

2.9. Reduction by hydride transfer-reagent:

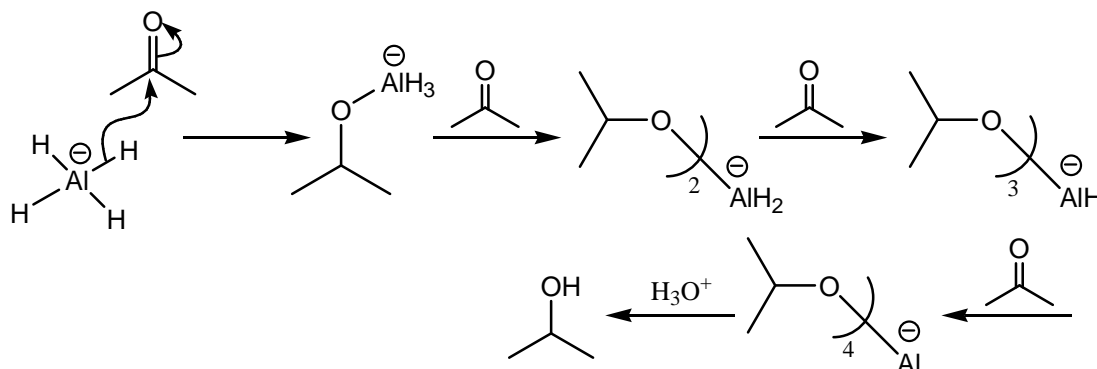
REACTIVITY OF HYDRIDE DONAR REDUCING AGENTS						
	Iminium ion	Acyl chloride	Aldehyde or ketone	Ester	Amide	Carboxylic salt
Hydride Donar	More Reactive			—————→	Least Reactive	
LiAlH ₄	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Red Al	—	Alcohol	Alcohol	Alcohol	Amine	Alcohol
LiAlH (Ot-Bu) ₃	—	Aldehyde	Alcohol	Alcohol	Aldehyde	—
NaBH ₄	Amine	—	Alcohol	Alcohol	—	—
NaBH ₃ CN	Amine	—	—	—	—	—
B ₂ H ₆	—	—	Alcohol	—	Amine	Alcohol
AlH ₃	—	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Disiamylborane	—	—	Alcohol	—	Aldehyde	—
DIBAL	—	—	Alcohol	Aldehyde	Aldehyde	Alcohol

2.9.1. Lithium aluminium hydride (LiAlH₄)

Most reductions of carbonyl compounds are done with reagents that transfer a hydride from boron or aluminium. Sodium borohydride is a mild reducing reagent that rapidly reduce aldehyde and ketones but not esters. Lithium aluminium is strongly donor reagent and it rapidly reduce ester acids, nitriles, amides as well as aldehyde and ketones. Neither sodium borohydride nor lithium aluminium hydride reacts with isolated carbon-carbon double bonds.

These reagents are nucleophilic and as such they normally attack polarized multiple bond such as C=O, C≡N by transfer of hydride ion to the more positive atom.

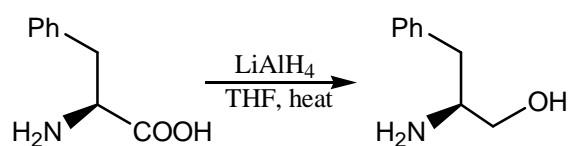
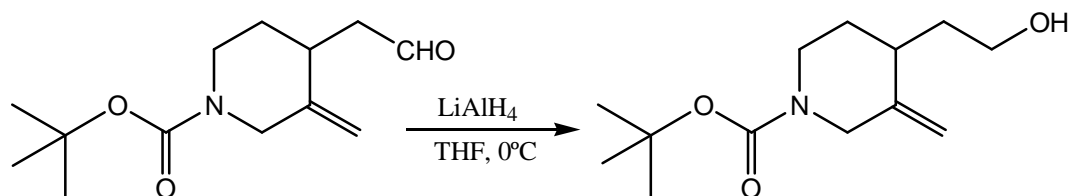
Lithium aluminium hydride is a more powerful reducing agent than sodium borohydride and reduces most of commonly encountered organic functional group.

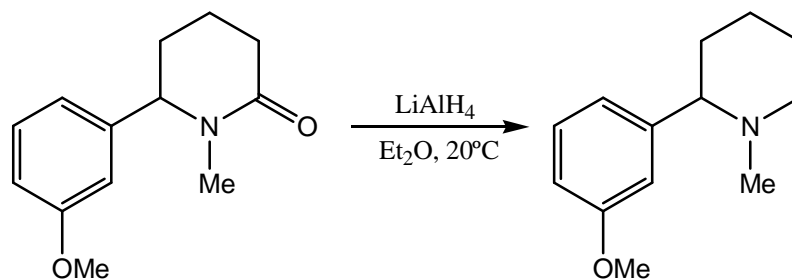


 Common Functional Groups, reduced by LAH

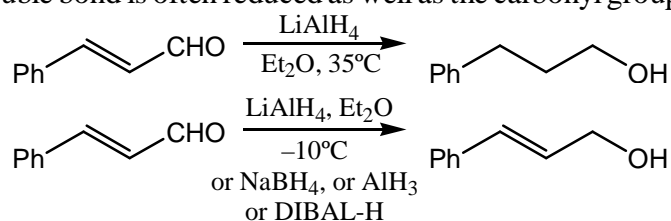
Functional groups	Reduction product
RCHO	\rightarrow R-CH ₂ OH
$\begin{array}{c} \text{R} \\ \diagdown \\ \text{C}=\text{O} \\ \diagup \\ \text{R} \end{array}$	\rightarrow $\begin{array}{c} \text{R} \\ \diagdown \\ \text{CH-OH} \\ \diagup \\ \text{R} \end{array}$
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{OR}' \end{array}$	\rightarrow R-CH ₂ OH + R'OH
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{OH} \end{array}$	\rightarrow RCH ₂ OH
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NHR}' \end{array}$	\rightarrow R-CH ₂ NHR'
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NR}'_2 \end{array}$	\rightarrow R-CH ₂ NR' ₂ or RCH(OH)NR' ₂ \rightarrow RCHO + R' ₂ (NH)
R-C \equiv N	\rightarrow R-CH ₂ -NH ₂ or $\begin{array}{c} \text{R}-\text{C}=\text{NH} \\ \\ \text{H} \end{array}$ \rightarrow RCHO
$\begin{array}{c} \text{R}-\text{C}=\text{N}-\text{OH} \\ \\ \text{H} \end{array}$	\rightarrow $\begin{array}{c} \text{H}_2 \\ \\ \text{R}-\text{C}-\text{NH}_2 \end{array}$
ArNO ₂	\rightarrow Ar-NH-NH-Ar or Ar-N=N-Ar
R-CH ₂ -Br	\rightarrow R-CH ₃
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{CH}_2-\text{O}-\text{S}-\text{Ar} \\ \parallel \\ \text{O} \end{array}$	\rightarrow R-CH ₃
$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{CH}_2 \\ \\ \text{H} \end{array}$	\rightarrow $\begin{array}{c} \text{OH} \\ \\ \text{C}-\text{CH}_3 \\ \\ \text{R} \quad \text{H} \end{array}$

Aldehyde, ketone, esters, carboxylic acids and lactones can all be reduced smoothly to corresponding alcohols under mild conditions. Carboxylic amides are converted into amines or aldehydes.

