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

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Lecture - 60
Course Summary and Conclusion

Hello and welcome you all to today's lecture. This is going to be our last lecture. And therefore, I am going to summarize what we have done in the last 59 lectures. So the course, as we started was, Essentials of Oxidation, Reduction and C-C Bond Formation, Application in Organic Synthesis.

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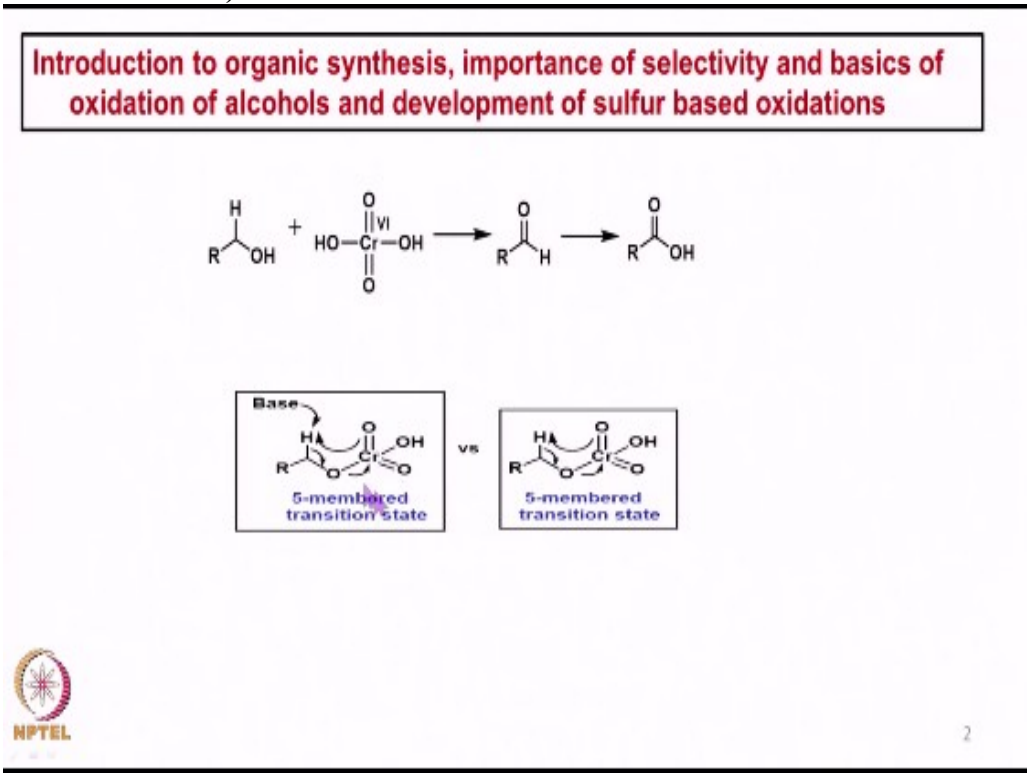

So initially we started with the introduction to organic synthesis and then importance of selectivity and basics of oxidations and development of sulfur based oxidations we discussed. Of course, initially we saw the chromium based oxidations and then we considered the two possibilities that is the oxidation in an intermolecular fashion or an intramolecular fashion via a 5-membered transition state.

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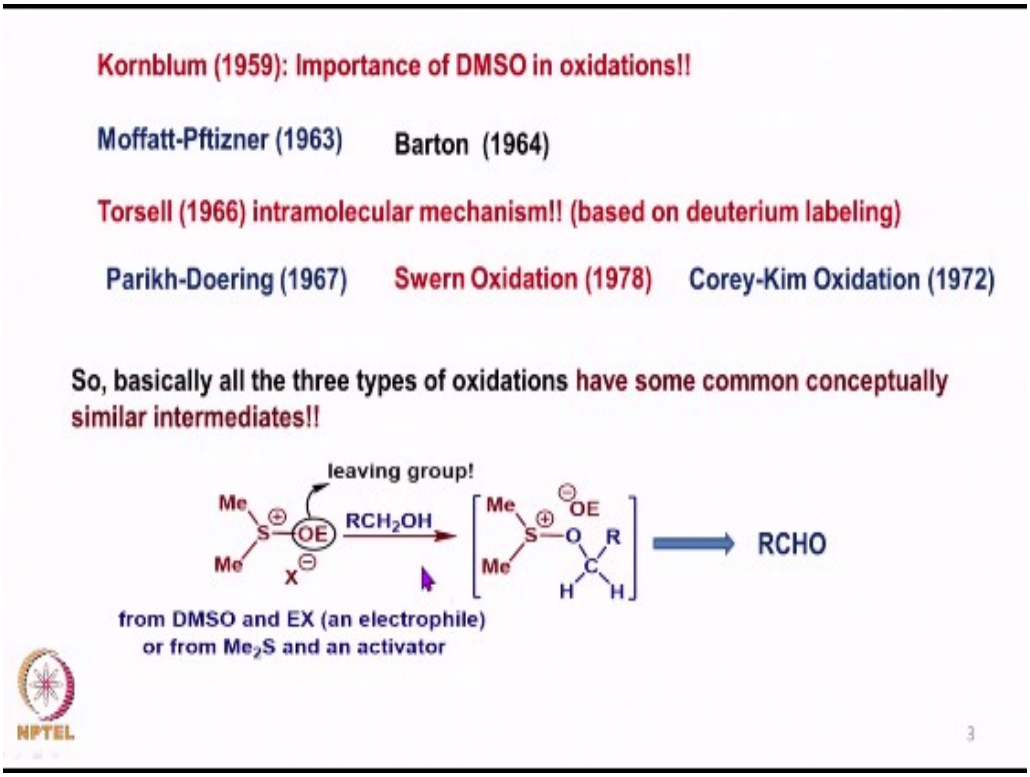

Then, of course, we looked at Kornblum type of oxidation. Then of course DMSO activated oxidation like Moffatt-Pftizner, Barton type of oxidations. And then we also discussed the Torsell studies which allowed to establish the intramolecular mechanism based on deuterium labelling. Then we of course discussed all these oxidations which are similar in concept that is Parikh-Doering, Swern oxidation, Corey-Kim oxidation.

As we discussed that they were all conceptually similar and they had similar type of intermediates first upon reaction with DMSO followed by alcohol to form this intermediate and then of course go to the aldehyde. So this intermediate of course was formed from DMSO and an electrophile or from DMS and an activator which is in the Corey-Kim oxidation.

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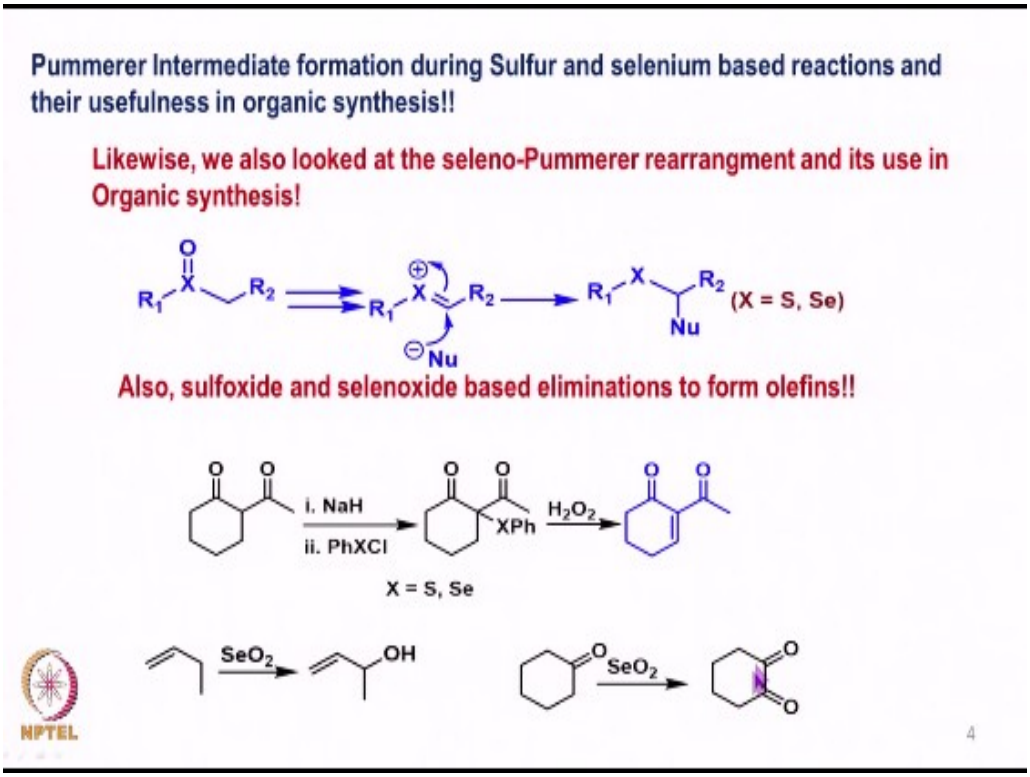

Then we looked at the Pummerer intermediates from sulfur as well as selenium based reactions and their use in organic synthesis by trapping this intermediate whether X is sulfur or selenium. So the sulfoxide and selenoxides lead to this particular seleno or sulfur intermediates.

And also we saw how sulfoxides and selenoxides, as I have shown here, that we take this particular compound and if we have the carbon X bond here, where x is sulfur or selenium, then via sulfoxide it can undergo elimination or via selenoxide it can undergo elimination to form the corresponding double bond. Then of course, with selenium dioxide base oxidations we saw that allylic alcohol oxidation.

That means, the allylic hydrogen on a substrate like this leads to the allylic alcohol formation and a ketone can lead to 1,2-diketone formation.

