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

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Lecture - 59
Simmons Smith Cyclopropanation: Mechanism, Stereochemistry and Synthetic Applications

Hello, all of you. I would like to welcome you all to today's class. We looked at in our last class some aspects of Peterson olefination after we had discussed the allyl and vinylsilane based chemistry. We saw very interestingly that if we have beta silanol then they can undergo syn elimination under basic conditions, which is what is called as Peterson olefination.

It is a very interesting reaction as an alternative to Wittig reaction. And we discussed the mechanism of that where we saw a four member oxygen silicon containing intermediate.
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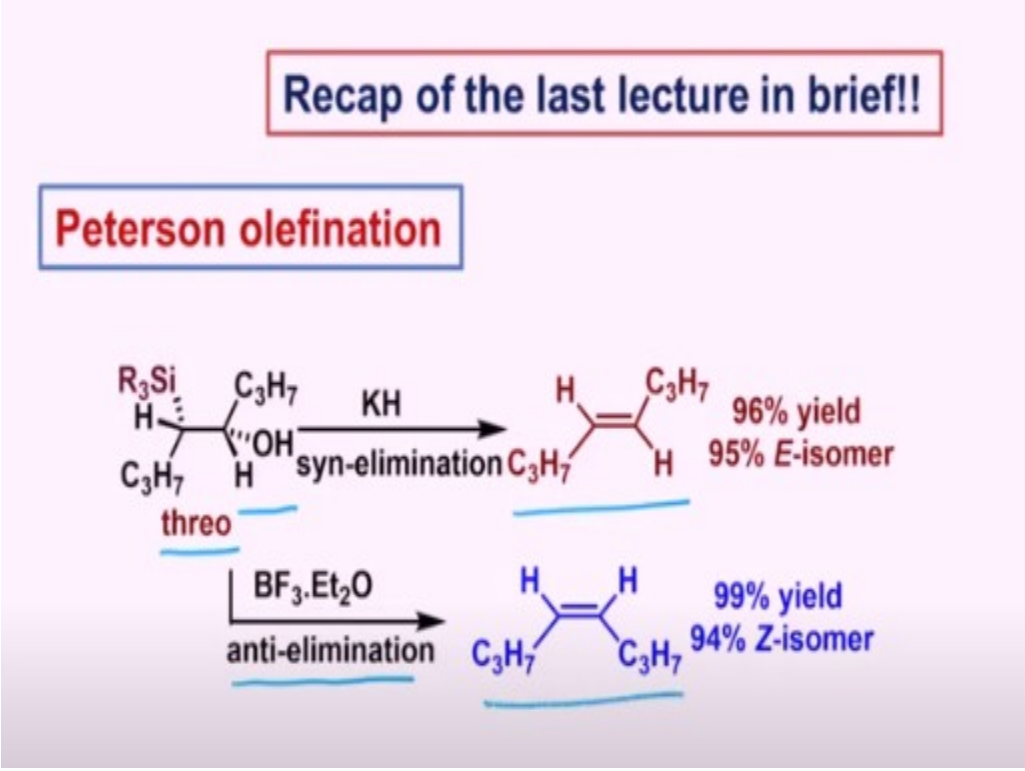

And then of course, as we saw that say for example, this kind of beta silanol, which is having a threo configuration can lead to the formation of the E isomer under basic conditions. And under acidic conditions, it can undergo anti-elimination to form the Z isomer and we discussed the mechanisms in detail. Then also we saw one cyclic case where cyclohexanol which is multiply substituted with various hydroxy groups and silane moiety.

That we saw how under different conditions the conformation allows the elimination of the beta silanol moieties to give the E or different types of regeoisomers of the cyclohexene substituted

molecules. Then, we also saw the carbanion stability and why the carbanions which are alpha to the silicon are more stable than normal carbanions which do not have silicon moiety.

And then finally, we looked at the epoxidation of the vinylsilanes and how these epoxides which are sensitive towards H+ that is the proton under water conditions can give to the ketone or aldehyde and under say HBr conditions also they can give the different types of double bonds depending on how the opening allows.

If the opening of the epoxy silanes are carried out to give beta silanols and if they are pursued in the same acidic medium, then of course we get anti-elimination similar to what we have discussed it here. And if they can be taken up separately after the beta silanol form, then of course under basic conditions, they give syn elimination to give this kind of E isomers. Now we will move into the final topic of our course and that is Simmons-Smith reaction.

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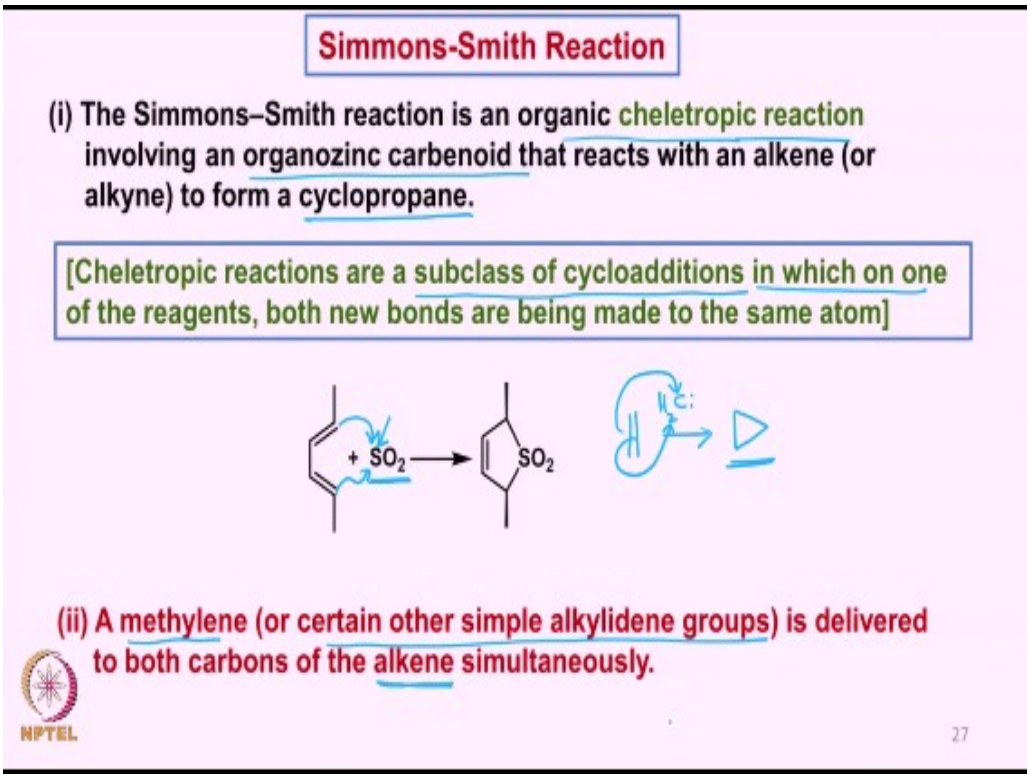

