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

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Lecture - 55
Further Synthetic Aspects of the Chemistry of Allylsilanes (Part 2)

Hello everyone. I would like to welcome you all to today's lecture. I hope you went through the contents of the last lecture. We will briefly look at what we did in the last class.

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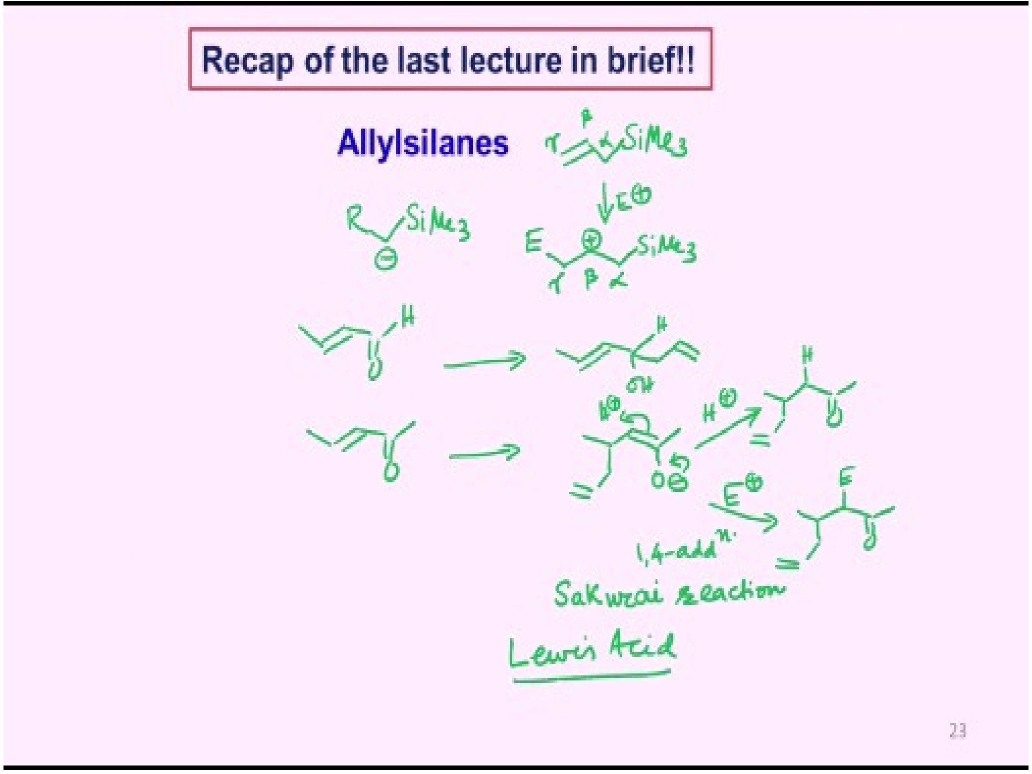

Recap of the last lecture in brief!!

Allylsilanes

We introduced the reagent which is allylsilane. And of course, we discussed that we can generate anion alpha to the silicon, whether the substrate is of any kind you can generate an anion alpha to the silicon. But we gave more emphasis on the fact that we can react the allylsilanes with an electrophile in such a fashion that the carbocation is formed at the beta carbon atom.

And therefore, if electrophile interacts with the double bond at the gamma position, so this is alpha this is beta and this is the gamma position. This is alpha, this is beta, and this is the gamma position and it generate a carbocation at the beta position. And then we discussed that the stability of such kind of cations at the beta position with respect to silicon are stabilized because of the hyperconjugation between the carbon silicon sigma bond and the empty p-orbital.

And then we did see a few reactions. And we also looked at that the reactions of such allylsilanes take place with stabilized carbocations which include allyl cation, benzyl cation or teriarybutyl cations. And of course, we saw the mechanism of it that how does the overlap of the carbon silicon bond with the empty p-orbital allows the geometry of the product to be formed.

Then we also looked at that allylsilanes can also react at the gamma position of that substitution with alpha, beta unsaturated aldehydes and also alpha, beta unsaturated ketone. So we checked accordingly that the reaction occurs in the presence of a Lewis acid. But the alpha, beta unsaturated aldehyde gives the 1,2 addition product that means of this kind here, where the allyl group acts on to the carbonyl itself and double bond remains as it is.

