Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

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Lecture 40

Dynamic Stereochemistry Asymmetric Aldol Reaction (Contd)

Hello. Welcome back to this course on Structure, Stereochemistry and Reactivity of Organic Molecules and Intermediates, A Problem Solving Approach. This is the last lecture of this course.

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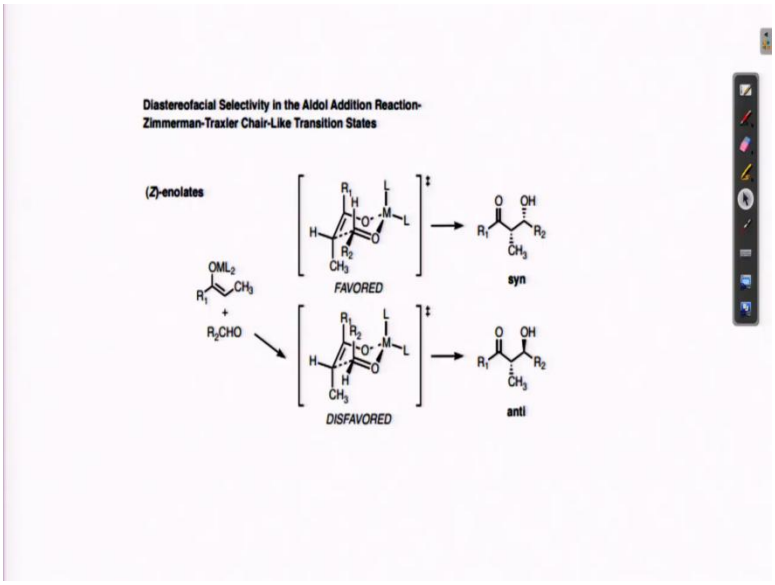

Remember, in the previous lectures, we are concentrating, we are discussing the Aldol Condensation, mainly the stereochemistry of Aldol Condensation. Strictly speaking, it is not the condensation, it is the formation of the Aldol and not the dehydration step, so that we do not want to lose the stereochemistry of the carbon which is (())(1:11) the hydroxy group. We do not want to dehydrate. Because there are many natural products which have this OH at the right position where aldol condensation brings the OH at a carbon. And that is present in many natural products.

Now, remember Aldol Condensation is, why it is so important, because it is a carbon, carbon bond forming reaction, number one. Number two, it creates two stereogenic, SP3 stereogenic centers at the same time and so that itself is a challenging if you want to develop an asymmetric synthesis. Now the trick to do a stereo selective that means an asymmetric Aldol

reaction, if you want to do that you have to keep something some points in mind, number one is the geometry of the enolate.

So, you have to have only one enolate which is produced and that is acting as a donor. Because in the aldol reaction, one part acts as a donor that is in the form of the enolate and the other part acts as an acceptor. So, the donor molecule is in the form of an enolate and the enolate geometry has to be fixed. Because the enolate geometry can be two, one is Z enolate or the Z enolate, and the other is that E enolate. And if there is equilibration going on between this Z and the E enolate then you will not get the desired selectivity. It will scramble.

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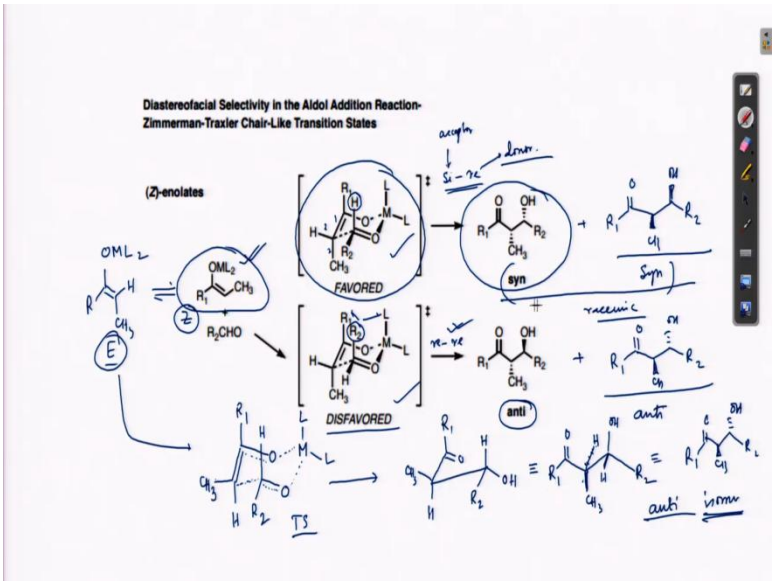

So, the first thing is to the form a particular type of enolate, whether Z or E. So, here we started with the, this slide shows that there is a sorry, there is a Z enolate or Z enolate that is this one. And then what is the E enolate, the E enolate is the other geometrical isomer, OM and M will have some ligand, here it is two ligands so that is shown here as an example. So, this is the E enolate and this is the Z enolate. So, you have to have a fixed geometry of the enolate.

