Essentials of Oxidation, Reduction and C-C Bond Formation Application in Organic Synthesis

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Lecture-26

Further Aspects of Luche Reduction, Stereochemistry in Reductions and Reduction with LiBH 4

Hello everyone, welcome to today's class. We will briefly go through matter that we discussed last time.

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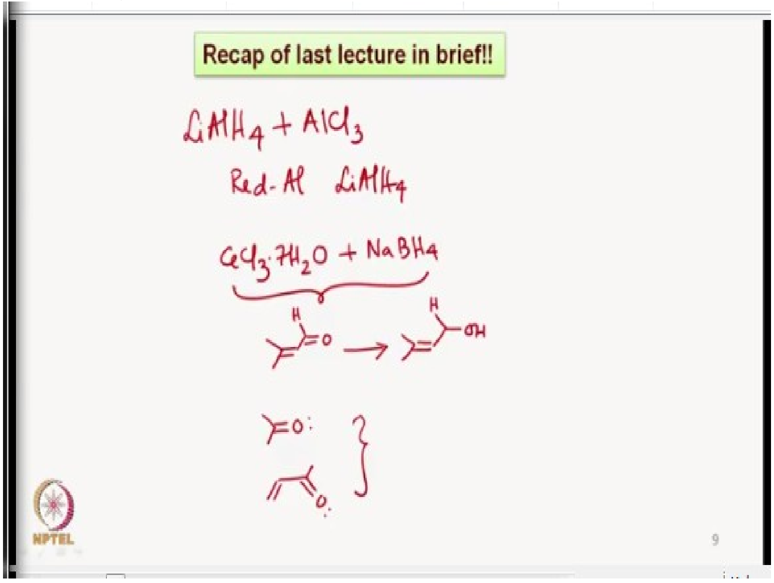
Recap of last lecture in brief!!

If you recall, we discussed initially the reductions using lithium aluminium hydride and aluminium chloride. And of course we saw how the selective reductions can be carried out? Then we proceeded to look at the reactions of Red -Al and the Red-Al comparison with lithium aluminium hydride. And we saw how important is this reducing agent, because it is better than lithium aluminium hydride in many sense for especially from handling point of view and it reduces the acid to the corresponding alcohol.

But interestingly, when you take epoxy alcohol both Red-Al and lithium aluminium hydride, they lead to selectivity which is different from that of DIBAL. We then of course discuss the mechanism involved in those reactions and saw how in the lithium aluminium hydride and Red-Al case intra molecular reduction of the epoxide gives 1, 3 diol as the major product.

And in the case of DIBAL it is an inter molecular reduction that allows the formation of 1, 2 diol as the major product. And then towards the end we discussed Luche reduction and as I mentioned after a lot of combinations, the Luche and Gemal found out that cerium chloride 7 H_2O, that means hydrated sodium chloride along with sodium borohydride very comfortably gives the reducing system which allows reduction of say particularly carbonyl which groups which are alpha beta unsaturated, can be aldehyde or can be ketone.

And that leads to specifically reduction with the reducing agent to the corresponding allylic alcohol. This is something very interesting because it is very easy to perform this reaction, and the selectivity is very high. Then of course we also discussed how the ketones oxygen and also alpha beta unsaturated ketones or aldehydes, oxygen here is more Lewis basic than the corresponding unsaturated ketones or say aldehydes.

So, this difference in the Lewis basic character of ketones and alpha beta unsaturated systems was also exploited by the Luche and Gemal in their reduction. So, we will look at some aspects of it now in this lecture today.