On the other hand, if we take alpha, beta unsaturated ketone, and then of course, the Michael edition does take place and then you get addition of the allylsilane and we saw that you can generate an enolate and this can either react with a proton to form the addition product in this fashion or where the proton comes in here. So that means this can react with the proton here or it can react with an electrophile.

So it can give the addition of the carbon electrophile bond and this is 1,4 addition or Michael addition product. So 1,4 addition or Michael addition product and such reactions are called as Sakurai reaction. We also saw that generally the reaction does not tolerate the bronsted acids except we had one exceptional case of an intramolecular cyclization using methanesulfonic acid.

Otherwise normally you need a Lewis acid for such reactions to take place. So now we look at some more aspects of this allylsilane based chemistry and that is allylsilanes in multicomponent reactions.

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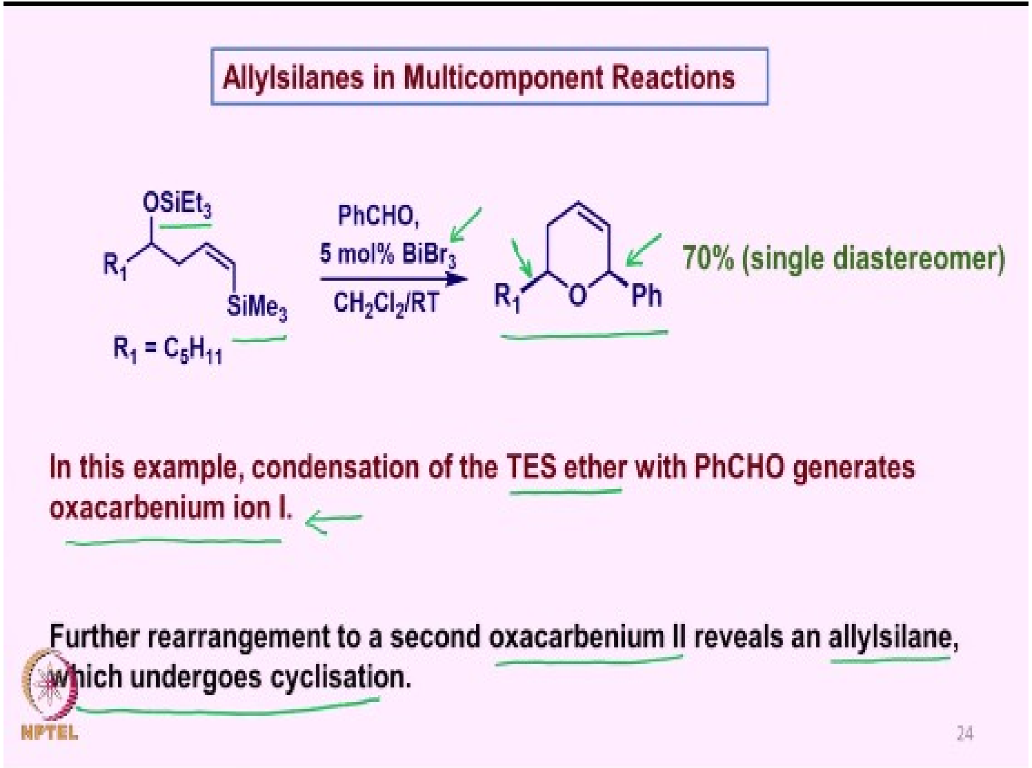

Allylsilanes in Multicomponent Reactions

70% (single diastereomer)

In this example, condensation of the TES ether with PhCHO generates oxacarbenium ion I.

Further rearrangement to a second oxacarbenium II reveals an allylsilane, which undergoes cyclisation.

For example, if we take this particular substrate, which is basically not an allylsilane but it is a vinylsilane. However, it is very interesting because now we have another moiety in the substrate here in the starting compound which is triethyl silyl ether. So this is the triethyl silyl ether as we have written here that reacts with an aldehyde in the presence of a Lewis acid like bismuth tribromide and in dichloromethane at room temperature.

