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

Prof. Yashwant D. Vankar
Department of Chemistry
Indian Institute of Technology-Kanpur

Lecture - 31

Silanes [R3SiH, Including Polymethyhydrosilanes (PMHS)] as Reducing Agents

Hello, welcome to today's lecture. I hope you had the opportunity to go through the notes of the last class. What we discussed was essentially the mechanism of the McMurry coupling, how McMurry coupling can allow direct formation of the olefins from the ketones in an intermolecular as well as intermolecular fashion forming different kinds of cyclic systems or acyclic systems.

But since the formation of the acyclic molecules did not have a control over stereochemistry we considered several possibilities of the mechanism. And we ruled out the two possibilities in which the hydroxy groups could be attached to a one titanium or to different titanium of these atoms. And of course, then we settle for the mechanism in which the coordination or the kind of attachment to the titanium zero surface allows the reaction to proceed.

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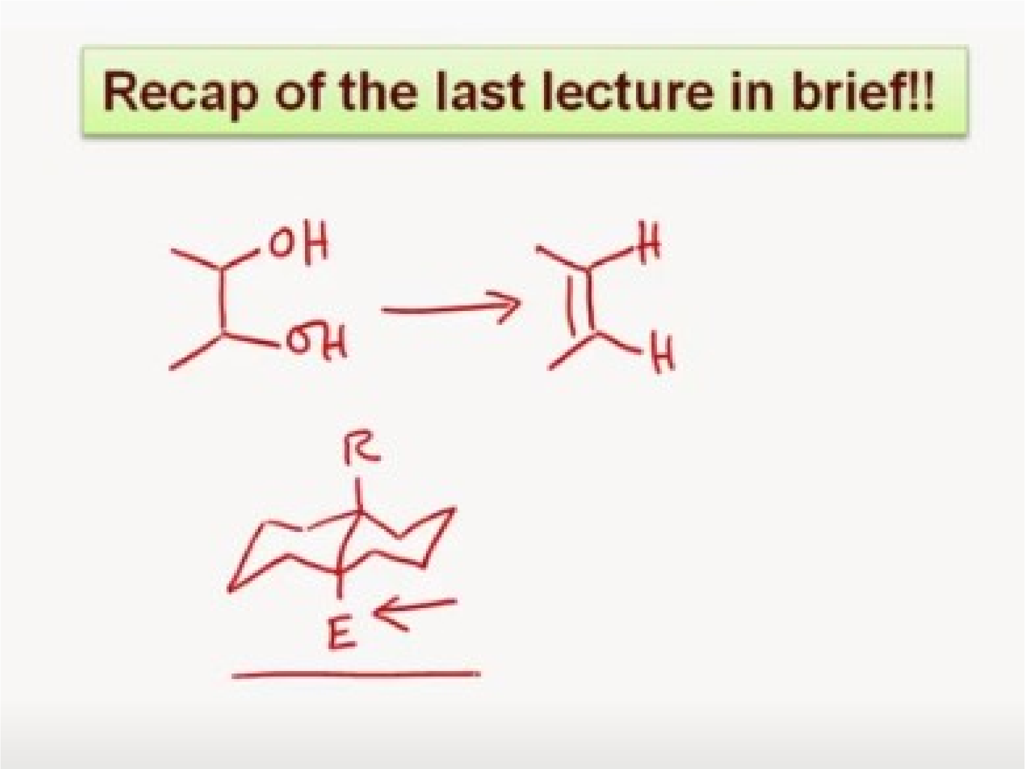

Recap of the last lecture in brief!!

The conditions we discussed also where we can straightaway stop the reaction after the coupling up to the diol stage, and we also can allow this diol under the same conditions in a refluxing way to form the corresponding olefin. This also can be done both in an intermolecular as well as intramolecular fashion.

So with this detailed titanium zero base McMurry coupling, we had discussed mechanistically and also saw the synthesis of humulin, which is relatively difficult to do under normal conditions, but this one step procedure allows the formation of medium size ring also. Of course, we discussed the disadvantages also that these conditions do not allow many other functional groups to be tolerated.

But then there are advantages of getting such a coupling in one step. Then we discussed the reduction of alpha beta unsaturated systems especially, the bicyclic enone systems where the hydrogen or the electrophile attaches at the junction. And obviously, we came out with a discussion in which the incoming electrophile attaches always from the axial side and not from the equatorial side.

There were again three possibilities that we considered, the three types of confirmations, cis-decalin having two different types of possibilities and trans-decalin having one possibility, and we ruled out based on steric factors as well as stereoelectronic factors and settled for the formation of a product like this, which is very useful in the steroidal systems or terpenoid systems based on the predictions or the rule devised by Gilbert Stork.

