Reagents in Organic Synthesis
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Lecture 25
Zn and Hg Based Reagents in Organic Synthesis

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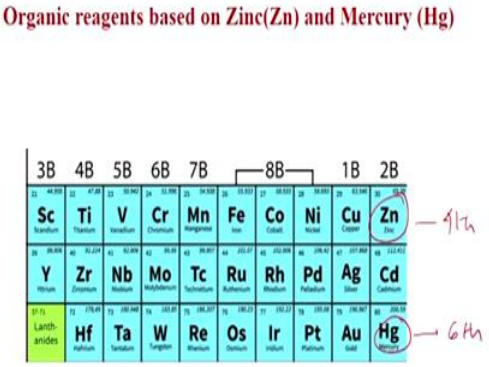

Welcome again. Today, we will discuss organic reagents based on Zinc and Mercury. So as you can see Zinc and Mercury are in the same group but they are in the different row. This is fourth row and this is sixth.

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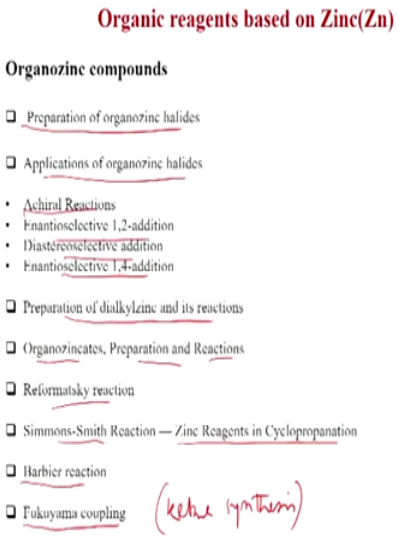

So, we will discuss first the Zinc. Organozinc compounds will discuss preparation of Organozinc halides; Applications of organozinc halides; Achiral reactions, Enantioselective 1,2-addition; Diastereoselective addition; Enantioseletive 1,4-addition we will discuss. Also we will discuss, Preparation of dialkylzinc and its reactions; Organozincates, preparation and reactions; Reformatsky Reaction; then Simmons-Smith Reaction - Zinc Reagents in Cyclopropanation, this is an important reaction for Cyclopropanation. Then Barbier Reaction we will discuss; and Fukuyama coupling, this is ketone synthesis.

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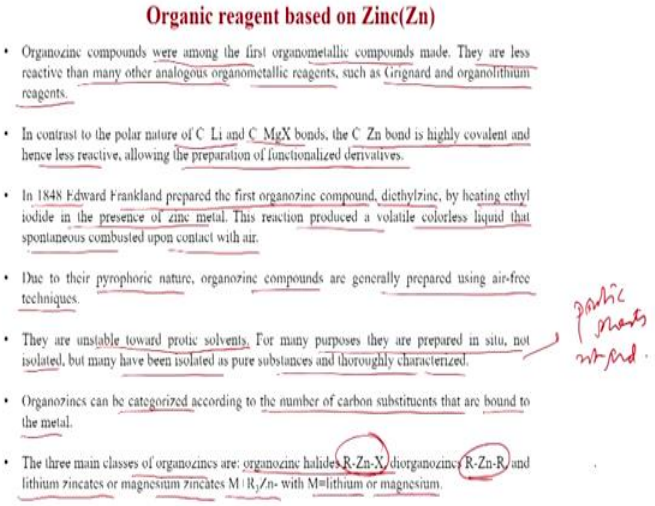

So, first we will discuss the basics about organozinc reagents. Organozinc compounds were among the first organometallic compounds made. They are less reactive than many other analogous organometallic reagents, such as Grignard and Organolithium reagents. This is an important thing. In contrast to the polar nature of C Li and C MgX bonds, the C Zn bond is highly covalent and hence less reactive, allowing the preparation of functionalized derivatives. So this is an important because the C Z bond is covalent, so we can incorporate functional groups.

In 1848 Edward Frankland prepared the first organozinc compound, dialkylzinc, by heating ethyl iodide in the presence of zinc metal. This reaction produced a volatile colorless liquid that spontaneous combusted upon contact with air. So they are pyrophoric in nature. Organozinc compounds are generally prepared using air-free techniques. They are also unstable towards protic solvents. For many purposes they are in situ, not isolated, but many have been isolated as pure substances and thoroughly characterized. So polar protic solvent is not good.

Organozincs can be categorized according to the number of carbon substituents that are bound to the metal. The three main classes of organozincs are organozinc halides R-Zn-X, that we will discuss; diorganozincs R-Zn-R, that also we will discuss; and lithium zincates or magnesium zincates M plus R3Z minus with M is equals to lithium or magnesium.

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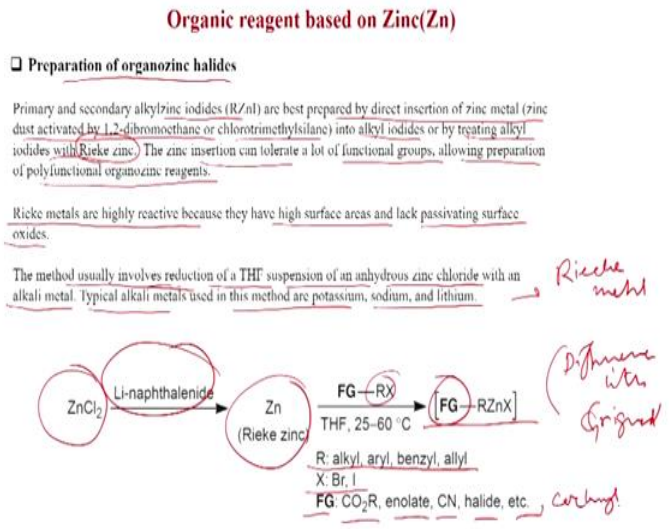

So, first we will discuss preparation of organozinc halides. Primary and secondary alkylzinc iodides are based prepared by direct insertion of zinc metal zinc dust activated by 1,2-dibromothane or chlorotrimethylsilane into alkyl iodides or by treating alkyl iodides with Rieke zinc. So this Rieke zinc we will discuss. The zinc insertion can tolerate a lot of functional groups, allowing preparation of polyfunctional organozinc reagents. This is important about zinc.

Rieke metals are highly reactive because they have high surface areas and lack passivating surface oxides. And this Rieke metal can be prepared. So the method usually involves reduction of a THF suspension of an anhydrous zinc chloride with an alkali metal. Typical alkali metals used in this methods are potassium, sodium and lithium. This way Rieke metal is generated.

So you put zinc chloride, then lithium-naphthalenide you get the Rieke zinc and then you can put functional group containing RX or simple RX then you can get functional group containing RZnX. That is the difference with Grignard. The functional group you can incorporate in the RZnX. So R is equal to alkyl, aryl, benzyl, allyl. X can be bromine, iodine. Functional group CO2R, enolate, cyanide, halide, etc. Even carbonyl also ketone.

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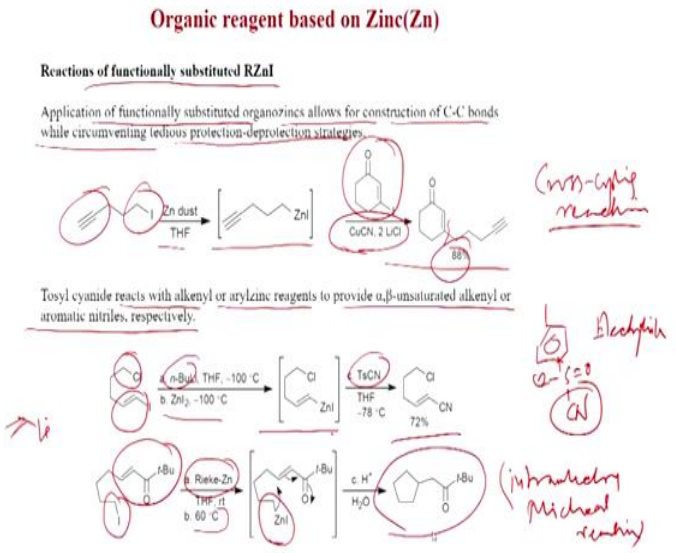

Reaction of functionalized substituted RZnI. This we will discuss application of functionally substituted organozincs allows for construction of C-C bonds while circumventing tedious protection-deprotection strategies. Like here, you see there is a triple bond and this primary iodine with zinc dust THF you get this alkylzinc iodide and now, 3-hydroxycyclohexenone with copper cyanide, lithium chloride then this coupling reactions happen. So this is cross-coupling reaction and likely the oxidative additions is happening with copper. Then you get this product in 88 percent yield, so this is the newly bond form.

Tosyl cyanide reacts with alkenyl or arylzinc reagents to provide alpha, beta-unsaturated alkenyl or aromatic nitriles, respectively. Like here, a chloro is there and vinyl iodide is there, first metal halogen exchange with n butyllithium you get the vinyl lithium. And then treatment with zinc iodide, you get this vinyl zinc iodide. So this is very important zinc iodide does not insert here, it insert here vinyl because already the lithium is there, so it is a nucleophilic reaction here is happening.

And now, the Tosyl cyanide if you put then this because this is a nucleophilic species, this is nucleophile and Tosyl cyanide is this, CN. So this is electrophilic species, electrophile. So you get this product in 72 percent yield. Also if a alpha, beta-unsaturated ketone is present and iodide here you can put directly Rieke zinc and this does not add here. So it inserts into this iodide, you get this alkylzinc iodide at 60 degree centigrade and then in acid treatment you get the cyclization, so this is the intramolecular cyclization is happening intramolecular Michael reaction. Then you get this cyclopentane derivative.

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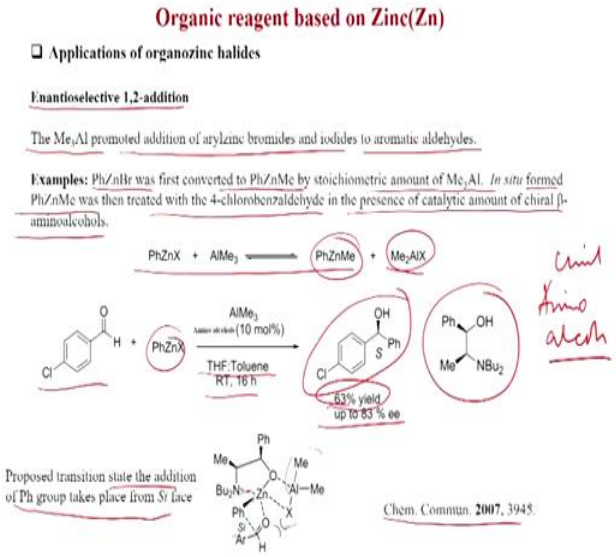

Now, we will see some Enantioselective version, Enantioselective 1,2-addition. Here you can add trimethylaluminum promoted addition arylzine bromides and iodides to aromatic aldehydes. PhZnBr was first converted to PhZnMe by stoichiometric amount of trimethylaluminum. Now in situ formed PhZnMe was then treated with 4-chlorobenzaldehyde in the presence of catalytic amount of chiral beta- aminoalcohol.