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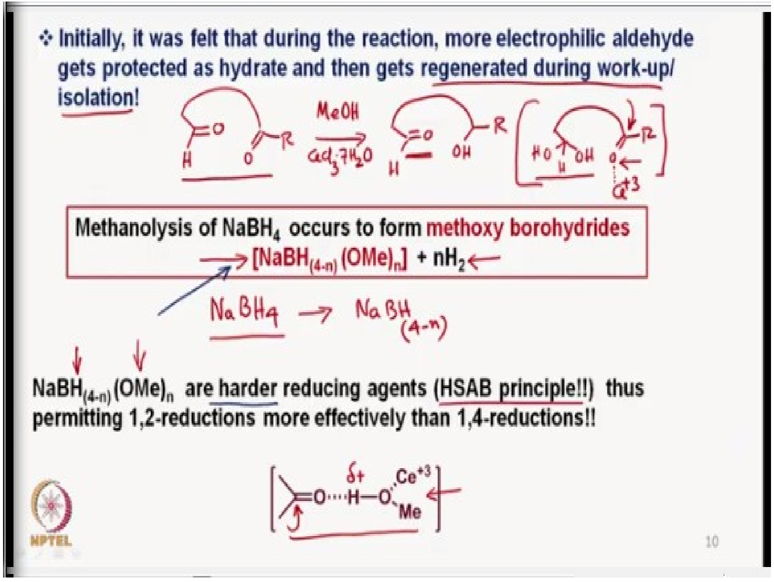

- Initially, it was felt that during the reaction, more electrophilic aldehyde gets protected as hydrate and then gets regenerated during work-up/ isolation!

Methanolysis of $NaBH_4$ occurs to form methoxy borohydrides
$[NaBH_{(4-n)}(OMe)_n] + nH_2$

$NaBH_4 \rightarrow NaBH_{(4-n)}$

$NaBH_{(4-n)}(OMe)_n$ are harder reducing agents (HSAB principle!!) thus permitting 1,2-reductions more effectively than 1,4-reductions!!

Initially, it was felt during the reaction that more electrophilic aldehyde gets protected as aldehyde hydrate and then gets regenerated during the work-up. That means, what is happening is that, if suppose you have a molecule that has say aldehyde here, and also it is a part of a corresponding ketone, so you have an R group here. So, this particular compound allows the reduction of the ketone over say for example aldehyde.

This is the selectivity that is particularly found in the case of reaction of a molecule that contains both an aldehyde and ketone. Under normal conditions aldehyde being more electrophilic in nature compared to the ketone should get reduced with sodium borohydride or with any reducing agent. But the combination of reagents such as cerium chloride, heptahydrate, and sodium borohydride allows a kind of aqueous medium because the reaction is also carried out in methanol as a solvent.

So, in methanol as a solvent everything is miscible and at that time initially it was felt that the aldehyde gets basically formed as hydrate and gets blocked, and does not react, will something like this and the ketone remains as it is. So, this is the intermediate that was proposed that under the conditions here when we have a cerium chloride, $7H_2O$ at that time, when molecule containing both aldehyde and the ketone is exposed to these condition is, the aldehyde basically gets blocked as a hydrate.

And now the reduction takes place onto this because this particular oxygen atom is more Lewis basic and therefore, the cerium +3 coordinates which is readily available. And then during the work-up the aldehyde is regenerated, that means once the reduction has taken place, this is what originally it was felt. Later on more detailed studies of these mechanisms of involved in this particular reaction were carried out.

And it was found that methanolysis of sodium borohydride occurs to form methoxy borohydride. That means, as I have already mentioned earlier that we take sodium borohydride, normally sodium borohydride is easily used in alcoholic medium. But I also mentioned the earlier time that sodium borohydride does react with methanol or ethanol but slowly.

So, under these conditions it is expected that what may happen is that methanol reacts with sodium borohydride and forms different species. That means you have NaBH say for example, it can be a 4^{-n}, that means, it can be 1, n can be 1, 2 or 3 or something of that kind forming this species, and of course the corresponding hydrogen goes off. So, this is the methoxy borohydride which are expected to form this particular junction when sodium borohydride is used in methanol along with cerium salt.

This sodium methoxy borohydrides are obviously harder reducing agents, because now you have methoxy groups attached to it, and therefore the electron withdrawing nature of the methoxy group due to inductive effect makes the corresponding hydride here of the sodium borohydride as harder based on acid base or of acid base principle. And thus it allows 1, 2 reduction to take place.

It is very clear that a species of this kind should be involved, because it is expected that even methanol has coordination with the cerium+. And of course now the modified methoxy borohydrides, then interacted and act as a reducing agent to this, where the carbonyl oxygen has a kind of interaction with the H. Now because you can expect that now this can become delta plus and therefore there is a coordination of the oxygen with the H+. And this is a part which is coming from the methanol.

