Hydride Transfer Reagents

Hydride Transfer Reagents

- Some of the most important reducing agents are hydrides derived from aluminium and boron.
  - There are numerous varieties differing principally in their reactivity.
- They all act as sources of nucleophilic hydride and therefore are most reactive towards electrophilic species.

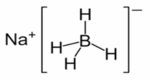
Hydride Transfer Reagents

- These two reagents are on the extremes of reactivityð whereas
  - **Lithium aluminium hydride** reacts with nearly all reducible functional groups,
  - **Sodium borohydride** reacts with a much more limited range of functional groups.

Sodium borohydride

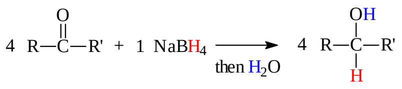
Sodium borohydride

- Sodium borohydride, also known as sodium tetrahydridoborate, and sodium tetrahydroborate is an inorganic compound with the formula $NaBH_4$.
- This white solid, usually encountered as a powder, is a versatile reducing agent

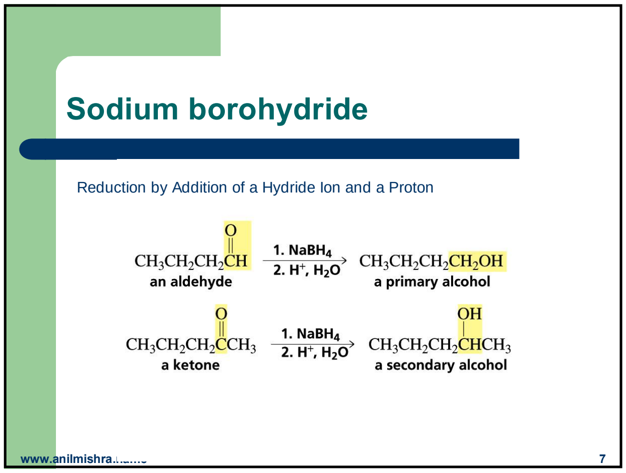


Sodium borohydride

- NaBH4 (sodium borohydride) is a versatile and useful reducing agent in organic chemistry.
- A reducing agent causes a reaction (a reduction) in which the product has more bonds from carbon to hydrogen (or fewer bond to oxygen)



$$4\ R-\overset{\overset{O}{\|}}{C}-R' + 1\ NaBH_4 \xrightarrow[\text{then } H_2O]{} 4\ R-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-R'$$



Sodium borohydride

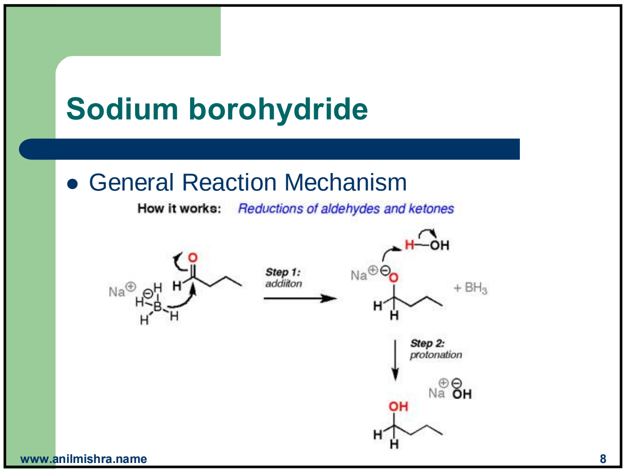
Reduction by Addition of a Hydride Ion and a Proton

$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H \xrightarrow[2.\ H^+,\ H_2O]{1.\ NaBH_4} CH_3CH_2CH_2CH_2OH$$

an aldehyde → a primary alcohol

$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[2.\ H^+,\ H_2O]{1.\ NaBH_4} CH_3CH_2CH_2\overset{\overset{OH}{|}}{C}HCH_3$$

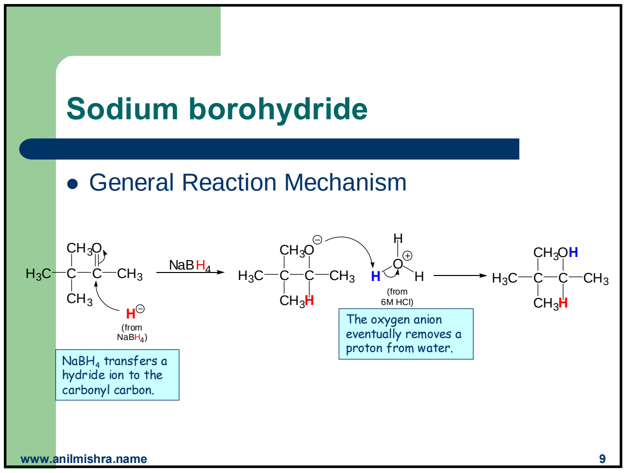
a ketone → a secondary alcohol



Sodium borohydride

- General Reaction Mechanism

How it works: *Reductions of aldehydes and ketones*

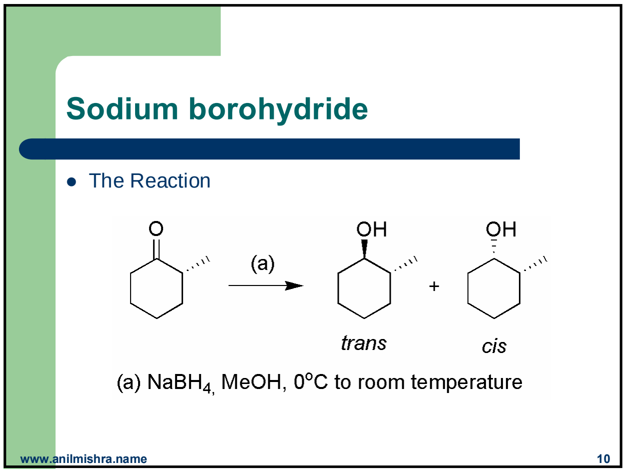


Sodium borohydride

- General Reaction Mechanism

$NaBH_4$ transfers a hydride ion to the carbonyl carbon.

