Reagents in Organic Synthesis
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Oxidation by Ru, Hypervalent Iodine, Al and Na Based Reagents
Lecture 06
Keywords: TPAP, Dess-Martin periodinane, DMP, and Oppenauer oxidation

Welcome Again. Today we will discuss, four oxidizing agents- Tetra n-propyl ammonium peruthenate, which is TPAP. Then, Dess-Martin periodinane, DMP, and Oppenauer oxidation, and fourth one is, sodium periodate.

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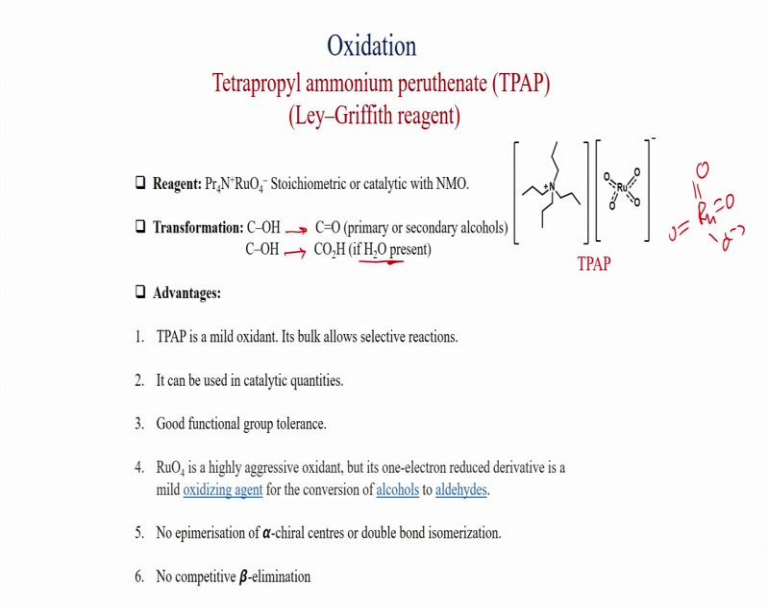

So TPAP, which is tetrapropyl ammonium peruthenate, which is also called Ley-Griffith reagent. And as you can see the structure, there is tetra n-propyl ammonium, salt is there. And, ruthenium. This is ruthenium, plus 7 state. So, this is peruthenate. And, this is; can be used in stoichiometric or catalytic with n-methylmorpholine oxide. And generally, this converts to the primary or secondary alcohol to the carbonyl compound. Also, it can convert alcohol to the carboxylic acid. And, when H_2 is present, that time it can convert to carboxylic acid.

It has several advantages, like it is a mild oxidant. Its bulk allows selective reactions. It can be used in catalytic quantities. Good functional group tolerance. Also, ruthenium

tetraoxide is a highly aggressive oxidant. But, its one electron reduced derivative, that is, this one is a mild oxidizing agent for the conversion of alcohols to aldehydes. That is the motive to generate this peruthenate species. And, no epimerisation of alpha chiral centers or double bond isomerization happen during oxidation. Also, no competitive beta elimination.

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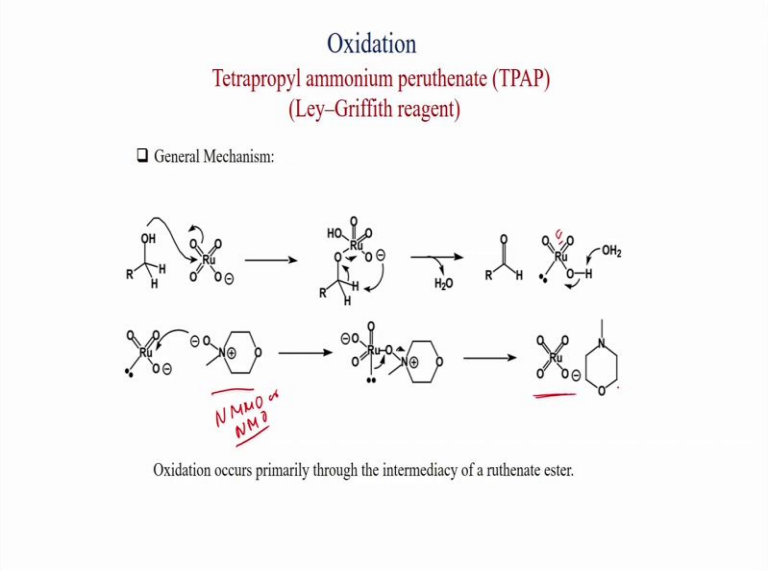

So, this is the general mechanism, that alcohol first attack to the ruthenium. And then, this ruthenate ester is generated. After that, this O minus attracts this acidic hydrogen of the alcohol. And then, the carbonyl compound is generated, after elimination of water. And, ruthenium 7 becoming ruthenium 5 here.

And then, water can attack, take this proton and it makes the ruthenium, this species O minus. And now, (morph) NMO; NMMO. So, this is called NMMO or NMO, N-methylmorpholine oxide, which re-oxidizes this one. And, then ruthenate is generated again.

So, how it does? This O minus attacks to ruthenium again. And now, this species is formed, which after elimination of morpholine. As, you can see, N-methylmorpholine is liberating here and you get the ruthenate species. That is the use of N-methylmorpholine

oxide. That it can regenerate the ruthenate species. And, this is the ruthenate ester that is the intermediate.

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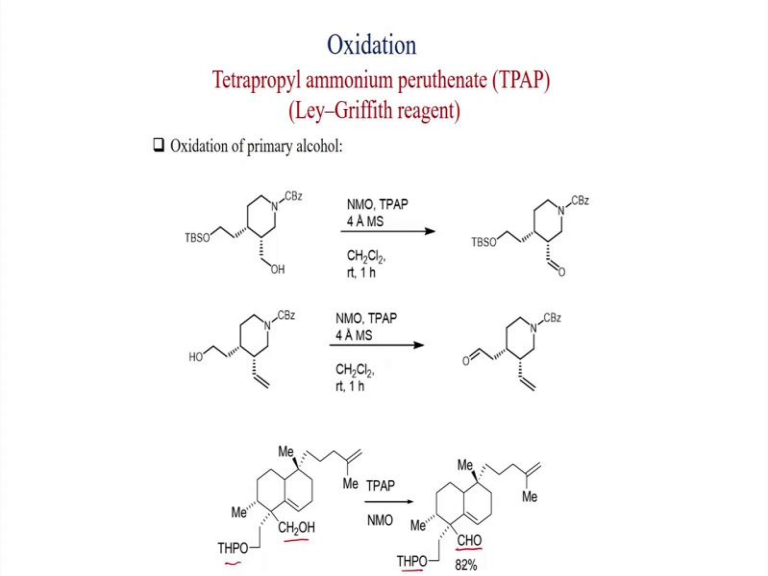

So, it main application is oxidation of primary alcohol. Like you can see, here is a primary alcohol is there. OTBS group is there. NCBZ group is there. And, selectively this alcohol is getting oxidized to aldehyde with NMO, TPAP, 4 angstrom molecular shift, dichloromethane, in room temperature condition. And, these two groups are not touched during the condition.

Also, here the double bond is present and similarly NCBZ group is there. Here, also the primary alcohol oxidize to the aldehyde. And, this is a complex molecule. As you can see, there is a THP, which is acid sensitive group. And, alcohol is there. And also, double bond present are there. So, in this TPAP NMO conditions, selectively this alcohol is getting converted to the aldehyde, without disturbing the THP group. That means, TPAP is a very mild oxidant. It cannot harm the acid sensitive group.

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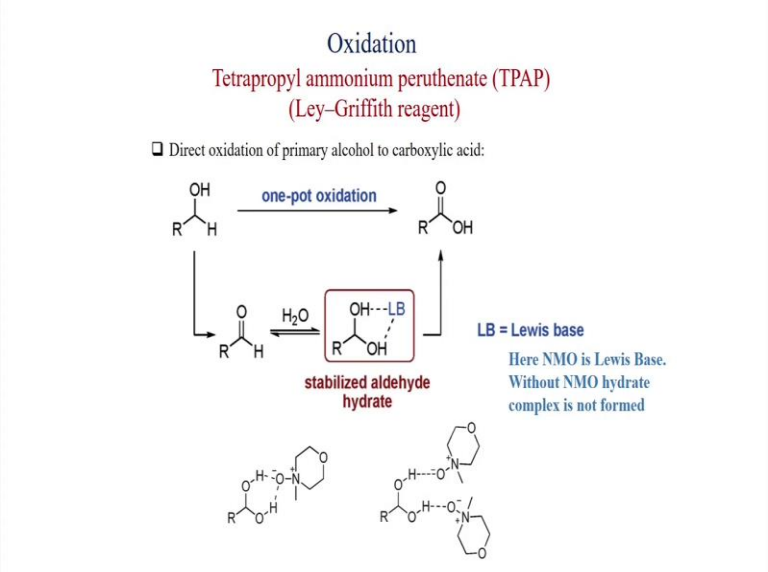

Also, direct oxidation of primary alcohol to carboxylic acid is possible. And, first the alcohol is getting oxidized to the aldehyde. And, then water attacks to the aldehyde, so stabilized aldehyde hydrate. And, this stabilization happens with a Lewis base, that is, the NMO. So, NMO acting as a Lewis base, that is, stabilizing the aldehyde hydrate. And, aldehyde hydrate ultimately going to carboxylic acid.

And here, you can see, one molecule of N-methylmorpholine oxide binding to the aldehyde hydrate. Here, two hydrogen bonded, they are with one O minus. And, here two NMO group is there. So, each one is binding with one OH group. So, this hydrogen bonding stability is very important, to stabilize the aldehyde hydrate, which ultimately going to carboxylic acid.

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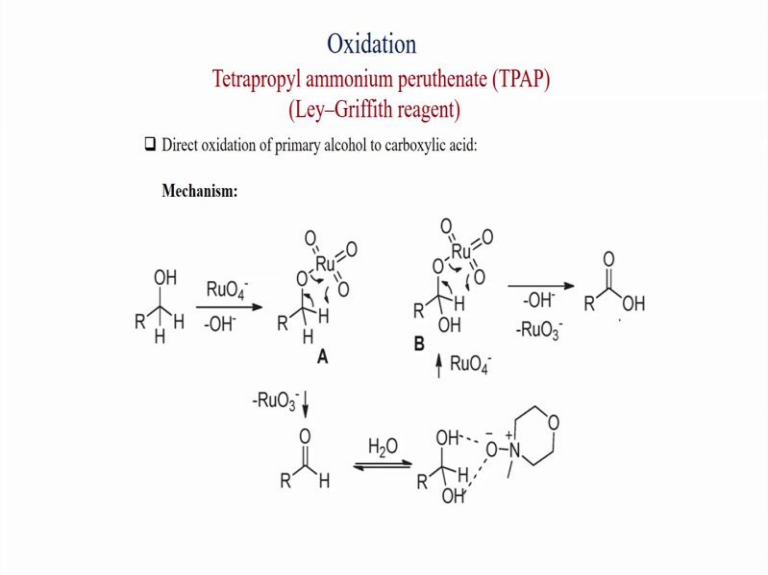

So, this is the mechanism. Again, we can see that, first the alcohol attacks to the ruthenate to generate this ruthenate ester. And then, after elimination of OH minus, this species is formed. And, now this ruthenium oxygen bond can take this proton here. And, the ruthenium O_3, RuO_3 minus is liberated and the aldehyde is generated.

