Essentials of Oxidation, Reduction and C – C Bond Formation
Application in Organic Synthesis
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Module No # 03
Lecture No # 15
Tetra-n-propylammonium Perruthenate (TPAP) Based Oxidations, and Tamao-Fleming oxidation

Hello everyone welcome to today's lecture what we discussed last time was introduction of ruthenium tetroxide as aggressive oxidizing agent. For the conversion of alcohols to the corresponding acids, cleavage of the C-C bond to the corresponding di aldehyde or di ketone or di carboxylic acids depending on the condition. Also we saw that the olefins can be converted to the corresponding epoxide if one uses a nitrogen ligand.

And we have also seen that how catalytic amount of ruthenium reagent such as ruthenium di oxide or ruthenium tri chloride is used in conjunction with co-oxidant such as sodium meta periodate for preparing the ruthenium tetroxide in the reaction medium. And thus only catalytic amount of the ruthenium salts can be utilized for this C-C bond cleavage. Now towards the end of the last class that; we saw that ethers or acyclic ethers or cyclic ethers can be converted to the corresponding esters or lactones.

And that was mainly because as we had discussed earlier that since the ruthenium tetroxide is a very strong oxidizing agent it is a very aggressive oxidizing agent it reacts with solvents such as ethers or pyridine or even benzene. That was the reason why oxidation of the acyclic ethers to the esters or cyclic ethers to the lactones took place. So we now will see in today's class the mechanisms of how does that oxidation occur.

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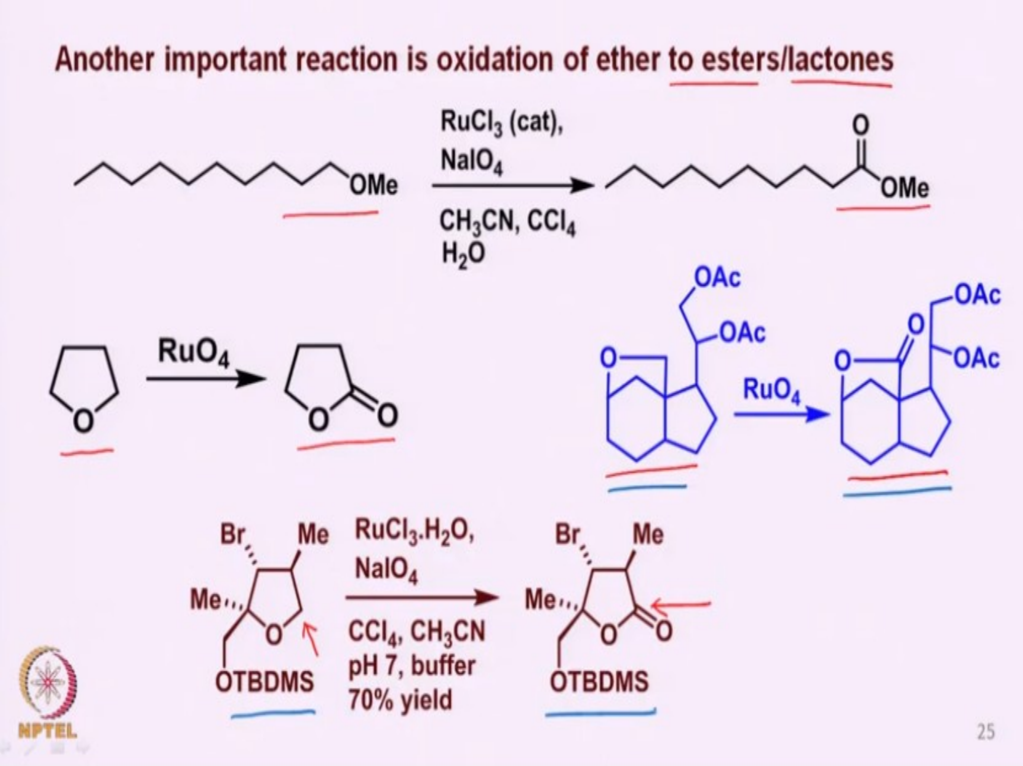

Another important reaction is oxidation of ether to esters/lactones

For example we can start with the cyclic ethers such as tetrahydrofuran this tetrahydrofuran then reacts with the ruthenium tetroxide and forms a species of this kind. Where there is a positive charge on the oxygen and of course this negatively charged ruthenium species which is attached to the oxygen. Now what can happen is this negatively charged part of the ruthenium species is able to take the proton from here and then in the process it breaks this in this fashion to form an oxonium ion.