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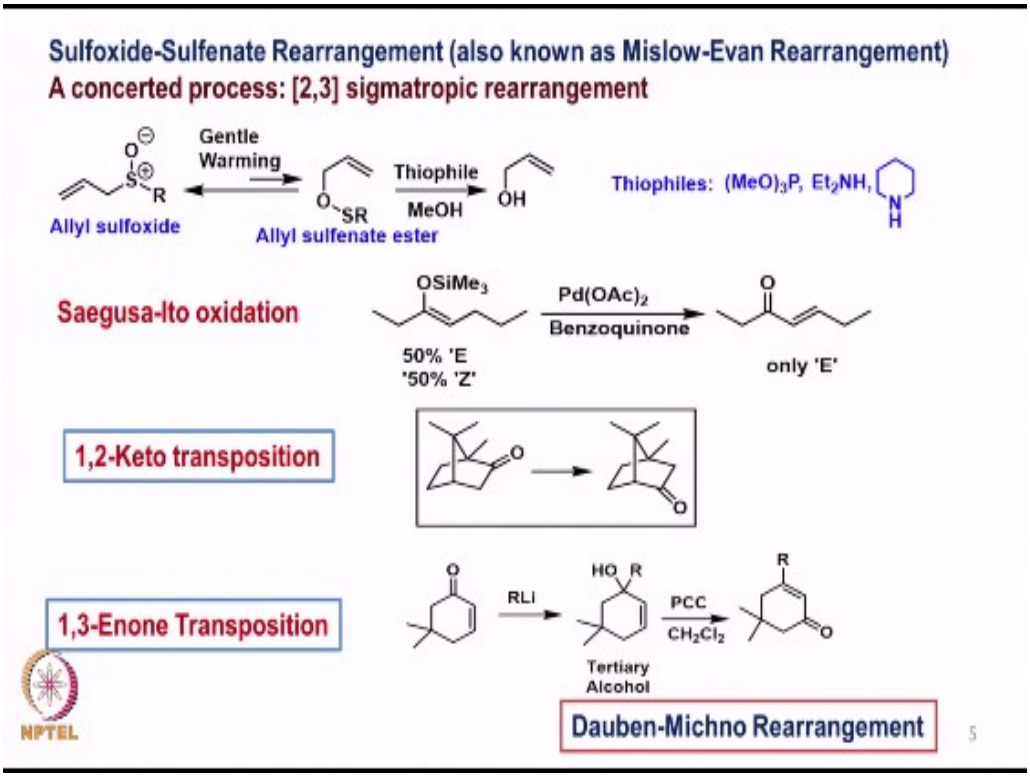

Then we saw sulfoxide-sulfenate rearrangement, which is also known as Mislow-Evans rearrangement. So a concerted process was kind of discussed with 2,3 sigmatropic rearrangement where this allyl sulfoxide goes to allyl sulfenate followed by of course cleavage of the oxygen sulfur bond by thiophile to form this allylic alcohol. The thiophiles, of course we used were of this kind.

And of course, the intermediates of these kinds were discussed based on mechanistic aspects. Then we saw Saegusa-Ito reaction, which is basically an oxidation of an enol silyl ether to the corresponding enone using palladium acetate and benzoquinone as co-oxidant. Then we also saw 1,2-ketone transposition, that is if we have a ketone like this, we can put it onto this next carbon using different types of chemistry.

And also in the same context we did 1,3-enone transposition. That means if we have an enone of this kind we can convert to the corresponding transpose enone of this type via this tertiary allyl alcohol using what is called as Dauben-Michno rearrangement, where an oxidant reacts with this allyl alcohol which is a tertiary or alcohol to form this enone. And we discussed the mechanism and its application.

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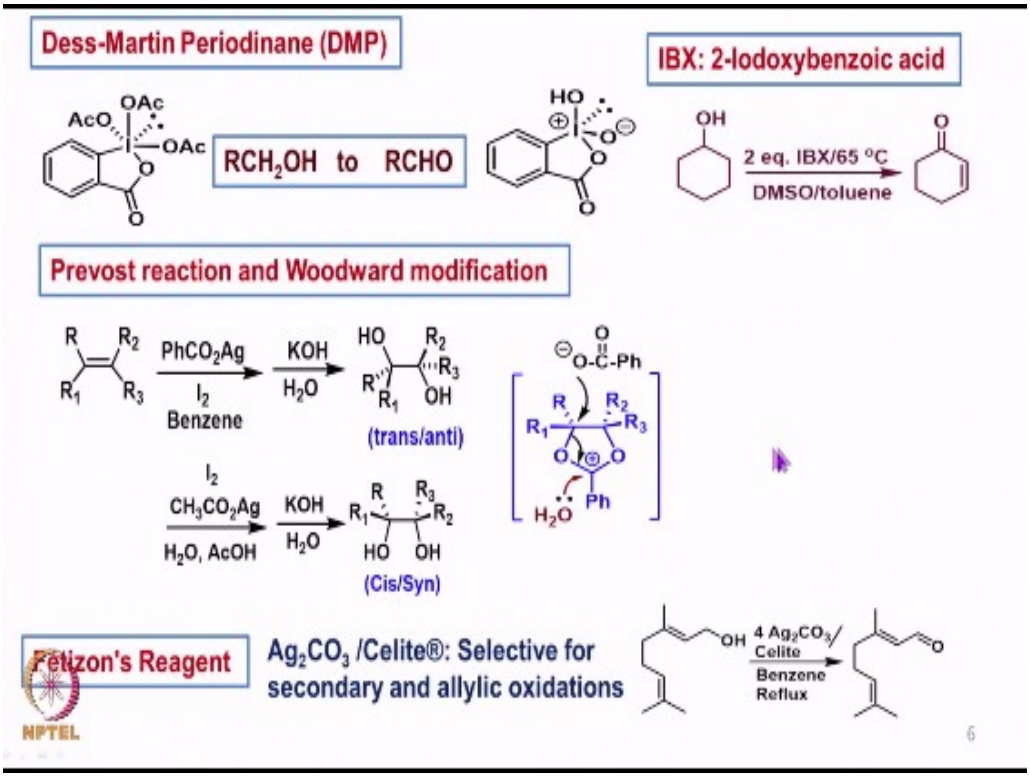

Then we saw Dess-Martin Periodinane based oxidations and also IBX that is 2-iodoxybenzoic acid based oxidations where the reagents of this type, this is Dess-Martin Periodinane and this is IBX converts alcohol to the ketone or enone. If we use two equivalents of the IBX then of course, we get the corresponding enone. The first equivalent converts alcohol to the corresponding ketone and the second one leads to the enone.

In the case of course Dess-Martin, we of course convert alcohol to aldehyde. So both of them they convert alcohol to aldehyde. But then here IBX converts to the corresponding enone if we take more than one equivalent of IBX. We saw then Prevost reaction and Woodward modification. That is you start with an olefin like this under two different conditions, under dry condition, under aqueous condition we get the trans or that is anti diol or a cis diol or a syn diol.

We discussed the mechanism and we went through this particular type of intermediate. If water is present, then this intermediate opens up to form the cis diol or a syn diol. Or if this nucleophile attacks on to this intermediate under non-aqueous condition, then of course we get the anti-attack to form this trans or anti diol. We also looked at Fetizon's oxidation using silver carbonate celite for selective secondary and allylic oxidations of this kind.

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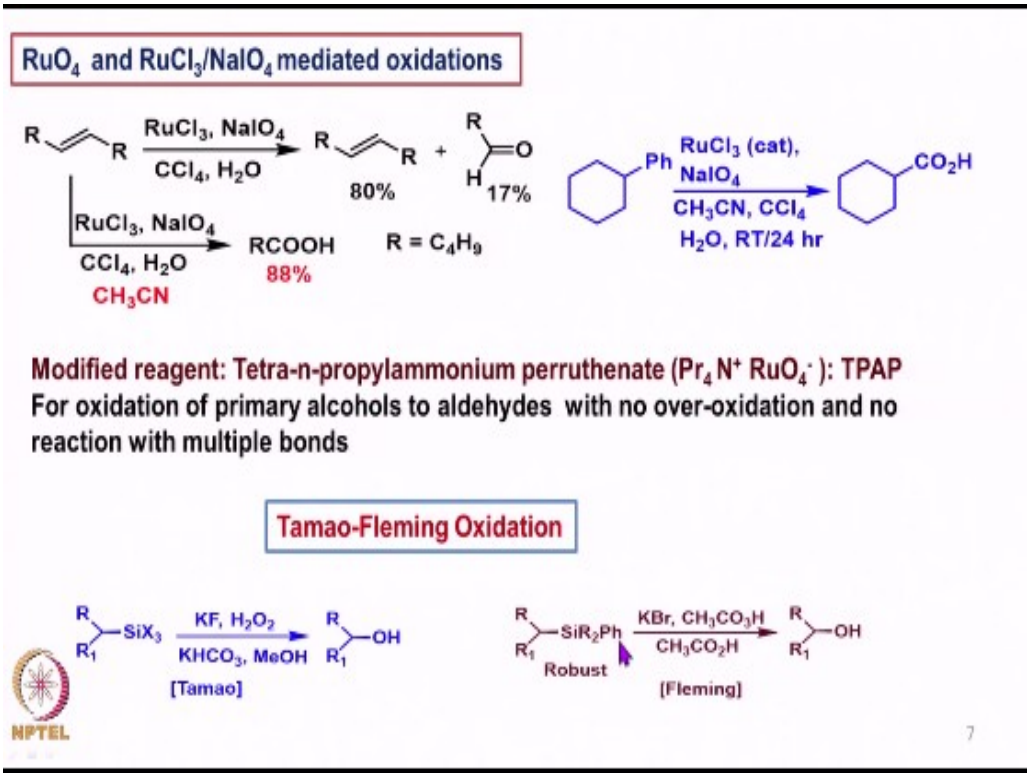

Then we proceeded further for ruthenium tetroxide based oxidations which can also be done using catalytic amount of ruthenium trichloride and sodium metaperiodate that lead to the cleavage of this double bond to the corresponding ketone or aldehyde. And of course if we use this condition here, we discussed in detail how the carboxylic acid can be formed.

