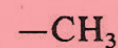
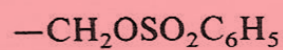
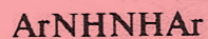
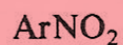
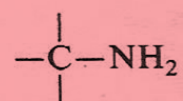
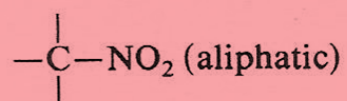
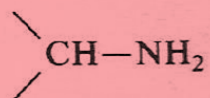
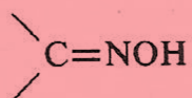




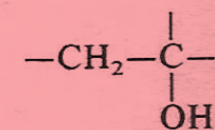
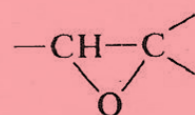
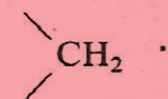
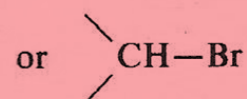
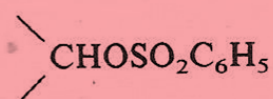
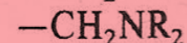
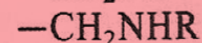
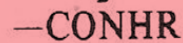
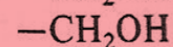
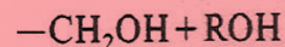
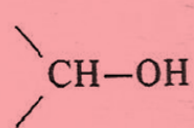
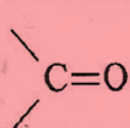
# Lithium Aluminum Hydride as a Reducing Agent [LiAlH<sub>4</sub>]

## General characteristics of Lithium Aluminum Hydride Reduction:

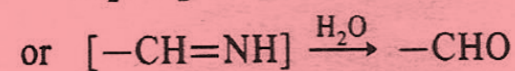
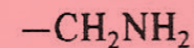
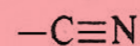
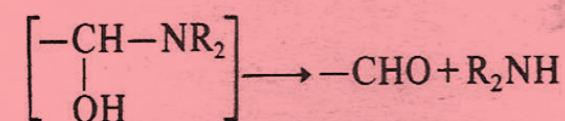
- Lithium aluminum hydride (LAH) is a strong reducing agent.
- It can reduce a variety of functional groups such as aldehydes, esters, acids, ketones, nitriles, epoxides and azides (carbon hetero-atom sigma and pi bonds)
- It vigorously reacts with water and all the reactions are performed in polar aprotic solvents.
- The anion of LAH are nucleophilic reagents and as such they normally attack polarized multiple bonds such as  $C=O$  or  $C=N$  or cyanide by transfer of hydride ion to the positive atom (electrophilic center).
- They do not usually reduce isolated carbon-carbon double or triple bonds.

**FG****Product**

or

**FG****Product**

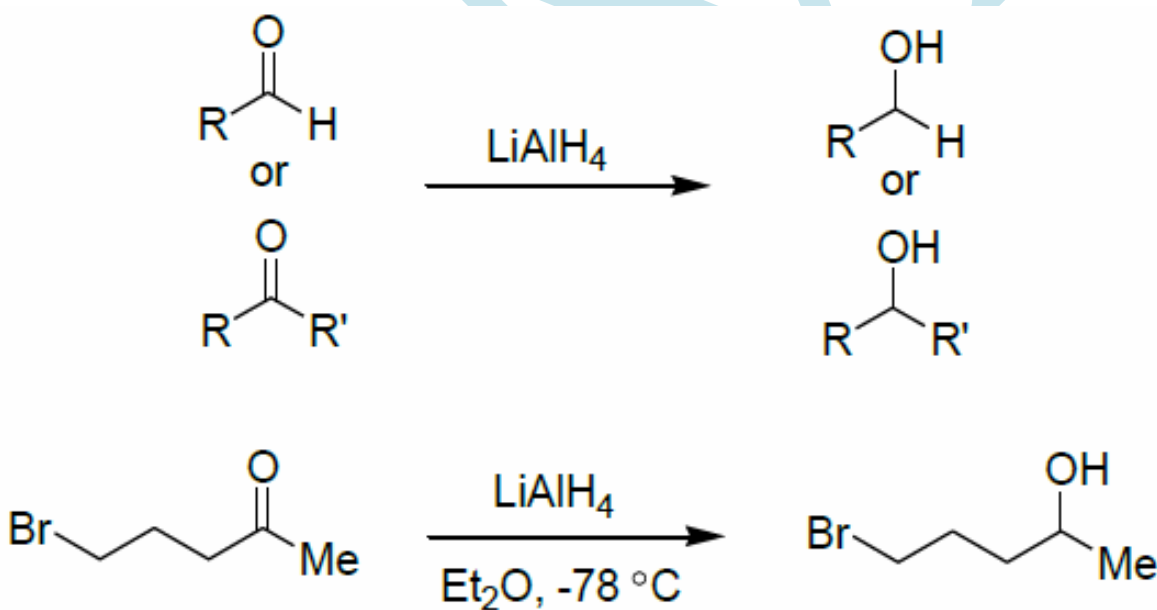
or



## 1. Reduction of Aldehydes and Ketones

The aldehydes and ketones are reduced to give the corresponding alcohols when treated with LAH. Complete reduction reaction involves two steps-

1. Transfer of hydride, which is generally performed in ether solvents at low temperature. 2. Work-up with acidified water.