And another ruthenium species of this type now this ruthenium species can go and react with the oxonium ion at the carbon which is electrophilic to form this species. And this species then undergoes oxidation to form this type of lactone and ruthenium species. This ruthenium species loses water to form ruthenium dioxide. So ruthenium tetroxide has got converted to ruthenium dioxide and in the process ether which is tetrahydrofuran has got converted to the corresponding lactone.

This is how the reaction occurs and it is a very useful reaction as we had seen different types of examples I can show once again those examples are here. For example you have this substrate of this kind going to the corresponding lactone and of this type to the corresponding lactone. Therefore this is a very useful conversion of ethers to the corresponding oxidized esters or lactone depending on whether it is acyclic or cyclic ether.

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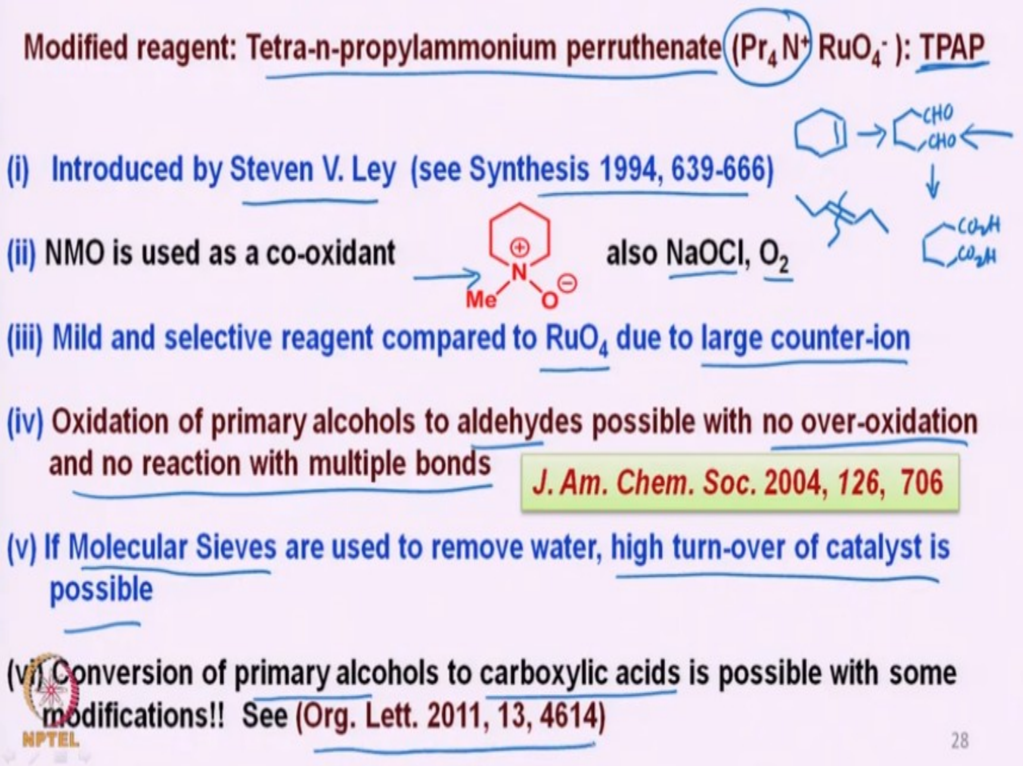

Modified reagent: Tetra-n-propylammonium perruthenate ($Pr_4N^+ RuO_4^-$): TPAP

(i) Introduced by Steven V. Ley (see Synthesis 1994, 639-666)

(ii) NMO is used as a co-oxidant also NaOCl, O_2

(iii) Mild and selective reagent compared to RuO_4 due to large counter-ion

(iv) Oxidation of primary alcohols to aldehydes possible with no over-oxidation and no reaction with multiple bonds

J. Am. Chem. Soc. 2004, *126*, 706

(v) If Molecular Sieves are used to remove water, high turn-over of catalyst is possible

(vi) Conversion of primary alcohols to carboxylic acids is possible with some modifications!! See (Org. Lett. 2011, 13, 4614)

Now there is a modification of the ruthenium tetroxide we saw in many cases that the aldehyde is oxidized to the corresponding acid that means if you allow a primary alcohol to react with ruthenium tetroxide it forms the corresponding acid. And I had already discussed the mechanism of the formation of the acid from aldehyde using ruthenium tetroxide. But many a times when such conversions are required to be stopped at the aldehyde stage then there is a problem.

And this becomes more important when say you carry out oxidative cleavage of a cyclic olefin or even an acyclic olefin. But with substrates which can give the corresponding aldehyde but then these aldehydes are oxidized to the corresponding acid. So basically what it means that we need to develop protocols which can allow the reaction to be stopped at the di-aldehyde stage. Because as I, showed one example that C-C bond cleavage does not occur with reagent such as ozone or $KMnO_4$ such reagents.

