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

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Module No # 03
Lecture No # 14
Ruthenium Tetroxide (and RuCl3/NalO4) mediated oxidations

Hello everyone I would like to welcome you to today's lecture where we will continue with the discussion of the Fetizon's reagent which we introduced last time. We saw that the Fetizon's reagent which is basically adsorption of silver carbonate on the surface of celite. And that allows the different kinds of oxidations of primary secondary allylic as well as benzylic type of alcohols and especially it is useful for the oxidation of a diol to form the lactone via lactol. So last time what we were discussing about the various aspects of steric factors and the polar factors towards the end.

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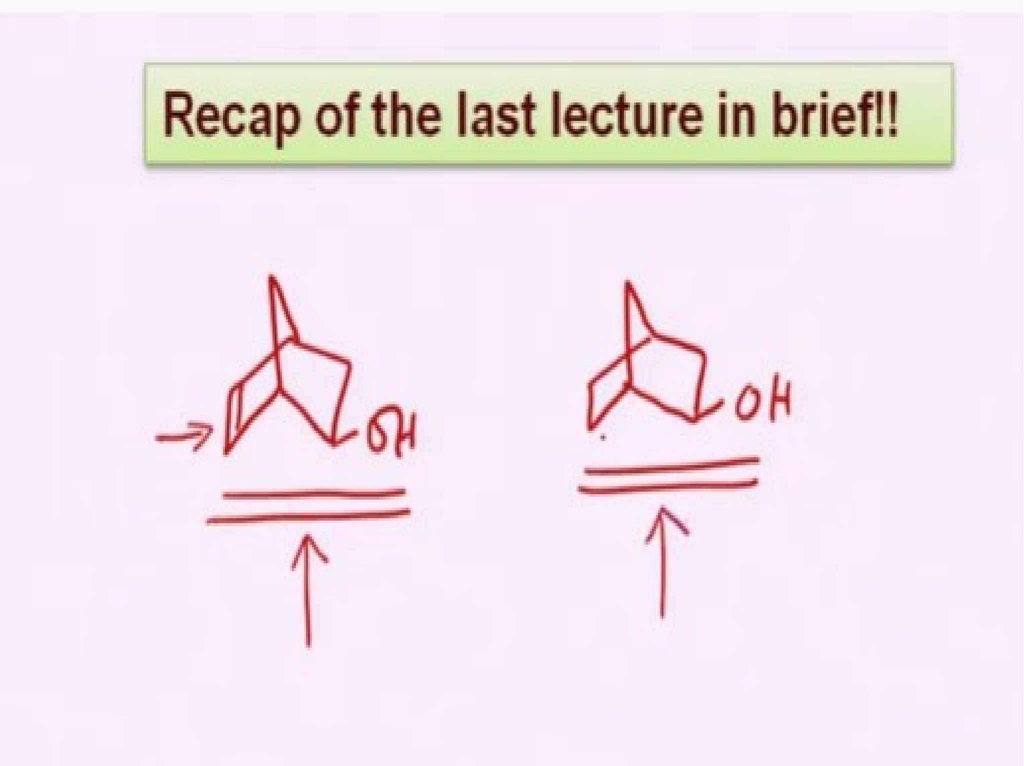

Recap of the last lecture in brief!!

I mentioned that an example of this kind which basically has an alcohol which is having a double bond versus another alcohol in which no such double bond is present. So, this particular alcohol reacts much faster than this alcohol. Obviously because there is a competition for the alcohol to get absorbed on the surface of the reagent with the double bond, which also tries to participate to act as a kind of nucleophile for the surface of the Fetizon's reagent.

So, there is a competition between the double bond and the OH and therefore this particular alcohol reacts slower than this alcohol which, is devoid of such a double bond.

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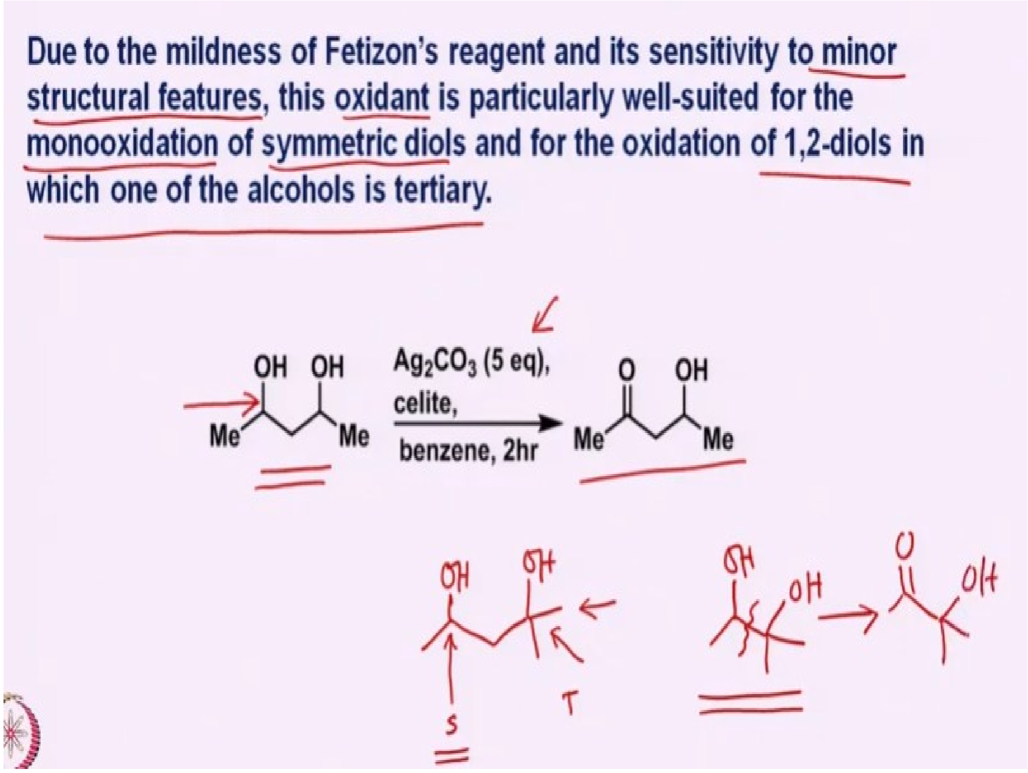

Due to the mildness of Fetizon's reagent and its sensitivity to minor structural features, this oxidant is particularly well-suited for the monooxidation of symmetric diols and for the oxidation of 1,2-diols in which one of the alcohols is tertiary.

