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

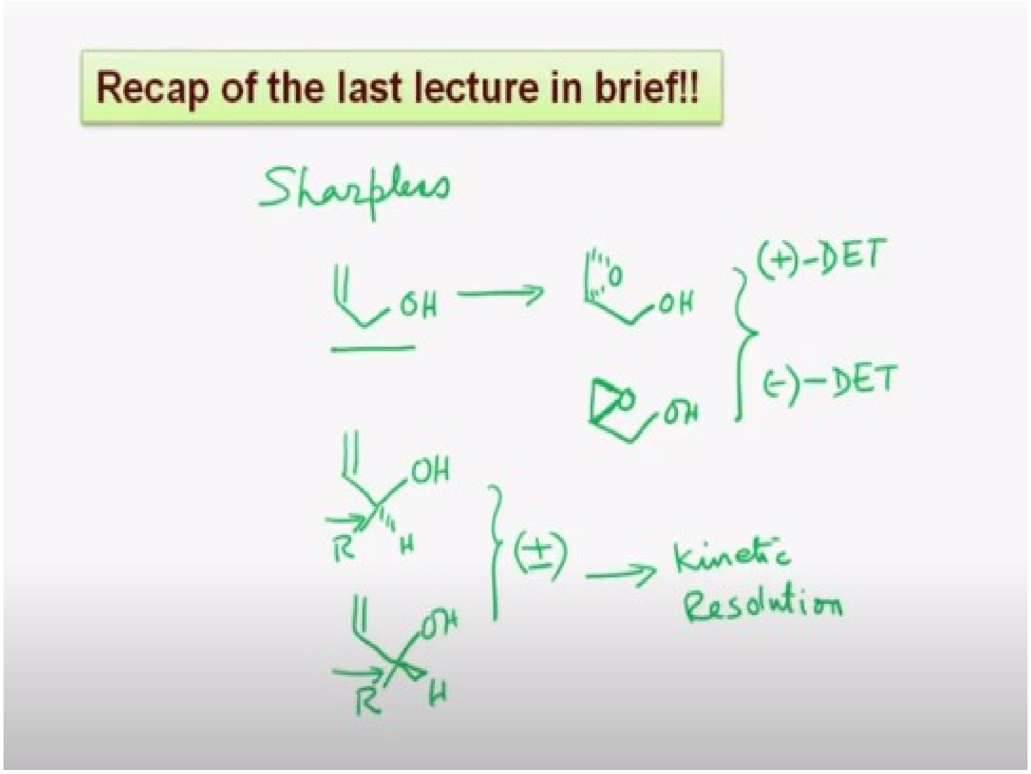
Prof. Yashwant D. Vankar
Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture - 36

Synthetic Utility of Chiral 2,3-Epoxy Alcohols Obtained From Sharpless Epoxidation

Hello everyone. I would like to welcome you all for the today's lecture. We will briefly look at what we did last time. As you recall, we started with asymmetric epoxidation developed by Sharpless.

(Refer Slide Time: 00:35)



Recap of the last lecture in brief!!

And we looked at how the mnemonic device allows the allylic alcohol to be oriented in this particular fashion and depending on whether it is L+ DET or D- DET we can get the corresponding epoxides and their orientation or stereochemistry in this fashion. These are two epoxy alcohols that can form. This one based on +DET that is diethyl tartarate and this one by from the –DET.

