Essentials of Oxidation, Reduction and C-C Bond Formation
Application in Organic Synthesis
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Lecture -08
Further synthetic applications of Mislow-Evans rearrangement and Saegusa-ito oxidation

Hello everyone welcome to the today's class as, you may recall that in the last class I discussed some aspects of the sulfoxide sulfenate rearrangement. The mechanism and the application of sulfoxide sulfienate rearrangement to some interesting molecule synthesis involving very interesting mechanistic aspects and applications of say for example Diels-Alder reaction or allyl alcohol to allyl sulfenate ester followed by allyl sulfoxide formation and subsequent reactions.

Now today I will discuss some more aspects of this allyl sulfoxide, allyl sulfenate rearrangement and its application in the synthesis of very interesting molecules. I also mentioned about the fact that in some cases when sulfoxide reactions do not work that means allyl sulfoxides to allyl sulfenate rearrangements do not work then even allyl selenoxides can be reacted, and they also work in a similar fashion as the sulfoxide work.

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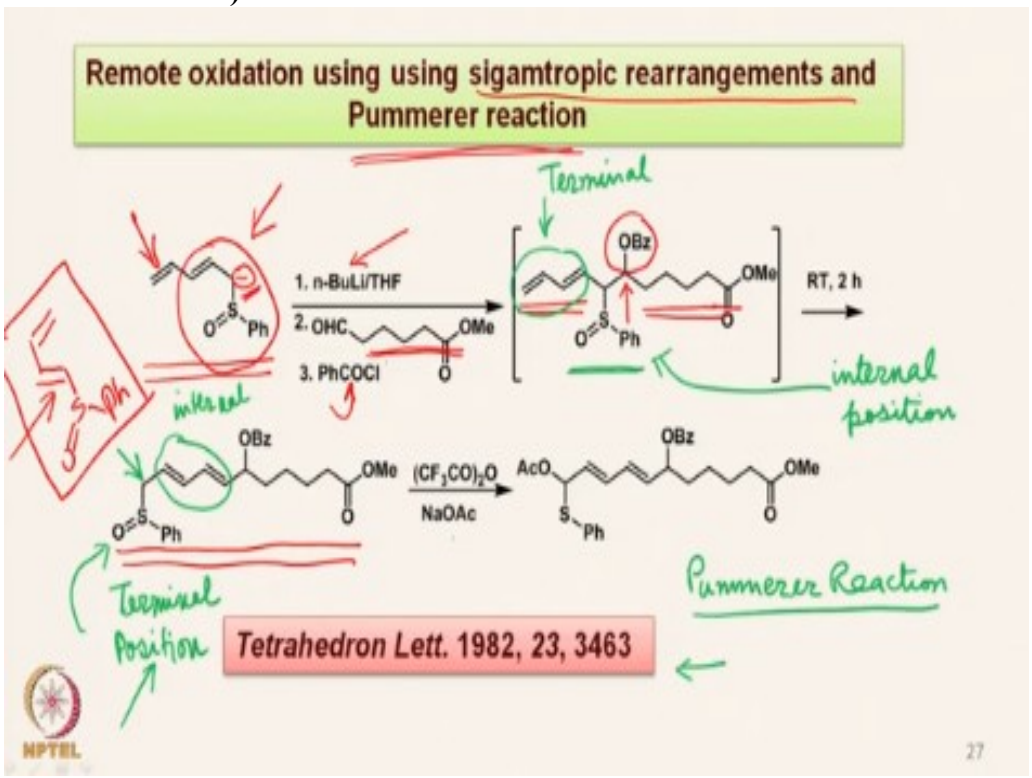

Now in this particular slide which I have presented here there is a combination of this sigmatropic rearrangement which is Mislow-Evans rearrangement which is nothing but 2, 3 sigmatropic rearrangement associated with Pummerer reaction. Now I have already mentioned a

few times that how allyl sulfoxide can be converted to the corresponding allyl sulfenate ester from different kinds of substrates.

Now let us take an example of this diene which is having an allyl sulfoxide part here, but is attached to another olefin at this part. So this is not the same diene which we took last time for the Diels -Alder reaction. In the Diels-Alder reaction case what we had taken was this particular vinyl sulfoxide as a diene where the sulfoxide part was directly attached onto the double bond, which is why it underwent Diels-Alder reaction.

But that is not the case here. In this particular case what you would have is allyl sulfoxide rather than vinyl sulfoxide. But then this diene containing an allyl sulfoxide is treated with a butyl lithium a base here to generate an anion alpha to the sulfoxide and reacted with this particular aldehyde. So it is like an aldol kind of form reaction and when this anion here reacts with the aldehyde and the generated OH is further reacted with Phenyl COCl (Benzoyl Chloride) then what you generate is a benzoate here.