We also saw how ruthenium tetroxide or this particular combination allows an aromatic ring also to be cleaved to the corresponding acid. Then, we modified the reagent as reported by Steve Ley to tetra N-propylammonium perruthenate like this and because of the negative charge here, the oxidation reactivity of this TPAP is somewhat less than that of ruthenium tetroxide.

And therefore oxidation of primary alcohols to aldehydes is possible without over oxidation to acid or without other oxidations such as that of a double bond. Then we talked about the Tamao-Fleming oxidation with lot of mechanistic details. We saw how Tamao oxidation occurs under basic conditions or neutral conditions or acid conditions and of course it is a stereoselective oxidation.

In a similar fashion, Fleming based oxidation we saw with the carbon silicon bond having a aromatic part here.

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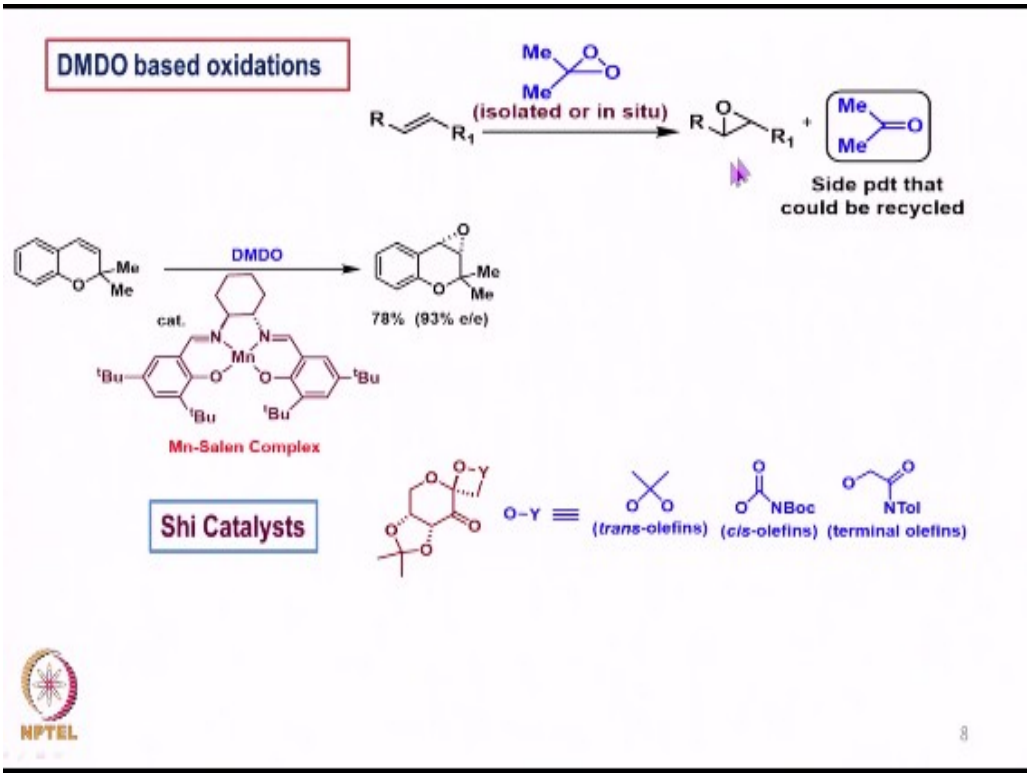

Then we did DMDO based oxidations where olefins can be epoxidized with dimethyldioxirane, which can be either isolated or can be reacted in situ. And then we also saw how DMDO is utilized in manganese salen based complexes of Katsuki-Jacobsen type of oxidations. And of course, from the fructose derived ketone we can make what is called a Shi catalyst and that leads to the epoxidation of olefins to chiral epoxides.

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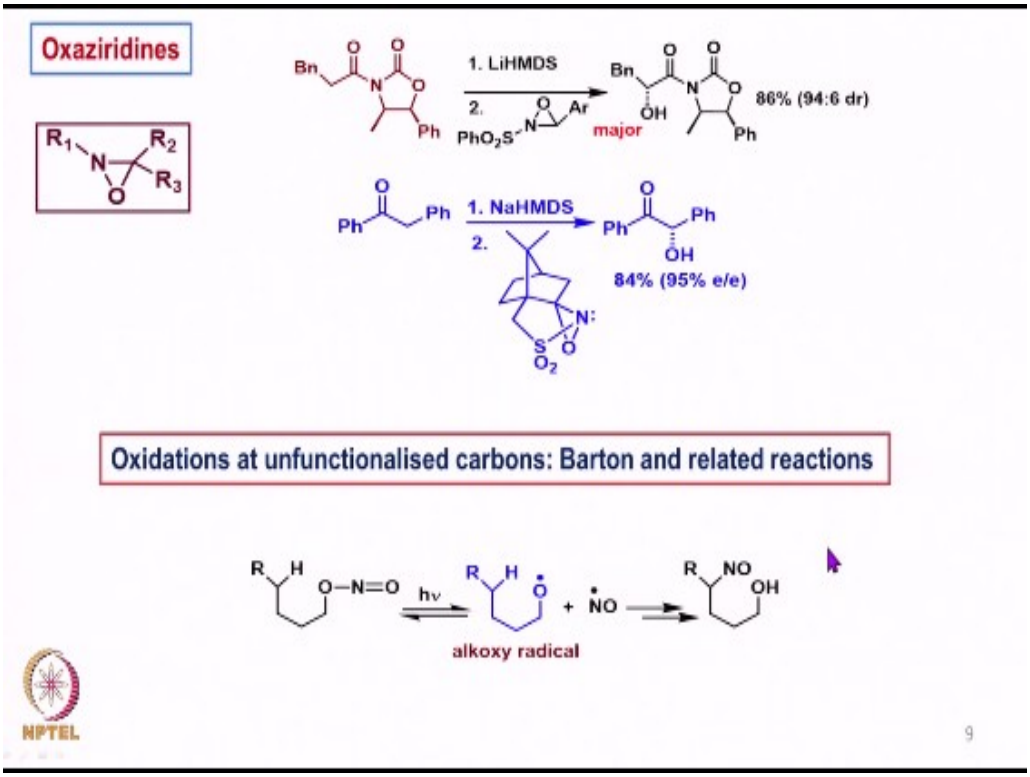

Then we saw the utility of oxaziridines of this type and starting from an optically active starting material having an auxiliary which is chiral auxiliary. We got the corresponding compound in which the hydroxyl group here can be stereoselectively introduced. And of course, we can also take the chiral oxaziridine and oxidize the ketones which are having a prochiral hydrogens here to the corresponding alpha hydroxy ketones with high enantioselectivity.

Then we also looked at oxidation at unfunctionalised carbons that is Barton and related reactions. Starting from this nitrite ester, we got the corresponding alkoxy radical here and then eventually we had this abstraction of the hydrogen here and the carbon NO bond formation and then of course such products were converted to many other products.

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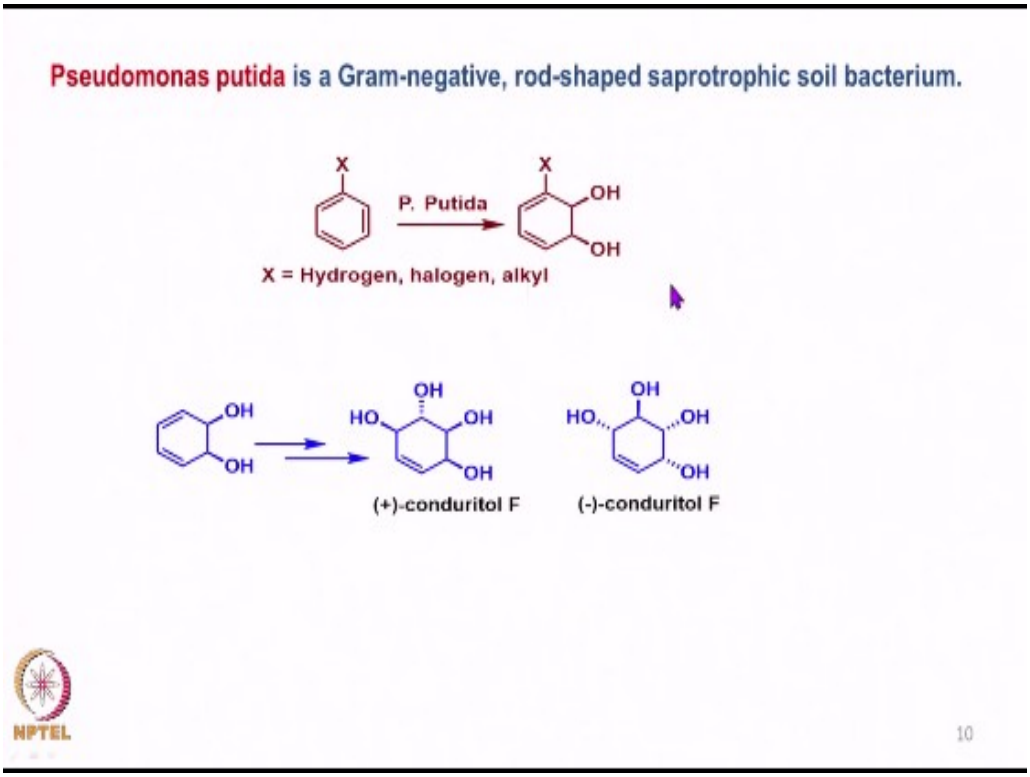

Pseudomonas putida was used as a interesting Gram-negative bacteria for the conversion of aromatics to diols and this happen to be optically pure. If we have other than hydrogen here, like halogen alkyl, then we can get this particular cis diol as optically pure compound. And then one of them we utilized it for the conversion of this diol which is not optically pure.