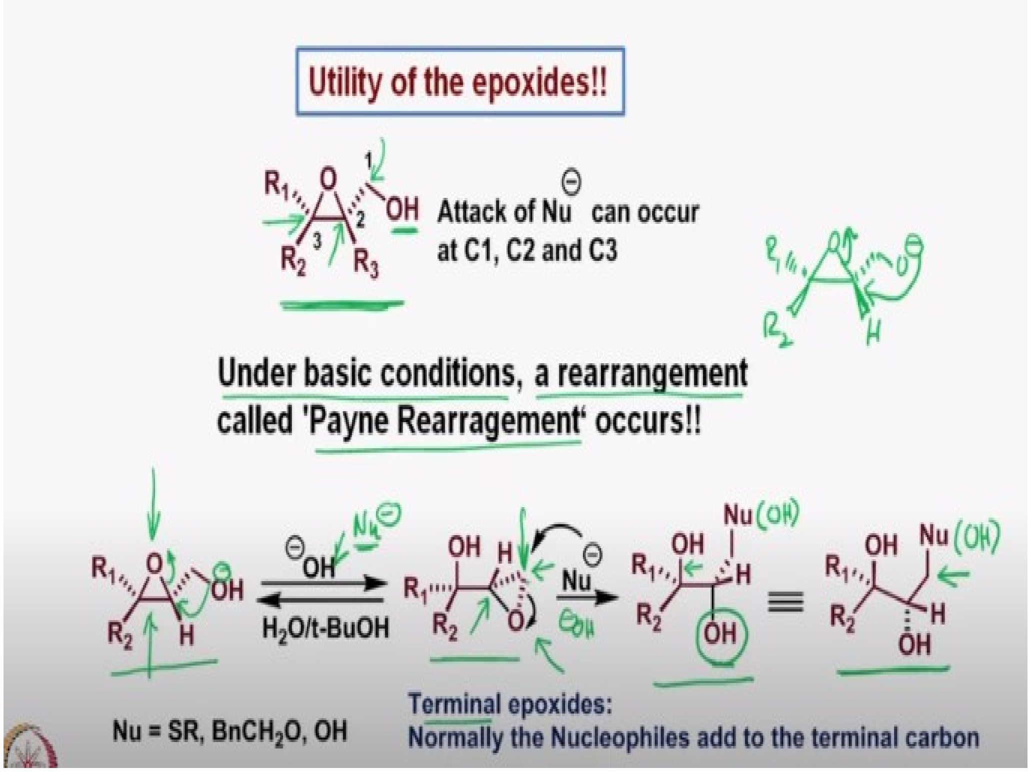
This is L+ and this is D-. So rest of the reaction conditions remain the same. And we also saw that not only this kind of prochiral allylic alcohols can be epoxidized under the Sharpless epoxidation conditions, where we can also take racemic allylic alcohol in which we have here say for example, R and H or we have R in differently oriented fashion and this particular racemic molecule.

So as we can see that if we write it here, this R group and this R group in such a way that they are basically enantiomers of each other. So they would be available as a racemic molecule. And if we carry out the reaction, we can carry out basically and kinetic resolution in which one of them reacts faster for epoxidation and the other one remains as allylic alcohol.

So up to here, we had seen and we also saw the mechanistic aspects of these reactions where how the dimeric species of the titanium catalyst allows this orientation of the epoxide to come from lower side in case of +DET and from the top side or the beta side when we use –DET.

So having obtained such epoxy alcohols in very high enantiomeric purity in a very catalytic fashion, we also saw the utility of molecular sieves to remove water and isopropanol from the reaction medium to make the reaction catalytic. Now what is the utility of these epoxy alcohols in the synthetic area, let us see that. So we have the epoxy alcohols like this.

(Refer Slide Time: 03:54)



Utility of the epoxides!!

Attack of $Nu^{\ominus}$ can occur at C1, C2 and C3

Under basic conditions, a rearrangement called 'Payne Rearragement' occurs!!

Nu = SR, $BnCH_2O$, OH

Terminal epoxides:
Normally the Nucleophiles add to the terminal carbon

And we can anticipate that there are essentially three centers where the nucleophile can attack. Like for example, one position where nucleophile can attack if we are in a position to make the hydroxy group as a leaving group. Then the nucleophile can attack at the carbon number 1. Then it can attack on carbon number 2. The epoxide can be opened at nucleophilic attack from at the carbon number 2 and also at the carbon number 3.

It all depends upon various conditions. And we will discuss that under what conditions such attacks are possible. But one thing which is very important is that under basic conditions, these epoxy alcohols undergo a kind of rearrangement called Payne rearrangement.

So if we take for example the epoxy alcohol of this type, when we react it with a base such as sodium hydroxide or potassium hydroxide, and we can anticipate that this epoxy alcohol should become a particular anion by the base that we have used and then we can expect that this particular O- opens up the epoxide in an intramolecular fashion and to give this epoxide.

That means this negative charge from here will attack onto this carbon and the carbon oxygen bond of the epoxide will break leading to this OH group in this fashion and the epoxide of course will now be terminal epoxide because we started with an epoxide which was having a position in the middle where on the one side we had this R 1 and R 2 group. On the other hand, we had the CH2OH and the H.

But now after the Payne rearrangement, the epoxide has now become the terminal epoxide and this terminal epoxide is sterically less hindered compared to this epoxide. So if you look at the reactivity of this epoxide and compare the reactivity of this particular epoxide, here the two carbons of the epoxide end are both sterically hindered. Whereas here, this is sterically more hindered and this is sterically less hindered.

