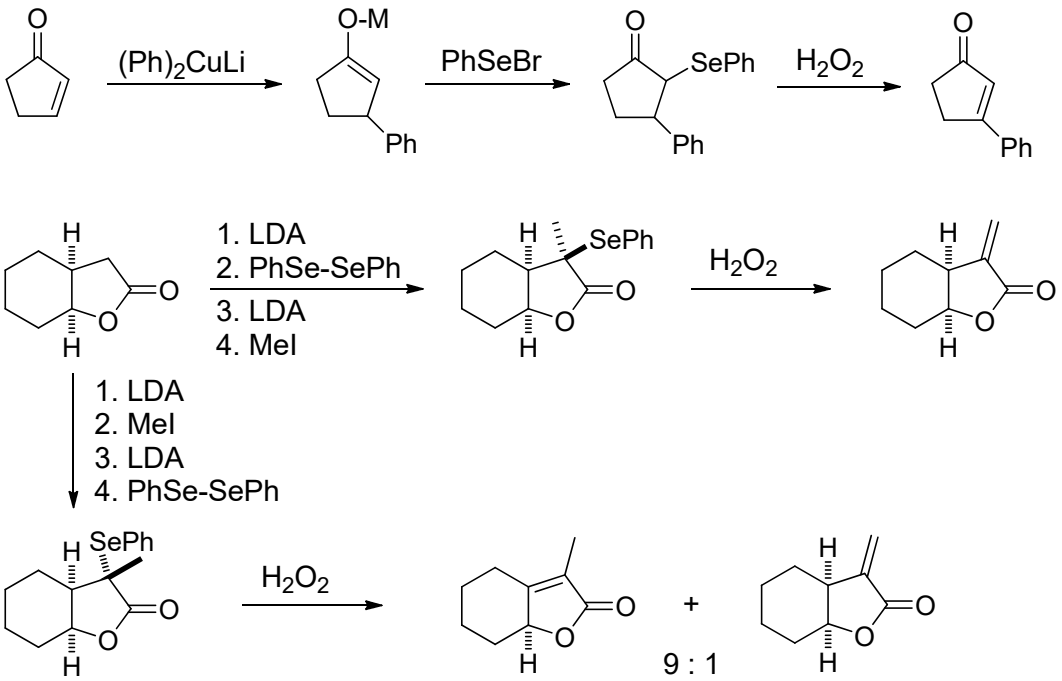


2.2 Pyrolytic **syn** eliminations (continued)

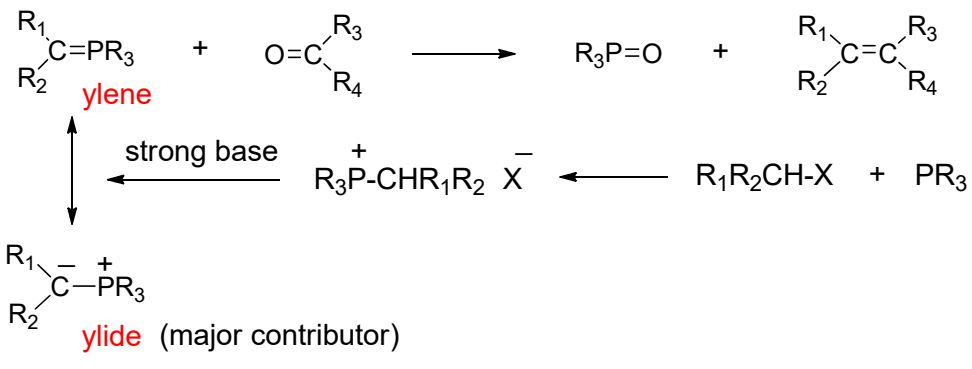
d. Sulfoxides (concerted cyclic pathway)



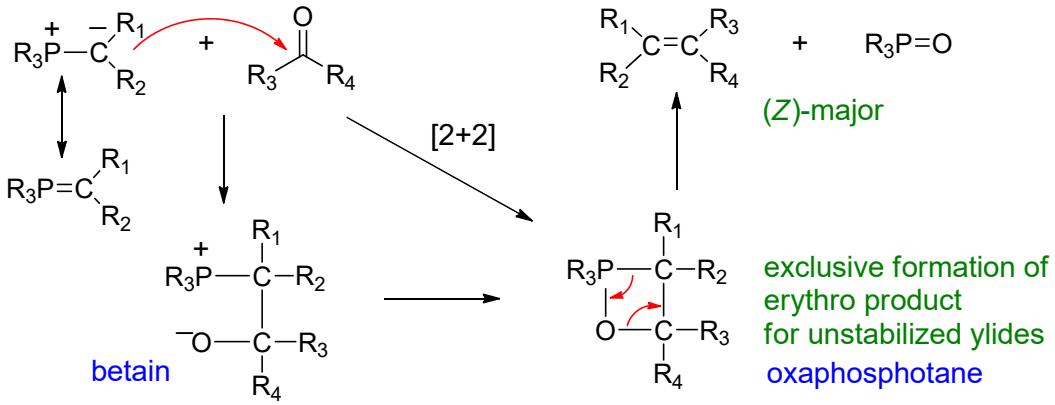
e. Selenoxides: milder conditions (at room temperature or below)



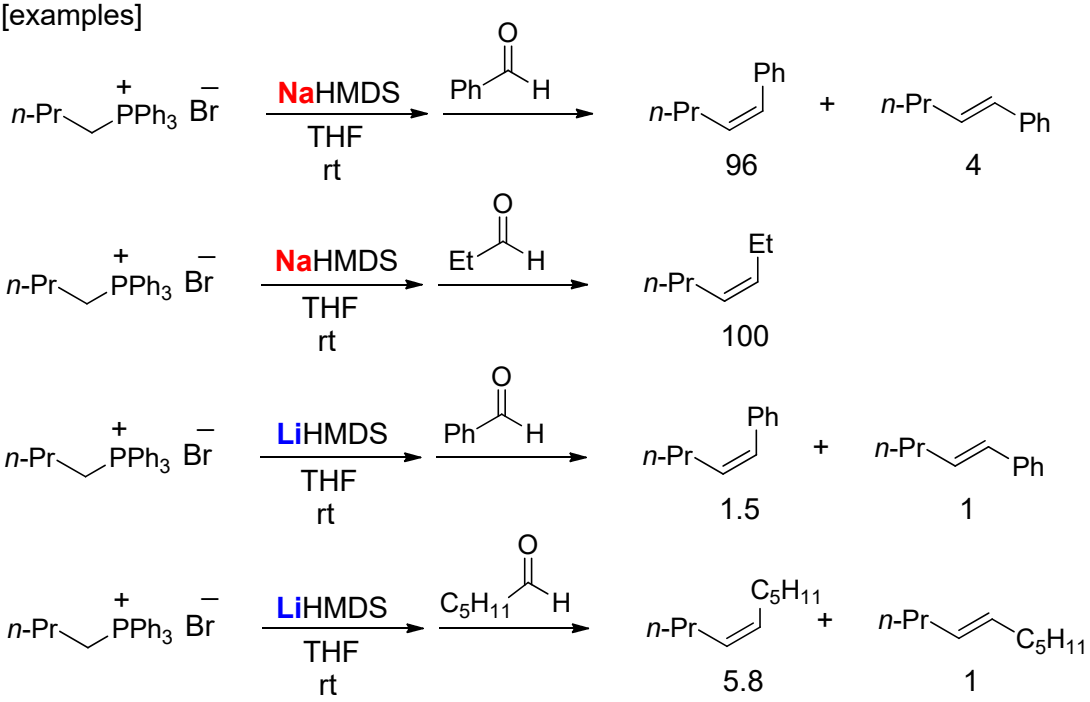
2.3 The Wittig and related reactions



a. The **mechanism** of Wittig reaction

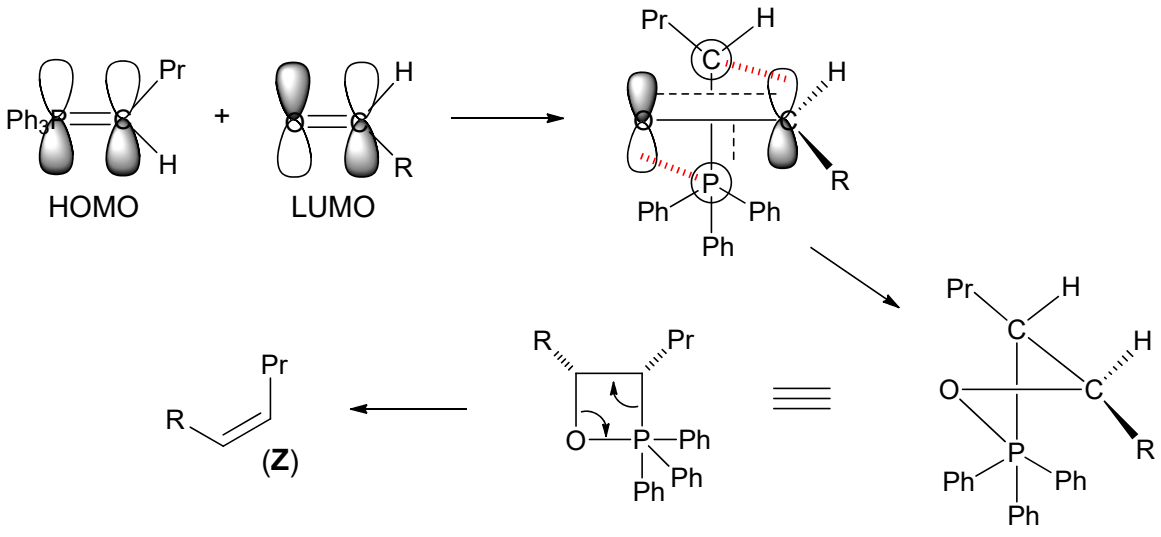


[examples]



Stereoselectivity

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



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

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

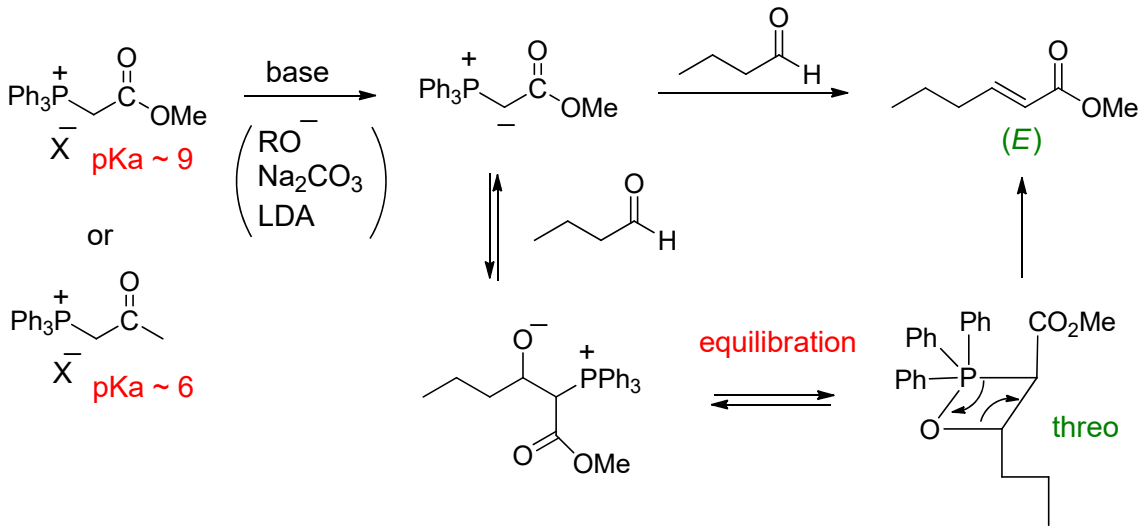
   K, Na as a counter metal ion

   Li-X forms a chelated complex with the reaction intermediate

2. Dipolar aprotic solvents

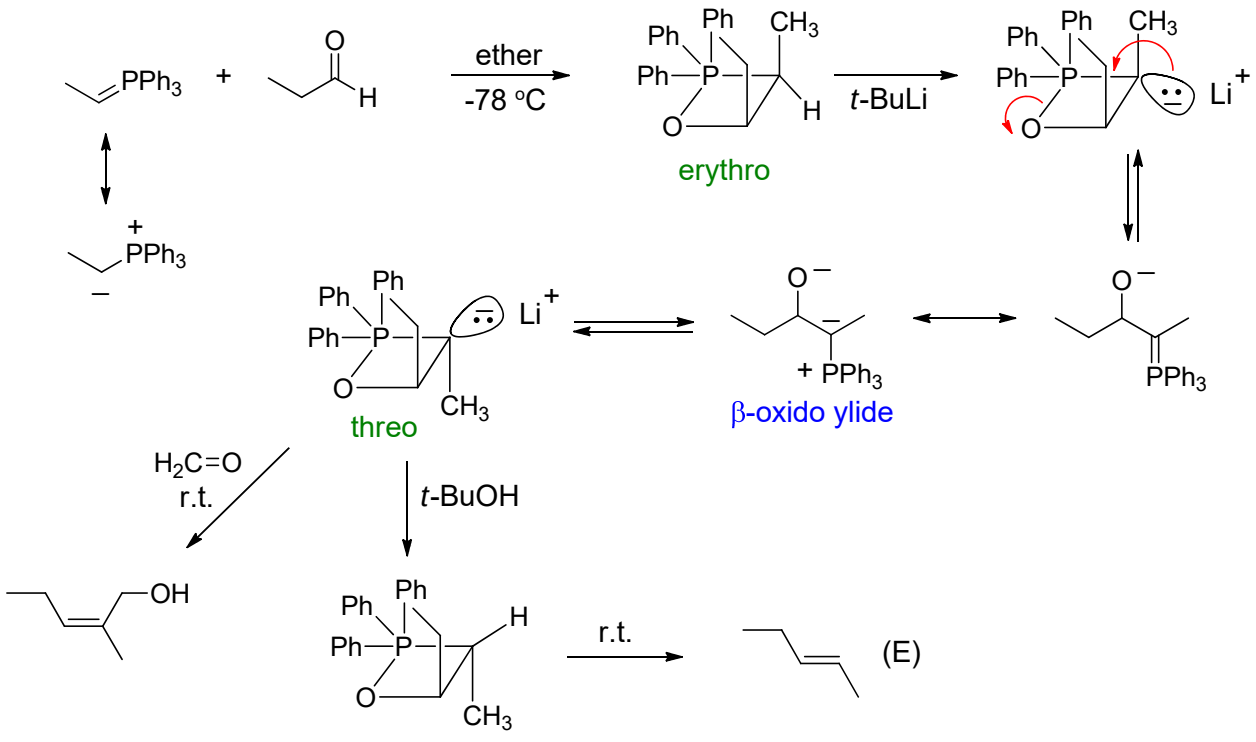
   THF, DMSO, DMF

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



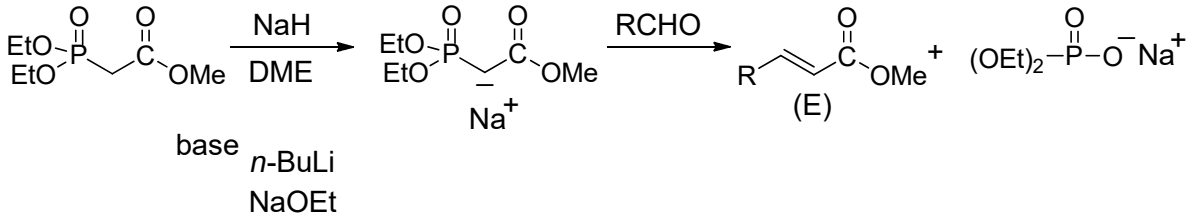
c. **Schlosser Modification** **nonstabilized ylides** ⟶ **(*E*)-alkene**

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



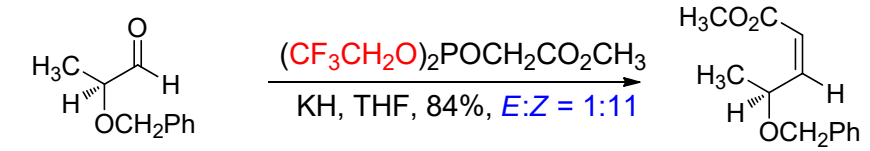
d. Horner - Wadsworth - Emmons Modification

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

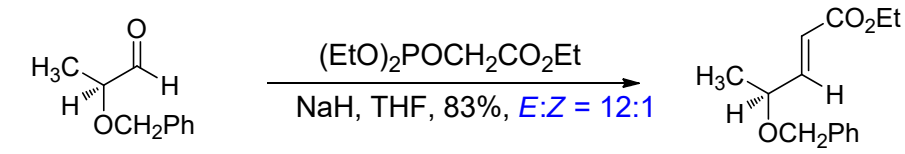


Z-selective HWE reaction

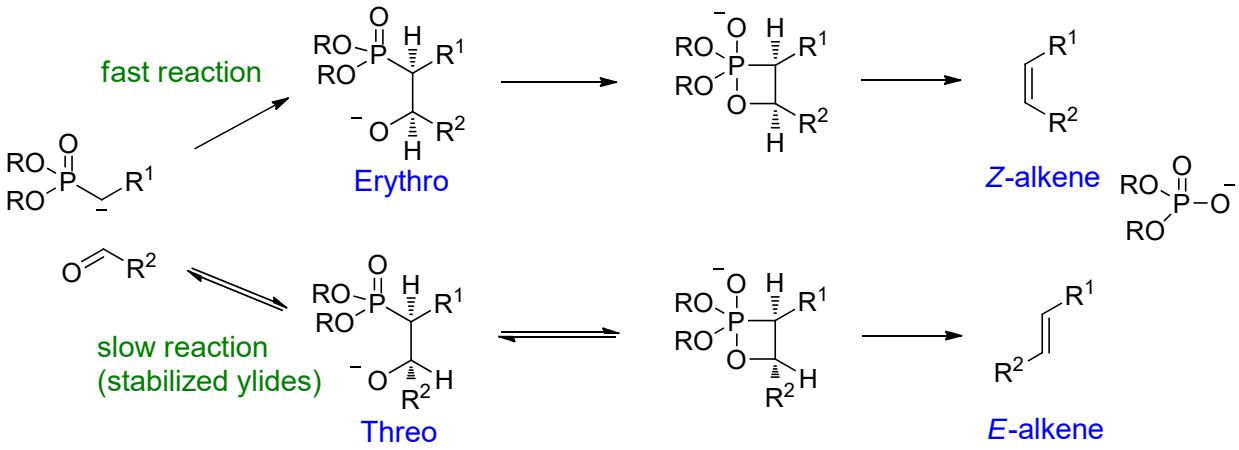
1. Still-Gennari modification: *TL* **1983**, *24*, 4405



c.f.

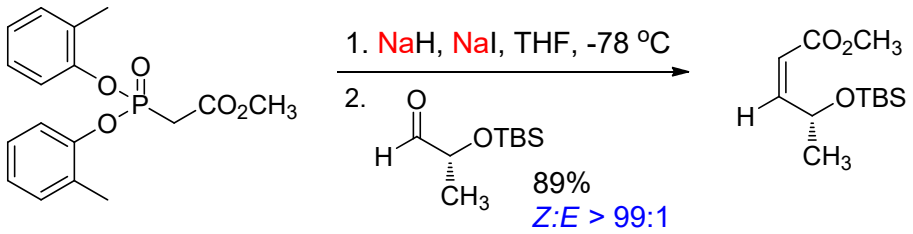


[Mechanism and Origin of Stereoselectivity]

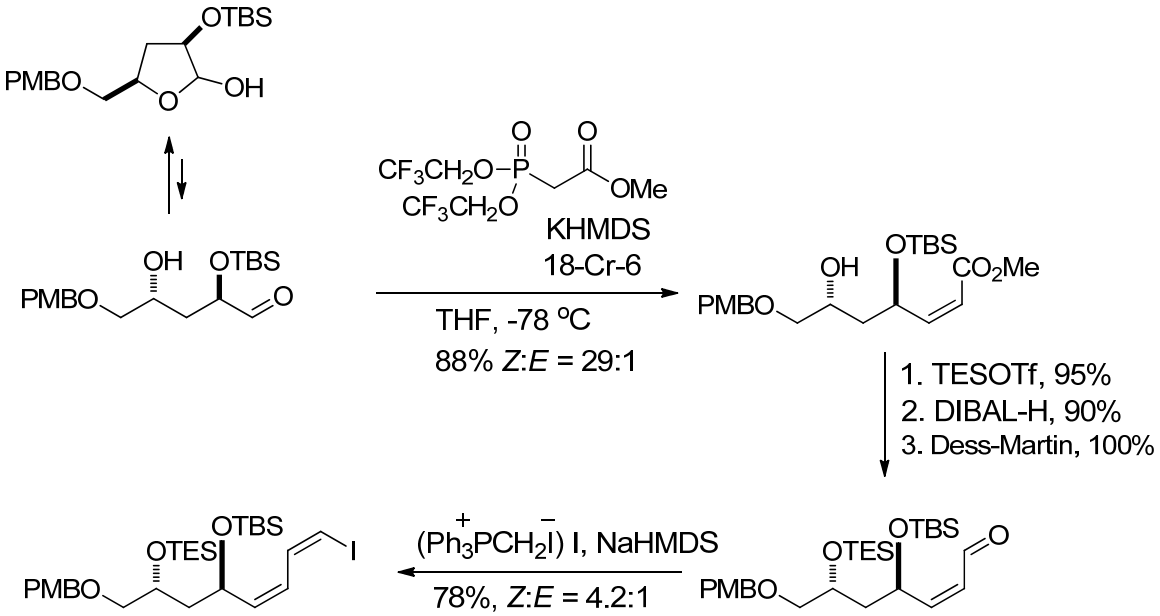


Large R or R^1 groups favor *E* alkene formation.

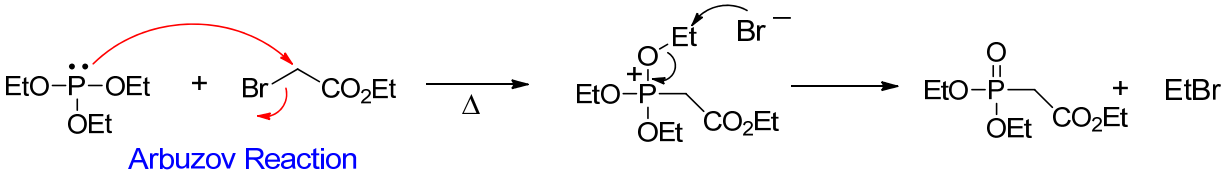
2. Ando method: *TL* **1995**, *36*, 4105; *JOC* **1997**, *62*, 1934.



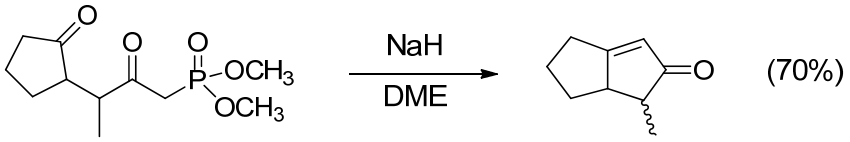
D. L. Boger et. al. *J. Am. Soc. Chem.* **2001**, *123*, 4161.



preparation of phosphonate

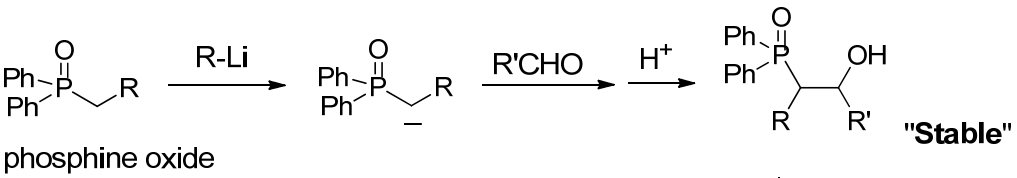


Arbuzov Reaction

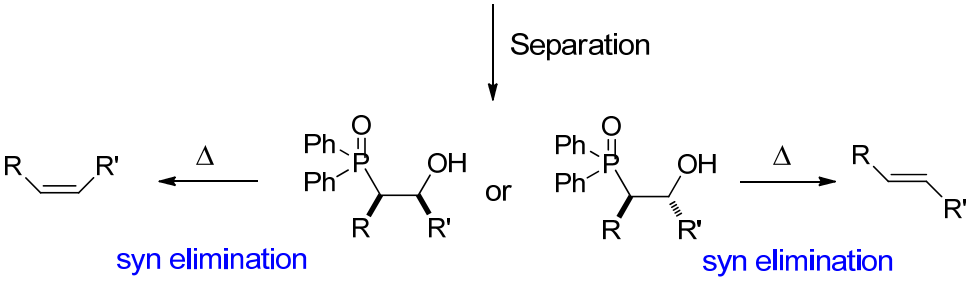


e. Horner - Wittig Reaction

Phosphine oxide carbanion

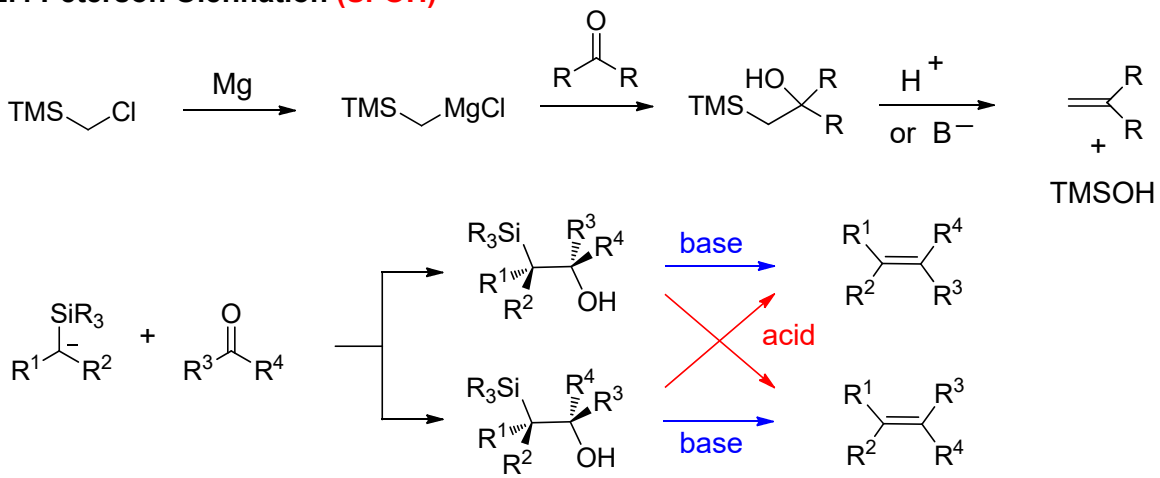


phosphine oxide

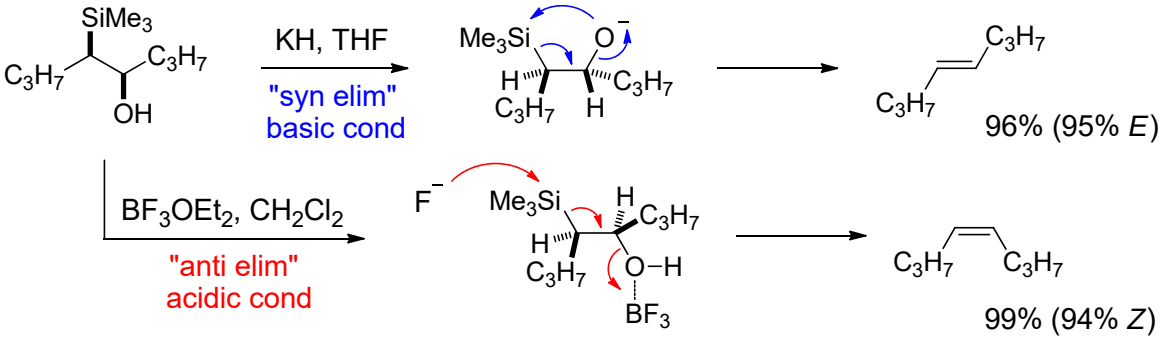


syn elimination　　syn elimination

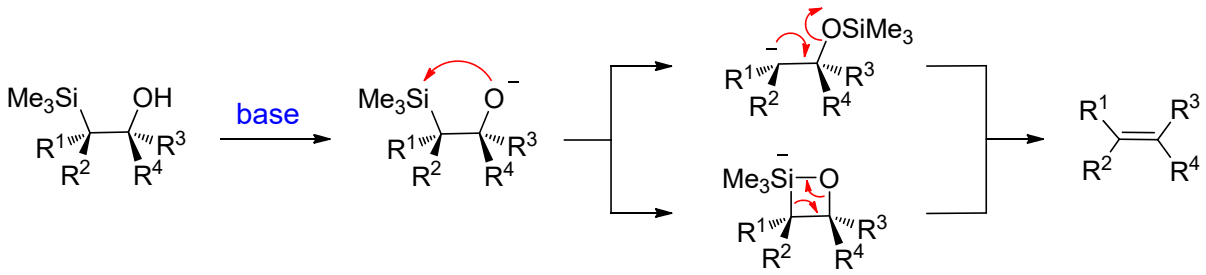
2.4 Peterson Olefination (Si-OH)



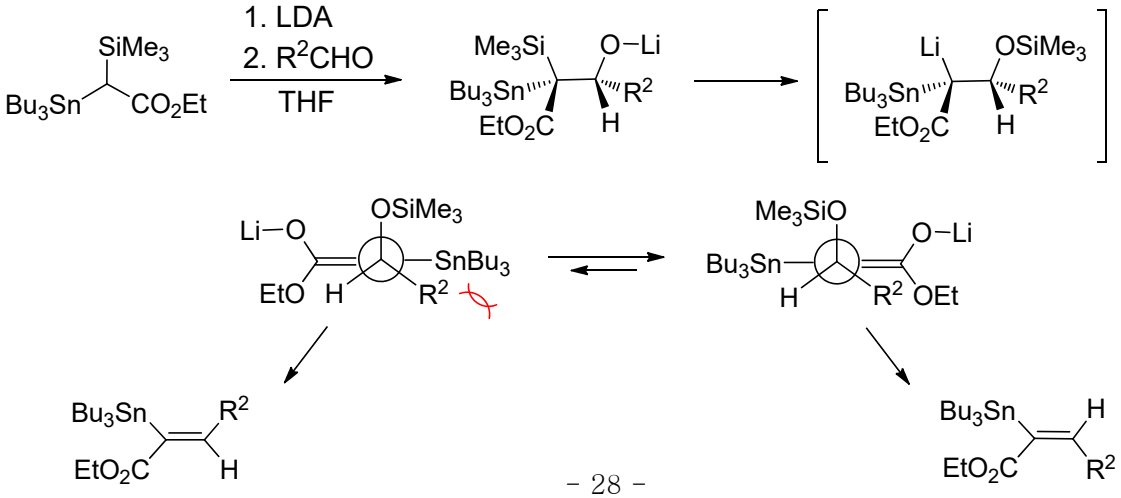
- The addition reaction is generally not stereoselective.
- The elimination is highly stereoselective.