So this particular part at this stage here is the same part as it is here the aldehyde, this is the aldehyde carbon that is attacked by the negative charge of the anion which is alpha to the sulfoxide, then the aldehyde gives O^- and that O attaches to the benzyl chloride to form this benzoate. Now this particular sulfoxide which is having a diene unit in this fashion, undergoes an interesting reaction to form another diene sulfoxide here.

Now look at it very carefully what you have is this sulfoxide here was internally oriented, this is an internal position. Now the same diene has now got interconverted to a terminal position. Now this sulfoxide has come to the terminal position. So obviously the diene part has moved into the internal position and here it was at on the terminal position. So the terminal diene has become an internal diene and internal sulfoxide has become a terminal sulfoxide.

And then this sulfoxide when it is treated with trifluoroacetic anhydride and sodium acetate, it allows functionalization at this center via so called Pummerer reaction. Now this work was published in 1982 in a very interesting paper by E J Corey and the mechanism for this reaction is very interesting which is discussed here.

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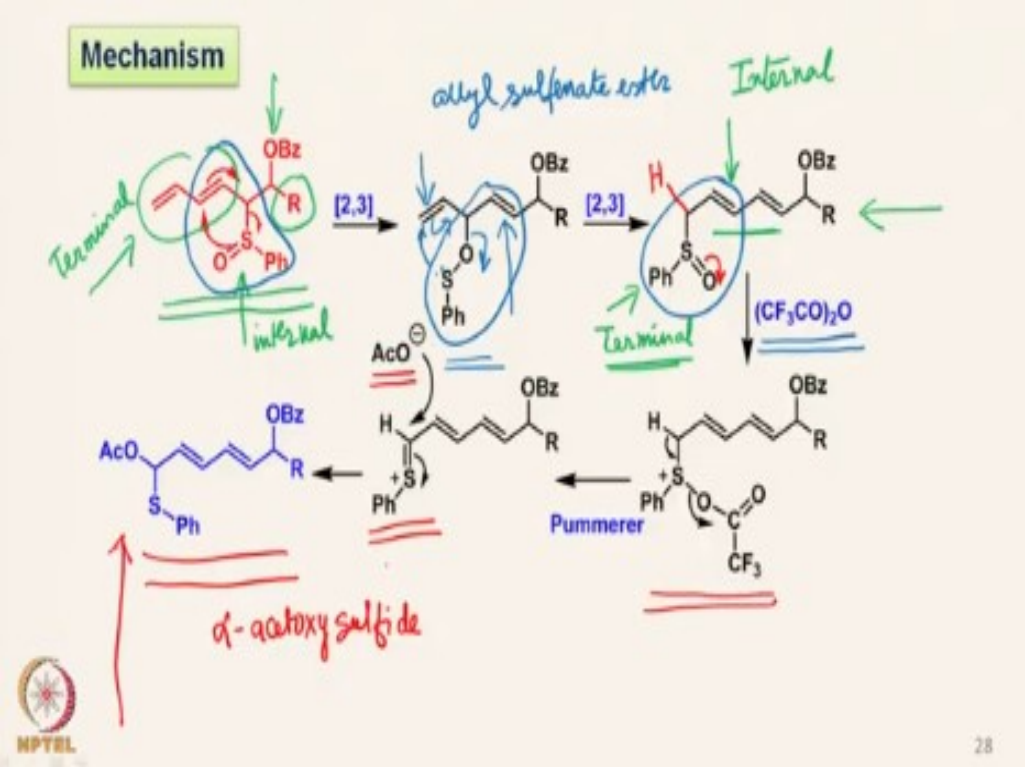

Now as you can see that after the aldol type of reaction one gets this part R is the remaining side chain of the aldehyde and this is the benzoate which is coming from the aldehyde. Now this is what is your internal sulfoxide and this diene is terminal diene. Now just like that it cannot get converted into this diene which is internal diene and terminal sulfoxide, so this is internal diene and terminal sulfoxide.

Now just like that it cannot undergo, but what it does it is very interesting. Now if one looks at the this part here only this part this particular part, which I have encircled with blue pen it is allyl sulfoxide. So that undergoes allyl sulfoxide sulfenate arrangement to form this unit, which is now is allyl sulfenate ester. Now this allyl sulfenate ester is basically flanked by two double bonds.

So this allyl sulfenate ester has a choice, either it undergoes to the same rearrangement back to the sulfoxide or it undergoes a new rearrangement and generate this unit. This is exactly what is happening. So that means that if you have a diene which has an allyl sulfoxide unit at in one end of the diene it can undergo allyl sulfoxide sulfenated rearrangement form this type of sulfenate ester which is now flanked by two double bonds in an allylic position and then it undergoes a different kind of allyl sulfoxide sulfenate rearrangement in a different way.

And give this terminal sulfoxide, now this terminal sulfoxide when it is treated with an electrophile like trifluoroacetic anhydride, then that allows the Pummerer rearrangement to take place. Now if you recall the Pummerer rearrangement, we had discussed it earlier time and here there is a proton which is what is expected to trigger. So I have repeatedly mentioned that unless there is at least one hydrogen atom adjacent to the sulfoxide Pummerer reaction would not take place.