Due to the mildness of Fetizon's reagent and its sensitivity to minor structural features something I mentioned that if there is a double bond versus there is no double bond. Therefore, this oxidant that is Fetizon's reagent is particularly well suited for the mono oxidation of symmetric diols. Now we have a symmetrical diol like this here and we can carry out that mono oxidation that means between the 2 of them only we can oxidize one of the alcohols.

Even if we use excess of silver carbonate because it is slow reaction and therefore one can monitor and stop when the oxidation of one of the hydroxy groups gets oxidized to the corresponding ketone. At the same time, we can also obviously take up an example where there is say you have a hydroxy group which is secondary hydroxy group and then we have another hydroxy group which is say for example here tertiary.

So, if this is secondary hydroxy group and this is the tertiary hydroxy group, we can specifically oxidize this and it does not get oxidized. Obviously, it will not be oxidized because it is tertiary. But at the same time, we can also take another example in which hydroxy group is secondary and at the next carbon you have another hydroxy group which is tertiary. Now substrates of this kind have been found to have problems for the C-C bond cleavage with other oxidizing agent such as chromium based or other oxidizing agents.

But that does not happen in the case of Fetizon's reagent and what one easily can get is this type of hydroxy ketone without affecting the C-C bond cleavage.

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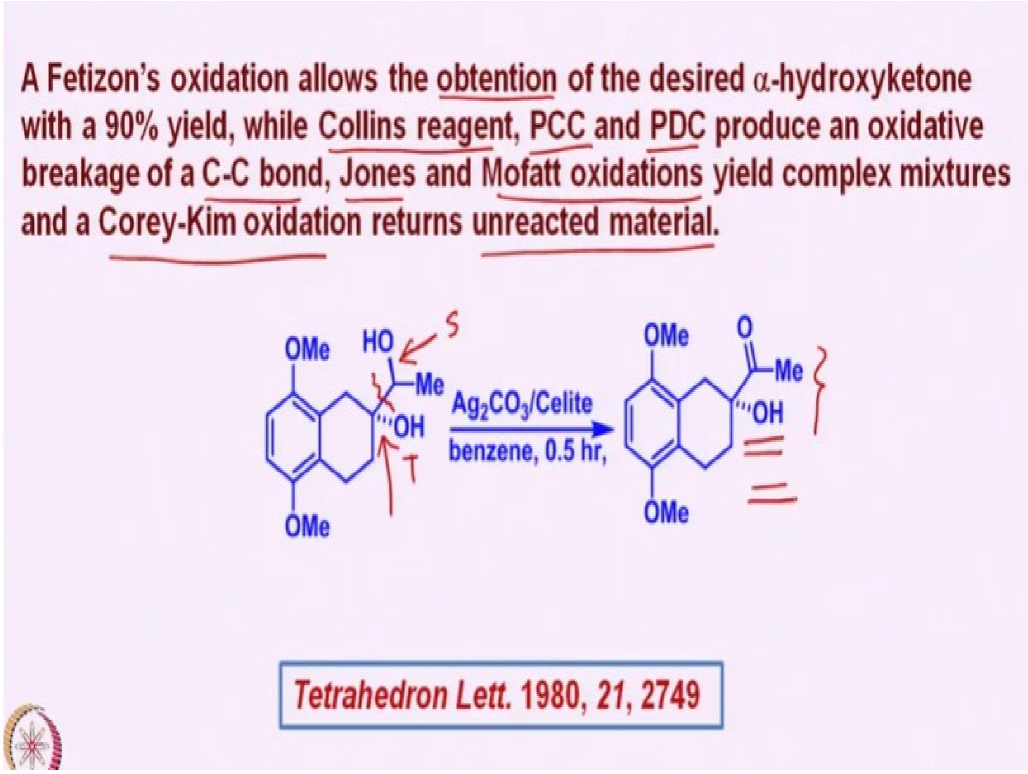

A Fetizon's oxidation allows the obtention of the desired α-hydroxyketone with a 90% yield, while Collins reagent, PCC and PDC produce an oxidative breakage of a C-C bond, Jones and Mofatt oxidations yield complex mixtures and a Corey-Kim oxidation returns unreacted material.

Tetrahedron Lett. 1980, 21, 2749

Now a Fetizon's oxidation allows the preparation or of obtaintionof the desired alpha hydroxy ketone of this kind. This is exactly what I mentioned before that if we have a tertiary hydroxy group here and the secondary hydroxy group here then the oxidation can be to the alpha hydroxy ketone without any cleavage of the C-C bond. Whereas Collins reagent, PCC pyridinium chlorochromate, pyridinium dichromate produce an oxidative cleavage of the C-C bond.

Similarly, Jones and Mofatt oxidations yield complex mixtures whereas, Corey-Kim oxidation does not give any oxidation and gives back the unreacted starting material. What it indicates is it is a mild oxidizing agent and therefore it is useful for the oxidation of a substrate having a hydroxy group which is a secondary hydroxy group and the tertiary hydroxy group here to form the alpha hydroxy ketone of this kind.

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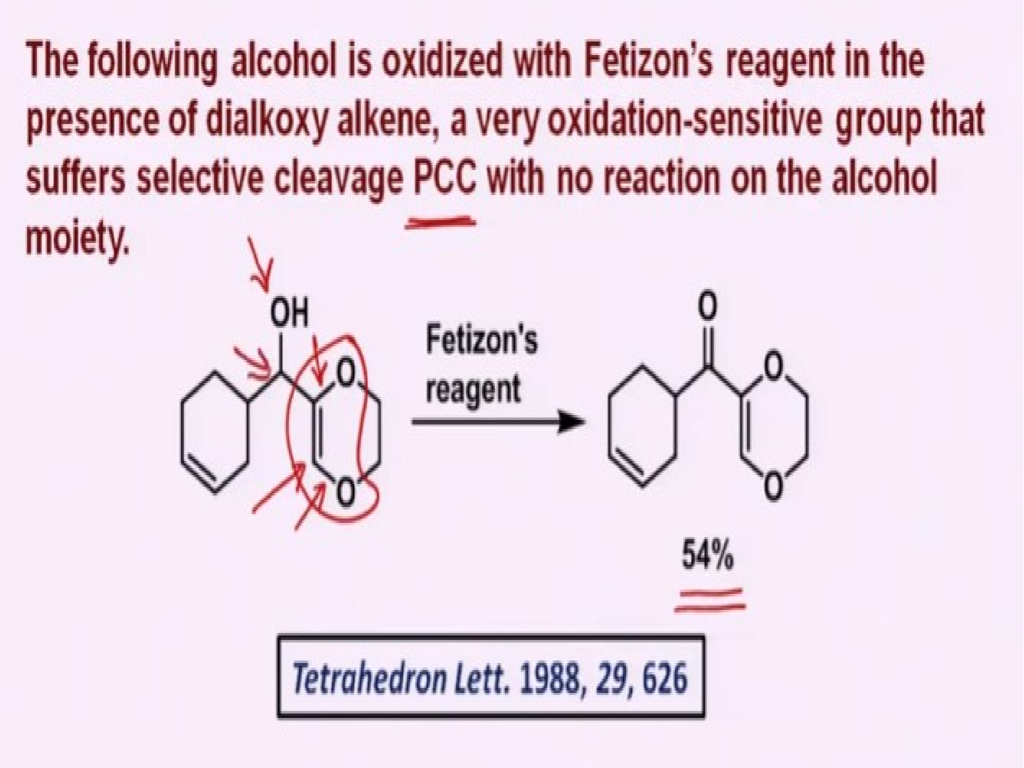

