Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3-sp3) bonds in asymmetric fashion

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Module - 08
Miscellaneous method of enolate alkylation of several carbonyl species
Lecture - 38
Organocatalytic methods for enolate alkylation (SOMO activation)

Welcome back everyone and particularly in continuation with the earlier module we are trying to discuss couple of new things. And today we will be talking in this lecture lecture 38, where we will be mainly discussing Organocatalytic methods for enolate alkylation. And we will discuss about a new concept SOMO activation method, which stands SOMO stands for Singly Occupied Molecular Orbital.

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We will be mainly discuss this concept in this lecture, organocatalytic alpha alkylation of carbonyls which earlier we have discussed through the enamine pathway. A reverse polarity of enolate functionalization and few case studies ok.

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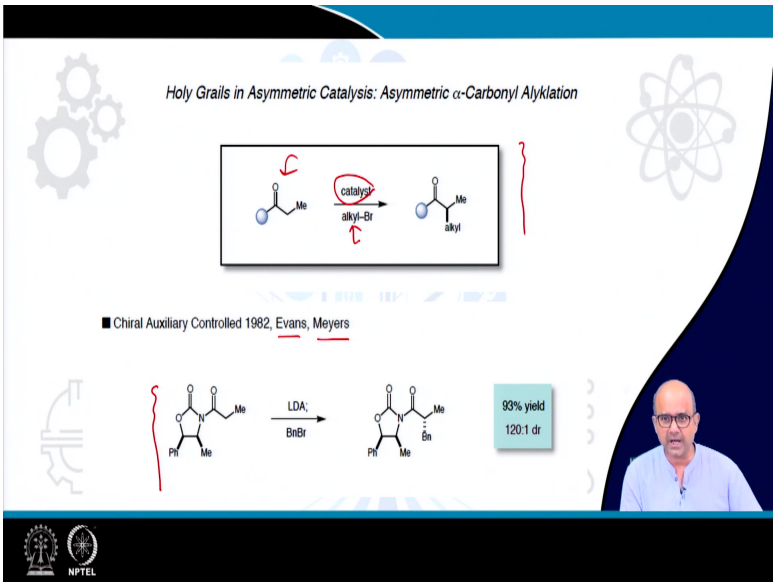

Now, let us talk about this new concept which is often regarded as a holy grails in asymmetric catalysis. So, means there are couple of new things we need to do in a different perspective and one of the interesting or challenging factor is how you can do a alkylation with the help of chiral catalyst, with an electrophile. This is usually the throughout this course work we talked about these things.

And the conventional examples which we have already highlighted mainly focuses on different auxiliary induced thing, either Evans or Meyers or other RAMP/ SAMP based different alkylation. So, these are already we talked about, but still there are too many things to do, in most of the cases this auxiliary seems to be expensive you need to have a stoichiometric amount of the auxiliaries. But can you do a catalytic version of this enolate alkylation?

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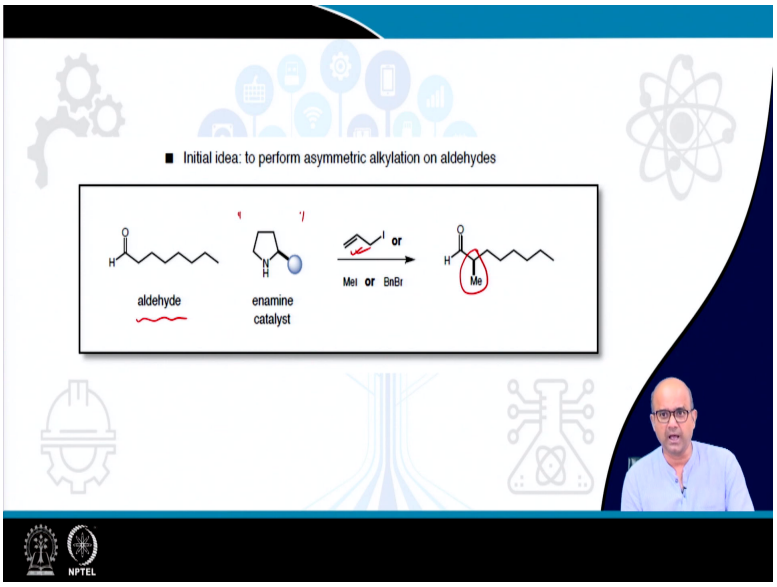

The initial idea was yes you can do it, but definitely then you need to do a different mode of activation. And normally if you think about the enolate alkylation at the end stage, we talked about aza enolate or enamine alkylation. We said that this aldehyde kind of compounds are very difficult to alkylate at the alpha position because the most competing reaction was the aldol reaction.

But still a properly substituted enamine can be covalently linked and then you can use different electrophiles to create new carbon containing stereo center adjacent to the aldehyde or carbonyl compound.

