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

Prof. Yashwant D. Vankar
Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture - 37
Katsuki-Jacobsen Epoxidation: Mechanism and Stereochemistry

Hello everyone. I welcome you all for today's class. I hope that you got the opportunity to go through the last class where I discussed some aspects of asymmetric epoxidation. So we will briefly look at what we did in the last class and then proceed further for other aspects of asymmetric reactions.

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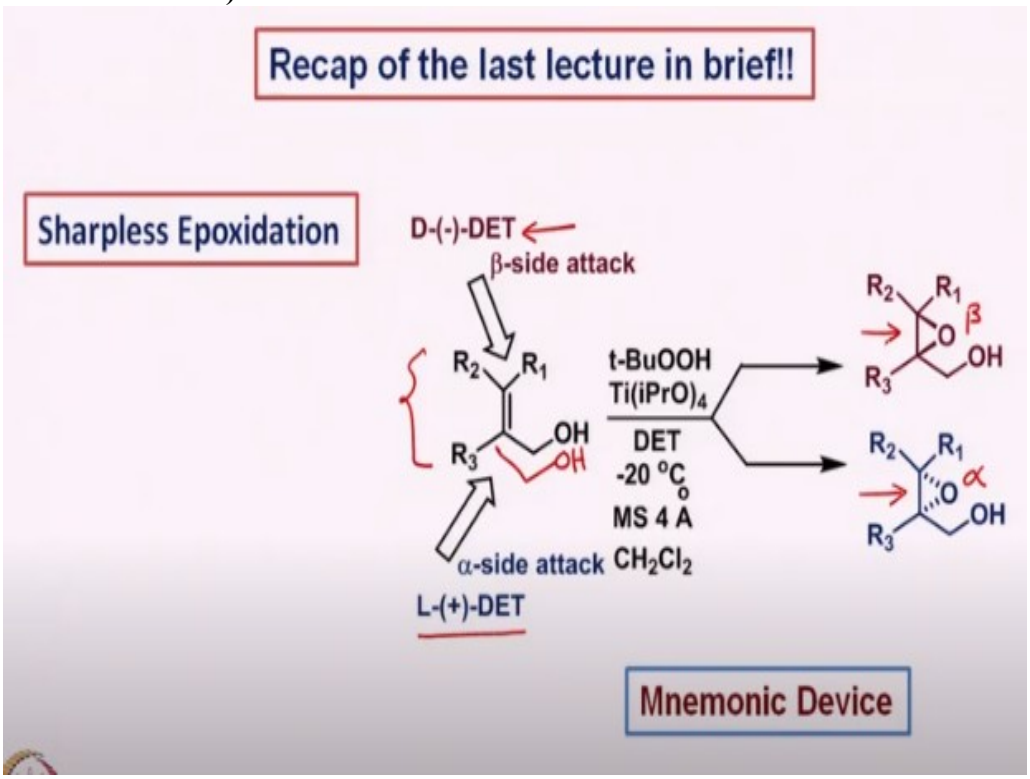

Last time we discussed the Sharpless epoxidation and as I told you that if we have an allylic alcohol, which is a prochiral molecule, and then we can epoxidize that using a protocol developed by Sharpless namely that involves tertiary-butylhydroperoxide, titanium isopropoxide and of course molecular sieves to remove water or isopropanol.

And the main reagent that is required which guides the enantioselectivity is diethyl tartarate optically active formed. If we take L+ DET and orient the allylic alcohol in this fashion, where we have the double bond like a vertically oriented and then on the right hand side on from the lower part of it, we have the CH2OH like this. Then of course, the L+ DET allows the epoxidation to take place from the alpha side as you can see it here.

On the other hand, if we take D- diethyl tartrate then of course, we get the epoxidation from the beta side and we discussed in detail how the mechanism allows the formation of these epoxides in a highly stereo selective fashion and obviously, they give enantiomerically pure epoxide.

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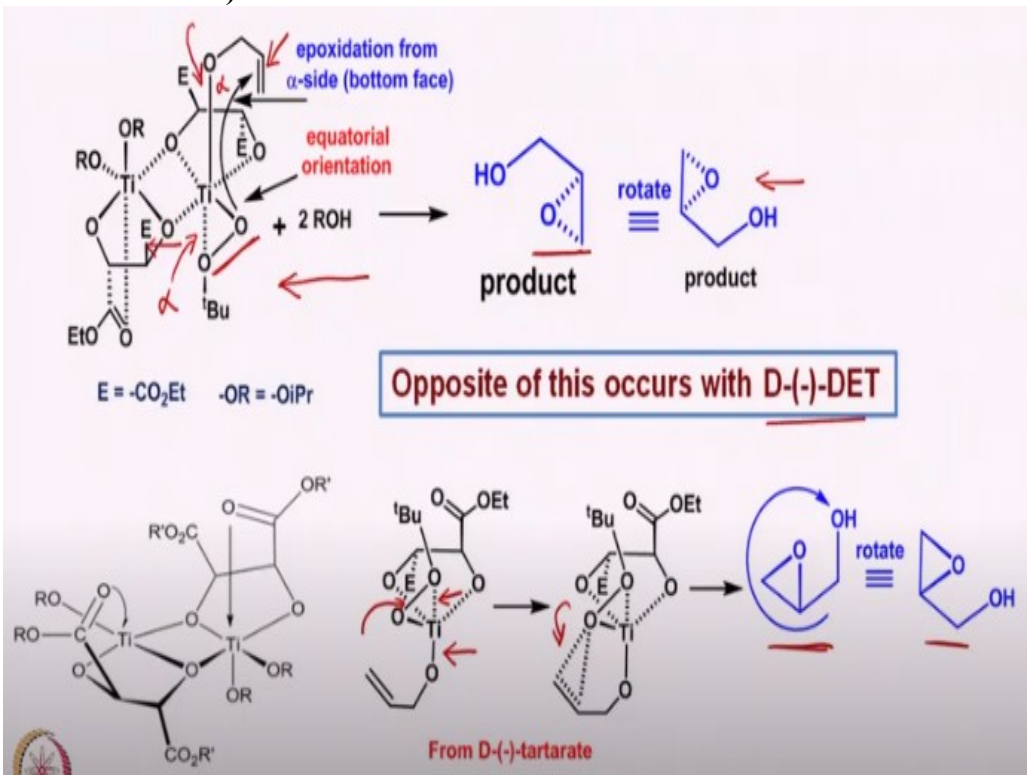

