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

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Lecture - 45
Further Aspects of Aldol Chemistry Including the Use of Boron and Silicon Enolates

Hello everyone, welcome to today's lecture. Before we proceed further, we will briefly look at what we did last time and then go to new aspects of the reaction that we were discussing. So last time towards the end we looked at many aspects of the SAMP and RAMP based C-C bond formation.

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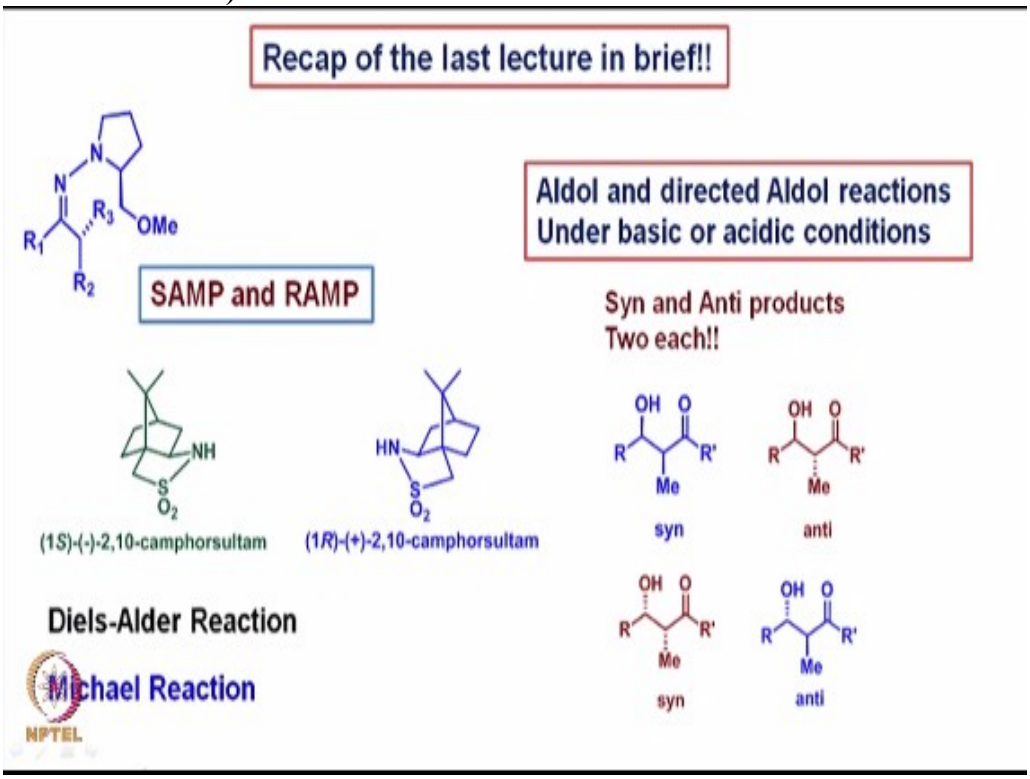

As you can see that this is a SAMP based hydrazone and when we carry out a C-C bond formation next to this hydrazone moiety then of course, we induce asymmetry. Likewise, we of course we have done the reactions with the RAMP. Now once we have got this particular product in which a C-C bond has been formed, then of course we did several reactions to release the auxiliary.

First one was of course the hydrolysis to go to the ketone. The second one was reduction of this particular hydrazone moiety to release the corresponding amine. The third one was to convert this into a thioketal and the fourth one was the case in which R1 was hydrogen. Then of course we through N-oxide bond formation here we got the corresponding nitrile.

In all these cases we had this carbon-carbon bond formed in an asymmetric fashion and which of course was high enantioselective products. Now we also looked at the camphorsultam based auxiliary as introduced by Oppolzer and saw the Diels-Alder reactions and Michael reactions in highly enantioselective fashions. Now towards the end, we looked at the aldol reactions and directed aldol reactions under basic or acidic conditions.