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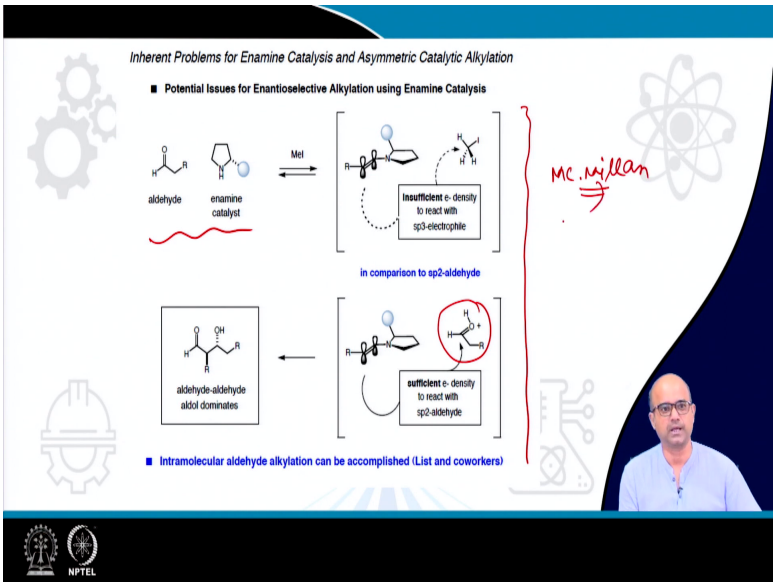

Now, the problem associated with the enamine alkylation was mainly, once you created a imine, the imine basically is a 4 π-system like this and definitely the HOMO of the enamine which actually reacts you know in normal cases. But it is in found that the insufficient electron density was the main drawback to replace or to react with the electrophile.

On the contrary, the aldol reaction seems to be more much more facile because the aldehydes are much more electrophile because they can be easily activated. And then this HOMO of this enamine reacts with this aldehyde to give you a competing aldol reaction, which is the most important reaction.

Now, Professor Benjamin List and Professor David Macmillan who actually got the Nobel Prize in this year chemistry both of them independently worked on this particular problem. And Professor David McMillan we will be explaining his work in the form of this SOMO alkylation or organocatalytic alkylation.

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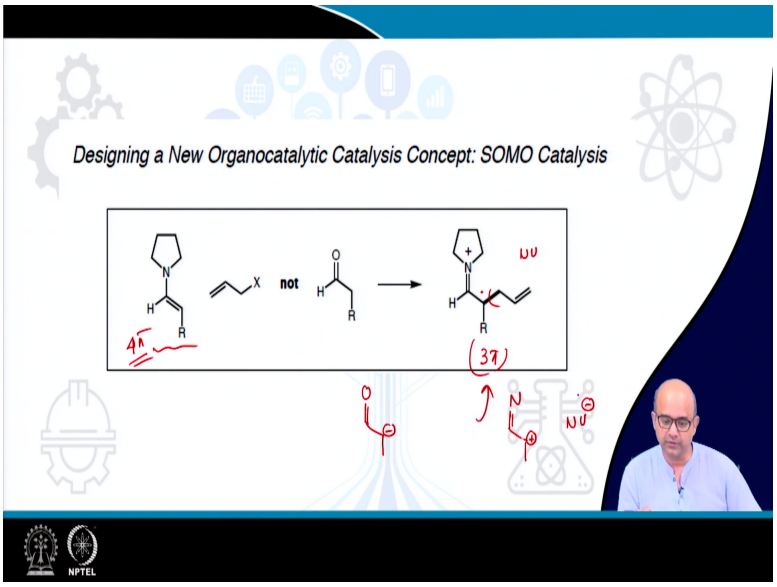

Now, the concept was basically you have an enamine and you have an electrophile. Now, what we do this enamine as I said the electron density was not very sufficient to react with this sp3 containing electrophile. So, probably this 4 π- enamine system you might convert a 3 π- iminium system and then you can actually tune the reactivity.

And then you will find that you can actually create not a negative charge here, you can create a singly occupied molecular orbital or a radical and then you react with another nucleophile or another radical containing species. And then you are basically what you are trying to see in the normal cases this is your minus, but in organocatalytic way this system contains a charge reversal, it is an umpolung system. And then you can actually react with a nucleophile. So, that will explain how these things are really happening.

