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

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Lecture-24

Further Aspects of DIBAL-H Based Reductions and Comparison with Mixed Chloride Hydrides

Hello everyone, I expect that you had gone through the material that I covered last time related to the reductions in organic chemistry. We will briefly look at what we did in the last lecture where we started with the reduction of the alpha beta unsaturated ester with lithium aluminum hydride where the corresponding alcohol was formed CH_2OH.

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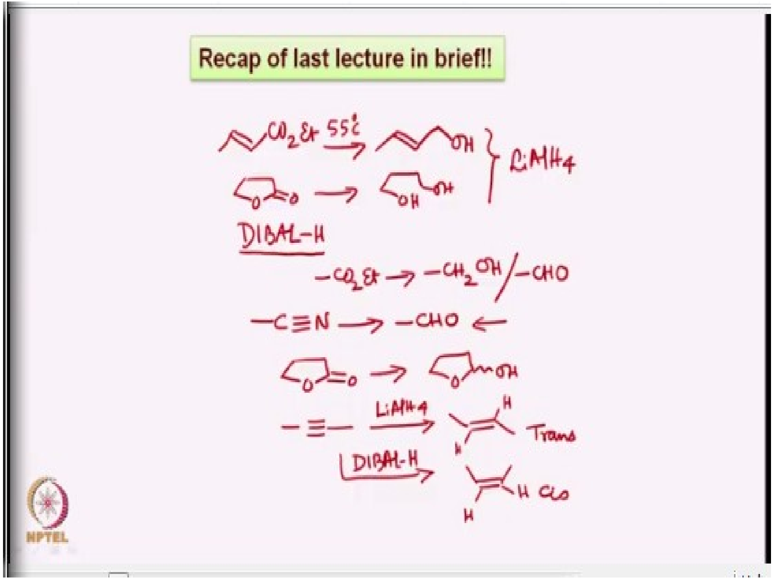

Recap of last lecture in brief!!

And then we also looked at the conditions where we had to heat it, so it required approximately 55 degrees temperature. As we can also look at it that the lactones give the corresponding diol. And we compare it with the DIBAL reductions, so these were the ones which we discussed with lithium aluminum hydride. On the other hand we introduced the reagent DIBAL-H.

And that allowed the conversion of the ester to the corresponding alcohol or aldehyde depending on the conditions. Such as solvent were participating or non participating solvents or temperature or say for example how many equivalents of diisobutylaluminum hydride are used. Then we also looked at the reactivity of diisobutylaluminum hydride with respect to the nitrile where it can be stopped at the aldehyde stage, which is very different from lithium aluminum hydride.

On the other hand we can also use lithium tri alkoxy aluminum hydride where only one hydrogen is there, and can also do the same transformation leading to the formation of aldehyde from nitrile, when we were also discussing the ester reduction to the corresponding alcohol or aldehyde. We also looked at how the lactones can be selectively stopped at the lactol stage. And then towards the end we were trying to look at the reduction of acetylene using first lithium aluminum hydride and that led to the trans olefin.

And I mentioned that the same reaction can be done by using DIBAL-H and that can be stopped at the DIBAL-H. And it can be stopped at the olefin stage but then the olefin can be cis olefin. So, this is how we ended in the last class. Now I would like to tell you why is it that in the case of lithium aluminum hydride we get trans olefin and in the case of DIBAL we get cis olefin. Of course we discussed last time that the lithium aluminum hydride case since aluminum hydride part is negatively charged.

And therefore when it attacks on to the acetylene the attack of the negatively charged aluminum hydride occurs from the side opposite to the side where the electron density is moving. That means the attack of the aluminum hydride occurs from let us say for example from the lower side the electron density of the pi cloud moves away from towards the upper side.