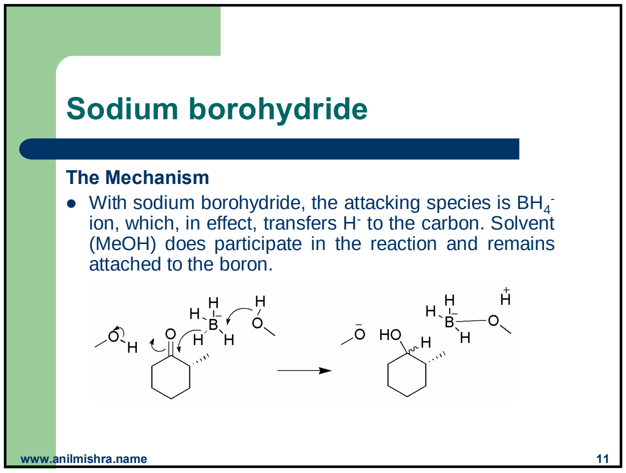
The oxygen anion eventually removes a proton from water.



Sodium borohydride

- The Reaction

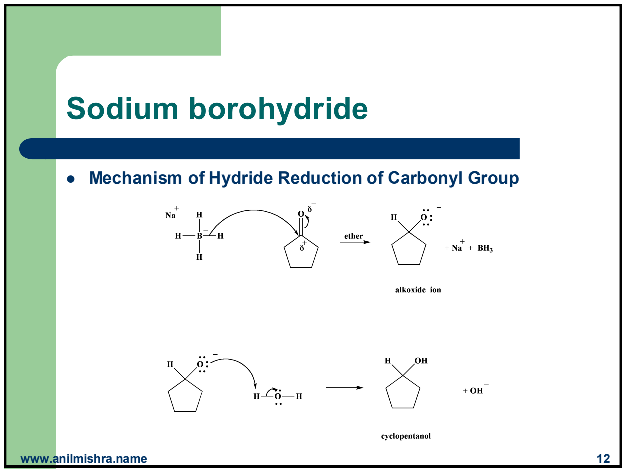
(a) $NaBH_4$, MeOH, 0°C to room temperature



Sodium borohydride

The Mechanism

- With sodium borohydride, the attacking species is BH_4^- ion, which, in effect, transfers H^- to the carbon. Solvent (MeOH) does participate in the reaction and remains attached to the boron.

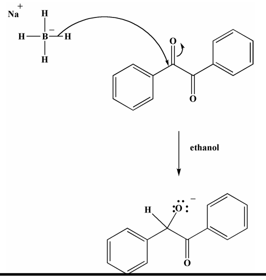


Sodium borohydride

- **Mechanism of Hydride Reduction of Carbonyl Group**

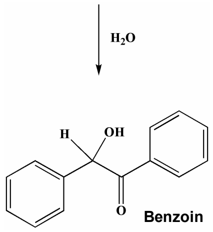
Sodium borohydride

- Reduction of Benzil (Step 1)



Sodium borohydride

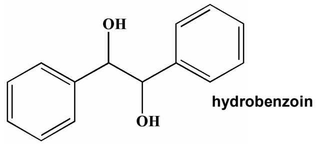
- Reduction of Benzil (Step 2)



- Reduction of Benzil (Step 3)
  - Repeat of Steps 1, 2
  - Reaction at the other C=O

Sodium borohydride

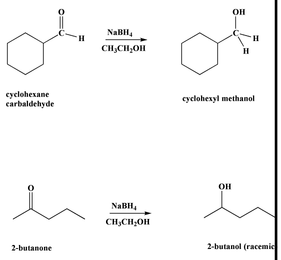
- Reduction of Benzil (Final Product)



Sodium borohydride

Selectivity

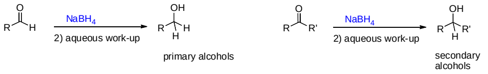
- Reduces aldehydes to primary alcohols, ketones to secondary alcohols
- Very selective:
  - Only reactive towards aldehydes/ketones
  - Will not reduce carboxylic acids or esters



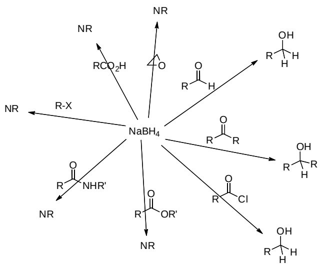
Sodium borohydride

Selectivity

- Less reactive; More selective Than $LiAlH_4$
- Won't reduce esters, amides, halides, epoxides, carboxylic acids



Sodium borohydride



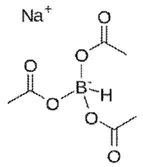
Sodium borohydride Summary

- **What it's used for**
  - It is a good reducing agent. Although not as powerful as lithium aluminum hydride ($LiAlH_4$),
  - It is very effective for the reduction of aldehydes and ketones to alcohols.
  - By itself, it will generally not reduce esters, carboxylic acids, or amides (although it will reduce acyl chlorides to alcohols).
  - It is also used in the second step of the oxymercuration reaction to replace mercury (Hg) with H.

Sodium triacetoxyborohydride

Sodium triacetoxyborohydride

- Sodium triacetoxyborohydride, also known as sodium triacetoxyhydroborate, commonly abbreviated STAB, is a chemical compound with the formula $Na(CH_3COO)_3BH$.



