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

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Lecture - 51
Introduction to Allyl Metal Additions for C-C Bond Formation

Hello everyone, I would like to welcome you all for today's lecture. We will briefly look at what we did last time. We looked at some aspects of Claisen rearrangement and their variations in terms of substrate structure.

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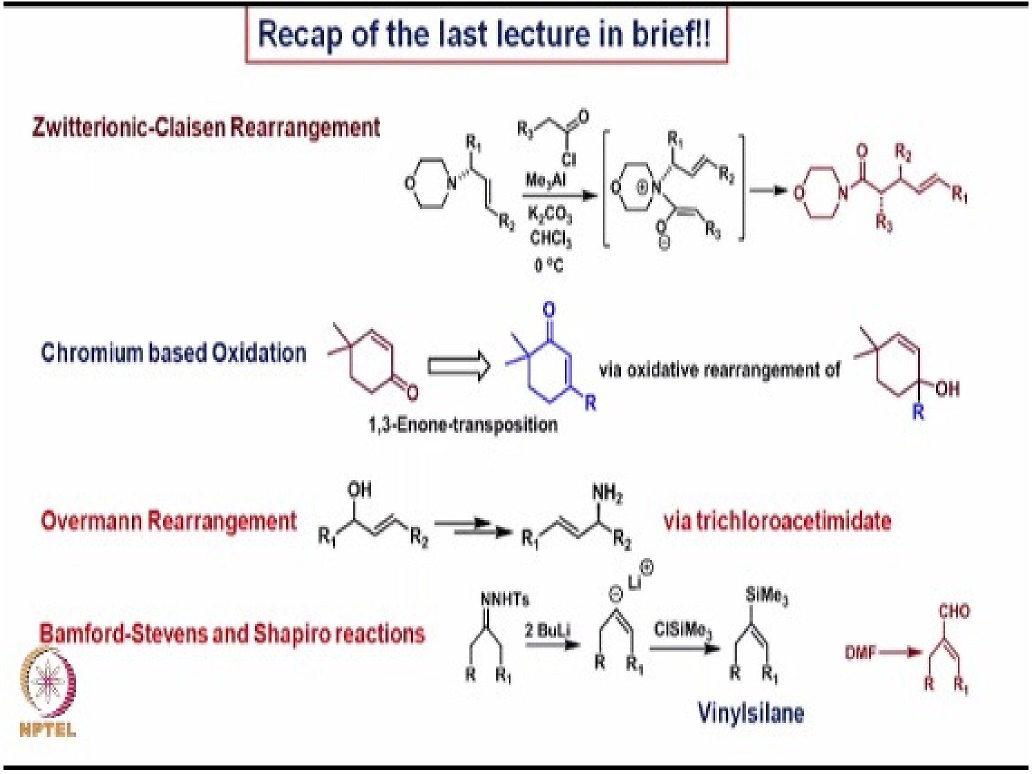

Recap of the last lecture in brief!!

Zwitterionic-Claisen Rearrangement

Chromium based Oxidation

1,3-Enone-transposition

via oxidative rearrangement of

Overmann Rearrangement

via trichloroacetimidate

Bamford-Stevens and Shapiro reactions

Vinylsilane

For example, the last one that we took was Zwitterionic-Claisen rearrangement, which was close to the ketene based reaction. Here the substrate was slightly different. For example, if we start with this allyl amine and react it with this acid chloride in the presence of a Lewis acid, then what we discussed was that the reaction proceeds through this enolate.

And of course, it leads to the formation of the corresponding product like this, in which the R2 and R3 groups were anti disclosed. But of course, we can take differently oriented this particular double bond. That means cis and then we can get different stereochemistry in the final product. Likewise, we also looked at the chromium based oxidation particularly in the enone transposition of this type to this type by introducing an R group here and carrying out the oxidative rearrangement of this kind of tertiary allylic alcohol.

This rearrangement was kind of reminiscence of the Claisen rearrangement. And therefore, we had a nice way of converting one enone to the other enone by introducing another substituent at the position where the ketone was present. Also we looked at the Overmann rearrangement, where conversion of allyl alcohol to the corresponding allyl amine via a transposition of the double bond was seen and it was proceeded via trichloroacetimidate.