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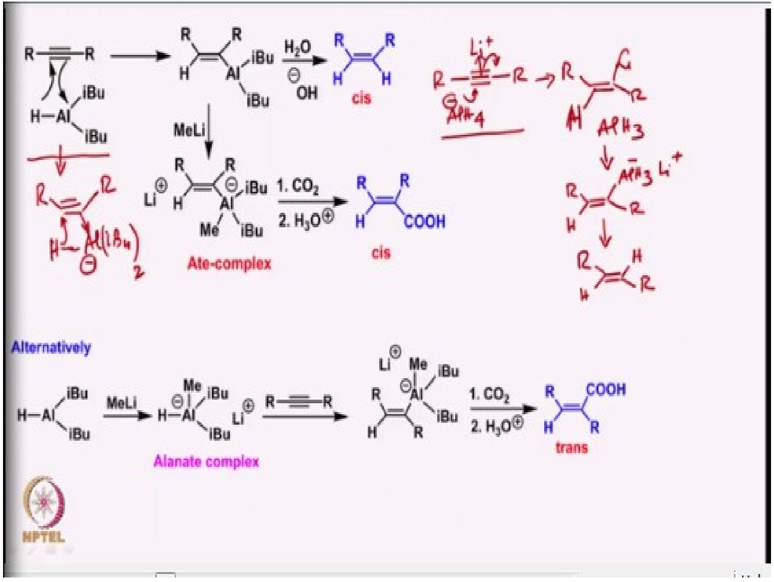

In the case of diisobutylaluminum hydride, since the DIBAL is trivalent and therefore electrophilic in the nature. That reaction of the diisobutylaluminum hydride does not occur unless and until the pi cloud of the triple bond interacts with the aluminum hydride and makes it negatively charged, the way I have shown it by arrow. For example in the case of lithium aluminum hydride what we had was.

We had the lithium+ which was interacting with the triple bond say for example here. I can write it a little bit below, so that it can be seen here as you can see that the triple bond interacts in the case of lithium aluminum hydride. In such a fashion that the lithium+ interacts first and therefore AlH_4^- attacks from the lower side. And then electron density moves to form the corresponding lithium here and hydrogen with AlH_3 released.

And this is what leads to the corresponding say AlH_3^-, lithium+ and R here, and then this leads upon protonation to the corresponding trans olefin. So, this particular reaction triggers in such a fashion that the aluminum hydride which is already a negatively charged and therefore nucleophilic in the nature initiates the reaction. So, that the electron density moves towards the top towards the lithium+.

But that is not the case in the case of DIBAL where the DIBAL first interacts with the triple bond. And in this particular case what you can imagine that you have a something like this.

You have a species of this type where now the aluminum of the DIBAL is interacting with the triple bond and generating a kind of positive charge here where the this hydrogen migrates. That means this triple bond has essentially interacted with the DIBAL and making it negatively charged here.

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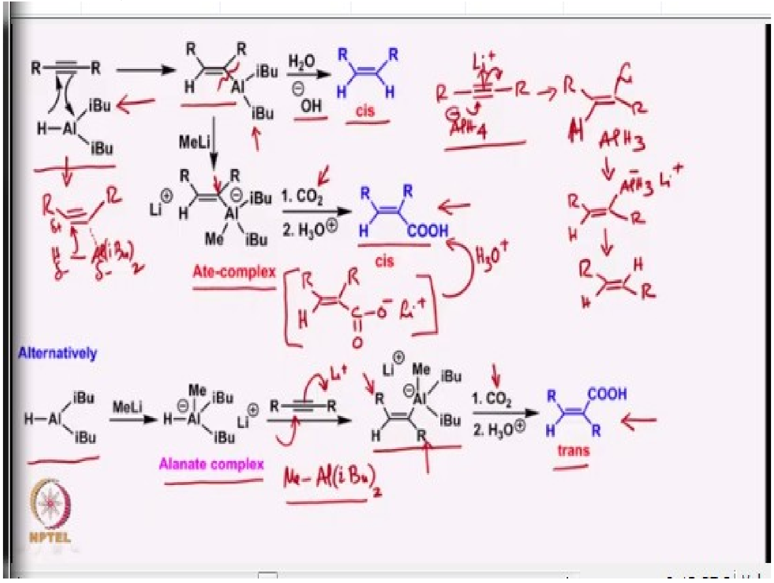

So, I can rewrite this part again in the sense that you have the triple bond to start with which should not be written like a bent bond. But then I am writing it because I want to show that you have aluminum here and negatively charge here. So, you have a delta negative here and you have a sort of delta negative here which is and of course you have a delta positive here. So, when this is interacting here then you have an interaction leading to the same side.

