Introduction to Organic Chemistry II

Dr. Harinath Chakrapani and Dr. Neeraja Dashaputre
Teaching Assistants: Harshit Singh and Utsav Dey Sarkar
Indian Institute of Science Education and Research, Pune

Lecture 30

Alcohols, Ethers, and Epoxides

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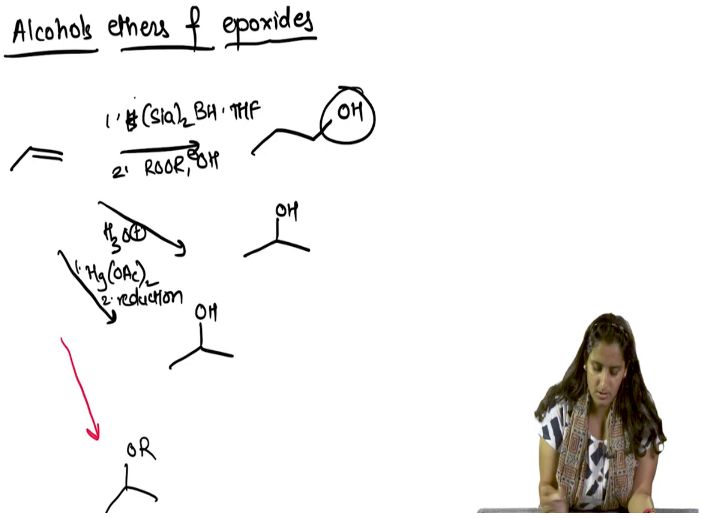

So, this chapter is alcohols, ethers and epoxides, and also carboxylic acid derivatives and in the course one of this particular introductory organic chemistry, we have covered alcohols, ethers and epoxides in a lot of detail. So, I am just going to go very quickly over some of the reactions that we have covered.

For those who wish to revise, the course is running right now, so the material is still available online. Please go back and look at Chapter 8, or Week 8 of Introductory Organic Chemistry I. I am just going to quickly write down the reactions here. I am not going to go over the details such as the reaction mechanism.

So, the first one we are going to cover is how to form alcohols, and there are various ways to form an alcohol from an alkene, for example. You could just react it with H_3O^+, or you could do oxymercuration, and then reduction, or you could do something like hydroboration. Now, hydroboration will form the OH on the less substituted carbon, (Sia)$_2$BH, and THF, and the second reaction will be an oxidation reaction, so it will be ROOR and OH$^-$.

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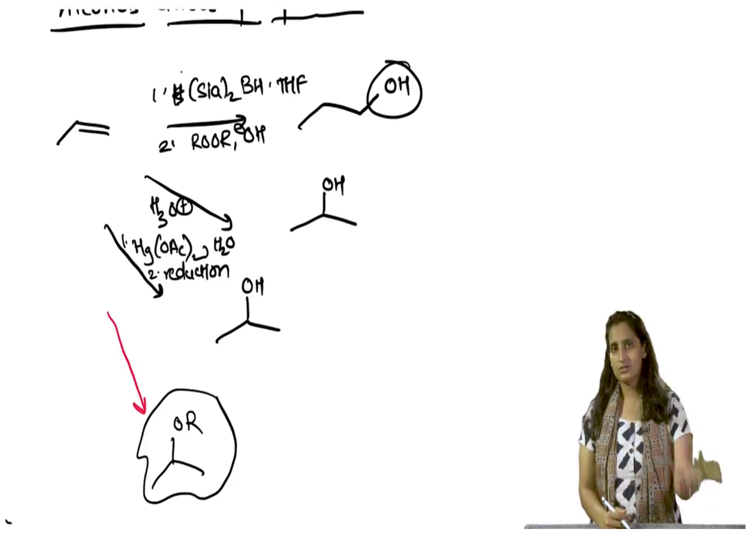

Now, in the same case, in the oxymercuration reaction, instead of taking water as the solvent if you take alcohol as the solvent you end up with an ether. So, that is a very good way to form an ether. Although, nowadays we do not use mercury for any of the synthesis that we do. We avoid ah use of mercury because of its poisonous nature.