And, then the aldehyde, in presence of water, makes this aldehyde hydrate, which stabilize by the NMO. As we have seen, either one or two molecule of NMO can stabilize the aldehyde hydrate. And, again ruthenate reacts with this aldehyde hydrate to generate this ester, ruthenate ester. Which similarly, like this intermediate like A, this eliminates the water or OH minus, RuO_3, you get the carboxylic acid.

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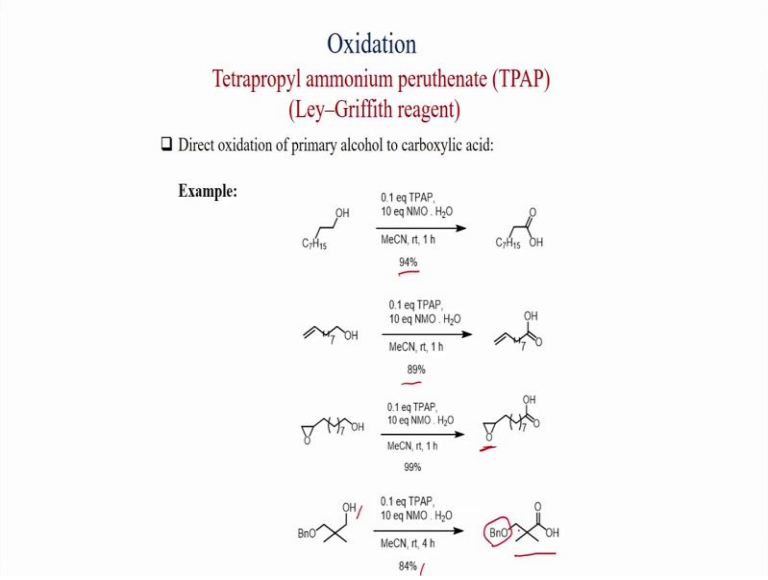

And, there are different primary alcohols can be oxidized directly to the carboxylic acid with this condition. Here, you can see a long chain alcohol. Primary alcohol can be oxidized to the acid, with point 1 equivalent TPAP, 10 equivalent NMO, plus water, acetonitrile solvent, room temperate, it gives 94 percent yield of this product.

Also, this long chain alcohol with a double bond can be oxidized to the carboxylic acid with point 1 equivalent TPAP, 10 equivalent NMO, water, acetonitrile condition, 89 percent yield it gives, the product. Also, there can be an epoxide in the alcohol. And, you can see, this a long chain alcohol with an epoxide is converted to the carboxylic acid without disturbing the epoxide group. So, epoxide group is untouched during this oxidation.

Also, a benzyl group is present here; benzyl and primary alcohol. So, under this TPAP NMO condition, you the carboxylic acid in good yield and benzyl group is undisturbed in this condition.

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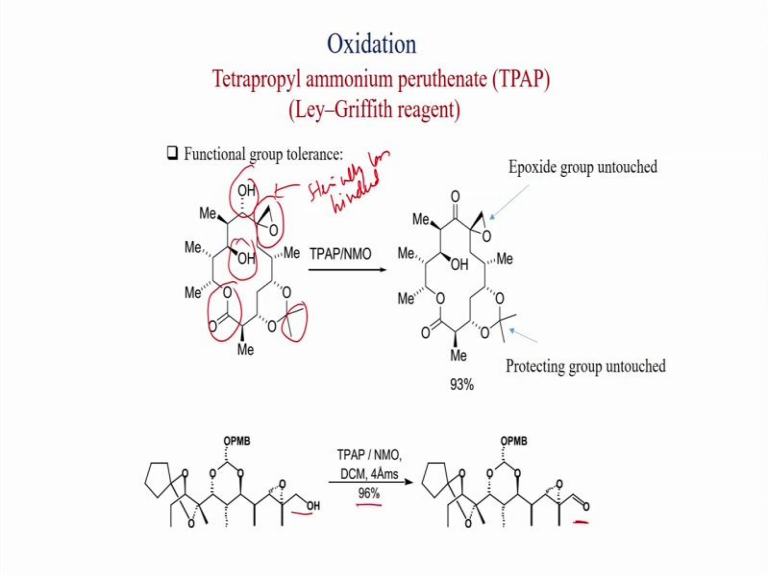

Also, this oxidation has been used in many natural product synthesis. Here, you can see a complex structure. There are many groups are there, like here, an epoxide is there. Here is a ketal group is there. Here, an ester motif is there. And, when this oxidation happens with the TPAP, here we can see that, only a secondary alcohol, which is sterically less hindered. Here, two OH is present. But, this OH is sterically hindered, because of, both side methyl group is there. So, this is sterically accessible. This is sterically less hindered. And, that is why, selectively this alcohol only go going to carbonyl. And also, other groups are not disturbed during this oxidation.

Here, also a complex molecule is present. Here, you can see, there is an acetal motif. There is a ketal motif. There is an epoxide. So, all these group are remain intact, when, when this primary alcohol getting oxidized to the aldehyde, with TPAP, NMO, DCM, 4 angstrom molecular shieves condition. And, it gives good yield, very good yield of this product.

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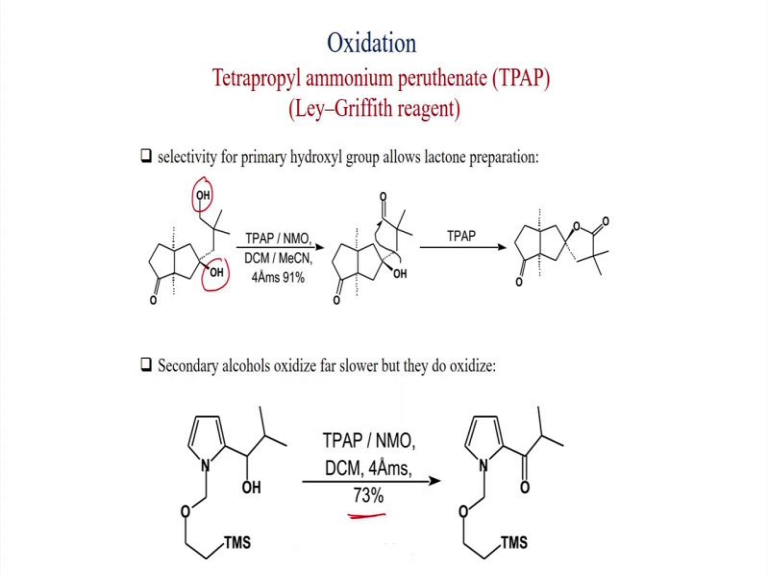

Also, selectivity for primary hydroxyl group allows lactone formation. So, here you can see, there is a tertiary alcohol is present and primary alcohol present. When, TPAP, NMO, DCM is used, 4 angstrom molecular shift, you get selectively the aldehyde. And, after that aldehyde, the lactone is formed. That OH attacks to the tertiary alcohol, attacks to aldehyde, to get the lactol, which finally goes to the lactone, with TPAP.

Here, secondary alcohol also oxidizes, but much more slowly. Like this, alcohol with an heterocyclic motif, pyrrole motif, it oxidize to the ketone, with TPAP, NMO, DCM, 4 angstrom molecular shift condition and it gives 73 percent yield. Also, long reaction time is required.

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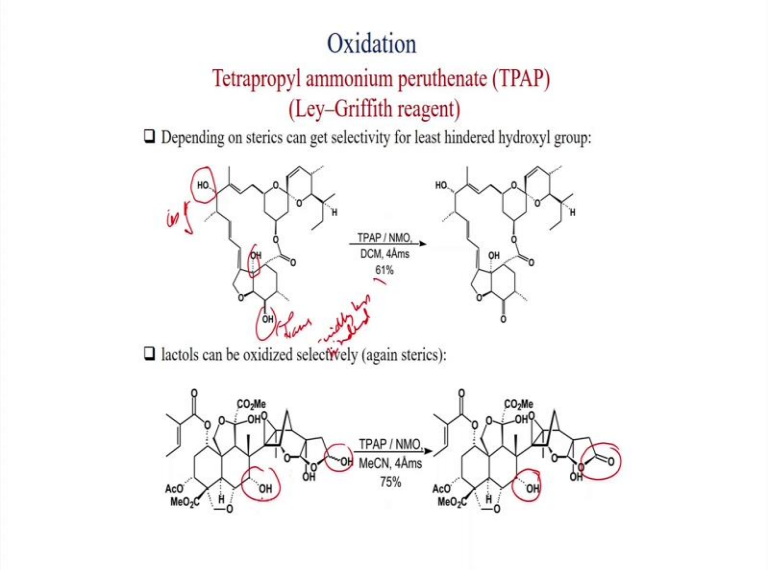

Here is a complex molecule. And that is what, we discussed last slide that depending on sterics can get selectivity for least hindered hydroxyl group. Here, is another example. Here, you can see, there are two secondary alcohol present. This tertiary alcohol cannot be oxidize. So, among these two secondary alcohols, this alcohol is cis with the methyl group. And, this alcohol is trans.

So, this is trans and this is cis. So, this alcohol is sterically more hindered and this is sterically less hindered. As this alcohol is sterically less hindered, when TPAP, NMO, 4 angstrom molecular sieve is used, then selectively this alcohol only getting oxidized to this ketone, with 61 percent yield. So, this tells that the steric is very important, because the alcohol first attacks to the ruthenium center. So, if the alcohol is sterically hindered, then it cannot attack to the ruthenium. And that is why, the selectivity is coming.

Here, is an example, that lactol can be oxidized selectively. Again, here sterics is operating. So, here you can see, there is a nalcohol present is there. And, there is a lactol present. So, when TPAP NMO is use, selectively this alcohol, this lactol is getting oxidized to the lactone, without disturbing the secondary alcohol. So, because secondary alcohol also cis with this oxygen ether bond. So, this alcohol is sterically more hindered position. That is why TPAP can oxidize less hindered lactol motif to the lactone.