And it gives an interestingly such kind of product, which is a single diastereomer as you can see that this and this are pointing to the same direction that is beta direction. Now the rationalization of this reaction has been done which leads to a so called oxacarbenium ion I. I will discuss it with it and basically it is a vinylsilane and therefore we need first to understand the chemistry of the vinylsilane.

And then after the first carbocation is formed or oxacarbenium ion is formed, oxacarbenium ion is formed, then it leads to another oxacarbenium ion II which is what allows the revealing of an allylsilane and that allows this cyclization to undergo to form the final product. We will see, it is a very interesting reaction.

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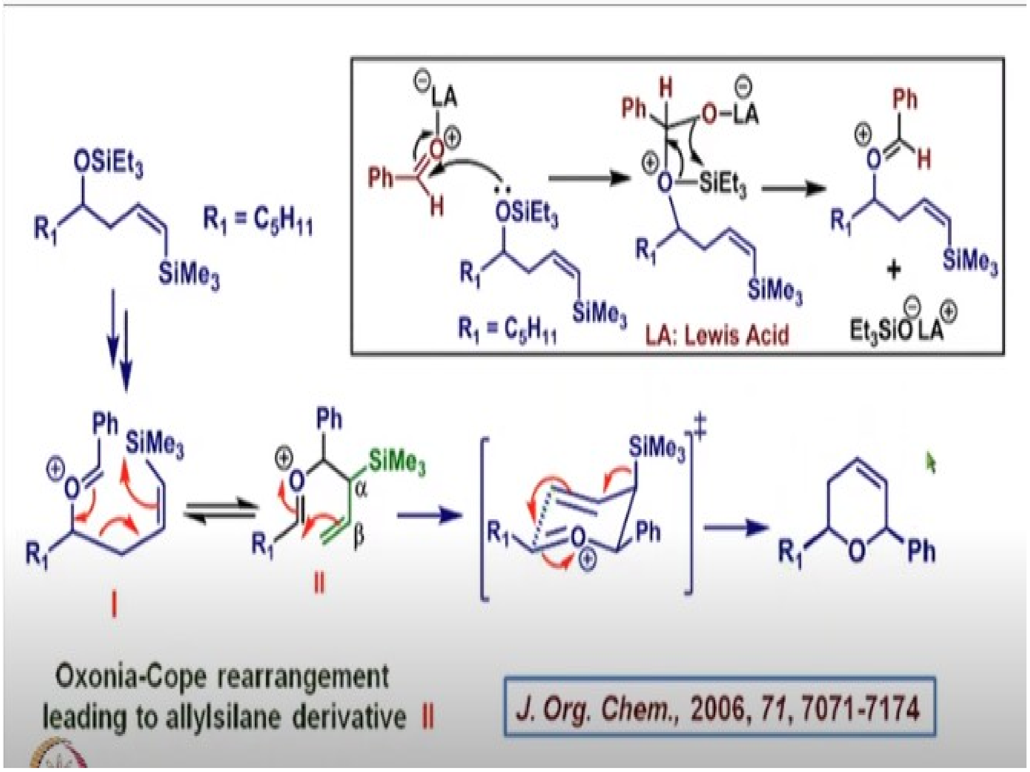

Oxonia-Cope rearrangement leading to allylsilane derivative II

J. Org. Chem., 2006, 71, 7071-7174

So what is happening is that you have this particular starting material in which you have triethyl silyl ether. So when this reacts with an aldehyde in presence of a Lewis acid then we can expect an interaction of this type where first the Lewis acid interacts with the aldehydic oxygen to make this carbon more electrophilic on which the silyl ether attacks in this particular fashion to lead to this particular ionic intermediate, which then releases this oxonium ion which has this vinylsilyl moiety.

Also of course, will be releasing the triethyl siloxy anion. Now this particular oxonium ion having vinylsilane which is shown here undergoes what is called as Oxonia-Cope rearrangement leading to this kind of allylsilane derivative. Now this allylsilane derivative as you can see, that can undergo easily pi cation cyclization the way I have shown in such a fashion that we generate a carbocation on this particular position, which is a beta position with respect to the silicon.