And the Simmons-Smith reaction is a very interesting way of carbon-carbon bond forming reaction. It is called as an organic cheletropic reaction which is involving an organozinc carbenoids. It is not a carbene but it is a carbenoid that reacts with an alkene forming a cyclopropane. What are cheletropic reactions? Cheletropic reactions are a subclass of cycloadditions in which on one of the reagents both the new bonds are being formed.

That means, if this is the reagent then both new bonds are being formed on the same atom that is this alpha. This is how the reaction is termed or classified as a cheletropic reaction. So if you have a double bond like this and suppose, you have formation of a molecule like this where you have a species which allows the incorporation of a single carbon.

So if you have something like this here with a carbene or carbenoid, whatever you can take it, then what you are doing it is that you are forming both the bonds like this here. And that is what is called as a cheletropic reaction. So a methylene or certain other simple alkylidene groups can be delivered to the alkene simultaneously forming a cyclopropane, and this is what is a cheletropic reaction.

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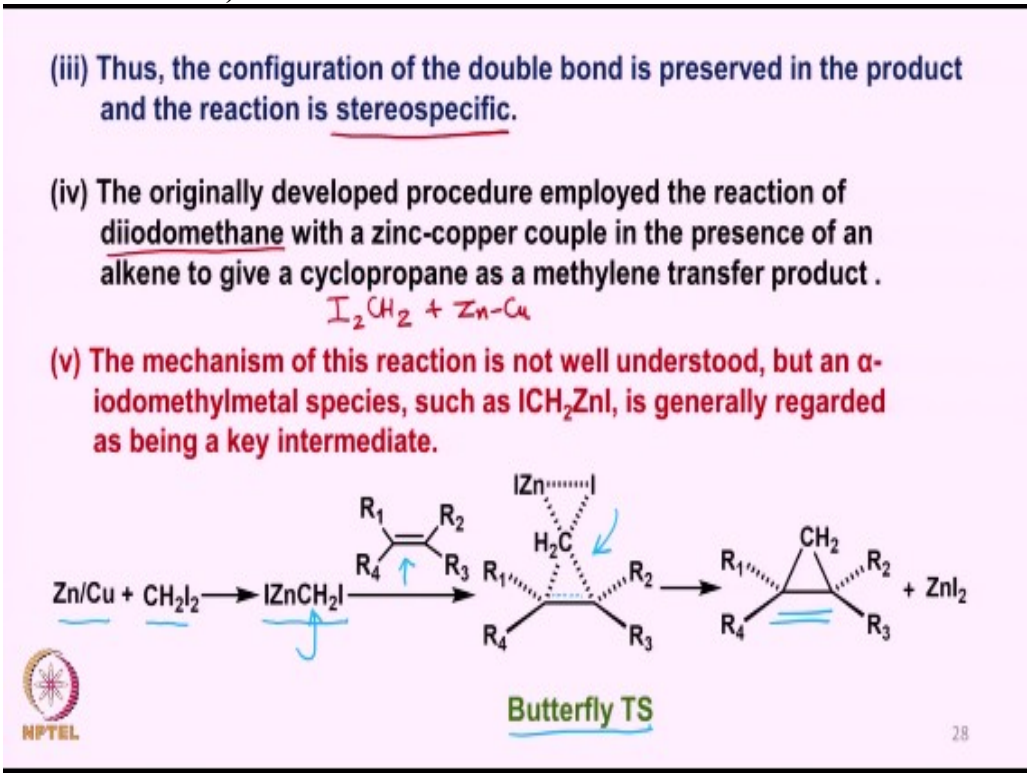

The configuration of the double bond is preserved in many of these reactions. And that is very important from the point of view of application in organic synthesis because the reaction is highly stereospecific. What we are talking about is the Simmons-Smith reaction. And the originally developed procedure that employs the reaction of diiodomethane, so you have a diiodomethane is something like this here CH_2 in the presence of zinc-copper couple.

So you have a zinc-copper couple which allows a finally divided or finally spread zinc species, zinc atoms and they allow the formation of cyclopropane in the, when in the reaction with olefins. Now this is what it is, the zinc-copper couple, diiodomethane. It is expected or believed to form an intermediate of this type which then interacts with the double bond.

So this is not a free carbene but it is a carbenoid type of intermediate, zinc carbenoid. And that the transition state that is proposed is like this, where if this olefin reacts with the carbenoid here, so there is a simultaneous bond formation between the carbon of this zinc intermediate with the double bond. Of course, you will have something like this and at the same time the carbon iodine bond is breaking.

The iodine and zinc bond is forming and carbon zinc bond would also break at the same time later on to form the cyclopropane and of course, you get the zinc iodide. So the this here, this

CH_2 part of the Simmons-Smith reagent gets transferred in this particular fashion. And this is also termed as butterfly transition state because it looks like a butterfly.