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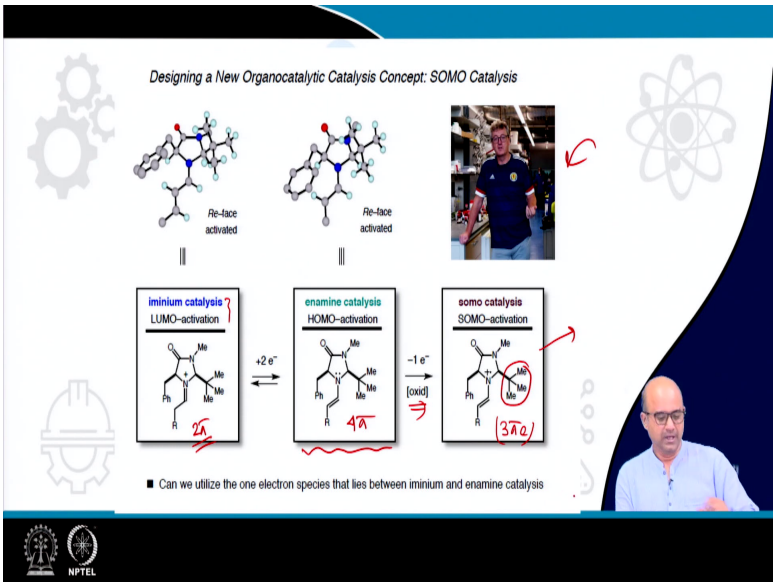

So, this gentleman professor David McMillan was the first pioneering in this field. So, initially now, let us talk about a typical enamine catalysis which all of us know ok. Now, this enamine it is basically a 4 π- system ok. Now, if you remove 2 electron for this enamine, you will actually get a iminium catalysis ok, this iminium catalysis this is normally a 2 π- system ok. And this it basically gives you a LUMO activation mode that is a standard way.

Now, if we apply an oxidant and then you only remove 1 electron, you are basically trying to get a radical cation system which is an iminium kind of thing and this is a 3 π- electron system. Now, these 3 π- electron system in principle that probably actually the main factor in the organocatalytic activation; the catalyst contain a steric directing group either tertiary butyl and the benzyl, both are in cis position or both are in beta.

That means, that the below face of the enamine seems to be approached by an incoming SOMOphile, it is not a nucleophile, it is a SOMOphile.

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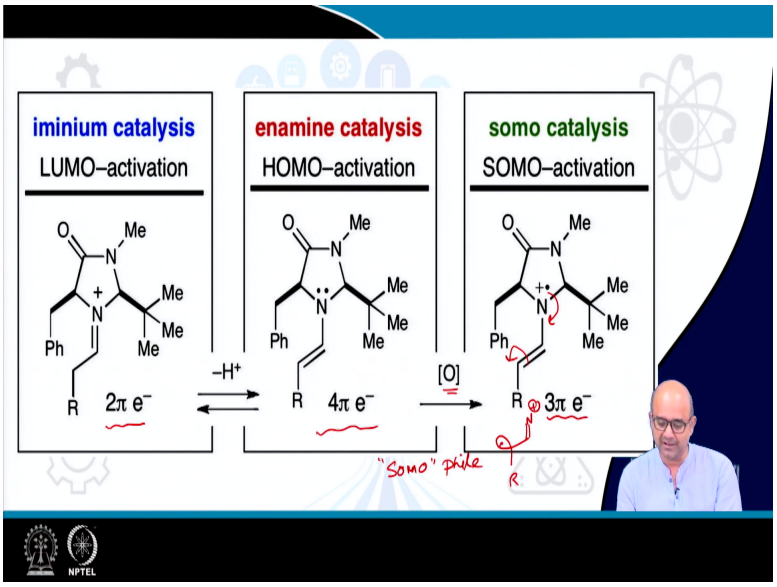

Now, how this SOMOphile can be generated. Now, we talk about that. So, this is the standard enamine 4 π electron system you have this nitrogen to lone pair with this 2 π that makes you 4 π. Now, you can eventually remove this lone pair and you get a 2 π electron system. And this is your enamine to iminium. This iminium now actually you can attack or you can abstract or you can do whatever way you can do the alkylation, which is probably known.

Now, if you use an oxidant here one of this electrons probably you can replace and you get this kind of iminium cation here. Now, this iminium cation you will try to first come here and you give here. So, basically what you are trying to get, you get a R and you get double bond N plus, you get a singly occupied molecular orbital SOMO. Now, this SOMO is the main factor in the organocatalytic alkylation.

And then you react with another SOMOphile which also contains another electron and this two electron electron combines and you get a new carbon carbon bond. So, now, you can find that this SOMOphile usually contains a single electron ok. So, it is the charge seems to be little bit reversed; it is not a normal negative charge alpha to the carbonyl ok; not alpha to the carbonyl. It is actually more of like a positive charge here or a radical cation kind of thing. We will explain these things little bit later on.

