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

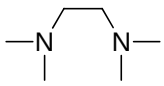
RLi	*In hydrocarbon solv.*	*In ethereal solv.*
MeLi	-	Tetramer
EtLi	Hexamer	Tetramer
n-BuLi	Hexamer	Tetramer
i-BuLi	Tetramer	-
BnLi	Dimer	Monomer
i-PrLi	Tetramer	Dimer
s-BuLi	-	Dimer
PhLi	-	Dimer
t-BuLi	Tetramer	Dimer

Half-lives of RLi

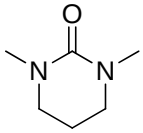
		Temperature (°C)					
RLi	*Solv.*	-70	-40	-20	0	+20	+35
t-BuLi	DME	11 m					
	THF		5.6 h	42 m			
	ether			8 h	1 h		
s-BuLi	DME	2 h	2 m				
	THF			1.3 h			
	ether			20 h	2.3 h		
n-BuLi	DME			1.8 h	<5 m		
	THF				17 h	1.8 h	10 m
	ether					153 h	31 h
PhLi	ether						12 d
MeLi	ether					3 mon	

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

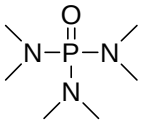
TMEDA



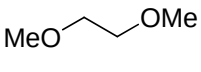
DMPU



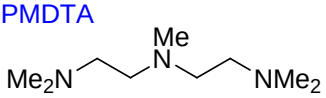
HMPA



DME

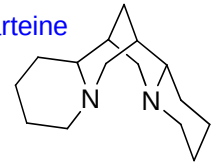


PMDTA

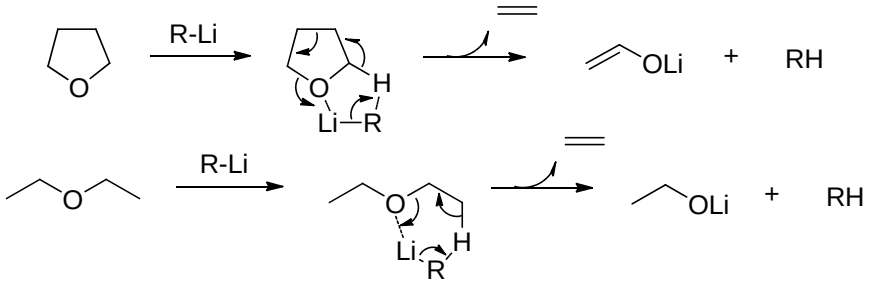


THF

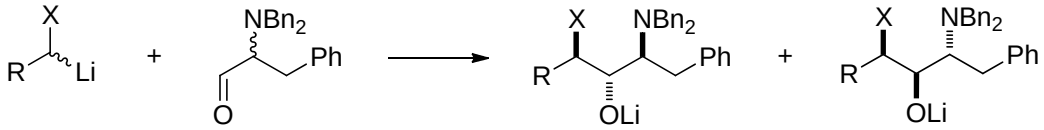
(-)-sparteine



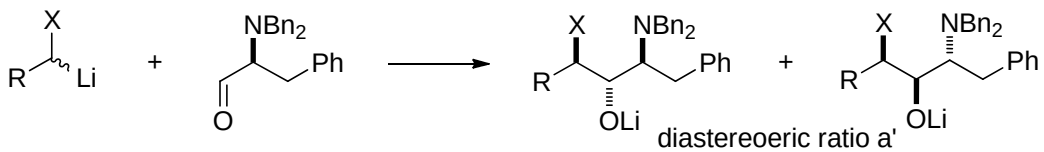
Thermal Decomposition in etheral solvents



Configurational Stability - The Hoffmann test



diastereoeric ratio a



diastereoeric ratio a'

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

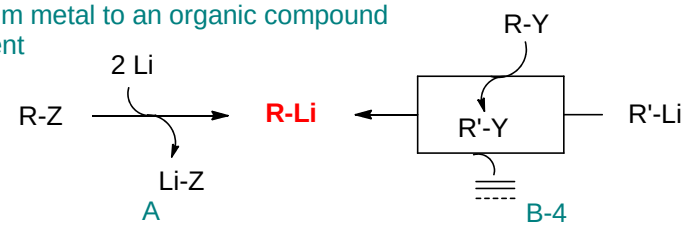
If a' ≠ a, then the organolithium compund is configurationally unstable

1.2 Methods for the Preparation of Organolithium Compounds

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

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



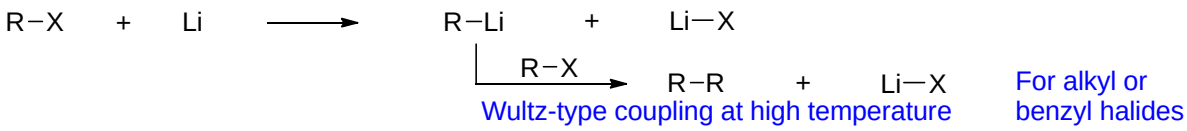
1.2.1 Reductive Lithiation using Lithium Metal

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

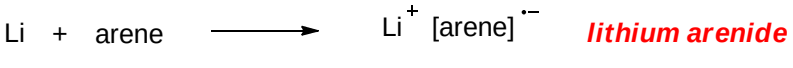
the order of reactivity: radical formation is the rate determining step

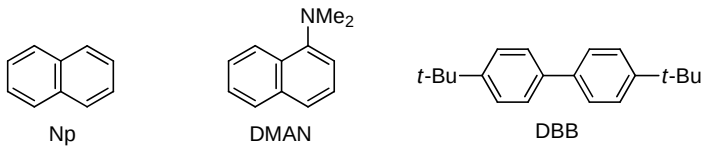
Alkyl-Li

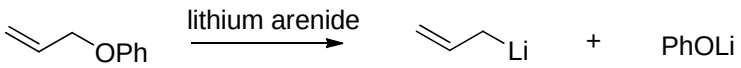
tert- > sec- > pri- > vinyl-Li > aryl-Li

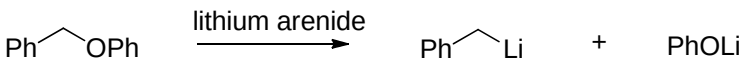


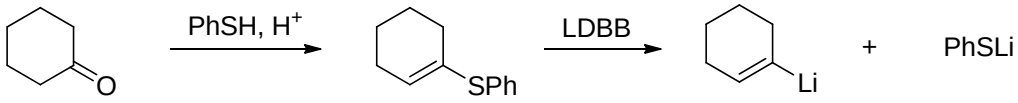
Use lithium arenides: the homogeneous solution lowers the reaction temeperature therby reduce the side reaction product











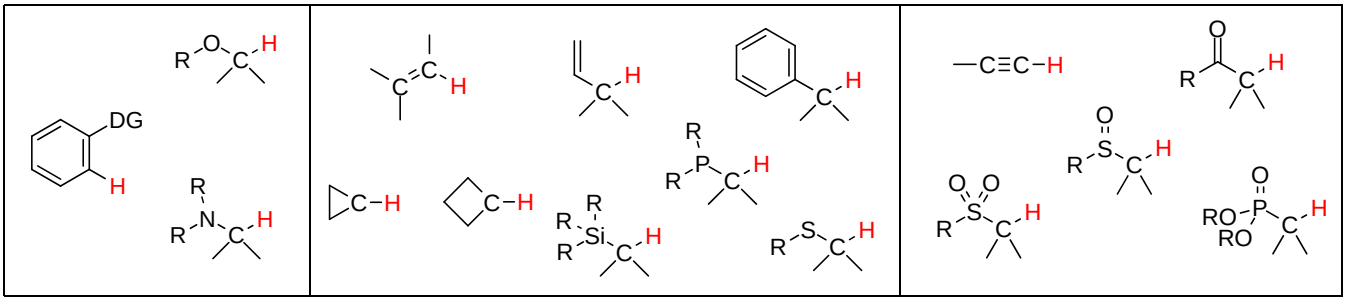
1.2.2 Preparation from Another Organolithium Compounds

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

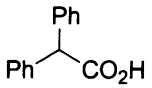
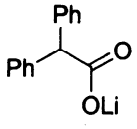
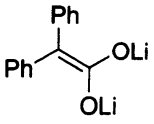
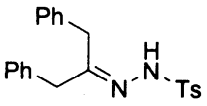
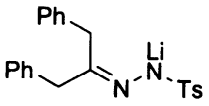
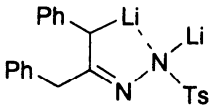
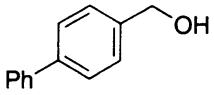
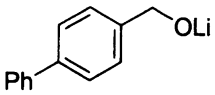
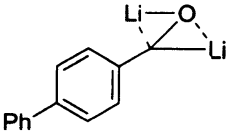
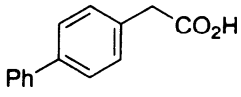
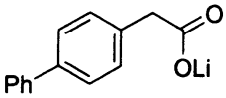
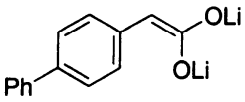
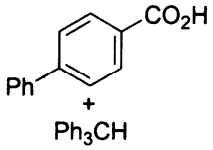
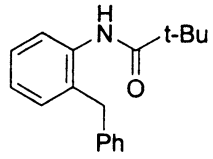
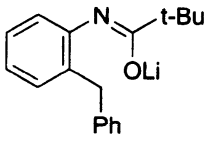
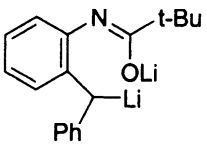
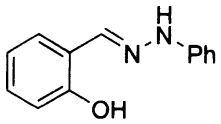
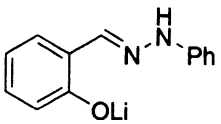
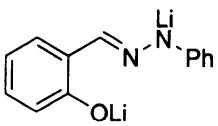
deprotonation of a C-H bond without sufficient acidity is facilitated by the introduction of heteroatom functionality at a neighboring position.

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

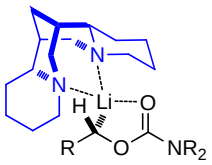
easier deprotonation

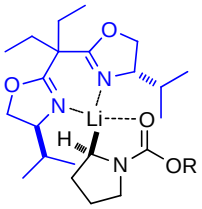


Tab. 1.4 Color indicators in titration

Color indicator	*Color change*	*Suitable RLi*	*Reference*
	 colorless →  yellow	MeLi n-BuLi	[21]
	 colorless →  orange	MeLi n-BuLi t-BuLi PhLi	[22]
	 colorless →  orange red	MeLi n-BuLi s-BuLi t-BuLi	[23]
	 colorless →  bright yellow	n-BuLi s-BuLi t-BuLi	[23]
	colorless → deep red	n-BuLi s-BuLi t-BuLi	[23]
	 colorless →  yellow orange	MeLi n-BuLi s-BuLi t-BuLi PhLi	[24]
	 yellow →  red	MeLi n-BuLi t-BuLi	[25]

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

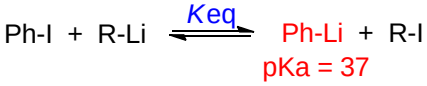


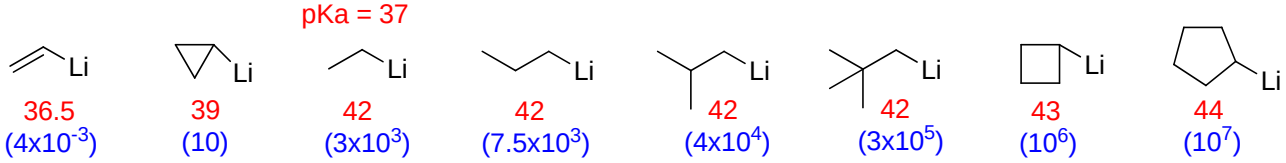


1.2.2 Preparation from Another Organolithium Compounds

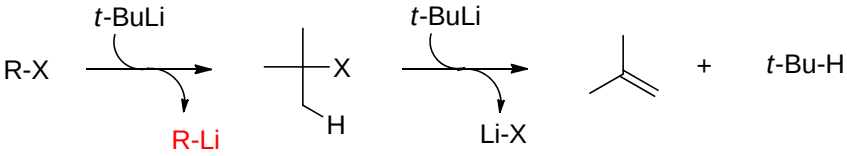
1.2.2.2 Halogen-Lithium Exchange - equilibrium process

Synthetically useful for the preparation of aryllithium or vinyllithium





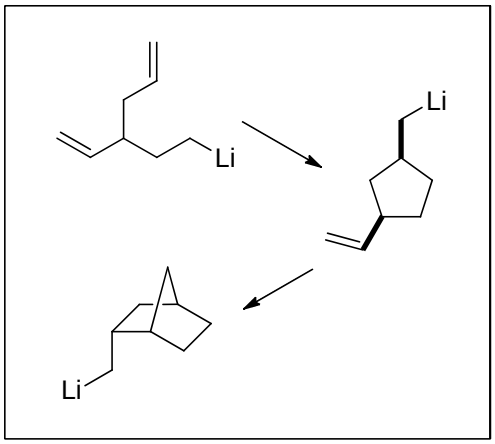
Use of 2 equiv of *t*-BuLi



The rate of halogen-lithium exchange

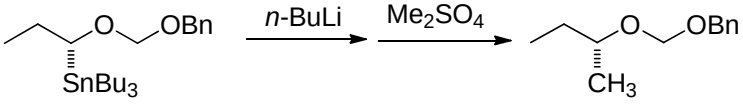
R-I > R-Br > R-Cl >> R-F

Accelerated by the presence of ethereal solvents



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

tin-lithium exchange



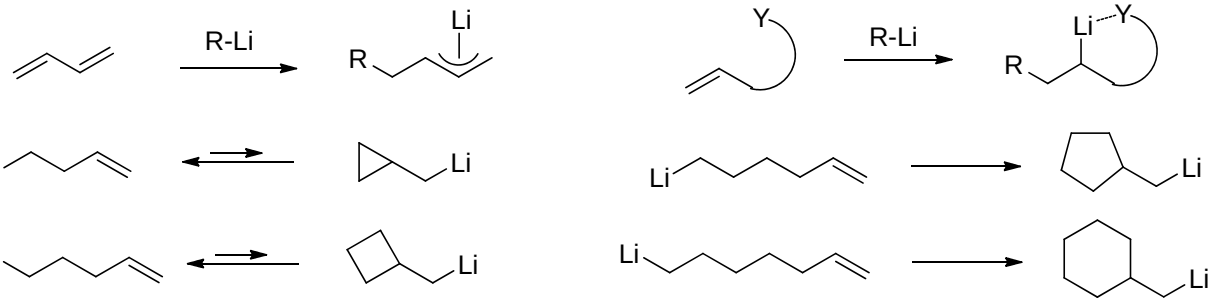
1.2.2.4 Carbolithiation

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

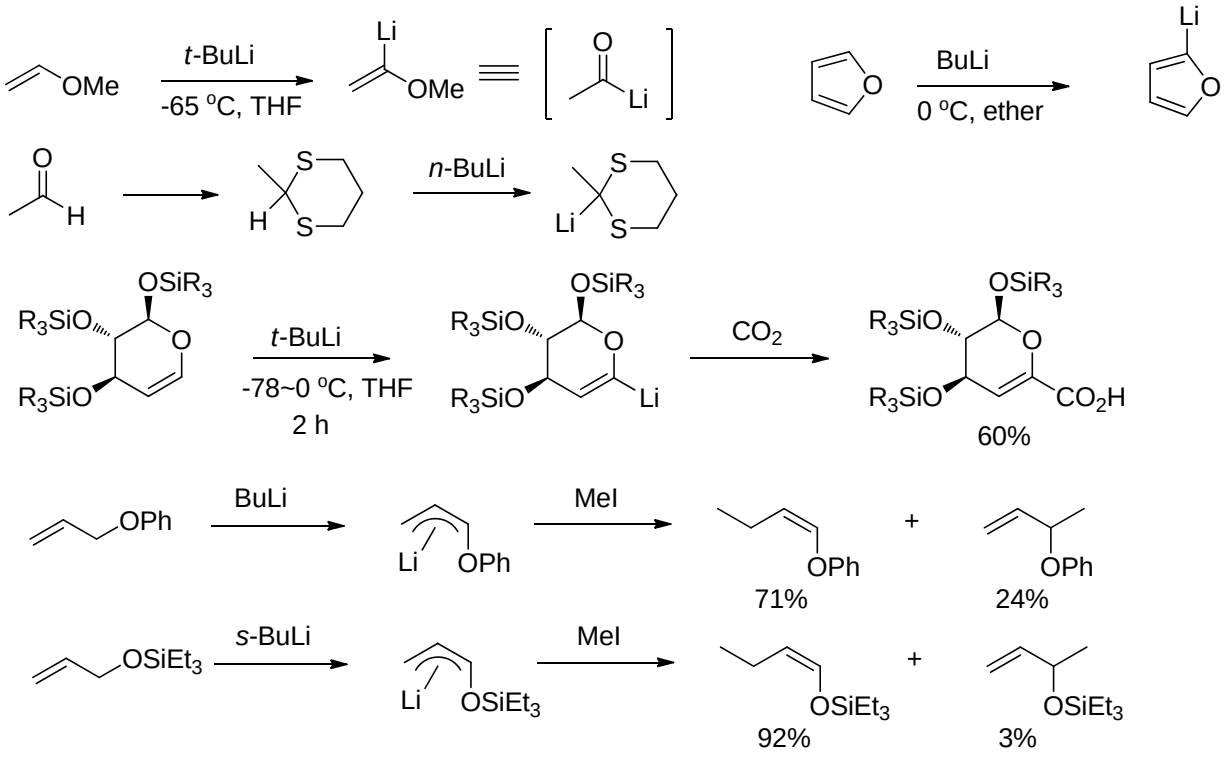
Activation by TMEDA, DABCO, or (-)-sparteine is advantageous



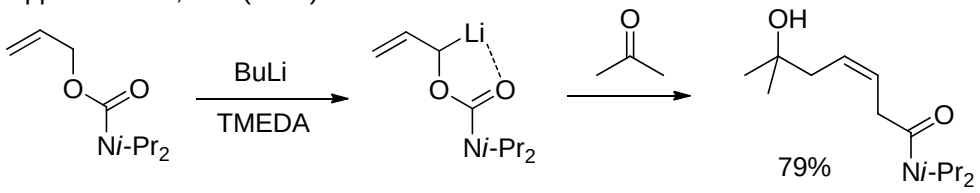
1.3. Examples of Lithiation

1.3.1. **Lithiation by Deprotonation**

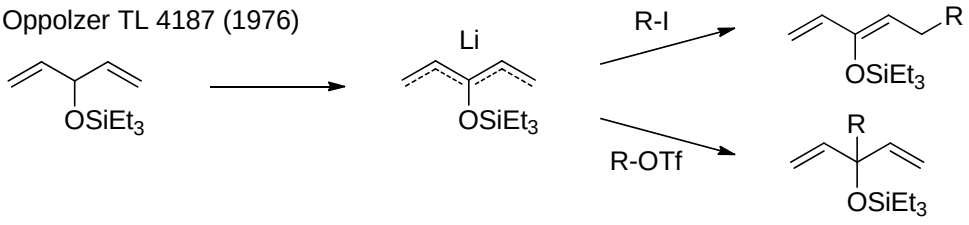
1.3.1.1. Formation of vinylic, allylic or benzylic organolithiums alpha to oxygen

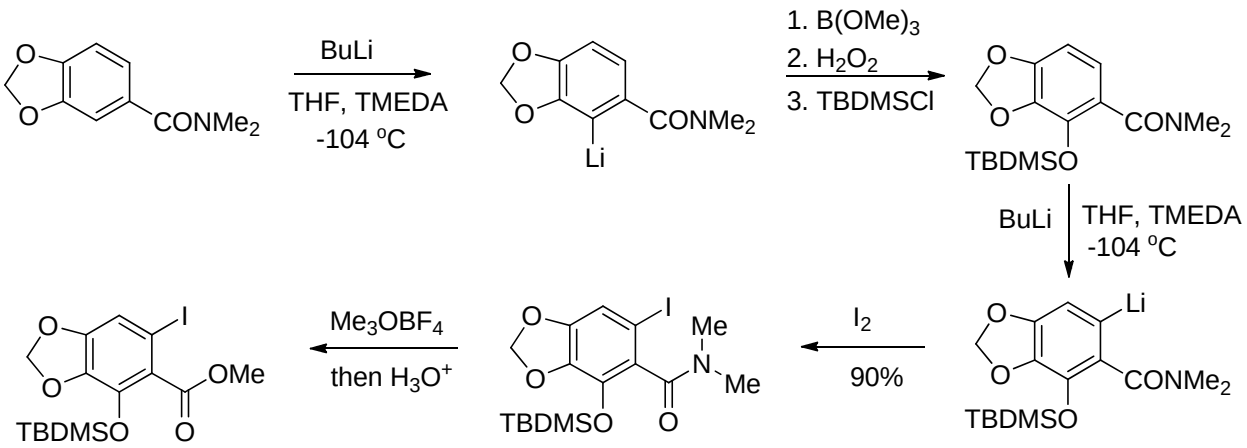


Hoppe ACIE **23**, 932 (1984)



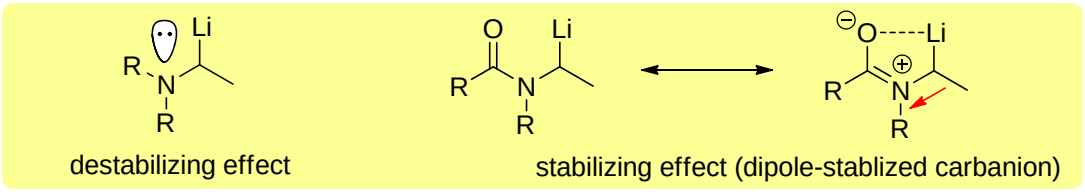
Oppolzer TL 4187 (1976)

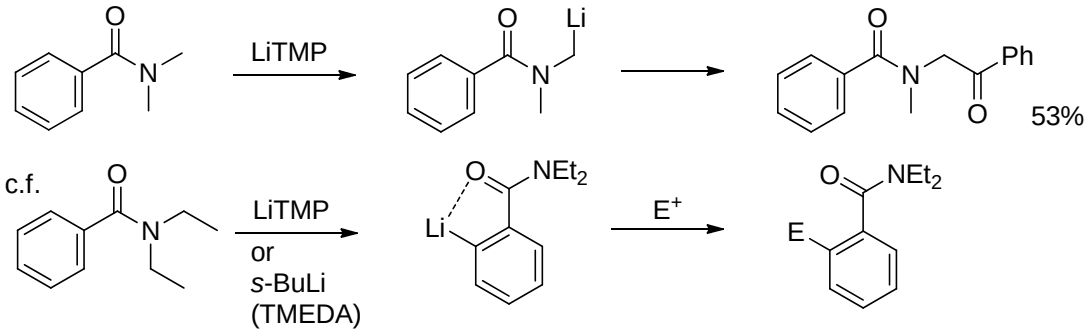




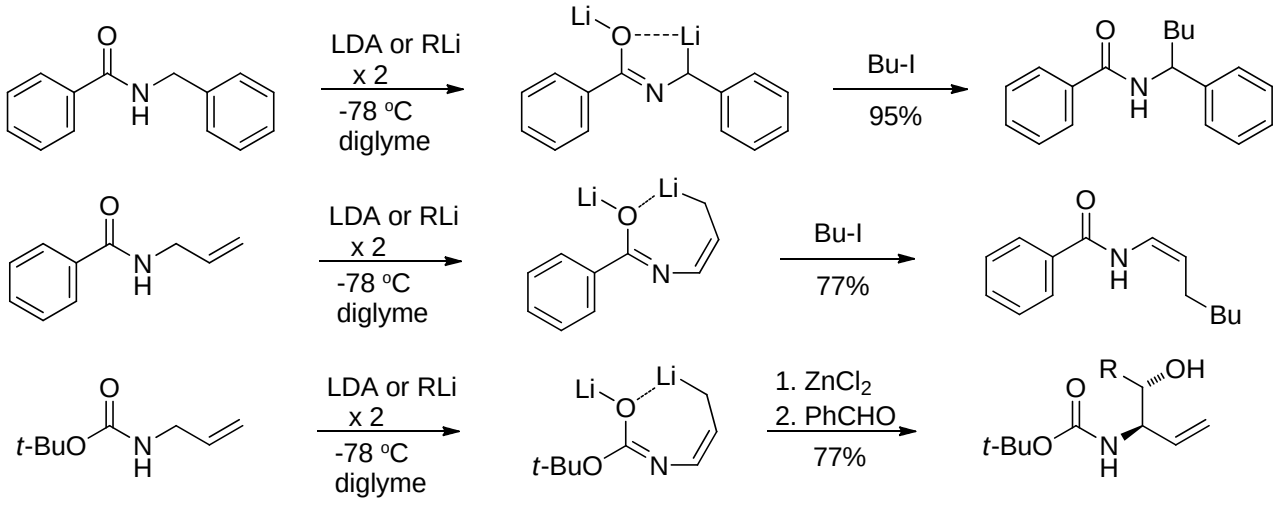
1.3.1. **Lithiation by Deprotonation**

1.3.1.2. Lithiation alpha to nitrogen

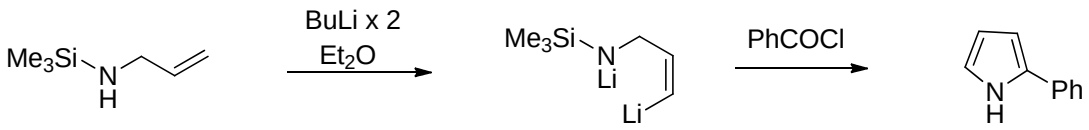


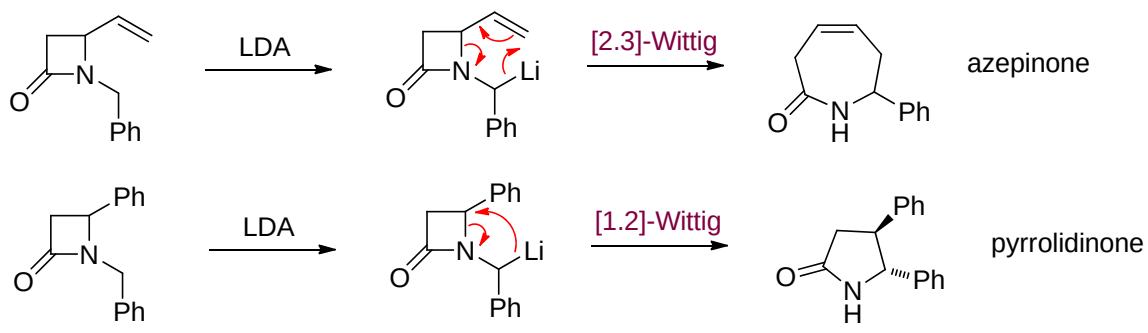


N-benzyl or *N*-allyl amide



c.f.

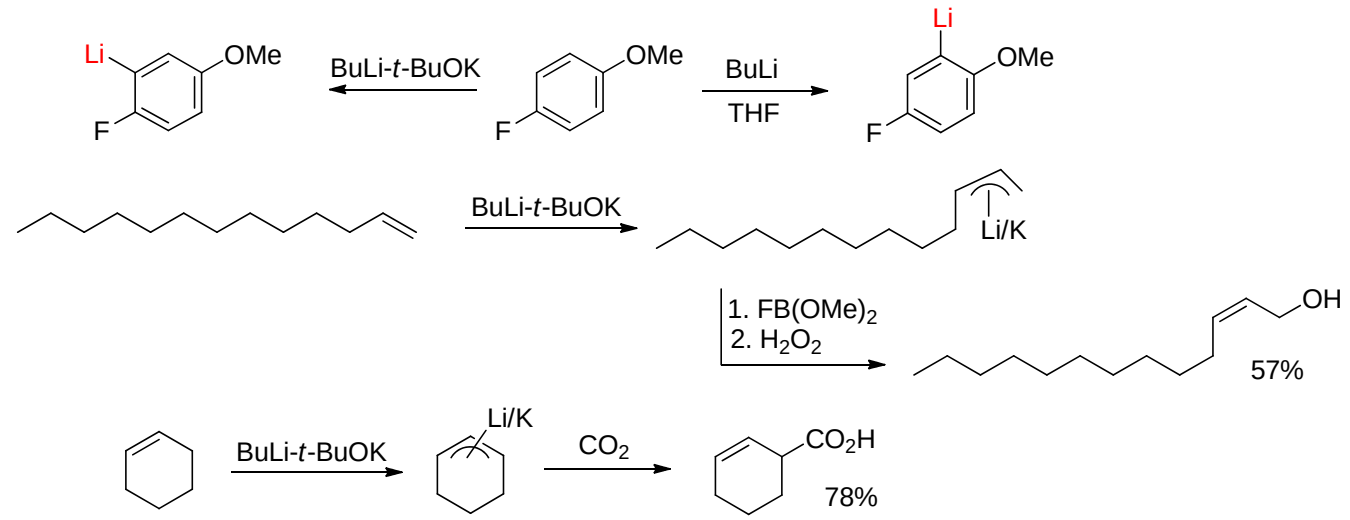




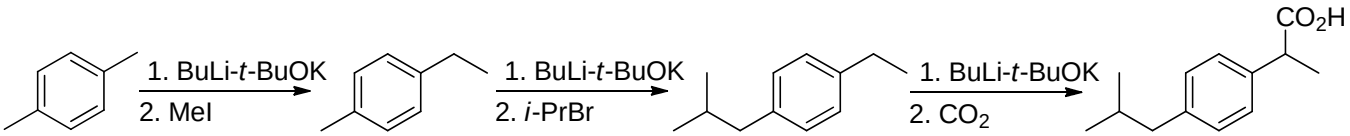
1.3.1. **Lithiation by Deprotonation**

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

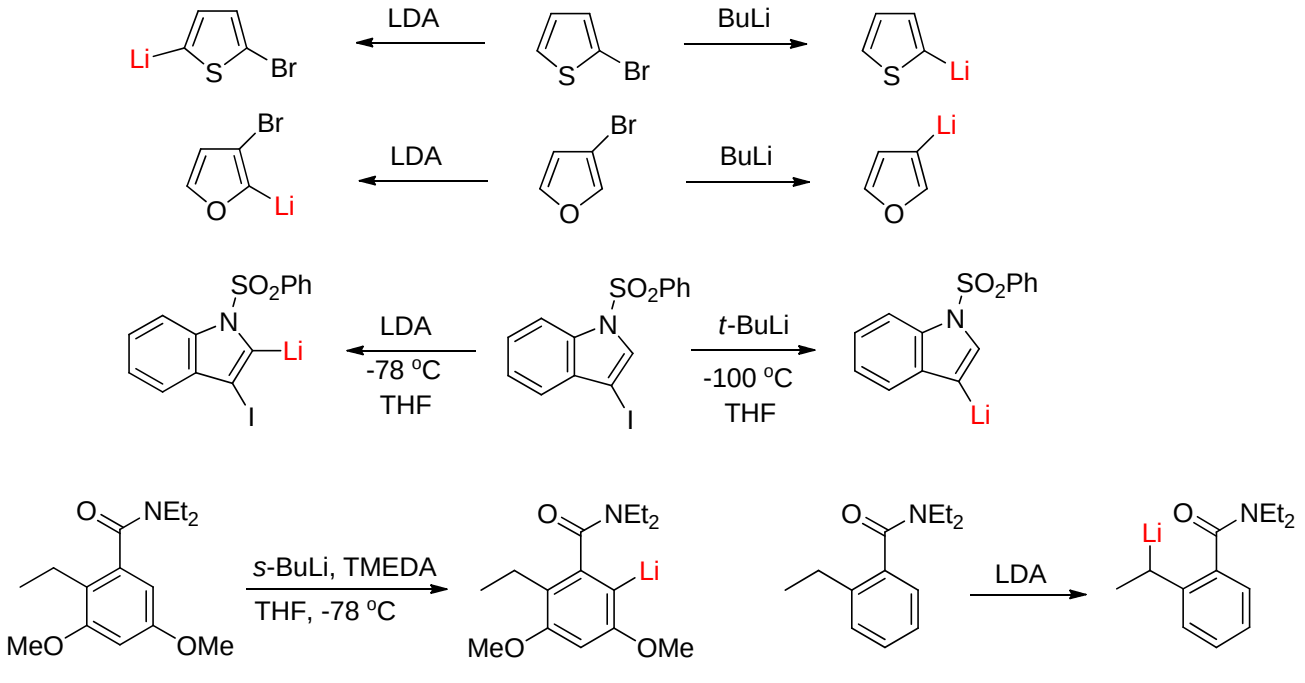
Deprotonate Allylic, Benzylic, Vinylic, Aromatic and Cycloprpane C-H with no Additional Assistance
Remove the Most Acidic Protone



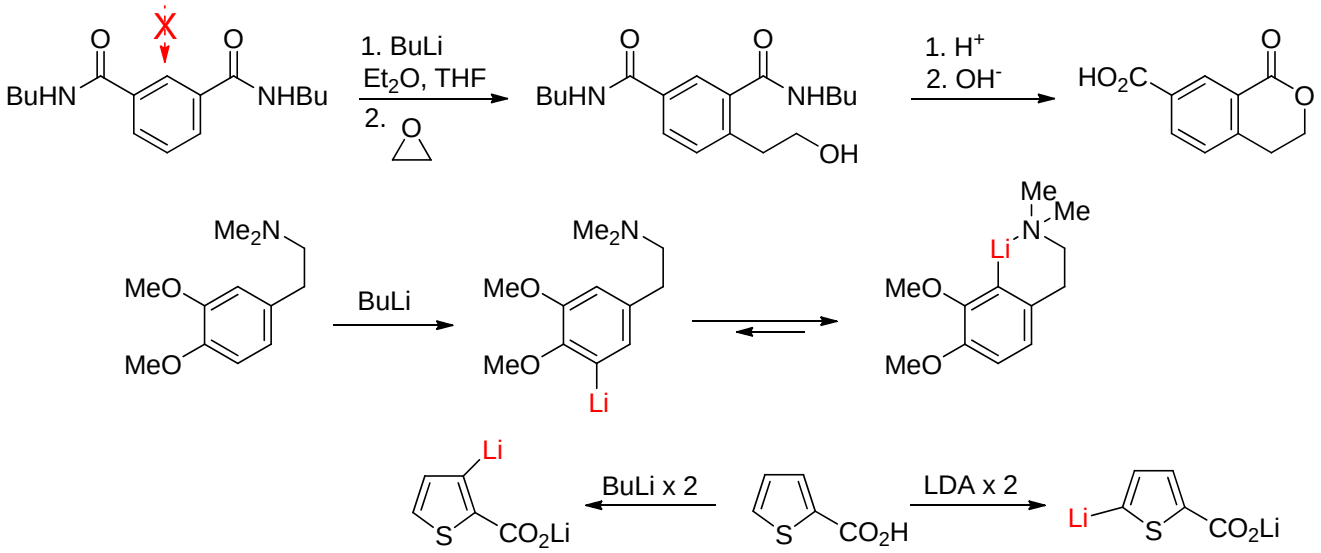
Ibuprofen Synthesis by Schlosser

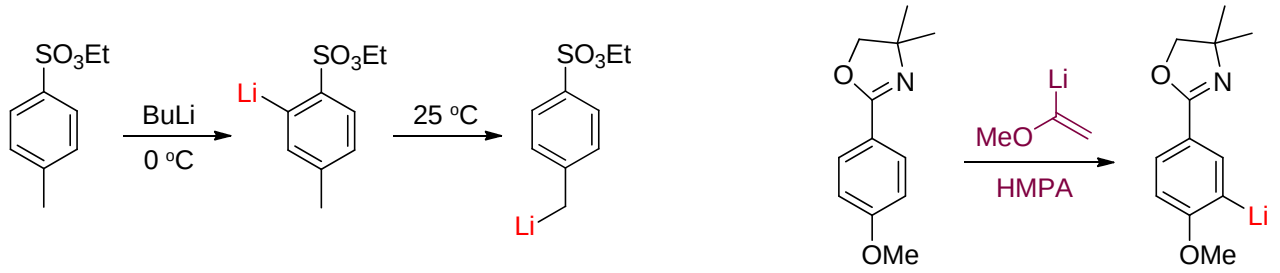


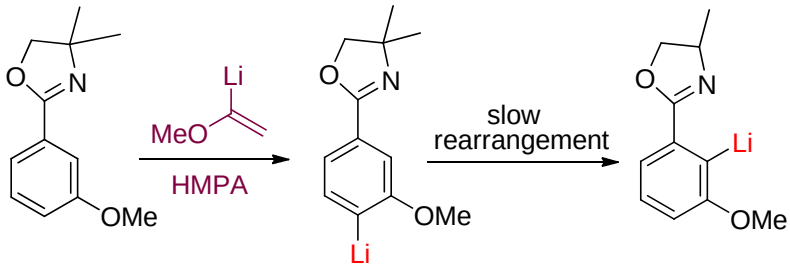
1.3.2. Ortholithiation vs. Halogen-metal exchange

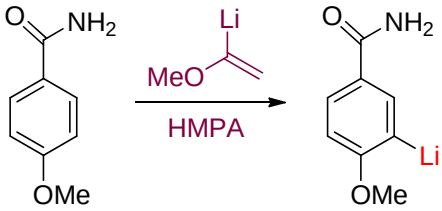


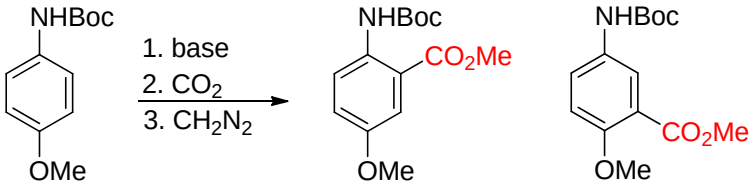
1.3.3. **Cooperation, competetion, and regioselectivity** in **Lithiation by Deprotonation**



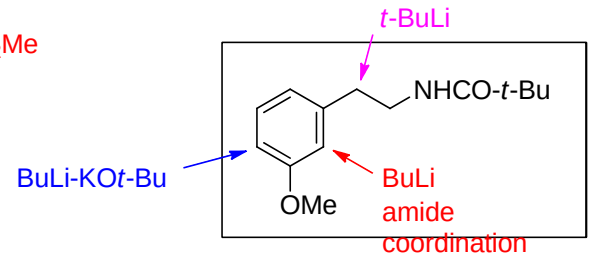


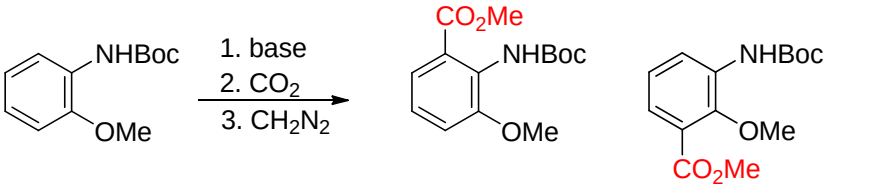






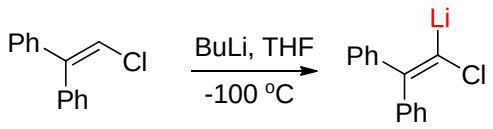
Steric hindrance control

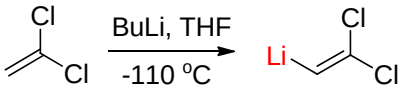


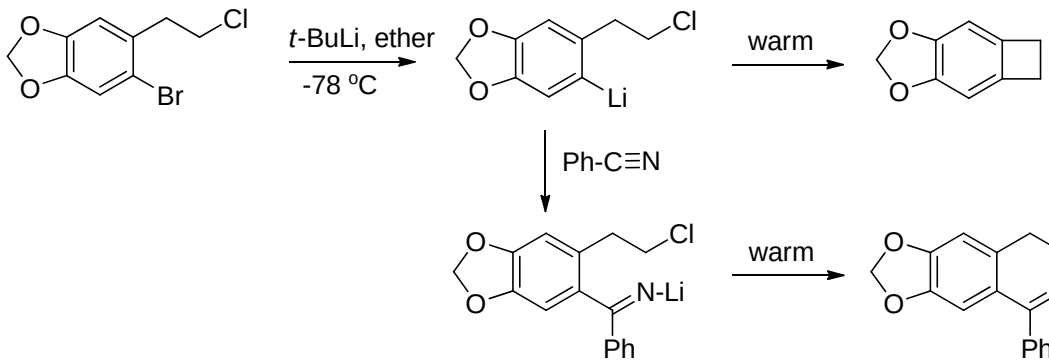


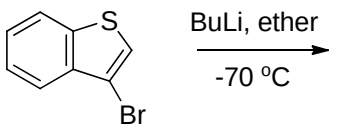
1.3.4. **Lithiation by X-Li Exchange**

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

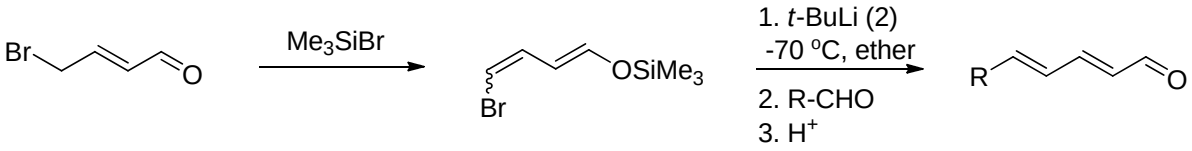




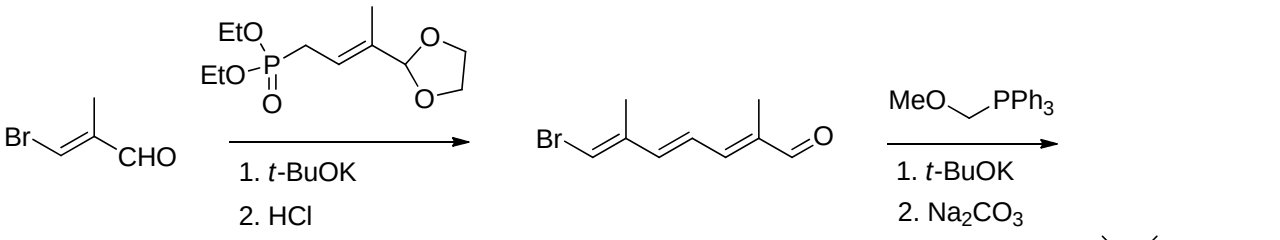


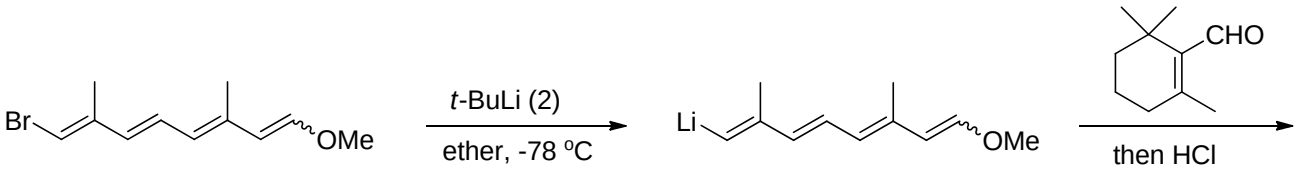


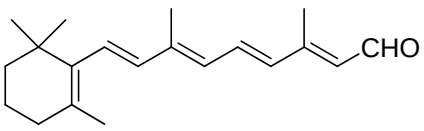
Dickinson
J. C. S. (C) **1971**, 3447



Retinal Synthesis

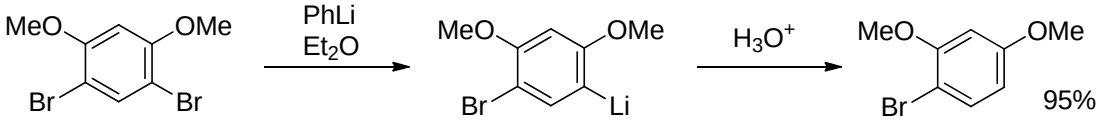




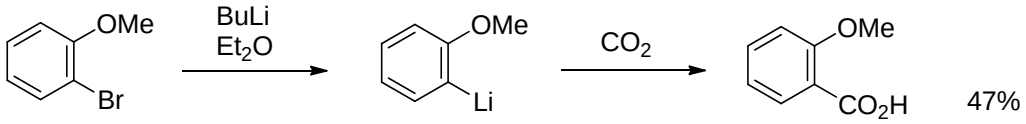


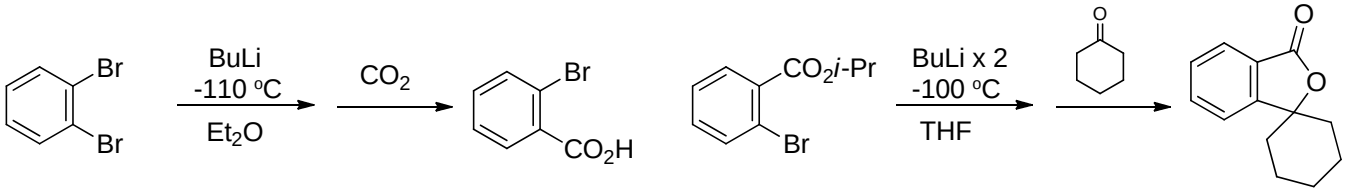
1.3.4. Examples of Lithiantion by **X-Li Exchange**

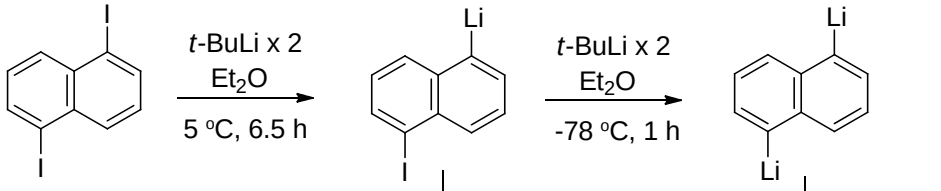
Wittig Chem. Ber. **71**, 1903 (1938)

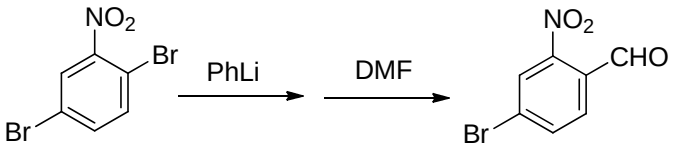


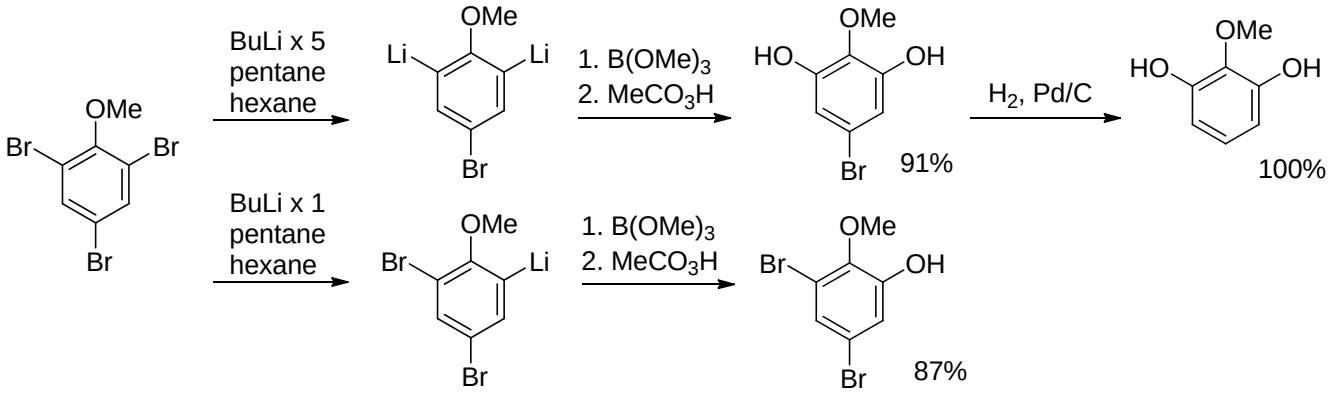
Gilman J. Am. Chem. Soc. **61**, 106 (1939)

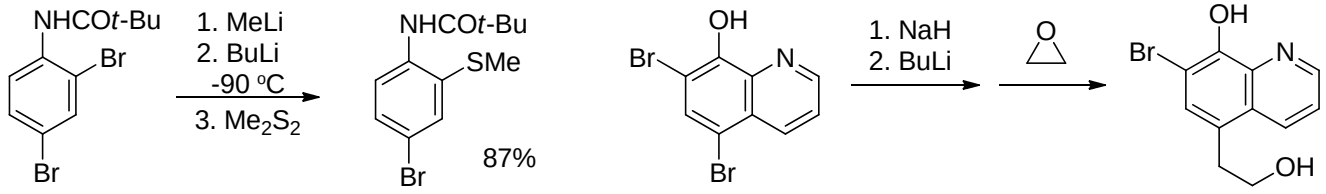




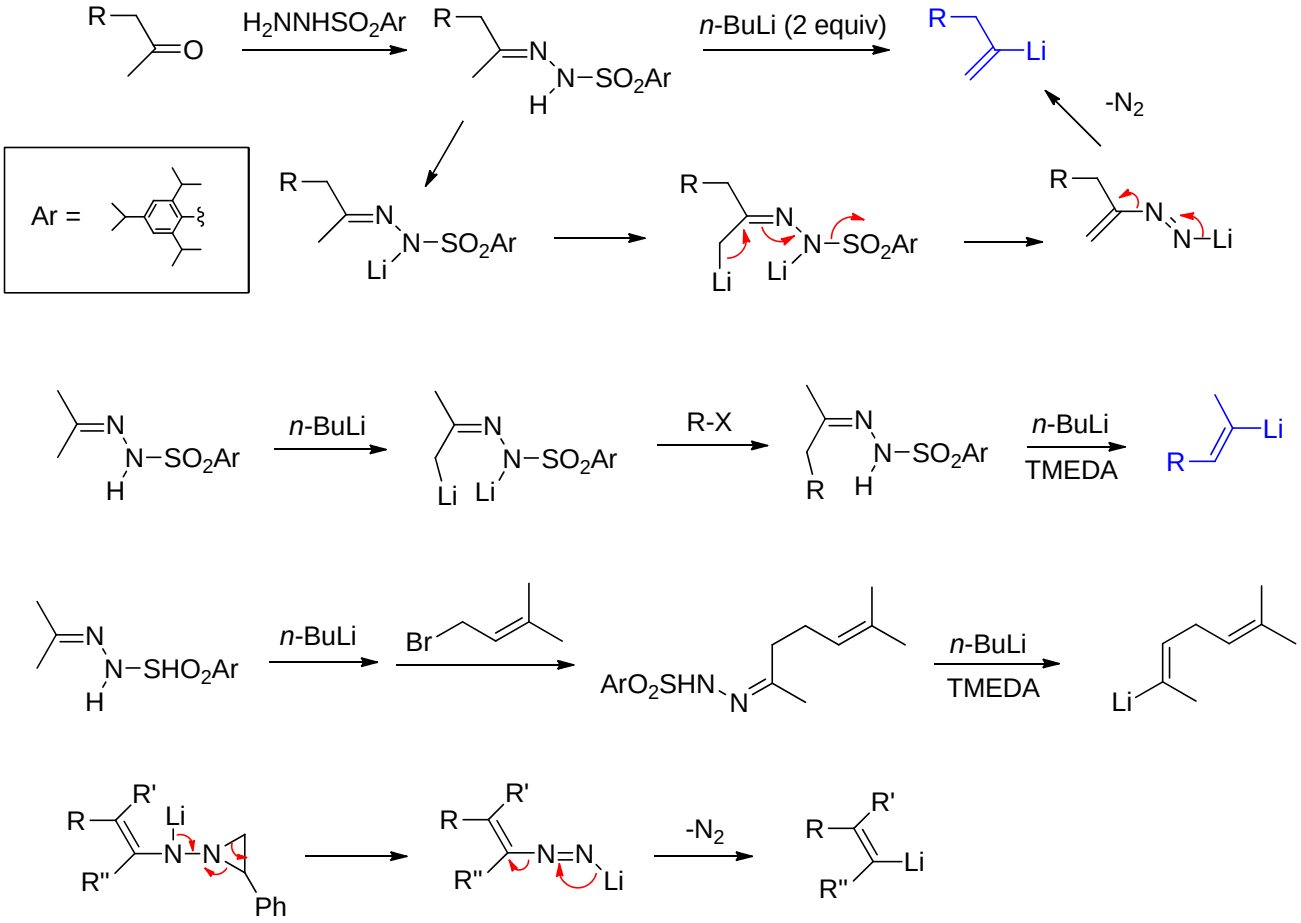








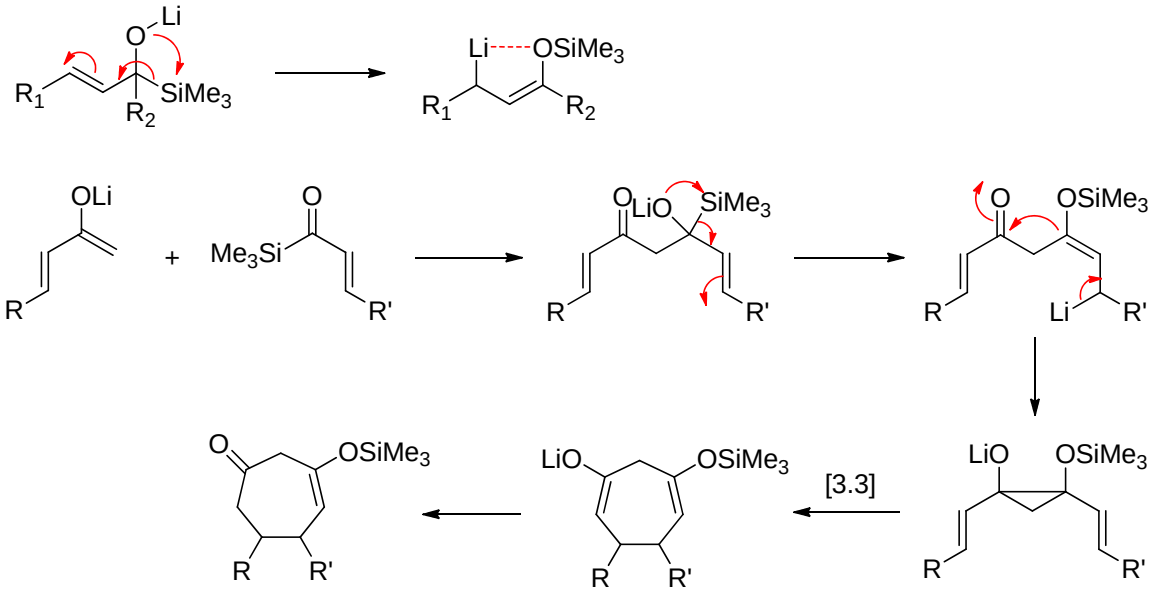
1.3.5. Preparation of Vinyllithium by Shapiro Reaction



from 1-amino-2-phenylaziridine

1.3.6. Miscellaneous

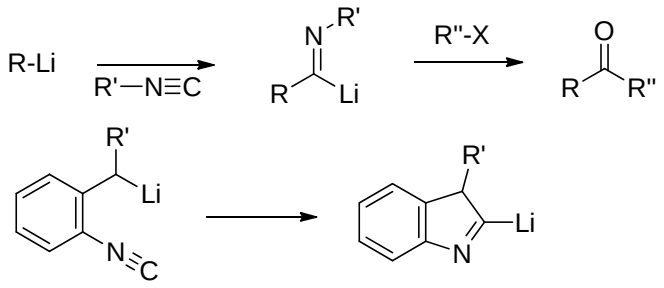
1.3.6.1. 1,2-Brook Rearrangement



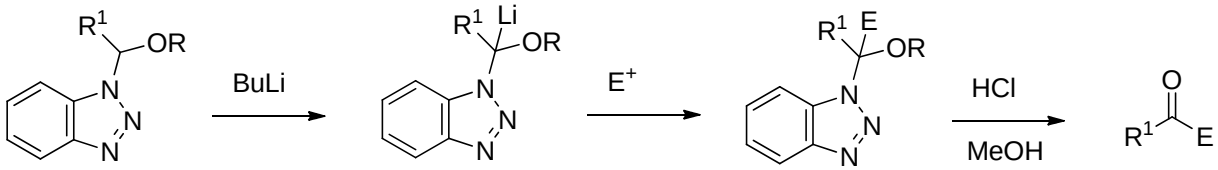
1.3.6. Miscellaneous

1.3.6.2. Acyllithium and Iminoacyllithium using CO and Isonitriles

Acyl anion equivalent



1.3.6.3. Benzotriazoles as acyl anion equivalents

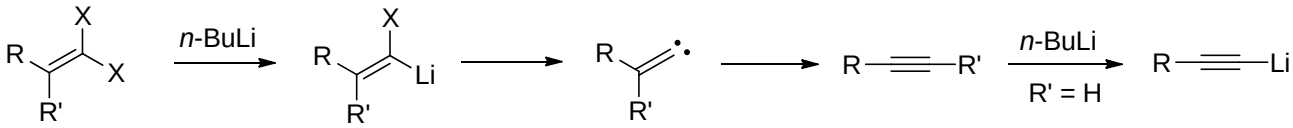


1.3.6.4. Akynyllithium Compounds from Aldehydes

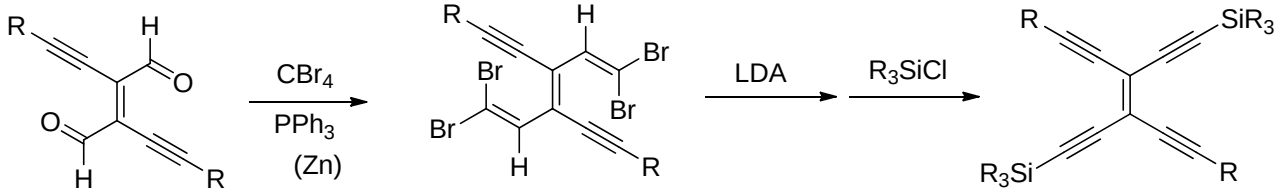
Vinyllithium compounds with a halogen in the α-position undergo Fritsh-Buttenburg-Wiechell-type rearrangement to give alkynes

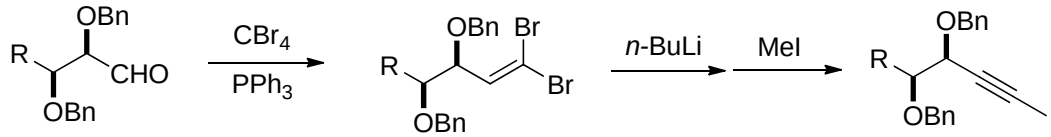
one of the β-substituents should be aryl, alkenyl, cyclopropyl, or H

