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

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Lecture - 54

Chemistry of Allylsilanes: Mechanism, Stereochemistry and Synthetic Applications (Part 1)

Hello everyone, welcome to today's class. Before we proceed further, we briefly look at what we did last time and I hope that you had the chance to go through that on your own based on what I discussed in the last class. So what we did was reaction of allyltin compounds or allylstannanes what they are called as.

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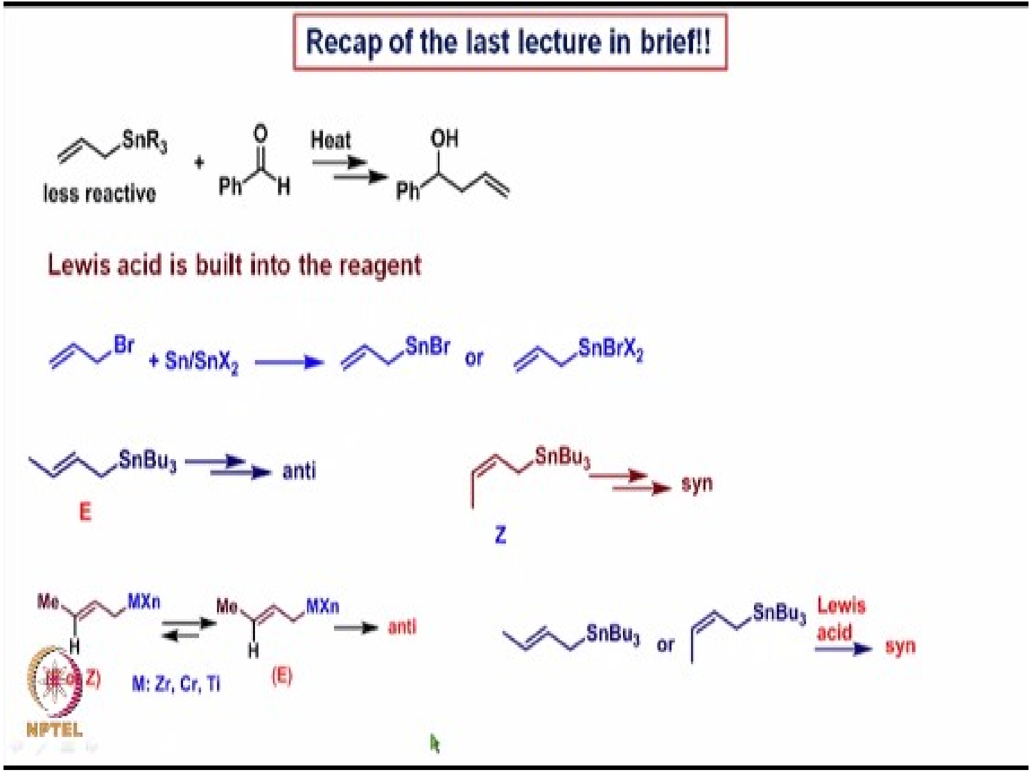

Recap of the last lecture in brief!!

So initially we took an allyltin compound of this kind was reacted with aldehyde, say for example benzaldehyde, under heating conditions to form the homoallyl alcohol. This required heating, but if we look at the reaction that we discussed, in which the allyltin species had a Lewis acidic character like this, which was prepared by reacting allylbromide or allylhalide with tin or tin halide.

Then these kinds of species which have inbuilt Lewis acidic character did not require heating to transfer the allyl group to aldehyde because there was a chelation between oxygen and the Lewis acidic part of the reagent or the allyltin compound. And we also looked at how crotyltin molecules with a specific geometry of the double bond lead to the formation of anti or syn products.

Thus for example, we saw that the E configurated crotyltin compound led to anti product and Z configurated crotyltin product led to the formation of syn compound. Now we also saw that if we take a crotyl compound in which the metal part is either zirconium, chromium or titanium, then irrespective of the geometry of the crotyl, this particular double bond here E or Z, eventually what was found that it leads to the formation of the E configurated crotyl molecule.

There is an equilibration between the two of them and then that leads eventually to the formation of anti product. Also we saw that crotyltin compounds, whether it is E or Z, if it is reacted with carbonyl compound in the presence of a Lewis acid then we get syn product as the major product irrespective of the geometry of the crotyl compound.

So this is how we saw a variety of reactions of allyl and crotyltin compounds and crotyl compounds containing other metals like zirconium, chromium or titanium. So we will now proceed further today looking at the allylsilanes for example.

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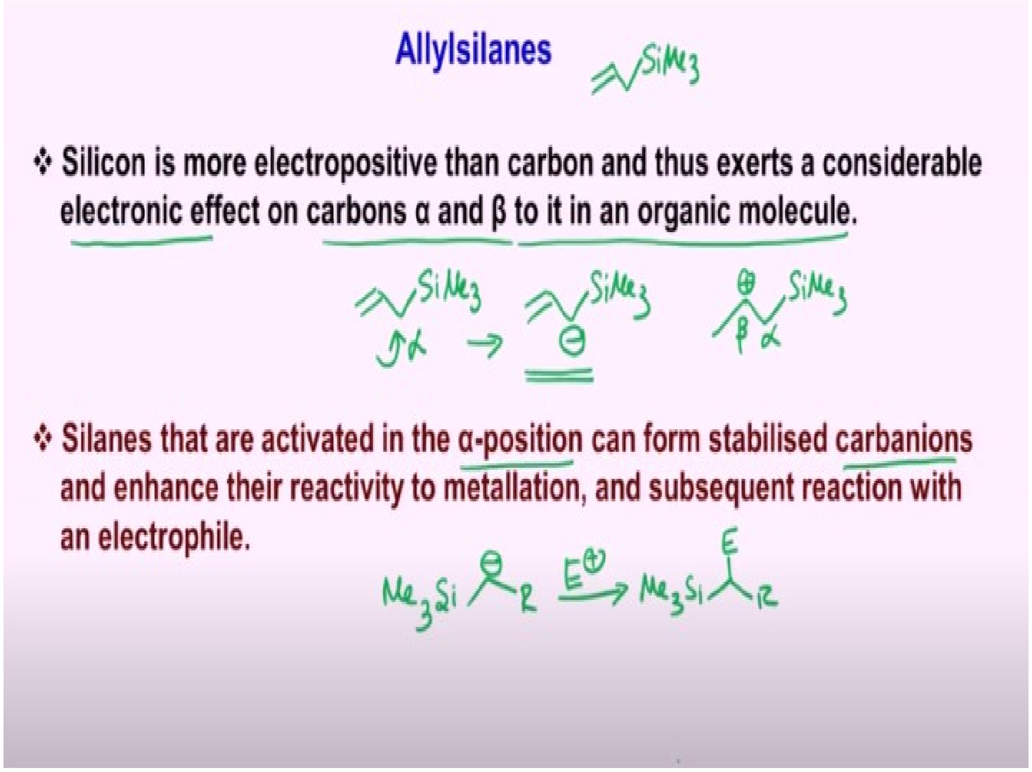

