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

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Lecture - 32
Further Aspects of Silanes as Reducing Agents & Barton-McCombie Deoxygenation

Hello all of you. I welcome you to today's lecture. We discussed some aspect of silane based reducing agents last time.

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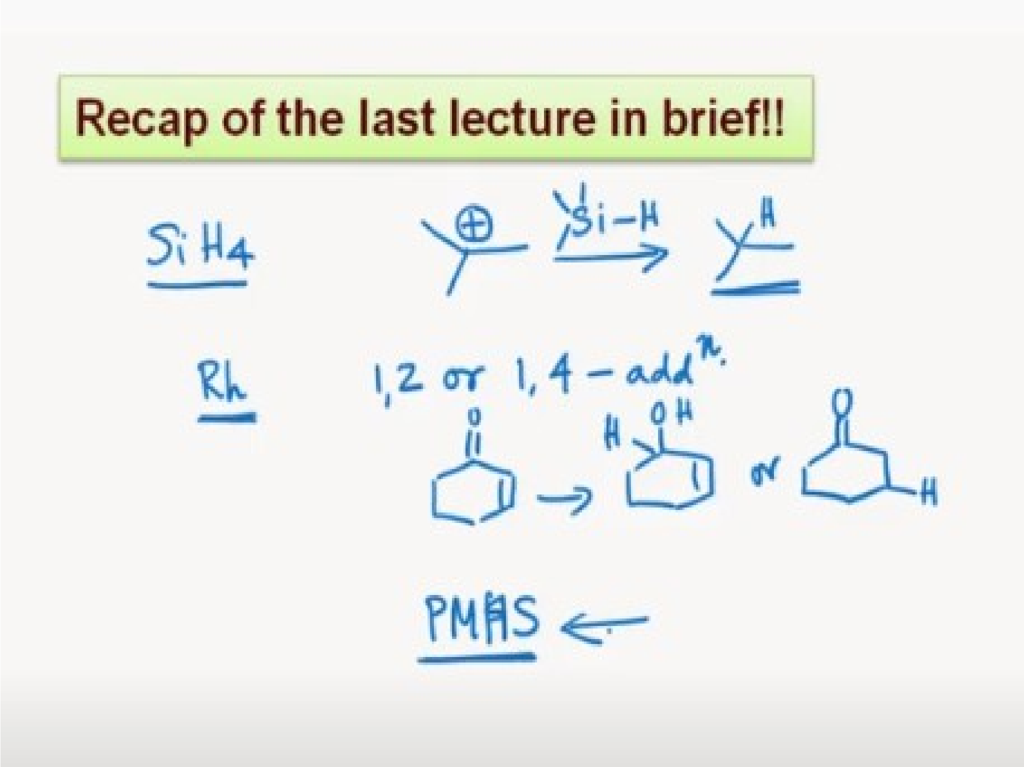

Recap of the last lecture in brief!!

SiH_4

Rh

1,2 or 1,4-add^{n}.

PMHS

We saw how silane gas can be modified and different types of organic groups, functional groups could be attached to silicon and different silane reagents can be prepared which are relatively more stable than the silane gas. And these modified silane base reagents can reduce a number of functional groups such as carbonyl group or an ester group or even halides which are capable of forming a carbocation.

So if we have a possibility of generating a carbocation, then the silane based reagents where this 1 or 2 silanes the hydrogens are present can lead to the formation of the corresponding reduced product.

Then we also saw how the rhodium modified reducing agents can be prepared and they lead to 1,2 or 1,4 addition of hydrogen and to an enone system and we can get either, from an enone we can get either a 1,2 product at a reduced product or a 1,4 reduced product depending on the bulk of the corresponding groups attached to silicon.

Then towards the end, we saw polymethylhydrosilane as PMHS which is something that is like a polymer and therefore, we can expect that such a polymeric molecule which is liquid to handle and it is stable, air stable and inexpensive and hope it can be used in reducing various kinds of molecules similar to the silanes that we discussed.

So off late if you see the literature, many people prefer to use PMHS as a reducing agent rather than triethylsilane or other reducing agents of similar type. Now we see how these reactions occur.

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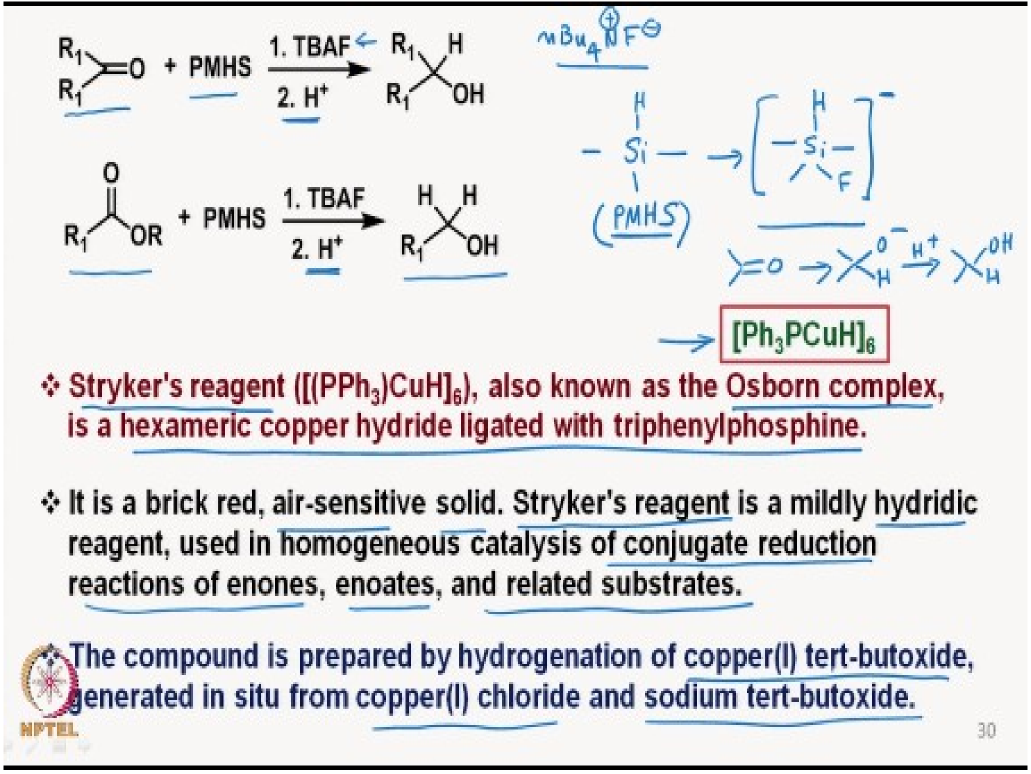

→ $[Ph_3PCuH]_6$

- Stryker's reagent ($[(PPh_3)CuH]_6$), also known as the Osborn complex, is a hexameric copper hydride ligated with triphenylphosphine.
- It is a brick red, air-sensitive solid. Stryker's reagent is a mildly hydridic reagent, used in homogeneous catalysis of conjugate reduction reactions of enones, enoates, and related substrates.
- The compound is prepared by hydrogenation of copper(I) tert-butoxide, generated in situ from copper(I) chloride and sodium tert-butoxide.