So here, first this exchange happens PhZnMe is form and this is the by-product Me2AlX. Now in situ if you prepare this trimethylaluminum PhZnX with 4-chlorobenzaldehyde if you react THF toluene solvent room temperature 16 hours, you get this product the pH group as to the 4-chlorobenzaldehyde with 63 percent yield and with this aminoalcohol, so this is chiral aminoalcohol, you get 83 percent ee. So, what could be the transition state?

As you can see here, this complex is forms the zinc coordinates with n butyl, this is the tertiary amine and the oxygen and now Ph is coordinating of course with the zinc and this is the PhZnX and also dimethylaluminum which is by-product that also coordinates here. And now, this orients like this aryl group will be this side because if the aryl group this side then there will be steric interaction with X. So aryl group this side. And now vinyl comes from the top phase, so this is Si phase attack, the addition of pH group takes place from the Si phase and you get this stereochemistry. This was published in Chem Commun, 2007.

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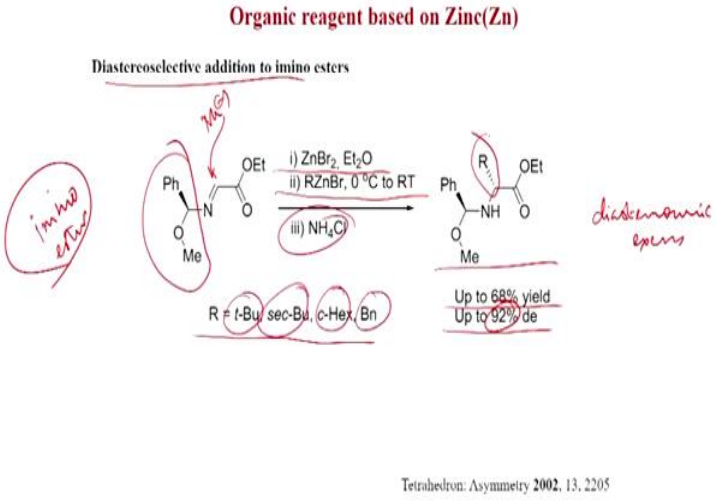

Now, Diastereoselective addition to imino esters is also possible. Like here, you can see this is imino ester and this imine is chiral, here this is the chiral auxiliary. And now, Diastereoselective addition can take place from nucleophile here. So with zinc, bromide, ether and RZnBR, 0 degree centigrade to room temperature after ammonium chloride treatment you get this compound. So the addition take place from this down phase, so you get this product, upto 68 percent yield and 92 percent de diastereomeric excess. So very good diastereomeric excess upto 92 percent and different groups like R is equal to tertiary butyl you can add secondary butyl, cyclohexyl, benzyl, etc.

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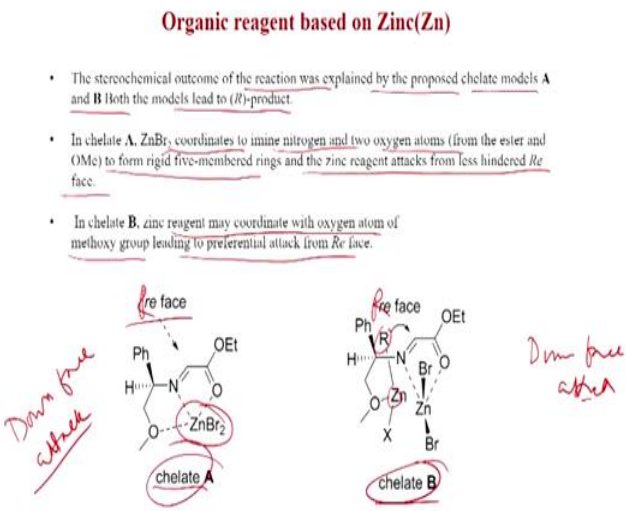

So what could be the mechanism of this reaction? The stereochemical outcome of the reaction was explained by the proposed chelate models A and B. Both the models lead to R-product. So this is the chelate A and this is chelate B. So there is slight difference. In chelate B, you can see the RZnX also is coordinate to the chiral auxiliary. So here the RZnBr is externally coming. So in chelate ZnBr2 coordinates to imine nitrogen and two oxygen atoms. So ZnBr2 has been added previously and it is coordinate to imine nitrogen as well as the two oxygen atoms, so this makes a tight geometry. And now, this rigid five-membered rings is formed and the zinc reagent attacks form the less hindered Re-face. So that is why Re-face attack is taking place. That is the down face. So down face attack.

In chelate B, zinc reagent may coordinate with oxygen atom of the methoxy group leading to preferential attack from Re-face. So here, the RZnX is coordinate with this methoxy group and this R now is taking place from the same, the down face, so it is also down face attack is happening. So either by chelate A or chelate B you can get the same product. So very Diastereoselective addition is taking place.

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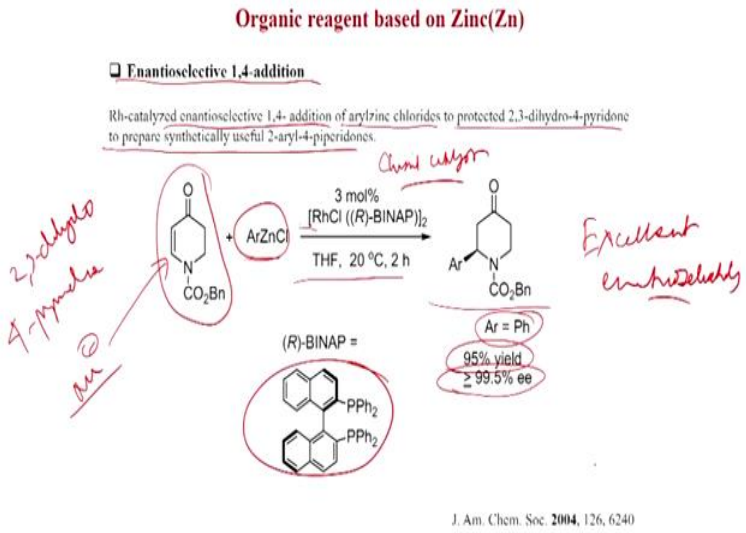

Now, Enantioseletive addition is possible also with chiral catalyst. So rhodium catalyzed enantioseletive 1,4-addition of arylzinc chloride to protected 2, 3-dihydro-4-pyridone to prepare synthetically useful 2-aryl-4-piperidones. So this is the substrate, you can say this is substrate 4-peridones, 2, 3-dihydro of course and here the nucleophile will add here. So one 1, 4 addition will take place, arylzinc chloride is the reactant and RhCL R-BINAP2, so this is the catalyst, chiral catalyst.

And THF 20 degree centigrade, you get this product. And you can get upto 95 percent yield Ar is equals to Ph and greater than 99.5 percent yield, so excellent enantioseletivity, excellent enantioseletivity. With this BINAP ligand. So rhodium R-BINAP ligand, you can get up to 99.5 percent ee. This was published in JACS, 2004.

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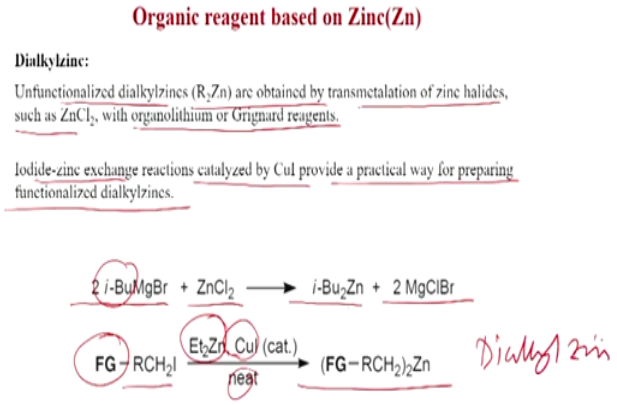

Now, we will discuss dialkylzincs. So unfunctionalized dialkylzinc are obtained by transmetalation of zinc halides such as zinc chloride with Organolithium or Grignard reagents.

Iodide-zinc exchange reactions catalyzed by copper iodide provides a practical way for preparing functionalized dialkylzincs. So this is the normal preparation. If you put equivalent of isobutyl magnesium bromide, 1 equivalent zinc chloride then 2 isobutyl goes to the zinc now. So diisobutyl zinc is formed and this is the by-product, 2MgClBr. Also, functional group containing RCH2I can be reacted with diethylzinc with copper iodide catalyst neat, you can get this functional group (RCH2)2 zinc. So dialkylzinc, dialkylzinc.

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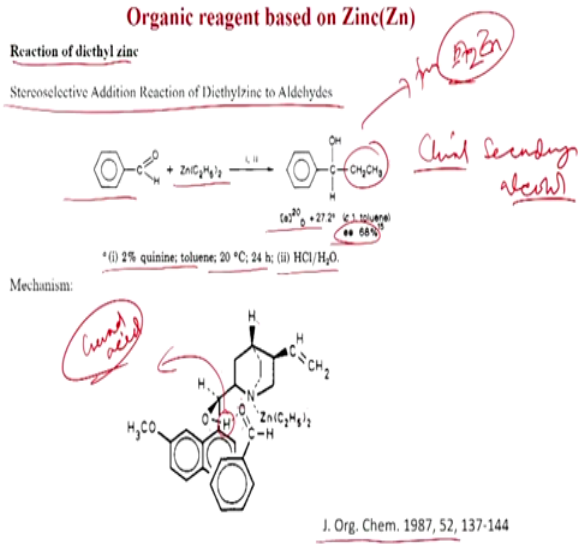

Now, we will discuss reactions of diethylzinc. First stereoselective additions reactions of diethylzinc to aldehydes. So here, benzaldehyde is there, this is diethylzinc and with two more percent quinine, toluene, 20 degree centigrade, 24 hours and after acid workup you get this chiral alcohol, chiral secondary alcohol is formed. And this is the rotation, so 68 percent is obtained.

