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

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Lecture - 39
Mechanism, Stereochemical Aspects and Synthetic Applications of Sharpless Asymmetric Dihydroxylation

Hello everyone and welcome you all for today's lecture. We will briefly look at what we did last time and then proceed further for the other aspects of asymmetric reactions.

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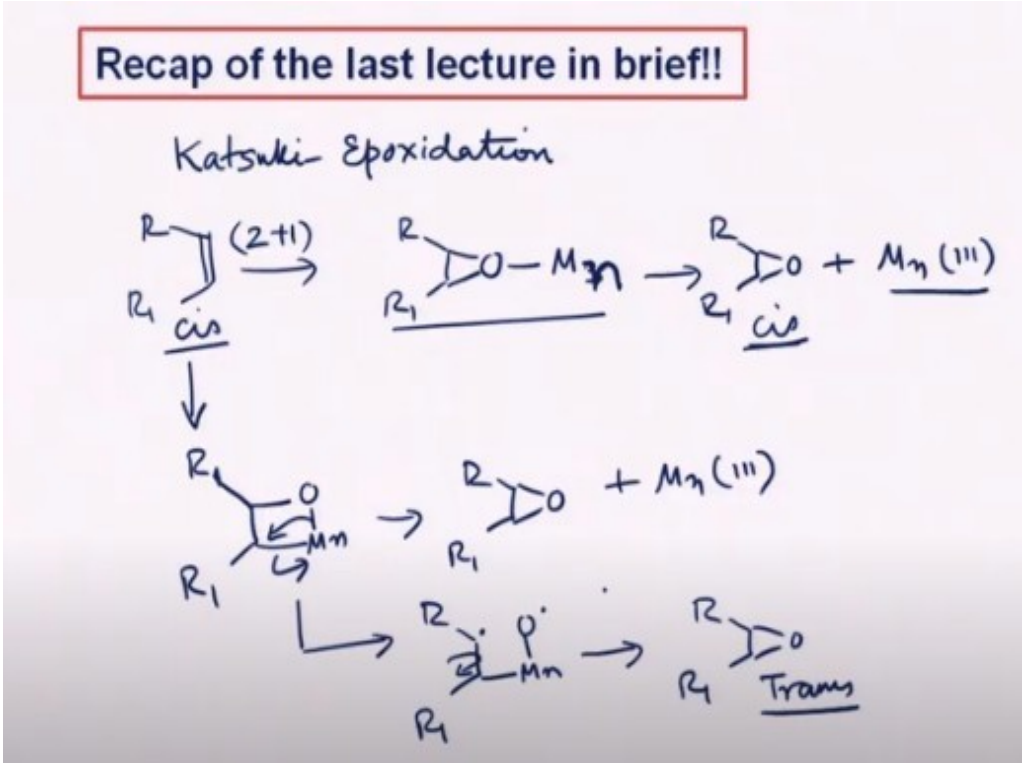

So last time what we discussed was Katsuki-Jacobsen epoxidation and the mechanistic aspects of it towards the end and followed by we did introduction of the dihydroxylation of olefins. So in the case of Katsuki epoxidation reactions various aspects of it we saw.

How the different types of C2 symmetric based 1,2 diamines and different aldehydes, which are basically salicylaldehyde derivatives are used to make the manganese oxo complex and that allows epoxidation to take place based on various factors and then allows highly enantioselective epoxidation.

In that respect, when we looked at the mechanism, if we start with a cis-olefin then we saw that there could be a possibility of manganese complex, which is basically having a 2+1 type of intermediate. That means, it gives you a 2+1 concerted process to lead to this, which allows the

epoxidation to complete by the release of manganese III. So we start with manganese V and then we release the manganese III upon epoxidation.

We also saw that since cis-olefin gives cis-epoxide therefore, this type of concerted process is important. We also saw that it can also be done by a metallooxetane type of intermediate where something of this kind can be proposed. And when this breaks up in this fashion, then we can also expect the cis epoxidation to take place and plus of course manganese catalyst goes away.

But this was also expected to form a sort of radical in some way or the other, so that we can expect that there is a possibility of a radical formation here and of course a radical can come in here. And then there is a rotation and then that can allow the epoxidation eventually to form in this way that some amount of trans epoxide is formed.

So considering these aspects, there is a possibility of such a radical based reaction to occur, especially in cases where the cyclopropane ring becomes a part of the starting material. So these are the aspects that we saw and then we also looked at the dihydroxylation of olefins using osmium tetroxide. But, since osmium tetroxide is expensive and toxic and therefore there is a need to use that in a catalytic amount.

And towards the end we looked at the use of co-oxidants and where we discussed sodium chlorate and also hydrogen peroxide, but then these lead to over oxidation. So there was a problem and therefore, there is a need to look at the co-oxidants in a different way. So later on Sharpless also did some work in his area and many other people.

