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

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Lecture 38

Dynamic Stereochemistry: Stereochemical Issues in Cyclohexanone Reduction and alpha-electrophilic Substitution in Carbonyls

Hello. Welcome back to this course on structures stereochemistry and reactivity of organic molecules and intermediates, a problem solving approach. In the last sessions, what we have been discussing is basically the different kinds of attacks, which are called parallel and anti-parallel attacks, during your alkalilation of an enolate or halogenation of an enolate. And we have seen that how steric factors can dominate in controlling the parallel or the anti-parallel attack.

In this lecture, we will continue again still with the carbonyl chemistry. First, we will discuss an interesting problem which is involving the reduction of an anode in a cyclohexanone. We have done some examples earlier, but the reduction of the cyclohexanone alpha, beta unsaturated carbonyl system by metal sodium liquid ammonia dissolving systems. Today we will just discuss one problem and then we will take up the final problem of this course and that is the aldol condensation or aldol reaction basically.

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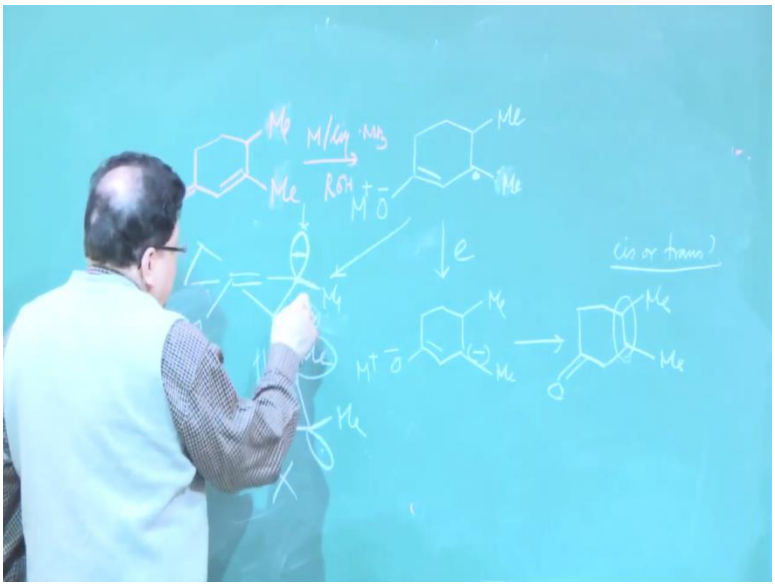

So, let us first do that problem. The problem is that if you have a cyclohexanone, let us put a particular group, suppose methyl here, methyl there. And if you are asked to remove the

double bond, there are many ways, one particular good way is metal liquid ammonia reduction, and in presence of a proton donor. Now, we know that metal liquid ammonia reduction goes via step-by-step electron donation. So, when one electron is added, it forms a system, which looks like this and enolate system this is the metal ion, this is a double bond, and a radical is formed at this position. So, that is your methyl and that is your methyl.

And then another electron is added, so that becomes an ion, so another electron is added and that becomes N ion and then this will be quenched by the proton donor. So, now you get the two methyl's and the double bond is reduced. And finally, it will tautomerize to go into the ketone form. So, this is the product.

Now, there is a question of geometry at this position, whether it is cis or trans, which type of product is formed. Now, that depends on the specific geometry of this radical, of this radical ion. This radical ion will be something like this cyclohexene, and then it will be the radical here, and that will be a methyl. This is one possibility, obviously, the methyl will try to adopt an equatorial orientation. Maybe, I can sorry, I can write this way this is methyl and that is the radical, this is one possibility.

And the other possibility is, let me just check, double check it, the initial one, just a second, now the initial one, let me write in this fashion. So, this is the radical that is methyl, and this is a methyl. So, that is one possibility, remember the way the radical is drawn is kind of SP3 character. And the other possibility is that, you change it, you invert it in this fashion. So, now the, this radical will be here, so the radical basically flips on this side, this is the methyl, and this is the methyl.

