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

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Lecture - 47

Ireland-Claisen Rearrangement: Emphasis of Enolate Geometry on the Stereochemical Outcome, and Claisen Rearrangements

Hello everyone, I welcome you all for today's class. We will briefly look at what we discussed last time and then proceed further. In the last class, we saw how the oxazolidinones were used for the formation of Z enolate. And how the Z enolates are then allowed to react with the alkylating species and the oxazolidinones are basically derived from different amino acids.

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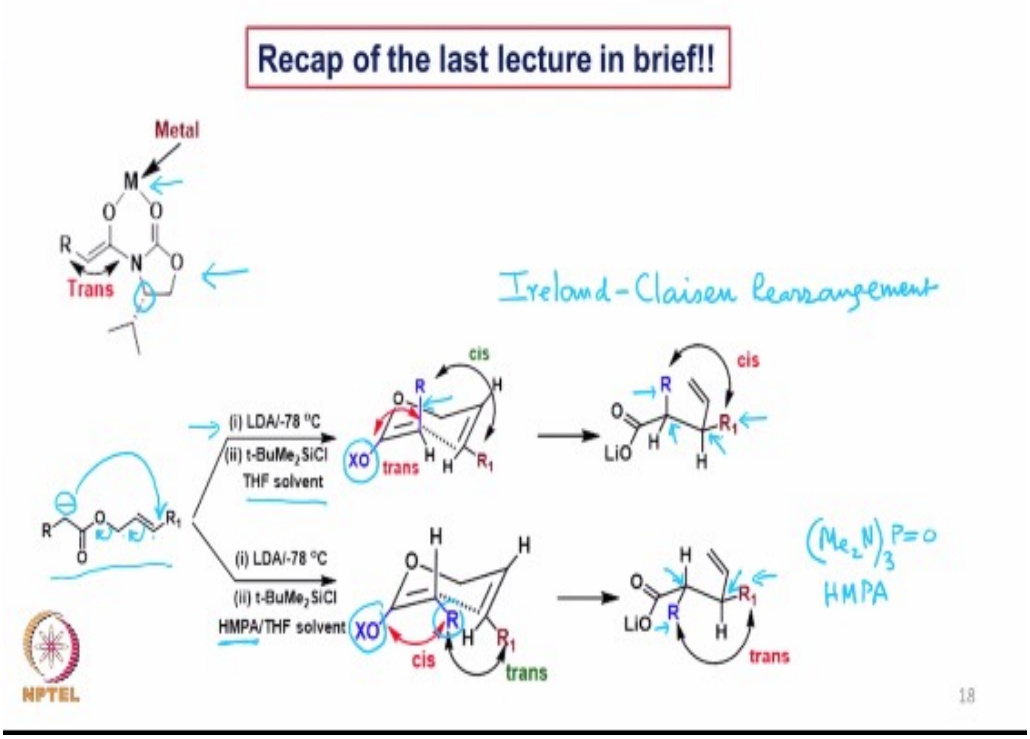

And the configuration of the substituents on the auxiliary such as this for example here propyl group, it determines the orientation of the incoming electrophile when the enolate is reacting with the electrophilic species. And we also saw how the aldol products are formed. In the formation of the aldol product that we saw that the oxygen metal bond which is boron enolate that is metal here is boron, how does that form is kind of intramolecular chelation to make this bicyclic system here.

And when the aldehyde comes in contact with this particular bicyclic enolate chelated species, then the oxygen boron bond breaks and the oxygen of the aldehyde comes in contact with the boron. And therefore, we see that Zimmerman-Traxler transition state and then we see the aldol product formed.

And during that process, we also looked at how the dipoles of this enol part and the oxygen carbon part of the auxiliary they repel each other when the aldehyde forms the chelation with the boron and therefore the orientation goes back. And then that allows the specific orientation of the aldehyde where R group is equatorially oriented followed by then the attack of the enolate from the si face leads to the product formation which is syn aldol.

Now when the syn aldol is formed we had no surprise because that is what was expected. But how do we get an anti aldol? For the anti aldol formation, we saw that if we use extra Lewis acid, then that extra Lewis acid does not allow the aldehyde to kind of break the enolate of the boron and so chelation remains intact as it is here.

