Reagents in Organic Synthesis
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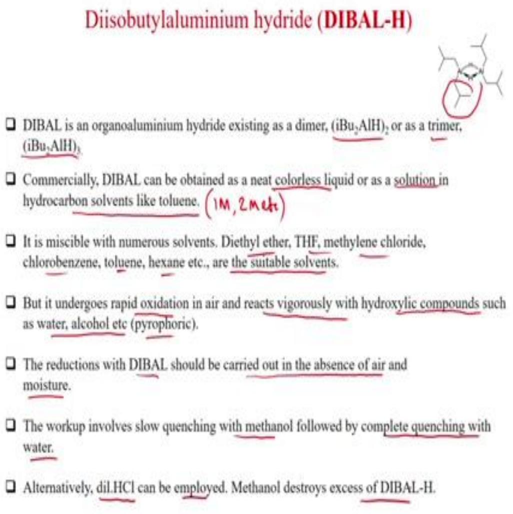

Diisobutylaluminium hydride (**DIBAL-H**)

- ❑ DIBAL is an organoaluminium hydride existing as a dimer, $(iBu_2AlH)_2$ or as a trimer, $(iBu_2AlH)_3$
- ❑ Commercially, DIBAL can be obtained as a neat colorless liquid or as a solution in hydrocarbon solvents like toluene. (1M, 2M etc)
- ❑ It is miscible with numerous solvents. Diethyl ether, THF, methylene chloride, chlorobenzene, toluene, hexane etc., are the suitable solvents.
- ❑ But it undergoes rapid oxidation in air and reacts vigorously with hydroxylic compounds such as water, alcohol etc (pyrophoric).
- ❑ The reductions with DIBAL should be carried out in the absence of air and moisture.
- ❑ The workup involves slow quenching with methanol followed by complete quenching with water.
- ❑ Alternatively, dil.HCl can be employed. Methanol destroys excess of DIBAL-H.

Welcome again today we will discuss four reduction reactions. First one is DIBAL-H then we will discuss Wolff-Kishner reduction and then Clemmensen reduction and finally reduction with LDA. So DIBAL is full name is diisobutylaluminum hydride as you can see this structure, this is the isobutyl group is they are aluminum and hydrogen bridge is there. So this exist as a dimer, (isobutylyl$_2$ AlH) 2 or as a trimer (isobutyl2 AlH)3. Commercially, DIBAL can be obtained as neat colorless liquid or as a solution in hydrocarbon solvents, like toluene exactly you can buy one molar two molar etc.

It is miscible with numerous solvents like diethyl ether, THF, methylene chloride, chlorobenzene, toluene, hexane etc. Are the suitable solvents, and that is why it is used because of its miscibility. It has advantage but it undergoes rapid oxidation in air and reacts vigorously with hydroxylic compounds such as water alcohol etc. So this is a pyrophoric. Thus, the reduction with DIBAL should be carried out in the absence of the air and moisture. So this should be dry reaction, because DIBAL reacts with the moisture, and also with protic solvents. The workup involves slow quenching with methanol followed by complete quenching with water. Because methanol quenching DIBAL as well as water also. Alternatively dilute HCl can be employed. Methanol destroys excess of DIBAL-H.

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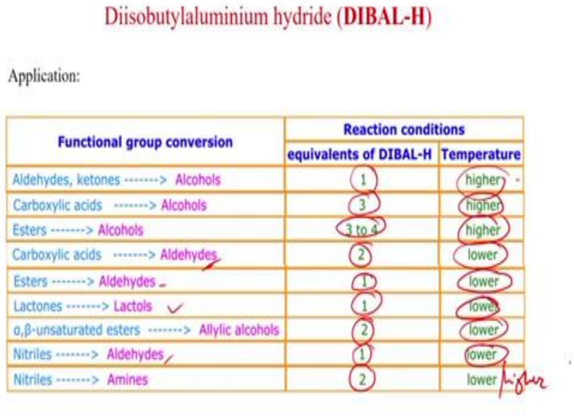

Diisobutylaluminium hydride (**DIBAL-H**)

Application:

Functional group conversion	Reaction conditions	
	equivalents of DIBAL-H	Temperature
Aldehydes, ketones -------> Alcohols	1	higher
Carboxylic acids -------> Alcohols	3	higher
Esters -------> Alcohols	3 to 4	higher
Carboxylic acids -------> Aldehydes	2	lower
Esters -------> Aldehydes	1	lower
Lactones -------> Lactols ✓	1	lower
α,β-unsaturated esters -------> Allylic alcohols	2	lower
Nitriles -------> Aldehydes	1	lower
Nitriles -------> Amines	2	lower higher

And there are various reduction can be carried out with the DIBAL-H. Suppose aldehydes and ketones can be converted to alcohol with one equivalent of DIBAL-H and the temperature will be higher. Also carboxylic acid to alcohol so its three equivalent of DIBAL-H temperature is higher. Esters to alcohols so its 3-4 equivalent DIBAL and higher temperature. Carboxylic acid to aldehydes this is important reaction that the aldehydes can be stopped here.

And 2 equivalent DIBAL-H and temperature will lower. Also Esters to aldehydes this is also an important reaction of DIBAL-H and only one equivalent DIBAL-H have to used for this case and the temperature will be lower. Lactones to lactose also an important reaction here also you have to use only one equivalent of DIBAL and the temperature is lower. Alpha beta unsaturated esters to allylic alcohols two equivalent of DIBAL-H will be used.

This is also an important reaction because with LAH you cannot carry out this reaction because double bond will be reduced. So in DIBAL this is very selective that double bond is untouched and the reaction also will be in lower temperature. Nitriles to aldehydes this is also an important reaction of DIBAL and the reaction can be stopped at aldehydes with only one equivalent of DIBAL-H and temperature will lower. Nitriles to amines this can be carry out with two equivalent of DIBAL-H and here lower or also higher temperature can be used.

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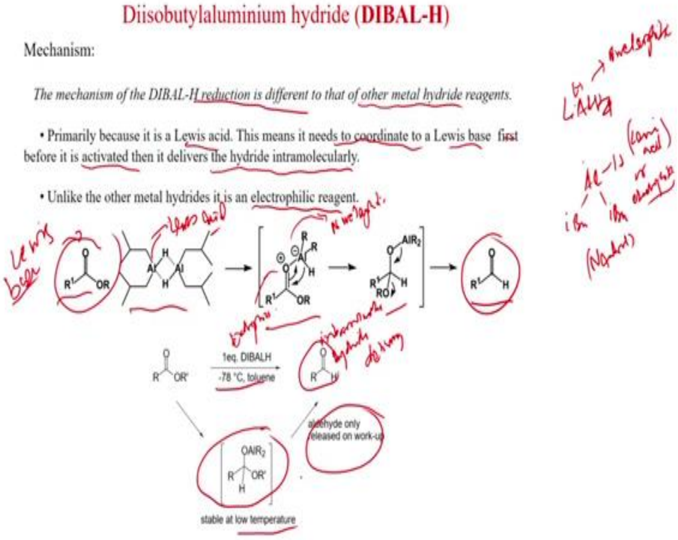

Diisobutylaluminium hydride (**DIBAL-H**)

Mechanism:

The mechanism of the DIBAL-H reduction is different to that of other metal hydride reagents.

- Primarily because it is a Lewis acid. This means it needs to coordinate to a Lewis base first before it is activated then it delivers the hydride intramolecularly.
- Unlike the other metal hydrides it is an electrophilic reagent.

Now we will discuss mechanism of DIBAL aluminium hydride, so mechanism of DIBAL-H reduction is different to that of other metal hydride reagents. Primarily because it is a Lewis acid. This means it needs to coordinate to a Lewis base fast before it is activated then only it delivers the hydride intramolecularly. Unlike the other metal hydride it is an electrophilic reagent. Suppose we have always seen lithium aluminum hydride there is a negative charge on aluminium, so this is a nucleophilic reagent. On the other hand DIBAL-H this is a Lewis acid Lewis acid or an electrophilic. So this is the different because diisobutyl aluminium hydride this is a neutral and this is an electrophilic reagent. And for that we need to react with suppose an ester this is a dimeric DIBAL-H this is a Lewis base Centre this is this Lewis base. And this is a Lewis acid.

First it coordinate with the Lewis basic centre. Now, this coordination will happen. That the oxygen alumina bond is formed and you can see there is a negative charge on the aluminium and positive charge on oxygen so what happens this becomes now nucleophilic centre. And this is electrophilic centre, so now because this aluminium has a negative charge now this is nucleophilic so that hydride deliver will takes place to the oxygen ion and this is called intramolecular hydride deliverey.

And then you get this intermediate and after the elimination of OR you get the aldehyde. So with DIBAL-H you can get an aldehyde from an ester. And this is the reaction that if you a ester if you treat with one equivalent DIBAL-H minus 70 degree centigrade toluene, then you get the aldehyde and what happens with one equivalent DIBAL and minus 78 degrees Centigrade. This intermediate is formed and this become stable at the low temperature. So further reduction is not possible. That is the aldehyde the further reduction is not possible because this intermediate is formed which is stable and only aldehyde is formed only after work up. So aldehyde is not generating in the reaction medium so that the alcohol cannot be formed because this intermediate is formed which after hydrolysis only generates the aldehyde so this is a very important.