So, these are the two possible confirmations that this radical can adopt. There are a few things to remember, first of all, this radical is not a SP2 radical. It is regarded as a SP3 and this radical can be pointing upwards like this in a cyclohexene system, this methyl now becomes pseudo equatorial, and this methyl will naturally try to become pseudo equatorial, because in order to avoid this that both split the flagpole positions. It wants to avoid. So, this is the methyl.

The other hand this can now in it in hart like you know the nitrogen that lone pair inversion. So, that type of inversion can take place, the lone pair can come here. So, if that be the case then the whole thing actually changes, and this methyl, so this is the lone pair now. And the methyl will go up and this methyl will now become will have to occupy a kind of a actual

orientation that both are the flagpole type of orientation, which is not very energetically stable.

So, this one will not be formed or this one will not be followed. So, one that will be followed will be this and that makes sorry, this is the O minus. Again, I am missing this, this is the O minus. Now, the O minus comes back, not comes back sorry, now an electron is dumped on to this, so that will become negative, and that will be quenched by the proton source. The ultimate result is that the two methyl's are actually, one is alpha, another is beta. So, that means the two methyl's, the product that will be formed will be a trans ring junction. That is the measure product, a trans ring junction is the major product.

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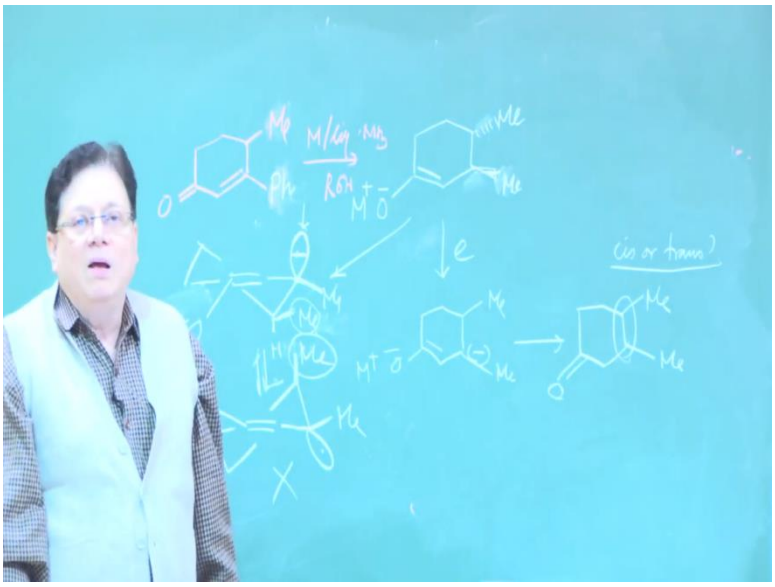

On the other hand, now, on the other hand, if it is suppose not methyl, suppose there is a -- this is phenyl group now, instead of a methyl you have a phenyl. So, if you have a phenyl then this radical in order to go into conjugation with the phenyl, will adopt an SP2 orient, so it will be, the carbonyl will be pure SP2 and the radical will occupy a P orbital. The radical will occupy a P orbital.

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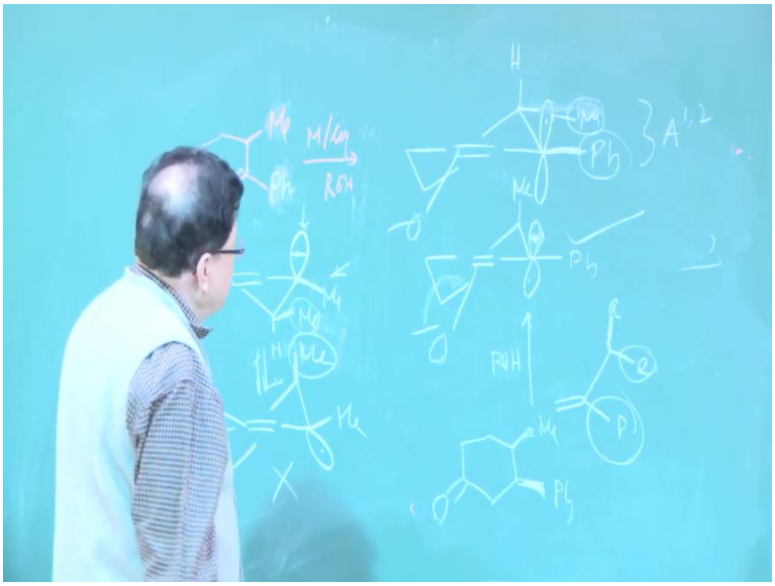

