# Essentials of Oxidation, Reduction and C-C Bond Formation
# Application in Organic Synthesis
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## Lecture -06
## SeO2 based oxidation of ketones and Sulfoxide - Sulfenate rearrangement (Mislow-Evans rearrangement)

Hello everyone, welcome to this today's lecture now. As we discussed last time towards the end the rules for the introduction of hydroxyl group at the allylic and benzylic positions using selenium dioxide. So we discussed four different rules in the last class. Now today we will continue the remaining rules of selenium dioxide based. So basically what we had seen was that the oxidation occurs on the disubstituted side of the double bond.

It does not occur at the bridge head position. It occurs on the cyclic ring rather than on the side chain, so there are certain restrictions and certain observations which have been made.

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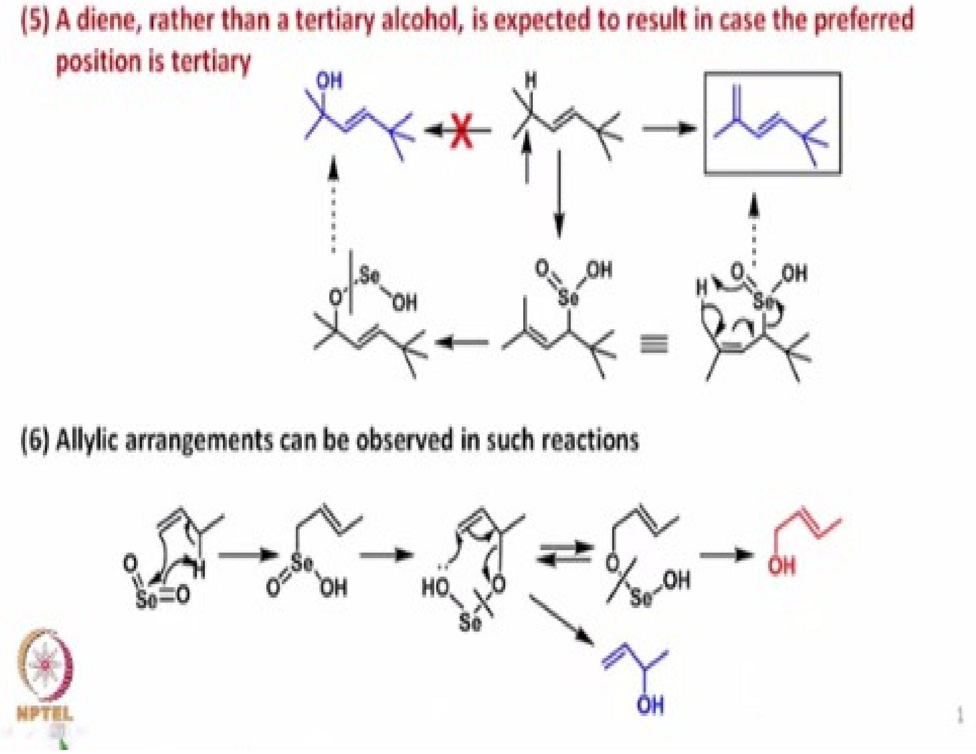

(5) A diene, rather than a tertiary alcohol, is expected to result in case the preferred position is tertiary

(6) Allylic arrangements can be observed in such reactions

And now according to the fifth rule, a diene rather than a tertiary alcohol results in case the preferred position is tertiary. For example if you take a compound of this type where the allylic hydrogen is tertiary as it is here, because on the right hand side we have three methyl groups and there is no allylic hydrogen. So what one would expect is this undergoes oxidation to form this tertiary allylic alcohol.

How the reaction takes place is, that there is a carbon selenium bond formation here accompanied by the proton loss to form a double bond. So this type of selenium intermediate then undergoes rearrangement to form an oxygen carbon bond accompanied by the migration of the double bond to form an intermediate of this kind where oxygen selenium bond is cleaved and that result into the tertiary allylic alcohol.

This is what one is expected to form. Now what happens is we do not get such a tertiary allylic alcohol but we get the corresponding diene. So what one could expect is that when such a selenium-based intermediate is formed one could expect that there is a migration of the double bond from here to here followed by cleavage of the carbon selenium bond and removal of a proton and of course formation of another double bond.