And we also looked at how if we start with a molecule that contains an asymmetric center and of course, we can resolve them in a kinetic fashion. So I have shown here the mechanism which I need not emphasize too much, but just as a recap, as you can see that the tertiary-butylhydroperoxide attaches from the equatorial side first to the titanium and then it has a choice to attach the tertiary butyl oxy this particular moiety to the titanium from the lower side or from the top side.

But since in the dimeric species, we have the ester moiety here, which is beta oriented and therefore, the titanium oxygen tertiary butyl bond formation occurs from the alpha side. And that decides that the allylic alcohol attaches from the beta side and therefore, epoxidation occurs to the double bond which is oriented in this fashion from the alpha side and that leads to the formation of the product like this.

And which can be written up by simply rotation in the plane of the paper to give this particular product. And exactly opposite of that occurs when we take the D- DET and of course, we get the product like this because the tertiary-butylhydroperoxide now attaches from the top side.

That means, once the titanium oxygen bond of tertiary butyl hydroperoxide has taken place from the equatorial side the other oxygen and tertiary-butyl that particular bond the attachment takes place opposite side to the side from where the allyl alcohol will attach. And that of course, as I mentioned depends upon the ester group of the dimeric species.

And in this particular case when we are dealing with D- diethyl tartarate the tertiary butyl O-bond attachment occurs from the top and therefore, the allylic alcohol attaches from the alpha side and therefore, the oxidation occurs from the beta side like this, which leads to the formation of this particular epoxy alcohol which is exactly opposite from the product that we have got from L+ DET.

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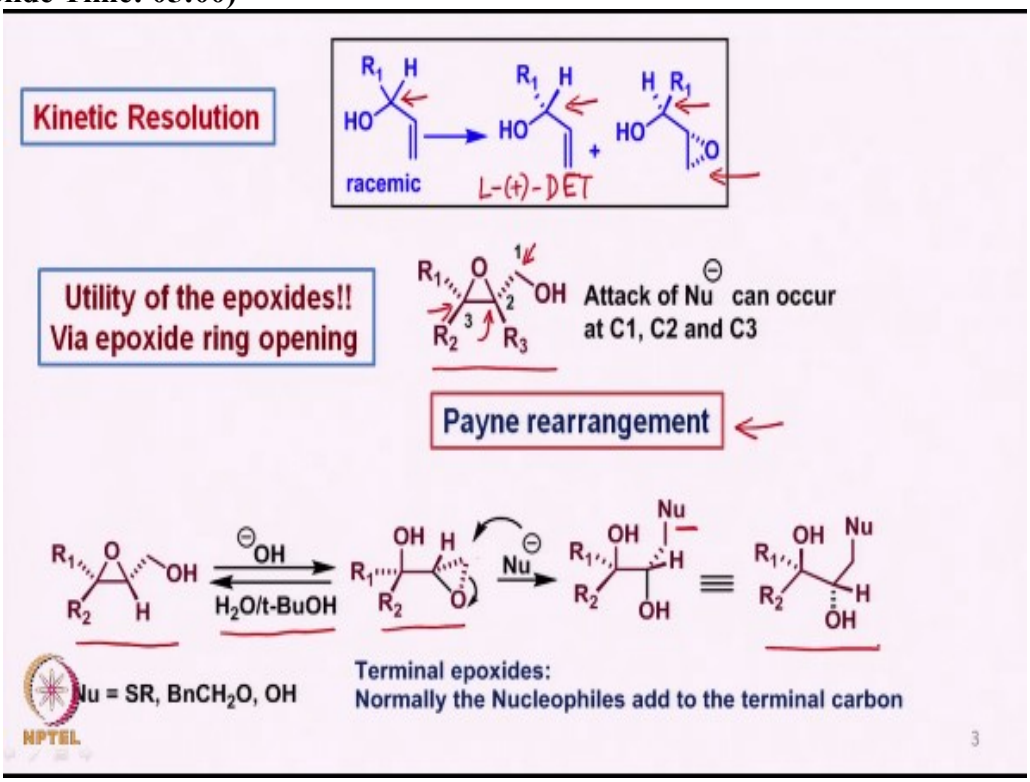

Now we come to the kinetic resolution part. We need not spend much time. We already have seen that if we take a L+ DET for example, L+ DET as the tartarate ester then of course, the two racemic molecules, which are here, because of the group R 1 they exist in racemic form and we are taking a racemic molecule.

