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

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Lecture - 38
Further Aspects of Katsuki-Jacobsen Epoxidation & Introduction to Sharpless Asymmetric Dihydroxylation

Hello and welcome you all for today's lecture. I hope you got the chance to go through what we discussed last time. After we had looked at the recap of the Sharpless epoxidation we looked at the how normal olefins, which do not have an allylic alcohol or any hydroxyl group in the vicinity of the double bond, simple olefins how can they be epoxidized using salen complex based metal oxo complexes.

And we initially looked at how the C2 symmetry based 1,2-diamines can be prepared.
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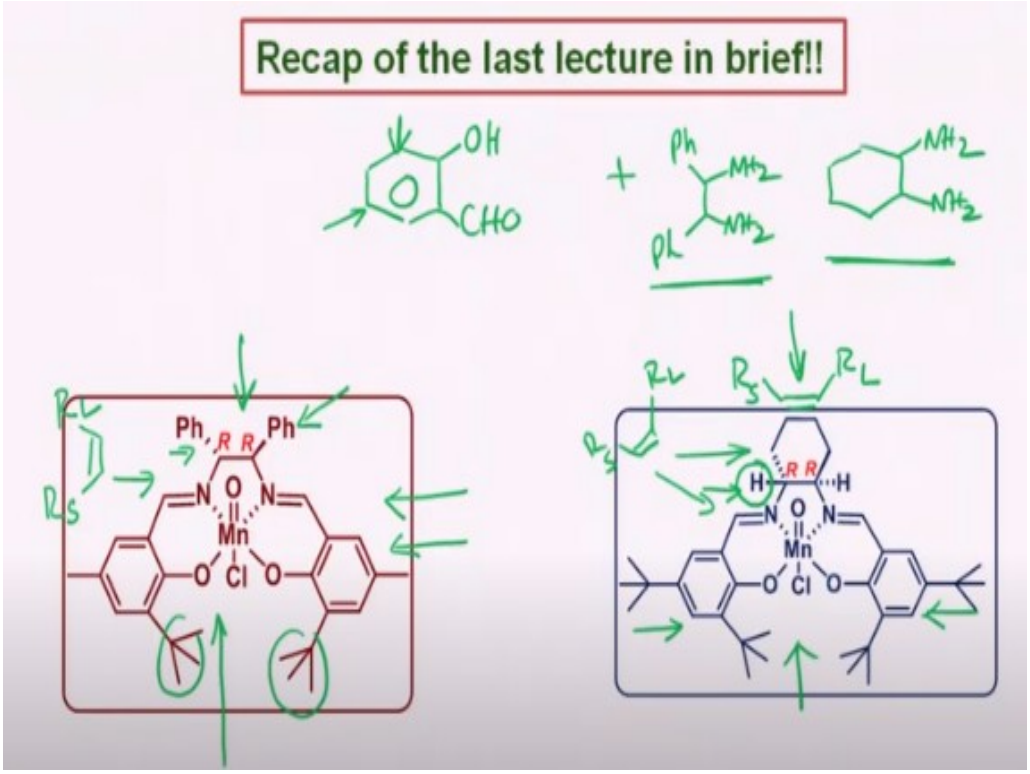

And also how we can get the aldehydes, especially the salicylaldehyde, which we discussed and they are not easy to prepare and therefore, we looked at the some method for making and we need substituent here and substituent here. That means, a substituent ortho to the hydroxy group and para to the hydroxy group is what is required. And of course, we use two different types of amines.

And one of them was of this kind, where of course, we had the C2 symmetry based amine and the other one was with the cyclic system. And this is how these two amines were taken up. And

of course, we tried to look at how we can resolve them or how we can get them optically pure and in a C2 symmetric fashion.

So what we looked at it is just one example is shown here is with this 1,2-diphenyl 1,2-diamino ethane type of C2 symmetry based amine leads to this complex. And the cyclohexane based 1,2-diamine leads to this particular manganese oxo complex. And we look at how the epoxidation prevents the particular phenyl group allows blocking up of the olefin approaching from this side.

It also blocks the approach from this side here. And it also blocks from this side where the tertiary butyl group blocks and eventually what is allowed is that you have an R L group on this side and R S group this side. The large group on the other side and the small group towards the lower side and that allows epoxidation to take place where this phenyl group does not come into the way and therefore, the epoxidation occurs.

Whereas with the cyclohexyl amine case, we very clearly saw that how this axially oriented hydrogen blocks the orientation of the large group onto this side. That means, if we have to epoxidize, the olefin has to be oriented in this fashion. Of course, we discussed that this side, this side and this side is blocked because of the tertiary-butyl groups from all the three sides. And this is the only side where the olefin can approach.

And this is the hydrogen which stops according to the Jacobsen's hypothesis. On the other hand, the same molecule can approach the oxo complex according to Katsuki. But then he invokes the pi-pi interaction, but the result is the same as we discussed. So we saw how these epoxidations take place, which are not dependent on the requirement that there should be a hydroxyl group in the vicinity of the olefin. And therefore, it is a very important reaction.

