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

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Lecture - 41
Asymmetric Reduction with Oxazaborilidines

Hello everyone, welcome to today's class. I hope you could go through what we discussed in the last class. We will briefly look at what we did and what we discussed in the last class.

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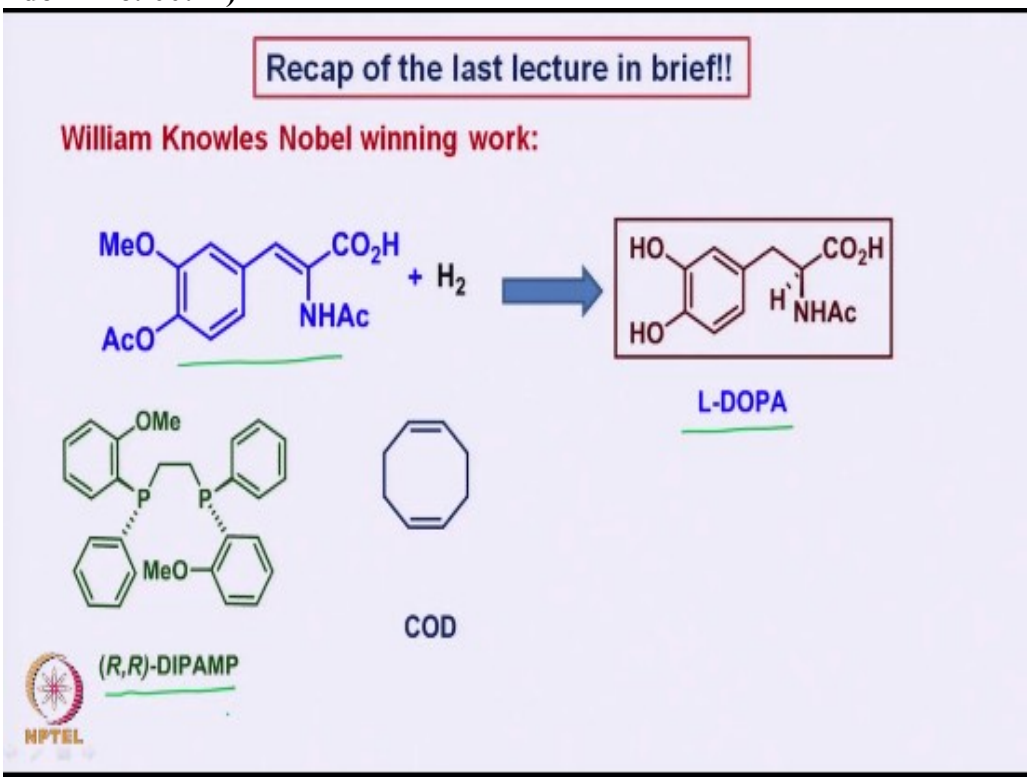

Now we looked at the asymmetric reduction part, where we discussed William Knowles Nobel Prize winning work where he developed an industrial method for the synthesis of L-DOPA, starting from an enamide like this where asymmetric hydrogenation was done using a rhodium catalyst where ligand was this DIPAMP and this led to the synthesis of L-DOPA in high enantiomeric purity.