And then the Lewis acid interacts with the aldehyde and disposes the aldehyde in such a fashion that the carbonyl of the aldehyde and this particular enolate they are away from each other, this particular carbonyl group of the oxazolidine part, they are away in the transition state and that allows the formation of the anti aldol.

Then more importantly, towards the end we tried to look at the enol silyl ether to be formed from a substrate like this and see what is known as Ireland-Claisen Rearrangement. So I have taken up this Ireland-Claisen Rearrangement first instead of taking Claisen rearrangement because in Ireland-Claisen Rearrangement there is a very strong influence of the formation or the geometry of, formation and geometry of the enolate.

And therefore, I thought it was relevant that we discuss it right along with this particular boron enolate part. So in that case, what we do is if we start with this and we carry out a deprotonation here, so basically it is allyl ester which is then converted into the corresponding ester with the possibility of generating an anion here. So you have 1, 2, 3, 4, 5 and 6.

And therefore you have a possibility of a rearrangement, which can occur in this fashion. So this is how the reaction takes place. And as you can see if the conditions are very stringent conditions, the LDA reacts with this particular compound or the ester in the presence of tertiary-butyldimethysilyl chloride but the solvent is THF.

And if the THF solvent is used what you can see that this is the new part of the enolate that is formed and the R group which is already present here, they are anti to each other or trans to each other. But if we keep everything else same, but add extra HMPA, which is hexamethylphosphoric triamide, which is having this structure. You have $(Me_2N)_3P$-O. This is what is hexamethylphosphoric triamide.

This is what is HMPA. So this particular solvent has the nitrogens, there are three nitrogens and they play a very crucial role. And in that situation as you can see here, the OX group and the R group are cis to each other. So since now the geometry of the enolate has been achieved by different conditions, they lead to different products as you can see here, the R group and R1 group are cis to each other.

And here R and R1 group are trans to each other in the final product. So the newly generated asymmetric centers are highly influenced in both the cases by the geometry of the enolate. And therefore, we need to understand why is it so.

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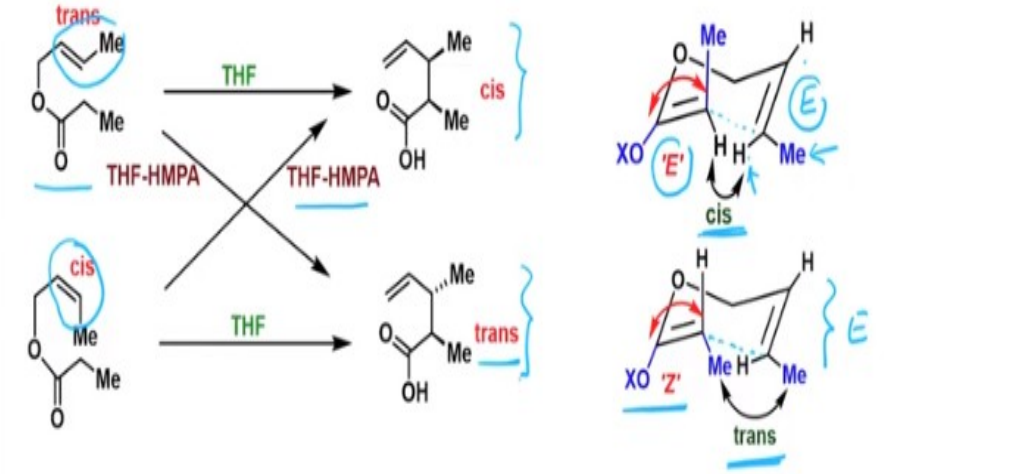

'*E*' double bond in SM leads to *E,E* (TS) (in THF) leading to '*cis*'-product

'*E*' double bond in SM leads to *Z,E* (TS) (in THF/HMPA) leading to '*trans*'-product

First of all we will see how this affects the product formations. For example, if we take a case like this, this kind of particular substrate here, where the geometry of the double bond here is trans and then of course we have the corresponding ester here. In this case, we have taken the geometry of the double bond as cis.

So if we start with a substrate like this, and you carry out the reaction in THF as we saw in the last transparency and then we get the product which is cis product, that is in THF. The same reaction if it is done in THF HMPA, here we get the trans product here. So the methyl orientations are trans to each other.