Allylsilanes

- Silicon is more electropositive than carbon and thus exerts a considerable electronic effect on carbons α and β to it in an organic molecule.
- Silanes that are activated in the α-position can form stabilised carbanions and enhance their reactivity to metallation, and subsequent reaction with an electrophile.

Now in the case of allylsilanes of this type here there are many interesting reactions apart from of course, normal allylations. Since silicon is more electropositive than carbon, it exerts a considerable electronic effect on carbons alpha and beta to it in an organic molecule. So say for example if you have a silicon here, say you have something like this, then you can expect this alpha position here to be very specifically converted to an anion for example.

So you can have very easily generating an anion alpha to the silicon. In a similar fashion if you can somehow manage to generate a cation and if that happens to be on the beta position, then of course, this particular beta carbocation here with respect to the silicon is also an important kind of contribution for the silicon based reagents and their reactions.

So silanes which can be activated in the alpha position lead to stabilized carbanions and therefore they allow the reaction of an electrophile to react on that carbanion. So irrespective of whether there is an allyl group or not, if you can generate the anion alpha to the silicon here, then we can expect that the E plus will react in this fashion to give the electrophile attached to the carbon, alpha to the silicon group.

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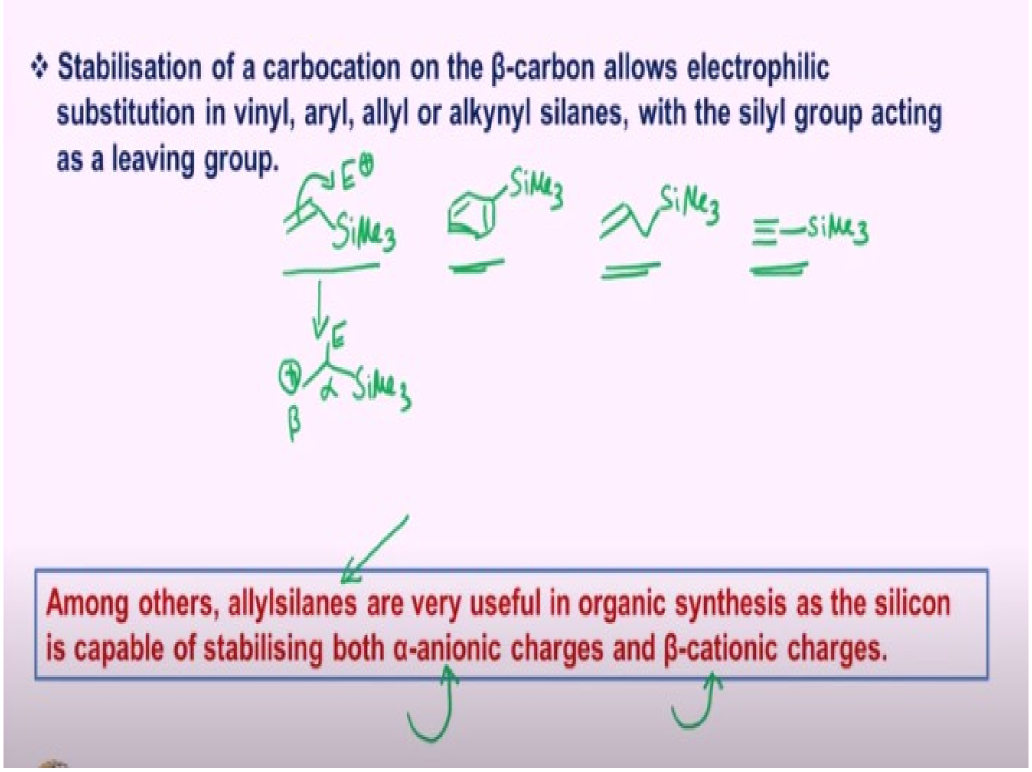

- Stabilisation of a carbocation on the β-carbon allows electrophilic substitution in vinyl, aryl, allyl or alkynyl silanes, with the silyl group acting as a leaving group.

Among others, allylsilanes are very useful in organic synthesis as the silicon is capable of stabilising both α-anionic charges and β-cationic charges.

Now as I said that you can stabilize the carbocation beta to the silicon and say you have a substrate something like this here or this is the vinylsilane and you have an allylsilane of this type here, say you have arylsilane or an allylsilane or say alkynylsilane, you have here something of this type or this kind of substrates that we have, then you can expect that for example, this can lead to the formation of a carbocation in here if the electrophile attaches to the carbon here.

So we can expect that you have an electrophile attaching and of course we generate the carbocation at the beta position. So this is alpha, this is beta. So likewise in this also this also and of course in here also we can generate the cation at the beta position, which is then stabilized by the silicon. So among all others basically different types of reagents, generally there is a lot of reactivity with respect to allylsilanes as well as vinylsilane of course.

