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

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Lecture-05
Organoselenium chemistry and SeO2 based oxidations

Hello everyone, I hope that you had a chance to go through the lectures that I gave last time. And you were able to go through the Swern oxidation and the Pummerer reaction that we discussed using sulfur compounds namely sulfoxides and also with selenoxides. So, in today's lecture what I am going to describe is oxidations using organo selenium compounds and also selenium dioxide. But first briefly we will have a recap of what we did last time in a very short while?

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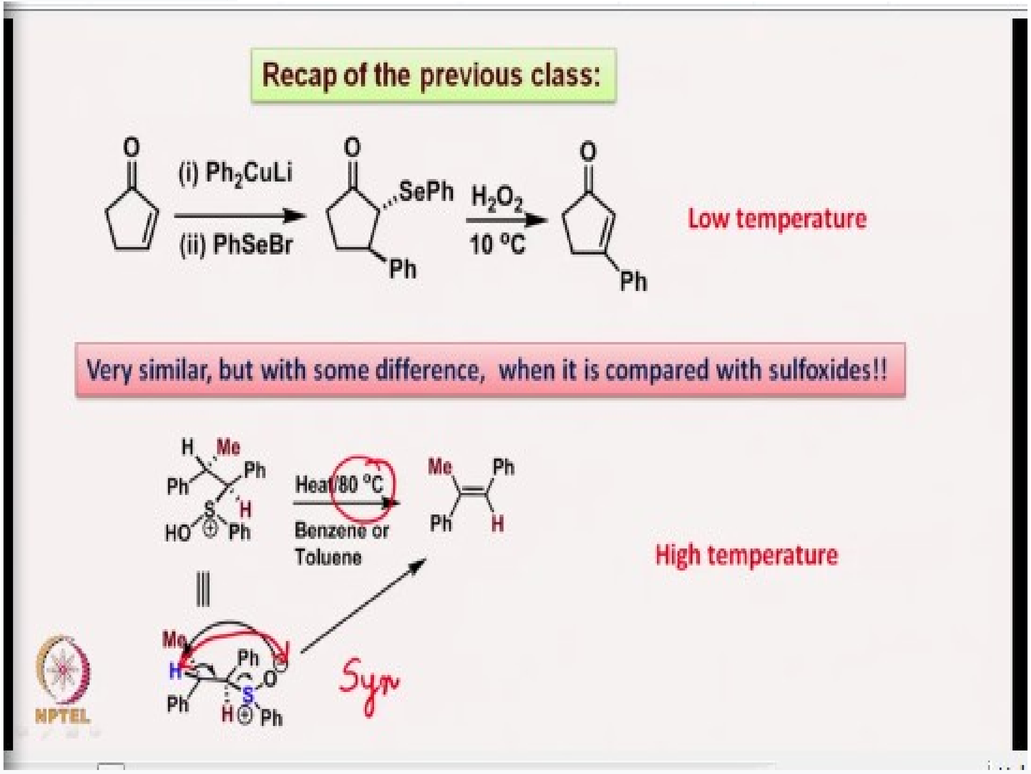
Recap of the previous class:

Low temperature

Very similar, but with some difference, when it is compared with sulfoxides!!

High temperature

For example what we did was we took an enone, say for example cyclopentenone. And when we did the cuprate addition and then trapped the enolate with the selenium electrophile, we got this phenyl and selenophenyl substrate compound. An intermediate in a trans fashion which upon oxidation led to the elimination of selenoxide. Now this selenoxide elimination is done at relatively low temperature like for example 10 degrees.

And on the other hand very similar but with some difference the use of sulfoxide is observed, that is when you take a sulfoxide of this type. The example that I have mentioned last time, when it undergoes an elimination it has to be a syn elimination because for compound to undergo syn elimination the sulfoxide here. This particular sulfoxide and hydrogen that is supposed to eliminate, this hydrogen here and the sulfoxide they have to be syn to each other and then the elimination occurs.

Now this particular sulfoxide elimination takes place at a relatively high temperature as you can see here, approximately 80 degrees which is the boiling point of benzene. So, the difference between the two of them is the temperature and therefore many a times selenoxide is preferred over sulfoxide eliminations. At the same time we would also look at the Pummerer rearrangement and also combine the two in the next slide.

