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

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Lecture - 53
Allytin Chemistry: Mechanism, Stereochemistry and Synthetic Applications

Hello everyone, welcome to today's class. I hope you went through the content of the last class. We will briefly look at what we did in the last class. We started with the allyl indium chemistry.

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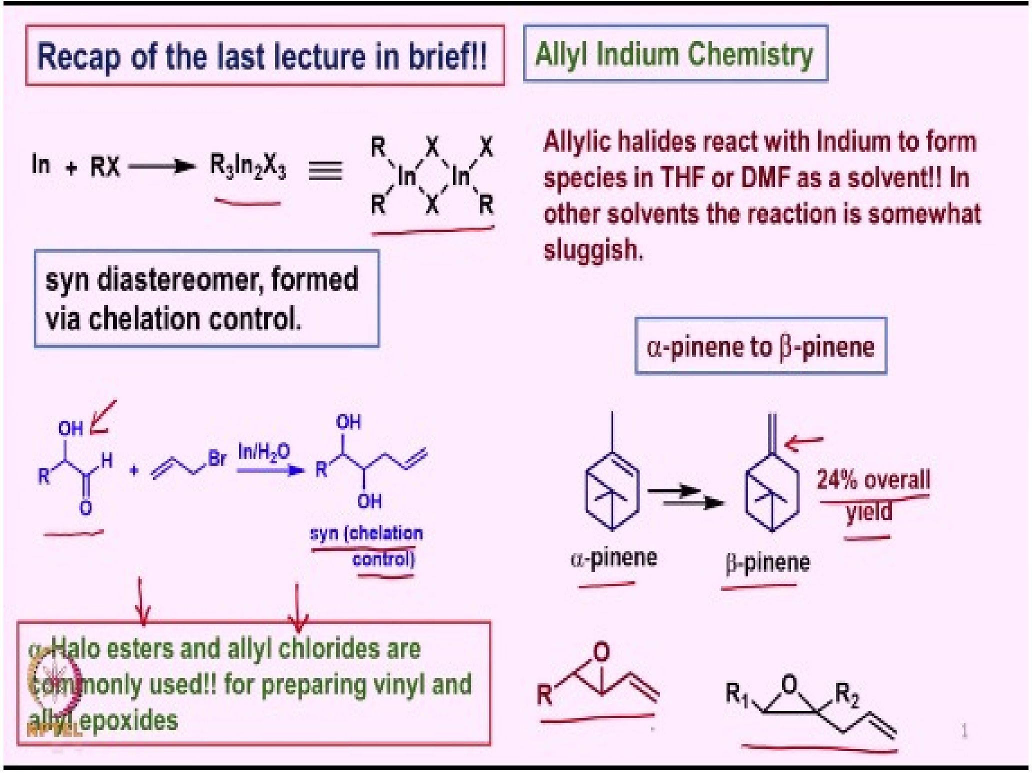

Recap of the last lecture in brief!!

Allyl Indium Chemistry

$In + RX \longrightarrow R_3In_2X_3$

Allylic halides react with Indium to form species in THF or DMF as a solvent!! In other solvents the reaction is somewhat sluggish.

syn diastereomer, formed via chelation control.

α-pinene to β-pinene

α-Halo esters and allyl chlorides are commonly used!! for preparing vinyl and allyl epoxides

And as you can see here that when indium metal is reacted with any halide particularly allyl halide, then we get as an intermediate of this type where, of this kind here, and which has a structure of this type. And that reacts with the aldehyde or a ketone, especially in a DMF or THF as a solvent, because in other solvents the reaction is somewhat sluggish. And in these cases, we get a mixture of syn and anti products.

However, if we have a chelation control, particularly of this type, when you have a hydroxy group, which is present alpha to the carbonyl group, then there is a chelation control. And we saw in the last class that we can get specifically syn product through chelation control. Then we also looked at how alpha pinene can be converted to the beta pinene although the yield is only 24%, overall yield.

But still it is a very important reaction since alpha pinene which is thermodynamically more stable olefin which is a trisubstituted olefin gets converted to beta pinene which is having an exomethylene group here, which is thermodynamically less stable. So therefore, it is a very important reaction. And therefore, it is a very good application of the indium based isomerization.

And then we also looked at the formation of such kind of vinyl epoxide or allyl epoxides using alpha haloesters of different kinds and allyl chlorides. And thus we were able to make these kinds of functionalized epoxides. Now we will proceed further today to see other reactions especially of the allyltin compounds.

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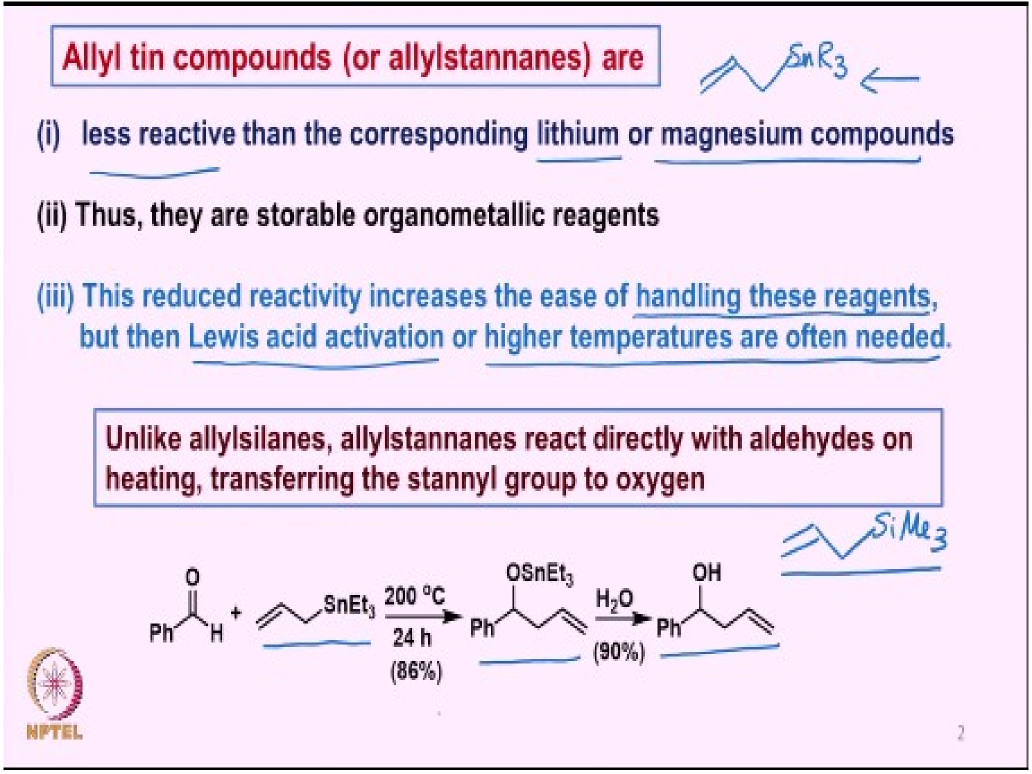