Sodium triacetoxyborohydride

- Like other borohydrides, it is used as a reducing agent in organic synthesis.
- This colourless salt is prepared by protonolysis of sodium borohydride with acetic acid

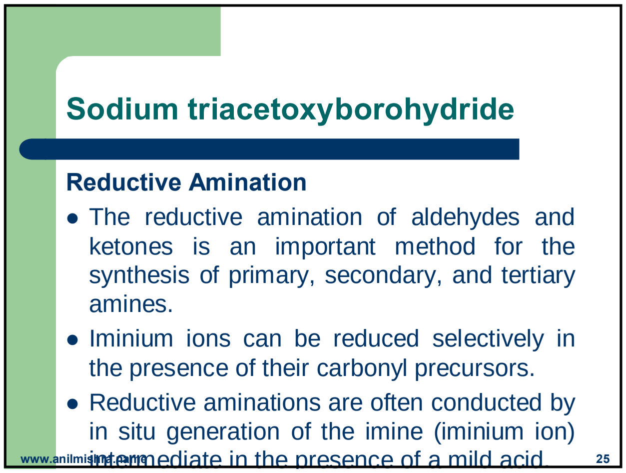
$$NaBH_4 + 3HO_2CCH_3 \rightarrow NaBH(O_2CCH_3)_3 + 3H_2$$

Sodium triacetoxyborohydride

- Owing to the steric and electronic effects of the acetoxy groups, sodium triacetoxyborohydride is a milder reducing agent than sodium borohydride
- $NaBH(OAc)_3$ avoids the toxic side-products

Sodium triacetoxyborohydride

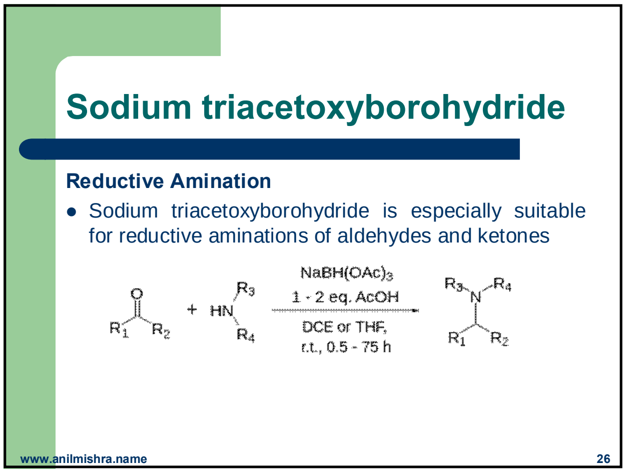
- Triacetoxyborohydride is **water-sensitive** and water cannot be used as a solvent with this reagent, neither is it compatible with methanol.
- It reacts only slowly with ethanol and isopropanol and can be used with these.
- The boron-hydrogen bond is stabilized by the steric and electron-withdrawing effects of the acetoxy groups, making sodium triacetoxyborohydride a mild reducing agent.



Sodium triacetoxyborohydride

Reductive Amination

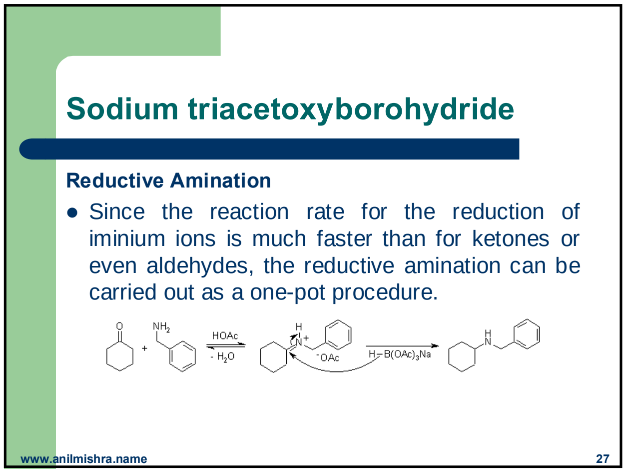
- The reductive amination of aldehydes and ketones is an important method for the synthesis of primary, secondary, and tertiary amines.
- Iminium ions can be reduced selectively in the presence of their carbonyl precursors.
- Reductive aminations are often conducted by in situ generation of the imine (iminium ion) intermediate in the presence of a mild acid.



Sodium triacetoxyborohydride

Reductive Amination

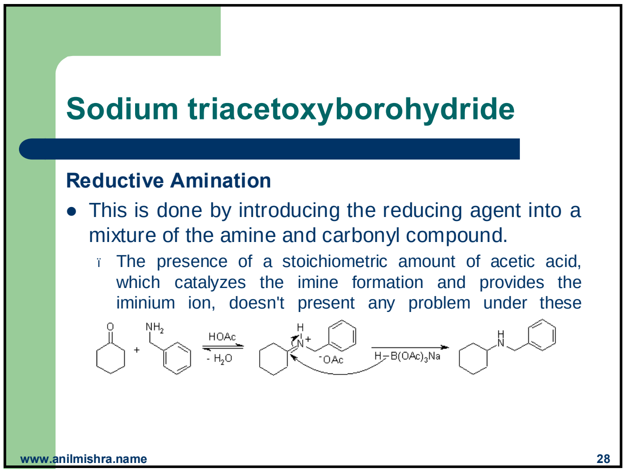
- Sodium triacetoxyborohydride is especially suitable for reductive aminations of aldehydes and ketones



Sodium triacetoxyborohydride

Reductive Amination

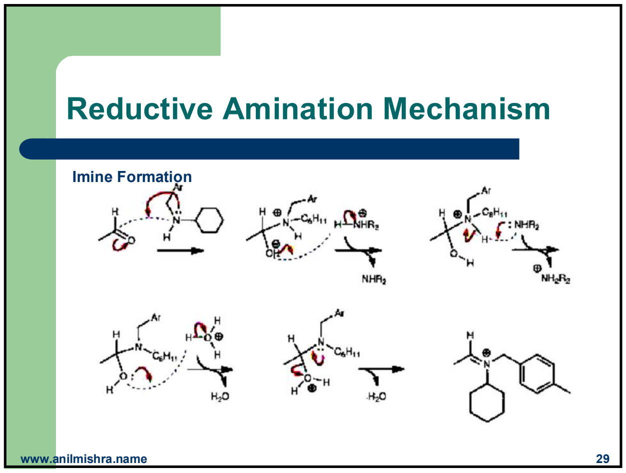
- Since the reaction rate for the reduction of iminium ions is much faster than for ketones or even aldehydes, the reductive amination can be carried out as a one-pot procedure.