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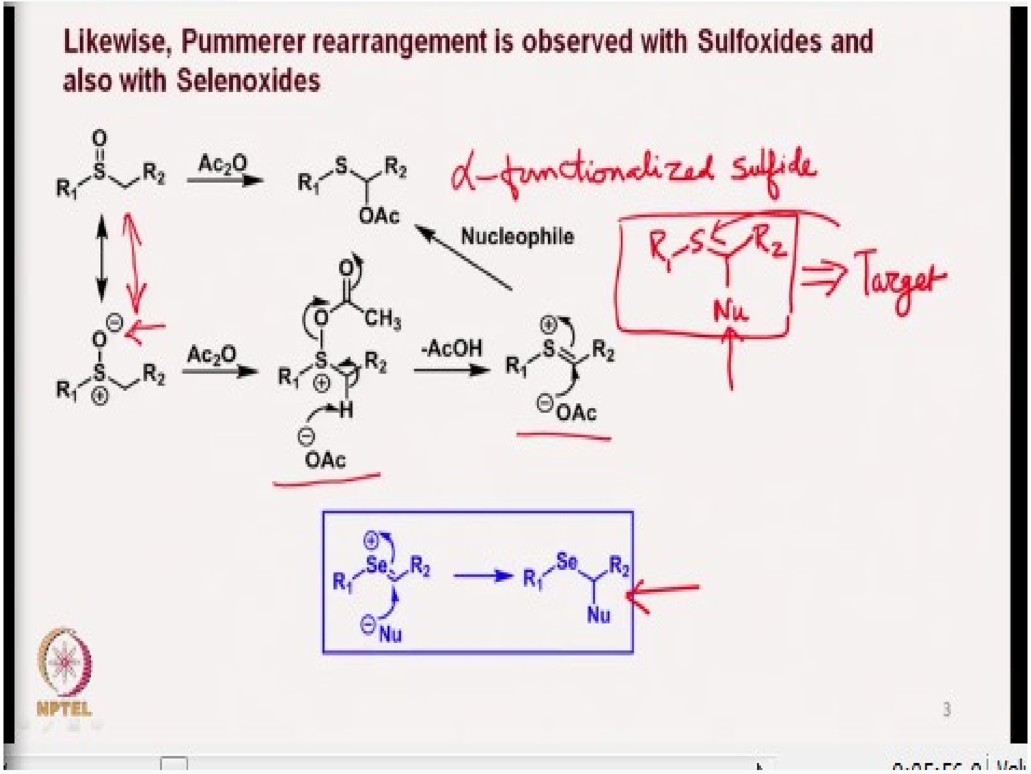

Likewise, Pummerer rearrangement is observed with Sulfoxides and also with Selenoxides

For example the Pummerer rearrangement which is observed with sulfoxides is also observed with selenoxide. So, I will not spend much time on it because we did it last time nevertheless the sulfoxide here, for example reacts with an acetic anhydride. And therefore one can write a resonance structure of the sulfoxide in this fashion here. And the nucleophilic oxygen here reacts with the electrophilic acetic anhydride to form this intermediate.

From where the acetate ion picks up the proton from here and that allows the elimination to take place to form this particular sulfonium ion and this sulfonium ion then is reacted with a nucleophile, in this particular case acetate is the nucleophile. So, when the reaction occurs you get an alpha acetoxy sulphide or say alpha functionalized sulfide. So, this is a very important substrate.

Because one can carry out the preparation of a number of such sulfides which have different kinds of nucleophiles attached. And now depending on the chemistry that one can think about of this sulfide one can prepare a number of important target molecules. So, this kind of sulfoxide based Pummerer rearrangement followed by nucleophilic attack. As well as selenium based

Pummerer rearrangement followed by nucleophilic attack is an important development that we discussed last time.

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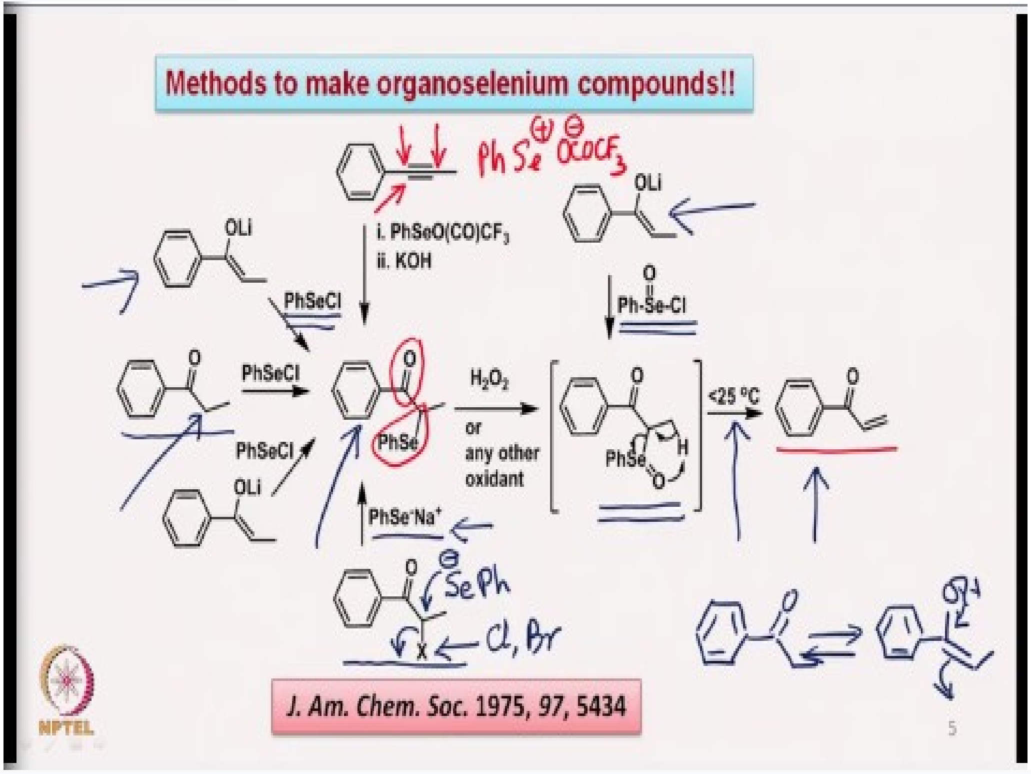