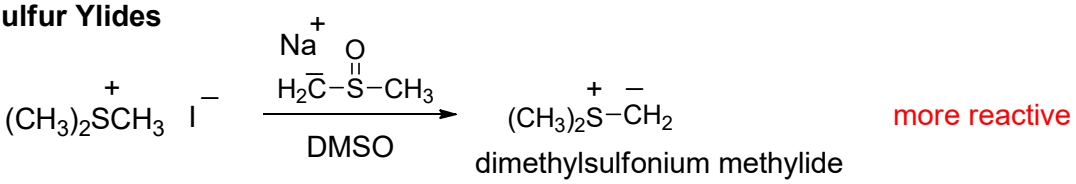
Elimination under basic condition: stepwise vs. concerted mechanism

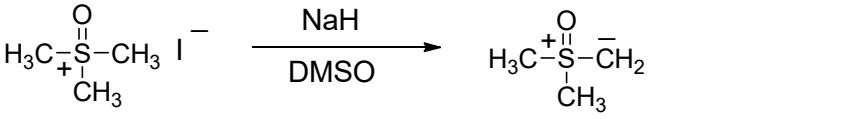


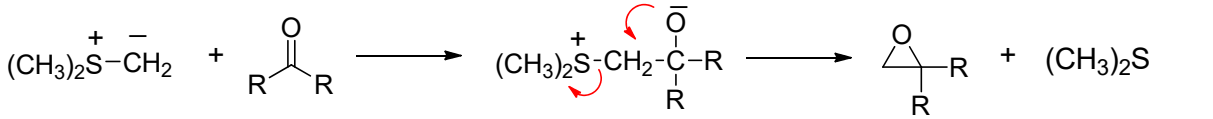
Stepwise mechanism for α-stabilized α-silylcarbanion

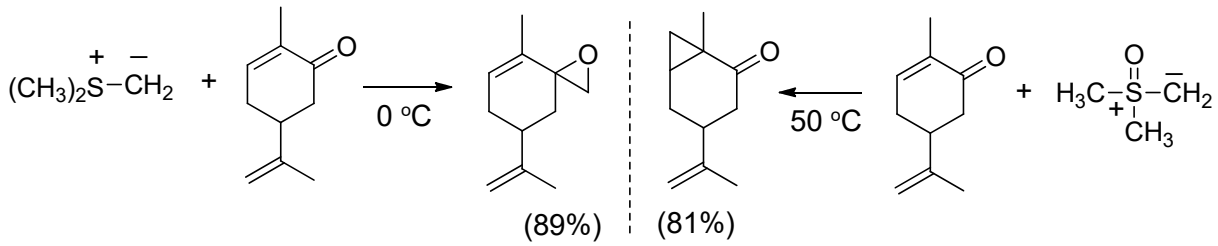


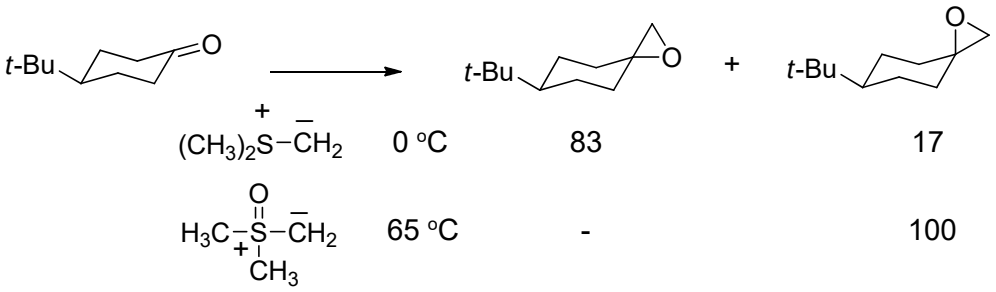
2.5 Sulfur Ylides



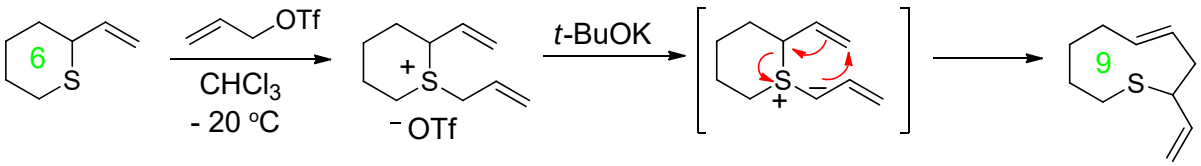


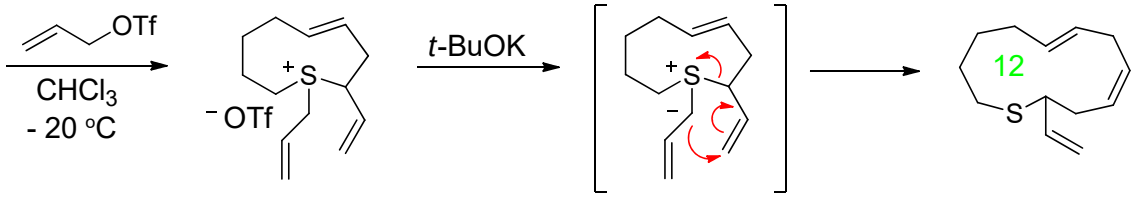






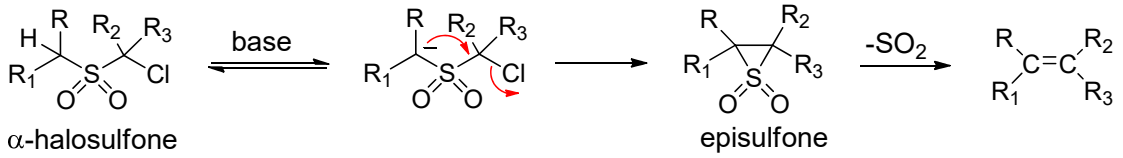
[2.3]-Wittig rearrangement - Ring expansion



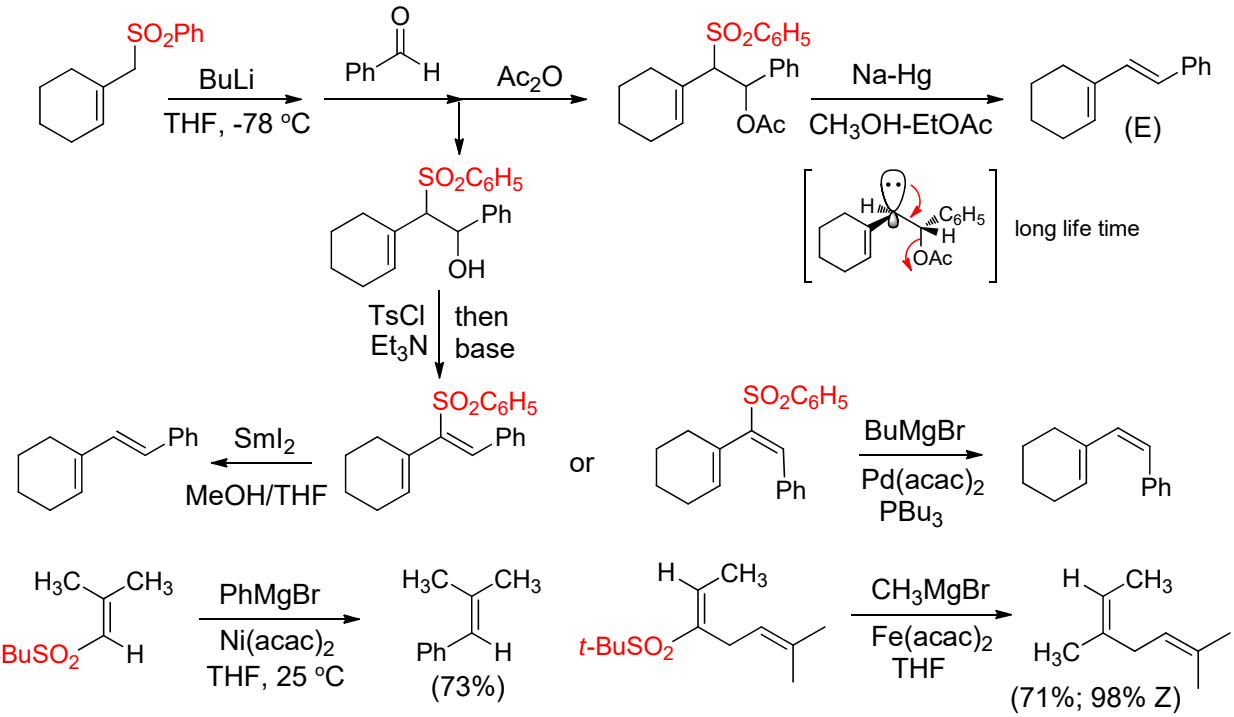


2.6 Alkenes from sulfones

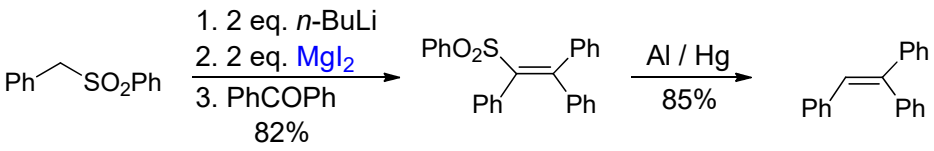
a. Ramberg-Bäcklund reaction



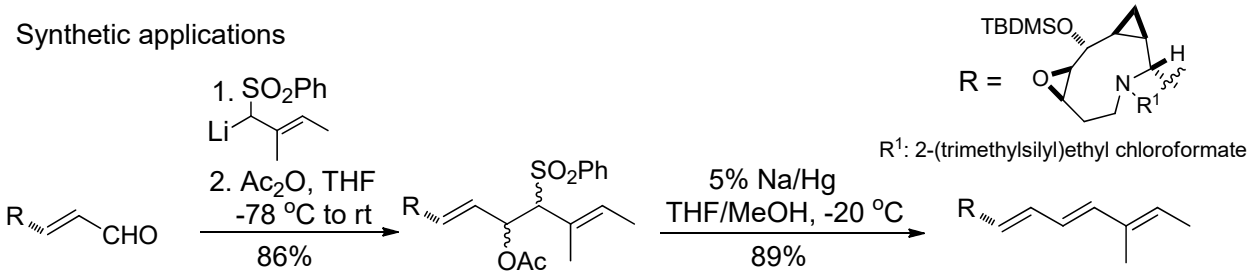
b. Julia olefination

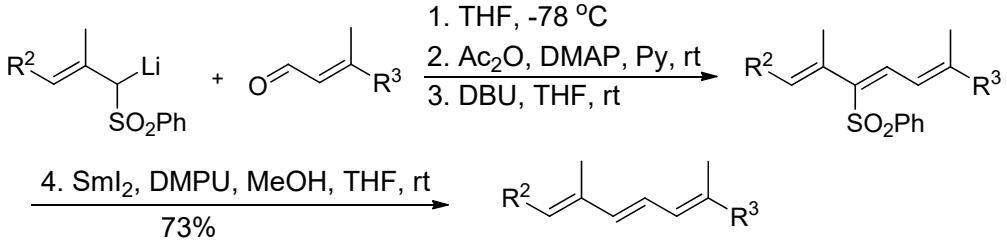


The first report on the sulfone-mediated olefination



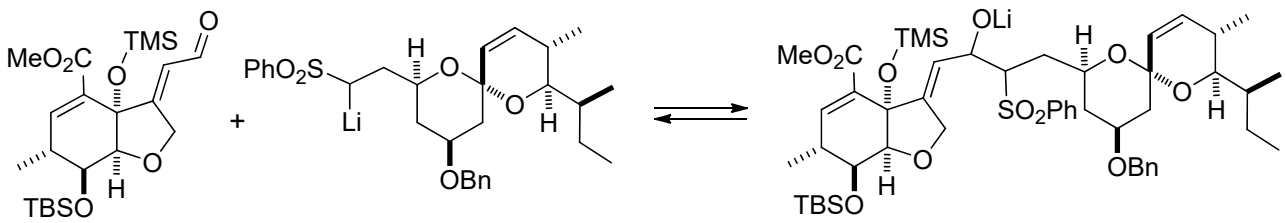
Synthetic applications

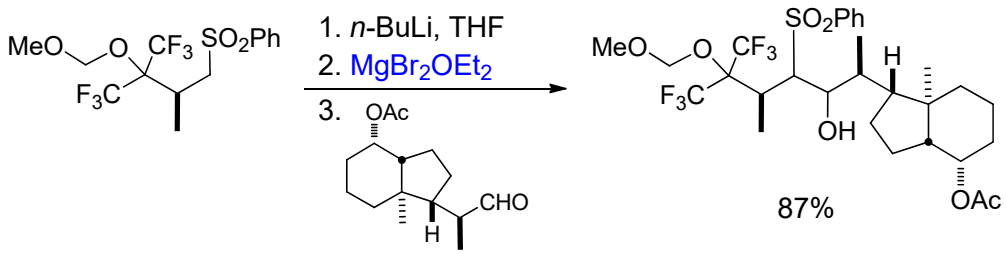


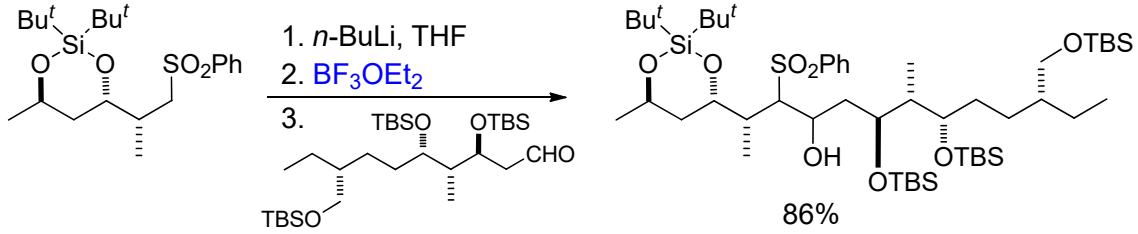


- Sulfone-mediated addition reaction

  Different counter metal ions can shift unfavorable equilibrium toward the addition product
  Replace lithium with magnesium or use BF_3OEt_2

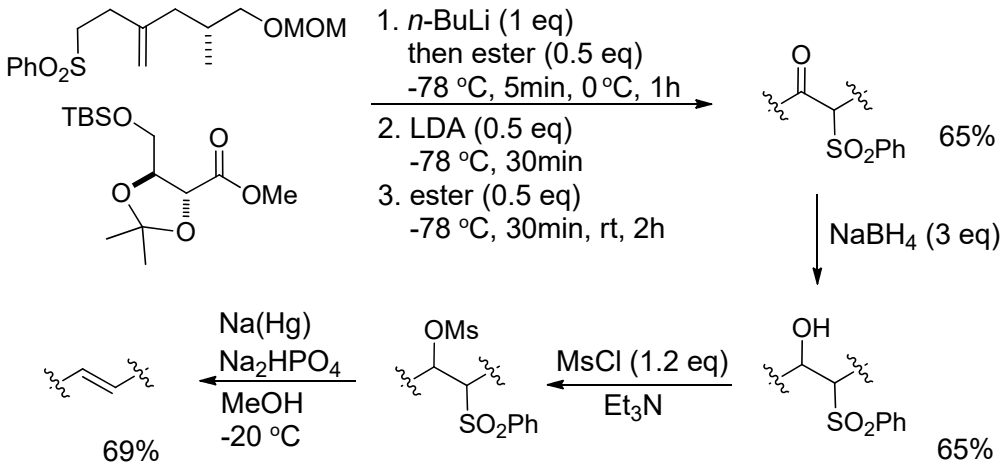






Trapping with Ac_2O, BzCl, MsCl or TMSCl can also shift unfavorable equilibrium toward the addition product

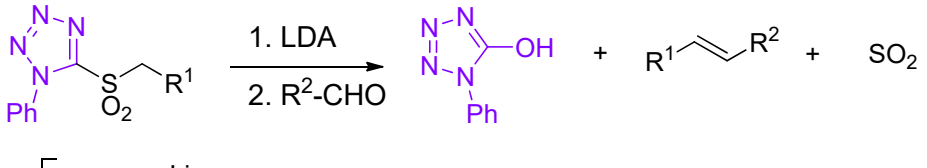
Addition to an ester and reduction of the resulting ketone to β-hydroxysulfone

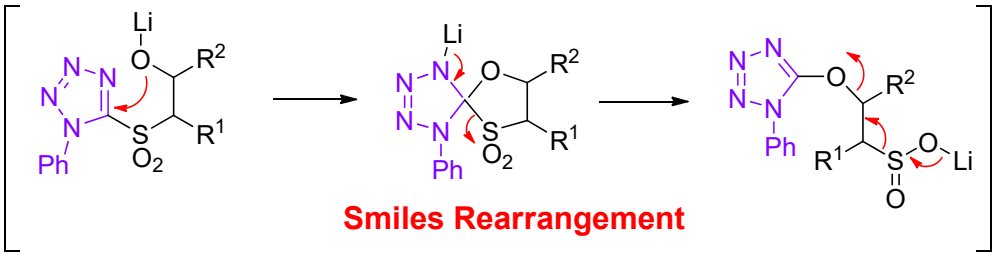


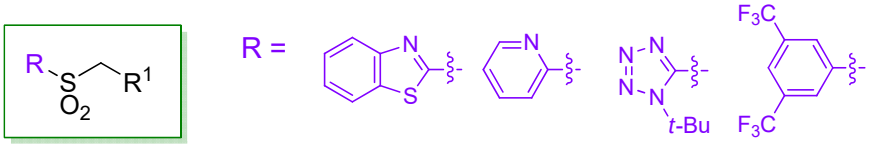
Using DME instead of THF sometimes suppresses the undesirable enolization

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

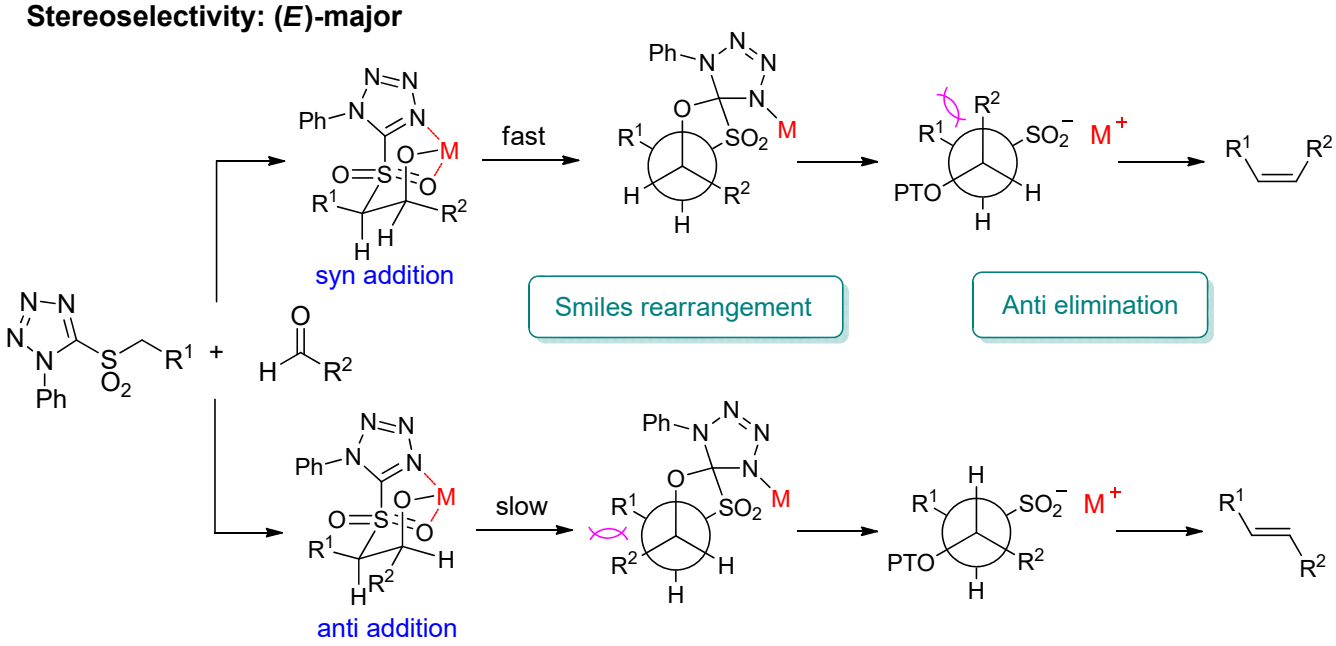
c. Julia-Kocienski olefination

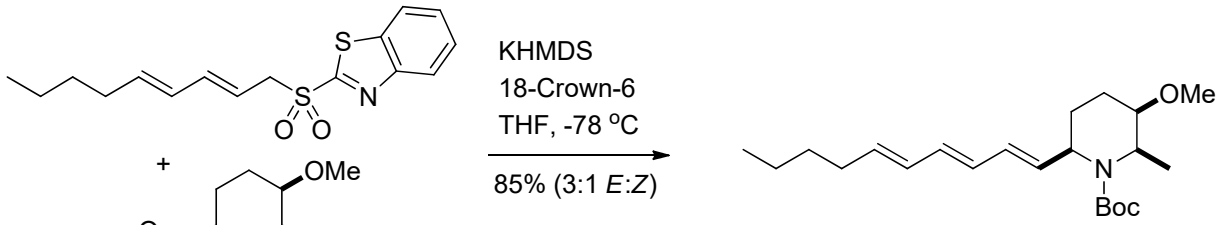


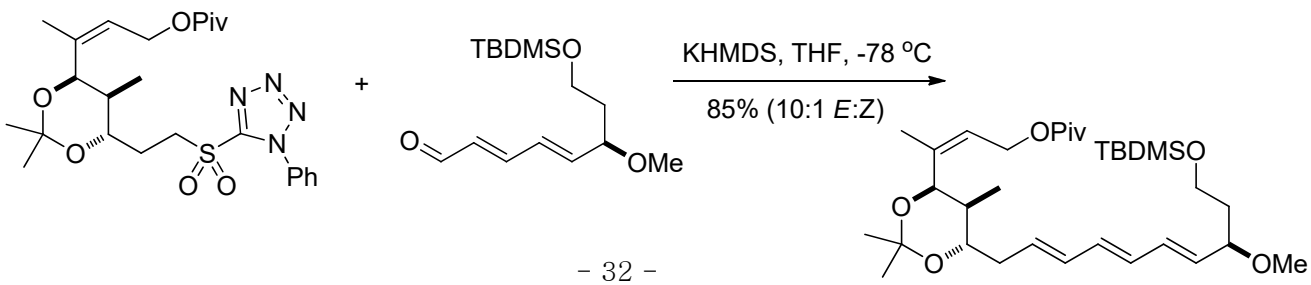




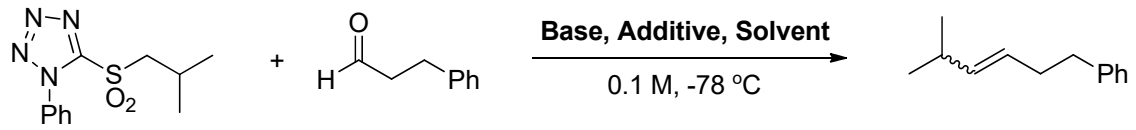
Stereoselectivity: (*E*)-major





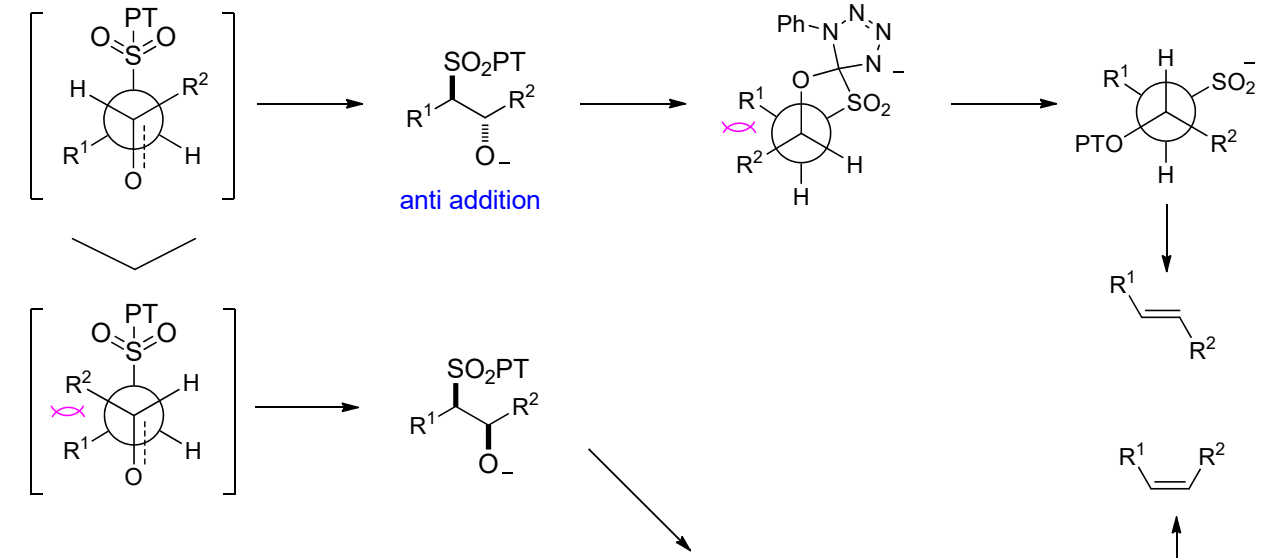


Stereoselectivity

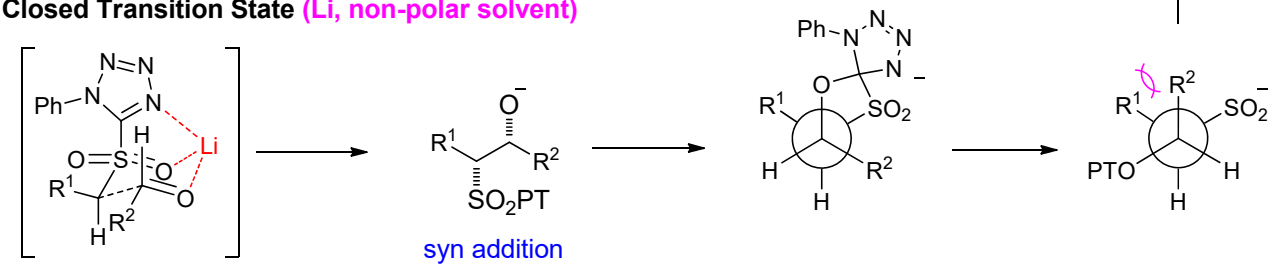


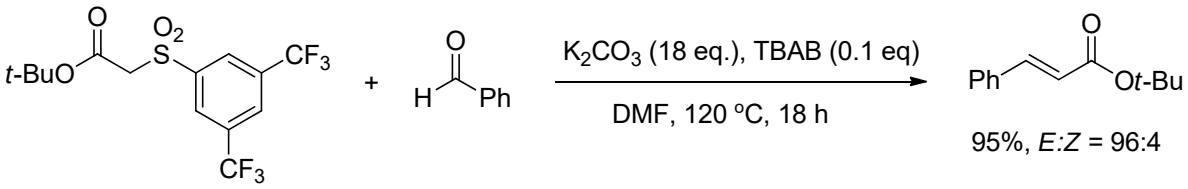
Entry	Base (equiv)	Additive (equiv)	Solvent	Yield	E/Z
1	KHMDS (1.1)		THF	88%	4.3:1
2	KHMDS (1.1)	18-Cr-6 (1.1)	THF	86%	15:1
3	KHMDS (1.1)	18-Cr-6 (2.0)	THF	84%	>50:1
4	KHMDS (1.1)	18-Cr-6 (2.0)	toluene	87%	>50:1
5	KHMDS (1.1)	18-Cr-6 (2.0)	DMF	78%	>50:1
6	NaHMDS (1.1)	18-Cr-6 (2.0)	THF	78%	4:1
7	LiHMDS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

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

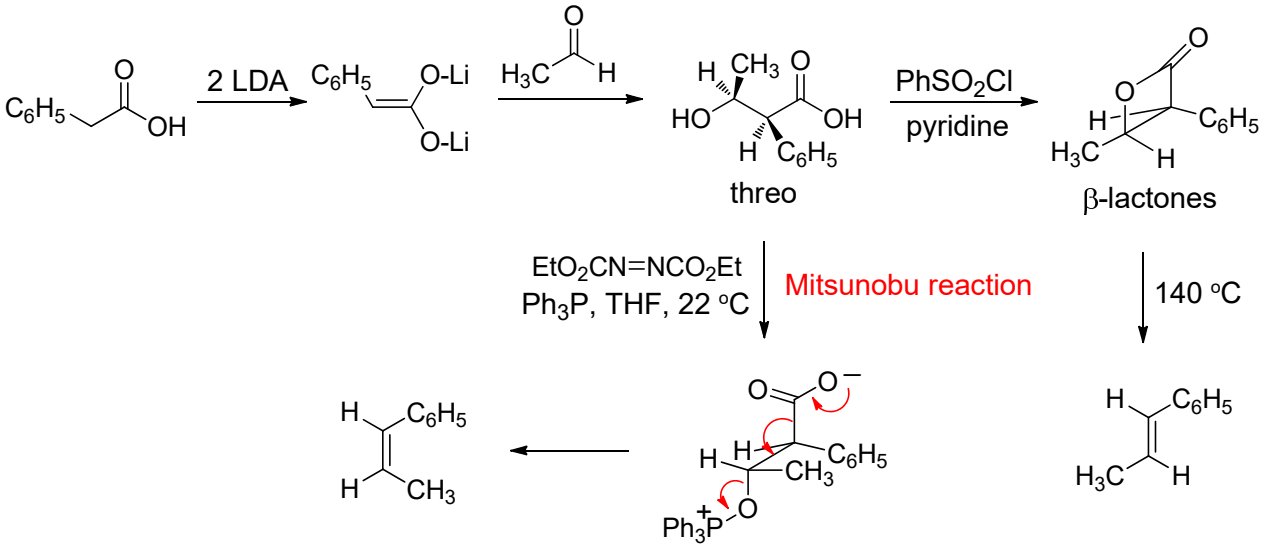


Closed Transition State (Li, non-polar solvent)



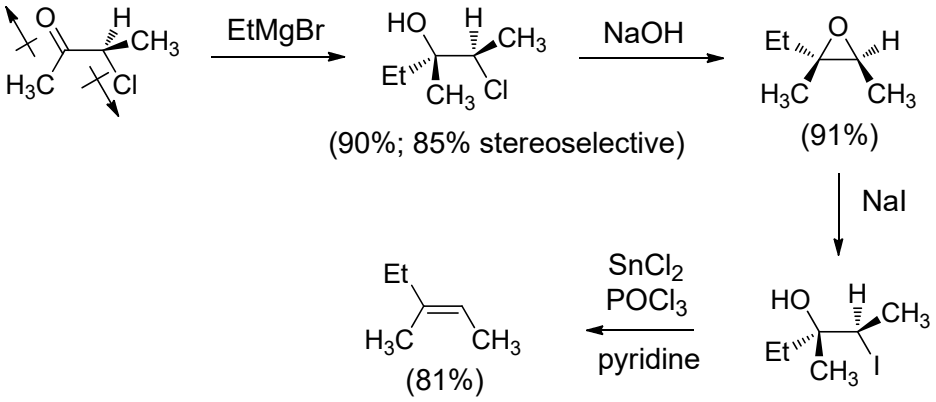


2.7 Decarboxylation of β-lactones

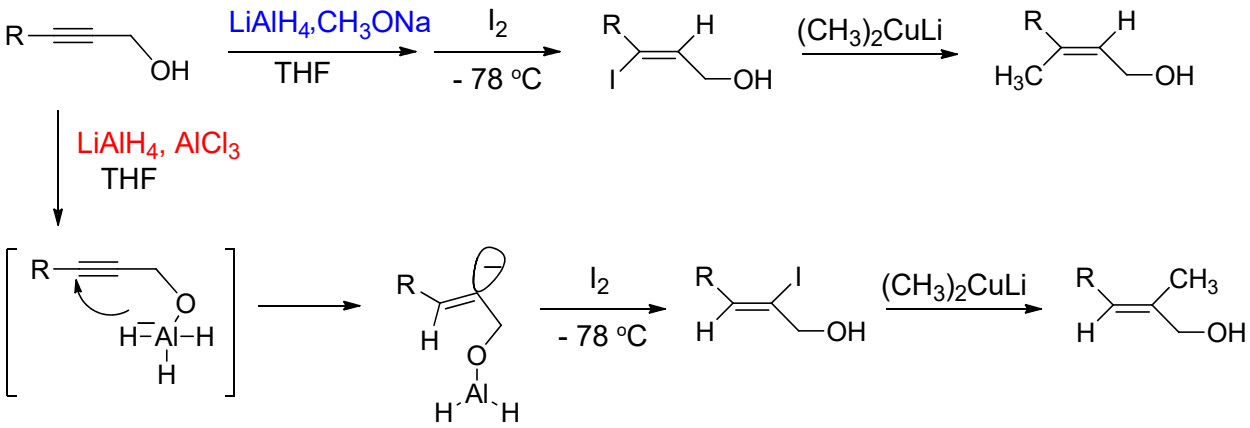


2.8 Stereoselective synthesis of tri- and tetra-substituted alkenes

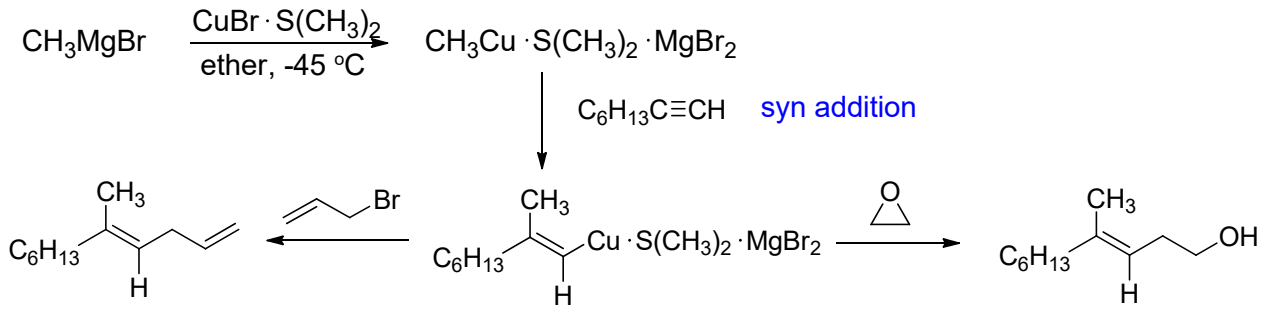
a. Grignard reagent with an α-chloroaldehyde or -ketone

