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

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## Lecture - 35

## Sharpless Asymmetric Epoxidation: Mechanism, Stereochemistry and Kinetic Resolution

Hello everyone. Welcome to today’s lecture. We will briefly look at the various aspects of asymmetric synthesis or asymmetric reactions that we started in the last class. What I introduced was the importance of optically active molecules or the chiral molecules.

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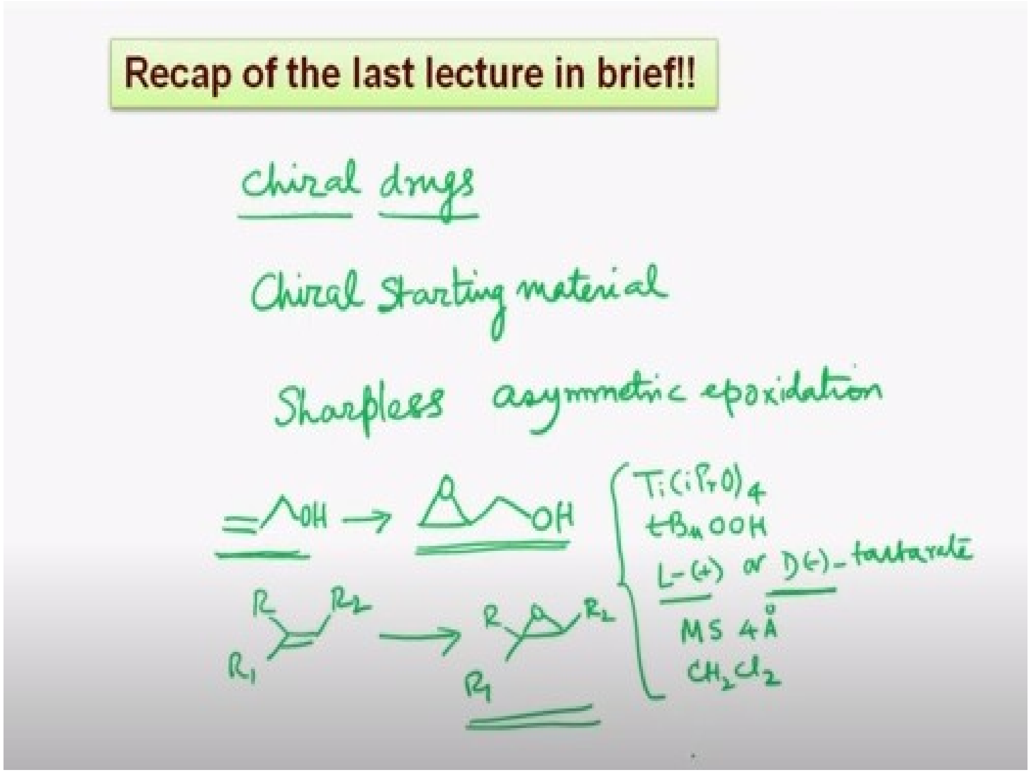

Recap of the last lecture in brief!!

Chiral drugs

Chiral Starting material

Sharpless asymmetric epoxidation

$Ti(iPrO)_4$
$tBuOOH$
L-(+) or D(-)-tartarate
MS 4Å
$CH_2Cl_2$

Because of the importance in our biological systems, the chiral drugs are important to obtain. In a similar fashion I also mentioned that some molecules could have a different odour or different smell. So that also depends on the enantiomer or the enantiomeric purity of the molecule. Then, we saw how the various aspects of asymmetric synthesis needed to be developed in order to get chiral molecules in a synthesis.

As I have discussed that as soon as possible the first possibility, at the first possibility a chiral starting material should be available at the beginning of the synthesis, so that the possibility of diastereo mixtures are reduced. And then, we went further to see how the three people got the Nobel Prize, the William Knowles, Ryoji Noyori and Sharpless.

These are the people who shared the 2001 Nobel Prize in Chemistry for their work in asymmetric synthesis. And towards the end, we started discussing Sharpless based asymmetric epoxidation.

And as I mentioned last time that these epoxides are very important because once we have a very pure epoxide in this particular case, an example of this type was taken, which was from the prochiral allylic alcohol.

So as I mentioned, that in the case of Sharpless based asymmetric epoxidation has to be done from an allyl alcohol. It is not possible to do this epoxidation of an olefin of this kind, for example of this kind, which does not have an allyl alcohol function. So epoxidation of this, it cannot be done by the conditions developed by Sharpless.

For that, we will see later on, there are other epoxidations, there are other assymetric epoxidation. For the time being, we will look at how this Sharpless based epoxidation of allylic alcohols to epoxy alcohols occurs. And we also looked at it that we can use a combination of reagents in which a titanium isopropoxide is used as a reagent. Then tertiary-butylhydroperoxide is used as another reagent.

