Essentials of Oxidation, Reduction and C-C Bond Formation.
Application in Organic Synthesis
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Lecture – 27
Reductions with Zn(BH 4) 2,LiBHEt 3(Superhydride) and L and K-Selectrides

Hello everyone, I would like to welcome you all to today's lecture. I hope you had the opportunity to go through what I discussed last time, we will see very briefly what we did last time and what are the aspects of reducing agents that we discussed. So, we looked at the chemo and stereo selectivity using the Luche Reductions. And sodium borohydride cerium chloride reducing agent system was utilised to specifically see If we can reduce in the presence of an aldehyde ketone or a ketone, in the presence of which is an alpha, beta unsaturated system.

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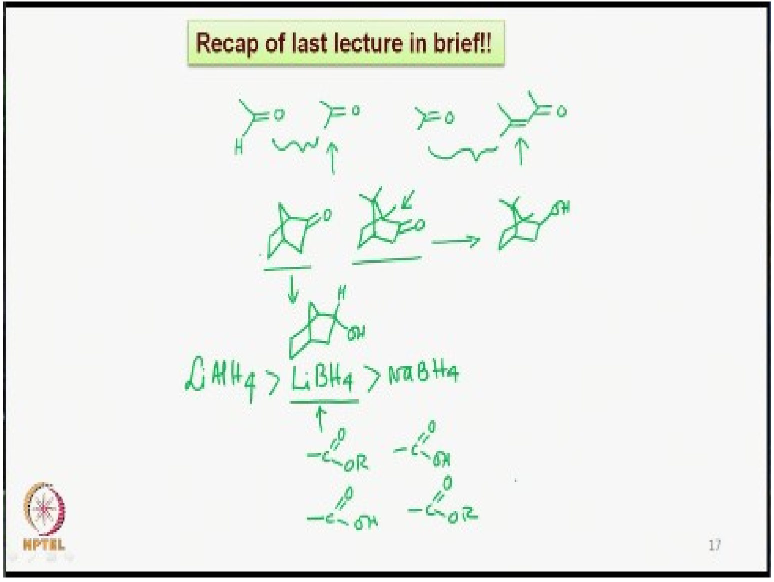

Recap of last lecture in brief!!

In the presence of these 2 the alpha, beta unsaturated system is reduced between these 2, this ketone is reduced. And therefore, various aspects of mechanistic considerations, we did it and found out that how methanol basically gets activated by a cerium chloride and releases the H plus to be attached to more basic ketone or more basic enone. And therefore, there is a selectivity in terms of reduction of a ketone in comparison to hydride or an enone in comparison to ketone.

Then, we also of course, discussed the stereo selectivity part of it, where if one particular side of the ketone is sterically bulky, therefore, the reduction occurs from the other side as one is normally expecting in all these cases. Then, we also looked at the stereochemistry of reductions of different kinds of reductions say with lithium aluminium hydride, etcetera, in a locked ketone, where we discussed norbornane systems.

So, we take a norbornane system like this and compared with another system where we had the methyl groups on the top and we saw that the reduction of such lock systems occurred specifically in one particular direction. In this case, for example, the reduction gives the alcohol which is on the top, because the top part of this particular molecule is sterically hindered. Whereas, in this case, we got the corresponding alcohol, which is endo alcohol because the top part is relatively free.

And therefore, we get the reduction from the exo side. Then, towards the end, we used lithium borohydride as a reducing agent. We try to see how the lithium borohydride is compatible with sodium borohydride and lithium aluminium hydride. So, we found out that lithium aluminium hydride is a stronger reducing agent compared to lithium borohydride which is stronger than sodium borohydride.

And one of the aspects of this lithium borohydride, we discussed was that it reduces esters in the presence of, corresponding carboxylic acid or when we compare with borane. The boranes reduce carboxylic acids to the alcohol and the esters are not touched. So, basically these are different reducing agents which have different power and selectivity in reductions.

