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

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Lecture - 52
Allylindium Chemistry: Mechanism, Stereochemistry and Synthetic Applications

Hello and welcome you all for today's class. Last time we were looking at the Shapiro reaction and some allylation of various kinds of aldehydes or carbonyl compounds using different allyl metal reagents. In the Shapiro reaction what we did was to make use of the vinyllithium for example of this kind.

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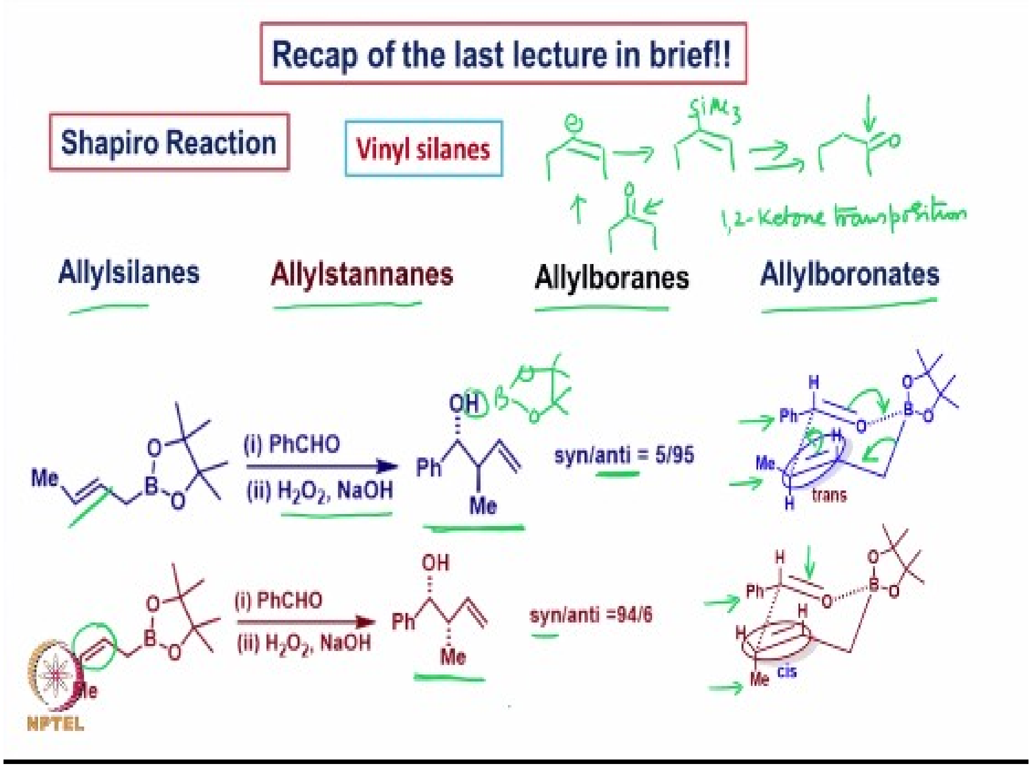

Recap of the last lecture in brief!!

Shapiro Reaction

Vinyl silanes

Allylsilanes

Allylstannanes

Allylboranes

Allylboronates

And then we converted into vinylsilane and then as we saw that we can convert this into the epoxide and eventually convert into a carbonyl group and the carbonyl group was actually started in the substrate to be in this particular position and now we have moved into this position and that is what is called as 1,2-ketone transposition.

So after that we looked at how allylsilanes, allyltin, allylboranes and allylboronates of this type of substrates. And of course, we also saw how crotyl substrates can be equilibrated in depending on which metal salt is used. And then towards the end, we looked at these allylboronates, how do they react with say benzaldehyde. And if the geometry is trans, then we get this anti product as the main product.

This reaction we discussed in detail. Of course, the vinyl group here for example, if we move the electron density in this particular fashion, then of course, we get this particular product here. As I mentioned that the phenyl group is equatorially oriented and therefore, that will always be in that particular position. It is only now remaining borons have to be boron has to be close to the oxygen and the geometry of the double bond is fixed.

And therefore now as you can see that the OH group is going down and the methyl group is going up. Therefore, this particular part of the molecule is also fixed. We have used hydrogen peroxide and sodium hydroxide as a reagent basically because product that will form will have a boron. So basically instead of having hydrogen here, first it would be a boron which will be then needed to be removed by oxidatively.

And that is what the role of the hydrogen peroxide and sodium hydroxide is. And in a similar fashion when we took the corresponding cis product, then of course, we have the product in which the syn product is formed in large amount as you can see it from here. Again phenyl group is in equatorial. The geometry of the double bond is fixed. And now if we look at it, the methyl is pointing downward.

The hydroxy group is pointing downward in the transition state and that is exactly what is being reflected here. So this is what we did it and we will now look at little bit more in detail about allylsilane, allyltin, allylboranes, etc., a bit later. But first we would also like to look at what is an allyindium. So indium is also one of the very important metal and has been utilized in organic synthesis quite well.