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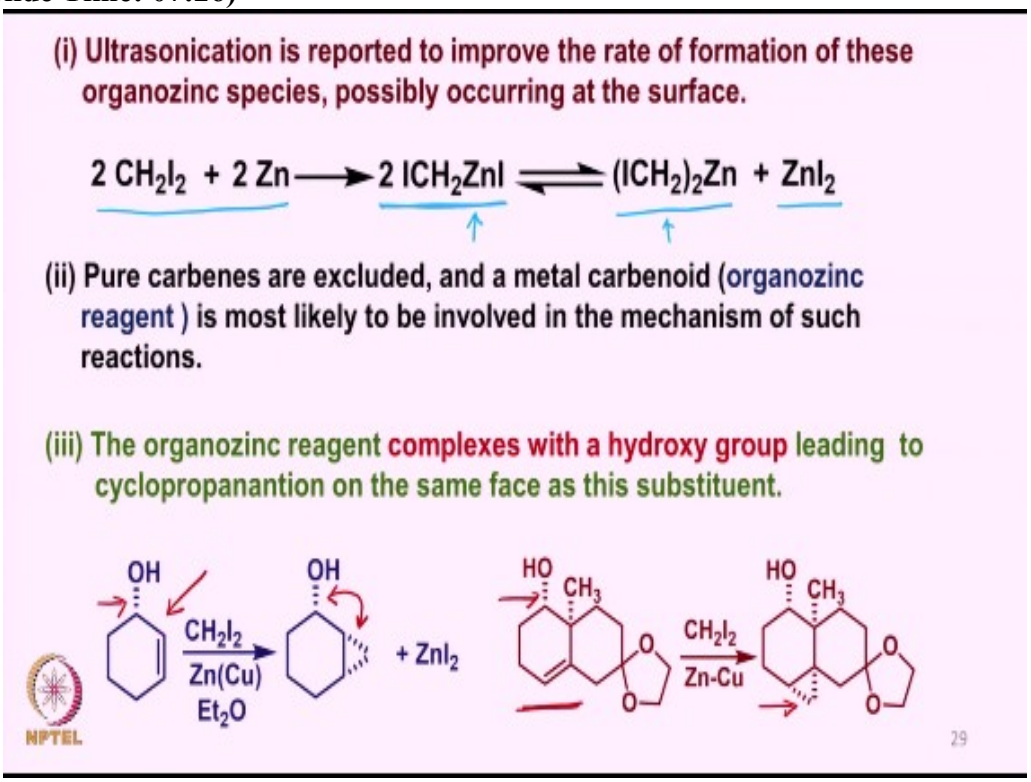

It is known that ultrasonication improves the formation of this organospecies, organozinc species. And therefore, the reaction occurs faster and that suggests that the reaction occurs at the surface of the zinc. It is believed that when diiodomethane reacts with zinc, it forms this species which can of course, be in equilibrium with another species and zinc iodide.

So it is expected or it is believed that either this or this, these are the species which are involved in the final cyclopropanation. Now pure carbenes are excluded and a metal carbenoid or organozinc reagent is likely to be involved in the mechanism of such reactions. Because what has been found that these kinds of reagents react with allyl alcohols of this type, where there is a specific stereochemistry of the OH group, for example alpha.

Then the cyclopropanation takes place from the same side of the OH group, and suggesting that there is some sort of chelation. Not only allyl alcohol, but even homoallyl alcohol of this type, where the hydroxy group is alpha and the geometry of the cyclopropane thing also becomes alpha. That means, there is some chelation that is involved with the species that is holding the zinc with it, so that it has some Lewis acidic character.

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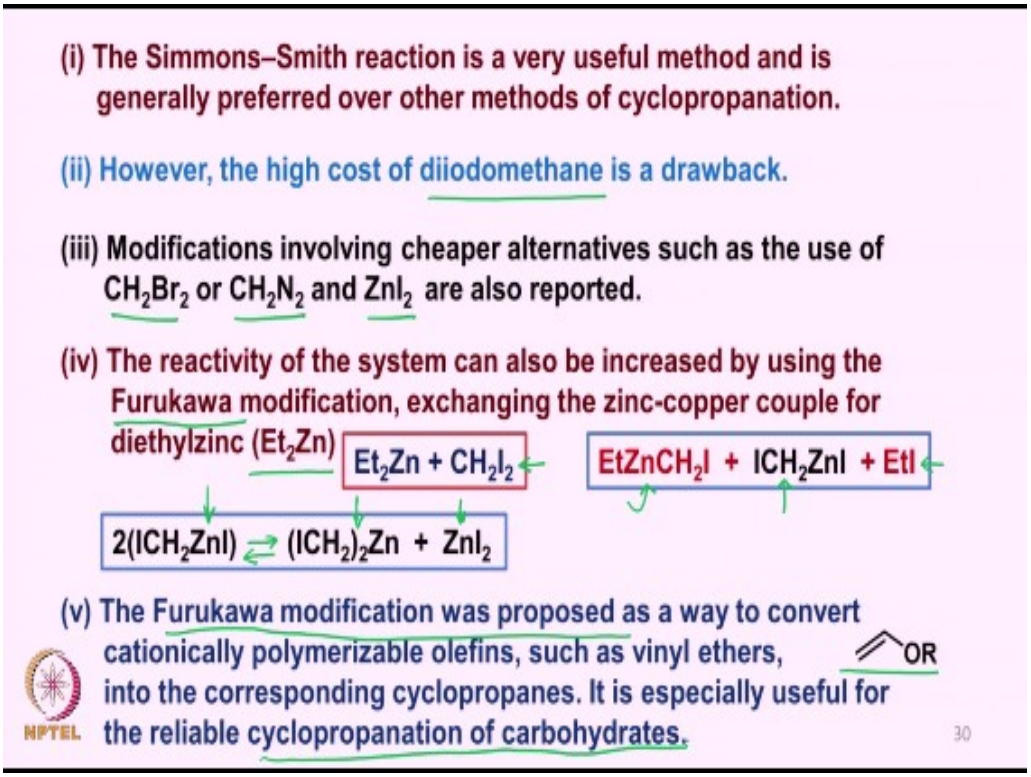

It is a very important reaction and very useful method and it is generally preferred over other cyclopropanations. The only drawback about this reaction is that, diiodomethane is somewhat expensive. But then alternatives like dibromomethane or diazomethane and zinc iodide are also reported, a combination of diazomethane and zinc iodide. But there also have been other improvements.

For example, Furukawa has made a modification where diethyl zinc is used along with diiodomethane and it is believed that species of this kind is formed along with the expected zinc iodide species like this and of course, ethyl iodide is also expelled. And it is believed as I have mentioned earlier that these are in equilibrium with this so that we have a species of this kind as well as of this kind.

And of course, we have zinc iodide. All of these help in kind of chelation with the hydroxy or any oxygen or nitrogen, this moieties which can then guide the stereochemistry of the cyclopropanes. The Furukawa modification is very useful, particularly when cyclopropanation is done of an enol ether and this has been utilized in the cyclopropanation of carbohydrates which are generally difficult to carry out.