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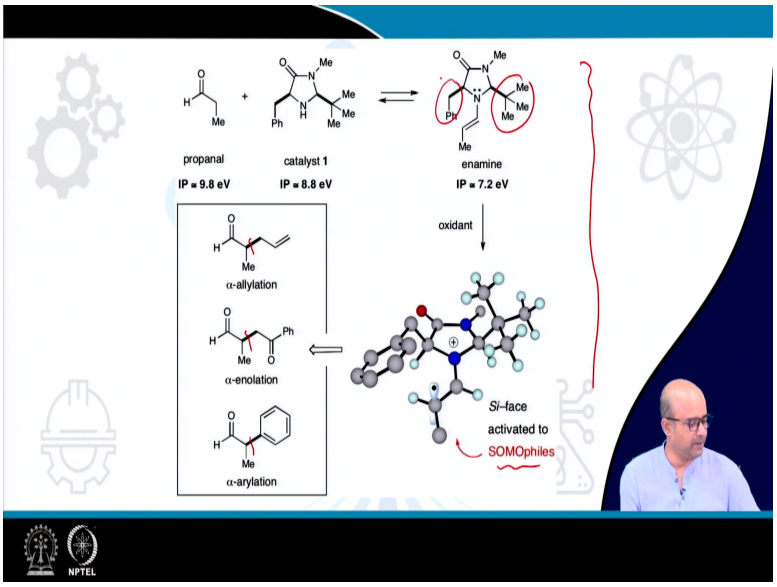

So, in principle it has been found that this kind of aldehyde reacts with this kind of imidazolinone, which was developed by Professor McMillan and actually in terms of ionization potential these two compounds have similar kind of ionization potential. So, they can be easily condensed and the enamine you can now add oxidant, mainly ceric ammonium nitrate or other oxidant, which helps to this electron removal.

So, now you what you are getting you basically get an iminium cation and this SOMO ok. Now, this SOMO you can now trap you can trapped with SOMOphile the SOMOphiles are different species, not the standard electrophile. And by the help of this you can actually create new carbon carbon bond, new carbon carbon bond. You can do alpha allylation, alpha enolization means you can react with a enolic species, you can do a alpha alpha allylation with the SOMOphiles in a enantioselective fashion because the compound contains two stereo directing group ok.

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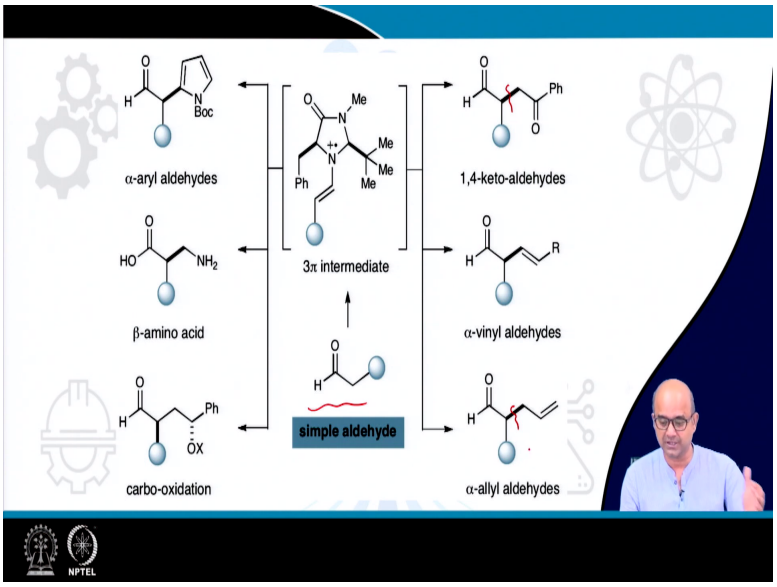

So, this is our main conceptual analysis, you have a simple aldehyde, you first create with this iminium cation and then subsequent reaction. Normally, the reaction which we will be mainly focusing in today's lecture just for a brief introduction how we can create new carbon carbon bond. So, this could be the most interesting part, which is very conventional traditional enolate alkylation looks like ok.

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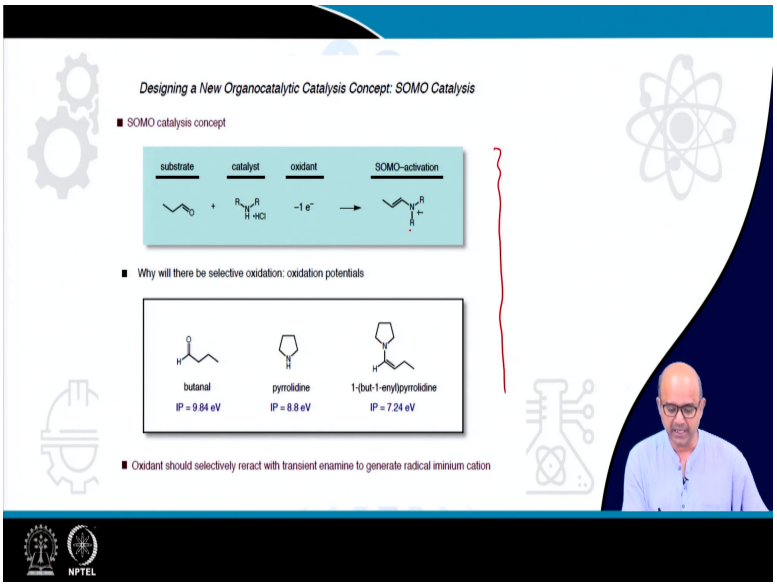

So, now let us again just go back to the normal thing as I said they this kind of compounds contain a similar kind of ionization potential. So, first you react to it substrate with 1

equivalent of this secondary amine, which is chiral in nature ok. Then you first get the enamine then you with the oxidant which actually abstracts the electron and you get the iminium one.