So what could be the mechanism? So this is quinine. As you can see this is the alcohol of the quinine and this is the amine part. So here, so the benzaldehyde is coordinated with the OH, so this is the acid. So this is general acid, so this is activating aldehyde. Now, your diethylzinc is coordinated with nitrogen. So both aldehyde and zinc are coordinated to the catalyst. So it is not tight geometry and that is why you can get enantiomeric excess, so the ethyl group, so ethyl group, this is coming from diethylzinc. So nucleophilic addition of ethyl group is happening here. And you can get the secondary alcohol. This was published in JOC, 1987.

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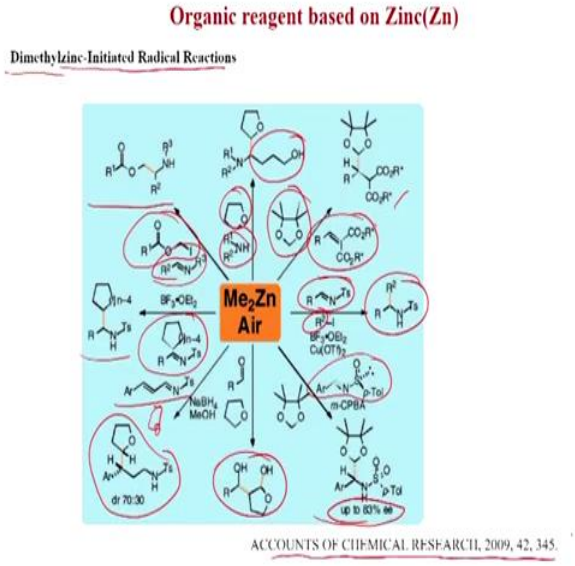

Now, we will discuss dimethylzinc-initiated radical reaction. They also can do radical reactions. There are a lot of radical reactions as you can see. So what happens, a radical is generated then it adds to different electrophile. Like here, the radical will generate from R2 and it can add to the imine. So this is imine, you can get a amine.

Here also, this radical will form will here from this acetal and it can add to the chiral imine and then this product can be formed up to 83 percent. Here also, you can see and tetrahydrofuran, the radical will form here. So here the radical is formed and then the, you can get this product. Also you can add this one, this tetrahydrofuran here missing here. Tetrahydrofuran should be there and you can add this dienamine then you can get this product. dr is 70 is to 30. Then this one is also possible, the cyclopentane and this imine then you can get this product.

Also with this esters, iodoester, so you can get radical here. This can add to the imine, you can get this product. Also tetrahydrofuran and the amine, you can get this product. So the one tetrahydrofuran is opening to give this component. Also this acetal and alpha, beta-unsaturated ester, it can do the conjugate addition, you can get this product. So various reactions can be done, various radical reaction by dimethylzinc air. And there is a Review Accounts Of Chemical Research, 2009.

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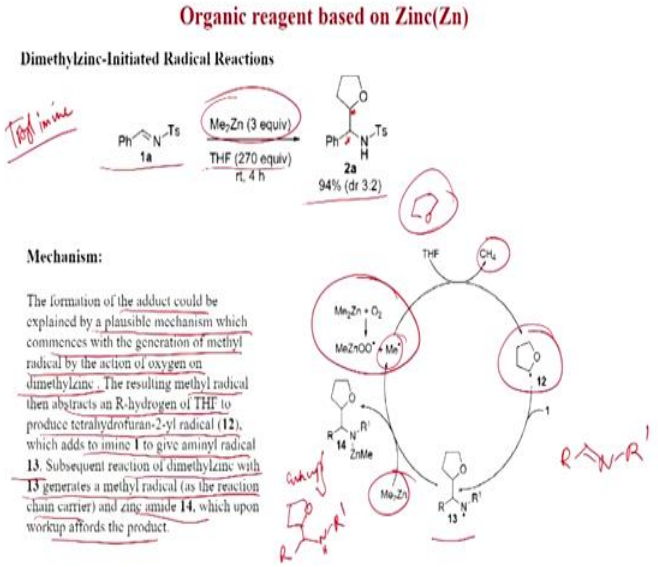

So this is an example like tosyl amine. So this is tosyl amine, reactively dimethylzinc 3 equivalent in THF solvent you can get this. So a radical is forming which is attacking the imine, so you can get the dr 3 is to 2. Because 2 chiral sensors are there, so you get diastereomeric excess.

So, what could be the mechanism of this reaction? So the mechanism that the formation of the adduct could be explain by a plausible mechanism which commences with the generation of methyl radical by the action of oxygen on dimethylzinc. So this is first forming. So dimethylzinc plus oxygen then you can get MeZnOdot and methyl dot, so that methyl dot is reacting with tetrahydrofuran. So tetrahydrofuran then this radical is forming. And CH4 will generate of course. So resulting methyl radical then abstract an R-hydrogen of THF to produce tetrahydrofuran to a radical 12. Now 12 can add to imine. So now, if there is imine then this tetrahydrofuran radical will add to the imine and you generate the 13. So which adds imine 1 to give aminyl radical 13.

Now subsequent reduction of dimethylzinc with 13 generates a methyl radical as the reaction carrier. So when dimethylzinc is added to here then you get ZnMe and methyl dot is generated and zinc amide is formed, so this is the amide, which upon workup affords the product. So this after workup, workup you get this product NHR1. So this is very important. The radical is formed, methyl dot radical and that is abstracting the R hydrogen are formed, tetrahydrofuran you get this radical and it is adding to the iminium ion or other electrophile and various reactions are possible.

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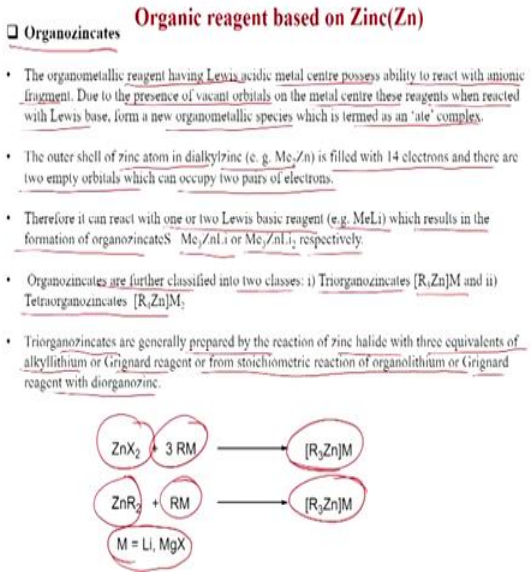

Now, we will discuss organozincates. So organometallic reagents having Lewis acidic metal center possess ability to react with anionic fragment. Due to the presence of vacant orbitals on the metal centre these reagents when reacted with Lewis base, form a new organometallic species which is termed as an ate complex.

So the outer shell of zinc atom in dialkylzinc like Me2Zn is filled with 14 electrons and there are two empty orbitals which can occupy two pairs of electrons. So it can more electrons. Therefore, it can react with one or two Lewis basic reagent. As for example methyl, lithium, which results in a formation of organozincates. Me3ZnLi or Me3ZnLi2 respectively. So dimethylzinc again can react with methy lithium and then you can get this trimethyl zinc lithium.

Organozincates are further classified into two classes Triorganozincates R3ZnM and tetraorganozincates R4ZnM2. And Triorganozincates are generally prepared by the reaction zinc halide with three equivalents of alkyl lithium or Grignard reagent or from stoichiometric reaction or Organolithium or Grignard reagant with diorganozincs.

So directly from zinc halide, you can prepare zinc halide then 3RM you have to put, 3RM, so this R3 will come here then R3ZnM will form here. Alternatively, with dialkylzinc react with one equivalent of RM, then you can get R3ZnM. So M is equal to lithium or MgX. So these eight complexes are very useful nucleophile that we will see and it can be used define additions reactions also.

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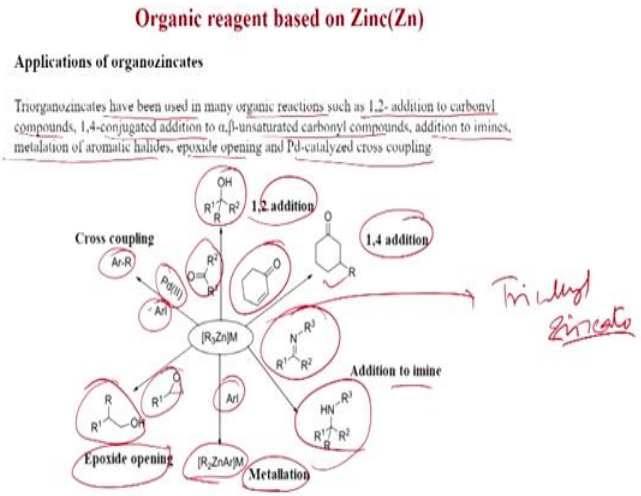

Triorganozincates have been used in many organic reactions such as 1,2-addition to carbonyl compounds, 1,4-conjugated addition to alpha, beta-unsaturated carbonyl compounds, addition to imines, metalation of aromatic halides, epoxide opening and palladium catalysed cross-coupling reactions. So many reactions can be carried out. As you can see here, this is the trialkyl zincate. So trialkyl zincate.

Now, when it add to cyclohexanone, you get 1,4 addition product, with imine you get the amine, addition to imine. Now, aryl iodide you can get R2ZnArM, so metallation is possible. Epoxide opening is possible. Epoxide opening you can get product like this, alcohol product. Then cross-coupling reaction with aryl iodide palladium 2 and then you get this cross-coupling product and with ketone, it can give the 1,2-addition product, so this is the product.

So this is a very useful reagent and with nucleophile it can add to various electrophiles like 1,2-addition, 1,4-addition, metallation and cross-coupling, etc.

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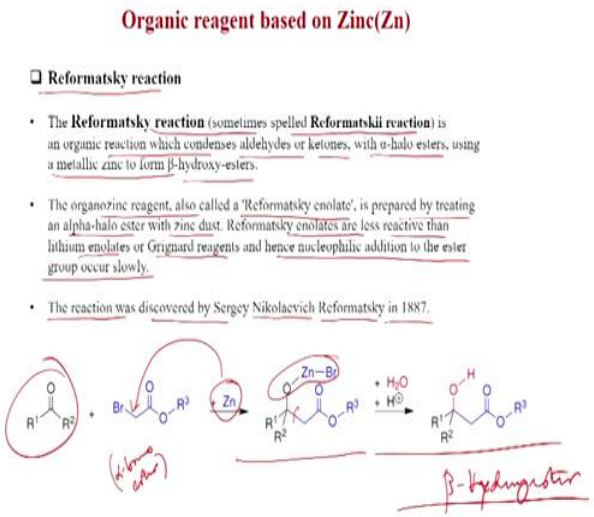

Now we will discuss Reformatsky reaction, this is very important reaction. The Reformatsky reaction sometimes spelled Reformatskii reaction, is an organic reaction with condenses aldehydes or ketones, with alpha-haloesters, using a metallic zinc to form beta-hydroxy-esters.

