Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

Department of Chemistry

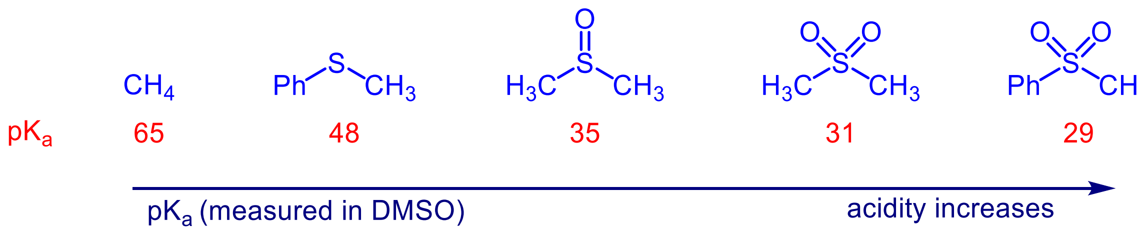
Indian Institute of Technology, Kharagpur

Lecture 51: Organosulfur

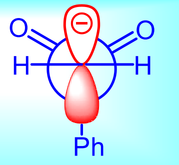
Welcome back to this NPTEL online certification course in "molecular arrangement and reactive intermediates". In the last class, I started talking about the organosulfur chemistry. So, I start with the different types of organosulfur compounds, I introduce you to the thiol, then disulfide, sulfone, and sulfoxide. And then I also talk about some of the important properties of these different compounds and some of the reactivity. In today's class, I am going to talk more about organosulfur chemistry and try to talk about some of the stabilized carbanion using sulfur and some of the reactions.

First, I am going to talk about the sulfur-stabilized carbanion, different reactions, and what is their pKa. We are going to discuss some of this. Then I think you must have heard about dithiane, if you talked about the protection of aldehydes you must have seen the dithiane protection, we are going to talk about that and the application. This Smith-Tietze coupling we are going to talk about this and then the most important thing is the sulfonium and the sulfoxonium ylide. So, these are the two important classes, you going to see different types of reactions and in the competitive exams the question comes from also these two important parts. And then I think we are going to talk about the stabilized and unstabilized versions of these ylides. And we are going to see if you have a particular substrate, if you use a stabilized ylide you get one product, if you use an unstabilized ylide you get another product.

So, the first thing we want to start with is that the α-carbanion can be stabilized by sulfides, sulfoxides, and sulfones. So, if you try to compare the pKa values, moving from methane, if you replace one of these hydrogen by SPh you can see the pKa jump from 65 to 48. If we replace one hydrogen of methane with S(O)CH_3 now pKa jumps to 35. If the hydrogen was replaced by SO_2CH_3 i.e. sulfone, then pKa jumps to 31. If you replace one

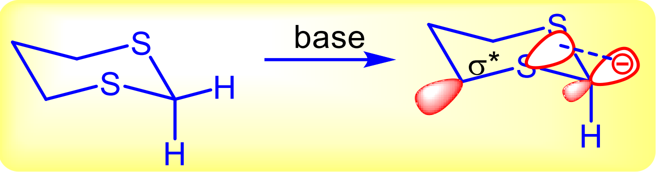


of these methyl with a phenyl, this proton becomes more acidic, pKa 29. So, what we are seeing is the effect of sulfur, we are seeing here once you are moving from sulfide to sulfoxide or sulfone, you are introducing an extra electron-withdrawing group. The electron-withdrawing capacity of the sulfone is much higher compared to sulfoxide and sulfide. So, the stabilization is also getting increased because of the increased stabilization from going from the sulfide to sulfoxide to sulfone, what you are seeing is that as the negative charge is getting more stabilized, the pKa is decreasing. So, if you remember, if you talk about the acidity then we always talk about that if the proton is more acidic that means, the corresponding conjugate base must be more stable. We are going to discuss them again why these are more stable we are going to come back to that also. And then another important factor is that once you are talking about this, a lot of studies have been done about the structure of this type of carbanion. So, from some of the studies, it was found that once you have this carbanion from a sulfone, So, these are some sort of a planar shape means I am not talking about this, but I am talking about this CH_2^-. I am talking about what we are saying here in this particular compound, this CH_2^-. So, once you have a CH_3 here what is the difference? So, once you have a CH_3 then this carbon will have sp^3 hybridization and it is pyramidal. But once it becomes CH_2^- this will achieve planarity, people have done some theoretical calculations also some carbon NMR studies, and from there they found that this carbanion from the sulfone is planar. But once you see about the carbanion from a sulfide this carbanion still has a pyramidal shape and once you have something like a sulfoxide which is actually in between the sulfide and the sulfone, it is neither sp^3 nor sp^2 something in between. So, now, we are going to learn about their some of the reactivity.