Methods to make organoselenium compounds!!

J. Am. Chem. Soc. 1975, 97, 5434

Now what are the ways to make organo selenium compounds, one is of course as shown here that one can take acetylene, for example phenyl methyl acetylene. And if one uses phenyl seleno tri fluoroacetate then you basically what you have is a source of phenyl S e $^+$. And of course you have $OCOCF_3^-$ as a leaving group. When this triple bond reacts with the selenium, it reacts in a markovnikov fashion.

And therefore the positive charge is formed on this particular carbon atom and the selenium comes on to this carbon atom. And then potassium hydroxide attaches to this end of the triple bond and finally the carbonyl groups comes in here and the selenide comes in here. So, this is one of the easier ways of getting a selenium compound adjacent to a ketone starting from a triple bond. How if one carries out oxidation or a with hydrogen peroxide or any other oxidant?

We can easily make the corresponding selenoxide which undergoes elimination to form this alpha beta unsaturated ketone. Alternatively one can also take the enolate of this type, this kind enolate and directly treat with this particular selenoyl chloride and get the corresponding selenoxide here directly without the use of any oxidizing agent, which upon as you can see that you require only lower than 25 degrees temperature to let the compound undergo selenoxide elimination and the same substrate is formed readily (08:10).

Now we can take the similar enolate and react with selenyl chloride instead of selenoyl chloride. And then introduce and make the selenide which of course again you can go via the same sequence of reactions which we saw earlier to form this particular enone. One can also take this ketone instead of the enolate and treat with the phenyl Se Cl phenyl selenyl chloride.

This particular substrate is actually existing like for example as a enol and this enol will then react as a nucleophile at this end of the double bond to introduce selenide at this particular carbon atom. And then one can carry out the same sequence of reaction to form the alpha beta unsaturated ketone. This reaction here is from alpha halo. For example here one can take chlorine or bromine any such leaving group and then have a nucleophilic selenide here.

For example sodium phenyl selenide at this stage here which can directly attack the selenium phenyl, the selenide here can directly attack at this and let the halide go and one can form the corresponding alpha seleno ketone which gives under the same conditions alpha beta unsaturated ketone. So, these are various ways by which one can carry out the reactions of introducing selenium bond or selenium atom or seleno group at the carbon atom of organic substrates. Now the mildness of the procedure is very much justified by the following examples.

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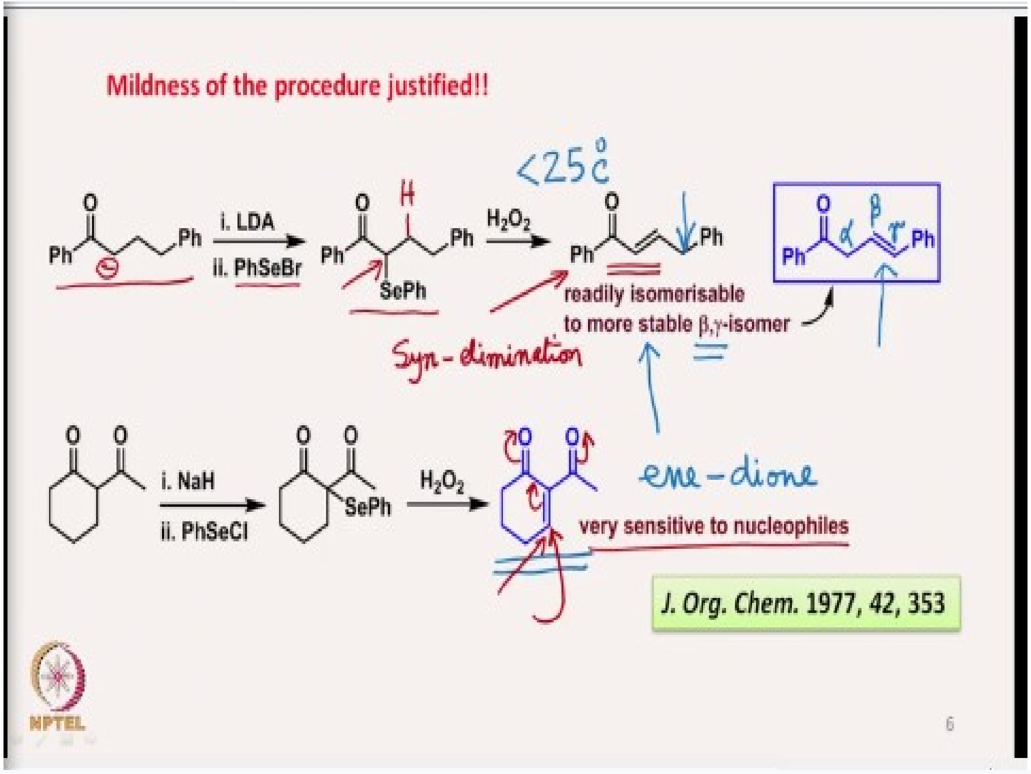

