Reagents in Organic Synthesis
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Lecture 27
Fe and Co based reagents in organic synthesis

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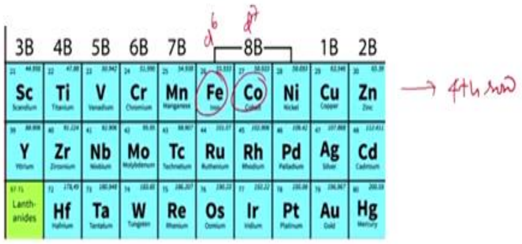
Iron and Cobalt based reagents in organic synthesis
(Fe & Co)



Welcome today we will discuss iron and cobalt based reagents so you can see in the periodic table iron and cobalt they are enabling elements and they are in the same row and iron is d6 system and cobalt is d7 system.

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Iron based reagents in organic synthesis
(Fe)

- ❑ Collman's Reagent ($Na_2Fe[CO]_4$)
- ❑ Binary Carbonyl–Iron Complexes
- ❑ Alkene–Iron Complexes
- ❑ Cyclopentadienylironcarbonyl
- ❑ Friedel–Crafts alkylation
- ❑ Epoxidation
- ❑ Kharasch Reaction
- ❑ Aminochlorination
- ❑ Allylic oxidation
- ❑ Cross Coupling Reactions (Kumada, Negishi, Suzuki)

So first we will discuss iron based reagents in organic synthesis we will discuss Colman's reagents which is Na2 iron tetra carbonyl then binary carbonyl iron complexes alkene iron complexes cyclopentadienyl iron carbonyl also we will discuss Friedel Crafts alkylation will discuss Epoxidation will discuss Kharasch reaction will discuss that is the di functionalization of alkenes amino chlorination will discuss allylic oxidation that is the allylic alcohol formation will discuss and cross coupling reaction Kumada Negeshi Suzuki kind of reactions will discuss.

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Iron based reagents in organic synthesis

(Fe)

- ☐ Organoiron chemistry is the chemistry of iron compounds containing a carbon-to-iron chemical bond.
- ☐ Organoiron compounds are relevant in organic synthesis as reagents such as iron pentacarbonyl, diiron nonacarbonyl and disodium tetracarbonylferrate.
- ☐ Organoiron chemistry was started by the discovery of pentacarbonyliron in 1891, independently by Mond and Berthelot.
- ☐ In complexes iron has an electronic configuration of $[Ar]4s^0 3d^8$.
- ☐ The most common oxidation states for iron are +2 and +3.
- ☐ For iron(II) complexes ($[Ar]4s^0 3d^6$) having a coordination number of six with an octahedral ligand sphere is preferred.
- ☐ Iron(III) ($[Ar]4s^0 3d^5$) can coordinate three to eight ligands and often exhibits an octahedral coordination.
- ☐ Iron(III) generally is a harder Lewis acid than iron(II) and thus binds to hard Lewis bases.
- ☐ Iron(0) mostly coordinates five or six ligands with trigonal bipyramidal and octahedral geometry.

So organoiron chemistry is the chemistry of iron compounds containing a carbon to iron chemical bond organoiron compounds are relevant in organic synthesis as reactions such as iron penta carbonyl diiron Nona carbonyl and disodium tetra carbonyl ferrate. Organoiron chemistry was started by the discovery of penta carbonyl iron in 1891 so 1891 first iron penta carbonyl was discovered, independently by Mond and Berthelot.

In complexes iron has an electronic configuration argon 4s0 3d8 the most common oxidation state for iron are plus 2 and plus 3. And iron 2 complexes argon 4s 03d6 having a coordination number of 6 with an octahedral ligand sphere is preferred. An iron 3 that is 4s 03d5 can coordinate 3 to 8 ligands and often exhibits and octahedral coordination so here also octa hydral coordination is observed.

Iron 3 generally is a harder Lewis acid then iron 2 and thus binds to hard Lewis bases. Iron 0 mostly coordinates 5 or 6 ligands with trigonal bipyramidal and octahedral geometry.

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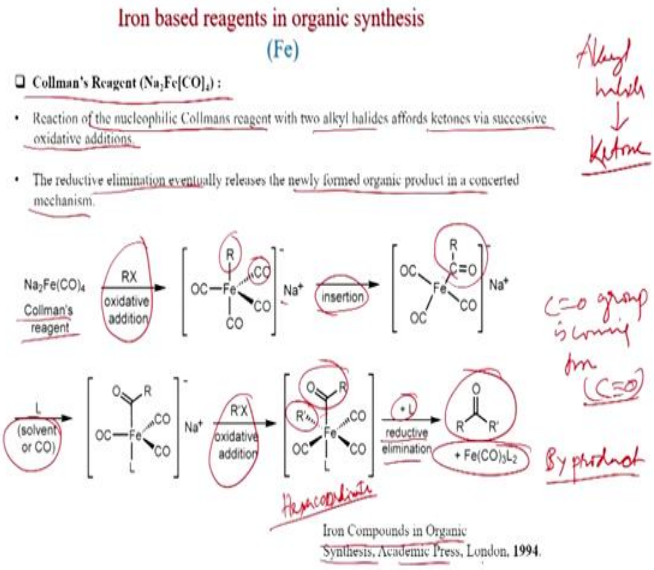

Iron based reagents in organic synthesis

(Fe)

☐ **Collman's Reagent ($Na_2Fe[CO]_4$) :**

- Reaction of the nucleophilic Collmans reagent with two alkyl halides affords ketones via successive oxidative additions.
- The reductive elimination eventually releases the newly formed organic product in a concerted mechanism.

Iron Compounds in Organic Synthesis, Academic Press, London, 1994.

So first we will discuss Colmans reagents Na2FeCO4 so reaction of the nucleophilic Colmans reagent with 2 alkyl halides affords ketones via successive oxidative addition. So alkyl halides goes to ketone that we will see. And of course the carbonyl group comes from the carbo monoxide the reductive elimination eventually releases the newly from organic product in a conserted mechanism so this is the reaction colmans reagent now, Rx comes oxidative addition happens and you get this penta coordinated iron one R is here and sodium plus is outside.

Now, the insertion will happen so one carbon monoxide inserts into this iron R bond so this is formed carbonyl and now, a ligand can be solvent or carbon monoxide again reacts with iron so that iron becomes penta coordinated now and oxidative addition again will happen with another alkyl halide R dash x so R dash adds here and iron now is hexacoordinate.

So iron becomes hexacoordinate so obvious is that now, the reductive elimination will happen so reductive elimination so R dash they are closed to this COR group so that is they are cis so this reductive elimination can be possible now and you get the ketone and also with another ligand comes then you get this FeCO3 l2 so this is the byproduct.

So what happens one alkyl halide and another alkyl halide reacts with colmans reagent and in this process you can get a carbonyl so, the carbonyl group is coming from carbon monoxide. This was reviewed in iron compounds in organic synthesis academic press London, 1994.

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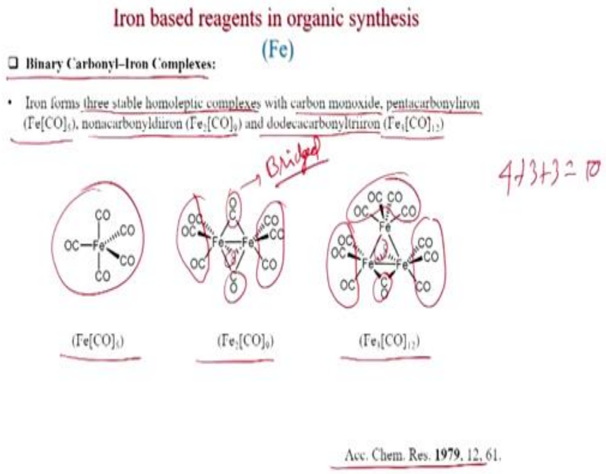

Iron based reagents in organic synthesis

(Fe)

❑ **Binary Carbonyl–Iron Complexes:**

- Iron forms three stable homoleptic complexes with carbon monoxide, pentacarbonyliron ($Fe[CO]_5$), nonacarbonyldiiron ($Fe_2[CO]_9$) and dodecacarbonyltriiron ($Fe_3[CO]_{12}$)

→ Bridged

4+3+3 = 10

($Fe[CO]_5$) ($Fe_2[CO]_9$) ($Fe_3[CO]_{12}$)

Acc. Chem. Res. **1979**, 12, 61.

So now we will discuss binary carbonyl iron complexes iron forms three stable homoleptic complexes with carbon monoxide penta carbonyl iron FeCO5 Nona carbonyl diiron Fe2CO9 and do deca carbonyl tri iron Fe3CO12 so iron can be only on be iron that is iron penta carbonyl to iron can be there that is Fe2CO9 and three iron is there Fe3CO12 so these are the structure iron penta carbonyl you can see 5 carbon monoxides are their around iron and this structure of Fe2 CO9 here you can see 3 carbon monoxides are here, 3 are here.

And remaining 3 are in the bridged so they are bridged and also there is a iron iron bond here that can be seen similarly Fe3COl2 here 2 iron has 3 carbon monoxide and 1 iron has 4 carbon monoxide so 4 plus 3 plus 3 is equal to 10. And remaining 2 carbon monoxide are in the bridge so they are bridged and also there is a iron iron bond so it is important in Fe3CO12 2 iron will have 3 carbon monoxide and 1 iron will have 4 carbon monoxide and 2 carbon monoxide are in the bridged.

So bridged carbon monoxide are labile of course and this was reviewed in account chemical research 1979.

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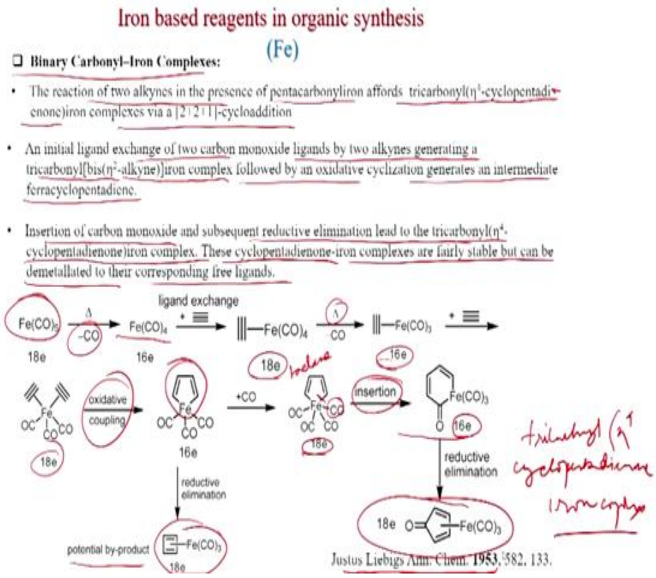

Iron based reagents in organic synthesis

(Fe)

❑ **Binary Carbonyl–Iron Complexes:**

- The reaction of two alkynes in the presence of pentacarbonyliron affords tricarbonyl(η^4-cyclopentadienone)iron complexes via a [2+2+1]-cycloaddition
- An initial ligand exchange of two carbon monoxide ligands by two alkynes generating a tricarbonyl[bis(η^2-alkyne)]iron complex followed by an oxidative cyclization generates an intermediate ferracyclopentadiene.
- Insertion of carbon monoxide and subsequent reductive elimination lead to the tricarbonyl(η^4-cyclopentadienone)iron complex. These cyclopentadienone-iron complexes are fairly stable but can be demetallated to their corresponding free ligands.

Justus Liebigs Ann. Chem. 1953, 582, 133.

So we will discuss more about binary crabonyl iron complexes reaction also the reaction of 2 alkynes in the presense of penta carbonyl iron affords tricarbonyl eta 4 cyclo penta di enone. complexes via a 2 plus 2 plus 1 cyclo addition and initially ligand exchange of 2 carbon monoxide ligands by 2 alkynes generating a tricarbonyl bis eta 2 alkyne iron complex followed by an oxidative cyclization generation intermediate ferra cyclo penta diene.

So this is the reaction if you see this is the iron penta carbonyl 18 electrons and after heating one carbon monoxide eliminates you get the 16 electrons tetra carbonyl iron and now the ligand exchange will happen so triple bond that is the alkyne can add to the iron and you get another 18 electrons and now again another carbon monoxide after heating can eliminate so it becomes again 16 electrons and again another alkyne will come so you get this 18 electrons species.

Now this oxidative coupling will happen so oxidative generation intermediate ferra cyclo penta diene. So this forms this is the oxidative coupling happens and you get this ferra cyclo penta diene. So this is the you can see cyclo penta diene with iron so that is called ferra cyclo penta diene and 3 carbon monoxide are there. And this can after reductive elimination gives the cyclo buta diene FeCO3 complex that is potential byproduct and major thing happens that again another carbon monoxide comes and you get this 18 electron and now the insertion will happen so insertion of carbon monoxide and subsequent reductive elimination lead to the tri carbonyl eta 4 cyclo penta dieneone on iron complex.

So, after insertion so here you see carbon monoxide inserts into this carbon iron bond and you get the 6 membering which is of course 16 electron system iron. And after reductive elimination you get this, this is the product 18 electron compound that is the tri carbonyl eta 4 cyclo penta dieneone iron complex. So this is the product after reductive elimination 18 electron and also this is a byproduct that is the cyclobuta diene tricarbonyl iron that is the byproduct and this is the major product.

