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

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Lecture 39
Dynamic Stereochemistry: Asymmetric Aldol reactions

Hello. Welcome back to this course on structure, stereochemistry and reactivity of organic molecules and intermediates, a problem-solving approach. In the last session, we were discussing the Aldol Reaction and we have seen that in the aldol reaction what happens there is basically possibility of formation of four stereoisomers, basically, two diastereomers, two diastereomeric peers I can say that one can be called a syn pair and the other is the anti-pair.

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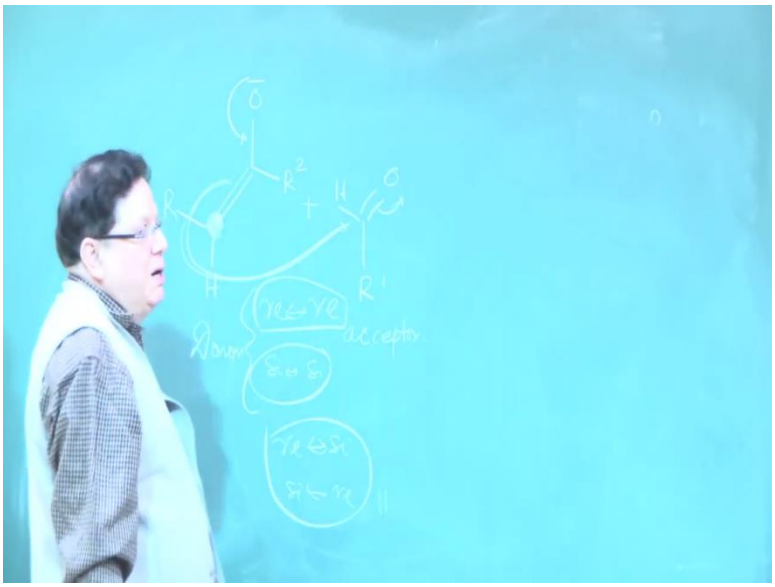

Now, the genesis of that formation of these four isomers, basically, this I did not mention in the last lecture is that the reaction that is happening is basically an enolate and another carbonyl system. So, this is the enolate which is basically the donor component and this is the acceptor, so that is the donor component and this is the acceptor component.

So, this comes back, attacks the carbonyl. Now, you know that there are two kinds of faces that are possible across a double bond or across a carbonyl. Like when this is these electrons are coming here and attacking this carbonyl, so obviously, this carbon has a face. So, either it is approaching the carbonyl from the top face or it can provide it is the face which is at the back to the carbonyl.

Similarly, the carbonyl can also have two kinds of faces, like the rear face of the surface, you know that. And so, depending on which face is reacting with what you get a type of stereoisomer. Like if it provides rear face and if also the re face is involved here, so you have a re, re combination or you can have a Psi combination that is possible.

See this is basically that gives you 1 diastereomer as an enantiomeric mixture. And the other one is the re and Psi or Psi and re, so this gives the other diastereomer existing as an enantiomeric pair. So, that is basically the genesis. It is the faces, the different types of faces that can add up together and that gives rise to 4 stereoisomers.

And we have seen in the last lecture that there is a natural preference for the syn, syn diastereomer, because of the fact that in the transition state, the alkyl group of the aldehyde wants to adopt an equatorial orientation in the Zimmerman and Traxler 6 member chair like transition state.

Now, let us try to see, that how we can, but that all about the diastereo selection, let us try to find out that how to introduce enantio selection or enantioselectivity in an Aldol Reaction. There are different ways to do that. Because in Aldol Reaction, there are two components, one is the enolate and another is the acceptor molecule.

The enolate if both are achiral, then what you can get is only diastereo selectivity like the syn selectivity, but you will not get any enantioselectivity there. If there is if you want to introduce enantioselectivity, you have to either introduce start with achiral enolate and an achiral aldehyde or carbonyl compound or a achiral or an achiral enolate and achiral carbonyl compound. Or you can have both as chiral, that means your enolate is chiral, your carbonyl compound acceptor is also chiral.

So, that you can basically, you are trying to amplify the asymmetry, that is possible, but there is no that is not mandatory. You need one chirality at least in the one of the components. On the other hand, there is another possibility that you can use a catalyst to do the Aldol Condensation like TiCl4 what Mukai Yama was using. So, some kind of catalyst that we use, but the catalyst itself is achiral catalyst.

