Reagents in Organic Synthesis
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Na and Li Based Metal Reduction
Lecture 07

Welcome to MOOC program. Today we will discuss 2 reactions, first is your Birch reduction and second one is Lithium Aluminium hydride reduction. So Birch reduction is Sodium or Lithium metal in liquid ammonia, generally this condition is treated.

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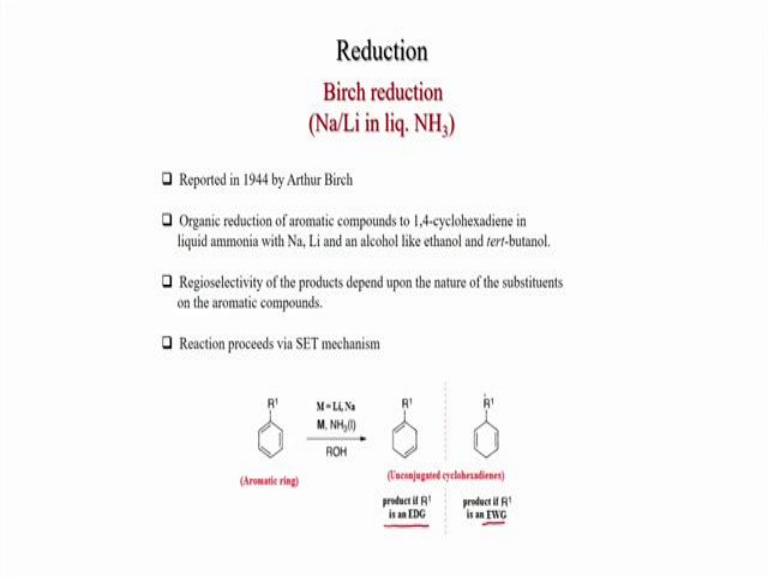

So reported in 1944 by Arthur Birth, that is why this reaction is called Birch reduction. And organic reduction of aromatic compounds to 1, 4- cyclohexadiene in liquid ammonia with Sodium, Lithium and an alcohol like ethanol and tert-butanol which are generally proton source. Regioselectivity of the products depend upon the nature of the substituents of the aromatic compounds and reaction proceeds via SET mechanism which is called Single Electron Transfer like if there is a substituent aromatic ring and when it is treated with Sodium Lithium metal in liquid ammonia with a proton source like alcohol, then you get unconjugated cyclohexadiene. In one case the double bond, the R1 is present with the double bond carbon.

When R1 is electron donating group then you get this kind of system and when R1 is electron withdrawing group then the cyclohexadiene system has a saturated carbon here which constitutes the R1.

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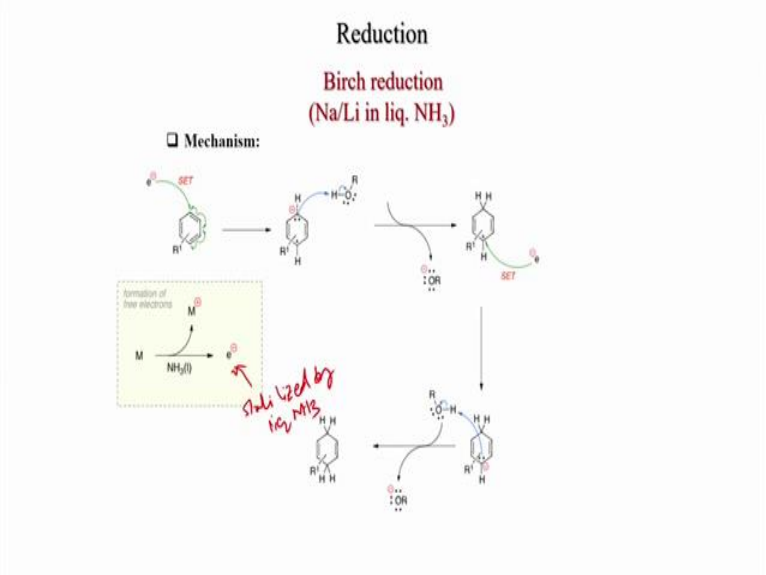

So what is the mechanism of this reaction? When metal is added in liquid ammonia then the metal becomes M plus and liberates one electron. And this electron is stabilized by liquid ammonia. So that is the importance of liquid ammonia, it stabilizes the electron, and that electron then adds to the benzene ring. And you can see that first radical anion will form and this radical anion, they wants to stay para to each other so that the repulsion will be minimum, and then these anion getting protonated by alcohol, and the alcohol will be OR^- and after protonation, this hydrogen comes here and then just a radical is formed, and that radical, again 1 electron adds to the radical and it becomes anion. And after, the anion is getting protonated by the alcohol and you get the cyclohexadienyl system.

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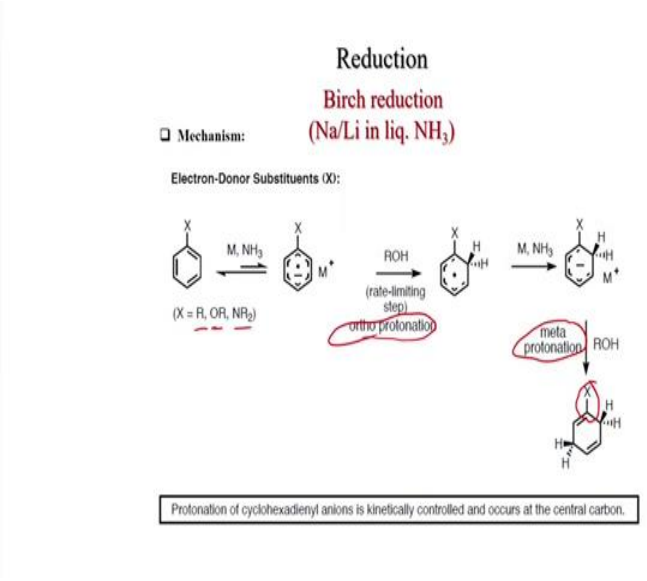

And what happens when the electron-donor substituents are there? So if we have a alkyl group, OR group, NR_2 group which are electron donating and after treatment with sodium or lithium in liquid ammonia you get the radical anion. And then this is the ortho protonation and this is the rate-limiting step. So the anion stage ortho position of the electron donating group, and that is why ortho (proto) protonation happens. And now again this Lithium, liquid ammonia will come then the radical becomes anion, and after that this anion stays to the meta position because earlier I told that here the radical was formed so there will be maximum para to each other, so ultimately this anion will stay here, and then that is why this is called meta protonation. So first will be ortho protonation and the second will be meta protonation.

And now you get the cyclohexadienyl system, where the substituents contest the double bond. So, protonation of cyclohexadienyl anions is kinetically controlled and occurs at the central carbon. So this is kinetically controlled process.

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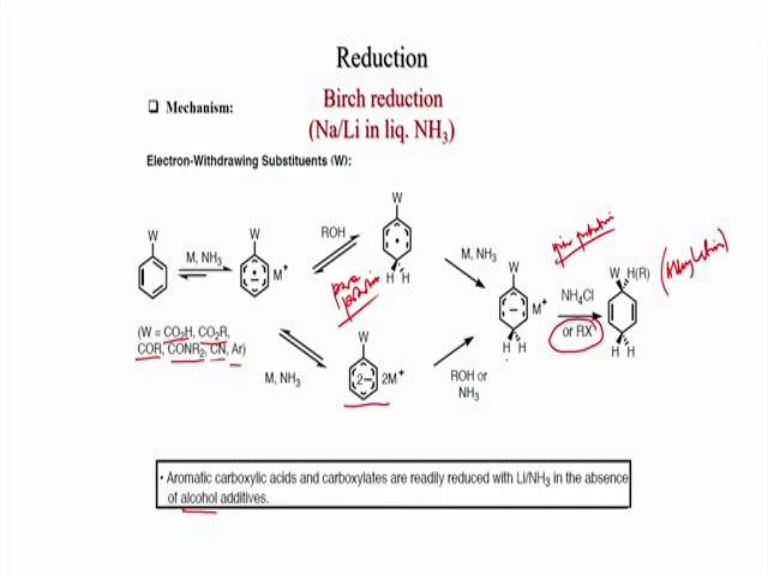

Now, if you have a electron withdrawing substituents, what will happen? Now electron withdrawing substituents like carboxylic acid, ester) COR, ketone, amides, cyanide and aryl group also. That time also the radical anion will generated, and now protonation, it becomes a radical and as I told, here, first the anion will stay on the carbon atom which is connected to the W, W because that is stabilized by the W group, electron-withdrawing. And this anion will be generated at the electron-withdrawing group. And now, initially this will be para protonation. So first will be para protonation. And now this will be ipso protonation later, but what I want to say that this anion can be generated also and particularly when proton source is not there, then this radical anion becomes dianion. That is also possible and this dianion later can react with alcohol or ammonia can get this anion.

This anion, then the ipso protonation. So, this called ipso protonation. So this carbon atom where W enters, there the ipso protonation or if you can treat with alkyl halide, then you can get the alkylation. So alkylation also possible at particularly only when the electron withdrawing group present in the aromatic system. So, aromatic carboxylic acids and carboxylates are readily reduced with Lithium liquid ammonia in the absence of alcohol derivatives. And in the absence of alcohol derivatives this is the method, that is following actually. So dianion and then the ammonia comes, become the anion and then ammonium chloride.

