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

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Module No # 03
Lecture No # 12
Silver Based Oxidations: Prevost Reaction and Use of Fetizon's Reagent

Hello everyone I welcome you to today's lecture what we discussed last time about IBX based oxidation iodoxy benzoic acid based oxidations. I hope that you had the chance to go through that and understand what I mentioned in the class where not only we did the oxidation of alcohols to the corresponding carbonyl compounds. But we also discussed how alcohols can be converted to the corresponding enone or dienone and how the mechanism allow the conversions of ketones to the enone using IBX you know involving radical base mechanisms.

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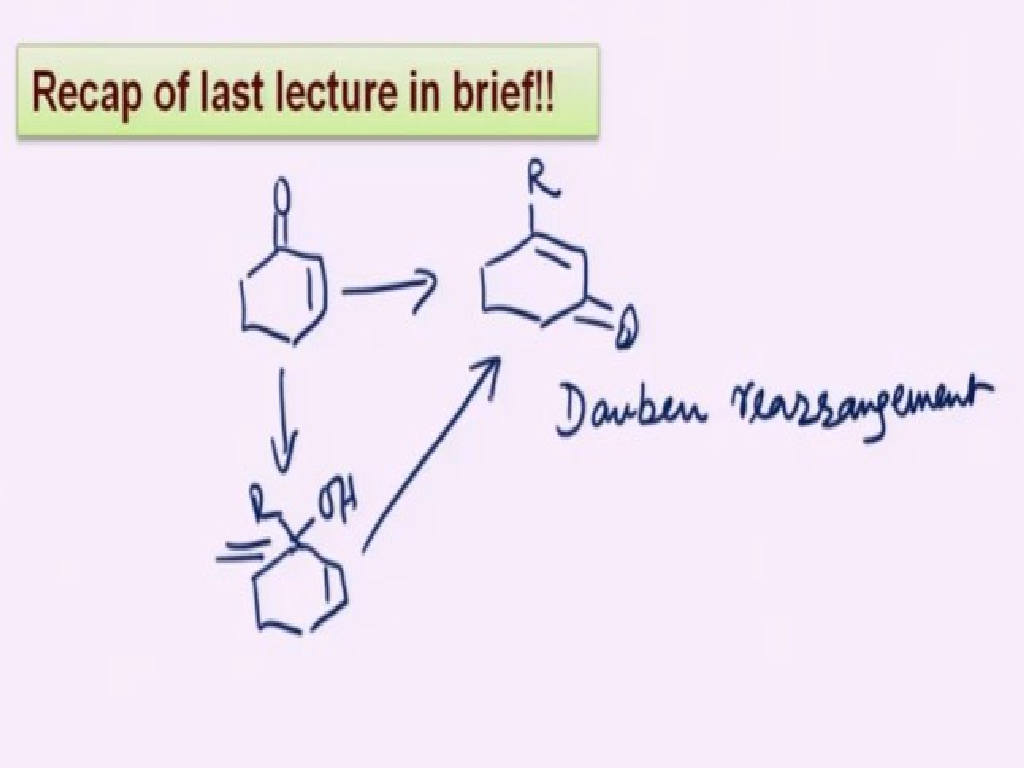

Recap of last lecture in brief!!

Now one of the oxidizing agents that we used for converting an enone or transposing an enone to the corresponding enone with on extra functional group such as this was Dauben rearrangement where we took the alcohol and reacted with PCC. Now that oxidizing agent pyridinium chlorochromate allowed this oxidation of the tertiary alcohol which can be formed from here if we add the corresponding alkyl or aryl group. And then we carry out this Dauben rearrangement.