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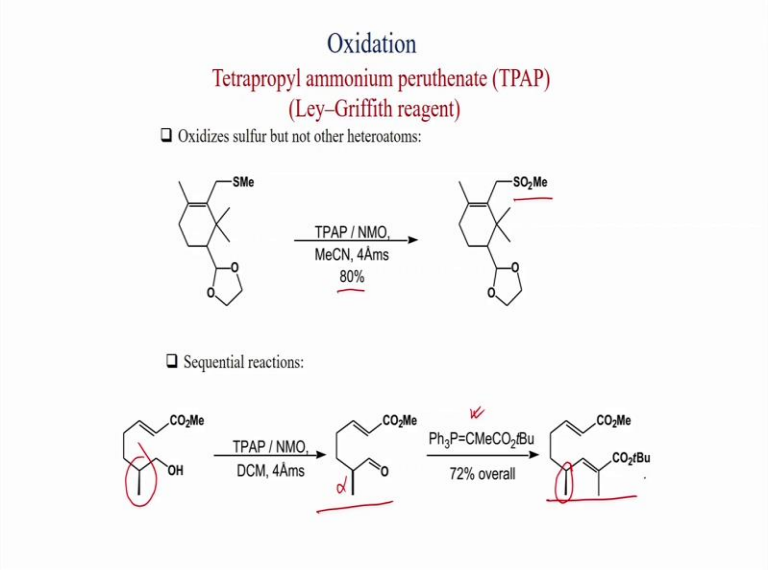

TPAP can also oxidize sulfur, but not other heteroatoms like this, thioeteher. Thioether can be oxidizes to the sulfoxide with TPAP, NMO, 4 angstrom molecular sieves condition and it can give 80 percent yield of the suphoxide. Also, sequential reaction is possible, like here chiral center is present with the alcohol. So, under this condition, there is a possibility that, aldehyde alpha position can epimerize. And, you get racemerisation.

But here, with TPAP NMO condition, you can get the aldehyde. And in-situ, if you trap with this Horner Wittig ylide, then the alpha beta unsaturated ester is possible and this chiral center is retained. So, that means TPAP is very mild. It does not, when in the aldehyde condition. It does not allow epimerization of the methyl group. And that is why you get, the methyl geometry is retained in the alpha beta unsaturated ester.

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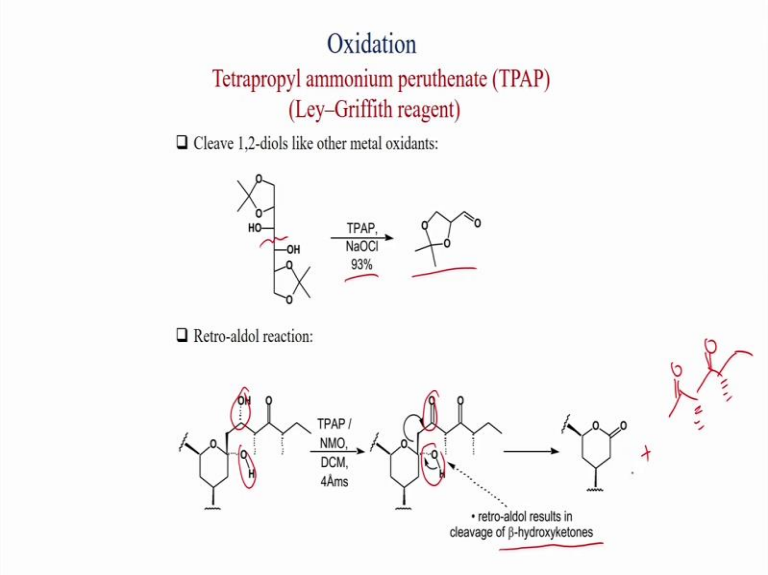

Cleavage of 1,2-diols is possible also with TPAP. We have seen, like earlier diol cleavage. But, here TPAP can also do with NaOCl, sodium hypochloride, it gives 93 percent yield of this aldehyde. So, this is symmetrical diol. If it cleaves, then it gives only this product, two molecules of this product.

Also, retro-aldol reaction is possible. So, here you can see, there is a tertiary alcohol is present. And, this is a secondary alcohol. So, with TPAP NMO, the secondary alcohol gets oxidize. Now, this is a beta hydroxy ketone. This is a beta hydroxyl ketone. This is a hydroxy, this is ketone. So, this is the aldol product. Now, the retro-aldol possible, that OH becomes a ketone here, and you get here, aldol donor. So, this becomes aldol acceptor and you get here, this. So, this two reactant on aldol reaction can give this product. So, here under this condition, retro-aldol reaction happens and you get these two reactants.

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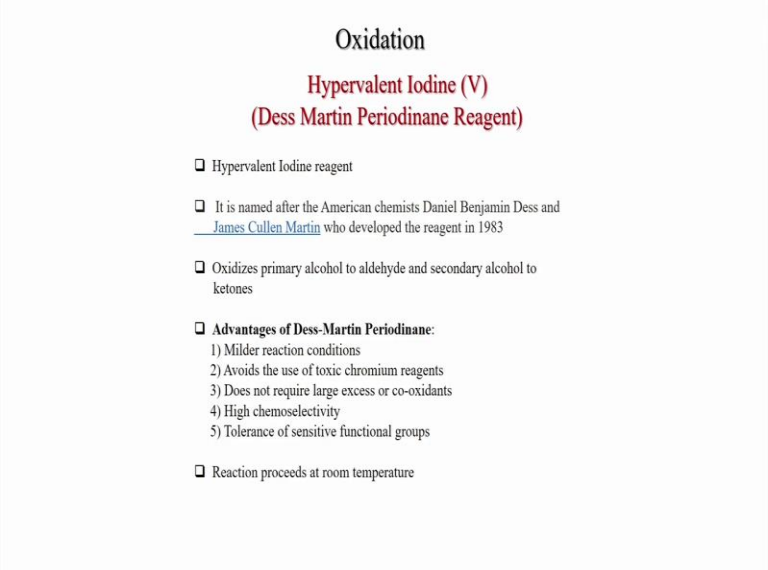

Now, we will discuss Dess-Martin periodinane. This is hypervalent iodine five reagent. And this is named after the American chemist, Daniel Benjamin Dess and James Cullen Martin, who developed the reagent in 1983. This oxidizes primary alcohol to aldehydes and secondary alcohols to ketones.

Advantage of Dess-Martin periodinane, it is milder reaction condition generally used. Avoids the use of toxic chromium reagents. So, this is hypervalent iodine. This is much less toxic. Does not require large excess or co-oxidants, like we have seen in TPAP, you need the N-methylmorpholine oxide. Dess-Martin periodinane itself can oxidize alcohol to aldehyde. High chemoselectivity is possible. Tolerance of sensitive functional group. Reactions proceed at room temperature.

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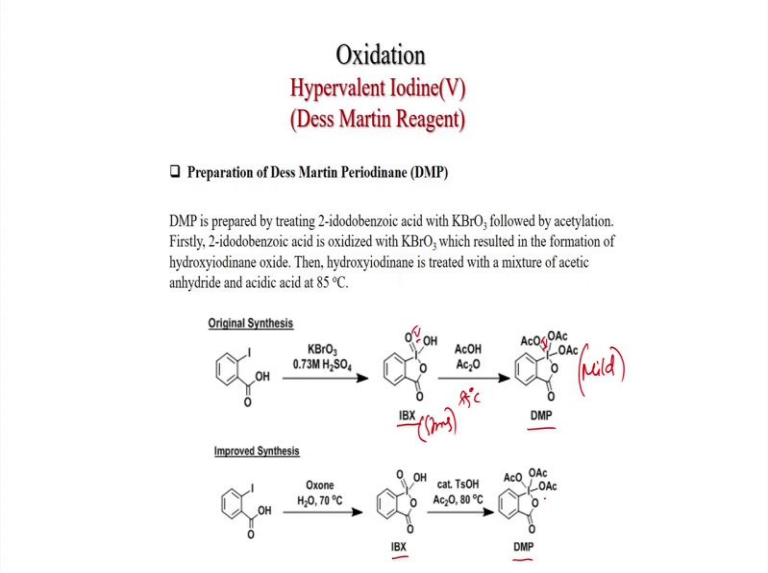

So, preparation of Dess-Martin periodinane, we will see first. Dess-Martin periodinane is prepared by treating 2-iodobenzoic acid with $KBrO_3$ followed by acetylation. Firstly, 2-iodobenzoic acid is oxidized with $KBrO_3$, in point 73 molar H_2SO_4 and it gives the iodoxybenzoic acid, which is the IBX. Here, you can see, iodine is plus 5. And then, the hydroxyiodinane, and so this is can be also called hydroxyiodinane, is treated with mixture of acetic anhydride and acetic acid at 85 degree centigrade. It gives the of Dess-Martin periodinane.

So, what happens? One acetate group attacks here and this OH gets protected. So, ultimately after that also, after attacking this O oxygen also takes another acetate molecule. So, here triacetate molecule is there. And, here also iodine is plus 5. So, what is the difference between IBX and DMP? Because if you convert this to acetate, this becomes very mild. So, Dess-Martin periodinane is very mild oxidizing agent compared to IBX. That is why, this reagent was developed.

Also, there is another procedure for this Dess-Martin periodinane, which is improved synthesis. Instead of potassium bromate, you can use oxone, water, 70 degree centigrade, you can generate the IBX. And instead of acetic acid, you can use catalytic para-toluene

sulfonic acid with acetic anhydride, 80 degree centigrade, you can get Dess-Martin periodinane.

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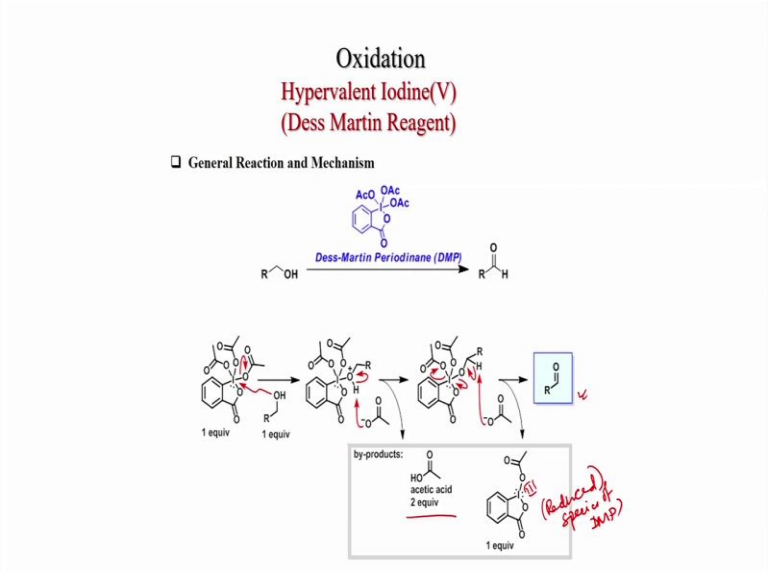

So, what is the general reaction? This is the alcohol to aldehyde oxidation. And, what is the mechanism? The mechanism is that, one equivalent of Dess-Martin periodinane reacts with one equivalent of alcohol. First, a substitution reaction happens. So, acetate group is liberated and oxygen makes bond with the iodine. And after that, this proton liberated by the acetate, ultimately it becoming acetic acid.

And now, that acetate again or this acetate can deprotonate this hydrogen, which is acidic enough after binding to the iodine. And now, this gets liberated and ultimately this bond will, i-oxygen bond will cleave. And, again another acetate will liberate and ultimately you get this. So, iodine 5 becomes iodine 3. I, there only one acetate molecule will be remain. So, here three acetate group was there.