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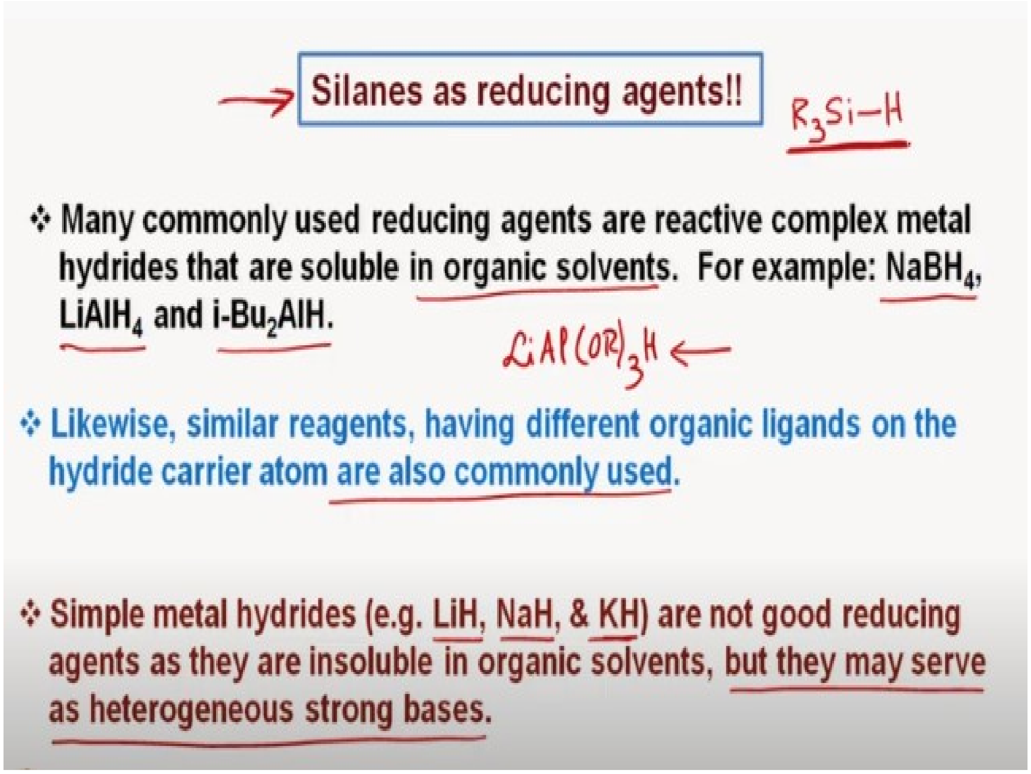

Silanes as reducing agents!!

R_3Si-H

- Many commonly used reducing agents are reactive complex metal hydrides that are soluble in organic solvents. For example: $NaBH_4$, $LiAlH_4$ and i-Bu_2AlH.

$LiAl(OR)_3H$ ←

- Likewise, similar reagents, having different organic ligands on the hydride carrier atom are also commonly used.
- Simple metal hydrides (e.g. LiH, NaH, & KH) are not good reducing agents as they are insoluble in organic solvents, but they may serve as heterogeneous strong bases.

Now we look at new reducing agents, which is basically a silane base reducing agent. So as we can see that there are many commonly used reducing agents, reactive complex metal hydrides that are soluble in organic solvents. So like for example sodium borohydride or lithium aluminum hydride or Dibal or likewise similar reagents having different organic ligands on the hydride carrier atom are also commonly used.

We have discussed all these rare cases. For example, if we take in the case of lithium aluminum hydride, we can have the OR here and we can have a reagent of this type where we increase the bulk and also the hydrophobicity. So these type of various molecules are soluble in organic solvents in or it is partially soluble in organic solvents and the reductions can be carried out.

Simple hydrides such as lithium hydride or sodium hydride and potassium hydride are not good reducing regions as they are not really soluble in organic solvents. Of course, they react violently with protic solvents, and obviously do not dissolve in other solvents such as ether or tetrahydrofuran. However, because they are ionic and they are kind of hard anions they behave as strong bases.

So these are used as strong bases to remove an acidic proton to generate an anion. So in this respect, we have to see other possibilities of developing reducing agents and in that respect this silanes behave as a good reducing agents. It is a new aspect of reduction and silanes such as see you have R3Si and there is a hydrogen attached. So such reducing agents have been utilized in organic chemistry and we will see what they are and how do they function.

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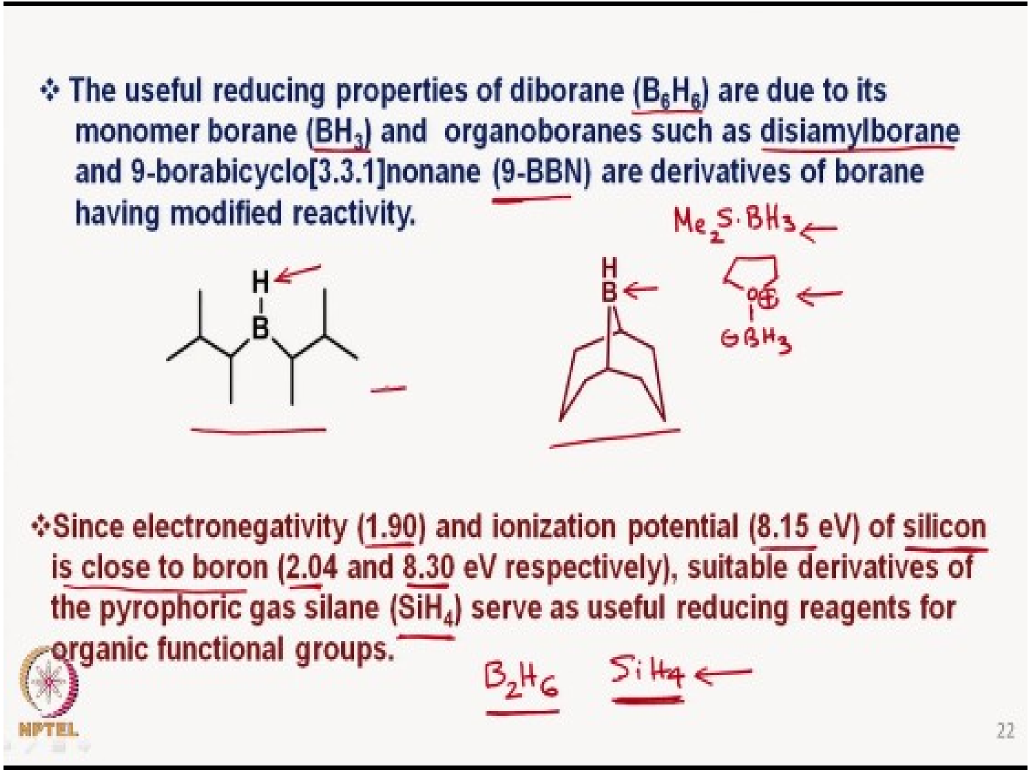

