**Reagents in Organic Synthesis**
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**Hydride Based Reduction**
**Lecture 08**

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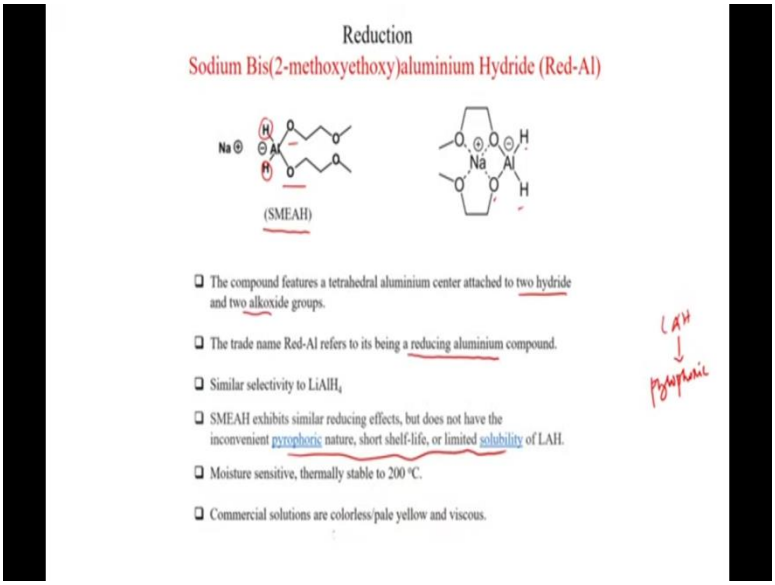


Welcome, today we will discuss different reducing agent. First one is Red-Al then we will discuss sodium borohydride, sodium cyanoborohydride, then zinc borohydride, lithium borohydride and K selectride or L selectride.

So first we will discuss Red-Al which is sodium Bis(2-methoxyethoxy)aluminium Hydride and the structure is like this where two alkoxy group is connected with aluminium and two hydrides are present on the aluminium anion. Also this structure can be drawn like this as sodium is connected to four oxygen and aluminium connected to two oxygen and the two hydride are attached to aluminium. This is also called SMEAH because S stands for sodium, M for methoxy, E for ethoxy, A for aluminum and H for hydride.

The compound features a tetrahedral aluminium centre attached to two hydride and two alkoxide groups. As we have seen, the trade name Red-Al refers to being a reducing aluminium compound. So Red means reducing, Al means aluminium. Similar reactivity to Lithium aluminium hydride, however though SMEAH exhibits similar reducing effects, but does not have the inconvenient pyrophoric nature.

Lithium aluminium hydride, it is pyrophoric. That means it gets fired when in, when it is in the air but SMEAH is quite stable. It has short shelf life or limited solubility of LAH. So it does not have limited solubility like LAH or short self life like LAH. So these are the properties of LAH which does not have with SMEAH or Red-Al. This is moisture sensitive. It is thermally stable to 200 degree Centigrade. Commercial solutions are colourless, pale yellow and viscous.

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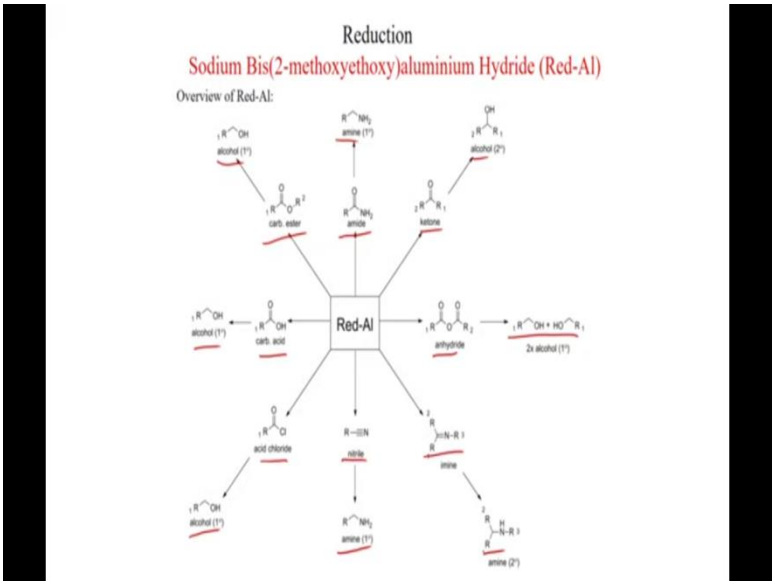


Reduction overview of Red-Al reduction. Red-Al, as we have told the Red-Al has the similar reactivity like lithium aluminium hydride. So whatever reductions lithium aluminium hydride undergoes, Red-Al also done similar reduction like anhydride gets to alcohol. Imines gets Amine. Similarly, nitrile goes to primary amine. Acid chloride goes to alcohol. Carboxylic acid goes to alcohol. Ester, also it goes to alcohol. Amide goes to amine. Ketone goes to alcohol. Also, aldehyde goes to alcohol. So, Red-Al has similar reactivity like lithium aluminium hydride but it is less pyrophoric. It is not pyrophoric like lithium aluminium hydride so it is more convenient to use, also a wide solubility.

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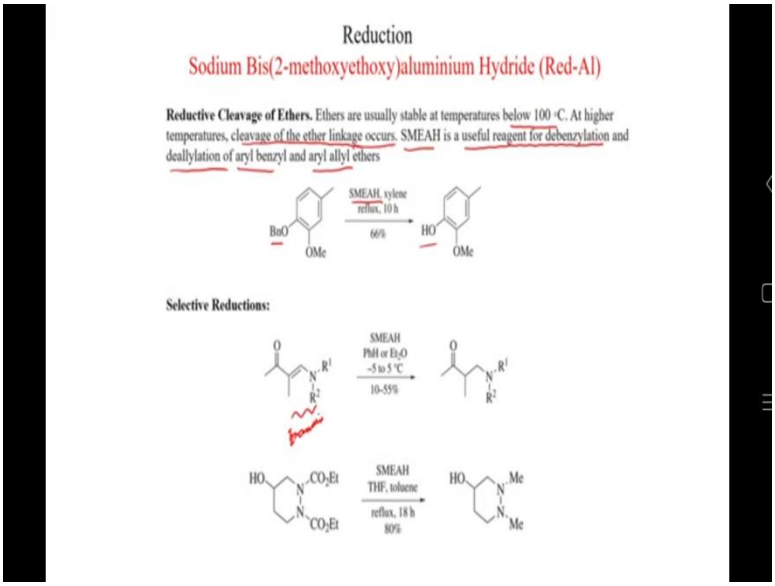


Also it can reduce ether and that is called reductive cleavage of ethers. Ethers are usually stable at temperature below 100 degree centigrade. At higher temperatures, cleavage of the ether linkage occurs and SMEAH is a useful reagent for debenzylation and deallylations of aryl benzyl and aryl allyl ethers. So we can see examples like these benzyl aryl ether, you can see this is benzyl group. This is aryl, and when it is treated with SMEAH xylene reflux, 10 hours, the benzyl group gets deprotected and you get the phenol derivative.

Selective reductions also is possible like here a carbonyl group is present and here this enamine, this is an enamine, and under this SMEAH condition, it's benzene or ether minus 5 to 5 degree centigrade, you get 10 to 55 percent yield of this double bond enamine reduction. That is the double bond gets reduced and carbonyl gets intact. Also, you can see there are 2 amide motifs are there, here and here. And these, these are actually carbonyl motifs and this carbonyl motifs are getting reduced with SMEAH and THF toluene under reflux condition and both becoming a tertiary amine motif and you get 80 percent yield of the product.

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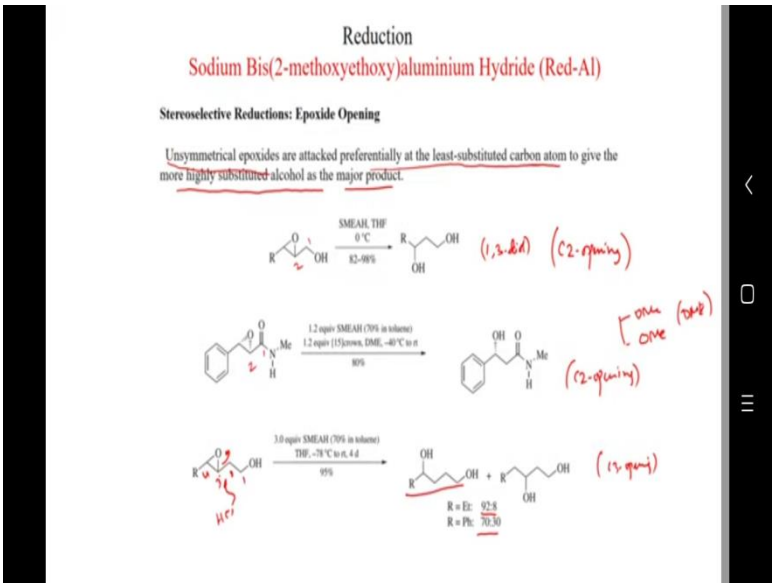


This is also an important reaction of Red-Al. Stereoselective reduction Epoxide Opening, so unsymmetrical epoxides are attacked preferentially at the least hindered or least substituted carbon atom to give the more substituted alcohol as the major product. Like this one, you can see this is, there is 2-3 Epoxy alcohol that is the allylic alcohol. If you do the epoxy dissent you will get this product. And now if you treat this compound with SMEAH THF 0 degree centigrade, you get this alcohol. So this is 1, 2, 3, 1,3 diol. And if you count the carbon atom, this is 1 2, so this C2 opening.

