Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Synthesis
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Module No # 04
Lecture No # 19
Asymmetric α-hydroxylations Using Oxaziridine Based Reactions

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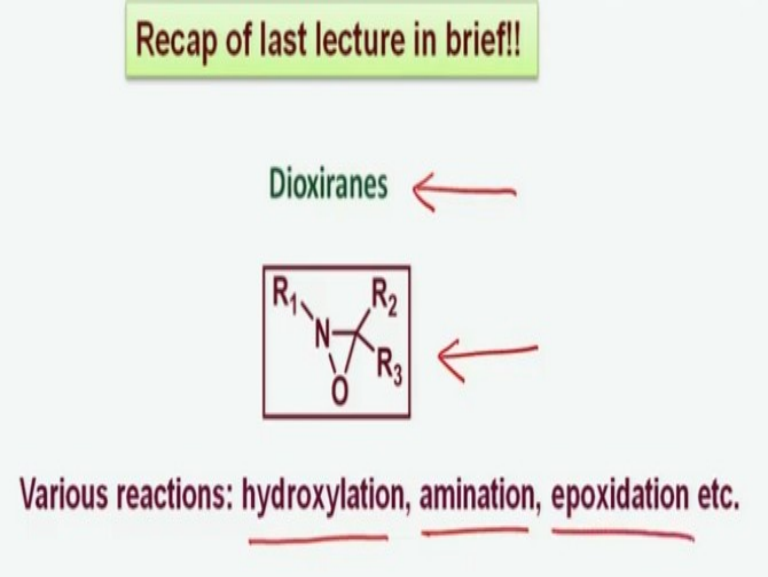

Hello everyone welcome, to today's class so what we discussed last time was briefly the dioxiranes where we discussed the mechanism and also the Shi's oxidation etc. And then we started looking at the transfer of oxygen or nitrogen via oxaziridines. And we discuss that how reaction such as hydroxylation, amination, epoxidation etc., can be carried out using oxaziridines. And different kinds of oxaziridine that; can be prepared and depending on the substituents that are present on the oxaziridines.

There is a possibility of the maneuvering or selectively doing nitrogen or oxygen as electrophiles transferring them to the nucleophilic substrate such as enolates or enamines, enol silyl ethers, simple double bond. And like that electron rich molecules, obviously electron deficient olefins do not react easily to such with oxaziridines. And now go further and see how we can make use of these in chiral fashions.

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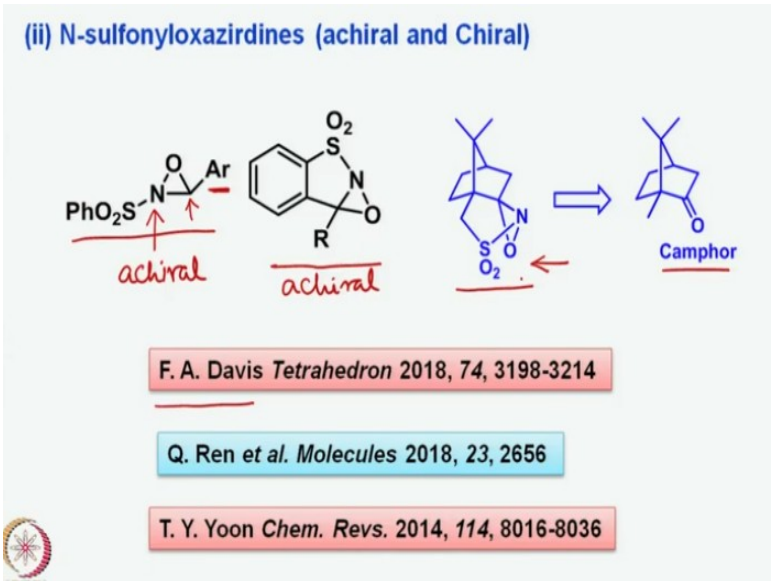

So what are the N-sulfonyloxazirdines as I discussed last time that preferentially people use N-sulfonlyoxazirdines more popular than other oxazirdines. And one of the most useful oxazirdines is this type where you have an aromatic ring onto the carbon of the oxazirdines and N- sulfonlyl group which is present here on the nitrogen. Now this is an achiral oxazirdines and this can be utilized for reactions with either achiral substrates or even chiral substrates.