- The useful reducing properties of diborane (B_6H_6) are due to its monomer borane (BH_3) and organoboranes such as disiamylborane and 9-borabicyclo[3.3.1]nonane (9-BBN) are derivatives of borane having modified reactivity.

- Since electronegativity (1.90) and ionization potential (8.15 eV) of silicon is close to boron (2.04 and 8.30 eV respectively), suitable derivatives of the pyrophoric gas silane (SiH_4) serve as useful reducing reagents for organic functional groups.

Now the useful reducing properties of diborane, for example B2H6 are essentially due to the monomeric borane. And these monomeric boranes can be prepared as say you have dimethyl sulfide borane complex or THF borane complex. So either we have, you have this positive charge here and the negative charge here. Either we have this complex or this complex. They are having or carrying monomeric borane.

In addition to these H.C. Brown has developed a large number of reducing agents based on boron and 9-borabicyclic nonane or disiamylborane, which we discussed. This is the disiamylborane and this is 9-borabicyclo nonane, some of the reducing agents based on boron, which are not dimeric because of the steric bulk.

And they need not be stabilized like dimethyl sulfide or tetrahydrofuran, are very useful reducing agents and they are a bulky reducing agents and they offer similar type of reactivity as normal borane but then with a modified reactivity in terms of steric hindrance.

Since electronegativity and ionization potential of silicon is close to boron, so as you can see here 1.90 and 2.04, 8.15 electron volt and 8.30 electron volt, so they are very close to each other the silicone and the boron. Therefore, suitable derivatives of the pyrophoric gas silane, now if we start analyzing BH3, which is existing as B2H6 and if we compare it with SiH4, there is a problem.

The problem is that this is like a low boiling gas and of course, it catches fire. B2H6 can be stabilized but this is not stabilized easily. And therefore, although there is a comparison in terms of electronegativity and ionization potential, it is not easy to use this silane as a reducing agent that is a gas. Then there are many modifications just the way. Such modifications have been done for the boron. They have the chemists have also done the modifications on the silicone.

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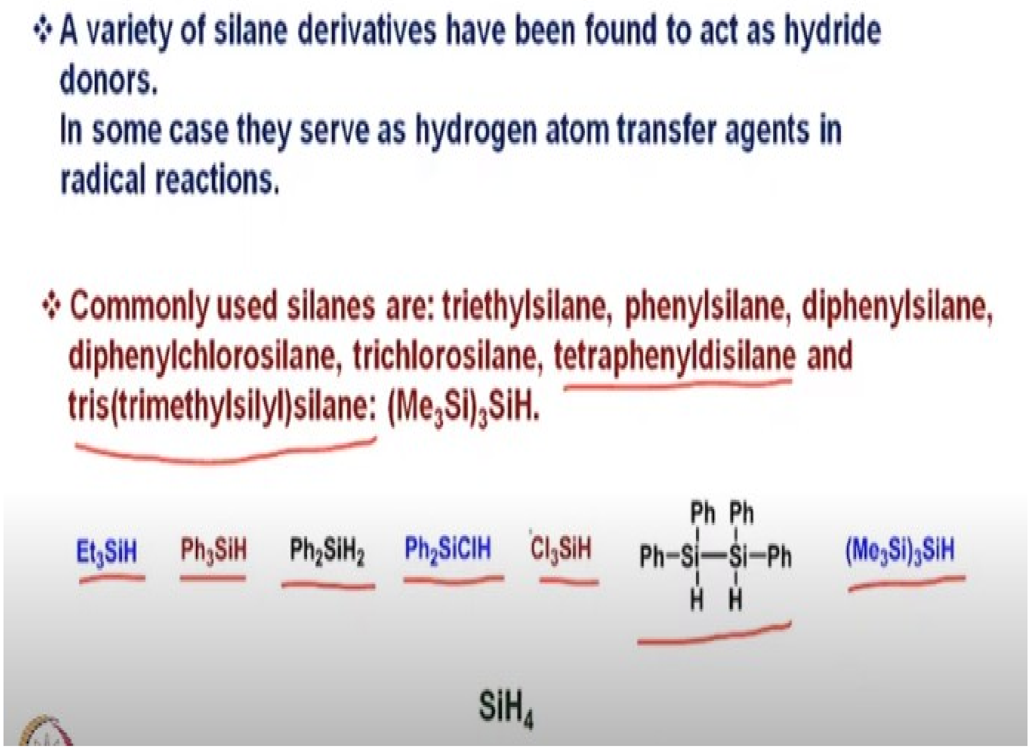

- A variety of silane derivatives have been found to act as hydride donors.
  In some case they serve as hydrogen atom transfer agents in radical reactions.