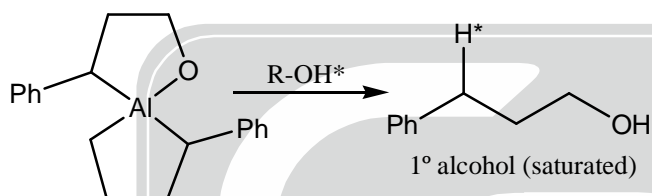




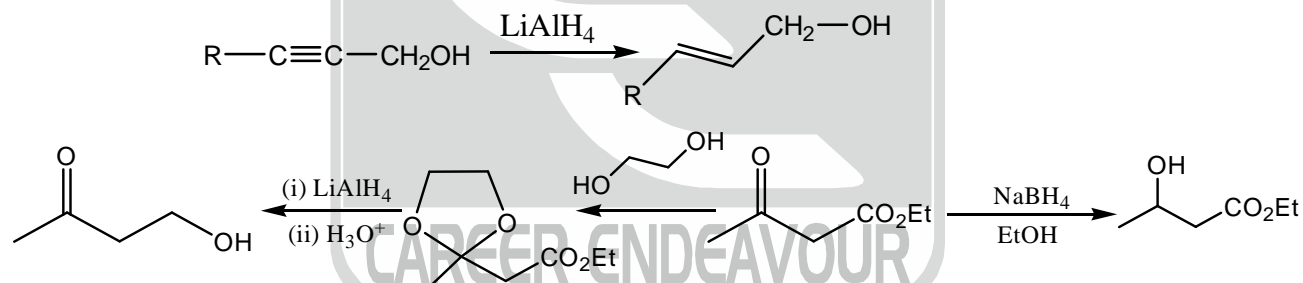
Reduction of β -aryl- α,β unsaturated carbonyl compounds with lithium aluminium hydride, where the carbon-carbon double bond is often reduced as well as the carbonyl group.



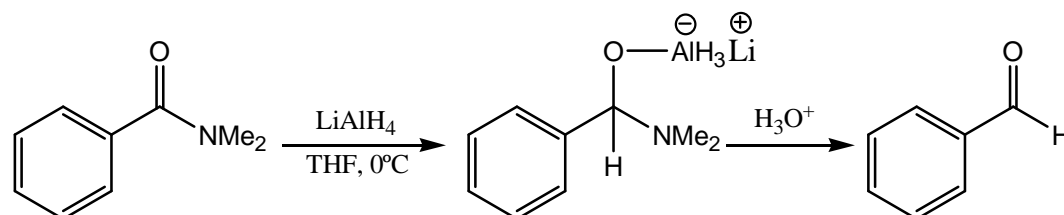
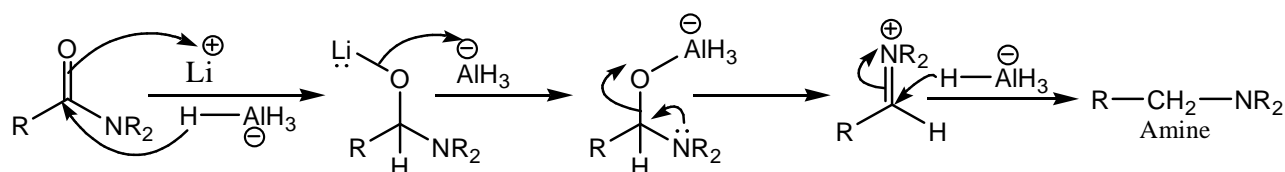
Cyclic organoaluminium compound is formed.



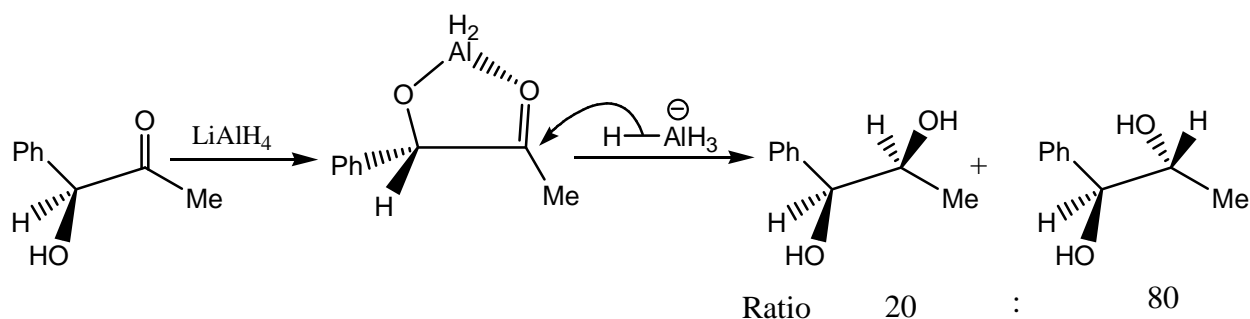
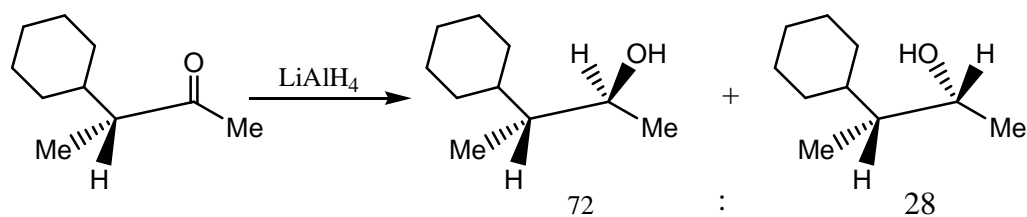
Reduction of propargylic alcohols ($\text{R}-\text{C}\equiv\text{C}-\text{CH}_2\text{OH}$) with lithium aluminium hydride to give trans alkenes.



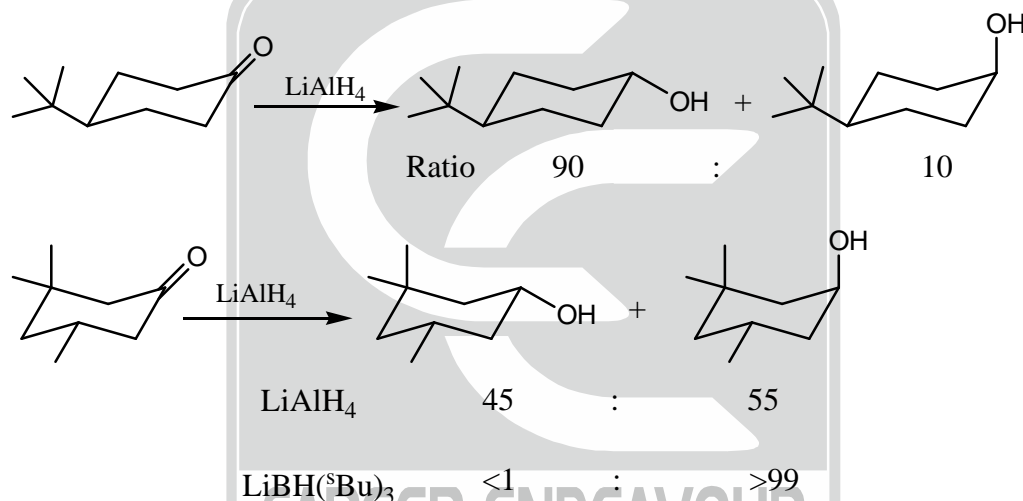
Reduction of amide to amine by Lithium Aluminium Hydride:



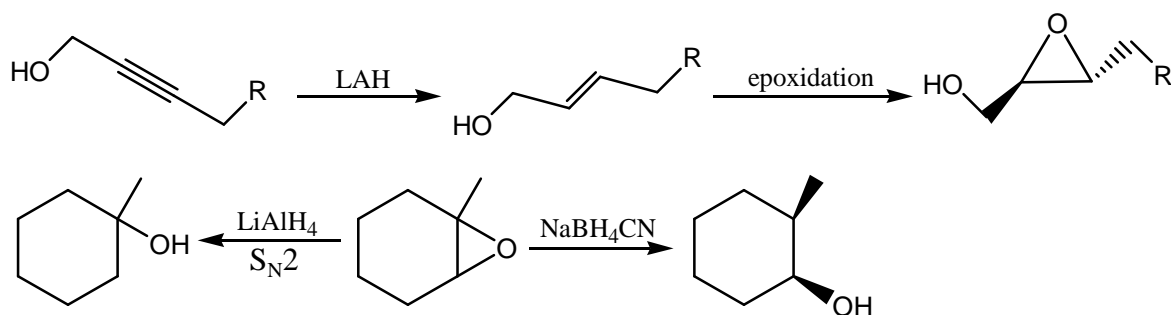
Stereoselectivity and chemoselectivity of LiAlH_4 :



Mixture of product is obtained, unhindered ketones react with LiAlH_4 , equatorial alcohols is the predominant product. When hindered ketones reacts with LiAlH_4 axial alcohol will be major product.



Alternative reagent can provide high selectivity. Dissolving metal reductions (Li, NH_3). Provides the thermodynamically more favourable equatorial alcohols almost exclusively from either two cyclic ketones.

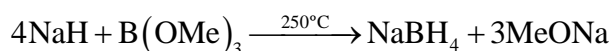


2.9.2. Sodium Borohydride (NaBH₄) :[NaBH₄/EtOH/25°C]**Common Functional Groups, reduced by NaBH₄**

Functional groups	Reduction product
RCHO	→ R—CH ₂ OH
$\begin{array}{c} \text{R} \\ \diagdown \\ \text{C}=\text{O} \\ \diagup \\ \text{R} \end{array}$	→ $\begin{array}{c} \text{R} \\ \diagdown \\ \text{CH}-\text{OH} \\ \diagup \\ \text{R} \end{array}$
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NHR}' \end{array}$	→ R—CH ₂ NHR'
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NR}'_2 \end{array}$	→ R—CH ₂ NR' ₂ or RCH(OH)NR' ₂ → RCHO + R' ₂ (NH)
$\begin{array}{c} \text{R}-\text{C}=\text{N}-\text{OH} \\ \\ \text{H} \end{array}$	→ $\begin{array}{c} \text{H}_2 \\ \\ \text{R}-\text{C}-\text{NH}_2 \end{array}$
R—COCl	→ R—CH ₂ NH ₂
RCOOCOCi	→ RCH ₂ OH
$\text{R}-\text{N}=\text{N}=\text{N}^{\ominus}$	→ RNH ₂
$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{R}-\text{C} \quad \text{CH}_2 \\ \\ \text{H} \end{array}$	→ $\begin{array}{c} \text{OH} \\ \\ \text{R}-\text{C}-\text{CH}_3 \\ \\ \text{H} \end{array}$

Sodium borohydride is a very selective reducing agent and reduce aldehyde and ketone to alcohols. Sodium borohydrides is a comparatively weak reducing agent. Because boron hydrogen has more covalent character than lithium hydrogen. It does not react or slow react in the case of ester or cyclic ester functional group. NaBH₄ is a chemoselective reagent for carbonyl compound in the presence of esters (cyclic or acyclic) and amide functional group.

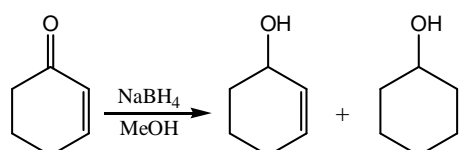
It is prepared by the reaction of sodium hydride and trimethyl borate.



NaBH₄ is insoluble in ether but soluble in alcohol and water. So, it is used in hydroxylic solvent like alcohol, isopropanol etc.

Reducing properties of sodium borohydride are substantially modified in the presence of metal salt, particularly in the presence of cerium (III) chloride.

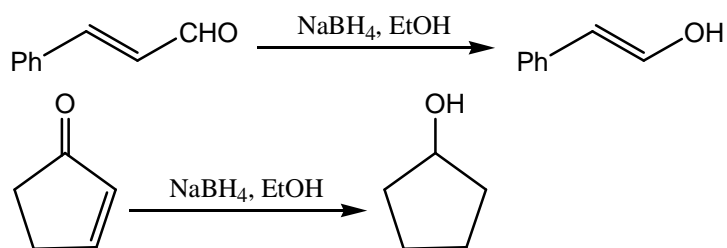
Sodium borohydride reduces α,β unsaturated ketone with extremely high selective, such that 1, 2, not 1, 4 reduction occurs to gives allylic alcohols.



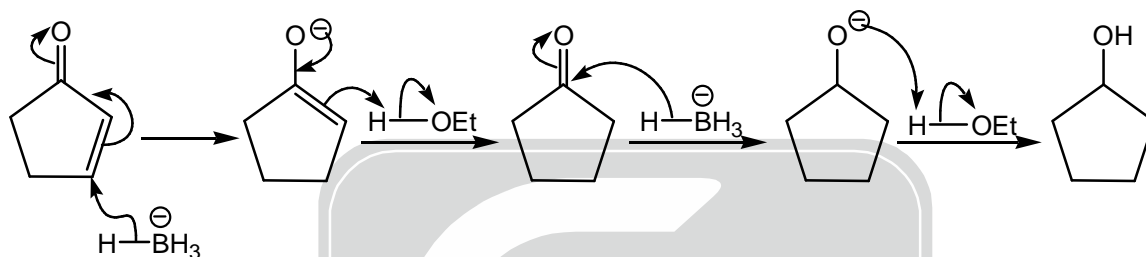
no CeCl ₃	59	:	41
CeCl ₃ ·7H ₂ O	99	:	1

Sodium borohydride is a nucleophile that you have seen reducing simple aldehyde and ketone to alcohols. But it will also do conjugate addition reaction, which of the alternatives actually takes place depends on the reactivity of the >C=O group.

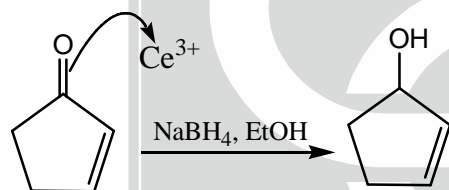
NaBH_4 usually react with α, β unsaturated aldehyde to give alcohols by direct addition to the carbonyl group.