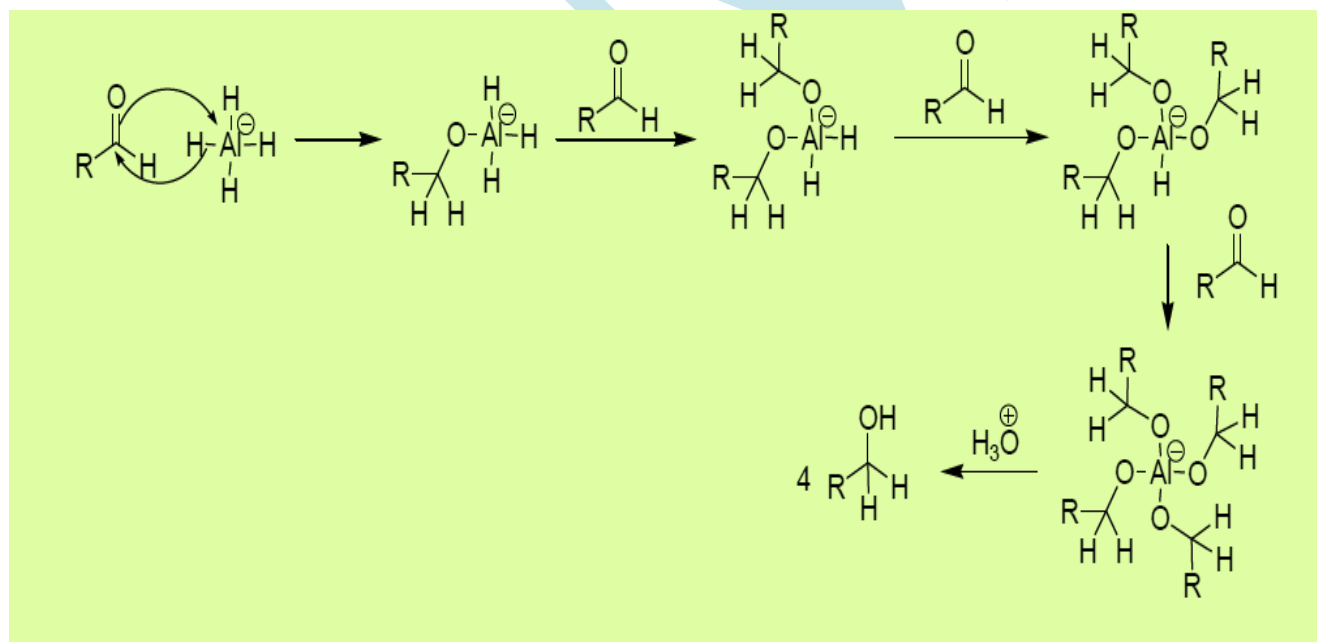
## Mechanism:

**Step-1:** The hydride from LAH is transferred to the carbonyl group to form alkoxy anion which then forms complex with aluminum.

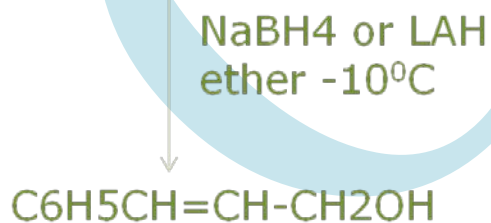
Similarly, four hydride atoms stepwise are replaced by four alkoxy groups and the aluminum complex thus formed.

The rate of hydride transfer gradually decreases.

**Step-2:** Hydrolysis by dilute acid to give the desired alcohol. (Workup of reaction)



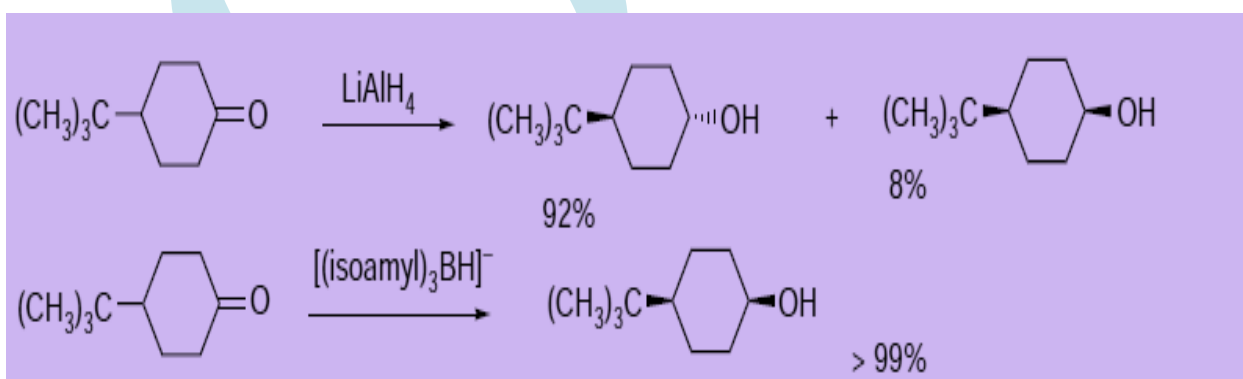
Note: An exception to the general rule that carbon-carbon double bonds are not attacked by hydride reducing agents is found in the reduction of  $\beta$ -aryl- $\alpha,\beta$ -unsaturated carbonyl compounds with LAH, where the carbon-carbon double bond is often reduced as well as the carbonyl group



