Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Systems
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Module No # 04
Lecture No # 17
Oxidations with Dimethyl Dioxirane (DMDO)

Hello everyone welcome, to today's lecture. I hope that you had the chance to go through the last lecture and we will briefly look at what we did last time before we start new topic today.
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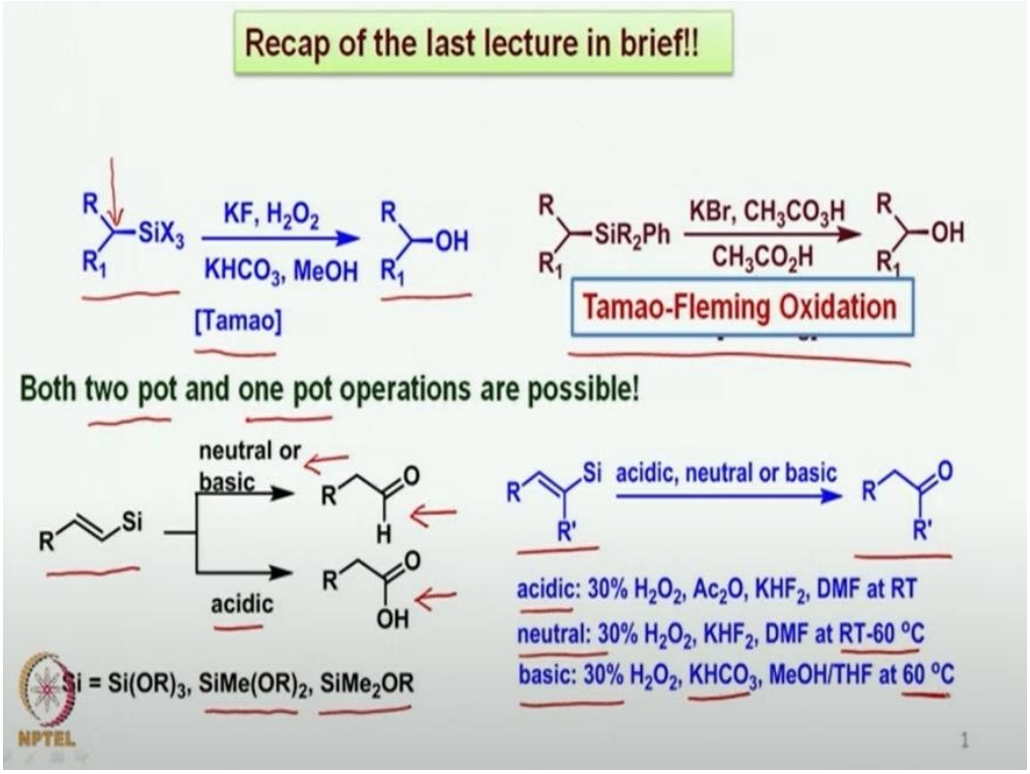

The last lecture we had discussed Tamao Fleming oxidation which is basically conversion of the chiral or even achiral but chiral is more important. If you have a chiral silicon bonded compound such as this here as shown. And if this is treated under at Tamao condition then we get the corresponding alcohol that means the carbon silicon bond is broken and carbon hydroxy bond is formed.

And this condition is that we discussed last time in detail in Tamao condition we have s different types of conditions. On the other hand the Fleming oxidation involves the 2 types of possibilities. As we discussed one is a 2 pot reaction and the other one is 1 pot operation or reaction. In both the cases in the Tamao's case as well as Fleming oxidation case eventually we get the same product as retention of configuration of the hydroxy group from the silicon bonded group that we started with.

So and both are important and in similar fashion when we had the alkenyl silene like this we discussed towards the end that if we have neutral or basic condition like this .And if it is a disubstituted olefin then we can get the corresponding aldehyde. Or if it is under acidic condition like this then we can get the corresponding acid provided that the silicon has substitutions like this. On the other hand when it is a tri substituted silicon containing alkenyl molecule then either whether it is acidic or neutral or basic condition.

We get only the corresponding ketone because there is no chance of getting any acid. And as we discussed that we have acidic condition in which we have hydrogen peroxide acetic anhydride and this fluorine source and the DMF at room temperature neutral is also the same except acetic anhydride is not there. And of course you heat from room temperature to 60 degrees and the basic condition requires potassium carbonate in methanol and 60 degrees temperature.

So this how the Tamao Fleming oxidation is utilized and it is a very important reaction as we discussed and we saw some applications.