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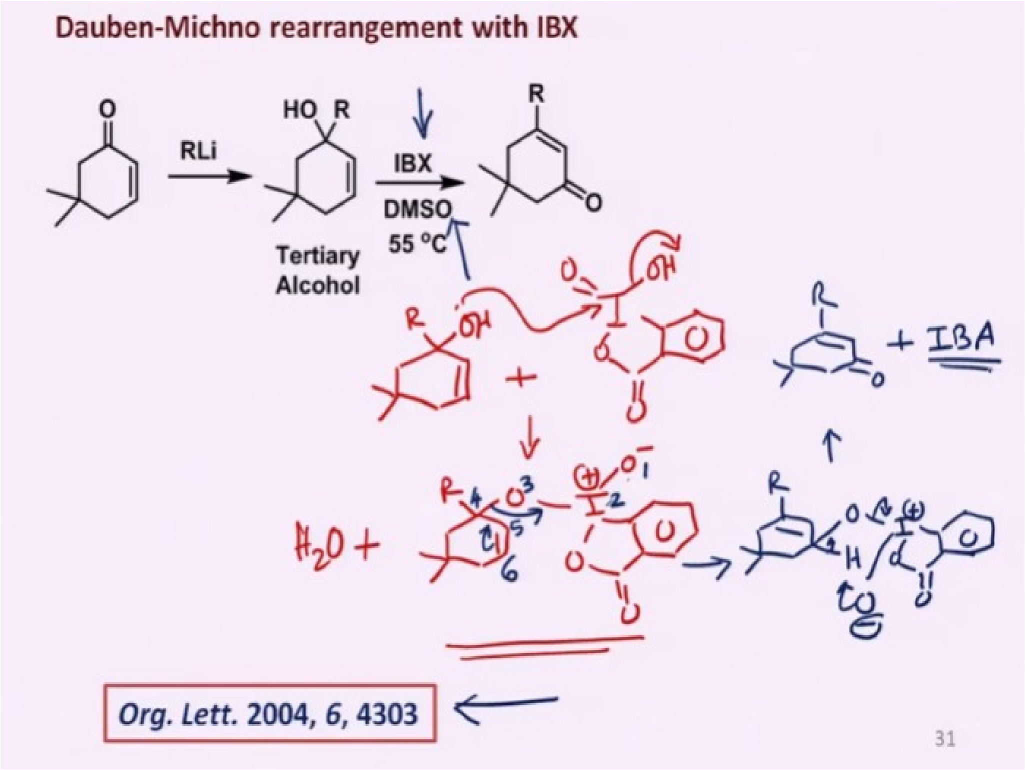

Dauben-Michno rearrangement with IBX

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So if one also looks at the IBX based reactions so in 2004 someone reported there can similar type of conversions using IBX in DMSO at 55 degrees temperature. So as one can see that we can have not only PCC but also IBX as a reagent to bring about this Dauben-Michno rearrangement now. As you can anticipate that the intermediate that can be expected to form on this intermediate would be something of this kind.

So one starts with substrate which is shown above and reacts with IBX that is what you have is something of this kind where you can put the Iodo here and oxygen here and of course OH and OH and iodine oxygen double bond and OH from the IBX. And what one can expect to form is an intermediate of this kind where you have the reagent in this fashion and with an O^- and positive charge.

So when this alcohol reacts with this iodine this goes off and what, we generate is some of this type by the loss of water in the from the reaction medium. Now when such an intermediate which is formed you can anticipate that the iodine here which is iodine here which is connected to the O^- which of course you can write as I double bond O or I^+ and O^-. Then we can anticipate that you this is 1, this is 2, this is 3, this is 4 and this is 5 and this is 6.

So you can anticipate that this oxygen can be attached to this with the double movement of this kind and of course here something of that type can occur to form the intermediate of this kind where now you have hydrogen. And you have an R and then you have an O then you have I then of course you have the bulk of the substrate here and oxygen here and this here. And at the same time what you will have is an O^- coming here which is what is like this.

Now this can undergo oxidation this allows oxidation to take place and one can get the enone here transposed and + IBA. So it is very similar to what we discussed earlier with pyridinium chlorochromate. But now you have another option of using IBX for the similar type of Dauben-Michno rearrangement would take place.

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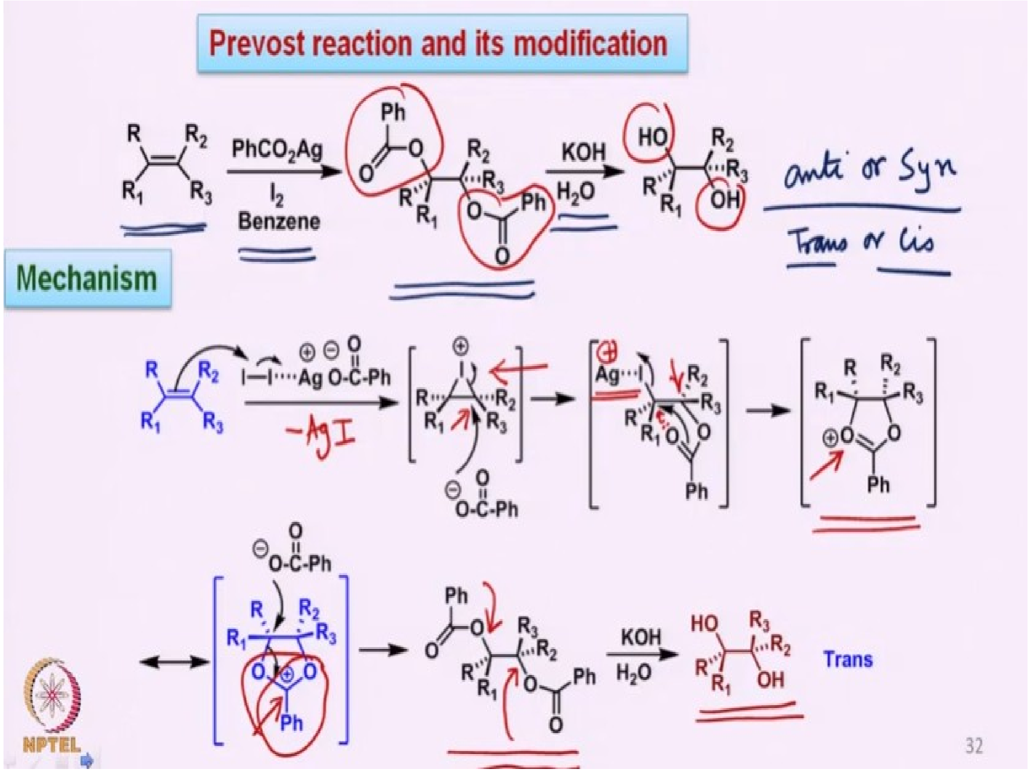

