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

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Lecture - 44
Asymmetric C-C Bond Formations Using Oppolzer's Camphorsultams and Introduction to Directed Aldol Reactions

Hello and welcome to today's class. I hope you could go through what I discussed in the last class. But we will have a brief recap of the last lecture today before we look at the other aspects of asymmetric C-C bond formation.

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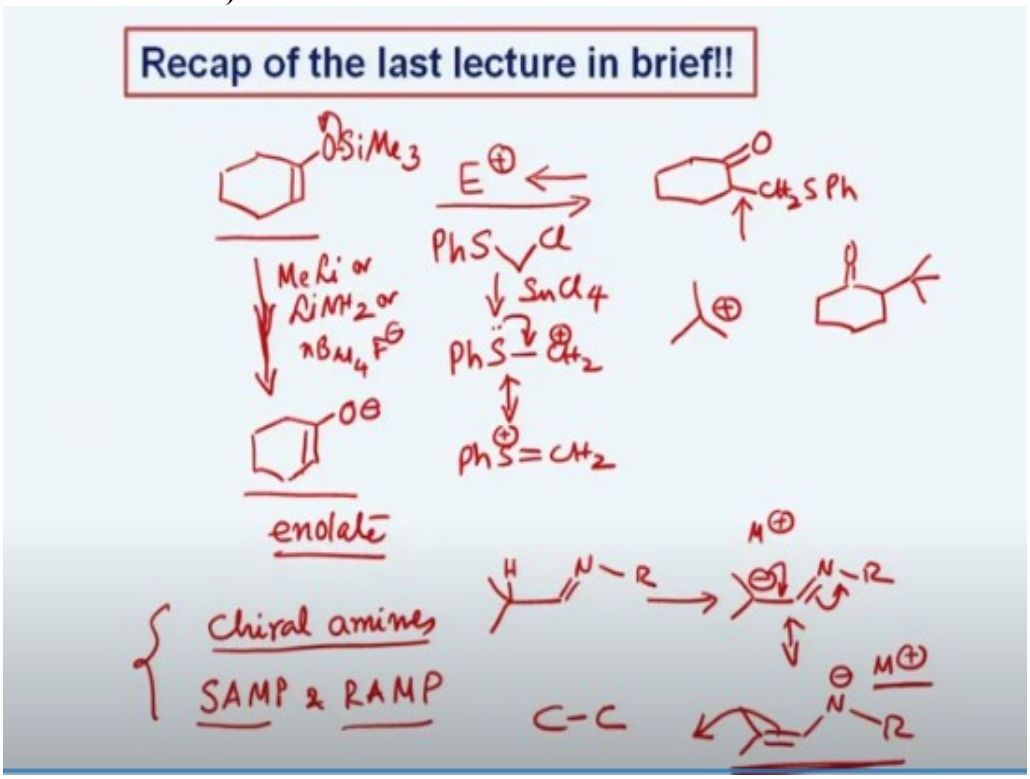

So towards the first part of our last lecture that we saw was how enol silyl ethers can be made to react with strong electrophiles we need strong electrophiles such as E+ as a carbocation or for example as we discussed towards the end we can have a CH_2Cl and generate upon reaction with Lewis acid say for example $SnCl_4$ or LCl_3 or anything and then of course we can generate the carbocation.

And this carbocation is generated because the sulfur stabilizes this carbocation. So this is how one can then allow the reaction of such electrophiles to take place with enol silyl ether and introduce CH_2Sphenyl group here and have a C-C bond formation. Now this is possible because the electrophile is very strong. But as a general rule enol silyl ethers are not a very strong nucleophiles.

They are weak nucleophiles and therefore we need to have a strong electrophile to react with it. We saw various aspects of it and saw even how a tertiary cation can be allowed to react with this enol silyl ether and we can get the ketones having a tertiary butyl group alpha to it, which is not easy to introduce by traditional means. So enol silyl ether is a good option to go for such reactions.

But then there are disadvantages as we discussed that only strong electrophiles can be reacted. But on the other hand, we can also react with this with say methyllithium or lithium amide as we discussed or even tetra-butylammonium fluoride and then we can generate the corresponding enolate upon the when this particular nucleophiles any one of them, this or this or this.

Then they react with the carbon silicon bond is broken and the enolate is generated. Now so enol silyl ether can be made reactive and as a reactive nucleophile or an enolate upon reaction with say the species like methyllithium or lithium amide or tetra-butylammonium fluoride. And then we saw the chemistry of imine.

So we had something like this where we had an imine where this particular proton alpha to the imine group can be deprotonated and we can generate an enamine of this type where we can write the resonance structure as this. And what it indicates is that the M+ which is what is going to come from base. So there has to be an M+ here, there has to be an M+ here as a counter-cation.

This counter-cation will remain close to the negative charge on the nitrogen because it is more electronegative and then this allows the C-C bond formation to take place. Then we also saw the other aspects of it where the imine chemistry was done with chiral amines and in with chiral amines we saw how asymmetric induction via C-C bond formation can be done.

And in the process, we also introduced SAMP and RAMP as two hydrazines, which allow the imine to form. And this imine upon deprotonation then allows enamine to form. Now this enamine is different enamine as compared to the enamine developed by Stork. Because in the Stork enamine case, the nitrogen did not have a negative charge.

Whereas, in this particular case we have a negative charge and the M+ plays a very crucial role. And that is exactly what is done in the case of chiral amines SAMP and RAMP cases where the methoxymethyl group next to the or attached onto the nitrogen is of course useful for the chelation and thus guiding the asymmetric induction. So these are the things we saw in the last class.