Finally, we looked at the Bamford-Stevens reactions and Shapiro reactions say particularly the Shapiro reaction, which we discussed in the end was basically converting a tosylhydrazone to the corresponding vinyllithium or vinyl anion. And first we looked at the reaction of this vinyl anion with DMF to form the corresponding vinyl aldehyde.

Now it can be possible to make use of this vinyl anion to react with chlorotrimethylsilane and generate a very important intermediate which is a vinylsilane. So today we would like to look at the reactions of vinylsilane and how do they give different types of products.

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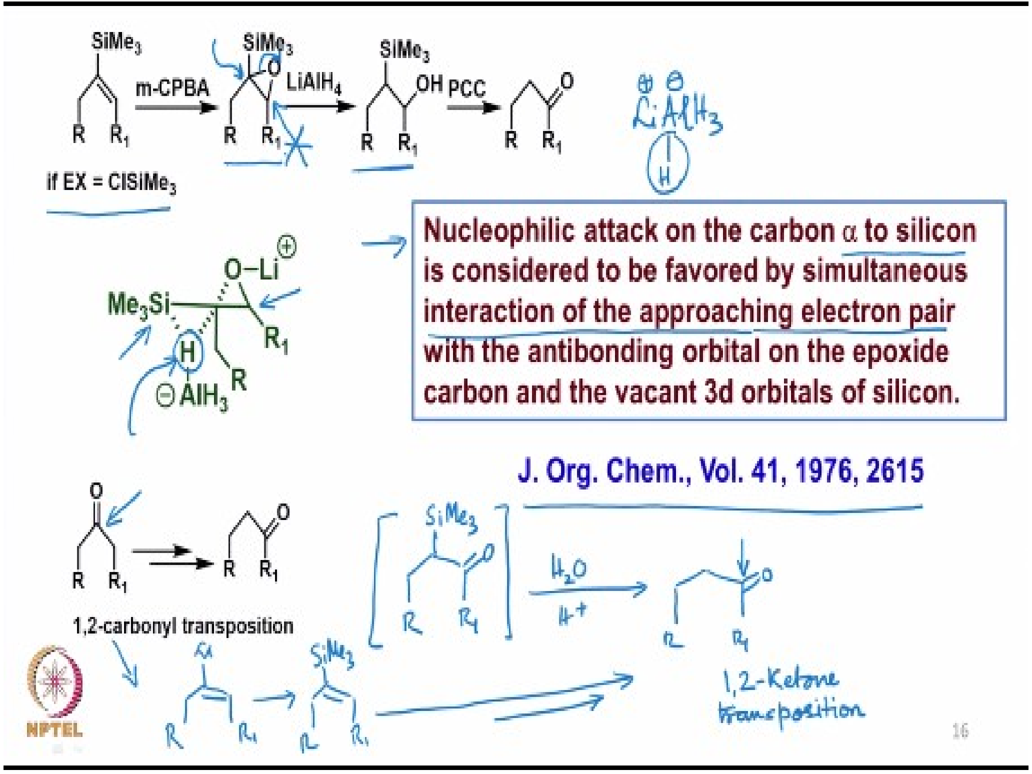

if EX = ClSiMe3

Nucleophilic attack on the carbon α to silicon is considered to be favored by simultaneous interaction of the approaching electron pair with the antibonding orbital on the epoxide carbon and the vacant 3d orbitals of silicon.

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So supposing if we take the vinylsilane, which is made by the method of Shapiro reaction, and if EX is used as you can as it is shown here is if $SiMe_3$, then we can carry out epoxidation using meta-chloroperbenzoic acid. And it is very interesting to see that such epoxides which are basically derived from vinylsilanes, when they are reacted with different nucleophiles say for example, lithium aluminum hydride.

So what you have in lithium aluminum hydride is a something of this kind. We have here H and minus here and a positive charge here. So this is what the lithium aluminum hydroxide. So this is the hydride that is what is going to act as a nucleophile. Now it is very interesting to see that there is a regioselectivity in terms of reduction of this particular epoxide and it opens up in this fashion.

So there is no reaction here. There is no reaction here, but there is a reaction at the center. Now this is very intriguing because the nucleophile actually should be expected to attack on sterically less hindered situation that is the carbon holding the R1, could be. And also because one could expect some other effects of silicon.