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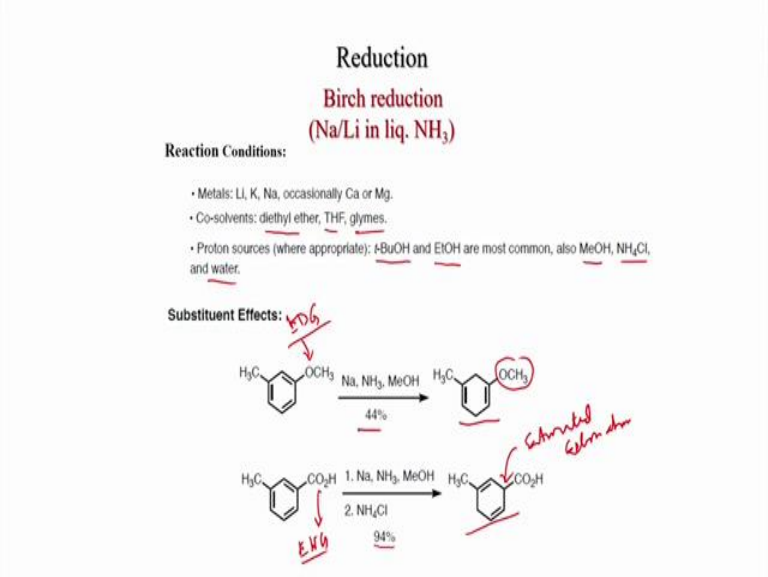

So what are the reaction conditions? Metals, you have to use lithium, potassium, sodium, occasionally calcium or magnesium. Co-solvents like diethyl ether, THF, glymes. Also, proton sources, where appropriate, generally tertiary butanol or ethanol are most common, also methanol, ammonium chloride, even water can also be used as a proton source. And substituent effects, already we have seen. Now, if you have this meta methyl anisole then after sodium, liquid ammonia in methanol, it gives 44 percent yield because here this is the major electron donating group. This is the stronger electron donating group than methyl.

So this only controls the reaction and you get the cyclohexadiene system where the methoxy group contains the double bond. Now, if you have a carboxylic acid, carboxylic acid, already we have discussed that this is electron withdrawing group. And now, if you have this meta methyl benzoic acid, then sodium, liquid ammonia, methanol condition and after that if you treat with ammonium chloride, you get 94 percent yield of this product where the carboxylic acid is present at the saturated carbon atom. So, for electron-withdrawing substituents the double bond will not be with the electron-withdrawing group. So, the electron withdrawing group will be on a saturated carbon atom.

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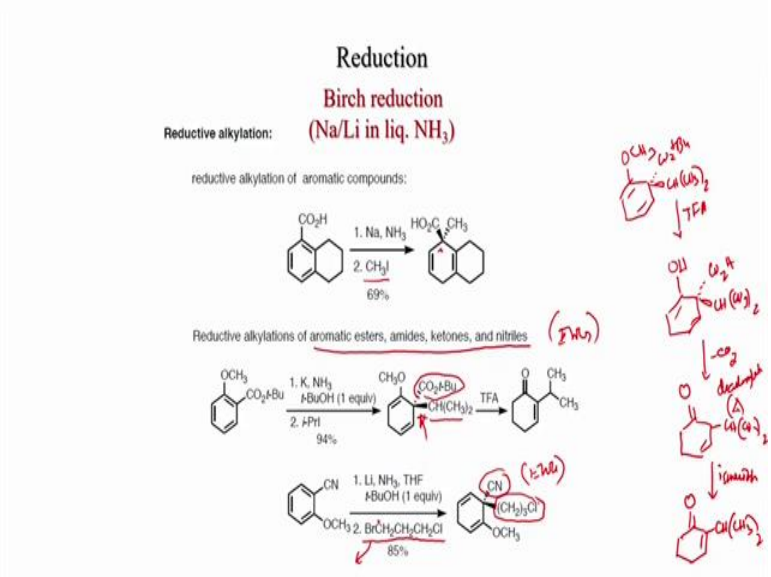

Reductive alkylation is possible, reductive alkylation of aromatic compounds like this one. This is benzoic acid derivatives with sodium, liquid ammonia. Then you add iodomethane and then you get this cyclohexadiene system with a quarternary stereogenic system centre. And here, the carboxylic acid and methyl groups at the same carbon atom. Reductive alkylation is possible with aromatic esters, amides, ketones and nitriles. So, they are all electron-withdrawing groups. Then only the radical, then only the anion will stabilized by the electron-withdrawing group and the alkylation is possible. Like this system, there is a ester and methoxy, here the control will come from the ester group, and if you treat this compound with potassium, liquid ammonia and tertiary butanol, one equivalent which is protic source and after treatment to its to iodopropane you get this isopropyl group here.

So this is the CO_2 tertiary butyl. So at the same centre you get the isopropyl. So you generate quarternary centre here. And now after treatment with trichloroacetic acid, you get the alpha beta unsaturated enone. So what is happening here? So TFA if you give, what happens? This become enol and this becomes CO_2H first. And, decarboxylation will happen and then you get the enol you can write as a carbonyl compound, sorry. And now the decarboxylation is possible if you heat it, and now you get a this one, $CH(CH_3)_2$. And now the isomerization will happen, which gives the conjugated enone. So you get his compound.

So, alpha beta unsaturated enone can be generated by reacting this ester with potassium, ammonia, tertiary butanol, then treated with 2 iodopropane and this isopropyl substituted enone you can write. Also, if you have a cyano and methoxy substituent in the compound with treatment of lithium, ammonia, THF and tertiary butanol one equivalent and after that if you treat with 3 chloro 1- bromopropane, then you get this compound. So here this is the electron withdrawing group. So the substitution will happen on the electron withdrawing group. And here, since bromine is a good leaving group compared to chlorine, so you get the bromine elimination, the substitution happens under this carbon atom and you get this product which is a chloro substituent.

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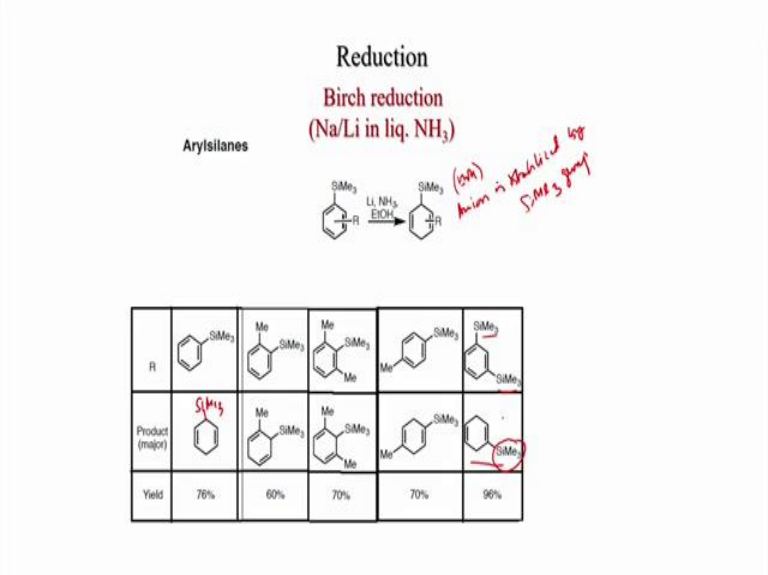

Arylsilanes, arylsilanes also on reaction with lithium, liquid ammonia in ethanol, it gives this cyclohexadiene system and this acts as electron withdrawing. So, the anion, anion is stabilized by $SiMe_3$ group. So this means that $SiMe_3$ acts as electron withdrawing group. And now if you treat phenyl trimethyl silane with sodium, lithium, liquid ammonia, ethanol then you get 76 percent yield of this cyclohexadiene. Now, if you have a methyl substituent then also you get this compound. Here $SiMe_3$ will be there. $SiMe_3$ will be on the saturated carbon atom. And when 2, 6-dimethyl substituent is there then you get 70 percent yield of this product. Also when you have para methyl group then you get 70 percent yield. And interestingly, when two $SiMe_3$ group are

there, then one $SiMe_3$ eliminates and you get cyclohexadiene system with $SiMe_3$ group with a double bond.

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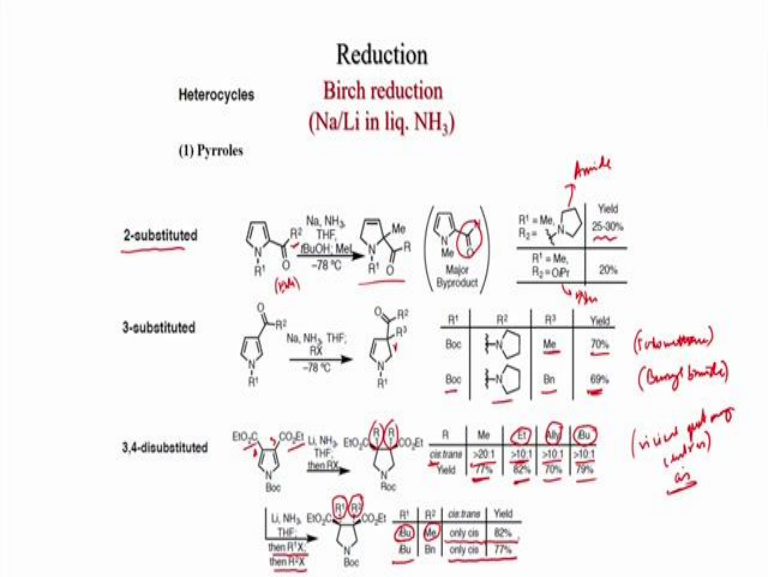

Pyrroles, pyrroles can also react with these conditions. Now we will discuss for 2-substituted pyrroles. And R^2 is generally ester, so this is generally ester or amide group which is electron withdrawing. So, this is EWG. And now if you treat these 2-substituted pyrrole, sodium, liquid ammonia, THF with tertiary butanol followed by alkylation in methyl iodide then you get 2,5-dihydropyrrole with a quaternary centre at the 2- position and the major by-product is this with ortho position aldehyde group also. And you can see here, if R^1 is equal to methyl and R^2 is equal to pyrrolidine, so if it is a pyrrolidine amide then you get 25 to 30 percent yield of the product. And if R^1 is equal to methyl and R^2 is equal to O-isopropyl, so this is amide and this is an ester, so you get 20 percent yield of the product. So yield is very not good.