So, if you use the chiral catalyst, then you can have this Aldol Condensation which can be enantio selective. So, these are basically the 4 possibilities. The chiral catalysts can be methyl catalysts or it can be enzymes also, because there are enzymes which do Aldol Condensation,

aldolase enzymes. And that also gives rise to high level of enantioselectivity. So, these are the three possibilities, your chiral enolate, or chiral acceptor or you can say chiral donor, chiral acceptor, or you can have both chiral or you can have chiral catalyst. So, these are the possibilities.

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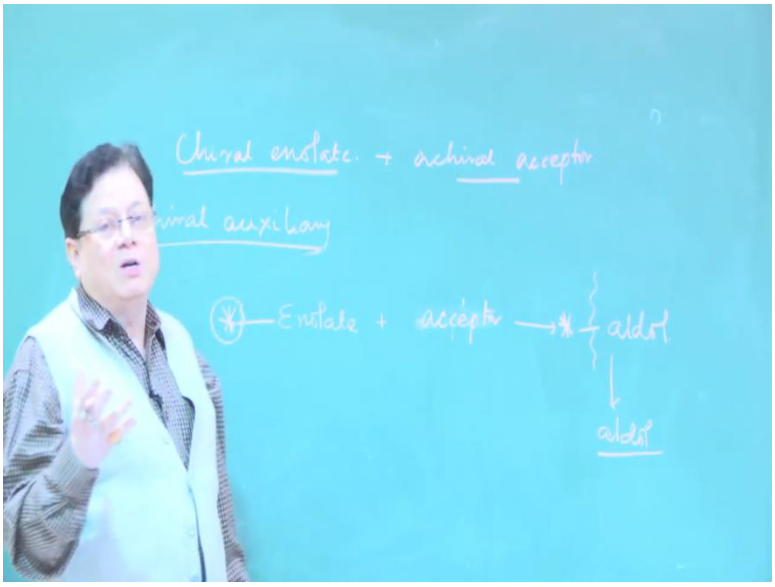

We will consider the only one where this is achiral enolate plus achiral acceptor. Now, chiral enolate, what sometimes reactions have to be taken, have to be carried out between only a achiral substrates, means your enolate is achiral, your acceptor is also achiral. But the interesting part of the reaction is that the reaction itself generates 2 stereogenic centers.

Now, in that case, how to induce enantioselectivity? So, what has been one particular very well known strategy is what is called chiral auxiliary based approach. So, in that case, what you do that when you have the enolate, so at the enolate level you attach something a temporary, a temporary group which has got chirality, built-in chirality. You attach that, built-in chirality, so that the whole thing becomes chiral and now you add these to the acceptor, sorry, to the acceptor to do the reaction get the aldol.

But remember the aldol will have is attached with this chiral appendage that you have started with from the enolate, and then after the reaction what you can do, you can take this off and get the aldol. So, that is the strategy of achiral auxiliary based method. Now, different chiral auxiliary groups are available. Chiral, see when you talk about any asymmetry synthesis, you have to start you have to have some chirality somewhere. It may be chiral catalyst, it may be

chiral auxiliary, whatever it is, or you may start with the chiral ketone also, chiral carbonyl compound.

The question is, what is the source of these compounds? What is the source? The source is from nature, because nature gives us, provides us molecule which are chiral molecules, and usually they are available when they are produced, they are mostly produced in one chiral form.

And from that chiral pull, what we actually get our either the chiral auxiliary or the chiral catalyst or the chiral substrate. All these are possible. There is another common approach for asymmetry synthesis, it is called Chiron Approach. That means you start with the chiral compound, and then, subsequently develop new chiral centers, new stereogenic centers, but that stereogenic centers chirality will be controlled by the existing chirality. So, that is what is called Chiron Approach.

But here it is auxiliary based approach, this auxiliary is also achiral compound, which is available from natural sources and the one that I am going to describe is actually obtained from amino acids. Because the amino acids are available in one particular chiral form and mostly in the L form, D forms are you can get it, but they are much more costly.

