Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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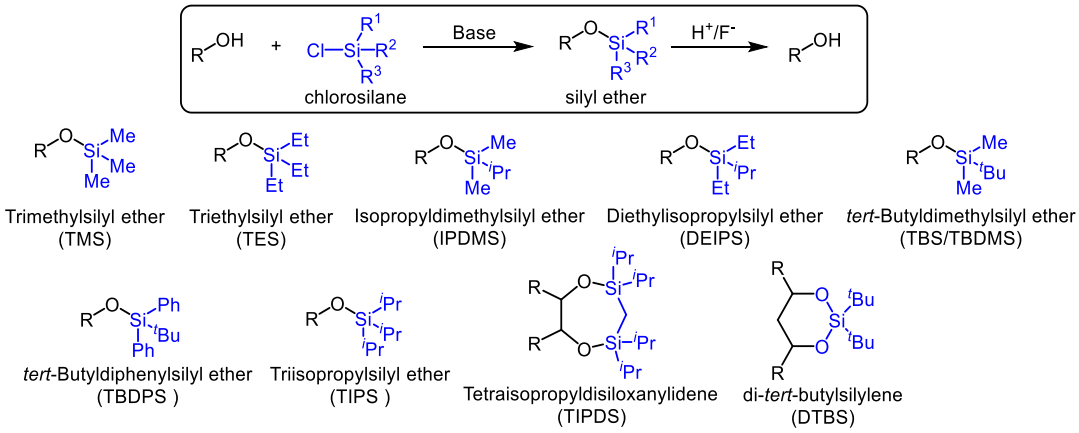
Lecture 48: Organosilicon

Welcome back to this NPTEL online certification course of molecular rearrangement and reactive intermediates. In the previous class we started learning about the organosilicon chemistry. We have learned about the organosilicon compounds their discovery, their bonding with oxygens with the halogens and we talk about the α-effect, β-effect, different type of reactions and end up with the formation of the polymer from the silicon. In the today's class my focus will be to start with the silicon base protecting group and then the reaction of vinyl and alkylyne silicon compound with the electrophile. We are going to learn about again this α-effect and β-effect in this class too. So, let start the today's class.

Here we are going to talk about first the silyl protection of the corresponding alcohols and their deprotection. Again the acetal formation using trimethylsilyl triflate. then there will be electrophilic substitution reaction of the different type of reaction of vinyl and alkynylsilane compounds in the hydrosilylation and the Peterson olefination. So, in this particular part we are going to learn about the protection of alcohol group using different silicon-based reagent.

Silyl Protection of Alcohols



- Rate of protection: primary alcohol > secondary alcohol

So, we are going to talk about that the different type of protein, I think we have already heard TMS chloride. I think this is a very common reagent you have seen. It is a very reactive silicon compound. So, if you have an alcohol here you can react with the corresponding TMS chloride with in base to quench, the HCl formed to form the OTMS. So, this is called trimethylsilyl ether.

But it is not only trimethylsilyl, but there are various different like it could be triethyl silyl, it could be isopropyldimethylsilyl ether. So, there is isopropyl comes in, there is a two ethyl and one isopropyl group. There could be a tertbutyl with dimethyl, tertbutyl with diphenyl and triisopropyl. There are so many different type of varieties. And you can see what is happening going from trimethyl to the tertbutyl dimethyl phenyl, we are seeing the steric hindrance around the silicon is getting increased.

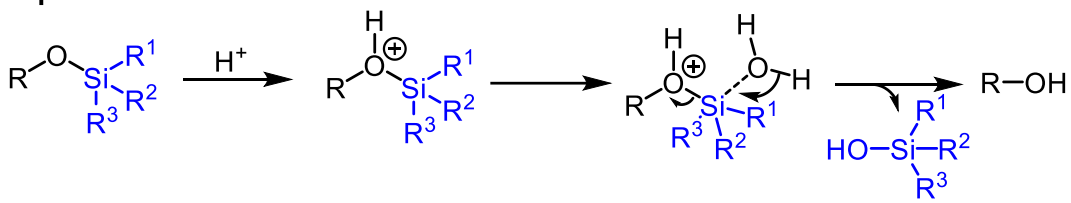
So, again if you have a very sterically hindered silicon, one of the problem going to happen if you try to do some sort of a reaction where the nucleophile going to approach to silicon that will be getting blocked once you have a very hindered group around the silicon. And not only that so, that is number one, the number two is if you have an alcohol here is secondary versus you have a primary. So, this is a primary. So, now, if I have to selectively do a protection, then we can use a bulkier group which can be only going to protect the primary one over the secondary. So, that we can be done using that.

So, that is the two advantage using this type of bulkier protecting group. Also they are very bulky then at the same time as I mentioned the nucleophile cannot able to approach they will be difficult to remove as well. So, after you form the protection means after you form this corresponding silicon ether then the next thing is how do you deprotect them. There is two different deprotection one is under acidic condition, another is under fluoride condition. So, under acidic condition if you have this silyl ether once you treat with the H+ this is going to bind with the oxygen and now if you treat with water can attack to the silicon that can able to break this bond to get your starting material back or get your compounds back.

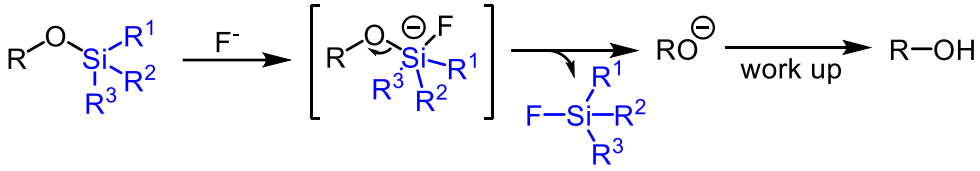
At the same time if you treat with the flouride ion then it is going to attack to the silicon as I mentioned first thing is formation of this pentavalent silicon compounds with trigonal bipyramidal structure. And now what is going to happen there will be cleavage of this silicon oxygen bond to form this RO- which going to take H+ to form the corresponding ROH. And because of this silicon flouride bond is very strong bond that is why end up forming this compound. So, these are the two different deprotection. Now, we are going to learn that they going to deprotect at the same time or what is that their difference on the order of the protection versus deprotection.