And therefore, there is a stability of the cation by beta silicon effect. Now we can write the transition state in this particular fashion, where R1 and the phenyl groups are equatorially oriented which then eventually by the loss of this carbon silicon bond and the cyclization here to form this C-C bond leads to this particular cyclic olefin. Now we can write it the same thing in a slightly different way.

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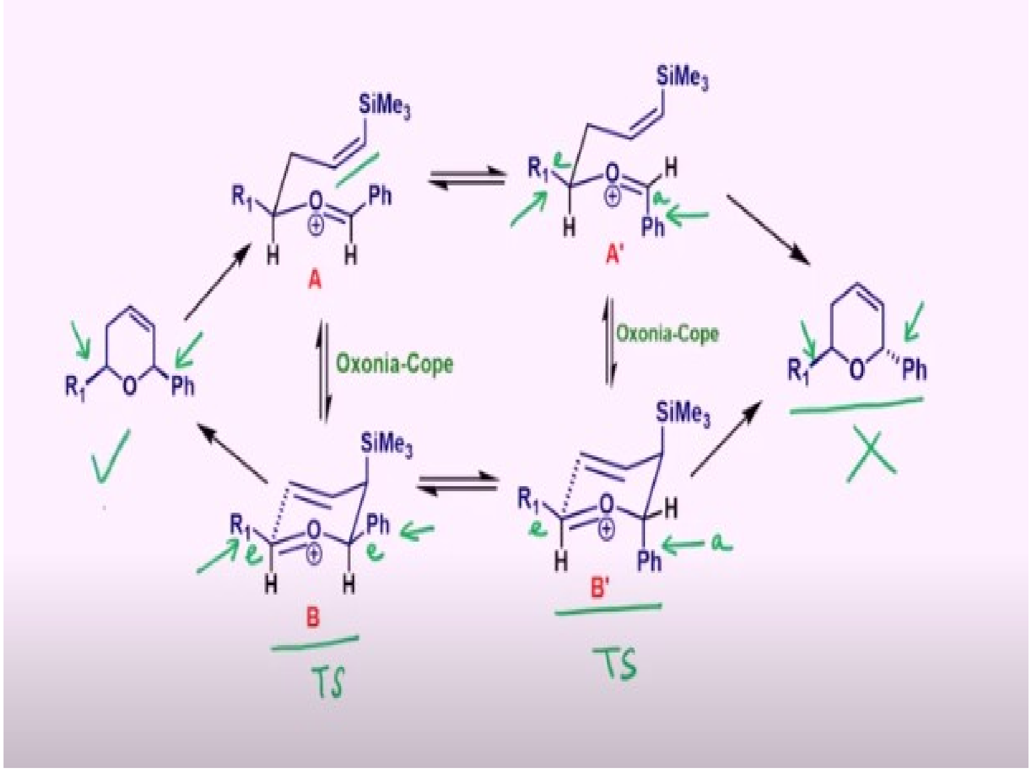

As you can see it here, that this is what the vinylsilane that we started with, here this part. And of course then once the Oxonia-Cope rearrangement occurs, we can think about getting a transition state of this kind in which now we have the phenyl group and the R1 group being equatorial. So they are equatorially oriented here. The other possibility is that we can orient the phenyl group as axial and let the R1 group being equatorial.

So you have equatorial and then you have an axial. Then in the transition state, this is the transition state in which now this is axially oriented and this is equatorially oriented. Then we will get at a product like this in which the phenyl group and R1 are the on the opposite side of the cyclic structure. On the other hand here we get this and this substituents on the same side of the product.

So obviously, this transition state is more stable than this transition state and therefore, this is not formed and this is the product that is formed.