So, let me draw that diagram. So, this is the phenyl and the radical will occupy something like this. Now, everything is linear, so this, this, that added along with the carbon, carbon bond between the phenyl and this carbon, the carbon bearing radicals. Now, why this is now P orbital because it wants to enter into conjugation with the phenyl. Now the next carbon has a methyl. Next carbon has a methyl group. The question is, where the methyl group will be? So, methyl has an option to be on this side, on the equatorial side, let me draw it, equatorial methyl or it can have a possibility to be axial, which one is favoured.

Now, you know that if there is a double bond, and then if there is a double bond where this alkyl group is there, the next group where there is axial or equatorial substituent is possible, then because the equatorial substituent is very close to eclipsing the group at this double bond position. So, like here phenyl and methyl, they are basically in generating what is called A12 strain.

So, A12 strain will definitely I am sorry, there is O, minus here, I always missing that, this O minus. So, because of this A12 strain, the methyl will adopt this confirmation. Although, it looks a little awkward, but this is because of that A12 strain between the phenyl and the methyl. So, this will be the favoured one and then what will happen, when it comes back, the no, no, it comes back basically it will tautomerize. Now, next electron is dumped here, so that will become negative. And because of this methyl the mostly the proton that will be delivered will be from this side, from the bottom side, because the methyl is like an axial group.

So, the proton will be delivered from the alcohol, from the alpha face. So, if that be the case, this phenyl will become beta, and the hydrogen will be alpha, methyl is already beta. So, your resultant product having a cis-geometry. The resultant product will have a cis-geometry. Again, I repeat this problem. The problem started with this, that if you have a cyclohexanone system with two methyl groups, then it has been found that methyl liquid ammonia reduction gives a trans product.

I framed the question now. If this the (())(11:43) methyl is replaced by a phenyl then the major product that is formed is the cis compounds, so there is a major departure from one case to the other. So, what is the explanation for that? The explanation was that, when there are two methyl's, out of the two radicals first of all, the radicals is occupying an SP3 kind of hybrid orbital. And that orbital is positioned in such a way that the two methyl's become trans to each other, because that is the more stable geometry of the radical. So, if that be the case, then the radical is taking another electron to become negatively charged, and then finally, the proton is delivered.

So, that gives majority in the trans product. So, the product is driven by what? The product is driven by the stability of the radical which is dominated by the disposition of the two methyl groups in the trans orientation. So, you get the trans product. In case of the phenyl, when this methyl is replaced by a phenyl, then this radical in order to have conjugation, enter a conjugation with the phenol occupies a P type character.

If it occupies a P type character then this methyl, in order to avoid A12 strain, like what is present here, occupies this kind of actual orientation, beta actual orientation. And then the electron comes, this becomes negatively charged, and the hydrogen is delivered, the proton is delivered from the bottom face because of this methyl. Because that top face not very accessible.

So, this is the accessible phase. So, that makes these phenyl again beta, that goes up, methyl was already beta, so that gives rise to the formation of a cis product. So, I thought that is a very good example of the geometry of radical how it is controlled and how it can give rise to different types of stereochemistry.

Now, let us go to the last topic of this lecture series and that is what is called the Aldol Reaction. Everybody knows Aldol Reaction any organic chemist who has been who had

started organic chemistry, they have what was told that a one of the major method for formation of carbon, carbon bond is via the Aldol Reaction.

