Essentials of Oxidation, Reduction and C-C Bond Formation Application in Organic Synthesis

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Lecture-25
Reductions with Red-Al, and Luche Reductions

Hello everyone, I would like to welcome you all for today's class. We will briefly look at what exactly we did it last time and then proceed further. What we looked at last time was the reductions of alkynes, nitriles with DIBAL-H and we saw that we can stereo selectively reduce alkynes to cis or trans alkenes. And we also can reduce the alkynes and convert them to corresponding alpha beta unsaturated acids which could be assist or trans depending on the conditions that we discussed.

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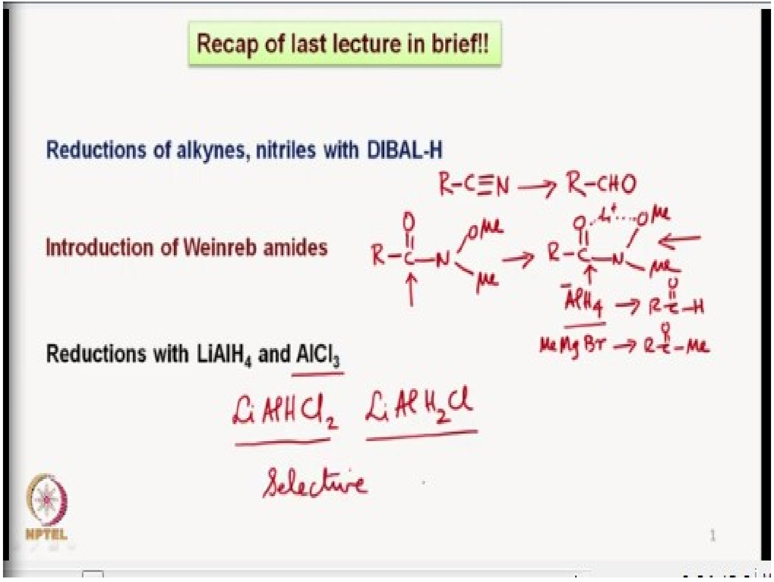

Recap of last lecture in brief!!

Reductions of alkynes, nitriles with DIBAL-H

Introduction of Weinreb amides

Reductions with $LiAlH_4$ and $AlCl_3$

We also looked at the conversion of nitriles to the aldehyde or ketone depending on what nitrile we take. I mean in the case of nitrile it will be of course aldehyde with the DIBAL, and how we could stop it from further reduction to the corresponding amine. Then we also looked at the Weinreb amides utility specially to stop the reaction at the aldehyde stage or a ketone stage where a nucleophile can be added to this.

And it can allow chelation as one of the parts by which we can have the stopping of the reaction at the aldehyde or ketone stage. For example if we have here Li+ then of course we can have the reduction of it leading to the aldehyde formation. Now the over reduction or over reaction of nucleophiles is stopped because of the chelation that is here. So, we discuss various types of nucleophiles that can be added to the Weinreb amides.

And in apart from the hydrogen addition like reducing agent we can also take say you have methyl magnesium bromide or any Grignard reagent that can be used. And the reaction can be stopped, say in this case up to the corresponding methyl ketone. Then towards the end we discussed the reductions with lithium aluminium hydride. We also discussed the reductions using lithium tri tertiary alkoxy hydride.

And lithium aluminium hydride in presence of aluminium chloride, where the use of aluminium chloride modifies the reducing agent to say for example you can have this or you can have this. And because of the electro negativity of the chlorine the reducing power of lithium aluminium hydride which is now modified to having 1 hydrogen, or 2 hydrogens, or 2 chlorines or 1 chlorine is reduced.

And accordingly the selective reductions can be carried out, what selective reductions can be carried out is something that we can look at it once again today is.