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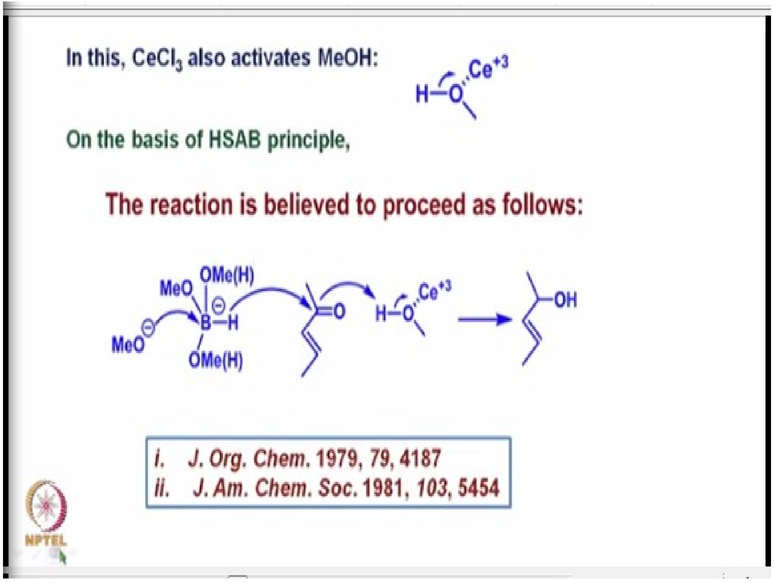

In this, $CeCl_3$ also activates MeOH:

On the basis of HSAB principle,

The reaction is believed to proceed as follows:

i. *J. Org. Chem.* 1979, 79, 4187

ii. *J. Am. Chem. Soc.* 1981, *103*, 5454

So, basically what is happening is cerium chloride activates methanol in this particular fashion and thereby makes the proton very labile and a harder acid. Now on the basis of HSAB principle, what we expect that, the reaction of an alpha beta unsaturated ketone may proceed in this particular fashion. So, what is the initiation that happens? That is when an alpha beta unsaturated ketone comes in contact with the proton that is being released from methanol, which in turn complexes with the cerium +3 salt.

And therefore this more basic ketone of the alpha beta unsaturated system, the more basic oxygen interacts with the harder H+ and thereby increasing the electrophilicity of this particular carbon atom making it harder Lewis acid. And to which hydride then attacks, this hydride is basically made up of tri methoxy borohydride, in which there could be 1 methoxy or 2 methoxy or 3 methoxy it could be a mixture of all, all the 3 types of methoxy borohydrides.

And therefore, they form a harder Lewis base in terms of H-, which then interacts with the harder Lewis acid at this particular carbon atom, which is due to the coordination of the oxygen, which is a harder base with the harder acid here H+, released by the complexation or as a result of the complexation of methanol with the same cerium 3+ salt resulting into an allylic alcohol.

This mechanism has been well studied and reported in these 2 papers. And we can therefore, assume that based on the HSAB principle, the reaction proceeds in this particular fashion. So, this is what is usually expected that the reaction allows the reduction of an alpha beta unsaturated ketone to specifically form the corresponding allylic alcohol.

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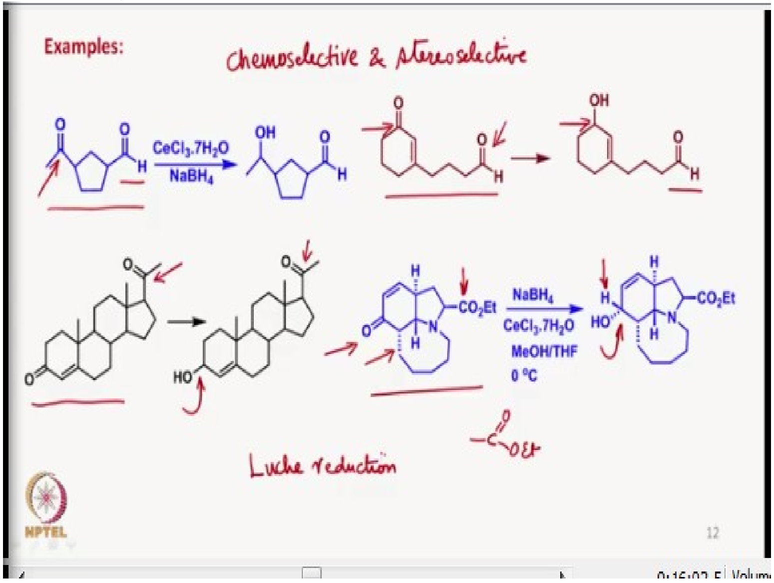