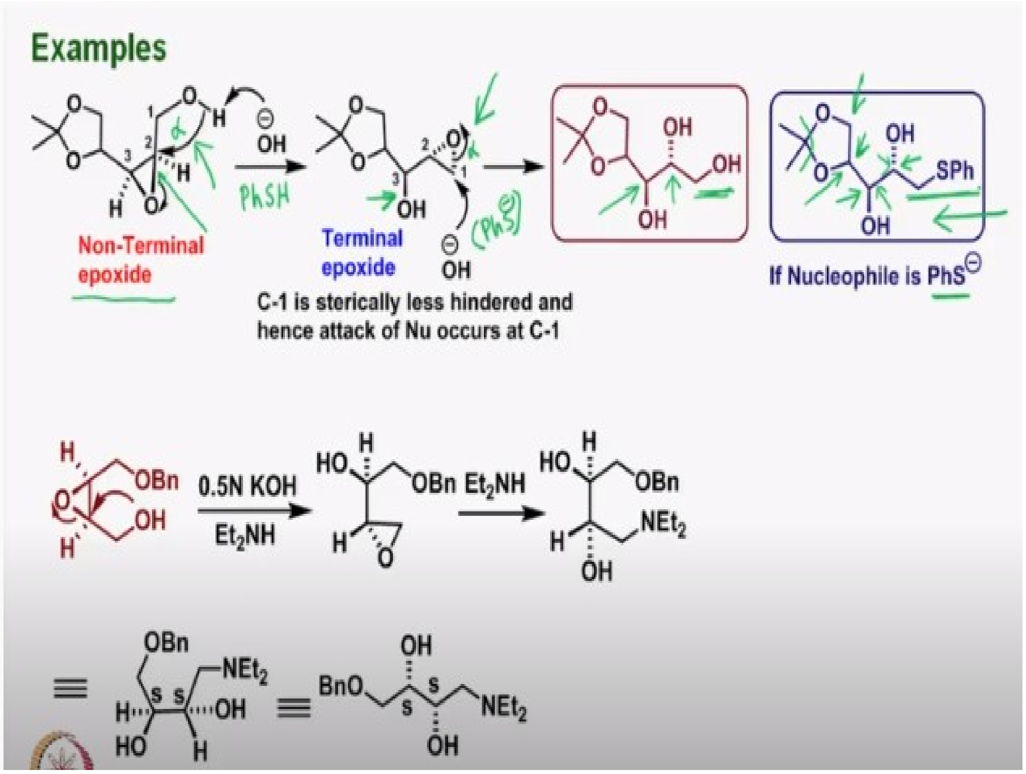
Therefore, the nucleophile can attack on to this carbon and then we can get the in fact in this particular case the nucleophile is OH- and therefore we are getting the OH- coming at this place, at this place it should be actually. And the epoxide opens up to form the OH group like this. So therefore, you have the nucleophilic attack taking place on to this carbon and the carbon oxygen bond breaks to get to this and in this case you have an OH here.

So this is how the reaction occurs. And of course, we can write the diol or the triol whichever way one wants to without actually changing the stereochemistry of the asymmetric center. So this is something as a very important reaction, where the utility of the epoxy alcohol can be looked at. And since the Payne rearrangement allows the conversion of one type of epoxide to another type of epoxide.

As you can see that both of them are essentially epoxy alcohols. In this case, the epoxide is not terminal, whereas in this case it is terminal. So one can also anticipate that the same Payne rearrangement can occur from this OH under basic condition and that opens the epoxide and it goes back to this. That is why there is an equilibrium that is shown on this side.

However, if in the present reaction conditions, OH is a nucleophile but one can also take any other nucleophile or a precursor of a nucleophile and that particular nucleophile will preferentially attack on to this particular end of the epoxide which is sterically less hindered. So this Payne rearrangement followed by nucleophilic attack has been well exploited in the organic synthesis.

(Refer Slide Time: 09:19)



Examples

C-1 is sterically less hindered and hence attack of Nu occurs at C-1

If Nucleophile is $PhS^{\ominus}$

So let us take a special case here. If we take a nonterminal epoxide now where the epoxy alcohol of this kind is generated or formed or prepared or synthesized according to the Sharpless method. And when we allow this reaction to take place in the presence of sodium hydroxide, so we expect this type of opening to take place.

