Reagents in Organic Synthesis
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Lecture 13
Mg and Na Based Reagents in Organic Synthesis

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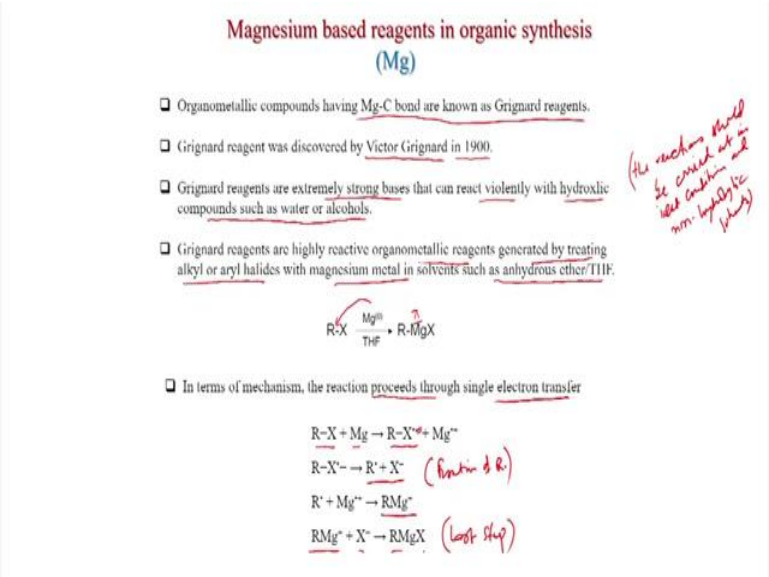

Welcome again today, we will discuss magnesium and sodium based reagents. So magnesium based reagents in organic synthesis, organometallic compound having magnesium carbon bonds are known as Grignard reagents. These are very well-known reagents. Grignard reagents was first discovered by Victor Grignard that is why it is called Grignard reagent and in 1900 it was discovered. Grignard reagents are the extremely strong bases that can react violently with hydroxlic compounds such as water or alcohol.

So that means the reactions, reactions should be carried out in inert conditions, and non hydroxylic solvents. So this is a very important. Grignard reagents are highly reactive organometallic reagents are generated by treating alkyl or aryl halides with magnesium metal in solvents such as anhydrous ethers and THF. This is the preparation, RX magnesium over THF, RMgX, so what happens the magnesium get inserted into this RX bond and magnesium 0 becomes magnesinum 2 here.

In terms of mechanism the reaction passes through single electron transfer. So, first what happens, alkene or aryl halide magnesium then RX dot minus so this minus is there and Mg dot plus, so this is the first happens, then magnesium became magnesium dot plus and now

this RX dot minus cleaves so RX dot is formed, so formation of formation of R dot here, so this is vital here. Then this R dot reacts with this magnesium radical magnesium dot plus cation radical to generate this RMg plus and now this is the last step, this is the electrophilic species, this is the nucleophilic, so just the addition reaction happens and RMgX is formed.

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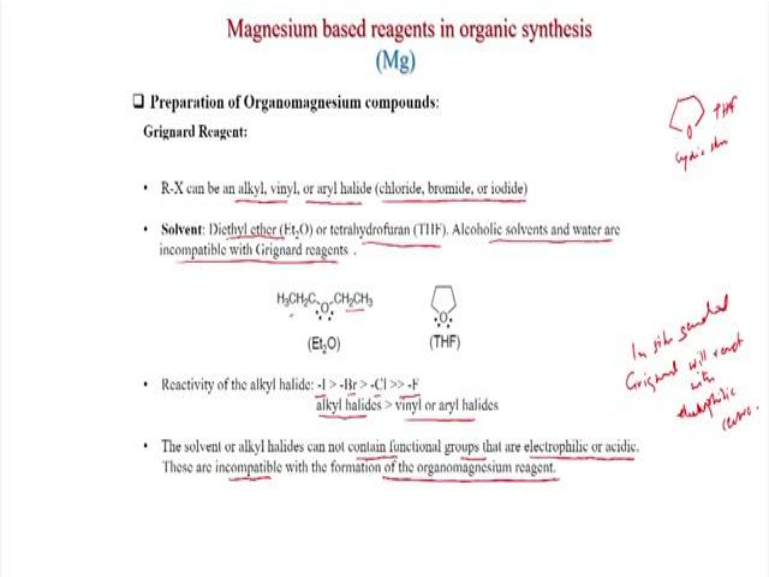

Preparation of organomagnesium compounds Grignard reagents, so we had already discussed, now RX can be alkyl, vinyl or aryl halide (chloride, bromide, iodide). Solvent diethyl ether, this is the ether solvent or tetrahydrofuran. So this is tetrahydrofuran, this is cyclic ether. Alcoholic solvents and water are incompatible with Grignard reagent. This is structure of diethyl ether to ethyl groups is there and this is cyclic ether tetrahydrofuran.

Reactivity of alkyl halide, iodide is most reactive than bromide, then chloride, chloride is much more reactive than fluoride, followed by alkyl halides, then vinyl or aryl halides. So, vinyl or aryl halides the reactivity will be less. The solvent or alkyl halides can contain functional groups that are electrophilic or acidic. So, this is important if you have electrophilic centre then Grignard will react with electrophilic centre, so in situ generated Grignard will react with electrophilic centre. So no electrophilic centre will be present in the substrate. These are incompatible with the formation of the organomagnesium reagent.

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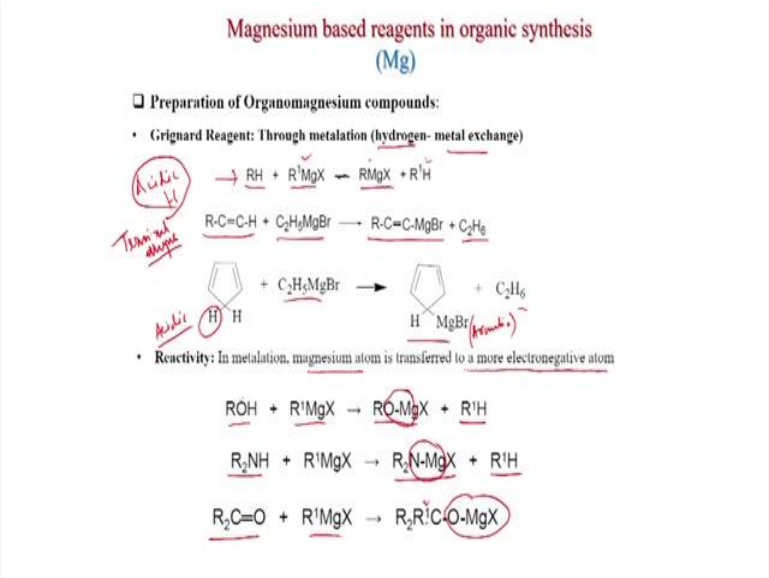

Preparation Grignard reagent, some more preparation through metalation, hydrogen metal exchange, so one Grignard you can convert to another Grignard when you treat with RH. So, this is the hydrogen metal exchange. This hydrogen is replaced by MgX. So, RH becomes RMgX, R1MgX becoming R^1H and this generally, this RH should be acidic, so acidic hydrogen should be there.

Then the reaction is more facile. Like this one, this alkyne, terminal alkynes, so this is terminal alkyne, so terminal alkyne when reacts with ethyl magnesium bromide you get this alkynyl magnesium bromide plus ethane, also cyclopentadiene we know this is acidic, acidic because this you know that cyclopentadienyl anion is aromatic in nature. So, this is very acidic in nature because this is aromatic.

So when you treat with ethyl magnesium bromide you get this cyclopentadienyl magnesium bromide plus ethane, reactivity in metalation, magnesium (ion) atom is transferred to a more electronegative atom. Like ROH, R1MgX, the oxygen is more electronegative here and the magnesium is going to there, so RO-MgX plus R1H is formed.

Similarly, when it reacts with amine the nitrogen makes up bond with magnesium. So these bonds are important, but these are more stable are. R2NH plus R1MgX you get this MgX plus R1H. Similarly, with Ketone R1MgX, so this this bond is forming also that the Grignard addition, this R1C is also important but what we want to show that the magnesium is going to

transfer to the more electronegative atom. So here the oxygen is the more electronegative and magnesium is transferred to there.

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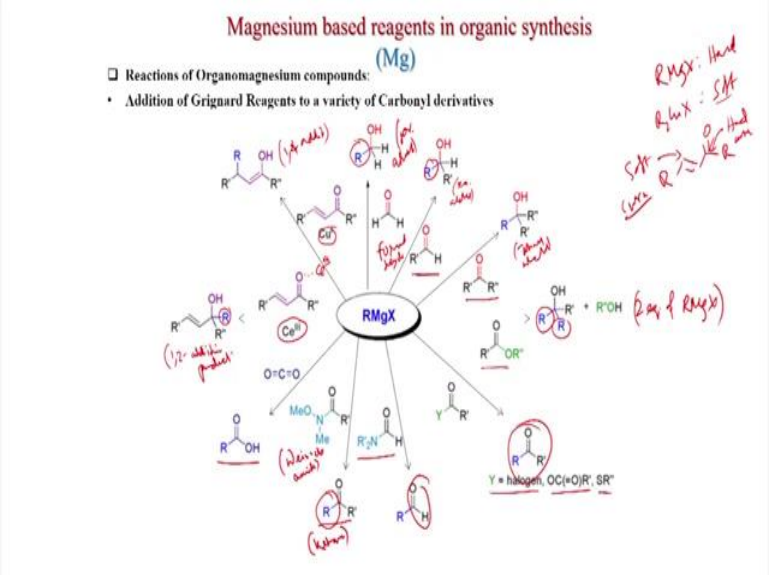

Addition of Grignard reagents to a variety of carbonyl derivative, this is the major reaction that Grignard reagents perform. So a variety of carbonyl compounds can be employed in the reaction with Grignard reagents, like if you react with formaldehyde, formaldehyde, then you get the primary alcohol. So, this is very important, with formaldehyde you get the primary alcohol alternatively other aldehydes you get a secondary alcohol. So these are coming from the Grignard reagents.

Also, with Ketone you get a tertiary alcohol so this is the preparation of different alcohol from Grignard reagents, these are very useful reaction that primary alcohol can be obtained from reaction with formaldehyde, other aldehydes can give you a secondary alcohol and Ketone will give us tertiary alcohol. Similarly, ester also give tertiary alcohol in situ Ketone is formed first then the Ketone reacts further to generate tertiary alcohol and two R groups come from the Grignard.

So two equivalent of Grignard is required. Surely, if Y is other leaving group then if you do the slow addition the Ketone isolation is possible but difficult like Y is equal to halogen, then OCOR which is anhydride, then SR, also formamide can give you the aldehyde, that is also useful method to get a aldehyde and generally this also has to be slow addition so aldehyde will not further react with Grignard and if you have Weinreb amide, this is also very useful reaction.