- Commonly used silanes are: triethylsilane, phenylsilane, diphenylsilane, diphenylchlorosilane, trichlorosilane, tetraphenyldisilane and tris(trimethylsilyl)silane: $(Me_3Si)_3SiH$.

Et_3SiH Ph_3SiH Ph_2SiH_2 Ph_2SiClH Cl_3SiH $Ph{-}\overset{Ph}{\underset{H}{Si}}{-}\overset{Ph}{\underset{H}{Si}}{-}Ph$ $(Me_3Si)_3SiH$

SiH_4

And a variety of silane derivatives have been introduced to act as hydride donors. This is of course, as I mentioned in view of the fact that SiH4 is pyrophoric and difficult to handle. Now in most of the cases they act as hydride donors, but in some cases, it has also been found that some of the silicon derivatives act as hydrogen transfer agents in radical fashion.

Now the commonly used silanes which have got lot of popularity include triethylsilane of this kind for example of this type triethylsilane. Then phenylsilane, which has the structure of this type. That means 3 hydrogens have been replaced by the phenyl group. Or diphenylsilane of this kind where 2 hydrogens have been replaced by 2 phenyls.

And of course diphenylchlorosilane in which one of the hydrogens has been replaced by the chlorine and of course 2 hydrogens have been replaced by the phenyl. Then you have trichlorosilane and then of course tetraphenyldisilane of this kind. And in a similar fashion, there is one very interesting reagent which is tris(trimethylsilyl)silane. This is what is the tris(trimethylsilyl)silane, which is sterically hindered.

So these are the various kinds of silanes, which have been introduced in order to avoid the usage of pyrophoric SiH4 and of course these reagents are relatively easy to handle.

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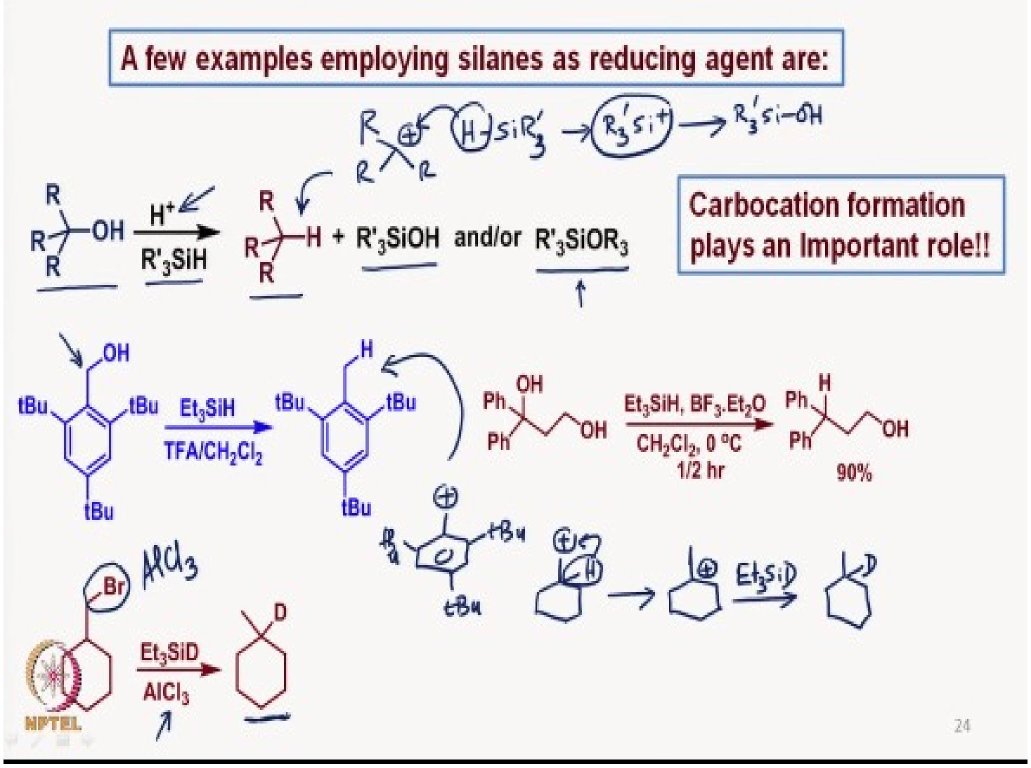

A few examples employing silanes as reducing agent are:

Carbocation formation plays an Important role!!