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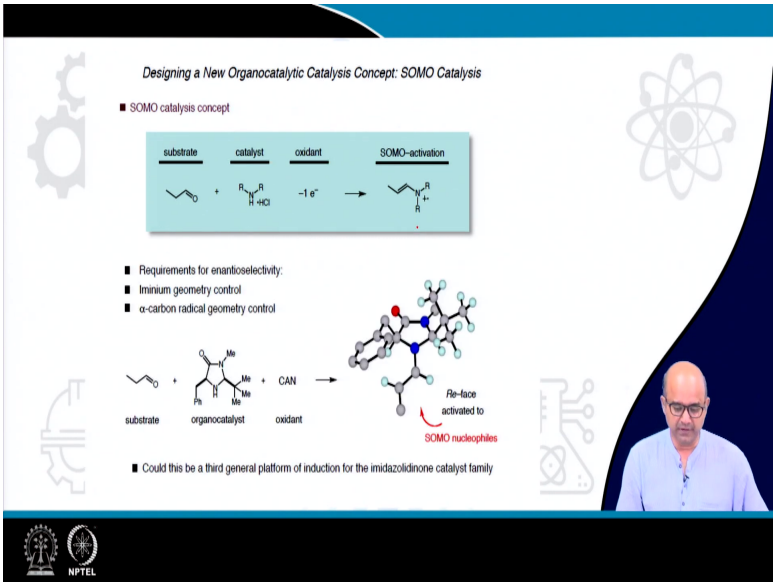

So, this iminium, once you get the iminium then you can see that the iminium as it is a having a bulky benzyl group and cis tertiary butyl group the top phase seems to be blocked ok. And the bottom face the SOMO or the nucleophile SOMOphile will basically reacting.

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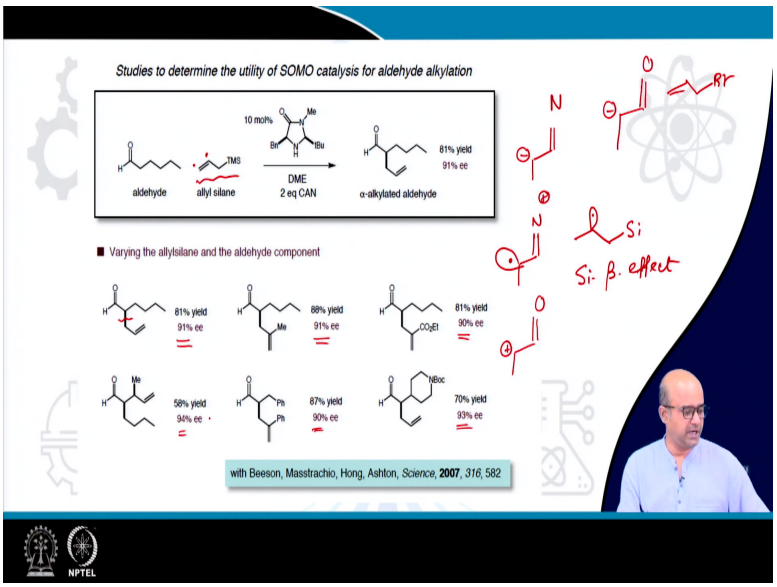

So, let talk about now this thing what this is really happening. Now, in conventional way you will find that this is a minus species and then you attack the electrophile. But, in this kind of a thing, this was not this is basically having a single electron species. So, means that you have to react with some other single electron species or a SOMOphile. So, this is not a normal allyl bromide, you can react to it allyl silane this allyl silane is a good SOMOphile.

Now, what is happening, this actually you this double bond allyl silane means this double bond means two electron. So, you can have one electron dot here, one electron dot here. So, this is basically reacting with this carbon carbon thing here ok. And then you get …..basically get this kind of single electron species with the silicon. And this is more or less named as silicon beta effect, which actually mainly responsible that silicon can stabilize a beta carbocation as well as beta free radical.

So, this is the main factor for taking this kind of SOMOphile, and then in the latter part you can further remove the silicon to generate the carbon carbon double bond. So, in reality if you compare with this system with the enolate alkylation you can think that this is a normal enolate alkylation, where you are having a carbonyl species and a minus, then you react with a allyl bromide, right.