So we will first consider the anion formation alpha to the silicon in an allylsilane substitutions type of starting materials and of course and also beta cationic charges. Both of these charges that we will consider with respect to the silicon and then see the reactivity of it.

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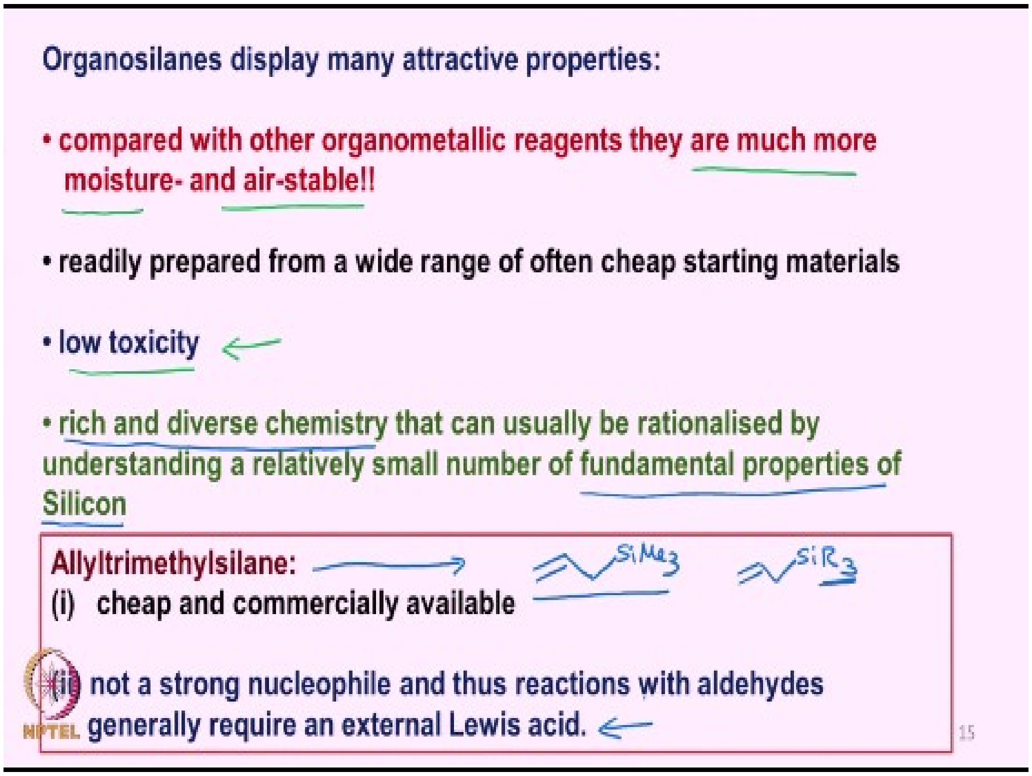

Organosilanes display many attractive properties:

- compared with other organometallic reagents they are much more moisture- and air-stable!!
- readily prepared from a wide range of often cheap starting materials
- low toxicity
- rich and diverse chemistry that can usually be rationalised by understanding a relatively small number of fundamental properties of Silicon

Allyltrimethylsilane:
(i) cheap and commercially available
(ii) not a strong nucleophile and thus reactions with aldehydes generally require an external Lewis acid.

Now organosilanes display a very useful alternatives or attractive properties that with respect to the other organometallic reagents. These reagents allylsilanes or vinylsilanes are more stable and they are moisture and air stable compared to other organometallic reagents. They can be easily prepared from wide range of starting materials. And of course, they have low toxicity in comparison to many other reagents.

And they actually lead to rich and diverse chemistry which can easily be understood and rationalized by a relatively small number of fundamental properties of silicon. Basically, as we have discussed earlier that anion alpha to silicon and cation beta to silicon are stabilized. And of course, we can have transition states which are well defined transition states with respect to cyclohexane chair form and that also helps in rationalizing the product formation.

Now we simply take simple allyltrimethylsilane. The basic allyltrimethylsilane reagent looks like this, allyltrimethylsilane. Of course there are many other substitutions which we can think of putting here. So we can have here anything else, not necessary only methyl, but we can also take other substitutions. And especially this one is relatively cheap and commercially available.

And it is not a very strong nucleophile unless and until we add an external Lewis acid. So allylsilanes are robust, strong and therefore they can react only in the presence of a Lewis acid.

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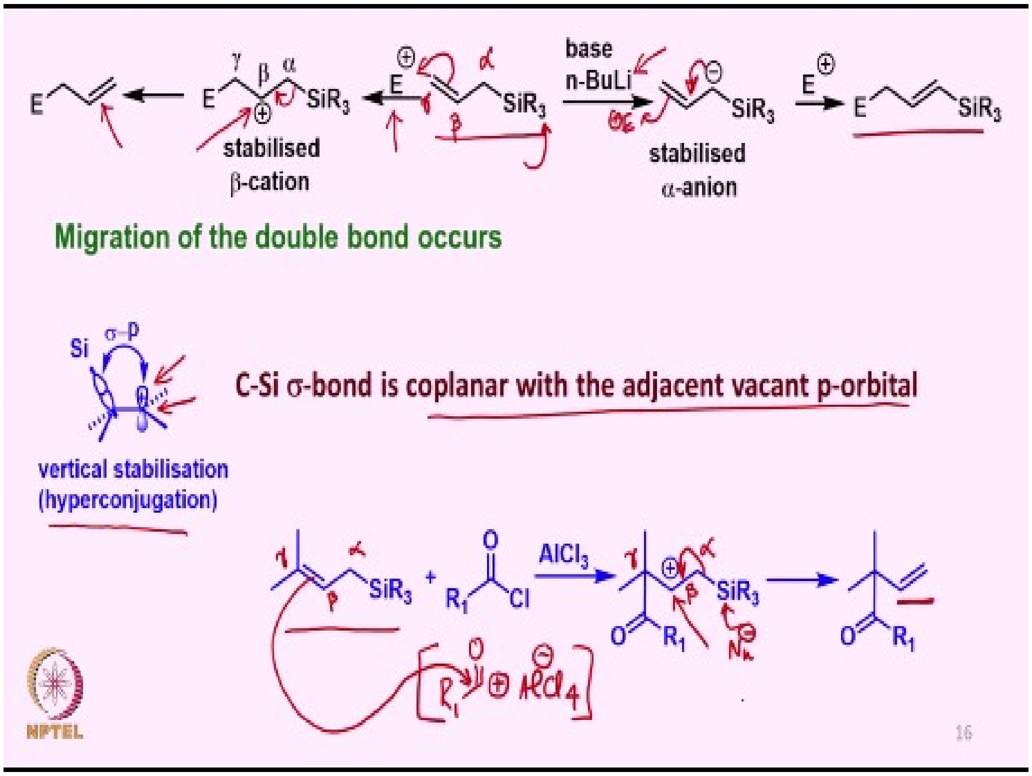