We saw that if the aldol reactions are not directed, then of course, we keep on getting different mixtures of the products. But if we have a directed aldol reaction, then of course we get only specifically these types of products in which the two enantiomers of the syn product and two enantiomers of the anti products are formed. And if the reaction is highly diastereoselective, then of course we would get one as the major over the other one.

So that is how we looked at the reactions of the directed aldol reactions. Now we will go further for today's lecture.

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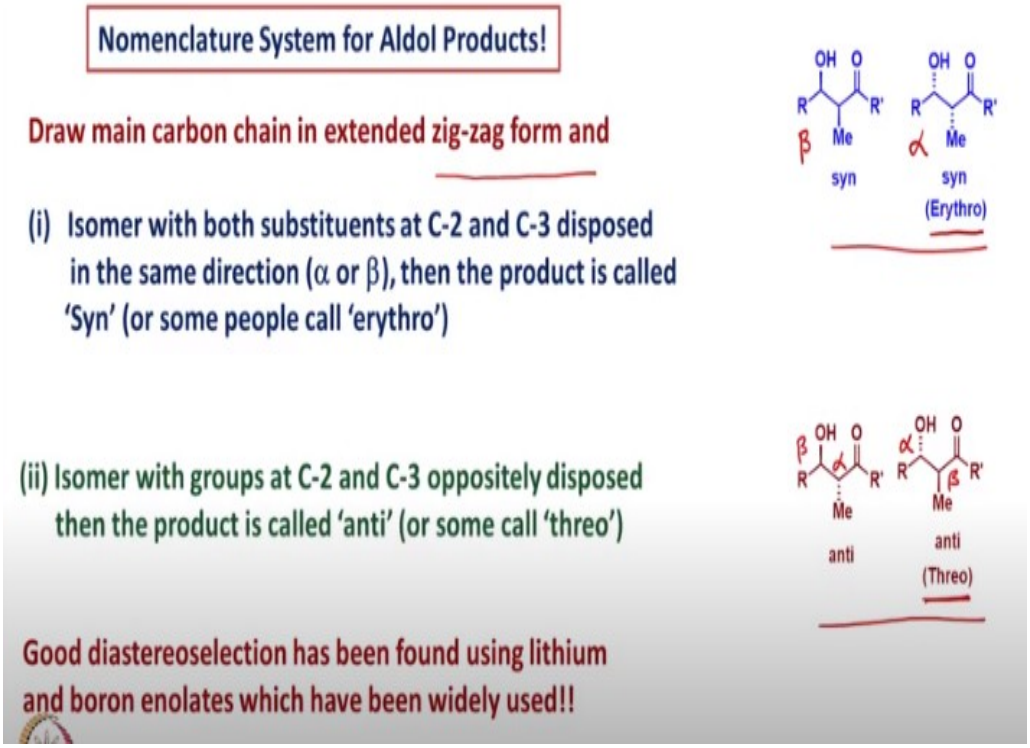

First of all these syn and anti products these are the syn and anti products we need to sort of define them and as you can see here, it is a syn product in which the two hydroxy groups are oriented in the same direction and the same is the case here. And first of all, what you have to draw is a main carbon chain extended in a zig-zag form. So this is the RCCCR prime.

This is the main chain of the, which is written in zig-zag form. And in such a case when the two substituents at C-2 and C-3, like this is C-2 and this is C-3. If suppose these substituents are oriented in or disposed in the same direction, like as you can see here they are exposed in beta direction or alpha direction here. So that means, these are called syn products.

When the C-2 and C-3 groups are oriented or disposed in different directions, like here this is an alpha and this is beta and here is alpha and this is sorry this is beta. It is not correct. This is beta. This is beta and this is alpha. And this is alpha and this is beta. So they are opposite to each other. Therefore, these are called anti products.

But some people call it as erythro although not many people accept it, but some people call such arrangements as erythro and this arrangement as threo. It has also been found that good diastereoselection is noticed using lithium and boron enolates which have been widely used.