In this case, we are starting with the Z enolate, suppose you have made the Z enolate. Then what you have to do, you have to bring in facial selectivity, that means when the aldehyde attacks the, when the aldehyde approaches or just the opposite way of saying, that when this enolate approaches the aldehyde molecule, there are basically two faces that are going to see each other.

Like in this transition state, remember, Aldol reaction goes through this six membered chair like transition state that is the Zimmerman-Traxler chair like transition state model. So, the transition state, if it is like this, that means here the enolate is at the backside and this is the carbonyl, the carbonyl that means the acceptor component. So, what is happening here? The face which is behind this laptop screen, this screen is actually reacting with the front face of this double bond.

So, that means if I asked you that what it represents, does it represent a Psi connection, or ray-Psi connection, or ray-ray, or Psi ray, these are the four possibilities and that leads to for a stereoisomer. Here if we do, suppose we think that okay, oxygen is one definitely, R2 will be two and hydrogen will be three. So, the side which is facing me that is becoming ray, so that actually the face which is reacting with the alki, with this enolate is the Psi face.

So, this represents a Psi and then this the double bond carbon that also has the facial nomenclature, so the top face is reacting with the bottom face of this carbonyl carbon. The top face here is this is one and that is two and this is three, so this is ray. So, it is a Psi ray combination, but we have to mention Psi is the acceptor and ray is the donor. So, that gives rise to a particular form of, particular diastereomer which is the syn-diastereomer.

Now, if there is no chirality involved here that none of these substituent's or the ligands have any chiral center that means the an SP3 stereogenic center. Then what will happen, you will have, during this reaction, you will have exact mirror image transition state of this, which will be equally probable. So, along with this molecule, you will also get the enantiomer of this that means the methyl and the OH and this is R2.

So, this is the other enantiomer of the syn-diastereomer, this is also syn. So, both these will be obtained in equal amounts. So, that is a racemic mixture. Why that will be racemic mixture, because you are not involving any chirality in the transition state. On the other hand, so what is the difference between this transition state and this one, which is says disfavored that you have now it is a double bond, the enolate remains the same, so it will be enolate is ray face and this is the ray face.

Because now I have put the R2 on the top and hydrogen here. So, that makes it, so the front face is the Psi face and the back face is the ray face. So, this is ray-ray combination, and that gives rise to an anti diastereomer. Again, there will be an equal probability of a mirror image

transition state of this and that gives the other anti-isomer that will be methyl beta and OH alpha, R2. So, this is also anti.

Now, because the ray-ray combination will not be very feasible, because of the fact that this R2 is having one three di-axial interaction with the R1 as well as R1 is a part of the enolate. And with the L, L is a part of the ligand attach to the metal. So, because of this, this is dis-favored and that one three di-axial interaction is not there because it is now or it is much less, I can say, because it is hydrogen not between R2 and R1 and R2 and L. Here it is L and H, and R1 and H

And obviously, this is much smaller interaction, so this will be the favored and you get the preferential formation of the syn-diastereomer. That we have seen in the beginning of the aldol reaction lecture, when we told about this natural selection of syn, formation of syn isomer because of the fact that the transition state of the anti-isomer is dis-favored.

Now, you have to also remember the fact that we have started with the enolate which is in the Z configuration. If it is in the E configuration, then what will happen? So, let us try to write it. That if it is in the E configuration, so that means we are taking this enolate. So, let us try to draw the transition state. So, everything is same only this is R1 and now the methyl because it is the E enolate, so methyl and R1 will be on the same side, this is the oxygen.

Now, the dotted line, the metal, this ligand and ligand and then you have the dotted line because there is a transition state, these are also dotted line, which are going to be broken. And this is the hydrogen because that will be the preferential orientation of the carbonyl, the hydrogen should occupy the axial and R2 should occupy the equatorial and then you have the carbonyl oxygen. So, the transition state you have again a broken bond here and a broken bond here. So, this is the preferred transition state from the E enolate.

So, let us see what is the ultimate product. The ultimate product is that you get CO R1 when the Aldol reaction is complete that means the carbon, carbon bond formation is complete, then you have this will be the back to the keto form, this is your methyl, this is the hydrogen, and then you have hydrogen R2, and this will be OH after workup, O metal and that will be OH after workup.

Now, the question is, what is this, this diastereomer? Is it anti or is it the syn-diastereomer? So, how to do that? You, what I do because in the way we are writing this molecule is in the

zigzag fashion, that means the main chain is in the zigzag fashion that is, that you have to do by just some manipulation. The manipulation is like that, that because you want to have the chain in this direction, so here it will be CO, R1, that is your ultimate target and that should be R2.