Sodium triacetoxyborohydride

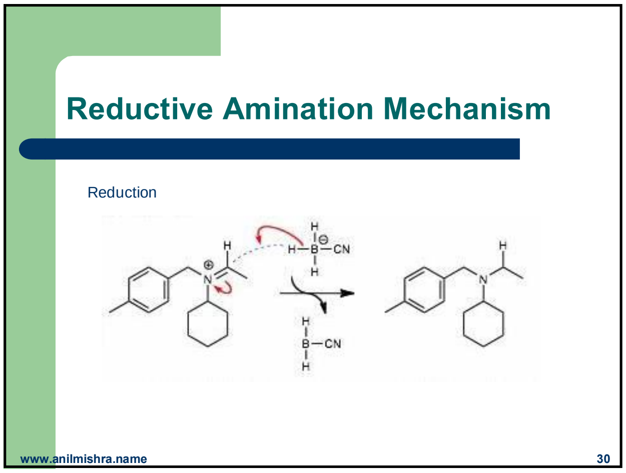
Reductive Amination

- This is done by introducing the reducing agent into a mixture of the amine and carbonyl compound.
  - The presence of a stoichiometric amount of acetic acid, which catalyzes the imine formation and provides the iminium ion, doesn't present any problem under these



Reductive Amination Mechanism

Imine Formation



Reductive Amination Mechanism

Reduction

Lithium Aluminum Hydride

Lithium Aluminum Hydride

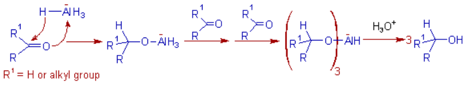
- Lithium aluminum hydride (LAH) is a strong reducing agent with chemical formula $LiAlH_4$.
- It can reduce a variety of functional groups such as aldehydes, esters, acids, ketones, nitriles, epoxides and azides.
- It vigorously reacts with water and all the reactions are performed in polar aprotic solvents.

Lithium Aluminum Hydride

- The reduction of a carbonyl group by $LiAlH_4$ is initiated by the attack of nucleophilic hydride ion on the carbonyl carbon to give a tetrahedral intermediate.
- $LiAlH_4$ is a nucleophilic reducing agent since the hydride transfer to the carbonyl carbon occurs prior to the coordination to the carbonyl oxygen.
- It reacts faster with electron deficient carbonyl groups. The reactivity of carbonyl compounds with this reagent follows the order:
  - Aldehydes > Ketones > ester > amide > carboxylic acid

Lithium Aluminum Hydride

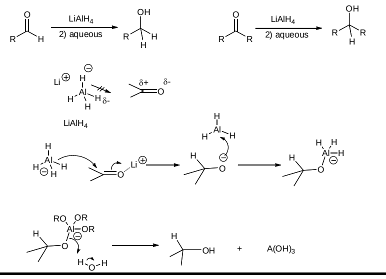
- **Reduction of Aldehydes or Ketones to 1^0 or 2^0 alcohols:**
  - Initially, a hydride ion is transferred onto the carbonyl carbon and the oxygen atom coordinates to the remaining aluminium hydride species to furnish an alkoxytrihydroaluminate ion, which can reduce the next carbonyl molecule. Thus three of the hydride ions are used up in reduction.



R¹ = H or alkyl group

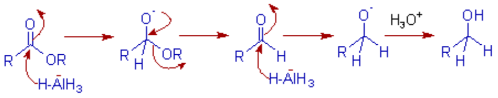
Lithium Aluminum Hydride

- Reduction of Aldehydes and Ketones

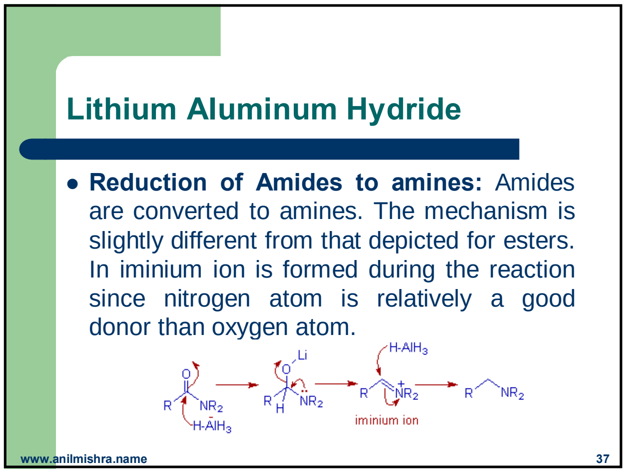


Lithium Aluminum Hydride

- **Reduction of Esters to 1^0 alcohols:** The ester is first converted to aldehyde which is further reduced to primary alcohol.

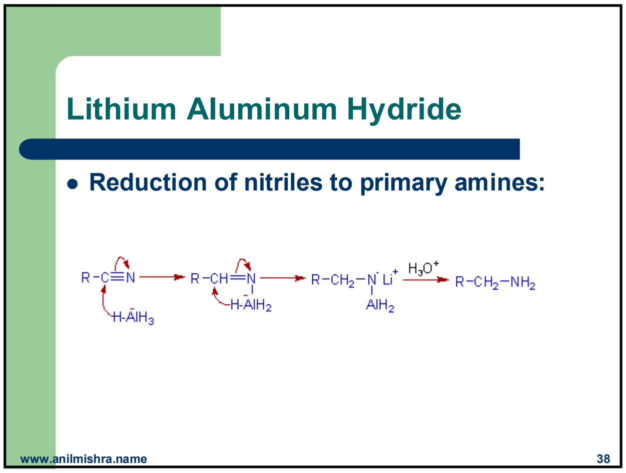


Lecture notes of Prof. Anil Mishra from www.anilmishra.name



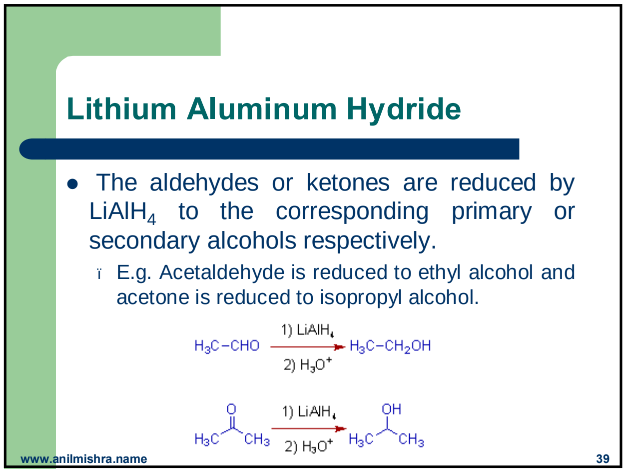
Lithium Aluminum Hydride

- **Reduction of Amides to amines:** Amides are converted to amines. The mechanism is slightly different from that depicted for esters. In iminium ion is formed during the reaction since nitrogen atom is relatively a good donor than oxygen atom.



