Reagents in Organic Synthesis
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Lecture No. 24
Chromium and Manganese Based Reagents in Organic Synthesis

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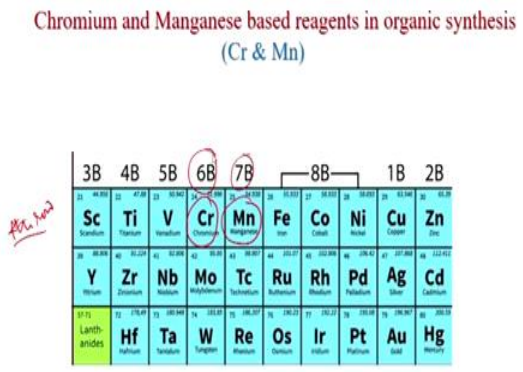

Welcome again. Today we will discuss chromium and manganese based reagents in organic synthesis. So this is chromium and manganese. They are side by side. So this is fourth row. And chromium is present in 6B group and manganese in 7B.

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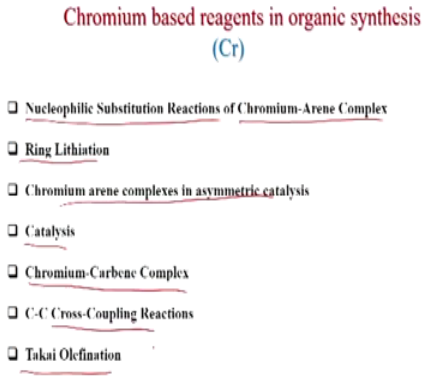

So first we will discuss chromium based reagents and the reactions nucleophilic substitution reactions of chromium-arene complex. Then we will discuss ring lithiation, chromium-arene complexes in asymmetric catalysis because if it is di-substituted, then it is chiral that we will discuss. Catalysis. Chromium-carbon complex. C-C cross coupling reactions and finally Takai olefination.

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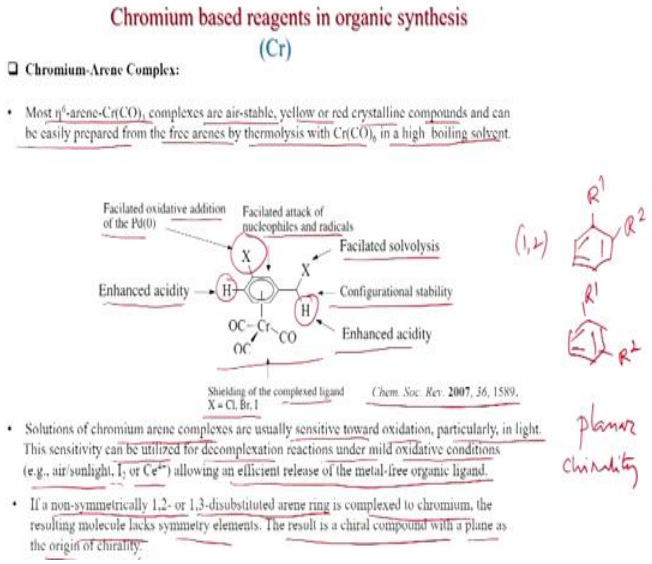

So chromium-arene complex, most eta 6 arene $CrCO_3$ complexes are air stable, yellow or red crystallines compounds and can be easily prepared from the free arenes by thermolysis with hexa-carbonyl chromium in a high boiling solvent. So this can be easily prepared by reacting hexa-carbonyl chromium with the arene.

So this is the structure. You can see here, 3 carbonyls are attached to the chromium. And this group can be facilated solvolysis is possible, then configuration is stable. And this is enhanced acidity that we will see also, the enhanced acidity. And shielding of the complexed ligand X is equal to Cl, Br, I. Enhanced acidity of this proton also and facilated oxidative addition of the palladium (0) at this group. We will see different reactions. And facilated attack of nucleophiles and radicals that also we will see. There is a nice review, chemical society review 2007.

So solution of chromium arene complexes are usually sensitive toward oxidation, particularly in light. The sensitivity can be utilized for decomplexation reactions under mild oxidative conditions, as for example air, sunlight, iodine or ceric salt allowing an efficient release of the metal free organic ligand. So it is possible to remove the chromium complex by under sunlight, air, or iodine or ceric salt.

Now if a non-symmetrically 1, 2- or 1, 3- di-substituted arene that means this kind 1, 2- or 1, 3- arene ring is complexed to chromium, the resulting molecule lacks symmetry elements. The result is a chiral compound with a plane as the origin of chirality. So this is called planar chirality. We will see also their examples.

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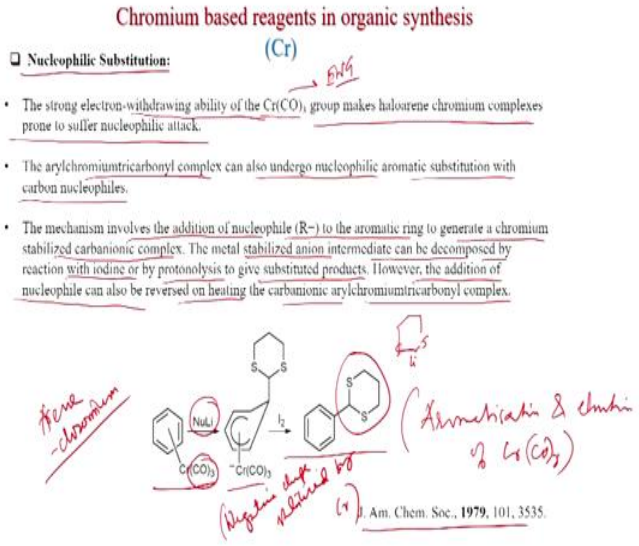

Now first we will discuss nucleophilic substitution reaction. The strong electron withdrawing ability of the CrCO3 group makes haloarene chromium complexes prone to suffer nucleophilic attack. So this actually EWG- electron withdrawing group. So nucleophilic substitution is possible on the arene ring. The aryl chromium tricarbonyl complex can also undergo nucleophilic aromatic substitutions with carbon nucleophile also is possible.

And the mechanism involves the addition of the nucleophile to the aromatic ring to generate a chromium stabilized carbanionic complex. The metals stabilized anion intermediate can be decomposed by reaction with iodine or by protonolysis to give substituted products. So with iodine you can remove the chromium. However, the addition of nucleophile, it can also be reversed on heating the carbanionic aryl chromium tricarbonyl complex. So by heating also, the addition is reversible.

So this is the arene complex, arene chromium complex. Here 3 carbonyl is there. Now nucleophile is adds, like this one 1, 3 diethyl lithium and you get this eta 5. And this negative charge is stabilized by chromium. And with iodine you get aromatization and elimination of CrCO3. So if you just put the iodine, then you get. So it is a very easy method to get a group like this nucleophile with just addition followed by iodine treatment. This was published in JACS 1979.

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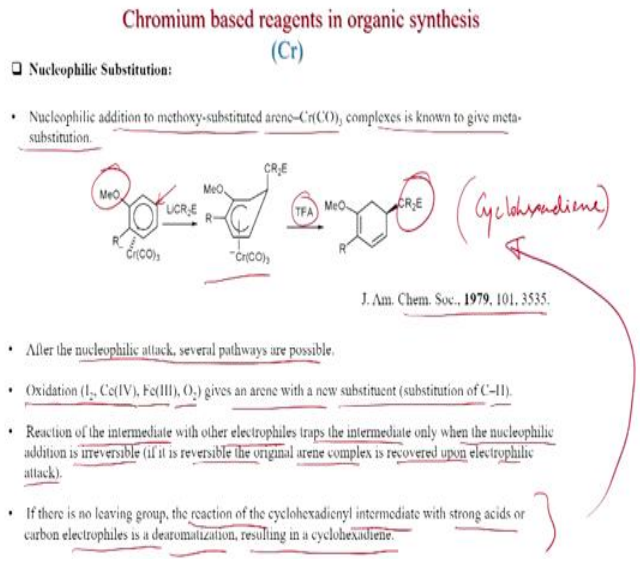

Some more examples. Nucleophilic addition to methoxy substituted arene- CrCO3 complexes is known to give meta-substitution. We will see. So if there is methoxy group is present in the arene, then the nucleophile adds to the meta position. So this is the meta. Here the attack will take place and you get this. And after trifluoroacetic acid, you get the cyclohexadiene. So earlier we have seen the aromatization happened with iodide. But if you put acid, then you get cyclohexadiene system with the nucleophile here. This was also published in JACS 1979.

So after the nucleophilic attack, several pathways are possible. Oxidation as we have seen iodine, ceric salt, iron salt, oxygen gives an arene with a new substituent, substitution of C-H. Reaction of the intermediate with other electrophiles traps the intermediate only when the nucleophilic attack is irreversible, if it is reversible the original arene complex is recovered upon electrophilic attack. And if there is no leaving group, the reaction of the cyclohexadienyl intermediate with strong acids or carbon electrophiles is a dearomatization, resulting in a cyclohexadiene. So this is happening here that cyclohexadiene is forming after treatment of a strong acid like trifluoroacetic acid.