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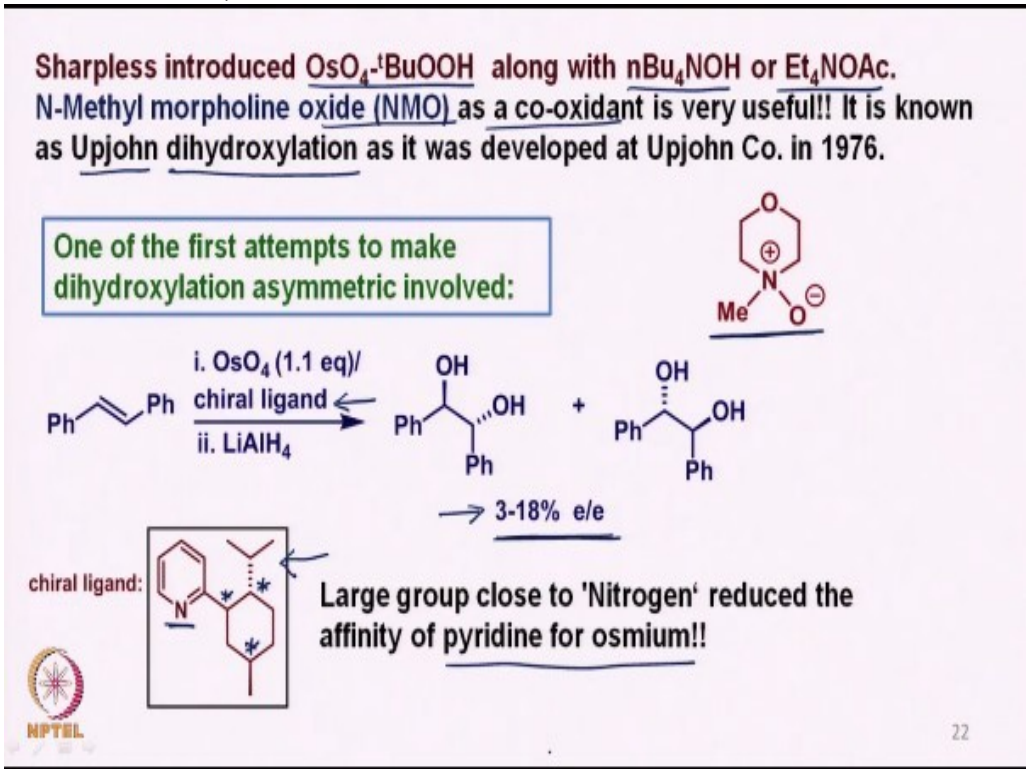

And accordingly Sharpless introduced the tertiary-butylhydroperoxide along with osmium tetroxide as a co-oxidant. And in the presence of these salts to kind of dissolve the reaction in the

aqueous condition. And also N-Methylmorpholine N-oxide NMO was used as a co-oxidant by Upjohn company, and that is why it is known as Upjohn dihydroxylation because it was they who first developed the use of N-Methylmorpholine N-oxide in the dihydroxylation.

So this is the, this NMO that is N-Methylmorpholine N-oxide, which is what is something that we had discussed earlier. And one of the first attempts to make it chiral was then looked at it. Because now since osmium tetroxide is not required in a stoichiometric fashion and therefore, one can now start looking at whether reaction can make it as a catalytic and also asymmetric.

Now we mentioned or we discussed earlier that there was a possibility of increasing the rate of reaction and increase the yield if a tertiary amine or a pyridine is added to the reaction mixture and that allows the attachment of the triethyl I mean the tertiary amine or the pyridine to the osmium atom and therefore, the reaction rate increases.

Considering that the chiral ligand, which is pyridine base was used for the first time and it was found that eventually there was an optical kind of induction or asymmetric induction and that gave the optically active molecules in 3 to 18% enantiomeric purity. However, this particular chiral ligand is this where there are three asymmetric centers.

And it was found that since pyridine moiety is very close to the isopropyl group and therefore, it is something could be sterically not desirable and therefore, the large group close to the nitrogen sort of prevents the pyridine to come very close to the osmium because of the steric hindrance.

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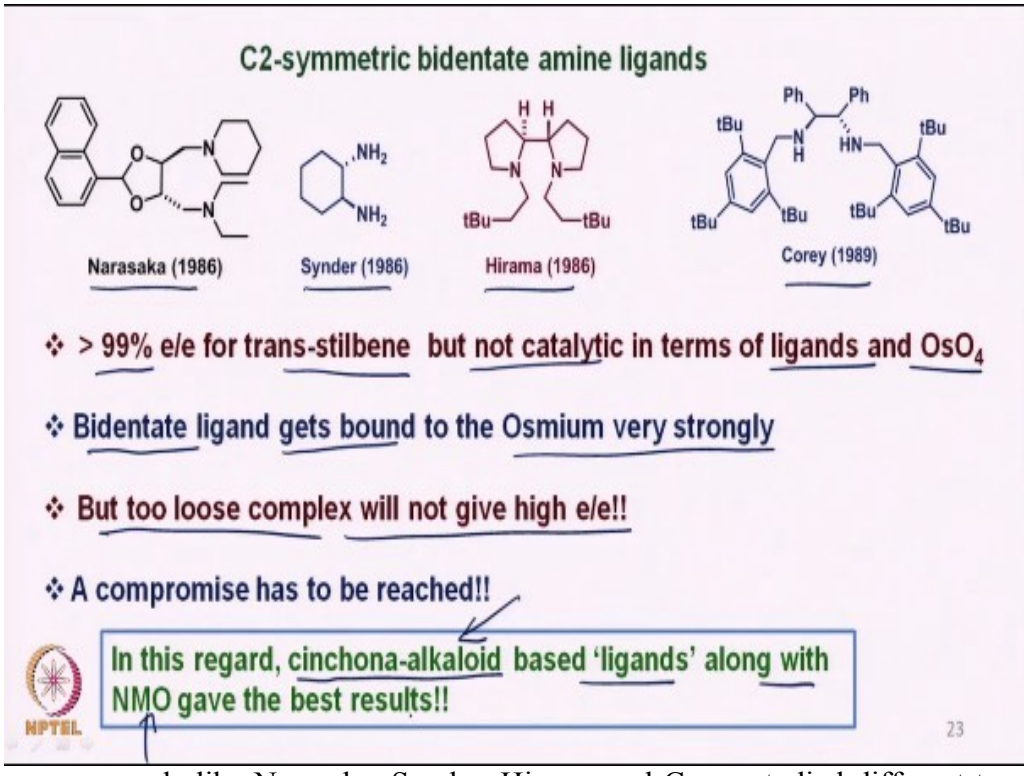

Later on, many people like Narasaka, Synder, Hirama and Corey studied different types of C2-symmetric based bidentate amine ligands which are shown here and different types of these ligands gave very high enantioselectivity more than 99% for trans-stilbene. But it was not catalytic in

terms of osmium tetroxide or the ligand. That means, even these chiral ligands, which are shown these structures of which are shown here are need to be used in stoichiometric way and also osmium tetroxide.