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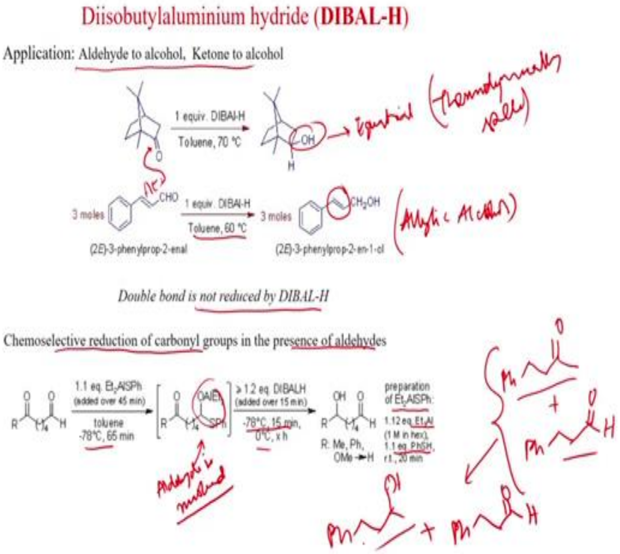

Diisobutylaluminium hydride (**DIBAL-H**)

Application: Aldehyde to alcohol, Ketone to alcohol

Double bond is not reduced by DIBAL-H

Chemoselective reduction of carbonyl groups in the presence of aldehydes

Its measured application to aldehyde to alcohol, ketone to alcohol like this case here this bridge system if you can see this hydride is coming from this down face and you get the alcohol at the equatorial. So this is thermodynamically stable. So in DIBAL-H case the steady factor is not so important only the thermodynamic. Now with alpha beta unsaturated aldehyde is one equivalent of DIBAL toluene 60 degree centigrade you get this allylic alcohol. And here also the double bond is untouched.

This is very important because DIBAL-H is not nucleophilic reagent; It is an electrophilic reagent so double bond is not getting reduced. Chemoselective reduction of carbonyl groups in the presence of aldehydes is possible, or that you have to use this diethyl thiophenolate and toluene minus 17 degrees Centigrade. What happened the aldehyde is getting masked like this so aldehyde is masked. And once the aldehyde is masked this then the Ketone is naked and then the DIBAL-H reduction will take place on the Ketone and interestingly under this condition minus 78 degree reduction followed by zero degree centigrade this moiety will give to the aldehyde.

So ultimately you get the ketone reduction and the aldehyde is untouched. How you will prepare this one this intermediate reagent can be prepared from 1.2 equivalent of triethyl aluminium and 1.1 equivalent of thiophenol. Also this reaction suppose you have a mixture of Ketone and aldehyde suppose if you have a ketone of aldehyde then under this condition what will happen the Ketone only will reduce. So this is like mixture also can work. This is not that in the same molecules the two carbonyl group has to be there but separately if you Ketone and Aldehyde also, the Ketone can be reduced to the alcohol and aldehyde is untouched.

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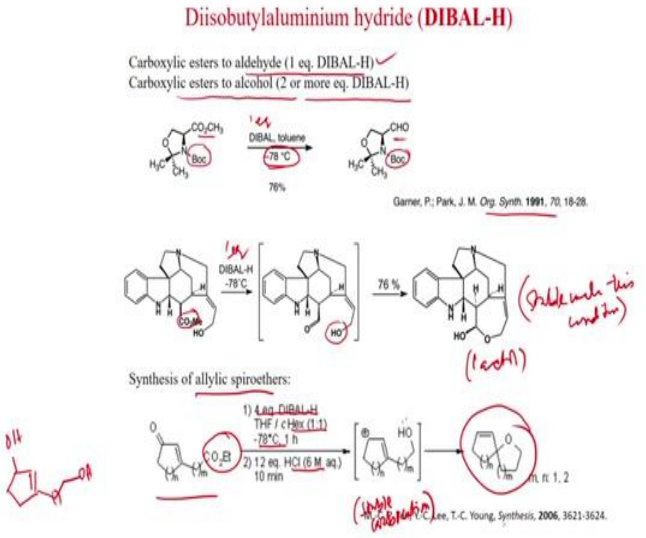

Diisobutylaluminium hydride (**DIBAL-H**)

Carboxylic esters to aldehyde (1 eq. DIBAL-H) ✓
Carboxylic esters to alcohol (2 or more eq. DIBAL-H)

Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18-28.

Synthesis of allylic spiroethers:

Lee, T.-C. Young, *Synthesis*, **2006**, 3621-3624.

Carboxylic ester to aldehyde with one equivalent of DIBAL-H and carboxylic ester to alcohol with two or more equivalent of DIBAL-H, this is very important reaction of DIBAL. That which one equivalent DIBAL like this condition. Here one equivalent DIBAL toluene minus 78 degrees Centigrade. This ester is converted to the aldehyde and other Boc groups are untouched. This was repeated organic synthesis. Also this alkyl halide here you can see there is a ester group is there and with DIBAL-H is should be one equivalent DIBAL-H minus 70 degree Centigrade you get the aldehyde and that insitu generated aldehyde reacts with the primary alcohol to generate the lactol and this lactol is stable under this condition.

So, in DIBAL-H condition lactol is very stable. It does not father react. Synthesis of allylic spiroethers is also possible with DIBAL-H for that you need a system like this alpha beta unsaturated Ketone and there is a ester group is here and with four equivalent DIBAL-H THF cyclohexene 1 is to 1 mixture minus 70 degree temperature followed by twelve equivalent of HCl six molar aqueous. So quiet acidic solution you have to treat. What happens first this alcohol is formed so this alcohol is formed and here also the alcohol is formed. And when you treat with HCl what happens the secondary alcohol gets eliminated because the allylic carbocation is formed and this is quite stable carbocation. And now this primary alcohol will react on this double bond and the double bond will isomerized actually then you get this allylic spiroethers in very good yield. And this was published in synthesis journal.

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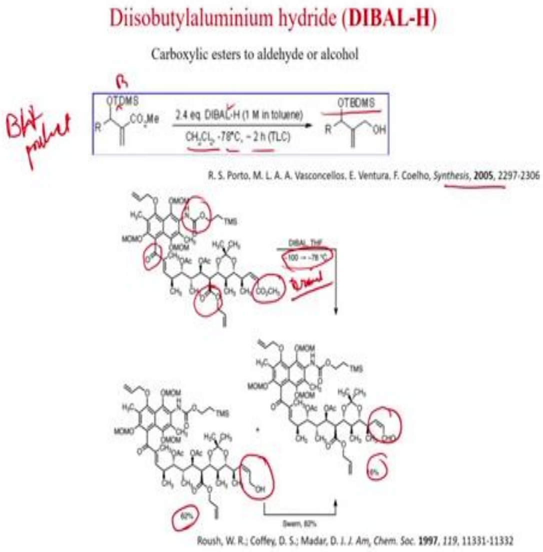

Diisobutylaluminium hydride (**DIBAL-H**)

Carboxylic esters to aldehyde or alcohol

R. S. Porto, M. L. A. A. Vasconcellos, E. Ventura, F. Coelho, Synthesis, **2005**, 2297-2306

Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331-11332

Carboxylic esters to aldehyde there are more examples. Suppose this one Baylis Hillman product actually and this is OTBDMS group. So this compound when treated with 2.4 equivalent DIBAL-H one molar in toluene dichloromethane minus 70 degree Centigrade after two hours studying you get this allylic alcohol and this TBDMS group is untouched. It’s also published in Synthesis journal and if you have this kind of complex structure. Here you can see various functional groups are there like the here is a carbonate group is there here is a alpha, beta unsaturated ketone is there, here is a allylic ester group is there and this is a terminal a ester this alpha beta unsaturated ester.

This is the terminal and under this condition DIBAL-H minus 100 to minus 70 degree Centigrade only the terminal alpha beta unsaturated ester getting reduced to the alcohol as well as aldehyde. So alcohol is found 62 percent yield and aldehyde 16 percent yield and also by Swan condition, you can combat to the allylic alcohol to the alpha beta unsaturated aldehyde. So this is remarkable that they are the various functional group is there and DIBAL-H very selective to reduce only the terminal ester group. This was published in JACS 1997.

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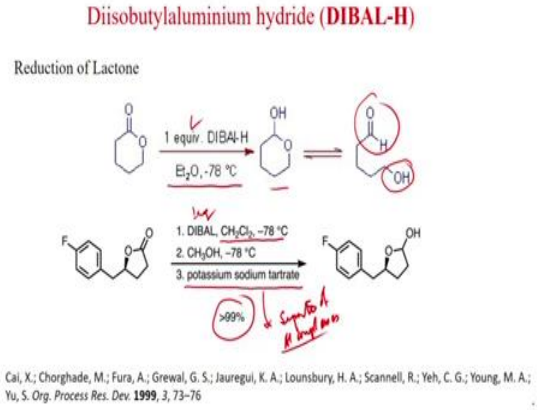

Diisobutylaluminium hydride (**DIBAL-H**)

Reduction of Lactone

Cai, X.; Chorghade, M.; Fura, A.; Grewal, G. S.; Jauregui, K. A.; Lounsbury, H. A.; Scannell, R.; Yeh, C. G.; Young, M. A.; Yu, S. *Org. Process Res. Dev.* **1999**, *3*, 73–76

Reduction of lactone to lactol also very important reaction of DIBAL for that you have to use one equivalent of DIBAL-H diethyl ether solvent minus 78 degree Centigrade you get the lactol and lactol can be equilibrium with the three form that the alcohol and the aldehyde is there. So suppose this butyrolactone if you treat with DIBAL-H dichloromethane minus 78 degree centigrade followed by quenching with methanol and potassium sodium tartrate you have used to this is used to first separate of aluminium complex. Separate of aluminium complex which are formed after the reaction. And you get this butyrolactol in 99 percent yield greater than 99 percent yield and this has published in organic process research division.