For example, if we take a carbonyl group, then PMHS in the presence of TBAF, TBAF is nothing but tetra-n-butylammonium fluoride. Basically it has a fluoride ion and counter cation as an ammonium ion. So what is done it is, this is the species that you have here and this is how the polymeric species of the PMHS is having hydrogen in the middle and then the fluoride makes a kind of pentavalent silicate.

And then what you have is a possibility of transferring hydrogen from this species to the carbonyl group. So basically this is the modified species is which is formed when the TBAF interacts with the PMHS. So the reduction occurs in a slightly different way than the normal reduction that we expect from normal silanes where we first make the compound under acidic conditions and then we carry out the reduction.

In a similar fashion, we can convert an ester to the corresponding alcohol if we use two equivalent of PMHS and a TBAF. And the anion which is going to be formed after the carbonyl group gets reduced. So even gets reduction and get the corresponding anion which then is protonated to form the corresponding OH. So you have to use a proton source later on during the next step.

Now there is a another reducing agent which is called as Stryker's reagent and which is having this copper hydride. Basically it is a hexameric copper hydride reagent ligated with triphenylphosphine. It is also called as Osborn complex. So this is a reducing agent. Now suddenly from silicon to this Osborn complex or hexameric copper hydride I am coming to mainly because this can also be prepared using a silane.

First let us see what is the utility or what is the use of such copper based complex. It is a brick red air sensitive solid which is known as Stryker's reagent. Is mainly hydridic because you have here hydrogen there attached to copper and therefore it is useful because it is relatively soft, because of the copper being present. This allows the conjugated reduction of enones, enoates and related substrates, different type.

So basically it allows conjugate addition of the hydrogen occurring. The compound is prepared, now this is where the silicon based things come into picture. The compound is prepared by hydrogenation of copper tertiary-butoxide generated in situ from copper chloride and sodium tertiary-butoxide.

That means this copper tertiary-butoxide is then hydrogenated and of course a triphenyl phosphine has to be put. Then we get the corresponding Osborn complex or the Stryker's reagent.

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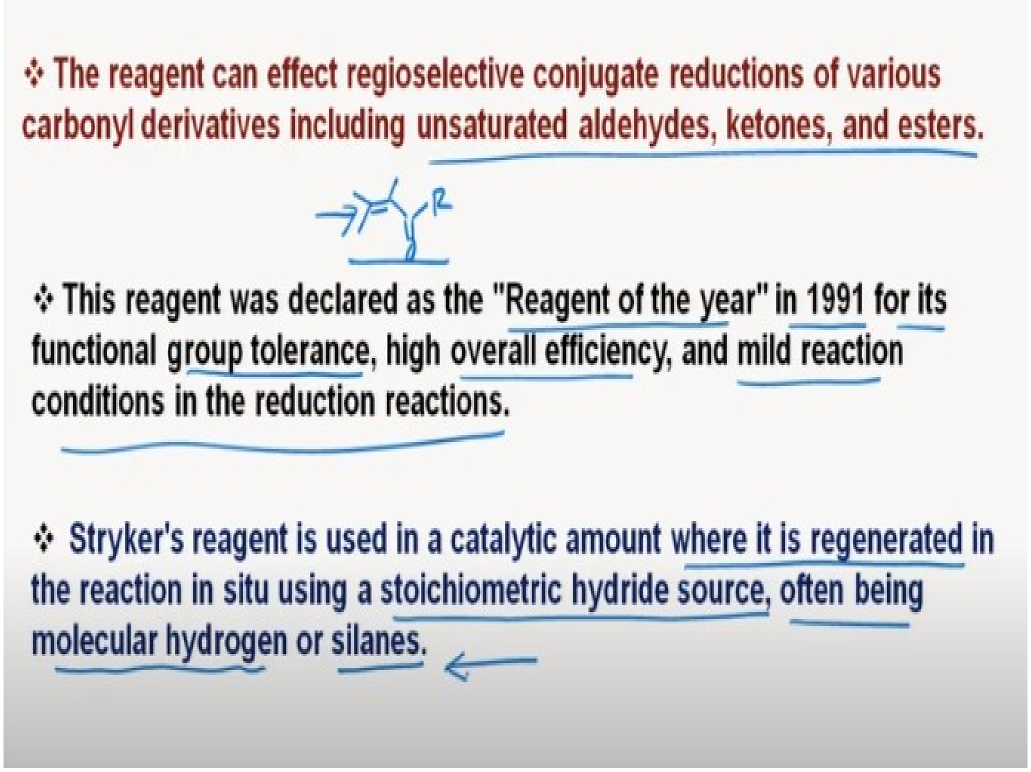

- The reagent can effect regioselective conjugate reductions of various carbonyl derivatives including unsaturated aldehydes, ketones, and esters.
- This reagent was declared as the "Reagent of the year" in 1991 for its functional group tolerance, high overall efficiency, and mild reaction conditions in the reduction reactions.
- Stryker's reagent is used in a catalytic amount where it is regenerated in the reaction in situ using a stoichiometric hydride source, often being molecular hydrogen or silanes.

The reagent can effect regioselective conjugate addition of various carbon derivatives including unsaturated aldehydes, ketones and esters, which we already seen that we can have of any kind of unsaturated system, where the reduction occurs at this end of the double bond. This was declared as the reagent of the year in 1991 as it could tolerate different types of functional groups tolerance, a high overall efficiency, mild reaction conditions in the reduction reactions.

So hope it is very easy to carry out such a reduction. Therefore it tolerates various functional groups and therefore, it is of great use. Now this is used in catalytic amount. You can use the Stryker's reagent in a catalytic amount where it is regenerated in the reaction and you can use some other source of hydride in a stoichiometric way. And in that respect, either you use molecular hydrogen or even silane.