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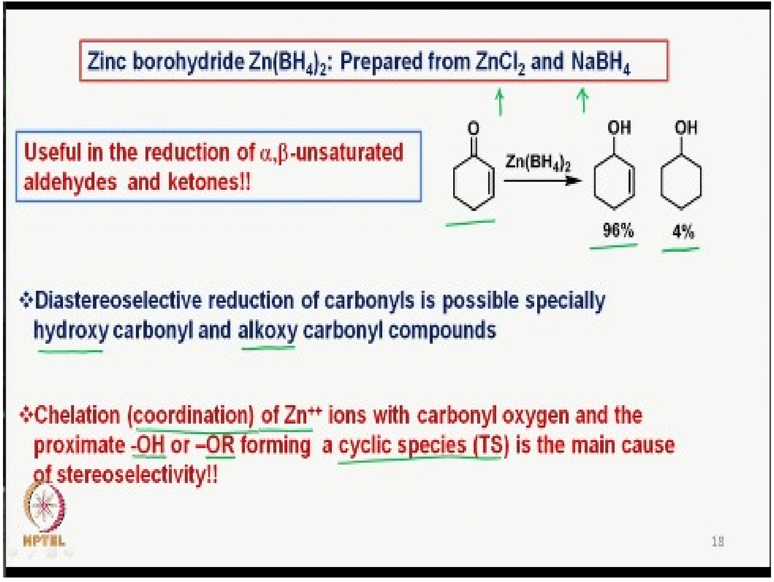

Zinc borohydride $Zn(BH_4)_2$: Prepared from $ZnCl_2$ and $NaBH_4$

Useful in the reduction of α,β-unsaturated aldehydes and ketones!!

- Diastereoselective reduction of carbonyls is possible specially hydroxy carbonyl and alkoxy carbonyl compounds
- Chelation (coordination) of Zn^{++} ions with carbonyl oxygen and the proximate -OH or –OR forming a cyclic species (TS) is the main cause of stereoselectivity!!

Now, we look at another reducing agent, which is zinc borohydride and it is readily prepared from zinc chloride and sodium borohydride. As you can see that sodium chloride would be off from the mixture as a by-product and we get the corresponding zinc borohydride. It is specifically useful in the reduction of alpha, beta unsaturated aldehydes and ketones. For example, this to the corresponding allylic alcohol and there is no very little reduction which leads to the corresponding saturated alcohol.

Now, this is very interesting because it has been reported in the literature that it allows a highly diastereoselective reduction of carbonyl compounds. If they have a say, if there is a hydroxy group present or an alkoxy group present in the vicinity of the particular carbonyl group that is to be reduced. It allows the reduction to take place due to the coordination of zinc ions with the carbonyl oxygen.

And also to the proximity based OH or OR group and thus, the form is cyclic transition state and that is the reason why there is a very high stereoselective or diastereoselective depending on molecule.

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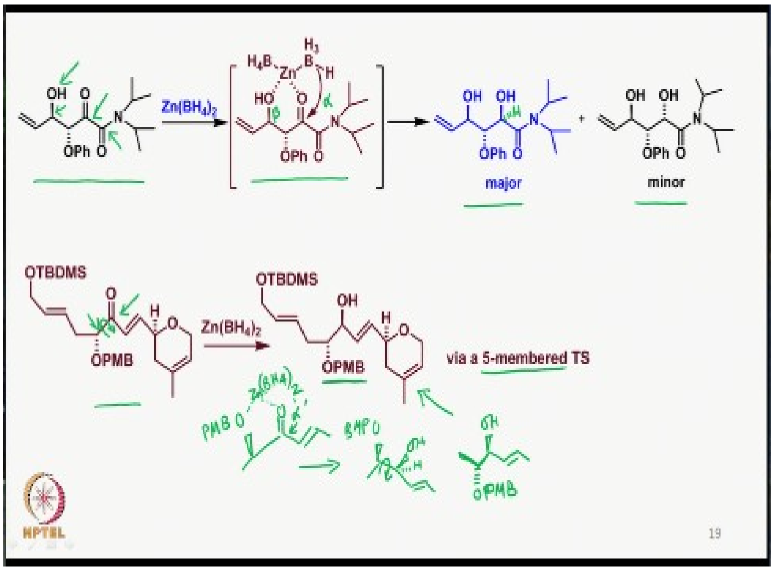

Say for example, if we have a case like this here, as you can see that there is a carbonyl group which is to be reduced, of course, there is another carbonyl group. But this is not going to be touched, because it is not a normal simple carbonyl. But, it is basically an amide. And therefore, this is less electrophilic compared to the other carbonyl group and therefore, that is reduced.