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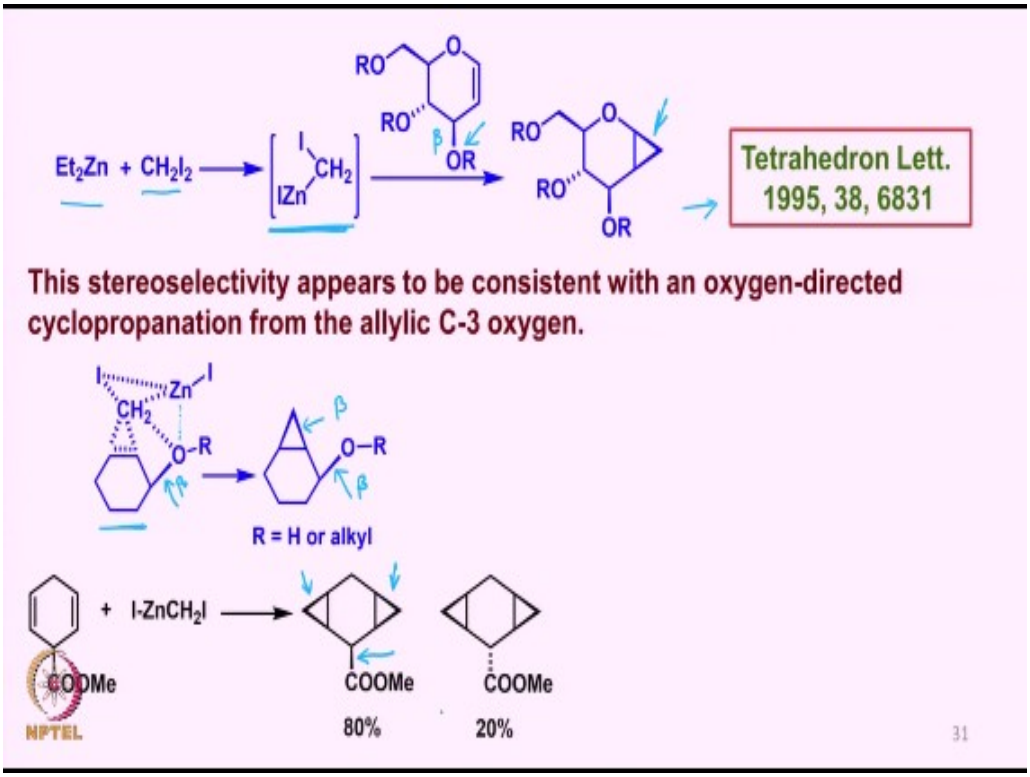

For example, if we take diiodomethane here, diiodomethane and of course diethyl zinc, we expect an intermediate of this kind to form and when the reaction is done this particular OR moiety, which is oriented in a beta fashion allows the cyclopropanation to take place from the beta side. It has been published in 1995 the reference. And of course, these are the kind of transition states that are proposed here.

As you can see, that oxygen of course will have a chelation with this. So this particular chelation, which is beta oriented allows the cyclopropane ring also to come from the beta side. So both of them are beta oriented. And if we take an ester of this kind here, as you can see, if this ester group becomes beta, then both the cyclopropanes are formed.

That is both double bonds are cyclopropanated from the same side as the ester, because the ester oxygens first chelate with the zinc carbenoid species and give the cyclopropanated product in such a way that the two cyclopropanes come in the beta oriented. As you can see, it is 80% and the other one is only 20%. So that means, the steric hindrance does not play so much an important role as it is the chelation with the ester group that dominates.

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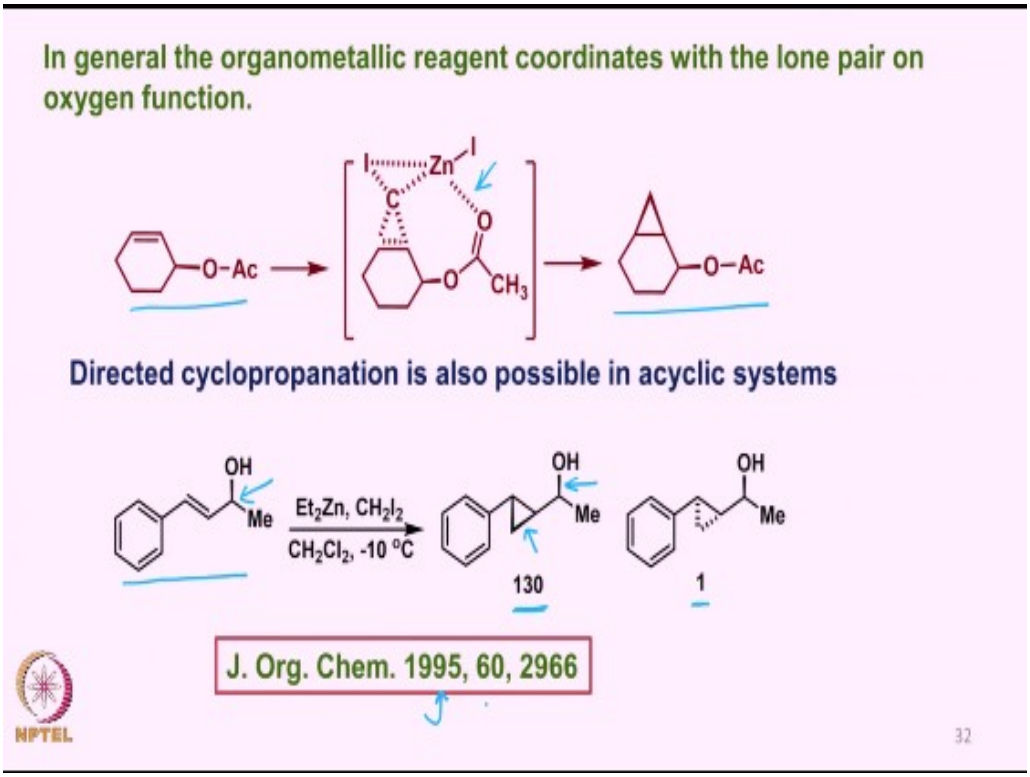

In a similar fashion even acetates have been found to give the cyclopropanation and the chelation as you can see is through the acetate oxygen to the zinc part of the zinc carbenoid. And even open chain type of molecules also give, if we have an asymmetric center like this in which OH group is beta oriented, if we orient the molecule in such a fashion, thus then you can see the OH group is beta. This is also beta.

So this is the ratio is 130:1. So this has again been published in 1995. So you can see that there is a huge effect of the chelation with the zinc carbenoid with the hetero atoms leading to the formation of the cyclopropanes.