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



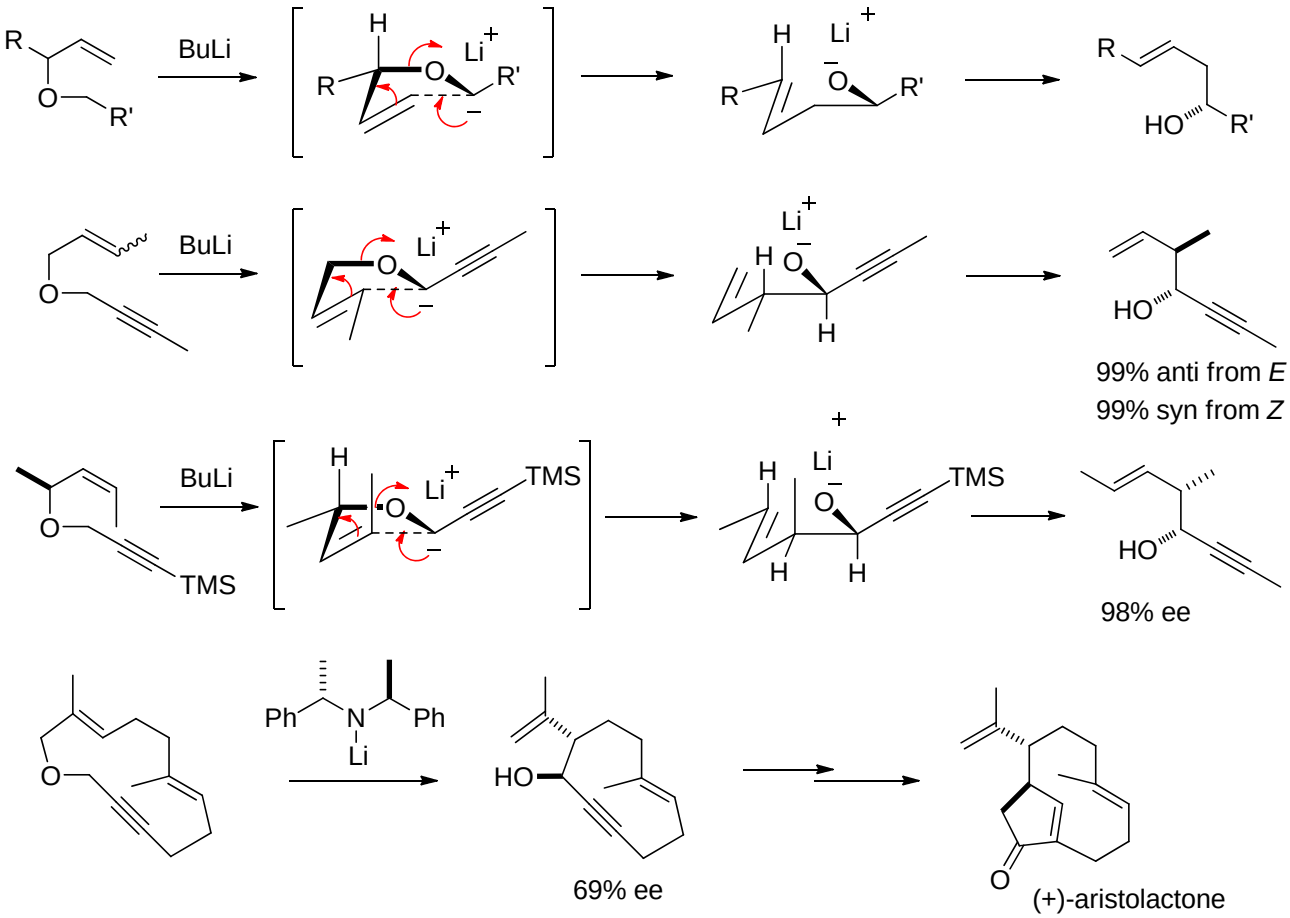
Corey-Fuchs method



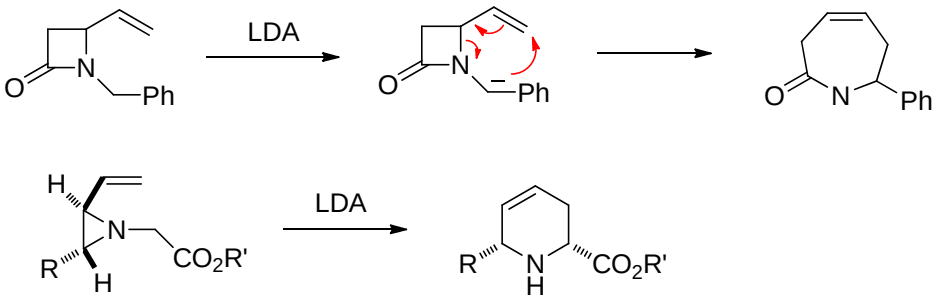


1.4. Synthetic Applications

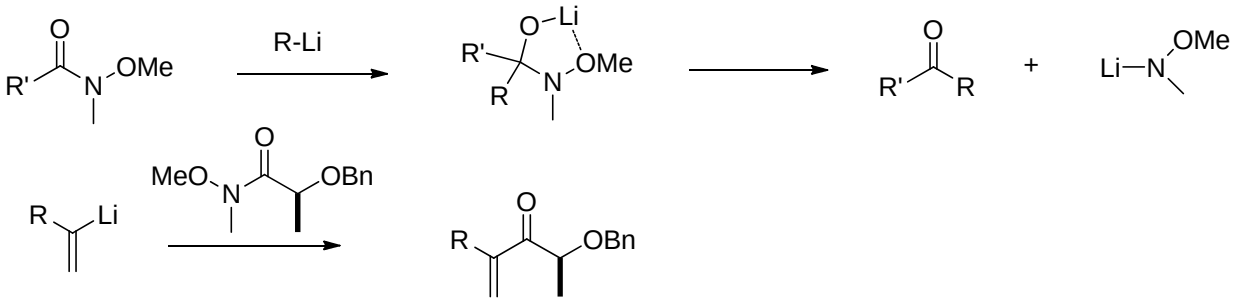
1.4.1. [2.3]-Wittig Rearrangement



1.4.2. Aza-Wittig

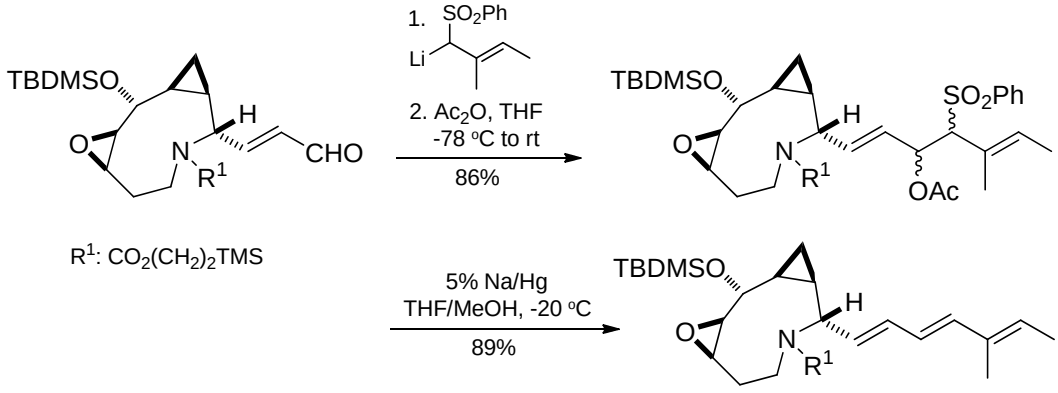


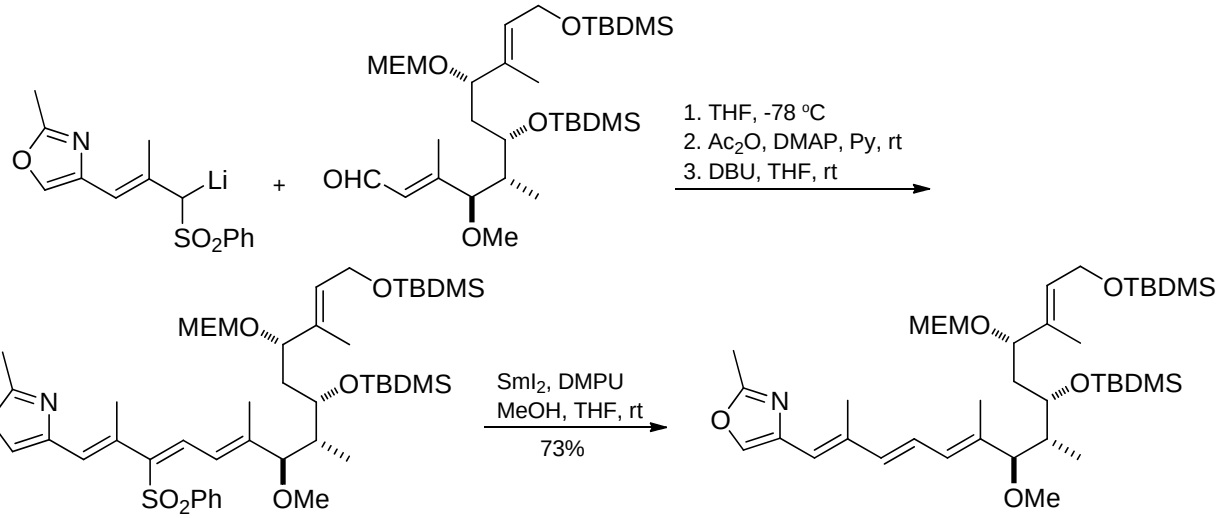
1.4.3. Weinreb Amide



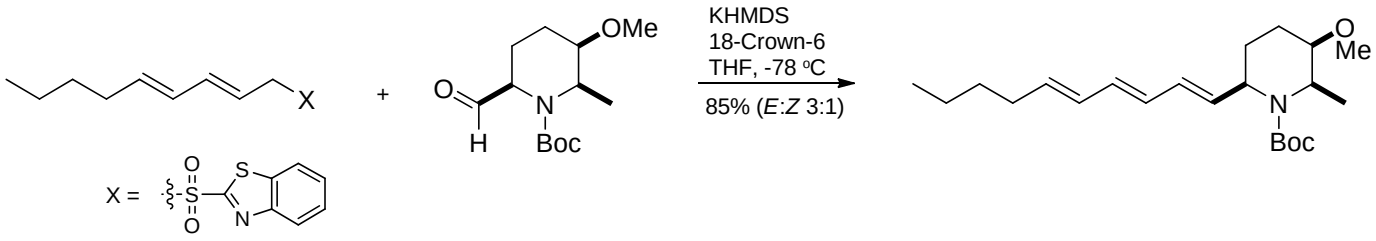
1.5. Application to polyene synthesis

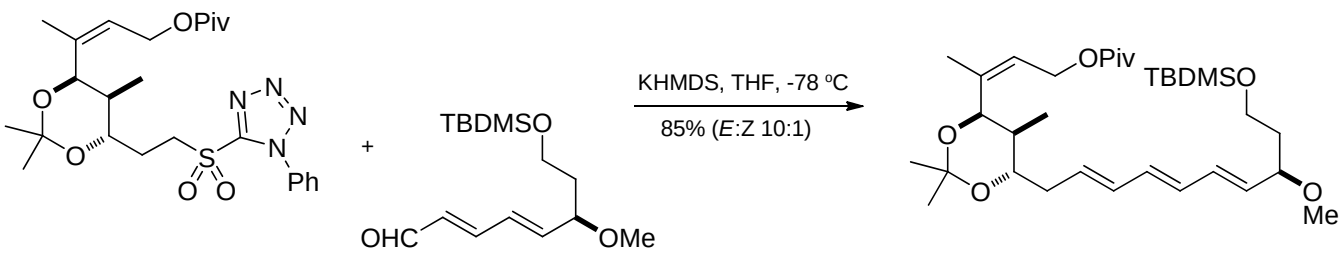
1.5.1. **Julia Olefination**



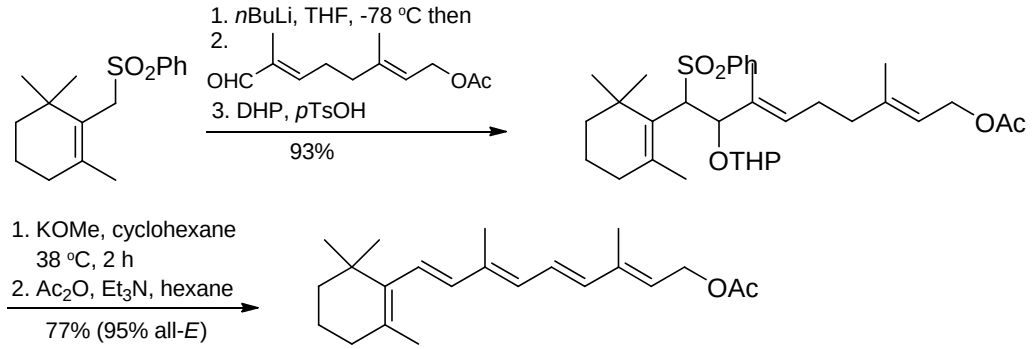


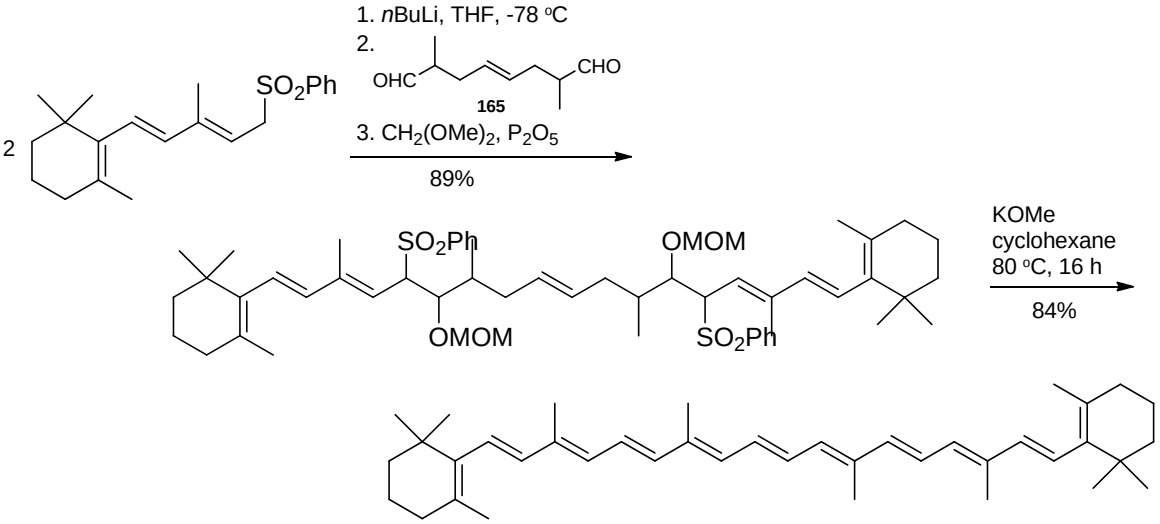
1.5.2. **Julia-Kocienski Olefination**

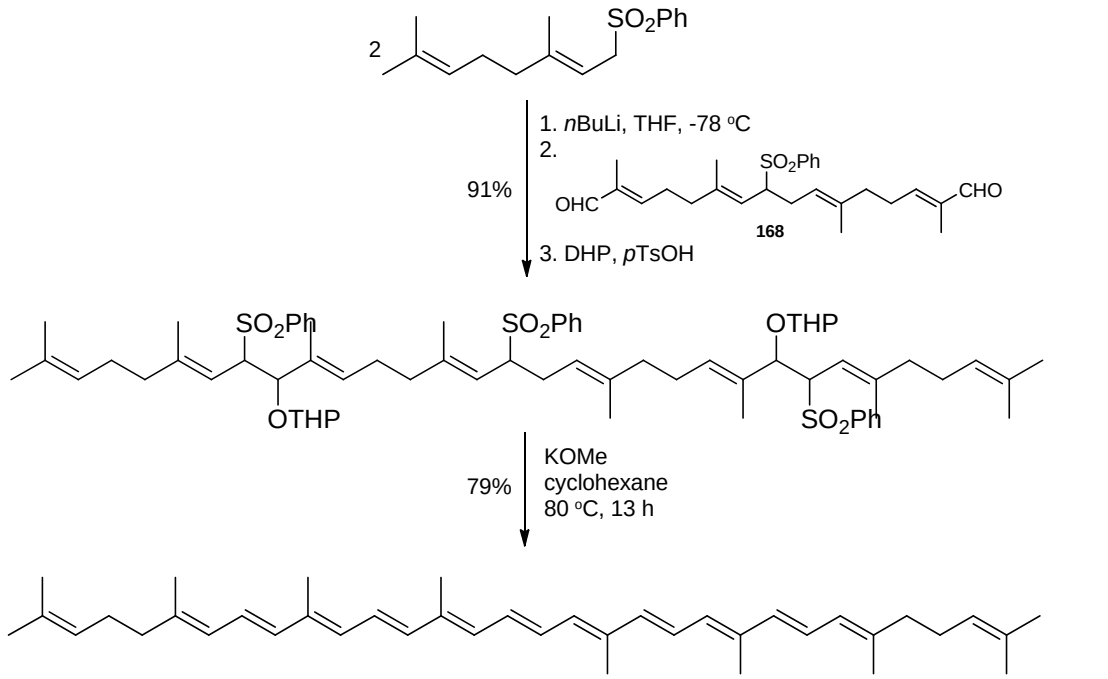




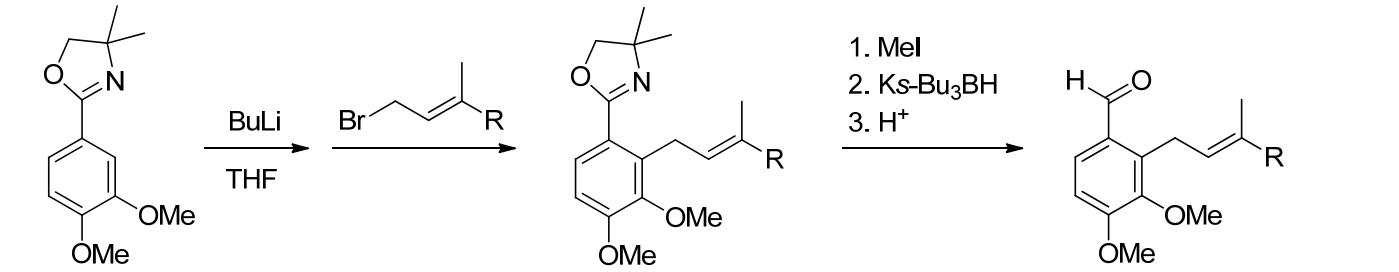
1.5.3. **Double Elimination Reaction for Carotenoid Synthesis**

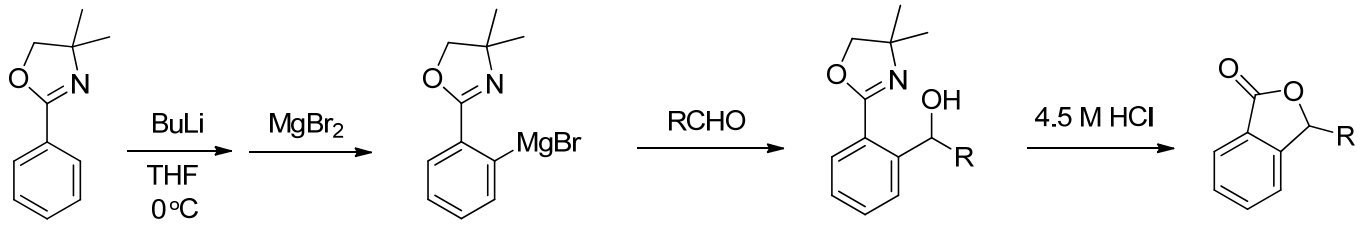


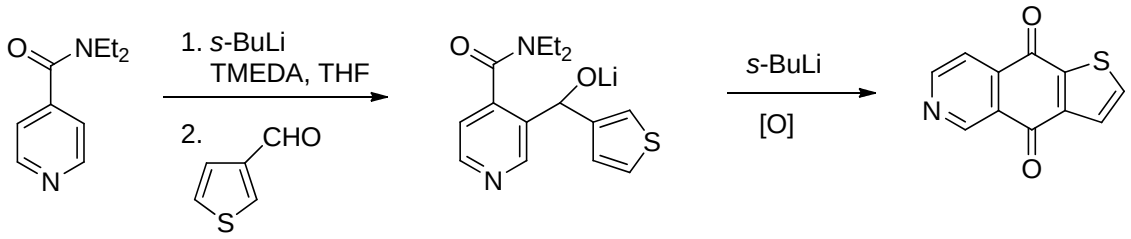




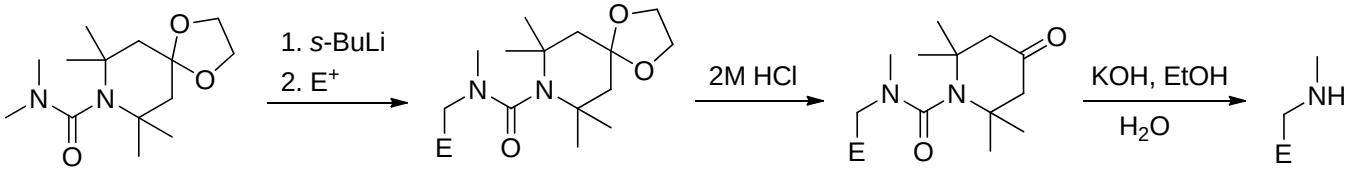
Oxazolines


BuLi
THF
Br
R
1. MeI
2. Ks-Bu3BH
3. H+
H
O
OMe
OMe

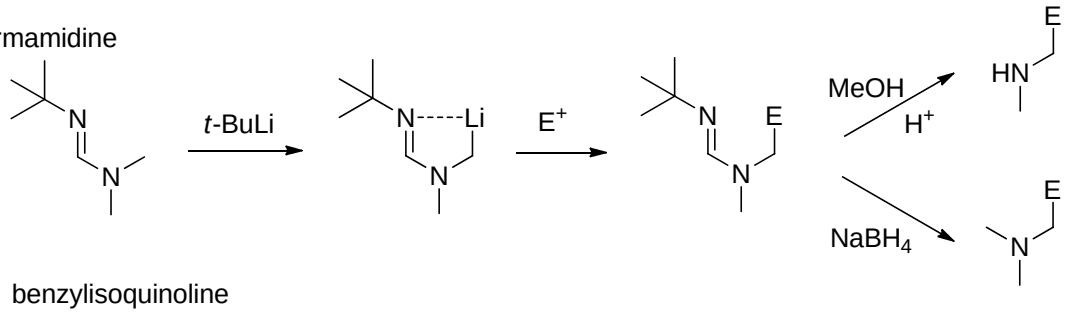

BuLi
THF
0 °C
MgBr2
MgBr
RCHO
OH
R
4.5 M HCl


NEt2
1. s-BuLi
TMEDA, THF
2.
CHO
OLi
s-BuLi
[O]
N
S

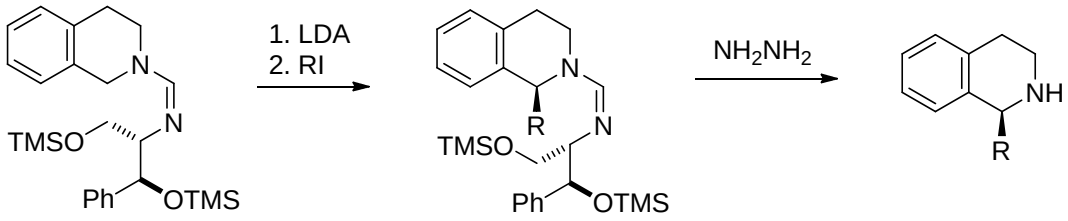
Addendum 1-1. Selective Lithiation by deprotonation - derivatization of amines

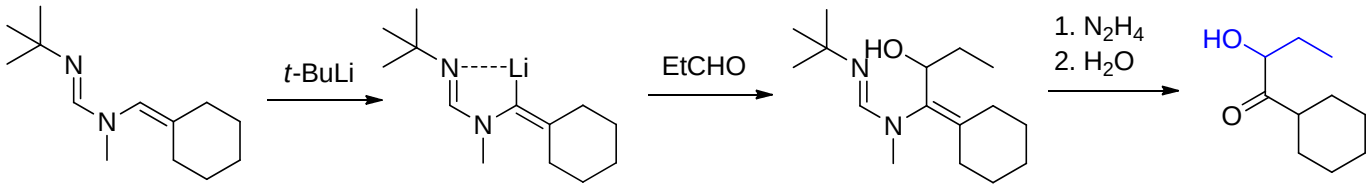


formamidine

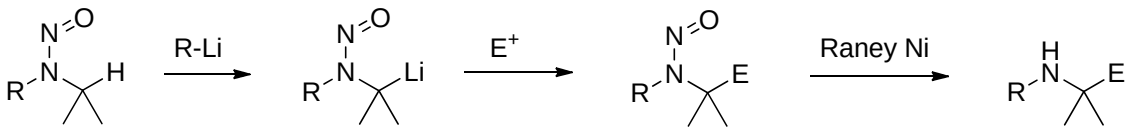


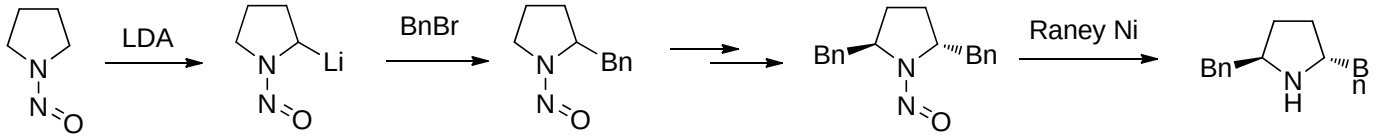
benzylisoquinoline

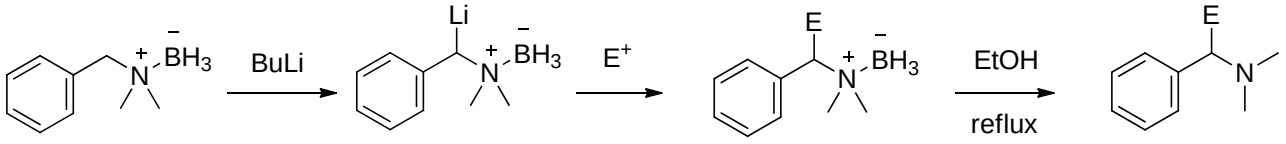




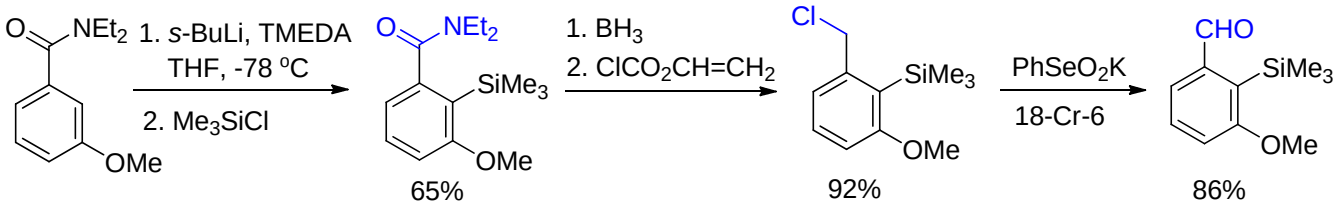
nitrosoamine

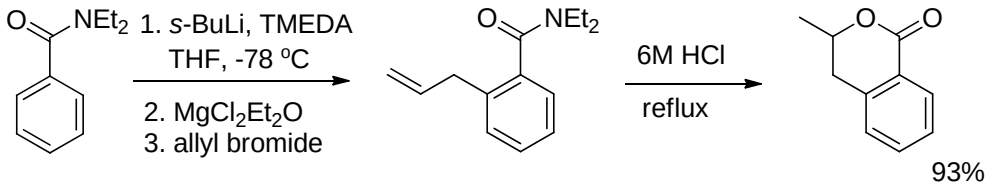


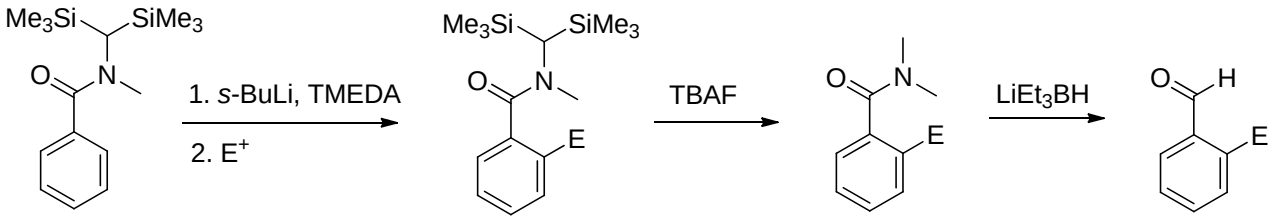


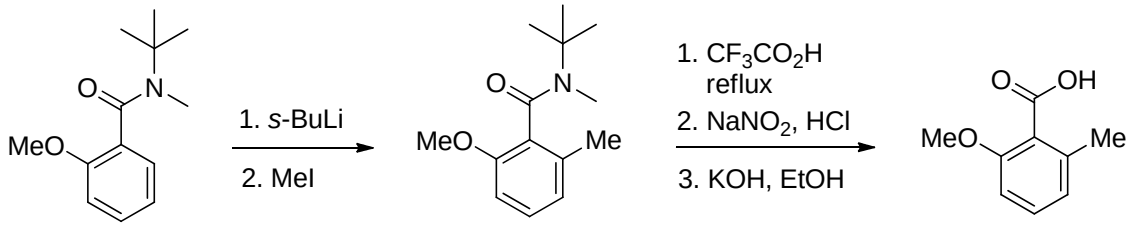


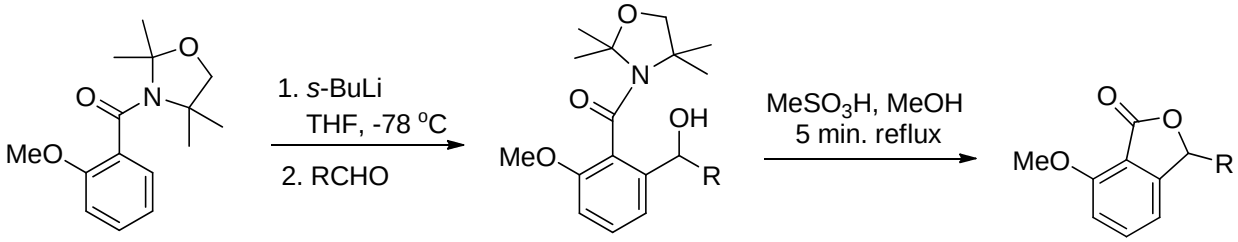
Addendum 1-2. Deprotonation directed by tertiary amides - FGI

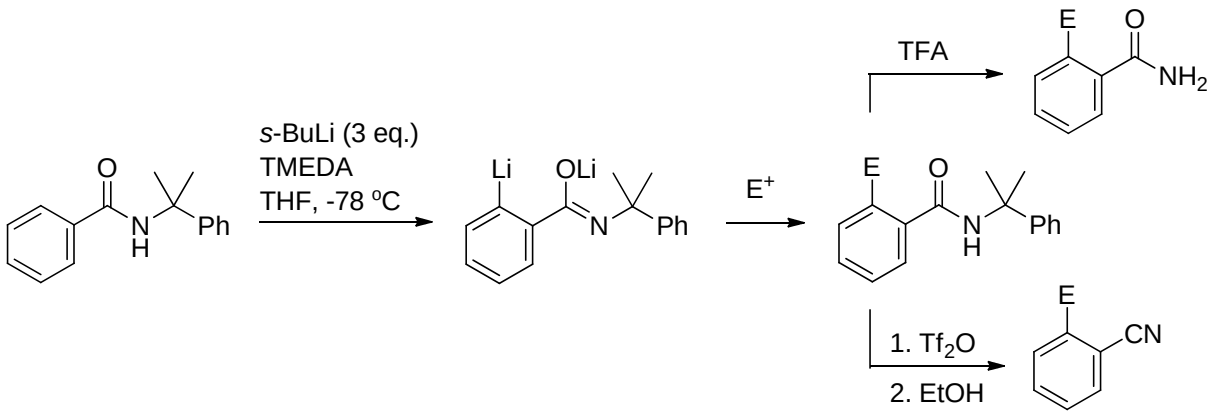






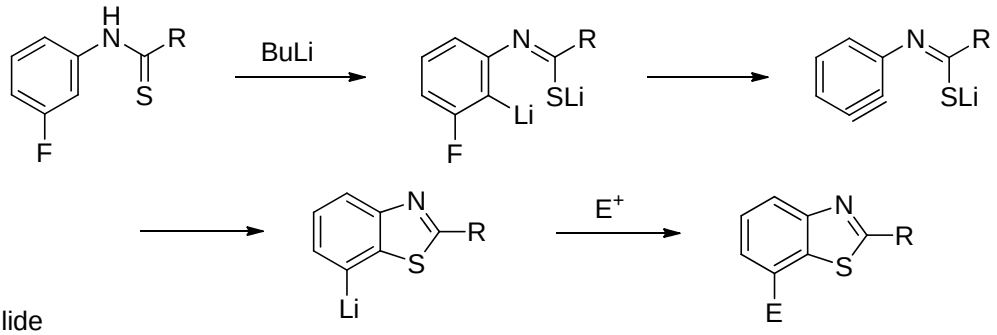




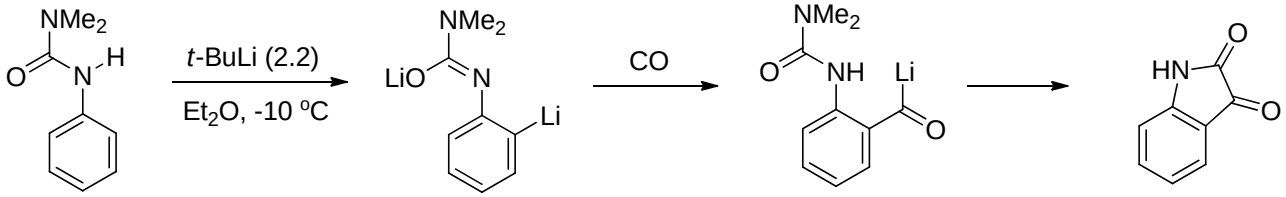


Addendum 1-3. Deprotonation directed by other functional groups

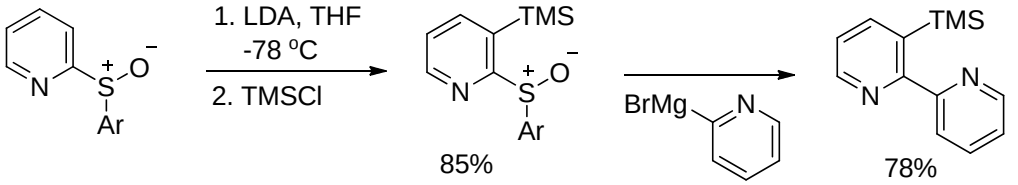
Thioanilide

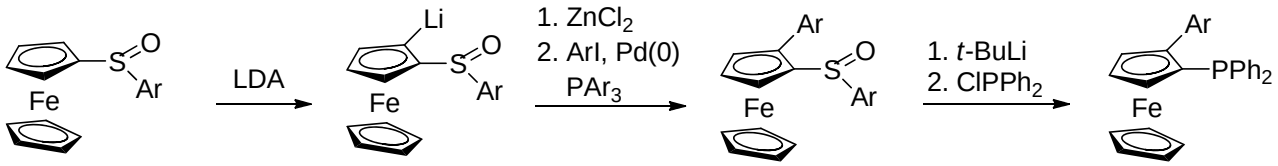


Urea anilide

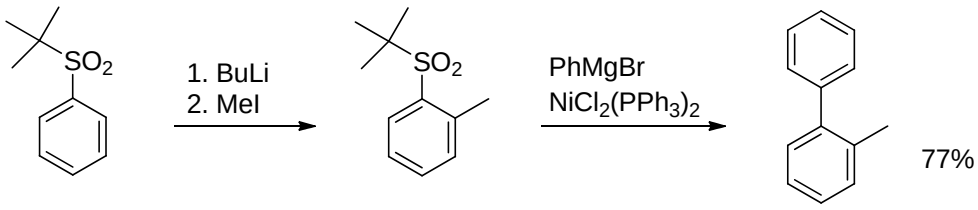


Sulfoxides - prone to nucleophilic attack - use LDA rather than alkyllithium as a base

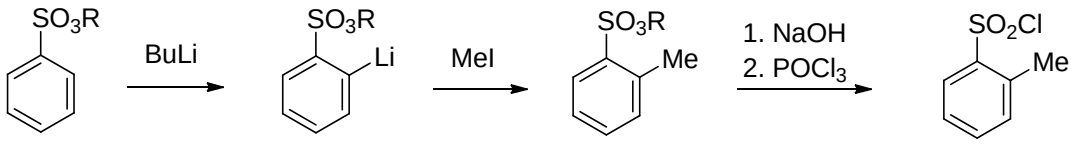




Sulfones

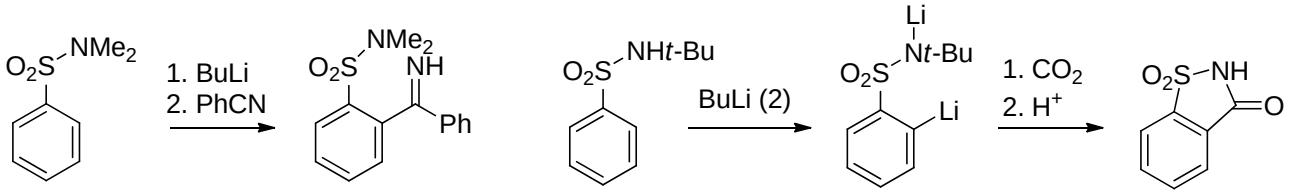


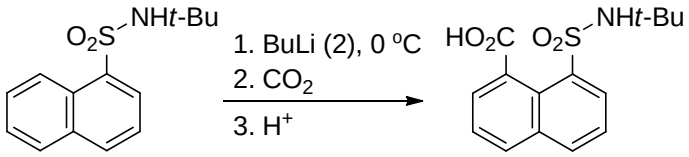
Sulfonate esters

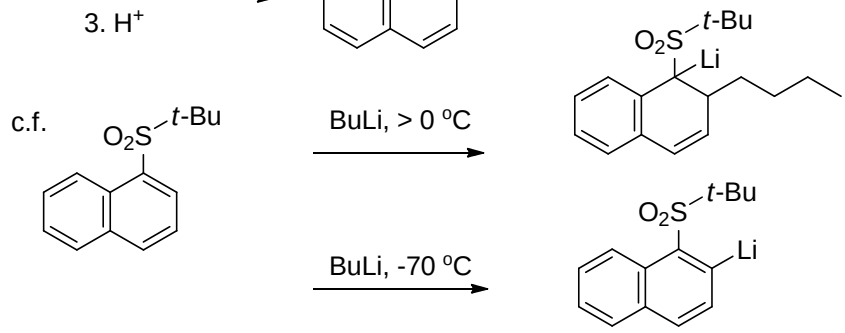


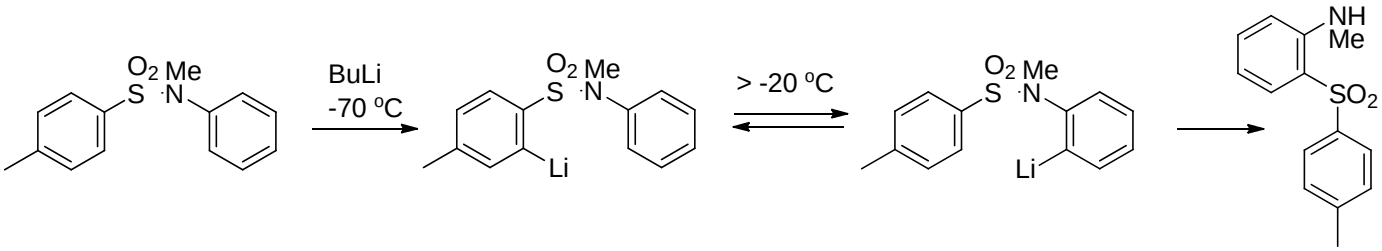
Addendum 1-4. Deprotonation directed by other functional groups

Sulfonamides

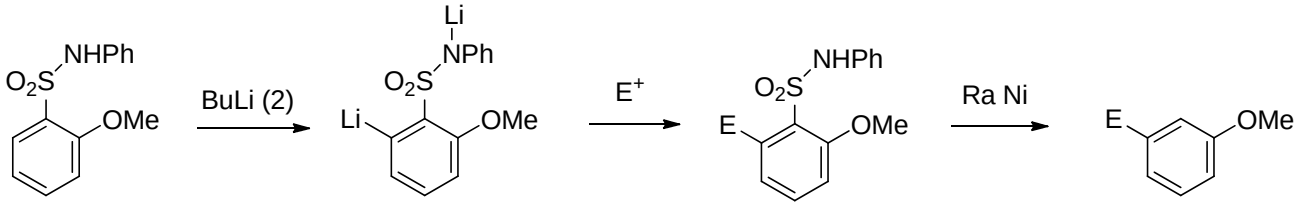




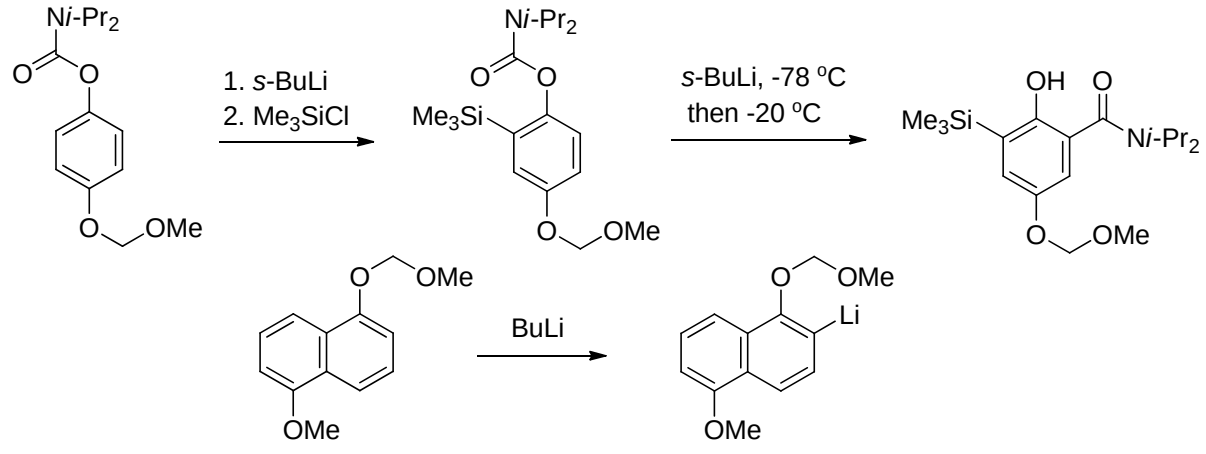




Benzenesulfinamide



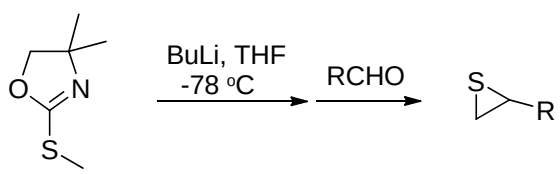
Directing efficiency - OCON*i*-Pr_2 > MOM > OMe



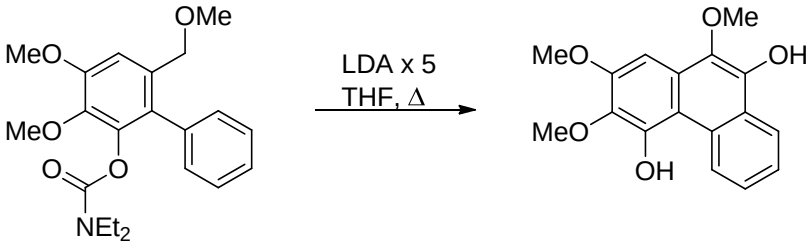
1.6. Problem Set

Propose the mechanism of the following reactions

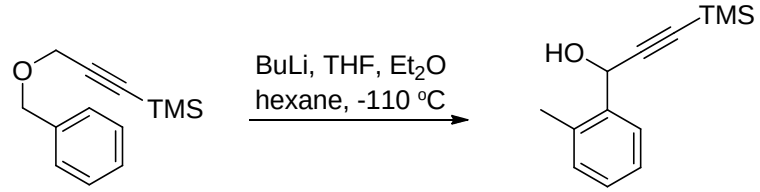
(1)



(2)

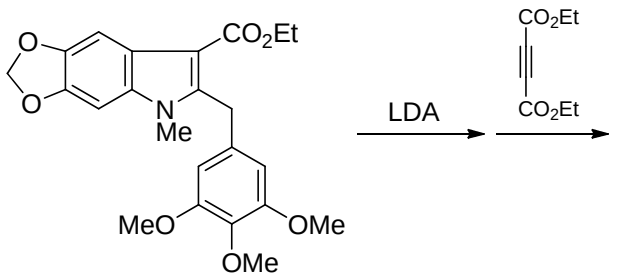


(3)

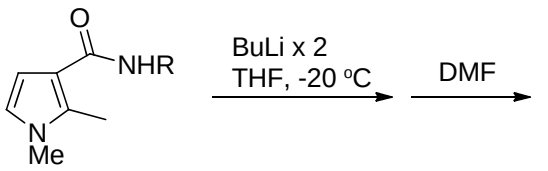


Draw the structure of the expected product

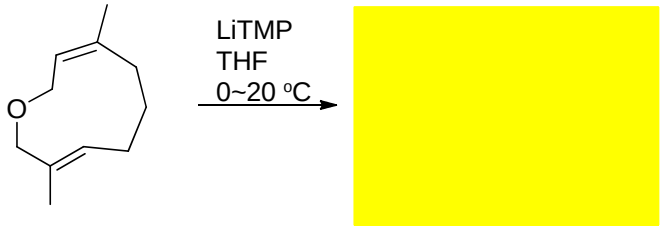
(4)



(5)

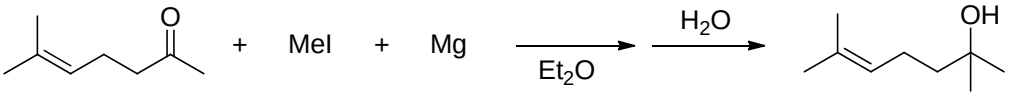


(6)

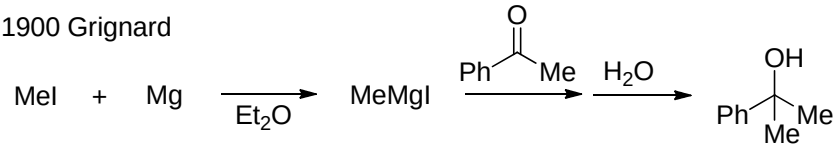


2. Magnesium in Organic Synthesis

1898 Barbier (1875 Wagner & Saytzeff for organozinc compound)



1900 Grignard



(Nobel Prize in 1912)

2.1 Preparation of Organomagnesium Compounds

2.1.1 Preparation from Alkyl Halides and Mg Metal [1]

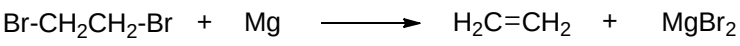
the purity and form of Mg is important - Mg turnings

Grignard Procedure:

Add 1 equiv of Et-Br to Alkyl Halide in Et_2O; Dropping the above mixture to excess Mg

Et-Br keeps Mg clean and active possibly by an exchange reaction

Use Br-CH_2CH_2-Br for the same purpose



Et_2O: the most commonly used solvent

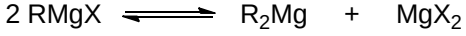
Solvate most alkylmagnesium compounds, should be dried

High vapor pressure creates a "blanket" over the surface - N_2 or Ar unnecessary

For the initiation, add MeMgI, I_2, or Br_2

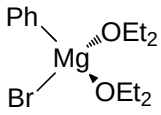
The Structure of a Grignard reagent

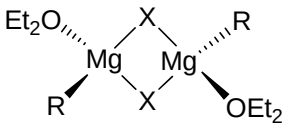
In solution - Schlenk equilibrium



association 3.7 @ 1.5 M

crystal structure: monomer, dimer (solvent incorporation)





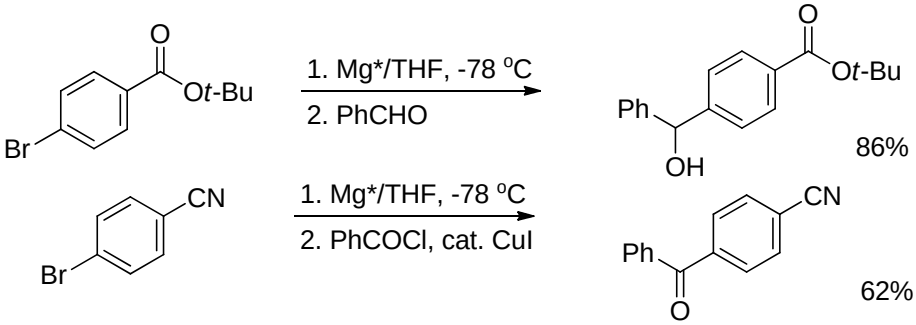
2.1.2 Preparation with Rieke Mg [2]

Preparation of slurries of highly reactive magnesium

1. Reaction of $MgCl_2$ with K in the presence of KI in THF
2. Magnesium halide is reduced with lithium, in the presence of naphthalene as electron carrier.

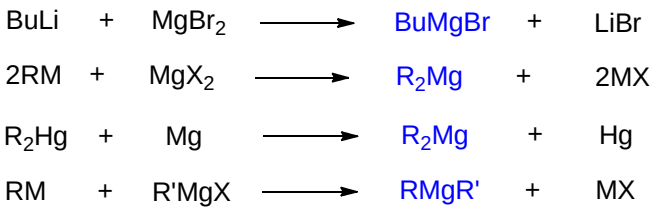
References: 1. Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674-3680.
2. Rieke, R. D.; Li, T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323-4324.

Preparation of functionalized Grignard reagent at -78 °C using Rieke Mg

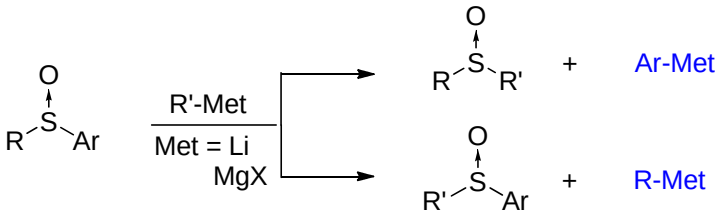


2.1 Preparation of Organomagnesium Compounds

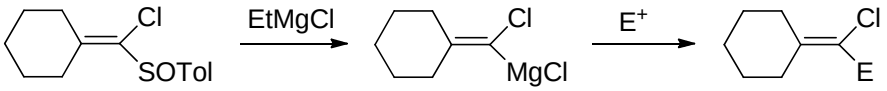
2.1.3 Transmetallation



2.1.4 Sulfoxide-Magnesium Exchange (Ligand Exchange Reaction of Sulfoxides with Grignard Reagent)



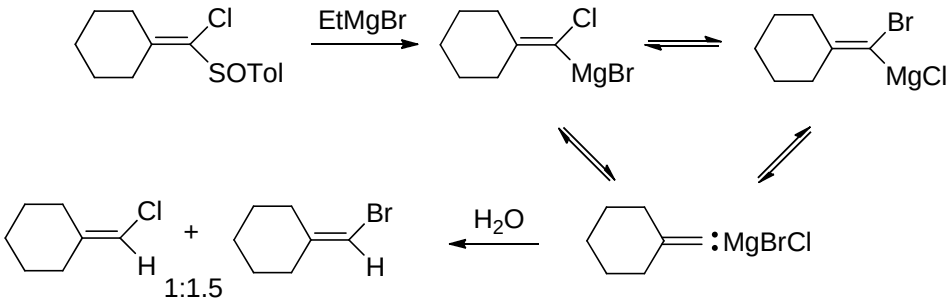
Satoh



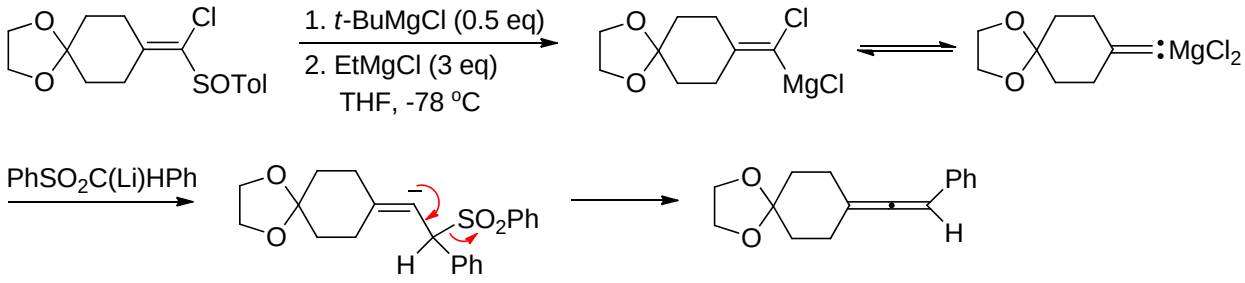
(stable at -78 °C for 30 min)

E = H_2O: 98%
PhCHO: 68%

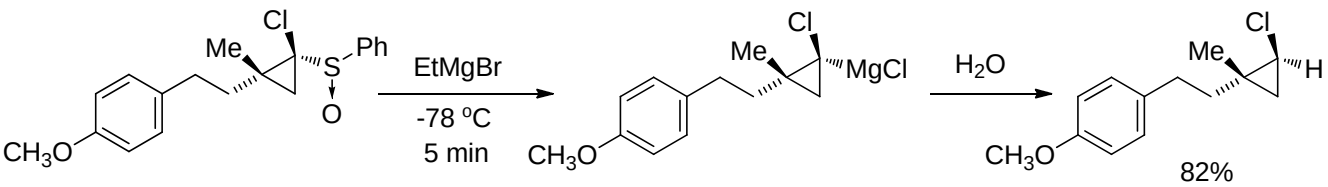
alkylidene carbene-magnesium complex



Synthesis of allenes



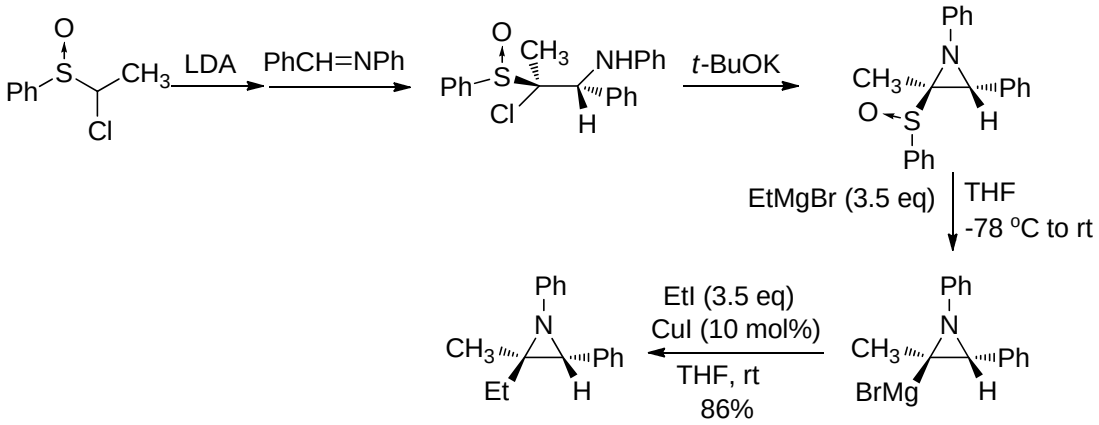
Magnesium cycloprpylidenes (stable at below -60 °C for at least 3 h)

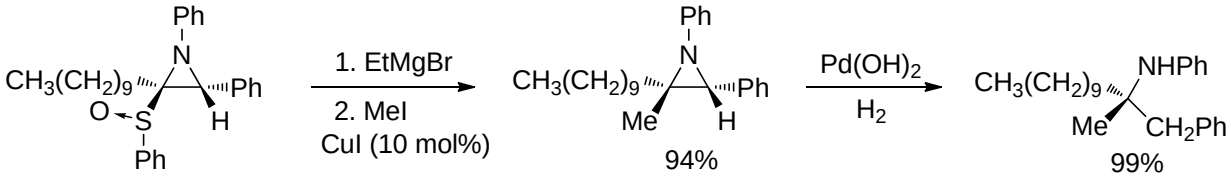


2.1.4 Sulfoxide-Magnesium Exchange (Ligand Exchange Reaction of Sulfoxides with Grignard Reagent)

Aziridinylmagnesium compounds

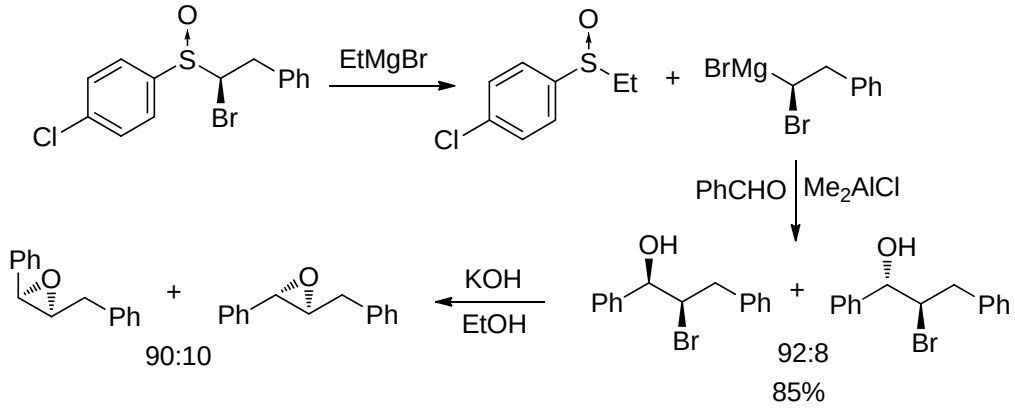
Satoh, T.; Matsue, R.; Fujita, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891-3898.



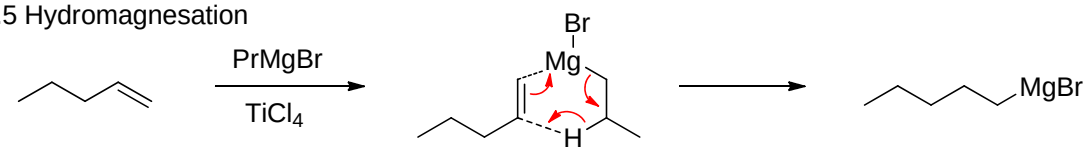


Enantioselective Preparation of α-Haloalkyl Grignard Reagents

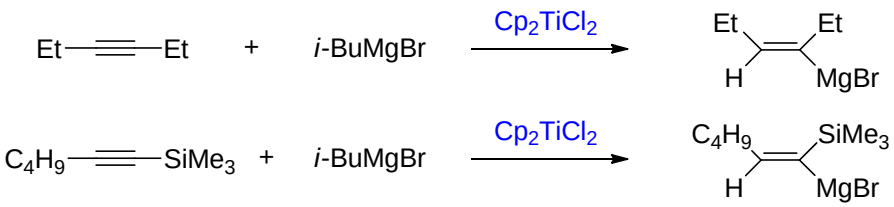
Configurationally stable at -78 °C and racemization begins at or above -60 °C.



2.1.5 Hydromagnesation

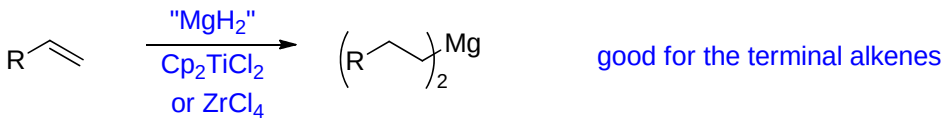


Syn-addition



2.1.5 Hydromagnesation

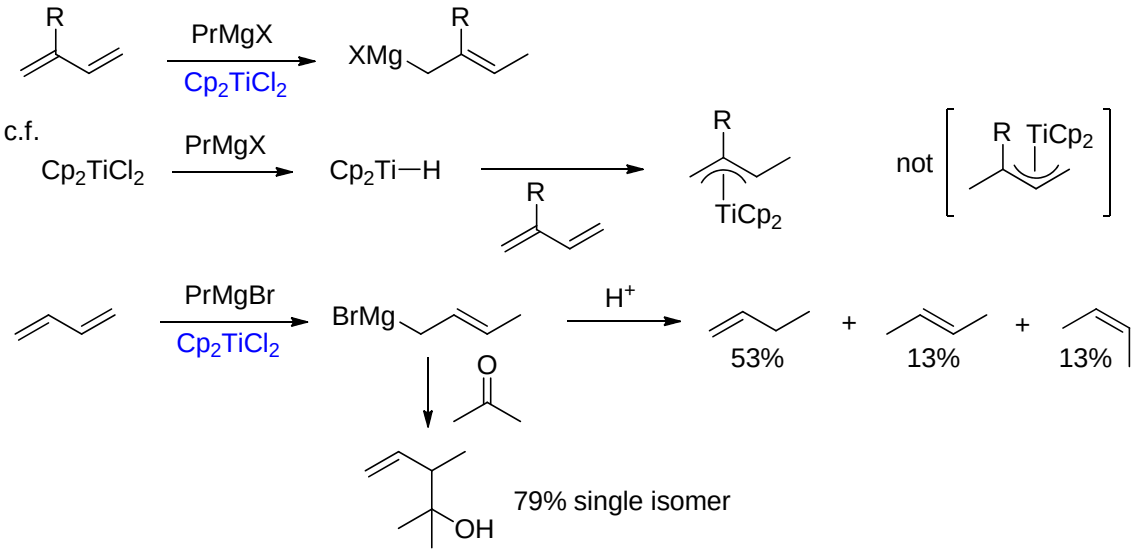
Preparation of Dialkylmagnesium Compounds



good for the terminal alkenes

Hydromagnesation to Conjugated Diene

Use Cp_2TiCl_2 instead of $TiCl_4$



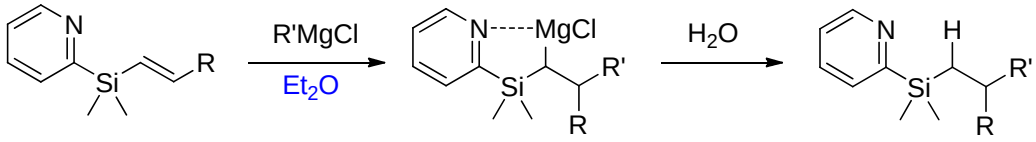
2.1.6 Metalation (Deprotonation)

$$RC{\equiv}CH + EtMgBr \longrightarrow RC{\equiv}CMgBr + C_2H_6$$

only good for C-H with pKa < 25; less powerful than Li reagents; stable even in boiling THF

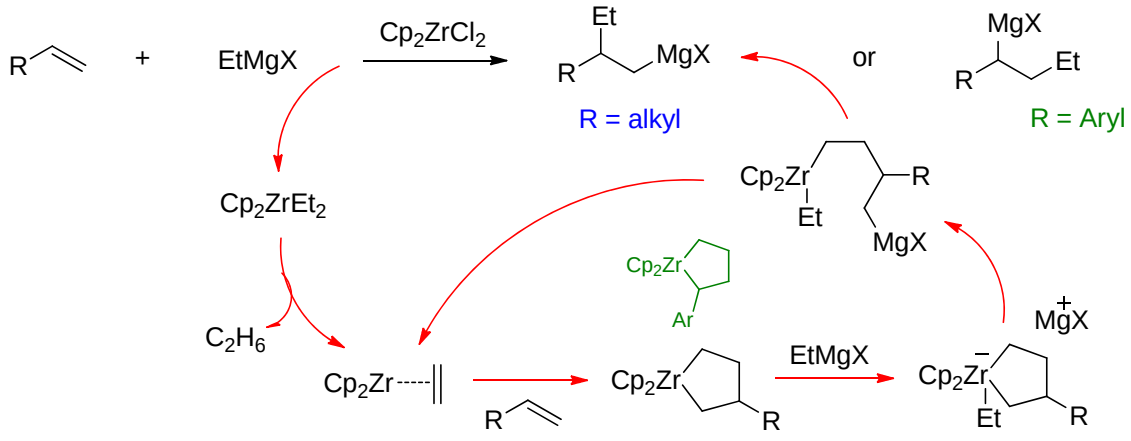
2.1.7 Other Preparative Methods

α-Silylcarbanion (activating group required, substitution at silcon as a side reaction)



R = H, R' = *i*-Pr: 91%
R = H, R' = Bu: 93%
R = H, R' = Ph: 73%
R = Bu, R' = Bu: 91%

Carbomagesation of 1-alkene

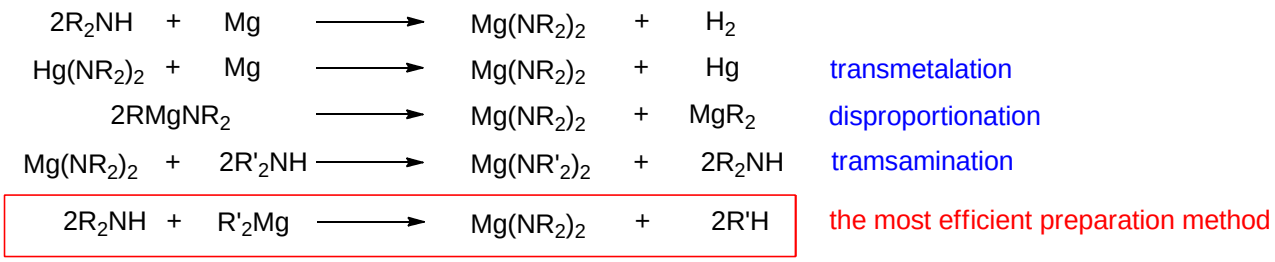


2.2 Reaction of Organomagnesium Compounds

- reaction with organomagnesium amide as a base
- Cp_2TiCl_2- or Cp_2ZrCl_2-catalyzed reaction with Grignard
- substitution with Grignard reagent
- addition to carbon-carbon multiple bonds

2.2.1 Reaction with Organomagnesium Amides

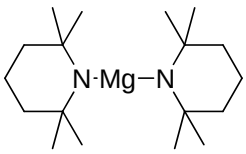
2.2.1.1 Preparation of Mg bisamides



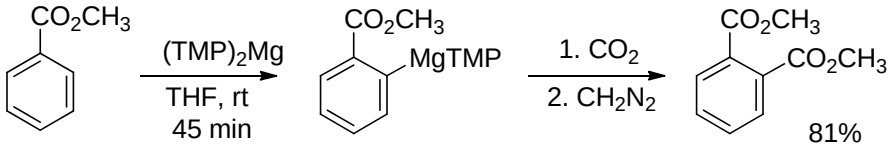
2.2.1.2 Reaction with Organomagnesium Amide

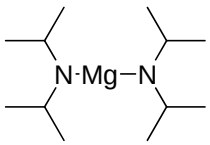
ortho-magnesation in the presence of ester

THF solution of $(TMP)_2Mg$ are stable on heating to reflux over several hours.