In order to form primary alcohols, you can also start from primary alkyl halides and do S$_N$2 reaction, secondary alcohols can also be formed similarly. For tertiary alcohols that is going to be a little difficult, so for tertiary alcohols you will need a different way, more likely you need to start from the corresponding alkene.

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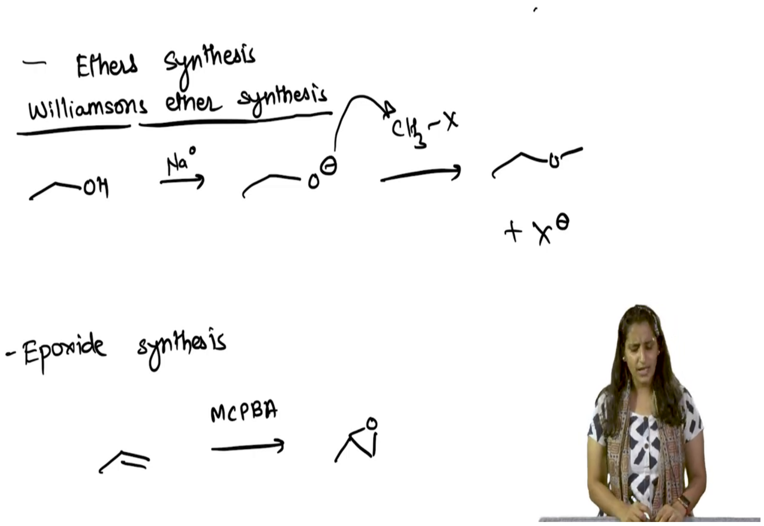

— Ethers synthesis

Williamsons ether synthesis

- Epoxide synthesis

Now, in the case of ethers, we have various ways to synthesize an ether. We just talked about one where in the oxymercuration reduction, instead of water as the solvent if you take alcohol as the solvent you end up forming an ether. In the case of Williamson's ether synthesis, you start with an alcohol, you react it with something like a sodium metal and you form this O^-, and this is going to react with an alkyl halide, RX, depending on what kind of ether you want to form, you can form an S_N2 reaction really and you end up forming that particular ether.

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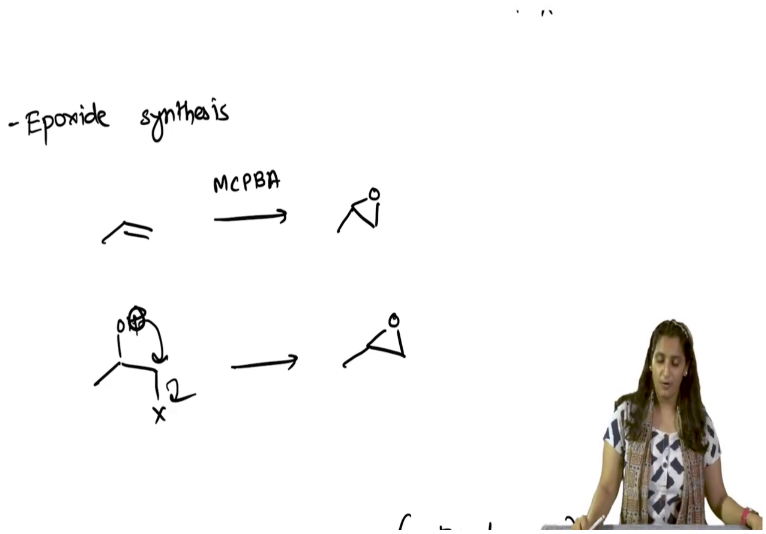

What other ways did we look at last time? We looked at various ways to form an epoxide. Epoxides can be formed in the presence of MCPBA, or any kind of peracids, and this method as we saw was such that it was stereoselective in the sense that depending on the stereochemistry of the starting material the end product also had a very particular stereochemistry for that epoxide. You can also form an epoxide wherein you start from halohydrin, and if it is a trans-halohydrin what you can do is, you can start with the oxygen and then do S_N2 type of reaction to form that epoxide.

