

Course Name: Methods in Organic Synthesis

Paper Number: 202 Section: B (Group V and VI)

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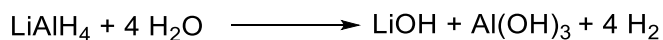
Study Material (Name of Topic/ Chapter): Reduction

Reduction by hydride-transfer reagents

Reactions through transfer of hydride ions play important part in organic chemistry. The most useful reagents of this type in the synthesis are Lithium aluminium hydride(LiAlH₄) and Sodium borohydride (NaBH₄). These reagents are nucleophilic and as such they normally attack polarized multiple bonds such as C=O or C-N by transfer of hydride ion to the more-positive atom. They usually do not reduce isolated carbon-carbon double or triple bonds.

Lithium aluminium hydride (LiAlH₄)

- Lithium aluminium hydride, commonly abbreviated to LAH, is a powerful reducing due to the weaker Al-H bond. It will convert esters, carboxylic acids and ketones to alcohols; and nitro compounds into amines.
- LAH violently reacts with water, including atmospheric moisture, and the pure material is pyrophoric. Commercial material is inhibited with mineral oil to allow handling in air. Therefore, it must be used under anhydrous conditions in a non-hydroxylic solvent; diethyl ether and THF.

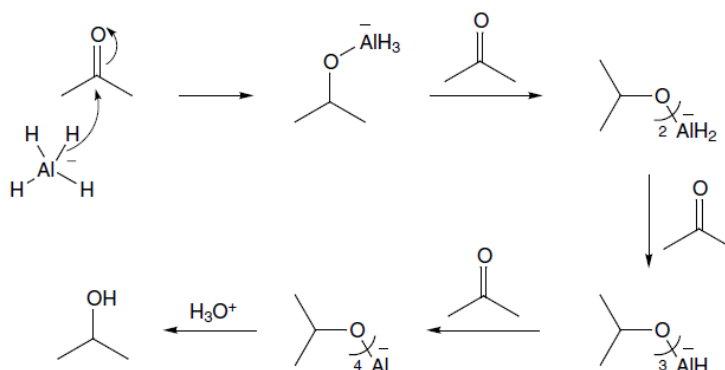


- Pure, recrystallized (from diethyl ether) LAH is a white solid. Commercial samples are almost always grey due to trace contamination with aluminum metal.

Reactions

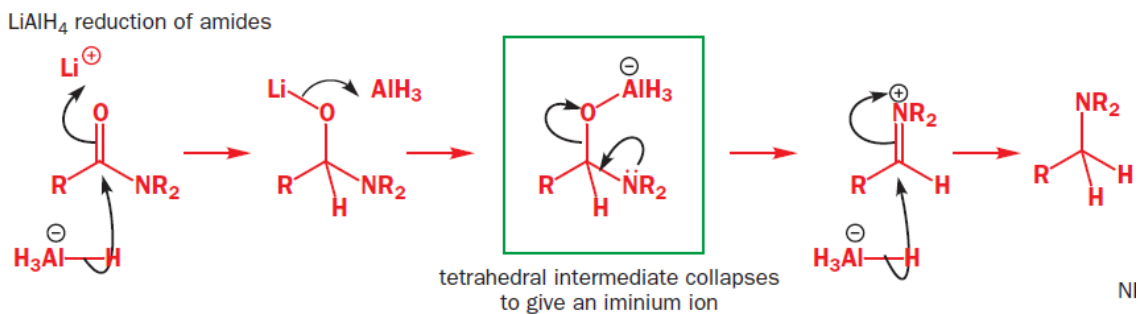
The reaction mechanism shows the involvement of all four hydrogen atoms that are being transferred in a stepwise manner. Each successive transfer of hydride ion takes place more slowly than the one before, and this has been exploited for the preparation of modified reagents that are less reactive and more selective than lithium aluminium hydride.