This is not really a cis and trans in terms of the double bond, but this is just a way of defining that that the methyl groups and methyl groups are basically or towards the same side. Similarly, methyl group and methyl group here are opposite side. Therefore, it is trans. It is not something to do with the double bond cis, trans or so. So we start with the trans double bond and we get a product which looks like this.

And if we do in THF HMPA, the product is opposite to this. And with this cis double bond here, if we carry out the reaction THF we get this product and opposite of that we get in THF HMPA. So there is enormous amount of difference in terms of the solvent effect. So as you can see in summarize here, E double bond in starting material leads to E,E transition state and leads to cis products.

So E, this is E and the double bond in starting material leads E,E transition state. So obviously, this and this are away from each other, this is also E. And therefore, E,E transition state leads to cis product. And if we take Z double bond in starting material leads to Z,E transition state. For example, here this is E and if it is THF HMPA, then we get Z here and that leads to trans product.

Now we can see here that when the rearrangement takes place here, this is the bond that is going to form here and therefore, this methyl is orienting up, this methyl is equatorial in the transition state. This is axial, this is equatorial. Therefore, axial equatorial on adjacent atoms will be cis to each other. And here as you can see that this is equatorially oriented and this is also equatorially oriented.

And therefore, the two equatorial groups on adjust carbon atoms in the cyclic transition state that will lead to the formation of the product would be trans to each other. Therefore, in the transition state as you can see, trans product is from here it is going to be a cis kind of orientation of the two methyl groups. So that is how it leads to the formation of the cis products here and the trans products here.

That is what we are basically trying to refer to. So it is very clear that with various kinds of product distribution that we can see with different stereochemistry of the double bond and different solvent systems, we can then expect the specific cis or trans orientations of the methyl groups in the product. Methyl groups in this case, but there could be different substituents.

So we have to see why is this THF and THF HMPA this combination helps to make this particular enolate to be cis or trans or E or Z.

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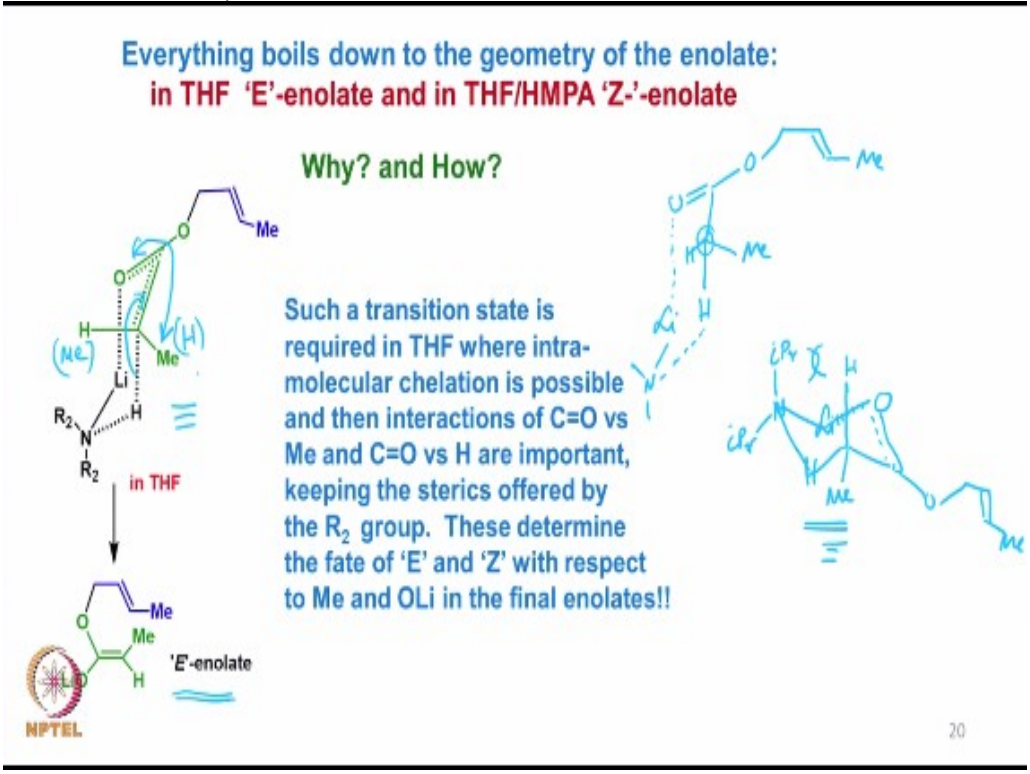

Now here as you can see that the orientation of the groups would be something like this, where you have where you have a carbonyl group here and of course, you have the oxygen here and then you have this particular here you have a CH_2 and you have a methyl group here and then of course, you have a hydrogen here.