Allyl tin compounds (or allylstannanes) are

(i) less reactive than the corresponding lithium or magnesium compounds

(ii) Thus, they are storable organometallic reagents

(iii) This reduced reactivity increases the ease of handling these reagents, but then Lewis acid activation or higher temperatures are often needed.

Unlike allylsilanes, allylstannanes react directly with aldehydes on heating, transferring the stannyl group to oxygen

So allyltin compounds or allylstannanes which are like of this type when you have say allyltin having different substituents. Now there is a more covalency between carbon and tin bond and therefore, they are generally less reactive than the corresponding lithium or magnesium allylated compounds. Thus they can be stored easily and therefore they are more easy to handle.

The reduced reactivity because of the covalency of the carbon-tin bond, the reduced reactivity increases the ease of handling as you can imagine that it is much easier to handle such compounds if they are relatively more stable and less reactive. And we need however, Lewis acid activation or we need high temperature. That is the only difference that we have it in comparison to allyl lithium or allyl magnesium compounds.

So for example, unlike allylsilanes, allylstannanes react directly with aldehydes on heating. That is, for example if you have which we will be taking up little later is you have an allylsilane for example here of this type, they require Lewis acid. So in comparison to that allyltin compounds of this type do not require necessarily Lewis acid, but they can also be at high temperature, allowed to react with aldehydes to form this type of intermediate.

So if we take an allyltin compound, which then reacts with an aldehyde at 200 degrees, then we see that we get this there is a transfer of the tin to the oxygen and therefore, we get this allyltin ether type of molecule or homo allyltin ether type of molecule which upon hydrolysis leads to the corresponding homoallyl alcohol. So this is done at high temperature.

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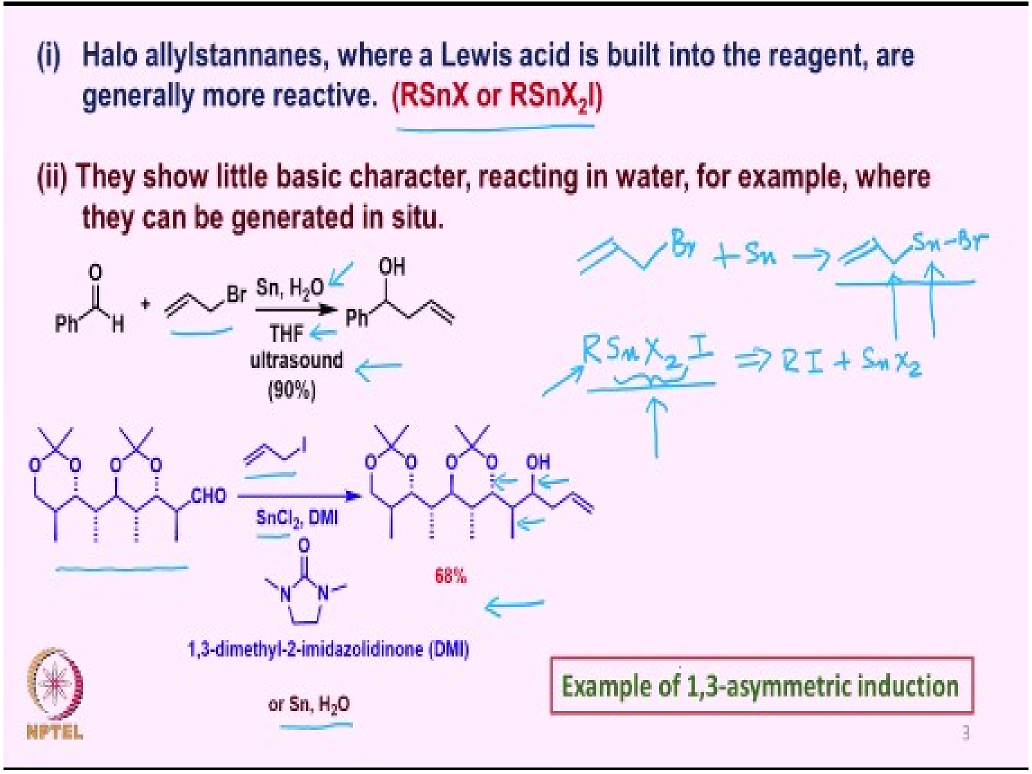

(i) Halo allylstannanes, where a Lewis acid is built into the reagent, are generally more reactive. (RSnX or $RSnX_2I$)

(ii) They show little basic character, reacting in water, for example, where they can be generated in situ.