But what is happening here is the nucleophile attacks on the carbon, alpha to silicon and it is favoured by simultaneous interaction of the approaching electron pair. That means the hydrogen is approaching with the electron pair with the anti-bonding orbital on the epoxide. So you have this particular anti-bonding orbital of the epoxide carbon-oxygen bond and the vacant 3d orbitals of the silicon.

So basically when this is approaching here, of course when it is approaching here also it will be the same thing as far as anti-bonding orbital of the carbon-oxygen bond is concerned. But here additional factor is that the anion interacts also with the empty d orbitals, 3d orbitals of the silicon simultaneously.

Therefore, this hydrogen here H- tries to interact with the empty 3d orbitals of the silicon as well as the anti-bonding orbital of the CO and thus it reflects the regiochemistry of the reduction that is observed. This is quite given in much detail in this particular reference that one can look at it if one wants to know little bit more detail about this particular observations.

And now if we oxidize this particular silanol we can get the corresponding ketone here and what one can do is if we simply work up this particular substrate here, then you can imagine that there will be desilylation readily happening and then one can get the corresponding ketone.

So if one looks at it, what we have done it is we started with a ketone and through the Shapiro reaction, we got the corresponding vinyllithium and if that vinyllithium, supposing if we say that the vinyllithium was something of this kind, vinyllithium here, so you have vinyllithium and that leads to the formation of the vinyl silane and then that eventually has been converted to the corresponding ketone.

So you can see that the ketone was here, now the ketone has come next to the R1 group. So this was one carbon away from the carbonyl group. So this is what is called as 1,2-ketone transposition. So this is a very interesting application of the silane based chemistry where vinylsilanes can be epoxidized, reduced, followed by oxidation to convert a ketone into another ketone and which is what is 1,2-ketone transposition.

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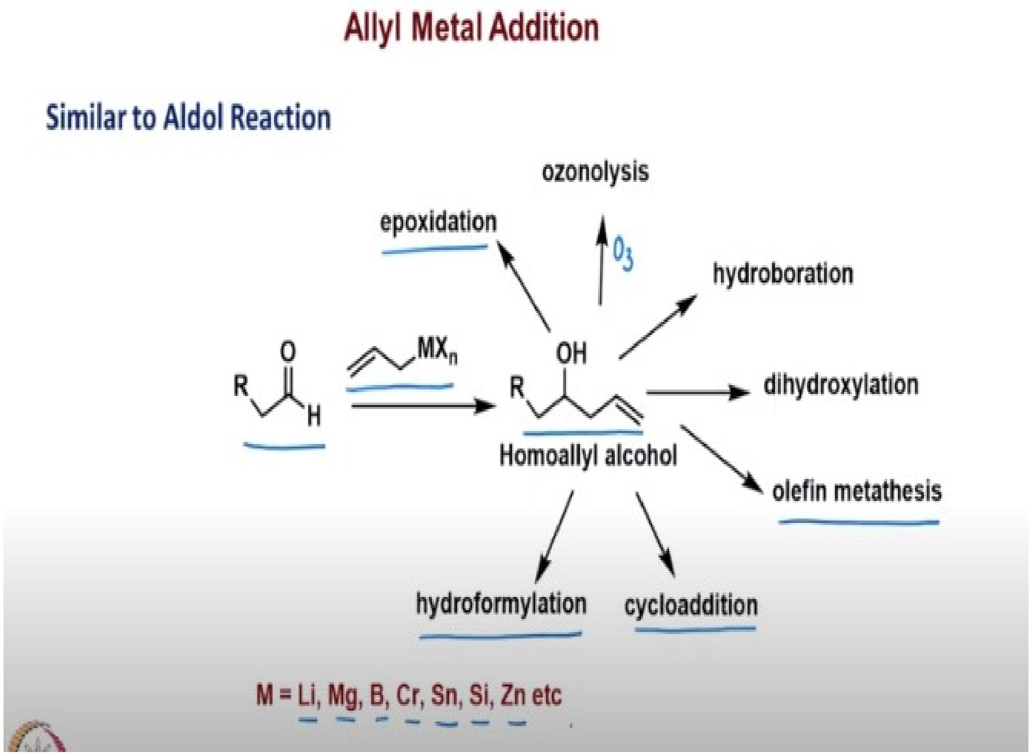

Allyl Metal Addition

Similar to Aldol Reaction

M = Li, Mg, B, Cr, Sn, Si, Zn etc

Now we go for another topic where we try to look at how allyl metal additions are taking place on a carbonyl group. Say for example, if we have a substrate of this kind, where we have an aldehyde and we try and take an allyl metal kind of substrate and if we attack the allyl group onto this, we can convert aldehyde into homoallyl alcohol here.