$(TMP)_2Mg$

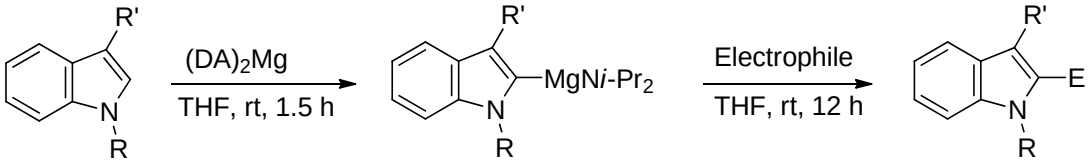




$(DA)_2Mg$

deprotonation at 2-position in Indole

R' = H, Me, CO_2Me or CN

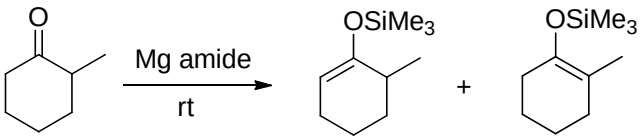


R = SO_2Ph or CO_2t-Bu

E = CH(OH)Ph, I, CO_2Me, allyl

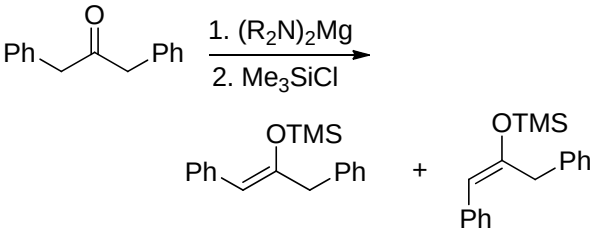
selective enolate formation

kinetic product at rt



1. $Mg(DA)_2$/THF	100	:	0
2. BrMgDA /THF	77	:	23
3. BrMgDA /DME	87	:	13
4. BrMgDA /ether	3	:	97

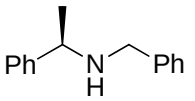
E-stereoselectivity



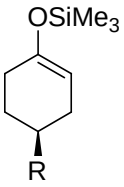
R = *i*-Pr	9	:	91
R = Me_3Si	2	:	98

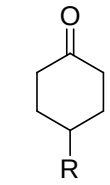
2.2.1.2 Reaction with Organomagnesium Amide

Enantioselective deprotonation using optically-pure Mg-bisamides

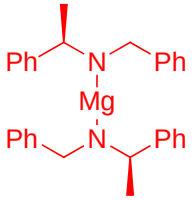


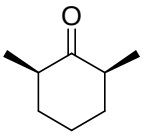
Bu_2Mg



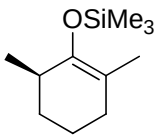


TMS-Cl
-78 °C
THF/HMPA





TMS-Cl
-78 °C
THF/HMPA

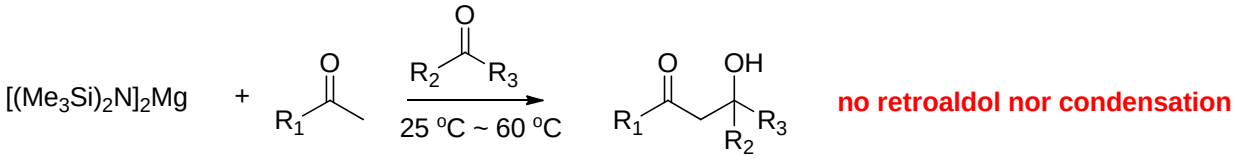


e.r.		e.r.	
R = *t*-Bu	91:9	75.5:24.5 (w/Li base)	-78 °C 97:3	64.5:35.5 (w/Li base)
R = Ph	87:13		-60 °C 93:7	
R = Me	91:9		-40 °C 92:8	

* DMPU can be used instead of HMPA
→ 89% yield; 90:10 e.r. for R = *t*-Bu

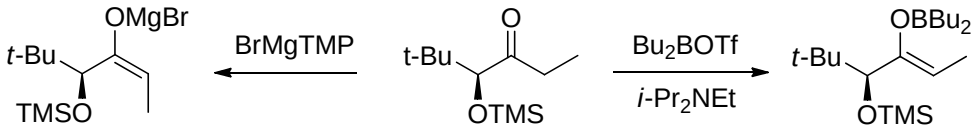
*conversion was increased from 17% to 99% as the temperature was raised from -78 to -40 °C

Aldol addition reaction at elivated temperatures



no retroaldol nor condensation

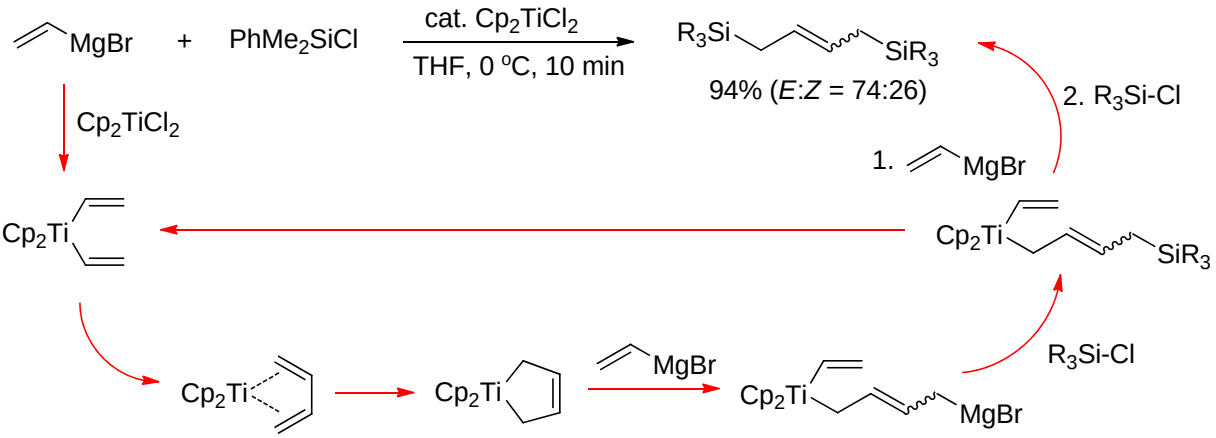
Stereoselective formation of enolates

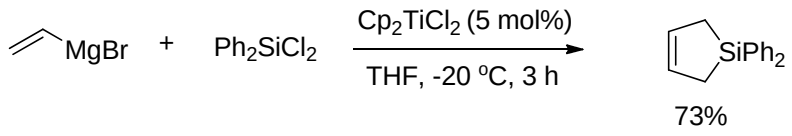


2.2.2 Cp_2TiCl_2- or Cp_2ZrCl_2-catalyzed Reaction with Grignard Reagents

Reduction of alkyl, aryl, vinyl bromides, alkoxy- and halosilanes etc.
Hydromagnesation of alkynes, dienes, and alkenes

Kambe et al. - Preparation of 1,4-disilyl-2-butene

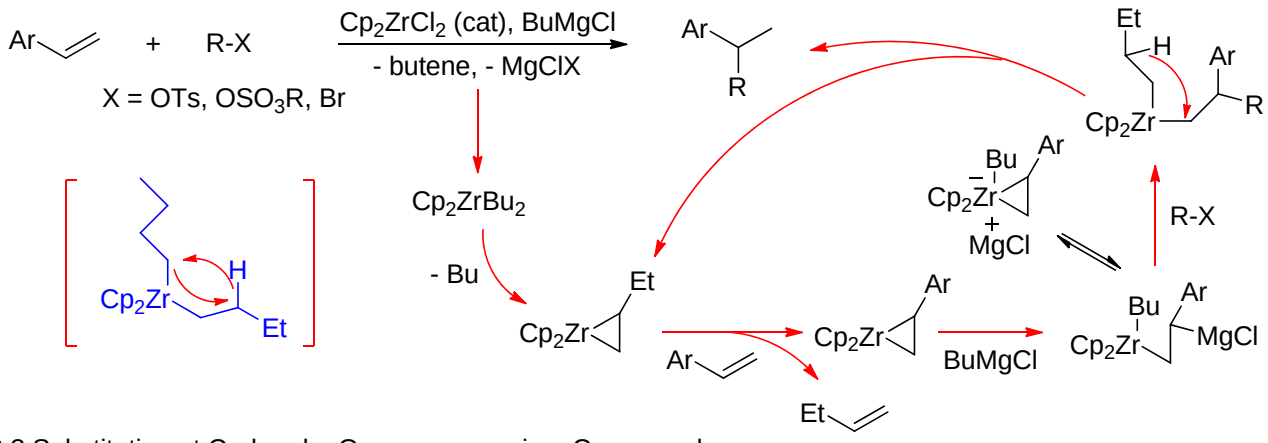




73%

w/ Zirconocene complexes

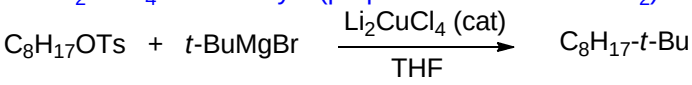
Addition of organometalics (aluminum, zinc, magnesium) to alkenes and alkynes



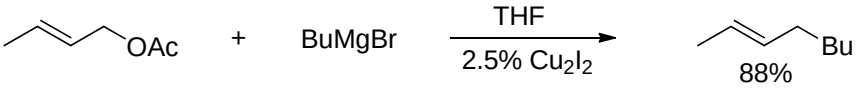
2.2.3 Substitution at Carbon by Organomagnesium Compounds

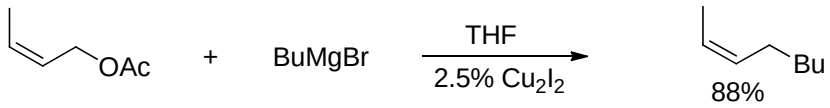
side reactions: metal-halogen exchange, deprotonation

Use Li_2CuCl_4 as a catalyst (prepared from LiCl + $CuCl_2$)

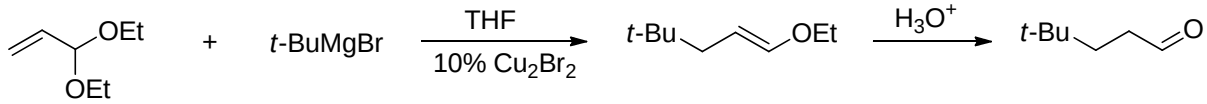


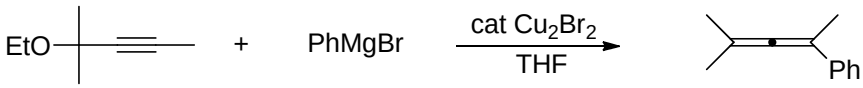
reaction with allylic acetates



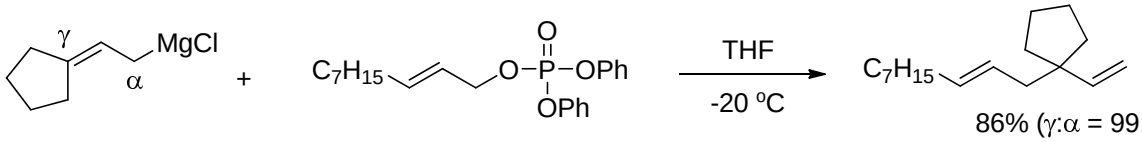


reaction with allylic ethers (allylic rearrangement)

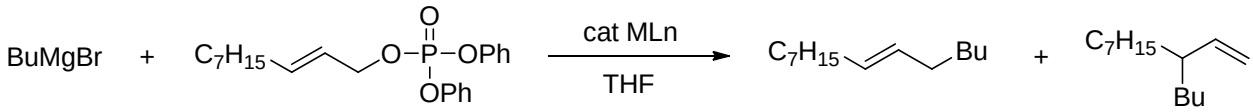




reaction with allylic diphenylphosphonate (γ-coupling)



86% (γ:α = 99:1)



$Fe(acac)_3$	99:1
CuCN-2LiCl	1:99

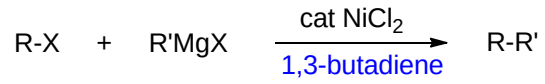
2.2.3 Substitution at Carbon by Organomagnesium Compounds

Nickel-catalyzed cross-coupling reactions of Grignard reagents with alkyl halides and tosylates

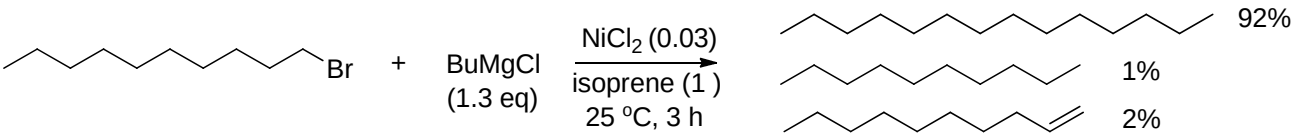
$NiCl_2$, $Ni(acac)_2$, $Ni(COD)_2$

problems in alkyl-alkyl cross-coupling reactions → slow oxidative addition step, facile β-elimination process

1,3-butadiene as additive



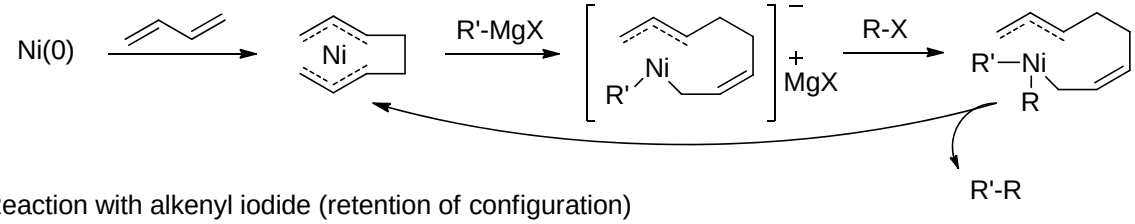
R = alkyl R' = alkyl, aryl
X = Cl, Br, OTs



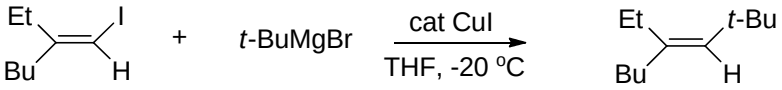
without isoprene the coupling product was obtained in only 2% yield

Optimized condition: 1 mol% $NiCl_2$, 10 mol% 1,3-butadiene, alkyl bromide (1 eq), 0 °C

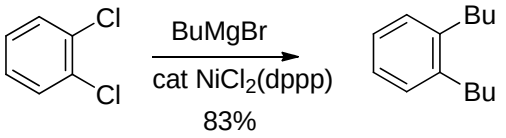
Reaction Mechanism



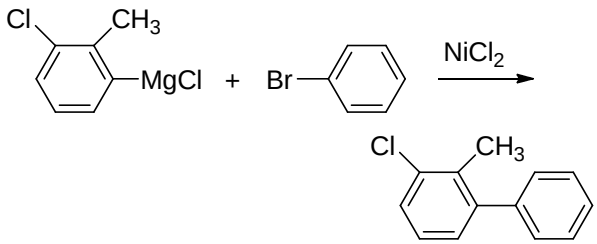
Reaction with alkenyl iodide (retention of configuration)



The most generally applicable Ni catalyst: $NiCl_2$(dppp)

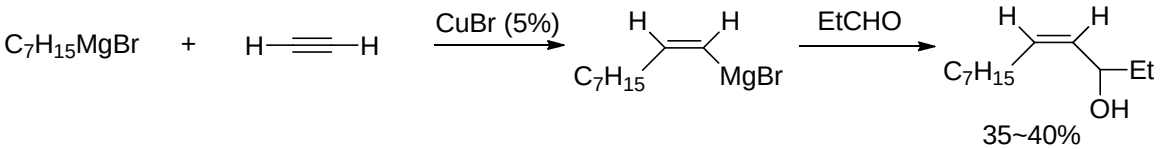


c.f. (no ligand)

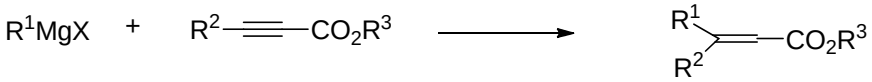


2.2.4 Addition to Carbon-Carbon Multiple Bonds

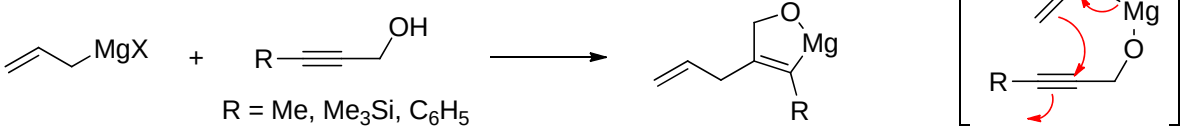
Syn addition to acetylene in the presence of Cu salt



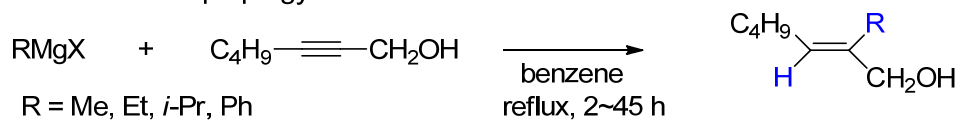
Conjugated addition to acetylenic acids, esters, and nitriles



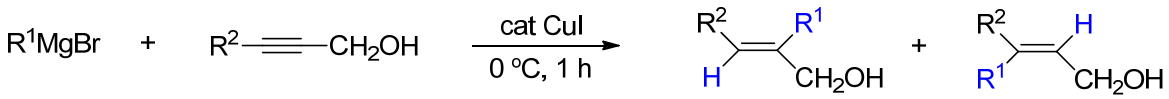
Reaction of allylic Grignard with acetylenic alcohol by anti-addition process



Anti-addition to propargylic alcohols

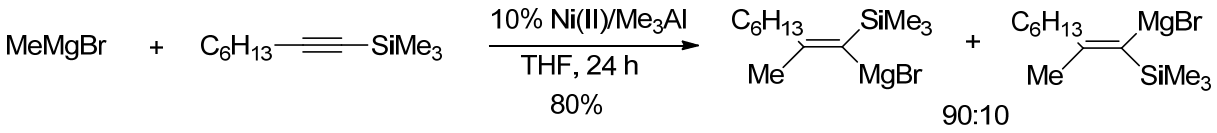


R = Me, Et, *i*-Pr, Ph

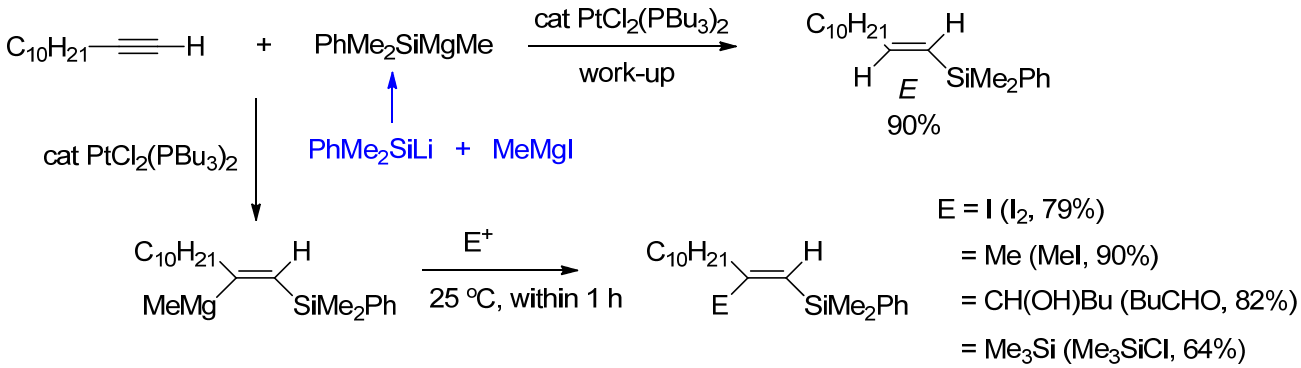


R^1 = Me, Et, *i*-Pr, *t*-Bu, Ph, allyl R^2 = H, Me, Bu, Ph, $SiMe_3$

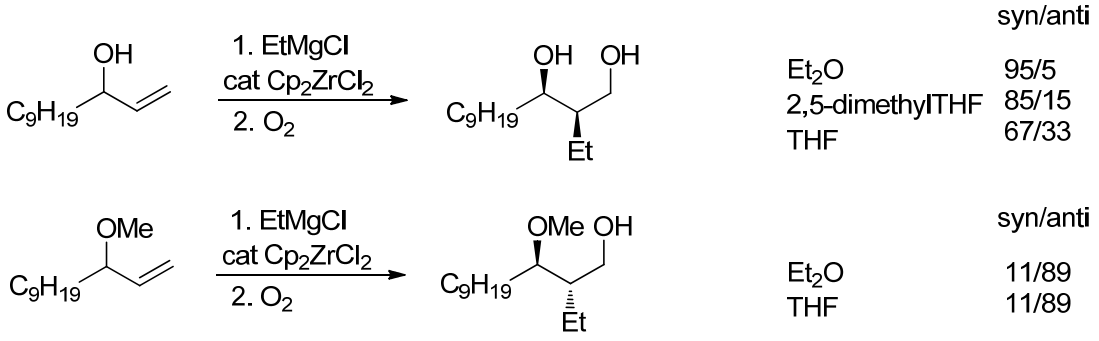
Regioselectivity controlled by the bulky TMS group



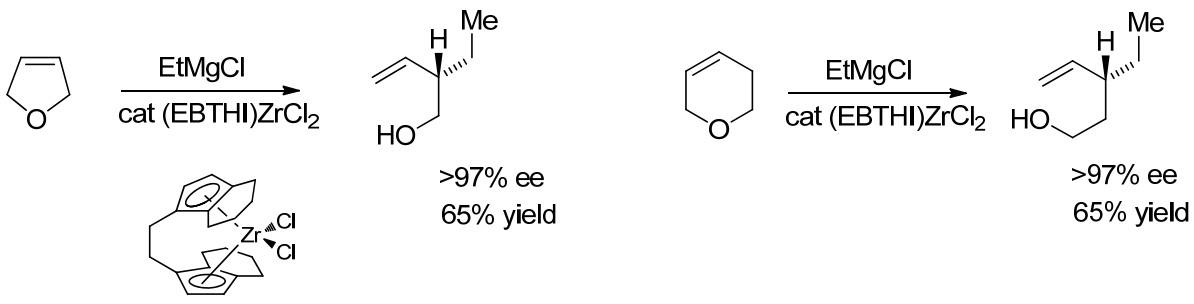
SilylImagnesation of acetylene (Pt or Cu catalyzed)



Hoveyda et al.



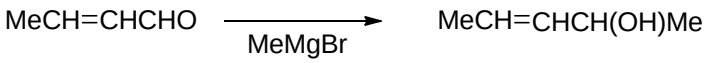
Enantioselective alkylation of alkene



2.2.5 Addition to Carbonyl Groups

Side reactions: Enolization and Reduction (by β-hydrogen of Grignard reagent)

1,2-addition to α,β-unsaturated aldehydes



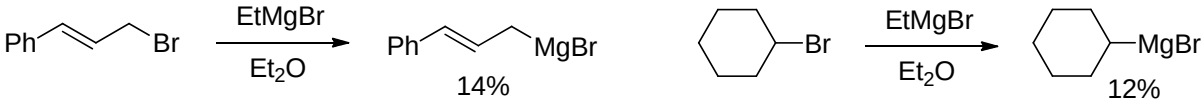
Chemoselectivity between formyl and keton groups

magnesium carboxylate and sulfonate give greater selectivity

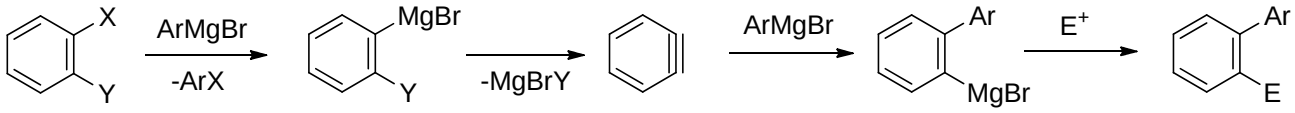
MeMgBr	55:45
MeMgOTf	95:5
$MeMgOCOCMe_3$	99:1
BuMgBr	60:40
BuMgOTs	99:1

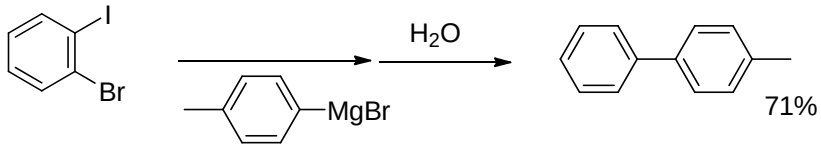
2.3 Halogen-Magnesium Exchange Reaction

Synthetically unuseful in general

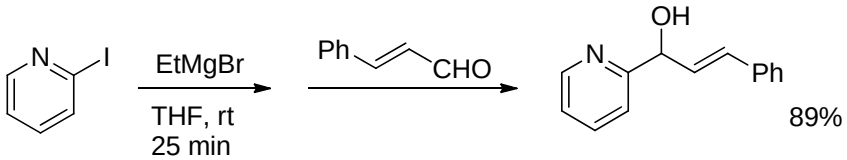


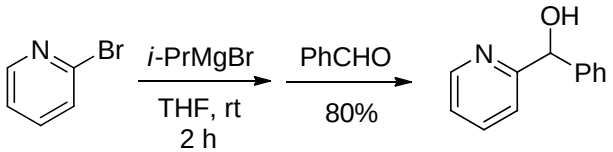
Benzyne formation

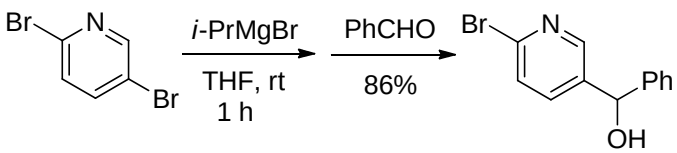




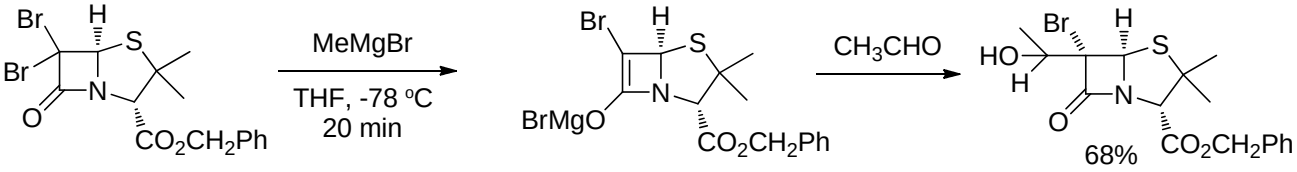
Heteroaromatic compound



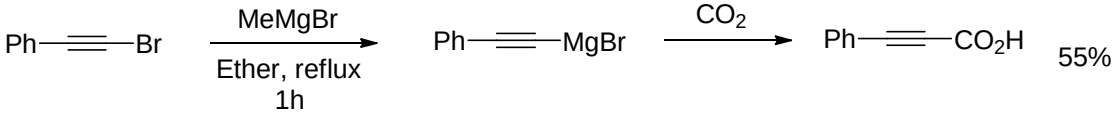




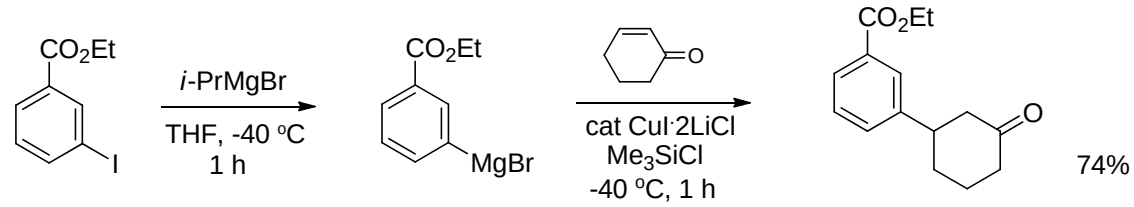
Enolate formation

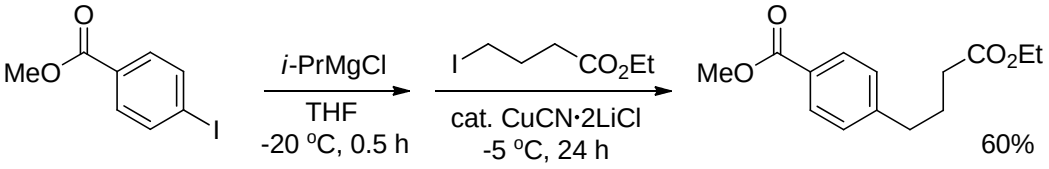


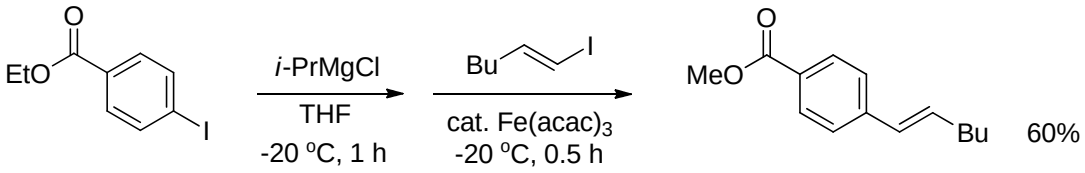
with Alkynyl Halides

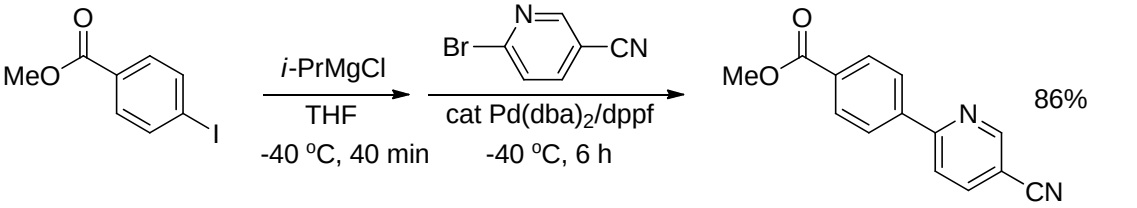


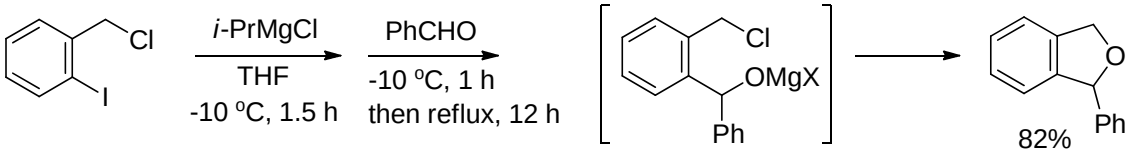
More examples for polyfunctional organomagnesium reagents (by Iodine-magnesium exchange)



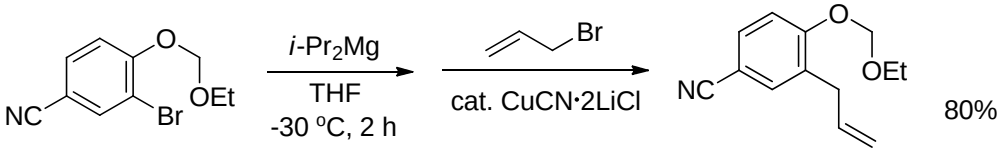


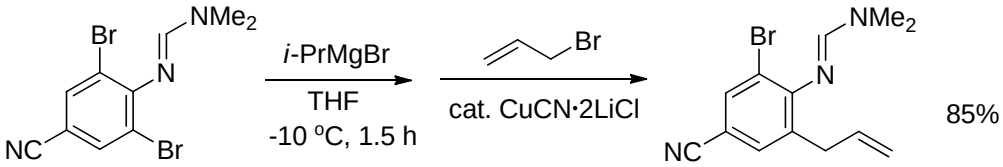




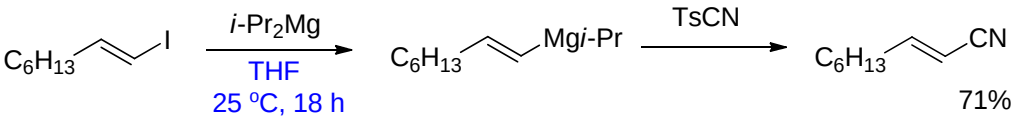


Polyfunctional organomagnesium reagents by bromine-magnesium exchange
(strong activation by electron-withdrawing or directing group is required)

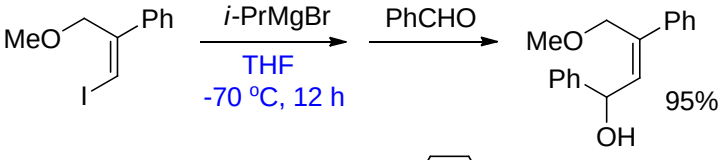


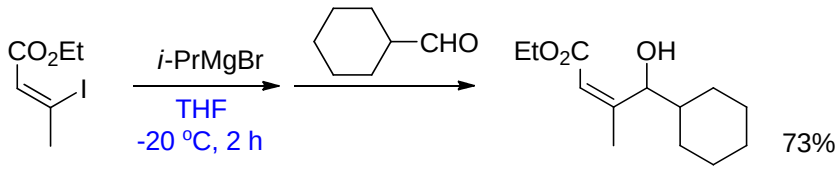


Exchange reaction of alkenyl halides

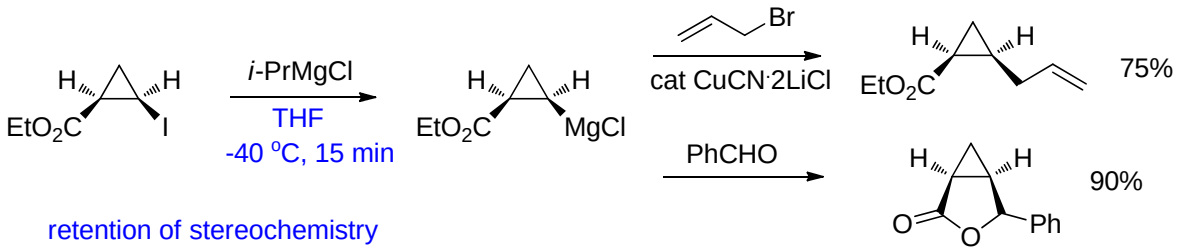


effect of directing groups

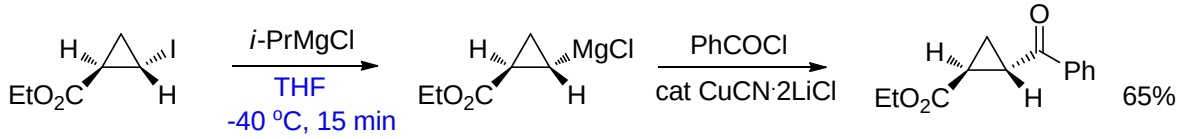




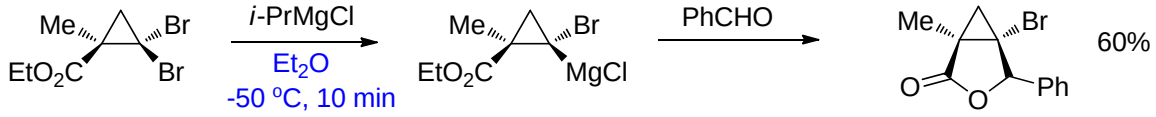
Functionalized cyclopropylmagnesium reagents



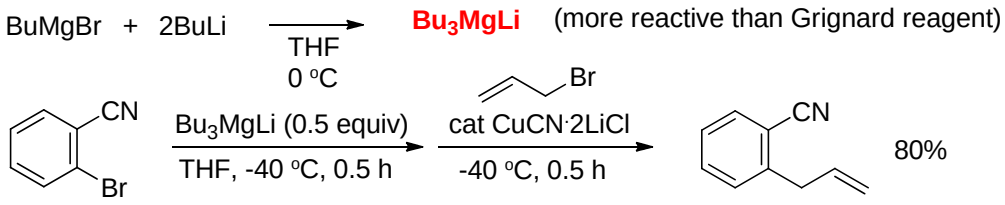
retention of stereochemistry

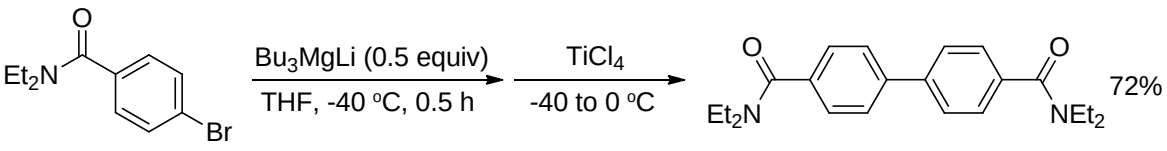


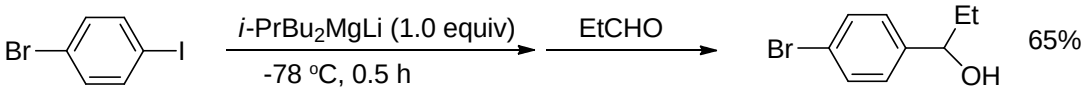
directing effect of the ester group



Trialkylmagnesate-induced halogen-magnesium exchange reaction

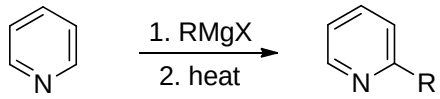


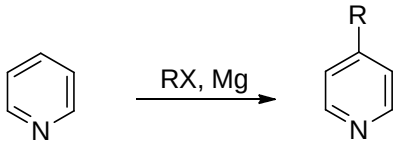




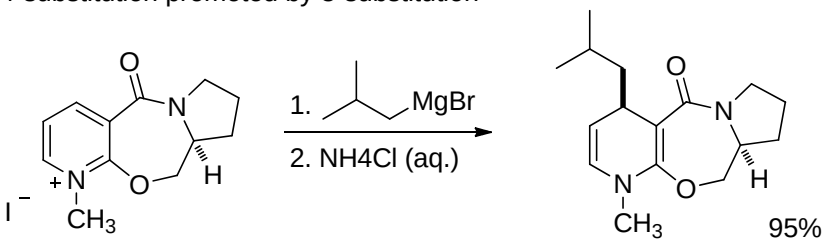
Addition to nitrogen heterocyclic aromatic compunds

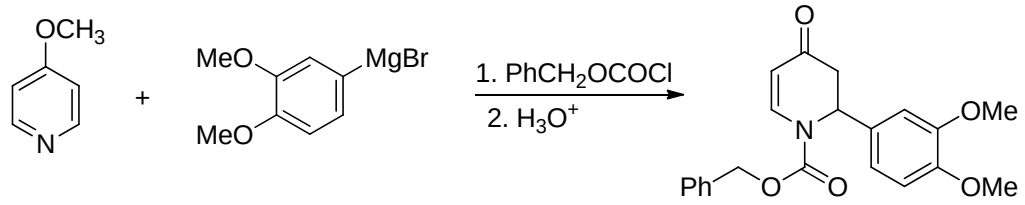
c.f. electron transfer mechanism favors 4-substitution

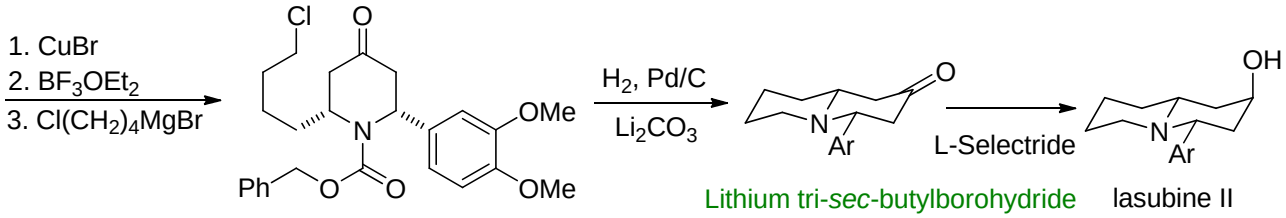




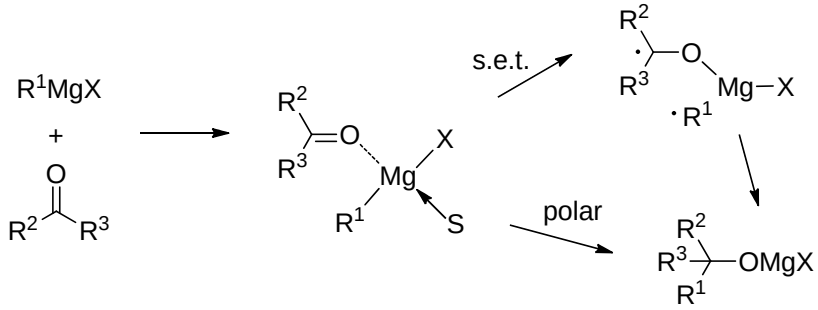
4-substitution promoted by 3-substitution







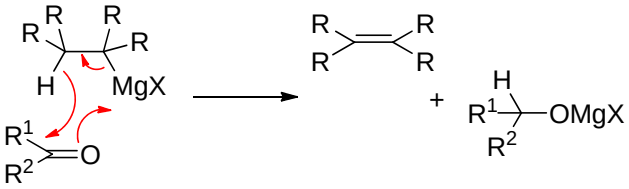
Addendum: Addition of organomagnesium compounds to carbonyl groups



three important side reactions

1. reduction

β-hydrogen transfer



favored for sterically hindered case

suppressed by the addition of metal salts

hydrogen abstraction by ketyls

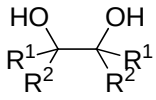
Meerwein-Ponndorf reduction

magnesium hydride reduction

are also possible for reduction

2. pinacol reduction

electron trsnafer $2R^1R^2CO$ →



promoted by transition metal or magnesium with aromatic ketones in polar solvents

3. enolization

recovery of cabonyl compound or aldol product

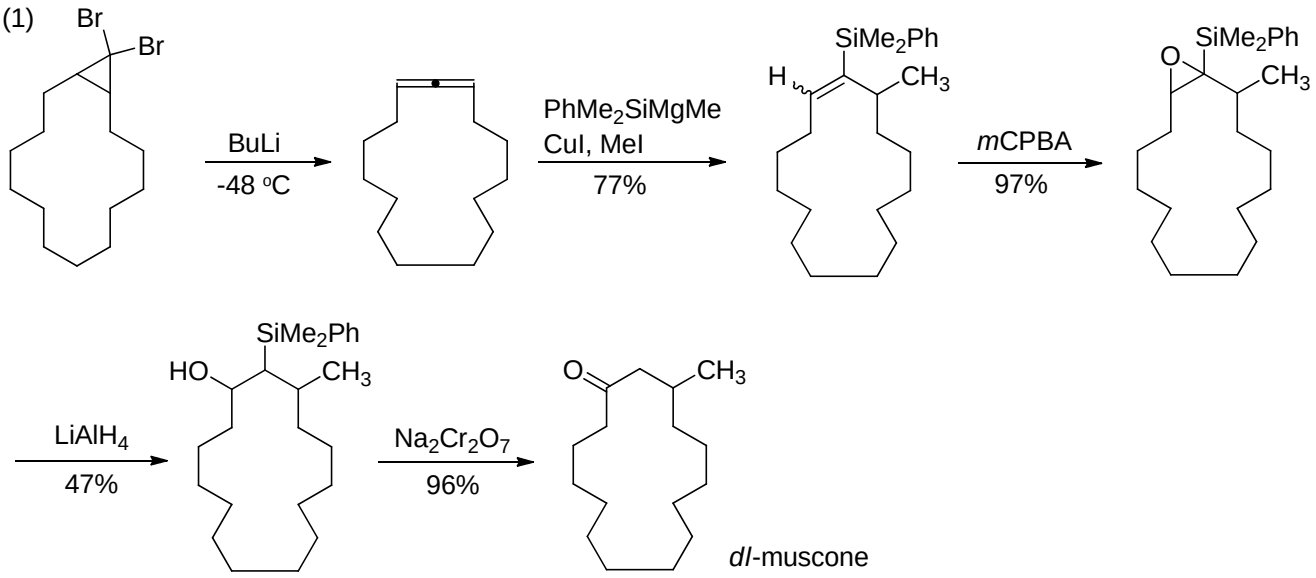
reduced by the use of less polar media or low temperature

in situ convertion to less basic Ti(IV) or Ce(III) salt

Problem Set - Organomagnesium

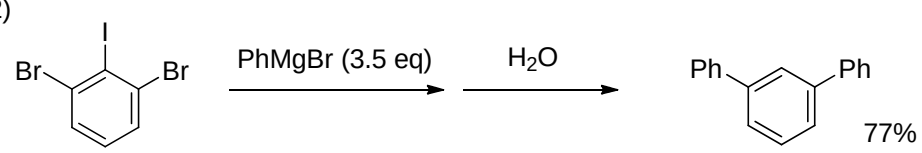
Explain the mechanism of the following reactions

(1)



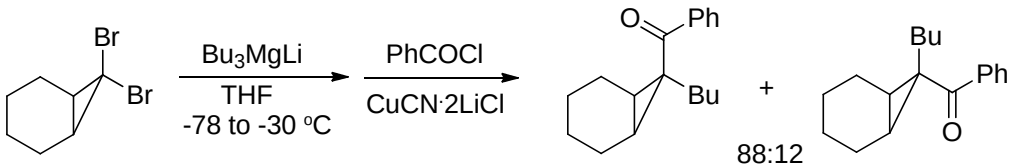
dl-muscone

(2)



77%

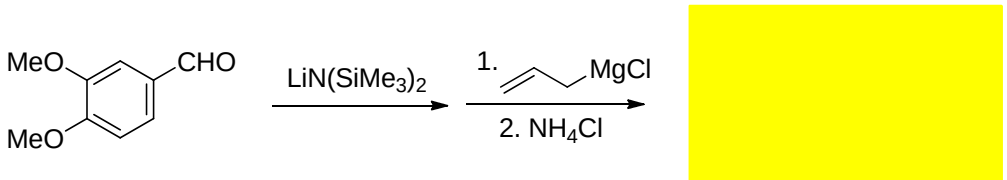
(3)



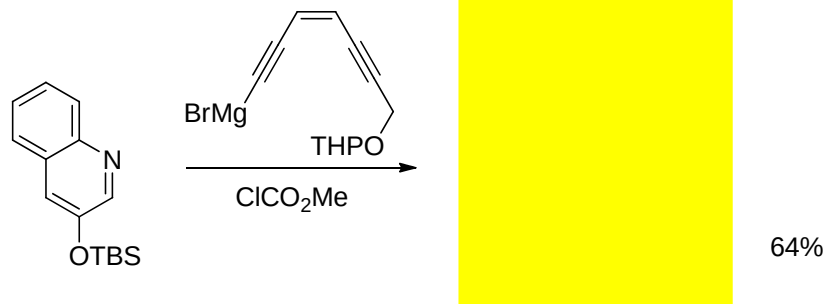
88:12

88%

(4)



(5)

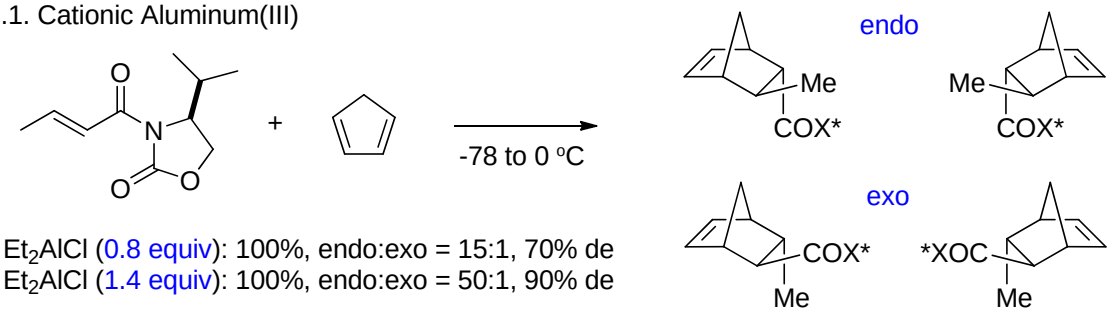


64%

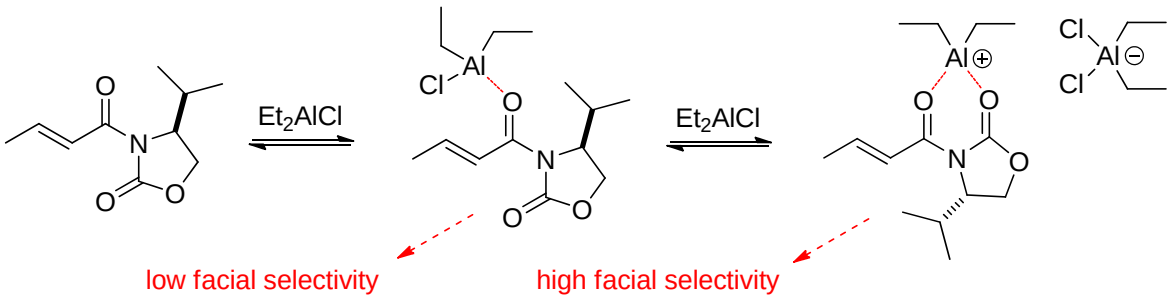
3. Aluminum in Organic Synthesis

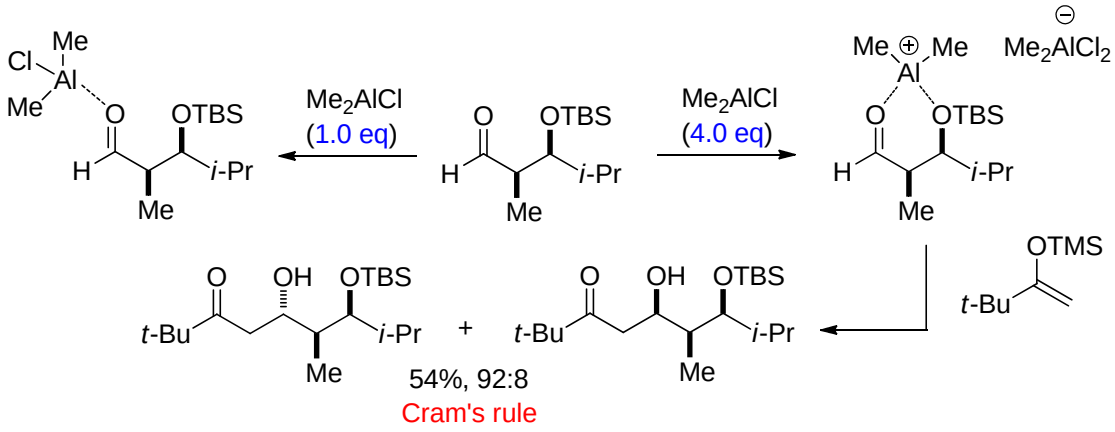
3.1. Interaction of Aluminum(III) with different functional groups

3.1.1. Cationic Aluminum(III)



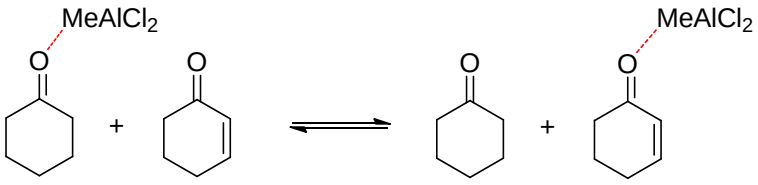
Et_2AlCl (0.8 equiv): 100%, endo:exo = 15:1, 70% de
Et_2AlCl (1.4 equiv): 100%, endo:exo = 50:1, 90% de



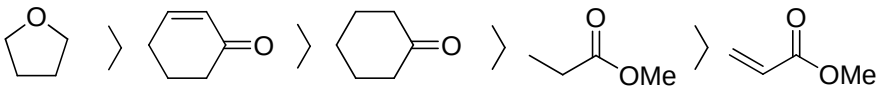


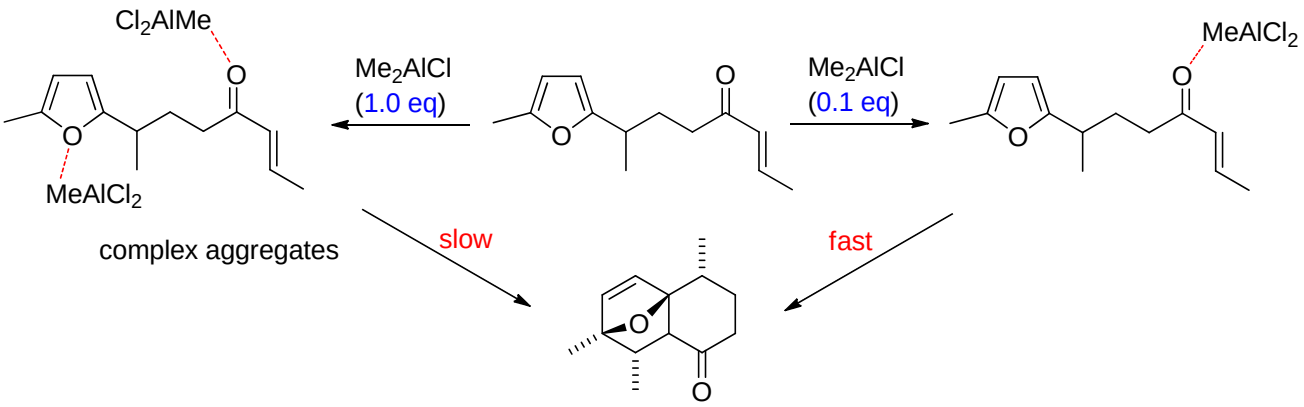
3.1.2. Neutral Aluminum(III)

Coordination aptitude



Relative basicity

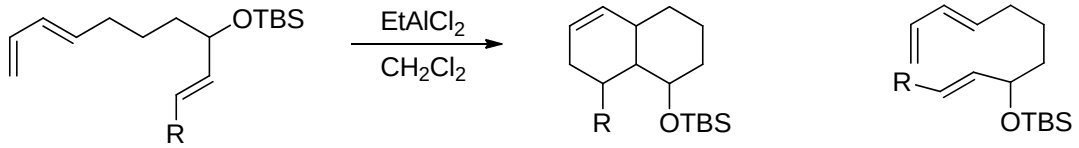




3. Aluminum in Organic Synthesis

3.1. Interaction of Aluminum(III) with different functional groups

3.1.2. Neutral Aluminum(III)



R: CHO, 0.2 equiv $EtAlCl_2$, -78 °C, 62%

R: CO_2i-Pr, 1.0 equiv $EtAlCl_2$, 8 °C, 60%

due to the basicity difference of the functional groups in SM and PD (conjugated or saturated)

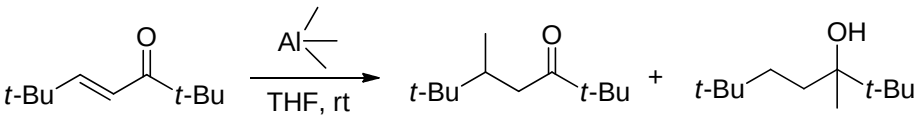
3.2. Aluminum reagents in selective organic synthesis

3.2.1. Carbon-Carbon bond formation
3.2.2. Reduction
3.2.3. Oxidation
3.2.4. Rearrangement and fragmentation
3.2.5. Radical reaction

3.2.1. Carbon-Carbon bond formation

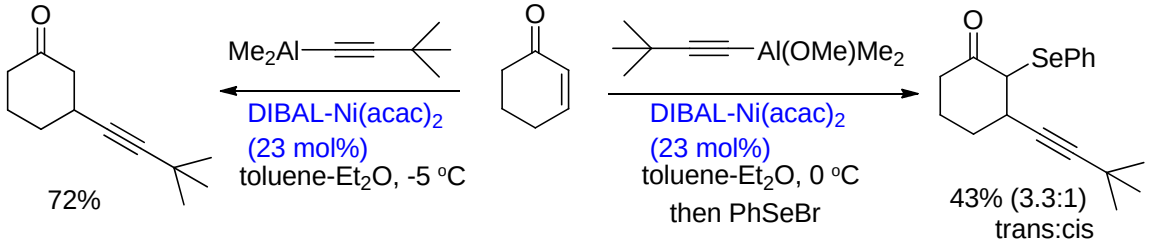
3.2.1.1. Generation and reaction of aluminum enolate

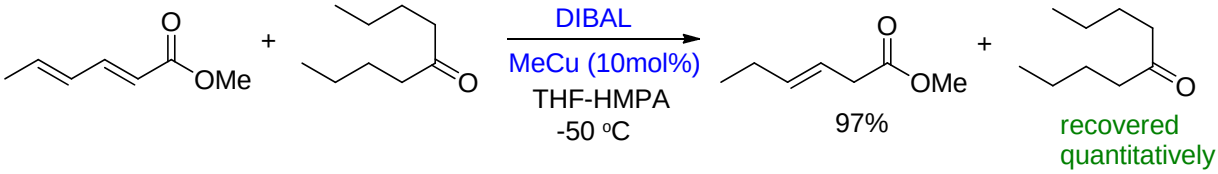
By Michael Addition

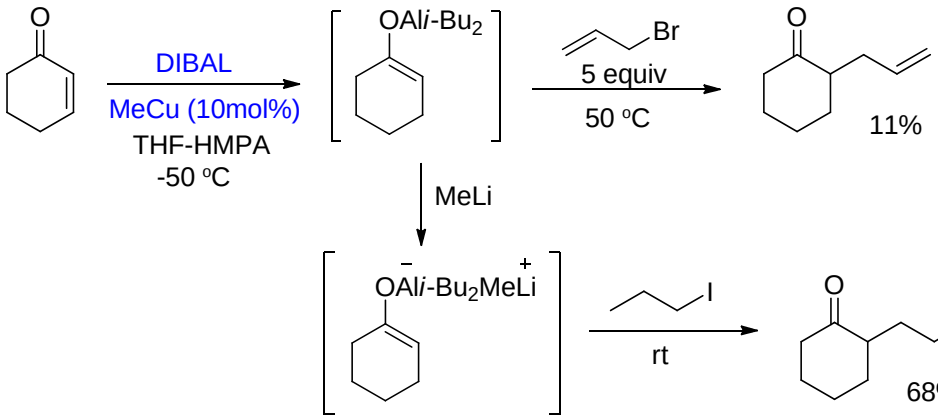


Me_3Al: 75% (0:100)
Me_2AlCl: 71% (6:94)
$MeAlCl_2$: 58% (20:80)
Me_2AlI: 42% (98:2)
$MeAlI_2$: 32% (100:0)

Transition metal catalyst

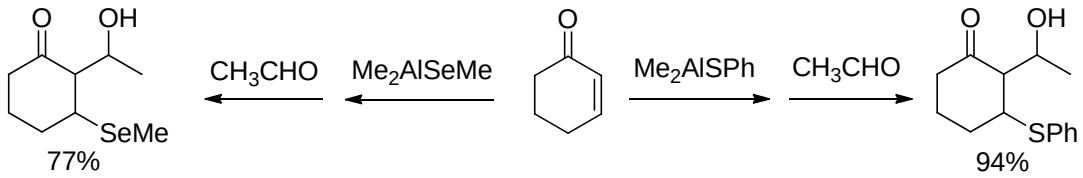




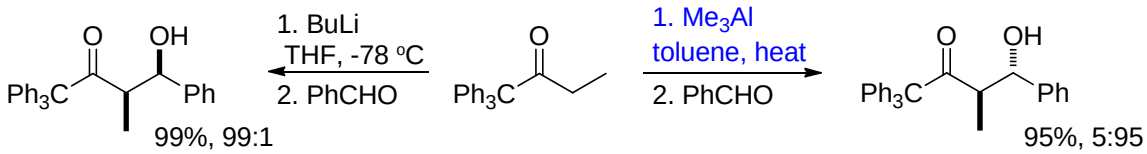


3.2.1.1. Generation and reaction of aluminum enolate

Heteroatom-containing aluminum reagent - no transition metal catalyst required

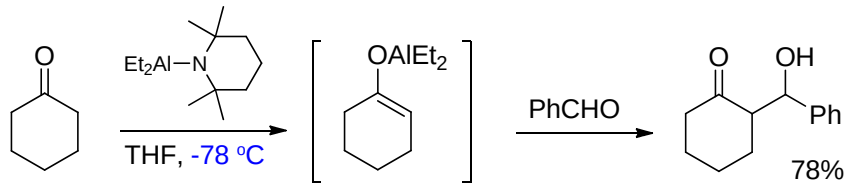


By Deprotonation with trialkylaluminum



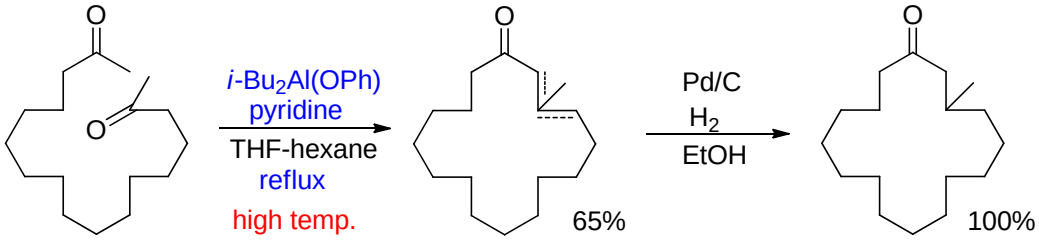
kinetic control thermodynamic control

By Deprotonation with aluminum amides - DATMP



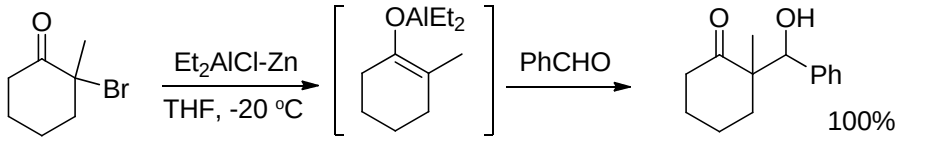
low temp.

By Deprotonation with aluminum phenoxides



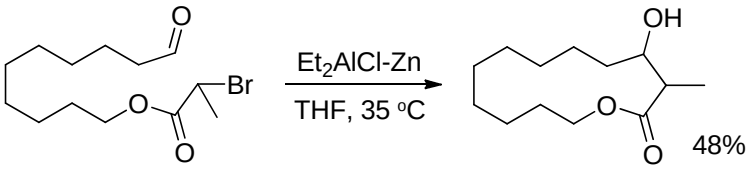
dl-muscone

By Reduction of α-bromo carbonyl compounds



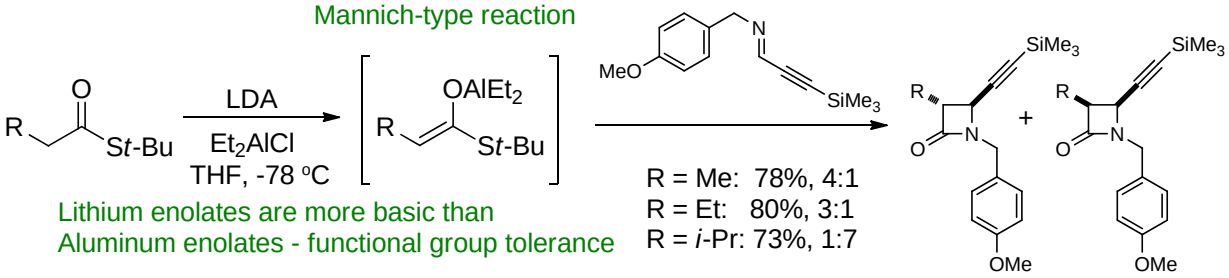
$Et_2AlSnBu_3$ works too Zinc enolate?