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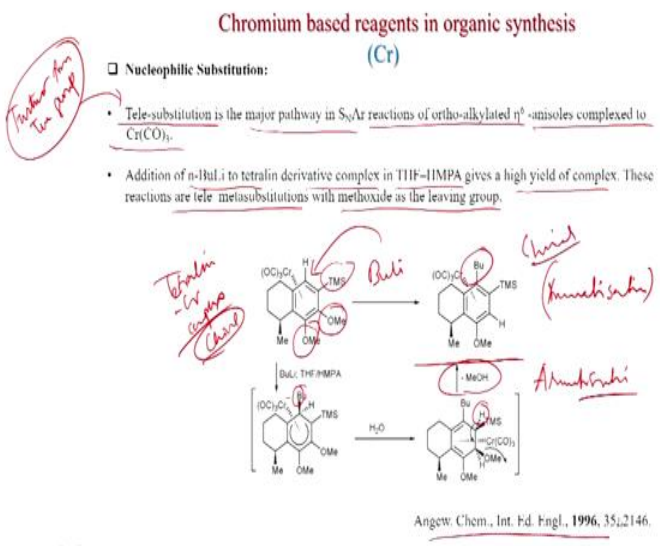

Some more examples of nucleophilic substitution teli-substitution. Teli means farther from the group, farther from the group already present. So like meta, para that is called tele-substitution is major pathway in SnAr reactions of ortho-alkylated eta 6 anisoles complexed to CrCO3. Addition of n-butyl lithium to tetralin derivative complex in THF-HMPA gives a high yield of complex. These reactions are tele metasubstitutions with methoxide as the leaving group.

So this is the reaction. This is tetralin derivative, tetralin chromium complex. So if you see, this is a anisole and there is also another methoxy and TMS group. Now butyl lithium, if you put butyl lithium, this butyl group adding at this position. And after aromatization you get this. So we will see the detailed mechanism. So if you add butyl lithium then it is adding here and this is also chiral. So butyl lithium is coming from the top side because chromium is down.

So butyl is coming from top side and attacking in this carbon selectively. Then you get this anion which is stabilized by chromium. And now if you treat with water, aqueous work up then what happens? This anion getting protonated and the aromatization will happen now. You see this methanol is eliminating. So this hydrogen is eliminating and this methoxide. So ultimately methanol is eliminating. So aromatization is happening. And you get the butyl substituted chromium complex. And this is also chiral. This was published in Angew Chem 1996.

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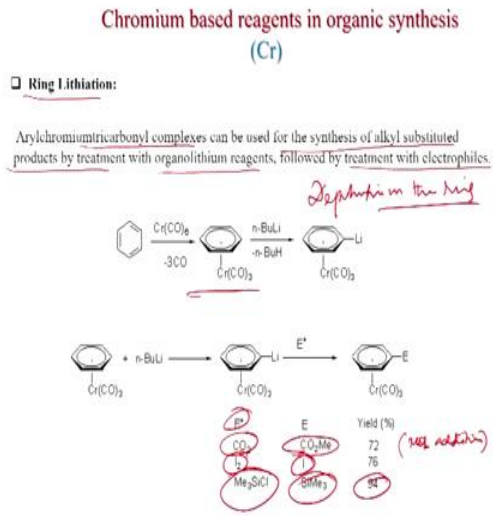

Ring lithiation is also possible. Arylchromium tricarbonyl complexes can be used for the synthesis of alkyl substituted product by treatment with organolithium reagents, followed by treatment with electrophiles. So this is an important reaction that is the arene chromium carbonyl complex. And with n-butyl lithium, you can deprotonate. So this acidity of the benzene ring increase because it is coordinal chromium. So with n-butyl lithium you can deprotonation is possible. So deprotonation on the ring.

And this one can be used for electrophilic reactions. So defined electrophiles like carbon dioxide, you get CO2Me. Of course here you have to add methyl iodide also, methyl iodide addition. Then iodine, if you put iodine then you get I, I in the aromatic ring. If you put dimethylsilyl chloride, then you get TMS group in the ring. And you get 94 percent yield. So this is very useful method for getting these kind of compounds.

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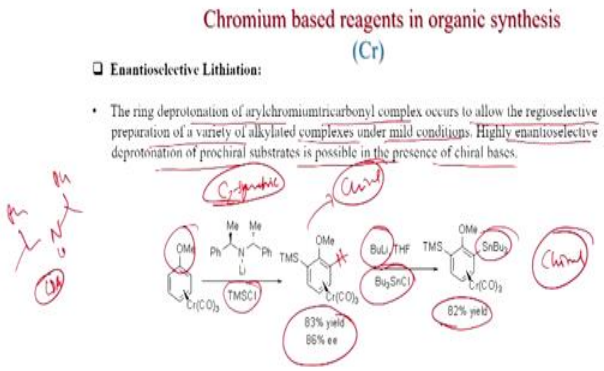

Now enantioselective version also possible. If the ring is di-substituted after lithiation, then you can get the chiral product. So the ring deprotonation of arylchromiumtricarbonyl complex occurs to allow the regioselective preparation of a variety of alkylated complexes under mild conditions. Highly enantioselective deprotonation of prochiral substrates is possible in the presence of chiral bases.

Like here, this is monosubstituted complex and now after lithiation followed by TMS quenching you get this chiral product. So this is chiral product. So if you know the LDA, LDA was diisopropyl. This is LDA. And this is, one methyl group is displaced by phenyl and this is also C2 symmetric. So this is chiral base. And with chiral base you get a selective lithiation, also enantioselectively. And you get this product, TMS substituted product in 83 percent yield with 86 percent ee.

Again you can put another equivalent of silyl butyl ether because this is now chiral. So n-butyl lithium if you put this lithiation takes place. This hydrogen is deprotonated and tributyltin chloride reaction tin substitutent coming here. And this product is formed 82 percent. So this is also chiral. So the enantioselective lithiation is possible with chiral base.

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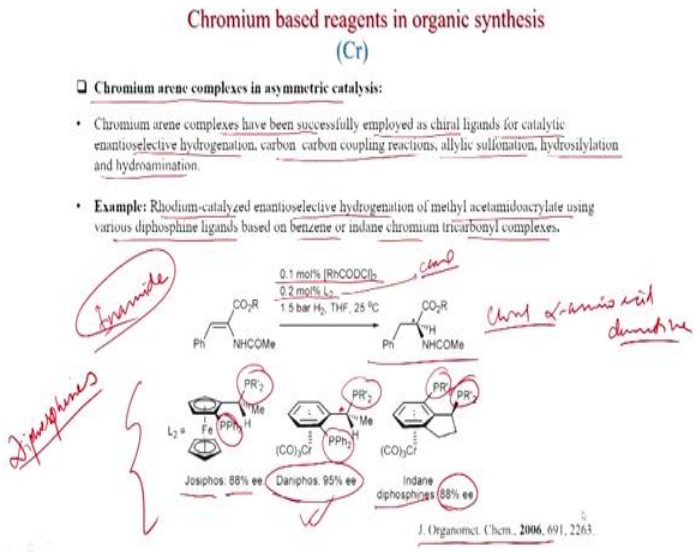

Now we will discuss this chiral chromium complexes in asymmetric catalysis. So chromium arene complexes have been successfully employed as chiral ligands for catalytic enantioselective hydrogenation, carbon-carbon coupling reactions, allylic hydrosilylation and hydroamination. So many reactions can be performed with this chromium arene complexes.

Example: Rhodium catalyzed enantioselective hydrogenation of methyl acetoimdoacrylate using various diphosphate ligands based on benzene or indane chromium tricarbonyl complexes. Like this is inamide. We have seen this kind of substrate earlier. So this is inamide. Now with 0.1 mole percent rhodium cyclooctadiene Cl whole 2, 0.2 mole percent of L2. So this we will see the structures chiral ligands. So this chiral. And 1.5 bar hydrogen, THF, 25 degree centigrade, you get the hydrogenation of the inamide and you get this chiral product. So these are the chiral alpha amino acid derivative.

And now we will see the ligand structure. So all of these are diphosphines. Now this is ferrocene based. So this is a phosphine, here is a phosphine. And this with ferrozine based, this is called Josiphos. You get 88 ee. Now this is our chromium arene complex, tricarbonyl complex. Here this phosphine is there, this is a phosphine. This is a chiral center. This is also planar chiral.

So this one is giving Daniphos, 95 percent ee of this product. Now if you make another cycle, that is the indane derivative. Here phosphine, here phosphine, then you get diphosphine, indane diphosphine which is giving 88 percent enantioselectively for this product. So this Daniphos catalysis is the base for this inamide hydrogenation and you get 95 percent enantiomeric excess. So this was published in journal Organometallic Chemistry, 2006.

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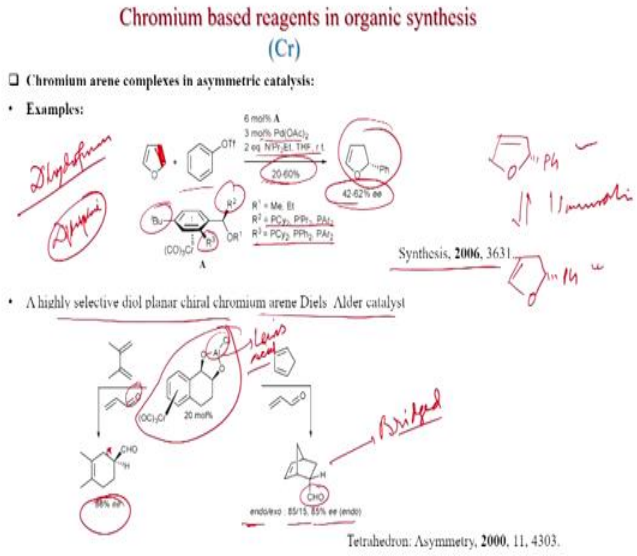

Some more reactions in asymmetric catalysis like Heck reaction. So this is mistake. This should be single bond. So this is dihydrofuran. So dihydrofuran reacting with this (triflate) aryl triflates with 6 mole percent A. So A is this. This is also diphosphine, diphosphine that earlier we have seen. Here A phosphine is there. R3 is equal to PCy2 and R2 also is a phosphine. And there is additional tertiary butyl substituent in the para position. And with ligand and this is the catalysis 3 mole percent palladium acetate, 2 equivalent of diisopropylethylamine, THF, you get 20 to 60 percent yield or this Heck coupling product and the enantiomeric excess is 42 to 62 percent.