And ultimately, this product, it becomes one acetate. So, two acetate liberated and in that process the alcohol became oxidized to aldehyde. And, Dess-Martin periodinane reduced to this one. So, this is the reduced species of Dess-Martin periodinane. And, two acetate molecules are liberated, generates two molecules of acetic acid. So, two molecule of

acetic acid this and this you will get, when you do the reaction of alcohol with Dess-Martin periodinane.

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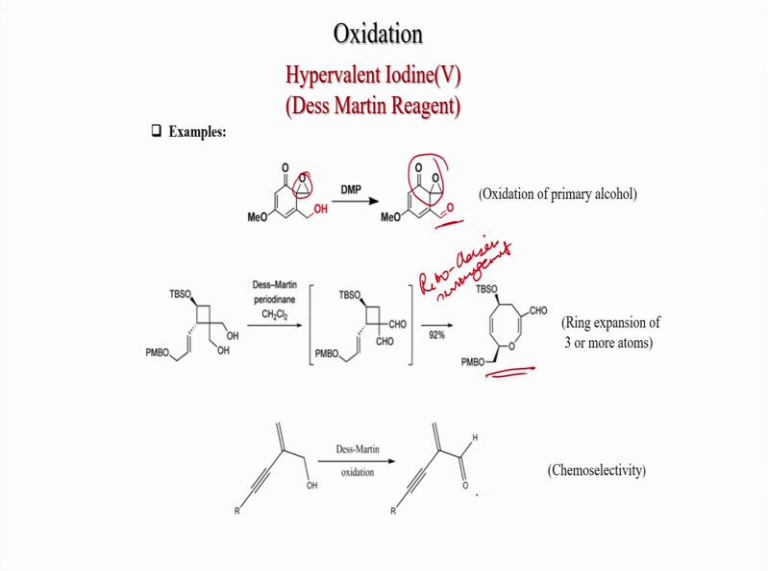

So, as we told earlier, that this is mild oxidizing agent. And, you can see this molecule, there is a dienone motif and also an epoxide is there. And under this condition, selectively the alcohol is oxidized to the aldehyde and other motifs remain undisturbed.

This is an oxidation cascade reaction. So, this is Dess-Martin periodinane oxidized this diol to the dialdehyde. And then, this 8 membered cycle is formed. So, this is called, retro-Claisen rearrangement. So, with retro-Claisen rearrangement, you can get the ring expansion of 3 or more atoms and you get this heterocycle in 92 percent yield. Also, if you have an allylic alcohol as well as a triple bond. Selectively, this alcohol is oxidized with Dess-Martin periodinane, to generate the alpha beta unsaturated aldehyde.

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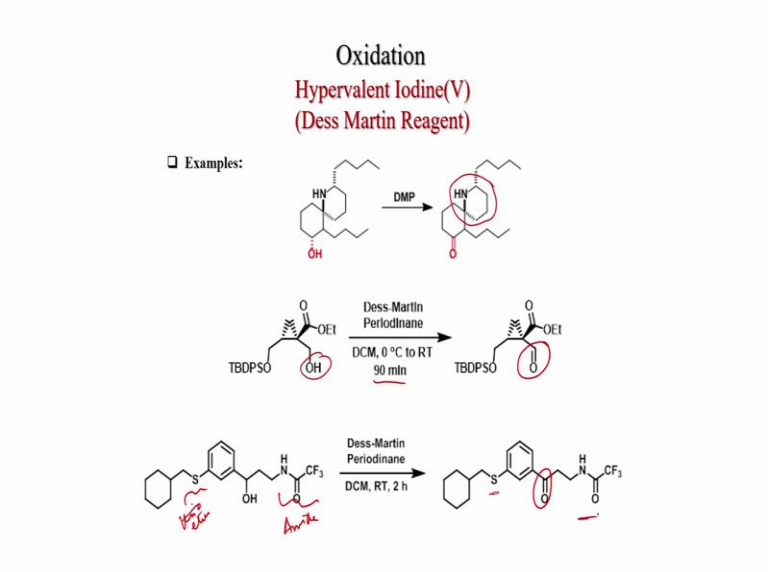

Also, secondary alcohol can be, also be oxidized to carbonyl group. Here, you can see there is a piperidine motif. And, during this oxidation, the piperidine motif untouched. And, only the secondary alcohol gets to the carbonyl. Also, here a cyclopropyl group is there. And, this is a quaternary center. This primary alcohol, selectively getting oxidized to the aldehyde, without disturbing the quaternary chiral center. And, this is very mild, DCM, 0 degree centigrade to room temperature, only 90 minutes, you can get very high yield of this product.

This is another substrate, where the secondary alcohol is present. There is an amide is present. And, this is thioether is present. So, under this condition, Dess-Martin periodinane, DCM room temperature, only a secondary alcohol is getting oxidized to ketone and other groups are not touched during this oxidation.

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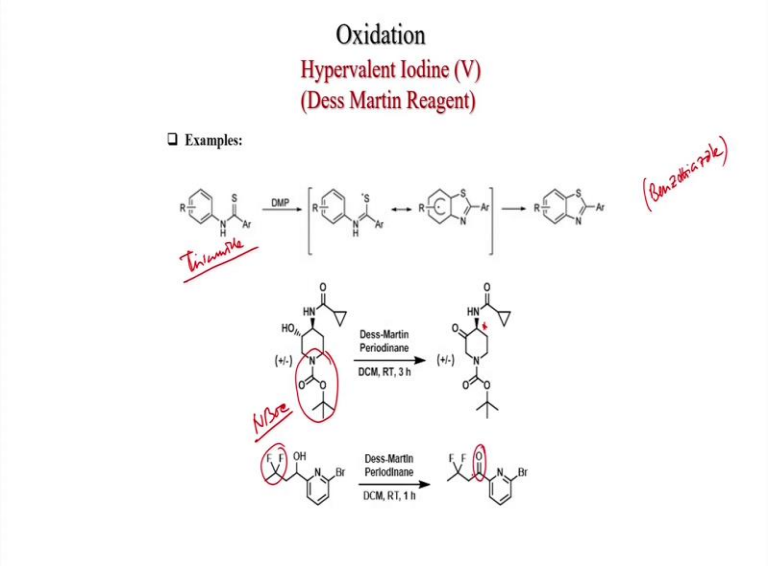

Also, from thioamide. This is thioamides on reaction with Dess-Martin periodinane, it can give the benzothiazole. So, this benzothiazole compounds are formed. So, what is the mechanism? Now, first Dess-Martin periodinane oxidized, there is a negative charge will form and that will be oxidized single electron oxidant, it gives a radical. And, then the aryl species reacts to the radical. And then, radical migrated to aryl group now. And, after oxidation of this radical, aryl radical, you get the benzene ring here. And ultimately, benzothiazole is formed.

Dess-Martin periodinane can also oxidize secondary alcohol with other groups. Like here, NBoc group. This is NBoc group is present. And this is, which is acid sensitive. And this one, amide group is present. And, with Dess-Martin periodinane, DCM, room temperature, 3 hours, you get good yield of this product. And, the geometry is retained here. So, this alpha amide; alpha amide geometry is not disturbed during this oxidation.

Here also, you can see, a heterocycle is present. And also, two fluorine group is there. And only, secondary alcohol selectively getting oxidized to the ketone, without disturbing the other groups.

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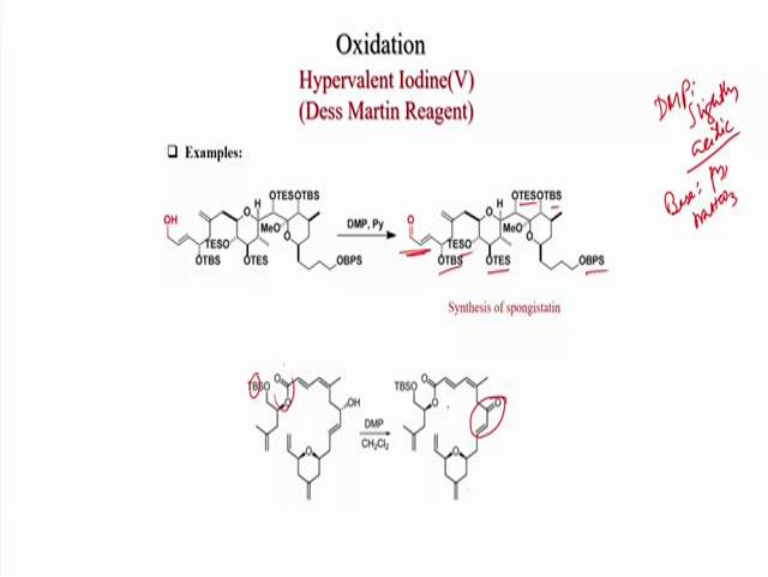

This is an complex molecule. Dess-Martin periodinane like TPAP also is use, many natural product synthesis. Here you can see, there are two tetrahydropyran species are there. And, also many chiral centers are present. And, this is an allylic alcohol. This allylic alcohol selectively getting oxidized to the aldehyde. And, also many silyl ether groups are present, like TES group, TBS group. So, these groups are not disturbed on this oxidation.

So, Dess-Martin periodinane is very mild. And, you have to use, pyridine, because Dess-Martin periodinane is slightly acidic. So, sometimes you have to use base like, base like, pyridine, sodium bicarbonate, you can use with Dess-Martin periodinane to make the solution neutral .

This is a complex molecule, where tetrahydropyran motif is there and different other groups, like ester motif is there, TBS group is present. So, with this condition, only the secondary alcohol gets to the ketone, enone actually, here allylic alcohol. So, other groups are not disturbed during this oxidation.

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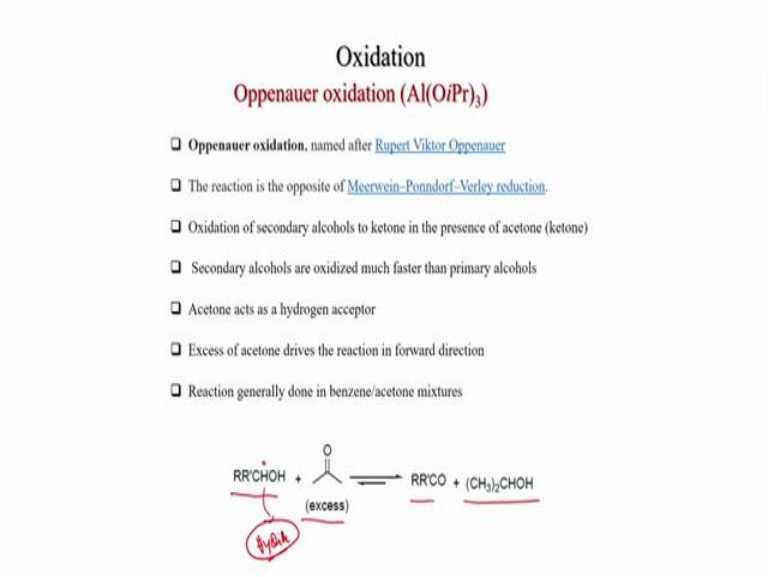

Now, we will discuss Oppenauer oxidation. This oxidation named after Rupert Viktor Oppenauer. And the reaction is the opposite of the Meerwein-Ponndorf-Verley reduction. This is generally oxidation of secondary alcohol to ketone, in the presence of acetone or other ketones. Also, aldehydes can be used. Secondary alcohols in general, are oxidized much faster than primary alcohols. Acetone acts as a hydrogen acceptor. Excess of acetone drives the reaction in forward direction.