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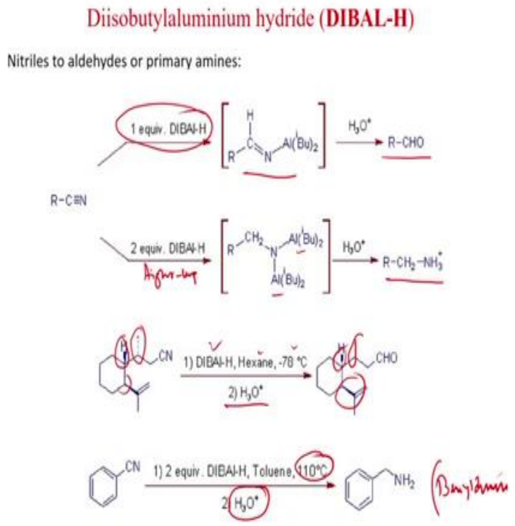

Diisobutylaluminium hydride (**DIBAL-H**)

Nitriles to aldehydes or primary amines:

Nitriles to aldehydes or primary amines also is an important reaction. So, nitriles when treated with one equivalent of DIBAL-H this kind of imine intermediate is formed and there amine nitrogen there is a bond with aluminium and with aqueous work up to get the aldehyde. On the other hand two equivalent DIBAL-H and you have to use little bit higher temperature and then you get this double reduction of the nitriles to get this amine where two DIBAL aluminium is present and after aqueous workup you get the amine. If you see this substrate there is a chiral centre is here here here and when it was treated with DIBAL-H section minus 78 degree centigrade followed by acidic workup you get the aldehyde. And this chiral centres are untouched so they are not disturbed under this reaction condition. Also if you have a benzonitrile with two equivalent DIBAL-H toluene 110 degree centigrade followed by acidic workup you get the benzyl amine in good yield.

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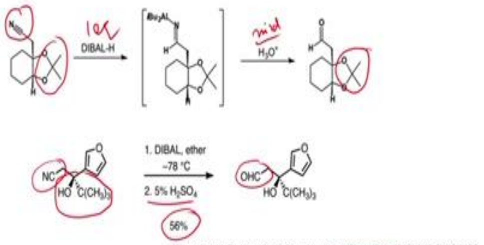
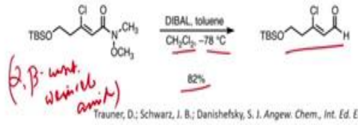
Diisobutylaluminium hydride (**DIBAL-H**)



Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146-3155

Reduction of Weinreb amides:



Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542-3545

Also if you see this substrate there is a nitrile motif here and also there is a ketal motif is here and with DIBAL-H one equivalent you get this imine complex and now acidic workup you get the aldehyde and this ketal motif is untouched. So, this is a mild acidic may be one normal HCL or ammonium chloride also low alcohol methanol and this you can see there is a chiral centre quaternary chiral centre here and this is the cyano group with DIBAL-H minus 78 degree centigrade selectively the cyanide goes to aldehyde and you have to do workup with 5 percent H2SO4 and the furan motif is untouched 56 percent yield you can get this was published also in JACS. Reduction of weinreb amides is also possible so this is alpha beta unsaturated Weinreb amide. And when it was treated with DIBAL toluene this is the toluene solution of DIBAL in dichloromethane solvent minus 78 degree centigrade you get the 82 percent yield of this alpha beta unsaturated aldehyde. This was published in Angewandte.

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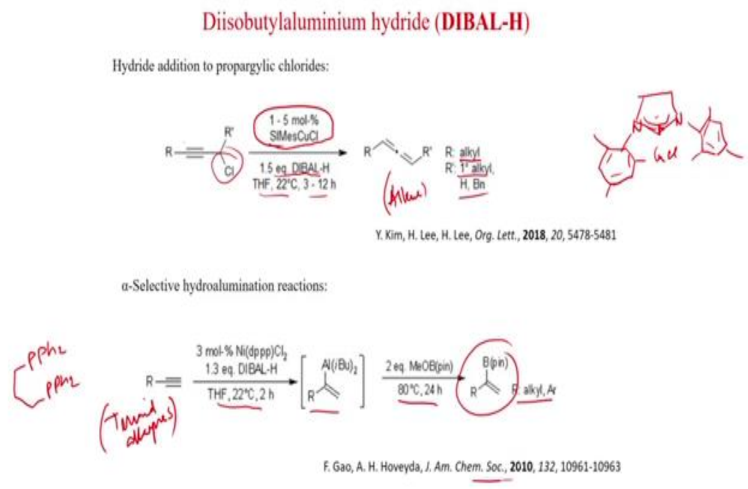

Diisobutylaluminium hydride (**DIBAL-H**)

Hydride addition to propargylic chlorides:

Y. Kim, H. Lee, H. Lee, *Org. Lett.*, **2018**, *20*, 5478-5481

α-Selective hydroalumination reactions:

F. Gao, A. H. Hoveyda, *J. Am. Chem. Soc.*, **2010**, *132*, 10961-10963

Hydride addition to propargalic chlorides is also possible and this is the regioselective additions which want to 5 mole percent of the n-heterocyclic complex. So this is the imidazole system, so imidazolidium n-heterocyclic carbon which want to 5 mole percent and then 1.5 equivalent of DIBAL-H THF 22 degree centigrade in three to four hours you get this allene. So what happens the DIBAL that hydride delivery takes place from here and followed by elimination of this chlorine you get this allene.

So R is equal to alkyl one and that can be 1 degree alkyl hydrogen benzyl group etc. This was published in Organic letters. Also alpha selective hydroalumination reaction is possible like this terminal alkynes terminal alkynes with 3 mole percent nickel dppp Cl2. So dppp is diphenyl phosphinopropane with 1.3 equivalent DIBAL-H THF 22 degree centigrade 2 hours stirring you get his intermediate and if you treat this with pinacol boronate and 80 degree centigrade 24 hours you get this double bond theres aluminium is replaced by pinacol boronate and this reaction R is equal to alkyl aryl group. This was published in JACS.

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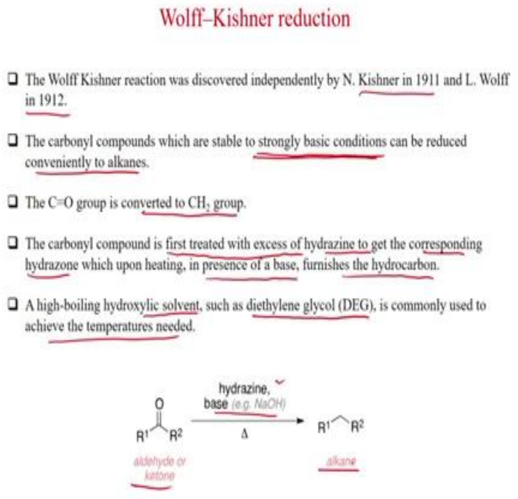

Wolff–Kishner reduction

- ☐ The Wolff Kishner reaction was discovered independently by N. Kishner in 1911 and L. Wolff in 1912.
- ☐ The carbonyl compounds which are stable to strongly basic conditions can be reduced conveniently to alkanes.
- ☐ The C=O group is converted to CH_2 group.
- ☐ The carbonyl compound is first treated with excess of hydrazine to get the corresponding hydrazone which upon heating, in presence of a base, furnishes the hydrocarbon.
- ☐ A high-boiling hydroxylic solvent, such as diethylene glycol (DEG), is commonly used to achieve the temperatures needed.

Now we will discuss Wolff-Kishner reduction, so Wolff-Kishner reaction as discovered independently by N. Kishner in 1911 and L. Wolff in 1912. The carbonyl compound which are stable to strongly basic conditions can be reduced conveniently to alkanes. So this is very important strongly basic condition is required for Wolff-Kishner reduction. The CO group is converted to CH2 group. The carbonyl compound is first treated with excess of hydrazine to get the corresponding hydrazone which upon heating, in presence of a base, furnishes the hydrocarbons. So hydrazone has to be form and then the base will furnace the hydrocarbon. A high boiling hydroxylic solvent, such as diethylene glycol DEG, is commonly used to achieve the temperatures needed. So this is the aldehyde and ketone and with hydrazine base as for example sodium hydroxide you get the alkane.