Now, how to do that? What you do that we have a exchange in a group of three. So, you bring this R1 CO in the place of methyl, bring the methyl down and this is your hydrogen. This is what is the famous rule of exchange in a group of three. That does not change the configuration of the carbon. So, you do the same thing R2 here, OH there, and this is your hydrogen. So, R2 goes into the position of OH, OH goes to the position of hydrogen, and hydrogen comes to the position of R2.

So, now this is you see that this is nothing but this hydrogen is beta and this is also and this hydrogen is alpha. So, that means, you are getting an anti-isomer, if I write it now R1 CO put alpha beta then this will be beta and the OH will be alpha. So, this is the anti-isomer. So, anti-diastereomer will predominate, this is interesting and important.

But if you start with Z enolate, then you get the syn-diastereomer pair, if you do not have any chirality involved here. And you will get the anti-diastereomer as the major product if you start with the E enolate. So, that is one important issue.

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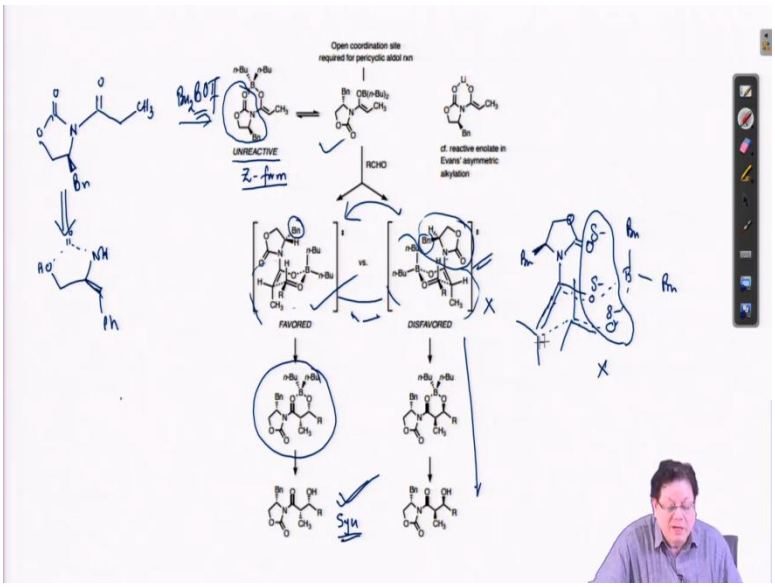

The next one now is that we know that if you want to make it let us see, erase all this. If you want to I think that is whatever I said is actually shown here, but with E enolate what happens, I think I have already explained this slide to you. So, let us go to the next slide.

Now, you know that the Evans chemistry right, Evans chiral oxazolidinone chemistry, where he uses a chiral auxiliary. If you want to now, we are talking about asymmetric synthesis. That means, if you start with the Z enolate, again our conclusion from the last two slides that if you start with Z enolate, then you get more of the syn, and if you start with E enolate, you get more on the anti. That is clear.

Now, both the syn or anti will be present in recimic form, unless you put some chirality somewhere, either in the enolate or in the carbonyl component which is the acceptor or in the ligand which is attached to the metal. So, all these possibilities are there. What Evans had chosen that he had chosen a group like which is called oxazolidinone, which is easily available from carbonyl compounds from amino acid, sorry, which is available from amino acid. So, this is the, that we are talking about the chiral auxiliary. We have already done this in the last lecture.

And we have seen that this forms the Z enolate, you can actually you are starting materials we are showing the enolate directly, but your starting compound means actually this one, this is your Benzyl, actually this comes from phenylalanine, the amino acid phenylalanine.

So, you can see that, if this is carboxy that is phenylalanine, so you have to reduce the carboxy to the alcohol, so that gives to this is phenylalanine all and then you do a formation of this oxazolidinone network by reacting with phosgene, you can react with phosgene or some other variants of phosgene. So, you get the chiral auxiliary, and then you attach it to your carbonyl component.

So, in this case, it was this, a CO and then CH2, CH3. Now, when you make the enolate, so here it is said that you get if you add dibutylboron triflet. So, you get an enolate which is in the Z form. So, you get preferential formation of the Z enolate, which is very critical, because you have to freeze the conformation configuration of the enolate in a particular Z or E. So, in this case, if you use dibutylboron triflate, you get the Z enolate.

The Z enolate is initially locked in this form and then it detaches from this oxygen, it can actually detaches from the oxygen by rotation around this carbon nitrogen bond. So, the

benzyl goes in the other direction and it will be alpha. So, in that case, it will be, it cannot chelate, both these oxygen cannot chelate to the boron at the same time.