Now when the LDA that lithium diisopropylamide comes into this, you are basically trying to have the anion from the N lithium here first chelates with this oxygen here. This is what is the is required here. And then of course we have the so something like this can be anticipated. So lithium coordinates with the with the oxygen here and then the we can write it here like this and this chelation allows the orientation of the hydrogen here to be in this direction of course.

Now at this stage the hydrogen can, the other hydrogen can be on this side or methyl can be here or vice versa. That means methyl can be. As we have seen it here it could also be methyl here or hydrogen here. So in this particular case, what is happening is now that in this such a transition state is required in THF where intramolecular chelation is possible and then interactions of the carbonyl versus methyl and carbonyl versus hydrogen are therefore important.

Now if we look at this transition state, we can also look at and put it in this fashion and we can say that something like this is happening. And we could put it in this fashion that we have lithium here, which is now chelating with this. Then you have a nitrogen here, when you have isopropyl, lithium diisopropylamide. And then you have a hydrogen here of course.

And then here there could be a hydrogen here and the methyl here is one possibility. Of course from here, you will have this. So this is the transition state that this is what I am referring it here. Now as you can see that in this particular position, when the hydrogen is axial, there is not much of steric hindrance. But if we try and look at the put it here, and instead of these two, if we put the methyl group here and the hydrogen here, then of course there will be steric hindrance.

Therefore this chelation, which is allowing the orientation of the hydrogen to be in this direction leads to the formation of the E enolate. So this E enolate is formed because now the double bond is being formed here. And therefore the oxygen here enolate comes in here and the methyl are opposite to each other.

So the intramolecular chelation with the LDA that is possible in THF makes the transition state look like this, which is what is here in which the hydrogen prefers to be in the axial position and therefore the methyl group is in the equatorial form. And when the chelation occurs, then the final product after deprotonation leads to the E enolate.

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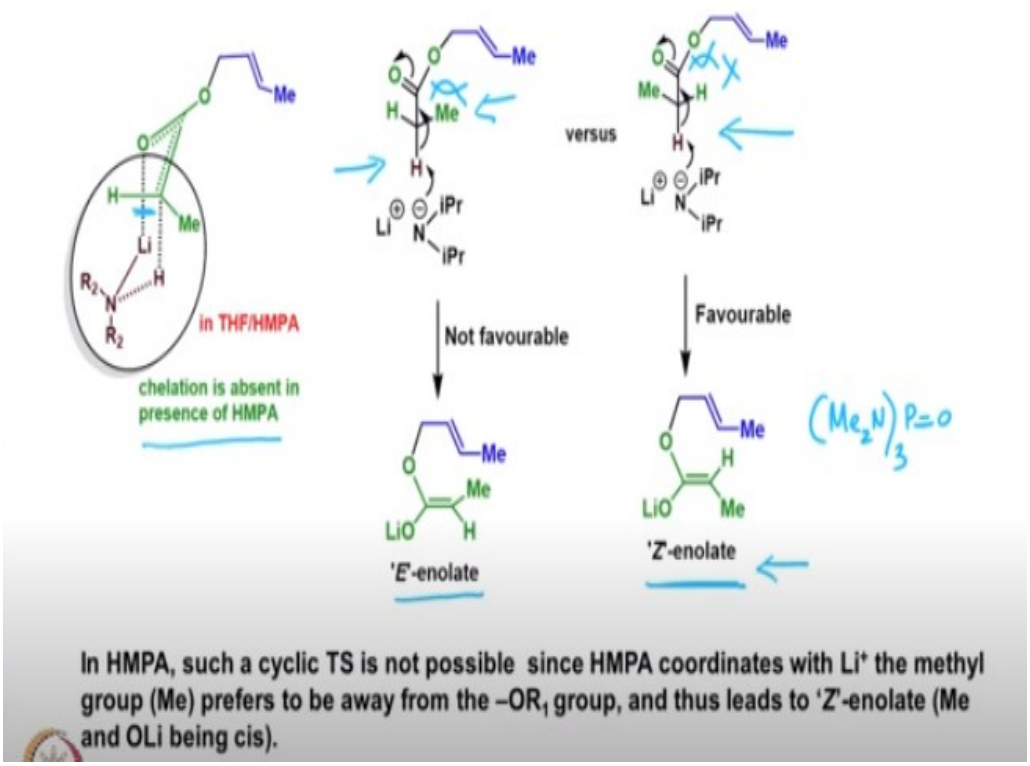