So one can make from the chiral substrates enolates or any of that kind enamines, enolates, enol silyl ether and then react with this and transfer oxygen on to the molecule. In a similar fashion even this type of N-sulfonyloxazirdines has also been utilized it. Now these are both achiral molecules whereas one of the most highly cited and used substrates from Camphor is this particular oxazirdines which is very useful and leads to very high optical induction or asymmetric induction.

And it has been popularized by Franklin Davis as I mentioned earlier so you can easily start from the Camphor and prepare these highly reactive and sterically hindered Camphor based oxazirdines.

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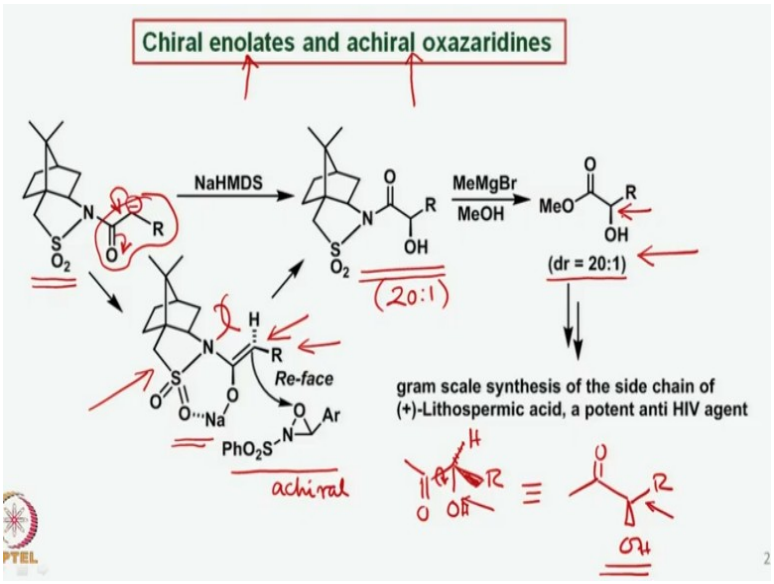

Now one can prepare chiral enolates that means enolates from chiral substrates and you can use a chiral oxazirdines I mentioned to you that oxazirdines of this type which is achiral can be utilized for transferring oxygen to a chiral enolate. So this is the path of the enolate which is formed from these substrates which is again Camphor based substrate. So as you can see that if there is nitrogen here and then SO_2 which is part of the Camphor based molecule. And then you generate or attached this particular part of a ketonic type of molecule.

Then there is a possibility of a deprotonation here this hydrogen can be deprotonated and you can make the corresponding enolate of this type and which can be like this. Now there is possibility of somewhat like this and since the large part of the molecule is on this side. Therefore the small group which is hydrogen goes back side. So this is a favored possibility of an enolate where the hydrogen the large group is coming towards us because the backside is having steric hindrance of this type.

So therefore the hydrogen goes backside and R group from this side. And now when the oxazirdines is reacted the reaction occurs from the lower side that means from the bottom side. The olefin is flat hydrogen is back side this path is back side and then this enolate and R, are cis to each other and the oxygen is transferred from the lower side and once oxygen is transferred from the lower side the geometry of the hydroxy groups comes in this fashion.

One can see very easily that you have here say you get a ketone here like this and the hydrogen is back side. So you have like this where the oxygen is coming below now if oxygen is coming below and if this is back side and the R group is in the front this can be rotated further and this can be equal to a ketone here and now we can imagine that we have we can remove this and redraw to see that this particular molecule is very similar to this.

So basically what is done is you rotate it here so that the R group which is coming towards us goes into the plane this is in the plane. If that happens then this hydroxy group which is in the plane will towards us that is how it is shown here. So basically the main thing that is happening is that enolate ion is formed in such a fashion that the R group which is the larger group is towards this side towards us and the small group goes behind.