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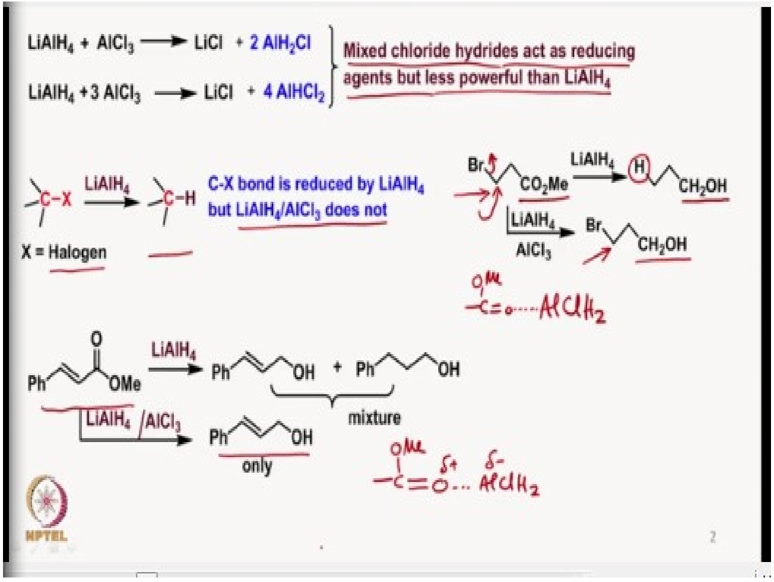

$LiAlH_4 + AlCl_3 \longrightarrow LiCl + 2\,AlH_2Cl$

$LiAlH_4 + 3\,AlCl_3 \longrightarrow LiCl + 4\,AlHCl_2$

Mixed chloride hydrides act as reducing agents but less powerful than $LiAlH_4$

C-X bond is reduced by $LiAlH_4$ but $LiAlH_4/AlCl_3$ does not

X = Halogen

We discuss this mixed chloride hydrides which act as reducing agents but less powerful than lithium aluminium hydride. We discussed that the C X bond, X is halogen can be reduced to the corresponding C H bond using this lithium aluminium hydride. But then the same reaction is not possible to be done using a combination of lithium aluminium hydride and aluminium chloride. On the other hand if we take another example of this type here. Say you have a bromide and an ester in the same molecule here.

If we do the lithium aluminium hydride base reduction then the lithium aluminium hydride reduces this carbon bromine bond, introduces this hydrogen here. And at the same time ester is reduced to the corresponding CH_2OH, but if we take lithium aluminium hydride in combination with aluminium chloride. Then this modified mixed chloride hydride reducing agent only reduces the ester and does not touch the carbon bromine bond.

So, there is a selectivity in terms of reducing power of this combination of lithium aluminium hydride and aluminium chloride. It is very clear that the mixed hydride chloride for example if it is something like this, then the chelation of the ester takes place more easily than the direct nucleophilic addition of the hydride to the carbon bond to reduce the carbon bromine bond and replace it by hydrogen.

Now it is also seen that we have an alpha beta unsaturated ester something like this. And if we reduce it with lithium aluminium hydride we get a mixture of allylic alcohol and the saturated alcohol. At the same time if we use the mixed chloride hydride reducing agent like lithium aluminium hydride, aluminium chloride, we only get this allylic alcohol as the major product.

So, it is very obvious that again here same thing is happening that only the chelation allows the reduction to take place. So, once this happens of course you have a delta positive here and a delta negative here then the hydride reduces this and goes further for the completion of ester to the corresponding primary alcohol.

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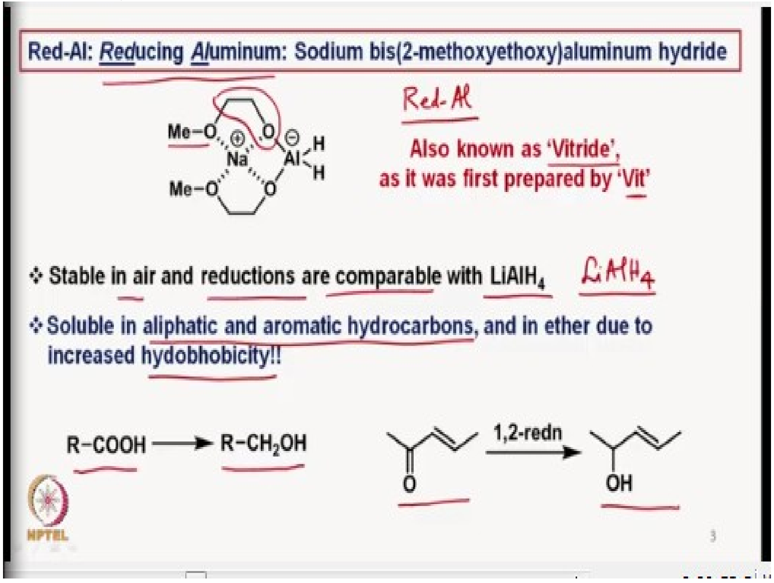