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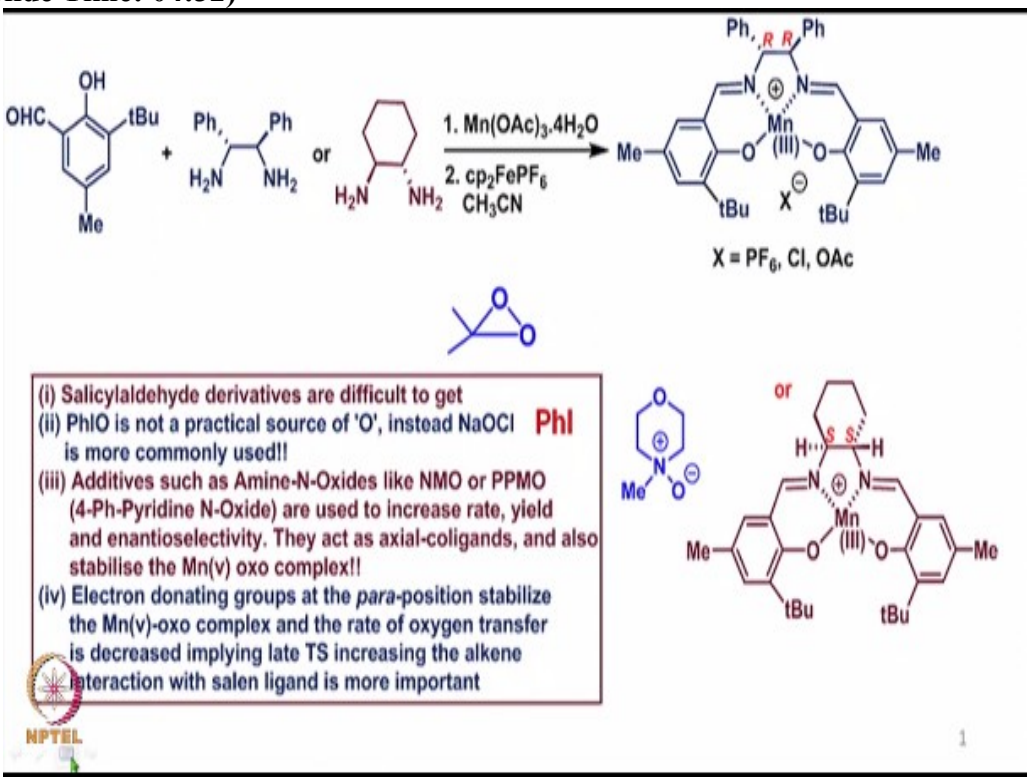

Now we look at the condensation of aromatic aldehyde that is salicylaldehyde derivatives with C2 symmetry based amines like these two to form the corresponding salen complexes in presence of manganese triacetate. In the preparation of these salen complexes, we have a choice where we can either have PF6, Cl or acetate ions as the counter ion, which also act as ligands.

Now what happens in these reactions that it has been found that the salicylaldehyde derivatives are not generally very easy to prepare, as we have seen in the preparation of one of them, where it was relatively difficult to get that particular salicylaldehyde derivative, which is this one.

Now I iodosobenzene is also not found to be a practical source of oxygen, because it leads to the formation of iodobenzene as a side product, which needs to be removed by chromatographic means, because it cannot be removed by simple washing with water. Instead of iodosobenzene people prefer to use sodium hypochlorite or DMDO because the byproducts that are formed are easily washable by water.

In addition to that, it has also been found that additives such as amine-N-oxides like n-methylmorpholineoxide NMO like this and above or 4-phenyl-pyridine N-oxide PPMO are used and they are found to be enhancing the rate, increase the yield and also the enantioselectivity. They act as axial co-ligands and also stabilize the manganese V oxo complex which is obtained by the oxidation of this manganese III salen- complexes.

It is also found that electron donating groups at the para position of the aromatic system stabilize the manganese V oxo complexes and thus the rate of oxygen transfer from that manganese oxo complex decreases, which implies late transition state that increases the alkene interaction with salen ligand being more important.

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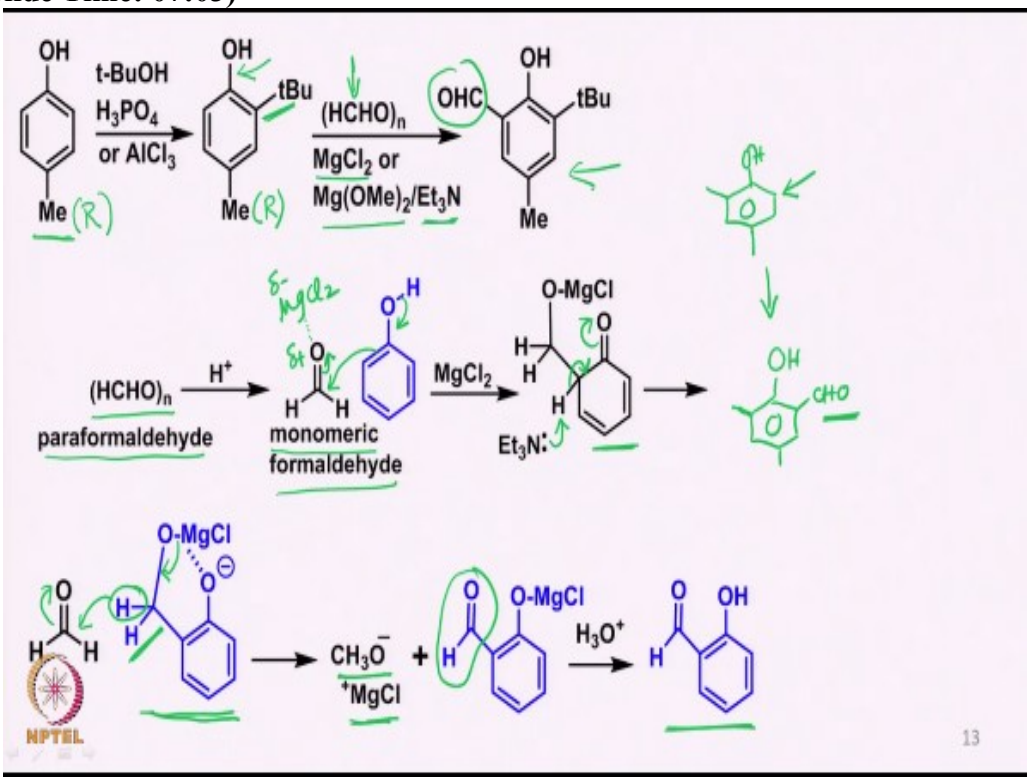