Scheme 1. Mechanism for LiAlH₄ reduction

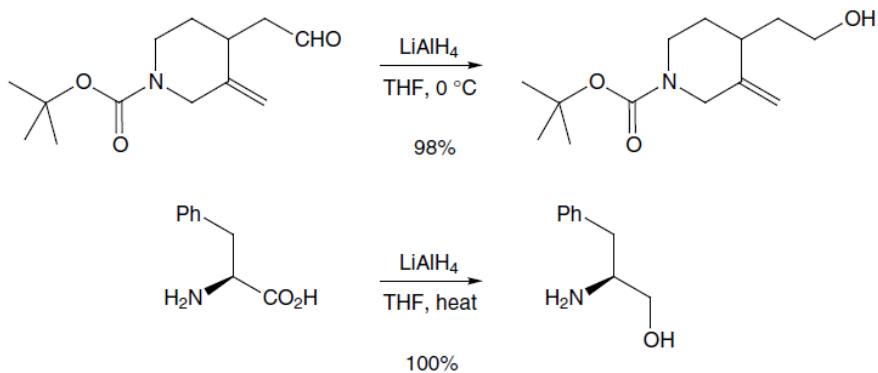


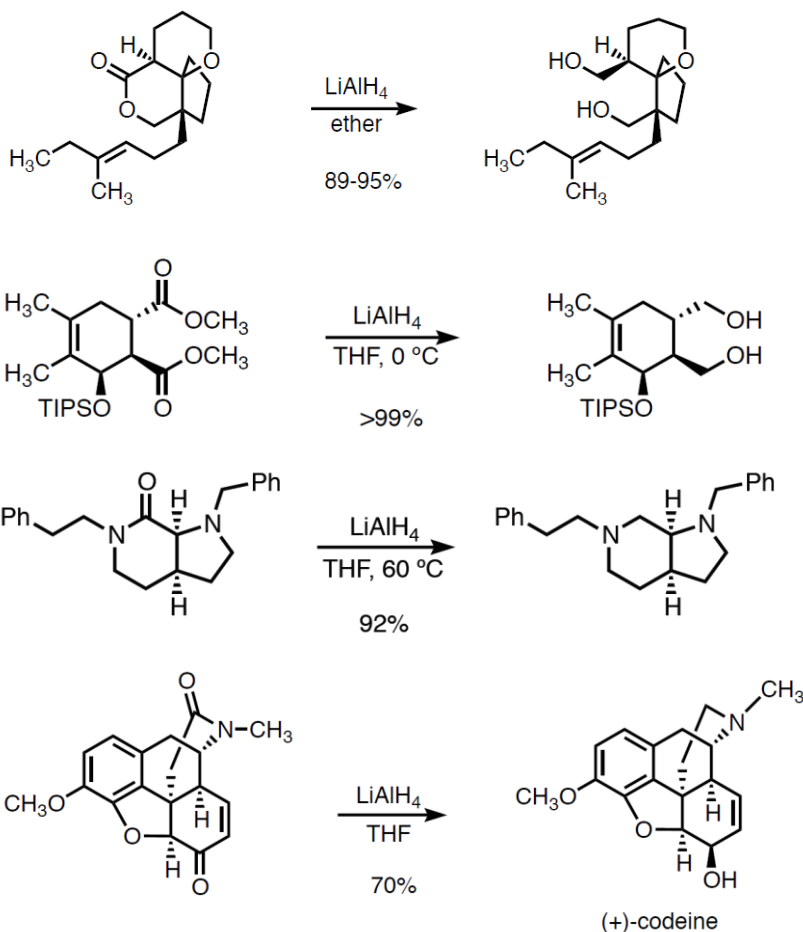
LiAlH₄ is a good reagent for the reduction of esters and amides, but there is a key difference in esters, ⁻OR is eliminated to give aldehyde which further reduces to alcohol, while in amides ⁻NR₂ is not eliminated.