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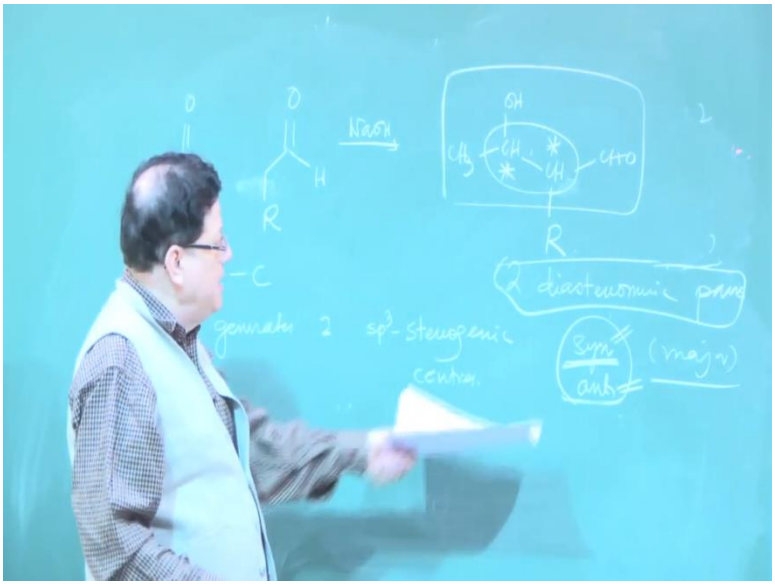

The Aldol Reaction is nothing but the reaction between two carbonyl systems and historically it was basically done with acetaldehyde. Two molecules of acetaldehyde and with the dilute sodium hydroxide it gives what is called a Aldol. And you know that if you hit this molecule, it loses the water and gives the that is the condensation product. So, that is Aldol condensation, that means the combining of the two reactions formation of this Aldol, aldehyde, and alcohol combined, and then the dehydration that is Aldol condensation.

But here we are not talking about dehydration, we are talking about the Aldol Reaction. That means we will consider up to this point. Now, this Aldol Reaction, you can see that already there is the formation of once asymmetric centred or the SP3 chirality centre is formed during this reaction. So, that means there is this question whether this type of reaction can be done in an asymmetric fashion, that means, whether you can get only one enantiomer over the other.

Remember, in absence of any chiral reagent, this will always give only the recipe mixture. Things become a little bit more complicated when you have a R group here, in one of the components of the aldehyde, then what will happen that the R group will end up at this position. Provided, of course, these two molecules react with each other, because they are always cross Aldol Condensation possible that means this reacting with self and this reacting with self.

But suppose you have a method of doing this in such a way that only this one reacts with that one to give the Aldol, then you get a Aldol like this, and now you see that you are generating another stereo genic centre. So, that is the scenario. That means is in this case, the beauty of Aldol chemistry is that it forms carbon, carbon bond formation, that is very important step in organic synthesis. And then it can generate, it generates two SP3 stereo genic centres.

So, two SP3 stareo genic centre means, now it can exist in the form of a two diastereomeric pairs. So, one can be called syn and other can be called anti. There are different ways of describing relative conformation relative configuration syn and anti syn to be the best amongst all of them.

So, the question is, how can we make this reaction more how can you make only one? If you do it, in absence of again, in absence of any chiral reagent, you will get all the diastereomers. But however, because it is two diastereomeric peers, a syn and anti, so their transition states will be also different in energy. So, there could be a natural selection, a diastereo selection, that is possible, even if you do not have any chiral reagent. Because you are getting pairs of diastereomers.

So, you can always expect that these diastereomers can be formed in different ratios. So, that is always possible. But if you want only one, if you want to bring an enantio selectivity into this system, enantio selectivity means first you get only one diastereomer, one diastereomeric pair that gives your diastereo selectivity and then out of that in that pair, what you get, if you can get only one of the enantiomer, suppose I get same as the major product.

So, I will say that this reaction is a diastereo selected because it gives more of the syn, because what is other diastereomer possible, that is anti. So, you get one diastereomer major over the other, so that gives the diastereo selectivity. On the other hand, now you have two syn molecules possible and then out of these two syn molecules which are enantiomers, if you can get only one as the major then that will be called an Enantioselective Aldol Reaction. So, basically you have to go step-by-step. First, how diastereo selection is taking place and then followed by how enantio selection can happen.