And now, this carbonyl group is very close to the hydroxy group here, which is beta oriented. So, if one can see that we can expect that there is a chelation of a 6 member. So, you have 1,2,3,4,5,6, 6 member transition state. And therefore, the chelation occurs from the beta side and therefore, the reduction occurs from the alpha side. So, this is an alpha side and this is a beta side.

And therefore, the chelation allows the availability of alpha side for the reduction to occur. And therefore, we get here hydrogen, which is coming from the alpha side. And therefore, this is a major product and this is the minor product. So, there is a high amount of the stereoselective that you can see. If we take the lower example here, then we have a ketone which is immediately next to the OPMB group, there is para methoxybenzyl group and that is alpha oriented.

But as you can see, that is pointing downward and therefore, when the chelation has to occur, this has to go up in a beta fashion O here and PMB. So, it would look like this, somewhat like this. And then what you have is a carbonyl group, which is now orienting itself in a fashion that will allow the say for example, we have something like this. And then you have carbonyl group coming here and then of course, something like this.

So, what we have done, it is that if we had done a rotation around here, so, that the PMB group goes on the top. And now, zinc would co-ordinate like this with BH_4 twice here. And now, the reduction also occurs from the alpha side, which is free. But then again after re-rotating, it would come to the original OPMB side. So, that means this would give a product like this OPMB.

And of course, we have here reduction taking place that means you have an OH here and alpha hydrogen like this, but then we re-rotate it here. And then we go to the formation of a product like this where now, we will have OPMB. So, this is the product that is formed, this is what is the product that is formed. So, it is via 5-membered transitional state. So, you could have either a 6 member transition state or a 5 member transition state.

But, the main idea here is that zinc easily coordinates with 2 oxygen around in the vicinity. And if they are properly oriented then accordingly the transfer of the hydrogen occurs to give highly diastereoselective reductions.

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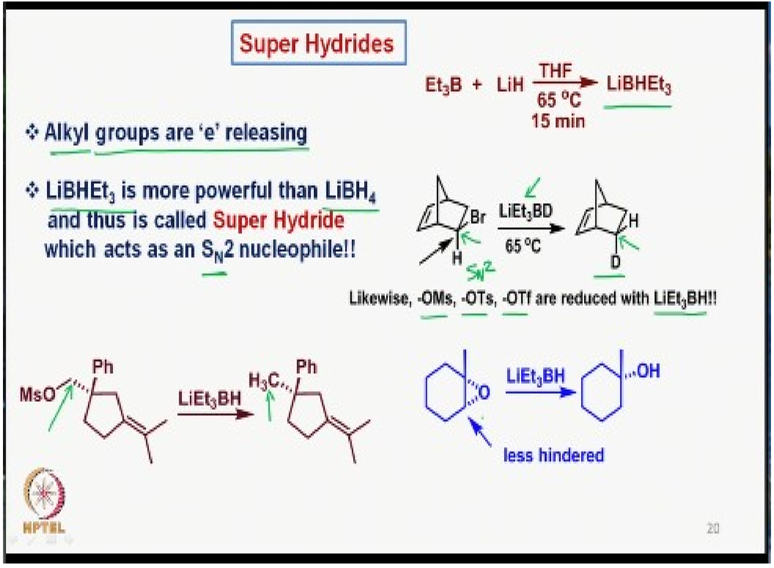

Super Hydrides

$Et_3B + LiH \xrightarrow[65\ ^\circ C,\ 15\ min]{THF} LiBHEt_3$

- Alkyl groups are 'e' releasing
- $LiBHEt_3$ is more powerful than $LiBH_4$ and thus is called Super Hydride which acts as an S_N2 nucleophile!!