A few examples that are shown here, where silanes can be used as a reducing agents are like for example, one starts with a tertiary alcohol and in the presence of H+. Now we can carry out reactions of different types of silanes very easily in the presence of acid. They are not affected, because the silicon hydrogen bond is not ionic, it is covalent and therefore, it is easy to carry out the reaction under both the conditions.

And as you can see here, if we take a tertiary alcohol, the hydride is transferred from the silane to the carbocation, which is what is going to form here as like this and to this the hydrogen from the silane say for example R3 prime here is transferred to this to this and the product is this formed. Now this particular cation which is formed here would obviously has to be taken care of.

So the positive charge that is going to form here will react with the nucleophile present in the reaction medium, which can be water or it can also original alcohol. So one can expect this to form. But essentially, this is what is going to form. This can form a little bit if the alcohol allows the reaction to take place on the silicon plus.

As you can see here this is the benzylic alcohol here and is relatively easy to form the corresponding benzylic cation. And once the benzylic cation is formed, so you have is relatively stable benzylic cation and that benzylic cation then gets reduced here, although it is a primary cation but it is benzylic, therefore reduction gives this particular product. Now we can see such a reaction occurring on a primary bromide but having a cyclohexane ring system.

I am very sure that most of you know what this reaction is going to be going through is if we form the corresponding cation here, which is what is going to happen when this bromide reacts with a Lewis acid like aluminium chloride. So the aluminium chloride will take away the bromide ion from here and will generate the corresponding primary cation.

But then this primary cation immediately undergoes a hydride shift, going to hydride shift leading to the formation of the corresponding tertiary cation. And then this tertiary cation as you can see that can react with triethylsilane having a deuterium. So it is a isotope of the hydrogen, which allows the introduction of a deuterium atom at this junction.

So we can easily get the corresponding deuterated molecule using triethylsilane which having deuterium.

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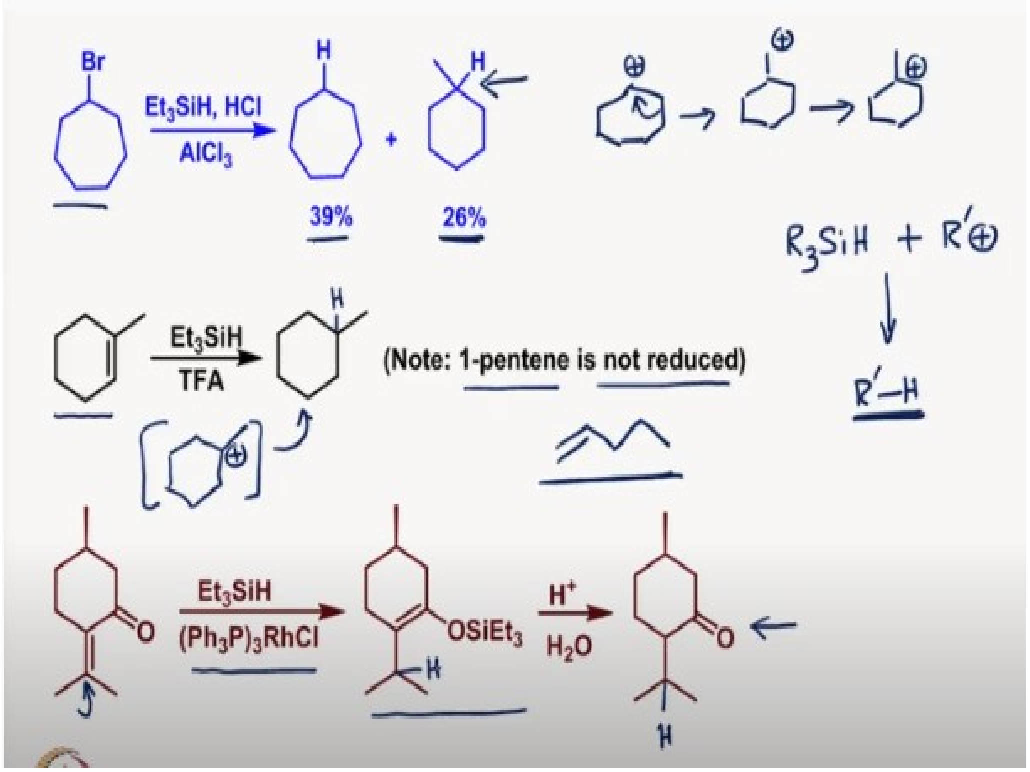

(Note: 1-pentene is not reduced)

We can also see as similar type of carbocation based reactions, if we start with a cycloheptyl bromide, they got 39% of the direct reduction and 26% after the rearrangement. That means, here again one can expect the cation to form in here, but then there is a shift of this particular bond to form a primary cation, which is what would look similar to what we did it earlier.

And then this leads to again carbocation shift and forming this tertiary cation and that is what is leading to the formation of this particular molecule in 26%. But it is interesting to see that if we take a simple one pentene, so something like this, if we take here 1, 2, 3, 4, 5 this does not get reduced, because we do not have a strong possibility of generating a stabilized or stable cation.

On the other hand, if we take 1-methyl cyclohexene it can easily form the corresponding tertiary cation, something like this, where the positive charge is here and the reduction can lead to the formation of such a molecule. So there is a contrast between the two of them. This cannot form a stable cation, whereas this can form stable cation and therefore the reaction takes place.