Then you have L+ or D- tartarate basically. It is a diethyl tartarate, it is an ester. So this is what is the most important aspect. Of course, we have to use molecular sieves, which are 4 angstrom molecular sieves and some solvent like dichloromethane or such solvent. So this is the protocol which is used for the asymmetric epoxidation. All these things are required to be done and this reaction has to be done in a dry medium in the sense that it should be moisture free. Now how this reaction is done?

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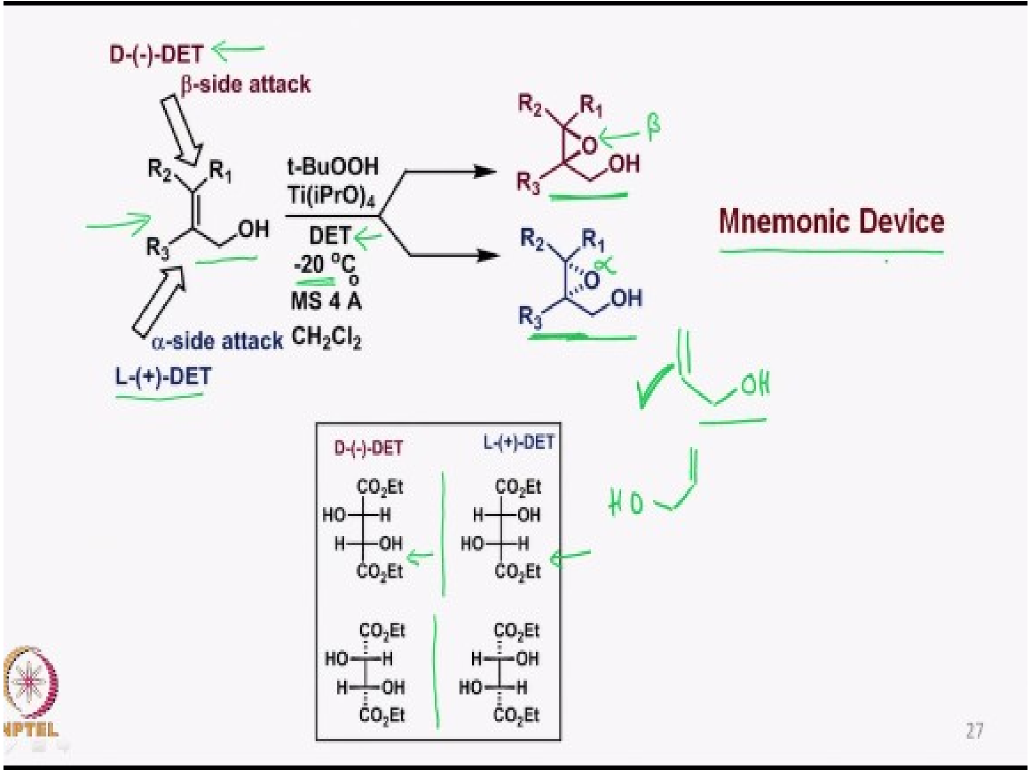

So if we have an allylic alcohol of this type here, where there are four substituents on the double bond, and one of which is CH2OH. So we are starting with a double bond like this and we are writing the allylic alcohol part like this. So there is something called a mnemonic device or device in which you can predict the possibility of which side of the double bond the epoxide will form.

So if the allylic alcohol is kept on the piece of paper, for example we draw in such a fashion that the CH2OH is on the lower side of the double bond and on the right hand side, not like this. So this is the way we have to orient on a piece of paper, the structure of the allylic alcohol that we are considering. So this is how it is shown here.

So if we have an allylic alcohol with a double bond like this and OH with the appropriate substituents and if we orient it in such a fashion, then if we use L+ DET then the epoxidation occurs from the lower side that is alpha side. This is the alpha oriented epoxide. That means, the oxygen comes to the double bond from the alpha side or from the lower side.

But if we take D- diethyl tartarate, then the epoxidation takes place from the beta side and the product that is formed looks like this. So these are basically the enantiomers of each other. If you look at the structure of L+ DET, this is what is the L+ DET and this is D- DET. We can also write the same, this is the Fischer projection and this is of course, the three dimensional structure like this.

So these are obviously the enantiomers of each other. And that is the reason why the products that are formed are enantiomeric in the nature. So what Sharpless has actually carried out is the oxidation at say -20 degrees and whichever diethyl tartarate that is taken, it can give either of the two enantiomers as the major product.