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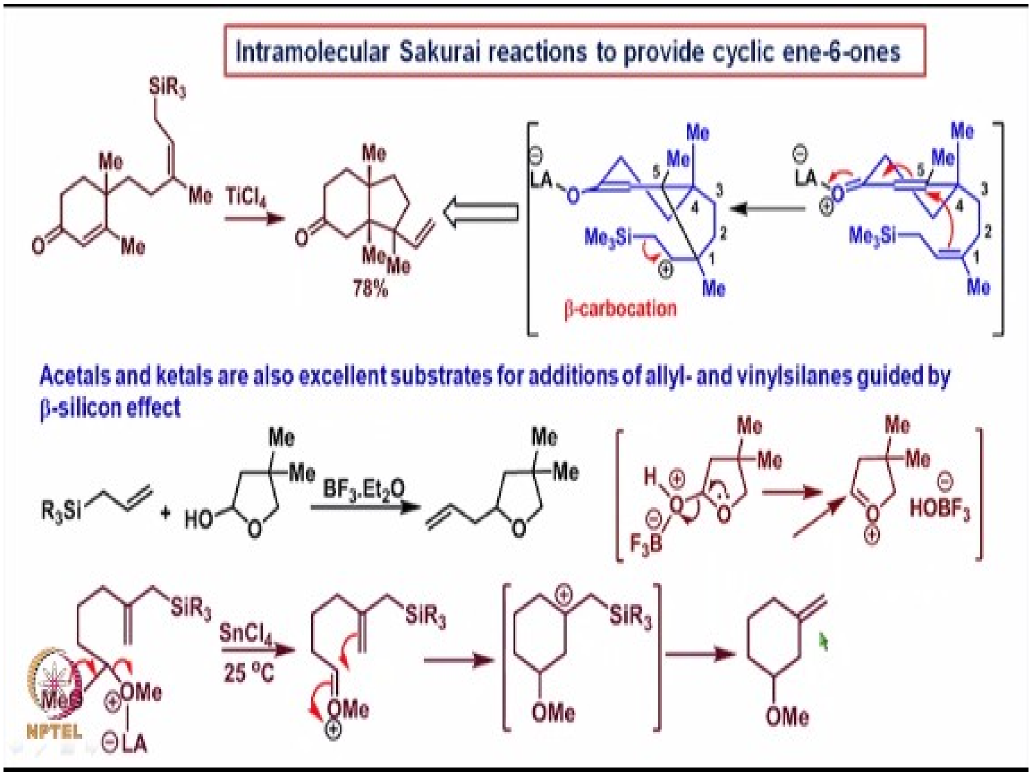

Intramolecular Sakurai reactions to provide cyclic ene-6-ones

Acetals and ketals are also excellent substrates for additions of allyl- and vinylsilanes guided by β-silicon effect

Now we can look at the intramolecular Sakurai reaction to provide cyclic enone of this kind. When a substrate of this kind in which there is a cyclic conjugated enone and allylsilane moiety is treated with titanium tetrachloride and Lewis acid a bicyclic ketone of this kind is formed which is an ene-6-one. So 1, 2, 3, 4, 5, 6. The transition state involved in this reaction can be written up like this, in which this particular part is a half chair confirmation.

And of course, when Lewis acid interacts with the carbonyl oxygen, we generate a delta positive at the carbon number 5, and then there is a reaction between this particular carbon atom and this carbon atom to form a C-C bond, because the cation that will be generated will be on this particular position, which is beta to the silicon.

And therefore, this beta silicon effects guides the regioselective cyclization in this particular fashion. And this loss of carbon silicon bond from here leads to the formation of this bicyclic product. It is also found that acetals and ketals are excellent substrates on which allyl and vinylsilanes can be added, which are guided by beta silicon effect.

If we take a substrate like this, a hemiacetal and react with the BF_3 etherate in the presence of an allylsilane, then this particular allylated product is formed. The reaction proceeds in this fashion that the hydroxy group gets knocked off by coordinating with the Lewis acid to form the oxonium ion of this kind to which allylsilane adds and then we get the allylated product, which again is guided by the beta silicon effect.

Similarly, if we take this acetal of this kind in which the allylsilane moiety is embedded, it upon treatment with tin tetrachloride looses one of the methoxy groups which first coordinates with a Lewis acid and then of course it gets expelled out to form this oxonium ion which then undergoes cyclization in such a fashion that the cation is generated beta to the silicon.

And then the carbon silicon bond breaks to release the cyclic molecule like this having an exomethylene.