Then ruthenium tetroxide becomes a better oxidizing agent to clean that but if such a cleavage does not allow to, stop the reaction at the aldehyde stage and even one wants aldehyde then you unnecessarily go to the acid stage. Keeping these kinds of requirements in mind, Steven.V. Ley in 1994 reported introduction of reagent which is tetra n-propyl ammonium perruthenate which is also popularly called as TPAP.

In this reagent system the good point is that it is having a large counter cation here and that is useful because it can allow the solvent to be used which are normal organic solvent. In this reagent system the co-oxidant which is also soluble in organic solvents can be used and mostly it is the NMO that is n-methyl morpholine oxide. This n-methyl morpholine oxide but also one can use sodium hypochlorite or oxygen as a co-oxidant.

It is obviously very selective reagent and mild reagent compared to ruthenium tetroxide because of the large counter ion and that is present. At the same time it is negatively charge ruthenium perruthenate species and therefore it is having a less reactivity compared to the ruthenium tetroxide. So using these the alcohols can be converted tit he corresponding aldehydes with no over oxidation or no reaction with multiple bonds.

In this case it was found that if molecular sieves are used which is nothing but alumino silicates as they absorb water to remove water high turnover of the catalyst is possible. Now when of course with the same reagent system there are conditions under which primary alcohols can be converted to the corresponding carboxylic acids. But then that is not so much really required but if wants to see this is the reference that you can check it.

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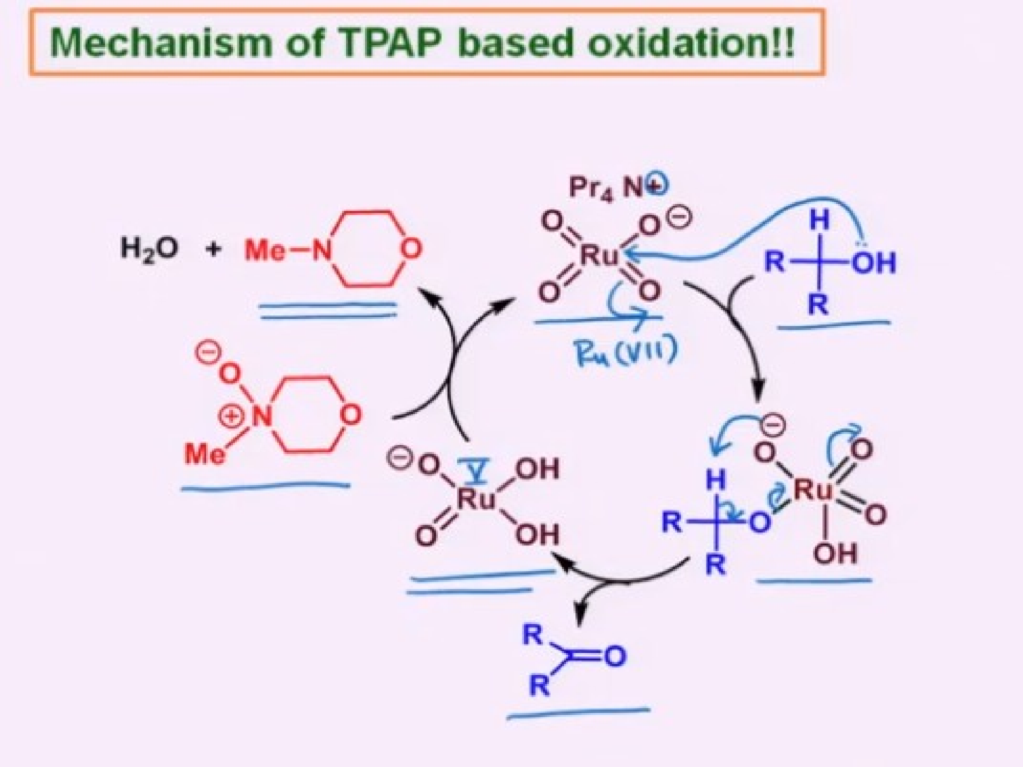

Mechanism of TPAP based oxidation!!

Now with what is the mechanism of the TPAP based oxidation it is very similar to the ruthenium tetroxide based oxidation. But here I have shown that the TPAP which is present here as this counter cation which is large tetra n-propyl ammonium species that reacts with the alcohol to form this kind of species where the lone pair of electron on the alcohol reacts with ruthenium with the movement of the electron density on to the oxygen forming this intermediate and this intermediate then can take up the proton allows the oxidation to takes place in this fashion.

