Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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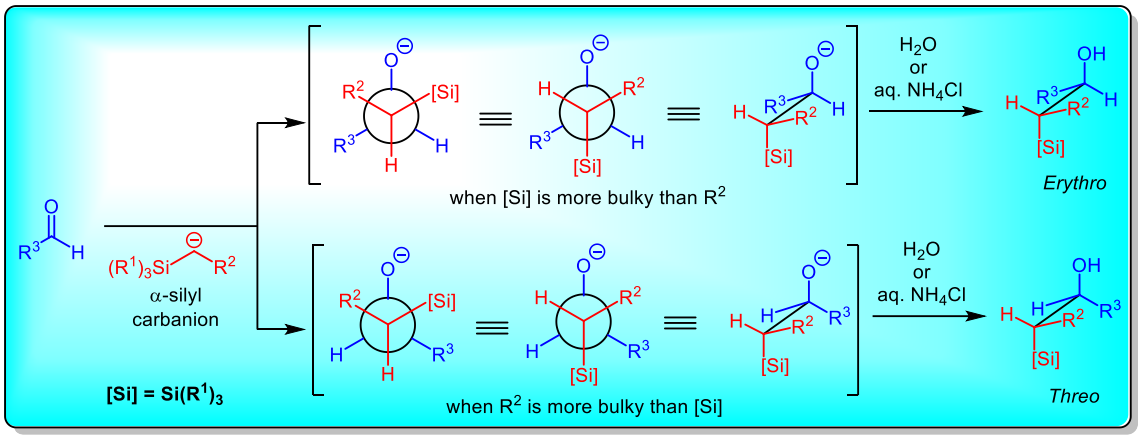
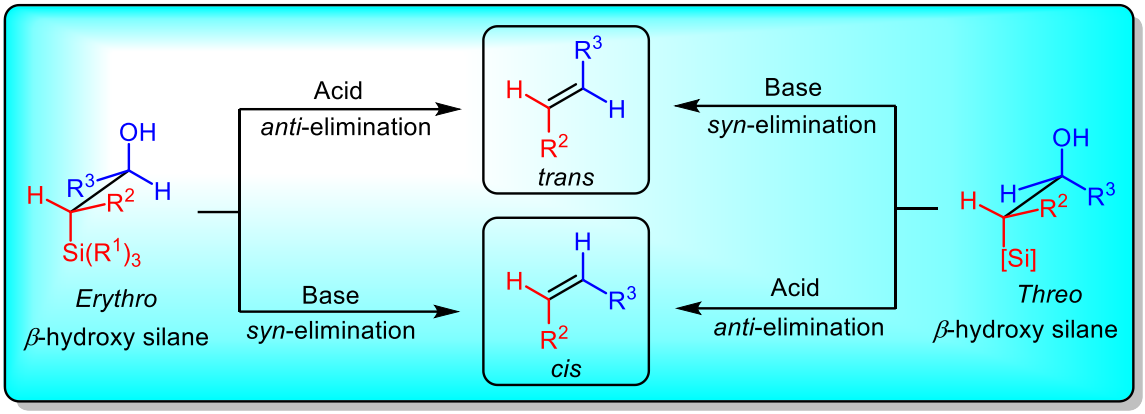
Lecture 49: Organosilicon

Welcome back to this NPTEL online certification course in "molecular rearrangement and reactive intermediate". So, I am continuing with the organosilicon chemistry. In the last two classes, I talked about organosilicon chemistry mostly the discovery of silicon and the different types of coordination numbers, you have seen tetrahedral versus the trigonal bipyramidal structure. If it is pentavalent silicon also I talk about some of the important effects like the α-effect and the β-effect. And also I think I also included one of the important reactions using organosilicon compounds which is Peterson olefination. I am going to continue with Peterson's olefination and then also I am going to include some of the other important reactions like the Brook rearrangement. This is a very important reaction using organosilicon chemistry. Then there is cross-coupling. So, I am going to talk about the Hiyama coupling, and Silyl-Heck coupling reaction, and my lecture will end with the Fleming-Tamao oxidation, another important reaction.

So, last class I talked about the Peterson olefination, and one of the things I think which I did not go into the deeper, I think I talked about that the generation of the α-silyl carbanion from the α-effect. So, from the α-effect, you can understand that it is going to stabilize this corresponding carbanion because there is a σ* and non-bonding interaction. Because of the electron donation to the σ* that is why this carbanion is stabilized. Then I also talk about that once you add to this aldehyde, you can think about like some sort of a very similar to organolithium or you have seen that this is a carbon with a negative charge is going to add to the corresponding aldehyde. So, it is a hard nucleophile. So, it is going to go for 1,2-addition, after 1,2-addition it is going to generate this corresponding β-hydroxy silane. So, once you have this type of intermediate, now there is an important thing because, in the last class, I only talked about the formation of β-hydroxy saline and if you give acid we have seen the formation of the *E*-selective olefin and if you give base we have seen the formation of the *Z*-selective olefin. But the other important thing is before we go into that this is very important that how this nucleophile is going to attack here. Here you can see once the nucleophile going to attack you are generating two chiral centers. So, there is a possibility of diastereomers. Now it could be a *threo* or it could be an *erythro*. So, now first if you try to think about the attacking of nucleophiles to the carbonyl compound then one of the important things is if you try to see when the