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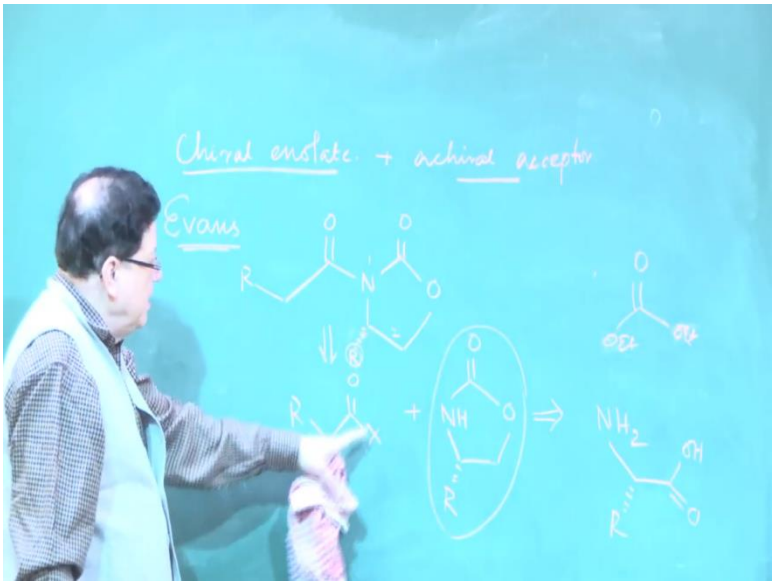

So, what famous scientist Evans Deed, so he made a auxiliary based Aldol Condensation which is extremely successful. So, what was the method? The method was basically that you

have suppose you have a compound like this, it is an amide type, but this amide is basically hooked as a chiral auxiliary.

So, if you look at this molecule, basically this is nothing but see some activated carbonyl compound plus NH oxazolidinones and there is a substituent, a group here, that depends on the type of amino acid you are starting with and also the configuration will depend on the if you want to make it an L compound then basically you have to see whether the R group is alpha or beta. If this is 1, that is 2, and that is 3, so 1, 2, 3, so, yeah, this is right. So, that is your L component. So, this is the starting source is an L amino acid. So, R could be isopropyl, that means it is valid, R could be methyl, it could be alanine, could be benzyl. That means, you are starting with phenylalanine.

So, depending on the if you want more steric bulk, so use benzyl, like phenylalanine or you can use isobutyl a isopropyl that will be valid. So, these are sterically more bulky or even you can have methyl that is alanine, but that will definitely give varying degree of enantiomeric access at the end of the reaction.

So, this is basically the chiral auxiliary that Evans made from amino acids, see this is the amino acid. If you reduce the alcohol by divalent so boron THF you can in one step you can reduce it to the alcohol and then this amino alcohol can be reacted with the carbonyl compound like CO, CL or CL, oxa this is your false gene that is possible or you can react that with OET, OET, that is so you make this Oxazolidinones as your chiral auxiliary and then react that with an activated acid and you get this amide. So, this is basically your starting point for the formation of the enolate.

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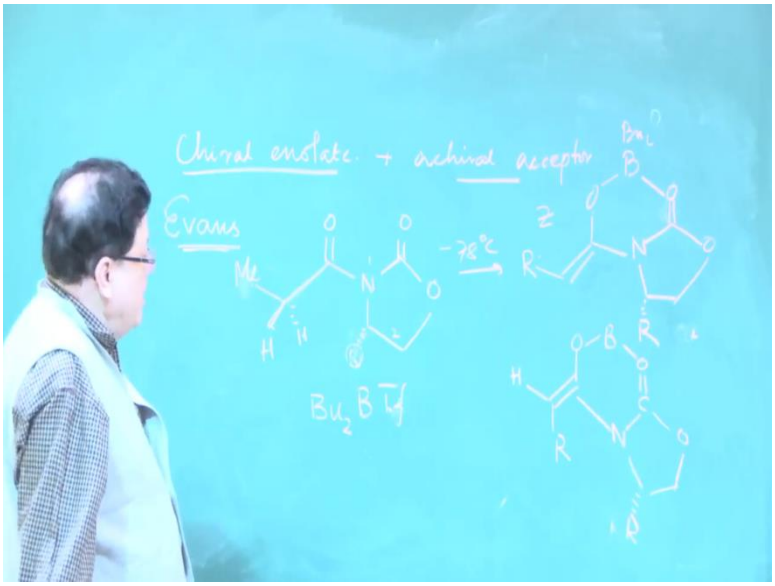

So, as you add now here he used a particular compound, dibutyl boron triflate, will form and enolate like this sorry, O double bond O in now, there are two types of enolate which are possible, either this or you have the other possible. So, the way the reaction was done, so the enolate that you get was basically the 1 where this is so, that is one that is one, so that means this is your Z enolate on Z enolate. So, that is what you are getting.