And then we are trying to react it with L+ DET and of course titanium isopropoxide and tertiary-butylhydroperoxide the one in which the R 1 group is away from the ester group in the transition state, that gets epoxidized faster and therefore, we get this particular epoxy alcohol and this particular allylic alcohol remains unreacted.

So this is how we can do the kinetic resolution. As I mentioned earlier that if we allow the reaction to go for a longer time, then of course, both the allylic alcohols will get epoxidized. So that is the reason why it is called as a kinetic resolution because it all depends upon which allylic alcohol reacts faster. We also looked at the utility of the epoxides basically, via the epoxide ring opening.

Now if we can look at the epoxy alcohol, we see there are three sides where the nucleophile can attack. That is carbon number 1, carbon number 2 and carbon number 3. And we looked at all the possibilities including the Payne rearrangement, where we could transpose the internal epoxide

into a terminal epoxide and then the reaction easily occurs at the terminal end of the epoxide because that is sterically less hindered.

And therefore, the SN2 reaction takes place as I have shown it here. So if we start with this epoxy alcohol, under the base condition basic conditions here OH-, water tertiary-butanol medium, we get the epoxide which is the terminal one. And then the nucleophile in this particular case will be OH- but any other nucleophile we discussed like thiols or amine.

Then they can attack on to this end of the epoxide and from this particular diol with a nucleophile being there at the terminal end of the epoxide and eventually we get this product. So like this one can easily transform the epoxy alcohol which is almost 100% optically pure into a large number of different types of molecules, which are highly functionalized molecules.

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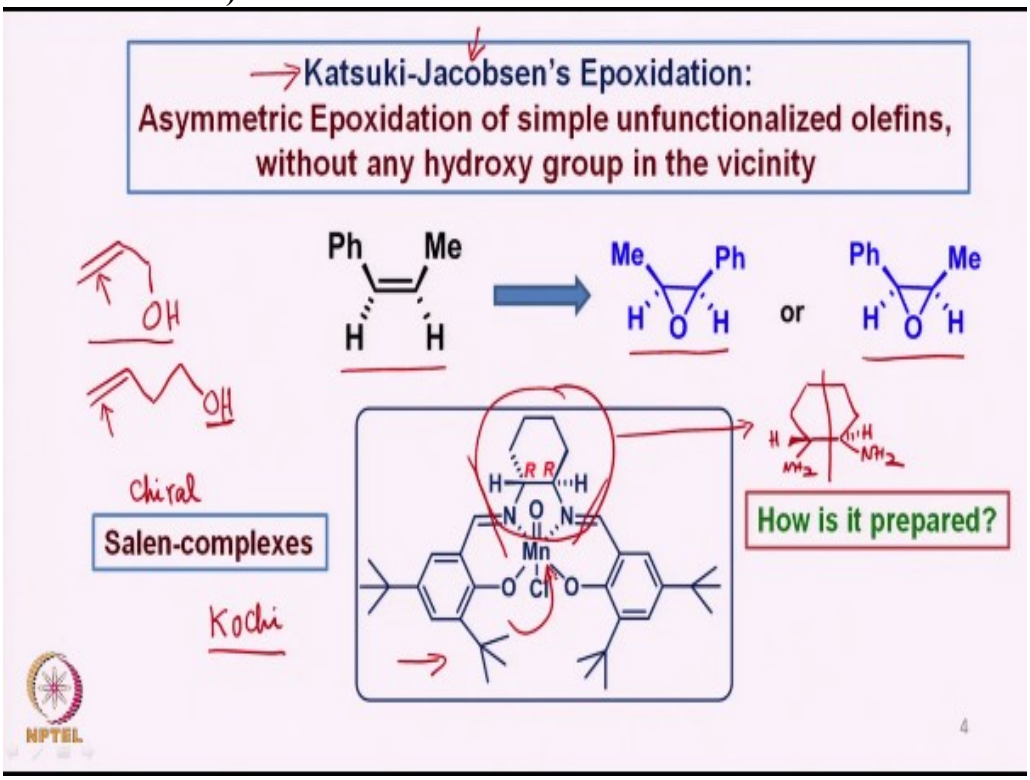

Now so far we discussed the epoxidation of allylic alcohol. So in the epoxidation using Sharpless conditions, the requirement was that allylic alcohol is a must. That means, the OH group has to be at the allylic position and very close to the double bond. It has been found that they also have studied the epoxidation of homoallylic alcohol, but of course, the epoxidation drops down.

Because the attachment to the titanium obvious OH group allows the transfer of the oxygen from tertiary-butylhydroperoxide on a double bond which is one more carbon away from the allylic alcohol. So the possibility of high stereoselectivity is somewhat less. Worst is or even more difficult is epoxidation of such kind of olefins which are not functionalized and how to carry out epoxidation to give the epoxide either this or this, they are basically enantiomers of each other.

Now in this respect Katsuki and Jacobsen have almost the same time developed method of epoxidation of these olefins using chiral salen-complexes. This is a chiral salen-complex. Of

course, these kind of complexes were originally described by Kochi. However, the asymmetric version has now been developed by Katsuki and Jacobsen.