If you have Weinreb amide then you can stop ketone, this mechanism already we discussed. So ketone formation is very useful method utilizing when Weinreb amide and Grignard, these are comes from the Grignard reagents. Also with carbon dioxide Grignard reagent can give the carboxylic acid and cerium 3 when it is added, then generally, it gives the 1, 2 addition with alpha beta unsaturated ketone but when you add the cerium 3 then specifically the 1-2 addition products have formation happens.

So 1-2 addition product, this because this is getting activated by cerium 3 and selectively RMgX as to the carbonyl group and you get an allylic tertiary alcohol. Alternatively, if you have the copper 1 then you get the 1,4 addition product, 1, 4 addition, why, because this is the Grignard reagent is a hard reagent, alternatively R_2CuX, it is a soft reagent and what happens this one, this is the hard centre, so this is hard center, hard center and this is the soft center.

So hard nucleophile will add to the hard electrophilic centers similarly, soft electrophile will add to the soft nucleophile center, so this is the double bond that is why the 1, 4 addition reaction happens.

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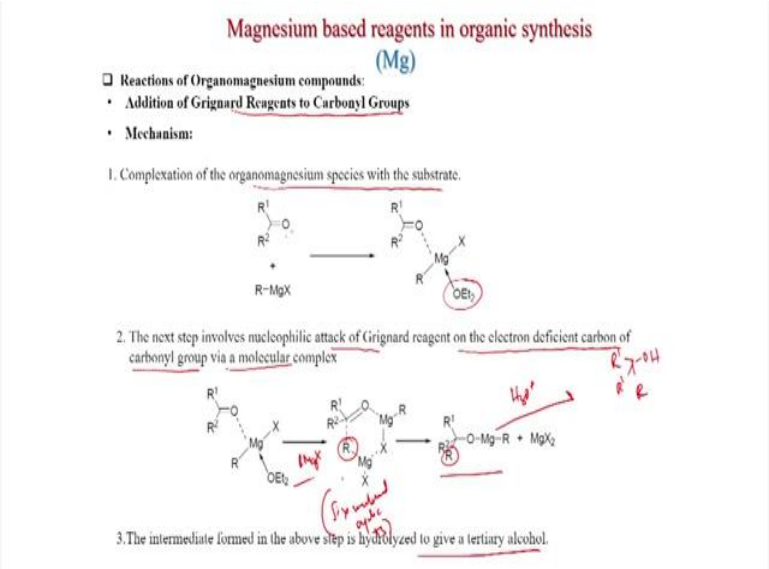

So, now more details, so we will discuss so first we will discuss Grignard reagent to carbonyl groups complexation of the ogranomagnesium species with the substrate. What is the mechanism? So, first the complexation happens. So here the carbonyl binds to the magnesium because this is the more electronegative that we discuss, that will come to with the magnesium and now this solvent is there, this can stabilize this transition state. And now

the next step involves nucleophilic attack of Grignard reagent on the electron deficient carbon of the carbonyl group by molecular complex.

So, here what happens this is the this one, now here another Grignard comes here, RMgX so 6 membered cyclic transition state is from, you can see here two magnesium are there that means two Grignard are there. So first this oxygen carbonyl oxygen binds to the magnesium or getting activated with magnesium, at this X again binds with another molecule of Grignard and finally, this R will be transferred to the carbonyl group.

This is the R, this is transferred, and this alkoxy compound is formed and now if you treat with acidic workup, then you get the tertiary alcohol. So the intermediate form in the above state is hydrolyzed to give a tertiary alcohol. So this is an useful method to generate a tertiary alcohol from carbonyl. That is the ketones here and you get it as a tertiary alcohol and this is important the 6 membered cyclic transition state is formed where two Grignard reagents.

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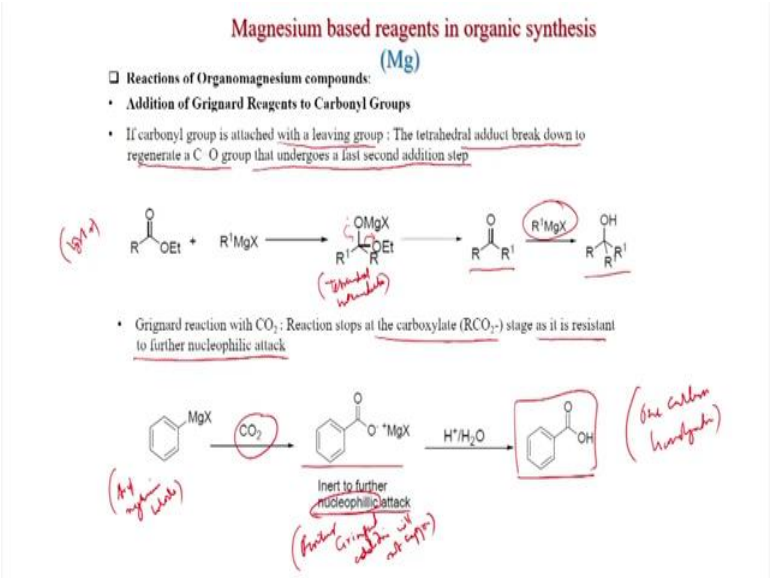

If carbonyl group is attached with a leaving group, the tetrahedral adduct break down to generate a C-O group that undergoes a fast second addition step. So, here if ester is there and now these Grignard reagents will add so this is the tetrahedral intermediate. So after the tetrahedral intermediate, this can collapse to a carbonyl compound, so this ethoxy group will eliminate here and you get this a carbonyl.

And this carbonyl group which is generated in situ can react further with a more equivalent of Grignard to generate tertiary alcohol. Grignard reaction with carbon dioxide, reaction stops at

the carboxylate stage as it is resistant to further nucleophilic attack. So this is the reaction here, this is aryl magnesium halide. Now carbon dioxide is added to this and this intermediate is formed carboxylate.

This is inert to the further nucleophilic so here further the Grignard reaction, so the further nucleophilic attack and so further Grignard addition will not happen and after aqueous workup you will get carboxylic acid. So this is very useful method to generate a carboxylic acid because the one carbon homologation, one carbon homologation, so this Grignard reagent reacts with carbon dioxide then this carboxylic acid can be generated after workup. So, this is very useful method to generate a carboxylic acid form aryl or alkyl halides.

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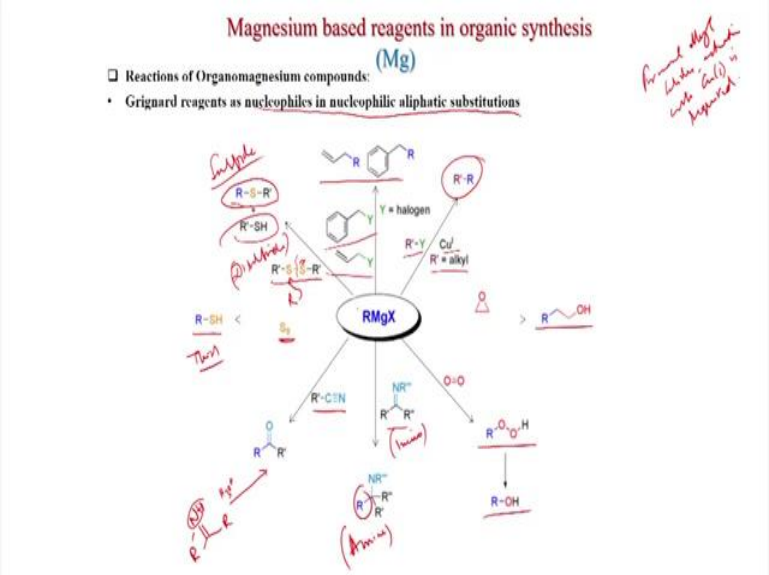

Grignard reagent in nucleophilic aliphatic substitution reactions also, it is very much used like here, if it is activated alkyl halide like benzyl bromide or benzyl chloride then allyl chloride or allyl bromide, then you can get this product. So, normal substitution reaction is possible with activated halides and now, if there is normal alkyl halide R' is alkyl then you need to add copper to activate this alkyl halide and then only the Grignard reaction will happen.

So for normal alkyl halide, for normal alkyl halides activation with copper (I) is required but if it is, if it is activated, then you do not need the copper(I) activation. Also epoxide can be reacted with Grignard to generate this primary alcohol, also oxygen this is also another

reaction, with oxygen you can get the hydro peroxide, later we will see that you can generate the alcohol also and the hydroperoxide can be used to convert to alcohol.

Also it can do reaction with the imines to generate amines, so this is very useful reactions imine to amine and with one alkyl or aryl group comes from the Grignard reagent. And with nitriles you can generate the carbonyl compounds. So, what happens, this is intermediate form here, so one intermediate forms here, this one might be and this after hydrolysis, it generates the carbonyl compound because this is unstable without here no alkyl group is there then it is unstable, simply imine then you get the carbonyl compound.

With sulphur S8 you get the thiol, and when it is reacted with disulphide, it generates the sulphide, sulphide as well as the thiol, so when it reacts so then what happens, this bond is getting breakage. So this bond is getting breakage and R, so here R comes, so R reacts here and S-S bond is cleaved. So, you get the sulphide from disulphide.

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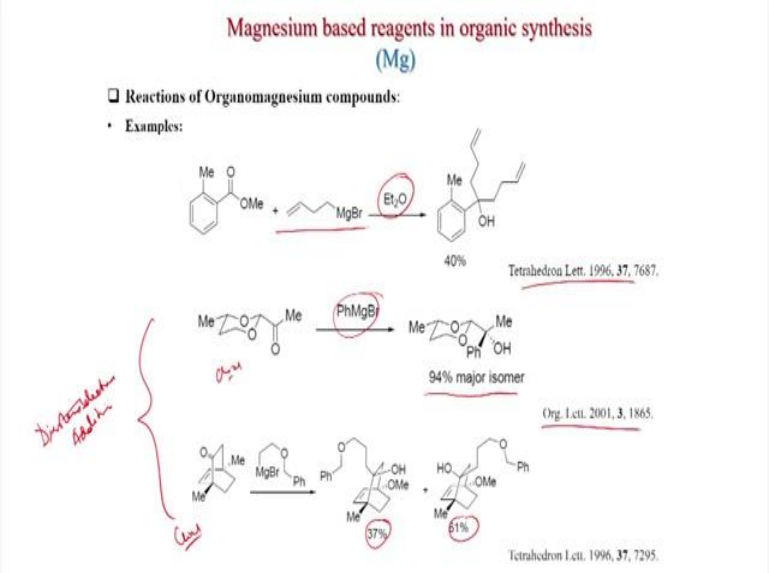

Some more examples of the addition of Grignard reagents like here, if you have ester group, the aromatic ester and this is Grignard reagent with double bond, so double bond is not a problem, and you get this tertiary alcohol, research published in Tetrahedron Letters, ether is a solvent. Also this is a chiral ketone and if you had phenyl magnesium bromide then you get the product and this is 94 percent major isomer, so this stereochemistry is important. Higher the phenyl as from the top face, because of this geometry phenyl is coming from the top face and this product is formed. This was published in Org letters.