Such a rearrangement can occur to form this conjugated diene and this particular conjugated diene is stable thermodynamically because it is conjugated and also any activity at the tertiary position of course involves steric hindrance. Therefore considering both the points the formation of the conjugated diene is normally observed. According to the sixth rule allylic rearrangements can be observed in such reactions.

For example if we take a case like this such allylic rearrangements do not happen in every case but it can be observed in some reactions. In this particular case where there is a terminal double bond and the allylic hydrogen is located here when the selenium dioxide reacts with this olefin, we can expect to get an intermediate of this type having a selenide species. And that can undergo rearrangement as in all the other earlier cases that we have seen.

And can form such an intermediate where of course one could expect that a cleavage of the oxygen selenium bond would lead to the formation of such an allylic alcohol. On the other hand there is a possibility of such a rearrangement where a new oxygen carbon bond is formed leading to such an intermediate which can again undergo similar type of rearrangement between oxygen and carbon bond here and lead to the formation of this particular intermediate.

In other words these two species could be in equilibrium with each other when this particular species is formed and if it gets cleaved form this allylic alcohol and if this particular selenium species is formed and if this undergoes a cleavage here then one can expect to form such an allylic alcohol. Both these allylic alcohols are actually seen and thus allylic rearrangements are accompanied by the formation of two different types of allylic alcohols.

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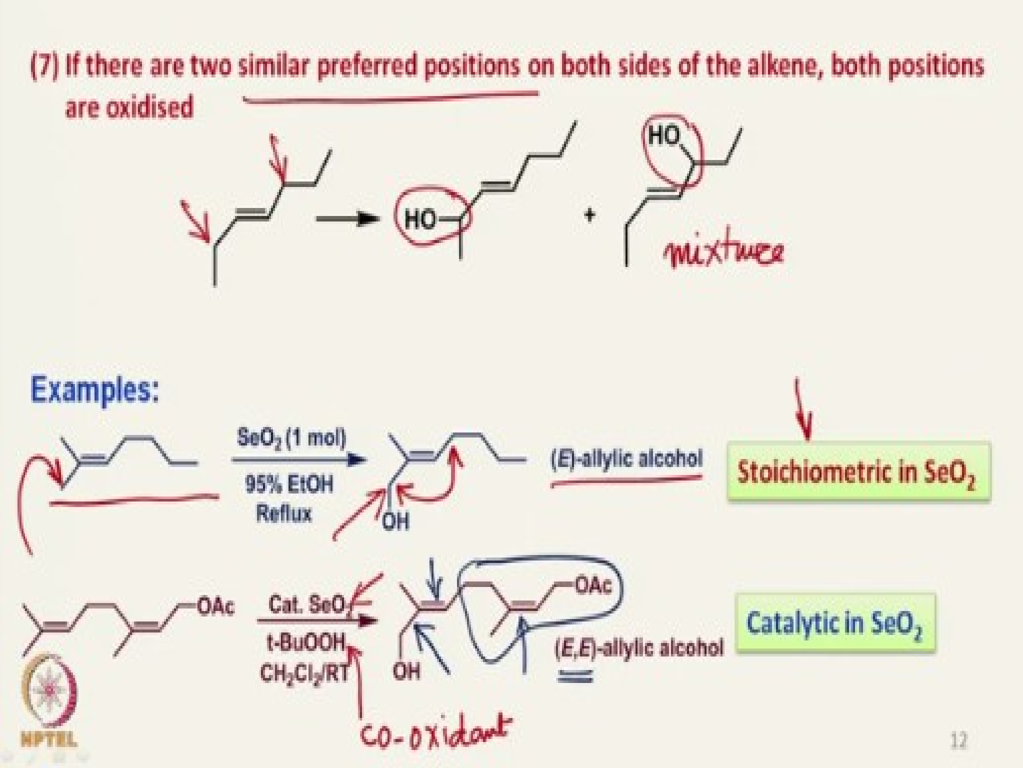

(7) If there are two similar preferred positions on both sides of the alkene, both positions are oxidised

Examples:

(*E*)-allylic alcohol

Stoichiometric in $SeO_2$

(*E,E*)-allylic alcohol

Catalytic in $SeO_2$

Now if there are two similar preferred positions on both sides of the alkene if such as this here and here so we can get oxidation here as well as here, so that is a mixture is formed. For example one can avoid this if one wants to have only one of them then of course you have to make sure that your substrate does not contain two similar positions which are preferred. Now in application point of view one can see that when takes a substrate of this type.