But in reality here what we do? You react with this kind of SOMO with another SOMOphile. Now, this is actually not a negative charge here it could be radical cation and this radical cation means the charge is kind of reversible, it is basically alpha carbonyl cation. So, it looks like something like this species.

So, the carbon, I mean the cation adjacent to carbonyl seems to be the polarity has been reversed is the umpolung polarity. So, this was that is why the polarity seems to be reversed. Now, by taking a different series of silane compound you can actually create a large variety of alpha functionalized aldehyde and you can you get a good amount of asymmetric induction and this was reported in 2007 in a science paper which seems to be opening the flood gate for this organocatalytic alkylation.

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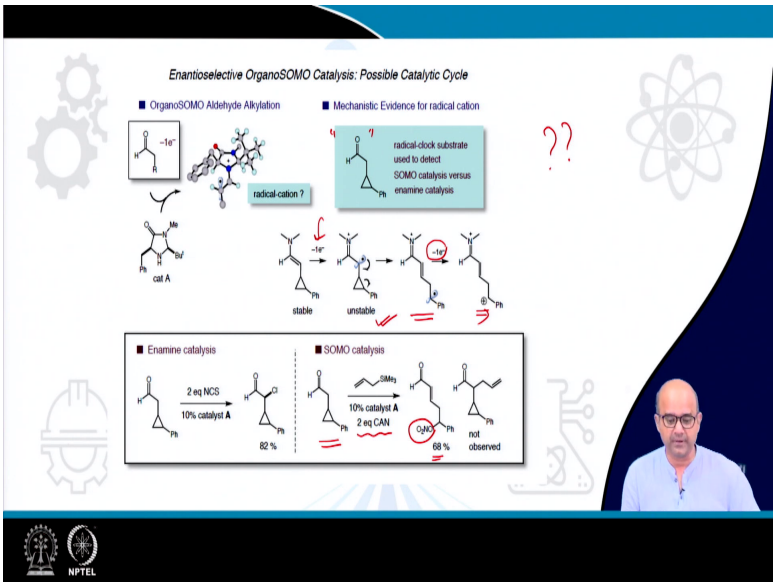

Now, coming to detailed mechanistic analysis, how these things are happening. So, initially this aldehyde react with this imidazolium secondary amide and you basically get a thing like a radical cation or the iminium cation. Now, how to prove it that in reality it is happening? Now, if you take the aldehyde in this kind of cyclopropane containing aldehyde. So, initially you get cyclopropane in amine system you add your oxidant ceric ammonium nitrate you get the radical cation of the SOMO.

Now, this cyclopropane alpha to this radical seems to be unstable, because the cyclopropane rings are strained. So, radical if there is a chance that it can open it up it tries to open it up the cyclopropane ring opens up and basically it will give you a this SOMO. Now, this SOMO you can have a 2nd electrophile sorry, the oxidant again abstract another electron and gives you a purely vacant carbocation ok.

Now, how you can identify? Now, if you take this as a main substrate you treat with two equivalent of oxidant ceric ammonium nitrate. Now you can actually observe once you get the cation the nitrate acting as a nucleophile and 68 percent of this compound was isolated.

That basically proves that first this kind of, this kind of unstable cyclopropyl methyl radical was formed which is the main SOMO species, then it rearranges to give you the homo allyl carbocation and then the further nucleophile taking from the scan ok. So, this gives you a clear cut indication and this is sometimes referred as radical clock substrates, where the radical adjacent to the cyclopropyl usually cleaves or opens up ok.

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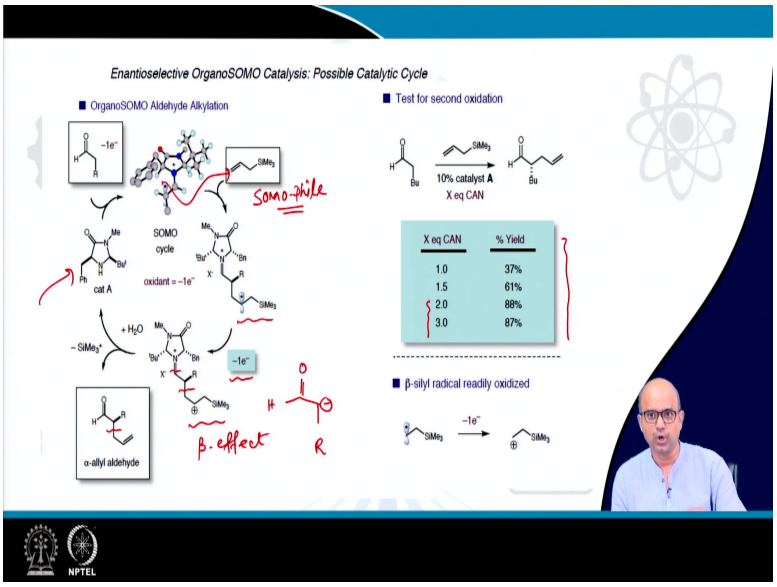

Now, let again come back to the original system. So, first you are having this aldehyde react with your chiral amine ok, secondary amine you basically get the iminium system ok. Now, iminium system in the SOMO ok. Now, this SOMO reacts with this allyl silane, as I said this radical recombines with this part and you get the beta silicon radical ok and this beta silicon.