Examples:

Chemoselective & Stereoselective

Luche reduction

If we take various examples of the Luche reduction, we find that as I mentioned earlier, one of the examples is that if we take a ketone and an aldehyde, only the ketone gets reduced and the aldehyde remains unreacted. If we take an alpha beta unsaturated ketone having an aldehydic group, then the ketone is reduced to the corresponding allylic alcohol and aldehyde remains unaffected.

So, these are the 2 examples, which I discussed where initially what was felt that the aldehyde group gets blocked under the reaction conditions as a hydrate. But then the mechanisms which we discuss were mixed methoxy borohydrides are formed where it is expected that the ketonic oxygen is more Lewis basic. And similarly, alpha beta unsaturated ketone's, oxygen is more basic than the corresponding aldehyde here, for example here.

And that is the reason why the aldehyde does not react with the reducing agent and specifically the ketone or the ketone of an alpha beta unsaturated ketone gets reduced, which is exactly opposite to what normally one would expect. Because aldehyde is more electrophilic than ketone or aldehyde is more electrophilic than the corresponding enone. In another example, in which an enone was taken and a ketone was taken in the same molecule.

As you can see that the enone gets reduced to the corresponding allylic alcohol and the saturated ketone remains as it is. Again we can think in the same fashion that the ketone here is more electrophilic in the nature whereas, enone is less electrophilic because of the double bond. And exactly on the basis of the larger Lewis basic character of an enone of oxygen versus saturated ketone, the reduction of the enone occurs.

And if one takes, an example of this type where an enone is there and an ester is there. We have already discussed that the Ester carbonyl here of course, is much less electrophilic here and enone because of the double bond being there reacts specifically to form this, and here also as one can see, that there is a stereo selectivity involved. Since this particular carbon-carbon bond is alpha oriented, the hydrogen which is coming is from the meta side.

So, not only that, there is a chemoselectivity these are the examples of chemoselective reduction. So, because you have one type of aldehyde or ketone and there are 2 different types of carbonyl compounds in each case, and therefore it is a chemoselective reduction. At the same time, this also has to stereo selective reduction, chemoselectivity and stereo selective reductions occur.

So, both these are very important aspects and a number of examples have been reported in the literature, where the utility of the sodium borohydride, cerium chloride combination which is known as Luche reduction is used in n number of synthetic transformations.

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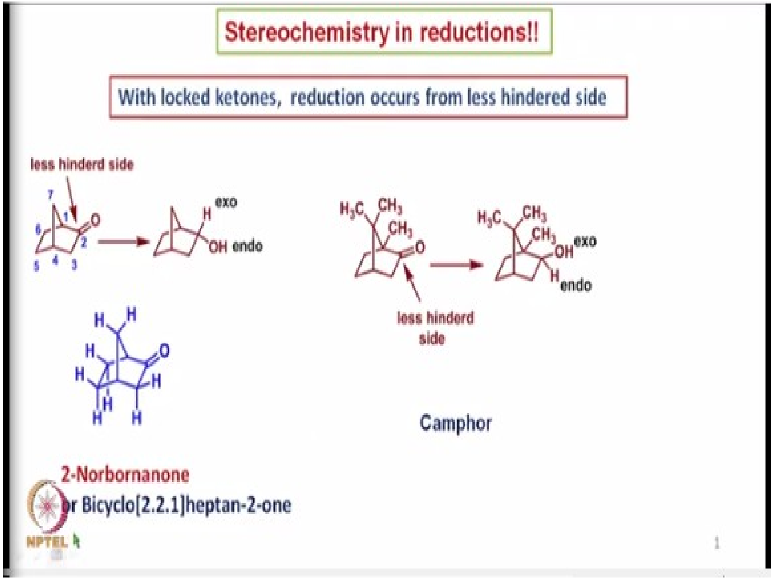

Stereochemistry in reductions!!