Also, this is a chiral, so all these are distereoselective addition. So here also this chiral and what happens, the when this addition happens, then it has been found that this side addition that is the double bonded side only 37 percent, on the other hand addition taking place from this side is 61 percent. So this is the Grignard reagent, you can see here, there is ether motif is present, but in Grignard condition the ether is stable and this was published in Tetrahedron Letters.

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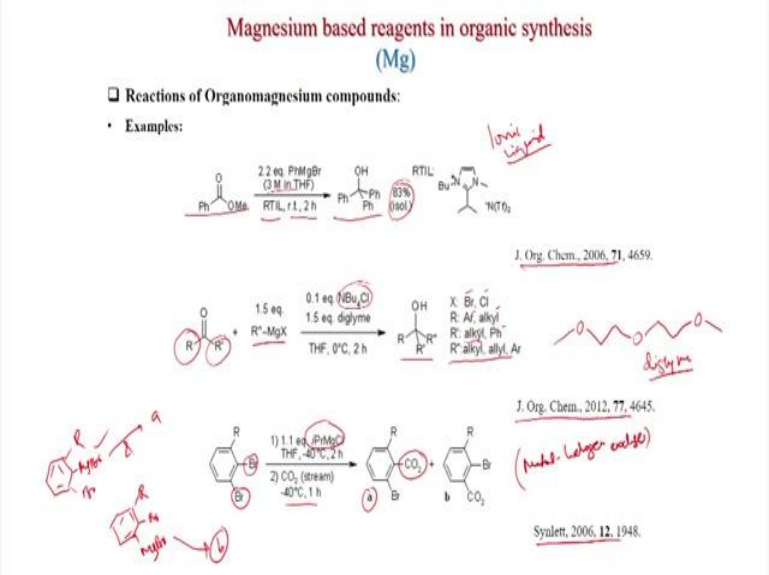

Some more examples here the ester is there and 2.2 equivalent phenyl magnesium bromide this is commercially available 3 molar in THF and this is RT ionic liquid that is the room temperature ionic liquid. So this is the ionic liquid and in this solvents the reaction is quite fast, because there is a charge, so ionic liquid means the charge is there, positive or negative, so the reaction will be faster because it would stabilize the Grignard reagent and you get the tertiary alcohol in 83 percent isolated yield, it was published in JOC.

Also not only ionic liquid you can use other ammonium salt like tetrabutyl ammonium chloride and with 1.5 equivalent diglyme and THF is the solvent, so what is the structure of diglyme, so this is diglyme and now this addition reaction will happen and you can get this product in very good yield. So, possibility is that X can be bromide chloride, R can be aryl alkyl, so this R can be aryl alkyl, R' can be alkyl phenyl, this can be alkyl phenyl, and R double dash can be alkyl, allyl aryl, so this can be alkyl allyl aryl.

So this scope is very broad and define Grignard reagent and ketones can be implied and very good yields are obtained. This has published in JOC. Also if you have a two bromide groups

in the aromatic system, then also you can get the product and here the metal halogen exchange have been performed.

So metal halogen exchange, because this bromide first reacted with this Grignard and you get this, MgBr, RBr and you can get this also or MgCl here. Whatever you get this one, the Grignard reagent and then with carbon dioxide you get this carboxylic group comes, this comes from this reagent, this gives to A and this gives to B, so you get two actually carboxylic acids from dihalide, this was published in Synlett.

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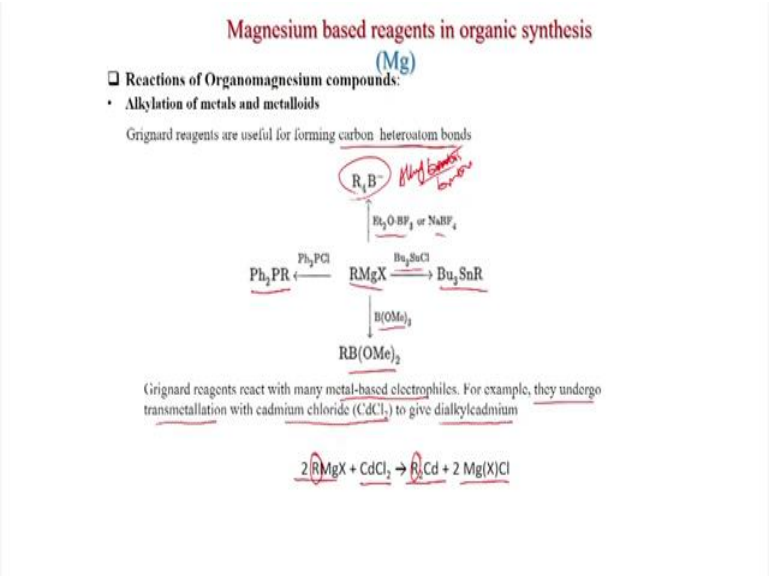

Grignard reagents useful for forming carbon heteroatom bonds so this is important. Like here RMgX is treated with tributyltin chloride and you get this stannane, also which BF3 etherate or sodium BA4 you get this boronate, so this is alkyl boronate, or alkyl borates, these are alkyl borates. And now diphenylphosphine chloride you get this PH2PR phosphine compounds, also $BOMe_3$ you get the dimethyl boronate.

And Grignard reagent reacts with many metal based neucleophiles, for examples, they undergo transmetallation with cadmium chloride to give dialkylcadmium, so other metal means electrophiles also can be reacted, like here 2RMgX with cadmium chloride you get the R2 cadmium plus 2MgX chloride. So, this is very important the R this RMgX is going to here with the cadmium to generate the dialkylcadmium.

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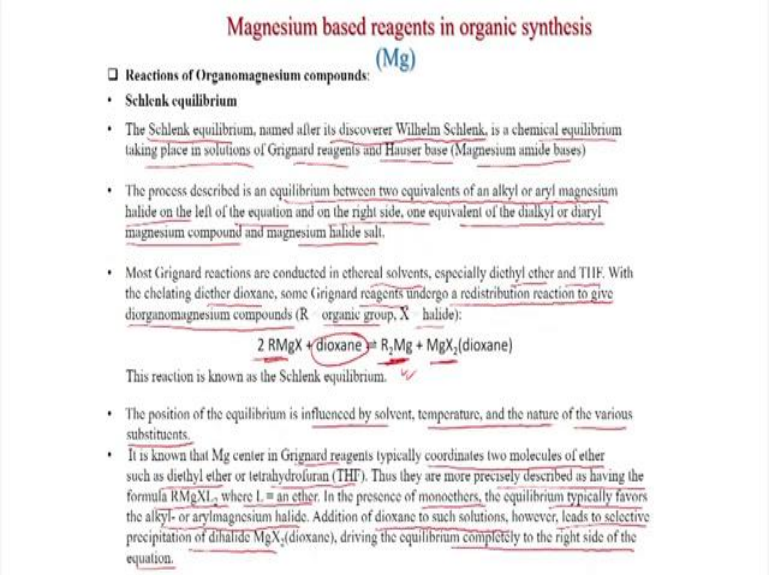

Magnesium based reagents in organic synthesis

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❑ **Reactions of Organomagnesium compounds:**

- **Schlenk equilibrium**
- The Schlenk equilibrium, named after its discoverer Wilhelm Schlenk, is a chemical equilibrium taking place in solutions of Grignard reagents and Hauser base (Magnesium amide bases)
- The process described is an equilibrium between two equivalents of an alkyl or aryl magnesium halide on the left of the equation and on the right side, one equivalent of the dialkyl or diaryl magnesium compound and magnesium halide salt.
- Most Grignard reactions are conducted in ethereal solvents, especially diethyl ether and THF. With the chelating diether dioxane, some Grignard reagents undergo a redistribution reaction to give diorganomagnesium compounds (R = organic group, X = halide):

$$2\ RMgX + dioxane \rightleftharpoons R_2Mg + MgX_2(dioxane)$$

This reaction is known as the Schlenk equilibrium.

- The position of the equilibrium is influenced by solvent, temperature, and the nature of the various substituents.
- It is known that Mg center in Grignard reagents typically coordinates two molecules of ether such as diethyl ether or tetrahydrofuran (THF). Thus they are more precisely described as having the formula $RMgXL_2$, where L = an ether. In the presence of monoethers, the equilibrium typically favors the alkyl- or arylmagnesium halide. Addition of dioxane to such solutions, however, leads to selective precipitation of dihalide MgX_2(dioxane), driving the equilibrium completely to the right side of the equation.

Schlenk equilibrium, now we will discuss Schlenk equilibrium. So, Schlenk equilibrium named after its discoverer William Schlenk is a chemical equilibrium taking place in solution of Grignard reagents and Hauser base (magnesium amide base), so in other Hauser bases also this equilibrium works. The process described is an equilibrium between two equivalents of an alkyl or aryl magnesium halide on the left of the equation, and on the right side one equivalent of the dialkyl or diaryl magnesium compound and magnesium halide salt.

So, this is the equation actually, 2RMgX it goes to R2Mg and MgX2. Most Grignard reactions are conducted in ethereal solvent, as diethyl ether and THF. With the chelating diether, dioxane, some Grignard reagents undergo a redistribution reaction to give diorganomagnesium compounds. R is equal to organic group and X is equal to halide. So, this reaction happens, this equilibrium goes to the right side when dioxane is used.

So with dioxane you get the R2Mg. This is equilibrium on the right side. This reaction is known as Schlenk equilibrium. The position of the equilibrium is influenced by solvent, temperature and the nature of the various substituents. Also it is known that magnesium centre at Grignard reagents typically coordinates two molecules of ether such as diethyl ether or tetrahydrofuran, this we have seen.

Thus they are more precisely described having the formula RMgXL2, where L is equal to an ether. In the presence of monoethers the equilibrium typically favours the alkyl or aryl magnesium halide. Now addition of dioxane which is diether, however, leads to selective

precipitation of dihalides MgX2 (dioxane) driving the equilibrium completely to the right side of the equation.

So if you use the monoether like diethyl ether or tetrahydrofuran then you get this RMgX, on the other hand when diethyl, like dioxane is used then you get the equation this is the R2Mg is the major so the equilibrium is on the right side.