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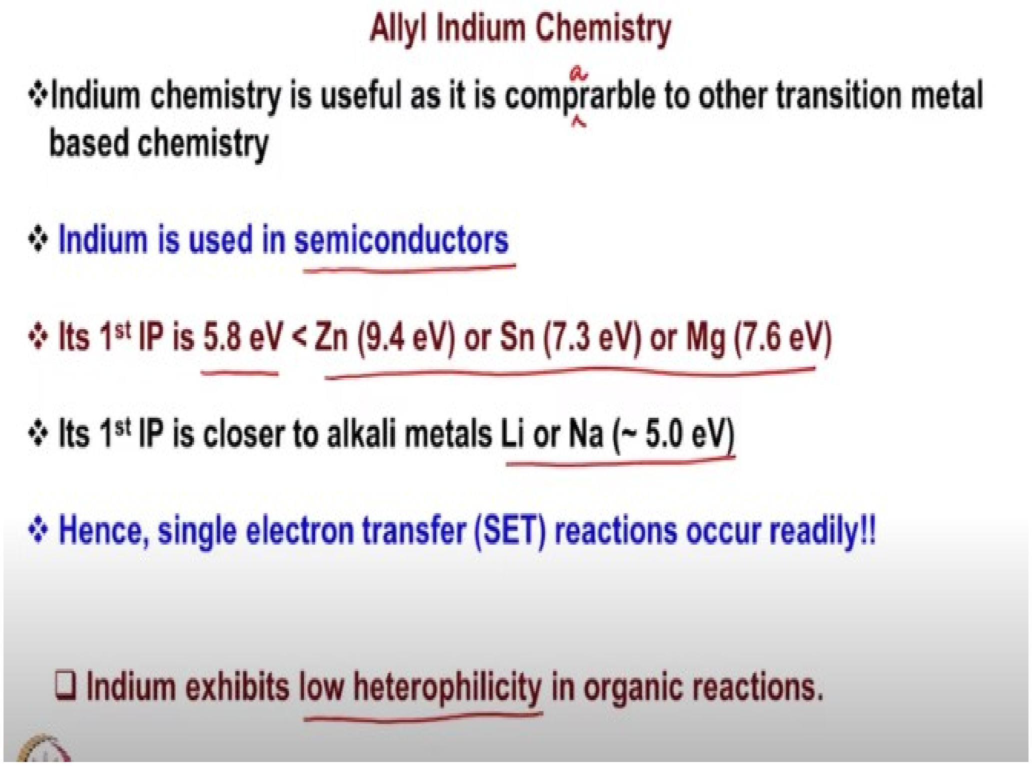

Allyl Indium Chemistry

- Indium chemistry is useful as it is comprarble to other transition metal based chemistry
- Indium is used in semiconductors
- Its 1st IP is 5.8 eV < Zn (9.4 eV) or Sn (7.3 eV) or Mg (7.6 eV)
- Its 1st IP is closer to alkali metals Li or Na (~ 5.0 eV)
- Hence, single electron transfer (SET) reactions occur readily!!

☐ Indium exhibits low heterophilicity in organic reactions.

And indium chemistry is useful as it is comparable as it is, this should be a, comparable to other transition metal based chemistry. Indium of course, as a utility is used in semiconductors, but that is not something that we are now right now worried about it. Its first ionization potential as you can see is 5.8 electron volt, which is less than that of zinc or tin or even magnesium for example.

So its first ionization potential is actually closer to lithium or sodium. Therefore, very readily it can transfer one electron. And since it is of a very large size that means it shows low heterophilicity in organic reactions. The hetero atoms do not easily attach to the indium species and therefore, the reactions can be tolerated in water or other medium.

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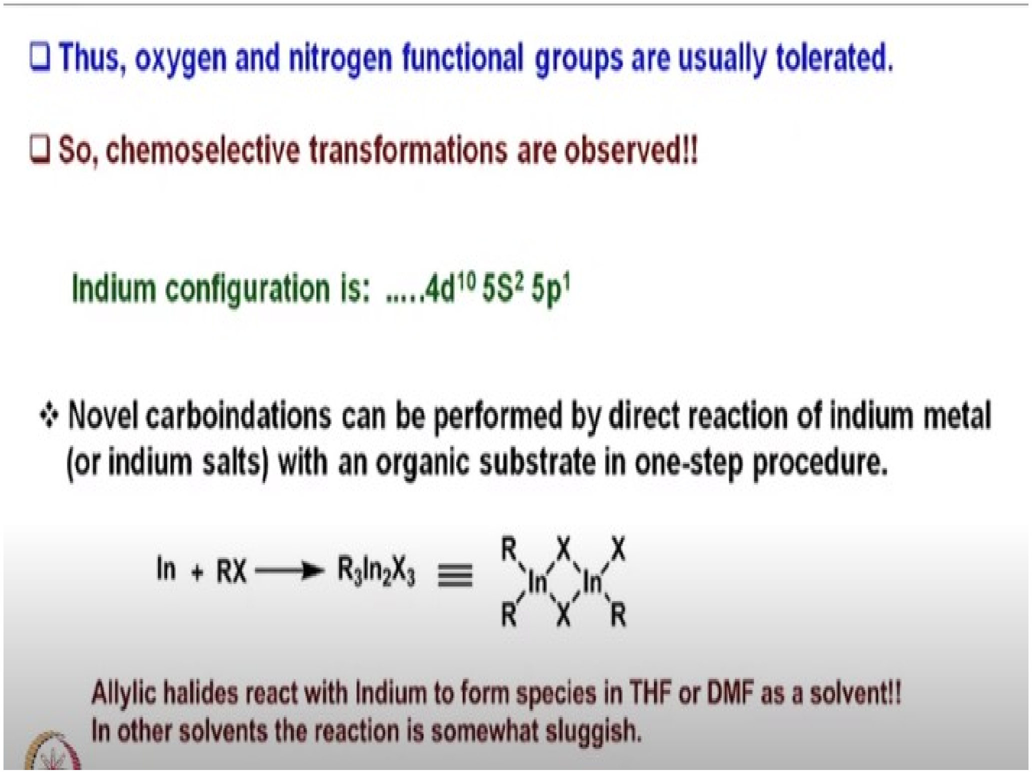

❑ Thus, oxygen and nitrogen functional groups are usually tolerated.