So, this is your SOMOphile, it is not standard conventional electrophile or nucleophile SOMOphile we can term it ok. Then further electron removal by oxidant you get a beta silicon cation this is very much stable species by silicon beta effect ok. And then you are trying to remove this trimethylsilyl group by standard carbon silicon bond cleavage, you can eventually react with other species also and then you can regenerate the see the this will be hydrolyzed to remove the thing and you get a double bonds here that will give you alpha allyl aldehyde.

So, in conventional, way what we do in conventional way if you have to do way this kind of compound synthesis you actually generate the enolate first and then do allyl bromide, but associate problem was aldol condensation of the main culprit or main drawback. But nevertheless, if you can react to a thing this kind of secondary imidazolium things then you add a oxidant that oxidant what it does it accepts the electrons of the initial 4 pi enamine system and you get a iminium cation this is the SOMO ok.

Now, this SOMO will react with the SOMOphile the allyl silane you get a beta silicon containing radical, the oxidant was still there can it can abstract further electron you get a

silicon beta containing compound ok. So, this is the bond you are normally creating ok and then further TMS removal you get alpha allyl aldehyde, this catalyst was regenerated ok.

And usually, such systems was very nice you can see the most yield was obtained with 2 equivalent to 3 equivalent of oxidant because the more oxidant you use normally 2 equivalent are sufficient. First to create the SOMOphile, 2nd if you use allyl silane second oxidant was used to create a beta silicon carbocation which seems to be much more stable.

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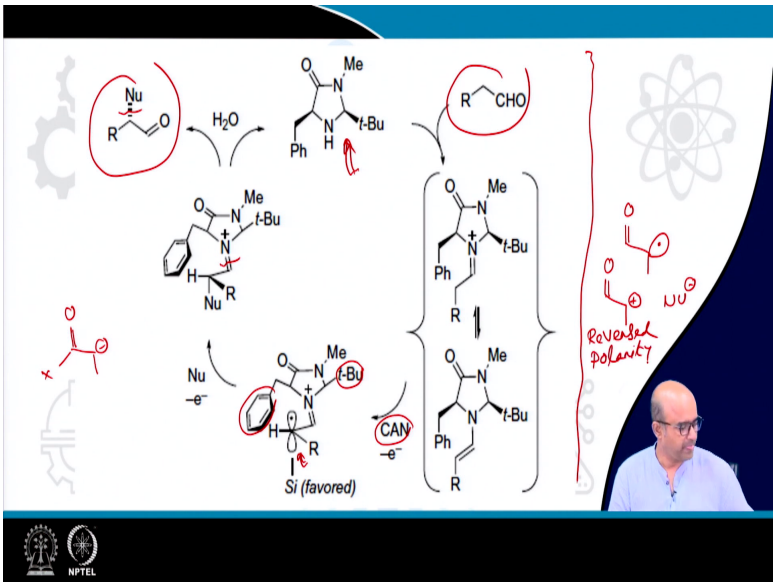

In another way you can also draw a catalytic cycle something like this. So, first take your precursor the aldehyde, then first this is your imidazolone based catalyst or the MacMillan catalyst. And then you first get the normal iminium species, then you apply your CAN, Ceric Ammonium Nitrate to abstract the electron, this is the iminium cation or the SOMO species which we are talking about.

Eventually you can see the top face seems to be blocked by this tertiary butyl, this benzyl group. So, only accessible phase of this thing is the bottom face ok. And you attack here and you get the iminium species, you have to hydrolyze and then you can basically get back the compound where new carbon nucleophile bond was created.

So, here we are talking about as a nucleophile, you can call a SOMOphile. So, usually the polarity of this alpha carbonyl compound has been reversed. So, usually in the most of the

cases, the enolate alkylation you have a carbonyl compound, you actually create a negative charge here.

But in this case you normally create a SOMOphile or you can so or you can think about you are basically creating a positive charge here. And then a nucleophile actually attacks. So, the polarity has been reversed that is what this is this organocatalytic thing we often called the polarity has been reversed fine.