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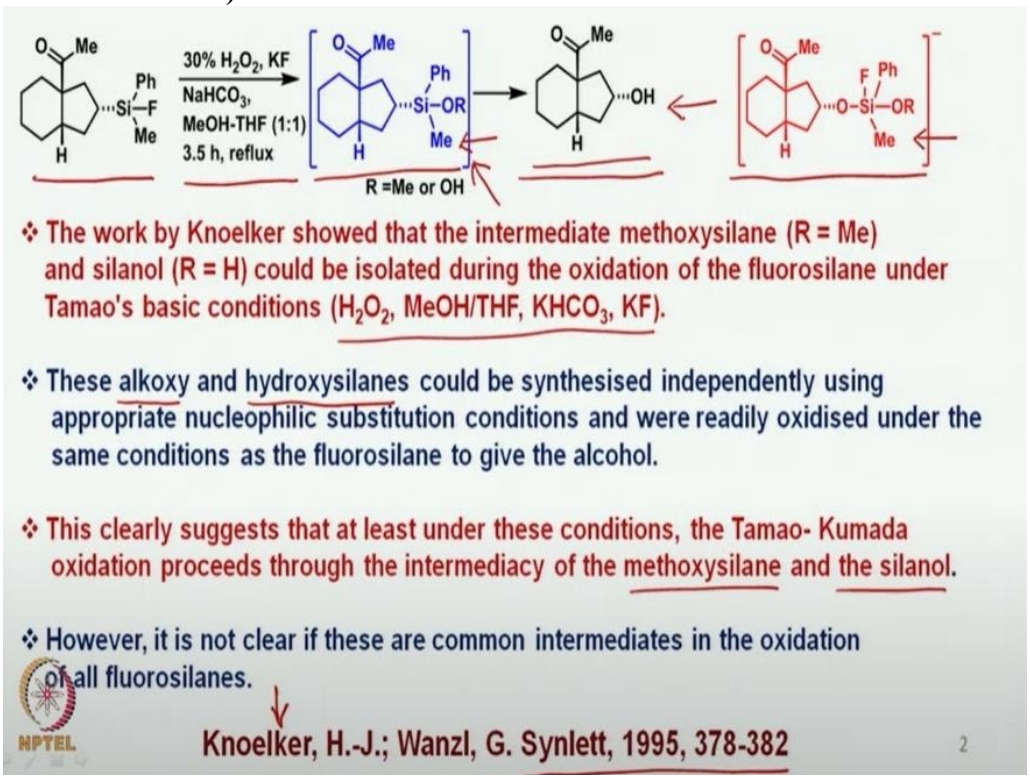

Now one more example that I had shown last time was this silicon molecule this molecule containing silicon group and a fluoride here at this position. And I showed that it forms a corresponding hydroxy group with the intermediacy of this kind, which essentially was shown by Knoelker. A German scientist Knoelker whose reference I have given here in Synlet 1995. He actually isolated when he did the work he actually isolated the corresponding methoxy or hydroxy group here.

So this particular molecule was isolated by Knoelker during the reaction of converting this particular silicon containing molecule to the corresponding hydroxy molecule and showed. So

the work by Knoelker showed that the intermediate methoxysilane when R is methyl or silanol when R is hydrogen could be isolated during the oxidation of the fluorosilane under Tamao's basic conditions.

So this is the condition under which they isolated. Now it is very clear that when they did prepare the alkoxy and the hydroxysilanes these molecules separately not under these conditions and then subjected these molecules under the same conditions of Tamao they did indeed get the hydroxy compound. So it is very clear that under these conditions at least these Tamao Kumada oxidation proceeds to the intermediacy of the methoxysilane and the silanol at least in these conditions or for this particular molecule.

It is very clear that intermediate would be something like this. Starting from this particular where intermediate where there is an OR or OH the hydrogen peroxide would attack, and eventually one would get something like this which finally will give the product of this type. So this is a very clear indication of how the Tamao oxidation can proceed and there is very clear evidence that some intermediate of this kind can be isolated.

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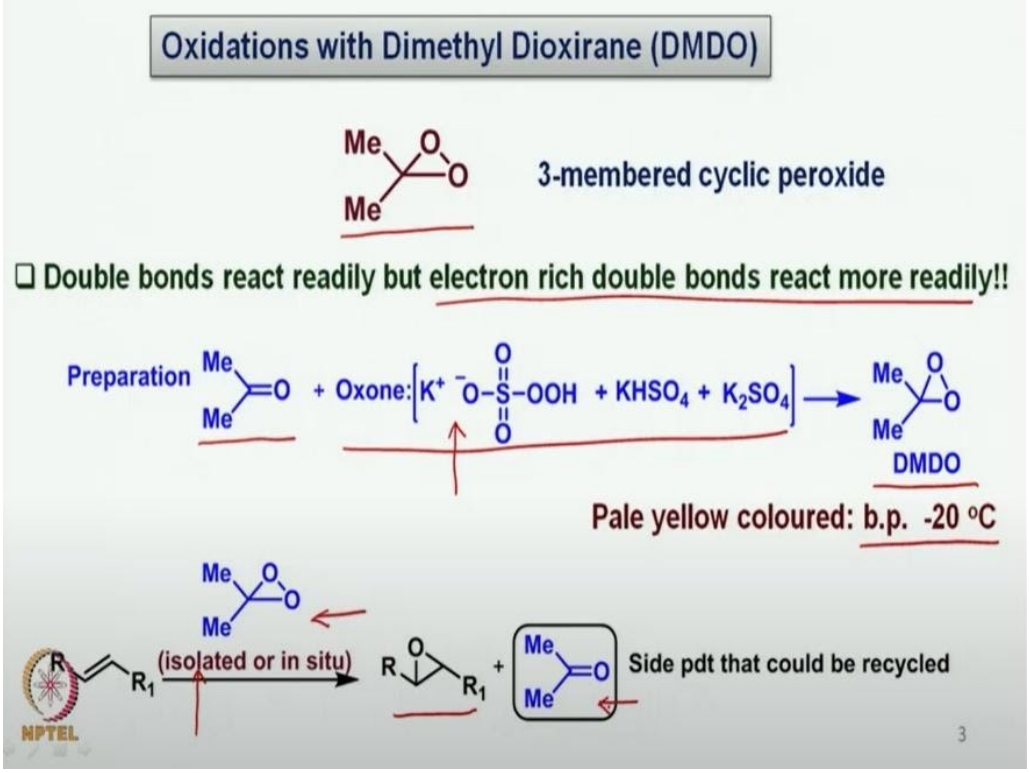