So what is happening? After coupling this product is forming first because we know in heck coupling, the double bond will isomerize. And this will isomerize this one because this will be stabilized more. So first this is forming and then this is isomerization is happening. And this product is obtained in 42 to 60 percent enantiomeric excess. This

was published in Synthesis 2006. Also a highly selective diol planar chiral chromium arene as Diels Alder catalyst. This one the catalyst. So here you can see this chromium arene is present and this is the diol aluminum. So aluminum is good Lewis acid. And this Lewis acid is activating the aldehyde group. And this acryldehyde when it is treated with this diene, this cyclic product is forming in 86 percent enantiomeric excess. So this is the chiral center.

And when it is treated with cyclopentadiene, then you get a bridge compound. So this is bridged. And endo is the major. So this is the endo structure, CHO is down. Endo is forming in 85 is to 15 ratio index, and the enantiomeric excess of endo isomer is 85 percent ee. This was published in Tetrahedron Asymmetry, 2000.

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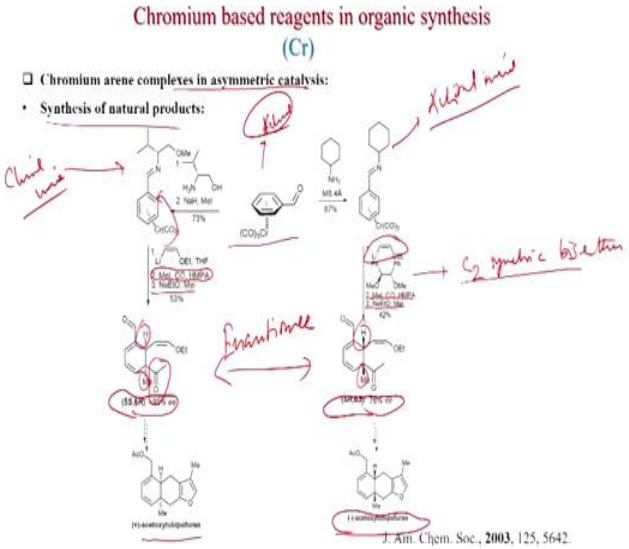

Chromium arene complexes now it can be applied for natural product synthesis also. Like this one. This is not chiral because it is monosubstituted. So this is achiral. Now if you make a imine. So this is chiral, this is venial and this is chiral imine. Chiral imine is formed here. Now if you add vinyl lithium to this aromatic ring, now this will add to here. And this addition will be enantioselectively like this one. And after that this anion will be form here. This anion you can react with carbon monoxide, methyl iodide so you

get a ketone and that ketone, alpha position again you can treat with sodium ethoxide, methyl iodide you get the methyl. And this product is formed 95 percent ee. And in this process this $CrCO_3$ also is eliminated.

So first addition here. Then the, so first the nucleophile, then the electrophile, that is the carbon monoxide and methyl iodide you get the ketone and then the alpha functionalization of ketone with sodium ethoxide and methyl iodide. And these two hydrogen and methyl, so these two are the cis position. And this intermediate can be converted to the natural product. This is the plus version, plus acetoxytubipofuran.

Now the other enantiomer you can also be form. So here you make a achiral imine. So this is achiral imine because cyclohexylamine is added. And now with a C2 symmetric ligand, so this is C2 symmetric bis ether- Ph-Ph, OMe-OMe. And with this C2 symmetric bis ether, the addition of this vinyl lithium also you can do in chiral fashion. So here the chiral ligand is vinyl. And with this, you get the other enantiomer. But the enantiomeric excess is low-76 percent.

So addition, second bimethyl iodide, carbon monoxide, HMPA, same reaction and then alpha functionalization, sodium ethoxide, methyl, so you get a quaternary center. And this hydrogen, methyl is in the opposite phase now. So these two are enantiomer. So this can be converted to the minus 1 minus acetoxytubipofuran. This was published in JACS, 2003, 125, 5642.

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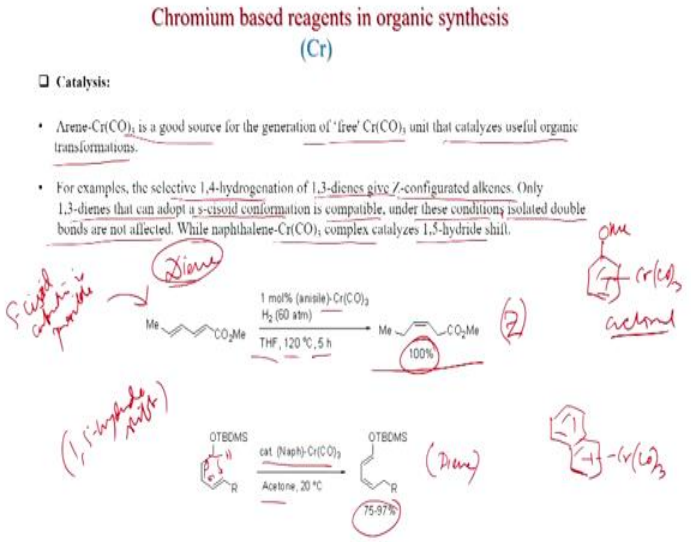

Now we will see simple catalytic reaction also can be carried out. Arene CrCO3 is a good source for the generation of free CrCO3 unit that catalyzes useful organic transformations. For example, the selective 1, 4-hydrogenation of 1, 3-dienes gives Z-configured alkenes. Only 1, 3-dienes that can adopt a s-cisoid conformation is compatible under these conditions isolated double bonds are not affected, so isolated double bond are not reacting. While naphthalene CrCO3 complex catalyze 1, 5- hydride shift.

So we will see this reaction. So this is diene and you can see this is linear. So this can take a s-cisoid conformation, so a s-cisoid conformation is possible and 1 mole percent anisole CrCO3. So anisole is this, anisole and CrCO3 this complex. And this also achiral, it is mono substituted. With hydrogen, 60 atmosphere, THF 120 degree centigrade in 5 hours, you get this olefin. This is Z-configured and the yield is 100 percent. So this is quite good that you get high yield for this olefin, Z olefin.

Also 1, 5- hydride shift is possible with this naphthyl CrCO3. So this is naphthyl and CrCO3 with acetone, 20 degrees centigrade, you get this. So what is happening? This hydride attacking here, then this because this carbocation will be stabilized by this oxygen, OTBS group. So this 1, 5- hydride shift is also now diene. And this product is forming in 75 to 97 percent yield.

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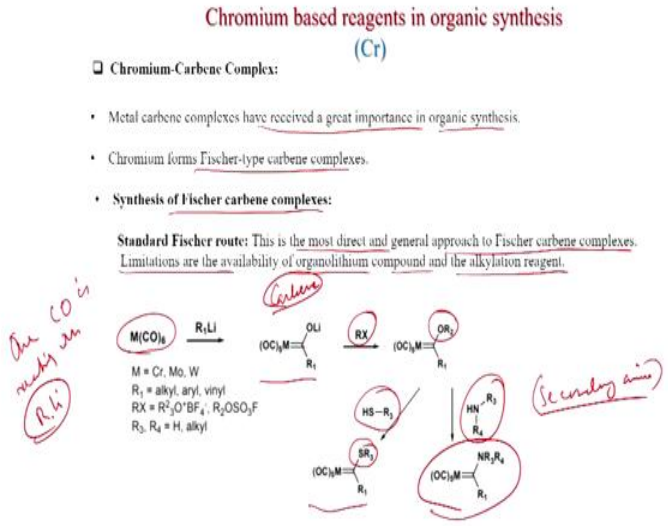

Chromium-carbene complex, metal carbene complexes have received a great importance in organic synthesis. Chromium forms Fischer-type carbene complexes. Synthesis of Fischer carbene complexes: standard Fischer route. This is the most direct and general approach to Fischer carbene complexes. Limitations are the availability of organolithium compound and the alkylation reagent.

So earlier we have seen that the chromium hexacarbonyl when reacted with arene then the arene chromium complex is formed. Now we will react this chromium hexacarbonyl with lithiated alkyl lithium and then you get the carbene. So this is the, what is happening? With the hexacarbonyl, one carbon monoxide; one carbon monoxide is reacting with R1 Li. And when this reaction is taking place, then you get this carbene.

So this one carbon of carbon monoxide. And you get this intermediate. Now this OLi can be reacted with an alkene halide so that this alkoxy substitution is possible. And this can be replaced with thiol. So if you react with thiol, then you get the SR3 group here, the carbene SR3 also with secondary amine, then you get the amine containing carbene complexes. So these reactions are useful. And you can generate these carbene complexes very easily.

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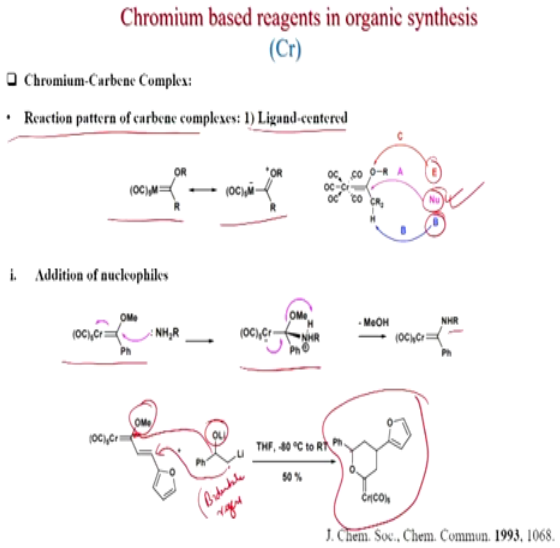

Now we will see the reactions of these carbene complexes. First we will discuss ligand centered; the ligand is involved in the reaction. So this carbene can be in resonance form with this because this metal can take an anion also, because it is coordinated with carbon monoxide, which are pi acceptor. Also this one, this hydrogen will be acidic. So with base you can deprotonate. Also nucleophile can be reacted, that we have seen already, the substitution reactions here. And electrophile can also react with oxygen. That kind of reaction also is possible.