That is because the bidentate, these are bidentate ligands, they get bound to the osmium very strongly and then they do not come out. So therefore, such tightly bound complex although gave very high enantioselectivity, but then it was not catalytic.

At the same time, if we have a loose complex that will also not give high enantiomeric purity because if it is loose that means it comes off and therefore, the reaction will definitely not give high enantiomeric purity because it can also react with unbound osmium tetroxide. So we need to have a compromise. So a compromise has to be reached.

And in this regard, what was found by Sharpless that cinchona-alkaloid based ligands along with NMO gave the best results. So NMO was used for as a co-oxidant but then cinchona-alkaloids were used as chiral ligands.

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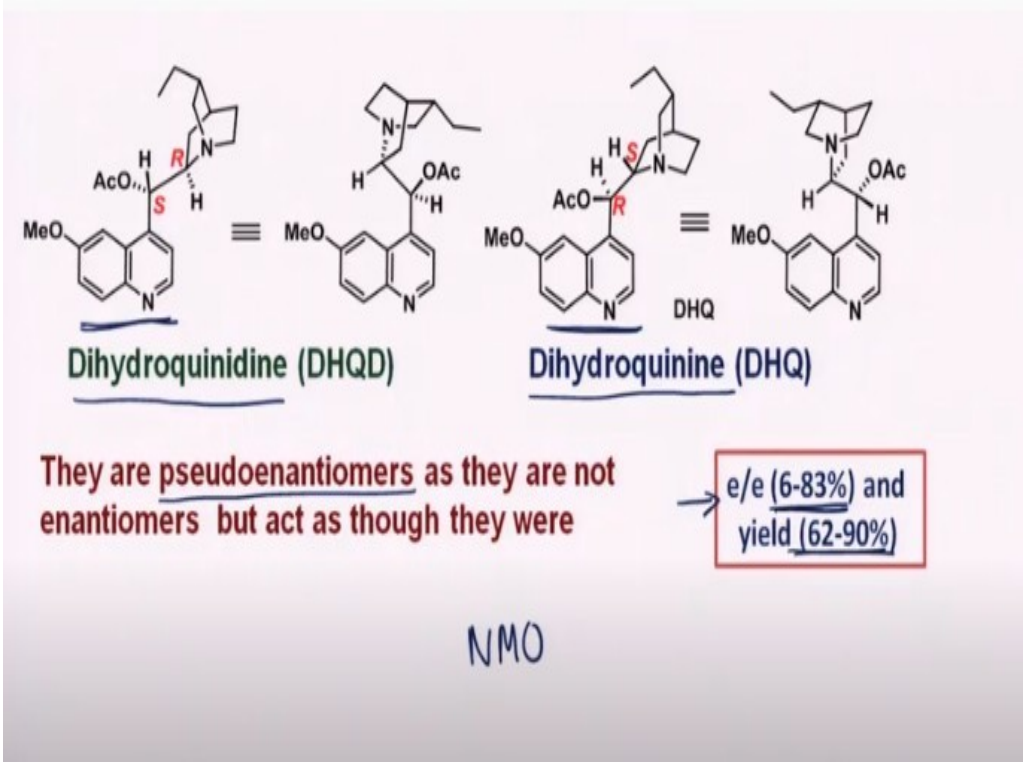

So these are the chiral ligands, which are used in the symmetric dihydroxylation. One of them is known as dihydroquinidine. The other one is known as dihydroquinine. They are pseudoenantiomers. They are called as pseudoenantiomer. They are not really enantiomers as they are not really in the mirror images of each other, but they give different enantioselectivity.

And therefore, they are considered as pseudoenantiomers. Now as you can see that the utility of such chiral ligands along with as I mentioned, NMO gave the optical purity or enantiomeric purity being 6 to 83% and yields ranging from 62 to 90%. So it seems to be pretty good, but then it is

something that we need to worry about it because why is it that the enantiomeric purity is as low as 6 and of course in some cases is as high as 83%.

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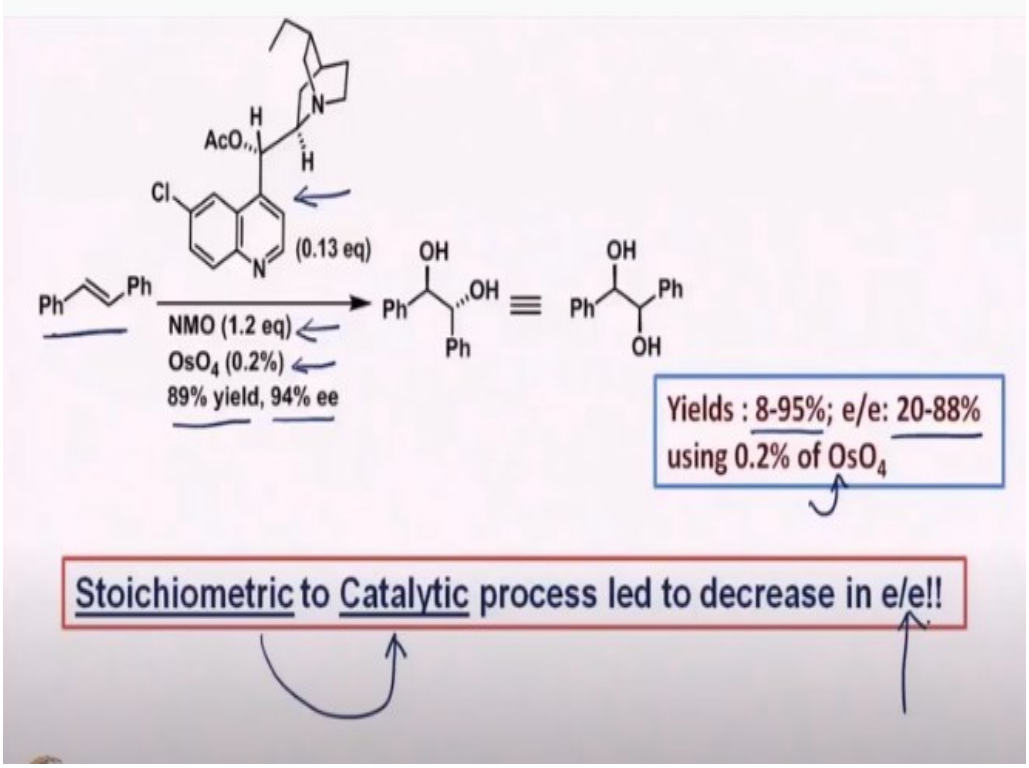

Now, if we look at one particular example, and if we can take this particular trans-stilbene, then under these conditions, this is the chiral ligand that was used and 1.2 equivalents of the NMO was used and 0.2% of osmium tetroxide we used that lead to 89% yield of the product and 94% enantiomeric purity.