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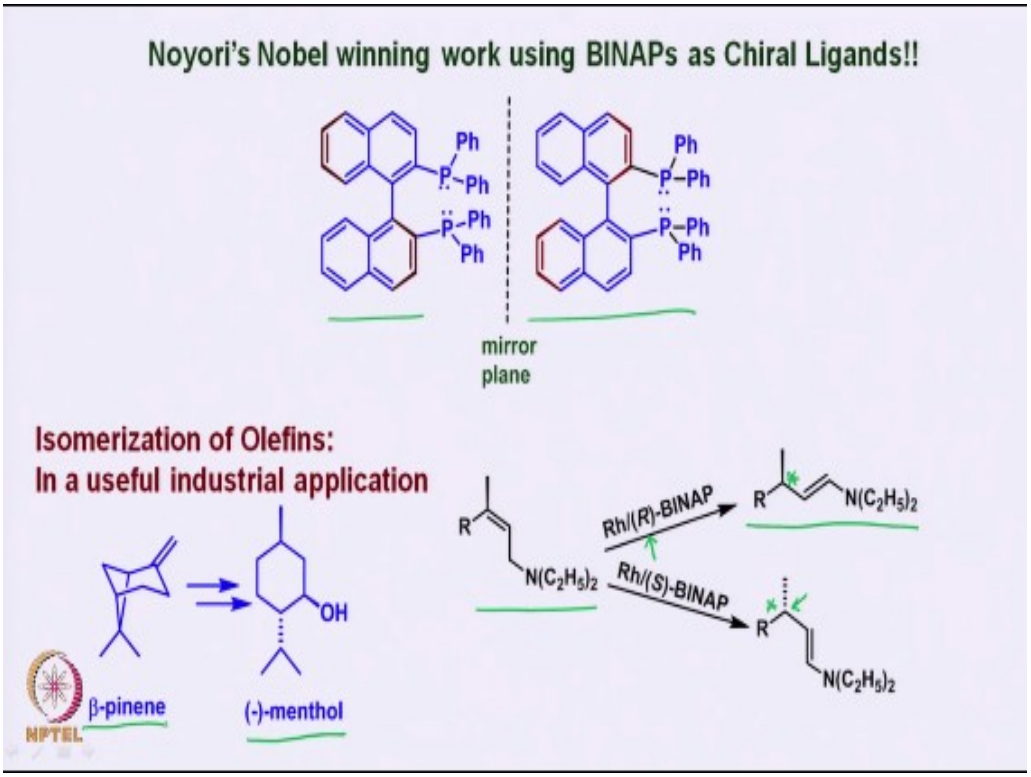

Then, we also discussed how Noyori's Nobel winning work using BINAPs as chiral ligands. So we saw two BINAPs, one of this and its mirror image. One of them is R, the other one is S configurated. And these BINAP ligands were very useful in leading to very high enantiomeric purity of the products wherever these ligands were used.

For example, isomerization of olefins was done and this kind of olefin which had a diethylamino group then could be isomerized to an enamine where this new asymmetric centre is being generated. And if we use R-BINAP, then we get the configuration of the asymmetric centre being like this. And if we took S-BINAP, then of course, we have this asymmetric centre configuration opposite to the above one.

And this kind of isomerization of olefins as one can imagine, that we can do the hydrolysis of these enamines and get the corresponding aldehyde. This is what was utilized in the synthesis of menthol by Takasago company and the beta pinene was eventually converted to this minus menthol using step of reactions involving one of them being isomerization of olefins using a rhodium BINAP catalyst.