And one can generate the corresponding ketone and the ruthenium species which is low valent compared to the starting ruthenium which is ruthenium 7 goes to ruthenium 5 here. And this is then re-oxidized with n-methyl morpholine n-oxide to the TPAP and one loses the corresponding n-methyl morpholine as a byproduct from the n-methyl morpholine oxide. So this is mechanism which is proposed for the oxidation of alcohols to the corresponding ketones. Obviously this does not react further with aldehydes to form the acid.

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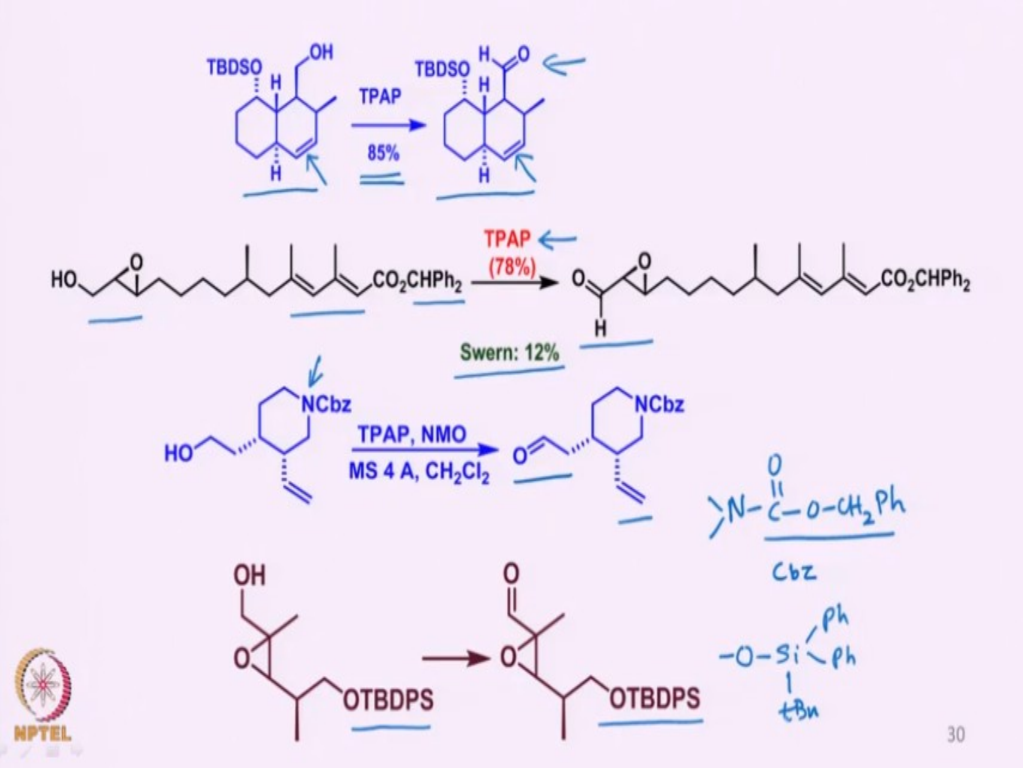

So examples are here this kind of alcohol having a double bond is converted to the corresponding aldehyde with the 85% yield. This kind of substrate having an epoxy alcohol and 2 double bonds and of course the phenyl rings here which can be oxidized and this substrate when it was reacted with the Swern's oxidizing agent it gave only 12% of the oxidized product. On the other hand with TPAP 78% of the corresponding aldehyde was formed.

But we can also see another example of course in this particular case also nitrogen has been protected as Cbz group. Cbz group is nothing but COO benzyl group CH2 phenyl this is the protecting group for the. And this is what is called Cbz. And therefore this is protected and that gives the corresponding aldehyde no over oxidation of the double bond. And another example is of course this lower one where this protecting group is also unaffected which; is tertiary butyl di-phenylsilyl that is this protecting group is like this.

We have 2 phenyl rings here and tertiary butyl so this is OTBDPS tertiary butyl di- phenylsilyl. So these kinds of different protecting groups are unaffected groups and the reagent allows oxidation in a selective and mild fashion. And therefore it has become a very popular oxidizing agent.