So if we start looking at various ligands and various kind of additives and then we see that the yield is ranging from 8 to 95% and the enantiomeric purity is 20 to 88%. But then use of osmium tetroxide has decreased considerably and therefore 0.2% of osmium tetroxide is needed for this particular kind of reaction. But then what are generally found that if we go from stoichiometric to catalytic process, it leads to decrease in enantiomeric purity.

So in general it was felt that the enantiomeric purity is still in these cases is not universally high in all the cases but it also needs to be looked at it from catalytic to stoichiometric fashion if one wants to make it high enantiomerically pure product to be obtained. Now why is it that when such a low enantiomeric purity is seen in cases where NMO is used as a co-oxidant.

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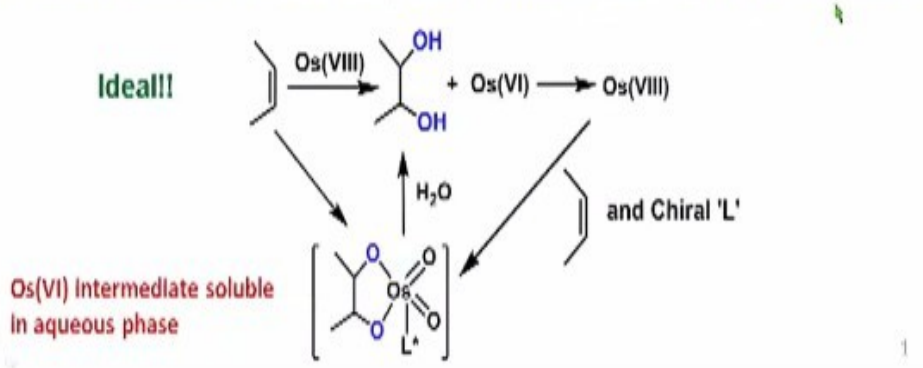
(i) This was due to the secondary catalytic cycle in which ligand was not involved!!

(ii) NMO (the re-oxidant) converts Os(vi) glycolate to Os(viii) glycolate along with the expulsion of the chiral ligand. This Os(viii) glycolate which is devoid of chiral ligand then dihydroxylates some of the olefins leading to low enantioselectivity!!

(iii) But, when $K_3Fe(CN)_6$-K_2CO_3/t-BuOH-H_2O is used, the oxidant remains in water phase. This allows Os(vi) glycolate to hydrolyze to release chiral diol and then Os(vi) is re-oxidized to Os(viii)!!

(iv) In general, e/e with $K_3Fe(CN)_6$-K_2CO_3/t-BuOH-H_2O system is much higher than with NMO!!



So it was felt that this was due to the secondary catalytic cycle in which ligand was not involved. Now when NMO is used as a re-oxidant it converts osmium VI glycolate of this type to osmium VIII glycolate along with the expulsion of the chiral ligand. That means when this osmium 6 intermediate is re-oxidized with NMO, it forms an osmium VIII glycolate but then ligand comes off.

Now this osmium VIII glycolate which is devoid of chiral ligand then dihydroxylates some of the olefins and that leads to low enantioselectivity. Because the osmium VIII glycolate is having osmium in oxidation state of VIII it can dihydroxylate some of the olefins. And that would of course be of low enantioselectivity because chiral ligand is not present.

But then when Sharpless used potassium ferricyanide, potassium carbonate, tertiary butanol water system in place of NMO, the oxidant remains in water phase and this allowed this glycolate osmium VI glycolate to get hydrolyzed like this and release the chiral diol, which is of course of high enantioselectivity.

And of course then releases the osmium VI, which then gets re-oxidized because the oxidant is soluble in water phase to osmium VIII, which is osmium tetroxide. Now this osmium tetroxide then interacts with the chiral ligand and subsequently the osmium VIII modified with the chiral ligand then reacts with the olefin and forms this type of osmium VI intermediate and the reaction continues.

Because of this in general it was found that enantioselectivity or enantiomeric excess of the diol with potassium ferricyanide, potassium carbonate, tertiary butanol water system is much higher than just with NMO.

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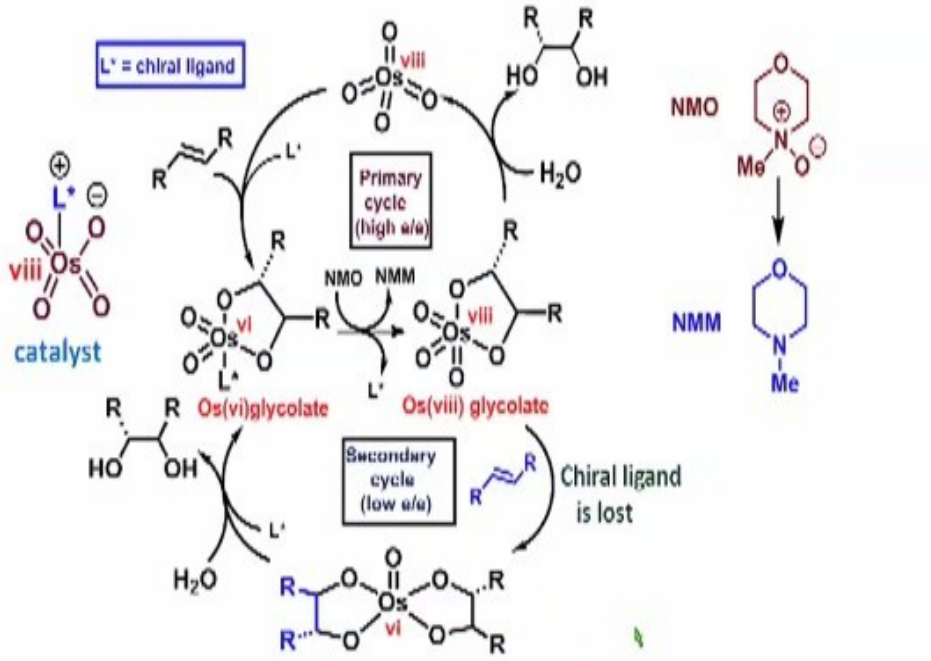