So mechanism we will see shortly but let's see more examples like here, the amide group is there as well as the epoxide is there with 1.2 equivalent SMEAH, 70 percent toluene and 1.2 equivalent crown ether DME solvent, DME is 1,2-Dimethoxyethane, so this is DME. And here also the selective opening of C2, so C2 opening is happening and you get this alcohol, beta hydroxy amide, you get this product.

Similarly if you have a 3,4-Epoxy alcohol. Then also you get the opening at this C3, C3 opening and you get, so regioselectively hydride is attacking at this position and you get this alcohol as major. When R is equal to ethyl you get 92 is to 8 ratio and R is equal to phenyl you get 70 is to 30, so when R is equal to phenyl you get slightly less but the major product is the same, that the C3 opening. So what we have observed? That the carbon centre which is close to the hydroxy group that is opening. So this might be the mechanism.

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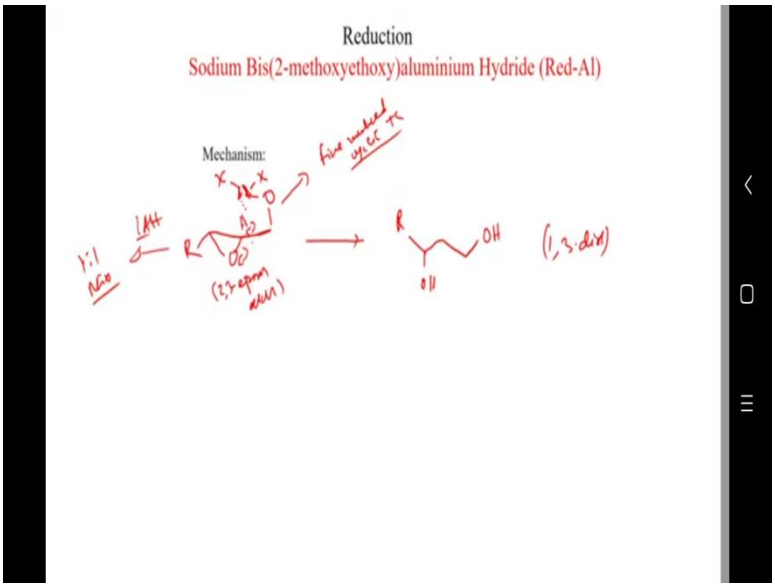


We can draw a mechanism like this. And this is the Red-Al and now a hydride attacks here. So what happen the hydroxy group bind with aluminium and the hydride, so this is a 5 membered intermediate is forming. 5 membered cyclic transition state possible and now you get the C3 opening so you get this alcohol. This is a very important that C2, 1, 1, 2, 3, 4, 5, this should be 1 less actually, so if we see this alcohol $CH_2OH$, so this will be $CH_2OH$ and now you get a 5 membered ring here, 1 2 3 4 5, 5 membered cyclic transition state and you get 1.3 diol and in fact, if you do a lithium aluminium hydride of this 2,3 Epoxy alcohol, 2,3 epoxy alcohol, then you get 1:1 mixture.

So this is very important that the Red-Al preferably binds with the aluminium complex and the hydride delivery takes place from the C2 atom, so that epoxide will open and you will get the more substituted alcohol, that is the 1-3 diol.

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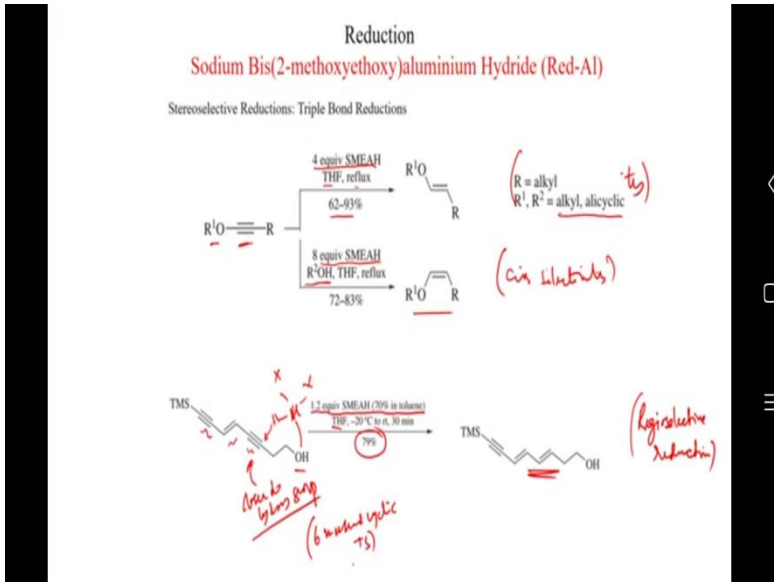


Some more reaction radon performs like triple bond reductions. If you see this, there is a triple bond here, there is a alkoxy group and when you treat this compound with 4 equivalent SMEAH THF reflux condition you get 62 to 93 percent yield of this trans product. So here trans selectivity. On the other hand, if you do the same reaction with 8 equivalent SMEAH and you take an alcohol which is a proton source, alcohol THF reflux and then you get the cis selectivity. And you can see which kind of groups you can tolerate here. You can see the R is equal to alkene, $R^1$, $R^2$ is equal to alkene alicyclic, so different groups can be tolerated.

Now if you do the reaction with this kind of alcohol where the conjugated alkyne, alkene, alkyne is there and selectively the alkyne which is close to the hydroxy group so this is the closer to hydroxy group. And this triple bond only will get reduce so this is a regioselective reduction. Because there are many groups, that is the olefin as well as alkyne is present. So the reduction takes place only this alkyne and you get the trans product and very good yield when you treat with 1.2 equivalent SMEAH which is 70 percent toluene, THF minus 20 degree centigrade. So similar like, whatever we told that, here also, here instead of 5 membered you get a 6 membered aluminium, so this kind of aluminium hydride and like this, it will form. So 1, 2, 3, 4, 5, 6, so 6 membered cyclic transition state will be there so that you get a trans product.

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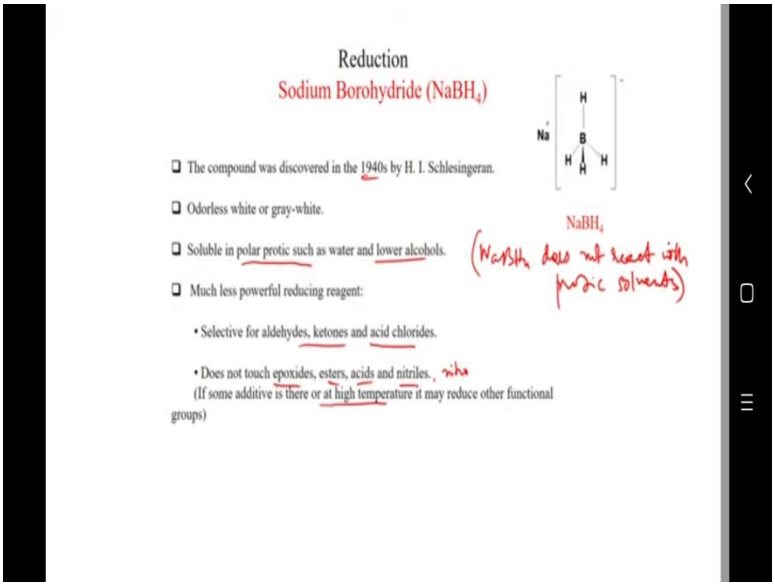


Now sodium borohydride reduction, this is also a popular reducing agent. And this structure is like this. There is a borhoydride minus because boron has 4 hydrogen attached and sodium plus. It was discovered in 1940's by H. I. Schlesingeran. This is odourless, white or grey white, soluble in polar protic such as water and lower alcohols. So this is important. sodium borohydride, sodium borohydride does not react with protic solvents.

So this is important that lithium aluminium hydride, they are so reactive or Red-Al, they are so reactive that they will reduce, they will react with protic solvents but here polar protic such as water and lower alcohols can be used. Much less powerful reducing agents selective for aldehydes, ketones and acid chlorides does not touch epoxide, esters, acids, nitriles, also nitro compounds. However, if some additive is there or at high temperature it may reduce or if you increase the equivalence of sodium borohydride then also it can reduce other functional groups. That we will see later.

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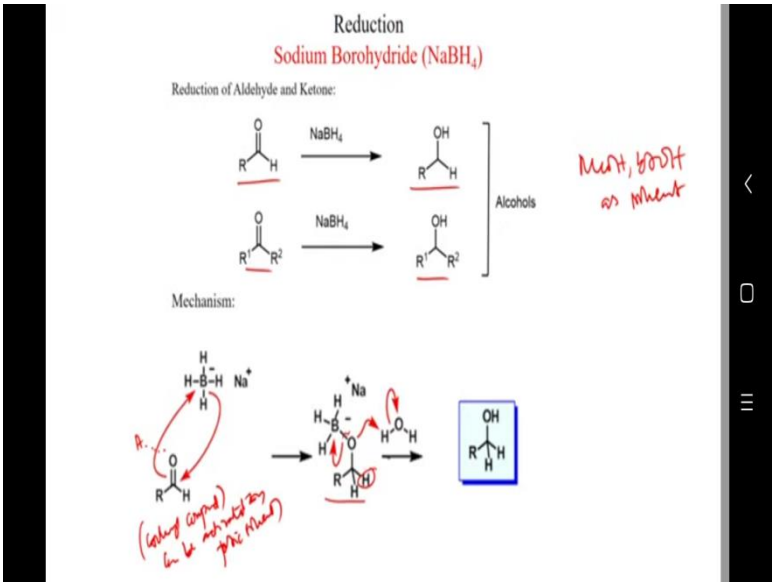


So this is the sodium borohydride reduction of aldehydes and ketones. So aldehyde gives primary alcohol, ketone gives secondary alcohol. And generally good yield under mild condition generally in methanol or ethanol, methanol, ethanol as a solvent. And what could be the possible mechanism of this reaction so here, it can be the, it can be possible that the protic solvent also slightly activates this hydrogen bond with carbonyl, it slightly activates that carbonyl compound. Carbonyl compound can be activated also by protic solvent.

