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

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Lecture - 33
Tributyltinhydride (n-Bu3SnH) Based Radical Based Reductions & C-C Bond Formations

Hello everyone. I would like to welcome you all for today's lecture. And before we proceed for the remaining part of the topics, we would like to recap of the last lecture in brief, as I have shown it here.

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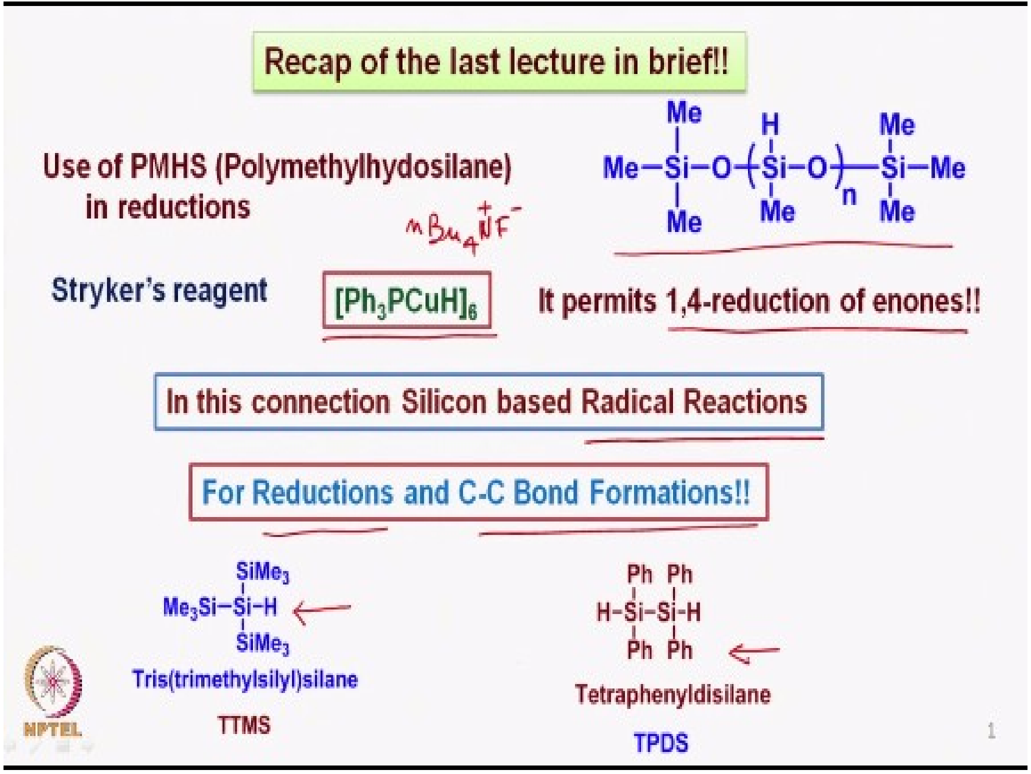

Recap of the last lecture in brief!!

Use of PMHS (Polymethylhydosilane) in reductions

$Me-Si(Me)_2-O-(Si(H)(Me)-O)_n-Si(Me)_2-Me$

$nBu_4\overset{+}{N}\overset{-}{F}$

Stryker's reagent $[Ph_3PCuH]_6$ It permits 1,4-reduction of enones!!

In this connection Silicon based Radical Reactions

For Reductions and C-C Bond Formations!!

$(Me_3Si)_3Si-H$

Tris(trimethylsilyl)silane

TTMS

$H-SiPh_2-SiPh_2-H$

Tetraphenyldisilane

TPDS

That what we learnt in the last class was the use of polymethylhydrosilane. This is the structure and we studied its reactivity in the reductions of carbonyl compounds in the presence of tetra-butylammonium fluoride. Then, we also looked at the reactivity of Stryker's reagent, which is what it is and it permits as you will remember, 1,4-reduction of enones because that is a very important reaction.

And in this connection, we also saw the effect of silicon based reducing agents, both this triethylsilane and also polymethylhydrosilane. Then, we also looked at the silicon based radical reactions. In that context, we saw both reductions using silane based reagents and also C-C bond formations using radical based chemistry.

In that context, we introduced this tris(trimethylsilyl)silane, which is a sterically hindered hydrogen containing silane and also tetraphenyldisilane, which is also a very nice reducing agent and also it allows C-C bond formation to take place.

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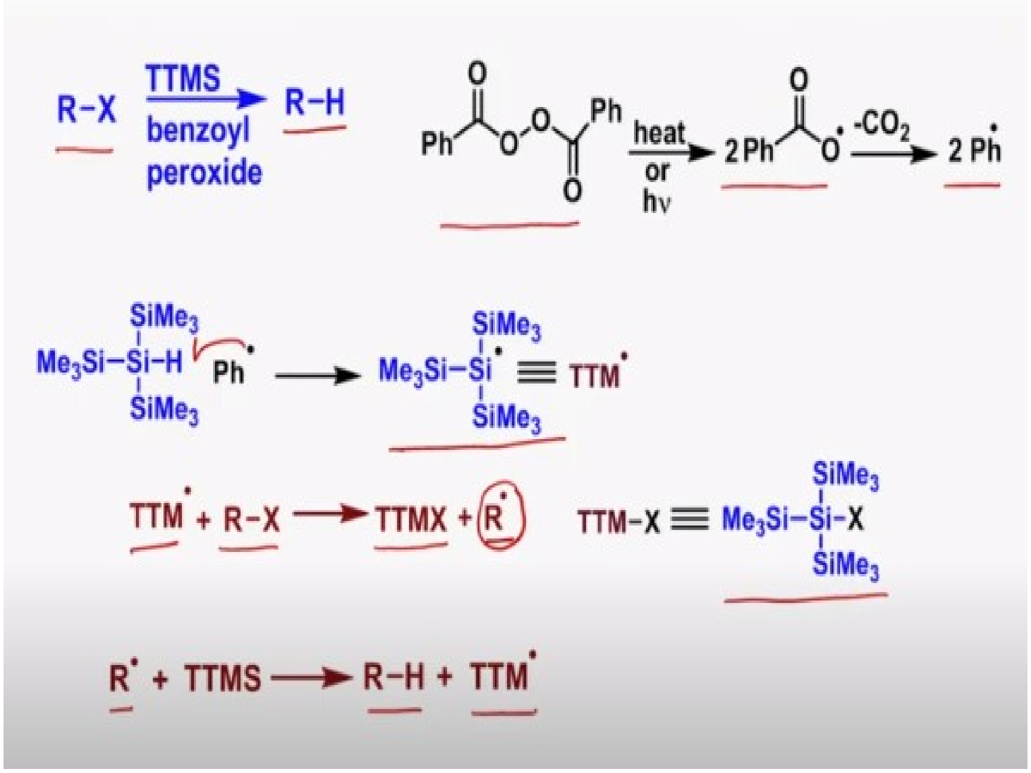

Now we looked at the reduction of halides like R-X where X can be especially bromine and iodine. And then in the presence of benzoyl peroxide it gives the corresponding R-H basically replacing X-R-R bond by H-R bond. What happens is that the benzoyl peroxide as I discussed last time upon heating or photolytic conditions, decomposes eventually to phenyl radical by the loss of carbon dioxide.