Reaction generally done in benzene acetone mixture. And this is the reaction, that the alcohol is there, secondary alcohol and acetone. This is the, acetone is the hydride acceptor actually. That we will see in the mechanism, that this hydrogen actually going as a hydride. So, this is special of Oppenauer oxidation. So, the hydride goes to the acetone. And, acetone becomes alcohol. And, this alcohol becomes ketone.

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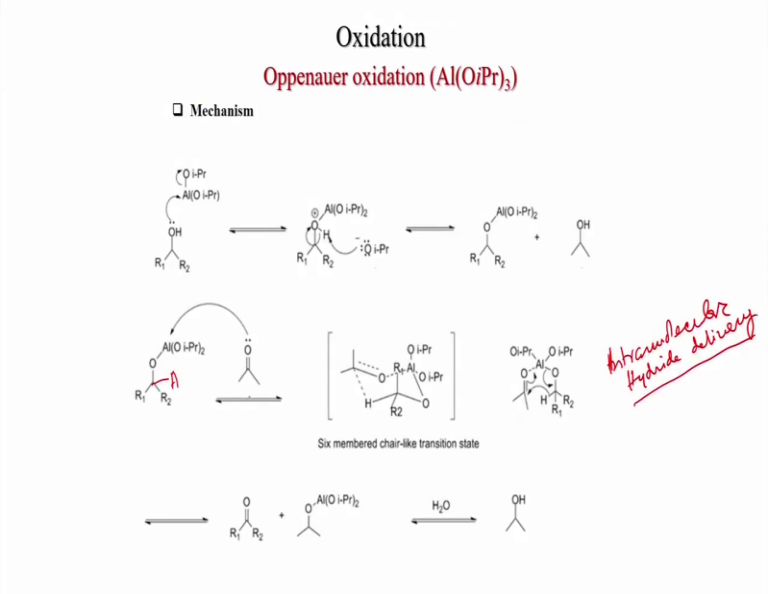

What is the mechanism? So, first the alcohol attacks to aluminum tri-isopropoxide and liberates one molecule of isopropoxide anion. And now, this acidic proton is taken by the isopropoxide anion to generate the isopropanol. And, this O-allyl bond, with this intermediate is formed now. And now, this intermediate again, this aluminum can bind with the acetone or other ketone. And, when it binds, then what happens? This binding helps the electrophilicity of the acetone motif will enhance.

And now, aluminum is binding with this oxygen of alcohol, that is the alcohol, through the aluminum oxygen bond, and also binding with the acetone. So, this is the acetone. This is also binding with the aluminum. And now, it can stay in a 6 membered chain-like transition state. And now, the hydride delivery will take place. So, you can see this way, the O aluminum bond is breaking. And, it is migrating to carbon oxygen bond. Here, the double bond is generating and hydride is going to the acetone, and it is becoming alcohol.

So here, intermolecular hydride delivery. So, this is special about Oppenauer oxidation. All other oxidation we have seen, that this hydrogen is going as the H plus. But, in Oppenauer oxidation, this is going as a hydride. And, this hydride is going to the acetone. Ultimately, this is going to oxidize to the ketone. And, this acetone becomes O-allyl

species now, intermediate. And, on hydrolysis, this will give isopropanol. So, acetone becoming isopropanol and your alcohol is becoming to the carbonyl compound.

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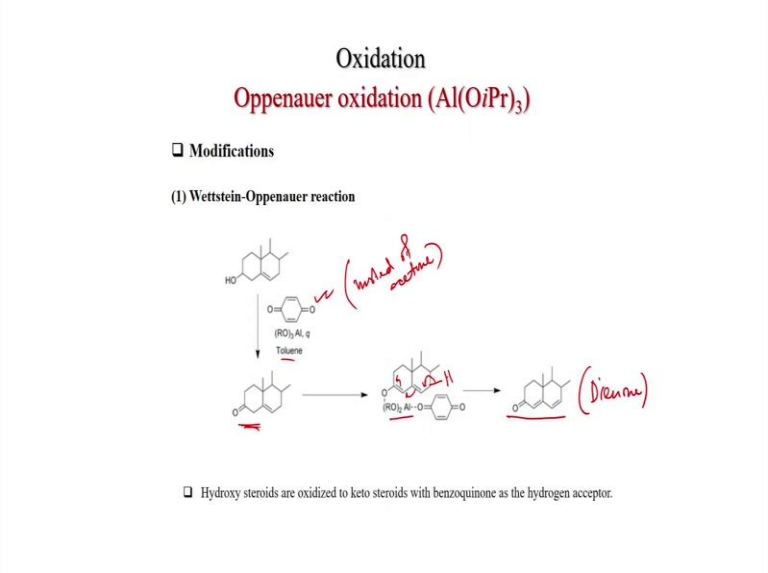

There are different modification of Oppenauer oxidation, is reported like Wettstein-Oppenauer oxidation. Under this oxidation, para-benzoquinone is used, instead of acetone. So, this is the hydride acceptor para-benzoquinone. And, when it was treated with this secondary alcohol with a double bond far, what happened? This gets oxidized to the carbonyl compound with this aluminum isopropoxide, para-benzoquinone, toluene. And now, this becomes enolate. And, this enolate binds with this aluminum and parabenzoquinone, ultimately it becomes dienone.

So, what happens? Ketone is becoming enolate. And, that enolate is binding with the aluminum and again it is getting oxidized. And, you get a, actually this hydrogen is moving and ultimately you get an oxidation. So ultimately, you get dienone with a double bond, new double bond generation. Hydroxy steroids are oxidized to keto steroids with benzoquinone as the hydrogen acceptor.

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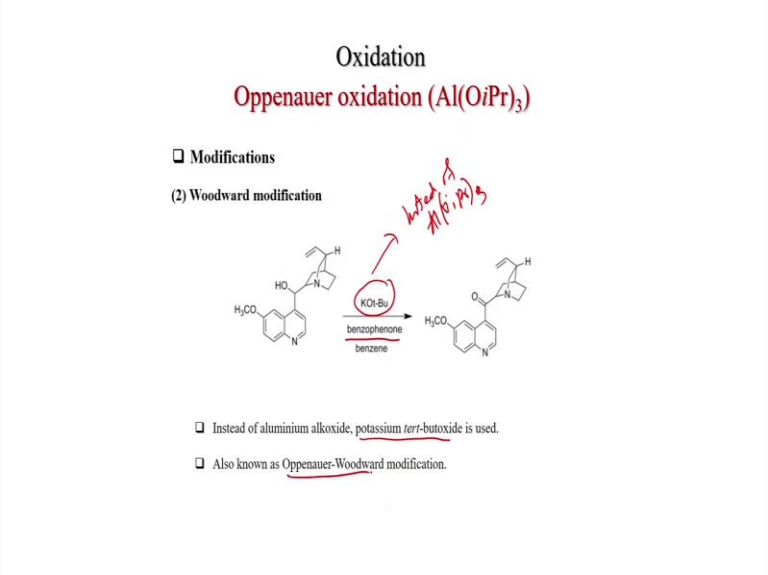

Another modification by Woodward. This is called Woodward modification. He used potassium tertiary butoxide base. So, instead of aluminum isopropoxide, Woodward used potassium tertiary butoxide. And also, benzophenone, like last case, benzophenone is the hydride acceptor. Instead of, aluminum alkoxide, potassium tertiary butoxide is used. And also, known as Oppenauer-Woodward modification.

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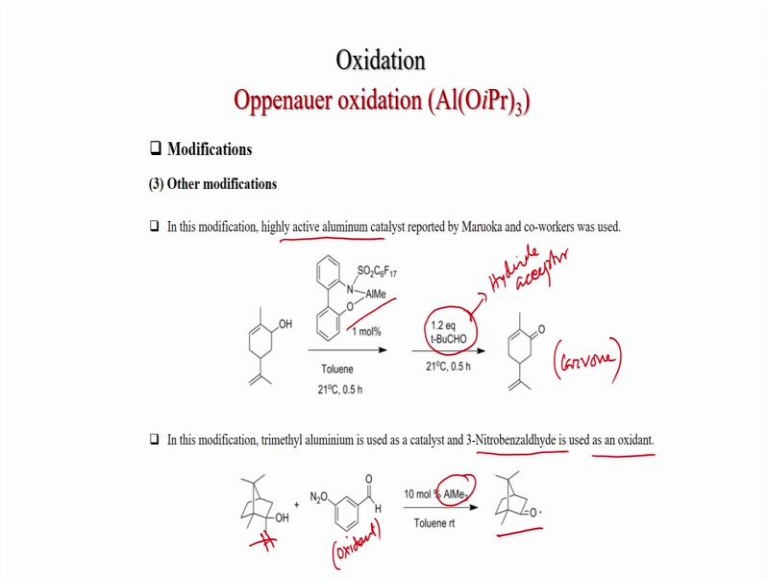

This is third modification. In this modification, highly active aluminum catalyst. So , instead of aluminum isopropoxide, this is an catalyst, highly reactive aluminum catalyst is used, which was reported by Maruoka and co-workers. Only, one mole percent catalyst is enough to do the oxidation. And, this tertiary butyl aldehyde, which is called pivaldehyde. So, pivaldehyde is the hydride acceptor. So that means, not only ketone, aldehyde can also exercise hydride acceptor.

And, now this alcohol is going to the carvone. So, carvone is generated from oxidation of this hydrocarvone. In this modification, trimethyl aluminium is used as a catalyst and 4-nitrobenzaldehyde is used as an oxidant. So, here 3-Nitrobenzaldehyde is a oxidant or hydride acceptor. And, under this condition, with aluminium trimethyl, aluminum 10 mole percent, this alcohol is getting oxidized to the ketone. So, this will be hydrogen. So, this secondary alcohol is getting oxidized to the carbonyl compound.

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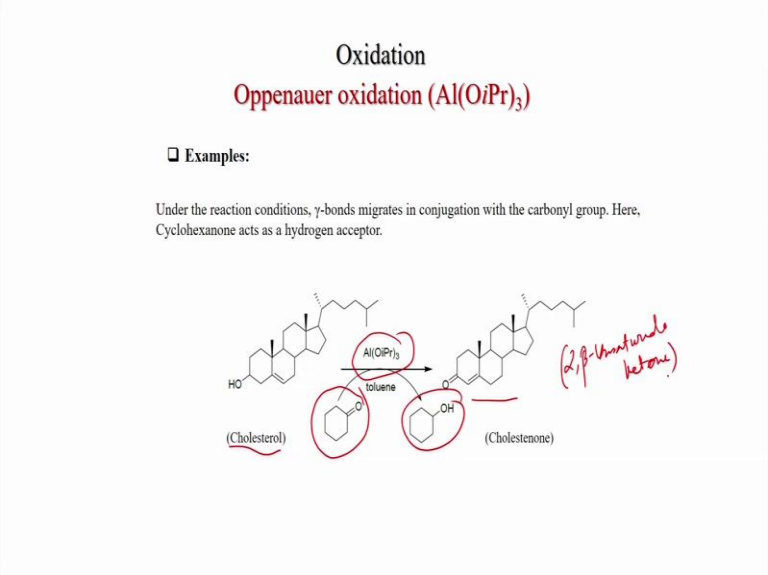

So, we have seen the migration of the double bond or dienone generation. And here, gamma bond migrates in conjugation with the carbonyl group. So, here what happen, Gamma bond that migrates to the alpha beta position of the carbonyl group. Here. cyclohexanone acts as a hydrogen acceptor.