Because once this sulfoxide is activated by this electrophile like a trifluoroacetic anhydride then you would get an intermediate of this kind and this kind of intermediate has to lose a proton from here and then generate this sulfonium ion. This sulfonium ion then is attacked by the nucleophile which is present as an acetate ion to attack on to this to form this particular alpha acetoxy sulphide.

So you have an alpha acetoxy sulphide from this particular rearrangement. So this is the beautiful mechanism is a beautiful way of converting a very interesting substrate to in a very regioselective fashion to this particular alpha acetoxy sulphide. So now one can carry out many different interesting applications of this particular highly functionalized molecule to convert into different intermediates, which could be useful in the synthesis of important natural products. Now this yet another example which is similar to the example that we took last time.

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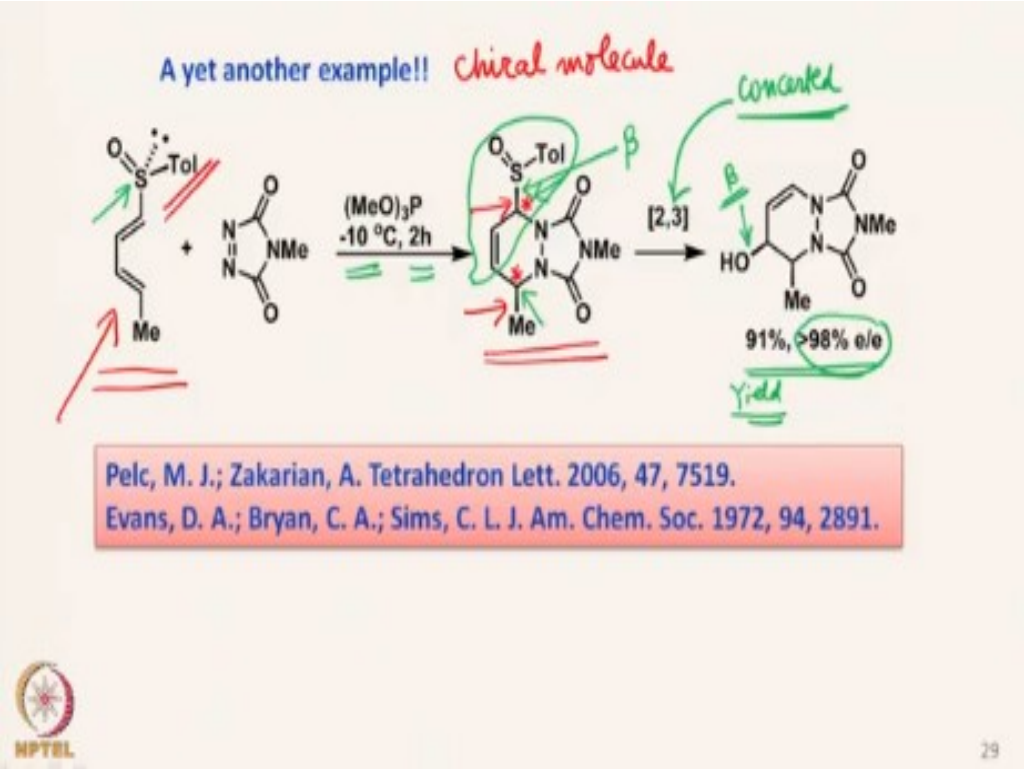

Where now we have a different vinyl sulfoxide, here the diene and sulfoxide are in conjugation with each other except to the fact that this is another example is basically a chiral molecule. So if the sulfoxide is made chiral, this is why it is made chiral this is a chiral sulfoxide because sulfoxides can exist as enantiomers. They are having three different groups like double bond O this carbon sulphur bond and carbon toluene bond and of course a pair of electron that allows the enantiomers to be formed.

So if this particular diene having a sulfoxide is made in a chiral fashion then the Diels Alder reaction gives this intermediate the stereochemistry here is governed by the Diels Alder reaction rules, which is not the scope of this particular course, however this is how it will happen. But now since there are two asymmetric centers which are formed that will be chiral centers. That is because the sulfoxide is chiral and therefore the reaction would give a highly diastereoselective reaction.

When; now you see that this particular molecule has this part as allyl sulfoxide. Now this will undergo already one has induced asymmetry into the substrate, based on the enantio selectivity governed by the sulfoxide. So now once you have these two centers here as chiral centers and now you have a allyl sulfoxide when this undergoes rearrangement and since this is a beta orientation here beta so the alcohol which is formed is also beta.

And it was found that the reaction is done at minus 10 degrees, 2 hours and yield is 91%, whereas enantiomeric excess that is optical purity is more than 98%. So this is a very beautiful example of combining the information obtained from the chirality of the sulfoxide, the Diels-Alder reactions stereochemistry and enantioselectivity from the sulfoxide followed by the concerted this is the concerted reaction.