This homoallyl alcohol is very useful because you can carry out epoxidation and get an epoxide here which can allow many more manipulations of the functional groups. You can cleave the double bond here by ozonolysis. And then of course, you can get the corresponding aldehyde. You can do the hydroboration oxidation and you can think about various different types of reactions of the double bond dihydroxylation.

You can also carry out something like called as olefin metathesis, which we will look at later on. Of course, a cycloadditions can be carried out. You have a double bond, so you can carry out cycloaddition reactions. And you also can carry out hydroformylation reactions. Now these types of substrate scopes and reaction scopes are numerous and therefore, what is this MX n or what is M.

M can be lithium, magnesium, boron, chromium, tin, silicon, zinc, etc. Many of these things have been studied and of course depending on which kind of metal has been used, there are different types of reaction parameters. And the stereoselectivity or the regioselectivity depends on various factors of this kind. So we will look at a few of them in this particular course.

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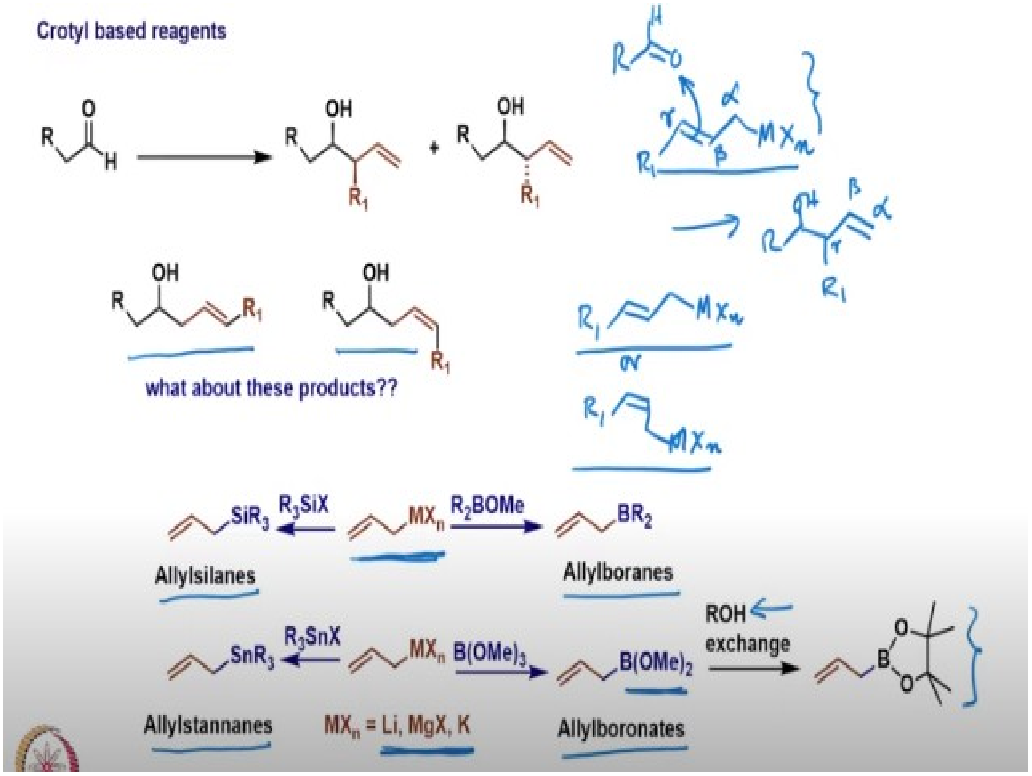

Now if we look at the crotyl based reactions, say for example if we look at something like this here. You have an MX here, then how does this reaction occur? Now it is seen that usually, you have the reaction going via this. That means, you have here RCH_2, RCHO for example here. Then we can carry out the reaction of the two and one can get the corresponding alcohol here with the double bond being here.