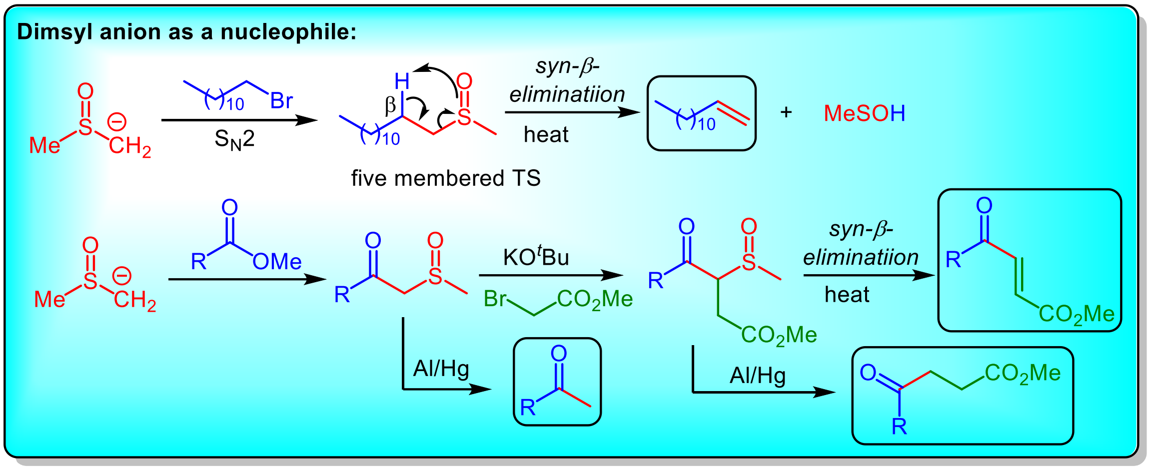


Probable conformation of sulfone-stabilized carbanion

So, again I think one of the other important things when you try to talk about the pKa of methane vs MeSPh, we talk about a change of pKa from 65 to 48. So, one thing you might be thinking is that sulfur has a vacant *d*-orbital and carbon does not have it. Because of sulfur *d*-orbital, this CH_2^- might be giving electron density to the corresponding *d*-orbital of sulfur and that is why it is getting stabilized. However, the calculation suggested that this is not the major factor, the major factor is the stabilization of this corresponding σ*. So, if this is a σ-bond between this carbon and sulfur then there is a σ*-orbital here. So, the donation of electron density of CH_2^- to the corresponding σ*-orbital is the most important reason for the stability of this type of corresponding carbanion which forms from sulfide. So, that is the important factor here and one of the evidence is here. So, you can think about this type of dithiane, we are going to come back and talk about them after a couple of slides. So, in the dithiane, if you have these two hydrogen here one is axial another is equatorial. Now, if you try to compare their acidity, it is saying that the equatorial one is more acidic than the axial one. So, why the equatorial one is more acidic than the axial one? The evidence is that in the case of the equatorial one when it is forming the corresponding conjugate base that means, this corresponding carbanion, this is giving electron density to this corresponding σ*-orbital. So, this σ*-orbital is getting electron density from this non-bonding orbital of this carbanion. That is how the corresponding conjugate base is getting more stabilized compared to the axial one. That is why the equatorial proton is more acidic than the axial one. So, I think from these data you are convinced that the stability is coming from the electron donation from this non-bonding carbanion electron to the σ*-orbital of the carbon-sulfur bond.