Now, there is a reason that why you will get this molecule, because there are two hydrogens here and this is kinetically formed if you treat this at minus 78 degree, you will get the loss of that hydrogen which will lead to this enolate. Let me just again check, double confirm, that this is the enolate that is formed, yes, that is the enolate, especially when R is equal to say methyl.

You can actually equilibrate this enolate by to the thermodynamic enolate, if you do it if you allow it to equilibrate allow it to arm into room temperature so that it can equilibrate to the E-enolate. But the way it is done that it is kinetically controlled so you get the Z enolate. So, this is the enolate form that is what is going to react with an aldehyde now. So, let us do that.

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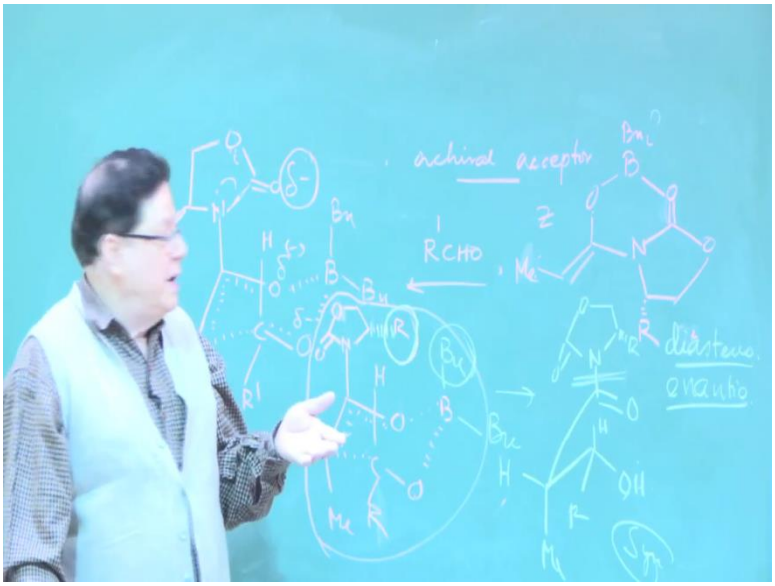

Now, I know that this reaction when I add RCHO, that reaction make it R1CHO, that reaction will go higher the Zimmerman and Traxler model. And Zimmerman and Traxler model basically what? The demands that this will be the now instead of lithium, you have boron here. You have boron and then you have this carbonyl carbon and here you have the formation of the carbon, carbon bond.

Now, the syn selectivity demands that your R1 group should be on this side, that is the syn selectivity demands that, so the hydrogen will be on that side. And here depending on the geometry of your enolate, so that means that your R if R is methyl, make it methyl, suppose a particular example.

So, the methyl will be here, hydrogen will be there, and this is your that chiral auxiliary. Now, you can write this in two fashion. If you write it in this fashion, let us see whether the R group is now alpha or beta, if this is one, that is two, if R is that one let' say the R has to be beta. Because that makes it L, because all natural amino acids except the system are is ACE, so that is that has to be ACE configuration 1, 2, 3, so that is ACE configuration.

So, this is one possibility, this is your butyl. The other one is so this is the other transition state is this one. You do not change anything here, because that has to be that is demanded by the syn selectivity that the R has to be in the equatorial position. This is your N. Just you rotate this, so now this is R, this is your carbonyl, this is the oxygen.

So, this Oxazolidinone ring that will either adapt this orientation or it can adapt the other orientation where the carbonyl will be on this side. Now, according to Evans, what happens is that because of these two conjugations, this will be delta negative. And here this oxygen is also delta negative, negatively charged.

So, there is there will be repulsion, this is also delta negative, especially this oxygen. So, all these negative charges will repel this Oxazolidinone not to adapt this confirmation, but to adapt the other confirmation, which is shown here, this one, where the carbonyl is just the opposite to the carbonyl, this one.

