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

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Lecture - 46
C-C Bond Formations Using Evans' Oxazolidinone Based Chemistry

Hello everyone, welcome to today's class. I hope that you had the opportunity to go through the last class. And we will briefly look at what we did last time. We started looking at the nomenclature of the syn and anti aldol, which were also called as erythro and threo respectively.
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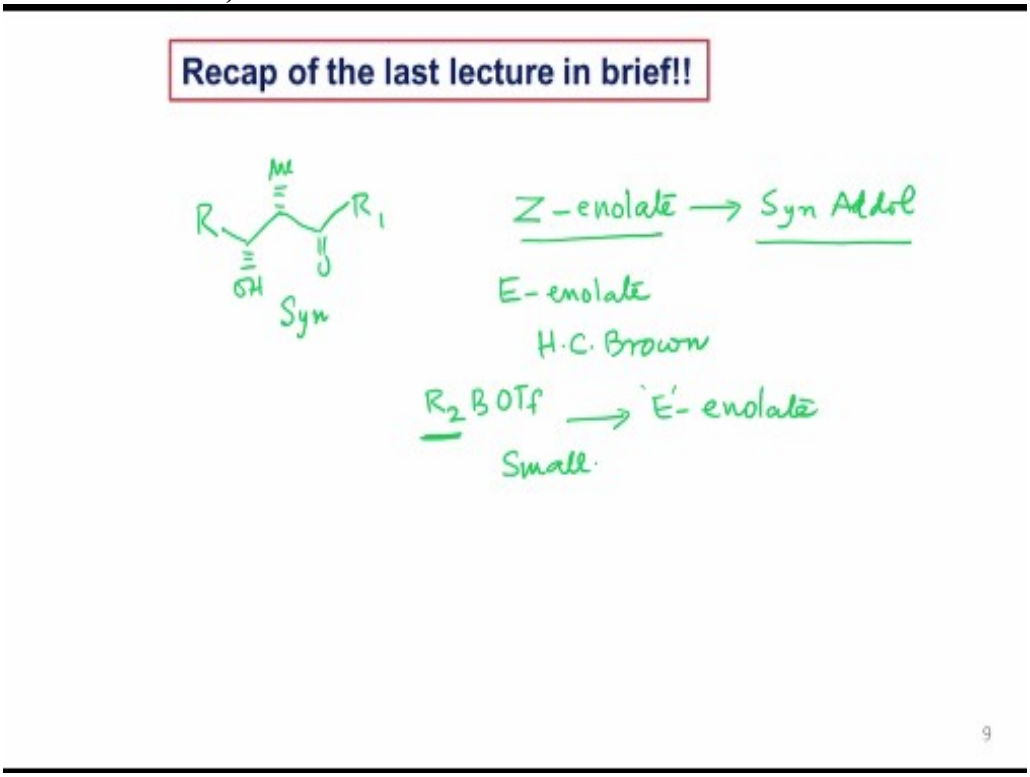

And we saw that if we draw a main carbon chain as zig-zag form and then of course we can then expect that the, once we have this here, then whatever the substituents are here, for example here methyl hydroxy or methyl in this direction, therefore we can anticipate and say that okay, this is a syn aldol. And likewise anti aldol. And of course these are called as erythro or the other one is called as a threo; that we looked at it.

Then we also saw that how Z enolate can give high selectivity in terms of syn aldol. We took all the four cases and we saw how the large ratio of the syn aldol is likely to form when we start with the Z enolate. Then we also looked at the various features that are needed for obtaining Z enolate. And we saw that the formation of the Z enolate is much better, much easier.

And also the formation of the corresponding syn aldol from Z enolate is also very much easy. Then this was the work that David Evans has reported. And so then the work related to the

formation of the E enolate was also taken up by other people and especially H C. Brown and as we saw that it depends on the size of the substituents. Say you have here R2 groups that is two R groups attached to boron and O triflate.

If this are to R group, which is two substituents has R, they are large in size, and then they allow the E enolate to form in case we use a small base. And the small base as we discussed forms irreversible complex with the boron. And therefore, it allows the formation of the E enolate. We discussed the transition state part.

And in the case of Z enolate, what we have also seen that if the base is very large then the base, like such as this Hunig's base, diisopropylethylamine, and such a base then allows the formation of the reversible complex with the boron and therefore that leads to the formation of the Z enolate as the major product. And based on these Z enolate and E enolates that we can anticipate to form syn and anti aldol products to form.

So now we will look at what are the other auxiliaries that are required to get highly enantioselective reaction. So far we were talking about the racemic products where there is a possibility of getting different types of products in terms of their syn or anti aldol. But now we will also look at how the enantioselective reactions can be done with which kind of chiral enolates.