With locked ketones, reduction occurs from less hindered side

Now we see the stereochemistry in reductions of ketones. If we take locked ketones, we find that reduction occurs from less hindered site. For example, if we take a case of this bi-cyclic ketone which is 2-Norbornanone or it is also called as bicyclo 2, 2, 1 heptan- 2- one. Now if we see the positions of the hydrogen around the carbonyl group, then we will see that the endo side of the molecule is sterically more hindered than the exo side.

For example there are 3 endo hydrogens which are at the lower side of the molecule, whereas there is only one hydrogen which is blocking the phase of the carbonyl due from the exo side. Therefore when a reducing agent approaches this particular molecule, it sees more steric hindrance from the endo side, and therefore it reduces the carbonyl group from the exo side or the hydrogen is transferred from the exo side resulting into the formation of the endo alcohol.

On the other hand, if we take somewhat similar example but with different substitution, like for example camphor. In the camphor case, the carbonyl group now, has a slightly different endo and exo selectivity. Here as you can see, that the exo phase has 2 methyls here on the top which are blocking the phase of the exo side. On the other hand, the endo side has only the 3 hydrogens which were present in the case of 2-Norbornanone.

But because of the closeness of the methyl groups here to the carbonyl group, the exo side is technically more hindered. And therefore the reducing agent approaches the carbonyl group form the less hindered endo side, resulting into an exo alcohol. So, basically what is happening is that in locked cases where there is no possibility of any confirmation change, the reduction always occurs from the less hindered side.

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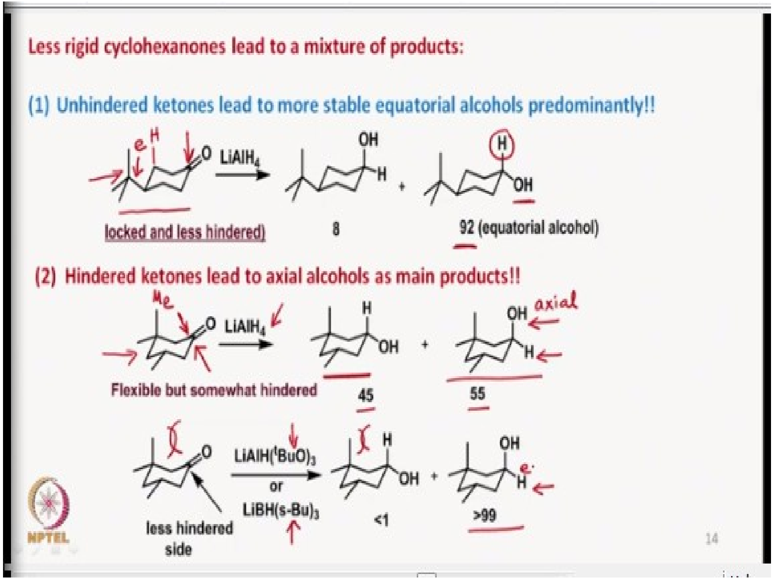

Less rigid cyclohexanones lead to a mixture of products:

(1) Unhindered ketones lead to more stable equatorial alcohols predominantly!!

(2) Hindered ketones lead to axial alcohols as main products!!

If we take less rigid cyclohexanones, then we obviously get mixtures, where we can see how the distribution of the products occur. For example, if we take a case like this, well of course, we have put tertiary butyl, so it is a kind of locked because the tertiary butyl group would always remain in an equatorial orientation of the molecule, and therefore when the lithium aluminium hydride attacks.

As you can see, what is found is that the reduction occurs mainly from the axial side. That means, the hydrogen approaches from the axial side leading to 92% of the equatorial alcohol. That means that since the OH group is bigger than the hydrogen obviously, and the aluminium part would react with alcohol of course when the reduction occurs, there is a chelation with the lithium+.

And then eventually the O^- which is going to form would interact with the AlH_3 which is released and that will give $OAlH_3$ and upon workup, we get the corresponding OH. But then with the lithium aluminium hydride is a small reducing agent, it prefers to attack in such a way that the larger OH or the OA l H_3^- goes to the equatorial side. But then if we say take a hindered ketone something like this, where now deliberately we have put a methyl group here.