That phenyl radical then picks up the hydrogen from here generating this TTM radical. This TTM radical then reacts with the R-X to form R dot which is what is important and then TTM-X which looks like this, that means the silicon X bond is formed and generate this R dot. This R dot then reacts with TTMS that is tris(trimethylsilane) which provides hydrogen and it forms the R-H which is the reduced product and of course, we recover the TTM radicals.

So this is how the chain continues and we have the reduction of R-X to R-H.

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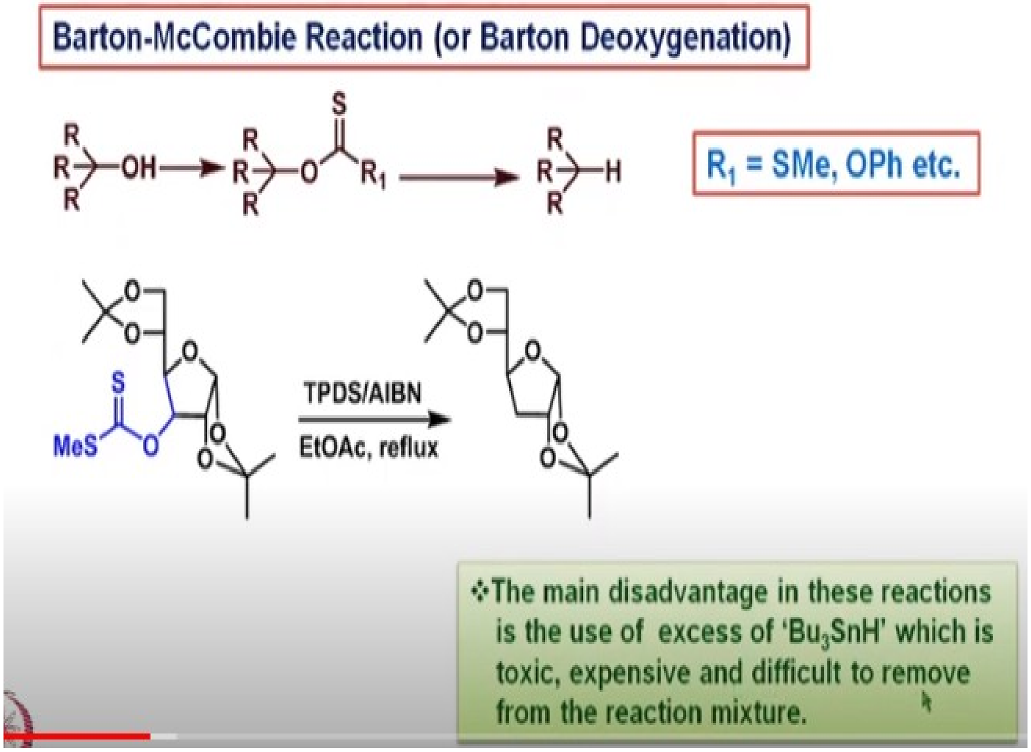

Barton-McCombie Reaction (or Barton Deoxygenation)

R_1 = SMe, OPh etc.

- The main disadvantage in these reactions is the use of excess of 'Bu_3SnH' which is toxic, expensive and difficult to remove from the reaction mixture.

Then we also looked at Barton-McCombie reaction or it is also known as Barton deoxygenation reaction in which we can convert a hydroxy compound to the corresponding hydrocarbon. Particularly it is very useful for the conversion of a tertiary hydroxy compound to the corresponding hydrocarbon. That means, the carbon hydroxy bond is replaced by the carbon hydrogen bond going via the corresponding thiocarbonate compound of this kind here where R 1 is S-Methyl, O-phenyl etc.

We made use of that in the conversion of a sugar derived thiocarbonyl compound like this to the corresponding deoxygenated product of this type here, but here we use tetraphenyldisilane as a reagent in place of the tributyltin hydride. However, wherever we use tributyltin hydride as a reagent, one of the main disadvantage is that we have to use excess of tributyltin hydride, which is toxic, expensive and very difficult to remove from the reaction mixture.

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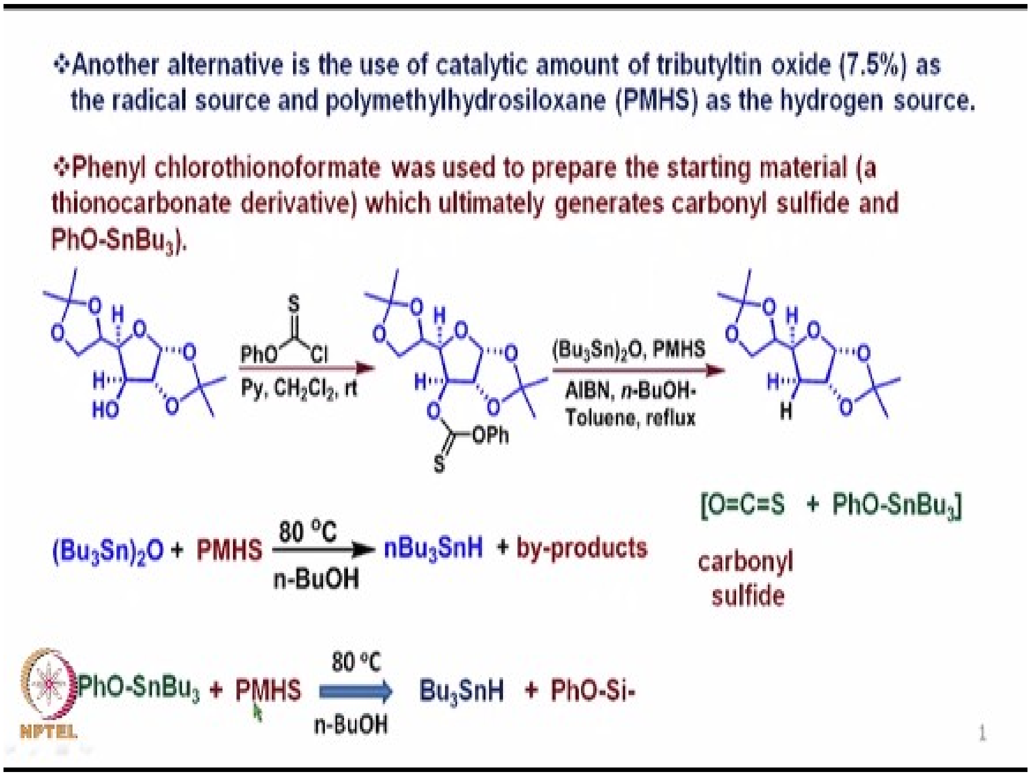

- Another alternative is the use of catalytic amount of tributyltin oxide (7.5%) as the radical source and polymethylhydrosiloxane (PMHS) as the hydrogen source.
- Phenyl chlorothionoformate was used to prepare the starting material (a thionocarbonate derivative) which ultimately generates carbonyl sulfide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

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

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

It is in that context I also mentioned another alternative usage of catalytic amount of tributyltin oxide that is 7.5% as a radical source in the presence of polymethylhydrosiloxane as the hydrogen source. What I mentioned last time was that we can take a hydroxy compound like this, which can be converted to the corresponding thionocarbonate derivative by using this reagent phenyl chlorothionoformate in the presence of pyridine.