Likewise, -OMs, -OTs, -OTf are reduced with $LiEt_3BH$!!

less hindered

Now, we will move on to super hydrides that are very strong and very sterically bulky reducing agents. For example, lithium triethyl borohydride is one of the super hydrides where there are alkyl groups attached to the reducing agent and they are electron releasing and therefore, the reactivity of such hydrides is very high. Now, one can see that if we compare it with lithium borohydride, obviously, this lithium triethyl borohydride is much more powerful than lithium borohydride.

And thus, it is called as a super hydrides which also acts like a nucleophile in an SN2 fashion. So, we had discussed earlier for example, if we have a carbon halogen bond like this here and if we react with say, lithium aluminium hydride, there will be a reduction of the carbon bromine bond to the carbon hydrogen bond. But, if we take sodium borohydride and lithium aluminium hydride and an aluminium chloride, the mixed chlorohydrides would not reduce this carbon bromine bond.

But, if we now take this super hydride lithium triethyl borohydride, for example, it reduces the carbon bromine bond easily and say in this particular case, you have lithium triethyl boro deuteride and deuterium has come in the fashion that is an SN2 type of reaction. And the stereochemistry of this centre has inverted here. Not only bromine but mesylate, tosylate, triflate are also reduced with lithium triethyl borohydride.

And as you can see here, there is a reduction of mesylate and it leads to the corresponding methyl group formation. It also allows reduction of epoxides and of course, as you can see very easily that reduction would occur from the less hindered side. So, basically lithium triethyl borohydride super hydride is comparable with lithium say aluminium hydride in many sense, but then there is a mixed reducing agent nature it has lithium and boron.

So, therefore, we can compare it with lithium borohydride. But then in comparison to the lithium borohydride because of the electron realising nature of the ethyl groups which are attached steric hindrance as well as the reducing power both of them contribute. And therefore, it acts like a super hydride and that is how it is used. It is called as a super hydride.

There is a very interesting example in which comparison is made with lithium aluminium hydride and lithium triethyl borohydride that means lithium aluminium hydride and the super hydride, if we see the reduction of this epoxide here.

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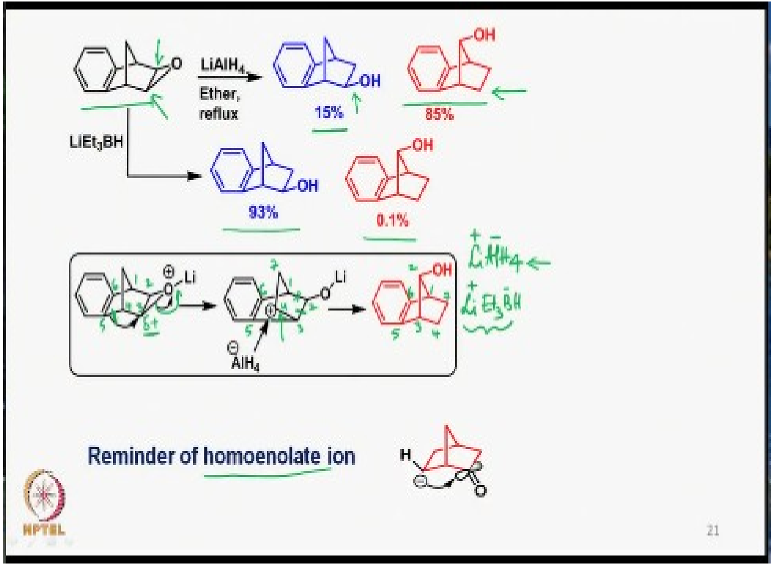

Reminder of homoenolate ion

And if lithium aluminium hydride is used under refluxing conditions in ether, it is actually symmetrical molecules it does not really matter, where the reduction takes place, whether it takes place here or it takes place here, but we have shown that the reduction takes place there to form the exo-alcohol that means this is an exo path which is pointing up. Therefore, the reduction is taking place from the lower side and we are getting an exo-alcohol.

But, at the same time as you can see that there is a somewhat strange molecule which is formed which cannot be expected either if the reduction takes place here or the reduction takes place here. We cannot expect this. We can only expect this to form. So, how it is formed? We will see it later. But then if we use lithium triethyl borohydride as a reducing agent, which is more nucleophilic in the nature.