So, by rotation, you can break this chelation or chelation with the oxazolidinone carbonyl. And what it says that this is the reactive form and this is the un-reactive form. So, the reaction goes via this form, but anyway by rotation you cannot change the Z to E, so the Z enolate remains in the Z configuration, so that part is clear.

Now, this reacts with the aldehyde, and with aldehyde and what is happening here that again there are two transition states that are drawn here, one is R as the equatorial and in and the other one, I now remind you that last time what I said that when you draw a transition state for the formation of the syn isomer from the Z enolate, we drew one transition state, but at the same time, we said that there is also another mirror image transition state, which is there which has got 50 percent probability of existing. Because there was no chirality involved in the system. So, you are getting a racemic mixture.

But once you have put a chirality in this molecule, actually the chirality is in the enolate and that chirality will now, what will happen you have a mirror image form of this, when you draw the other transition state, the mirror image transition state, but used a chiral auxiliary has a particular absolute configuration that you have to maintain. You cannot have these two transition states which are perfectly mirror image of each other, because, to have mirror image you have to change the configuration of the chiral auxiliary, which is actually fixed.

So, here are the two transition states by incorporating a chirality here in the form of the chiral auxilary, what you have done, you have made the two transition states diastereomeric, diastereomeric like this. So, this is one transition state and this is the other transition state. Remember, again I remind, up to this point without the chiral auxiliary, the everything looks perfect mirror images of each other.

But then when you add the chiral auxilary with a particular well defined configuration, then it becomes diastereomeric transition state. That is number one point or the most important point in this asymmetric synthesis. And the second point is that this carbon nitrogen bond is a single bond, we are talking about the rotation of carbon nitrogen bond to disturb the chelation to the boron.

So, we can also write another transition state where the carbonyl is on the on this side, so it rotates and the carbonyl is on this side. If that be the case, the benzyl we will be beta here, this is the oxygen, this is the carbonyl and you have now the enolate, this is the system now, let me, so dibutylboron triflate. So, this is the situation.

So, the oxazolidinone can also adopt this type of orientation where the carbonyl is pointing towards the boron. But, whatever is the interesting point to note is that, this is not favored because of this is delta minus, this is delta minus, this is delta minus. So, there is now a repulsive scenario that is existing in this orientation, if this adopts, oxazolidinone adopts this type of orientation, so there will be repulsion between all these negatively charged oxygen's.

So, this will prefer see these two cannot change because they are predefined by the formation of the this chair like transition states. The only thing that can change is that it rotates and gets to the confirmation which is shown here. So, that is why the carbonyl will be away from the boron. So, it is away from the boron and that is another important issue, because if it is freely rotating, then also that would have killed the degree of asymmetry that is achieved in this asymmetric synthesis.

So, basically what is happening now, that number one is you have to fix the enolate geometry, once you do that, then the next one is that the two transition states become diastereomeric, because you have already incorporated the chiral auxiliary. And number three is that the chiral auxiliary is not also freely rotating, because of the repulsive scenario in one direction, it takes the other confirmation.

And in the other confirmation what is happening now, if you consider these two transition states, what is happening here benzyl is alpha and in this case, in order to make the carbonyl away from the boron, so you have the carbonyl here, so the benzyl will be beta, represented as beta. So, here what happens the approach from this top side will be hindered by the beta benzyl group.

On the other hand, here the benzyl is alpha, so approach from the top side actually is welcome, but not the approach from the backside. So, backside approach, backside of the enolate, the carbonyl, will not approach because there is benzyl which will hinder its approach. On the other hand, in this transition state, the front side is now blocked because of this benzyl.

So, this will be the favored transition state and not this one, and not the other one, not this one. And that gives rise to the formation of this product and ultimately, you can write this in this form. Again you can add up that exchange in a group of three you do that and try to find out write the molecule in the zigzag fashion, in the correct form, and then put the substituents and find out whether it is syn or anti.

In this case, it is syn, because you started with a Z enolate. And so it will be syn, but there are two syn products one is coming from the dis-favored transition state. Why dis-favored? Because this approach is hindered by the benzyl group. The benzyl is at the top position, is facing the approach of the carbonyl components. So, that is dis-favored and this is the favored one.

So, you get very high and enantiomeric access of the syn-isomer. So, this is what is the Evan's chemistry. Now, the question is, if you want to make the anti, because many compounds maybe there natural compounds where the steric disposition of these two centers are such that it is actually giving an anti isomer, anti stereoisomer.