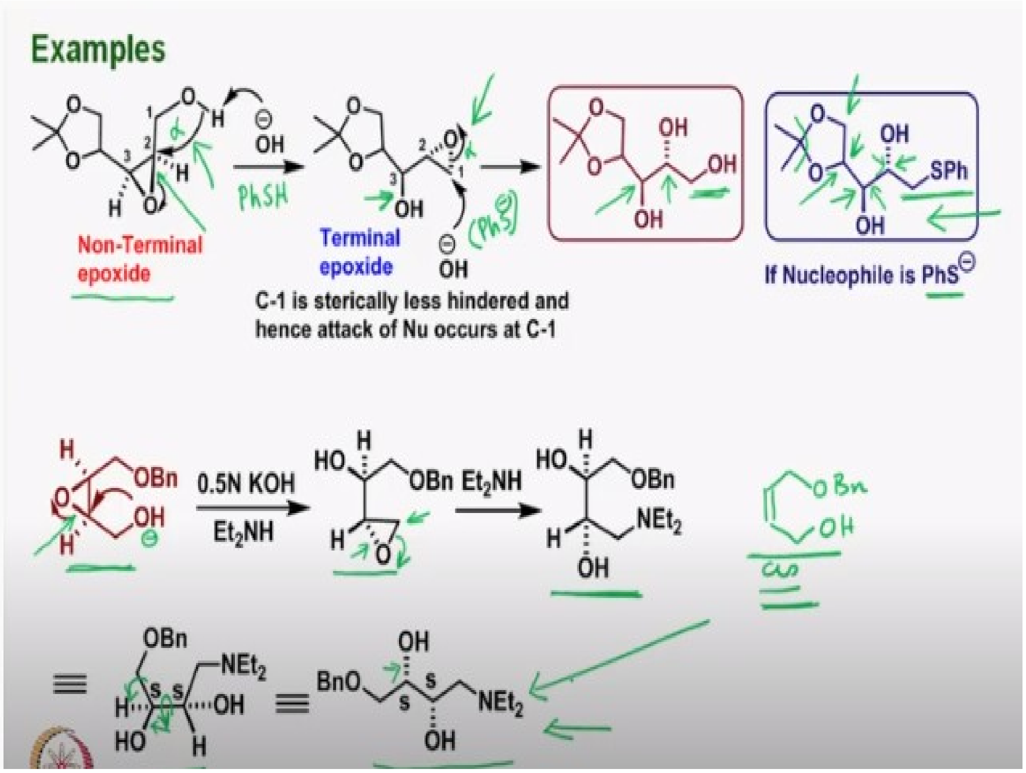
And generating the terminal epoxide of this type where the O- attacks from the, as you can see that the epoxide here is beta oriented, the carbon oxygen bond is beta oriented and therefore, the O- attacks from the alpha side. So this is an alpha side attack. So you have this carbon oxygen bond is broken and on the third carbon the carbon oxygen bond is beta oriented.

Whereas the terminal epoxide, the epoxidation is occurring from the alpha side opposite to the original epoxide which was beta. And to this now the OH- which is what is the nucleophile in the reaction medium attaches to the carbon number 1 and this carbon oxygen bond is broken to form the OH group here at the alpha oriented here the beta oriented and of course we get hydroxy group at the terminal end.

Under these conditions, if we also add say for example phenyl SH as a reagent or reactant in the medium, then we can expect the phenyl S- forming. So in place of this nucleophile we could expect that PhS- can act as a nucleophile leading to the formation of such thio compounds. These kinds of thio compounds are very important and as one can see very carefully that we have this asymmetric centers.

Of course, there is also one asymmetric center here. And we have functionality in which there is possibility of hydrolyzing this particular acetal moiety and we can generate two hydroxyl groups here. So we have one hydroxy group coming here, another hydroxy group coming here, we already have the third one here and the fourth one here and the possibility of manipulating the carbon S bond and therefore leading to highly functionalized optically pure molecules.

(Refer Slide Time: 12:33)



Examples

Non-Terminal epoxide

Terminal epoxide

C-1 is sterically less hindered and hence attack of Nu occurs at C-1

If Nucleophile is $PhS^{\ominus}$

Let us take another example of this type which is easily derived from a molecule of this kind. So one can start with this cis double bond where there is an allylic alcohol and you can carry out whichever way one wants to have the epoxide using L+ or D- DET under Sharpless epoxidation conditions.