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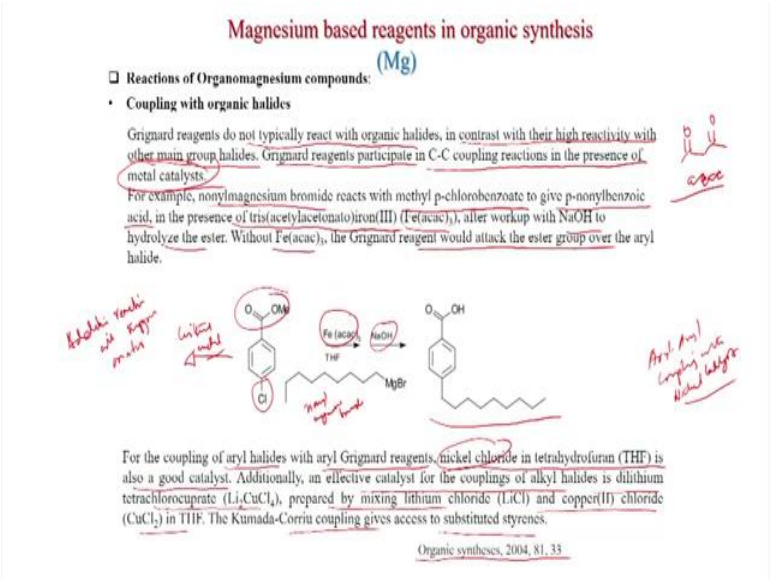

Coupling with organic halides also is possible with Grignard reagent, once we have seen the metal halogen exchange but also you can do some coupling reaction. Grignard reagents typically react with organic halides in contrast with their high reactivity with other main group halides. Grignard reagent participates in carbon carbon coupling reactions in the presence of metal catalyst, so this is important you have to use metal catalyst for the carbon carbon bond formation.

For example, nonylmagnesium bromide reacts with methyl parachlorobenzoate to give paranonylbenzoic acid in the presence of tris acetylacetonate iron 3, Fe(acac)3 so which is (ac ac) so this is acetylacetone. After workup with NaOH to hydrolyse the ester, without acetylacetonate iron the Grignard reagent would attack the ester group over the aryl halides.

So, this is important, you have two groups here, ester group and chloride. Now, if you put this nonyl, nonylmagnesium bromide, and with this one the group is activated and, now, the addition happens to this ones, so what happens iron insert in this one, carbon chlorine bond

and then activation happens and you get the cross coupling to get this product, interestingly here the after NaOH you get the hydrolysis from the ester to carboxylic acid.

Now, if you do not use metal, without metal, without metal the normal reaction will happen so addition reaction will happen on ester. So, if you do not use the metal then this group will not be activated, so only the normal addition product will happen, the tertiary alcohol. On the other hand if you use the iron, then this carbon chlorine bond is getting activated and now the Grignard addition will happen. So, first two metal oxidative additions, reaction will happen like Kumada coupling reaction and now you get this product.

Also the coupling of aryl halides with aryl Grignard reagent, nickel chloride in tetrahydrofuran is also a good catalyst, additionally an effective catalyst for the coupling of alkyl halidesis is di lithium tetrachlorocuprate prepared by mixing lithium chloride and copper chloride in THF. The Kumada-Corriu coupling gives access to substituted styrenes and this work has been reviewed in Organic Synthesis 2004.

So these are useful methods for the cross coupling reaction with Grignard reagent and these are called the Kumada coupling reactions. So here the alkyl halide is used with a alkyl magnesium bromide used the iron and with nickel you can get the aryl aryl coupling. So aryl aryl coupling with nickel catalyst. So aryl magnesium bromide and then aryl chloride then you get the nickel catalyst.

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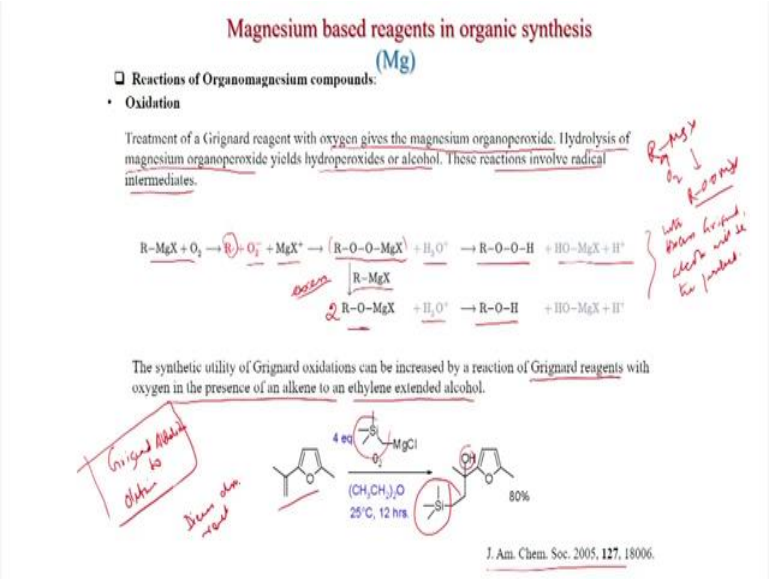

Oxidation reaction also possible, the treatment of a Grignard reagent with oxygen gives the magnesium organoperoxide. Hydrolysis of magnesium organoperoxide yields hydroperoxides or alcohol. These reactions involve radical internediates. So, here you can see that Grignard reacts with oxygen, now this R dot is formed and O2 minus MgX plus and now this R dot again reacts with oxygen and to generate this O-O MgX, so what actually happens, so here this oxygen, RMgX is there, so now oxygen is adding to this bond the RMgX bond.

So, that is why in presence of oxygen this RMgX got cleaved and it is going to be ROOMgX, so oxygen inserts in this RMgX more generate this. After hydrolysis you get the hydroperoxide plus this bi-products HOMgX plus H plus, alternatively this compound can react with excess Grignard. So, if you have excess Grignard then you can get, this will be two molecules ROMgX and which after hydrolysis generates the alcohol.

So excess Grignard, with excess Grignard alcohol will be the product otherwise the hydroperoxide. The synthetic utility of Grignard oxidation can be increased by a reaction of Grignard reagent with oxygen in the presence of an alkene to an ethylene extended alcohol. So this oxygen chemistry that this intermediate or this is forming can be useful, like Grignard excess is used so this intermediate will be formed, and this chemistry was nicely exploited in this Jacs's paper, where the olefin, this oxygen Grignard has been added to the olefin and you can get the alcohol here.

So, what happens the alkyl group from this Grignard adds to the olefin, this was the olefin and also the oxygen, OH group is added, and this is a very nice method to generate this Grignard addition to the olefins, Grignard addition to the olefin because olefins generally are unreactive to Grignard. So, this was the major discover that olefins can be also used in the Grignard chemistry if you use oxygen, also this olefin should be like styrene derivatives or vinylic, like diene also, dienes also react.

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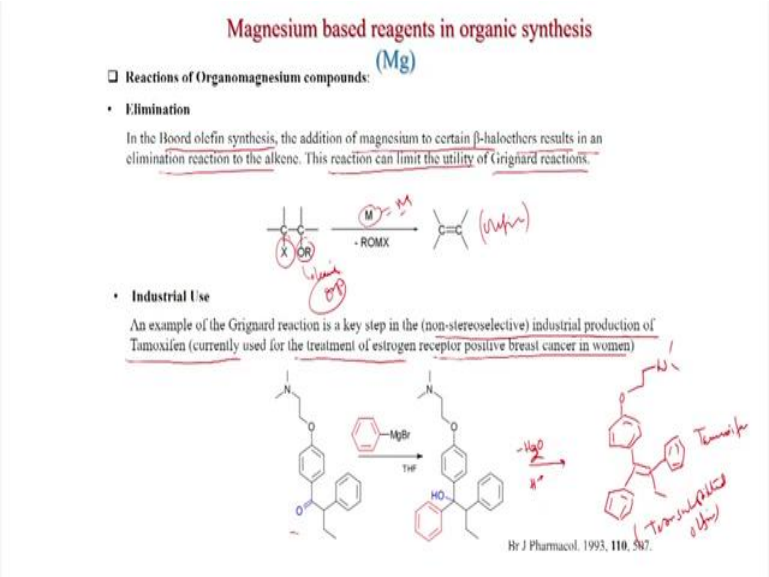

Elimination reaction also is possible with Grignard in the Boord olefin synthesis, the addition of magnesium to certain beta halo ethers results in an elimination reaction of the alkene. This reaction can limit the utility of Grignard reactions. So, suppose this is the leaving group, this is the leaving group and when the Grignard will form, so first Grignard will form here with metal that is the Grignard magnesium here and now this elimination will happen and you get the olefin.

Industrial use and example of the Grignard reaction is a key step in the non-stereoselective industrial production of tamoxifen currently used for the treatment of estrogen receptor positive breast cancer in women. So, this was the substrate here, this was the ketone and now this phenyl magnesium bromide which is commercially available is added to this and now this can be converted to tamoxifen. So, just H plus if you add, then water will eliminate minus H2O.

So, this is very important, this compound this is tamoxifen, this is tetra substituted olefin, so olefin is tetra substituted here and this olefin is called tamoxifen can be prepared easily if you add Grignard phenyl magnesium bromide to this ketone followed by acid treatment, the elimination of water.

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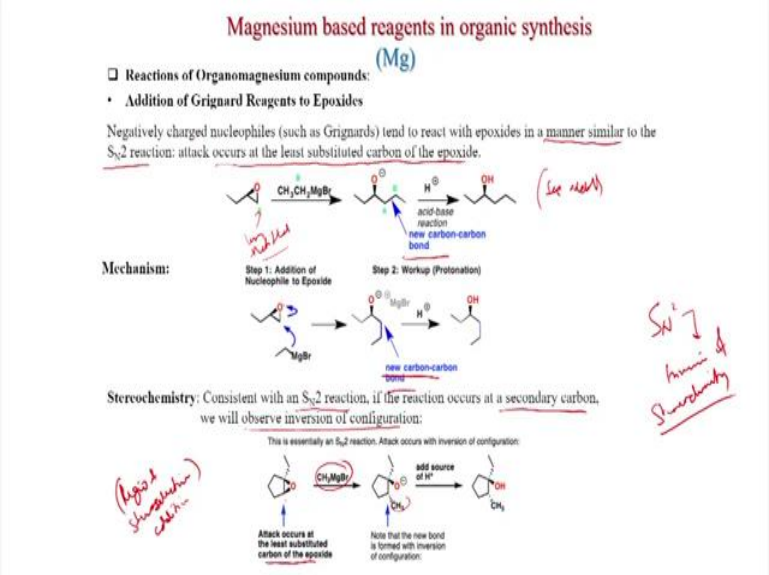

Addition of Grignard reagent to epoxides we already discussed this now more details, negatively charged nucleophile such as Grignard tend to react with epoxides. Epoxide in a manner similar to the SN2 reaction, attack occurs at the least substituted carbon of the epoxides. Like here this epoxide, this is the less substituted, this is more substituted, so this is less substituted and now if you use the ethyl magnesium bromide, this less substituted carbon the attack will, new carbon-carbon bond formation.