Example of 1,3-asymmetric induction

Now if we take a halo allylstannanes where a Lewis acid is built into the reagent are generally more reactive. So if we have the reagents of this type here like this, which can be prepared from the corresponding allyl halides such as allyl bromide. So if we take an allyl bromide, it can be expected that, that reacts with say tin and it forms an intermediate of this type where there is an oxidative addition.

And this is the one that acts as a kind of inbuilt Lewis acid as well as the allyl transfer reagent. So there is an allyl transfer reagent from here. And of course, you have a kind of Lewis acidity associated with this particular part of the reagent. So these molecules of this type or if we can also prepare something of this type we have here $RSnX_2I$, which can be prepared from say for example, it can come from our RI and SnX_2.

So if we take a tin halide and react with a corresponding ally iodide or so, so we can get a reagent of this type where there will be transfer of the R group and in the presence of this part which acts like a Lewis acid. Now these reagents of this type which is RSnX or $RSnX_2I$ type of reagents are kind of relatively stable in water and they can be reacted in the aqueous medium also.

Therefore, we can use water as well as THF as a co- solvent. And ultrasound is expected to also help. And therefore, the yield can be increased if we use ultrasound as a medium for the reaction. Likewise, for example, the second example is like $SnCl_2$ and allyl iodide.

This is what is of this type of reagent and that also reacts with the if the complicated molecule of this type, where there is an aldehyde with a with several carbon-carbon bonds or carbon-oxygen bonds with a specific stereochemistry being there. So this particular reaction can also be done either in the presence of tin chloride and allyl iodide or you can take allyl iodide and tin. And you can also do the reaction in aqueous medium.

And this is the product with high degree of selectivity that is obtained with respect to this and with respect to this. So we get the 1,3 asymmetric induction. So it is a kind of 1,3 asymmetric induction, because we are now going to react the aldehyde which is now reacting with the allyl iodide in the presence of either tin chloride or tin and therefore, there is an asymmetric induction which is of 1,3 type.

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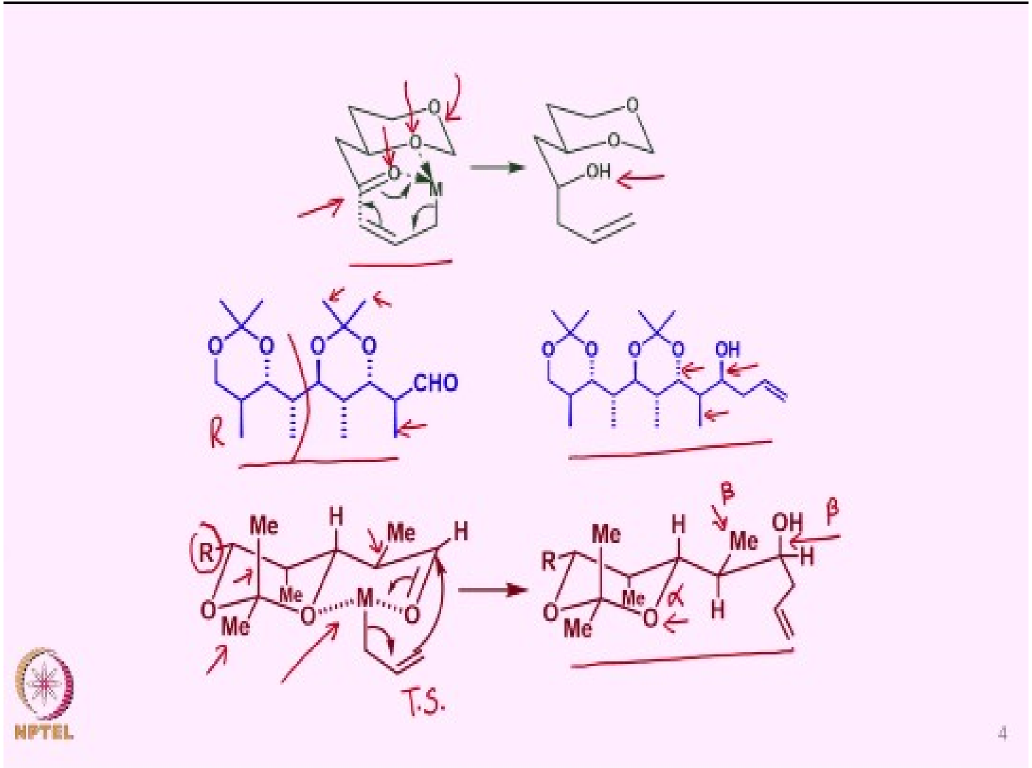

So this is how it can be seen. So if we try and write the intermediate or the transition state of this kind here, where there is an acetyl moiety present here of this kind, acetyl moiety. And when the aldehyde, which is present here reacts with the Lewis acid part of the allyl reagent, then of course there is a chelation from this oxygen here as well as through the aldehyde oxygen here.

And this is the type of transition state that is formed where allyl group is transferred. And of course, you would eventually get here OM, which is the O metal and then of course upon hydrolysis that releases the corresponding homoallyl alcohol. So this OH group is released from the OM that is O tin particular moiety.

So if we take this specific compound which we converted into this, where we said that this stereochemistry here, this stereochemistry here with respect to this stereochemistry is formed upon allylation. So we can write this particular part here, say if we can take this part here as written as R and this is what is the R group here. And then of course we have oxygen, carbon, oxygen.

This is the acetyl part, these are the two methyl groups here. This is a methyl group, this is a methyl group, that is what we have written here. These two methyl groups and of course this is the second oxygen. And then you have this methyl group here, here, this is the methyl here and then you have an aldehyde.

When such a chelation occurs as it is shown here, if such a chelation occurs, then of course what we have is, if we have this, then of course, allyl group gets transferred from the lower side and this is what the lower side is the allyl group coming. And therefore, the oxygen goes into the mode of beta hydroxy.