We start now with oxidations of different kind which is oxidation with di methyl dioxirane as you can see the name dimethyl dioxirane. So this is the structure of the dimethyl dioxirane. So it is 3, member cyclic peroxide as you can see there is a peroxide bond. And since it is a 3 member ring with 2, oxygen's obviously it is a very reactive substrate it is very reactive reagent. And it reacts readily with all kinds of double bonds but obviously it would react much faster with electron rich double bond.

As we go along we will see how the reactivity of this dimethyl dioxirane can be understood. How do we make this? It is very easy to prepare on paper but it is not that easy to prepare in the

laboratory that is because the boiling point of this DMDO which is dimethyl dioxirane is -20 degrees. That means it is a very low boiling compound and it can be easily prepared from acetone and the Oxone which we discussed about Oxone last time.

Oxone is nothing but potassium monoperoxy sulphate along with potassium hydrogen sulphate and potassium sulphate. But this is the main oxidant, and it is a very useful oxidizing agent. Now when acetone reacts with Oxone you get the corresponding DMDO which has to be distilled out very carefully at low temperature with all protection so that the molecule the DMDO does not escape out.

Now there are several ways by which this reaction can be done. You can either isolate this DMDO by distilling and cooling it at low temperature so that you can isolate this DMDO and then you carry out the reaction. So you can have an isolated way of doing it or you can also do it in-situ. In-situ means inside a reaction we put acetone and also Oxone and as soon as the DMDO is formed the DMDO reacts with the olefin and the epoxidation occurs.

So basically olefins react with this DMDO to form the corresponding epoxide. Now the side product as you can see what 1, oxygen of the DMDO is transferred to the olefin the side product is nothing but acetone. So it is a very useful way of regenerating the starting ketone that means you are starting ketone is acetone that reacts with Oxone forms DMDO and if that DMDO reacts with olefin you get the corresponding epoxide and acetone back in.

It means that we can start with the small amount of acetone and a large amount of Oxone. And as soon as the reaction of olefin occurs with the DMDO and acetone is back and that acetone again reacts with the Oxone to prepare to form DMDO and then reaction continues. This is a very general way of reacting.

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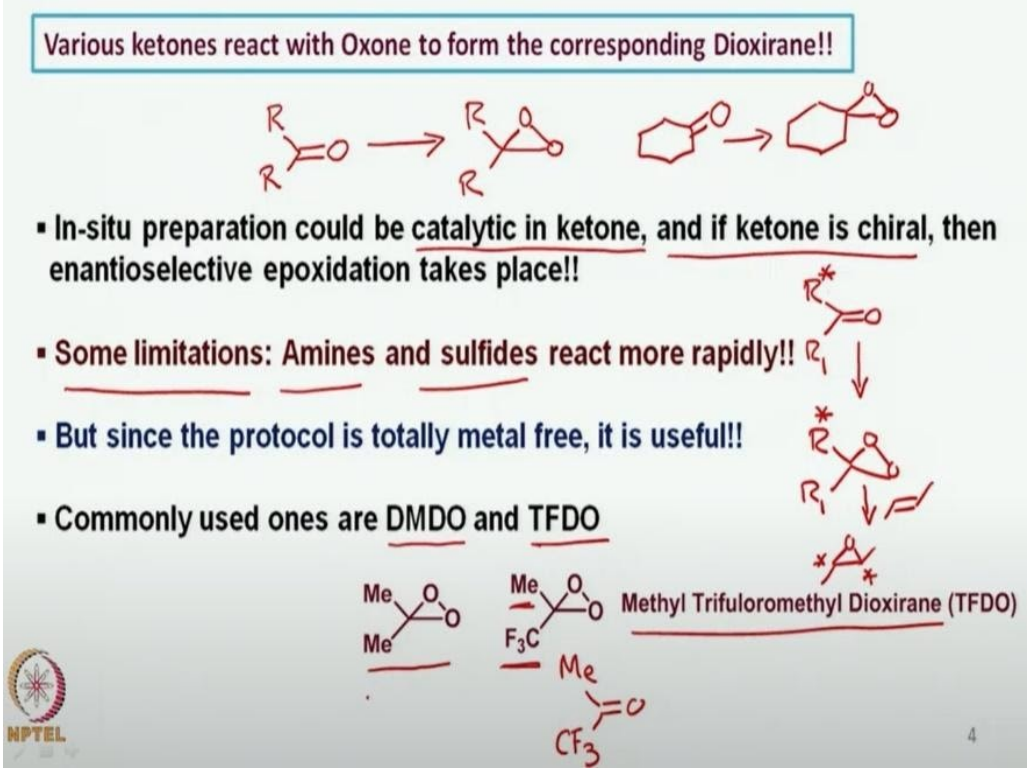

So, various ketones of different kind have been found to react with Oxone to the form the corresponding dioxirane. So that means we can here write a general way of representing that we have ketone which is an acyclic ketone right now can form the corresponding dioxirane. So irrespective of what R groups are. You can have the corresponding dioxirane. In a similar fashion you can also have corresponding cyclic ketone that can give the dioxirane of this type.