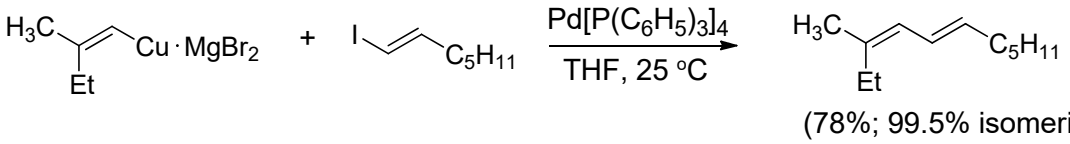


b. Reduction of propargylic alcohol with $LiAlH_4$

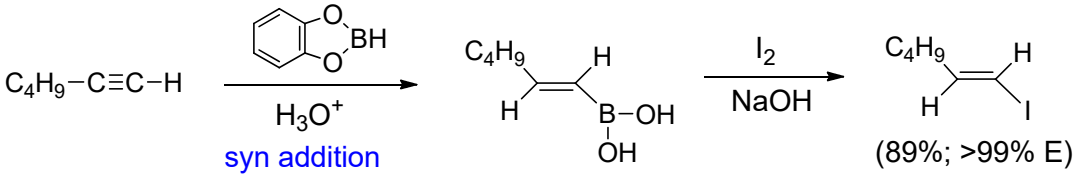


c. Reaction of organocopper or organoborane with alkynes

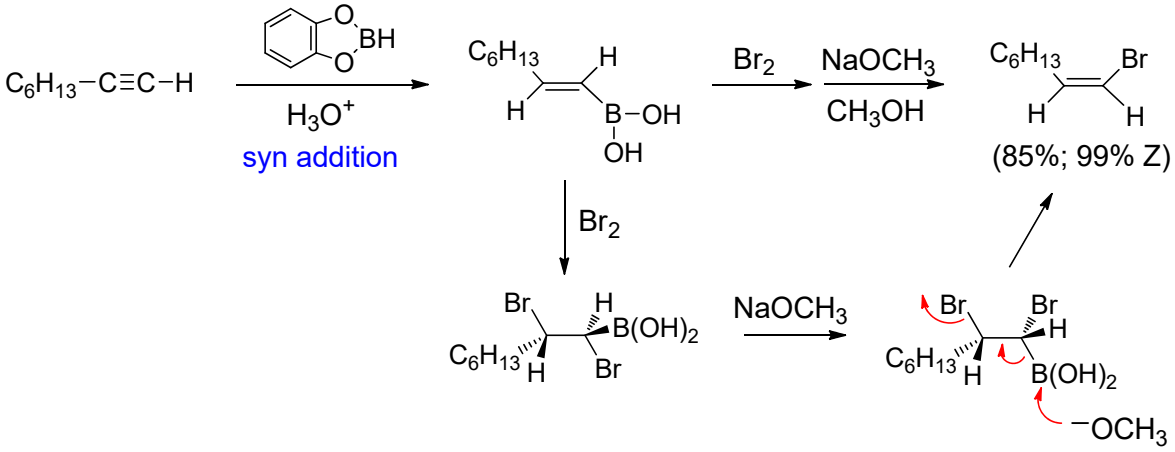




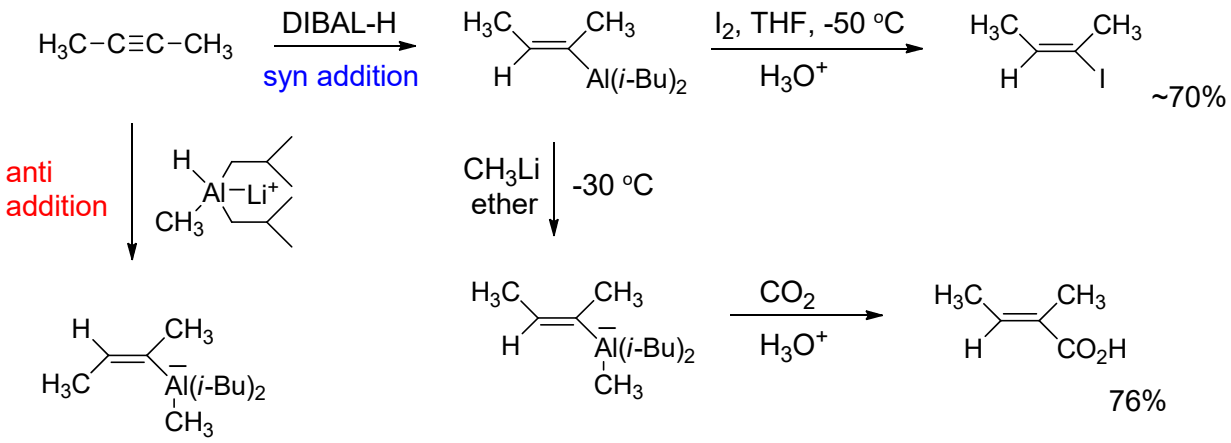
(78%; 99.5% isomeric purity)



(89%; >99% E)

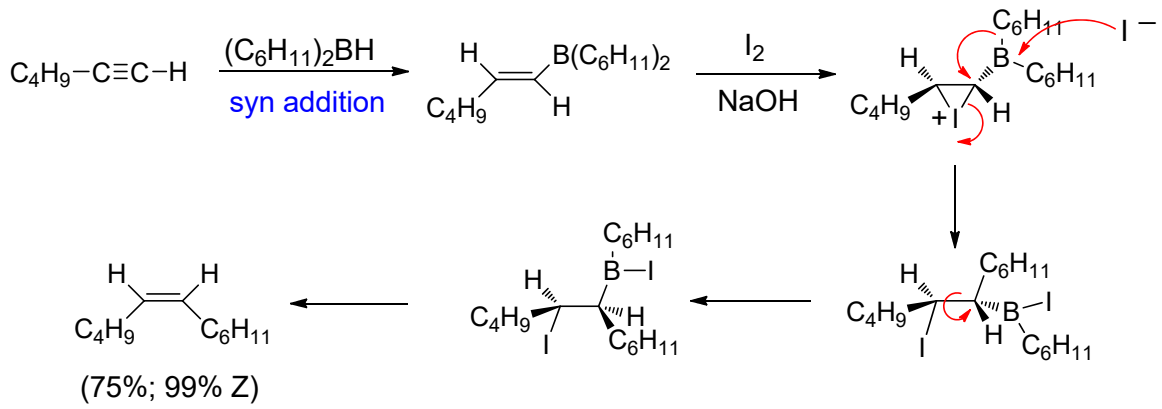


(85%; 99% Z)

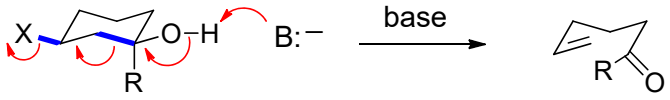


~70%

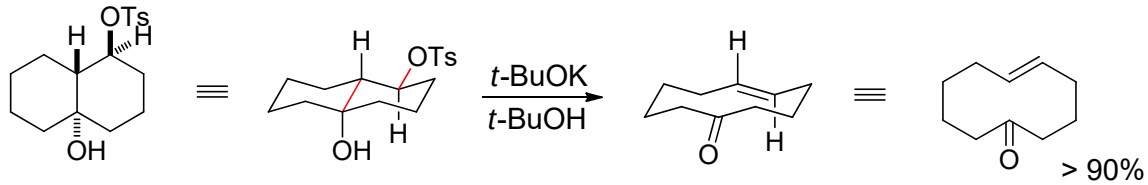
76%

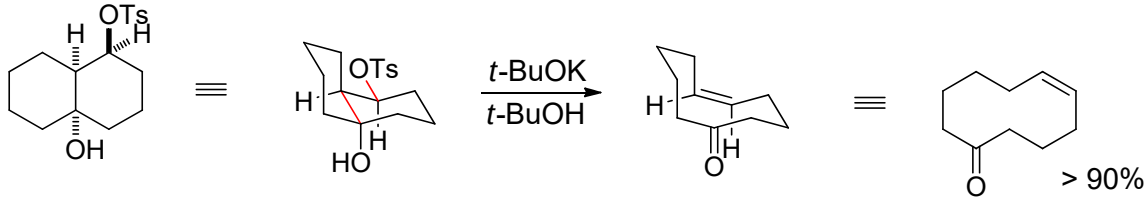


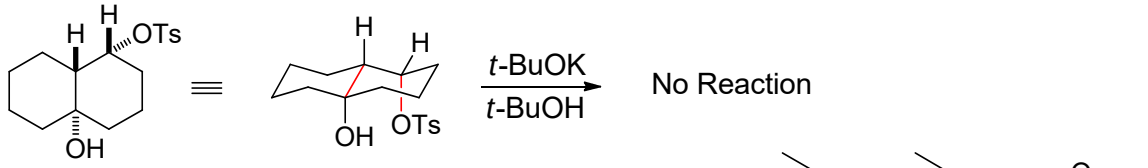
2.9 Fragmentation reactions

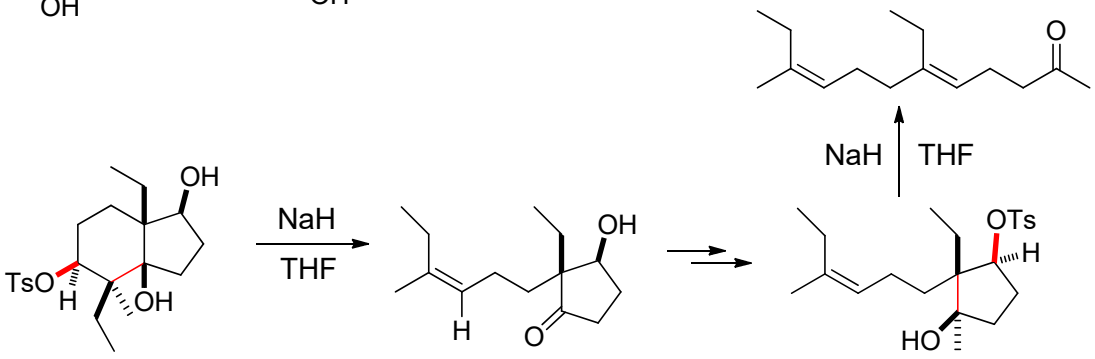


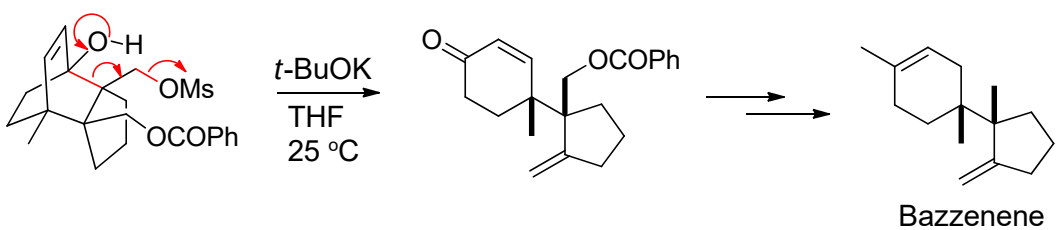
X = OTs, OMs





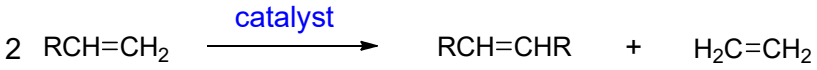






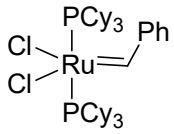
Bazzenene

2.10 Olefin Metathesis



ruthenium or molybdenum alkylidene (carbene) complex

A

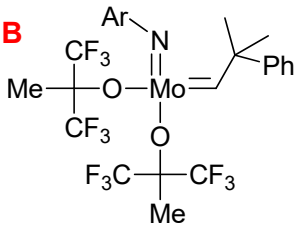


Cy: Cyclohexyl

Grubbs I

(stable but less reactive)

B

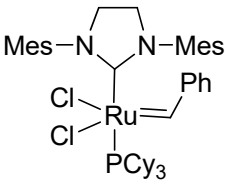


Ar: 2,6-diisopropylphenyl

Schrock

(useful for tri- or tetra-substituted alkenes)

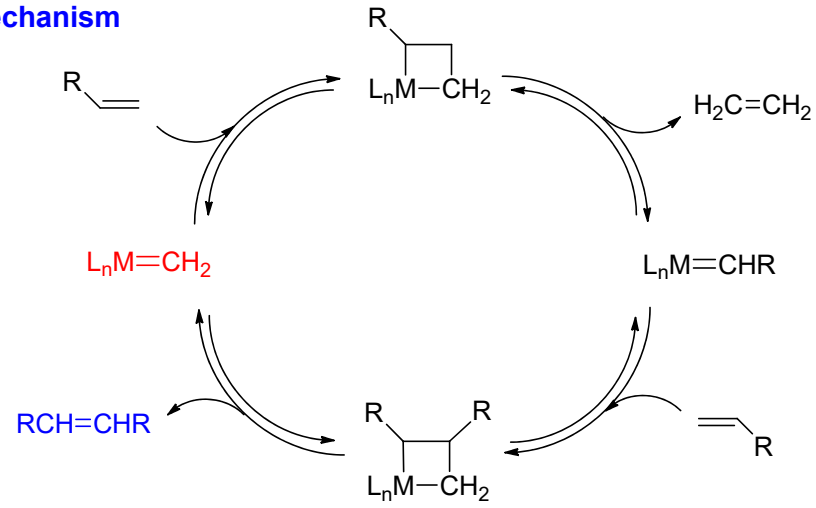
C



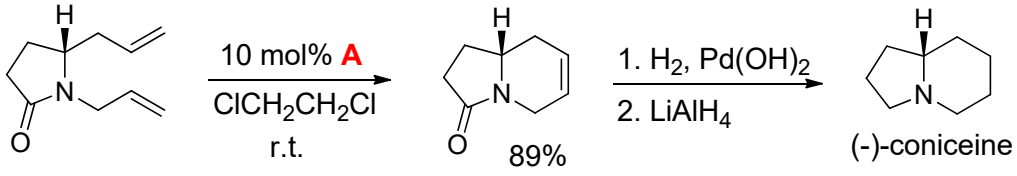
Mes: 2,4,6-trimethylphenyl

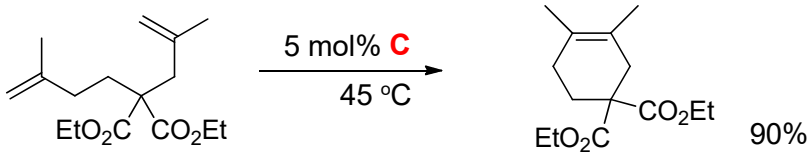
Grubbs II

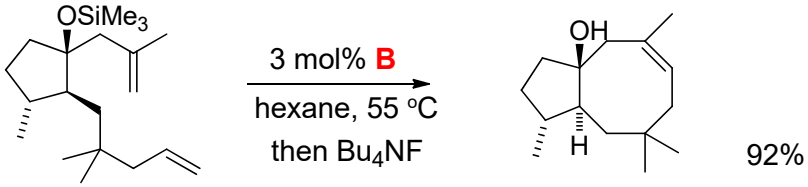
Mechanism



RCM (Ring Closing Metathesis)







1. Lithium in Organic Synthesis

1.1 Nature of Organolithium Compounds

senstive to oxygen and moisture

stable in anhydrous hydrocarbons under a nitrogen or argon atmosphere at ambient temperature

exists as hexamers, tetramers, or dimers

RLi	*In hydrocarbon solv.*	*In ethereal solv.*
MeLi	-	Tetramer
EtLi	Hexamer	Tetramer
n-BuLi	Hexamer	Tetramer
i-BuLi	Tetramer	-
BnLi	Dimer	Monomer
i-PrLi	Tetramer	Dimer
s-BuLi	-	Dimer
PhLi	-	Dimer
t-BuLi	Tetramer	Dimer

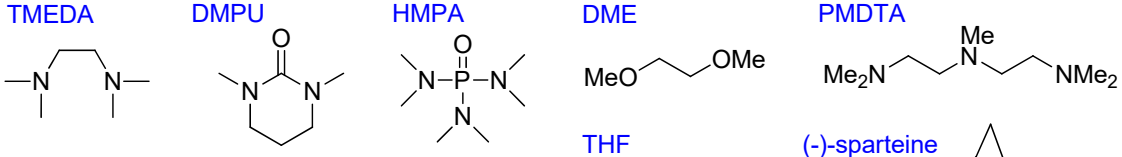
Half-lives of RLi

Temperature (°C)

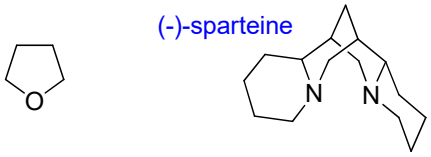
RLi	*Solv.*	-70	-40	-20	0	+20	+35
t-BuLi	DME	11 m					
	THF		5.6 h	42 m			
	ether			8 h	1 h		
s-BuLi	DME	2 h	2 m				
	THF			1.3 h			
	ether			20 h	2.3 h		
n-BuLi	DME			1.8 h	<5 m		
	THF				17 h	1.8 h	10 m
	ether					153 h	31 h
PhLi	ether						12 d
MeLi	ether					3 mon	

The following coordinating solvents increase the reactivity of organolithium by reducing the extent of aggregation

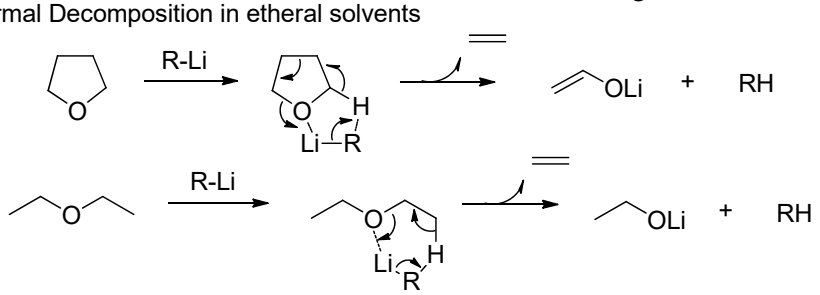
TMEDA DMPU HMPA DME PMDTA



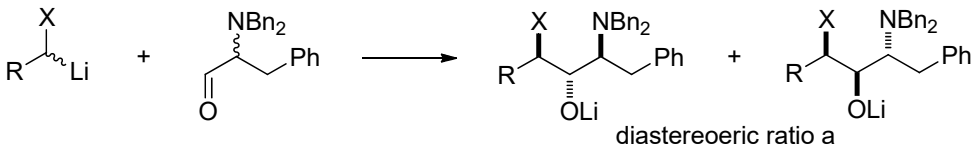
THF (-)-sparteine



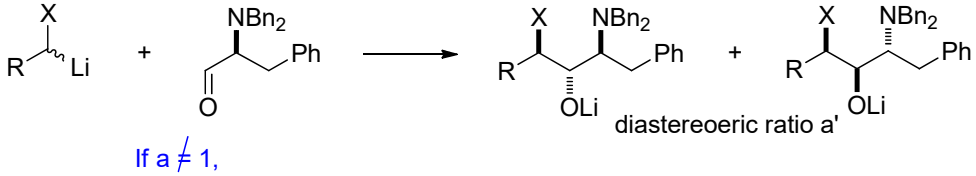
Thermal Decomposition in etheral solvents



Configurational Stability - The Hoffmann test



diastereoeric ratio a



diastereoeric ratio a'

If a ≠ 1,

If a' = a, then the organolithium compund is configurationally unstable

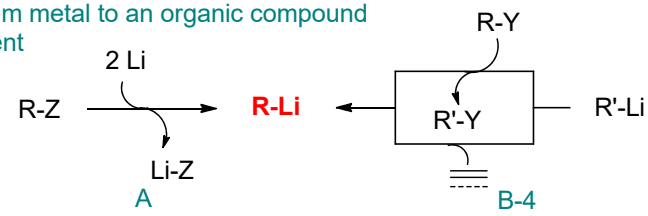
If a' ≠ a, then the organolithium compund is configurationally stable

1.2 Methods for the Preparation of Organolithium Compounds

Overview

A. de novo synthesis: reductive insertion of lithium metal to an organic compound
B. preparation from another organolithium reagent
1. deprotonation
2. lithium-halogen exchange
3. transmetallation
4. carbolithiation

B-1: Y = H
B-2: Y = halogen
B-3: other metal



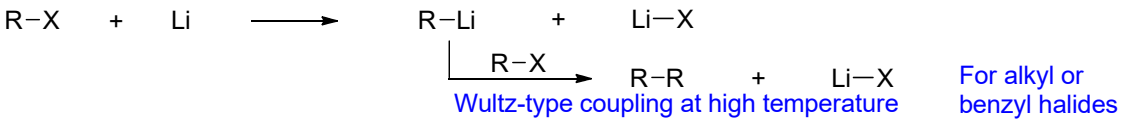
1.2.1 Reductive Lithiation using Lithium Metal

preparation of simple, unfunctionalized organolithium compounds at ambient temperature or above

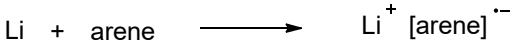
the order of reactivity: radical formation is the rate determining step

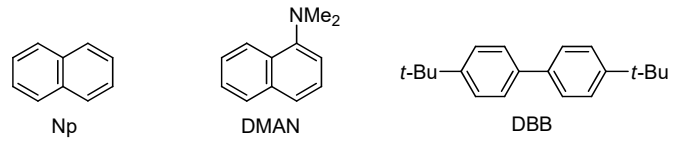
Alkyl-Li

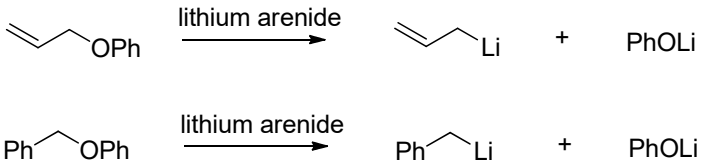
tert- > sec- > pri- > vinyl-Li > aryl-Li

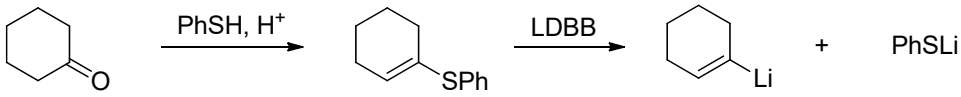


Use lithium arenides: the homogeneous solution lowers the reaction temeperature therby reduce the side reaction product









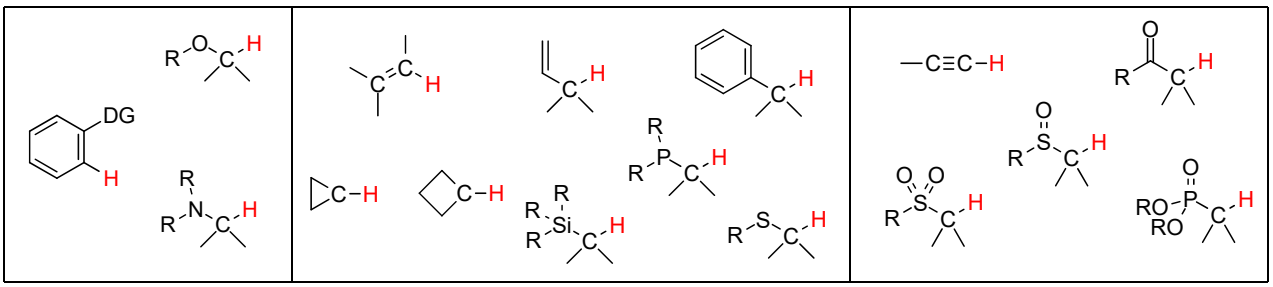
1.2.2 Preparation from Another Organolithium Compounds

1.2.2.1 Deprotonation (to form more stable C-Li bond)

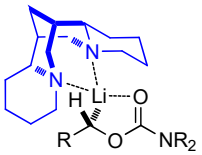
deprotonation of a C-H bond without sufficient acidity is facilitated by the introduction of heteroatom functionality at a neighboring position.

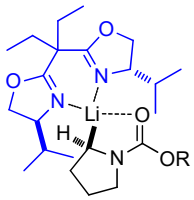
n-BuLi, *s*-BuLi, *t*-BuLi, LDA, LTMP

easier deprotonation



Enantioselective alkyllithium reagent by use of (-)-sparteine or (s,s)-bis(oxazoline)

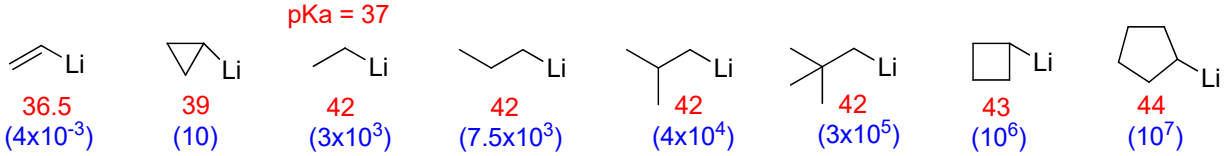




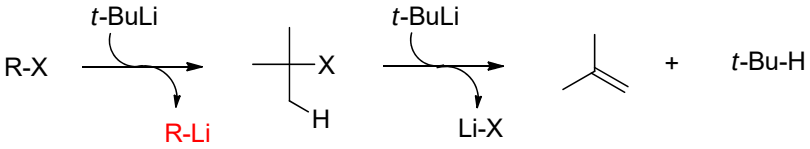
1.2.2 Preparation from Another Organolithium Compounds

1.2.2.2 Halogen-Lithium Exchange - equilibrium process

Synthetically useful for the preparation of aryllithium or vinyllithium



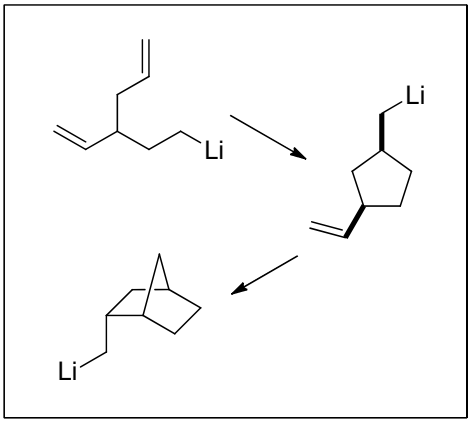
Use of 2 equiv of *t*-BuLi



The rate of halogen-lithium exchange

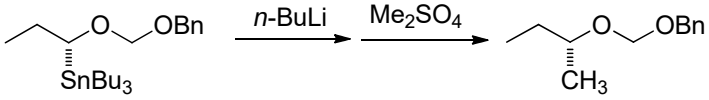
R-I > R-Br > R-Cl >> R-F

Accelerated by the presence of ethereal solvents



1.2.2.3 Transmetallation B, Si, Sn, Pb, and Hg

tin-lithium exchange



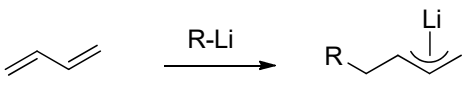
1.2.2.4 Carbolithiation

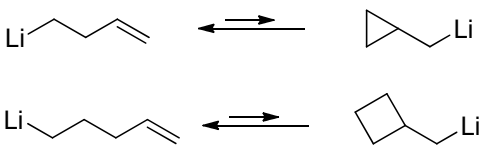
Addition of an organolithium to an unactivated, non-polarized alkene - new organolithium compounds

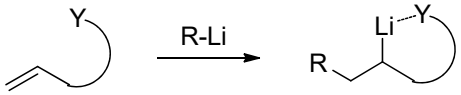
Rate $3^o > 2^o > 1^o$ organolithium

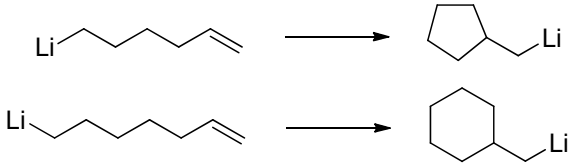
Equilibrium process: more stable organolithium compound can be formed

Activation by TMEDA, DABCO, or (-)-sparteine is advantageous





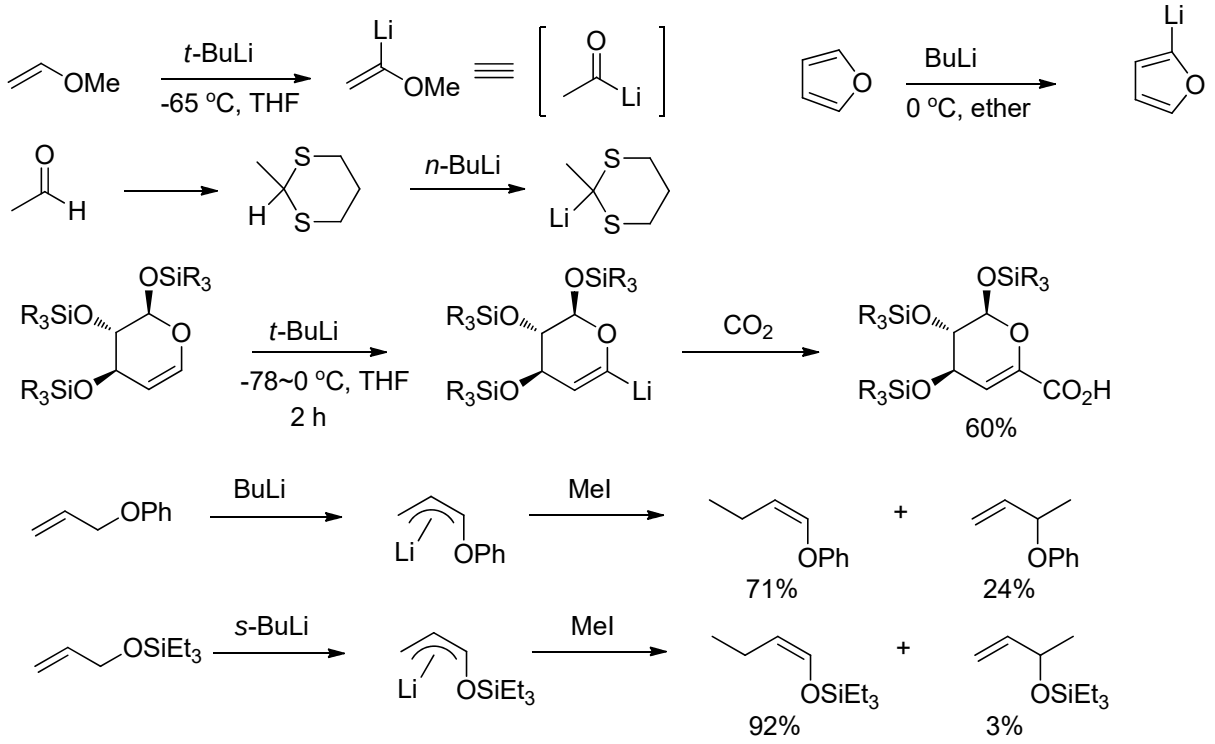




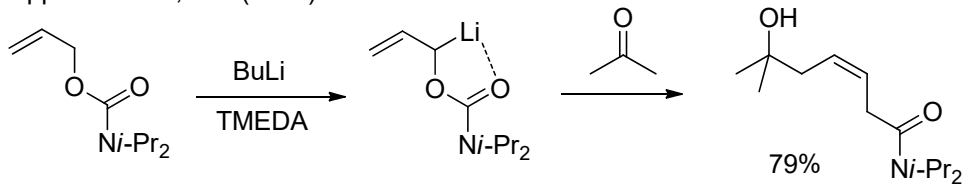
1.3. Examples of Lithiation

1.3.1. **Lithiation by Deprotonation**

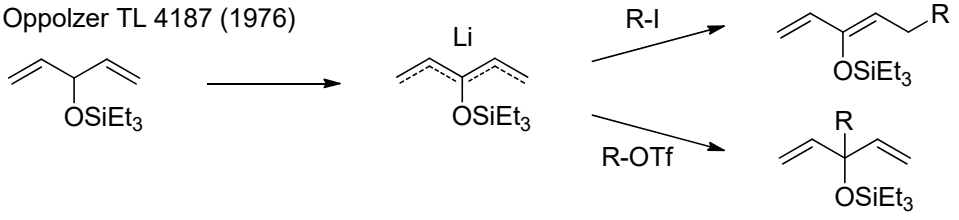
1.3.1.1. Formation of vinylic, allylic or benzylic organolithiums alpha to oxygen

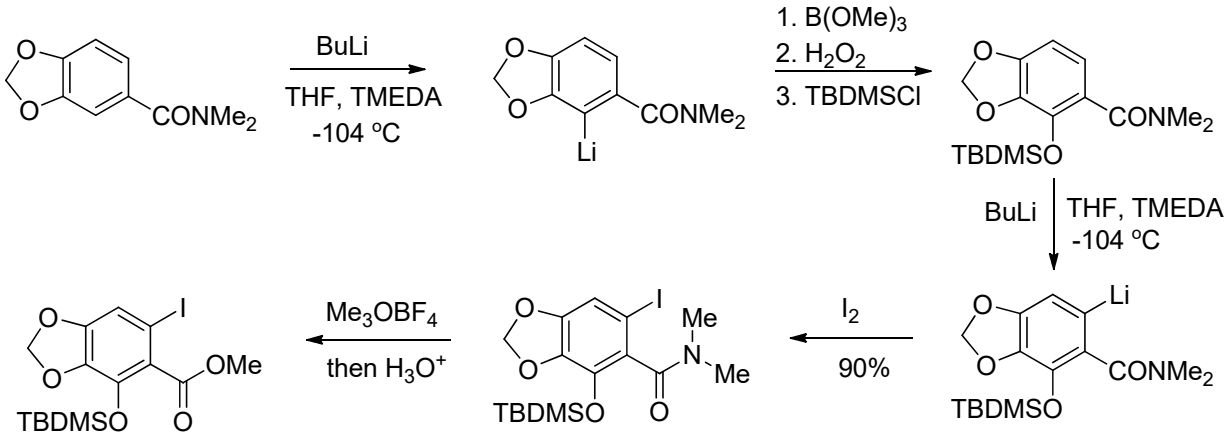


Hoppe ACIE **23**, 932 (1984)