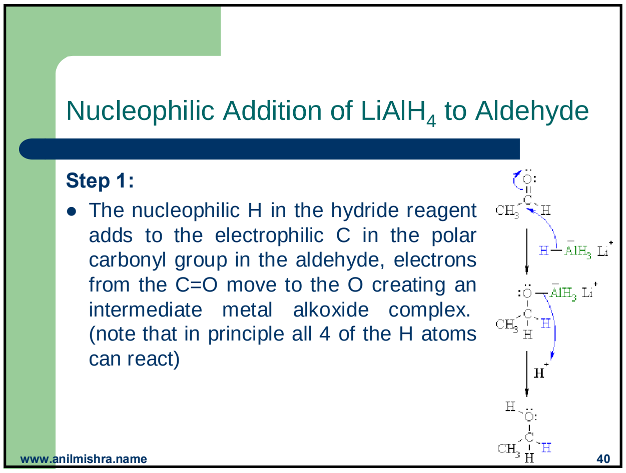
Lithium Aluminum Hydride

- **Reduction of nitriles to primary amines:**



Lithium Aluminum Hydride

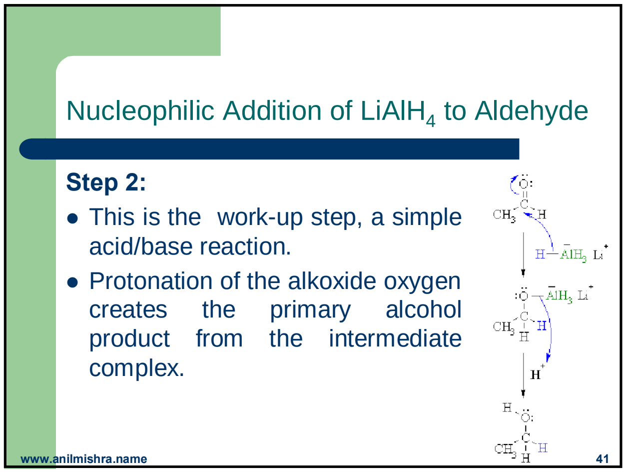
- The aldehydes or ketones are reduced by $LiAlH_4$ to the corresponding primary or secondary alcohols respectively.
  - E.g. Acetaldehyde is reduced to ethyl alcohol and acetone is reduced to isopropyl alcohol.



Nucleophilic Addition of $LiAlH_4$ to Aldehyde

Step 1:

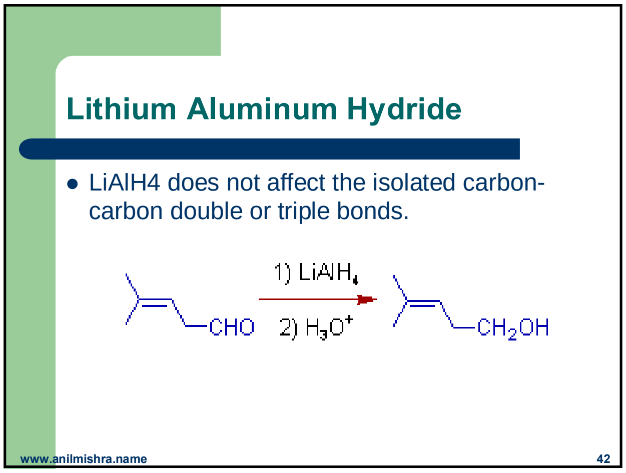
- The nucleophilic H in the hydride reagent adds to the electrophilic C in the polar carbonyl group in the aldehyde, electrons from the C=O move to the O creating an intermediate metal alkoxide complex. (note that in principle all 4 of the H atoms can react)



Nucleophilic Addition of $LiAlH_4$ to Aldehyde

Step 2:

- This is the work-up step, a simple acid/base reaction.
- Protonation of the alkoxide oxygen creates the primary alcohol product from the intermediate complex.



Lithium Aluminum Hydride

- LiAlH4 does not affect the isolated carbon-carbon double or triple bonds.

Lithium Aluminum Hydride

- The carboxylic acids, esters and acid halides are reduced to corresponding primary alcohols by Lithium aluminium hydride.
  - ï E.g. The reduction of Acetic acid, methyl acetate and acetyl chloride by $LiAlH_4$ furnish the same ethyl alcohol.

$$H_3C{-}COOH \xrightarrow[\text{2) } H_3O^+]{\text{1) 3 equiv. } LiAlH_4} H_3C{-}CH_2OH$$

$$H_3C{-}COOMe \xrightarrow[\text{2) } H_3O^+]{\text{1) 2 equiv. } LiAlH_4} H_3C{-}CH_2OH + MeOH$$

$$H_3C{-}COCl \xrightarrow[\text{2) } H_3O^+]{\text{1) 2 equiv. } LiAlH_4} H_3C{-}CH_2OH$$

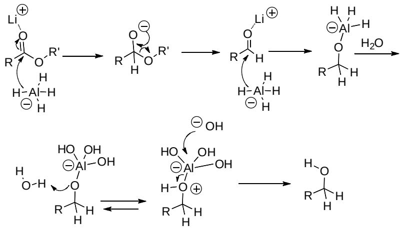
Lithium Aluminum Hydride

- The **amides** are reduced to amines by LAH. Especially this method is used to get secondary amines.
  - ï E.g. Diethyl amine can be prepared starting from acetyl chloride as follows:

$$H_3C{-}COCl \xrightarrow[\text{-HCl}]{EtNH_2} H_3C{-}CONHEt \xrightarrow[\text{2) } H_3O^+]{\text{1) 2 equiv. } LiAlH_4} H_3C{-}CH_2NHEt$$