Migration of the double bond occurs

C-Si σ-bond is coplanar with the adjacent vacant p-orbital

vertical stabilisation (hyperconjugation)

So suppose we consider the reaction of say an electrophile with an allylsilane of this type where it is not necessarily methyl, but it can be anything else. So if we react with an electrophile here, then the electrophile reacts in this fashion from the gamma position. If we say this is alpha, this is beta, and this is gamma, then of course we have at the beta position the cation comes because now you have a carbon electrophile bond formation at the gamma position.

And therefore we generate a stabilized carbocation here. And then there is a loss of carbon silicon bond that leads to the formation of the double bond here. On the other hand, we can generate the anion alpha to the silicon by removal of proton by a base such as n-butyllithium. And this anion then reacts with the electrophile at the gamma position here, something like this.

And this electrophile reacts in this fashion and to lead to the formation of the product of this kind where now we get the vinylsilane. Now why is the beta carbocation more stable is because there is a kind of hyper conjugation between the carbon silicon bond and the p-orbital, which is an empty p-orbital at the beta carbon of the substrate on which there is a formation of a carbocation after the electrophile reacts.

And therefore, this particular p-orbital which is an empty p-orbital interacts with the sigma bond of the carbon silicon and they are actually coplanar with respect to each other. And therefore there is an overlap like hyperconjugation. Now if we say react this type of allylsilane which is now substituted allylsilane react with acid halide in the presence of aluminum chloride.

So we would expect that it would form something of this kind, where the aluminum chloride has abstracted the carbon chlorine bond and we generate an intermediate of this type where there is a non-nucleophilic AlCl$_4$ minus and of course you have a acyl carbocation. This acyl carbocation then reacts with the double bond in this fashion here, it will come and react here.

And then you generate a beta carbocation here. Now this is the alpha position and this is the beta position. And the beta position the carbocation is formed because at the gamma position here, this is alpha, this beta and this is the gamma. So the gamma position the double bond reacts with the acyl cation and then leads to the formation of a beta carbocation.

And now you have the loss of the carbon silicon bond. So whatever nucleophile that is present in the medium, say for example, Cl- or anything, that reacts with the carbon silicon bond. And of course, there is a breaking of the carbon silicon bond leading to the formation of the double bond. So this is how the reaction occurs with an electrophile and that is driven by the stability of the beta carbocation with respect to the silicon.

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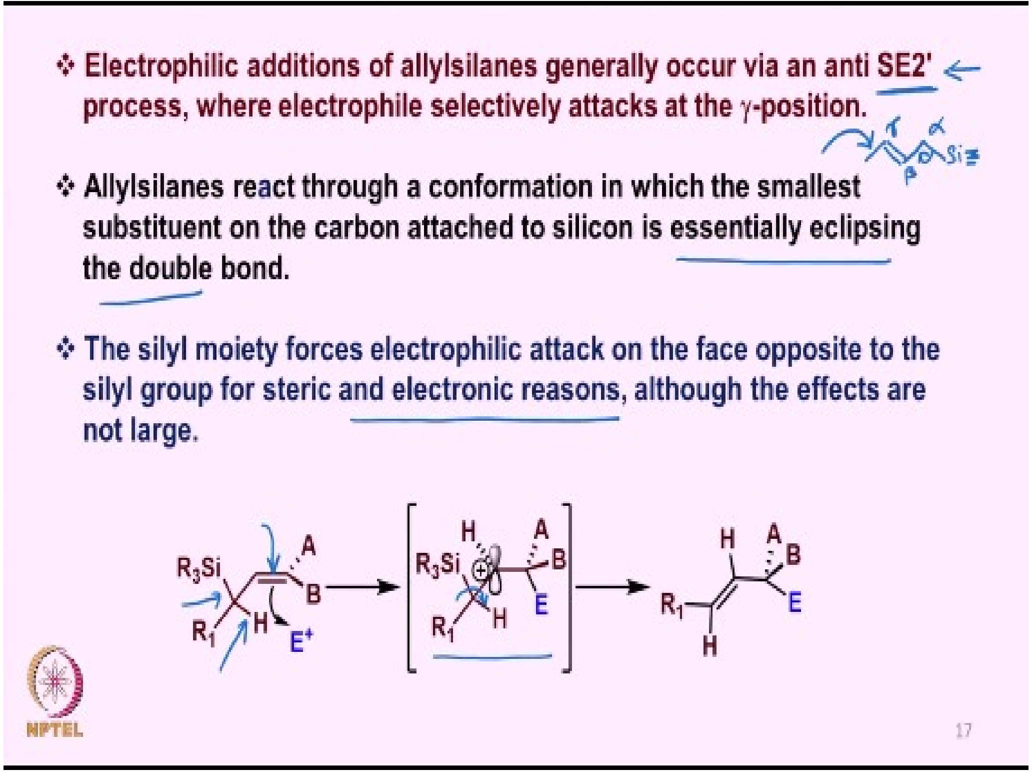

- Electrophilic additions of allylsilanes generally occur via an anti SE2' process, where electrophile selectively attacks at the γ-position.
- Allylsilanes react through a conformation in which the smallest substituent on the carbon attached to silicon is essentially eclipsing the double bond.
- The silyl moiety forces electrophilic attack on the face opposite to the silyl group for steric and electronic reasons, although the effects are not large.