Cyclo penta dieneone this cyclo penta dieneone iron complexes are fairly stable but, can be demetalated to their corresponding free ligands. So here also you can demetalate that iron can be removed and you can get free cyclo penta dieneone this was published in Justus Liebig's and chemist 1953.

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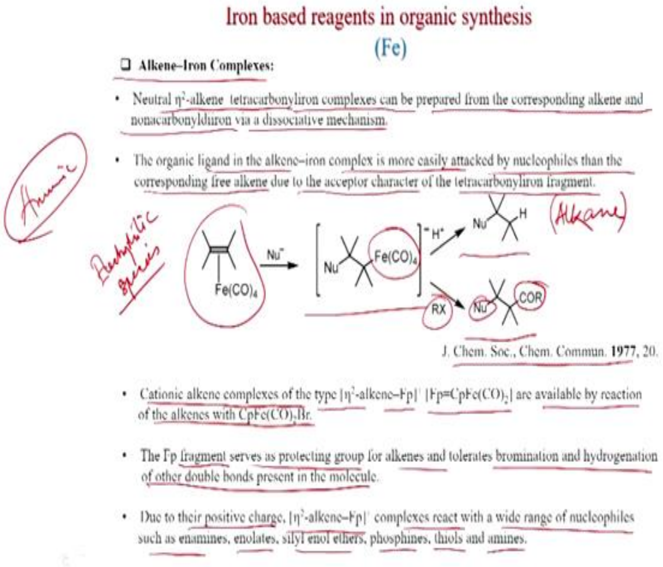

Iron based reagents in organic synthesis

(Fe)

❑ **Alkene–Iron Complexes:**

- Neutral η^2-alkene tetracarbonyliron complexes can be prepared from the corresponding alkene and nonacarbonyldiiron via a dissociative mechanism.
- The organic ligand in the alkene–iron complex is more easily attacked by nucleophiles than the corresponding free alkene due to the acceptor character of the tetracarbonyliron fragment.

J. Chem. Soc., Chem. Commun. **1977**, 20.

- Cationic alkene complexes of the type [η^2-alkene–Fp]$^+$ [Fp=CpFe(CO)$_2$] are available by reaction of the alkenes with CpFe(CO)$_2$Br.
- The Fp fragment serves as protecting group for alkenes and tolerates bromination and hydrogenation of other double bonds present in the molecule.
- Due to their positive charge, [η^2-alkene–Fp]$^+$ complexes react with a wide range of nucleophiles such as enamines, enolates, silyl enol ethers, phosphines, thiols and amines.

Now we will discuss alkyne iron complexes neutral eta 2 alkyne tetra carbonyl iron complexes can be prepared from the corresponding alkyne and Nona carbonyl diiron via dissociative mechanism. The organic ligand in the alkyne iron complexes is more easily attacked by nucleophiles than the corresponding 3 alkynes due to the accepter character of the tetra carbonyl iron fragment so this is important when olefin is connected to iron tetra carbonyl this becomes an electrophilic species.

So electrophilic species, and now a nucleophile can come and you get this complex so you can see the nucleophile added and this FeCO4 now connected to one carbon and overall negative charge is there, and now, this can react with H plus so if you react with H plus then this iron tetra carbonyl can be removed and you can get formal addition of nucleophile to olefin so an alkene is formed here so this is alkyne with the nucleophile. Also if you put RX this is interesting if you put RX then a COR group will come so, one carbon monoxide inserts into the carbon iron bond and then R add so you get this compound so one side nucleophile another side COR group and this was published in chem com 1977.

On the other hand cationic alkyne complex so this is anionic; now cationic alkyne complex of the type beta 2 alkyne f plus f is equal to CpFeCO2 are available by reaction of the alkynes with CpFeCO2 Br the Fe fragment serves as protecting group for alkynes and tolerates bromination and hydrogenation of other double bonds present in the molecule due to their positive charge eta 2 alkyne Fe plus complexes react with a wide range of nucleophile such as enamines enolates silylenol ethers phosphines thiols and amines.

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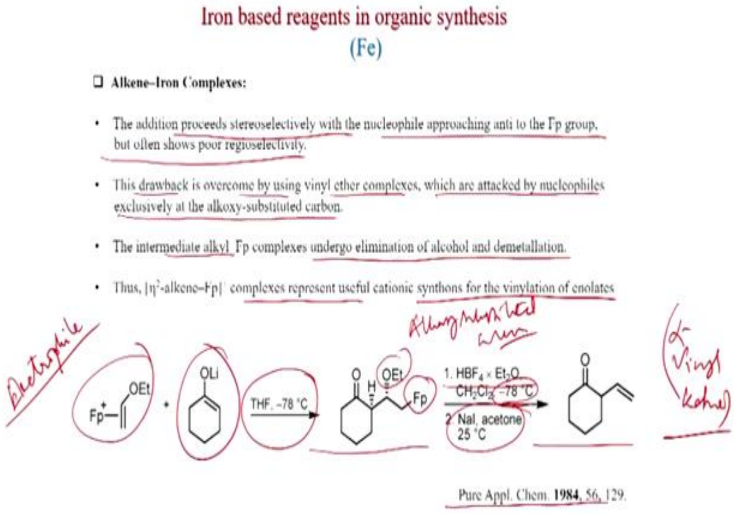

Iron based reagents in organic synthesis

(Fe)

❑ **Alkene–Iron Complexes:**

- The addition proceeds stereoselectively with the nucleophile approaching anti to the Fp group, but often shows poor regioselectivity.
- This drawback is overcome by using vinyl ether complexes, which are attacked by nucleophiles exclusively at the alkoxy-substituted carbon.
- The intermediate alkyl Fp complexes undergo elimination of alcohol and demetallation.
- Thus, $[\eta^2\text{-alkene-Fp}]^+$ complexes represent useful cationic synthons for the vinylation of enolates

Pure Appl. Chem. **1984**, 56, 129.

So alkyne iron complexes the addition proceeds stereo selectively with the nucleophile approaching anti to the Fe group but often shows poor regeoselectivity. And this drawback is overcome by using vinyl ether complexes which are attacked by nucleophiles exclusively at the alkoxy substituted carbon. So this is important if you use vinyl ether then the nucleophiles adds exclusively at the alkoxy substituted carbon.

And this intermediate alkyl Fe complex undergo elimination of alcohol and demetalation so this is the reaction Fe so Fe connected this, this is electrophile and this the enolate derived from cyclo hexanone lithium elonate now if we do the reaction THF minus 78 degree centigrade you get this carbon carbon bond formation and OEt comes here attack is happening alkoxy substituted carbon.

And now, this ether as well as Fe can be removed in two step process first treatment with HBF4 ether dicholoromethane minus 78 degrees centigrade followed by NaI acetone you get this, and this is very interesting product this is actually a vinylation of enolates so this is alpha vinyl ketone which can be obtain so this alpha vinyl ketone are important compounds and difficult to obtain but, in this strategy you can get this alpha vinyl ketone this was published in pure applied chemistry 1984.

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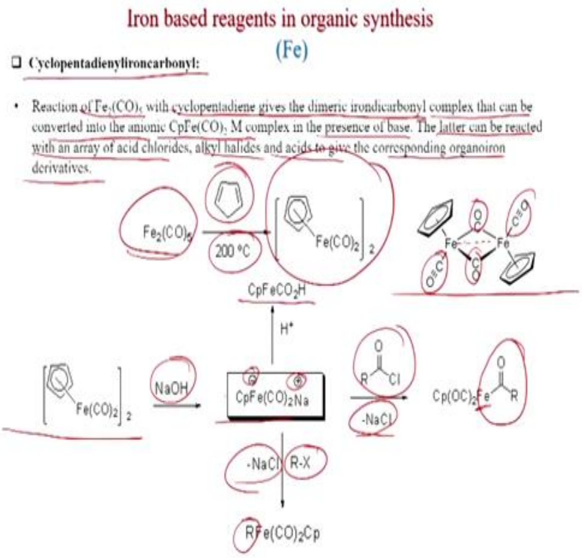

Iron based reagents in organic synthesis

(Fe)

❑ **Cyclopentadienylironcarbonyl:**

- Reaction of $Fe_2(CO)_5$ with cyclopentadiene gives the dimeric irondicarbonyl complex that can be converted into the anionic $CpFe(CO)_2M$ complex in the presence of base. The latter can be reacted with an array of acid chlorides, alkyl halides and acids to give the corresponding organoiron derivatives.

Now we will discuss cyclo penta dienenyl iron carbonyl so reaction of Fe2CO5 this is Fe2CO5 with cyclo penta diene gives the dimeric iron dicarbonyl complex so this is the cyclo penta diene iron dicarbonyl complex this can be obtain after heating with cyclo penta diene at 200 degree centigrade and this is the structure of cyclo penta diene iron dicarbonyl so this you can see this is dimeric and there is a bridging CO. So one CO is connected to iron is and another toward in the bridge also this is a debate the their might be iron iron bond also.

And now if you put base then this can be converted to anionic Cp FeCO2N so suppose this is the iron cyclo penta diene dicarbonyl if you treat with sodium hydroxide then you get this anion this can be obtain in the presense of base like sodium hydroxide and the latter can be reacted with an array of acid chloride alkyl halides and acids to give the corresponding organoiron derivatives.

So different reactions can be performing on this and if you see this structure there is a negative charge on the iron. And sodium of course is plus now if you treat with H plus then you get this CP FeCO2H alternatively if you react with RCOCl then this iron is reacting so iron is reacting with RCOCl and you get this FeCOR with the elimination of minus sodium chloride on the other hand if you react with RX then the iron takes the R and again you get sodium chloride elimination so this is very important if you put with sodium hydroxide then you can get this CP FeCO2M like sodium and the you can treat either acid or acid chloride or alkyl halide to get different organoiron compounds.

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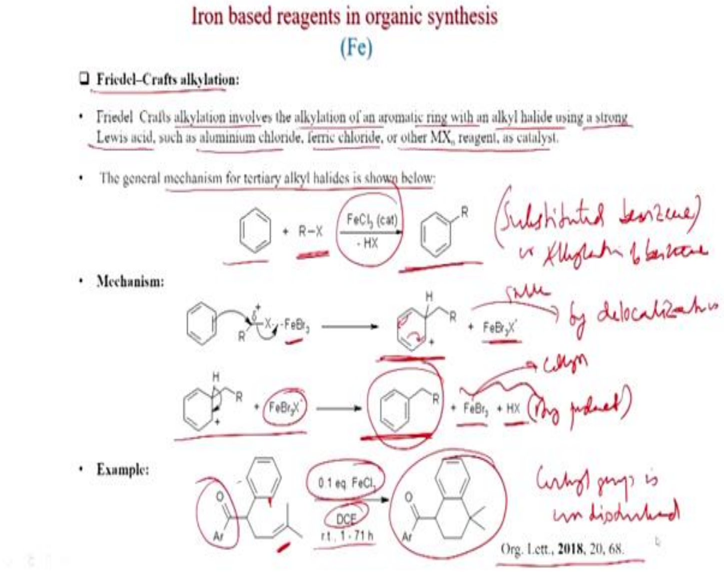

Iron based reagents in organic synthesis

(Fe)

❑ **Friedel–Crafts alkylation:**

- Friedel Crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid, such as aluminium chloride, ferric chloride, or other MX_n reagent, as catalyst.
- The general mechanism for tertiary alkyl halides is shown below:

(Substituted benzene) or Alkylation of benzene

- **Mechanism:**

stable by delocalization

catalyst

(by product)

- **Example:**

Carbonyl group is undisturbed

Org. Lett., **2018**, 20, 68.

No we will see different reactions of iron, iron is generally Lewis acid catalyzed so we will see first the Friedel crafts alkylation, Friedel crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid such as aluminum chloride ferric chloride or other MX and reagent as catalyzed the general mechanism for tertiary alkyl halides is shown below so like this benzene RX so this can be tertiary also tertiary alkyl halide because their the carbocation will form much easier and now ferric chloride is the catalyst with minus HX you get this.

So this benzene becomes substituted benzene or this is called alkylation, alkylation of benzene so what could be the mechanism so FeBr3 is Lewis acid so it can react with X and there will be delta plus charge on the carbon connecting to R and that is the stabilized so here you get this carbocation after addition and FeBr3 X minus is the byproduct.

Now, this carbocatal is stable actually, so this is stable by delocalization because this pi bonds will help in the delocalization this so this is quite stable and different resonating structure can be drawn for this, and after that FeBr3 X minus can take up this proton and the aromatization will happen and you get this product plus FeBr3 and HX. So FeBr3 HX are the byproducts and this is actually the catalyst so HX is the byproduct catalyzed regenerated.

For example, this one if you see this substrate there is a olefin is here and there is a ketone is here, but if you see this benzene has the substituted here now this ortho-position is here or here, but both are same now this one if it attacks here and the carbo cation which is stable that will form so this is the tertiary carbo cation like so this will be stable so this carbon attacks here. So Fridel cabs reaction will happen to here and you get this compound so this is very important the carbonyl group is un disturbed in this reaction.

So only point one equivalent ferric chloride di chloro ethane solvent room temperature 1 to 71 hours you get this product this was published in organic letters 2018.