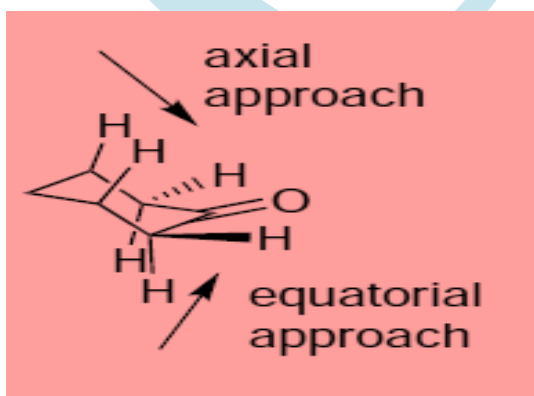
## 2. Reduction of cyclic ketones:

- Unhindered cyclo-hexanones normally reacts with  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  by preferential reagent approach from the **axial direction** forming mainly the equatorial alcohol.
- The presence of axial substituents or use of more sterically demanding reagents, such as alkyl-borohydrides leads to selective equatorial approach and formation of axial alcohols.

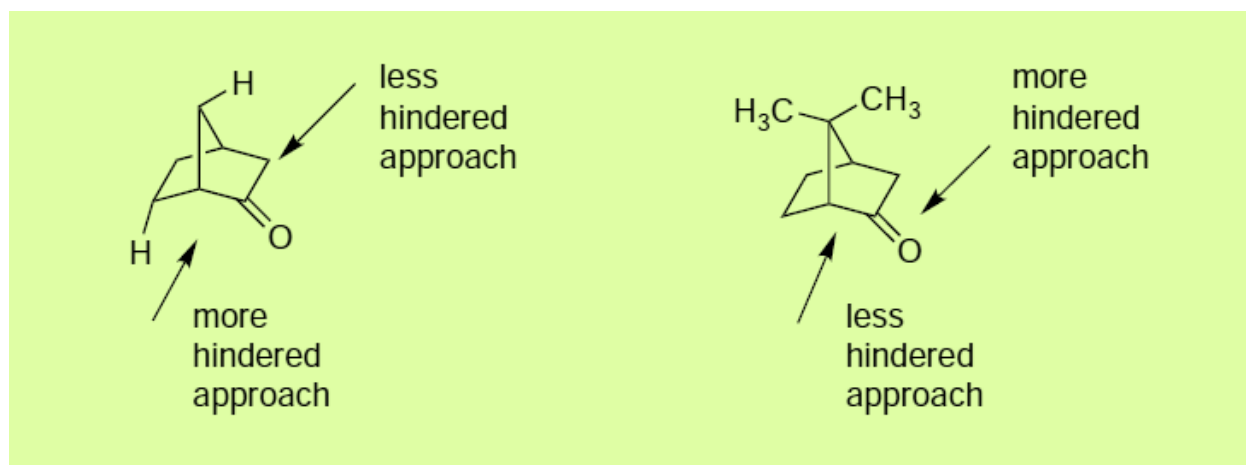
Bi-cyclic ketones are generally reduced by hydride approach from the less hindered face of the carbonyl group



- The stereo selectivity in cyclo-hexanones is determined by the preference for approach of reactants from the axial or equatorial direction.
- The chair conformation of cyclo-hexanone places the carbonyl group in an unsymmetrical environment. The axial face has C (2, 6) -H equatorial bonds that are nearly eclipsed with the C=O bond and the C (3, 5)-di-axial hydrogens point toward the trajectory for reagent approach.
- In contrast, the equatorial face has axial C-H bonds at an angle of roughly 120° to the carbonyl plane. There is more steric bulk, including the 3, 5-axial hydrogens, on the axial face.
- Remember also that the reagent interaction is with the LUMO and that the optimal trajectory is at an angle somewhat greater than 90° to the carbonyl plane.