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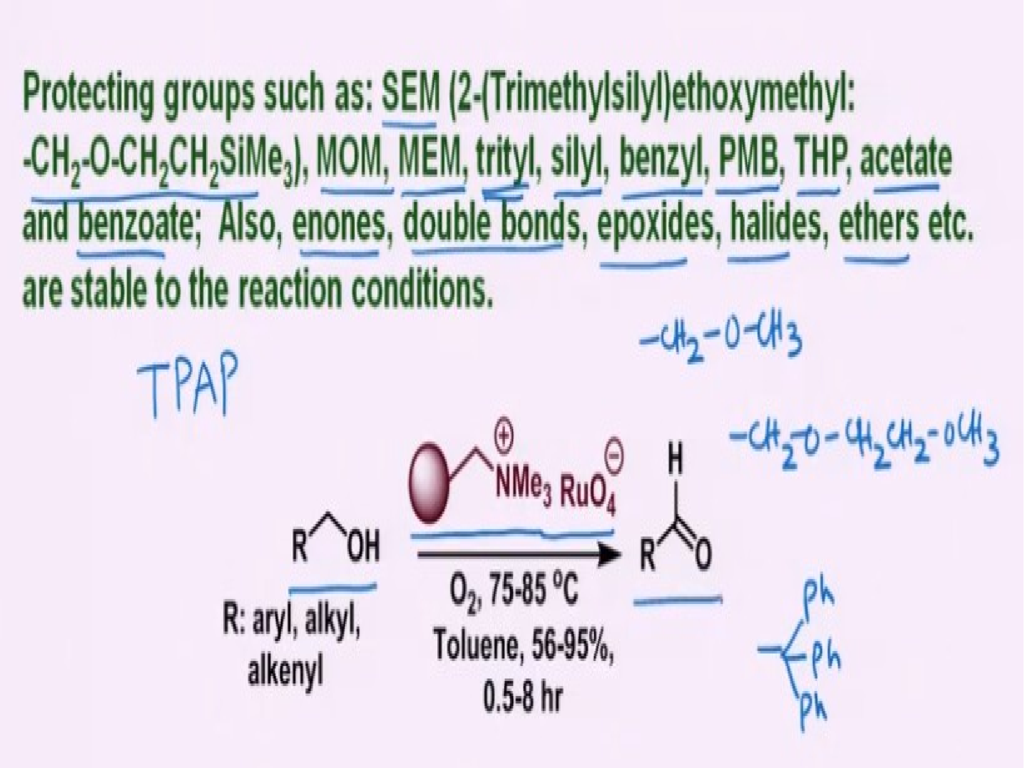

Protecting groups such as: SEM (2-(Trimethylsilyl)ethoxymethyl: $-CH_2-O-CH_2CH_2SiMe_3$), MOM, MEM, trityl, silyl, benzyl, PMB, THP, acetate and benzoate; Also, enones, double bonds, epoxides, halides, ethers etc. are stable to the reaction conditions.

TPAP

$-CH_2-O-CH_3$

$-CH_2-O-CH_2CH_2-OCH_3$

So as I said that different protecting group such as SEM which is 2-trimethylsilyl ethoxy methyl like this MOM which is; nothing but CH2O methoxy methyl protecting group for the alcohol or any of alcohol type or MEM which is methoxy ethoxy methyl ether. So you have CH2 CH2O CH3 then trityl group which is nothing but this type of substrate from the oxygen here of course then you have a silyl group, benzyl group. Paramethoxybenzyl group, tetrahydropyranyl group, acetate and benzoate protections.

Also functional group such as enones, double bonds, epoxides, halides, ethers are stable under the reaction conditions. So therefore TPAP is a very useful alternative of converting primary alcohols to the corresponding aldehydes or without and without cleaving various kinds of double bonds or tolerating different types of function groups. It is also found that one can introduce this type of solid phase catalyst where you have the part of the nitrogen is attached to say polystyrene based group and such an oxidizing agent also is useful because you can recover and reuse it.

Simply filter it off and the solid phase ruthenium reagent can be reused for the oxidation of alcohol to the corresponding aldehydes. So this is what it was related to the ruthenium tetroxide based oxidizing agents which where conveniently made useful for various transformations. And of course introduction of the TPAP as for as mild, and selective oxidizing agent. Now we go to another oxidizing agent oxidation rather and that is called as Tamao-Fleming oxidation.