The following alcohol is oxidized with Fetizon's reagent in the presence of dialkoxy alkene, a very oxidation-sensitive group that suffers selective cleavage PCC with no reaction on the alcohol moiety.

Tetrahedron Lett. 1988, *29*, 626

Now the following alcohol is oxidized with Fetizon's reagent in the presence of dialkoxy alkene. Now this is example where we have this dialkoxy alkene there is an alkene on which you have 2 of the alkoxy groups here present. So therefore, this is a very reactive substrate and of course when it was reacted with PCC there was cleavage and there was no oxidation of the alcohol. That means the C-C bond was cleaved and there was no alcohol oxidation.

On the other hand, Fetizon's reagent allows the oxidation to take place even though the yield is low still oxidation does take place and the reagent allows oxidation of such allylic alcohol which is a sensitive substrate.

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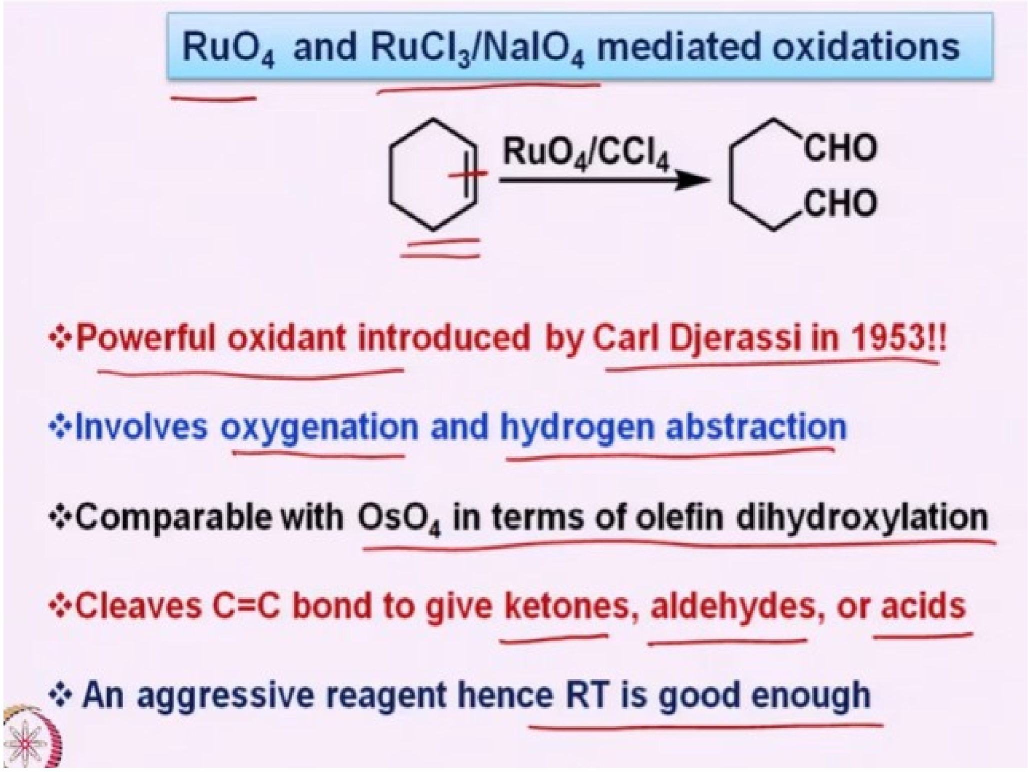

RuO_4 and $RuCl_3/NaIO_4$ mediated oxidations

- Powerful oxidant introduced by Carl Djerassi in 1953!!
- Involves oxygenation and hydrogen abstraction
- Comparable with OsO_4 in terms of olefin dihydroxylation
- Cleaves C=C bond to give ketones, aldehydes, or acids
- An aggressive reagent hence RT is good enough

Now we will move on to a new oxidizing agent which is ruthenium tetroxide or we can also use a combination of ruthenium trichloride and sodium metaperiodate. But let us first see what was initially done that it was found by Carl Djerassi in 1953. That olefins can be cleaned the C-C bond can be cleaved using ruthenium tetroxide in carbon tetrachloride. This was found to be a very powerful oxidant and it basically involves oxygenation and hydrogen abstraction.

We will discuss about the mechanism a bit later it is comparable with osmium tetroxide in terms of olefin dihydroxylation which we will also discuss in a while. And it cleaves the C-C bond to give ketones aldehydes or even acids. It is a very aggressive reagent hence room temperature is good enough for the cleavage of the C-C bond taking place.