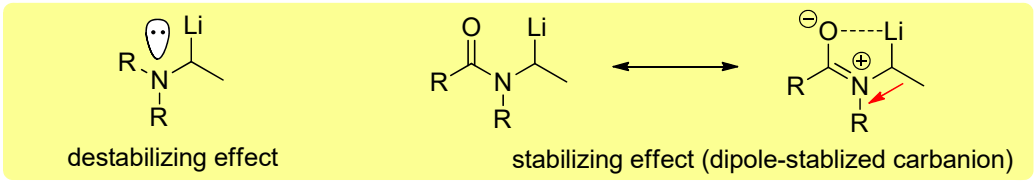
Oppolzer TL 4187 (1976)

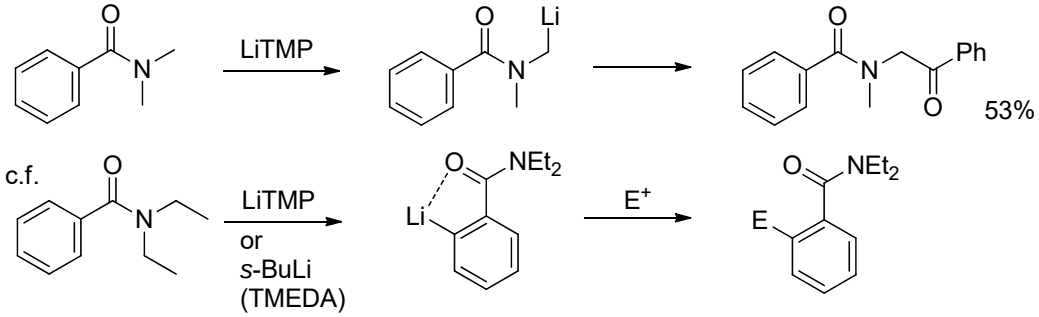




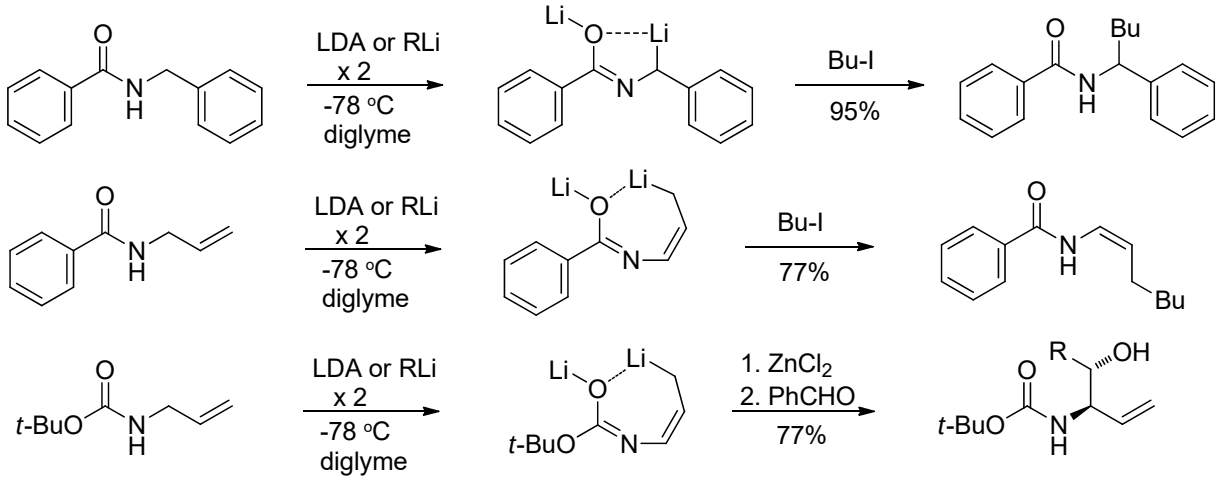
1.3.1. **Lithiation by Deprotonation**

1.3.1.2. Lithiation alpha to nitrogen

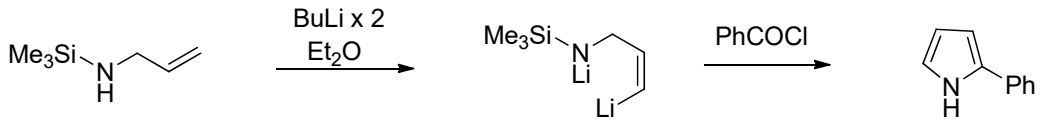


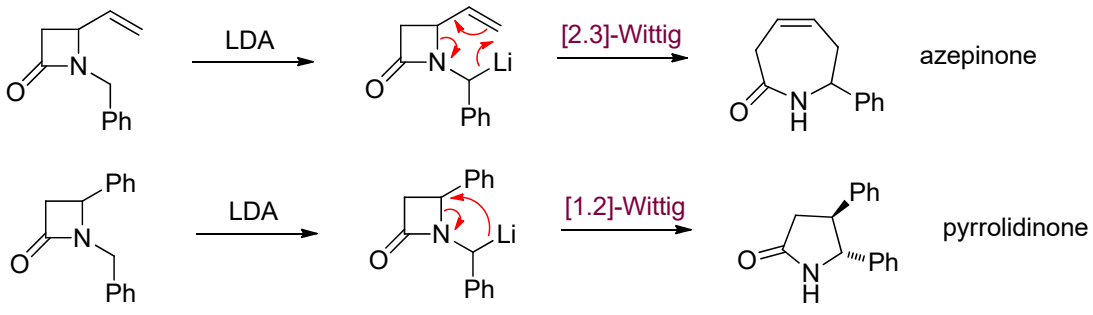


N-benzyl or *N*-allyl amide



c.f.

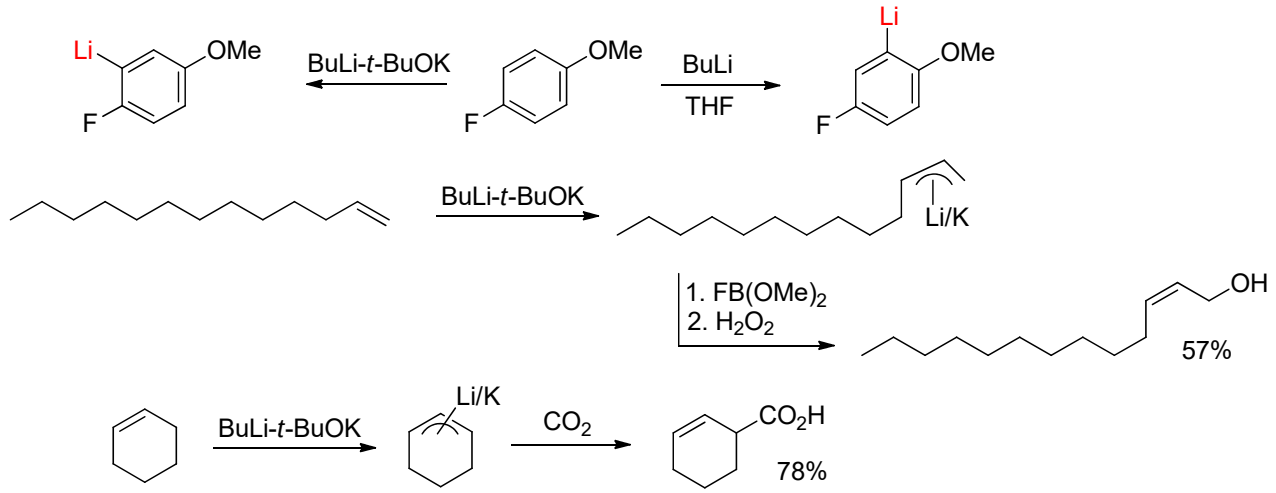




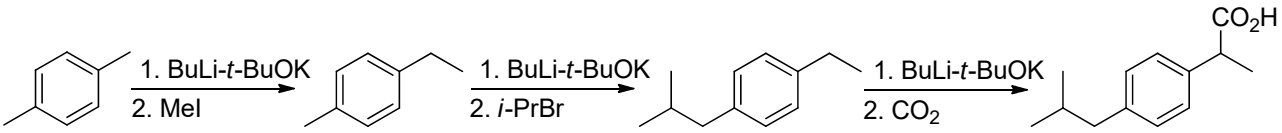
1.3.1. **Lithiation by Deprotonation**

1.3.1.3. Super Base (BuLi + KO*t*-Bu)

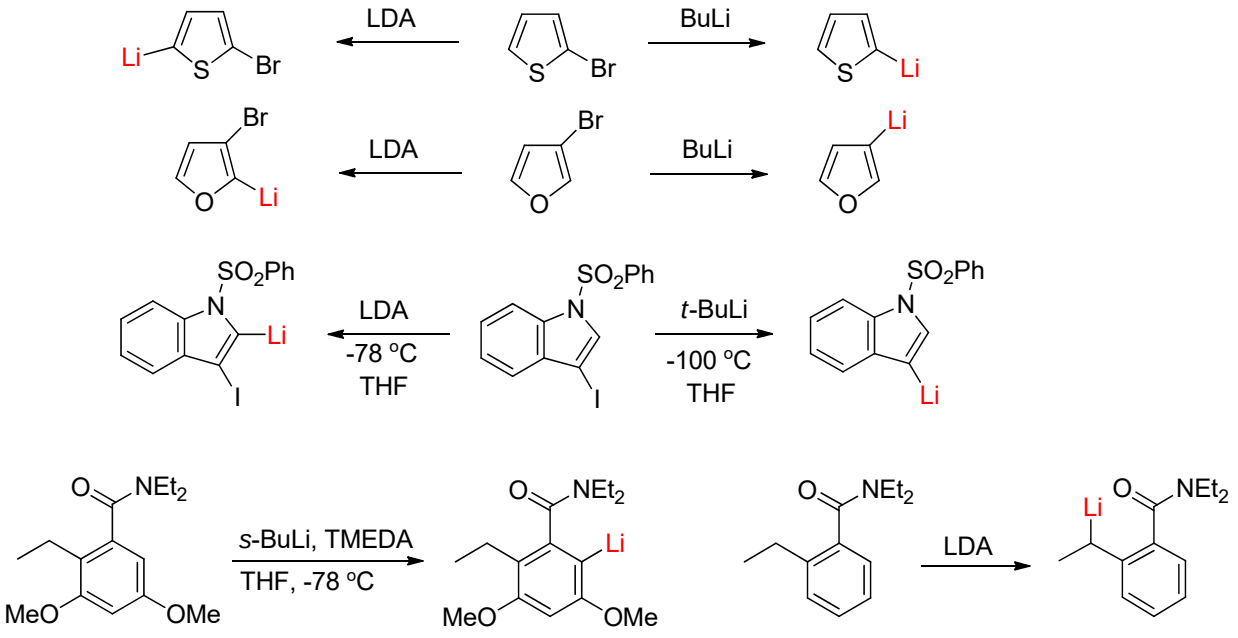
Deprotonate Allylic, Benzylic, Vinylic, Aromatic and Cycloprpane C-H with no Additional Assistance
Remove the Most Acidic Protone



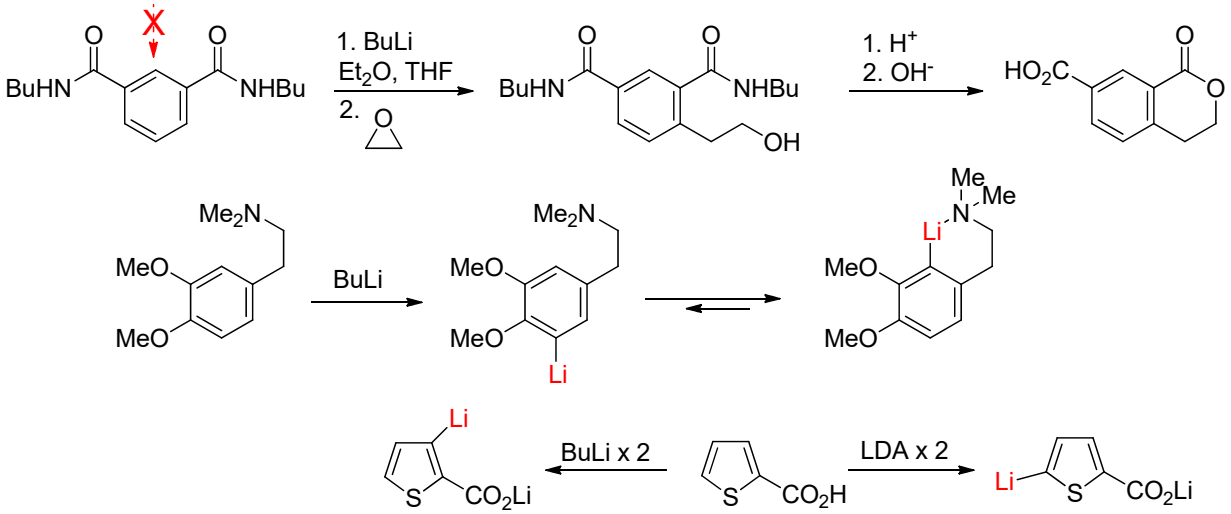
Ibuprofen Synthesis by Schlosser

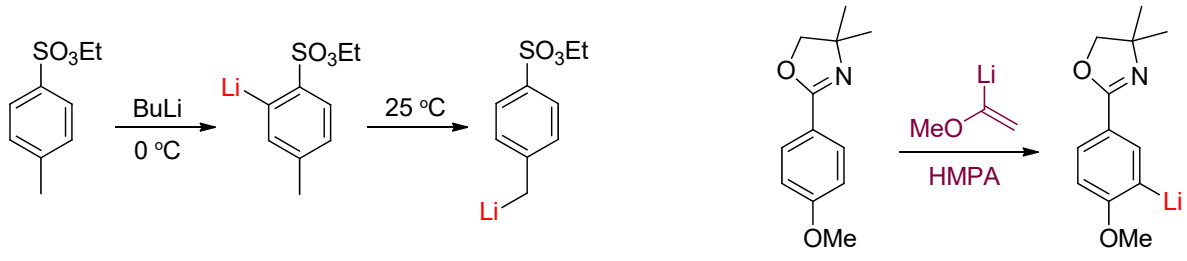


1.3.2. Ortholithiation vs. Halogen-metal exchange

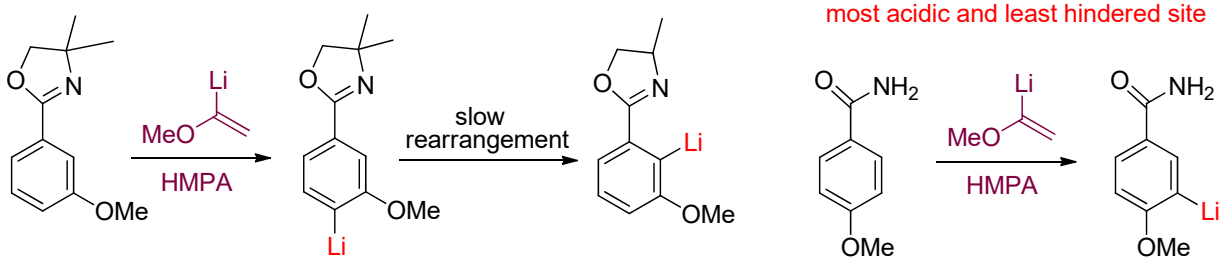


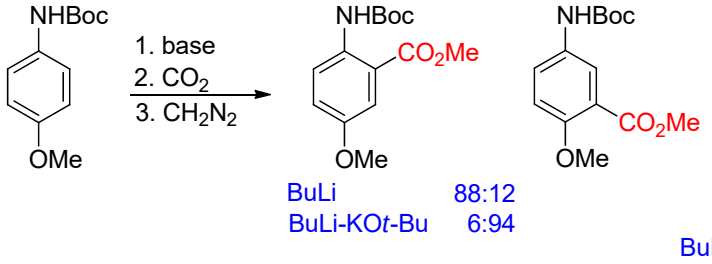
1.3.3. **Cooperation, competetion, and regioselectivity** in **Lithiation by Deprotonation**





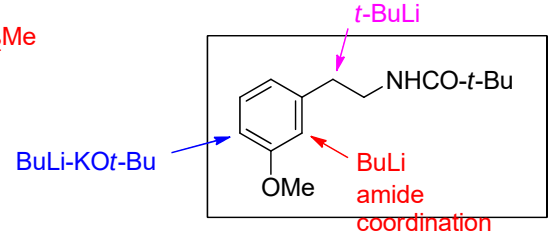
most acidic and least hindered site

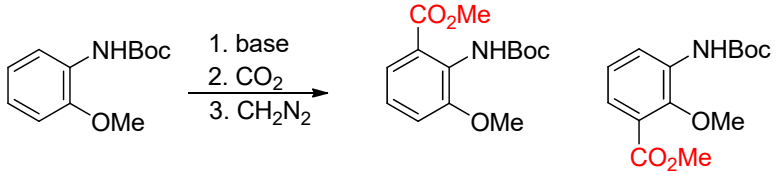




BuLi 88:12
BuLi-KO*t*-Bu 6:94

Steric hindrance control



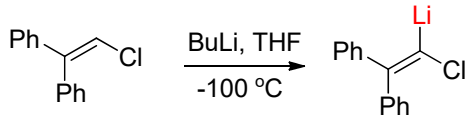


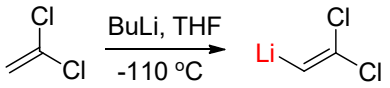
65% with BuLi

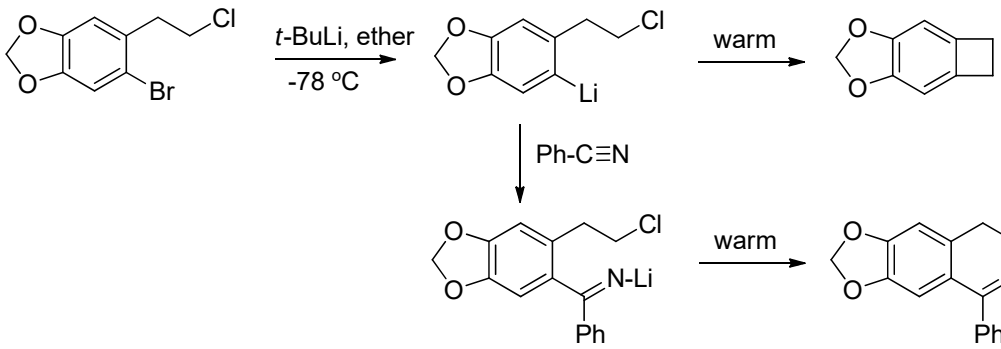
78% with BuLi-KO*t*-Bu

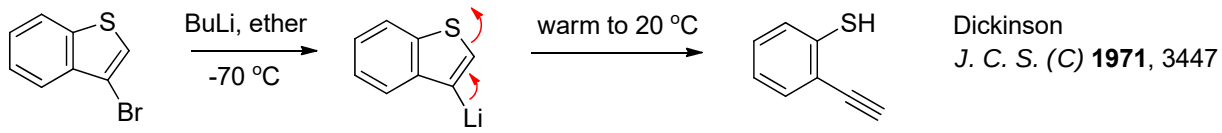
1.3.4. **Lithiation by X-Li Exchange**

Ar-Cl and Ar-F are not synthetically useful for exchange reaction,
and tend to undergo deprotonation, leading to benzyne

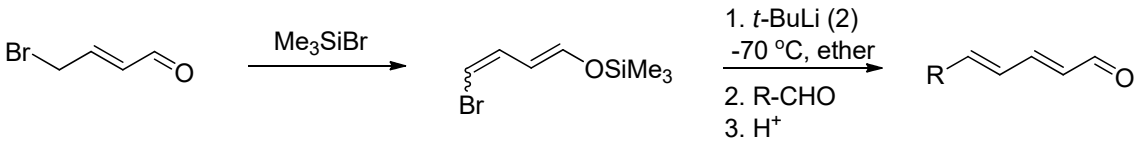




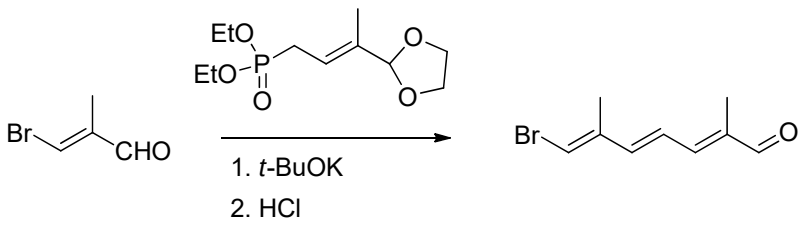


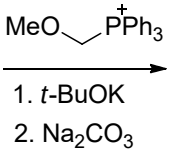


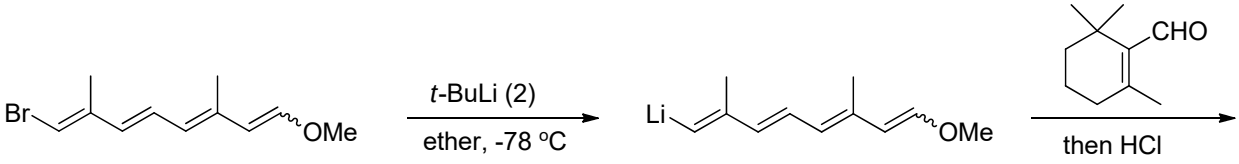
Dickinson
J. C. S. (C) **1971**, 3447

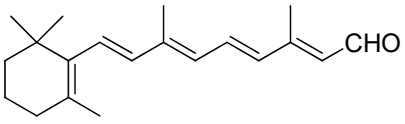


Retinal Synthesis



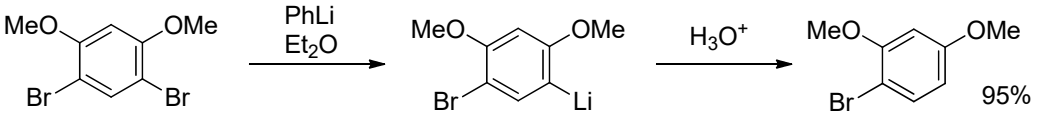




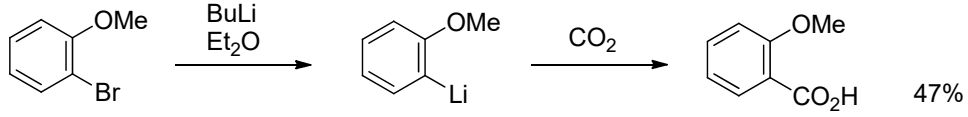


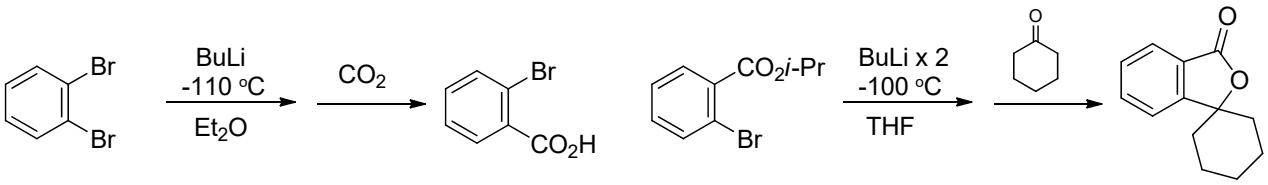
1.3.4. Examples of Lithiantion by **X-Li Exchange**

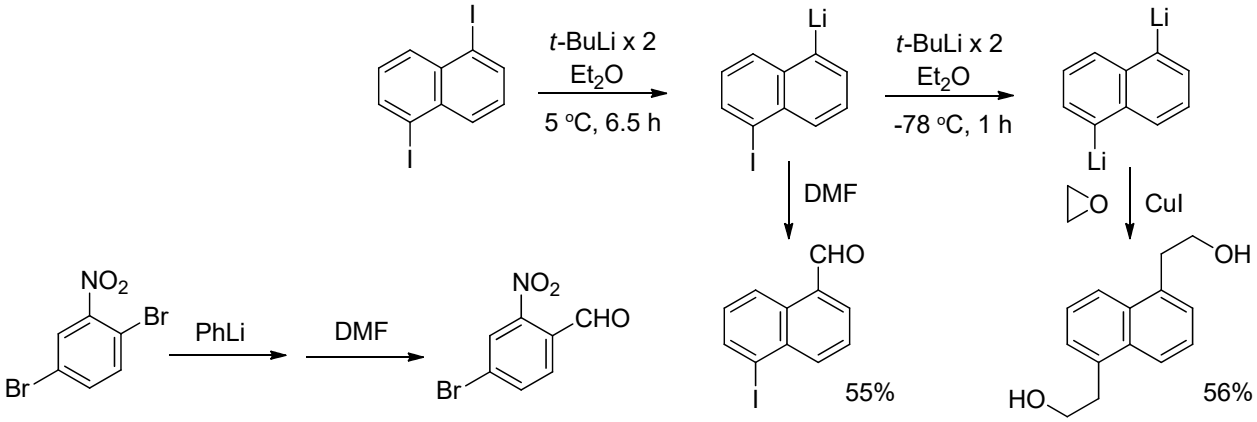
Wittig Chem. Ber. **71**, 1903 (1938)

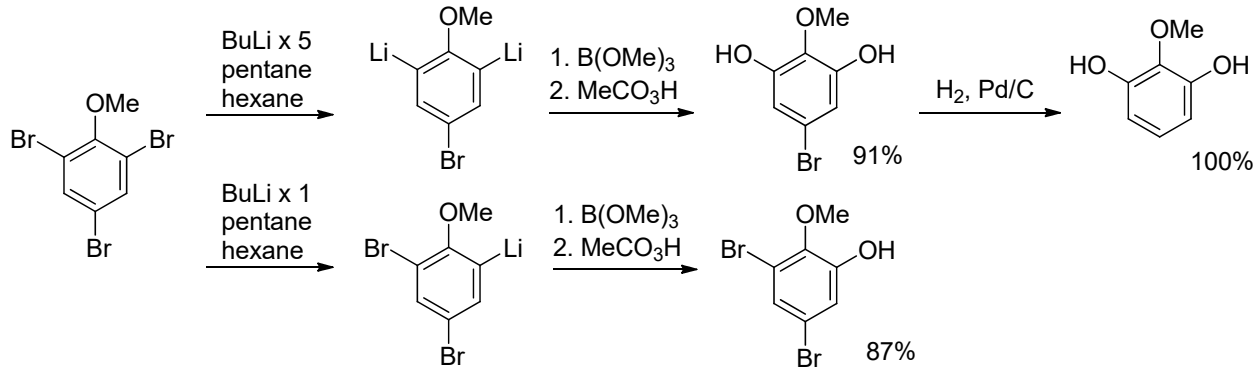


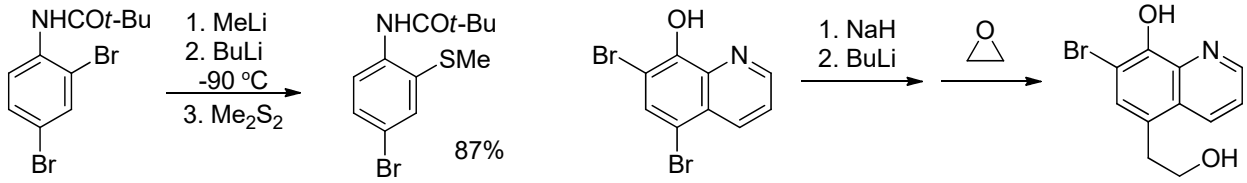
Gilman J. Am. Chem. Soc. **61**, 106 (1939)



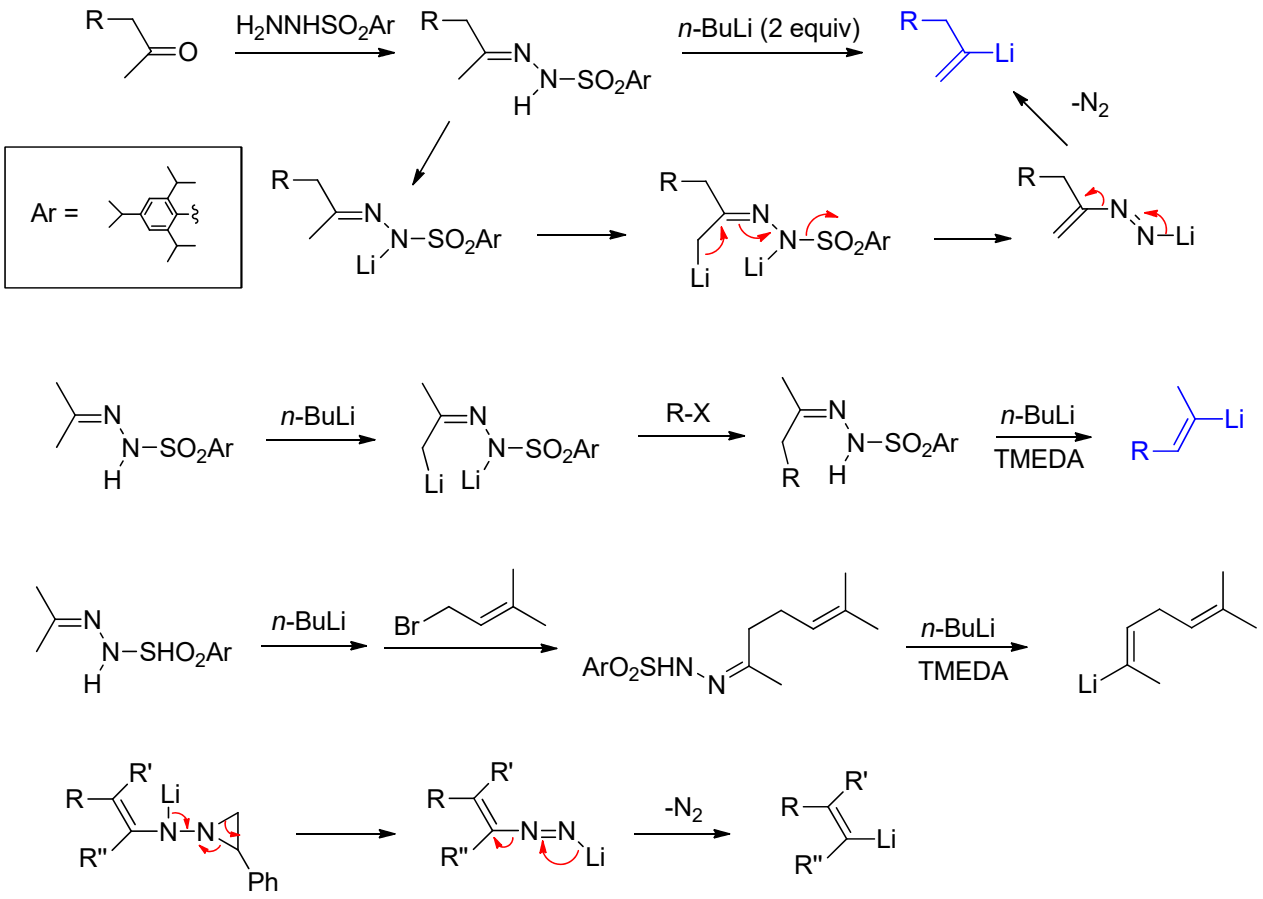








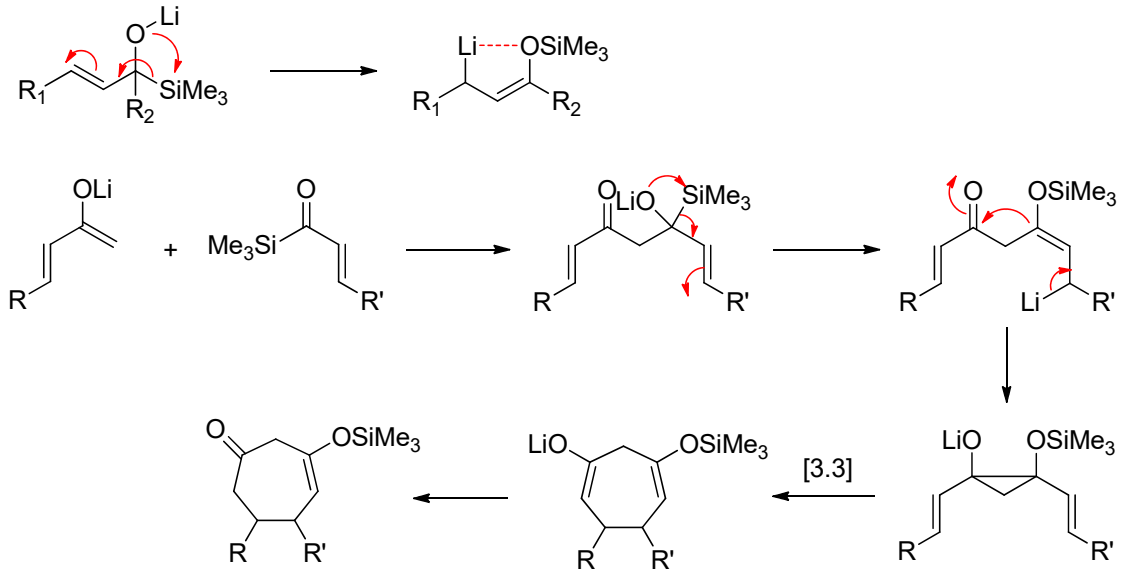
1.3.5. Preparation of Vinyllithium by Shapiro Reaction



from 1-amino-2-phenylaziridine

1.3.6. Miscellaneous

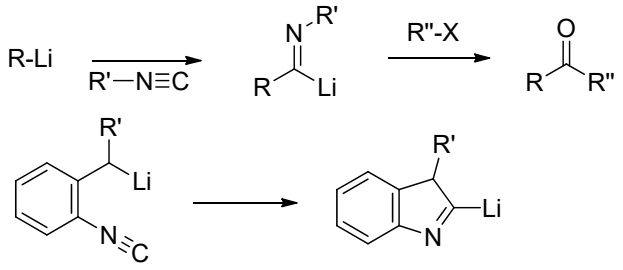
1.3.6.1. 1,2-Brook Rearrangement



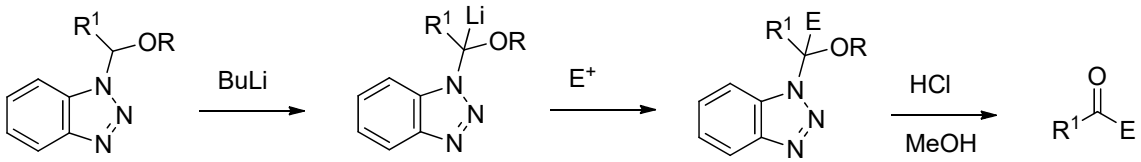
1.3.6. Miscellaneous

1.3.6.2. Acyllithium and Iminoacyllithium using CO and Isonitriles

Acyl anion equivalent



1.3.6.3. Benzotriazoles as acyl anion equivalents

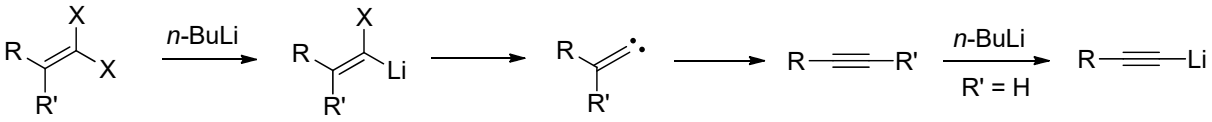


1.3.6.4. Akynyllithium Compounds from Aldehydes

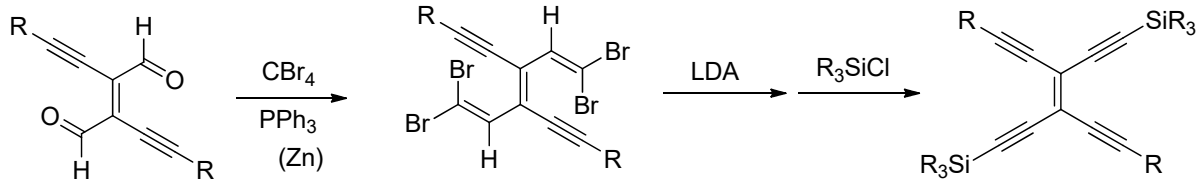
Vinyllithium compounds with a halogen in the α-position undergo Fritsh-Buttenburg-Wiechell-type rearrangement to give alkynes