So that is where the silane part comes in. So this is very important that you can modify the Stryker's reagent by basically using in a catalytic amount and reusing along with that silanes or molecular hydrogen. So obviously, when you have to have a choice between molecular hydrogen and silane, you might want to have silanes over hydrogen.

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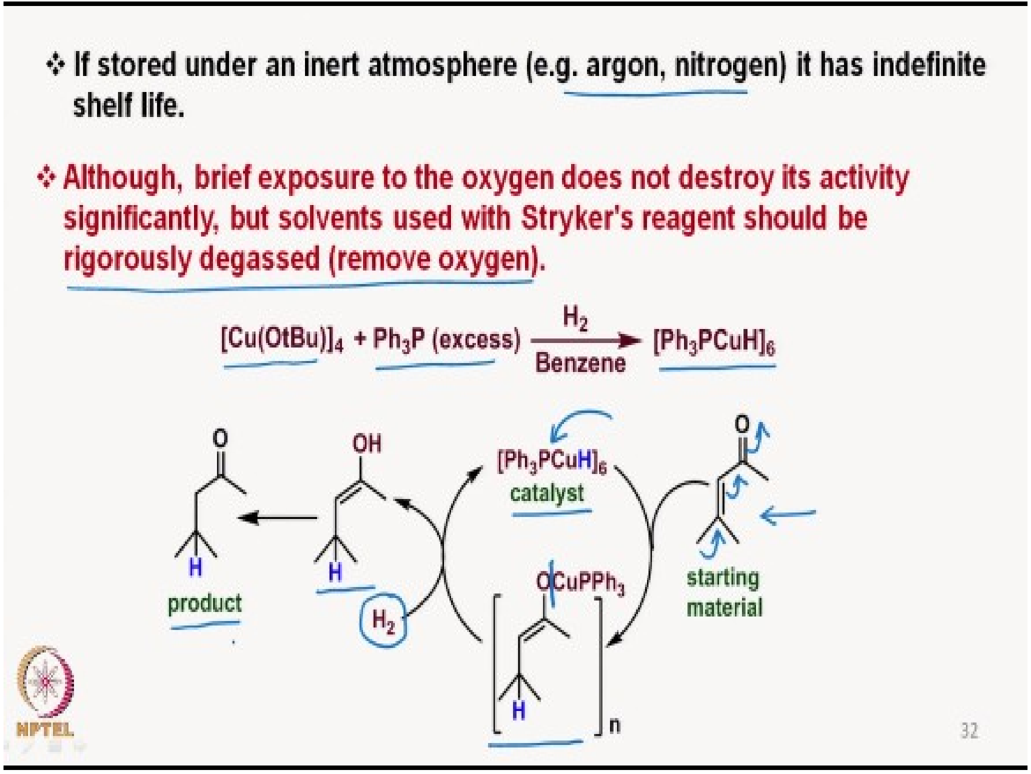

- If stored under an inert atmosphere (e.g. argon, nitrogen) it has indefinite shelf life.
- Although, brief exposure to the oxygen does not destroy its activity significantly, but solvents used with Stryker's reagent should be rigorously degassed (remove oxygen).

$$[Cu(OtBu)]_4 + Ph_3P \text{ (excess)} \xrightarrow[\text{Benzene}]{H_2} [Ph_3PCuH]_6$$

If it is stored under inert atmosphere, for example argon, nitrogen, it has indefinite shelf life. Although brief exposure to the oxygen does not destroy its activity significantly, but solvents used with Stryker should be rigorously degassed to remove oxygen. So oxygen has to be removed.

Now how it is made is that you take this copper tertiary-butoxide and use excess of triphenyl phosphine and in the presence of hydrogen in benzene solvent it gives this hexameric Osborn complex or Stryker's reagent. When this Stryker's reagent reacts with an enone hydrogen is transferred on to this end of the double bond.

And as one can expect, that we can have an intermediate of this type, enol cuprate and this enol cuprate on this reduction will break the oxygen copper bond and of course, you regenerate the catalyst here and you have the enol and that enol gives the product ketones.

So basically, this is how the catalyst is used, where now molecular hydrogen is used as in a stoichiometric way essentially to cleave the oxygen copper bond here and regenerate the Osborn complex or the Stryker's reagent and the reduced product the ketone is formed.

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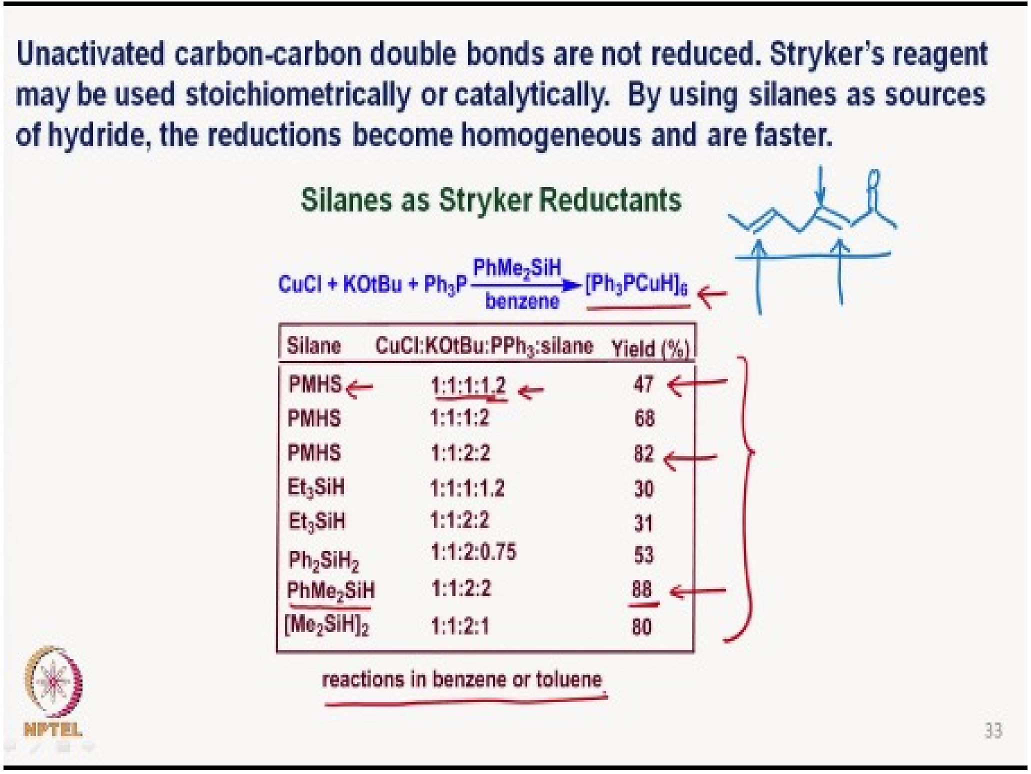

Unactivated carbon-carbon double bonds are not reduced. Stryker's reagent may be used stoichiometrically or catalytically. By using silanes as sources of hydride, the reductions become homogeneous and are faster.