So electrophilic additions of allylsilanes generally occur via an SE_2 prime as I mentioned that the reaction occurs at the opposite end of the double bond. So you have something like this here and then you have a silicon see here and therefore, the reaction occurs at this position, the alpha, beta and gamma. And since this occurs at the electrophile adds on to the gamma position and then this breaks up here.

And therefore this is called as an SE_2 prime reaction that is at the allylic position. So allylsilanes react with a conformation in which the smallest substituent on the carbon is that is attached to the silicon is essentially eclipsing with the double bond, eclipsing double bond. For example here, as you can see, this is a double bond of the allylsilane and this is the smallest substituent of the carbon that contains the silicon.

And therefore, this carbon hydrogen is essentially eclipsing with the carbon-carbon double bond. Now what happens is when the electrophile reacts with the double bond, the reaction occurs on the opposite face of the silyl group for steric and electronic reasons.

That is, now once the smallest group has been oriented in such a fashion that the smallest group is essentially eclipsing with the double bond, then the electrophile attaches like from the opposite face of the carbon silicon bond to avoid the steric hindrance. And of course, what happens also is that once we get this intermediate of this type when the electrophile has attached, then there is a small rotation here.

The carbon silicon bond rotates here like this here, so that there is an overlap between the carbon silicon bond and the p-orbital just the way as we saw earlier in order for hyperconjugation type of effect to occur. So and that leads to the formation of the double bond. So this overlap of the carbon silicon sigma bond to the empty p-orbital of the carbocation is very important.

And that can happen only by slight rotation around the carbon -carbon bond in such a way that the carbon silicon bond overlaps with the p-orbital.

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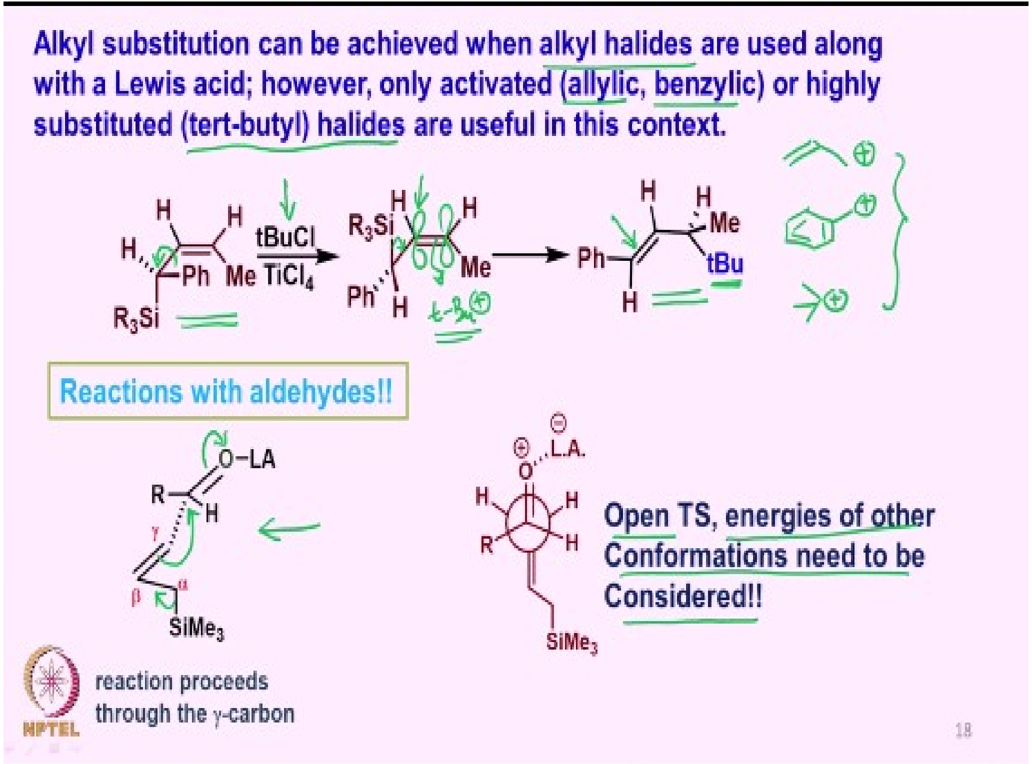

Alkyl substitution can be achieved when alkyl halides are used along with a Lewis acid; however, only activated (allylic, benzylic) or highly substituted (tert-butyl) halides are useful in this context.

Reactions with aldehydes!!

Open TS, energies of other Conformations need to be Considered!!

reaction proceeds through the γ-carbon

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Now we can also do the same thing using some other molecule such as alkyl halides, alkyl halides for example, especially which can allow the formation of a stable carbocation. So you have an allylic or a benzylic or a tertiary butyl halides such as say tertiarybutylchloride. So what we need to do is we need to generate a carbocation of this type or we need to generate a carbocation of this type here or we generate a carbocation of this type.

So you have an allylic carbocation, benzylic carbocation or say tertiary carbocation, because they are stable and therefore, they can easily be produced. So in that situation, if we have an allylsilane of this kind here, then what happens is of course, is the tertiarybutyl cation here reacts with the double bond. And once the double bond interacts in this fashion here, so what we have done it is we have rotated the bond here and here in such a way that the carbon silicon bond goes up.