That means the reaction takes place at alpha, beta and the gamma position. So this is the gamma position, this is the beta position, this is the alpha position. But what about how can we carry out the reaction at the alpha position for example to get to a molecule like this or a molecule like this. That means, depending on which direction, say for example, if this happens to be R1 and then of course, you will have this as R1.

But if it wants to get something like this from a trans crotyl substrate or a cis crotyl substrate then or you have something like this. So how are we going to get it, that we will look at it little bit later. Now there are many other substrates which are very important like such as allylsilanes.

So if we have an allyl MX n bond, then if we react with say chlorotrimethylsilane or any other silyl halide or triflate whatever, then we can get the allylsilane. And if we react with this R_2BOMe, then we can get the corresponding allylboranes. If we react with trimethyl this trimethoxyborane here for example, then we can get allylboronate. And if we react with the tin X then we can get the allystannane.

So we have allylboranes, allylboronates, allylstannanes and allylsilanes reacting with any one of these substrates where lithium, magnesium or potassium is generally used. Of course, you can also exchange these particular this methoxys by other alcohol and accordingly one can prepare these types of boronates. So this various kinds of such allyl substrates have been utilized in organic synthesis.

And these are some of the very popular reactions in which the silicon, tin and boron based reactions have been utilized it.

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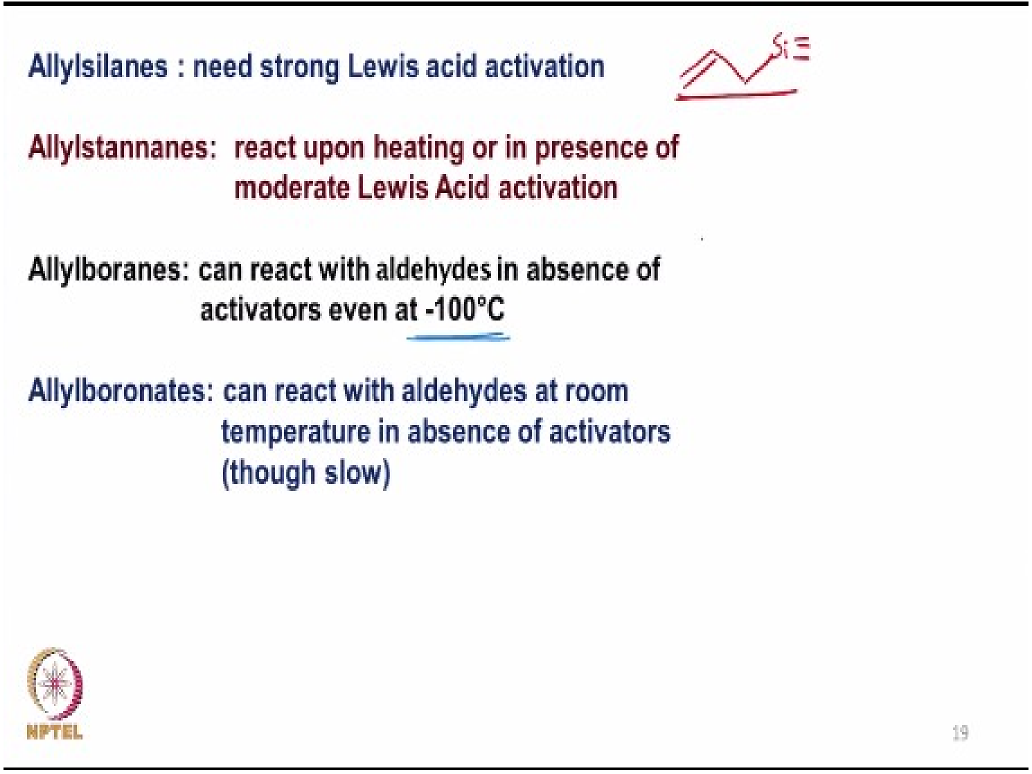

Allylsilanes : need strong Lewis acid activation

Allylstannanes: react upon heating or in presence of moderate Lewis Acid activation

Allylboranes: can react with aldehydes in absence of activators even at -100°C

Allylboronates: can react with aldehydes at room temperature in absence of activators (though slow)

Now what happens is that when we have an allylsilane then you have to have a very strong activation, because the carbon-silicon bond here is fairly strong and covalent bond and it is not possible to react the double bond with any electrophile unless it is strongly activated. We will study about that a little bit later.