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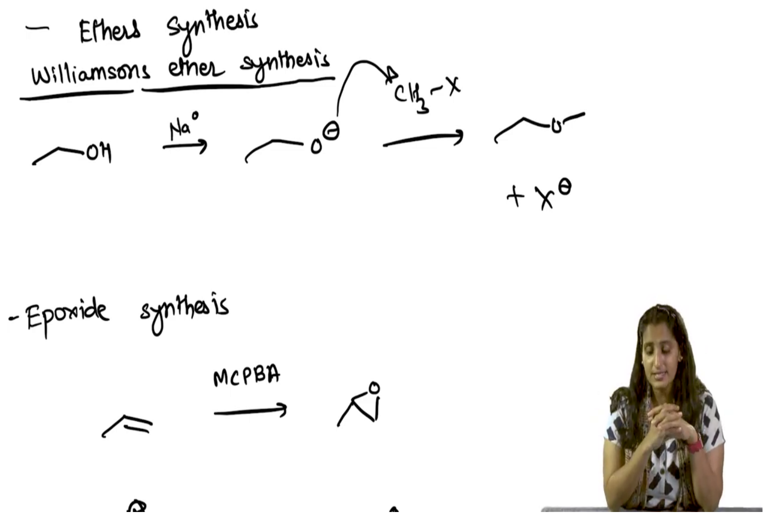

Last time we also looked at couple of reactions of ethers, and epoxides, how ethers break down, in the presence of acids.

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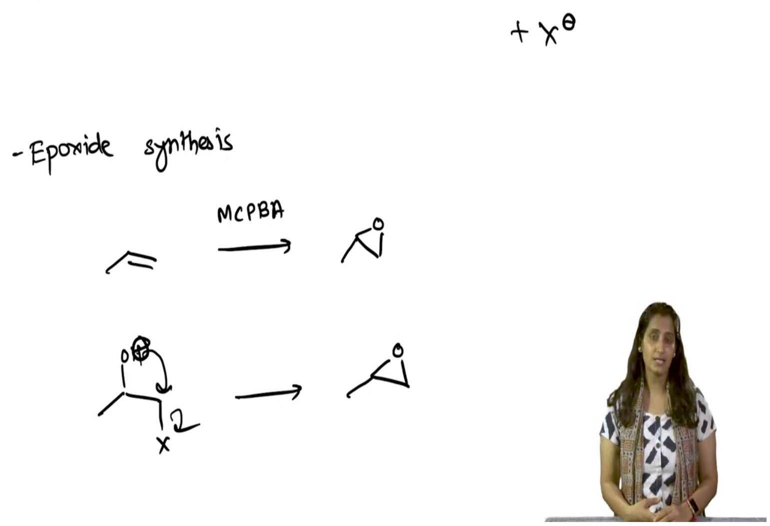

Or we can even talk about how epoxides open up in the case of acidic medium. There is a different way of reaction happening, in the case of basic medium, or a nucleophilic attack, it is going to open up in a different manner. So, we did look at the reactions of epoxides as well. Do go back and check out those reactions.

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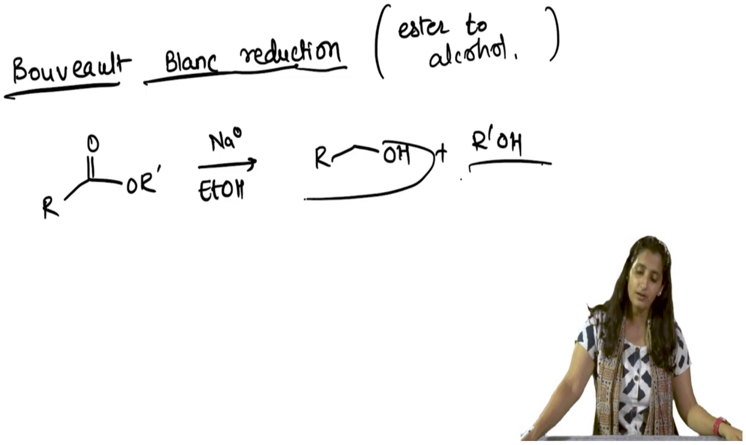