Now we look at other oxidizing agent which, is called as Prevost reaction and its modification. Now Prevost reaction give either trans or the anti or syn alcohols depending on the condition that one uses or trans or cis alcohols. Now what is used is the Olefin is allowed to react with silver salts of a benzoic acid or acetic acid that means silver benzoate or silver acetate. And in the presence of iodine in a reaction where benzene is used as a solvent and what is formed is the di-benzoate which is formed from the olefin which can be hydrolyzed under basic condition to form the diol.

As one can see from here that the benzoate which is here is coming opposite to the other benzoate which is present that is the reason why this hydroxyl group and these hydroxyl groups are opposite to each other onto the double bond site. So what is exactly happening is silver benzoate interacts with the iodine and polarizes the iodine to form silver iodide. And you generate I^+ this, I^+ then interacts with double bond to form an intermediate iodonium ion of this type.

And of course here in this case you will be loosing silver iodide now benzoate can attack see on this carbon atom here and this bond breaks the carbon iodine bond breaks. And you now have benzoate attacked so this that there is an inversion of stereochemistry at this centre so the R^2 group and R^3 groups are pointing upwards and from the lower side benzoate is attacking. And now you have iodine going on the top where now the next silver benzoate there should be positive charge here on the silver.

Now this interacts with the iodine tries to pull it off at the same time this oxygen lone pair of electrons can attack here and by pushing the iodine out which is assisted by the silver salt to form an oxonium ion intermediate of this kind. This of course we can write as a resonance structure with a positive charge either on oxygen or on carbon. Of course you will prefer to write the positive charge on the carbon which is next to the phenyl group.

And in this case now this symmetrical intermediate then it is attacked by the benzoate onto this carbon. Now when this attacks on this carbon now this particular benzoate has come from the opposite side of the other benzoate. Because now this particular part becomes benzoate so now you have a di-benzoate where the 2 benzoate groups have come from opposite direction. And then the hydrolysis under basic condition is carried out the benzoates gets oxidized and you get the corresponding diol.

So this is where one of the aspects of Prevost reaction which was discovered long back as been used. One of the disadvantages as you can see is the use of silver salt which is somewhat expensive if the reaction is to be carried out on large scale. But it is very interesting from the mechanism point of view.