Allylstannanes on the other hand react upon heating or in presence of moderate Lewis acid activation because carbon silicon versus carbon tin bond the polarization is somewhat different. Allylboranes can react with aldehydes in absence of activators even at -100 degree. So allylboranes are extremely reactive. And on the other hand, allylboronates can react with aldehydes at room temperature in absence of activators, though they are slow.

So as you can see that each one of them has some merit and some demerit. So we will look at the reactions of some of these and see how they lead to different products under different conditions.

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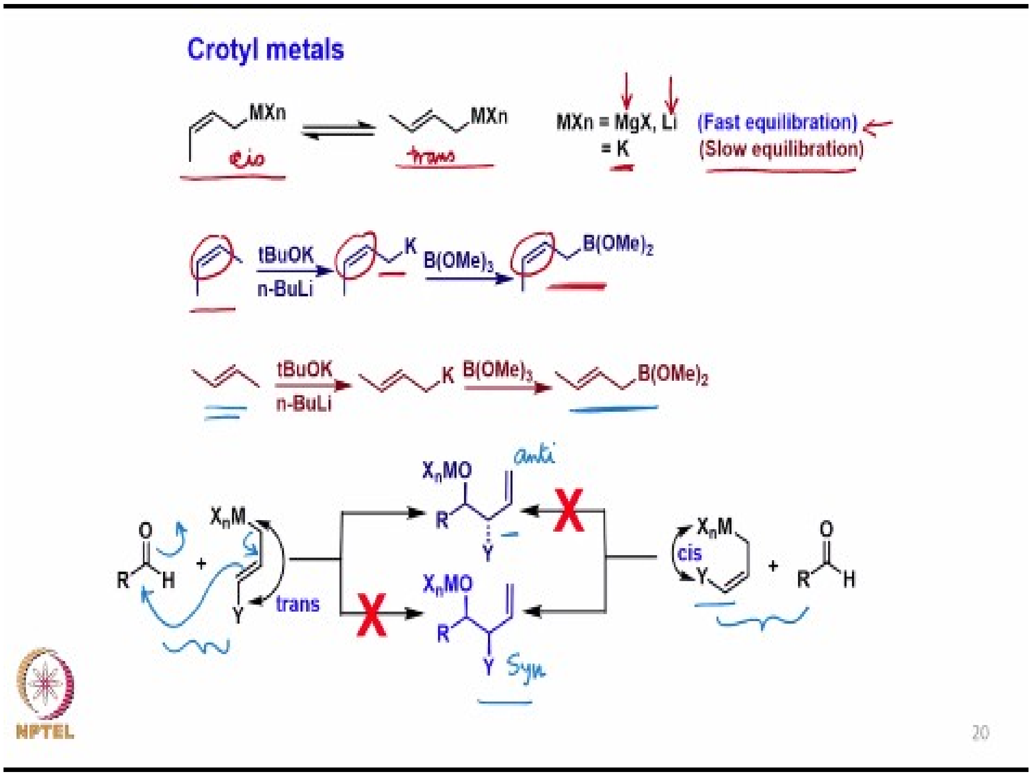

Crotyl metals

MXn = MgX, Li (Fast equilibration)
= K (Slow equilibration)

Now if we look at the crotyl metals, then crotyl metal somewhat like this can be written up, is in equilibrium with this. And it is found that if MX n that is the metal is either MgX or lithium, then there is a fast equilibration. On the other hand, when this is a potassium here, it is supposed to be going via a slow equilibration.

So basically what is happening is that MgX or lithium plus could easily coordinate with the double bond and undergo rearrangement. So that means, if we start with a cis double bond here and it can be in equilibrium with the trans double bond. Obviously, the trans double bond is more stable and therefore many reactions proceed via trans products. But if we start with a potassium metal containing substrate then it does not undergo equilibration that fast and therefore we can stop it.

For example here if we deprotonate this particular olefin using a combination of potassium tertiary butoxide and n-butyllithium which is supposedly called as a super base because the tertiary butoxide interacts with lithium plus and then you generate a strong base as n-butyl minus and that takes the proton away from here and it forms a potassium salt of the corresponding anion.