Mildness of the procedure justified!!

J. Org. Chem. 1977, 42, 353

For example if one takes this kind of substrate here which now we can use LDA and react with phenyl Se bromide here for example as a selenium source. So, obviously you will first generate an anion here with the LDA which is lithium di isopropyl amide. And react with the phenyl SeBr to introduced the Se phenyl group here, which upon oxidation with hydrogen peroxide will allow the elimination, of course in a syn fashion, the syn elimination will occur.

Syn elimination to form this particular compound, as one can expect that we have a double bond which is in conjugation with the ketone. And of course this will first form because selenide was present at this particular carbon atom. However this particular compound can also undergo easy elimination on this side or isomerization on this side. It can undergo an isomerization on this side because here now the double bond is in conjugation with the phenyl ring.

So, this particular substrate is very easily isomerizable to the more stable beta gamma, so this is the alpha position, and this is the beta position and this is the gamma position. So, one can do such a isomerization if one needs it. However the mildness of the procedure, that means this particular elimination takes place as I mentioned earlier below 25 degrees centigrade. So, such a temperature gives mostly this particular substrate easily.

But if the temperature is increased then one will isomerize to the beta gamma isomer, so this is the mildness of the procedure which is justified. Now another substrate which is very interesting is this enedione this is an enedione. Now this enedione as one can see easily that this can undergo very easy attack by a nucleophile on to this particular carbon atom.

Mainly because there are two electron withdrawing groups which are present and they are in conjugation with one double bond. So, one double bond and two electron withdrawing groups makes this particular carbon atom here very, very electrophilic, this carbon atom is highly electrophilic. And therefore very sensitive to the nucleophiles present in the reaction medium, so if the reaction temperature is relatively high then such nucleophilic attacks will easily happen during the reaction.

So, the mildness of the procedure that means the elimination of the selenoxide occurs at less than 25 degrees centigrade. And therefore formation of such a enedione which is sensitive to nucleophiles can be readily prepared.

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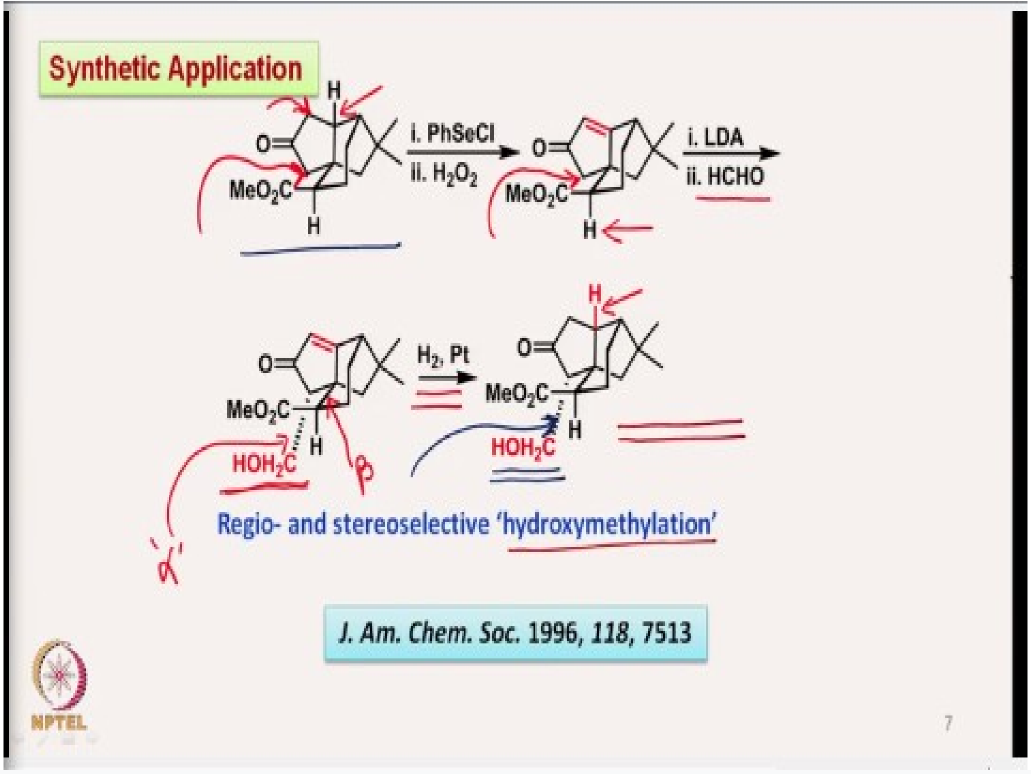