Now, there is one more reaction of alcohol formation that we did not cover last time. So, I am just going to use it here. And this is the Blanc reduction. It starts from an ester and we end up forming an alcohol. It is in the presence of sodium and ethanol. So, as you can guess, because it is sodium, it is going to be doing one-electron reduction at a time.

And that is the reason why it is not so preferred, and nowadays we do not do a Blanc reduction unless it is really, really impossible to do any other kind of reaction because for this reaction you would need sodium in excess. So, you start from an ester, you end up forming two alcohol molecules.

So, that is one reason. I do not want to go over the mechanism of it, but if you want to go over the mechanism, I do not mind putting it up in the corresponding material, but really the reason why I do not want to go over the mechanism is that we do not use it anymore. We now have much better reducing agents for ester.

I mean, just to begin with, the lithium aluminum hydride does a much better job than sodium and ethanol. The other reason is that there is a risk of lab accidents or fire accidents working with sodium. So, that is also a reason people prefer using some other reducing agents that are there.

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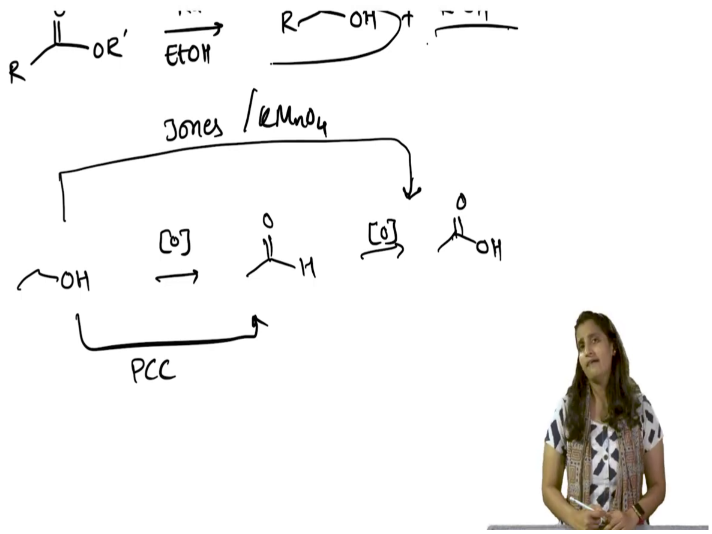

Okay, I will thus prefer going over some of the reducing and oxidizing agents. So, what do we know about reduction and oxidizing agents so far? We have seen that primary alcohols can get oxidized to aldehydes and which can further get oxidized to carboxylic acids, and then of course we know how to form various carboxylic acid derivatives starting from these carboxylic acids.

We know that primary alcohols can go all the way to carboxylic acids if we use a very strong oxidizing agent like Jones reagent or like manganese-based reagent $KMnO_4$ or Chromium (VI). I am going to write Jones, or $KMnO_4$ here, all of these are going to give you carboxylic acid. It is very difficult to stop at that aldehyde and form an aldehyde in excess. So, for doing that we use a milder oxidizing agent which is pyridinium chlorochromate, so PCC. You can look at the reaction for that.

So, that is the oxidizing agents that we know. There are various other oxidizing agents to be really fair, and for exams or for most of the preparatory exams, you would need to know a lot more reagents than these but in lab you can do some other different kind of oxidation.

If you want to have a look at the list I am going to add it as a resource so that you can prepare for other exams as well, but we do not need the details of these oxidizing agents for this course. So, do look out for resources. I am going to put up list of oxidizing agents and list of reducing agents. You can look that up.