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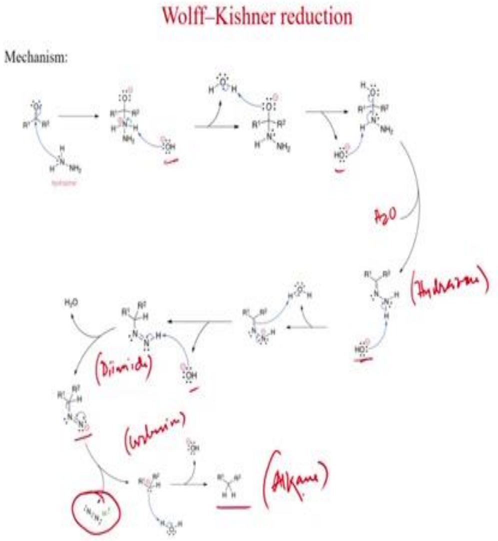

What is the mechanism? First the aldehyde and ketone can be reacted with hydrazine to generate this aminal then this OH minus will take up this proton to generate the water and after that again this OH minus with abstract this proton from the NH and now elimination of water will generate this one hydrazone so this is hydrazone. And now this hydrazone again will be reacted with the base.

So base you need many times actually here here many times you need the base and then again this NH will be abstracted by the base to get the water and now a negative charge is formed on the nitrogen. And now this intermediate is formed diimide. After that diimide hydrogen also be accepted by OH minus and to generate this negative charge on nitrogen. And now a nitrogen gas will be eliminated to generate this carbon ion so this is carbon ion. And this carbon ion will be protonated by the solvent to get this alkane. So there are quite steps are there in this mechanism.

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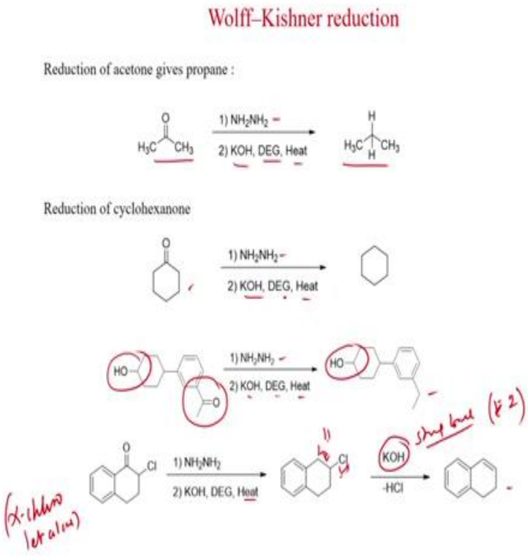

Wolff–Kishner reduction

Reduction of acetone gives propane :

Reduction of cyclohexanone

Reduction of acetone gives propane so if you treat acetone with hydrazine KOH diethyl glycol heat you get the propane. Similarly cyclohexanone with hydrazine KOH diethyl glycol heat you get the cyclohexane and if you have a hydroxyl group is present and this is the ketone motif here with hydrazine KOH diethylene glycol heat you get the alkane here and the hydroxylic group is untouched in this reaction. Also if it is alpha chloro tetralone so this is alpha chloro tetralone is treated with hydrazine KOH diethyl glycol heat you get this compound tetrahydro naphthalene chloro. And since KOH is a strong base, so the elimination will happen. So E2 elimination is possible. And to get this unsaturated compound, so this elimination happens here.

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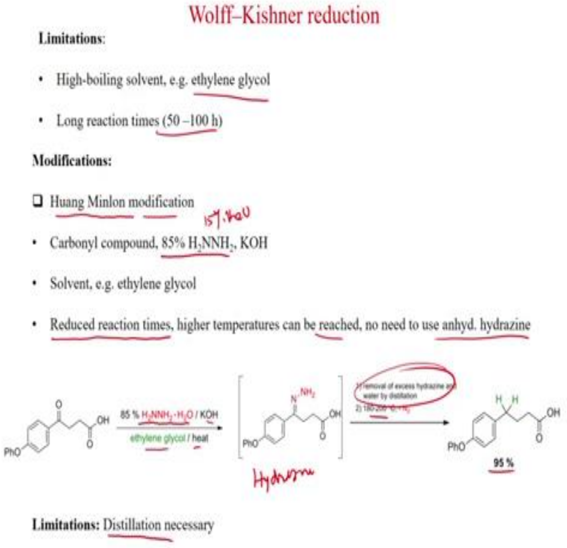

Wolff–Kishner reduction

Limitations:

- High-boiling solvent, e.g. ethylene glycol
- Long reaction times (50 –100 h)

Modifications:

☐ Huang Minlon modification

- Carbonyl compound, 85% H_2NNH_2, KOH
- Solvent, e.g. ethylene glycol
- Reduced reaction times, higher temperatures can be reached, no need to use anhyd. hydrazine

Limitations: Distillation necessary

What are the limitation of Wolff-Kishner reduction high boiling solvent such as ethylene glycol long reaction times 50 to 100 hours. That is why several modification of Wolff-Kishner reduction has been reported first was reported by Huang Minlon which is called Huang Minlon modification. Here he used 85 percent NH NH2 water so remaining 15 percent is water and KOH as the base. Solvent is ethylene glycol. Here the reduced reaction time is important, higher temperatures can be reached no need to use anhydrous hydrazine.

Suppose if you have a keto-carboxylic acid here and if you treat with 80 percent, 85 percent hydrazine Hydrate with KOH base ethylene glycol heat you get this intermediate hydrazone. And now this hydrazone can be removed, removal of excess hydrazine and Water by distillation at 180 to 200 degree Centigrade will generate this alkane. So one limitation of this is the distillation is required. So this is the excess hydrazine and water you have to remove by distillation that is a drawback. However, the advantage is reduced reaction times.

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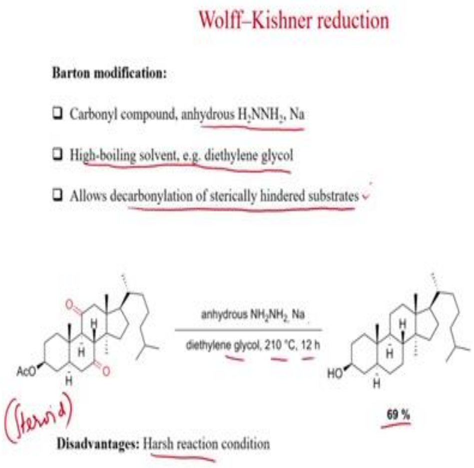

Wolff–Kishner reduction

Barton modification:

- ☐ Carbonyl compound, anhydrous H_2NNH_2, Na
- ☐ High-boiling solvent, e.g. diethylene glycol
- ☐ Allows decarbonylation of sterically hindered substrates ✓

Disadvantages: Harsh reaction condition

Barton modification, carbonyl compound here then anhydrous hydrazine sodium has to be used. High boiling solvent such as diethylene glycol allows decarbonylation of sterically hindered substrates. So this is a very important sterically hindered substrates it can be useful like this steroid system. Steroid system when treated with anhydrous NH2 hydrazine and sodium diethylene glycol 200 degree centigrade, 12 hours you get both ketone reduced here and you get this product 69 percent yield. So what disadvantage of this Harsh reaction condition. But useful is the sterically hindered substrates.

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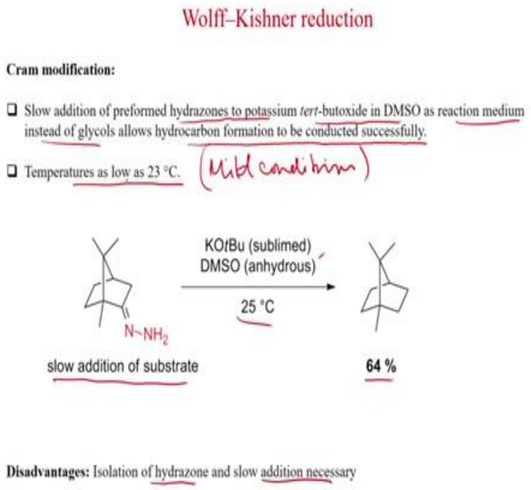

Wolff–Kishner reduction

Cram modification:

- ☐ Slow addition of preformed hydrazones to potassium *tert*-butoxide in DMSO as reaction medium instead of glycols allows hydrocarbon formation to be conducted successfully.
- ☐ Temperatures as low as 23 °C. (Mild condition)

Disadvantages: Isolation of hydrazone and slow addition necessary

Cram modification, here he developed this strategy slow addition of preformed hydrozones to potassium tetra-butoxide in DMSO as reaction medium instead of glycols allows hydrocarbon formation to be conducted successfully. And temperatures as low as 23 degree centigrade so this is very mild, mild conditions. Suppose this one this hydrazone is the substrate and it can be added slowly to potassium tertiary butoxide in DMSO. And in 25 degree Centigrade, you get 64 percent yield of this bridge compound. Isolation of hydrazone and slow addition is necessary this is a disadvantage, but advantage is that temperature can be very low 23 degree centigrade.