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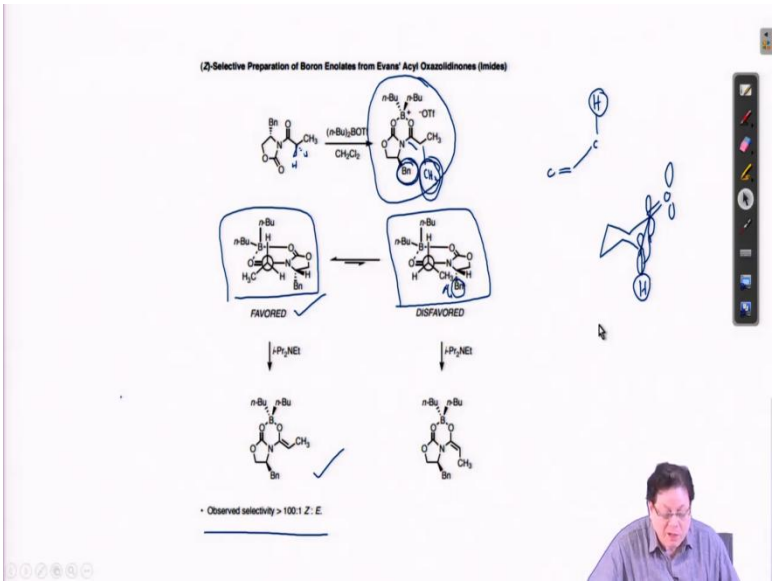

So, what to do in that case? How to get the anti stereoisomer? I gave you already the clue that you have to change the enolate geometry. If you change the enolate geometry, let us see where is that. Okay, this is another one. We have not said why this will form the Z enolate preferentially. Why this oxazolidinone with dibutylboron triflate forms the enolate in the preferentially the Z configuration.

One very simple way of explaining this is that if you draw the, remember this is the more stabilized form of the boron enolate. So, in that case the benzyl is on this side, on the right hand side, and if you now draw the enolate, the double bond here, if the methyl is now on the bottom side, that means that is the E enolate. So, you have a problem with the benzyl and the methyl, there will be steric repulsion between these two.

So, methyl will tend to be away from the benzyl group, and that is the genesis for formation of the Z enolate, preferential formation of the Z enolate. And however, if you go a little bit in a that is one way of explaining, but the actual confirmation analysis if you do, that is shown here, that when enolization takes place, remember, this carbon is actually orthogonal to the plane of the carbonyl, because that is we told you about this that when there is a carbonyl it is the axial one which is lost. Because the orbitals that are involved in the process, they are perfectly aligned to become conjugated with each other.

So, that is why the hydrogen which will be lost that will be orthogonal or perpendicular to the carbonyl. Now, you can actually there are two hydrogens here, these are di-astereotopic hydrogens. And if you want to draw the take out the hydrogen which will give the Z enolate then you will have an orientation like this. And if you want to make the conformation which will lead to the E enolate, then you will have a Newman projection like this.

You just see actually I said in very simple terms here the methyl group is on the right side and your benzyl is also here. So, there will be now repulsion between these two. And in this case, the methyl is away from the oxazolidinone, so that will be favored and ultimately you get see the observed selectivity is greater than 100 is to 1. That is Z is to E is greater than 100 is to 1. So very good selectivity.

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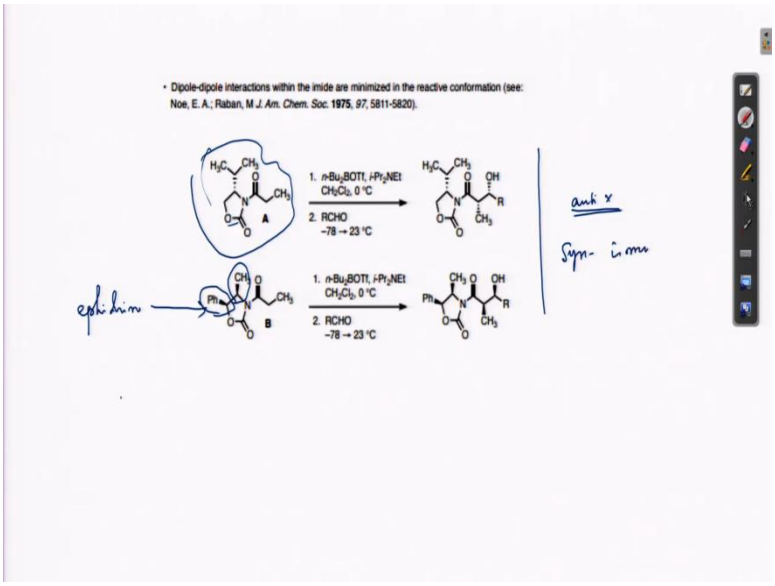

So, now, the question is, that how to get the anti-isomer? Sorry, here, how to get the anti-isomer? Let us see, there are series of papers that are published in this domain that actually maybe a very large number of papers are dedicated to asymmetric aldol reaction. Now this is the Evans chiral auxiliary, here the starting material is it reminds that because there is an isopropyl, so here the Evan started with L value.