Now what happens when we have the HMPA added to it. When HMPA is added to it, this particular chelation breaks. This particular chelation breaks and this particular chelation breaks here and the molecule remains free, there is no chelation at all. So there are two orientations that are possible. One is like this here, the and the other one is like this here. So now we have two possibilities.

One the in the transition state when the proton is being abstracted from here, the methyl can have orientation like this where you can expect the steric hindrance like this or like this where there is no steric hindrance, there is no steric hindrance here. There is a steric hindrance here. Therefore, this when methyl group is orienting towards this side, it is upon deprotonation leads to E enolate.

On the other hand, when the methyl group is on this side away from this large group here, then of course the deprotonation leads to Z enolate. This is what happens because HMPA basically with the its nitrogen as I mentioned earlier it has three. These nitrogens chelate with the lithium and therefore the lithium is not available for the intramolecular chelation with the oxygen that we saw in the case of only THF as a solvent.

So this was the chelation that was possible in the absence of HMPA this chelation was possible, but that chelation is absent when we add HMPA. And therefore, Z enolate formation occurs.

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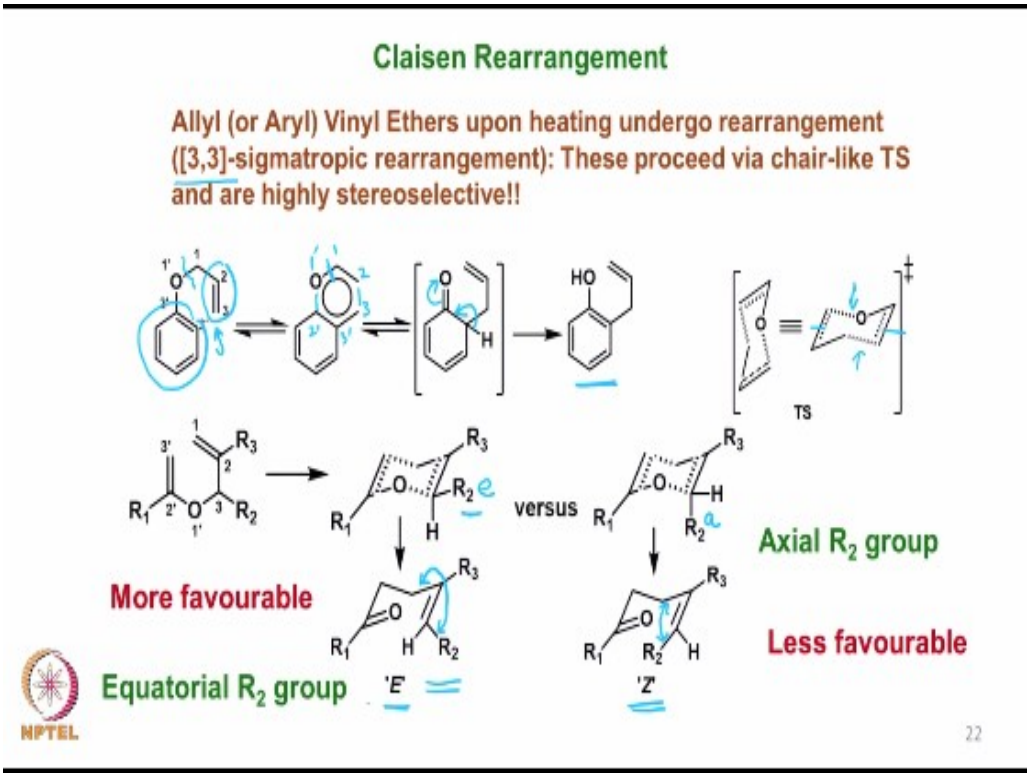

So this is how the effect of the solvent of HMPA versus no HMPA, the formation of E enolate versus Z enolate occurs. And that influences the geometry of the final product. Now we look at the Claisen rearrangement which is not really dependent on the enolates. It is slightly different from what we have been doing it so far. It does not have a enolate but we are dealing with allyl or allyl vinyl ethers.