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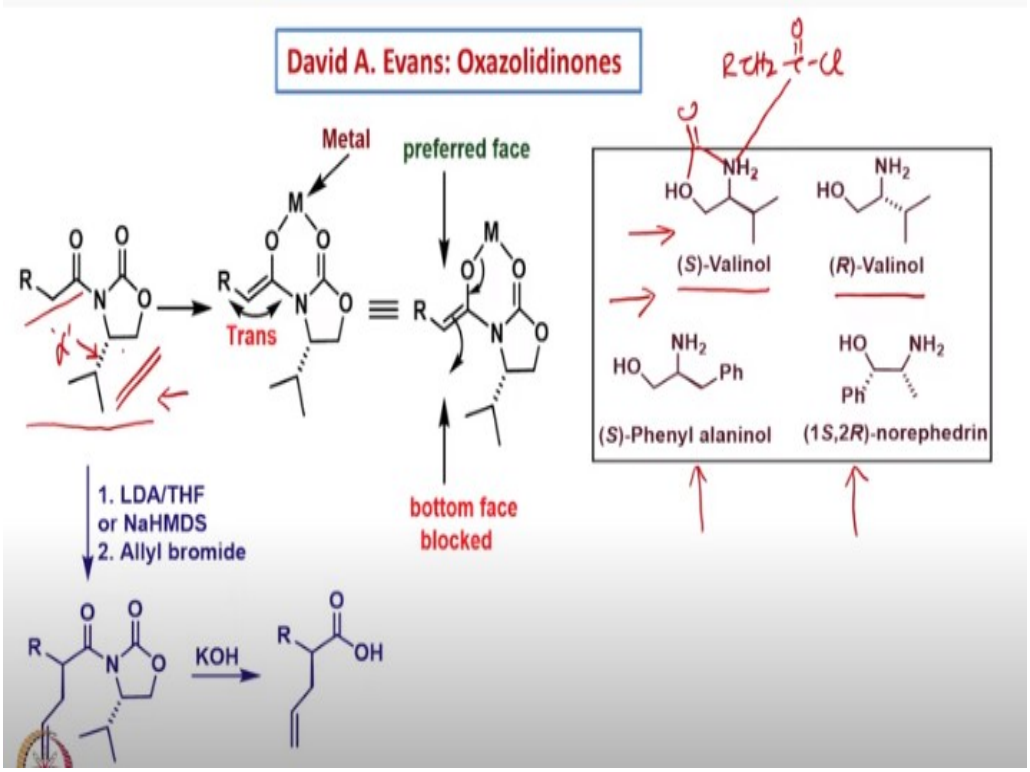

So as I have repeatedly been telling that David Evans name and David Evans of course has introduced this oxazolidinones, which we have earlier also considered.

So now what we have is if we take a ketone and take a compound such as this in which the this particular part is attached to the auxiliary that is made from some of these amino acids, if you

start with (S)-Valinol or (R)-Valinol, then as you can see from here this particular auxiliary which is shown here is prepared from this particular (S)-Valinol.

And if we convert this particular oxygen and nitrogen and make it as a carbon a group here then of course we get a auxiliary like this and from the nitrogen you can then attach with the help of say suppose if we have R-CH_2-COCl and if we have NH here, we deprotonate, then we can make a bond between the two of them. And that is what would lead to if we just turn it around this is what is the product that is going to form.

So this comes from (S)-Valinol. Likewise if we take (R)-Valinol then this will be beta. Right now this is alpha oriented, it can be beta oriented if we take from (R)-Valinol. And of course, we can use many of these kinds of chiral auxiliaries to make different types of oxazolidinones like this where the substituents here would be fixed in terms of their configuration.

So this is how these various kinds of chiral auxiliaries from different amino acids have been reported. And of course, this is norephedrine and the corresponding oxazolidinones can form. So let us see what can we do with it.

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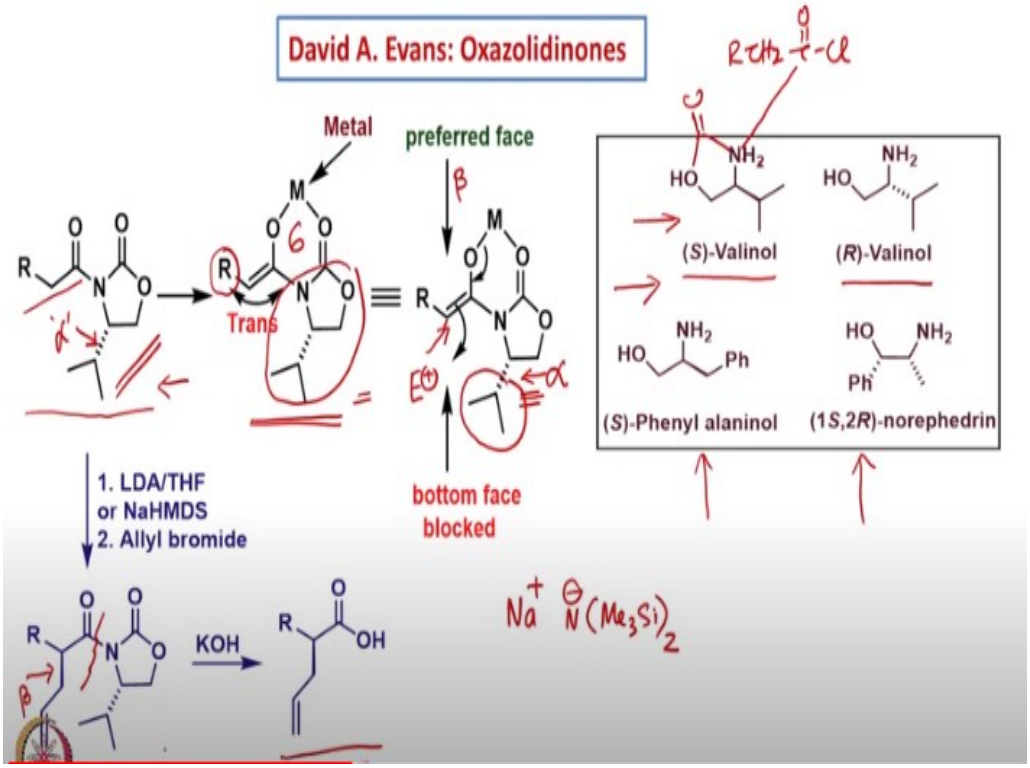