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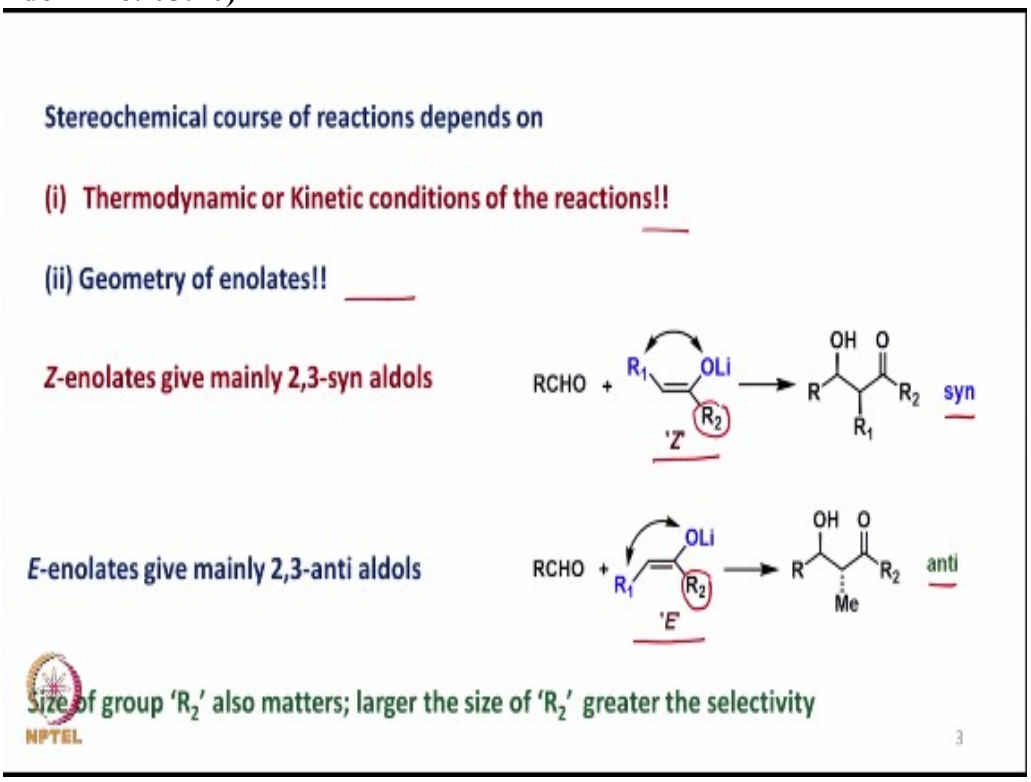

The stereochemical course of reaction depends on thermodynamic and kinetic conditions. Different kinds of thermodynamic and kinetic conditions are employed. It also depends on the geometry of the enolates. And for example, this is a Z enolate and this is an E enolate. So the R 1 group is apposite, R1 group group is opposite to the enolate here and therefore, this is an E enolate.

Whereas R1 group is in the same direction as enolate and therefore this is Z configuration. And it is noticed that the Z enolates lead to syn products and E enolates give to anti products. It also depends upon the size of the R group here. For example, if the size of R2 is large, then there is a better selectivity or higher selectivity that is observed.

So that means, everything boils down to the fact that how can we ensure that Z enolate is formed or E enolate is formed depending on what we want to do it. So selectivity in terms of formation of E and Z enolate is therefore important.