But then we could get to these optically pure glycosidase inhibitors through various transformations. And we also we saw the conversion of other substituted diols into some important intermediates.

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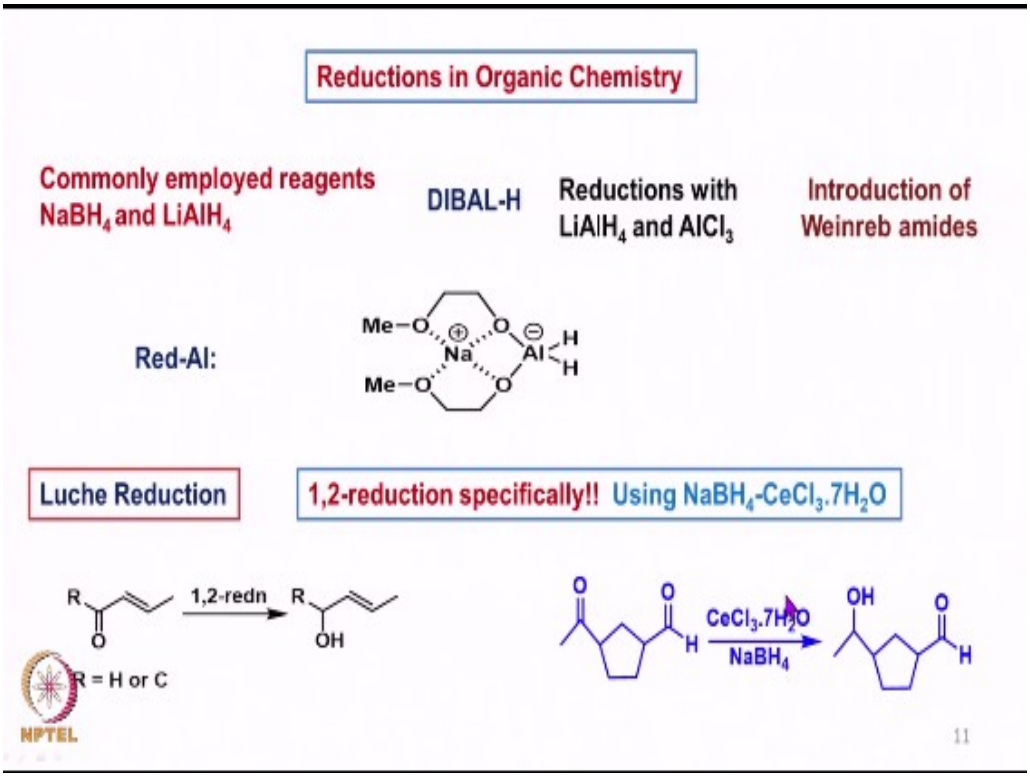

Then we looked at the reductions in organic chemistry utilizing commonly employed reagents like sodium borohydride, lithium aluminium hydride, DIBAL-H, reductions with lithium aluminum hydride, aluminium chloride and of course Red-Al of this kind. And we looked at the merits and demerits of these compounds or reagents for the reaction of various kinds of carbonyl compounds or esters or nitriles or triple bonds or various reductions.

During that process, we also introduced Weinreb amides for selective reductions or selective reactions. Then we looked at how Luche reduction which is a combination of sodium borohydride cerium chloride allows reduction of enones to allyl alcohols or this type of selective reductions.

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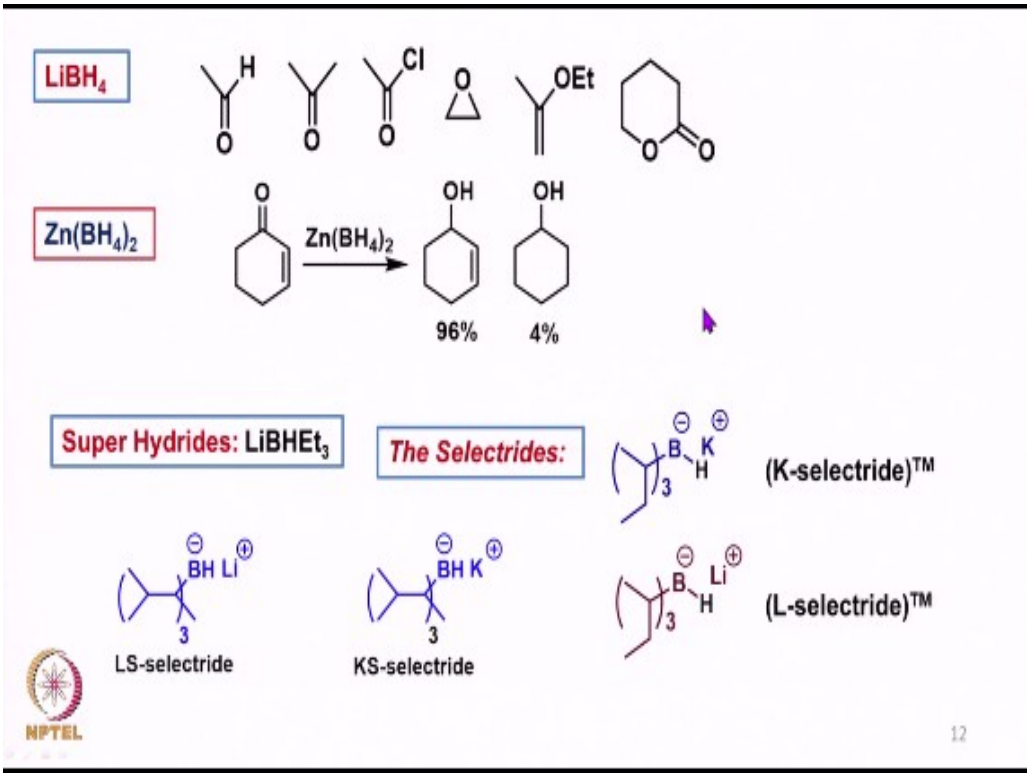

Then we looked at lithium borohydride, zinc borohydride, super hydride, selectrides, all these kinds of reducing agents we looked at it. Gradually we increased the steric hindrance and selectivity. And then of course, we also saw the selectivity aspect in terms of how lithium borohydride and how zinc borohydride are different from sodium borohydride or lithium aluminium hydride.

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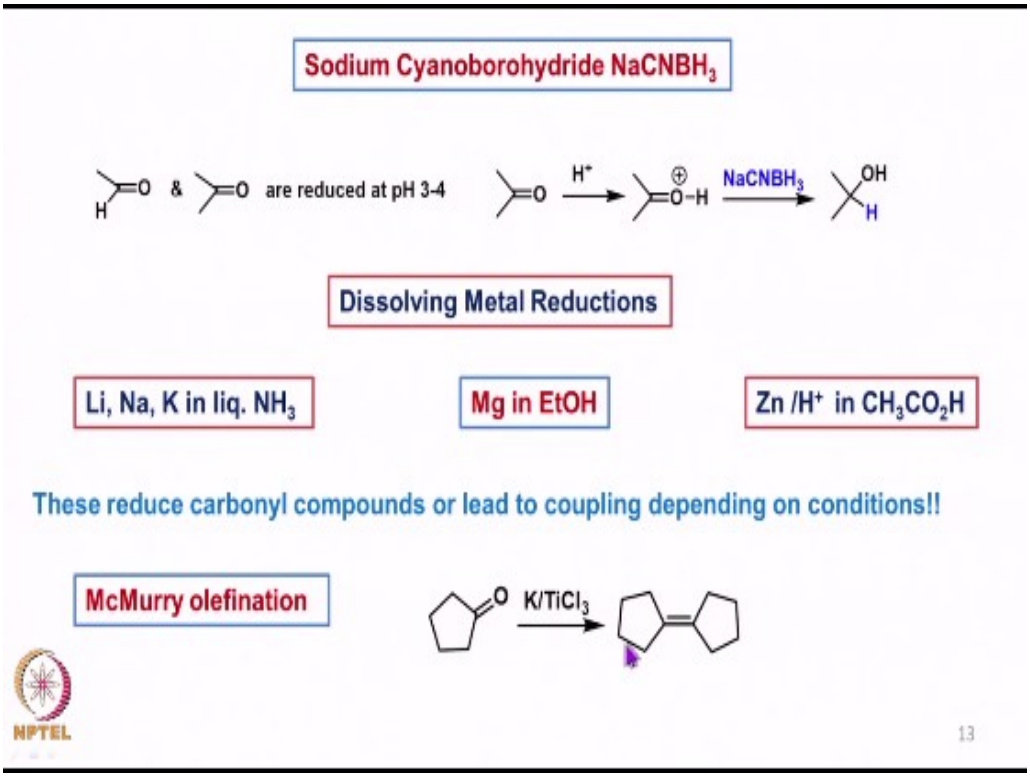

Then we saw sodium cyanoborohydride how it can allow the reduction of aldehydes or ketones under acidic conditions because sodium cyanoborohydride is stable under acidic conditions. And then we saw dissolving metal reductions using these kind of monovalent metals or bivalent metals. And finally, we saw McMurry olefination where we used titanium based reagents.

We saw of course in these cases whether reduction occurs or C-C bond formation occurs when we take monovalent or bivalent metals. And then in the case of McMurry of course, coupling also occurs of this kind.