So this advantage of this is that we can prepare the dioxirane from a chiral ketone. So if the ketone is chiral that means optically active. Then we can have a small of or a catalytic amount of ketone we can use it and react it with the dimethyl to react with Oxone and then epoxidation is expected to take place because the chiral ketone. So any chiral ketone will give the corresponding chiral dioxirane.

So supposing if you have R group here and here is R 1 group and your ketone is like this and one of this is having a chiral centre here. So once the corresponding dioxirane is formed which contains now elements of chirality here in terms of R group here. So when this transfer the oxygen to the corresponding olefin then one can expect that the epoxide that is going to form would be optically active.

So I will show the so you have 2 asymmetric centres here and if these 2 groups are different of course then you will have chiral epoxide. I will show the example later on. So now epoxidation can take place but since if we take a chiral ketone and if we have to use one equivalent of chiral ketone then it is not going to be a very easy process. It is not going to be cheap process and therefore it is nice to see that after the transfer of the epoxide after the transfer of the oxygen to the double bond.

And when the epoxide forms the ketone which is now in this present case it will be chiral that chiral ketone can be recovered and will be reused during the in-situ means inside the reaction. We will continue to keep on generating the chiral dioxirane. Now this particular dimethyl dioxirane or any dioxirane is very reactive because of the main reason that it is a 3 membered ring with 2 oxygen's and therefore it is very strained ring and transfers the oxygen readily.

And that is the reason why there are some limitations such as amines and sulfides also react with the dimethyl dioxirane even more rapidly than with the double bond. Obviously because we; have a lone pair of electrons on the amine as well as on sulfide. But since this is a metal free protocol it is useful and people use it. The only disadvantage of this use of this dimethyl oxirane is that it is a bit a difficult to handle because of the lower boiling nature and also in some instances it has been found that it is an explosive.

So it can explode if the reaction is not carried out at appropriate temperature. But then the formation of the in-situ method for dimethyl dioxirane or any other dioxirane is very useful and can avoid the isolation of the corresponding dioxirane. Commonly used dioxirane's are DMDO that is dimethyl dioxirane and also this some methyl trifluoromethyl dioxirane. So you have a methyl and trifluoromethyl dioxirane these are the 2 which are used very often of course both by in-situ preparation.

And this can be easily isolated this will be little difficult to isolate but the in situ preparation would be relatively easy. So for the in-situ preparation in this case you will have to take this ketone which is relatively easy to handle. In this case of course you will have the acetone though so both the cases we can easily do the in-situ preparation.

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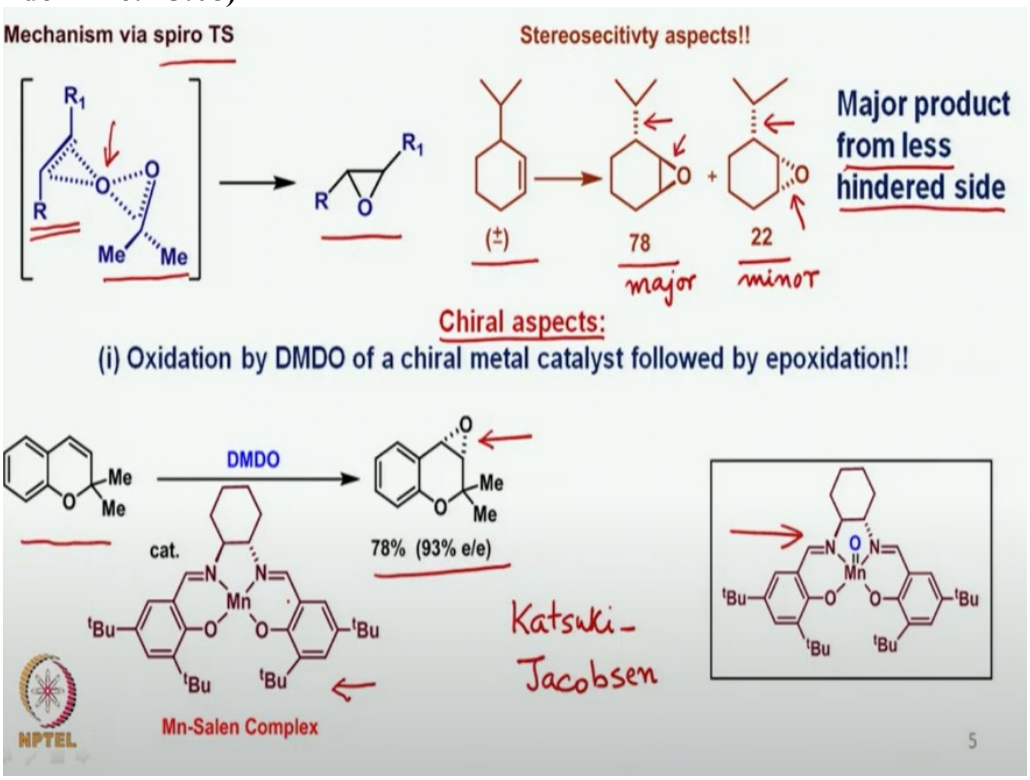

Now what is the mechanism? The mechanism is via spiro transition state. So as you can see here we have the dimethyl dioxirane which is transferring its oxygen to the olefin which is present here. And the transition state is kind of spiro transition state which is this is the spiro centre in the middle. And the transition state involves transfer of the oxygen in a more or less like a concerted process. So if we start with a trans double bond we get corresponding epoxide we retaining the stereochemistry of the double bond.