And this is what the mnemonic device allows you to essentially predict the stereochemistry of the epoxy alcohol before you actually carry out the reaction. That is very, very important part of the asymmetric epoxidation developed by Sharpless.
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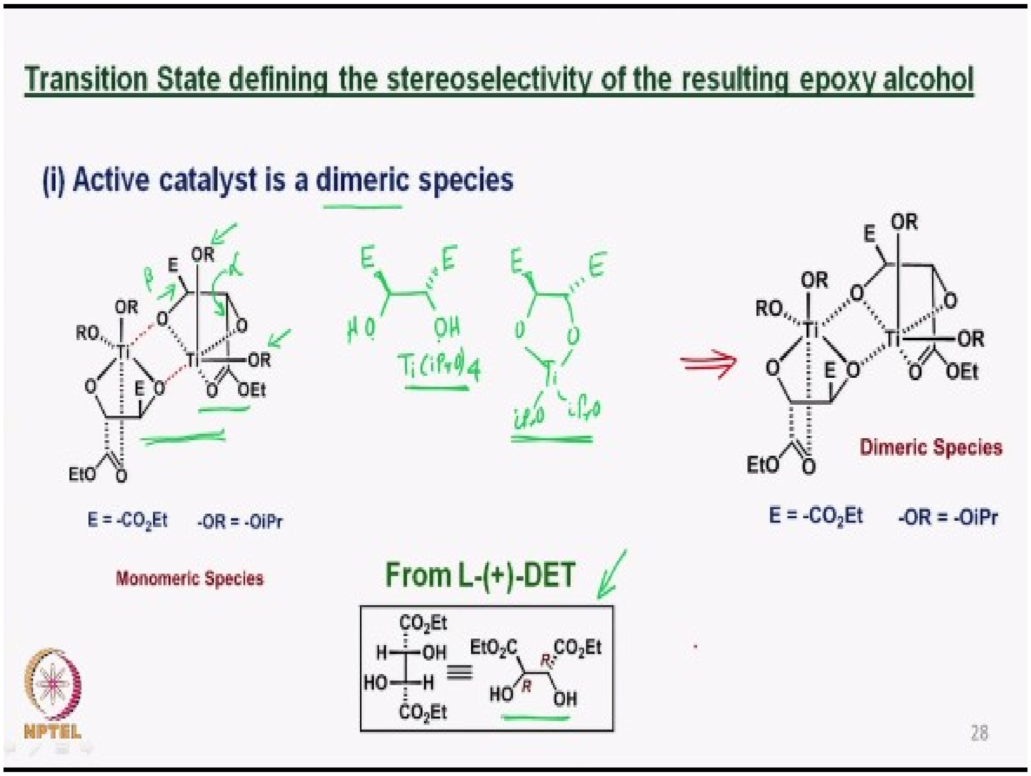

Transition State defining the stereoselectivity of the resulting epoxy alcohol

(i) Active catalyst is a dimeric species

$E = -CO_2Et$   $-OR = -OiPr$

Monomeric Species

Dimeric Species

$E = -CO_2Et$   $-OR = -OiPr$

From L-(+)-DET

Now the transition state which defines the stereo selectivity of the resulting epoxy alcohol is something that we need to really look at it. If we take say for example, if we look at the diethyl tartarate, which I have shown it here, we can write it in this particular fashion, the same molecule. And if we see that you have ester group as E, written as E, then of course we can write it that we have something like this.

We have OH here, and then we have an OH here. And this is beta. So the other epoxy ester path of the diethyl tartarate would have an ester like this. And this is exactly what is shown here. And when this comes in contact with titanium isopropoxide, then you have four of the groups attached to the titanium.

And then we can expect that two of the isopropoxy moieties are lost when these two hydroxy groups react with it. And of course, we can expect something like this to form where we have now titanium and you have an isopropoxide and you have isopropoxide here. It should be through the oxygen of course. So this is how it is shown in here.

So we have the ester group, on the left hand side, which is a beta. And then this is the ester, which is at the alpha side, which is pointing below. So this is alpha and this is beta. And then of course, you have the isopropoxide parts coming in here and the ester group and the could have a chelation with the titanium. And what is found is that the species which is a real catalyst is a dimeric in the nature.

And therefore, we can have to the similar molecules are aligned in this particular fashion. And they will have kind of chelation, something of this kind. We have here, chelation of this type and the dimeric species can form, which is what is shown here. Now this is the first dimeric species, which is actually there is enough evidence to see that such a dimeric species is present during the reaction.