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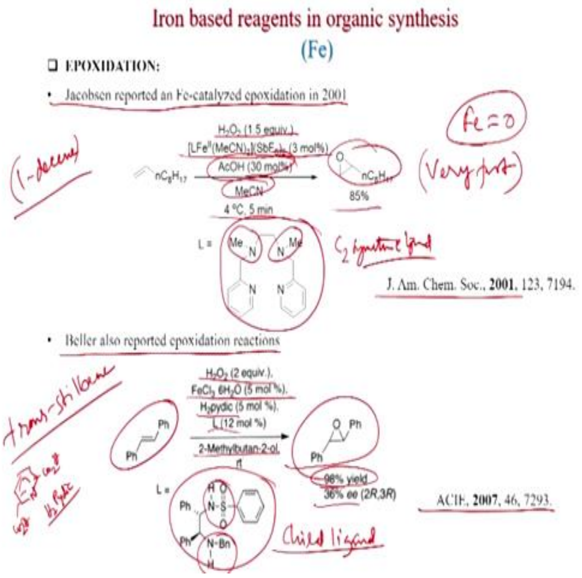

Iron based reagents in organic synthesis

(Fe)

❑ EPOXIDATION:

- Jacobsen reported an Fe-catalyzed epoxidation in 2001

J. Am. Chem. Soc., **2001**, 123, 7194.

- Beller also reported epoxidation reactions

ACIE, **2007**, 46, 7293.

Now we will discuss epoxidation, so Jacobsen group reported an iron catalyzed epoxidation in 2001 so this is 1- decene when treated with hydrogen peroxide 1.5 equivalent ligand iron2 MeCn2 SbF6 2 3 mole percent. So this is the ligand if you see this is C2 symmetric, C2 symmetric ligand and here this is tertiary amine and also pyridine motifs this binds with iron of course and iron reacts with H2O2 to generate this, iron oxo bond is formed and that is why the epoxidation is happening also acetic acid is require 30 mole percent acetonitrile and solvent 4 degree centigrade temperature in 5 minutes you get this epoxidation so this is very fast process. Very fast you get this epoxide in 85 percent yield. This was published JACS 2001.

Now Bellor also reported the epoxidation reaction suppose this is trans stilbene when reacted with hydrogen peroxide to equivalent FeCl3 6 H2O 5 mole percent H2 pydic this is actually peridyne di carboxidic acid this called H2 pydic short form and ligand 12 mole percent so this is the structure of ligand here you can see a sulphoromide group is there and a secondary amine is there and this is the solvent 2 methyl butanol room temperature you get this epoxide

98 percent yield however the enantiomeric excess is low only 36 percent enansomaric axis excess obtain.

So with this chiral ligand they got 36 percent enantiomeric excess and this was published in Angewandte Chemie International Edition 2007.

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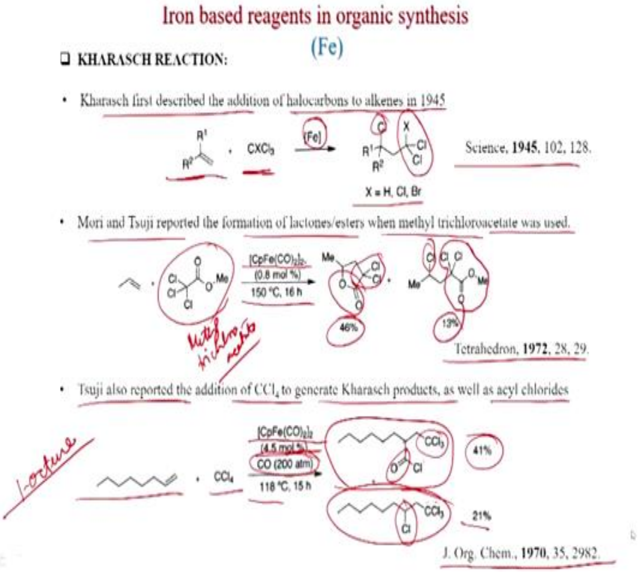

Iron based reagents in organic synthesis

(Fe)

☐ **KHARASCH REACTION:**

- Kharasch first described the addition of halocarbons to alkenes in 1945

Science, **1945**, 102, 128.

- Mori and Tsuji reported the formation of lactones/esters when methyl trichloroacetate was used.

Tetrahedron, **1972**, 28, 29.

- Tsuji also reported the addition of CCl₄ to generate Kharasch products, as well as acyl chlorides

J. Org. Chem., **1970**, 35, 2982.

Now we will discuss Kharasch reaction, so Kharasch first described the addition of halocarbons to alkenes in 1945. So this is the reaction the alkene CXCl3 with iron here the di functionalization happens and you get this, RC Cl here and X Cl2 here X is equal to hydrogen chlorine bromine. So this was published in science 1945.

Now Mori and Tsuji reported the formation of lactones ester when, methyl trichloro acetate was used here you see with this one methyl trichloro acetate so methyl trichloro acetate you get this product so here, this enter the this group is coming and 2 chlorine CCl2 group adding here, this carbon earlier we have seen here the Cl coming and this group CXCl2 is coming here terminal carbon so here this product you can get in 46 percent yield after treating with cyclo penta diene FeCO2 whole 2 that structure we have seen earlier 0.8 mole percent and 150 degree centigrade temperature 16 hours you get this product 46 percent yield along with this product here chlorine comes this group comes at the terminal carbon. And you get this product in 13 percent yield this was published in Tetrahedron 1972.

Now Tsuji also reported the addition of carbon tetra chloride to generate Kharasch products as well as acyl chloride so this you can see this is 1 octene, 1 octene when treated with carbon tetra chloride same compound Cp FeCO whole 2 dimeric 4.5 mole percent only also carbon monoxide you have to add 200 atmosphere. This is the reaction in general in 118 degree centigrade 15 hours you get this product. So this is of course coming from the carbon monoxide and that is the COCl group is coming here and the terminal carbon there is CCl3.

So earlier, also the terminal carbon we have seen CCl3 is adding at this product is forming 41 percent and this product here the chlorine is adding. And CCl3 terminal carbon this is product is obtaining 21 percent yield and this was published in journal of organic chemistry in 1970.

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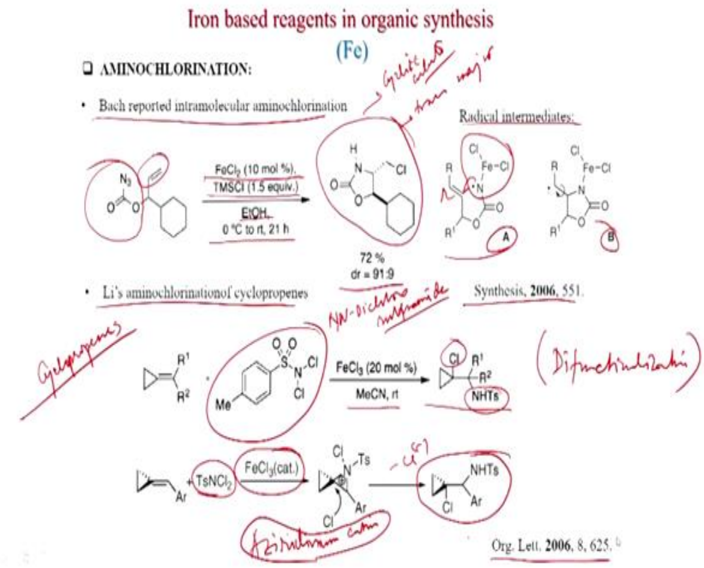

Iron based reagents in organic synthesis

(Fe)

❑ AMINOCHLORINATION:

- Bach reported intramolecular aminochlorination

Radical intermediates:

72 %
dr = 91:9

Synthesis, 2006, 551.

- Li's aminochlorinationof cyclopropenes

Org. Lett. 2006, 8, 625.

So now we will see a different reaction an amino chlorination so this is also di functionalization of olefins Bach reported intra molecular amino chlorination and with this acyl azide and there of course is olefin is there now, with ferrous chloride 10 mole percent TMs chloride 1.5 equivalent ethanol 0 degree centigrade to room temperature in 21 hours you get this product.

So cyclic carbamate is formed, and there is 2 stereo center you can see so, a major is forming trans in 91 is to 9 ratios and the most likely the mechanism follows Radical intermediates so first Radical A will form if you see from this azide and ferrous chloride you get this, so there is a radical of nitrogen which is connected to iron. Now, this radical of course will add to this double bound because a 5-member ring will form and after the 5-member ring formation you get this radical B and with a radical add this carbon. Which is connected to R and this was published in synthesis 2006.

This radical of course will react with the solvent and can be quenched so that formal or it can react with Cl group or it can react with Cl to get a Cl group here. Leads amino chlorination of cyclopropanes so this is cyclopropane and this is NN di chloro sulphonamide with ferric chloride 20 mole percent acetonitrile you get this. So what happens the chlorine adds here of course chlorine is nucleophiles and NH tosyl is here the most substituted carbon atom. So this is the di functionalization of olefins. So what could be the mechanism, so with ferric chloride catalatic amount because 20 mole percent is added and with this reagent you get this.

So, Aziridinium cation is forming here the nitrogen as a positive charge so tosylNCl2 in presence of acid first makes the aziridinium ion. Now, the Cl minus will attack here so you get this Cl here and this group is open also is Cl minus elimination you get this product. So 1 side chlorine and another side NH2 tosylgroup adds. This was published in organic latter 2006.

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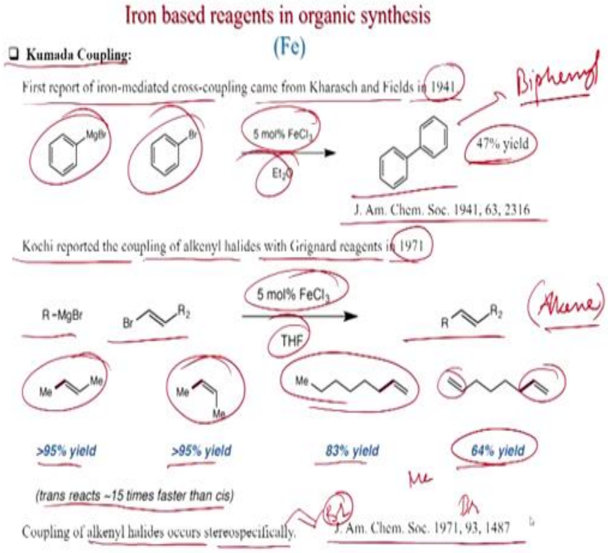

Iron based reagents in organic synthesis

(Fe)

❑ **Kumada Coupling:**

First report of iron-mediated cross-coupling came from Kharasch and Fields in 1941

J. Am. Chem. Soc. 1941, 63, 2316

Kochi reported the coupling of alkenyl halides with Grignard reagents in 1971

(trans reacts ~15 times faster than cis)

Coupling of alkenyl halides occurs stereospecifically.

J. Am. Chem. Soc. 1971, 93, 1487

Now we will see different cross coupling reactions so we have earlier seen the palladium, and copper purpose many cross coupling reactions here we will see iron can also perform because iron is very chip first report of iron mediated cross coupling came from kharasch and fields in 1941. So phenyl magnesium bromide with bromo benzene only 5 mole percent ferric chloride ether will give this. bi phenyl, biphenyl will be form in 47 percent yield this was published in journal of American chemical society in 1941.

Kochi reported the coupling of alkenyl halides with Grignard reagents in 1971. So exactly after 30 years Kochi developed the reaction again with alkenyl bromide. So RMgBr alkenyl bromide 5 mole percent ferric chloride THF you get this alkene so here alkene is formed which are much useful alkene synthesis and you see here trans alkene trans 2 butene cis 2 butene is formed in very high yield here a long chain can be formed in 83 percent yield here also 2 olefins are there this selectively forms in 64 percent yield.

And trans reacts 15 times faster that cis, so if you have a trans one that will react 15 times faster that cis, of course for the steric reason and the olefin geometry will be retain so coupling of alkenyl halides occur stereo specifically, so the geometry will remain intact so trans will give trans olefin cis will give cis olefin. This was published in journal of American chemical society in 1971.

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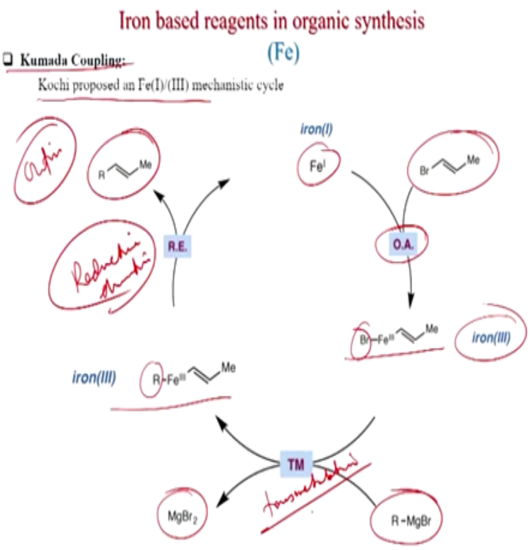

Iron based reagents in organic synthesis

(Fe)

❑ **Kumada Coupling:**

Kochi proposed an Fe(I)/(III) mechanistic cycle

Now we will discuss the mechanism, so Kochi proposed an iron 1, iron 3 mechanistic cycle so if you see the cycle iron 1 is the active catalyst here and with this alkenyl bromide oxidative addition happens like palladium here this iron will be 3 now, after oxidative addition and now ,this R-MgBr will come and so this is called the trans-metalation trans metalation TM so R-MgBr the R group will coordinate with iron and MgBr will react with this Br so MgBr 2 will formed and here also iron is 3. And now reductive elimination will happen.