Now if you have a 3-substituted, suppose here the electron withdrawing group at the 3-substituted, and interestingly, now the desired reaction happens, however you get 2-3 dihydropyrrole. And here the electron withdrawing carbon, there the alkylation happens. So, here electron withdrawing group earlier was in the 2 position, there the alkylation happened, now it is at the 3 position, and 3 position the alkylation happens. And now if R^1 is equal to Boc and R^2 is equal to pyrrolidine so if it is a pyrrolidine amide, and R^2 is equal to methyl if the alkylation with iodomethane, then you get 70 percent yield. So this is with iodomethane. And now, again you

have a Boc group and pyrrolidine amide, now if you alkylation you do with benzyl bromide , suppose.

Now we get 69 percent yield of the product. Now what will happen with 3, 4-disubstituted? Like two ester groups are there at 3 and 4 position, 3 and 4. Interestingly, when this compound is treated with lithium, liquid ammonia, THF and then alkylation with RX, interestingly the disubstituted means, the disubstitution happened and two quaternary. So this is vicinal quaternary centres.

So 2 quaternary centres side by side and also their stereochemistry is cis, so cis is the major as you can see. When R is equal to methyl, suppose, iodomethane, you get 77 percent yield. And *cis* to trans cis is greater than 20:1,so cis is the major product. Now if you have ethyl iodide, then you get greater than 10:1 cis product and 82 percent yield. If it is allyl bromide then you get greater than 10:1 for the cis and 70 percent yield and if it is isobutyl then also you get greater than 10:1 and 79 percent yield. So the cis substitution is important. So always you get the cis as the major. Now, if you have a two different alkyl halide, like first one is with R^1 and second one is with R^2, that also you can do. Now you can, one carbon will contain R^1 and another contain R^2. Suppose if you treat first in the system, after lithium, ammonia treatment if you add first the isobutyl iodide and then iodomethane, then you get the product, 82 percent yield.

So this is symmetrical compound does not matter, where R^1 comes first you get the same compound, but the geometry is important cis. Now again if you treat with isobutyl iodide and then benzyl bromide, here also you get the product, cis product with 77 percent yield.

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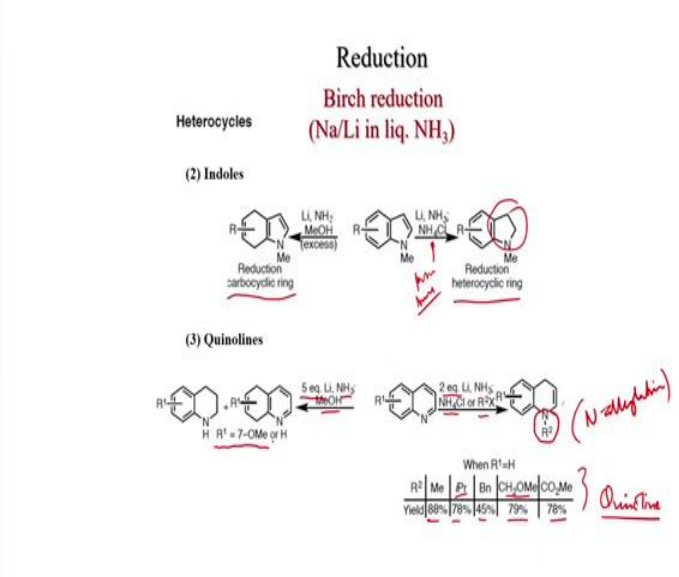

Not only pyrroles, indoles can also be treated with this condition. And here this N methyl indole, if you with treat lithium, ammonia, ammonium chloride as the proton source, so this is the proton source, then the reduction happens in the heterocyclic ring. So heterocyclic ring is reduced and this is very important. The Birch reduction, here electron is the reducing agent, not hydrogen source, so the electron adds to this system and reduced. So this is the reduction of heterocyclic ring. And here, when you treat with lithium, liquid ammonia with methanol excess. Methanol is a proton source now. Here reduction of carbocyclic ring is observed, and here an isolated double bond is there. So this pyrrole is there N-methyl pyrrole motif and here a cyclohexene motif is present.

Quinolines also can be treated with this condition. Suppose, here 2 equivalent lithium, liquid ammonia, ammonium chloride or R^2X, here the N alkylation is possible and the heterocyclic motif is reduced. And now only 1 double bond is present. So this is like N amine system here. And now we can see if R^1 is equal to H that means this is with quinoline only. So, if you do the reaction with quinoline and then different alkyl halide, suppose iodomethane 88 percent yield, and the alkylation happens on the N atom. So the N arylation, N alkylation is happening. Like isopropyl 78 percent, benzyl group 45 percent, CH_2OMe 79 percent, CO_2Me 78 percent yield. So here N alkylation is happening. Now, if you increase the amount of lithium, so what will happen? 5 equivalent lithium, ammonia, and methanol as the protic source.

Now, we get a mixture of products. In one case, the heteroaromatic group or heterocyclic group, heterocyclic group completely reduces, and another case, this group partially reduce, the benzene group. So, here if R^1 is equal to 7-methoxy or hydrogen, you can get this kind of products.

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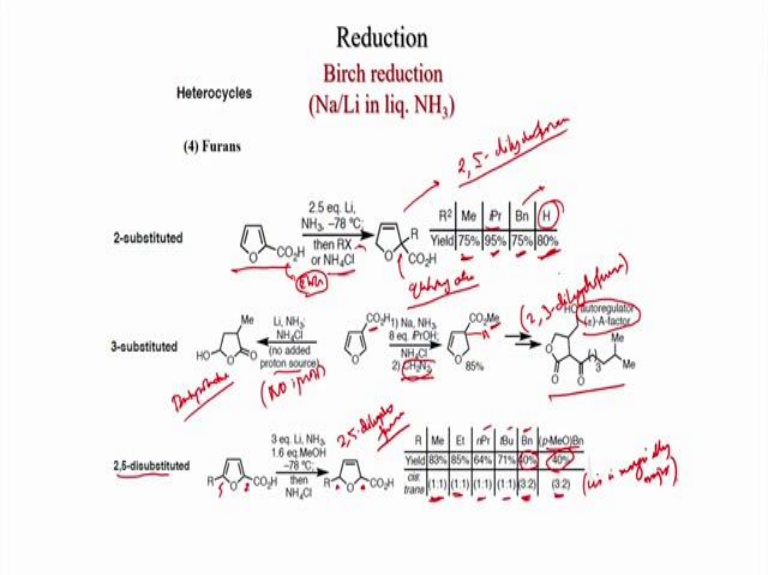

Furans, furan also, can also be reduced under Birch reduction condition. Here 2-substituted furan first used and CO_2H, we know this is electron withdrawing group. And now after treat with 2.5 equivalent lithium, liquid ammonia condition at minus 78, then you treat with alkyl halide or ammonium chloride which is a proton source, and you get 2, 5 dihydrofuran. 2, 5 dihydrofuran, and at this 2 position, here the quaternary centre is formed if you treat with alkyl halide. Suppose, if you have a methyl, suppose if you treat it with iodomethane you get 75 percent yield of this product. If it is isopropyl, that it means 2 iodopropane. If you do the reaction, then you get 95 percent yield, so yield got enhanced. Now if you treat it with benzyl bromide then what we will get? 75 percent yield.

And if you have proton source, like ammonium chloride is treated, then you get, carboxylic acid will be there, this will be not a quaternary centre but this will be a stereogenic centre, you get 80 percent yield. 3 substituted, suppose if the carboxylic acid at the 3 position, then like our earlier case, pyrrole case, here also, here the reduction will change now.

So now you will get 2, 3 dihydrofuran, because you are 2 or 3 position formally, hydrogen had been added. So sodium, liquid ammonia, and 8 equivalent of isopropanol ammonium chloride. So this is the proton source. So here, this proton comes from ammonium chloride, and now that ester you can convert to, sorry the carboxylic acid you can convert to ester with treatment to diazomethane, you get the methyl ester. And this compound can be converted to a biologically active compound which is auto regulator or plus A factor like this. So this you can derivative to this compound. Alternatively, if you treat this compound, lithium ammonia ammonium chloride, no added proton source, so no isopropanol, then what will happen?

No isopropanol, then what will happen? Then the butyrolactone derivative is formed. So butyrolactone, so butyrolactone derivative is forming. So here, here this compound completely reduce. The furan motif is completely reduced to give a saturated compound, which is called here butyrolactone. And now if you have a 2,5-disubstituted furans, so this is 2 and this is 5, and now again you get, like earlier 2-substituted, here also you get 2, 5 dihydrofuran. And depending on R you get different yield. Suppose R is equal to methyl, you get 83 percent yield and in this case the selectivity is not good, 1:1 cis trans mixture because this is a stereogenic centre, this is a centre, so cis and trans will be 1:1 mixture.

If alkyl halide is ethyl then you get 85 percent, here also 1:1, if it is N propyl, then also 1:1. Tertiary butyl 1:1. Benzyl group 3:2, and the yield also got reduce 40 percent and this is a para methoxybenzyl group, the yield is 40 percent only and 3:2 is the ratio. So cis is the major but cis is marginally major in some cases.

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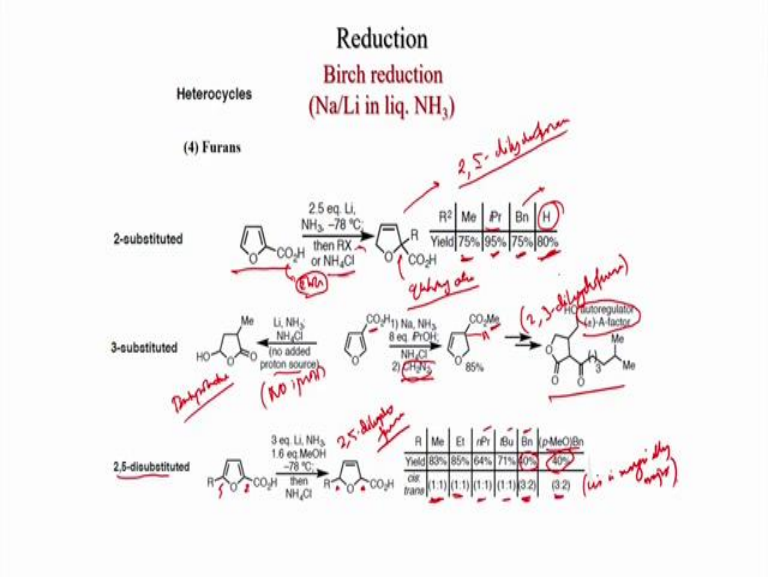

Asymmetric Birch reduction also is possible, like you have a this kind of chiral compound, there is a amide group. This is amide, amide group. This is ether. And now if you treat with lithium or sodium, liquid ammonia, THF followed by tertiary butanol 1 equivalent, then you get this kind of enolate, conjugated enolate system. Now this is the proposed convex attack, so the convex side is open and the alkylation happens from the top face. So top face, top face is open and the attack will take place from the top face. And you can see the selectivity if it is methyl iodide you get 60 percent yield, this is 60 percent yield of the product. Now, if it is ethyl iodide, then you get 82 percent yield and greater than selectivity.