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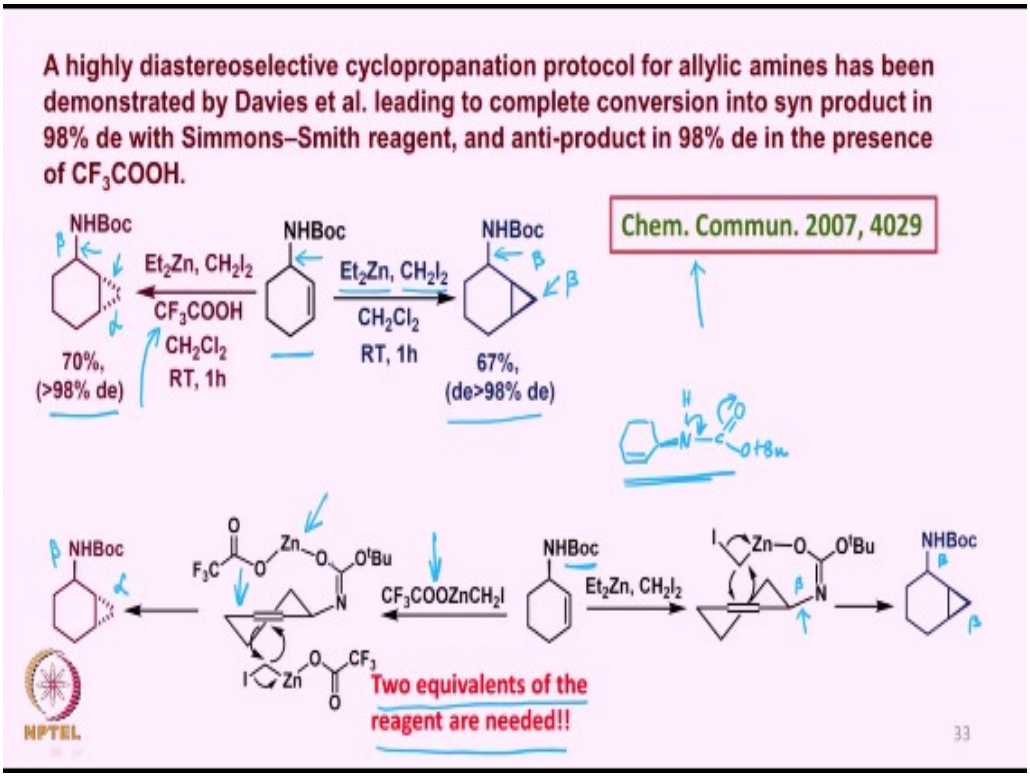

It is an interesting example, where it has been found that if the even if the nitrogen is present that allows the cyclopropanation to take place in a very interesting fashion where, for example if you had diethyl zinc and diiodomethane, then you get the cyclopropanation as expected from the same side as this. If this is beta, then this is also beta. And of course, as you can see, the diastereoselectivity is more than 98%.

But it has been found that in case the reaction is put along with trifluoroacetic acid, then what is found is that the geometry of the cyclopropane is opposite to the geometry of the carbon nitrogen bond. So here it is beta, here it is alpha. And again this stereoselectivity or the diastereoselectivity is very high. How it has been rationalized?

And this work has been published in 2007 in Chem. Commun as you can see here, that the NHBoc, what is NHBoc? NHBoc is nothing but say if you put a double bond here, then you have here N, here NH and Boc is CO O tertiary butyl. So this can be expected to be in this way. There is a kind of enolization or formation of an iminol. And that oxygen then reacts with the zinc and forming this intermediate.

And of course, then the geometry of this allows the cyclopropanation to form from the same side as beta. So if this is beta, then this is beta and this is beta. But in this particular case when trifluoroacetic acid is added, this is the intermediate that is formed. This is what reacts, but before that this particular species reacts with this intermediate to form an intermediate of this kind here.

Where now the Boc group, this is the Boc group, that now is made in a large group having zinc species and trifluoroacetate species, and therefore blocks the top face for the cyclopropanation. So here the steric hindrance comes into the picture and therefore, the olefin attacks from the

alpha side. So this is the alpha side and this is the beta side. So beta side is blocked and therefore the reaction occurs from the alpha side.

And in this case, it was also found that two equivalents of the reagents are needed. If the two equivalents are not used, the cyclopropanation does not take place. That means, the first equivalent of the reagent makes the Boc group kind of derivatized and make bulky and then blocks the beta face. And the second equivalent of the reagent then allows the cyclopropanation to take place from the lower side.

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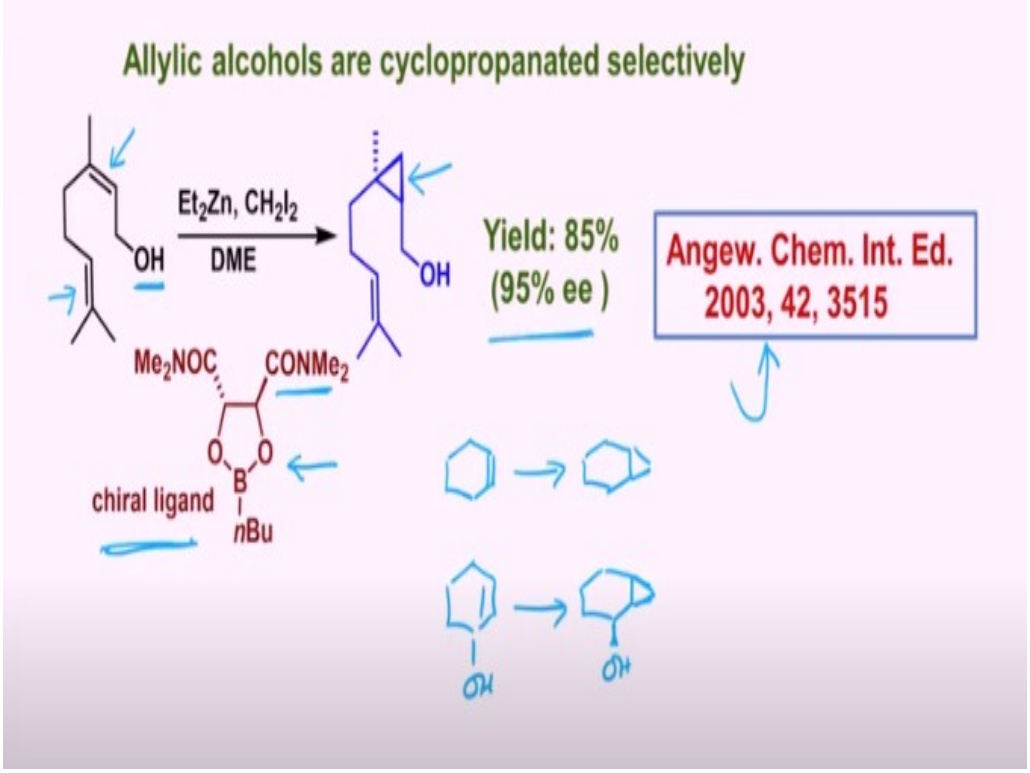