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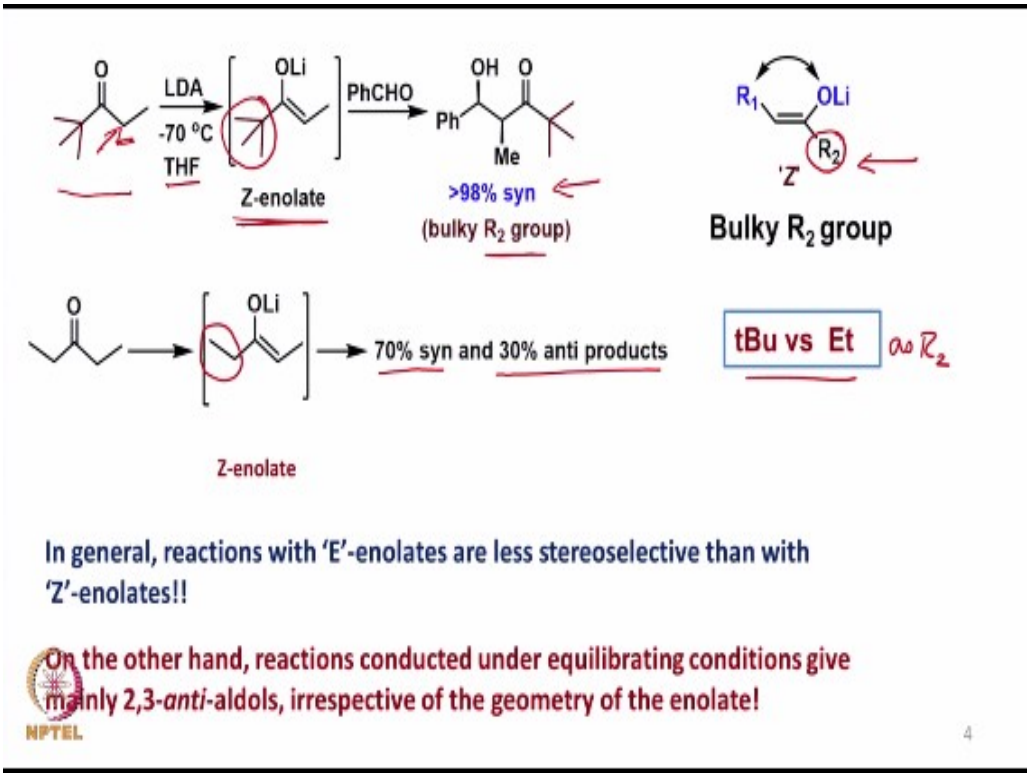

Now for example, if we take a compound like this in which there is if there is a tertiary butyl group here and ethyl group is here, and if the reaction is carried out in THF at low temperatures like -70 degrees using a base like LDA, lithium diisopropyl amide, then the enolization would occur from this position here obviously, and we get the enolate like this, which is a Z enolate.

Now when this is reacted with benzaldehyde for example, the product that is formed is syn product which is more than 98% syn and the group that you can see here is bulky R2 group. So this is what we were saying that the R2 group should be bulky. So here as you can see that this bulky tertiary butyl group has been put and therefore the selectivity turns out to be very high.

Now if we take, in contrast we take this diethyl ketone, where the tertiary butyl group is now replaced by the ethyl group, then we of course will get this as Z enolate. However, the Z enolate gives 70% of syn and 30% of the anti product. So that means now since the bulkiness of the R2 group is reduced. So this is the R2 group and here it was tertiary butyl. So it is ethyl versus tertiary butyl group as R2.

So clearly the size of the R2 group makes a lot of difference in terms of selectivity of syn versus trans. So in general it has been found the reactions with E enolates are less stereoselective than with Z enolates. Now on the other hand reactions conducted under equilibrating conditions give mainly 2,3-anti-aldols irrespective of the geometry of the enolate.

That means that the thermodynamically 2,3-anti-aldols are formed if the reaction is allowed to continue or the reactions are conducted under equilibrating conditions. So eventually it forms thermodynamically more stable anti aldol product. But if the reactions are not performed under equilibrating conditions, then of course Z enolates give better selectivity than the E enolates and then we will see how does that happen.