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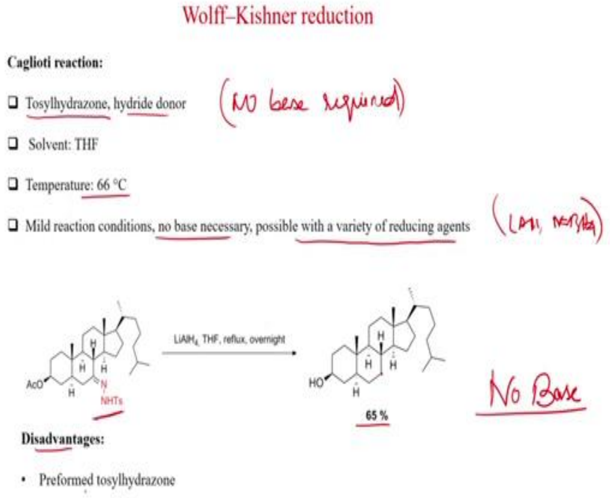

Wolff–Kishner reduction

Caglioti reaction:

- ☐ Tosylhydrazone, hydride donor (No base required)
- ☐ Solvent: THF
- ☐ Temperature: 66 °C
- ☐ Mild reaction conditions, no base necessary, possible with a variety of reducing agents (LAH, NaBH$_4$)

Disadvantages:

- Preformed tosylhydrazone

Then Caglioto developed and he developed the tosylhydrazone instead of hydrazine he used tosylhydrazine so that tosylhydrazone will be intermediate and hydride donor is required. So here no base is required. This is very important, no base is require only hydride donor temperature can be 66 degrees centigrade. Mild reaction condition, no base necessary, possible with a variety of reducing agents like LAH, Sodium borohydride can be used. For an example this kind of structure with tosylhydrazone with lithium aluminium hydride THF reflux overnight to get this product. So this become reduced here and you get 65% yield. So this is very important no base. That means a base sensitive group is present that can be reduced under this condition. However, one disadvantage is there preformed tosylhydrazone is required.

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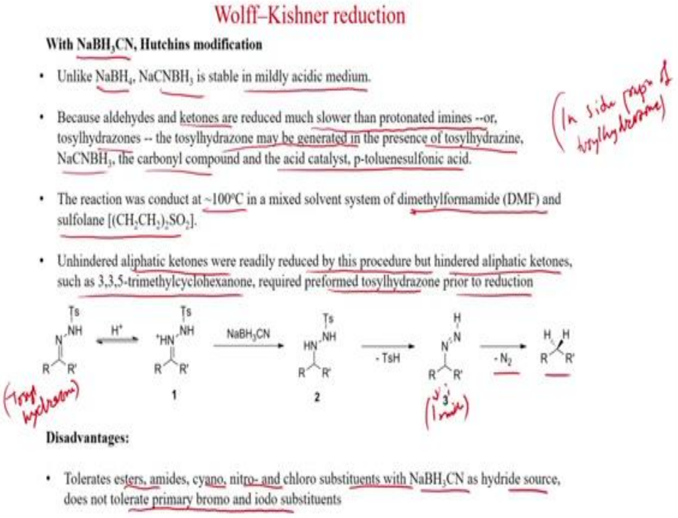

Wolff–Kishner reduction

With $NaBH_3CN$, Hutchins modification

- Unlike $NaBH_4$, $NaCNBH_3$ is stable in mildly acidic medium.
- Because aldehydes and ketones are reduced much slower than protonated imines --or, tosylhydrazones -- the tosylhydrazone may be generated in the presence of tosylhydrazine, $NaCNBH_3$, the carbonyl compound and the acid catalyst, p-toluenesulfonic acid.
- The reaction was conduct at ~100°C in a mixed solvent system of dimethylformamide (DMF) and sulfolane $[(CH_2CH_2)_2SO_2]$.
- Unhindered aliphatic ketones were readily reduced by this procedure but hindered aliphatic ketones, such as 3,3,5-trimethylcyclohexanone, required preformed tosylhydrazone prior to reduction

(In situ prepn of tosylhydrazone)

Disadvantages:

- Tolerates esters, amides, cyano, nitro- and chloro substituents with $NaBH_3CN$ as hydride source, does not tolerate primary bromo and iodo substituents

And then Hutchins modified this strategy using sodium cyanoborohydride as the reducing agent. Unlike sodiumborohydride sodium cyanoborohydride is stable and mildly acidic medium. And because aldehydes and ketones are reduced much slower than protonated imines or tosylhydrazones the tosylhydrazone may be generated in presence of tosylhydrazine, sodium cyanoborohydride, the carbonyl compound and the acid catalyst. So this means in situ preparation of tosylhydrazone.

So that is a contribution by Hutchin. The reaction was conducted at 100 degree centigrade in mix solvent system of dimethylformamide and sulfolane. Unhindered aliphatic ketones are successfully reduced by this procedure but hindered aliphatic ketone, such as 3, 3, 5 trimethylcyclohexanone, required preformed tosylhydrazone prior to reduction. So unhindered aliphatic ketones that can be in situ the tosylhydrazone can be generated but for hindered one you have to preformed tosylhydrazone should be used.

So this is the mechanism that mild acidic condition this can be protonated the tosylhydrazone then sodium cyanoborohydride reduces and now the sulphinate will eliminated to get this imide this is imide and diimide, and now the nitrogen will eliminate to generate this alkane. Disadvantage, it tolerates ester, amides, cyano, nitro and chloro substituents with sodium cyno boride as hydride source, however, does not tolerate primary bromo and iodo substituents. So primary bromo and iodo can not be used under this reaction condition.

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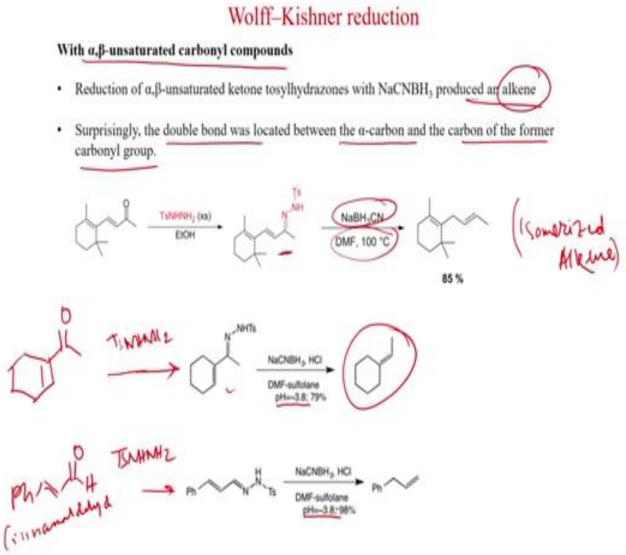

Wolff–Kishner reduction

With α,β-unsaturated carbonyl compounds

- Reduction of α,β-unsaturated ketone tosylhydrazones with $NaCNBH_3$ produced an alkene
- Surprisingly, the double bond was located between the α-carbon and the carbon of the former carbonyl group.

With alpha beta unsaturated carbonyl compound this reduction also can be carried out and here instead of alkane it generate produced an alkene. Surprisingly, the double bond was located between the alpha carbon and carbon of the former carbonyl group. Suppose this substrate when treated with tosylhydrazone ethanol this hydrazone is form and now… so there is a double bond now with sodium cyano borohydride the DMF 100 degree centigrade you get the reduced and also the double bond is isomerized.

So isomerized alkene is formed. So this is very important this also we have discussed earlier suppose this hydrazone which can be generated from one acetyl cyclohexene this hydrazone with treated with sodium cyano borohydride HCL and DMF sulfolane and pH will be 3.8 you get 79 percent yield of this alkene. Also cinnamaldehyde derived hydrazone, so this is cinnamaldehyde, its reaction with tosylhydrazine generate the hydrazone. When treated with sodium cyano borohydride HCL DMF sulfolane pH 3.8 you get this alkene in 98 percent yield.

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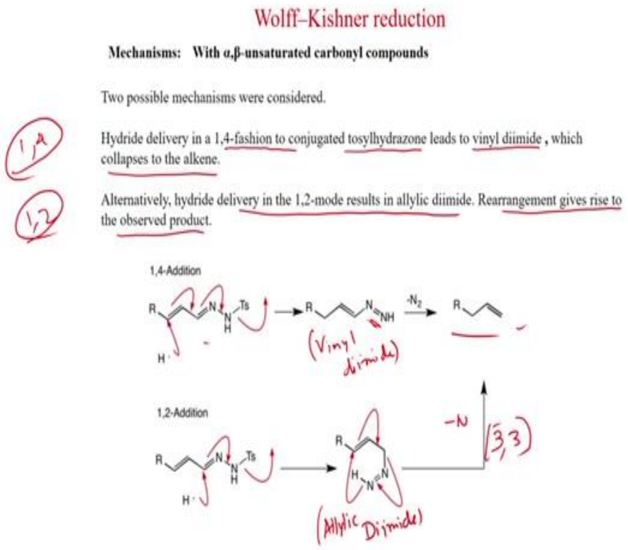

Wolff–Kishner reduction

Mechanisms: With α,β-unsaturated carbonyl compounds

Two possible mechanisms were considered.

Hydride delivery in a 1,4-fashion to conjugated tosylhydrazone leads to vinyl diimide , which collapses to the alkene.

Alternatively, hydride delivery in the 1,2-mode results in allylic diimide. Rearrangement gives rise to the observed product.

So mechanism there are two possible mechanism are considered. First one is hydride delivery in a 1, 4- fashion to conjugated tosylhydrazone leads to vinyl diimide, which collapses to the alkene. So 1, 4 addition like this way so if in 1, 4 case this hydrazone is formed and then the hydrides 1, 4 fashion and this hydride will adds here then the double bond become here and this the imide form so this is vinyl imide, vinyl diimide and after nitrogen elimination you get the alkene. Alternatively, hydride delivery in the 1, 2 mode results in allylic diimide. So 1, 2 possible also and rearrangement gives rise to the observed product. So in 1, 2 cases so this cases the hydride attached to this imide nitrogen here you can see this and after that the… so this is allylic diimide so here vinyl diimide here allylic diimide and then 3, 3 sigmatropic rearrangement will take place to generate after nitrogen elimination you generate this alkene.