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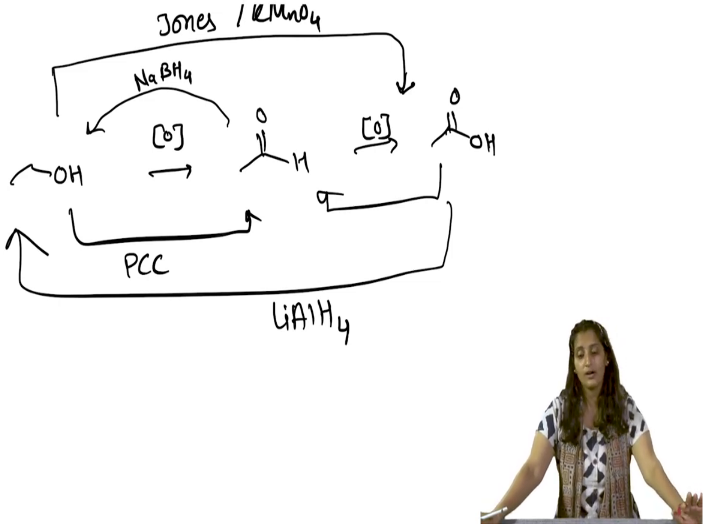

How do we go back though? We have not really discussed reduction in that much detail in the previous course as well. So, to go back from carboxylic acids all the way to alcohols we use reagents like $LiAlH_4$, lithium aluminum hydride. So, that is a reagent that will take you all the way back. In order to go one step back, there are ways to do it, and I am going to go over them.

And then, we have very selective reagents or milder reagents that will work on aldehydes to get to the alcohol which is sodium borohydride, so $NaBH_4$ will be here. So, that is pretty much what we had covered last year or last course, and I am going to go over some of the selective oxidizing and reducing reactions now more often of carboxylic acids and their derivatives going back to either aldehydes or alcohols.

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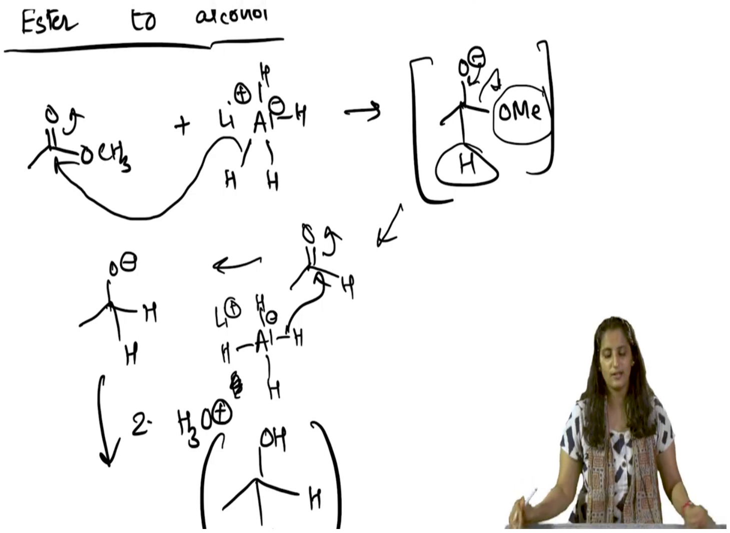

So, let us start with the reagent that we have written here, lithium aluminum hydride. Now, it is a wonderful hydride agent because it can give off that H^- which is the main reducing agent, in excess when we use this. So, let us start with an ester, so converting an ester to an alcohol.

So, we are going to start with an ester, and I am going to react it with lithium aluminum hydride, so as you can see it has aluminum attached to 4 hydrogens and has a negative charge and thus it is a very good source of H^-, and that is going to attack here, and open this up.

So, what do we have here? Look at this tetrahedral intermediate. Now, in this case, the hydride is not going to be a good leaving group. And since we are in a basic medium, we can kick out the OMe. So, we are going to kick that out forming an aldehyde.

But the moment you form that aldehyde you have so much more lithium aluminum hydride in the solution which is going to further react and because aldehydes are much more reactive, it is going to again add here and it is going to form that O^-. Now, you have your alcohol almost there.