And therefore there is no possibility of the loss of stereochemistry and that is what is transpired into an enantio selective Diels-Alder reaction giving this bicyclic interesting allylic alcohol.

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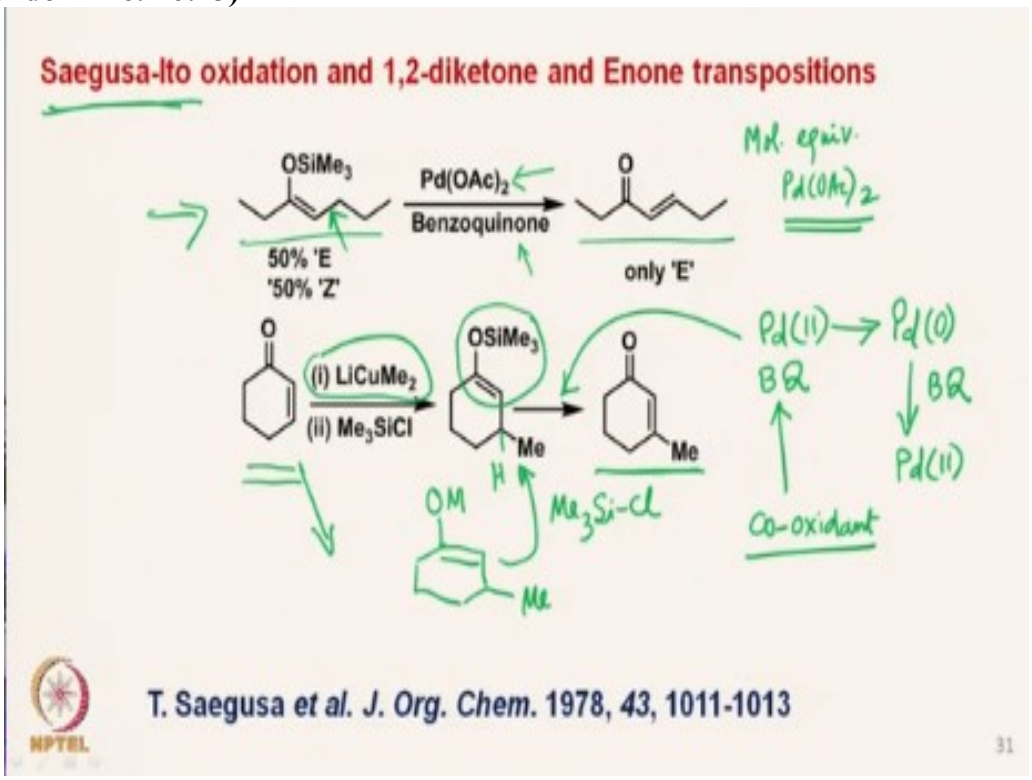

Now we would move to another topic which is called Saegusa - Ito oxidation and if time permits then we carry out the two interesting transpositions one is 1, 2 diketone and enone transpositions. Now what is Saegusa- Ito oxidation, first we will take that. Now what is interesting in this particular reaction is if one takes an enol silyl ether of this kind and if one treats with palladium acetate and in the presence of benzoquinone one gets this enone formation.

That means there the double bond is coming on this and this in enol silyl ether gets converted with ketone. Now initially when this reaction was done, it was found that one can do this reaction with mole equivalent of palladium acetate. But then palladium acetate is very expensive

and therefore the reaction will not be of much use unless it is made in catalytic fashion. But the reaction is very interesting.

Because once you are in a position to make an enol silyl ether of this kind in a highly regioselective fashion, then the formation of the enone will occur only in a particular fashion, like for example if enol silyl ether is formed here then you can always get the double bond in this particular place. It will not go on to the other side. Now if one extends this and applies in a different way one can start with an enone say cyclohexenone add methyl group in by lithium dimethyl cuprate.

And the particular cuprate that is going to form would look something like this here O and M, M is like copper and lithium species and then this is converted into this enol silyl ether by Me_3Si-Cl Me $_3$ Si-Cl and once that enol silyl ether is now generated this is the enol silyl ether that regenerated similar to the one it is shown above would now undergo a Saegusa- Ito reaction that means palladium acetate palladium 2 in the presence of benzoquinone. Now that gives elimination from here this hydrogen goes off and you generate this enone.

Now two things which are important one of course is that Saegusa was a Japanese chemist and Ito they were the ones who did the reaction first and therefore this is called as Saegusa-Ito reaction.
Now here palladium 2 is the one that actually does the reaction but then this palladium 2 is converted into palladium 0 and which then reacts with benzoquinone and then gets converted into palladium 2.