Now once we do the selenium dioxide base reaction 95% ethanol you reflux it, so the preferred position according to the rule number 1 takes place and the introduction of the hydroxy group occurs at this disubstituted side of the double bond and as you can see as I mentioned earlier that it is trans to the other side of the double bond and one gets E-allylic alcohol. However as you can see that in this particular reaction stoichiometric amount of the selenium dioxide is used which is not very comfortable or not good.

Because selenium compounds are toxic in nature and therefore there have been efforts to use catalytic amount of selenium dioxide, so that one can avoid using excess of selenium dioxide. For this purpose catalytic amount of selenium dioxide is used along with a co oxidant which is tertiary butyl hydroperoxide, it is a co oxidant and that also gives similar type of introduction of the hydroxy group on the disubstituted side and of course trans to the corresponding other side of the function, this double bond.

So one gets E E that means E is here and also E is here, so you get allylic alcohol which is acetoxy alcohol but has E E geometry around. So these are the rules which are useful in predicting the regiochemistry of the hydroxy group in this case.

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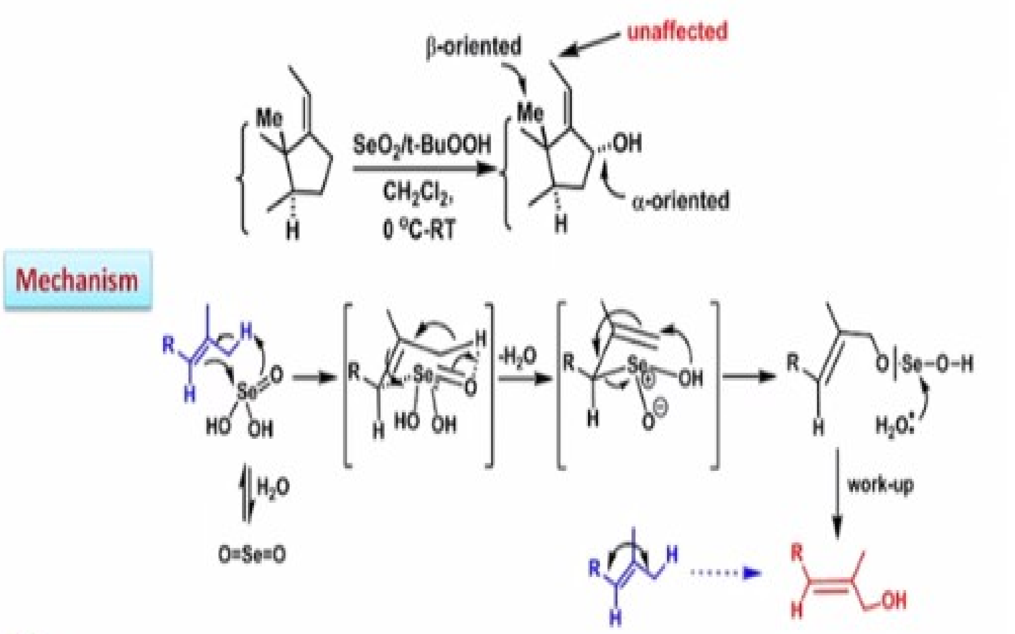

Now we take another example of a cyclic case and then we will look at the mechanism of the reaction. For example if we take a case like this where there is a cyclic substrate having two different types of hydrogens, one is allylic hydrogen here which is not a part of the ring, on the other hand these allylic hydrogens are part of the ring and as one expects that based on the one of the rules that the oxidation occurs in the cycle rather than on the side chain and therefore the oxidation would occur here with selenium dioxide.

Now because this methyl group is beta oriented the hydroxy group comes from the alpha side, thus this is an example which is not only indicating a regio selectivity but also stereo selectivity in selenium dioxide based oxidation. Now what exactly is the mechanism of this reaction if we take a simple substrate of this type where there is an allylic hydrogen and we can write the selenium dioxide in aqueous medium in this particular form which is in equilibrium with the selenium dioxide.