What is the exact mechanism of this reaction? Initially, what happens is that this osmium tetroxide gets attached to the chiral ligand and the modified osmium species then reacts with the olefin to form this osmium VI glycolate having the chiral ligand. Now this osmium VI glycolate then gets oxidized with NMO, which is N-Methylmorpholine oxide and releases NMM that is N-Methylmorpholine.

This osmium VIII glycolate upon hydrolysis releases the chiral diol and the osmium tetroxide. This entire cycle then of course continues and this would be of high enantioselectivity because the chiral ligand is attached to the osmium tetroxide before it dihydroxylates the olefin.

Now what happens is this particular osmium VIII glycolate which has been formed by the oxidation of osmium VI glycolate oxidizes some other olefins present in the reaction medium and then makes this particular osmium VI species. Now, this oxidation of olefin by the osmium VIII glycolate is of low enantioselectivity because chiral ligand is not involved in this particular process.

When this osmium VI species gets hydrolyzed it releases the diol, but this diol will be of low enantiopurity. And so what needs to be done is of course, this particular osmium VI glycolate should get hydrolyzed to the chiral diol, which will be of high enantiopurity before it is oxidized to this osmium VIII species because this is the osmium VIII species that is the culprit to oxidize the olefins present in the reaction medium.

And there is a competition between this osmium species which has a ligand and this particular osmium VIII species which does not have a ligand for the dihydroxylation of the olefin and because of, the enantioselectivity of the chiral diol is low.

So the modified reagent system of potassium ferricyanide introduced by Sharpless takes care of this particular problem and allows the hydrolysis of this osmium VI species to the diol and the oxidant is present in the reaction medium and is soluble in water that oxidizes the released osmium VI species directly to osmium tetroxide.

That means in the modified system, the hydrolysis is taking place first to release the diol and subsequently in the same medium, the osmium VI gets oxidized to osmium VIII that is osmium tetroxide. And therefore, this primary cycle is basically operating when potassium ferricyanide system is used.

And that is the reason why potassium ferricyanides based system is of high enantioselectivity and gives the diol of high enantiopurity.

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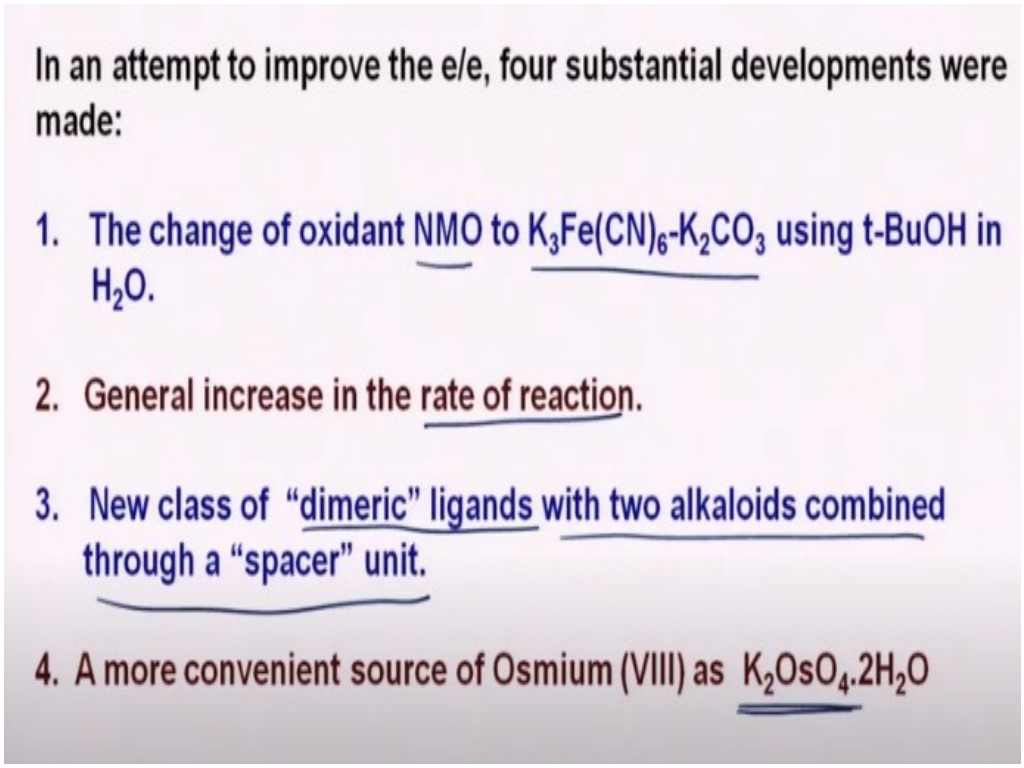

So basically four substantial developments were made. The change of oxidant from NMO to potassium ferricyanide in water and tertiary butanol medium that led to the increase of the rate. And of course, they also introduced some new dimeric ligands with the same two alkaloids, but as a spacer unit. And a more convenient source of osmium tetroxide was used as this particular salt of the osmium tetroxide.

