Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Systems
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Module No # 04
Lecture No # 18
Mechanistic aspects of DMDO based Oxidations and Oxaziridine Mediated

α-hydroxylations of Ketones

Hello everyone I would like to welcome you all for today's lecture. Before we continue with where we left last time.
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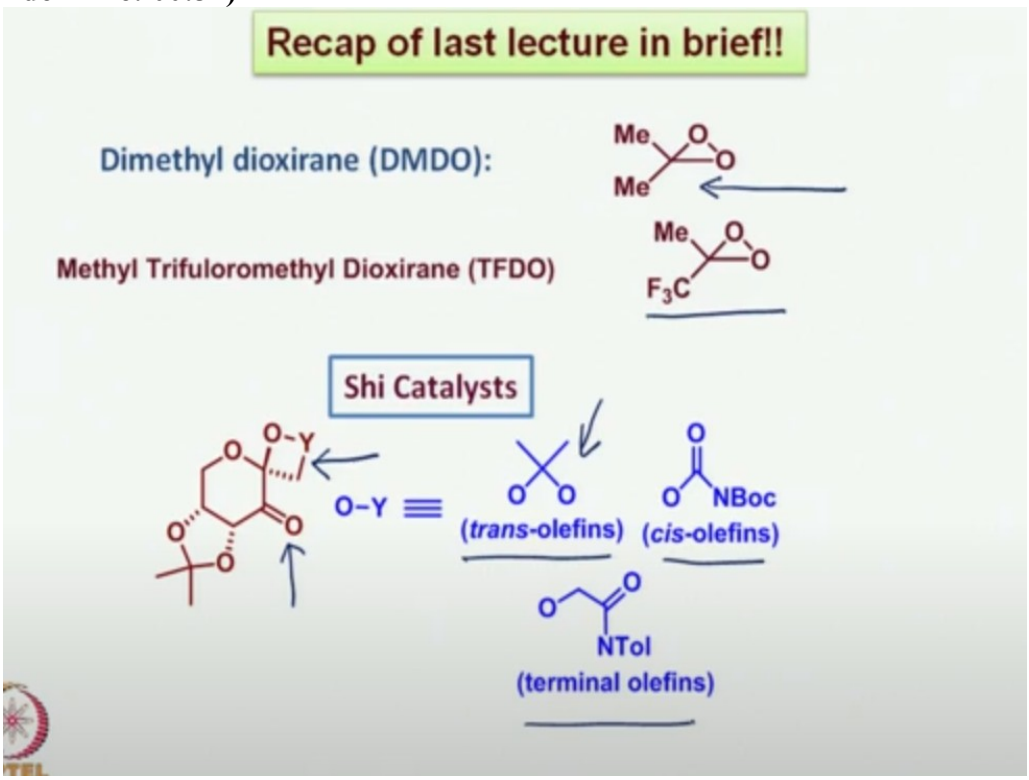

We would like to have a brief recap of the last lecture what we discussed in the last lecture was the use of dimethyl dioxirane and some other dioxiranes which are useful for the conversion of olefins to the corresponding epoxide. So the first one and the most popular dioxirane is dimethyl dioxirane whose structure is this. And I mention last time that we can take different ketones and one can prepare the corresponding dioxirane particularly in-situ.

That means inside the reaction and carry out the epoxidation of olefins it becomes more useful if one has reactive dioxirane somewhat like this. Having an; electron with drawing group such as CF 3 mainly because such dioxirane react with the electron deficient olefin a bit faster. And of course we can also take the chiral ketones and carry out the formation of the dimethyl dioxirane and they can transfer the chirality to the olefins to prepare chiral epoxide.

In this process I had mention a Shi catalyst and particularly from the D fructose. So if we have here this particular path attached to the fructose derived molecule here. Here is the ketone from the fructose and if this part here is having oxygen as a di acetonide protection. Then the trans olefins can be readily be oxidized. We will discuss more later on about how are the other substituents that affect the cis olefins and the terminal olefins. So this is what we did last time. Now let us go further today with the utility of the dimethyl dioxirane or other dioxiranes in organic chemistry.

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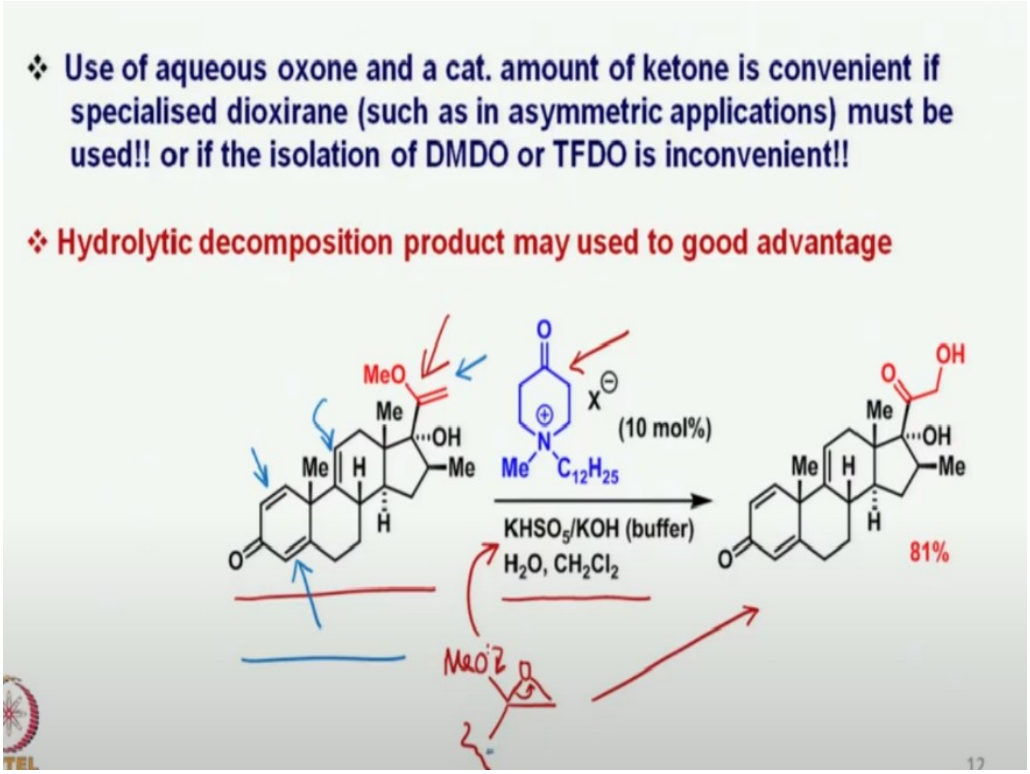

The use of Oxone and the catalytic amount of ketone is thus convenient we discussed it last time also. And particularly everyone wants to make use of it is in optically active preparation of the epoxides then one can easily use it. If one wants to isolate DMDO or TFDO that is trifluoromethyl methyl dioxirane if it is inconvenient then of course you can do the in-situ preparation. An example of this kind is here for example you have a substrate of this kind.