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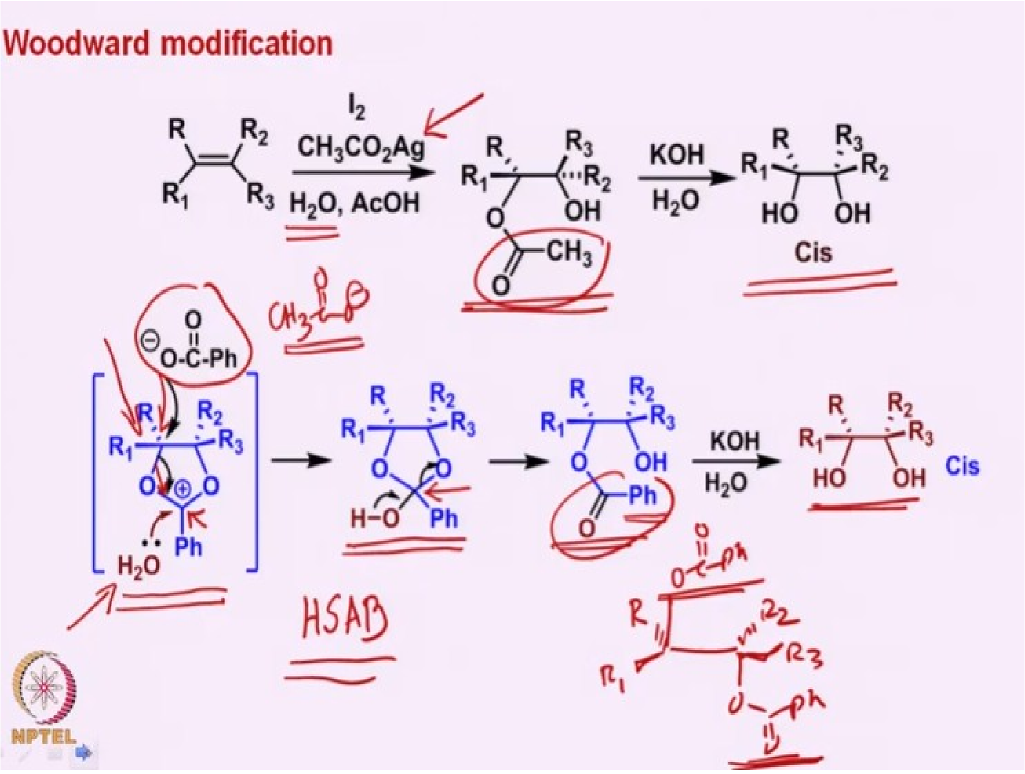

Woodward modification

And now there is some modification which is done and that has been reported by the famous organic chemist R.B.Woodward at Harvard who found out that if the reaction is carried out in the presence of water. In this case of course the reagent that has been taken is silver acetate but it does not matter one can also take silver benzoate. Idea here is that you have a source of any carboxylate which eventually gives the hydroxy group.

So when the reaction is carried out in the presence of water what is observed is the formation of the cis hydroxy group. That means the 2 hydroxy groups are coming from the same side. Now if one looks at the mechanism that we discussed without the presence of water you get an intermediate of this kind. Now this intermediate is the one in which we had attacked benzoate in this case.

Of course it would be acetate but in the case of benzoate the benzoate attacks on to this carbon here in this carbon here and this opens up here from here to here and you get the corresponding trans di acetate or di-benzoate. So we one what we have observed last time was the like this here and of course OCO phenyl and you get an OCO phenyl. So basically we were saying that this part and this part are opposite to each other.

So that is the case when benzoate or in this case acetate you can also have an acetate reacting. So that attacks opposite to on the opposite side but if we take water as a medium I mean as a nucleophile present in the medium then water now is competing with the acetate or the benzoate moiety. And the water is small is present in a large amount and it attacks on to this particular carbon atom rather than attacking on to this carbon atom.

And that is to do with hard soft acid base principle that is this carbon is a positively charged carbon with 2 oxygen's, around and water is harder than the benzoate or the acetate where the negative charge is delocalized over the carbonyl group. Whereas in the water case it is not delocalized therefore this is hard base and this is a hard acid therefore the reaction preferential gives this particular OH group attaching on to the carbon where there is a phenyl ring.

Now this obviously will immediately breakup and releasing the OH and the benzoate which of course on the hydrolysis will give the OH now. In the 2 OH groups are on the same side. Obviously here we are writing benzoate because we are comparing with the previous reaction that we did it. But we can also have the acetate as I mentioned here. So in place of this benzoate part here you can have the acetate part also. So one gets the diol which is sys diol so, this is a very interesting modification that has been introduced by R.B. Woodward.