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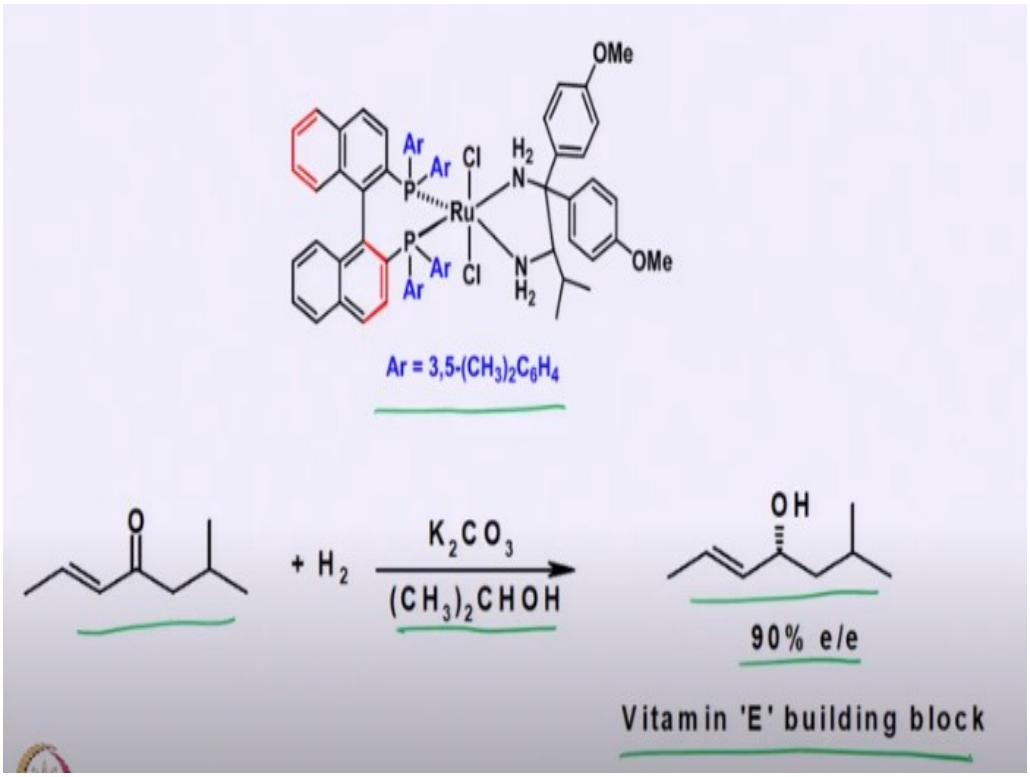

And towards the end, we saw that a ruthenium catalyst of this kind can be used for the reduction of these enones to the corresponding allylic alcohols in the presence of hydrogen and isopropanol. And this gave the corresponding allylic alcohol in 90% enantiomeric purity, which is a good vitamin E building block. So this was one of the methods of reduction of ketones.

So we will try to look at in today's class, what other methods are there for the reduction of ketones to enantiomerically pure alcohols.

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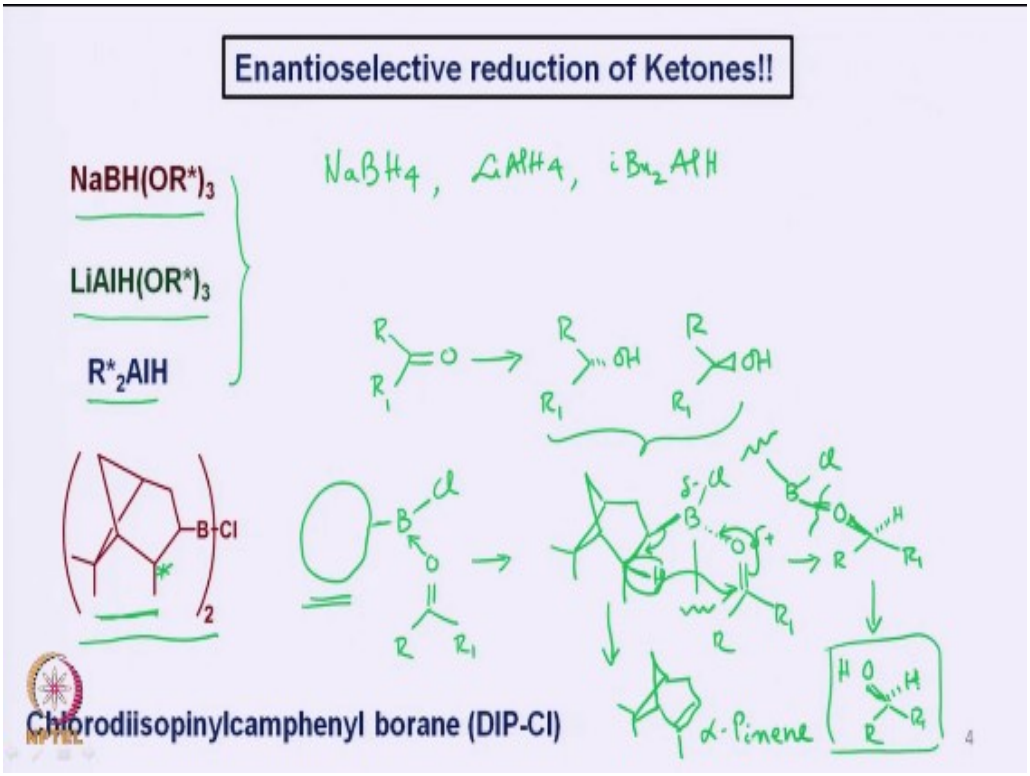

