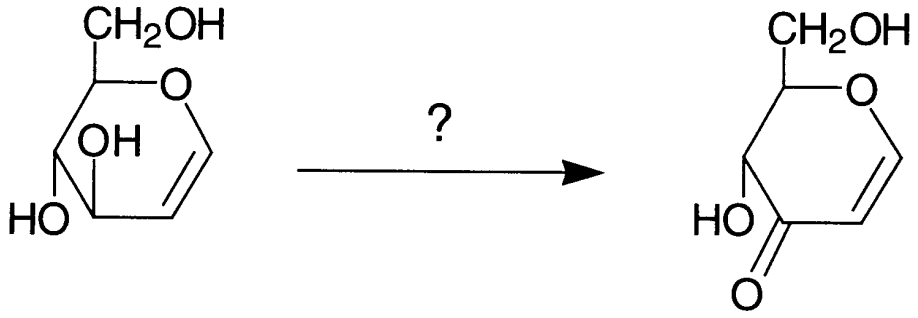
Chapter 4.

Functional Group Transformations: Oxidation and Reduction

Chapter 4. Functional Group Transformations: Oxidation and Reduction

4.1 Oxidation of Alcohols to aldehyde and Ketones



Classical oxidation is using chromium(VI) reagent.

Oxidation of primary alcohol to aldehyde requires anhydrous conditions.

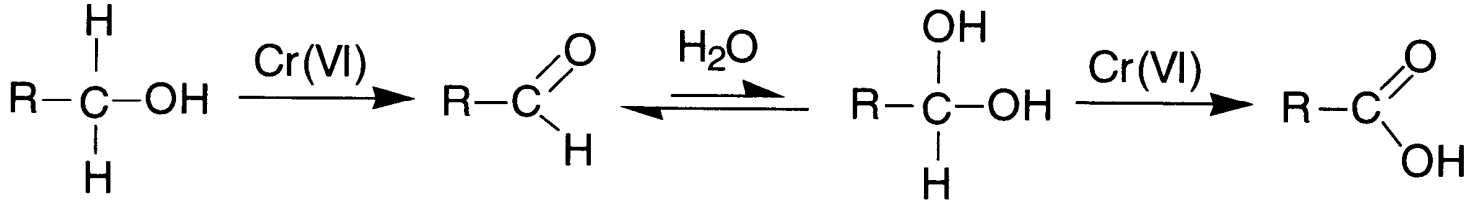
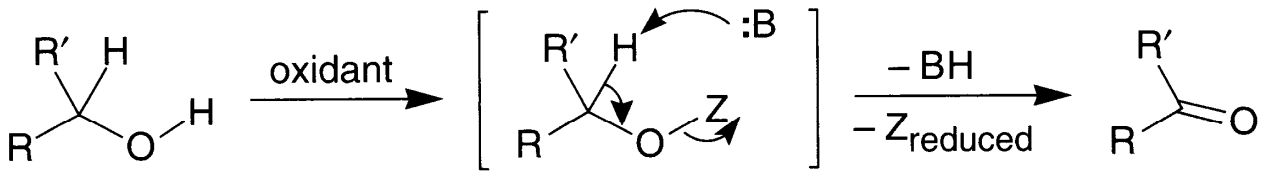
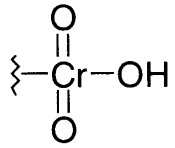
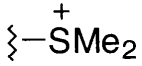
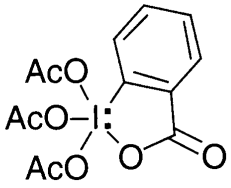
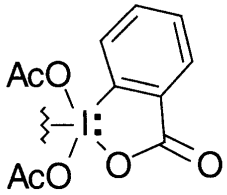
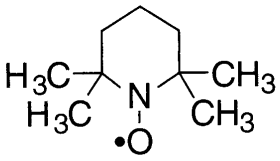
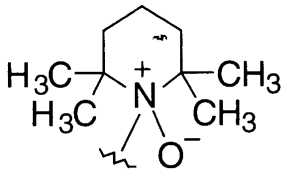
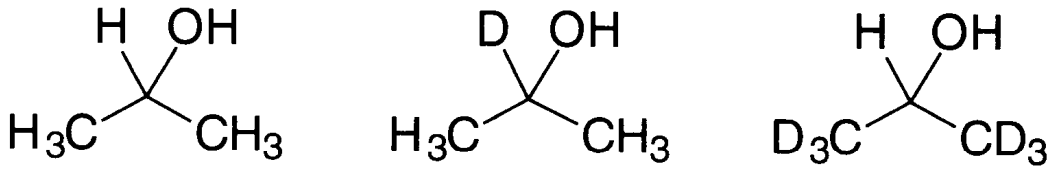


Table 4.1 Methods for Alcohol Oxidation



Name	Reagents	Z
Jones	CrO_3, H_2SO_4, H_2O	
Swern	DMSO, oxalyl chloride	
Dess–Martin		
TEMPO	 NaOCl, NaBr	

The E2-like process is supported by the observation that deuterium substitution of the a-H in isopropanol slows the rate of chromic acid oxidation by seven fold.



Relative rate of oxidation with H_2CrO_4	1.0	0.16	1.0

Since C-D bonds are broken more slowly than C-H bond, these results suggest that the a-H is removed in a slow step.

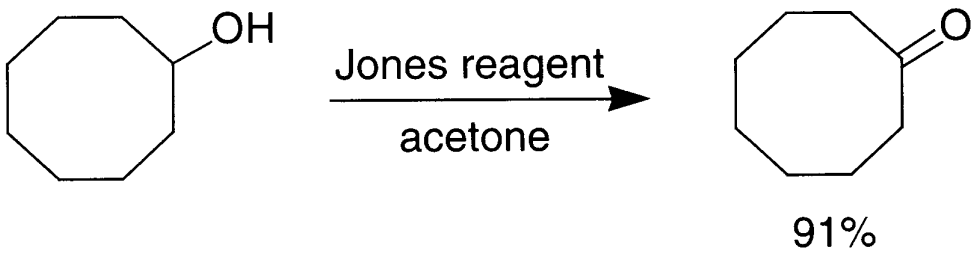
4.2 Reagents and Procedure for Alcohol Oxidation

Jones reagent

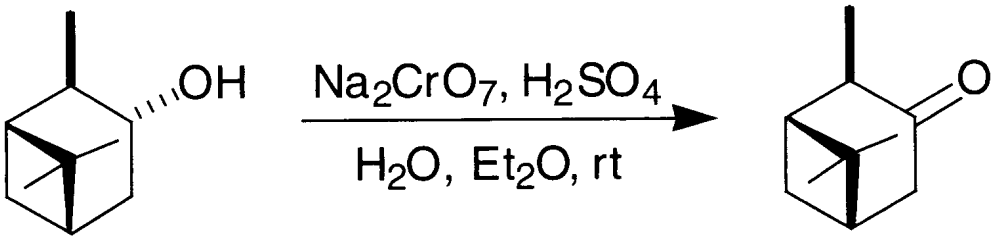
$$CrO_3 + H_2SO_4 + H_2O + \text{acetone}$$

or $$Na_2Cr_2O_7 + H_2SO_4 + H_2O + \text{acetone}$$

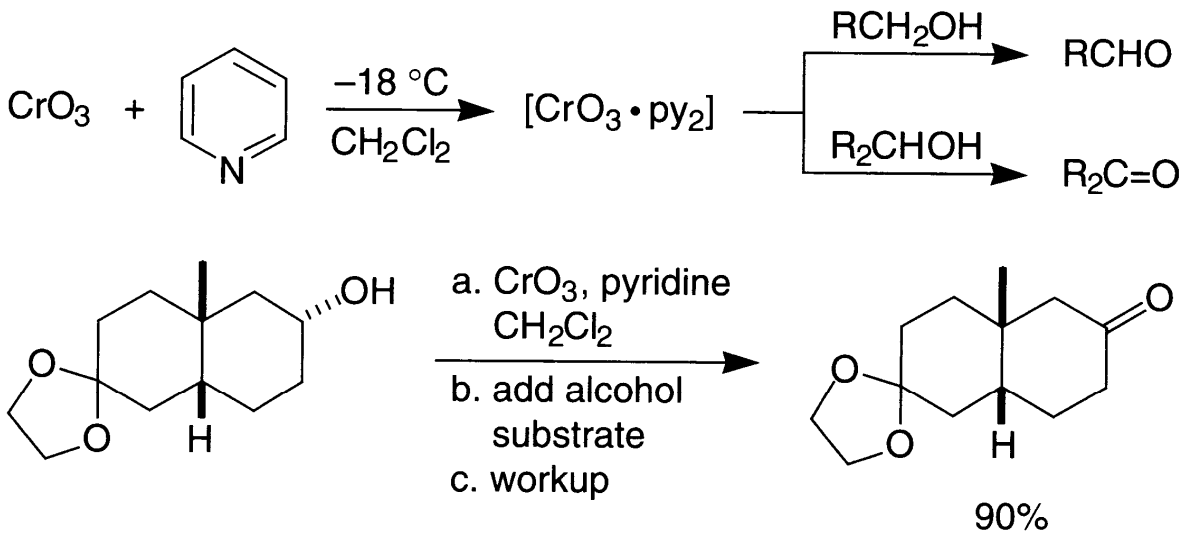
Excellent reagent for the oxidation of secondary alcohol that do not contain acid-sensitive groups such as acetals.
Primary alcohol can be converted into carboxylic acid by oxidation of initially formed aldehyde followed by further oxidation.
Excess Cr(VI) is destroyed in the reaction workup by adding some isopropyl alcohol (color change from orange to blue green)



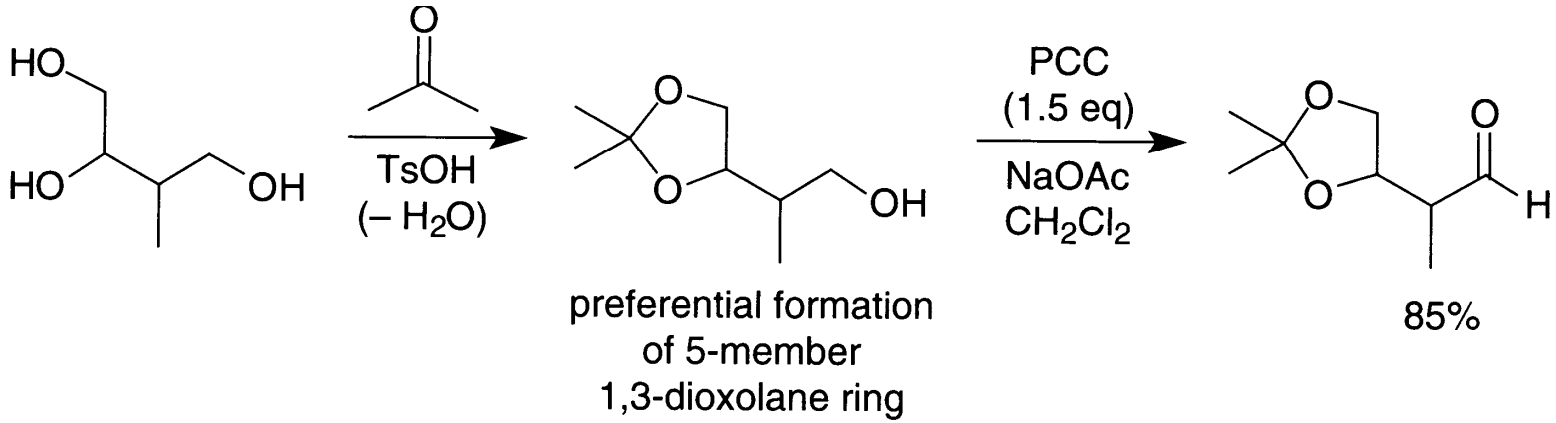
The reaction can be performed even in the presence of water.



Collins-Ratcliff reagent: mild reagent for the oxidation of alcohols that contain acid sensitive groups.

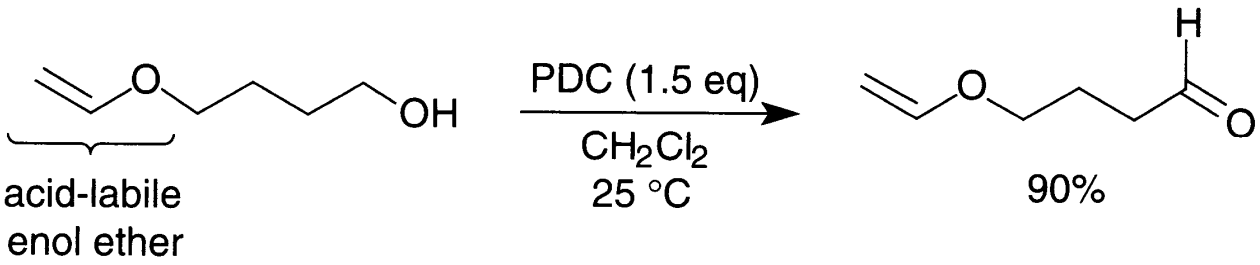


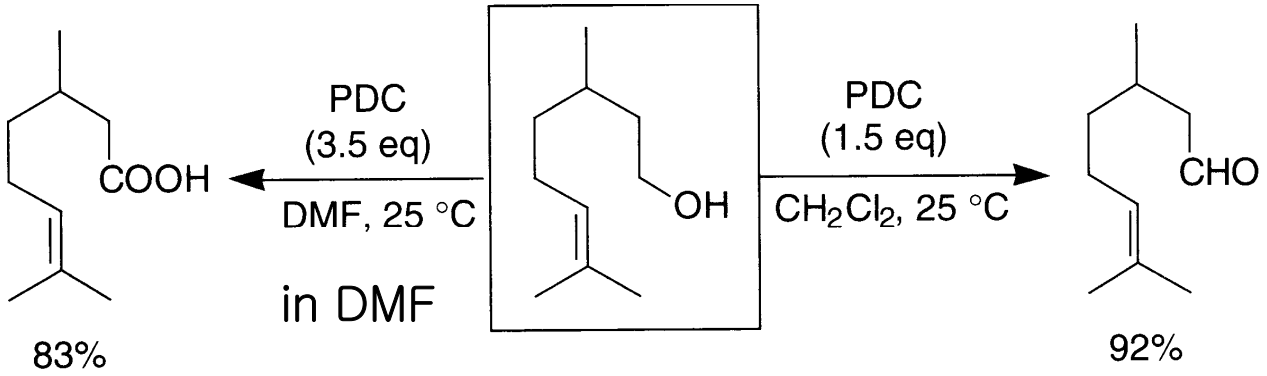
Pyridinium Chlorochromate (PCC)



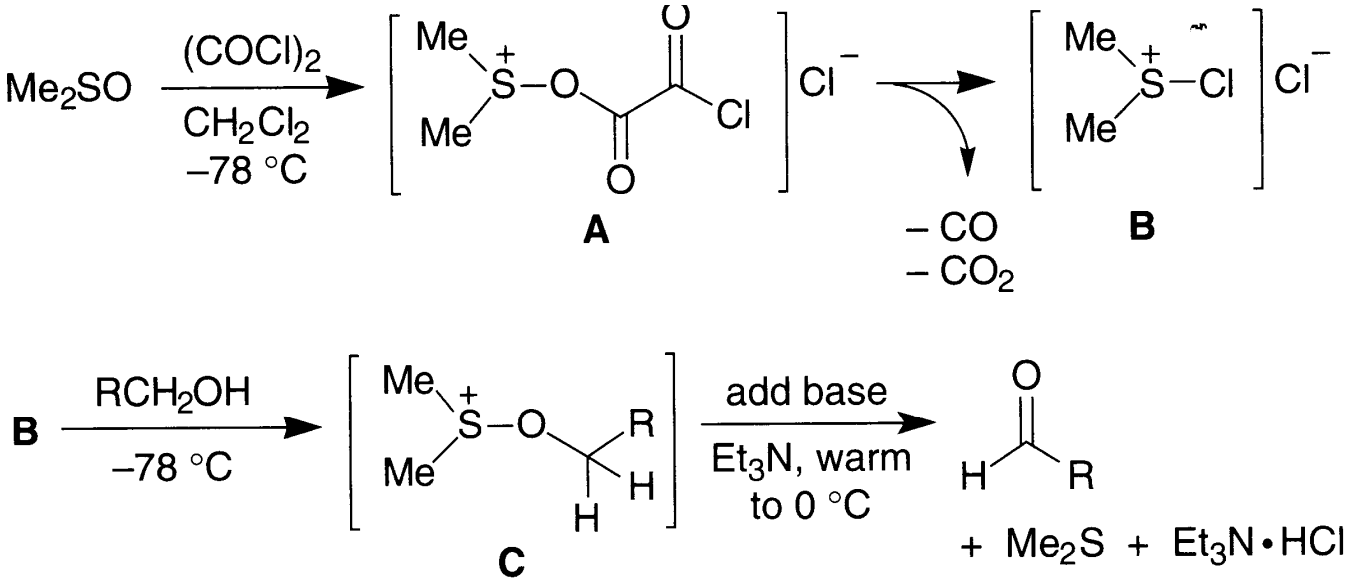
If alcohol contains acid sensitive group, powerded NaOAc is added.

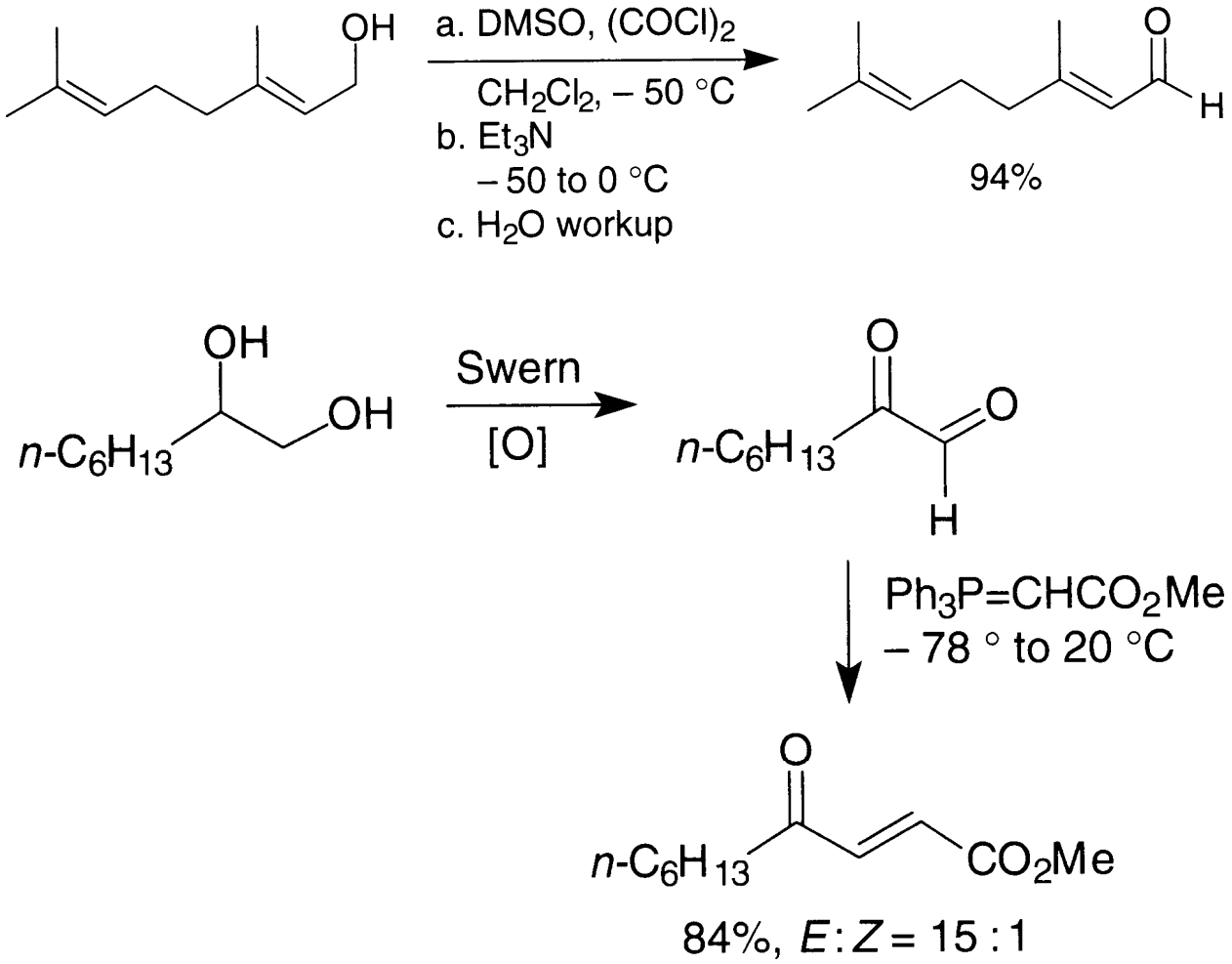
Pyridinium Dichromate (PDC): the reaction can be carried out at neutral conditions.