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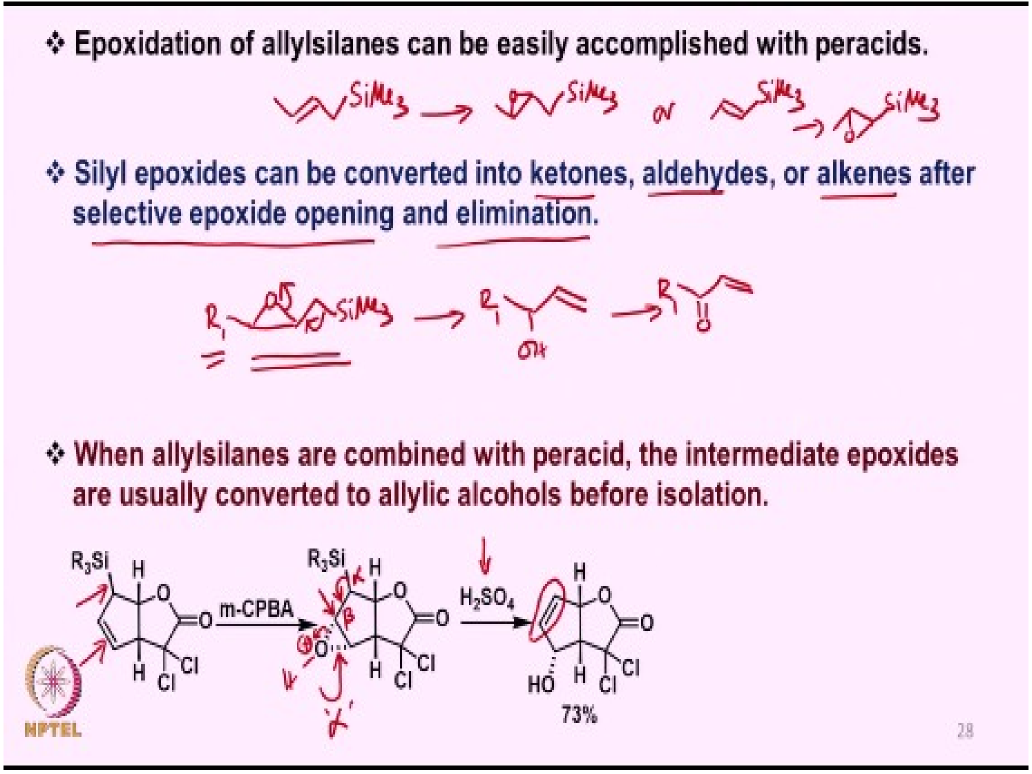

❖ Epoxidation of allylsilanes can be easily accomplished with peracids.

❖ Silyl epoxides can be converted into ketones, aldehydes, or alkenes after selective epoxide opening and elimination.

❖ When allylsilanes are combined with peracid, the intermediate epoxides are usually converted to allylic alcohols before isolation.

Now epoxidation of allylsilanes can also be accomplished by peracids. So you have an allylsilane of any kind that can be reacted with a peracid to form allyl epoxide of the allylsilane in this particular fashion. And products of this kind or even from the vinylsilane, you can also generate epoxides from vinylsilane. And all these products, all these epoxides lead to the formation of different kinds of ketones, aldehydes or alkenes after selective epoxide opening and elimination.

Say you have an epoxide of this kind and now this can lead to the formation of an OH here and this double bond. So suppose if this is how it opens, then you can get the allyl alcohol and this can be converted to the ketone or aldehyde depending on what is the substituent here. So if it is R1 then of course we get a ketone. If it is proton, then of course we get the aldehyde.

So there are different ways by which the reaction can be triggered or can be directed. Now say for example, if you have an epoxide, particularly from allylsilane, then the intermediate epoxide as we shown it, have shown it here, if the conditions of the epoxidation are such that they allow the opening of the epoxy silane then of course, this itself can undergo either within the reaction or by the addition of say extra sulfuric acid.

So with this gets protonated with sulfuric acid and this bond particularly breaks. Now there are two possibilities whether this bond breaks or this bond breaks. But this bond breaks because you generate a positive charge on this carbon atom which is a beta carbon atom. So you have a possibility of beta carbocation formation and then of course, the carbon silicon bond breaks and then you generate the corresponding double bond here.

So this is how the opening of the epoxide allows regioselective opening in this fashion. Now the epoxide formation here has taken place from the alpha side as you can see. The epoxide is formed from the alpha side. That is because this silicon bond here is beta oriented and therefore to avoid the steric hindrance, the epoxidation occurs from the alpha side.