That is what is important. Now in this case what happens is it undergoes a sigmatropic rearrangement, (3,3)-sigmatropic arrangement. If we have this aryl vinyl ether, so this is the vinyl part here and this is the aryl part here. If we take this and we number them as, this is the bond that is to be broken. And this is the, here the bond will be formed. So the bond that is being broken is numbered as 1, 2, 3 and 1 prime, 2 prime, 3 prime.

This is how it is undergoing cleavage at the 1 and 1 prime and the bond formation will take place. So this is 1 prime and this is 1, 2 and of course it is 3 here. And here is going to be 3 prime, 2 prime and of course 1 prime. So bond is being formed here and the bond is being broken here. Of course this is already a bond present here in fact.

So when this breaks of course, we are writing in this two part, because there is a reason for that, I will discuss in a while. And once the bond formation takes place, then of course you have enolization and that leads to the formation of the corresponding phenol. So allyl vinyl ether lead to 2-allylphenol formation.

And of course, the transition state would look somewhat like this where the bond is being formed and the bond is being broken as you can see. The two double bonds are breaking here and the two single bonds are being formed here. Now as we can see here, if we look at the transition

state with substituents around in non-aromatic substrates, then we can see that the R2 group here versus R2 group here.

Now here it is equatorially oriented and here it is axially oriented. And rest of the things are of course the same. So now if we look at this particular part we can see that this particular transition state where the R2 group is equatorially oriented is definitely more favorable. So what here is the E geometry is basically what we are referring to is R2 verses this particular group and here it is R2 verses this.

So this is what is Z and this is what is E. So it is less favorable, and that is more favorable. But we will look at it little more detail.

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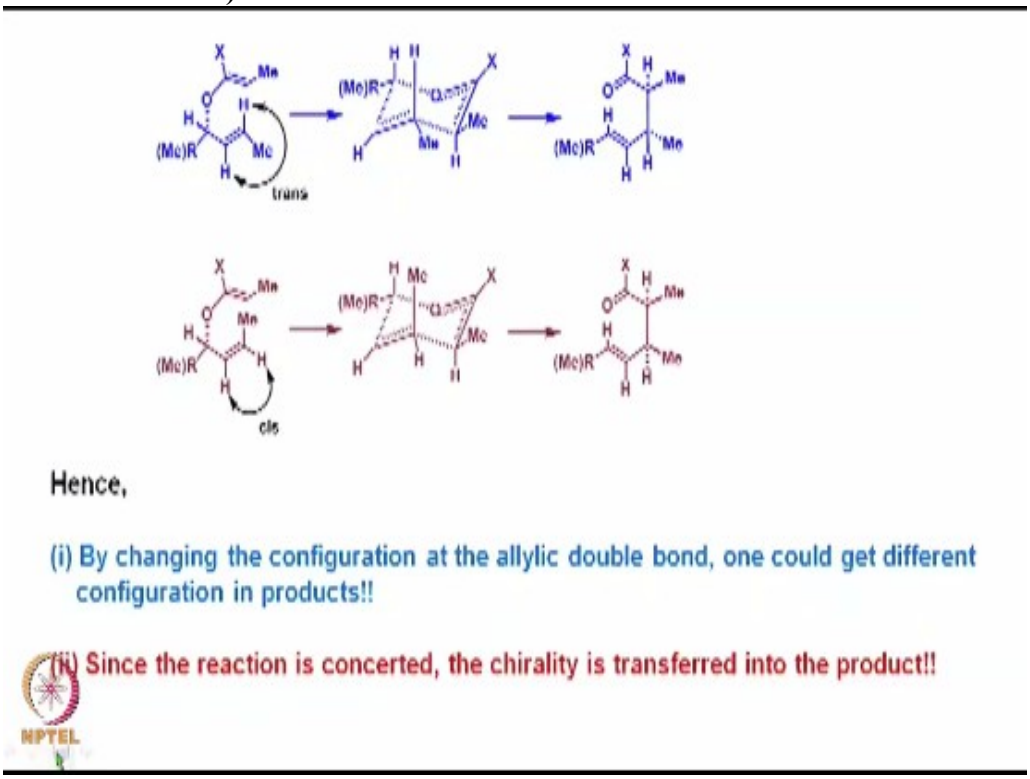

Now if we start with two molecules of this kind having an asymmetric center here and if these are chiral molecules, but they have two different types of double bonds in which in this case it is a trans double bond, in this case it is a cis double bond. And since this reaction is a concerted reaction, so what we get is a product of this kind from this starting material and a product of this kind with this starting material.