So after reductive elimination, you get this olefin product olefin is formed and your iron 3 becomes now iron 1. After reductive elimination, so the mechanism, similar like palladium catalysis here iron 1 is the active catalyst and in the reaction is becomes iron 3 also and after catalytic cycle again it is coming back to iron 1.

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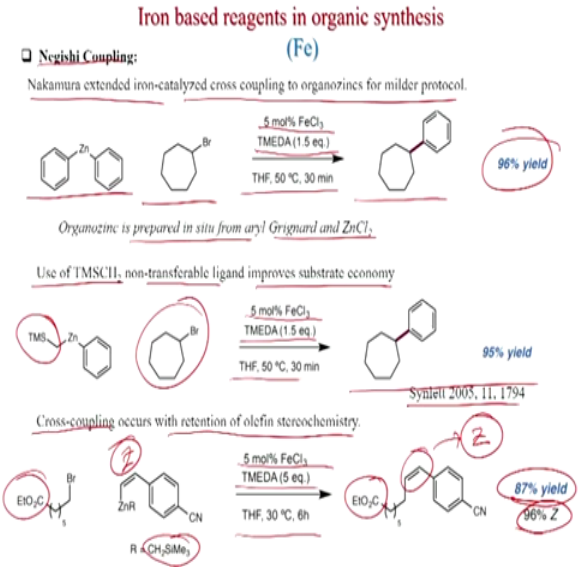

Iron based reagents in organic synthesis

(Fe)

❑ **Negishi Coupling:**

Nakamura extended iron-catalyzed cross coupling to organozincs for milder protocol.

Organozinc is prepared in situ from aryl Grignard and $ZnCl_2$

Use of $TMSCH_2$ non-transferable ligand improves substrate economy

Synlett 2005, 11, 1794

Cross-coupling occurs with retention of olefin stereochemistry.

Now we will discuss Negishi coupling Nakamora extended iron catalyzed cross coupling to organozincs for milder protocol where di phenyl zinc with cyclo heptanyl bromide with 5 mole percent ferric chloride TMEDA 1.5 equivalent ThF 50 degree centigrade 30 minutes you get this cross coupled product in 96 percent yield. Organozinc is prepared insitu from aryl Grignard and zinc chlorine that also we have seen earlier.

And use of TMSCH2 nontransferable ligands improves substrate economy like here instead of a another phenyl group if you put this CH2TMS which is much smaller in size with the same bromides cycloheptyl bromide 5 mole percent ferric chloride TMEDA 1.5 equivalent THF 50 degree centigrade you get this product again 95 percent yield, this was published in Synlett 2005.

And cross coupling occurs with retention of olefin stereo chemistry like earlier also we have seen for Kumada coupling here also Negishi coupling this suppose is z configuration this is alkyl bromide also functionalize 5 mole percent feericchloride TMEDA 5 equivalent THF 30 degree centigrade you get this olefin and here also this is z.

So the stereo chemistry is retained and R is equal to here CH2SiMe3 lie here and 96 percent z and 87 percent yield Co2 Et group is untouched in this reaction.

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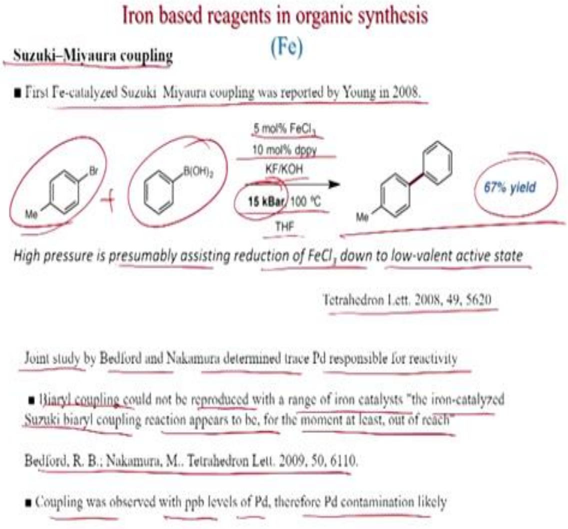

Iron based reagents in organic synthesis

(Fe)

Suzuki–Miyaura coupling

- First Fe-catalyzed Suzuki Miyaura coupling was reported by Young in 2008.

High pressure is presumably assisting reduction of FeCl$_3$ down to low-valent active state

Tetrahedron Lett. 2008, 49, 5620

Joint study by Bedford and Nakamura determined trace Pd responsible for reactivity

- Biaryl coupling could not be reproduced with a range of iron catalysts "the iron-catalyzed Suzuki biaryl coupling reaction appears to be, for the moment at least, out of reach"

Bedford, R. B.; Nakamura, M., Tetrahedron Lett. 2009, 50, 6110.

- Coupling was observed with ppb levels of Pd, therefore Pd contamination likely

Now, Suzuki Miyaura coupling first iron catalyzed Suzuki Miyaura coupling was reported by Young in 2008, this is the aryl bromide aryl bonronic acid with 5 mole percent ferric chloride 10 mole percent DPPI di phenyl peridyne KF/KOH 15 kilo per 100 degrees centigrade THF you get this. cross coupled product in 67 percent yield. High pressure is presumably assisting reduction of FeCl3 down to low valiant active state. Iron 1 state that is why high pressure is required this was published in Tetrahadron latter 2008.

However, there was a problem like Joint study by Bedford and Nakamora determine trace palladium responsible for reactivity and Biaryl coupling could not be reproduce with a range of iron catalyzed the iron catalyzed Suzuki Biaryl coupling reaction appears to be for the moment at least out of rich. This was published in Tetrahedron latter 2009, The comments.

And coupling was observed with ppb levels of palladium therefore palladium contamination is likely so Suzuki Miyaura coupling may occur with this palladium contamination which is present in iron.

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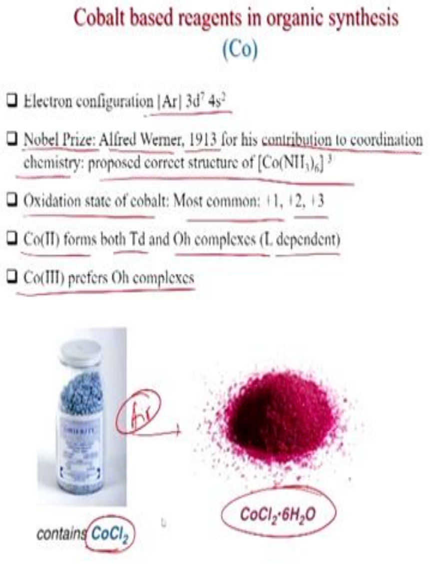

Cobalt based reagents in organic synthesis
(Co)

- ❑ Electron configuration [Ar] $3d^7 4s^2$
- ❑ Nobel Prize: Alfred Werner, 1913 for his contribution to coordination chemistry: proposed correct structure of $[Co(NH_3)_6]^{3+}$
- ❑ Oxidation state of cobalt: Most common: +1, +2, +3
- ❑ Co(II) forms both Td and Oh complexes (L dependent)
- ❑ Co(III) prefers Oh complexes

So now, we will discuss Cobalt based reagent in organic synthesis so electronic configuration is Argon3d7 4s2. And noble prize was obtain by Alfred Werner in 1913 for its contribution to coordination chemistry proposed correct structure of CONH3 6 3 plus so, he proposed the structure and he got noble prize in 1913.

Oxidation state of Cobalt most common plus 1, plus 2, plus 3 cobalt to forms both tetrahedral and octahedral comolexes of course ligand dependent ligand is strong then the geometry will change and cobalt 3 prefers octahedral complexes. This one is blue this is CoCl2, and if you put it in air then it becomes red so this is CoCl2 6 H2O. So this is very important the colour chemistry.

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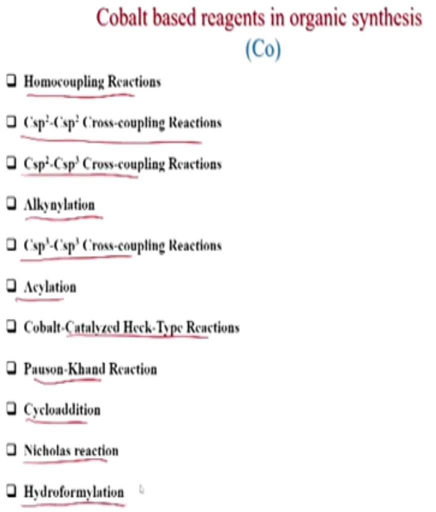

Cobalt based reagents in organic synthesis
(Co)

- ❑ **Homocoupling Reactions**
- ❑ **Csp^2-Csp^2 Cross-coupling Reactions**
- ❑ **Csp^2-Csp^3 Cross-coupling Reactions**
- ❑ **Alkynylation**
- ❑ **Csp^3-Csp^3 Cross-coupling Reactions**
- ❑ **Acylation**
- ❑ **Cobalt-Catalyzed Heck-Type Reactions**
- ❑ **Pauson-Khand Reaction**
- ❑ **Cycloaddition**
- ❑ **Nicholas reaction**
- ❑ **Hydroformylation**

Now we will discuss many reactions like homo coupling reactions Csp2, Csp2 cross coupling reaction Csp2, Csp3 cross coupling alkylnilation Csp3 Csp3 cross coupling reactions acylation will discuss, cobalt catalyzed heck type reactions will discuss. Pauson Khand reaction will discuss cyclo addition will discuss, Nicholas reaction also will discuss, and hydro formylation will discuss.

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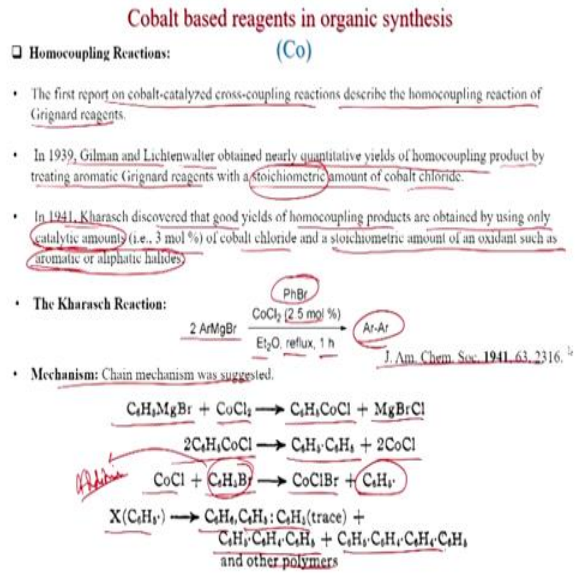

Cobalt based reagents in organic synthesis

❑ **Homocoupling Reactions:** (Co)

- The first report on cobalt-catalyzed cross-coupling reactions describe the homocoupling reaction of Grignard reagents.
- In 1939, Gilman and Lichtenwalter obtained nearly quantitative yields of homocoupling product by treating aromatic Grignard reagents with a stoichiometric amount of cobalt chloride.
- In 1941, Kharasch discovered that good yields of homocoupling products are obtained by using only catalytic amounts (i.e., 3 mol %) of cobalt chloride and a stoichiometric amount of an oxidant such as aromatic or aliphatic halides.
- **The Kharasch Reaction:**

$$2\ ArMgBr \xrightarrow[Et_2O,\ reflux,\ 1\ h]{PhBr \quad CoCl_2\ (2.5\ mol\ \%)} Ar\text{-}Ar$$

J. Am. Chem. Soc. **1941**, 63, 2316.

- **Mechanism:** Chain mechanism was suggested.

$$C_6H_5MgBr + CoCl_2 \longrightarrow C_6H_5CoCl + MgBrCl$$

$$2C_6H_5CoCl \longrightarrow C_6H_5{\cdot}C_6H_5 + 2CoCl$$

$$CoCl + C_6H_5Br \longrightarrow CoClBr + C_6H_5{\cdot}$$

$$X(C_6H_5{\cdot}) \longrightarrow C_6H_6, C_6H_5 : C_6H_5 (trace) + C_6H_5{\cdot}C_6H_4{\cdot}C_6H_5 + C_6H_5{\cdot}C_6H_4{\cdot}C_6H_4{\cdot}C_6H_5 \text{ and other polymers}$$

So first we will discuss homo coupling reaction first report on cobalt catalyzed cross coupling reactions describe the homo coupling reaction of Grignard reagents. In 1939 Gilman and Lichtenwalter obtain nearly quantative yield of homo coupling product by treating aromatic Grignard reagents with a stoichiometric amount of cobalt chloride.

Here of course stoichiometric amount was used in 1941 Kharasch discovered the good yields of homo coupling products obtain by using only catalytic amounts that is 3 mole percent of cobalt chloride. And stoichiometric amount of an oxidant such as aromatic or aliphatic halide so this is important contribution from Kharasch so this is the Kharasch reaction ArMgBr and this is the stoichiometric amount of aromatic halides CoCl2 only 2.5 mole percent ether reflux 1 hour you get this Ar, Ar cross coupled product.