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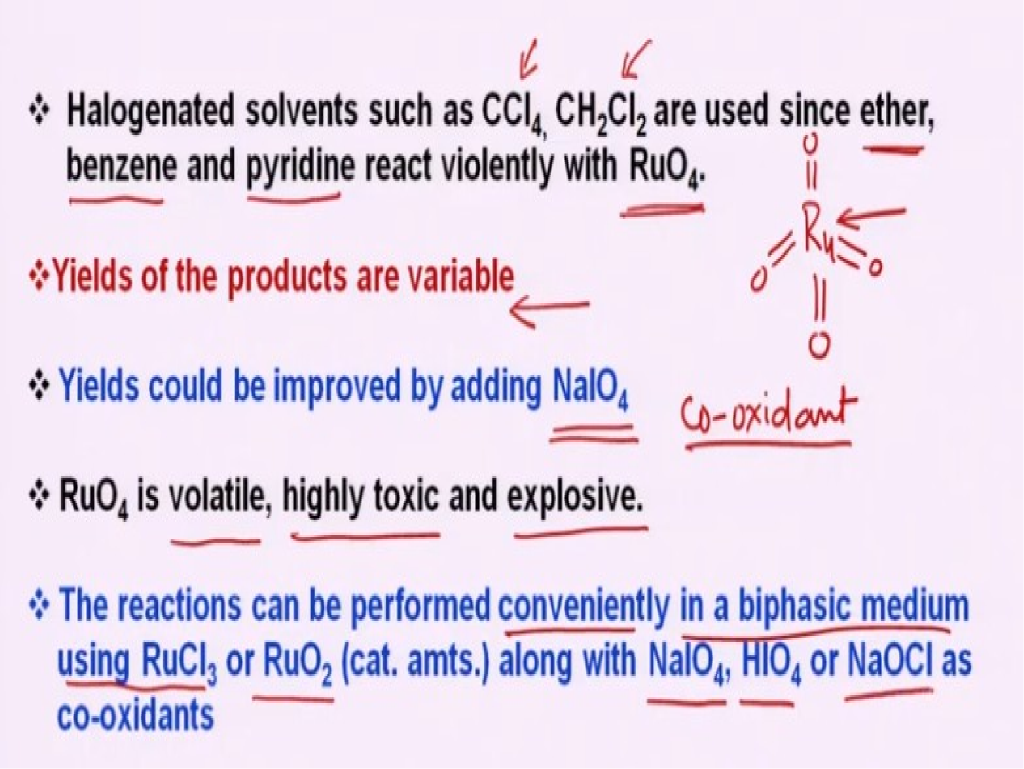

- Halogenated solvents such as CCl_4, CH_2Cl_2 are used since ether, benzene and pyridine react violently with RuO_4.
- Yields of the products are variable
- Yields could be improved by adding $NaIO_4$

Co-oxidant

- RuO_4 is volatile, highly toxic and explosive.
- The reactions can be performed conveniently in a biphasic medium using $RuCl_3$ or RuO_2 (cat. amts.) along with $NaIO_4$, HIO_4 or NaOCl as co-oxidants

Halogenated solvents such as CCl_4 ,dichloromethane are used because ether, benzene and pyridine react very violently with the ruthenium tetroxide. If one sees the structure of ruthenium tetroxide then you have of 4 oxygen's attached to the ruthenium. And therefore, the ruthenium here is highly electrophilic. Therefore, the ether benzene and pyridine all of them they react very violently with ruthenium tetroxide.

Unfortunately, the yields of the products are variable that means it depends on the substrate to substrates. But at the same time, it has been found that instead of using ruthenium tetroxide if one tries to add sodium metaperiodate as a co-oxidant the yields can be improved. What it means that the ruthenium tetroxide when it oxidizes or cleaves a double bond it gets reduced to the low valent ruthenium species.

And that can be re-oxidized using sodium metaperiodate and that is where the efficiency of the reagent increases by the addition of sodium metaperiodate that acts as a co-oxidant in these reactions. On its own ruthenium tetroxide is volatile and highly toxic and it also reported to be known as an explosive. The reaction therefore can be performed conveniently in a biphasic medium using ruthenium tri-chloride or ruthenium tetroxide in catalytic amounts.

Since ruthenium tetroxide is an expensive reagent people have tried to make use of other ruthenium source such as ruthenium tri-chloride or ruthenium dioxide in catalytic amounts along with co-oxidants such as sodium metaperiodate or periodic acid or sodium hypochlorite as Co-oxidants.

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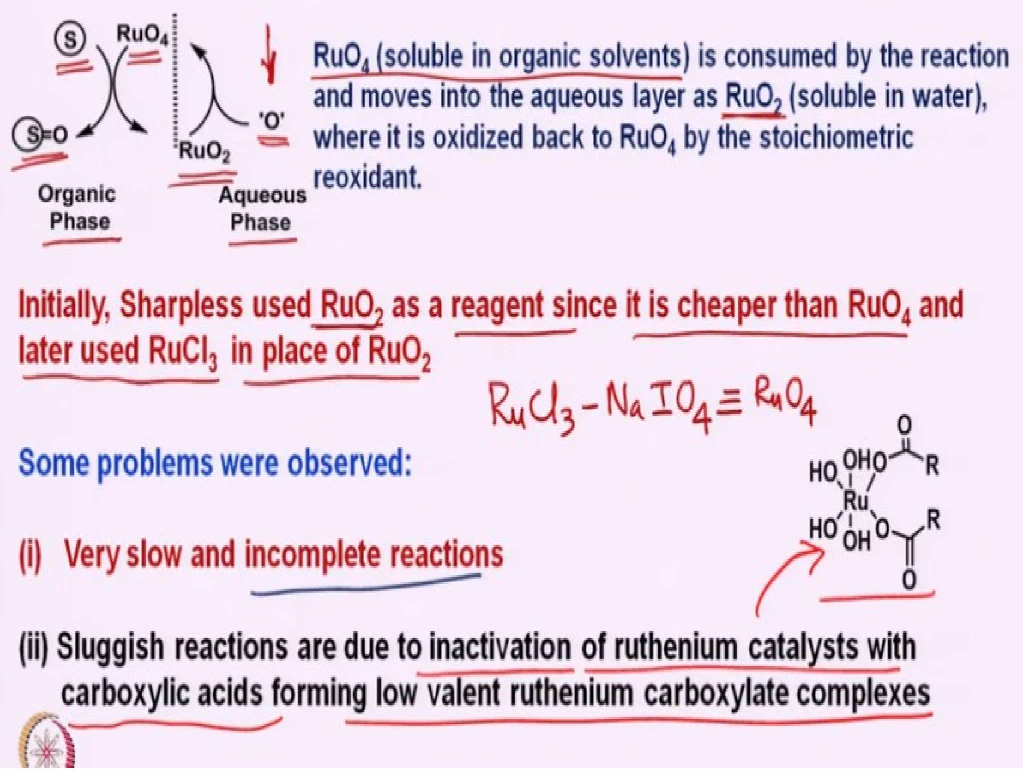

RuO_4 (soluble in organic solvents) is consumed by the reaction and moves into the aqueous layer as RuO_2 (soluble in water), where it is oxidized back to RuO_4 by the stoichiometric reoxidant.