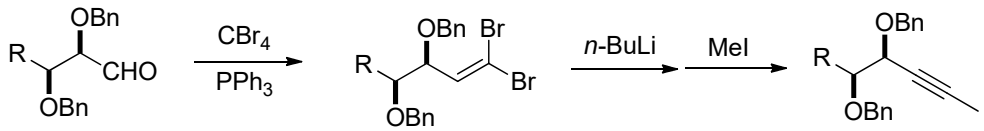
one of the β-substituents should be aryl, alkenyl, cyclopropyl, or H

Hydride shift occurs at temp. above -70 °C and alkynyllithium compounds are obtained by the reaction with excess BuLi



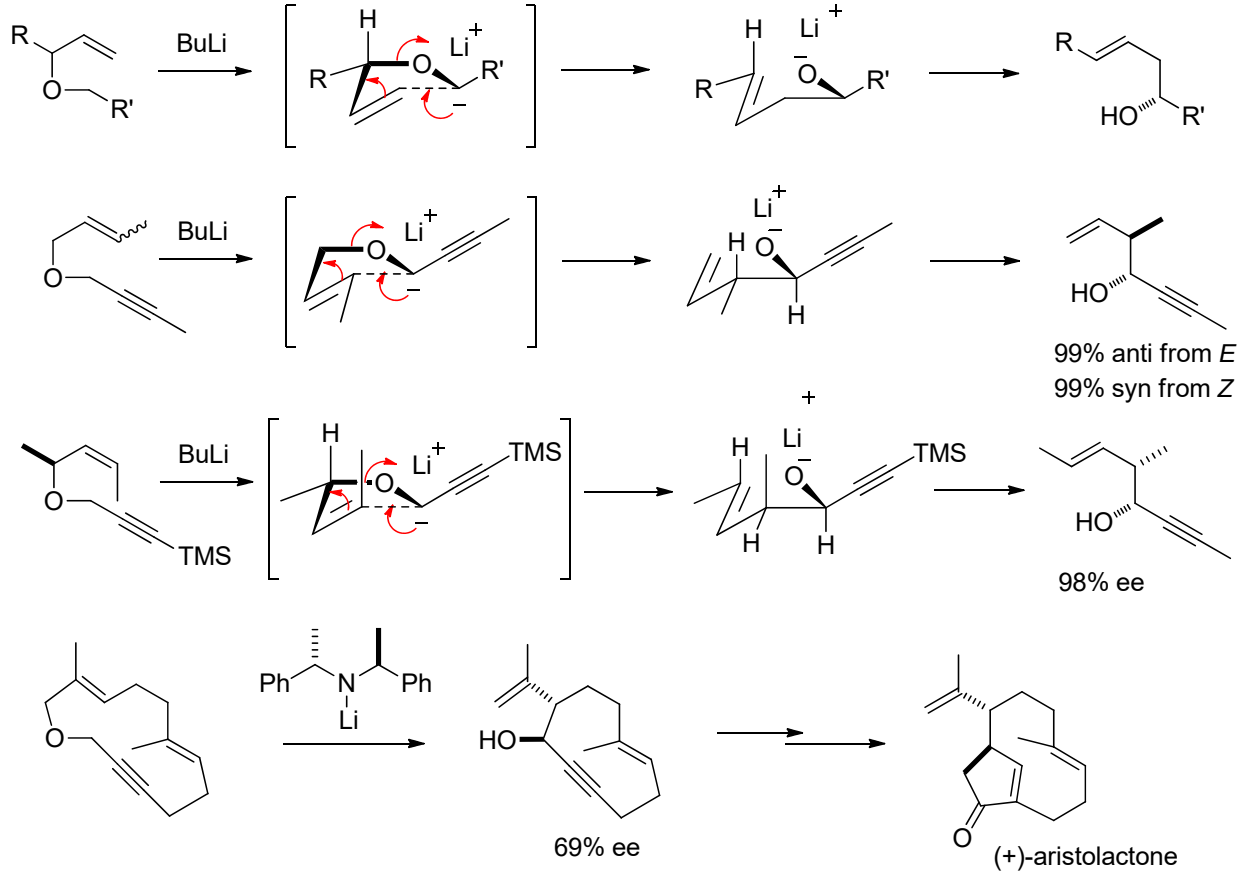
Corey-Fuchs method



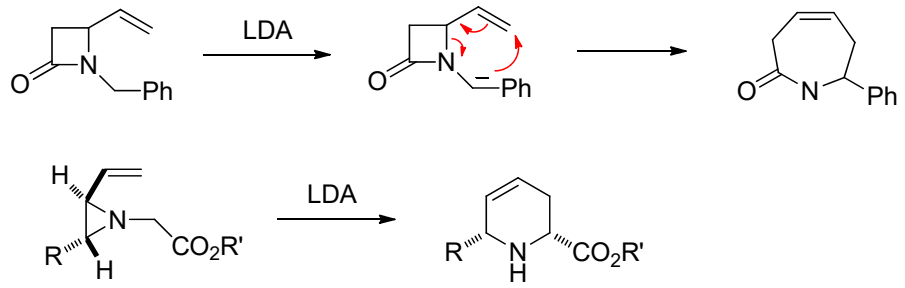


1.4. Synthetic Applications

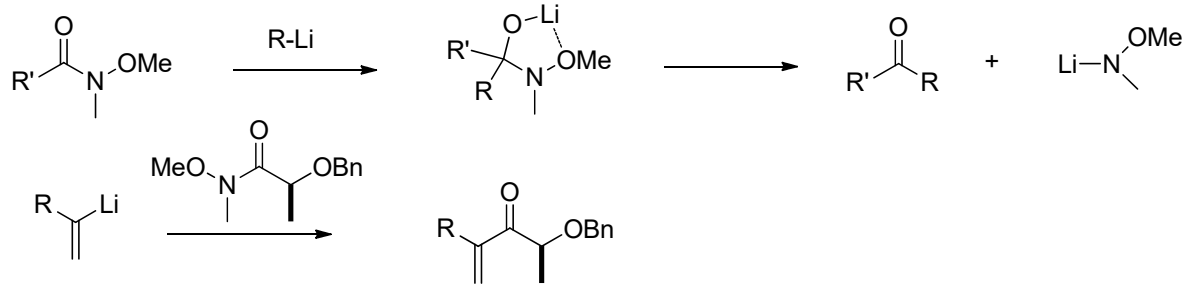
1.4.1. [2.3]-Wittig Rearrangement



1.4.2. Aza-Wittig

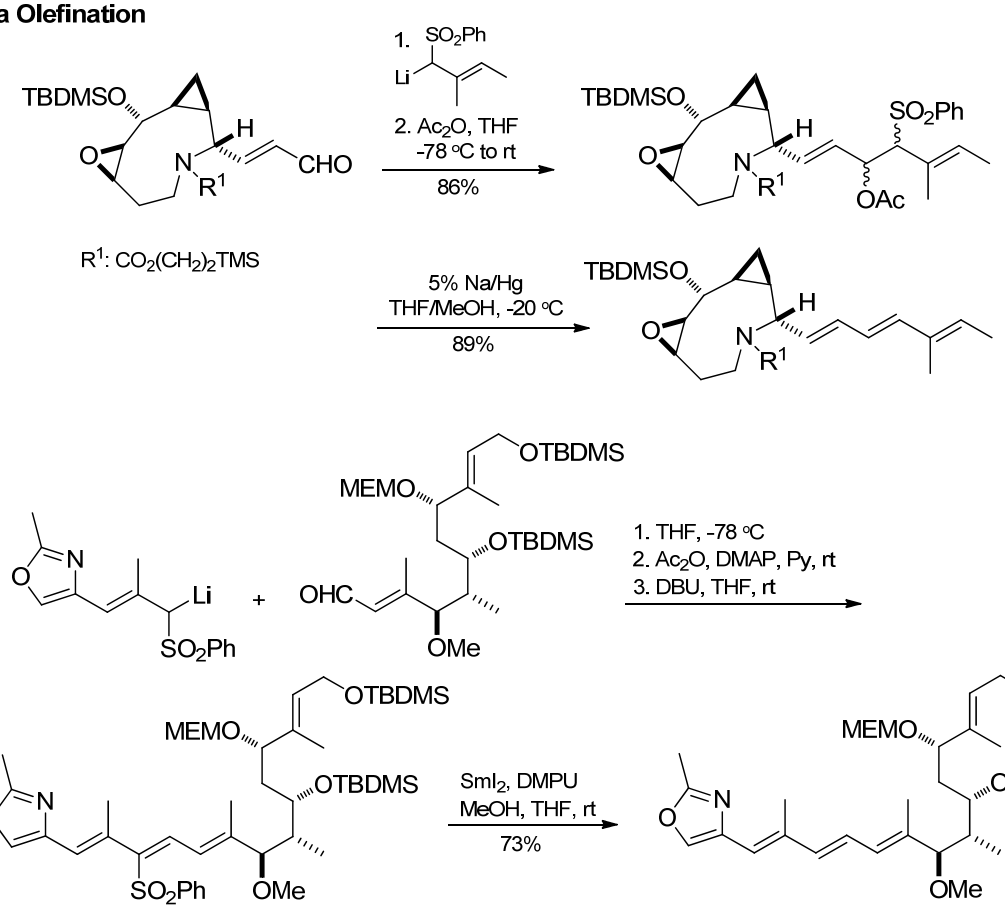


1.4.3. Weinreb Amide

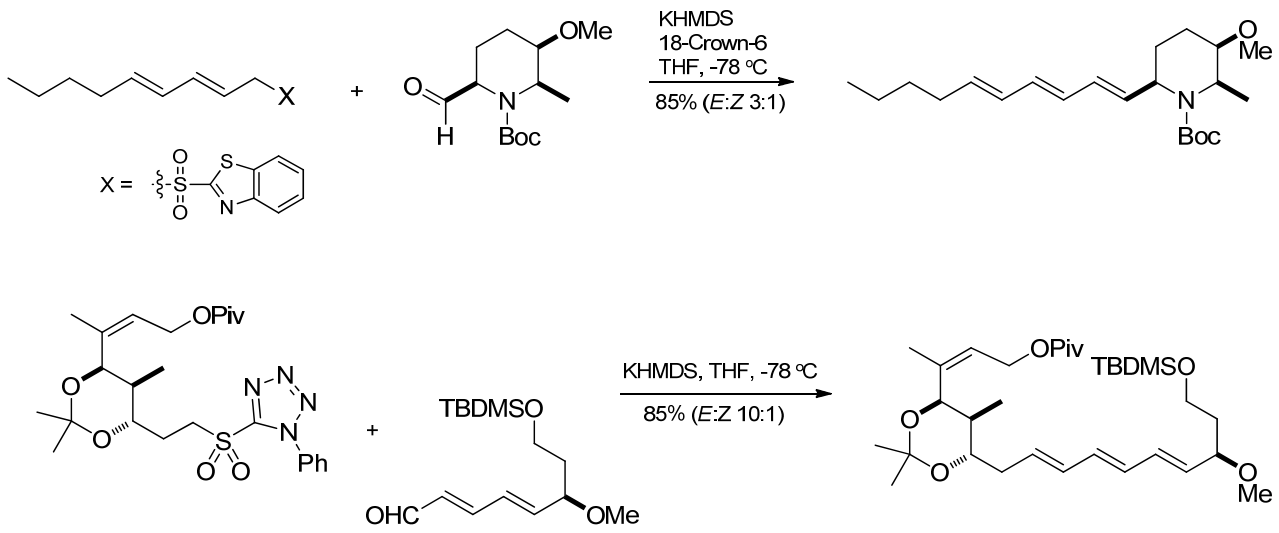


1.5. Application to polyene synthesis

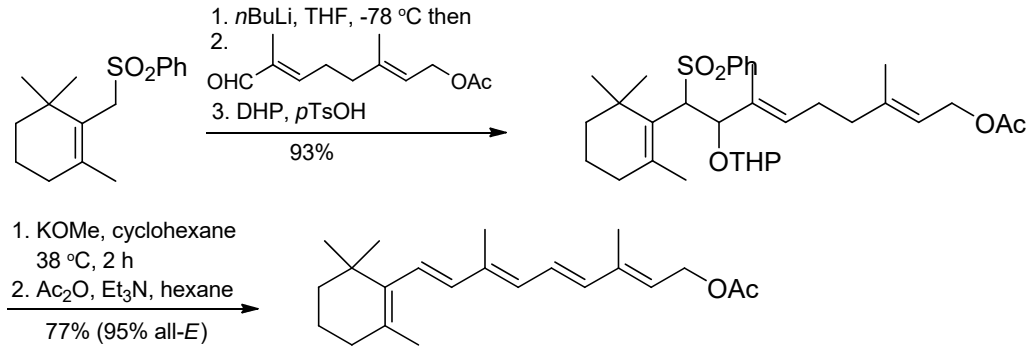
1.5.1. **Julia Olefination**

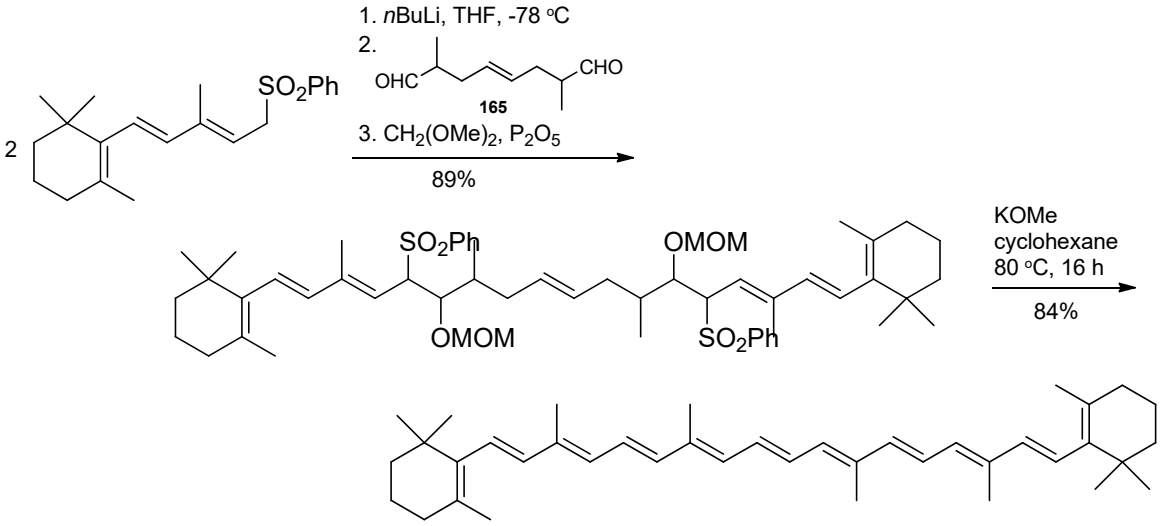


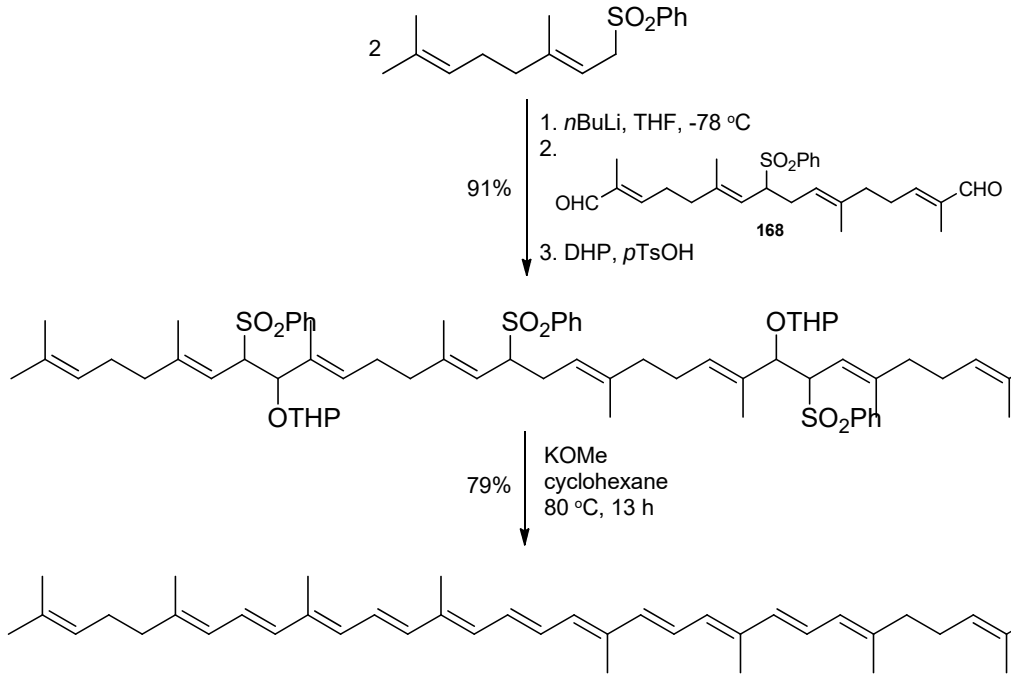
1.5.2. **Julia-Kocienski Olefination**



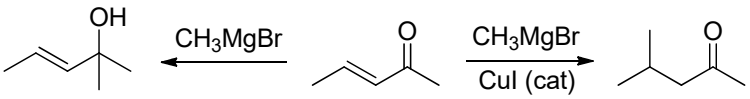
1.5.3. **Double Elimination Reaction for Carotenoid Synthesis**







6. Organocopper Reagent



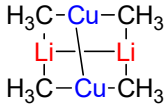
6.1 Preparation of organocopper reagents

a. Alkyl Copper

R-Li + Cu(I) ⟶ R-Cu + Li^+ [CuI, CuBr·$S(CH_3)_2$, CuCN]

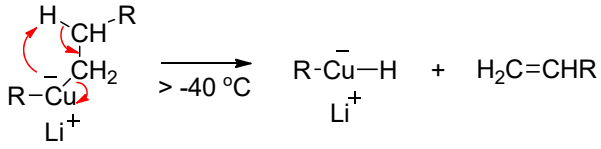
b. Cuprate

2R-Li + Cu(I) ⟶ R_2CuLi + Li^+



Dimeric structure in solution (ether, THF) - $[LiCu(CH_3)_2]_2$

β-Hydride elimination



c. Higher-order Cuprate

3R-Li + Cu(I) ⟶ R_3CuLi_2 + Li^+

d. Mixed Cuprate

[RC≡C-Cu-R]Li, [ArS-Cu-R]Li, [$(CH_3)_3$C-O-Cu-R]Li, [(cyclo-Hex)$_2$N-Cu-R]Li, [Ph_2P-Cu-R]Li

[CH_3-S(O)-CH_2-Cu-R]Li, [N≡C-Cu-R]Li

Efficiency of ligand transfer

vinyl, Ph > Me > Et > *i*-Pr > *t*-Bu >> PhS, R_2N, RC≡C

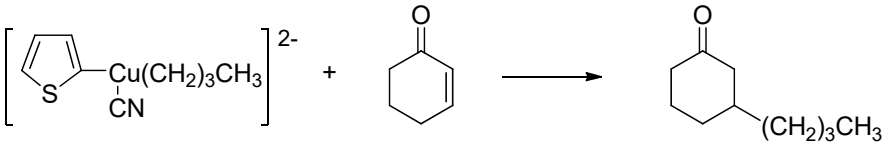
dummy ligand

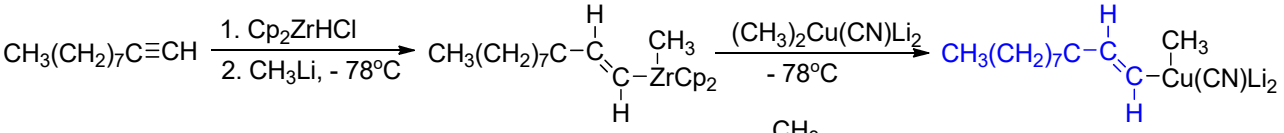
e. Higher-order Cyanocuprats (stable)

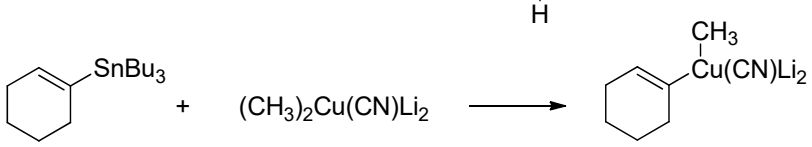
2R-Li + CuCN ⟶ $R_2CuCNLi_2$ ⟷ $[(R_2CuCN)_2]^{4-}$ $4Li^+$

$[R_2Cu]^-[Li_2CN]^+$ dimer

f. Mixed Higher-order Cyanocuprates





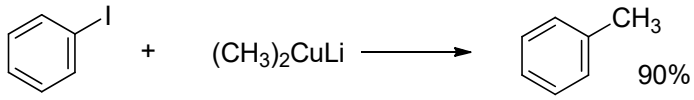


$(CH_3)_2C$=$CHCH_2Cl$ $\xrightarrow[CuCN,\ LiCl]{\text{Li-Naphthalene}}$ $[((CH_3)_2C{=}CHCH_2)_2CuCN]Li_2$

6.2 Reactions

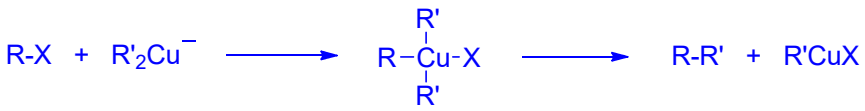
6.2.1 Nucleophilic displacement on halides and sulfonates

a. Aryl or vinyl halides

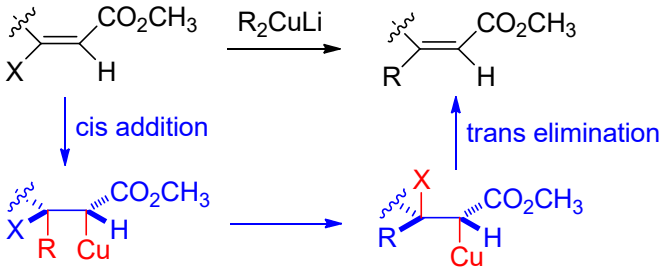


PhCH=CHBr + $(CH_3)_2CuLi$ → PhCH=CHCH$_3$ 81%

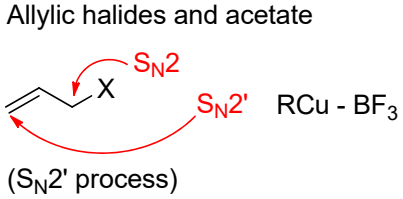
Mechanism: Oxidative addition and migration

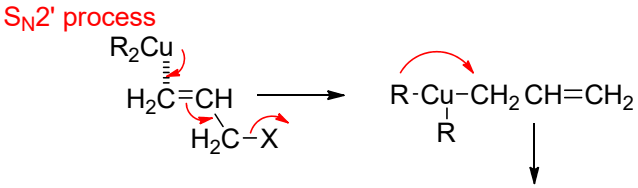


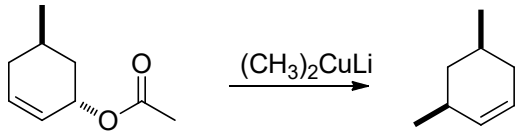
b. Vinyl halides with β-EWG

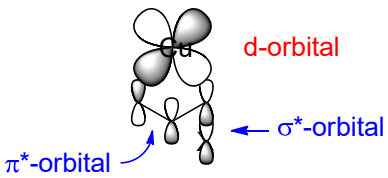


c. Allylic halides and acetate

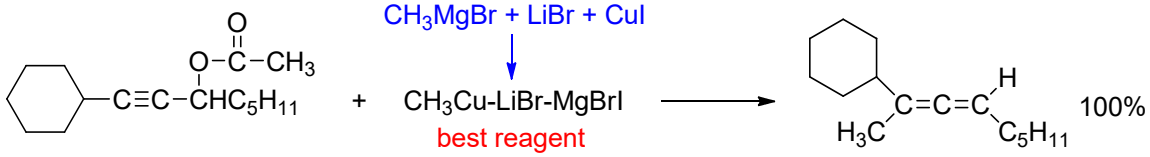








d. Propargylic acetates, halides, and sulfonates



e. Coupling of Grignard reagents using Li_2CuCl_4 catalyst

1° halides and tosylates:

$H_2C{=}CH(CH_2)_9MgCl$ + $Br(CH_2)_{11}CO_2MgBr$ $\xrightarrow[2)\ H^+]{1)\ Li_2CuCl_4}$ $H_2C{=}CH(CH_2)_{20}CO_2H$ >90%

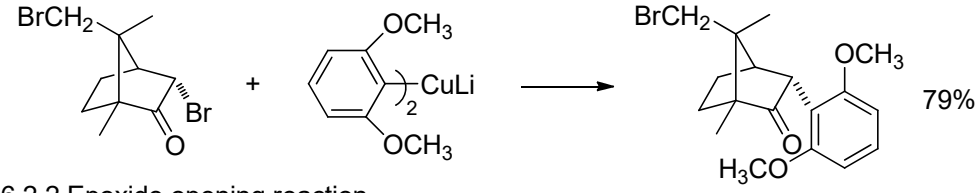
2° sulfonates:

$CH_3(CH_2)_9MgBr$ + $CH_3CHCH_2CH_3$ ($O{-}SO_2CH_3$) $\xrightarrow{\text{cat.}}$ $CH_3(CH_2)_9CHCH_2CH_3$ (CH_3)

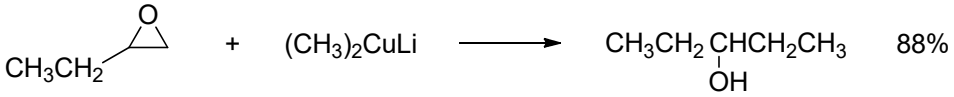
Li_2CuCl_4	17%
CuBr/HMPA	30%
CuBr-$S(CH_3)_2$, LiBr, LiSPh	62%

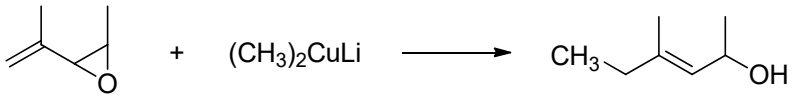
6.2 Reactions

f. α-Halocarbonyl compounds



6.2.2 Epoxide opening reaction

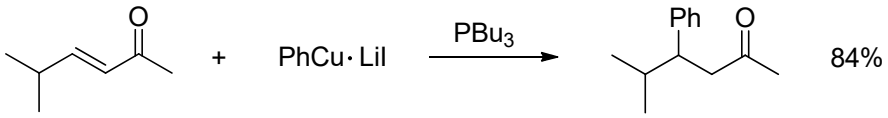




6.2.3 Conjugate addition to α,β-unsaturated carbonyl compounds

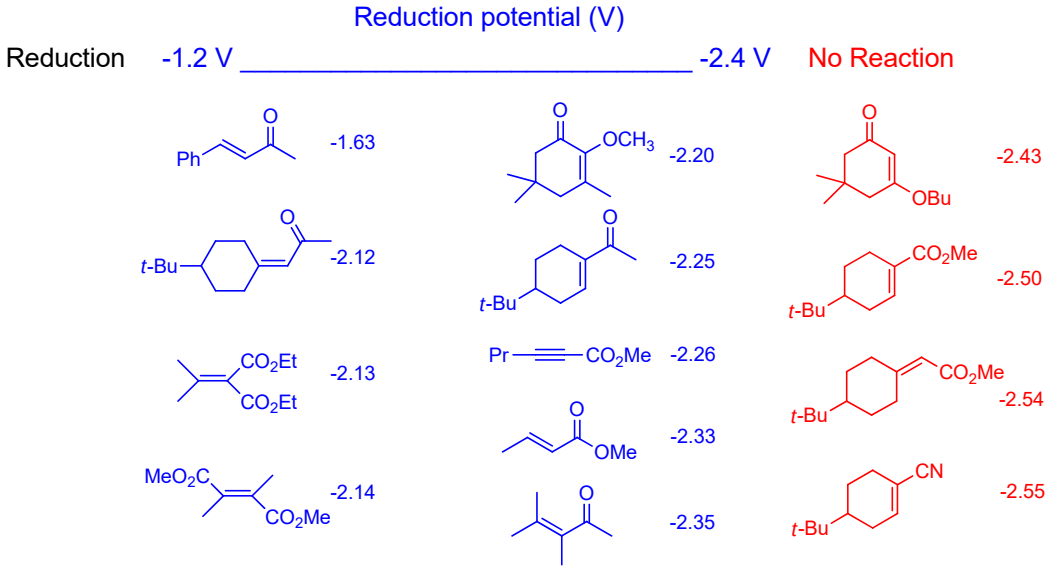
best copper salt: CuBr - $S(CH_3)_2$ or CuCN

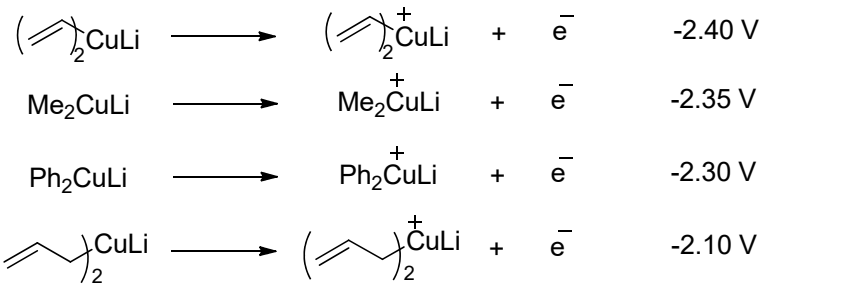
add PR_3 to improve the reactivity (Noyori, *Tetrahedron Lett.* **1980**, 1247)

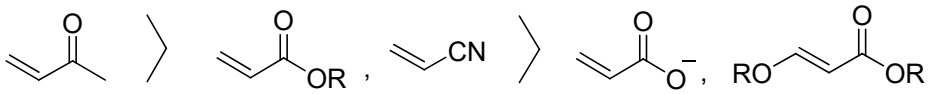


not a free radical mechanism

a. corelation of the reactivity towards 1,4-addition with the reduction potential of the carbonyl compounds







6.2 Reactions

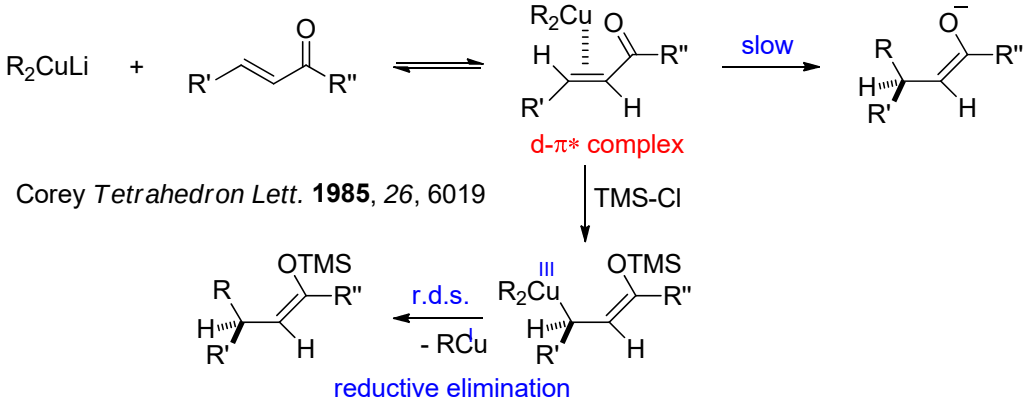
6.2.3 Conjugate addition to α,β-unsaturated carbonyl compounds

b. α,β-Unsaturated esters, nitriles: reduced reactivity with dialkyl cuprate (R_2CuLi)

Use RCu - BF_3 (RLi + CuCN + $BF_3 \cdot OEt_2$) Yamamoto *J. Am. Chem. Soc.* **1978**, *100*, 3240.