And now your tertiarybutyl group reacts with it. And then of course, the here this is how it will be, tertiary butyl. And then we of course, get the product which is like this. That means since the carbon silicon bond is pointing upward, so the double bond interacts with the tertiary butyl cation from the opposite face and from below. That is why the tertiarybutyl group has come below here.

And we generate a carbocation at this center here and that will then interact with the carbon silicon bond, sigma bond to lead to the formation of the double bond. This is how the product formed. Now the reaction of course, has to be seen through open transition state and then energies of other conformations have to be considered in each case. So this is how it happens then the reaction occurs.

When the Lewis acid interacts with the aldehyde the reaction occurs via the gamma carbon atom in this fashion.

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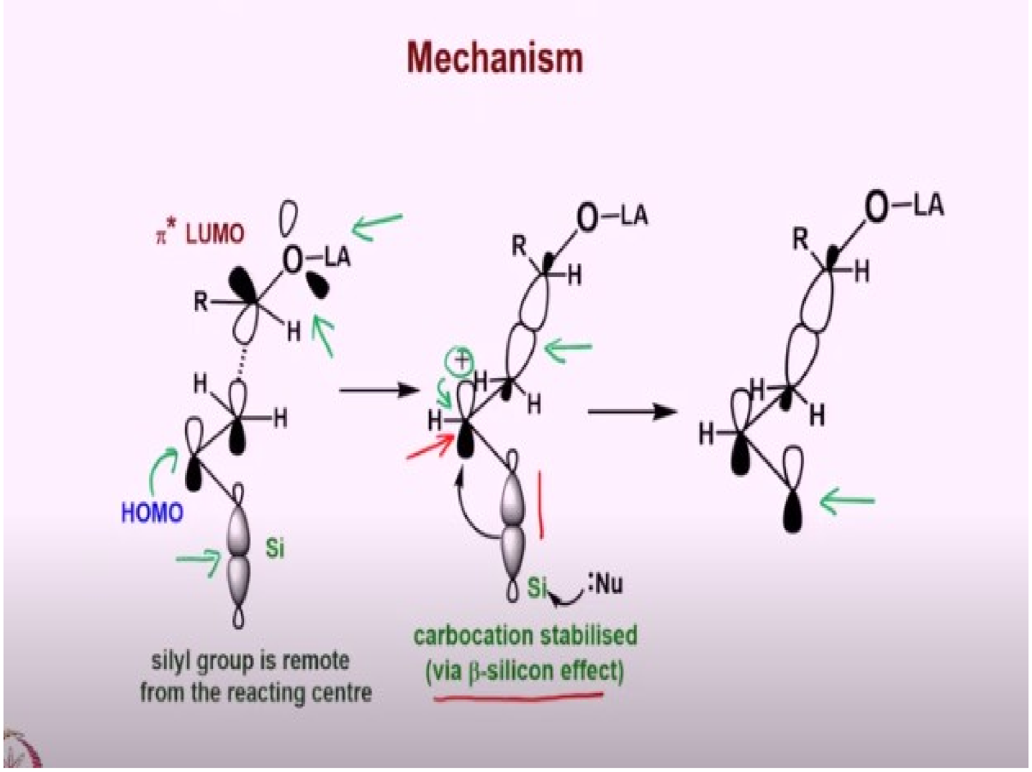

Mechanism

silyl group is remote from the reacting centre

carbocation stabilised (via β-silicon effect)

Now the mechanism can be understood if we take the HOMO the highest occupied molecular orbital of the allyl substrate. Then we can say that this is the carbon silicon bond here and this is the double bond and we are talking about the HOMO of the double bond here.

And if we take the LUMO of the carbonyl group, then of course, when the Lewis acid interacts with the oxygen here, then we can write the pi*LUMO of the aldehyde in this fashion where there is a there is an interaction with the P pi interaction and leading to the formation of the sigma bond here.

And then of course, we generate a carbocation on this particular carbon atom, which then of course, when the nucleophile reacts the carbon silicon bond breaks and then we generate a double bond here. So this is how the mechanism looks like and this is basically nothing but the beta silicon effect and this carbon silicon bond and the positive charge the p-orbital here, they interact like hyperconjugation.

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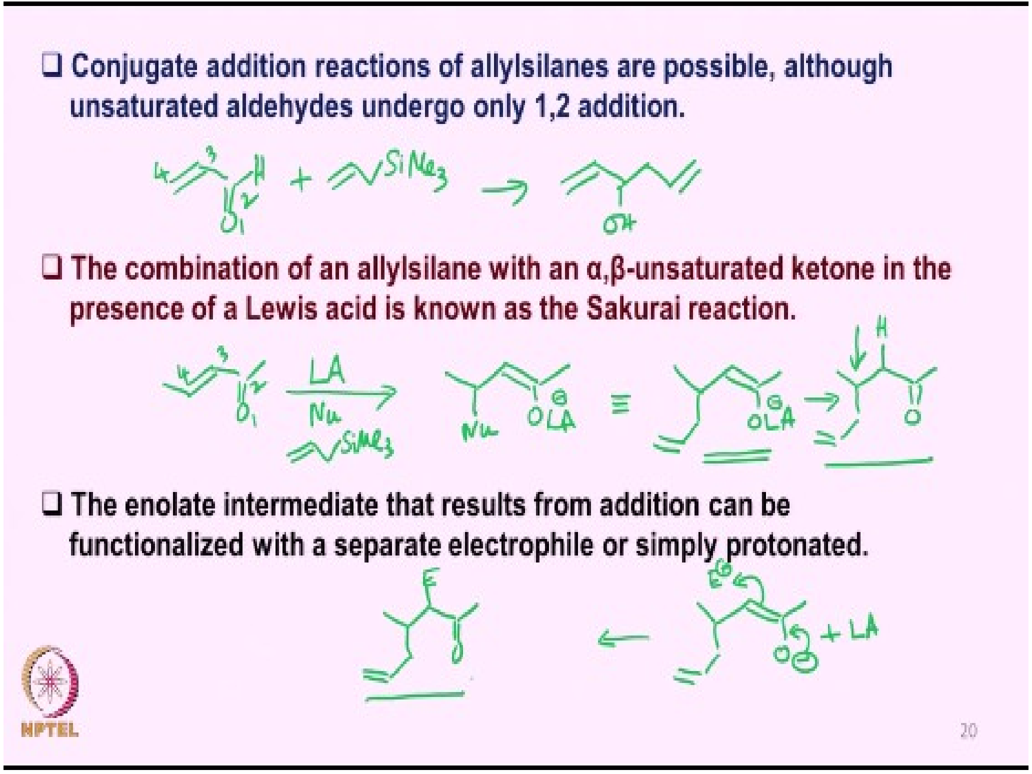