Deprotection of Silyl Ether

Deprotection under acidic condition:



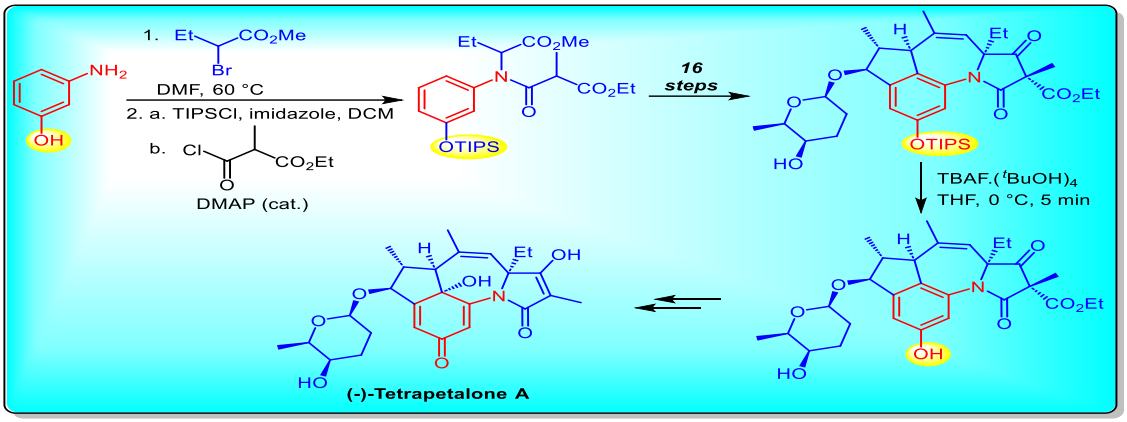
Deprotection under fluoride condition:

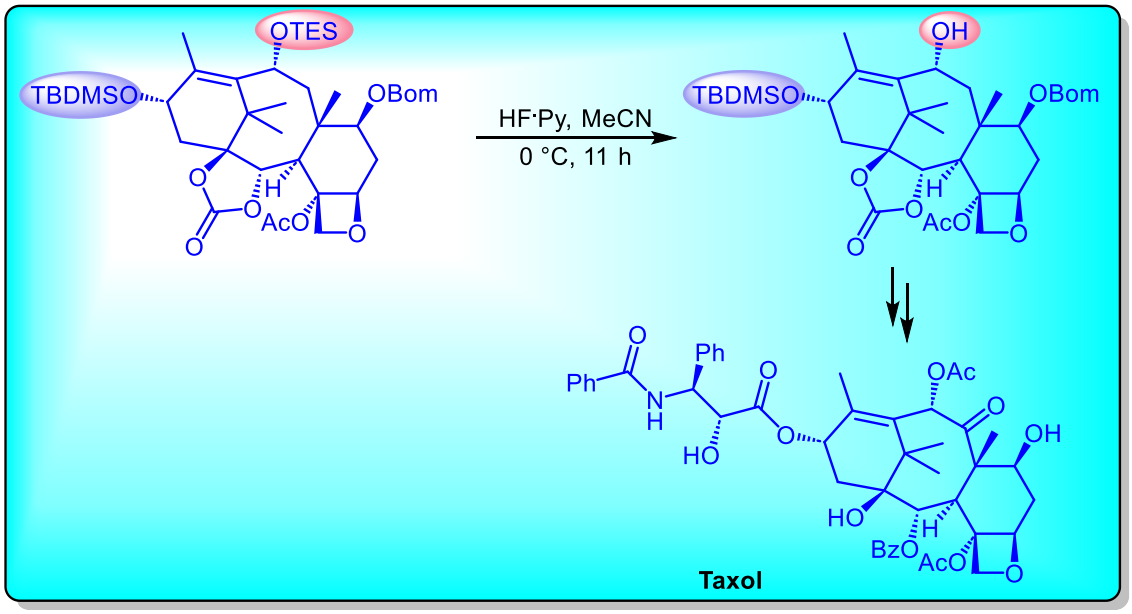


I think in terms of protection as I mentioned that if you have primary versus secondary and using a bulky silyl ether protecting group, then always the primary will be protected faster than the secondary that is number one. But now if you come to the deprotection, then the TMS will be deprotecting very faster the trimethylsilyl. So, this is the order then triethylsilyl, tributyl, triisopropyl and then you have this the tributyl diphenylsilyl. Very similarly if you have a basic medium also I think if you using the corresponding the fluoride ion there you also going to the TMS will be the one going to deprotect fasters. Again you can see as the steric bulk is increasing in this direction you are seeing that their stability is increasing.

We can also able to compare their half-life in the basic medium, but in the acidic medium you can see in this direction you are getting the steric bulk is getting increased and you can see at the same time once the steric bulk is getting increased stability is getting increased too. So, this tricks of the stability in terms of acid and basic condition can help to do the protection first and then to conduct many different transformations. So, here you can see this phenolic -OH groups were getting protected using triisopropylsilane, here it is a TIPS chloride. So, first thing in this reaction you can see first there is alkylation of nitrogen with the aniline happening and then there is a protection of this.

Silyl Ether	Half life in basic media	Half life in acidic media
$^{n}C_6H_{13}OTMS$	≤ 1 min	≤ 1 min
$^{n}C_6H_{13}OTBDMS$	2.5 min	≤ 1 min
$^{n}C_6H_{13}OTIPS$	24 h	55 min
$^{n}C_6H_{13}OTBDPS$	24 h	225 min





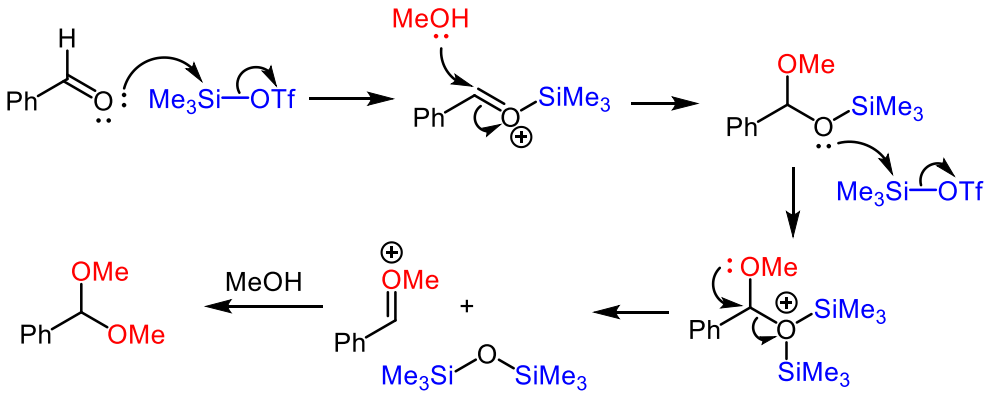
Then further what is going to happen they are going to go for a N-acylation to form this compound and after several step they able to prepare this and you can see in this 16-step this OTIPS- group is remain stable.

So, after they have done their synthesis when they want to go close to their final product now they can do the deprotection using TBAP, Tertbutyl Ammonium Fluoride, which have a F-source which can able to now deprotect to form the corresponding phenol. Then I think in the total synthesis of Taxol, you can see there is a TBDMS group here, there is triethylsilane here and in place of the HF. pyridine at 0°C, you can able to selectively deprotect this particular protecting group keeping the other remain protected. So, that is what is happening you can see there is a difference in this size of the silicon protecting group and the steric environment can allow to deprotect selectively this secondary one compared to this one, to form this as the corresponding alcohol which can be able to convert to the natural product. So, the other important thing.

So, these are can be used the TMS triflate which also used in the laboratory very often. So, if you think about TMS triflate, then people also use them for this conversion that if you want to go for a acetal from the corresponding aldehyde, if you want to form a acetal you can also use TMS triflate. Of course, you can think about using PTSA or parietal sulfonic acid or, but again I think if you use those acid source the one of the problem if there is a trace of little bit of water there then you will not able to get to the equilibrium towards this product, you might get back to the corresponding starting material. So, there will be mixter and it will be difficult to control, but TMS triflate can be used it can do the job. So, here what is happening the oxygen lone pair is attacking first to the silicon to get of this triflate. and then what is happening, in the methanol is attacking here to this corresponding carbon here forming this compound. Again, you have the oxygen lone pair, so it is going to react with another TMS triflate to form this compound. Now you can see your oxygen is bind with two TMS-group for this oxygen lone pair can come back and get this compound. Now once you have this corresponding oxonium, now the methanol can now easily attack here to form this corresponding acetal.