And of course the chirality is also transferred in the product. That means the products are also chiral because the starting materials are chiral. So what it means that by changing the configuration at the allylic double bond, this is the allylic double bond, one can get different configurations in the products. For example, in this particular case, the two methyl groups are beta oriented and in this case one is beta and the other is alpha oriented.

And of course, as I mentioned, since the reaction is concerted, the chirality is transferred into the product.

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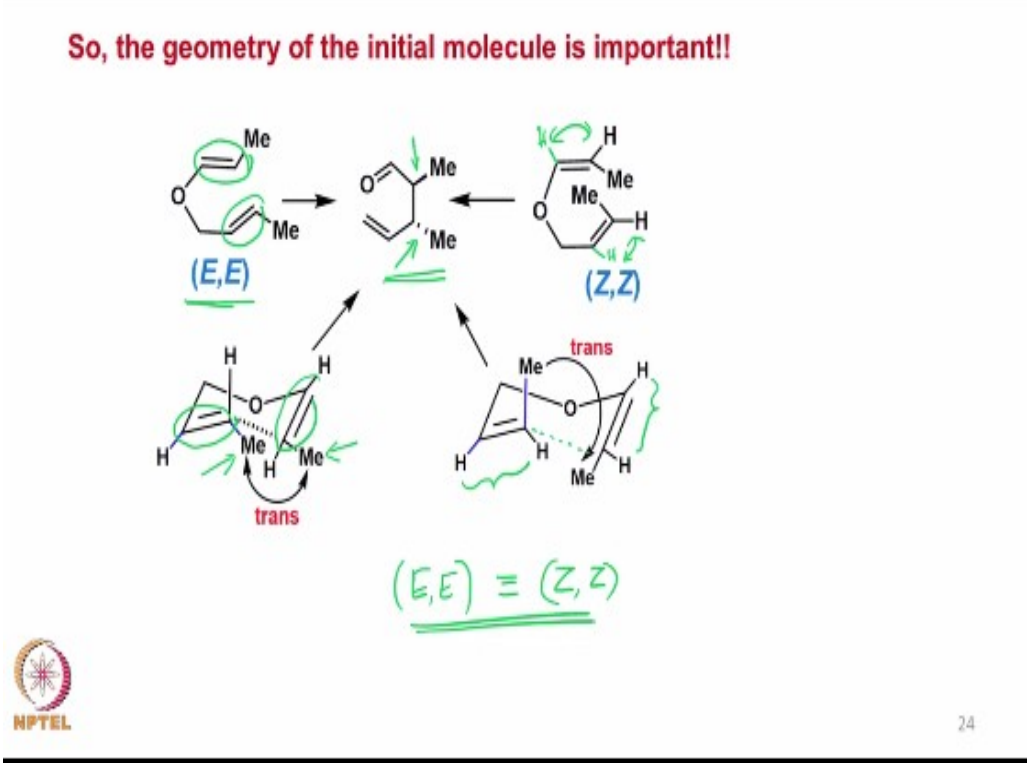

So the geometry of the initial molecule is very important. Now we are looking at this slightly differently here is that we take, without taking the absolute configuration into picture, we take the allyl vinyl ether the Claisen rearrangement starting material like this for example, then we can look at it in a slightly different way and see how does it happen.

Like for example here, if we start with E,E that is this is also E and this is also E, then the transition state would look like this where we have maintained the E here and we also maintained the E here . When that transition state is formed and the C-C bond is being formed as then can see this methyl is pointing downward and this is pointing upward. And therefore here we have these two anti to each other.

On the other hand, if we take the Z double bond here and the Z double bond here, and then the transition state would look like something like this where you have this Z and this Z and therefore when the bond is formed here, then we can see that the methyl group here is pointing upward, the methyl group here is pointing downward. So this is how it is coming here.

So E,E gives the similar type of product as Z,Z gives. So this is an interesting thing of course and therefore, the geometry of the initial molecule becomes very important.