And now this hydride delivery will take place from the borohydride and this oxygen of the aldehyde or carbonyl compound can react with boron, and you get this kind of alkoxy borane intermediate. This is $BH_3$ now because 1 hydride comes here and now this is also, because oxygen is now binding with borane and now the proton source like water or alcohol will react with this and it will cleave the oxygen boron bond will cleave and you get the alcohol here. So this is the mechanism that hydride delivery will take place and oxygen will bind with borane so alkoxy borane intermediate will form which cleaves in protic solvent like water or acidic workup you get the alcohol.

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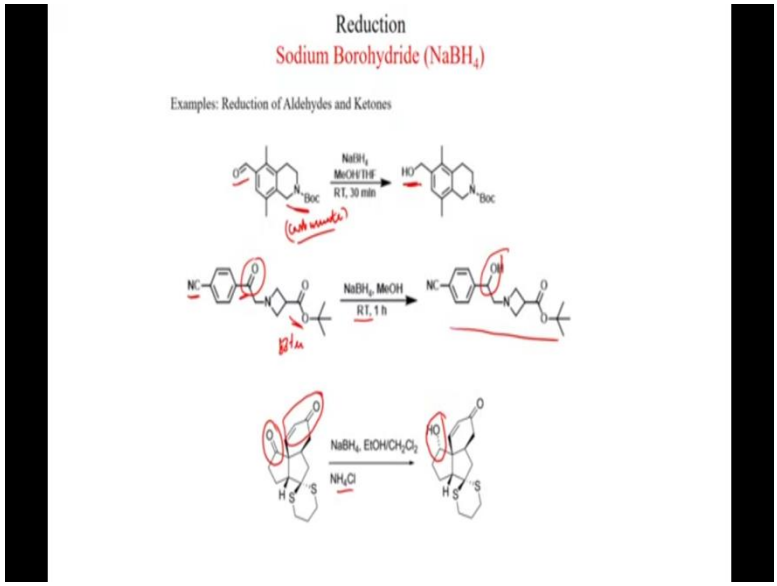


Example, reduction of aldehydes and ketones like this compound you can see there is an aldehyde group but also an N-Boc group is present so this is carbamate and with sodium borohydride, methanol, THF at room temperature condition, you gets only the primary alcohol. So aldehyde group only reduce. That means sodium borohydride is a mild reducing agent. Also you can see here, three functional groups are there. Cyano is there, carbonyl is there and this is an ester motif and sodium borohydride and methanol room temperature within one hour, it can give high yield of this product. So only the ketone group reduced to the alcohol.

The ester and cyano group are untouched. Similarly here, you can see a thioketal motif is there, a ketone is there and also alpha beta unsaturated ketone is there, and with sodium borohydride, ethanol, chloroform and ammonium chloride as the proton source, so under this condition you get selectively only this carbonyl group is reduced. So here this alpha beta unsaturated ketone cannot be accessed might be due to the steric region, that's why only the carbonyl group is, saturated carbonyl group is getting reduced and it is getting reduced from the top face so, you get the alpha alcohol.

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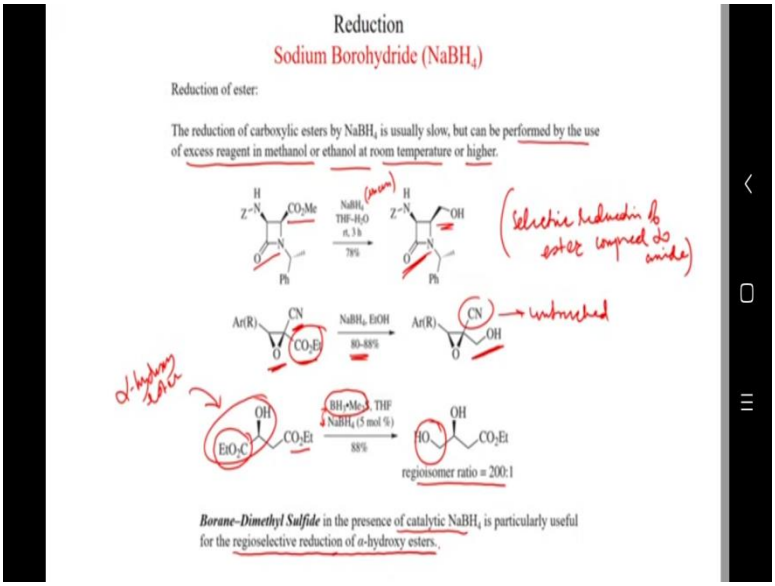


Reduction of ester, so that also told that sodium borohydride in general does reduce ester but under more equivalent of sodium borohydride or at high temperature, sometimes it can reduce carboxylic acid ester like carboxylic ester is usually slow but can be performed by excess reagent in methanol or ethanol even at room temperature or higher. So excess reagent you have to use like this one. Here you can see that there is a lactam motif beta lactam and also a methyl ester is there and with sodium borohydride, so this would be excess at THF, water, solvent and room temperature within 3 hours you get this alcohol, primary alcohol and this lactam motif is untouched.

So selective reduction of ester compared to amide because LAH will reduce both so that way sodium borohydride in high excess it can reduce ester. Similarly here, there is an epoxide motif is there, there is cyano, there is ester and with sodium borohydride ethanol you get 80 to 88 percent yield of this alcohol. So only the ester group gets reduced to the alcohol. Cyano group is untouched. This is untouched. Another reagent, this is sodium borohydride 5 mol percent and borane dimethylsulfide. So both reagents are there and under this condition you can selectively reduce this ester. So there are two ester motif, this and this and this is alpha hydoxy ester so this motif is called alpha hydroxy ester.

And this ester getting reduced to the alcohol and the regioisomeric ratio 200 is to 1 so, very high regioselectivity so only this ester which is alpha to the hydroxy group is

getting reduced. The other one is not reduced. So this is in the presence of catalytic sodium borohydride is particularly useful for the regioselective reduction of alpha hydroxy ester. So this is very selective reduction when sodium borohydride is mixed with borane dimethylsulfide in THF solvent.

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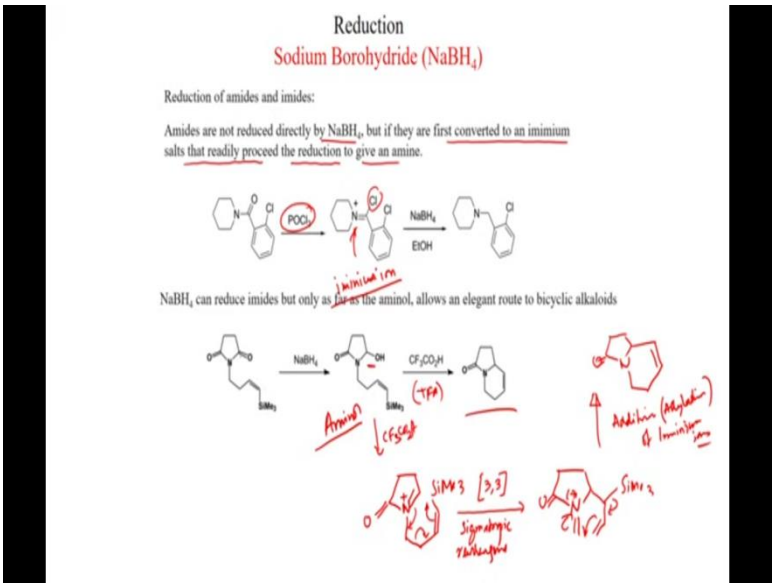


Reduction of amides and imides. Amides are not reduced directly by sodium borohydride, but if they are first converted to an iminium salts that readily proceed the reduction to give an amine. Like here, the amide is treated with $POCl_3$ and it converted to the iminium ion, iminium ion and now sodium borohydride can react with this iminium ion. Here, reduction as well as this group leaves, so you get a tertiary amine. $NABH_4$ can reduce imides but as far as the aminol, aminol allows an elegant route to bicylic alkaloids. Look this imide is there.

Now it would, sodium borohydride you treat. Then you get this aminol. Aminol, and now, $CF_3$, that is the TFA, trifluro acetic acid. So if you treat the acetic acid, then you get this product. This cyclisation happens. So what could be the possible mechanism? So, most likely this one will give an iminium ion. So if you see, this is a cis double bond, cis to this, so we can write like this. So now we can see, there will be the positive charge here. Now we can see there are 6 atoms are present and now these 3, 3 sigmatropic rearrangement is possible. So 3, 3 sigmatropic rearrangement. Now, you get this one, there is an iminium ion and now your silyl will be here.