And if now we react it with this trimethyl borate here, then we can get the corresponding boronate here. Now here the double bond geometry is retained. So all throughout the double bond geometry is retained. On the other hand, if we start with the trans double bond, then of course, we can also retain that in the substrate that is obtained in the end, that is the boronate.

Now if reaction is carried out with the aldehyde for example here, then what is obtain is something like this here that goes in here, that goes in here and that comes in here. And that is how one gets the corresponding product as it is here. On the other hand, when it is cis, now here Y and MX n are trans to each other and that is what is happening here.

Now as you can see that when they are cis to each other, this syn product is formed. And this is anti product. But interestingly, this is not formed with this and this is not formed with this. So that means it is a highly stereospecific reaction. So if we take these two, we get this product. And if we take these two, then we get this product.

How does this reaction occur? We will discuss about it through the various transition states that we can think about it.

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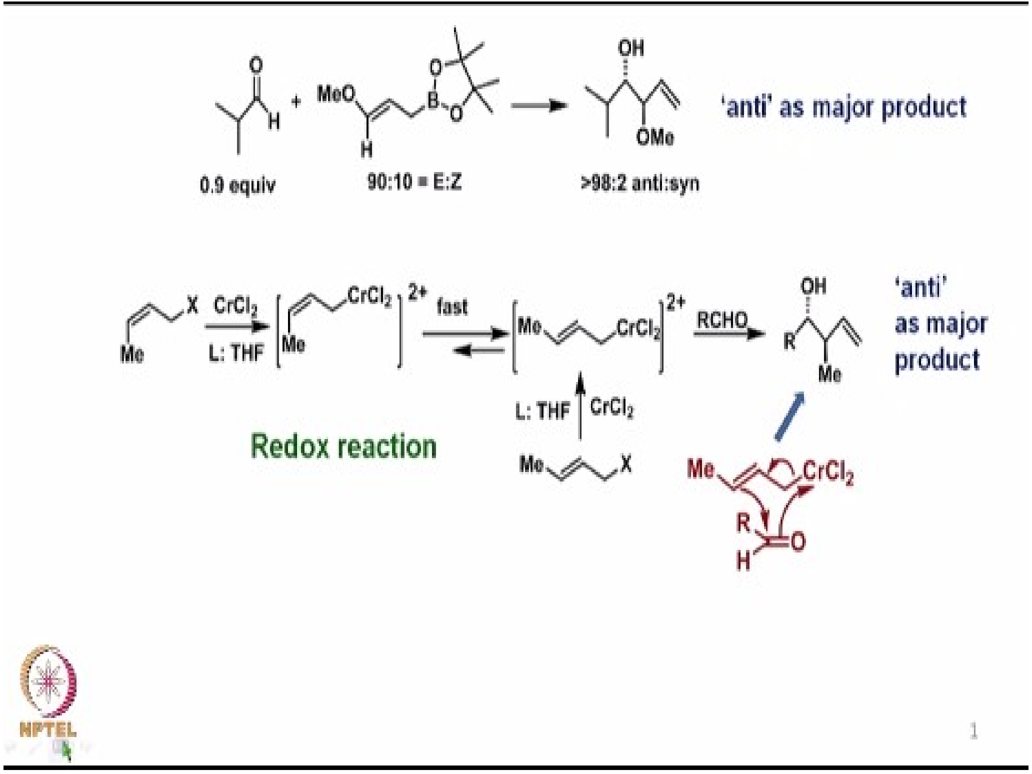

But before that, as you can see, we have some examples. If we start with an aldehyde of this kind and react with the allylboronate of this type in which the double bond has a mixture of E and Z isomers in which the E isomer is dominating, that is 90:10. Then when the reaction occurs, we get the corresponding homoallyl alcohol as the product in which the anti syn ratio is 98:2.

That means anti product is the major product. On the other hand, if we start with an allylhalide or allyl substrate of this kind in which the double bond is cis oriented and react with chromium chloride, then what happens is initially there is an oxidative addition to form this kind of chromium species, which still has that double bond in the cis orientation.

But then, it undergoes fast equilibration to the chromium species of this kind in which the double bond now has become trans oriented, which can also be obtained if we start with the corresponding trans allyl starting material instead of cis allyl starting material. Then we get this mainly as the chromium species having the trans oriented double bond.