And of course because of the electron releasing nature, it is electronically more dense and therefore, reduction is somewhat different. So, if we see this, the reduction in a normal fashion gives this particular molecule as in 93% yield, whereas that was formed only in 15%. And the strange molecule which we notice above in 85% yield while using lithium aluminium hydride gives only 0.1% of that molecule. How does this strange molecule form that where the hydroxy group is far away from the expected position.

What is happening is that in both the cases the lithium+ is available, but if we can see that in the case of lithium aluminium hydride, because there is no electron releasing group. So, we have a normal ionic nature of the lithium+, but if you look at lithium triethyl borohydride. In this case, because of the electron releasing nature of the ethyl groups, this particular part here is not as ionic as in the case of lithium borohydride, because of the electron realising nature of the ethyl groups.

Therefore, in the case of lithium aluminium hydride, the lithium+ very readily coordinates to the oxygen here. And this particular bond which is present here, this bond migrates in and breaks the carbon oxygen bond here. This carbon oxygen bond is broken. Why does that happen is because this carbon-carbon sigma bond and this carbon oxygen sigma bond basically they are antiperiplanar to each other essentially.

And it is very easy for this kind of overlap of the orbitals to take place, when there is a developing positive charge here, which is possible because of the coordination or the chelation of the lithium+ to the oxygen. And therefore, the moment there is a possibility of a delta plus here, this bond breaks and attaches to this and generates the positive charge at this centre. So, if we look at it, if you number these you have 1, 2, 3, 4, 5 and 6. So, we have here 1, then 2, then 3, then 4 here, then 5, 6 and 7.

Now, if you look at the same position here so, you have 1 here, then we have 2 here, then we have 3 here, then we have 4 here, then we have 7 here and then this is 5 and this is 6. So, that is how the bridge that has formed is specifically this part here, this and this is the bridge, which is 1, 2, 3. This is how it has come on the top and then the hydroxy group is coming from here.

So, when such a migration occurs, you generate a positive charge here, which then gets reduced and then immediately you form this of course, it can go back to the same molecule and we get a part of the reduction in like 15%. Now, this particular migration of the carbon-carbon bond to this carbon here, where the epoxide opens should remind you of homoenolate ions where basically, we have a carbonyl group here, the negative charge attaches in this fashion.

So, basically, it is nothing but a kind of proper orientation of the orbitals, which allow the overlap and then migration in such a way that there is a movement of the bonds leading to the formation of a cations in a slightly different way.

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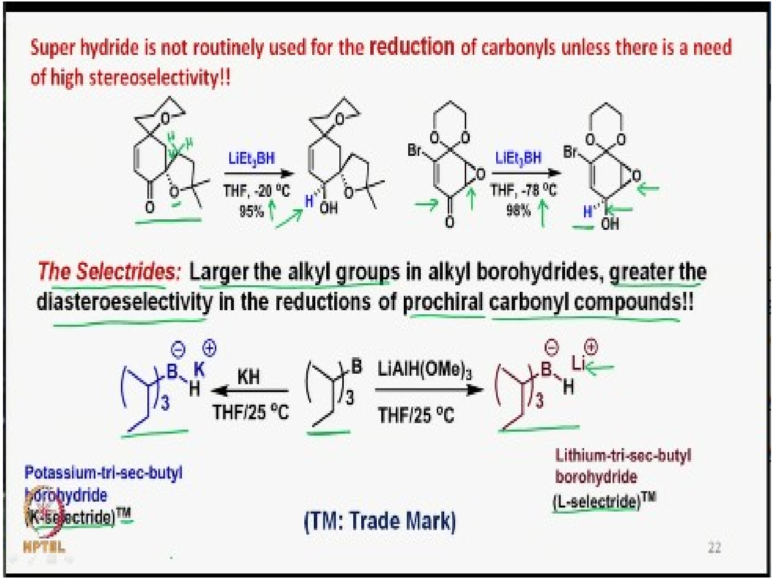

Super hydride is not routinely used for the **reduction** of carbonyls unless there is a need of high stereoselectivity!!

The Selectrides: Larger the alkyl groups in alkyl borohydrides, greater the diasteroeselectivity in the reductions of prochiral carbonyl compounds!!