Now allylic alcohols also can very easily be allowed to react in the presence of isolated double bond. As you can see, this is the allylic alcohol and this is the isolated double bond. If we do not have a double bond that contains an allylic or if we do not have a substrate that contains an allylic alcohol moiety, simple double bond is there, then the cyclopropanation would occur in this fashion.

Or if we have an allylic alcohol here and then simple cyclopropanation would give a cyclopropane. Suppose here it is OH beta, then it is beta. But in a substrate like this in which we have both allylic alcohol as well as an isolated double bond, it is the chelation that allows the reaction of the specifically this double bond to form the cyclopropane in this way.

Now it is found that if you add chirally ligand like this, then of course, we can also do the cyclopropanation in an enantioselective fashion and the work has been published in this particular journal in 2003. So you can look at this particular reference to see how the reaction has been carried out.

But the main point here is that the amide part of the reagent interacts with the zinc along with the OH group of the allylic alcohol and they form a transition state that allows the chirality of this particular chiral ligand to be transferred in such a fashion that you get 95% enantioselectivity of the cyclopropanated product.

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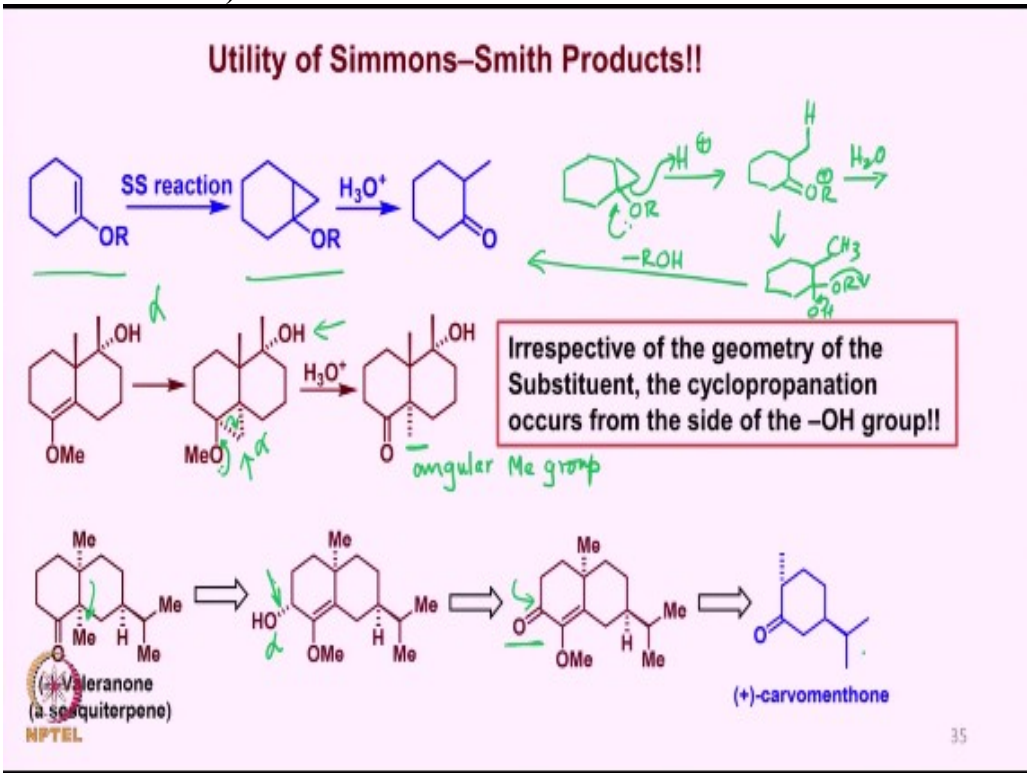

Now we look at the uses of Simmons-Smith product. For example, if we look at the cyclopropanation of an enol ether of this type for example, if you carry out Simmons-Smith reaction, then we can get a cyclopropane like this. And now if we treat with H_3O+ to this cyclopropane which is called as oxycyclopropane because it is having a OR group.

So when proton is added to it, then this particular cyclopropane opens up and forms an intermediate of this type where positive charge in OR and of course you get hydrogen here. And now this particular part of the oxonium ion gets hydrolyzed with water where the water attacks on to this intermediate to form hemiacetal and OR. And here there will be methyl group.

And then this opens up and loses the ROH to form the corresponding minus ROH and you get the corresponding methyl ketone. Now if we have in an enol ether, the hydroxy group which is having a particular orientation such as alpha hydroxy, then of course cyclopropanation occurs from the alpha side.

And in the same concept, if we allow the H_3O+ to react with it, then of course as you can see that you can open up and here you get the methyl group having the alpha orientation. So it is a very interesting way of introducing angular methyl group here. This is basically angular methyl group, angular methyl group and with a proper stereochemistry which is dictated by the stereochemistry of the hydroxy group in the vicinity.

So this has been employed in various natural products synthesis. For example, this valeranone has been synthesized. For example, this valeranone can be expected to come from this kind of enol ether since the geometry of the methyl group is alpha. Therefore, if this is alpha, then of course we can expect the cyclopropane to form in the similar fashion as we have shown it here.

And then the methyl group at the junction would be then the alpha because the cyclopropanation would take place from the alpha side because this is alpha. So and this can be expected to come from this ketone where we can clear out the reduction of the ketone and then this can come from the corresponding carvomenthone. So where geometry of this cyclopropane, this particular isopropyl group here is fixed.