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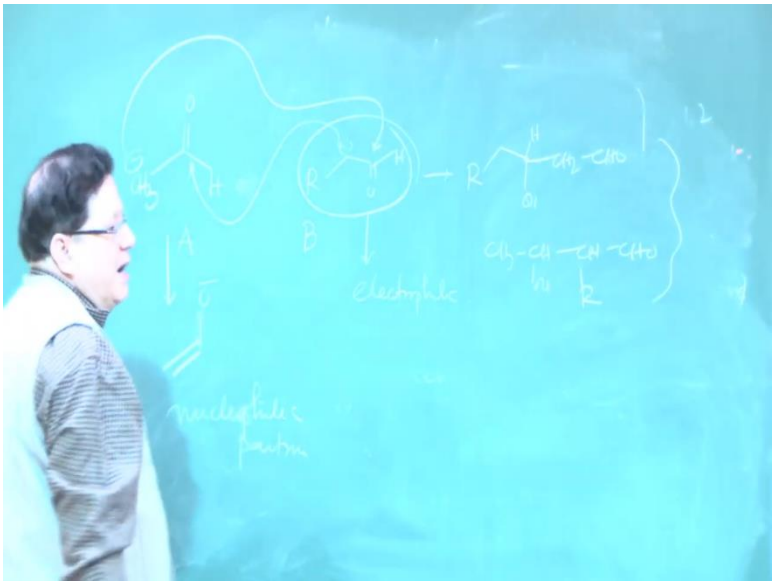

Now, before going into that, as this we have talked about this formation, the possibility of Self Aldol Condensation versus Cross Aldol Condensation, if you want to really do only the Cross Aldol Condensation, that means I have one carbonyl compound, and another carbonyl compound, and I want reaction between them, not only that, that also I forgot to mention that also can give rise to two products, that one is R, CH2, CHOH, and then CH2, CHO, that is one and another is CH3, CHOH, and then R, CH, CHO.

So, then also two types of Cross Aldol product are possible. This is simply because that either this N ion is reacting with this or this N ion and is reacting with the carbonyl. And you know that these N-ions are not bare-ions actually they are present as enolates. That means, if you want to make only one compound, so you have to make convert one of the component as the enolate, and this is what is the basically that is the nucleophile and this is the electrophilic partner.

So, the enolate becomes the nucleophilic partner, because that is what was dumping the electrons and attacking the carbonyl. So, this is a nucleophilic partner and this is your electrophilic partner. You can do the reverse also, that first generate enolate from this and then add it to the aldehyde, then that becomes then you will get more of this product, if you can make the enolate of this. And if you make the enolate of these and then add this one then you get more of the other product.

So, that is how the aldol reactions are controlled. So, these were the some of the historical development of aldol reaction. It is a very well known but very old reaction, I would say, old reaction discovered long back, long back means it is aldol reaction was discovered in 1864, discovered by Charles-Adolphe Wurtz, you know Wurtz reaction, in Germany. And also, someone in Russia, they almost together at the same time they discovered the aldol reaction. And at that time, it was done with the help of sodium hydroxide. If you do with the help of sodium hydroxide then actually it is very difficult to control, if you have different types of aldehydes. It is difficult to control the self-condensation versus the cross condensation.

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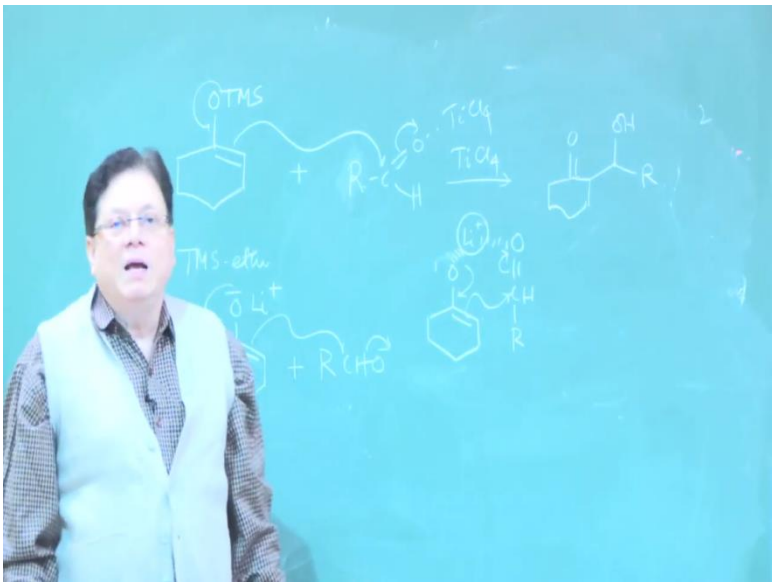

Then it was one big development take place, when Mukai Yama from Japan, he showed that you can actually trap one of the enolate as a TMS ether. So, if you take cyclohexanone form the enolate and then and then add TMS steroid, so that becomes O-TMS, so this is the TMS ether.