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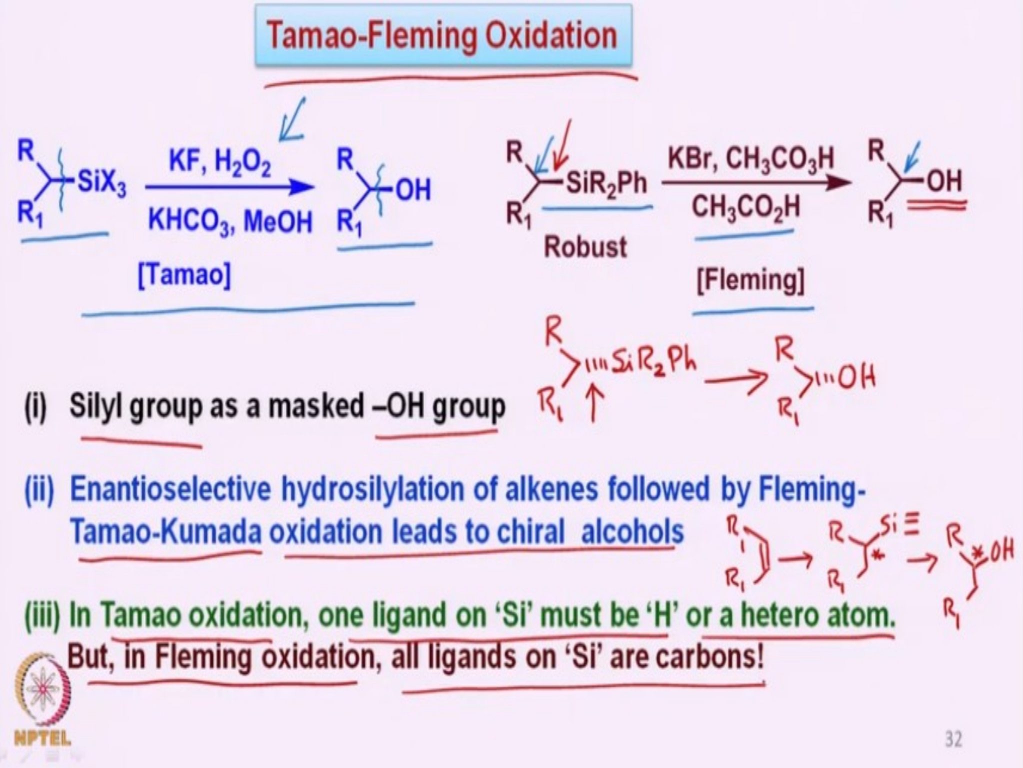

Tamao-Fleming Oxidation

KF, H_2O_2

$KHCO_3$, MeOH

[Tamao]

KBr, CH_3CO_3H

CH_3CO_2H

[Fleming]

(i) Silyl group as a masked –OH group

(ii) Enantioselective hydrosilylation of alkenes followed by Fleming-Tamao-Kumada oxidation leads to chiral alcohols

(iii) In Tamao oxidation, one ligand on 'Si' must be 'H' or a hetero atom. But, in Fleming oxidation, all ligands on 'Si' are carbons!

In Tamao-Fleming oxidation what is used is a carbon silicon bond of this type is converted to the corresponding carbon oxygen bond. That means this bond here is basically converted to the corresponding oxygen this was introduced by Tamao where he used a slightly different types of silicon based substrates and slightly different conditions. As one can see here with, potassium fluoride hydrogen peroxide potassium bicarbonate in methanol.

At the same time Fleming introduced a somewhat robust silicon based substrate where there are only carbons which are attached on the silicon carbon based groups which are attached. And this in the presence of potassium bromide par acetic acid in acetic acid medium allows the conversion of this type of substrate to the corresponding alcohol. What it does it is clearly one can see that it allows the silyl group to be used as a masked OH group.

Interestingly what is very important in this oxidation is whatever, is the stereochemistry of the original silicon substrate that means if this substrate which is used has this type of silicon group attached where the absolute stereochemistry is like this or like this. So if one starts with this type of absolute stereochemistry the hydroxy group also is coming from the same side. So if, one takes this substrate then one can get the corresponding alcohol which would look like this.

So Enantio selective hydrosilylation of alkenes followed by Fleming-Tamao-Kumada of course Tamao and Kumada did together the oxidation. So this called as Tamao-Kumada oxidation but popularly it is called as Tamao-Fleming oxidation can lead to the chiral alcohols. That means if one starts with any olefin like this where there are 2 different substrates attached or say for example something like this.

And if one converts into the silyl group which; is present here in this fashion where you have now asymmetric center that is being created. And if this is chiral compound then of course you can get the, upon this oxidation the corresponding alcohol in a chiral fashion. So you start with a chiral substrate and you get the corresponding chiral alcohol because the oxidation that occurs is highly stereo specific or stereo selective reaction.

Now in Tamao oxidation one ligand on silicon must be hydrogen or a heteroatom that is the condition. But in Fleming oxidation all ligands on silicon are carbons so there is a slight difference in the reaction conditions and therefore the requirements are slightly different.