Silanes as Stryker Reductants

$$CuCl + KOtBu + Ph_3P \xrightarrow[\text{benzene}]{PhMe_2SiH} [Ph_3PCuH]_6$$

Silane	CuCl:KOtBu:PPh$_3$:silane	Yield (%)
PMHS	1:1:1:1.2	47
PMHS	1:1:1:2	68
PMHS	1:1:2:2	82
Et$_3$SiH	1:1:1:1.2	30
Et$_3$SiH	1:1:2:2	31
Ph$_2$SiH$_2$	1:1:2:0.75	53
PhMe$_2$SiH	1:1:2:2	88
[Me$_2$SiH]$_2$	1:1:2:1	80

reactions in benzene or toluene

Unactivated carbon-carbon double bonds are not reduced. So if you have something like this here, a molecule of this kind and you also have both the possibilities, you have a simple double bond, unconjugated double bond and of course a conjugated double bond with the carbonyl group only this will get reduced at this center.

So it is a very useful reagent and since it can be used only on catalytically, if one wants to use in stoichiometric way we can do that, but also catalytic way. And now there have been many studies in which different types of silanes that have been utilized for the reduction of this particular complex in such a way to form the Stryker's reagent.

So in order to form the Stryker's reagent, when the copper chloride potassium tertiary-butoxide, triphenylphosphine and the silane that is used. So this silane is used in 1.2 equivalent. So the ratio is shown here. So if you have 1:1:1:1.2 that means silane is used as 1.2. Then they kept on modifying and you see the effect of that on the yield. So we have a PMHS in this ratio of different reagents.

Then you get 47% and you see the best one is here 1:1:2:2 as ratios. Then you get 82% yield and one can also see that you can get 88% of this when you use this dimethylphenylsilane. So there are several possibilities of this type, where you can use different silane based reducing agents where instead of using molecular hydrogen one can use these and form the corresponding Stryker's reagent.

So it is very clear that we can take a catalytic amount of this and also use any one of these silanes as stoichiometric reagents and these reactions are generally performed in benzene or toluene and they allow reductions to take place in a conjugated fashion.

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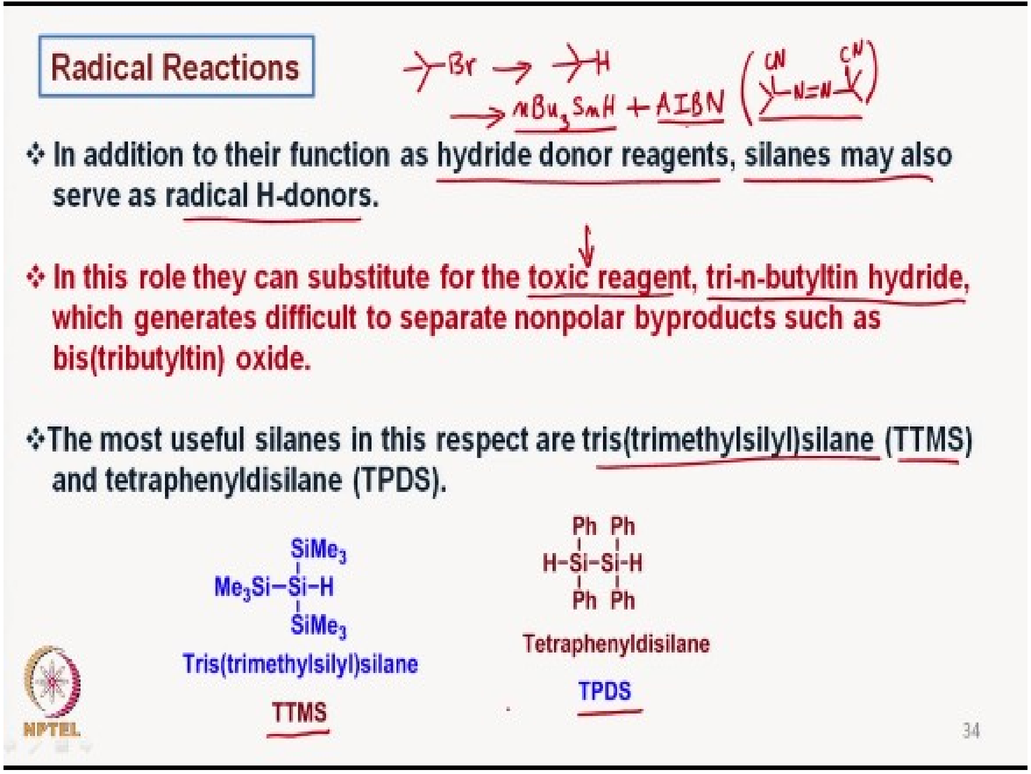

Radical Reactions

- In addition to their function as hydride donor reagents, silanes may also serve as radical H-donors.
- In this role they can substitute for the toxic reagent, tri-n-butyltin hydride, which generates difficult to separate nonpolar byproducts such as bis(tributyltin) oxide.
- The most useful silanes in this respect are tris(trimethylsilyl)silane (TTMS) and tetraphenyldisilane (TPDS).

Tris(trimethylsilyl)silane

TTMS

Tetraphenyldisilane

TPDS

Now we see how this silanes can act as reactions as in the reactions where radicals are involved. In addition to their function as hydride donor silanes also may act as a radical hydrogen donors. In this role, they can substitute for the toxic reagent tri-n-butyltin hydride. Before we proceed further, various kinds of radical based reactions have been carried out particularly reduction.

So if one wants to carry out a reduction, say for example of Br here and if you want to carry out reduction to form H here, what is used is tributyltin hydride as a reagent, as a hydrogen source. In the presence of something called as AIBN which is azoisobutyronitrile, which looks like this. So you have here CN. Then you have this particular azo group. And then you have here CN.

So this is how, this is what is called as azoisobutyronitrile, which we will discuss it later on. So these two combination by heating allow such a reduction to take place and there are many other reactions that occur using, but in these cases, the hydrogen source is basically tributyltin hydride and this is what is considered to be a toxic reagent.