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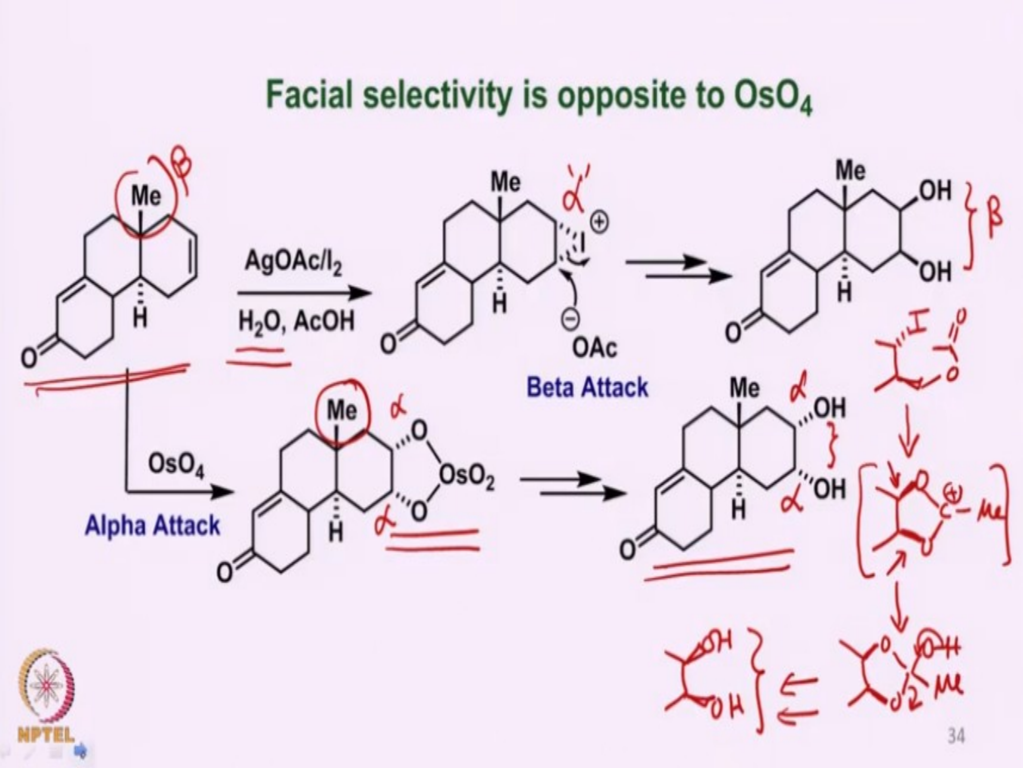

Facial selectivity is opposite to OsO_4

Now if one looks at a complicated example such as this which is an intermediate for a steroid type of synthesis. Now if one takes silver acetate and iodine so obviously since the methyl group is beta oriented the sterically less hindered side will be from the alpha side. Therefore iodonium ion formation takes place from the alpha side now if one then attacks the acetate. Now this reaction we are carrying out in the presence of water.

So it is since the iodonium ion is formed from the alpha side the attack of the acetate ion would always occur from the beta side. And on the less hindered side of the iodonium ion but it does not really matter eventually because we get anyway the diol. But the reaction occurs from the beta side that is the reason why what we are getting is an intermediate where this diol would eventually come from the beta side. Because the intermediate that is going to form will be something like this and here you have OCO and methyl.

So now if this reaction goes further then we will get O which is beta C then this here O and this so this is also beta and this is also beta. And then of course you will have methyl group here and the positive charge here this is what is going to happen. And when this is attacked by the water then of course what we would get is an intermediate of this type where you have an OH here and the methyl here.

When this part breaks up in whichever way eventually finally what you would get is OH here and of course OH here. So this is how the reaction is carried out now that means if the iodine reacts with silver acetate and the iodonium ion is formed from the alpha side the diol is beta. Now if one can carries out the dihydroxylation using osmium tetroxide. Then similar to the iodonium ion formation osmium tetroxide would also attack from the alpha side because there is steric hindrance from the beta methyl group.

So the osmium tetroxide will make an intermediate of this kind which is from the alpha side and since it is a cyclic intermediate involving both the oxygen of the osmium tetroxide attacking on the double bond from alpha side eventually one would get the diol in which both of these hydroxyl groups are alpha oriented. So, one can see that the difference between the 2 of them is eventually the outcome of the diol stereochemistry. So this kind of application has been very well utilized in the reaction of the Prevost type.