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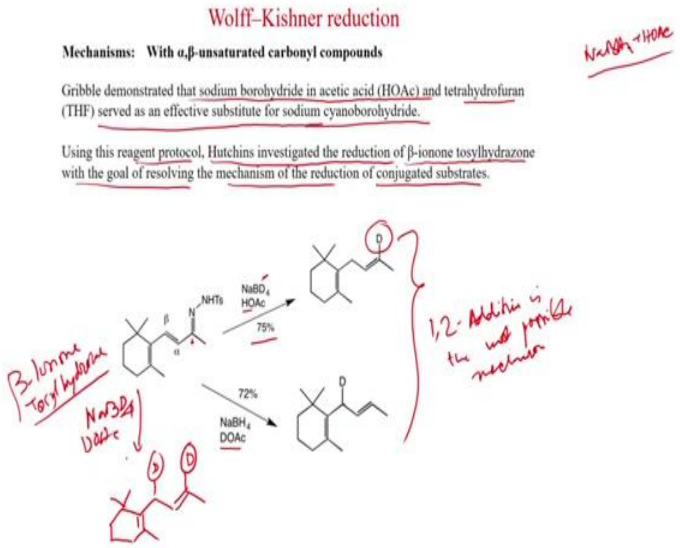

Wolff–Kishner reduction

Mechanisms: With α,β-unsaturated carbonyl compounds

Gribble demonstrated that sodium borohydride in acetic acid (HOAc) and tetrahydrofuran (THF) served as an effective substitute for sodium cyanoborohydride.

Using this reagent protocol, Hutchins investigated the reduction of β-ionone tosylhydrazone with the goal of resolving the mechanism of the reduction of conjugated substrates.

So to verify that weather 1, 2 or 1, 4 so they started some deuterium started. So Gribble demonstrated that sodium borohydride in acetic acid and tetrahydrofuran served as an effective substituent for sodium borohydride, so sodium borohydride and acetic acid is a good substitute for sodium cyano borohydride. Using this reagent protocol, Huchins investigated the reduction of beta ionone toslhydrazone with the goal of resolving the mechanism of the reduction of the conjugated substrates.

So this was the beta ionone, beta ionone tosylhydrazone and when this was treated with the sodium BD4 in acetic acid you get the 75 percent yield of this. So deuterium is here where the hydrazone that carbon there the deuterium is there and double bond of course has migrated. Alternatively when sodium borohydride and DOAc is used. Then the deuterium is here the allylic position at this tails the 1, 2 addition is the possible mechanism so 1, 2 is the most possible mechanism. Also if you treat this substrate with NABD4 and DOAc then both deuterium will be incorporated. So here both deuterium will come so this tells that 1, 2 addition is the most possible.

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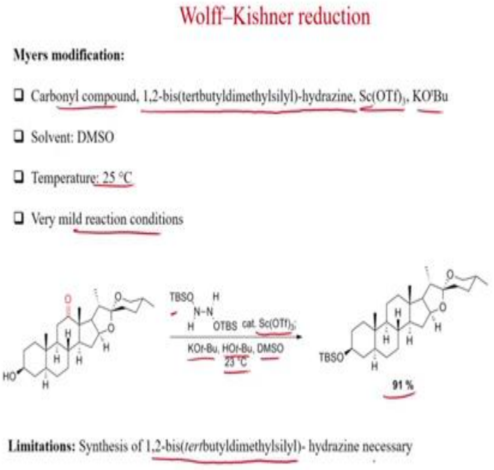

Wolff–Kishner reduction

Myers modification:

- ☐ Carbonyl compound, 1,2-bis(tertbutyldimethylsilyl)-hydrazine, $Sc(OTf)_3$, KO^tBu
- ☐ Solvent: DMSO
- ☐ Temperature: 25 °C
- ☐ Very mild reaction conditions

Limitations: Synthesis of 1,2-bis(*tert*butyldimethylsilyl)- hydrazine necessary

Myers modification here carbonyl compound is used and 1, 2 bis tertbutyldimethylsilyl - hydrazine, scandium triflate Lewis acid and potassium tertiary butoxide base. Solvent is DMSO, temperature is mild condition 25 degree centigrade so this is very mild reaction conditions. And this complex substrate when treated with this hydrazine tosyl derivative with catalytic scandium triflate, potassium butoxide, tert butanol DMSO 23 degree centigrade you get this reduction and product is formed 91 percent yield. Limitations, synthesis of 1, 2 bis tertbutyldimethylsilyl - hydrazine is necessary.

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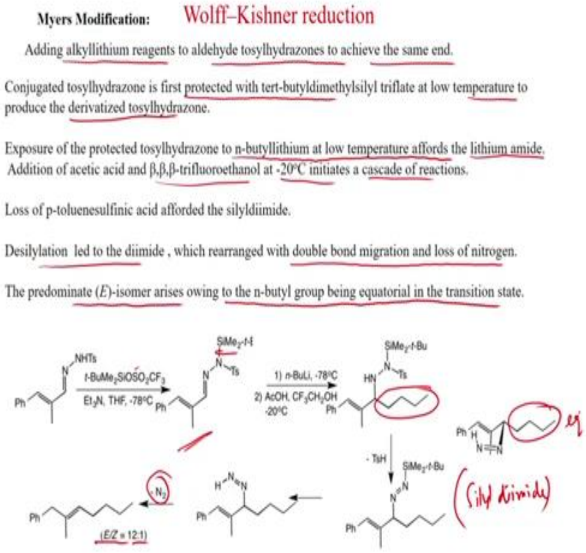

Myers Modification: Wolff–Kishner reduction

Adding alkyllithium reagents to aldehyde tosylhydrazones to achieve the same end.

Conjugated tosylhydrazone is first protected with tert-butyldimethylsilyl triflate at low temperature to produce the derivatized tosylhydrazone.

Exposure of the protected tosylhydrazone to n-butyllithium at low temperature affords the lithium amide. Addition of acetic acid and β,β,β-trifluoroethanol at -20°C initiates a cascade of reactions.

Loss of p-toluenesulfinic acid afforded the silyldiimide.

Desilylation led to the diimide , which rearranged with double bond migration and loss of nitrogen.

The predominate (*E*)-isomer arises owing to the n-butyl group being equatorial in the transition state.

So Myers also did this modification that adding alkyllithium reagents to aldehyde tosylhydrazone to achieve the same end. Here conjugated tosylhydrazone is first protected with tert-butyldimethylsilyl triflate at low temperature to produce the derivatized tosylhydrazone, so this compound is formed. So hydrazone is treated with this triflate triethylamine you get this silyl group here.

Now exposure of the protected tosylhydrazone to n-butyllithium at low temperature affords the lithium amide. So lithium amide is formed here you can see this butyl group has added to the hydrazone here and acetic acid this is a solvent trifluoroethanol at minus 20 degree centigrade initiates a cascade of reactions. So loss of para-toluenesulfonic acid afforded the silyldiimide. So this is the silyldiimide. So elimination of this group and desilylation lead to the diimide, which rearranged with double bond migration and loss of nitrogen.

So now silyl group is eliminated you get this diimide and after loss of nitrogen and double bond migration here you get this compound with E/Z 12 is to 1 selectivity. The predominated E isomer arises owing the n-butyl group being equatorial in the transition state. So this is the transition state n-butyl group in the equatorial position. So you get E isomer as the major.

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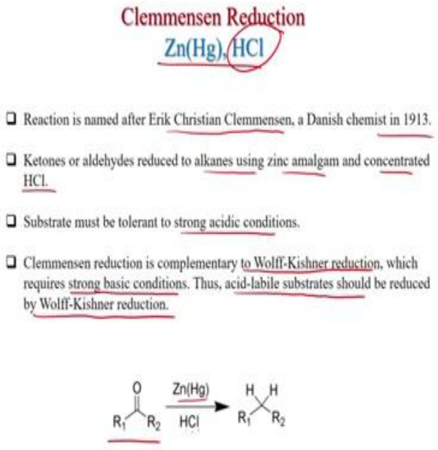

Clemmensen Reduction

Zn(Hg), HCl

❑ Reaction is named after Erik Christian Clemmensen, a Danish chemist in 1913.

❑ Ketones or aldehydes reduced to alkanes using zinc amalgam and concentrated HCl.

❑ Substrate must be tolerant to strong acidic conditions.

❑ Clemmensen reduction is complementary to Wolff-Kishner reduction, which requires strong basic conditions. Thus, acid-labile substrates should be reduced by Wolff-Kishner reduction.

Now we will discuss Clemmensen reduction. So in Clemmensen reduction zinc amalgam HCl is used. Reaction is named after every Christian Clemmensen a Danish chemist in 1913. Ketones or aldehyde reduced to alkanes using zinc amalgam and concentrated HCl. Substrate must be tolerant to strong acidic conditions. Clemmensen reduction is complementary to Wolff-Kishner reduction, which requires strong basic conditions. Thus, the acid labile substrates should be reduced by Wolff-Kishner reduction. So here it is complimentary here acid is used and a Wolff-Kishner base is used. So this is the overall reaction a ketone and aldehyde with treatment zinc amalgam HCl you get the alkane.