❑ So, chemoselective transformations are observed!!

Indium configuration is: .....$4d^{10}\ 5S^{2}\ 5p^{1}$

❖ Novel carboindations can be performed by direct reaction of indium metal (or indium salts) with an organic substrate in one-step procedure.

$In + RX \longrightarrow R_3In_2X_3 \equiv$

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

Thus indium is low heterophilic in nature and thus oxygen and nitrogen functional groups are usually tolerated. That means, in the substrate we can have functional groups which can be of oxygen and nitrogen origin. Also we see chemoselective transformations using indium based reactions. Since indium configuration is 4d10 5s2 5p1 it is found that it reacts with the RX that is halides, R could be allyl or any other organic halides.

And then form this kind of species R_3 IN $_2$ X $_3$ whose structure has been found to be of this kind. And this allows carboindations to take place with organic substrates in one-step procedure. That means, now we react this with say aldehydes or any other ketones. Then what we can do is carry out a C-C bond formations. And such reactions can be done in solvents like THF or DMF.

In fact, THF or DMF solvents are generally preferred, because in other solvents the reaction is found to be somewhat sluggish. Now we do not really have to isolate this organometallic species, we can simply mix indium or indium salts with the halides and along with them the aldehyde or a ketone to which the reaction has to be done. And we then of course, let the reaction complete and isolate the product as is required.

And we do not really have to isolate the organometallic species unlike in cases where such organometallic species have to be isolated. But this is the advantage of using indium based reaction.

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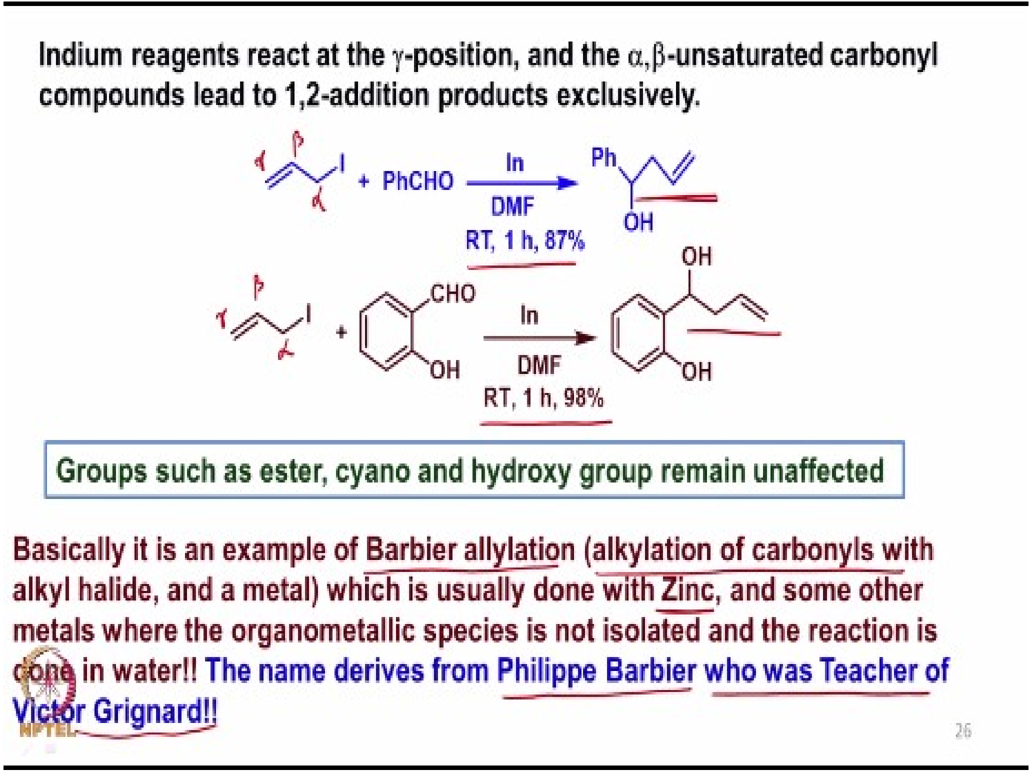

Indium reagents react at the γ-position, and the α,β-unsaturated carbonyl compounds lead to 1,2-addition products exclusively.

Groups such as ester, cyano and hydroxy group remain unaffected

Basically it is an example of Barbier allylation (alkylation of carbonyls with alkyl halide, and a metal) which is usually done with Zinc, and some other metals where the organometallic species is not isolated and the reaction is done in water!! The name derives from Philippe Barbier who was Teacher of Victor Grignard!!