Now, silicon can be used as a protection group for the alkyne.

Acetal Formation Using Trimethylsilyl Triflate

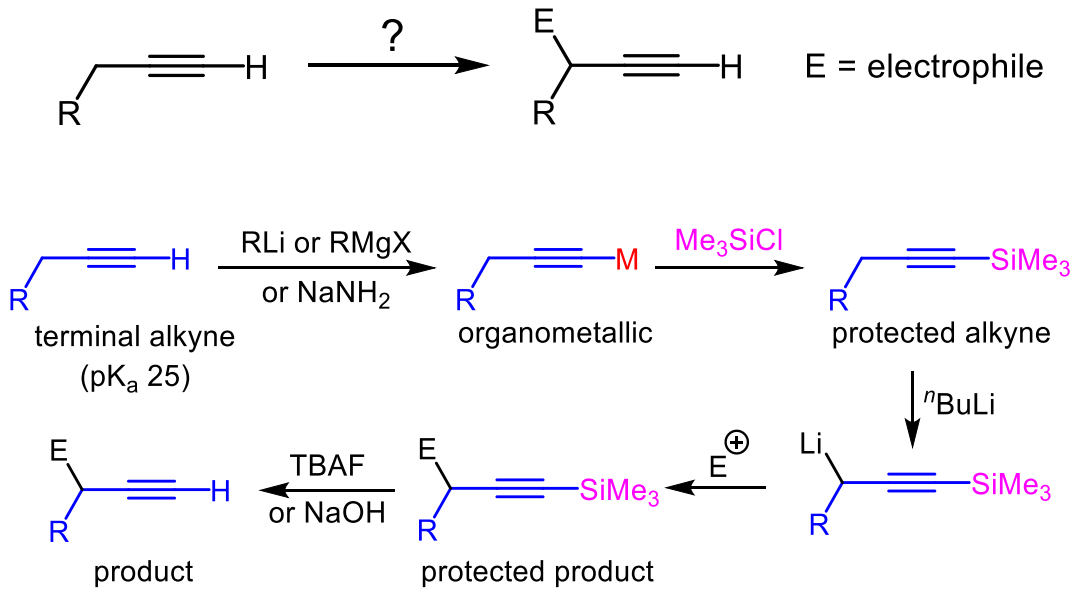


Suppose you have a alkyne here and now if you try to compare the acidity of different proton. So, which proton will be the more acidic? I think if you know about the pKa, you will be agree with me that this is the hydrogen which attached with the sp-hybridised carbon atom. So, you can see this is the sp-carbon versus this is the sp^3. If you remember in the carbon stability, I think I talk about at the beginning when the carbanion at the time if you remember the anion in the sp- carbon will be more stable because it can pull the electron density towards the nucleus. So, this proton will be more acidic, but if I want to do functionalization here suppose I want to do a functionalization here in this particular

carbon for you know how do that. For that we can use a trick we can do a silicon protection and a deprotection study. That means, first thing is we know that we can able to abstract this photon very easily using RLI. We have learned about that pKa around 25. If you use a n-butyllithium this photon can be abstracted and then if you use a corresponding you know it can form the corresponding

So, if you treat a n-butyllithium this can able to generate the carbanion at that carbon and now you can do some you can treat with the electrophile, you get corresponding product and now you just use TBAF for the deprotection. TBAF can react with the silicon attack on the silicon and get it to this corresponding alkyne to get to the corresponding product. So, here silicon job is just masking the alkyne and then at the end it is going to demask to get to the corresponding product. The other important fact is if you try to compare in general if you see a normal alkyne versus a silicon alkyne. So, if you have a carbon versus silicon these are the corresponding silicon analog is much more reactive that means, this alkanyle silane will be much more reactive compared to alkyne towards electrophile.

Alkynyl Silanes for Protection and Activation



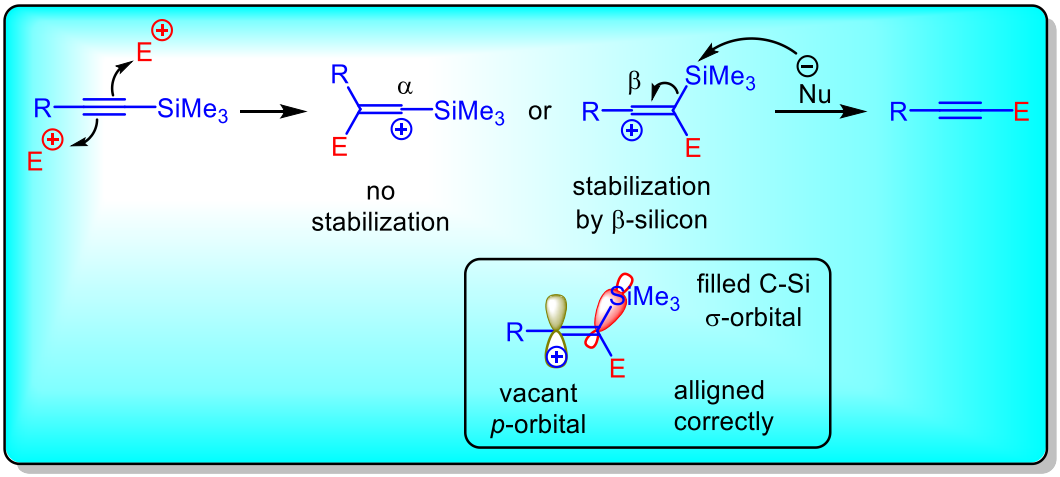
Why it is that? Because of the stability which is forming in the corresponding transition state because of the β-effect of silicon that means, once this electrophile will take the electron density from the alkyne it is going to form the corresponding carbocation. So, now this carbocation is going to form in the β- position here. compared to this one it is not in the α-position because this will be not going to get stabilized.

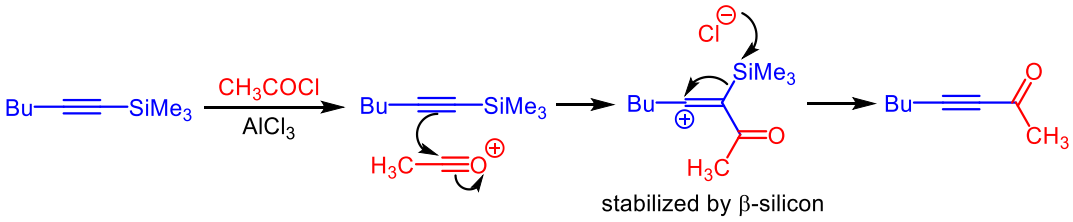
This is the one which is going to get stabilized when it is going to form at the β-position. Because, if it is the carbocation is going to form with the β-position, then the carbon silicon sigma bond electron density can be given to that to that empty orbital.