Mechanism:

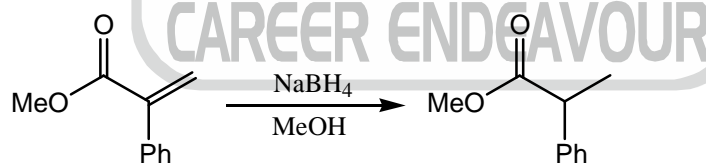


Lucas reduction:

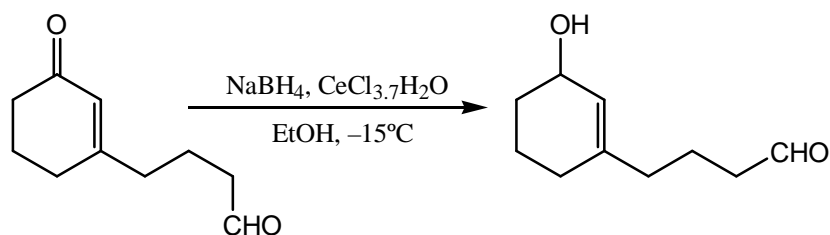


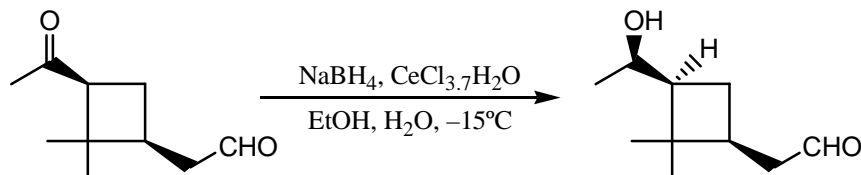
CeCl_3 : Hard Lewis acid model salt

For ester and other less reactive carbonyl compounds, conjugate addition takes place because NaBH_4 does not reduce ester or amide.

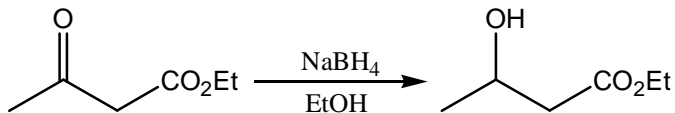


α, β unsaturated ketones are reduced selectively in the presence of saturated ketones or aldehydes. ketones can be sometimes be reduced in the presence of an aldehyde. More reactive aldehyde group is protected as the hydrate, which is stabilised by complexation with cerium ion and is generated during isolation of the product.

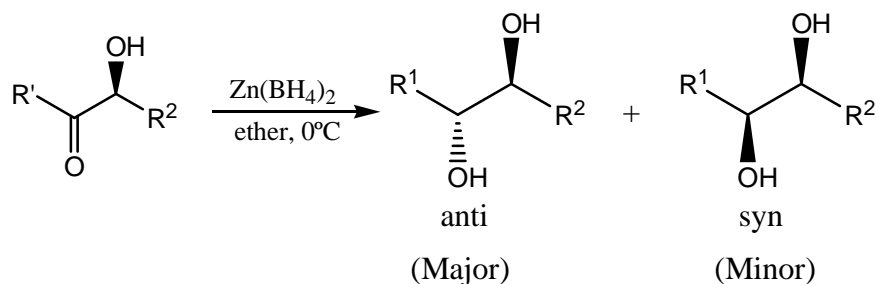
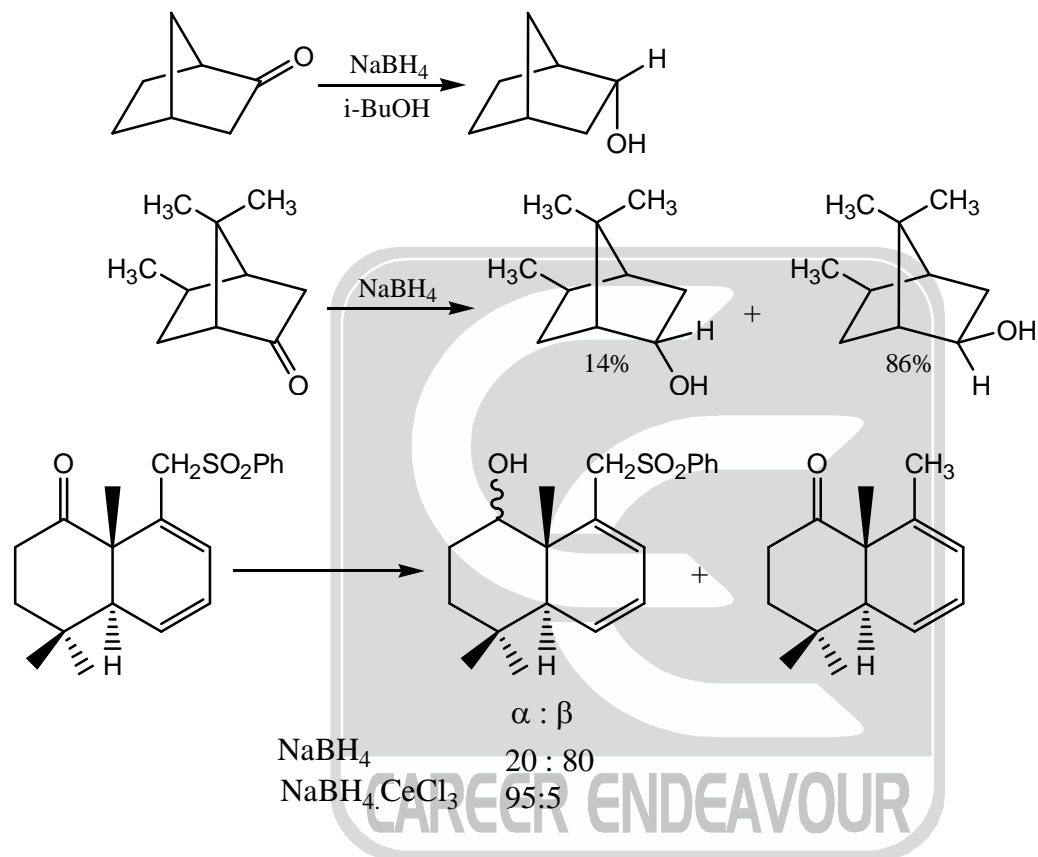




NaBH_4 is more chemoselective than LiAlH_4 . At room temperature in ethanol it readily reduce aldehyde and ketone but it does not generally attack esters or amide

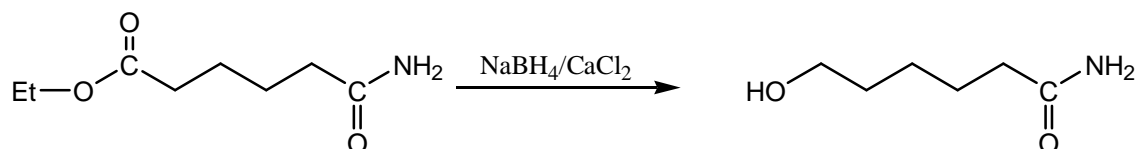


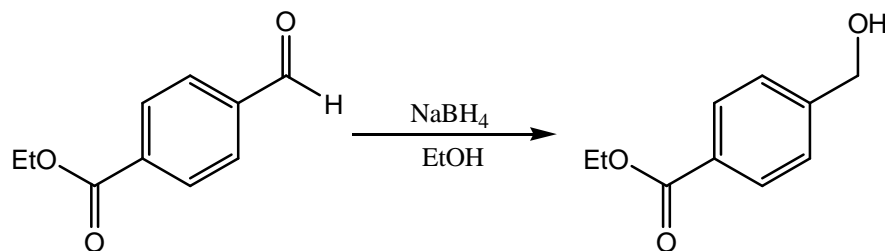
Stereoselectivity:



Chemoselectivity:

Reduction of carboxylic ester in the presence of carboxylic amide is possible using sodium borohydride and calcium chloride.