Because at the back side there is a big steric hindrance due to this large Camphor based group Camphor based substituents. And that is how as you can see that the hydroxylation that has been introduced that has been the hydroxy group that has been introduced is having a chiral center at this stage. And if we hydrolyze this then we can get the corresponding alpha hydroxy ester for this diastereomer reaction which is shown is actually for this molecule and you can see that it is 20 is to 1. So only very small amount of the corresponding other enantiomer will form during this process.

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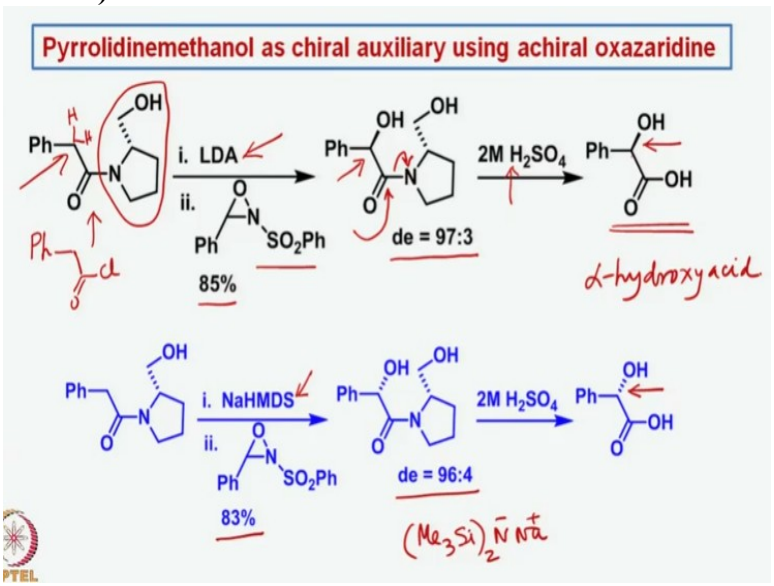

Now there is another pyrrolidinemethanol based chiral auxiliary that also has been used. Now this is the auxiliary in which this path is actually the chiral path and it is introduced with ketone like this. So one can easily prepare it say one can start with you can start with this and if one takes the corresponding chloride here then we can make this by taking this nitrogen based nucleophile to attack on to this acid halide.

Once this substrate is formed we can do the LDA that means deprotonation of this proton here there are 2 protons we can do the deprotonation and we can make the corresponding enolate. And then react it with this oxazirdines to introduce the hydroxy group here. So as you can see that if we take LDA lithium di-isopropyl amide you introduce the hydroxy group in this particular fashion with the enantiomeric induction being at this stage like this.

On the other hand the same substrate is taken and the base is sodium hexa methyl di silylamide actually it is like hexa-methyl silylamide that deprotonates again in the similar fashion. And it introduces the oxygen in a different way than the corresponding lithium diazopropylamide and both the cases the diastereomeric excess or diastereomeric ratio is very high than the 97 is to 3 and 96 is to 4. And the yield is also fairly good now how does this happen?

We should see that like in the case of lithium as a counter cation. When the deprotonation occurs when the deprotonation of this hydrogen occurs from here also oxygen of the OH is also deprotonated and we have the lithium here which is coordinating to both the oxygen's. And due

to this the lower path of the, because this is alpha oriented or it is a bottom of the double bond it is towards the lower path of the double bond.

Therefore the nucleophile attacks from the top side which is what is C, orientation? C means now we have something like S configuration we talk in the case of double bond in C configuration. So we have the top part if you can see that it is C configuration it is rotating in the anti-clock wise. So it is from the top the hydroxy group interacts and therefore what we get is this product.

On the other hand when the sodium's base is used then sodium is a counter cation and sodium is a counter cation which is not a very good in terms of chelating as much as lithium plus is there. Now we have also have enolate which is having this type of counter action where there is a sodium plus and here also the OH is deprotonated and you have a sodium plus. Now in comparison to lithium plus, the sodium plus, the anion is more separated and therefore there is a repulsion dipole repulsion.