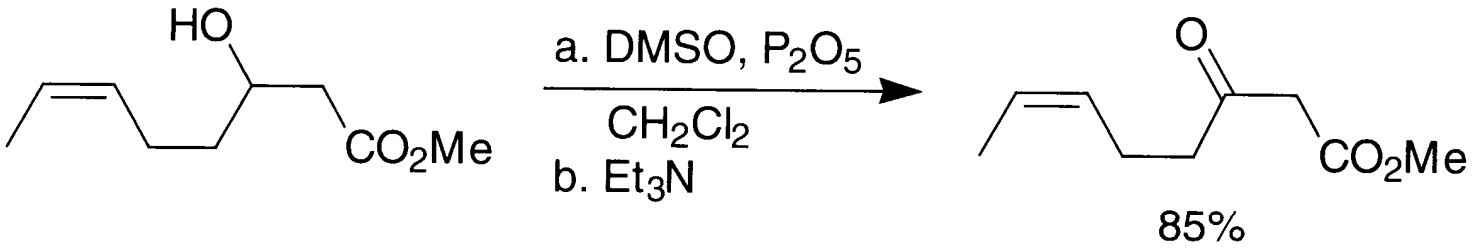


Swern Oxidation:

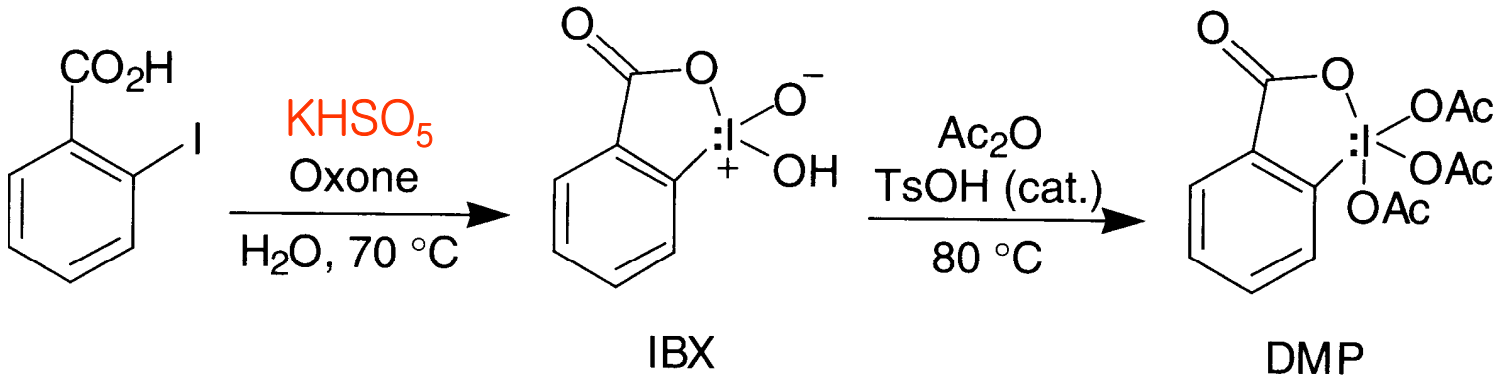




If formation of chlorinated side products is a problem, the Swern oxidation can be performed with DMSO, P_2O_5, and Et_3N.



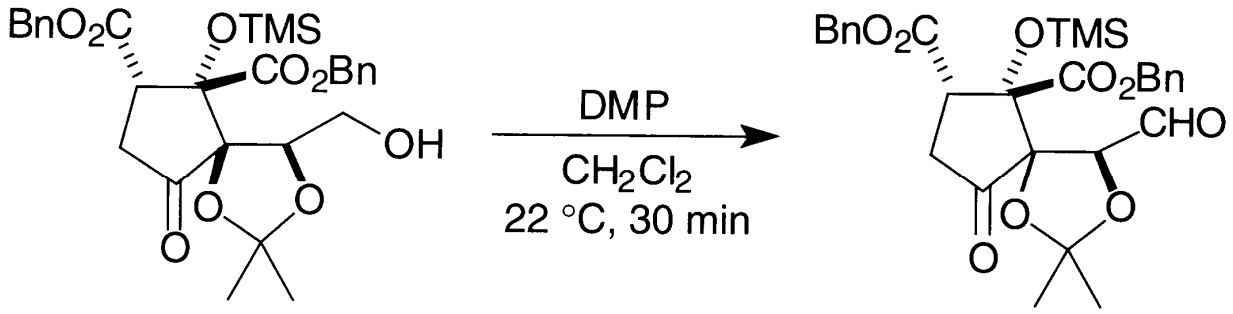
Dess-Martin Periodinane (DMP) Oxidation



Oxidation of 2-iodobenzoic acid with Oxone ($2KHSO_3$-$KHSO_4$-K_2SO_4) furnishes the oxidizing agent o-iodoxybenzoic acid, IBX, a periodinane.

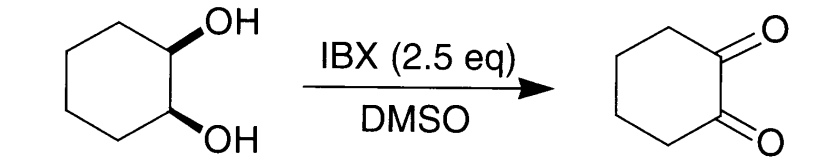
IBX is explosive when heated >130°C. Acetylation of IBX with Ac_2O in the presence of a catalytic amount of TsOH produces the Dess-Martin periodinane, DMP.

This reaction is suitable for multifunctional substrates containing acid-sensitive groups.

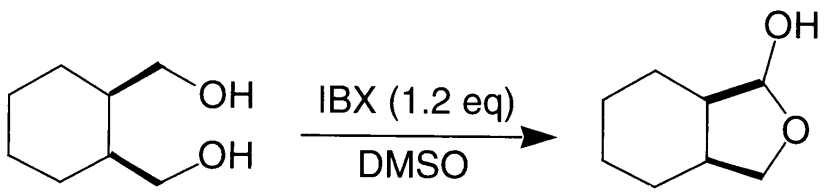


93%

Merits compared with Cr(VI)- and DMSO based oxidants
1) relative easy preparation, 2) short reaction time, 3) simplified work-ups
4) lower toxicity

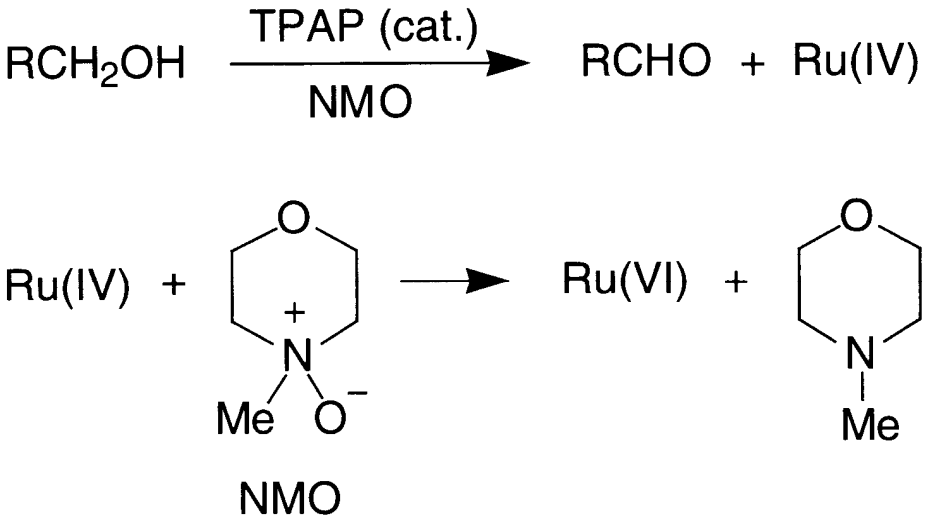


81%

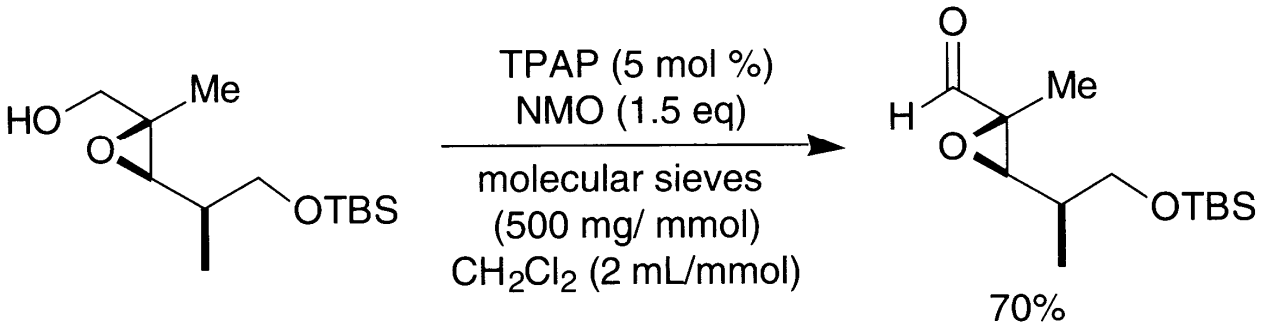


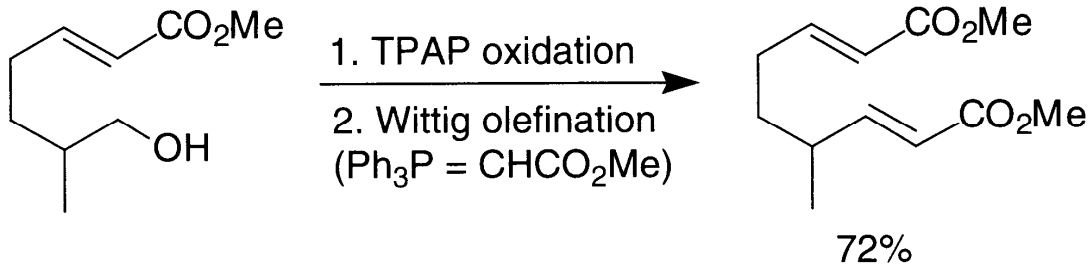
88%

Tetrapropylammonium Perruthenate (TPAP)



TPAP tolerates a wide variety of functional groups, including double bonds, enones, halides, epoxides, esters, and lactones. Protecting groups, such as MEM, trityl, silyl and benzyl ethers, THP and acetals, are not affected.

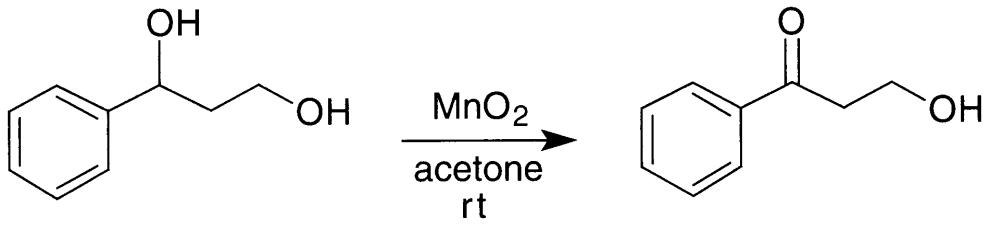




4.3 Chemoselective agents for oxidizing alcohols

MnO_2 is a highly chemoselective oxidant–allylic, benzylic, and propargyl alcohols are oxidized faster than saturated alcohols.
Solvent: H_2O, acetone, or $CHCl_3$.

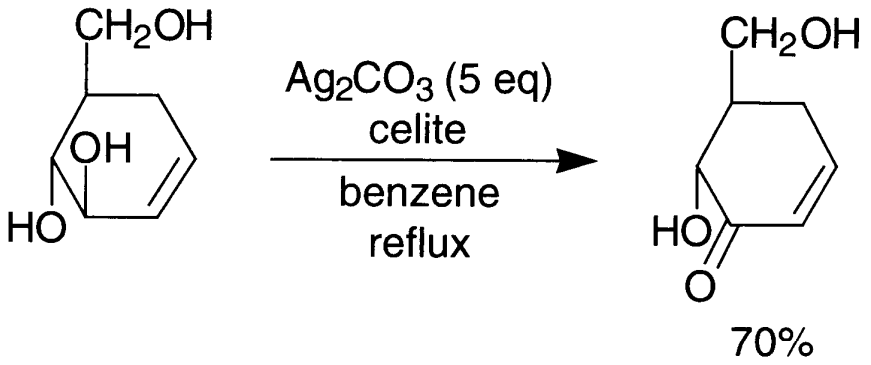
Low reactivity: use large amount of oxidant



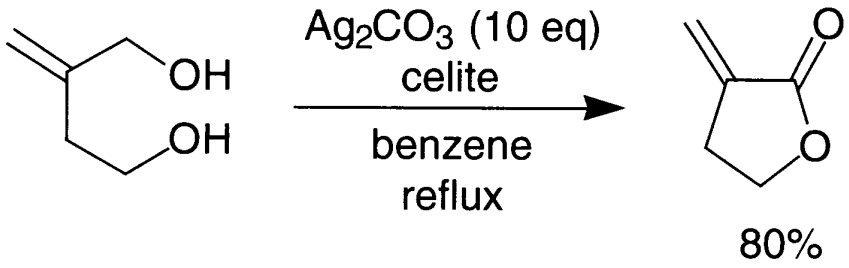
Silver Carbonate on Celite

The ease oxidation follows: allylic, benzylic-OH>2° ROH> 1° ROH

Highly hindered alcohol is not oxidized.



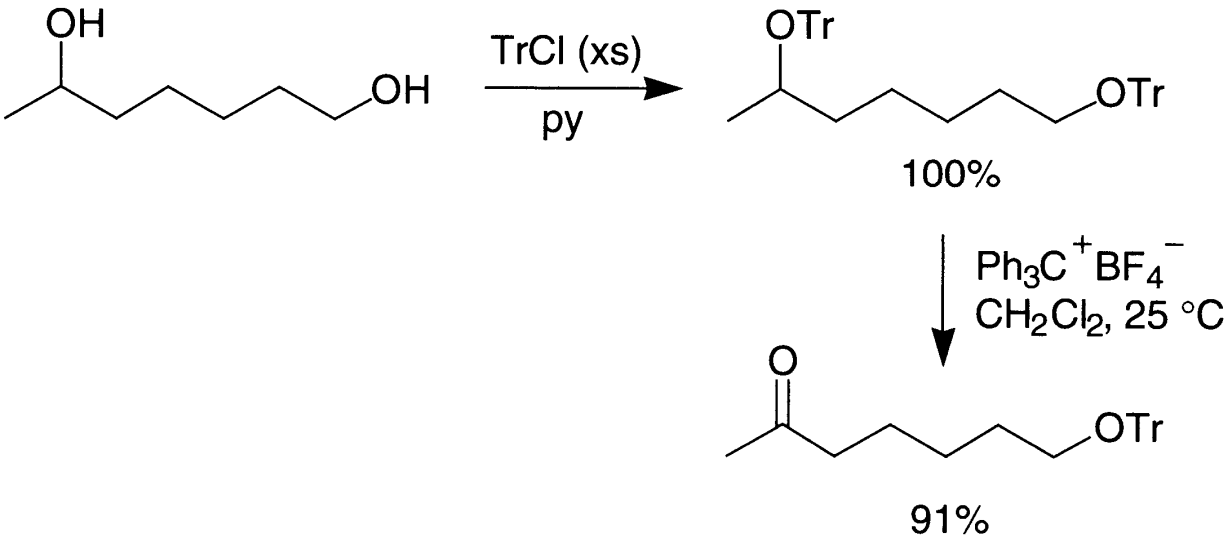
70%



80%

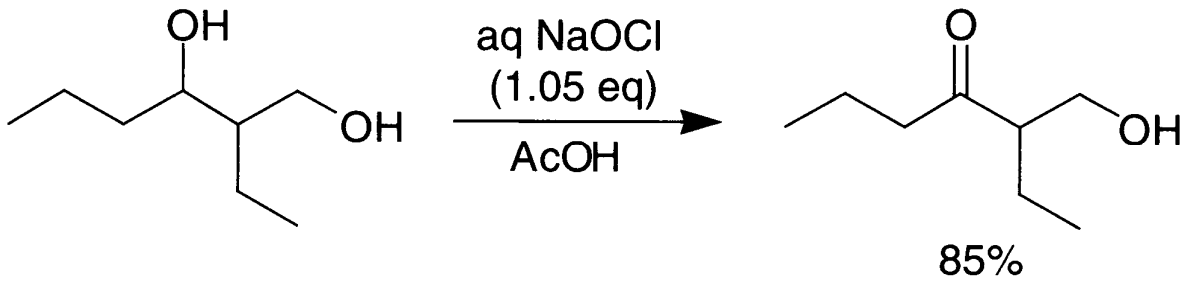
Triphenylcarbenium tetrafluoroborate

Oxidation of secondary alcohol over primary alcohol



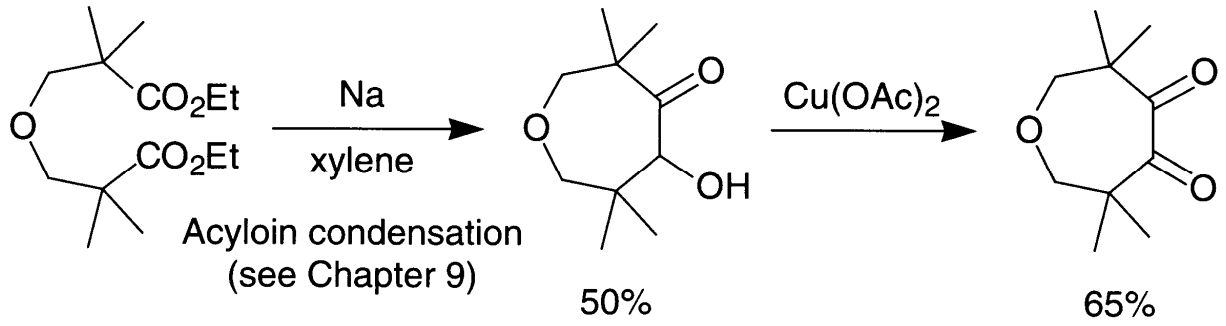
The secondary over primary selectivity results from preferential formation of an oxocarbenium ion intermediate at the secondary center (R_2^+C-OTr is formed faster than RH^+C-OTr)

Sodium Hypochlorite



4.4 Oxidation of Acyloins (α-hydroxy ketone) to α-diketone

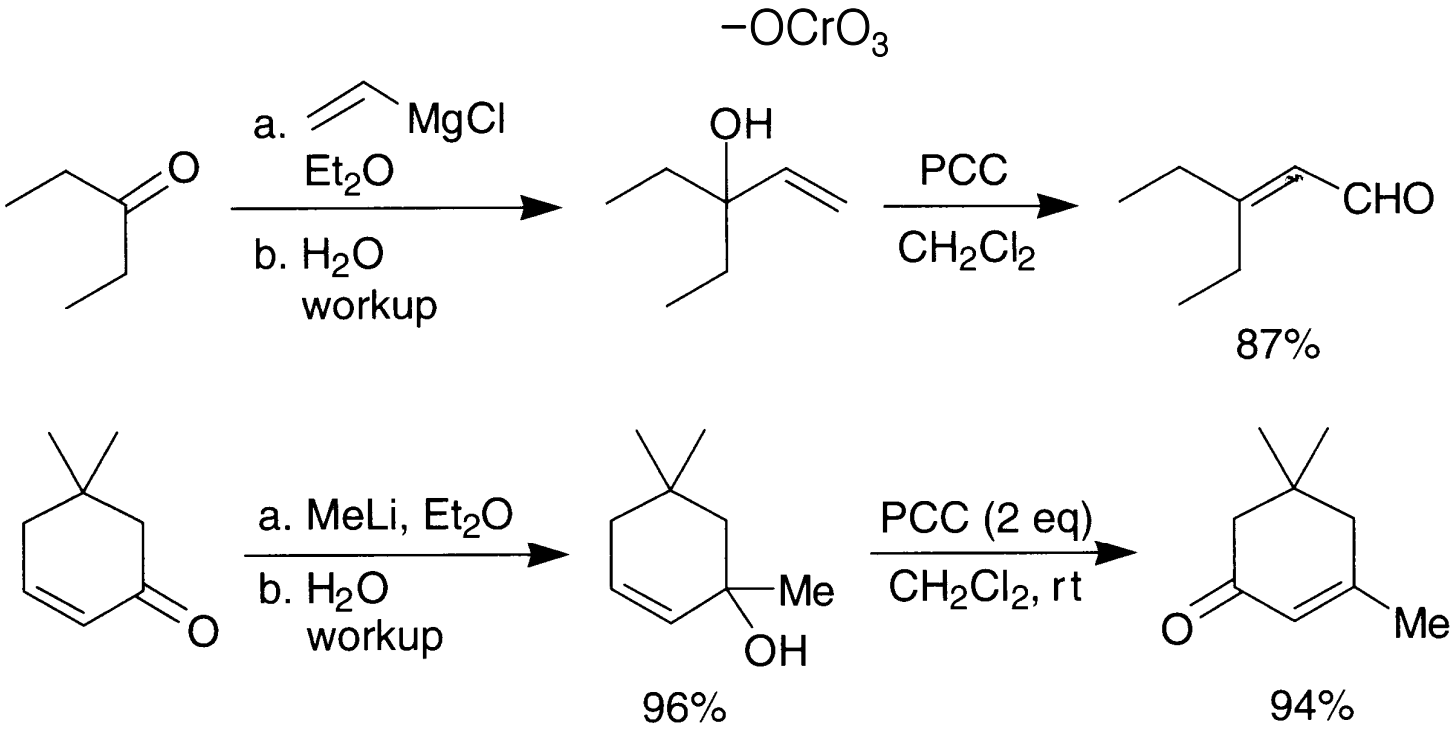
stoichiometric



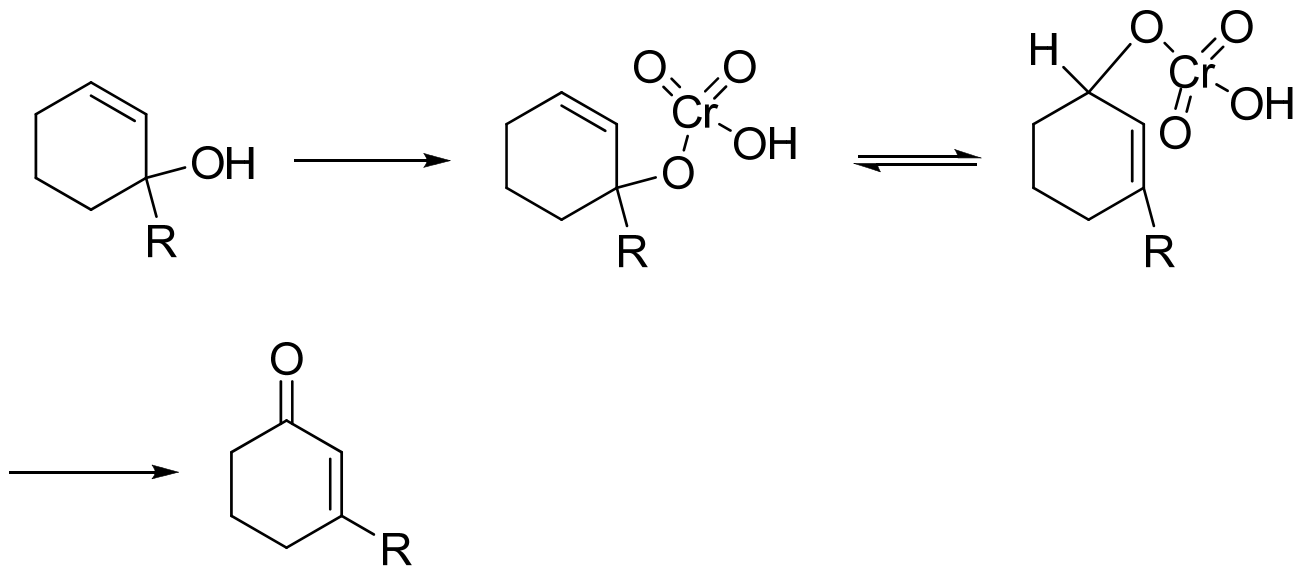
Catalytic with ammonium nitrate

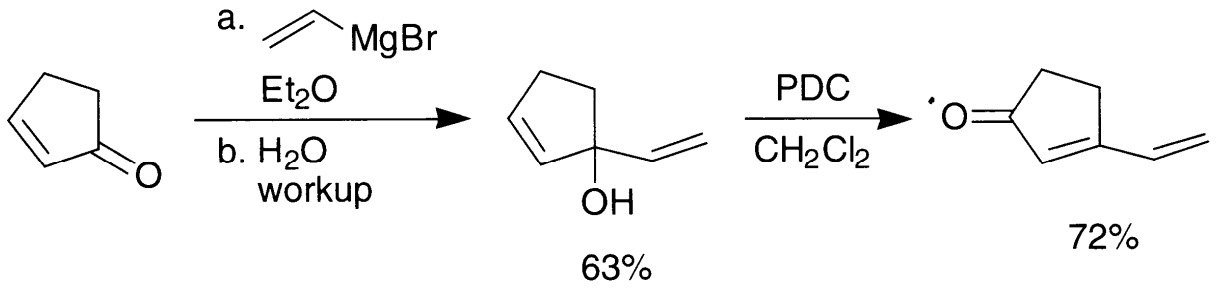
4.5 Oxidation of tertiary allylic alcohols (The Babler Oxidation)