It is also when the reaction occurs with this tributyltin hydride the byproduct which is formed is tributyltin oxide or other tin based products, which are very difficult to remove from the reaction and create problems during the workup of the reaction. So in that respect, people have tried to use tris(trimethylsilyl)silane of this type TTMS or tetraphenyldisilane of this type, tetraphenyldisilane of this type.

So these two reagents have been used in many places where people want to carry out radical based reactions. Radical based reactions have their own utility not only reductions, but they allow also C-C bond formations to take place when radicals are invoked as intermediates.

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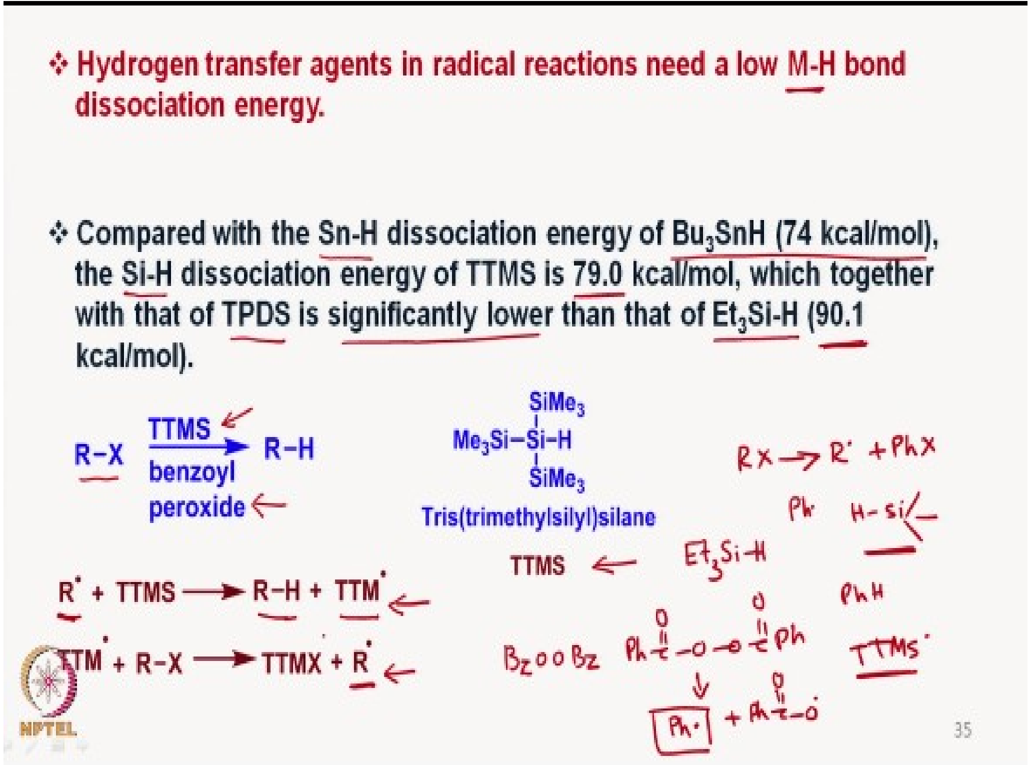

- Hydrogen transfer agents in radical reactions need a low M-H bond dissociation energy.
- Compared with the Sn-H dissociation energy of Bu_3SnH (74 kcal/mol), the Si-H dissociation energy of TTMS is 79.0 kcal/mol, which together with that of TPDS is significantly lower than that of Et_3Si-H (90.1 kcal/mol).

$$R{-}X \xrightarrow[\text{benzoyl peroxide}]{\text{TTMS}} R{-}H$$

Tris(trimethylsilyl)silane

$$R^{\bullet} + \text{TTMS} \longrightarrow R{-}H + \text{TTM}^{\bullet}$$

$$\text{TTM}^{\bullet} + R{-}X \longrightarrow \text{TTMX} + R^{\bullet}$$

Now this hydrogen transfer agents in radical reactions need a low M-H bond dissociation energy. Obviously because we need to do these reactions not at very high temperature. So compared with tin hydrogen dissociation energy of tributyltin hydride which requires 74 kilo calories per mole, the silicon hydrogen dissociation energy or TTMS is approximately 79.

So it is very close which together with that of TPDS which is significantly lower than that of triethylsilane. So if we compare the reducing ability of this versus a triethylsilane, so the triethylsilane based reagent requires high energy. That is the reason why this TTMS tris(triethylsilane) or TPDS that is tetraphenyldisilane is used.

Now what does happen is that if you take an R-X where X is halide for example, and if you use TTMS in the presence of benzoyl peroxide, then you generate R dot from here. And basically what is happening is that benzoyl peroxide which is benzoyl peroxide or we can write it something like this. You have O-O-C=O phenyl. When this is heated it eventually breaks to phenyl radical or phenyl C=O-O radical.

But eventually it forms this phenyl radical which can take the X from there. So you have here RX that leads to the formation of R dot plus PhX here. So this is how one possibility can be. The other possibility is that here Ph dot takes the hydrogen from the silicon of the PMHS of this TTMS and form PhH and TMS, TTMS or TTMS dot.

So and therefore, this the TTMS dot can of course react with R-X to form R and then the R will react with remaining TTMS to form R-H and TTM radical. This TTM radical will take the X from here and regenerate R dot. So essentially what is happening is that benzoyl peroxide initiates the reaction to generate a TTMS radical or TTM radical that takes the X from there, generate R dot.

And the remaining TTMS then reacts with the R dot to get to the product which is R-H and then regenerate the TTM radical which re-reacts with the R-X to generate R dot. So this is how the reaction keeps on taking place.