And if you have this enol ether then one can prepare the very interesting way of making the corresponding dioxirane is to use. This ketone which has a ammonium salt so that it is soluble in water and one can have the Oxone and potassium hydroxide buffer. And under these conditions the epoxide which is going to form from this double bond that means this is the epoxide that is expected to form.

If this is the other part of the molecule then this can open up in this fashion particularly and form the corresponding hydroxy ketone which is what is done in this case. So as you can see that this double bond is highly electron rich. These 2 are electron deficient olefins and this is highly sterically hindered. So this, such a molecule which has 4 different double bonds but then only one of them reacts and since it form an electron rich epoxide under the conditions then it cleaves to the corresponding hydroxy ketone.

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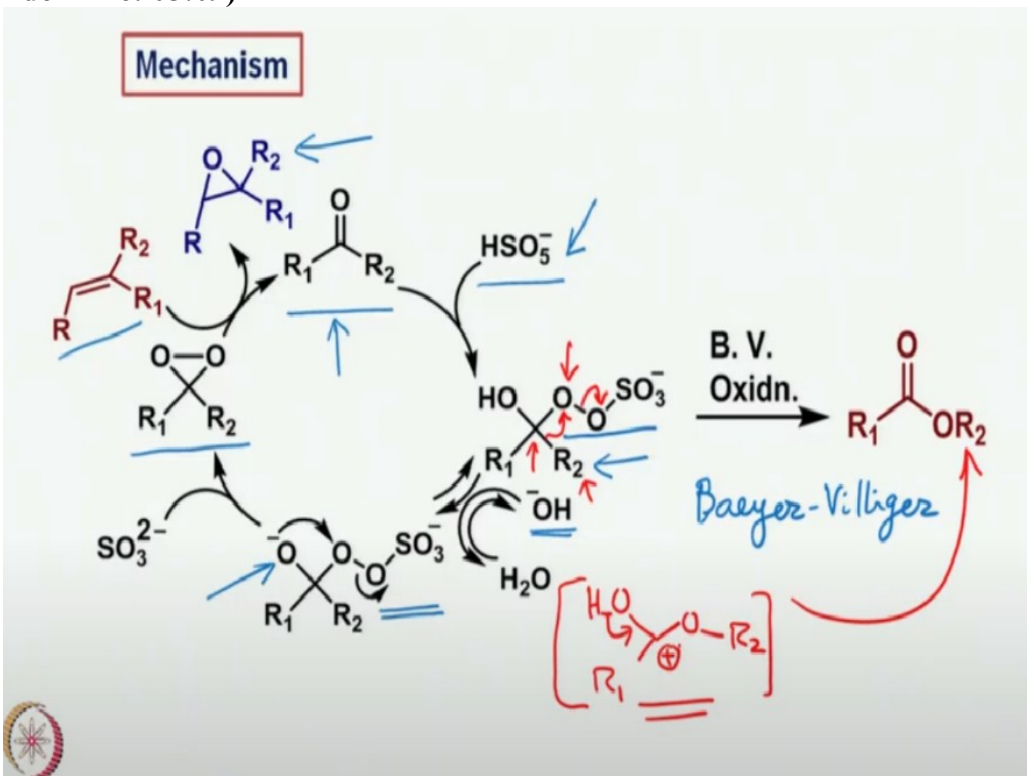

What is the mechanism of the reaction that is taking place in by using this Oxone to the corresponding epoxide? So what happens is that it starts with the ketone which ever ketone that you start with. It reacts with the Oxone that is mainly the mono peroxy potassium per sulfate. And that reacts to form to the ketone this particular intermediate. Now this intermediate is formed because of the attack of the peroxy sulphate moiety.

And now this under basic condition the OH minus takes up the proton from here to form this O-. And that under intra molecular condition opens up to form the dioxirane here. Now this dioxirane reacts with the olefin present forming the epoxide and regenerates the, corresponding ketones that is this type of ketones. So we have started with ketone and then under the basic condition it allows the intra molecular attack of O^- on to the oxygen because you have this sulphate ion as a leaving group and then it undergoes the corresponding formation of the dioxirane and of course epoxidation.

And one of the problems that is found that if the conditions is not much of basic then there is a possibility of Baeyer Villiger oxidation to take place. So you have a possibility of Baeyer Villiger oxidation that is because what you have is this path as a leaving group. So if this path is a leaving group then there is a possibility that the R 2 group or R 1 one of the 2 groups can migrate from here and this can go forming an intermediate of this type where you have a possibility of positive charge being formed.

Now this is what we see in the Baeyer Villiger oxidation we have 3, centre that is this one this one and this one 3 centre 2 electron that is carbon R 2 bond and therefore we formed this type of intermediate. And this what eventually leads to the formation of this ester. So this possibility can

also occur if the condition is not properly maintained. But then we there are ways to circumvent this.