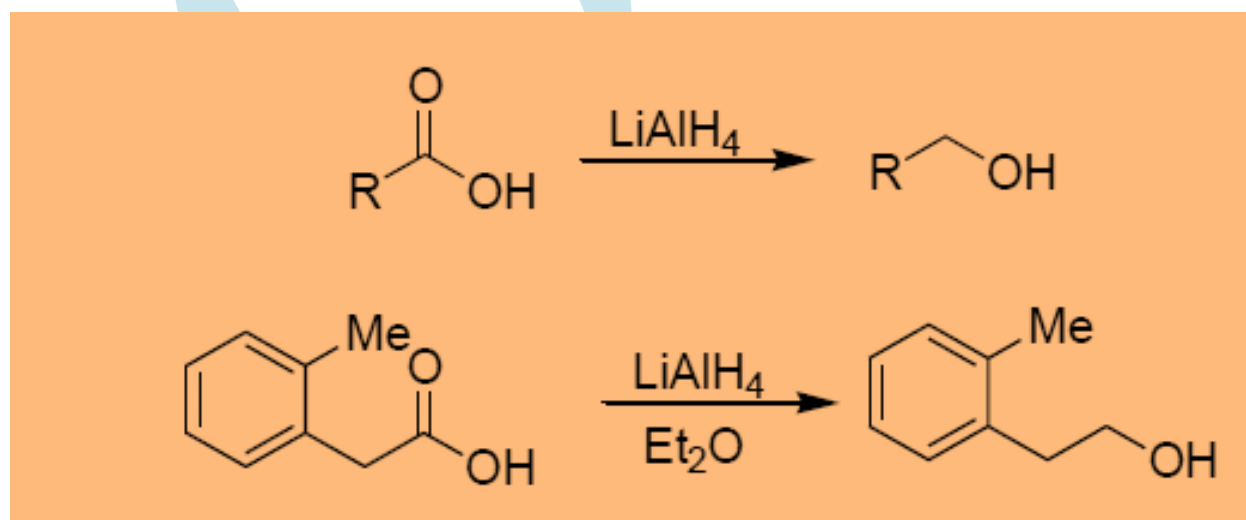






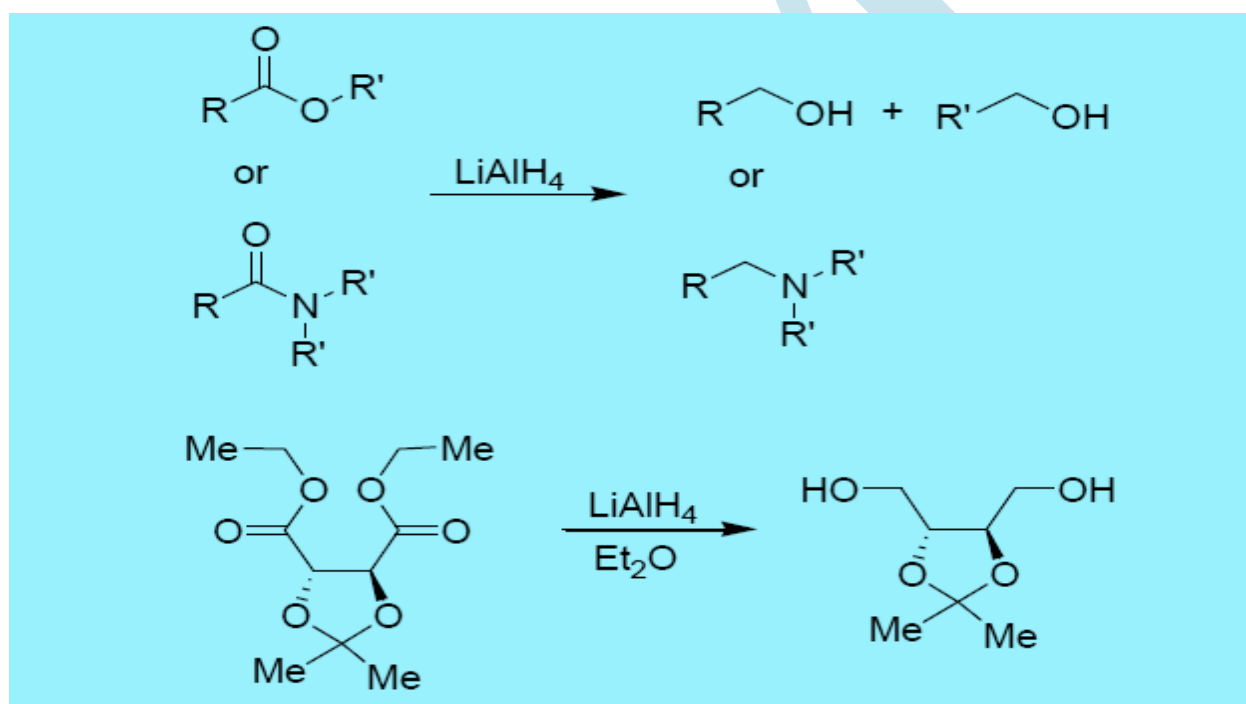
### 3. Reduction of Acids:

The acids are often reduced with LAH to prepare the corresponding alcohols. The other comparable method for reduction of acid is using  $\text{BH}_3$  as a reducing agent. The three hydride ions are consumed for reducing one acid group.