Now we look at how the aldehyde can also be introduced onto the aromatic system by using another reaction where a paraformaldehyde is taken. This is paraformaldehyde. Basically, it is a polymer of formaldehyde; that is how it looks like. You have paraformaldehyde which in the presence of acid would decompose. So you can start with a simple phenol and you can introduce the tertiary butyl group here like this.

But of course, we can here have any other group also. So in any case that is not so important. The important point is that you have a hydroxy group, which is what allows the introduction of the aldehyde group on to the ortho position.

So once we have introduced the tertiary-butyl group then paraformaldehyde is reacted with it in the presence of Mg++ that is Mg 2+ either as magnesium chloride or this type of magnesium salt in the presence of base like triethyl amine. So what is happening is that this polymeric formaldehyde decomposes in the presence of acid to form monomeric formaldehyde.

And then the protonation or say you have a Lewis acid in the form of magnesium chloride for example, here something like this that allows delta positive to form here and delta negative to form here. And then of course, we can expect something like this to happen to form this intermediate. And then this intermediate then is allowed to interact with the triethyl amine.

And then of course, we can expect that something of this kind will happen. And of course, we can get the aromatic system becoming like this. Now what we have done in the process is, we have introduced here this group adjacent to the alpha position of the hydroxy, that means ortho position and now what can happen is that this particular bond can break.

And we can anticipate that there is a hydride transfer to this and we can get the CH3O- coming out and MgCl+ coming out. Of course, will eventually come out and then we get this hydroxy group attached. That means, this CH2O MgCl has now become the formyl group and which upon acidification gives the corresponding aldehyde.

So this is how a phenol can be converted to the corresponding ortho formyl phenol or salicylaldehyde. So if we take any derivative of phenol of having a substituents at ortho and para position and one vacant position here, then of course, we can carry out such a reaction to form the corresponding formyl group onto the vacant ortho position here.

So we can not only have simple salicylaldehyde, but many substituted salicylaldehydes as we have seen it here. So this is how the mechanism of the introduction of the formyl group at the ortho position of the phenol occurs.

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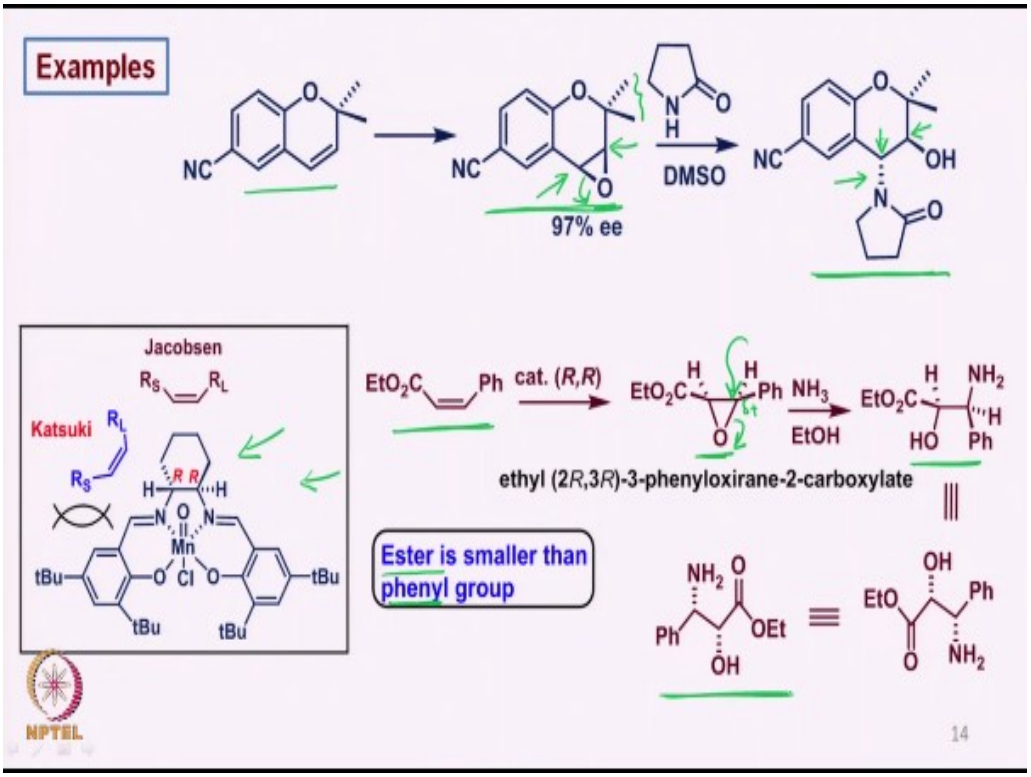