JACS **1977**, *99*, 7705



By transmetalation of lithium enolates

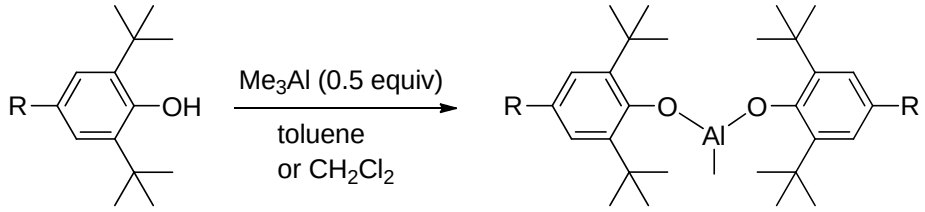
Mannich-type reaction

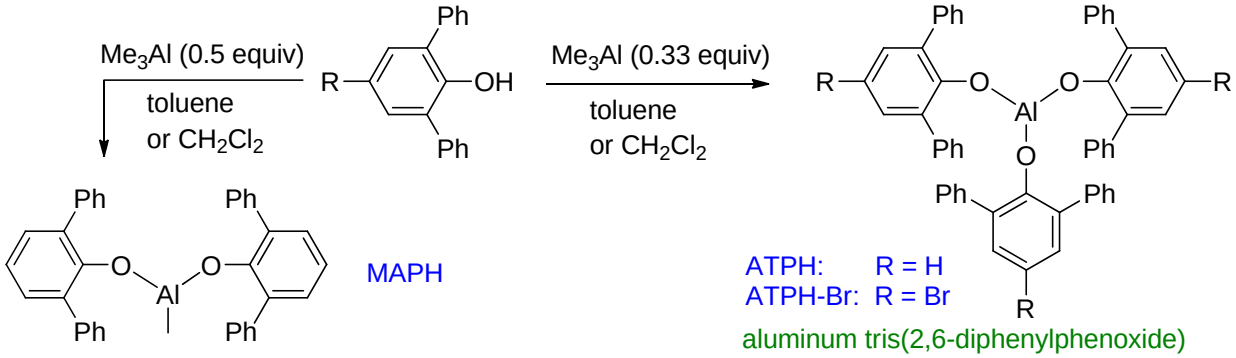


Lithium enolates are more basic than Aluminum enolates - functional group tolerance

3.2.1.1. Generation and reaction of aluminum enolate

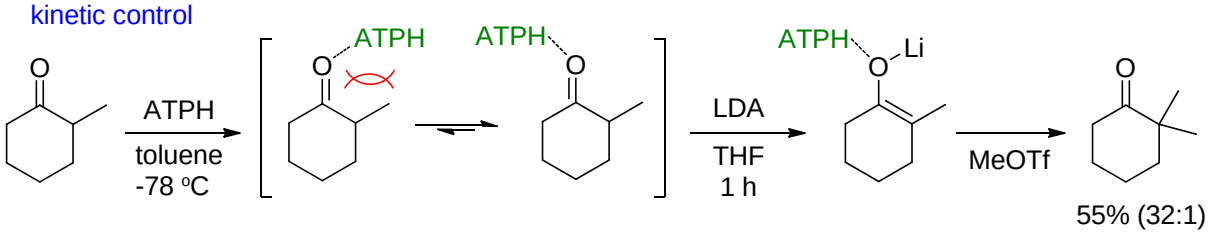
Well designed aluminum reagents

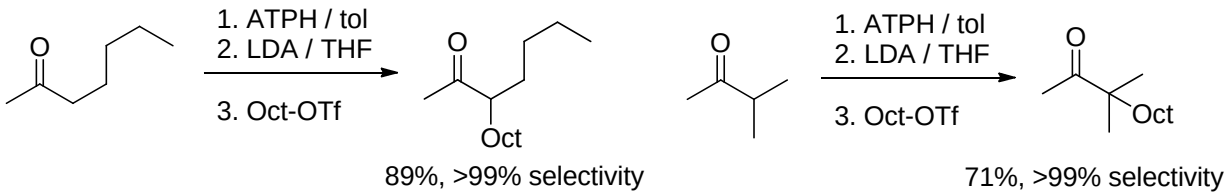


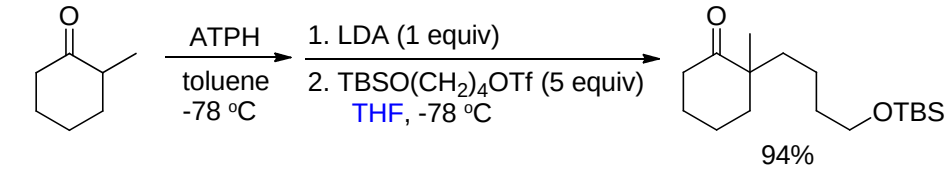


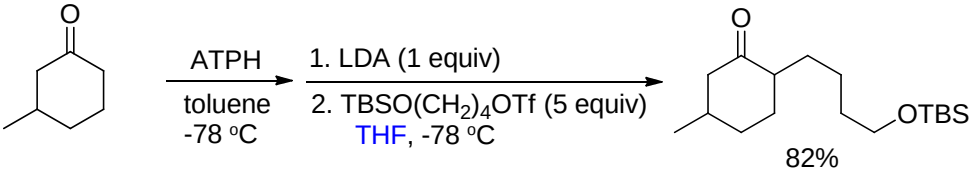
By Complexation with aluminum reagents

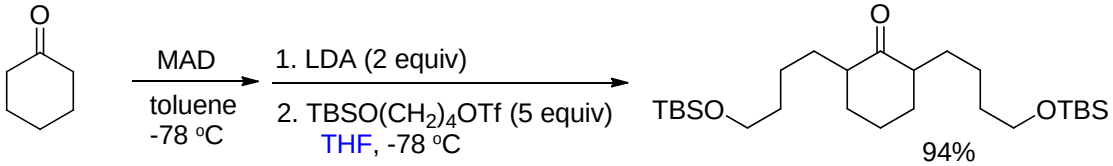
kinetic control







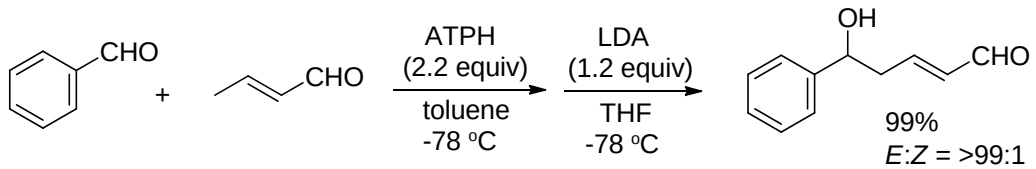




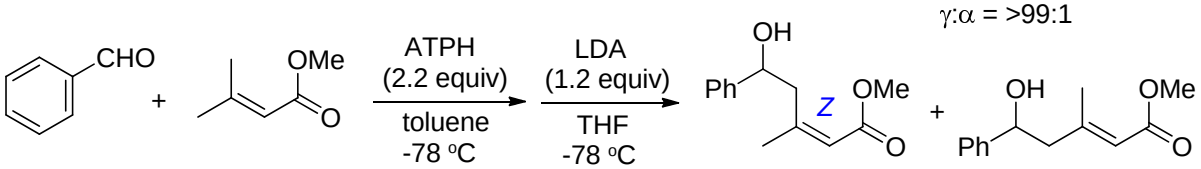
3.2.1.1. Generation and reaction of aluminum enolate

By Complexation with aluminum reagents

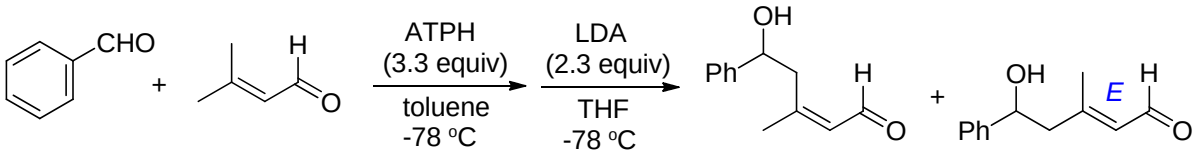
γ-Alkylation of α,β-unsaturated carbonyl compounds



99%
E:*Z* = >99:1
γ:α = >99:1



91% (13:1)

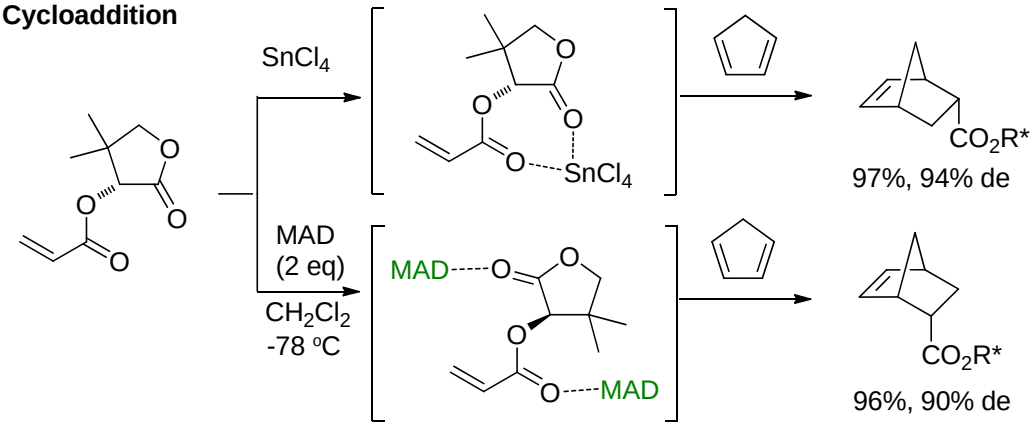


99% (1:99)

3.2.1.2. Aluminum-carbonyl complexation, activation, and nucleophilic reaction

Pericyclic reaction and asymmetric reaction

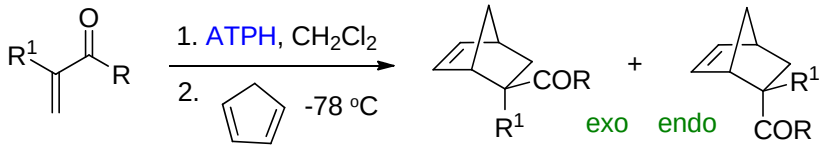
[4+2] Cycloaddition



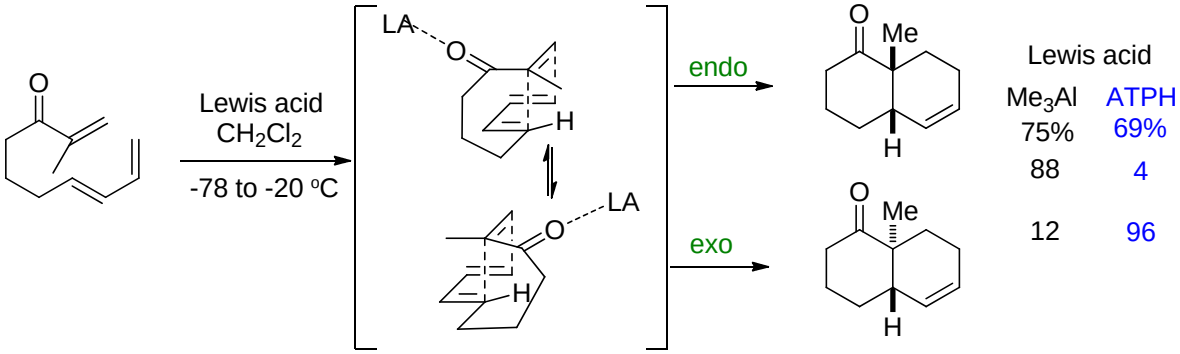
97%, 94% de

96%, 90% de

Exo-selectivity

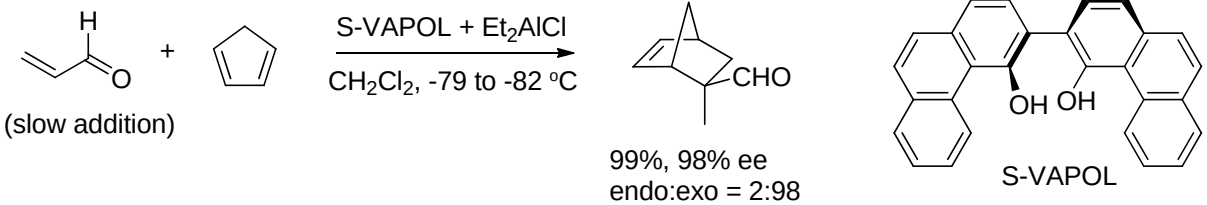


R = Ph, R^1 = H : 81% (73:23)
R = Ph, R^1 = Me : 81% (96: 4)
R = Me, R^1 = H : 87% (87:13)

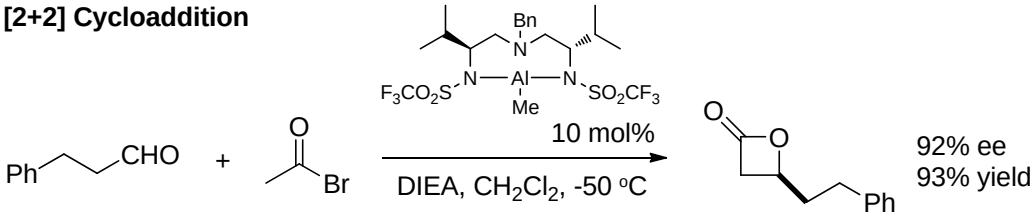


Lewis acid	Me_3Al	ATPH
	75%	69%
endo	88	4
exo	12	96

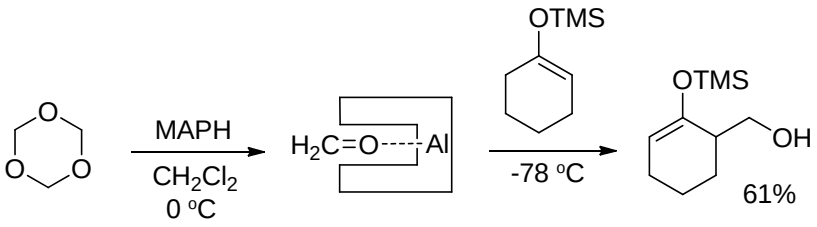
Catalytic asymmetric [4+2] Cycloaddition



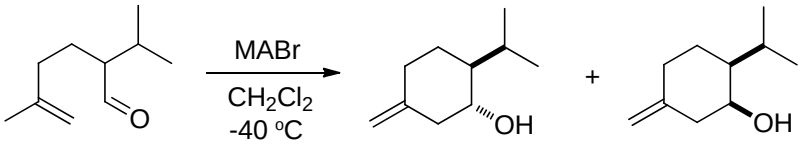
[2+2] Cycloaddition



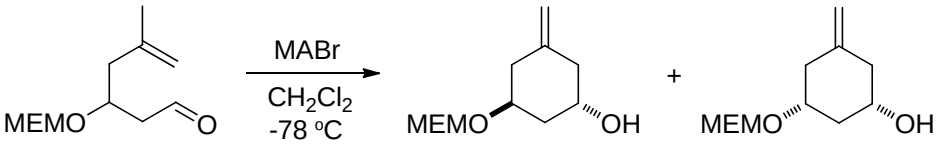
Ene reaction and asymmetric reaction



unusual trans selectivity

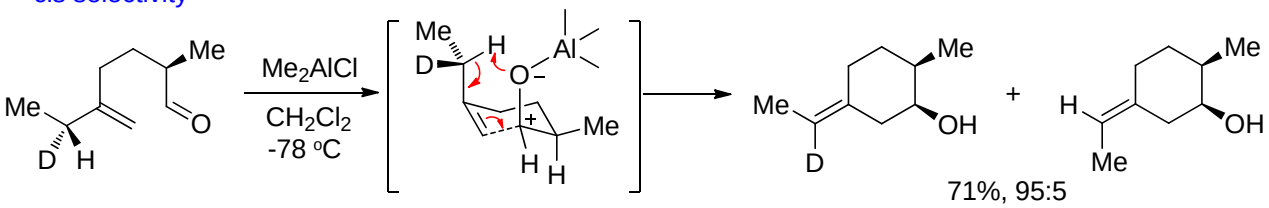


85%, 17:1



83%, 97:3

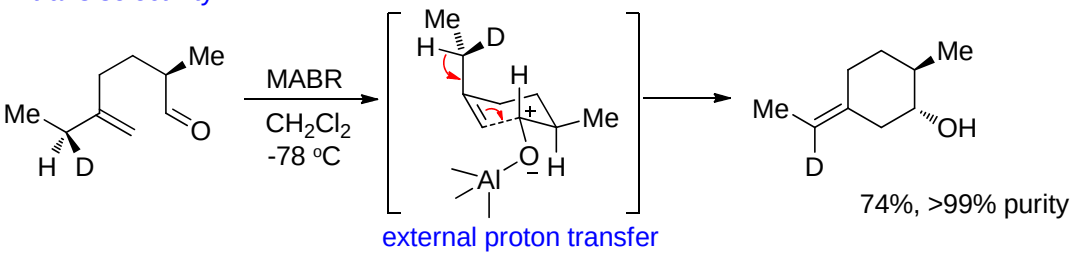
cis selectivity



internal proton transfer

71%, 95:5

trans selectivity

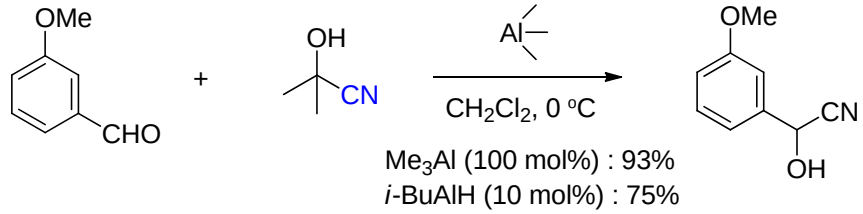


external proton transfer

74%, >99% purity

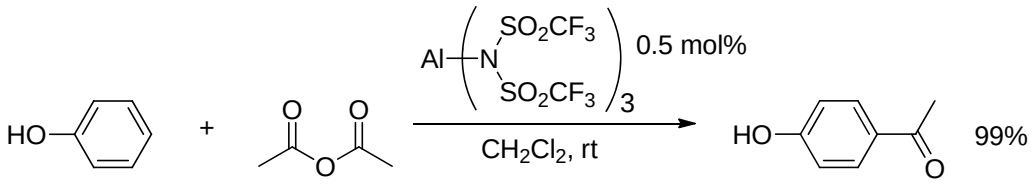
Hydrocyanation

Meerwein-Pondorf-Verley type

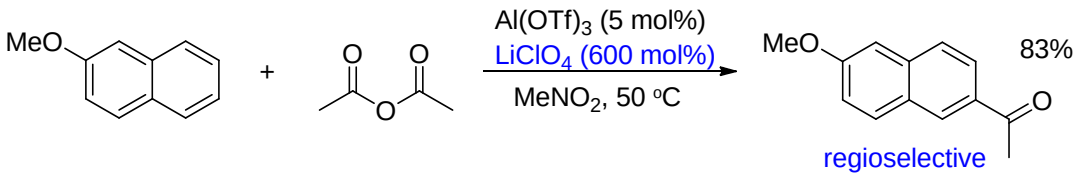


Friedel-Crafts Reaction

requires strongly electron-withdrawing aluminum(III) reagents: AlX_3 (X = Cl, Br, I, OTf)

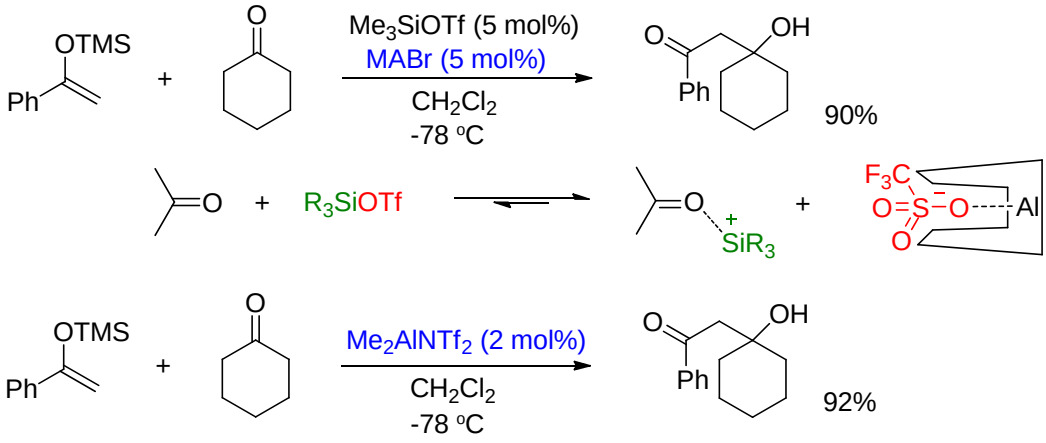


salt effects on reactivity and selectivity

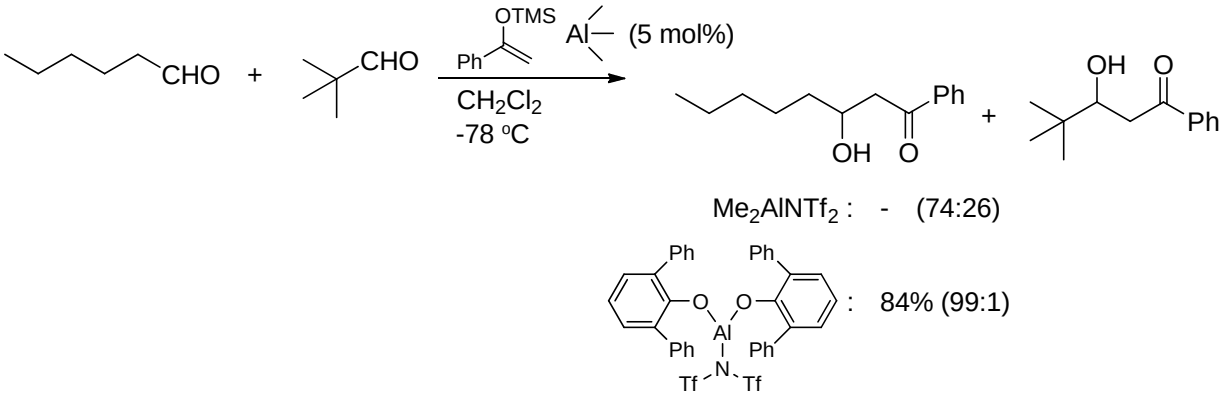


Aldol reaction and asymmetric reaction

The reactivity of **silyl cations** is increased by making more **naked species** by use of **bulky aluminum reagents**

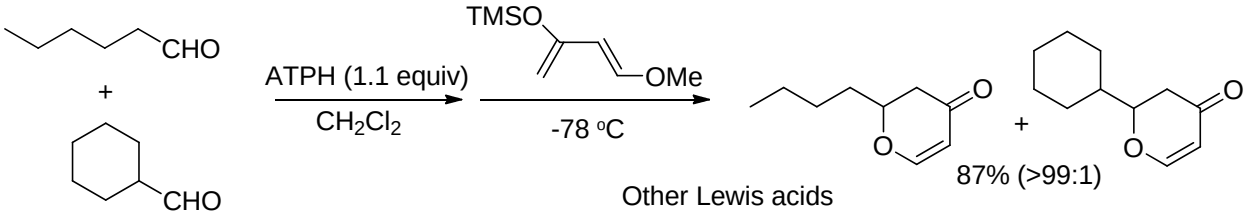


Recognition and activation of a less-shielded carbonyl functionality



Aldol reaction and asymmetric reaction

Recognition and activation of a less-shielded carbonyl functionality

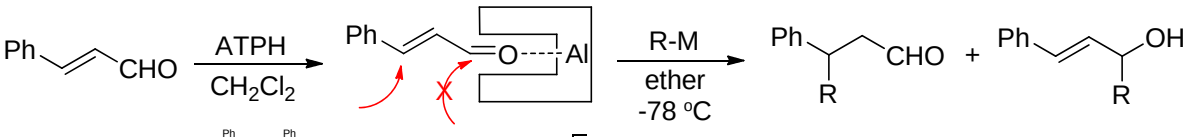


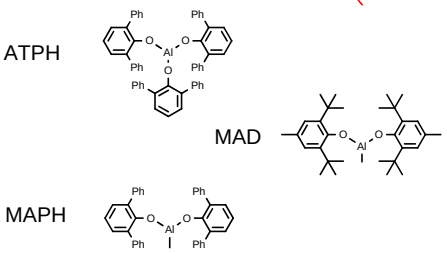
Other Lewis acids

$(i\text{-PrO})_2TiCl_2$	=	6.2 : 1
Me_3Al	=	5 : 1
MAD	=	3.7 : 1
$TiCl_4$	=	2 : 1
BF_3OEt_2	=	1.3 : 1
MAPH	=	1 : 3.4

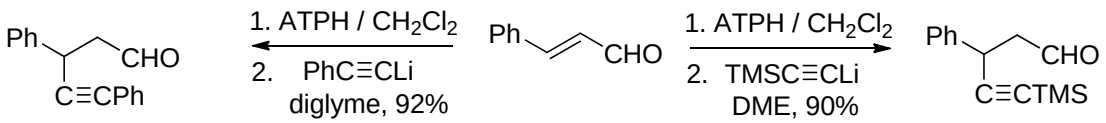
Conjugate addition and asymmetric reactions

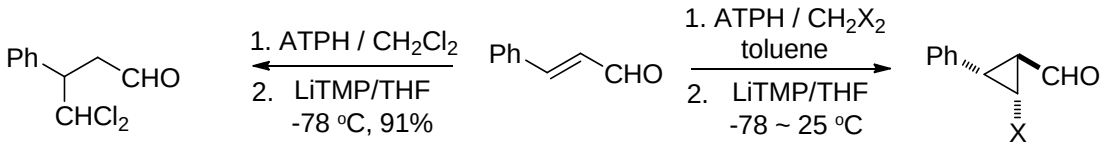
ATPH can be used as a carbonyl protector on complexation





ATPH	RM =	*n*-BuLi	: 92% (49 : 51)
		n-BuMgCl	: 99% (90 : 10)
		n-BuCaI	: 88% (98 : 2)
		n-BuSrI	: 60% (95 : 5)
		n-BuBaI	: 97% (97 : 3)
MAD		*n*-BuMgBr	: 95% (7 : 93)
MAPH		*n*-BuMgBr	: 98% (49 : 51)

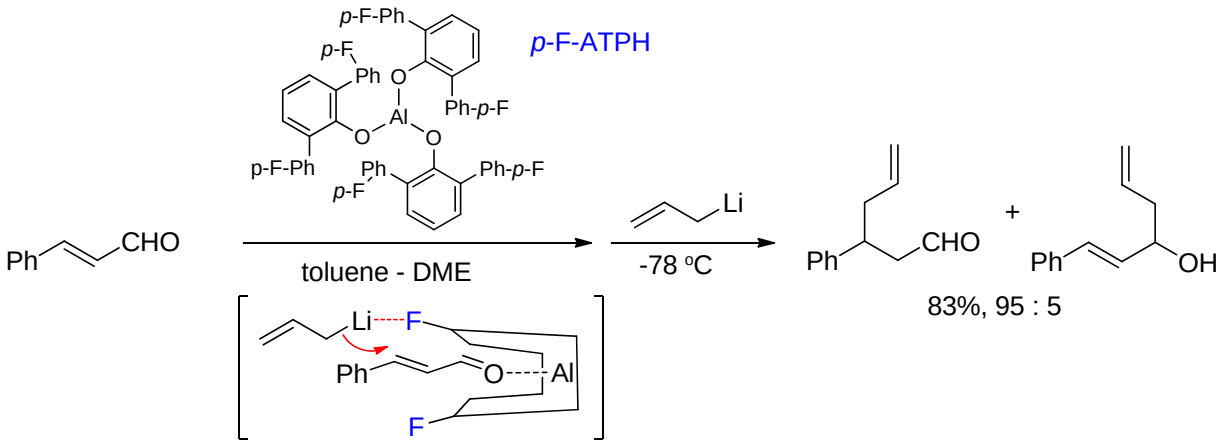




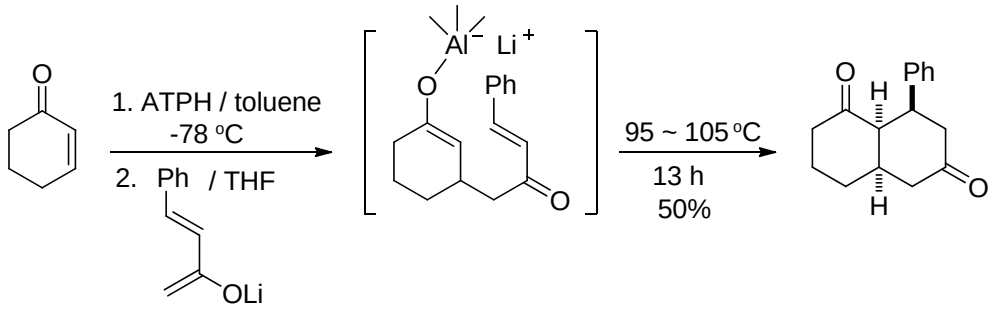
X = Cl : 86%
X = Br : 80%

* MeLi and allyllithium are prone to 1,2-addition

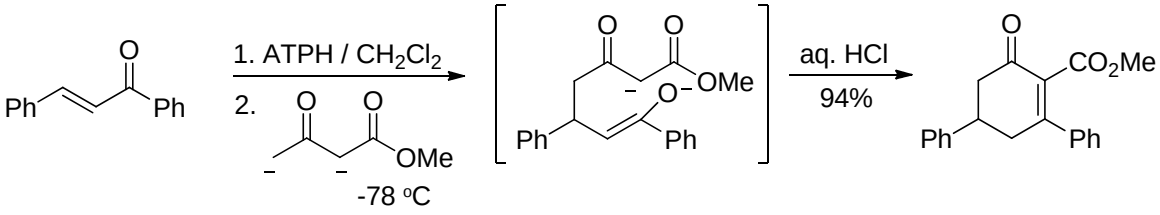
1,4-addition by ATPH analogue bearing fluorine directing groups - chelation control



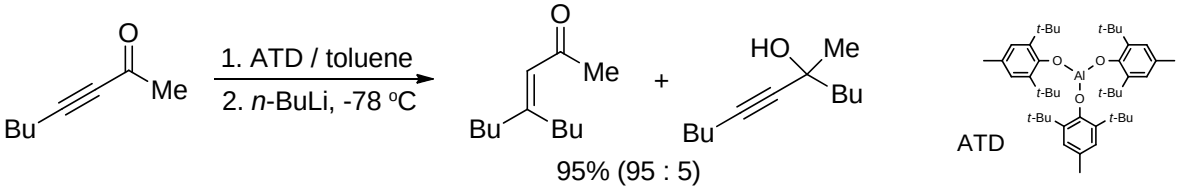
Tandem inter- and intramolecular Michael addition



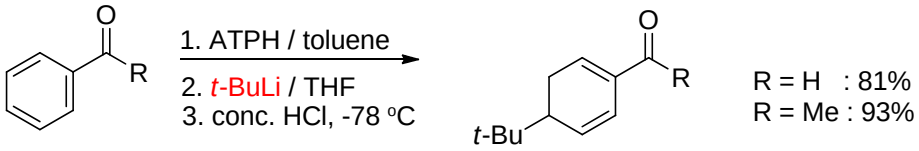
Michael addition and intramolecular aldol condensation



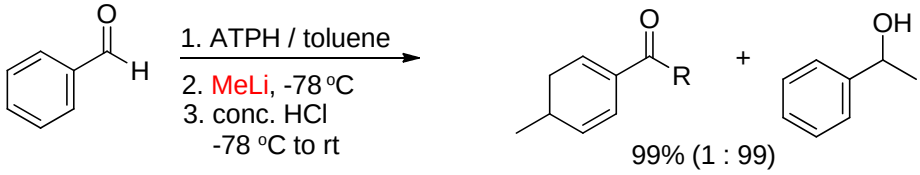
ATD is superior to ATPH or MAD as a carbonyl protector in **ynones**



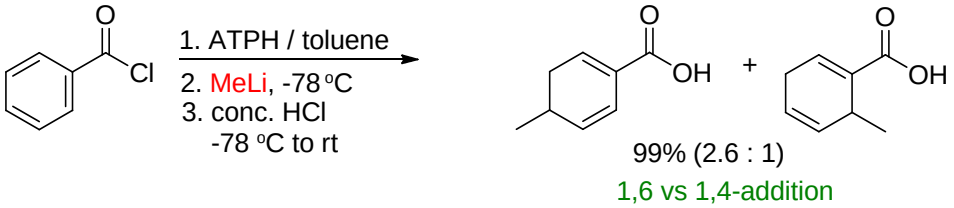
1,6-Addition to aromatic carbonyl compounds



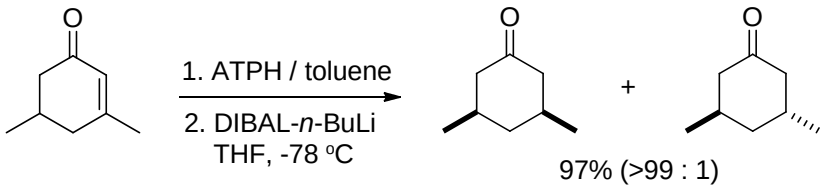
not effective for small nucleophiles - MeLi or lithium acetate

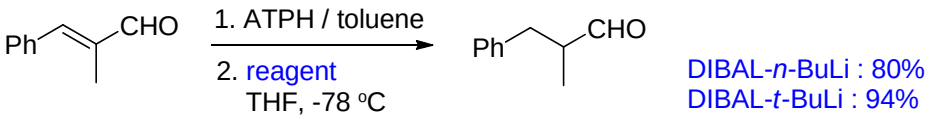


conjugate addition of MeLi to PhCOCl

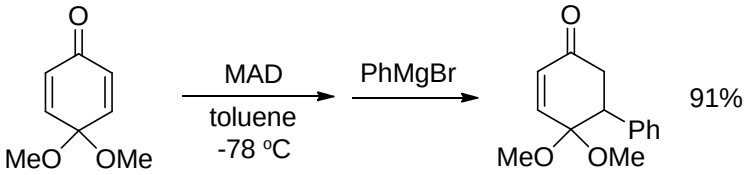


Conjugate reduction by ATPH - (DIABL-*n*-BuLi) ate complex

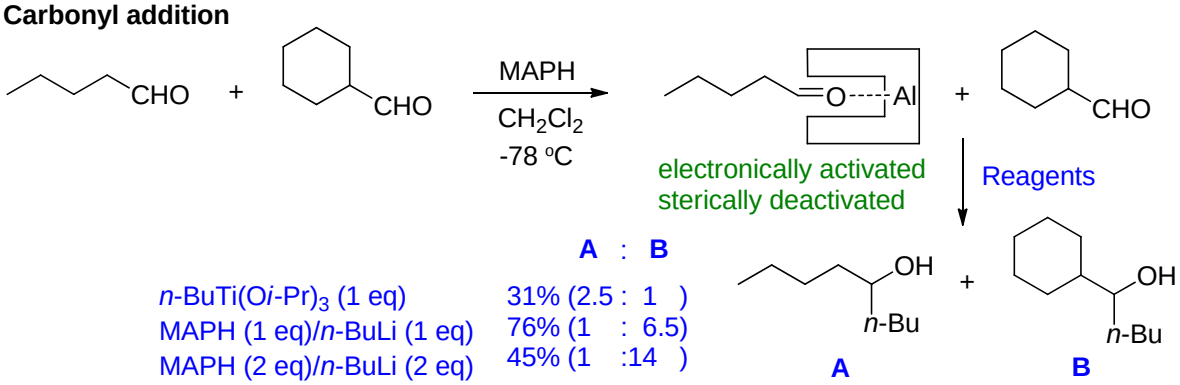




Addition to quinone monoketals



Carbonyl addition

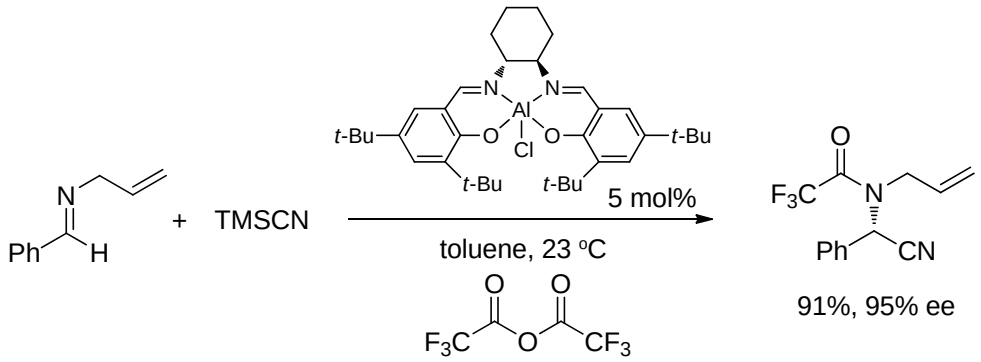


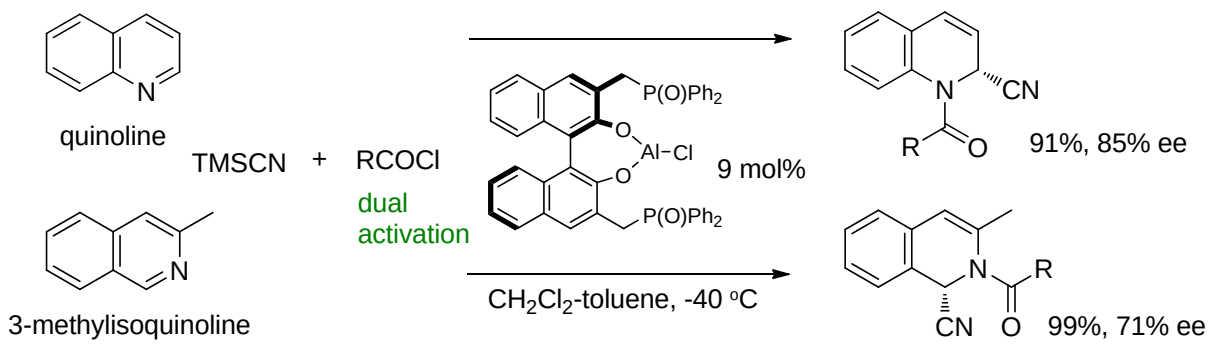
3.2.1.3. Strecker Reaction (Addition of CN^- to C=N Bonds)

preparation of optically active α-amino acids

chiral salen-Al-Cl catalyst was used for activation of aldimines

no reaction under strictly anhydrous conditions --> reacting species is HCN





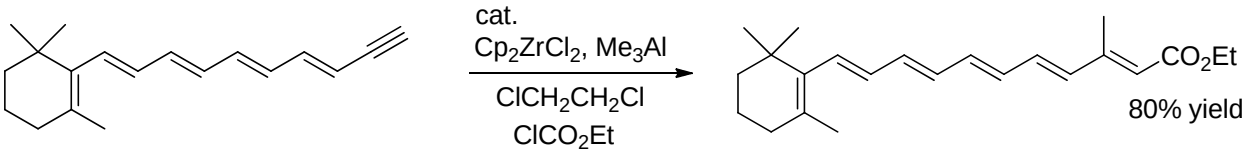
3.2.1.4. Carboalumination

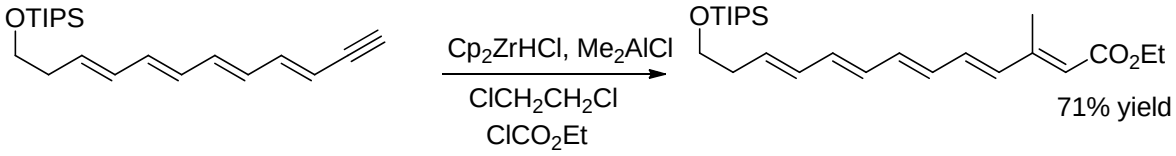
addition of C-Al bonds across the unsaturated C-C bonds

transition-metal catalyst is required alkynes are more reactive than alkenes

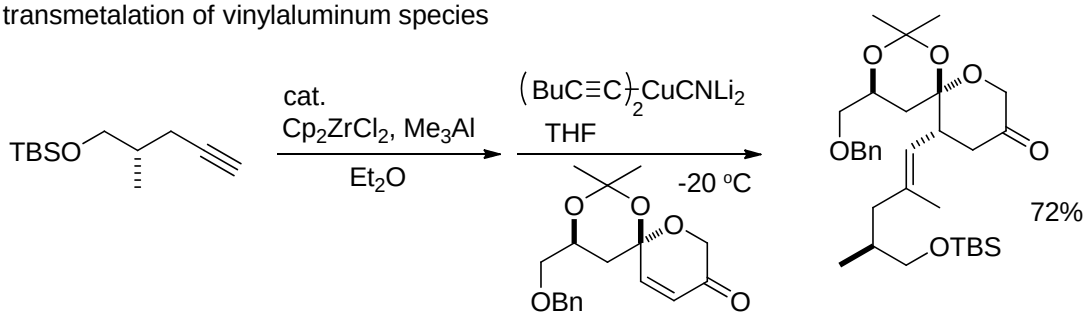
Cp_2ZrCl_2

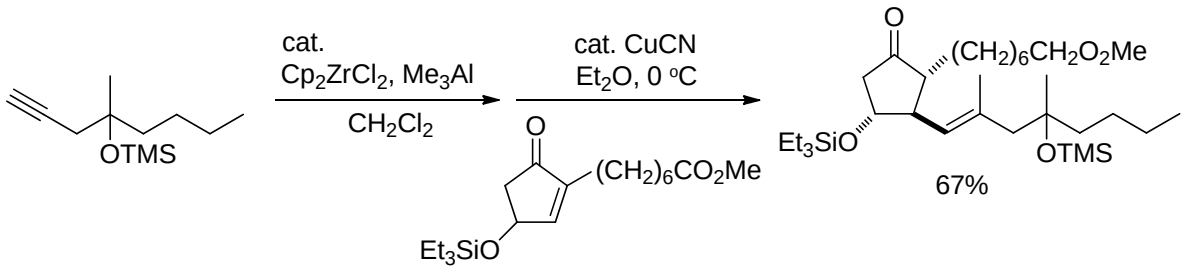
methyl-alumination (no β-elimination nor hydroalumination)





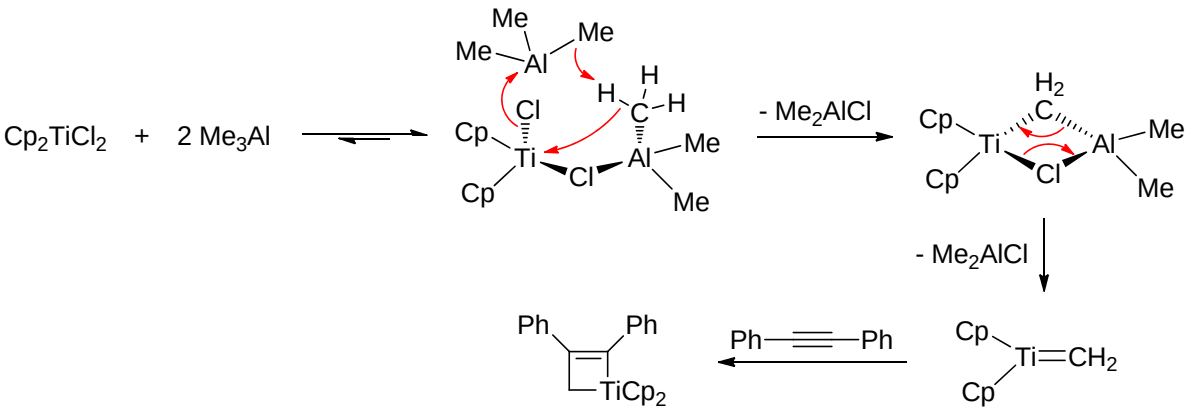
transmetalation of vinylaluminum species





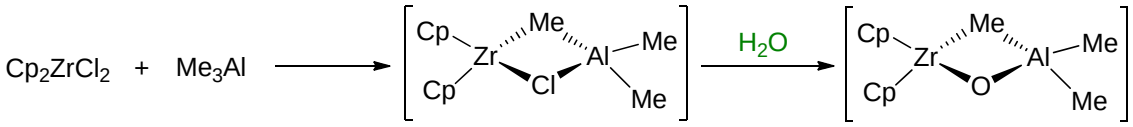
c.f. Tebbe reagent: Cp_2TiCl_2 - $2Me_3Al$

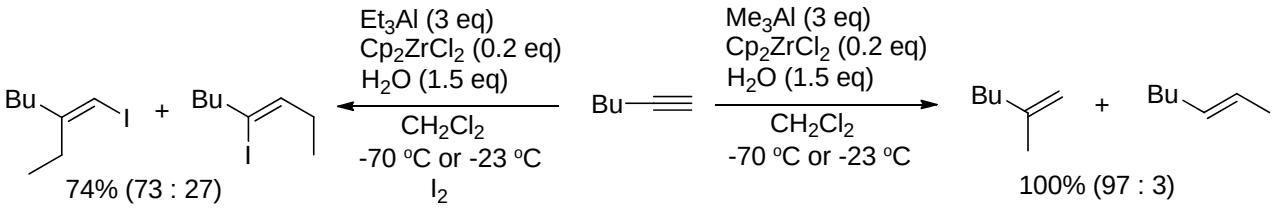
reqires a stoichiometric amount of Ti, sometimes difficult to control, limited in scope



3.2.1.4. Carboalumination

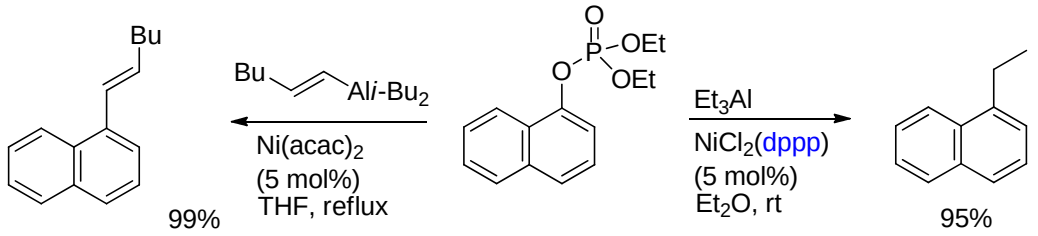
addition of H_2O leads to a considerable increase in the reaction rate
the formation of a thermodynamically labile, but catalytically active **oxo-bridged dimer** at temp. below 0 °C



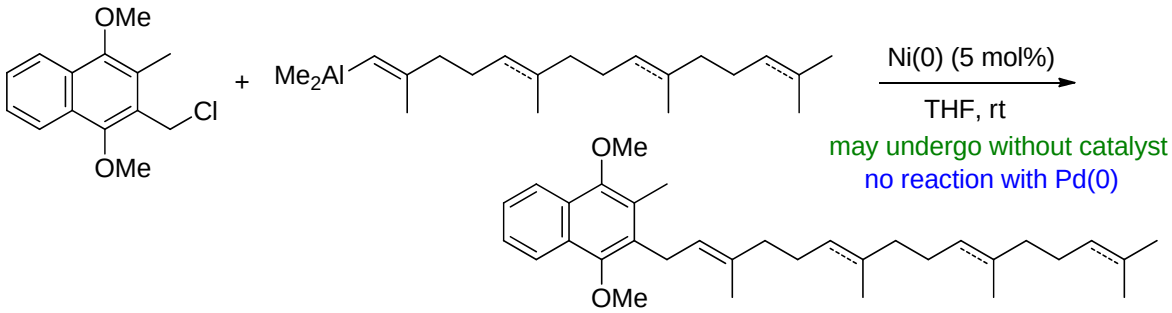


3.2.1.5. Coupling Reaction with Transition Metals

Ni-catalyzed cross-coupling of arylphosphonates - Grignard reagents as well as Aluminum Alkyl reagents
dppp ligand effect on **alkyl nickel species** - no β-hydride elimination
transmetalation of Al-R to Ni-Cl

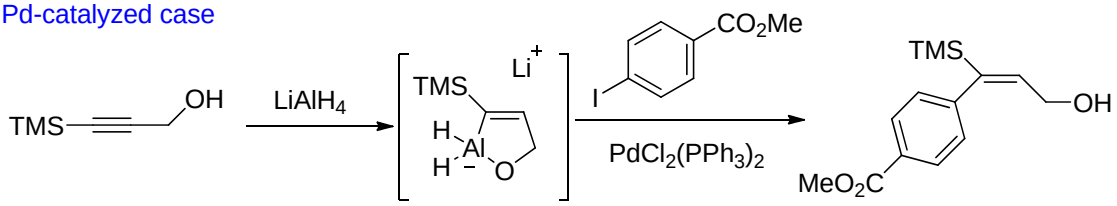


Coupling of benzylic halides



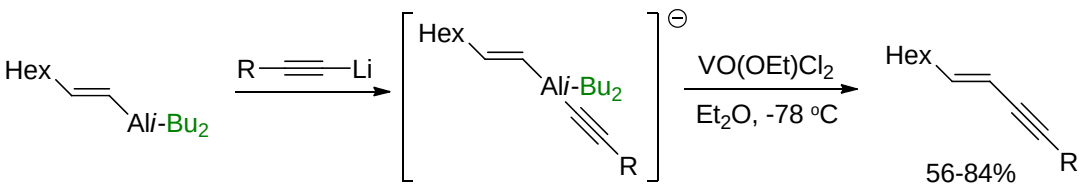
vitamin K_1 : 87%
vitamin $K_{2(20)}$: 91%

Pd-catalyzed case



without $ZnCl_2$: 11%
with 60 mol% $ZnCl_2$: 90%

Alkynyl coupling of ate complexes in the presence of stoichiometric oxo-vanadium reagents
selective cross-coupling ; neither alkynyl-alkynyl nor alkenyl-alkenyl coupling products was obtained.



3.2.2. Reduction

3.2.2.1. Carbonyl Reduction

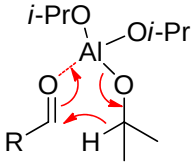
$LiAlH_4$, X_nAlH_{3-n} (X = halogen or alkoxy) are the most convenient reagents for reduction

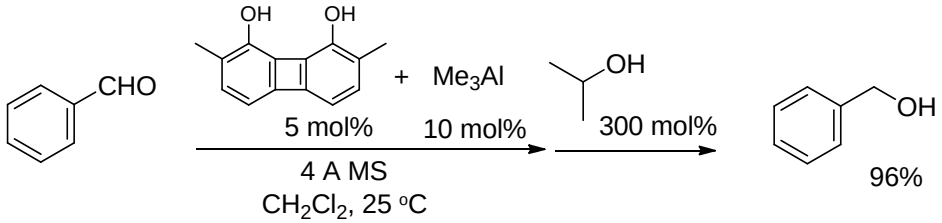
Meerwein-Ponndorf-Verley (MPV) reduction

environmetally benign, easy handling, commercial availability, and low cost

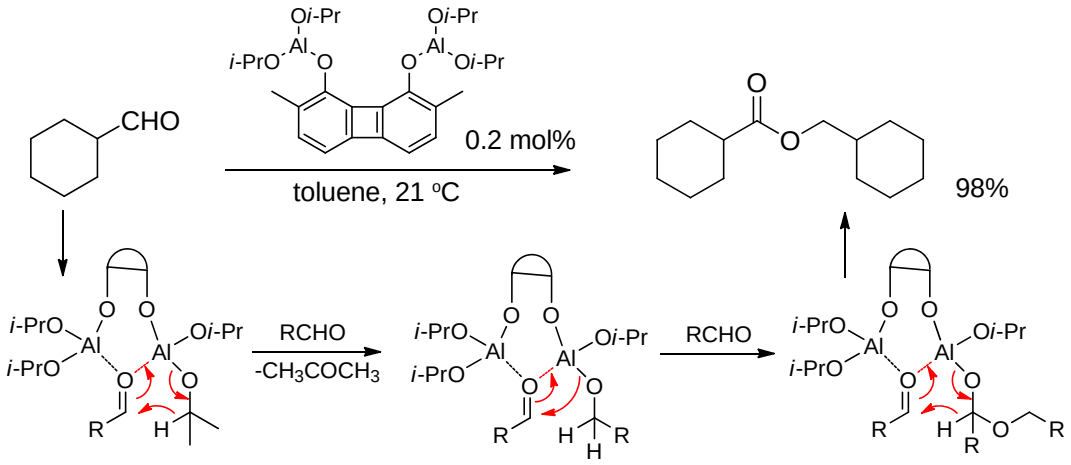
The original version uses Al(O*i*-Pr)$_3$, which proceeds very slowly.

Use **bidentate aluminum catalyst** for improvement

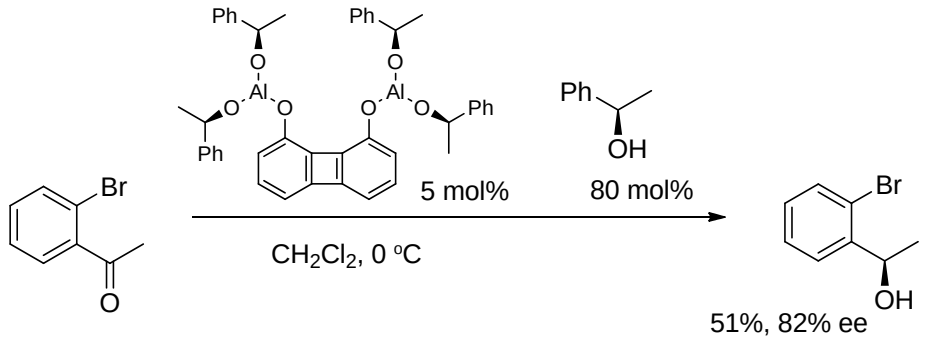


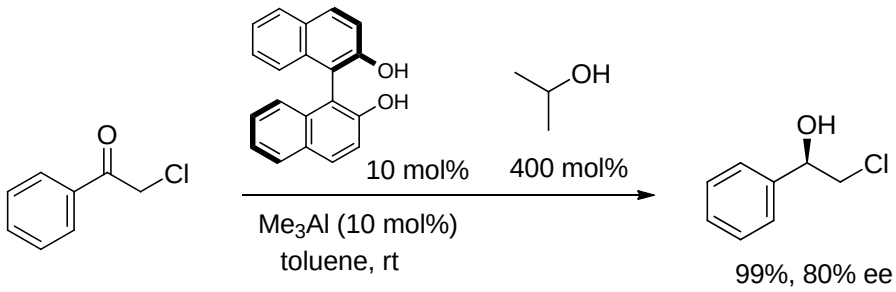


Tischenko reaction



Asymmetric MVP reduction

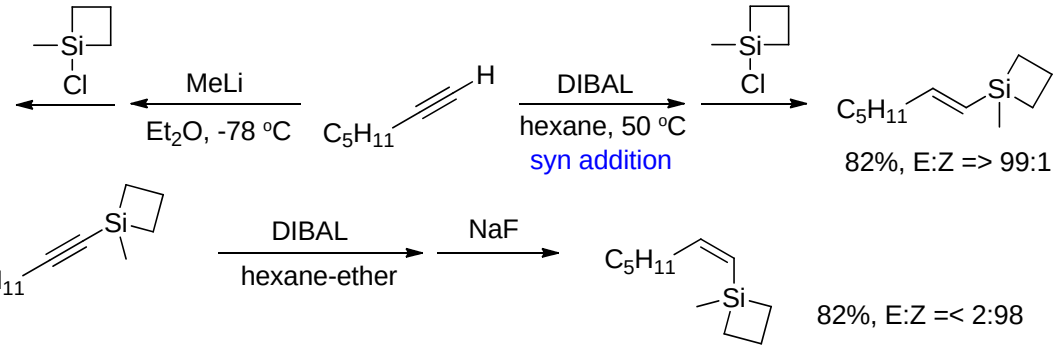




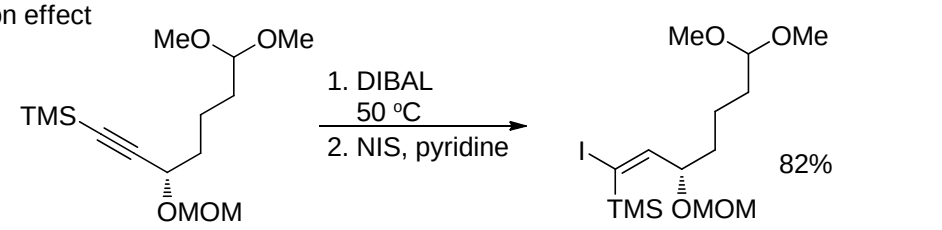
3.2.2. Reduction

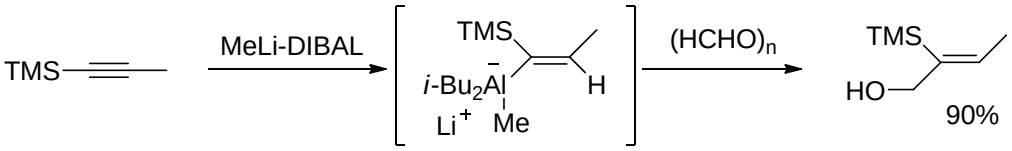
3.2.2.2. Hydroalumination

Hydroalumination of Alkynes Stereoselective synthesis of vinylaluminum species

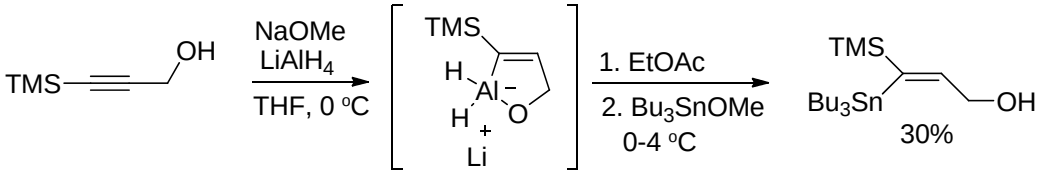


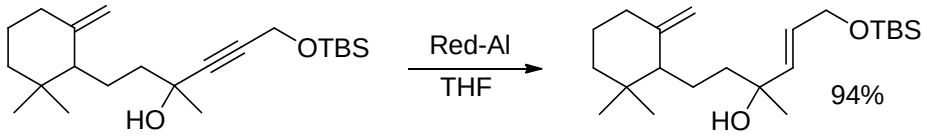
α-Silicon effect



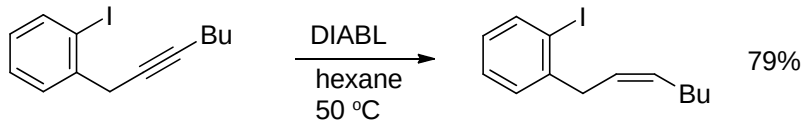


Propargylic alcohols ⟶ ***E*-alkenes**

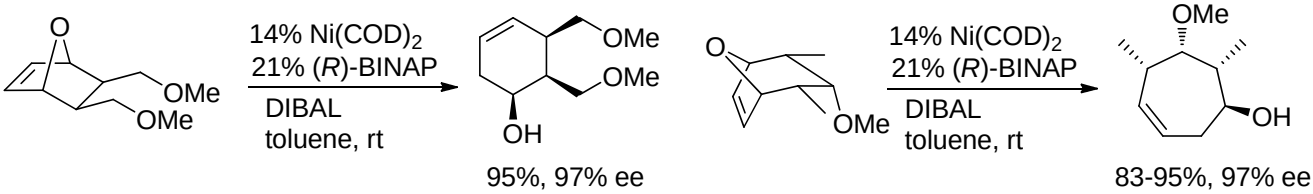




Ordinary alkynes ⟶ ***Z*-alkenes**

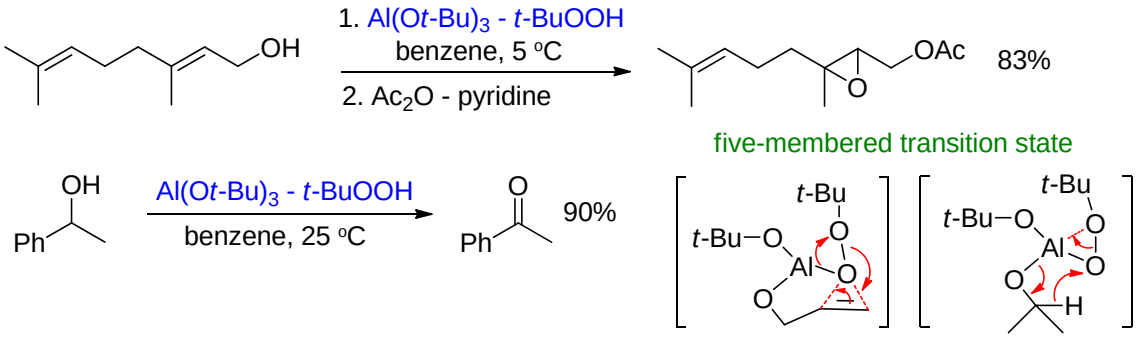


Hydroalumination of Alkenes: rather inert to hydroalumination
requires transition metal catalysts



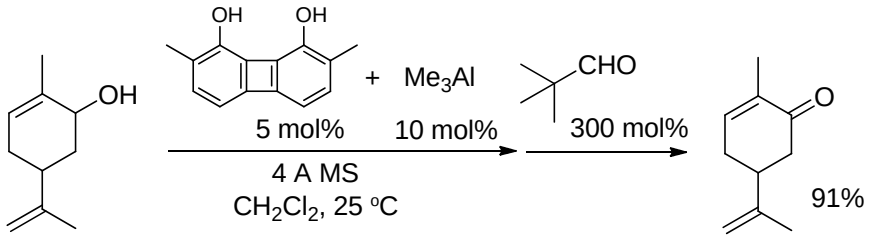
3.2.3. Oxidation

Epoxidation of allylic alcohol and oxidation of secondary alcohol by Al(O*t*-Bu)$_3$ and *t*-BuOOH



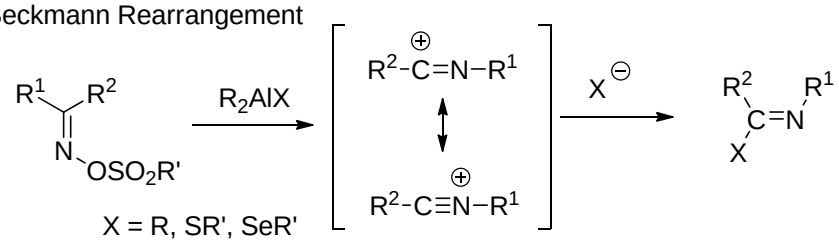
Oppenauer oxidation of secondary alcohols - pivalaldehyde (hydride capturing agent)

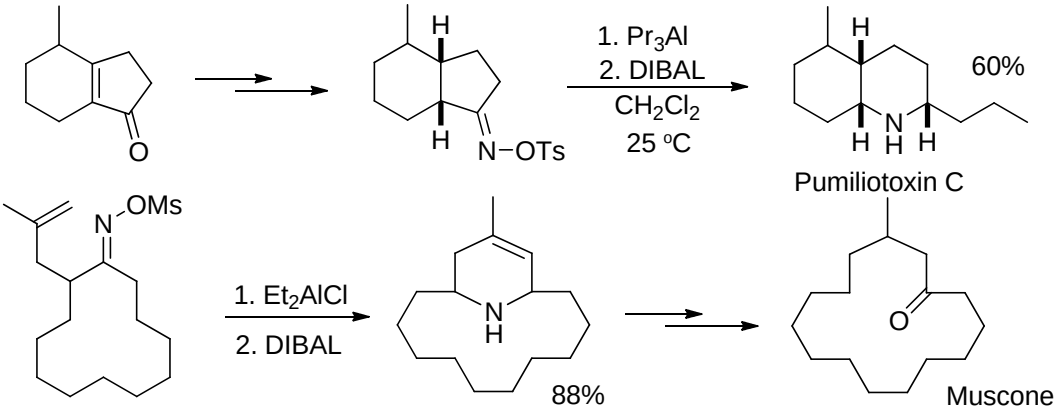
use of bidentate aluminum catalyst



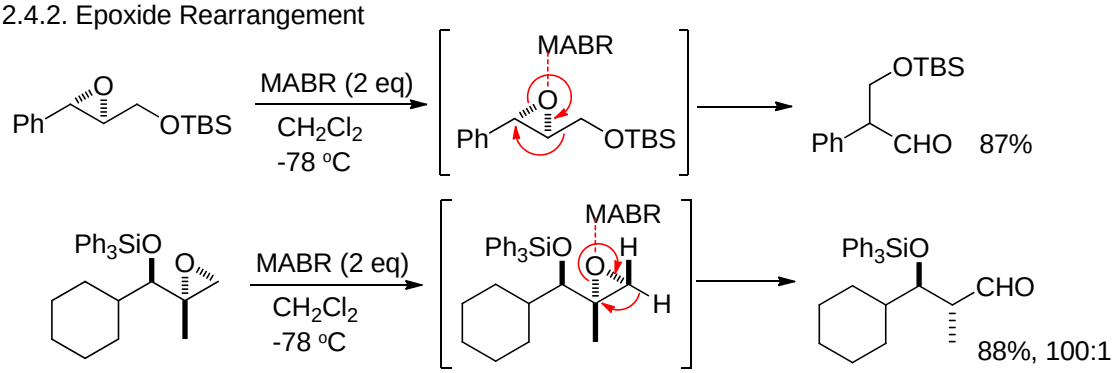
3.2.4. Rearrangement and Fragmentation

3.2.4.1. Beckmann Rearrangement

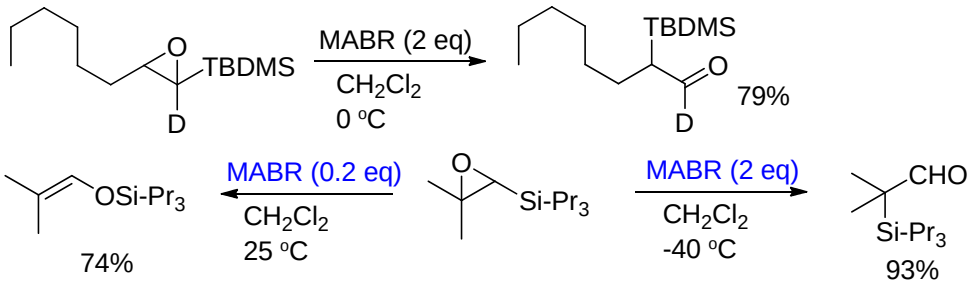




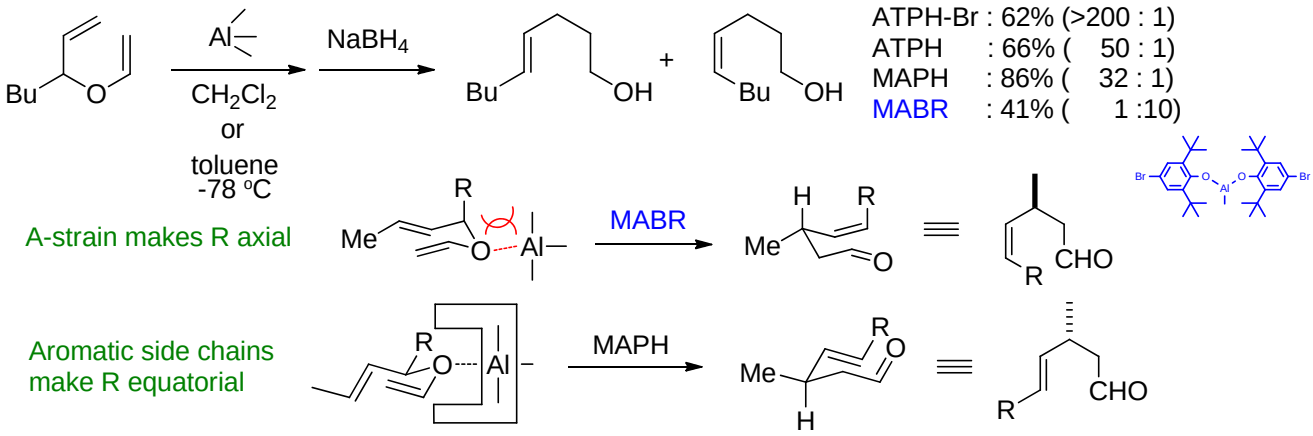
3.2.4.2. Epoxide Rearrangement



3.2.4.2. Epoxide Rearrangement



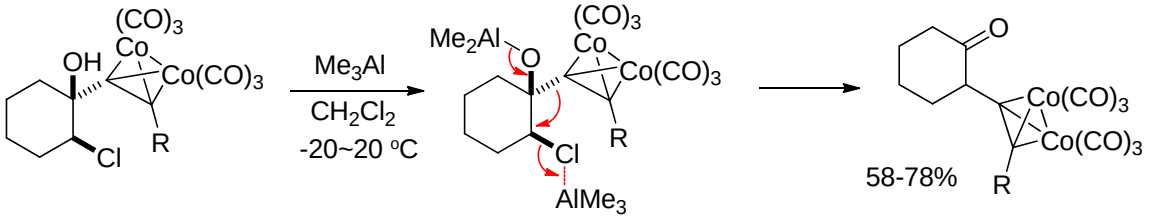
3.2.4.3. Claisen Rearrangement

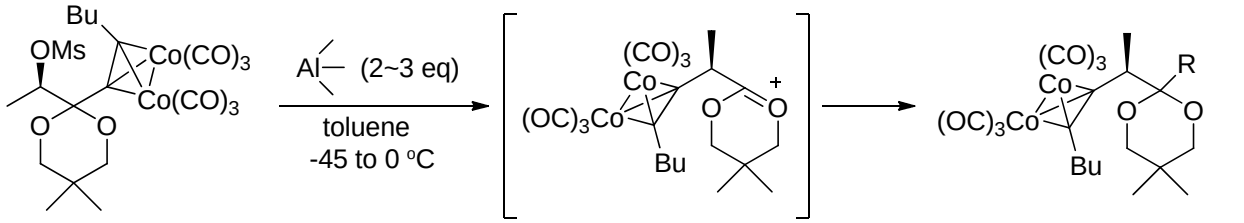


3.2.4.4. Meerwein Pinacol Rearrangement

Alkyne-Co complex strongly stabilzes a cationic charge at α-position

⟶ neighboring group participation toward the β-cation





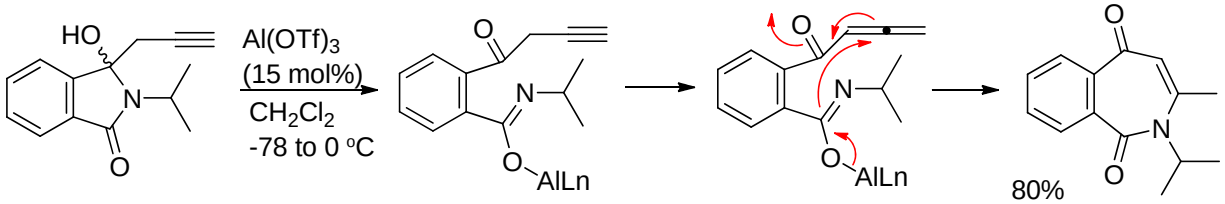
Me_3Al + BuLi : R = Me : 83%, 99% ee

Et_3Al + BuLi : R = Et : 73%, 99% ee

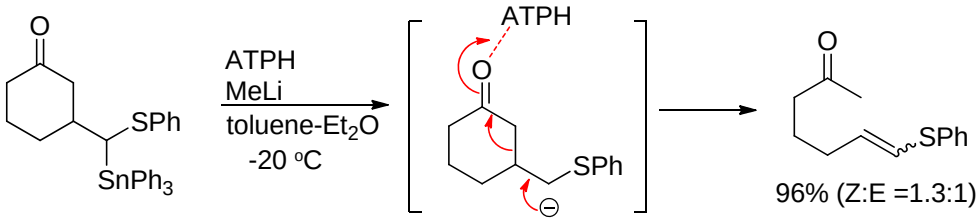
$(Me_3SiCC)_2AlEt$: R = Me_3SiCC : 85%, 99% ee

Et_3Al + DIBAL : R = H : 94%, 99% ee

3.2.4.5. Other Rearrangement and Fragmentation



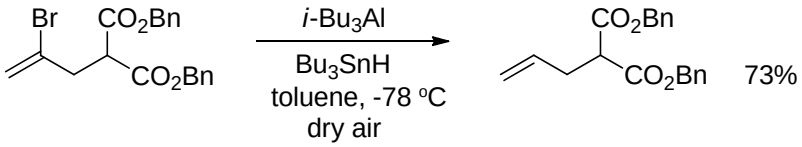
3.2.4.5. Other Rearrangement and Fragmentation

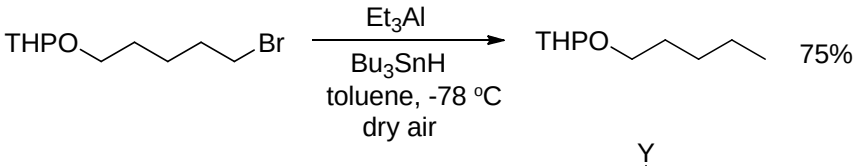


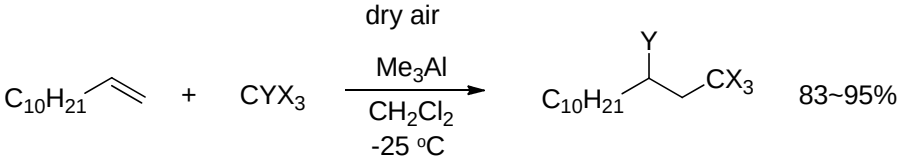
3.2.5. Radical Initiation and Reaction

Reduction of alkyl halides - aluminum alkyls (Et_3Al or *i*-Bu_3Al) and Bu_3SnH

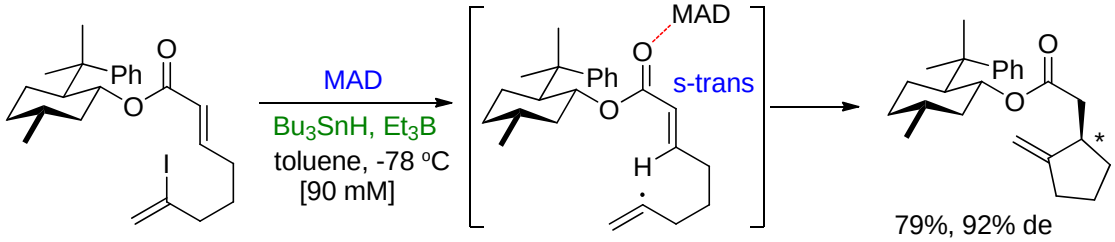
Alkyl aluminum - radical initiator (Pr_3Al, O_2 or UV)



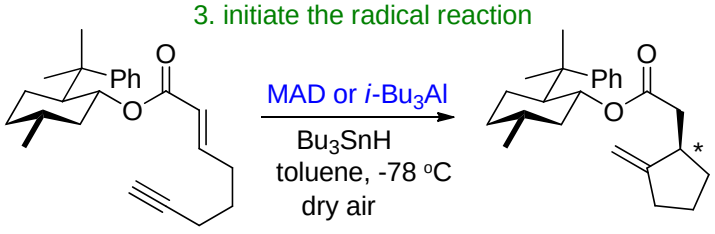




Stereocontrolled addition to α,β-unsaturated carbonyl compounds

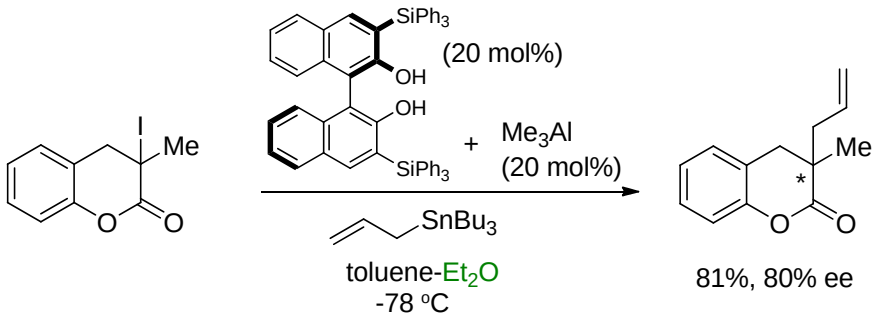


the function of MAD:
1. reduce the LUMO of the β-carbon
2. fix the conformation of the unsaturated ester
3. initiate the radical reaction