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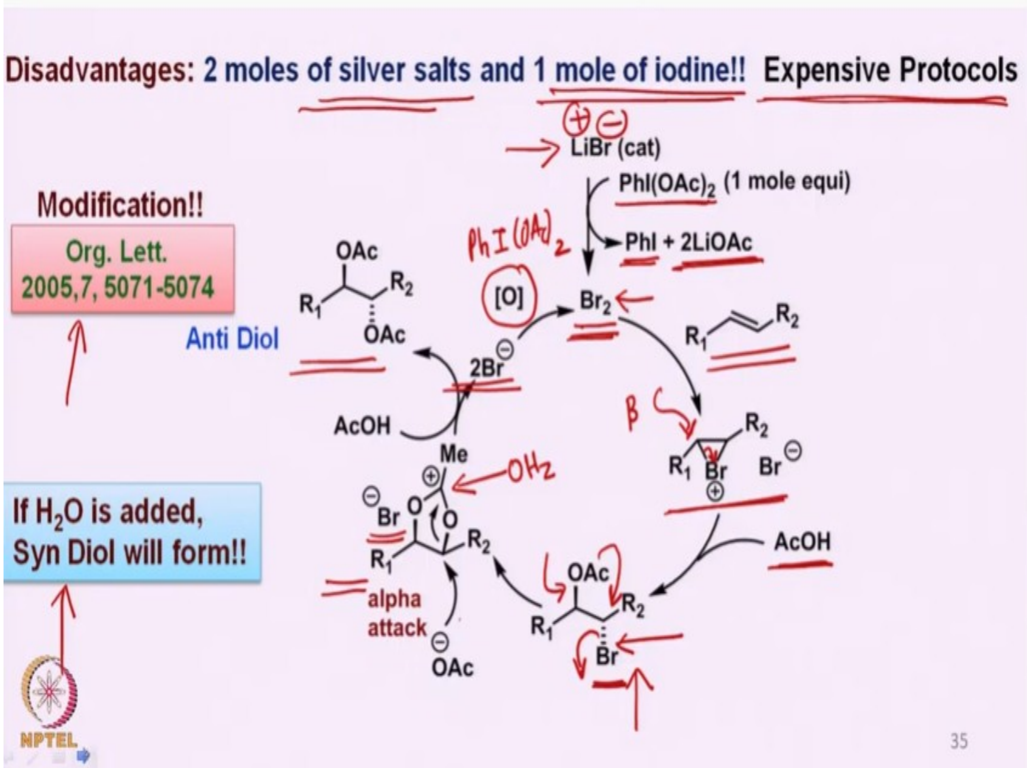

Disadvantages: 2 moles of silver salts and 1 mole of iodine!! Expensive Protocols

Modification!!

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If H_2O is added, Syn Diol will form!!

Now there are disadvantages as I mentioned that used 2 moles of silver salt and 1 mole of iodine it is something which is not very good because if one carries out the reaction on a large scale then you have this as expensive protocol. So; this protocols involving silver salt and iodone are expensive. So what has been recently reported in 2005 is you take lithium bromide as in a catalytic amount as a source of Br$^-$ and lithium$^+$ and this can be reacted with a 1 mole equivalent of oxidizing agent which is phenyl iodo di-acetate.

Now this phenyl iodo di-acetate oxidizes the Br $^-$ to Br$^+$ and of course that Br+ and Br- whole eventually become bromine. So now this molecular bromine in the process of course you use you get hydro benzene and lithium acetate from the oxidizing agent which is phenyl iodo di-acetate. So basically what you have done is you have oxidized the Br- the bromide ion to the corresponding molecular bromine which then reacts with the olefin.

In a similar fashion as the iodine was reacted with the double bond in the Prevost reaction where silver salts of the benzoate or silver benzoic acid or acetic acid was used as silver salt. So when this bromomium ion is formed you will get of course the attack of the double bond or on to the Br+ taking place exactly in an identical fashion as iodine type of reaction. And then when the attack of the acetic acid or in this case acetate or acetic acid occurs then one can imagine that the nucleophile coming from the beta side.

And this particular bond breaking from the lower side and therefore the acetate and the bromine would be opposite to each other. Or it is very clear that this is what exactly will happen similar to the Prevost type of reaction. Now obviously you have the acetate which is a now going to react it from the opposite side in the presence of this bromine leaving group in the form of bromide and you generate a similar intermediate to the Prevost type of intermediate.

Now or it is very clear that the acetic acid or acetate ion would now attack from the opposite side and then you get an anti-diol or anti di acetate which can be hydrolyzed to the corresponding anti-diol. But if water is added like a Woodward's modification then this is the intermediate that can be attacked by the water. And then you have a similar situation as Woodward's case and you can get the cis-diol or syn-diol that will form when water is added.

So it is exactly similar to the Prevost reaction the only difference is that in place of iodine as a molecular iodine and silver salt of the benzoate what one is using is basically nothing but lithium bromide in a catalytic fashion. Now as you can see from here when the reaction takes place you have a bromide ion coming from here is also bromide and coming from here. So, you have 2 of the bromide ions which have come out of the reaction medium.

And the acetic acid or acetate they react and then of course you generate the intermediates which are di-acetates or either in anti-form or a syn form. But these bromide ions then are re-oxidized by the same oxidizing agent which is phenyl $(HIOAC)^2$ and you regenerate the bromine here. So you do not have to use molecular bromine or and you can take the corresponding lithium bromide and then carry out by reacting with phenyl iodo di-acetate as an oxidizing agent to form the corresponding syn or anti-di-acetate.

So this is a very interesting modification and new modification and relatively cheap modification.