Because, so there is this filled carbon silicon sigma bond can be sigma electron density can be given to the vacant p- orbital to stabilize this corresponding carbocation. Again, I think this alignment is very important, so that the electron density can be given, so that can stabilize. Now, what is going to happen if this is giving electron density, I mentioned clearly if this is giving electron density here. Now, a nucleophile can easily come because now the carbon silicon bond is becoming weak because the sigma bond is already giving electron density to stabilize the carbocation. So, weak nucleophile can come and attack to the silicon and cleave this bond to generate the alkyne again.

Electrophilic Substitution in Alkynyl Silanes

❖ **Reaction of silylated alkyne with electrophile:**



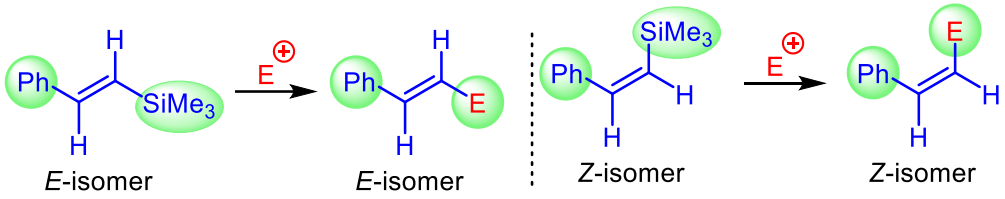


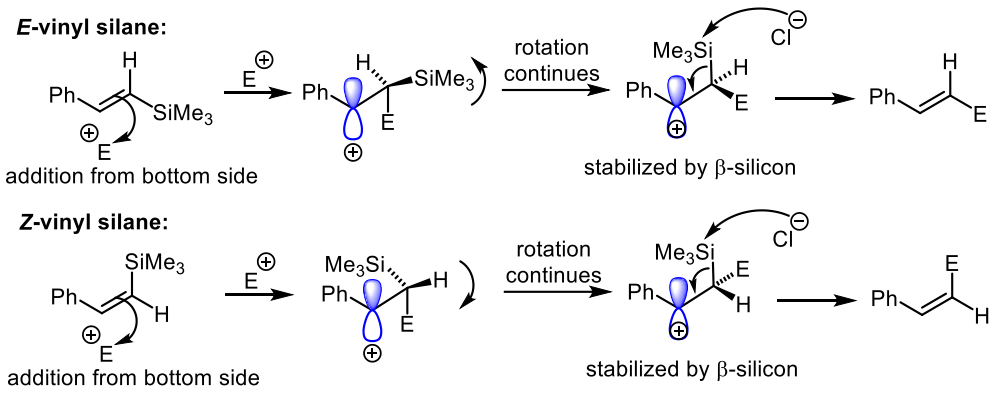
That is why what is happening from the starting to the product? If you start with the silicon you are replacing silicon by electrophile in the product. Again, there could be several different electrophiles, we are showing here first with $AlCl_3$ and acetyl chloride. It can able to introduce the $COCH_3$ groups in the place of silicon. So, silicon is gone and introduce CH_3CO- group. Very similar mechanism here, I think about that once you have this CH_3COCl, I already shown you that once you have the $AlCl_3$ as a Lewis acid it can form this species here.

So, now you can see once this is forms the alkyne can react with that and now there is a formation of this plus in the. So, there is a β-position due to the β-effects, if it will be stabilized which finally, then the Cl- can come in attack here cleave this bond because the bond getting weak to get to the corresponding product. We have learned about reaction with the alkyne, but now we are going to learn that if you have vinyl silicon compound here or the vinyl silane then if you have a E versus z- isomer if you treat with the corresponding electrophile from E- isomer you will get to the corresponding E- product that means, again the silicon will be replaced by the corresponding electrophile here. So, there will be no change from E to E you will get E.

Electrophilic Substitution in Vinyl Silane

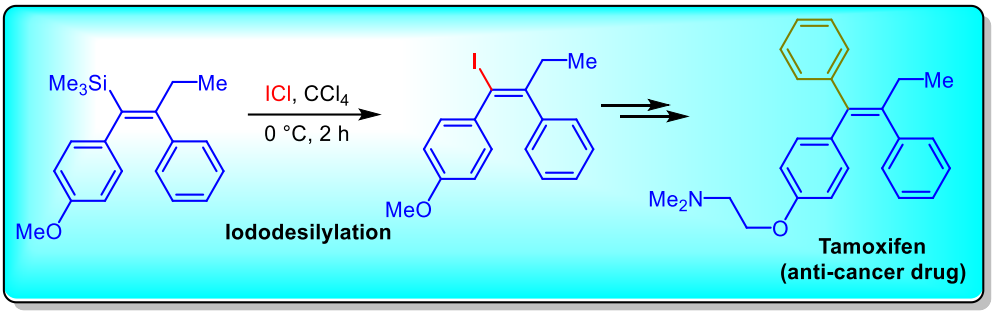
- Vinyl silanes undergoes *ipso*-substitution with retention of geometry in presence of electrophile.

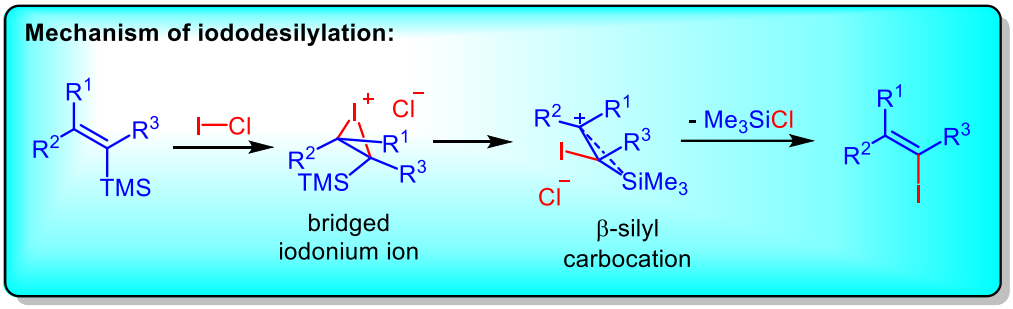




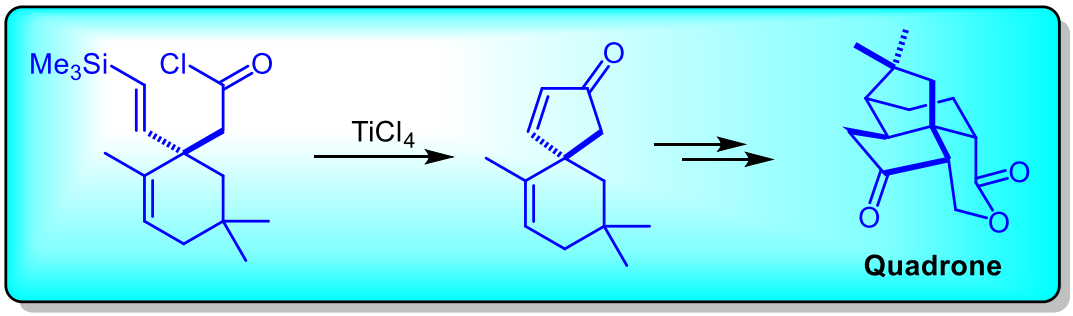
So, that will be very you see the reactions are going to be very stereospecific and from z- are going to end up getting to the Z-isomer as well. So, again what is happening here once E-vinyl silane react with the corresponding electrophile, it can generate a carbocation which is again if you see this α this is β. And to give electron density they have to be in the anti-periplanar orientation that the silicon sigma bond electron density can be given to that the empty orbital in the carbocation and finally, because of the electron donation this carbon silicon bond becoming weak. So, Cl- can be able to cleave it to form this corresponding vinyl product. If you start with the Z- vinyl silane that can also react with the electrophile generate the carbocation again it can rotate this bond between this carbon-carbon bond can rotate.