So basically benzoquinone is a co-oxidant that is required to convert palladium 0 to palladium 2. Of course in the literature as we go along we will see that there are many other co-oxidants which people have reported in the literature.
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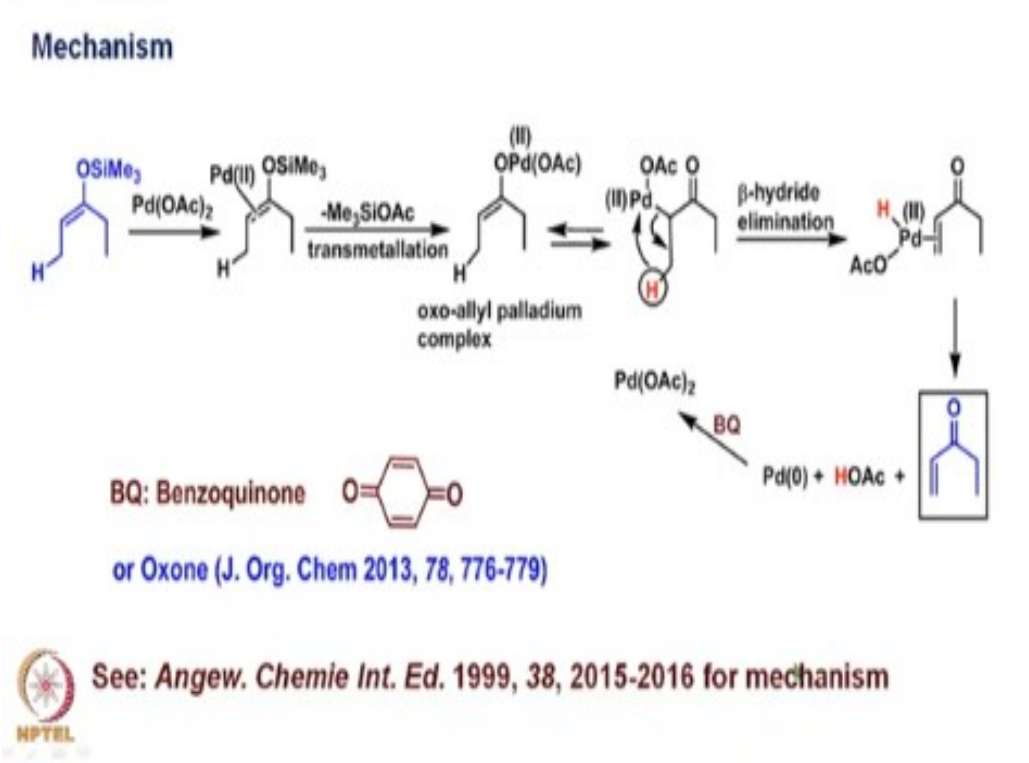

Now what is the mechanism of the Saegusa-Ito reaction. For that we have to understand that palladium 2 salts such as palladium chloride, palladium acetate or palladium trifluoroacetate react with a double bond particularly an electron rich double bond to form a pi complex, say for example if we have a compound of this type which is an electron rich double bond that is an enol silyl ether then we can expect that if this is reacted with palladium acetate.

Then we have a pi complex of this type that can easily form and this particular pi complex undergoes transmetalation by the expulsion of tri-metal silyl acetate in the sense that this oxygen silicon bond is broken and oxygen palladium bond is formed. This is what is trans metallation this results in the formation of oxo allyl palladium complex which is in equilibrium with this particular palladium species.

Now in this case you have oxygen palladium bond and since it is an enol ether type of species it breaks and can form a carbon palladium bond. In both the species the palladium remains in oxidation state of 2. Now these two species would be in equilibrium and this particular species which has a hydrogen at the beta position for example this is an alpha position and this is the beta position so there is a possibility of a hydride transfer from here to here and subsequently there is a loss of carbon palladium bond here to make it double bond.

That leads to the formation of this particular species in which now the newly formed palladium 2 species has a pi complexation with the double bond that has been regenerated. Now this palladium species then looses acetic acid and palladium 0 and generates an enone which is; what is the product of the expected Saegusa- Ito reaction. Now this palladium 0 then undergoes oxidation to palladium 2 with benzoquinone which is used in stoichiometric amount and thus this particular reaction is essentially catalytic in terms of palladium salt.

And stoichiometric in terms of the co-oxidants such as benzoquinone. This also has been reported in the literature where in place of benzoquinone oxone has been used as a co-oxidant. This entire mechanism is reported in the literature in 1999.