So as you can see it here, we have the salen-complex in which if you look at this particular part on the aromatic part here, this is basically a salicylaldehyde derivative. And if we look at the upper part, that is this particular part here, this particular part comes from the C2 symmetry based chiral amine. So what we have here is here you have NH2 and here also you have an NH2 and of course you have hydrogen here which is beta and the hydrogen here is alpha.

So you have a C2 symmetry basically. So such C2 symmetry based 1,2 diamines also have been utilized to prepare such a complex. And this complex then when it is present here having a manganese at the core then of course, the oxo manganese complex allows the oxidation to take place. We will study the mechanistic aspects in detail.

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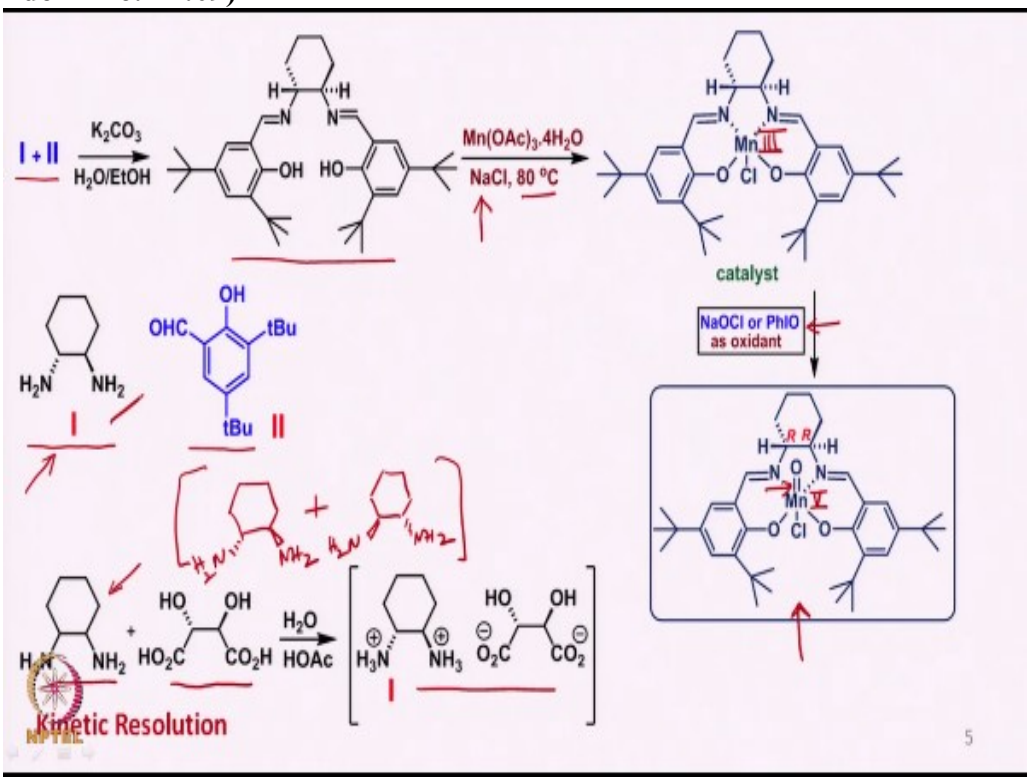

Now how do we make this kind of salen-complex and how do we incorporate the metal manganese into it. First of all we start with this C2 symmetric based diamine and we take the tertiary butanol and as I have written here, we mix them together in the presence of potassium carbonate and of course, water ethanol we remove basically it allows the condensation to take place and we get this particular molecule.

As you can see two molecules of salicylaldehyde derivatives have reacted with the primary amine and of course, we got imino molecule which on reaction with manganese triacetate at 80 degrees in the presence of sodium chloride we get here manganese III and such a complex is formed which can now be oxidized to the corresponding oxo complex here using an oxidant such as sodium hypochlorite or iodosobenzene as oxidant. And of course, this exists in the manganese V form.

Now this is the one that is utilized for the epoxidation of olefins which are unfunctionalised. Now how do we get this particular molecule here? There are several methods that have been developed in the recent past but one of the oldest ones is that we can start with a racemic molecule. Of course, it has to be a trans oriented. But then it would be a mixture of this and it is an enantiomer.

So we have mixture of this and this. So this is how it is here. I have not shown any stereochemistry here, but we mean that this is going to be a mixture of these two enantiomers as a racemic molecule. And when this is treated with tartaric acid, which is an optically active diacid that allows the resolution to take place and we get of course one of them coming out as a crystal, which we can recrystallize and separate out.

And then we can kind of basify it in order to release the corresponding free amine. That is what is utilized here. But there are several methods which can be employed to get to this particular 1,2-diamine.