Actually it is this one which allows the reaction to proceed. How does a reaction take place?
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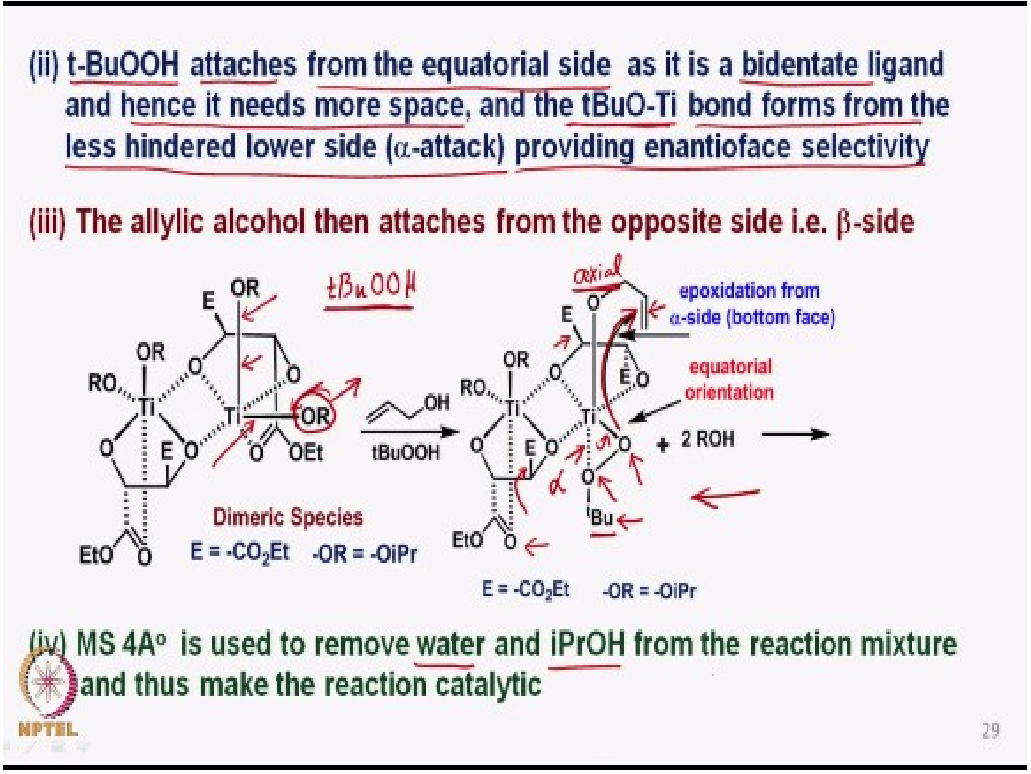

(ii) t-BuOOH attaches from the equatorial side as it is a bidentate ligand and hence it needs more space, and the tBuO-Ti bond forms from the less hindered lower side (α-attack) providing enantioface selectivity

(iii) The allylic alcohol then attaches from the opposite side i.e. β-side

(iv) MS 4A° is used to remove water and iPrOH from the reaction mixture and thus make the reaction catalytic

Now what happens is that, we have this dimeric species to which the tertiary-butylhydroperoxide, now tertiary-butylhydroperoxide as we can expect that you have here tertiary butyl group, which is a large group and of course, you have the corresponding hydroperoxide part. Then this dimeric species in which this is a isopropoxide and this is also isopropoxide. And the tertiary-butylhydroperoxide as you can see is here.

The tertiary-butylhydroperoxide attaches from the equatorial side. Now this is the equatorial side and this is the axial side basically. As it is a bidentate ligand, it is a bidentate ligand as you can see it here. So this is the tertiary-butylhydroperoxide part and this is the tertiary butyl group.

So the one of the OR groups one of the isopropoxy group is replaced when the tertiary-butylhydroperoxide attaches from the equatorial side and replaces this particular isopropoxide group off and gets attached and of course, the oxygen tertiary butyl bond is something that is very important to look at it.

So when tertiary-butylhydroperoxide attaches from the equatorial side it needs actually more space because tertiary-butylhydroperoxide is large in size and therefore, it does not go to the axial side, but it goes to the equatorial side and that is the reason why this attachment of the tertiary-butylhydroperoxide takes place in such a way to avoid the steric hindrance.

Once that has attached then there is a possibility of attachment of the second oxygen either from the lower side or from the top side. And that is where the tertiary-butyltitanium, tertiary-butyloxide-titanium bond forms from the less hindered lower side that is alpha attack providing enantioface selectivity.

That means, once this particular bond is formed the O-tertiary-butyloxy bond here attaches from the lower side, alpha side. That is because this particular ester group is beta oriented. So this particular part does not come from the top, but it comes from the alpha side. And also of course, we have this also being beta.

So it comes from the alpha side where only one of the esters here for example, in the vicinity is alpha oriented. So this orientation of the titanium O-teriary-butyl bond is very important. As you can see that the only other possibility now is left for the allylic alcohol is to attach from the axial side, this is what is the axial side.

And therefore, the alcohol, allylic alcohol path comes in in this particular fashion. And molecular sieves is used basically to remove water and isopropanol from the reaction mixture and thus the reaction is actually catalytic, because the isopropanol sorry isopropanol and water are basically removed continuously by molecular sieves.

So once we have decided that the attachment of the tertiary-butylhydroperoxide and the allylic alcohol takes place in such a fashion that the chirality or the absolute configuration or orientation of the L+ DET in this particular case decides from which direction the titanium-O-tertiarybutyl bond is formed and accordingly the allylic alcohol comes from the opposite side.