For example one can see that if we start with the molecule like this which is a racemic molecule which has an isopropyl group as a substituent on the top when the reaction is done what is found is that this particular epoxide where the isopropyl group and the epoxide group are opposite to each other that forms a major product with 78% yield. On the other hand the cis product where the epoxide and the isopropyl group are cis to each other it forms a in a minor way.

So it is very clear that the product is formed from less hindered side the major product is formed on the less hindered side. Of course here we are talking about the relative stereochemistry we are not talking about absolute stereochemistry because we have started with racemic compound. Now what do we do to make the molecule that is epoxide as chiral? What are the ways by which we can use this dioxirane to get epoxides which are chiral?

There are 2 ways by which one can do it for example if this is the olefin that is taken and if we want to convert into the corresponding epoxide in a chiral fashion here and here what has been utilized is manganese Salen complex this is the manganese Salen complex which was reacted with DMDO to form this reagent in the reaction. That means if we begin with this manganese Salen complex and react with DMDO in the reaction it forms the corresponding manganese.

This oxygen double bond based reagent which then transfers the oxygen to the olefin to form this particular epoxide. This is something that we will discuss little more in detail later on when we do the asymmetric epoxidation. This is called Katsuki Jacobson epoxidation and I have mentioned here mainly because it utilizes DMDO in the reaction. Of course, you can also use some other oxidizing agent. But again advantage of using DMDO is that the side product is of ketone that is acetone.

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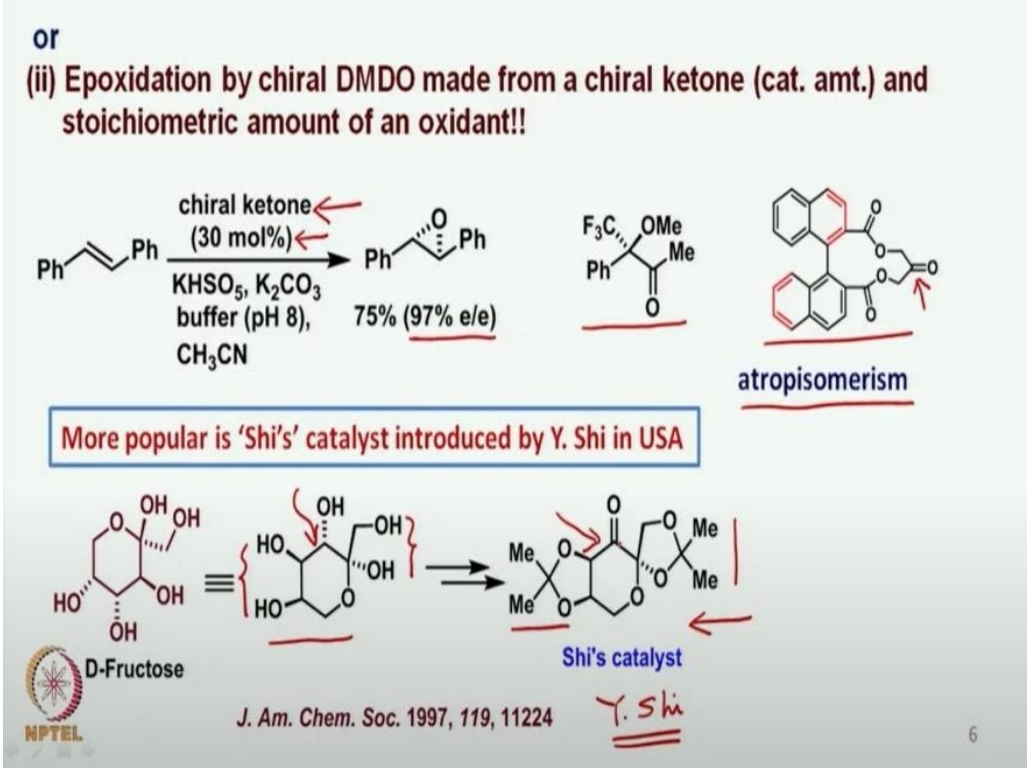

Now this is one way of doing the epoxidation in a chiral fashion what is the other, way of doing chiral epoxidation is you can start with the chiral ketone. So as I discussed earlier the chiral ketone can be utilized in a small amount. Like for example in this case conversion of this stilbene to the corresponding stilbene oxide in 97% enantiomeric excess under these conditions where chiral ketone is used which is only 30% more.

Various kinds of chiral ketones have been utilized for example this is one of the chiral ketone which has the CF 3 methoxyphenyl, and this particular methyl ketone or this type of ketone where this chirality comes from the corresponding atrope isomerism. So this is the ketone which is going to be reacting with the Oxone to form the corresponding chiral dioxirane. But more than these is the Shi's catalyst which is utilized which is reported by Y Shi in the United States.