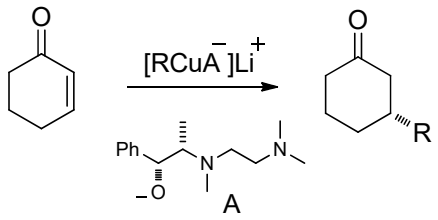
TMSCl: accelerate the addition of cuprate - good for α,β-unsaturated esters and amides

Mechanism



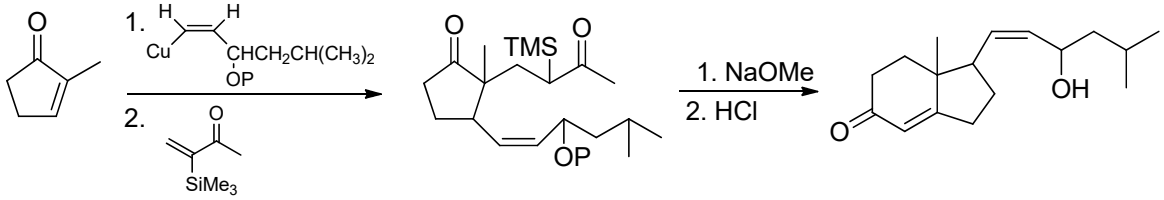
c. Enantioselectivity

mixed cuprate reagents with chiral anionic ligands

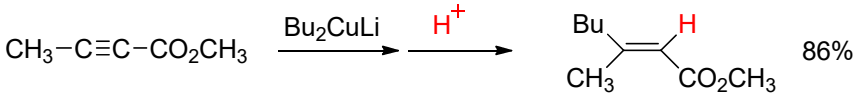


R	ee
Et	92
Bu	89
$(CH_3)_3COCH_2$	85

d. Tandem conjugate addition / alkylation



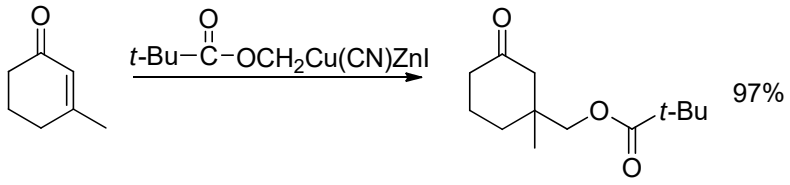
e. Conjugate acetylenic esters - syn addition (kinetic product)



f. Mixed copper-zinc organometallics

compatible with many functional groups; mild nucleophile; useful in conjugate addition

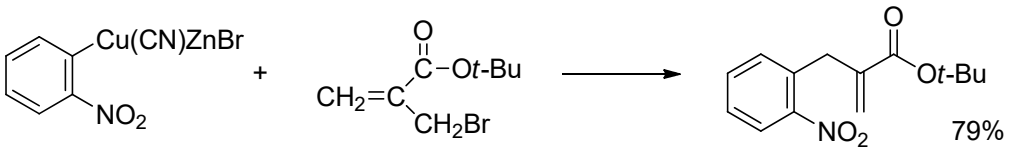
Preparation: add CuCN to R-Zn-I



6.2 Reactions

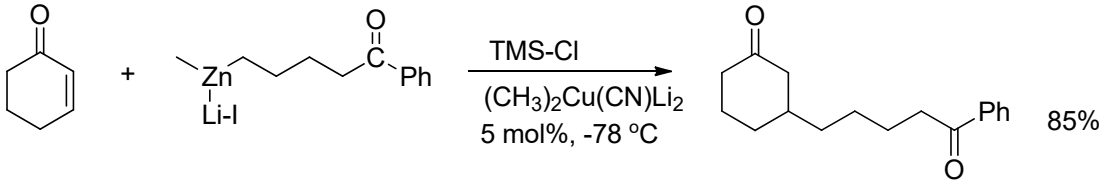
6.2.3 Conjugate addition to α,β-unsaturated carbonyl compounds

f. Mixed copper-zinc organometallics

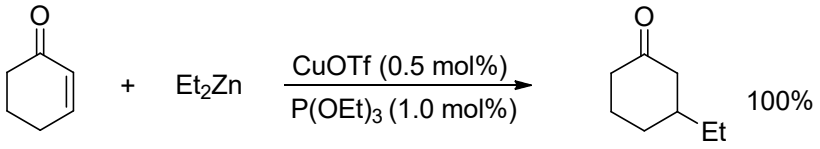


- Catalytic copper species with organozinc reagents

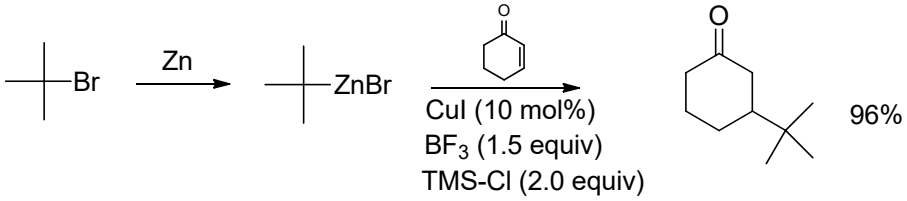
LiI + TMSCl + cat. $(CH_3)_2Cu(CN)Li_2$



dialkylzinc + 0.5 mol% CuOTf + phosphines or phosphites

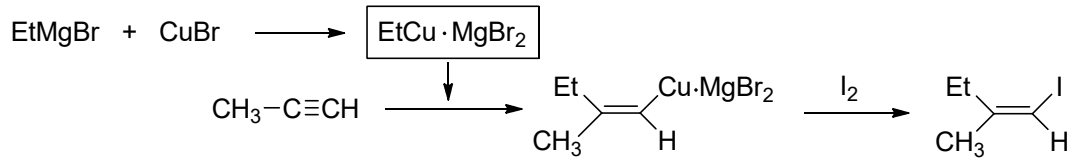


CuI or CuCN (10 mol%), BF_3 and TMS-Cl



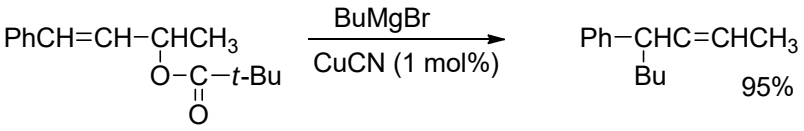
g. Mixed copper-magnesium reagents (Normant Reagents)

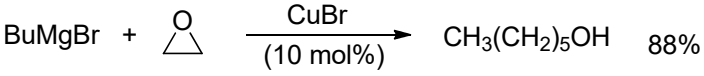
Addition to terminal acetylenes ⟶ Alkenylcopper reagents (syn addition)

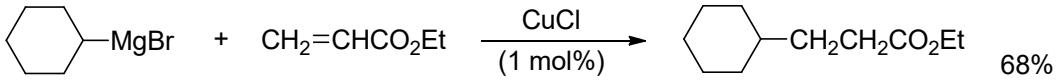


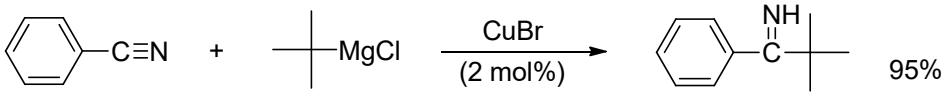
- Catalytic process

Grignard reagent + catalytic copper salt





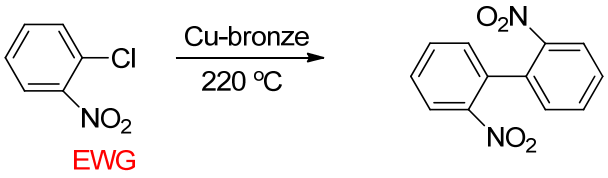




6.2 Reactions

6.2.4 Ullman coupling - coupling of aryl halide

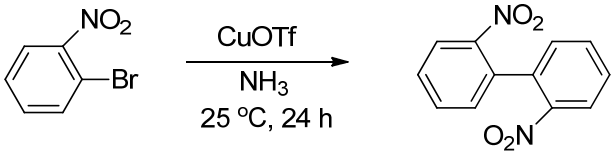
(Organocopper Intermediate)



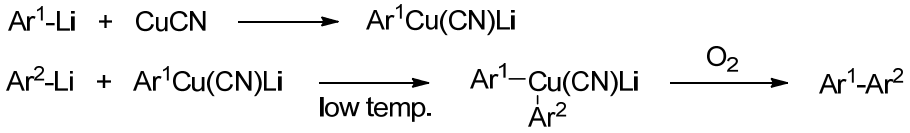
EWG

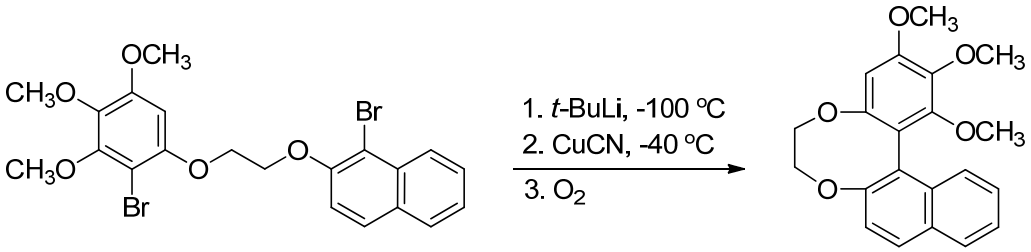
lower the reaction temperature by the use of soluble Cu(I) salts: CuOTf

homogeneous condition



New type of Ullman coupling - mixed diarylcyanocuprate



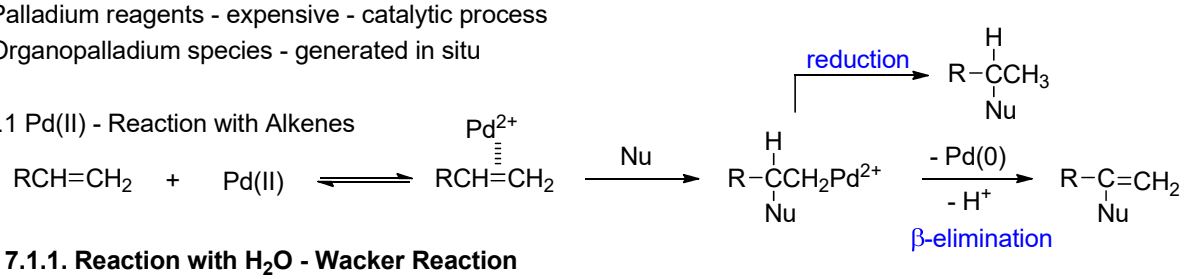


7. Reaction Involving Organopalladium Intermediates

Palladium reagents - expensive - catalytic process

Organopalladium species - generated in situ

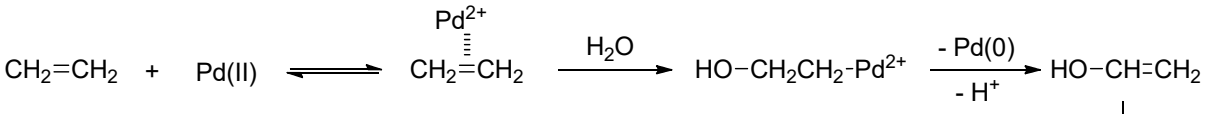
7.1 Pd(II) - Reaction with Alkenes



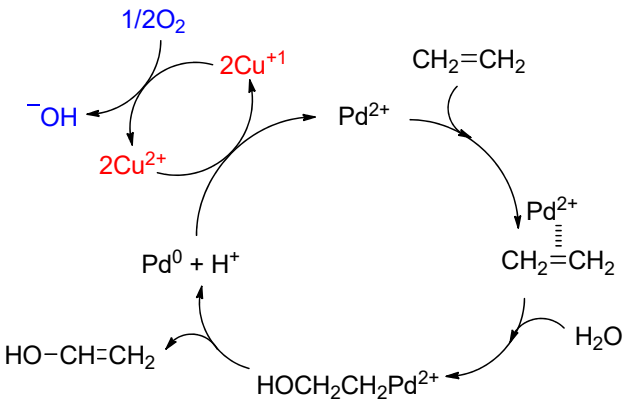
7.1.1. Reaction with H_2O - Wacker Reaction

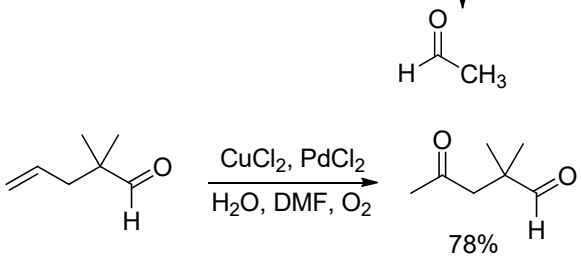
ethylene ⟶ acetaldehyde

Pd(II) catalyst, O_2 (stoichiometric oxidant), $CuCl_2$ (catalytic oxidant)

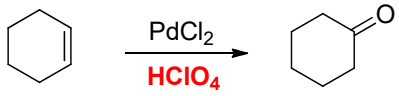


<mechanism>

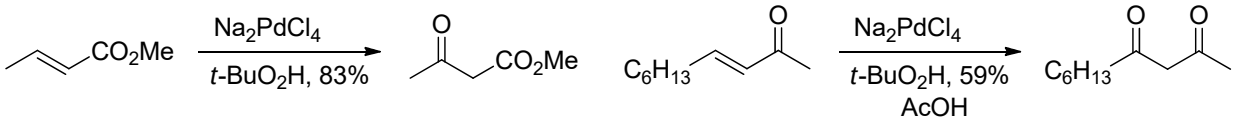




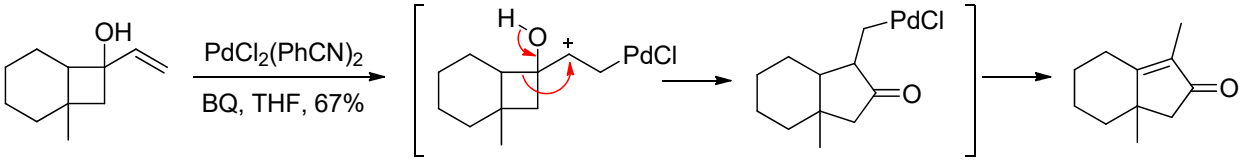
Oxidation of simple internal alkenes is very slow

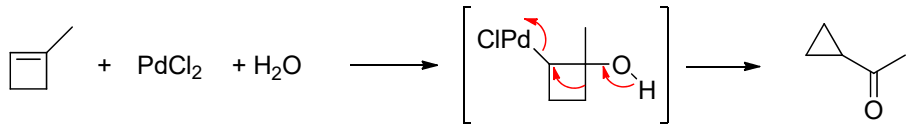


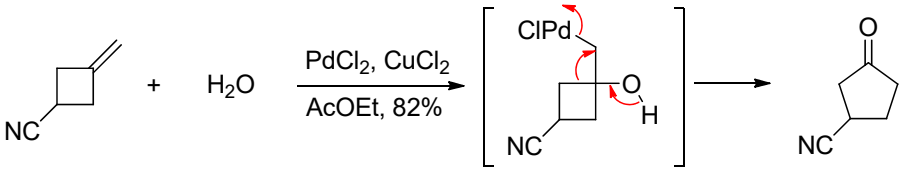
Neighboring group participation



Oxidative rearrangement

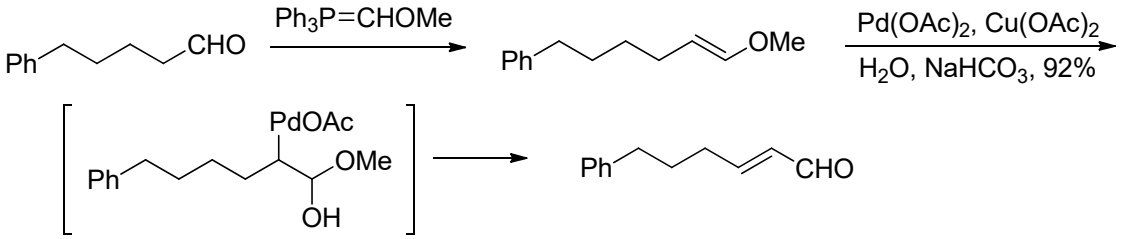




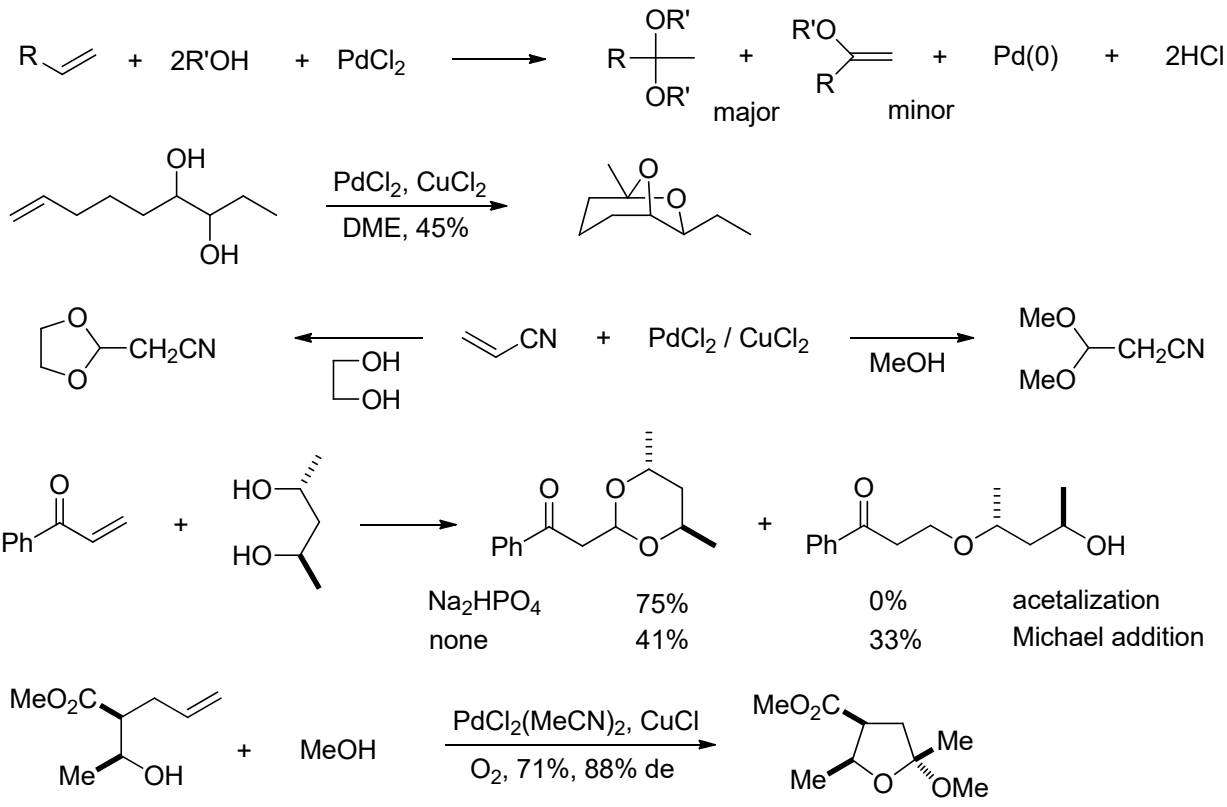


7.1. Pd(II) - Reaction with Alkenes

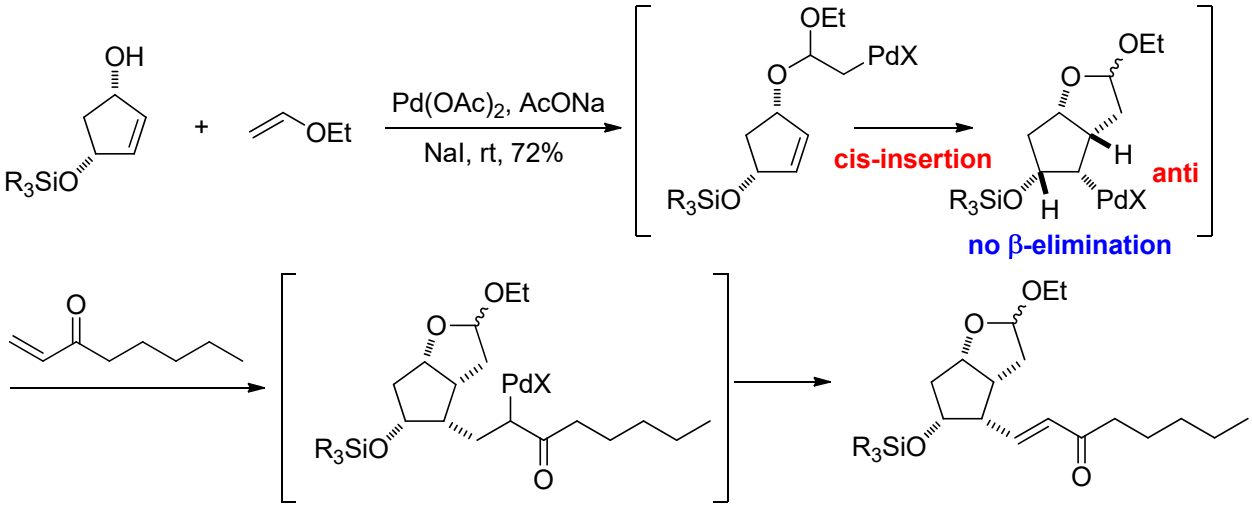
Methyl enol ether



7.1.2. Reaction with Alcohols

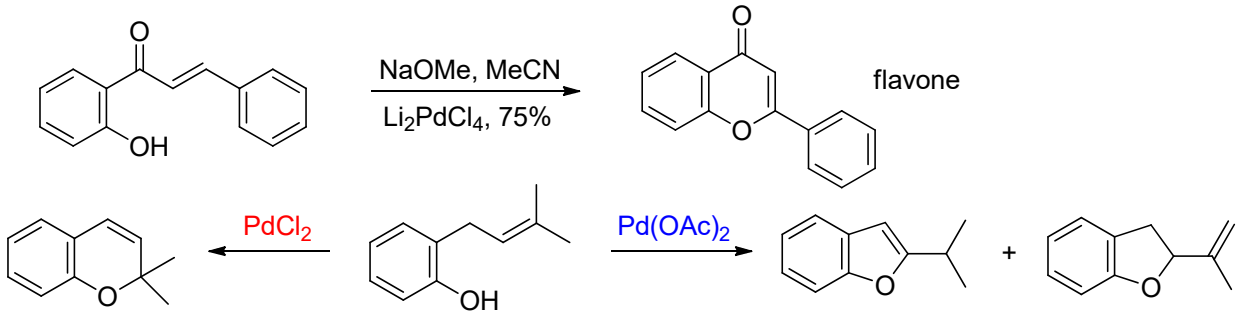


Oxypalladation / alkene insertion

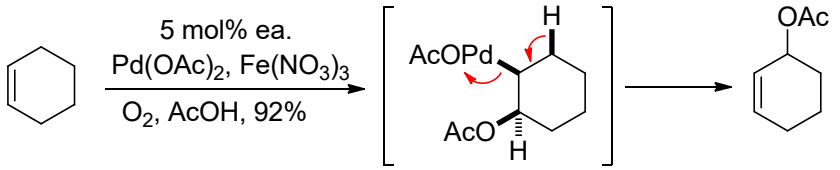


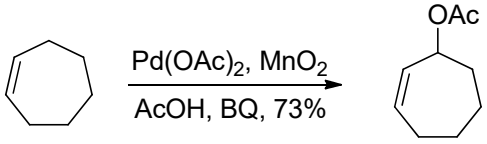
7.1. Pd(II) - Reaction with Alkenes

Phenolic Oxypalladation

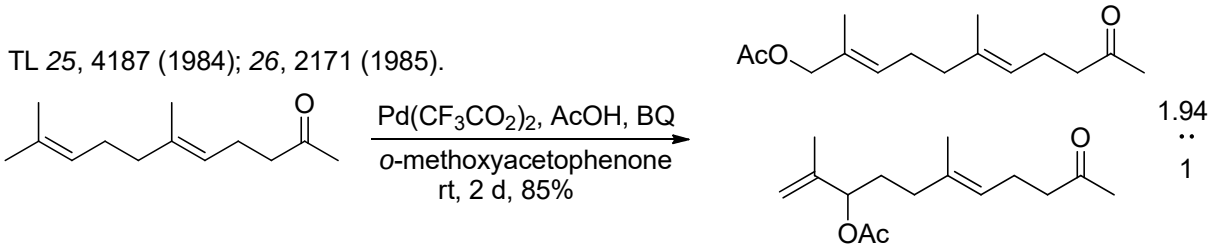


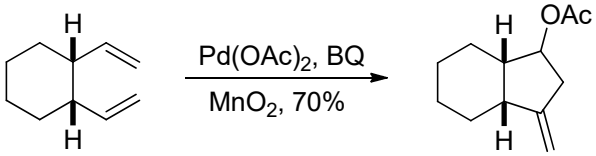
7.1.3. Reaction with Carboxylic Acids

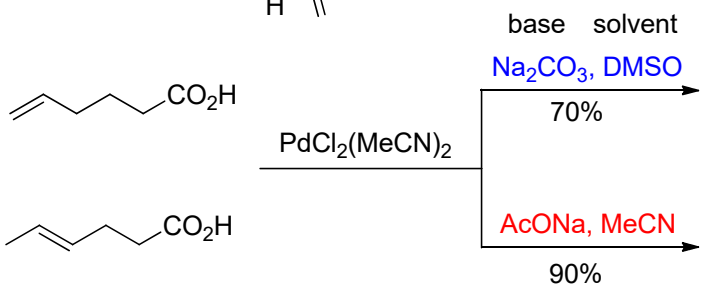


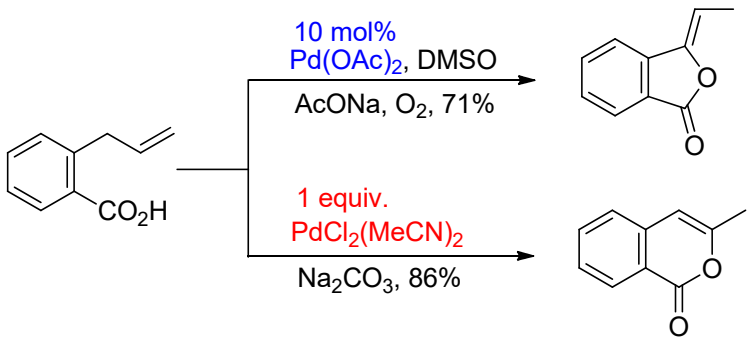


TL *25*, 4187 (1984); *26*, 2171 (1985).



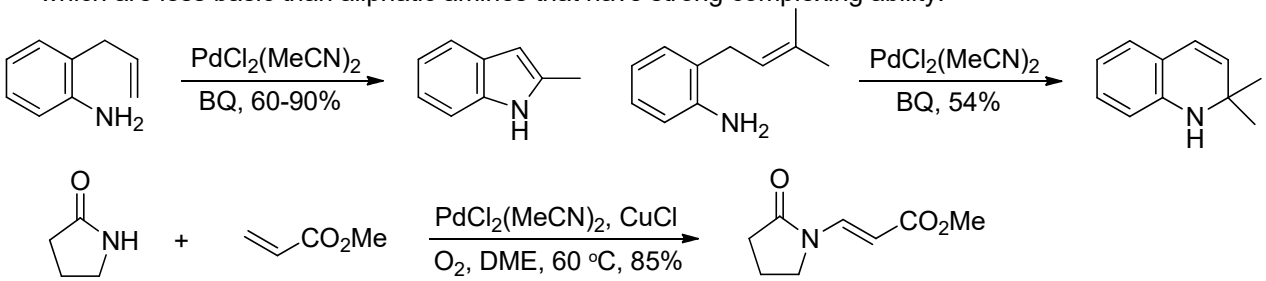




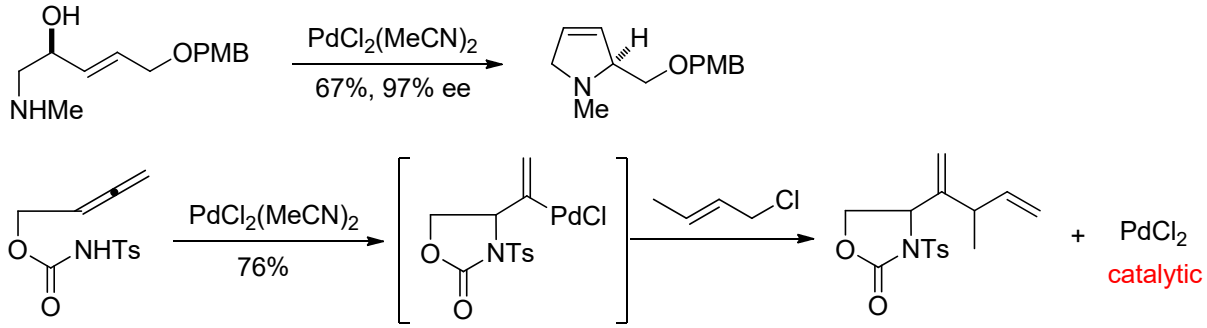


7.1.4. Reactions with Amines - aminopalladation

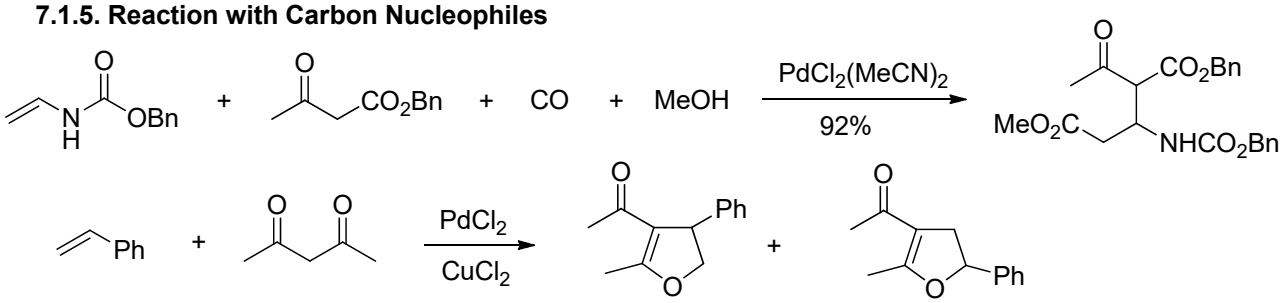
Oxidative amination proceeds smoothly for aromatic amines, amides, and tosylamines which are less basic than aliphatic amines that have strong complexing ability.