So once the allylic alcohol is attached from the axial side, as you can see now the epoxidation on to this double bond takes place from the lower side. That means allylic alcohol path is on the top and the epoxide is here and from the bottom side the epoxidation is essentially taking place.
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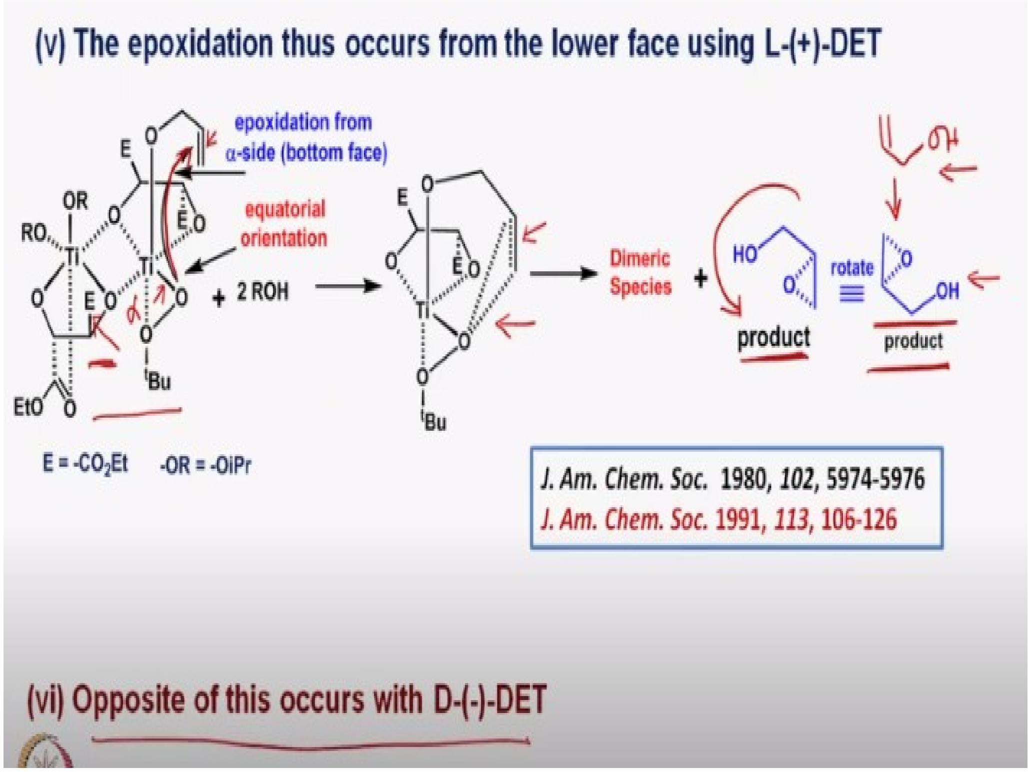

(v) The epoxidation thus occurs from the lower face using L-(+)-DET

E = $-CO_2Et$ -OR = -OiPr

*J. Am. Chem. Soc.* 1980, *102*, 5974-5976
*J. Am. Chem. Soc.* 1991, *113*, 106-126

(vi) Opposite of this occurs with D-(-)-DET

If it takes place from the bottom side what do we get is as you can see here, that in the transition state the double bond is here which is what is here double bond, which is what is shown here and the oxygen is here. That attachment is allowing the epoxidation to take place from the lower side.

So if we orient in this fashion, the parts where this allylic alcohol is epoxide is coming from the lower side and that is how we are writing the epoxide like this. If we rotate it 180 degrees in this fashion, then of course we get this particular product as epoxide. So if we look at the starting material, what we had was the starting material was like this, and we got the product which is like this.

So it is very clear that when we take L+ DET then L+ DET allows the epoxidation to take place in such a fashion that if the allylic alcohol is written in this way, the mnemonic device allows epoxidation to make the product or lead to the product which has such an orientation.

So again once again I want to reemphasize that in the dimeric species, the tertiary butyl group, the tertiary-butylhydroperoxide attaches from the equatorial side and then the attachment of the tertiary-butyl-O bond occurs based on the orientation of the ester group. In this case the ester group is beta and therefore, the attachment takes place on the alpha side.

And this leads to the attachment of the OH of the allylic alcohol from the top and then accordingly the oxygen of the tertiary-butylhydroperoxide is transferred to give the corresponding epoxidation from the alpha side. Exactly opposite of that happens in the case of reactions dealing with D- DET.