Now what are the examples that we can look at the Jacobsen-Katsuki based reaction. That is if we take an olefin of this kind that gives the epoxide that is formed on this choosing this oxo complex and as one can anticipate that this is sterically hindered position because of the two geminal dimethyl groups.

And therefore, the opening occurs from this side and the nucleophile from here with carbon nitrogen bond is formed here from the alpha side because the epoxide is beta and therefore, such a product is formed. So we can have a regio and stereoselective opening of the epoxide and lead to now as you can see, there are two asymmetric centers with two different functional groups attached to it.

Now if we take an alpha beta unsaturated ester of this kind, which has a phenyl group on one hand and ester group on the other hand, other side of it, and then we have a cis double bond and if we react with the same catalyst and same oxo complex as is here and considering that the ester group is smaller compared to a large phenyl group, then of course, epoxidation would occur the same way as we discussed earlier in the case of 2-methyl styrene.

And of course, when this epoxide is formed, the ammonia attacks on to this particular carbon atom. This goes off, because we have we can anticipate that the carbon oxygen bond can break and developing a positive charge at the benzylic position. So you can expect a slightly delta positive here under these conditions where amine attacks and we get this particular amino alcohol.

And then of course, we can expect that essentially we can convert that into this particular kind of orientation of the amino alcohol or alpha hydroxy ester.

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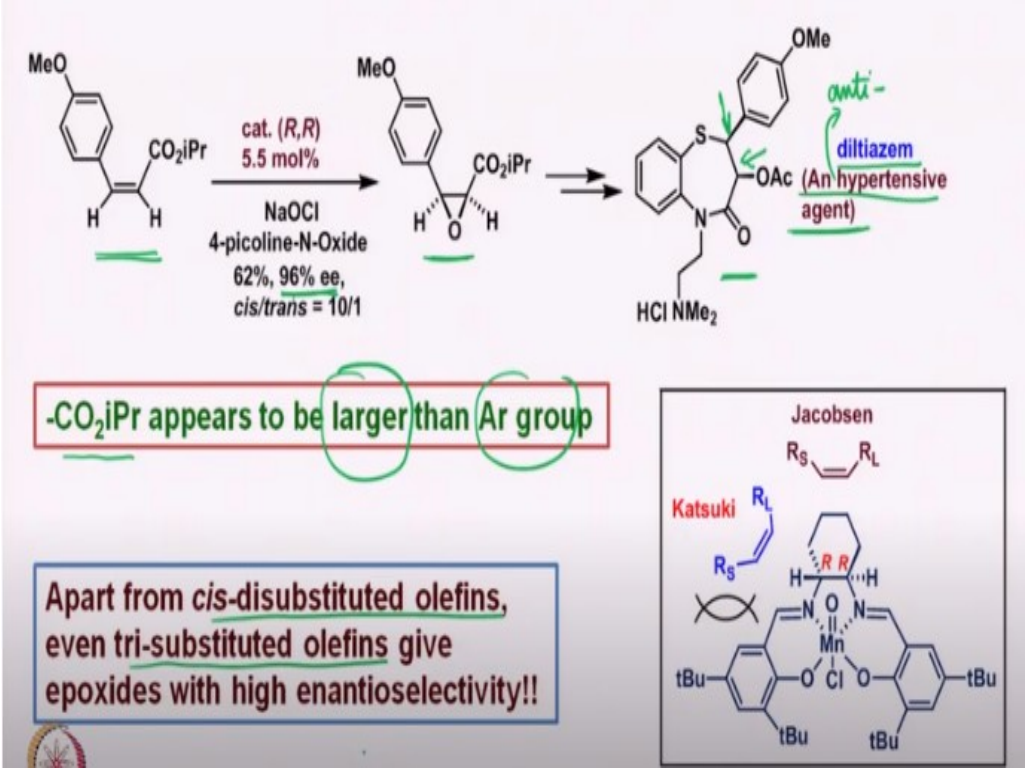

And what is found that if we take isopropyl ester, that seems to have a different epoxide like for example, if we have a CO2iPr that is isopropyl group, then it appears that this particular group seems to be acting as a larger than aryl group here. And then we get this epoxide when we take this particular olefin, which is cis double bond alpha beta unsaturated ester.

And that gives this epoxide which has been converted into an hypertensive agent, and antihypertensive agent. Actually it should not be an hypertensive agent, it is an antihypertensive agent. So diltiazem. So this is the structure of that where this hydroxy group is of course coming up there and this particular aryl group is also coming up from this epoxide. So it is a long synthesis.