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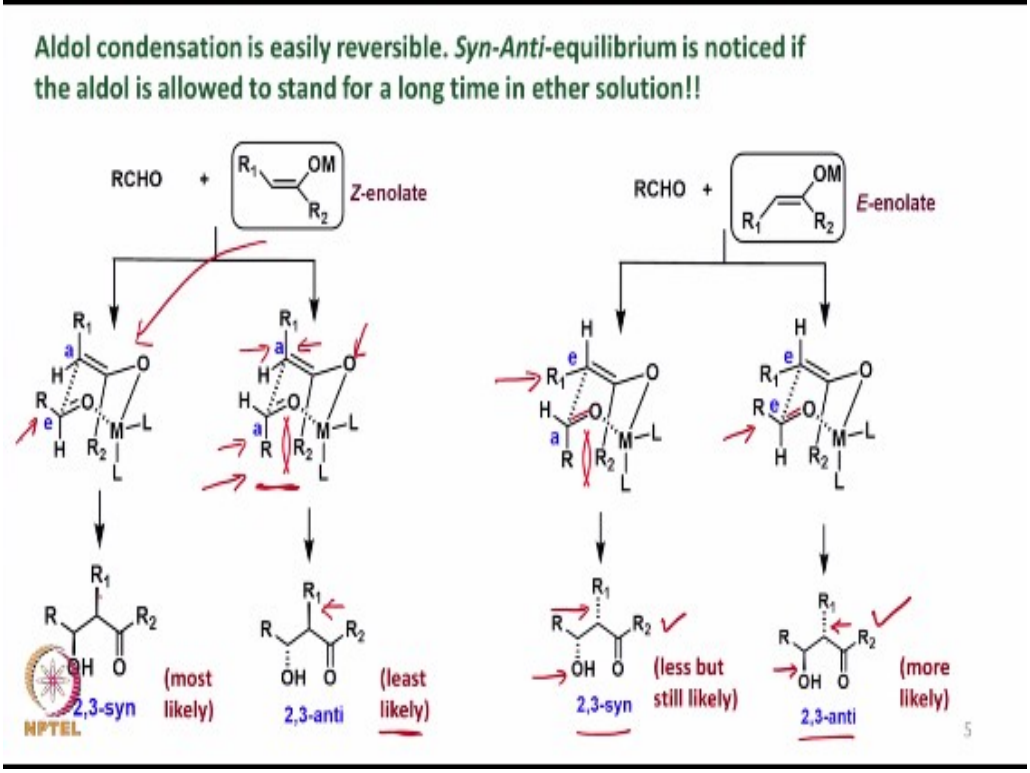

Now here aldol condensation that you can see is generally reversible, because unless and until it is worked up, the reaction is worked up with acidic conditions or basic conditions, depending on what kind of enolates are used. And the reactions are basically reversible. And syn anti equilibrium is noticed if the aldol is allowed to stand for a long time in ether solution.

So now why is it that the Z enolate gives syn product more and E enolate gives a kind of mixture that you can see. Suppose you allow this aldehyde to react with Z enolate like this, Z enolate, so we can make this kind of six member transition state, where we have this particular enolate part shown in here for example. And aldehyde can orient itself in such a way that the R group is in equatorial orientation.

And the carbonyl group is now having a chelation with the metal. So this particular OM is oriented here, so that the boron or the lithium or whatever the metal is, can have an inter chelation with this and this six member transition state, which is a cyclic chair form can be anticipated. So if you can see now here that the R group is equatorial and this R1 is axial. Of course, and this R2 is hanging here below.

In such a situation when the aldol condensation takes place, then we can anticipate that this particular geometry is formed. For example, this the C-C bond when it forms in here, then what we have is a hydroxy group pointing it upward and the R1 group is also pointing upward. Therefore, these two are beta and therefore this is 2,3-syn product. Now this is most likely the product between the two of them.

In the second possibility we can orient the aldehyde in such a way that R group now becomes axial. So now we have two axials here, the R as well as R1. Here the R1 being axial does not

matter much, because we do not have any substituents on this particular position and therefore there is no 1,3 diaxial interaction.

On the other hand, when this becomes axial here, then what we have is on 1, 2 and 3 now we have a 1,3-diaxial interaction and therefore, we can expect that such a steric hindrance would create a problem. At the same time the ligands attached to the metal will also have an interaction with the R group that is here or even R2.

And as you can now see that the R1 group is pointing up as in the previous case, but now if we turn around this R group, so that it orients in this particular fashion, then of course the OH will come down and therefore this is anti orientation of the aldol product. Now this is what we call it as least likely and that is because of the tremendous steric hindrance that the R and R2 groups and also the ligands on the metal are basically experiencing.