And then of course, we use catalytic amount of tributyltin oxide in the presence of PMHS and AIBN of course and n-butanol as one of the very important solvents in toluene and refluxing condition that allow the deoxygenation to take place to form this particular product. Of course, the side products turn out to be carbonyl sulfide which goes away and this tributyltinphenoxy compound.

Basically what happens in these reactions is the tributyltin oxide reacts with PMHS to form the tributyltin hydride, which then of course, in the presence of AIBN forms tributyltin radical and that leads to the formation of the deoxygenated product from this thionocarbonate derivative. And the side product which has come out from the tin based reagent and that is phenoxytributyltin derivative.

Then that reacts with PMHS to regenerate the tributyltin hydride. So and of course, there will be some silane derivative. So this is how the catalytic amount of tributyltin oxide is utilized to kind of carry out the reaction for the deoxygenation of alcohol to the corresponding hydrocarbons under these conditions.

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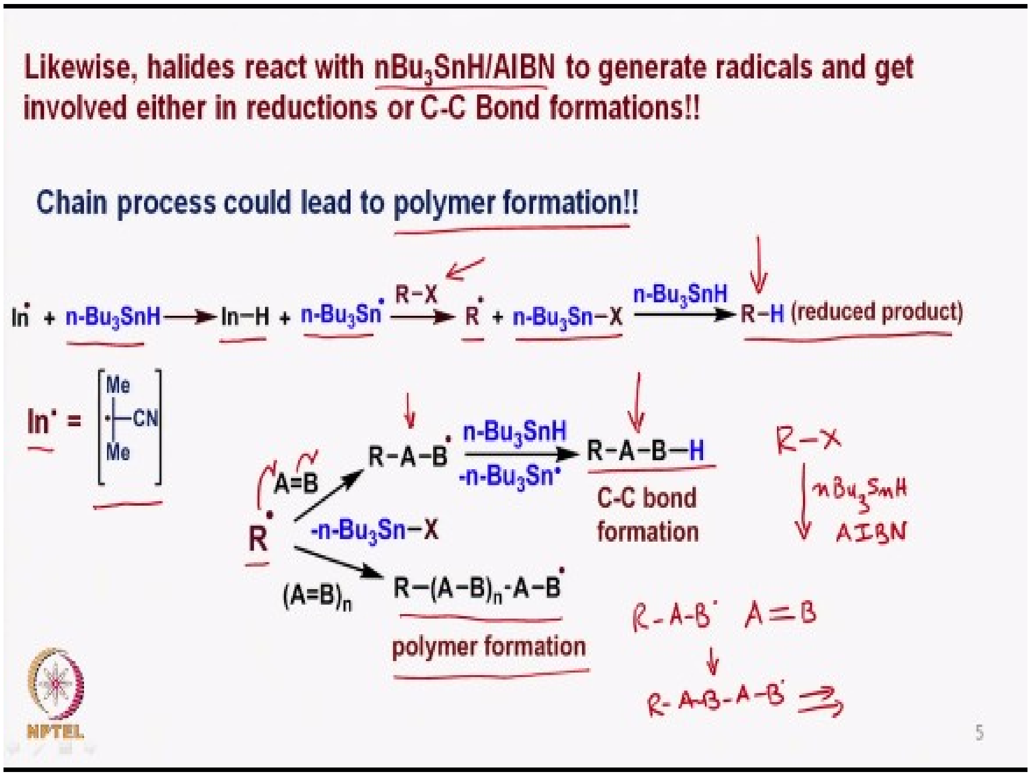

Likewise, halides react with nBu_3SnH/AIBN to generate radicals and get involved either in reductions or C-C Bond formations!!

Chain process could lead to polymer formation!!

$$In^{\bullet} + n\text{-}Bu_3SnH \longrightarrow In\text{-}H + n\text{-}Bu_3Sn^{\bullet} \xrightarrow{R-X} R^{\bullet} + n\text{-}Bu_3Sn\text{-}X \xrightarrow{n\text{-}Bu_3SnH} R\text{-}H$$

(reduced product)

$In^{\bullet} = \left[Me\text{-}\overset{\bullet}{C}(CN)\text{-}Me \right]$

$$R^{\bullet} \xrightarrow[-n\text{-}Bu_3Sn-X]{A=B} R\text{-}A\text{-}B^{\bullet} \xrightarrow[-n\text{-}Bu_3Sn^{\bullet}]{n\text{-}Bu_3SnH} R\text{-}A\text{-}B\text{-}H$$

C-C bond formation

$$R^{\bullet} \xrightarrow{(A=B)_n} R\text{-}(A\text{-}B)_n\text{-}A\text{-}B^{\bullet}$$

polymer formation

$$R\text{-}X \xrightarrow{nBu_3SnH,\ AIBN}$$

$$R\text{-}A\text{-}B^{\bullet} \quad A=B$$
$$\downarrow$$
$$R\text{-}A\text{-}B\text{-}A\text{-}B^{\bullet} \Rightarrow$$

Now likewise halides also react with tributyltin hydride and AIBN to generate radicals and get involved either in reductions or C-C bond formations. Now this chain process could lead to the polymer formation. Since, we are discussing about the radical based reactions and reductions at the same time it is possible that we can look at the C-C bond formation using the radical based chemistry.

So what is happening is that, in these case is, if you have an R-X here and you reacted with tributyltin hydride in the presence of radical initiator like AIBN, as we discussed last time it would form this particular radical which is what is we call it as initiator dot.

That interacts with the tributyltin hydride and it forms a In-H which is what is this particular molecule or radical interacts with the hydrogen and forms this and releases the tributyltin radical which interacts with the R-X to be reduced and then R dot is formed and tributyltin X is released and then this radical interacts with the tributyltin hydride to go to the reduced products.

Now this is something that we had also seen similar to silicon based reactions. Now what can happen is, this particular R dot can react with an olefin of this type where there is a double bond between A and B. And when this radical attacks onto this, you can generate a another radical here like after the C-C bond formed, which then can abstract the hydrogen radical and release this particular molecule which is what is a C-C bond formed molecule.