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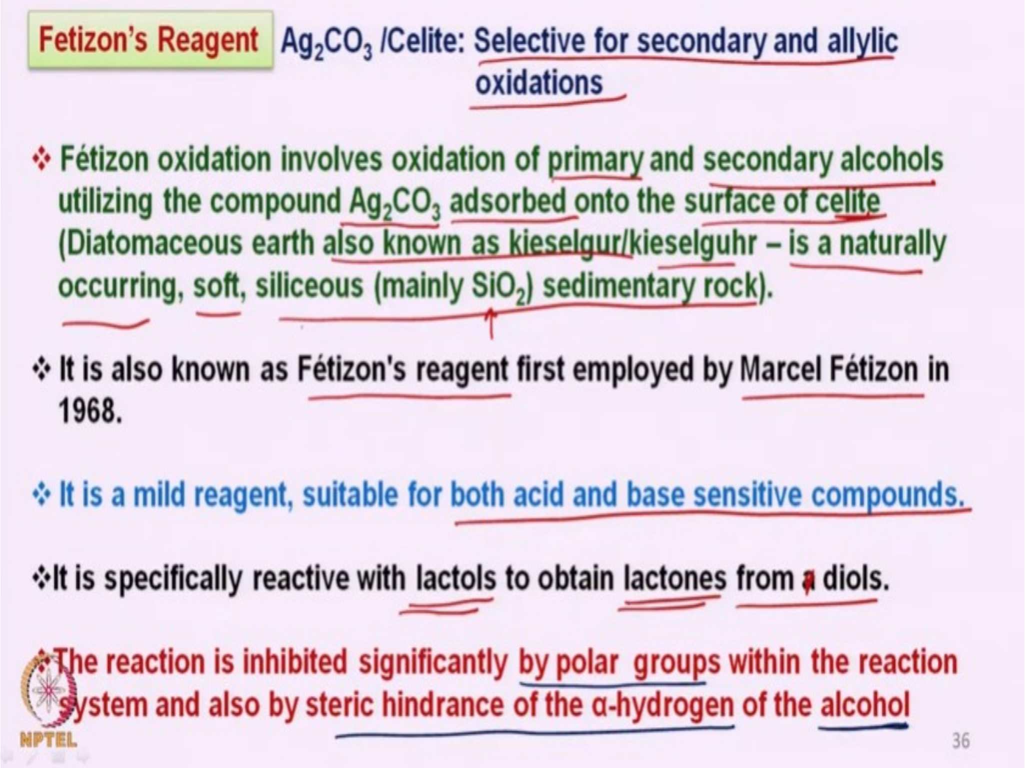

Fetizon's Reagent Ag_2CO_3 /Celite: Selective for secondary and allylic oxidations

- Fétizon oxidation involves oxidation of primary and secondary alcohols utilizing the compound Ag_2CO_3 adsorbed onto the surface of celite (Diatomaceous earth also known as kieselgur/kieselguhr – is a naturally occurring, soft, siliceous (mainly SiO_2) sedimentary rock).
- It is also known as Fétizon's reagent first employed by Marcel Fétizon in 1968.
- It is a mild reagent, suitable for both acid and base sensitive compounds.
- It is specifically reactive with lactols to obtain lactones from a diols.
- The reaction is inhibited significantly by polar groups within the reaction system and also by steric hindrance of the α-hydrogen of the alcohol

Now we have another reagent which is called as Fetizon's reagent which exploits the utility of the silver carbonate which is essentially absorbed on the surface of celite. And although this allows the oxidation of primary, secondary alcohols both but it is more selective for the oxidation of secondary and allylic oxidations. Or in other words the secondary and allylic alcohols are preferentially oxidizing over primary if the substrate as such both the kind of alcohols which are present.

Now Fetizon's oxidation involves oxidation of primary and secondary alcohols utilizing the compounds silver carbonate which is absorbed on the surface celite. Basically celite is nothing Diatomaceous are also known as Kieselgur is a naturally occurring soft siliceous sedimentary rock. So basically it is a fine powder white color powder which has mainly SiO_2 as the technical present however it allows adsorption of different kinds of chemicals on its surface.

It is known as Fetizon's reagent because it was first employed by Fetizon's in 1968 it is a mild reagent suitable for both acid sensitive and base sensitive compounds. And it is specifically reactive with lactols to obtain lactones now this something that we will discuss from diols not from a diols. It is obviously it is an expensive reagent because it is a silver salt which as to be utilized however it as lot of advantages. One has I have mentioned above it as selectivity in terms of secondary and allylic alcohols are oxidized faster than primary.

The diols can be interestingly oxidized to the corresponding lactones the only disadvantage or one of the disadvantages of this reaction is that it can be utilized but if there are polar groups present on the substrate then there is a problem. Because; those, polar groups can have a competition with the silver carbonate for the alcohol adsorption. Because ultimately; silver carbonate which is adsorbed on the surface of celite interacts with the hydroxyl group of the alcohol.