So, as the last step or second step you do hydrolysis, acid hydrolysis to really form OH here. So, that is what we have. We have alcohol starting from an ester. Wonderful. So, reagents like $LiAlH_4$ will work on acids, they will work on amides, they will work on esters, they will also work on ketones and aldehydes because they are really, really reactive. On the other hand, to selectively reduce ketones and aldehydes we use milder reagents because we do not need to use such a strong reagent. We use milder reagents like $NaBH_4$ for reducing the ketones and aldehydes.

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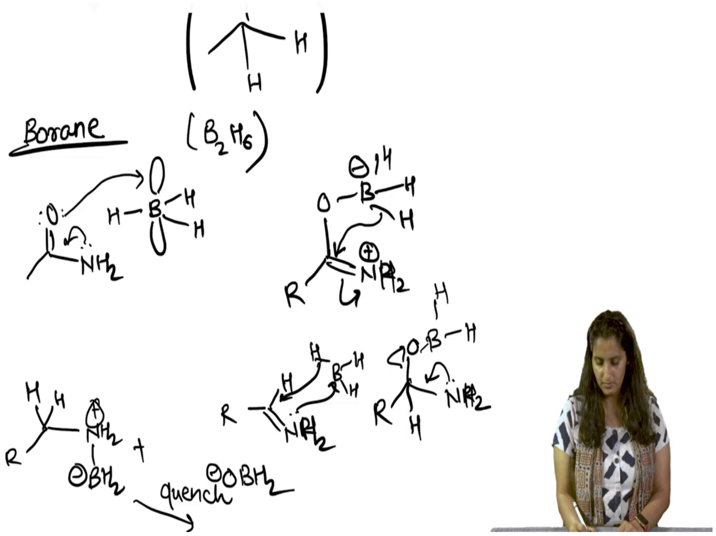

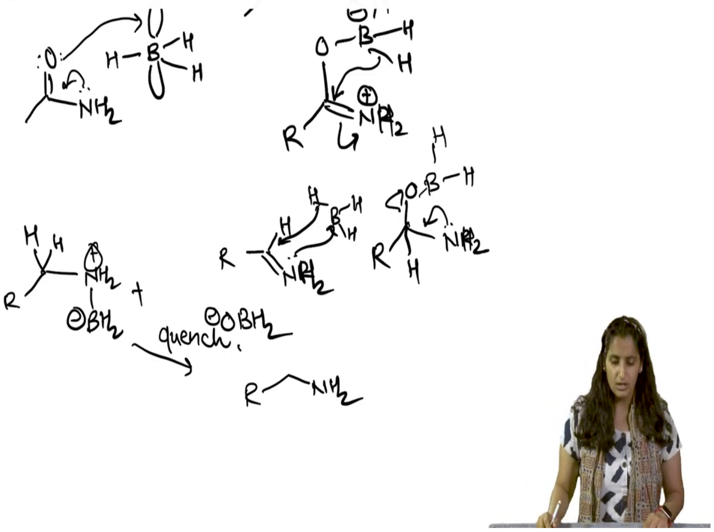

The other reducing agent I want to discuss is Borane. So, Borane, we have looked at it when we were doing hydroboration and oxidation in the case of alkenes. Now, here borane is a reducing agent, borane is BH_3 or it exists as B_2H_6, we know, and let us look at the mechanism.

I am going to start from an amide. Now, amide and we have borane now, let us write down the structure of borane. I am going to simply take BH_3 for the simplicity sake, but remember it does not exist as BH_3, it exists as B_2H_6, as a dimmer. What do we know here? We know that the boron has an empty p orbital and that is what is going to happen.

In the first step, this oxygen is going to put electrons into that empty p orbital forming an oxygen boron bond. What do we have here? We have a negative charge on this boron, and as a result of which this hydride is going to shift here and open this up. So, we have now added hydrogen where we wanted to add it in order to make the corresponding alcohol. Let us look at the next step.