When this comes in contact with this substrate having an allylic hydrogen, then we can anticipate the transition state of this type to form which then undergoes a reaction with the allylic hydrogen in this particular fashion where the oxygen of the selenium dioxide takes away the hydrogen from here in the form of a proton forming a double bond of this type here followed by carbon selenium bond formation which is accompanied by the loss of water.

And this selenium intermediate then undergoes rearrangement to form the carbon oxygen bond here and the cleavage of the carbon selenium bond to form this species which can undergo upon work up a cleavage of the oxygen selenium bond, resulting into the allylic alcohol of this type which indicates that this particular substrate has undergone allylic oxidation retaining the geometry of the double bond, as you can see this R group and the $CH_3$ group are trans to each other and that is what is also reflected here.

This R group and this particular $CH_3$ group which has undergone oxidation are trans to each other. So this is an example of how the reaction occurs, what is the mechanism of the reaction.

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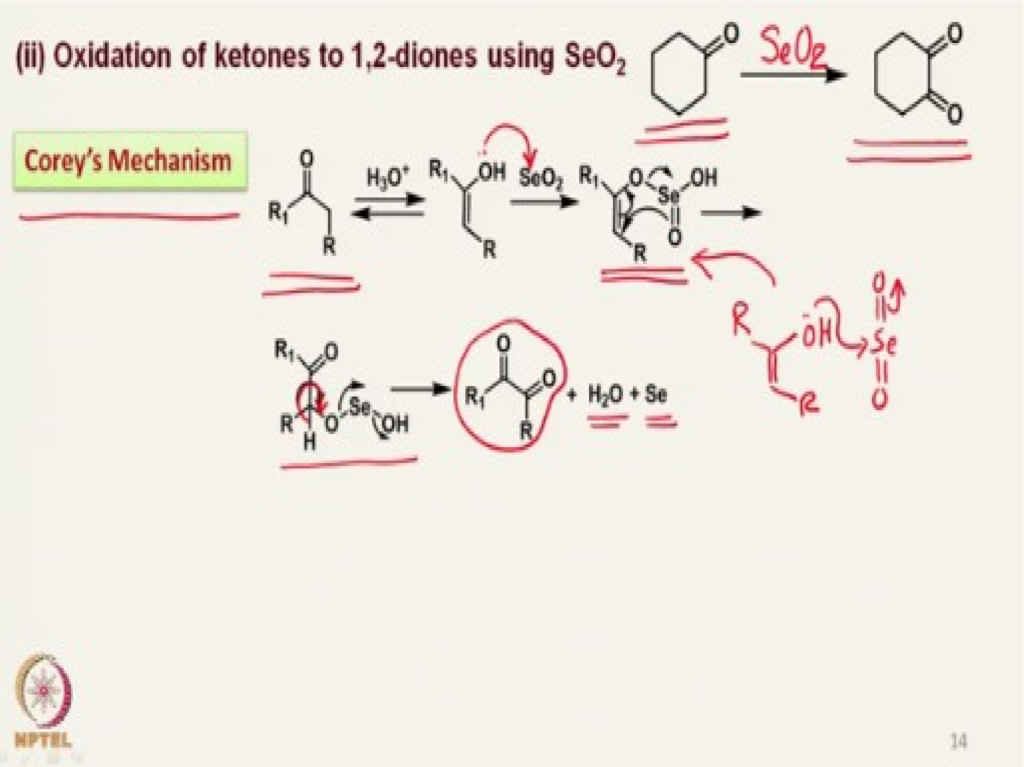

(ii) Oxidation of ketones to 1,2-diones using $SeO_2$

Corey's Mechanism

Now we go to the next topic which is oxidation of ketones to 1,2 diones using selenium dioxide. Now this is the typical example which shows how a cyclohexanone can be converted into cyclohexane 1,2 dione, now you use selenium dioxide to carry out such a reaction. Now there are two mechanisms which have been proposed, one is of course that the ketone of this kind, I have taken an example of a very general kind instead of taking a cyclohexanone.

And under this conditions it is done in water under these conditions and the slightly acidic conditions this will exist as a keto in all tautomeric equilibrium and according to the Corey's mechanism, EJ Corey at Harvard university has proposed that the oxygen directly attaches to the selenium. That means you have here a double bond and this OH, this is an enol and the selenium dioxide, then is attacked by the lone pair of electrons onto the selenium directly and this particular intermediate that is formed.