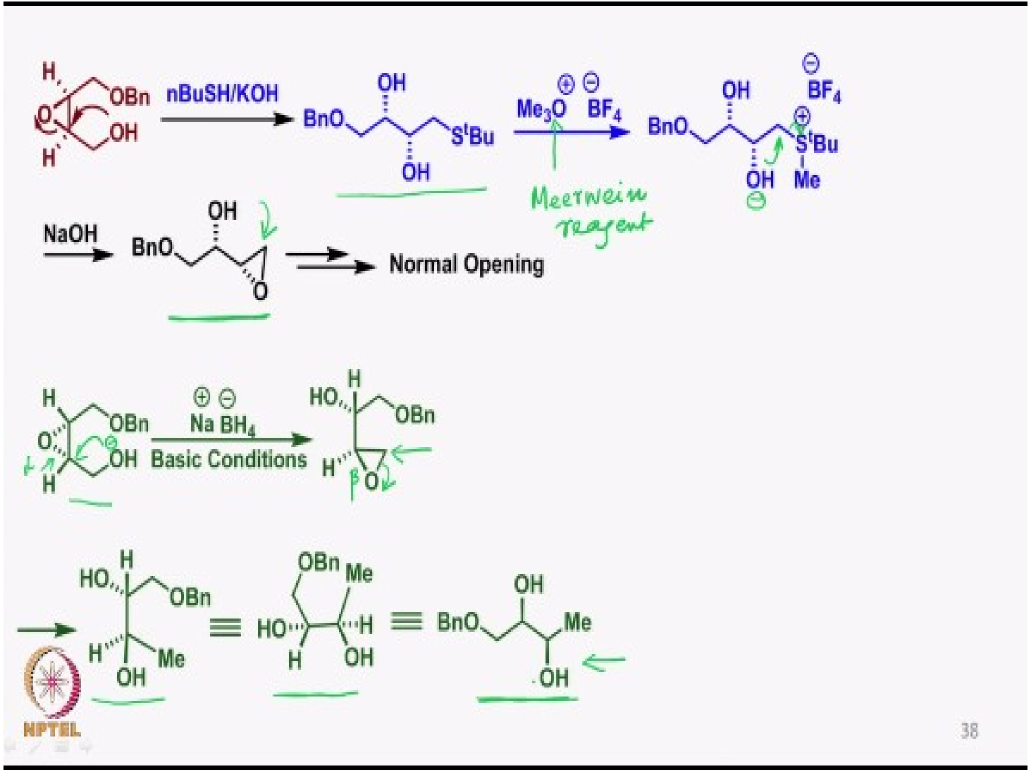
So having got the epoxide like this, if we treat with potassium hydroxide and say diethyl amine, so we could expect the anion to form at this center, which attacks to open the epoxide and this terminal epoxide can form. Again as you can see that the carbon oxygen bond here was beta oriented.

And now since the oxygen minus is now reacting from the opposite side of the carbon oxygen bond, therefore this is now alpha oriented to which now diethyl amine as a nucleophile can attack onto this particular carbon atom. And when this bond opens here, we get this diol, which can be written up in this fashion without changing the stereochemistry and also we can write it in this way in a zigzag fashion, where we can rotate it in this particular part here so that it points below.

If it points below the hydroxy group will go in a different orientation than what it was in here. So basically we are allowing the carbon-carbon bond rotation around here. So this is the product that is formed after the reaction has done, has been done.

So you start with a cis allylic alcohol and we get the product like this via essentially two steps, one epoxidation followed by opening of the epoxide and a nucleophilic attack in one step and with predictable stereochemistry in all the reactions. So this is a very important transformation and one can carry out such transformations in very under mild conditions and get high yield, not only high chemical yield but also high optical yield.

(Refer Slide Time: 15:18)



Now if the same epoxide is reacted with say butane thiol and as basic conditions we expect this kind of particular molecule to form and when this diol is reacted with a source of Me+, this is called Meerwein reagent and it is a useful source of methyl plus especially for the methylation of sulfur here.