Now as you can see here, that when such a compound is deprotonated we expect this type of intermediate to form. The reason for that is it forms a six member chelate with the metal. And once that happens, as you can see here, the R group here the R group and the large auxiliary here are basically trans oriented to each other. So we can expect that actually this and this is the same essentially, there is no difference.

And when the group attaches to the any electrophile is reacted with this enolate, thus we can see that since this large isopropyl group is alpha oriented, then the incoming electrophile which is

going to attach on to this particular carbon atom, because this has to break, this particular oxygen metal bond will break and this enolate will then be having a nucleophilic center on this particular carbon atom.

This nucleophilic center will then react with an electrophile, which is an electrophile here and of course you will get the product. It can also go onto the other side that is on the top. Basically what it means that when the enolate is going to react with the electrophile it would like to be oriented away from this particular large isopropanol group. Since isopropyl group is alpha oriented, therefore the attachment will take place from the beta side.

So for example, if we take this particular compound and react with LDA in the presence of THF or sodium hexamethyldisilazide. So basically it is sodium plus hexamethyldisilazane. You have N- and $(Me_3Si)_2$. So it is hexamethyldisilazide and then when that reacts with allyl bromide, you see now that gives a beta orientation of the allyl group.

And then we can hydrolyze it with the base and therefore the hydrolysis takes place here and we get the corresponding acid in a very high enantioselectively pure product. Of course then auxiliary comes out and you can recycle the auxiliary. So this is how the enolate reacts with an electrophile in an alkylation fashion.

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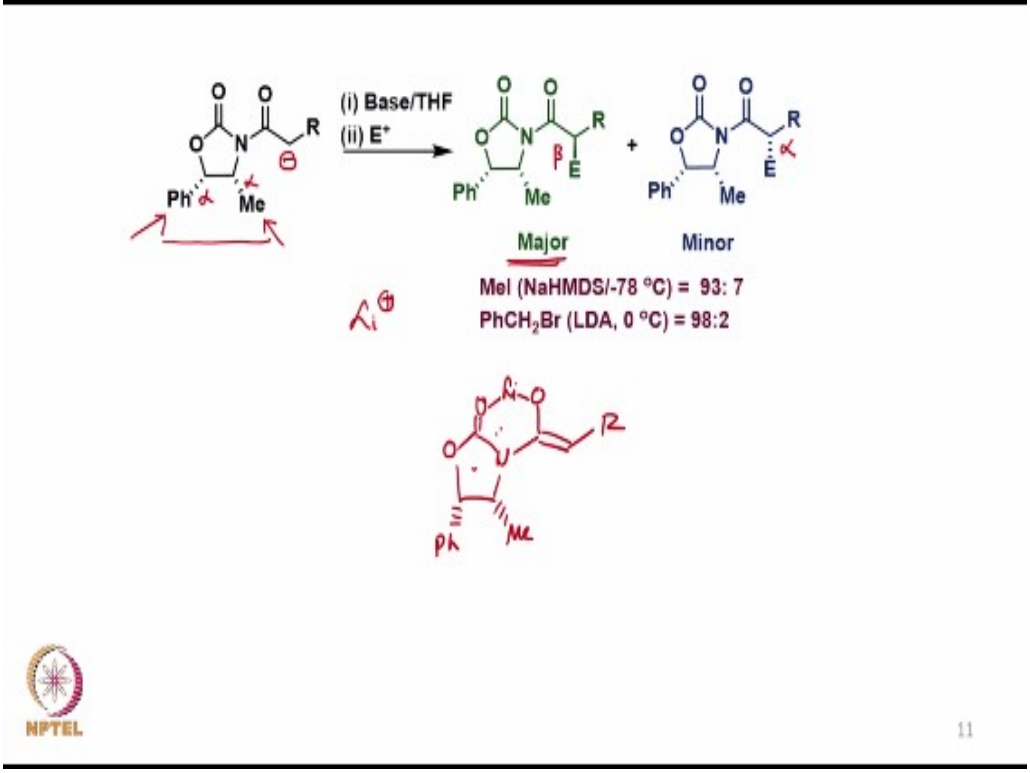

If we take for example, this type of auxiliary here like this, in which phenyl as well as the methyl, both of them are alpha oriented. This is even better, because now you have two big larger groups oriented in alpha fashion. Therefore, if we do the deprotonation here and react with an electrophile the major product will form here like this, because these two are alpha oriented.