And then you can add any aldehyde of your choice. Suppose, I add benzaldehyde, of course benzaldehyde has an advantage, benzaldehyde itself cannot undergo Aldol Condensation because of the lack of alpha hydrogen, but it is not just that you have to have benzaldehyde you can take any aldehyde, maybe the first example that was given by Mukai Yama was with benzaldehyde.

And if you add a Lewis acid, like TiCl4, then what happens, then this falls off and that attacks the carbonyl, basically that attacks the carbonyl and it becomes you get the Aldol

Reaction. So, that is a significant development in having a desired reaction between one carbonyl component and with the other carbonyl component.

Then came that in 1981, the type of before that before 1981, it was proposed that if you do not have suppose TMS, there is another way of making enolate is the simple way is that you add some alkyl lithium reagent, so it becomes lithium enolate. Because there are different types of hydrogen's, different types of acidity. So, one standard we are making the enolate is by adding the alkyl lithium.

So, if you add alkyl lithium, so it will form the enolate, the lithium enolate. And then if you add the aldehyde that will do that reaction that actually does not need any catalyst, because it is just a bare O minus. So, that goes and forms the Aldol Condensation. Now, regarding this mechanism, that is a bio-molecular process and bio-molecular process, but it actually can go through if you look at the number of atoms that are involved here. And let us suppose again I write specifically that this is O minus and then you have R CH and double bond O.

So, if you see the number of atoms, there is a lithium here, number of atoms involved in this reaction. So, that will be this 1, 2, 3, 4, 5, and you have the lithium also, that is complex between the two carbonyls. So, that gave rise to the suspicion, that there may be a 6 member transition state which is driving this reaction. So, basically what you are having that you are having a lithium which is related to both the carbonyls. And then these type of cyclization this type of cyclic process takes place.

So, that is nothing but Aldol Condensation. But this now gives a mechanistic outlook of that reaction. And why these reactions are so fissile? Because it is going through a 6 member transition state. Now the question is, if it is going through a 6 member transition state, 6 membered can be chair, can be boat, all these possibilities are there.

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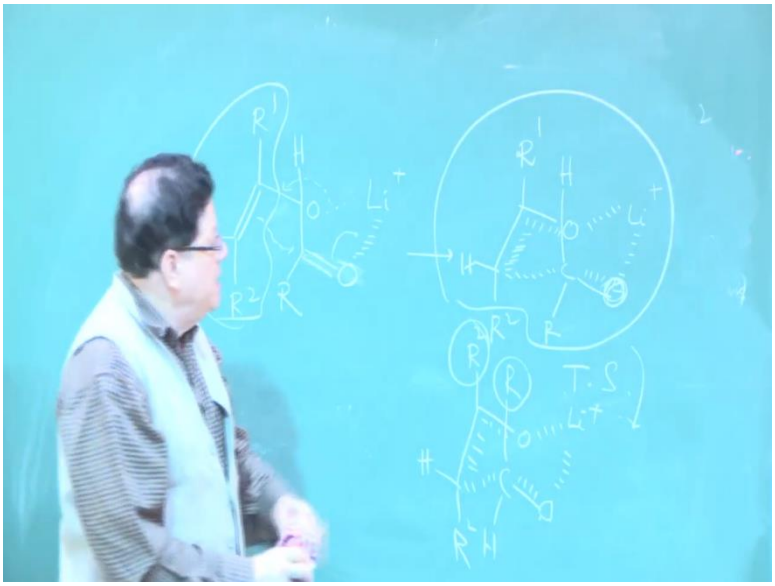

So, Zimmerman and Traxler they first actually gave this mechanism, and proposed, and which is accepted that this type of aldol reaction goes via a 6 membered chair like transition state. So, if you have suppose you have the enolate, so what is the enolate, enolate is like this. I put the substituent's of the enolate, suppose R1 and this is R2. Enolates, they have their particular geometry, and this is the lithium.