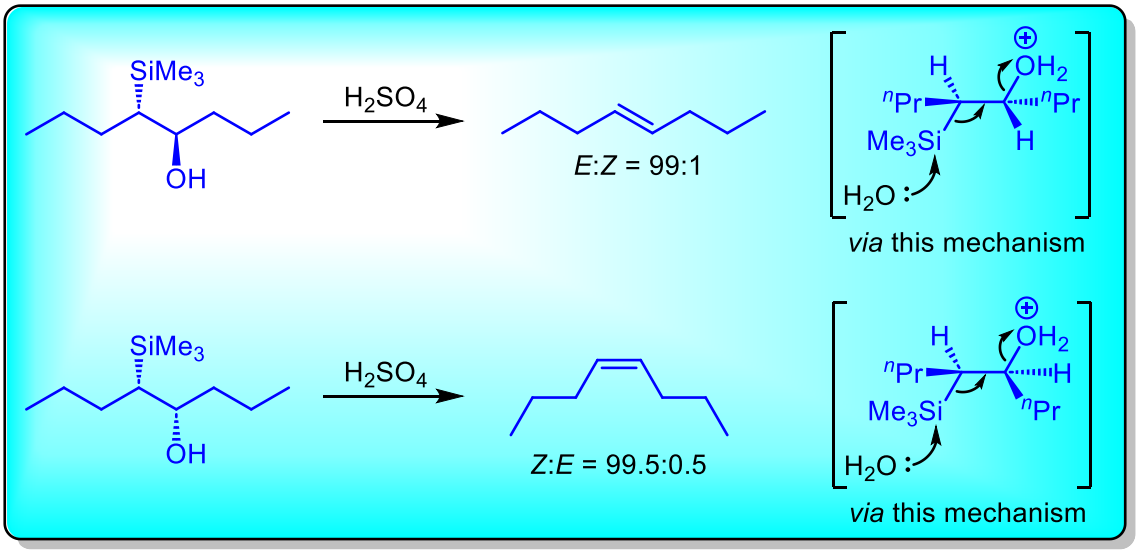


nucleophile is approaching there are two different things that can happen once you have an R_2 group. So, there are three important groups one is R_3 which is with the carbonyl, one is R_2 which is attached to this CH_2 and another is a silyl group. So, if you see based on the structure of these three you can either able to get to *erythro* or you can able to get to *threo*. So, now the question is once the nucleophile is attacking there if the silicon is bulkier than R_2. What is going to happen when this is going to attack this corresponding aldehyde if the silicon is bigger then it is going to be anti to this R_3 group of the aldehyde. Because if R_3 is a bigger group silicon is a bigger group they try to be as far as possible so this is the position they want to be. So, then what is going to happen? then you can see there is the possibility that you can put silicon here R_3. You try to draw in the different types of projection and at the end you can see you are ending up forming an *erythro* compound. Once you quench with the water the O- will get the proton to form the alcohol. So, you end up getting this β-hydroxysilane, but it is an *erythro*, if R_2 is bulkier than silicon, So, then the R_2 will try to approach in such a way that R_2 will be opposite to the R_3. Because that will be the more stable conformation where these two bulky groups will be far from each other in the anti-conformation. In that case, you can end up after the quenching forming the *threo* isomer. So, in one case you can get *threo*. So, depending on the size of the silicon or the R_2 which one is bulkier you can get either *threo* or *erythro*. So, that is a very important thing and sometimes this is a problematic thing for Peterson olefination because if the sizes are not much different then it will be difficult to control the formation of the ratio of *threo* and *erythro*. So, in that case from both the diastereomers you can able to get to the corresponding *Z* versus *E* olefin based on the next condition that you choose, which means if you use an acid or a base from either of these *threo* or *erythro* you can end up getting to the *E* or *Z* olefin. So, now if you have a mixture of *erythro* and *threo* then that is going to make the selectivity a big challenge. That is why a lot of time you see that Peterson olefination was mostly used for the formation of the terminal olefin where you do not have to deal with *E* or *Z*. I think I already talked about this once you use an acid it is going to form OH_2^+ and now the silicon can give electron density to the corresponding σ*-orbital from the σ-orbital and that is going to weaken this O-H bond. So, you can write this mechanism like that. So,

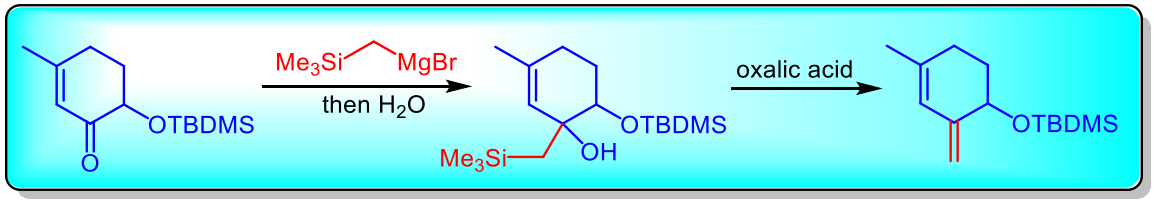


that can also weaken the carbon-silicon bond. So, there will be *anti*-elimination to form the corresponding trans product. In the case of base, what is going to happen? In the case of the base we know that we are not going to end up with the corresponding silanol, there will be this O^- after the addition to the aldehyde then O^- can attack the silicon from the same side, formation of the corresponding carbanion and then the formation of the double bond. So, that will end up forming the cis-product. So, this reaction is stereospecific. So, this was not a problem. the problem is the generation of *threo* or *erythro*. I hope I think you guys understand this particular problem in the Peterson olefination.

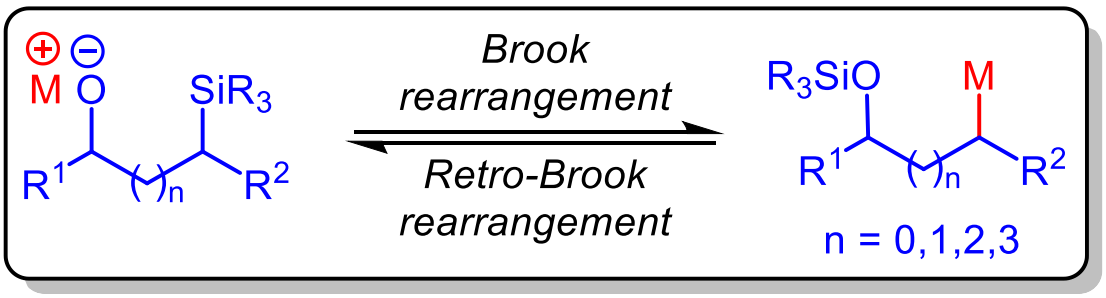
So, now, you can see once you have a particular diastereomer either you started with the *threo* or from the *erythro*. Once you put acid you can end up getting the corresponding *E*-product and from the *threo* you can end up getting the corresponding *Z*-product. Again I think I already talked about this mechanism before. So, here in these cases also the mechanism will be similar because depending on the acid or base, you will end up getting opposite selectivity, which means here in the case of getting an *E* you end up getting a *Z* whereas in case of getting a *Z* you end up getting an *E*.



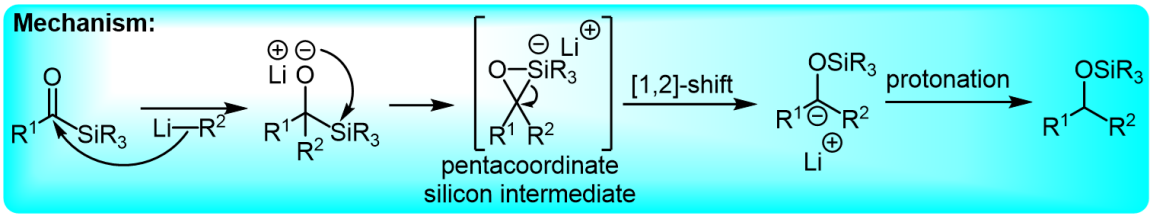
Peterson olefination is particularly used for the synthesis of exocyclic double bonds. So, when you are thinking about synthesis some sort of a terminal olefin or you can think about something like some sort of an exocyclic double bond like this. Again there is an example given here, in this reaction, the Grignard reagent going to attack. So, you can see there is a possibility of 1,4- vs 1,2-addition, but this is a hard reagent so it will go for 1,2-addition here, and then after the elimination it is forming this exocyclic olefin. So, that is all about the Peterson olefination.