And now we see what after the C-C bond formation has taken place using SAMP or RAMP type of hydrazines. And then what happens to the products or what can be done to the products which are obtained after the C-C bond formation has occurred.

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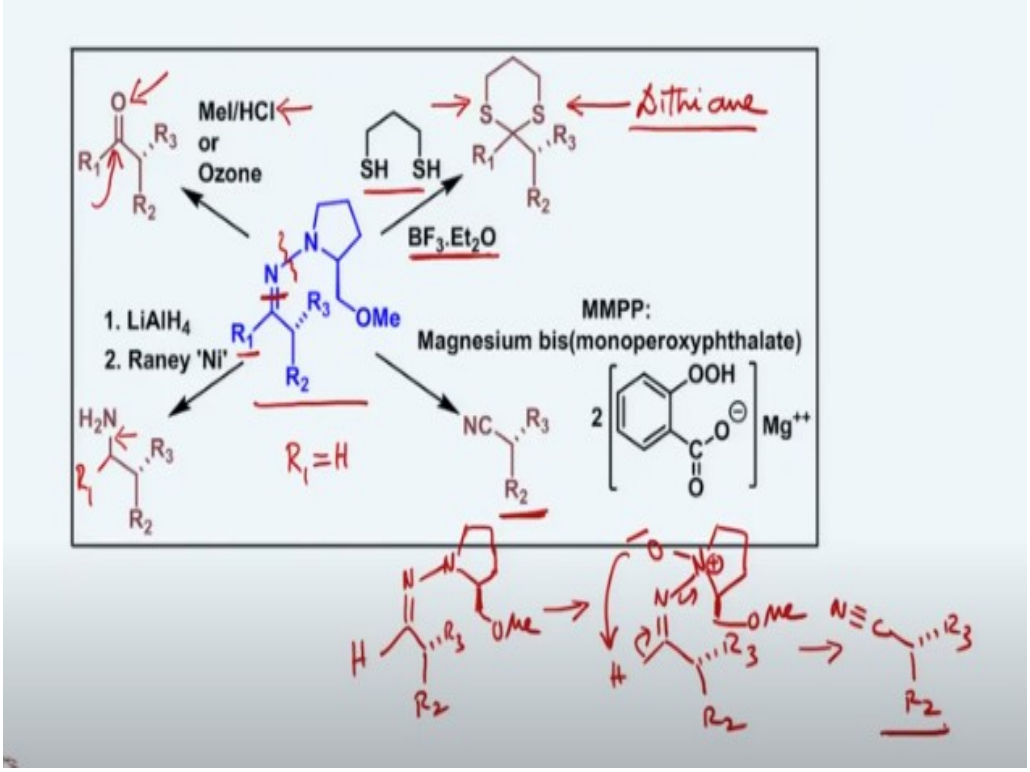

Now this is how the product of the SAMP or RAMP type is written and now what can be done with it. Of course, we can do the ozonolysis of the carbon-nitrogen bond or we can do the hydrolysis of the carbon-nitrogen bond with the help of methyl iodide and hydrogen chloride to form the corresponding ketone. So now this we can regenerate.

On the other hand, we can directly react with this dithiol to prepare the dithiane like this in the presence of BF_3 etherate. So without hydrolyzing this hydrazone to the ketone and then reacting with this dithiol in the presence of Lewis acid to get this we can directly react this hydrazone itself, because then the carbon-nitrogen bond acts like a leaving group. So it is very similar in terms of its reactivity to like a carbonyl group.

And therefore we can prepare the dithiane, this is 1,3-dithiane in the same pot. Now we can also reduce the carbon-nitrogen double bond first with lithium aluminum hydride to go to the corresponding amine and then when we do the Raney nickel based reduction then of course we have a nitrogen-nitrogen bond cleavage and that leads to the formation of if R1 is H.

Otherwise, there should be R1 here and then of course we get to the corresponding amine. So we have this particular reduction leading to amine. So we can get to a ketone or we can prepare a protected ketone as a dithiane or we can go to the corresponding amine. Now if R1 is H then we can expect this type of intermediate product to form which upon reaction with peracid like this.

So we have R3 here and R2 here and we have hydrogen here. So if we do a peracid treatment to this, we expect that we can have this intermediate to form where the N-oxide can form. And this N-oxide then allows this type of cleavage. Of course there will be positive charge to form and then that leads to the formation of the corresponding nitriles C triple bond N. So this is how this particular molecule has been obtained.

And of course now this nitrile group can be then converted into different other functional groups. So these are various conversions, which we can carry out of the hydrazone that is formed from SAMP and RAMP based hydrazines after the C-C bond formation has occurred.