Therefore, the electrophile comes from the beta side and this is the alpha side. So as you can see here that under two different conditions, the selectivity is 93:7, 98:2. Normally the lithium salts are better because when this forms this kind of enolate when we have auxiliary like this and the enolate that is going to form would be better in terms of chelation when it is lithium than when it is potassium or sodium.

And therefore, that reflects also because this bicyclic enolate has a better effect in terms of selectivity, because then there is no rotation around here. But if this particular chelate formation is somewhat loose, then there is a rotation around here and then that can lead to the E enolate to form and that will lead to less selectivity. That is why this particular selectivity as you can see, one is 98:2, other is 93:7.

Therefore, generally as we have seen, lithium and boron enolates are better in terms of achieving better selectivity. Now we look at the chiral aldol reaction. We saw so far chiral reactions, but that was alkylation reaction. Now this is a little bit chiral aldol reaction, is somewhat complex. Then we will have to look at it very carefully.

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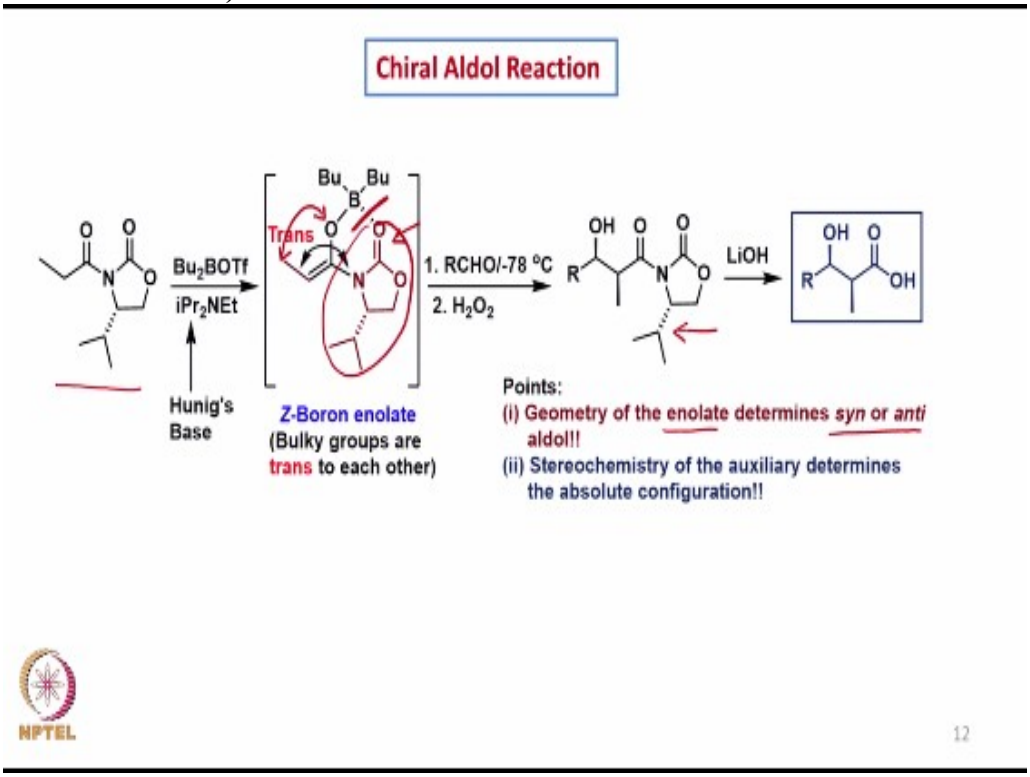

So the same way as we did it in the earlier case, if we start with this particular product, which is formed from the oxazolidinone auxiliary in which isopropyl group is alpha oriented. Now you react this with now the Hunig's base diisopropylethylamine and Bu_2BOTf. We discussed how this can lead to the formation of Z enolate. So now what we have here is this is Z enolate and in which the methyl group and the auxiliary are of course trans to each other.

Now once this Z enolate is formed, there is a better chelation between boron and oxygen just the way as we saw in the case of lithium. And therefore, this is a bicyclic enolate where everything is

pre-fixed. Now here as you can see that the Z boron enolate, which has a bicyclic structure involves the boron and the oxygen of the auxiliary in chelation.

Therefore, the boron enolate and the auxiliary itself has a chelation in it. But when the aldehyde comes into the reaction mixture, when it is dropped into the reaction mixture at low temperature of -78 degrees, then further reaction to occur to give aldol product there has to be a chelation between boron and the aldehyde oxygen. And therefore this particular chelation has to break down.

So it is very important that how does this the chelation break and how does the new chelation occur? That becomes a very important part. So now it is something that we already know that the geometry of the enolate determines whether syn or anti aldol is going to form. And of course, as we have seen that Z enolate will give syn aldol and E enolate will give anti aldol.

And stereochemistry of the auxiliary, that means here this particular auxiliary, the absolute configuration of the auxiliary would also determine the absolute configuration of the aldol products.