And therefore the 2 anions as oppose to the lithium type of thing where you can have coordination to both the oxygen's. There is no possibility of such coordination with the sodium plus therefore there is dipole repulsion. And the molecule turns that his particular part of the auxiliary turns in such a fashion that now this is beta oriented. So this path and this path are away from each other and during the process where this was alpha it has now become beta.

So therefore the beta means the above part so the top part or the beta part is now blocked because of this particular group. And therefore the attack of the nucleophile occurs from the lower side that is alpha side and that leads to the formation of the alpha hydroxy group which is eventually leads to the alpha hydroxy acid.

What is done is that after the transfer of the oxygen as I showed you earlier you can hydrolyze this particular carbon nitrogen bond by means of 2 mole sulphuric acid 2 molar sulfuric acid. And then you can cleave it and get the corresponding acid so basically it is an alpha hydroxy acid which is formed in a chiral fashion by this use of auxiliary which is pyrrolidinemethanol chiral auxiliary and deprotonation and reaction with oxazirdines.

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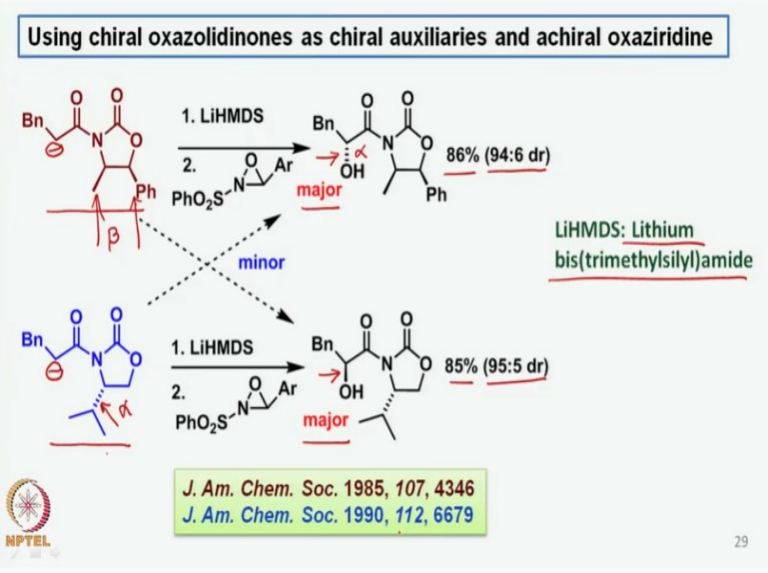

We can also look at the other auxiliary such as this oxazolidinones kind of substrates of these 2 types and you can use the lithium bis trimethylsilyl amide. We used earlier sodium bis trimethylsilyl amide and also use lithium and you can deprotonate here and once the deprotonation is done then of course the corresponding enolate reacts. Now since these 2 groups here are beta oriented therefore the hydroxy groups from the alpha side.

On the other hand if one takes this as alpha oriented substituent the group which is transfer comes from the beta side. So opposite to this side and as you can see the diastereomeric ratio is very large and yield is also good. Obviously this is the major product in both the cases and the minor products from here the minor product will be this one and from here the minor product will be this one. So we can control the reaction in such a fashion that we can get the major product depending on what kind of oxazolidinones we use it.