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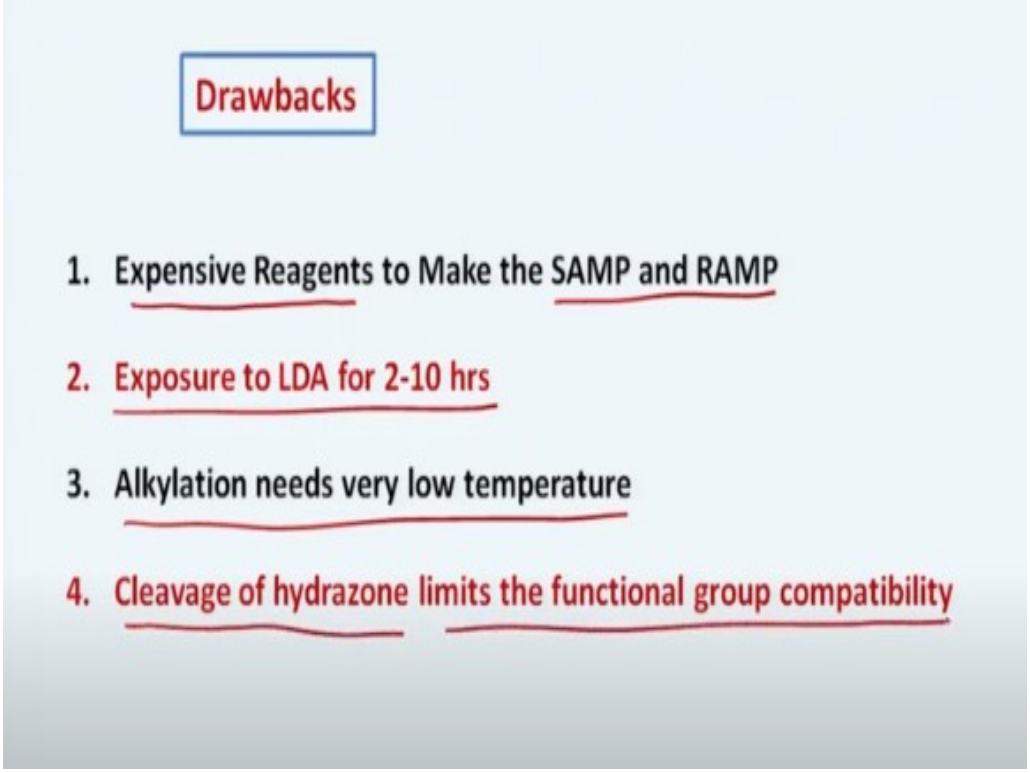

The drawbacks of these reactions are that these are expensive reagents. And they are definitely going to contribute to the cost of the product that needs to be evaluated at the end of the reaction. Of course, you have to expose to LDA for several hours to carry out the deprotonation and the alkylation needs to be done at very low temperature as you saw as low as -100 degrees temperature of course.

And then after the alkylation has been done, you slowly bring the reaction to the room temperature. And then you have to cleave the hydrazone. And this limits the functional group compatibility because suppose as we saw in the case of preparation of the nitrile we cleaved it by means of peracid treatment. Suppose your molecule contains a double bond then there will be a problem in terms of the peracid reacting with the double bond also.

So functional group compatibility has to be seen. So these are some of the drawbacks which are associated with SAMP and RAMP. But then these were found to be very useful reactions at the beginning of the asymmetric induction based C-C bond formations were looked at it. So it is a very useful contribution that needs to be appreciated and also learnt how these were introduced and how they were useful.

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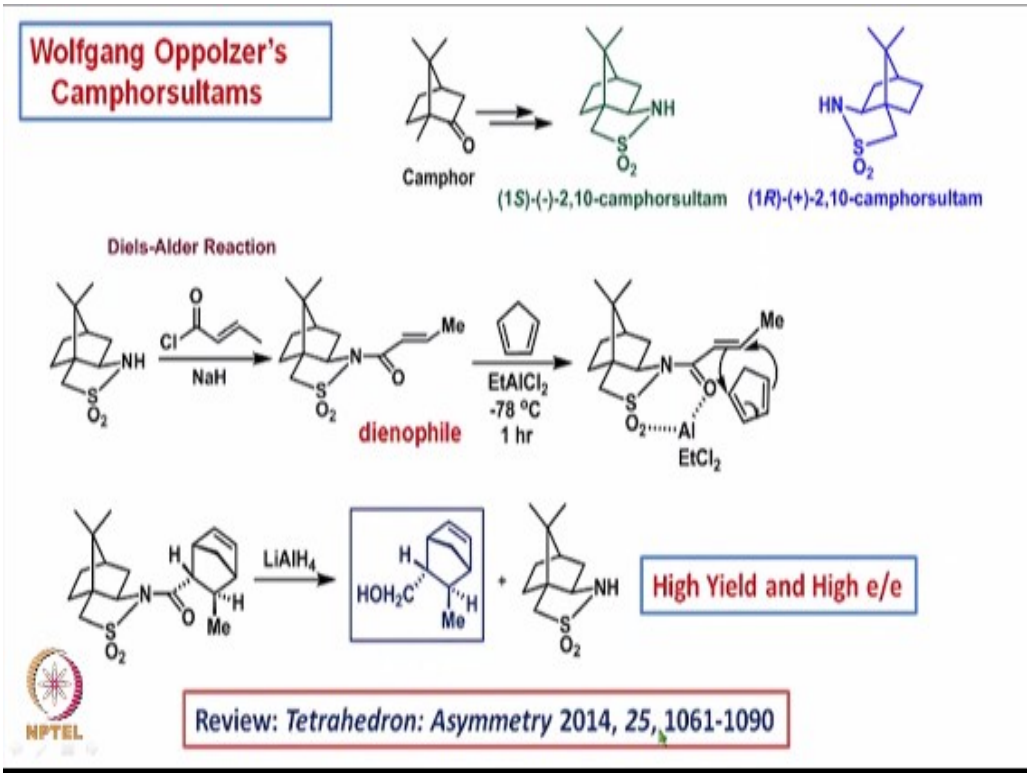

Then at the same time, Wolfgang Oppolzer in Switzerland introduced camphorsultams as interesting chiral auxiliaries. The camphorsultams look like this, which is (1S)-(-)-2,10-camphorsultam or like this, which is (1R)-(+)-2,10-camphorsultam. Now these are derived from camphor, which is a naturally occurring molecule.