This bond will form and you get this. Now, what will happen, now the allylation of imines like this. Because this iminium ion now again. This addition will take place. So after that you get this product. So like addition or allylation, allylation of iminium ions and then you get this bicyclic alkaloid. So this means the sodium borohydride can selectively reduce the imide to the aminal because LAH can reduce to the amine so the better you convert to aminal and then you can make this bicyclic alkaloid. So this is very useful strategy.

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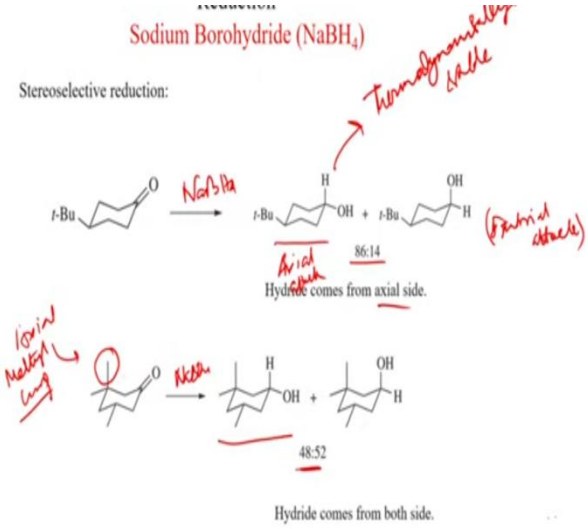


Sodium hydroxide stereoselective reduction also possible, like if you use this 4 tertiary butyl cyclohexanone, then if you treat sodium borohydride. Now you get mixture of products. This is actually through axial attack, axial attack and this is through equatorial attack equatorial attack. And now you see the ratio is 86 is to 14 so this is the major. This is minor. So axial attack is preferable. Hydrides comes from axial side. And now if you use this one where 3,3-Dimethyl and 5-Methyl cyclohexanone, so this compound when treated with sodium borohydride, it gives almost 1 is to 1 mixture so here hydrides come from both side.

So what happens here, because there is a axial methyl group, axial methyl group, sodium borohydride when it comes from the axial side then there will be a steric hindrance with this methyl group and this axial attack will give the product which is actually thermodynamically stable because you get an equatorial alcohol. So this is thermodynamically stable. This one. So axial attack gives a thermodynamic alcohol, thermodynamically controlled product which is equatorial alcohol but when you put a

methyl group in the axial position, then this selectivity because then the hydride delivery is getting steric hindrance from the methyl group.

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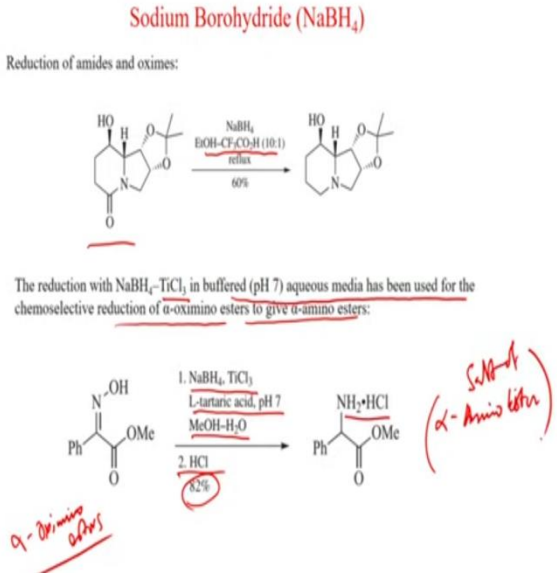


Reduction of amides and oximes also possible, like if you treat this compound, this is the amide with sodium borohydride, ethanols, trifluro acetic acid 10 is to 1, reflux condition, you get the amide to amine. The reduction with sodium borohydride titanium chloride and buffered aqueous media has been used for the chemoselective reduction of alpha oximino ester to give alpha amino esters. So this you can see, this is alpha oximino ester. So this is the oxime.

This is the the ester and with this sodium borohydride-titanium chloride, L-tartaric acid, pH 7, methanol water followed by HCl treatment, you get 82 percent yield of this salt actually. This is the $NH_2HCl$, so this is the salt of alpha amino ester. So, salt of alpha amino ester. So this is a very important reaction that oxime can be reduced to sodium borohydride titanium chloride in the L-tartaric acid.

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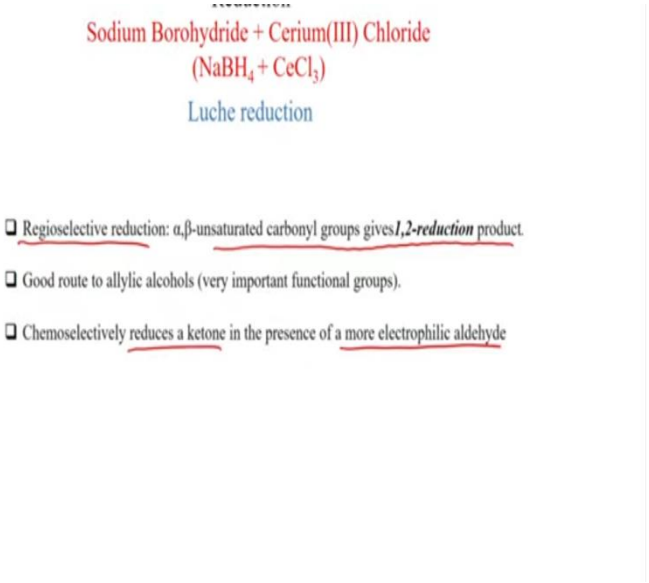


Now sodium borohydride cerium chloride, which is called also Cerius chloride. This one is discovered by Luche, that's why it is also called Luche reduction and this has some special selectivity like regioselective reduction of alpha beta unsaturated carbonyl compounds give 1,2-reduction product. Good route to allylic alcohols, very important functional groups. Chemoselectively reduces a ketone in the presence of more electrophilic aldehyde. This is also an important reaction. It can reduce a ketone in the presence of an aldehyde.

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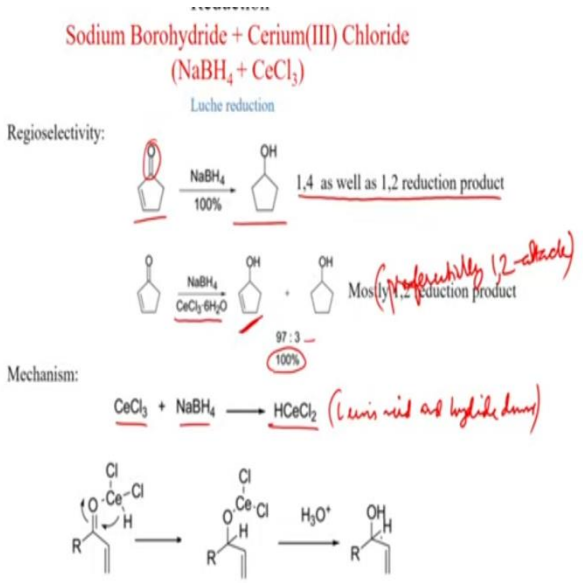

So this kind of enone, like cylopentenone. So cyclopentenone, if you treat with sodium borohydride, you get 100 percent yield of this product, cyclopentanol. So what happens here, here actually 1,4 as well as 1,2 reduction so both groups getting reduced, cyclo ketone as well as the double bond. However, when you do this reaction with sodium borohydride cerius chloride, you get selectively this allylic alcohol and the saturated alcohol you get only 3 percent.

This is the 100 percent yield of the mixture product and now 97 percent is this one. So, what happens here preferentially, 1,2 attack is happening. So 1,4 attack, that is the attack on the double bond is not happening here. Only the carbonyl group is getting reduced. The double bond is untouched. Mostly, 1,2 reduction product. So what is the mechanism. There are two mechanism.

The first, is the cerius chloride which reacts with sodium borohydride, it generates another hydride source which is $HCeCl_2$, and now $HCeCl_2$ is a Lewis acid also. Lewis acid and hydride donor. So it does both purposes as you can see here, it binds with oxygen that is a carbonyl oxygen and now this hydride, so that's why, it gets activated. Now hydride can deliver to the carbonyl group and you get this intermediate where O-Cerium bond is formed. And now after acidic work up you get the alcohol.

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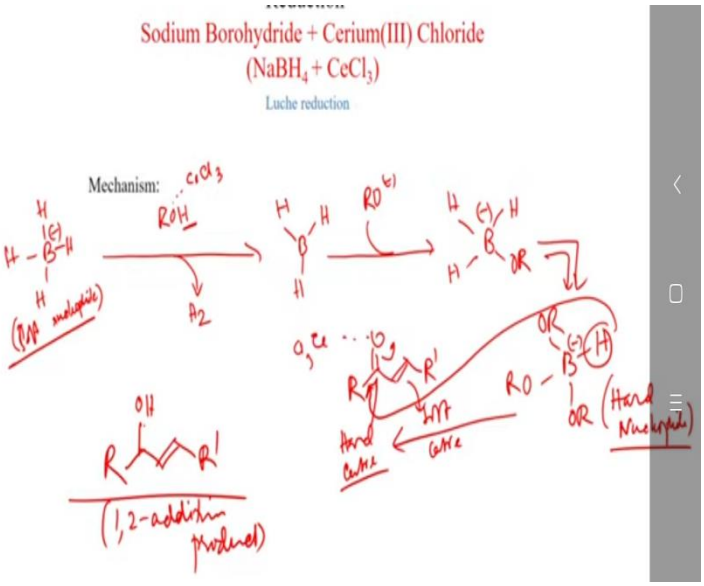

So another mechanism is also there which we can discuss that when $BH_4$ is there, that is the sodium borohydride. This is an soft nucleophile and now if you treat with ROH which is activated by cerous chloride and now what will happen, with cerous chloride alcohol you get elimination of hydrogen. So 1 hydride goes here and 1 H plus comes from alcohol so you get this borane.