This is diastereo selectivity, so 98 percent selectivity you get. $PhCH_2$, if it is allyl bromide you get 75 percent yield, greater than 96 percent selectivity. Benzyl bromide, you get greater than 96 percent. And this is another alkyl bromide, you get 96 percent selectivity. And if it is a $ClCH_2CH_2Br$, you get 91 percent, and this is not measured. Now, if you cleave this ether, and there ether motif is, this is open now. Now what will happen? Now the product will be different. Here also lithium, liquid ammonia, we get the dienolate, now the control will come from this CH_2 only, since is in the top face.

The reaction will take place from the downside, so down face attack, and R group will came from downside and you get this kind of cyclohexadiene system. And here, RX can be defined like earlier case, methyl iodide, ethyl iodide, benzyl bromide, this is another alkyl bromide, this

is Cl and Br containing alkane. And here that is the important thing, opposite facial selectivity is observed. So when it is a cyclic system, then you get the convex attack, and now you get the concave attack when it is open.

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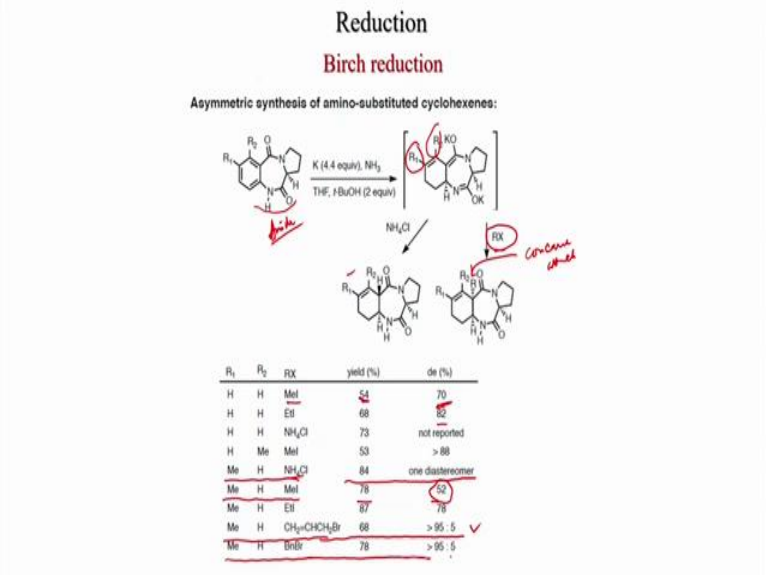

R_1	R_2	RX	yield (%)	de (%)
H	H	MeI	54	70
H	H	EtI	68	82
H	H	NH_4Cl	73	not reported
H	Me	MeI	53	> 88
Me	H	NH_4Cl	84	one diastereomer
Me	H	MeI	78	52
Me	H	EtI	87	78
Me	H	CH_2=$CHCH_2Br$	68	> 95 : 5
Me	H	BnBr	78	> 95 : 5

Also, if you replace, earlier it was ester, now if you have a amide here, now if you treat this compound with potassium, 4.4 equivalent liquid ammonia THF, tertiary butanol 2 equivalent, you get this kind of enolate, conjugated enolate. And now, ammonium chloride treatment, the hydrogen comes from the top side. However, when alkyl halide is there, then the alkylation takes place from the concave attack. So from the concave side, so it is attacking from the downside. And here, the selectivity you can see if R^1 is equal to hydrogen, R^2 is equal to hydrogen, alkyl halide will be methyl iodide, you get 54 percent yield and 70 percent selectivity. So, selectivity is not very good like earlier, but still you get 70 percent selectivity.

With ethyl iodide you get 82 percent selectivity, and with ammonium chloride, when R^1 is equal to methyl hydrogen ammonium chloride, you get 84 percent yield and only one diastereomer. So this is very important. When R^1 is equal to methyl, so this is methyl group, this is methyl and this is hydrogen, then you get only one diastereomer for this product. And similarly, for this product you get methyl iodide treatment, but you get the selectivity only 52 percent. However, when you change the alkyl halide to allyl bromide, then 95, greater is to than 95:5 selectivity, you observed. Both methyl iodide allyl bromide as well as benzyl bromide cases.

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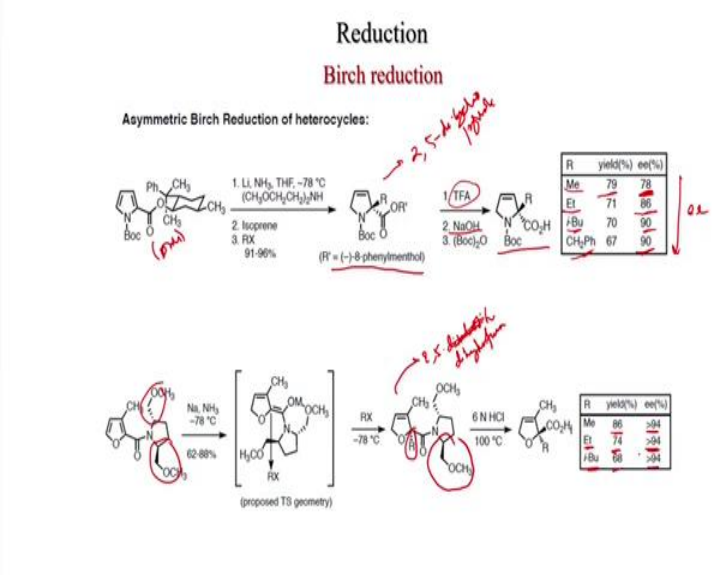

This is another chiral auxiliary was used for N-Boc pyrrole derivative like here, 8-phenylmenthol is used as a chiral auxiliary and this is actually EWG, 2 position EWG is there and we know that 2,5 dihydropyrrole will form. And here, if you treat with alkyl halide, this will be a quaternary centre and alkylation will happen to this carbon, ortho carbon of the 2 position. And this 8-phenylmenthol, you can cleaved with TFA, after that you can treat with sodium hydroxide and then again you have to treat with Boc because Boc will eliminate when TFA is treated, and now the Boc prtection again you have to do and then you get this carboxylic acid.

And you can see the selectivity, R is equal to methyl, with iodomethane you get 78 percent. And if R is equal to ethyl iodide, then 86 percent ee you can get. Isobutyl case, you get 90 percent enantioselectivity, and CH_2Ph benzyl group is added then you get 90 percent enantioselectivity. So depending on the group, so ee increases. That is the steric. Now if you have a chiral auxiliary, this is C2 symmetric chiral auxiliary, and now if you treat this compound with sodium, liquid ammonia at minus 78 degree centigrade, you get this enolate. And now this enolate will react with RX, and this group, which is closer here, if you see this group, this is top side.

Now, this will be down, so the alkylation will take place from the downside, and this is also 2,5-disubstituted furan, 2,5 dihydrofuran. And now if you treat with 6 normal HCl then this chiral aixiliary and you get a carboxylic acid, and depending on R, if R is equal to methyl, then you get greater than 94 percent enantioselectivity with 86 percent yield. If R is equal to ethyl then you

get greater than 94 percent enantioselectivity, 74 percent yield but if it isobutyl here also, get a greater than 94 percent enantioselectivity with 68 percent yield.

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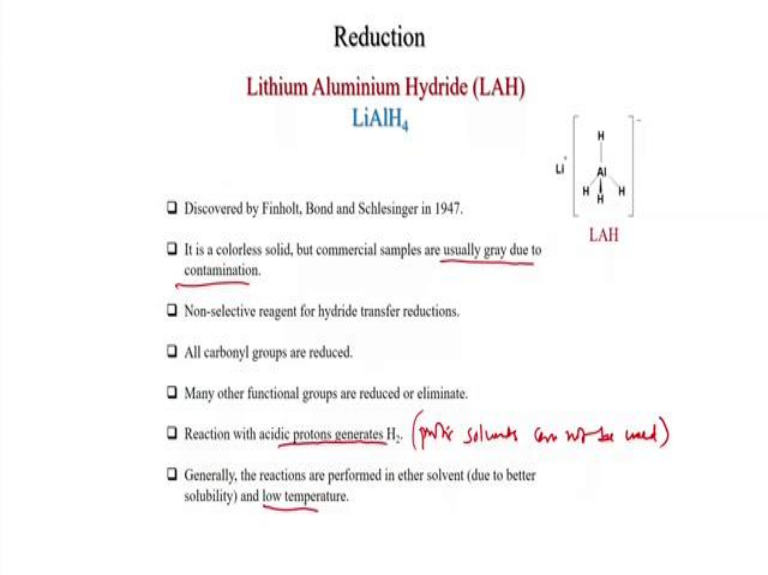

Now we will discuss lithium aluminium hydride reduction. So this is the structure of lithium aluminium hydride, lithium plus Al four hydride are there. It was discovered by Finholt, Bond and Schlesinger in 1947. It is a colorless solid, but commercial samples are usually gray due to contamination. So whatever we seen in the lab that is gray color because of contamination. Non-selective reagent for hydride transfer reduction, all carbonyl groups are reduced, generally. Many other functional groups are reduced or eliminate. Reaction with acidic protons generates hydrogen. So protic solvent cannot be used. Then, lithium aluminium hydride will be quenched.