Now this intermediate now undergoes this type of oxygen transfer to form this intermediate, where what is proposed by Corey is basically a loss of this water and selenium metal at the same time there is oxidation that is occurring to form this 1,2 diketone. Now this is the mechanism which is proposed by Corey.

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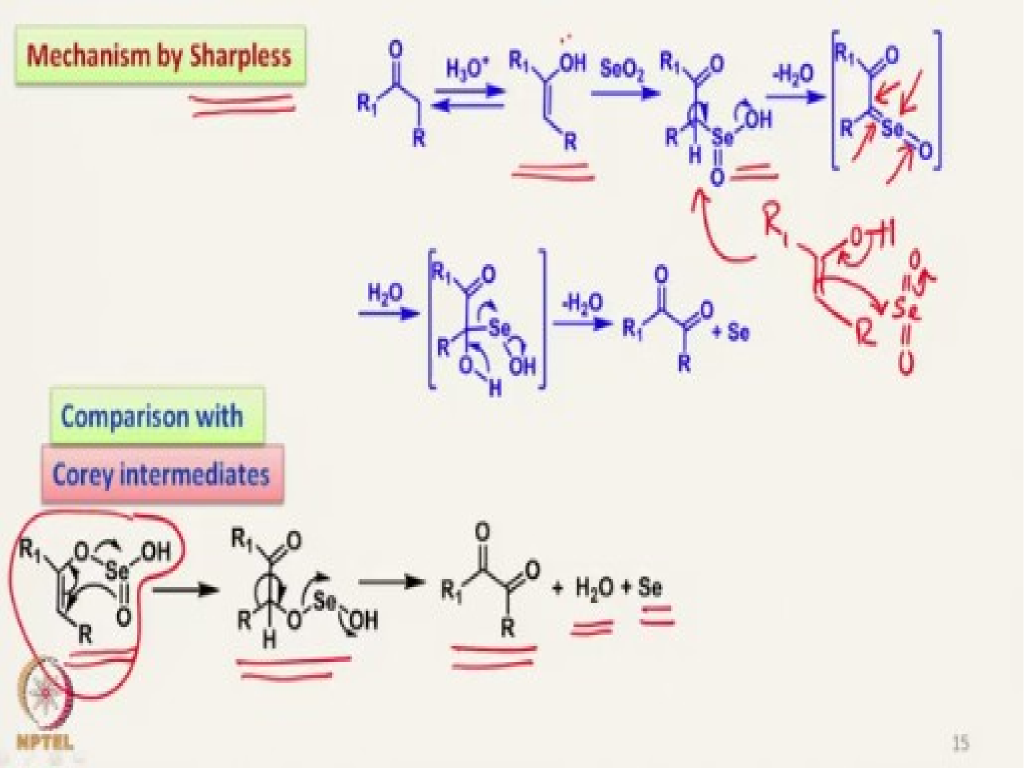

Mechanism by Sharpless

Comparison with

Corey intermediates

On the other hand, Sharpless proposed a mechanism very similar. This is the Corey mechanism, these are the Corey intermediates and a diketone is formed and of course selenium and water gets out of the reaction medium. So the only difference that mechanism by Sharpless and Corey is that when this enol reacts with selenium dioxide, so in the Corey case, this intermediate is formed where oxygen from here attaches onto the selenium dioxide.

On the other hand in the case of Sharpless epoxidation, this enol reacts onto the selenium here to form this intermediate. So that is the only difference that one can see in the case of mechanism by Sharpless and Corey. But there is a slight difference also that is, this intermediate then looses water molecule to form this selenium intermediate which has a carbon selenium double bond and of course carbon oxygen selenium double bond.

To which water re-attacks on to this particular carbon atom to form the carbon oxygen and carbon selenium type of intermediate and this again looses water to form of course the diketone with the loss of selenium metal and water. So essentially they are similar except the attack whether it occurs of the enol to the oxygen or to the carbon and of course subsequent manipulations of the; or subsequent fate of the remaining intermediates.