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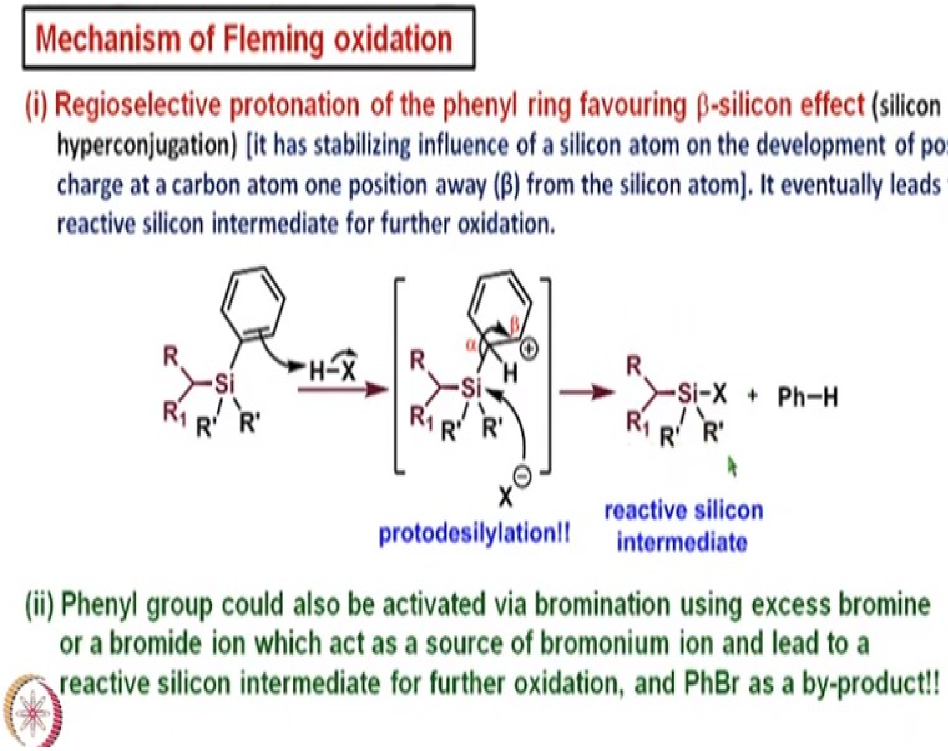

Mechanism of Fleming oxidation

(i) Regioselective protonation of the phenyl ring favouring β-silicon effect (silicon hyperconjugation) [it has stabilizing influence of a silicon atom on the development of positive charge at a carbon atom one position away (β) from the silicon atom]. It eventually leads to a reactive silicon intermediate for further oxidation.

(ii) Phenyl group could also be activated via bromination using excess bromine or a bromide ion which act as a source of bromonium ion and lead to a reactive silicon intermediate for further oxidation, and PhBr as a by-product!!

What is the mechanism of the Fleming oxidation? The Fleming oxidation essentially involves as we saw that a conversion of a stable silicon containing starting material to a reactive silicon intermediate for further oxidation. So under the protic conditions which was the initial condition that was reported by Fleming it basically involved a region-selective protonation of the phenyl ring favouring beta silicon effect. That means this particular phenyl ring undergoes protonation.

In such a fashion that the proton gets attached to this particular carbon atom and positive charge is formed at the next carbon atom which is the beta carbon atom. And this is because of the favouring beta silicon effect which is nothing but a silicon hyper-conjugation. It has stabilizing influence of a silicon atom on the development of a positive charge at a carbon atom one position away that is a beta position from the silicon.

This is the alpha position and this is the beta position so this particular formation of a positive charge at the beta carbon. Then eventually allows a proto desilylation because that negative charge that has come on the X that is say for example if we use HBr then it is a bromide ion. That bromide ion then interacts with the silicon and this carbon silicon bond is broken to regenerate aromatic system here like benzene here.

And in the process we generate the reactive silicon intermediate so essentially this is nothing but a regio-selective proto desilylation to form reactive silicon intermediate for further oxidation. This is the basis of the Fleming oxidation now in principle one can use any electrophile in place of H$^+$ and carry out the cleavage of the carbon silicon bond. And generate the corresponding aromatic compound for example we could also use a source of bromonium ion.

That means a phenyl group could also be activated via bromination using either excess of bromine which will of course give a source of Br$^+$ as well as B^{r-}. Or a bromide ion under oxidation condition that leads to the formation of a bromonium ion eventually for aromatic system to react with the aromatic species. And in the case of bromine then of course we get bromobenzene as a byproduct. And of course the same silicon which is reactive silicon intermediate for further oxidation will form.