So, the rotation continues to get to the spot place where it can able to give electron density to the empty P- orbital and finally, the Cl- can attack to the silicon to get to the corresponding photon. So, starting from either starting from E, you are getting E and from Z, you are ending up getting to the Z-isomer. Here some of the example here using ICl- as electrophile you can introduce a iodine here, Again I think as I say mechanistically very similar mechanism happen and once you have this compound it can be convert to a very important anticancer drug called Tamoxifen. Again, the mechanism is given here if you have a TMS then first the Iodinium formation going to happen and then you can see this can able to keep the Iodinium, there will be in the decomposition of Iodinium going to form this corresponding carbocation which is again in the β-position and finally, the Cl- can attack to the silicon even to form a double bond here, to get to the corresponding product. So, you can use a Lewis acid and it could be an intramolecular reaction where the vinyl silane can react intramolecularly to acyl chloride.





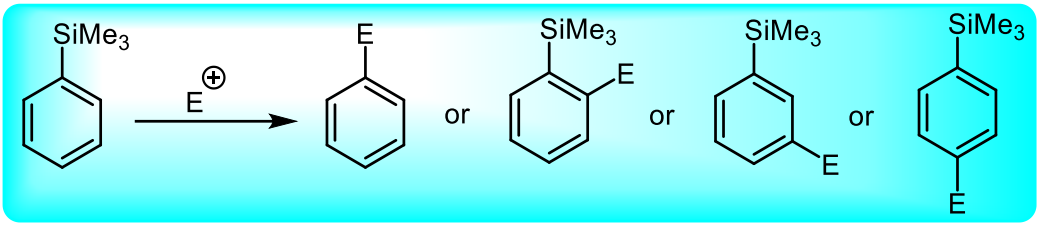
I think I talk about reaction of acyl chloride with $AlCl_3$ if you remember in case of alkynyl silane. Here very similarly in case of tritium tetrachloride, there is a very similar thing going to happen once you have a Lewis acid. and that can go for intramolecular attack. So, that intramolecular attack going to take place.



So, this can able to form first this type of species here, the Cl will go form this species which going to get attack from the silicon to generate.

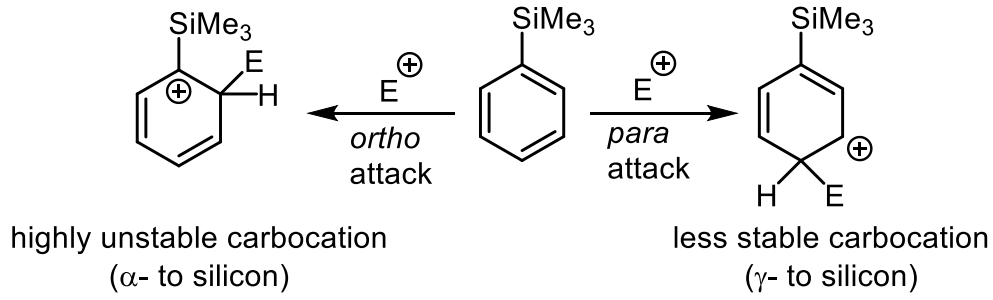
So, if you think about this going to go for attacking here and you have a corresponding silicon here. and you will be forming a carbocation here and now what is going to happen the Cl- going to come back because this bond is giving electron density to the corresponding carbocations the sigma bond that is why this bond will be weaker to form the corresponding product. So, we have learned about the reaction of alkynyl silane and then the vinyl silane. Now, we are going to learn about the aryl silane. If you have aryl silane you try to treat the electrophile.

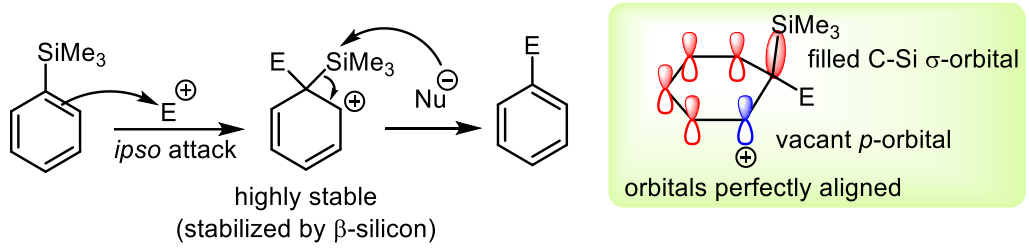
What is going to happen? You end up getting several different products, I have mentioned here. There are several different possibility, but what is going to happen? The major product will be formed through the corresponding ipso- substitution. So, we end up getting to this product the ipso-substitution product as a major product. So, what is happening here? Again, you can think about that if you go for an ortho attack here, then you are generating a carbocation which is α-to the silicon. Again, we know that silicon stabilized carbon ion in the α-position not the carbocation because so that is why this carbocation will be highly unstable.

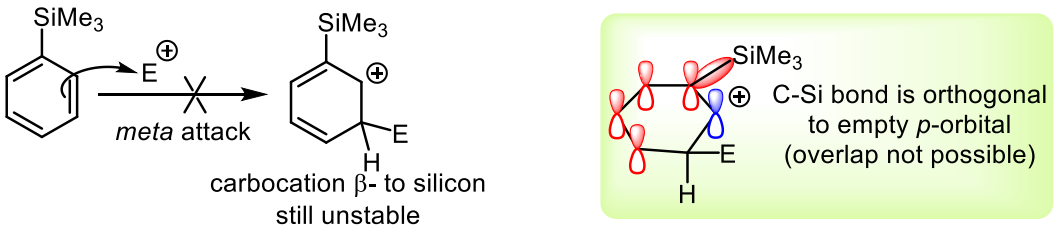


If you go for a para-attack, then you are generating a carbocation here which is not even α- not even β-it is or it is a γ-carbocation. So, it is not stable, but if you go for an ipso attack, you generate a carbocation which is β. Now again if you have a β-carbocation what is happening here, it can able to So, orbitals are perfectly aligned here you can see we have already discussed this in the previous case also that once the orbitals are aligned like that that you have a carbocation here and you have this silicon sigma bond then this can give electron density to that corresponding carbocation which is happening here. Orbitals are perfectly aligned for stabilizing this corresponding transition state which can now the nucleophile can attack here to get to the corresponding product. And then if you think about there is another possibility there you know what about if you have a meta-attack, then carbocation is forming to the β-position, you might here also carbocation is forming β-position why it is not going through this route.