Like for example, indium reagents react at the gamma position as we have discussed earlier. For example, this is the substrate that we have here. You have alpha, beta and gamma position here. So alpha, beta and gamma position here. So reaction occurs at the gamma position basically. And it can react with aldehyde in the presence of DMF and it is only 1 hour reaction, it is very fast.

And you can also carry out such reactions in aqueous medium and the corresponding allyl alcohol is obtained, homoallyl alcohol is obtained. Actually, it is an allylic substrate that is being used. And therefore, we get the homoallylic alcohols. And as you can see, the yields are fairly high. Interestingly in such cases, ester groups, cyanohydroxy groups remain unaffected. So the reaction is fairly mild.

It is actually an example of what is called as Barbier allylation or alkylation of carbonyl groups with alkyl halide in a metal. It is usually done with zinc but some other metals also can be used in such a reaction. And the name actually derived from Philippe Barbier who was actually teacher of Victor Grignard, who introduced the Grignard reaction. So it is a very interesting Barbier allylation, which is very much utilized in organic synthesis.

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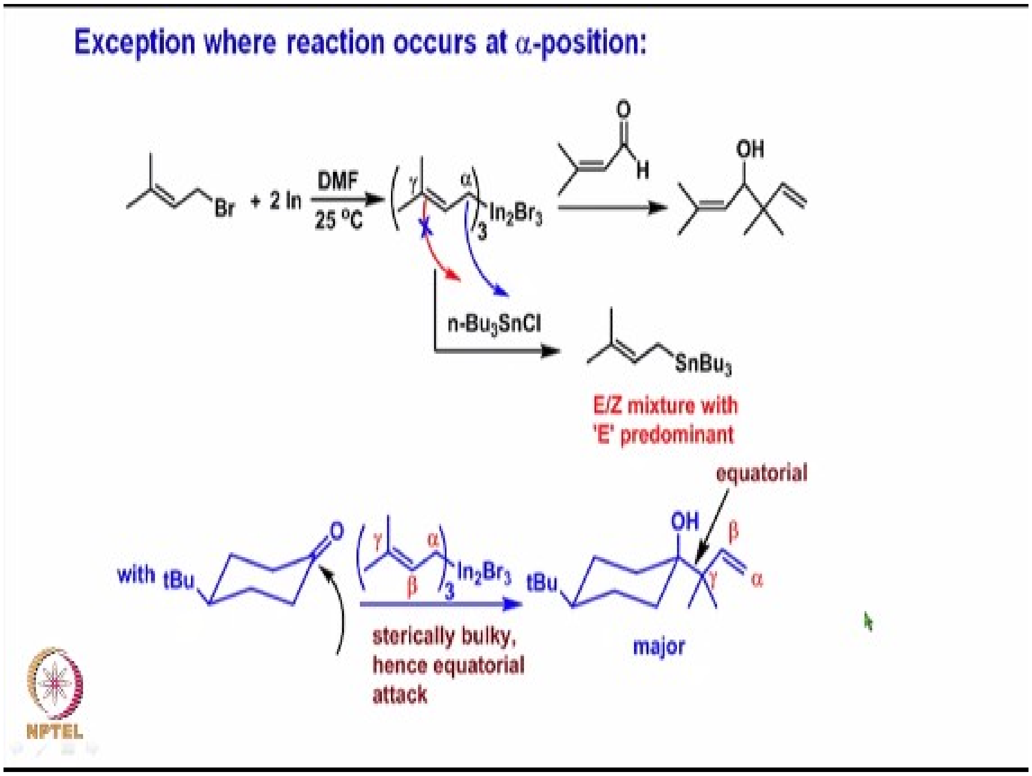

Exception where reaction occurs at α-position:

And we can see that majority of the times it is the gamma position where the reaction occurs. But if you have a sterically hindered substrate, then sometimes one can see alpha position being attacked. For example, if we take an allyhalide of this type and react with indium, which will in situ form this type of indium species.

And if we react it with say this particular alpha, beta unsaturated aldehyde, then the reaction occurs from the gamma position to this aldehyde leading to the formation of this type of product. On the other hand, if the same indium species which is formed in situ is allowed to react with sterically hindered tri-n-butyltin chloride, then the alpha attack takes place to form this type of allyl tributyltin in which of course the E product is the major product.

Now in the reaction of ketones of this kind, which is a cyclic ketone, obviously the attack will be preferred from the equatorial side. But in this particular case, there are no substituents around a ketone and therefore, the reaction occurs from the gamma position only but from the equatorial side to lead to the formation of this type of a major product.