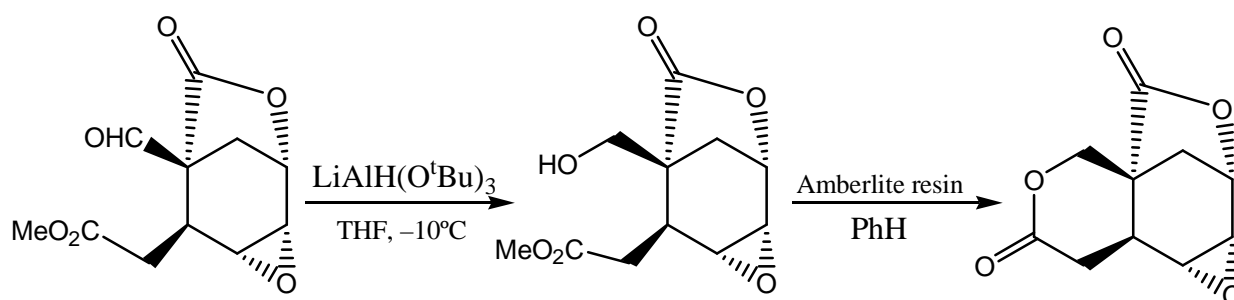


2.9.3. Lithium tri-*t*-butoxyaluminium hydride (lithium hydridotri-*t*-butoxyaluminate) $[\text{LiAlH}(\text{O}^t\text{Bu})_3]$:

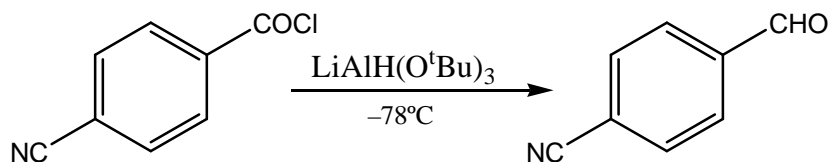
Common Functional Groups, reduced by $[\text{LiAlH}(\text{O}^t\text{Bu})_3]$

Functional groups	Reduction product
	$\text{R-CH}_2\text{OH} + \text{R}'\text{OH}$
	$\text{R-CH}_2\text{NHR}'$
	$\text{R-CH}_2\text{NH}_2$
RCOOCOCI	RCH_2OH
$\text{R-C}\equiv\text{N}$	RCH_2NH_2

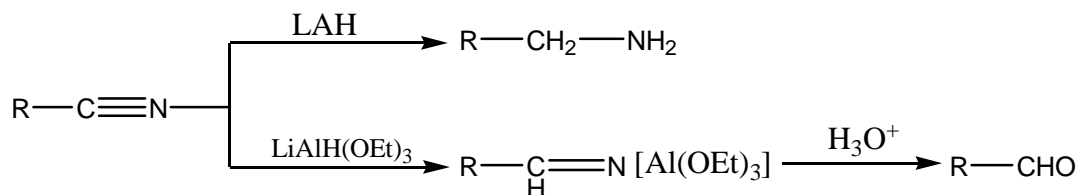
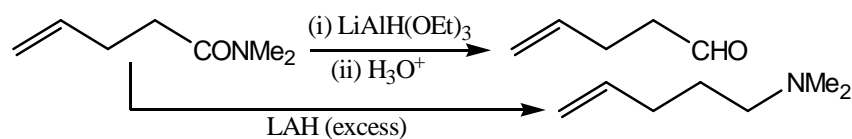
$[\text{LiAlH}(\text{O}^t\text{Bu})_3]$ is prepared by the action of three equivalent of *t*-butyl alcohol on lithium aluminium hydride. Lithium tri-*t*-butoxyaluminium hydride is a much milder reducing agent than lithium aluminium hydride. Aldehyde and ketones are reduced normally to alcohols, carboxylic ester and epoxides react only slowly and halides, nitriles and nitro group are not reduced.



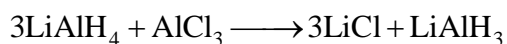
$\text{LiAlH}(\text{O}^t\text{Bu})_3$ reduce carboxylic acid, acid chloride and di-alkylamides into aldehyde.



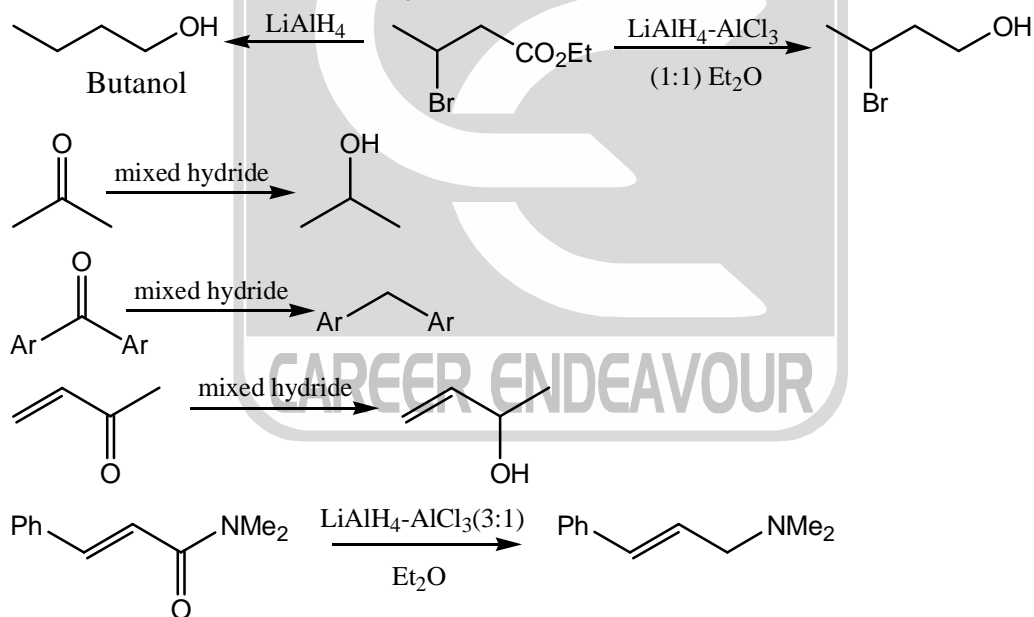
$\text{LiAlH}(\text{O}^t\text{Bu})_3$ reduce tertiary amide into aldehyde.



2.9.4. Mixed lithium aluminium hydride-aluminium chloride reagent:



The general effect of the addition of AlCl_3 is to lower the reducing power of LiAlH_4 .



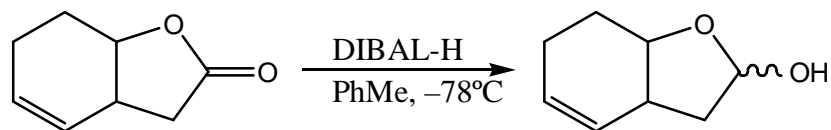
2.9.5. Diisobutylaluminium hydride (DIBAL-H):