And the reason to choose such kind of auxiliaries or ligands was basically because the exo part that is the upper part of the camphor here in all the cases is basically highly sterically hindered and therefore the reactions occur from the endo side, from the lower side. So now let us see some reactions.

For example, if we take one of these camphorsultam and react with this acid chloride in the presence of sodium hydride, then we get this kind of dienophile, which is a chiral auxiliary containing dienophile. Now if we allow this dienophile to react with cyclopentadiene in the presence of ethyl dichloro aluminum at -78 degrees, then the Diels-Alder reaction occurs from the lower side because the upper side as I mentioned is sterically blocked.

And therefore the reaction occurs from the lower side and leads to the formation of this kind of Diels-Alder adduct which contains the chiral auxiliary. But when lithium aluminum hydride mediated reduction is done, then this particular part gets cleaved and the corresponding alcohol is released. And of course, we regenerate the chiral auxiliary. Now these reactions have been found to be in high yield and high enantioselectivity.

A full account of the lot of work that has been done by camphorsultam based asymmetric synthesis has been reviewed recently in tetrahedron asymmetry.

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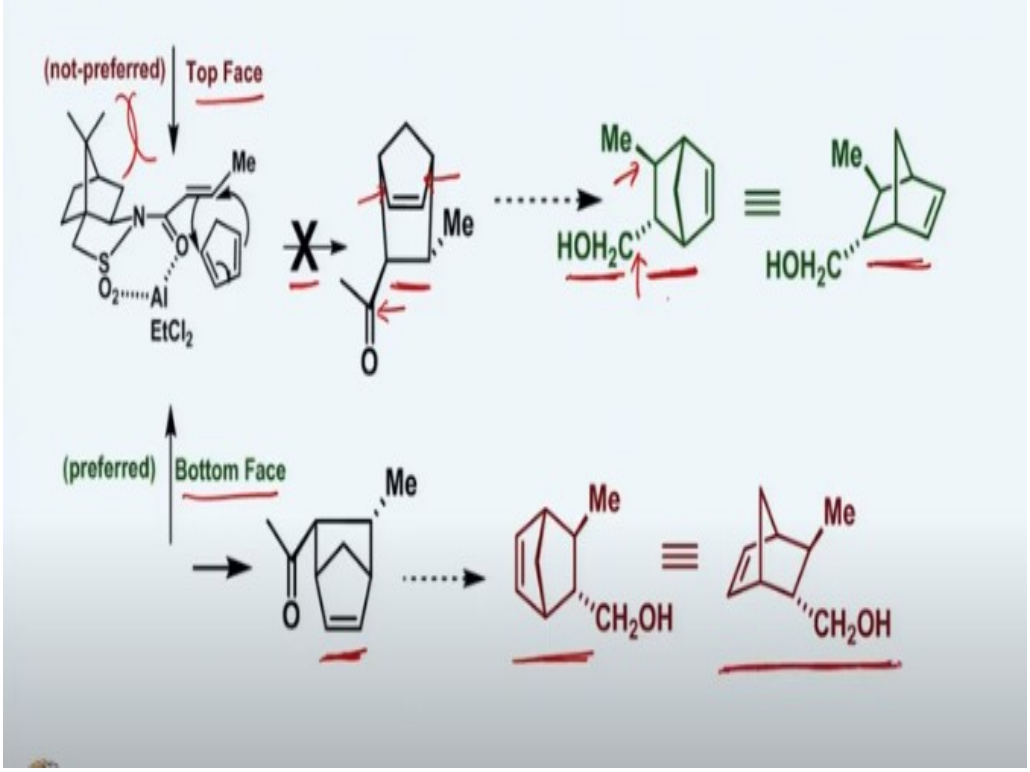

Now what is happening is basically the reaction from the top phase when the cyclopentadiene is approaching the dienophile, it could approach either from the top face or it could approach from the bottom face and the top face is not preferred because of this steric hindrance here. The lower face is the one that is what is preferred or the bottom face is preferred.

Now as you can see that when the diene is approaching from the top face, if this is what is the top face, which is not preferred, then this is the kind of intermediate that will form where this carbon-carbon bond basically is pointing towards us. And that we can see that if we just turn around on the paper of around 90 degrees of the paper, we can come up to this particular.

So this and this are basically same except that we have carried out the reduction here. So basically, if you just turn it around, you will see that the double bond comes on the right side. And then of course, we will have the methyl group which is going backside will turn towards above upper side, and then you get to this particular geometry, which is what is reflected here.

On the other hand when the reaction takes place on the bottom face, then this is the intermediate that is going to form and which again by simply twisting or turning, not breaking any bonds, twisting appears like this. So this particular product and this are basically as you can see they are mirror images of each other.

And thus, if we see that there is a facial selectivity, so if the Diels-Alder reaction is allowing a discrimination of the face, therefore this product is going to form exclusively.