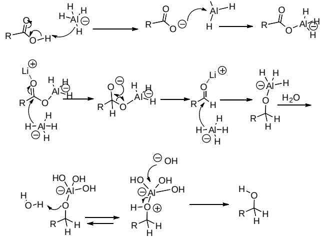
Lithium Aluminum Hydride

Esters and acid chlorides



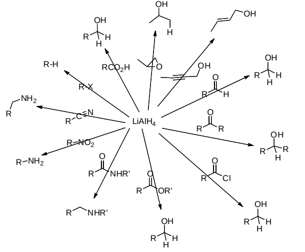
Lithium Aluminum Hydride

Aldehyde intermediate is more reactive than carboxylic acid and is immediately reduced to alcohol

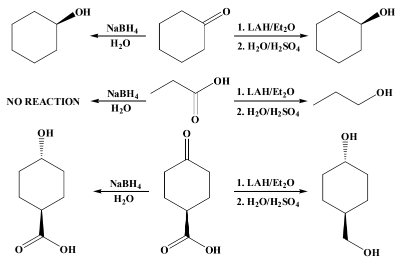


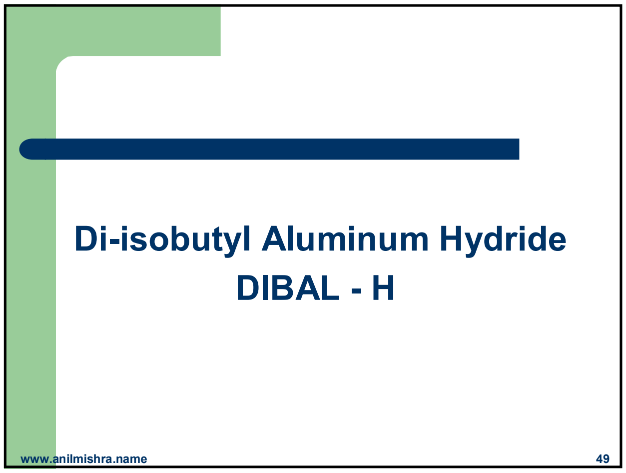
Lithium Aluminum Hydride

Strong reducing agent. Not very selective

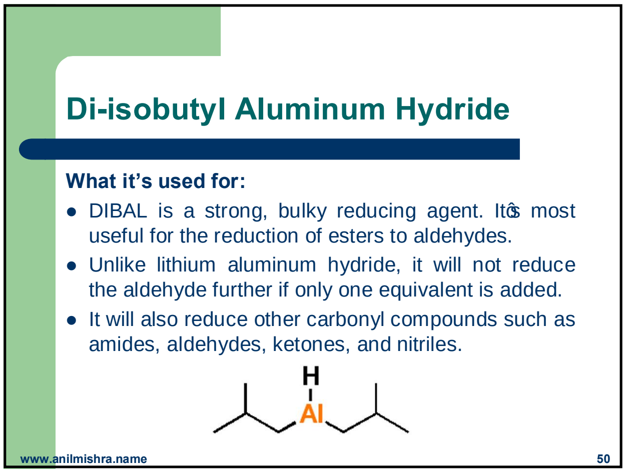


$NaBH_4/LiAlH_4$ Comparision





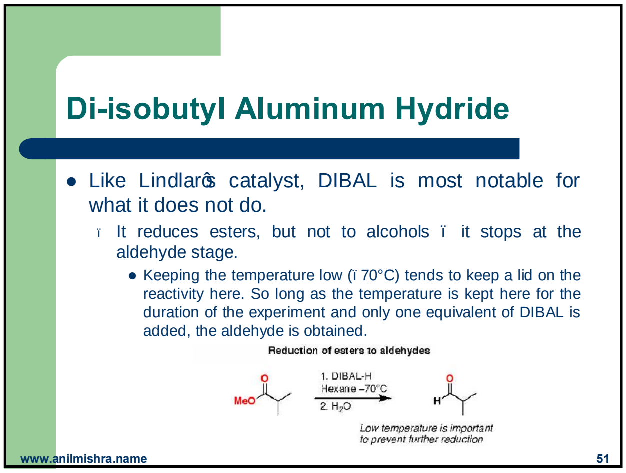
Di-isobutyl Aluminum Hydride
DIBAL - H



Di-isobutyl Aluminum Hydride

What it’s used for:

- DIBAL is a strong, bulky reducing agent. Itõs most useful for the reduction of esters to aldehydes.
- Unlike lithium aluminum hydride, it will not reduce the aldehyde further if only one equivalent is added.
- It will also reduce other carbonyl compounds such as amides, aldehydes, ketones, and nitriles.

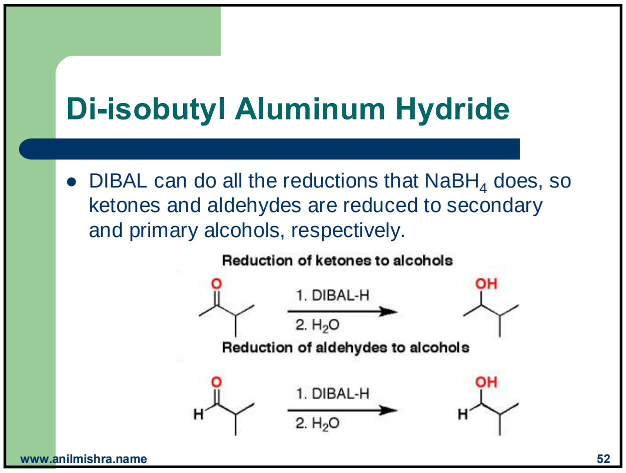


Di-isobutyl Aluminum Hydride

- Like Lindlarõs catalyst, DIBAL is most notable for what it does not do.
  - ï It reduces esters, but not to alcohols ï it stops at the aldehyde stage.
    - Keeping the temperature low (ï 70°C) tends to keep a lid on the reactivity here. So long as the temperature is kept here for the duration of the experiment and only one equivalent of DIBAL is added, the aldehyde is obtained.