- ❑ Conjugate addition reactions of allylsilanes are possible, although unsaturated aldehydes undergo only 1,2 addition.

- ❑ The combination of an allylsilane with an α,β-unsaturated ketone in the presence of a Lewis acid is known as the Sakurai reaction.

- ❑ The enolate intermediate that results from addition can be functionalized with a separate electrophile or simply protonated.

Now the conjugate addition of allylsilanes are also possible, although alpha, beta unsaturated aldehydes undergo 1,2 addition. For example, we can think about whether we allow Michael reaction to take place, conjugate addition to take place. So if we have something like this here, an aldehyde and if we react with allylsilane, then of course, in this situation generally what is observed is 1,2 addition here of this type.

So this is 1,2 addition. So you have 1, 2, 3 and 4. And therefore, 1, 2 addition takes place. This is the 1,2 addition product. But if we take an alpha, beta unsaturated ketone, then there is a possibility of reaction in a Michael fashion in the presence of a Lewis acid and that is known as you have something like this here, Lewis acid here and you have here a nucleophile that is added here.

So if you have a nucleophile that is added, which is an allylsilane type of thing, so example you have an allylsilane here as a nucleophile then of course, we expect the reaction to occur in this is what is the Lewis acid. When we put a Lewis acid we can put a negative charge here. And then you have here allylsilane. So if the nucleophile happens to be an allylsilane, that allylsilane can add in a Michael fashion or a conjugate addition on to the gamma or the fourth carbon.

You have 1, 2 and 3, 4. So it is more like a 1,4 addition. And that is where you get an enolate. And of course, this upon workup can lead to the formation of the conjugate addition. So basically it is nothing but a conjugate addition. However, this enolate intermediate, this is an enolate intermediate basically, because we can write it as this. Here if we remove the Lewis acid from there, then it would be like this plus Lewis acid.

So if the Lewis acid has an interaction with the oxygen, then of course, we get the OA Lewis acid minus. Otherwise you have this O- and Lewis acid is separate. Of course, we will always have a counter ion which comes from the nucleophile which is present or whichever. And now if it is possible, then of course we can either do a deprotonation of it or we can also react with an electrophile here.

It is a different electrophile and that can lead to the formation of electrophile here and you can get this. So such kind of products or such kind of products are possible. Here of course, you are getting a proton as an electrophile, here you are getting a separate electrophile which can be either sulfur or nitro or any other or even a carbon based electrophile we can get an addition of this kind.

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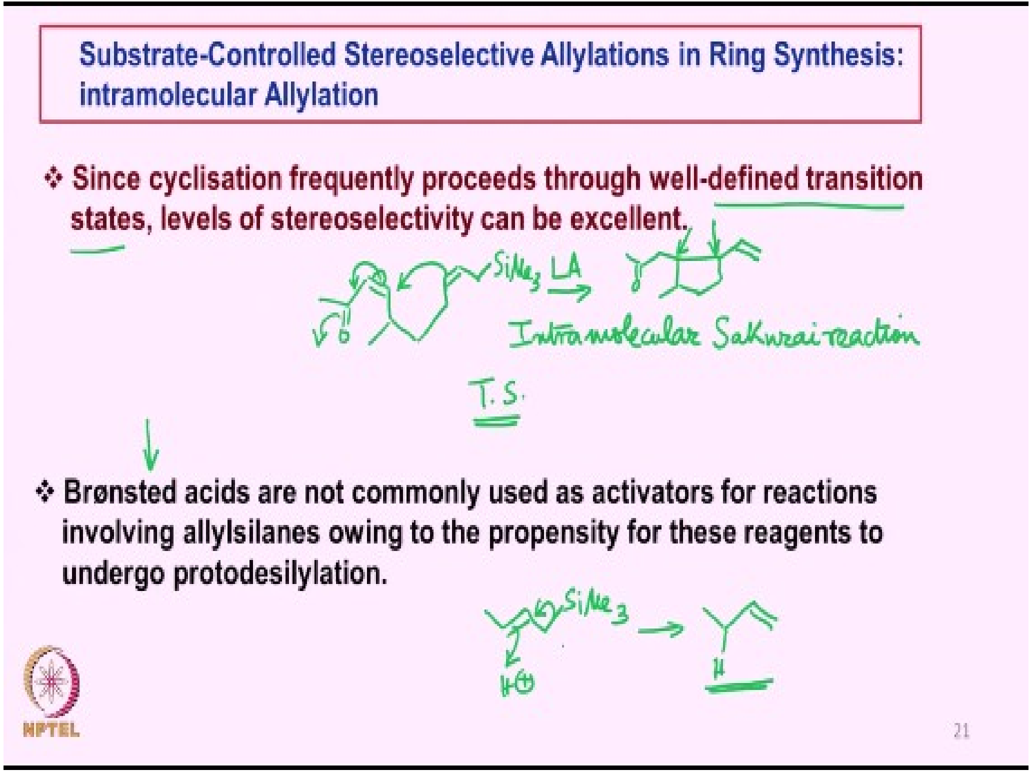

Substrate-Controlled Stereoselective Allylations in Ring Synthesis: intramolecular Allylation

- Since cyclisation frequently proceeds through well-defined transition states, levels of stereoselectivity can be excellent.