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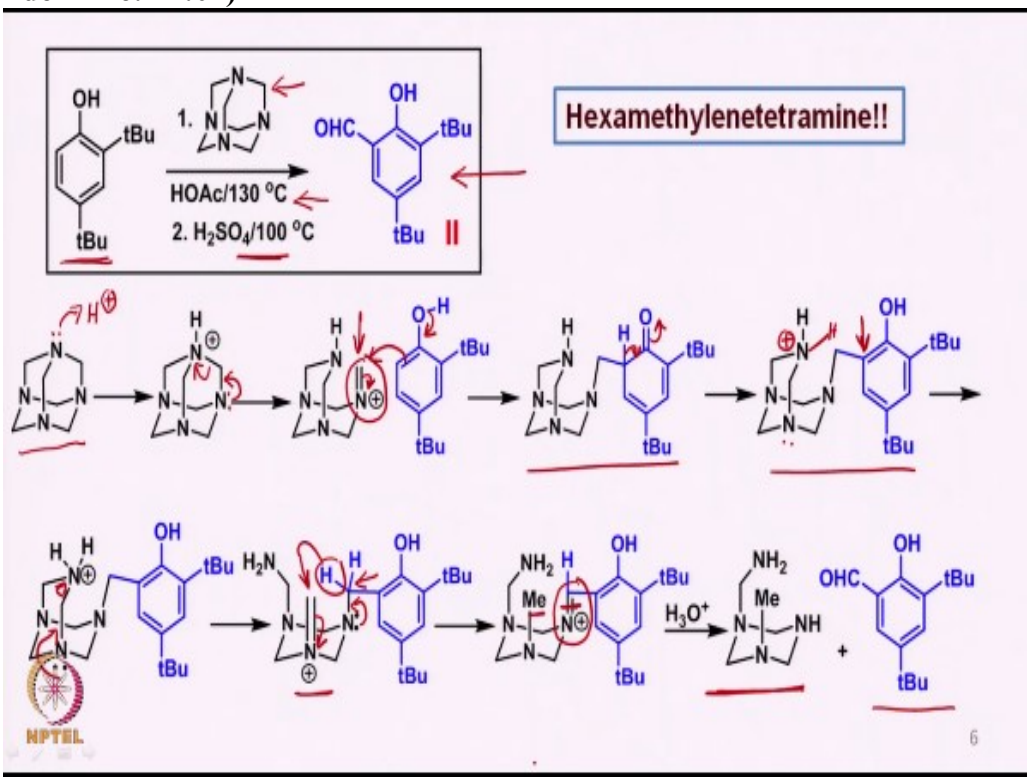

Now how do we get the corresponding aldehyde? This is a little bit of a little difficult aldehyde or salicylaldehyde to get it. But one of the ways by which we can introduce the aldehyde group into an aromatic molecule is by reacting the aromatic moiety with hexamethylenetetramine. So hexamethylenetetramine has this cyclic structure as you can see. There are 4 nitrogens and 6 methylene groups which are present.

When the phenol which is already substituted at the proper position is allowed to react with this hexamethylenetetramine in the presence of acetic acid at 130 degrees followed by of course hydrolysis using sulphuric acid at 100 degrees, we get the corresponding aldehyde. Now what

exactly is the mechanism and how does this act as a source of formyl group is something that is shown here.

If we take this hexamethylenetetramine it gets protonated. It can get protonated at any position, but we are writing it here on the top. So we protonate this and we form this ammonium ion. And then we have this pair of electrons here, which allow the opening of the particular carbon nitrogen bond which is next to the ammonium ion.

And then you generate this particular species in which now we have this electrophilic carbon here and therefore, the aromatic group will attack and then we get this particular part where now the aromatic group has attached to the hexamethylenetetramine. And of course it regains the aromaticity and we get this particular molecule.

And this molecule which is now basically an ortho-substituted amine which will now get reprotonated on to this particular nitrogen atom and we can push this out from here as you can see it here. Then we can push it out and neutralize the positive charge generating this species, which is now having an electrophilic carbon present at this position. And now we have a very kind of vulnerable carbon hydrogen bonds, two of them.

One is it is benzylic carbon and second is it is next to the nitrogen and therefore, it is ready to undergo a kind of hydride transfer to form the methyl group here and neutralize the positive charge on the nitrogen and of course, you generate this imonium ion. And this can be hydrolyzed. That is what is the next step. Sulfuric acid in the presence of water hydrolyzes and releases the corresponding aldehyde.

And of course, you can get the amine which is released from hexamethylenetetramine. So this is how the mechanism of the transfer of aldehyde occurs on to the aromatic ring system using hexamethylenetetramine.

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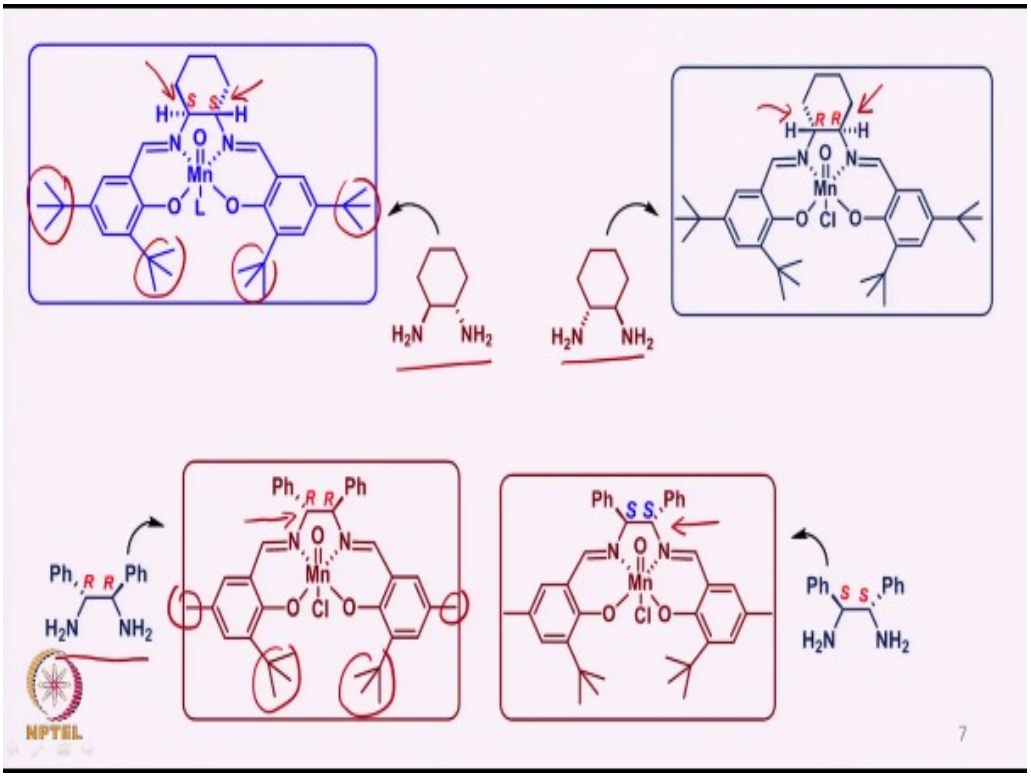