So this is what the beta hydroxy which is upon the reaction of the allyl group or upon transferring of the allyl group from the lower side, the OH group becomes on the top side which is the beta side. And this is also already a beta side and this is of course coming as an alpha side. So this is alpha oxygen. That is this particular carbon-oxygen bond is alpha oriented.

So this is the stereochemistry that is what is expected and the transition state is this, the transition state which leads to the formation of this particular product. So essentially what is happening is that the carbon tin bond which is carbon M bond as we have shown here acts as a Lewis acid.

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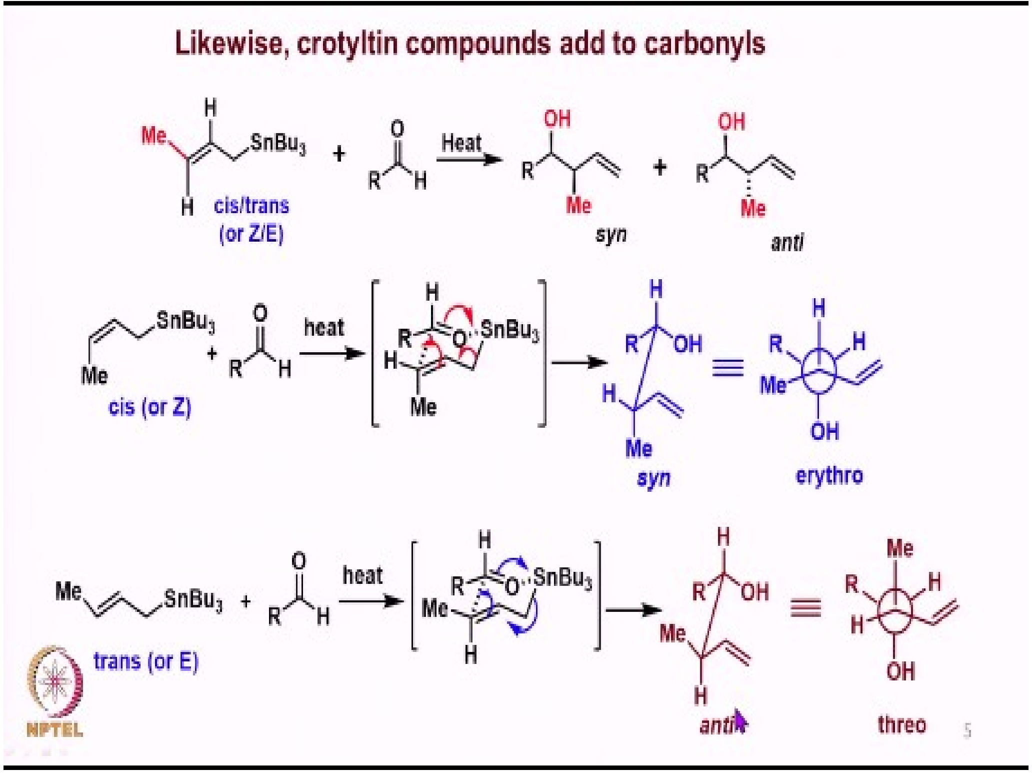
Likewise, crotyltin compounds add to carbonyls

So likewise, we can react crotyltin compounds with aldehydes and then allow C-C bond formation to take place. For example, if we take a crotyltin compound like this, which could be either cis or trans double bond, that means Z or E double bond and if we react with an aldehyde under heating conditions, then we can get either a syn product from Z olefin or a trans product or anti product from trans olefin.

So likewise we can react crotyltin compounds with carbonyl compounds to form C-C bonds. For example, if you start with a crotyltin molecule like this in which the double bond is either Z or E oriented, then upon reaction with aldehyde under heating conditions, we can get either syn product or anti product. That means from Z olefin, we get the syn product and from the E olefin we get the anti product. How does it happen?

Like for example, if we start with this Z oriented crotyltin compound and react with aldehyde then we can expect to have a transition state of this kind in which now carbon-carbon bond will form where R group is equatorially oriented. And since this double bond is cis oriented, therefore we are writing the methyl group in this particular position.

When this C-C bond forms, as you can see that the OH group is pointing below and also the methyl group is pointing below and therefore, this is a syn oriented or syn configured compound, which we can write it as Newman projection like this, which is also called as erythro compound. In a similar fashion, we start with this E configured crotyltin compound and react with aldehyde, then now we have this kind of transition state where the R group is still equatorially oriented.

But now the methyl is also oriented equatorially in the transition state because it is now a trans double bond here. So this transition state then leads to the formation of this particular compound here, which is anti configured because now methyl group is pointing upwards and then alcohol is pointing downwards. This can be written up as Newman projection like this, which is called a threo compound.

So this is how the crotyltin compounds add two carbonyls and lead to C-C bond formation specifically from Z crotyltin compounds to syn products and from E crotyltin compounds to anti products.