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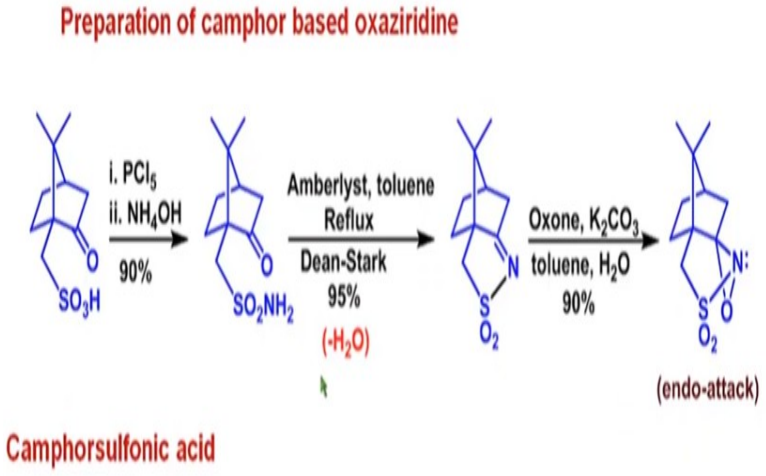

Now how do we make camphor based oxaziridine molecules which will be useful for reacting as chiral oxazirdines for introducing alpha hydroxy group next to a ketone or any other, oxidation.

We start with camphor sulfonic acid which looks like this and reacted with PCl_5 so that we get the corresponding sulfonyl chloride that is SO_2Cl. And then it is reacted with ammonium hydroxide so that we get the corresponding sulfonamide.

Now this sulfonamide is then heated in toluene in the presence of Amberlyst catalyst which is an acidic resin catalyst. And there is apparatus which is called a Dean-Stark apparatus which continuously removes the water from the reaction medium. It is required that we continuously siphon off the water from the reaction medium otherwise the product that is going to form that means if this amine here sulfonamide condenses with the carbonyl group here then we get this particular intermediate.

But then this particular intermediate and this Amberlyst catalyst condition can get protonated and further hydrolyzed and go back to the starting material or even it can go back to the sulfonic acid. And therefore water has to be continuously removed by the use of these Dean-Stark apparatus. And once this particular product is formed then this is reacted with oxone on the basic conditions.

Since there is a methyl group on the exo side therefore the oxidation of this emine path of the molecule occurs from the endo side that is from the lower side and then we get this reagent which has a complete endo attack of the oxygen. So this is how camphor based oxaziridines is prepared.

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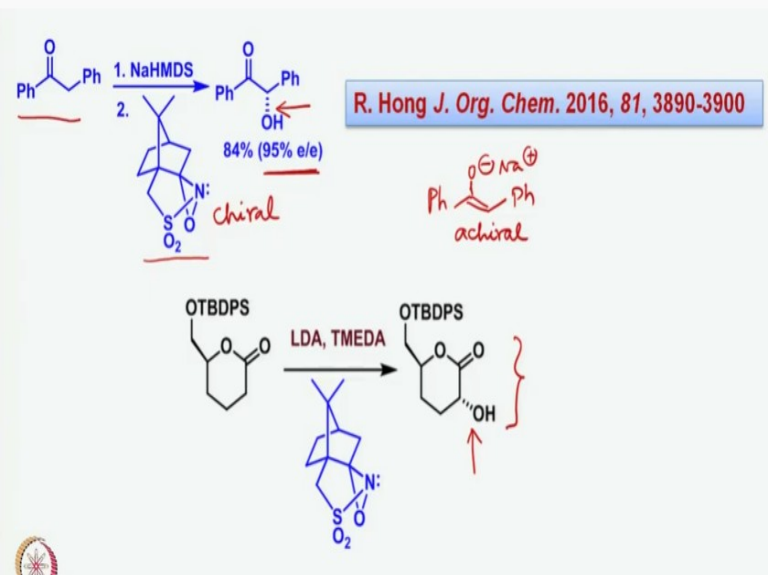

Now we can also see that this type of camphor based oxaziridines can be utilized that means before the introduction of the camphor based oxaziridines I had discussed the enolates to be formed from chiral auxiliary based molecules. Now what we are doing it is we have the substrate of this kind where enolate is formed from this achiral substrate. So if we can say for example you take this substrate this enolate here like this so this is achiral.

So we have achiral enolate that reacts with the chiral oxaziridines and the transfer of the hydroxy group occurs from the lower side and we get the 84% yield of molecule with 95% enantiomeric excess finally. In a similar fashion here also one can introduce the hydroxy group from chiral this

alpha side and can get the corresponding alpha hydroxy lactone here or the hydroxy ketone there with high enantiomeric purity.