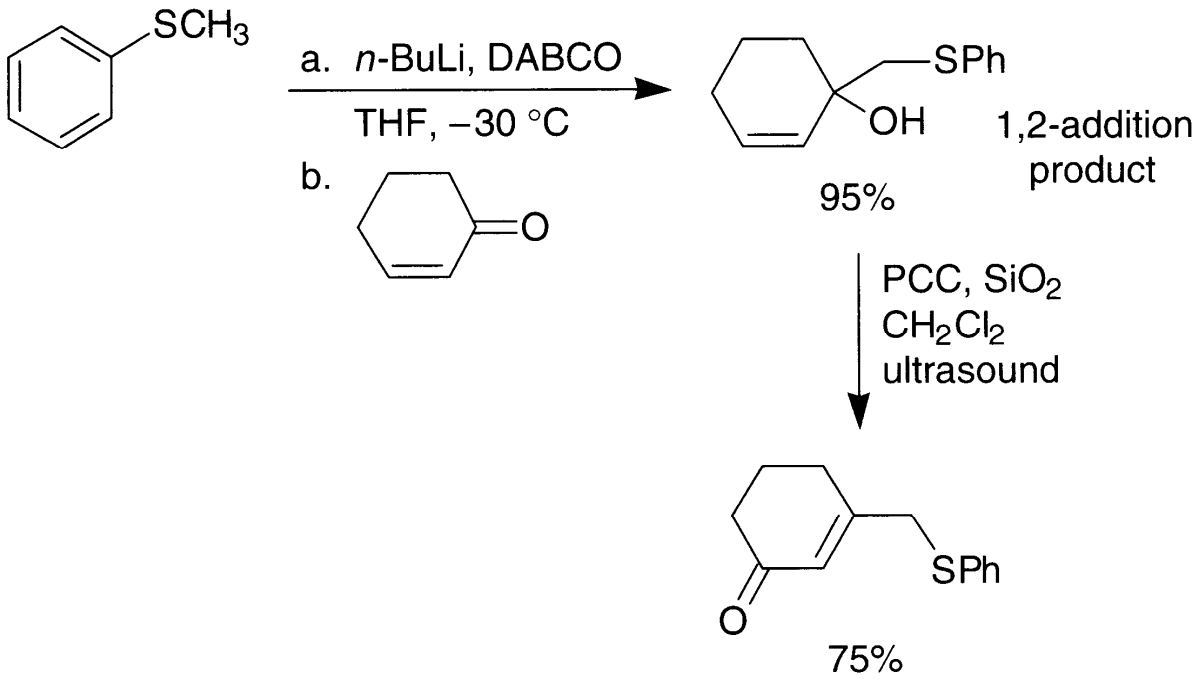
A carbonyl transposition can be effected via addition of a vinyl or an alkyl Grignard reagent to an α,β-unsaturated ketone.



Mechanism of Babler oxidation

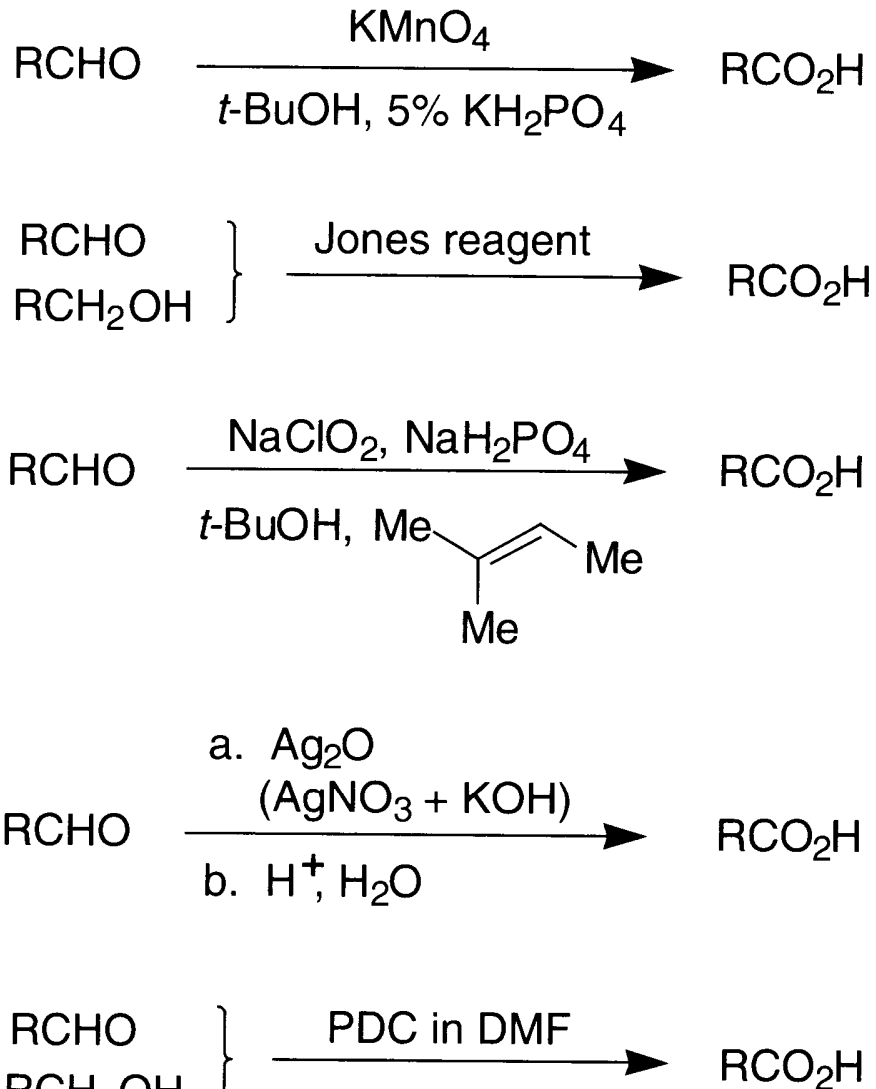



a.
MgBr
Et_2O
b. H_2O
workup
OH
63%
PDC
CH_2Cl_2
O
72%


SCH_3
a. *n*-BuLi, DABCO
THF, −30 °C
b.
O
SPh
OH
95%
1,2-addition
product
PCC, SiO_2
CH_2Cl_2
ultrasound
SPh
O
75%

4.6 Oxidative Procedure to Carboxylic acid

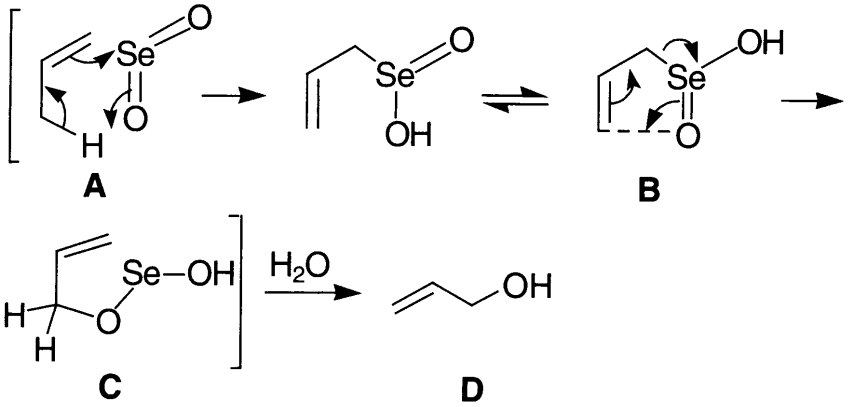
Oxidation of aldehyde to carboxylic acid

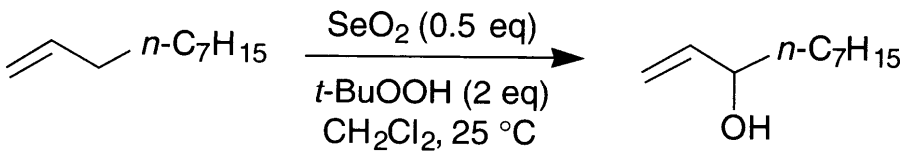


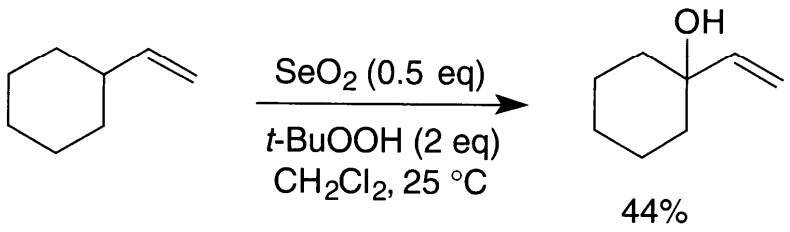
4.7 Allylic Oxidation of Alkene

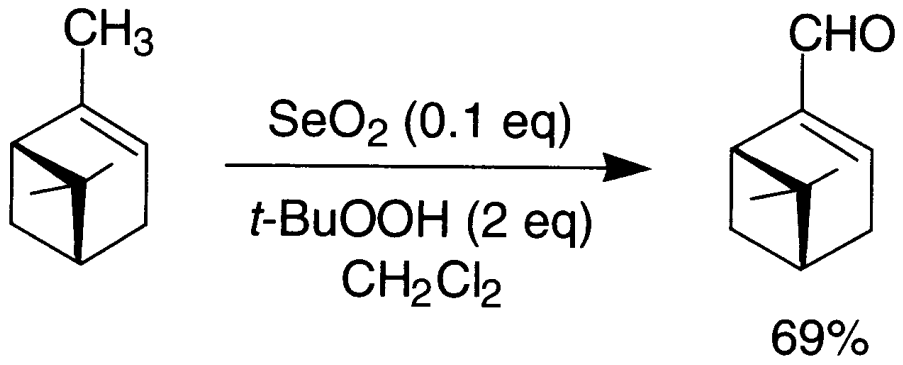
Selenium Dioxide

Alkenes possessing allylic C–H bonds are oxidized by SeO_2 either to allylic alcohols or esters or to α,β–unsaturated aldehyde or ketones. The reaction involves ene type reaction followed by sigmatropic [2,3]–shift.



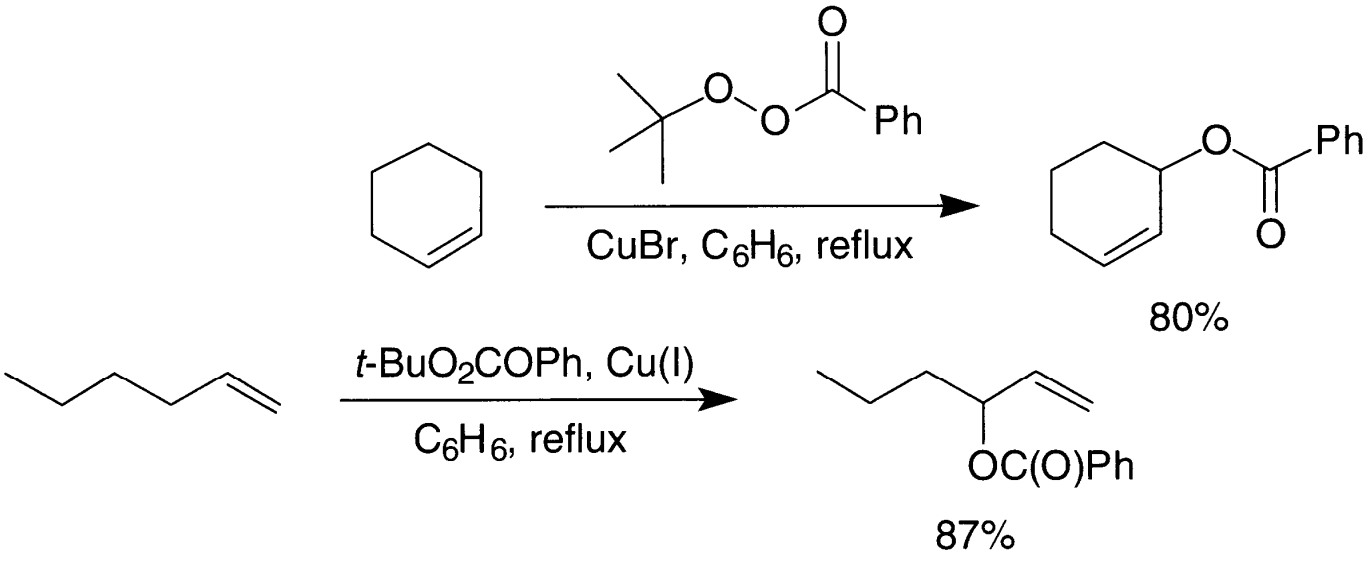




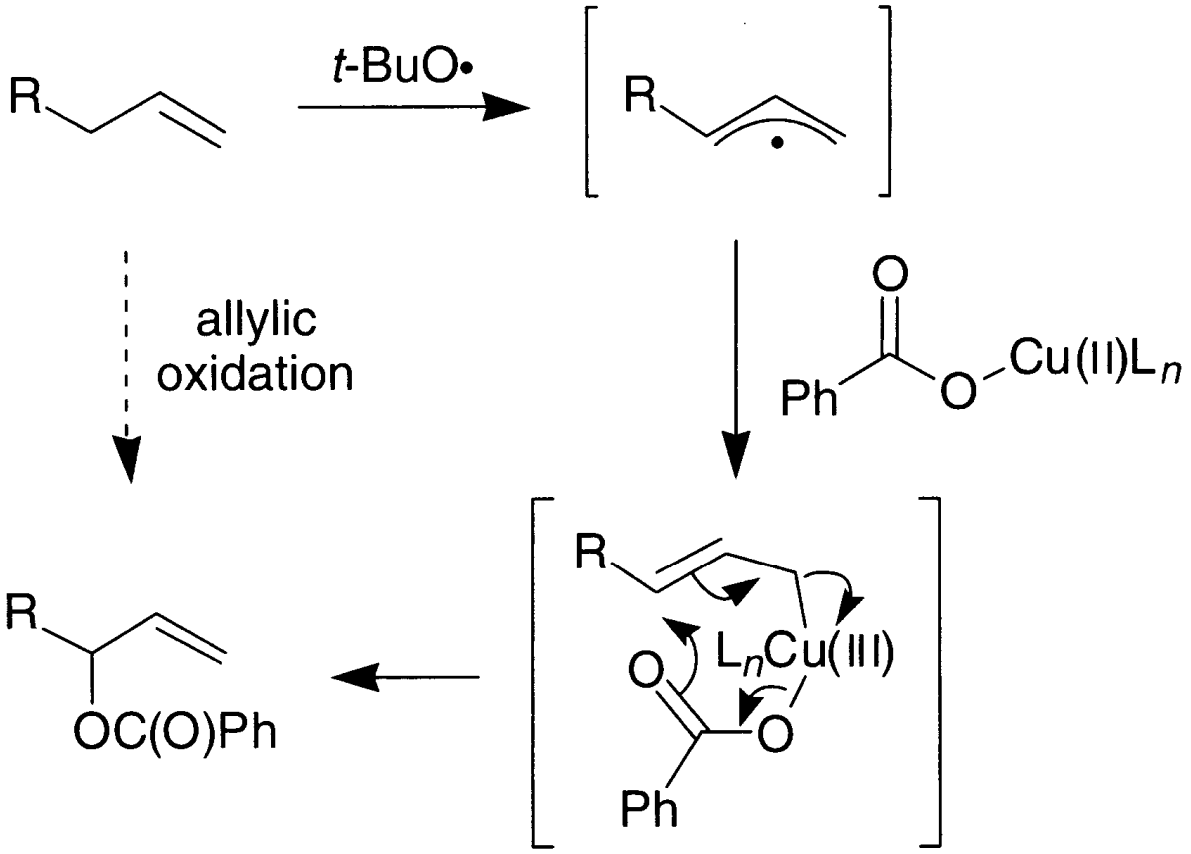


Lower yield of products were obtained when using stoichiometric amount of SeO_2. t-Butyl hydroperoxide is used to reoxidize selenium.

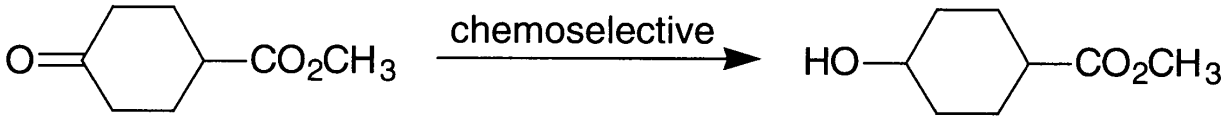
t-Butyl Peroxybenzoate: copper(I) salts catalyze the allylic oxidation of alkenes in the presence of peresters, such as tert-BuO_2COPh, to afford the corresponding allylic benozate esters.

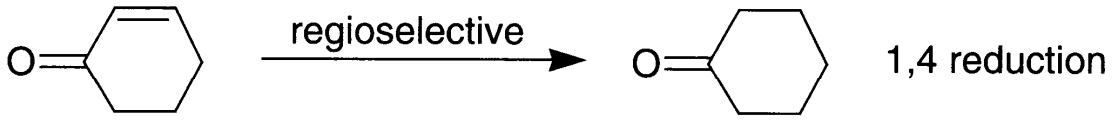


The mechanism is believed to involve addition of an allylic radical to copper(I) benzoate. Rearrangement of the copper(III) intermediate then produces the product and regenerates the copper(I) catalyst.

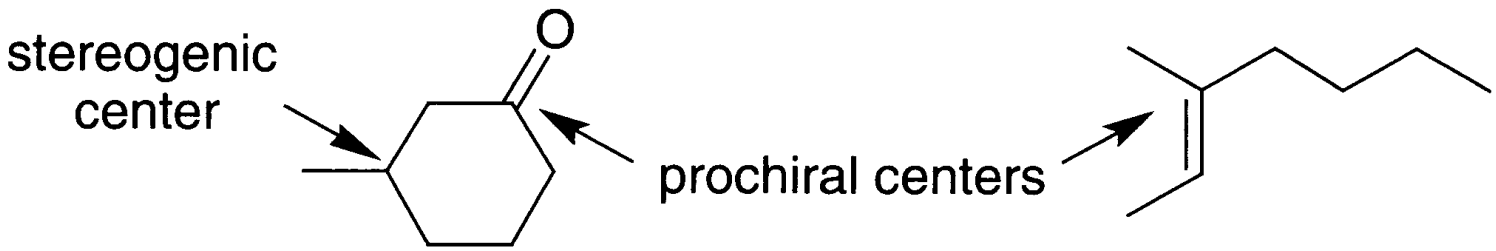


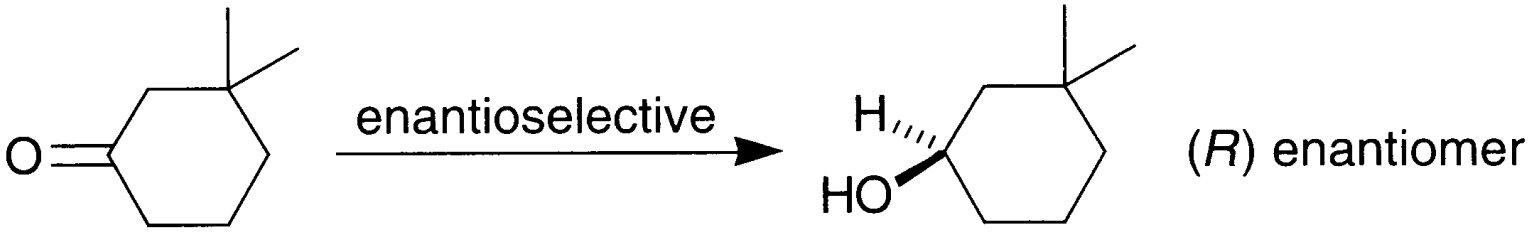
4.8 Terminology for reduction of carbonyl compounds.



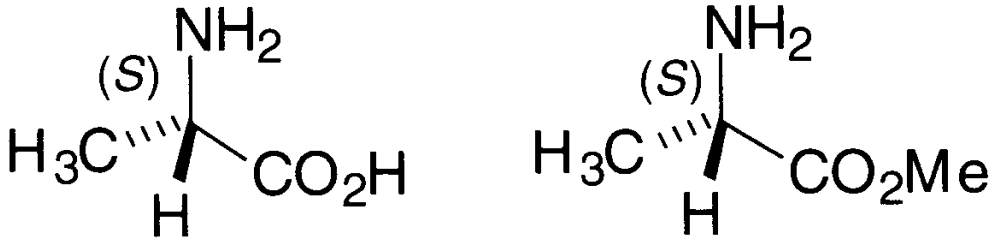


Prochiral center is a trigonal carbon of C=O and C=C that is not a stereogenic center but can be made chiral by addition reactions.