Now, we have BH_2 here, that boron is still having two hydrides to transfer, so what we are going to do next is, this attacks here and this opens up forming, NH_2. So, it is an imine that forms as an intermediate step, and in the next step, we have another molecule of boron attacking. Okay, so that is the structure. And in the final step, you are just going to quench it to form the corresponding amine.

So, borane can be used to reduce amides, it can be used to reduce esters, it also is a wonderful reagent to reduce acids, carboxylic acid, so $LiAlH_4$, for example, the first step in $LiAlH_4$ and carboxylic acid reduction is the H^- from $LiAlH_4$ is going to go and attack the carboxylic acid proton and thus really creating a carboxylate molecule there and thus the further reduction is a little difficult, although $LiAlH_4$ works wonderfully for carboxylic acids. Borane reductions are also really good reagents for this particular reaction.

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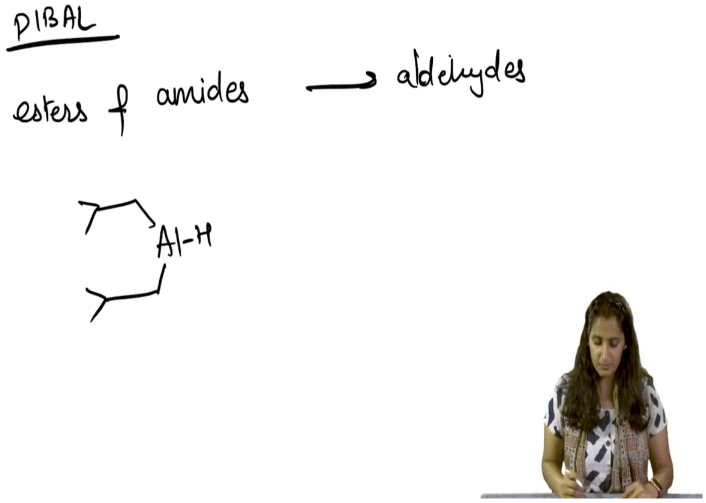

Now, the next reagent that we want to look at is DIBAL. And this is a very selective reagent. DIBAL is a way to convert esters and amides to aldehydes only. So, remember, so far, we have seen that most of these reducing agents will do the reduction all the way to either alcohols or amines, but in the case of DIBAL, because the reaction conditions are such that we end up forming aldehydes in excess.

So, DIBAL, let us look at the reagent. It is, di-isobutyl aluminum hydride. And remember, now in the case of $LiAlH_4$ you had 4 hydride ions, now in this case you have one hydride ion per molecule of DIBAL. And what we are going to see is that, that is why it becomes bulkier for it to do very quick reactions and they stabilize basically the hydride.

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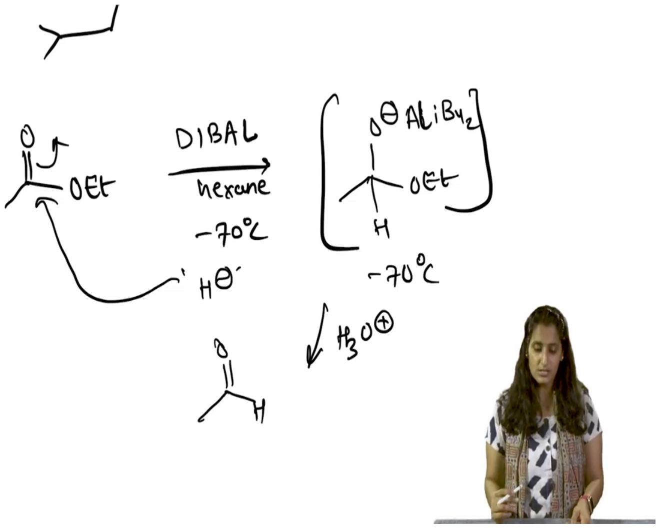

It exists as a bridge dimer and the reaction that it does is somewhat like this, such that you start from an ester and you react it with DIBAL, in the presence of hexane and -70°C. Now, again it is the source of hydride. So, it is going to attack and open this up. What do we end up forming? This forms CH_3CHO^- Al (isobutyl)$_2$ OEt.