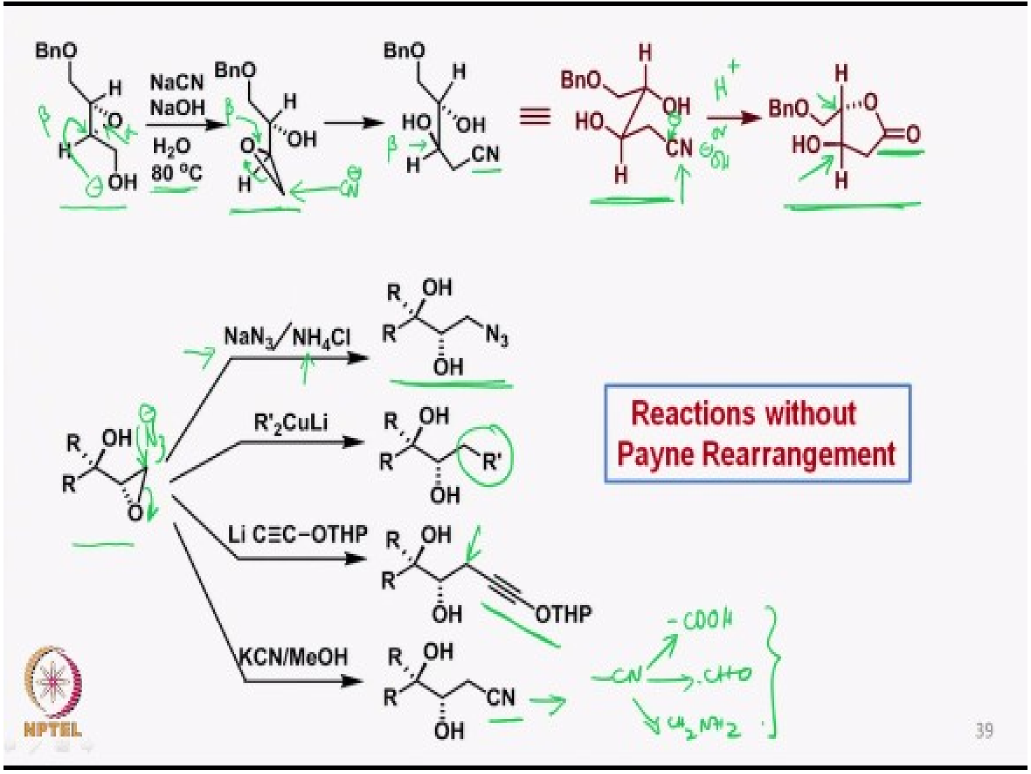
And once that is done, you can imagine that when it is treated with base, you can deprotonate the OH group here and that can go on attack on to this to remove this carbon sulfur bond because now this part has become a leaving group. And then of course, we can expect the epoxide to form in this way and then this allows the normal opening or the terminal epoxide opening the way we have seen in other cases.

If we take an epoxide of this type, then even sodium borohydride has been found to react with this as I have earlier mentioned that in a certain conditions in certain cases, sodium borohydride can do reduction of epoxides. For example here under basic conditions, the Payne rearrangement takes place and the anion will form from the opposite to the carbon oxygen bond.

This is alpha oriented, therefore this is now beta oriented. And when this gets reduced with sodium borohydride here, then this bond opens up and we get this product which can be written up in this fashion. And of course, we can then turn around and expect that the orientation of this molecule having a zigzag possibility being like this.

So this is how the epoxy alcohols are used in various kinds of transformations. We have few more cases. For example, we can also start with this epoxide.

(Refer Slide Time: 18:11)



Reactions without Payne Rearrangement

And treat with sodium cyanide under basic conditions in water at 80 degree centigrade so one can expect anion formation to take place from here. So and this particular carbon oxygen bond is alpha oriented. Therefore, the attack takes place from the beta side to form this epoxide where this is beta oriented. And then of course, it is a terminal epoxide.

So CN- reacts onto this particular carbon and then this carbon oxygen bond opens up to give the hydroxy group which is now beta oriented and then cyano and rest of the part which can be written up in this fashion, which now allows that if we take say for example H+ or under basic conditions, the H+ or under basic conditions followed by acidification can lead to the formation of the oxygen carbon bond eventually to give the to the lactone.

Essentially, what is happening is this is getting hydrolyzed or this is getting attacked by the O- and then hydrolyzed to the corresponding lactone. So one can prepare such kind of lactones where there are two asymmetric centers and we can get them in high enantiomeric purity. Now the other possibility is that, we can carry out the reaction without Payne rearrangement.

What is required for the Payne rearrangement is a basic condition, is a strongly basic condition so that the proton of the OH is deprotonated and O- is formed which then opens intramolecularly the epoxide on the next carbon of the molecule. But suppose if we take an epoxy alcohol of this type and treat with sodium azide in the presence of ammonium chloride.