Red-Al: Reducing Aluminum: Sodium bis(2-methoxyethoxy)aluminum hydride

Red-Al

Also known as 'Vitride', as it was first prepared by 'Vit'

- Stable in air and reductions are comparable with $LiAlH_4$ $LiAlH_4$
- Soluble in aliphatic and aromatic hydrocarbons, and in ether due to increased hydobhobicity!!

$R-COOH \longrightarrow R-CH_2OH$

Now there is another reducing agent which is comparable with lithium aluminium hydride but is in some sense better than lithium aluminium hydride which is called as Red-Al, which is reducing aluminium basically. It is a sodium bis 2 methoxyethoxy aluminium hydride. So, this is the methoxy, this part is ethoxy, so and an aluminium hydride, so it exists as this 2 methoxyethoxy aluminium hydride which is known as Red-Al.

And also it is called as Vitride by the name of it is discoverer which is Vit. So, the Vitride or the Red-Al is more stable in air and reductions are comparable with lithium aluminium hydride. One of the problems with lithium aluminium hydride as I mentioned last time is, it is very unstable towards water and therefore not easy to handle but in comparison to that Red-Al is more stable in air.

And it is also soluble in aliphatic and aromatic hydrocarbons because of the increased hydrophobicity. That is not the case in lithium aluminium hydride, lithium aluminium hydride is somewhat more ionic and more polar than Red-Al, and therefore this needs to be dissolved in ether or THF whereas this is possible to dissolve in aliphatic and aromatic hydrocarbons.

Now this Red-Al allows reduction of the acids to the corresponding alcohol similar to the reductions with lithium aluminium hydride. And also allows in a similar way reduction of alpha beta unsaturated ketones to the corresponding allylic alcohols. And these Vitride can also be available as a solution in the market, and therefore one can easily take it and use it for reductions of various kinds. We will also see how further things can be done.

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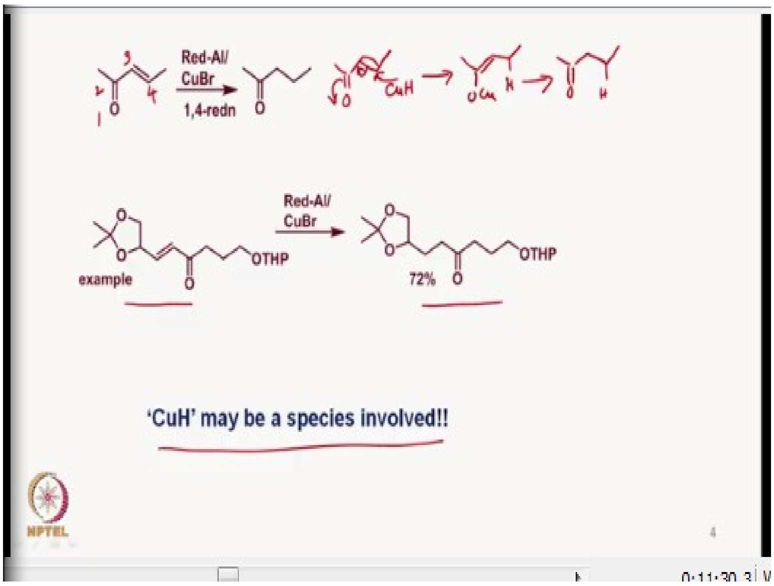

'CuH' may be a species involved!!

For example when the reduction of an alpha beta unsaturated ketone is carried out with Red-Al in the presence of copper 1, like cuprous bromide, this 1, 4 reduction takes place. Last time I told that this is 1, 2, 3 and 4, so 1, 4 reduction has taken place and essentially what is happening it is more or less like a copper hydride type of species, that is expected to be involved. And then copper hydride being softer adds on to this in this fashion and we have 1, 4 addition where we can expect a species like this to form and then this leads to the saturated ketone.