So first we will see this kind of reaction- the nucleophile is reacting at the carbene. So with amine, this intermediate is forming because this anion is stabilized by chromium. And now methanol is eliminating. You get this amine here. Also this is bidentate reagent, bidentate. So this one, this one will react here and this one will react here because the methoxy will displace by this. So ultimately you get this cyclic product, cyclic also the carbene is present. So this oxygen is this oxygen and this phenyl, so this is very important that you get this product. And this was published in journal of chemical science Chem. Commun, 1993.

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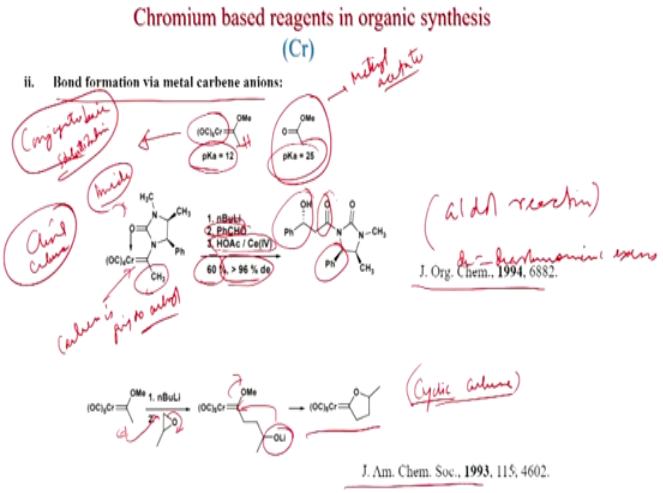

Now bond formations via metal carbene anions. So this is methyl acetate, methyl acetate and the pKa is 25. On the other hand, this carbonyl is displaced by chromium carbene, then this pKa is 12. So because this hydrogen is acidic, so when it is carbene complex then the hydrogen is very much acidic because it is in the resonance. This chromium can take a negative charge and so this is because the conjugate acid stabilization, sorry sorry, conjugate base, so conjugate base stabilization. Conjugate base stabilization and that is why you get the high acidity.

So this is a chiral, chiral carbene because this chiral imide is present. So this is imide and this carbonyl also will be coordinated with the chromium. And now, as we told that this hydrogen is acidic, so with n-butyl lithium you can deprotonate this one and then you can react with benzaldehyde. So this reaction, that is the aldol. So aldol reaction. An aldol reaction can be done in enantioselectivity.

So newly generated chiral center is this OH will be down because this is the Ph up and after that if you treat to it with acetic acid and cerium IV, then you can eliminate this carbene. And this carbene, actually this carbene is going to carbonyl. So this carbonyl is generated from this one. So carbene is going to carbonyl. And you get this compound in high yield, 60 percent moderate yield and greater than 96 percent diastereomeric excess.

So de is diastereomeric excess, greater than 96 percent. This is a very important reaction. You get high diastereoselectivity. And this was published in J.O.C, 1994.

Not only reacting with aldehyde, epoxide can also be reacted. An epoxide can be reacted at the less substituted carbon atom. And after that the epoxide opening happen and you get this O lithium. And what happens this O lithium also reacting here. This O lithium is reacting here. So this exchange happens methoxide is replacing by this O lithium and you get the cyclic, cyclic carbene is forming here. And this was published in J.A.C.S 1993.

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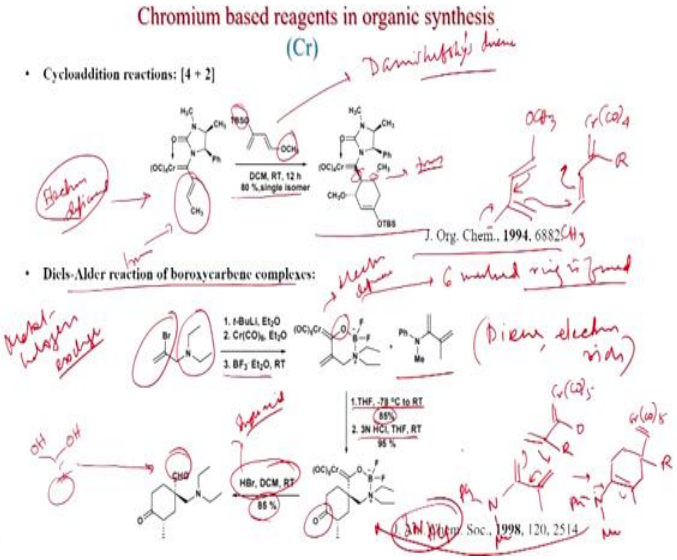

Now we will discuss cycloaddition reactions. So in this, earlier we have seen methyl. Now if you put a double bond here. So what will happen? This double bond is electron deficient. So this double bond is electron deficient. And suitable diene, so electron it is diene. So this diene, if you see the structure there is OTBS methoxy group. So this is called danishefsky's diene. And this diene after reaction with this one, with DCM, room temperature and 80 percent single isomer, you get this one

And here you see, this CH3 and they in the double bond they are trans and here also they are trans. So this is trans. And we know this reaction is happening like this- OTBS OCH3 and if you have this CH3, this is the carbene, chromium, CO4. This is the R. So the reaction will happen like this, so that you get this product. So the double bond will be, the

carbonyl will be connected with the OTBS group. This was published in J.O.C 1994, 6882.

Also, Diels-Alder reaction of boroxycarbene complex is also is possible. So this one, now here we have to generate a carbene. So this is the vinyl bromide and also a-tertiary amine is present. And with tertiary butyl lithium, this metal-halogen exchange will happen, metal-halogen exchange with tertiary butyl lithium. And that vinyl lithium will add to the hexacarbonylchromium to generate this carbene. And this alkoxy group will react with BF3 ether, and this 6 membered, 6 membered ring is formed. And in this 6 member, this boron is coordinated with oxygen as well as the amine. And one fluorine also is liberated.

And now if you react this one, so this is electron deficient, electron deficient. And this diene, diene is electron rich. So the Diels-Alder reaction will happen and this Diels-Alder is carried out in minus 78 degrees to room temperature, you get 85 percent yield. And other 3 normal HCl you get this ketone. So this also you can draw like this. This N, Ph, methyl and this is your the a CrCO5 carbene. So the reaction will happen like this, this, this, this. So you get an enamine. Here a methyl and here a this substituent. So here a quaternary center will be formed.

And this enamine can be hydrolyzed to ketone because this enamine can be converted to imine with acid. So with 3 normal HCl, this enamine is going to carbonyl with 3 normal HCl. And this ring is still there. Now if you put with HBr, so HBr is stronger acid. HBr, dichloromethane, room temperature, now we can hydrolyze the carbene and you get a aldehyde here. And this BF3 is eliminated; you get this product in 85 percent.

So most likely this one, this will be aldehyde acetal and this finally going to the aldehyde moiety. And this was published in J.A.C.S 1998. so this is an important reaction because you get this kind compound in the diastereoselective fashion.

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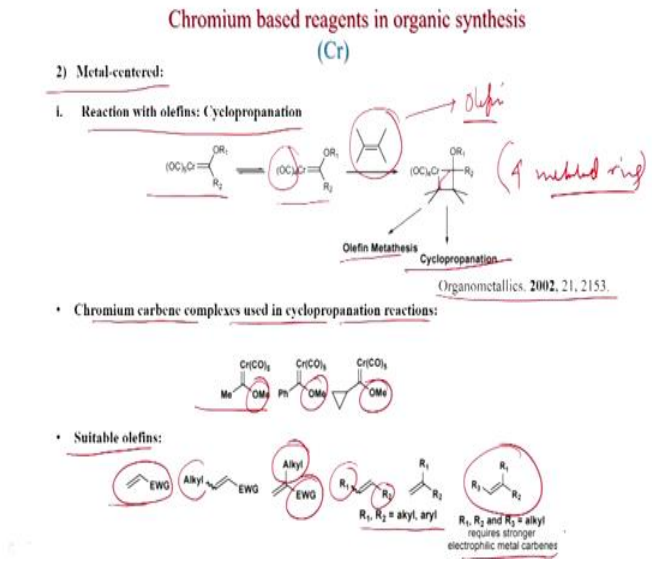

So far we have seen the reactions at the ligand. Now we will see the metal-centered reactions. Reactions with olefins: cyclopropanation first we will discuss. So this is the metal carbene and this can eliminate one carbon monoxide. Then the tetra carbonyl is present and this tetra carbonyl can react with a olefin, so olefin. And then this four membered ring is formed, four membered ring. And this four membered ring can give olefin metathesis product. Also it I possible to give cyclopropanation because this one can react here. And this was published in Organometallics 2002.

So we will see now examples of cyclopropanation reactions. Chromium carbene complexes used in cyclopropanation reaction. So this kind of chromium carbene complexes, so all cases you see methoxy is present- because it stabilizes the intermediate, we will see and suitable olefins. Of course, electron withdrawing group is better. Also alkyl group can be present. Also 1, 1 di-substitution is possible. Also R1 is possible. R1 is equal to alkyl, aryl, R1, R2. And when this tri substitutent is present, then it requires electrophilic metal carbenes.