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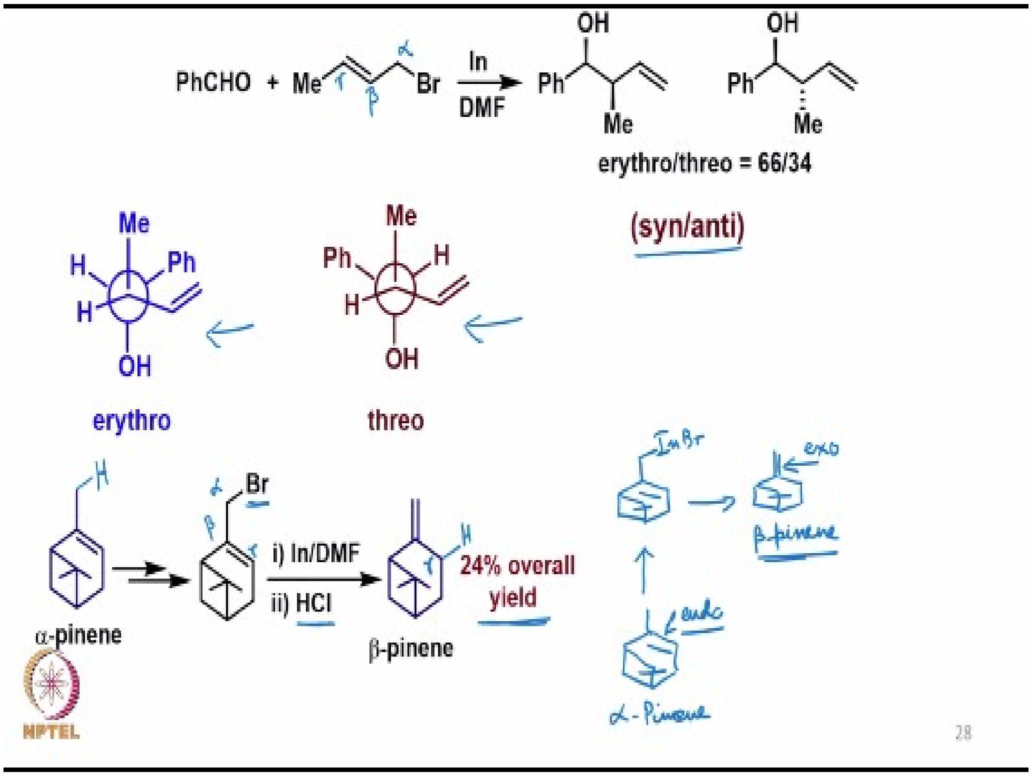

Now if we react with crotyl based substrates, then we can see that the reaction does occur. This is the alpha position and this is the alpha position, this is the beta position and this is the gamma position. The reaction as obviously as expected is taking place via gamma orientation. And as we have already seen that when we have a substrate like this as you can see here, syn and anti is forming 66 into and 34 ratio for example.

So this is erythro and this is the threo and if we look at the, that means in this particular case, we do not have that strong this ratio difference in terms of syn and anti as we had seen in the case of boron. But nevertheless, the reaction does take place and of course you get larger amount of the syn product here, erythro and the threo product in this particular fashion.

And now if we look at the further reactions of this is alpha-pinene. If we take alpha-pinene and we carry out the functionalisation at this particular higher carbon atom and make the corresponding bromide and react with indium. And once the indium reaction occurs, now this is the alpha position, this is the beta position, and this is the gamma position.

Now you see what is happening is that the reaction is occurring with the protonation at the gamma position. So this is the gamma position where the proton is coming. So basically what is happening is that, when reaction of pinene, which occurs in such a fashion that the say you have an indium bromide, I will put it in this fashion. And then you are getting it a product which is this.

So we start with this thermodynamically more stable product, which is an alpha pinene and we are getting a beta pinene in which the double bond is exo double bond here. It is exo whereas here it is endo double bond. So this is more stable, whereas this is less stable. And therefore the yield is not very high, the 24% only is there. But nevertheless, this is a very useful conversion of the alpha pinene to the beta pinene.

Now I suggest that you people can take up and see how this erythro and the threo products are formed, what is the transition state. That we discussed it in the boron case. You can try and work it out and see how it is and we can discuss about it in more detail when we have the question answer sessions.

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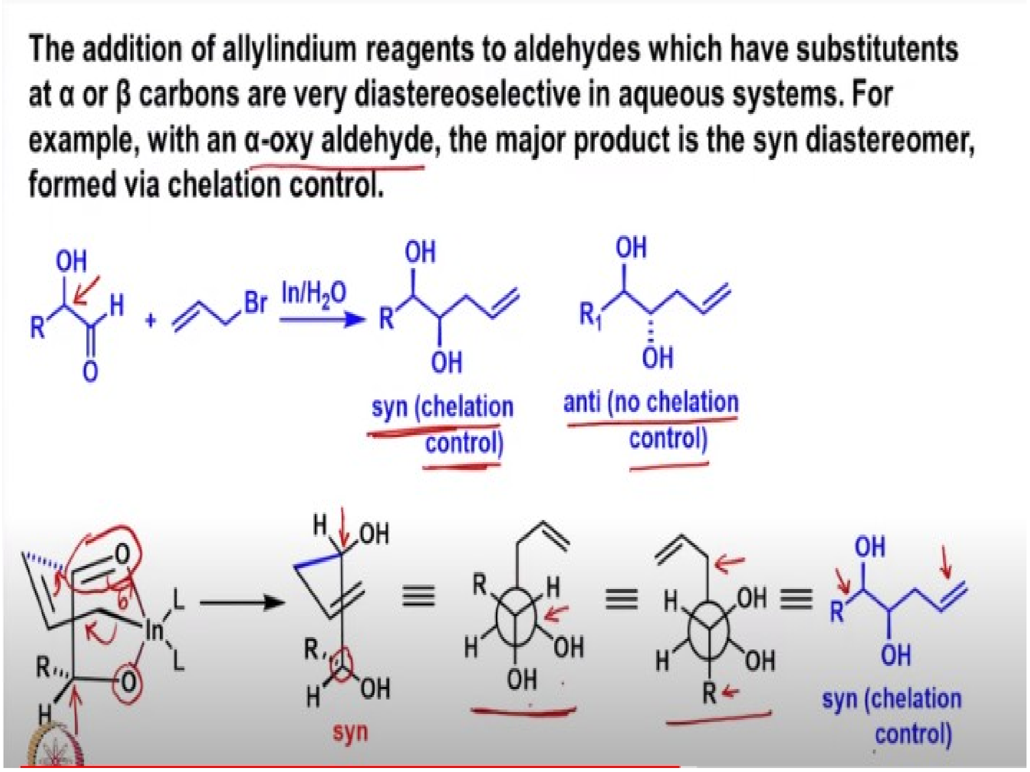