Initially, Sharpless used RuO_2 as a reagent since it is cheaper than RuO_4 and later used $RuCl_3$ in place of RuO_2

$RuCl_3 - NaIO_4 \equiv RuO_4$

Some problems were observed:

(i) Very slow and incomplete reactions

(ii) Sluggish reactions are due to inactivation of ruthenium catalysts with carboxylic acids forming low valent ruthenium carboxylate complexes

Ruthenium tetroxide is soluble in organic solvents and it is consumed in the reaction and moves into the aqueous layer as ruthenium dioxide. Ruthenium tetroxide when it oxidizes the substrate or oxidatively cleaves the double bond it forms eventually ruthenium dioxide. And therefore if one, uses biphasic medium containing an organic phase and an aqueous phase. And in the aqueous phase the co-oxidants such as sodium metaperiodate or sodium hypochlorite or periodic acid is used.

So, when ruthenium tetroxide which is soluble in organic solvent oxidizes the substrate to the corresponding oxidized species either C-C bond cleavage or whatever. And in the mean in the process it forms ruthenium dioxide which passes to the aqueous phase. And in the aqueous phase the oxidant the co-oxidant which is present re-oxidizes the ruthenium tetroxide ruthenium dioxide to go to ruthenium tetroxide.

So, one can start with only catalytic amount of ruthenium tetroxide and this reaction can be done. However initially Sharpless used ruthenium dioxide only as a reagent since it is cheaper than ruthenium tetroxide. And later he used ruthenium tri-chloride in place of ruthenium dioxide. So, right now lots of people who want to use this protocol prefer to use ruthenium tri-chloride and sodium metaperiodate as a combination of reagent which is a source of ruthenium tetroxide.

However, there are some problems which are observed for example if one takes the ruthenium reagents. So, there are cases which it has been found that the reaction becomes slow and there is an incomplete reaction. Now this happens in cases where carboxylic acid is formed the sluggish reactions which are observed are due to the inactivation of ruthenium catalysts with carboxylic acids that form low valence ruthenium carboxylate complexes such as this.

So, such kind of complexes with the carboxylate, reduces the activity of the ruthenium catalyst and therefore the reactions are slow and incomplete.

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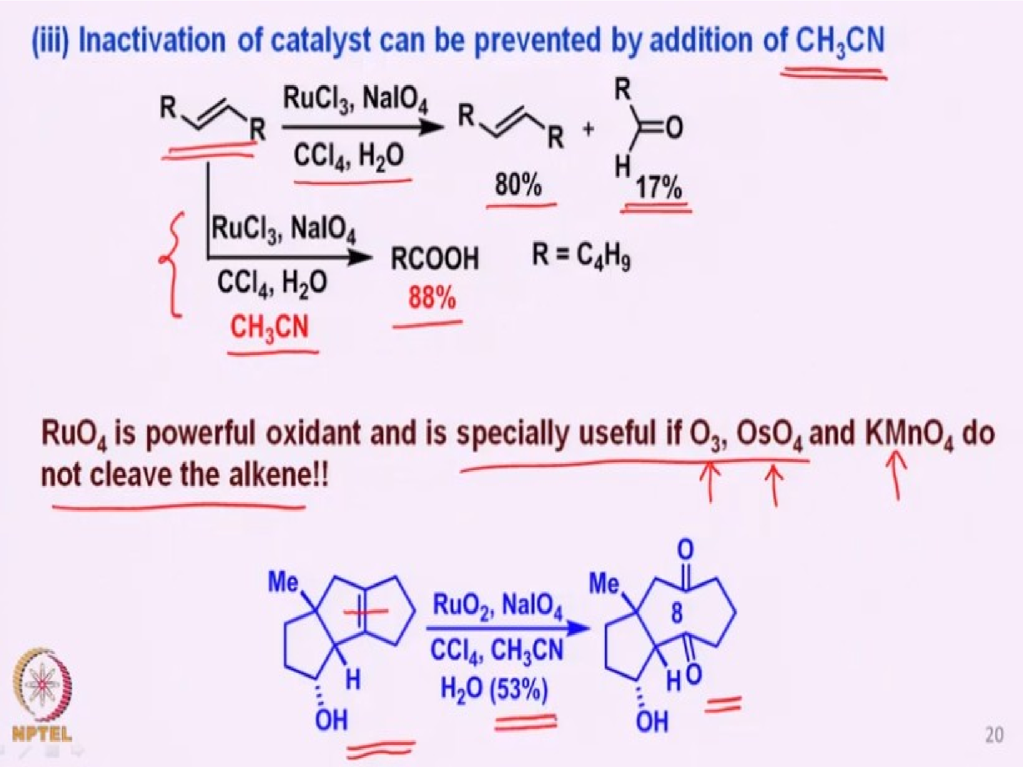

(iii) Inactivation of catalyst can be prevented by addition of CH_3CN

RuO_4 is powerful oxidant and is specially useful if O_3, OsO_4 and $KMnO_4$ do not cleave the alkene!!

At the same time, it was observed that the inactivation of catalyst like this can be presented if we add acetonitrile as a solvent or a molecule of acetonitrile. Now we will have competition with the carboxylic acid or the carboxylate to form the complex that we saw that is that forms with the carboxylate complexes. So, the nitrile blocks the site of the ruthenium species and does not allow carboxylates to form complexes.

It only temporarily allows the site protection and therefore the oxidation is completed and for example we can see here the C-C bond cleavage of this double bond with ruthenium tri-chloride sodium metaperiodate In the presence of CCl_4 and water gives 17% of the corresponding aldehyde and 80% of the starting material is recovered. On the other hand, if acetonitrile is used as a solvent then one gets the 88% yield of the corresponding carboxylic acid and all the starting material gets completely consumed.

So therefore the inactivation of the catalyst can be presented if one adds acetonitrile. So the protocol which is now generally followed is this protocol, in which one takes ruthenium tri-chloride and sodium metaperiodate in a reagent solvent system such as CCl_4 water and acetonitrile. And then the oxidative cleavage occurs now ruthenium tetroxide is powerful oxidant and especially it is useful where say.