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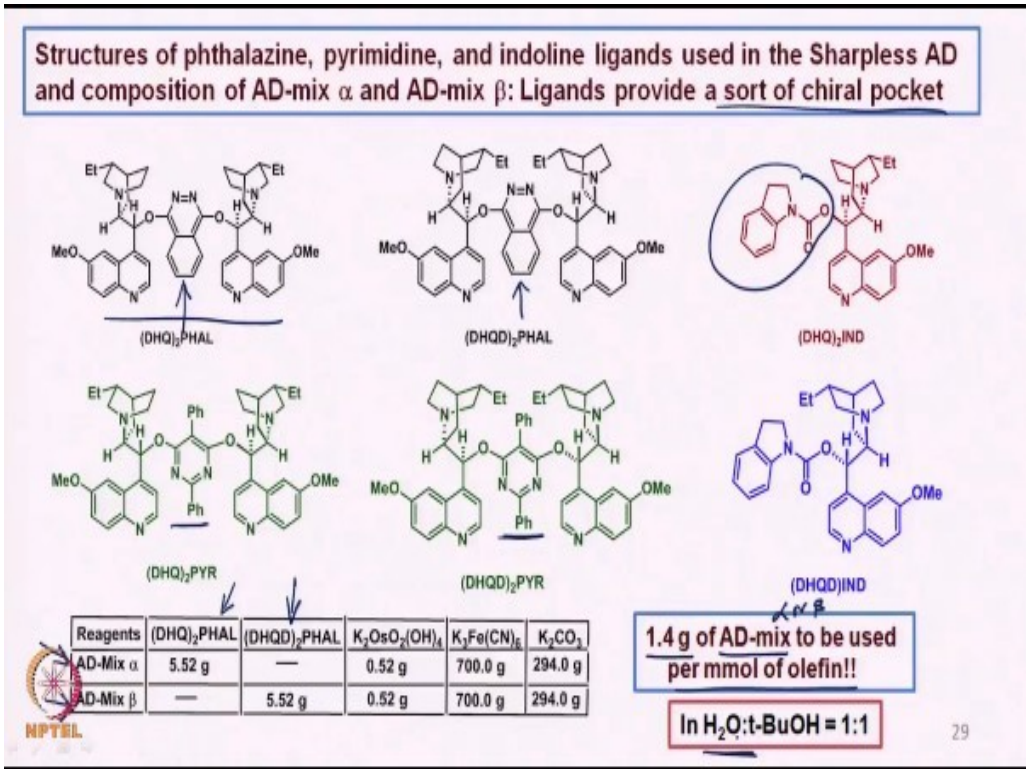

So these are the structures of various spacers which have been used and this is the structure where phthalazine is used as a spacer and this is DHQ and this is the DHQD. This is another spacer here. Then you have this type of spacer is used, which then allows two molecules to come in to the picture and then we have this kind of pyrimidine system as spacer.

And this type of spacers have been found to allow a sort of pocket of chiral nature that allows the dihydroxylation to occur to give high enantiomeric purity. What is also found that if one takes the chiral ligand of any one of this type, say in this case phthalazine is 5.52 grams and then 0.52 gram is that osmium salt and then potassium ferricyanide 700 grams and potassium carbonate is 294 gram.

This particular combination of salts is known as AD-mix alpha. And the other one in which this is different is known as AD-mix beta. If we take a mixture of these and this we use only say 1.4 grams of AD-mix, any one of them alpha or beta, whichever one wants to use it, per millimole of the olefin in tertiary butanol and water medium, it is enough to give the dihydroxylation of high enantiomeric purity.

So this has been introduced by Sharpless and therefore is commercially available with chemical companies such as Aldrich. And therefore, one can simply buy these particular mixture of an oxidizing agent and simply put 1.4 gram of it per millimole of olefin and get the dihydroxylation.
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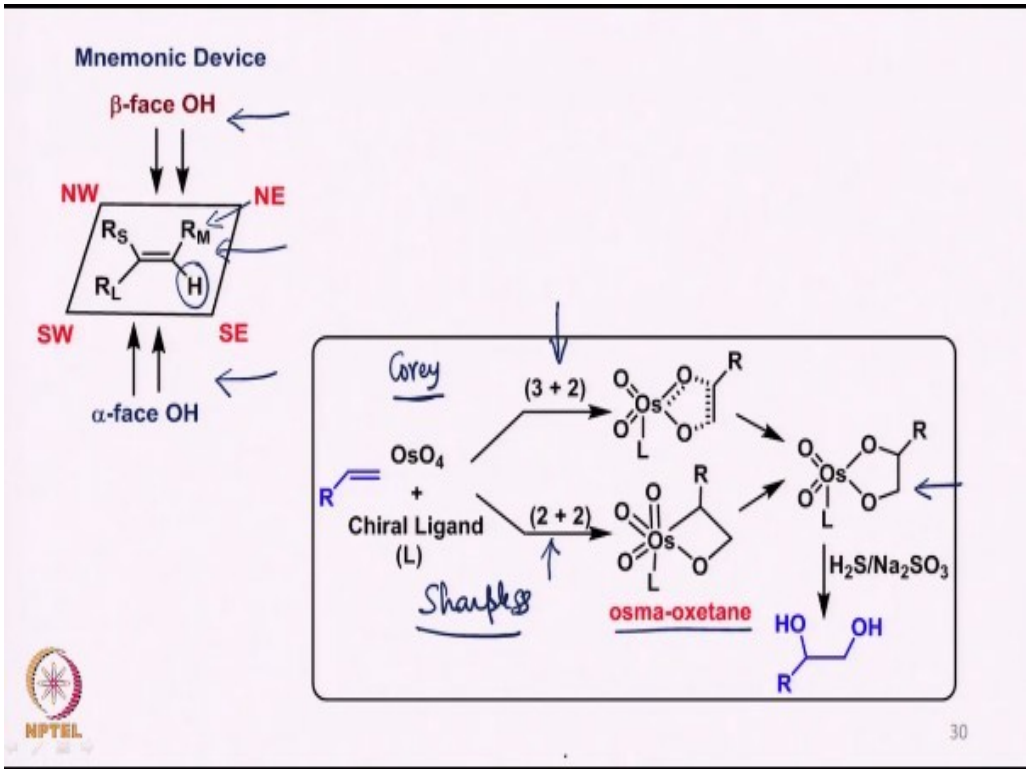