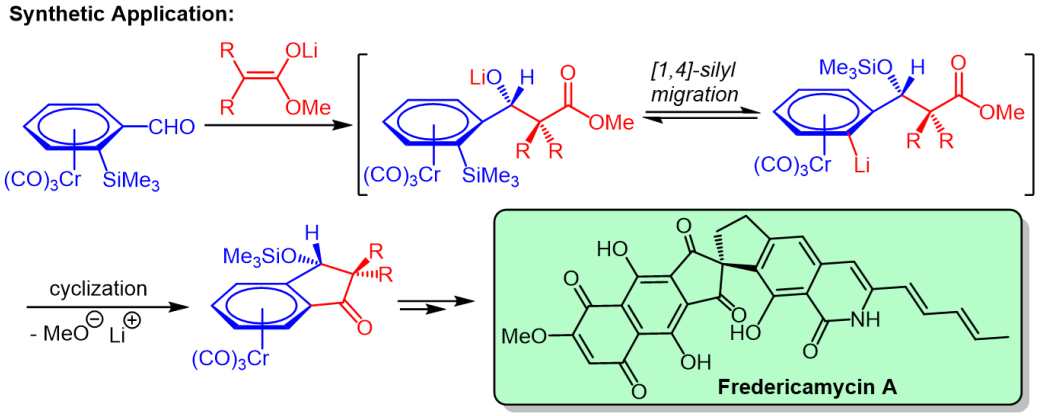


Now we are moving to another important reaction called Brook rearrangement. It was discovered by Canadian chemist Professor Adrian Gibbs Brook in the 1950s. It is a migration of the silyl group from carbon to the silicon under basic conditions or if you have an aldehyde or acyl silane you take a nucleophile and add it to the carbonyl that will generate this O^- species that can also participate in a Brook arrangement which we are going to discuss in a minute. If you have something like 1,2- or 1,3- silicon and OH then if you treat with base it can generate the O^- that can also participate in the migration of the silyl group from the carbon to the oxygen. So, the formation of silicon-oxygen bonds is very important. In the beginning, I talked about the bond energy, so the two strongest bonds are the Si-F and Si-O bonds. So, because these bonds are going to be stable. So, this is the driving force and then sometimes you can see there are retro Brook arrangements we will discuss some of this. The important thing is migration occurs with the retention of configuration in the silicon center. So, the migration occurs with the retention of configuration which I am going to explain also during the mechanism. So, there are a couple of different things which you put by n, n could be zero. So, both are in the same carbon which means we are talking about the formation of O^- and the silicon is in the same carbon, in that case also it is going to take the silicon and then form the corresponding carbanion. So, you end up generating a carbanion here with an $OSiR_3$. So, this is called Brook rearrangement.



Now if you have this acyl silane and take a nucleophile and add it to the acyl silane. If you have the corresponding organolithium, Grignard reagent, and other nucleophiles, once you attack the carbonyl group, you are generating this O^- here. Now that can react with this silicon from here and once it is giving electron density to the silicon it is going to form this *penta*-coordinated silicon intermediate. We talk about that in the silicon chemistry carbon which does not have a *d*-orbital cannot form this *penta*-coordinated species, but silicon does. That is the important thing here because once this *penta*-coordinated species forms then there will be a *[1,2]*-shift. There will be a *[1,2]*-shift of silicon moving from carbon to oxygen and generating a carbanion. Now, that carbanion can be trapped with a proton to introduce H, it can trap with the electrophile and more. This is an example of Brook rearrangement. Here you can see both CHO and the $SiMe_3$ group are in the *ortho*-position and this is again a chromium-aryn complex here. So, once this enolate is attacking the aldehyde, it is forming this OLi which now has a *[1,4]*-silyl migration. So, now, you can see this is a *[1,4]*-Brook rearrangement happening to generate this corresponding lithium in this carbon. So, the O^- is forming this *penta*-coordinated species. Once it is forming the *penta*-coordinated species it gives electron density that is weakening this carbon-silicon bond to generate this corresponding carbanion here and then that can able to do further intermolecular cyclization to form this compound which was converted to the important natural product.

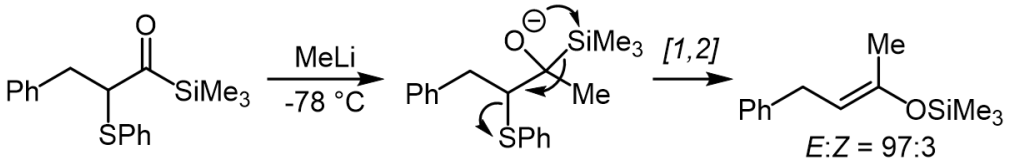




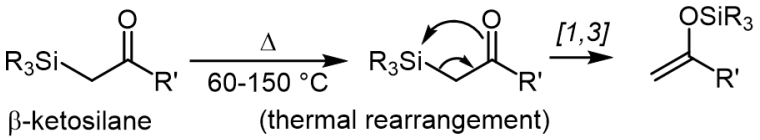
Now we will talk about *[1,2]*-Brook rearrangement, in this case, the methyl lithium is attacking here, formation of the O^- and the silicon going to transfer from the carbon to the oxygen formation of this carbanion going to happen first. And you end up forming $OSiMe_3$ and then methyl and then this minus which can remove the SPh group to generate the olefin here with a 97:3 *E* vs *Z* selectivity. Then there is *[1,3]*-Brook

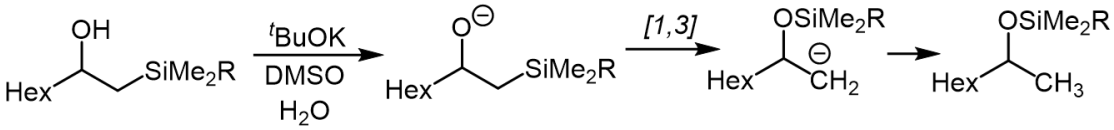
Classification:

***[1,2]*-Brook rearrangement:**



***[1,3]*-Brook rearrangement:**

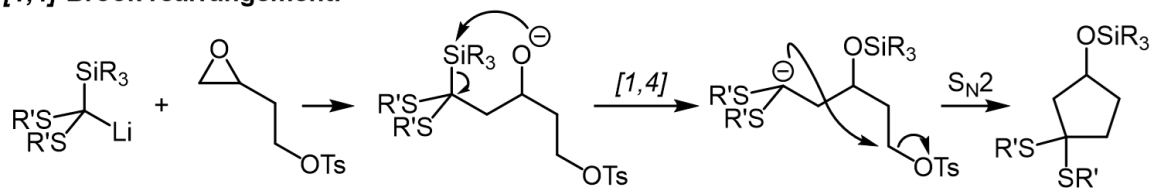




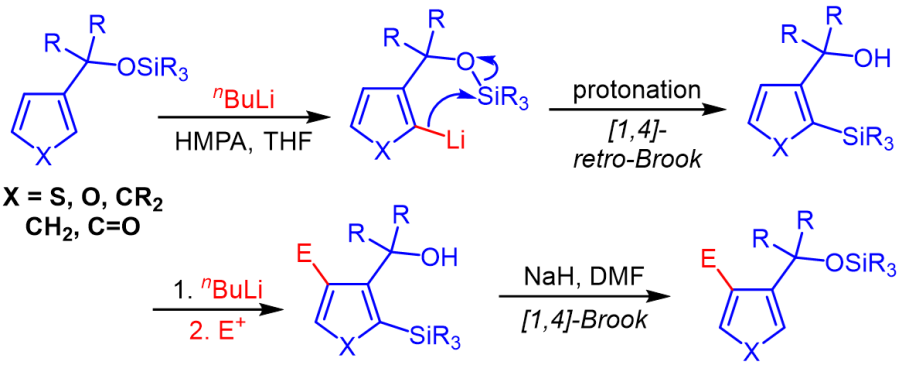
rearrangement here, here what is happening once you have a β-ketosilane. So, this is you have this α-keto this is a β -keto. Once you have this β-ketosilane, once you heat up then there is a thermal rearrangement happening to generate this silyl enol ether. Which can react with the corresponding electrophile. You can see another example here instead of this thermal arrangement instead of carbonyl you have alcohol here. If you treat it with KO^{t}Bu that can abstract this proton from this OH to generate the O^- which is again going to give electron density to the silicon to form this *penta*-coordinated species. Because silicon has a vacant *d*-orbital now it is going to weaken this carbon-silicon bond to generate this corresponding carbanion here. which can take a proton to form the corresponding product.