Borane, and now this borane can react with this alkoxide to generate this one, one. So the alkoxide group is connected to the boron and now, similarly two more possibility will be there, ultimately you can get this, this, this. One hydrogen you have to keep so that the reduction will happen. And now because of the alkoxy group, this reducing ability increases, so this is actually hard nucleophile. And now if you treat an alpha beta unsaturated ketone, which is activated also with cero3us chloride.

Now because this is the hard centre, hard centre and this is soft centre. So the reduction of this will happen at the hard centre and you will get only this one. Only 1, 2 addition product. So this is a soft nucleophile borohydride and this is hard nucleophile so hard nucleophile reacts at the hard centre which is carbonyl group and you get 1,2 addition product. So that means the selectively alpha beta unsaturated enone, only the carbonyl group is getting reduced and the double bond is untouched.

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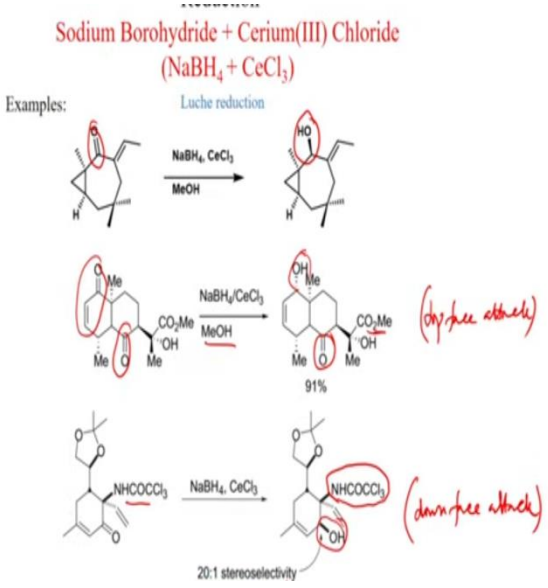


The examples you can see here. A cycloheptanone with a double bond, exocyclic double bond is present and with this condition only the carbonyl group getting

reduced to the alcohol. Also the product is forming in a very highly stereoselective manner so hydride delivery is coming from the down face, so that you get the beta alcohol. The alcohol is in the up. Also this enone, cyclohexanone and here also a carbonyl group is there and a cyclohexanone motif is there.

And under this condition sodium borohydride, cerous chloride, methanol, only this carbonyl group getting reduced. Only this one and also, this selectivity is also playing a role. So here also, from the top face it is attacking because of two methyl groups, the attack is from the top face. So top face attack. Also the ester groups and this carbonyl group is untouched. This might be due to steric region. There is this groups are present so this sodium borohydride cannot access this carbonyl group.

Here also a enone is there, also an amide group is present and with sodium borohydride and cerous chloride you get only this reduction and also a beta alcohol. So this is actually down face attack so hydride come from the down face so you get a beta alcohol and here also, might be this group is dominating. So this, because of this group is in the top face, the hydride comes from the down face and you get a beta alcohol. This is greater than 20 is to 1 stereoselectivity.

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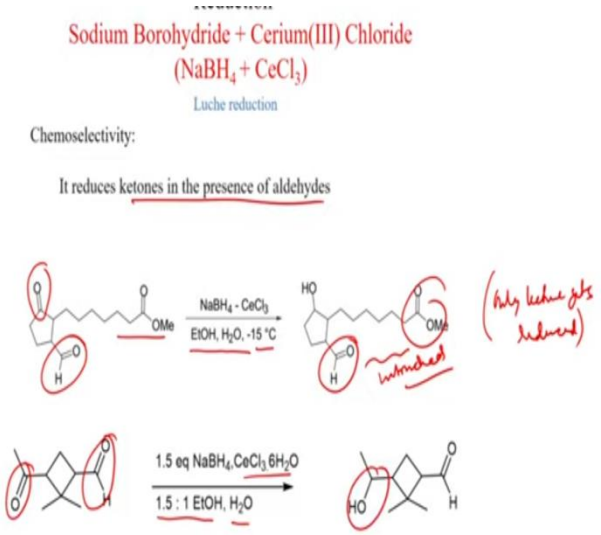


Also, sodium borohydride cerius chloride mixture, it can reduce ketone in the presence of aldehydes. So this is also an important reaction. Like this compound if you see, there is a carbonyl group. That is a ketone, this is aldehyde, this is ester and

when sodium borohydride cerius chloride is used with ethanol water mixture at minus 15 degree centigrade, you get only the reduction of the ketone group and this and this are untouched. So this is very important reaction.

Only ketone gets reduced. Now, if you consider this compound, there is a ketone group here, there is an aldehyde here also with 1.5 equivalent sodium borohydride cerius chloride, water and also ethanol water mixture. This is the cerius chloride $6H_2O$ and this is the solvent 1.5 is to 1 ethanol water, you get only the ketone group gets reduced.

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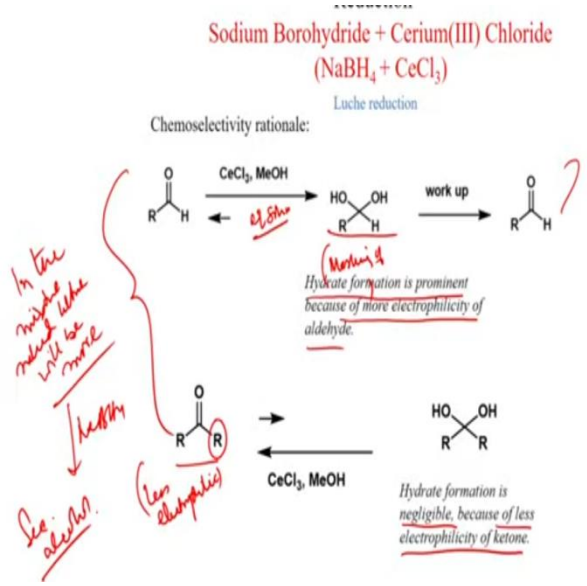


So what will be the mechanism for this reaction? So when cerous chloride methanol is added to aldehyde what happens in aqueous solution. In aqueous solution, the hydrate formation happens and this is the masking of aldehyde. So aldehyde getting masked as an hydrate and this hydrate formation is prominent because of more electrophilicity of aldehyde. And this masking can be cleaved if you work up because this is aldehyde hydrate and you finally get the aldehyde.

On the other hand, if in ketone, this hydrate formation will be very less because of your steric reason. Hydrate formation is negligible because of less electrophilicity of ketone. So this is less electrophilic. Less elctrophilic due to another alkyl group is there, also steric but a hydrate formation on aldehyde will be very fast and this way naked, so in the mixture what will happen if you have this one in the mixture, in the mixture naked ketone will be more.

So aldehyde is masked as a hydrate, naked ketone is more so the sodium borohydride will reduce the naked ketone and you get the secondary alcohol. So you get a secondary alcohol. That is the reduction happens on the ketone.

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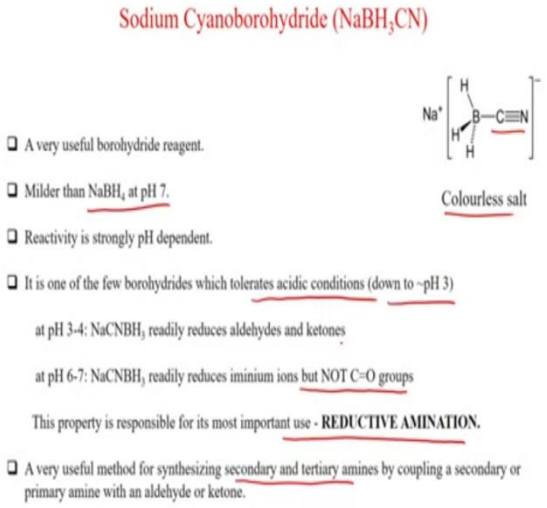


Sodium cyanoborohydride is another reducing agent. Here, and the structure is like this, there is a cyanide group attached to boron. This is colourless salt. A useful borohydride reagent, milder than sodium borohydride at pH 7. Reactivity is strongly pH dependant. If one of the borohydrides, it is one of the few borohydrides which tolerate the acidic conditions down to pH 3. At pH 3 to 4 sodium cyanoborohydride readily reduces aldehydes and ketones.

At pH 6 to 7, sodium cyanoborohydride readily reduces iminium ions but not CO group. So this is very important. At pH 6 to 7, sodium cyanoborohydride readily reduces iminium ions. This property is responsible for its more important use, reductive amination. A very useful method for synthesizing secondary and tertiary amines by coupling a secondary or primary amine with an aldehyde or ketone. So this is an important reaction of sodium cyanoborohydride which can be carried out at pH 6 to 7.