Synthetic Application

Regio- and stereoselective 'hydroxymethylation'

J. Am. Chem. Soc. 1996, *118*, 7513

Now what are the synthetic applications? For example a good synthetic application of it is in the preparation of such interesting and of course complicated substrate, final product. This requires a regio and stereoselective hydroxymethylation. This is the hydroxymethylated group, the hydroxymethyl group that has been introduced on to this particular substrate. Now if one starts with this particular tricyclic ketone, one can easily see that if one wants to introduce a hydroxymethyl group at this particular carbon atom.

At this carbon atom here then one also has to see that this carbon is also which is alpha to the carbonyl group available for functionalization. Therefore one has to do something to kind of protect this particular carbon atom. Now if one can look at it this carbon atom here is sterically more hindered because of this group here or this ring here. And therefore anything that one has to do will occur here.

So, one of the ways by which this reaction was carried out and which is reported in 1996 in the journal of American chemical society, is that first the selenium was introduced at this carbon which is what is required to be done to introduce a double bond here, and once the double bond is introduced this side of the carbonyl group is now blocked, there is no proton that is available to be removed.

And therefore once this particular enone is formed the LDA lithium diisopropylamide would deprotonate this proton here. This proton which is alpha to the carbonyl group and then with the help of an electrophile such as formaldehyde one can introduce the CH_2OH group. Now one can ask this question here that this particular proton is alpha to the carbonyl group, at the same time this particular hydrogen is alpha to the ester group also.

But this proton is next to a carbonyl group whereas this proton is next to an ester group and therefore the acidity of the proton here is higher than the acidity of this proton. Therefore deprotonation will occur preferentially at this carbon atom and then one introduces the CH_2 OH group. And since this particular C-C bond or this entire 6 member ring here is beta oriented and therefore the CH_2OH group is alpha introduced.

Once this addition or the substitution of the CH_2OH group has occurred at the alpha position next to the carbonyl group. Then the hydrogenation is carried out with the hydrogen and platinum here to saturate the double bond and get back the hydrogen here which is what was present in the beginning. So, this is a very interesting application of a regio and stereo selective hydroxy methylation. Regio because you are carrying out the reaction on one side of the carbonyl group here, and stereo because you are getting alpha hydroxymethylation.

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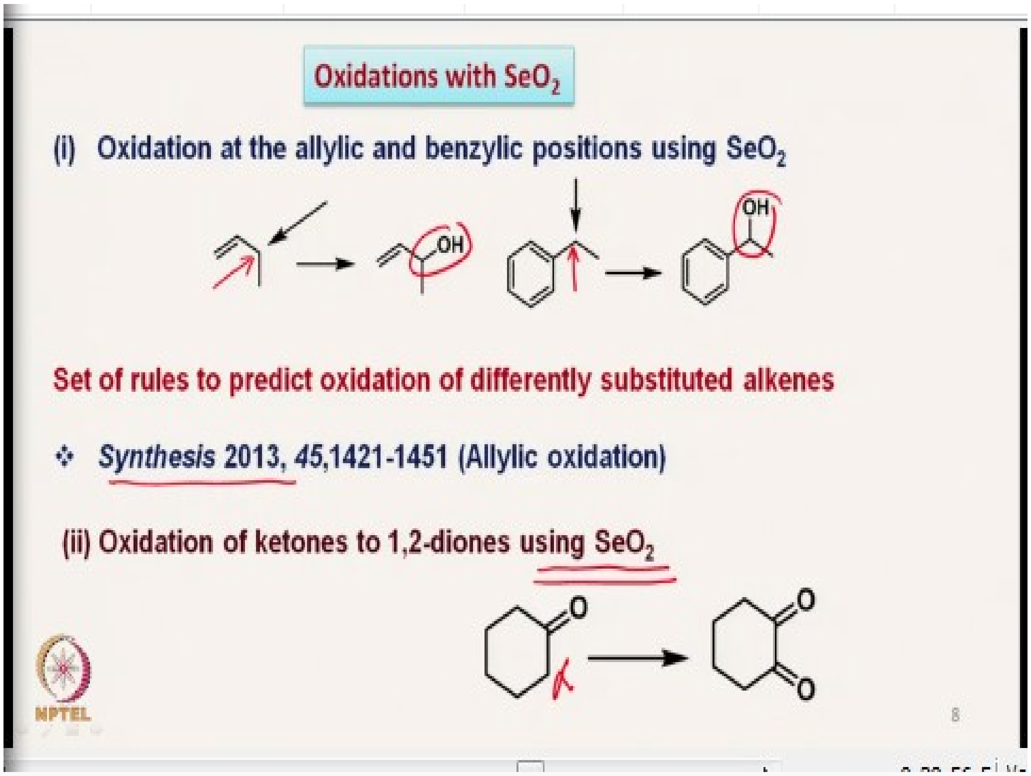