If we look at various traditional methods of enantioselective reduction of ketones what basically is done is modify say sodium borohydride or lithium aluminum hydride or DIBAL for example, into some sort of reducing agents in which we have a chiral ligand attached to it. Say for example one can make sodium borotrialkoxy hydride, where the R group of the alkoxy part is chiral.

In a similar fashion one can also make the lithium aluminum trialkoxy hydride where again we have the R as chiral ligand. And of course, one can also do the same with DIBAL. And one of the very interesting methods developed by Brown was the use of this particular borane compound which has a chlorine attached to it. And this particular part is coming from a pinene part.

So it is a chiral molecule and these kinds of reducing agents have been found to convert a ketone, which is a prochiral ketone. So if we take R and R1 we expect the reduction to give optically active either this or this one of them, or one of them being major optically active alcohol. Now these reductions are straightforward reductions of the ketone to the corresponding alcohol. We need not discuss that in detail.

Of course, in the case of DIBAL which is modified by a chiral ligand would of course behave not as a nucleophile to start with, but once it has coordination with the oxygen of the ketone, then of course it behaves like a nucleophile. But in all these cases, the enantiomeric purity of this or the extent of asymmetric induction depends upon various factors of course, including the chirality of the R ligand.

In this particular case, when this boron attaches to the ketone, so you have a attachment to the ketone, which is a prochiral ketone, and of course you have this coordination like this, and it is

attached to the part which is shown here. So we have this part, which is here and this part is essentially this part. So what is exactly happening is something that we can write it in one step here.

For example, if we have written in this fashion, then we can expect the boron from here. We have written only one part of it, and you can write the other part, which is attached to this same thing. Now we need to have the attachment of the boron. It will be something like this here, boron and chlorine. And of course, we will have attachment of the other part being here.

So one expects that what will happen is when this has a coordination to the oxygen, then we generate a kind of delta positive here and the delta negative here. And then this hydrogen attaches as a hydride to the carbon of the carbonyl group. And this goes in here and this again comes back here. So this allows the reduction to be completed. So you have R, R1 and of course the hydrogen whichever way the hydrogen has to say assume hydrogen comes in this way.

So then boron would be attached to the oxygen and we have this particular part attached here. So once then of course we hydrolyze it under basic conditions or under acidic conditions and then we get the corresponding chiral alcohol. And during this process, what releases from here is it is very interesting is something that one can think about it is basically it is nothing but a pinene.

So this is pinene. This is alpha pinene because the double bond is internal double bond and this is alpha pinene that comes off. So the reducing agent is chlorodiisopinylcamphenyl borane. And what is interesting is that this, the chirality of this particular part is guiding the hydride transfer to the carbonyl group.

And then the asymmetric reduction leads to this particular chiral alcohol which is of very high enantiomeric purity. So these are the various reducing agents that are needed for the reduction of ketone to the alcohol. But as you can see that the hydrogen which is being transferred to the carbonyl group as a hydride is essentially coming from the modified reducing agent.

That means, whichever one we take it, we need at least one mole equivalent of it, because each molecule will deliver one hydride. So it is a bit expensive in the terms of chiral ligand to be used. And therefore, there have been efforts to modify various reducing agents and see that if the chiral part of the ligand which is being used as chiral ligand to modify the reducing agent, whether it can be in a catalytic fashion or not.