So, this is something similar to adding say dimethyl cuprate or such copper based reagents. So, in a similar fashion we can take a somewhat more difficult example and reduce it to the corresponding saturated ketone. So, there are many such examples in the literature where such a copper hydride type of species is believed to be involved in the reduction of alpha beta unsaturated ketones to the corresponding saturated ketone using Red-Al.

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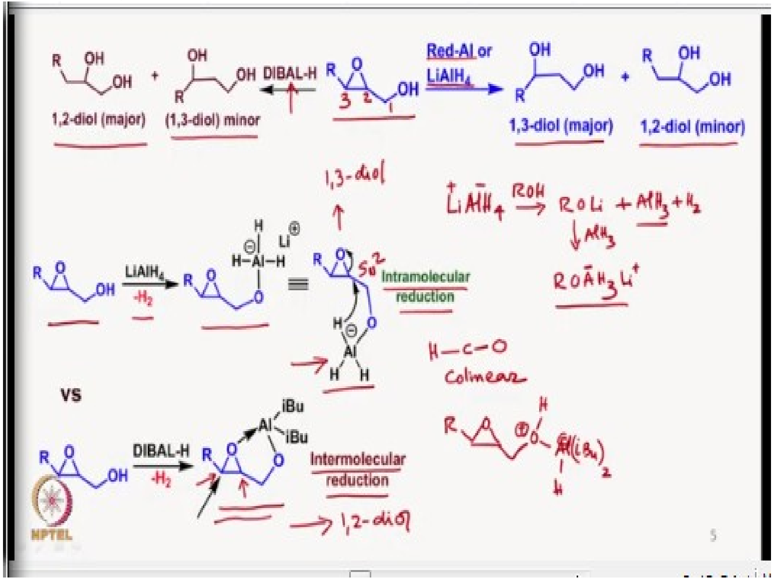

There is another interesting reduction which is a very specific and selective reduction, that is of epoxy alcohols. This 2, 3 epoxy alcohols, so you have 1, 2 and 3 so this 2, 3 epoxy alcohol is a very easily available via Sharpless epoxidation of the corresponding allylic alcohol. And therefore the utility of these 2, 3 epoxy alcohols become very important. And thus their reduction to give the corresponding 1, 2 or 1, 3 diol is important.

And therefore if there are reagents that can selectively reduce 2, 3 epoxy alcohols to either 1, 3 diol or 1, 2 diol then of course the reaction becomes more meaningful and synthetically useful. What is found? That if one takes Red-Al or a lithium aluminium hydride both of them are as I said comparable in terms of reactivity. They lead to 1, 3 diol as the major product and 1, 2 diol as the minor product.

On the other hand if one uses DIBAL for the same reduction and then what is found is that the 1, 3 diol is found in minor amount and 1, 2 diol is form in the major amount. Now how does this reaction occur, why should there be a selectivity. Now lithium aluminium hydride when it comes in contact with any alcohol as I mentioned earlier is something that leads to the expulsion of hydrogen gas after the OH of the alcohol or water reacts with the lithium aluminium hydride.

So, you have lithium aluminium hydride as a species which is having a negative charge here and a positive charge here. And when it comes in contact with ROH we get here ROLi and of course AlH_3 and hydrogen comes off. So, same thing happens even in this case hydrogen comes off and now as this species can interact with AlH_3 which is released here, and can form the corresponding negatively charged lithium+ species.

So, this is exactly what is here, but this is coming from the epoxy alcohol. Now we can also write the same thing in this particular form here, as we can slightly rotate the bond. And now we can see that the reduction of the carbon oxygen bond of the epoxide occurs in such a fashion that the hydrogen from this particular part of the reducing end attacks at the carbon bond sorry carbon atom of the epoxide carbon bond. where we have an SN2 type of reaction.

That means the hydrogen carbon and oxygen of these species should be sort of collinear then you have the proper SN2 type of reaction taking place. And this is exactly what happens, so you have an intramolecular reduction after the lithium aluminium hydride has reacted with the alcoholic part of the epoxy alcohol. And the reaction occurs in an SN2 fashion in an intramolecular fashion.