Objects and molecules are said to be homochiral when they possess the same sense of chirality. For example, L-alanine and its methyl ester derivative shown below are said to be homochiral.



4.9 Nucleophilic Reducing reagents

The majority of reductions of carbonyl compounds and nitriles with nucleophilic reducing reagents, such as $M[AlH_4]$ and $M[BH_4]$, proceed via nucleophilic transfer of a hydrogen atom with two electrons called a "hydride" from the reducing agent to the carbonyl or cyano carbon.

The rate of reduction and the chemoselectivity of a reducing agent toward a given substrate depends on factors such as

1. the nature of the metal cation (Li^+, Na^+, Zn^{2+}), which serves as a Lewis acid to activate the carbonyl or cyano moiety toward hydride transfer.

2. substitution of the reducing agent hydrogens by alkyl, -OR, or –CN groups

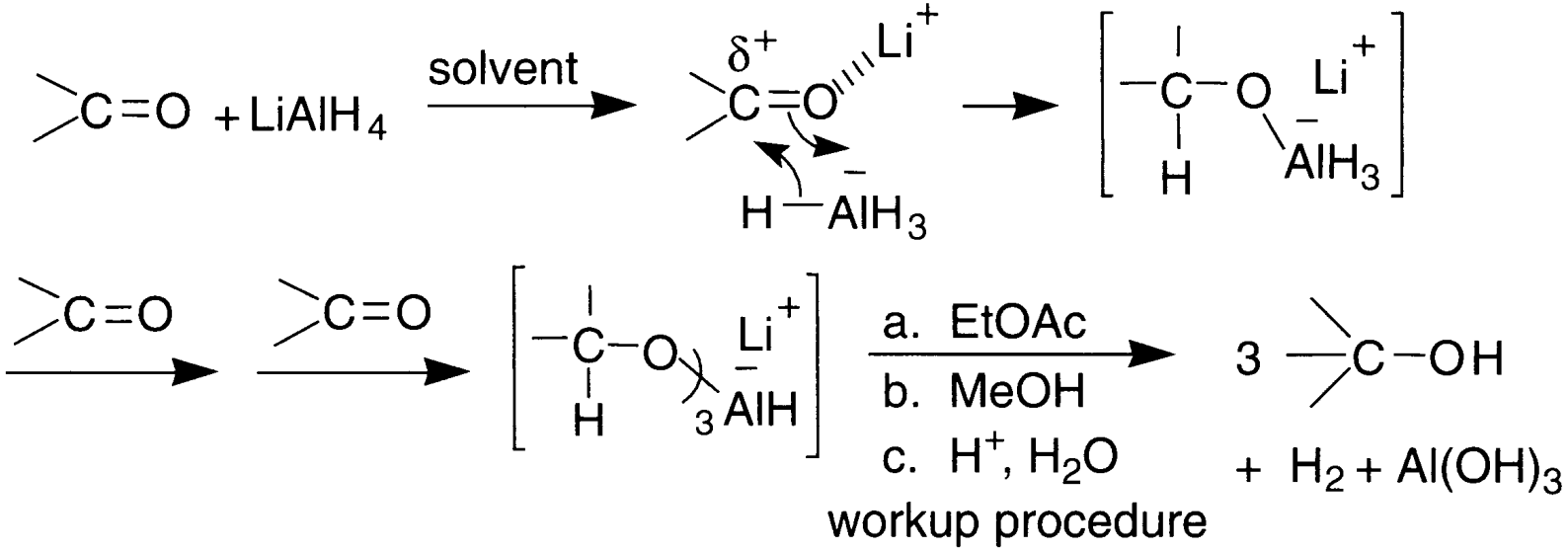
3. the reaction medium (Et_2O, THF, ROH, H_2O)

4. the reactivity order of substrates is: $RCHO > R_2CO > RCO_2R' > RCONR_2 > RCO_2H$

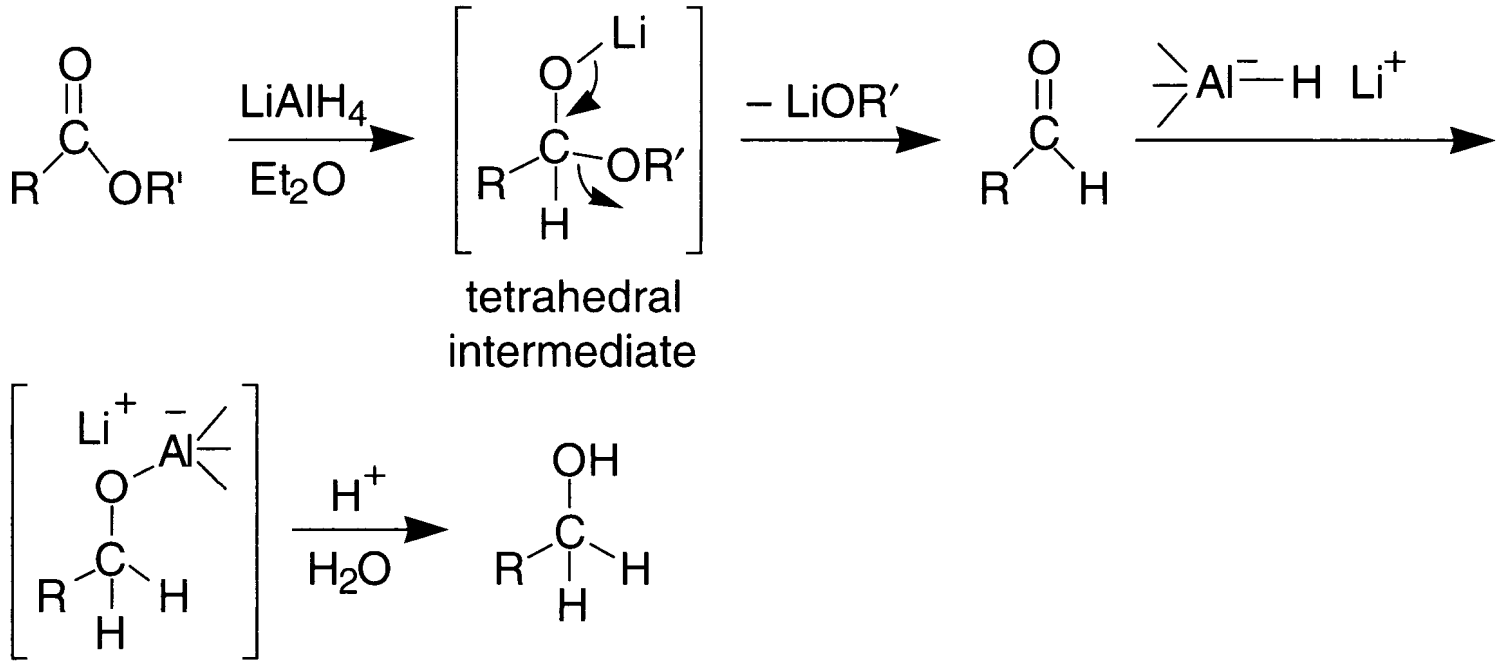
Aluminum Hydride Lithium Aluminum Hydride-$LiAlH_4$

Powerful reducing agent but not very chemoselective.
It must be used in nonprotic solvents such as Et_2O or THF.

To decompose any excess Al-H, first add ethyl acetate, followed by methanol and then H_2O.



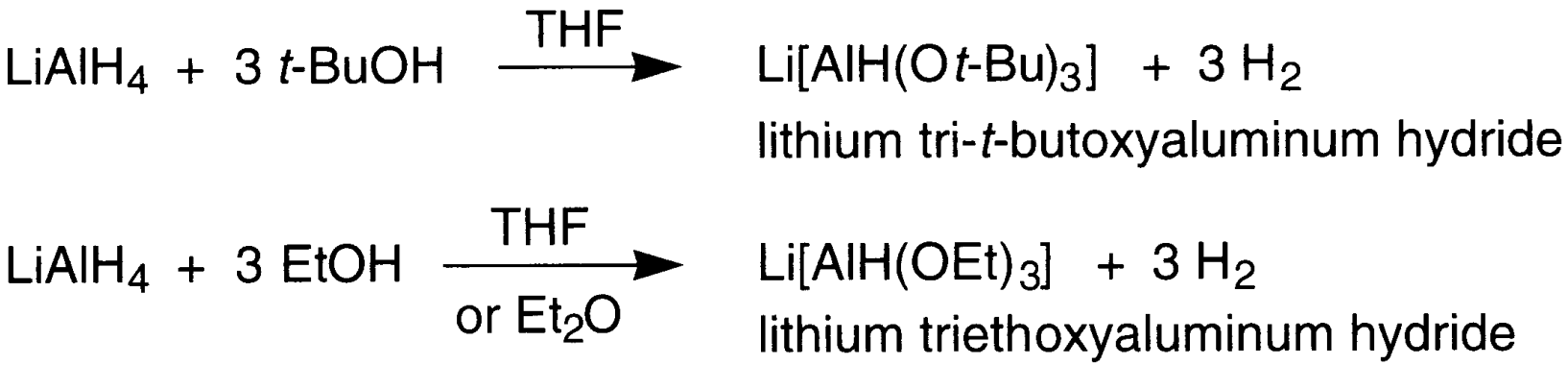
The reduction of esters to primary alcohols and the reduction of amides to amines requires two hydrides, whereas reduction of caboxylic acids to primary alcohols consumes three hydrides.

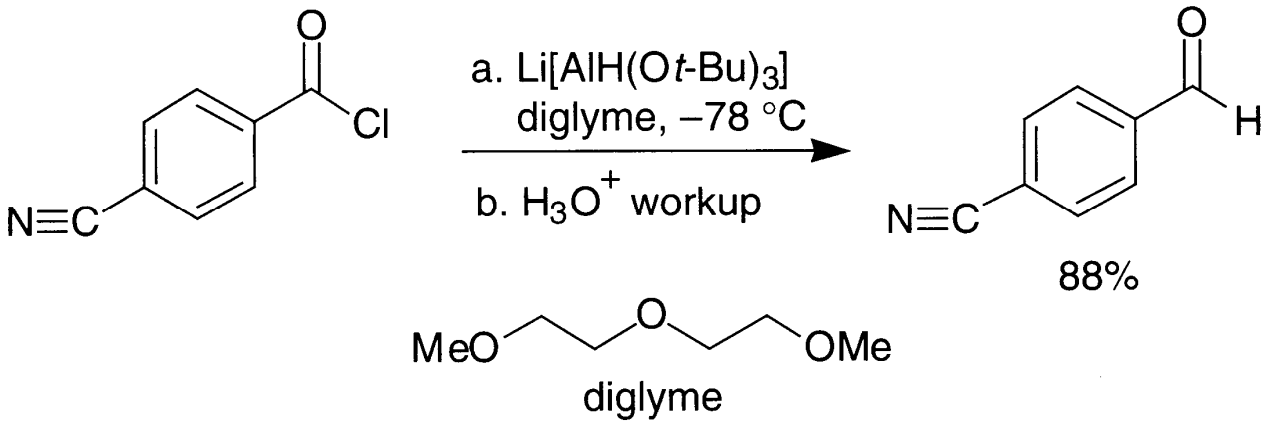


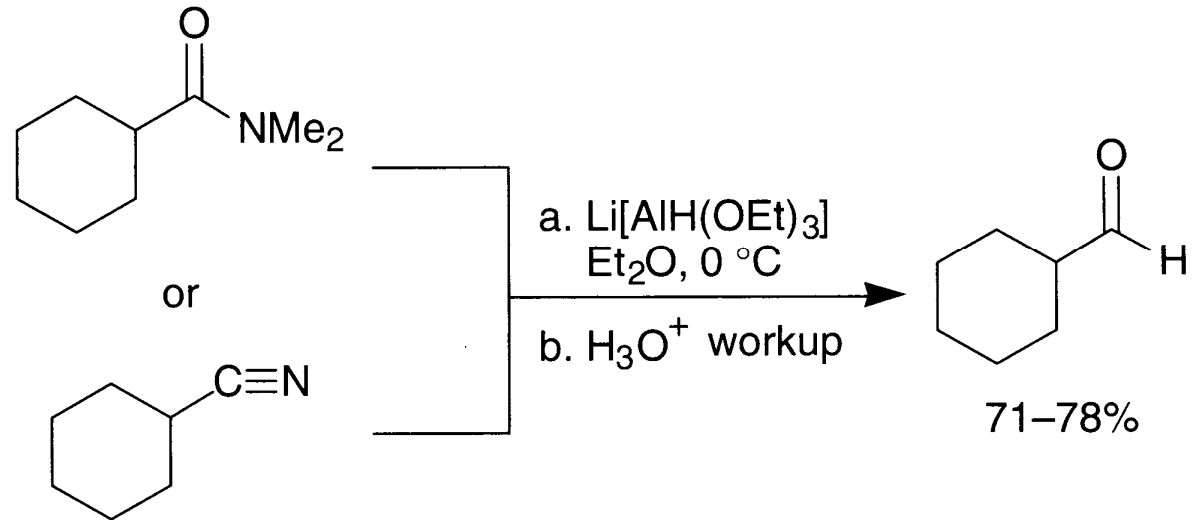
Reference Table 4.2

Lithium Trialkoxyaluminum Hydride- $Li[AlH(OR)_3]$

They are less reactive but more selective than LAH and are best prepared just prior to use *in situ*.

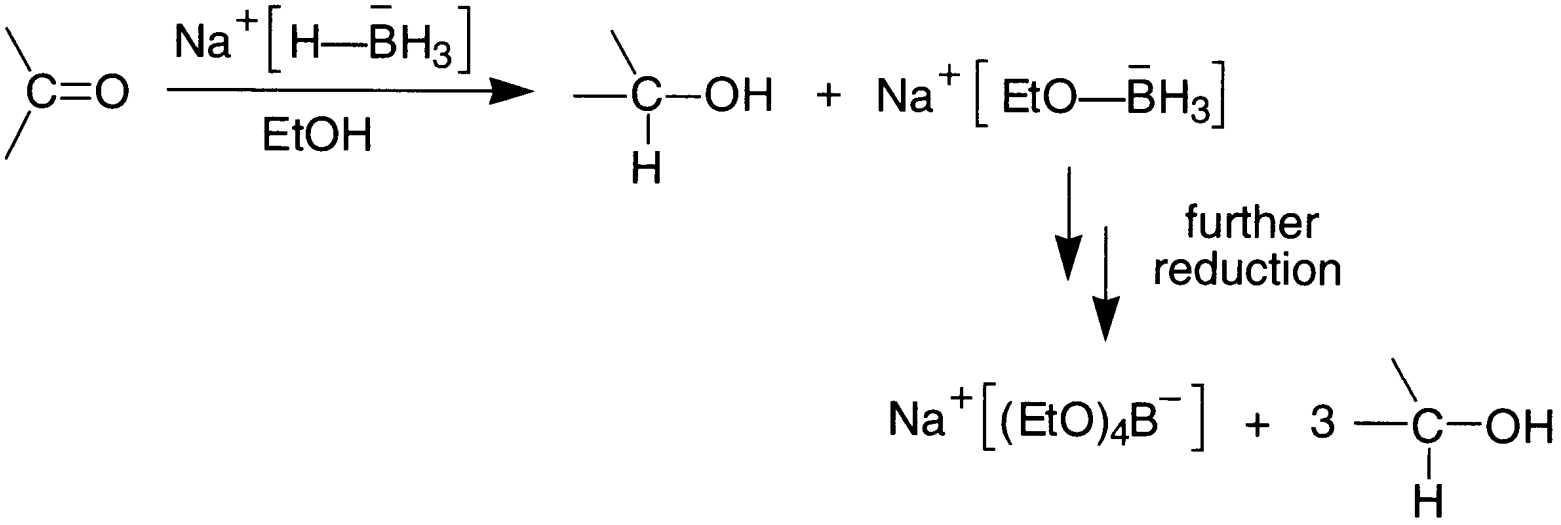


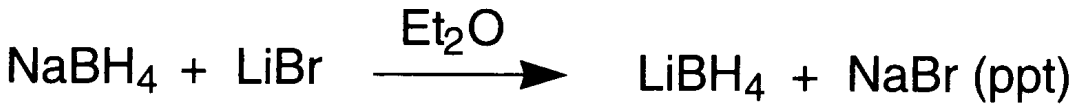

O
Cl
N≡C
a. Li[AlH(Ot-Bu)3]
diglyme, –78 °C
b. H3O+ workup
O
H
N≡C
88%
MeO
O
OMe
diglyme


O
NMe2
or
C≡N
a. Li[AlH(OEt)3]
Et2O, 0 °C
b. H3O+ workup
O
H
71–78%

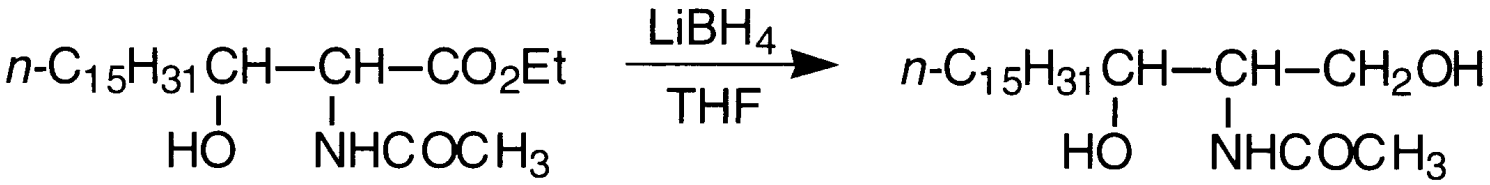
Borohydrides

Sodium Borohydride: a mild, selective reducing agent, its handling does not require special precautions. EtOH is usually the solvent of choice. It reduces RCHO and R_2CO in EtOH or aqueous solutions rapidly at 25°C to the corresponding alcohols.





The Li^+ cation is stronger Lewis acid than the Na^+ cation. Li^+ coordination with the carbonyl group enhances the electrophilicity of the carbonyl cation. Thereby facilitating hydride transfer. Lithium borohydride is a more powerful reducing agent than sodium borohydride: it reduces esters to primary alcohol but is unreactive towards amides.

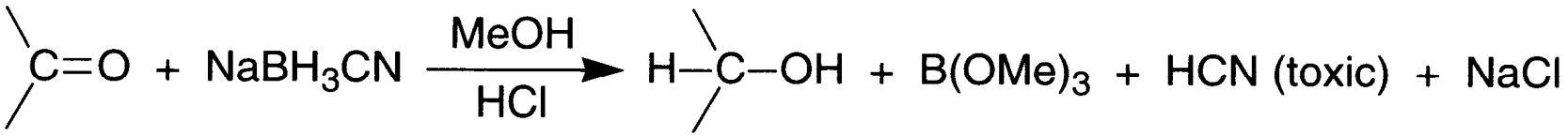


Sodium Cyanoborohydride-$NaBH_3CN$

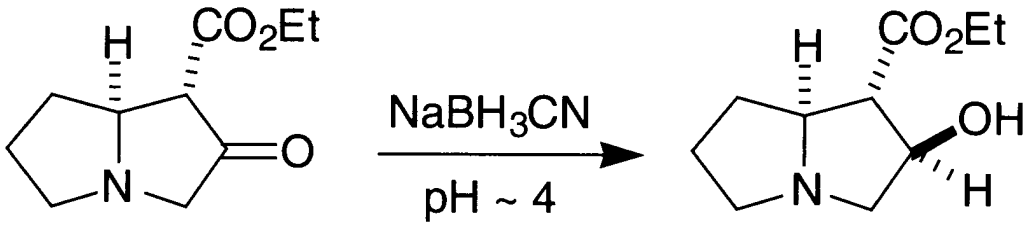
Because of the presence of the electron withdrawing cyano group, $NaBH_3CN$ is less nucleophilic and hence is more selective than $NaBH_4$.

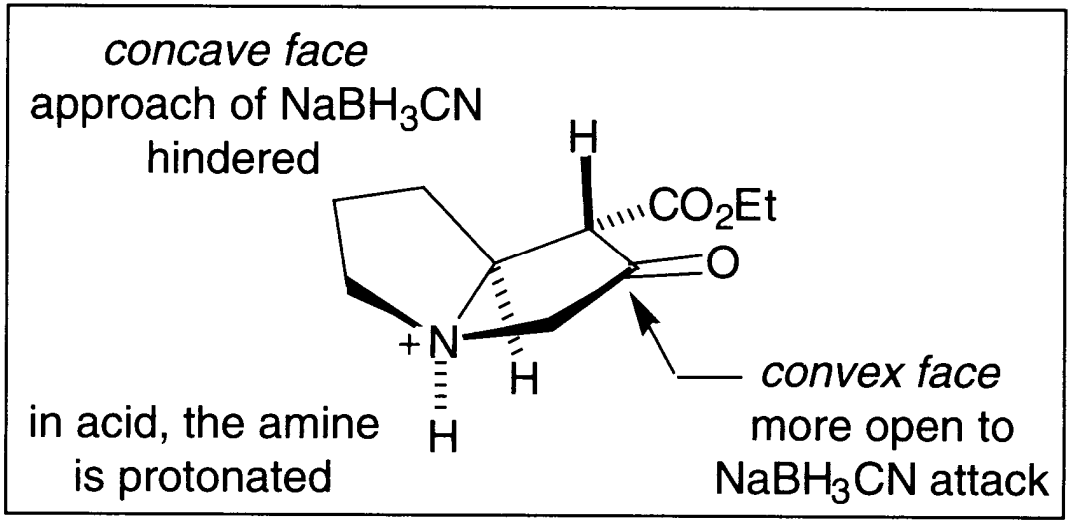
The utility of $NaBH_3CN$ as a reducing agent is greatly enhanced by its stability toward low pH (stable to pH 3).

In acidic condition, carbonyl reduction does occur (protonated carbonyl group)>



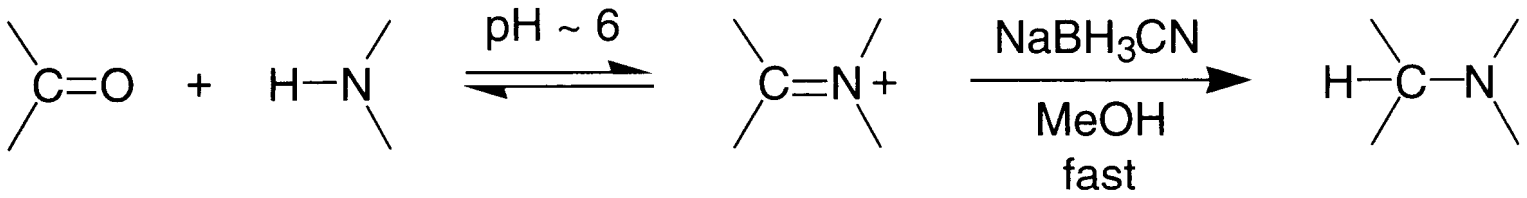
$NaBH_3CN$ is a chemoselective reducing agent. For example, it is possible to selectively reduce an aldehyde in the presence of keto group or a keto group in the presence of an ester group using $NaBH_3CN$.