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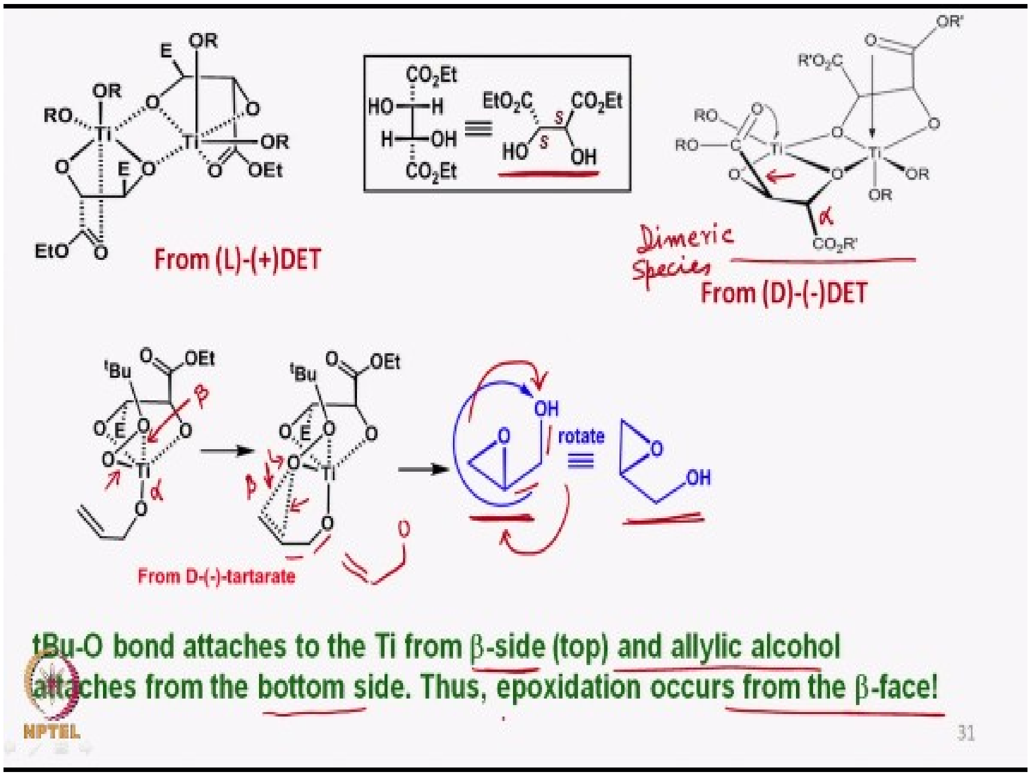

tBu-O bond attaches to the Ti from β-side (top) and allylic alcohol attaches from the bottom side. Thus, epoxidation occurs from the β-face!

For example, if we take the D- DET, the D- DET would look something like this. And very clear that when we have a dimeric species, this is the dimeric species from the D- DET. And as you can see this is pointing actually below, it is going below, alpha oriented, but it is coming towards us below. Whereas, this is going up on the top exactly opposite of what it is here.

And then what happens in such a situation as I have shown it here that the tertiary-butylhydroperoxide again come from the equatorial side, but then because this particular group is alpha, so the attachment of the tertiary-butyl-O bond takes place from the top side, this is the beta side. And since it is coming from the beta side, the allylic alcohol attaches from the alpha side.

So and then the epoxidation takes place in this particular fashion that you have the epoxide forming from the tertiary-butyloxy part and this is basically pointing above the double bond part. So you have O here and the epoxidation is taking place from the beta side. If it is taking place on the beta side and if this is how this part is here, this part is here, then epoxide takes place from the beta side.

We can get the epoxy alcohol like this because this is the epoxide oxygen. Now if we simply rotate it in this fashion, so we will if we rotate it in this fashion as I have shown it here then we get the epoxy alcohol having this configuration. So again the tertiary-butyl-O bond attaches to the titanium from beta side and allylic alcohol attaches from the bottom side that is alpha side as epoxidation occurs from the beta-face.

So you can see how different they are with each other, exactly opposite. We can also look at it in a slightly different way.

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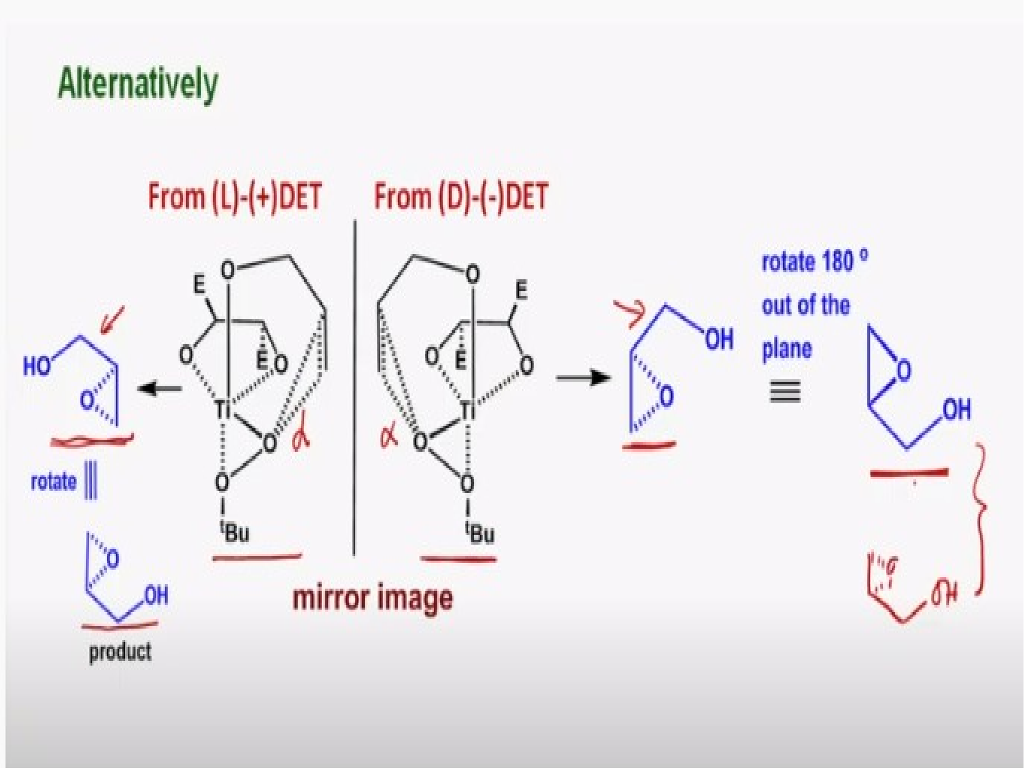