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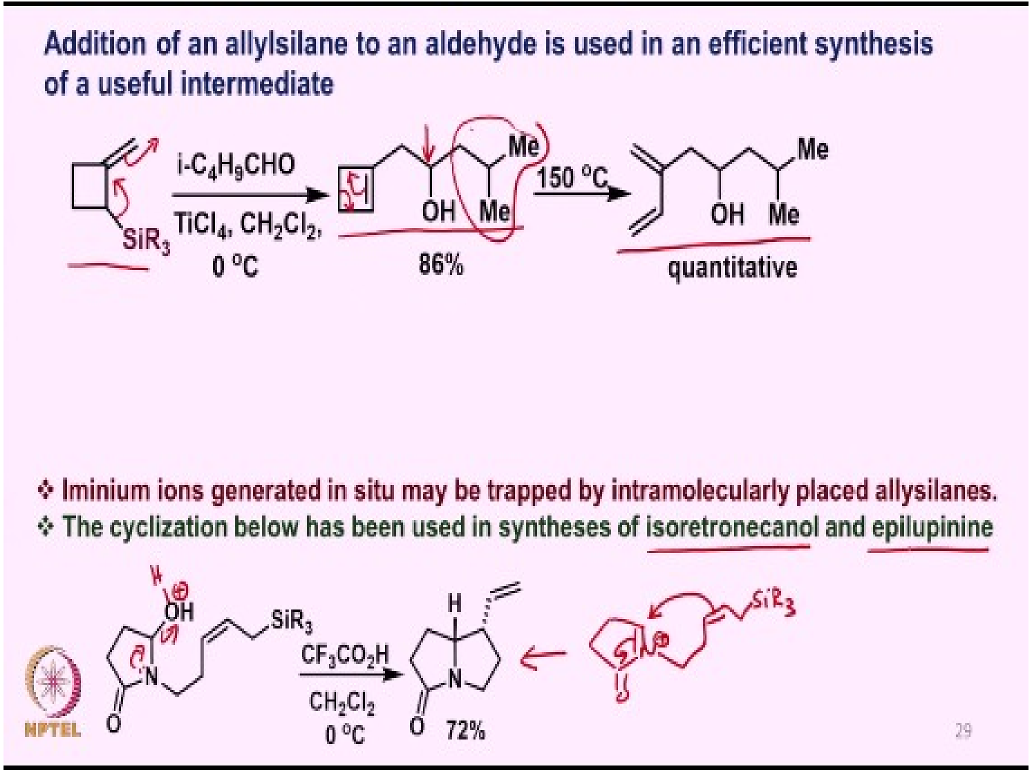

Addition of an allylsilane to an aldehyde is used in an efficient synthesis of a useful intermediate

- Iminium ions generated in situ may be trapped by intramolecularly placed allysilanes.
- The cyclization below has been used in syntheses of isoretronecanol and epilupinine

Now we can also add allylsilane to an aldehyde in such a interesting fashion, that if we take an aldehyde and react with a allylsilane which is made up of a cyclobutane ring, then of course, we can see that the aldehyde reacts at this end, which is the gamma end to form the product of this type, where this i-C_4H_9 is basically this part here, aldehyde.

And this is the aldehydic part and therefore, the reaction allows the formation of this homoallyl alcohol. Now if we heat this particular substrate, then of course, this 4-membered ring opens up to form this diene of this kind. And this diene is a useful diene for various kinds of Diels-Alder reactions. Now another possibility is that this iminium ions which can be generated in an intramolecular fashion can trap the allylsilanes.

If for example if you have a substrate of this kind, and if you treat with trifluoroacetic acid, this is another example of a bronsted acid. And the moment this gets protonated here, then what is happening is that the lone pair of electrons from here to here can push this out. And once that happens, then of course, you have iminium ion of this kind, where sorry this is from here, from here.

So now you have a positive charge at this particular position, where the reaction occurs and of course, it gives this particular product. Now this has, this particular substrate also another substrate they have been converted in two natural products. This 5,5 compound has been converted to isoretronecanol and then 6,6 membered ring has been converted to epilupinine.