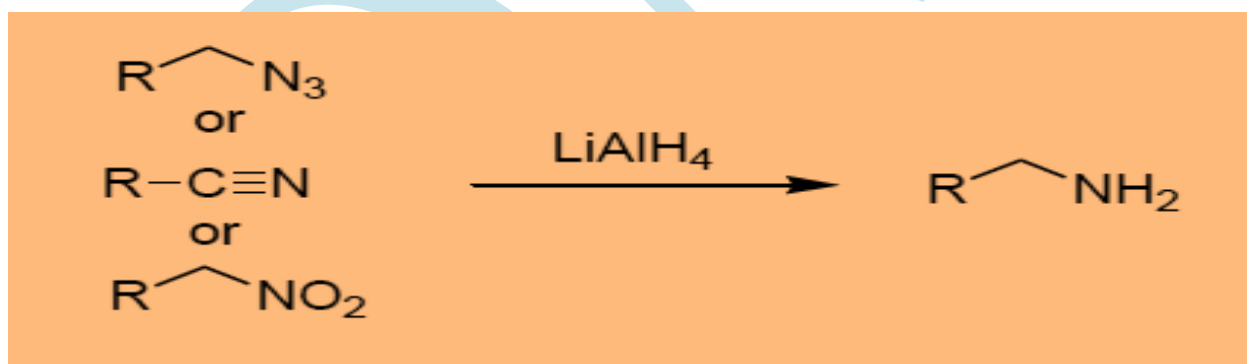
## 4. Reduction of Esters and Amides:

The esters and amides are reduced to the corresponding alcohols and amines, respectively, when treated with LAH. Each molecule of ester or amides consumes two molecules of hydride ions.



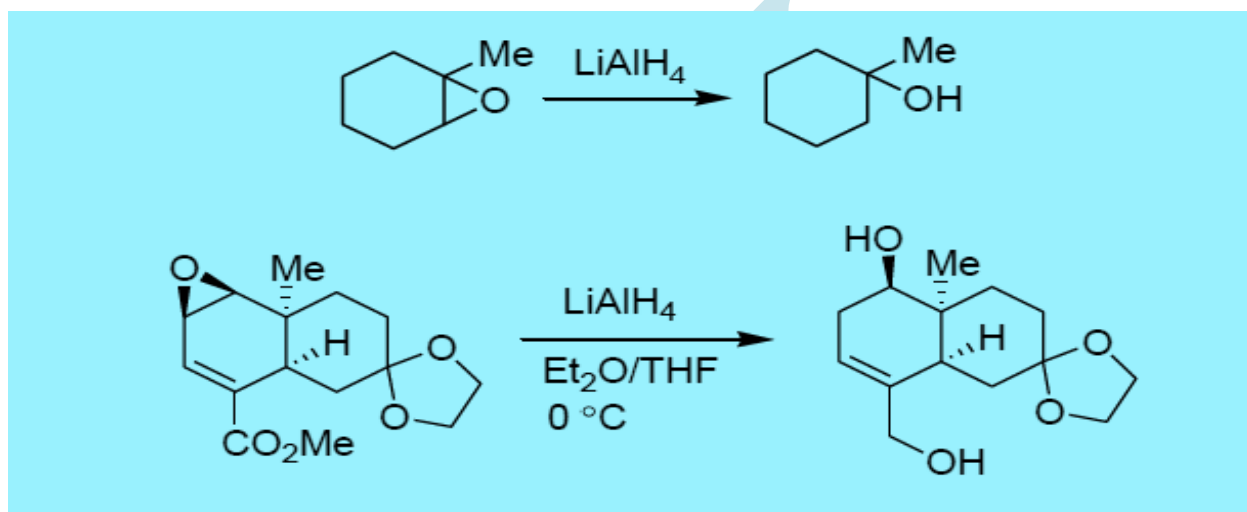
## 5. Reduction of Azides, Nitriles and Nitro Compounds:

The azides, nitriles and aliphatic nitro compounds are reduced to the corresponding amines in presence of LAH. The aromatic nitro compounds do not give the desired amines; they converted into corresponding azocompounds/hydroazocompounds.



## 6. Reduction of Epoxides:

The epoxides are reduced to the corresponding alcohols. The hydride ion is transferred to the less hindered carbon of the epoxides.



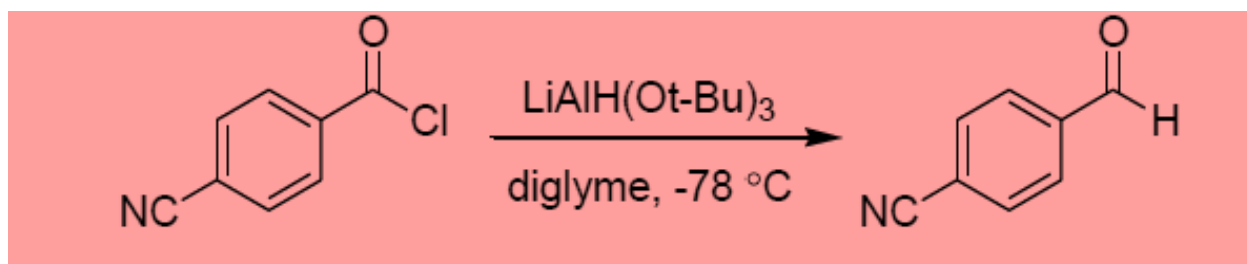
## Some Selective Aluminum/Boron based Reducing Agents:

### a. Lithium Tri-alkoxy-aluminum Hydride [LiAlH(OR)<sub>3</sub>]

Though LAH is a powerful reducing agent but is less selective. The reactivity and selectivity can be modified by replacing the three hydride ion with alkoxy groups such as *tert*-butoxy or ethoxy group. The resulting reagents are less reactive but more selective than LAH.