MAD : 80%, 84% de
i-Bu_3Al : 68%, 64% de

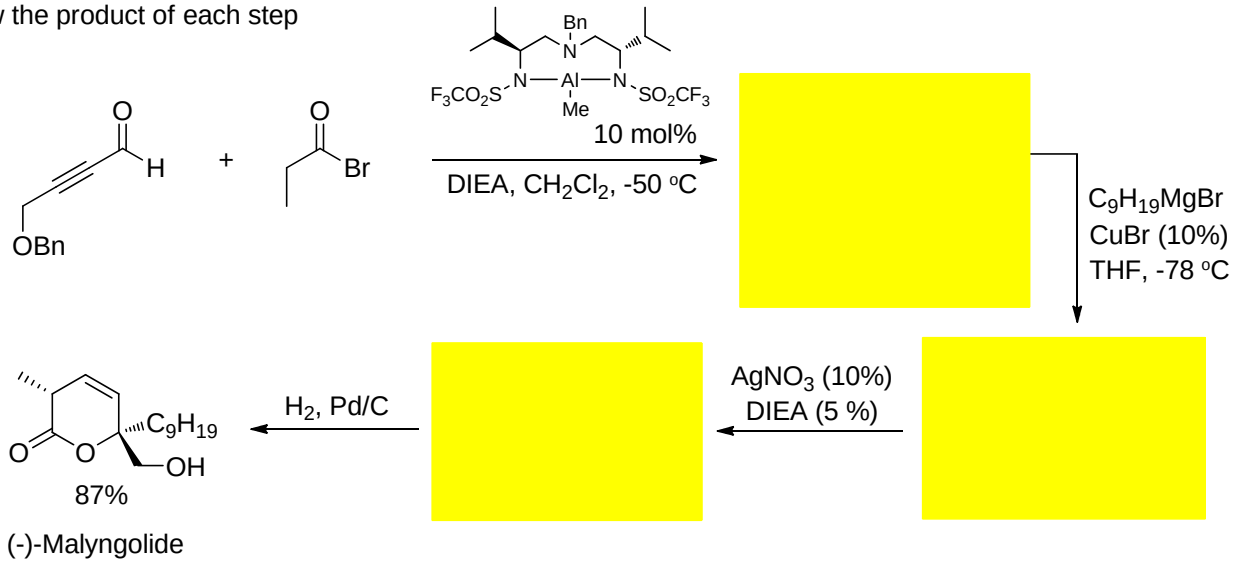
Effect on the α-position of carbonyl groups - high stereoselectivity (Et_2O effect is also noteworthy)



Problems - Organoaluminum

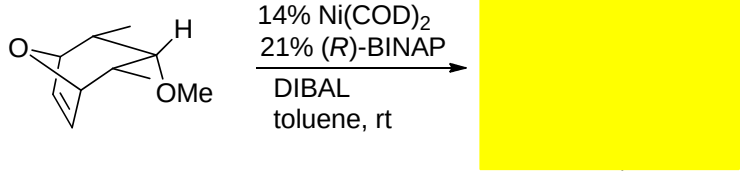
Draw the product of each step

(1)

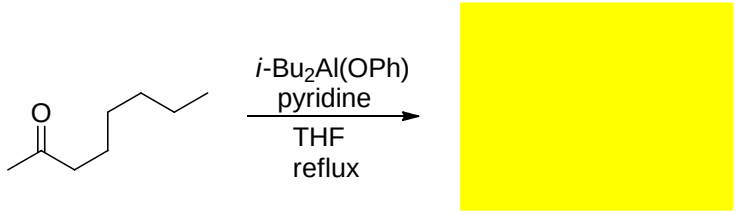


(-)-Malyngolide

(2)

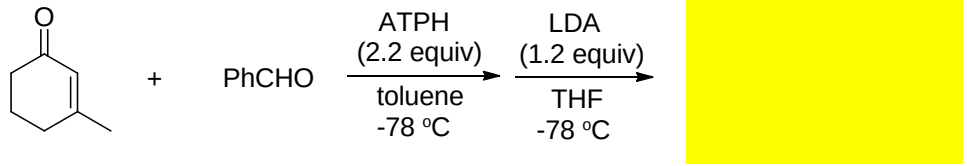


(3)

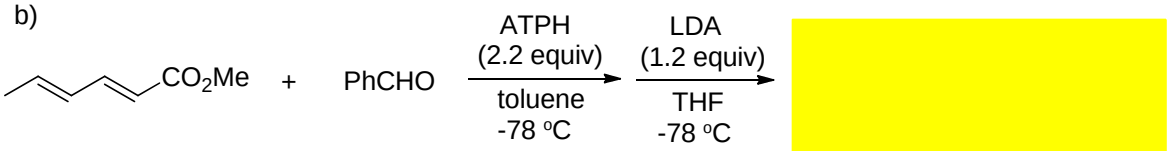


(4)

a)



b)



(5)

4. Indium in Organic Synthesis

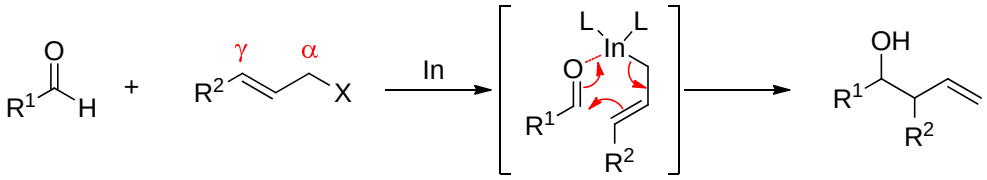
Indium is stable in air, nontoxic, tolerant of water, environmetally benign regents
1st ionization potential: 5.8 eV - effective s.e.t. agent

4.1. Allylation and Propargylation

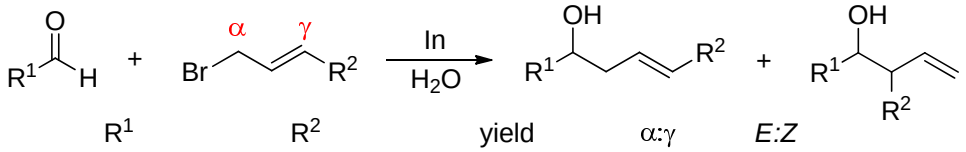
4.1.1. Allylation and Propargylation of Carbonyl Compounds

4.1.1.1 Regioselectivity

In general γ-allylation with carbonyl compounds with no sterically bulky group involved

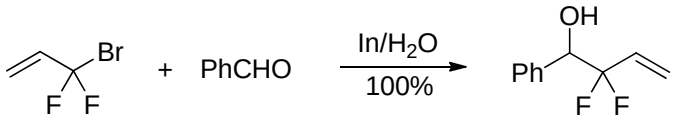


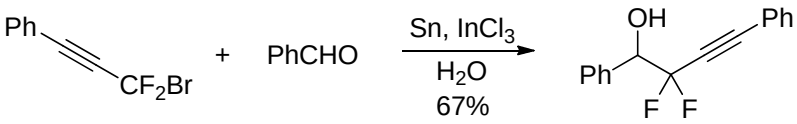
α-addition in the presence of 10 M water - T.P. Loh
γ-adduct was converted to the more stable α-adduct by oxonia-Cope rearrangement

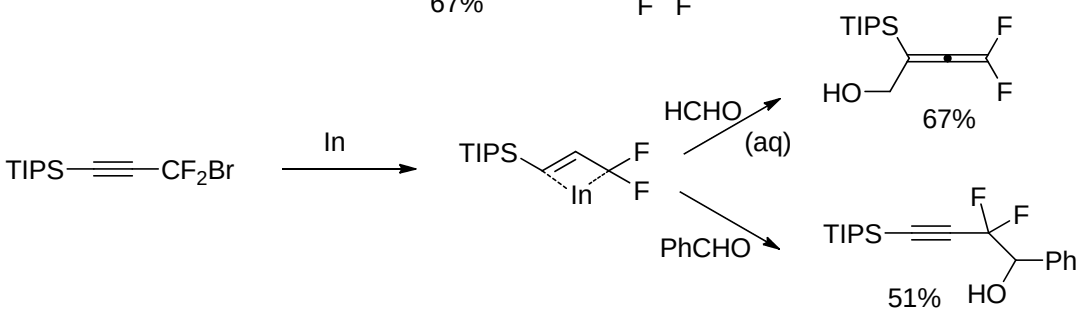


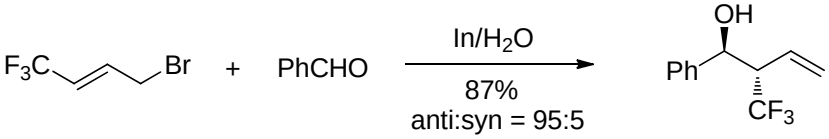
R^1	R^2	yield	α:γ	*E:Z*
Ph	Me	60%	99:1	55:45
Ph	Ph	72%	98:2	*E*
c-C_6H_{11}	Me	85%	99:1	70:30
c-C_6H_{11}	Ph	71%	99:1	90:10
$PhCH_2CH_2$	Me	67%	97:3	55:45
$PhCH_2CH_2$	Ph	50%	99:1	95:5

Fluorinated organoindium reagents



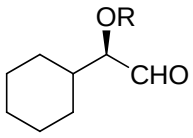






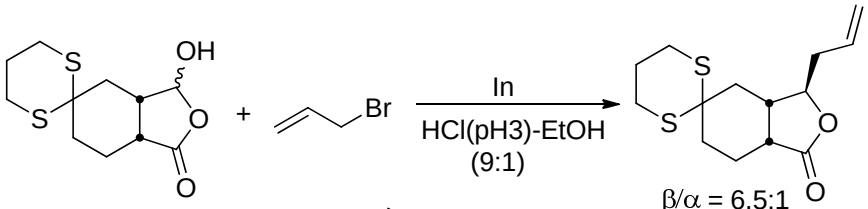
4.1.1.2 Diastereoselectivity

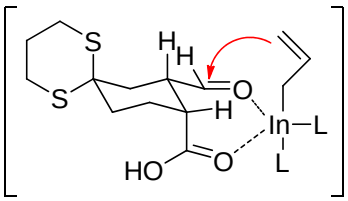
Effect of proximal groups on diastereoselectivity in the addition of allylindium to carbonyl group

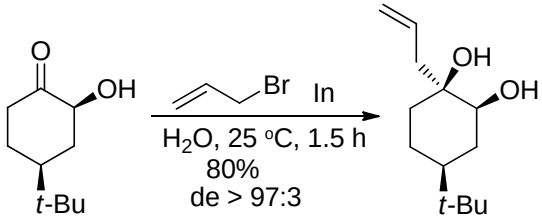


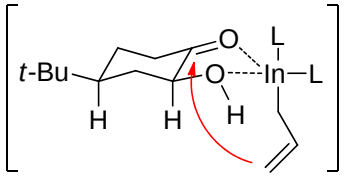
R	Solvent	Time (h)	syn:anti	Yield (%)
TBS	H_2O	3.5	1:3.9	90
TBS	H_2O-THF	2.5	1:4.2	87
TBS	THF	36-50	1:4.0	92
H	H_2O	5	9.8:1	85-90

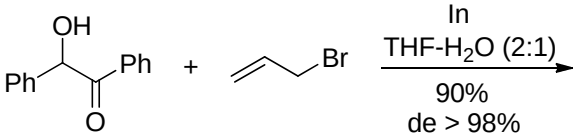
free OH - *syn*-1,2-diol
anti-1,3-diol
protected OH - anti-1,2-diol

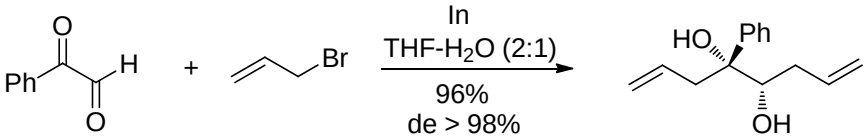


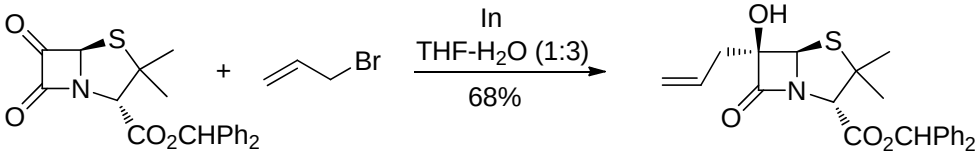




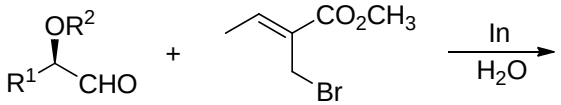


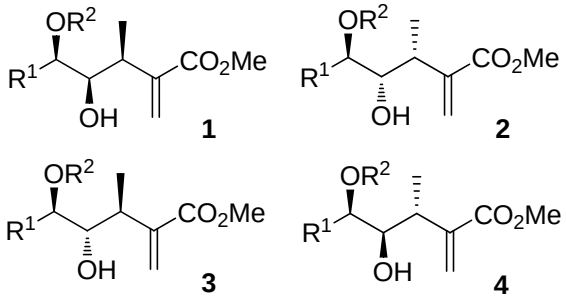




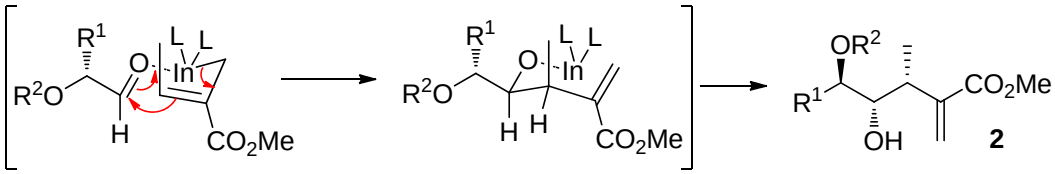


Felkin-Ahn Selectivity





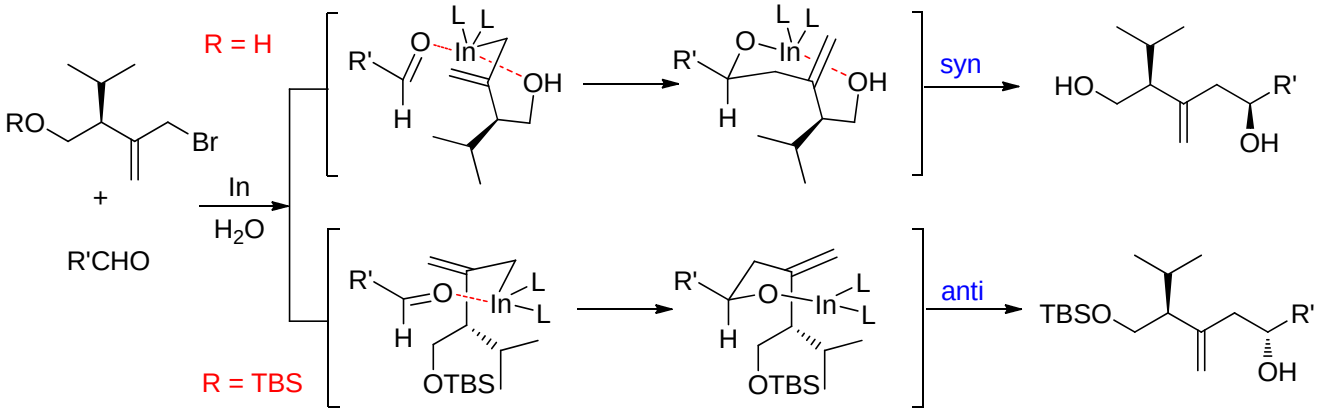
R^1	R^2	**1:2:3:4**	yield (%)
CH_3	TBS	3:97:0:0	75
Ph	TBS	5:95:0:0	92
c-C_6H_{11}	TBS	13:87:0:0	72
c-C_6H_{11}	Bn	7:88:5:0	79



4.1.1.2 Diastereoselectivity

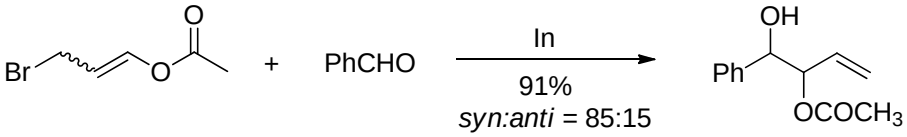
Oxygen-bearing Allylindium Reagents for 1,4-asymmetric induction

O-Silylated allylindium - anti selectivity; hydroxy-allylindium - syn selectivity

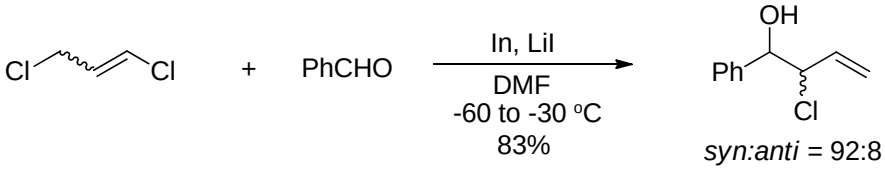


R	R'	yield (%)	*anti*:*syn*
TBS	*i*-Pr	72	76:24
TBS	Ph	83	75:25
TBS	c-C_6H_{11}	71	75:25
H	*i*-Pr	95	11:89
H	Ph	79	13:87
H	c-C_6H_{11}	91	14:86

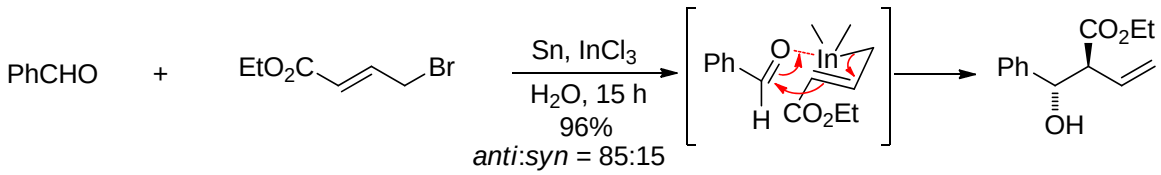
γ-Oxygenated allylindium to give vic-diols

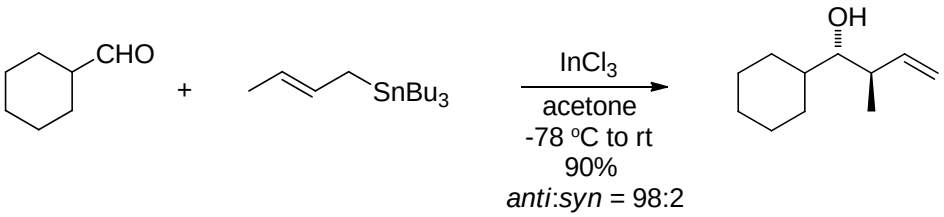


1,3-Dichloropropene in the presence of LiI



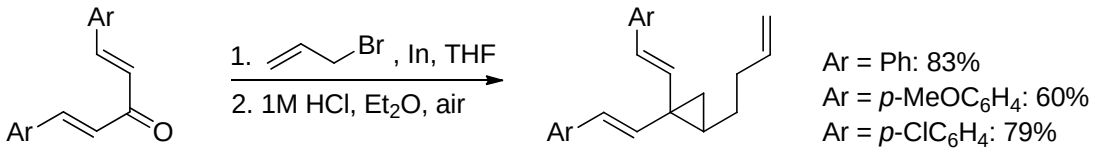
Allylindium Reagents prepared by Transmetalation





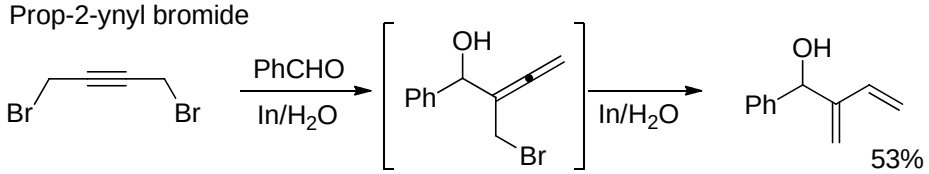
4.1.1.3 Other Allylation Reactions

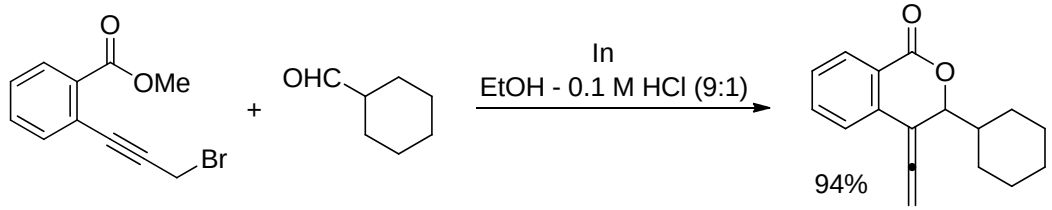
Cyclopropane Synthesis



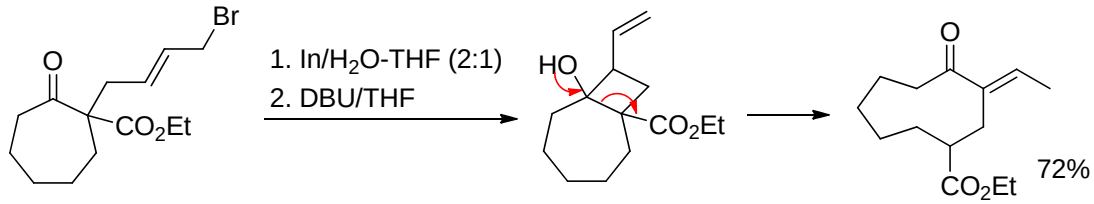
Miscellaneous

Prop-2-ynyl bromide

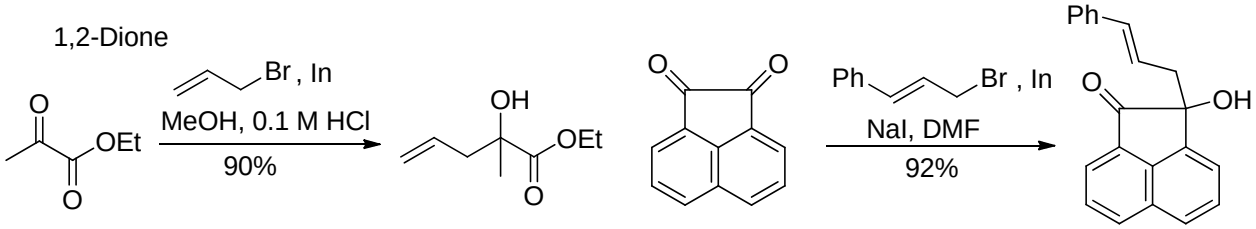




Two-atom ring-enlargement reaction

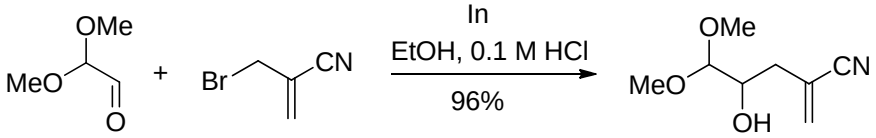


1,2-Dione

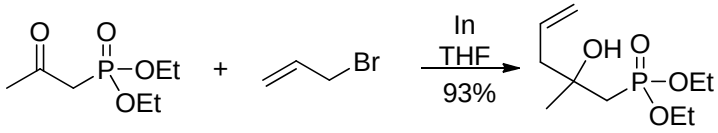


Glyoxal monoacetal

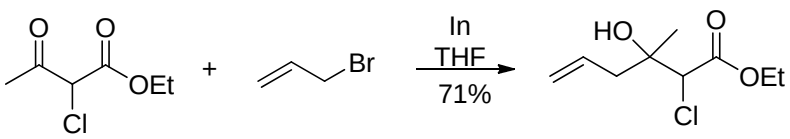
masked α-hydroxy aldehyde



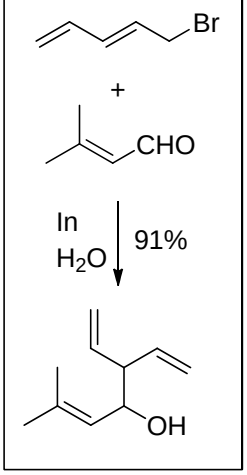
β-Keto phosphonate



α-Chlorocarbonyl compound



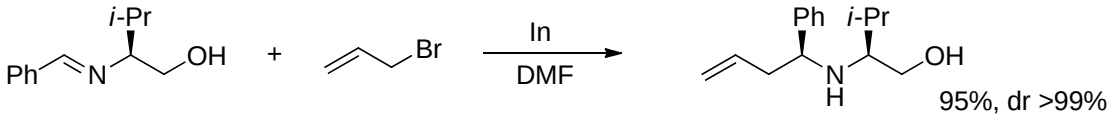
γ-Allylation



4.1.2. Allylation and Propargylation of Compounds other than Carbonyl

4.1.2.1. Imines and Enamines

Stereochemistry was controlled by the chelation between the nitrogen and the hydroxyl group of the imine with indium

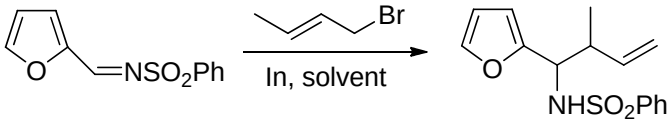


95%, dr >99%

Imine allylation in aqueous media are limited compared with the carbonyl compounds

1. Lower electrophilicity of the C=N group
2. Ease of hydrolysis to carbonyl compounds

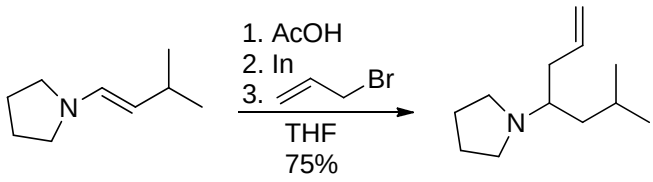
⟹ Sulfonimines are used in aqueous conditions



Solvent THF:H_2O	Yield (%)	*syn:anti*
0:100	90	76:24
50:50	94	93:7
10:1	99	93:7

Enamines

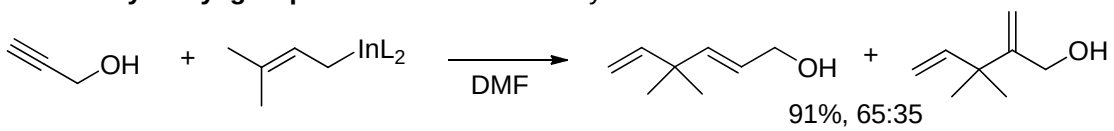
Addition of one equivalent of acetic acid accelerates the reaction



4.1.2.2. Alkenes and Alkynes

Allylindation with terminal alkynes proceeds in DMF to give **1,4-diens**

Proximal hydroxyl group is essential for clean allylation

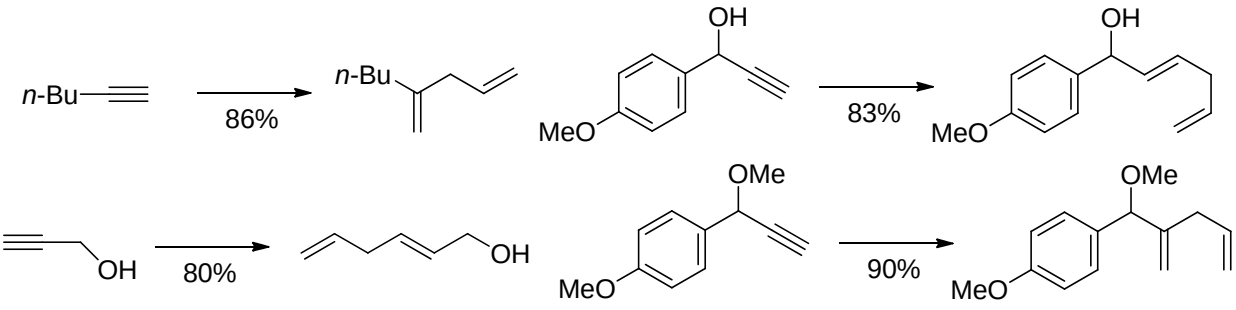


91%, 65:35

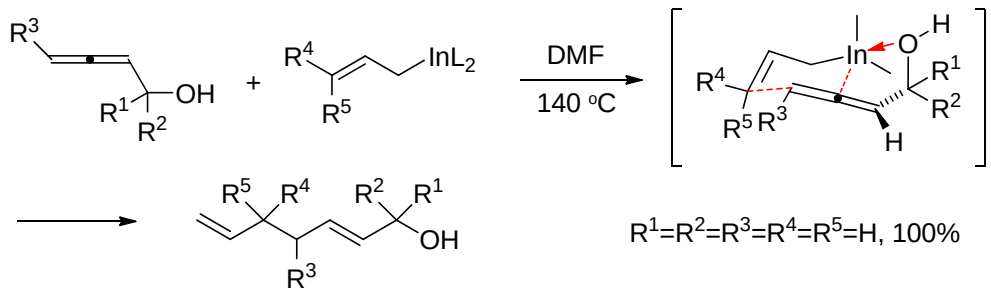
Regioselectivity depends on the presence of an adjacent **free OH group**

Free OH ⟶ linear 1,4-dienes

Protected OH or No OH ⟶ branched 1,4-dienes



Allylindation of **allenols** affords **1,5-dienes** via hydroxy-chelated bicyclic transition state

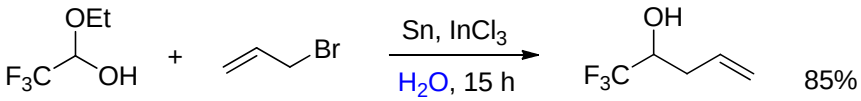


R^1=R^2=R^3=R^4=R^5=H, 100%

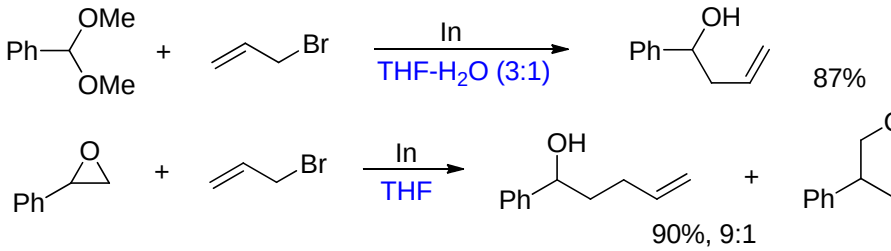
4.1.2.3. Other Compounds

Reaction with Acetals and Epoxides

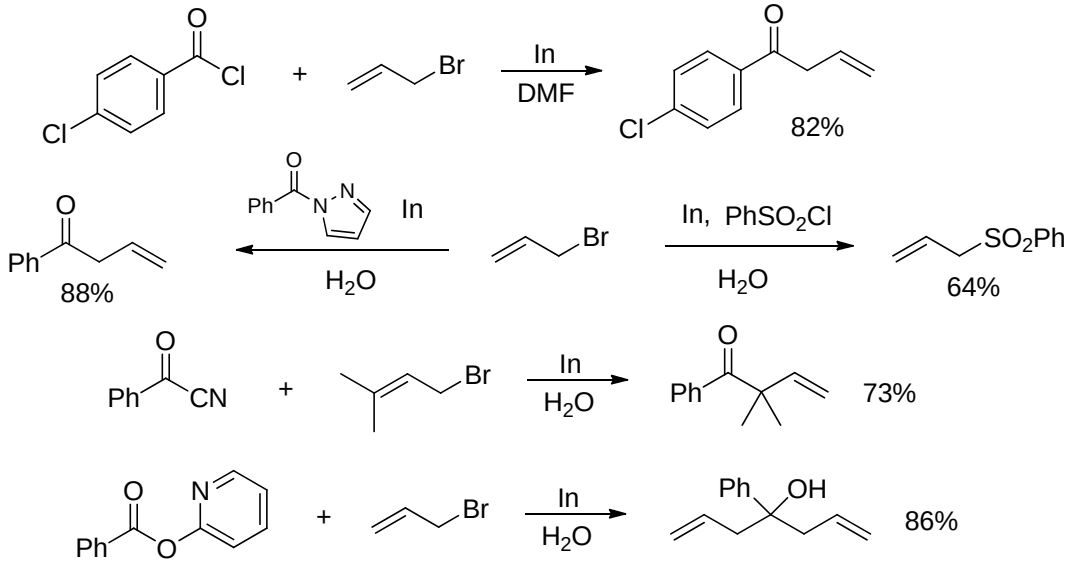
Trifluoroacetaldehyde hydrate or hemiacetal in H_2O



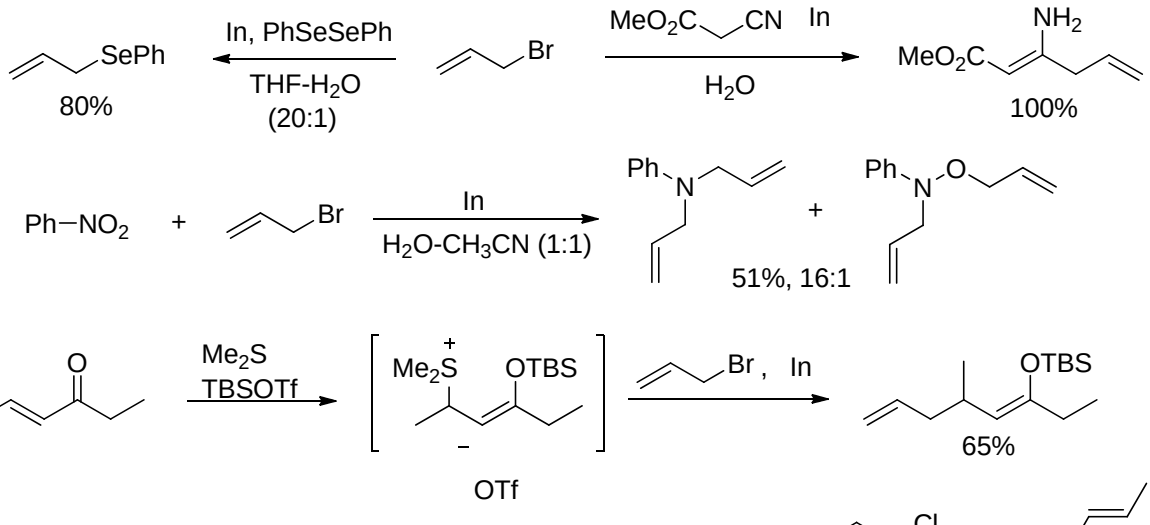
Aldehyde dimethyl acetals in aqueous THF



Reaction with Acid Chlorides and Related Compounds

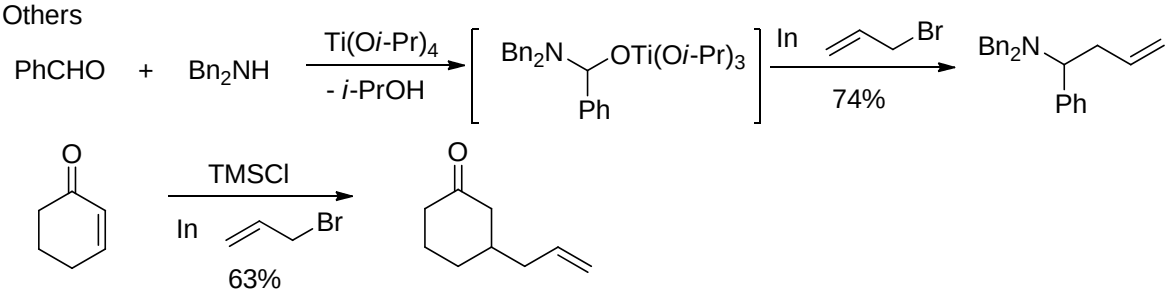


Others

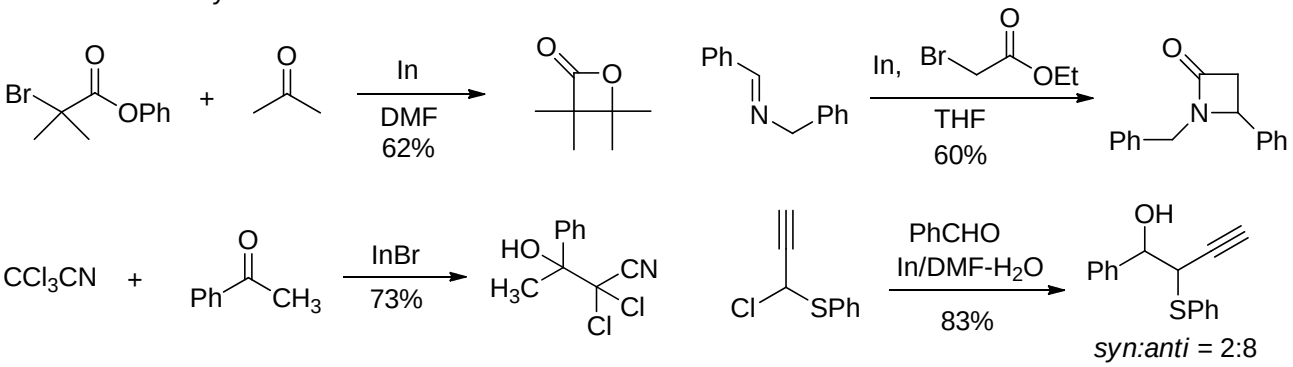


4.1.2.3. Other Compounds

Others

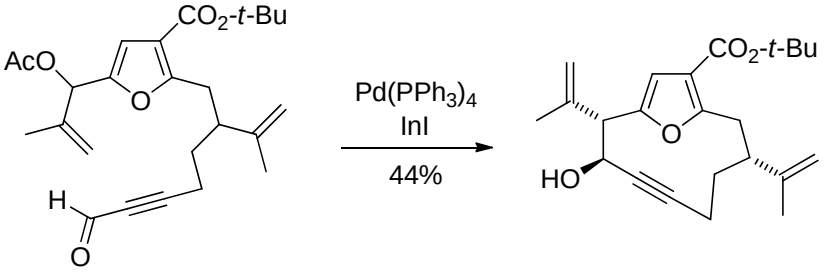


4.2. Reformatsky and Other Reactions

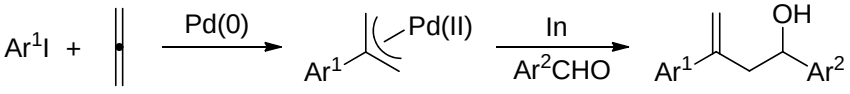


4.3. Reaction in Combination with Transition Metal Catalysts

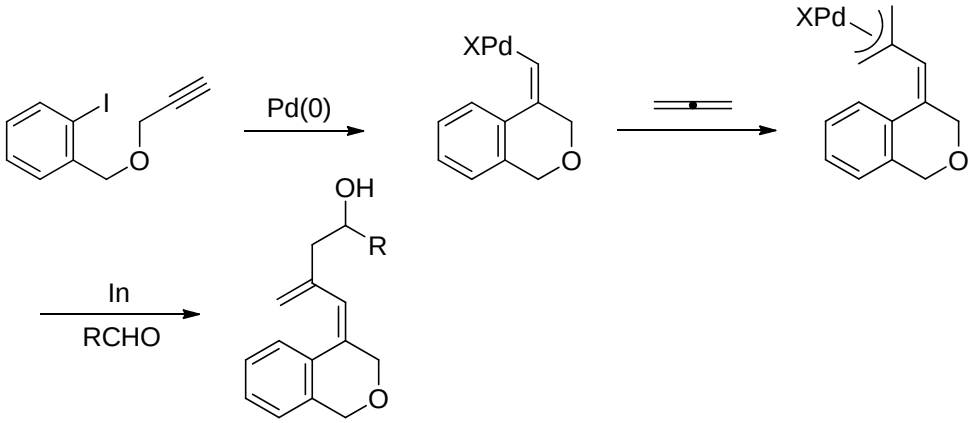
The reaction proceeds via a π-allylpalladium(II) complex then reductive transmetalation with InI to give allylindium compound



Cascade reaction with allenes (three component coupling)



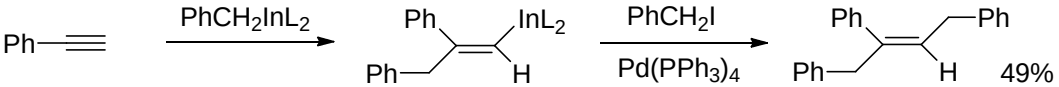
Ar^1	Ar^2	Yield (%)
Ph	4-$MeOC_6H_4$	64
	4-$MeOC_6H_4$	66
Ph	Ph	43

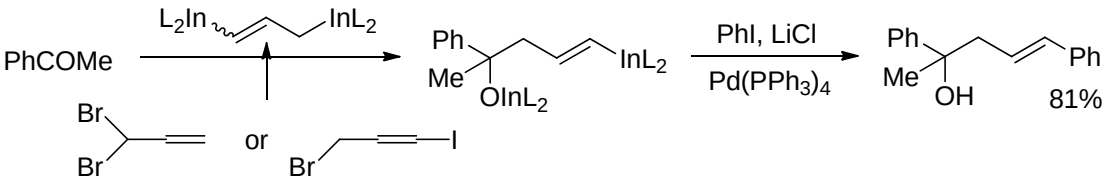


R	Yield (%)
Ph	52
	51
	50

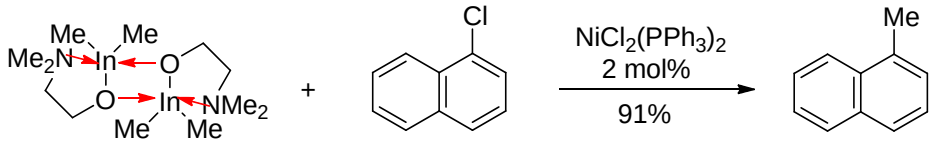
4.3. Reaction in Combination with Transition Metal Catalysts

Coupling of **vinylindium** with organic halide in the presence of a palladium-catalyst

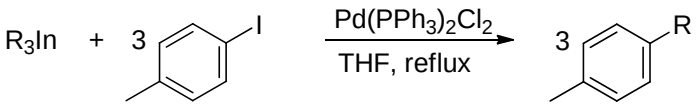




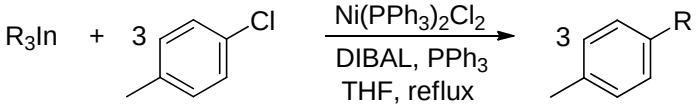
Alkylindium compounds react with chloroarenes in the presence of $NiCl_2(PPh_3)_2$



Palladium-catalyzed cross-coupling of **triorganoindiums** with vinyl and aryl triflates or iodides

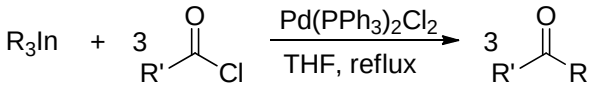


R	Yield (%)
Ph	96
H_2C=CH	89
PhC≡C	90
Bu	82
Me	85



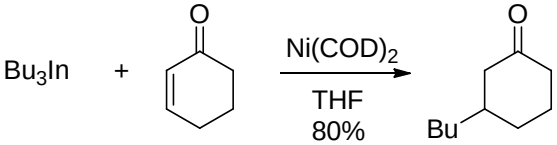
R = Ph: 74%
R = Bu: 83%

Palladium-catalyzed cross-coupling of **triorganoindiums** with acid chlorides

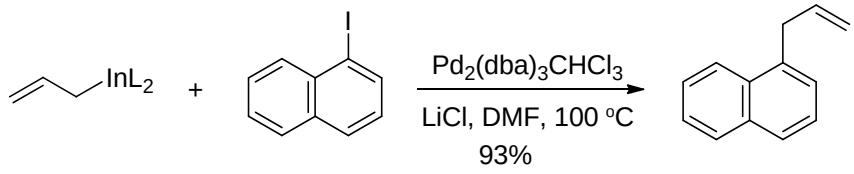


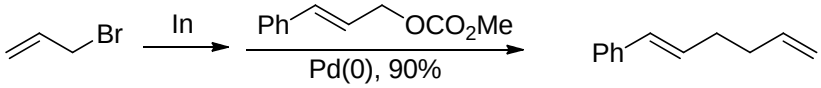
R	R'	Yield (%)
Ph	Ph	89
PhC≡C	Ph	94
Me	Ph	97
Ph	Me_2C=CH	87
PhC≡C	Me_2C=CH	90

Ni-catalyzed conjugate addition of **triorganoindiums** to enones



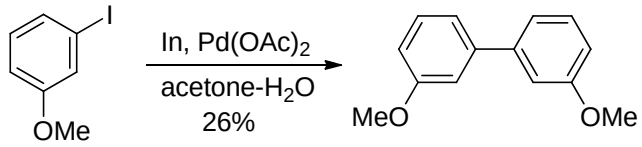
Palladium-catalyzed cross-coupling of allylindium





4.3. Reaction in Combination with Transition Metal Catalysts

Indium-mediated palladium-catalyzed Ullmann reaction



4.4. Reduction

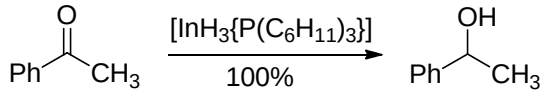
4.4.1. Reduction of Carbonyl Groups

$LiInH_4$, prepared in situ by 4 x LiH and $InCl_3$ in ether, reduces aldehydes.

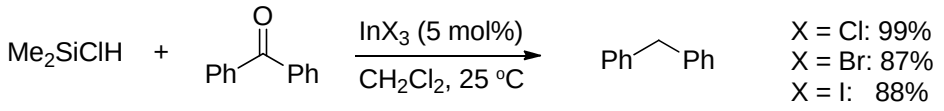
Acid chlorides are converted to esters by $LiInH_4$, and esters are little affected.

The reducing power is increased by introduction of phenyl groups: $LiPhInH_3$, $LiPh_2InH_2$ etc.

Cl_2InH, prepared by $InCl_3$ and Bu_3SnH, reduces carbonyl compounds and debrominates alkyl bromides



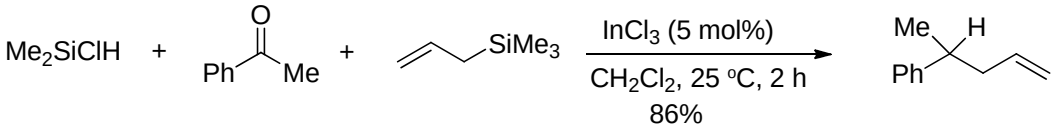
Selective deoxygenation of carbonyl groups in the presence of halogen, ester, ether, and nitro groups by a combination of **chlorodimethylsilane (Me_2SiClH) and 5 mol% of $InCl_3$**.



X = Cl: 99%
X = Br: 87%
X = I: 88%

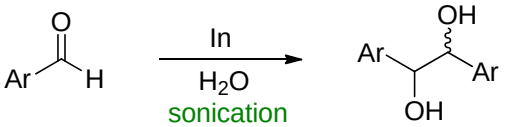
Deoxygenative allylation of **aromatic ketones**

by chlorodimethylsilane, allyltrimethylsilane, and catalytic $InCl_3$ in CH_2Cl_2 or $ClCH_2CH_2Cl$

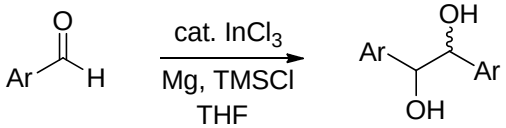


4.4.2. Reductive Coupling

Indium-mediated pinacol coupling of aromatic aldehydes in H_2O is promoted by sonication

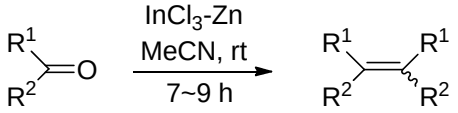


Ar = Ph: 70% (*dl*:*meso* = 5:3)
Ar = 4-MeC_6H_4: 80% (5.5:1)
Ar = 4-FC_6H_4: 51% (2:1)



Ar = Ph: 67% (*dl*:*meso* = 68:32)
Ar = 4-ClC_6H_4: 59% (50:50)
Ar = 4-MeC_6H_4: 69% (56:44)
Ar = 4-$MeOC_6H_4$: 43% (85:15)

$InCl_3$-Zn-mediated deoxygenative coupling of carbonyl compounds gives ***E*-alkenes**



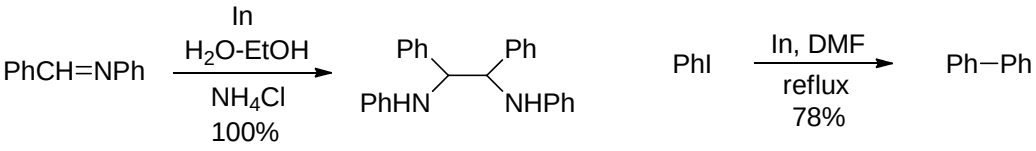
R^1	R^2	Yield (%)	E/Z
Ph	H	93	98:2
4-ClC_6H_4	H	90	86:14
4-MeC_6H_4	H	88	90:10
4-$NO_2C_6H_4$	H	70	70:30
Ph	Me	60	80:20
n-pentyl	H	72	70:30

4.4. Reduction

4.4.2. Reductive Coupling

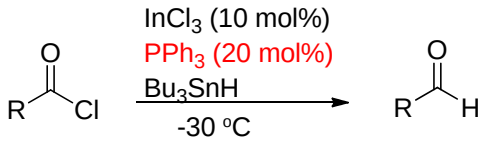
Aldimines by In in aqueous EtOH or by $InCl_3$, TMSCl and Al in THF

Reductive homocoupling of alkyl and aryl iodides with In in DMF



4.4.3. Dehalogenation

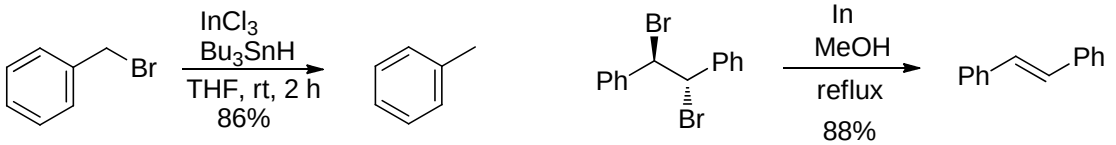
Cl_2InH - reactive species

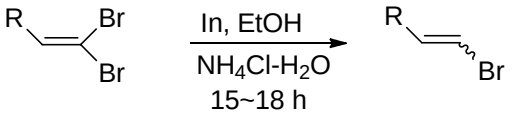


Cyano and nitro substituents tolerate the reduction condition

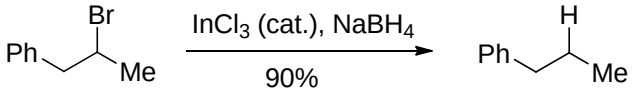
R	Solvent	Yield (%)
Ph	toluene	97
4-MeC_6H_4	toluene	93
4-ClC_6H_4	toluene	80
$Cl(CH_2)_5$	THF	83
$H_2C{=}CH(CH_2)_8$	THF	92

Cl_2InH as a radical initiator

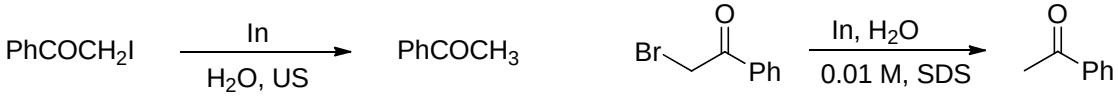




R	Yield (%)	E/Z
Ph	95	95:5
4-ClC_6H_4	92	82:18
4-$MeOC_6H_4$	88	75:25
4-MeC_6H_4	90	76:24
3-MeC_6H_4	91	70:30
PhCH=CH	80	60:40

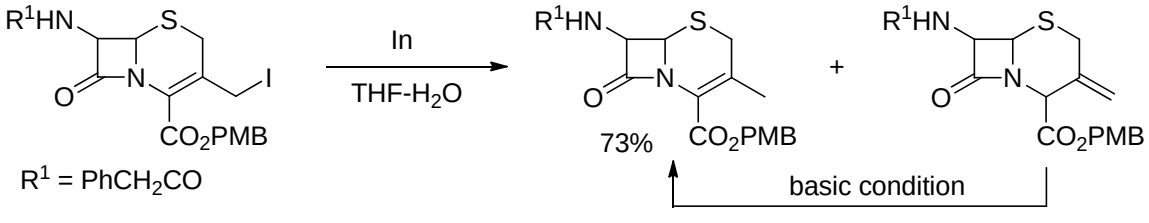


Reduction of **α-halocarbonyl** and **benzyl iodides** by indium metal in H_2O with sonication (Simple alkyl and aryl iodides remain inert)

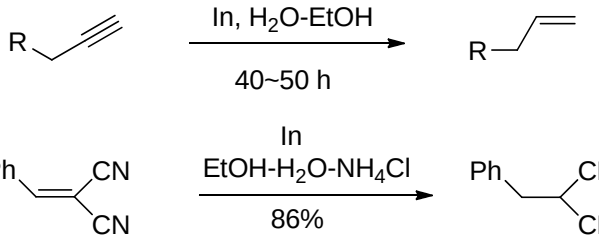


sodium dodecyl sulfate - micellar system

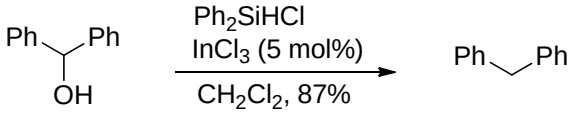
Allylic iodides or **acetates**

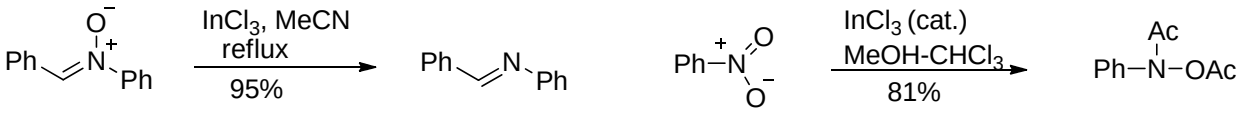


4.4.4. Reduction of Other Functional Groups

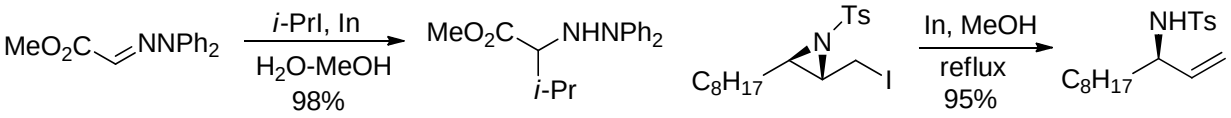


R	Yield (%)
PhO	90
$PhCH_2O$	45
PhNH	90
c-$C_6H_{11}NH$	20
PhCOO	95

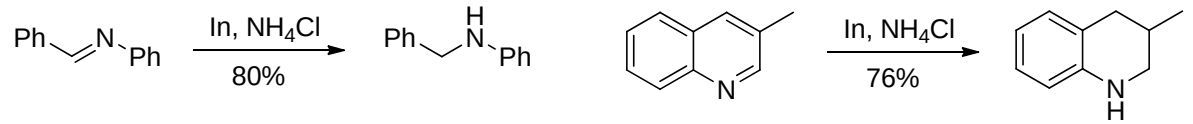


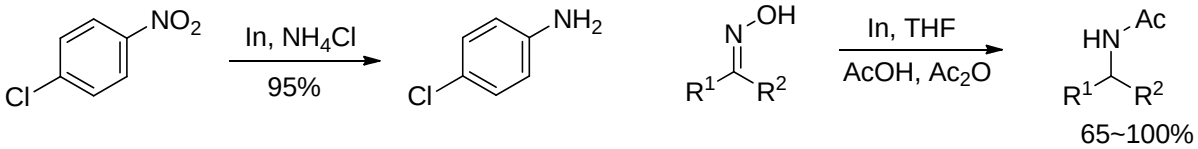


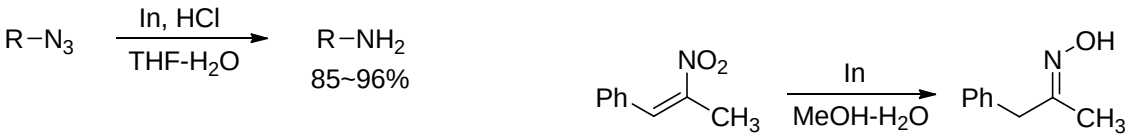
Alkyl radical addition to imine

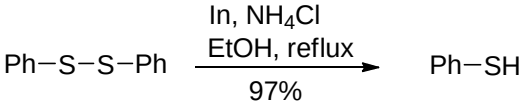


Indium reduces imines, iminium salts, quinolines, conjugate alkenes, nitro groups, azides, and oximes





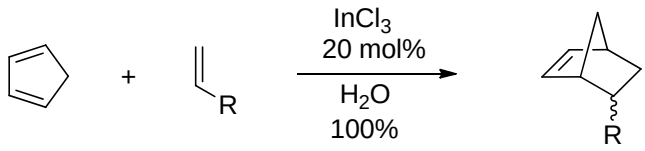




4.5 Indium Salts as Lewis Acids

$InCl_3$ and $In(OTf)_3$

4.5.1. Diels-Alder Reaction

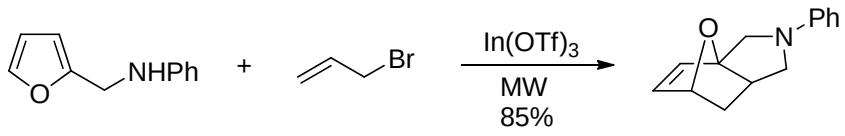


R = CHO, endo:exo = 91:9

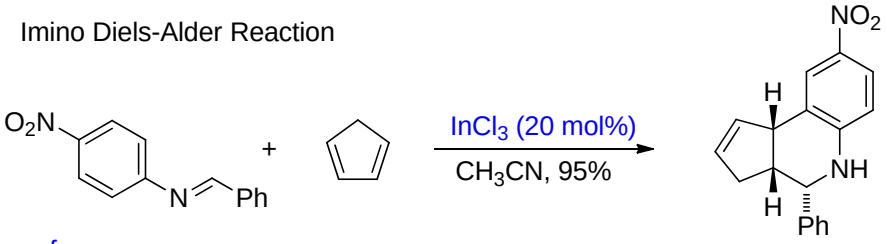
R = CO_2Me, endo:exo = 90:10

Without catalyst, the reaction yield is 60% (endo:exo = 74:26)

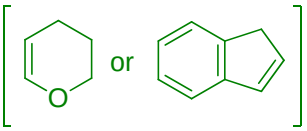
4.5.1. Diels-Alder Reaction



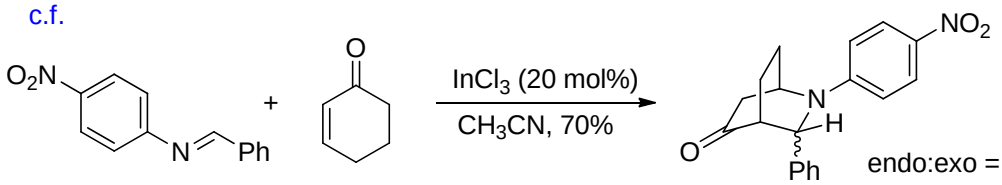
Imino Diels-Alder Reaction



other substrates for imino DA

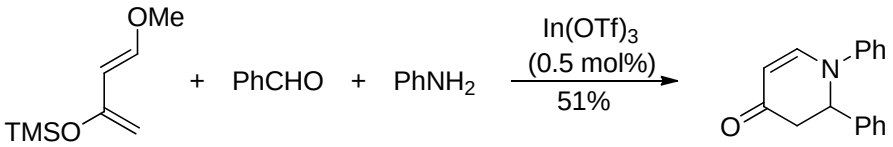


c.f.