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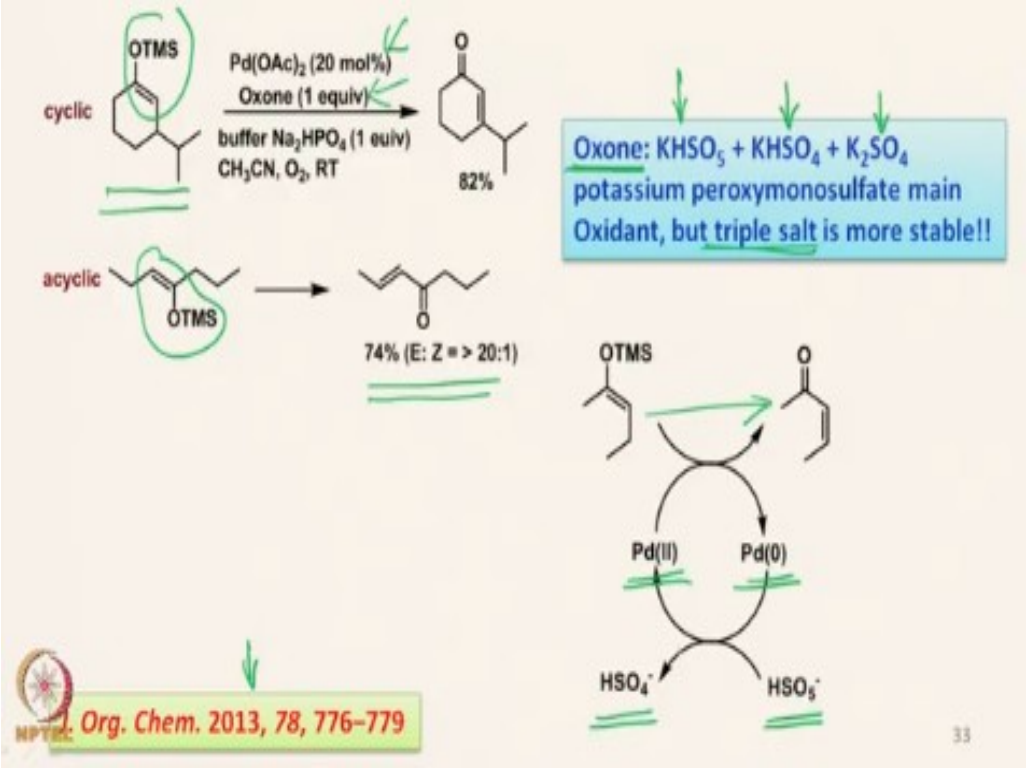

Now you can also carry out this reaction which is published in 2013 by using oxone. Oxone is a basically a triple salt which is primarily potassium peroxymonosulfate and this potassium hydrogen sulphate and potassium sulfate are essentially to stabilize the salt, because it is a peroxy salt. Such combinations have been reported in 2013 to convert this enol silyl ether for example of this kind where only 20 mole percent of palladium acetate is used along with one equivalent of the oxone to form an enone from this enol silyl ether.

This can also be done on acyclic systems and you can get the corresponding enone. So this is a very interesting and cheap method by which instead of using benzoquinone you can use oxone as a co-oxidant and carry out the reaction. So as you can see from here that the enol silyl ether is converted to the corresponding enone where palladium 2 is gone to palladium 0 and the palladium 0 reacts with this potassium peroxy monosulphate.

And then of course that gets reduced and the palladium 0 gets oxidized to the palladium 2. This is what is the; one of the latest applications of the Saegusa reaction.

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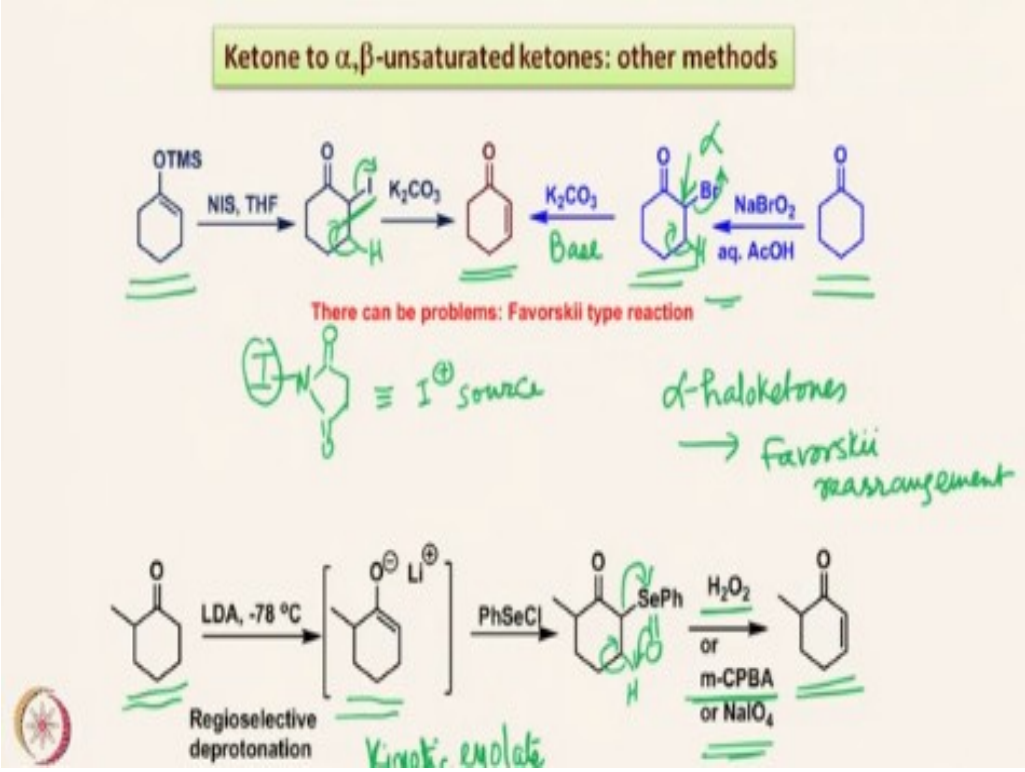