### Lithium tri-*t*-butoxy-aluminum Hydride [LiAlH(O<sup>*t*</sup>-Bu)<sub>3</sub>]

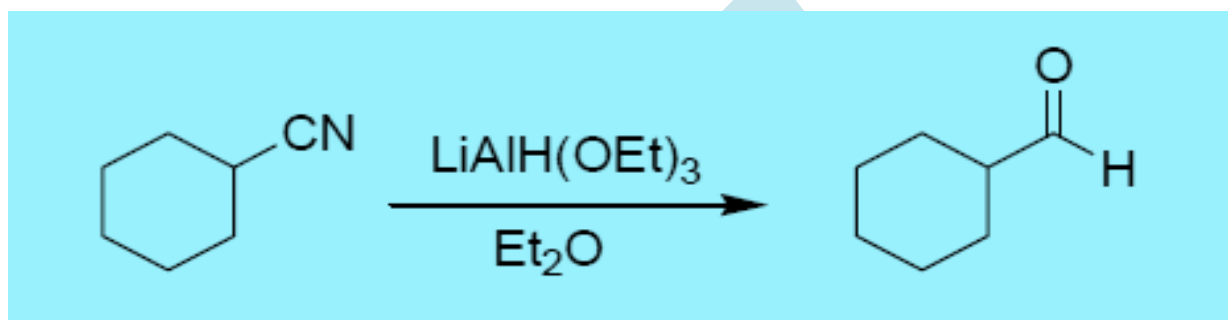
This is less reactive compared to LAH and reduces aldehydes and ketones to alcohols and acid chlorides to aldehydes. The other functional groups such as acids, amides and nitriles do not react or react very slowly.



## Lithium tri-Ethoxy-aluminum Hydride

### [LiAlH(OEt)<sub>3</sub>]

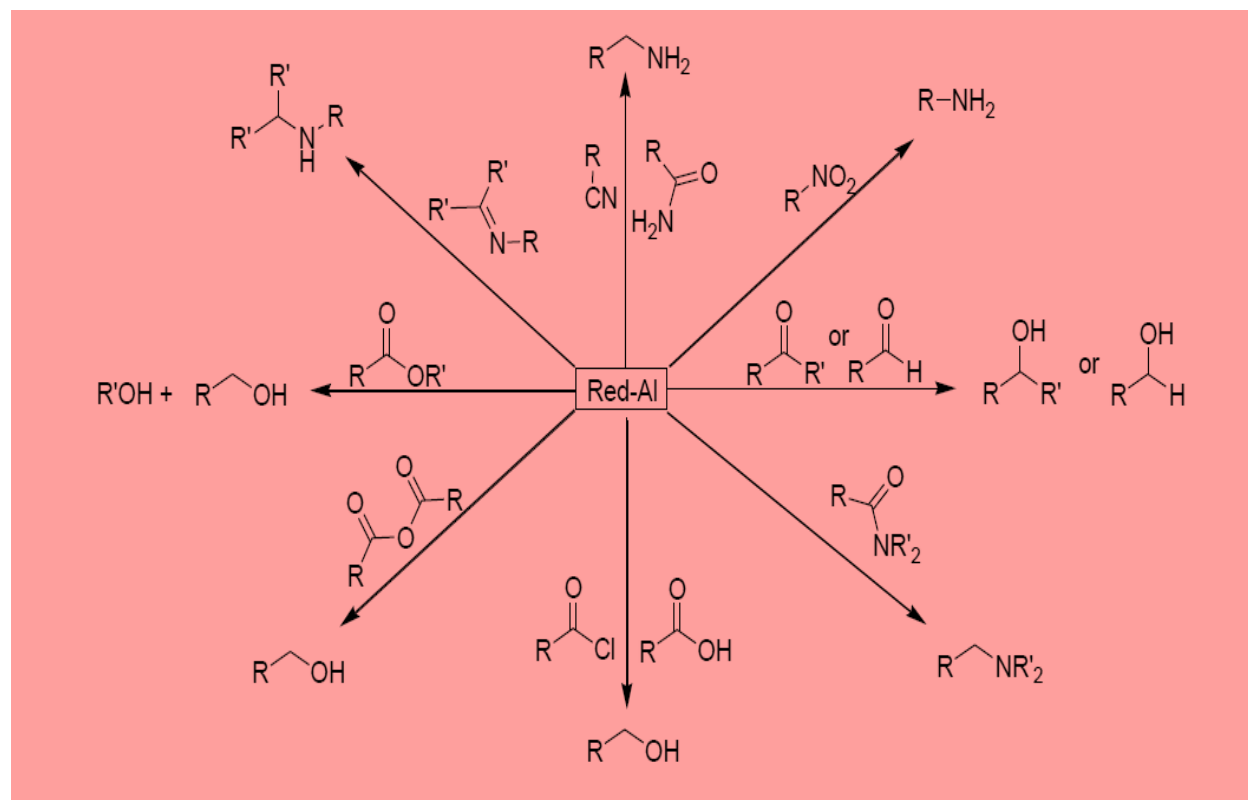
Lithium tri-ethoxyaluminum hydride is comparatively stronger reducing agent than lithium tri-*t*-butoxyaluminum hydride. It can reduce amides and nitriles to the corresponding aldehydes in good yield.