At the same time when we take DIBAL and react with these epoxy alcohols. So, in a similar fashion as lithium aluminium hydride when the DIBAL comes in contact with the epoxy alcohol. Then also you have a hydrogen here then if DIBAL comes in contact with this OH, we can expect this type of species to form. And this also looses, this is a negative charge and this is a positive charge, this also loses hydrogen and forms an intermediate of this type.

Now this particular intermediate where there is an aluminium species will have a coordination or with the oxygen that is of the epoxide oxygen. And it forms a kind of chelate complex which is strongly helded. Because aluminium here is trivalent and therefore it is highly electrophilic, therefore the oxygen of the epoxide coordinates with the aluminium and forms this.

Now since this aluminium part as against the aluminium part of the lithium aluminium hydride, here does not have any hydrogen for allowing the reduction to take place. Therefore the another part of the similar molecule or DIBAL then reacts to this part in an intermolecular fashion. So, there is no intramolecular fashion and therefore the possibility of attack of the hydrogen or the hydride to this particular carbon atom would be much better.

If between the two this carbon is attacked which is relatively sterically free compared to this particular carbon. And thus the reduction here leads to 1, 2 diol whereas in the case of lithium aluminium hydride it leads to the 1, 3 diol, this basically leads to 1, 3 diol. So, this is how the reductions occur of the 2, 3 epoxy alcohols with lithium aluminium hydride or DIBAL. And since lithium aluminium hydride is similar to Red-Al the Red-Al also gives 1, 3 diol as the major product very similar in a fashion that lithium aluminium hydride does it.

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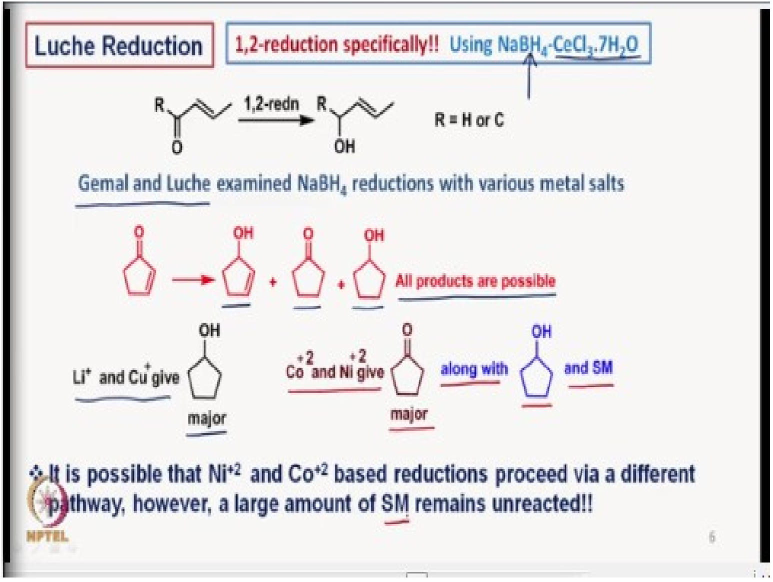

Luche Reduction

1,2-reduction specifically!! Using NaBH$_4$-CeCl$_3$.7H$_2$O

Gemal and Luche examined NaBH$_4$ reductions with various metal salts

- It is possible that Ni^{+2} and Co^{+2} based reductions proceed via a different pathway, however, a large amount of SM remains unreacted!!

Now we have another reducing agent which is known as a Luche reduction, which is named after the discoverer which is Luche. And it allows 1, 2 reduction to take place and particularly when there is a alpha beta unsaturated ketone. So, the reagent that is utilized is a combination of sodium borohydride and cerium chloride which is hydrated with 7 waters. This specifically allows the reduction of even alpha beta unsaturated aldehydes to the corresponding allylic alcohols.

We discussed earlier in one of the lectures that the reduction of alpha beta unsaturated ketones and alpha beta unsaturated aldehydes with lithium aluminium hydride is not straight forward, it all depends upon many factors. But then we also said that alpha beta unsaturated aldehyde reduction can take place with some other reducing agents. And that is what the one that we are now talking as the sodium borohydride, cerium chloride based reducing agent which allows the reduction of the alpha beta unsaturated aldehydes also to the corresponding allylic alcohols.