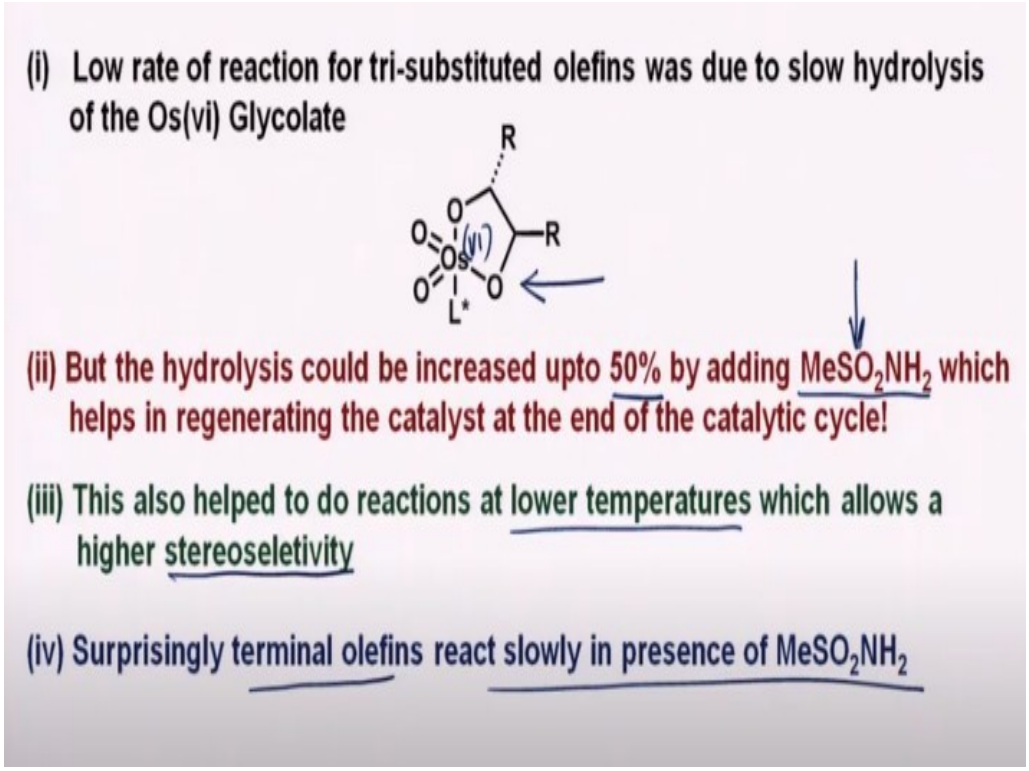
What is a mnemonic device that has been proposed by Sharpless based on a large study of various examples is that if the olefin is put it in this particular fashion, where a small group and a large group and the medium and the hydrogen etc., is substituted.

Olefin if we can orient it in this particular fashion, such that the small group is closer to the northwest side, the large group is on the southwest side and the northeast side is having this medium group and the smallest group is towards the southeast side, if we orient it, then the epoxidation allows in such a fashion that you get the beta dihydroxylation.

Whereas in cases where AD-mix alpha is used, then you get the dihydroxylation from the alpha side. So the AD-mix alpha and AD-mix beta are basically designed based on such a mnemonic device and therefore, it is expected that if we put the olefin in this particular framework, in this particular orientation, then if we use AD-mix beta, the dihydroxylation will occur from the top face.

And if we use AD-mix alpha, then the dihydroxylation will take place from the lower face. Now it is proposed that the reaction proceeds via this four membered, osma-oxetane via 2+2 cycloaddition. Whereas, it is also proposed that it goes via a 3+2 cycloaddition. And then of course, eventually they come to this particular intermediate and then the reduction leads to the formation of the diol.

This particular 3+2 proposition was made by Corey on the basis of the fact that this four membered ring could be sterically bulky. Whereas, the four member intermediate was proposed by Sharpless. So there is a controversy, but then the results of course are the same and one gets the diol no matter what happens and we get the diol through this expected mnemonic device based dihydroxylation. **(Refer Slide Time: 24:11)**



Now the low rate of reaction of tri-substituted olefins, as we discussed was due to slow hydrolysis of the osmium VI glycolate and this is what the osmium VI glycolate is and we saw that the hydrolysis of it is a must before it undergoes re-oxidant or re-oxidation. But the hydrolysis was found to be increased by about 50% if this methyl sulphonamide is used, and this allows the hydrolysis to be fast.

And therefore the enantiomeric purity is also affected by this. And it also allowed to do reactions at low temperature and therefore, high stereoselectivity is observed. Surprisingly the terminal olefins react slowly in the presence of methylsulphonamide and this is something that is not very clear, why is it so.

However, it is very clear that the addition of methylsulphonamide is something that allows the hydrolysis to be increased and the molecules in which the tri-substituted olefins were slow to hydrolyze could definitely be improved and high stereoselectivity is also observed.