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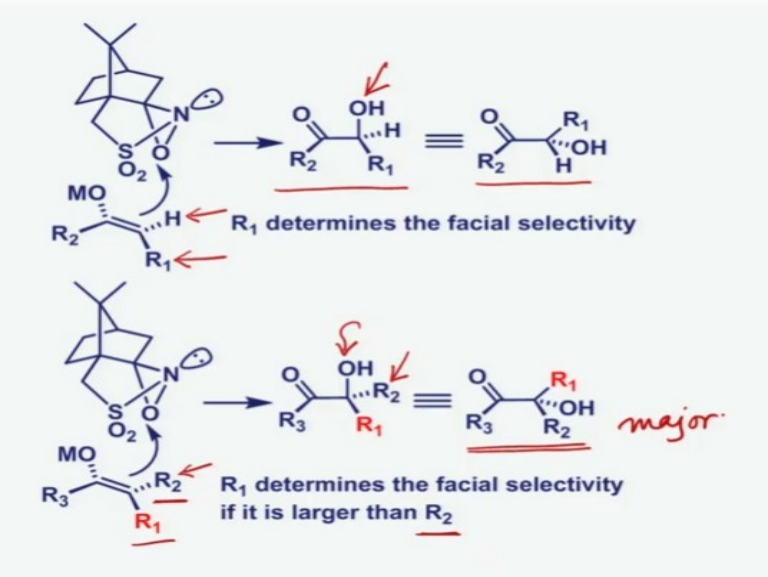

Now how does this happen? Why should, it happen in from the lower side as I mentioned earlier that the enolate attaches to the lower part of the oxaziridines with hydrogen group that is smaller than R1 group being back side and the larger group comes towards this side. And thus the oxygen is transferred from the top and that leads to formation of this molecule here where the hydroxy groups have come from the top as one can see that see that this is the same as this there may be just turn.

In such a fashion that R 1 group goes on the top the hydroxy group will come at the bottom. Now if we have a substrate like this when there is no hydrogen where there are 2 different substrates like R 1 and R 2. And if R 2 is smaller that means R1 is large then R 1 group will come towards us and between the 2 the smaller R 2 group will go on the back side. And accordingly the hydroxy group will come from the top when the smaller is on the back side. And we get the chiral molecule of having configuration of this kind as the major product.

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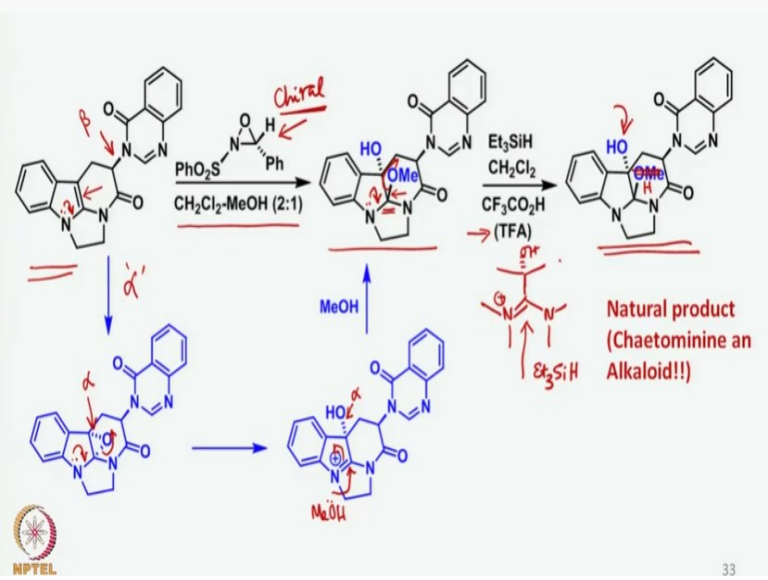

So you have a major product so we have seen now 2 types of things where we have one achiral oxygen oxaziridine is chiral oxaziridine. Now what can also be done is interestingly that the olefins can react with a molecule of this type here one can take even as a chiral substrate here. For example of this kind and when this is reacted with an olefin of this kind which is highly electron rich olefin is like an enamine.