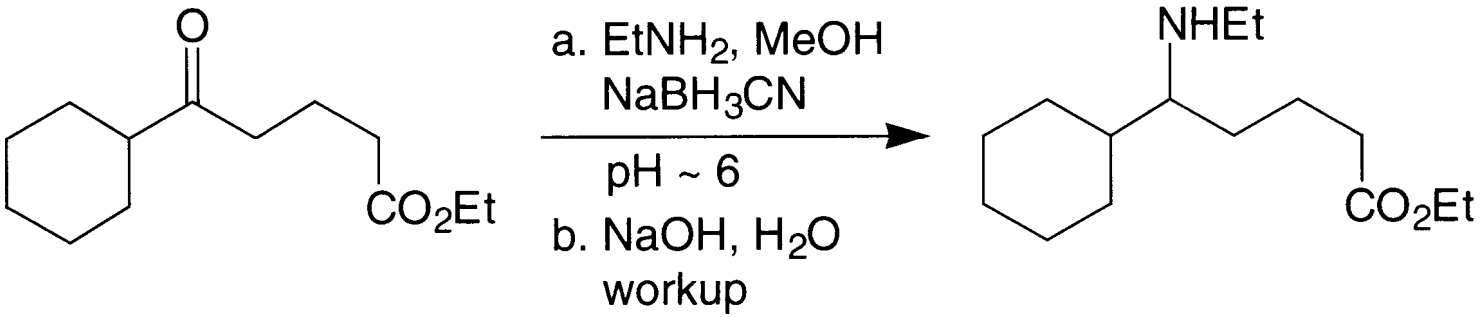




Reductive Amination with $NaBH_3CN$

Since the reduction of an iminium salt by $NaBH_3CN$ occurs more readily than the reduction of a carbonyl group, $NaBH_3CN$ is the reagent of choice for the reductive amination of aldehyde and ketones.





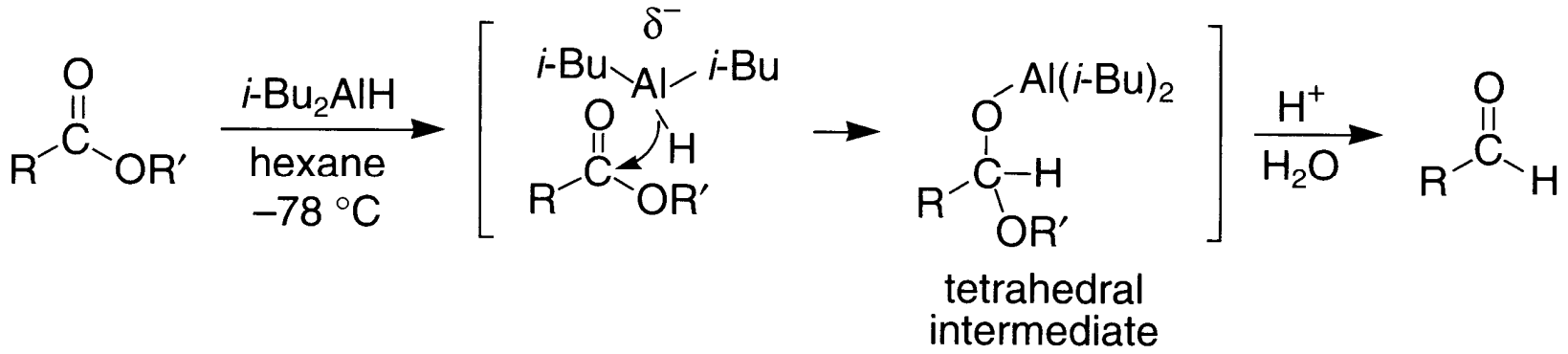
4.10 Electrophilic Reducing Agents

Whereas nucleophilic reducing agents react fast with electron-deficient carbonyl groups, the reactivity of electrophilic reducing agents such as R_2AlH and BH_3, characterized by their coordination with the carbonyl oxygen prior to hydride transfer, favor reductions of electron-rich carbonyl groups.

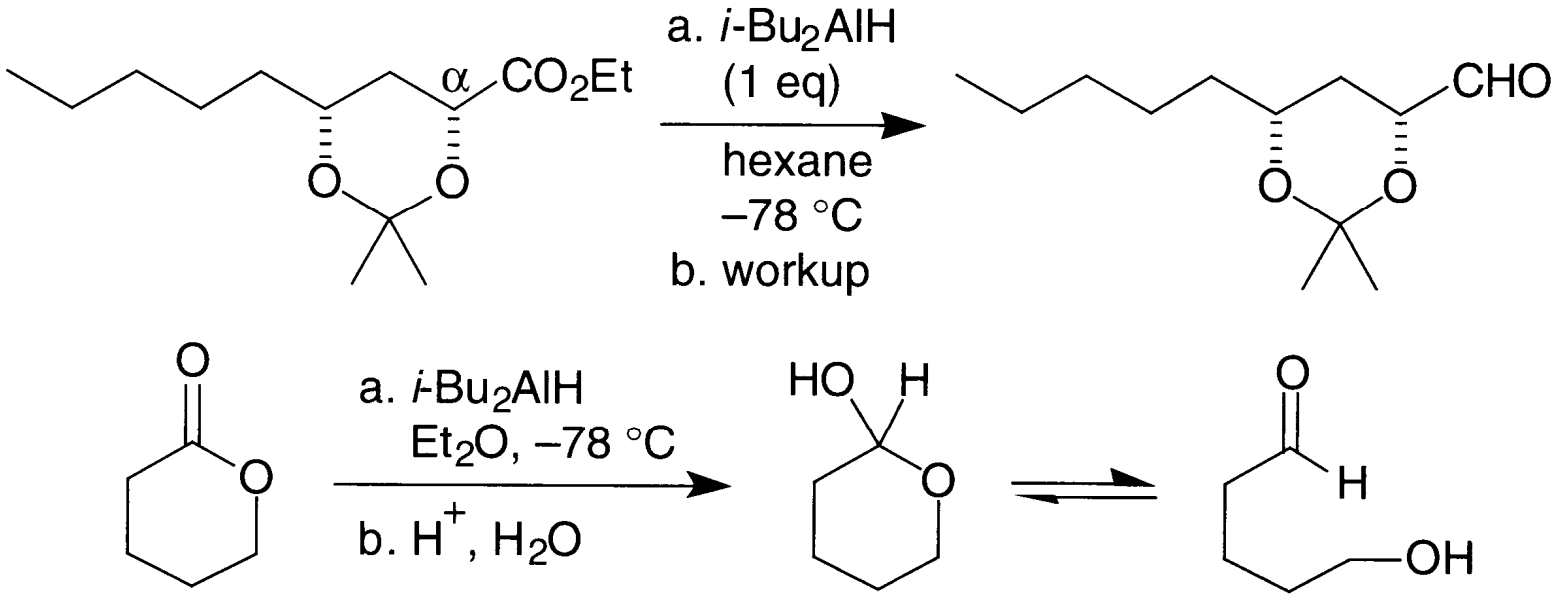
Diisobutylaluminum hydride (DIBAL-H)

Reductions with DIBAL-H must be carried out in the absence of air and moisture. DIBAL-H is a very versatile reagent for the selective reduction of appropriately substituted esters or nitriles to the corresponding aldehyde and for the reduction of lactones to lactole.

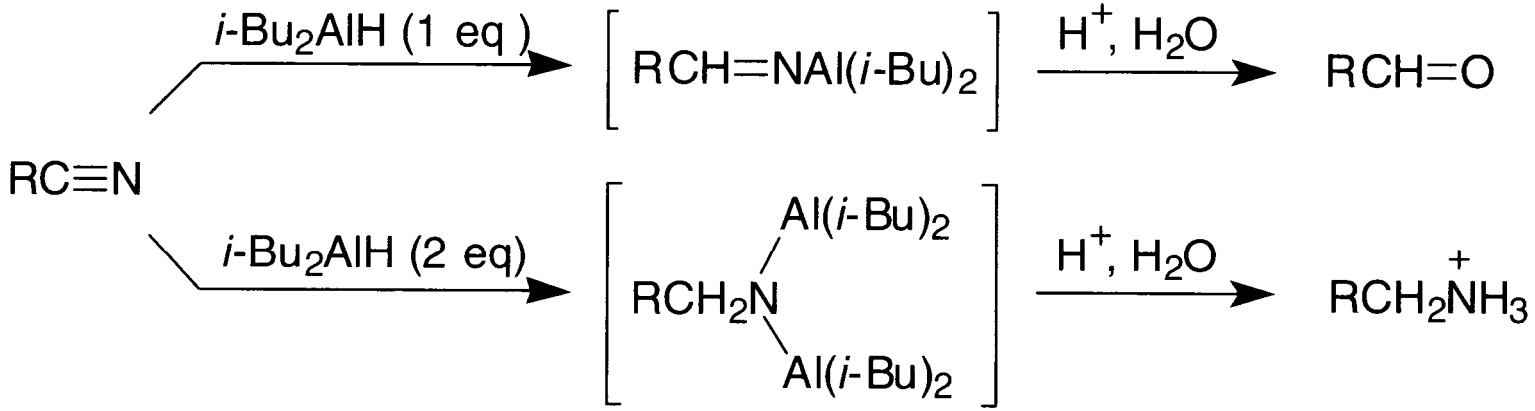
Reduction of Esters to Aldehyde

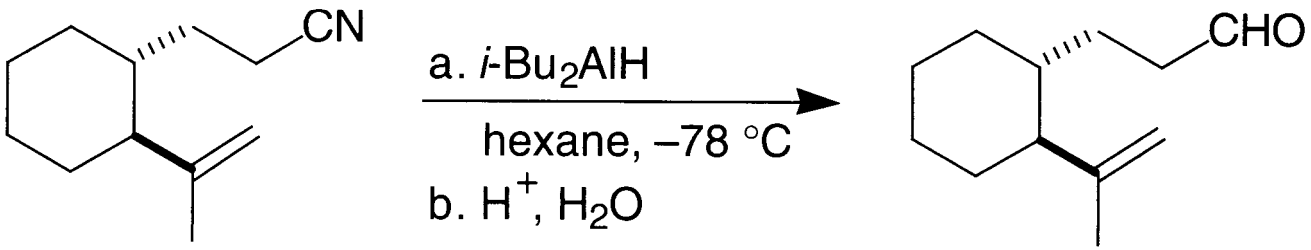


A neighboring alkoxy group will stabilize the tetrahedral intermediate through chelation and prevent overreduction.



Reduction of Nitriles to Aldehyde

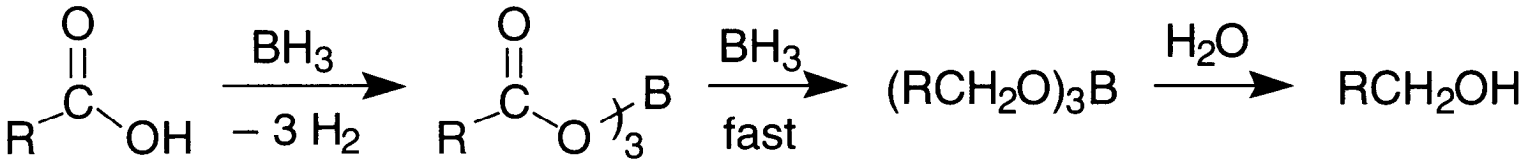


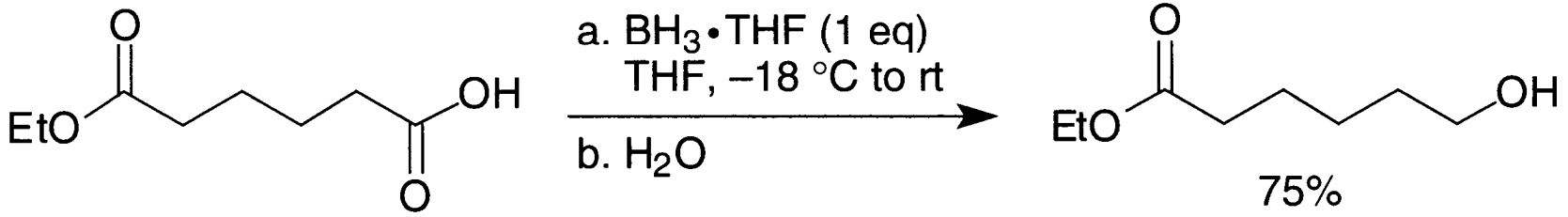


Borane•Tetrahydrofuane and Borane•Dimethylsulfide

Commercially available

These reagents can do facile reduction of carboxylic acids to primary alcohols, and selective reduction of a $-CO_2H$ group in the presence of other functional groups.





Thexylchloroborane

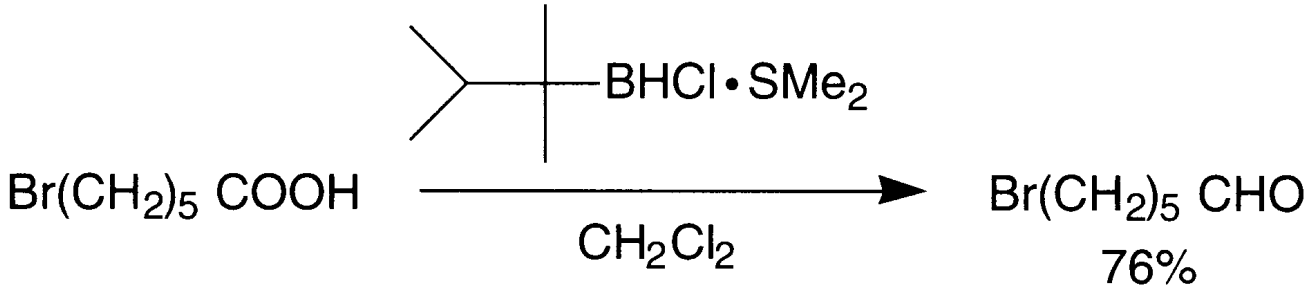
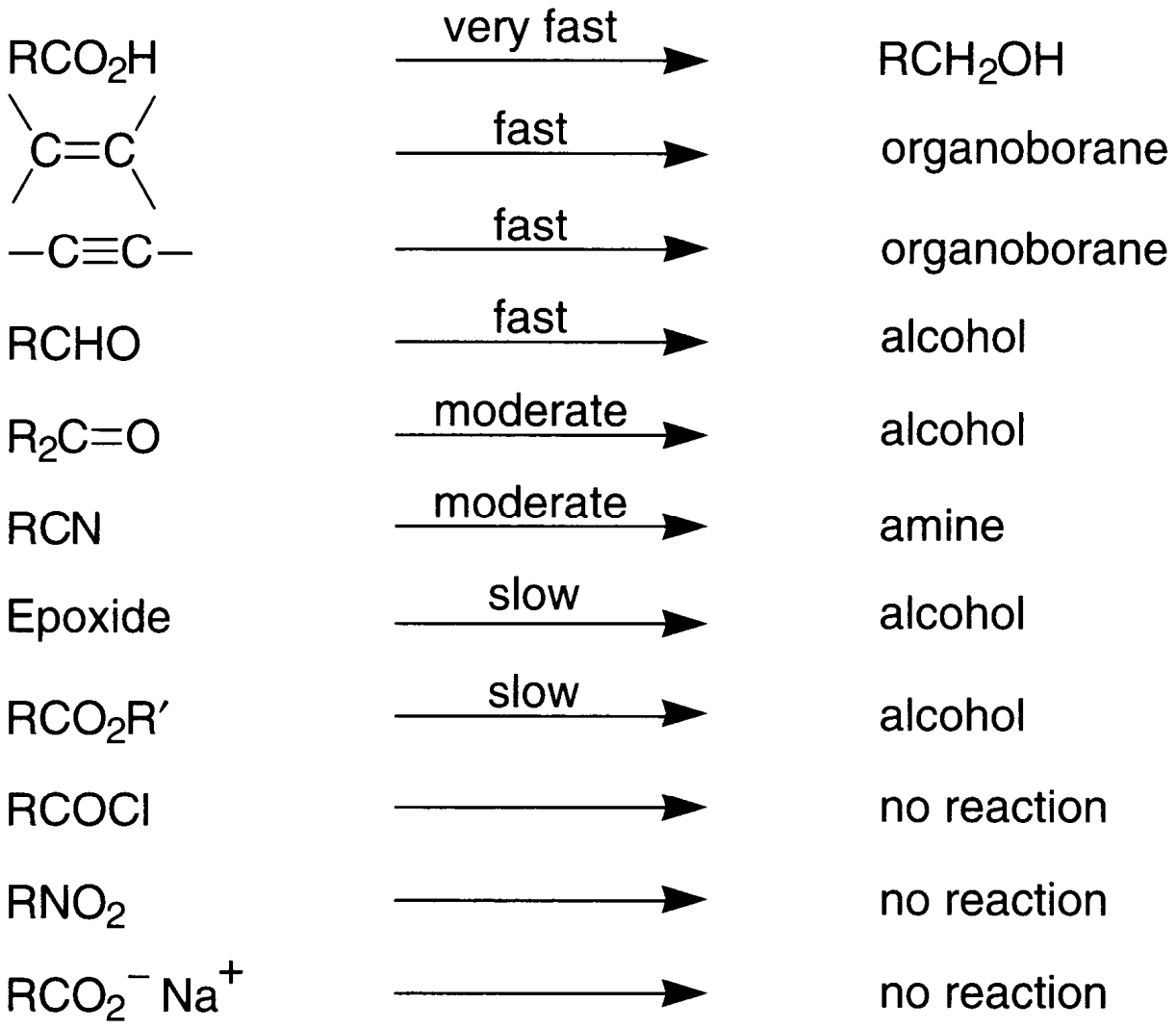
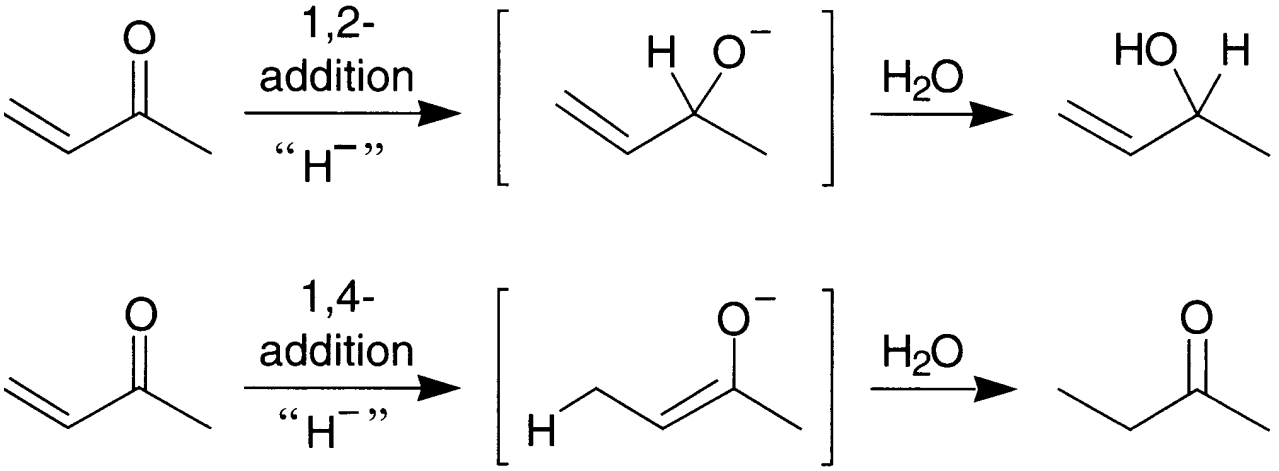


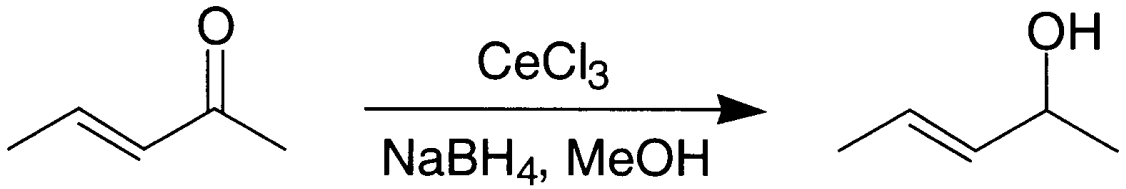
Table 4.3 Selectivity in BH_3•THF Reduction