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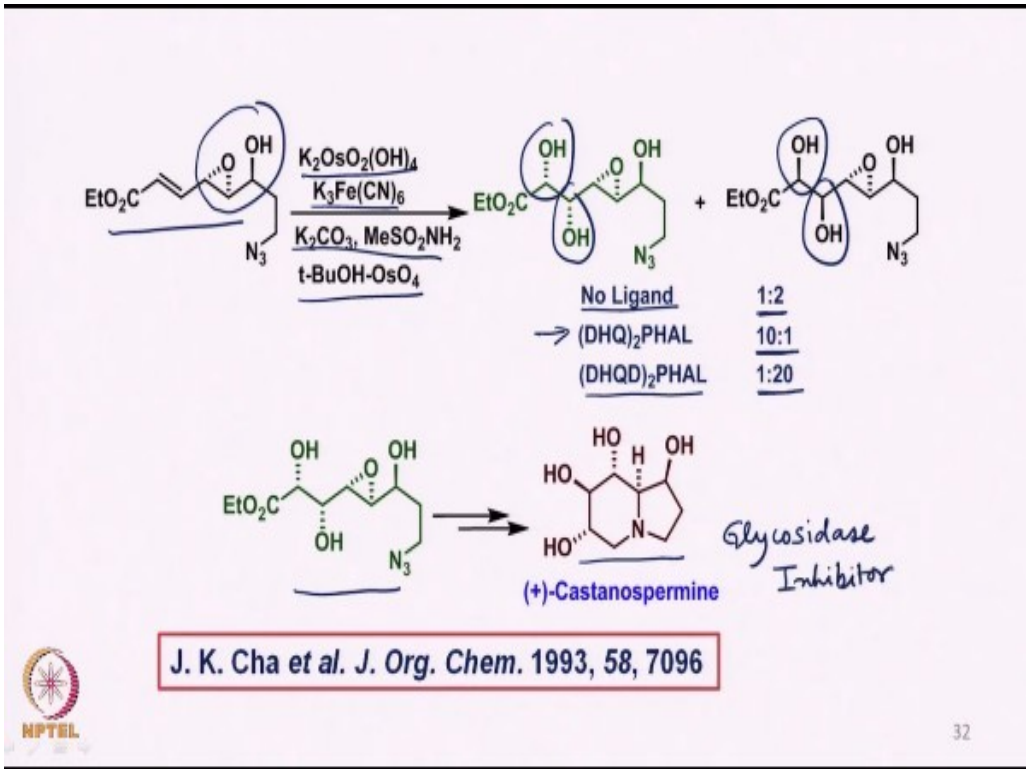

Now these are some examples of the osmium tetroxide based reactions. For example, we can take this epoxide having an olefin. Of course, this path of the molecule can also be prepared. In fact, it has been prepared by using Sharpless epoxidation and the dihydroxylation was carried out using this protocol, which we discussed just now. And of course, if we take no ligand we get both the molecules and the ratio is 1:2.

That means this cis-diol and this particular diol they are both formed in 1:2 if there is no ligand. If we use DHQ phthalazine as this particular reagent system, then we get 10:1 ratio and if we use DHQD PHAL, then of course we get 1:20 ratio of these two diols. So it is very clear that one can choose based on what one wants and accordingly one can get the dihydroxylation.

And one of these molecules was converted to castanospermine which is a good glycosidase inhibitor. And therefore, it comprises of a very important synthesis of such a molecule which is useful in biologically.

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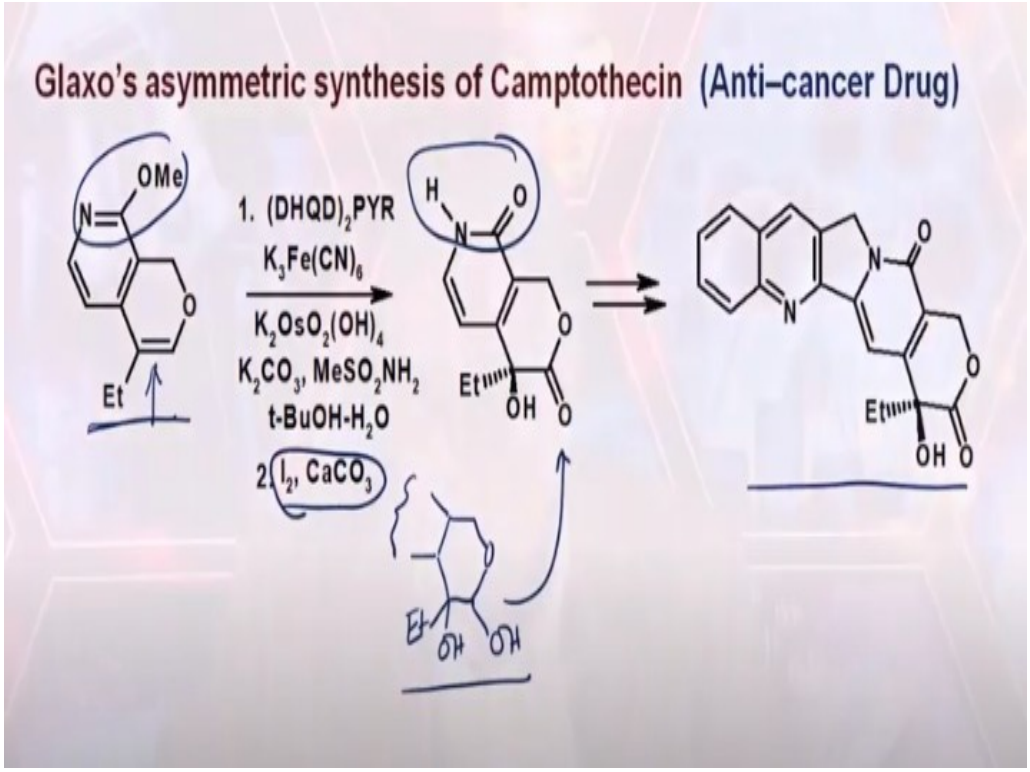

We can also make an anti-cancer molecule as camptothecin where this particular olefin was dihydroxylated, and as you can see that the dihydroxylation leads to the formation as you can see from here, this part has to be hydrolyzed of course to go to this particular amide and the double bond was dihydroxylated. And as we can see from here that, if we have dihydroxylation here taking place, then we can get this part, I am not writing it.

So this is what we will get it. And then with this iodine calcium carbonate, this was oxidized to form the corresponding lactone. And this intermediate has been converted to the anti-cancer drug Camptothecin. So one can easily see that how one can make use of such dihydroxylations in the synthesis of important molecules.

So we will stop it at this stage and we will take up the remaining aspects of asymmetric reactions, especially the reduction of molecules in such a way that they lead to optically pure, reduced products. So till then bye and thank you. We will see you next time.