On the other hand, if this radical interacts with the double bond and there is no tributyltin hydride to stop the reaction, then we can expect a polymer formation of this kind because this radical which is formed R-A-B dot that again reacts with next molecule to form R-A-B-A-B dot. That continues further to form a polymer.

So such polymerizations are known in radical based chemistry for example polyethylene or many such kind of molecules are formed basically by such reactions. But then from the organic synthesis point of view, we also need to have both the alternatives that is either we reduce the R-X to R-H or we have the stopping of the reaction at this stage when one C-C bond is formed.

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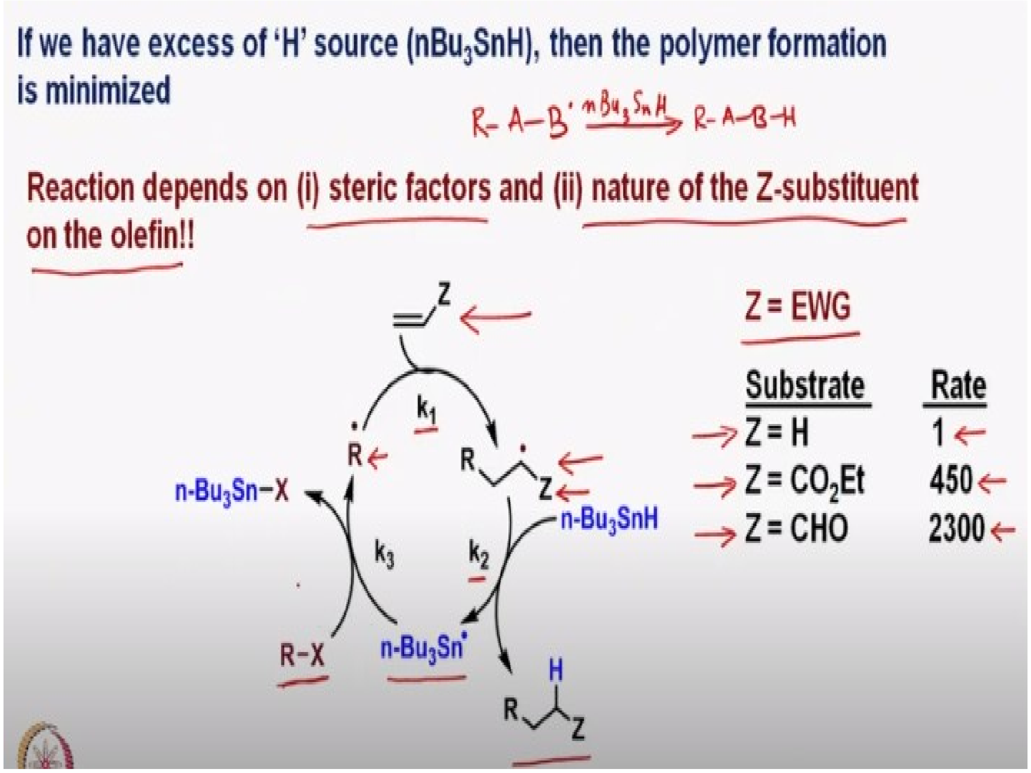

If we have excess of 'H' source (nBu_3SnH), then the polymer formation is minimized

$R\text{-}A\text{-}B^{\bullet} \xrightarrow{nBu_3SnH} R\text{-}A\text{-}B\text{-}H$

Reaction depends on (i) steric factors and (ii) nature of the Z-substituent on the olefin!!

Z = EWG

Substrate	Rate
Z = H	1
Z = CO_2Et	450
Z = CHO	2300

If we have excess of hydrogen source, then the polymer formation could be minimized as you can understand that, if we have say R-A and B dot form, in order for this reaction to get arrested, we need to have tributyltin hydride in a sufficient quantity, so that that reacts to form the corresponding terminated product after one C-C bond is formed. What has been done is that a large number of studies have been carried out for these kinds of reactions.

And it is found that the reaction depends on steric factors and also the nature of the substituent Z on the olefin. What is found that if one takes an olefin of this kind where there is one Z substituent and if Z happens to be an electron withdrawing group then the formation of the first C-C bond could be arrested.

See, what is found is that if Z is H the rate is if it is considered as 1 then if you take ester as that Z electron withdrawing group, the rate turns out to be 450. And if some more electron withdrawing group like aldehyde, then the rate is 2300. So basically what it means that the reaction can be arrested at the first C-C bond formation and reaction could be quenched by tributyltin hydride if we have electron withdrawing group attached to the double bond.

So if we take a catalytic cycle, then we have this R dot which is formed from this R-X and if this R dot reacts with the olefin then we generate another radical here, which is situated alpha to the Z group, next to the Z group.

And if that has a rate k 1 and then the k 2 is the one in which the tributyltin hydride interacts and it releases the end product like this, where hydrogen is attached to the carbon, where there was a radical alpha to the Z group. And of course, then you release tributyltin radical and then that reaction continues.

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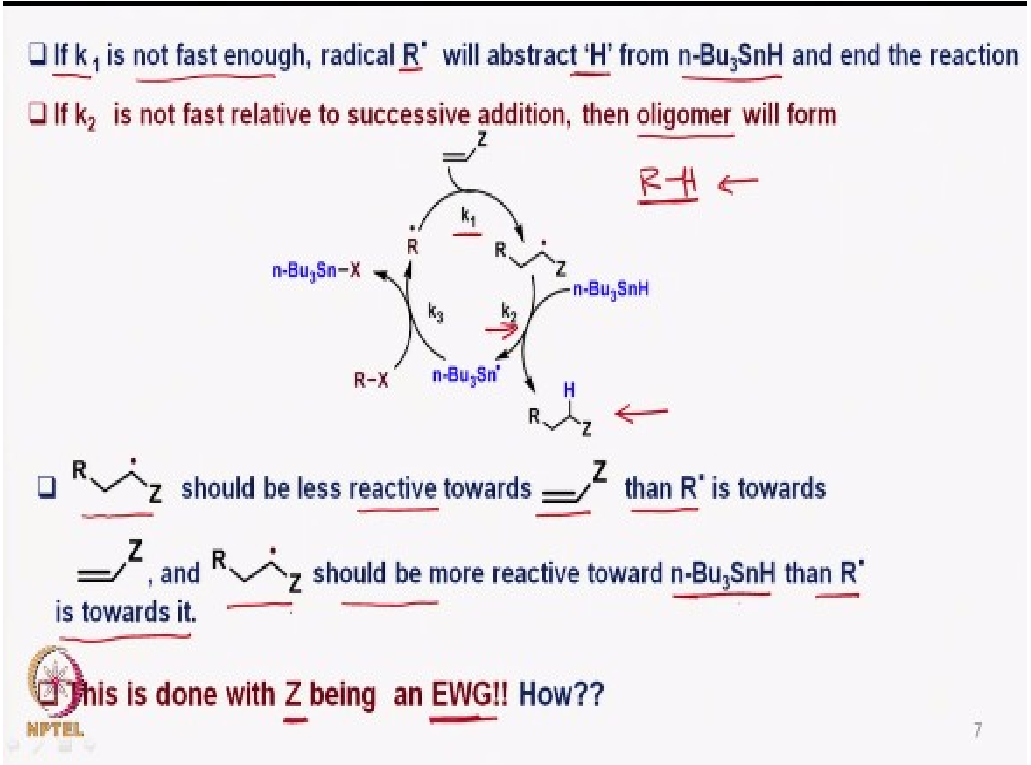