Alternatively, we look at L+ DET. This is the transition state the right part of the transition state or when we did L+ DET and we can imagine that its mirror image would be D- DET. So if we look at it this way, we can this is exactly the opposite of each other. And if this gives a product like this, as we discussed, this is the alpha side and this is also alpha side, but it is a mirror image.

So we can look at this as the product taking place, forming taking place whereas in the case of L+ DET this is the product that is forming. If this is the product, which is what we looked at it last time, last case and then the rotation leads to the product here. On the other hand here now we are looking at the mirror image and of course in the mirror image again the epoxidation is taking place from the lower side also.

But now this is the product which is formed which is exactly opposite of this. They are basically mirror images of each other. And now if we just turn out of the plane, then we get this particular product. So this product and this product basically are enantiomers of each other and they conform to the mnemonic device that we have looked at it in the beginning.

So this is another way of looking at the transition state by simply considering the fact that L+ DET is a mirror image of D- DET. And therefore, the transition state that we are looking at it can also be the mirror image of each other, when we take either L+ DET or D- DET. So in both ways, we can see that the product that is formed is basically an enantiomer of each other.

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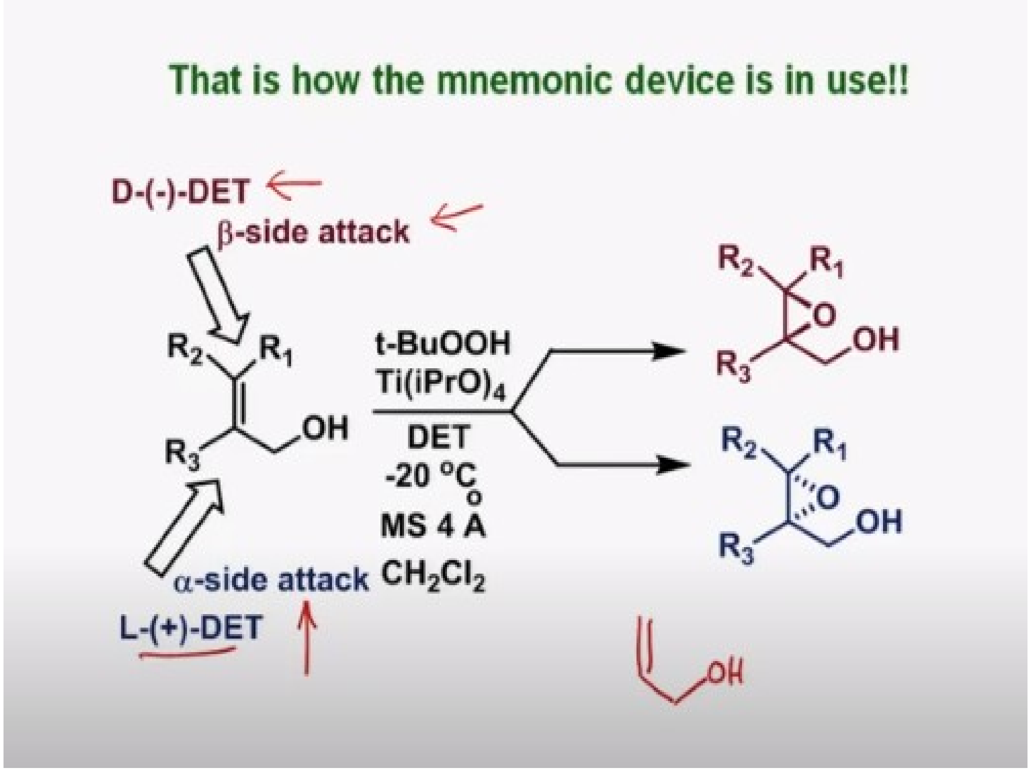
That is how the mnemonic device is in use!!

Now this is something that we looked at it last time from the mnemonic device and now we can very clearly understand that how does this mnemonic device allow the alpha-side attack when L+ DET used and beta-side attack when D- DET used. So we can imagine the orientation of the allylic alcohol in such a way that when the double bond is written on a piece of paper in a vertical fashion, the CH2OH group should be oriented on the right hand lower side.

And then accordingly we can predict the absolute configuration of the epoxy alcohol during this reaction.