So what I want to imply here is that the reduction of molecules which are easy to form a cation can easily give the reduction reduced product and one can get the corresponding deoxygenated product if it is from an alcohol or if it is from halide then obviously, it is also a replacement of the carbon halogen bond with carbon hydrogen bond.

If we take the triethyl silane and we use rhodium reagent or a catalyst, then it is found that it proceeds via an enol silyl ether. That means a reduction does occur at this junction because it is now modified reducing agent and it forms the corresponding enol silyl ether, which upon hydrolysis give the corresponding ketone where there is a hydrogen attached here. So there is hydrogen attached. Now how does this reaction occur, we would like to see.

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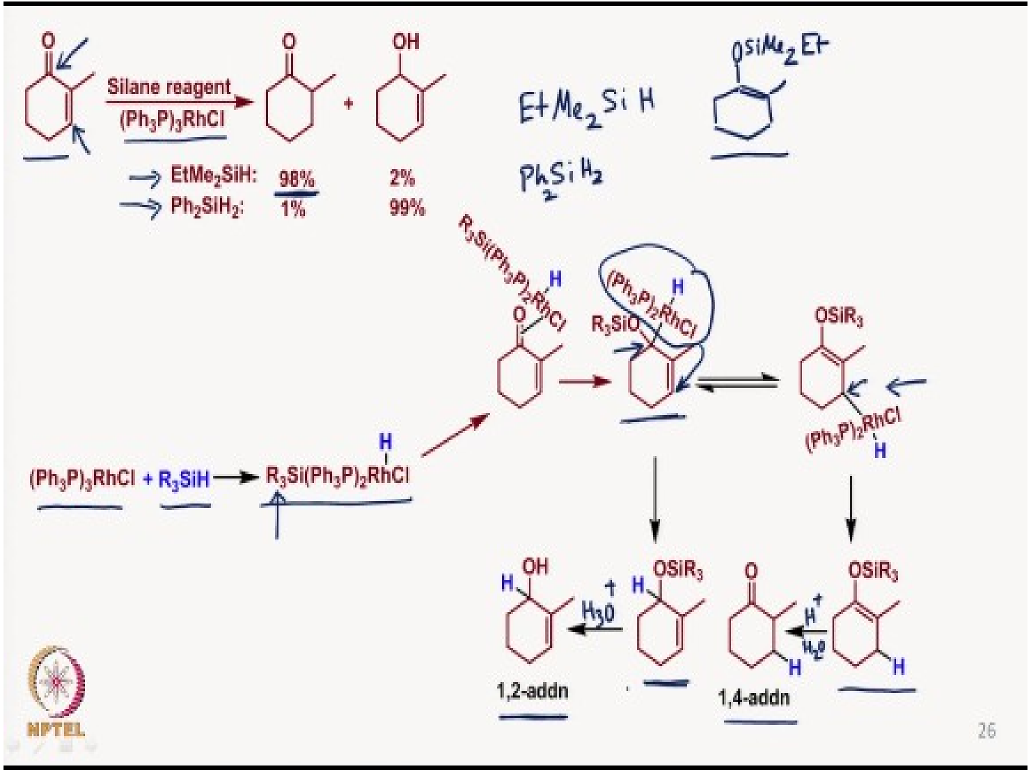

So if we take an enone of this kind and react with a silane reagent in the presence of this Wilkinson’s catalyst, then it is found that these two different types of reducing agents were basically utilized and they lead to two different types of products. For example, the first reducing agent in which there is only one hydrogen, that means this particular reagent contains one hydrogen and that gives the 98% of the corresponding saturated ketone via obviously enol silyl ether.

That means, this reaction must be going via the enol silyl ether and this gives the corresponding ketone. So this is the intermediate that must be formed. While in the second case when there are two hydrogens Ph2SiH2 it is seen now that the reduction takes place directly onto the carbonyl carbon. In this case the reaction had taken place at the fourth carbon here. So we have to see that how does it happen?

So if we have this catalyst rhodium catalyst and react with any silane, this is what we are expecting to get it. There R3 can be these three R's can be two R's and one more hydrogen or whatever. So when this particular modified reagent interacts with the enone, it is proposed that this interacts with the rhodium here through the oxygen and immediately there is a carbon rhodium bond forming such an intermediate.

Now this is the first intermediate that can form. Now this intermediate can be in such a way that this particular part of the intermediate can go to the fourth position that is on the other end of the double bond forming this intermediate where if the hydrogen is transferred to this carbon, then we get this intermediate which is 1, 4 addition and after hydrolysis here H+ water can give this ketone.

But if this hydrogen is directly transferred to this particular carbon atom and the rhodium goes off, then we get 1, 2 reduction product which upon hydrolysis, so we can say that upon hydrolysis of the oxygen silicon bond, we get 1, 2 addition. So you can have either a 1, 2 addition or a 1, 4 addition, if we invoke such intermediates.