❑ If k$_1$ is not fast enough, radical R$^{\bullet}$ will abstract 'H' from n-Bu$_3$SnH and end the reaction

❑ If k$_2$ is not fast relative to successive addition, then oligomer will form

❑ should be less reactive towards than R$^{\bullet}$ is towards , and should be more reactive toward n-Bu$_3$SnH than R$^{\bullet}$ is towards it.

❑ This is done with Z being an EWG!! How??

So in this respect what has been found that if k 1, which is shown again here, if k 1 is not fast enough, then if this particular rate is not fast enough, then R dot obviously will abstract the hydrogen from tributyltin hydride and the reaction will end in the reduction and this is the product that is going to form.

But if k 2 is not fast relative to successive addition, so if this particular rate here is not fast enough, then what will happen is this radical will not get quenched, but it will then react further and then oligomer or the polymer will form. So what is important is that this radical should be less reactive towards the original double bond than R dot is towards this.

That means, this particular radical should not react with the next olefin, but then that particular rate should be less than the rate in which the R dot is reacting with the double bond. And then this particular one should be more reactive towards the tributyltin hydride than R dot is towards it. Very clear that this should react faster with tributyltin hydride than R dot reacts with tributyltin hydride.

Because if R dot reacts with tributyltin hydride you will get the R-H. But if this reacts with tributyltin hydride, then you would get the reduced product that is this here, the reduced after the C-C bond formation. So this is how it is done by Z group being an electron withdrawing group. Now exactly why and how the electron withdrawing group allows such a reaction to occur?

That means to stop the reaction after the first C-C bond has formed and then the reaction is arrested.

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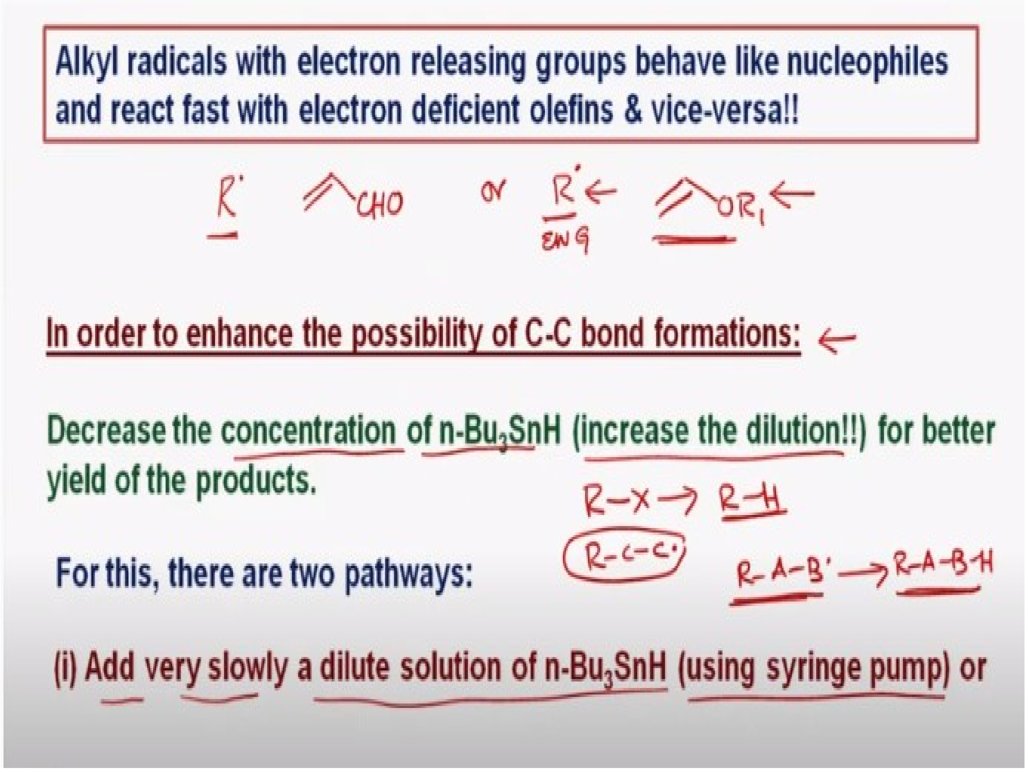

Alkyl radicals with electron releasing groups behave like nucleophiles and react fast with electron deficient olefins & vice-versa!!

$R^{\cdot}$ CHO or $R^{\cdot} \leftarrow$ EWG $OR_1 \leftarrow$

In order to enhance the possibility of C-C bond formations: ←

Decrease the concentration of n-Bu_3SnH (increase the dilution!!) for better yield of the products.

$R-X \rightarrow R-H$

For this, there are two pathways:

$R-C-C^{\cdot}$ $R-A-B^{\cdot} \rightarrow R-A-B-H$

(i) Add very slowly a dilute solution of n-Bu_3SnH (using syringe pump) or

What is found is that alkyl radicals with electron releasing groups behave like nucleophiles and react fast with electron deficient olefins and vice versa. So suppose if you have say R dot, which is a carbon radical and it behaves more like a nucleophile and that reacts with say you have an electron withdrawing group such as CHO attached to the olefin then this reacts faster.

And or you have a radical which is having electron withdrawing group here or electron deficient radical then it reacts faster with say you have an electron rich olefin. That is how it is vice versa. Alkyl radicals with electron releasing groups behave like nucleophiles and react fast with electron deficient olefins and electron withdrawing groups which they are attached to the radicals they react with electron rich olefins.

Now in order to enhance the possibility of C-C bond formation and stopping after the first C-C bond has formed, what needs to be done is that and also at the same time to make sure that the reduction that is R-X does not get reduced to R-H this could be one competing reaction, but what we want is a C-C bond formation. So we need to have this particular bond to be formed or as we wrote earlier then you have A and B here.

So basically we want to stop the reaction after this radical is formed which then quenched with tributyltin hydride to form this. So the competition is between this and this formation. For that you have to decrease the concentration of tributyltin hydride. That means, the concentration decreasing means the in the solution of the reaction, you increase the dilution.