The addition of allylindium reagents to aldehydes which have substitutents at α or β carbons are very diastereoselective in aqueous systems. For example, with an α-oxy aldehyde, the major product is the syn diastereomer, formed via chelation control.

Now the addition of allylindium reagents to aldehydes which have substituents at alpha or beta carbon atom. For example, if you have a substituent which is something like this here, then a very diastereoselective reaction is possible in aqueous medium. For example, with an alpha oxyaldehyde, this is what we are talking about here. The major product is the syn diastereomer.

So actually it is a chelation control, anti is no chelation actually. So what is happening is that, if you look at intermediate here, as you can see, this is the aldehyde portion here, the aldehyde portion is here. Then you have the aldehyde carbon is attached to the next carbon atom and then the OH is here. So this part is basically an OH part and this part is of course, the R group which is present here.

Now if you orient, if we orient the allylindium in such a fashion that if the carbonyl group is oriented here, then you have this 1, 2, 3, 4, 5, 6 this is six-member transition state here, a six-member transition state in which now alcohol is also having a chelation with the indium. So therefore, this geometry is restricted here and this is the transition state in which both the oxygens are attaching to the indium and therefore the transition state is restricted.

Now once the indium gets transferred to this, then of course, as you can see that you can put it in this version that you have, this is how the carbon-carbon bond will form, allyl group comes in here. And of course, the orientation of this particular diol remains in this fashion. Now if we put it in a Newman projection formula, it would look like this, as we can imagine that this particular carbon atom being at the back of it.

And if we turn it around, then the hydroxy group comes below, hydrogen comes below and the allyl group goes on the top. And of course, if we turn this particular portion towards us or the hydroxy group going behind or in such a fashion that you know R group comes on the top and the hydrogen goes on the top then the hydroxyl comes in the plane of the blackboard the way it is shown here.

Of course, you can see now that in both the cases we can also rotate it and bring it to this new position being equivalent to this particular position here. And if we see that this R group and this allyl group are actually in a form in a zigzag fashion in this particular way it is shown then the two hydroxy groups would be pointing in the same direction. That is the reason why they are called as syn products basically.

So there is chelation control and therefore, since as you can directly see from here for example, these two are pointing downward and when you turn it around, then R and allyl group will be opposite to each other. So this is how the syn product is formed. And that is not the case if there is no chelation control.

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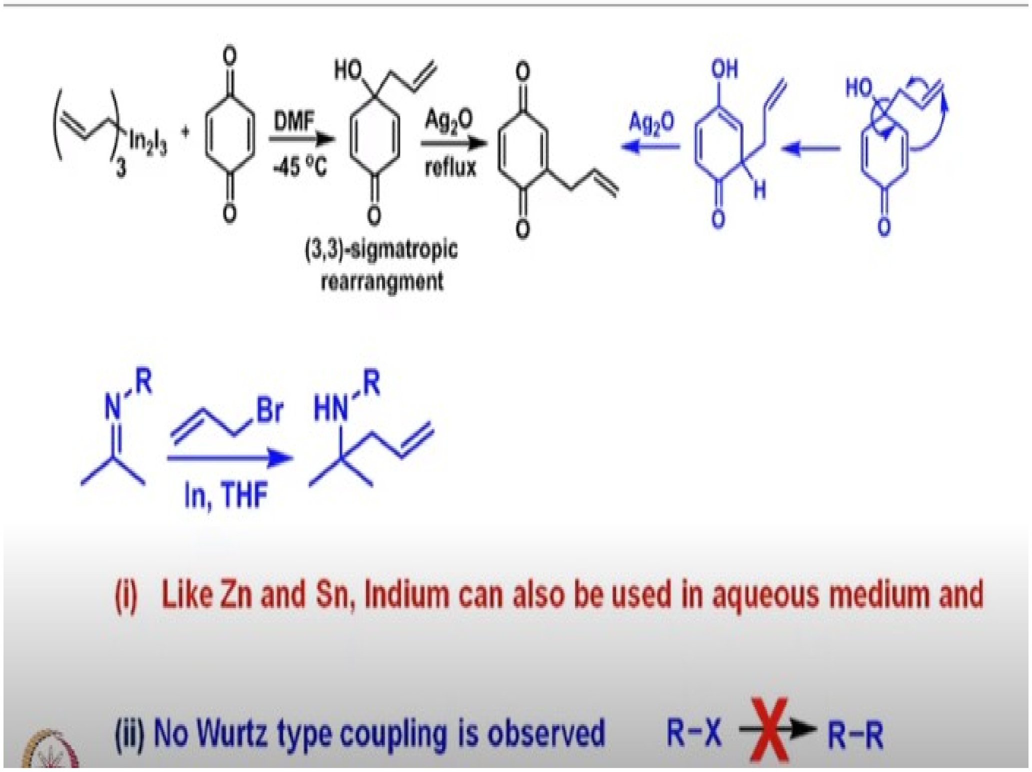