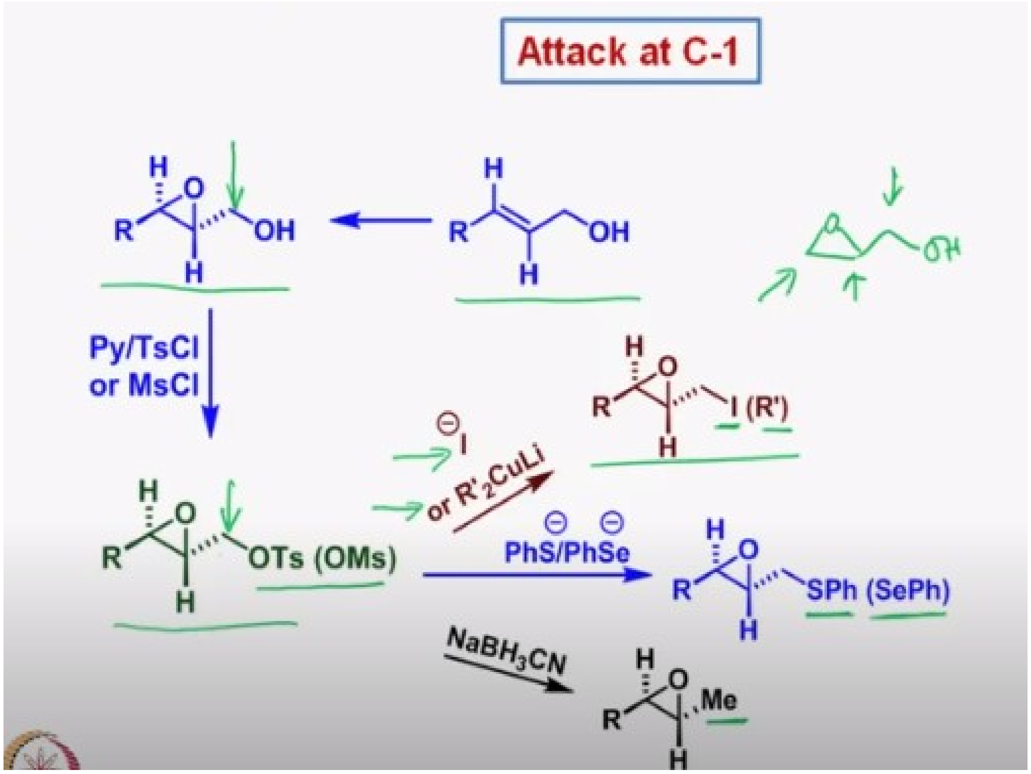
Now ammonium chloride is very mildly acidic, which allows epoxide to be deeply protonated and then the nucleophile which is N3- directly attacks onto this terminal epoxide and this carbon oxygen bond breaks to form the corresponding azido alcohol. Now this has not required any basic condition and therefore the Payne rearrangement does not take place.

Now we have lithium cuprates of this type which are actually not basic or ionic enough to allow the deprotonation and then opening to take place and therefore, such a reagent leads the attack at the terminal end and this is how the R prime group comes onto the terminal end of the double bond.

We can also take this lithium acetylide of this type where the epoxide carbon is getting attached with this terminal particular acetylenic part. And we can also take reaction in such a direction that we can introduce another interesting functional group such as potassium cyanide in methanol.

We can allow the opening of the carbon epoxide bond oxygen bond to give to the corresponding cyanide, which can of course be converted into different functional groups such as if we have a cyanide, we can go to the corresponding COOH. We can also go to the corresponding CHO. We can also go to the corresponding CH2O NH2O. That is something that we discussed at the time when we were doing the reactions using dibal.

(Refer Slide Time: 22:37)



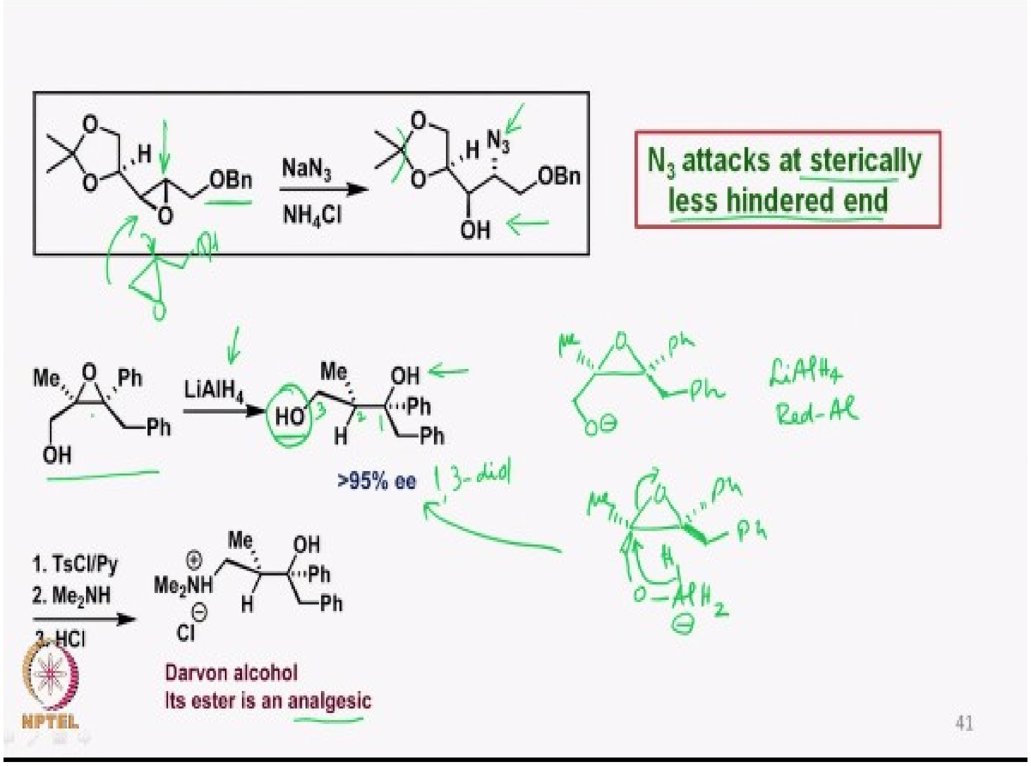
Now attack at this epoxide at the carbon number 1 can also take place in a way that if we convert the OH group of the epoxy alcohol to a leaving group and we do not have any strong basic conditions, then we can allow the opening to take place the way we want it at the carbon number 1.