If we increase the dilution that means, the concentration of tributyltin hydride has decreased. Now for this there are two pathways. One is to add very slowly a dilute solution of tributyltin hydride. That means at a particular time, the amount of tributyltin hydride, which is present in the reaction should be as less as possible. And this is done using syringe pump. It is a kind of device.

It is a pump in which you take a very dilute solution of the tributyltin hydride and time it out to add very tiny drop in say over a period of three minutes or five minutes you can work it out and add very slowly drop wise over a period of say two hours or three hours so that the concentration of the tributyltin hydride at any time is very less. Of course, you have to use more than one equivalent of the tributyltin hydride.

But then it is put it in a solution which is very dilute solution so that the possibility of reduction is reduced.

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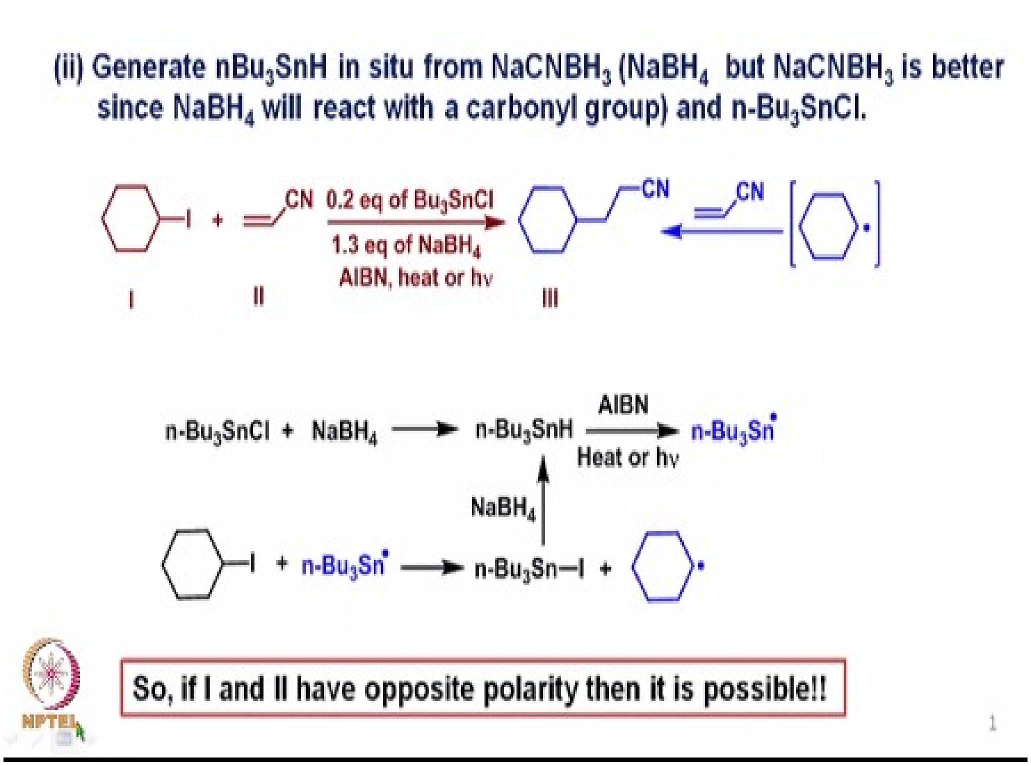

(ii) Generate nBu_3SnH in situ from $NaCNBH_3$ ($NaBH_4$ but $NaCNBH_3$ is better since $NaBH_4$ will react with a carbonyl group) and $n\text{-}Bu_3SnCl$.

So, if I and II have opposite polarity then it is possible!!

One can also generate tributyltin hydride in situ by using sodium cyanoborohydride or even sodium borohydride. But sodium cyanoborohydride is a better alternative than sodium borohydride because sodium borohydride does react with a carbonyl group. And along with the sodium cyanoborohydride or sodium borohydride one can use tributyltin chloride in catalytic amount.

So what exactly happens is the catalytic amount of tributyltin chloride reacts with say sodium borohydride or sodium cyanoborohydride to make the corresponding tributyltin hydride and this tributyltin hydride then, under the conditions were we use AIBN as a catalytic amount and of course, we either heat or we photolyze the reaction medium and then of course, we generate the tributyltin radical.

Now this tributyltin radical will then abstract the iodine from here as I have shown in here to generate a cyclohexyl radical and this cyclohexyl radical will add on to the acrylonitrile to form the corresponding C-C bond.

So basically, what is happening is that during the process, when we regenerate the tributyltin iodide from the starting material, then of course this tributyltin iodide is then reduced with sodium borohydride, which is used in more than one equivalent as shown here is 1.3 equivalents of sodium borohydride.

So this is how by using catalytic amount of tin material, tin based starting reagent and of course using excess of reducing agent like sodium borohydride or sodium cyanoborohydride can be made use of particularly to avoid the generation of a large amount of tributyltin hydride or a large amount of tin impurities in the reaction mixture, which are difficult to remove.

Now in addition, if we have then I and II having opposite polarity then it is possible that the reaction will be facile because they complement each other in terms of electronics.

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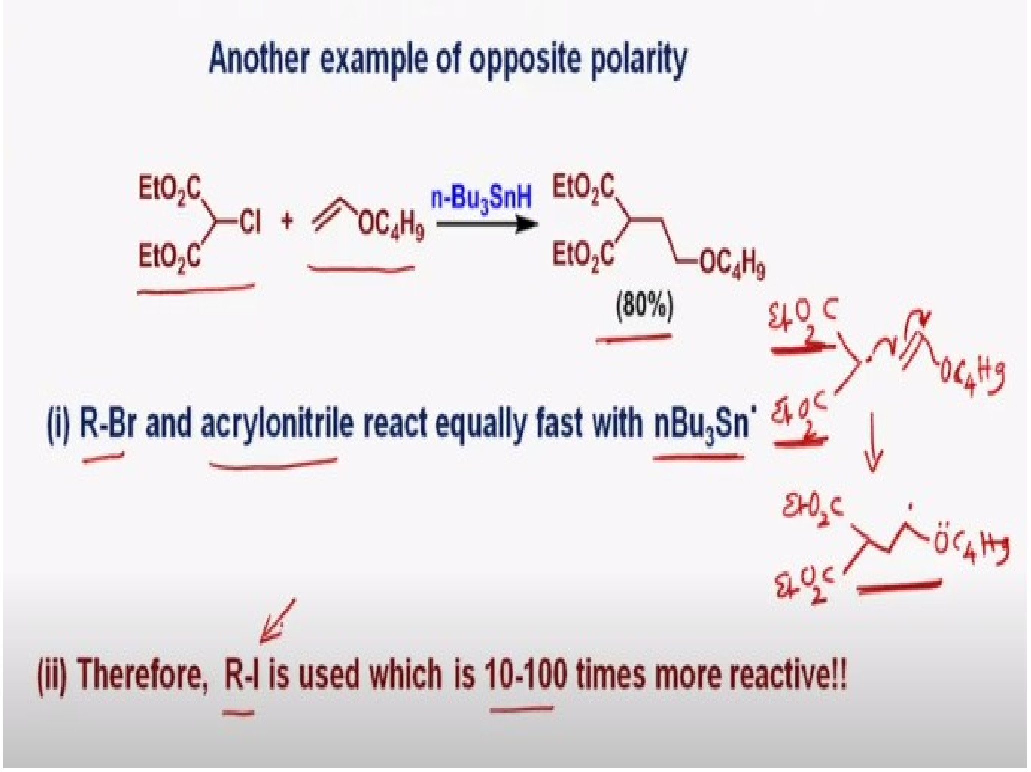