This is an example of *[1,4]*-Brook rearrangement, this lithium compound can add to the less hindered side of the epoxide to generate this O^-. Again which can participate in the *[1,4]*-Brook rearrangement. The O^- can give electron density to the silicon *d*-orbital to form the pentagonal species. Then you can see this bond is getting cleaved to form this corresponding carbanion here which is ready for an S_N2 reaction. Because this is a stabilized carbanion, again you can see this is stabilized by two sulfur groups next to it. This carbanion participates in the S_N2 reaction to get to this product. There could be a retro-Brook rearrangement can happen. Not only the Brook arrangement after that also there could be something called retro-Brook rearrangement. Here you have this oxygen or sulfur, this can go for a directed lithiation. We have learned in organolithium chemistry that there will be directed lithiation to generate the organolithium which can now react with the silicon to cleave the oxygen-silicon bond to generate an alcohol which is again treated with *n*-butyllithium and an electrophile, then you treat with the sodium

***[1,4]*-Brook rearrangement:**



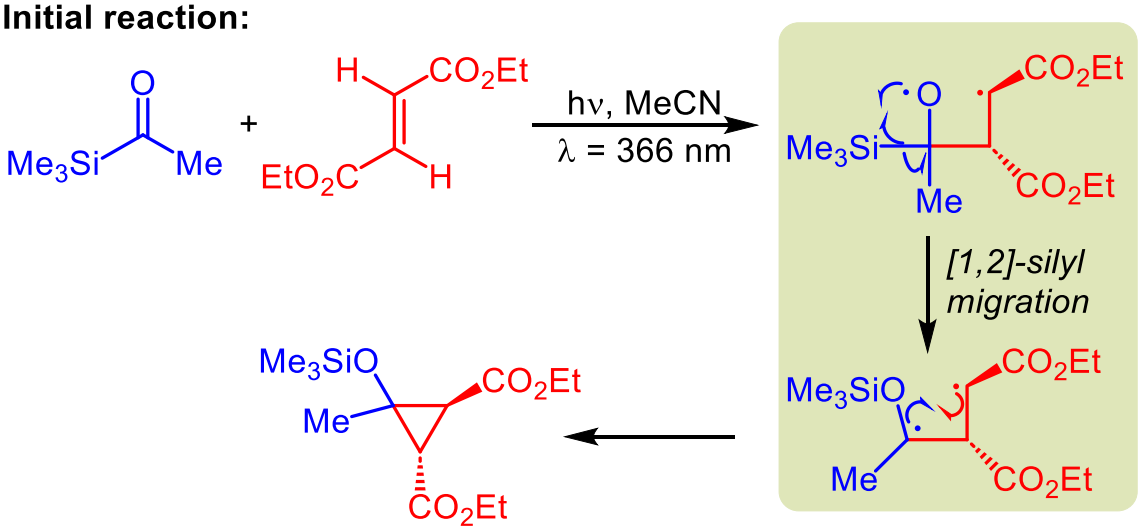
Retro-Brook rearrangement:



hydride and DMF, there will be the O^- can go for another Brook rearrangement, the O^- can come and take the silicon here. So, this is the Brook rearrangement going to happen. First, there is a retro-Brook happening here because this is cleaving the oxygen-silicon bond, and here is a Brook rearrangement happening, the O^- is taking the silicon and formation of this carbanion which can take a proton to get to the corresponding product. So, in this reaction what we have seen? We have seen first there is a retro-Brook and then there is a Brook rearrangement.

There is a radical Brook rearrangement. So, you can see if you have this acyl silane species, then if you can generate the radical from acyl silane under light, then that radical can be added to this α,β-unsaturated compound. Once the radical is added here, it generates this radical next to the ester and you have the oxygen radical here. Now, once

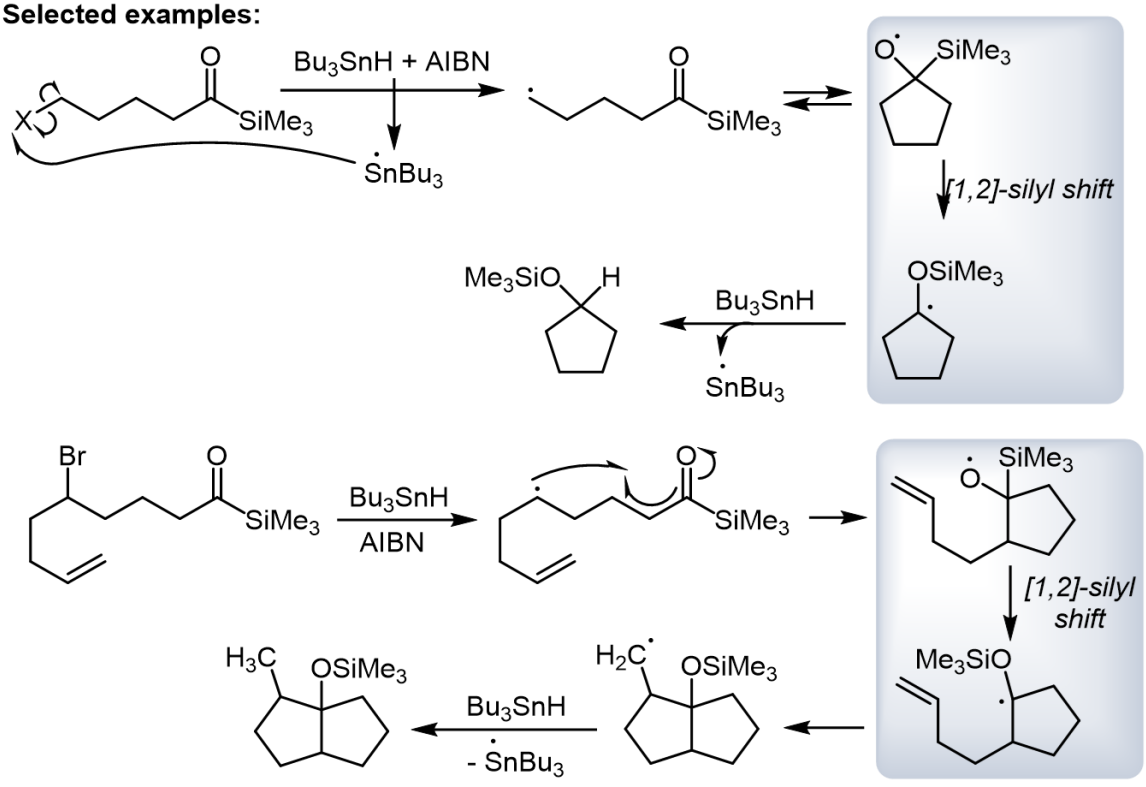
Initial reaction:



you have oxygen radical it can participate in the 1,2-silyl migration. It can interact with the silicon and then cleavage of this carbon-silicon bond to generate radicals, both the radicals can recombine to form this corresponding cyclopropane.