And that can be easily prepared from the D-fructose. As you can see here, the top one which I shown here are the ketones which are not sterically hindered. They are chiral they are optically pure but they are not sterically hindered. On the other hand if we take the D fructose which can look somewhat like this and can be converted to the corresponding ketone by the oxidation of this hydroxyl group. After the protection of these 2 hydroxy groups as the corresponding acetonides you can oxidize the hydroxyl group into the corresponding ketone.

And this ketone as you can see, is flanked by the 2 bulky groups are present here this part and this part. So therefore if the dioxirane is formed in the middle we can expect a fairly good amount of stereo selectivity because of the steric hindrance.

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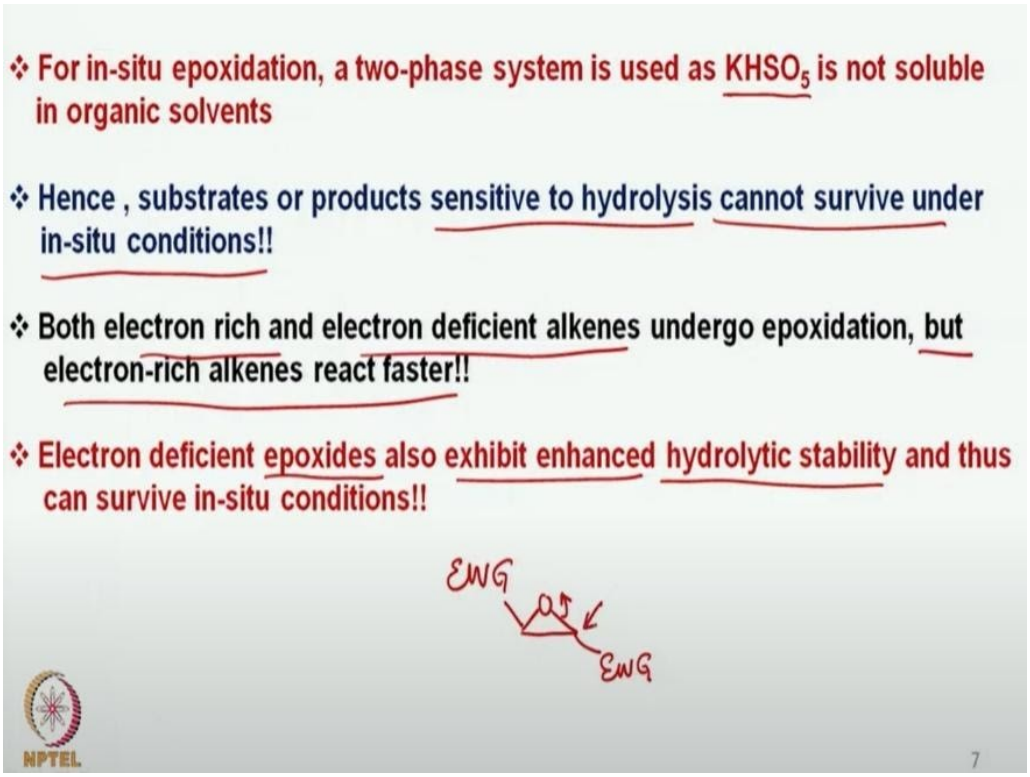

For the in-situ epoxidation a 2 phase system is used as this potassium mono peroxy sulphate is not soluble in organic solvent. So we can use water dichloromethane or something of that sort. Hence substrates which are the product which are sensitive to hydrolysis cannot survive under these conditions. So if we do the in-situ epoxidation inside the reaction we take the ketone and add Oxone. And if you are starting olefin or the epoxide which are formed is sensitive to hydrolysis then obviously it cannot survive under these conditions.

So there are advantage of using in-situ epoxidation but there is also a somewhat disadvantage. Both electron rich and electron deficient alkenes undergo epoxidation but as one can expect the electron rich alkenes would react faster. Electron deficient it epoxides also exhibit enhanced hydrolytic stability that means although the electron deficient alkenes would undergo epoxidation somewhat slower than that of electron rich alkenes.

But the product formed with electron deficient substituents and the corresponding epoxide which is formed would obviously not undergo easy hydrolysis. Say for example if you have an electron with drawing group here on the epoxide and you have another electron with drawing group here obviously this formation would be somewhat slow. But then during the hydrolysis this bond would not easily be breaking because we will be generating here some positive charge.

And that would be next to the electron drawing group. So there is a advantage of hydrolytic stability once the epoxide is formed after the epoxidation of electron deficient olefins has occurred.