The organozinc reagent also called a reformatsky enolate is prepared by treating an alpha-haloester with zinc dust. Reformatsky enolates are less reactive than lithium enolates or Grignard reagents and hence nucleophilic addition to the ester group occur slowly. So this is very important and ester group will be incorporated in the reformatsky reagent but the cell condensation will not happen, so that will happen very slowly, so that is why you can use this reagent. The reaction was discovered by Sergey Nikolacvich Reformatsky in 1887.

So this is the reaction. You have to use the alpha-bromo esters and ketone or aldehyde, then you put the zinc, then of course this reformatsky reagent will happen, zinc will insert in this bond, severe bond. And after that nucleophilic you get this addition. So then the zinc will coordinate with the oxygen because this will alkoxide it will produce this and this bond is forming after acidic workup you get this compound. This is beta-hydroxy ester. So these are very important compound. Beta-hydroxy ester because simply ketone addition with this reformatsky reagent that is the alpha-haloester and with zinc then you get this intermediate after aqueous workup you get this product.

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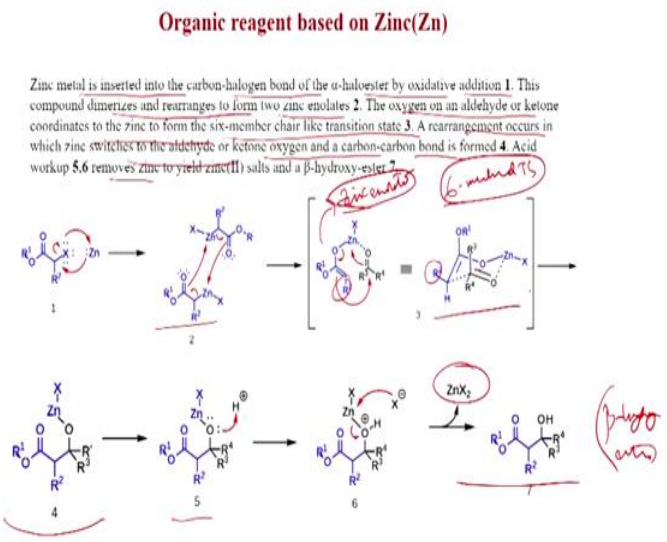

So, we will see first the mechanism. So zinc metal is inserted into the carbon-halogen bond alpha-haloester by oxidative addition 1. So this happens first, the oxidative addition, this compound dimerizes and rearranges to form two zinc enolates. So two zinc enolates are forming here because you can see there is a ester motif, so of course the enolate possibility will be there. The oxygen of an aldehyde or ketone coordinates to the zinc to form six-member chair like transition state 3. So it is the enolate. So this is very important, the zinc enolate is forming actually, zinc enolate is forming. So this is the zinc enolate formation, you can see here.

Now, zinc enolate is reacting with the carbonyl compound and six-membered transition state, so this is a six-membered transition state. This we have seen earlier also. And here if you see this R2 and this OZnX are trans. So here also R2 and OZnX they are trans, so you have to maintain in the chair also. And now, this carbonyl also will be coordinating with the zinc and it can take orientation like this then a rearrangement occurs in which zinc switches to the aldehyde or ketone oxygen and carbon-carbon bond is formed.

So after carbon-carbon bond forms, you get this. So this is a newly bond form is forming and there this carbonyl group will form here and this will be the OZnX. Acid workup 5, 6 removes zinc, so this will form. Now acid workup removes zinc to yield, zinc to salts and beta-hydroxy esters. So acid workup, this will be by-product and this is the beta-hydroxy ester. Because acid workup will remove the zinc. X minus will react here and then you get the free alcohol. So this is the reaction that is the zinc enolate and a six-membered chair like

transition state will form, these are the main things and after that you can get the, after acidic workup beta-hydroxy esters.

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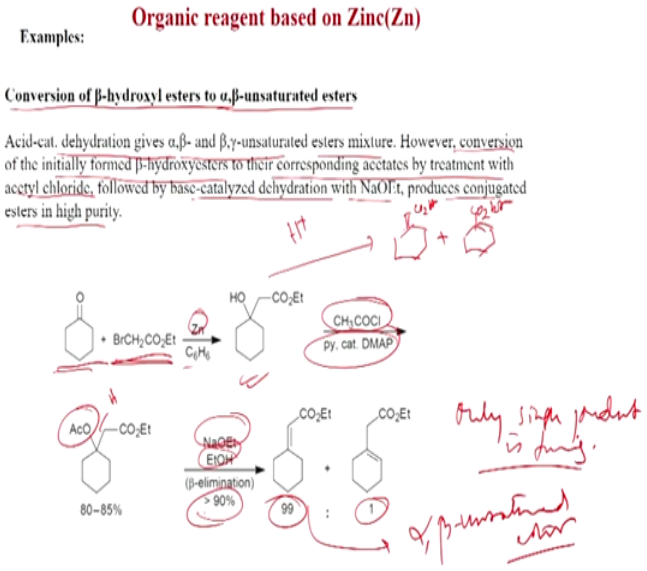

So we will see now different application of this reaction because the beta-hydroxy esters you can of course convert to alpha, beta-unsaturated esters also. Acid-catalyzed dehydration gives alpha, beta and beta, gama-unsaturated esters mixture. If you see the substate cyclohexanone and BrCH2CO2Et alpha bromo esters with zinc, benzene, you can get this product that is the Reformatsky reaction beta-hydroxy ester.

Now, on this if you put acid what happen, you can get two products. So CO2Et plus the internal double bond is also possible. CO2Et. So that is why the acid catalyzed dehydration gives alpha, beta and beta, gamma, so this is alpha, beta, this is beta, gamma. However, conversion of the initially formed beta-hydroxy esters to their corresponding acctates. So by treatment with acctyl chloride, followed by base-catalyzed dehydration with sodium ethoxide produces conjugate ester in high purity.

So now, if you do not do the acid treatment alternatively you can put with acid chloride and DMAP pyridine then you can take this hydroxyl the acetate. So acetate formation happens and now, if you put sodium ethoxide as a base in ethanol solvent, the beta-elimination greater than 90 percent and selectively you get this.

So selectively alpha, beta-unsaturated ester is forming because it is now base elimination, so this proton must be more acidic, so the elimination will happen from there, you can get this alpha, beta-unsaturated ester in greater than 99 is to 1 ratio. So this is the beta, gama. So here,

only single product is forming. So this is very important reaction. If you treat with acid chloride then you get the acetate after base treatment, you can get the alpha, beta-unsaturated ester.

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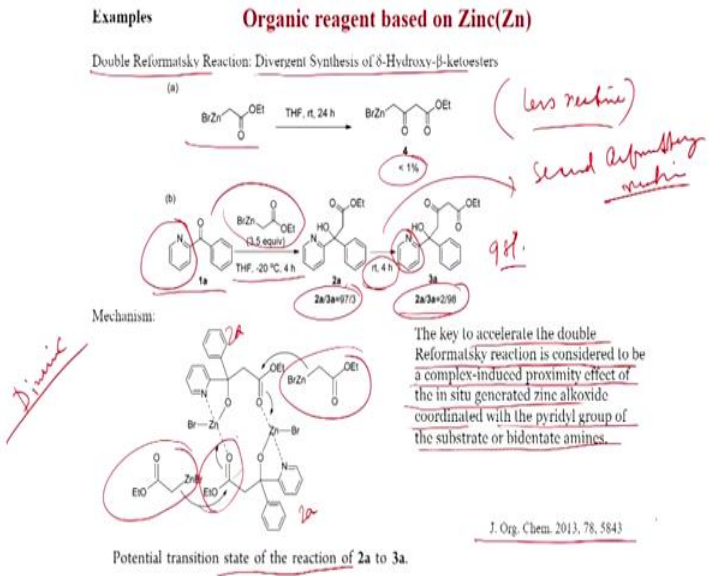

Now double Reformatsky reaction also is possible and here divergent synthesis of delta-hydroxy-beta-ketoesters. Simple this zinc ester they do not dimerize, see this is 1 percent because already we told that this zinc they are much less reactive. So this says they are less reactive and that is why it does not react with esters.

But some cases like this one, this is the special ketone a pyridine motif is there and a phenyl group. Now, you put this reagent Reformatsky reagent 3.5 equivalent THF minus 20 degree centigrade, 4 hours, you get this product. This is a normal product, beta-hydroxy-esters forms 97 percent and 3 percent this one. This is the double Reformatsky.

So, if you run this compound again because excess is there the second Reformatsky reaction will happen. So this step second Reformatsky reaction is possible, this is unusual. We will see the mechanism. The pyridine group is important for this reaction. Now, if you start for room temperature 4 hour, then 2A become 3A and 98 percent 3A is formed. So 98 percent and 2 percent only 2% remains as 2A.

So, what is the mechanism here? The key to accelerate the double Reformatsky reaction is considered to be a complex-induced proximity effect of the in situ generated zinc alkoxide coordinated with the pyridyl group. So this pyridine motif is important of the substate or bidentate amines. So this is the mechanism. As you can see this is 2A, 2A this is a dimeric

structure, dimeric. And this is the Reformatsky reagent here, here also. So what happens, if you see this structure, now this ester is activated by zinc bromide which is coordinated with the pyridine. So this is important, this is again activated so that nucleophilic addition will happen again.

So, how it is activated? Now this way is activated, this nitrogen and this oxygen coordinate with the zinc and that activated zinc will coordinate with the ester carbonyl. Similarly, here also, this is the dimeric here also the ester carbonyl is coordinated with this zinc which is activated with this hydroxyl and pyridine motif. So this is very important, the pyridine group, if you have a pyridine group then the double Reformatsky reaction can work. This is the potential transition state of the reaction of the 2A to 3A and this was published in Journal of Organic Chemistry 2013.