And now after acetate but you get the secondary alcohol, mechanism, the addition of nucleophile to epoxide, so this is the, also this oxygen can be activated if the magnesium and then this ethyl group will be added to this centre and now this is the new carbon-carbon bond formation happens and after acid workup you get the alcohol. Stereochemistry consistent with an SN2 reaction, so this reaction is a SN2 that you can prove also if the reaction occurs at a secondary carbon we will observe inversion of configuration.

So this is important because you know SN2 reaction, the inversion of stereochemistry. This is a property which is associated with SN2 mechanism. Suppose if you have this chiral epoxide, one cyclopentyl group is present and now this is the tetra substituted, this is tri substituted, so this is the least substituted carbon, this centre, now the methyl magnesium bromide will add in the down phase because the epoxide is on the up.

So this is up epoxide so the down face will happen methyl and you get this one so this is regio and stereoselective. So, regio and stereoselective addition, this carbon only reacts, so

this is regio and also stereoselective only attack takes place from the bottom face and you get the methyl group at the bottom and now the acidic workup will give you this alcohol.

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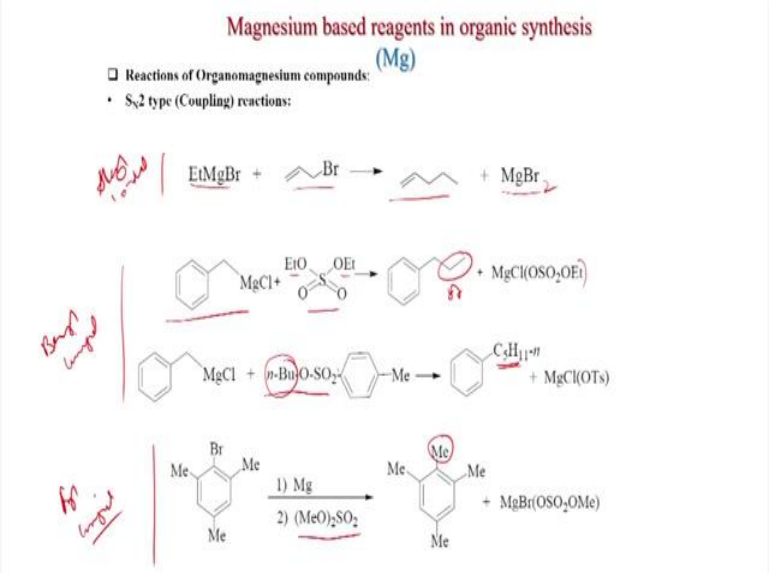

SN2 type coupling reaction already we have seen here are some more examples like ethyl magnesium bromide, allyl bromide, you get this double bond olefin and magnesium bromide. Also this benzylic magnesium chloride can react with this sulphonate and this ethyl group, this is the ethyl groups come from this sulfonate and this is the bi product, also benzyl magnesium chloride can react with this sulfonate n butyl OSO2 and you get this N butyl group.

So N butyl group comes to this one and ultimately it become pentyl group, also an aryl Grignard, so aryl Grignard can be generated from this bromide react with the magnesium and now it can react with this dimethyl sulphate and methyl group can be incorporated. So, these reactions are very useful, so this is with alkyl Grignard, this is benzylic Grignard and this is aryl Grignard. So, all of these undergoes substitution reaction.

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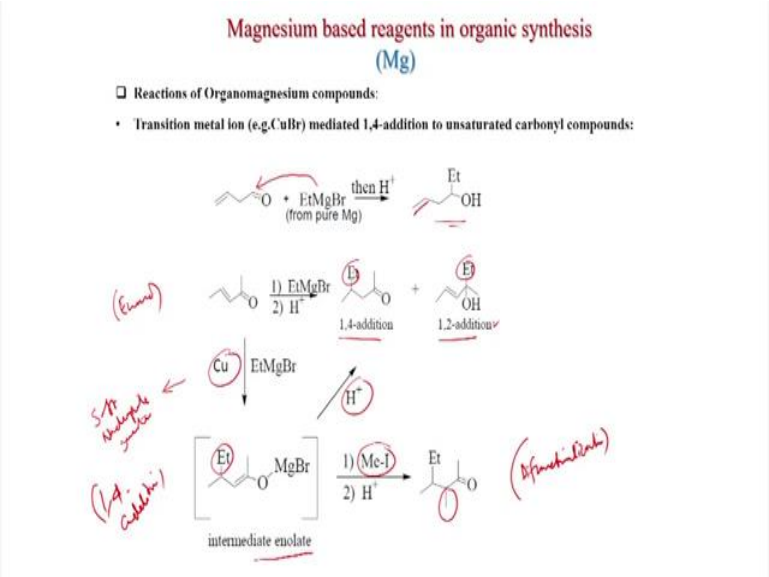

Transition metal ion such as copper bromide in mediated 1, 4-addition to unsaturated carbonyl compounds, so if you have this there will be double bond here. So, if you have this aldehyde with a double bond then with ethyl magnesium bromide if you generate from your magnesium ethyl bromide and then you add to this, then this alcohol will generate. Also with alpha beta unsaturated here this is ketone so this is enone.

Enone also undergo this reaction, suppose there are two possibilities, 1,4-addition and 1, 2 ethyl can add can 1, 4 or 1, 2 this already we have discussed, here is more details. Suppose simple ethyl magnesiun bromide H plus you get the 1, 2 addition, on the other hand if you have copper then this 1, 4-addition. So, with copper then this 1, 4-addition because this becomes copper may generate soft nucleophile generates.

It reacts with the Grignard generate the soft nucleophile EtCuBr and now this adds to the ethyl here and intermediate enolate is formed which after acid treatment it gives the 1, 4-addition product. Also a methyl group can be used, so this is the di-functionalisation, so this enolate, whatever is enolate is generated that can be reacted with alkyl like iodomethane and you get this methyl group here after acidic workup you get the ketone.

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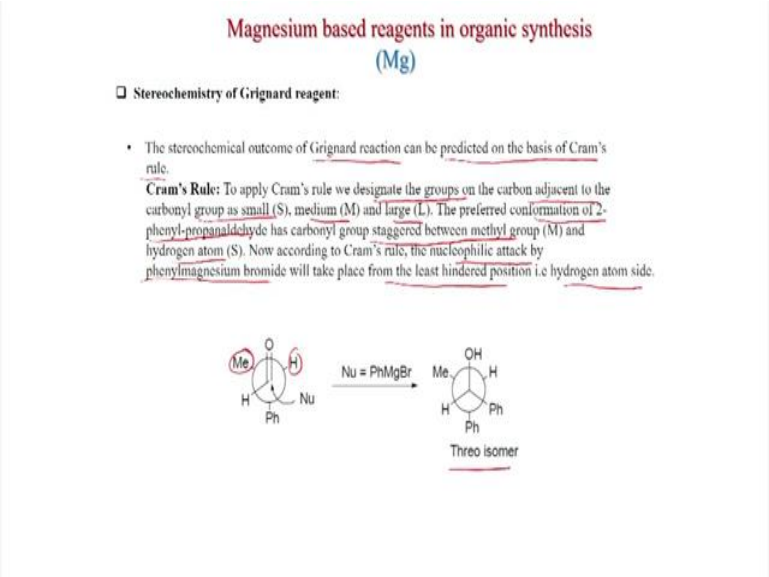

Stereochemistry, the stereochemical outcome of Grignard reaction can be predicted on the basis of Cram's rule. Cram's rule, to apply cram's rule we designate the group on the carbon adjacent to the carbonyl group as small, medium and large. The preferred confirmation of 2 phenyl propanaldehyde has carbonyl group staggered, so the carbonyl group staggered between methyl group and hydrogen atom.

So methyl and hydrogen, and this according to the Cram rule you have to put the carbonyl group in between this medium and small group. Now, according to Cram's rule the nucleophilic attack by phenylmagnesium bromide will take place from the least hindered position that is hydrogen atom side. So, if you put the aldehyde in the similar line with phenyl and methyl hydrogen in between then the nucleophile will come to the hydrogen side and you get this threo isomer.

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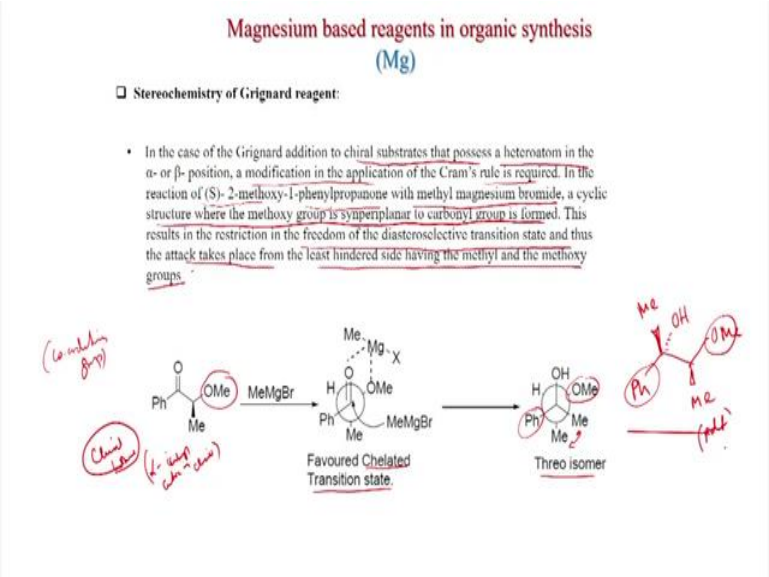

In the case of the Grignard reagent to chiral substrates that possess a heteroatom in the alpha or a modification in the application of the Cram's rule is required. In the reaction of S 2 methoxy 1 phenylpropanone with methyl magnesium bromide, a cyclic structure where the methoxy group is synperiplanar to carbonyl group is formed. So, this is a chiral ketone, chiral ketone and the chiral centre alpha to the carbonyl, this is also important, alpha carbonyl centre is chiral.

And if you have methoxy group is there, so this is the coordinating group, with coordinating group the stereochemistry will be such that this methoxy is binding with the magnesium so not only the carbonyl, this carbonyl as well as the methoxy group binds with the Grignard reagent. This results in the restriction in the freedom of the diastereoselective transition state and thus the attack takes place from the least hindered side having the methyl and the methoxy groups.

So this way you have to orient the substrate and this is the chelated transition state. So methoxy group as well as the carbonyl group will bind with the Grignard and another equivalent of Grignard will attack such that between methyl and O-methoxy group. And you get this threo isomers, this is in the Newman projection and if you draw in the zig-zag and this is your chiral centre already.

Now, if you add the methyl group, so here in the newman you can see the phenyl and methoxy are trans, so here I put phenyl and methoxy in zig-zag. Now, what happens, this

methyl and methyl are the syn to each other, so in the zig-zag they will also be syn and here this alcohol will be there. So, this is the compound that is formed when we add methyl magnesium bromide with this methoxy containing carbonyl compound.