Now, this is number 1 point, that confirmation of the Oxazolidinone. The number 2 is that in this case the enolate is coming from the backside and aldehyde is coming from the front side, from our side. And you have to now check the orientation of this group, the substituent which is at the attach to the R group. This time this R group is alpha, that means, this is okay that the R group is actually behind and your molecule is now approaching from the side, so there is no interaction with the R group.

On the other hand, had there been that this is the preferred confirmation then the R group would have been on this side and the aldehyde will have a lot of steric hindrance to the approach of this to the approach to that to approach to enolate from the side of the R group. Again, I repeat, first of all, the Oxazolidinones adapts this type of confirmation and not this one, that is because of electronic reasons.

Next is, the approach of the aldehyde. The aldehyde should approach to the enolate in such a fashion that the side chain of the Oxazolidinone group should be away from the approach of the and from the side the side should be away from the side from where the aldehyde or the carbonyl group, the acceptor group, is approaching.

Now, the way it has been drawn is perfect. This carbonyl and this R group is alpha. So, that means this approach what is shown here is the favoured approach. One thing, another important point we should remember that the existence of this axial butyl group at this position, in addition to this axial Oxazolidinone, that actually further reduces or further enhances the syn selectivity of this reaction.

Because, now, if R is axial, then it will suffer not only from the di-axial interaction from the Oxazolidinone but also from this butyl, and that is because of the boron, had it been lithium

that would have been absent. Because boron has another, this axial butyl group. So, then that increases the syn selectivity.

So, syn selectivity is enhanced, number 1, number 2, is your facial selectivity is also there, because it is only approaching from this side and that leads to the formation of only one compound and that compound will be CON, this is the Oxazolidinone, R and then OH, and this will be H, this will be your methyl and this will be your hydrogen.

So, this is syn. If you draw it correctly, then OH will be alpha and methyl will be alpha, both are alpha. So, that is the syn selective and enantio selective, so it is both enantio selective as well as diastereo selective. But remember diastereos electivity comes from natural origin, but it is still further enhanced, it is still augmented by the existence of this butyl. And enantioselectivity comes from the Oxazolidinone that your auxiliary and the auxiliary gives the enantioselectivity to this reaction.

I hope this is clear now. So, this is the syn selectivity which is there in Evans Aldol Condensation. Now, there are a few questions that how do you really remove this group, because that has to be removed. And it will be nice if you can again utilize this Oxazolidinone, if you can utilize, because that is another important issue of organic synthesis that to reuse the system over-and-over again.

So, that to make the reaction that sustainable, because economically economic sustainability is very important step. It is not only yield, but whether you are removing certain things and you are just discarding that is also not very good and people have realized that. So, nowadays reactions which are very attractive are basically these reactions where you can reuse whatever is coming out of the system.

So, what happened? If this is fitted with lithium hydroperoxide, that is lithium hydroxide, hydrogen peroxide, then it has been found, Evans has shown that this chiral auxiliary comes up, it becomes acid and you can recover this chiral auxiliary and you can reuse the chiral auxiliary. So, that is one of the brilliant way of doing this.

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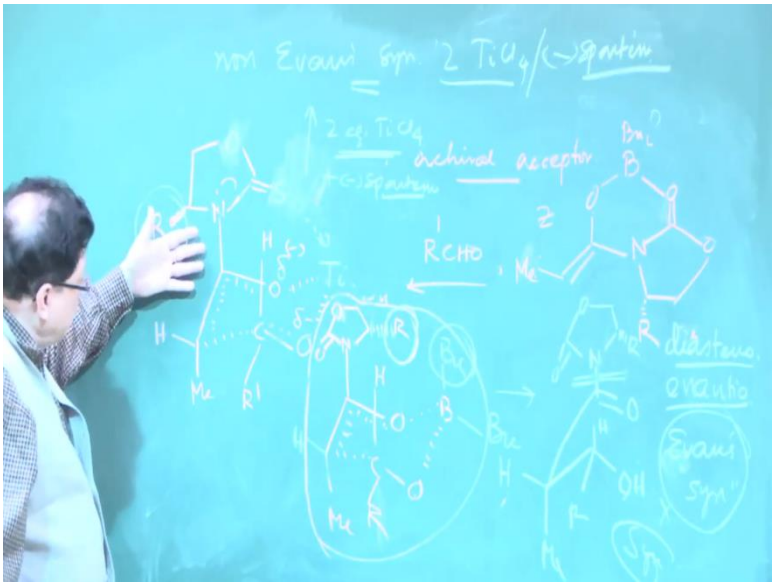