Now this particular trans oriented double bond containing chromium species then reacts with the aldehyde and leads to the formation of the anti homoallyl alcohol as the major product. Now the way reaction works is this chromium species interacts with the aldehyde where there is a chelation between chromium and the oxygen of course.

And then there is a C-C bond formation here leading to the expected homoallyl alcohol as the major product in anti stereochemistry as shown here.

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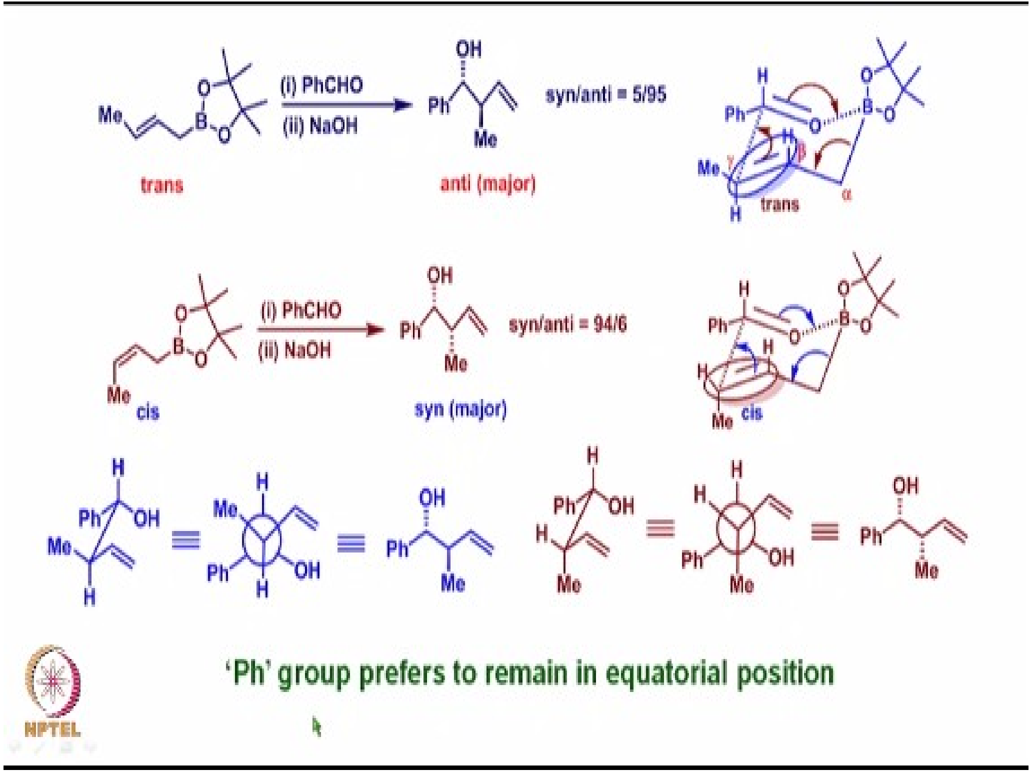

'Ph' group prefers to remain in equatorial position

Now how do these reactions of allylboronates proceed with aldehydes then we can look at it carefully and what is the transition state. For example, if we start with this allylboronate in which the double bond is trans oriented and react with say benzaldehyde followed by basic workup, it leads to the formation of the corresponding homoallyl alcohol in which the syn anti ratio is 5:95.

That means anti product is the major product. Now we look at the transition state which is like this, in which the benzaldehyde is oriented in such a way that the phenyl group is equatorially placed. And then oxygen interacts with the boron of the allylboronate, which has a trans double bond as shown here. In this condition then the carbon-carbon bond formation takes place and of course, that leads to the formation of the anti as the major product.

Likewise, if we start with the cis allylboronate, then we get the corresponding homoallyl alcohol as the major product in which syn anti ratio now is 94:6. That means, now syn product is the major product. Again we can write the similar type of transition state. We write that the benzaldehyde is put in such a fashion that oxygen of course chelates with the boron, but the phenyl group again remains in the equatorial position.

Now the products that are formed from these two transition states could be written up like this here as a sawhorse projection or a Newman projection or in a zigzag fashion. And also from here we can write the similar type of orientations of the product. Now we will stop it today and we will look at some of the aspects of these types of reactions next time. Till then, bye and thank you and take care. I will see you next time.