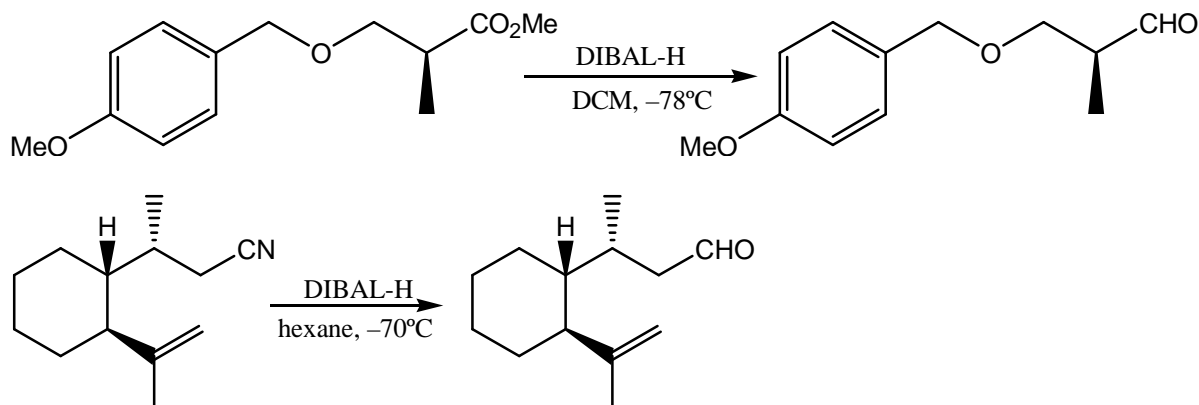
[DIBAL-H or DIBAL or $i\text{Bu}_2\text{AlH}$]

Common Functional Groups, reduced by [DIBAL-H or DIBAL or $i\text{Bu}_2\text{AlH}$]

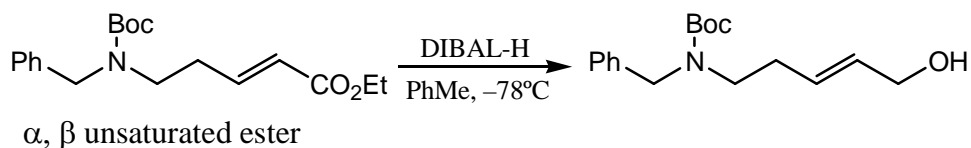
Functional groups	Reduction product
R-CHO	$\text{R-CH}_2\text{OH}$
	R-CHO
	R-CHO
	R-CHO
	R-CHO
	$\text{R-CH}_2\text{-NH-R}$
	R-CHO
	RCH_2NH_2
	$\text{R-CH}_2\text{OH} + \text{R'OH}$

DIBAL reduce esters and ketone into alcohols. DIBAL on reduction of nitriles gives amines and epoxides are cleaved to alcohols. At low temperature, esters and lactones are reduced directly to aldehydes (or lactols); nitriles and carboxylic amide gives amines which are readily converted into aldehydes by hydrolysis.

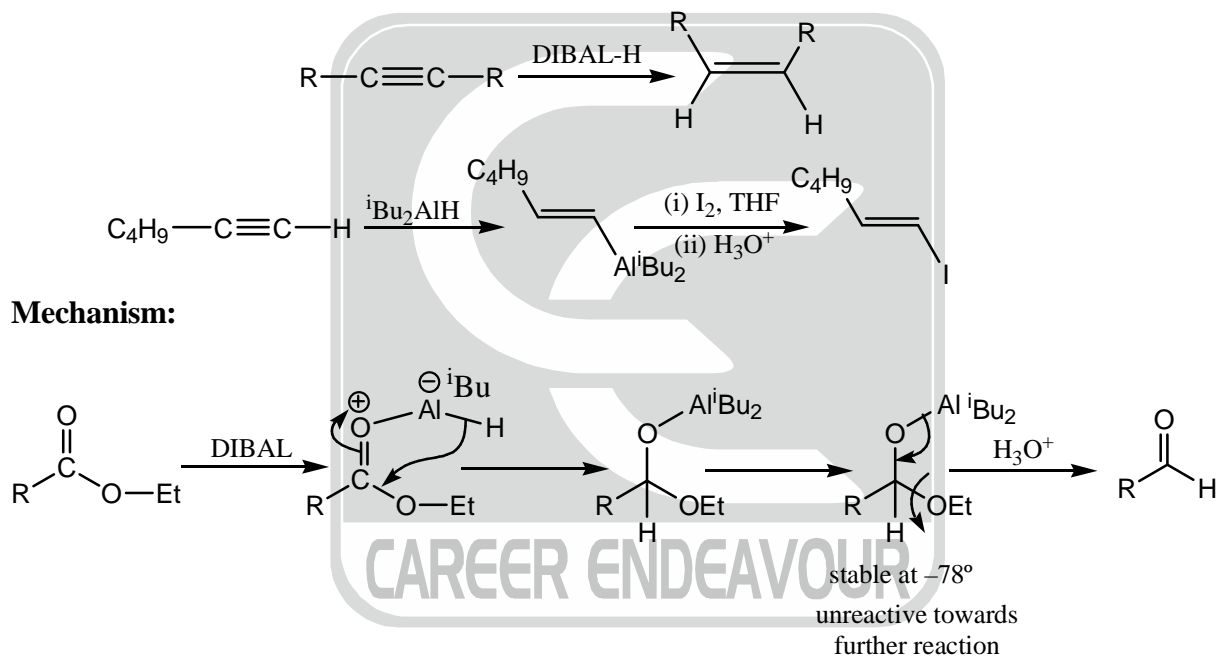




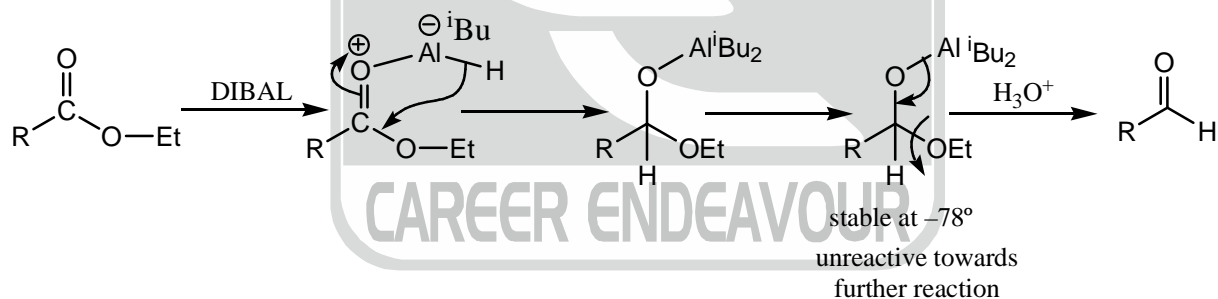
DIBAL reduce the α, β -unsaturated carbonyl compound to allylic alcohols



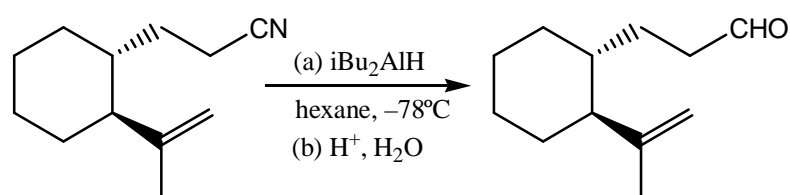
Note: DIBAL reduce to alkyne cis alkene

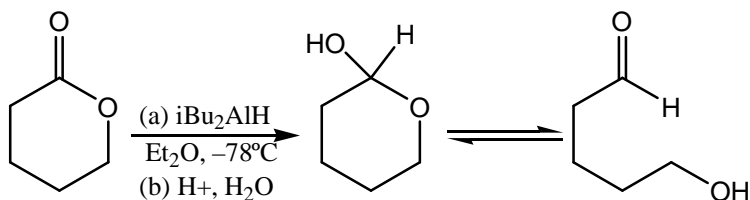


Mechanism:



Reduction of Nitrile:





Summary : At ordinary temperature DIBAL reduce

Ester and ketone \longrightarrow Alcohol

Nitrile \longrightarrow Amine

Epoxide \longrightarrow Alcohol

Lactone \longrightarrow Lactols

Carboxylic acid \longrightarrow Imine

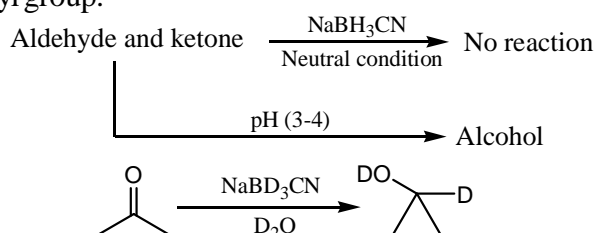
Alkyne \longrightarrow cis-alkene

2.9.6. Sodium cyanoborohydride (NaBH_3CN) and Sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$) :

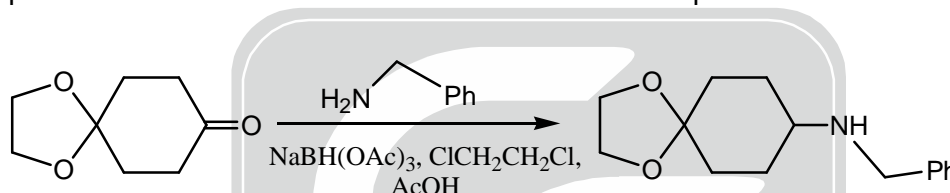
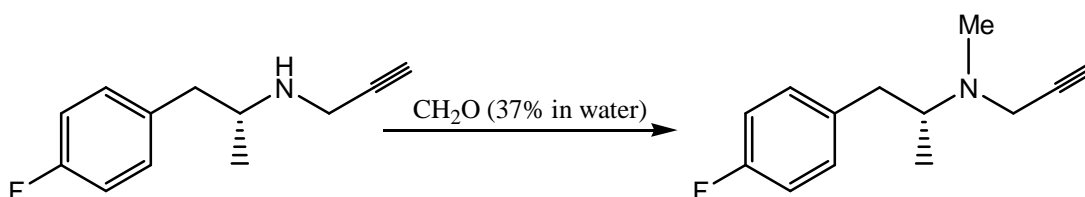
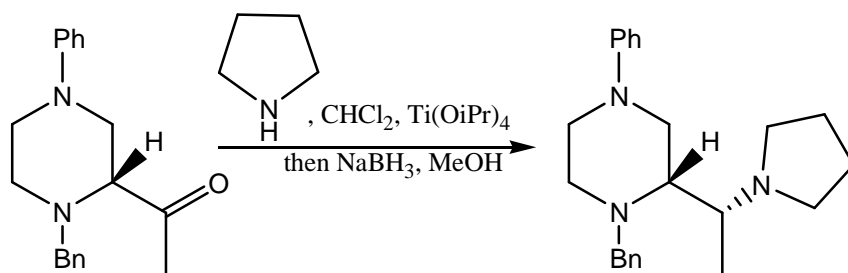
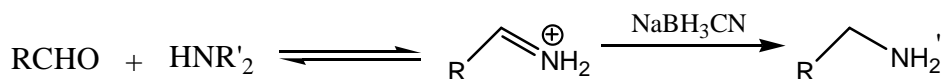
Common Functional Groups, reduced by ($\text{NaBH}(\text{OAc})_3$) and (NaBH_3CN)

Functional groups	Reduction product
R-CHO	$\text{R-CH}_2\text{OH}$
	R-CHO
	$\text{R-CH}_2\text{-NH-R}$
	R-NH_2
	$\text{CH}_3\text{-CH}_2\text{-OH}$

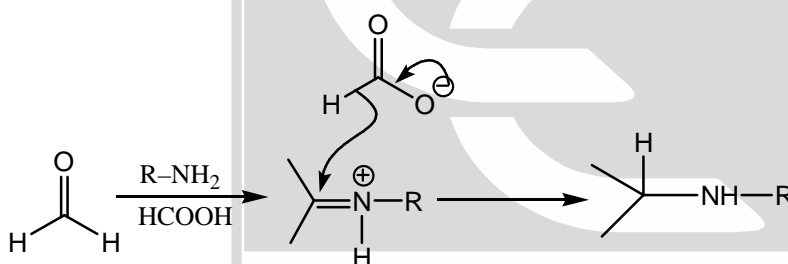
Sodium cyanoborohydride is more selective reducing agent than sodium borohydride because of electron-withdrawing effect of the cyano group. Aldehyde and ketone are unaffected by sodium cyanoborohydride in neutral solution but they are readily reduce to corresponding alcohol at pH = 3-4 by way of protonated carbonyl group.



Iminium groups are more easily reduced than carbonyl group in acid solution. Reductive amination of aldehyde or ketones by way of the iminium salt formed from the carbonyl compound. A primary or secondary amine, typically at pH > 5 at this pH carbonyl group unaffected.



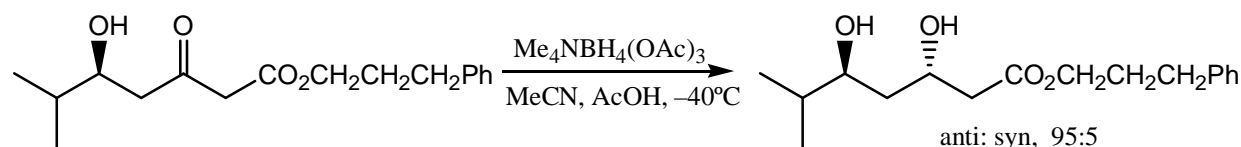
Eschweiler-Clark reaction:



Note: Sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$):

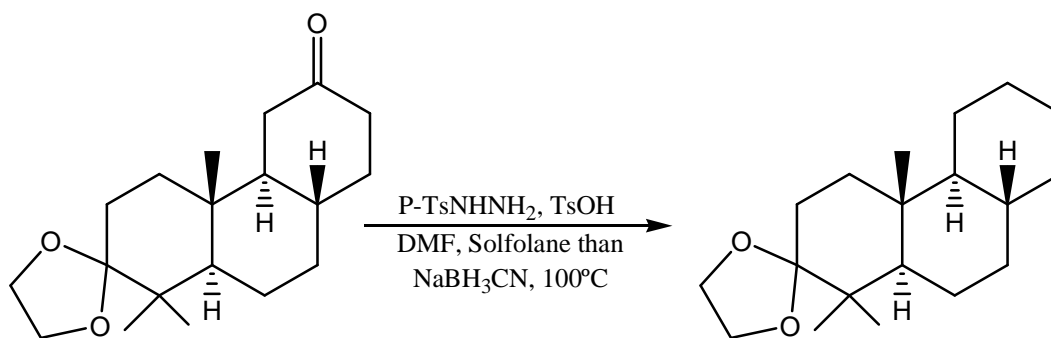
Reduce aldehyde selectively in the presence of ketones. However, α , β hydroxy ketones are reduced with this reagent and stereoselectively gives anti-diol product. The reagent tetramethyl ammonium triacetoxyborohydride, $\text{Me}_4\text{NBH}(\text{OAc})_3$ has shown excellent selectivity for this transformation.

Exchange of one of the acetoxy groups for alcohol is thought to proceed stereoselective intramolecular transfer of hydride.