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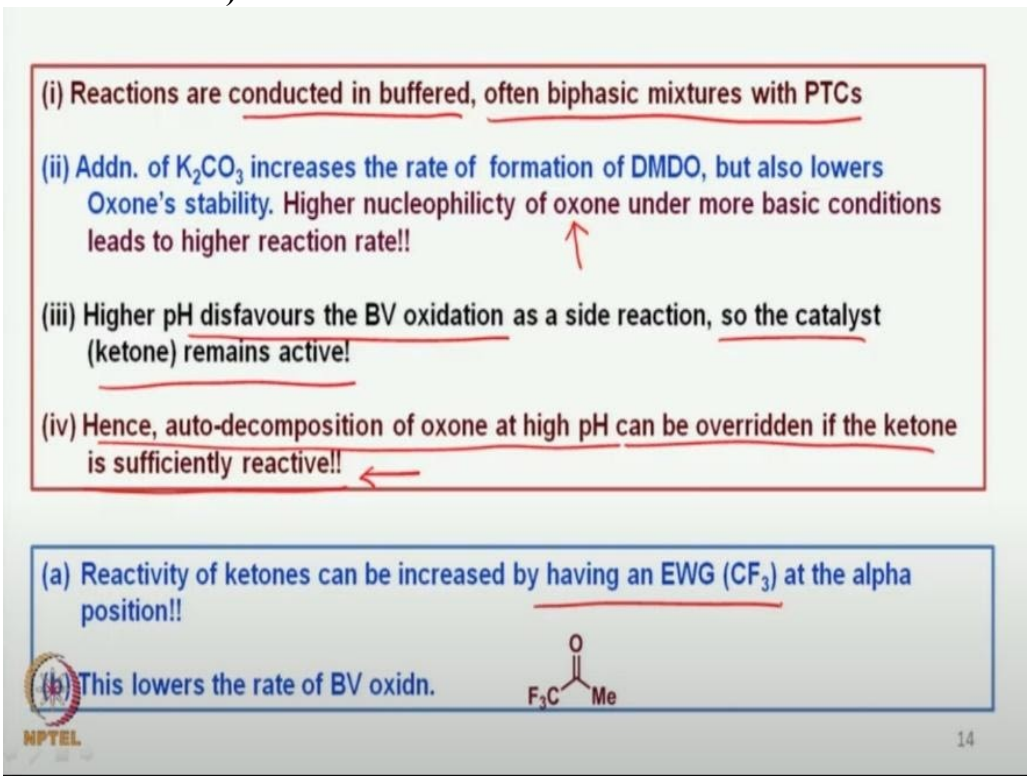

So the reactions are conducted in buffer medium often biphasic mixture with phase transfer catalyst which is what is PTC. Additional potassium carbonate increases the rate of formation of the DMDO but also lowers Oxone stability. It is found that the Oxone under the basic condition is somewhat less stable. But then if we add potassium carbonate as we did it in the previous case here.

The potassium carbonate allows the deprotonation of this hydrogen easily and then this negative charge attacks on to this oxygens and forms the corresponding dioxirane. So this can be increased by the addition of potassium carbonate or by increasing the basic medium. But then under the basic medium the Oxone stability is somewhat less. Obviously it is very clear that the Oxone nucleophilicity is high because of the deprotonation or the proton under basic condition and that leads to higher reaction rate also.

But at the same time higher pH disfavors the Baeyer Villiger oxidation as the side reactions. As we discussed we can go back to the last slide that this Baeyer Villiger oxidation occurs by the loss of the sulphate moiety. When the sulphate goes away that there is a migration of the carbon R2 bond to the oxygen which will now be kind of electron deficient. Because once, the sulphate leaves R is about to leave then you generate a delta positive on this particular oxygen.

You have delta positive to be formed and then the carbon R 2 bond goes there to form this intermediate. So this is Baeyer Villiger oxidation and then we want to avoid such a Baeyer villiger oxidation. So you can use basic condition so basic condition helps in decreasing the

Baeyer Villiger oxidation increasing the oxirane formation. But of course, it allows a somewhat decomposition of the Oxone.

Hence auto decomposition of Oxone at high pH can be overridden if the ketone is sufficiently reactive. So what you can even do is the higher pH as I said higher pH disfavors the Baeyer Villiger oxidation as a side product formation. So the catalyst remains active. So basically you start with the ketone and make the oxirane dioxirane but then you have to use basic condition. And if, we increase the reactivity of ketone then the possibility of Baeyer Villiger oxidation is less.

The nucleophilicity obviously of the oxirane this Oxone increases and then reaction becomes more or less like very sufficiently fast. So reactivity of ketones can be increased by having an electron drawing group and very clearly it leads more to the dioxirane and does Baeyer Villiger oxidation is reduced.

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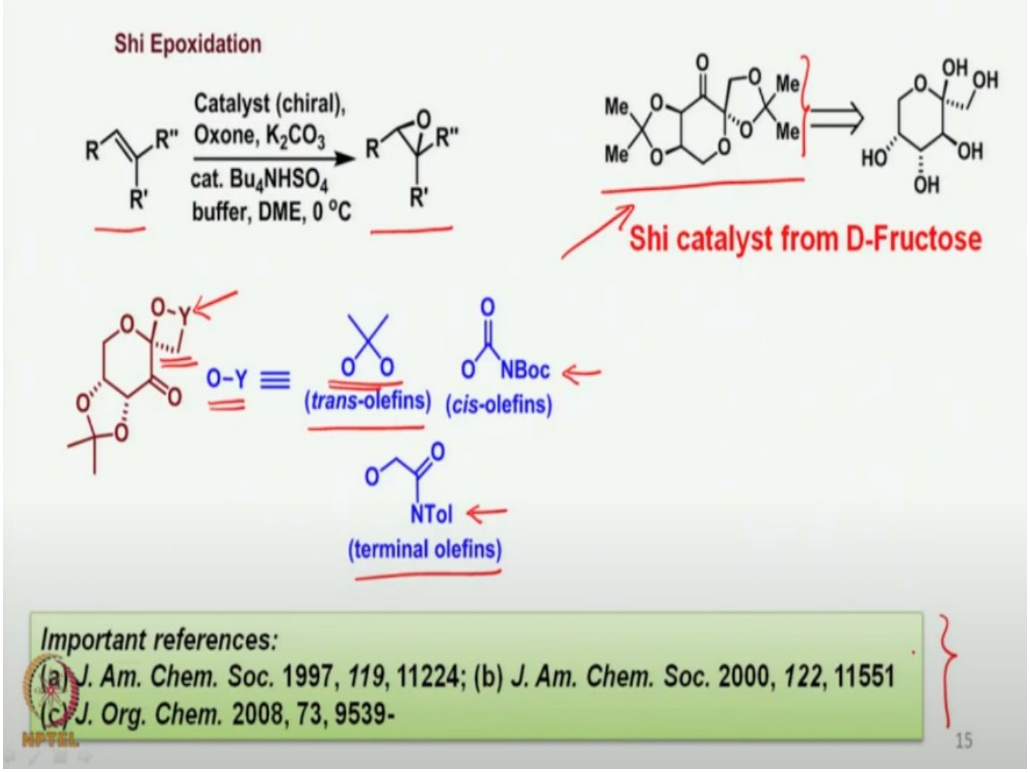

As I discussed and introduced we have Shi epoxidation so the one can start from D fructose and prepare this particular ketone which is what is used in the Shi's epoxidation of converting an olefin to the corresponding epoxide which is chiral. And their reference which is mentioned here are very important references. What is found is that instead of this acetonide here if we increase and change the substituent here say, Y so O Y is this which is what we have written here in this form.