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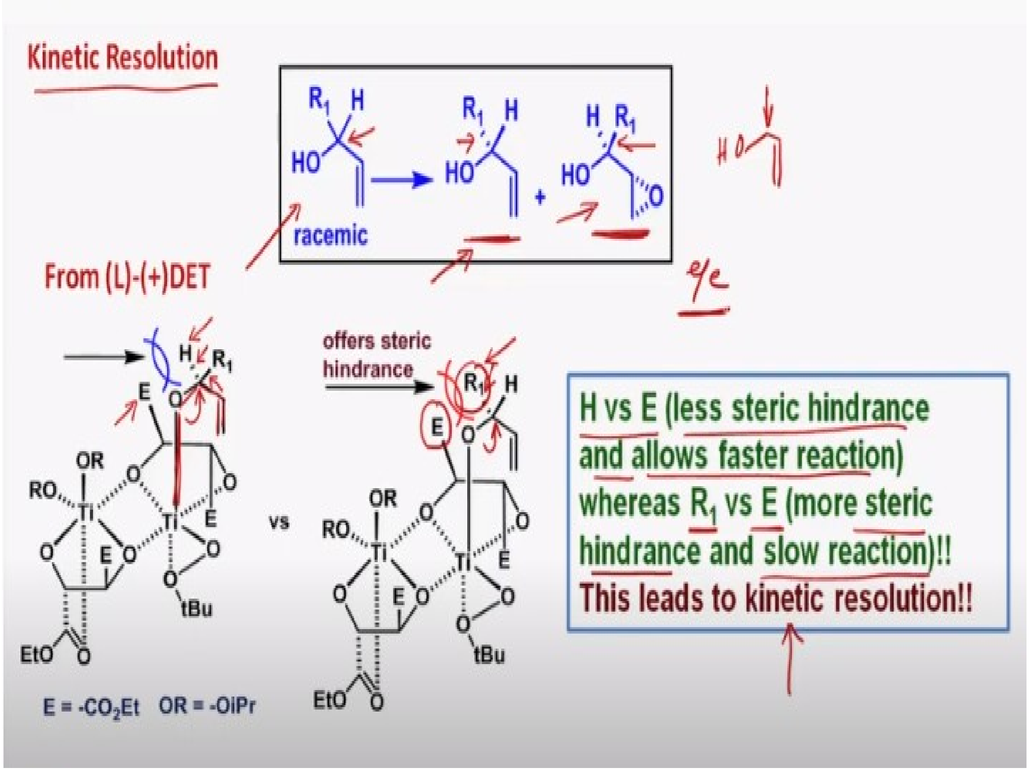

Kinetic Resolution

From (L)-(+)DET

offers steric hindrance

H vs E (less steric hindrance and allows faster reaction) whereas $R_1$ vs E (more steric hindrance and slow reaction)!! This leads to kinetic resolution!!

E = $-CO_2Et$ OR = -OiPr

Now what is the further development in these reactions? We can start the reaction with allylic alcohol, which could be racemic. That means, we need not start all the time alcohol, which is like this, but we can also have a racemic molecule.

So if we have a racemic molecule where there is a particular R 1 group attached and then what happens is out of the two enantiomers of the starting allylic alcohol, one of them reacts faster towards the epoxidizing reagent and gets epoxidized, whereas the other one does not react. Obviously, if we leave the reaction for a very long time, then the reaction will give epoxides from both the enantiomers of the starting allylic alcohol.

That is the reason why this is called as kinetic resolution. That means, one of the two enantiomers of this starting allylic alcohol reacts faster. Now how does this reaction happen and why is it so that when the R 1 group is beta oriented, the epoxidation takes place. When R 1 is alpha oriented epoxidation is slow. Like if we look at the transition state with L+ DET here, so we can orient the racemic the asymmetric center of the allylic alcohol in these two fashions.

That means, for example, we have the R 1 group as beta here and here we have R 1 group as alpha. So if it is beta that means it is coming towards us. Whereas, this particular entire part of the molecule is this part here contain is all attached to this one. And the hydrogen is going behind and to which this ester group is now having some interaction.

Obviously, this ester group will have less interaction with a small H compared to the interaction of the ester group with the R 1 group. When R 1 is alpha oriented, that means it is going backside and it is facing the ester group we will have more steric hindrance. So it is H versus E. E is ester, which is offering less steric hindrance and therefore faster reaction.

And that is the reason why this epoxide has formed first and then you have R 1 versus ester which is sterically more hindered and it is therefore, it is a slow reaction. And this is how it leads to the kinetic resolution. Interestingly, when this reaction is carried out, we can get almost 100% optically pure epoxide and almost 100% pure optically active allylic alcohol, which is not epoxidized almost like 95, 98% enantiomeric excess that we can expect.

So this is how the kinetic resolution occurs. So we will stop it at this particular stage today. And then next class we will see how the utility of these epoxy alcohols can be done in synthetic transformations. Till then bye and thank you.