Oxidations with SeO_2

(i) Oxidation at the allylic and benzylic positions using SeO_2

Set of rules to predict oxidation of differently substituted alkenes

- *Synthesis* 2013, *45*,1421-1451 (Allylic oxidation)

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

Now the next sub class of oxidations that we are going to look at is with oxidations of organic substrates using selenium dioxide. Now there are two things that we are going to look at, one is of course oxidation at the allylic and benzylic positions with selenium dioxide. As I have shown here that you can carry out the oxidation at allylic position here or at the benzylic position here.

Now what are the ways by which we can directly introduce a hydroxy group here? One way of doing it is with selenium dioxide. Now there is a very interesting review which is published in 2013 in the journal synthesis on allylic oxidation using selenium dioxide. There is another way of introducing a carbonyl group alpha to the ketones which is also by using selenium dioxide, so we will take up these transformations.

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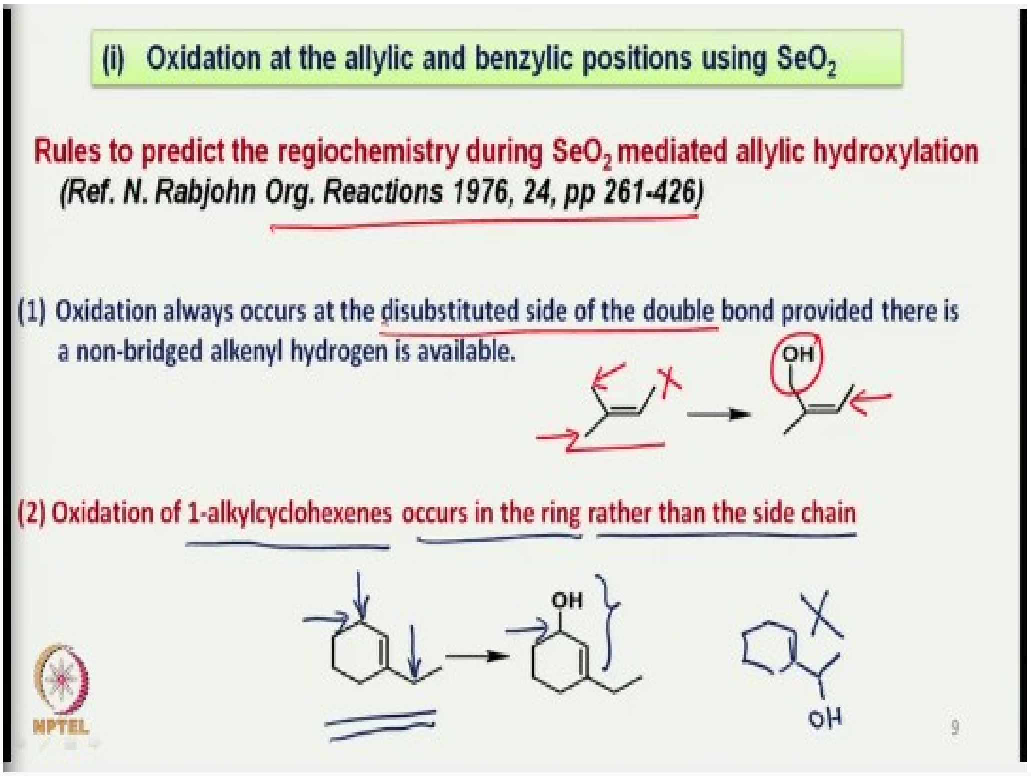

(i) Oxidation at the allylic and benzylic positions using SeO$_2$

Rules to predict the regiochemistry during SeO$_2$ mediated allylic hydroxylation

(Ref. N. Rabjohn Org. Reactions 1976, 24, pp 261-426)

(1) Oxidation always occurs at the disubstituted side of the double bond provided there is a non-bridged alkenyl hydrogen is available.