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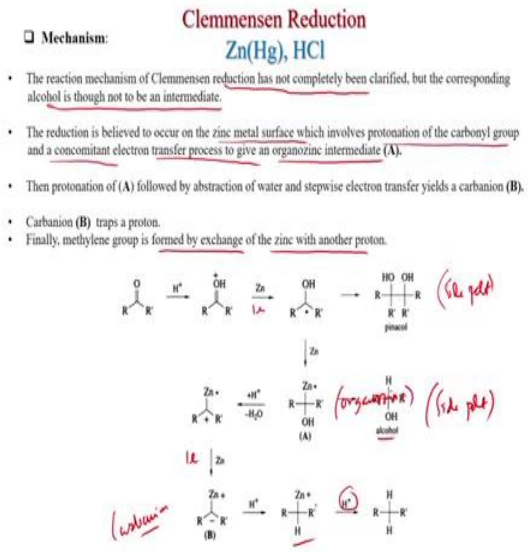

Clemmensen Reduction

Zn(Hg), HCl

❑ **Mechanism**:

- The reaction mechanism of Clemmensen reduction has not completely been clarified, but the corresponding alcohol is though not to be an intermediate.
- The reduction is believed to occur on the zinc metal surface which involves protonation of the carbonyl group and a concomitant electron transfer process to give an organozinc intermediate **(A)**.
- Then protonation of **(A)** followed by abstraction of water and stepwise electron transfer yields a carbanion **(B)**.
- Carbanion **(B)** traps a proton.
- Finally, methylene group is formed by exchange of the zinc with another proton.

Mechanism the reaction mechanism of Clemmensen reduction has not completely been clarified, but the corresponding alcohol is though not to be an intermediate. So this is an important thing that the alcohol is not intermediate the reaction is believed to occur by the zinc metal surface which involves protonation of the carbonyl group and the concomitant electron transfer process to give an organozinc intermediate A. So first the protonation and then the zinc comes so zinc gives one electron and this radical is form so the radical can give the pinacol this is a side product.

Alternatively this radical react with zinc to generate this organozinc intermediate so this is organozinc. And now is can goes to the alcohol, alcohol is also a side product if it forms actually and now the protonation of A followed by abstraction of water and stepwise electron transfer yields a carbonion B. So this organozinc compound is treated with acid then water will eliminate you get this carbocation here, and this carbocation after treated with zinc here also one electron is coming then the carbanion is form so this is a carbanion. And carbon ion traps a proton to generate this organozinc. Finally, methylene group is form by exchange of the zinc with another proton. So this organozinc become alkane by reaction with acidic proton.

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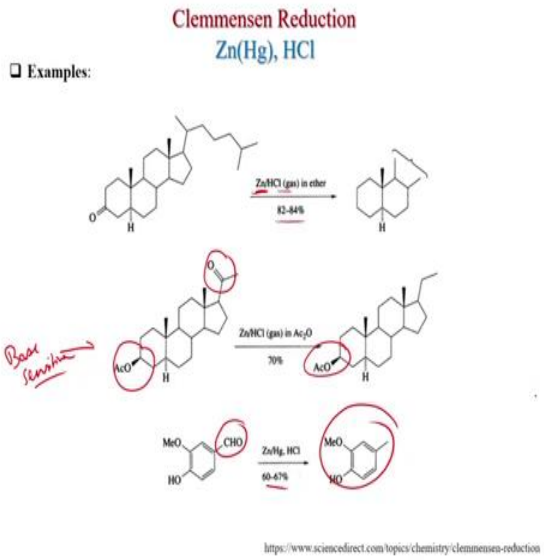
Clemmensen Reduction
Zn(Hg), HCl
❑ Examples:

https://www.sciencedirect.com/topics/chemistry/clemmensen-reduction

Examples this kind of steroid system can be used also here zinc metal itself can do this with HCl gas in ether 80 to84 percent yield you get this product. Also if you have an acetate group under this condition acetate group we know this is a base sensitive so with acetic condition this group is untouched and you get only reduction of this ketone to generate the alkane. Similarly if you have a benzaldehyde derivative with zinc amalgam HCl you get this toluene derivatives in 60-67 percent yield.

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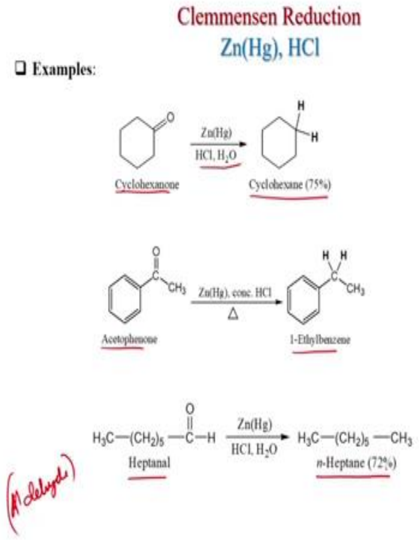
Clemmensen Reduction
Zn(Hg), HCl
❑ Examples:

More examples like cyclohexanone, if it is treated with zinc amalgam HCl water you get the cyclohexane 75 percent yield. Also acetophenone with zinc amalgam concentrated HCl you get 1-ethyl benzene in good yield. And aldehydes like long chain aldehyde heptanal with zinc amalgam HCl whether it gives n-heptane 72 percent yield. So ketone as well as aldehyde can be used.

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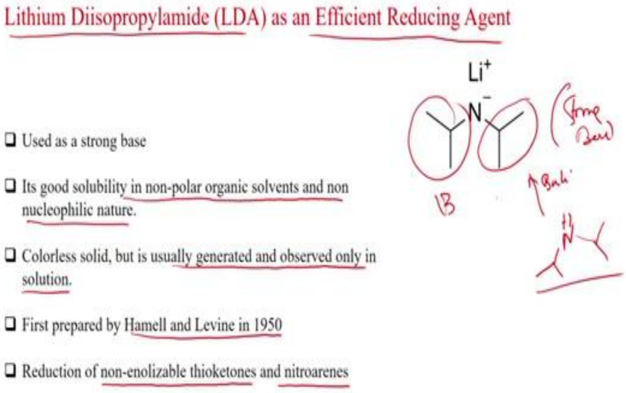

Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent

- Used as a strong base
- Its good solubility in non-polar organic solvents and non nucleophilic nature.
- Colorless solid, but is usually generated and observed only in solution.
- First prepared by Hamell and Levine in 1950
- Reduction of non-enolizable thioketones and nitroarenes

Now we will discuss Lithium Diisopropylamide as an Effective Reducing Agent. So this is the diisopropyl group so isopropyl here so this is secondary amine. And now the secondary amine one hydrogen is replaced by lithium this is a strong base. This can be formed if you treat with butyl lithium with this diisopropyl amine you get this aldehyde. This used as a strong base its good solubility in non-polar organic solvents and non-nucleophilic nature. So this is also important this is bulky so does not act as a nucleophile. Colorless solid but is usually generated and observed only in solution. First prepared by Hamell and Levine in 1950. And reduction of non enolizable thioketones and nitroarenes. So it’s main reaction as reducing agent with non enolizable thioketone and nitroarenes.

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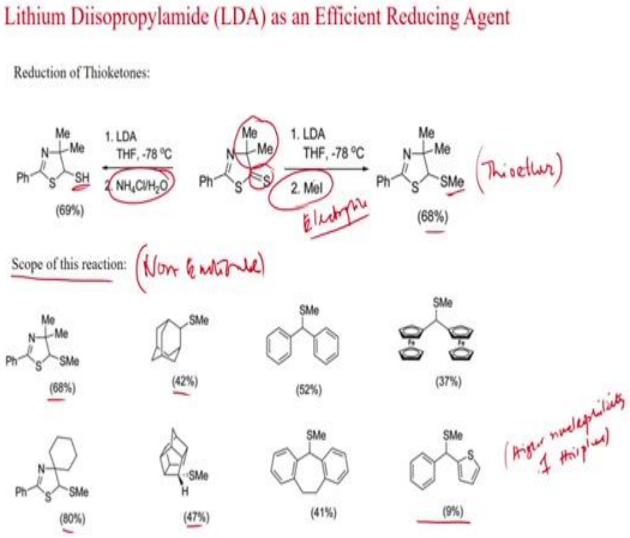

Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent

Reduction of Thioketones:

Scope of this reaction:

So reduction of thioketones like if you have a non enolizable here this is a quaternary centre and with LDA THF followed by iodomethane, so iodomethane is electrophile. And this double bond is getting reduced to single bond followed by reaction with iodomethane give this thioether in 68 percent yield. Alternatively, if you treat with ammonium chloride water then you get the thiol here. So methyl group coming from this iodomethane. Scope of this reaction.

So different non enolizable like this compound is form 68 percent yield this is adamantane system here also quaternary quaternary system and here you get 42 percent yield, this system 52 percent yield, this one ferrocene system 37 percent yield, this one instead of dimethyl cyclohexyl group is here the yield got enhanced to 80 percent yield. Here this is a chiral you get 47 percent yield, this system you get 41 percent yield. And this one when the thiophene group is there the yield is less so this might be this might be higher nucleophilicity of thiophene. So that means there is a thioketone is becoming conjugated with the thiophene system. That is why it’s not getting reacted well in this condition.