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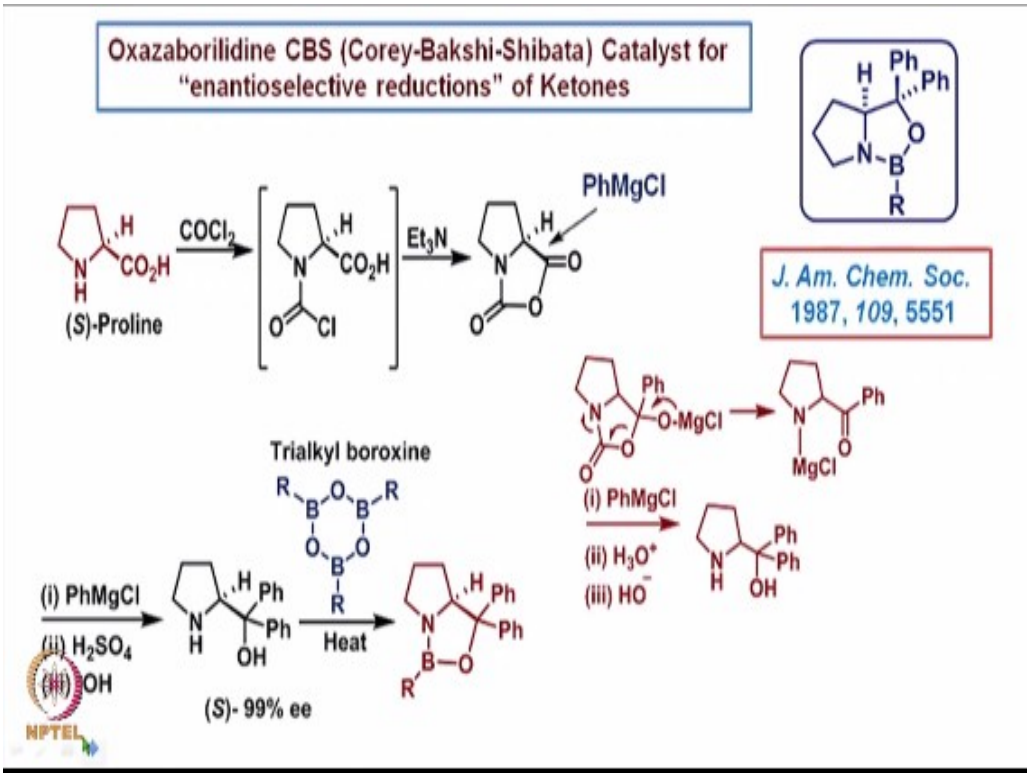

In this context, there is a very interesting chiral catalyst introduced by Corey which is known as oxazaborilidine catalyst or Corey-Bakshi-Shibata catalyst, which is useful for the enantioselective reductions of ketones. The structure of such a catalyst is shown here, which has a bicyclic 5-5 system in which there is a nitrogen, boron and oxygen in a continuous fashion.

Now this particular type of Corey-Bakshi-Shibata catalyst can be prepared from either S-Proline or R-Proline. Now because there are two 5-member rings which are attached to each other, the shape of this particular Corey-Bakshi-Shibata catalyst will be of a bowl type in which one side of the bowl is sterically hindered and the other side is sterically free.

Now depending on whether one uses S-Proline or R-Proline, the side of the pole would be differently accessible. How is this particular catalyst made? We will see from say for example, we start with S-Proline. Then we react with phosgene, which converts the N-H to N-COCl and then we use triethylamine to deprotonate the carboxylic acid to the corresponding carboxylate which then reacts with this particular carbamoyl moiety to form this bicyclic intermediate.

Now this bicyclic intermediate is then treated with phenyl magnesium chloride. Now phenyl magnesium chloride preferentially interacts on to this particular carbonyl carbon because this carbonyl carbon is less electrophilic because there are two hetero atoms which are on the either side of this particular carbonyl carbon. Therefore, this carbonyl carbon is more electrophilic for Grignard reagent to attack.

When this Grignard reagent attacks we get this kind of first intermediate which then breaks to release carbon dioxide and of course N-MgCl will be forming and also the corresponding ketone will be liberated. Now with the excess of phenyl magnesium chloride being around this ketone would again react with the phenyl magnesium chloride to form the corresponding O-MgCl.