Of course the ketones, alpha beta unsaturated ketones also get reduced. Now this Gemal and Luche are the 2 people who initiated examining the reduction of alpha beta unsaturated carbonyl compounds with various metal salts along with sodium borohydride as a reducing agent. As we can see here that there are possibilities of all the three types that one can anticipate, so all three types of products are possible.

So, you have allylic alcohol, saturated ketone and completely reduced saturated alcohol. So, a lithium and copper was found to give the corresponding completely reduced product as the major product. And if one uses cobalt and nickel salts along with sodium borohydride, they give this saturated ketone as the major product along with saturated alcohol. And of course a lot of starting material remains unreacted.

It is possible that nickel 2+ and cobalt 2+ base reduction proceed via a different pathway. But since a large amount of starting material SM, SM basically stands for starting materials which is nothing but alpha beta unsaturated carbonyl compound and if that is the case then it is not a very good reaction.

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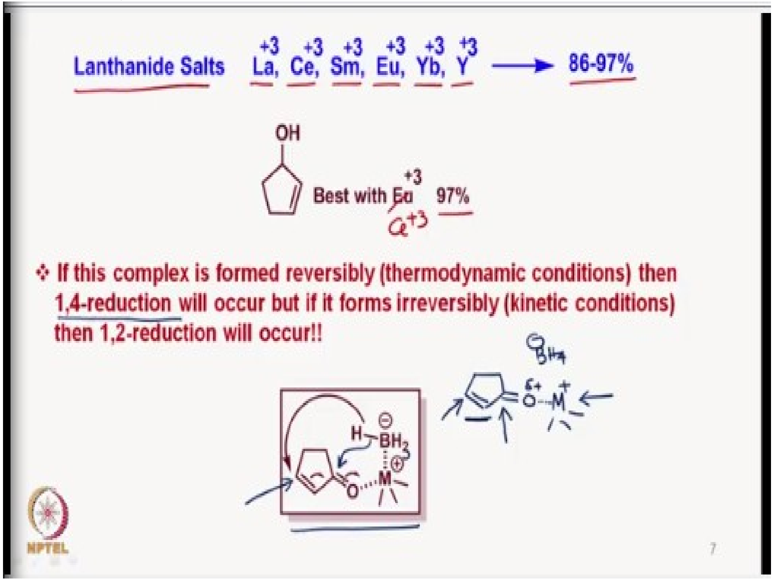

Lanthanide Salts $\overset{+3}{La}$, $\overset{+3}{Ce}$, $\overset{+3}{Sm}$, $\overset{+3}{Eu}$, $\overset{+3}{Yb}$, $\overset{+3}{Y}$ $\longrightarrow$ 86-97%

Best with ~~Eu~~$^{+3}$ Ce^{+3} 97%

- If this complex is formed reversibly (thermodynamic conditions) then 1,4-reduction will occur but if it forms irreversibly (kinetic conditions) then 1,2-reduction will occur!!

So, they did with some other salts and particularly with lanthanide salts when they carried out the reaction. Like lanthanum, cerium, samarium, europium, Ytterbium, Yttrium and they all gave the reductions in good yield from 86 to 97%. And particularly it was found that the it should not be europium it should be cerium. So, the cerium+ gave the corresponding allylic alcohol in about 97% yield.

So, what was then discussed or discussed in the papers that were published later on is, how does the reaction occur? What was initially found and accepted, that if this complex is formed for example one could expect that we have an enone like this. And it is obvious that the metal salt which is used for the reaction with whatever the atoms are attached to this. Now we can expect some sort of chelation with this and then we have a delta positive here and of course you have BH_4^- from the corresponding sodium borohydride.

And one can expect the reduction to take place either at this carbon to give the corresponding allylic alcohol or on to this carbon to eventually reduce the double bond and make the corresponding enolate which leads to the saturated alcohols or saturated ketone. That means the double bond gets reduced in one case, in the other case the carbonyl group gets reduced. So, what was proposed what?

If this particular complex type of should be CH_3 and if it this type of complex is reversibly formed. That means under thermodynamic condition it attaches to the carbonyl and then again detaches, again it attaches. If that happens then there is a possibility of attack onto this particular carbon atom. So, 1, 4 reduction is more easily feasible if it is reversibly formed, that will of course depend upon the nature of the M+ that is there and of course the groups which are attached.