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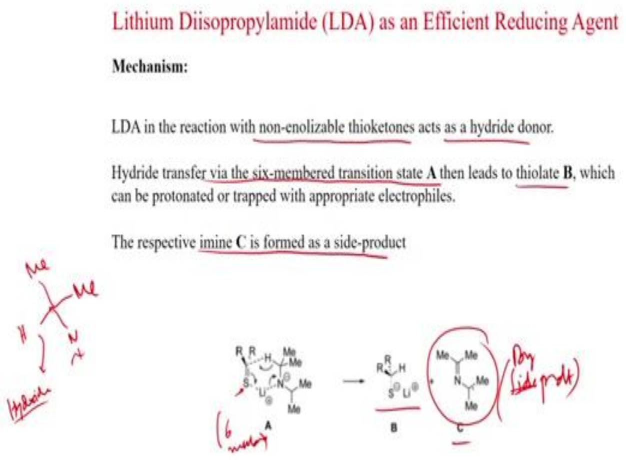

Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent

Mechanism:

LDA in the reaction with non-enolizable thioketones acts as a hydride donor.

Hydride transfer via the six-membered transition state **A** then leads to thiolate **B**, which can be protonated or trapped with appropriate electrophiles.

The respective imine **C** is formed as a side-product

So what is the mechanism, LDA in the reaction with non enolizable thioketones acts as a hydride donor? Hydride transfer via six membered transition state A. So this is the 6 member transition state A and here you can see that the lithium it binds with the sulphur and this is the hydride because isopropyl group like earlier also isopropanol and isopropyl group there is a hydrogen, hydrogen is there and this hydrogen is acting as a hydride. So from one of the isopropyl group hydride is delivered to this double bond and now lithium coordinates so this is a six membered and here a double bond is formed so leads to thiolate B, thiolate B is formed and this imine is form the respected imine C is formed as a side product, so this is a side product. Side product or better is a by-product actually because it is forming from the reaction so this byproduct this imine. So the hydride is delivered to this double bond and you get the thiol and you get the imine.

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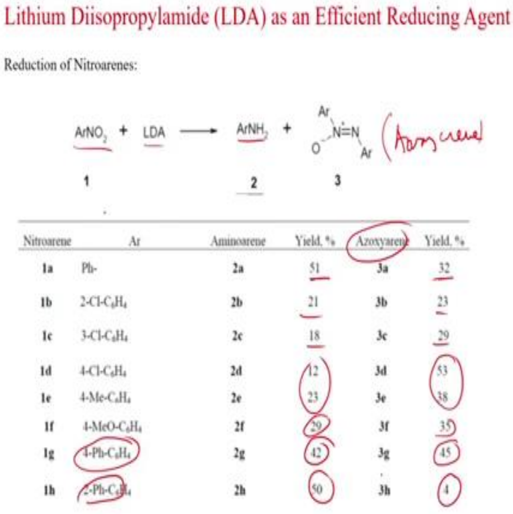

Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent

Reduction of Nitroarenes:

$ArNO_2$ + LDA ⟶ $ArNH_2$ + 3

1, 2, 3

Nitroarene	Ar	Aminoarene	Yield, %	Azoxyarene	Yield, %
1a	Ph-	2a	51	3a	32
1b	2-Cl-C_6H_4	2b	21	3b	23
1c	3-Cl-C_6H_4	2c	18	3c	29
1d	4-Cl-C_6H_4	2d	12	3d	53
1e	4-Me-C_6H_4	2e	23	3e	38
1f	4-MeO-C_6H_4	2f	29	3f	35
1g	4-Ph-C_6H_4	2g	42	3g	45
1h	2-Ph-C_6H_4	2h	50	3h	4

Reduction of nitroarenes also is possible like ARNO2, different nitroarenes with LDA the aniline derivative and azoxyarene so this is azoxyarene is also formed. Suppose when nitrobenzene is treated with LDA to get aminoarene 51 percent yield 32 percent yield of azoxyarene. Two chloro it gives similar yield of both compounds. Three chloro here also little bit higher azoxyarene. Four chloro four methyl you get higher yield of azoxyarene. And this compound is called little low arene. Four methoxy you get almost similar yield and when four phenyl is there that is the biphenyl system you get 42 percent yield of aniline and 45 percent yield of this azoxyarene. So yield got enhanced. And two phenyl cases you get 50 percent yield of this aniline and 4 percent only of the azoxyarene.

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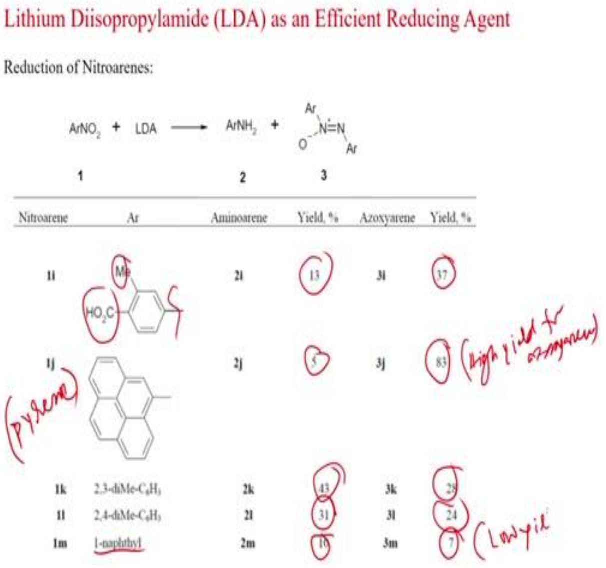

Lithium Diisopropylamide (LDA) as an Efficient Reducing Agent

Reduction of Nitroarenes:

$ArNO_2$ + LDA ⟶ $ArNH_2$ + 3

1, 2, 3

Nitroarene	Ar	Aminoarene	Yield, %	Azoxyarene	Yield, %
1i		2i	13	3i	37
1j		2j	5	3j	83
1k	$2,3\text{-diMe-C}_6H_3$	2k	43	3k	28
1l	$2,4\text{-diMe-C}_6H_3$	2l	31	3l	24
1m	1-naphthyl	2m	10	3m	7

Reduction of nitroarenes there are more examples, here you can see if the nitroarenes so here the nitro group is attached. If this nitroarenes contain a carbocylic acid and methyl derivative this gives aniline compound with 13 percent yield on the other hand azoxyarene is found 37 percent yield and this is pyrene system. So pyrene system gives interestingly only 5 percent yield of the amino derivative on the other hand azoxyarene is formed 83 percent yield so high yield for azoxyarene. Then 2, 3 dimethyl phenyl system give almost similar amount 43 percent of aniline and 28 percent of azoxyarene. Also 2, 4 dimethyl similar yields 31, 24 percent yield.

Interestingly, one naphthyl system does not react so when in this condition with LDA only 10 percent yield of the aminoarene and 7 percent yield of the azoxyarene is form so very low yield. Of esters to aldehyde also nitriles to aldehyde and alpha beta unsaturated esters can be convert in to the allylic alcohols also alpha beta unsaturated aldehydes converted into allylic alcohol. So this reactions cannot be possible with lithium aluminium hydride because the mechanistic difference between lithium aluminium hydride and DIBAL. DIBAL-H is a neutral compound and it is an electrophilic reagent and also a Lewis acid. So the aluminium should bind with a Lewis base then only the hydride delivery will take place. Then we have discussed Wolff-Kishner reduction.

This is reduction of ketone to alkane with hydrazine and strong base like KOH is used also a high temperature and different groups can be used for this reduction. However, the drawbacks are the high reaction temperature and strong bases so different modification has been developed first one was developed by Huang and who use the hydrazine 85 percent hydrazine hydrate and with this condition reaction time was reduced then then Barton developed another reaction condition with hydrazine and sodium here what happen here the sterically hindered substrate can also be used and then Cram came another strategic Cram used that hydrazone can be slowly added to potassium tertiary butoxide and DMSO solution and under this condition the reaction temperature can be lowered to room temperature like 23 degree centigrade and then another strategy was developed with tosylhydrazone and with tosylhydrazone the requirement of the strong bases was eliminated.

And in this case hydride source like lithium aluminium hydride, sodium borohydride was used. And then Huskin came up to use sodium cyanoborohydride because sodium cyanoborohydride is a mild reducing agent and also it can survives slightly acidic condition. So under this condition tosylhydrazone can be generated in situ from ketone and tosylhydrazine. Also alpha beta unsaturated ketones can be reduced with sodium cyanoborohydride and under this condition sodium cynoborohydride and tosylhydrazine under this condition the rearrangement of double bond was observed and most likely the mechanism follows 1, 2 addition.

Then we have discussed Clemmensen reduction and Clemmensen reduction its zinc amalgam and acidic condition is used like HCl also instead of zinc amalgam simple zinc can be used so this reaction is only useful when base sensitive group is present because acid level groups will react under this condition. And last we have discussed LDA as a reducing agent, so LDA is generally use as a base is a non-nucleophilic base so it can reduced selectively non enolizable thioketones as well as nitroarenes. So thioketone are selectively reduced so thoiethers or thiols if we treat with methyl iodide you get the methyl group in the thiol alternatively with ammonium chloride water you get the thiol also nitroarenes can be reduced to aniline derivate and azoxyarene. Thank you.