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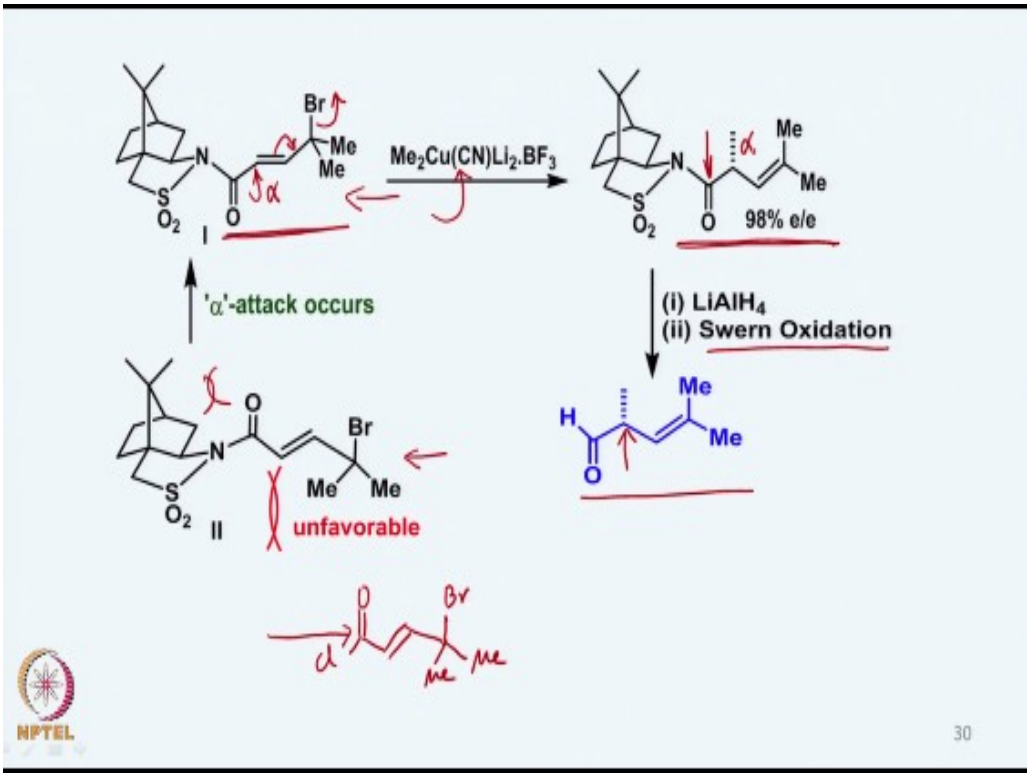

This is also reflected in another example in which if we take this type of group attached to the ligand, then we are favoring it to put it in this particular fashion, but we can also think about another way of attaching. So basically this is coming from, say you have an acid chloride and then we have this group here and to which the ligand or the auxiliary is attached.

When the nitrogen based auxiliary attaches, attachment takes place here and we can either write it in this fashion or we can write it in this fashion. This is the one that is more preferred, because for the reason that on the top face is going to be sterically hindered and this particular one is not sterically hindered. And therefore, the carbonyl group orients in this fashion to which the cuprate then attacks onto this carbon.

And then this goes as a leaving group leading to the formation of this auxiliary contained intermediate, which of course can be reduced with lithium aluminum hydride. And then once we get the corresponding CH_2OH after this part is reduced, the amide part is reduced, you can carry out the Swern oxidation and eventually to form this beta-gamma unsaturated aldehyde having a C-C bond formed here by the cuprate that we have added.

So the reaction is obviously taking place from the alpha side. So the attack is taking place from the alpha side. That is the reason why this alpha group has come because the lower side is relatively sterically less bulky.

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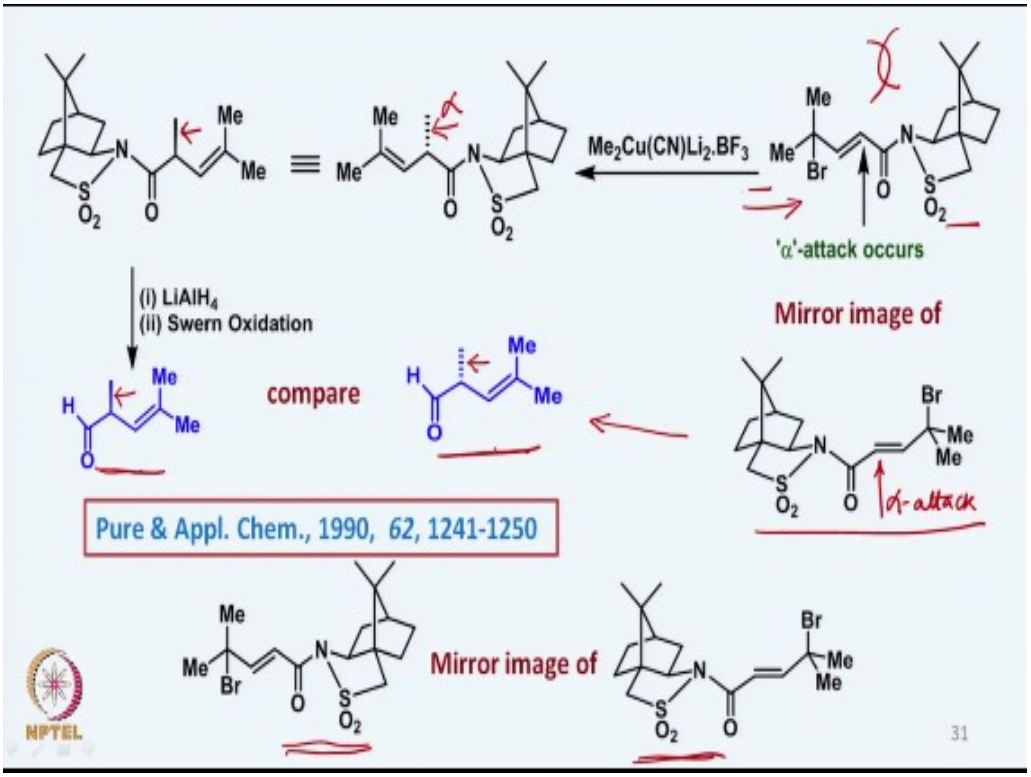