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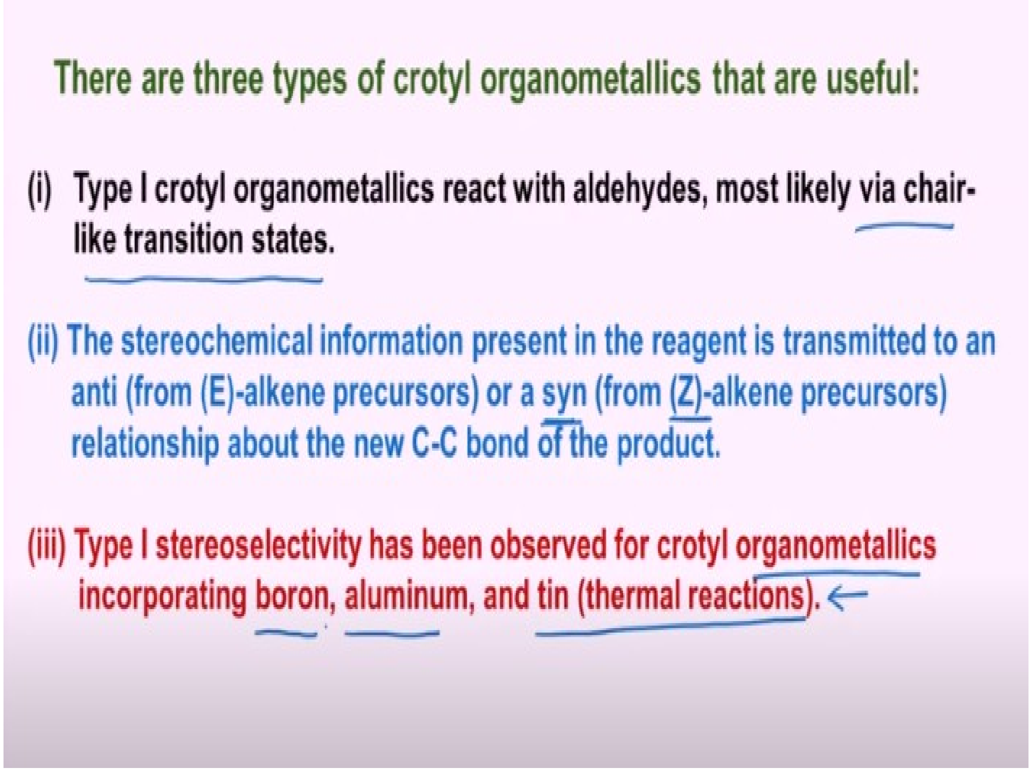

There are three types of crotyl organometallics that are useful:

(i) Type I crotyl organometallics react with aldehydes, most likely via chair-like transition states.

(ii) The stereochemical information present in the reagent is transmitted to an anti (from (E)-alkene precursors) or a syn (from (Z)-alkene precursors) relationship about the new C-C bond of the product.

(iii) Type I stereoselectivity has been observed for crotyl organometallics incorporating boron, aluminum, and tin (thermal reactions). ←

Now there are three types of crotyl organometallics that are useful. Type I crotyl organometallics are basically reacting with aldehydes mostly via a chair like transition states, of course as we saw. And the stereochemical information present in the reagent is transmitted to an anti as we saw just now that the anti product is formed from E alkene precursor.

If suppose you have allyl or crotyltin molecule which has a E alkene, then of course we get the anti product and of course from Z we get a syn product. So this is the first type of crotyl organometallics type of reagents. And the selectivity or the stereoselectivity is observed for this kind of crotyl organometallics which have a boron, aluminium and a tin type of molecules particularly via thermal reactions.

So the boron aluminium actually lead to kind of chelation in an intramolecular fashion and that leads to the formation of the product and the products are based on which kind of allyl crotyltin molecule that one is taking.

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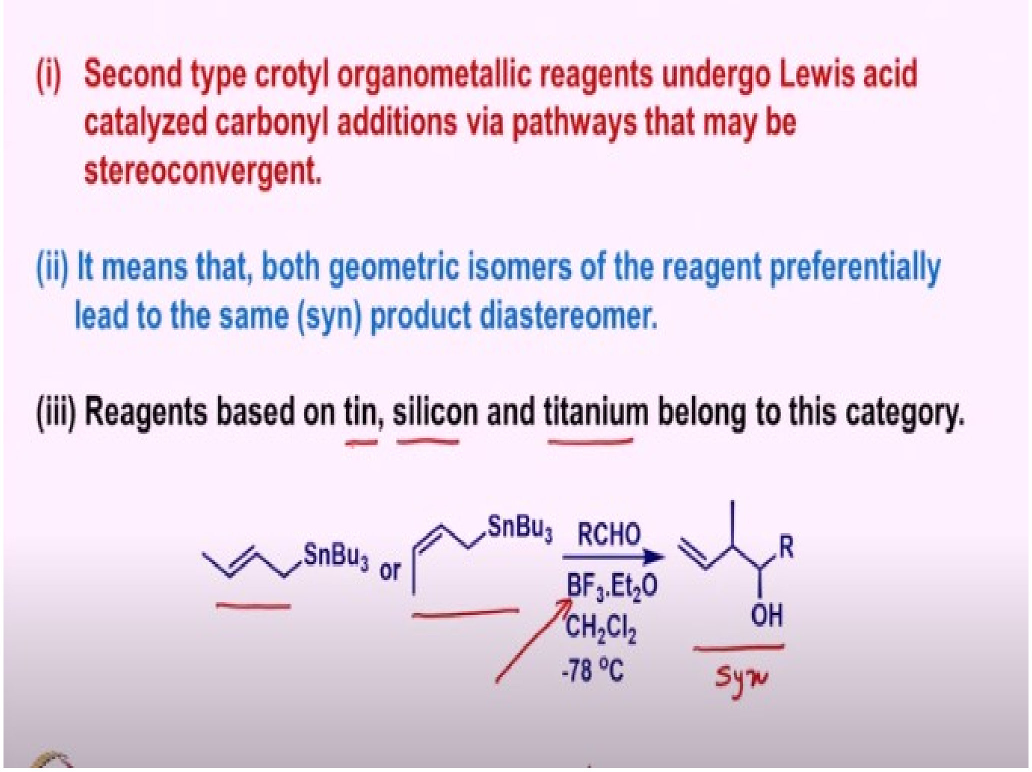

(i) Second type crotyl organometallic reagents undergo Lewis acid catalyzed carbonyl additions via pathways that may be stereoconvergent.

(ii) It means that, both geometric isomers of the reagent preferentially lead to the same (syn) product diastereomer.

(iii) Reagents based on tin, silicon and titanium belong to this category.