Then this is useful for trans olefin. If we change the substituent there and make it like O NBoc here this is found to be more useful for the cis olefin. And if we have this NTolyl here then of course it is useful for terminal olefins. The mechanism and this and the transition states are

somewhat complicated. So I would not like to discuss it here but one can check this references and get to know what how does this affect the corresponding olefins.

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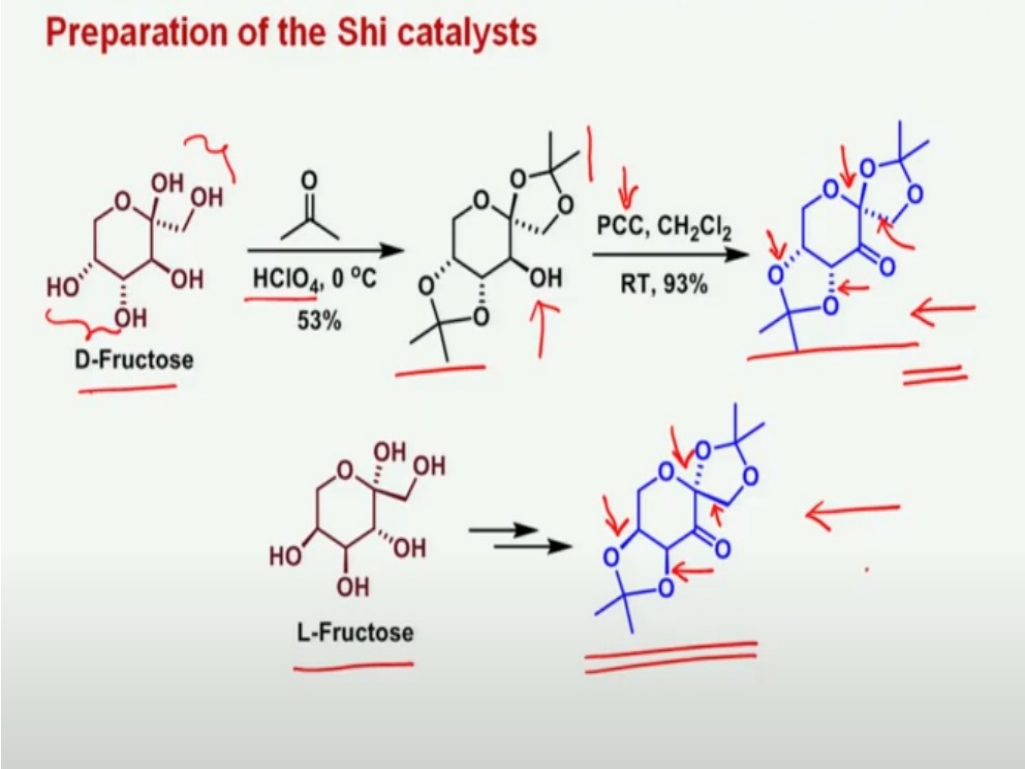

Now how do we make the Shi catalyst is very easy you can take the D fructose. And you can put the acetone in the presence of per chloric acid as an acid catalyst. And these diol which is a cis diol and this diol which is relatively free away from the steric point and can easily react. So both of them react to form the corresponding diacetonide and then you can oxidize the hydroxy group using PCC pyridinium chlorochromate. And we can prepare this particular ketone which is what is reacted with Oxone to form corresponding dioxirane.

On the other hand if this gives certain type of chiral reduction then opposite of that can be expected to form from the L fructose based ketone. If this is the L fructose ketone as you can see that there is a exactly opposite of the D fructose-based ketone. These 2 are beta where they were alpha here in a similar fashion this was alpha. So it is now beta and this is beta and here it was alpha. So it is exactly opposite because D fructose and L fructose are actually mirror image of each other.

So whatever chirality is going to come of the epoxide which is here by using this ketone it will be exactly opposite by using this ketone. So there is a great advantage and it is very easy to prepare from the D fructose and L fructose.

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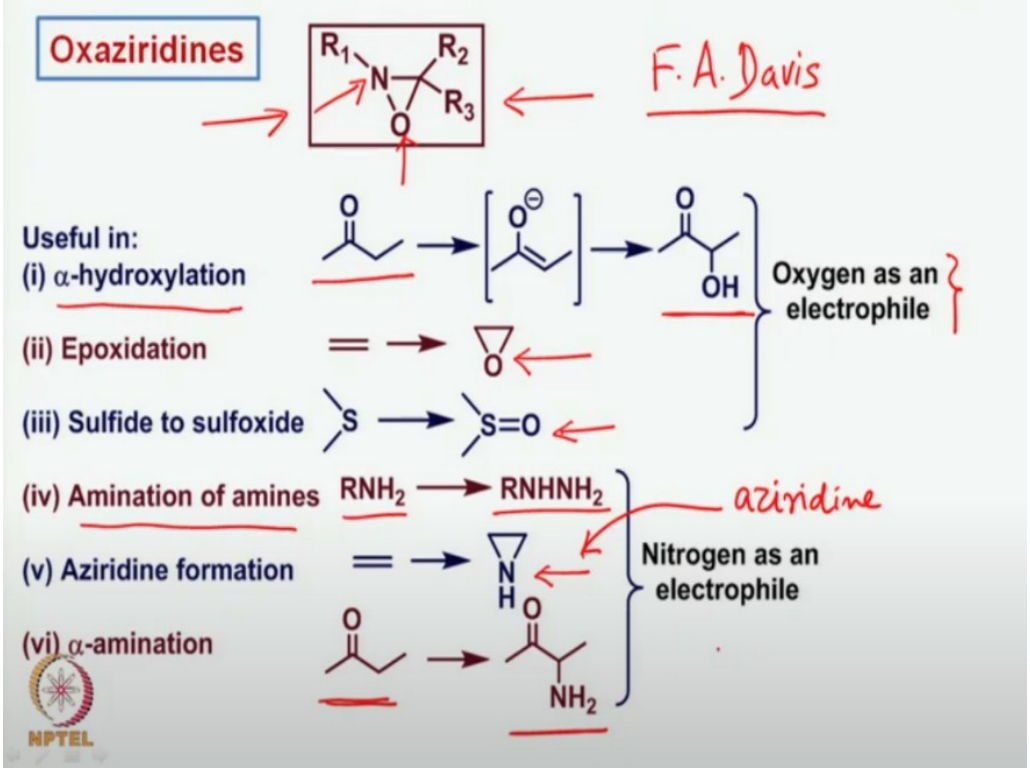

Now we go to the next topic that is oxaziridines and they are shown like this the structure. So we used dioxirane but now we are going to use the oxaziridines. Now what are those oxaziridines they are exactly similar to the dioxirane but then one of the oxygen is replaced by the nitrogen. Now this leads to interesting possibility and it has been popularized by Franklin A Davis and it leads to variety of different types of reaction.