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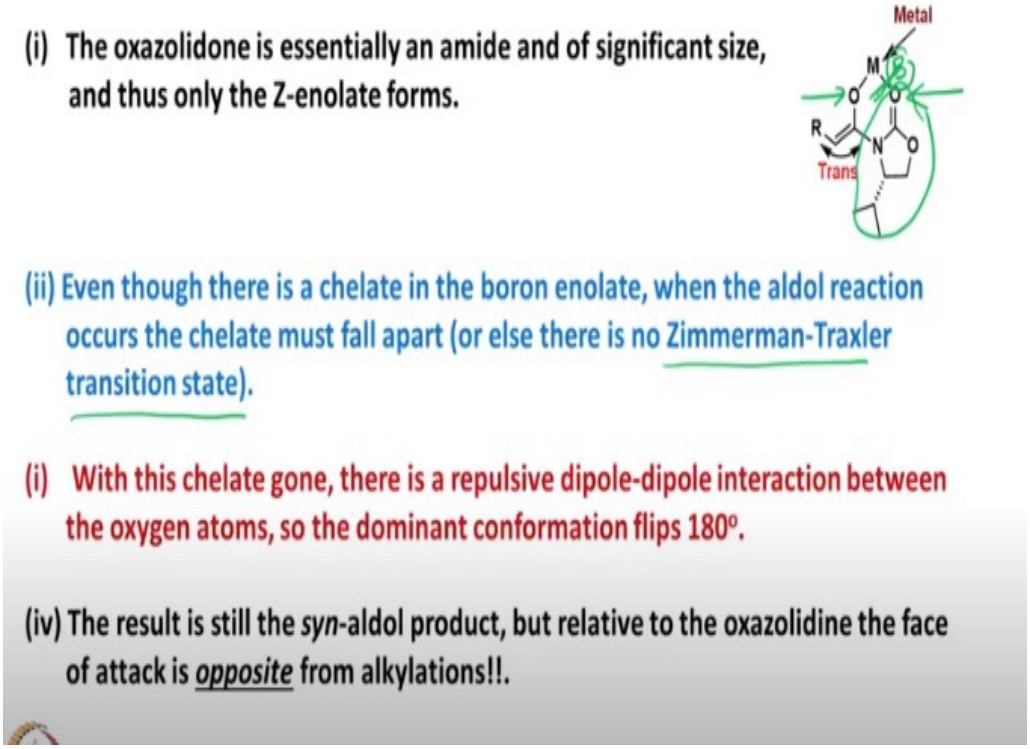

Now we look at the oxazolidinone, basically is an amide, and this particular part is essentially a carbamate and it is a very large size and therefore, the Z enolate formation occurs preferentially. Even though there is a chelate in the boron enolate, like this is what is the boron enolate, this is the boron where the metal is, the aldol reaction will occur when the chelate forms and breaks.

Otherwise, there will be no Zimmerman-Traxler transition state, something that we will discuss soon. With this chelate gone with the chelate that we saw it up with the enolate and the auxiliary, there is a repulsive dipole-dipole interaction.

Like for example, once this breaks, then there will be repulsive dipole-dipole interaction between the oxygen atoms because this oxygen atom and this oxygen atom there will be once this is broken from here, then we will see how these have dipole-dipole repulsion and that allows the confirmation to flip by 180 degrees.

The result is still the syn-aldol product, but relative to the oxazolidinone the face of attack is opposite when we were doing alkylations. So you will see that how does that happen. So this is how it is.

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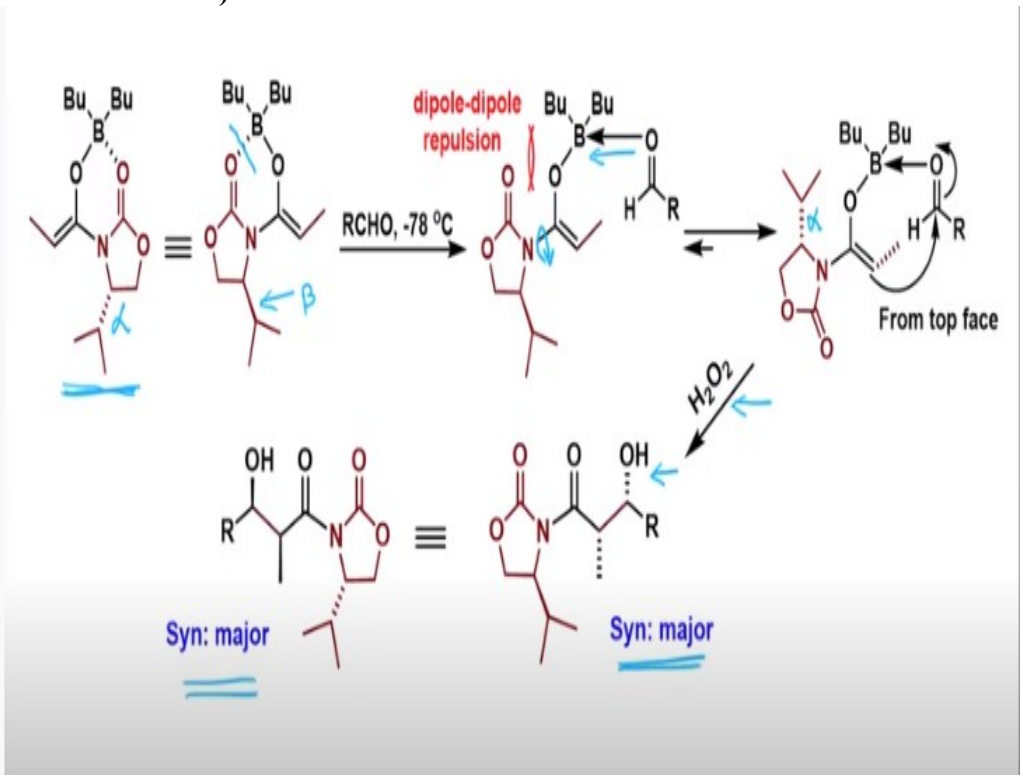