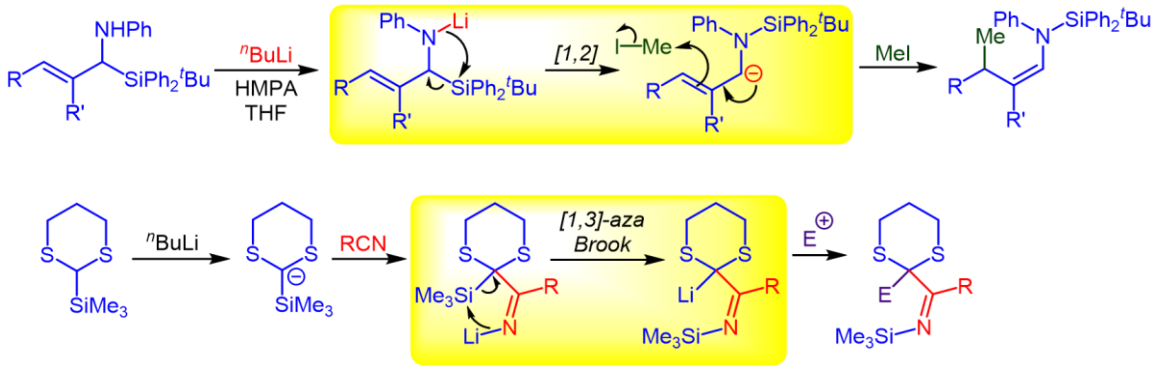
There is another example of a radical Brook rearrangement here, you have this acyl silane and you have this corresponding halide. Now, if you treat with TBTH and AIBN, we have already discussed the radical chemistry that will generate this corresponding tin radical. So, the tin radical can allow the homolytic cleavage of this carbon-halogen bond to generate the radical here. Now, if you have this radical it can add to this acyl silane to generate this species, which can participate in a 1,2-silyl shift to generate this radical on the carbon which can go for a hydrogen atom transfer from the TBTH. So, hydrogen atom transfer going to happen to get to the corresponding product. Another example here, first, the formation of this tin radical can allow the cleavage of this carbon-bromine bond to generate the radical species that can add to this corresponding acyl silane. Then there is a 1,2-silyl shift, the generation of this carbon radical which can go for 5-*exo*-*trig* cyclization and then finally, hydrogen atom transfer happens to form the corresponding product.

Selected examples:

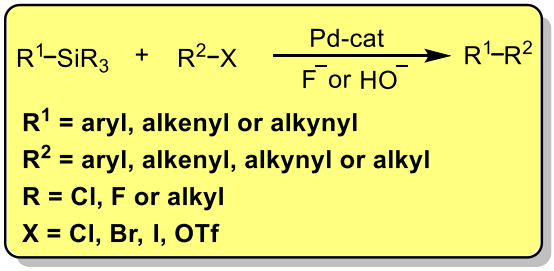


So, we have learned about the radical Brook now this is called *aza*-Brook rearrangement. So, it is not only that always there will be oxygen if there is nitrogen, particularly for this type of compound where the carbon has some sort of an amine at the same time having a silicon. Now, if you treat with the *n*-butyllithium first thing is this is the acidic proton

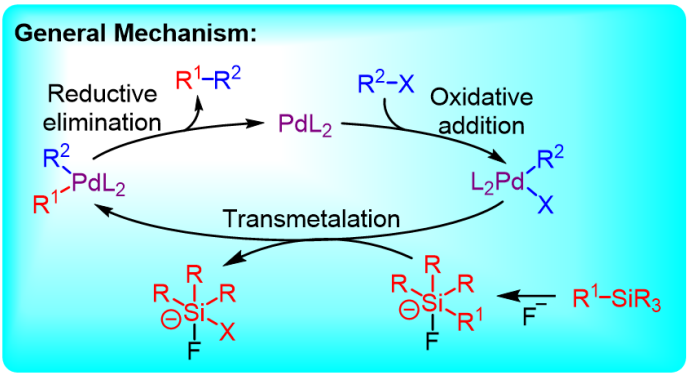
going to be abstracted to generate this *N*-lithium which can participate in *[1,2]*-Brook rearrangement to generate this carbanion here. which can finally, going to trap the methyl iodide because this is the allyl carbanion, going to form this corresponding vinyl amine. There is another example about this dithiane compound, if you have a silicon group here then if you treat it with *n*-butyllithium, then this is the proton going to be abstracted to generate the corresponding carbanion here. If you treat with the corresponding RCN, it is going to add to generate this N^- and Li^+, which can participate in a *[1,3]-aza* Brook rearrangement to form this *penta*-coordinated species. Then cleavage of this bond, generation of the corresponding organolithium here which can be trapped with an electrophile.



So, we talk about the Brook rearrangement, I think there will be some problems given in the assignment for your practice for the final exam. I am going to talk about another important reaction called Hiyama coupling. So, we have learned about lots of cross-coupling in this particular course, we have learned the Suzuki coupling, Negishi coupling, Kumada coupling, and Sonogashira reaction, and we are going to see about the Hiyama coupling. So, here you can see this reaction is a cross-coupling reaction between organosilane and organic halide or triflate. So, you need an organic halide or triflate for the oxidative addition we have learned previously. Once you have a palladium(0), if you have an aryl halide it can participate in the oxidative addition of aryl halide or vinyl halide. And then the important step which I am telling you again and again is the transmetalation step. At that step, if you use a boron then that becomes a Suzuki coupling, if you have an organozinc that becomes a Negishi coupling, if you have a Grignard reagent then that becomes a Kumada coupling and if you have a silicon species that becomes a Hiyama coupling. Sometimes this is also called the Hiyama-Denmark coupling as well. We we going to discuss the mechanism of this reaction. Generally, the organosilicon is activated using fluoride or hydroxide to form the pentavalent silicon. We are going to come to that point where you have seen for Suzuki coupling also we need to use the base to form the boronate



species. Here also you have to make a pentavalent silicon species to activate this organosilicon using fluoride or hydroxide which can generate this type of pentavalent silicon species which can allow the transmetalation step to take place. Because the oxidative addition will take place we have already learned about this the important step is this one where you have a fluoride source that can attack the silicon to generate this pentavalent species that will allow the transmetalation of this R^1 group from silicon to the corresponding palladium. So, once the transmetalation happens then the next step is reductive elimination to give the corresponding cross-coupling product and get back to the catalyst in the reaction cycle. So, there is a reaction here that you have this vinyl TMS and you have this α-naphthyl iodide. So, that is going to participate in the Hiyama coupling, again you have to use a fluoride source here which can allow this transmetalation step to happen to get to the corresponding product. Of course, if you want to do the same reaction you can also use a Suzuki coupling in that case you have to use a corresponding vinyl B(pin). Another reaction here you can see again there is an aryl bromide with two fluorine. Now, if you use a palladium source and NaOH which can activate the corresponding silicon for forming the pentavalent species for the transmetallation, then you can able to form the biaryl from there also. So, it is very similar to the Suzuki or the Negishi coupling, but the only thing is here the other precursor is organosilicon.