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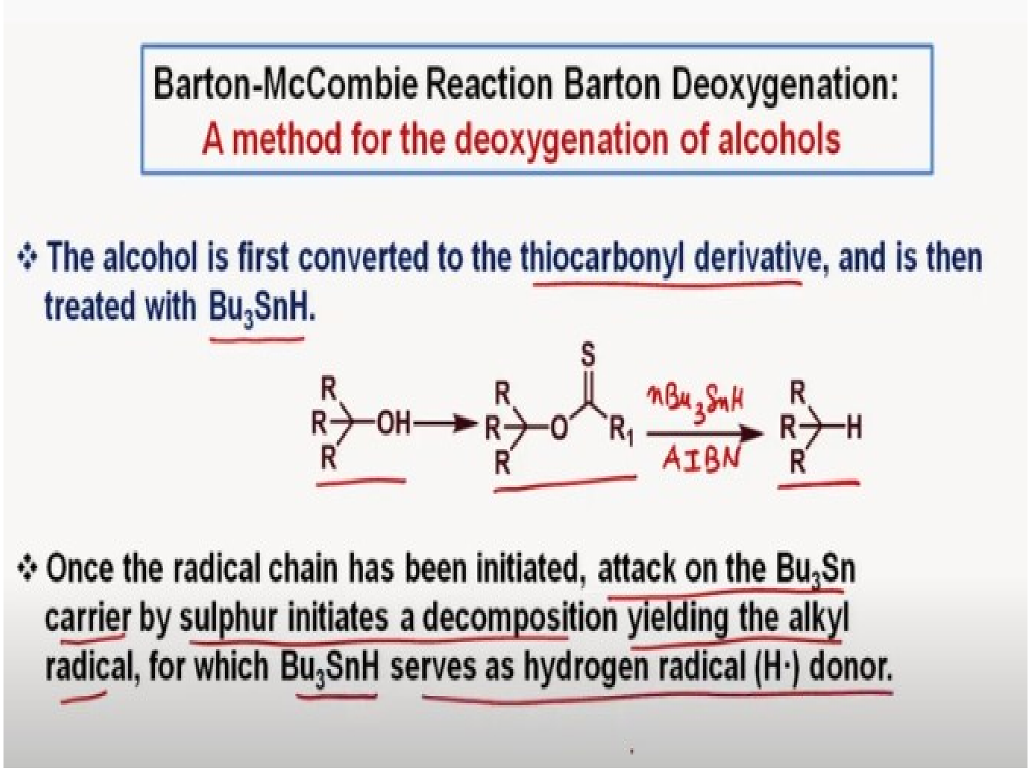

Barton-McCombie Reaction Barton Deoxygenation:
A method for the deoxygenation of alcohols

- The alcohol is first converted to the thiocarbonyl derivative, and is then treated with Bu_3SnH.

- Once the radical chain has been initiated, attack on the Bu_3Sn carrier by sulphur initiates a decomposition yielding the alkyl radical, for which Bu_3SnH serves as hydrogen radical (H·) donor.

Now there is another reaction which is called Barton-McCombie reaction or Barton deoxygenation. It is a method for the deoxygenation of alcohols. So if we have an alcohol of this type, we can convert into a thiocarbonyl derivative, which is how it looks like. And then that can be reacted with tributyltin hydride under conditions of similar type where we use tributyltin hydride and its AIBN, which I discussed earlier.

And it allows the formation of the corresponding deoxygenated product. Once the radical chain has been initiated attack on the tributyltin carrier by sulfur initiates decomposition yielding the alkyl radical for which this serves as hydrogen radical donor. We will see how the reaction takes place.

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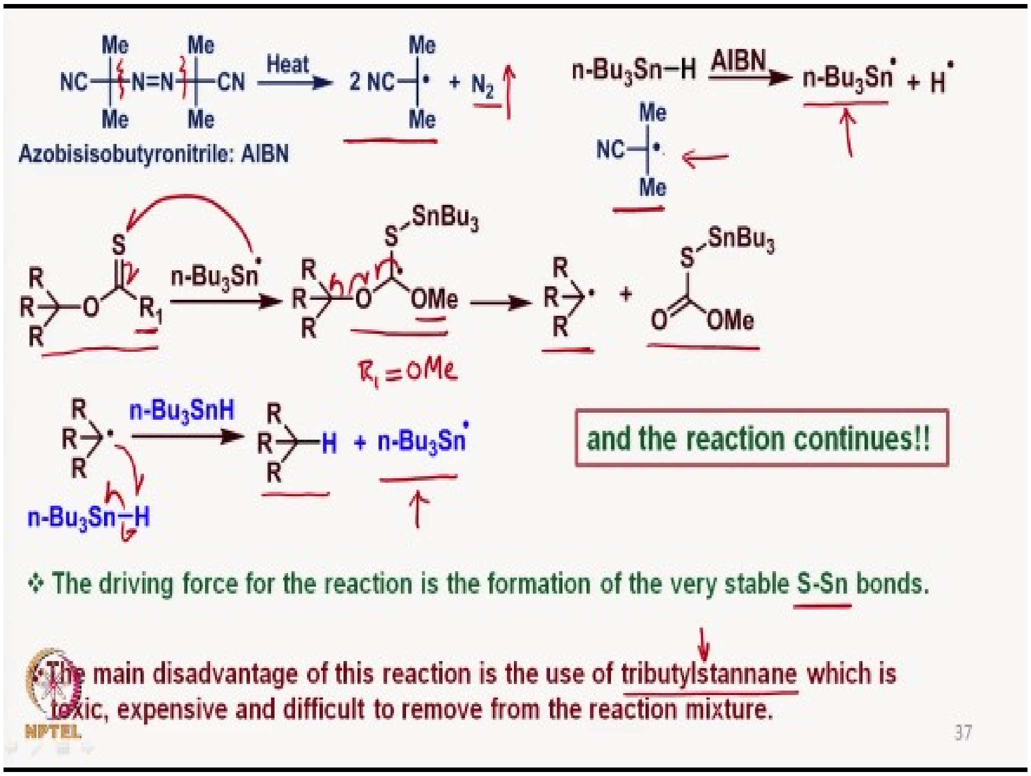

❖ The driving force for the reaction is the formation of the very stable S-Sn bonds.

❖ The main disadvantage of this reaction is the use of tributylstannane which is toxic, expensive and difficult to remove from the reaction mixture.

This is what is azobisisobutyronitrile where as you when you heat it, it breaks homolytically from here to form this particular radical intermediate and the nitrogen goes off from the reaction. When this radical reacts with the tributyltin hydride in a similar fashion as we discussed earlier that the benzoyl peroxide gives a phenyl radical that reacts with the TTMS to form the corresponding radical.

So similarly, this tributyltin hydride reacts to form this tributyltin radical. And of course, this radical will couple with the hydrogen dot and will go away. Now this tributyltin radical then reacts with the thiocarbonyl compound in this particular fashion, in this way and generates an intermediate of this kind where R 1 is O-Methyl, if R 1 is O-Methyl.

Now this decomposes in this fashion here like this and forms this as a byproduct and then you generate a radical of this kind. This radical then reacts further with tributyltin hydride generating this reduced product and you generate the same tributyltin radical which was generated here. So it is exactly similar to what we saw, where TTMS and benzoyl peroxide was used. Instead of benzoyl peroxide, here we are using AIBN which is generating a radical like this.