So we can write something like this here. As you can see, we can write the oxazolidinone with alpha oriented isopropyl group. We can turn around 180 degrees and make it look like this also. Therefore, now it is beta oriented. We have not broken the bond but we have simply changed 180 degrees. Now when this comes in contact with the aldehyde here, now this particular oxygen boron chelation breaks and then what happens is of course, there is a dipole-dipole repulsion.

Here there is an delta negative, here there is an delta negative and therefore the orientation has a dipole repulsion. And this turns around, there is a rotation around here, here to form this so that the carbonyl group comes down. So now this enolate is the dipole is here whereas this dipole is here, therefore there is no interaction between the two of them.

In this situation now the ketone has a chelation with the boron here and at this situation the attack since this is alpha oriented and therefore the attack occurs from the beta face from the top face and the enolate reacts with the aldehyde with a with the concomitant chelation and the C-C bond formation takes place from the beta face.

And that happens then of course the boron will be transferred to the oxygen and this oxygen boron bond is now broken by the oxidation with hydrogen peroxide. And then of course, the boron is released, taken out of the system and oxygen comes out in the form of OH and is released as the corresponding aldol. Of course, we can write the same thing in a different form by just turning around by 180 degrees.

So this is how the syn diol is formed as the major product. Now we can look at this in a slightly different way from the conformational angle. So we can look at the Zimmerman-Traxler transition state.

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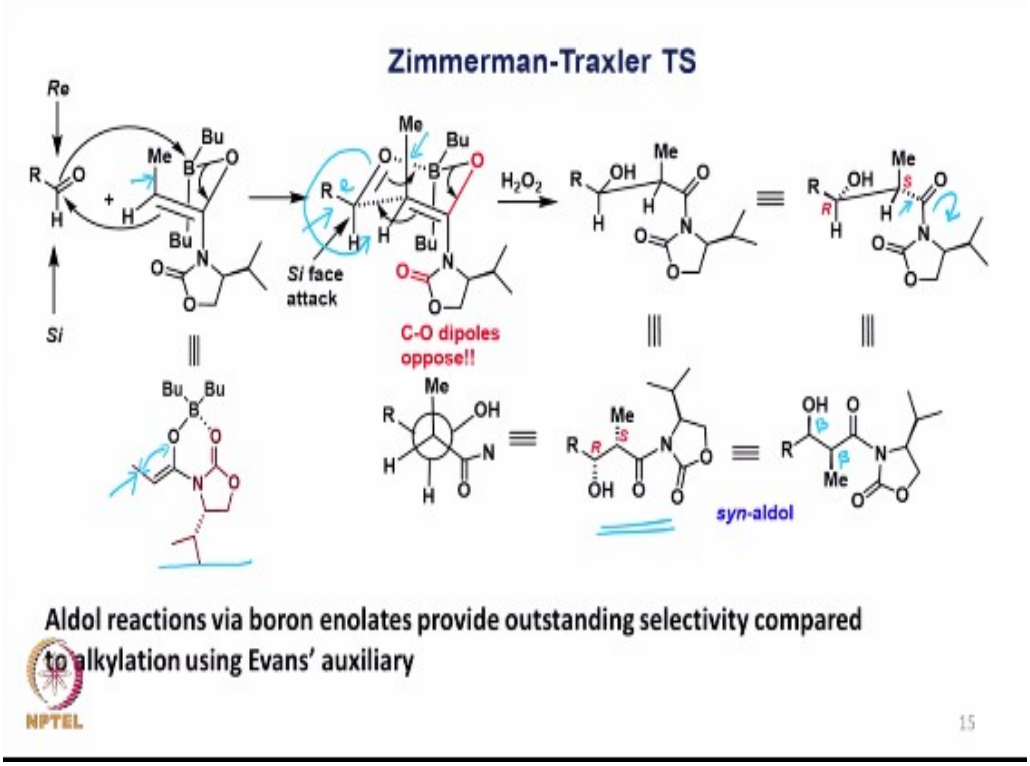

For example if we look at, this is how we started, this is the product that this is the enolate that we started. The same enolate can be written up in this particular fashion, where as you can see that the methyl group here is the methyl group here, double bond is here. Then the enolate and the methyl group are in the same direction as you can see here, they are in the same direction here.