And then mechanism, chain mechanism was suggested so C6H5MgBr reacts with cobalt chloride to generate this C6H5 COCl plus MgBrCl is a byproduct now 2C6H5COCl will generate this bi phenyl and 2COCl will formed. Now this CoCl will react with C6H5Br which is the additive here so this is additive and you get this CoClBr plus the radical phenyl radical is form and this phenyl radical can give bi phenyl benzene bi phenyl then this trimer tetramer plus other polymers is possible. This was published in JACS 1941.

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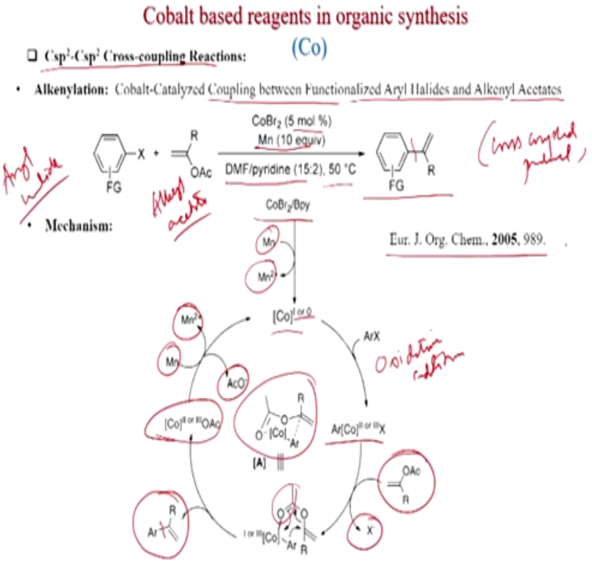

Cobalt based reagents in organic synthesis

(Co)

❑ Csp^2-Csp^2 Cross-coupling Reactions:

- **Alkenylation:** Cobalt-Catalyzed Coupling between Functionalized Aryl Halides and Alkenyl Acetates
- **Mechanism:**

Eur. J. Org. Chem., **2005**, 989.

Now we will discuss Csp2 Csp2 cross coupling reaction cobalt catalyzed coupling reaction between functionalize aryl halides and alkenyl acetates so this is aryl halide this is alkenyl acetate or vinyl acetate and with CoBr2 5 mole percent manganese 10 equivalent DMF pyridine solvent 15 is to 2, 50 degrees centigrade you get this cross coupled product. So a CC bond is formed this bond is formed in this reaction.

So what could be the mechanism so CoBr2 with manganese, so manganese is reductant manganese itself is going to manganese 2 plus and it is converting cobalt 2 to cobalt 1 or 0. So cobalt 1 or 0 is forming and now ArX will add so this is the oxidative addition like earlier we have seen this will form and now this vinyl acetate will displace 1X so X minus will eliminate and you get this, so this carbonyl group coordinates with cobalt. And it can take geometry like this so carbonyl coordinates with cobalt and cobalt also coordinates with iron and now the 6-member transition state is formed now this aryl will coordinate with this is aryl this CC bond will form here.

Like here, and you get this is the product so this is the newly generated bond and this is form down cobalt 2 or 3 acetate now again manganese becomes manganese 2plus acetate liberates and becomes a cobalt 3 becomes cobalt 1. So oxidative addition and reductive elimination like this happens and you get this cross coupled product. This was published in European JOC 2005.

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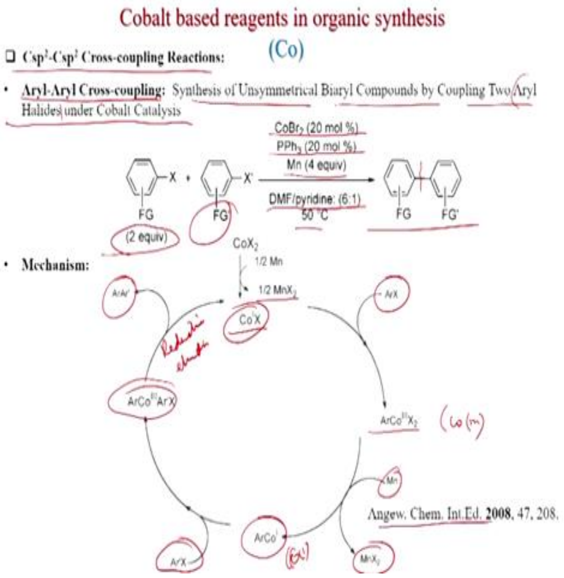

Cobalt based reagents in organic synthesis

(Co)

☐ **Csp²-Csp² Cross-coupling Reactions:**

- **Aryl-Aryl Cross-coupling:** Synthesis of Unsymmetrical Biaryl Compounds by Coupling Two Aryl Halides under Cobalt Catalysis
- **Mechanism:**

Angew. Chem. Int.Ed. **2008**, 47, 208.

Some more Csp2 Csp2 cross coupling reactions aryl aryl cross coupling earlier we have seen aryl vinyl now we will see aryl aryl cross coupling synthesis of un symmetrical bi aryl compounds by coupling of 2 aryl halides. Under cobalt catalysis so 2 aryl halides can be coupled to give bi aryl compounds.

So this is 2 equivalent excess this is another functional group containing aryl halide with CoBr2 20 mole percent tri phenyl phosphine 20 mole percent manganese 4 equivalent similar solvent DMF pyridine 6 is to 1 50 degree centigrade you get this so, the cross coupled product here this bond is formed carbon carbon so what could be the mechanism here similarly, this manganese becoming manganese plus 2 cobalt 2 become is cobalt 1 or 0.

Now this aryl X will do the oxidative addition and so cobalt 1 becoming cobalt 3, and now this manganese will go to manganese X2 and this will form, manganese will reduce this one because here cobalt is 3, cobalt 3 and this is cobalt 1. So after the addition of a different molecule Ar dash X will oxidatively add here. So you get this cobalt 1 again becomes cobalt 3 and now the reductive elimination will happen, reductive elimination so cobalt 3 becomes cobalt 1 and you get this cross coupled product. This was published in Angewandte Chemie International edition 2008.

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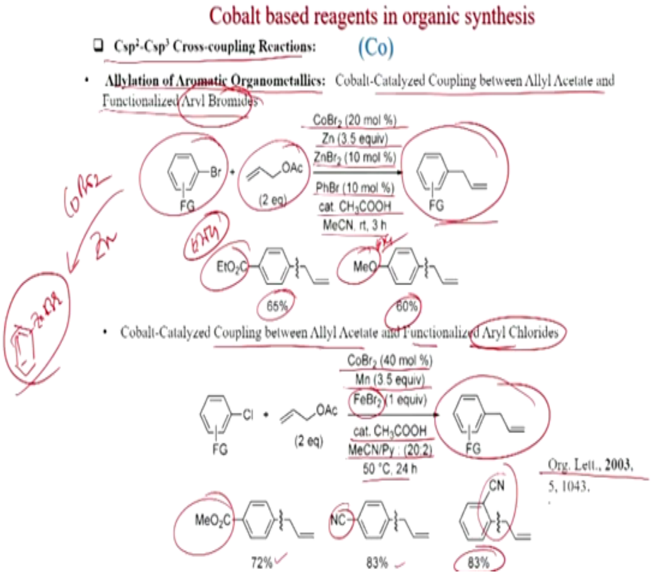

Cobalt based reagents in organic synthesis

❑ **Csp²-Csp³ Cross-coupling Reactions:** (Co)

- **Allylation of Aromatic Organometallics:** Cobalt-Catalyzed Coupling between Allyl Acetate and Functionalized Aryl Bromides
- Cobalt-Catalyzed Coupling between Allyl Acetate and Functionalized Aryl Chlorides

Org. Lett., 2003, 5, 1043.

So Csp2 Csp3 cross coupling also is possible allylation of aromatic organo metalized cobalt catalyzed coupling between allyl acetate and functionalize aryl bromides so this is the aryl bromide allyl acetate with cobalt bromide 20 mole percent zinc 3.5 equivalent zinc bromide 10 mole percent PhBr 10 mole percent catalytic acetic acid acetonitrile room temperature 3 hours you get this allyl containing aryl group.

So here electron withdrawing group so this is EWG group can be tolerated this product is form 65 percent and methoxy this is EDG group electron donating also the product is form is 60 percent yield. Now if you use allyl acetate and functionalize aryl chloride so earlier, we have seen aryl bromide these are aryl chloride now is aryl chloride similar condition we can use cobalt bromide 40 mole percent manganese 3.5 equivalent instead of zinc now here manganese and instead of zinc bromide here you have use ferrous bromide 1 equivalent catalytic acetic acid MeCn pyridine 20 is to 2 50 degree centigrade 24 hours you get this same product.

Here also electron withdrawing groups is tolerated nicely 72 percent 83 percent and here also you get this is the ortho position you get this product in 83 percent yield. So most likely cobalt and zinc, cobalt bromide and zinc you are getting this ZnBr and after that ZnBr this is reacting with allyl acetate which is again of course activated by cobalt and that is why this allyl product is forming so this was published in organic latter 2003.

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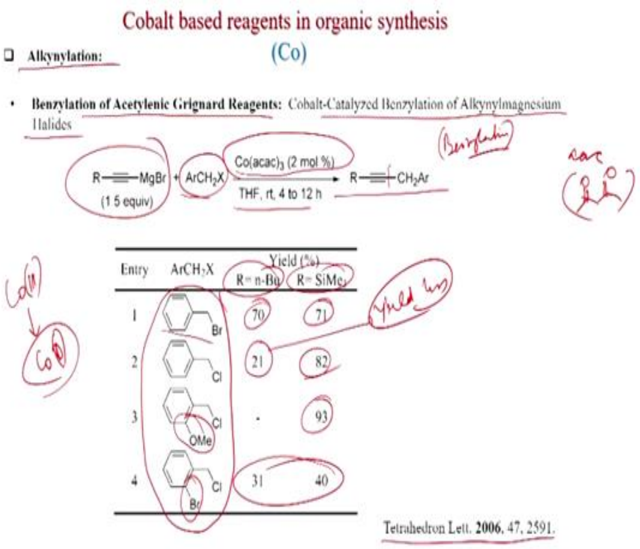

Cobalt based reagents in organic synthesis

(Co)

❑ **Alkynylation:**

- **Benzylation of Acetylenic Grignard Reagents:** Cobalt-Catalyzed Benzylation of Alkynylmagnesium Halides

$$\underset{(1.5\ \text{equiv})}{\text{R}{-}{\equiv}{-}\text{MgBr}} + \text{ArCH}_2\text{X} \xrightarrow[\text{THF, rt, 4 to 12 h}]{\text{Co(acac)}_3\ (2\ \text{mol}\ \%)} \text{R}{-}{\equiv}{-}\text{CH}_2\text{Ar}$$

Entry	ArCH$_2$X	Yield (%)	
		R = n-Bu	R = SiMe$_3$
1	Br	70	71
2	Cl	21	82
3	Cl OMe	-	93
4	Cl Br	31	40

Tetrahedron Lett. **2006**, 47, 2591.

Now we will discuss alkynylation benzylation of acetylic Grignard reagents cobalt catalyzed benzylation of alkenyl magnesium halides. So here alkenyl magnesium bromide is there ArCH3X with cobalt acetyl acetone acac so acetyl acetone 2 mole percent THF room temperature 4 to 12 hours you get this product so this is the bond is formed carbon carbon that is the benzylation so benzylation happens, and if you see the scope of this rection different benzyl groups containing compounds can be used like benzyl bromide and here this alkyne when R is equal to n butyl you get 70 percent yield.

R is equal SiMe3 you get 71 but if you use benzyl chloride then for n butyl case R is equal to n butyl you get only 21 percent yield so yield is less here. However, if you use SiMe3 yield is going to 82 percent. A ortho group can be also be tolerated like methoxy bromo in this case very good yield R is equal SiMe3 will 93 percent here almost similar yield n butyl SiMe3 so the mechanism will be most likely with Grignard that we will see later that cobalt 3 becomes cobalt 0, with this Grignard and this cobalt 0 then coordinates with the alkyne magnesium as well as this ArCH2X so that the cross coupling happens and this was published in Tetrahedron latter 2006.

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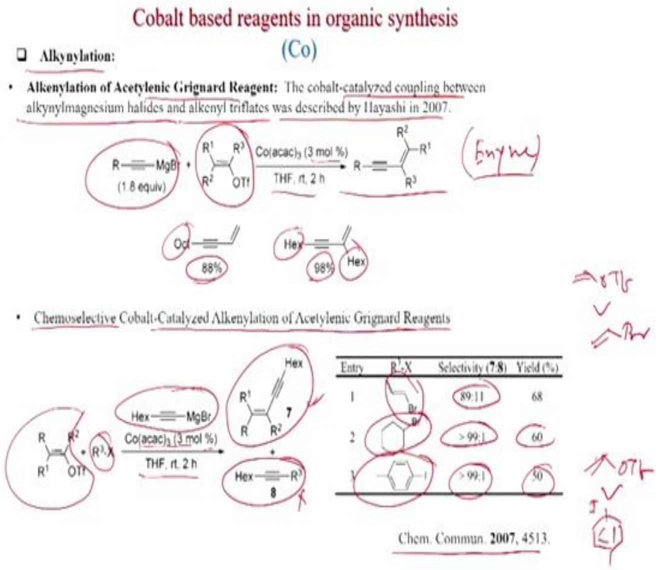

Cobalt based reagents in organic synthesis

(Co)

☐ **Alkynylation:**

- **Alkenylation of Acetylenic Grignard Reagent:** The cobalt-catalyzed coupling between alkynylmagnesium halides and alkenyl triflates was described by Hayashi in 2007.