So the driving force, of course here you take the radical form here and then you generate this tributyltin radical. The driving force for the reaction is the formation of the stable sulfur tin bond. The main disadvantage of this reaction, the only problem that with this reaction is the as I earlier mentioned is the use of this tributyltin based molecules which is difficult to remove and toxic, expensive.

And so there are problems and that is the reason why some modifications have been carried out.

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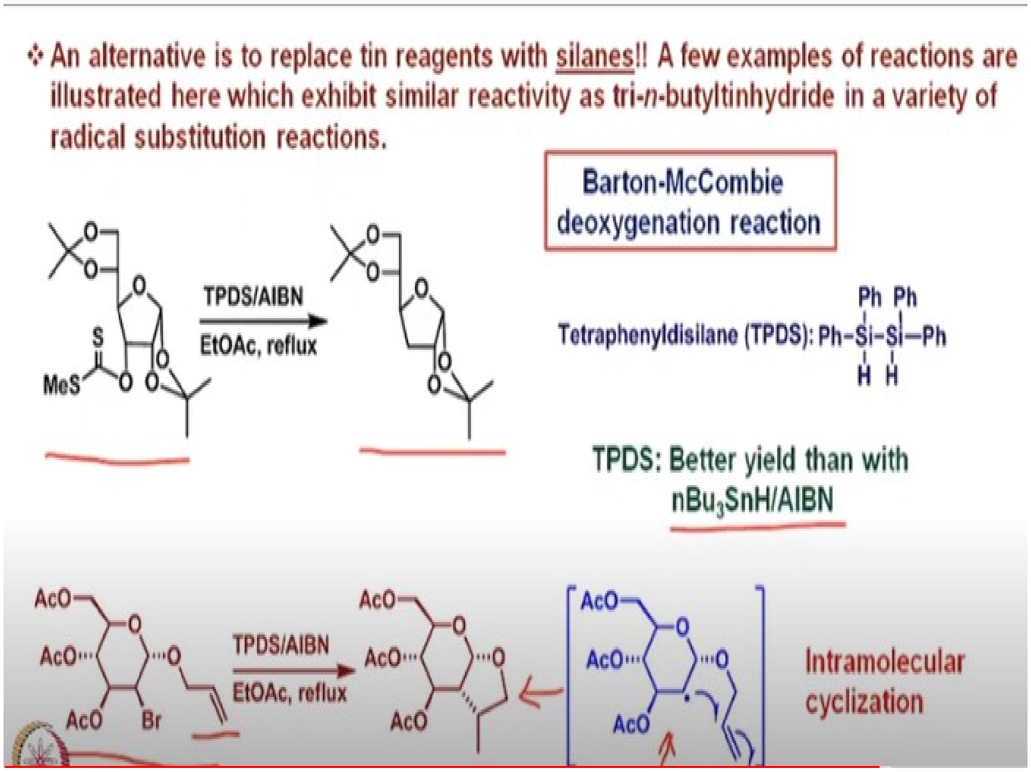

- An alternative is to replace tin reagents with silanes!! A few examples of reactions are illustrated here which exhibit similar reactivity as tri-*n*-butyltinhydride in a variety of radical substitution reactions.

Barton-McCombie deoxygenation reaction

Tetraphenyldisilane (TPDS): $\mathrm{Ph{-}\overset{Ph}{\underset{H}{Si}}{-}\overset{Ph}{\underset{H}{Si}}{-}Ph}$

TPDS: Better yield than with $n\mathrm{Bu_3SnH/AIBN}$

Intramolecular cyclization

An alternative is to replace tin reagents with silane based reagents. A few examples of reactions are shown here, which exhibit similar reactivity as tributyltin hydride in a variety of radical reactions. An example of the Barton-McCombie deoxygenation reaction using tetraphenyldisilane that is TPDS whose structure is here as shown.

Now TPDS is a better reagent than tributyltin hydride, not only in terms of toxicity, but also it gives better yield. So if we take an example of this kind, which is sugar derived xanthate then with TPDS, AIBN combination in refluxing ethyl acetate, the deoxygenation leads to the formation of this particular product.

Now not only xanthates can be reduced to the corresponding deoxygenated product, but it is also possible to generate a radical if we have a halide, carbon halide bond can be cleaved to the corresponding radical as it is shown here. So if we start with a brominated molecule like this and react with TPDS, AIBN combination in refluxing ethyl acetate what we first generate is of course this radical.

If this double bond was not present, then of course this radical would have taken the hydrogen and then we could have got the correspondingly reduced product. However, since there is a properly oriented double bond, which is present in the molecule, therefore this radical undergoes intramolecular cyclization to form this type of bicyclic molecule.

So it is also possible not only that we can reduce the carbon halide bond, but also we can allow the radical to undergo a intramolecular cyclization. So this kind of C-C bond formations are also possible and thus tetraphenyldisilane or similar types of silane reagents make a better alternative than the tributyltin hydride.

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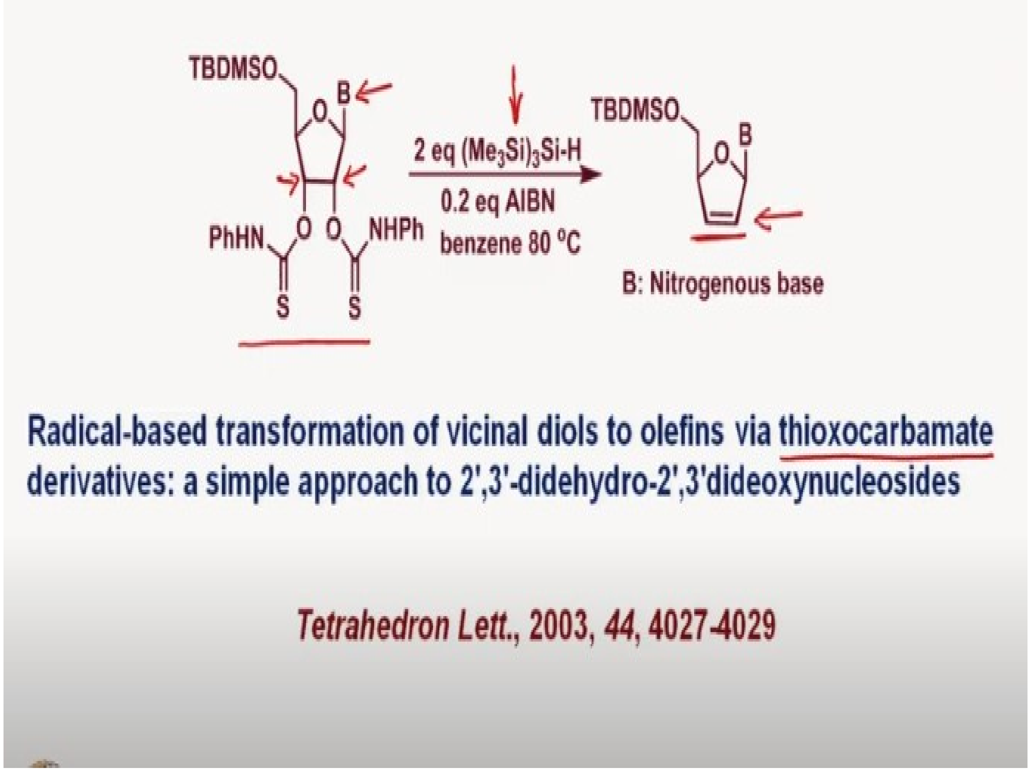