Amino acids are mostly available in the L form. So, the L form is available, D will be very costly, because you can say that, Sir, I will start with the D form to make the anti-compound. But that is not very available. So, the other option is that, so there are options. So, you start with a deform of the amino acid, but those amino acids are costly.

The number two is that you change the configuration of the enolate make from Z to E, that is your another option. And the third option, you start with the another chiral auxiliary, where you get these groups, here it is alpha, because of the L configuration of the amino acids. So, you get other natural products, which are chiral natural products, where these alkyl groups or benzyl or aldol groups, whatever it maybe, they are in the opposite side, that means they are beta.

Interestingly, there is a compound called ephedrine, a natural product, from which you can make these chiral auxiliary where the absolute configuration is just opposite to what is happening in the L amino acids. So, these groups are now in the sorry, this is actually not the

anti-form, this gives the, this is not the antiform, this is actually giving the other syn isomer, I am sorry.

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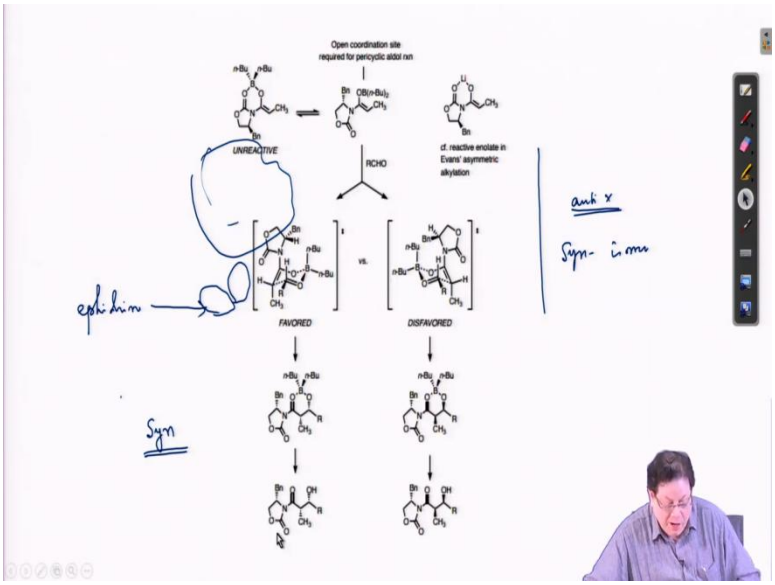

If you go to the previous slide, sorry, if you go to the previous slide. Our question was that we are getting sorry, we are getting a syn compound. One particular enantiomer of the syn-diastereomer we are getting, and that is where both are alpha. Again, go back to there, both are alpha. See there, this is the major compound.

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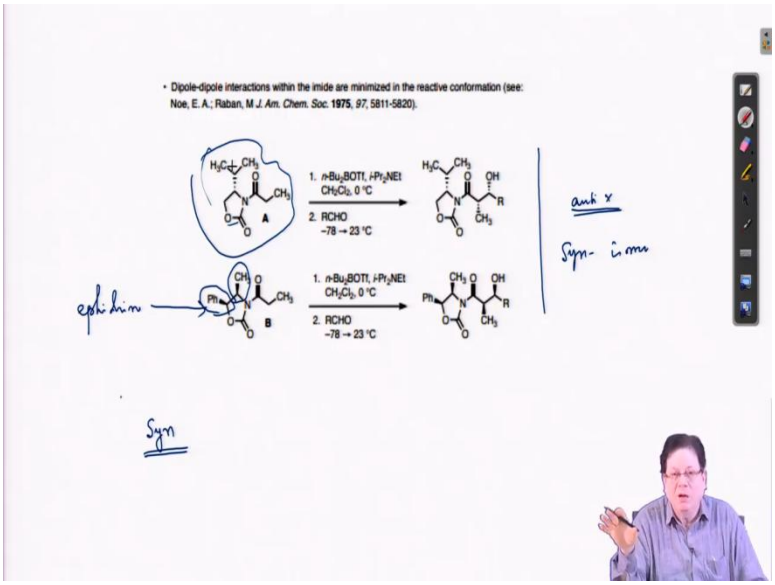

And so, how to get the other enantiomer? That is the question. The other enantiomer can be obtained if you can invert the configuration here of the chiral auxiliary. So, that is what we

are trying to say here, not the how to get the anti. We will come to the anti later on. So, I said that the amino acids are difficult to get, so you can get ephedrine which is a natural compound.

And from a particular chiral form of ephedrine you can get this chiral auxiliary where these groups are beta. So, that will force the carbonyl compound to come from the backside. And if it comes from the backside of the enolate then you will get the other isomer like this. So, this is the normal Evans chemistry starting from the L amino acid as the chiral auxiliary.