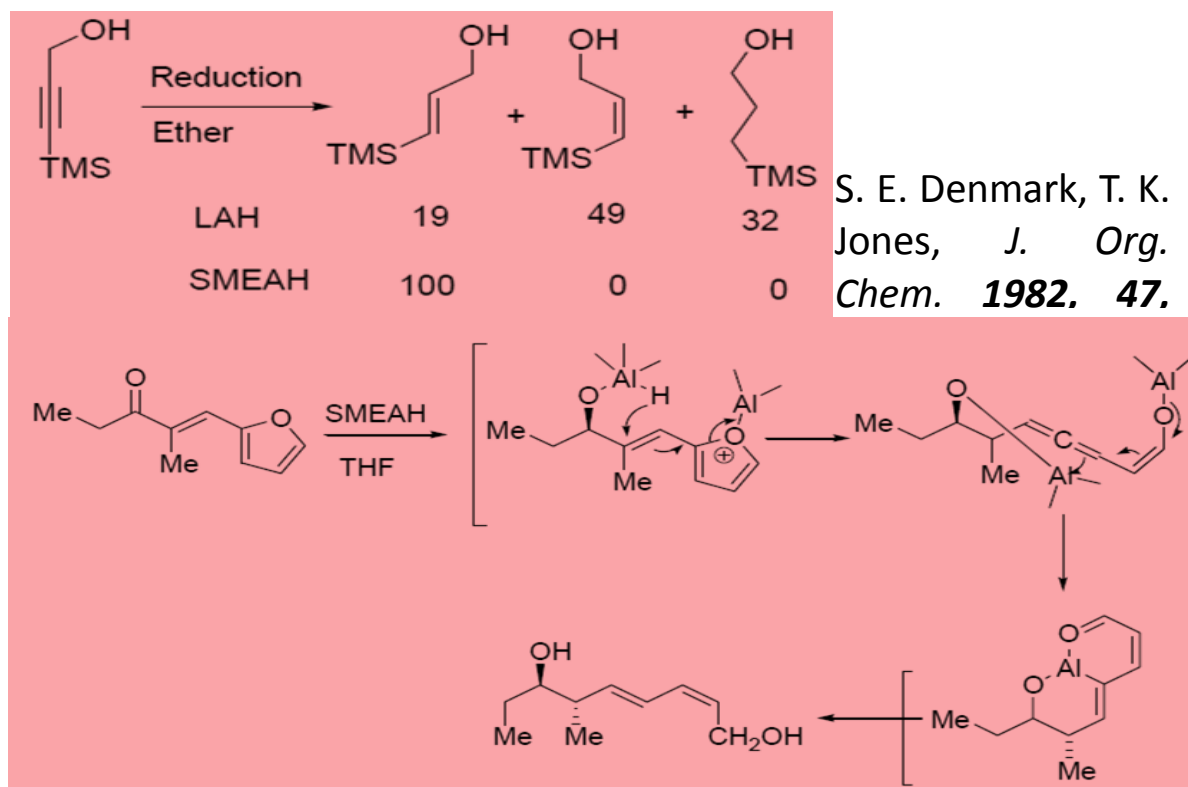


## Sodium bis(2-Methoxyethoxy)aluminum Hydride (SMEH) [NaAlH<sub>2</sub>(OCH<sub>2</sub>CH<sub>2</sub>OMe)<sub>2</sub>]

Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) is a commercially available reducing agent with trade name **Red-Al**. It is more selective than LAH and the reduction can be carried out in aromatic hydrocarbons as well as other ethers solvent.

M. Gugelchuk, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons., Inc., L. A. Paquette, Ed., New York, 1995, 7, 4518





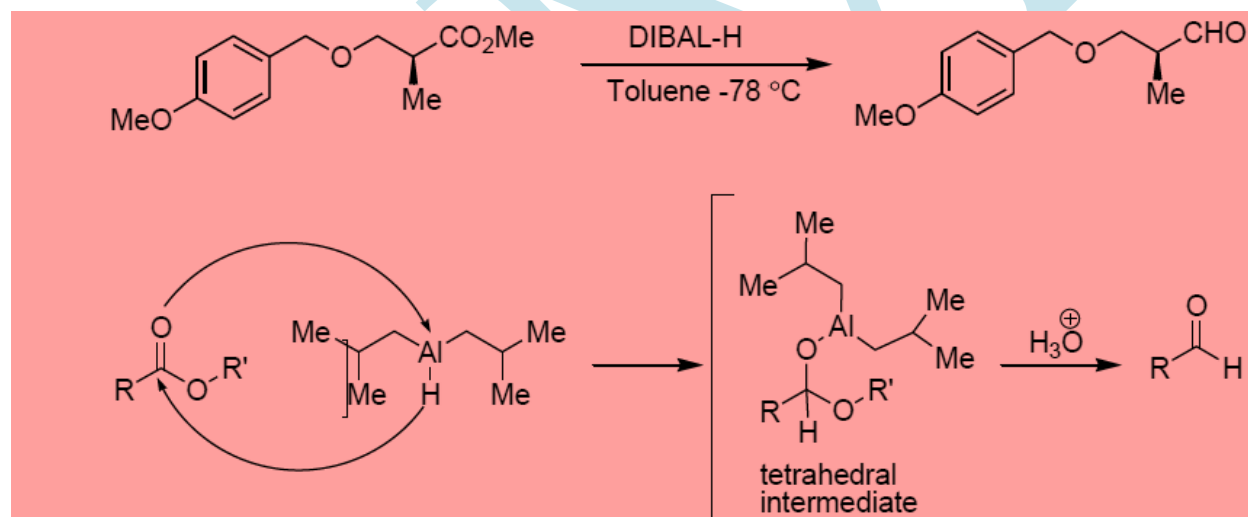
## Di-iso-butyl-aluminum Hydride (DIBAL-H):