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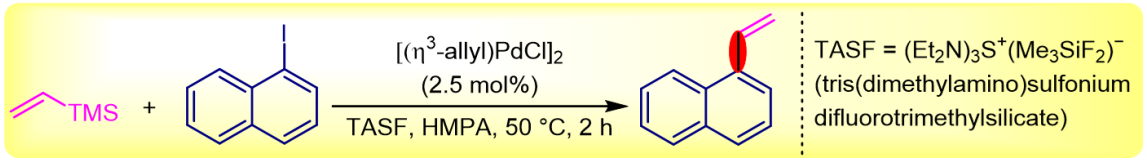
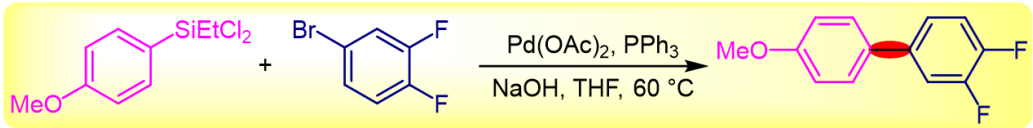
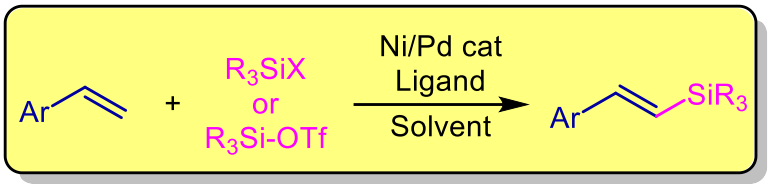


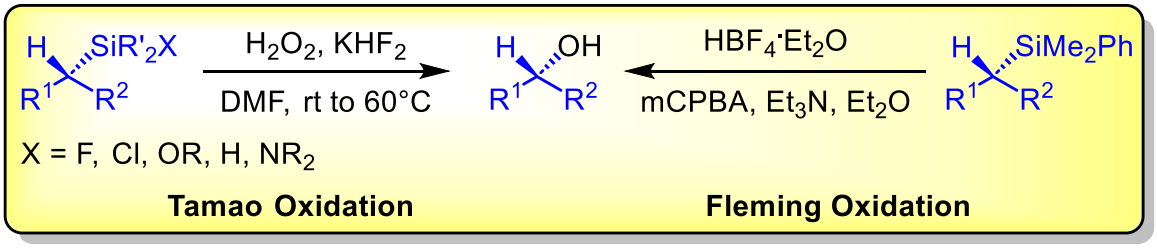


Then there is silyl-Heck coupling. We have not talked about the Heck coupling here which happens if you have a terminal olefin and an aryl halide. If you use this palladium catalyst and ligand and solvent you can end up forming this type of compound here. So, that is going to be the Heck, but the difference here is we are talking about silyl-Heck

which means, one compound will be R_3SiX or R_3SiOTf. If you have this thing then that can also participate in the Heck coupling with the olefin, some sort of styrene, or some sort of an olefin you have seen about the Heck coupling. Here the only difference is this type of silyl reagent was used with the palladium or nickel to get to the corresponding vinyl silicon compound. Again you can see this is a very good method for the synthesis of vinyl silane. The cross-coupling of styrene derivative with the silyl halide or silyl triflate is called the silyl heck coupling. Again silyl triflates failed to participate in the palladium catalytic silyl-Heck reaction without iodide additives. The strong silicon-oxygen bond prevents the oxidative addition of silyl triflate. Generally, bulky phosphine ligands are optional for this reaction.

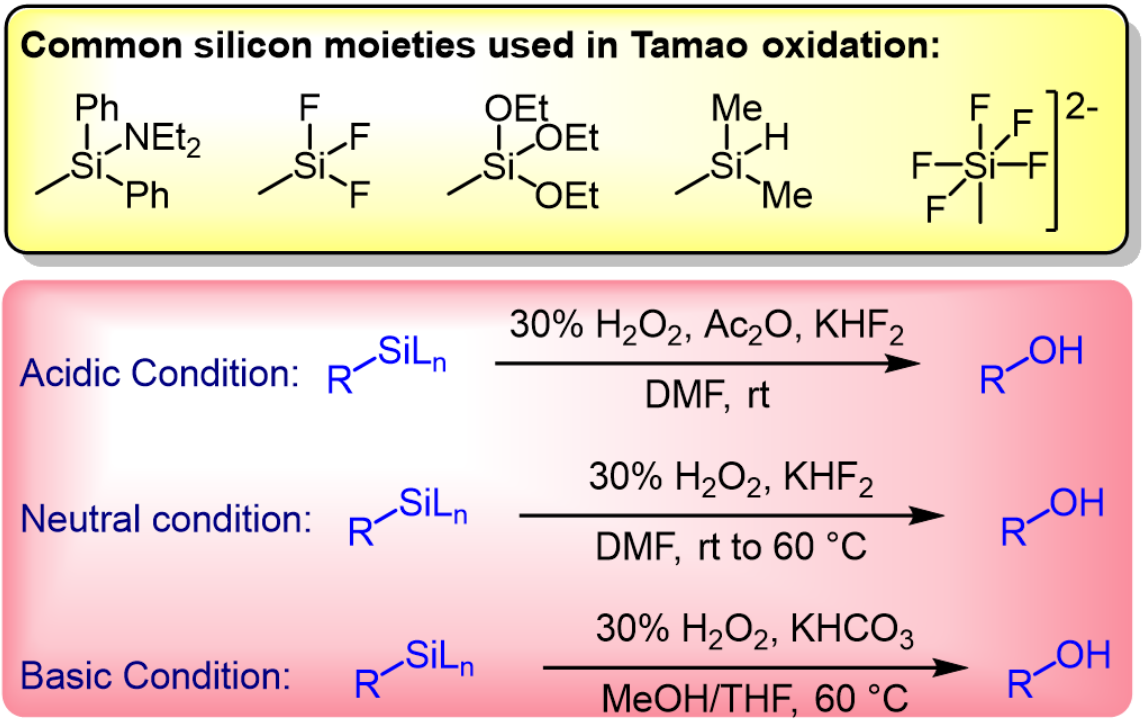


So, we are going to move further and going to talk about the last important reaction for this particular talk, which is the Fleming-Tamao oxidation. So, that is an oxidation reaction I think we have heard that if you have a carbon-boron bond you can convert the carbon-boron bond to OH, you have learned about hydroboration-oxidation discovered by Prof. Brown. Now, we are talking about similarly if you have a carbon-silicon bond. How do you convert the carbon-silicon bond to the carbon-oxygen bond? How do you do that? For that, Prof. Tamao and Prof. Ian Fleming have discovered an oxidation protocol called Fleming-Tamao oxidation. So, this is the protocol that was developed by Tamao H_2O_2, KHF_2, DMF, room temperature to 60°C, and Fleming condition HBF_4. Et_2O with mCPBA, triethylamine, and diethyl ether again. So, again you can see this is the oxidation reaction. So, the other important thing is we have drawn here a particular stereochemistry just to show you that this reaction you will be expecting the reaction to be stereospecific with retention of the configuration. That is very important because there is a retention of configuration. So, you are going to see the stereochemistry retained. So, you see the silicon was down here and also the alcohol is forming from the same side. So, there is a retention of configuration happening here.