Now second type of crotyl organometallic reagents required Lewis acid and in this particular case, what happens there is a stereo convergent reactions are observed. It means that the irrespective of the geometry of the starting allyltin product, whether it is this or it is this, we generally get the syn product here. This is the syn product.

So both geometric isomers of the reagent preferentially lead to the same product and this type of molecules are basically from the reagents that contain tin, silicon and titanium because each one of them does require the presence of a Lewis acid for example BF$_3$ etherate or tin chloride or say titanium tetrachloride or anything of that kind that is required.

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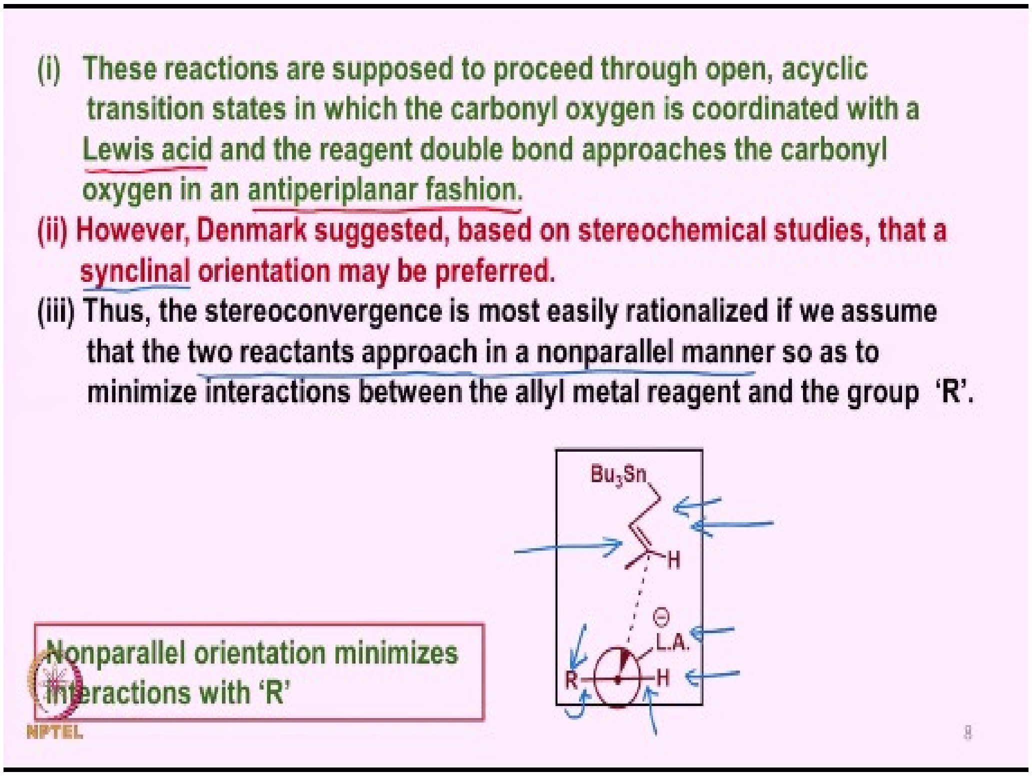

(i) These reactions are supposed to proceed through open, acyclic transition states in which the carbonyl oxygen is coordinated with a Lewis acid and the reagent double bond approaches the carbonyl oxygen in an antiperiplanar fashion.

(ii) However, Denmark suggested, based on stereochemical studies, that a synclinal orientation may be preferred.

(iii) Thus, the stereoconvergence is most easily rationalized if we assume that the two reactants approach in a nonparallel manner so as to minimize interactions between the allyl metal reagent and the group 'R'.

Nonparallel orientation minimizes interactions with 'R'

So the third type of, of course these reactions are supposed to proceed through open chain acyclic transition states in which the carbonyl oxygen is coordinating with the Lewis acid. So the carbonyl oxygen coordinates with the Lewis acid and then the reagent approaches the carbonyl oxygen in anti-parallel fashion. This is what was basically expected because it is obvious that once the chelation occurs, the approach of the nucleophile or the allyl part will happen from the antiperiplanar fashion.

But Denmark suggested based on various kinds of stereochemical analysis that the synclinal orientation is preferred. So like for example, here, as it is shown here. So basically what is happening is that when the aldehyde is oriented in this way that we have shown as a Newman projection type of orientation, the carbon oxygen bond is going backside, because R and H are here.

This is carbon R bond, this is carbon H bond of the aldehyde. And the carbon oxygen double bond is going backside to which the Lewis acid has actually interacted. And therefore, instead of the antiperiplanar fashion, this is how the synclinal fashion the allyltin product proceeds or reagent proceeds. And therefore, it is in a nonparallel fashion the reagent approaches.

So what we can say that stereo convergence easily rationalize if it is assumed that the two reactants approach in non-parallel manner so that they minimize interactions. For example, this is going away from the backside and it is approaching the aldehyde and it is coming in a synclinal fashion. So there is not much interaction with the R group.