So, you get this syn-compound, and if you use the ephedrine based chiral auxiliary, you get the other syn-compound, the mirror image. So, both the enantiomers can be obtained in very pure form, in one the chirally pure form. So, this is one aspect.

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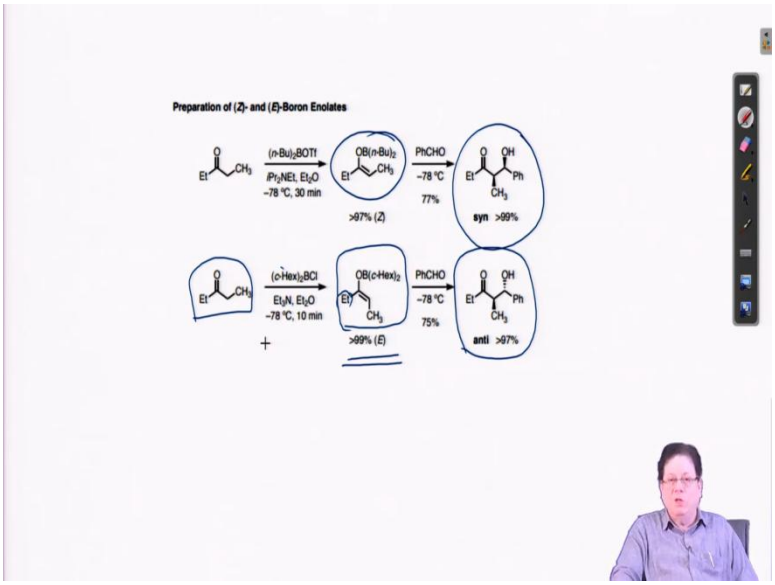

The other aspect is how to get the anti compound? Let us see. I think we will come back to this slide later on. So, the next question is, we know now know how to get both the forms of syn-diastereomer. One is amino acid derived chiral auxiliary as proposed by Evans, other is ephedrine derived chiral auxiliary that is also following the same Evans chemistry.

Now, if you want the anti-form, then obviously you have seen that in order to get the anti as the major product, you have to change the configuration of the aldol. So, the Z enolate sorry, the Z enolate gives the syn compound. And whereas, the E enolate will give the anti. How to get the E enolate? If you use extremely bulky cyclohexyl boron system dicyclohexyl. So, this is much bulkier than the di-n-butyl.

So, in this case ultimately you get the thermodynamically more stable enolate. This is the E enolate that you ultimately get, so greater than 99 percent. So, this is how you get the E enolate. So, if you put the like the auxiliary instead of the ethyl, you put the auxiliary, so ultimately you will get the anti-aldol as the major product, as in particular one enantiomeric form.

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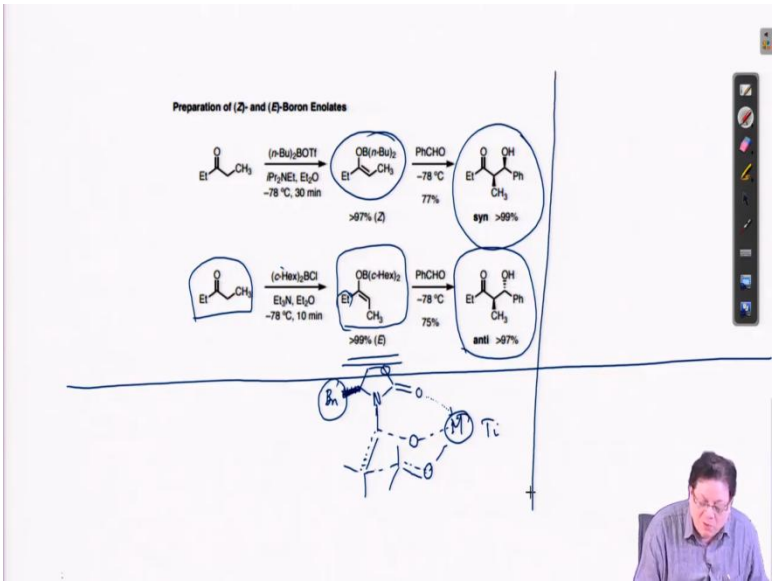

So, the trick is that you change dibutylboron triflate and go to the other enolate. Remember, there is one more we will end up by saying that if you see this is the sorry, how to draw the transition state, better first draw this dotted chair, put the metal here, the enolate oxygen here, the carbonyl oxygen here, the acceptor carbonyl, and then you have this bond is there, this is the no, sorry, that bond is not there, sorry.