Now, the question is now, the next question is, suppose, instead of this boron. If you have another metal ion, like titanium, then what happens then there is a possibility that this can act as a another ligand to be hooked into the titanium. If that be the case, then what will happen then there is a drastic change in the course of that in the enantioselectivity of the reaction. The diastereo selectivity is, it remains the same, but enantioselectivity will be a problem, because enantioselectivity at least the product that you got earlier by using the boron triflate will be totally different when you use the titanium.

When you use titanium what happens, first of all, what was found that Oxazolidinone, was very effective, but what was very effective was if you make thio, if you make the thio derivative of this and if you make thio derivative then what happens that the titanium now that means, the Oxazolidinone is basically adopting a conformation which was earlier ruled out in case of the boron triflate. That is what is interesting.

Let me just check one thing then I will whether it is there or not, the titanium enolate. Yes, the titanium enolate is there. Now, this is by the way this is syn compound and this is called Evans syn compound. On the other hand, if you now use actually, this is still oxygen, this is not sulphur. If you use this type of complex, titanium enolate, make the titanium enolate and use one equivalent of titanium reagent to do this reaction.

In that case what happened you get the whatever you expected from the Evans boron chemistry, that means, if you take titanium as one equivalent then you do not see any change in the product stereoselectivity. That means the same Evans syn product is obtained. On the

other hand, if you take equivalence of titanium chloride. If you take two equivalence of titanium chloride and supported by some natural base like Spartin, then what happens that you get the other see the problem is, if you have this complexation form. First of all, these forms when two equivalence of titanium chloride was used. And some base which is Spartin, a natural product Spartin.

So, what happens this adopts now this type of complexation, so that now rotates. The earlier one which was forbidden that rotates and forms these titanium complex. If that be the case, if this is the major transition state then the aldehyde cannot approach from this side, from the side which is above this plane of the board, towards us. Because these R group is now facing us. So, you cannot get this Evans syn product if you have two equivalence sub-titanium and then forms which actually forms this complex.

So, in that case what will happen, the aldehyde will definitely come from the opposite side, from the side of the from behind the board, and this one, this thio Oxazolidinone will come from the side of this in the front of the board. So, whatever stereochemistry you got here that Evans syn, so you will get just the other syn compound. Syn selectivity will not be compromised, what will be what will get changed is the ultimate configuration of the syn isomer. So, you get Evans syn in case of boron triflate, and you get the non-Evans syn product, if you get if you use the TiCl4 two equivalence, and it increases, if you use, Spartin as the base.

So, that is I think the chemistry or the reason is the logic is sound. The logic is that, now the Oxazolidinone earlier there was this electronic repulsion, so that force the Oxazolidinone to push the carbonyl on this side and the R group was going backward. So, the aldehyde could have approach from the front side of the board, but when this is a sulphur, it relates to the titanium. And the R group is now coming towards us, so the aldehyde will approach from the backside and that will invert both the stereochemistry's. But then you will get again another syn compound and that will be called the non-Evans syn compound.

So, that is what is the chiral auxiliary based one beautiful example of chiral auxiliary based Aldol Reaction. There are many such reactions. I think, we will take one more class where we will discuss some of the problems, because we have not drawn the stereochemistry very carefully, we have just kept it in the sawhorse projection formula, but we will convert it into the zigzag, the anti-form, and then we will show all the products.

And but that we will discuss in a problem-solving session. So, we hope that we will take another definitely we will take another class while all the problems which have been which are generated by our discussion through all these 20 all these 40 lectures, for 30-minute 40 lectures, we will compile them and in a 1 hour problem solving session that is the final session will solve all those problems and to clarify any doubt which is there in the mind.

There must be, there will be definitely, because stereochemistry after all is a complex subject and proper drawing of the molecule maintaining the proper stereochemistry is an art in organic stereochemistry. And that will be mastered only if you practice more-and-more. And if you try to visualize as you grow in your visualization process of three-dimensional molecule. So, we will have one problem solving session dedicated to all the concepts that have been discussed in this lecture. Thank you very much.