For example it is useful in converting a ketone to the corresponding alpha hydroxy ketone. So alpha hydroxylation is one of the reactions that is found to take place and this is how it works very well. So here this oxaziridines as one can imagine could be a source of nitrogen or could be a source of oxygen. So these examples which are shown here illustrate that oxygen acts like an electrophile.

So alpha hydroxylation is one product the olefin can react with the oxaziridines to form the corresponding epoxide. It can also oxidize sulfide to sulfoxide by transfer of oxygen. So these 3 examples are basically of oxygen transfer. Nitrogen can also be transferred if one takes amine for example so you can start with an amine and you can make this hydrazine we are transferring nitrogen.

There are possibilities of transferring nitrogen similar to the epoxide type of formation. One can also get the corresponding aziridines. So you can get this type of aziridine molecule which is nitrogen analog of epoxide. And just the way alpha hydroxylation was done you can also use alpha amination and get the corresponding amino ketone and this is basically because of the nitrogen transfer. So these are the example of nitrogen as an electrophile.

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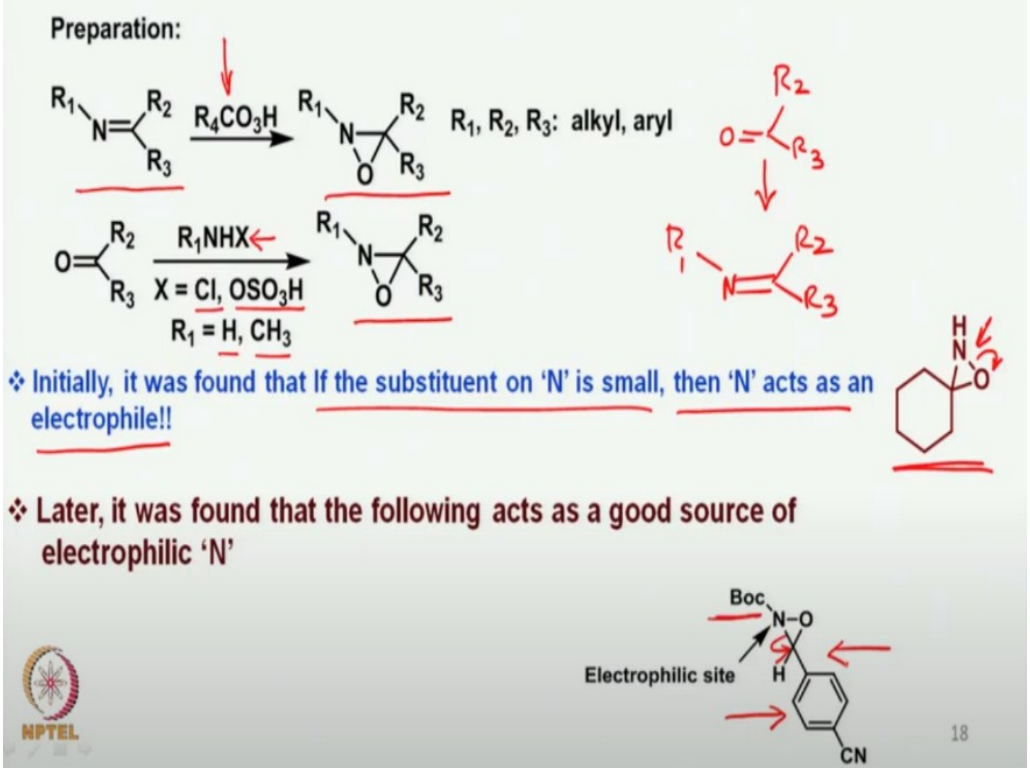

How do we prepare this oxaziridines there are several methods but I have shown here 2 methods that one can start with emine starting from the corresponding ketone. So, if we start with the R2 R3 ketone here and, we can prepare the corresponding emine easily and we can then react it with any percaid. So any perocaid such as metachloro perbenzoic acid peracetic acid or any other peracid we can easily epoxidize this emine to form the corresponding oxaziridines.

Otherwise one can take on this nitrogen some sort of leaving group. So a molecule of these, kind where x is chlorine or any kind of leaving group like OSO_3H. And of course R1 can be hydrogen methyl or any other substrate or a group and then it forms the corresponding oxaziridines. Initially it was found that if the substituent on nitrogen is small somewhat like this you have a, hydrogen or a methyl or a acetyl a small group.

Then nitrogen acts as an electrophile because there is unlike dioxirane which is dimethyl dioxirane or any other dioxirane. Here the 2 different possibility is one is oxygen as an electrophile other is nitrogen as an electrophile. Therefore one has to be little bit careful so it is always possible that nitrogen be careful and a lot of work has been done.

And as I mentioned that if we have a small substituent on the nitrogen then there is a possibility of nitrogen transfer. That is because if nitrogen has small substituent and this bond can easily break and you can transfer the nitrogen. On the other hand if was also found that if we have a group somewhat like this here para cyano phenyl. For example then it is possible with the group of like BOC group present on the nitrogen.

You are making this particular nitrogen as more electrophilic nitrogen. And also there is a possibility that you can break this bond here. And the negative charge here will be, stabilize because of the electron with drawing cyano group attached to the para position of the phenyl

ring. So it was found that this can also act as a good source of nitrogen. So there are examples in the literature where these 2 and somewhat similar have been utilized for the transfer of the nitrogen from oxaziridines.