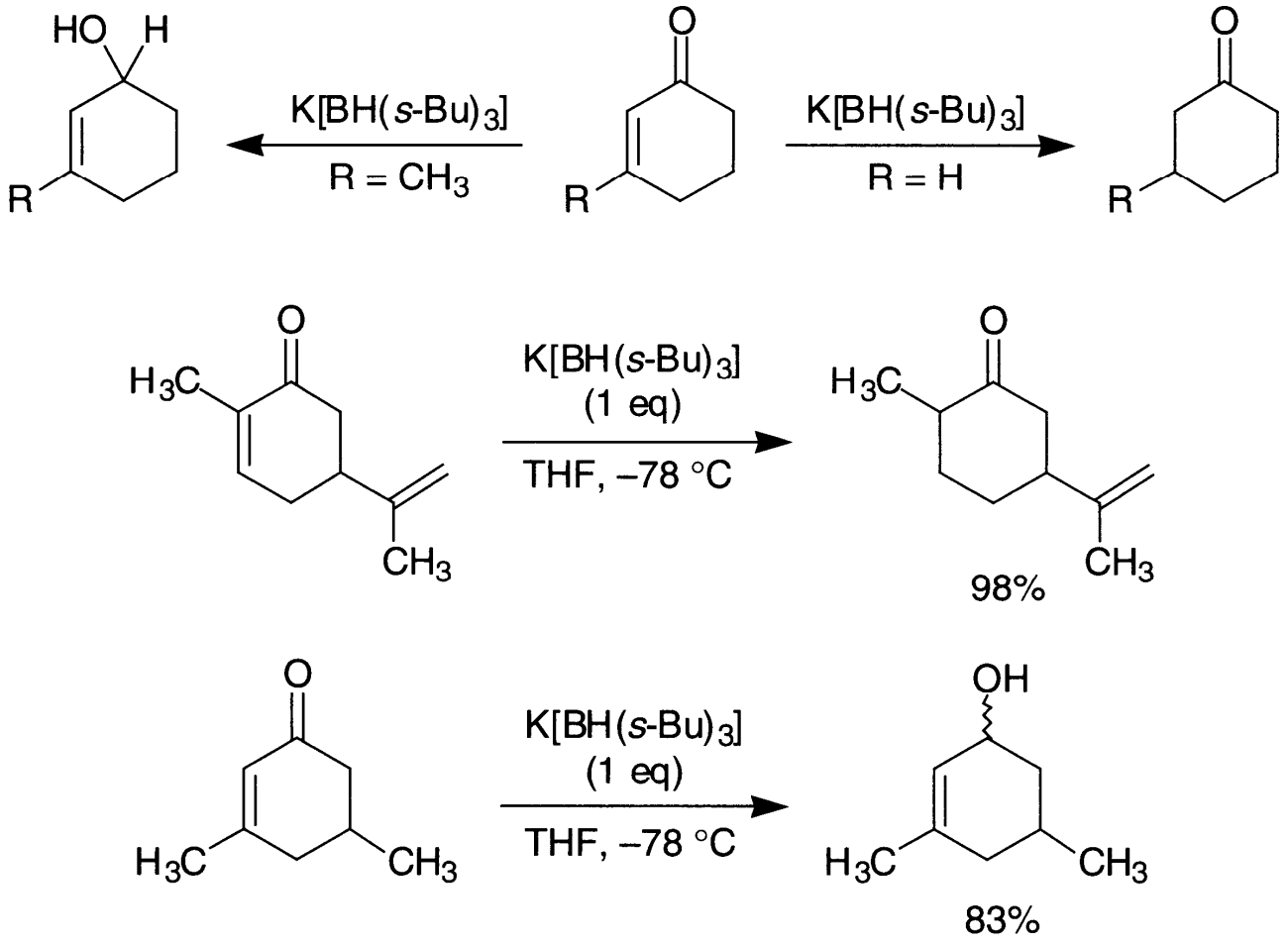
4.11 Regio- and Chemoselective Reductions



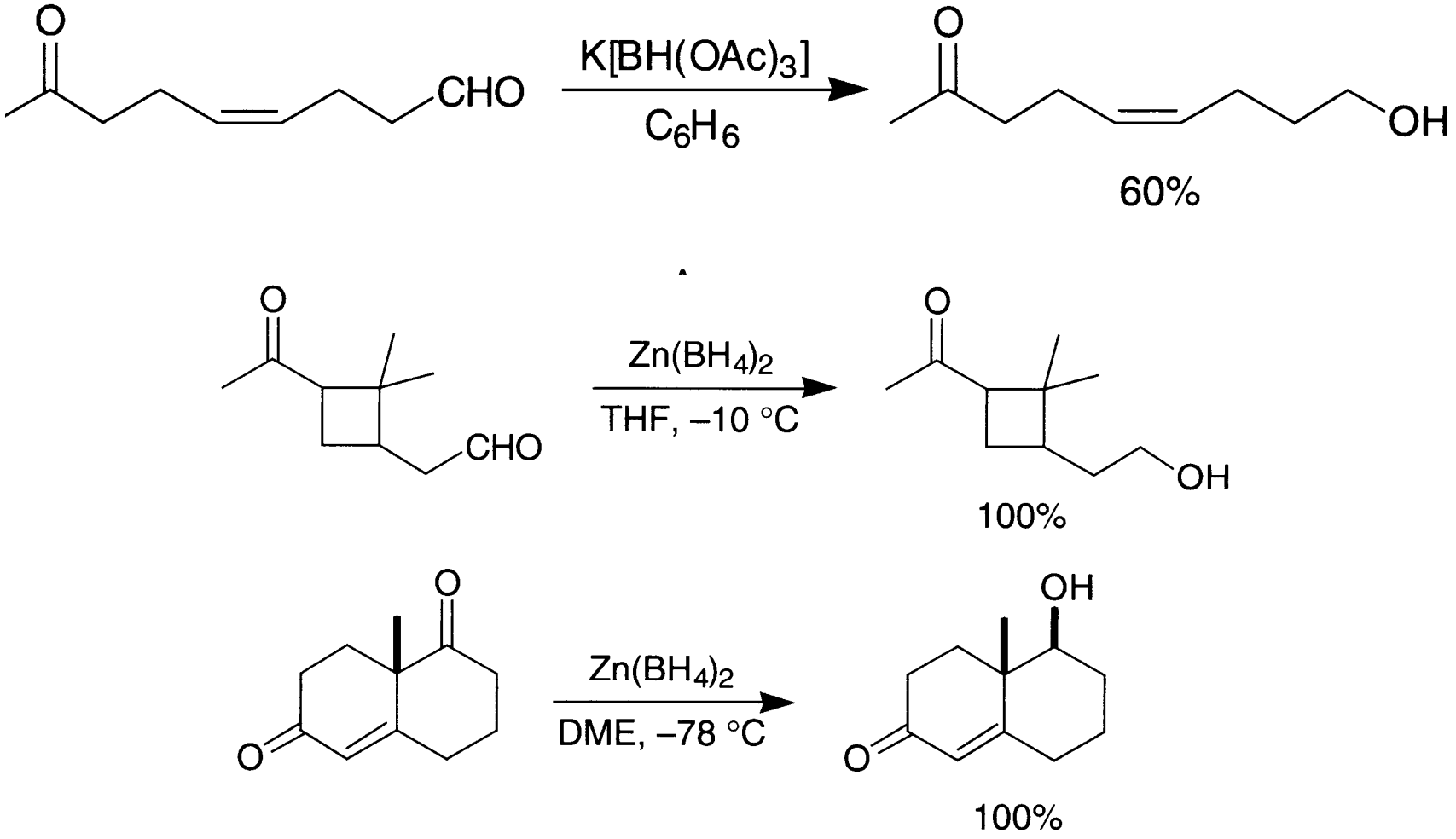
1,2-Additions: iBu_2AlH, $Zn(BH_4)_2$, $(i\text{-}PrO)_2TiBH_4$, 9-BBN,
$CeCl_3$-$NaBH_4$ (Luche reagent)

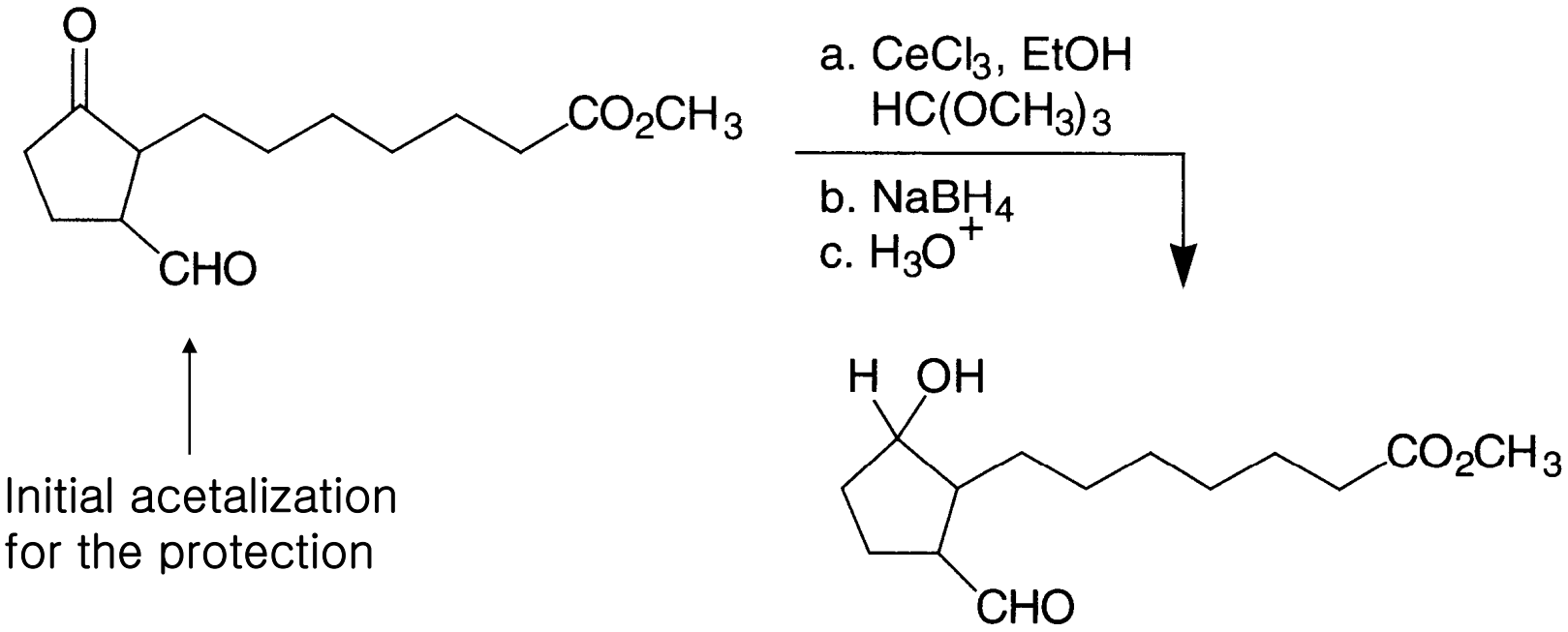


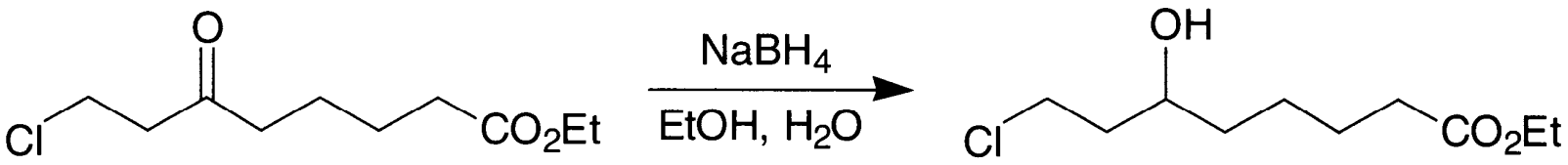
K-Selectride reduces β-unsubstituted cyclohexenones to cyclohexanones (1,4-addition) and β-substituted cyclohexenones to the corresponding allylic alcohols (1,2-additions).



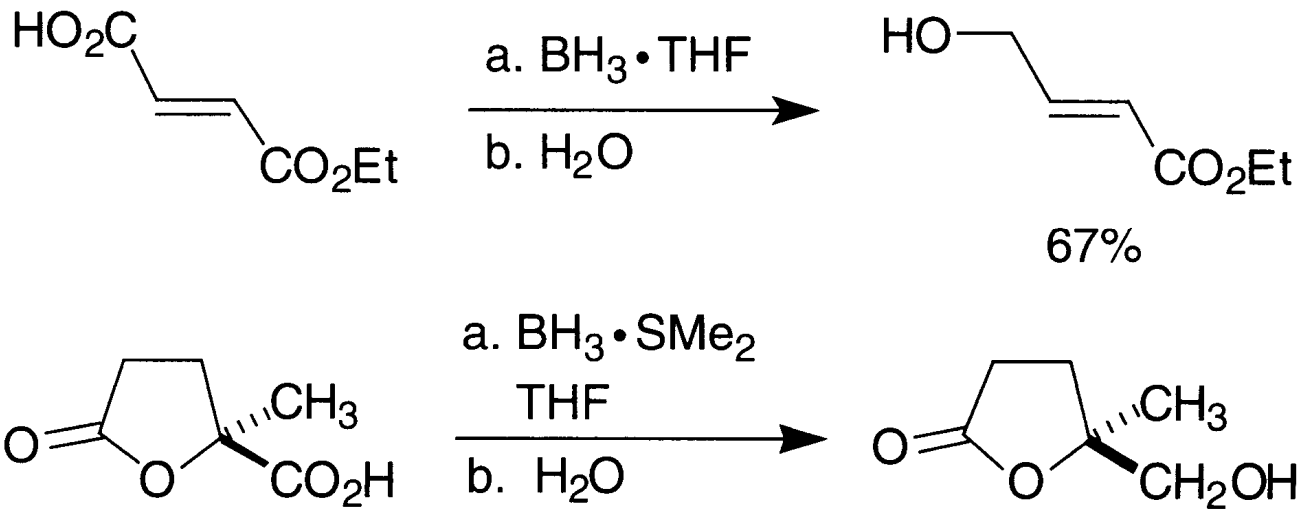
Aldehyde is more reactive than ketone with $K[BH(OAc)_3]$.



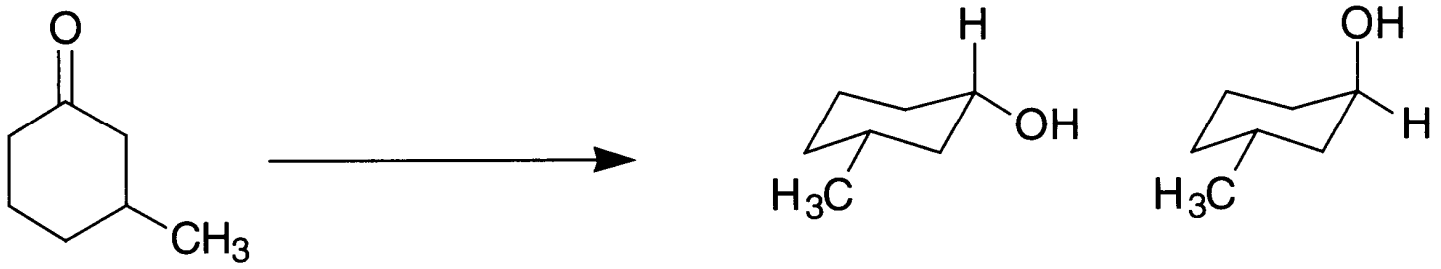

O
CO2CH3
CHO
a. CeCl3, EtOH
HC(OCH3)3
b. NaBH4
c. H3O+
H OH
CO2CH3
CHO
Initial acetalization
for the protection



Reduction of carboxylic acids in the presence of Ketones or esters.

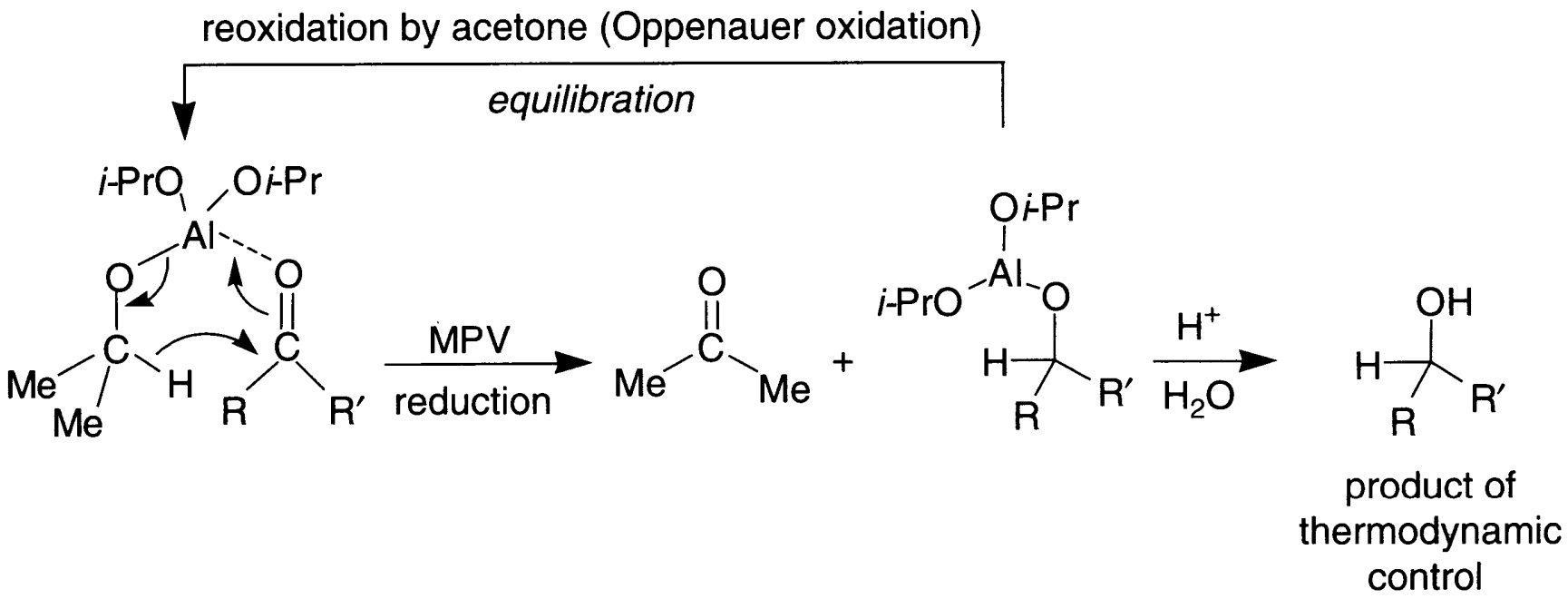


4.12 Diasterreoselective Reduction of Cyclic Ketones

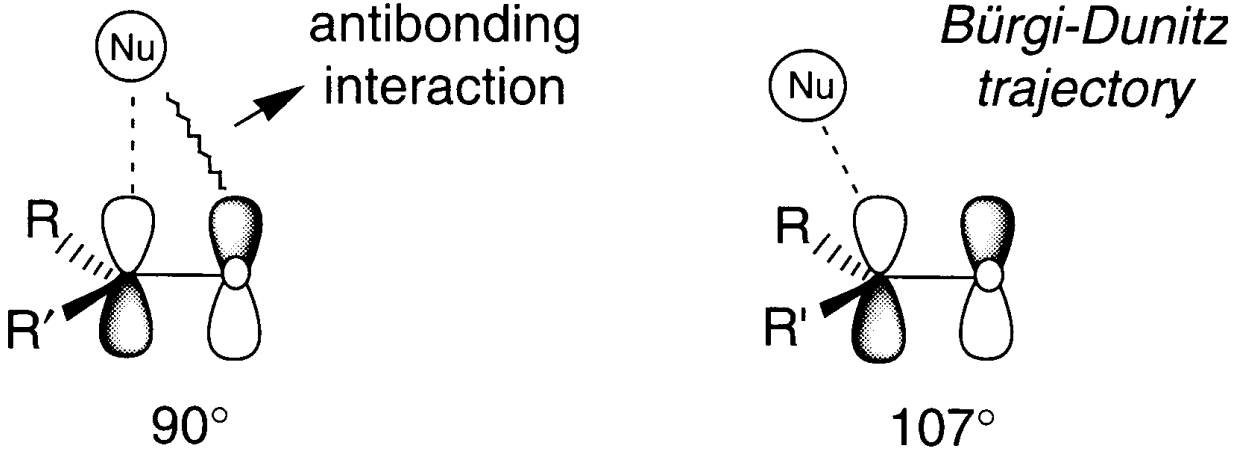


This reaction is called Meerwein-Ponndorf-Verley (MPV) reduction, which involves treatment of ketone with aluminum triisopropoxide [$Al(OCHMe_2)_3$].

This is an equilibrium process favoring the more stable stereoisomer.
In the case of an alkyl-substituted cyclohexanone is the equatorial alcohol.


reoxidation by acetone (Oppenauer oxidation)
equilibration
i-PrO
Oi-Pr
Al
O
O
C
C
Me
Me
H
R
R′
MPV
reduction
O
C
Me
Me
+
Oi-Pr
i-PrO
Al
O
H
R
R′
H+
H2O
OH
H
R
R′
product of
thermodynamic
control

Although perpendicular attack would result in maximum overlap between the HOMO of the nucleophile and the p-orbital at the carbonyl carbon that makes Up part of the LUMO π*, there is a significant antibonding overlap with the Other p-orbital on oxygen. Therefore, the best compromise is an angle of Attack of ~107° (Bürgi-Dunitz trajectory).