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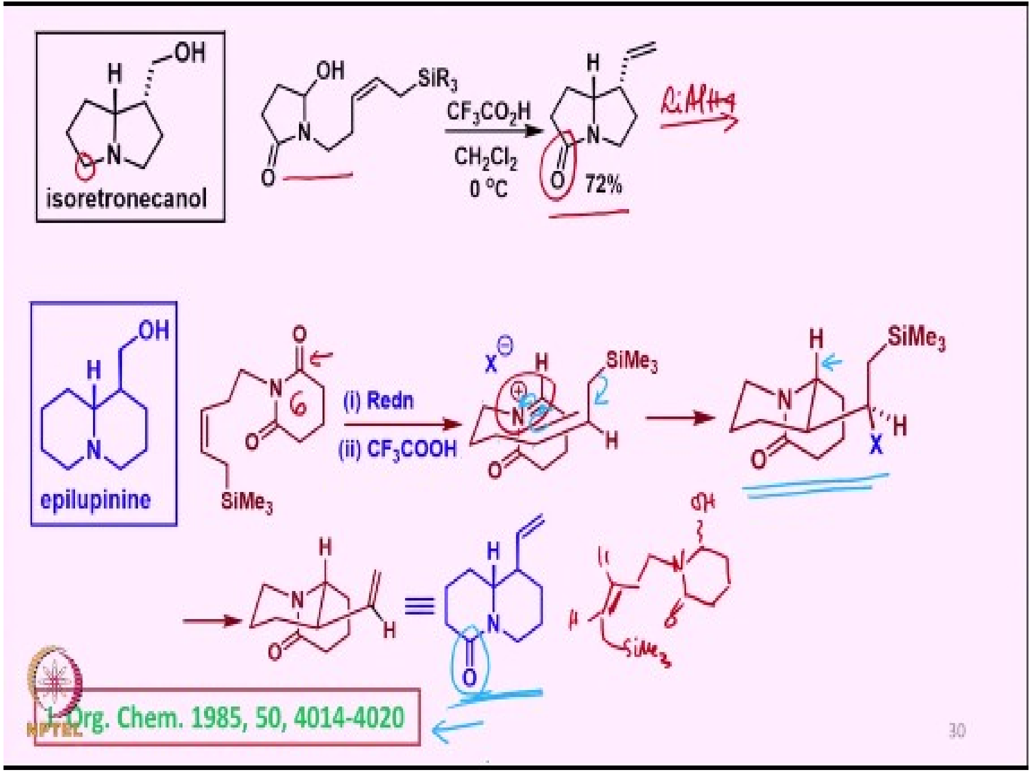

It is something like this, that this is the structure of the isoretronecanol as you can see that there is the this particular compound when it undergoes cyclization as we saw just now. It formed this intermediate and then now you have to reduce the carbamide, this lactam part. So you can do it by various different types of reducing agent. For example, you can also use lithium aluminum hydride here and then one can get the corresponding CH_2 group of the isoretronecanol.

Now in a similar fashion, if we take a 6-membered ring like this and the possibility of a reduction of one of the two carbonyl groups it is symmetrical and therefore, once the reduction of one of them takes place, then we can generate in a similar fashion as we did the earlier case. So if this undergoes a reduction, then of course you can generate the corresponding alcohol.

And that alcohol undergoes, here this is what is going to form. And then of course you have, and then this will interact with trifluoroacetic acid and form the corresponding imonium ion like this, which undergoes cyclization from here like this, from this carbon atom. So this is 1, 2, 3, 4 5 and 6. So you have cyclization to take place in this fashion to form this intermediate.

And this intermediate can then be understood that the lead to the formation of this particular product. And therefore, that particular product again has this lactam part and this lactam can be reduced to form the corresponding epilupinine. So you have this intermediate which undergoes cyclization from the lower part and therefore, the hydrogen comes on the top.

And therefore, the stereochemistry can be easily understood that we have the product with desired stereochemistry. So we will stop it at this particular stage today and look at the other aspects of the silane chemistry in the next class. If you wish, you can also look at this particular reference and see the more details of this reaction. So till then take care and bye. See you in the next class. Thank you.