This is the methyl group, whereas here it was only hydrogen, so this was not that much sterically hindered. So, if we put a methyl group here and it is not a locked particularly molecule as such but it has a methyl group which is axial. So, if this is reduced as you can see that the major product is the one that is between the 2 it is 45:55, but even then, it is slightly more than the equatorial alcohol.

So, you can see that the preference of reduction occurs from the equatorial side, so that we get axial alcohol. So, the axial alcohol formation occurs, because the equatorial side is somewhat. So, this side is somewhat less in hindered compared to this side, and therefore we get 55% of the alcohol which is axial alcohol via the reduction from the equatorial side, whereas the axial side reduction gives 45%.

Now, if we increase the bulk of the reducing agent, because lithium aluminium hydride is relatively small in terms of steric size. And therefore, if we increase say lithium aluminium tri tertiary butoxy hydride or lithium secondary butoxyl borohydride or any of these kind, where there are big bulky groups present on the reducing agent. And there as you can see that reduction occurs preferably from the equatorial side and then 99% more than 99% of the axial alcohol is formed.

Because of this particular portion being sterically hindered and therefore a reduction preferentially occurs from the equatorial side, this is the equatorial hydrogen. So, this is how one can expect that the reduction of cyclohexanones can be predicted.

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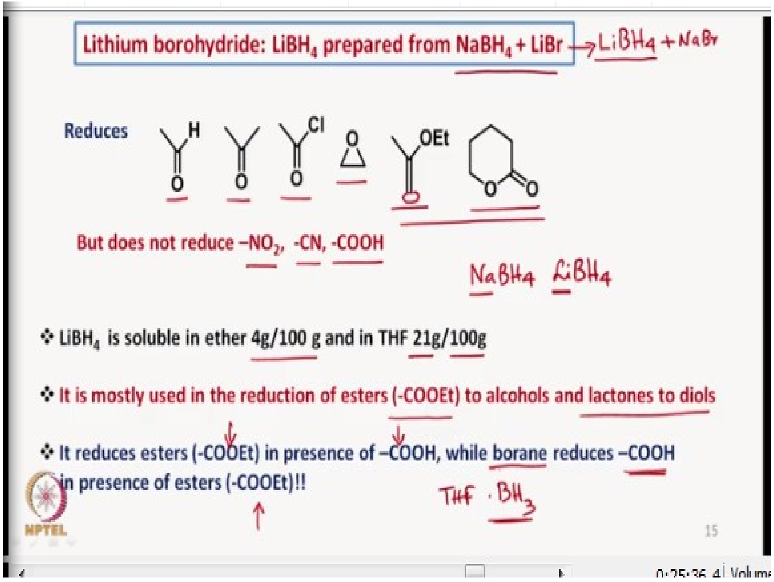

Lithium borohydride: $LiBH_4$ prepared from $NaBH_4$ + LiBr → $LiBH_4$ + NaBr

Reduces

But does not reduce $-NO_2$, -CN, -COOH

$NaBH_4$ $LiBH_4$

- $LiBH_4$ is soluble in ether 4g/100 g and in THF 21g/100g
- It is mostly used in the reduction of esters (-COOEt) to alcohols and lactones to diols
- It reduces esters (-COOEt) in presence of –COOH, while borane reduces –COOH in presence of esters (-COOEt)!!

THF · BH_3

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Now we have lithium borohydride as a reducing agent which can be easily prepared from sodium borohydride and lithium bromide. We take the combination of the 2 and then as you can expect that sodium bromide will precipitate off. From here of sodium and then lithium borohydride will form and there will be sodium bromide as a byproduct. So, we get the lithium borohydride very readily.

Because of the lithium+ nature which is harder compared to sodium+ the reduction occurs not only of aldehyde and ketone but also as it chloride, epoxides, this should be ester and the lactone. So, we can expect the reduction of these types of molecules to take place. But it is interesting that we are basically trying to compare sodium borohydride with lithium borohydride here. So, because there is a difference in terms of sodium versus lithium+ and lithium+ is harder, therefore it is able to reduce even like epoxide, esters and lactones.