Radical-based transformation of vicinal diols to olefins via thioxocarbamate derivatives: a simple approach to 2',3'-didehydro-2',3'dideoxynucleosides

Tetrahedron Lett., 2003, *44*, 4027-4029

We can also use this type of substrates where we have this particular reagent. This is TTMS and AIBN and of course here base this is like a different types of nucleic bases and we can then have two radicals that are going to form, one here and one here. They couple or they form the corresponding double bond.

So radical based transformation of vicinal diols to olefins this is this can come from the corresponding diol via thioxocarbamate derivative and that leads to the formation of this. So you can start with the corresponding sugar based molecule and carry out the reaction which has been published in 2003.

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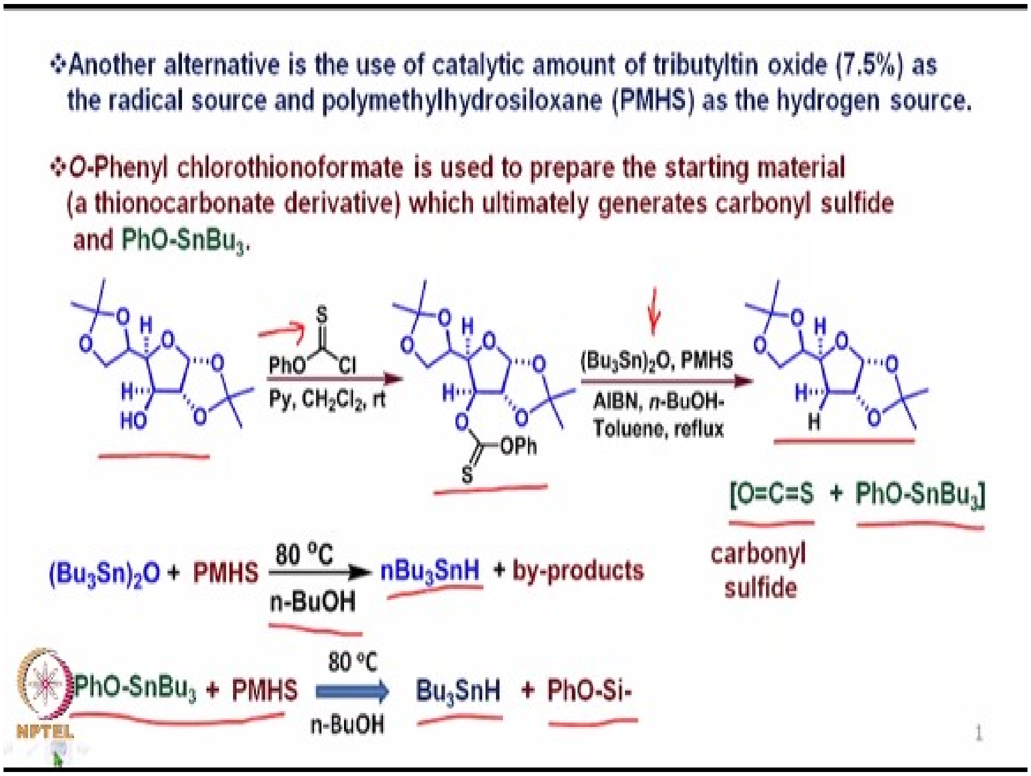

- Another alternative is the use of catalytic amount of tributyltin oxide (7.5%) as the radical source and polymethylhydrosiloxane (PMHS) as the hydrogen source.
- O-Phenyl chlorothionoformate is used to prepare the starting material (a thionocarbonate derivative) which ultimately generates carbonyl sulfide and PhO-SnBu$_3$.

[O=C=S + PhO-SnBu$_3$]

carbonyl sulfide

$$(Bu_3Sn)_2O + PMHS \xrightarrow[\text{n-BuOH}]{80\ ^\circ C} nBu_3SnH + \text{by-products}$$

$$PhO\text{-}SnBu_3 + PMHS \xrightarrow[\text{n-BuOH}]{80\ ^\circ C} Bu_3SnH + PhO\text{-}Si\text{-}$$

Now another alternative is the use of the catalytic amount of tributyltin oxide approximately 7.5% as the radical source and polymethylhydrosiloxane PMHS as the hydrogen source. Now what is done is that the substrate which is a hydroxy compound can be converted to the corresponding thionocarbonate derivative like this by reacting with phenyl chlorothionoformate like this in the presence of pyridine.

And we can react them this particular thionocarbonate derivative with tributyltin oxide in the presence of PMHS and of course AIBN but the solvent n-butanol is a very important solvent and a mixture of n-butanol and toluene is used and it is refluxed in that particular medium to form this deoxygenated product.

Now what happens is you get a side product as this carbonyl sulfide which is a gas which goes away and of course, we get this phenoxy tributyltin derivative. So this tributyltin oxide actually reacts with PMHS at 80 degrees in n-butanol to release the tributyltin hydride and that is what is basically reacting here in this particular stage in the presence of AIBN to generate tributyltin radical which of course interacts with this thionocarbonate and leads to the deoxygenation.

Now this byproduct which is phenoxy tributyltin derivative then reacts with PMHS again at 80 degrees in n-butanol and releases tributyltin hydride and of course there will be silane derivative here. So this is how the reaction is perceived and it gives an alternative to the use of stoichiometric amount of tin hydride based compound.

So we will stop it at this stage and in the next class we will take the radical based reactions because they are very close to these and therefore, how the radical based reactions can permit not only reduction, but also C-C bond formation in many cases. We will take up that next time. Till then you can go over whatever I discussed in today's class. Thank you and see you next time.