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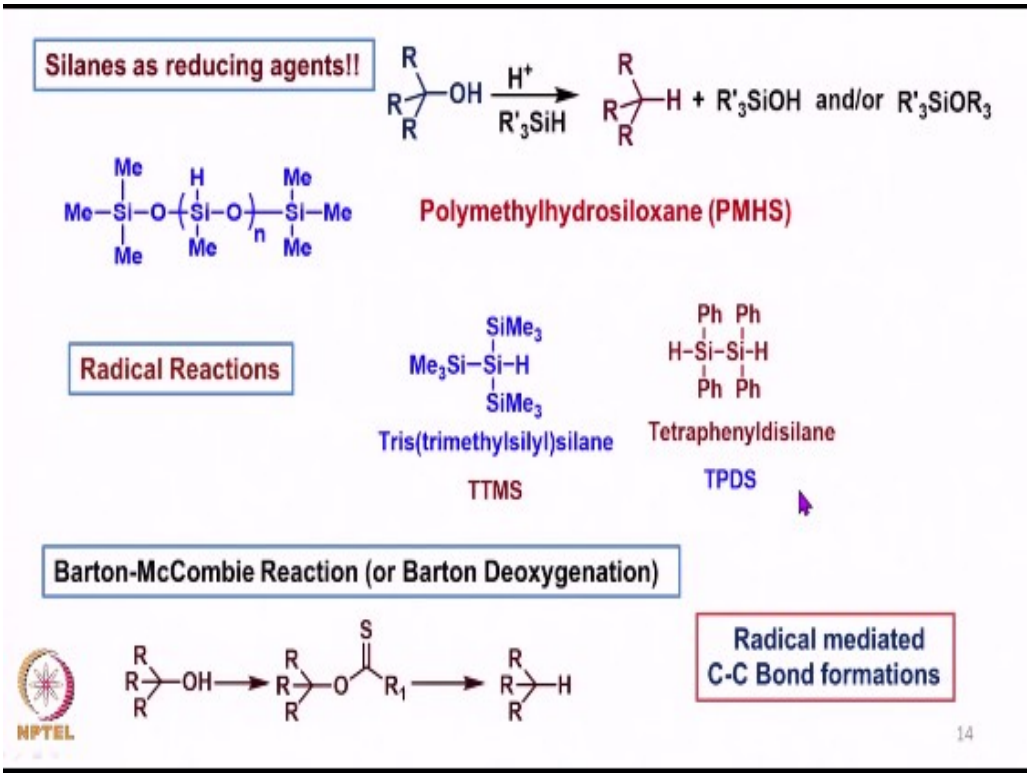

Then we looked at reducing agents such as silanes of different kinds like trialkyl silanes, which reduce an alcohol for example, to the corresponding hydrocarbon here under acidic conditions because they protonate, generate a carbocation and then reduction leads to the hydrocarbon here. In that context, we also saw the utility of this polymethylhydrosiloxane.

And in that context radical reactions, C-C bond formation and deoxygenation of this kind which is also known as Barton deoxidation. And of course many C-C bond formations where you seen using tributyltin hydride as well as this tris trimethylsilyl silane or tetraphenyldisilane. We looked at various kinds of reactions.

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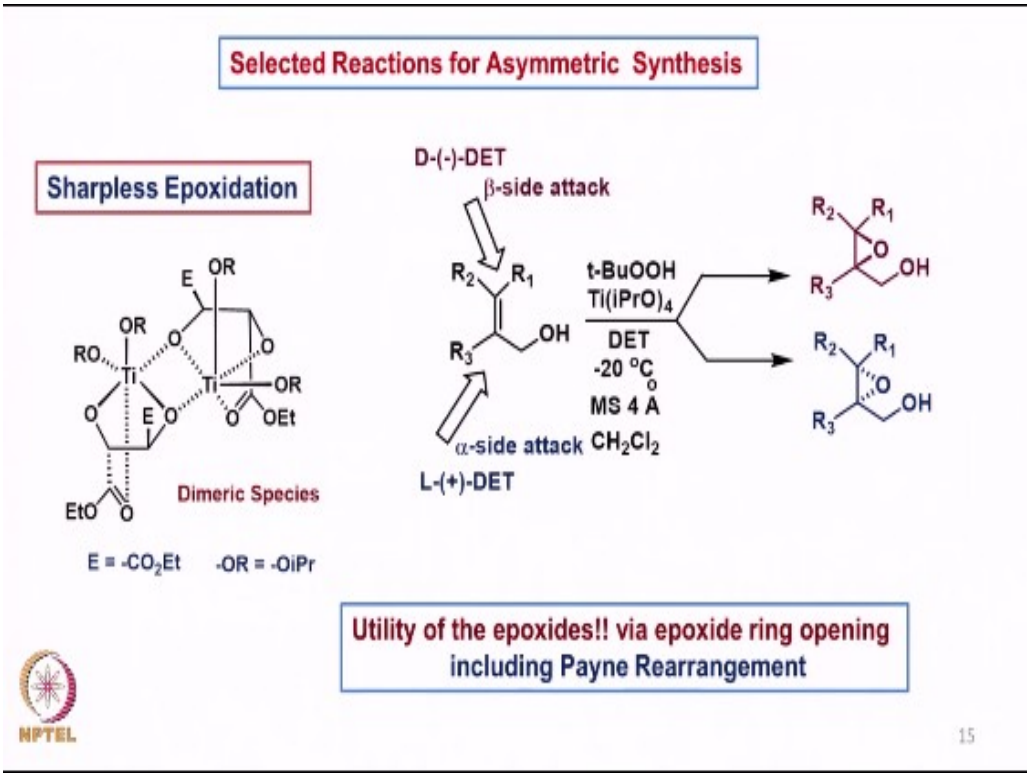

Then we went to asymmetric synthesis of this kind where initially we discussed Sharpless epoxidation where the allylic alcohols can be converted into epoxy alcohols with different kinds of enantioselective products. And also we saw the utility of these epoxides that is epoxide opening in a very regioselective and stereoselective fashion including Payne rearrangement. So under a neutral condition and under basic conditions, we saw different reactions.

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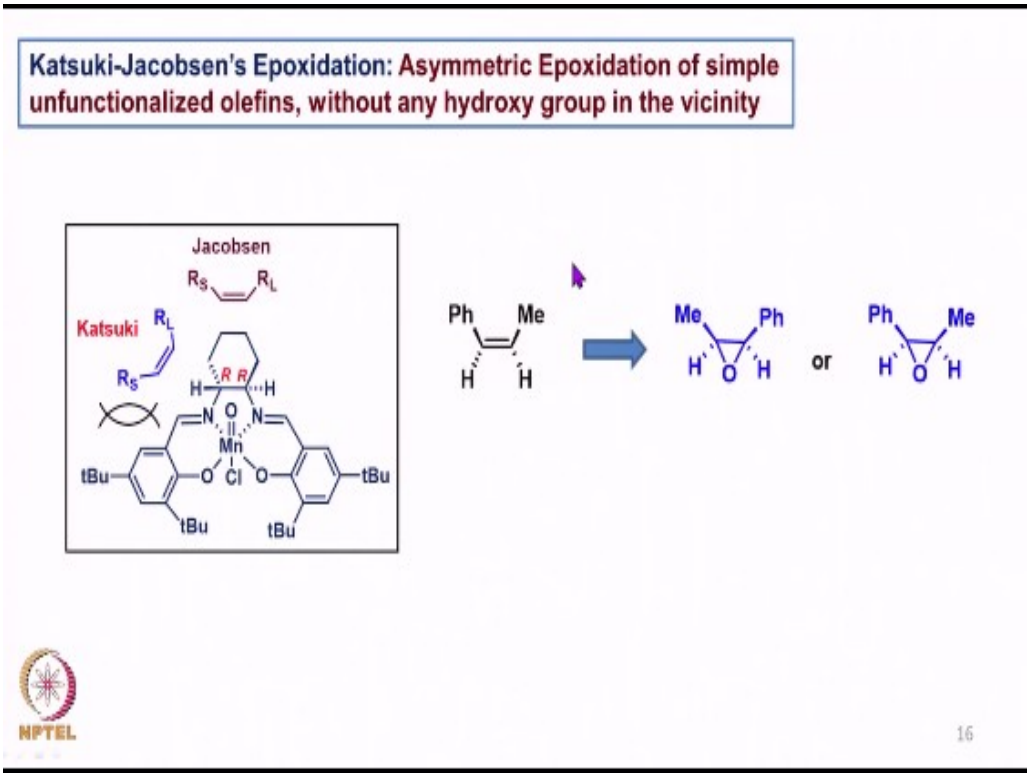

Then we looked at Katsuki-Jacobsen epoxidation using this kind of salan complexes. This involves basically epoxidation of unfunctionalized olefins to the corresponding epoxides. And of course we saw how the mechanistic aspects of Jacobsen and Katsuki type of proposals were implemented in these oxidations.

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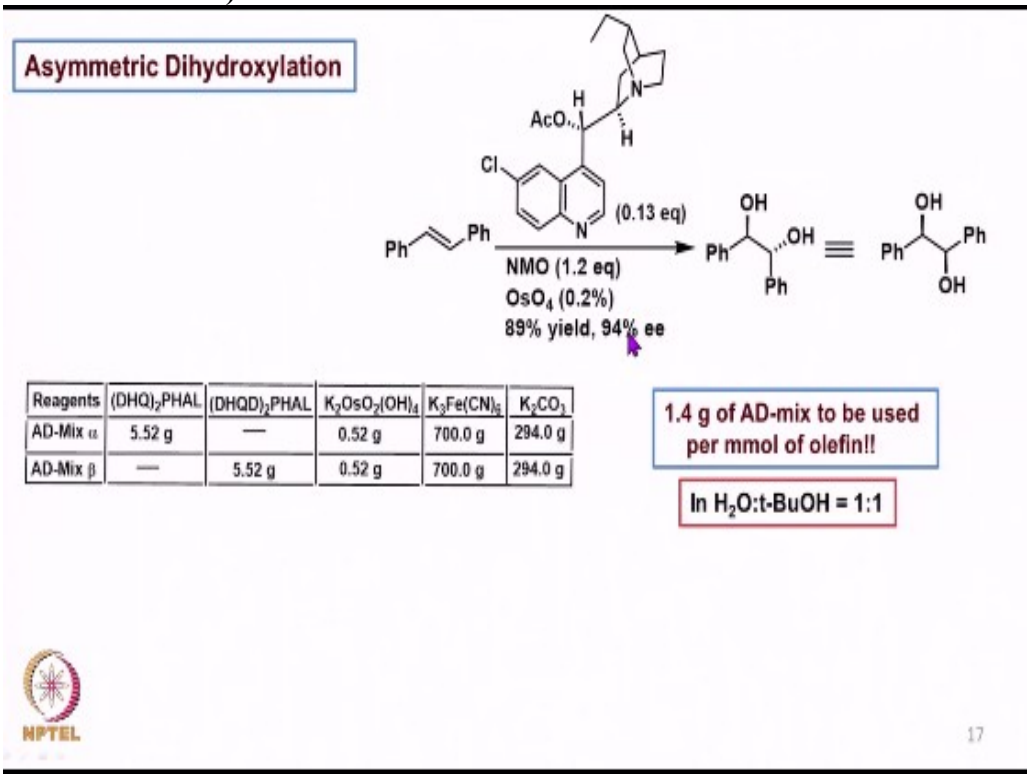

Then we looked at asymmetric dihydroxylation, that is Sharpless based dihydroxylation where double bond were converted to the corresponding diols, the syn diols. And during that process, we saw how this kind of alkaloids were utilized and the AD-Mix alpha and AD-Mix beta, how can they be in a predictable fashion utilized in organic synthesis.