So, first, we are going to talk about the Tamao process, at least one group on silicon must be heteroatom or hydrogen which is one important criterion. We are going to come back to the mechanism also you understand from there that the rate of oxygen decreases with an increase in the steric bulk on the silicon atom. You are going to learn in a minute that

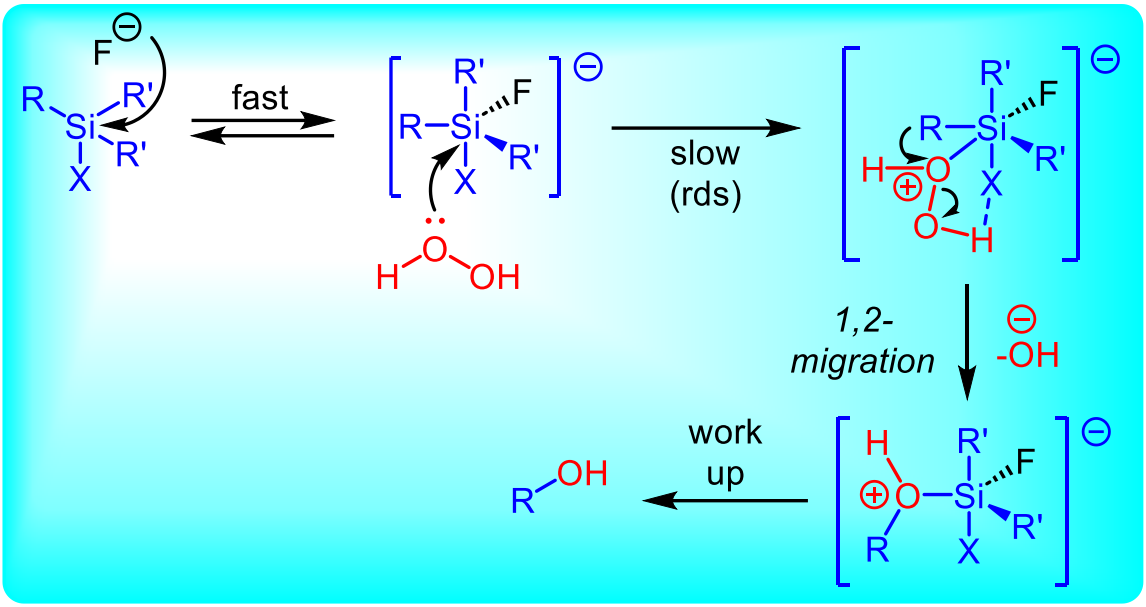
you have to use some sort of fluoride for the oxidation to take place. When we talked about silicon as a protecting group for alcohol. If you remember we talked about if the silicon has a bulkier group around silicon, then deprotection becomes difficult because approaching of the F^- becomes difficult. So, very similarly, if the Tamao process needs an F^- to be attacked then if silicon has a bulkier group around it then the oxidation rate will be much slower. Again the Tammao oxidation can be carried out with a variety of pH when H_2O_2 is the oxidant. You can see mCPBA is also commonly employed as an oxidant here. Under acidic conditions, you can use 30% H_2O_2, acetic anhydride, and KHF_2 to get to the alcohol. You can use the neutral condition again in the presence of DMF, 30% H_2O_2, and KHF_2, or under basic conditions also it can give the corresponding



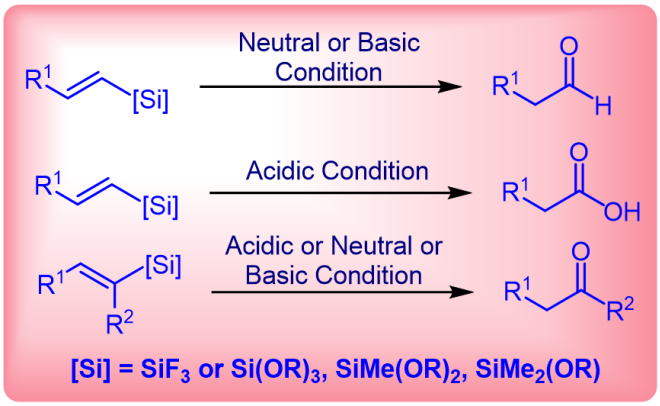
alcohol.

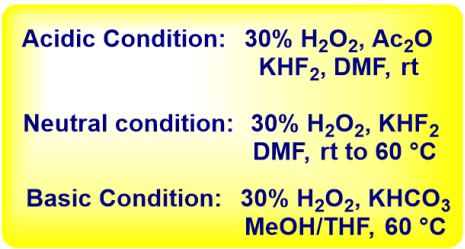
So, now, we are going to learn about the mechanism of this Tamao process. So, as I mentioned once you are using a fluoride source this F^- is going to attack the silicon to form this pentavalent species. You have to understand once you put an F^- into that, this becomes also a very electrophilic species. So, now, if you have this type of nucleophilic H_2O_2, then these oxygens are very nucleophilic they can attack the silicon to form this. Now, you have six different groups here like six groups attached from pentavalent it went to the hexavalent. Hexavalent silicon species here which can now take part in a 1,2-migration very similar to boron, if you remember in the case of boron because now this R group can migrate from silicon to oxygen. and the OH can get out from here because this oxygen-oxygen bond in the peroxide is the weakest bond. So, that will allow the cleavage of this bond to form this species here which after workup gave the corresponding alcohol.

Again you can think about this species because if you again do the work-up then water can attack the silicon and get rid of this particular alcohol out from the silicon.

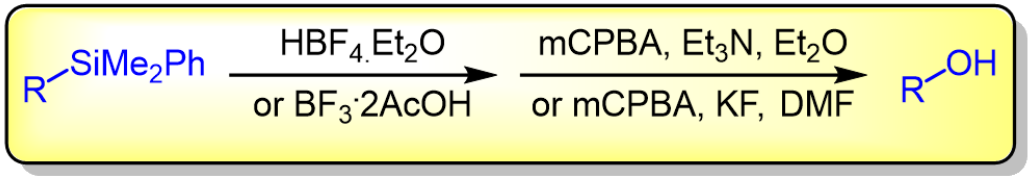


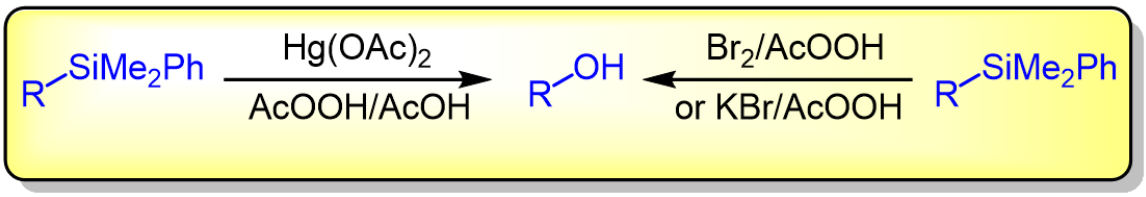
Then I am going to talk about that depending on the condition So, we talk about the acidic condition and neutral condition, but mostly I talk about once you have an alkyl silane means it is the silicon which attached to a carbon which is sp^3. Now, we are talking about silicon attached to a carbon which is sp^2 which means, we are talking about this vinyl silane. Now, if you have a vinyl silane under neutral or basic conditions what you going to end up that once you have a silicon will be OH. So, that will be an enol that can be converted to the corresponding aldehyde, but under acidic conditions, it is not going to stop there it is going to continue oxidizing to the corresponding carboxylic acid. And if you have an acidic neutral or basic condition if you have this scenario of course, this can be converted to aldehyde. If you have an R^2 group here, you can clearly see it is going to convert this to corresponding OH and R^2. That means this is going to convert to the corresponding ketone, because of the presence of the R^2 it will be a ketone. If R^2 equal to H then it will be aldehyde which I have shown here.