Scheme 2. Mechanism for the reduction of amides



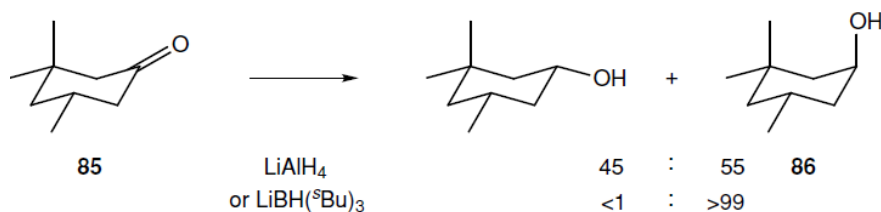
Scheme 3. Reduction of carbonyls





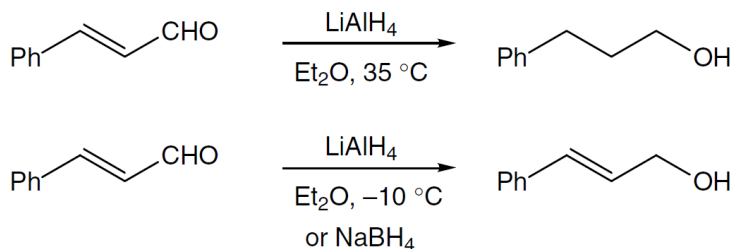
With less-rigid cyclohexanones, the stereochemical course of the reduction is less easy to predict. To rationalize the stereoselectivities in the reaction, it is supposed that in general there is a tendency for approach of the reagent to the carbonyl group in an axial direction, leading to the equatorial alcohol. In hindered ketones, however, axial approach may be hampered by steric factors, thereby favouring equatorial approach of the reagent and formation of the axial alcohol. Thus, reduction of 4-*tert*-butylcyclohexanone with lithium aluminium hydride gives predominantly the equatorial *trans*-4-*tert*-butylcyclohexanol, whereas the hindered 3,3,5-trimethylcyclohexanone **85** gives a mixture containing mainly the axial alcohol **86**. The latter is almost the only product when a more hindered and hence more selective reducing agent such as *l*-selectride [$\text{LiBH}(\text{sBu})_3$] or lithium hydrido-tri-*tert*-butoxyaluminate [$\text{LiAlH}(\text{OtBu})_3$] is used.

Scheme 4. Stereoselective synthesis of cyclohexanol derivatives



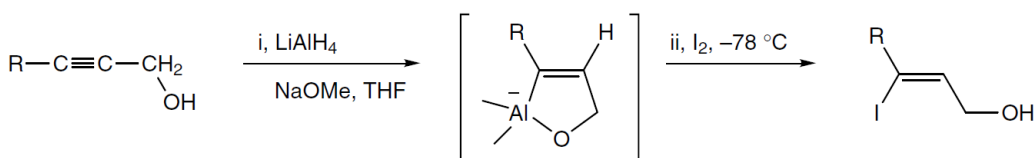
- The carbon-carbon double bonds are not attacked by hydride reducing agents is found in the reduction of β -aryl- α,β -unsaturated carbonyl compounds with lithium aluminium hydride, where the carbon-carbon double bond is often reduced as well as the carbonyl group. To achieve the selective reduction of the carbonyl group, the reaction was performed at low temperatures or by using sodium borohydride.

Scheme 5. Reduction of α,β -unsaturated carbonyl compounds



Similarly, aluminium compound is thought to be involved in the reduction of the triple bond of propargylic alcohols with lithium aluminium hydride to give *trans* alkenes.

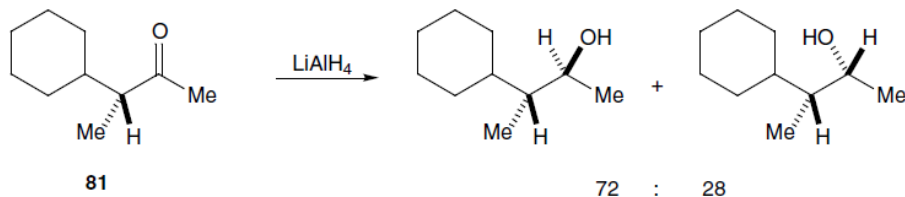
Scheme 6. Reduction of propargylic alcohol



- Usually, the reduction of the carbonyl group of an unsymmetrical ketone such as ethyl methyl ketone leads to the racemic alcohol. With ketones that contain an asymmetric centre, however, the two diastereomers of the alcohol may not be produced in equal amount. For example, in the

reduction of the ketone **81** with lithium aluminium hydride, the *anti* stereoisomer of the alcohol predominates in the product.

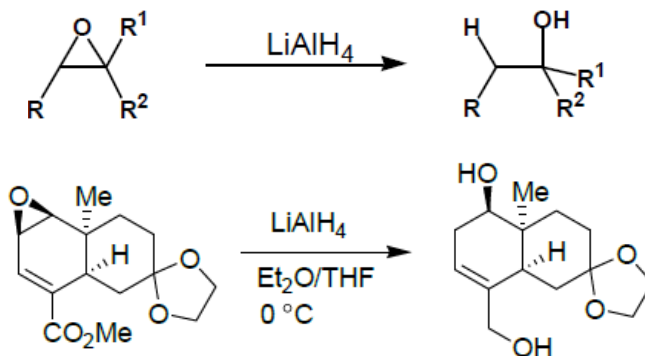
Scheme 7.