For example, ozone, osmium tetroxide or $KMnO_4$ types of reagents do not cleave the alkene. This is an example which is a tri-cyclopentenoid. Example in which there was a need to cleave this bond and this bond cleavage was not easily possible using the reagents such as ozone, osmium tetroxide that $KMnO_4$. But ruthenium tetroxide which is formed by from ruthenium dioxide in presence of sodium metaperiodate allows the cleavage of C-C bond to form this product in 53% yield. So, there are advantages of this reagent and therefore it is used in organic synthesis quite a lot.

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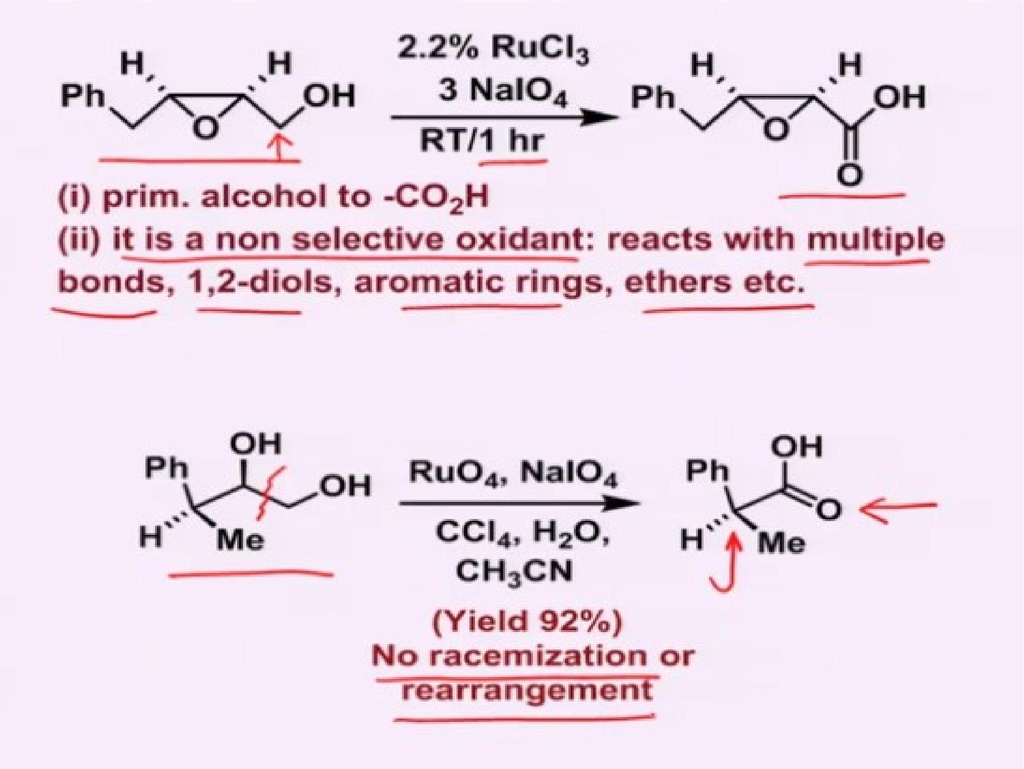

(i) prim. alcohol to $-CO_2H$

(ii) it is a non selective oxidant: reacts with multiple bonds, 1,2-diols, aromatic rings, ethers etc.

(Yield 92%)
No racemization or rearrangement

Interestingly when you have a substrate of this type where there is a primary alcohol. And that primary alcohol under these conditions of ruthenium tri-chloride sodium metaperiodate allows oxidation to give the corresponding carboxylic acid in a very short time such as 1 hour. Now, it is a non-selective oxidant, have been telling all the time that the ruthenium tetroxide is a very violent or aggressive reagent.

And therefore, it reacts with many other functional groups such as multiple bonds like double bond or triple bond, diols, aromatic rings ethers etc. Now for example here we take a diol of this type which undergoes a cleavage here to form eventually via the corresponding aldehyde the corresponding acid. So, there is no racemization or there is no rearrangement that occurs during this process.

So, which is an advantage by using such a reagent which is a bit of aggressive reagent but then reactions are done at milder conditions and therefore this is no side products that are formed.

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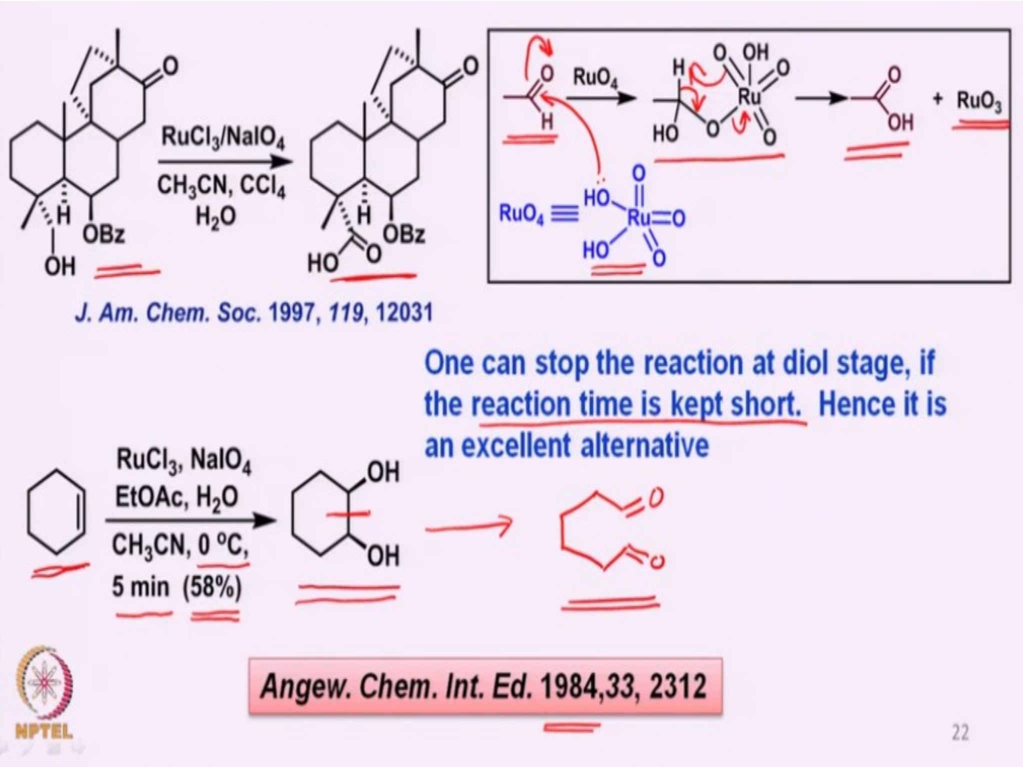

J. Am. Chem. Soc. 1997, 119, 12031

One can stop the reaction at diol stage, if the reaction time is kept short. Hence it is an excellent alternative

Angew. Chem. Int. Ed. 1984,33, 2312

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Now we have another example in which such a complicated tri-cyclic molecule can be converted to the corresponding carboxylic acid which is normally difficult with using other oxidizing agent. So, this example simply illustrates that how the primary alcohols can be oxidized to the corresponding acid under these conditions what exactly happens is? If we have the aldehyde then the ruthenium tetroxide will react to form this intermediate because we can write the ruthenium tetroxide under the water medium to be somewhat like this.