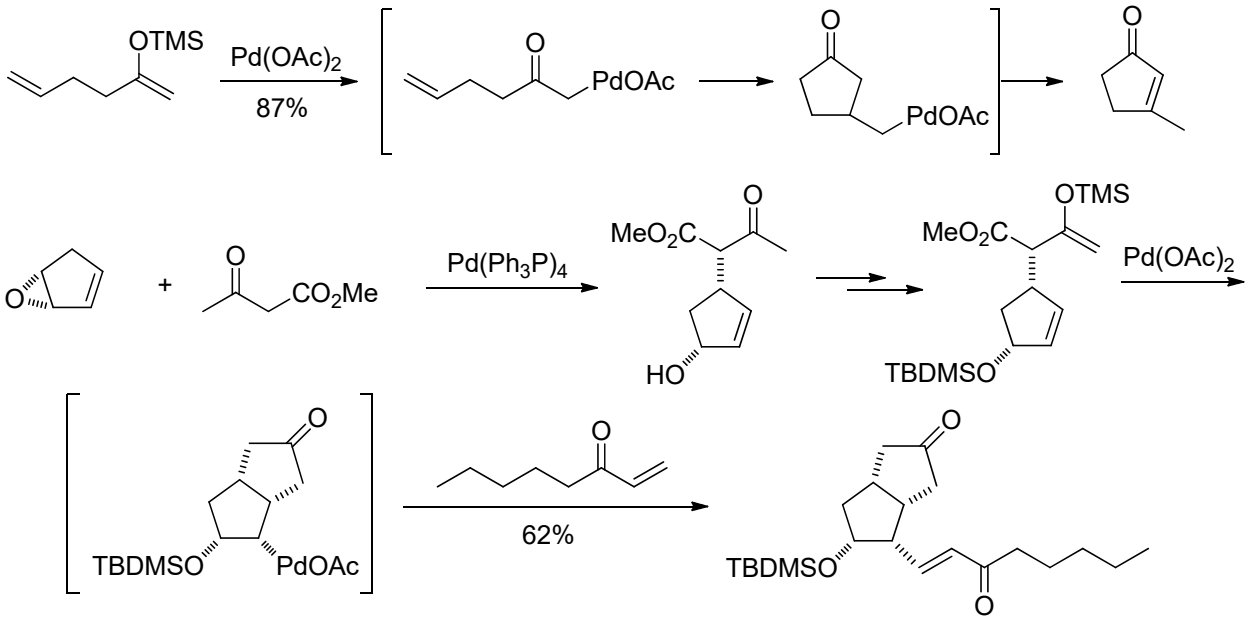
Aminopalladation is stoichiometric reaction. When β-OH is eliminated instead of β-H, Pd(II) is the elimination product (HO-PdCl) and the reaction is catalytic without a reoxidant.



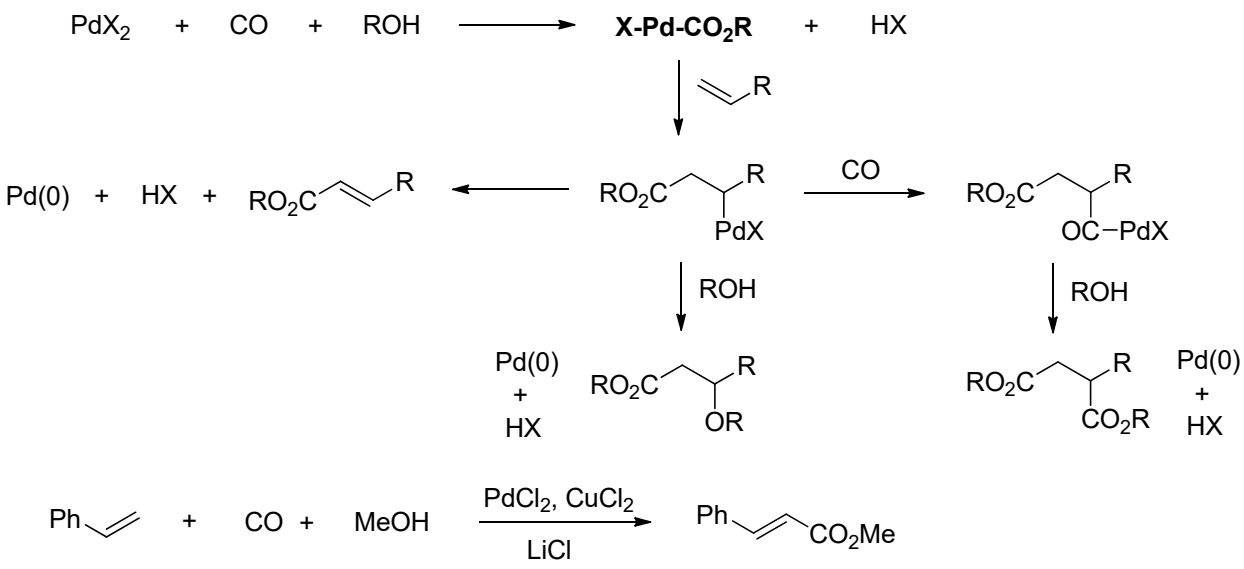
7.1.5. Reaction with Carbon Nucleophiles



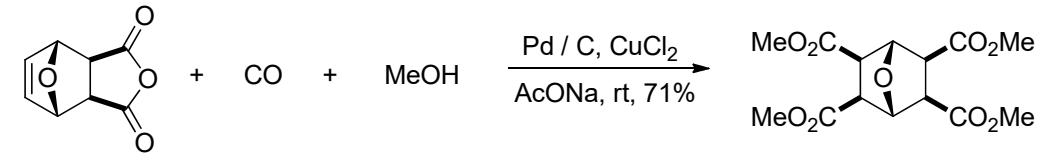
Pd enolates by transmetallation of silyl enol ehters with $Pd(OAc)_2$

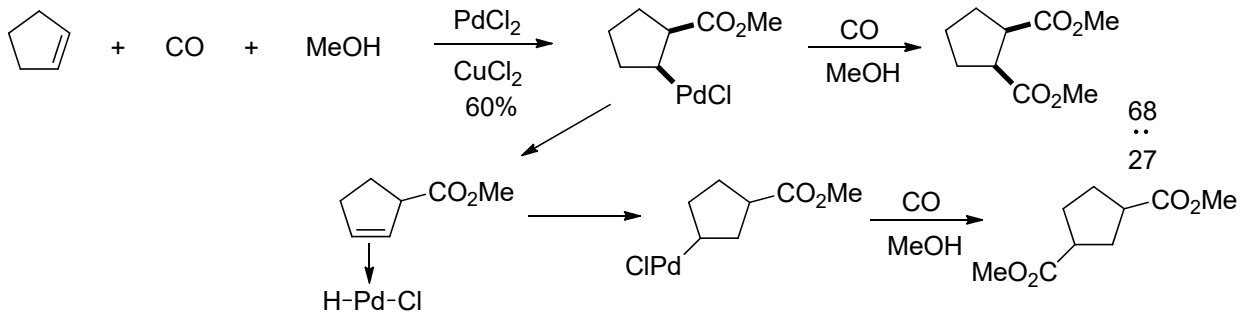


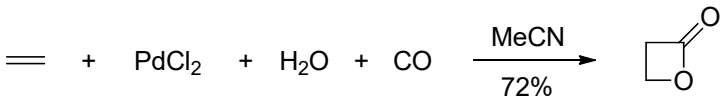
7.1.6. Oxidative Carbonylation

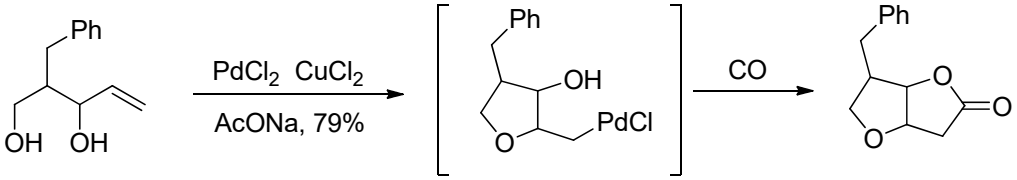


Dicarboxylation of cyclic alkenes

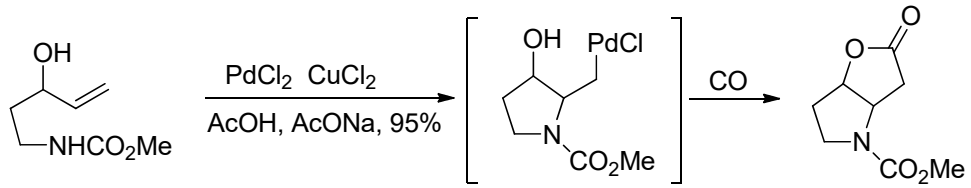




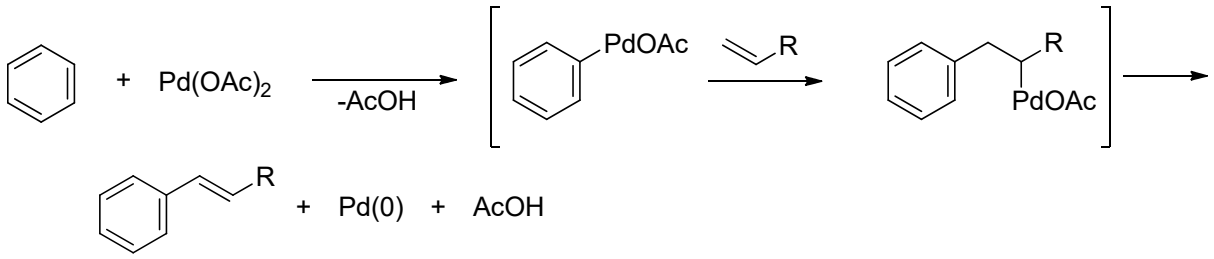


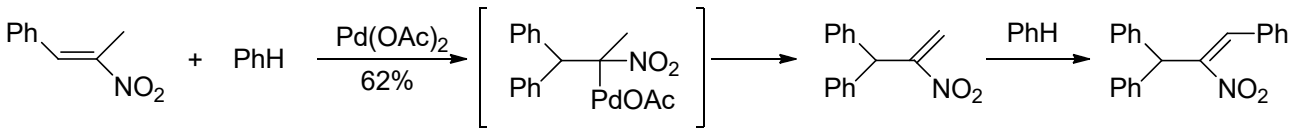


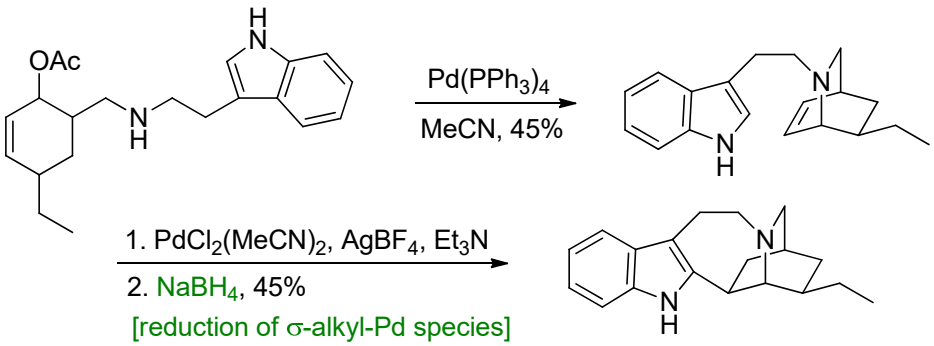
Aminopalladation / carbonylation

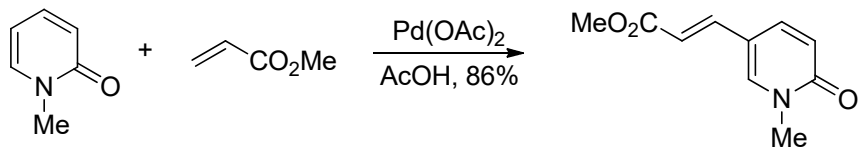


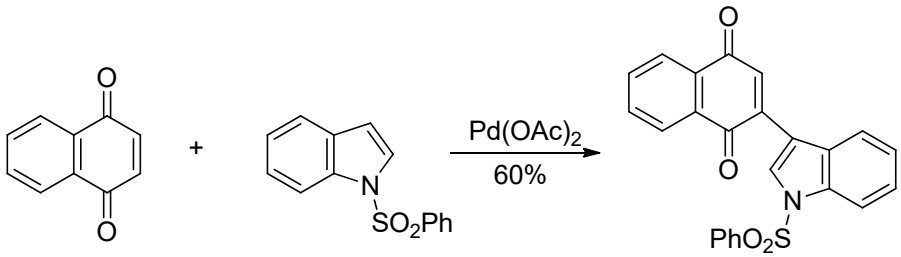
7.1.7. Reaction with Aromatic Compounds





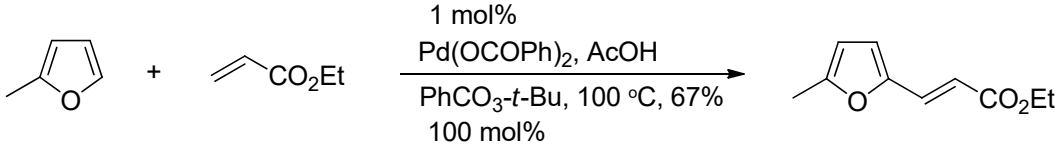






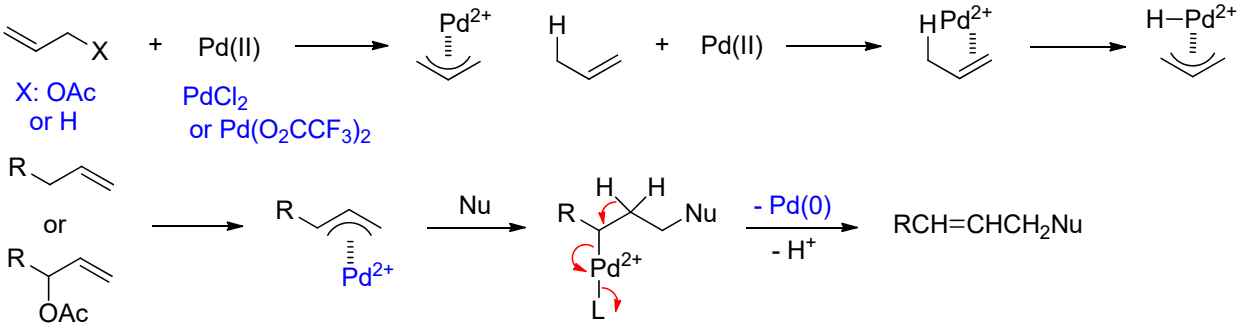
Catalytic Arylation of Alkenes

Catalytic turnovers are generally not high. ***tert*-Butyl perbenzoate** - an efficient reoxidant.

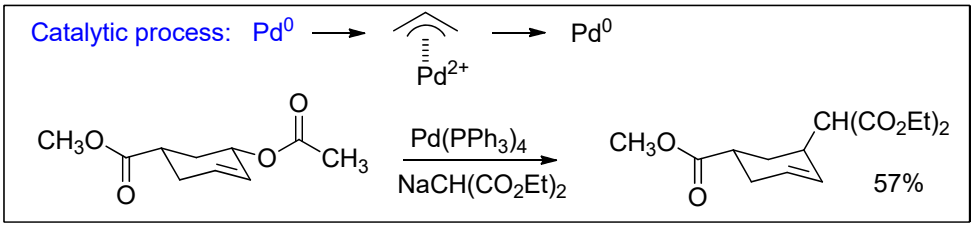


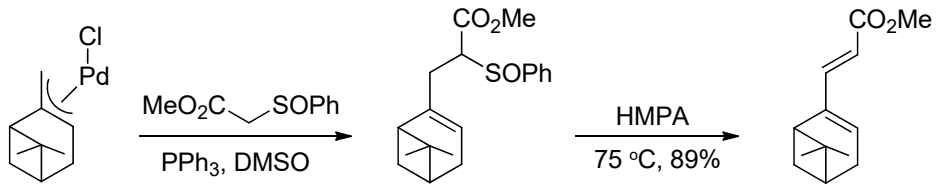
7.2 Pd(II) - Reaction with Allylic Compounds - **stoichiometric reagent**

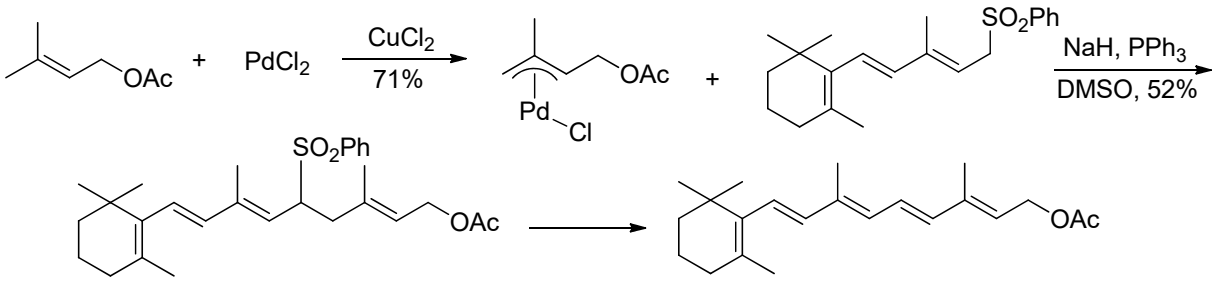
Formation of π-allyl complex

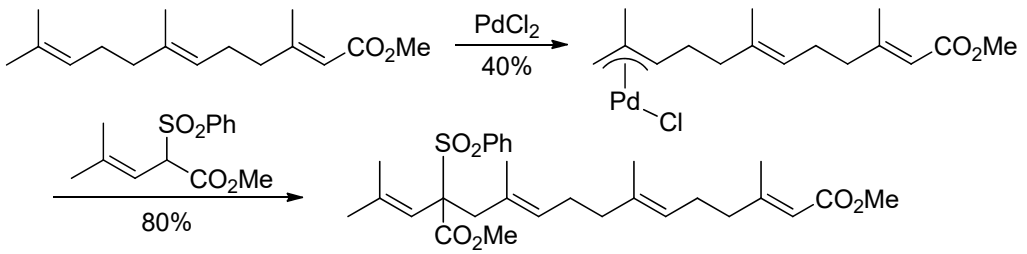


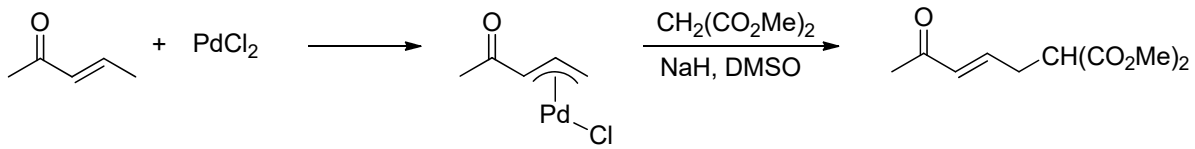
Efficient complex formation - Base in DMF or $CuCl_2$ and NaOAc in AcOH



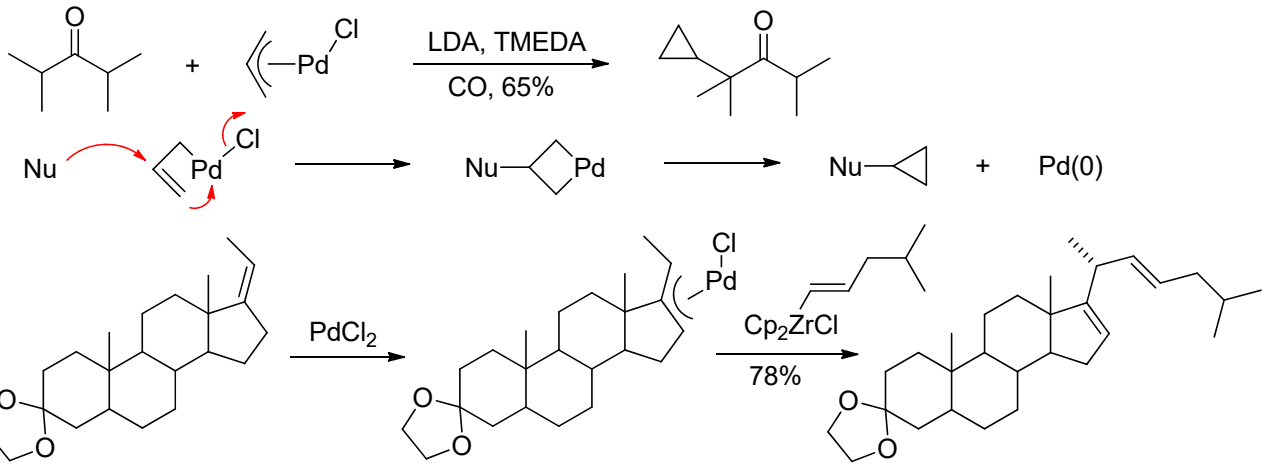




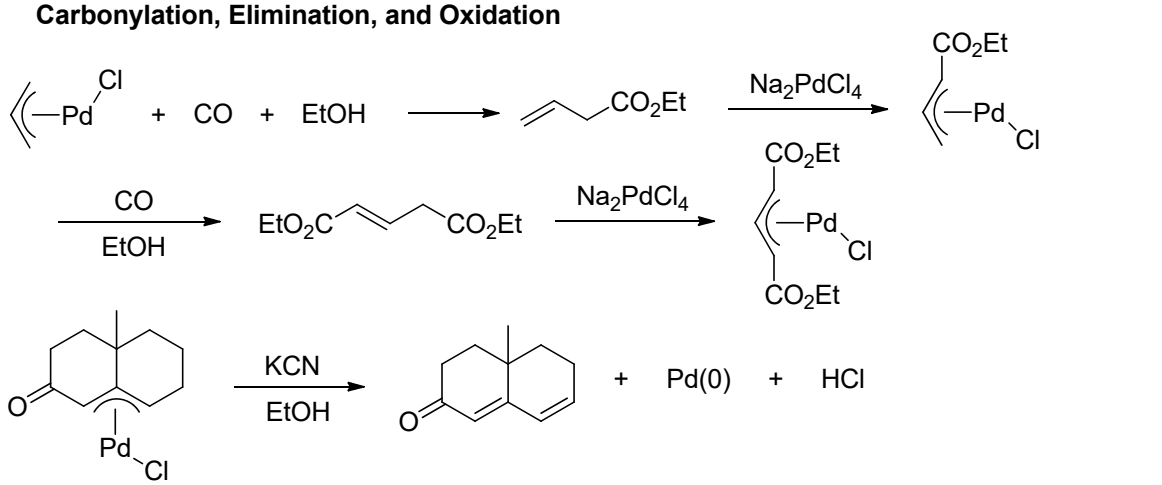


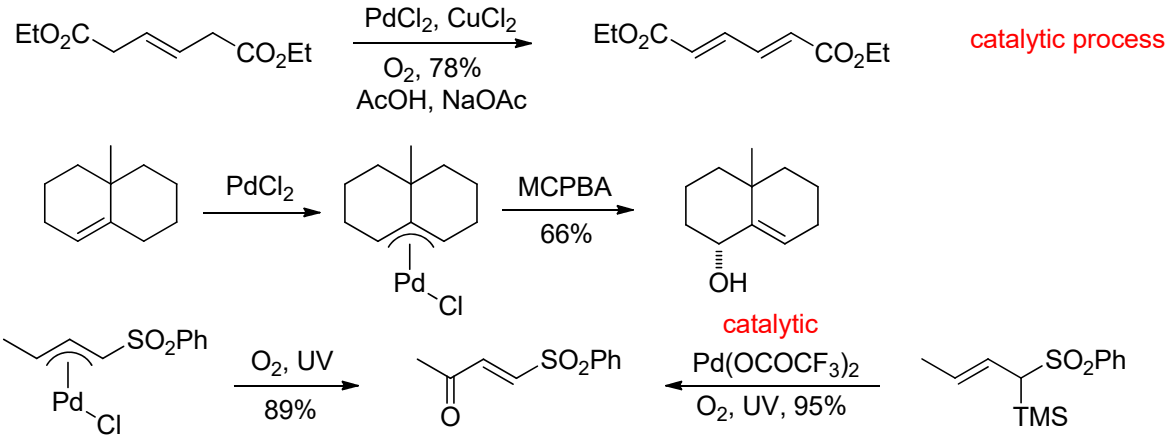


Formation of π-allyl complex

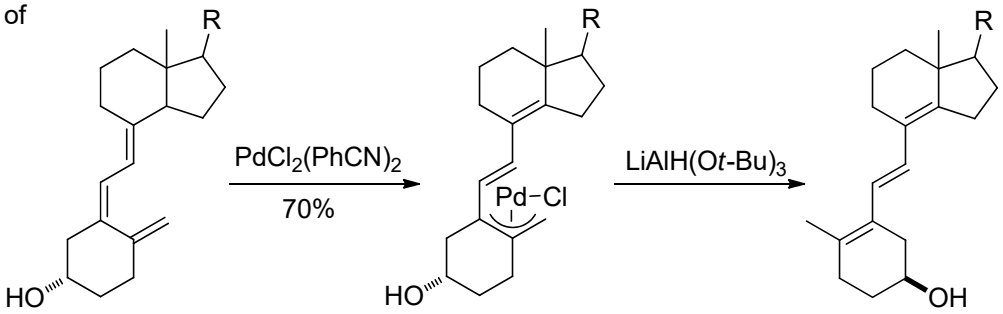


Carbonylation, Elimination, and Oxidation

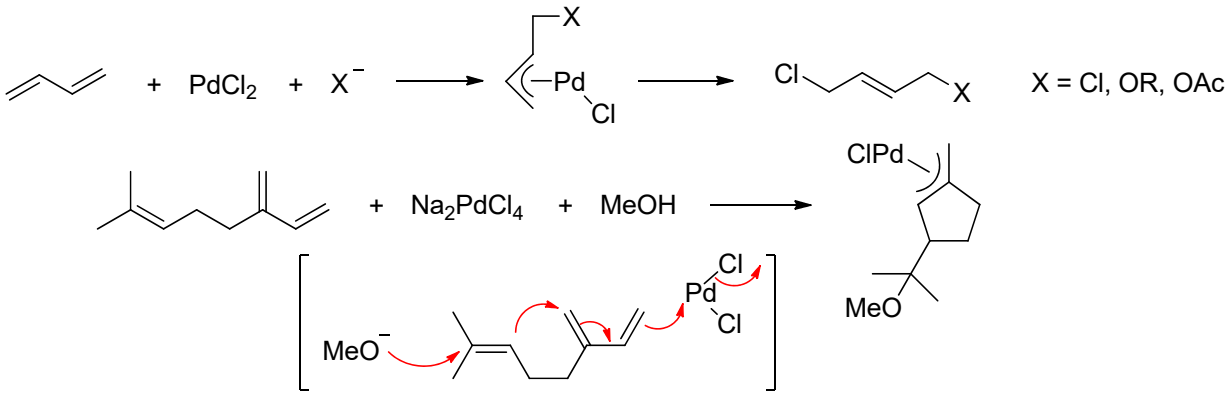




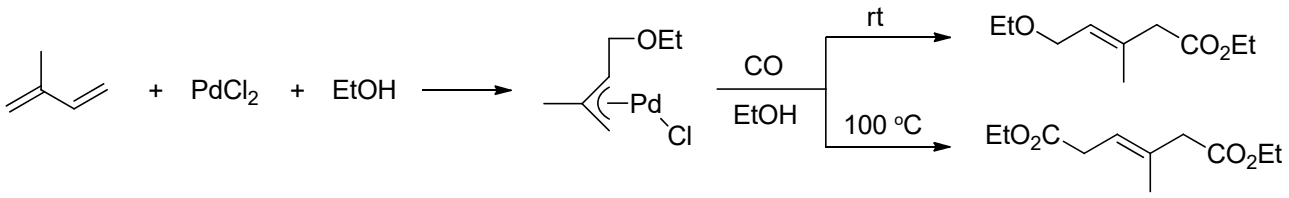
Isomerization of C=C bonds

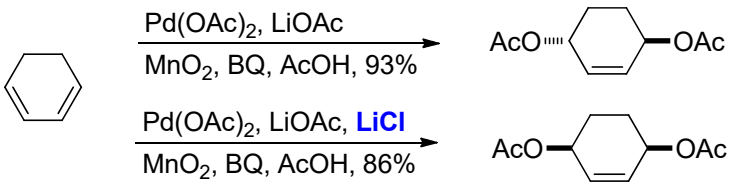


7.3. Pd(II) - Reactions with Conjugated Dienes

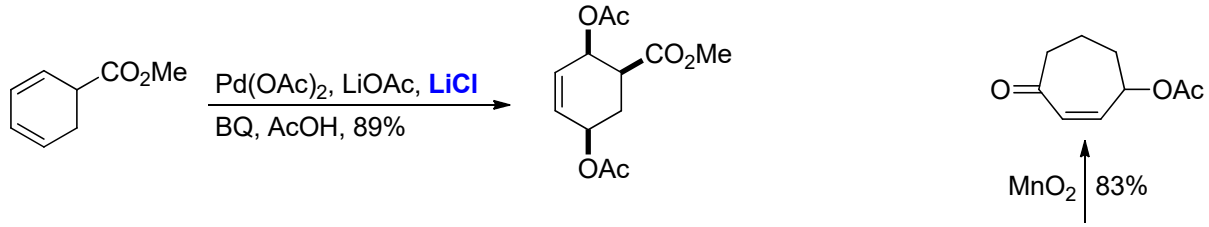


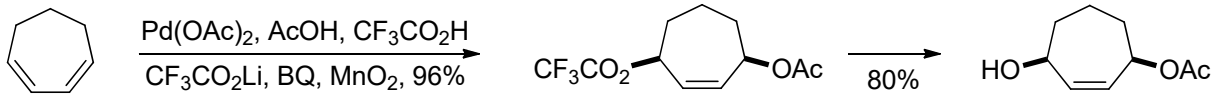
The reaction is stoichiometric with respect to Pd(II) salts, but can be made catalytic by the use of reoxidants.

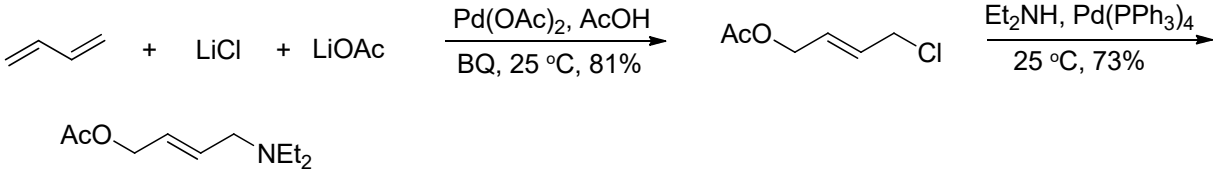


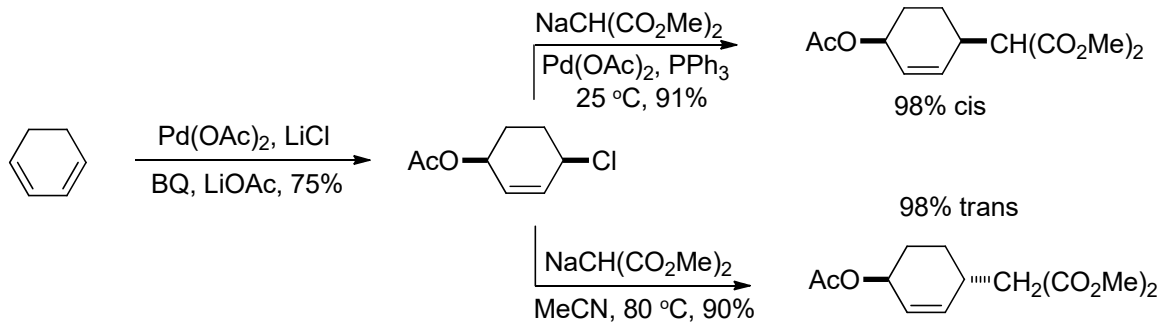


The coordination of a chloride ion to Pd makes the cis migration of the acetate from Pd impossible.