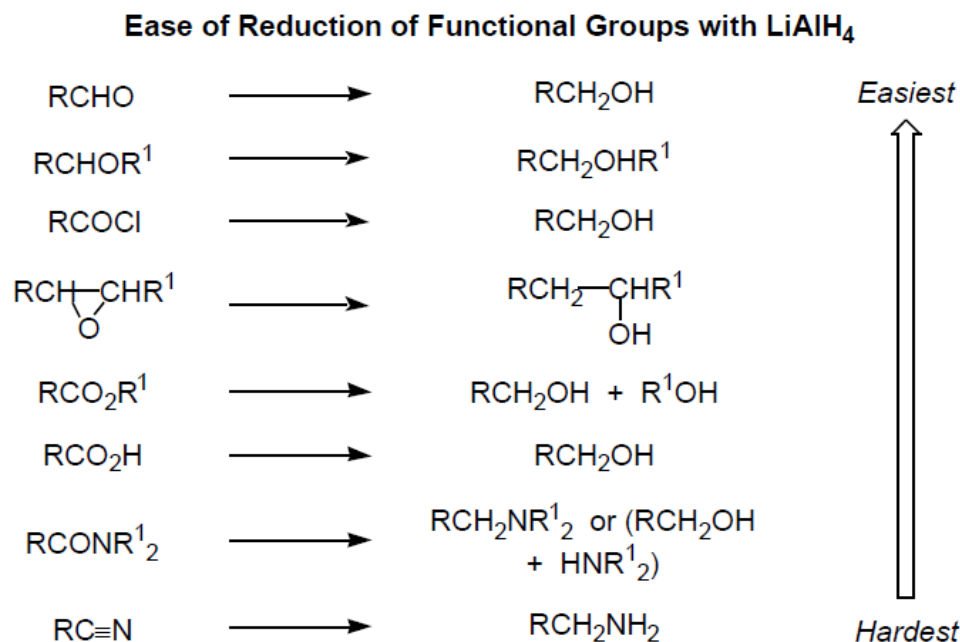
The main product formed in these reactions can be predicted on the basis of the Felkin–Anh model. The diastereomer which predominates is that formed by approach of the reagent to the less-hindered side of the carbonyl group when the rotational conformation of the molecule is such that the largest group on the adjacent chiral centre is perpendicular to the carbonyl group.

- LAH also used for reductive opening of epoxides which proceeds with $\text{S}_{\text{N}}2$ substitution by hydride ion to form a new C-H bond with overall inversion of configuration at the carbon atom attacked. Epoxides can therefore be reduced to alcohols. With unsymmetrical epoxides, reaction takes place at the less-substituted carbon atom to give the more substituted alcohol product.

Scheme 8. Reduction of epoxide



Scheme 9.



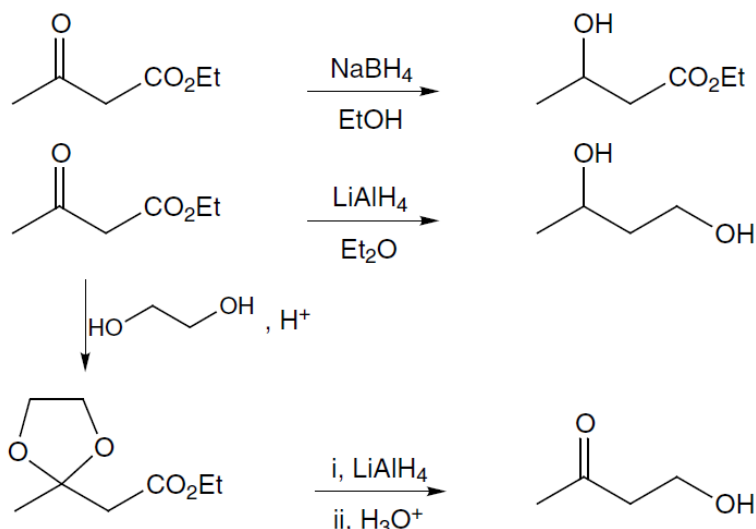
Sodium borohydride (NaBH₄)

- Sodium borohydride is less reactive than lithium aluminium hydride and is therefore more discriminating (chemoselective) in its action.
- It reacts only slowly with water and most alcohols at room temperature and reductions with this reagent are often effected in ethanol solution.
- At room temperature in ethanol it readily reduces aldehydes and ketones but it does not generally attack esters or amides and it is normally possible to reduce aldehydes and ketones selectively with sodium borohydride in the presence of a variety of other functional groups.