That we will not go through it, but then the idea is that the simple epoxide which can be easily made in optically pure form as you can see is like 96% enantiomerically pure. And then of course, you can convert it into the important anti-hypertensive agent. Apart from cis-disubstituted olefins, even trisubstituted olefins have been found to give high enantioselectivity in the epoxidation cases.

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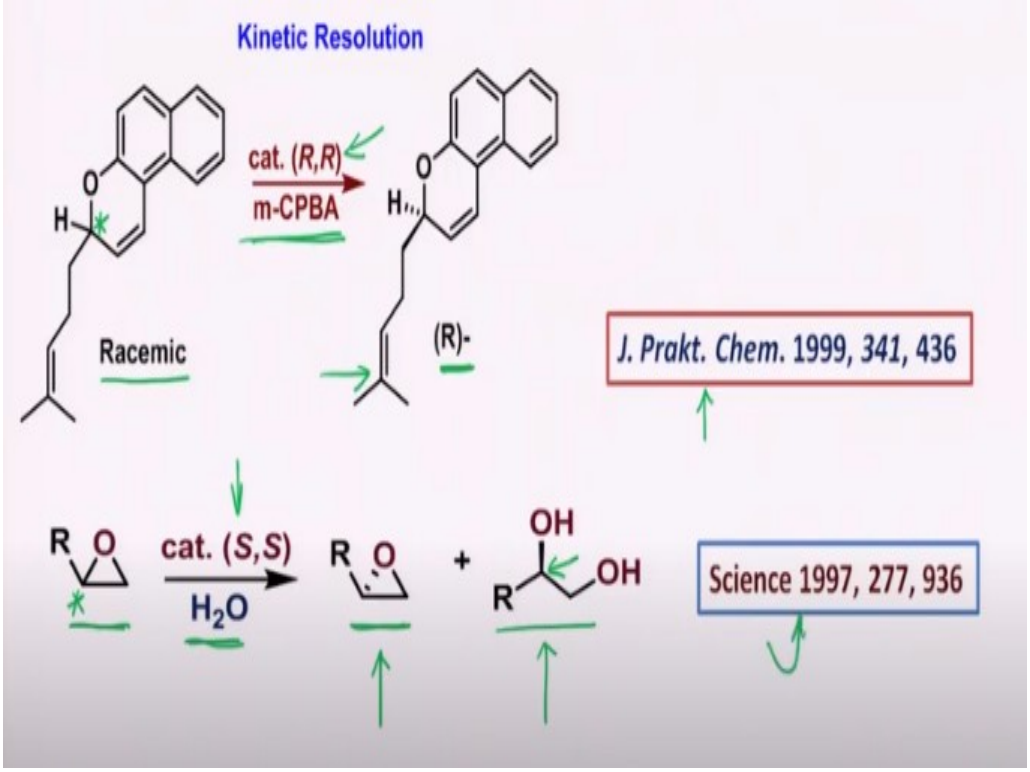

We can also carry out kinetic resolution using these catalysts that have been found. For example, if we start here as an asymmetric center, and we begin with a racemic molecule. That means we do not have an optically pure molecule and then we take a catalyst which is R,R oriented one of the manganese III complex and react with a oxidizing agent such as meta-chloroperbenzoic acid.

And what is found which is mentioned here in the Journal of Practical chemistry in 1999 that one of the two enantiomers gets epoxidized and the other one, which is what they wanted to use for something else which gets unepoxidized and therefore resolved. So this is a kinetic resolution in terms of which olefin gets epoxidized faster and which one does not. And therefore, we can resolve it.

But this kind of salen complex also has been used as a more or less like a Lewis acid catalyst which is chiral. Like for example, if we start with this kind of racemic epoxide, a simple small molecular weight epoxide like this. And if we use this catalytic amount of the manganese III complex and intention is not to do epoxidation because there is no olefin. Epoxidation does not occur.

And therefore, what happens is that the catalyst behaves more like a Lewis acid and from the racemic epoxide when the Lewis acid attaches to it, the water which is present in the medium and that is the reason why we take low molecular weight so that molecule is somewhat soluble in water. And one of them gets opened at this particular position and the other one remains unopened.

So the rate of reaction of the rate of opening of the epoxide is different for two different enantiomers of the same epoxide. So that also allows as a result, you can get this epoxide here or

you can get the diol having a hydroxyl group here, which is determined from the epoxide that has been utilized for this purpose. And this has been published in 1997 in Science.