So these two mechanisms are generally believed to occur. Now we go to the sulfoxide sulfenate rearrangement and this particular reaction is an interesting reaction which starts with;

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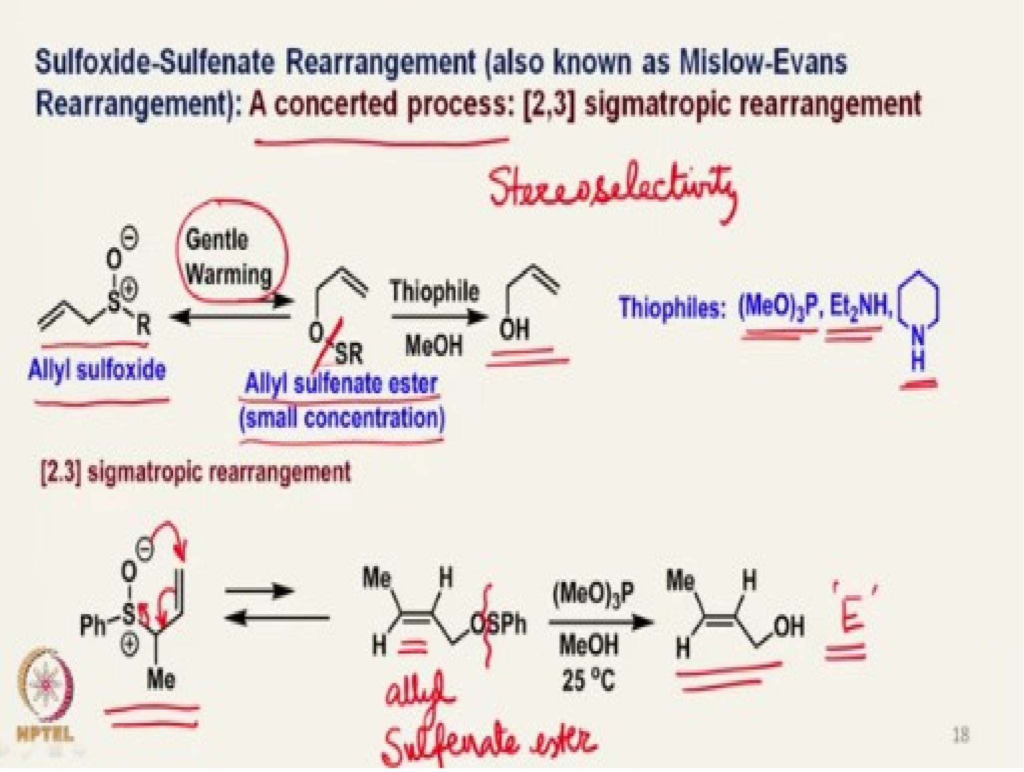

Sulfoxide-Sulfenate Rearrangement (also known as Mislow-Evans Rearrangement): A concerted process: [2,3] sigmatropic rearrangement

Stereoselectivity

Allylic sulfoxide and which exists as in equilibrium with allyl sulfenate ester, a very small concentration of this is observed when you do a gentle warming here. So essentially this allylic sulfoxide and this allyl sulfenate esters they exist in equilibrium and when a thiophile in the methanol, for example thiophiles such as triethyl phosphate or diethylamine or even a secondary base like this which allows the cleavage of the oxygen sulphur bond to form the allylic alcohol.

This is an example of 2,3 sigmatropic rearrangement which I will discuss in detail in a short while. However it is important to know that this particular process, this entire process is a concerted process and therefore there is huge a possibility of observing stereo selectivity in these reactions. And that is exactly why this reaction has become very popular. Now as one example I am showing here.

For example one typical example is phenyl sulfoxide base reaction which now gives essentially like this, that you have this coming like this and coming like this and coming like this. And you get the corresponding sulfenate ester, but this sulfonate ester is allyl sulfonate ester. So and then of course the cleavage with the thiophile you go to the corresponding and this is an E allylic alcohol.