So, the hydroxy group here attacks onto this aldehyde and you move this electron pair from there to form this intermediate and that undergoes oxidation here like this to form the corresponding carboxylic acid. And during the process you release the ruthenium low valent ruthenium substrate which again of course reacts further. But it is interesting that when one carries out the reaction with a double bond one can also stop the reaction at the diol stage.

Because this is diol that undergoes further reaction and allows the cleavage to take place. So, this of cleavage can be prevented in one stop’s the reaction at the diol stage by keeping the reaction time short. So, if one carries out the reaction say at 0 degrees and only allows within 5 minutes to, check the reaction can be stopped at the diol stage. So, one can isolate the corresponding diol so, this is an interesting observation which was published in 1984.

That means that you have an alternative as compared to the osmium tetroxide to go to the corresponding diol and if one wants this diol to be converted to the corresponding di-aldehyde a bond for the cleavage of the C-C bond. And of course, you can allow the reaction to go further for a longer time and the cleavage can take place. But getting the diol is also an alternative and which is a good alternative for the reaction.

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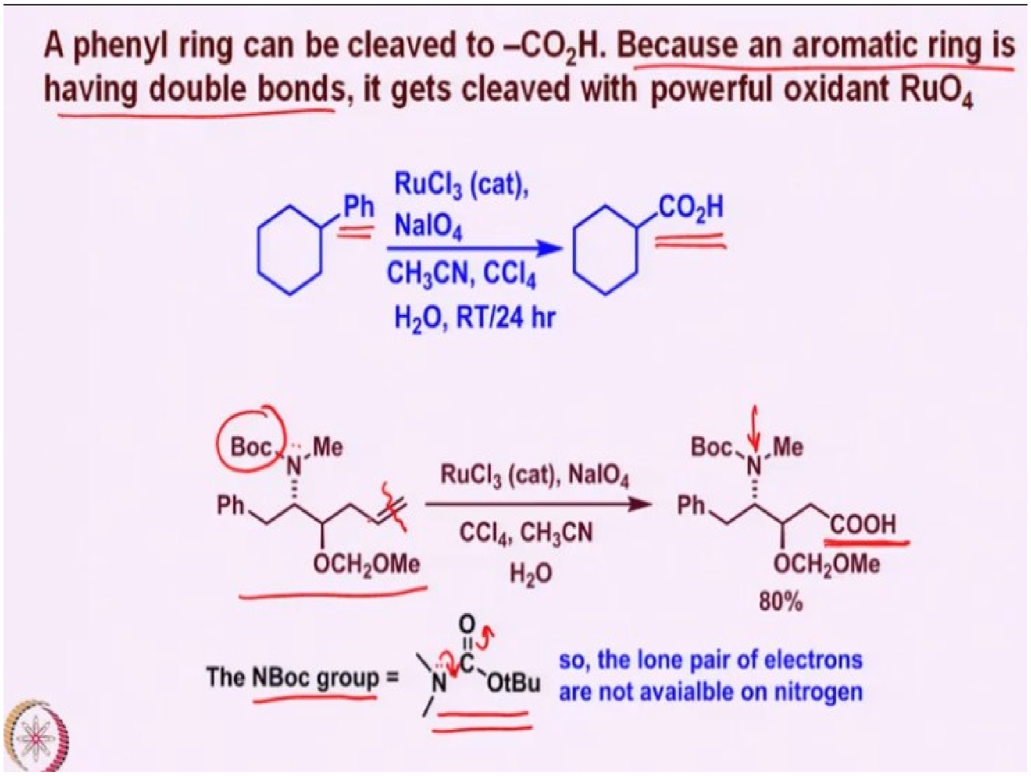

A phenyl ring can be cleaved to –CO$_2$H. Because an aromatic ring is having double bonds, it gets cleaved with powerful oxidant RuO$_4$

RuCl$_3$ (cat), NaIO$_4$, CH$_3$CN, CCl$_4$, H$_2$O, RT/24 hr

RuCl$_3$ (cat), NaIO$_4$, CCl$_4$, CH$_3$CN, H$_2$O

80%

The NBoc group =

so, the lone pair of electrons are not avaialble on nitrogen

Interestingly a phenyl ring can also be cleaved to the corresponding acid because an aromatic ring is basically nothing but having several double bonds. Since the ruthenium tetroxide is a very aggressive reagent is a powerful oxidant so even the phenyl ring gets oxidized to the corresponding acid. This, kind of conversions of the aromatic rings or electron rich aromatic rings to the corresponding acids have been utilized in organic synthesis.

Now here we have another example in which we have a lone pair of electrons on the nitrogen blocked by the using of this protecting group which is a Boc pro group which is nothing but this kind of where the lone pair of electrons on the nitrogen in conjugation with the carbonyl group. Therefore, the lone pair of electrons here is not available for the oxidation for the oxidant to give any problem.

And therefore a substrate of this kind can be cleaved to the corresponding acid without any problem even protects the nitrogen here as a NBoc protection. So, the conversion of such substrates to the acid can also occur readily with using the ruthenium tetroxide formed in-situ by ruthenium tri-chloride and sodium metaperiodate.