So if we take this, this is the one that we took, where the alpha attack was taking place from this side. And if we take its mirror image, which is what is this particular one, so if we write the same one as here, so this is going to be its mirror image. And that is what is shown here. So if we take this its mirror image, even then again the alpha attack will take place because alpha attack is more preferable because this side attack is sterically blocked.

And therefore, again alpha attack will give this methyl group to be formed from the alpha side. But then if we just turn it around 180 degrees, then of course this becomes beta oriented which will upon reduction and oxidation will give you a product like this. So from this we had got this product and from this particular mirror image we have got this product here.

So this leads to the product having beta oriented methyl group whereas, here it is alpha oriented. So they are two enantiomers of each other. So we can carry out such C-C bond formations by two different types of camphorsultam based dienophiles or Michael acceptors or stoichiometries which would allow SN_2 prime of reaction to take place.

It is essentially an SN_2 prime type of reaction that is taking place and we can get two different types of enantiomers in very high enantioselectivity and high yield.

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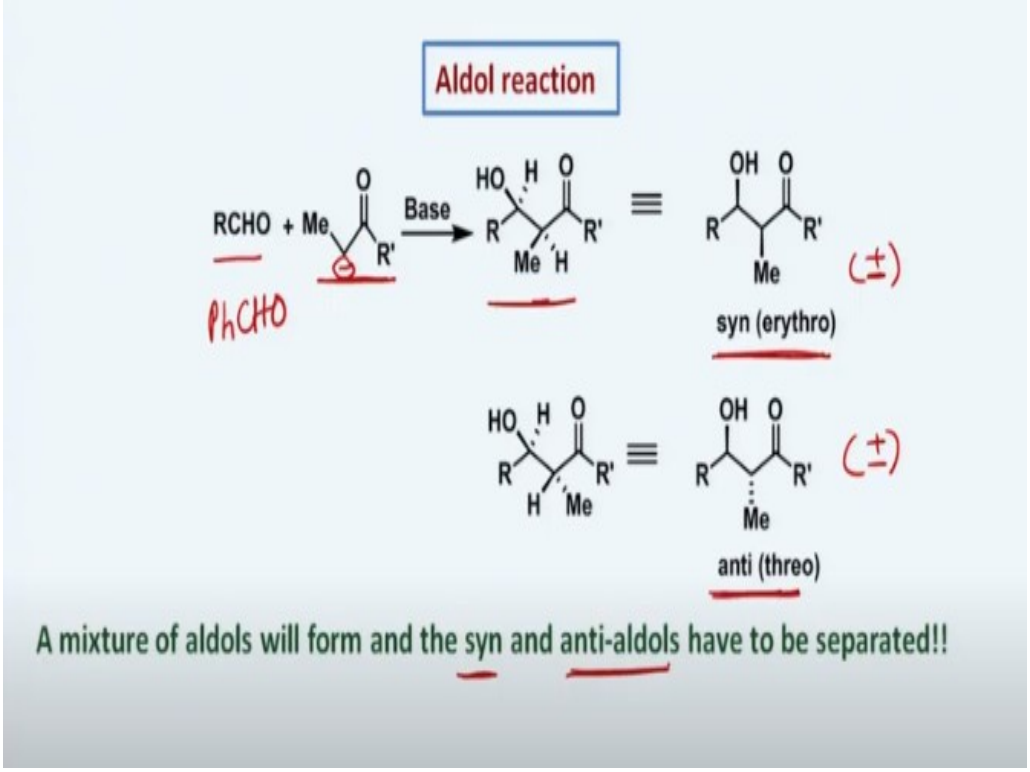

Now we go to the next set of reactions, which is basically an aldol type of reaction. So if we start with an aldehyde and react with a ketone of any kind, then what we can expect that if the aldehyde does not have an alpha hydrogen. So suppose we have benzaldehyde, then what we can expect is that anion can form here and then we can expect a syn product to form or an anti product to form.

So right now we have not taken any base or any product which has any elements of symmetry or asymmetry. So what we are doing right now is we are producing this syn diol or the anti diol as racemic. So basically they are forming racemic products. But now right now we are thinking about diastereomers. So we can expect either this syn product which is called as erythro product or anti product which is called thre product generally is something that we need we can form.

So if we carry out this aldol reaction, basically it will form this mixture, wherefrom syn or anti aldols need to be separated. Now is there a way by which we can control these reactions and get only one of them as the major product, because we will have to eventually see how they can be done as an asymmetric aldol reaction. For that purpose, there is a directed aldol reaction.