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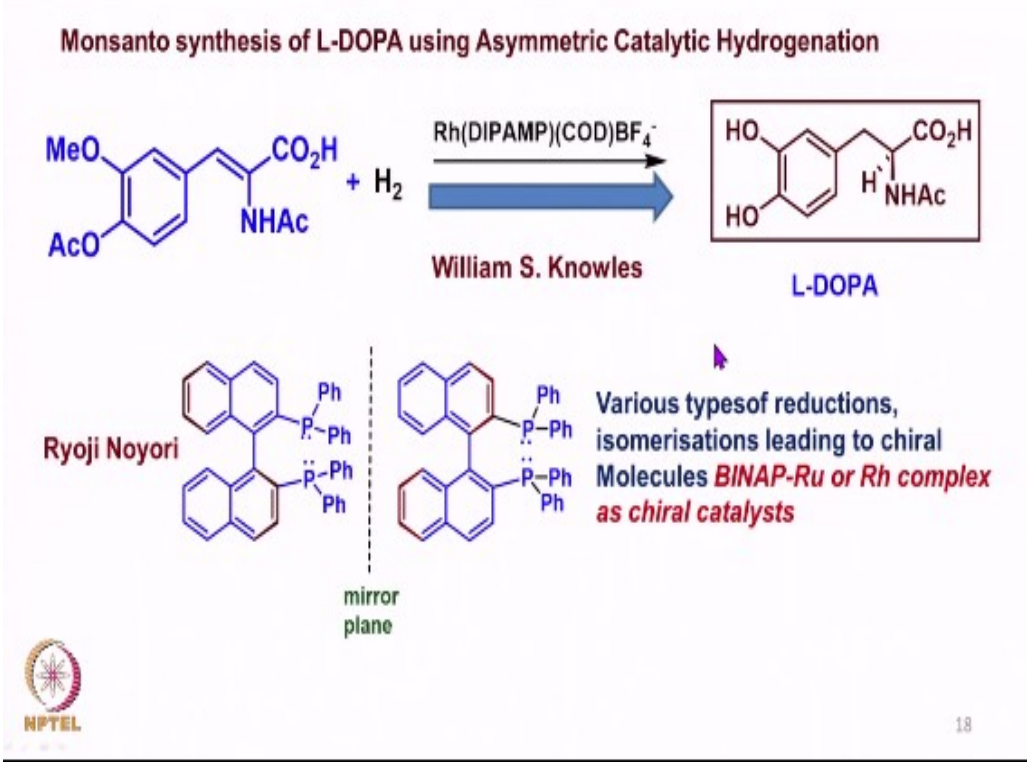

We also looked at the Monsanto synthesis of L-DOPA using asymmetric catalytic hydrogenation. What is something very important was basically initially developed by William Knowles to form L-DOPA, which is a very important compound on an industrial scale. Of course, he used this kind of rhodium catalyst and then Noyori modified the ligand to this particular BINAP based ligands, chiral ligands.

And then made use of various kinds of BINAP ruthenium or BINAP rhodium complexes as chiral catalyst. And allowed these reactions to take place in a highly enantioselective fashion.

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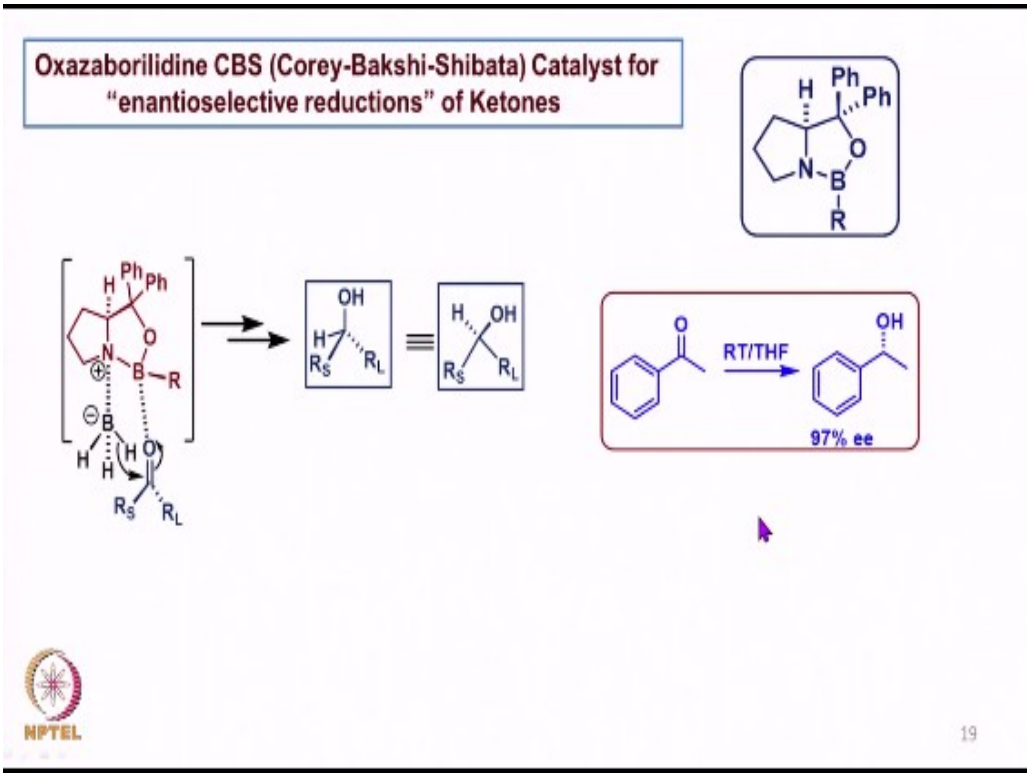

Then in this asymmetric reduction based studies, we also looked at the utility of the Corey-Bakshi-Shibata catalyst of this type for the reduction of ketones to alcohols here like this in a highly enantioselective and highly predictable fashion. And we invoked the transition state of this kind where this ligand or this chiral catalyst allows the reducing agent that is BH_3 or any diborane or any borane to attach here and then allow highly enantioselective reduction.

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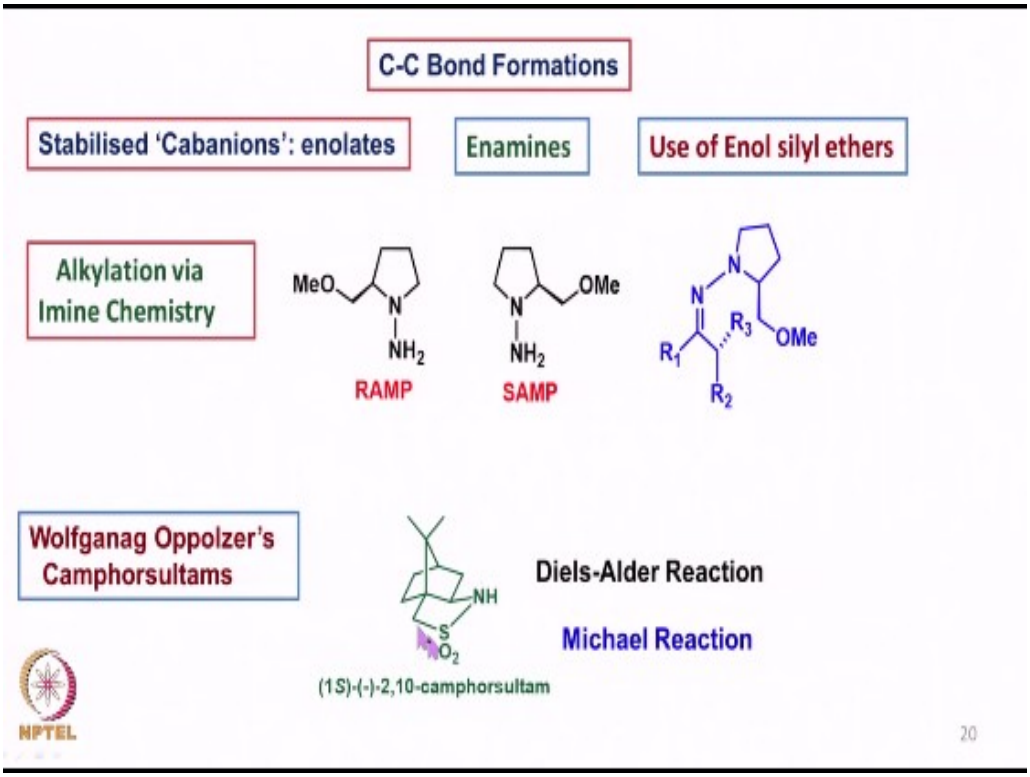

Then we did the C-C bond formations of various kinds starting with how the enolates allow C-C bond formation and what are the drawbacks. Then how the enamines emerged. Then how the use of enol silyl ethers emerged and what are the limitations and the positive aspects of these reactions. Then we proceeded via alkylation through imine chemistry, which eventually led to the formation of this.