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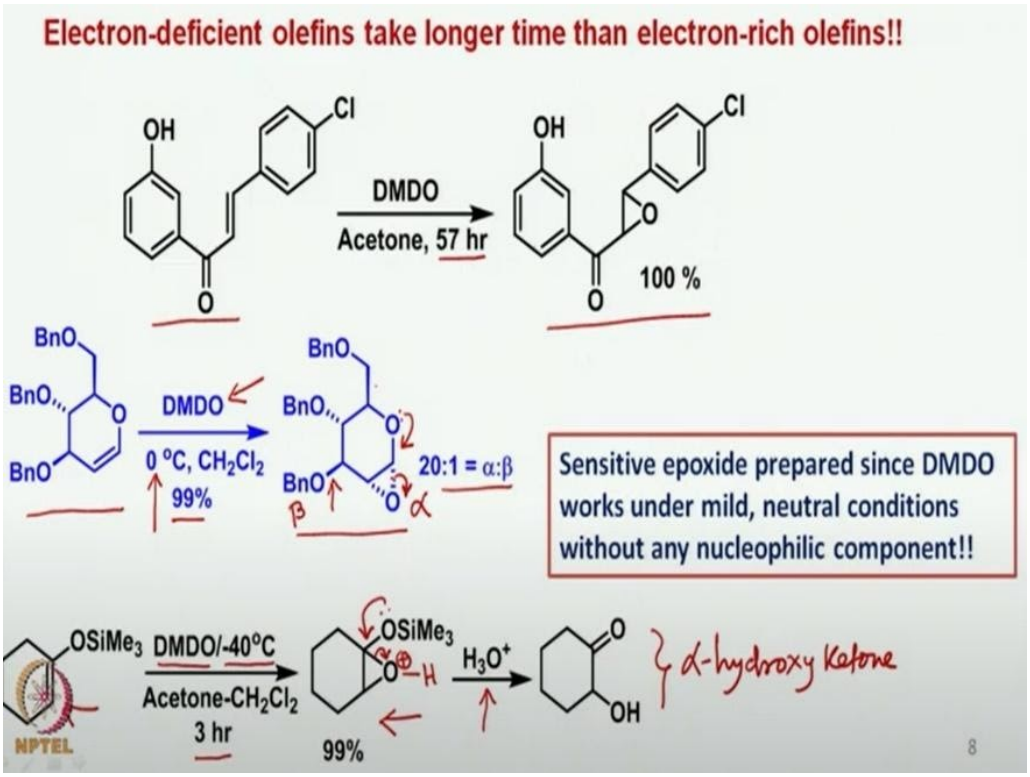

Now electron deficient olefins as I mentioned take longer time as you can see here this is an electron deficient olefin it gives 100% of the epoxide but then it has taken 57 hours in time. So it does not really matter the time but then at least it is not unstable molecule because of hydrolytic stability and as you can see that the yield is 100%. Now one can also use quite sensitive substrate such as this sugar derived olefin which can react with the DMDO

And at 0 degree centigrade in dichloromethane this is the reaction after isolating the DMDO that it leads to 99% of this epoxide. Since these groups are here or particularly this group is beta oriented here the epoxide attacks or epoxide forms from the alpha side. So you can see here 20 is to 1 is the alpha beta ratio. But then this epoxide is a very sensitive epoxide because the lone pair of electron can easily open the epoxide here.

So therefore there should not be any possibility of cleavage of the epoxide compound. But you can make use of this epoxide which is formed from an olefin which is electron rich and it can be hydrolyzed to the corresponding hydroxyketone. Say for example if you start with enol silane ether which is an electron rich double bond. And if we do the reaction at -40 degrees with DMDO in acetone dichloromethane reaction mixture within 3 hours this particular epoxide is formed.

And as one can imagine that H_3O^+ is the acidic condition this epoxide can easily open the protonation would occur here. And then the bond will break and eventually you would get a hydroxyketone. So you can get alpha hydroxyketone readily if you start with enol silyl ether. So sensitive epoxide prepare since, DMDO works under mild neutral condition without any nucleophilic component.

So this is the sensitive epoxide which is formed and since there is only acetone as a side product therefore there is no nucleophile present or under neutral condition epoxide does not open.

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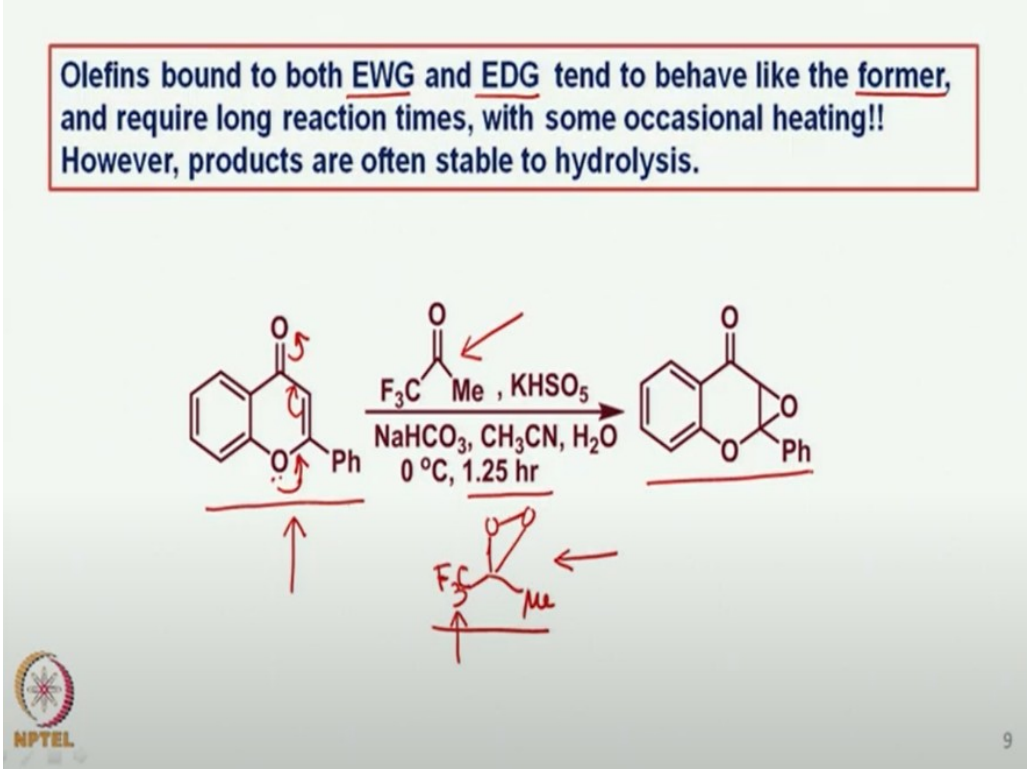