Potassium-tri-sec-butyl borohydride (K-selectride)™

Lithium-tri-sec-butyl borohydride (L-selectride)™

(TM: Trade Mark)

Now, the super hydride is not routinely used for the reduction of simple carbonyl groups, unless there is a need to observe high stereoselectivity, because, it is sterically bulky and also it is very nucleophilic. For example here, as you can take an example of this kind here, as substituent next to the carbonyl groups are basically in the form of tetrahydrofuran but then we can imagine that this part of the molecule which is beta oriented here.

Due to this, the hydrogens are on the top, but if you look at this part, you have oxygen and which will have only a pair of electrons. So, it is obvious that the bigger CH_2 group blocks the beta side and therefore, the reduction occurs from the alpha side. On the other hand, if you look at this here, the epoxide is beta oriented and therefore, the reduction occurs from the alpha side.

And you have the reduction leading to the formation of the hydroxy group in a beta oriented fashion even though this is beta. Obviously and as you can see, the reducing nature of such super hydride is so much that the reaction has to be done at minus 78 degrees or at minus 20 degrees that means that we need to control the reaction in a proper fashion so, that the reaction can be done at a lower temperature.

There is also, reduction reducing agents which are stronger than these more bulky compared to the super hydrides there called selectrides. So, larger the alkyl groups in alkyl borohydrides, there is a greater diastereoselectivity in the reduction of say, prochiral keytones obviously. It is obvious that if we have very strongly bulky reducing agents, then we can expect that there is a high diastereoselectivity.

Now, there are 2 in fact, there are 3 but more popular are 2, is, one is called as K selectride here. TM means trademark and the other one is L selectride. So, the structures are here, this is L selectride is because of the lithium, it is lithium-tis-secondary-butyl borohydride. So, we had that tri-borohydride. Now, we have secondary butyl borohydride. And of course, here we have potassium tri-secondary-butyl hydride.

And therefore, because of the K, we have K selectride. It can easily be made from the corresponding borone. So, you take tri-secondary-butyl borane and reduce it by lithium aluminium tri-methoxy hydride to lead to this particular L selectride. And if we take potassium hydride, then of course, this K selectride is formed. So, these are 2 new reducing agents, which have been introduced by H.C. Brown who got the Nobel Prize in 1979 for his reductions using this borane type of molecules or various kinds of borohydride.

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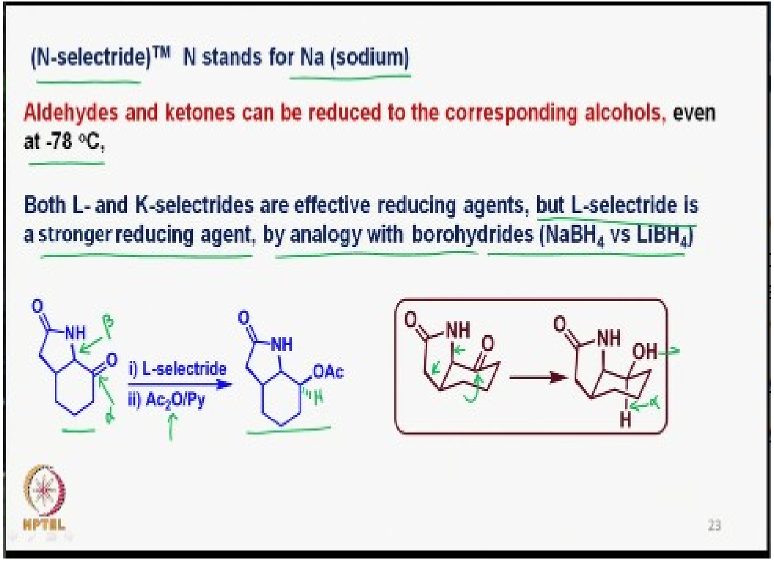

(N-selectride)™ N stands for Na (sodium)

Aldehydes and ketones can be reduced to the corresponding alcohols, even at -78 °C,

Both L- and K-selectrides are effective reducing agents, but L-selectride is a stronger reducing agent, by analogy with borohydrides ($NaBH_4$ vs $LiBH_4$)

If we; take N selectride, so, instead of potassium and lithium, will have sodium in the reaction in the as a counter ion. Both aldehydes and ketones can be reduced to the corresponding alcohols even at minus 78 degrees. Obviously, but then both are reducing agents which are very effective both L and K and of course N but more easily L selectride is normally utilised it because of the chelation nature of the lithium+ which is comparable with say, sodium borohydride versus lithium borohydride.