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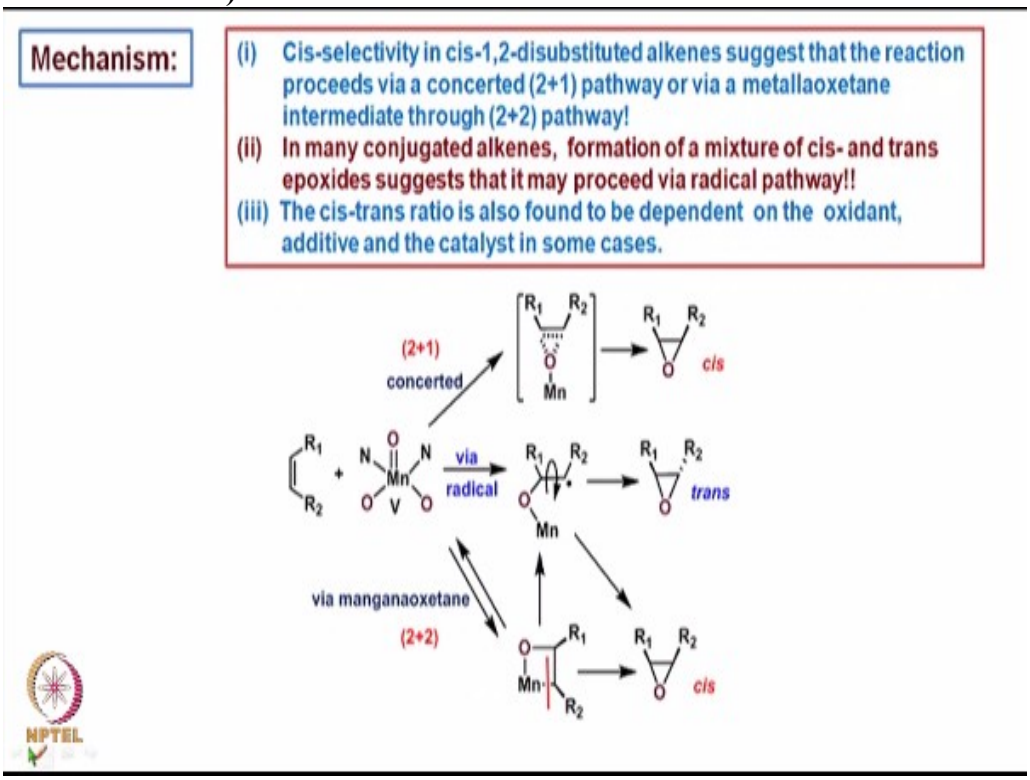

Now what exactly is the mechanism of this reaction? A lot of work has been done in this regard and we can summarize the observations and also the suggestions. It has been observed that cis-1,2-disubstituted alkenes lead to the formation of cis epoxides. That means, there is a cis selectivity in these cases. This suggests that the reaction may proceed via a 2 + 1 concerted pathway like this.

For example, if this olefin comes in contact with this manganese V oxo complex then there is a possibility of a 2+1 cycloaddition leading to this particular transition state, which then releases the cis epoxide and of course, manganese III complex for further oxidation. Alternatively, what they have suggested that, the reaction might proceed via metallaoxetane intermediate through 2+2 pathway.

For example, this manganese V oxo complex when it comes in contact with this cis olefin, them we can expect that 2+2 cycloaddition occurs to form this manganaoxetane intermediate, which if it collapses without any intermediate to be formed, then of course, we can get the cis epoxide. On the other hand, what has also been found that in conjugated alkenes from mixture of cis and trans epoxide is formed.

And that suggests the possibility of a radical pathway and that has been proposed in this particular manganaoxetane type of pathway, that if this particular carbon manganese bond cleaves homolytically, then of course we can get a radical at this particular carbon atom. And then that will allow a C-C bond rotation here and eventually lead to the formation of the trans epoxide.

Of course, it can also lead to the formation of cis epoxide. So a mixture of cis and trans epoxide can form. Now the cis and trans ratio has also been found to be dependent on the oxidant, additive and the catalyst in some cases. So these are the observations and these are the solutions. So there is a possibility of this kind of mechanism that may be operating and therefore, it is relatively acceptable to invoke such a mechanism.

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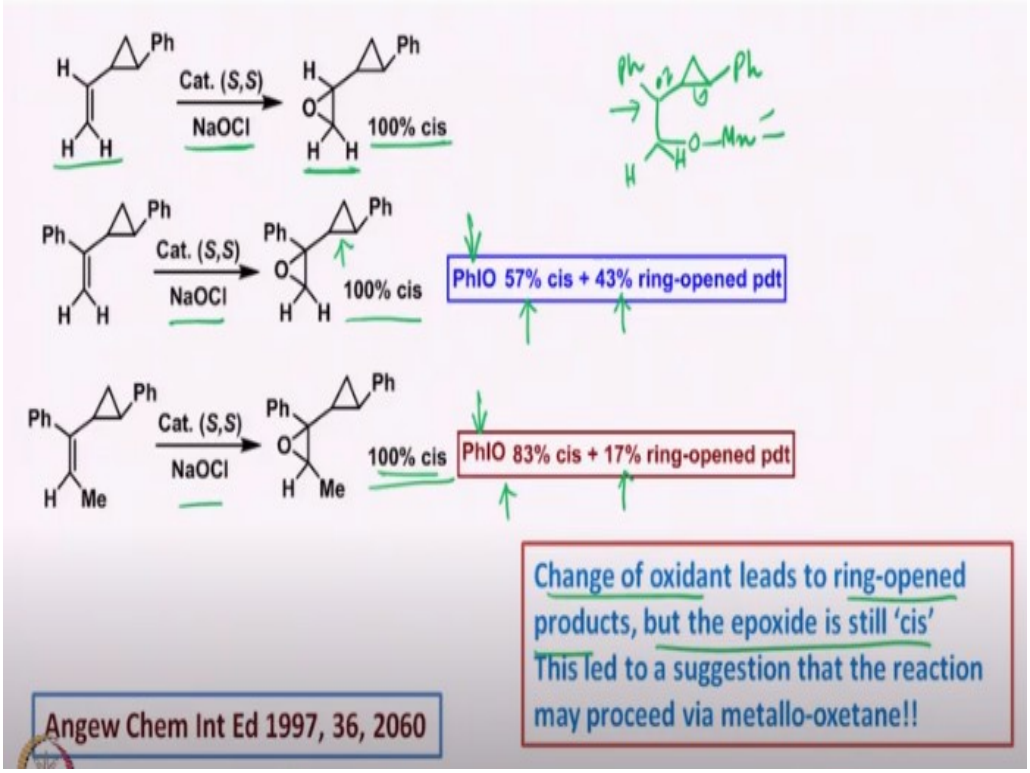