So, when this steroid or cholesterol compound, is oxidized with aluminum trioxopropoxide, and cyclohexanone as the oxidant. Cyclohexanone becomes cyclohexanol. And, it becomes, first the carbonyl group is formed and then isomerization happens. So, alpha beta unsaturated ketone is generated. So that means, double bond isomerization is happening here.

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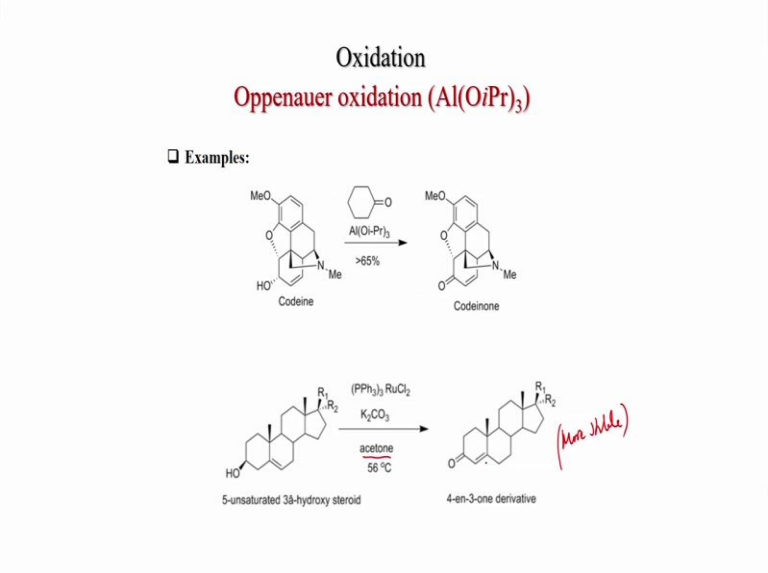

This is an example of Oppenauer oxidation. And this is a compound called codeine, and allylic secondary alcohol is present. Also, with heterocycle motif is present. And, with this condition, only the allylic alcohol is getting oxidized with aluminum tri-isopropoxide and cyclohexanone condition, you get greater than 65 percent yield of this product,

Also, we have seen this isomerization. So, this compound can also isomerize, with PPh_3 whole 3 ruthenium chloride, potassium carbonate and acetone is the hydride acceptor. So, acetone is the oxidant. And, in this condition also, double bond is migrating to the alpha beta position because this is the more stable. So, we have seen that, steroids can isomerize into the alpha beta unsaturated enone with this Oppenauer oxidation condition.

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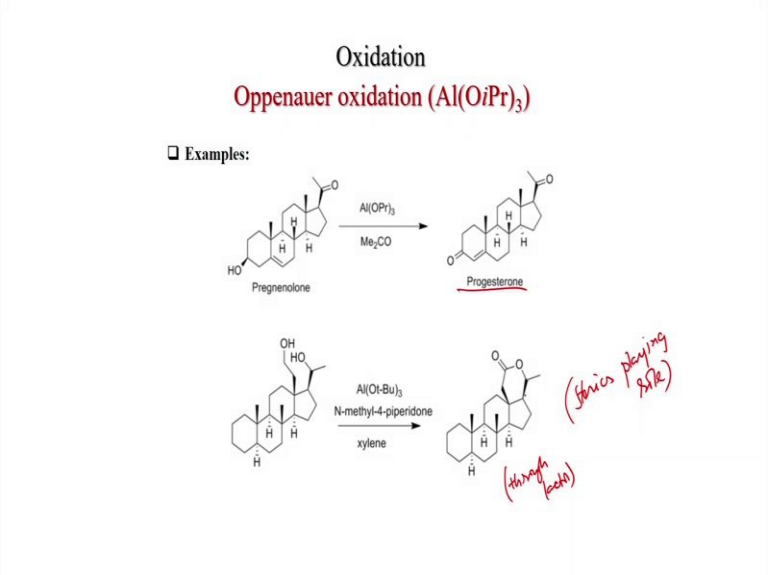

Here, one more example is there. This is pregnenolone. Here also, triisopropoxide aluminum with acetone, it gives the progesterone. And this is, here a secondary alcohol and primary alcohol is present. So here, selectively the primary alcohol is getting oxidized, because might be, steric is the factor might be, because there; these two groups are close to each other. And that is why, the steric, steric playing role.

In general, we told that secondary alcohol is reactive than primary with Oppenauer oxidation. But, here sterics is playing role. So, primary alcohol is getting oxidized to the aldehyde. Then this alcohol is making the lactol. And, lactol is going to lactone. So, through lactol; through lactol, lactol will be first formed and then it oxidized to the lactone.

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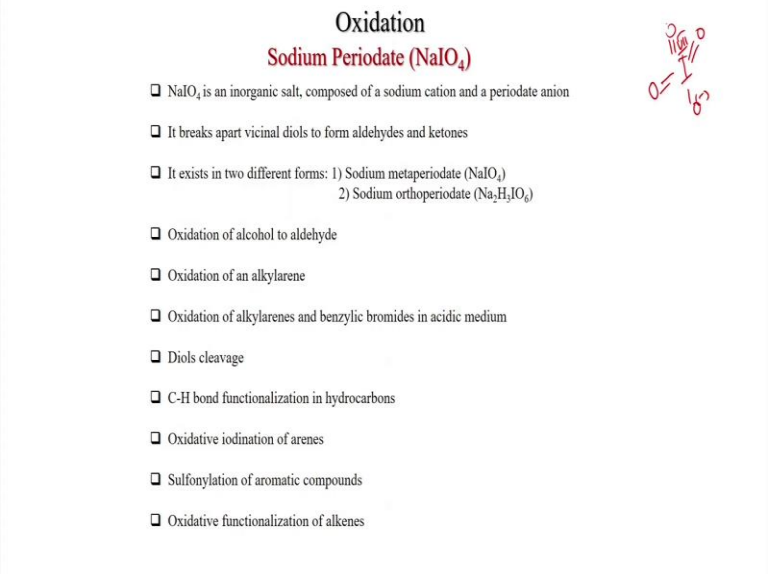

Now, we will discuss another oxidizing agent, which is sodium periodate. So here, iodine is in plus 7 oxidation state. So, Dess-Martin periodinane, it has plus 5. Here, plus 7 oxidation state. $NaIO_4$ is an inorganic salt, composed of sodium cation and periodate anion. It breaks apart vicinal diols to form aldehydes and ketones. It exists in two different forms- sodium metaperiodate, sodium orthoperiodate, which is $Na_2H_3IO_6$.

Oxidation of alcohol to aldehyde. Oxidation of an alkylarene. Oxidation of alkylarenes and benzylic bromides in acidic medium. Diols cleavage. C-H bond funtionalization in hydrocarbons. Oxidative iodination of arenes. Sulfonylation of aromatic compounds. Oxidative functionalization of alkenes. So, sodium periodate performs many reactions that we will discuss.

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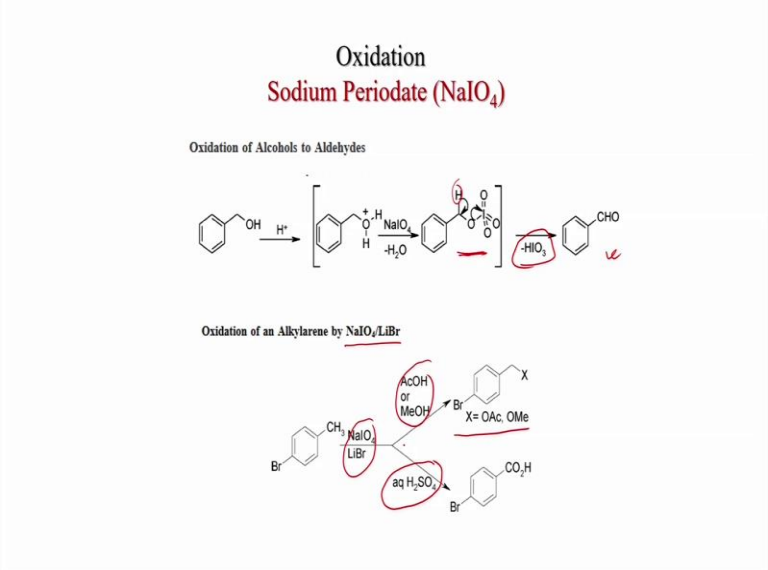

First is the oxidation of alcohol to aldehydes. So, this is the mechanism. In presence acid, the alcohol is getting protonated. And now, sodium periodate reacts with this alcohol to generate this iodoester. And now, this alpha hydrogen will be eliminated and HIO_3 will be generated, and you get benzaldehyde as the product.

Also, oxidation of alkylarene by sodium periodate, metaperiodate with lithium bromide is possible. So, when sodium periodate lithium bromide is treated, followed by acetic acid methanol, you get this benzylic acetate or benzylic ether. On the other hand, if you treat with aqueous H_2SO_4 this intermediate. The intermediate mostly is a bromide, that intermediate you get carboxylic acid.

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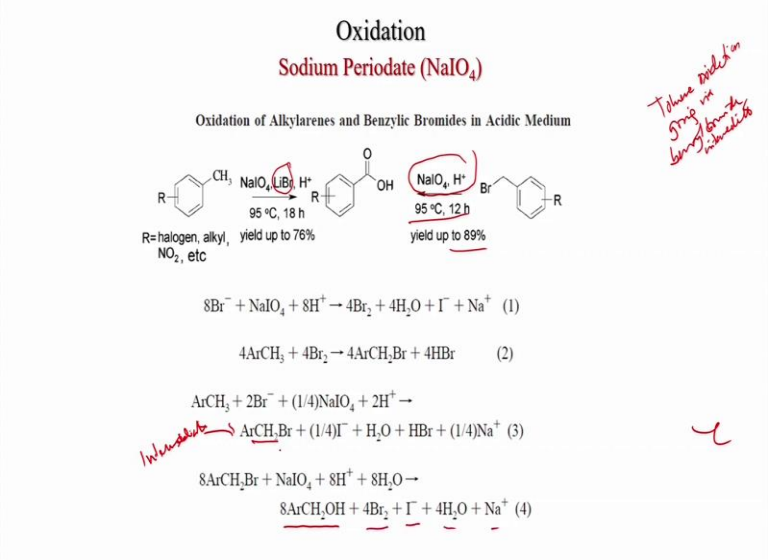

So, what happen; this is the reaction, that toluene derivative can be oxidized to the carboxylic acid, with sodium periodate lithium bromide in acid condition, like here H_2SO_4 is used. Also, it has been observed that if benzylic bromides are used; benzylic bromides are also, when you do not use lithium bromide here. Lithium bromide is not used here and other two reagents keeping intact, sodium periodate and H plus. And, same condition, it giving 89 percent yield of the carboxylic acid.