For example under very mild condition with mild base such as pyridine tosyl chloride or mesyl chloride we can convert the OH group without affecting the epoxide to the corresponding tosylate or mesylate. So we are starting with this allylic alcohol and we are getting this epoxy alcohol and we convert that epoxy alcohol to epoxy tosylate or mesylate.

And now we have nucleophiles such as say for example we have I- a good nucleophile or cuperate as a good nucleophile we can directly substitute the carbon tosylate or carbon mesylate bond to the corresponding I or R prime. We can also take relatively soft nucleophiles such as PhS- or PhSe- and introduce carbon sulfur bond or a carbon selenium bond.

Or we can react it with sodium cyano borohydride and reduction takes place at the carbon bond, carbon center where carbon tosylate or mesylate bond is there and that leads to the corresponding methyl group to form. So this is how the reactions can be carried out at the three centers of the epoxide. As we discussed, we can carry out the reactions of this epoxy alcohol at this, this, or this center depending on how the reaction can be carried out.

(Refer Slide Time: 25:06)



N$_3$ attacks at sterically less hindered end

>95% ee

Darvon alcohol
Its ester is an analgesic

So we will look at one more example in which a very interesting Darvon alcohol, which is an analgesic has been prepared. So we take this particular epoxy alcohol, which is derivatized to the corresponding O-benzyl group now here. That means, we are starting from the corresponding epoxide here and basically converting into the O-benzyl.

Now this is not the same as opening of the epoxy alcohols that we discussed so far. Here now sodium azide and ammonium chloride based reaction occurs at this center. So basically at this center here. So it is not a terminal epoxide but the opening of the epoxide is taking place in such a fashion that sterically less hindered end of the epoxide is in the reaction where the azide attacks.

Now this particular molecule of course we can then carry out further transformations by hydrolyses, by reduction and so on. And another example is epoxide of this type, where we have already discussed how the epoxy alcohol can be converted into, say for example we have in this case like this, how can we convert the epoxy alcohol of this type into 1,2-diol or 1,3-diol.

So if you recall the reduction part that I had discussed with using lithium aluminium hydride or Red-Al, we can allow the reaction to proceed in such a fashion that we get here. So you have one particular position 2 and 3. So you have 1,3-diol to form. So this is 1,3-diol and that is happening because the epoxy alcohol under lithium aluminium hydride condition this is what we are using it.

It is going to react, negative charge will come in here. And of course then we have the hydride to attach in such a fashion that we can expect that the opening of the epoxide which is accompanied by reduction takes place because here we have we are basically trying to write a negative charge here O-. And this O- then will obviously react with the AlH2 and H here and a negative charge here.

So this is how it is now going to be the intermediate and which attacks onto this carbon to form the corresponding diol here. So 1,3-diol is formed basically because of this reduction taking place in a similar fashion that we had discussed earlier. Of course, then we can look at that this particular alcohol here is a primary alcohol and this is a tertiary alcohol.

So primary alcohol can be tosylated so that we convert this into a tosylate as a leaving group. And then the nucleophile from the dimethylamine will replace and then we can do the hydrochloride formation. And this is what is called as Darvon alcohol which is an analgesic if its ester is used. So basically we have a simple way of getting optically pure Darvon alcohol from the epoxy alcohol made from a molecule which is having a double bond here.

And of course we can carry out the epoxidation according to asymmetric Sharpless method and followed by combining the regioselective ring opening of the epoxy alcohol with lithium aluminium hydride. So we will stop it today at this stage and discuss more aspects of such asymmetric reactions in the next class. Till then bye and thank you. See you next time.