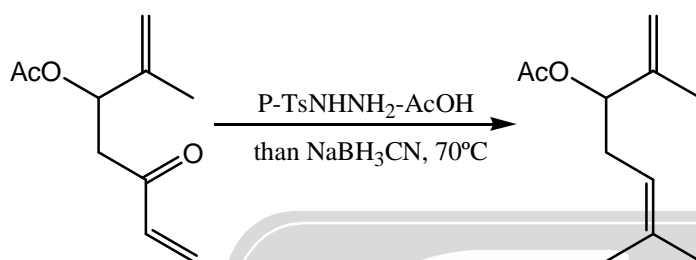


Reduction of tosylhydrazone of aliphatic carbonyl group (in acidic modify):

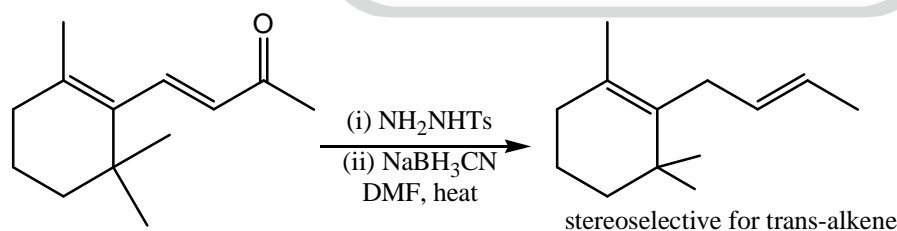
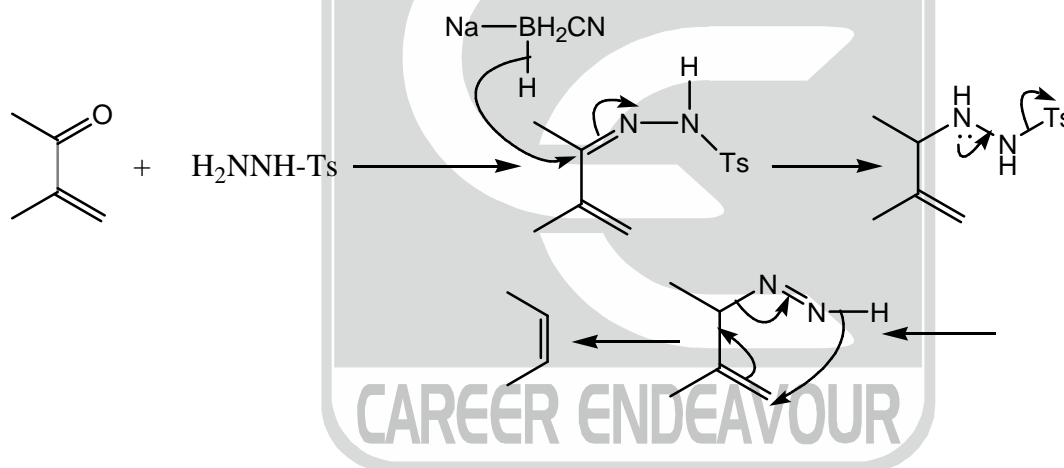
Carbonyl compound into corresponding hydrocarbons involves reduction of the derived toluene-*p*-sulfonyl (tosyl) hydrazones with sodium cyanoborohydride in acidic dimethylformamide (DMF). The reaction is specific for aliphatic carbonyl compound, aromatic compound are normally unaffected.



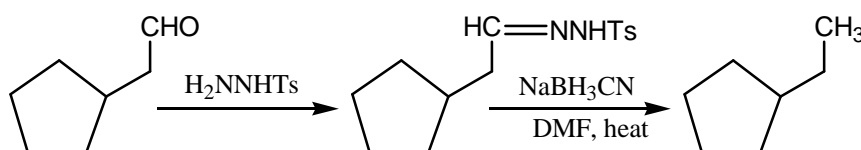
Reduction of α, β unsaturated carbonyl compound with tosylhydrazone followed by the migration of double bond.



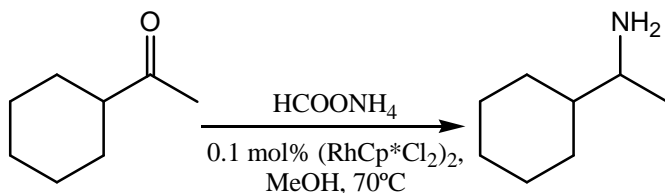
Mechanism:



Note: $\text{Zn}(\text{BH}_4)_2$ is a particularly effective agent for the reductive amination of α, β unsaturated aldehyde and ketone.



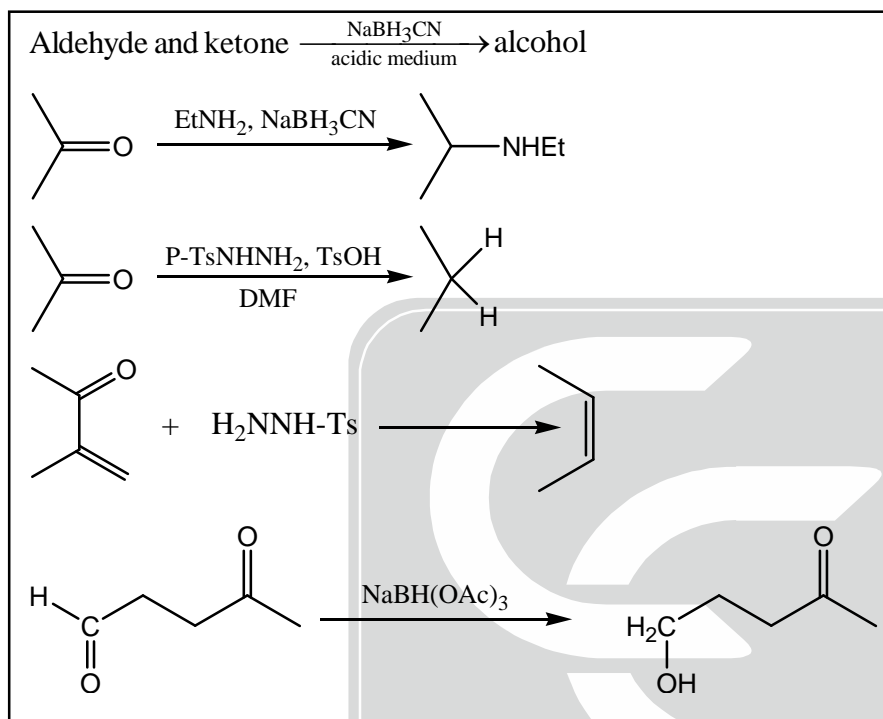
Selective formation of primary amine uses the rhodium (III) complex $[\text{RhCp}^*\text{Cl}_2]_2$ as a catalyst and ammonium formate (HCOONH_4), which acts as the source of the ammonia and the hydride.



$\text{Cp}^* = (\text{Pentamethylcyclopentadienyl anion})$

Note: Sodium triacetoxy borohydride can reduce aldehyde selectively in the presence of ketones.

Summary:



2.9.7. Borane and its derivatives:

Table: Functional groups reduced by borane

Functional Group	Reduction Product
RCOOH	RCH_2OH
$\text{RHC}=\text{CHR}$	
RCHO	RCH_2OH
$\text{R}_2\text{C}=\text{O}$	$\text{RCH}(\text{OH})\text{R}$
$\text{R}-\text{C}\equiv\text{N}$	RCH_2NH_2
RCONR_2	RCH_2NR_2
RCO_2COR	RCH_2OH
	$\text{R}-\text{CH}_2-\text{CH}_2-\text{OH}$
$\text{RCO}_2\text{R}'$	$\text{RCH}_2\text{OH} + \text{R}'\text{OH}$ (slow rate of reaction)
RCOCl	No reaction
RNO_2	No reaction