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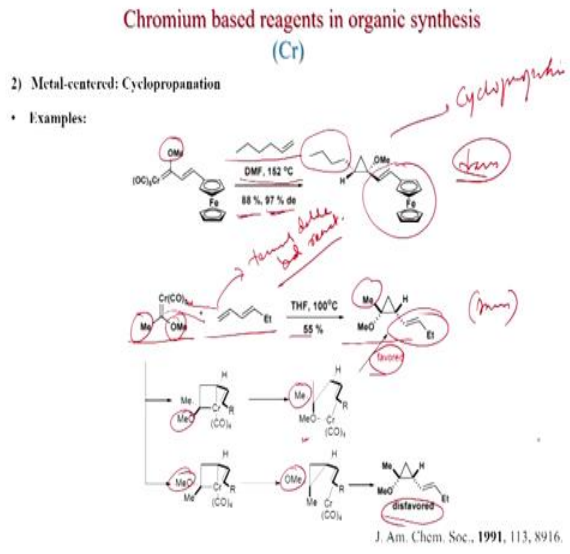

So some examples we will see. So this methoxy is present. Also there is an external double bond but that will not take part in the cyclopropanation and the ferrocene motive is present. And this is the normal olefin. With DMF, 152 degree centigrade, you get 88 percent yield and 97 percent diastereomeric excess. So you get 97 percent diastereomeric excess. You see this group and this group, they are trans. And methoxy is in the cis of this group. So this is the cyclopropanation happen.

And this is much simpler carbene. Methoxy group is there, methyl group is there and this is the diene. And here selectively this terminal, terminal double bond will react. And after the cyclopropanation, you get this. Here also, this methyl and this group are trans. So we will see why so much good diastereoselectivity you get. So we will see the model now.

This carbene reacts with this diene. What happens, this four membered ring is forming. So this chromium like this 2 plus 2, you can think of 2 plus 2 reaction here, here. And now this is forming. And here, this methoxy and this diene are in the same side. And that because this methoxy can coordinate also. This coordination is possible. See this is the coordination of the methoxy with the chromium as well as the double bond. So this will be much stable and this process will be favored. So methoxy and the this, they are in the same side and the methyl is much far.

On the other hand, when methoxy is far, it cannot coordinate with the chromium. So this coordination will not happen because methoxy is far. So this will be less stable and this process is disfavored. So you get high diastereoselectivity for these reactions. And this was published in J.A.C.S, 1991.

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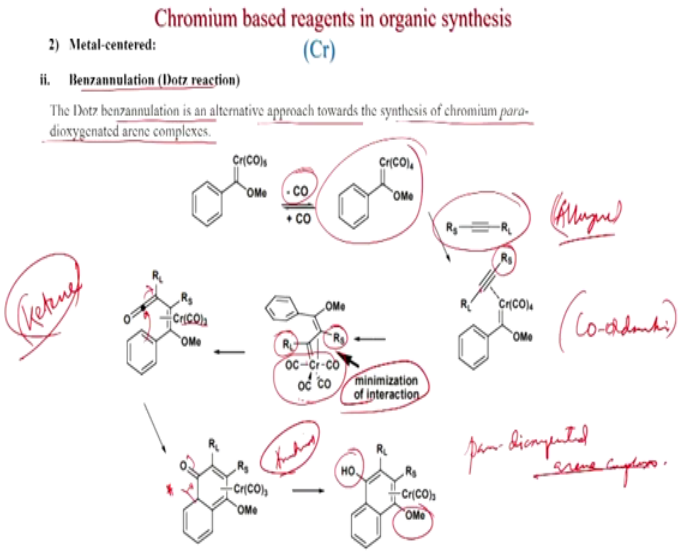

Now we will discuss another reaction that is benzannulation. So this is also metal centered. The Dotz benzannulation is an alternatively approach towards the synthesis of chromium para-dioxygenated arene complexes. So here, this is also same. Like earlier, we have seen carbon monoxide will be eliminated, you get this. And this can react with alkyne, with alkyne. So this is the alkyne. And it can make first coordination; this is the coordination and then the addition.

So this addition is taking place in such a way that Rs side is coming. So this carbene is reacting at the Rs side. And this stereochemistry is such that this Rs and this chromium will be in the cis. So that minimization of the interaction is possible. So Rs and R_L are trans. And this Rs and chromium are in the cis. So this kind of thing is possible.

And now, if you see, this carbene is changed now. Carbene came to this carbon now. So chromium carbene is now this carbon. And after that what will happen? 1 carbon monoxide will react and you get a ketene. So 1 out of 4 carbon monoxide 3 are there and

1 carbon monoxide reacted here. So the insertion happens and so that you get a ketene. And chromium then coordinates with the double bond.

And this is a very important intermediate, this ketene because immediately this will be reacted with the aromatic ring to get another ring. So this kind of reaction will happen. And you get a carbonyl, of course. You get a carbonyl here. And after aromatization, so this aromatization will happen. And you get this- dioxygenated. So this is para-dioxygenated, dioxygenated arene complex. So this is very important reaction- that a chromium carbonyl aryl reacting with an alkyne giving a bicyclic compound.

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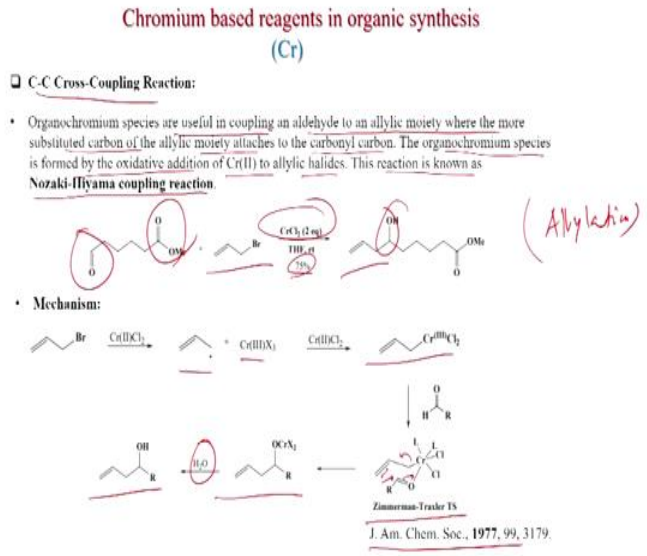

Now we will see cross coupling reaction. Organochromium species are useful in coupling an aldehyde to an allylic moiety, where the more substituted carbon of the allylic moiety attaches to the carbonyl carbon. The organochromium species is formed by the oxidative addition of chromium to the allylic halide. This reaction is known as Nozaki-Hiyama coupling reaction.

So this allyl bromide, this is aldehyde, this is ester. So selectively it is reacting to the aldehyde. And with chromous chloride, 2 equivalent THF, room temperature you get this

secondary alcohol with the allyl group in 75 percent. So this is allylation reaction, allylation.

So what is the mechanism? First the allyl radical is forming, chromium III, then allyl anion. And this stabilized by chromium III. And now the reaction will take place. And this will take Zimmerrman-Traxler transition state. So like this way, it will react. This is the new bond forming. And after that you get this one- OCrX2. Of course after hydrolysis, you get the alcohol. On hydrolysis you get the alcohol with the allyl group. And this was published in J.A.C.S, 1977.

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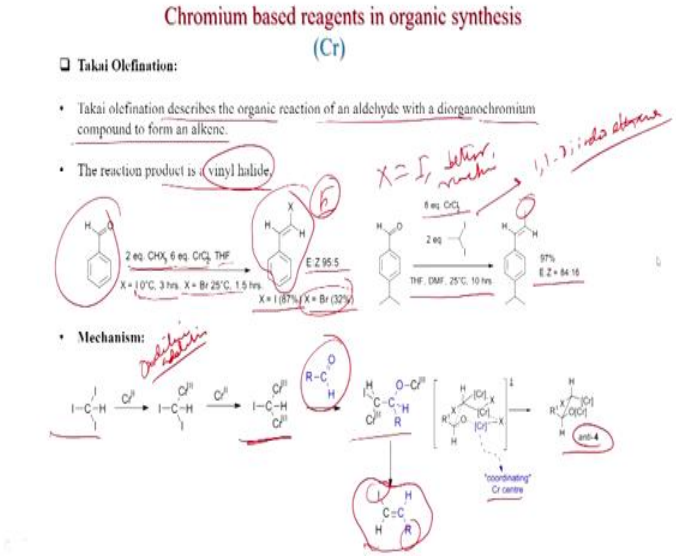

And last for chromium, we will discuss Takai olefination. So Takai olefination describes the organic reaction of an aldehyde with a diorganochromium compound to form an alkene. The reaction product is a vinyl halide. So this is benzaldehyde. With 2 equivalent CHX3, if iodine that is called iodoform, 6 equivalent CrCl2, THF, you get this- vinyl halide. And selectively E is formed. As major, E is Z is 95 is to 5.

And when X is equal to I, the 0 degree centigrade reaction occurs and you get 87 percent yield for this vinyl halide. And when X is equal to Br, you need room temperature, 1.5 hours and you get 32 percent yield. So when X is equal to I, then the reaction better, better reaction.

In the mechanism, because iodine can be displaced by chromium easily. So this is iodoform with chromium II. So this is oxidative addition is happening. So, 2 iodine will be reacted and generate this one- C-Cr3-Cr3. Now it will react with aldehyde and we will get this kind of intermediate. And this is the extra chromium. So here this 2 chromium are present in the nucleophile and it is reacting with the aldehyde. Aldehyde is activated by another coordinating chromium center. It will take this kind of orientation because of steric reason, of course.