Now if we take this particular amine, we get this complex in which we have the configuration here as S S. And if we take this particular amine then of course, we have exactly opposite. We have this R R configurated oxo manganese complex. In addition to this particular cyclic amines, these amines also have been employed and they can also be readily prepared by kinetic solution method or many other chemical methods.

So again we have two possibilities. We have here R R giving us this complex and S S giving us this particular complex. So these are the four different types of oxo complexes that have been employed in the Katsuki-Jacobsen epoxidation. Of course, you can see that substituents could be different. Like here they have put two methyls and then you have a tertiary butyl. But in this case there are tertiary butyl.

So one can play with the substituents which are present onto the aromatic ring particularly at the ortho and the para position next to compared to the hydroxy group. And these lead to a variety of different possibilities and therefore, we can impose steric hindrance or electronic factors into it.

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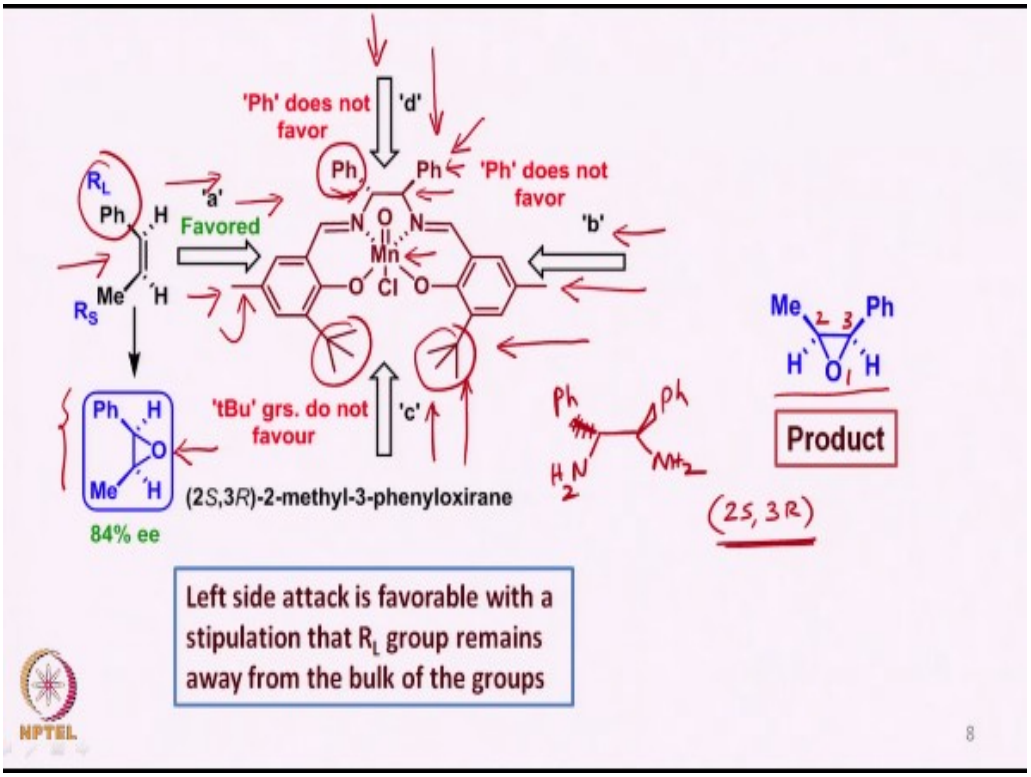

Now if we try and look at this particular oxo complex for the epoxidation of simple olefin like this, then what we see that the epoxidation is possible from four different sides. So if this is the manganese oxo complex which is there, so which is kind of, the manganese oxygen bond is orthogonal to the plane of the entire molecule.

And then the olefin can attack from either say, this side from the top side which is which I have referred as d side or it can be from the b side or it can be from the c side or it can be from the a side. So if this phenyl group here and this phenyl group here they are oppositely oriented, one is alpha and the other one is beta.

However, when the olefin is trying to come from this side, obviously the olefin will have an interaction with this particular phenyl group and also from the backside the phenyl group. But particularly this phenyl group will have a interaction. In a similar fashion when from this side when the reaction is occurring, then we can see that again the phenyl group will have the steric hindrance.