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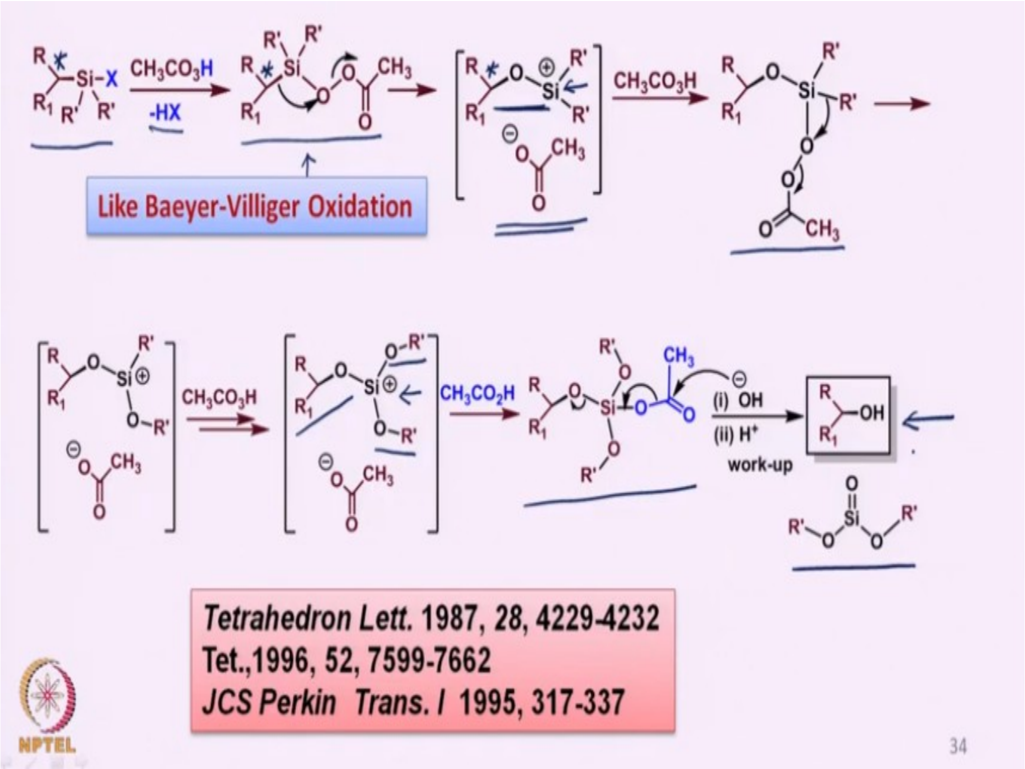

Like Baeyer-Villiger Oxidation

Tetrahedron Lett. 1987, *28*, 4229-4232
Tet.,1996, 52, 7599-7662
JCS Perkin Trans. I 1995, 317-337

Now this is the substrate that we have got that reacts with peracetic acid where the peracetic acid replaces the X from here H X is out and we can get an intermediate of this type which undergoes. Now this is the chiral centre that we are talking about it this is the chiral centre that we are talking the asymmetric centre. Now this substrate looks very similar to a substrate that can be seen as equivalent to undergoing as Baeyer-Villiger oxidation.

And in the Baeyer-Villiger oxidation also if you recall that the chiral centre does not lose the chirality and therefore this migration from here leaving the acetate ion out gives this intermediate. Now here the chirality is not last which now then reacts with another mole of peracetic acid where peracetic acid attaches to the silicon here forming this intermediate. And the remaining R primes which are present that which are the common substrates they undergo Baeyer-Villiger oxidation type of oxidation similar to the one that I have shown it here.

Undergo to form with the first R prime you get the transfer like this here to give the substrate which is again attacked by the paracetic acid. To eventually give via Baeyer-Villiger oxidation the 2 O R primes here. So we have 1 O R substrate which is what is derived from the alcohol and then 2 O R primes from the silicon substituents. And then the acetic acid attacks on to this silicon substrate and we get this particular product as the stable ultimately stable silicon substrate which upon basic workup like sodium hydroxide followed by protonation releases the alcohol and the silicon side product.

So this is the Fleming oxidation in which 2 steps first the silicon substrate which has 1 phenyl ring and 2 carbon substrates to form of carbon based groups undergoes proto desilylation to form silicon X bond. And then with peracetic acid eventually one gets this alcohol which is having same chirality as the starting silicon substrate. So we will stop it at this stage today and we will take it up in the next class the other aspects of this Fleming-Tamao oxidation and their utility in organic synthesis.

So you can go through some of the references I have mentioned already you can go through those references as well as revise what I have discussed today. Till then bye and thank you and we will see you in the next class.