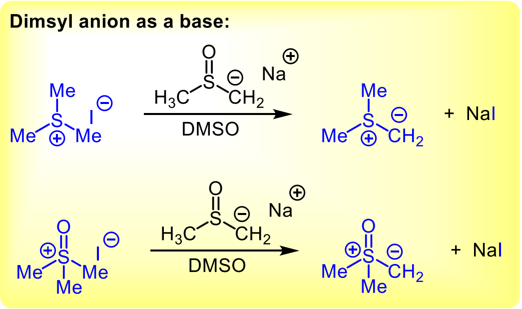


Now, we are going to talk about the dimsyl anion. Dimsyl anion is nothing but if you form a sulfoxide if you use a base like sodium hydride or sodamide it can comfortably able to abstract a proton, of course, you can also use *n*-butyllithium that can able to abstract this proton from here to generate a corresponding carbanion it is called dimsyl anion. So, once you have this anion this can act as a nucleophile because this is a carbanion forming. So, this can act as a nucleophile. So, we will learn some of the reactivity of this dimsyl anion. So, once you have this dimsyl anion it can participate in S_N2. You can see it is forming from the corresponding sulfoxide. So, we talk about, there is some sort of resonance stabilization, we said that is not achieving sp^2 all the way, but again there will be some sort of stabilization. So, this type of stabilized one can participate in the S_N2 reaction to get to this compound. So, this is a simple S_N2 product. So, you can think this is a derivative of DMSO. So, if you remember I talked about in the last class this is the structure of dimethyl sulfoxide. What is happening here? In the dimethyl sulfoxide, you are now changing one of the methyl groups to an *n*-butyl group that is what is done here. You are forming a carbanion and then going for an S_N2, but now if you take this compound and heat it at high temperature, then there is a thing is going to happen called *syn* β-elimination or it is called some sort of an Ei mechanism elimination internal or elimination intramolecular. So, thermal *syn* elimination happening here. You can think about this oxygen lone-pair can take this proton to form this double bond here and then this sulfoxide can get out to form the corresponding olefin. Again there are different types of varieties of this type of Ei mechanism it could be a five-member, six-member, or four-member. In this particular case, it is going through a five-member transition state. If I try to draw you will see it is



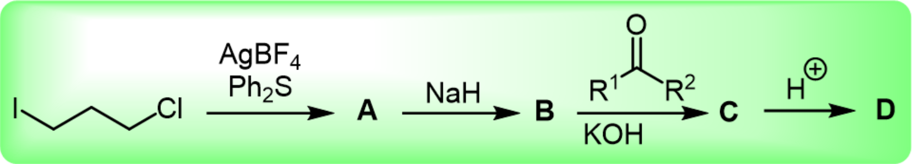
going through a five-member transition state, after the elimination forming the corresponding terminal olefin. There is another example here instead of S_N2, now this CH_2^- can attack the corresponding ester to form this compound here. So, you are having this β-carbonyl with respect to the corresponding sulfoxide. Now, if you have potassium *tert*-butoxide you can think of this type of compound very similar to this 1,3-dicarbonyl compound. So, if you remember I think in the case of the 1,3-dicarbonyl compound this is the proton which is the most acidic proton because of the stabilization of this corresponding negative charge that is forming there. So, now the corresponding carbanion is forming here, very similarly this is the proton that is most acidic. So, this is going to form in the presence of a base, it is going to form the corresponding carbanion. Again this is a stabilized one going to perform an S_N2 reaction and then again the *syn*-elimination can generate this corresponding α,β-unsaturated carbonyl compound. There is another option, after forming this compound if you use aluminum in Hg this can able to cleave this carbon-sulfur bond to generate this ketone. From this stage if can do the cleavage of this carbon-sulfur bond using aluminum-mercury to get to the corresponding carbonyl compound as well.