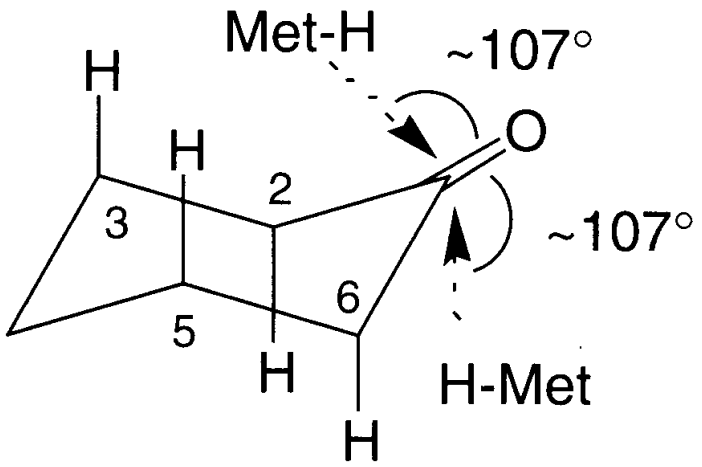


Two factors are competing with each other

(1) Steric interaction of the incoming "hydride" with the 3,5-diaxial hydrogens in the axial attack

(2) Torsional strain of the incoming "hydride" with the 2,6-diaxial hydrogens in the equatorial attack

Axial attack ($LiAlH_4$, $NaBH_4$) --→ equatorial alcohol



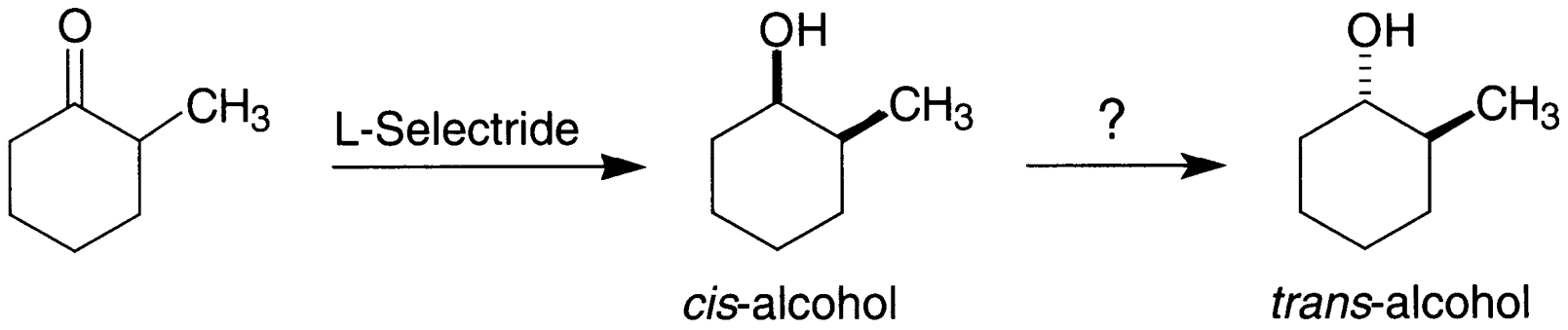
Steric interaction with the axial H_3 and H_5

Equatorial attack (Selectride, LTSBH) -→ axial alcohol

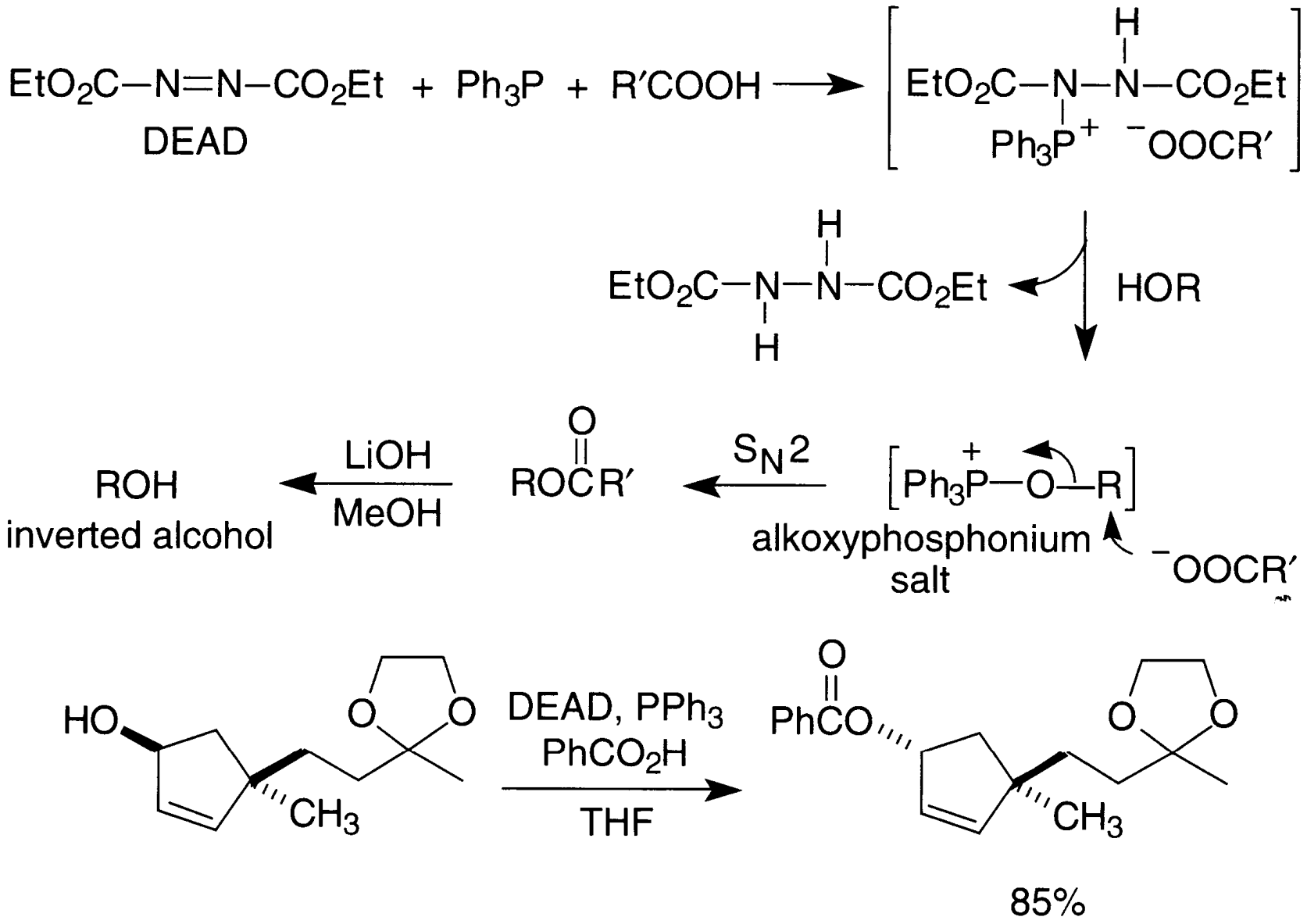
torsional strain with the axial H_2 and H_6

LTSBH: Li-tri-1,2-dimethylpropylborohydride

4.13 Inversion of secondary alcohol stereochemistry (the MITSUNOBU reaction)

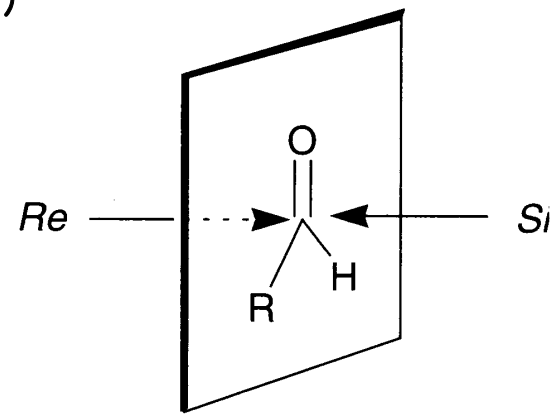


The mechanism of the Mitsunobu reaction is proposed to involve an Alkoxyphosphonium intermediate that undergoes S_N2 inversion.

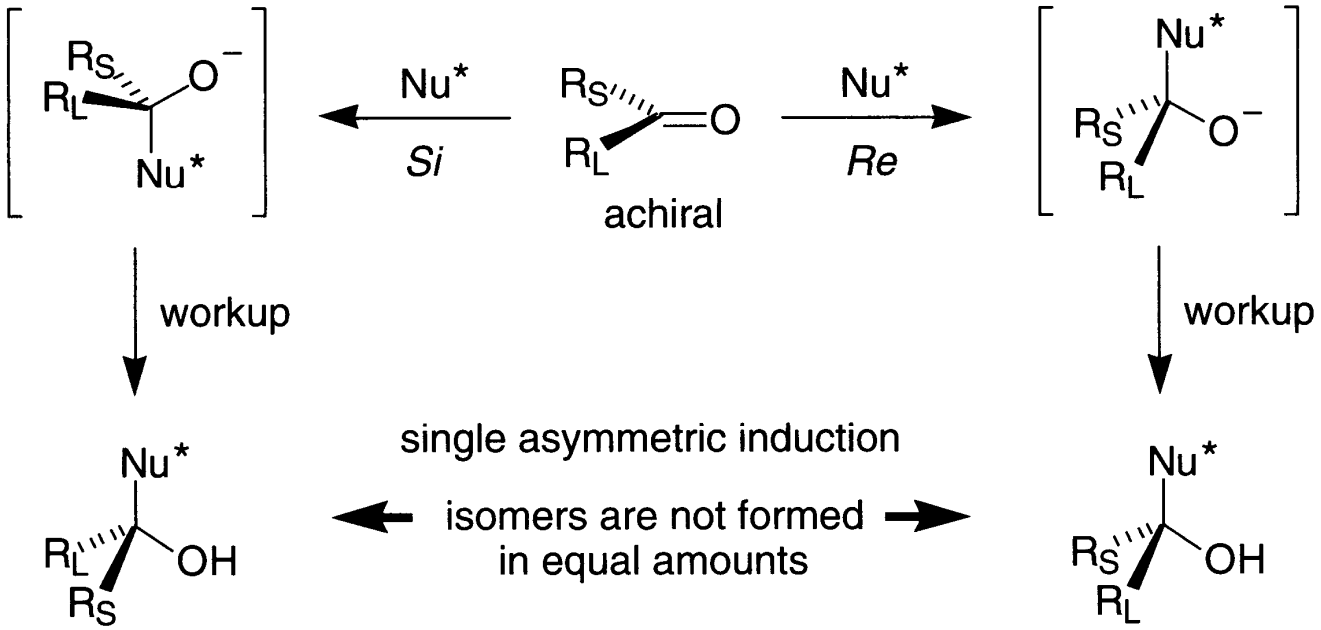

EtO2C–N=N–CO2Et
DEAD
+ Ph3P + R′COOH
EtO2C–N(H)–N(H)–CO2Et
Ph3P+ −OOCR′
EtO2C–N(H)–N(H)–CO2Et
HOR
[Ph3P+–O–R]
alkoxyphosphonium salt
−OOCR′
SN2
ROCR′
LiOH
MeOH
ROH
inverted alcohol
HO
CH3
DEAD, PPh3
PhCO2H
THF
PhCO
CH3
85%

4.14 Diastereo Selectivity in Acyclic System

We may distinguish between enantiotopic or diastereotopic faces in trigonal Moieties (>C=O and >C=C<)



Enantiotopicity

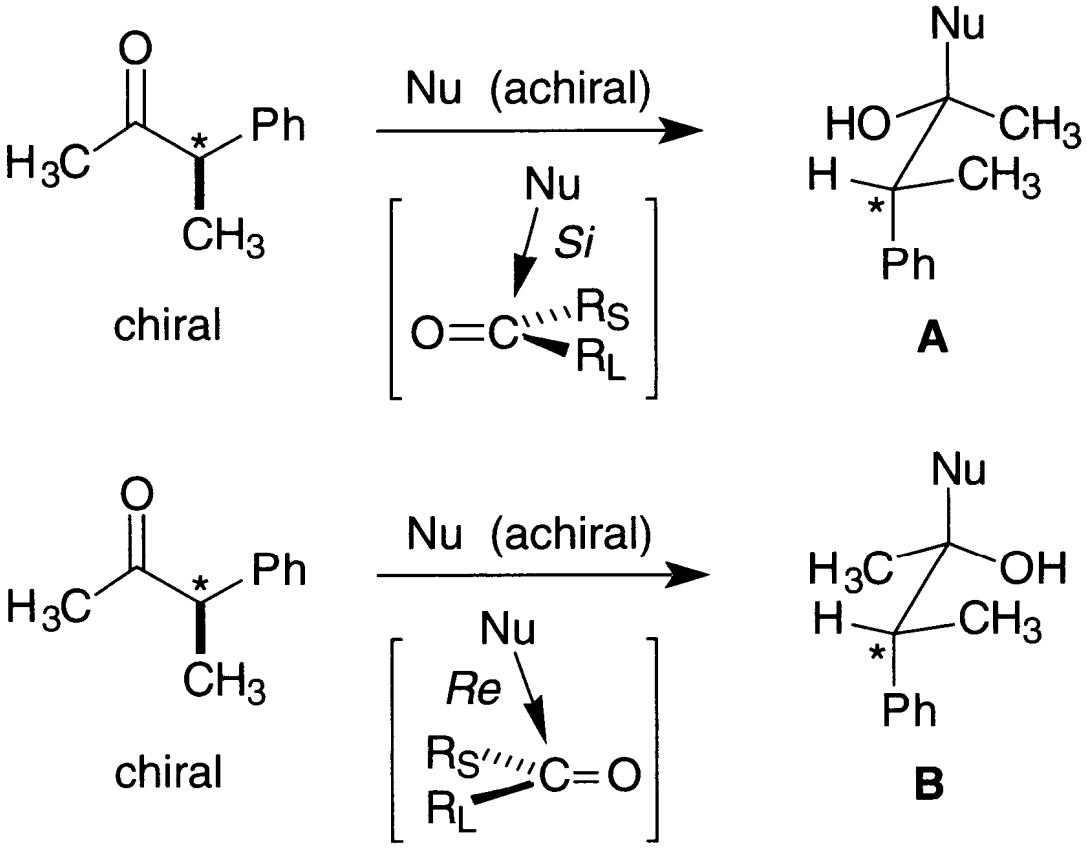


Diatereotopicity–Asymmetric Induction

The two π–faces of an aldehyde or of a ketone with at least one Stereogenic center are diastereotopic.

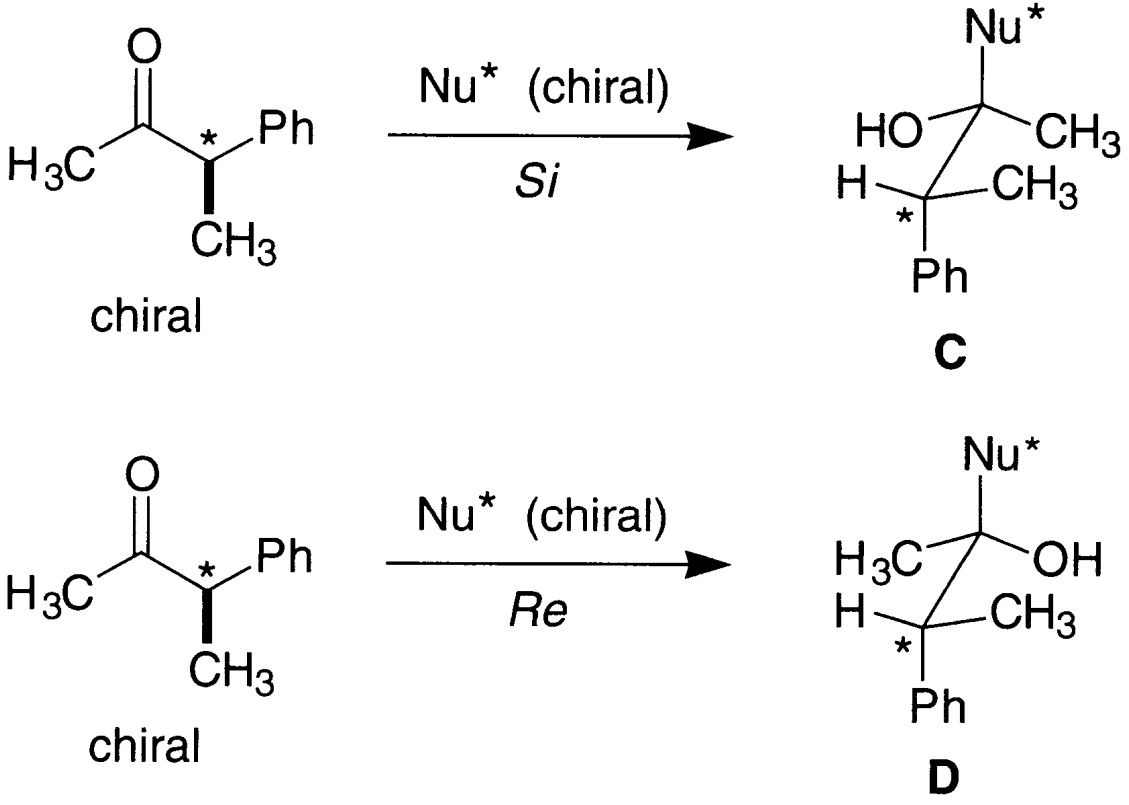
As a result, the Re and Si attack by an achiral nucleophile (i.e., LiAlH4, EtMgBr, PhLi) or an achiral enolate ion differ in energy, so unequal amount Of products are formed (A:B≠1).

single asymmetric induction



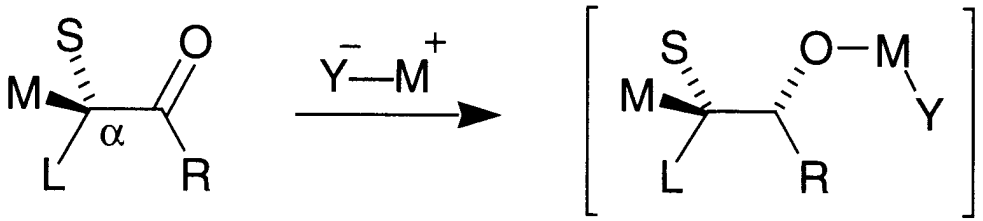
If two reactants are chiral,
the chirality elements of each elements of each reactant will operate either in concert (mached pair) or in opposite (mismatched pair) and together influence the stereochemical outcome of the reaction. In this case, C:D≠1.

double asymmetric induction

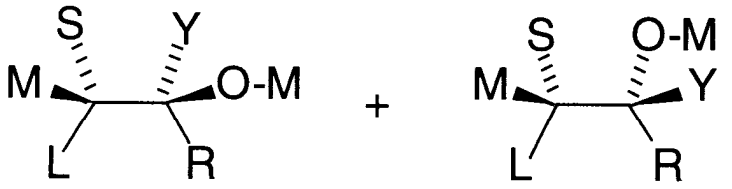


Prediction of Re vs. Si Addition: Cram's rule

A-carbonyl group coordinate with metal hydride or with organometallic Compounds, making the carbonyl group sterically more encumbered and More electrophilic. Then, nucleophile of the reagent attacks the carbonyl Carbon at the less hindered diastereoface, furnishing an excess of product C.



A M = Li, Mg, Zn, etc. **B**
Y = hydride, alkyl, etc.



C

major product
Cram product

D

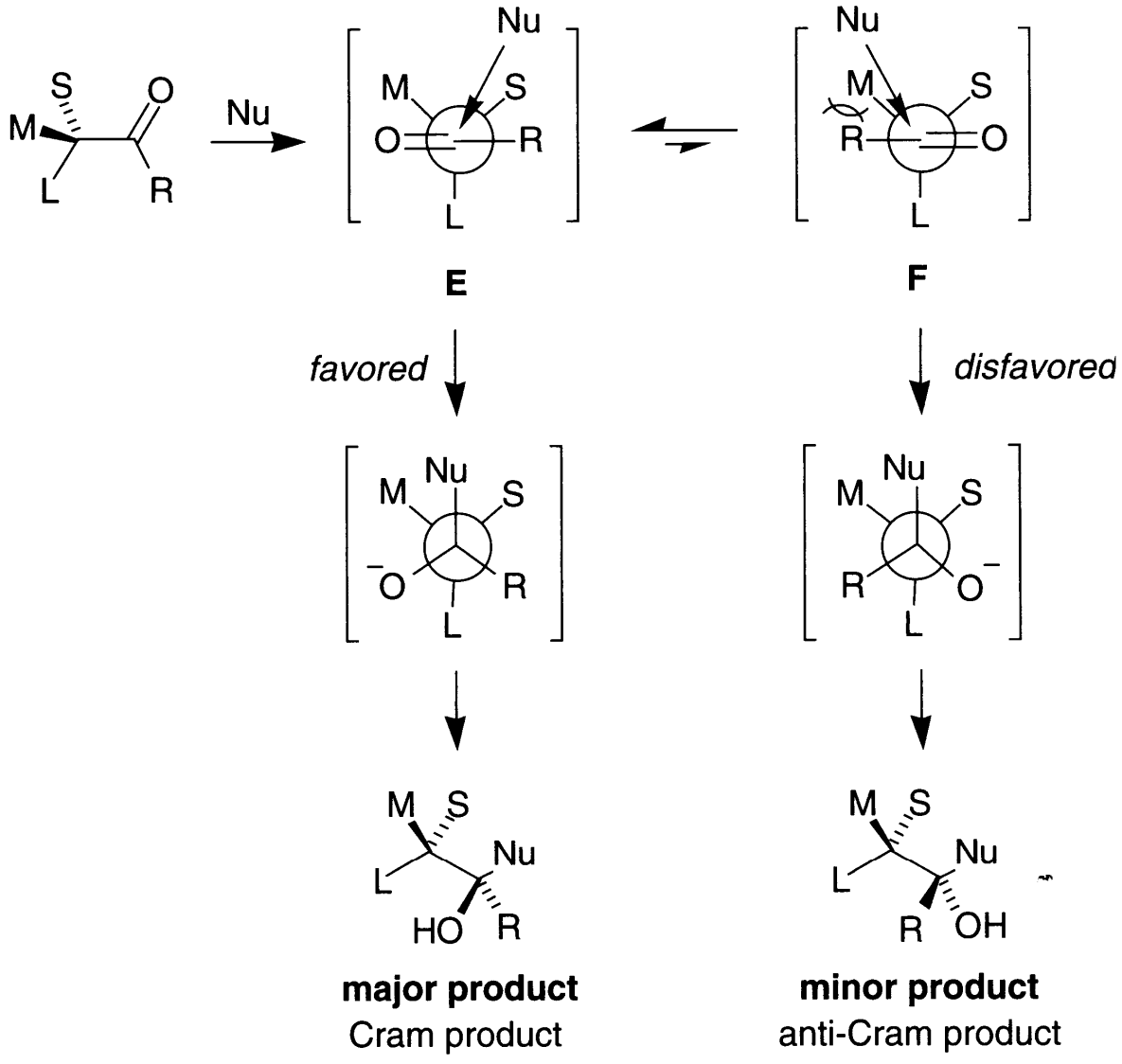
minor product
anti-Cram product

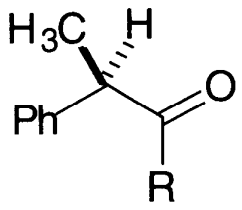
The Cram's rule is only valid when there is no chelating group attached to the Substrate and so neglects any dipolar interactions with the nuclophile. Moreover, there is considerable torsional strain between the L and the R groups.

Several subsequent models has addressed these shortcomings, the Felkin-Ahn model being the most popular.

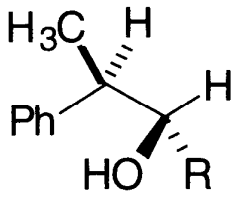
Felkin-Ahn Model.