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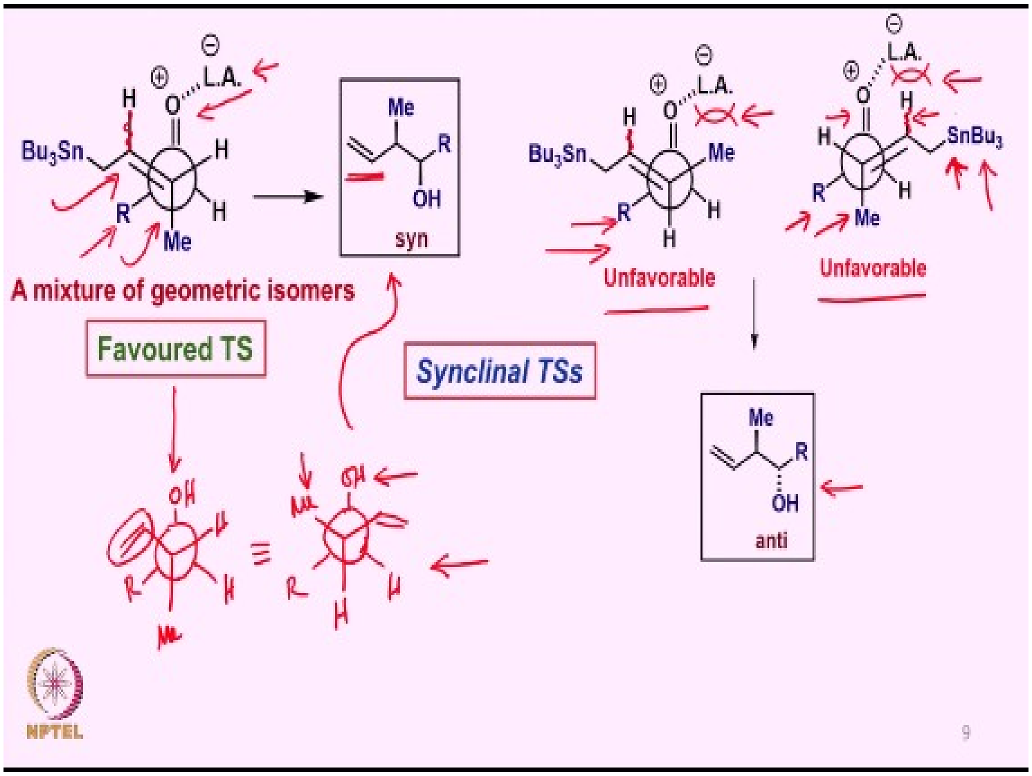
A mixture of geometric isomers

Favoured TS

Synclinal TSs

Unfavorable

Unfavorable

We can show this in a slightly different way as we can see it here, that here we are basically talking about the mixture of the stereoisomers. So we can say that this is a mixture of the stereoisomers here and therefore, it is mixture of E and Z both isomers.

So if suppose the Lewis acid interacts with the aldehyde in this particular fashion and therefore now the approach of this ally reagent occurs not in an antiperiplanar fashion, which means that it is not going to be from this direction, but it is going to be from this direction. This is what is the synclinal orientation.

And if we look at the three possibilities, where the interaction of the allyl moiety, allyltin moiety is considered with respect to the Lewis acid which is attached to the oxygen of the aldehyde, then this is supposed to be the most favoured transition state because there is no interaction of the Lewis acid with any of the substituent, either hydrogen or any other part of the molecule.

And therefore, if we can see now here, if R group and the particular vinyl group here or is oriented in a zigzag fashion, then of course, we can write it that when this reaction occurs, basically what we are trying to get it is something of this kind, OH here and H here and of course we will have this and methyl group here and H and R.

So if we can write it in this fashion that the OH group remains as it is, R group is here and H is here. And now if we orient it the methyl group here and of course, we can write it in this fashion. So both of them are same, because now what we have done it is we have brought this vinyl group up anti to the R so that we can then write as a product which is in this fashion.

And in such a situation you can see the OH group and the methyl group, both of them are pointing in the same direction and therefore this is a syn product. On the other hand, we can also write two more transition states in this particular fashion. Each one of them is synclinal orientation with respect to aldehyde.

And therefore, if we put the same reagent here like this, then of course, we expect that there is going to be a steric hindrance here with Lewis acid and the methyl group. And in this case, there is a steric hindrance with respect to either hydrogen here or the tin depending on which the stereoisomer that we are taking. Because we have started with a mixture of the olefin, the allyltin molecule.

In each case, as you can see, that if we orient in a similar fashion as we did it here, then we will see that the methyl group and the OH group are anti here as well as here anyway here, this R group is opposite to the vinyl group which will come. So therefore now hydroxy group here and the methyl group are anyway anti.

In a similar fashion you can also write it down this particular molecule or this particular orientation in such a way that if we rotate the vinyl part opposite to this carbon R bond, then we will see that we get the same product as an anti product. Therefore, considering this kind of synclinal transition states, if we look at it, then of course we expect that we get the favored product as the syn product.

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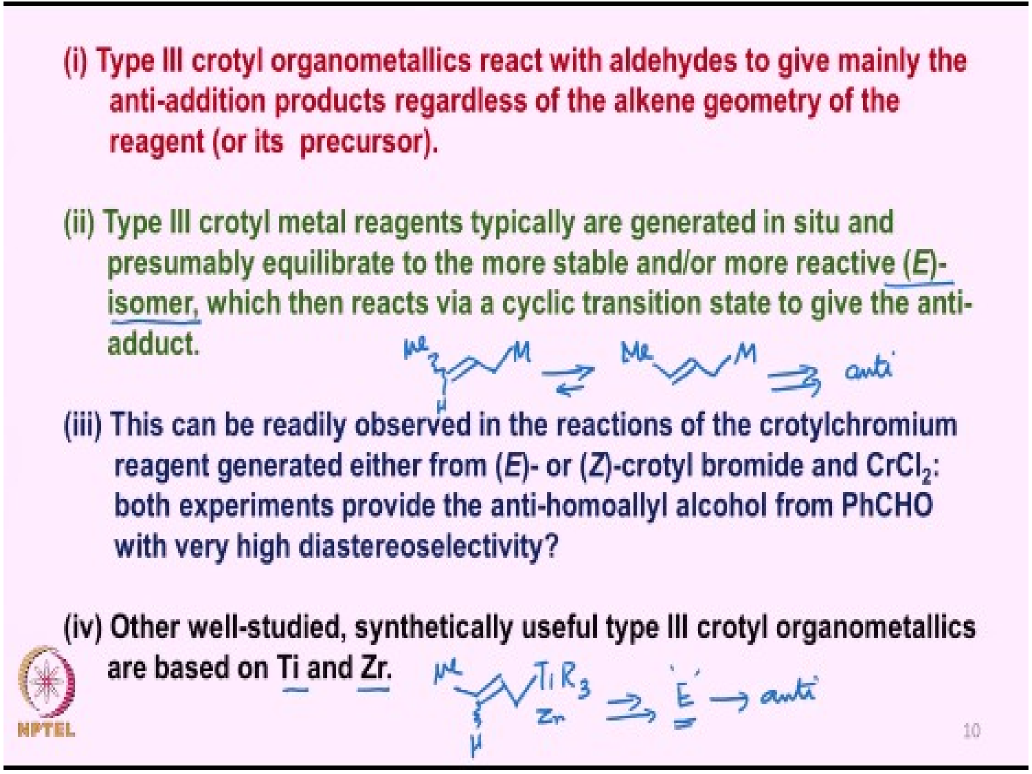