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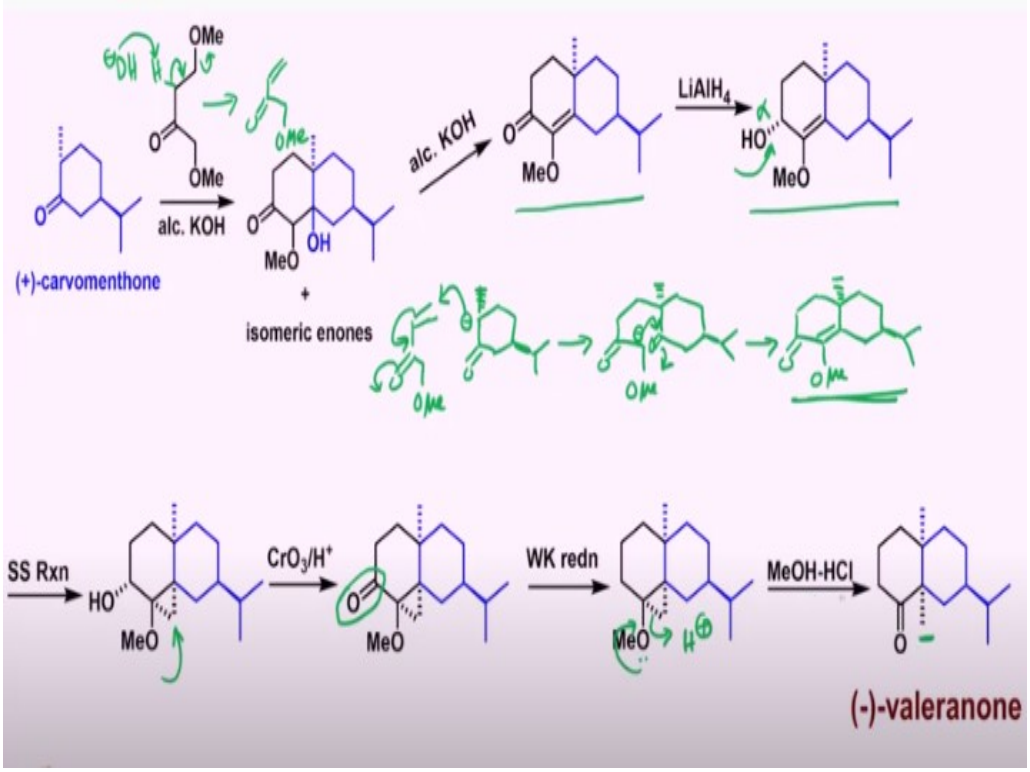

Now how it has been done? I would like to show the synthesis of it, is that you start with plus carvomenthone and react it with this particular intermediate under basic conditions. Then what happens is of course, that it undergoes an elimination of this kind under basic conditions and then there is a, so this intermediate undergoes elimination to form this particular product here.

So you have an elimination of proton, not here. The elimination of the proton takes place here and methoxy group goes off. So base takes the OH-, takes up the proton from here. And once this is formed, then of course, you can write it in this way that you have here ketone. And now what you have is O-methyl. So negative charge here and the basic condition will allow Michael addition to take place.

And this is what will happen that leads to the formation of this intermediate. Of course, the stereochemistry we are not right now worried about it. And then of course, we get this and then you will have the ketone as it is here, ketone here. Now the anion again will form at this center

and then of course, you will get cyclization that leads to the formation of eventually condensation takes place and you get the elimination and then you get the product being like this.

And then the reduction of this particular moiety here. So what is going to happen is that you are allowing the condensation to take place here like an aldol condensation. And now the reduction of this ketone gives one of the products to be this where the hydroxy group is alpha oriented. Now if we do the cyclopropanation of this particular allylic alcohol, then of course, you get the cyclopropanation from the alpha side because this is alpha oriented.

I suggest that the reduction of this particular species you can try and write down the conformation of this enone and then see how the lithium aluminium hydride allows the reduction to take place to give you alpha hydroxy group. So we can discuss that when the question answers will be discussed. Now the cyclopropanation happens, then of course, you can oxidize it in this fashion and then you carry out the Wolff-Kishner reduction to remove this.

And so the ketone goes away and now if we simply use methanol and HCl then of course, this going to open and you get the methyl group in a similar fashion as we discussed earlier. The opening would allow to open in this fashion with the proton being here. And therefore, you get eventually under the acidic water condition valeranone.

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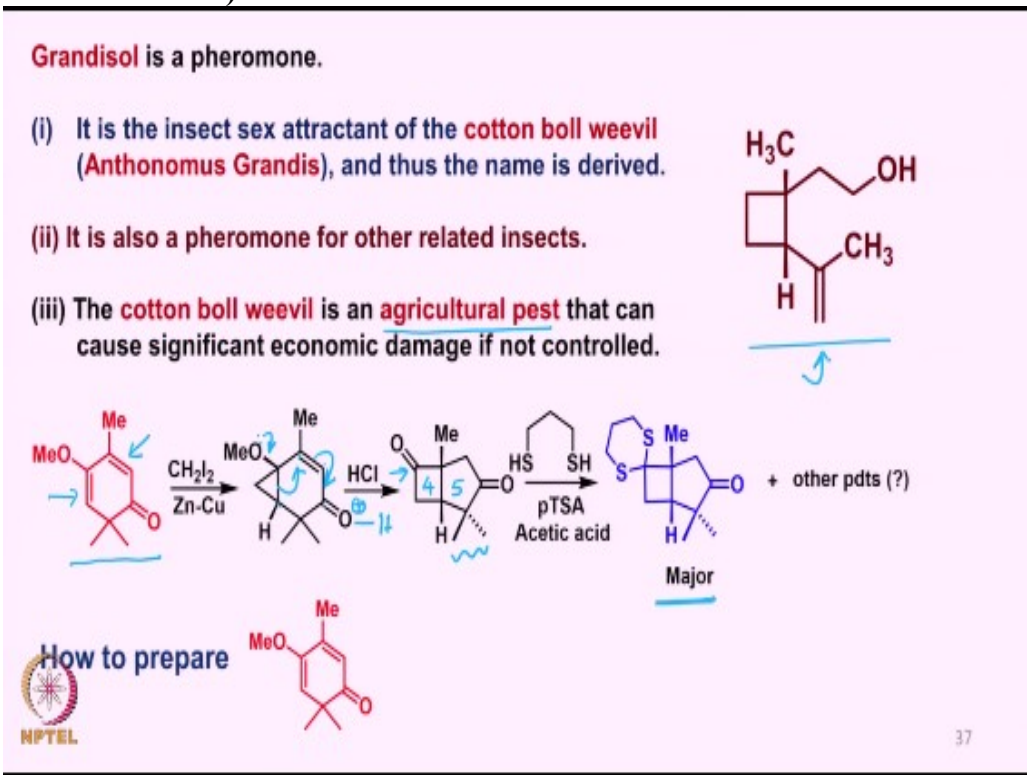

Now Grandisol is a pheromone and is an insect sex attractant of the cotton boll weevil and thus the name is derived from this particular Grandis. And this is an interesting molecule here as you can see, and it actually spoils the cotton field and therefore, there is a lot of interest in the synthesis of this molecule. One of the synthesis that has been done is utilizing the cyclopropane based chemistry.