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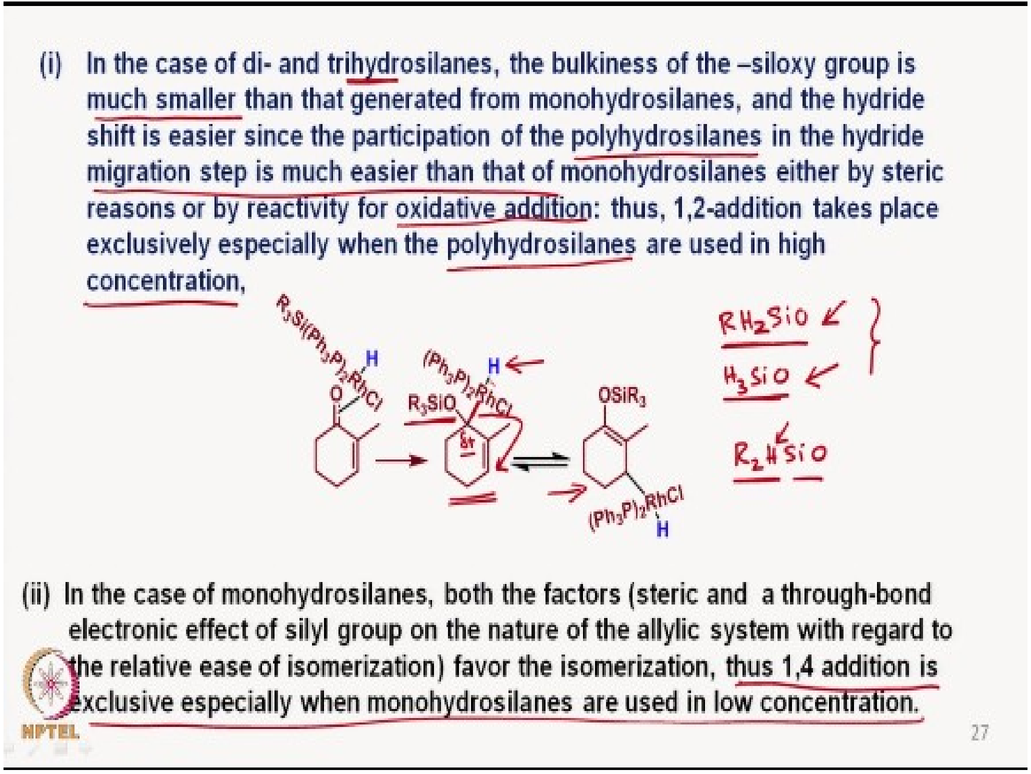

(i) In the case of di- and trihydrosilanes, the bulkiness of the –siloxy group is much smaller than that generated from monohydrosilanes, and the hydride shift is easier since the participation of the polyhydrosilanes in the hydride migration step is much easier than that of monohydrosilanes either by steric reasons or by reactivity for oxidative addition: thus, 1,2-addition takes place exclusively especially when the polyhydrosilanes are used in high concentration,

(ii) In the case of monohydrosilanes, both the factors (steric and a through-bond electronic effect of silyl group on the nature of the allylic system with regard to the relative ease of isomerization) favor the isomerization, thus 1,4 addition is exclusive especially when monohydrosilanes are used in low concentration.

Now we see now how it is happening. What has been suggested is in the case of di and tri hydro silanes that means if we have more of hydrogens attached, the bulkiness of the siloxy group is much smaller. So that means, if this particular part is considered and if the trihydro di or trihydro, that means we are talking about RH2SiO kind of species we are talking about it. Or trihydro, you have H3SiO part of it.

That means, the bulkiness of the siloxy group is reduced smaller than that one can think about monohydrosilane. So for example, if you have here R2HSiO. So you have two of the R groups and only one hydrogen here. So this is a monohydrosilane. This is a dihydrosilane. This is a trihydrosilane. So the bulkiness of the siloxy group is much smaller in these cases compared to monohydrosilanes.

And the hydride shift is easier since the participation of the polyhydrosilanes in the hydride migration step is much easier. Like for example, if we have something like this, then the hydrogen is immediately migrated here than of monohydrosilanes either by steric reasons or by reactivity for oxidative addition. Thus 1,2 addition takes place.

So in such cases where the bulkiness is reduced, we get the hydrogen transfer because there is not much steric hindrance and therefore, this is relatively stable and immediately hydrogen is transferred. Now a 1,2 addition takes place especially when the hydro polyhydrosilanes are used in high concentration. So you use you allow this where the R3 groups are more of hydrogens and therefore, this is relatively stable.

There is not much steric hindrance and it goes. In the case of monohydrosilanes when there is hydrogen only is 1 present that means, on the rhodium there is only one hydrogen has come from the silane that we have used and R3 is larger group both the steric and through bond electronic effect of silyl group on the nature of the allylic system with regard to the relative ease of isomerization.

Now this is particularly isomerizing to this. While isomerizing, this particular carbon rhodium bond is breaking and going to this one here. During the process there will be a delta positive which will be generated here, which is an allylic system. That is what is allowing it to migrate and also the steric hindrance.

The steric hindrance between the siloxy group and the rhodium part is large when it is monohydrogen containing silane and therefore, the steric hindrance allows it to move and away from the system and it goes to the other end of the double bond and also during the process you have delta positive. That delta positive will be stabilized by the double bond as well as by the silicon through a beta silicon effect.

And therefore, thus we get the 1,4 addition exclusively, especially when monohydrosilanes are used in low concentration. So this is how the reaction is perceived and the reaction occurs in a way that we can tune the reducing agent and therefore, you can have either 1,2 reduction or 1,4 reduction.