And now we have the aldehyde, so aldehyde carbonyl is here. You have the aldehyde alkyl group, suppose this side, and now the reaction this forms the complex, so the reaction will be something like this, that this attacks the carbonyl this goes here takes up the lithium and that comes and forms the carbonyl.

So, what is the transition state? The transition state will look like something like this, lithium, so there is from a bond formation here some partial bond here and then some partial bond that is the critical carbon, carbon bond formation. This is half broken and this is also half formed, and this is the different groups, our appendages to the enolate as well as to the carbonyl, to the aldehyde.

So, this is the transition state, this is Zimmerman and Traxler models. And obviously, you have different possibilities now. If your enolate geometry is fixed suppose, if your enolate geometry is fixed like this, then this aldehyde this oxygen, sorry this aldehyde can have the R group oriented in the equatorial position that is one possibility or it can orient in the axial position.

So, I write the other transition state, the other transition state is like this. Now, obviously, one thing is certain, that this is the one which will be problematic, this 1,3-diaxial, interaction. So, there may be a natural preference for the reaction to adapt this transition state, this transition state over this one.

And what are basically these to leading to? If this leads to one particular diastereomer or a diastereomer particular diastereomer, but remember the both the enantiomers of the diastereomer that is possible. And so, this will lead both the enantiomers of other diastereomer.

So, if it leads to suppose it leads to syn and if it then this will lead to anti or vice versa, but we have to check which one leads to what. But anyway, this shows that there could be a natural preference for one of these diastereomers, either the syn diastereomer or the anti-diastereomer. That preference maybe there.

So, let us take some so, basically up till now, what we have found is that the aldol reaction, if you want to do a particular type of aldol reaction, one component as the donor then you make it as the enolate and then add it to the other aldehyde, which is the electrophile, which is the acceptor.

So, the donor has to be converted into enolate and the acceptor remains like that, and then you add the enolate to the acceptor molecule and then the aldol reaction takes place. Mukai Yama, use the O-TMS sorry, he protected the enol as the ether system, TMS ether, and then broken down the TMS ether to generate the donor.

On the other hand, you can make lithiated enolates, lithium enolates, and then add it to the carbonyl compound and then through the Zimmerman Traxler model, it can go to the different aldol products, syn or anti. Now, as I told you, as I showed you through the two chair forms, that there could be a natural selection that is possible.

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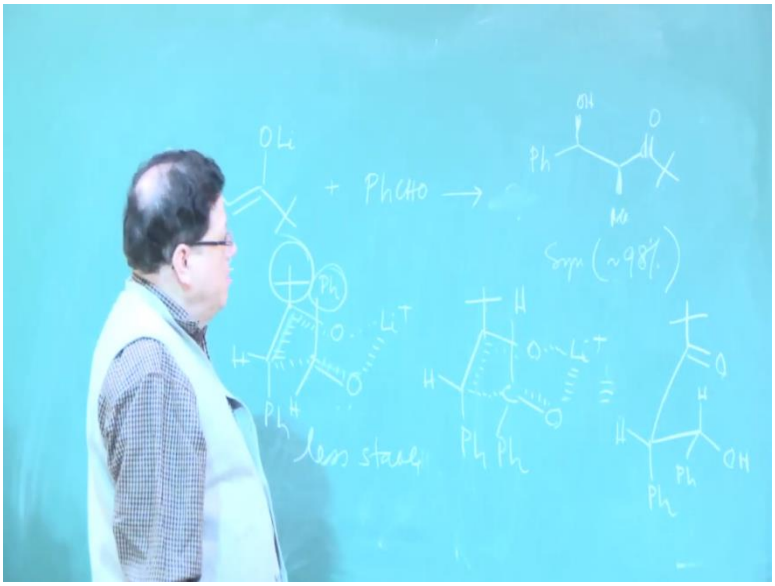

So, let us see what is that natural let us take a problem, I think if we take a problem then that will make it clear. Suppose, we have an enolate like this, OLI, and this is the tertiary butyl. So, this is a (())(32:39) stable enolate this is the Z enolate. Because these two are very bulky groups, so that is in the Z form. And suppose you are reacting that with PhCHO, benzaldehyde, so the question is, which one what was the result?