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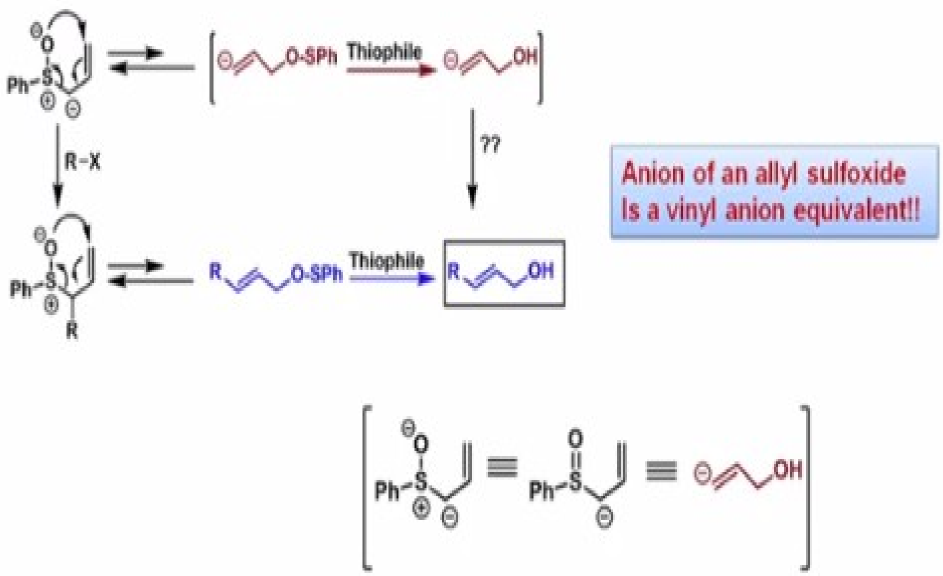

Anion of an allyl sulfoxide
Is a vinyl anion equivalent!!

Now we can do a lot of interesting reactions with this allyl sulfoxide sulfenate rearrangement reaction. For example if we take this allyl sulfoxide we can imagine that this will be in equilibrium with allyl sulfenate ester, of course without anion here, without anion here and if we react with the thiophile then we get the corresponding allyl alcohol of course without anion. On the other hand hypothetically if we think that we generate an anion at this position here alpha to the sulfoxide which is relatively easy to generate.

Because; this proton here would be acidic because it is next to the sulfoxide and also next to the double bond. And therefore we can generate this anion and hypothetically we can think that this particular allyl sulfoxide anion will be in equilibrium with the allyl sulfenate ester with a vinyl anion and when it reacts with the thiophile it can lead to the corresponding allyl alcohol with an vinyl anion at this particular position.

And if we treat with an electrophile like $R^+$or a source of $R^+$, then of course we can get the corresponding allyl alcohol where the R group is attached to the vinyl position. So this is all hypothetically, but in practice what one can do is to generate this anion here and react with an electrophile such as R-X, R can be like any alkyl group and X is a leaving group, then we can generate a carbon R bond here which then of course will be in equilibrium with this particular allyl sulfenate ester.

And this upon treatment with the thiophile should give this particular allyl alcohol having an R substitution. So basically what we are trying to do is to convert an allyl sulfoxide into an allylic alcohol within substitution here via basically going through a vinyl anion equivalent of this type. So what does it mean that this allyl sulfoxide, which we can write it like this and the corresponding anion which we can easily generate.

We can write the same allyl sulfoxide with an anion as like this and this allyl sulfoxide anion is basically equivalent of this vinyl anion type and such anion equivalents or vinyl anion equivalents have been utilized in organic synthesis very much.