- Chemoselective Cobalt-Catalyzed Alkenylation of Acetylenic Grignard Reagents

Entry	R³-X	Selectivity (7:8)	Yield (%)
1	Br	89:11	68
2	Br	> 99:1	60
3	I	> 99:1	50

Chem. Commun. **2007**, 4513.

Some more on the alkynylation, alkynylation also with the cobalt catalyzed coupling between alkenyl magnesium halides and alkenyl triflates so earlier, we have seen aryl bromide now alkenyl triflate was described by Hayashi by 2007, here this alkenyl magnesium bromide and vinyl triflate is used the same catalyzed cobalt acetyl acetonate 3, 3 mole percent THF room temperature you get this so this is enyne.

Enyne compounds are very useful you can get this very easily suppose this one with octyle group containing you get 88 percent with hexyle and here the substitution is there you can get this so in 98 percent yield. Also chemoselective possible cobalt catalyzed alkynylation of acetolanic Grignard reagents so here this is the vinyl triflate this is the Grignard that is what we are looking for the reaction and you get this, enyne product.

Now if you put R3X R3 can be also aryl also so this product could be form that is what last reaction we have seen earlier, this is when aryl the aryl group is coming and cobalt acetyl acetone 3 mole percent THF room temperature with the 2 hours you can get the selectivity. So R3 reacts when it is vinyl bromide you get 89 is to 12.

So that means vinyl triflate, is much more reactive than vinyl bromide now if you use cyclohexyl bromide of course you get greater than 99 is to 1 so this is the forming this is not forming and this is 60 percent. Interestingly if you have this one, paratolyl iodide here this is product is form selectively so what happens, this OTf is much more reactive now this with idotoluene so, here also selectivity is very good greater than 99 is to 1 and you get this product 50 percent yield.

So this is very important chemo selectively if you have a aryl iodide and vinyl triflate the vinyl triflate will selectively couple to the alkenyl magnesium bromide this was published in Chem Commun 2007.

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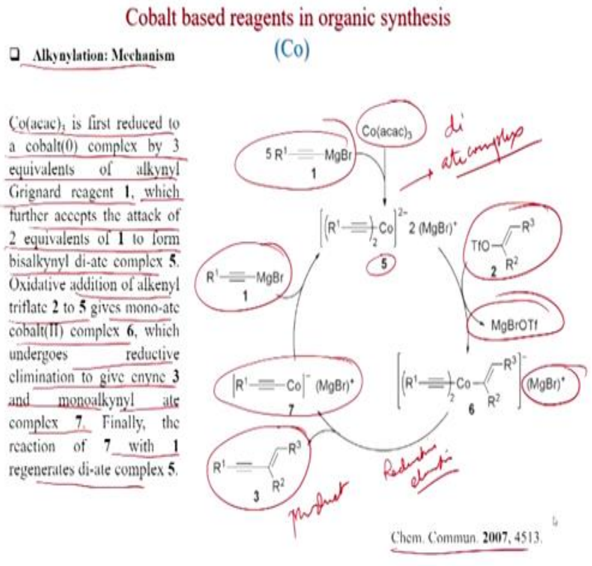

Cobalt based reagents in organic synthesis

(Co)

❑ Alkynylation: Mechanism

$Co(acac)_3$ is first reduced to a cobalt(0) complex by 3 equivalents of alkynyl Grignard reagent **1**, which further accepts the attack of 2 equivalents of **1** to form bisalkynyl di-ate complex **5**. Oxidative addition of alkenyl triflate **2** to **5** gives mono-ate cobalt(II) complex **6**, which undergoes reductive elimination to give enyne **3** and monoalkynyl ate complex **7**. Finally, the reaction of **7** with **1** regenerates di-ate complex **5**.

Chem. Commun. **2007**, 4513.

Now alkynylation mechanism we can discuss so, as i told earlier the cobalt 3 is first reduced to a cobalt 0, complex by 3 equivalents of alkenyl Grignard reagent 1, so this is the Grignard reagent this is cobalt acetyl acetone, this is reducing to cobalt 0 which further accepts the attack of 2 equivalents of 1 to form bisalkynyl di-ate complex 5. So again 2 equivalent attacks to the cobalt 0 so the cobalt here become 2 minus ate complex. So this is ate complex is formed.

Now oxidative addition of alkenyl triflate 2 to 5 gives mono ate cobalt to complex 6 so this is alkenyl triflate now, it adds to here to the cobalt of course so this adds to the cobalt and 1 MgBr will eliminate like this MgBrOTF and 1 MgBr will reside like this plus charge now this one both alkyne and vinyl group is present so, the reductive elimination will happen now. Which undergoes reductive elimination to give enyne 3 so this is the product and mono alkenyl ate complex 7.

So mono alkenyl ate complex 7 will form finally again it will react with alkynyl Grignard reagent with 1 to generate di ate complex 5 so this is di ate complex 5 this is the paper chem commun 2007.

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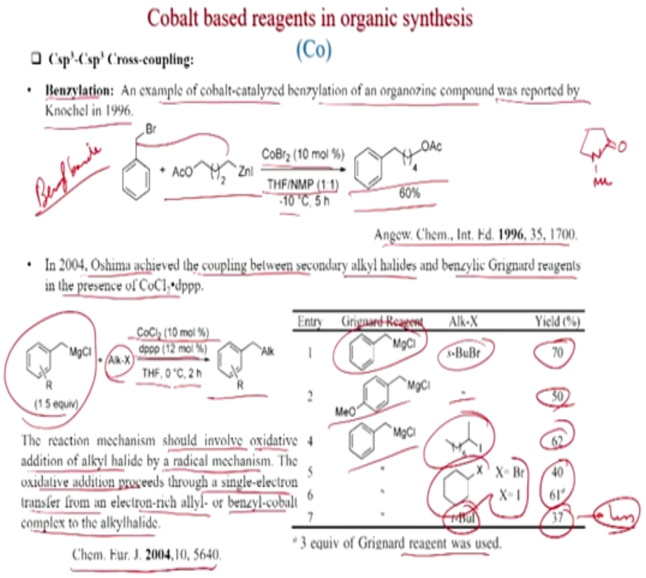

Cobalt based reagents in organic synthesis

(Co)

❑ Csp^3-Csp^3 Cross-coupling:

- **Benzylation:** An example of cobalt-catalyzed benzylation of an organozinc compound was reported by Knochel in 1996.

Angew. Chem., Int. Ed. **1996**, 35, 1700.

- In 2004, Oshima achieved the coupling between secondary alkyl halides and benzylic Grignard reagents in the presence of $CoCl_2$•dppp.

Entry	Grignard Reagent	Alk-X	Yield (%)
1	MgCl	s-BuBr	70
2	MeO MgCl	"	50
4	MgCl	I	62
5	"	X X= Br	40
6	"	X= I	61ᵃ
7	"	t-BuI	37

ᵃ 3 equiv of Grignard reagent was used.

The reaction mechanism should involve oxidative addition of alkyl halide by a radical mechanism. The oxidative addition proceeds through a single-electron transfer from an electron-rich allyl- or benzyl-cobalt complex to the alkylhalide.

Chem. Eur. J. **2004**,10, 5640.

Now we will discuss Csp3 Csp3 cross coupling, so benzylation will discuss now and example of cobalt catalyzed benzylation of an organo zinc compound was first reported by Knochel in 1996. So this is the reaction benzyl bromide and this is the functionalize zinc iodide cobalt Br2 10 mole percent THF NMP so NMP is n methyl pirolidone that is also solvent and minus 10 degree centigrade you get this so this carbon and this carbon reacts. And you get this product in 60 percent yield this was published in Angewandte Chemie international edition 1996.

In 2004 Oshima achived the coupling between secondary alkyl halides and benzylic Grignard reagents in the presence of CoCl2 Dppe di phenyl phosphino propane so this is the benzyl magnesium chloride now alkyl X with CoCl2 10 mole percent here dppe is the ligand with THF 0 degree centigrade 2 hours you get this cross coupled product.

And you can see the scope here so Grignard reagents is benzyl magnesium chloride secondary butyl bromide is the alkyl source and 75 percent yield you can get with paramethoxy same you get 50 percent yield also it benzyl magnesium chloride and secondary iodide also gives 62 percent yield and cyclo hexyle bromide or iodide gives good yield tertiary butyl iodide yield is less. And in this case 3 equivalent of Grignard reagent was used. So what could be the mechanism for this case the reaction mechanism should involve oxidative addition of alkyl halide by a radical mechanism.

The oxidative addition proceeds to a single electron transfer from an electron reach allyl or benzyl cobalt complex to the alkyl halide so, single electron transfer will take place from an electron rich allyl or benzyl cobalt complex. And this was published in chemistry journal 2004.

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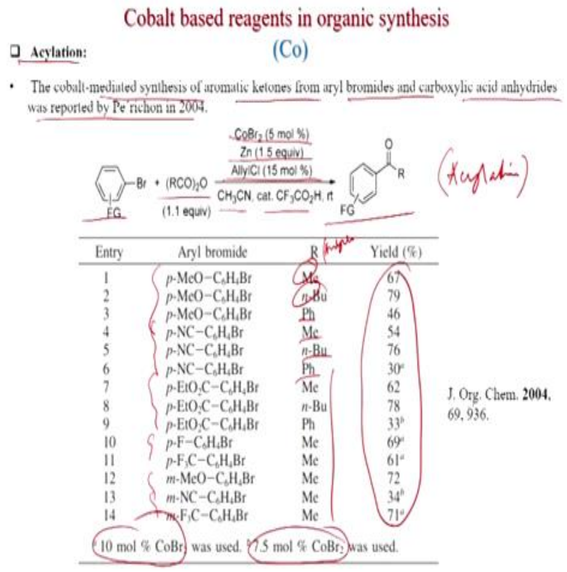

Cobalt based reagents in organic synthesis

(Co)

❑ **Acylation:**

- The cobalt-mediated synthesis of aromatic ketones from aryl bromides and carboxylic acid anhydrides was reported by Pe'richon in 2004.

Entry	Aryl bromide	R	Yield (%)
1	*p*-MeO−C_6H_4Br	Me	67
2	*p*-MeO−C_6H_4Br	*n*-Bu	79
3	*p*-MeO−C_6H_4Br	Ph	46
4	*p*-NC−C_6H_4Br	Me	54
5	*p*-NC−C_6H_4Br	*n*-Bu	76
6	*p*-NC−C_6H_4Br	Ph	30[a]
7	*p*-EtO_2C−C_6H_4Br	Me	62
8	*p*-EtO_2C−C_6H_4Br	*n*-Bu	78
9	*p*-EtO_2C−C_6H_4Br	Ph	33[b]
10	*p*-F−C_6H_4Br	Me	69[a]
11	*p*-F_3C−C_6H_4Br	Me	61[a]
12	*m*-MeO−C_6H_4Br	Me	72
13	*m*-NC−C_6H_4Br	Me	34[b]
14	*m*-F_3C−C_6H_4Br	Me	71[a]

[a] 10 mol % $CoBr_2$ was used. [b] 7.5 mol % $CoBr_2$ was used.

J. Org. Chem. **2004**, 69, 936.

Now we will discuss acylation the cobalt mediated synthesis of aromatic ketones from aryl bromides and carboxylic acid anhydride so as reported by Perichon in 2004, so aryl bromide this is anhydride with cobalt bromide 5 mole percent zinc 1.5 equivalent allyl chloride 15 mole percent acetonitrile catalytic tri fluoro acetic acid room temperature you get this so this is the acylation.

And you can see the scope of this reaction paramethoxy paracyano CO2 Et FCF3 methoxy meta methoxy meta cyano meta CF3 different group and are defined anhydride so this is anhydride with methyl n butyl phenyl methyl n butyl phenyl n butyl methyl n butyl methyl you get, moderate to good yields some case 10 mole percent has to be use CoBr2 and some cases 7.5 mole percent CoBr2 was used. This was published in journal of organic chemistry 2004.