Now if you look at the literature or the earlier methods one can say why do we want this palladium and co oxidant etcetera. Why cannot we simply take a ketone such as this convert into the corresponding alpha halo ketone here and then of course you take a potassium carbonate like a base it is a base and then of course you can lose the proton from here and this proton gives a enone. So it is essentially a kind of ketone to enone in on a simple substrate.

Of course in a similar fashion you can take the enol silyl ether which is what we took in the Saegusa- Ito reaction and treat with N- iodosuccinimide, N iodosuccinimide is nothing but is this like N bromosuccinimide it is this here which is the source of I^+ in instead of is a source of I^+. So you can introduce here this iodo group here and then in a similar fashion as this reaction here this elimination of HI under basic condition here gives an enone.

So one can do it but the problems associated with these are the fact that some of these alpha halo ketones like alpha halo ketones can undergo under basic conditions to give Favorskii rearrangement, so one can reaction or rearrangement. So there is a danger when you have substrates of this kind where alpha halo ketones are reacted with base so you may have a side reaction but that is not the case with this particular Saegusa reaction.

The other way of course is we can take this ketone, for example which we have already discussed it is that you can treat with the strong base at low temperature and you generate an kinetic enolate and react with phenyl selenyl chloride to form this alpha phenyl seleno ketone which upon oxidation with either hydrogen peroxide or m-per benzoic acid or sodium metaperiodate basically you have to do the reaction under careful conditions so that you make selenoxide here.

And the selenoxide then undergoes a elimination to form the double bond O. So this is definitely an alternative, but then you have to have different alternatives to carry out the same reaction so that on certain substrates with certain functional groups certain reactions work and other reactions do not work. Therefore for any particular transformation you have to have many different ways of carrying out the reaction different methods to be developed for such a also to provide different alternatives.

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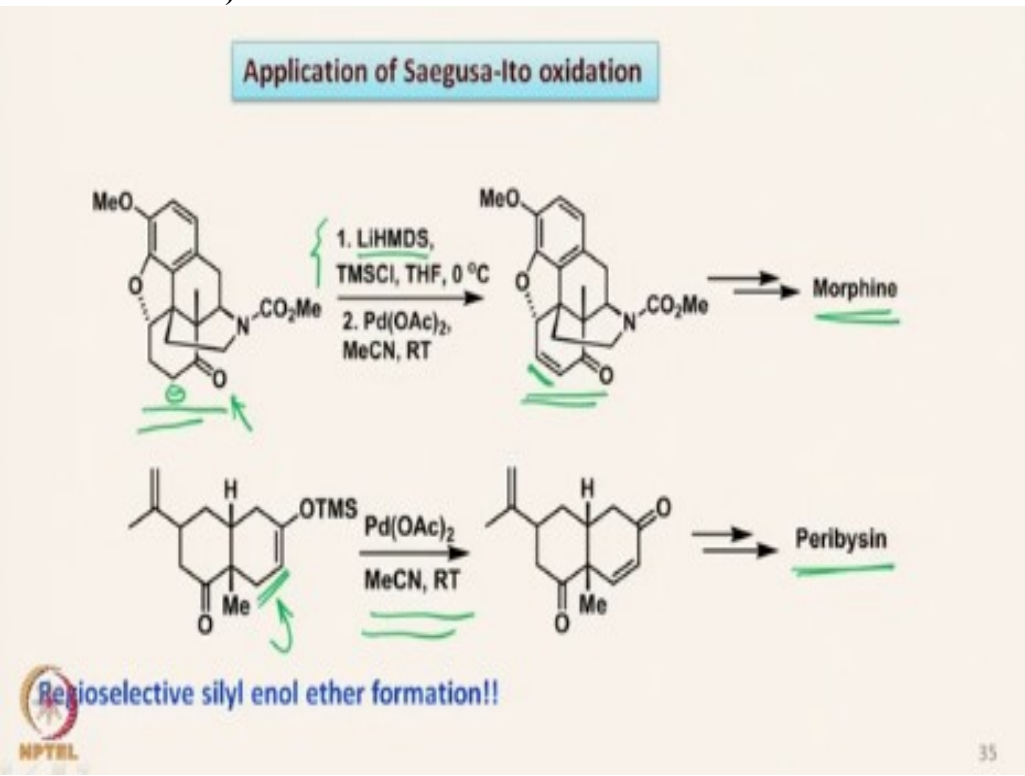

Now another example where simple applications are done is of course taking this ketone and making the corresponding enone. So here it is a very simple case you can generate an anion here which will form the corresponding in all silyl ether with the help of this this is lithium hexamethyldisilazane and then of course you generate an anion here make the enol silyl ether and you generate a double bond at this particular position.