Reduction of esters to aldehydes

Low temperature is important to prevent further reduction

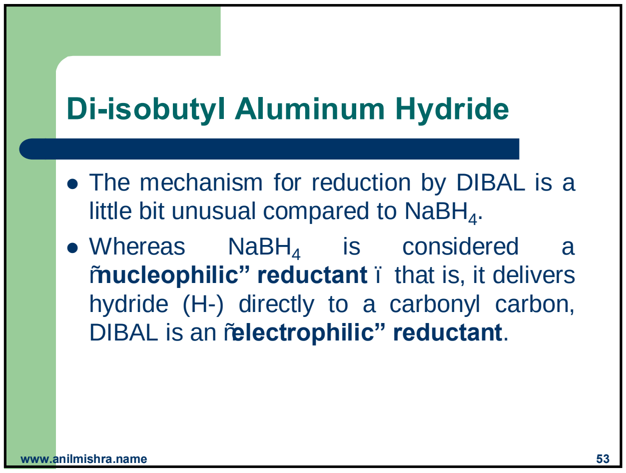


Di-isobutyl Aluminum Hydride

- DIBAL can do all the reductions that $NaBH_4$ does, so ketones and aldehydes are reduced to secondary and primary alcohols, respectively.

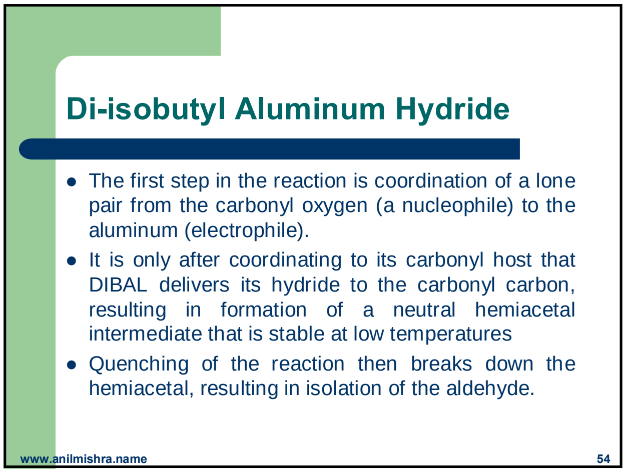
Reduction of ketones to alcohols

Reduction of aldehydes to alcohols



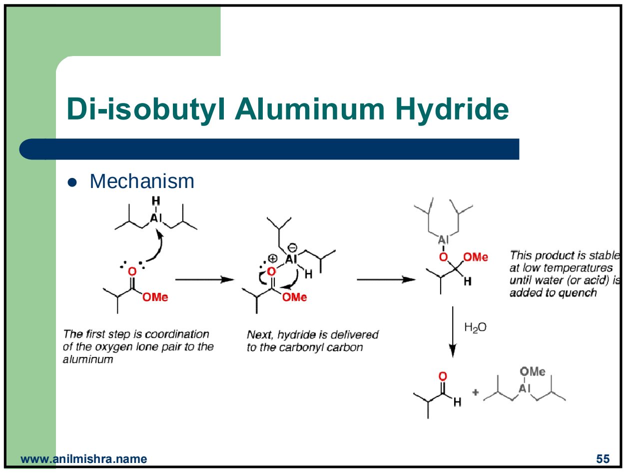
Di-isobutyl Aluminum Hydride

- The mechanism for reduction by DIBAL is a little bit unusual compared to $NaBH_4$.
- Whereas $NaBH_4$ is considered a ñ**nucleophilic” reductant** ï that is, it delivers hydride (H-) directly to a carbonyl carbon, DIBAL is an ñ**electrophilic” reductant**.



Di-isobutyl Aluminum Hydride

- The first step in the reaction is coordination of a lone pair from the carbonyl oxygen (a nucleophile) to the aluminum (electrophile).
- It is only after coordinating to its carbonyl host that DIBAL delivers its hydride to the carbonyl carbon, resulting in formation of a neutral hemiacetal intermediate that is stable at low temperatures
- Quenching of the reaction then breaks down the hemiacetal, resulting in isolation of the aldehyde.



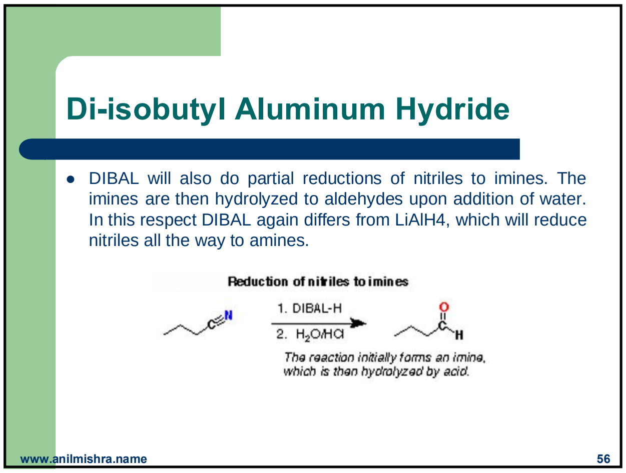
Di-isobutyl Aluminum Hydride

- Mechanism

The first step is coordination of the oxygen lone pair to the aluminum

Next, hydride is delivered to the carbonyl carbon

This product is stable at low temperatures until water (or acid) is added to quench

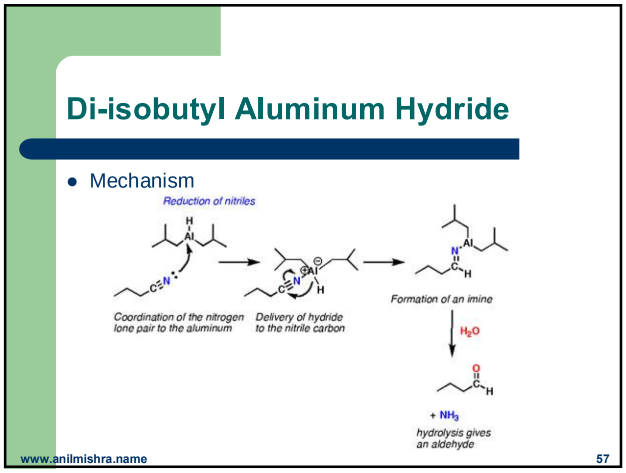


Di-isobutyl Aluminum Hydride

- DIBAL will also do partial reductions of nitriles to imines. The imines are then hydrolyzed to aldehydes upon addition of water. In this respect DIBAL again differs from LiAlH4, which will reduce nitriles all the way to amines.