So if we start with a molecule like this, the cyclopropanation has been done using Simmons-Smith reaction. Now between these two olefins this particular olefin is electron rich, therefore the cyclopropanation is specifically occurs with this particular double bond. And once this happens, we treat this with HCl.

So the protonation of the ketone occurs here and now what happens is this moves in here with the movement of the double bond and opening of the cyclopropane ring in this fashion. So it gives 1, 2, 3, 4 membered ring here and of course, you have 1, 2, 3, 4 and 5, this 5-membered ring is here. Now this is how this particular oxycyclopropanes have been utilized it now apart from the angular methyl formation.

Now between the two carbonyl groups, this carbonyl is relatively less sterically hindered, because here there are two methyl groups. So if we do the formation of the thioacetal, then you can get specifically this. Of course, you will get some mixtures and now this particular intermediate has been utilized it for the synthesis of this Grandisol, which I would like to show you how it has been done.

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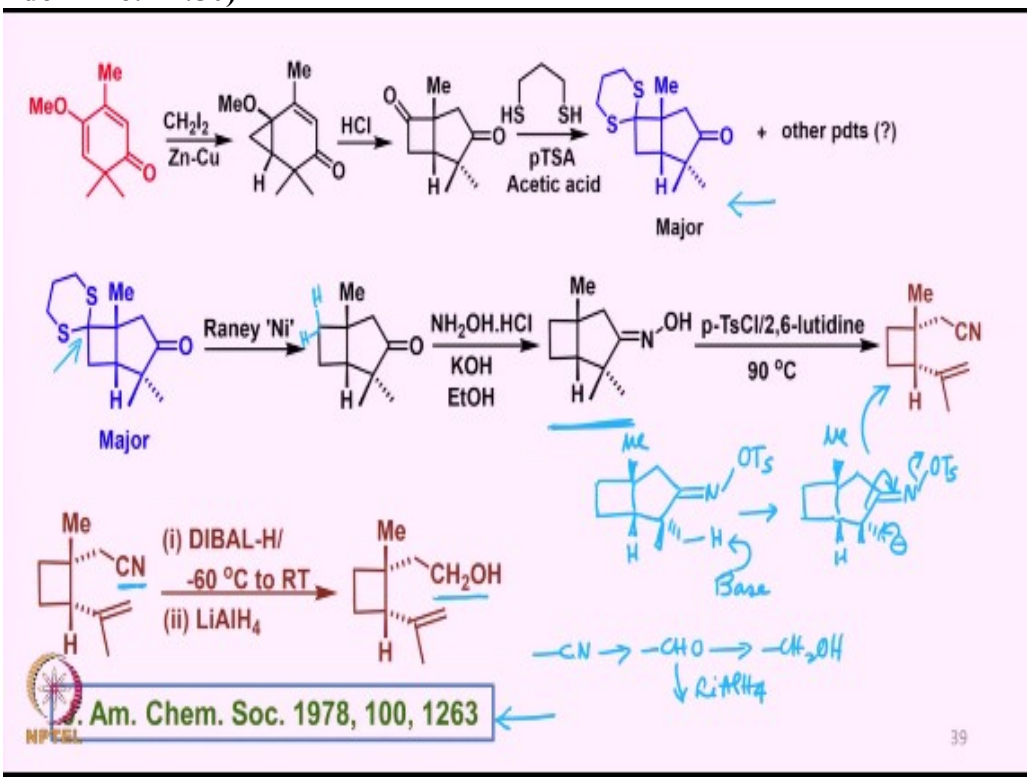

So once you get this particular intermediate here, here this intermediate, then you can then as I discussed earlier that you can specifically prepare this thioketal here, sterically less hindered. Then you do the Raney nickel based reduction of the thioketal where the carbon sulfur bond breaks and you get two hydrogens here. So basically it is an equivalent of Wolff-Kishner reduction in a different way.

Now if we react it with a hydroxylamine hydrochloride, then you get the corresponding oxime. And this oxime can be reacted with para-Toluenesulfonic acid and in the presence of a base, which is 2,6-lutidine at 90 degrees. Then what happens is basically here you have nitrogen and it

forms O tosylate. And then you have a methyl group here and then you have a hydrogen group here, hydrogen atom.

Then you have a methyl here. Now what can happen is that one of the hydrogens from here under the basic conditions is picked up by this base, which is the lutidine and then takes up the proton from here forming the anion. And then what you have, then there is a elimination of this type and that leads to the formation of the corresponding nitrile. So it forms a nitrile. And of course, you get this double bond here.

Once this double bond is done, then you can reduce the nitrile to the corresponding CH_2OH via aldehyde. We have discussed this reaction where the nitrile can be reacted with the DIBAL and lead to the formation of the aldehyde and that can with the excess of DIBAL can give the corresponding CH_2OH. So this is how the reaction can be done.

Or alternatively, you can also react this aldehyde with lithium aluminium hydride instead of DIBAL and that can lead to the formation of the corresponding CH_2OH. This is what the work that has been published in 1978. So these are the applications of the Simmons-Smith reaction in organic synthesis. As you can see that the Simmons-Smith reaction is a very important reaction.

Even the chiral version of this has been introduced. And therefore, it is a very important carbon-carbon bond forming reaction. So we will stop it here today and we will see you in the next class. Till then you can go to these cyclopropanations and various kinds of silicon based chemistry that we have talked. And then we will see what is now, how we can solve various kinds of organic synthesis problems using various kinds of reactions that we have discussed in this course. Till then take care. Bye, thank you. See you next time.