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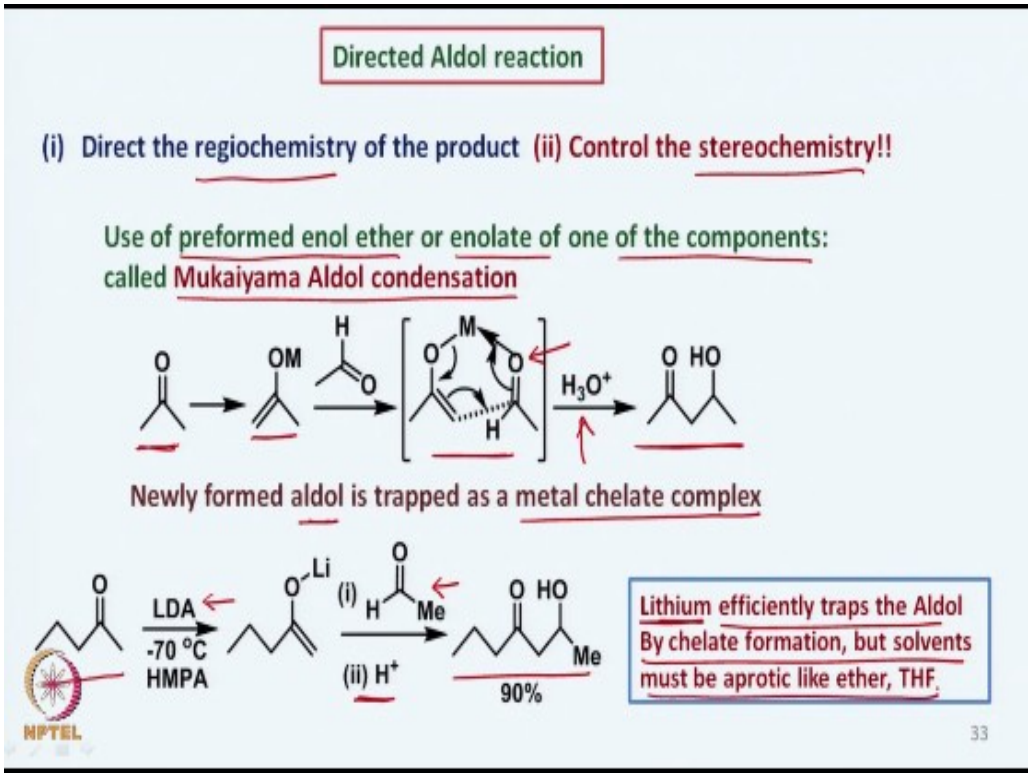

That is you direct the regiochemistry as well as control the stereochemistry. So you can have a preformed enol ether or enolate of one of the components and then carry out the aldol condensation, which is what is called a Mukaiyama aldol condensation.

So that means, we start with a ketone and we can make an enolate and then we react with the aldehyde here and then we can have the corresponding aldol product, where the electrophilic carbonyl group could have a chelation with the M that is the metal attached to the enolate and then that leads to the formation of the corresponding aldol after the hydrolysis has taken place.

Now this newly formed aldol is essentially trapped as a metal chelate complex and that is the reason why we need the hydrolysis to take place. Now this trapping can efficiently be done if we have a lithium ion as a counter ion.

And therefore if the reaction say for example of such a ketone is done with LDA at -70 degrees in the presence of HMPA basically, to allow the nucleophilicity of the LDA to be high, because the HMPA coordinates with the lithium plus and the LDA becomes more basic or better as a base. And then you generate, at that temperature we generate an enolate from the less substituted side.

And that reacts with the acetyl this propanaldehyde to form this aldol, which upon of course, has to be hydrolyzed and we get the 90% of it. The lithium essentially traps the aldol by chelate formation, but solvents must be aprotic like ether or THF. We cannot use obviously protic solvents because we are using LDA and therefore ether or THF is used.

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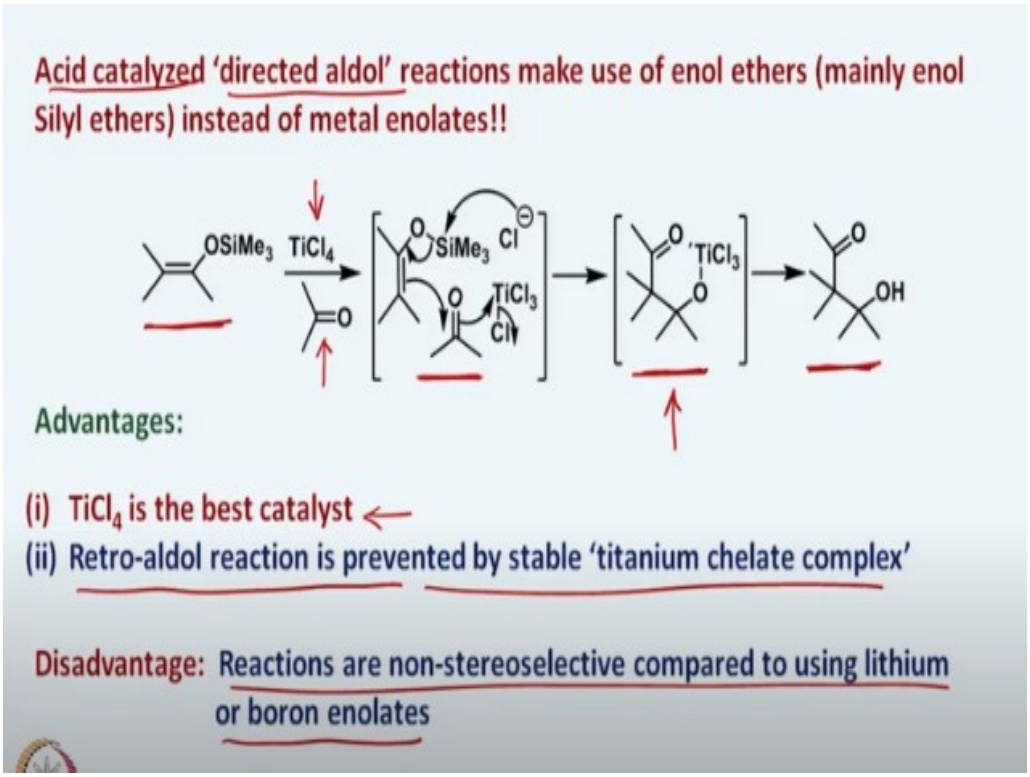