Generally, the reactions are performed in ether solvent due to better solubility and also low temperature because it is quite vigorous.

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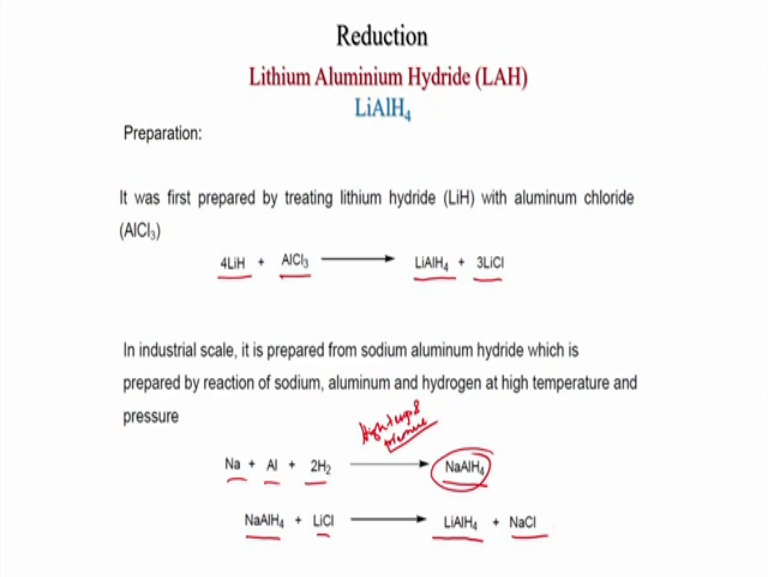

So how lithium aluminium hydride is prepared? It was first prepared by treating lithium hydride 4 equivalent with aluminium chloride you get LiAlH4 and 3 molecule of lithium chloride as a by-product. In industrial scale, it is prepared from sodium aluminium hydride. So, sodium aluminium hydride which is prepared by reaction of sodium, aluminium and hydrogen at high temperature and pressure. So, at high temperature and pressure you get hydrogen with aluminium, the bondage happens. And now this sodium aluminium hydride treated with lithium chloride you get the exchange, so lithium aluminium hydride is formed and sodium chloride is the by-product.

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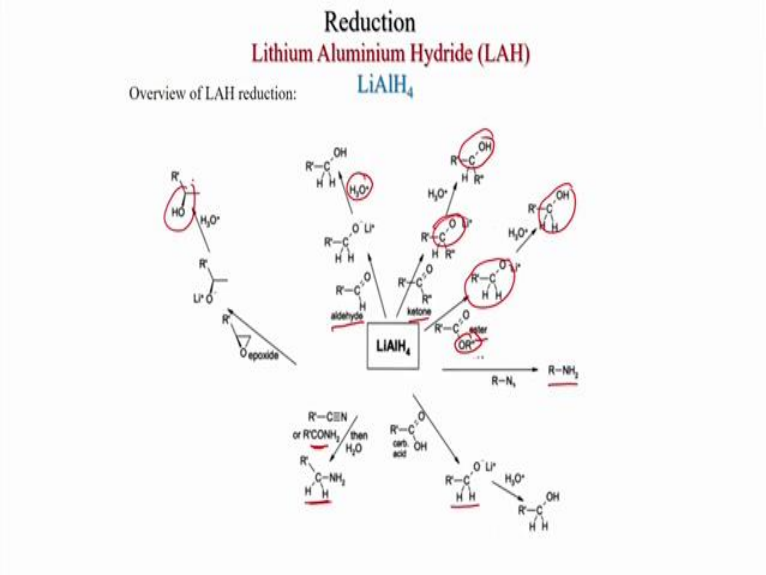

Overview of LAH reduction, LAH can reduce various carbonyl groups. Here aldehyde is used, here ketone, here ester. So aldehyde goes to first, the alkoxide, then proton source comes, you get the alcohol. Similarly, with ketone, you get the alkoxide, and now proton source come, you get the alcohol. Ester case, this group will eliminate you get a alkoxide here after elimination and reduction and then again proton source you get the alcohol. So, aldehyde, ketone, ester, all cases you get the alcohol. If you have an azide, then you get the amine. If you have a carboxylic acid also, this OH group will eliminate, you get alkoxide and which is treated with protein source, protic source, you get the alcohol.

Also nitrile can be reduced to amide, even amide, amide goes to amine. Epoxide can be cleaved to alcohol, generally less interface it attacks you get a, here you get a alcohol at the secondary carbon.

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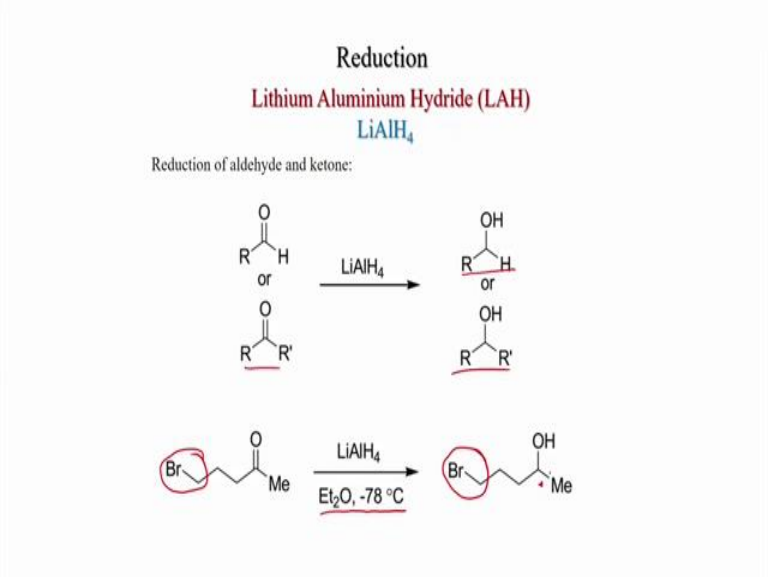

So reduction of aldehyde and ketone, generally aldehydes and ketones are reduced to lithium aluminium hydride to get their corresponding alcohols. And if you have a ketone like this with a bromo substituent, now lithium aluminium hydride ether minus 78 centigrade, this substituent is untouched, only the ketone group reduced to the alcohol.

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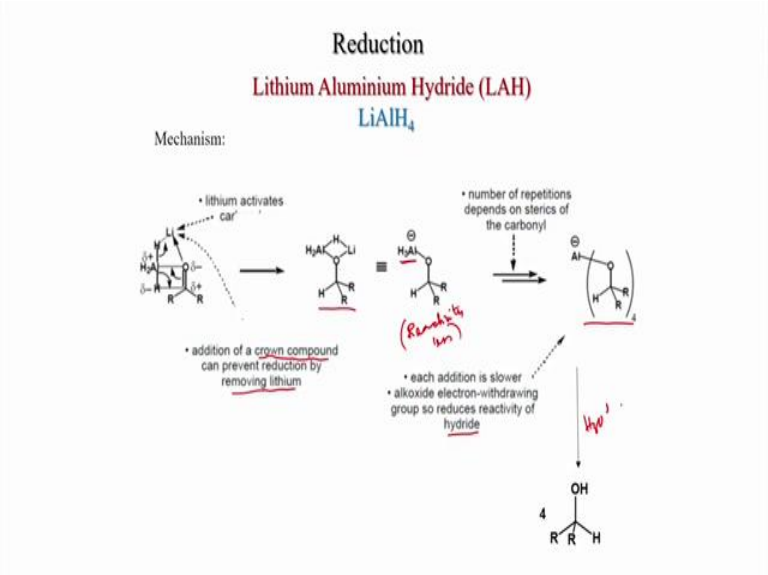

What is the mechanism of carbonyl reduction? Now here it is important that both the aluminium and lithium binds with oxygen and lithium actually, in facts activates carbonyl. It has been

observed that addition of a crown compound can prevent reduction by removing lithium. So, if you remove lithium, then the reduction will not happen, and then this hydride, there hydride bond is there between aluminium and lithium and this hydride is coordinated at this carbonyl carbon, and now the hydride delivery will take place to generate the alkoxide derivative. Where, bond like this will be there, first aluminium hydride lithium and this will go to H_3Al negative charge here.

Now you can see this is also a reducing agent, there are 3 hydride is present, so it can react another 3 molecules of carbonyl compound, ultimately 4 molecules of carbonyl compound gets reduced and you get a alkoxide like this, where Al minus will be coordinate to 4 oxygen atom. Number of repetition depends on sterics of the carbonyl group. This is important. Also each addition is slower because alkoxide electron withdrawing group so reduces reactivity of hydride. So, so this reaction, this is reactivity less. So reactivity less compared to lithium aluminium hydride, and ultimately if you treat with proton source, then you get the alkoxide to alcohol.

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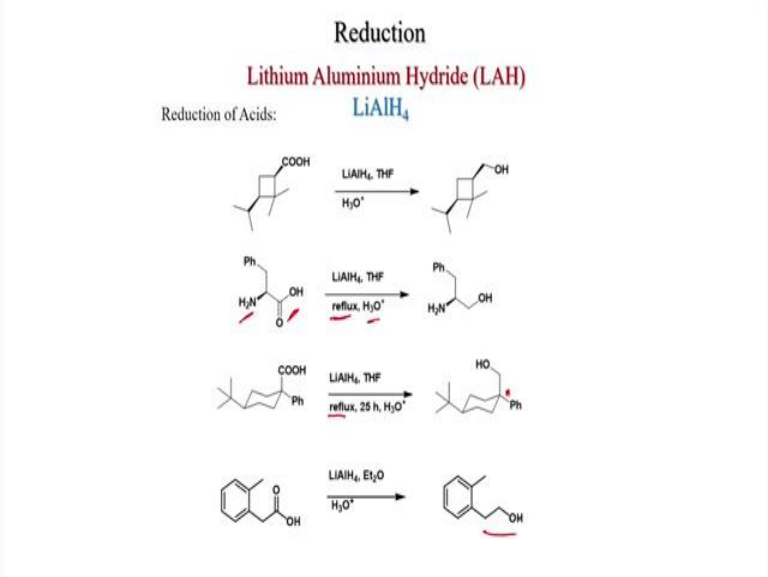

Reduction of acids. Various acids can be reduced in lithium aluminium hydride. Here, you can see cyclobutane carboxylic acid reduced to the alcohol with lithium aluminium hydride THF and then treated with protic source. And here, in amino group is present and a carboxylic acid, this is alpha amino acid, it is reacting with lithium aluminium hydride, THF, in reflux condition followed by acid treatment gives the alcohol and here is cyclohexyl group, carboxylic acid is

present here. Lithium aluminium hydride reduces under reflux condition to the alcohol. And this is a quaternary centre. Here, a phenyl acetic acid like a group is there and this on reduction lithium aluminium hydride generates this primary alcohol.