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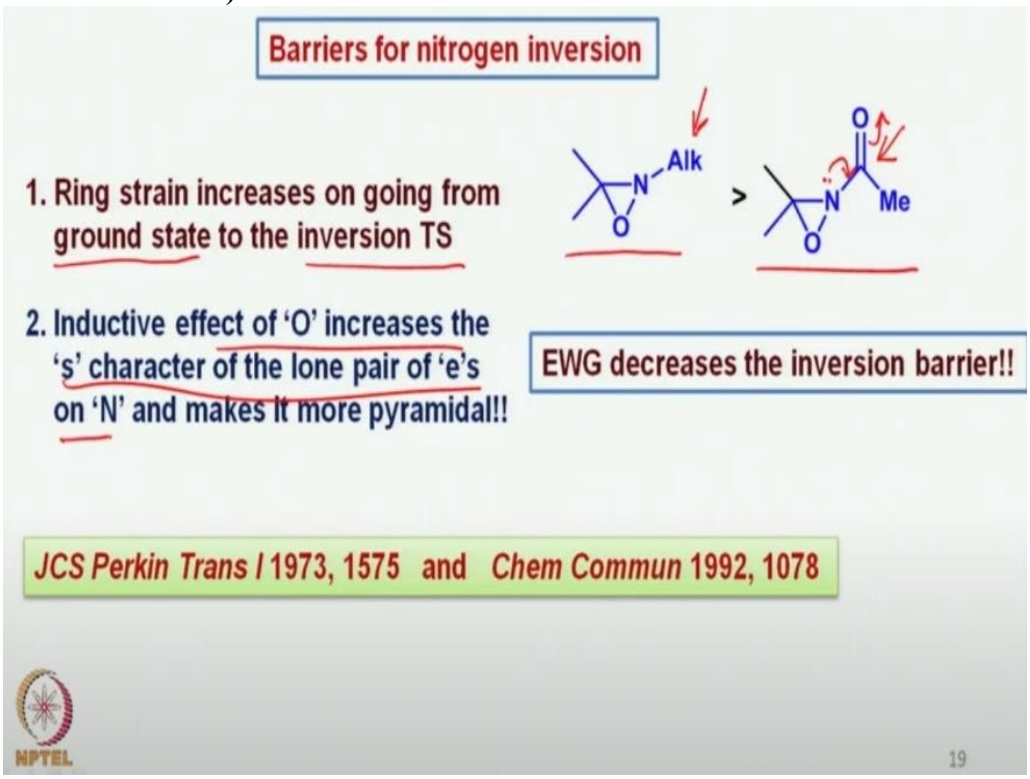

Now just to tell you about what are the barriers for the nitrogen inversion obviously we go from ground state to the transition state inversion of the transition state the strain will increase. And when you have an n alkyl substituent versus n acyl substituent the strain increases when we have the alkyl group and strain decreases when we have electron with drawing group. So, inversion barrier basically decreases with the electron withdrawing groups.

Because the lone pair of electron on the nitrogen here would now be in conjugation with this. Therefore there is an easy possibility of the inversion of the configuration here on the nitrogen. At the same time inductive effect of the oxygen increases the s character of the lone pair of electron on nitrogen and makes it more pyramidal. So that is another property of this type of oxaziridines.

So basically it is just to illustrate or show that what kind of properties these oxaziridines can have.

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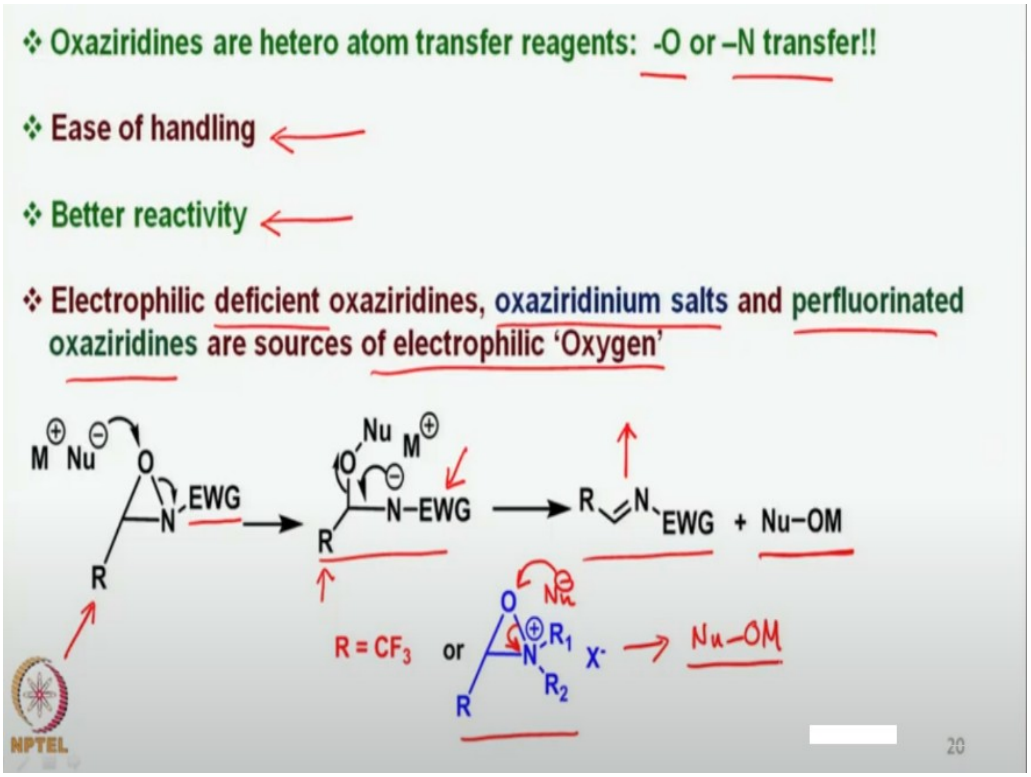

Now as I am already have discussed that they are can oxaziridines can transfer heteroatoms such as oxygen and nitrogen they are easy to handle. That is one advantage that there very easy to handle they are not unstable like dioxirane like dimethyl dioxirane or something like that. Of course they are reactive but we have a possibility of having an electron withdrawing group on the nitrogen Thus making the reaction the stability of the oxaziridines bit more.

And the same time they are fairly reactive. Now there are several ways by which one can make the oxaziridines with having a property of electron deficiency. For example oxaziridinium salts and per fluorinated oxaziridines are sources of electrophilic oxygen how? Now for example if one has an electron withdrawing group here so and also an electron withdrawing group on the nitrogen.

Then there is a possibility of ready cleavage of this oxygen nitrogen bond to form this particular anion on the nitrogen which is basically due to the influence of the electron withdrawing group on the nitrogen. At the same time because R is also an electron withdrawing group therefore it is easy possibility of such cleavage, and that lead to the formation of the nucleophile reacting specifically with the oxygen and the emine is regenerated.

So the regenerated emine can again be epoxidized and oxaziridines can form. At the same time one can also take oxaziridines with ammonium salt here such as this. This is going to be also a source of oxygen here electrophilic oxygen because your nucleophile will preferentially attack onto the oxygen and cleave this oxygen nitrogen bond. And therefore we can get the same as above that you have the transfer of oxygen to the nucleophile. So there are ways of manipulating the condition for this reagent to see if nitrogen is transferred or oxygen is transferred.