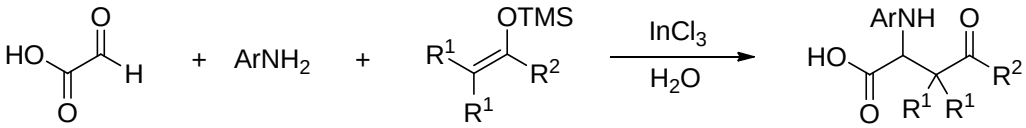
endo:exo = 67:33

Three-component coupling reaction



4.5.2. Aldol and Mannich Reactions

R	Yield (%)
Ph	88
H	91
CO_2H	91
2-Py	96
4-Py	96



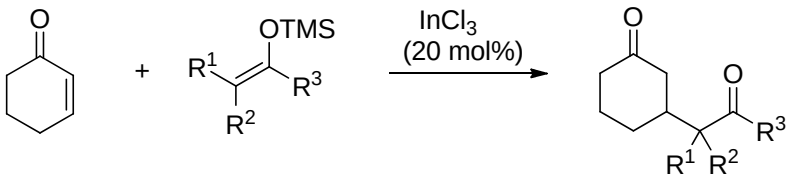
Ar = 4-ClC_6H_4

R^1 = Me, R^2 = OMe, 31%

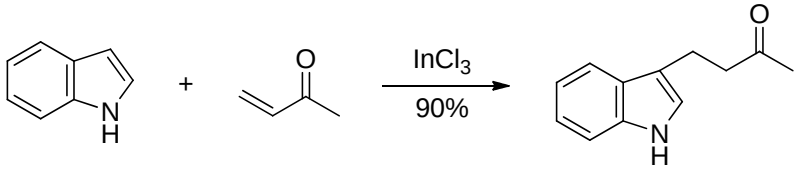
R^1 = H, R^2 = Ph, 63%

4.5.3. Michael Addition

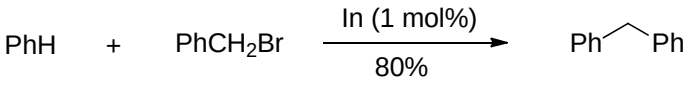
The conjugate addition of 1° and 2° amines to α,β-unsaturated carbonyls is promoted by $InCl_3$ in H_2O



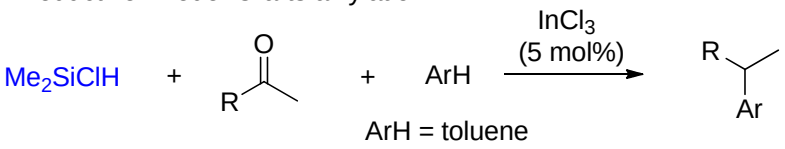
R^1	R^2	R^3	Yield (%)
H	H	Ph	67
Me	Me	OMe	82
Me	H	Ph	86 (syn:anti = 65:35)
H	$(CH_2)_3$		90 (de 65:35)



4.5.4. Friedel-Crafts Reaction

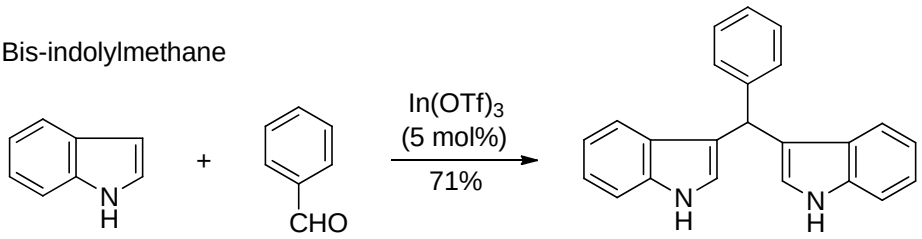


Reductive Friedel-Crafts alkylation

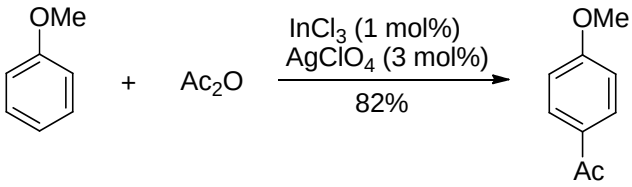


R	Yields (%) (*o:m:p*)
Ph	99 (15:4:81)
4-ClC_6H_4	91 (16:3:81)
4-CNC_6H_4	97 (32:10:58)
4-$NO_2C_6H_4$	87 (29:10:61)

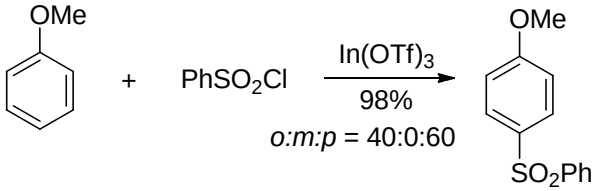
Bis-indolylmethane



Catalytic acylation

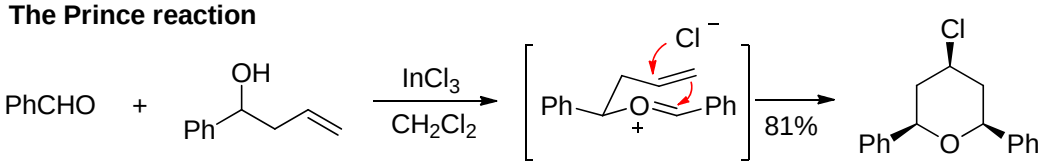


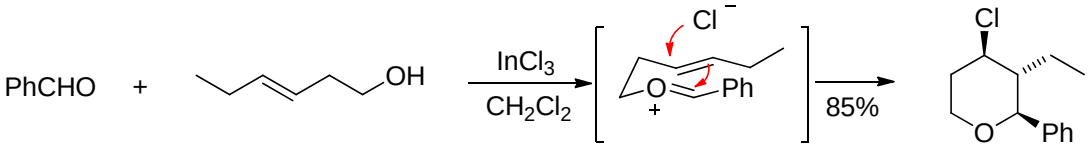
Sulfonylation

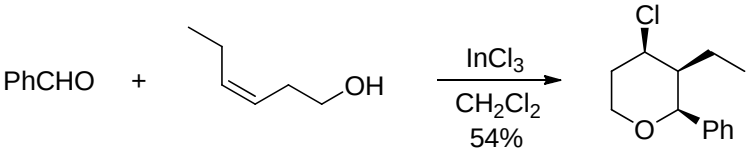


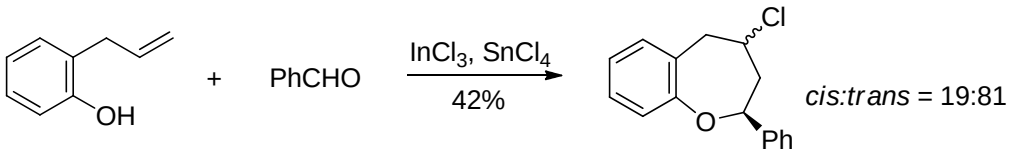
4.5.5. Heterocycle Synthesis

The Prince reaction



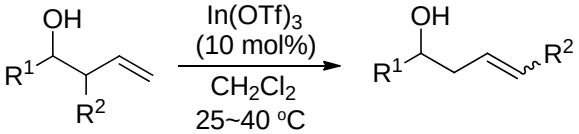






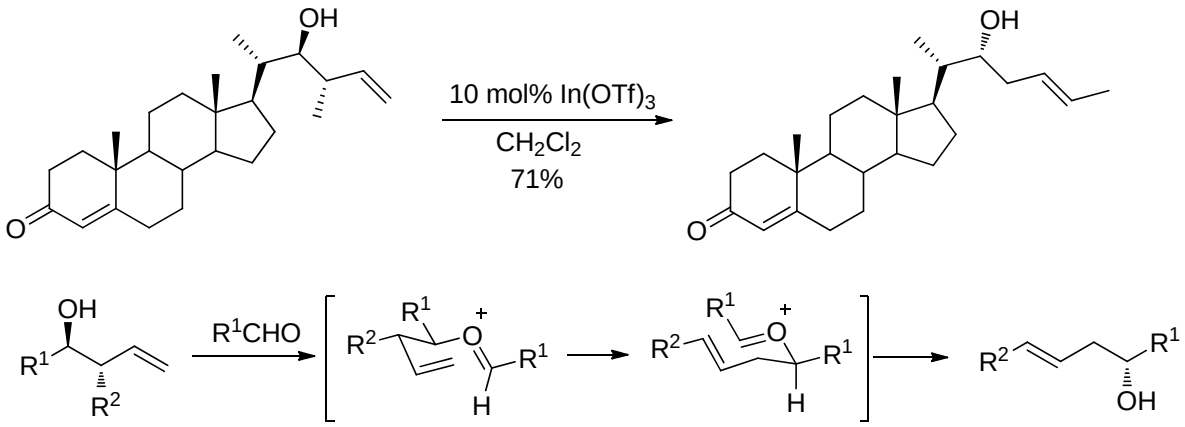
[3.3] Oxonia-Cope Rearrangement

Branched homoallylic alcohols are converted to the thermodynamically preferred linear regioisomers

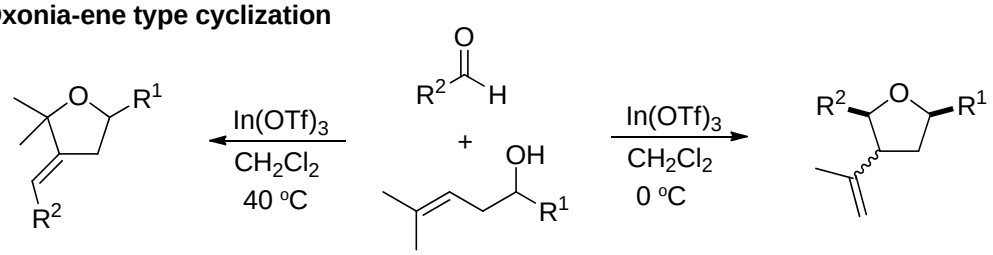


R^1	R^2	anti:syn	Yield (%) (*E*/*Z*)
c-C_6H_{11}	Me	80:20	78 (68/32)
c-C_6H_{11}	Ph	98:2	81 (*E*)
c-C_6H_{11}	CO_2Et	85:15	69 (85/15)
Ph	CO_2Et	86:14	19 (*E*)
$PhCH_2CH_2$	Me	50:50	72 (55/45)

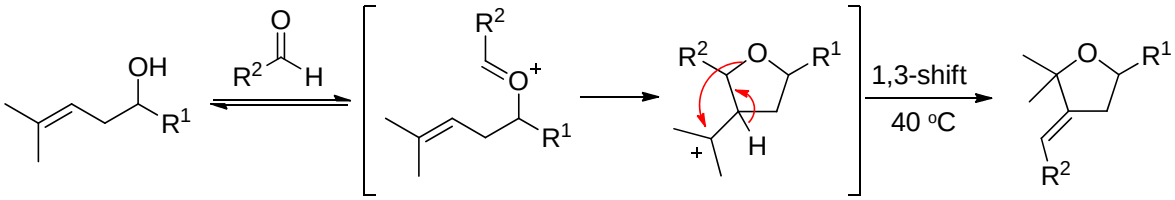
[3.3] Oxonia-Cope Rearrangement



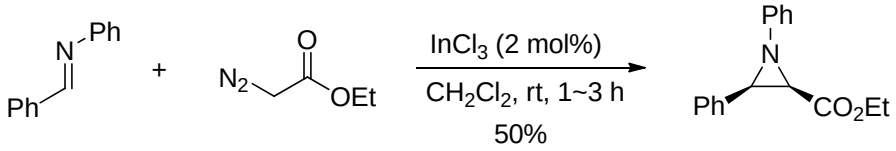
Oxonia-ene type cyclization



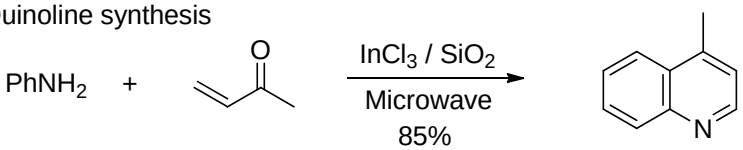
Yield (%)	R^1	R^2	Yield (%) (2,3-*trans*:*cis*)
65	*c*-C_6H_{11}	$PhCH_2CH_2$	95 (65:35)
81	*c*-C_6H_{11}	$CH_3(CH_2)_7$	69 (62:38)
97	*c*-C_6H_{11}	Ph	72 (80:20)
75	*c*-C_6H_{11}	*c*-C_6H_{11}	77 (87:13)



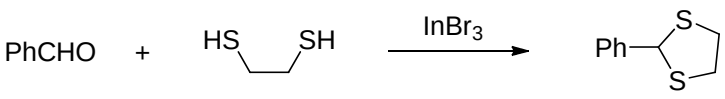
Aziridine synthesis



Quinoline synthesis



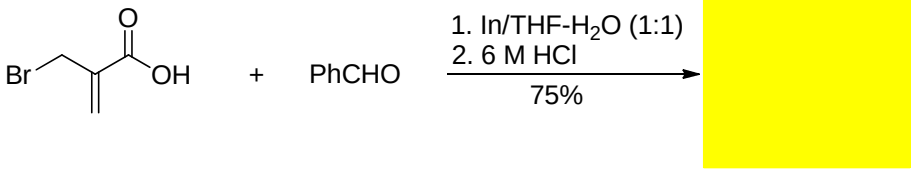
Thioacetalization



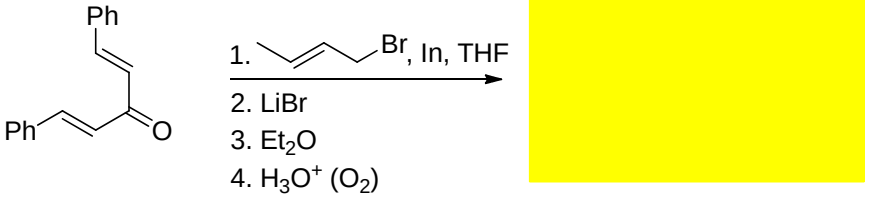
Problem Set - Organoindium

Draw the major product of the following reaction

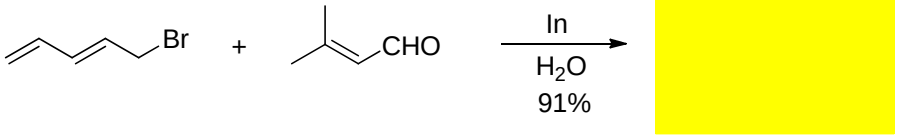
(1)



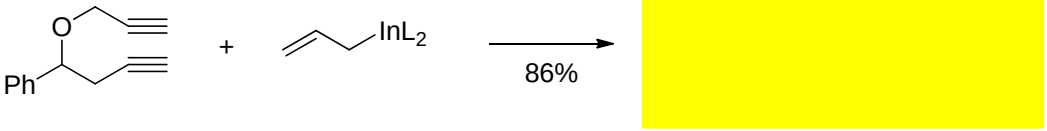
(2)



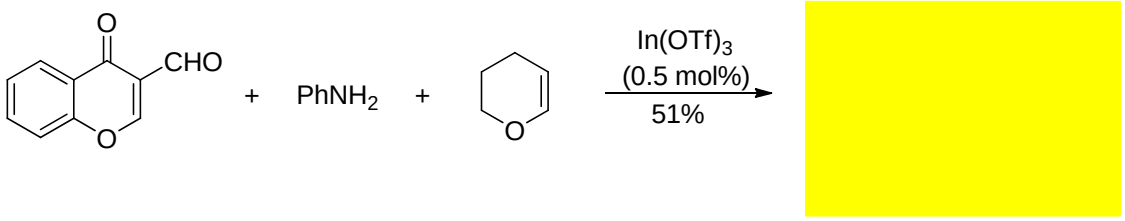
(3)



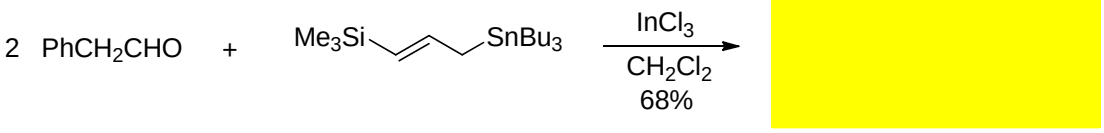
(4)



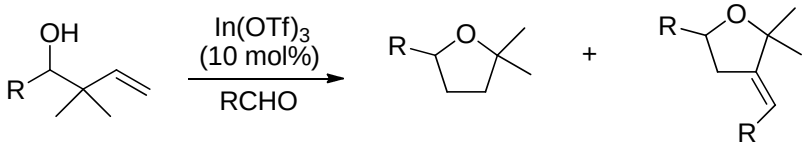
(5)



(6)



(7) Explain the mechanism of the following reactions



R = $PhCH_2CH_2$ RCHO (0.1 equiv); 25 °C, 54% (81:19)
RCHO (1.0 equiv); 40 °C, 60% (3:97)

5. Zinc in Organic Synthesis

Zn: relatively low abundance in nature; easily isolated from ores; non-toxic metal

Organozinc: easy preparation; high functional group compatibility; excellent reactivity in the presenece of the appropriate catalyst

5.1 General overview

5.1.1 Historical perspective

1849, Frankland (Germany) - searching for the preparation of ethyl radical

Et-I + Zinc powder $\xrightarrow[\Delta]{}$ Et-Zn-Et (colorless liquid) reacts violently with H_2O and explodes in O_2

Organozinc reagents were replaced by organomagnesium reagents due to their low reactivity; moderate yields

Only a few synthetic application - Reformatsky reaction (zinc enolate)

1942, Hunsdiecker - preparation of functionalized zinc reagents

Insertion of zinc powder into various **alkyl iodides** bearing an ester group at a remote position

$RO_2C\text{-}(CH_2)_n\text{-}I + Zn \longrightarrow RO_2C\text{-}(CH_2)_n\text{-}ZnI$ n>5

1962, Wittig and Jautelat - new functionalized zinc: Zinc carbenoid

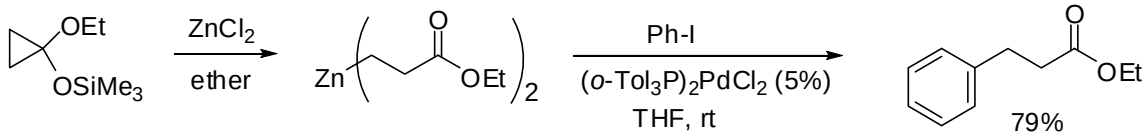
$PhCO_2CH_2\text{-}ZnI$ $PhCO_2(CH_2)_4\text{-}ZnI$

Simmons-Smith reaction: cyclopropanation

Modern organozinc chemistry

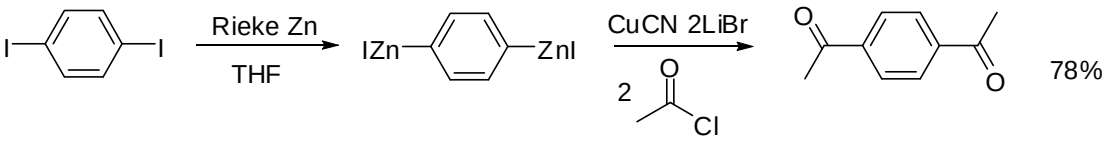
Nakamura and Kuwajima - Homoenolates

Negishi - Pd-catalyzed cross coupling reaction

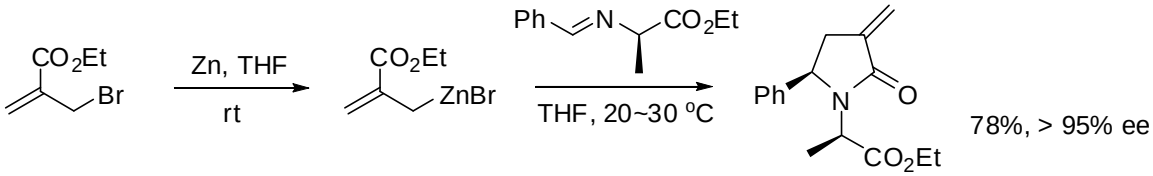


Rieke Zinc: prepared by the reduction of zinc halides with lithium naphthalenide

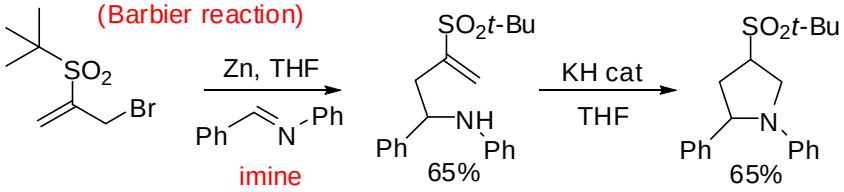
Zinc reagents from **aryl iodides** and **aryl bromides**



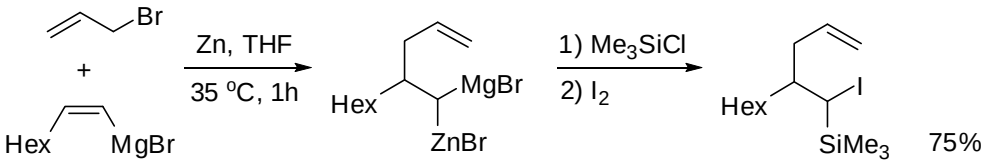
Gaudemar - Preparation of functionalized allylic zinc reagents



(Barbier reaction)

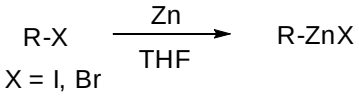


- Preparation of 1,1-bimetallic reagents



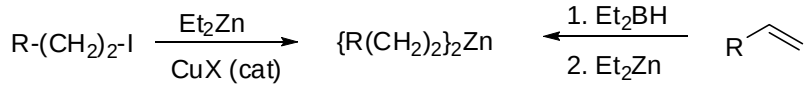
5.1.2 Nature of the organozinc reagents

I. Organozinc halide: **RZnX**

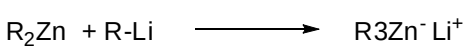


II. Diorganozinc: **R_2Zn** - **enhanced chemical reactivity** compared to alkylzinc halide

iodine-zinc exchange **boron-zinc exchange**

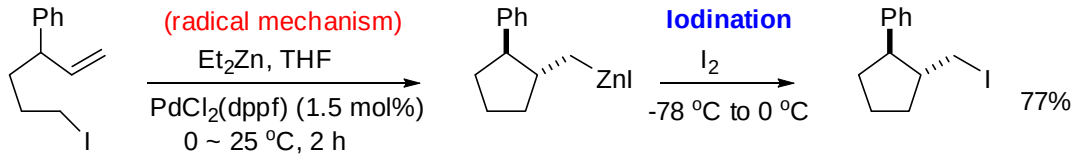


III. Lithium or magnesium zincate: **$M^+R_3Zn^-$** - more reactive than diorganozinc

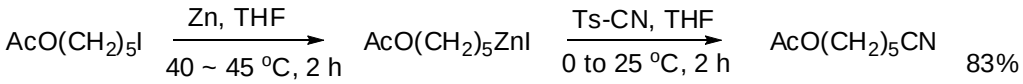


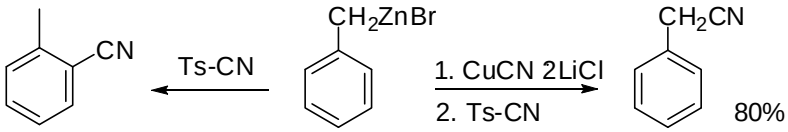
5.1.3 Uncatalyzed reactions of organozinc reagents

halogenation, oxidation, cyanation, phosphorylation, stannylation, silylation,



cyanation



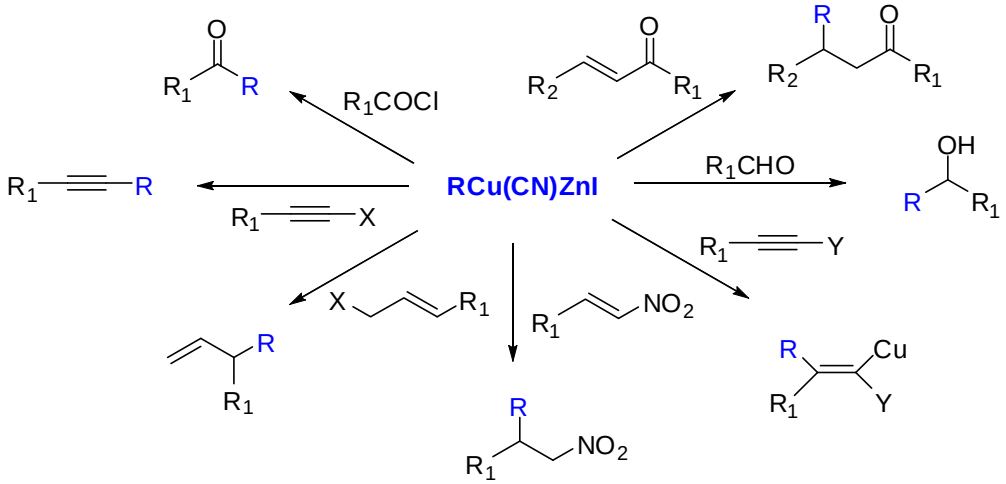


5.1.4 Catalyzed reactions of organozinc reagents

transmetallation and subsequent reaction except MnX_2 or $CeCl_2$

Negishi reaction - Pd(0) catalyzed cross coupling reaction

RCu(CN)ZnI from RZnI and CuCN 2LiCl - preparation of reactive polyfunctional copper organometallic reagent

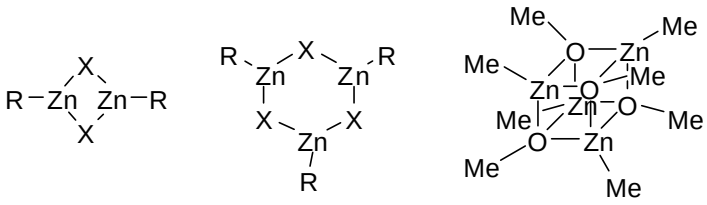


5.1.5 Structures of organozinc reagents

Diorganozincs (**R_2Zn**) are **monomeric** with the exception of dialkynylzincs

Organozinc halides (**RZnX**) form **dimers or higher associates** via halogen bridges

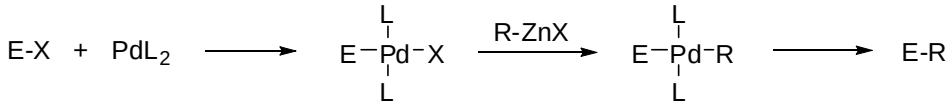
More **complex structures** for **organozinc alcoholates**

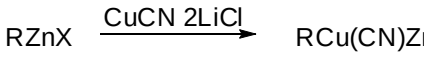


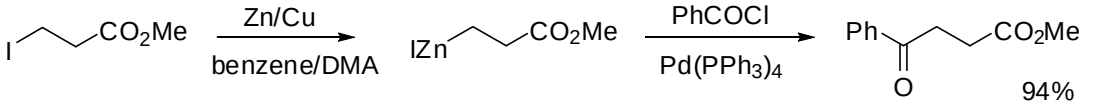
5.2 Preparation and use of organozinc halides

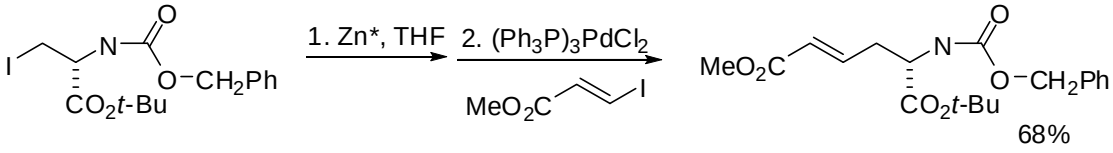
1. R-X + Zn ⟶ R-ZnX
2. R-Li + ZnX_2 ⟶ R-ZnX + LiX (less used)
3. BrCO_2Et —(Et_2Zn (2 eq), $Ni(acac)_2$ (5 mol%), 55 °C, 1.5 h)→ BrZnCO_2Et

General reaction: Transmetallation and coupling reaction





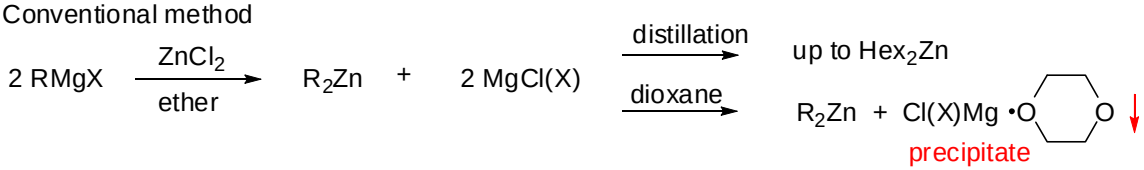




5.3 Preparation methods of diorganozincs

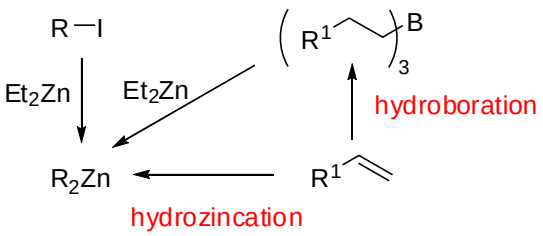
Higher reactivity than organozinc halides; transfer only one of the two organic groups

Conventional method



New Methods

1. Iodine-zinc exchange reaction
2. Boron-zinc exchange reaction
3. Nickel catalyzed hydrozincation reaction

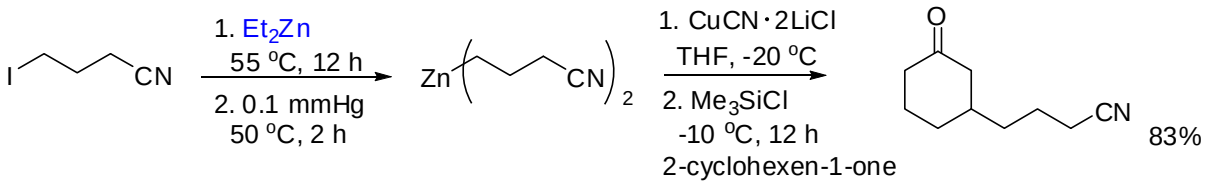


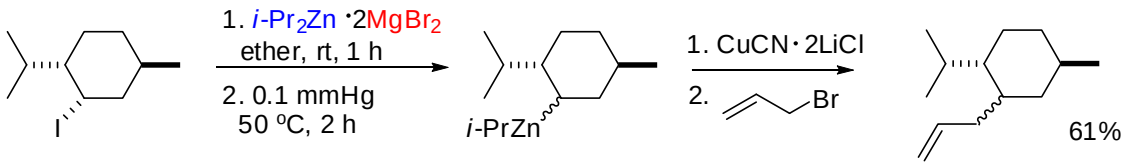
5.3.1 Iodine-zinc exchange reaction

Radical mechanism, catalyzed by Cu(I) salt

for alkyl iodides - without solvent, 50 °C, 2~10 h, requires 1.5~3 equiv of Et_2Zn

functional group compatibility: ester, ether, halide, or cyanide

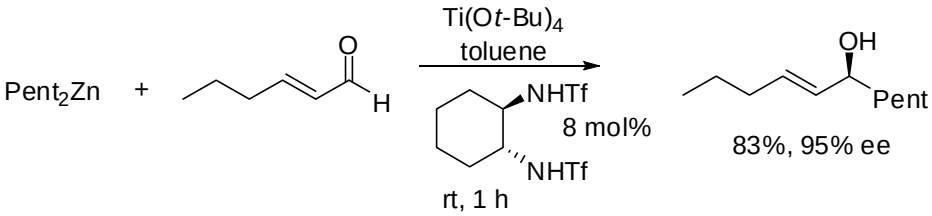




in situ generation of *i*-Pr_2Zn by the reaction of *i*-PrMgBr and $ZnBr_2$

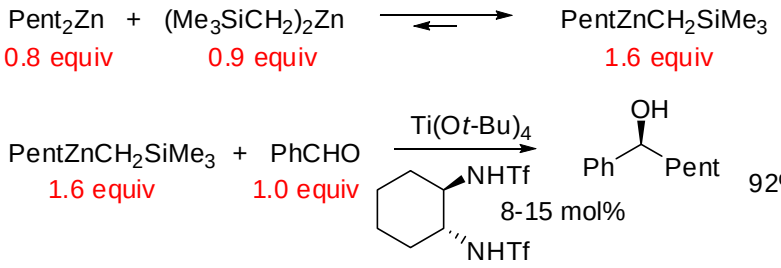
$MgBr_2$ facilitates the iodine-zinc exchange

Asymmetric addition to aldehydes using chiral catalyst



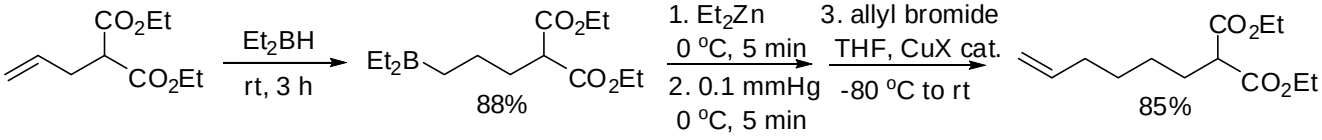
Mixed diorganozinc reagents - reduce the required amount of diorganozinc reagents (from 2~3 to 0.8 equiv)

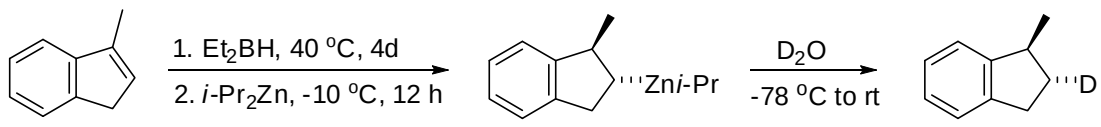
Me_3SiCH_2 group: non-transferable group



5.3.2 Boron-zinc exchange reaction

Exchange for primary diethylalkyl borane proceeds at rt within a few minutes.



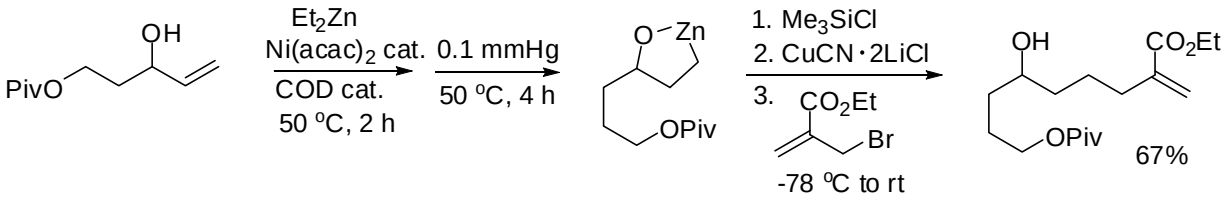


47%, 98:2 dr

5.3.3 Hydrozincation of olefins

Using Et_2Zn in the presence of cat. $Ni(acac)_2$ and COD

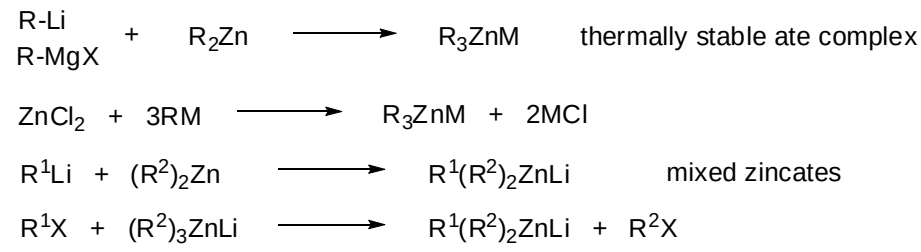
Good for allylic alcohols or amines



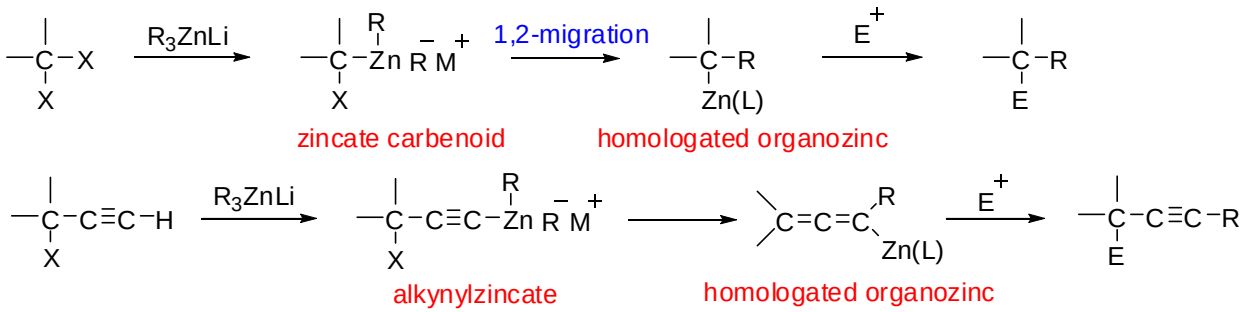
5.4 Preparation and reaction of triorganozincates

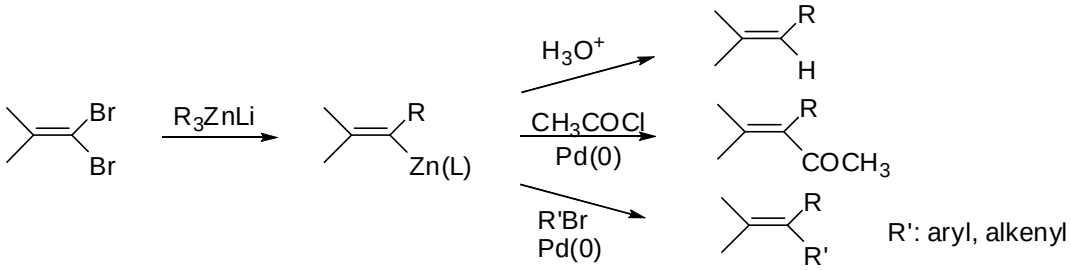
more reactive than organozinc halides and diorganozincs

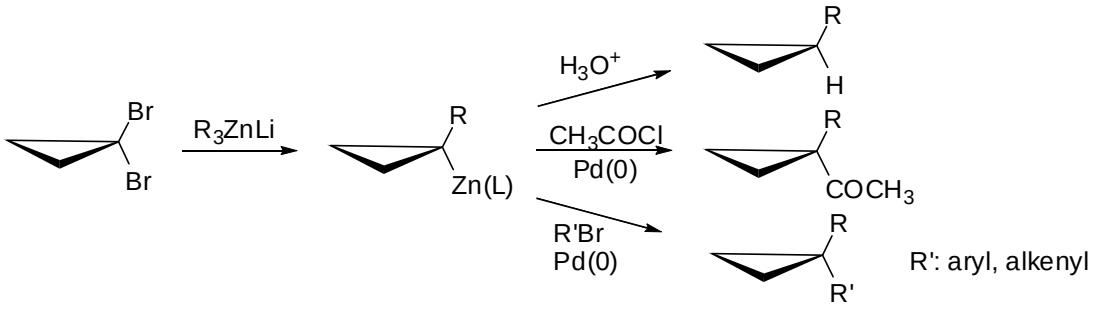
1,2-addition to aldehydes and ketones; 1,4-addition to conjugate enones

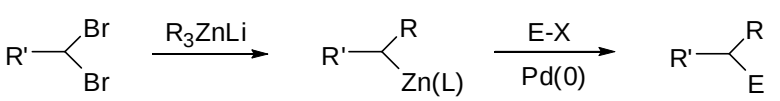


Homologated organozincs



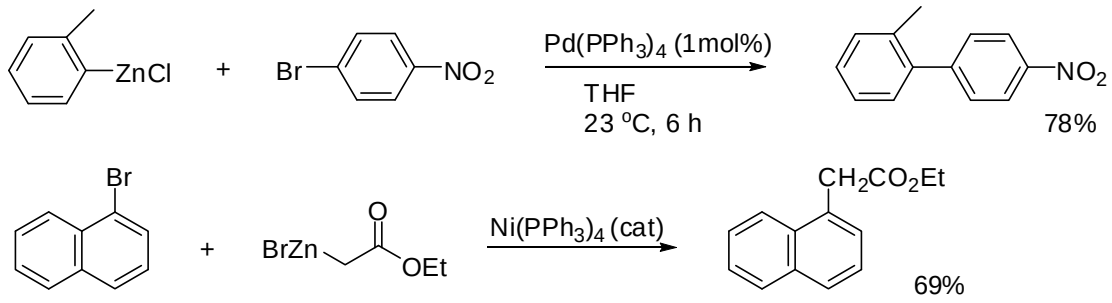




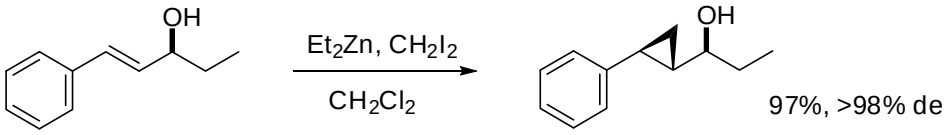


5.5 General Reactions

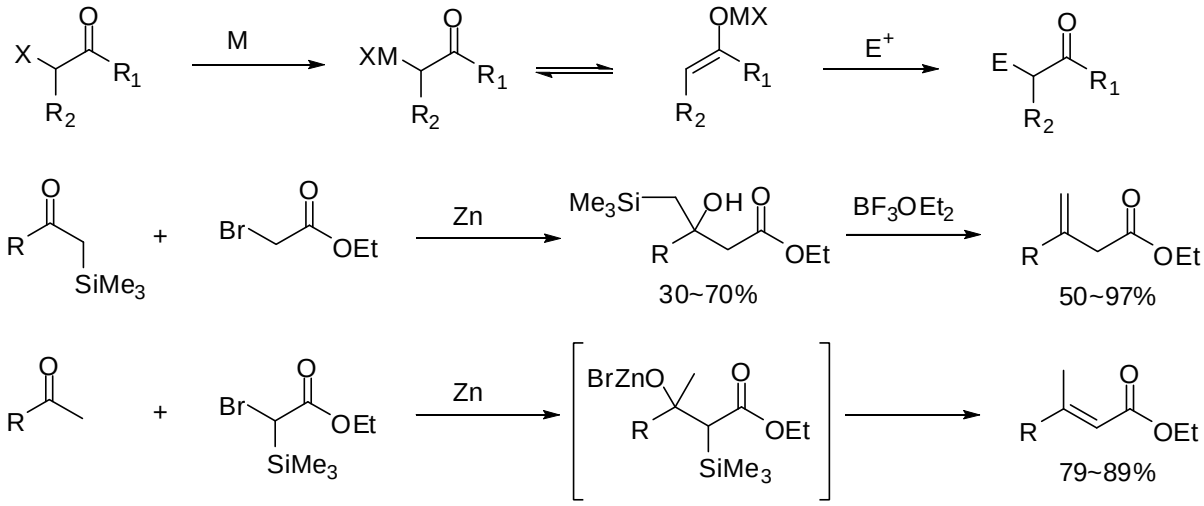
5.5.1. Palladium and nickel catalyzed reactions



5.5.2. Simmons-Smith cyclopropanation

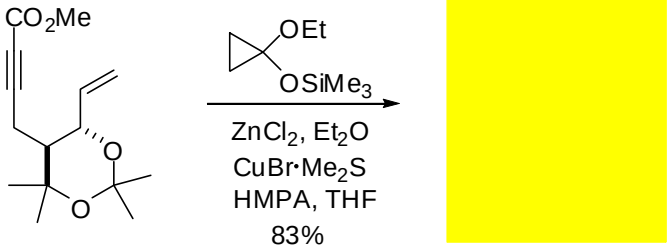


5.5.3. Reformatsky reaction



Problem Set - Organozinc chemistry

(1)



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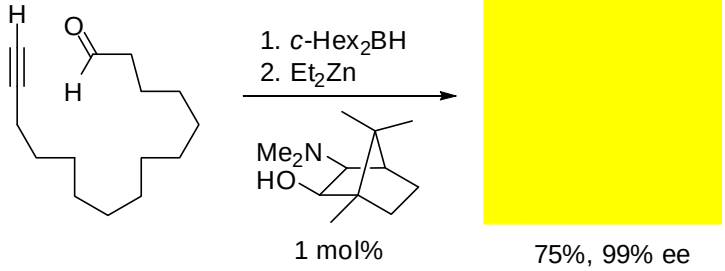

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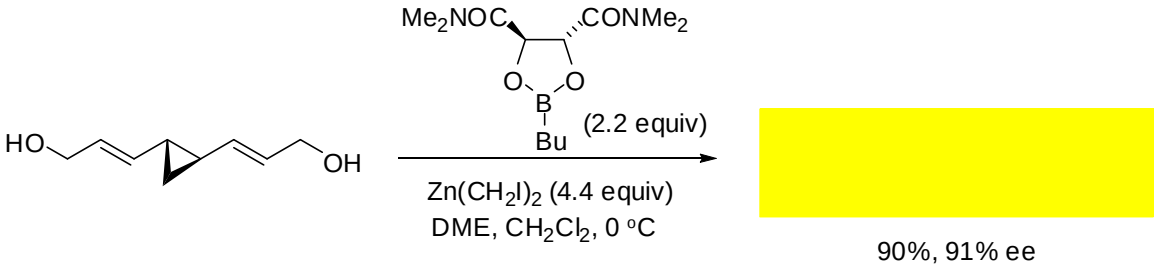

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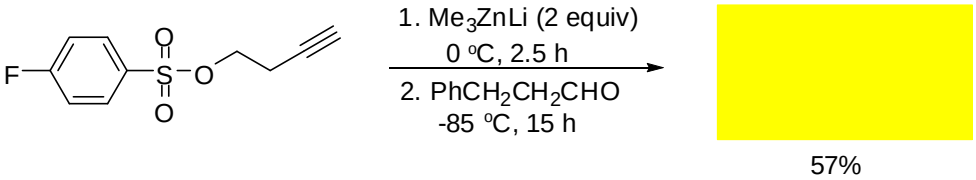

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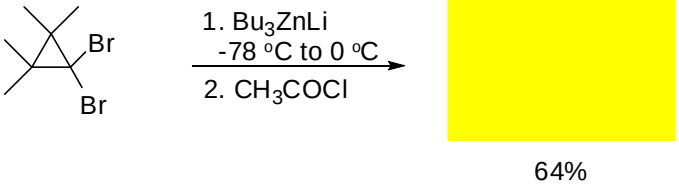

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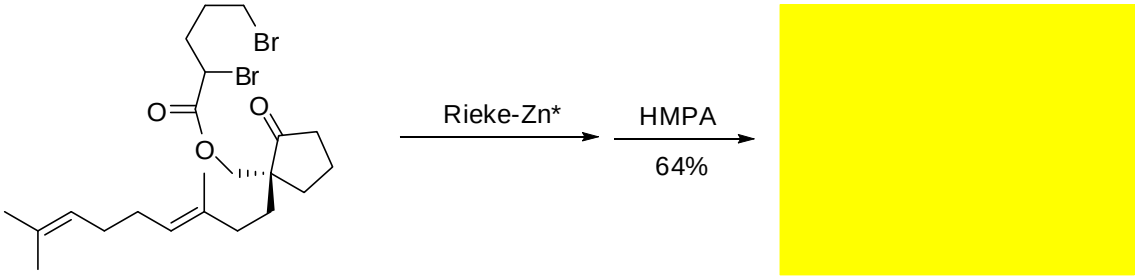
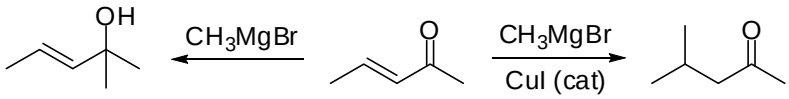
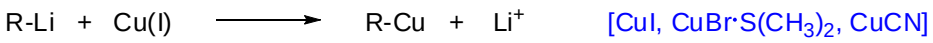


6. Organocopper Reagent

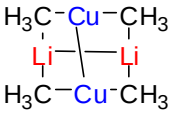


6.1 Preparation of organocopper reagents

a. Alkyl Copper

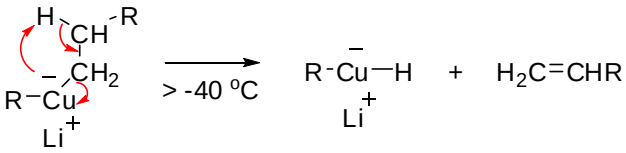


b. Cuprate

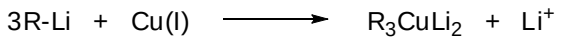


Dimeric structure in solution (ether, THF) - $[LiCu(CH_3)_2]_2$

β-Hydride elimination



c. Higher-order Cuprate



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

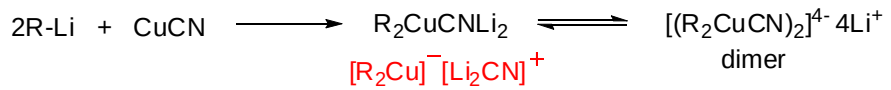
[CH_3-S(O)-CH_2-Cu-R]Li, [N≡C-Cu-R]Li

Efficiency of ligand transfer

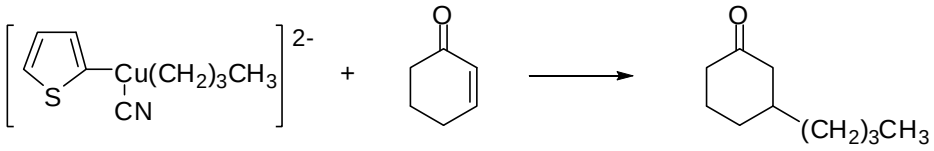
vinyl, Ph > Me > Et > *i*-Pr > *t*-Bu >> PhS, R_2N, RC≡C

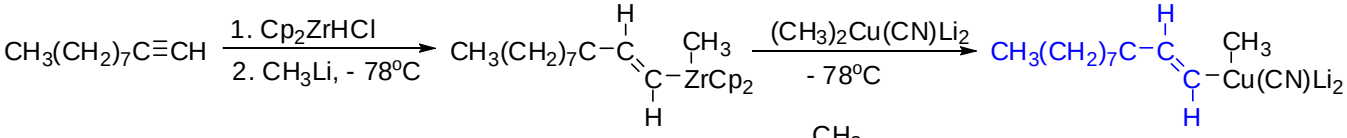
dummy ligand

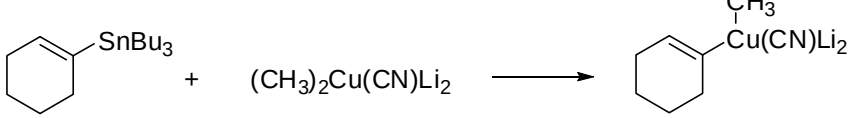
e. Higher-order Cyanocuprats (stable)

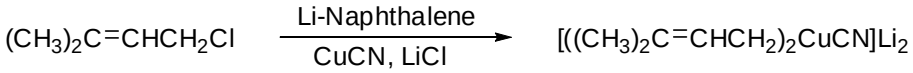


f. Mixed Higher-order Cyanocuprates





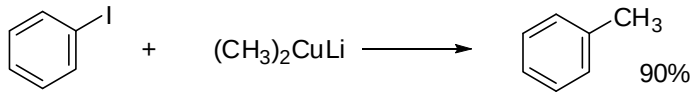




6.2 Reactions

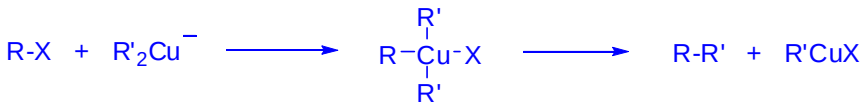
6.2.1 Nucleophilic displacement on halides and sulfonates

a. Aryl or vinyl halides

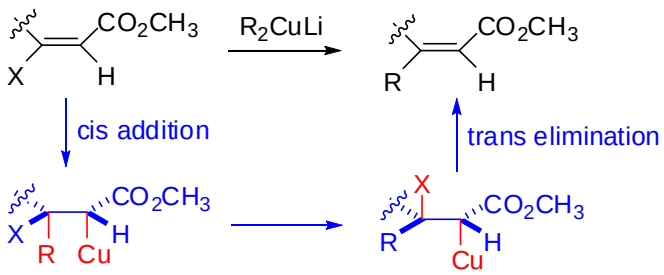


PhCH=CHBr + $(CH_3)_2CuLi$ → PhCH=CHCH$_3$ 81%

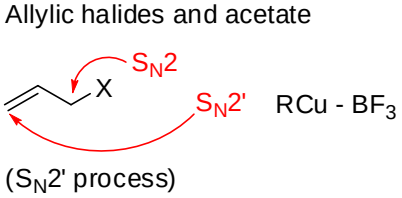
Mechanism: Oxidative addition and migration



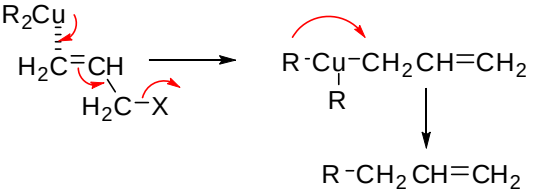
b. Vinyl halides with β-EWG

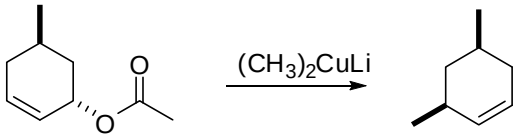


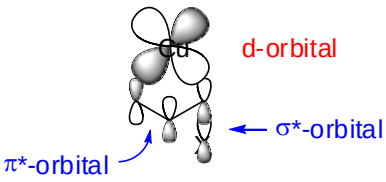
c. Allylic halides and acetate



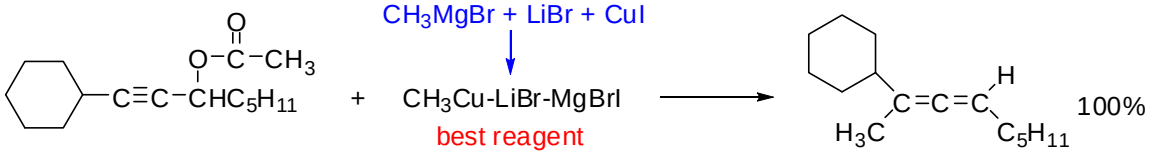
SN2' process







d. Propargylic acetates, halides, and sulfonates

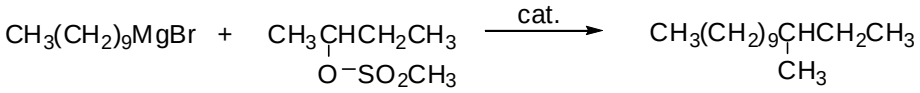


e. Coupling of Grignard reagents using Li_2CuCl_4 catalyst

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%

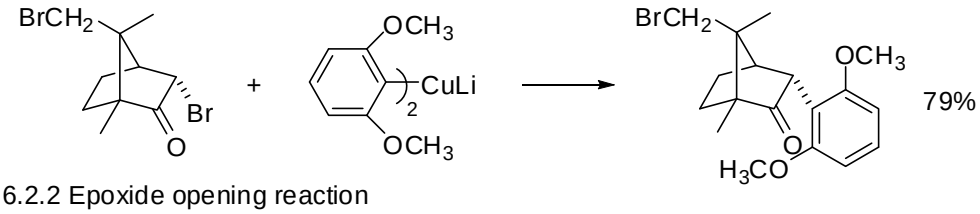
2° sulfonates:



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

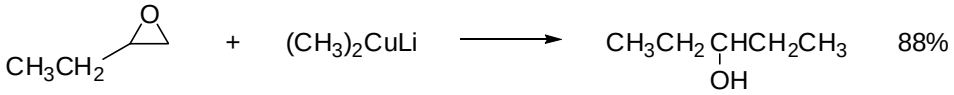
6.2 Reactions

f. α-Halocarbonyl compounds

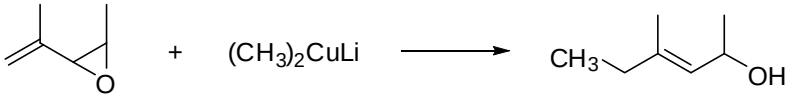


79%

6.2.2 Epoxide opening reaction



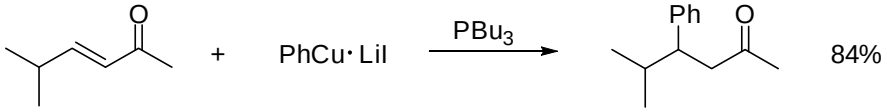
88%



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)



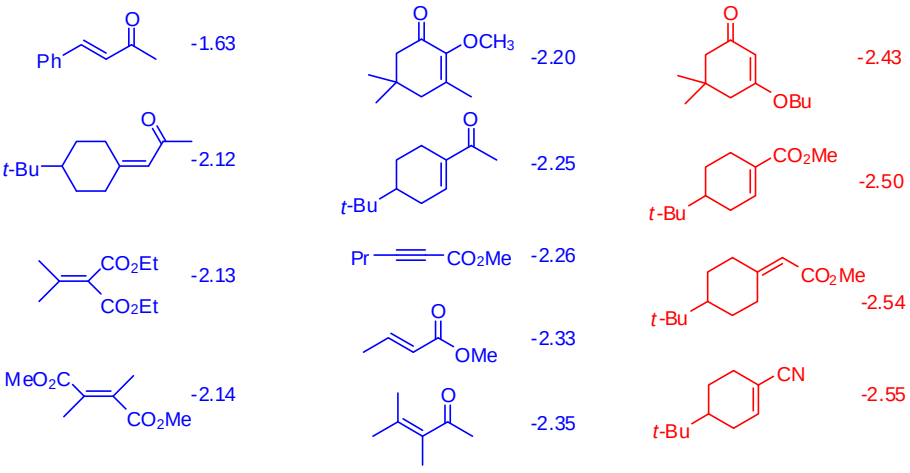
84%

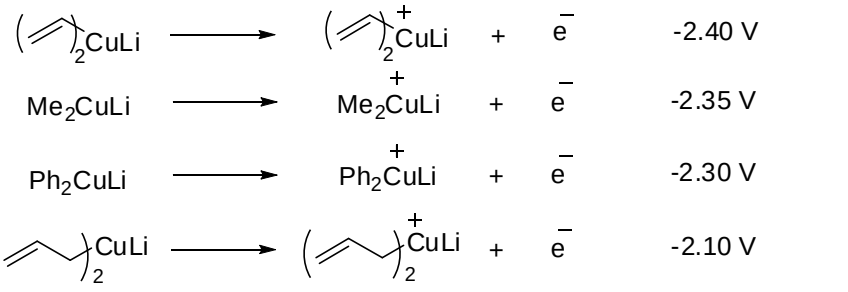
not a free radical mechanism

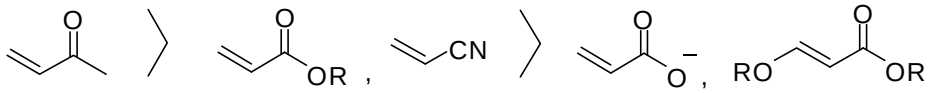
a. corelation of the reactivity towards 1,4-addition with the reduction potential of the carbonyl compounds

Reduction potential (V)

Reduction -1.2 V _____ -2.4 V No Reaction







6.2 Reactions

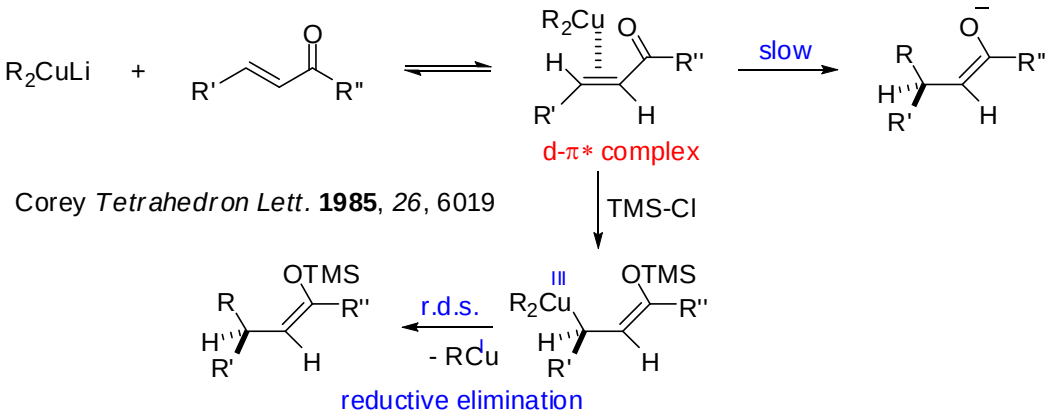
6.2.3 Conjugate addition to α,β-unsaturated carbonyl compounds

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

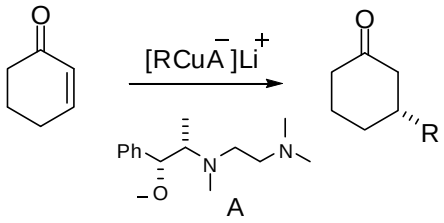
Mechanism



Corey *Tetrahedron Lett.* **1985**, *26*, 6019

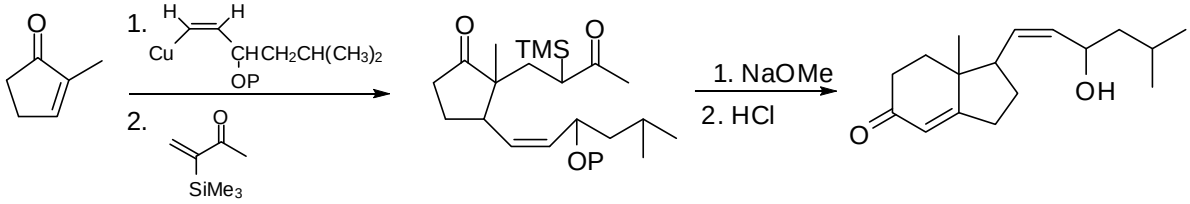
c. Enantioselectivity

mixed cuprate reagents with chiral anionic ligands

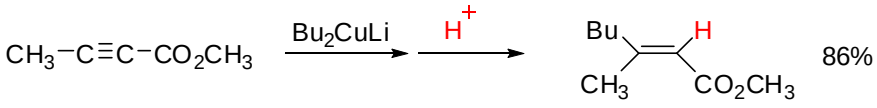


R	ee
Et	92
Bu	89
$(CH_3)_3COCH_2$	85

d. Tandem conjugate addition / alkylation



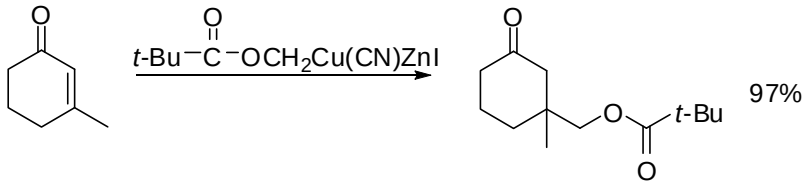
e. Conjugate acetylenic esters - syn addition (kinetic product)



f. Mixed copper-zinc organometallics

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

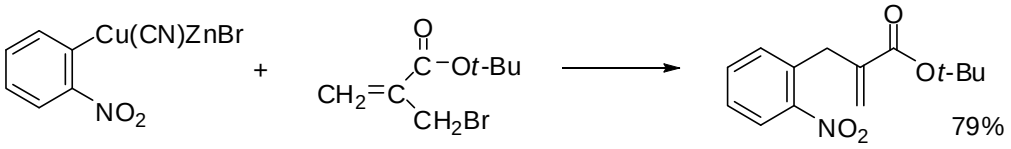
Preparation: add CuCN to R-Zn-I



6.2 Reactions

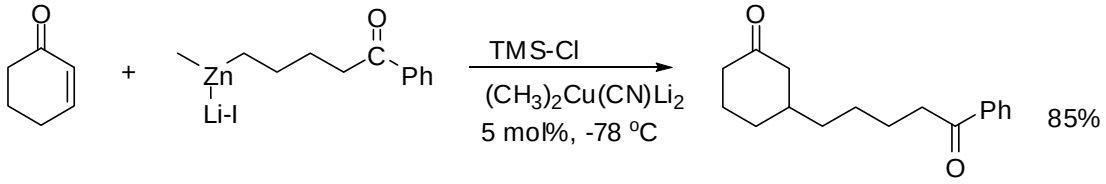
6.2.3 Conjugate addition to α,β-unsaturated carbonyl compounds

f. Mixed copper-zinc organometallics

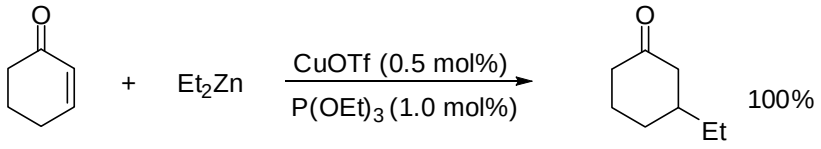


- Catalytic copper species with organozinc reagents

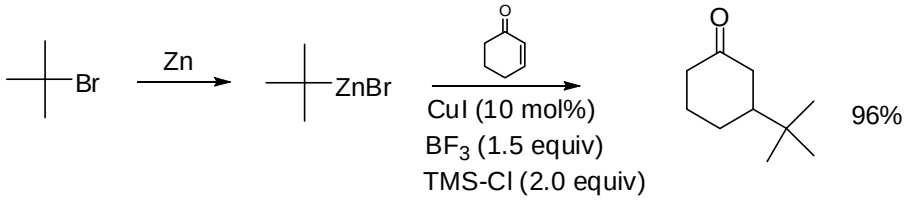
LiI + TMSCl + cat. $(CH_3)_2Cu(CN)Li_2$



dialkylzinc + 0.5 mol% CuOTf + phosphines or phosphites

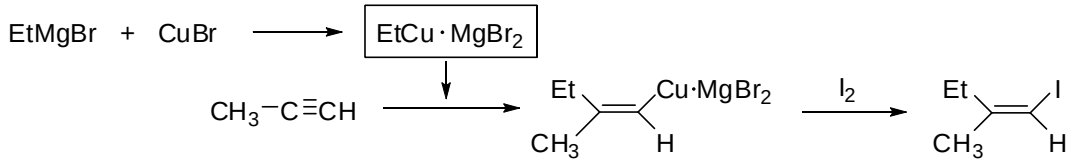


CuI or CuCN (10 mol%), BF_3 and TMS-Cl



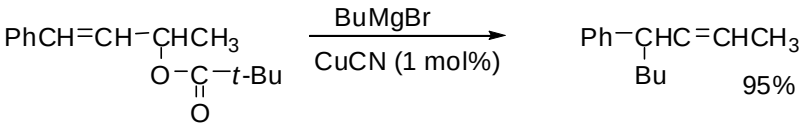
g. Mixed copper-magnesium reagents (Normant Reagents)

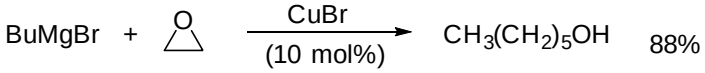
Addition to terminal acetylenes ⟶ Alkenylcopper reagents (syn addition)

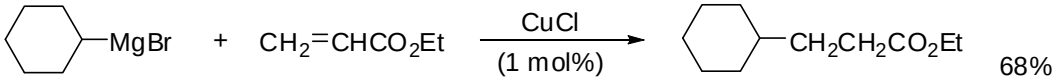


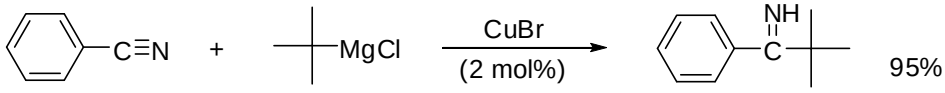
- Catalytic process

Grignard reagent + catalytic copper salt





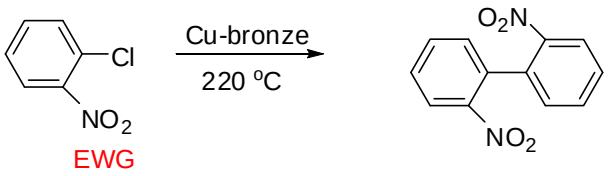




6.2 Reactions

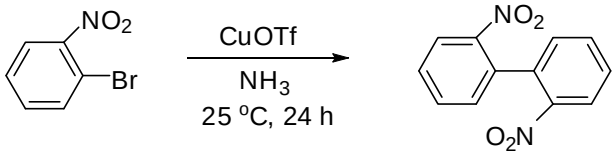
6.2.4 Ullman coupling - coupling of aryl halide

(Organocopper Intermediate)

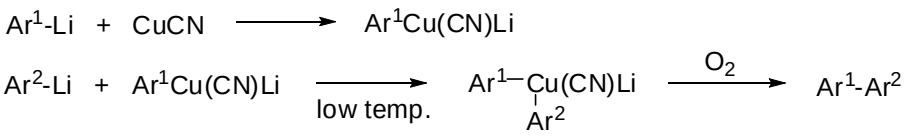


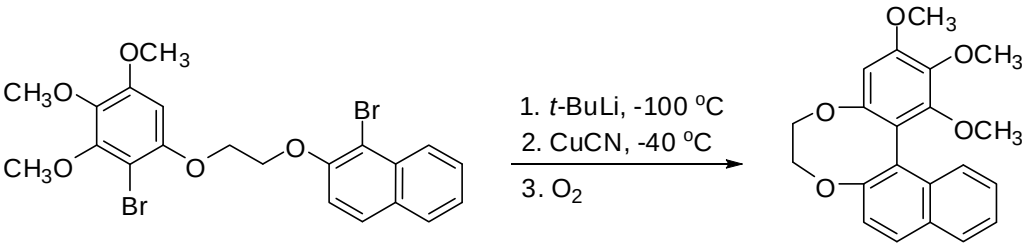
lower the reaction temperature by the use of soluble Cu(I) salts: CuOTf

homogeneous condition



New type of Ullman coupling - mixed diarylcyanocuprate



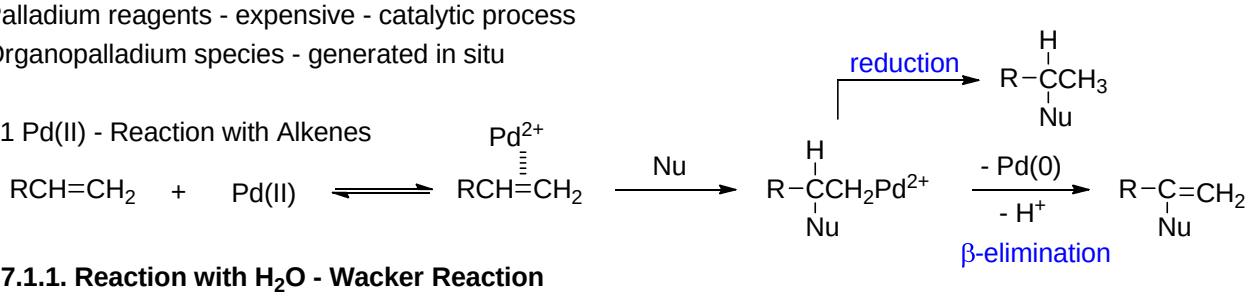


7. Reaction Involving Organopalladium Intermediates

Palladium reagents - expensive - catalytic process

Organopalladium species - generated in situ

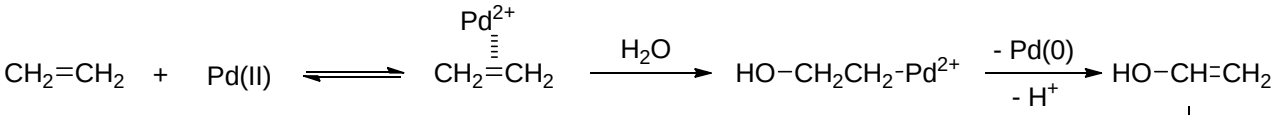
7.1 Pd(II) - Reaction with Alkenes



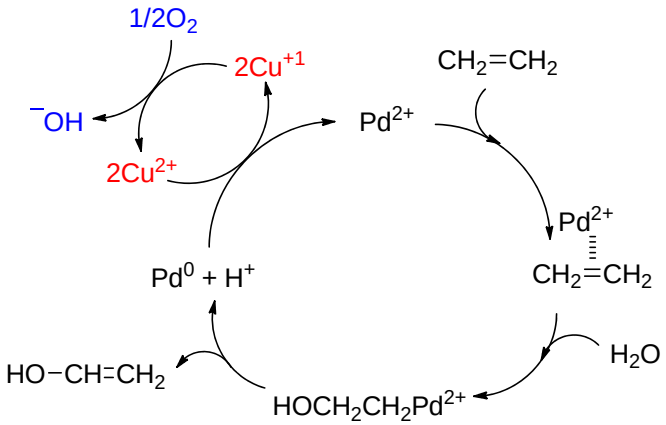
7.1.1. Reaction with H_2O - Wacker Reaction