So R1 and X, they are in the anti, if you see here. If you give a rotation also, then you see R1 and X are anti in a zigzag. And ultimately after elimination, you get this olefin, where R and iodine are in the trans. So E is the major. Now, if you put another methyl group here. So it is- 1,1-di iodo ethane. With this, you get a methyl group. And of course, 8 equivalent is required, THF, DMF, 25 degree centigrade, 10 hours- you get this olefin. And here E : Z equal to 84 is to 16. So still E is the major.

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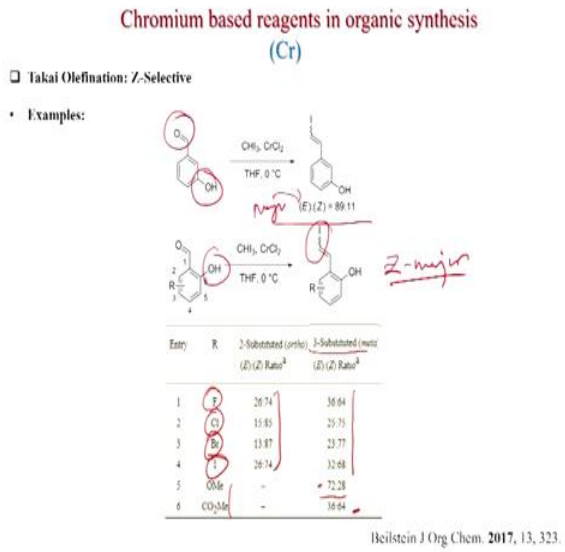

So now we will discuss Z selective Takai olefination. So Z selective is also possible because that intermediate, if you make stable. So we will see an example. So when meta hydroxybenzaldehyde is there, then the Takai olefination is this. So E is still major. Here, E:Z is equal to 89 is to 11. And when ortho hydroxybenzaldehyde, that is the salicylaldehyde, then you get Z major. So we will see an examples.

So this hydroxyl group is important. And you can see, this substitution input like 2 substituted that is the ortho here and with fluorine, chlorine, bromine, iodine- all cases you get Z as the major. Also if it is 3 substituted that is meta, these same group, also you see the Z is major. Also methoxy and CO2Me, if it is in the 3 substituted. Only in methoxy case, you get little bit E major. Otherwise, CO2Me case you get the Z major. So what is the reason? What would be the selectivity factor here? So Beilstein J. O. C, 2017 this work was published.

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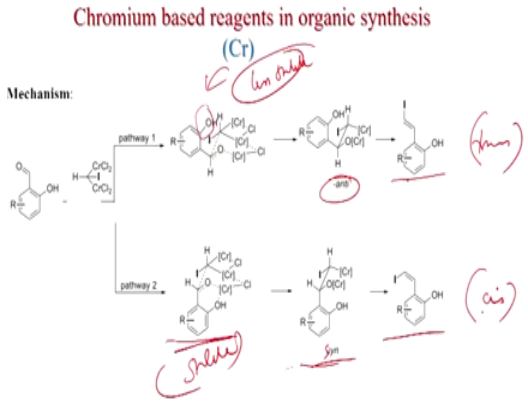

So this could be the possibility that for anti cases this hydroxy is in the other side. If you see, this is anti and hydroxy-this one is on the other side. So it cannot be coordinated chromium. So this will be less stable; less stable this one. And this will give cis, of course, and this will give the anti. So this will be trans product.

Now cis cases, this will be the intermediate and this hydroxy is binding with chromium. So binding is very important. So this is stable. And this of course will give this one syn. And this will give you cis product. So that is the reason. Because the hydroxy group is in the ortho position, then it can coordinate with the chromium. And that is why the Z intermediate is stable and you get the Z-olefin.

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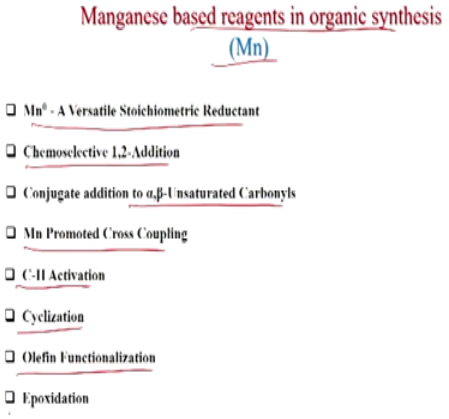

Now we will discuss manganese based reagents in organic synthesis. So manganese is a versatile stoichiometric reductant. Chemoselective 1,2 addition also it can be used. Conjugate addition to alpha beta unsaturated carbonyls. Manganese promoted cross coupling reactions and C-H activation reactions. Cyclization reactions, olefin functionalization reactions and epoxidation reactions.

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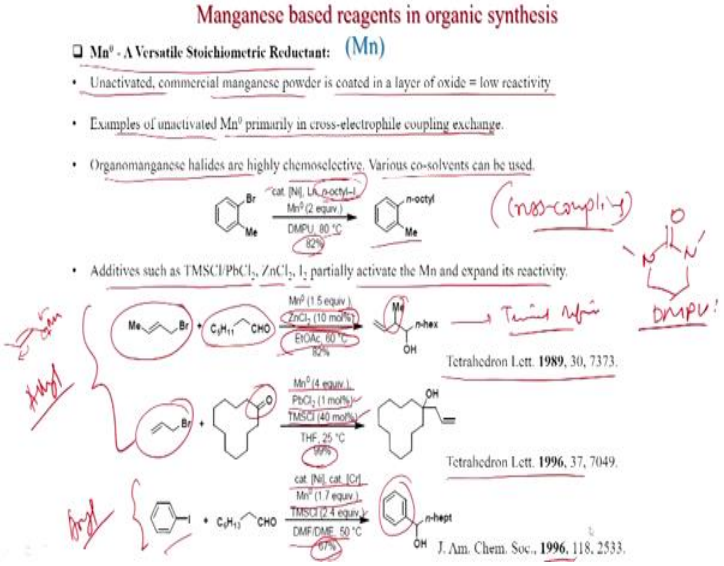

So we will see now examples. Manganese is a versatile stoichiometric reductant. So like Grignard reagent, the arlyl or alkyl manganese can also be used for different reactions. So we will see examples. So unactivated, commercial manganese powder is coated in a layer of oxide, so that is low reactivity. Examples of unactivated manganese 0 primarily in cross electrophile coupling exchange reaction.

An organomanganese halides are highly Chemoselective. Various co-solvents can be used. So they are not reactive like Grignard. They are much less reactive. So solvents like ethyl acetate can also be used, we will see example. So here an example of cross coupling reaction, cross coupling. So here catalytic nickel is there. And ligand n-octyl iodide. So this is the n-octyl group will come. And manganese 0, 2 equivalent. So in-situ, you generate the n-octyl magnesium. And with DMPU solvent, so this is DMPU n,n dash dimethyl propylene urea. And then 80 degree centigrade, you get 82 percent yield for this product. So this is very important.

Additives such as TMS chloride, lead chlorine, zinc chloride, iodine, partially activates the manganese and expands its reactivity. So here the zinc chloride is present, catalytic amount that enhances reactivity. Now here this allyl bromide is present. So allylic bromide will react with first manganese to generate allyl manganese. And it will react with n-octonal with ethyl acetate solvent. So this you see ethyl acetate can be used as solvent, 60 degree centigrade.

And here, this one so this manganese is giving a reaction from a more substituted. So the more substituted carbon is adding to the aldehyde. So you get a terminal olefin here. That means this more substituted carbon atom is reacted with methyl, and these are the newly generated chiral center. And this was published in Tetrahedron Letters, 1989.

Also a cyclic ketone can be used for the allylation. So with allyl bromide, manganese 0, 4 equivalent, lead chloride and TMS chloride are added. Lead chloride only 1 mole percent is enough and TMS chloride 40 moles percent, THF, 25 degree centigrade you get this product in 99 percent yield, so the allylation of the cyclic ketone. And this was also published in Tetrahedron Letters, 1996.

And we will see similar example to aldehyde addition the aryl. So this was allyl addition to aldehyde and this is aryl. So aryl iodide, that is the iodobenzene here, with catalytic nickel, catalytic chromium, manganese 0 1.7 equivalent, TMS chloride 2.4 equivalent, in DMF/DME, 50 degree centigrade- you get 67 percent yield. So yield is little less for aromatic group but still you get the product. And this was published in J.A.C.S 1996.

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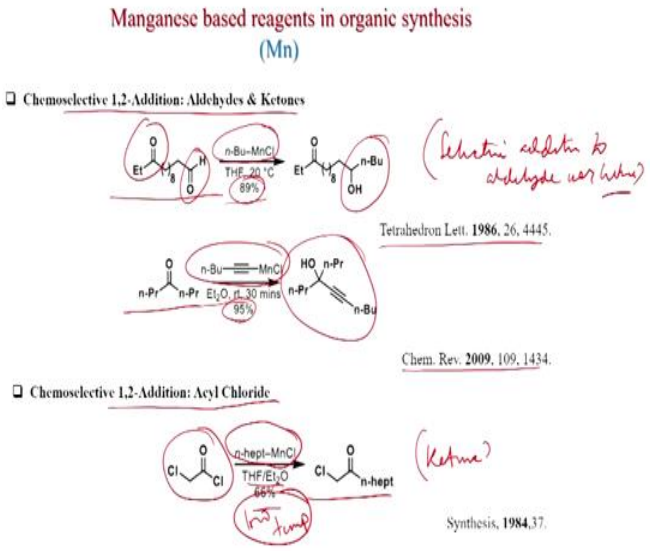

Now chemoselective 1, 2 addition is also possible, so that the aldehyde can be reacted selectively in presence in ketones. Suppose here, this dicarbonyl complex this is aldehyde and this is ketone and the when you add n-butyl manganese chloride in THF, 20 degree centigrade, you will get 89 percent yield for this product. So selective addition, selective addition to aldehyde over ketone. But ketone can also be reacted. That we will see that later. So this was published in Tetrahedron Letter, 1986.