(i) Like Zn and Sn, Indium can also be used in aqueous medium and

(ii) No Wurtz type coupling is observed $R{-}X \not\rightarrow R{-}R$

Now it is also seen that if we start with an allyindium species like this and react with benzoquinone, then even at -45 degrees in DMF, the corresponding homoalcohol is easily formed. And it is found that if one refluxes this species in the presence of silver oxide, then the corresponding substituted benzoquinone is formed.

The way reaction takes place is this homoallyl alcohol which can be written like this here, it undergoes 3,3-sigmatropic rearrangement of this kind, where the allyl group now has attached itself on this particular position and then under the oxidation conditions with silver oxide, it gets oxidized to form this substituted benzoquinone.

In a similar fashion for example, we can also carry out the allylation of an imine, which leads to the formation of this homoallyl amine. Now like zinc and tin based reactions, indium based reactions can also be used in aqueous medium. And it is also found that there is no Wurtz type of coupling that occurs in these reactions. Like for example, this R-X cannot undergo a coupling to form R-R.

So this is how interesting reactions take place with indium. However it is the only disadvantage is to some extent is that it is a somewhat expensive reagent.

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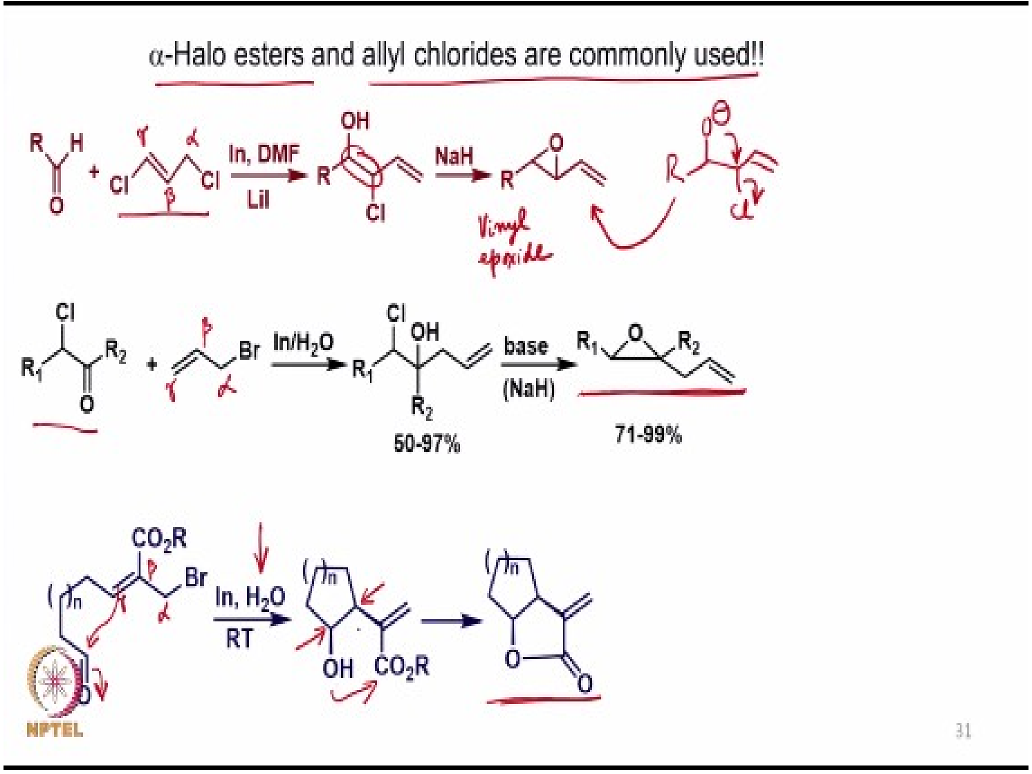

α-Halo esters and allyl chlorides are commonly used!!

Now if we take say for example, alpha-halo esters, for example if we take this alpha-halo esters or allyl chlorides are commonly used in many of these reactions. Say for example, we take this allyl chloride and we put an indium to it. So obviously, this is an alpha position, this is a beta position and this is the gamma position. The reaction takes place through the gamma carbon atom.

And therefore we can get an orientation of the hydroxy and the chloride chlorine as this. And once we react such a vicinal chlorohydrin with sodium hydride, which is a base. Then of course, you can deprotonate this and we can have a O- here which can then react with intramolecularly and the chloride can go and one can form the corresponding vinyl epoxide. So this is a vinyl epoxide.

And as I mentioned earlier, you have alpha-halo ketones, alpha-halo esters, for example this kind. If we do this alpha, beta and gamma, although in this case it does not really matter because unsubstituted. However, we get this and of course, in a similar fashion we have a base. Then we can get the corresponding this epoxide here. So this was vinyl epoxide or this is of course is allyl epoxide.