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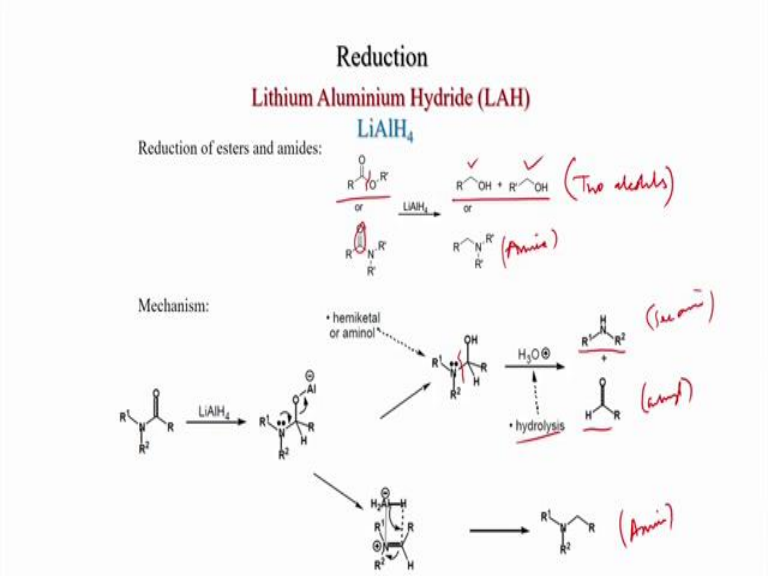

Esters and amides can also be reduced. Generally esters on reduction cleave this and generates two alcohol, this is one alcohol, this is another alcohol. Amides, this carbonyl gets to CH_2 so you get an amine. Here two alcohols are generated. What is the mechanism of this reaction? So amide, first this carbonyl group gets reduced to generate the alkoxide, and now, now this alkoxide on elimination will generate a imine and imine will be activated again like carbonyl compound, this aluminium will bind to the imine and hydride delivery at the, this carbon, imine carbon and you get ultimately amine. Alternatively, this hemiketal amine or aminol will be formed after protonation, and this can cleave, the hydrolysis can happen and you get hydrolysis.

On hydrolysis you get secondary amine and carbonyl compound, so this is also possible. So, secondary amine and carbonyl compound, so instead of a amine you can get this also side reaction.

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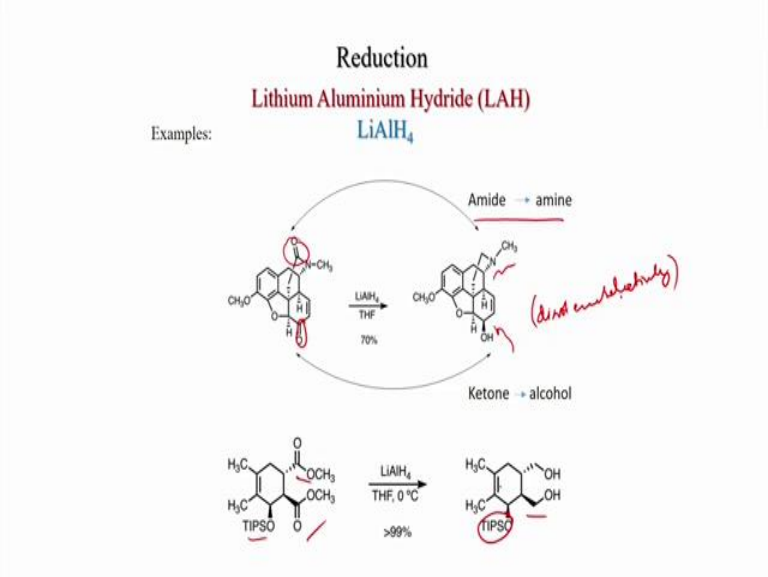

This is an example that lithium aluminium hydride is used in many complex structure, this is a complex structure where there is a enone motif, also there is a amide motif and you can see with lithium aluminium hydride THF reaction you get the amide to amine. So amide to amine happens here and selectively the carbonyl group is getting reduced to alcohol and also the geometry of the compound, this reduction happens diastereoselectivity. So, diastereoselectivity reduction happens, the hydride comes from the down face. And here you can see a silyl group is present and 2 ester motifs are present, both ester getting reduced to lithium aluminium hydride you get a diol without disturbing the TIPS group.

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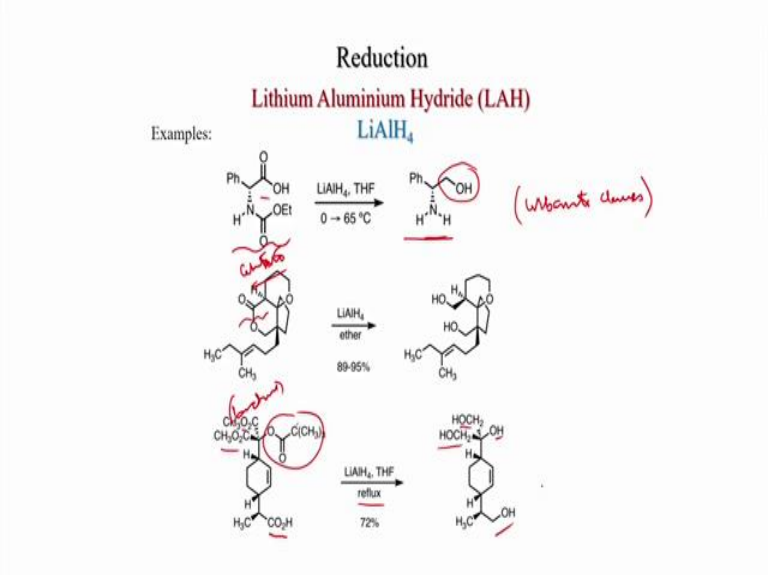

Here is another example, here a carbamate group is there, so this is carbamate, and here a carboxylic acid, so here in N- protected amino acid is present. Now the carboxylic acid goes to the alcohol and carbamate also getting cleaved. Carbamate cleaving is giving you a primary amine, so carbamate cleaved or cleaves. Carbamate cleaves under this condition. And this is N compound, there is a lactone is there. Lactone on lithium aluminum hydride reaction, it gives diol, so this is very important. This bond is getting cleaved and you get an aldehyde, then that insitu generated aldehyde get reduced to the alcohol.

Also, if you have a many ester groups like as well as carboxylic acid, here is an ester, here ester, here is an ester group and all groups with lithium aluminium hydride reflux condition getting reduced, this alcohol this alcohol this alcohol and this alcohol.

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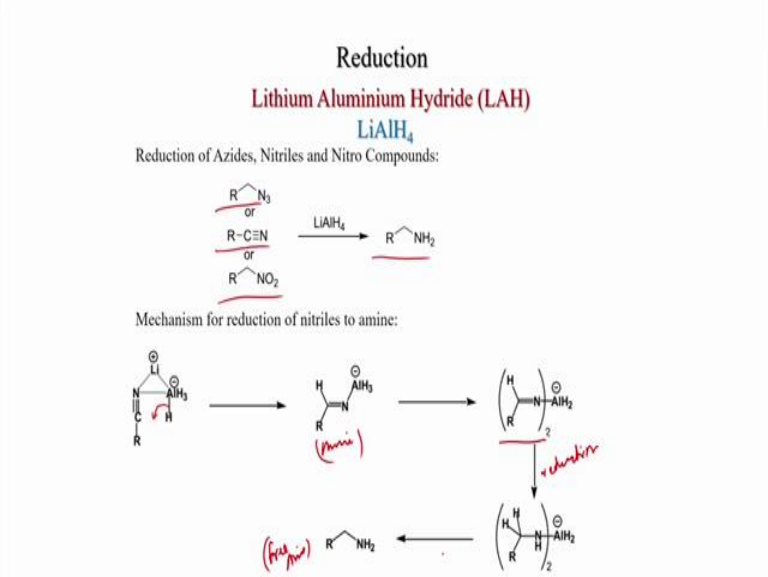

Reduction of azides, nitriles and nitro compounds, so azides nitriles and nitro alkanes on lithium aluminium hydride reduction generates the amine. What is the mechanism of the reduction of nitriles to amine. Here also the nitrogen binds both with lithium and aluminium and now this hydride delivery will take place to generate first the imine, with N aluminium bond and now this can again reduce another nitrile to generate this species where 2 imine bonds are connected to aluminium. And ultimately this imine will get again reduce, so on reduction you generate the amine and after on protonation you will get the free amine. So, this is the free amine. So what is the intermediates, nitrile goes to imine, imine goes to amine and after proton or acidic workup you get the free amine.