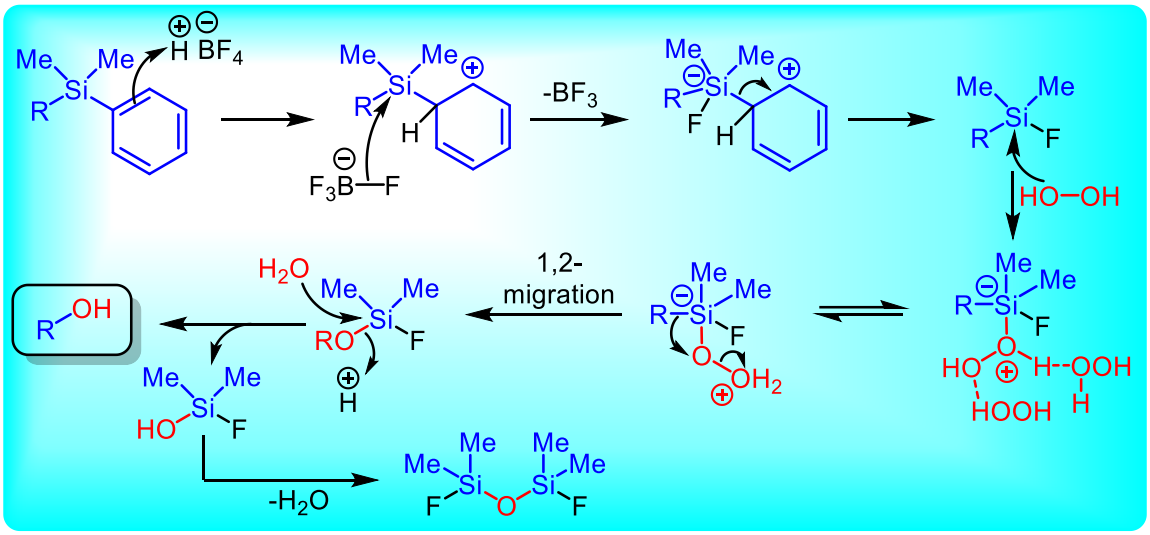




In Fleming process, as I mentioned it could be a two-pot sequence, HBF_4 or BF_3. AcOH then mCPBA; or it could be a one-pot variation which they have later developed with mercury acetate with acetic acid and acetyl peroxide or it could be the bromine or it could be the KBr with this peroxide, that can also convert this corresponding RSi to ROH. So,



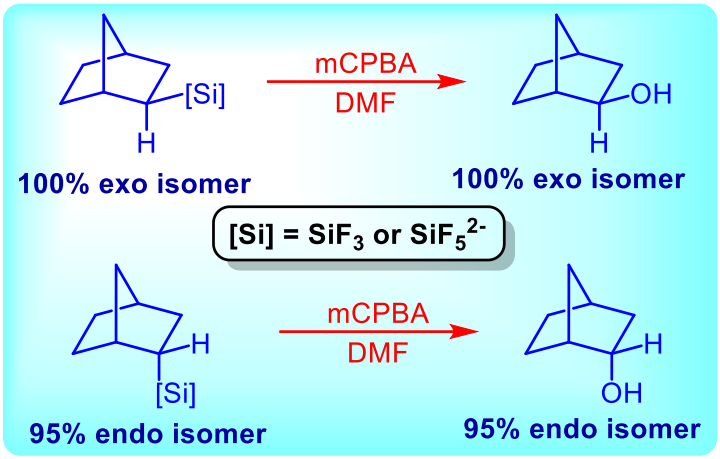




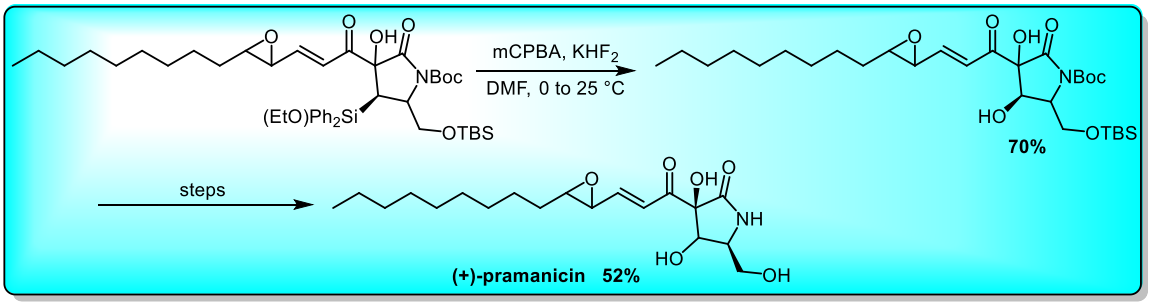
we try to understand the mechanism of this reaction if you have this corresponding silane species if you treat it with HBF_4 then there will be an *ipso*-substitution. So, we have learned about the *ipso*-substitution if you remember at the beginning we talk about that once you go for *ipso*-substitution we will be generating a carbocation at the β-position. According to the β-effect, the β-carbocation will be stabilized because of the electron donation from this carbon-silicon σ-bond. So, we have learned after the formation of the carbocation what is going to happen. This is going to weaken the carbon-silicon bond as well. So, if you have an F^- attacking the silicon it can able to form the double bond here to give you the silicon compound out from the phenyl ring. And now if you have this H_2O_2 that can attack on the silicon to form this pentavalent species. Now from the pentavalent species also it can participate in 1,2-migration from the silicon to the oxygen. After the 1,2-migration, it can go for hydrolysis to get to the corresponding alcohol. As I mentioned, very similarly to the last mechanism, you have seen from this intermediate it

can go for hydrolysis because water can attack here and it can give to the corresponding alcohol and form this $SiMe_2(OH)F$. Two of these species can form this silyl ether.

The retention of stereochemistry, I think I mentioned at the beginning that in this reaction there will be retention of stereochemistry during this Tamao or the Fleming oxidation. You can see if you start with 100% *exo*-isomers under this standard condition you end up getting 100% *exo*-isomers. So, you can see the *exo*-isomer will give the *exo*-product very similarly if you have an *endo*-isomer it will give you the *endo*-product.



Another synthetic application, this Tamao and the Fleming oxidation was applied in the natural product synthesis. One of the examples was the synthesis of (+)-pramanicin. So, the (+)-pramanicin natural product was synthesized, and one of the important steps here where they convert this carbon-silicon bond to a carbon-oxygen bond using the mCPBA and KHF_2. So, you see that this neutral Tamao oxidation condition was useful for the total synthesis of natural products.



So, in this particular class, I talked about Peterson olefination some of the things that I did not talk about in the last class. Of course, I talked about Brook rearrangement, and its several different variations, radical Brook, then aza-Brook rearrangement, the Hiayama coupling, the silyl-Heck coupling and I ended up with the Fleming-Tamao oxidation. Again here are some of the references and again thank you so much for coming to the class. I am going to see you guys in the next class. Thank you.