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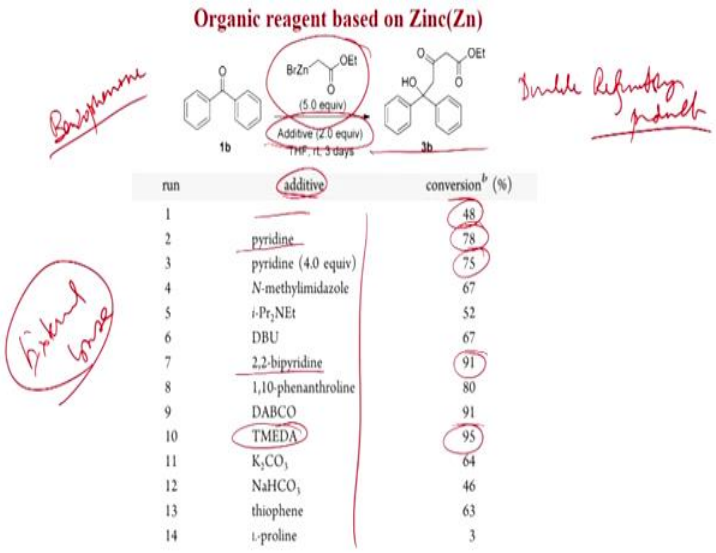

run	additive	conversion[b] (%)
1		48
2	pyridine	78
3	pyridine (4.0 equiv)	75
4	*N*-methylimidazole	67
5	*i*-Pr_2NEt	52
6	DBU	67
7	2,2-bipyridine	91
8	1,10-phenanthroline	80
9	DABCO	91
10	TMEDA	95
11	K_2CO_3	64
12	$NaHCO_3$	46
13	thiophene	63
14	L-proline	3

Now, if you add bases externally like this benzophenone is there. So this is benzophenone and with this Reformatsky reagent 5 equivalent, if you add different basis, so this are the additives different of course basis are there and THF room temperature three days, so this is the double Reformatsky product, as you have seen. So here you can see, if there is no additive also you can get 48 percent yield. But if you add bases like pyridine, it is given 78 percent, pyridine 4.0 equivalent 75; 2,2-bipyridine is giving 91 and the base is TMEDA which can give 95 percent yield. So what is happening here because the amine is coordinate with the zinc, free zinc and that is activating the ester. So that is why the external base, so this is the external base can give double Reformatsky product. So this is very important.

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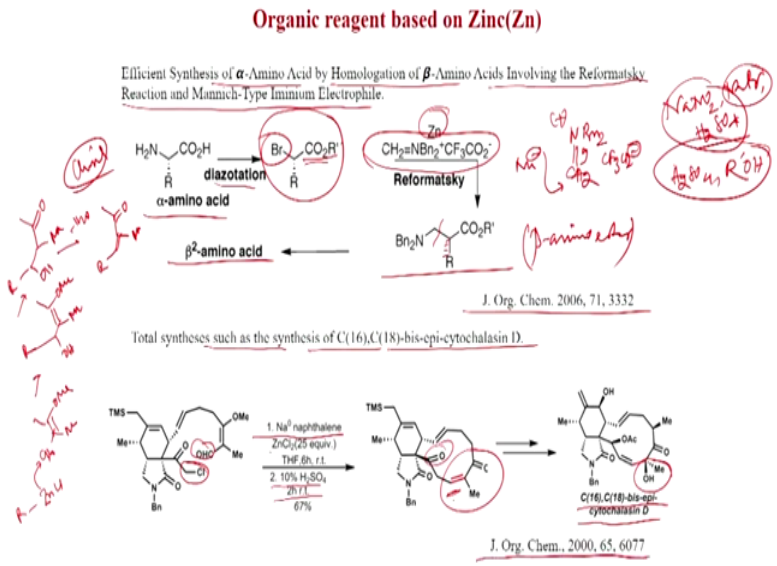

Efficient synthesis of alpha-amino acid by homologation of beta-amino acids involving the Reformatsky reaction and Mannich Iminium Electrophile. So this is another application of Reformatsky reaction. So this is alpha-amino acid, so this is chiral, alpha-amino acid. Now, if you diazotisation, so if you put NaNa2, NaBr and H2SO4 then you can get this bromine here. So first the diazotisation will take place then NaBr will react, you can get this bromine here. And also the acid can be converted to the ester. So acid if you put H2SO4 and R dash OH that is the alcohol. So acid catalyzed ester synthesis can be formed to get the ester.

Now this you can get the Reformatsky reagent after react with zinc and that reagent you can react with this iminium ion. So this is the iminium ion double bond and benzyl to CH2. Also CF3CO2 minus is there. Now your nucleophile will attack here. And you get this. So the chiral center will not be disturbed here. So like this. So this is the newly bond formed. So this is beta-amino ester, beta-amino ester. And after that of course, after hydrolysis, you can get the beta 2 amino acids. So this is very important, you can convert alpha amino acid to beta amino acid and this was published and Journal of Organic Chemistry, 2006.

Also, total synthesis it has been applied, total synthesis, such as the synthesis of C16, C18 bis-epi-cytochalasin D. So suppose this was the intermediate and you can see here of course electrophile is there and also this alkyl chloride is there. Now, if you put zinc that was the interest thing about zinc that it can add selectively to this bond. So you have to activate the zinc that is the activated zinc with sodium naphthalene, zinc chloride.

Then it adds to here and after that the addition takes place and after acid treatment, you get this alpha, beta-unsaturated ketone. So what happens, if you see the mechanism, so zinc chloride are CHO here of course the OMe group is there, so this will add, so you get OH.

Now if you put acid, what happens? Acid because this will become ketone of course in acid, a methyl OHR, so this will form and this after elimination of water it will give the alpha, beta-unsaturated ketone. So air methyl group will be there. So that is what here is happening, you see, this is the double bond and alpha, beta-unsaturated ketone.

Now, this compound can be converted to this. So here, you have to convert this to hydroxyl here a double bond has doing properly and then quartnery center. So this is the C16, C18 bis-epi-cytochalasin D. So that is why Reformatsky reaction is very important and this was published in Journal of Organic Chemistry, 2000.

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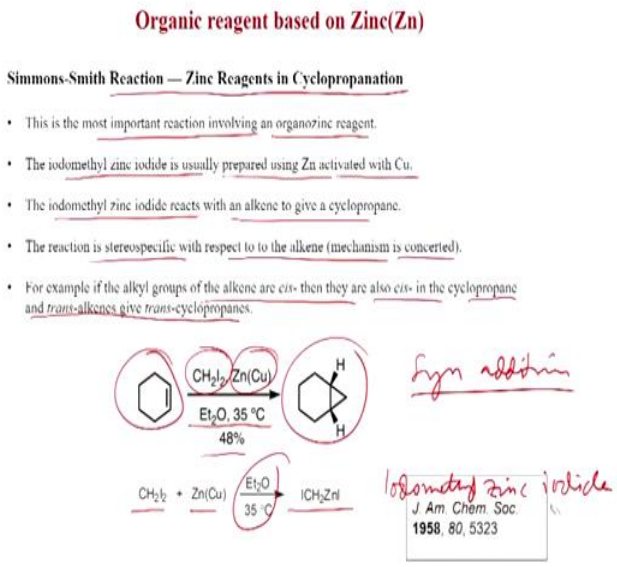

Now, we will discuss another reaction Simmons-Smith Reaction, this is Cyclopropanation. Zinc reagents in Cyclopropanation, this is the most important reaction involving organozinc reagent. The iodomethyl zinc iodide is usually prepared using zinc activated with copper. The iodomethyl zinc iodide reacts with an alkene to give a cyclopropane. The reaction is stereospecific with respect to the alkene mechanism is concerted.

For example, if the alkyl groups of the alkene are cis then they are also cis in the cyclopropane and trans-alkene give trans-cyclopropane. So this is a syn addition and like cyclohexene if you put with CH2I2 and zinc copper couple with ether 35 degree centigrade you get this product. So this is syn addition. And what happen if you put this CH2I2, zinc

copper couple with ether 35 degree centigrade, this is the active intermediate that is forming ICH2 zinc iodide, iodomethyl zinc iodide, so this is forming and which is reacting with the double bond. So mechanism we will see. It was published in JACS, 1958.

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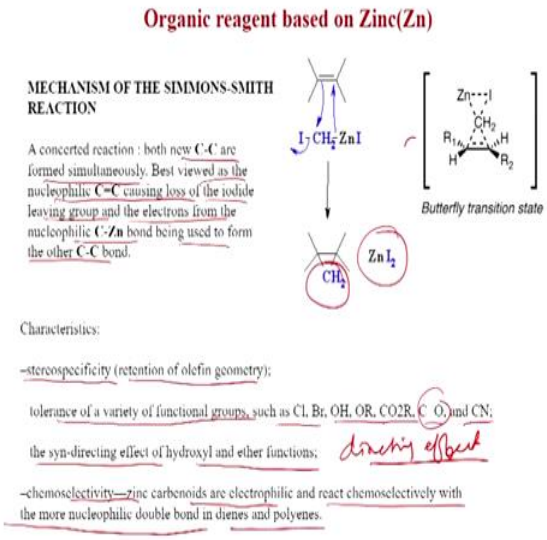

Now, mechanism. So a concerted reaction both new C-C are formed simultaneously best viewed as the nucleophilic C double bond C causing loss of the iodide leaving group and the electrons from the nucleophilic C-Zn bond being used to form the other C-C bond. So this -C bond is forming like this. This is in the leaving group and this is now nucleophilic, so this bond is attacking to the double bond, so that you get this CH2 group and ZnI2 will be by-product. So this is concerted reaction.

And butterfly like transition state also is possible, you can see here the CH2 group is adding to the double bond the Pi electron cloud are delocalized, there are two three membered rings are there. And now the characteristics. We have already told the stereospecificity retention of the olefin geometry tolerance or variety of functional group such as chloride, bromide, OH, OR, CO2R, carbonyl and cyanide.

This is very important, so selectively only reacts to the double bond, not to the carbonyl. The syn-directing effect of hydroxyl and ether functions. This we will discuss, the directing effect, so this is directing effect. And chemoselectivity-zinc carbenoids are electrophilic and react chemoselectively with the more nucleophilic double bond in dienes and polyene. So if you have many double bonds then the more nucleophilic double bond will react.