And then if we look at from the bottom side, from this side attack, if we are looking at the approach of the olefin towards the Mn double bond O, then of course, it will also come across with tertiary butyl groups. So the sides b, c, d are blocked or kind of sterically congested and hindered. And therefore the olefins, no matter which way you orient it would not approach easily.

On the other hand, if we look at from the a side, if we look at from this side, we see that if we orient the large phenyl group on the other side of the molecule that is on the top side of the molecule and leave the small group towards the lower side of the molecule, then the approach

would not come in the way like for example, the phenyl group will not be putting a steric hindrance.

But since it is going to be alpha oriented, therefore it is pointing downward. And if we have the hydrogens going down and the phenyl and the methyl is pointing up and then that molecule is approaching towards this manganese double bond O, then we do not anticipate any steric hindrance particularly when we have put here the small methyl group.

And therefore, in that situation when the epoxidation occurs into the plane of this particular black board or paper, then of course, we expect that the epoxidation will give a geometry being like this, where the phenyl group is on the top side, methyl group is on the lower side of the plane. And of course, both of them are pointing towards the beta side. The hydrogens are pointing alpha side and the epoxidation has occurred into the plane.

It has transferred the oxygen into the plane. And so this is the product that we get it, which is what is 2S, 3R. That means you have 1, 2 and 3. So you have here 2S and a 3R is actually the configuration at the newly formed asymmetric center. So this is something to do with the catalyst that is derived from this particular chiral amine which is also C2 symmetric.

And it is basically it is it should be like this here and particular diamine. We can also take the other diamine and of course get opposite of this particular configuration.

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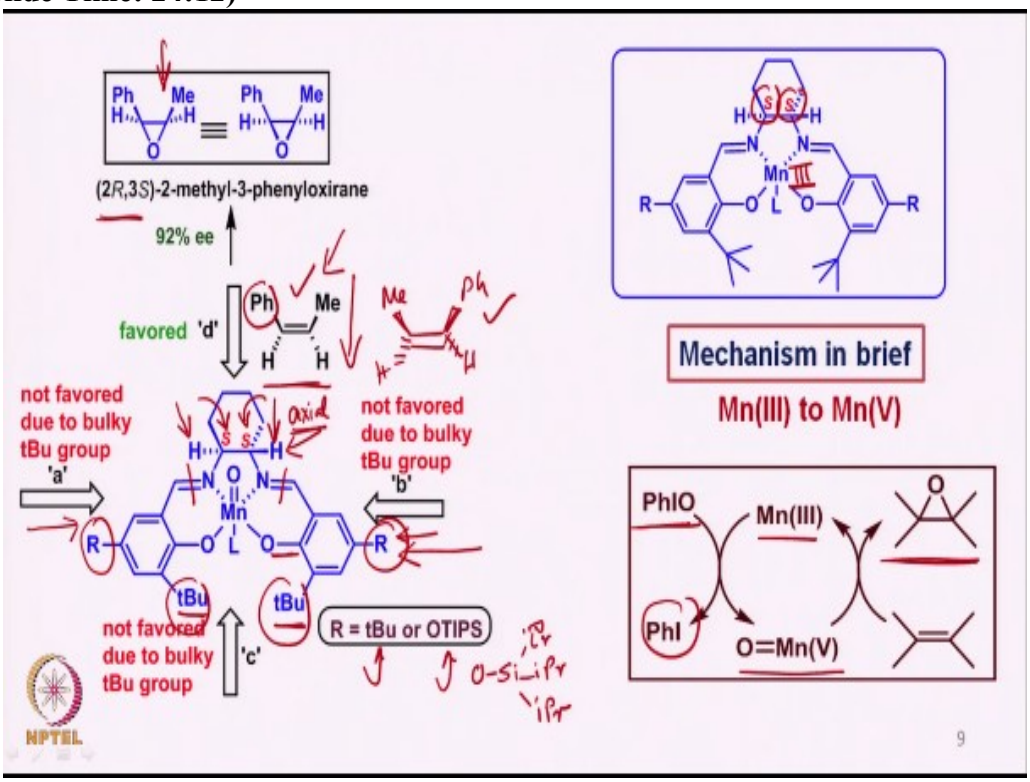

Now if we look at the cyclic amine based complex, like for example, this particular one here, where we have S and S as configurations, then we can see how the olefin approaches. Now if we can see the substituents on the aromatic ring, they have put here two tertiary butyl groups, ortho to the OH bond of the particular aldehyde, which is what is this particular aldehyde.

So if we have the carbon oxygen bond which is a phenolic OH bond next to that tertiary butyl groups are put and para to that R group is put, which R group is either tertiary butyl or O-triisopropyl. So basically isopropyl is silent. So you have the O-Si isopropyl isopropyl and isopropyl. So we can put this bulky substituents around or so that they kind of impart lot of steric hindrance.

So we can see now that if the olefin is trying to approach from a side here, then we have the tertiary butyl group which is not going to be favouring. Similarly on the b side the tertiary butyl group will not favour. And of course, from the c side we have these tertiary butyl groups not favouring.

So from a, b and c sides as we can very clearly see that the tertiary butyl groups which are deliberately put R-O triisopropylsilyl group which is put specifically because of allowing the blockage of the attachment of the olefin from these three sides. And therefore, now what is left is only the top side, the d side where the olefin can approach. Now olefin can orient the way I have shown it here or it can also be oriented in this particular fashion.