So this is an example of ketone. So ketone with this alkynyl manganese chloride, in ether solvent, room temperature, 30 minutes, you get this alkyne group addition in 95 percent yield. And this was published or reviewed in chemical review, 2009.

Now acyl chloride. Earlier we have that copper can react with acyl chloride to generate ketone. Similarly, the manganese can also react. So here, this n-heptyl manganese chloride, when reacted with this acyl chloride in THF, ether, 66 percent you get this

ketone. So this is very important, ketone. Maybe this is low temperature. So the ketone is further non-reactive with this n-heptyl manganese chloride. So you can isolate the ketone. This was published in Synthesis 1984.

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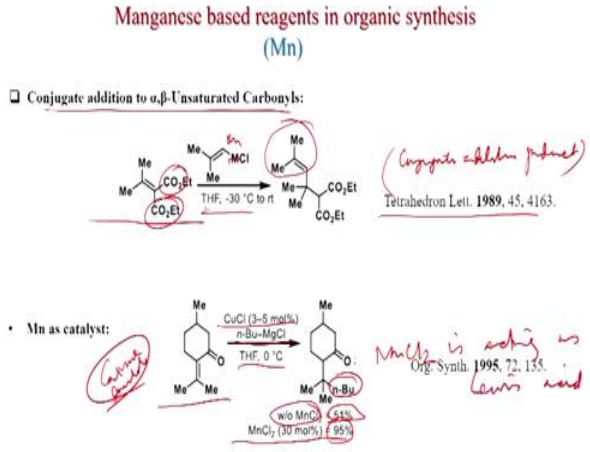

Now conjugate addition. So far, we have seen 1, 2 addition. Now conjugate addition also is possible to alpha beta unsaturated carbonyl. So here you can see, this is alpha beta unsaturated ester. Two ester moieties are present and this is the manganese here. This is the vinyl manganese. And in THF, minus 30 degree centigrade to room temperature, you get the conjugate addition. So this group is adding to this. And you get this conjugated addition product, conjugate addition product. This was published in Tetrahedron Letter, 1989.

Now, so far we have seen manganese as reagent. Now manganese as catalyst also is possible. We have earlier told that manganese can also be catalyst. So here you can see this reaction, carbon derivative and here with copper chloride, 3 to 5 mole percent n-butyl manganese chloride, THF 0 degree centigrade this n-butyl addition is happening, conjugate addition. Without manganese chloride, you get 51 percent. Now if you put manganese chloride, 30 mole percent, 95 percent yield you get. So what is happening here? The manganese chloride is acting as a Lewis acid, is acting as Lewis acid. And this was published in Organic Synthesis, 1995.

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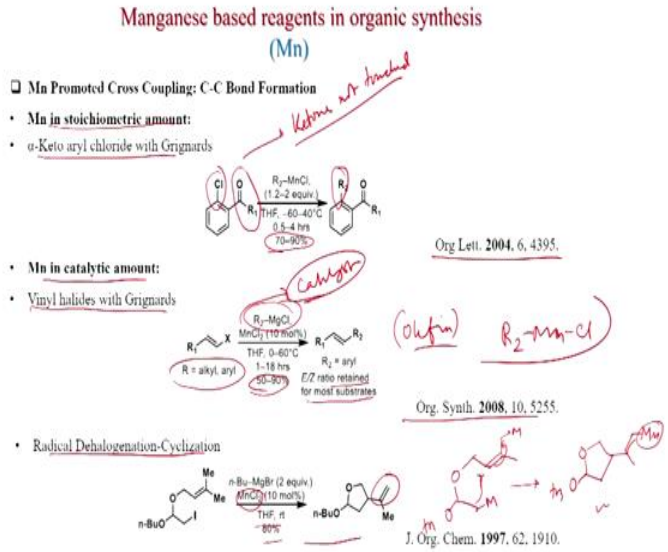

Now we will see manganese in stoichiometric amount also and cross coupling reactions. Alpha keto aryl chloride with Grignards. So here it is interesting that you have a ketone group and aryl chloride. So under this condition, R2MnCl the ketone group is not touched. So ketone not touched. And selectively the aryl chloride is doing a coupling reaction and R2 is coming here. This was published in Organic Letters, 2004. And you get high yield for this product 70 to 90 percent yield.

Now manganese in catalytic amount is also is possible. Vinyl halides with Grignards. So here, this manganese chloride again is a catalyst here. And this is the Grignard-R2MgCL, this is vinyl halide. And with manganese chloride 10 mole percent, THF, 0 to 60 degree centigrade, you get 50 to 90 percent yield for this olefin, olefin. And this is E:Z ratio retained. So if it is, vinyl halide is E:Z, then this geometry will be retained for more substrate.

So what happened? This magnesium, of course it is changing with manganese and then it is adding. Because simple magnesium, simple Grignard cannot add to the vinyl halide, so only when it is activated by manganese. So this R2MnCl, this is forming and this is adding to the vinyl halide. This was published in Organic Synthesis, 2008.

Also radical dehalogenation-cyclization reaction also is possible. Here, n-butyl magnesium bromide and manganese chloride 10 mole percent, THF, room temperature, 80 percent yield of this cyclic compound you are getting. So what could be the mechanism? So most likely, the metal halogen exchange will happen. So here a metal. So suppose metal is here and O n-butyl. This will add and this, the metal will come here. So most likely, the manganese will be metal there. So what will happen?

O n- butyl this, this, this, this will be the manganese most likely. And this manganese can be removed in, to get a terminal olefin. So this olefin is generated here. So this olefin is generated here. So this kind of mechanism is possible, the cyclization. And this was published J.O.C, 1997.

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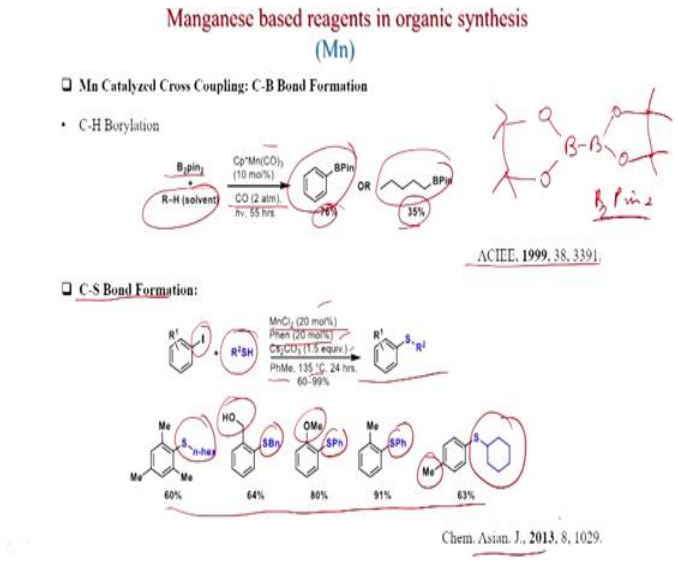

Now, not only C-C coupling, the C-B bond formation is also possible. So C-B borylation. So if you put B2pin2, so we know this is the structure. So this is B2pin2. And with Cp star manganese tricarbonyl 10 mole percent with carbon monoxide also you have to add additionally 2 atmosphere, RH that is aromatic or aliphatic. So 76 percent yield for benzene, you get this BPin. And normal 1, 2, 3, 4, 5- pentane, you get this 35 percent yield. So not only benzene but the aliphatic also can be borylated. This was published in Angewandte Chemie, 1999.

Now, C-S bond formation is possible with manganese. Manganese chloride, 20 mole percent, phenanthroline 20 mole percent, cesium carbonate 1.5 equivalent and toluene solvent 135 degree centigrade. This thiol is adding to this aryl iodide and you get this aryl thio derivative. And different thiol can be used here n-hexyl, here benzyl, here phenyl, phenyl and here also hexyl. And different substituent on the aromatic ring is also possible methoxy, hydroxy methyl, methyl, and you get moderate to high yield for this product. This was published in Chemistry Asian Journal, 2013.

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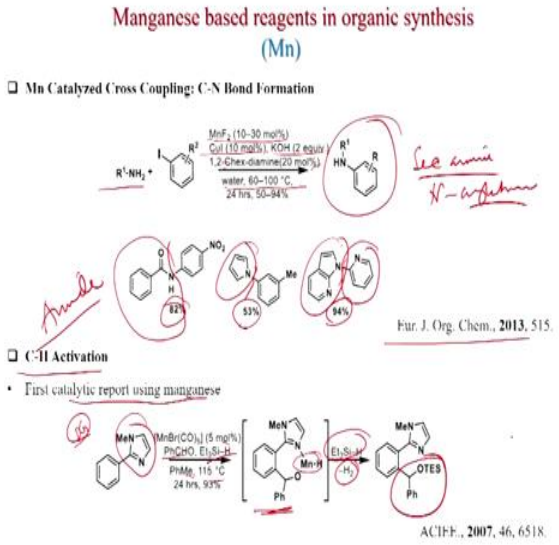

Now manganese catalyzed cross coupling. So far we have seen the C-C, C-B and C-S. Now we will see C-N bond formation. So amine also can take part in this cross coupling reaction with manganese fluoride, 10 to 30 mole percent, copper iodide 10 mole percent, KOH 2 equivalent and this is cyclohexyl diamine Chex-diamine 20 mole percent, water 60 to 100 degree centigrade, this cross coupled product you can get. So this secondary amine is forming from primary amine. N-arylation, N-arylation is happening.