And then when the aldehyde comes into the contact with the boron then it has of course the R group will remain in the equatorial form as we saw in the last time how the two possibilities of aldehyde in the transition state, it can be either axial or equatorial, but the axial one is sterically more hindered. Therefore, it prefers to be equatorial here. There are again two choices that you have to see.

Which direction the attack will occur from as we say that it will attack from the top side, that is si side or the re face, si face or the re face. As you can see here the oxygen will have a chelation with the boron and therefore this chelation will be somewhat like this. If this happens, the R group is equatorially oriented and therefore the enolate will attack from the top side which is

what is si face because you have this is the oxygen of the aldehyde, this is the R and this is hydrogen.

Therefore we have a anti-clockwise rotation of this particular face and therefore this is the si face where the enolate is going to attack. Once the attack takes place R comes into this particular form, OH comes from here, of course after the hydrogen peroxide reaction. C-C bond formation takes place. Methyl is here axial. Hydrogen is equatorial.

And of course, we get the auxiliary attached to the carbonyl group there which we can also write something like this that the hydroxy group is going behind and the R group is coming towards us and the hydrogen is in the plane of the blackboard or this particular board and then of course, we have a methyl group in the plane, hydrogen is coming towards us and this particular bond is going behind.

And the same thing can be written up in this way. You can see that, that for example if we turn the R group which is beta oriented, bring it to the into the plane of the board below, then the hydroxy group will go up and therefore, it is beta. And similarly, for example if we bring the methyl group down this side, then this particular broken bond here, which is alpha bond goes into the plane.

If it goes into the plane that means it is coming towards, if we just rotate it around here like this, then it comes into the plane towards us. In that situation, the methyl group will of course come down and then that is why it is looking like a beta oriented here. So basically it is a syn aldol and we can also write the same syn aldol like this. So this is the way the syn aldol forms and the syn aldol forms.

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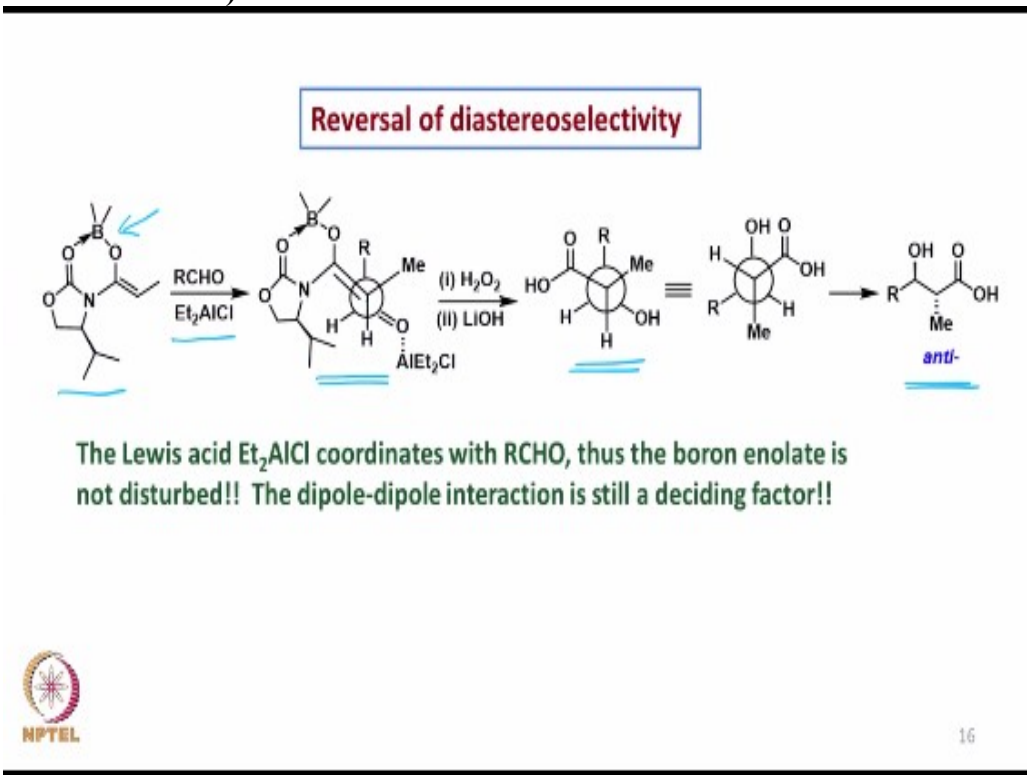

Now we look at the reversal of diastereoselectivity. Now how do we get the anti aldol? If we have to get the anti aldol, how do we get it? Now what has been done that if we start with say for example this type of enol boron enolate and react with aldehyde. Now if we add extra Lewis acid such as diethylaluminum chloride, then what happens is that this particular chelation does not break.

And the aldehyde comes in to contact with this enolate in this particular fashion, because the aldehyde oxygen has this extra Lewis acid interacting with its oxygen. That means the aldehyde oxygen interacts with this. So it does not have any need to go and break the boron enolate and then interact with the boron. If that happens, then of course we have such a situation which is coming into the picture.