When, olefin is bound both to electron with drawing group as well as electron donating group. The olefin more like more or less like behaves like the former that is the electron drawing group and generally takes long time with some occasional heating. We may have to heat in some cases obviously people try to avoid as much as possible. However as we discussed earlier these products are relatively stable to hydrolysis. Now one example is some what like this here you have an electron withdrawing olefin here as well as you have donation of electron from this side.

When the reaction is occurred in an in-situ fashion now you can see here the starting ketone is taken as trifluoromethyl methyl ketone. And this is mainly because if the epoxide is to be formed you need to have a very reactive dimethyl dioxirane. And since there are there is an electron with drawing CF_3 groups present here the reactivity of this dioxirane is very high. Therefore now if this particular starting olefin has an electron withdrawing group and therefore the nucleophilicity of the double bond is somewhat less than electron rich olefin.

Therefore you increase the electrophilicity of the dioxirane that you have you are going to use. And therefore if one makes the dioxirane of this type which has a CF 3 group attached here the oxygen can easily be transferred. And that is the reason why it just takes say 1.25 hours to form the corresponding epoxide. So basically you have to have a balance between the reactivity of the olefin as well as the reactivity of the dioxirane that is used under the condition. So this is how one can carry out various kind of reaction of different olefin that can lead to the corresponding epoxide formation.

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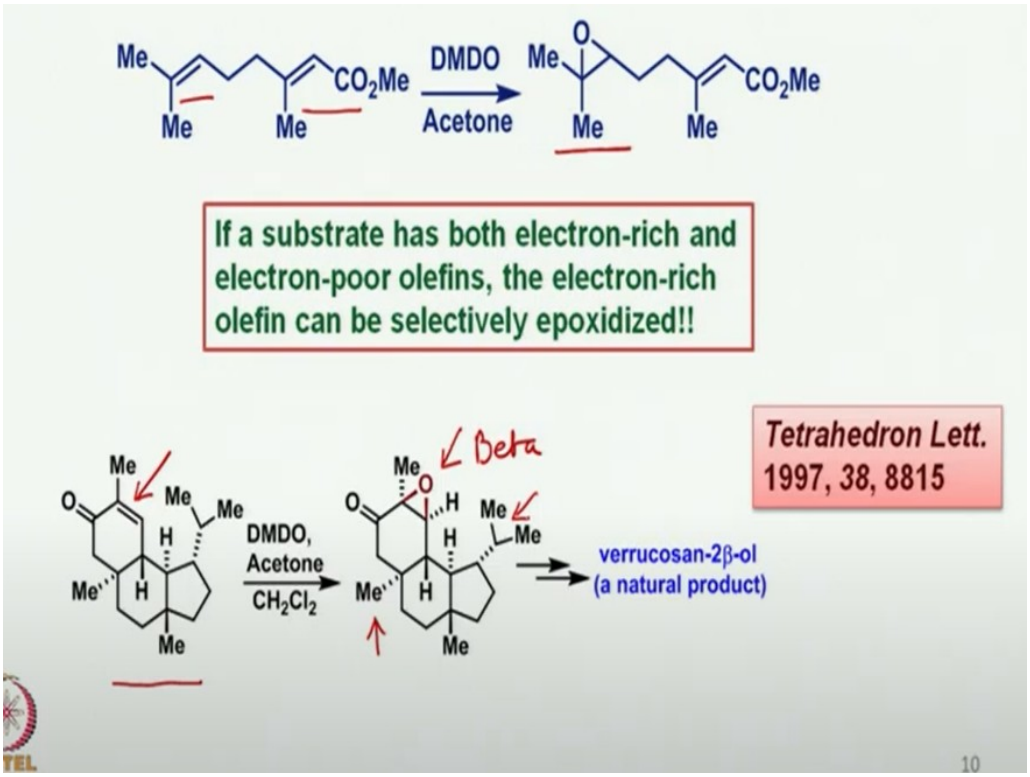

Now if we have a substrate which has both electron rich and electron deficient olefin such as here like this is an electron rich and this is an electron deficient olefin. Obviously the electron rich would react faster than the electron deficient. Therefore the epoxide forms from this end of the molecule. And one can also see that in application wise that is somewhat complicated example this tricyclic molecule which has an electron deficient olefin here reacts to form the corresponding epoxide.

Now you can see the formation of the epoxide is taking from the beta side because the groups which are present here they are all alpha oriented. So due to steric hindrance the formation of the epoxide occurs from the beta side. So we will stop at this stage today and then take up the other examples or other application of the dimethyl dioxirane and the mechanism how does it happen the next class? So till then you can go through these things which we have discussed today. Thank you.