But if there are other polar groups which are present in the reaction medium or on the substrate then there is a competition. Now this is also a possibility of steric hindrance of the alpha hydrogen that means the alcohol which is getting oxidized that alcohol. If it has the hydrogen which is sterically hindered kind of hydrogen. Then there is a possibility of a rate slowing down because of the steric hindrance that is exhibited by that particular substrate. So in case the reaction is carried out in a solvent which is, polar then also there is a problem.

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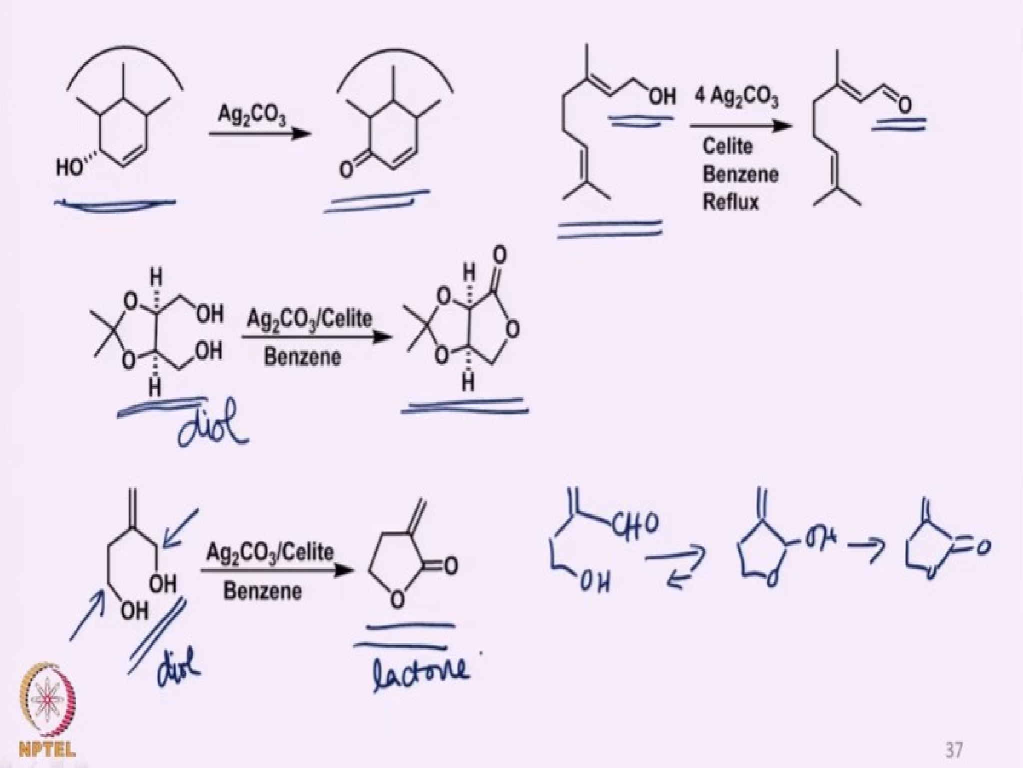

Now I just want to show 1 or 2 examples here for example if this allylic alcohol can be oxidized to the corresponding enone this allylic alcohol can be converted to the corresponding alpha beta unsaturated aldehyde. And as I mentioned that you can take diol of this type and it is a symmetrical diol so you get only one particular lactone and then if you have this diol which is not a symmetrical diol.

But then as you can see the difference there is an allylic alcohol here and which is a non-allylic alcohol here. So this particular the OH groups gets oxidized to the corresponding aldehyde which is an equilibrium with this lactol and this lactol then is again a allylic alcohol and it gets oxidized to the corresponding lactone. So this is how the lactone as formed. So, one can go to the diol to the lactone in 2 different ways as it is seen 1 diol which is symmetrical diol which does not have allylic alcohol.

But then this is allylic alcohol so allylic alcohol is oxidized faster than the non-allylic alcohol and that allows the electron formation in a very regio-selective fashion. So these are the example which indicates the utility of silver carbonate on celite which is called Fetizon’s reagent. So I will stop it today at this stage and take up the further aspects of this Fetizon’s reagent in my next class.

In the mean while you can go through these oxidations which I discussed just now both Prevost reaction as well as the silver carbonate based reaction and prior to that I discussed the IBX based Dauben-Michno reaction or rearrangement and you can carefully look at the mechanistic aspects and application of those reagents in organic synthesis. And we will look at further aspects of these in the next class thank you.