Or introduction of this RAMP and SAMP based auxiliaries and thus this type of imine formation which allowed the C-C bond formation to take place in an enantioselective fashion. In the same context then Wolfganag Oppolzer's camphorsultams were introduced to allow Diels-Alder and Michael reaction to take place using this type of camphorsultams.

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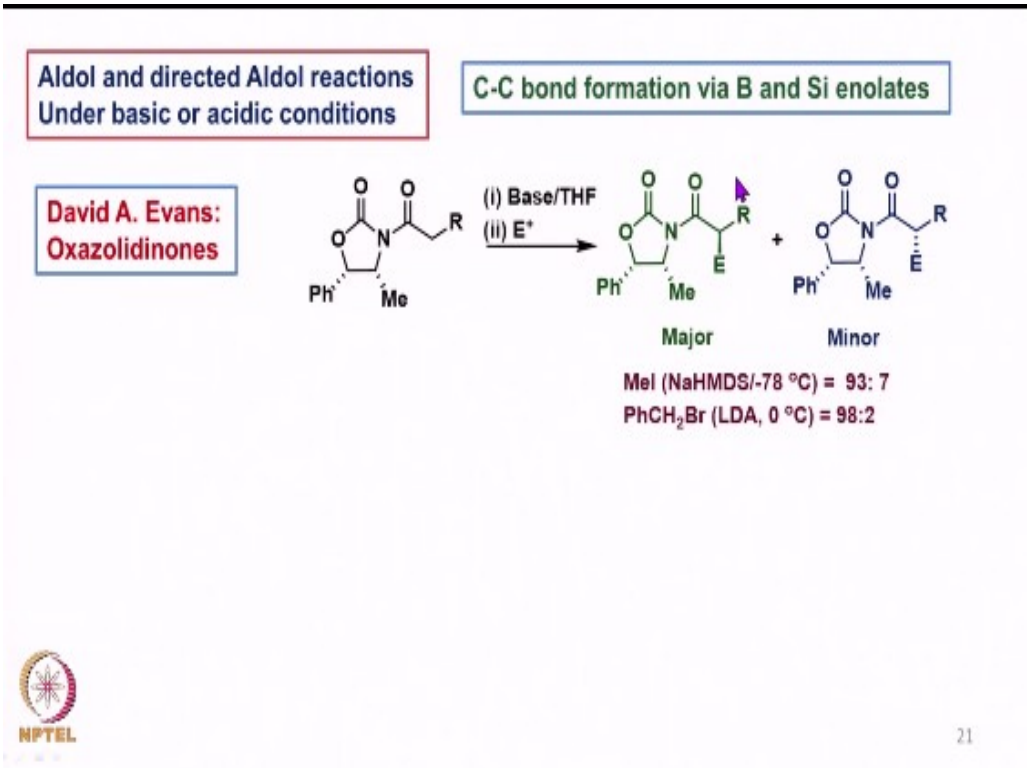

Then of course, we did the C-C bond formation via boron and silicon enolates. David Evans introduced oxazolidinones of this kind. And then we could do this carbon-carbon bond formation like what I have shown here using different types of bases like this NaHMDS or LDA. And of course in this context, we also discuss various kinds of boron and silicon enolates.

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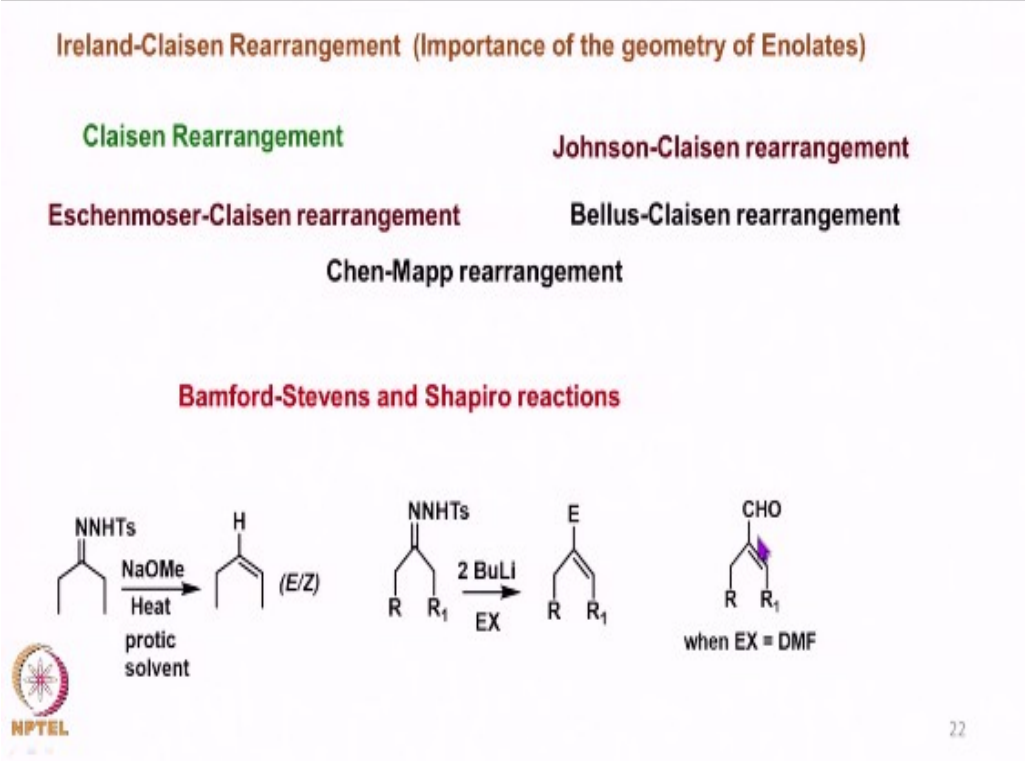

Then we looked at Ireland-Claisen rearrangement, where we looked at and discussed the importance of geometry of enolates. First the formation of the enolates itself was very important and how does the presence or absence of HMPA in THF lead to one enolate and over the other enolate. Now in that context, we looked at Claisen rearrangement basically.

And then various modifications, Johnson-Claisen rearrangement, Eschenmoser-Claisen rearrangement, Bellus-Claisen rearrangement, Chen-Mapp rearrangement. Like this various aspects of Claisen rearrangement, including aza-Claisen rearrangement, thio-Claisen rearrangement.

Then finally, we saw Bamford-Stevens reactions and Shapiro reactions, which also allow C-C bond formation to take place, which proceed through an intermediate of tosylhydrazone of this kind, which allow the formation of E or Z olefins depending on the solvent. And also we saw that how Shapiro modifications of this reaction using two equivalents of butyllithium and an electrophile allow vinyl anion to form onto the same carbon where tosylhydrazone was formed.

And this vinyl anion then leads to the introduction of an electrophile. For example, when we have a DMF as an electrophile, we got the corresponding aldehyde. So we can convert this tosylhydrazone to this vinyl aldehyde.

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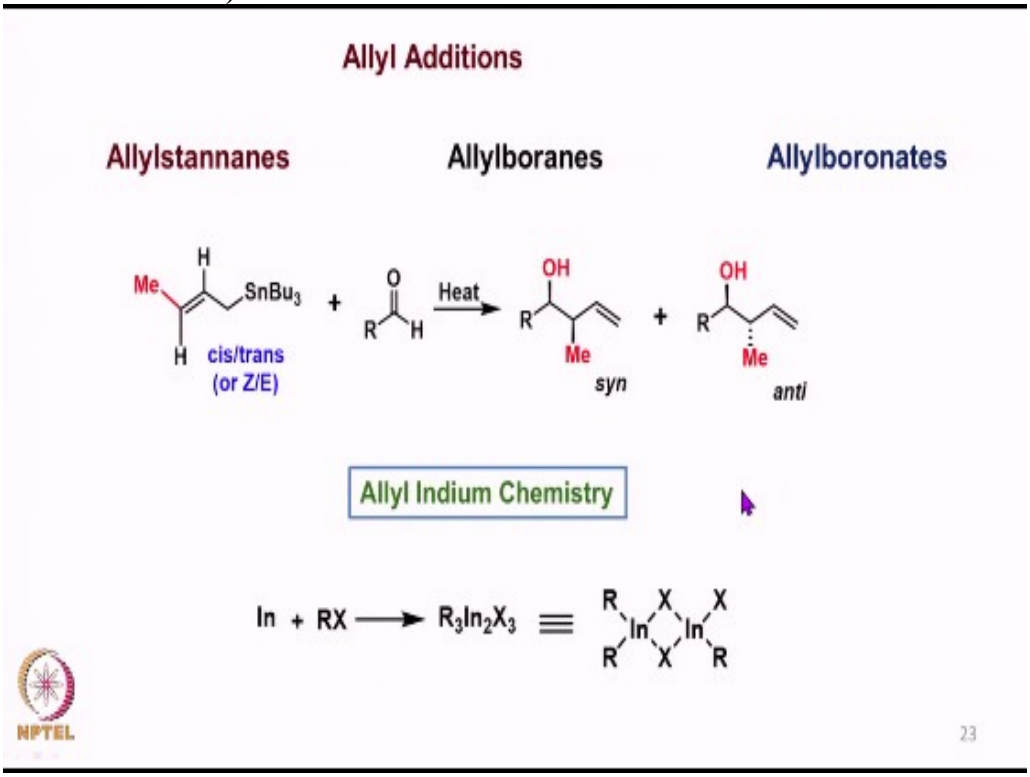

Then in the domain of allyl additions to carbonyl compounds to allow C-C bond formations what we looked at was reactions of allylstannanes, allylboranes, allylboronates and allylindiums to various kinds of carbonyl compounds.