Therefore, this is least likely and this is most likely. Now we turn towards the E enolate and as you can see the same type of orientation that we can show. But in here, now since the E enolate is there, therefore R1 group is opposite to the OM and therefore, it is orienting in a equatorial position. Now if we put the aldehyde in which we have the R group here in the axial orientation.

Of course there has to be a double bond O and in such a situation when the reaction occurs, as you can see R 1 is pointing downward and if we orient R up then OH will come down and therefore this is 2,3-syn. Now here there is a possibility of the same sort of interactions as they are here in this case. And therefore it is also not a product for choice.

And when we convert the other orientations where the RCHO group is such that the R group is equatorially oriented. Now we have R as well as R1 group, both are equatorially oriented. And then now if you look at the products that is formed, in this case if R group is already in the same direction as up and this particular part is also here. Therefore, as such you can see that the OH is pointing upward and the R1 group is pointing downward and therefore they are also anti to each other.

So now this is 2,3-syn and this is 2,3-anti and therefore what we expect that in this case since the steric hindrance is not there, therefore we expect this product to form in a larger amount. To some extent this product is form and a larger amount of this particular product is formed. And therefore, we say that the Z enolate is very good enolate to lead to the 2,3-syn product.

And in this case we get some what a mixture of the products because in this case this is less but still likely. Why do we say still likely because R1 group is in equatorial position. Whereas in this case the R1 group is in the axial position. Therefore, between the two of them this one and this one, this is little bit likely to be formed more, but this is less likely to be formed.

Therefore, in this Z enolate case when there are two possibilities, clearly the 2,3-syn product is most likely and therefore, the selectivity turns out to be high. In the case of E enolate, because the R1 groups are equatorially oriented, therefore both the possibilities to some extent one large one less is there and therefore selectivity becomes somewhat less.

Now the C-C bond formation via boron and silicon enolates have been very much used in the aldol of chemistry and we will look at some of these things in little bit more detail.

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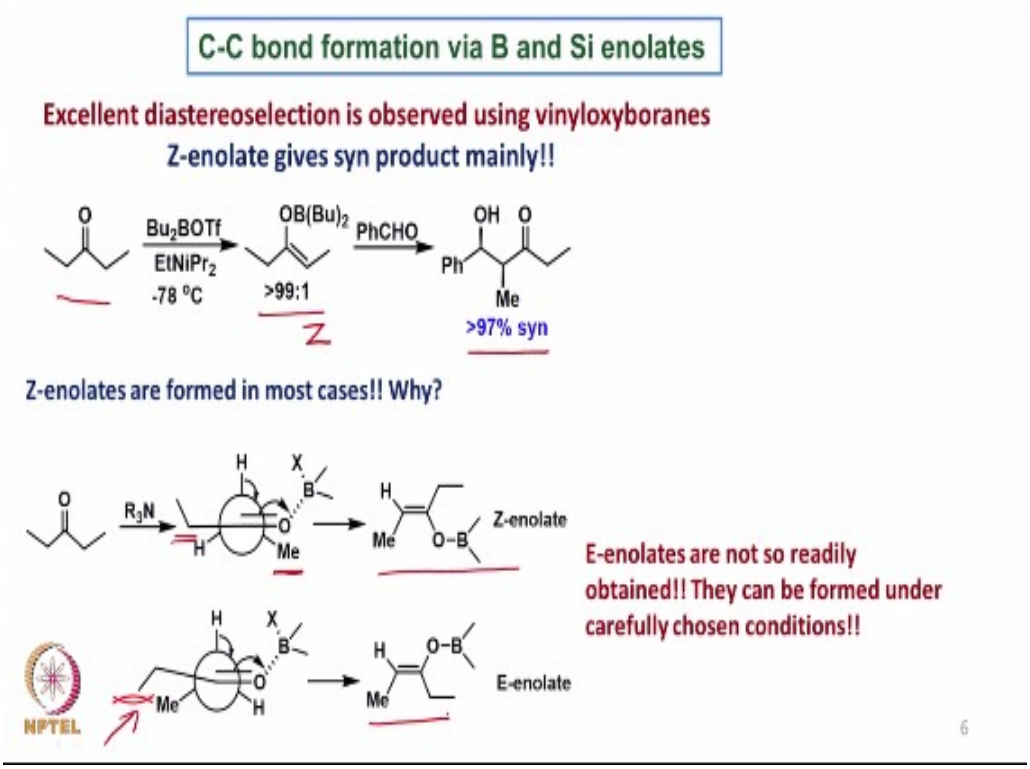