We can also use enol silyl ether as we discussed the chemistry of the enol silyl ether for directed aldol condensation and the acidic conditions and like as I shown here, the $TiCl_4$ can be used as a Lewis acid to activate the carbonyl group and the carbonyl group when it is activated by titanium tetrachloride the Cl- which is released from here reacts with the silicon and cleaves the oxygen-silicon bond.

And eventually it is trapped as the titanium complex like this which upon hydrolysis leads to the formation of the aldol. The advantage is the $TiCl_4$ is the best catalyst. Retro-aldol reaction is prevented, because every aldol reaction in principle can be a reversible reaction. But the titanium chelate complex like this here stops the reversion. And the disadvantage of course is that such reactions are non-stereoselective compared to using lithium or boron enolates.

So this is something that we need to very carefully address. And this enol silyl ether based chemistry although it is useful developed by Mukaiyama but it has some disadvantages.

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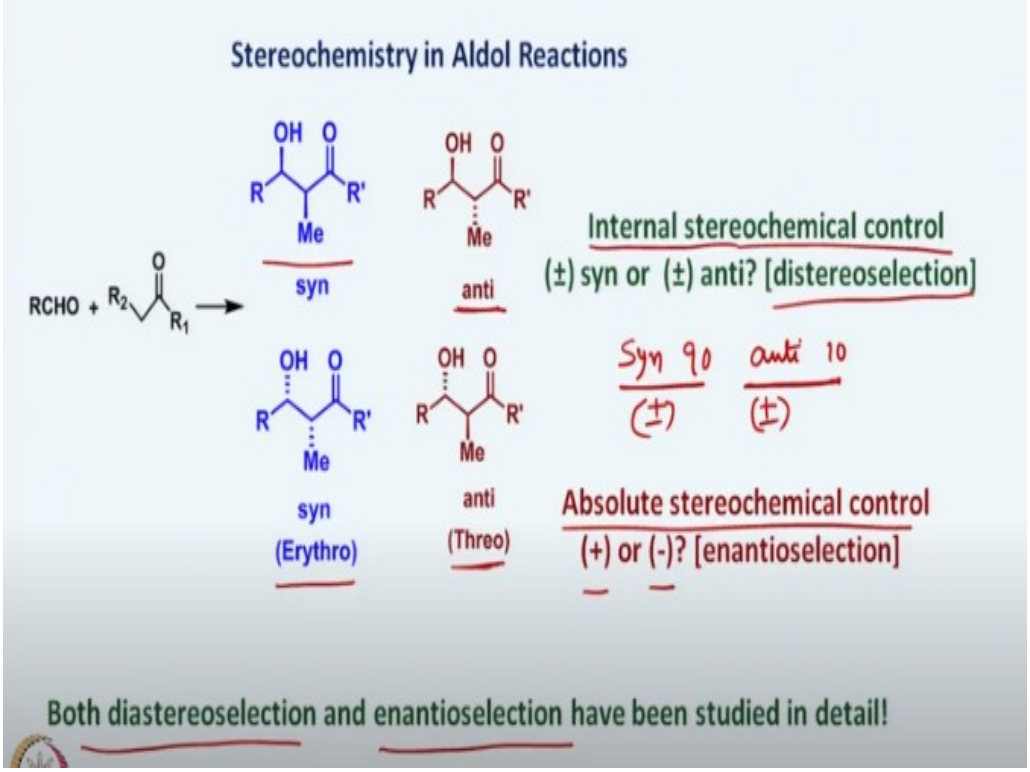

Now the stereochemistry in aldol reactions, one can see that we can get a syn product as I mentioned, but it will also be its mirror image present as the corresponding syn product. And in a similar fashion we can have anti and also its mirror image. So basically there has to be an internal stereochemical control, which of course will lead to diastereoselection.

That means that between syn and anti if we get a syn as say 90 and anti as 10 then we have basically a diastereomeric selection or diastereoselection control, because we are still dealing with the 90, this plus minus enantiomers. On the other hand, we have to have absolute stereochemical control.

That means either plus or minus or that means that out of all these four possibilities, if we can get only one as the major product, then of course we have to say that it is going to be an absolute stereochemical control or enantioselective reaction. So we have to have both diastereoselection as well as enantioselection.

Both we need to have so that we can get out of these four possibilities only one product as the major product, then such a reaction will be highly useful and it will be an enantioselective reaction in terms of aldol chemistry. A lot of work has been done and lot of auxiliaries that have been introduced for such aldol reactions and we will study one of them which is very useful.

But then that requires the enolate based understanding of what kind of enolates are useful. As I mentioned just now that boron and lithium based enolates are very useful. So we will stop it today at this stage and look at the enolates which are boron or lithium based enolates and how do they allow the enantioselective aldol reaction to occur and how they are useful in modern day organic chemistry.

Till then I think you should go through this whatever I have taught in this class and we will see you in the next class. Till then bye and thank you.