So, basically the pi clouds is interacting with the aluminum and the hydrogen from the same side. And that is why we have shown by arrows the interaction in this fashion. And that leads to the intermediate of this type which upon workup using aqueous condition, cleaves the carbon aluminum bond and forms the cis double bond. On the other hand if we take the same intermediate in fact this intermediate can easily be isolated if is required.

And instead of adding water or basic conditions to cleave the carbon aluminum bond, if it is reacted with methyl lithium for example. The methyl lithium forms reaction with aluminum to make lead to an 8 complex. And this particular 8 complex which is now negatively charged has now this particular carbon atom as a kind of nucleophilic carbon atom that interacts with the carbon dioxide.

If we bubble carbon dioxide through it, then of course this carbon aluminum bond acts like a nucleophile to the corresponding electrophilic carbon dioxide. And that allows the formation of an intermediate you can imagine that it will allow you to form the carboxylate. And here and of course you will have a lithium+ or the other electrophilic species around. So, this is the intermediate that can form which upon acidic workup leads to the formation of the corresponding acid alpha beta unsaturated acid.

But then since the hydrogen and the aluminum from diisobutylaluminum hydride reacted from the same side of the double bond. Already we had the R groups on the alkene path towards cis oriented and therefore the hydrogen and the carbon dioxide they come from the same side. So, there is a stereo selective formation of the corresponding acid in the reduction of acetylene. And then eventually converting into the corresponding alpha beta unsaturated acid.

On the other hand if one wants to prepare a trans alpha beta unsaturated acid. Then we start with the DIBAL which is a trivalent and electrophilic in the nature. First we add methyl lithium to it and make an alanate complex instead of a trivalent species. We have a tetravalent aluminum species which is now nucleophilic in the nature. So, it behaves very similar to the lithium aluminum hydride, so in the case of lithium aluminum hydride we had the negatively charged aluminum species.

And now when this interacts with the triple bond the approaching negatively charged hydride attack takes place. Say for example from the bottom phase then the movement of the electrons will towards the Li+ would occur from the opposite side. And which eventually again interacts with the trivalent aluminum species, this is the aluminum species which is a trivalent aluminum species after the hydride has been transferred.

And this interacts with the carbon lithium bond here leading to the formation of this particular intermediate now. Here we can see the R group here and the R group here are already trans oriented. And when such a species reacts with the carbon dioxide as an electrophile eventually it leads to the trans alpha beta unsaturated acids. So, this is one of the very interesting aspects of the DIBAL based chemistry which can allow transformation of an alkyne to a cis or a trans olefin depending on what one wants to.

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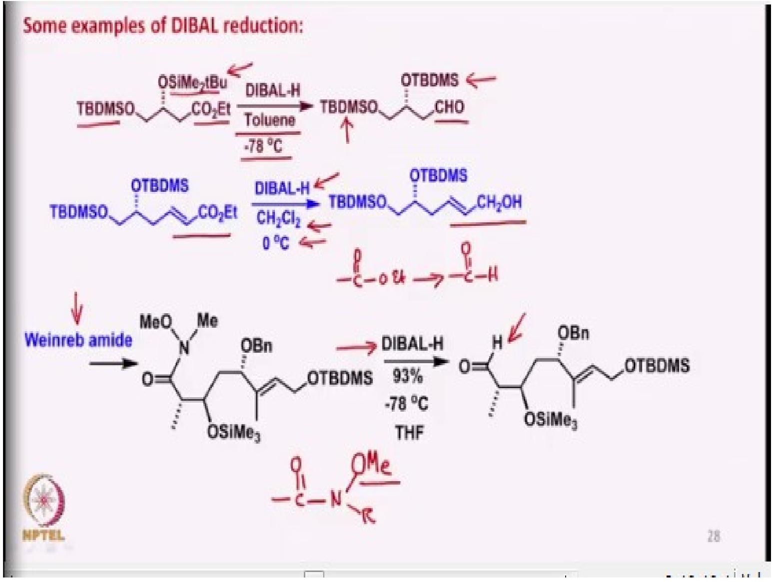