(2) Oxidation of 1-alkylcyclohexenes occurs in the ring rather than the side chain

Now one by one, the first one that we take is oxidation at the allylic and benzylic positions using selenium dioxide. Now there are certain rules which are published in this organic reactions in 1976 which is what is generally observed when the reactions are carried out. For example when we have an oxidation to carry out on a olefin of this type which has three substitutions on the double bond. So, the first rule says oxidation always occurs at the disubstituted site of the double bond provided there is non bridged alkenyl hydrogen available.

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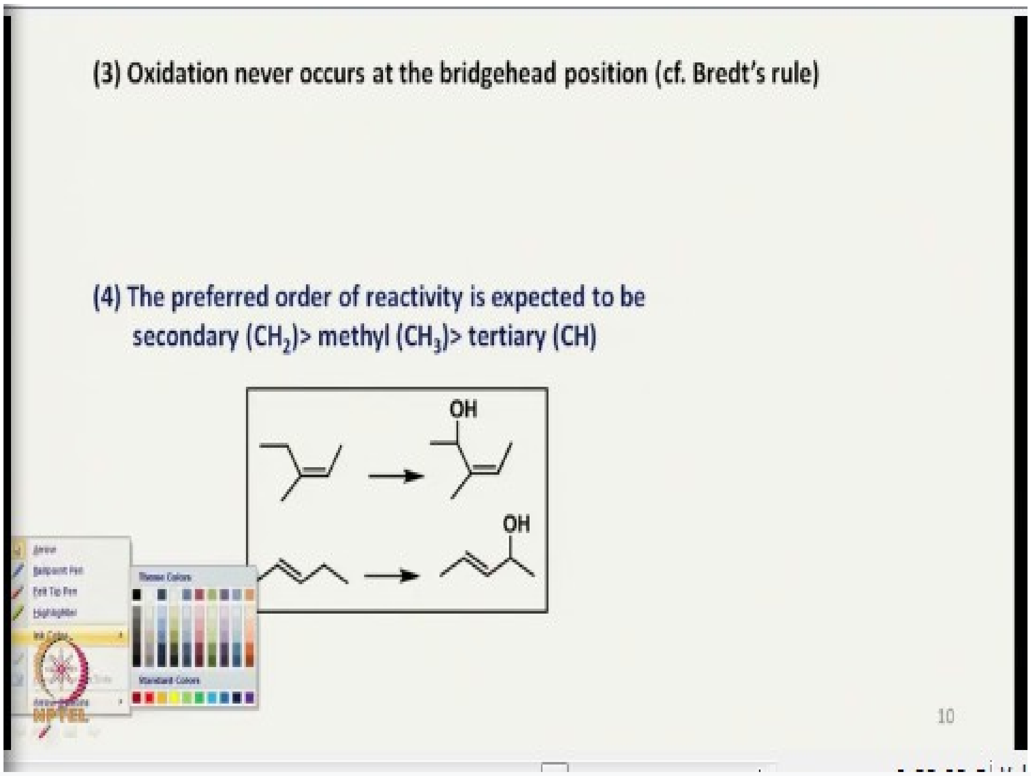

(3) Oxidation never occurs at the bridgehead position (cf. Bredt's rule)

(4) The preferred order of reactivity is expected to be secondary (CH_2)> methyl (CH_3)> tertiary (CH)

So, oxidation occurs either at this side of the double bond or on this side of the double bond but not on this side. That means the oxidation always occurs at the disubstituted side of the double bond. Obviously when we think about it, we have to think that the oxidation occurs to give hydroxy group attachment. In many cases trans to this particular methyl group for steric reason. Oxidation of 1 alkylcyclohexenes, for example here of this kind the oxidation occurs in the ring rather than on the side chain.

That means oxidation occurs here rather than taking place onto this particular carbon atom. So, that means this is not formed, so it is always on the ring that is what the introduction of the hydroxy group occurs.