Ipso Substitution in Aryl Silane



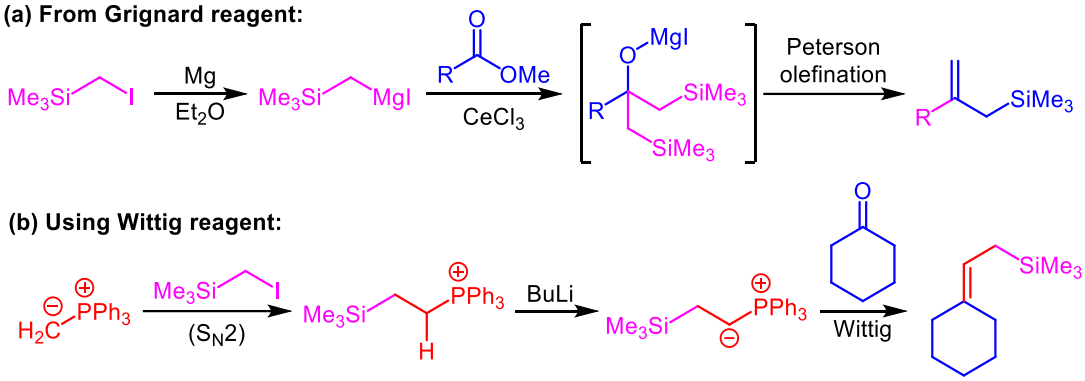




The problem is that here the silicon carbon bond is orthogonal in terms of this empty p-orbitals of the carbocation. So, if there orthogonal then they cannot able to give electron density, the sigma bond cannot able to give electron density to the to the p- orbital of the carbocation. So, that is why this is not possible, that this ipso substitution which is favorable because of this corresponding the stabilization of this positive charge which is in the β- position to the silicon. Then I am going to talk about some of the chemistry of the $TMSCH_2I$ compound. So, this is an important compound here because people can able to convert this iodo to the corresponding Grignard because you can see are literally generating some sort of you can compare this species of some sort of a carbanion here.

So, you have a carbon and some sort of anion here you can think about like that. So, if you can see once you are making a Grignard means you are making some sort of a C- and M +. So, this is α- position of the silicon and α- position of the silicon is always silicon stabilize the corresponding carbanion. That is why these compounds can be synthesized and can be used can be react with corresponding esters here and after the two equivalent of the silicon two equivalent of the Grignard can attack here if you remember. then after that Peterson olefination can happen between these two group there will formation of the olefin.

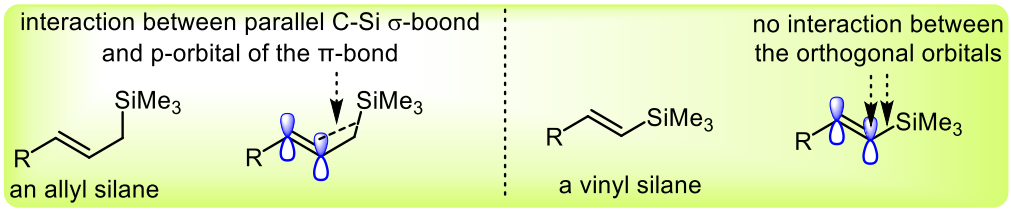
❖ **Synthesis:**



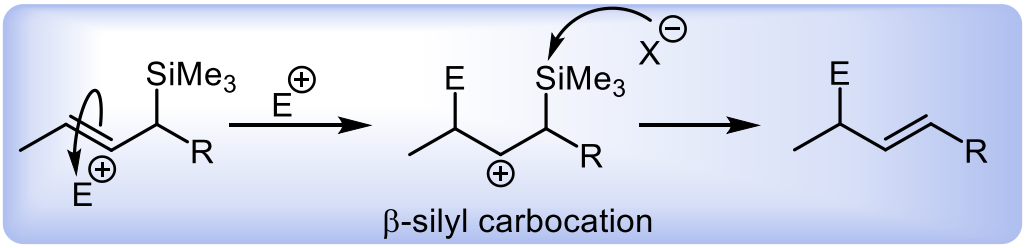
So, the oxygen silicon bond formation happen and then there is a once that is going to form happen this will allow formation of this corresponding double bond. It can also act as a Wittig reagent. So, you can take this you treat with that corresponding CH_2 -PPh_3+ the phosphorus ylides. Finally, if you treat with the butyl lithium it will able to form the corresponding Wittig ylides which can react with the corresponding carbon group to form these corresponding allyl silane compounds. So, you can able to synthesize allyl silane compound from starting from this particular compound here.

Or you can start with again from. So, you can use you know two different technique from using this Me_3SiCH_2I either you can use the Grignard technique or you can use this Wittig reagent to get to the corresponding allyl silane. Of course, there are more method there are several other cross coupling strategy also you can use for this. and also there are some hydrosilylation strategy. So, I think now we have learned about the synthesis of the allyl silane we are going to talk about some of the reactivity. So, one of the important thing is as I said before also that once you have this allyl silane the interaction between this parallel carbon silicon sigma bond and the p- p-orbital of the pi bond.

So, these interaction are possible here this sigma bond can interact with this π- bonds, but here once you have a vinyl that is not possible. So, now if you have a electrophile as I mentioned that can this olefin electron density can be given to the electrophile to generate this β-silyl carbocation.



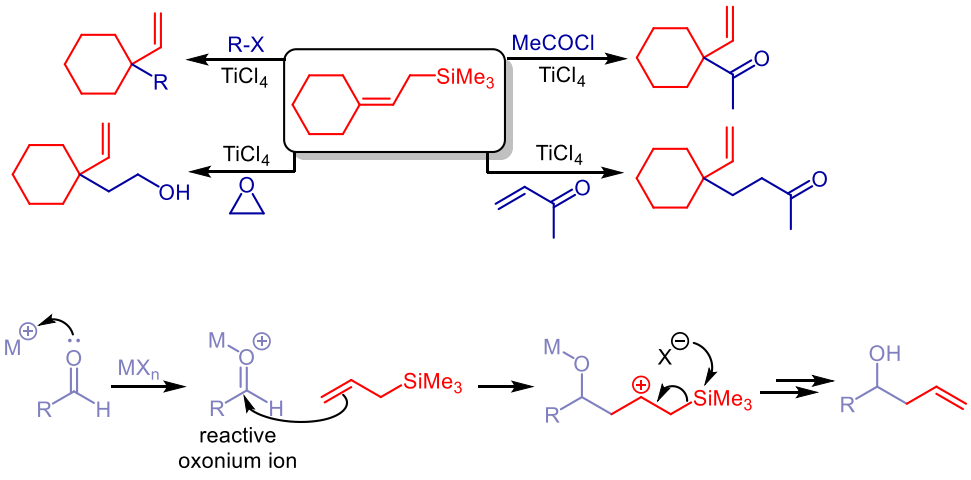
Because now of the sigma bond is giving electron density here to stabilize this β-silyl carbocation. So, this carbon silicon bond is weak.