In this model, nucleophile addition to ketone occurs from a conformation That places the entering group (Nu) in an antiperiplanar arrangement with The largest group L at the adjacent chiral center

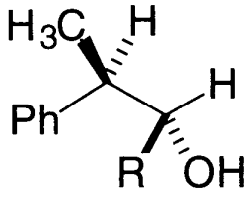

S
O
M
L
R
Nu
Nu
M
S
O
R
L
E
F
favored
disfavored
Nu
M
S
−O
R
L
Nu
M
S
R
O−
L
M
S
L
Nu
HO
R
M
S
L
Nu
R
OH
major product
Cram product
minor product
anti-Cram product



hydride

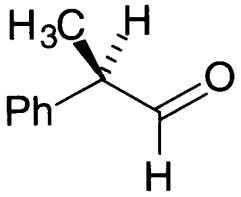


A



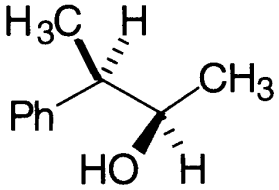
B

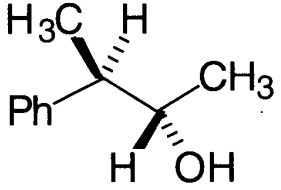
R= t-Bu, Et, Me $LiAlH_4$ A is major (Cram's product)



CH_3^-

THF

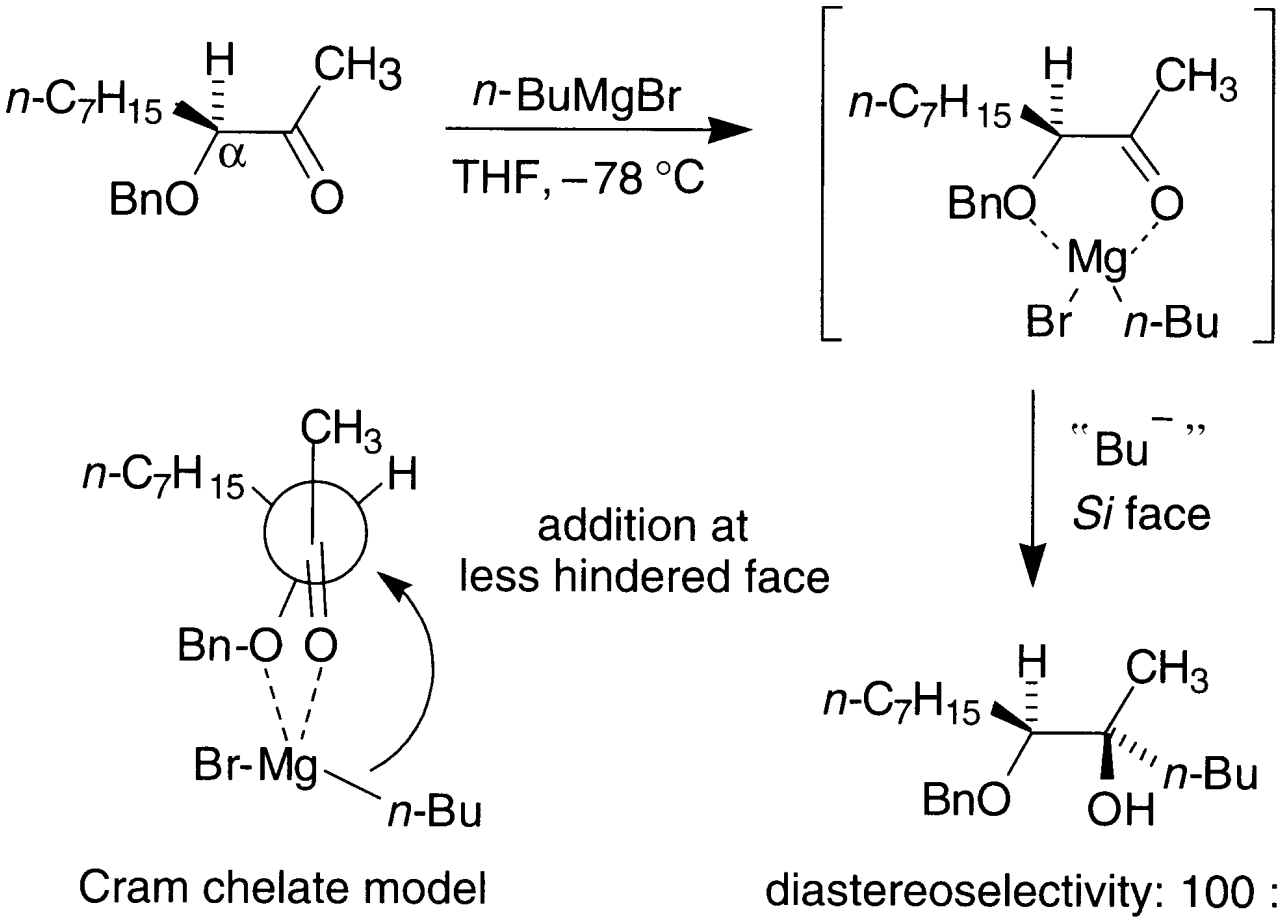




Generally, aldehydes reacts with lower stereoslectivity than ketones with The same reagent.

Chelation-controlled Addition Reactions

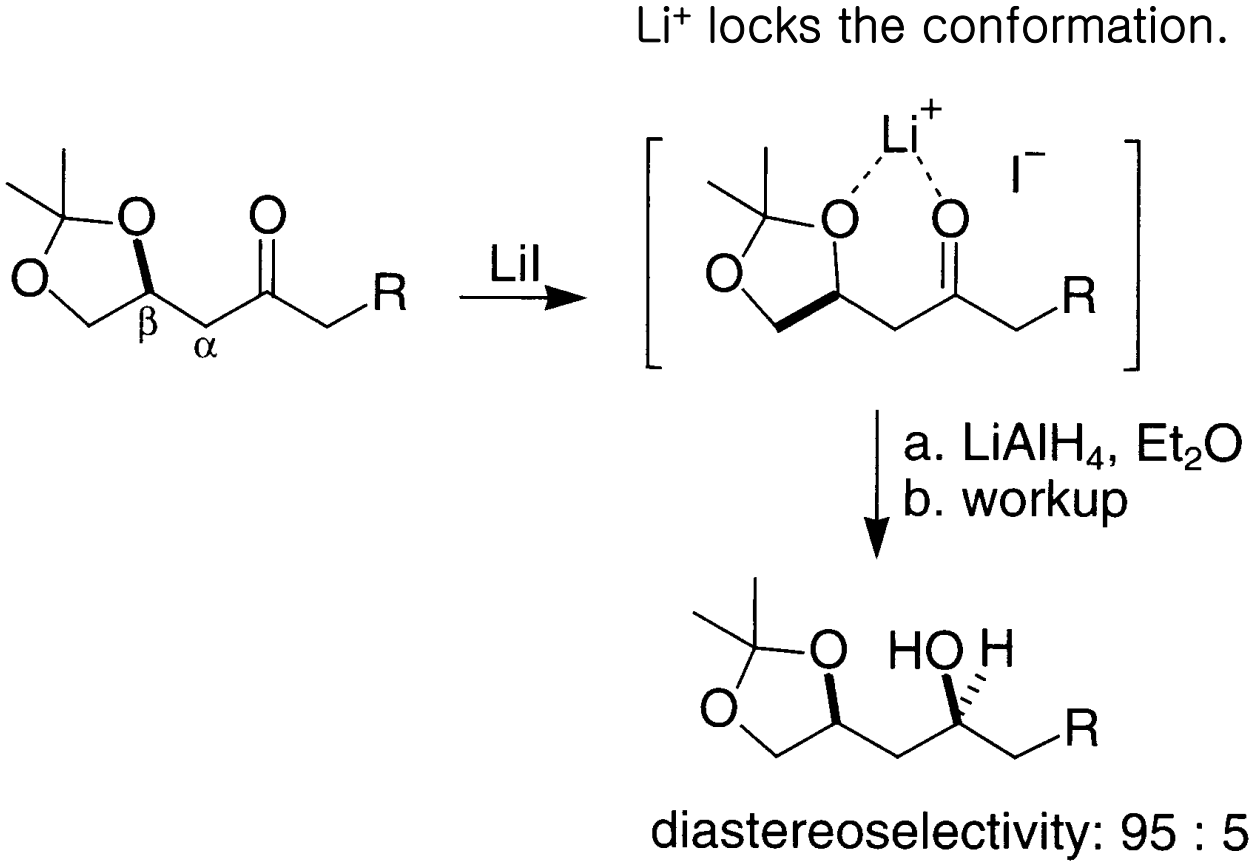
Cyclic model for nucleophilic addtions to chiral carbonyl compounds Containing an a-alkoxy, a-hydroxy, and a-amino group capable of Forming a chelate with the organometallic reagent.



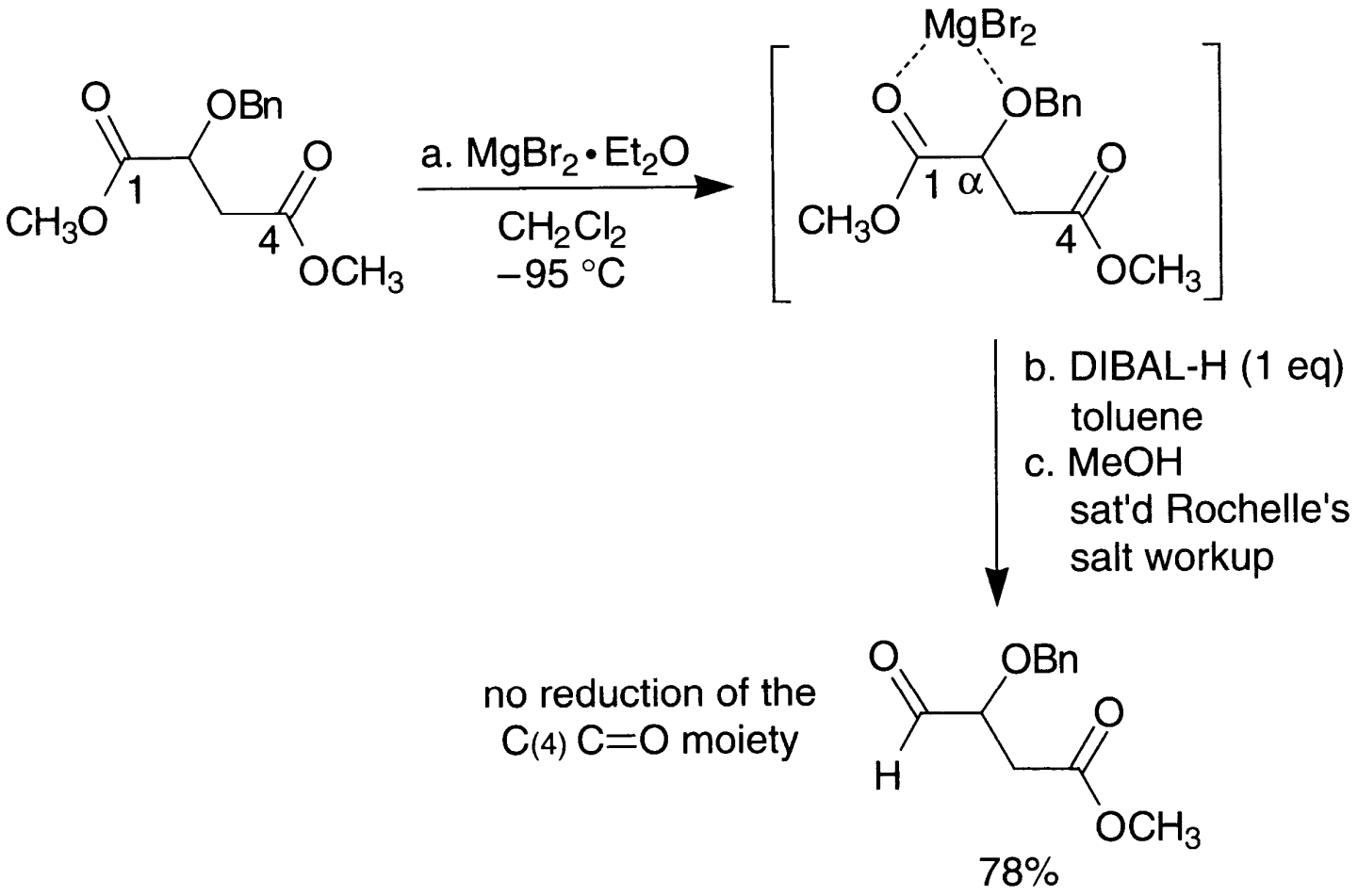
Cram chelate model

diastereoselectivity: 100 : 1

High diastereoselectivities in β-chelation-controlled reactions have also Been observed with aldehyde and ketone in the presence of a Lewis acid.

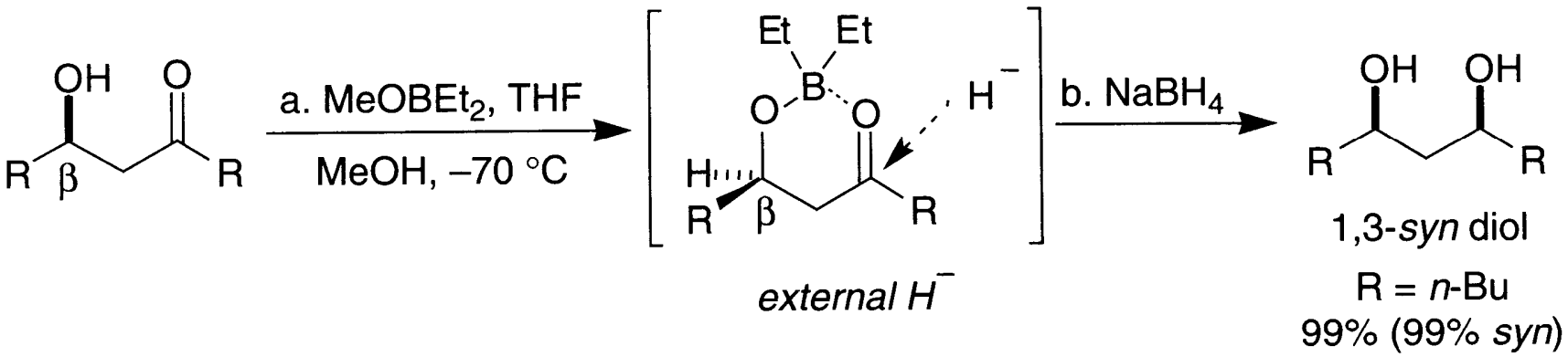


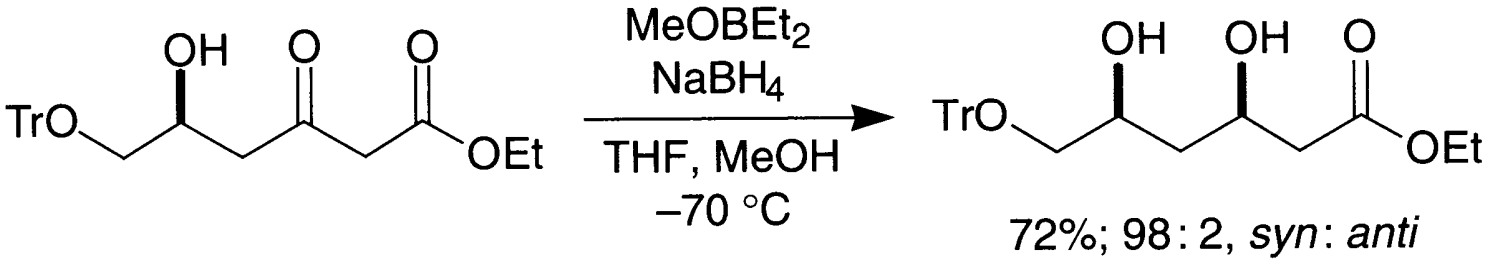
In general, five-membered ring chelates are formed in preference over Six-memebered ring chelates.



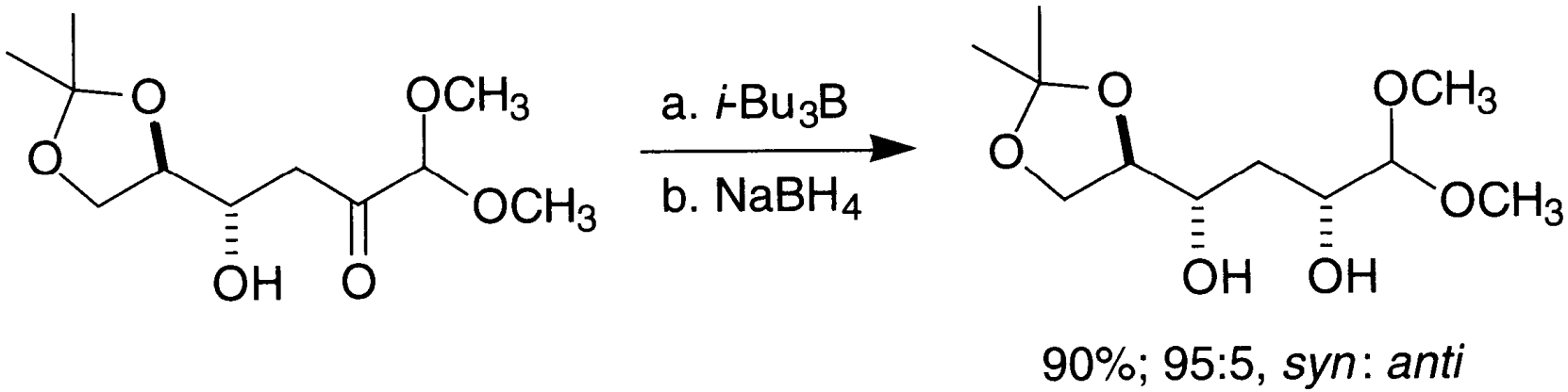
Hydroxy-directed Reduction of β-hydroxy ketones

Alkoxydialkylboranes ($R'OBR_2$) reacts with β-hydroxy ketones to form Boron chelate intermediates that on subsequent reduction give the 1,3-syn diols. Methoxydiethylborane and $NaBH_4$ are the reagents of Choice for this transformation.



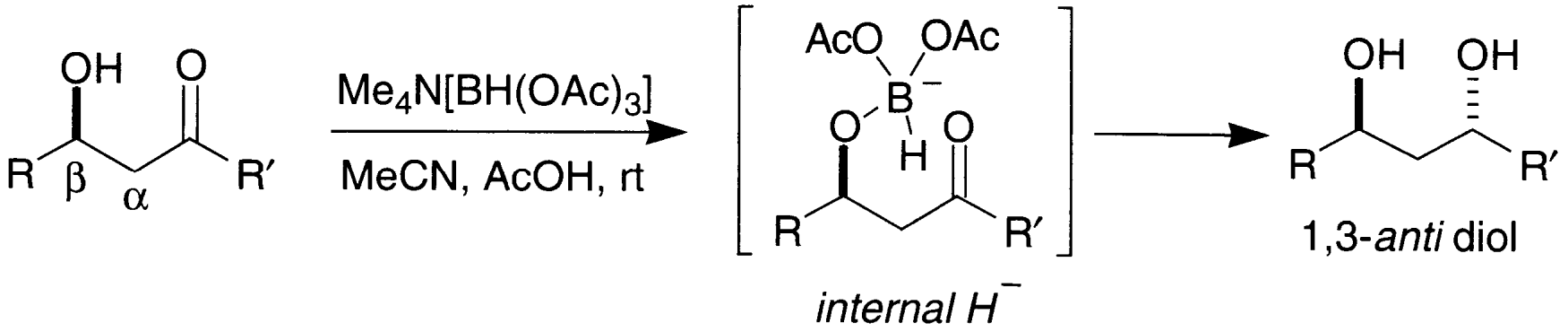


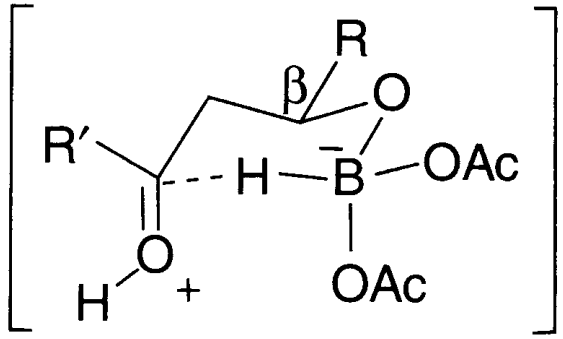
Trialkylboranes are also effective chelation agents in stereoselective $NaBH_4$ Reductions of β-hydroxy ketones to 1,3-syn diols.



90%; 95:5, *syn*: *anti*

However, treatment of β-hydroxy ketones with tetramethylammonium triacetoxy Borohydride complements the chelation approach described above by affording 1,3-trans diols.





intramolecular hydride delivery

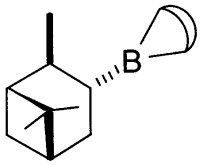
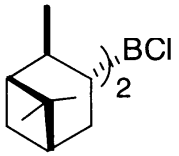
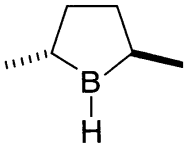
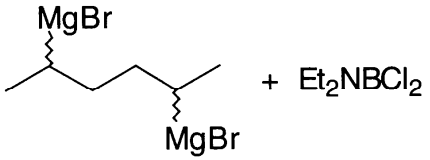
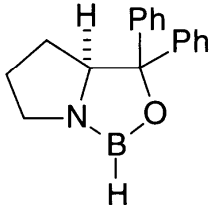
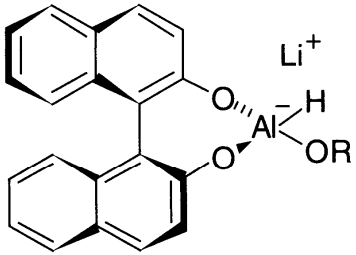
4.15 Ennatioselective Reductions

Three main strategies to obtain enantiomerically enriched (nonracemic) materials are listed below.

1) Optical resolution of a racemic mixture: not vey economical, since 50% of the product is lost.

2) Derivatization: start with a chiral compound and manipulate it in such a way as to maintain chirality through the reaction (SN_2 reaction or chirality transfer in pericyclic reactions.)

3) Asymmetric synthesis: (1) Use a chiral auxiliary (2) Use a chiral reagent (3) Use a chiral catalyst

Ipc-9-BBN [*R*- and *S*-Alpine-Borane]		(+)- or (−)-α-pinene + 9-BBN	136
Ipc_2BCl [(+)- and (−)-DIP Cl]		(+)- or (−)-Ipc_2BH + HCl in Et_2O	139
trans-2,5-Dimethylborolane [(*R*,*R*)- and (*S*,*S*)-DMB]		 (optical resolution required)	142
2,5-Oxazaborolidines (CBS reagents)		D- or L-Proline + PhMgBr, then BH_3	144
BINAL-H [(*R*)- and (*S*)-BINAL-H]		(+)- or (−)-binaphthol + $LiAlH_4$, then MeOH or EtOH	147

Alphine–Borane