But it is not sufficiently since even then there is a borohydride part which is relatively mild reducing part, and therefore the nitro, cyano or carboxylic acids are not reduced. And the lithium low hydride is found to be soluble like 4 grams in 100 grams of ether or 21 grams in 100 grams in tetrahydrofuran. It is mostly used in the reduction of esters and lactones to diols, as we have already shown it here that can be easily done.

But if we have a molecule in which there is an acid to be reduced, then of course we use borane diborane or BH_3 say THF complex or any such thing which is a source of BH_3, reduces the acid to the corresponding alcohols. So, we see it very clearly that if we take lithium borohydride, it reduces esters in presence of acid in presence of carboxylic acid, but borane reduces acids in presence of ester.

So, this is something that it is important for all of you to remember that lithium borohydride and di borane, they complement each other in terms of reactivity. And as I mentioned esters are easily reduced, similarly lactones are reduced to the corresponding diols.

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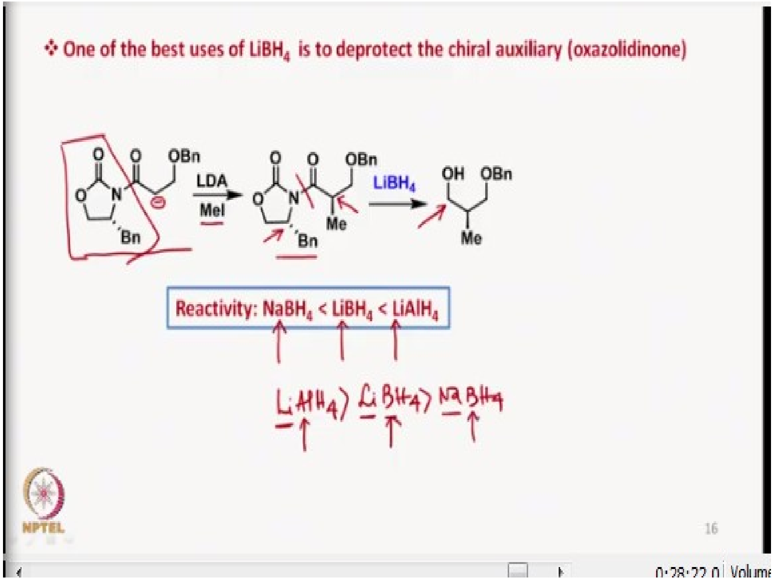

❖ One of the best uses of $LiBH_4$ is to deprotect the chiral auxiliary (oxazolidinone)

Reactivity: $NaBH_4 < LiBH_4 < LiAlH_4$

$LiAlH_4 > LiBH_4 > NaBH_4$

One of the best uses of lithium borohydride is to deprotect chiral auxiliary like we can see that we can take this particular molecule in which this part is a chiral auxiliary, this part here. And because of this part, we can make an anion here with say LDA and say add methyl iodide here as an electrophile, we can introduce here the methyl group. So, after the methyl group has been introduced, here which is based on the side chain which is present and this is an optically active, and therefore this is a highly diastereoselective alkylation.

And when we need to remove the auxiliary from here, what is done is simply use lithium borohydride which is soluble in ether or THF. And we can completely reduce this particular part which is an easily reducible part with lithium borohydride equivalent to ester type of thing is and then we can get the corresponding CH_2OH. So, this is one of the best examples where lithium borohydride has been used in terms of deprotecting the chiral auxiliary.

So, if we look at the reactivity profile, sodium borohydride is much less reactive which is comparable with lithium aluminium borohydride which is more reactive than sodium borohydride as we have see in these examples. And which is more, now again comparable with lithium aluminium hydride and lithium aluminium hydride is much more reactive than lithium borohydride.

So, we have the lithium aluminium hydride versus lithium borohydride which is then compared to sodium borohydride the reducing power keeps decreasing. And that has to do with the lithium+ here and of course comparison with sodium+ and boron versus aluminium, so this is how the reactivity profiles have been found. So, we will stop it at this stage today and you can go through these reactivity profiles of sodium borohydride, lithium borohydride and lithium aluminium hydride and try to understand what I discussed.

And we will continue with the reductions of various kinds in organic chemistry using other reducing agents, and see how do they compare with reducing agents that we have discussed so far. So, we stop it here and thank you, see you next time.