But if it is irreversibly formed, that means that immediately attaches to the oxygen and because of the electro negativity of the oxygen and electropositive character of the lanthanide salts. The moment carbonyl group attaches to that and if it is an irreversible attachment then it is obvious that 1, 2 reduction would be much more facile something like this. So, it is much easier to get 1, 2 reduction. So, therefore that the reaction depends upon thermodynamic conditions and kinetic conditions.

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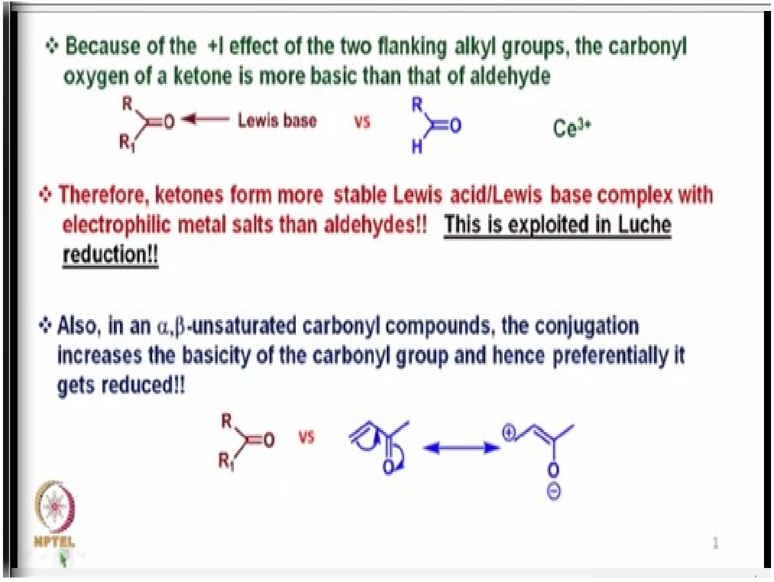

❖ Because of the +I effect of the two flanking alkyl groups, the carbonyl oxygen of a ketone is more basic than that of aldehyde

❖ Therefore, ketones form more stable Lewis acid/Lewis base complex with electrophilic metal salts than aldehydes!! **This is exploited in Luche reduction!!**

❖ Also, in an α,β-unsaturated carbonyl compounds, the conjugation increases the basicity of the carbonyl group and hence preferentially it gets reduced!!

Because of the +I effect of the 2 flanking alkyl groups, the carbonyl oxygen of a ketone is considered to be more basic than that of aldehyde. It is obvious that if a ketone has two alkyl group the +I effect would increase the electron density on the carbonyl oxygen. In comparison to aldehyde in which there is only one alkyl group. And therefore the cases where ketones and aldehydes are compared obviously ketones will form more stable Lewis acid, Lewis base complex with electrophilic metal salts than aldehydes.

This is exactly what is exploited in Luche reduction. In Luche reduction for example cerium 3+ salts are utilized for the selective reduction of ketone over aldehydes. And that is because of the stable Lewis acid, Lewis base complex formation with ketone in comparison to aldehydes. In a similar fashion when we compare an alpha beta unsaturated carbonyl compound with a saturated carbonyl compound.

We can see that while in the case of saturated ketones, it is only the inductive effect that increases the basicity of the oxygen. In case of alpha beta unsaturated ketone it is the electron density from the pi system that is in conjugation with the carbonyl group. And we can write a resonance structure like this in indicating that more electron density is residing on the oxygen of the alpha beta unsaturated system compared to the oxygen of the ketones.

And therefore it is very clear that an alpha beta unsaturated ketone would form a more stable Lewis acid, Lewis base complex with say cerium salts in comparison to saturated ketone. And therefore alpha beta unsaturated ketones are reduced more preferentially in comparison to the saturated ketone. So, these are the things which have been exploited in the Luche reduction.

We will stop it today here and look at the further reactions of the Luche reagent with different types of carbonyl compounds, and what exactly is the role of solvent in modifying the Luche reagent in and how do they affect the selective reductions of various types of carbonyl compounds. So, you can go through these aspects of the reagent that I have discussed and we will see you next time, thank you.