Initially, we saw that say in the case of stannane additions, we saw that if we take either Z oriented crotylstannane or E oriented crotylstannane and add on to an aldehyde under heating

conditions, then we get syn product from Z oriented crotylstannane and anti product from E oriented crotylstannane.

In the case of allylindium chemistry, we saw that we can carry out the reaction in situ upon reaction of indium metal with halides, say allyl halides for example, and it leads to the formation of this particular indium species which then reacts with the aldehydes or ketones in situ and leads to the formation of C-C bonds. So this is how we looked at various kinds of allyl moiety additions to carbonyl compounds.

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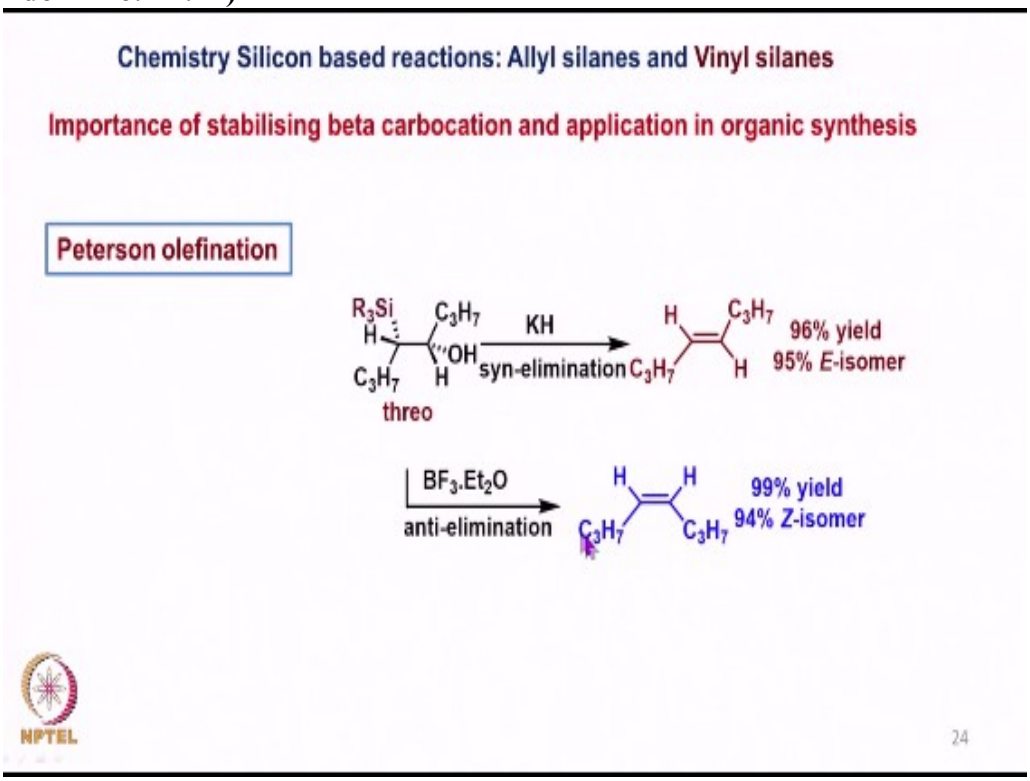

Then we looked at the chemistry of silicon based reactions where ally and vinyl silanes were used. And we very categorically looked at the importance of stabilizing beta carbocations and then application in organic synthesis. We also looked at not exactly C-C bond formation, but a very important reaction which is called Peterson olefination reaction.

Under basic condition it leads to syn elimination to form this product and under acidic condition or under Lewis acidic condition via anti-elimination to form this particular kind of product.

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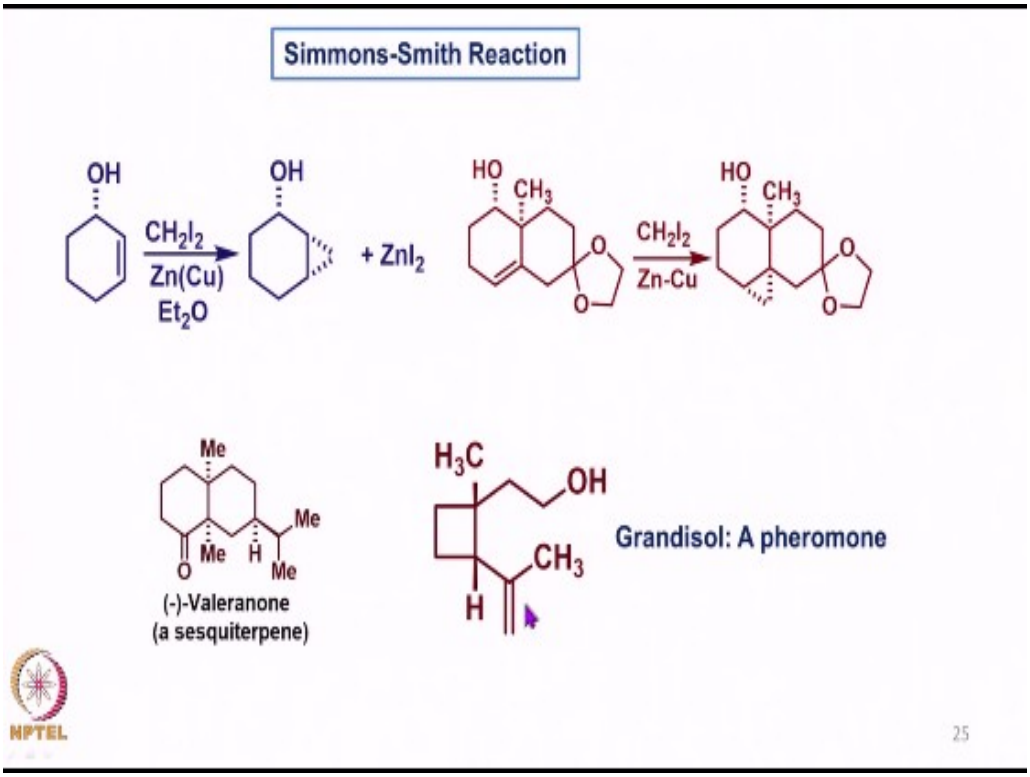

In the end, we looked at Simmons-Smith reaction to form a cyclopropane ring which is a C-C bond formation using this type of protocol where you used a diiodomethane and zinc copper couple in ether and this gives the corresponding cyclopropane where the geometry of the cyclopropane was similar to the geometry of the hydroxy group. And we also saw the mechanistic aspects of it.

Likewise, when we had this homoallyl alcohol also we got the corresponding cyclopropane having the similar type of geometry as a carbon hydroxy bond. Utility of this kind of cyclopropane reactions with Simmons-Smith type of reaction was also utilized to prepare molecules like this, which is a natural product. And then of course, we applied this for the synthesis of a pheromone which is called as Grandisol using the cyclopropane based chemistry.

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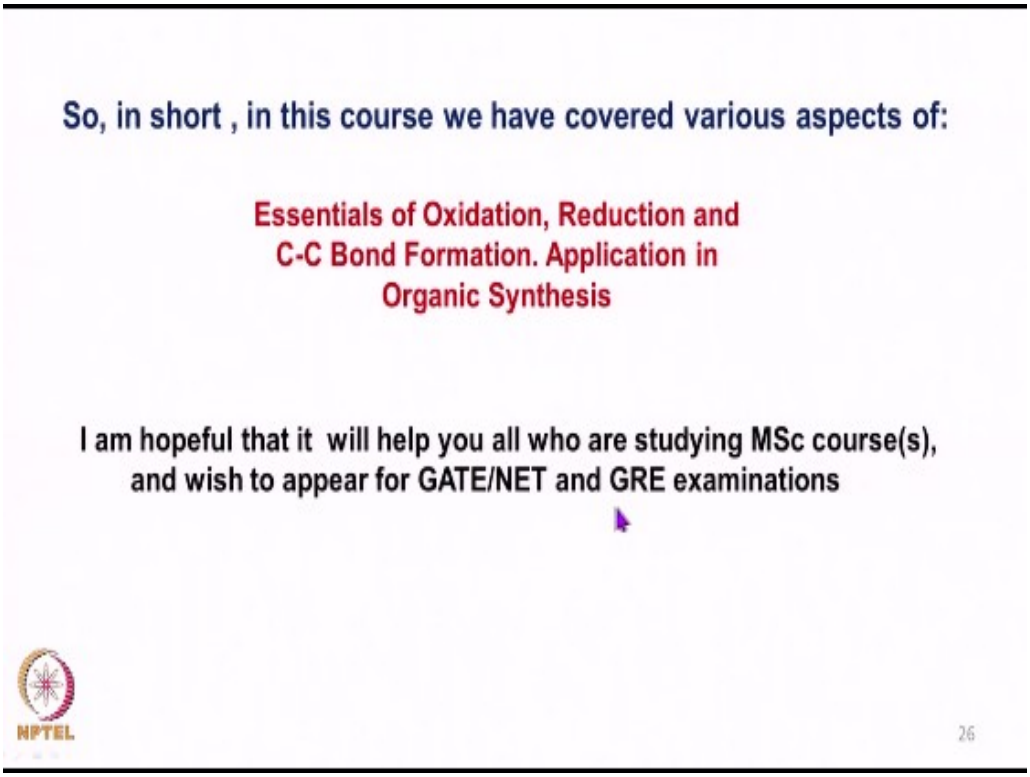

So in short, in this course we covered various aspects of essentials of oxidation, reduction, and C-C bond formation and their application in organic synthesis. I am hopeful that it will help you all who are studying MSc courses and wish to appear for GATE/NET and GRE examination. So we will stop it here.

And I wish you all the best for the examination pertaining to this particular course and also in the future, other examinations and also for your future as a researcher in chemistry. Thank you and bye.