And in a similar fashion if we do intramolecular reactions like this, then of course you have alpha, beta and gamma. From the gamma carbon the reaction takes place in this fashion and you get this particular hydroxy ester moiety. And the reaction of the hydroxy group with the ester group intrarmolecularly leaves the formation of the corresponding alpha methylene gamma butyrolactone.

So this is a very interesting way of in situ generating and as you can see, the reaction can be carried out in the water medium. Of course, in this case, the stereochemistry of the product would again depend on the kind of transitional state that we are going to look at, because the transition state would be again 6-member transition state because indium will be here 1, 2, 3, 4, 5, and 6.

So again I suggest that please work it out the transition state and see how does the geometry of the two groups here which are at the junction are beta oriented or in the same direction.

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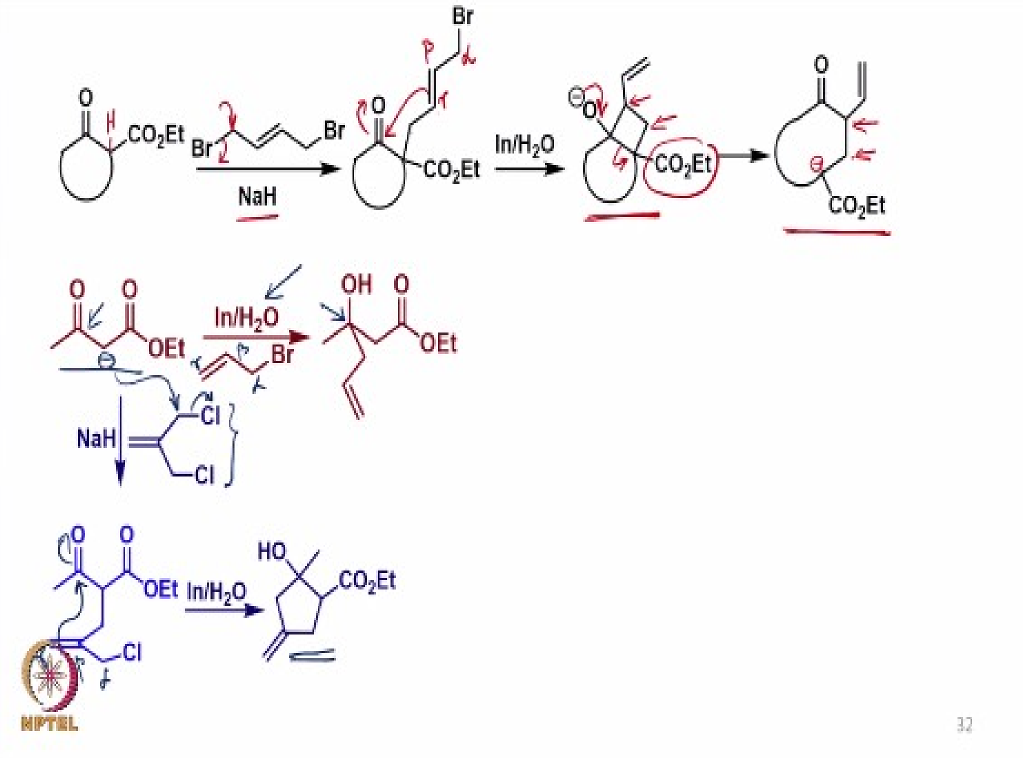

Now we can also carry out very interesting reactions, say for example you take this particular keto ester and if we take the proton from here of by base like sodium hydride, then we can generate an anion. Then anion goes and it reacts at the allylic position here for example and the C-C bond is formed. And we can generate this particular allyl bromide. Now if we react this with indium, so you have alpha, beta and gamma.

So from the gamma position the reaction occurs and then you form this intermediate which is what is going to be 1, 2, 3, 4, 4-member intermediate. The negative charge and breaks up in this fashion and this carbon-carbon bond breaks because the negative charge that is going to be formed here would be stabilized here. So basically this is the carbonyl group.

This is the next carbon atom, this is the next carbon atom this here, here, this is here and then your negative charge is stabilized by the ester group and that is where you get the proton of. So this is the product that is going to form. So it is a very neat way of converting keto esters into a ring expanded compound.

Likewise, we can start with this beta keto ester and we can do the alkylation here in a similar fashion as with this diallyl chloride and we can generate anion here and attack on one of them. And then we can remove and we can get this. And this then reacts the alpha, beta and gamma position. So this goes 1, 2, 3, 4, 5. This attacks on to this carbon atom and this is what is formed.

On the other hand if we take directly like this, then of course you have alpha, beta and gamma that directly goes and attacks on to this and this is the position where the allylation has taken place. So one can carry out such kind of allylations using indium. And again as you can see in the water medium it can be carried out. So the message here is that you have a carbonyl group or you have a carbonyl group in which there is an ester group or anything of that kind.

Then allylation can allow the C-C bond formation to take place and then the C-C bond formed product can be accordingly depending on the structure can be manipulated and get further products. So we would look at little bit more detail in the next time. And till then you can go through these allylations which I have discussed today with indium and also with tin.

And then we will take up in the next class more in detail about these reactions. And of course, some exceptions and some more synthetic transformation that will be carried out. Till then take care, bye. Thank you and see you next time.