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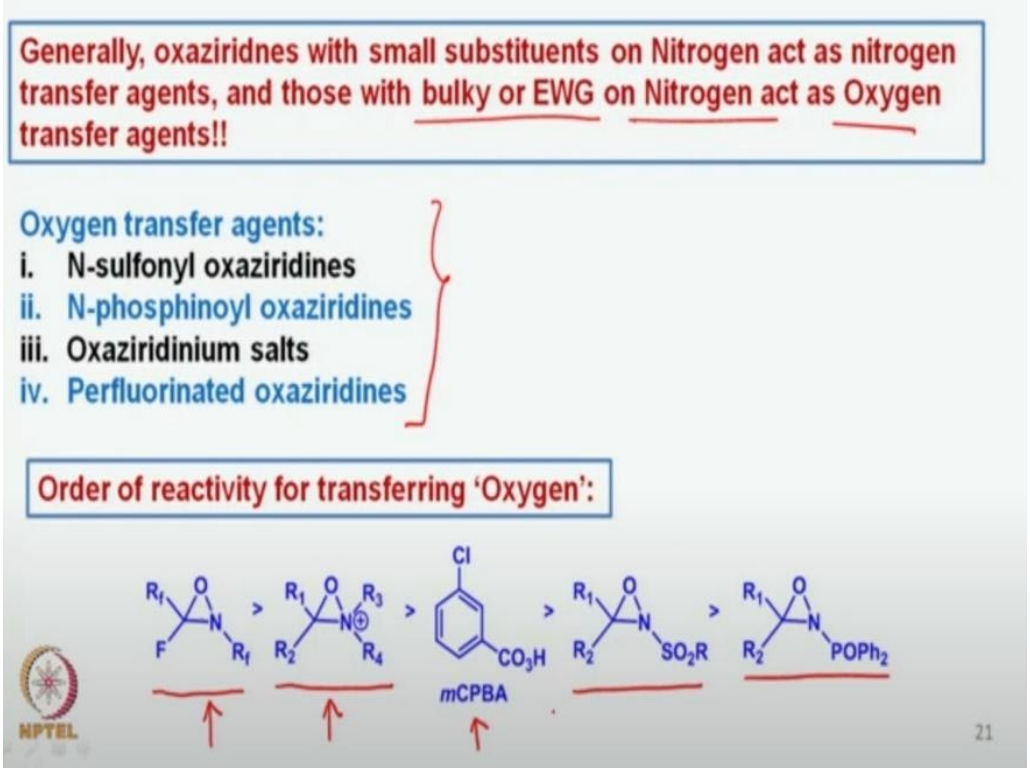

Now as I already discussed earlier that we have oxaziridines with small substituents on nitrogen act as nitrogen transfer with bulky or electron with drawing group on nitrogen act as oxygen transfer reagents. So what are the oxygen transfer reagents? There are 4 of these, kind I have already shown here N sulfonyl oxaziridines as it is shown here. Then N phosphinoyl oxaziridines then you have oxaziridinium salts which are here.

Then we have perfluorinated oxaziridines these are the 4 different types of molecules which can act for the transfer of oxygen on it to a nucleophile. Now what; are the order of reactivity for transferring such oxygen in comparison to say meta chloro perbenzoic acid. And this is how it has been found that we have for the perfluorinated oxaziridines react very fast. Then you have the corresponding salt of this kind of oxaziridinium salts.

Then that is more than meta chloro perbenzoic acid which then is more than the corresponding sulfonyl type of oxaziridines and then phosphinoyl type of oxaziridines are less reactive than the corresponding sulphonyl type of oxygen. So this is the reactivity pattern of the oxaziridines that one can think about it. Now that depends upon the reactivity of the nucleophile that we have it.

So based on that if we have a possibility of the order of reactivity of the nucleophile then one can match readily with the oxygen source as well as the enolate nucleophilicity and decide which combination one can take.

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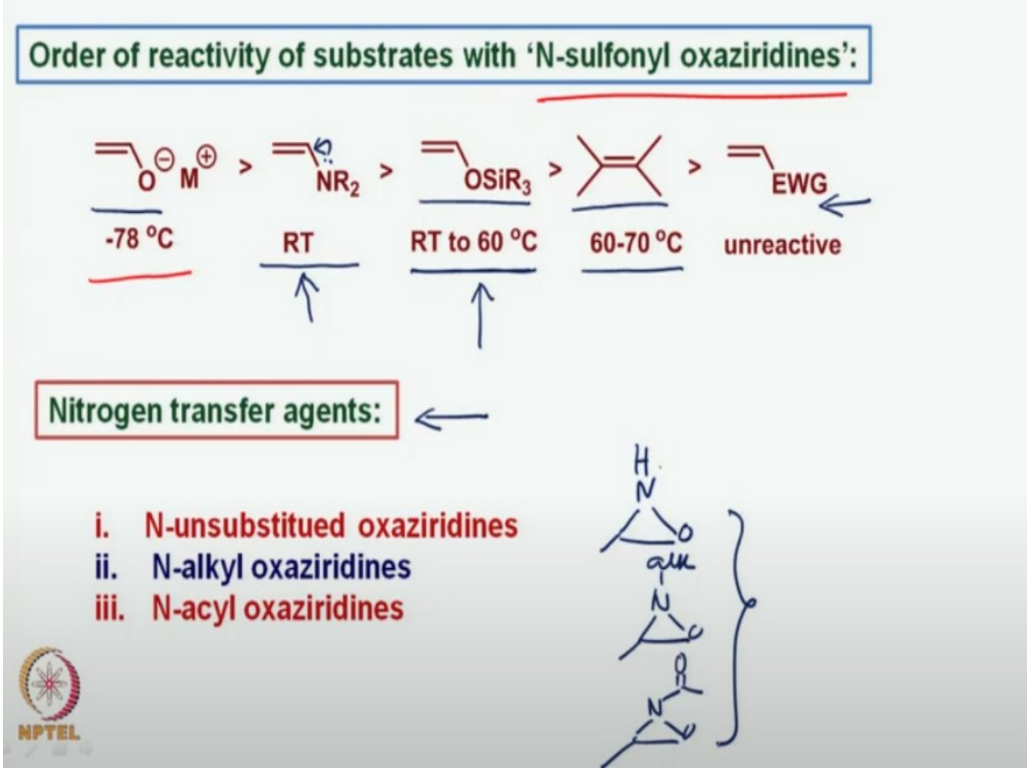

Now order of reactivity of olefins or the olefin type of substrates is as follows with respect to the N sulphonyl oxaziridines. Normally N sulphonyl oxaziridines are more often used they are stable easy to prepare and for the reactivity that has been very much studied with N sulphonyl oxaziridines. Now you can see that the enolate ions can easily prepared at low temperature such as -70 degrees and this enolate ions can react with the N sulphonyl oxaziridines very fast.