And when such a situation comes, of course in this case also as we can anticipate that the carbonyl group would be away from this particular enolate, here this particular double bond it would be away to allow the repulsion to be less, the dipole-dipole repulsion. And therefore, the perfect orientation of this group would be somewhat like this where R H and ketone would be oriented in this way.

That is carbonyl group will be oriented in this fashion. When this happens this allows the formation after the hydrogen peroxide and of course hydrolysis of the auxiliary that this particular part will give the acid. The methyl group is here. R is here H is here and OH is here. And this is if we trans can convert into the final orientation it would look like an anti aldol.

So this anti aldol formation is essentially taking place because we have not broken the enolate, the boron enolate and therefore this diethylaluminum as a Lewis acid allows the orientation of the transition state in such a way that we get the anti aldol which is the reversal of the diastereoselectivity. Now we will try and look at the enol silyl ether. That means silyl enolates with having a silyl group.

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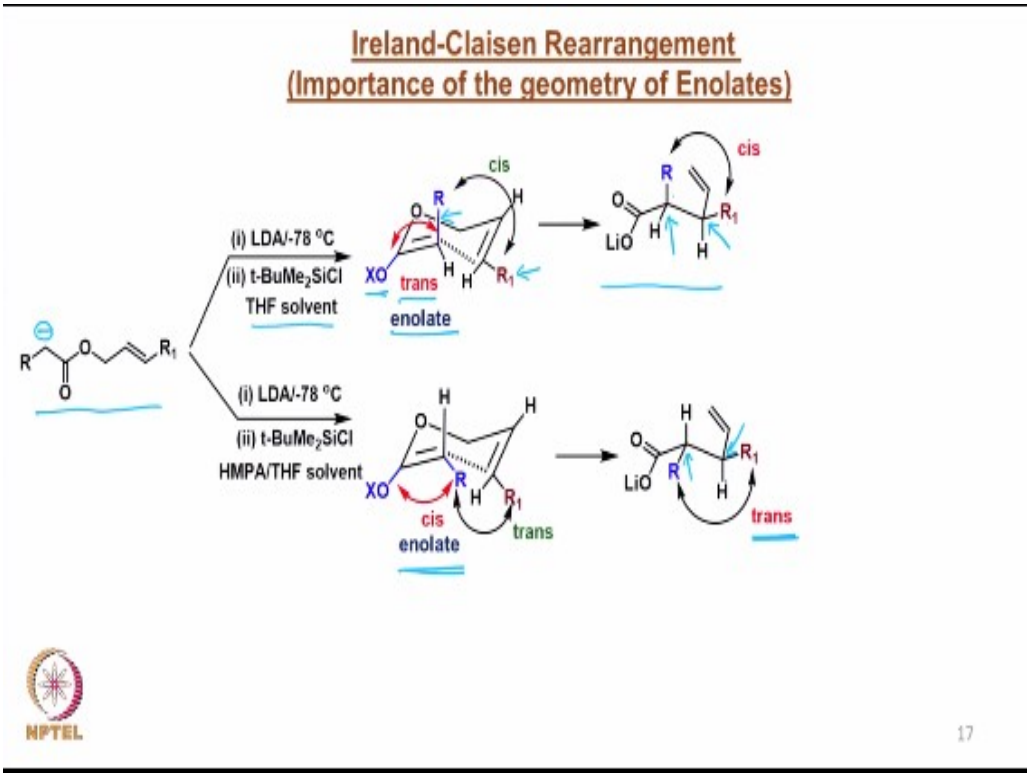

Now in this case, Ireland-Claisen Rearrangement is an important reaction, which depends on the geometry of the enolate. We also saw the geometry of the enolates influencing the formation of the syn product, syn aldol and anti aldol. Of course, there we also saw that the Lewis acid made a difference. But in this particular case if we start with allyl alcohol and its ester, that is allyl ester, where you have a possibility of deprotonation here.

And if the deprotonation is done and the enolate is trapped as a silyl ether or silyl enolate and if the reaction is done at low temperature in the solvent THF, then what is found is that we get this type of enolate of course, but where this OX group and the R group are trans to each other. And here we have in the presence of HMPA and THF as a solvent, the enolate gets changed. It forms OX and the R group.

They are now cis to each other. So this is a cis enolate and this is a trans enolate. Now that allows the formation when the rearrangement takes place, the Claisen rearrangement takes place here, then what happens is that the product that is going to be formed is such where the R1 group here and the R group here are cis to each other. And in this particular case, R group and R1 group are trans to each other.

So this is a basically the process in which two new asymmetric centers are being created here. There is an asymmetric center here and there is an asymmetric center here. So these new asymmetric centers are as a consequence of the formation of the enolate, because this double bond geometry is fixed in both the cases. The only difference is between the geometry of the enolates.

And based on the geometry of the enolates the configuration of the final product is of course determined. Obviously, in these cases we are talking about only the achiral molecules and

therefore, this product will be anyway achiral unless we use chiral auxiliary into it. So we will stop it at this stage to end today's class. You could go ahead and look at what I have talked in this today's class and be prepared for the next class. Till then bye and take care.