Excellent diastereoselection has been observed using vinyl oxy boranes. As we checked before that we can make the enolates the way we wanted. Now if we take diethyl ketone for example, something like this, something like this, then if we use dibutylboron triflate and in the presence of this Hunig's base that is diisopropylethylamine at -78 degrees then this is the enolate that is boron enolate that is formed which is a Z enolate which is more than 99 is to 1 ratio of the Z and E enolate.

And then this reacts with benzaldehyde. Then of course you get syn product, syn aldol, which is more than 97% in terms of its ratio. Now why is it that the Z enolates are formed in most cases? One of the reasons for this is that if we take the kind of Newman projection of the transition state, then as you can see it here that this particular methyl group and this ethyl group are away from each other.

And whereas, if we look at this below here, then the methyl group and the ethyl group are towards the same side. So obviously, there is a tremendous amount of steric hindrance here and that allows the methyl group to be away from the ethyl group and it prefers to remain in this direction. And when that particular orientation of the methyl group is preferred, then when the deprotonation occurs, of course you get the Z enolate as the major product.

Here you will get the E enolate. But E enolates are generally not easily obtained and they have to be obtained under carefully chosen conditions. Lot of work has been done in this area and especially by David Evans and also to some extent by H C. Brown in this case. Now we will see

what exactly happens when we change the substituents or we change the bases or we change the kind of size of the bases or the size of the substituents on the boron or even the leaving group.

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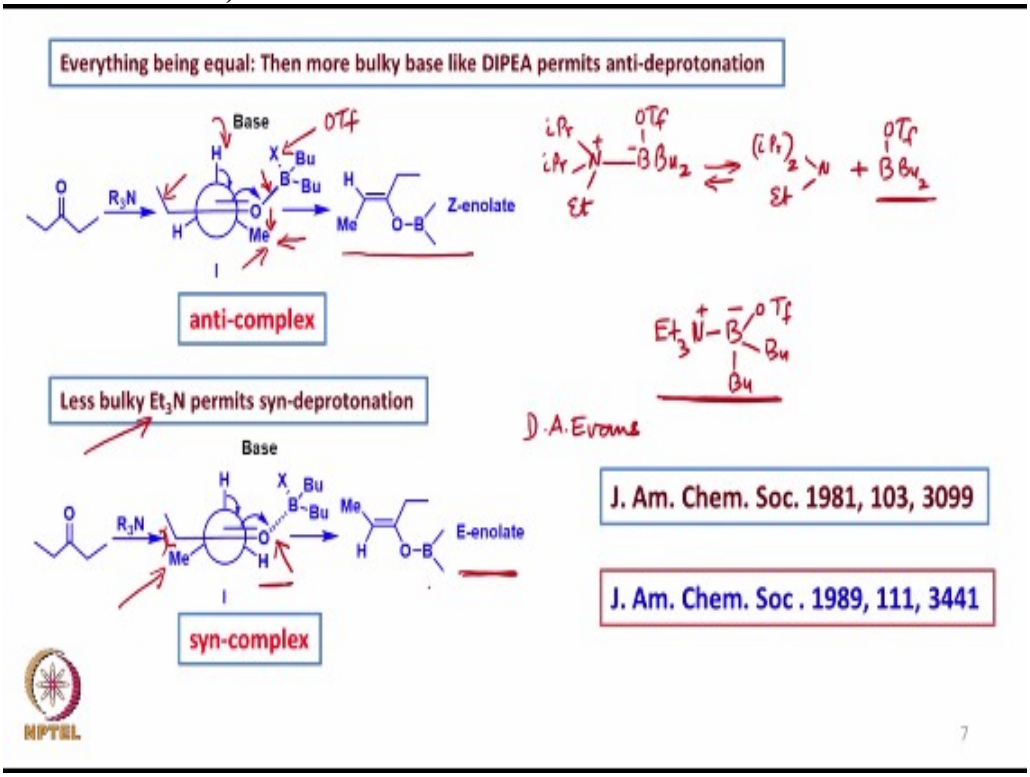