Now this is an example in which what is seen that as I mentioned that the reaction depends upon oxidant, additive and the catalyst that is used. So if we use S,S catalyst and here use sodium hypochlorite, what is found is that if we start with this olefin we get 100% cis olefin. The epoxidation does not make any change in terms of stereochemistry. In a similar fashion this gives you 100% cis. And in this case, it also gives 100% cis.

But when you use iodosobenzene in both the cases, then of course what is found is that we get 57% cis product and 43% is ring-opened product. Ring-opened product means, this cyclopropane gets opened. And in a similar fashion here 83% and 17% is cyclopropane ring-opened product. So how is it expected that the cyclopropane ring will open.

It is only possible if there is a possibility of cyclopropane opening through a radical intermediate. So we can expect, supposing if this is what is the case, then if we put it here phenyl group here, then this intermediate has to come somehow of this kind epoxidation would allow the radical to form in this fashion. So we can expect the oxygen to come here and manganese to come in here.

And then rest of the things, but then radical has to be here, which allows the opening of the cyclopropane to take place. So this is what is found in the case of phenyl iodosobenzene, but that

does not happen in the case of sodium hypochlorite. So actually the change of oxidant leads to ring-opened products but the epoxide is still cis, as you can see, that the epoxide is still cis.

So it means that there is a possibility of the reaction proceeding via metallaoxetane intermediate and then opens up to form the ring-opened product via radical means or it closes immediately without isomerization to form the cis epoxide. So this is what is mentioned in this particular paper that you can read it.

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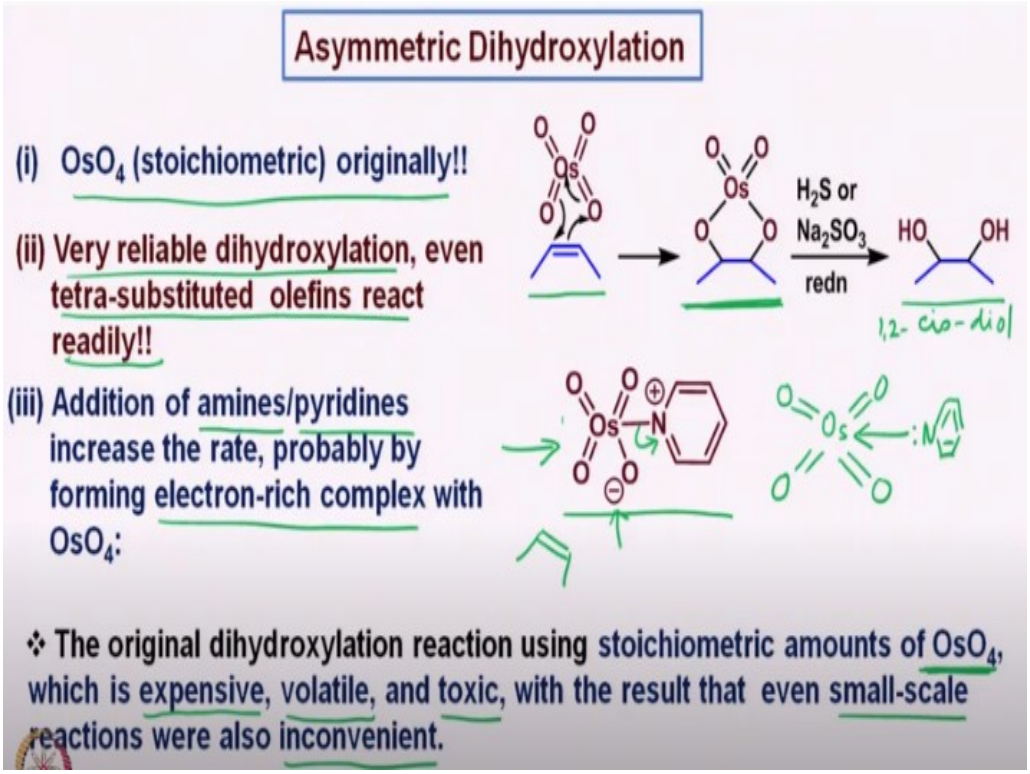

Now we start another topic, which is asymmetric dihydroxylation. Originally the dihydroxylation of an olefin, for example if we start with an olefin and we can get the corresponding diol which is a cis-diol, which is 1,2-cis-diol and this kind of 1,2-cis-diol has been found by reacting olefins with osmium tetroxide.