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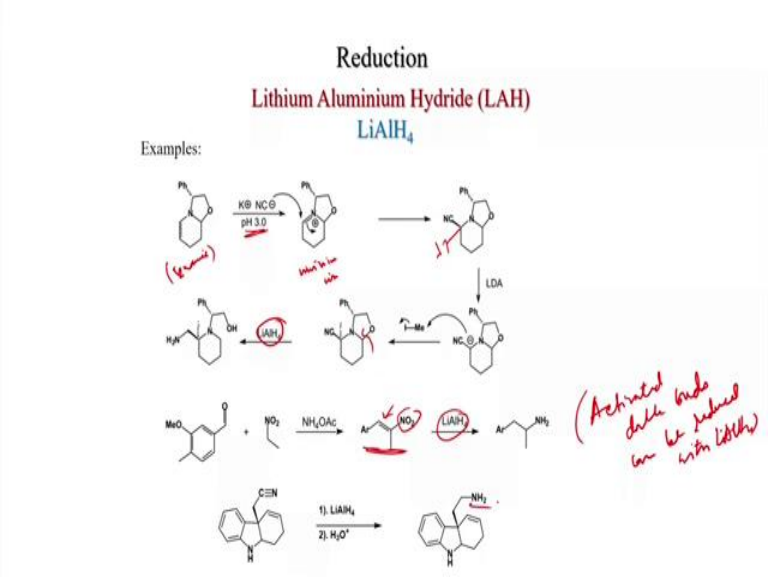

Example like here this is an enamine. Enamine with K plus and cyanide nucleophile, first in the protons, when you get the acidic medium, pH is equal to 3, then you get the iminium ion. And now the cyanide adds to the iminium ion to get this as cyano containing product and now LDA can take this proton and generate an anion. And after alkylation, you get this compound. Now if you treat this compound with lithium aluminium hydride, what will happen? This bond will cleave. So the aminal is cleaved to this free alcohol. Also if you make the nitroalkene, and now with treatment of lithium aluminium hydride. The first reduction will take place of the double bond because this is, the double bond is activated.

So activated double bonds can be reduced with lithium aluminium hydride and ultimately you get the amine. Here a nitrile is there with lithium aluminium hydride reduction followed by acidic workup, you get the amine.

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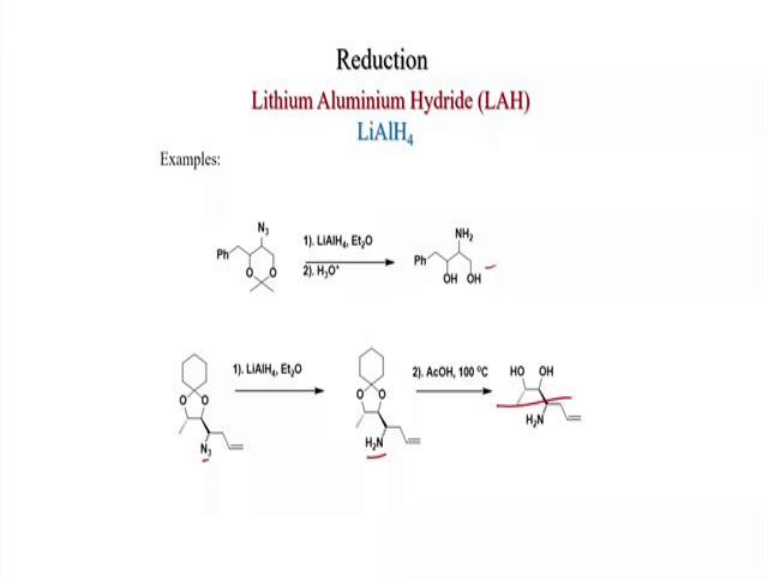

Here is a more example, like a secondary azide is there with lithium aluminium hydride condition you get a primary amine. Here also azide is present, you get a primary amine and after acetic acid you get the cleavage of the ketal you get 3 diol.

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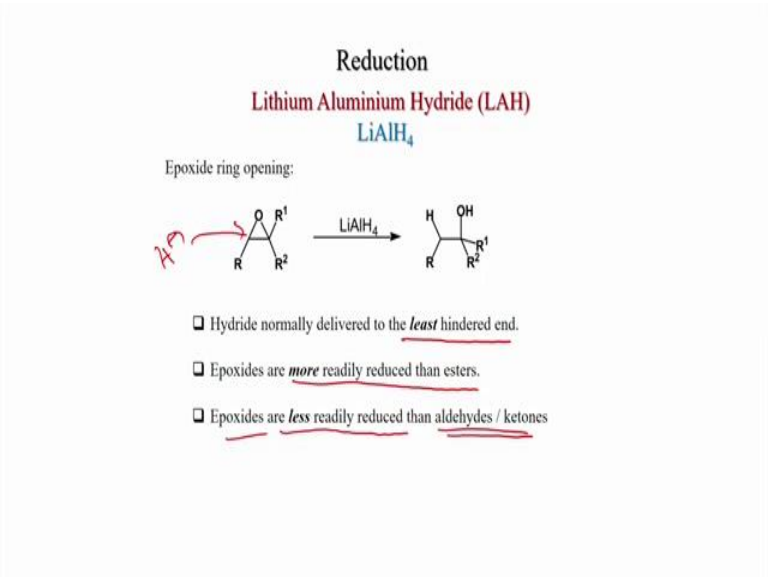

Epoxide ring opening is a very important reaction and here the regioselectively at the least hindered end. So here the hydride will take place from this side. Epoxides are more readily reduced than esters. If you have ester functionality and epoxide, then epoxide will reduce fast.

On the other hand if aldehyde ketone are there then the reduction will take place on the aldehyde and ketone because epoxides are less readily reduced.

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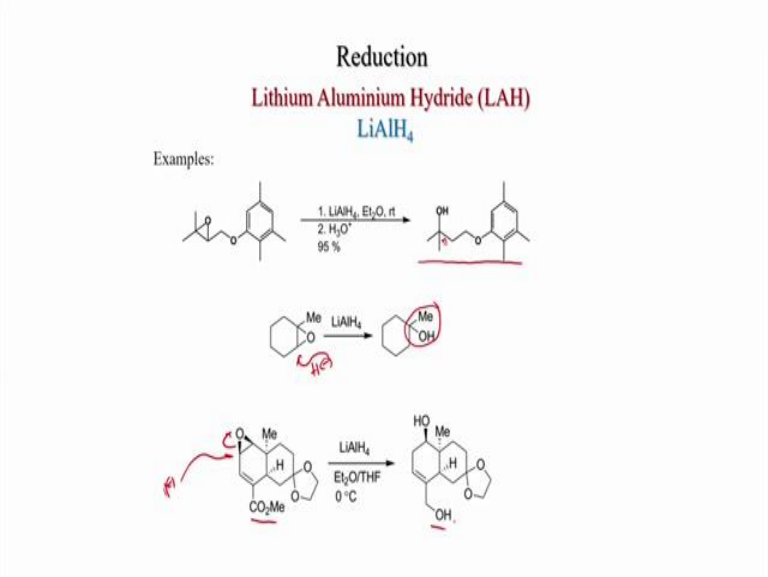

Example, here is an epoxide is there lithium aluminium hydride treatment gives this alcohol. With a quaternet centre here. Here also regioselectively this cyclohexene epoxide then gives this quaternary center and this complex molecule when treated with lithium aluminium hydride then hydride delivery takes place from the side. You get this secondary alcohol. Also the ester group getting reduced to alcohol.

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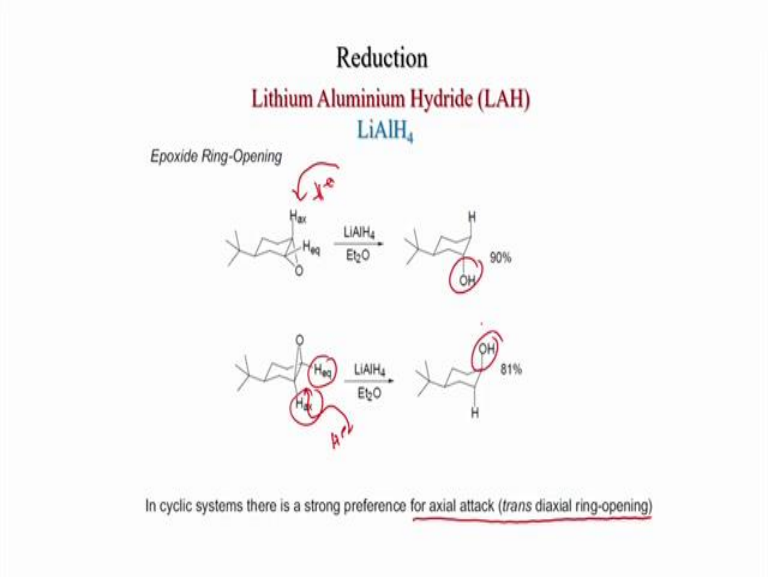

Epoxide ring opening, more examples is there it is cyclohexane system is there and if you have a epoxide like this, so if you draw in the downside then the hydride delivery takes place from this side. So hydride comes from here. So axially, mostly it attacks at axially. Strong preference for axial attack, trans diaxial ring opening. Suppose this system, if the epoxide is up now and this becomes equatorial and this axial, so hydride will come from this one axial side, you get this alcohol. Here it is down, here it is up.

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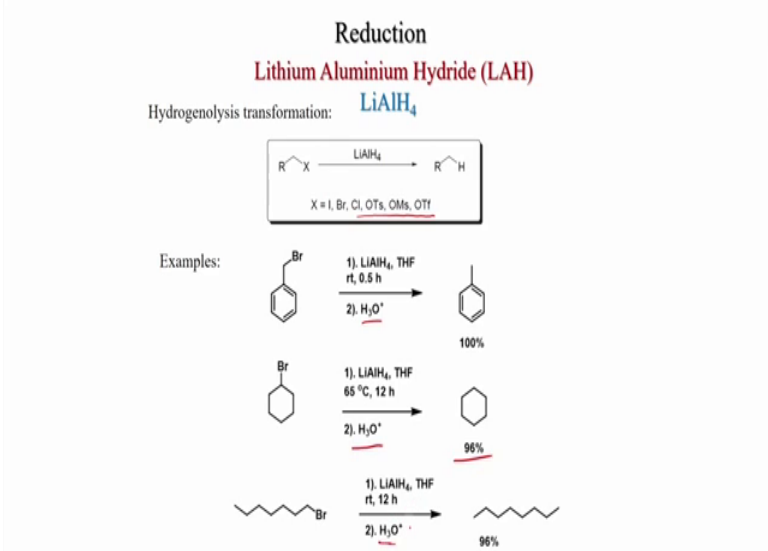

Hydrogenolysis transformation, also lithium aluminium hydride does like X is equal tim bromine, iodine, bromine, chlorine, o-tosyl, o-mesyl, o-triflate, you get this alkene. Examples like benzyl bromide when treated with lithium aluminium hydride THF and followed by acidic workup you get toluene, similarly cyclohexyl bromide with lithium aluminium hydride THF 65 degree centigrade followed by acetic workup, you get cyclohexane in 96 percent yield. And this is a normal long chain alkyl bromide also with lithium aluminium hydride H_3O you get the alkane.