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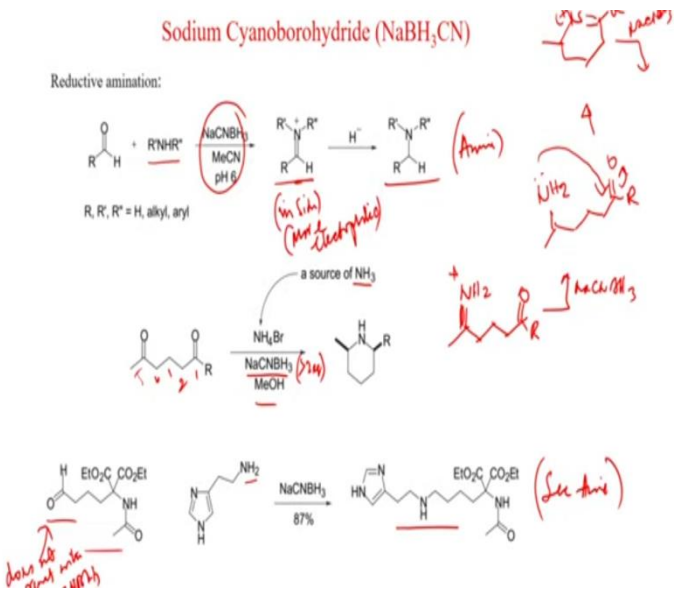


Let us see some examples. So this is the overall reaction, if you have an aldehyde also with ketone and a primary or secondary amine when sodium cyanoborohydride, acetone nitrile at pH 6 is condition then the iminium ion is generated which, so this is in situ. In situ, iminium ion is generated which getting reduced by sodium cyanoborohydride to get the amine. Like this one, 1, 2, 3, 4, 5, 1,5-Diketone with ammonium bromide which is source of ammonia, with sodium cyanoborohydride, methanol it gives cis-2,6 disubstituted piperidine.

So what is happening here? If you see the mechanism, first might be this one, this iminium ion will form. Then this will be sodium cyanoborohydride reduction. So minimum, this will be more than two equivalent. Now, sodium cyanoborohydride gives this primary amine. Now, this one will get an intramolecular reaction will happen and now you get this one. This one, so this will be, now if it is protonated then it will be iminium ion. And now sodium cyanoborohydride will reduce. So, two molecule of sodium cyanoborohydride is required and now we get this product.

Also, this compound with functionalized group, there is amide is there, aldehyde is there and this is an heterocyclic group is there, primary amine. Here also, with sodium cyanoborohydride you get reductive amination, so you get a secondary amine. So, secondary amine is generated. So this is very useful reaction that two component, aldehyde and amine, so aldehyde does not react with sodium cyanoborohydride. This

is also important because this one, which is imine, this is more electrophilic. So this is more electrophilic. That is why the reduction of imine is possible in presence of aldehyde.

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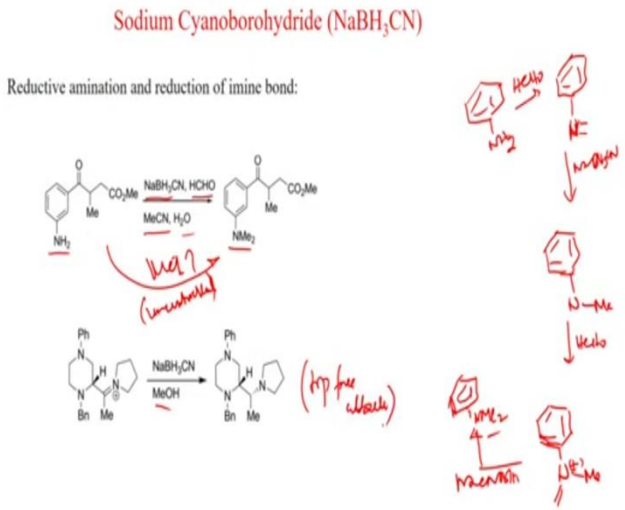


Reductive amination and reduction of imine bond. There are some more examples like this one. Here is aniline derivative is there and aniline converted to N,N-Dimethylaniline which treatment with sodium cyanoborohydride, formaldehyde, acetone nitrile and water. So what is happening here, so aniline so aniline first reacts with formaldehyde. And you get this one. Now this one and this imine will be protonated might be and then sodium cyanoborohydride will get to this one. So first methyl came. Again formaldehyde, so formaldehyde, N-methyl and now iminium ion is formed.

Now sodium cyanoborohydride, sodium cyanoborohydride will give the product aniline $NME_2$. So this is important because if you treat with methyl iodide then you cannot control because maybe another methyl will come. So total three methyl can come so this is uncontrolled. On the other hand, with formaldehyde and sodium cyanoborohydride you can control. Here also an iminium ion is reduced with sodium cyanoborohydride methanol. Here there is also selectivity, so hydride come from the top face, top face attack. And you get this amine chiral.

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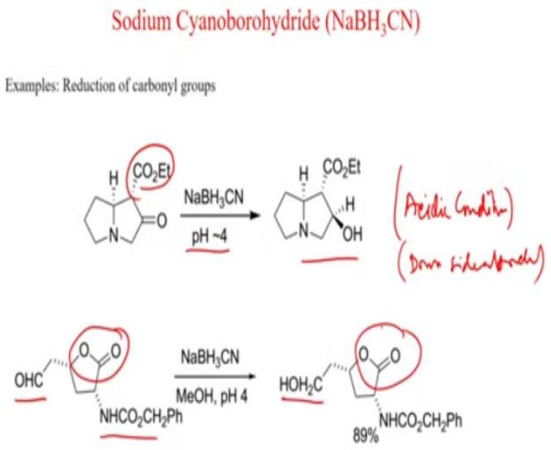


Reduction of carbonyl groups also is possible. So only you have to use pH 4, so acidic condition. More acidic. So in acidic condition sodium cyanoborohydride can reduce carbonyl compound to get a beta hydroxy ester here. Here, down side attack is happening. So hydride is coming from the down side because might be these groups are there so the hydride come from the down side so that you get a beta alcohol. Here also you can see an aldehyde group is there, a lactam motif is there. Here is also a carbamate group is there and with sodium cyanoborohydride methanol pH 4, only the aldehyde getting reduced, the lactone is untouched.

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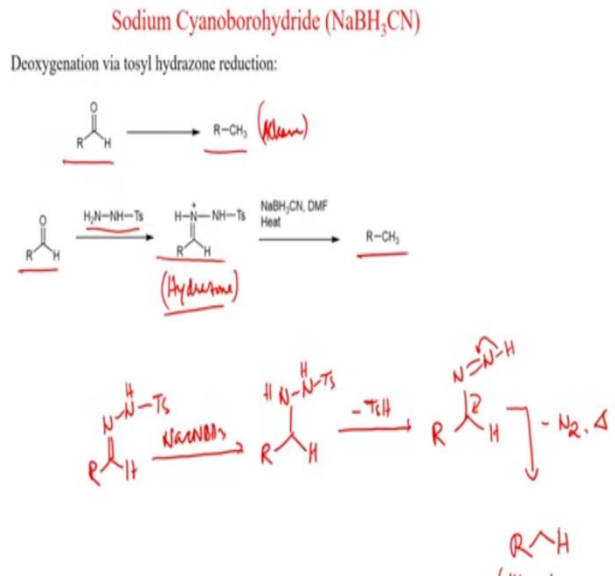

Deoxygenation reaction. This is also an important reaction of sodium cyanoborohydride like aldehyde or ketone can get the alkane. So this is alkane is forming. So deoxygenation happens. So first when we treat aldehyde with tosyl hydrazine, you get a hydrazone. So hydrazone, tosyl hydrazone in this case and now with sodium cyanoborohydride, DMF, heat, you get the alkane. So what is happening here? So what will be the possible mechanism?

So RH double bond N N NH Ts. So what will happen, sodium cyanoborohydride will reduce this one, will generate N NH Ts, and now minus TsH, so elimination will happen. Sorry, there is a NH. Minus TsH, now you get a this one. This compound and this minus $N_2$, you get this alkane. This is the alkane. So you need heat actually. Here you have to eliminate nitrogen and this heated condition you get the alkane.

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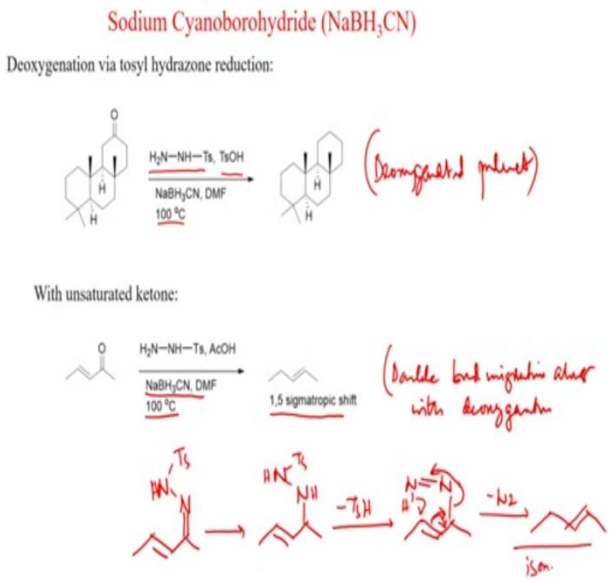


This is a example that tricyclic compound with a carbonyl group when is treated with tosyl hydrazine, acid, so you need a acid. That is important, the acid will enhance the reactivity, the reducing ability. And now sodium cyanoborohydride, DMF, 100 degree centigrade, you get the deoxygenated product. So deoxygenated product. And now this is important, when alpha beta unsaturated ketone is treated with tosyl hydrazine acetic acid sodium cyanoborohydride DMF 100 degree centigrade, you get a double bond migration. 1,5 sigmatropic shift.