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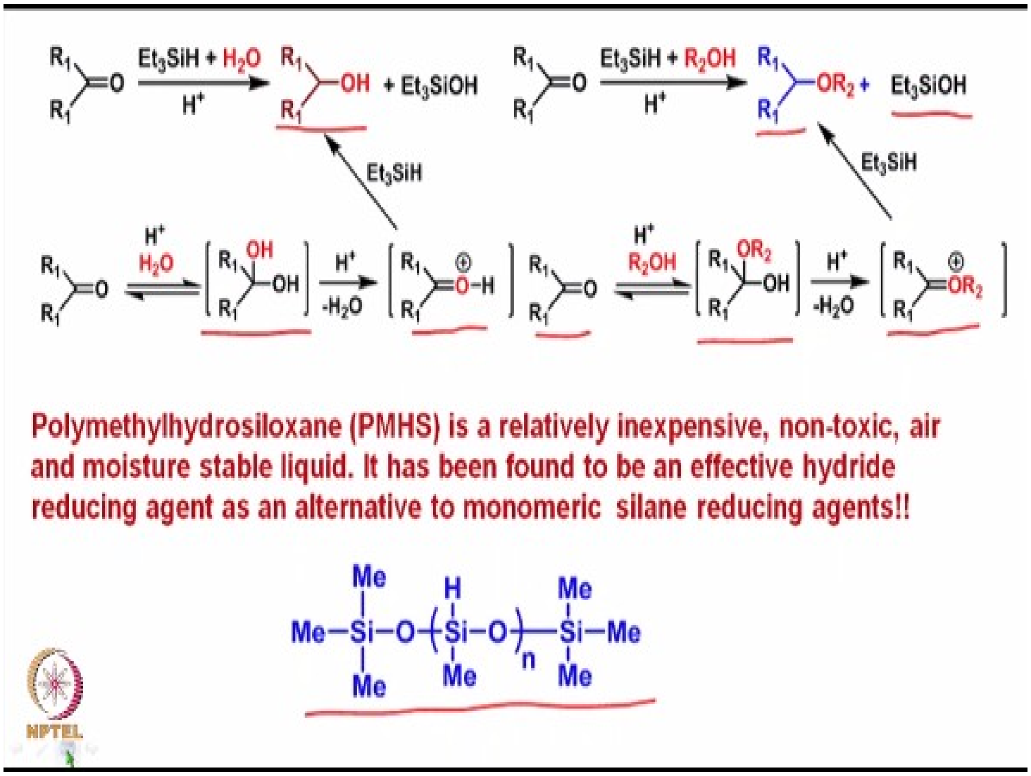

Polymethylhydrosiloxane (PMHS) is a relatively inexpensive, non-toxic, air and moisture stable liquid. It has been found to be an effective hydride reducing agent as an alternative to monomeric silane reducing agents!!

$$\mathrm{Me{-}Si(Me)_2{-}O{-}\left(Si(H)(Me){-}O\right)_n{-}Si(Me)_2{-}Me}$$

We can also carry out reductions of ketones or aldehydes using triethylsilane. And for example, if we take a ketone of this type with triethylsilane in aqueous medium if we have an acid then of course, we get the corresponding alcohol and triethylsilanol as the byproduct.

And in a similar fashion if we take ketone and reduce in the presence of an alcohol like R2OH then under acidic conditions with triethylsilane, what we get is the corresponding ether and again triethylsilanol comes out as the byproduct. The way it has been perceived or rationalized is that the ketone under acidic condition gets first protonated and the water attacks on to this particular carbon atom.

And then, one forms the particular dihydroxy compound geminal dihydroxy compound which is unstable. Of course, it will be in equilibrium with the ketone. Now if one of the two hydroxy groups, say for example, this one gets protonated, then what one could expect to get is a oxonium ion of this kind by the loss of water.

Now this particular oxonium ion then can react with triethylsilane and get reduced to lead to the formation of this particular alcohol. And of course, triethylsilanol will come out.

In a similar fashion if we take this ketone and react with an alcohol in the presence of H+, then of course, what you expect to form as a hemiacetal of this kind because, proton will protonate the carbonyl oxygen and alcohol will attack as a nucleophile to form this hemiacetal, which can of course loose water to form this oxonium ion similar to what we saw it here, but now we have this OR2 in the molecule.

And now when this oxonium ion gets reduced with triethylsilane then of course, we get the corresponding ether. And of course, we will get the triethylsilanol as the byproduct. Now this is how the triethylsilane has been utilized for the reduction of carbonyl compounds under different conditions.

But in addition to triethylsilane or different kinds of silanes people have also started using polymethylhydrosiloxane PMHS, which is shown as like this here. And it is a relatively inexpensive nontoxic air and moisture stable liquid. It is of course a polymeric liquid and it has been found to be an effective hydride reducing agent as an alternate to monomeric silane reducing agents such as triethylsilane.

So we will see how the reactivity of this PMHS can be utilized for the reduction of different kinds of substrates. So till the next class we will stop it here and we will discuss other aspects of this PMHS and other reducing agents in the next class. Till then bye. Thank you.