Of course, that has to be neutralized and followed by basification to release this particular amino alcohol. Now this amino alcohol then reacts with trialkyl boroxine and there is a formation of a bond between nitrogen boron and oxygen. That means, this particular part of trialkyl boroxine gets inserted between nitrogen and a oxygen to liberate the Corey-Bakshi-Shibata catalyst.

Now as you can see, that we have not lost any asymmetric center or we have not done any epimerization. Therefore, the enantiopurity remains close to 99%. So this particular Corey-Bakshi-Shibata catalyst can then be utilized for the reduction of ketones along with a reducing agent such as diborane or any other boron producing agent.

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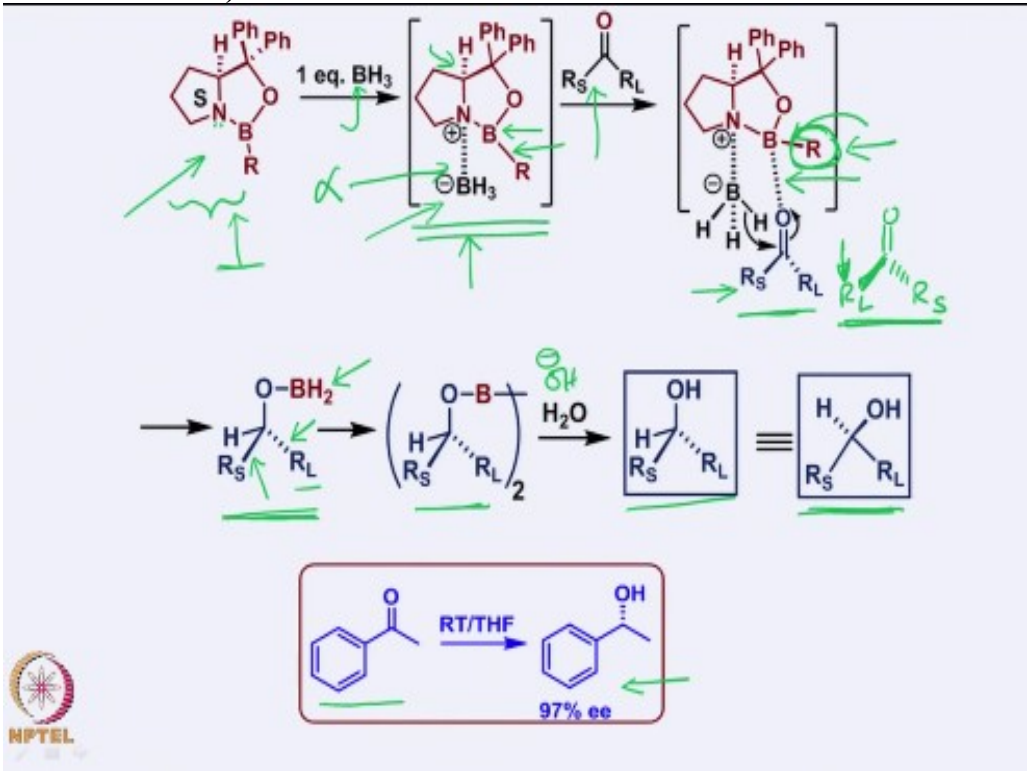

Now when we take such a bicyclic ligand and react with say borane, so the nitrogen lone pair of electron from here interacts with the electrophilic borane and forms this intermediate and this is the intermediate that is very important. Now what we have here is this R group. This R group is a very crucial group. And what happens is that, since the bowl, the hydrogen at the junction is alpha oriented.

So the bowl is, the major bulk of the bowl is like this. It is going to be pointing out up and the hydrogen is pointing below. So basically the bowl is like this. So what happens is that, since the hydrogen is pointing down because the bowl is pointing up the major part of the bowl and therefore, the nitrogen attaches to the borane from the alpha side. That means the lower side, from the same side as the hydrogen is.