So, let us erase that, again we have to redraw it. So, this is the enolate oxygen. There is a double bond here. So, the double bond is being broken, so it will be one full bond and a partial bond and this is the carbonyl there was a double bond here. So, one bond is being broken and this is your that oxazolidinone. Now there is a trick that you can put this oxygen in this form, see benzyl, that means towards the metal ion. But you have to change the metal ion in that case, because boron cannot accommodate beyond four.

If boron cannot accommodate I told you that the trick is that you have to change it to the titanium enolate. If you put it titanium then what happens this oxygen these negative charges dispersed by chelation to the metal ion. So, now the syn-compound that you are getting

earlier in when you are using the boron enolate, the other syn compound you will get if we use the titanium enolate.

So, now we have this is very interesting, that if I ask you that, how do you get the other syn-isomer by a, other syn-isomer relative to the syn-isomer that you get by the normal Evans chemistry? There are two ways, either use ephedrine based chiral auxiliary, that is number one, or you use titanium enolate, change the boronil in order to titanium. And then the oxazolidinone takes the form where the carbonyl oxygen is pointing towards the metal ion.

So, that will force the benzyl group if it is derived from phenylalanine to be beta and the aldehyde will preferentially approach from the backside. So, that gives definitely the other syn compound. And so, that is titanium enolate or you can use ephedrine based chiral auxiliary to get to the other syn compound. So, there are different tricks.

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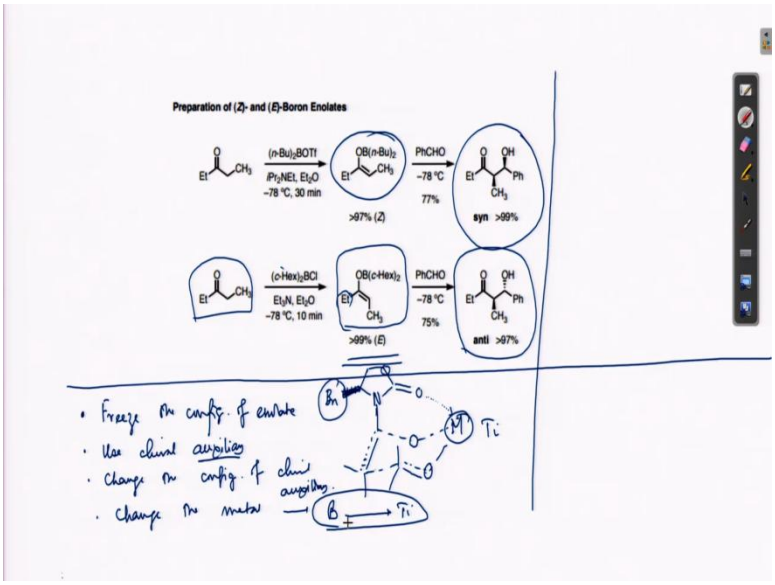

Now, to summarize what I can say that in order to achieve stereo selective aldol reaction including asymmetric synthesis, so what you have to do, freeze the configuration of the enolate then there are changes that you can do, use chiral auxiliary. You can change the configuration of the chiral auxiliary or you can change the metal from boron to titanium.

So, there are different techniques by which you can get to the different forms of syn-isomer or you can get different forms of the anti-isomer. So, this is basically what we are covering. Remember, what is something is missing, I have not deliberately included, because these days there is a vast number of aldol reaction which has, which can be carried out, asymmetric

aldol reaction, which has been carried out by the use of small organic molecules has catalysts. Like prolene is one amino acid, prolene assisted or prolene catalyzed asymmetric aldol reaction.

And now organic catalysis mediated aldol reaction has become a very important and very well developed topic in aldol chemistry. All these are inspired by nature because they are in nature. The nature always do aldol chemistry by using enzymes, which are called aldolase enzymes.

So, inspired by that, it has been shown by scientists that it is possible to do aldol reaction using small organic molecules. But that is another entirely different domain of aldol reaction which is catalyzed by small molecules. Here only we were considering the metal involved, metal mediated asymmetric aldol reaction.

So, I hope after going through these 40 lectures, you will have a good grasp of overall concept which are required in organic chemistry, especially we started with some stereo chemical aspects, the point group, the symmetric group analysis, then we went for determination of configuration where we utilize spectroscopy to determine the absolute configuration of molecules.

Then we went for the reactive intermediates. We have discussed radicals. We have discussed key teens. We have discussed alkynes. We have discussed diradicals all these as intermediates. In between we had a very important topic which was called stereo electronic effects in organic molecules. So, that is how the orbital should be aligned during a reaction or even during in the ground state, how does it dictate the adoption of a particular conformation all these things.

And then finally, we went for some of these reactions, especially the reactions involving the carbonyl group. So, there are many things in organic chemistry but this is a G stuff what is there which are considered very important if you want to study organic chemistry beyond whatever is covered here. Thank you very much. I hope you will enjoy going through this course.