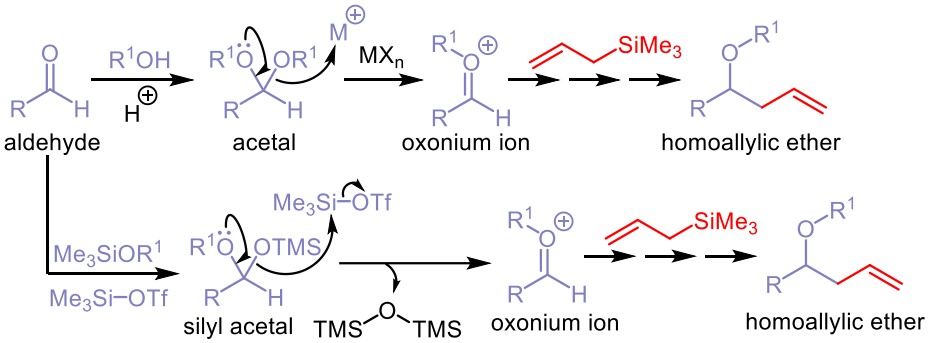
So, X- can attack here to form this olefin here. So, finally, what is happening the overall process is electrophilic substitution with an allylic rearrangement you can think about. In general, if you try to think about allyl silicon, we generally write this way that if we have a electrophile we generally write this way that it can able to trap electrophile and form this sort of a product, but in general if you I think this is the mechanism you know what is

happening to form this product. So, it is going through some sort of mechanism like that, where it is forming this some sort of a β-silyl carbocation. Again, if you have this compound, you can be able to treat with, Lewis acid. If you have titanium tetrachloride and Lewis acid, you can treat the alkali halide to introduce this R- group here.

You can take acyl chloride to introduce the $COCH_3$- group here. Acetyl group can be introduced. It can go for a1,4- addition in place of titanium tetrachloride. it can also open up epoxide. So, if you have a Lewis acid and then this corresponding allyl silane can attack to the epoxide here, to open up the epoxide to get to this corresponding product.

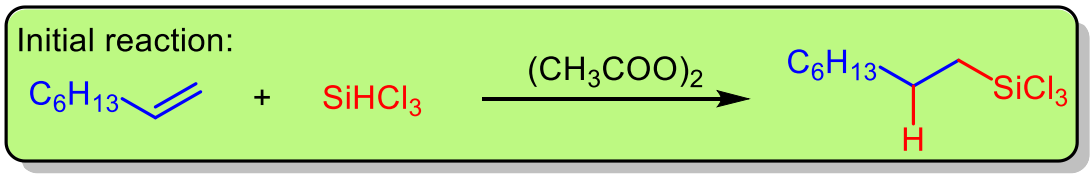


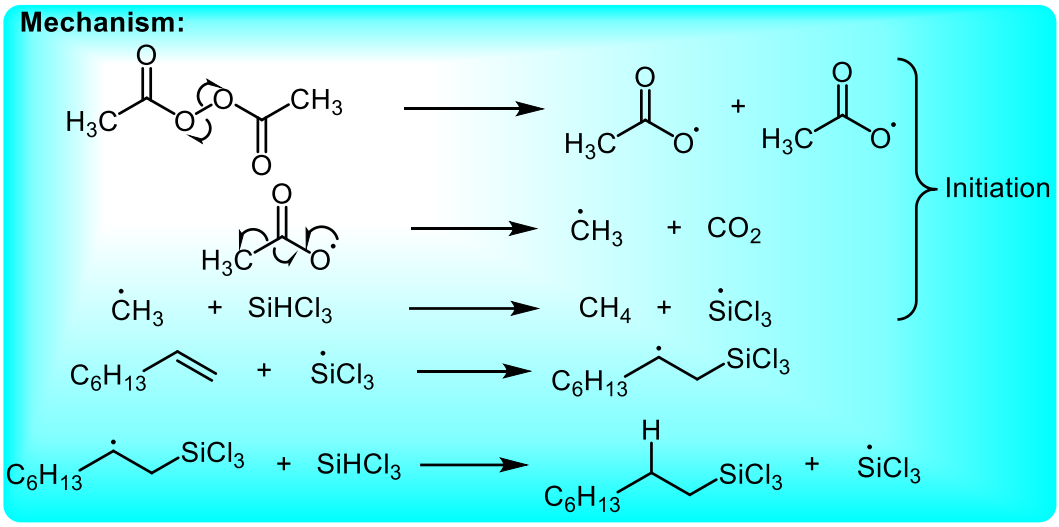
So, again the very similar thing we are saying that if you have a Lewis acid what is happening it is forming this reactive oxonium ion. Once it is forming this oxonium ion then now this double bond electron density can be given here forming this the we are forming this the carbocation in the β-position, now this X-can attack on the silicon to get to the corresponding product. Here you can see I think the mechanism is given here very you can use the TMS-triflet to form this corresponding silyl acetal to get to this corresponding oxonium ion or you can use the corresponding ROH and H+ either way you can able to generate this corresponding oxonium ion which can able to react with the allylsilane to form this corresponding homoallylic ethers. So, this is the way you can able to form the corresponding homoallylic ether. So, this is a problem given here if you want to go for intramolecular cyclization because now you have to use a Lewis acid which can activate this or the OMe.



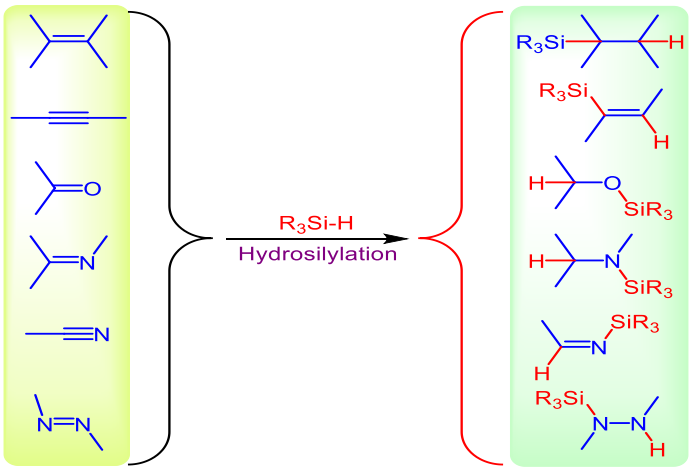
So, once it will be activated it can able to form some sort of a intermediate like that, once you have a Lewis acid then it can you know this can come back and get it of this forming this oxygen plus which can now allow this cyclization to happen to form this compound. So, here what is happening at the end you are generating a homoallylic ether.

The hydrosilylation reaction it was in 1947, it was discovered by F.C. Whitmore and the co-worker actually discovered the hydrosilylation reaction of 1-octene. Here it is happening. So, in this hydrosilylation reaction 1-octene react with the trichlorosilane in the presence of diacetyl peroxide. So, in place of diacetyl peroxide what is happening? The $SiHCl_3$ and this H-is adding in that two different part of this. And what you are seeing very similar to the hydroboration we are also seeing the anti-Markovnikov selectivity here. Again, what is happening in this reaction first thing this reaction is going through some sort of a radical pathway.