Now we have the only now electrophilic part that is left out is this particular boron and we have the carbonyl group which can have one small group and one large group. So the oxygen of the carbonyl group comes in contact with the electrophilic boron and has this chelation or the

coordination. Now at that stage, there are two possibilities of orienting. One of course, as I have shown it here.

And the other possibility is that the oxygen attaches in this fashion and we have R large group coming here and the small group coming here. So what it means that this particular R group which is pointing upward, because the oxygen of the carbonyl group from the lower side has attached and the steric hindrance caused by the R group would allow which direction the carbonyl group would be oriented.

Since this R group is beta oriented, therefore the small R part, the group which is smaller orients towards the beta side to avoid steric hindrance. If we had put this kind of orientation, then what would have happened is that there is severe steric interaction between this R and this R large group, that is the larger group attached to the carbonyl.

So therefore, in such a situation, the carbonyl group orients in such a way that the large group goes behind and the small group comes towards us, which is kind of more towards the R group. In that situation, then the hydride is transferred and the way I have shown it here. And suppose if R L group was going behind, R S group is coming towards us. R S means small substitution and the R L is the larger substitution.

Then the hydrogen is transferred into the plane and therefore, we get the intermediate of this kind. Of course, we can use the remaining hydrogens also and eventually get two or three. And finally upon workup, with a basic workup, we of course will get the boron oxygen bond cleaved and the hydroxy group would be released.

And this way we have converted carbonyl group to the alcohol and with the predictable geometry of the newly formed asymmetric carbon atom. And that is the configuration that is what is seen. And there are many examples that have been done. Say for example, if this acetophenone is taken room temperature in THF and we carry out this particular reduction, then we get this alcohol in 97% enantiomeric purity.

Of course during this process, this particular chiral ligand which is what modifies the reduction part of the borane into such an intermediate. So essentially this is the reducing agent which is a modified reducing agent and therefore, this particular chiral ligand is only used in a small amount, one or two mole percent. And whereas, we use one equivalent of the corresponding reducing agent.

So as we can understand that the borane would not reduce the ketone unless it is activated to make it as a nucleophilic reducing agent and that is exactly what is done by this oxazaborilidine by modification. Now here we have a negative charge on the boron and thus the reduction occurs of the ketone via this kind of chelation.

So this is a very nice method, where only catalytic amount of a chiral ligand is used and one equivalent of borane is used as a reducing agent.

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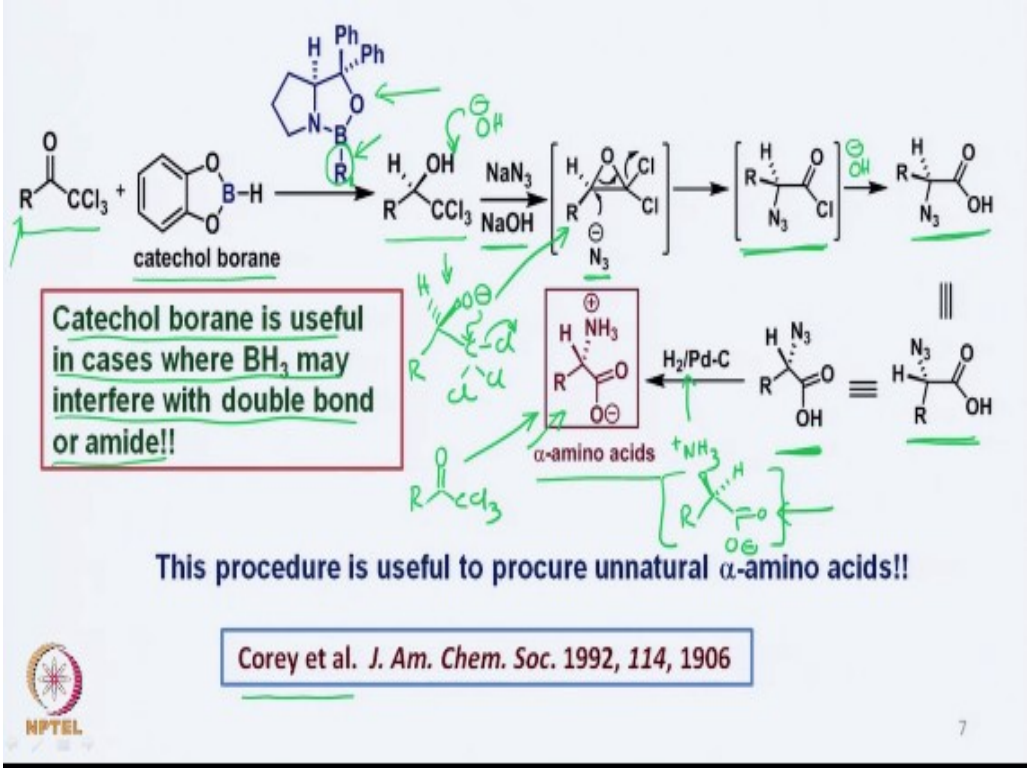