Another example of opposite polarity

(i) R-Br and acrylonitrile react equally fast with nBu$_3$Sn$^{\cdot}$

(ii) Therefore, R-I is used which is 10-100 times more reactive!!

Now another example of opposite polarity can be seen that we have a halide in which there are two electron withdrawing groups like esters are attached and we have this electron rich double bond. So it is clear that when tributyltin hydride reacts with this particular chloride you generate this radical here. And this radical is having two electron withdrawing groups.

Therefore, it is much easier for it to react with electron rich double bond where the radical is generated at the center. So basically what is formed is this type of molecule in which you have a radical which is now next to the oxygen and therefore, it is a stabilized radical because of the lone pair of electrons on the oxygen here. So this is how the example of opposite polarity can be taken up.

And yes, you can see the yield is very good, 80%. It is also found that the carbon bromine bond of the original starting material R-Br and say acrylonitrile they react equally fast with tributyltin radical. But then what is found is that R-I reacts 10 to 100 times more than the R-Br and therefore, many a times the possibility of using R-I is explored. However, there is a little problem.

Sometimes some of these iodo compounds are not as stable as R-Br at particularly high temperature during the reaction. So one has to look at the compromise between the two and then carry out the reaction. But the use of dilution avoids the reduction of the radical at the first stage and therefore, C-C bond formation occurs and then subsequently the reaction stops.

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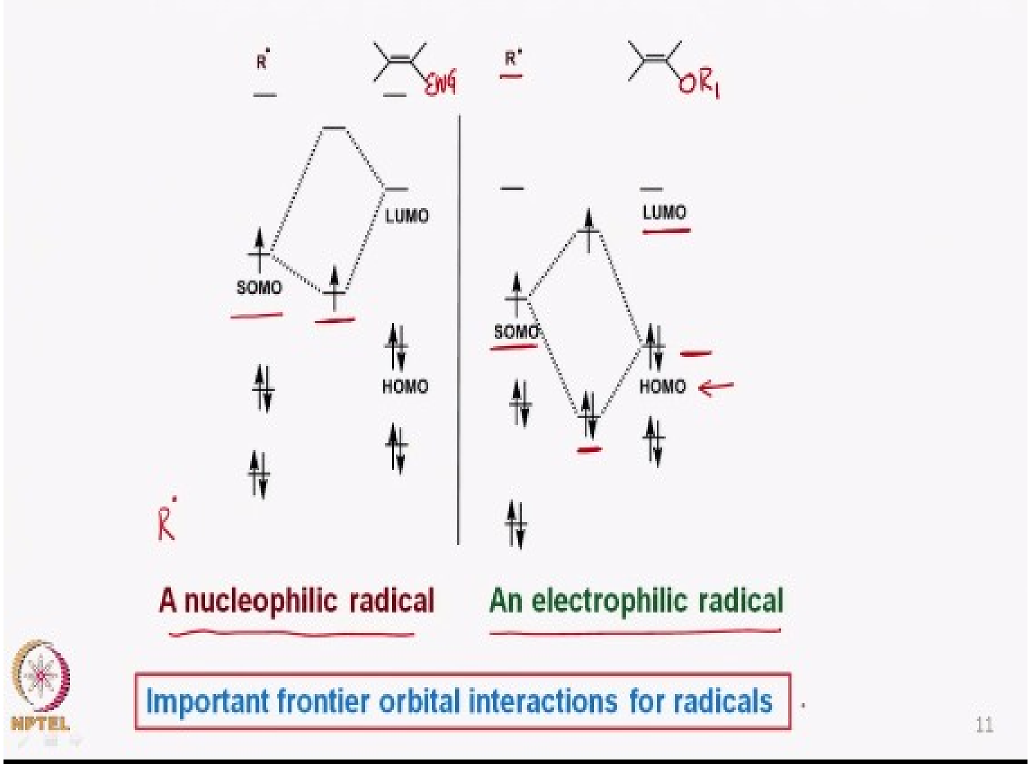

A nucleophilic radical

An electrophilic radical

Important frontier orbital interactions for radicals

One can look at the radical's reactivity, if you have nucleophilic radical and if you have an electrophilic radical, then this one can look at the singly occupied molecular orbital obviously, would be of higher energy, because the radical which is generated, if it is having an electron donating group, then its orbital having a single electron would be of a higher energy.

And complementarily if the olefin has electron withdrawing group say here, electron withdrawing group is attached to the olefin, then of course its LUMO would be of a lower energy and therefore, there is a possibility of interaction of the SOMO that is singly occupied molecular orbital with the LUMO that is lowest unoccupied molecular orbital, because energy gap would be less and therefore, the reaction occurs and then the product forms of this type.

On the other hand, if we have an electrophilic radical, then we expect that we use say you have an electron donating group attached to the olefin and if the dot is having an electron withdrawing group, so the singly occupied molecular orbital will be of lower energy and therefore it will go down. On the other hand, the lowest unoccupied molecular orbital will be of higher energy.

On the other hand the HOMO, the highest occupied molecular orbital would be of a also higher energy, but then the SOMO of the electrophilic radical and the HOMO of the olefin would be easy to interact with, the energy will be less and therefore, one generates the corresponding radical with this kind of arrangement like this.

And therefore, these are the important frontier orbital interactions of two different types of radicals with two different types of olefins, one with electron withdrawing group and the other with electron rich olefin.