And what is found that the action proceeds very likely through such kind of osmium intermediate, which can be reduced and we can get the corresponding diol. The reduction can be done with hydrogen sulfide or sodium sulfide. And of course, we can get the corresponding diol.

Originally, osmium tetroxide was used in a stoichiometric fashion and but then it was very reliable, the hydroxylation, that even tetra substituted olefins react readily. That means, the reactivity of the osmium tetroxide is very high. Then, it was also found, which is very important observation that the addition of amines or pyridines increase the rate, probably forming such an electron rich complex as it is here.

As you can see that the osmium tetroxide here is an electron deficient in terms of oxygen being there as oxygen double bond O, four of them, and therefore this particular osmium atom is very electrophilic and therefore any nitrogen would prefer to bind it very easily. And therefore, such a

intermediate can allow. When such a reaction happens, then of course, we will now we have a leaving group here.

At the same time we have a nucleophilic oxygen here and of course, we have three of the osmium oxygen double bond, which are electrophilically oriented and therefore this dihydroxylation occurs very fast. And the original dihydroxylation reaction using stoichiometric amount of osmium tetroxide as I mentioned above is that it is very reliable and useful, but it is expensive.

And since the osmium tetroxide is volatile and it is also extremely toxic, so even to do a reaction on a small scale people were not particularly very comfortable with it and it was not a convenient proposition to do the reaction at small scale involving the use of osmium tetroxide in a stoichiometric fashion.

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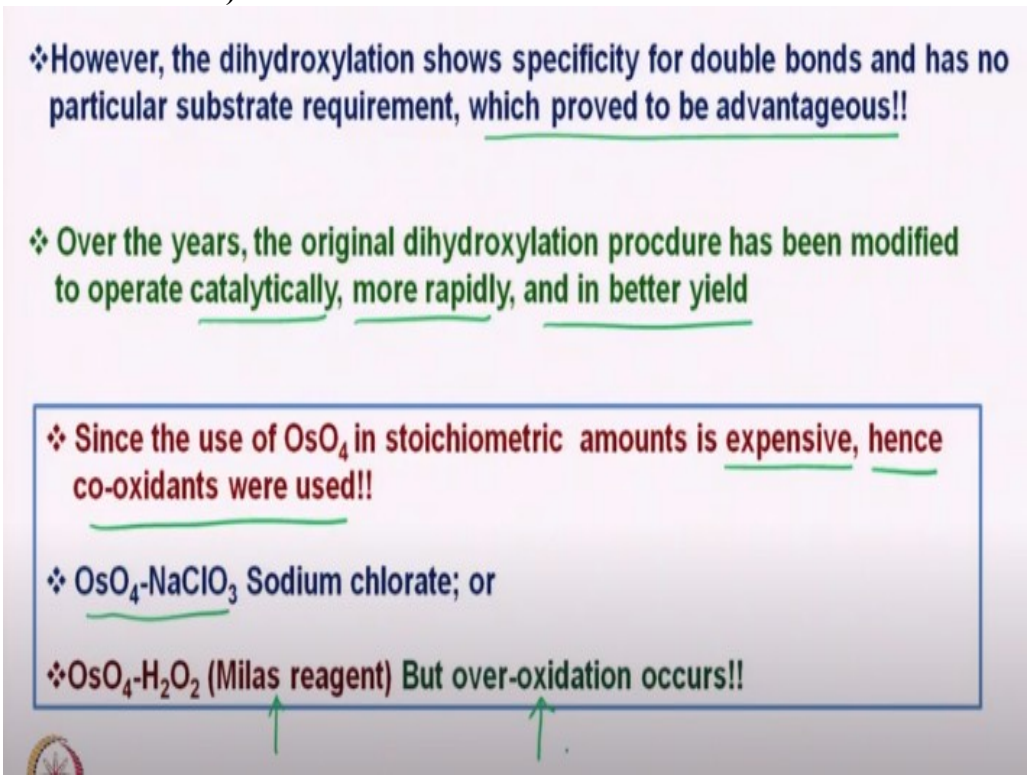

However, since there was this very important observation that any kind of double bonds can react, and therefore there was a need to improvise this particular procedure, as this proves to be a very advantageous situation that any kind of double bonds can react. And therefore, over the years, the dihydroxylation procedure has been modified to operate catalytically and more rapidly and giving better yield.

That means in terms of osmium, if the osmium tetroxide could be made catalytic in terms of its usage, then the reaction is definitely going to be very useful. And therefore, because of the expensive nature, toxic nature, the co-oxidants were used. And one of the co-oxidant was this sodium chlorate, osmium tetroxide. And the other one was osmium tetroxide and hydrogen peroxide, which is known as Milas reagent.

But in these cases over oxidation occurs and the aldehyde or the ketone are formed and therefore, it was not a very convenient method for making use of these kinds of oxidants. But then, there have been many other modifications which are reported in the literature and eventually the osmium tetroxide was made to be used in a catalytic fashion.

And we will discuss the remaining part of the osmium tetroxide based dihydroxylation in the next class. Till then you can go through what I have mentioned today and then see you next time. Till then bye and thank you.