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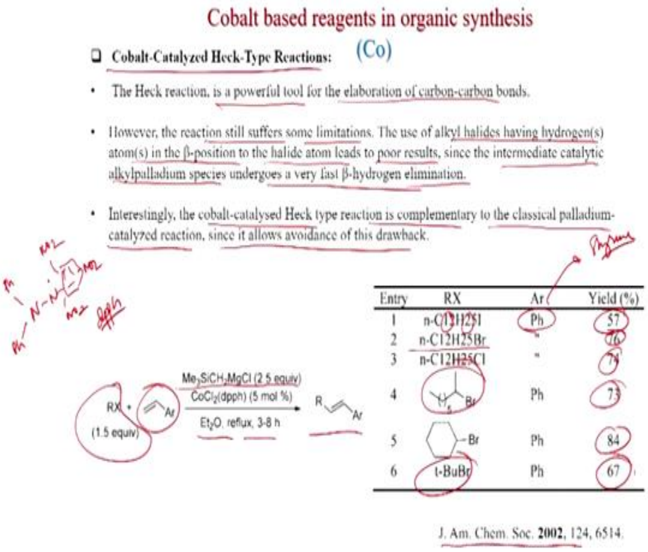

Cobalt based reagents in organic synthesis

❑ **Cobalt-Catalyzed Heck-Type Reactions:** (Co)

- The Heck reaction, is a powerful tool for the elaboration of carbon-carbon bonds.
- However, the reaction still suffers some limitations. The use of alkyl halides having hydrogen(s) atom(s) in the β-position to the halide atom leads to poor results, since the intermediate catalytic alkylpalladium species undergoes a very fast β-hydrogen elimination.
- Interestingly, the cobalt-catalysed Heck type reaction is complementary to the classical palladium-catalyzed reaction, since it allows avoidance of this drawback.

RX (1.5 equiv) + Ar-substituted olefin $\xrightarrow[\text{Et}_2\text{O, reflux, 3-8 h}]{\text{Me}_3\text{SiCH}_2\text{MgCl (2.5 equiv)},\ \text{CoCl}_2\text{(dpph) (5 mol \%)}}$ R–CH=CH–Ar

Entry	RX	Ar	Yield (%)
1	n-C12H25I	Ph	57
2	n-C12H25Br	"	76
3	n-C12H25Cl	"	74
4	Br	Ph	73
5	–Br	Ph	84
6	t-BuBr	Ph	67

J. Am. Chem. Soc. **2002**, 124, 6514.

Now we will discuss cobalt catalyzed Heck type reaction, now Heck reaction is a powerful tool for the elaboration of carbon carbon bonds however the reactions still suffers some limitation. The use of alkyl halide having hydrogens atoms in the beta position to the halide atom leads to poor results since, the intermediate catalytic alkyl palladium species undergo very fast beta hydrogen elimination.

So this is the problem in Heck reaction if you want to is alkyl halide and if there is a beta hydrogen that can be eliminate but we will see which cobalt this problem can be solved the cobalt catalyzed Heck type reaction is complementary to the classical palladium catalyzed reaction since, it allows avoidance of this drawback. Like here RX alkyl halide with olefin Me3SiCH2MgCl 2.5 equivalent CoCl2 dppH so dppH is this n dot No2, No2, No2 Ph Ph. So this is dppH with ether reflux 3 to 8 hours you get this heck coupled product and this is the scope this is of course same C12 H25i PPH Ar is equal Ph and it is the styrene you get this product in 57 percent yield.

N C2l H25 Br you get 76 percent here also 74 percent also secondary alkyl bromide can also be used you get 73 percent cyclohexyle gives 84 percent and tertiary butyl can also be used in this heck coupling. And you can get 67 percent yield so this is very interesting. Different primary secondary and tertiary can be use in this heck coupling, this was published in JACS 2002.

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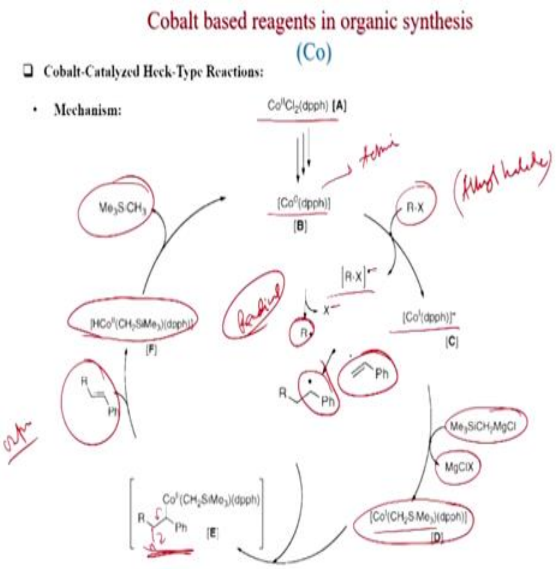

Cobalt based reagents in organic synthesis

(Co)

❑ **Cobalt-Catalyzed Heck-Type Reactions:**

- **Mechanism:**

So, what could be the mechanism for this heck coupling reaction so CoCl2 dpph goes to cobalt 0, and after that RX so this is the alkyl halide will react and generate RX dot minus so there is a minus dot minus and cobalt 0 become cobalt 1. Now this Me3SiCH2MgCl will coordinate with cobalt so to generate this and MgCl acts to will be byproduct. Now, this RX dot minus after elimination of X minus it generates R dot.

So this is radical. So R dot radical is formed and that will attack to the styrene so it attacks regio selectively at this carbon so that this radical will stabilize by phenyl group so that is the benzylic radical. And now this radical react with cobalt 1 system, to generate this cobalt become now cobalt 2. And after that elimination so this elimination will take place like this you get this olefin and this hydrido F is formed.

So this should be like this, so HCo2 this ligand and dpph after Me3SiCH3 you get this active catalyzed so this is the active catalyzed cobalt 0.

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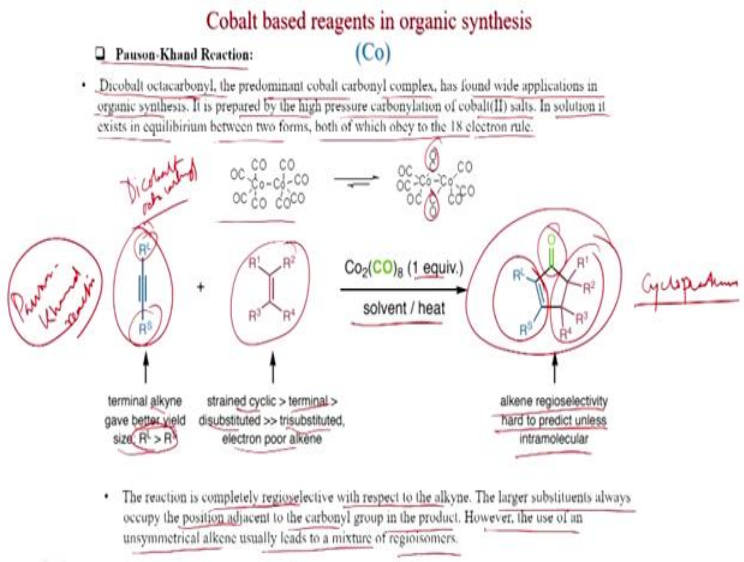

Cobalt based reagents in organic synthesis

- ❑ **Pauson-Khand Reaction:** (Co)
- Dicobalt octacarbonyl, the predominant cobalt carbonyl complex, has found wide applications in organic synthesis. It is prepared by the high pressure carbonylation of cobalt(II) salts. In solution it exists in equilibrium between two forms, both of which obey to the 18 electron rule.

$Co_2(CO)_8$ (1 equiv.)

solvent / heat

terminal alkyne gave better yield size $R^L > R^S$

strained cyclic > terminal > disubstituted >> trisubstituted, electron poor alkene

alkene regioselectivity hard to predict unless intramolecular

- The reaction is completely regioselective with respect to the alkyne. The larger substituents always occupy the position adjacent to the carbonyl group in the product. However, the use of an unsymmetrical alkene usually leads to a mixture of regioisomers.

Now we will discuss Pauson Khand reaction this is very important reaction, dicobalt octa carbonyl the predominant cobalt carbonyl complex has found wide applications in organic synthesis. It is prepared by the high pressure carbonylation of cobalt2 salts. In solution it exists in equilibrium between two forms both of which obey to the 18 electron rule.

So this is dicobalt octa carbonyl, and this can stay like this so, here all connected to cobalt two carbon monoxide are in the bridged. And this is the Pauson Khand reaction. Here an alkyne will be used RL so this can be di substituted RL, RL means this is the larger side because we will see the regeoselectivity is an issue so, terminal alkyne gets better yield size RL greater than Rs now, an olefin strained cyclic greater than terminal greater than de substituted, greater than tri substituted then electron poor alkene.

So electron poor alkenes are not very good substituted for this and Co2CO8 1 equivalent that is this solvent heat you get this. So what is this, this is cyclo pentenone so you can see this is 3 components, this carbonyl group comes from carbon monoxide this is the triple bond part and this is the olefin part. So triple bond becomes double bond, olefin becomes carbon carbon and carbon monoxide inserts to give this carbonyl. Alkene regeoselectivity hard to predict unless intramolecular.

The reaction is completely regeoselective with respect to the alkyne the larger substituted always occupy the position adjacent to the carbonyl group in the product. However, the use of an un symmetrical alkyne usually leads to mixture of regeo isomers.

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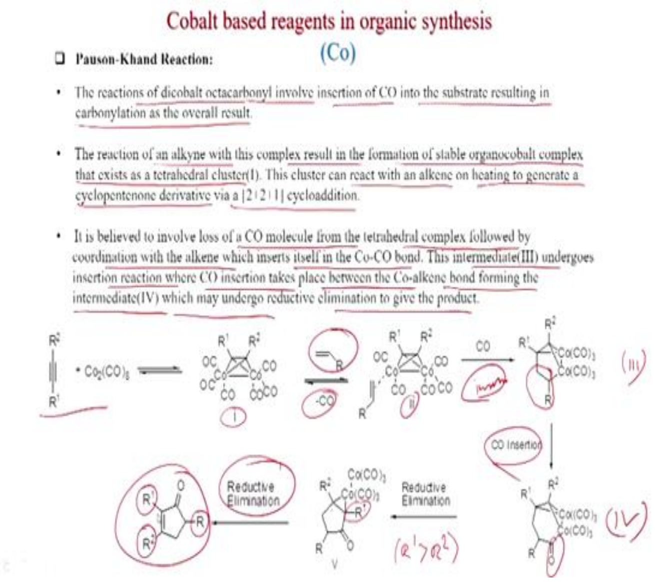

Cobalt based reagents in organic synthesis

(Co)

❑ **Pauson-Khand Reaction:**

- The reactions of dicobalt octacarbonyl involve insertion of CO into the substrate resulting in carbonylation as the overall result.
- The reaction of an alkyne with this complex result in the formation of stable organocobalt complex that exists as a tetrahedral cluster(I). This cluster can react with an alkene on heating to generate a cyclopentenone derivative via a [2+2+1] cycloaddition.
- It is believed to involve loss of a CO molecule from the tetrahedral complex followed by coordination with the alkene which inserts itself in the Co-CO bond. This intermediate(III) undergoes insertion reaction where CO insertion takes place between the Co-alkene bond forming the intermediate(IV) which may undergo reductive elimination to give the product.

So now, we will see the mechanism so the reaction of dicobalt octa carbonyl involved, insertion of carbon monoxide into the substituted resulting in carbonylation as the overall result. And similar way the reaction of an alkyne with this complex result in the formation of stable organo cobalt complex that exist at tetrahedral cluster 1.

So this is the reaction and tetrahedral cluster 1 is formed so this is very important, a alkyne reacts with dicobalt octa carbonyl to generate this. Here you can see that is the both pi bonds has been used to react with cobalt. And with this is formed tetrahedral cluster.

This cluster can react with an alkyne on heating to generate a cyclo pentenone derivative where 2 plus 2 plus 1 cyclo addition.

So this is the detailed mechanism now an olefin will comes after elimination of 1 carbon monoxide the coordination will happen so intermediate 2 is formed, so it is believed that the loss of carbon monoxide molecule from the tetrahedral complex followed by coordinates with the alkene which insert itself in the CO bond. So now the insertion will happen.

So this is the insertion, this double bond inserts into cobalt carbon monoxide bond, this intermediate 3 now this is the intermediate 3 undergoes insertion reaction where carbon monoxide insertion take place between the CO alkene bond forming the intermediate 4. So this is the intermediate 4, is formed and which may undergo reductive elimination to give the product.

So, here you can see this bond has broken and this alkene gets insert and now, carbon monoxide gets insert into this bond so here carbon monoxide comes and this is the olefin part of course.

And now CO inserts here so you get this and after reductive elimination you get this 5-member ring is formed and here this R2 R1 stays like so here, R1 is bigger in size than R2. So then you can get this selectivity R1 will be close to the carbonyl and after reductive elimination you get this cyclo pentenone. So this is R1, R2 and this is the olefin R.