So as you can see here, the same thing I have written here now except that we have dibutyl this substituents on here and we have put here X, X as a leaving group. So it could be say for example a triflate. So what has been observed by David Evans, D. A. Evans that everything being equal, everything being equal, more bulky base like DIPEA, that is diisopropylethylamine, which is what is used in many cases and that allows anti-deprotonation.

Now anti-deprotonation means, this is the anti complex in which the methyl group and the ethyl group are away from each other. This is the, here the complexation is taking place with the boron triflate. Now what has been found that if we take bulky base such as DIPEA, so you have isopropyl, isopropyl and you have N and of course ethyl. So this is what is Hunig's base or DIPEA, diisopropylethylamine.

This is a large base and therefore when this reacts with a boron triflate, say for example this Bu_2, then it forms a kind of a complex like this, which is in equilibrium with the free form. That means you have $(iPr)_2$ N and ethyl and of course we have the boron here Bu_2O triflate. So this actually the it is an equilibrium with each other. That means, it attaches to the boron and it dissociates from it.

So in that situation when it comes in contact with the carbonyl group, then the when boron attaches with and boron then tries to be away from the methyl group here. That is where it is shown as a in the beta orientation. That means it is coming towards us and avoiding the interaction with the methyl group. So the methyl has a choice. Either it remains in this direction or it goes into this direction.

If it goes into this direction, then of course, we have steric hindrance with the ethyl group. But if suppose, it remains in the same position here as a methyl group then the since there is an equilibrium between the two of them, the boron gets attached to the oxygen, but from away from the side of the methyl group. And now the large base which is a Hunig's base goes and deprotonates the hydrogen from there which then leads to the formation of the Z enolate.

And if the methyl group goes into the other direction, then of course we would expect the E enolate to form. But then that does not happen in the case when we have large bases such as Hunig's base or diisopropylethylamine. Because they are in equilibrium and therefore the boron can easily interact with the oxygen and keep it itself away from the methyl group.

But if the base is relatively small, then such as triethylamine, less bulky, then there is a possibility of the deprotonation from the syn complex here. In that situation what happens if methyl group goes on to the left hand side, it has an interaction with the ethyl group; that is fine. But at that time, the boron actually with the less bulky groups, less bulky bases, form irreversible complex with the boron.

So you have say triethylamine and it forms irreversible say like this, you have minus and plus. So this does not dissociate readily and therefore it remains attached to the nitrogen. And since the base is required for the deprotonation, so therefore this particular orientation, that means oxygen boron bond is going backside. If it goes backside, then it will have a steric hindrance with the methyl group.

Therefore methyl group goes away from it and it prefers to stay here. And in this situation when a relatively small base, that is the diethylamine then picks up the proton from here and in turn deprotonation leads to E enolate formation. So you have a choice where the steric hindrance between this methyl and ethyl versus the methyl versus this group. Obviously, this group is very large.

Therefore methyl group tends to prefer to go away from it and has some interaction with the ethyl group. But then this is how E enolates are formed. And since this is a situation where it is not a very easy situation and therefore one gets the E enolate as the product, but with not high selectivity. That is the reason why Z enolate is formed with high selectivity when the large base is used in the deprotonation.

Now this is how it is summarized. So we will stop it here today and we will take the reactions of these for condensation and see how these are leading to the formation of the syn and the anti products in aldol reactions. So you please study whatever I have told and I have also given you some references, you can check more in detail and till then bye and see you in the next class.