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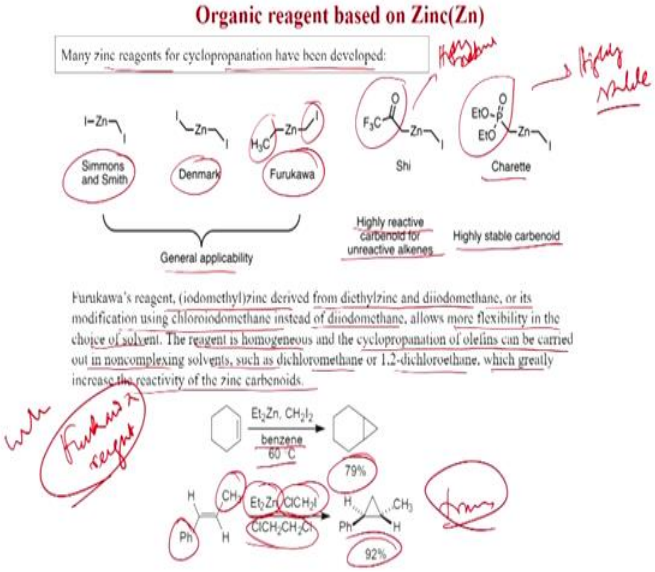

So now many zinc reagents for Cyclopropanation have been developed. The alternatives like this is the Simmons and Smith that is the iodomethyl zinc iodide. Then here the Denmark develop then Furukawa develop with diethylzinc actually, the ethyl group, this is CH2I group. So these are general applicability we will see. And Shi group develop a trifluoro ketone is there. And this is highly reactive carbenoid for unreactive alkenes. So this is highly reactive. And Charette developed with this phosphate and this is highly stable. So one is highly reactive, another is highly stable. When the phosphate is there at that time it has become highly stable.

So this is the Furukawa reagent, iodomethyl zinc derived from diethylzinc and diiodomethane or its modification using chloroiodomethane instead diiodomethane, allows more flexibility in the choice of solvent. The reagent is homogeneous and the cyclopropanation of olefins can be carried out in non-complexing solvents, such as dichloromethane or 1,2-dichloroethane, which greatly increase the reactivity of the zinc carbenoids.

So this is very important this Furukawa reagent, the other non-complexing solvent like dichloromethane 1 to dichloroethane can be used. So this is an example, this is Furukawa reagent. With Furukawa reagent this reactions cyclohexene, diethylzinc, CH2I2 benzene is a solvent 60 degree centigrade, you get this product 79 percent yield. Also here, trans-alkene is there Ph, CH3 with same reagent, diethylzinc but here CLCH2I and 1,2-dichloroethane solvent, you get this product. So this is the trans-product, you are getting 92 percent yield. So that is the importance of Furukawa reagent. You can use different solvents.

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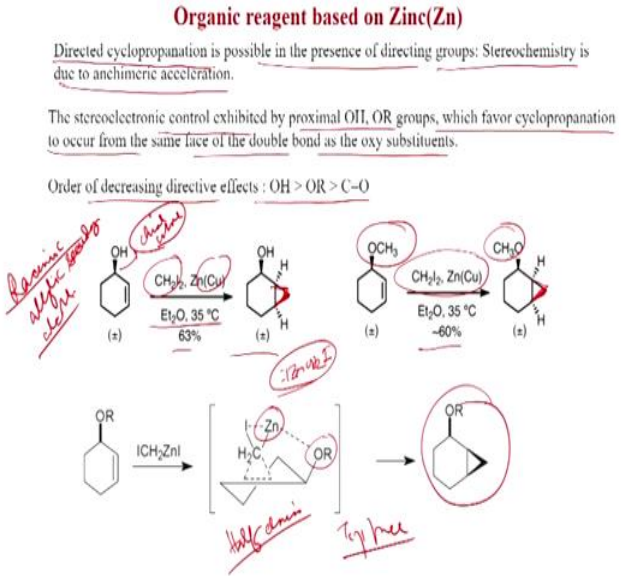

Now, we will discuss directed cyclopropanation is possible in the presence of the directing groups. Stereochemistry is due to anchimeric acceleration. The stereoelectronic control exhibited by proximal OH, OR groups, which favor cyclopropanation to occur from the same face of the double bond as the oxy substituents. An order of decreasing directive effects: OH is greater than OR greater than carbonyl.

So this is you can see, this is of course racemic, racemic allylic alcohol, allylic secondary alcohol. So what happens, this alcohol of course, this is a chiral center. So in the product, you see this cyclopropyl group is in the same side of the hydroxyl. So with CH2I2 zinc, copper, ether, 35 degree centigrade you get 63 percent yield of this product. So cyclopropyl, in the same side with hydroxy like epoxidation. Not only hydroxide, the ether, so this is defined with epoxidation, here the ether also can direct. So ether CH2I2 zinc, copper, you get the same product. So cyclopropyl group is the same side of the methoxy and you get 60 percent yield.

So, what could be the mechanism? So here, you can see this half chair conformation. So this is a half chair conformation. Here, the cyclohexene group, this is a double bond and OR in the top. Now, this OR will complex with the zinc, so this is important. OR or OH is complex with zinc IZnCH2I, so that is the active reactant. Here this is the active reactant is coordination happen. So the addition is taking place from the same side of OR. So here from the top face. So this is the product, you get the cyclopropanation from the same side of the OR group. So because of this coordination, you get this geometry.

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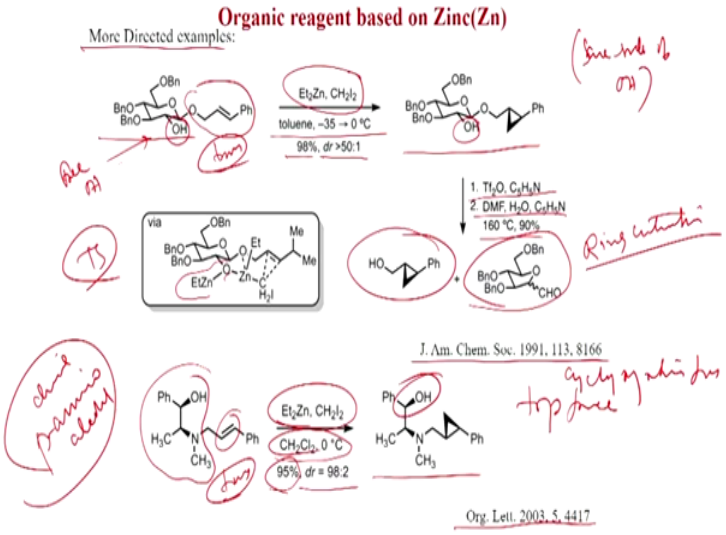

Now, we will see some more directed example. Like here this is an sugar motif and interesting one OH is free. So this is free OH and you see this ether, a double bond is present here. This is of course trans-alkene. Now, with diethylzinc CH2I2 that is the Furukawa condition toluene minus 35 to 0 degree, 98 percent yield and dr greater than 50 is to 1. So this cyclopropanation happens. So same side of OH.

So cyclopropanation happens same side of OH. Of course, this is chiral auxiliary, so that has to be clean. So if you put first triflic anhydride pyridine, you get this O triflate and after that DMF waser, pyridine condition you can get this product, alcohol product, cyclopropyl alcohol and this ring contraction happen. So here ring contraction and aldehyde is formed.

So this is the transition state. So here you can see this cyclopropanation happening is double bond, so here this CH2I group is present. Now zinc is coordinate with of course the hydroxy, this is the hydroxy group, as well as this ether group. So double coordination is happening and now the cyclopropyl group will come from the same phase of the OH group and you get this geometry. This was published in JACS, 1991.

Not only this, this is also you can see chiral beta-amino alcohol is the chiral auxiliary, so this is the double bond. Here also trans double bond is present. Of course, this is the chiral auxiliary, amine hydroxyl is present and with diethylzinc CH2I2 same condition, dichloromethane, 0 degree centigrade you get 95 percent yield and dr is equal is 98 is to 2. So it is very important. Here also, the top face, cyclopropanation from top face that is from the

top face hydroxy side, so the coordination is happening similar way and you get this product. This was published in Organic Letters, 2003.

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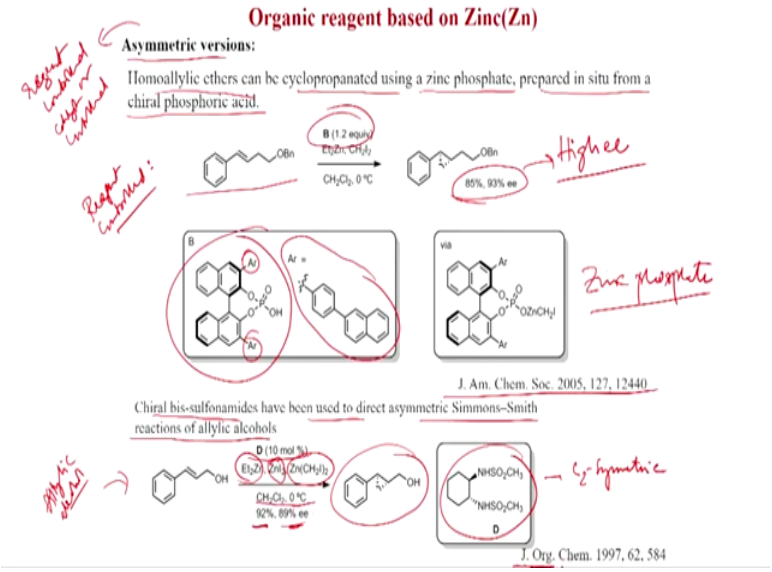

Now, we will discuss asymmetric versions reagent controlled or catalyst controlled that we will see. So homoallylic ethers can be cyclopropanated using a zinc phosphate prepared in situ from a chiral phosphoric acid. So, if you have this homoallylic ether O benzyl ether and B is this phosphoric acid with this substituent Ar is here, three prime substituent and when it is treated diethylzinc CH2I2 then this zinc phosphate is formed. So this in chiral environment and this is used in 1.2 equivalent and the products, cyclopropanation happens in 85 percent yield with 93 percent enantiomeric excess, so this is very high ee. And this group are required for this control of high enantiomeric induction this work was published in JACS, 2005, Page Number 12440. So this is reagent control because you want equivalent unit**.**

And now we will see catalyst control, so chiral B sulfonamides have been used to direct asymmetric Simmons-Smith Reaction of allylic alcohols. This is allylic alcohol and with this B sulfonamide, this is C2 symmetric, this is 10 mole percent only then diethylzinc, zinc iodide plus zinc CH2I whole 2 with dichloromethane solvent 0 degree centigrade, you get this cyclopropanation products in 92 percent yield with 89 percent ee. So this is very important. Only 10 mole percent of this catalyst can give very high yield as well as very high ee. This work was published in Journal of Organic Chemistry 1997, Page Number 584.