Some examples of DIBAL reduction:

Now some more examples of DIBAL reduction are shown here. For example one can of course use toluene as a non participating reagent at low temperature. And the ester can be converted to the corresponding aldehyde. As you can see that here this is the same as this, this is tertiary butyl dimethyl silyl groups. So, I have written here OTBDMS in both the cases and they are basically nothing but this OSiMe 2 tertiary butyl.

Now we can convert ester at low temperature using toluene to the aldehyde, this has been done in the literature. And this we can also take alpha beta unsaturated ester and can convert to the corresponding alcohol at 0 degree centigrade in dichloromethane. In this case as you can imagine that you will obviously use more than 2 equivalents of the diisobutylaluminum hydride. If one wants to stop the reduction of an ester to the corresponding aldehyde, there are methods which are other than the DIBAL.

Now there is something called as Weinreb amide, it has been introduced by Weinreb. Now what happens is such an amide is like you have here carbonyl group and you have an nitrogen. But then for normal amide it is this could be hydrogen or it could be alkyls. But if one takes a heteroatom such as this and of course you have an R group here something different. But you have to have a heteroatom here as a substituent on the nitrogen and that is called as Weinreb amide and if such an amide is used and this of course can be easily prepared from the corresponding ester or acid halide.

And then when if it is reacted with a reducing agent or any nucleophile. For example in this case here diisobutylaluminum hydride, then one can easily stop the reaction at the aldehyde stage without worrying about over reduction. So, as in this example I have shown that we have a double bond, we have various other substituents, but the reaction can easily be stopped at this particular stage.

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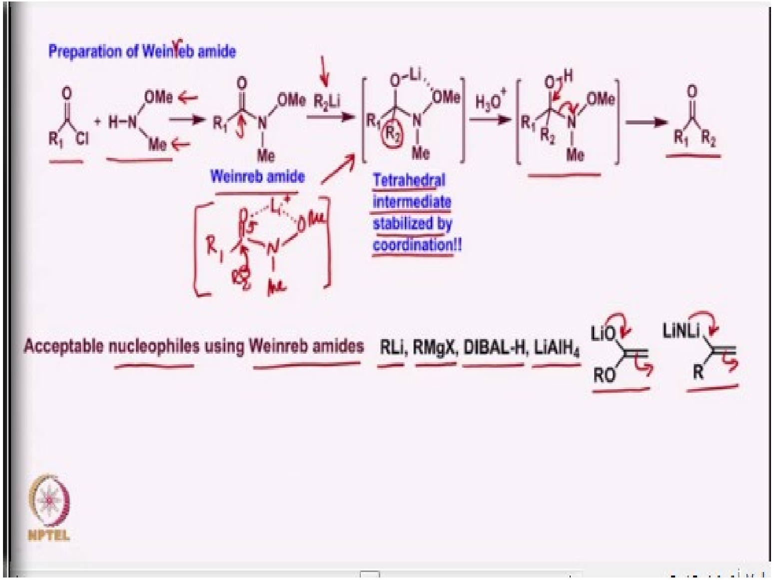

Preparation of Weinreb amide

Weinreb amide

Tetrahedral intermediate stabilized by coordination!!

Acceptable nucleophiles using Weinreb amides RLi, RMgX, DIBAL-H, $LiAlH_4$

Why it is so and how it is so? We can look at it now, here it is Weinreb amide R, and how is it prepared? You can prepare it from the corresponding acid halide and react it with this particular nitrogen compound. Where there is already a methoxy group, this is an amine this is like ammonia derivative. So, you have a methoxy and the methyl on the nitrogen, when they react and they form the corresponding Weinreb amide.