- Brønsted acids are not commonly used as activators for reactions involving allylsilanes owing to the propensity for these reagents to undergo protodesilylation.

So there are several ways in which you can perform such a Sakurai type of reaction, which is what is conjugate addition or the Michael addition of allylsilanes to alpha, beta unsaturated ketone. We can also do it in a in an intramolecular fashion.

So if we have something of this kind here, so suppose you have an alpha, beta unsaturated ketone, and you have now say you have allylsilane of this kind here, then there is a possibility of doing this, oh sorry this is it should be here, of alpha, beta unsaturated system.

And therefore, now we can consider as having an intramolecular Michael addition of allylsilanes or intramolecular what is called a Sakurai reaction, intramolecular Sakurai reaction and that could lead to the formation of this type of product. Now we can see that the new centers, which are asymmetric center, which are being created here.

And therefore, there is a possibility of looking at them from the point of view of the various transition states that one can think about it in all these reactions. So there is a there is a possibility of cyclization which is proceeding via very well defined transition states and therefore, the stereoselectivity has been found to be excellent.

In all these cases, we have to use a Lewis acid because very less cases the protic acids like bronsted acids have been used. Because what happens is if you have an allylsilane of this kind, then very often what happens is this undergoes protodesilylation. That means, the proton itself reacts with this particular double bond and then one can get the proton addition at this stage here and the reagent itself gets desilylated.

So you basically have the formation of this. So the allylsilane does not react with the substrate if we have a bronsted acid in case of a Lewis acid that has been observed.

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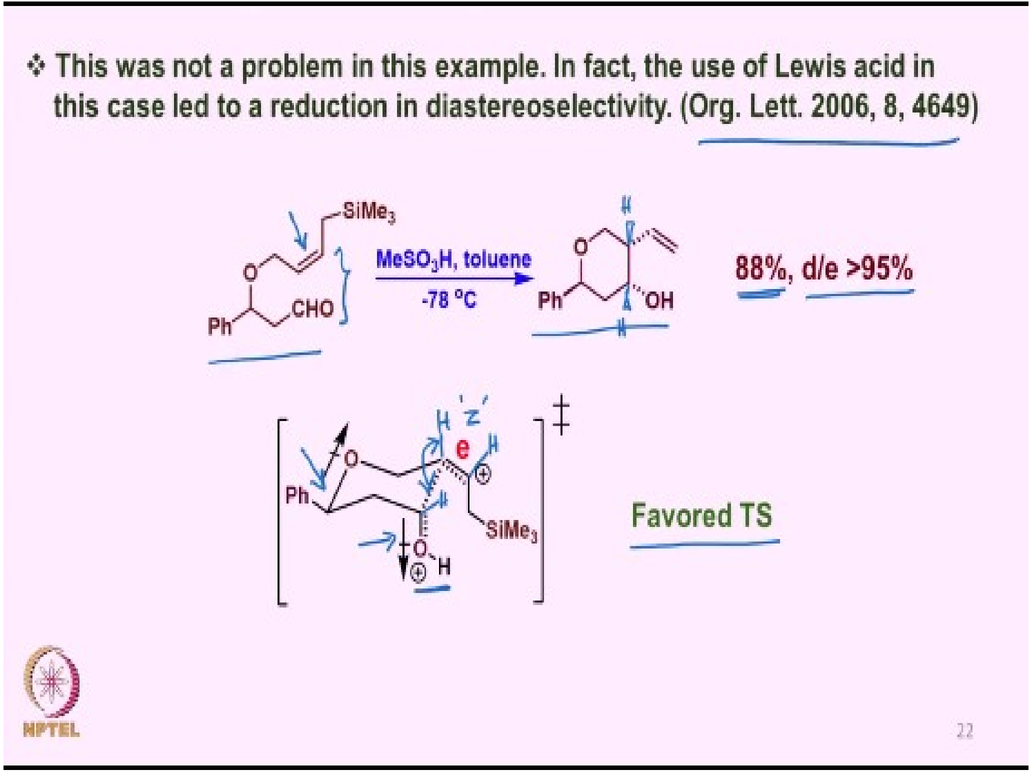

❖ This was not a problem in this example. In fact, the use of Lewis acid in this case led to a reduction in diastereoselectivity. (Org. Lett. 2006, 8, 4649)

However, there is an exception. In this case, for example in fact, the Lewis acid was not found to be useful in this case, and they found that substrate of this kind reacts with the methanesulfolic acid at low temperature and that gives a product of this kind in 88% yield in which the diastereoselectivity was more than 95%. What they understood or they rationalize is through favored transition state.

Possibly, everything is lined up here. And this substrate allows immediately a protonation through the bronsted acid like methanesulfonic acid to the aldehyde. And the aldehyde when upon protonation forms a particular part in this fashion, which now the dipole of this is oriented opposite to the dipole of this particular carbon-oxygen bond to avoid the dipole-dipole interaction.

And therefore, this allylsilane moiety here being Z in orientation and therefore, the hydrogen here and the hydrogen here are cis oriented, because the double bond here is of course, also going to be Z oriented here. This is the part which is the double bond part and when this interacts here, the hydrogen is oriented above and therefore, this and this are cis to each other.

And that is where the hydrogen here is cis to the hydrogen here. And that this particular favored transition state leads to the formation of the product that is rationalized here. So this is an exception, but of course in majority of the cases, the reaction needs a Lewis acid. So we will stop at this stage and we will take up the other aspects of the allylsilane addition, next time.

Till then you can go through this and if you wish, you can see the reference here which I have mentioned, and see the details of this particular reaction. Till then you take care and we see next time. Bye. Thank you.