So, this tell that converting of the toluene, it is going to the benzylic bromide intermediate. So, toluene oxidation going via benzyl bromide intermediate, when lithium bromide is used. So, what is the reaction equation? Now, lithium bromide, sodium periodate in acid condition, it is becoming bromine, water, I minus, plus Na plus. So, this is the stoichiometry. And now, your toluene can react with bromine and generate the benzylic bromide and HBr. So, this is toluene. CH_3 is getting activated under this condition, to get a bromine compound, benzylic bromide.

So, this is the overall reaction. $ArCH_3$ plus 2 Br minus, plus 1 by 4 $NaIO_4$, plus 2H plus, it is giving $ArCH_2Br$, plus 1 by 4 I minus, plus H_2O plus HBr, plus 1 by 4 Na plus. Now, this benzylic bromide can react with sodium periodate. So, this is the intermediate. It can react with sodium periodate, 8 H plus and 8 water, it becomes 8 $ArCH_2OH$, plus 4 Br_2, I minus, plus H_2O, plus Na plus. So, benzyl bromide is converting to benzyl alcohol.

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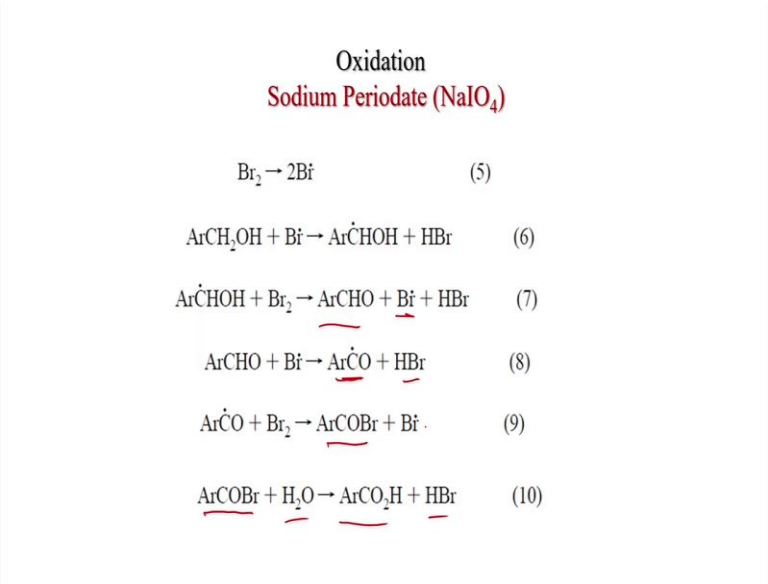

And now, Br_2 can generate bromine radical. And, this alcohol, benzylic alcohol reacts with bromine dot, to generate a benzylic radical and HBr. This radical reacts with bromine to generate the aldehyde. And, Br dot is regenerated. And now, the aldehyde is going to react with Br dot, to generate the ketyl radical plus HBr. And, this ketyl radical reacts with bromine to generate- ArCOBr plus Br dot also. And now, finally ArCOBr plus H_2O, $ArCO_2H$ plus HBr.

So, when toluene is going to the carboxylic acid, it is going through many intermediates. First, the benzylic bromide is formed. Benzylic bromide goes to the benzylic alcohol. Benzylic alcohol goes to the benzaldehyde derivative. And, benzaldehyde derivative goes to ArCOBr, acylbromide. And now, acylbromides on hydrolysis, giving the carboxylic acid.

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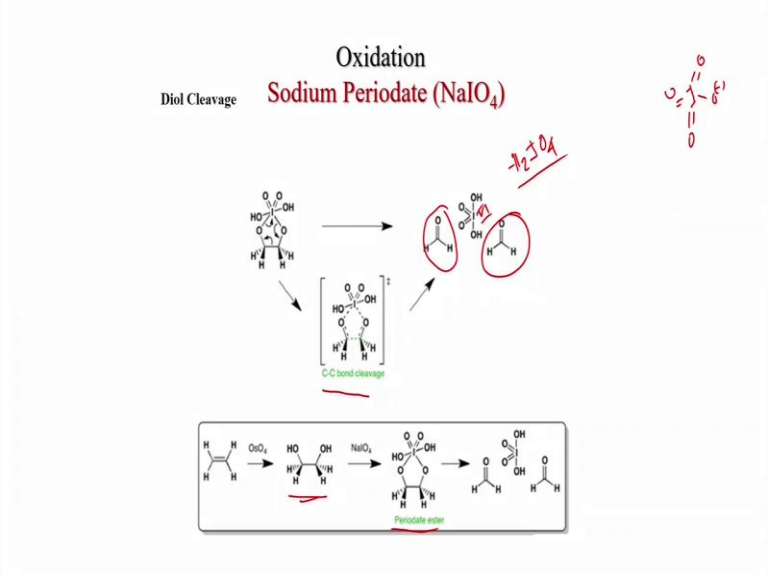

Diol cleavage. Sodium periodate main application is in the diol cleavage. So, diol binds to this peruthunate ion like this, intermediate is formed. And, when cleaves, as you can see, this intermediate. So, earlier this was the perethunate. And now, the diol interacts with this and generate this species. And, after C-C bond cleavage, like this way, you generate two molecules of the aldehyde. And, iodine 7 becomes iodine 6, two OH. So, this is, H_2IO_4.

So, H_2IO_4 is generated on oxidation. So, sodium periodate is converting; sodium periodate is getting reduced to H_2IO_4. And, this diol is converted to two molecules of aldehydes. Also, this is generally, one part procedure is followed from alkenes. So, alkenes can be assimilated with osmium tetraoxide to provide the diol. And, diol is sodium periodate reaction, which generate the periodate ester, like we have seen here. And, periodate ester on cleavage will give two molecules of aldehyde and H_2IO_4. So, this is very important reaction, that alkene can be treated with osmium tetraoxide and followed by sodium periodate. That will give directly to aldehyde.

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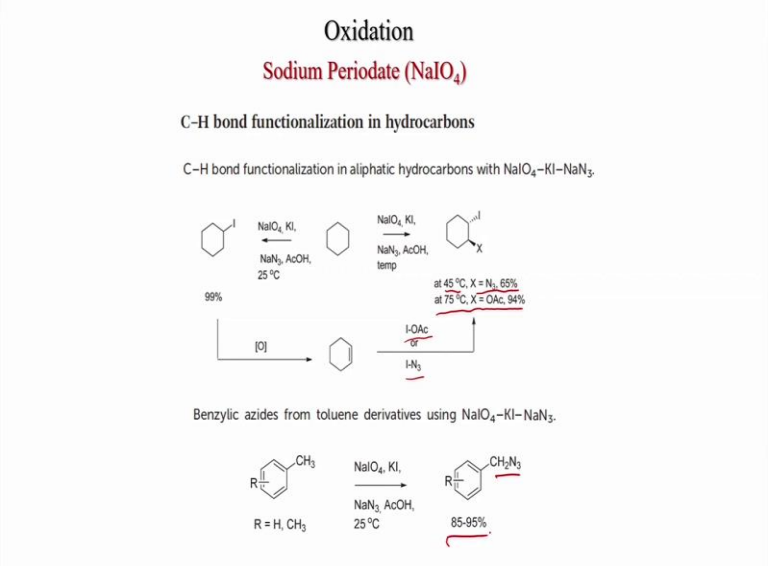

Sodium periodate has also been used in C-H bond functionalization in hydrocarbons. Like, when cyclohexane is treated with sodium periodate, KI, sodium azide, acetic acid condition, it gives the iodo-cyclohexane in 99 percent yield. On the other hand, when sodium periodate, potassium iodide, same reaction, but the temperature was increased to 45 degree centigrade, then you get this compound, iodo, azide in 65 percent yield and at 75 degree centigrade you gets the O acetate iodo compound.

So, what is going on? So, that means that on oxidation, this first, this iodo-cyclohexane is formed. And, on oxidation it generating the cyclohexene. And, potassium iodide as well as sodium azide on oxidation with sodium periodate generate this species, IOAc or IN_3. And, these reacts with this double bond to make this iodo-azide or iodo acetate derivatives.

Benzylic azides from toluene derivatives also possible. So, if you, instead of cyclohexane, if you use toluene derivative, then with sodium periodate, potassium iodide, azide and acetic acid condition, you get CH_2N_3 species in 85 to 95 percent yield.

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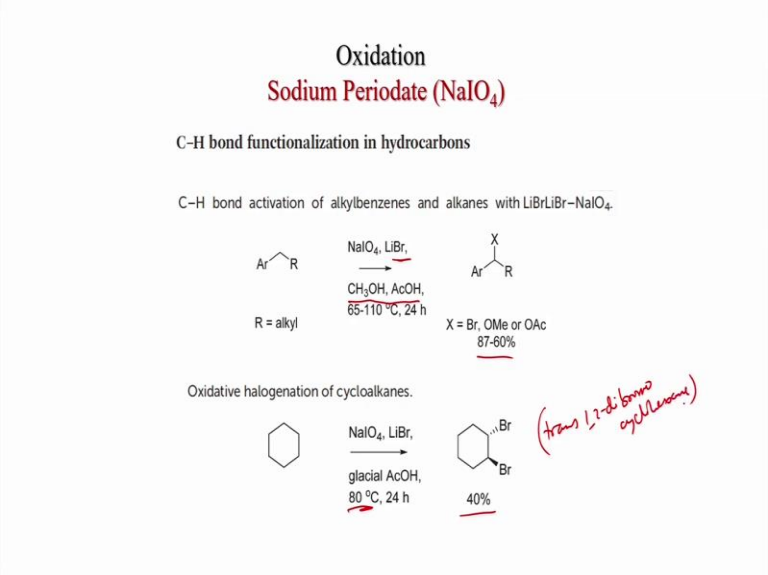

Also, if benzylic derivatives are present. And, if you change the reaction condition to sodium periodate, lithium bromide, methanol, acetic acid condition, you can get mixture of product, X is equal to Br, OMe, benzylic bromide or benzyl ether, acetate is formed in 87 to 60 percent yield.

And, if you use cyclohexane. Like earlier, with sodium periodate, lithium bromide, glacial acetic acid and 80 degree centigrade, you can get the trans-dibromide. So, trans 1,2-dibromo cyclohexane is formed in 40 percent yield, with sodium periodate, lithium bromide, glacial acetic acid condition.