Now, this is at -70 degrees, and this particular tetrahedral intermediate because we are doing the reaction at such a low temperature, it is stable enough, and that is the reason why you kind of quench the reaction at that and when you add H_3O^+ to this, separately later, it can form the aldehyde.

The only reason why DIBAL does not go all the way to corresponding alcohol is that we are doing this reaction at a very low temperature and thus stabilizing the tetrahedral intermediate. And that is one way to form the aldehyde. So, DIBAL is one reagent that we wanted to introduce here.

Of course, from an ester you can go all the way to the alcohol and then do a selective oxidation with PCC to really form this aldehyde. But that is it regarding oxidizing agents and reducing agents. There are quite a bit of them as we discussed early on. In fact, here is a good summary of some of the reagents that we have seen.

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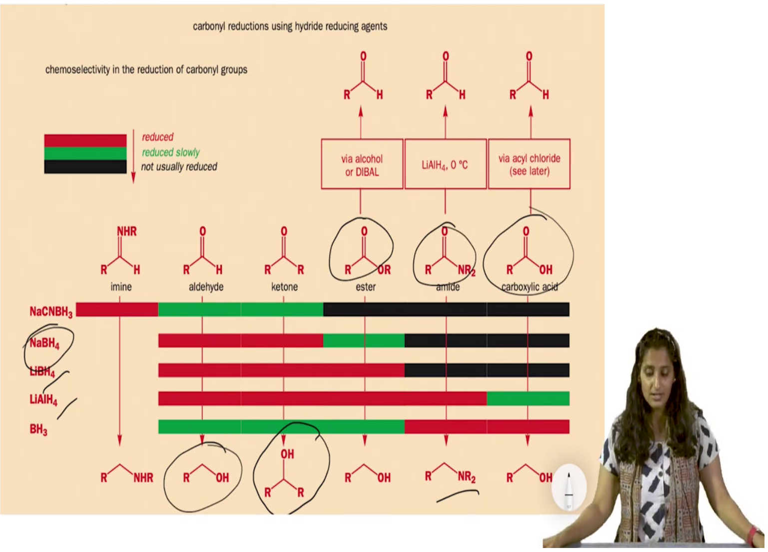
carbonyl reductions using hydride reducing agents

chemoselectivity in the reduction of carbonyl groups

So, that is it about oxidizing and reducing agents, and in fact here is a good summary of various oxidizing and reducing agents that we have seen and this is from the book Clayden. As you can see we looked at esters, amides and carboxylic acids, and all of these can be reduced, although they are not usually very easily reduced using, let us say, sodium cyanoborohydride.

But they can be very easily reduced using LiAlH$_4$ and the reason why we looked at borane for carboxylic acid was the reason that it gets reduced very slowly. So, that is why we used borane, BH$_3$, for carboxylic acids and when they get reduced they form corresponding alcohols.

In the case of esters also you end up with alcohol, in the case of amides you end up with an amine. Ketones and aldehydes require milder agents. So, for reduction of these, for ketones and aldehydes, you can use simply use NaBH$_4$ or LiAlH$_4$, or LiBH$_4$ and you will form the corresponding alcohol. So, in the case of ketones, you will form a secondary alcohol, in the case of aldehydes, you will form primary alcohol.

We also looked at how to use DIBAL. Starting from an ester, it forms an aldehyde. Starting from an amine it is going to form an aldehyde as well. So, LiAlH$_4$ and at 0°C temperature, amine is going to form the aldehyde. So, remember that in order to form the aldehyde and stop there, the reaction conditions have to be such that they stabilize the tetrahedral intermediate, and for that, we are going to use really low-temperature conditions. So, that is it regarding oxidation and reduction reactions of carboxylic acids and their derivatives. We will see you next week. Thank you.