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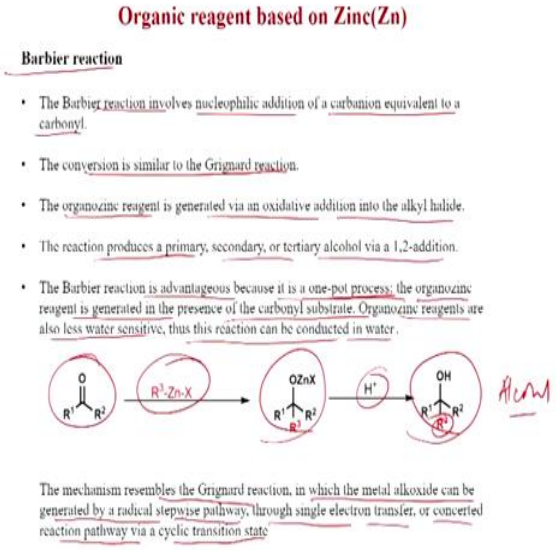

Now we will see another reaction the Barbier Reaction involves nucleophilic addition of a carbanion equivalent to a carbonyl. The conversion is similar to the Grignard reaction. The organozinc reagent is generated via an oxidative addition into the alkyl halide. The reaction produces a primary, secondary or tertiary alcohol via 1,2-addition.

And the Barbier Reaction is advantageous because it is one-pot process, the organozinc reagent is generated in the presence of the carbonyl substrate. Organozinc reagents are also less water sensitive, thus this reaction can be conducted in water.

So this is very important, it can be conducted in water also. So carbonyl compound R3ZnX, the 1,2-addition happens and after aqueous acid workup, you get this alcohol. So this R3 is coming from the zinc. The mechanism resembles the Grignard reaction, in which the metal alkoxide can be generated by a radical stepwise pathway through single electron transfer or concerted reaction pathway via a cyclic transition state. So this kind of possibility is there either by a radical pathway or concerted reaction pathway.

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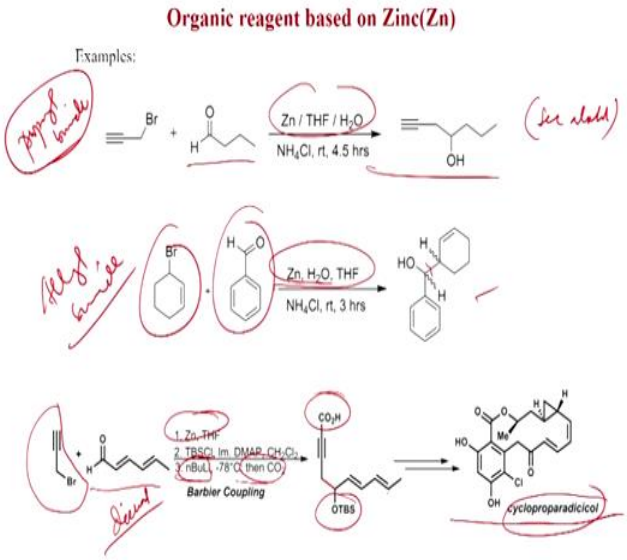

Now we will see examples, so this is propargyl bromide. So with zinc, THF, first this propargyl zinc bromide will form that will add to the aldehyde and you get the secondary alcohol. Also, allyl bromide, allyl bromide if you put zinc water, so this is very important water can be solvent zinc water, THF, and with benzaldehyde you get this product.

So here the zincate formed, so this is the newly bond form and propargyl bromide can also be reacted with this dienal, so this is dienal with zinc THF then the protection TBS chloride, so alcohol is protected as TBS and this terminal CH that is the alkyne CH can be deprotonated with n-butyl lithium then carbon dioxide treatment will give you CO2H group and this intermediate can be converted to this cycloproparadicicol. So this you can see this geometry. So some functionalities are coming from here like this one most likely.

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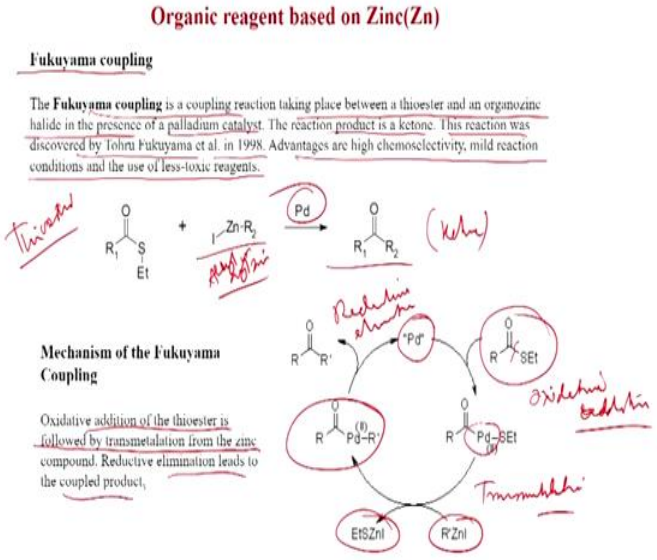

Now, we will discuss Fukuyama coupling that is the last reaction of zinc. So Fukuyama coupling is a coupling reaction taking place between a thioester and an organozinc halide in the presence of a palladium catalyst. The reaction product is a ketone. This reaction was discovered by Tohru Fukuyama et al in 1998. Advantages are high chemoselectivity, mild reaction condition and the use of less toxic reagents. So this is an important thioester and zinc, alkyl or aryl zinc.

With palladium catalyst of course you get the ketone. So this is very important reaction and the mechanism like this oxidative addition of the thioester is followed by transmetalation. Now palladium zinc of course here, now thioester, the oxidative addition happening. So oxidative addition, COS bond here the palladium is insert, palladium two now. Now, the transmetalation will happen, transmetalation. From the zinc compound, so R dash will come to palladium and this will be by-product, EtSZnI and now, this is the reductive elimination will happen, so ketone will get and palladium will re-generate this to the coupled product.

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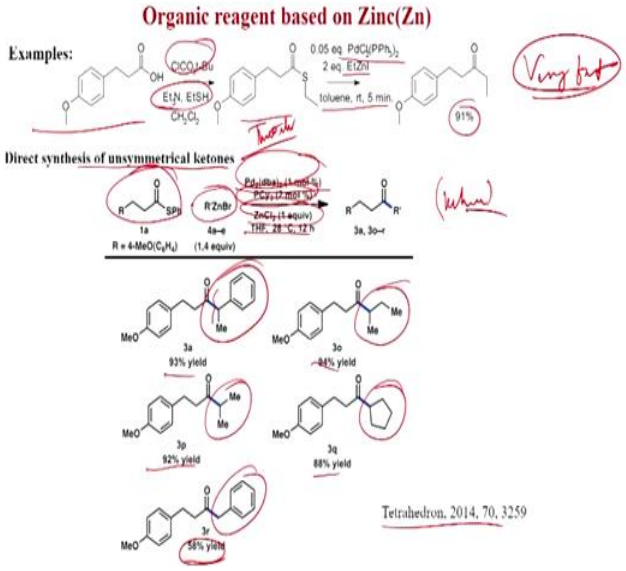

So we will see some examples. Like here, a carboxylic acid you have to first convert to acid chloride then you treat with diethyl I men ethanethiol, you get this thio ester, so this is thio ester and with palladium chloride PPh3 whole 2 EtSZnI toluene room temperature only 5 minutes you get this product, ketone. So this is very fast process, only 5 minutes you get this ketone product.

Direct synthesis of unsymmetrical ketones. So this is the thio esters, R dash ZnBr, Pd2dba whole 3 1 mol percent PCy3, 2 mol percent zinc chloride one equivalent THF 28 degree centigrade, 12 hours you get this ketone. And here, various zinc can be used. So this is the thio ester, so this is zincade part. Here also aliphatic, here also aliphatic here cyclopentyl group and here the benzyl group. So the yields are good here 92 percent, 93 percent, 94 percent, 88 percent and this one 58 percent. This was published in Tetrahedron, 2014

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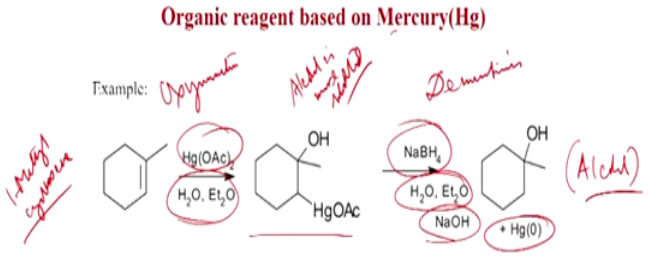

Now we will see example. Like here, this is 1-methyl-cyclohexene if it react with mercury acid what are ethanol then you can get this one regioselectively so alcohol is more substituted. And after that sodium borohydride treatment if water diethyl ether with a base you can get the removal of the mercury and you can get this alcohol, free alcohol. So this is oxymercuration and this is demercuration.

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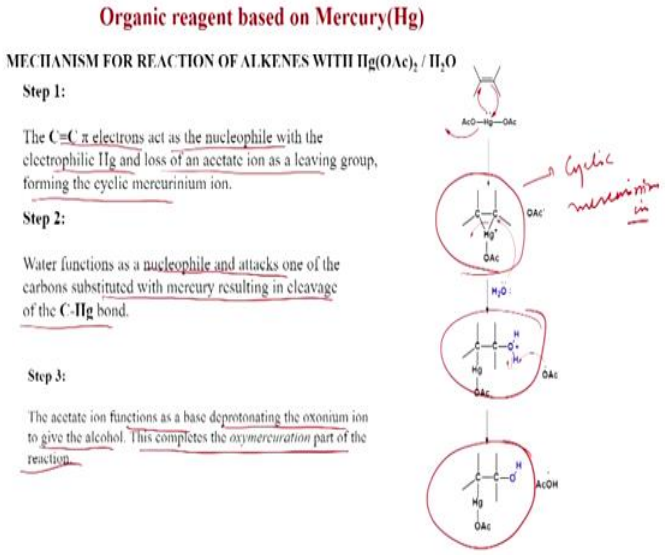

So we will see now detail mechanism. So Step 1: the C double bond C pi electrons act as nucleophile with the electrophile mercury and loss of an acetate ion as a leaving group forming the cyclic mercurinium ion. So it is happening like this. So this is the cyclic mercurinium ions. Now water attacks as a nucleophile and carbon substituted with the

mercury resulting in cleavage of the C-Hg bond. So this will form. And now acetate ion function as a base deprotonating the oxonium ion to give the alcohol. This completes the oxymercuration part of the reaction. So now, this you get and the alcohol are the more substituted carbon atom because of the Markovnikov addition.