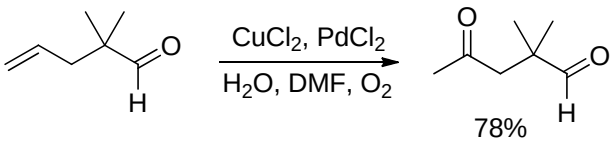
ethylene ⟶ acetaldehyde

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

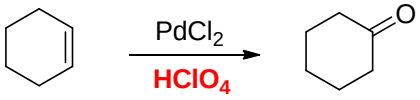


<mechanism>

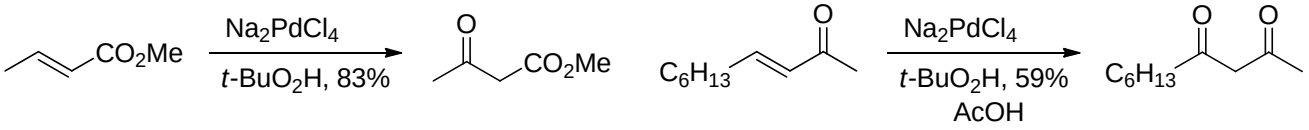




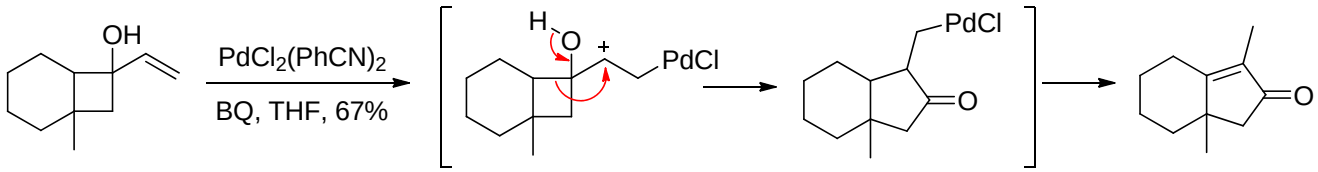
Oxidation of simple internal alkenes is very slow

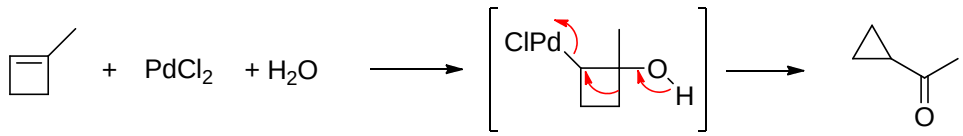


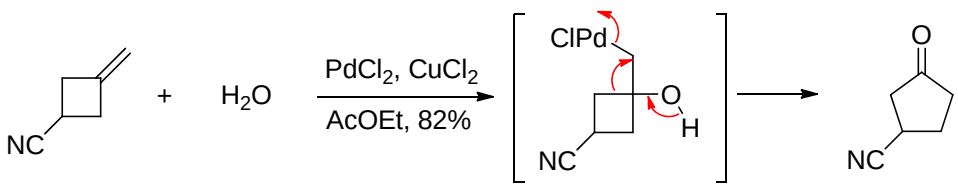
Neighboring group participation



Oxidative rearrangement

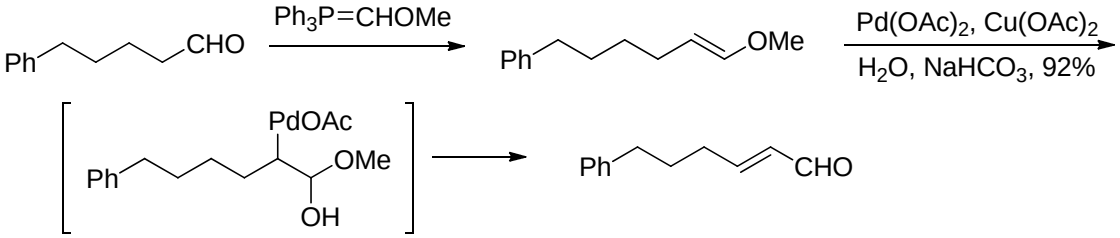




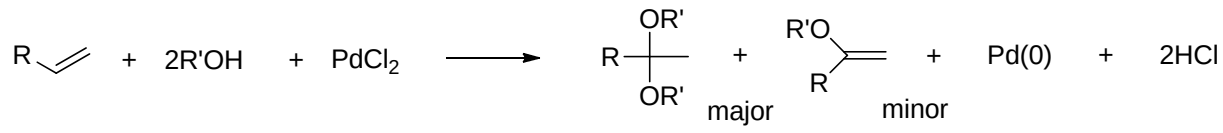


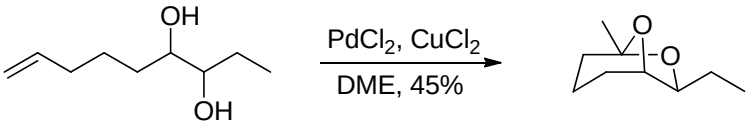
7.1. Pd(II) - Reaction with Alkenes

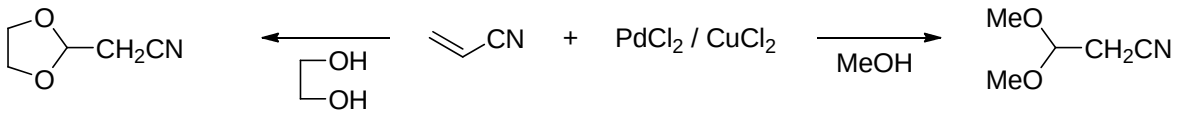
Methyl enol ether

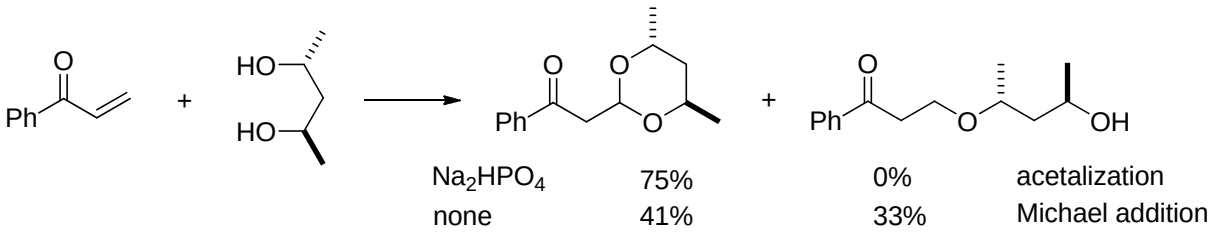


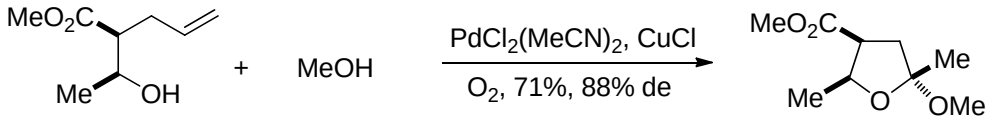
7.1.2. Reaction with Alcohols



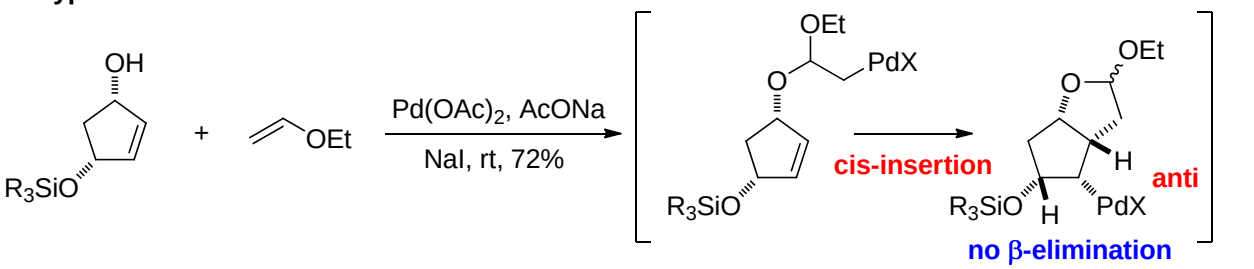


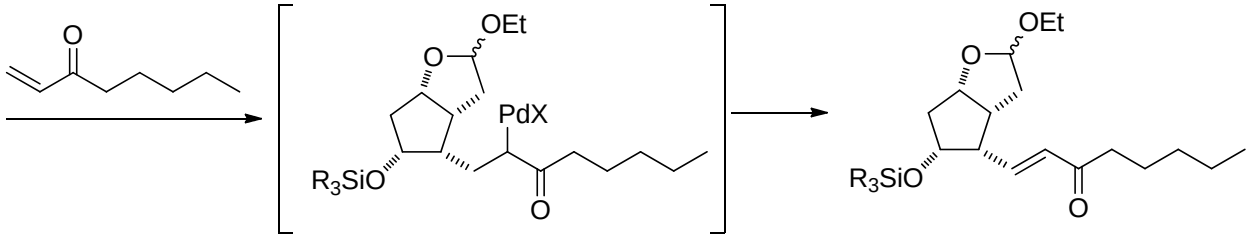






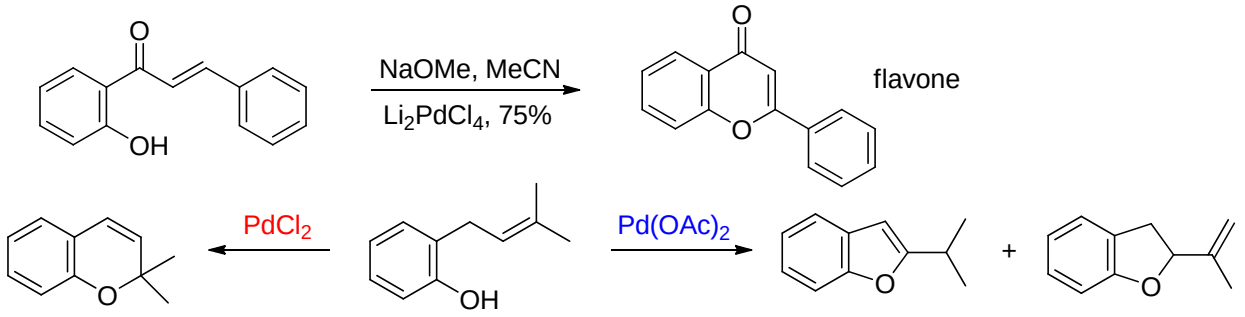
Oxypalladation / alkene insertion



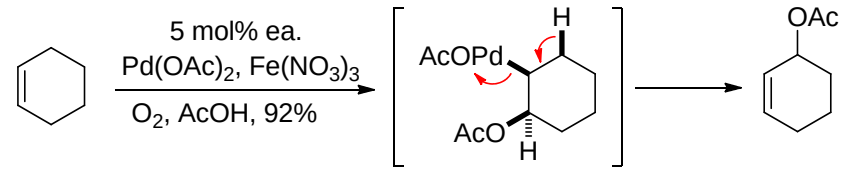


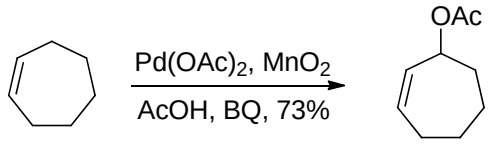
7.1. Pd(II) - Reaction with Alkenes

Phenolic Oxypalladation

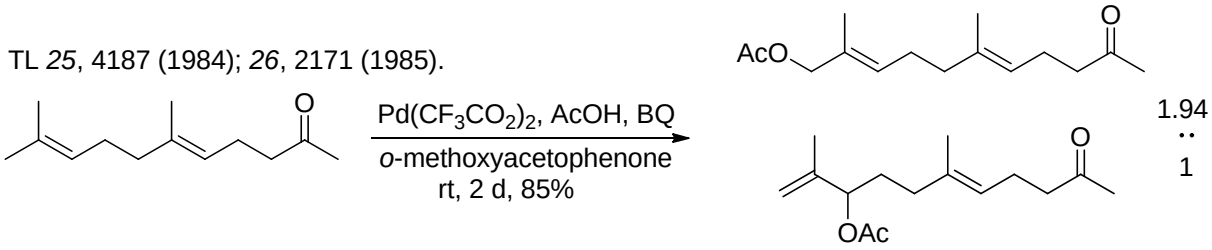


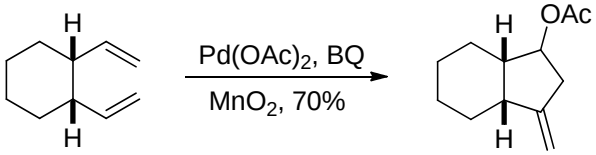
7.1.3. Reaction with Carboxylic Acids

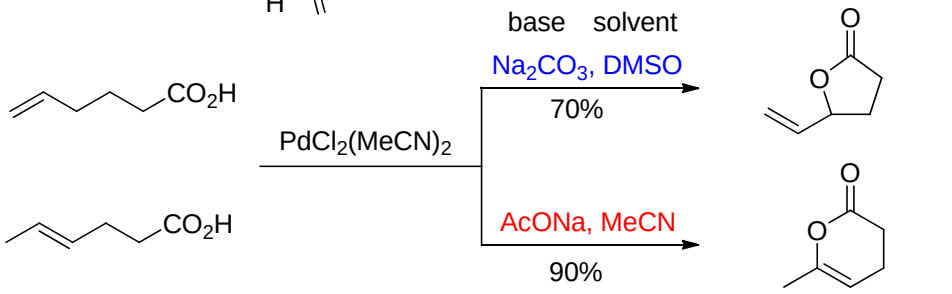


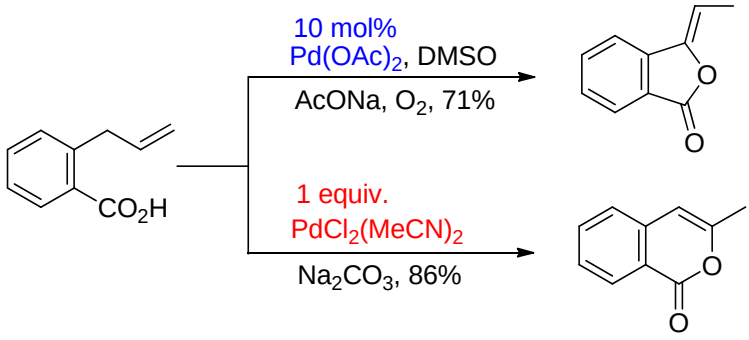


TL *25*, 4187 (1984); *26*, 2171 (1985).



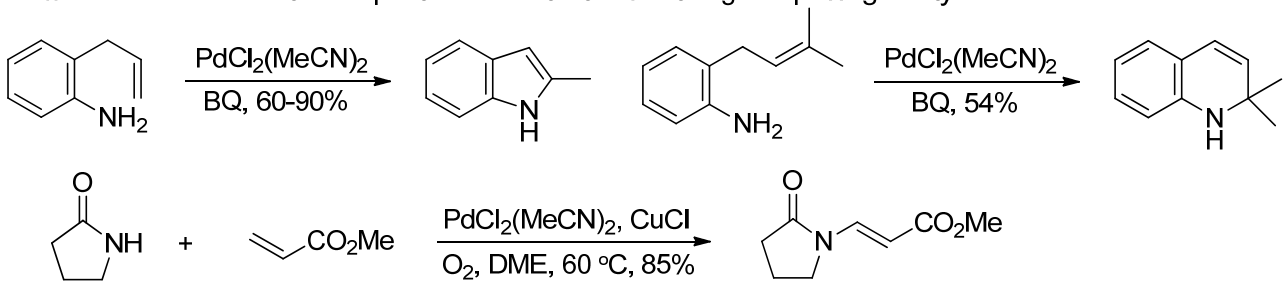




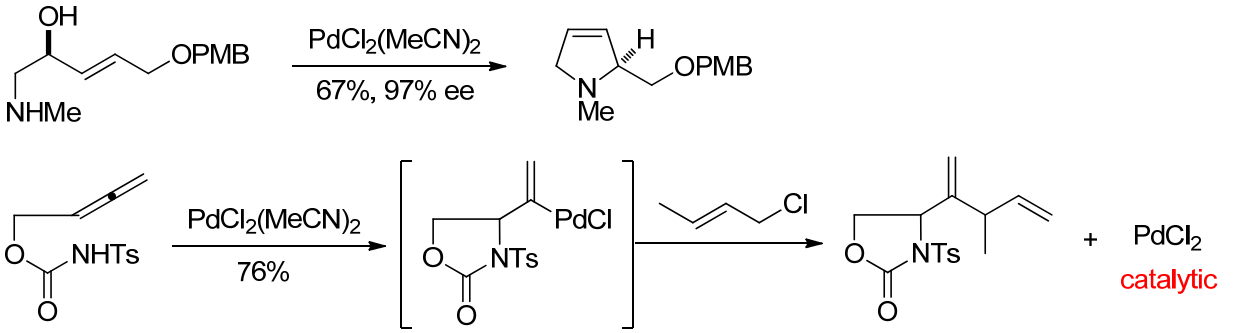


7.1.4. Reactions with Amines - aminopalladation

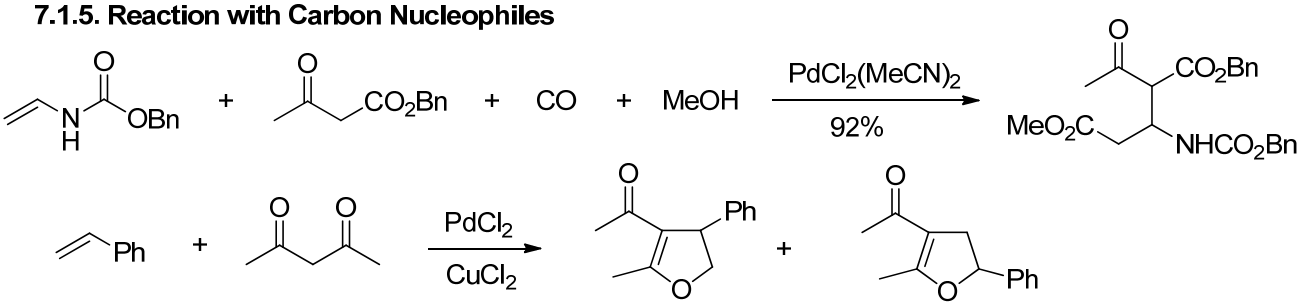
Oxidative amination proceeds smoothly for aromatic amines, amides, and tosylamines which are less basic than aliphatic amines that have strong complexing ability.



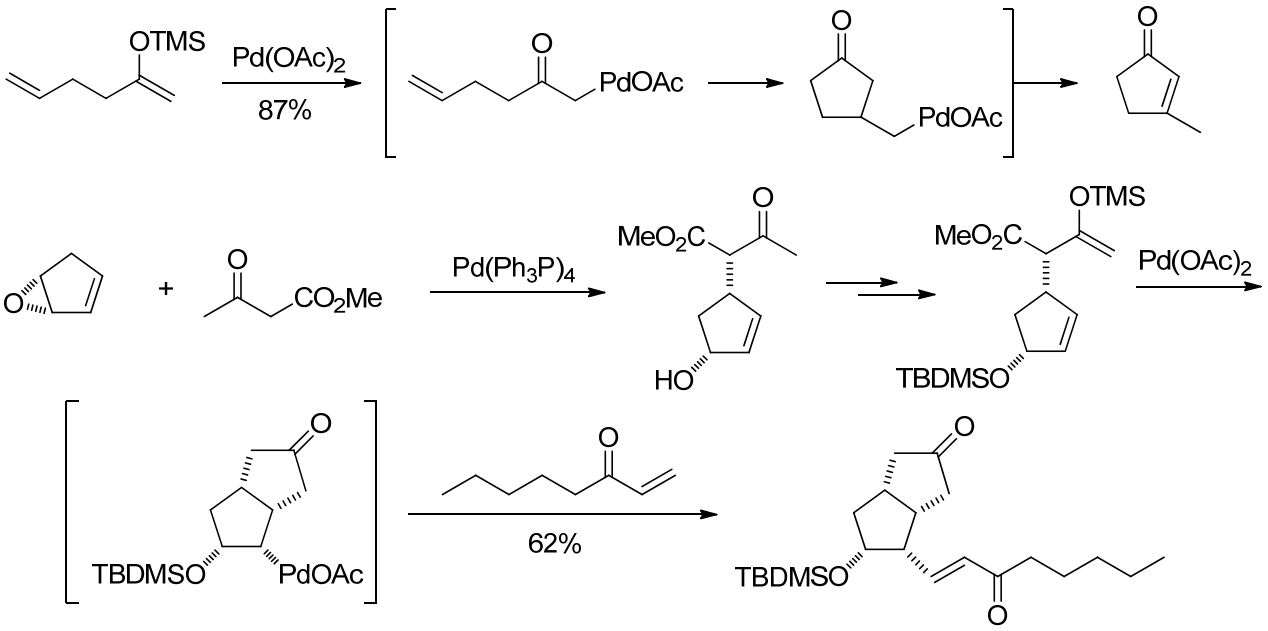
Aminopalladation is stoichiometric reaction. When β-OH is eliminated instead of β-H, Pd(II) is the elimination product (HO-PdCl) and the reaction is catalytic without a reoxidant.



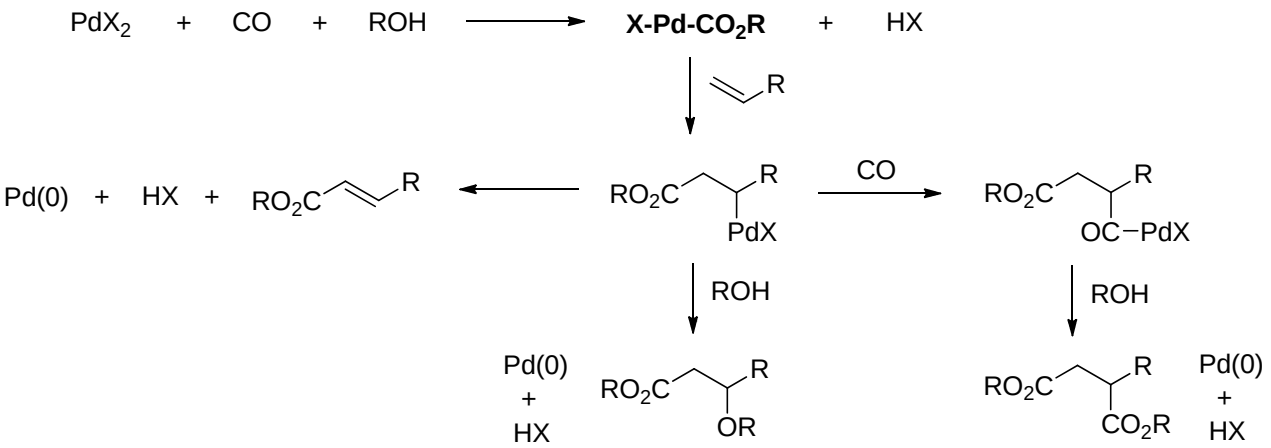
7.1.5. Reaction with Carbon Nucleophiles

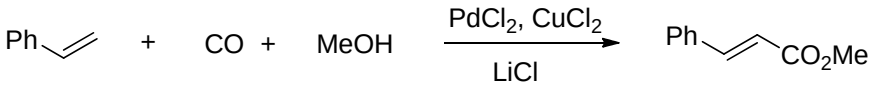


Pd enolates by transmetallation of silyl enol ehters with $Pd(OAc)_2$

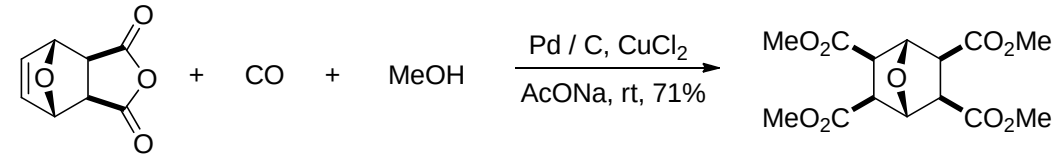


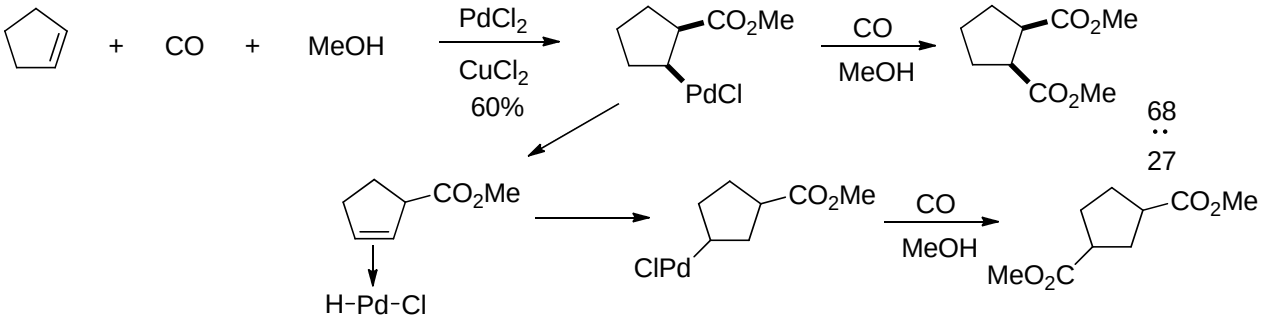
7.1.6. Oxidative Carbonylation

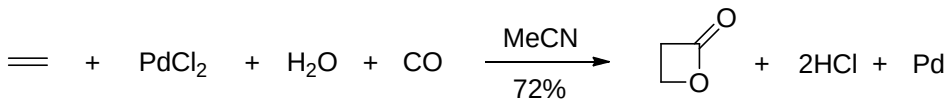


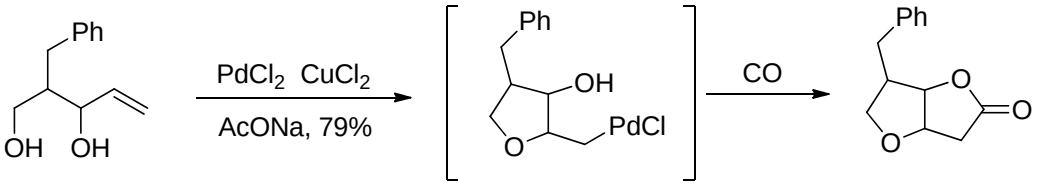


Dicarboxylation of cyclic alkenes

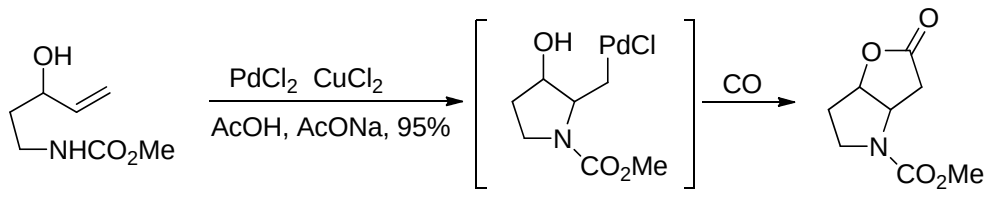




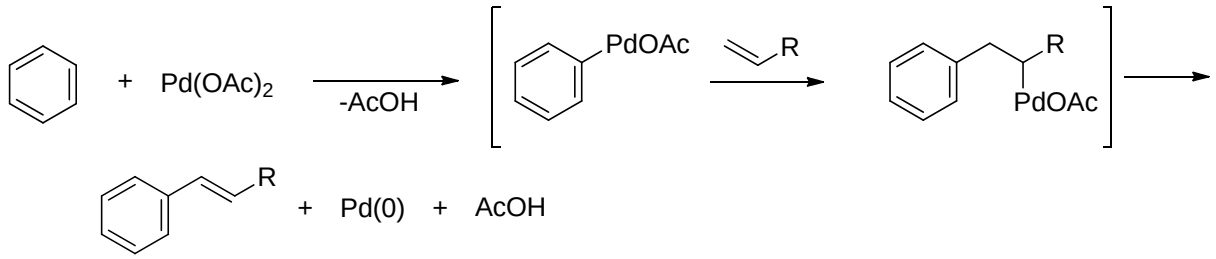


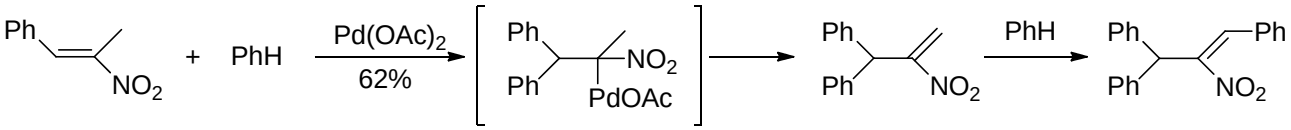


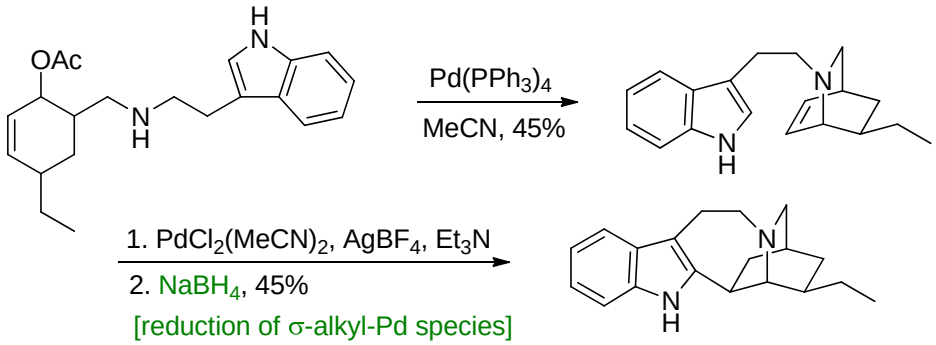
Aminopalladation / carbonylation

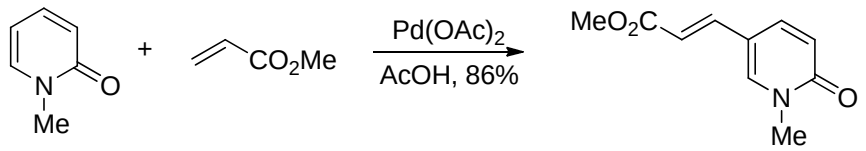


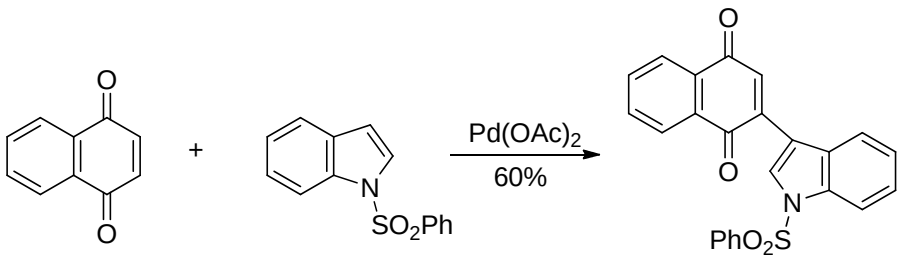
7.1.7. Reaction with Aromatic Compounds





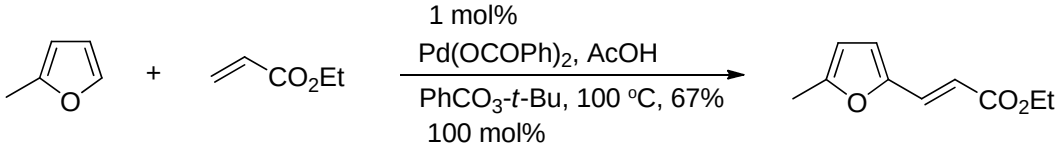






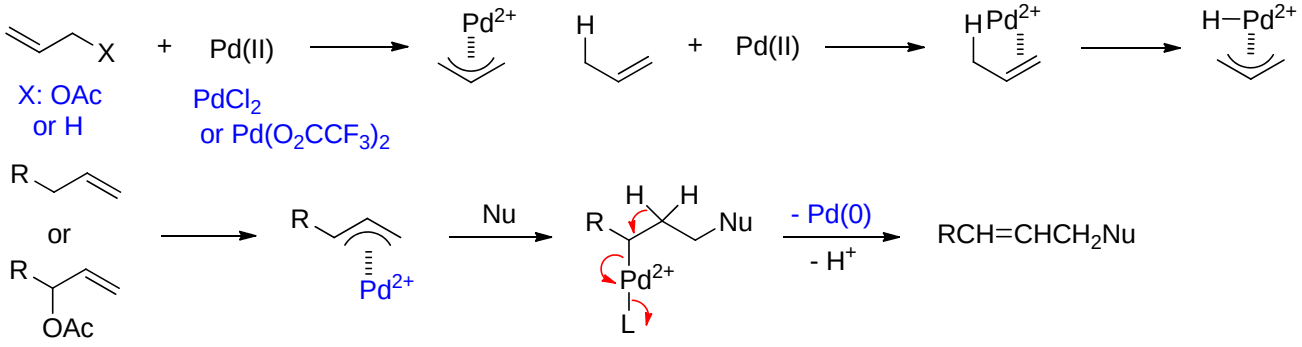
Catalytic Arylation of Alkenes

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

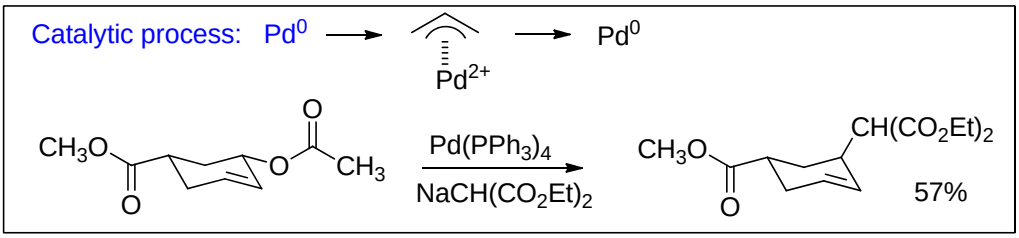


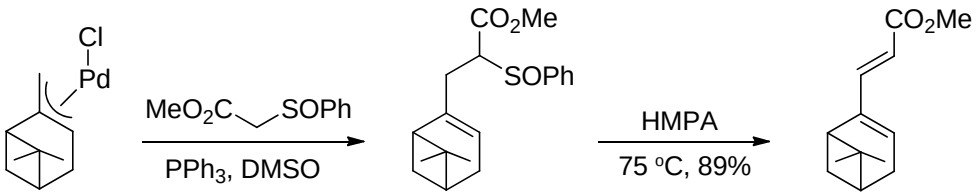
7.2 Pd(II) - Reaction with Allylic Compounds - **stoichiometric reagent**

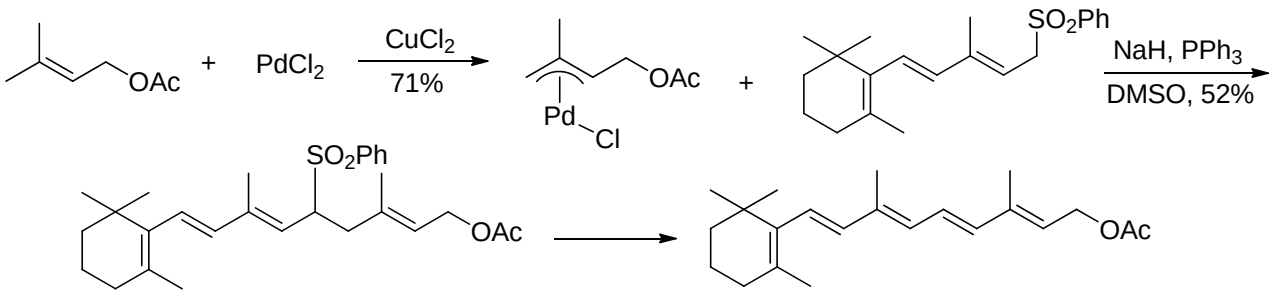
Formation of π-allyl complex

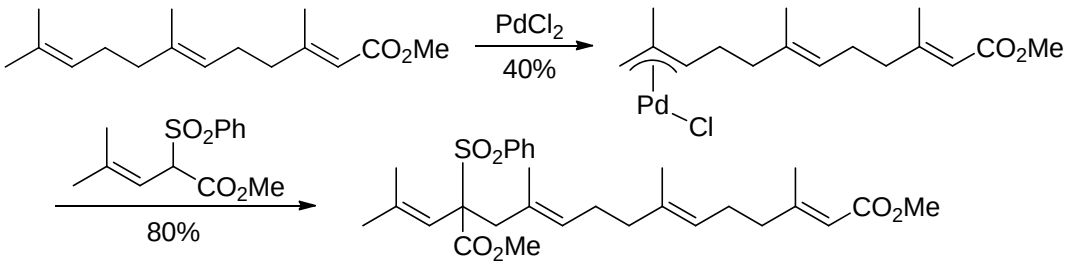


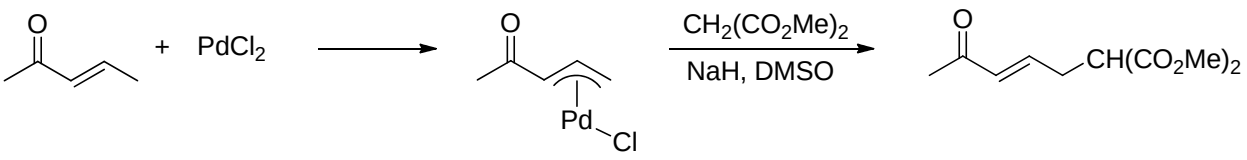
Efficient complex formation - Base in DMF or $CuCl_2$ and NaOAc in AcOH



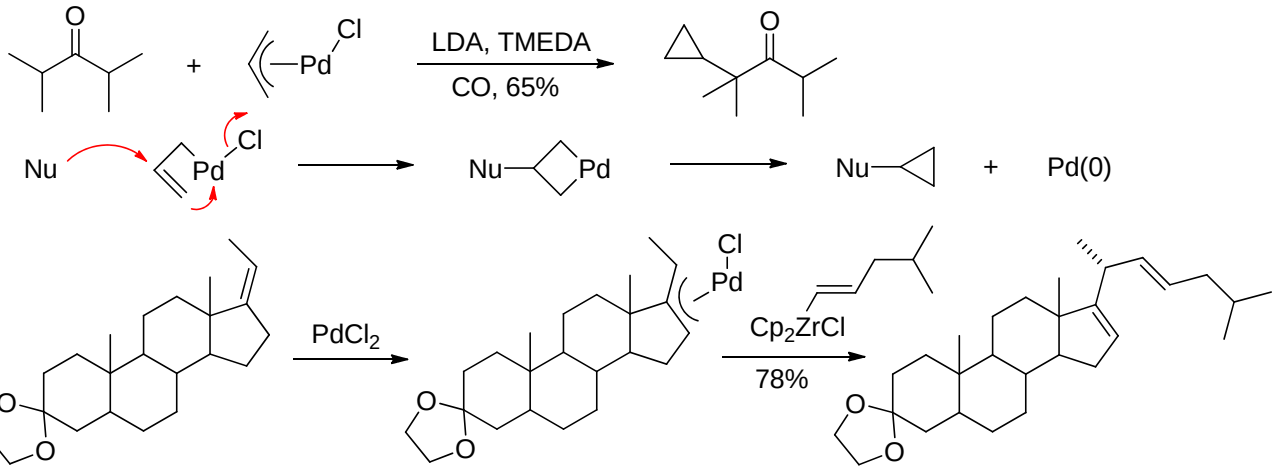




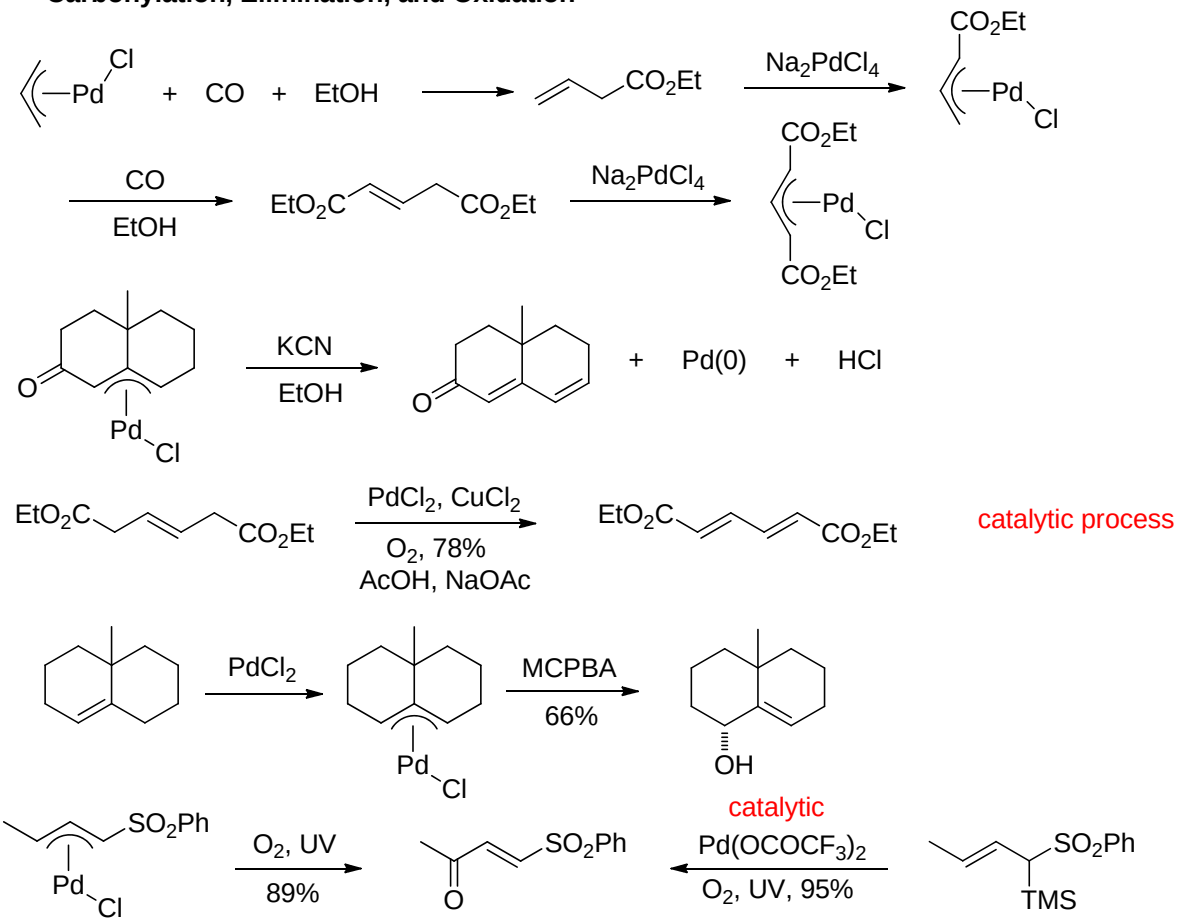




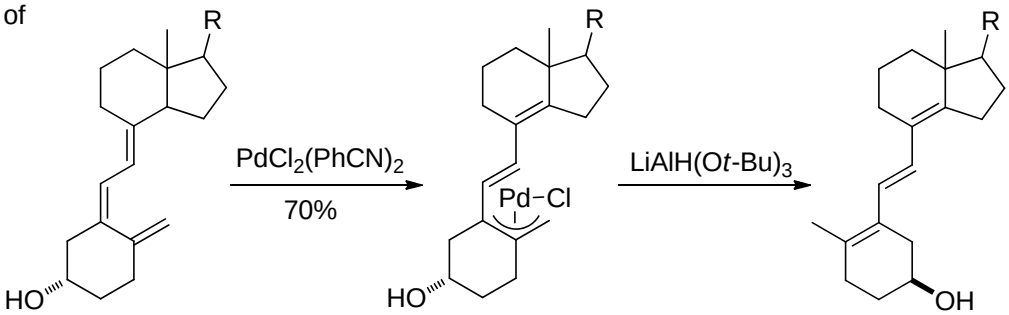
Formation of π-allyl complex



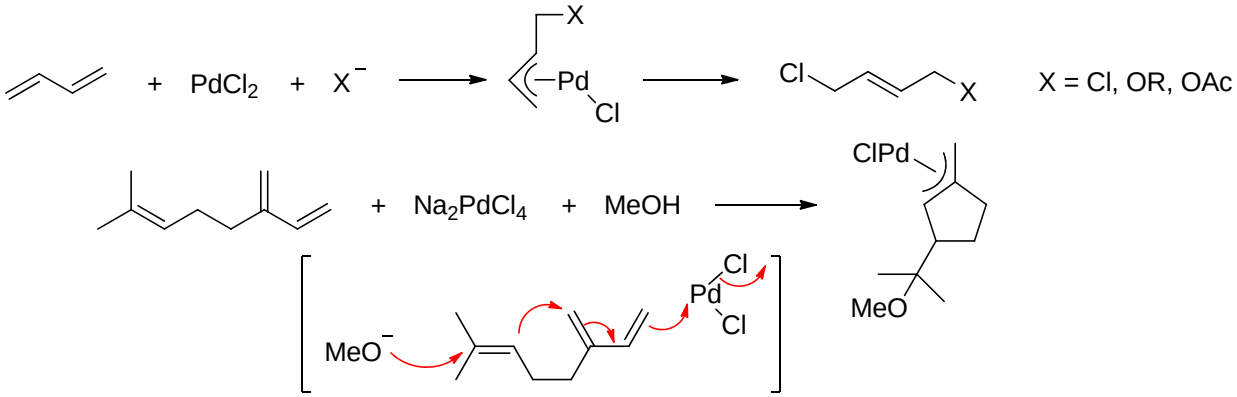
Carbonylation, Elimination, and Oxidation



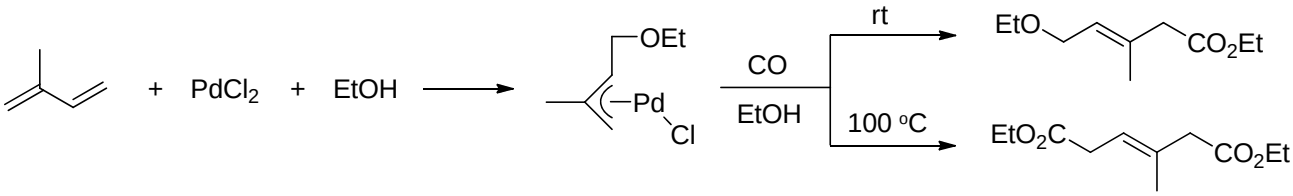
Isomerization of C=C bonds

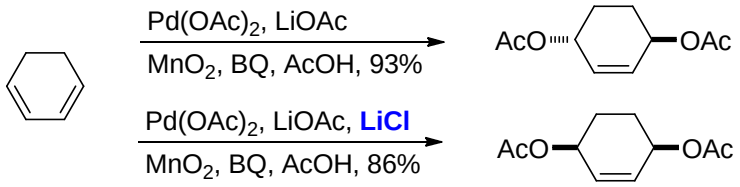


7.3. Pd(II) - Reactions with Conjugated Dienes

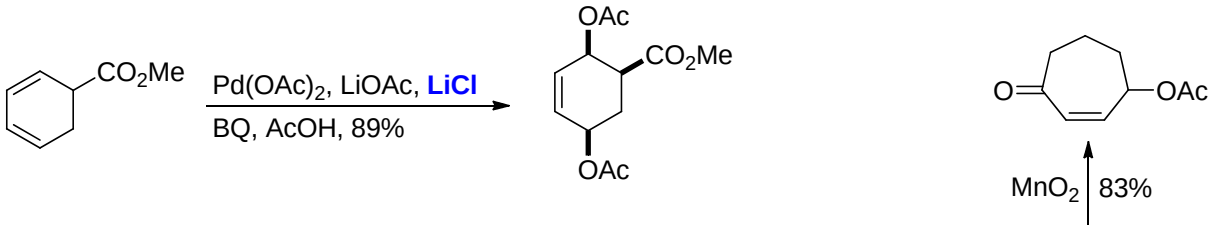


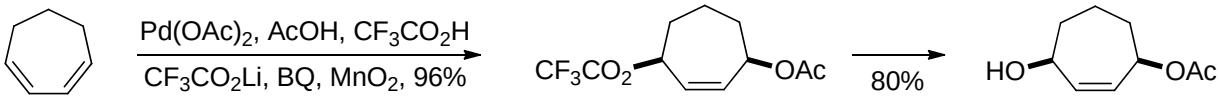
The reaction is stoichiometric with respect to Pd(II) salts, but can be made catalytic by the use of reoxidants.

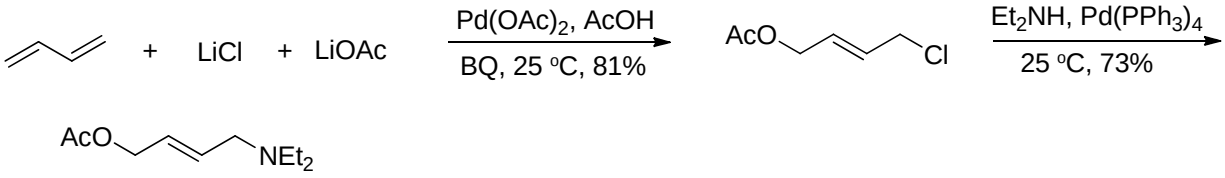


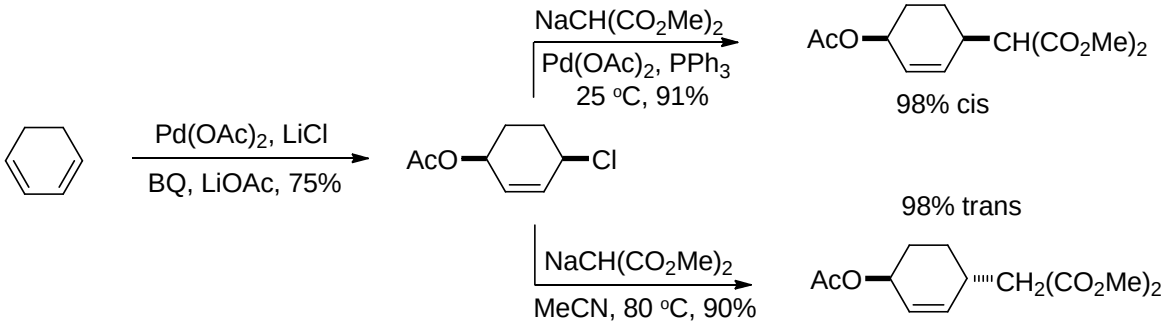


The coordination of a chloride ion to Pd makes the cis migration of the acetate from Pd impossible.



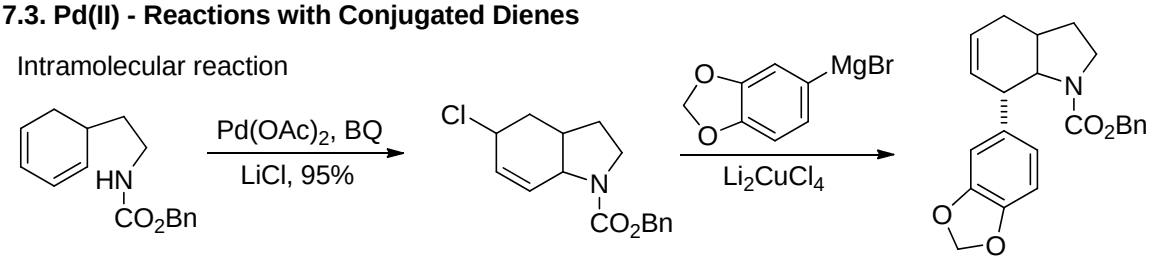


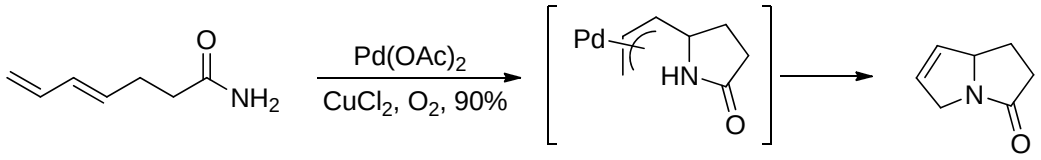


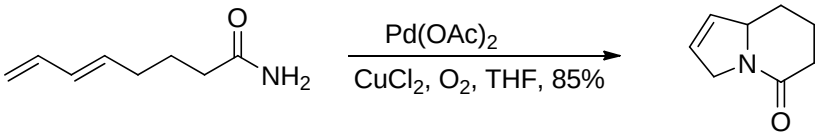


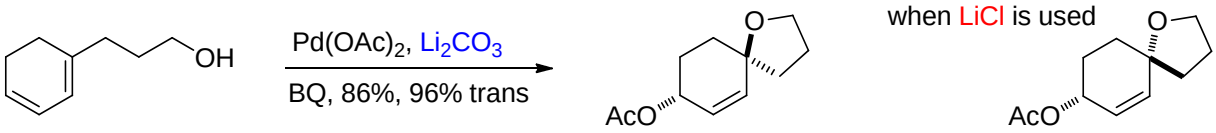
7.3. Pd(II) - Reactions with Conjugated Dienes

Intramolecular reaction







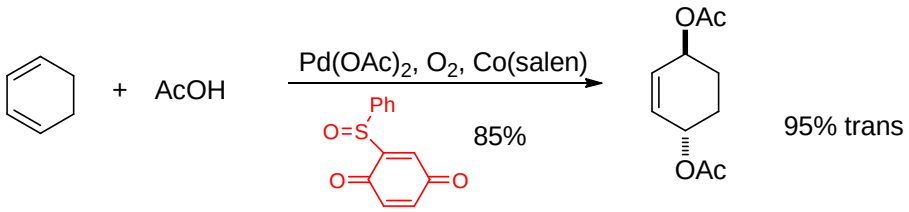


Catalytic reaction - use reoxidant of Pd(0)

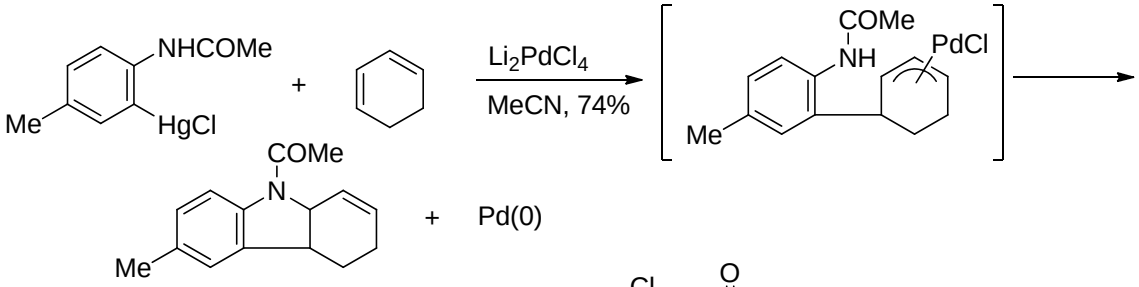
stoichiometric benzoquinone or

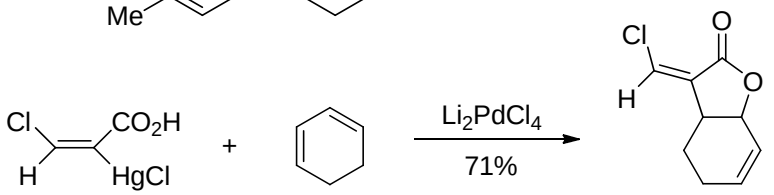
Fe-phthalocyanine complex or Co-salen complex is used to reoxidize hydroquinone to benzoquinone

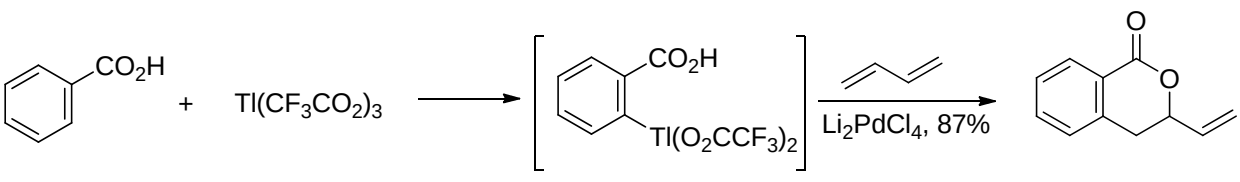
Faster reaction and Higher in stereoselectivity is obtained when (phenylsulfinyl)benzoquinone is used.



Aryl- or alkenylpalladium by transmetallation

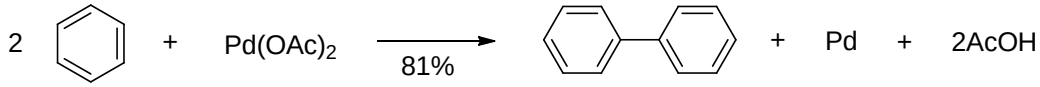




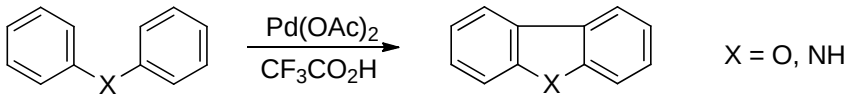


7.4. Pd(II) - Reactions with Aromatic Compounds

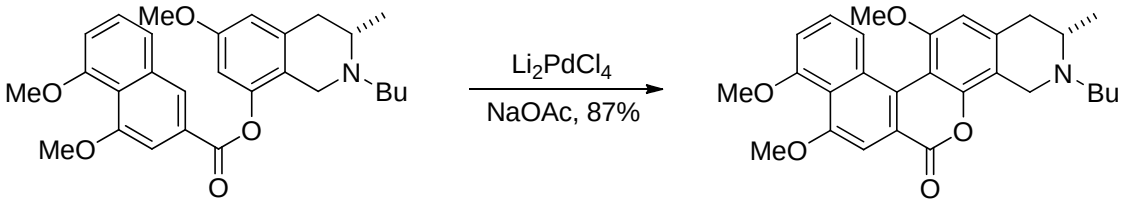
7.4.1. Homocoupling



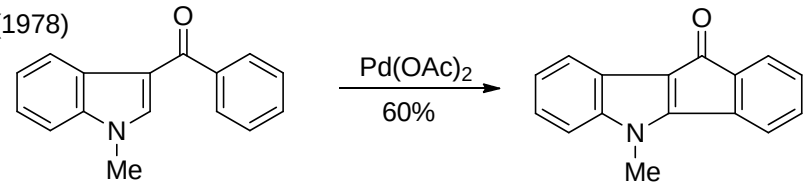
JOC, *40*, 1365 (1975)

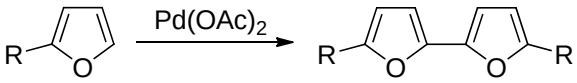


TL, *30*, 5249 (1989)

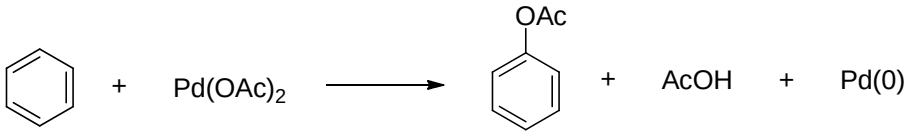


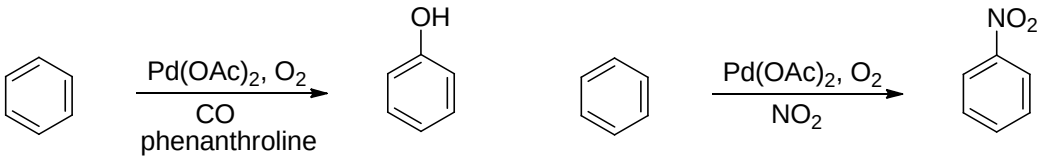
Synthesis, 607 (1978)

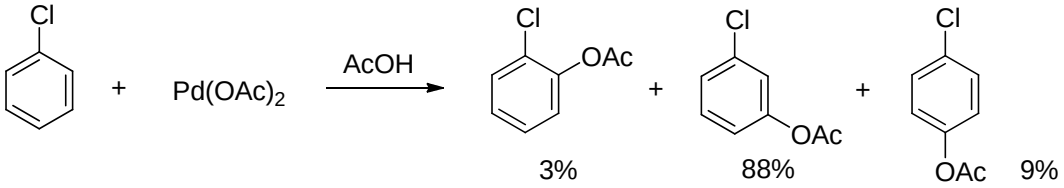


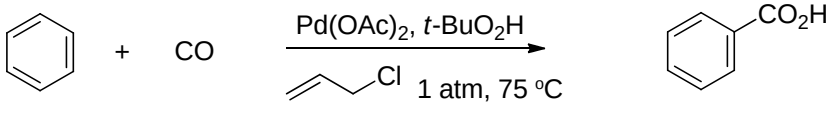


7.4.2. Oxidative Substitution

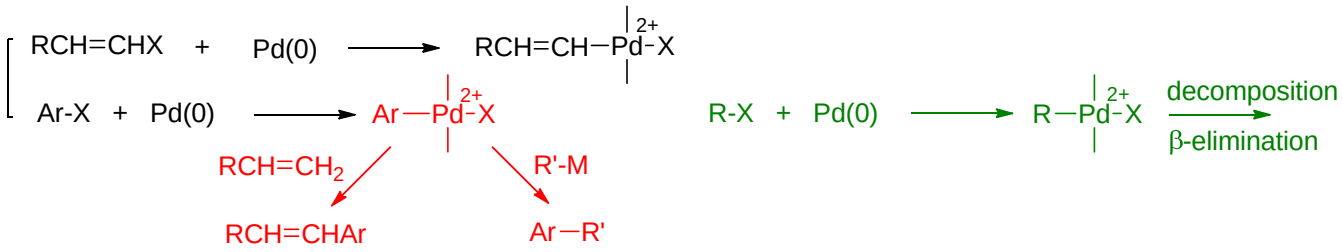




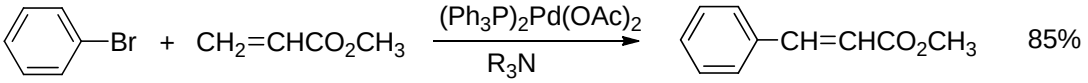




7.5. Pd(0) - Oxidative addition to halides or sulfonates (σ-bond)

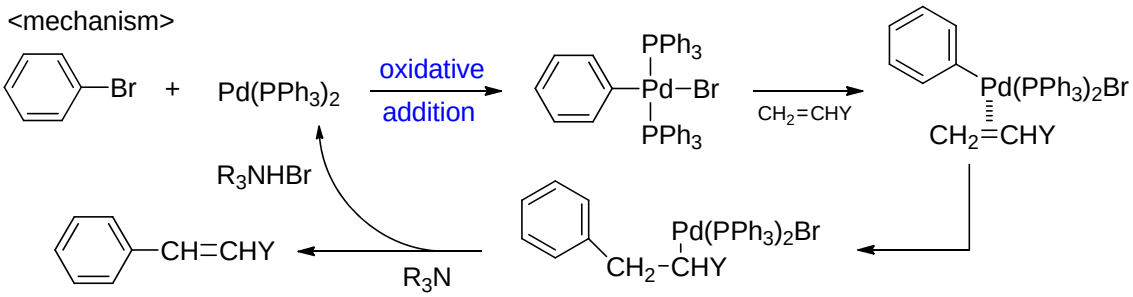


7.5.1. Heck reaction (reaction with alkenes)

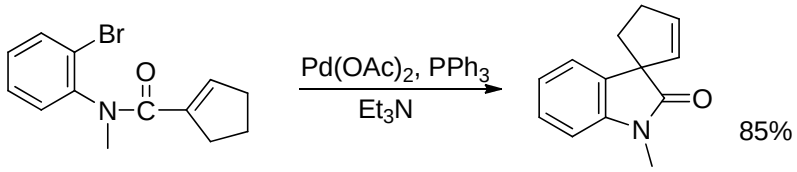


in situ reduction of Pd(II) to Pd(0): $Pd(OAc)_2$ + $2PPh_3$

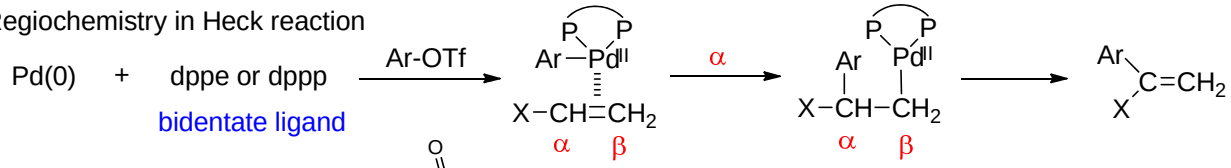
<mechanism>



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

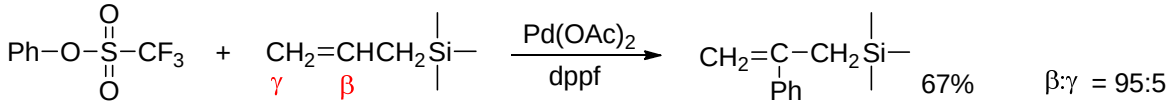


Regiochemistry in Heck reaction



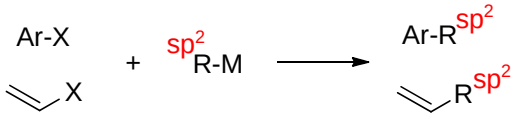
α: X = -OR, -OAc, $-CH_2OH$,  , ERG β: X = EWG

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

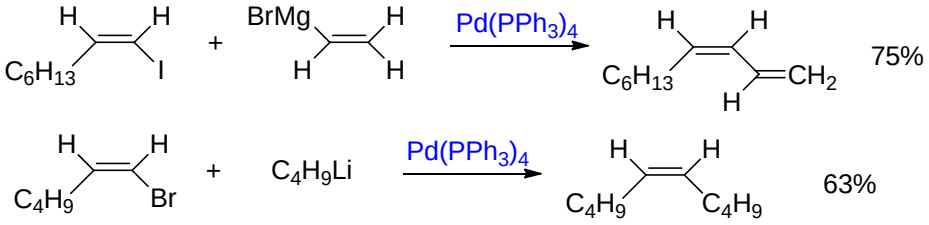
Steps in cross-coupling reaction:

oxidative addition - transmetallation - reductive elimination

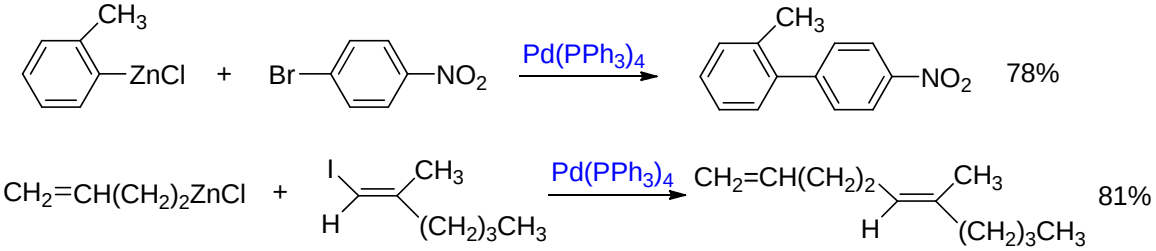
7.5.2. Palladium-catalyzed cross coupling reaction