Reduction of nitriles to imines

The reaction initially forms an imine, which is then hydrolyzed by acid.



Di-isobutyl Aluminum Hydride

- Mechanism

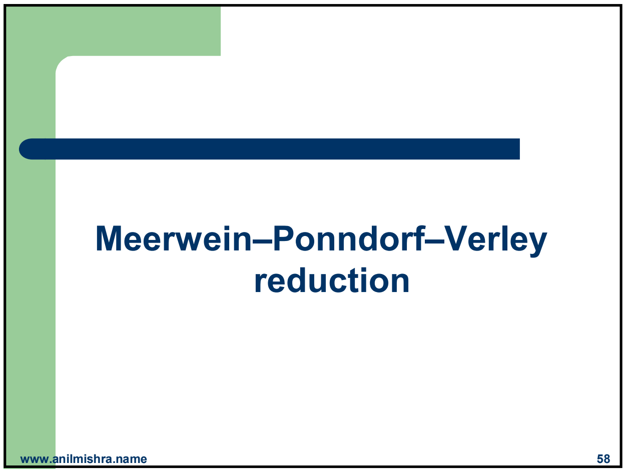
Reduction of nitriles

Coordination of the nitrogen lone pair to the aluminum

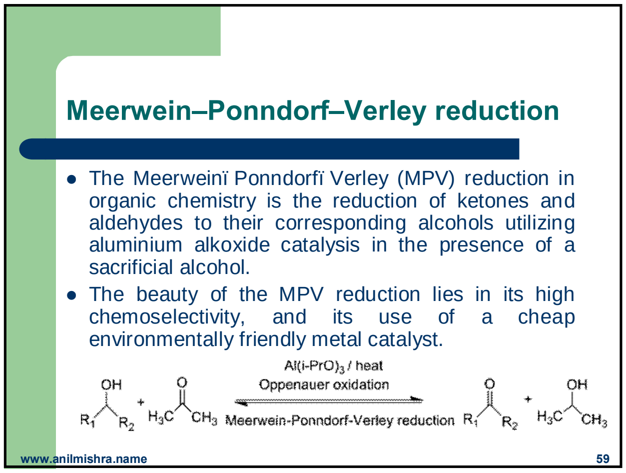
Delivery of hydride to the nitrile carbon

Formation of an imine

hydrolysis gives an aldehyde

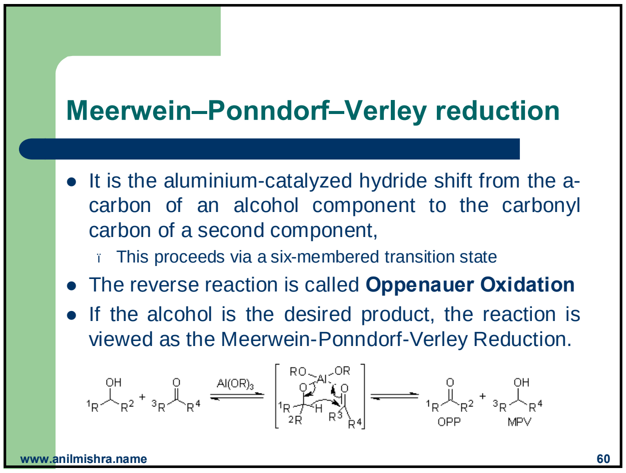


Meerwein–Ponndorf–Verley reduction



Meerwein–Ponndorf–Verley reduction

- The Meerweinï Ponndorfï Verley (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a sacrificial alcohol.
- The beauty of the MPV reduction lies in its high chemoselectivity, and its use of a cheap environmentally friendly metal catalyst.

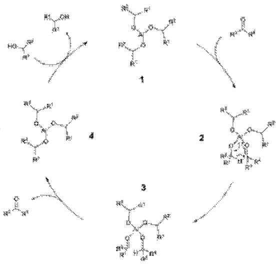


Meerwein–Ponndorf–Verley reduction

- It is the aluminium-catalyzed hydride shift from the a-carbon of an alcohol component to the carbonyl carbon of a second component,
  - This proceeds via a six-membered transition state
- The reverse reaction is called **Oppenauer Oxidation**
- If the alcohol is the desired product, the reaction is viewed as the Meerwein-Ponndorf-Verley Reduction.

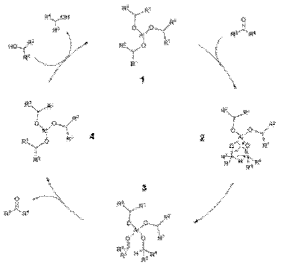
Meerwein–Ponndorf–Verley reduction

- The MPV reduction is believed to go through a catalytic cycle involving a six-member ring transition state.
- Starting with the aluminium alkoxide 1, a carbonyl oxygen is coordinated to achieve the tetra coordinated aluminium intermediate 2.



Meerwein–Ponndorf–Verley reduction

- Between intermediates 2 and 3 the hydride is transferred to the carbonyl from the alkoxy ligand via a pericyclic mechanism.
- At this point the new carbonyl dissociates and gives the tricoordinated aluminium species 4.
- Finally, an alcohol from solution displaces the newly reduced carbonyl to regenerate the catalyst 1.



Meerwein–Ponndorf–Verley reduction

- Each step in the cycle is reversible and the reaction is driven by the thermodynamic properties of the intermediates and the products.
- This means that given time the more thermodynamically stable product will be favored.

Meerwein–Ponndorf–Verley reduction

Chemoselectivity

- One of the great draws of the Meerweinï Ponndorfï Verley reduction is its chemoselectivity.
  - Aldehydes are reduced before ketones allowing for a measure of control over the reaction.
  - If it is necessary to reduce one carbonyl in the presence of another, the common carbonyl protecting groups may be employed.
  - Groups, such as alkenes and alkynes, that normally pose a problem for reduction by other means have no reactivity under these conditions.