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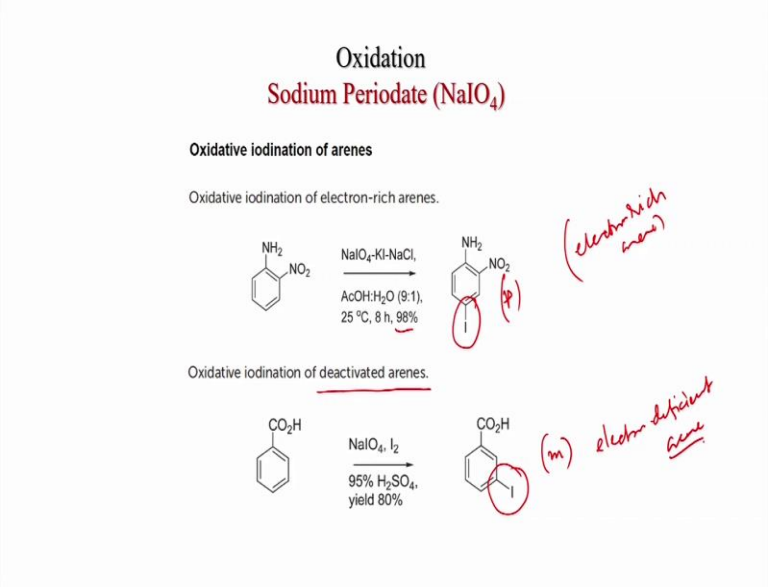

Also, oxidative iodination of arenes is possible. Like this, 2-nitrotoluene, 2-nitroaniline, when reacted with sodium periodate, potassium iodide, sodium chloride with acetic acid water, 9 to 1, 25 degree centigrade, it gives 98 percent yield to the iodo-derivatives. So, para of NH_2 form the iodo species.

And now, deactivated arenes can also be reacted with this species, sodium periodate, iodine, 95 percent H_2SO_4 and meta, so this is meta selectivity. This is para selectivity because this is electron deficient or arene. So, electron deficient arenes gives meta selection. And, this is electron, slightly electron rich arene. So, this is para selective.

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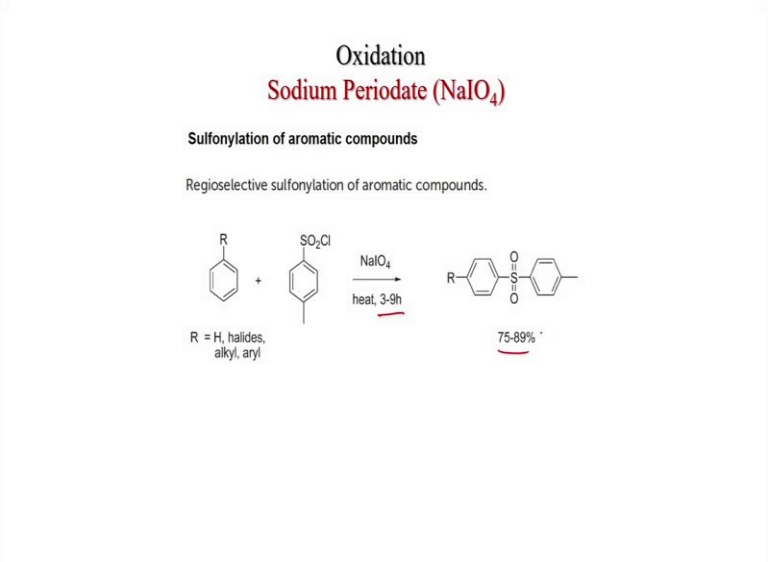

Sulfonylation of aromatic compounds is also possible with sodium periodate. Like, this benzene derivatives, when reacted with sulfonyl chloride with sodium periodate, heating condition in 3 to 9 hours, it gives this sulfoxide in 75 to 89 percent yield.

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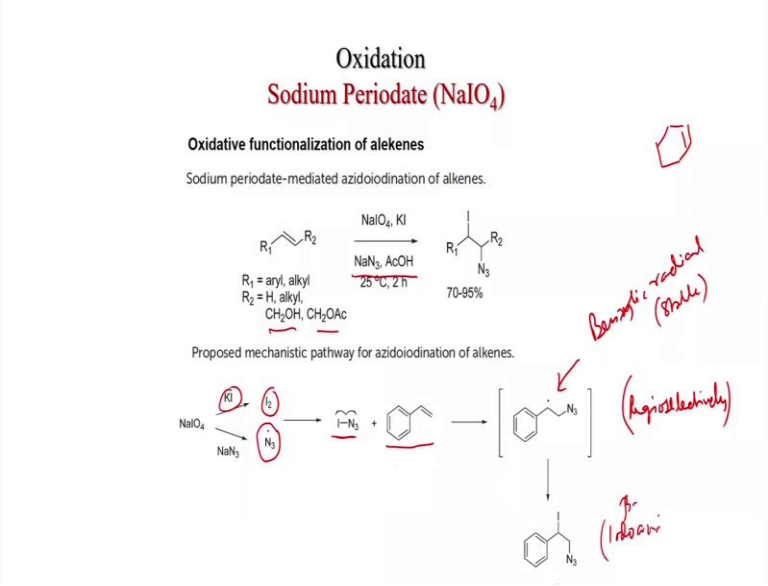

Other oxidative functionalization of alkenes is possible. Like this type of alkenes can be aryl or alkyl substituted. Also, CH_2OH, CH_2OAc group. And, when sodium periodate,

potassium iodide, sodium azide, acetic acid is present, under this condition this iodoazide is formed. So, this we have seen with cyclohexene also.

Cyclohexene, when is treated with this condition, and we have seen the iodoazide formation at 45 degree centigrade. Here, acyclic olefins can also, generate this iodoazide. So, what will be the mechanism here? Most likely sodium periodate oxidize potassium iodide to iodine. And, sodium azide to N_3 dot N_3 radical. And, this to bind to generate the IN_3, iodoazide.

And, iodoazide then, adds to the styrene and this is regioselectively. So, regioselectively it adds, so that the benzylic radical is formed. So, this is benzylic radical. And, benzylic radical is stable. So, azide attacks to the terminal carbon. And now, this benzylic radical reacts with I_2 to generate the iodoazide. So, beta iodoazide is formed.

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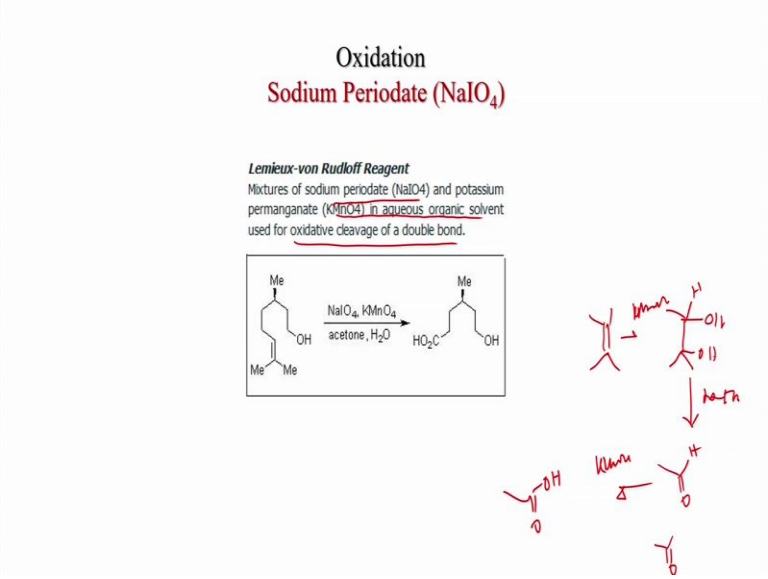

Also, this is a modification of sodium periodate oxidation. So, this is a mixture of sodium periodate and potassium permanganate, in aqueous organic solvent used for oxidative cleavage of double bond. So, here the double bond is cleaved to the carboxylic acid. So, most likely, the double bond is going to diol. Diol is cleaved. So, because potassium

permanganate, potassium permanganate will make the diol. And, the diol cleaved with sodium periodate to carbonyl compounds.

And now, if there is a hydrogen is there, then this aldehyde, with $KMnO_4$ getting oxidized to the carboxylic acid. So, that is what is happening here. This is a, this purpose actually, diol formation cleavage, followed by oxidation, when you treat sodium periodate, potassium permanganate together, with in acetone water condition.

So, today we have seen four oxidizing agents. First one was TPAP, tetra n-propyl ammonium peruthenate. This is mild oxidizing agent, we have seen and the steric is important. We have seen that sterically less hindered alcohol is getting oxidized. Mainly, the primary alcohol goes to the aldehyde. However, when water is present, then that time alcohols can also give carboxylic acid.

Then we discussed Dess-Martin periodinane. Dess-Martin periodinane is a mild oxidizing agent and it mainly oxidize alcohol to carbonyl compound. Primary alcohol to aldehyde and secondary alcohol to ketone. And, this is slightly acidic but it can be made neutral with sodium bicarbonate or pyridine. And, this is also very selective. Without disturbing other ether groups, this primary alcohol or secondary alcohol can be oxidized, without disturbing THP or ketal or acetyl motif, silyl ethers can also be untouched during this oxidation.

Then, we discuss Oppenauer oxidation. This is opposite of MVP oxidation. And, here generally acetone is the hydride acceptor. And, compared to other oxidation mechanism, this mechanism is different. Here, the H of the OH, alcohol is going as a hydride. And, that hydride is taken by a carbonyl compound, mostly acetone. Also, you can use cyclohexanone, para-benzoquinone. Also, aldehydes can be used. And in general, the secondary alcohols are more reactive than primary alcohol. But also, we have seen that, when sterics is playing a role, if a secondary alcohol is sterically hindered position, then the primary alcohol oxidize and then lactol is formed. And, the lactol is going to lactone.

And, lastly we discussed sodium periodate. This also can oxidize alcohol to aldehyde. Also, it cleaves diol to; mainly its application in the diol cleavage. Diol to carbonyl compounds. And also, different functionalization reactions can be carried out. Like cyclohexane to iodo; cyclohexane or cyclohexene. Also, iodoazide species is formed. And, when toluene derivatives are reacted with sodium periodate, sodium azide, acetic acid condition, then we have seen IN_3 is formed. And, benzylic position can be also, activated to generate the benzyl bromide species.

And, we have seen, the oxidation of here, CH_3 to carboxylic acid also, with sodium periodate, lithium bromide condition, in acid condition. And, here generally, the $ArCH_3$ is going to $ArCH_2Br$. First, the benzylic bromide. Benzylic bromide is going to benzylic alcohol. Benzylic alcohol to benzaldehyde, follows by bromo, acylbromide is formed. And, the acylbromide on hydrolysis is giving the carboxylic acid. And, lastly we have seen the iodination of arenes. When electron rich arene is used, then the para position is getting iodinated. And, when electron deficient arene is used, then the meta position is getting iodinated, with sodium periodate, potassium iodide condition.

And, lastly we have seen, the mixture of sodium periodate and $KMnO_4$, which is very strong oxidizing agent, where a olefin is converted to carboxylic acid. So, first diol is formed. Then, diol is cleaved to the aldehyde. And, the aldehyde is getting oxidized to the carboxylic acid. So thank you.