So double bond migration along with deoxygenation. So what will happening here so you can think that this one and this hydrazone, so whatever intermediate we had earlier like this, this will reduced, this N NH tosyl and now minus TsH, you get this one. Now 1, 2, 3, 4, 5, 6, so this hydride comes here and now, sorry this now this happens. So minus $N_2$ and now you get a double bond, it is here. So this is the double bond. Migration is happening and with elimination of nitrogen you get this sigmatropic shift product. So this is the isomerized product.

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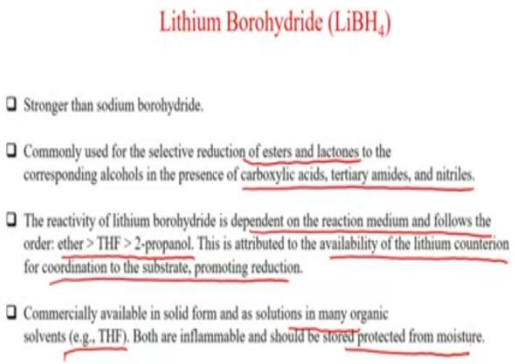


Lithium borohydride, it is stronger than sodium borohydride. Commonly used for the selective reduction of esters and lactones to the corresponding alcohols in the presence of carboxylic acid, tertiary amides and nitriles. So this is very important for the reduction of esters and lactones. The reactivity of lithium borohydride is dependent on the reaction medium and follows the order ether greater than THF greater than 2-propanol.

This is attributed to the availability of the lithium counteranion for coordination to the substrate, promoting reduction. So in ether is better than THF than 2-propanol because the lithium counterion will be available when it is non protic., non protic ether solvent. Commercially available in solid form, also a solution in many organic solvents such as THF. Both are inflammable and should be stored protected from moisture.

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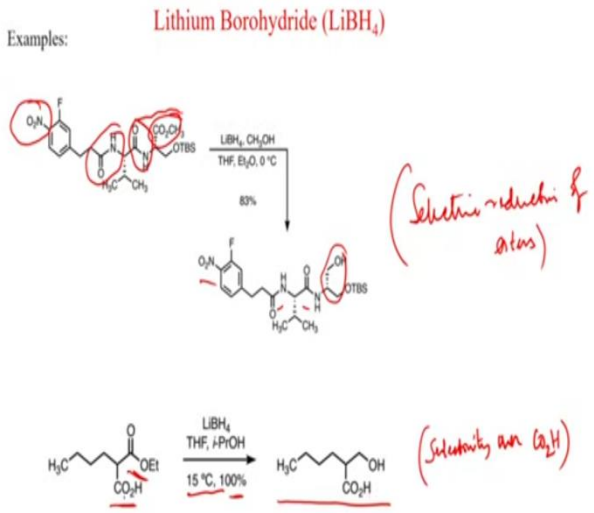


Ok so lithium borohydride, if you this is useful for selective reduction of ester. Like here, if you see this compound, it is a nitro group is there. There is a amide group is there and there is another amide and there is another ester group is there. So only out of four groups, only the ester getting reduced to the alcohol and this amide and this amide and nitro groups are untouched, so this is very selective reduction.

Selective reduction of ester and this compound if you see there is a carboxylic acid and there is an ester with lithium borohydride, THF, isopropanol solvent and 15 centigrade, 100 percent yield you get of this product. So here selection or selectivity over $CO_2H$. So $CO_2H$ group is not reduced. So if you want to reduce an ester in presence of a carboxylic acid, you have to use lithium borohydride.

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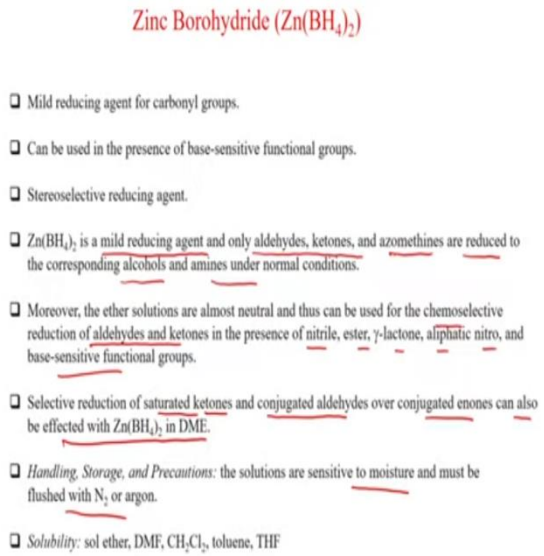


Zinc borohydride, it is a mild reducing agent for carbonyl groups. Can be used in the presence of base sensitive functional groups. This is stereoselective reducing agent and this is a mild reducing agent. Milder than sodium borohydride and all the aldehydes, ketones, azomethines are reduced to the corresponding alcohols and amines under normal conditions. Moreover the ether solutions are almost neutral and thus can be used for the chemoselective reduction of aldehydes and ketones in the presence of nitrile, ester, gamma lactone, aliphatic nitro and base sensitive functional groups.

Selective reduction of saturated ketones and conjugated aldehydes over conjugated enones can also be effected with zinc borohydride in DME solvent. So this is an also important reaction that saturated ketones can be reduced in presence of unsaturated ketones. Handling, storage, these solutions are sensitive to moisture and must be flushed with nitrogen or argon. Solubilities, ether, DMF, $CH_2Cl_2$, that is the dichloromethane, toluene, THF.

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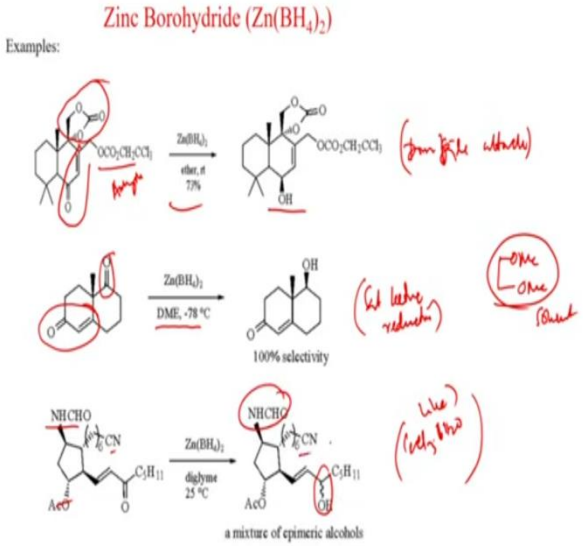


So examples of reduction. Here you can see an anhydride group is there. This is also an anhydride and this is the enone. So selectively zinc borohydride ether, it gives only the carbonyl reduction and from the down side attack and you get thus, product. So other groups are untouched. This is important reaction. That is what we told that saturated ketone, so this is unsaturated ketone and this is saturated ketone. And with zinc borohydride in DME, so DME again, this is this compound, this is the solvent, DME solvent. And you get only saturated ketone reduction.

So saturated ketone reduction and you get also a special selectivity, down side attack is happening so you get a beta alcohol. This is another example. Here NHCHO carbamate, acetate, nitrile and the alpha beta unsaturated ketone group is there and when you treat with zinc borohydride diglyme, you get the alcohol, so this is like, selectivity like cerous chloride, like cerous chloride as $6H_2O$ like. So you get preferentially 1,2 attack here and you get epimeric alcohols. However, other groups are untouched.

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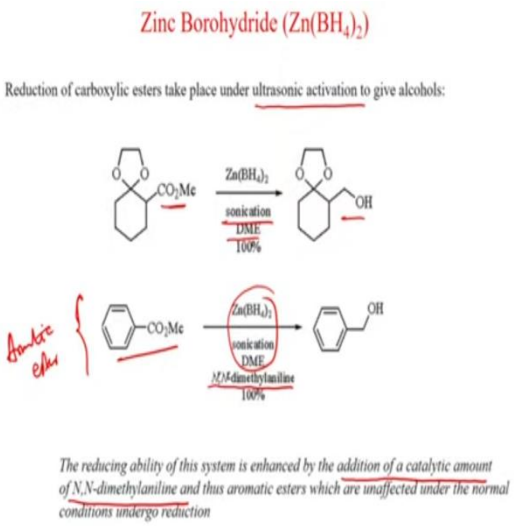


Reduction of carboxylic esters takes place under ultrasonic activation to give alcohols. So in general, esters are not reduced. Only aldehydes and ketones, whatever we have seen. However, in sonication condition, in DME, it can give the ester reduction to alcohol. This is aromatic, aromatic ester and here this condition is required but still you need N,N-dimethyl aniline and then only you get the benzylic alcohol.

So the reducing ability of this system in enhanced by addition of a catalytic amount of N,N-dimethyl aniline and thus, aromatic esters which are unaffected under the normal condition, undergo reduction. So zinc borohydride can reduce ester with ultrasonic activation so this we have to remember that zinc borohydride can reduce esters with ultrasonic activation.

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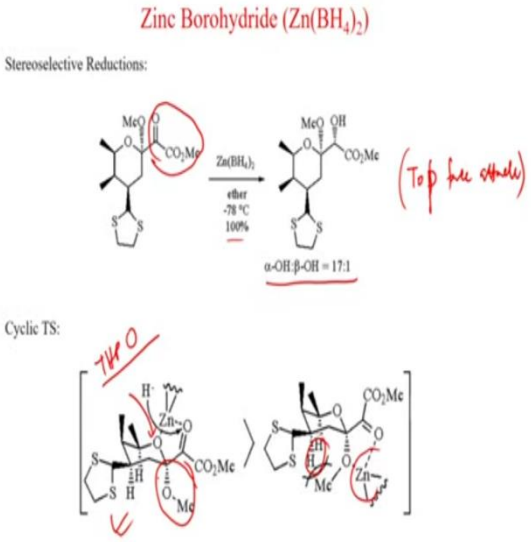


Stereoselective reduction is also possible like this one alpha keto ester when it is treated with zinc borohydride ether minus 78 degree centigrade you get 100 percent yield of this product and selectivity is 17 is to 1. So this is the alpha hydroxy ester and here hydride come from the top face. So, top face attack. So, hydride come from the top side and you get the alpha alcohol. And this can be explained by this transition state.