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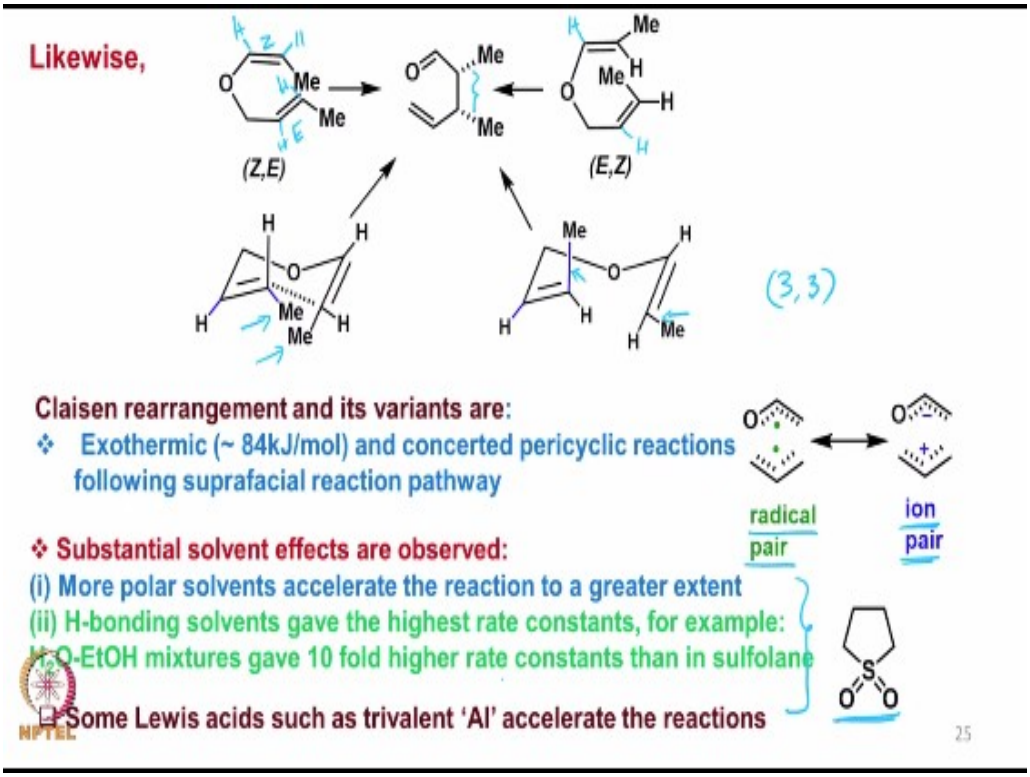

In a similar fashion, if you start with Z,E as we have here Z and E, then of course, we can say that this is H,H this is Z and this is H here and H here, this is E and this is of course Z and this is E. So same thing happens and in the transition state as you can see methyl is down, this methyl is down here, here this methyl is up and this is also up. So basically cis to each other. So they are cis to each other.

And here also they will be cis to each other. It does not really matter up or down in this particular case, because this is a racemic molecule. Now this Claisen rearrangements and its variants are basically exothermic reactions as you can see 84 kilojoule per mole and they are concerted pericyclic reactions now following suprafacial reaction pathway. So basically they are 3,3 sigmatropic rearrangement, which is what is the pericyclic reaction.

But there is a substantial solvent effects that are observed. The more polar solvents accelerate the reaction to a greater extent. Hydrogen bonding solvents give the highest rate constants. For example water ethanol mixture gives 10 fold higher rate constant than in sulfolane. Sulfolane is this kind of nonpolar solvent and some Lewis acid such as trivalent aluminum accelerate the reaction.

But this part is something very important. And that is the reason why this radical pair or more so as ion pair type of rearrangements or the intermediates that are the transient intermediates, which do not affect the orientation of the double bond. But they are transiently available when the bond breaking and bond formation takes place.

And that has the reason, that is the reason why these things are observed that the polarity of the solvent makes the reaction rate faster because of such ion pair intermediates that are involved in it. So we will stop it here and take some other aspects of Claisen rearrangement in the next class,

because there are say various alterations in terms of the Claisen rearrangement and they have huge amount of application in organic synthesis.

So please look at these carefully and go through whatever content that I have discussed today and be prepared for the next class. Till then bye and have a good study period. Thank you.