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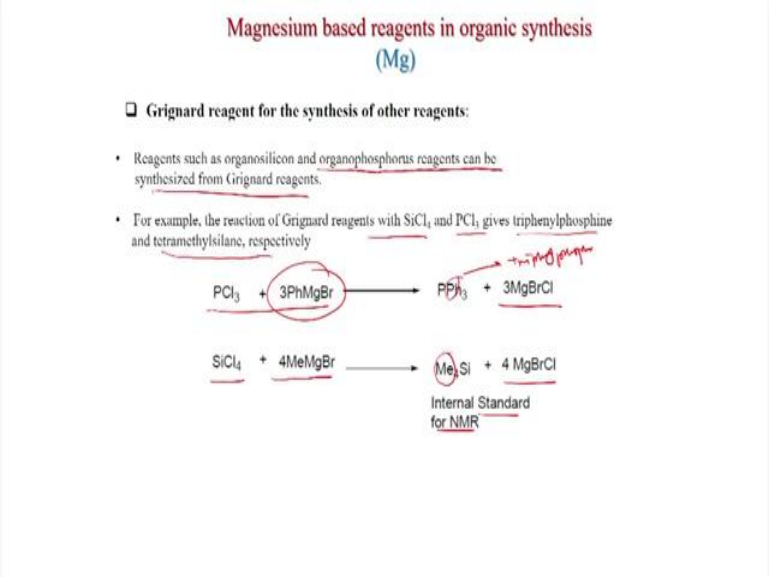

Grignard reagent for the synthesis of other reagents, reagents such as organosilicon and organophosphorus reagents can be synthesized from Grignard reagents. We already seen the transmetalation, also here you can generate organosilicon and organophosphorus reagents can be generated, if you treat with a tetrachlorosilane and phosphorus trichloride, gives triphenylphosphine and tetramethylsilane, respectively.

So, here if you treat with 3 equivalents of phenyl magnesium bromide, then what happens, this 3 phenyl groups, 3 phenyl groups transform the Grignard and you get this triphenylphosphine and 3MgBrCl, so triphenylphosphine is formed. And this one tetrachlorosilane reacts with 4 equivalent of methyl magnesium bromide then 4 methyl groups come. 4 methyl groups come on the silicon and this is tetramethylsilane, this is very useful for Internal Standard for NMR, so always in CDCl3 we add this, this is the Internal Standard and bi-products 4MgBrCl.

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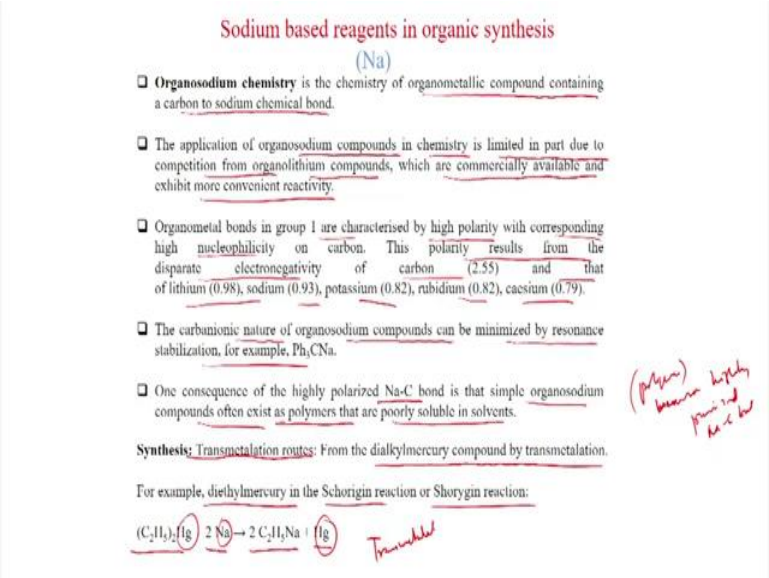

Now we discuss sodium, so organosodium chemistry is the chemistry of or organometallic compound containing a carbon to sodium chemical bond. The application of organosodium compounds in chemistry is limited in part due to competition from organolithium compounds, which are commercially available and exhibit more convenient reactivity. Organometal compounds in group one are characterized by high polarity with corresponding high nucleophilicity on carbon.

This polarity results from the disparate electronegativity on carbon. And that of lithium, sodium, potassium, rubidium and cesium. So, this is very important that the electronegativity defines the high polarity of the bonds forming. The carbanionic nature of the organosodium compounds can be minimized by resonance stabilization, for example, Ph3CNa.

One consequence of the highly polarized Na-C bond is that simple organosodium compounds often exist as polymers that are poorly soluble in solvent. So, this is important, polymer formation because they are highly polarized, polymer formation because highly polarized sodium carbon bond. However, it can be synthesized also by transmetalation route: like dialkylmercury compound by transmetalation, you can generate also.

For example, diethylmercury in the Schorigin reaction or Shoryngin reaction and this mercury compound when treated with, so diethylmercury can react with 2 equivalent of sodium and then you can get this ethylsodium plus mercury. So, this is like transmetalation

this mercury is becoming 3 here this sodium is displacing the mercury, so this is called transmetalation.

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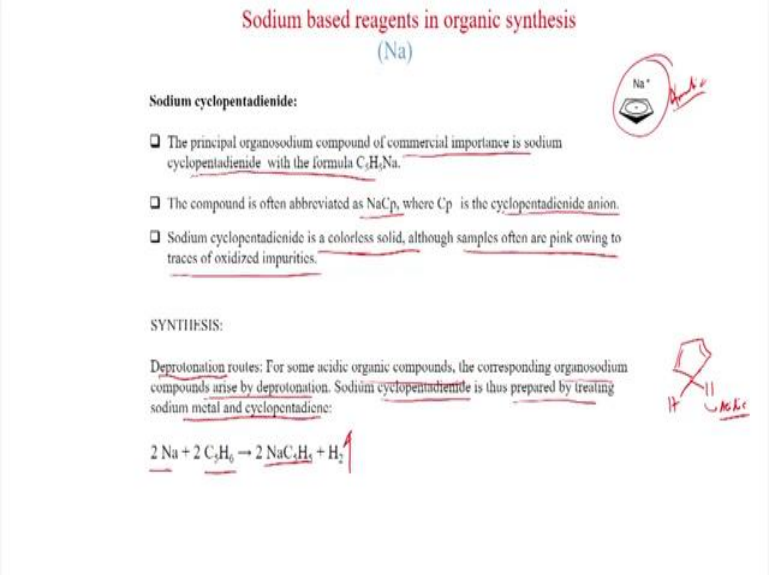

Sodium cyclopentadienide, so this is Sodium cyclopentadienide, this is aromatic, you have seen cyclopentadienide magnesium bromide that is also aromatic. The principal organosodium compound of commercial importance is sodium cyclopentadienide with the formula C5H5Na. The compound is often abbreviated as NaCp, where Cp minus is the cyclopentadienide anion.

Sodium cyclopentadienide is a colourless solid, although samples often are pink owing to traces of oxidized impurities. And we say it can be synthesized, also this mercury route you can synthesize also because this is acidic, so this we have already seen that this hydrogen is acidic, so this is acidic, similarly, like Grignard here the sodium reagents can also be formed from reacting cyclopentadienide.

So, this is the deprotonation route from some acidic organic compound the corresponding organosodium compounds arise by deprotonation. Sodium cyclopentadienide is thus prepared by treating sodium metal and cyclopentadiene. So, with 2 equivalent of sodium 2 equivalent of cyclopentadiene you get this cyclopentadienyl and hydrogen, so hydrogen gas is liberated.

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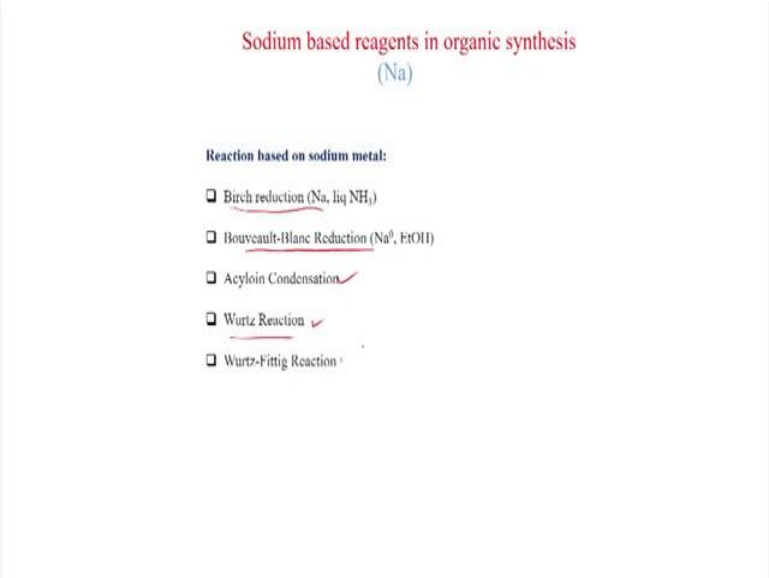

Reaction based on sodium metal. There are various reactions. Birch reduction this we have already discussed so we will not be discussing that again. Bouveault-Blanc Reduction this also we have discussed. Acyloin Condensation this we discussed today. Wurtz Reaction we will discuss and Wurtz-Fittig Reaction we will discuss. So, first we will discuss acyloin condensation.

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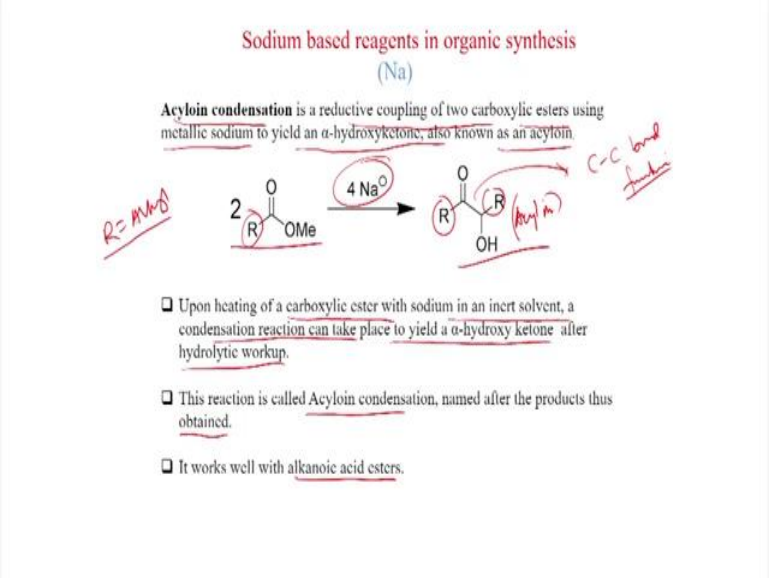

So Acyloin condensation is a reductive coupling of two carboxylic esters using metallic sodium to yield an alpha-hydroxyketone, also known as acyloin. So this is known as acyloin,

alpha hydroxyketone and 2 equivalent of ester with 4 equivalent of sodium generate the acyloin, alpha hydroxycarbonyl compound.