In the case of lithium borohydride, we have seen that because of the lithium plus coordination that is a stronger reducing agent than the sodium borohydride in a similar fashion, a K selectride are less effective as reducing here as compared to L selectride. Now, we have 2 examples, we take a reduction of this which goes to the corresponding acetate after reduction and acetylation.

As you can see, that reduction occurs from the alpha side that means, this particular group being beta oriented, the alpha side is free and therefore hydrogen comes from alpha side. As we can see the same molecule in its conformation, then we can say that these groups are beta oriented and therefore reduction occurs from the alpha side. So, you have the reduction in highly diastereoselective fashion and then of course, you take acetic anhydride and pyridine to convert this to the corresponding O-Acetate.

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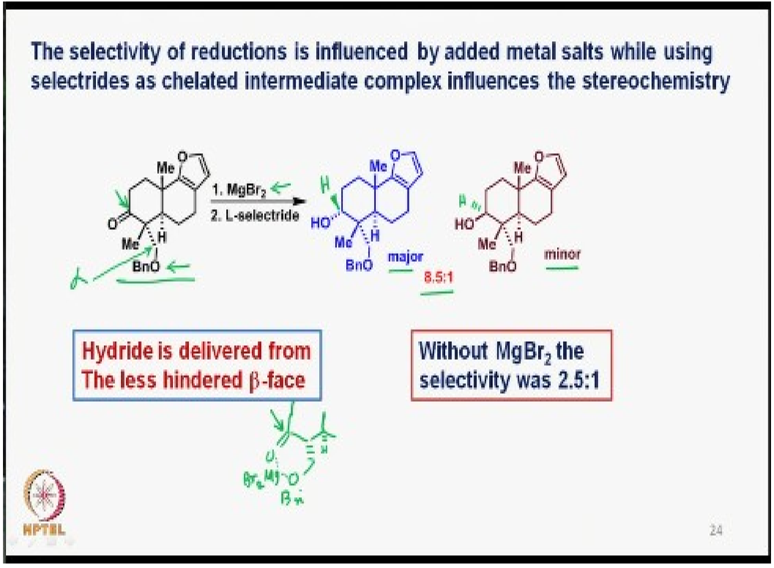

The selectivity of reductions is influenced by added metal salts while using selectrides as chelated intermediate complex influences the stereochemistry

Hydride is delivered from The less hindered β-face

Without $MgBr_2$ the selectivity was 2.5:1

So, this is an example in which we can expect the reduction to take place in a similar fashion, there is a reduction which is added influenced by added metal salts, while using these kinds of selectrides, these are called selectrides and because of the selective nature of the reducing agents. And if we take this example here, we can see that the group here which is benzyloxy group is very close to the carbonyl group here and this is alpha oriented.

And if we add magnesium bromide to this, we can expect that there is a chelation between this benzyloxy group and the oxygen group with the magnesium bromide. And therefore, the magnesium bromide allows the OBM group here and so, now, you have magnesium and then bromide here. So, you can expect such type of coordination, I will not write the other part of the molecule.

And therefore, one can see that the alpha side is blocked and therefore, the reduction occurs or this carbon atom or this carbon atom from the beta side. So, you have the hydrogen coming from the beta side. So, now, we get 8.5 is to 1 ratio of these 2 molecules in which this is minor, this is the major as you can see, without magnesium bromide, the selectivity was only 2.5 is to 1.

Therefore, one can expect that such chelation by an added extra Lewis acid type of molecule such as magnesium bromide makes it kind of chelated complex. And which then directs the reactivity of the carbonyl group in such a way that the less hindered beta phase is then open for the reduction to take place. We will stop today at this stage and take up the remaining part of the reducing agents and reactivity of various compounds in the next class.

You can go through these aspects of whatever we have discussed today and be ready for the next class. Thank you. See you next time.