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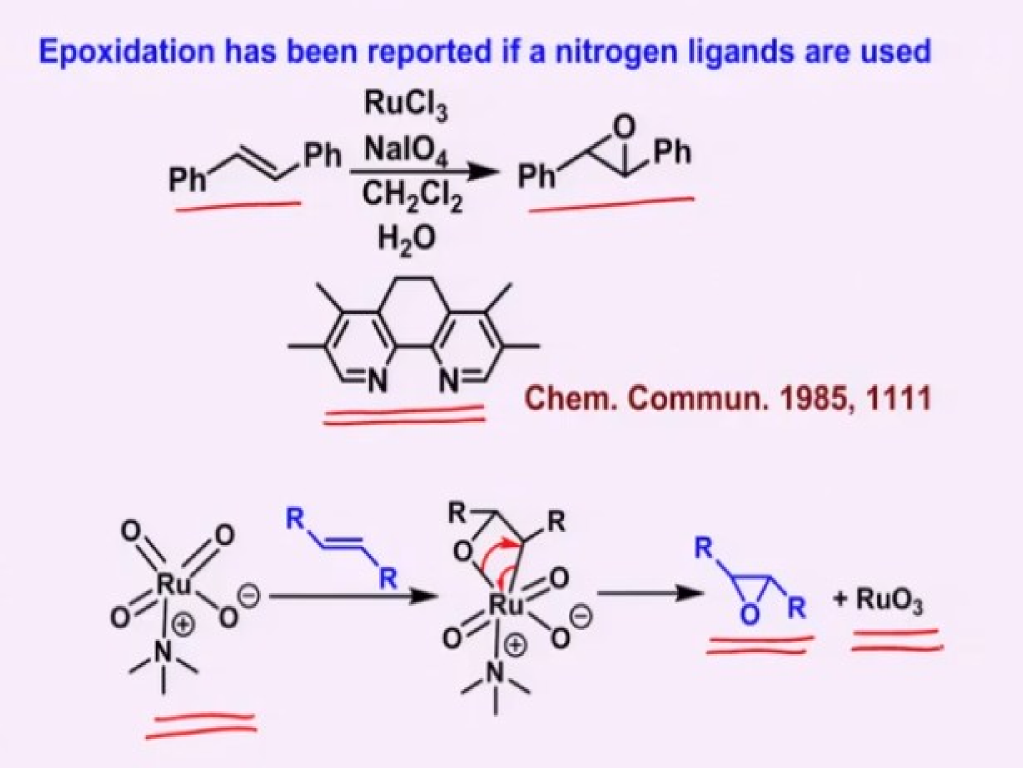

Epoxidation has been reported if a nitrogen ligands are used

Chem. Commun. 1985, 1111

It is also observed that if one uses a nitrogen ligand of this types, we can convert an olefin to the corresponding epoxide which is interesting reaction because the lone pair of electrons or the nitrogen will react with the ruthenium tetroxide to form this species. Now if this species comes in contact with the olefin one can have a 2 + 2 cyclo-addition of the ruthenium oxygen double bond and the double bond of the olefin here forming this intermediate which can undergo a cleavage forming the epoxide and low valent ruthenium species.

So, this is one of the very rare examples of a conversion of olefins to the corresponding epoxide but nevertheless one can carry out such a reaction in the presence of nitrogen ligands. Essentially what they do is to reduce the activity of the ruthenium tetroxide by this particular nitrogen ligand.

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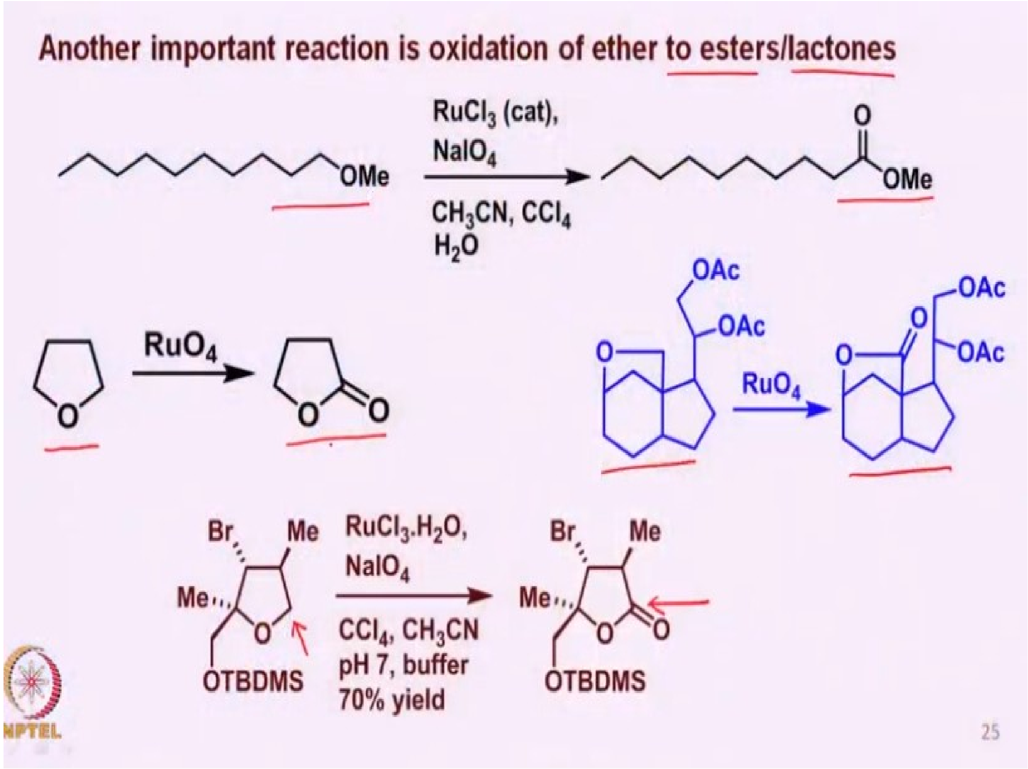

Another important reaction is oxidation of ether to esters/lactones

There is another important reaction which is conversion of ethers to the esters corresponding esters or to lactones. So, if we have ether of this kind one can get the corresponding ester if one starts with a cyclic ether one can get the corresponding lactone. In a similar fashion this cyclic ether goes to the corresponding lactone even this type of cyclic ether having many functional groups and a site where there is a possibility of lactone formation can allow the lactone formation to take place.

Now why should this happen? This happens mainly because as we have discussed earlier that ruthenium tetroxide is a very powerful oxidant and we cannot use solvent such as ether or pyridine or benzene such solvents. Because they can also react this is precisely the reason why ethers, can formed corresponding ester of the cyclic ethers can form the corresponding lactone. Now we will stop at this stage today and in the next class we will try and see what is the mechanism by which this ether which are acyclic or cyclic ethers are converted to the corresponding esters or lactones.

And further development of the ruthenium reagents for other reactions that will see you can go through these notes and then get ready for the next class till then good bye and thank you.