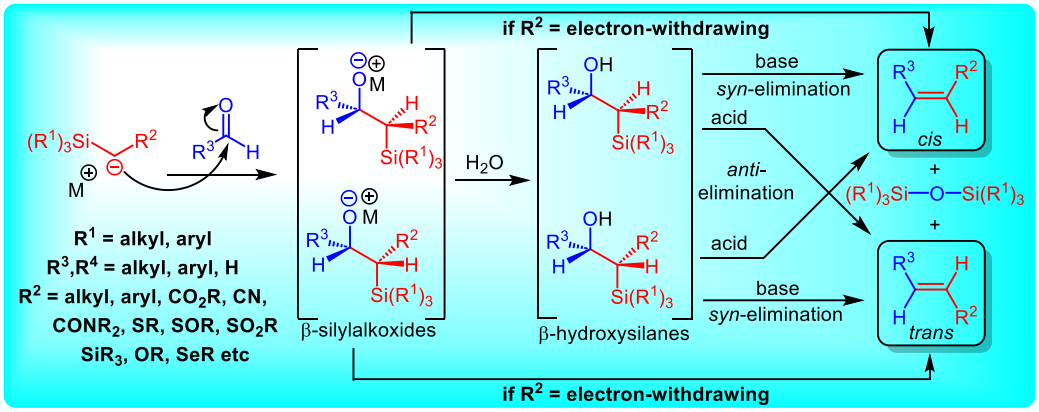
You can see because of this you have this type of the peroxide linkage here which is going to get cleaved in case of heating to generate CH3COO radical after the CO_2 getting eliminated it can form CH_3 radical which can able to form this corresponding silicon radical here.



Now, silicon radical can act to the olefin ,It is going to form the β-radical in the silicon, if you remember that can silicon can stabilize radical in the β-position which can now go for a hydrogen atom abstraction to get to the corresponding product. Again, I think this chemistry was developed for last 4 and 5 decades there are several different methods was developed for hydrosilylation reaction. They are from olefin to alkyne to carbonyl to imine, cyanide, every single different compounds, you can able to introduce the silicon and hydrogens. So, this method can be done in presence of transition metal or in the absence

of transition metals. So, now I am going to talk about another very important topic which is the last part of the today's talk is the Peterson olefination.

Peterson olefination

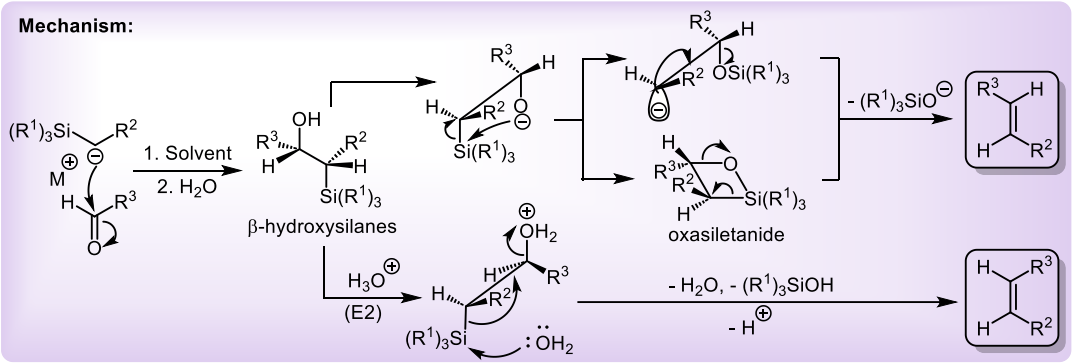


So, here you are going to see that this is I think we have learned in the previous part that once you have this you are generating carbanion alpha to the silicon. So, now this can able to react with the corresponding aldehyde to form this β-silyl alkoxide. Once you have this β-silyl alkoxide under basic condition it can undergoes a corresponding stereospecific syn elimination and in case of acidic condition it is going to participate in a stereospecific anti elimination. So, now if you can see here depending on this syn and anti-elimination you can end up getting a stereoselective formation of the olefins. We are going to explain in the details how this olefin formation is happening.

It was discovered by prof. Donald John Peterson. So, first once you have this anion here alpha to the silicon it can act with the corresponding aldehyde from the β-hydroxysilanes. And now you can see that there is two different cases if you have acid versus base.

In case of acid what is happening OH can be getting protonated. So, it can form the H_2O+ here. Now you can see there is anti-elimination is happening because this silicon can give electron density to the corresponding antibonding sigma orbitals here the sigma to the sigma electron density can donation can be happening. Now, because of this the silicon bond is weak. So, this bond can be cleaved to form corresponding cis olefin. But once you have treated with the corresponding base, now they will be syn elimination happening. This O- can be attacking the silicon forming this sort of a carbanion here or can be an oxasiletanide intermediate. Either way what is going to happen it is going to get it of the silicon going to form corresponding trans olefin.

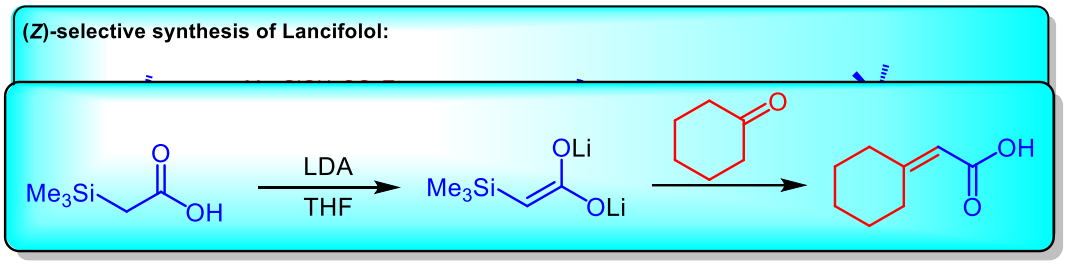
So, I think you understood how this two mechanism is operating to giving you the cis. So, anti-elimination going to give the corresponding cis product and syn elimination going to give the corresponding trans product. Here you can see again I think it is starting from this $Me_3SiCH_2CO_2Et$ already you can able to generate this anion and now you can able to react to this carbonyl compound to form this corresponding olefin. Again, you can see the Z-selectivity is very high you can end up getting to the corresponding Z-product and which can be convert to the natural products here. Again, another example here you can treat with LDA- here you need excess LDA because you have acidic proton here to get to this corresponding compounds.



Then you can treat with the corresponding carbonyl group here to get to the olefin here. So, that they are although you have carbosilicate group is unprotected, but that does not make any problem here because once you have this carbonyl next to the silicon it is going to act with the corresponding carbonyl group and then after the elimination it will form the corresponding product. So, in this part I think I talk about a couple of important thing about the silicon you have learned about at the end the Peterson olefination how you can able to get to the corresponding E versus Z. And then in the previous part I think the most important thing I am going to talk about I think I have talked about is the protecting

group for alcohol, different silyl ether protecting groups how that is important that if you want to protect primary versus secondary.

And, then also I talk about that if you have a vinyl silane or alkynylsilane, if you treat with electrophile it is just replace the silicon with the electrophile.



So, if you start with the E, the vinyl silane you end up getting the E- product, starting from Z- end up getting to the Z-product. Again, these are the references and again thank you somuch for coming to the class. I am going to see you guys in the next class. Thank you.