Now when this Weinreb amide reacts with a nucleophile say for example I have written here R_2 Li but it can be DIBAL or it can be anything where R_2 is a nucleophile and then this R_2 attacks on to the particular carbon of the carbonyl moiety here. Now what is happening in this case is essentially initiating the reaction with the coordination of the lithium+ one can put it here lithium + and one can have such coordination.

And this leads to the increase in the electrophilicity of this particular carbon atom where the nucleophile R_2^- attacks and this stage and reaction leads to the intermediate which is now stabilized by coordination. Basically here the lithium coordination with the oxygen allows this tetrahedral intermediate to be stable under that condition, which is against what we have done with using lithium aluminum hydride where the intermediate the tetrahedral intermediate that was formed was ionic in nature, and therefore it would decompose.

But here due to the coordination this does not decompose and when water is added under acidic conditions, then we have the formation of this type of intermediate which then breaks in this fashion to form the corresponding carbonyl group. Now the nucleophiles which have been utilized Weinreb amides R phenyl lithium, Grignard reagents, the DIBAL or even lithium aluminum hydride for example.

And a nucleophile such as this or this where you have this nucleophilicity coming in like this. So, you have nucleophilicity coming like this where you can put an amide group or an ester group onto the electrophilic side of a Weinreb amide.

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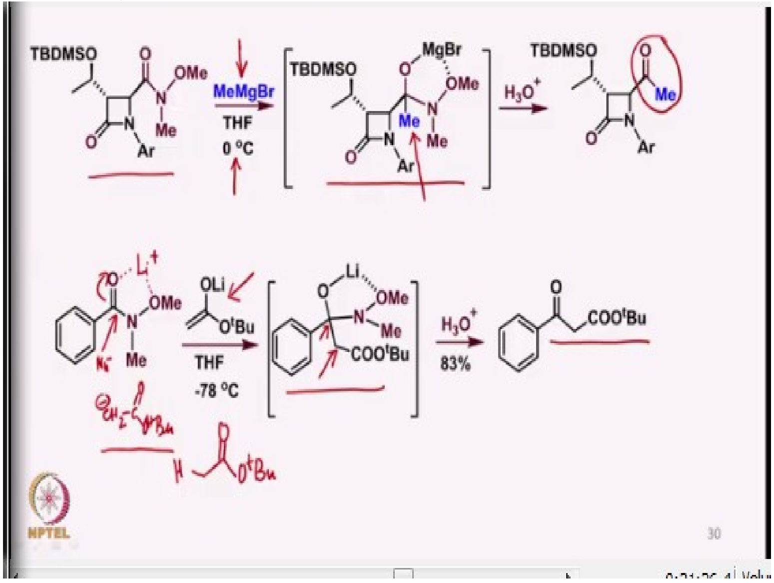

So, example which is a little bit more complicated is shown here. Then if we have Weinreb amide of this kind where to which methyl magnesium bromide is added at 0 degrees in THF, we go through this particular intermediate. As you can see it here the magnesium Br part of the Grignard reagent interacts both with the oxygen of the carbonyl and also the OMe of the Weinreb amide and allows the nucleophilic attack at the particular carbon atom.

And that stops because of the coordination and then after the hydrolysis one gets the corresponding methyl ketone. Now I also told that we can introduce a nucleophile like this. Here which is basically derived from the corresponding ester, so if we have an ester of this type where we deprotonate here and generate the nucleophile like this which has a lithium+ to coordinate.

So, you have a lithium+ to coordinate like this and the nucleophile attacks on to this carbon atom and to form the corresponding intermediate of this type. Where basically what we have done is, this nucleophile is nothing but a nucleophile of this type here. So, we have here the negative part coming from the alpha to the ester anion. And that leads to this particular carbon-carbon bond formation to take place and eventually to form the beta keto ester. So, this is how one can stop the reaction in the Weinreb amide case from over reacting with nucleophiles.