So Corey also showed, Corey is the one who is a professor at Harvard University and 1990 Nobel Prize winner. And what he has also shown that if we take a ketone of this kind, where there is a trichloromethyl group attached to it, and we use a borane, which is a catechol borane we can use, different types of borane molecules, depending on what kind of enantiomeric purity is given.

So we can also change this path. Like for example catechol borane is useful in cases where BH3 may be interfering with the double bond or amide. For example, if there are extra hydrogens attached after the ligand has coordinated with the borane part, then those extra hydrogens, for example in the case of BH3 would also affect some other part of the molecule if that gets affected.

The same time, the modification of the borane can be also done in such a way that gives more steric bulk to the reducing agent. So we use this particular part so we can also modify this based on initial Corey-Bakshi-Shibata preparation. And when this reaction was done on to this ketone, they got this particular optically active alcohol which was treated with sodium azide in the presence of a base like sodium hydroxide.

So you can imagine that this epoxide which is formed is basically nothing but, if we can imagine that we have here molecule like this, and you have an O- becoming because of the two the OH group which is there and the base takes up the proton from the OH and generates an anion. And this anion then internally attacks and removes one of the chlorines to form this particular dichloro epoxide.

And this dichloro epoxide then under the conditions is attacked by the azide group and in the way I have shown the arrows, the nucleophile attacks on to the carbon atom, which is

asymmetric. And then there is a loss of chlorine and eventually forming this acid chloride which under the conditions because there is a basic condition is hydrolyzed. Of course, we can write the configuration of this in this fashion and in this fashion, whichever way we like it.

And then finally, when we do the hydrogenation using a normal palladium catalyst, then the hydrogenation leads to alpha amino acids. So this is basically a very convenient and a fantastic way of converting a simple ketone of this kind to an alpha amino acid of this type. Now here depending on what the R group is, this R group coming from the, of course I must emphasize that this R group is different from this R group.

So basically one can write here is that, this being as R1 to distinguish from this R. So we can imagine that we can also get this alpha amino acid with a different configuration. That means, we can think about getting, say you have an amino group here coming as NH_3^+ and you have hydrogen coming like this and you have the carboxylate ion.

So this is also possible if we use the other enantiomerically pure Corey-Bakshi-Shibata catalyst. That means, if we start with S-Proline we get, say for example, this kind of alpha amino acid and we start with R-Proline we can get this kind of amino acids. And therefore, we have the possibility of getting both the enantiomers of the same alpha amino acid.

And thus one of them would of course be natural or we have a possibility of making unnatural amino acids, alpha amino acids of both enantiomeric type. This is something very useful because unnatural amino acids are important for making different types of peptides or proteins to study their effect in the biological systems. So this is how this particular reduction has been done.

So we will stop it today at this stage and we will take up the other aspects of asymmetric reactions in the next class. Till then you could go through this whatever I have discussed it today and be ready for the next class. Till then bye and thank you.