What is formed under these conditions with dichloromethane and methanol is final product which is formed is basically this and this can be converted to the corresponding actually it should be hydrogen here. So what happens is the epoxidation takes place from the alpha side to form this alpha epoxide. Because this group which is the large group which is the beta therefore the double bond forms an epoxide and then this particular lone pair of electron pushes it out and opens up the epoxide to form this alpha hydroxy emmonium ion here to which methanol attacks.

So the methanol basically is attacking on to the emmonium ion here and this positive charge is utilized to form this where the emthoxy group has come from the beta side. Now under acetic conditions here trifluoroacetic acid this oxygen is lost and you can generate the similar type of emmonium ion. But then instead of that means we get this here I will not write the lower part of it. But then you have positive charge here and hydroxy group here and of course the remaining part.

Now this is the one that is reduced with tri ethyl silane it is a reducing agent and that introduces the hydrogen at this stage. So one can convert a molecule of this kind to a natural product which is of this type where there is hydrogen. And the hydroxy group has been introduced in a highly stereo selective fashion.

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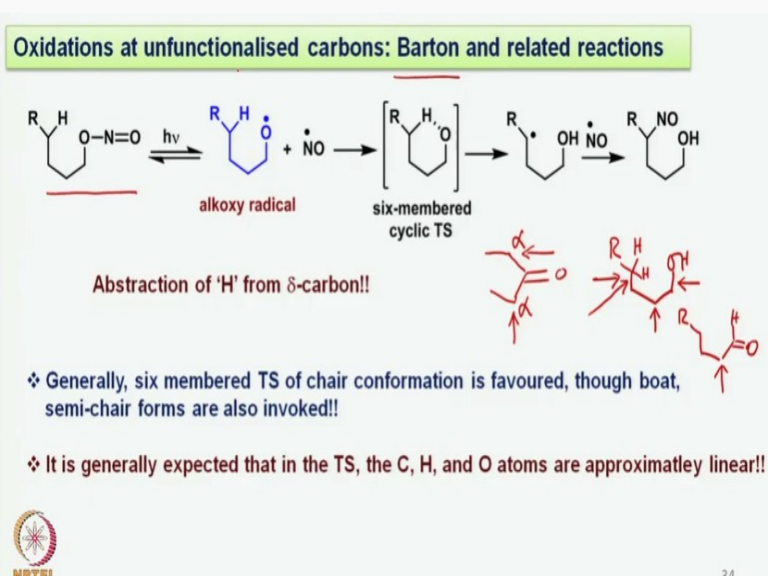

Now we will start with another interesting oxidation which is oxidation at the un-functionalized carbons. It is called as Barton reaction and then there are variations of a Barton reaction they are called different types of reagents are utilized and therefore we will group them in Barton and related reactions. Now what is un-functionalized carbon it is very easy for say you have a ketone and if this hydrogen which is alpha to the carbonyl group.

Or if we take a symmetrical substrate and both the alpha carbons are equally available so the alpha carbons are basically activated because of the carbonyl group. And therefore that is easy for functionalizing the alpha carbon. But if we have a substrate of somewhat like this we have a substrate where we have hydroxy group here and the hydrogen that we want to functionalize is away here.

If we want to functionalize this particular carbon atom then we can oxidize this to the corresponding aldehyde and then one can easily prepare the aldehyde of this type and you can functionalize here you have. But functionalizing here it is not that easy that is what has been done by DHR Barton who got the Noble prize in 1968. And he has shown how this type of nitrate esters can be utilized for the functionalization at un-functionalized or oxidation at un-functionalized carbon.

So we will take it up this particular part in the next class and in the mean while you can go through the oxaziridines and look at what are the advantages and disadvantages of that reagent thank you we will see you next time.