That means or the phenol group is put on the right side. So we can have the hydrogen here and of course a double bond here. So we can either have this or we can have this. Now what is found is that this particular hydrogen here in this case is actually beta oriented in an axial fashion. So it is an axially oriented hydrogen and therefore it is assumed that this comes into the way.

And therefore, the olefin tries to orient in this way that the large R group is avoiding this particular hydrogen here. And therefore, it goes on the left hand side where the hydrogen is pointing downward. And therefore, the epoxidation occurs to give this particular epoxide where the phenyl group is on the left hand side, methyl group is on the right hand side. And that particular epoxide is having 2R, 3S configuration.

If we want exactly opposite of that to happen, then of course, we can take the, in place of this we can take the corresponding R configurated amine we can take it. Now what exactly is the mechanism in brief? Basically, we are starting with this manganese III complex and oxidized during the process. Say for example using this particular PhIO as an oxidant.

So the manganese III gets converted to the corresponding manganese V oxo complex. In the process we will release iodobenzene and the double bond gets epoxidized to the corresponding oxirane or the epoxide. And of course, we release the manganese III in the process, which is again reoxidized to the corresponding manganese oxo complex.

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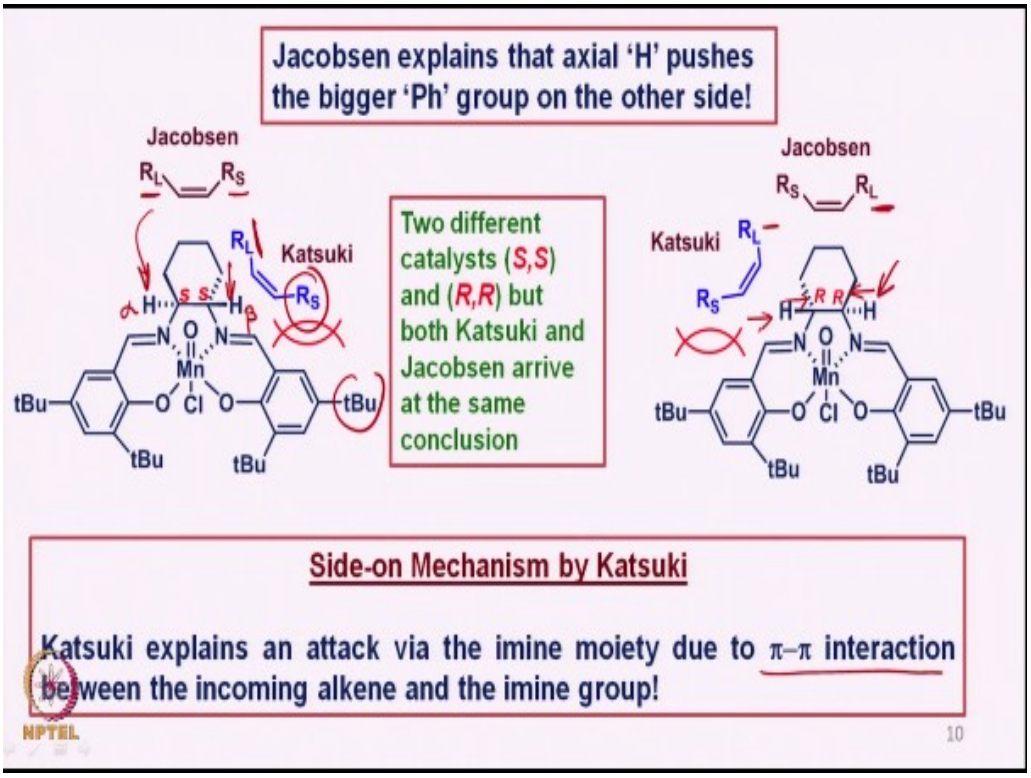

Now what is the explanation for such a reaction? Jacobsen has a slightly different view than the Katsuki, but both of them arrive at the same conclusion. For example, Jacobsen says that as I mentioned earlier that this particular hydrogen which is axially oriented does not allow the R large group that is the larger substituent on the right hand side, therefore the smaller substituent is kept on the right side.

And the large substituent goes on the left hand side to avoid the interaction with this particular hydrogen which is beta oriented here and alpha oriented here. On the other hand Katsuki says that the approach of the olefin is towards the imine so that there is a pi-pi interaction. And pi-pi interaction is such that, that allows the olefin to be closer to the oxo complex.

But during the process what is seen that the large tertiary butyl group here is kind of repels the larger substituent on the other side like this. So eventually this the result of the epoxidation is the same irrespective of which way one looks at it, whether it is through the pi-pi interaction of the olefin and the imine or is it because of the double bond trying to avoid the axial hydrogen of the cyclohexyl 1,2-diamine.

It gives the same epoxidation. And as you can see that with S,S this is what the situation is and with R,R complexes we see that the R L group the large group in both the cases Jacobsen as well as Katsuki case avoids the hydrogen and orients to the right hand side.

That means wherever there is a hydrogen which is not axial towards that side the large group goes and the smaller group goes on the side when there is a hydrogen which is axially oriented. So we will stop it at this stage today and look at other aspects of this Katsuki-Jacobsen epoxidation in our next class. Till then you can work through this whatever I have told and bye and thank you for today's class.