Upon heating of a carboxylic ester with sodium in an inert solvent, a condensation reaction can take place to yield alpha-hydroxyketone after hydrolytic workup. So, an ester is converted to and, of course, 2 equivalents is required because two R is coming here, so there is a C-C bond formation is happening, this we can see will also see in detail also in mechanism C-C bond formation.

This reaction is called acyloin condensation, named after the product thus obtained. It works well with alkanoic acid esters. So, if you have alkyl group here R, R is equal to alkyl then the reaction is much more facile.

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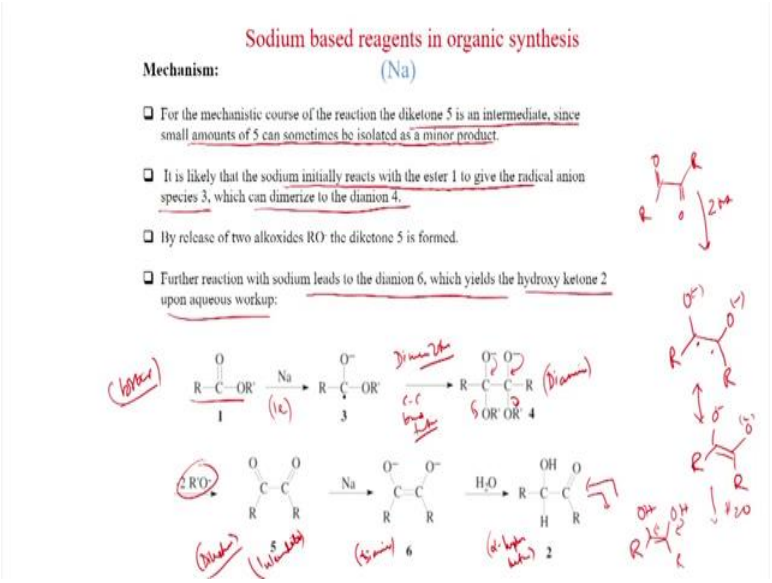

Mechanism for the mechanistic course of the reaction the diketone 5 is an intermediate, since small amount of 5 can sometimes be isolated as a minor product. It is likely that sodium initially reacts with the ester 1 to give the radical anion species 3 which can dimerize to the di anion 4. So this the reaction that this ester, ester first reacts with sodium, one electron is given to the ester, then this and a radical is formed and now this will dimerize.

So this dimerization will happen here, radical will react with another radical and generate this dianion and by the release of two alkoxides RO, the diketone 5 is formed. So, here what happens this alkoxide groups will be eliminated and diketone will be formed, so this diketone

was a, because this minor product sometimes is obtained, so this diketone is an intermediate here.

Intermediate and further reaction with sodium leads to dianion 6 which yields the hydroxy ketone 2 upon aqueous workup. So this is the in dianion 6 and after aqueous workup you get this one. So, what happens when you add two, two equivalents of sodium, so what happens here are dot O minus and here also dot if we write same side also dot O minus and this dot, this can be drawn like this because two radical, di-radical will make a bond here and you get a double one here.

That is why the 6 is formed and after aqueous workup you get this diol, in diol and now one enol will tautomerize to the carbonyl and that is where the alpha hydroxy ketone is formed. So this is the mechanism, this is very important dimerization the C-C bond formation. So, C-C bond formation is happening followed by the elimination of two alkoxide groups to generate a di-ketone and then sodium attacks again.

So 4 equivalent of sodium is generally required for this reaction and dianion will generate with the double bond here. Now, the aqueous work up will generate the alpha hydroxy ketone.

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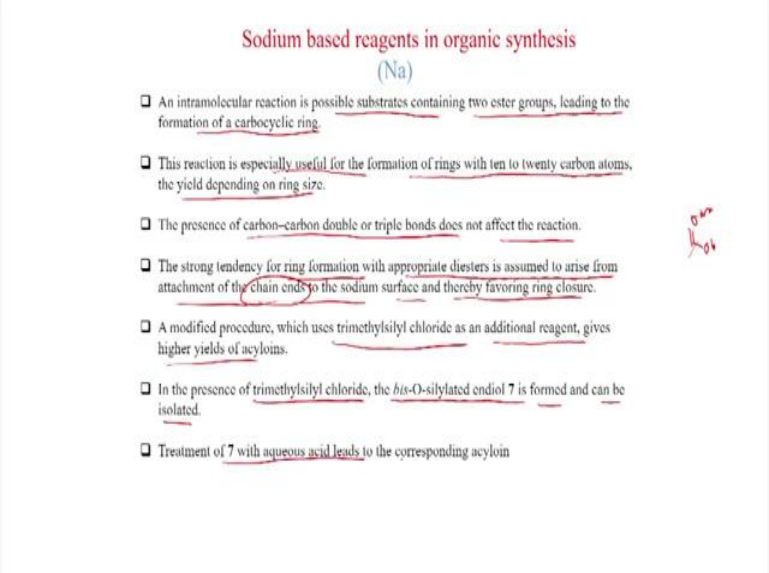

An intramolecular reaction is possible substrates containing two ester groups leading to the formation of a carbon cycling ring. This reaction is especially useful for the formation of rings with 10 to 20 carbon atoms, the yield depending on ring sizes, the presence of carbon

carbon double or triple bonds does not affect the reaction. The strong tendency for ring formation with appropriate diesters is assumed to arise from attachment of the chain ends to the sodium surface and chain ends.

So it binds to the chain ends the sodium that is the ester group and thereby, favouring the ring closure because this ester group the sodium can bind, right. A modified procedure, which uses trimethylsilyl chloride as an additional reagent, gives higher yields of acyloins. In the presence of trimethylsilyl chloride, the bis-O-silylated enediol 7, which we will see in the next slide, is formed that can be isolated. Treatment of 7 with aqueous acid leads to the corresponding acyloin.

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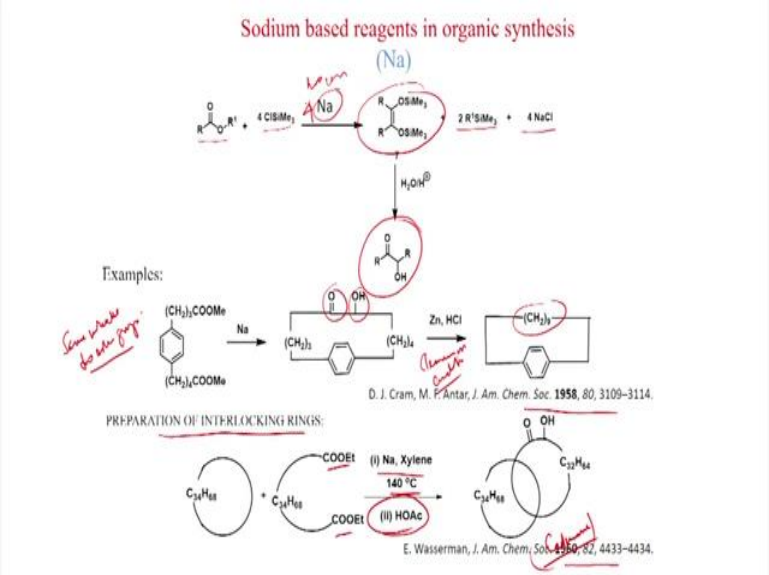

So, if you have a trimethylsilyl chloride and sodium then excess sodium, then you get this, disilane species and now which aqueous workup you get this alpha hydroxy ketone and these are the bi products R1 SIMe3 plus 4 equivalent of sodium chloride. So here minimum 4 equivalents you need. Examples like here these are the two ester groups here and in the same molecule same molecule two esters group.

Now, what will happen, another ring will form here, the alpha hydroxy ketone is formed here and now with Clemenson conditions Zn/HCl you get this alkyl. So this groups are eliminated and alkyl groups come here, research published in 1958 in JACS. Also interlocking rings can be prepared by this method which sodium xylene 140 degree centigrade followed by acetic acid treatment.

If you have a normal cyclic ring and another cyclization with the diester where the cyclization will happen and this called catenin, so this catenin species will form, that interlocking happens. So not only the Acyloin the reaction but interlocking also happens because these are large rings and you get the catenin species when you do the reaction under this Acyloin condition. So this was published in JACS 1960.

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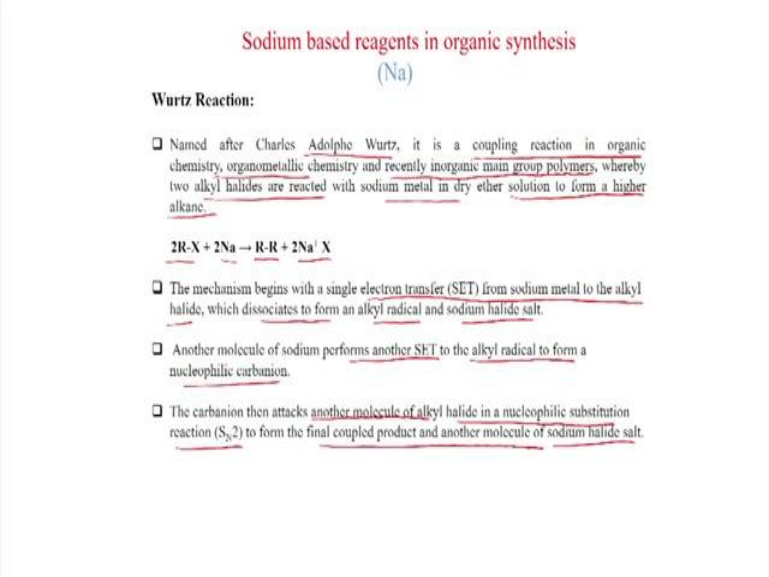

Wurtz reaction named after Charles Adolphe Wurtz, it is a coupling reaction in organic chemistry, organometallic chemistry and recently inorganic main group polymers, whereby by two alkyl halides are reactive sodium metal diether a solution to form a higher alkane. So here 2RX plus 2 sodium RR plus plus two NaX, the mechanism begins with a single electron transfer from sodium metal to the alkyl halide which disassociates to form an alkyl radical and sodium halide salts.

Another molecule of sodium performs another SET to the alkyl radical to form a nucleophilic carbanion. The carbanion then attacks another molecule of alkyl halide, the nucleophilic substitution reaction to form the final couple product and another molecule of sodium halide salts.