So if you see the 6 membered cyclic, this tetrahydropyran, if you draw like 6 member chair like transition state then you see this all methyls, these two methyls are up. This also up and this methoxy is down and now your zinc coordinate with this carbonyl group as well as this oxygen, tetrahydropyran oxygen. So this is THP oxygen and after this binding then the hydride come from the top side and then you get the down alcohol.

Because from the down side you can see this group is there, this is also there. So it comes from the top side and you get a down alcohol. So another possibility that zinc can bind also with this oxygen. This methyl oxygen but here there will be a steric hindrance. So once it binds with zinc this way then this methyl has to go this way, left side, and when it comes left side then there is a steric interaction with this hydride. So this is the transition state. Through this, the product is forming.

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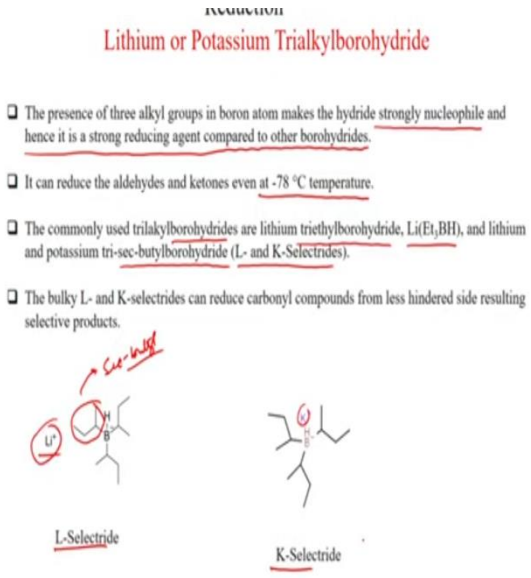


Ok now we will, lastly we will discuss reduction with lithium or potassium trialkyl borohydride. The presence of three alkyl groups in boron atom makes the hydride strongly nucleophile and hence it is a strong reducing agent compared to other borohydrides. It can reduce the aldehydes and ketones even at minus 70 degree centigrade temperature. The commonly used trialkyl borohydrides are lithium, triethylborohydride lithium, that is Li $Et_3BH$ and lithium and potassium tri-sec-butylborohydride which are very popular as L and K selectrides.

The bulky L and K selectrides can reduce carbonyl groups from less hindered side resulting selective products. This is the L selectride structure there is a lithium is there that is called the L and you can see the sec-butyl, 3 sec-butyl groups are there. So these are sec-butyl, sec-butyl group, because methyl is connected at the first carbon. So sec-butyl group is there. Similarly, K selectride, here also this sec-butyl is there. Only instead of lithium, there is a potassium that is why it is called K selectride.

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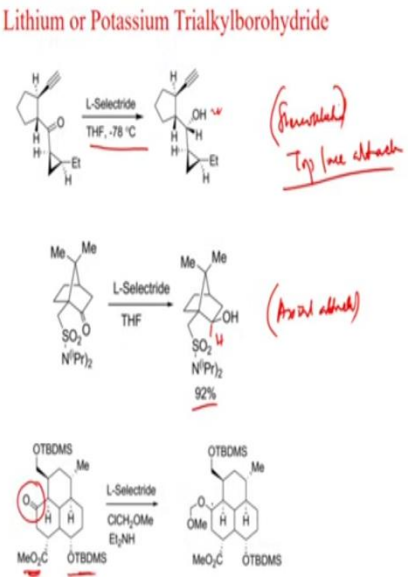


So as we told that these are highly reactive borohydride because there are three alkyl groups are present and that is why the reaction has to be done at minus 78 degree centigrade and because of its bulkiness, it is selective. So stereoselective, like this compound the hydride come from the top face. So top face attack and you get this alcohol. Alpha alcohol you get selectively.

Similarly this compound you can see this is cyclic ketone. Here also L selectride gives this equatorial alcohol. So axial attack is happening. You get the equatorial alcohol in 92 percent yield. And similarly this one, you can see there are many chiral centres present in this molecule. There is an ester group is there, OTBDMS group is there. Only this group is getting reduced to the alcohol in 90 percent yield.

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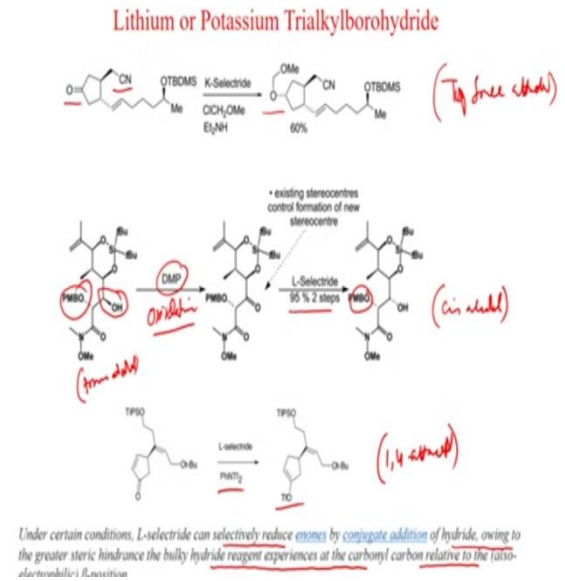


Some more examples, here is a cyano group is there, carbonyl is there and with K selectride you get the secondary alcohol. Also here, you get the top face attack. Because of this group maybe, this is down so you get the top face attack so that you get the alpha alcohol. This is an important reaction that if you want to change the stereochemistry of an alcohol, we know that Mitsunobu is a reaction but sometimes mistunobu may not work so this is the reaction you have to do, the oxidation reduction.

So this is with Dess-Martin periodinane you can oxidize this alcohol to the ketone and now, so this was trans, and now when L selectride is there then you get a cis alcohol. So this is very important that L selectride can do very stereoselective reduction. So this is the trans alcohol with respect to this group and here now with Dess-Martin, this become cis. Also under certain conditions, L-selectride can selectively reduce enones by conjugate addition of hydride owing to the greater steric hindrance of the bulky hydride reagent experience at the carbonyl carbon relative to the beta position.

So carbonyl group, it tell, it may face higher, higher steric repulse and that is why it may reduce in the 1,4 attack. So 1,4 attack is happening and after that you can make the enolate you can trap with triflamideand you get the o-triflate. So that means it can selectively reduce enone to an enone double bond. So 1,4 reduction is possible. So it is opposite like cerous chloride sodium borohydride.

So whatever we have seen that, today we have first discussed Red-Al. So Red-Al is an similar reactivity like lithium aluminium hydride but it is less pyrophoric, wide solubility and we have seen that similar reaction, whatever lithium aluminium does like ester, amide, ketone, nitrile reduction it does. Also we have seen the epoxy alcohol, this is very important reaction of Red-Al and preferentially it adds, the hydride adds to the carbon which is closer to the oxygen like 2,3 epoxy alcohol, you get 1,3 diol and on the other hand, LAH does not give any selectivity.

You get 1:1 mixture of products. Then we have seen sodium borohydride which is milder reducing agent. And sodium borohydride, we have seen that, if you can use higher amount or higher temperature then also it can reduce ester not only aldehydes and ketones, it can also reduce esters. Also we have seen the sodium borohydride cerius chloride which is very useful reagent.

Which is called also Luche reduction condition, which is very useful [re] reducing agent for selective 1,2 reduction of enones. So if you have enone, then if you use sodium borohydride cerius chloride then you get only the carbonyl reduction. That is called the 1,2 reduction. Also, we have seen the selective reduction of ketones in the presence of aldehyde is possible when you use sodium borohydride cerous chloride in aqueous ethanol. So what happens in this case, aldehyde makes the hydrate in that water ethanol mixture and that way it is getting masked. So only naked ketone can be reduced with sodium borohydride so the ketone reduction is happening.

Then we have seen lithium borohydride. Lithium borohydride is stronger than sodium borohydride and it is very selective reduction, used for selective reduction of esters and lactose also. So it can selectively reduce esters in presence of nitrile, in presence of nitro, in presence of carboxylic acid. So, if you want to selective reduce ester then you have to use lithium borohydride.

Then we have seen zinc borohydride. Zinc borohydride also is a mild reducing agent even in fact it is milder than sodium borohydride and we have seen in a compound where saturated ketone and alpha beta unsaturated ketone is there, zinc borohydride selectively reduces the saturated ketone so that is why it is very selective compared to the sodium borohydride. It can selectively reduce the saturated ketone in presence of unsaturated ketone. Also under sonication reaction condition we have seen that it can reduce the ester like aliphatic ester and aromatic ester, then you need an additive

N,N-Dimethyl aniline, something base additive you have to use where the reactivity is increased.

Then we have discussed K selectride and L selectride which are very strong boron hydride reagent because there are three alkyl groups present in the boron atom so that is why it is very reactive and the reaction has to be done at minus 78 degree centigrade. Also we have seen that because of its bulky nature it can do the stereoselective reduction of aldehydes, ketones, etc. Thanking you.