(i) Type III crotyl organometallics react with aldehydes to give mainly the anti-addition products regardless of the alkene geometry of the reagent (or its precursor).

(ii) Type III crotyl metal reagents typically are generated in situ and presumably equilibrate to the more stable and/or more reactive (*E*)-isomer, which then reacts via a cyclic transition state to give the anti-adduct.

(iii) This can be readily observed in the reactions of the crotylchromium reagent generated either from (*E*)- or (*Z*)-crotyl bromide and $CrCl_2$: both experiments provide the anti-homoallyl alcohol from PhCHO with very high diastereoselectivity?

(iv) Other well-studied, synthetically useful type III crotyl organometallics are based on Ti and Zr.

And the type III crotyl organometallics react with aldehydes to give mainly the addition products regardless of the alkene geometry. This is exactly opposite of what we just now talked. And the reason for that is that this type of third type of crotyl metal reagents are basically such reagents which equilibrate to the more stable and more reactive E isomer. So this equilibration is very important.

Because irrespective of which geometry that you have of the allyl metal bond, here if we have something like this, whether it is here, there is a orientation of the methyl group, it is a mixture. And eventually it equilibrates to the E isomer. And if that happens, then of course, we always get the anti product. This will lead to anti product. So and this is possible in cases where there is a titanium and zirconium based organometallics are used.

So you have something like this here. And if we have a mixture of the reagents and if we have a titanium here and whatever the R3 here or zirconium, you have a zirconium, then they equilibrate to the E isomer. And of course, that leads to the anti product. So this is how it happens.

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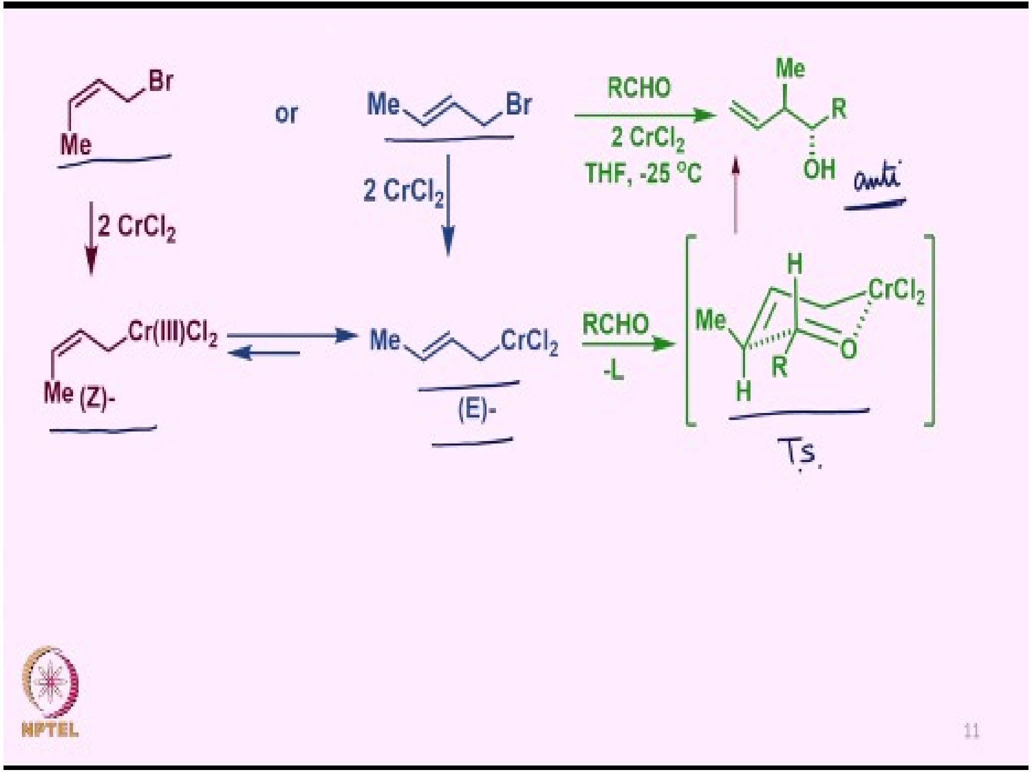

We can see here for example or even chromium based reagents. So you have here a chromium reagent which is formed from by reacting Z isomer or E isomer of the crotyl bromide and if they react with chromium chloride, then what they form is reagent of this type or this type, which then equilibrate and majority of it forms in this fashion which reacts with the aldehyde through this transition state.

And this transition state leads to the formation of the anti product. So this is how the reaction occurs in the third type of crotyl reagents. And therefore, we have a choice of different types of reactions that we can think. First one is of course syn product formation. The other one is the anti one.

And in some cases you get a mixture of anti and syn, especially when it is a heating compound using heating condition using allyltin reagents. So we will stop it here today. And then we take up the some other aspects in the next class. So take care of it and we will see next time. Thank you.