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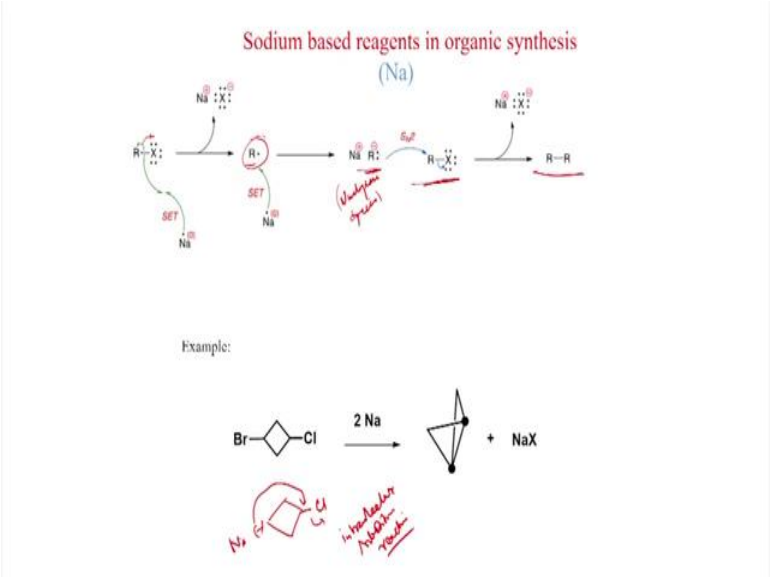

So this is the mechanism that the single electron transfer happens, the RX and here what happens the R dot is formed. This should be this side because X gives minus and this is a single electron transfer is showing here, so R dot and X minus is formed and Na becomes Na plus again, another electron is given to the R dot. So, what will happen, so again R dot become R minus and now this R minus sodium so this is a nucleophilic species.

So, R minus Na is a nucleophilic species, which can do SN2 reaction with unreacted RX, and now you get this RR bond. Example like here, so what will happen, first this bromide will react because this is good leaving group. So, this will form minus Na, now a substitution intramolecular substitution reaction will give this, intramolecular substitution reaction.

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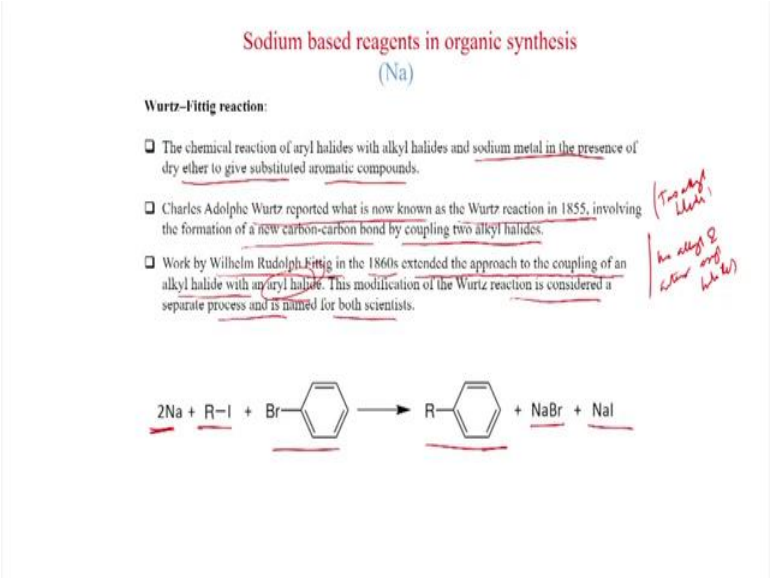

Wurtz Fittig reaction is the chemical reaction of aryl halides which alkyl halides and sodium metal in the presence of dry ether to give substituted aromatic compounds Charles Aldophe Wurtz reported what is known as Wurtz reaction in 1855, involving the formation of a new carbon-carbon bond by coupling of two alkyl halides. On the other hand, Fittig, Wilhelm Rudolph Fittig, in 1860, after 5 years, extended the approach to the coupling of an alkyl halide with an aryl halide.

So, here two alkyl halides in the Wurtz reaction, here one alkyl and another aryl halide, so that is the Fittig contribution that aryl halide were used. This modification of the Wurtz reaction is considered to a separate process and named for both scientists. Like here an alkyl halide and aryl halide is reacted with two equivalent of sodium, you get this R carbon-carbon bond formation, R aryl, sodium bromide, sodium iodide are the by-products.

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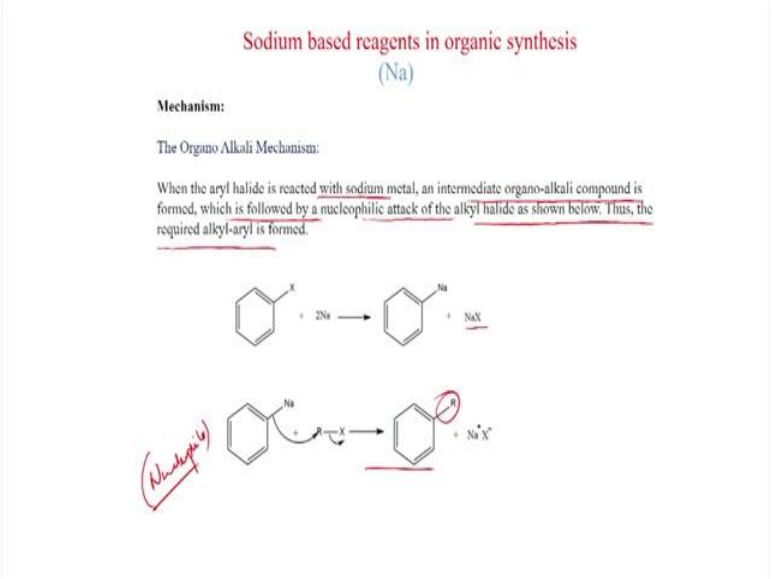

So the mechanism is alkyl mechanism when they aryl halide is reacting with sodium metal and intermediate organo-alkali compound is formed which is followed by a nucleophilic attack of the alkyl halide as shown below. Thus, the required alkyl aryl is formed. So, first aryl halide reacts with two equivalent of sodium, which generate this anion sodium species. So here minus is there, plus NaX and now this is a nucleophile. And now this aryl nucleophile will react with this alkyl halide to generate this carbon carbon bond formation happens and NaX is the by-product.

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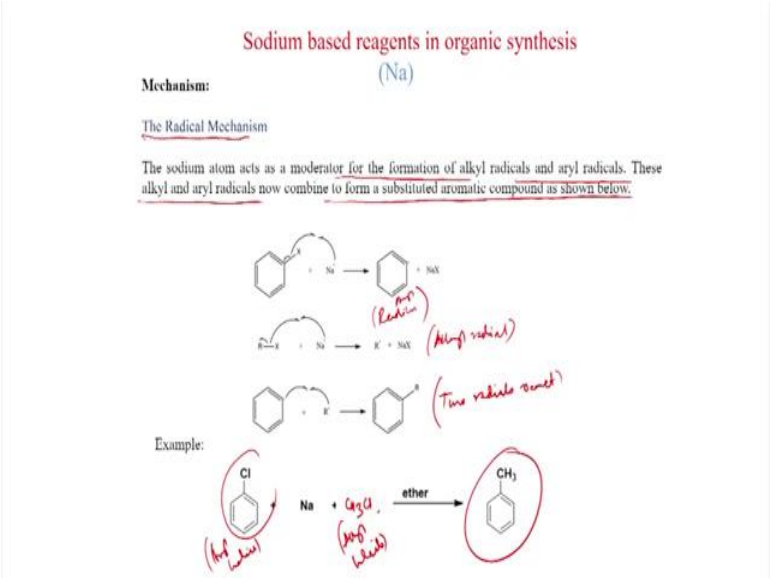

Also, the radical mechanism also is possible. So, here the sodium atom acts as a moderator for the formation of alkyl radical and aryl radicals. This alkyl and aryl radical now contribute to form a substituted aromatic compound as shown below. Like here single electron transfer. So this was the first formed actually the radical and then the carbanion and so here the radical is formed first. So, aryl radical is forming here, also alkyl radical.

So separately, the sodium is reacted with aryl halide and alkyl halide and two radicals are formed. Now, these two radicals will react, two radicals react. So, C-C bond formation a substituted aromatic compound is formed. Example, here is CH3Cl will be, so this is the aryl halide, this is the alkyl halide and in presence of sodium ether you get the toluene, so chlorobenzene is converted to toluene. This is the method that with sodium Wurtz-Fittig condition you can get this substituted aromatic compound.

So today first we have discussed Grignard reactions and Grignard reagents are very useful for the reaction with carbonyl compound, also substitution reactions and addition reaction. So, carbonyl compounds are reacted, if you have a simple formaldehyde that can give primary alcohol, then aldehyde. Then other aldehyde give the secondary alcohol and ketone give the tertiary alcohol.

Also Weinreb amide can give ketone also it can add 1, 4 fashion to the, and as well as 1, 2, fashion. So, normally Grignard reagents are hard nucleophile, they add 1, 2 fashion and with Ce(III) it is 1, 2 product and with copper or what happens it becomes a soft reagent in presence of copper and 1, 4 addition products are formed.

Also Grignard reagents have been used to for transmetallation like cadmium chloride, the R2 cadmium can be formed. Also different tin compounds, phosphorous compounds, boron compounds can be reacted with Grignard reagents and different, this Grignard R can be added to this boron team species. Also, it can react with PCl3 and tetrachlorosilane to generate respectively like phenyl magnesium bromide on reaction with PCl3 can generate triphenyl phosphine.

And tetrachlorosilane on react with methyl magnesium bromide can generate the tetramethylsilane which are used in the NMR solvent. Also the selectivity and regio selectivity of Grignard addition has been observed in epoxide addition, it attacks selectively from the less hindered side, and in SN2 function that is the inversion of stereochemistry is observed.

Also Grignard reagent is used for the coupling reactions. Normally when iron is used then the coupling reaction between alkyl Grignard and aryl halide compound can be, the coupling reaction can be performed with iron tris acetylacetonate. On the other hand, both are aryl, like aryl Grignard and aryl halide then nickel catalyst is used. Then we have seen the sodium and already Wurtz reaction and Bouvea-Blanc reaction already discussed earlier so it was not discussed today.

So, today we have discussed first the acyloin condensation and here two equivalents of ester generate the alkanoic ester, generate the alpha hydroxy ketones, which are called Acyloin and this is the radical process where this radical is formed, carbon dot O minus which dimerise to generate the carbon-carbon bond and then the diketone is formed, ultimately further addition of sodium to diketone generate the alpha hydroxy ketone.

Also we have discussed the Wurtz reduction, this is the sodium mediated reaction between two alkyl halide and the alkyl alkyl bond is formed, on the other hand when the aryl halide as well as the alkyl halide is used that is the Wurtz contribution, that is called Fittig contribution that is called Wurtz Fittig reaction between and aryl halide, alkyl halide and sodium then you get the substituted aryl compounds. Thank you.