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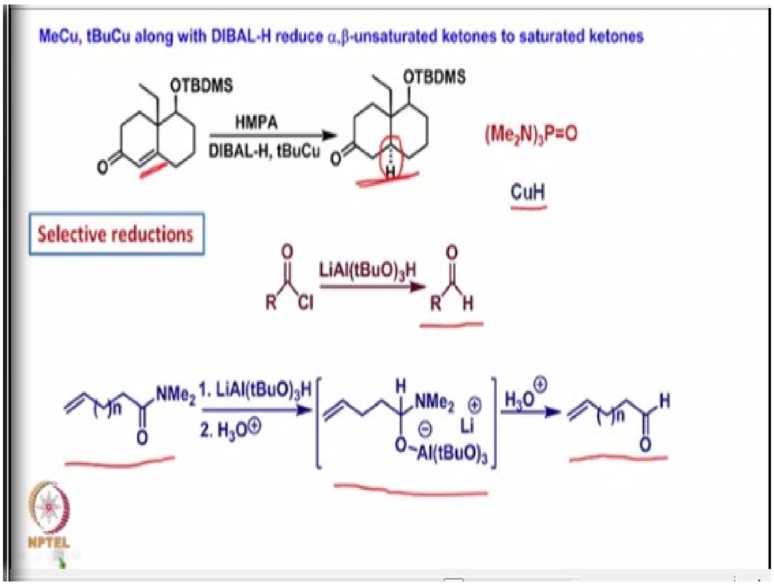
MeCu, tBuCu along with DIBAL-H reduce α,β-unsaturated ketones to saturated ketones

Selective reductions

Now in the reductions using diisobutylaluminum hydride, if one uses alpha beta unsaturated ketones. Then if one allows the reduction to take place in the presence of these kind of copper species like methyl copper or tertiary butyl copper along with diisobutylaluminum hydride in solvents like HMPA. For example the HMPA has already mentioned earlier hexamethylphosphoric triamide.

Then what has been observed is the reduction of this particular double bond to the corresponding saturated species. And the hydrogen is approaching the molecule from the side opposite to this particular carbon-carbon bond. Since this particular carbon-carbon bond is beta oriented and therefore the hydrogen comes from the alpha side. It is believed that this particular reagent system that is using diisobutylaluminum hydride along with this copper species leads to the formation of copper hydride which is a kind of soft hydride.

And therefore there is a Michael addition of this hydride species to take place on to this particular enone, and thus we get the corresponding saturated ketone. And of course the stereochemistry is defined by the stereochemistry of this carbon-carbon bond. Now we can also carryout selective reductions of say acid chloride. For example with a reagent which is lithium aluminum tri tertiary butoxy hydride.

Basically it has only one hydrogen and therefore since it is sterically hindered molecule, it only transfers one hydrogen to this particular acid chloride leading to the formation of the corresponding aldehyde. In a similar fashion we can also use this amide which is sterically hindered and of course we can also use the same reagent, that is lithium tri tertiary butoxy aluminum hydride.

And that proceeds via this intermediate which is now kind of stabilized, because now this lithium + will chelate it with the nitrogen and will be closer to the aluminum and therefore it will not undergo decomposition. And once we hydrolyze with H_3O^+ that is under acidic condition then this particular species gets cleaved to the corresponding aldehyde, and therefore we stop the reaction at the aldehyde stage.