7.5.2.1. Coupling with organometallic reagents

7.5.2.1.1. Grignard and organolithium reagents with Alkenyl halides

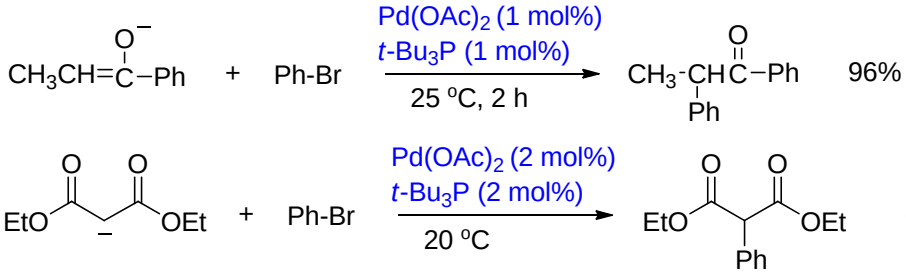


7.5.2.1.2. Organozinc reagents

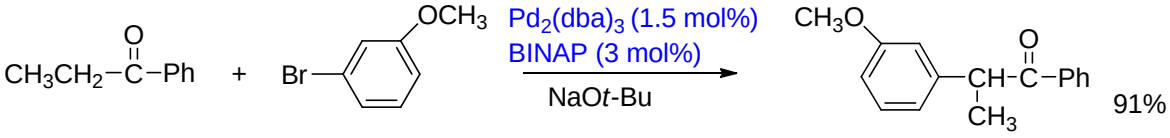


7.5.2.1.3. Arylation of enolates

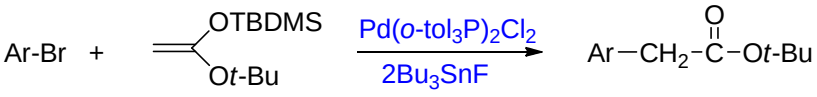
a. using *t*-Bu_3P, $Pd(OAc)_2$



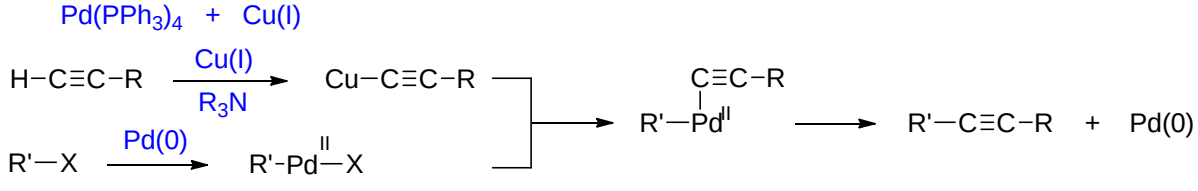
b. using BINAP ligand



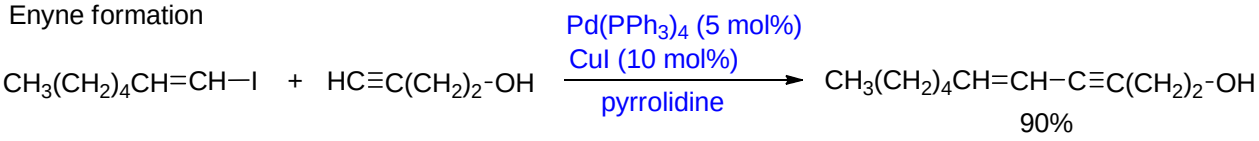
c. O-silyl ketene acetals with Bu_3Sn-F



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



Enyne formation



7.5.2. Palladium-catalyzed cross coupling reaction

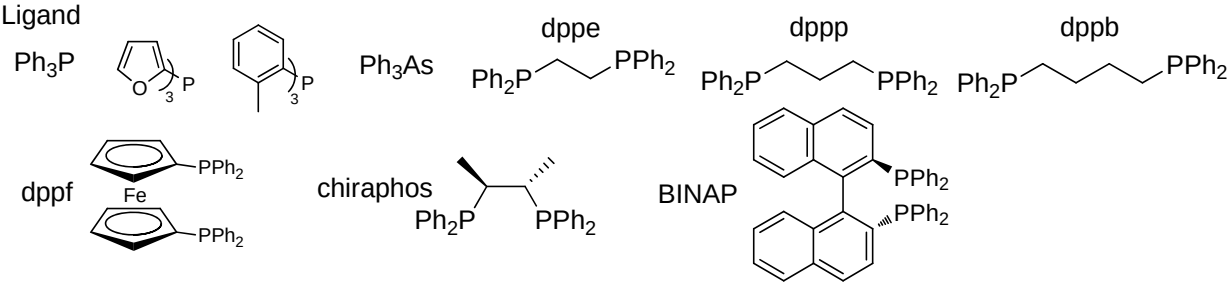
7.5.2.2. Coupling with stannanes

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

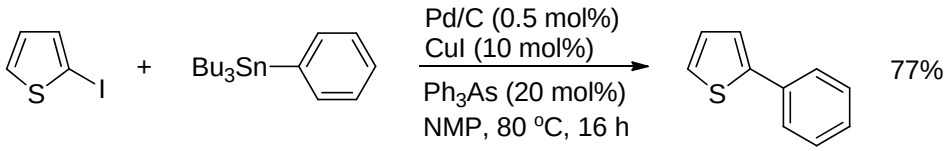
Group that can be transferred from tin:

alkynyl > alkenyl > aryl > methyl > alkyl

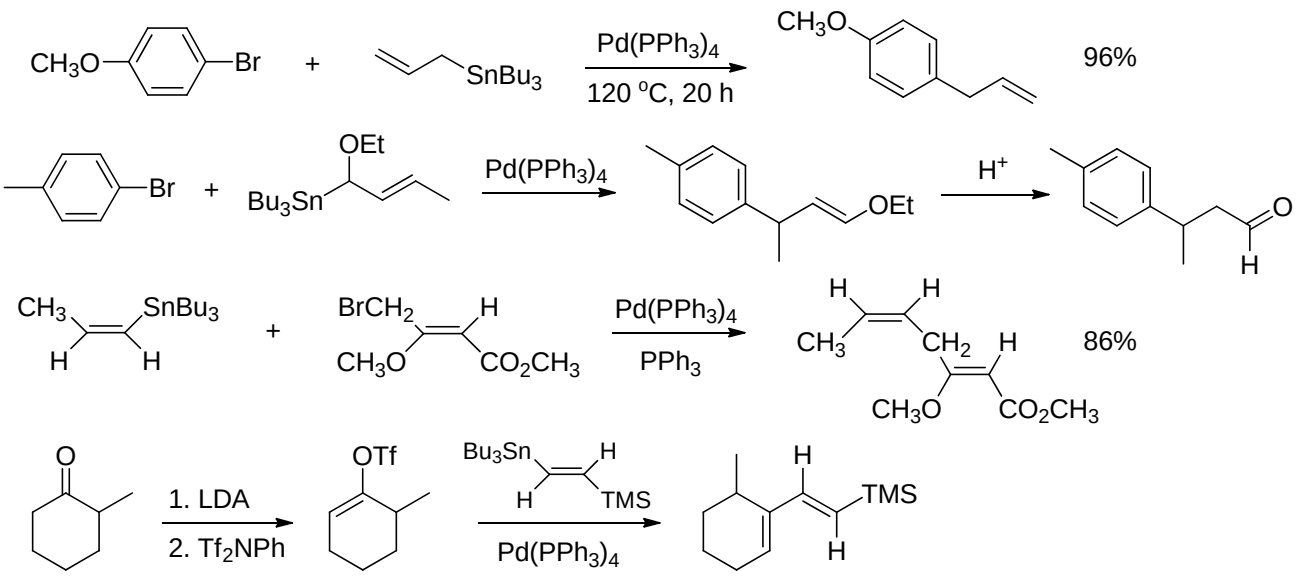
Ligand



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



Eaxamples



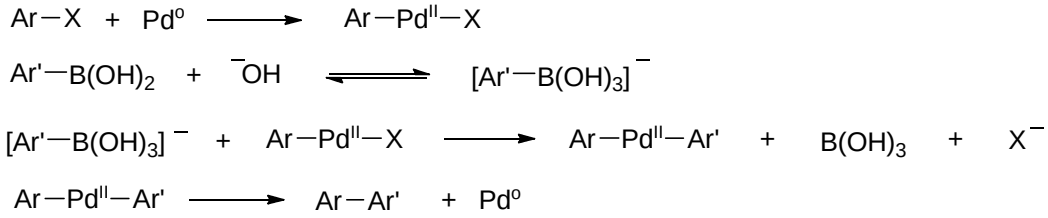
7.5.2.3. Coupling with organoboranes

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

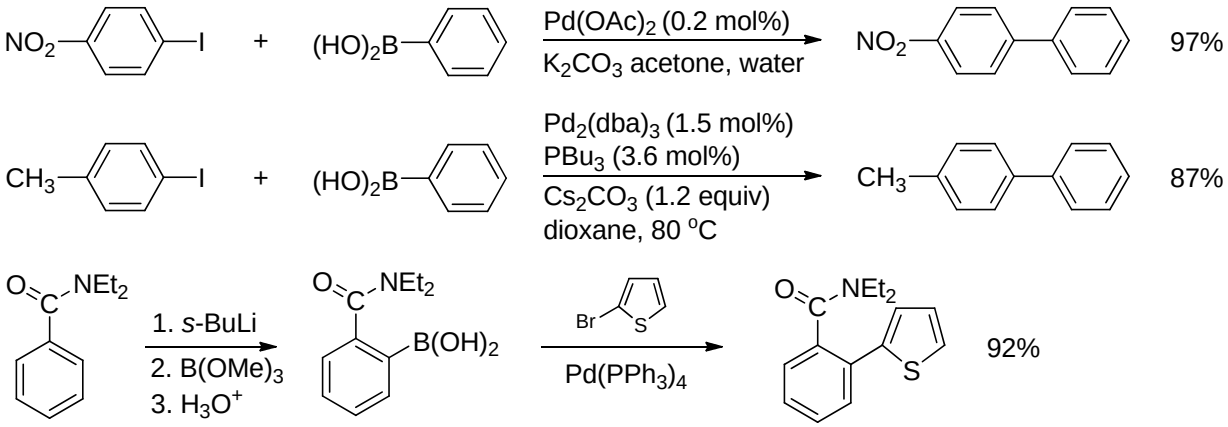
Base catalysis is required for boronic acids to generate more reactive boronate anion.



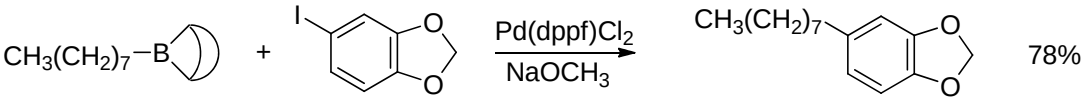
7.5.2. Palladium-catalyzed cross coupling reaction

7.5.2.3. Coupling with organoboranes

Eaxamples



Alkyl-aryl coupling using 9-BBN

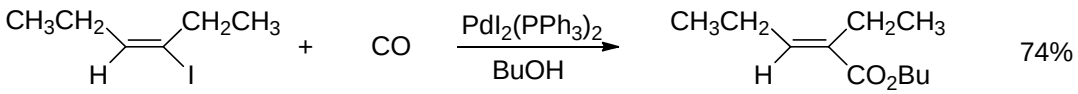


Bases

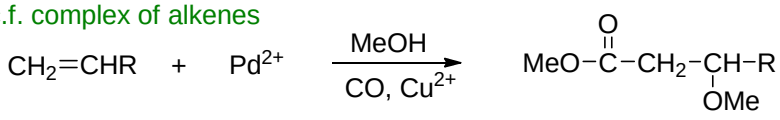
Cs_2CO_3 or TlOH > NaOH

7.5.2.4. Reaction with carbon monoxide (CO)

7.5.2.4.1. Reaction in ROH



c.f. complex of alkenes



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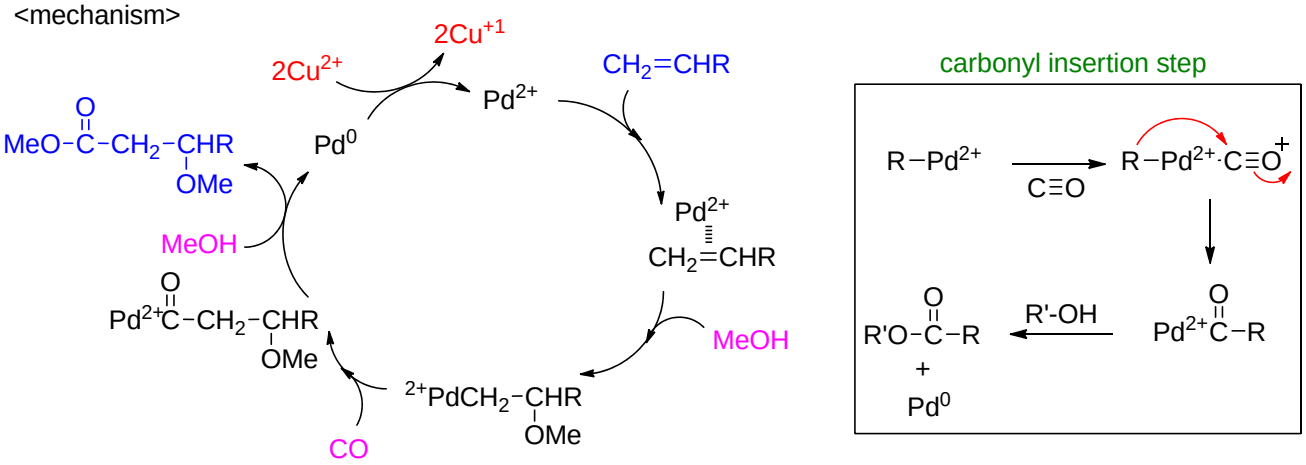
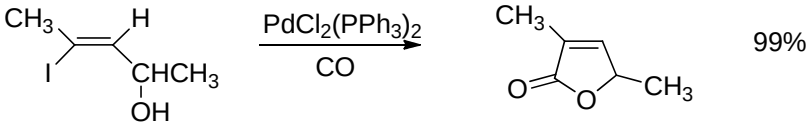


7.5.2. Palladium-catalyzed cross coupling reaction

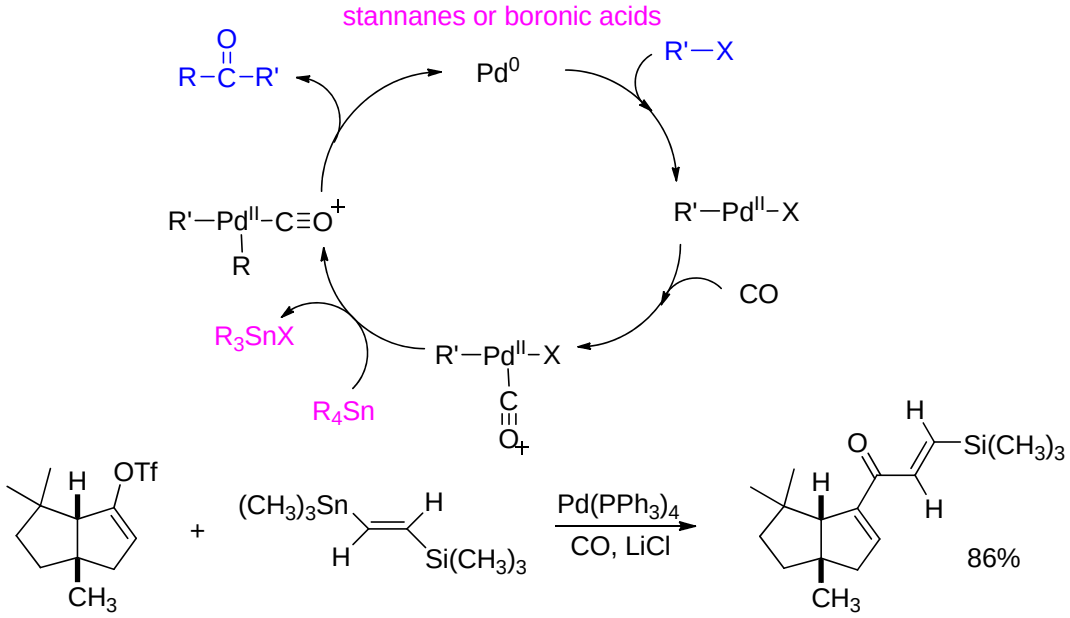
7.5.2.4. Reaction with carbon monoxide (CO)

7.5.2.4.1. Reaction in ROH

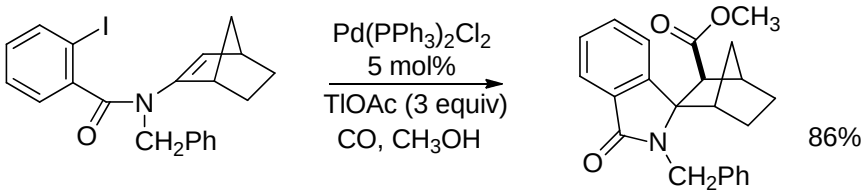
Intramolecular version



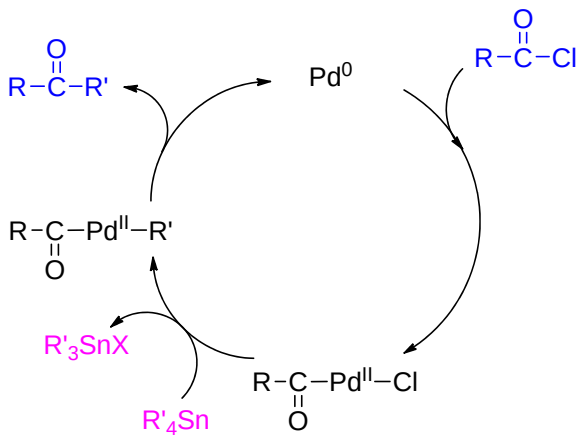
7.5.2.4.2. Coupling of organometallic reagents with aryl or vinyl halides



7.5.2.4.3. Tandem intramolecular Heck-carbonylation reaction

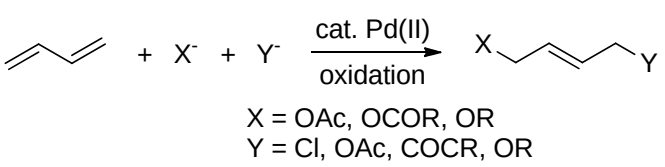


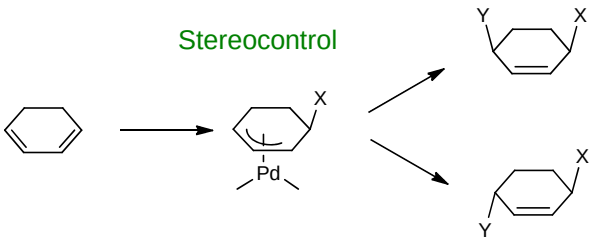
7.5.2.5. Coupling of organostannane with acyl chlorides

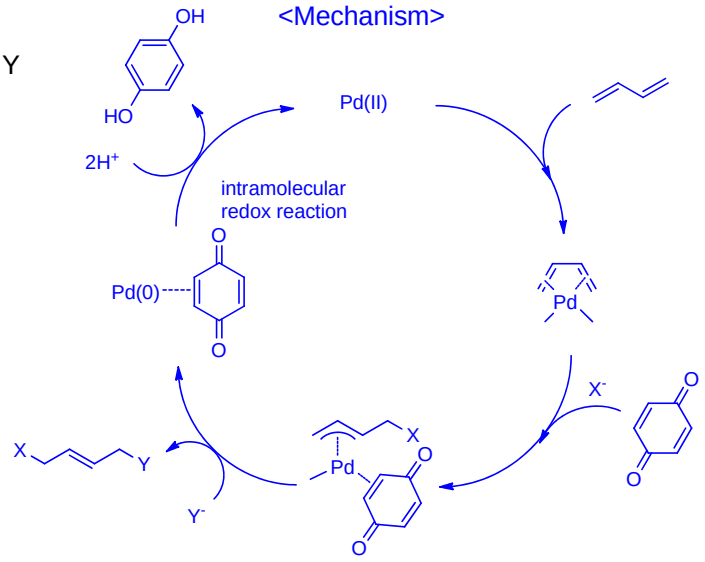


7.6. Synthetic Applications using Pd catalyst

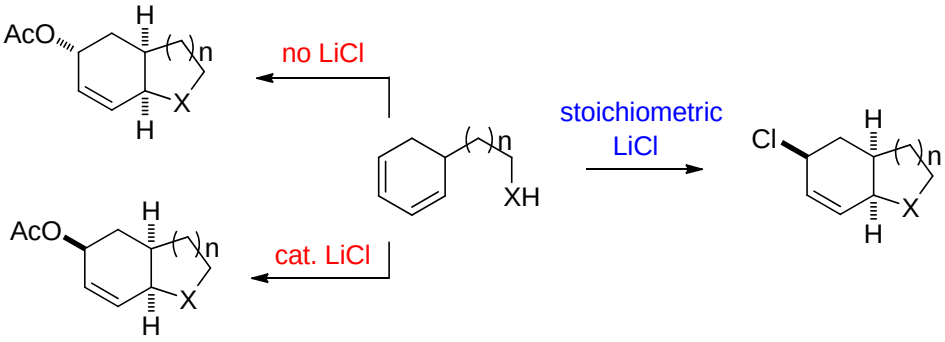
7.6.1. 1,4-Functionalization of 1,3-butadiene - Backvall, J. E.

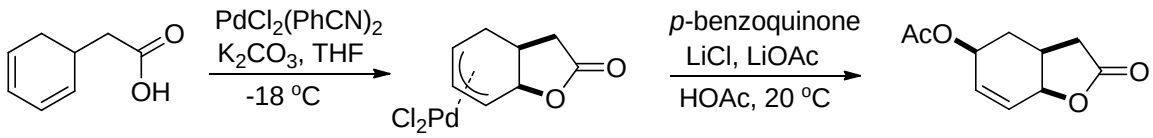


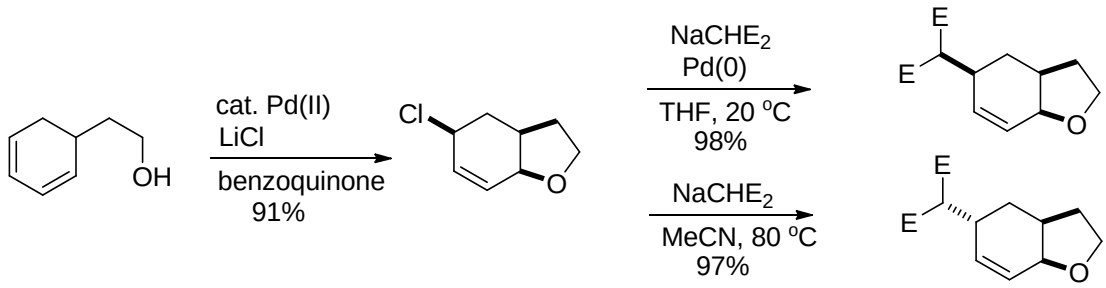


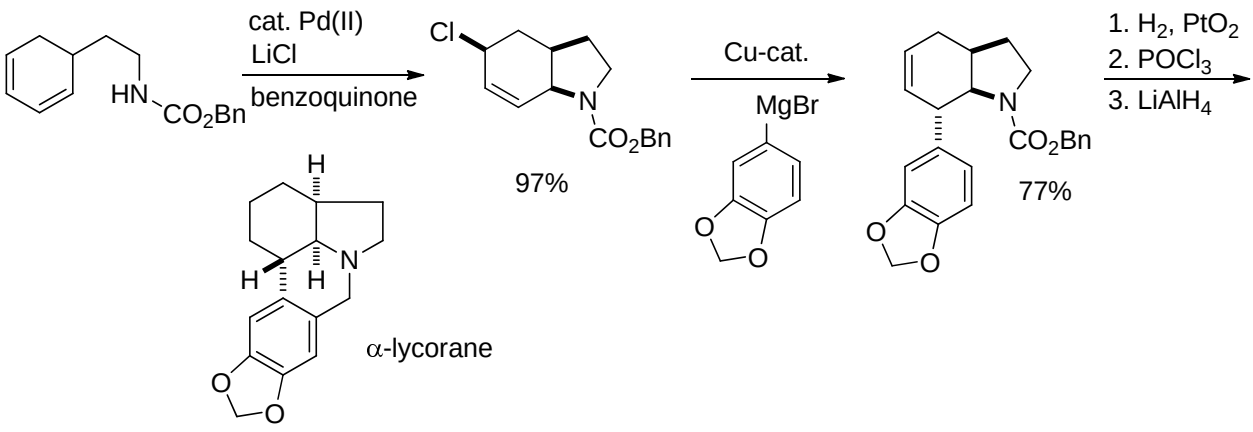


7.6.1.1. Heteroannulation



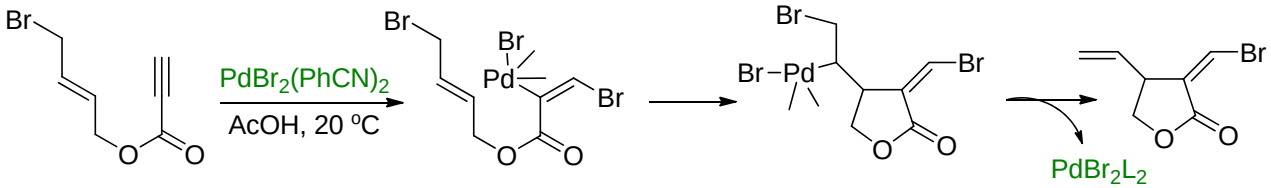


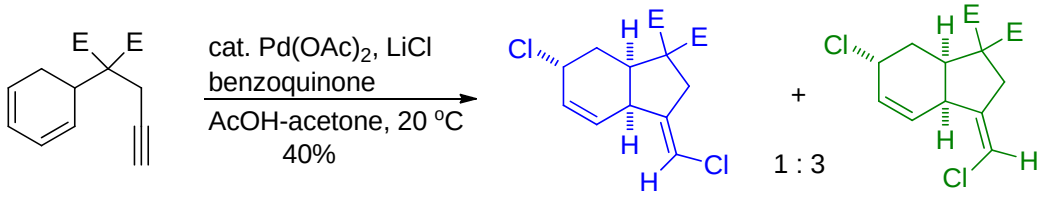




7.6.1.2. Carboannulation

Addition of vinylpalladium intermediate to olefins, which is formed by halopalladation of an acetylene





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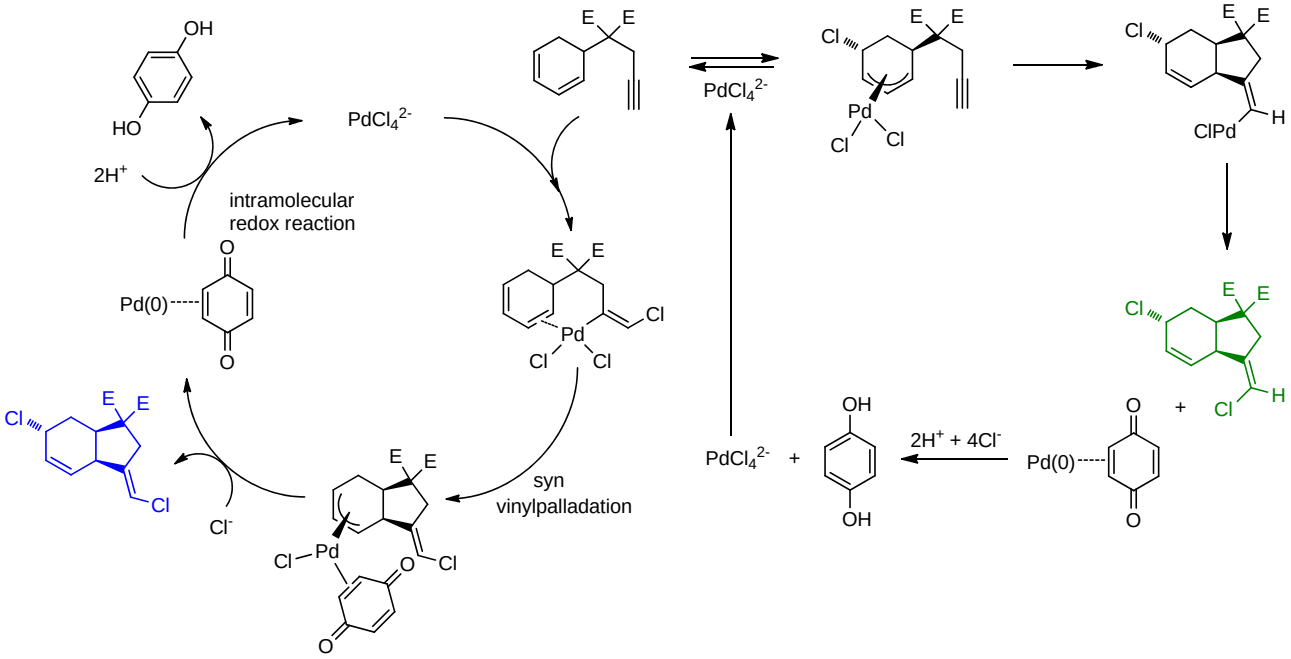
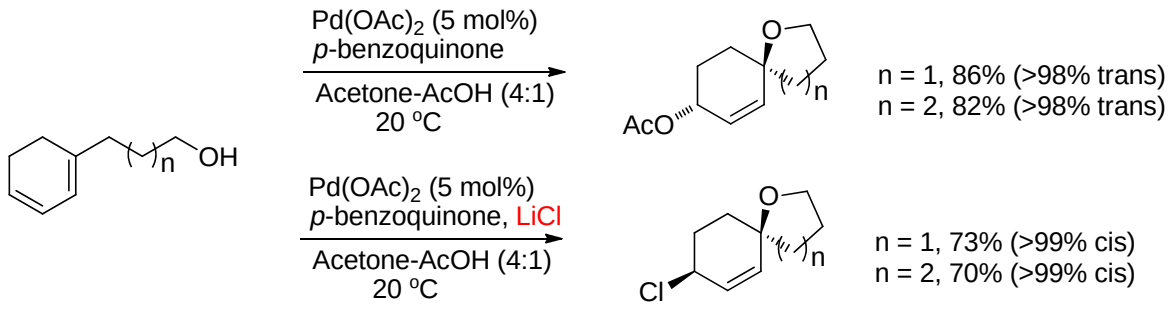
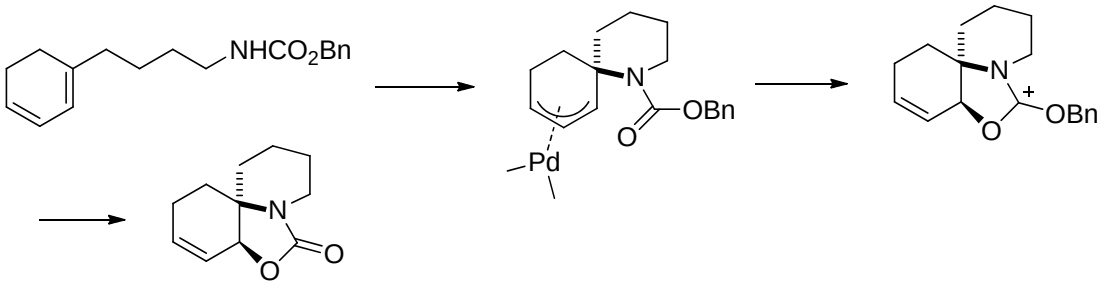
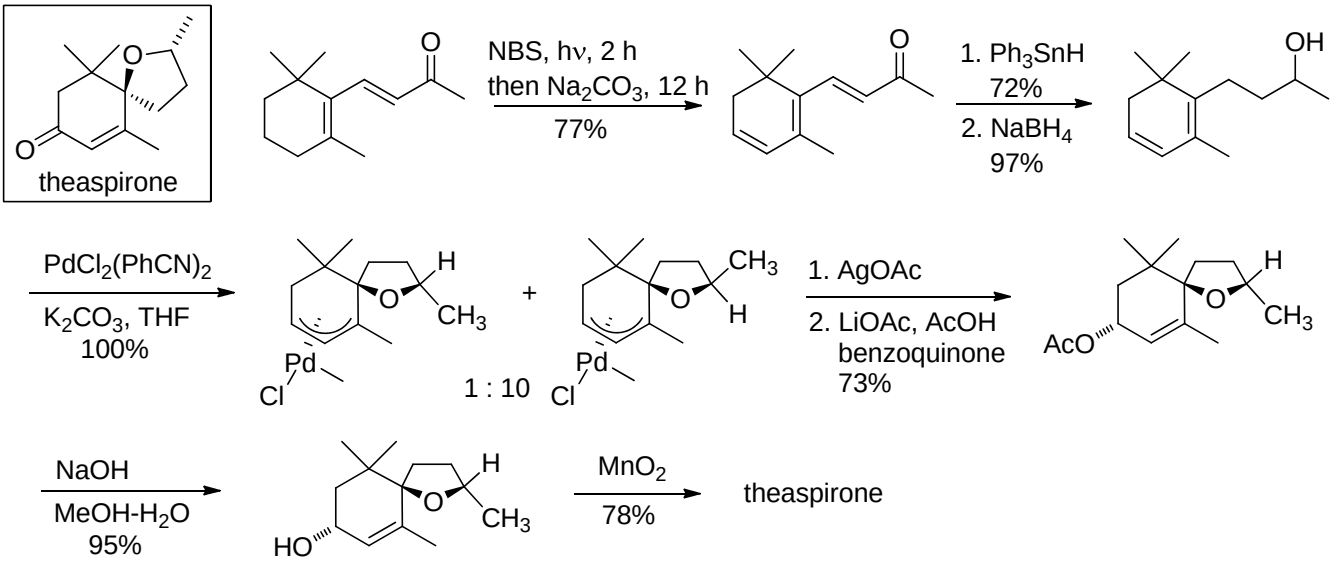


7.6.1.3. Spirocyclization



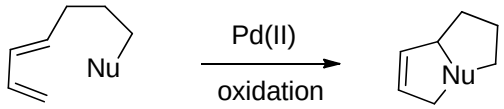


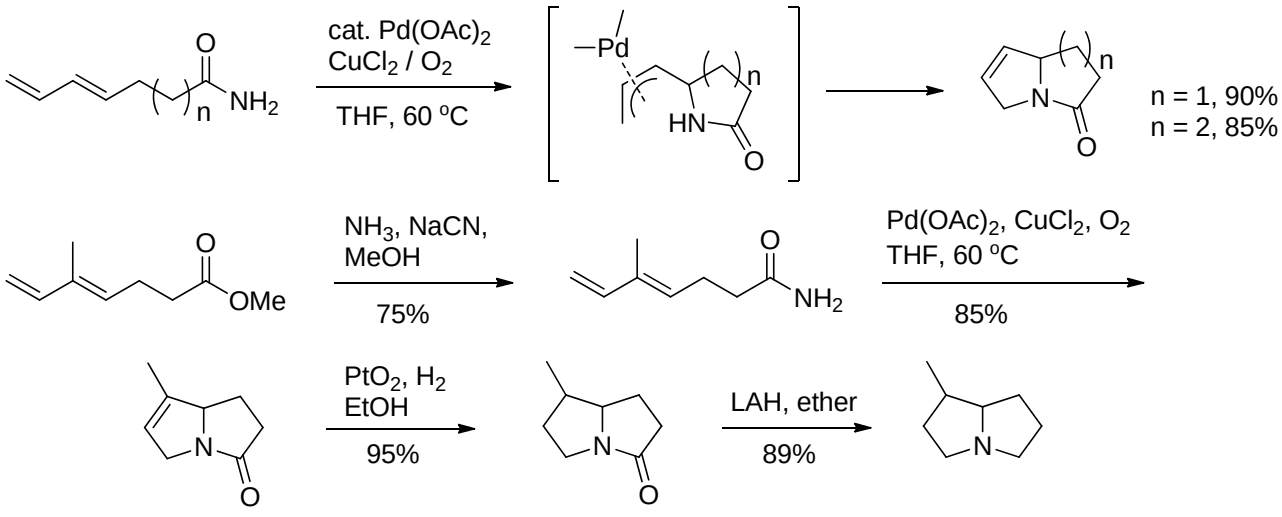
7.6.1.3. Spirocyclization



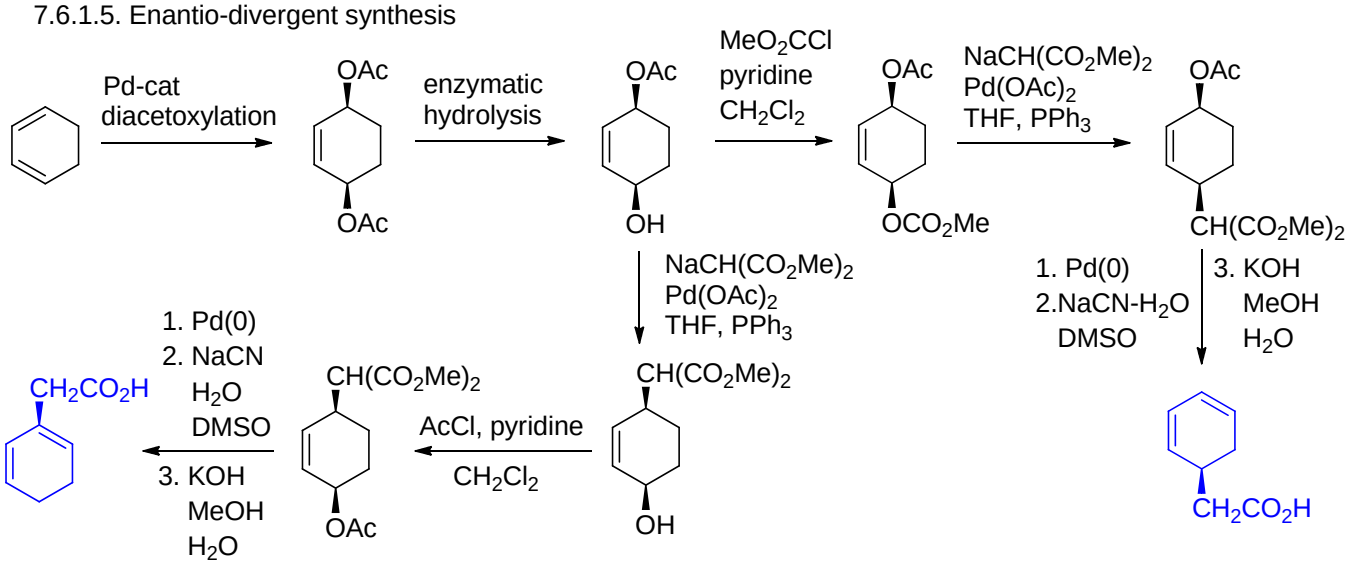
7.6.1.4. Tandem cyclization

[4+1] Cycloaddition
preparation of pyrrolizidine and indolizidine

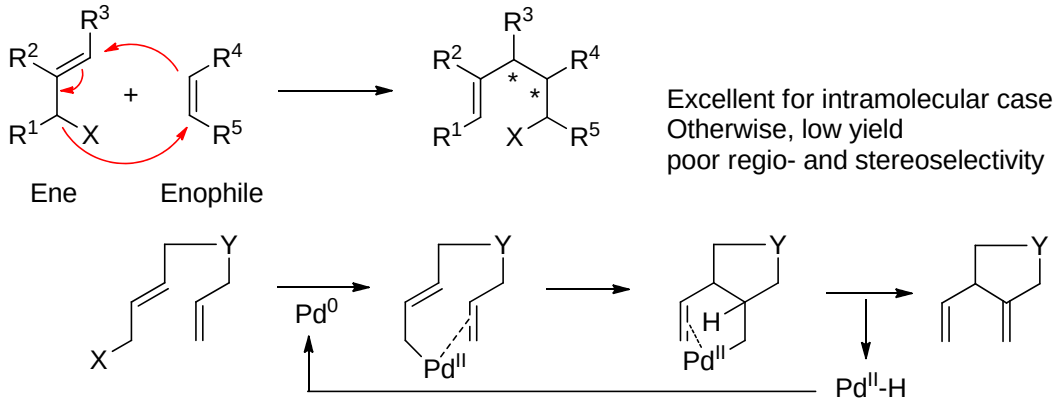




7.6.1.5. Enantio-divergent synthesis

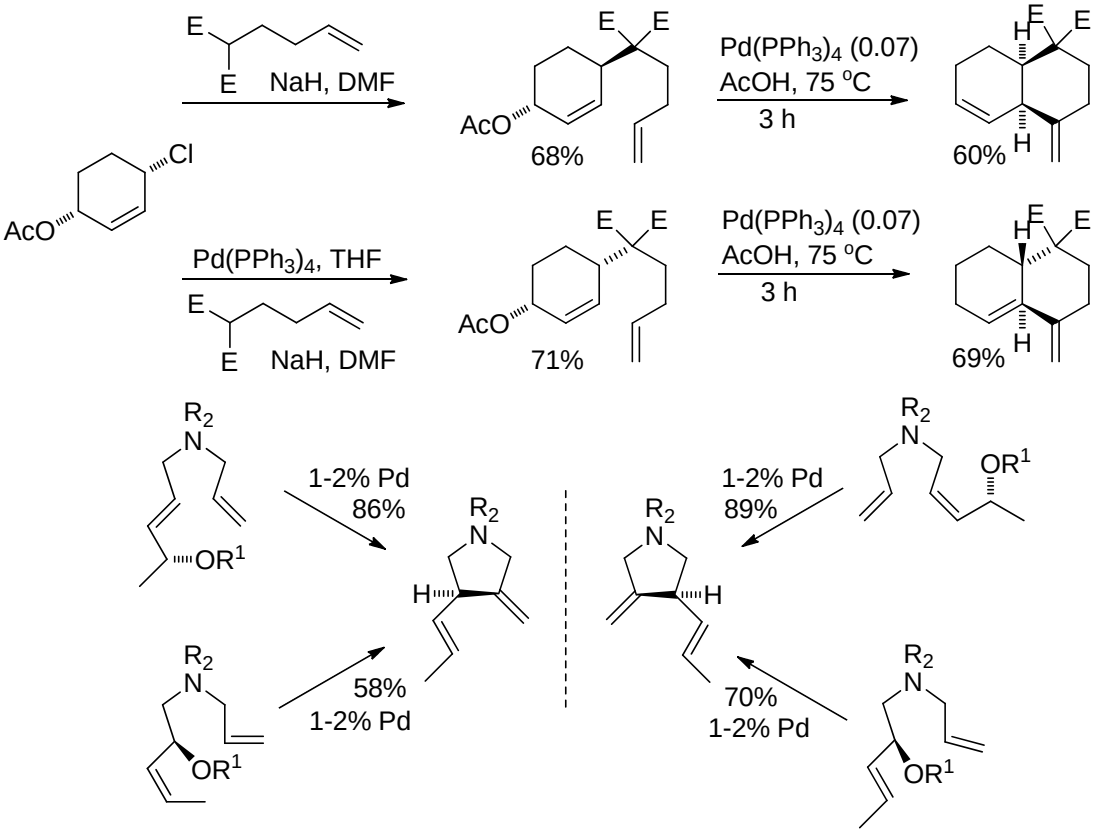


7.6.2. Palladium-catalyzed Metal-Ene type Cyclization



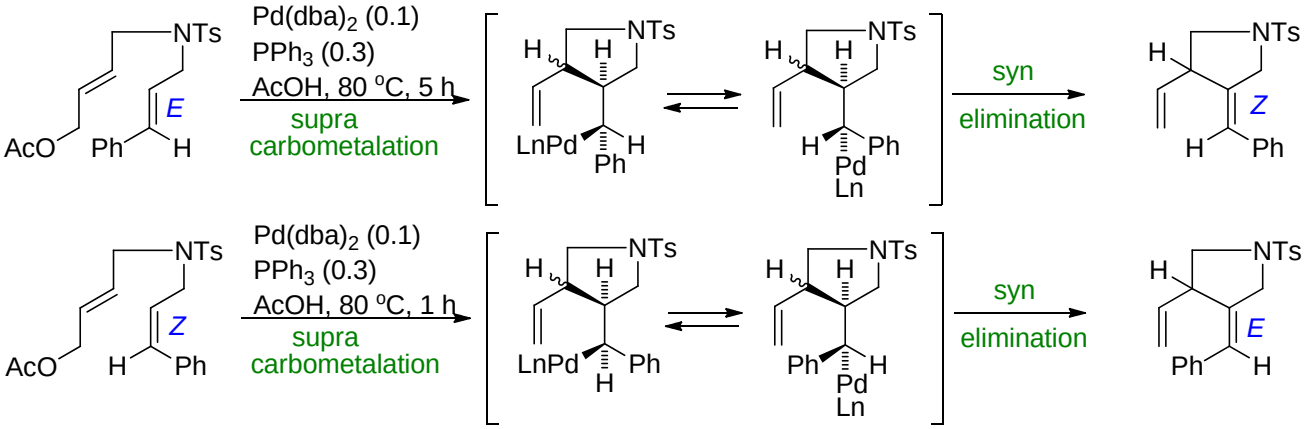
7.6.2.1. Allylmetal-alkene cyclization/β-elimination

7.6.2.1.1. Allyl Faciality

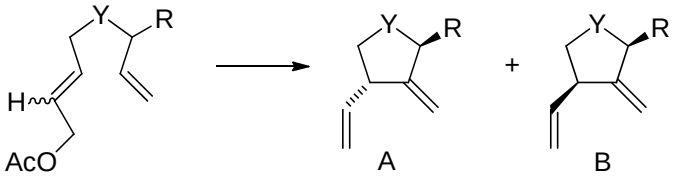


E-dienyl acetate - inversion at the allylic center; retention of the olefinic configuration
Z-dienyl acetate - retention at the allylic center; *Z*-*E* isomerization

7.6.2.1.2. Alkene Faciality



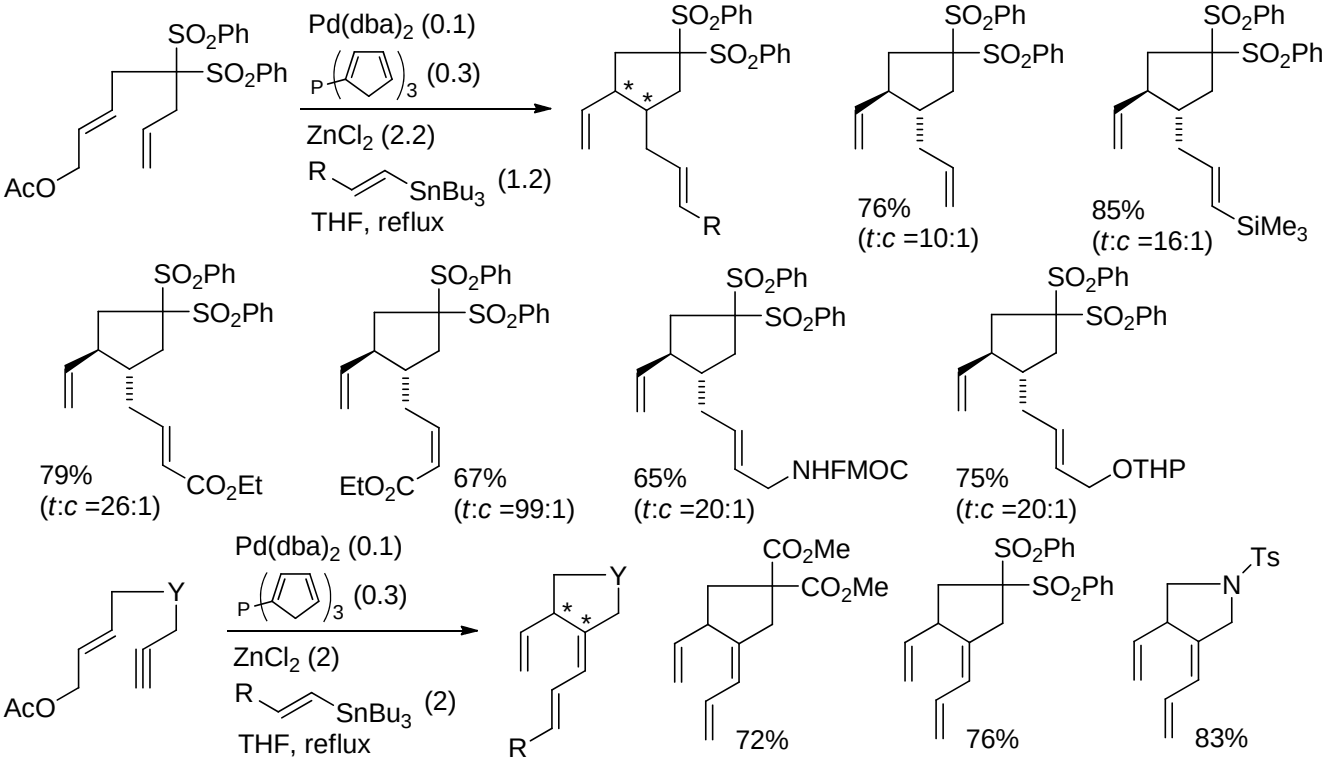
7.6.2.1.3. Resident Stereocenters



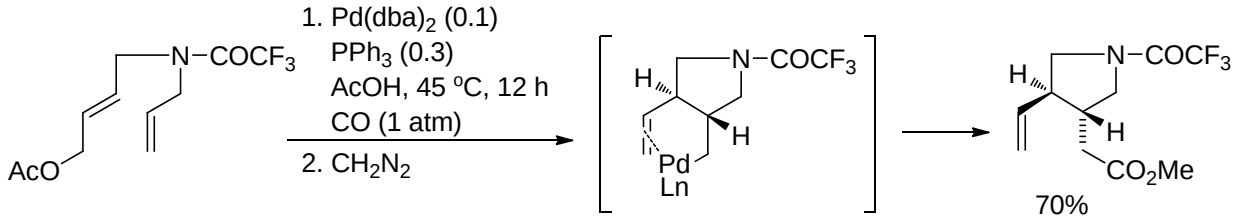
Y	R	Cat (%)	Yield	A:B
O	n-Hex	Pd (5)	62	52:48
O	n-Hex	Ni (10)	79	99:1
CH_2	CH_2OBn	Pd (10)	67	72:28
CH_2	CH_2OBn	Ni (10)	88	97:3

Pd: $Pd(dba)_2$:PPh_3 (1:3), AcOH, 80 °C
Ni: $Ni(COD)_2$:dppb (1:1), THF, 20-50 °C

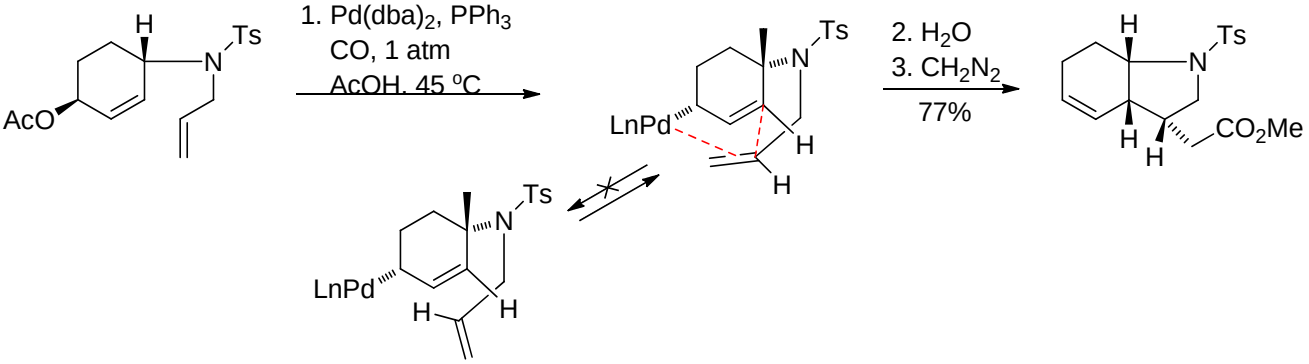
7.6.2.2. Allylpalladium-alkene cyclization / alkenylstannane coupling



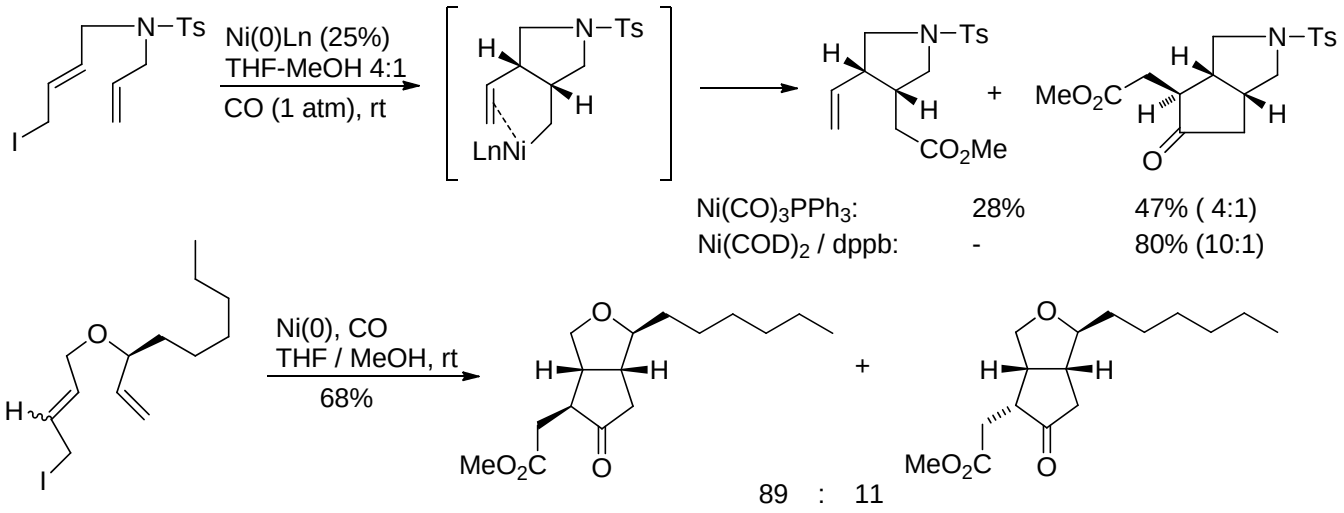
7.6.2.3. Allylmetal-alkene cyclization / carbonylation



Pd(0) catalysis: Endo diastereoselectivity → trans
Ni(0) catalysis: Exo diastereoselectivity → cis

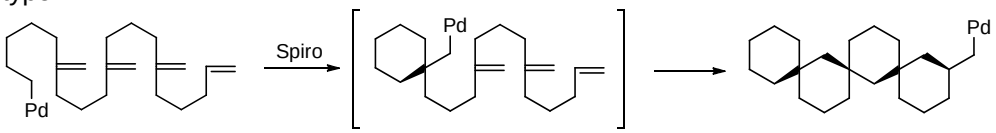


7.6.2.4. Allylmetal-alkene cyclization / carbonylation - Ni(0)-catalyzed case

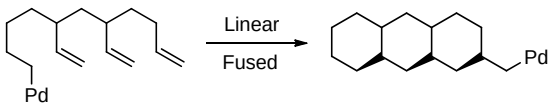


7.6.3. Palladium-catalyzed polyene cyclization

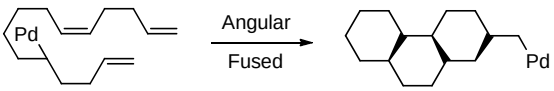
type-1



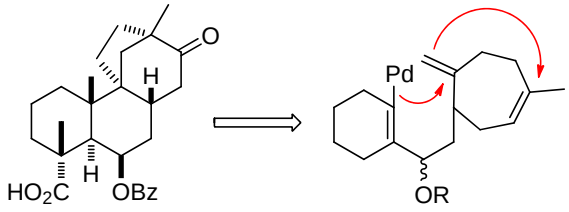
type-2



type-3

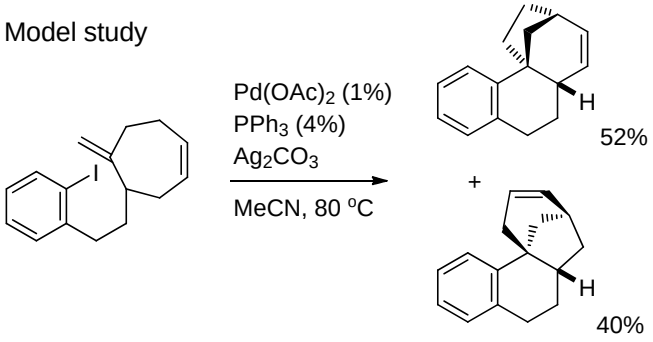


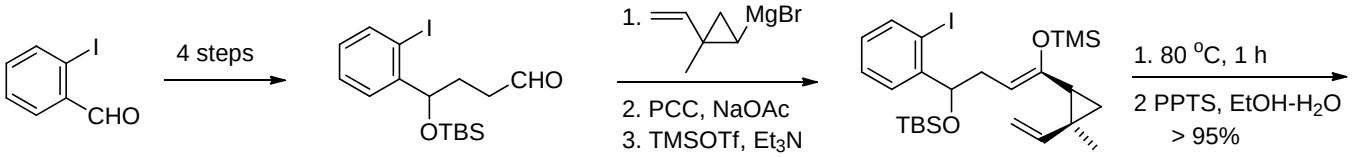
Total synthesis of Scopadulcic acid B

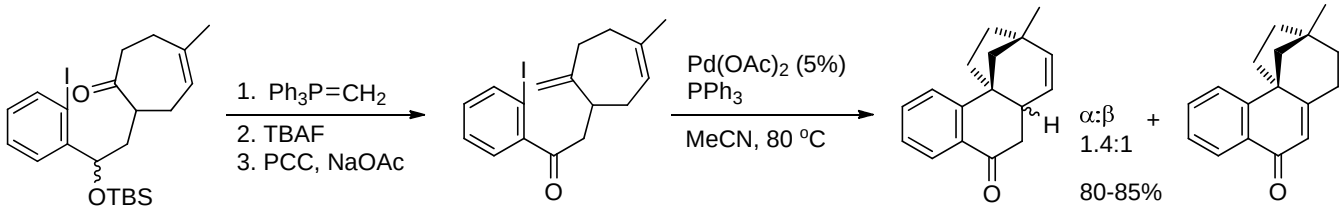


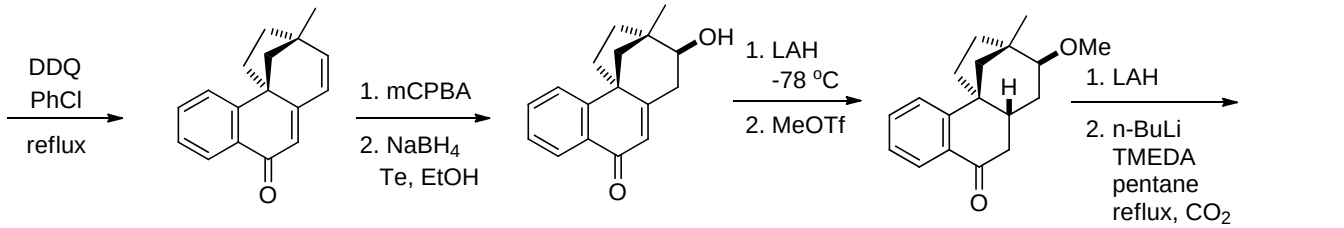
Scopadulcic acid B

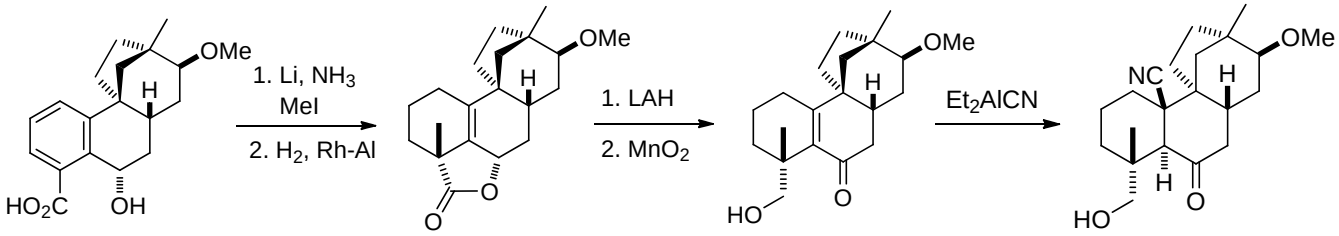
Model study

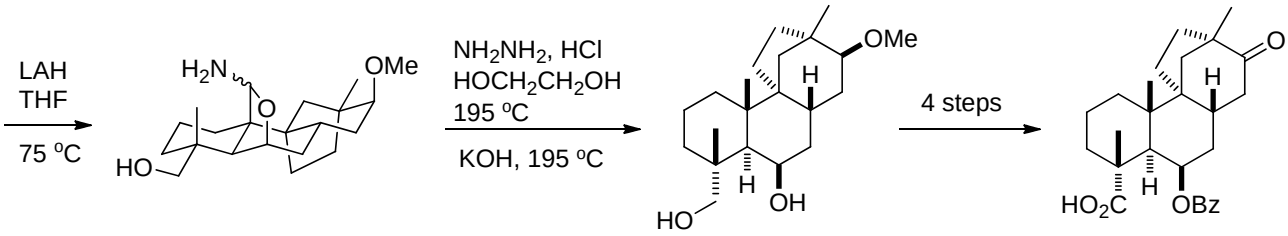




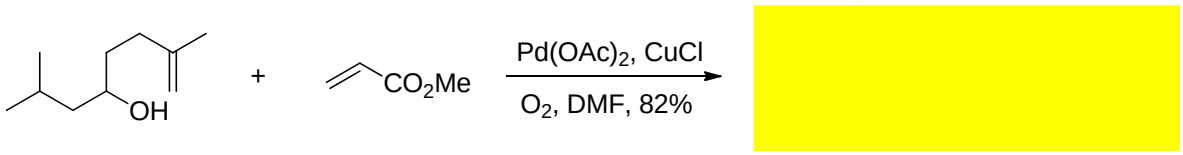




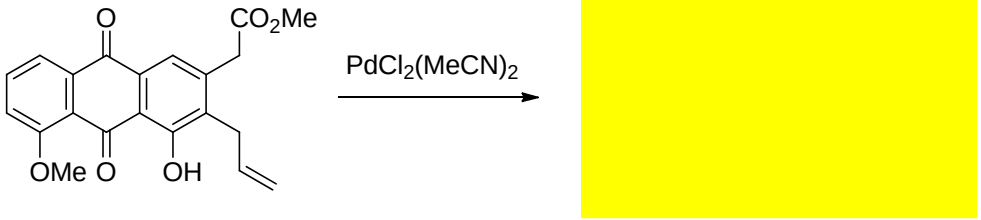




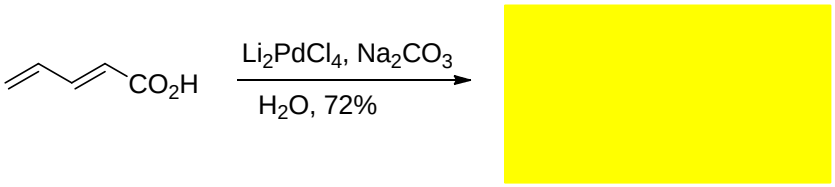
(1)


OH
+
CO2Me
Pd(OAc)2, CuCl
O2, DMF, 82%

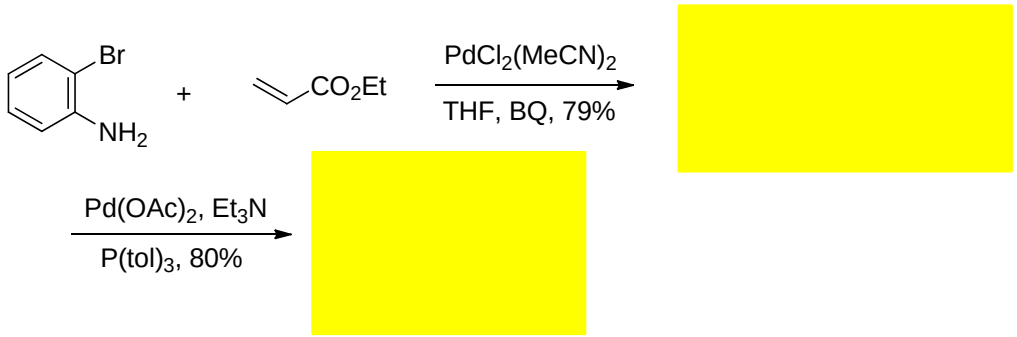
(2)


O
CO2Me
OMe
O
OH
PdCl2(MeCN)2

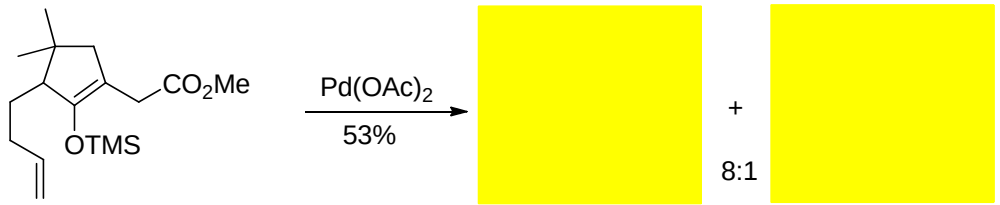
(3)


CO2H
Li2PdCl4, Na2CO3
H2O, 72%

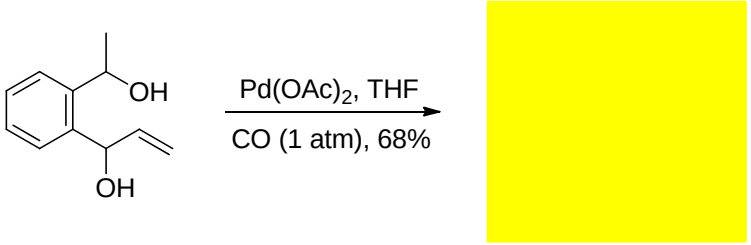
(4)


Br
NH2
+
CO2Et
PdCl2(MeCN)2
THF, BQ, 79%
Pd(OAc)2, Et3N
P(tol)3, 80%

(5)


CO2Me
OTMS
Pd(OAc)2
53%
+
8:1

(6)


OH
OH
Pd(OAc)2, THF
CO (1 atm), 68%