The di-iso-butyl-aluminum hydride (DIBAL-H) is a commercially available selective reducing agent. It can selectively reduce esters and nitriles to the corresponding aldehydes. The reaction is carried out in inert and moisture free atmosphere.



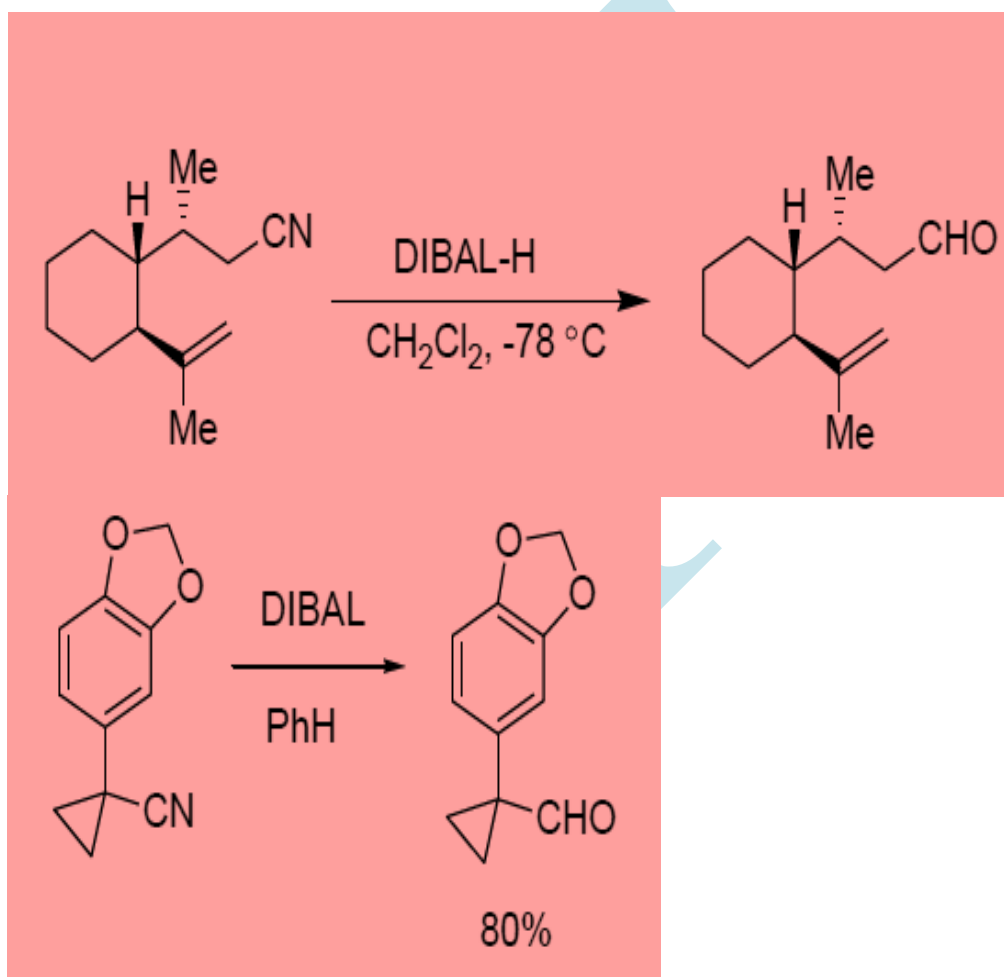
## Reduction of Esters to Aldehydes

The esters are selectively reduced to the corresponding aldehydes at low temperature. The DIBAL-H transfer one hydride to the ester group and forms a tetrahedral intermediate which is stable at low temperature. The hydrolytic work up of the intermediate gives the desired aldehydes. The presence of alkoxy or amino group to the close proximity can stabilize the tetrahedral intermediate and hence give better result.



## Reduction of Nitriles

The nitriles are selectively reduced to the corresponding aldehydes with one equivalent of DIBAL-H at low temperature. The use of two equivalent of DIBAL-H gives the corresponding primary amine.



R. V. Stevens, L. E. Dupree, P. L. Lowenstein, *J. Org. Chem.*  
**1972, 37, 977**