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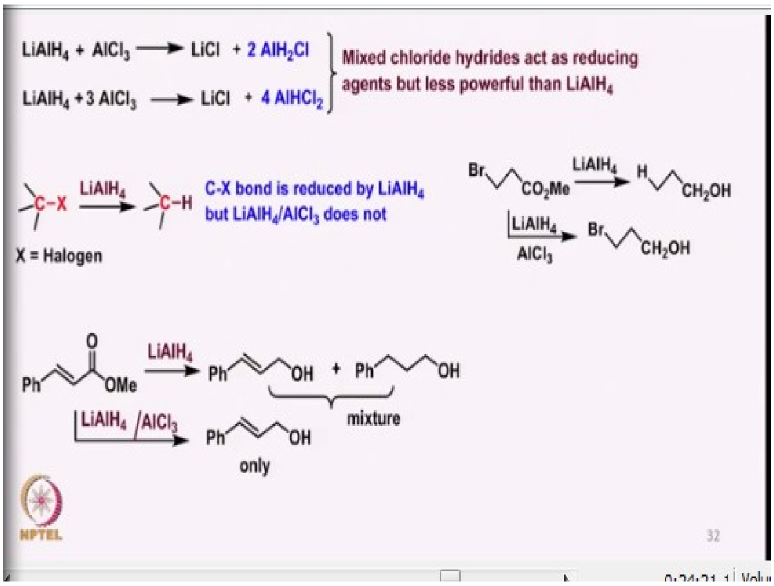

$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2\,AlH_2Cl$

$LiAlH_4 + 3\,AlCl_3 \longrightarrow LiCl + 4\,AlHCl_2$

Mixed chloride hydrides act as reducing agents but less powerful than $LiAlH_4$

C-X bond is reduced by $LiAlH_4$ but $LiAlH_4/AlCl_3$ does not

Before diisobutylaluminum hydride as I mentioned that AlH_3 was utilized AlH_3, but since AlH 3 is not a very easy reagent to handle. That is the reason why diisobutylaluminum hydrides were used. So, this was basically converted into or an alternative as this was used. Idea was to have a trivalent aluminum which is electrophilic in the nature and that initiates the reaction only after the carbonyl oxygen interacts with the aluminum.

In this regard various combinations have been utilized, for example lithium aluminum hydride with aluminum chloride which leads to lithium chloride. And these 2 molecules of aluminum hydride having 1 chlorine, so it is a mixed chloride hydride. And in a similar fashion if one starts with lithium aluminum hydride and uses 3 equivalents of aluminum chloride one can get 4 equivalents of aluminum hydrogen chloride which is basically having only 1 hydrogen.

And these mixed chloride hydrides act as reducing agents but because of the electro negativity of the chlorine the electron density is being pulled towards the chlorine. And therefore the hydride nature of these mixed chloride hydrides is somewhat less. And therefore is a less powerful reagent than lithium aluminum hydride. Obviously because of the electron withdrawing nature of the chlorine that is attached to it.

And therefore for example we can easily convert a halogen, if it is a halogen compound we can convert a halogen in to the corresponding hydrogen here, the carbon X bond is cleaved and carbon hydrogen is formed if lithium aluminum iodide is used. But this reaction does not happen if we take a combination of lithium aluminum hydride and aluminum chloride. On the other hand for example if we take an alpha beta unsaturated ester of this type and we use lithium aluminum hydride as a reducing agent.

We can easily get a mixture of this allylic alcohol and saturated alcohol as a mixture where this is somewhat larger in a measure than this, but then reduction gives a mixture of both. On the other hand when lithium aluminum hydride is used along with aluminum chloride only this is formed. That means in this particular case if we have R group instead of phenyl.

I am just trying to write in the general way that if we have something like this and if we take a mixture of lithium aluminum hydride and aluminum chloride it could be either AlH_2Cl or it could be an $AlClH_2$. That means any one of them or any one of them, that interacts with here and the transfer occurs at this position only, and there is no chance of a reduction taking place in such a way that we can get this particular molecule.

So, therefore it is the electrophilic nature of the trivalent less reactive aluminum species such as this aluminum H_2Cl or aluminum chloro H_2 which allows mild reduction to take place only of the ester moiety to the corresponding alcohol. Therefore this forms as the only product that is the case. So, we will stop it today at this stage and continue further in the next class of where such mixed hydride chlorides are used.

Or and some other reducing agents are introduced for specific and selective conversions of some functional groups. You can go through these reducing agents from the books that I have mentioned. And whenever there is a need I will also give the references for other reducing agents, and you can see these transformations understand the mechanism and will be ready for the next class, till then good bye and thank you.