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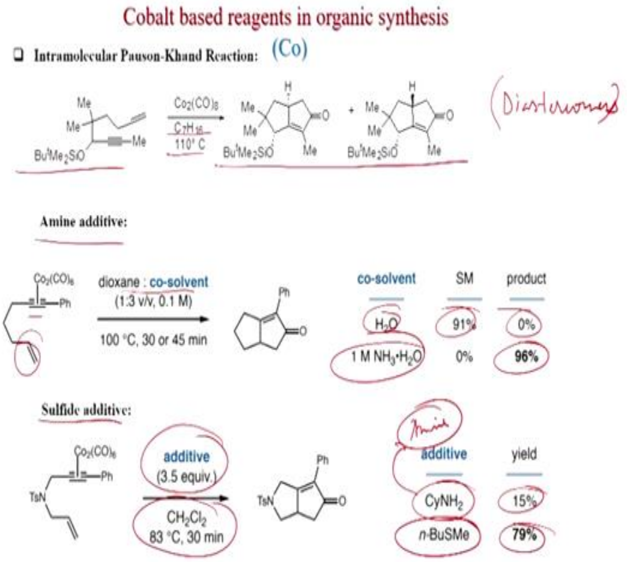
Cobalt based reagents in organic synthesis

❑ **Intramolecular Pauson-Khand Reaction:** (Co)

Amine additive:

co-solvent	SM	product
H_2O	91%	0%
1 M $NH_3 \cdot H_2O$	0%	**96%**

Sulfide additive:

additive	yield
$CyNH_2$	15%
n-BuSMe	**79%**

Now we will discuss some intramolecular Pauson Khand reactions, so here the double bond and triple are in the same molecule with Co2CO8 C7 H16 100 degree centigrade you get the two products so both are, these are diastomer, diastomer are formed and this intramolecular reaction, different additive has been used like amino additive here this one, the triple bond double bond is there, with amine additive like ammonia.

So if you see the solvent co-solvent diocesan what are you get only 0 percent yield so 91 percent starting material for this particular reaction now, if you react with 1 molar ammonia what are you get 96 percent yield, so base is effective.

Sulfide additive can also be used like for this reaction if you see additive 3.5 equivalent dichloro methane 83 degree centigrade 30 minutes with additive like cyclohexyle amine you get 15 percent this is the amine, amine additive that is not good but if you is sulfide like n butyl methyl sulfide you get 79 percent yield. So amine and sulfide can increase the yield.

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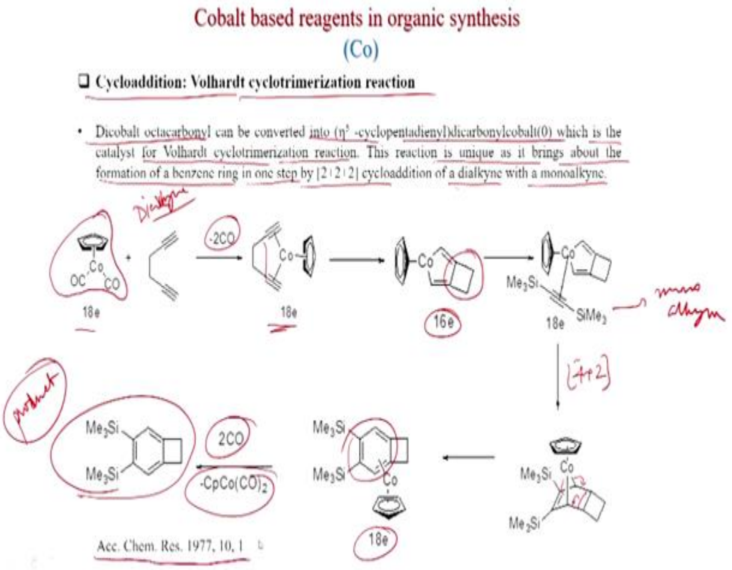

Cobalt based reagents in organic synthesis

(Co)

☐ **Cycloaddition: Volhardt cyclotrimerization reaction**

- Dicobalt octacarbonyl can be converted into (η^5 -cyclopentadienyl)dicarbonylcobalt(0) which is the catalyst for Volhardt cyclotrimerization reaction. This reaction is unique as it brings about the formation of a benzene ring in one step by [2+2+2] cycloaddition of a dialkyne with a monoalkyne.

Acc. Chem. Res. 1977, 10, 1

Now, we will discuss cyclo addition reaction that is the Volhardt cyclo trimerization reaction so, dicobalt octa carbonyl that we have seen can be converted to eta 5 cyclopenta dienyl dicarbonyl cobalt 0, which is the catalyzed for Volhardt cyclo trimerisation reaction this reaction is unique as it brings about 3 formation of a benzene ring in one step by 2plus, 2plus, 2 cyclo addition of a dialkyne with a mono alkyne. So this is the dialkyne, and this is the dicobalt this is the monomer dicobalt octa carbonyl 18 electron now, after two carbon monoxide elimination you get this coordination happens.

And now, this bond is formed so this you see 1, 2, 3 so this bond is formed here, so the cyclobutane ring is formed and here also cyclo pentadienyl cobalt, cobalt is connected with cyclopenta diene this is 16 electron system again another alkyne will come, so this is monoalkyne also again 18 electrons it will get cobalt.

And now, the 4 plus 2 reactions will happen here a double bond will be there, so after that you get this 4 plus 2 there is a bridged cobalt. And this bridged cobalt then eliminates like this and again it coordinates with the pi system so here the aromatization happens actually. If you see this is 6 membered aromatic compound and with cobalt it is connected cobalt is 18 electrons and after that cobalt elimination 2 carbon monoxide and minus Cp CoCO2 you get this product.

So this is very important a dialkyne and mono alkyne can give this bicyclic product in good yield. This was reviewed in account of chemical research 1977.

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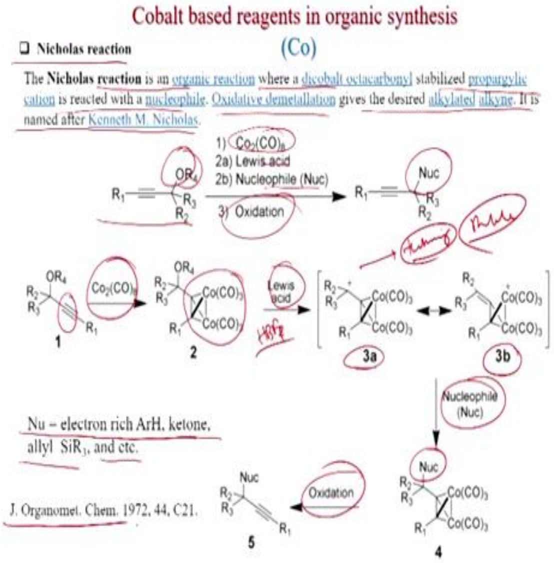

Cobalt based reagents in organic synthesis

(Co)

☐ **Nicholas reaction**

The **Nicholas reaction** is an organic reaction where a dicobalt octacarbonyl stabilized propargylic cation is reacted with a nucleophile. Oxidative demetallation gives the desired alkylated alkyne. It is named after Kenneth M. Nicholas.

Nu – electron rich ArH, ketone, allyl SiR_3, and etc.

J. Organomet. Chem. 1972, 44, C21.

Now we will discuss Nicholas reaction so Nicholas reaction is an organic reaction where a dicobalt octa carbonyl stabilized propargylic cation is reacted with a nucleophile oxidative de metalation gives the desired alkylated alkyne it is named after Kenneth M Nicholas.

So this is the substrate here, if you see this is propargylic system and of course this is a quaternary center and with Co2CO8 Lewis acid nucleophile oxidation lasted then you get this, OR4 group is replaced by nucleophile what could be the mechanism so as we have seen the alkyne will coordinate with this, so alkyne protection happens and now with Lewis acid or strong acid like HBF4 you can generate this carbo cation because, this carbocation is tertiary carbocation so it is stable also it can isomerize like this see this isomerization that is the resonance form is here and then a nucleophile will attack here to get this so nucleophile will attack to the carbocation and after oxidation you can remove this cobalt system.

So this is cobalt here acts as a protecting group and you can functionalize a propargylic system. Nucleophile can be electron rich ArH ketone allyl Si R3 etc. and this was published in general oregano metallic chemistry 1972.

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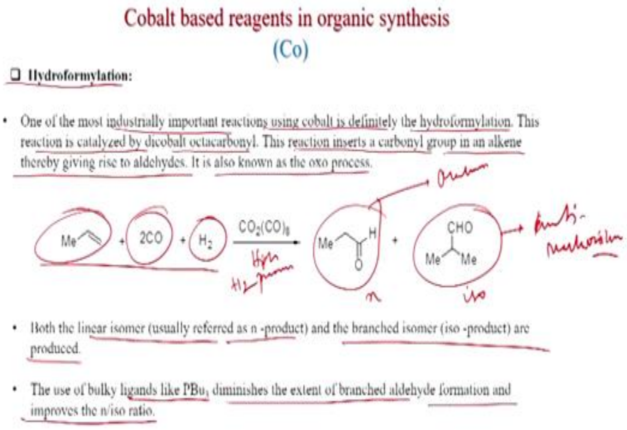

Cobalt based reagents in organic synthesis

(Co)

❑ **Hydroformylation:**

- One of the most industrially important reactions using cobalt is definitely the hydroformylation. This reaction is catalyzed by dicobalt octacarbonyl. This reaction inserts a carbonyl group in an alkene thereby giving rise to aldehydes. It is also known as the oxo process.

- Both the linear isomer (usually referred as n -product) and the branched isomer (iso -product) are produced.
- The use of bulky ligands like PBu_3 diminishes the extent of branched aldehyde formation and improves the n/iso ratio.

Last reaction we will discuss hydro formylation so one of the most industrial important reaction using cobalt is definitely the hydro formylation this reaction it catalyzed by dicobalt octa carbonyl this reaction inserts a carbonyl group in an alkene thereby giving rise to aldehydes it is also known as the oxo process.

So this is the reaction so high hydrogen pressure of course you have to maintain high hydrogen pressure. This is propene 2 carbon monoxide H2O gives this propnal and also this. this is the Markovnikov product Markovnikov this is anti Markovnikov product. This is n and this is iso. So both the liner isomer usually refers to as n product and the branch isomer isoproduct are produced the use of bulky ligands like tri butyl phosphine diminishes the extent of branched aldehyde formation. Improves the n, iso ratio.

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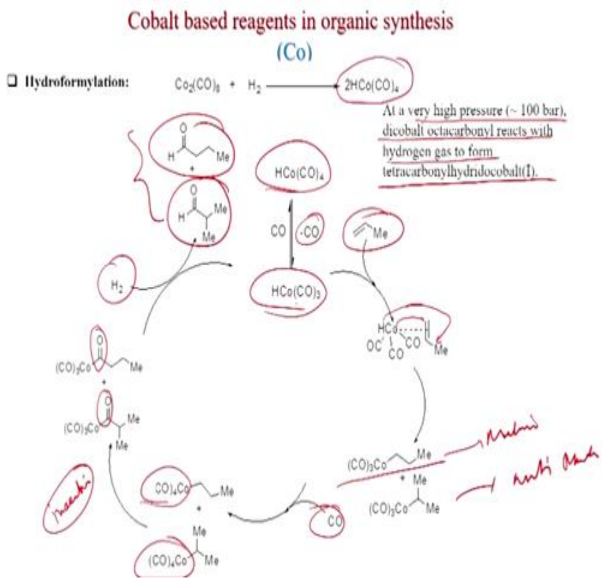

Cobalt based reagents in organic synthesis

(Co)

❑ Hydroformylation: $Co_2(CO)_8 + H_2 \longrightarrow 2HCo(CO)_4$

At a very high pressure (~ 100 bar), dicobalt octacarbonyl reacts with hydrogen gas to form tetracarbonylhydridocobalt(I).

So this is the mechanism so at a very high pressure like 100 dicobalt octa carbonyl reacts with hydrogen gas to form tetra carbonyl hydrido cobalt. So this is the tetra carbonyl hydrido cobalt is formed, this is the active catalyzed so HCOCO4 after carbon monoxide elimination you get this, and then the alkene so here propene, coordinates with the cobalt and you get this so, what happens here, H also reacts and CO also reacts so if CO reacts here, and hydrogen reacts here that is the Markovnikov so this is the Markovnikov, and this is anti Markovnikov.

Again one carbon monoxide comes so the cobalt coordinates with 4 carbon monoxide and this formed and now, the insertion will happen so, insertion so one carbon monoxide inserts into this C cobalt bond so you see this carbonyl group inserts and H2O comes it generates this one is, hydro tricabonyl cobalt and you get this product. So these two products are formed.

So in today’s lecture first we have discussed iron based reagents, so in iron based reagent we have discussed Colmans reagent also we have seen the sodium hydroxide treatment and then the functionalization binary carbonyl iron complexes we have seen alkene iron complexes we have seen then we have discussed cyclo pentadiene iron carbonyl this we have seen. Phenyl cubs alkynylation we have discussed because ferrichloride is a good Lewis acid then we have seen the epoxidation reaction then we have discussed Kharasch reaction we have seen.

Amino chlorination reaction we have seen, and we have seen also different coupling reactions like Kumada coupling Nigishi coupling this reaction can be perform also with iron. And then we have discussed Cobalt chemistry in the cobalt chemistry we have first discussed homo coupling reactions we have discussed, Csp2 sp2 cross coupling reactions Sp2 Sp3 cross coupling reactions, alkynylation reactions, Csp2 Csp3 cross coupling reactions we have seen, different alkyl halide like primary secondary tertiary can be used.

Then we have seen the acylation then we have seen the cobalt catalyzed heck type reactions then we have seen the Pauson Khand reactions this is very important reaction a alkyne a alkene and cobalt carbonyl, ultimately we will gives cyclo pentenone compound so this is very useful reaction then we have seen the Nicolas reaction we have seen.

And cyclo addition reaction also we have seen. And lastly we have seen hydroformylation and aldehydes that is the linier aldehyde also Branched aldehyde can be obtained. And if you use tri butyl phosphine then the normal isomer can be increased, Thank You.