Because you have a clear negative charge and therefore a nucleophilicity of double bond is very high. So we use at -70 degrees which is that means at a very low temperature. Now we have an enamine that also is very reactive, because now you have a lone pair of electron on the nitrogen that donates electron density to the double bond the reaction can be carried out at room temperature.

So it does not require very low temperature but room temperature is good enough. On the other hand, if you have enol silyl ether lots this kind and that that requires room temperature to 60 degrees as a temperature for the epoxidation to take or reaction with oxaziridines to take place. If you have a normal olefin like this it takes around 60 to 70 degrees. That means this can react even at room temperature depending on the reactivity of enol silyl ether.

But can be done up to 60 degrees temperature but then you have less nucleophilic olefins such as simple olefin then you need 60 to 70 degrees. And if you have electron with drawing group on the double bond then the molecule is somewhat unreactive. For the nitrogen transfer reagents of this time what you need is an N-unsubstituted oxaziridines so we have somewhat like this or you have an N alkyl.

So you have N alkyl group here and you have this oxaziridines or N acyl. So you have here somewhat like this. So these are the oxaziridines which are generally used for the transfer of the

nitrogen for a nucleophile. So there are different ways by which one can choose the reaction condition and also the substrates and also the oxaziridines and accordingly one can carry out the reaction depending on what is required?

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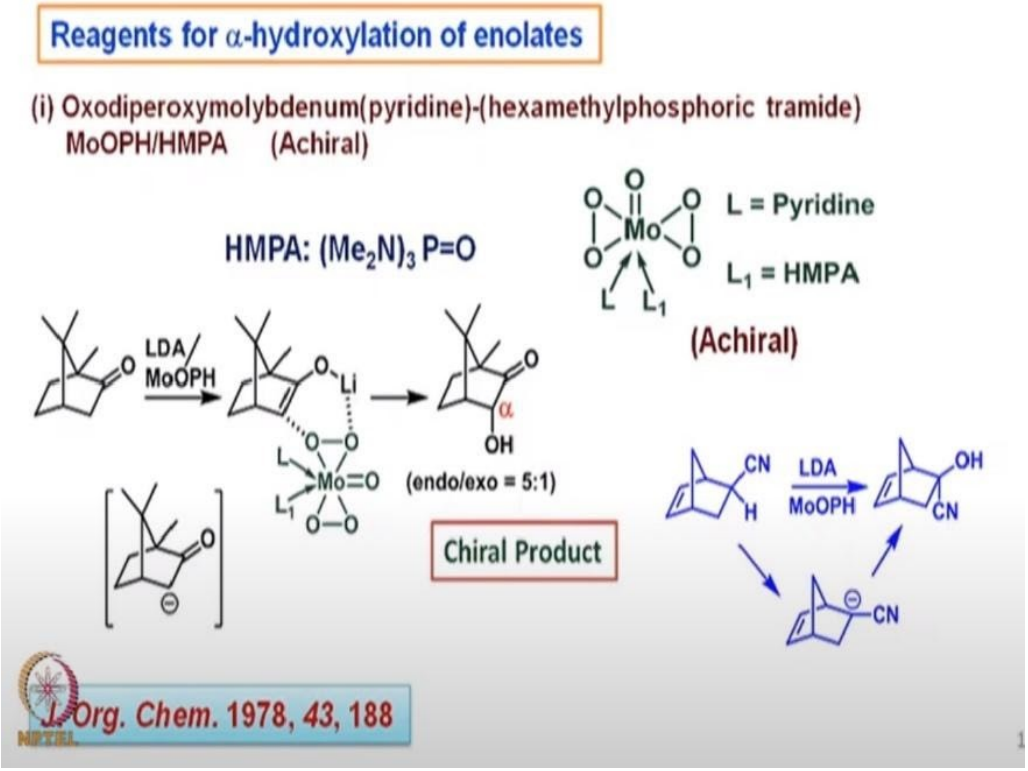

Now what are the reagents for the alpha hydroxylation of enolates to form achiral alpha hydroxy ketones. One of the reagents that has been used is oxodiperoxymolybdenum pyridine hexamethylphosphoric triamide complex which is shown here. L is pyridine and L1 is HMPA which is hexamethylphosphoric triamide. So these 2 are the ligands which are a chiral and therefore this particular complex is an achiral complex.

Now this acts as an oxidizing agent and if we; react achiral molecule like this which is camphor with a base like LDA and this MoOPH this is what the reagent is. Then under basic condition like LDA it would deprotonate the proton alpha to the carbonyl group leading to this particular anion which will exist as an enolate and then there will be a nucleophilic reaction, of this enolate from this carbon to the oxygen of this particular complex allow to form this alpha hydroxylation.

And since the beta side that is the upper side or the exo side of the molecule is sterically hindered because of this methyl group. We get a mixture of 2, alpha hydroxy ketone in which, the endo hydroxy group or the compound having endo hydroxy group is the major product as you can see here. The endo exo ration is 5 is to 1. Now although the reagent is achiral since the molecule the starting molecule the camphor is optically pure so the product that we get is a chiral product.

So this is one of the ways by which we can get the chiral alpha hydroxy ketone. Now in a similar fashion if we take instead of a ketone if we take a cyano compound of this kind in which there is no steric hindrance from the top side that means the exo side is sterically unhindered then if we

do the deprotonation with LDA and react with the same molybdenum based oxidizing agent MoOPH. Then once we get the anion of this type after the deprotonation alpha to the cyano group here.

This can react with the reagent from the exo side because the endo side in the particular case is sterically more hindered when compared to the exo. And therefore we get this cyanohydrin in which the hydroxy group is exo oriented. So this is one of the ways by which one can easily deprotonate a proton which is a highly acidic under basic condition we can deprotonate that particular hydrogen and introduce a hydroxy group.

So we will stop at this stage today and take up the remaining parts of the oxaziridines such as chiral based reagents and the mechanism and other aspect of it in the next class. So please study whatever I have discussed today and thank you and we will see you next time. Thank you.