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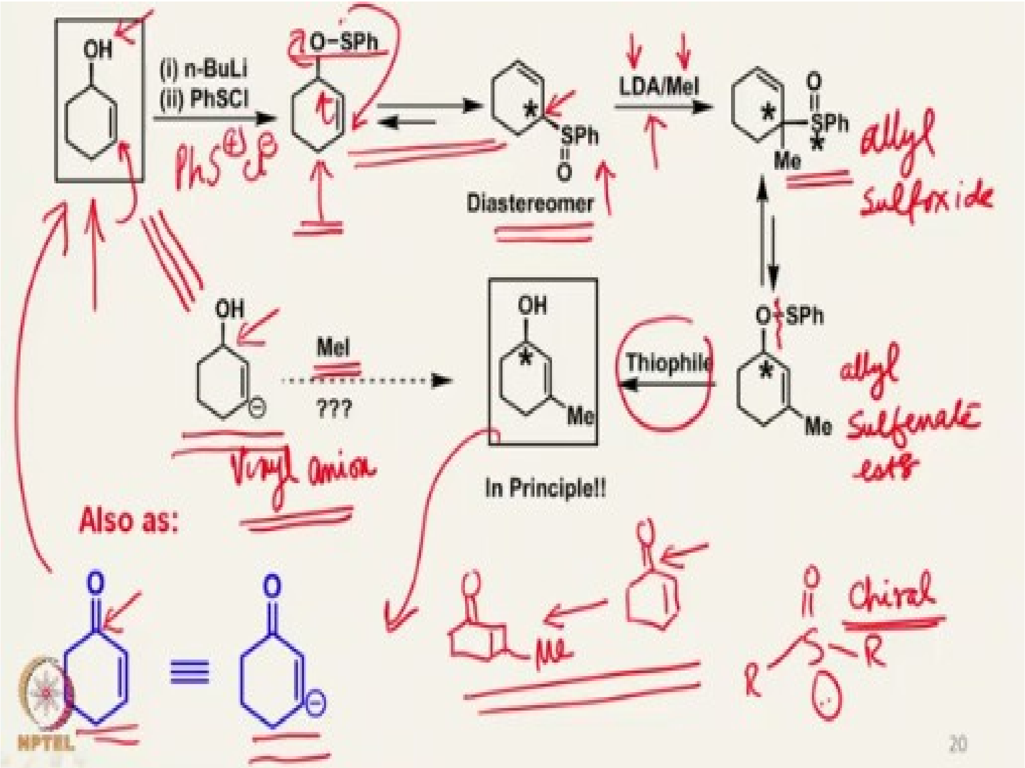

So one can carry out such reactions and one of the examples which I have shown here is of course you start with allyl alcohol, you deprotonate the OH group here by butyl lithium and react with the phenyl SCl where you have a source of phenyl S$^+$ and of course Cl$^-$ this is the electrophile. So the anion form here reacts with the sulfur to form this OS phenyl which is itself is allyl sulfenate ester.

Now this allyl sulfenate ester will be in equilibrium with the allyl sulfoxide. But now this is the sulfenate ester and this is the sulfoxide, therefore this reaction will occur in this fashion to form the sulfoxide. Now this center of course, now is asymmetric center and you can do the deprotonation of this proton with LDA and say for example you add an electrophile such as methyl iodide.

And then one can form this sulfoxide which is substituted with a methyl group adjacent to the sulfoxide center. Again this will be an equilibrium this is allyl sulfoxide and this is allyl sulfenate ester, again this equilibrium will be more in this for a favor rather than in this favor but when the thiophile is added to it the cleavage of the oxygen sulfur bond takes place and you get this particular allyl alcohol.

So now what we have done is we have started with this allyl alcohol which was not having a substitution at this center, but we made the sulfenate ester here, allyl sulfenate ester which was in equilibrium with the allyl sulfoxide. Now we have generated an acidic proton alpha to the sulfoxide did the deprotonation here, you used methyl iodide as an electrophile but one can use any other electrophile.

You make another sulfoxide which then is in equilibrium with the allyl sulfonate ester and thiophile cleavage and then you get the methyl. So essentially what we have done is this particular compound is we have made it as an equivalent of an anion which is a vinyl anion, so basically it is a vinyl and ion equivalent and to which we have added the methyl iodide. We can also do is after we have done this particular set of reactions one can start with even enone.

And essentially what we are saying is it is an equivalent of a vinyl anion equivalent. That means we can reduce this alpha beta unsaturated ketone to the corresponding allylic alcohol and we can oxidize this allylic alcohol to the corresponding methyl here. So that means we have started with a substrate of this kind reduce it to the corresponding alcohol, allylic alcohol then carry out this allyl sulfoxide sulfenate rearrangements then finally oxidize to go to this.

So this indicates that, through this process we are having two different types of equivalence, one is vinyl anion equivalent of this kind with a hydroxy grouping here and the other is this vinyl anion equivalent which is of an enone. Now we will take up some other aspects of this particular reaction later on in the next class because we can also carry out such reactions in an enantiomeric fashion.

Particularly when we know that a sulfoxide can exist if the two groups are different and then of course you have a lone pair of electron here extra. So this can be made chiral and if it is made as a chiral substrate then one can carry out such reactions and we have to see how the diastereoselectivity occurs. So we will take up the remaining part of the sulfoxide sulfenate rearrangement next time and I hope that you will be able to go through these and see the references that I have mentioned and be prepared for the next class thank you.