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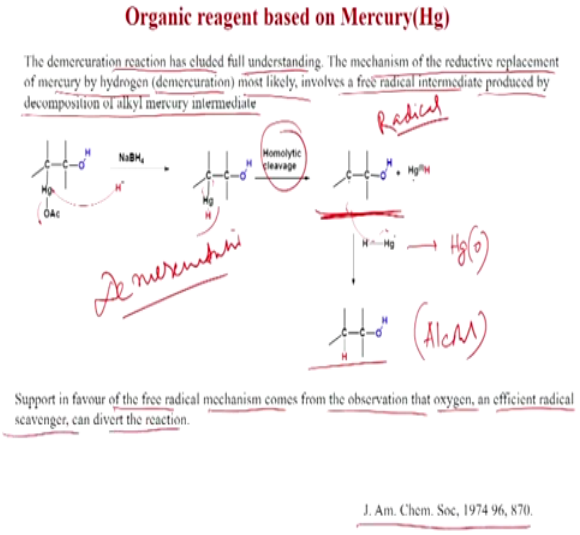

Now the demercuration reaction has eluded full understanding. The mechanism of the reductive replacement of mercury by hydrogen demercuration, most likely involves a free radical intermediate produced by decomposition of alkyl mercury intermediate. So most likely hydride will react with this mercury and this HgH bond will form and after that hemolytic cleavage will happen and this radical will form, is the radical and Hg dot H occurs and now again it will react this is radical with H and this will go to mercury 0, so you can get the alcohol. So this is the demercuration is happening. Supporting favor the free radical mechanism come from the observation that oxygen and efficient radical scavenger can divert the reaction and this was published in JACS 1974.

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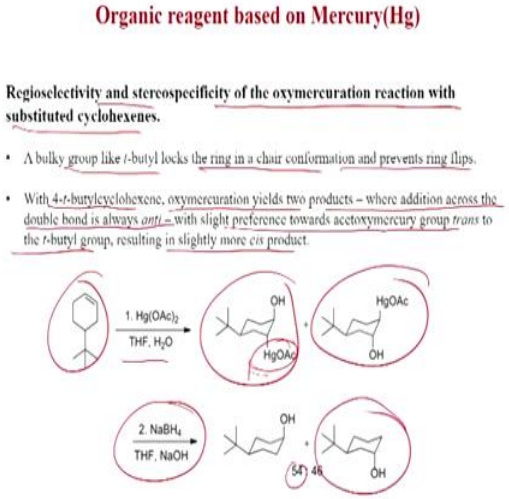

And the regioselectivity and stereospecificity of the oxymercuration reaction which substituted cyclohexenes. A bulky group like tertiary butyl locks the ring in a chair confirmation and perverts ring flips with 4-tertiary butyl cyclohexene, oxymercuration yields two products where addition across the double bond is always anti with slight preference towards acctoxymercury group trans to tertiary butyl group resulting in the slightly more cis product.

So here you can see four tertiary butyl cyclohexene, oxymercuration reaction gives two product. This is almost equal amount because after sodium borohydride THF, sodium hydroxy treatment you get this. So mercury addition to the downside is a little bit measure, it is forming 54 percent and this is 46 percent this one.

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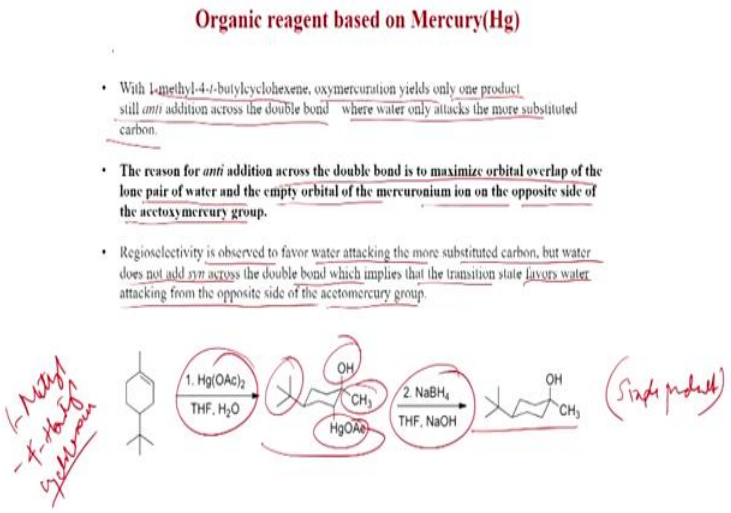

Now with 1-methyl-4-tertiary-butyl- cyclohexene, oxymercuration yields only one product still anti addition across the double bond where water only attacks from the more substituted carbon. And the reason for anti-addition across the double bond is to maximize orbital overlap of the lone pair of water and the empty orbital of the mercuronium ion on the opposite side of the acctoxymercury group.

Regioselectivity is observed to favor water attacking the more substituted carbon. But water does not add syn across the double bond which implies that the transition state favors water attacking from the opposite side of the acctomercury group.

So this is the 1-methyl-4-tertiary-butyl- cyclohexene and now if you do chair like after mercury acetate you get this product where this mercury acetate opposite of the tertiary butyl. And of course, water attacks from the opposite side OH is like this and methyl will be down and with sodium borohydride treatment you get only the single product. So only single product is forming. So this is very important mercury acetate will be trans to the tertiary butyl, so water will come from the opposite side anti phase, so you get this product.

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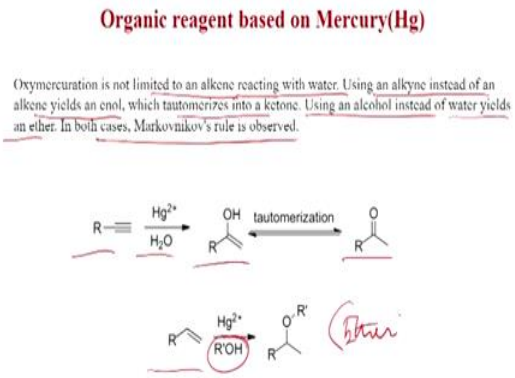

Oxymercuration is not limited to alkene reacting with water using an alkyne instead of an alkene yields an enol, which tautomerizes into a ketone. Using an alcohol instead of water yields an ether. In both cases, Markovnikov's rule is observed. So this is alkyne Hg2plus you get the enol tautomerization to ketone and with an alkene that we told earlier that which alcohol you can get ether, so this is an ether is forming.

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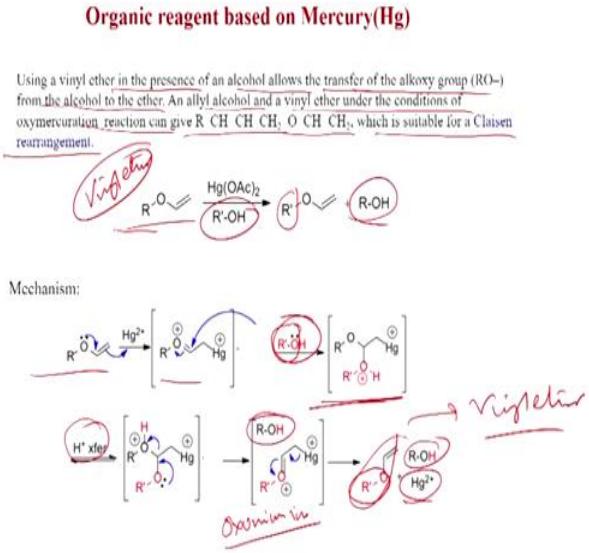

And using a vinyl ether in the presence of an alcohol allows the transfer of the alkoxy group RO from the alcohol to the ether. An allyl alcohol and a vinyl ether under the condition of oxymercuration reaction give R CH double bond CH CH2 O CH double bond CH2 which is suitable for a Claisen rearrangement.

So this is the reaction. RO vinyl ether, so this is vinyl ether and with an alcohol R dash OH, so R dash coming here and ROH is the by-product. So this is the exchange is happening, we will see the mechanism. So what could be the mechanism? So this vinyl ether first coordinates with the mercury to generate the oxonium ion and to the oxonium ion, the alcohol will add to generate this acetyl derivative and after that deprotonation or HX plus transfer will happen. So here, the proton goes to this part now.

And again another oxonium ion, so again oxonium ion will form oxonium ion and ROH is the by-product. And after H removal, so after removal you get this vinyl ether Hg2 plus and ROH, so this is a vinyl ether. So this is the mechanism of the vinyl ether the transfer of the alkoxy group. So it is the alkoxy group, R dash O that is because here you can see this is the red oxygen, earlier oxygen were black, this is red oxygen. So the R dash O alkoxy group is transferring.

So today in the class, first we have discussed preparation of organozinc halides. Then we have discussed the application of organozinc halide. First the Achiral reactions we have discuss then Enantioselective 1,2-addition, Diastereoselective addition then Enantioselective 1,4-addition reaction with rhodium catalyst also we have discussed.

Then we have discussed preparation of dialkylzinc and its reaction, it undergoes many radical reaction because dialkylzinc it generate the methyl dot radical and which generate the tetrahydrofuran suppose then the tetrahydrofuran radical will form which can add to different electrophiles then organozincates their preparation we have discuss and reactions, it can add different addition products 1,2-addition, 1,4-additions and also palladium catalysed coupling reactions it can do.

Then we have discussed the Reformatsky reaction, it is an important method for generation of beta-hydroxy esters. Also we have seen the double Reformatsky reaction, if you have pyridine in the ketone then the double Reformatsky reaction can happen because the pyridine coordinate with the zinc.

Simmons-Smith Reaction, this is very important reaction for cyclopropanation and also we have seen the more reactive double bond will react and will be a directing group if you have a hydroxyl group also an ether group that can coordinate with the zinc and the cyclopropanation will happen from the same face.

Then we have discussed the Barbier Reaction, this is like Grignard addition, so it is similar but here you can use the water as the solvent. And lastly, we have seen the Fukuyama coupling which ketone formation from thio ester and alkylzinc compound with palladium catalyst. And in the mercury, we have discussed oxymercuration, demercuration this is the Markovnikov addition to generate alcohol from olefin and you can get the more substituted alcohol here. Thank you.