The result was that the syn product now, what is the syn product, the syn product is this. Methyl. The syn product is obtained is around 98 percent. So, it is highly syn selective reaction. So, why is that? So, that is clarified if you do the if you draw the transition state for the reaction. So, let us try to draw that transition state.

So, this is that lithium, the enolate, so this is the T-butyl and the phenyl is opposite to the T-butyl, so the phenyl will be here, and this will be the hydrogen. And now this is the carbonyl carbon, the phenyl either it could be in the axial position, the hydrogen is here, this is the double bond O, and now the transition state will be something like this. So, this is one transition state versus the other one. The other one this is the other one.

So, if that would be the case, so these are the two transitional states. Obviously, this is having lot of 1,3-diaxial interaction. So, this is less stable, much less stable. So, the major product will come from that transition state. The question is, whether that is really the syn compound or not? So, you have to draw the compound first, the product, the product is this. This is the product and if you draw it properly, you will see that, that actually matches with that one.

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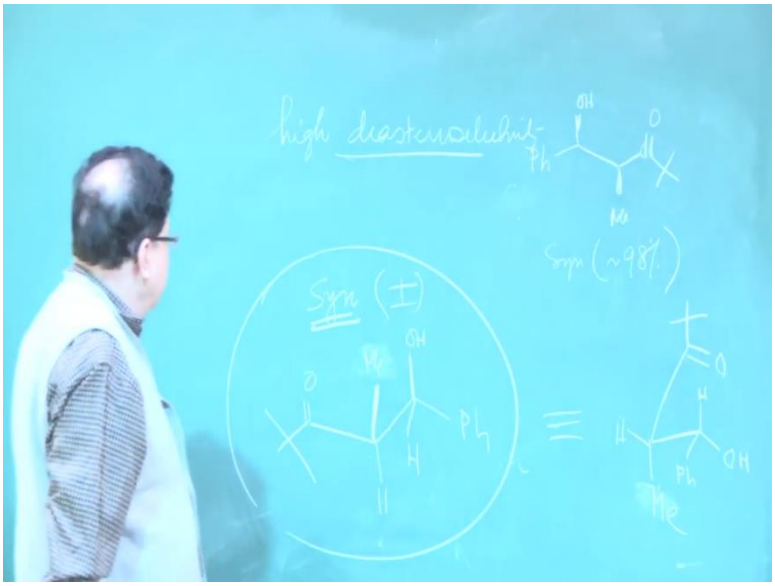

Let me just show you, because it is drawn in this zigzag fashion, so you put the phenyl here, and then you have the OH here then and you have H here. Basically, you are doing three exchanges and then here you have CO T-butyl, it is just the other form is like the mirror image form we are drawing. And so, this is here, so you have changed it to here, so that will be your this will be the phenyl, so hydrogen will come here, and that will be your phenyl.

Let me see whether both are phenyl, no, that is actually methyl. I am sorry, this is the methyl group, because we started with the methyl compound not the phenyl. So, this is the methyl. So, in this case, you see this is actually beta and that is also beta, both are on the same side. So, this is the syn product.

So, the syn product is predominating, but remember this is the plus minus mixture. You do not go to any enantio selectivity here. Here, the reaction goes with high diastereomeric selectivity. So, it appears that there is already a natural preference for one set of aldol product and that is the reaction is syn selective.

The reaction is syn selective, and why is that because of the disposition of this group attached to the aldehyde. In this case it is very high because there is a T-butyl group here and there is the phenyl. So, when they are in the 1,3-diaxial position, there is lot of interaction. So, that destabilizes that transition state quite a bit. So, that is almost very negligible less than about 1 percent, 1 percent to 2 percent that product is formed, and this is around 98 percent.

So, that is diastereo selectivity in an Aldol Reaction. Again, I repeat, this is the natural diastereo selectivity that one can introduce into an aldol reaction without encountering any enantioselectivity. In the next lecture, we will discuss the enantio selective reactions.