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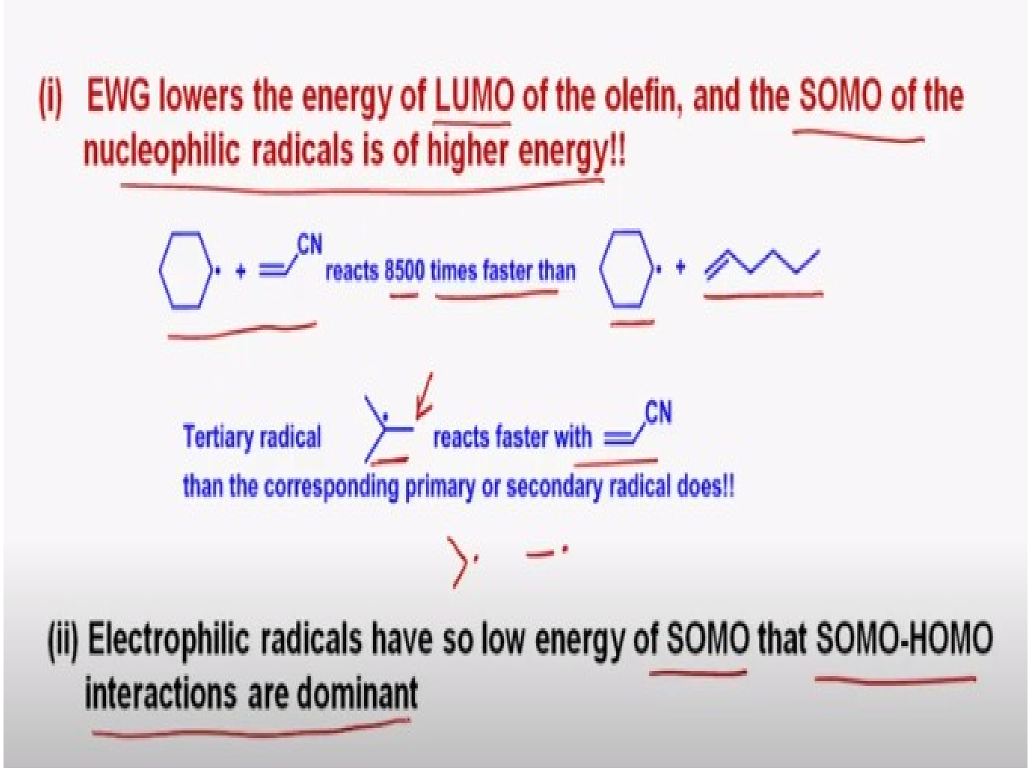

(i) EWG lowers the energy of LUMO of the olefin, and the SOMO of the nucleophilic radicals is of higher energy!!

reacts 8500 times faster than

Tertiary radical reacts faster with

than the corresponding primary or secondary radical does!!

(ii) Electrophilic radicals have so low energy of SOMO that SOMO-HOMO interactions are dominant

At the same time, we can also look at the couple of more aspects of it. One is that as we discussed the electron withdrawing groups lowers the energy of LUMO of the olefin and SOMO of the nucleophilic radicals is of higher energy. That is how for example, if you take simply the cyclohexyl radical, it reacts at 8500 times faster than the same radical reacting with an ordinary olefin having no electron withdrawing group.

Tertiary radical which is electron rich reacts faster with acrylonitrile than the corresponding say for example, you have a secondary radical or a primary radical in comparison that this tertiary radical reacts faster obviously, because of electron releasing nature of the substituents on the tertiary radical. Similarly electrophilic radicals will have low energy of the singly occupied molecular orbital and therefore, SOMO-HOMO interactions are dominant.

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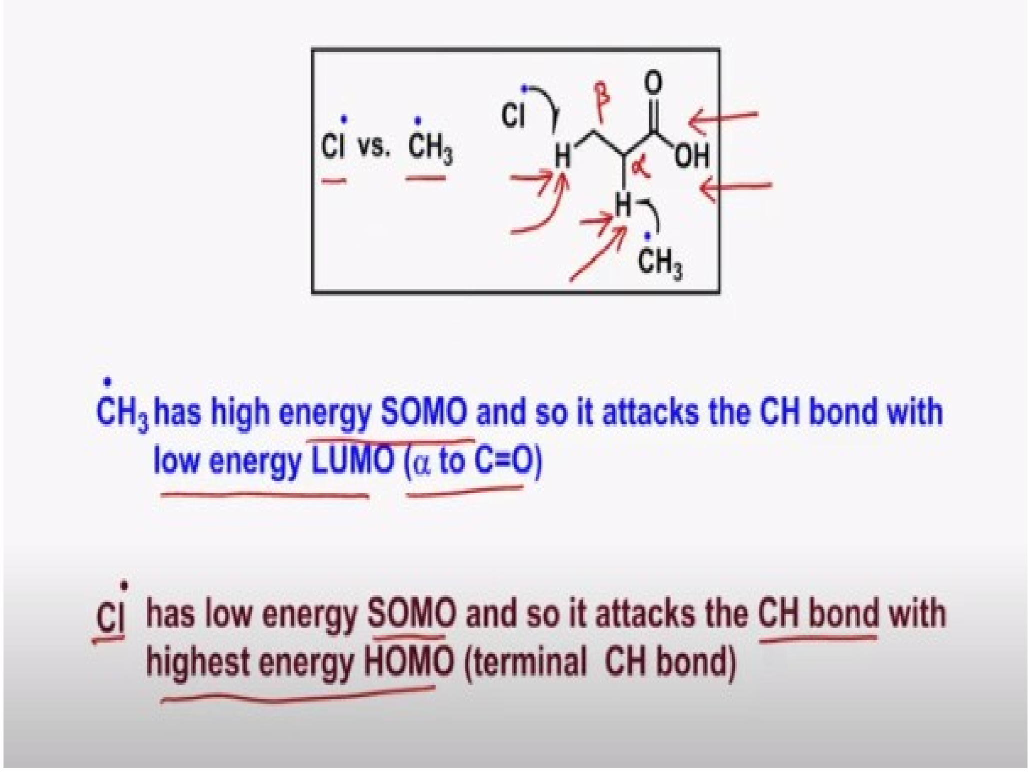

$\dot{C}H_3$ has high energy SOMO and so it attacks the CH bond with low energy LUMO (α to C=O)

$\dot{Cl}$ has low energy SOMO and so it attacks the CH bond with highest energy HOMO (terminal CH bond)

Finally, in this regard, we have one example in which if we take a molecule like this, where there are two hydrogens which are likely to be abtracted by different radicals, so if we compare chlorine radical versus say methyl radical, methyl radical has high energy SOMO and so it attacks the hydrogen bond with low energy LUMO that is LUMO which is alpha to the carbonyl group.

So you have, this is the alpha position and this is the beta position. So this particular hydrogen CH bond will be of low energy LUMO and therefore the methyl radical reacts there. On the other hand Cl dot will have low energy SOMO and so it attacks the CH bond with highest energy of HOMO, which is what is this particular CH bond which is away from the carboxylic acid.

So even such kind of abstraction of hydrogens are also affected by the similar type of reactivity as we discussed with the nucleophilic and electrophilic radicals reacting with double bonds having either electron withdrawing or electron donating group. So we will stop it at this stage and then we will carry on the discussion in the next class on some other aspects of reactivity of the molecules using radical chemistry or other reactions.

So we stop it here and you try to study whatever I have told today and till then, goodbye and thank you.