And this was different amine can be used. So here you can see, this is indole. So indole was used. Here this 2 iodo pyridine. This is the N actually. So this is the amine part. And here, this is most likely the amine part. So this is the amide. So this is amide here. So amide can also take part. And this product is forming 82 percent yield, this is 53, this is 94 percent yield. And this was published in European J.O.C, 2013.

Now C-H activation, we will see C-H activation is also possible with manganese. First catalytic report is manganese. So here this is the directing group, DG directing group and with manganese BrCO5, 5 mole percent, with benzaldehyde, triethylsilane, toluene, 115 degree centigrade, you get this kind of intermediate. So this addition benzaldehyde forms at this ortho position. And this intermediate is formed when manganese hydrogen is present. And with triethylsilane, you get hydrogen elimination and this OTES group coming here. So this product is forming, so selectively ortho position. And this was published in Angewandte Chemie, 2007.

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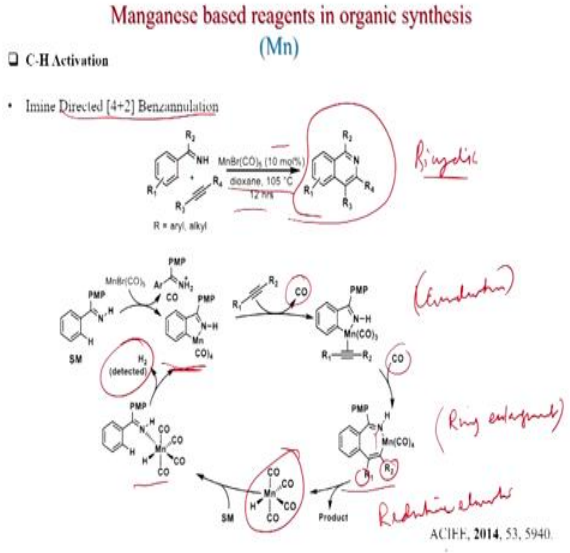

So some more C-H activation reaction we will see. Imine directed 4 plus 2 benzannulation is possible. So this imine, this is alkyne with manganese BrCO5, 10 mole percent dioxane, 105 degree centigrade, 12 hours you get this product, bicyclic product. So this is called benzannulation because this carbon is reacting to the triple bond and also the imine nitrogen.

So this could be the mechanism that first this type of intermediate is forming. Nitrogen and this CH is activated with manganese, manganese CO4. Now triple bond will come with elimination of 1 CO. So this coordination will happen, coordination. And now another carbon monoxide may come. So you get the ring enlargement or ring expansion is happening here. So R1, R2. This is from the triple bond has become the double bond

and manganese is here. Also we will look coordinated nitrogen. Then you get the product. So then you get the product here. So this will add.

So this is like reductive elimination will happen. You get this and this will react with starting material again to generate this. And after elimination of hydrogen; which can be detected also, you get this active intermediate. So this is very important. This triple bond activation by the manganese and then the ring expansion and then the reductive elimination will give you the product. So this was published in Angewandte Chemie, 2014.

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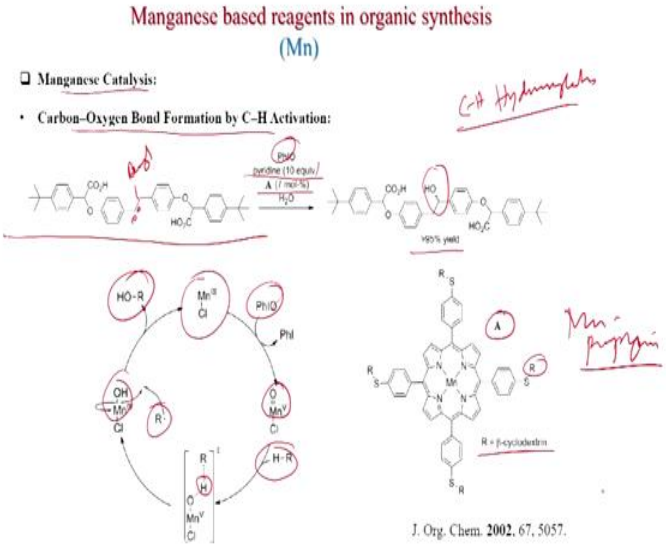

Now we will see some manganese catalysis. Carbon oxygen bond formation by C-H activation. Like here, if you see this substrate, there is a benzylic, this or this. This 2 are benzyl group. And when you treat with iodoxybenzene, pyridine 10 equivalent, A we will the structure, in H2O solvent, you get this hydroxylation. So this is hydroxylation, C-H hydroxylation at the benzyl position and you get 95 yield.

So this is the structure of A that is the manganese porphyrin, manganese porphyrin. And R are beta cyclodextrin. And with this, you get very high yield. So what could be the mechanism? Manganese 3Cl will be oxidized to manganese oxide here imine double bond O. manganese is equal to 5 now. PhIO is oxidized. And now your alkane will come.

So this is most acidic hydrogen, of course will coordinate with this oxygen. So that is the benzylic hydrogen. And after that, R dot and OH will come here. And after that, this because this radical is also stabilized by aromatic, that is the benzylic radical. And you the R-OH and this you get this back again. This was published in J.O.C, 2002.

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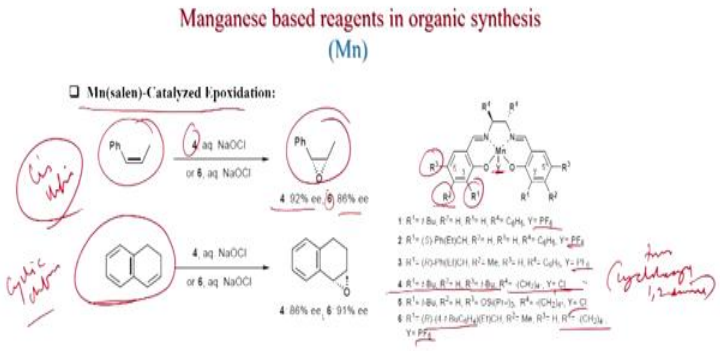

Now we will discuss manganese salen catalyzed epoxidation reaction. This is also a powerful reaction. The olefin, generally the cis olefin, cis olefin is better for this epoxidation; you get this epoxide with 4 chiral. Ligand 4, you get 92 percent. Chiral ligand 6, 86 percent. So these are the structures of chiral ligand. Mostly this is ortho, para substituted. R2 mostly hydrogen or methyl. And you can see this Y can be PF6 or chlorine.

And 4 is this one. R1 is tertiary butyl. So R1, R3 is tertiary butyl. R2 is H and R4 is equal to CH2 whole 4. So this cyclohexyl, cyclohexyl 1, 2 diamine system. Of course trans, trans so that the chiral will formed. And this also, you see tertiary butyl, R4 also this cyclohexyl. So what could be the, okay there is another substrate this one, cyclic olefin. This is cyclic olefin. This is already cis configured. So here also you get very high ee with 4, 86 percent and with 6 you get 91 percent.

So today we have discussed first this chromium based reagents in organic synthesis. In chromium based reagents we have discussed nucleophilic substitution reaction of chromium arene complex because this is electrophilic. When it is connected with chromium that becomes, arene ring becomes electron deficient. So different nucleophilic substitution reaction can be carried out.

Also, you have seen ring lithiation. If you treat with butyl lithium, then different electrophile can be added. Chromium arene complexes, in asymmetric catalysis we have seen different hydrogenation, heck coupling this chiral catalyst can be used. Also simple catalysis we have seen. Then chromium carbene complexes we have seen. We have seen the cyclopropanation reaction. So there are ligands centered as well as metal centered reactions are possible. C-C cross coupling reactions we have seen. And Takai olefination we have seen. In Takai olefination, you get selectively E Isomer E, vinyl iodide, if you react with iodoform. Alternatively, salicyladehyde derivative gives the Z olefin as the major product.

Then we have discussed manganese based reagents in organic synthesis. So manganese 0 is versatile stoichiometric reductant. So manganese they are much more less reactive then the Grignard reagent. This can be used in solvents like ethyl acetate also. And different cross coupling reaction with aryl iodide can be added and different coupling reactions that is why C-S bond formation, C-B bond formation, C-N bond formation can be carried out in manganese catalyst.

Also chemoselective 1, 2 addition is possible. So selectively addition to aldehyde motif in presence of ketone group is possible. Also acid chloride addition will give ketone. That ketone, if you do a reaction at lower temperature that ketone will not further react. Conjugate addition to alpha, beta unsaturated carbonyls also we have seen. That alpha beta unsaturated resistors can be used as a Michael acceptor.

Then C-H activation reaction we have seen, the suitable directing groups are there, then the C-H activation is possible. Like benzaldehyde addition is possible. Also triple bond, the benzannulation we have seen. Olefin functionalization is also possible that it can add

this O lithium species or C lithium can add to the oxygen, and you get the, to the double bond and you can get the terminal olefin and with a cyclic system.

Also we have seen the epoxidation and hydroxylation. So C-H hydroxylation we have seen the manganese porphyrin and iodoxy benzene. If you treat with substrate having benzylic C-H hydrogen that will be benzylic C-H hydroxylation will happen. Also with manganese VII catalyst, you can get the epoxidation and particularly if it cis olefin, then you can get high enantiomeric excess. Also cyclic olefin also gets high enantiomeric excess. Thank you.