Here is already any enol silyl ether with the palladium acetate acetonitrile at room temperature the reaction takes place to form this ketone. Now this has been converted into the alkaloid morphine where this has been converted to another natural product called peribysin. So it is of course you have to get to these enol silyl ethers in a very regioselective fashion in this case there is no problem.

But in this case one has to develop differently how one can get to this you know once you have got the enol silyl ether the formation of this see you can see that at room temperature just one step and one can get this reaction done.

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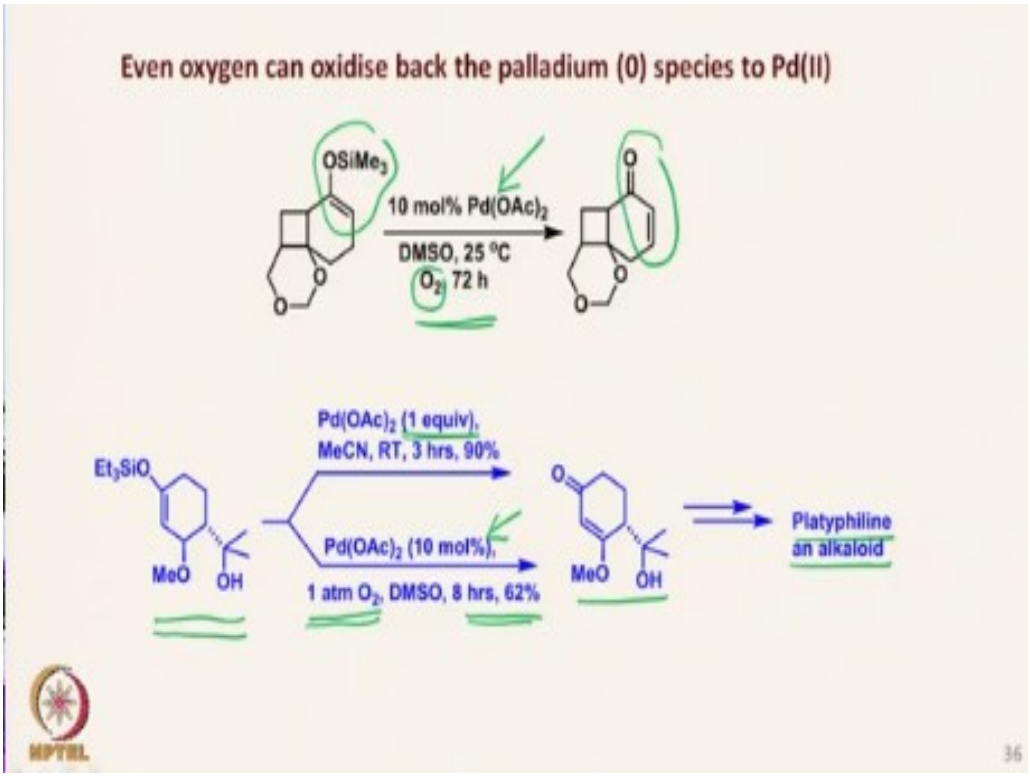

So this is what I have discussed so far and there are many more examples in the literature for example one can also use the DMSO and an oxygen as a co-oxidant or in place of benzoquinone or oxone, so as you can see here only 10% palladium acetate is used to form convert is enol silyl ether to the corresponding enone using oxygen as a co oxidant. Now in this example for example here enol silyl ether is already formed here with palladium acetate with one equivalent the reaction was done to get to this particular enone.

But on the other hand if one takes one atmosphere oxygen and only 10 mole percent of palladium acetate and you can get in 8 hour 62% yield and then that has been converted to an alkaloid. So these are new developments which are replacing the standard benzoquinone co-oxidant to something simple as oxygen as a co-oxidant. So I think that we will stop today on this particular reaction note.

I hope you have understood some new aspects of sulfoxide sulfenate rearrangement and I am sure that you will be able to make use of or at least theoretically construct different allyl sulfoxides and convert them into allyl sulfenate esters and place them in such a fashion that they lead to very interesting applications in organic synthesis and also similarly you can make use of the Saegusa-Ito reaction for converting in all silyl ethers or some other silyl ethers not necessarily coming from ketone or aldehyde.

But in some other fashion for example from nitro and then of course you introduce the double bond adjacent to the functional groups like ketone to enone or nitro to nitro olefin like this one can do it. So I have given examples I have given literature references you can go and read them also and ponder over the mechanism and of course we can always discuss it in the question answer sessions and we will take it up from here for the next 1, 2 ketone transposition next time, thank you and see you next time.