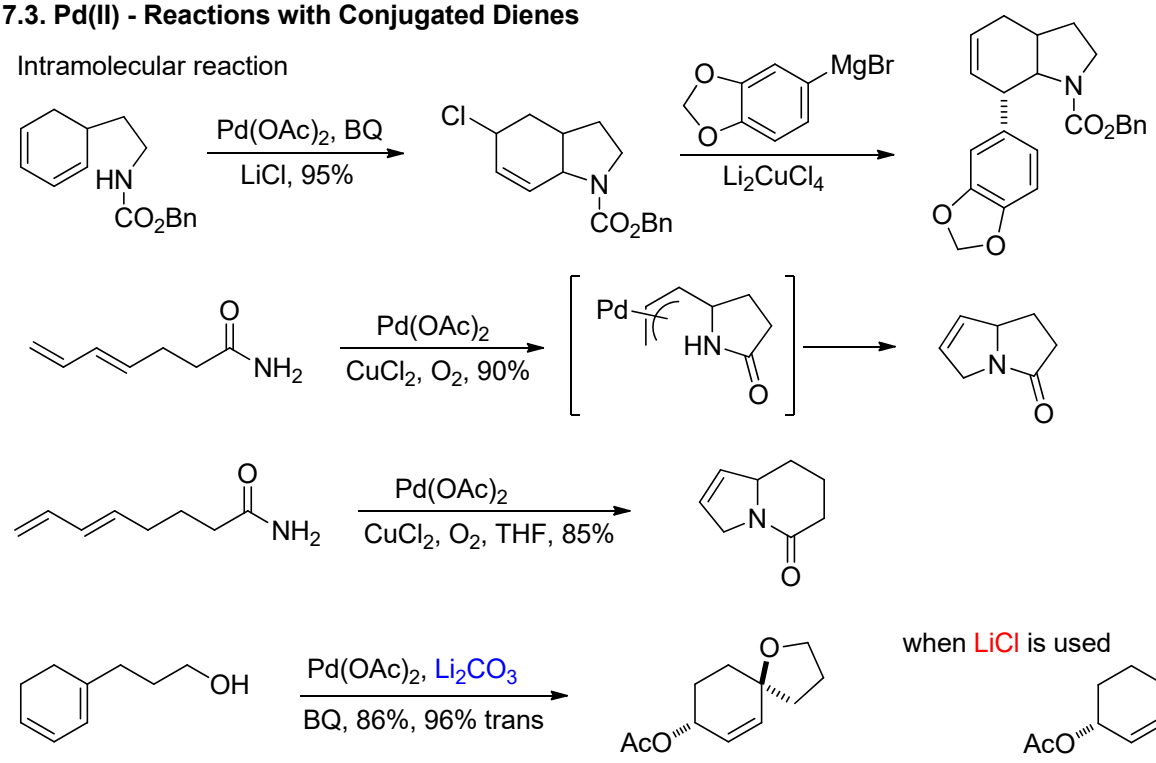






7.3. Pd(II) - Reactions with Conjugated Dienes

Intramolecular reaction

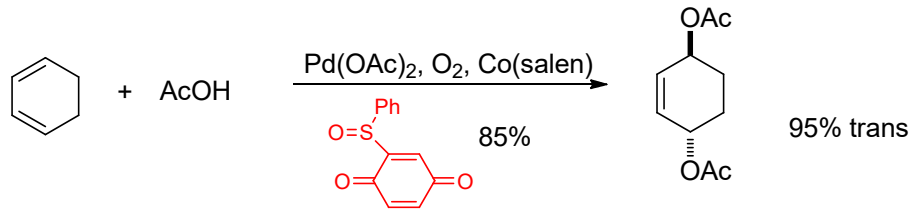


Catalytic reaction - use reoxidant of Pd(0)

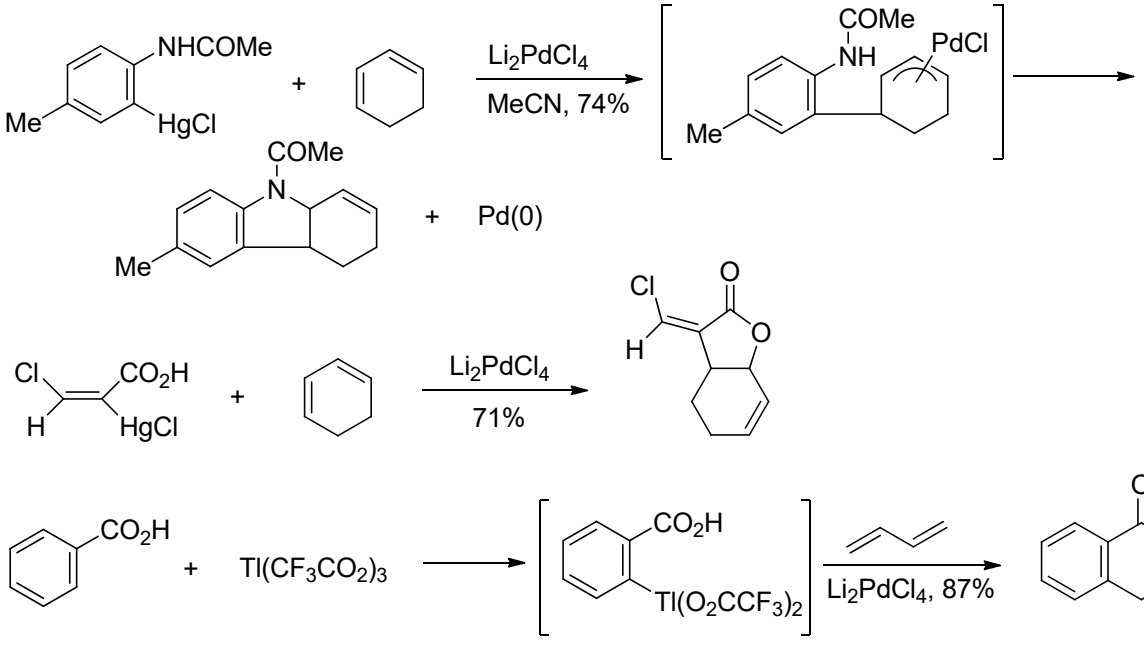
stoichiometric benzoquinone or

Fe-phthalocyanine complex or Co-salen complex is used to reoxidize hydroquinone to benzoquinone

Faster reaction and Higher in stereoselectivity is obtained when (phenylsulfinyl)benzoquinone is used.

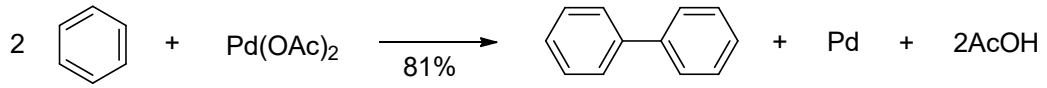


Aryl- or alkenylpalladium by transmetallation

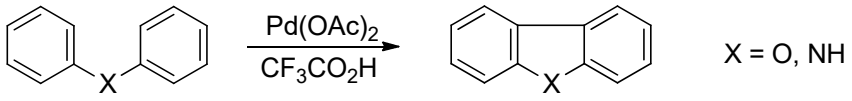


7.4. Pd(II) - Reactions with Aromatic Compounds

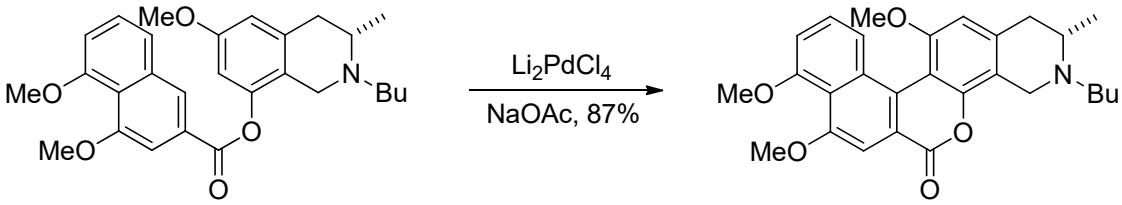
7.4.1. Homocoupling



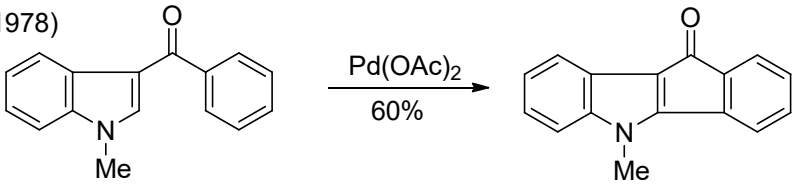
JOC, *40*, 1365 (1975)

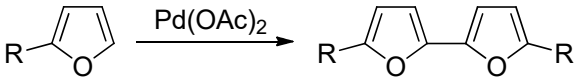


TL, *30*, 5249 (1989)

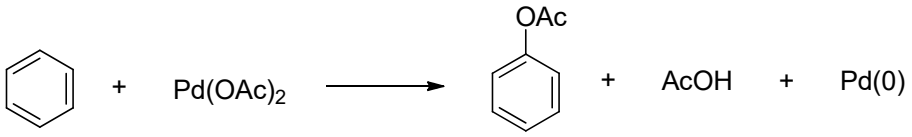


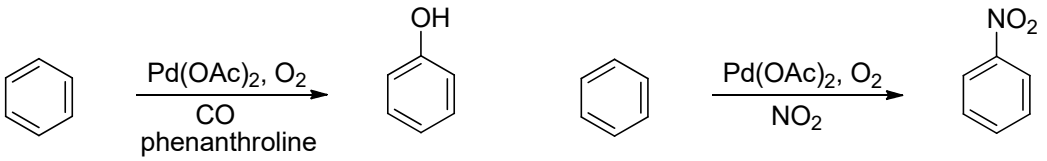
Synthesis, 607 (1978)

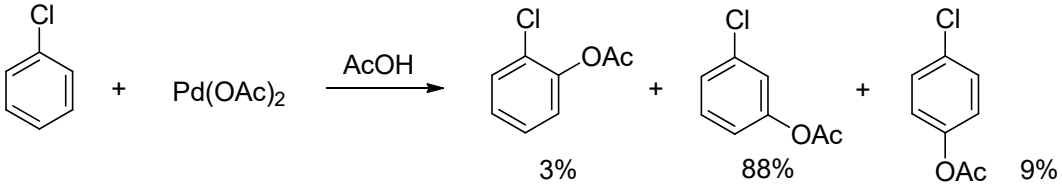


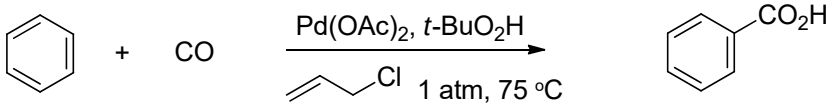


7.4.2. Oxidative Substitution

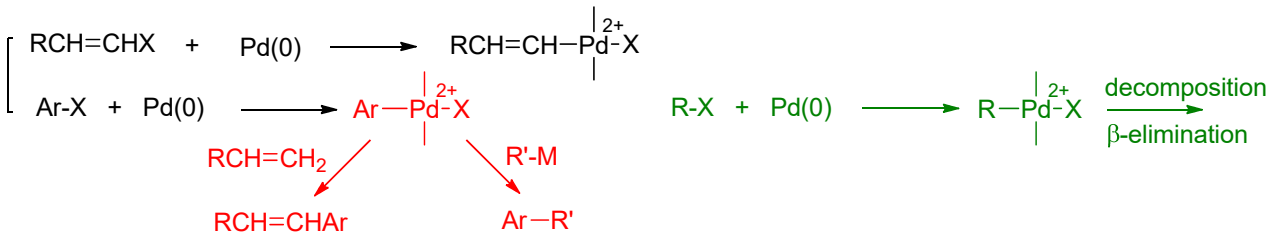




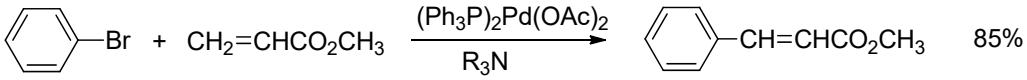




7.5. Pd(0) - Oxidative addition to halides or sulfonates (σ-bond)

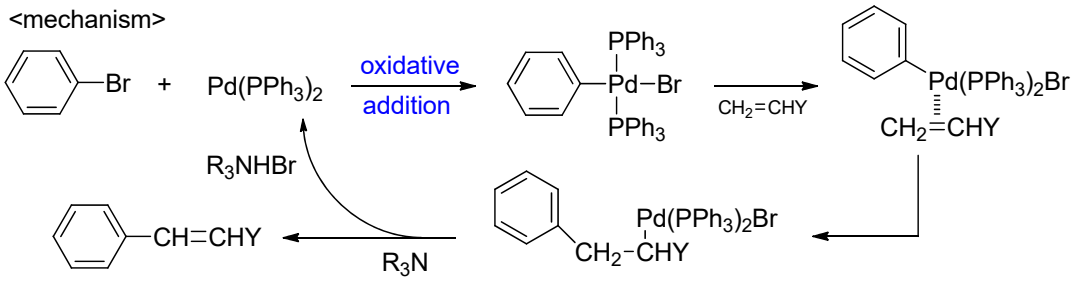


7.5.1. Heck reaction (reaction with alkenes)

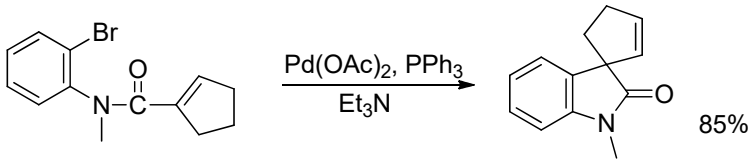


in situ reduction of Pd(II) to Pd(0): $Pd(OAc)_2$ + $2PPh_3$

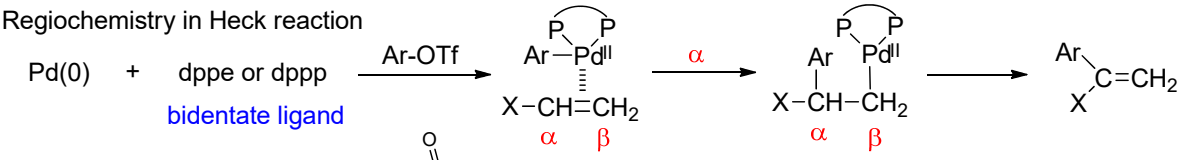
<mechanism>



* High halide concentration promote formation of $[PdL_2X]^-$, which retards coordination to double bonds.
Use -OTf instead of -X to accelerate complexation with alkenes.

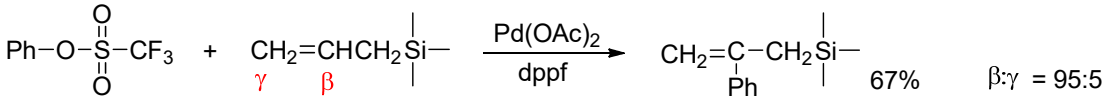


Regiochemistry in Heck reaction



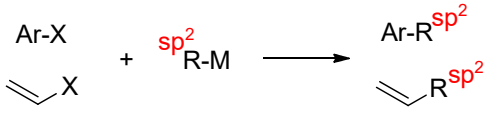
α: X = -OR, -OAc, $-CH_2OH$,  , ERG β: X = EWG

Silicon effect



7.5.2. Palladium-catalyzed cross coupling reaction

7.5.2.1. Coupling with organometallic reagents



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

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

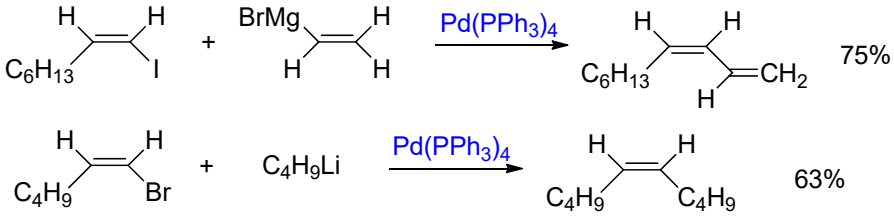
Steps in cross-coupling reaction:

oxidative addition - transmetallation - reductive elimination

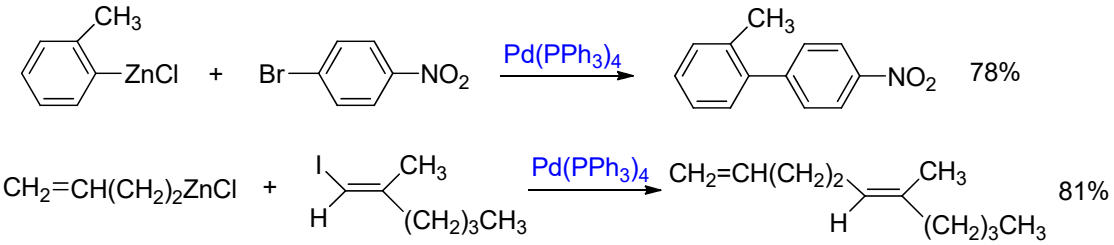
7.5.2. Palladium-catalyzed cross coupling reaction

7.5.2.1. Coupling with organometallic reagents

7.5.2.1.1. Grignard and organolithium reagents with Alkenyl halides

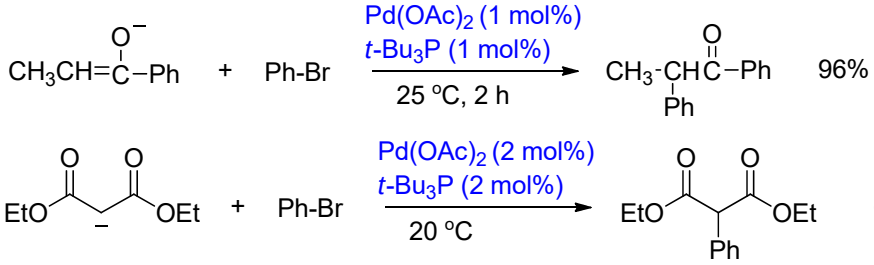


7.5.2.1.2. Organozinc reagents

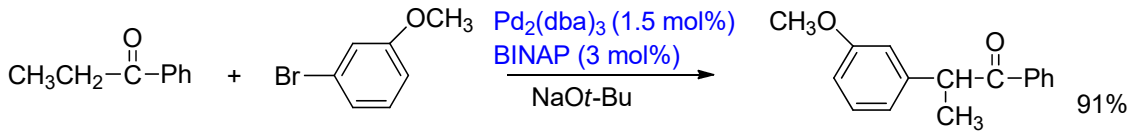


7.5.2.1.3. Arylation of enolates

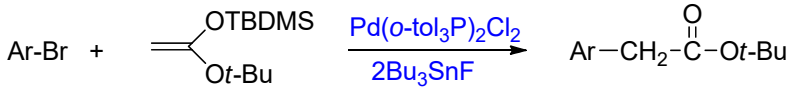
a. using *t*-Bu_3P, $Pd(OAc)_2$



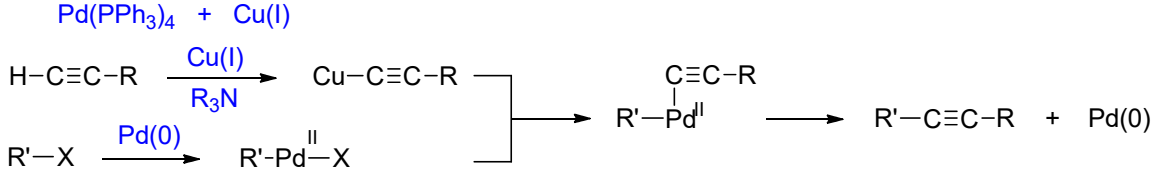
b. using BINAP ligand



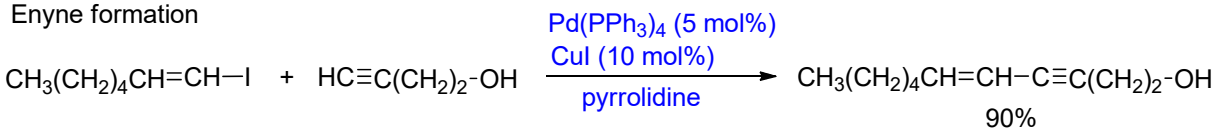
c. O-silyl ketene acetals with Bu_3Sn-F



7.5.2.1.4. Terminal alkynes with vinyl or aryl halides "copper acetylide"



Enyne formation



7.5.2. Palladium-catalyzed cross coupling reaction

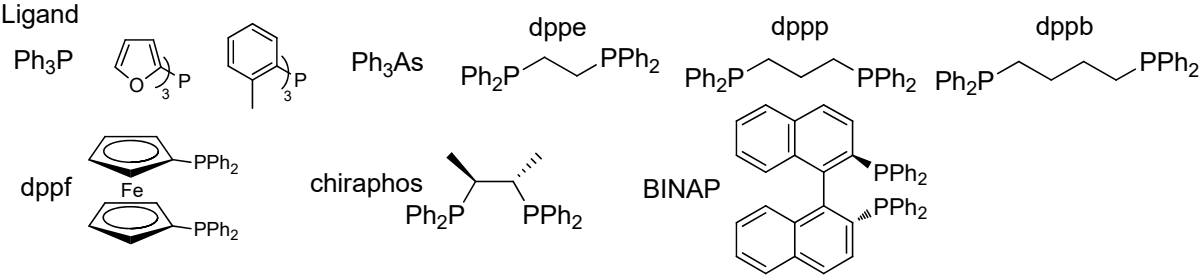
7.5.2.2. Coupling with stannanes

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

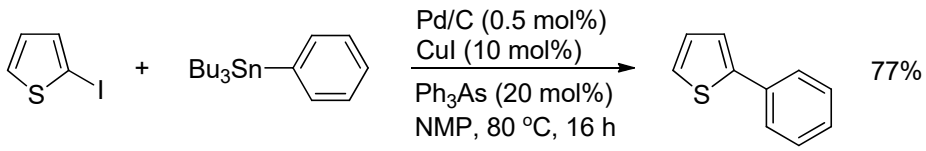
Group that can be transferred from tin:

alkynyl > alkenyl > aryl > methyl > alkyl

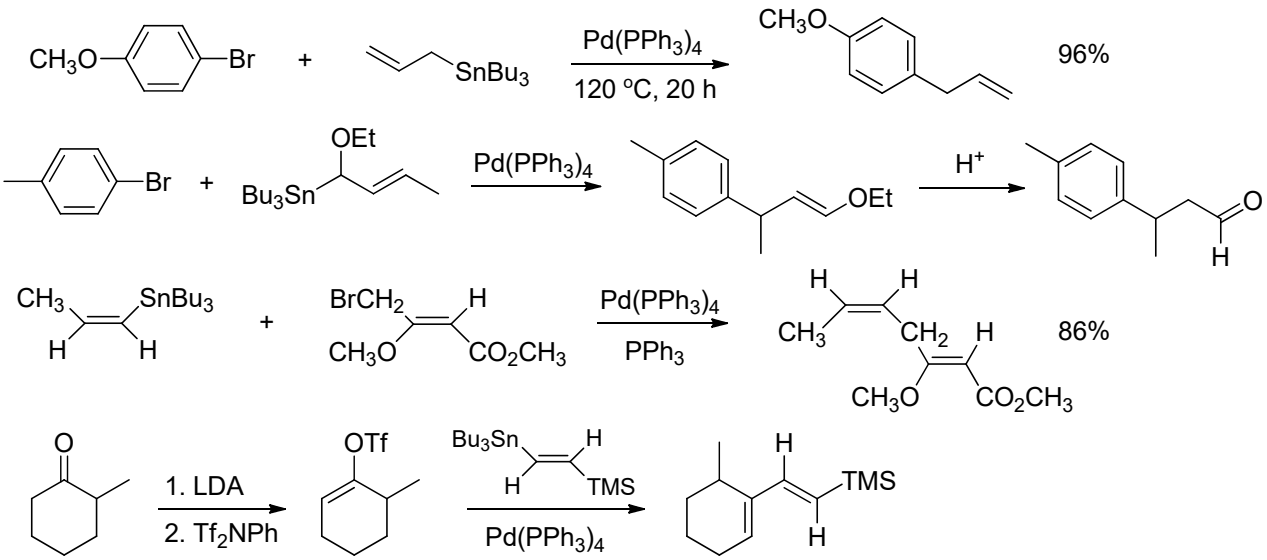
Ligand



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



Eaxamples



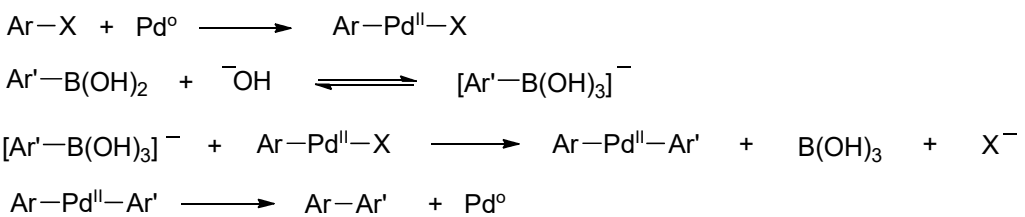
7.5.2.3. Coupling with organoboranes

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

boric acid as a biproduct

Rate-determining step: oxidative addition or transmetallation

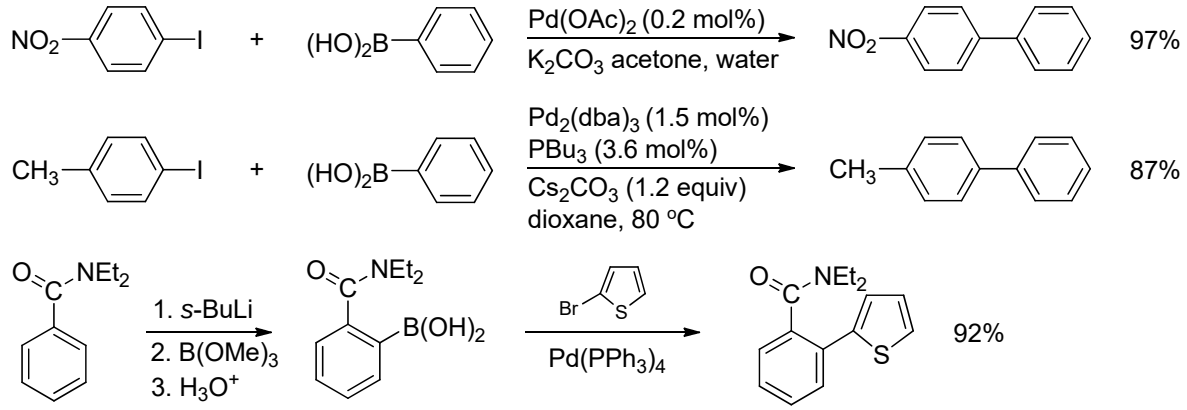
Base catalysis is required for boronic acids to generate more reactive boronate anion.



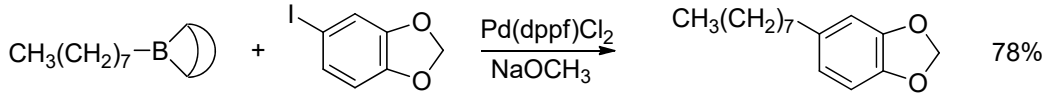
7.5.2. Palladium-catalyzed cross coupling reaction

7.5.2.3. Coupling with organoboranes

Eaxamples



Alkyl-aryl coupling using 9-BBN

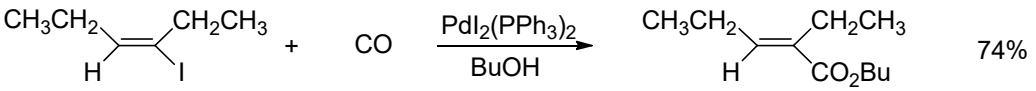


Bases

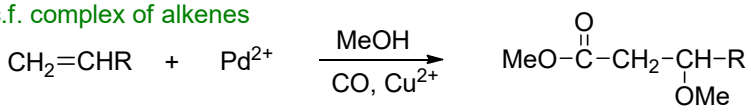
Cs_2CO_3 or TlOH > NaOH

7.5.2.4. Reaction with carbon monoxide (CO)

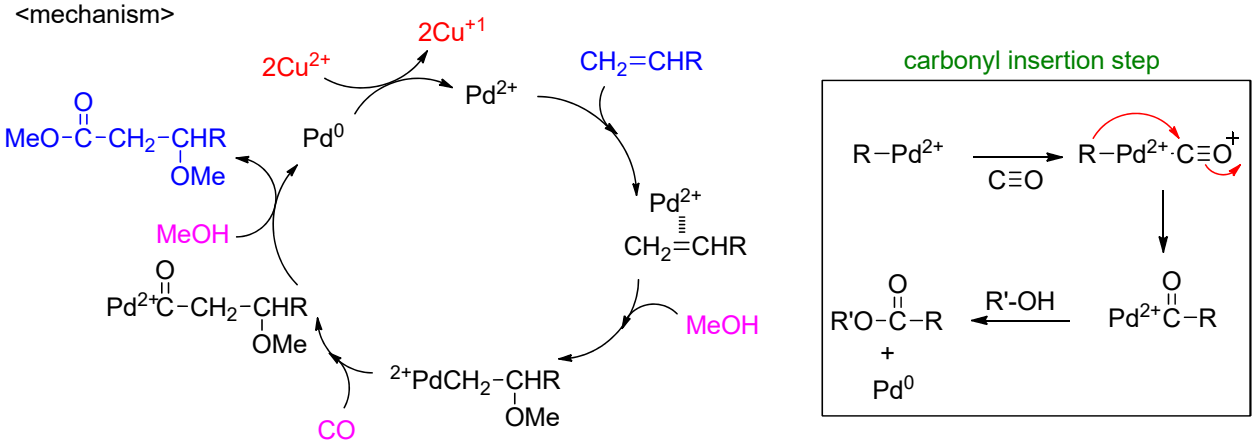
7.5.2.4.1. Reaction in ROH



c.f. complex of alkenes



<mechanism>

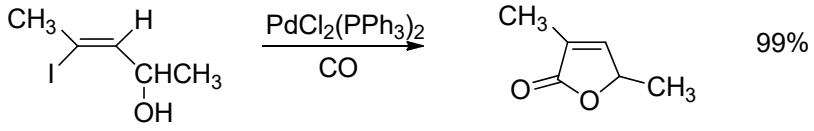


7.5.2. Palladium-catalyzed cross coupling reaction

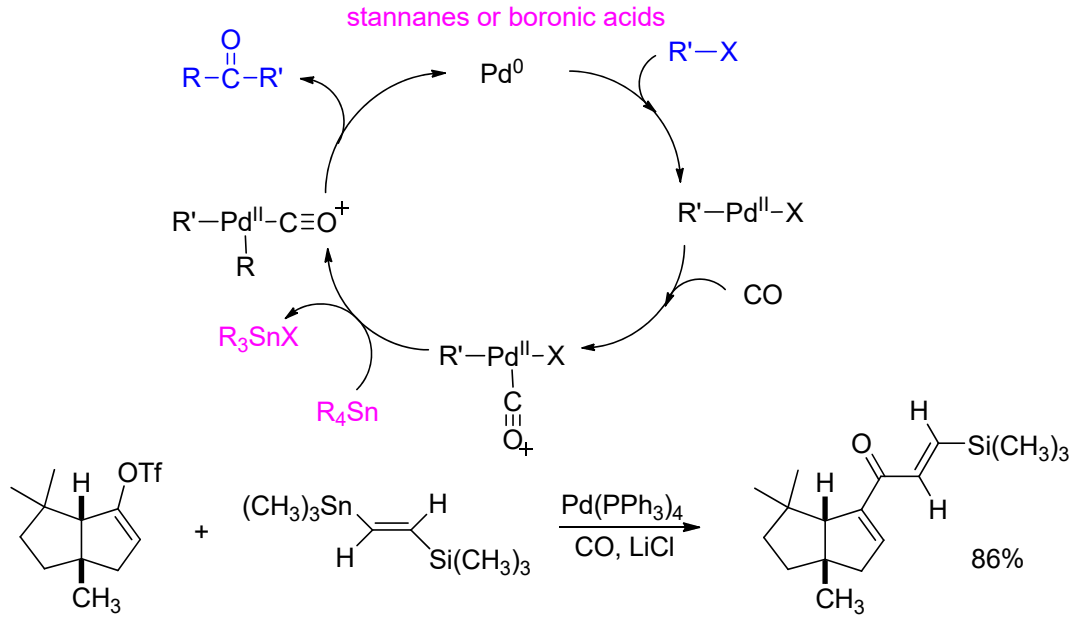
7.5.2.4. Reaction with carbon monoxide (CO)

7.5.2.4.1. Reaction in ROH

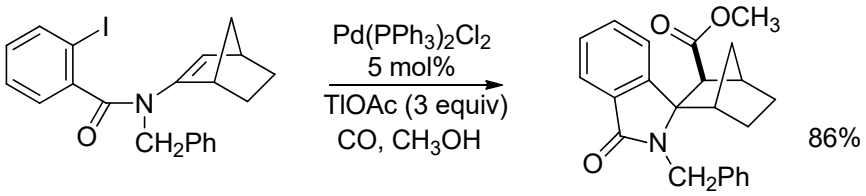
Intramolecular version



7.5.2.4.2. Coupling of organometallic reagents with aryl or vinyl halides



7.5.2.4.3. Tandem intramolecular Heck-carbonylation reaction



7.5.2.5. Coupling of organostannane with acyl chlorides