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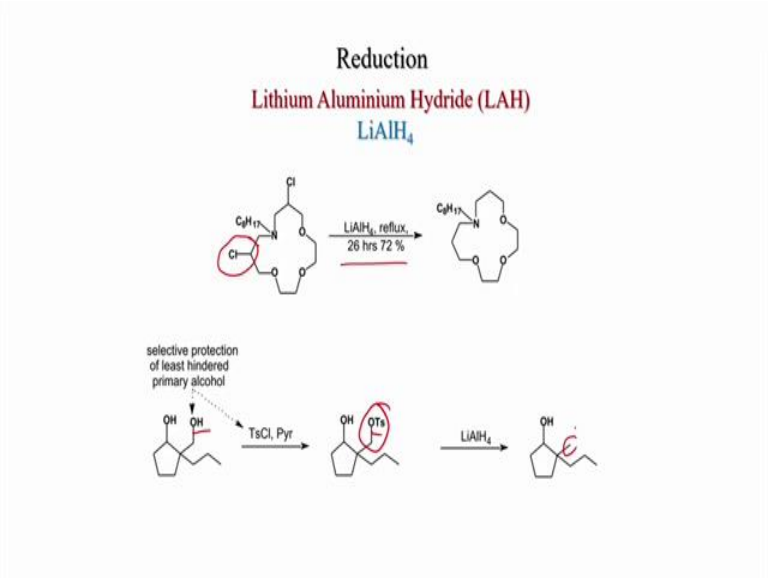

Reduction, if you have a caged compound like this then this chlorine can be removed with lithium aluminium hydride reflux condition, and also if you have a diol, now if you selective protection of this primary alcohol to the tosyl derivative and then lithium aluminium hydride reduction can remove this o-tosyl group, so that the alkyl group is generated here.

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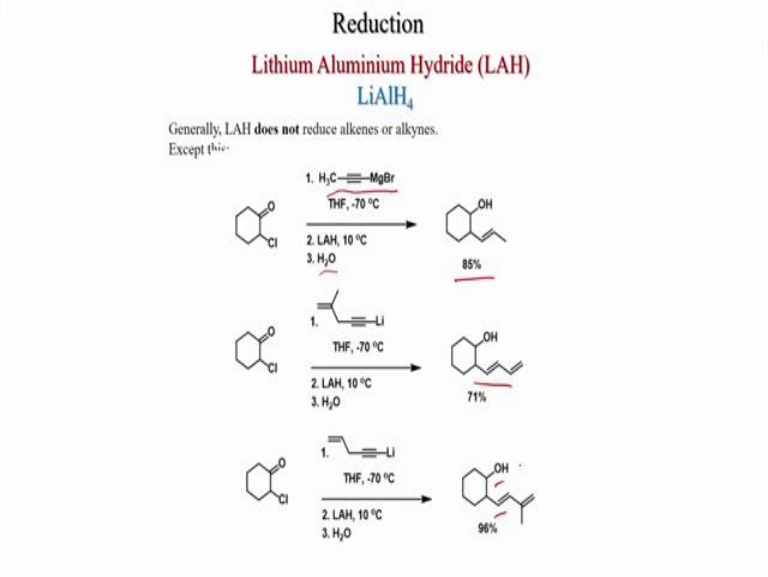

Generally LAH does not reduce alkenes or alkynes, but we have seen the activated alkenes it get reduced. Suppose if we have a compound like this 2 chloro cyclohexanone and if you treat with this propargylic Grignard reagent and with THF minus 70 degree centigrade followed by lithium aluminium hydride and H_2O condition, you get this alcohol. Where triple bond becomes double bond, similarly here also triple bond addition and followed by reduction generate this diene, and here also the triple bond becomes double bond. So what is the mechanism of this reactions, that we will see.

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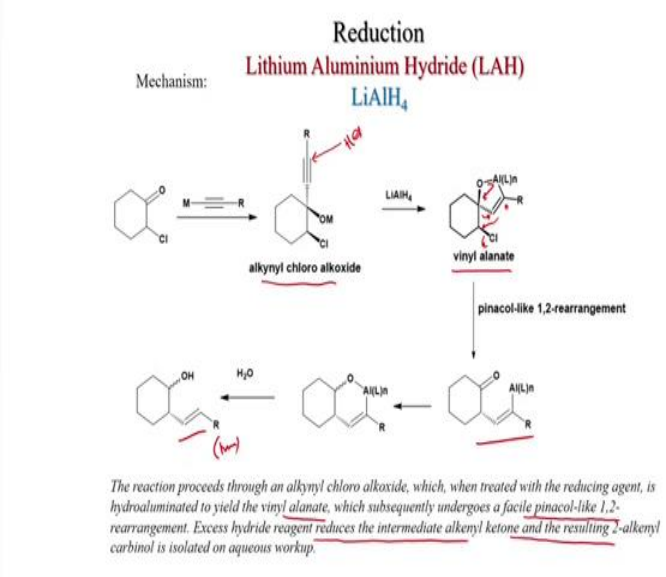

So first, a carbonyl group is getting attacked by this Grignard reagent to generate this alkynyl chloro alkoxide, which after treatment with lithium aluminium hydride generates this. Reduction happens like this. So the aluminium selectively, hydride selectively comes from this way so that aluminium will be there on this a carbon atom and it can bind with the oxygen, so this is called vinyl alanate. And after pinacol-like 1,2- rearrangement you get a carbonyl compound, so it will be like this. So carbonyl compound and you get this one, so this is a SN2 substitution reaction here you get from the alpha attack and after that, after acidic workup you get a double bond here, which is trans.

So the reaction proceeds through an alkynyl chloro alkoxide, which, when treated with reducing agent, is hydroaluminated to yield vinyl alanate, which subsequently undergoes a facile pinacol-like 1, 2-rearrangement. Excess hydride reagent reduce the intermediate alkenyl ketone and the resulting 2-alkenyl carbinol is isolated on aqueous workup.

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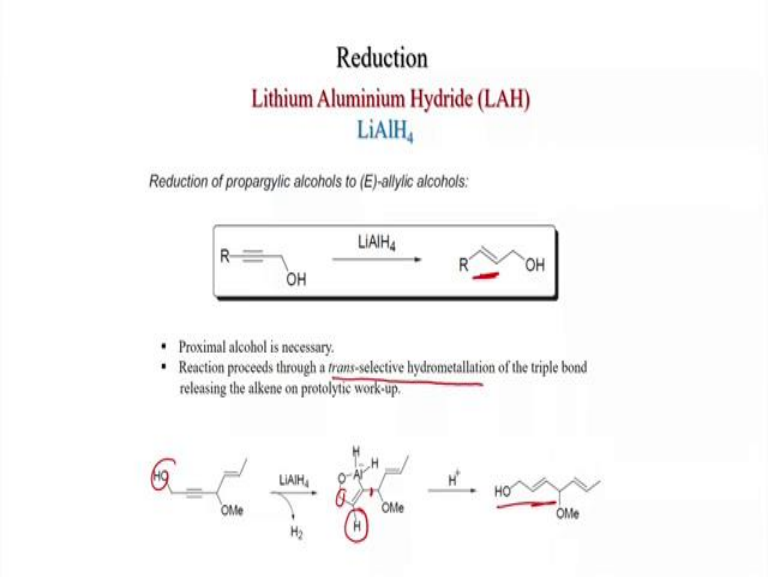

This is the similar process, here also happens when you take propargylic alcohol with lithium aluminium hydride, you get a trans allylic alcohol. So here proximal alcohol is necessary and reaction proceeds through a trans-selective hydrometallation of the triple bond releasing the alkene on protolytic workup. So this is the mechanism that that alcohol binds with aluminium and the hydride delivery takes place from this side, you can see this is the hydride. And now this species will be generated after elimination of hydrogen. And now after proton source, you can see this is the trans actually, this and this, they are trans to each other. So you get a trans allylic alcohol.

So whatever we have seen today, the first is the Birch reduction. So in Birch reduction we have that benzene derivatives can be reduced and when depending on the substitution you get two kind of cyclohexadiene systems. If you have an electron donating group, then the double bond will contain the group, electron donating. On the other hand, if electron withdrawing group is there, then the cyclohexadiene system will be generated, where electron withdrawing group will be on the saturated carbon atom. Also we have seen that chiral Birch reduction is possible, like if you have a substituent, then you can do.

And Birch reduction followed by alkylation, and it is only possible when electron withdrawing group is present, and you can derive the quaternary centre. And this reduction was successfully applied to furan, pyrrole, indole, quinoline system. On the other hand, lithium aluminium hydride

is very strong reducing agent, and it reduces all kinds of carbonyl compounds and aldehydes, ketones, esters, amides, nitriles. Nitriles azide and nitroalkenes gives the amine. On the other hand, if you have an allylic alcohol with propargylic system, then you can get a trans selective allylic alcohol, and this is, the mechanism follows that aluminium bind with the alcohol and then a 5 member ring is formed.

So, also generally this is important that the double bond can also be reduced with lithium aluminium hydride, particularly when it is conjugated, like nitro olefin on reduction with lithium aluminium hydride, both nitro and the double bond gets reduced. So this is the difference between Birch reduction and LAH. In Birch reduction the electron is the reducing agent. On the other hand, lithium aluminium hydride, the hydride minus is the reducing agent. Thank you.