Reactions

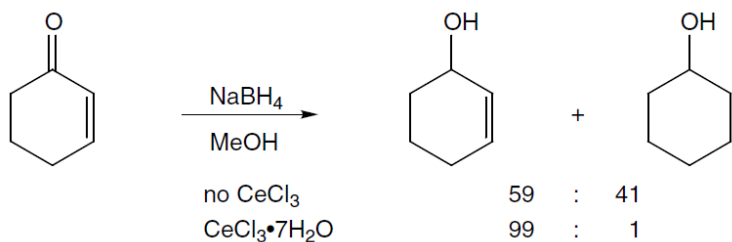
- Ethyl acetoacetate, having both an ester and a ketone functional group, on reduction with sodium borohydride gives ethyl 3-hydroxybutanoate, the product from selective reduction of only the keto group. In contrast, the more reactive lithium aluminium hydride gives 1,3-butanediol, by reduction of both carbonyl groups. To effect selective reduction of the ester, the keto group must be protected as its acetal, and the ester reduced with lithium aluminium hydride. Mild acid hydrolysis then regenerates the ketone to give the keto-alcohol.

Scheme 10. Selective reduction of ethyl acetoacetate



- The reducing properties of sodium borohydride are substantially modified in the presence of metal salts, and particularly useful in this respect are lanthanide salts. In the presence of cerium(III) chloride, for example, sodium borohydride reduces α,β -unsaturated ketones with extremely high selectivity, such that 1,2- and almost no 1,4-reduction occurs to give allylic alcohols. This reagent system has therefore found some use for the formation of allylic alcohols from α,β -unsaturated ketones that otherwise lead to reduction of the carbon-carbon double bond as well

Scheme 11.

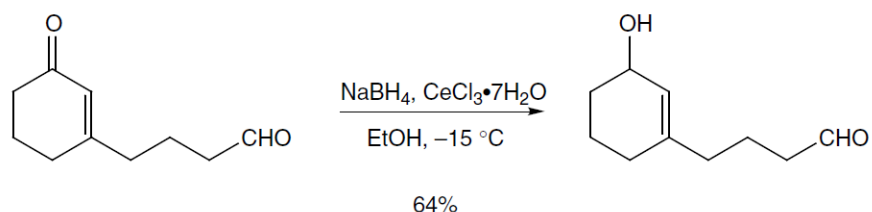


Interestingly, sodium borohydride- CeCl_3 can discriminate between different ketone and aldehyde groups, effecting the selective reduction of the *less*-reactive carbonyl group. For example, α,β -unsaturated ketones are reduced selectively in the presence of saturated ketones or aldehydes. Ketones can be sometimes be reduced in the presence of an aldehyde

- Changing the counter-cation can have a profound effect on the reactivity of NaBH_4

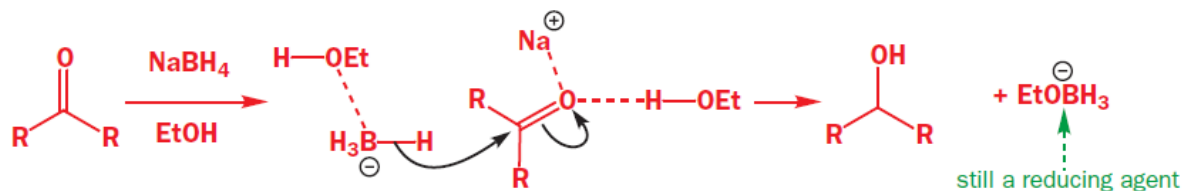
- Addition of CeCl_3 (**Luche Reduction**) gives very selective 1,2-reduction of conjugated aldehydes and ketones.
- The reason might be: the more-reactive aldehyde group is protected as the hydrate, which is stabilized by complexation with the cerium ion, and is regenerated during isolation of the product.

Scheme 12.



- Sodium borohydride is one of the weakest hydride donors available. The fact that it can be used in water is evidence of this as more powerful hydride donors such as lithium aluminium hydride, Sodium borohydride reacts with both aldehydes and ketones, though the reaction with ketones is slower: for example, benzaldehyde is reduced about 400 faster than acetophenone in isopropanol.
- Sodium borohydride does not react at all with less reactive carbonyl compounds such as esters or amides: if a molecule contains both an aldehyde and an ester, only the aldehyde will be reduced.

Scheme 13. Mechanism for the reduction of carbonyl



The transfer of a hydrogen atom with two electrons (called **hydride transfer** though no hydride ion is involved). In addition, the developing negative charge on oxygen gets help from the alcohol or the sodium ion or both and a molecule of alcohol adds to the boron during or immediately after the reduction. The by-product, an alkoxyborohydride anion, is itself a reducing agent, and can go on to reduce three more molecules of carbonyl compound, transferring step-by-step all of its hydrogen atoms.