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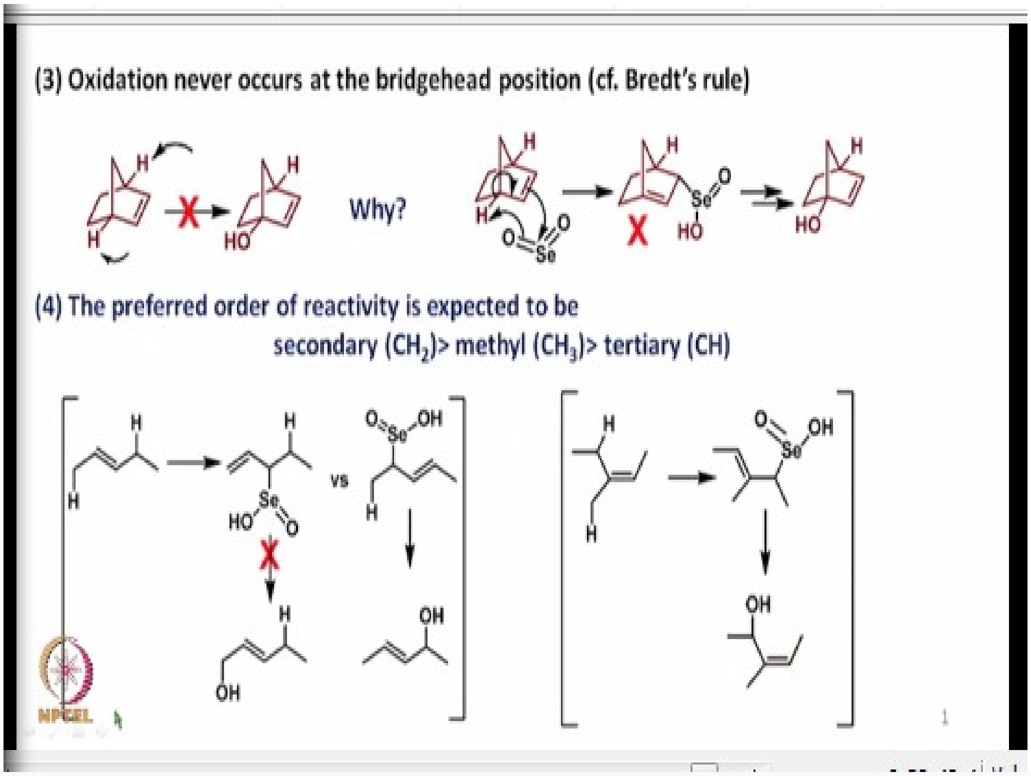

(3) Oxidation never occurs at the bridgehead position (cf. Bredt's rule)

Why?

(4) The preferred order of reactivity is expected to be

secondary (CH_2)> methyl (CH_3)> tertiary (CH)

According to the third rule oxidation never occurs at the bridgehead position and that is because of the Bredt's rule. If we take a compound of this kind which has two bridgehead allylic hydrogens which are symmetrical, we expect the oxidation with selenium dioxide to give this particular allylic hydroxy compound. But since this hydroxy group is at the bridgehead position, we do not get this molecule.

That is because when selenium dioxide reacts with this bridgehead based compound. Then what we expect is to form a selenium intermediate of this type where carbon selenium bond has formed between this carbon and the selenium followed by the removal of a proton from here which leads to the formation of a double bond at the bridgehead. Now this particular selenium intermediate then undergoes rearrangement to allow the introduction of the hydroxy group at the bridgehead position and the double bond is returned to the original position.

That means this particular compound when it undergoes oxidation with selenium dioxide, the allylic hydrogen is replaced by the hydroxy group at the bridgehead position. But because the intermediate that is formed has a double bond at the bridgehead position which according to the Bredt's rule it is not allowed. And therefore the oxidation never gives this type of allylic hydroxy group where there is hydroxy group at the bridgehead position.

According to the fourth rule the preferred order of reactivity is that the secondary allylic hydrogen that is of CH_2 type is oxidized over say allylic methyl hydrogen which is oxidized preferentially over allylic tertiary hydrogen. Say if we take an example of this kind where there are two possibilities this is allylic secondary hydrogen and this is allylic methyl hydrogen, if this gets oxidized, we get the particular hydroxy group at this position.

And if this position gets oxidized then we get this allylic hydroxyl molecule. Now if we see the intermediates that are formed then we expect that based on similar type of mechanistic consideration as we discussed above. We expect the formation of this selenium intermediate in which as we can see that the double bond is at the terminal position. And that eventually leads to the hydroxy group at the terminal position.

Whereas if we take this secondary hydrogen into consideration then the intermediate involving a selenium species that is formed is this particular intermediate. In which as one can see that the double bond is 1, 2 di substituted and that leads to the formation of the allylic hydroxy group like this. Now between the two selenium intermediates one can easily see that this particular selenium intermediate is more stable than this.

And therefore the formation of the allylic hydroxy group involving a secondary allylic hydrogen is allowed and this does not form. In a similar fashion if we take another example in which we have now 3 possibilities. There are 2 methyl allyl hydrogens and one secondary allyl hydrogen. According to the first rule the more substituted side of the double bond is preferentially oxidized than the less substituted side.

Now these are the two more substituted sides of the double bond and between the two of them this is secondary CH_2 which is allylic. And this is the methyl allylic hydrogen obviously according to the fourth rule that we discussed just now. Oxidation here occurs and that happens proceeding via this particular selenium intermediate which is obviously tri-substituted double bond.

And therefore that leads to the formation of this particular allylic hydroxy compound. And I think you should read these, whatever I have told today and we will discuss more aspects of this selenium dioxide base oxidation next time, thank you.