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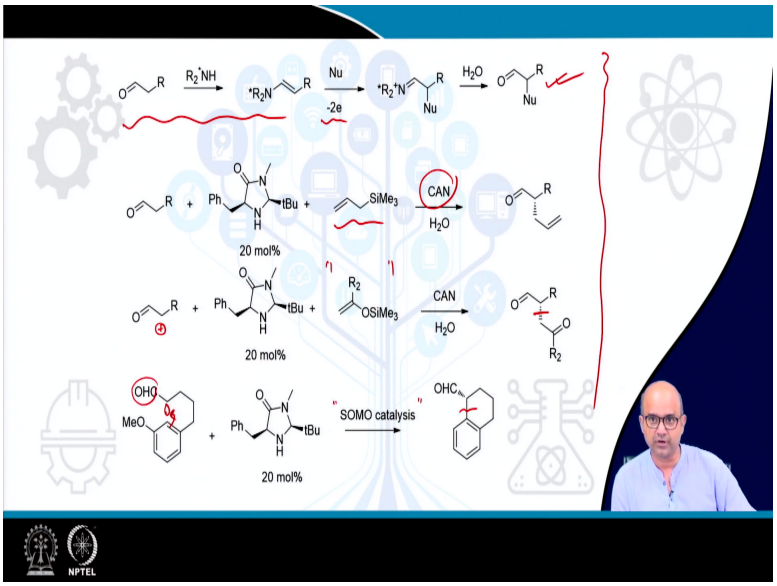

So, this is the again the schematic diagram what you can do it. So, to have concluding remarks, basically you start with this kind of compound, you react with this two electron oxidation system, you get the SOMOphiles and then final nucleophilic attack this could be your main final product.

Allyl silane is one of the SOMOphile you use, CAN is the oxidant, what are the extra SOMOphiles you can use this is an enol silyl ether as a nucleophile. So, mean in this position you basically, it is a plus and then your enol attacks here ok and you get a new carbon carbon bond in asymmetric fashion. Intramolecular version also can be reacted this is very interesting. If you take a electron rich aromatic substrates, where initially you this aldehyde reacts with this imidazolium and you get the SOMO.

Now, this SOMO, this SOMO species this SOMO you will be having electron rich aromatic in its vicinity. And so this aromatic rich electro nucleus act as a nucleophile and you can

create the new carbon carbon bond in asymmetric fashion. So, this was the probably one of the finest example of this intramolecular SOMO based alkylation, with a non conventional electrophile basically it is a electron rich aromatic system in a intramolecular fashion.

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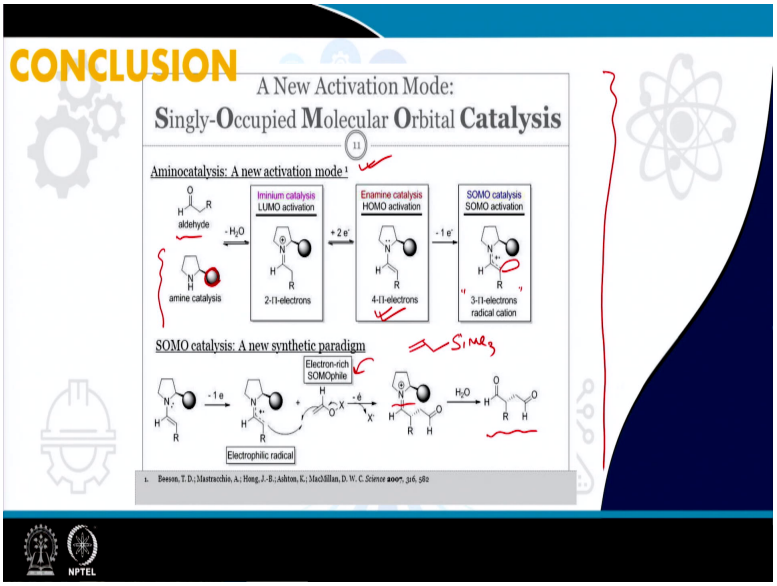

So, in concluding remark, you can say that what you can do amino catalysis basically a new activation mode as we are talking about. So, first you take the aldehyde, you have a amine catalyst which contains a chiral center a point chirality, first you get a usual the conventional you first get a iminium or a enamine which contains 4 π electron.

Now, there this 4 π and 2 π there must be something lies in between, if you abstract single electron for this is the 4 pi system of this 2 nitrogen lone pair by oxidant you actually get a 3 π electron system, which is radical cation. Now, this radical cation basically contains a SOMO ok, singly occupied molecular orbital. So, this singly occupied molecular orbital you can now get it here and this is basically electrophilic radical ok.

This electrophilic radical you now reach react with electron rich SOMOphile or you can call it nucleophile, like your allyl silane. Allyl silane was usually chosen because the silicon containing group contains or usually responsible for stabilizing the beta radical ok. And then further one round of oxidant addition you can actually get the beta silicon carbocation, then simply hydrolysis you will get to different kind of activation mode.

So, this is a similar concept, but doing a disconnection in a different approach ok. So, in the next lecture we will be talking about a phase transfer catalyzed asymmetric alkylation and that will be our 39th lecture. And then finally, we will conclude and sum up with a; sum up with whatever we taught throughout the entire 40 hour lecture.

Thank you and see you in next class.