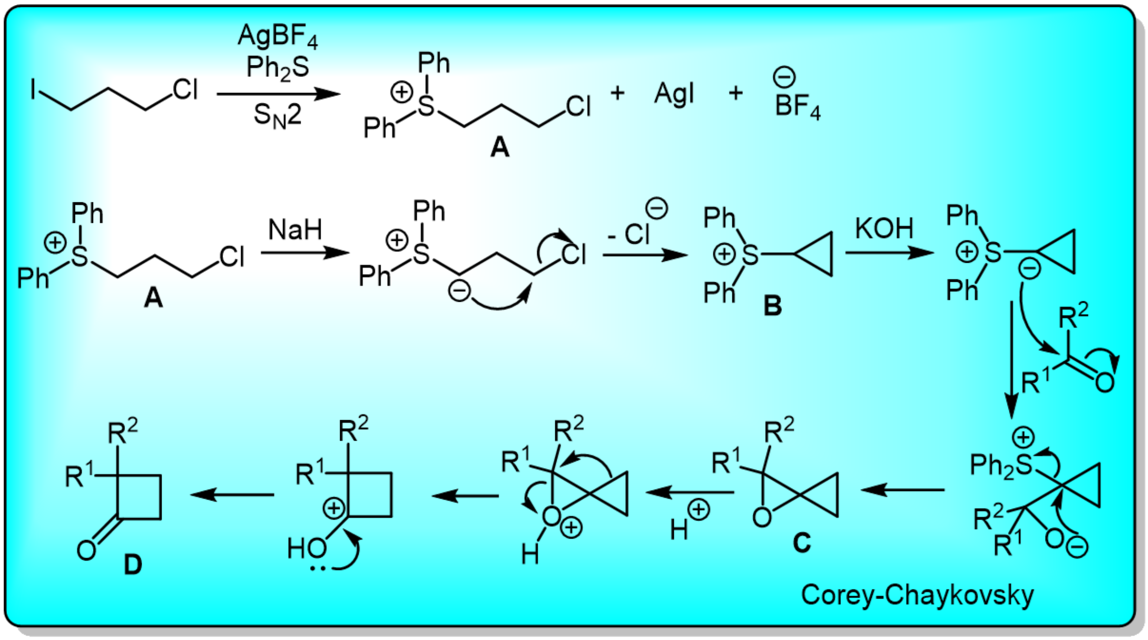
So, dimsyl anion can act as a nucleophile. Here I am showing you that this can also act as a base. So, this can act as a base to abstract protons from this corresponding salt. So, this is a sulfonium salt. So, from this trimethyl sulfonium iodide, you are generating a sulfonium ylide. So, this proton from the methyl you can see it is next to a sulfur with a positive charge. So, you can understand that it is an acidic proton. So, this can be abstracted by this dimsyl anion to generate the corresponding sulfonyl ylide. We are going to talk a lot about the reactivity of this sulfonyl ylide. It can also generate sulfoxonium ylide if you use the dimsyl anion that can also abstract a proton from the corresponding sulfoxonium iodide and it can generate the corresponding sulfoxonium ylide. Again we are going to



come back to this, you are going to see in a minute this is going to be a stabilized one and this is going to be an unstabilized one and there will be a difference in the reactivity.

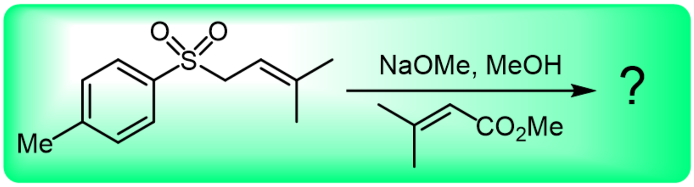
Before going to that we have some problem to discuss. So, here we are talking about a problem, because in sulfur chemistry, we have not talked about any problem yet, but here you can see in this particular compound if you use $AgBF_4$ and Ph_2S. So, you can think about a sulfide here. So, you know that sulfur can act as a better nucleophile. So, going to participate in an S_N2 reaction first to form this compound. So, now, what is going to happen after forming the compound you have sodium hydride you treated a sodium hydride. Now, once you have a sodium hydride then if you think about the pKa of different protons, this is the proton which is next to a sulfur with a positive charge. So, this corresponding anion will be stabilized. So, that is why sodium hydride can able to generate this corresponding carbanion once it is formed it is going to participate in the S_N2 reaction to generate corresponding cyclopropane. Now, again if you treat with KOH then it can able to abstract protons from here again this will be stabilized this is going to form a ylide here which is going to react with the corresponding carbonyl compound. So, we are going to talk about this reaction, the Corey-Chaykovsky reaction, and we are going to come back in a minute. So, this is a reaction between the sulfonium ylide and the carbonyl compound to generate epoxide. Once you form this type of epoxide and cyclopropane which of course, is a strained molecule that is why once you have an H^+

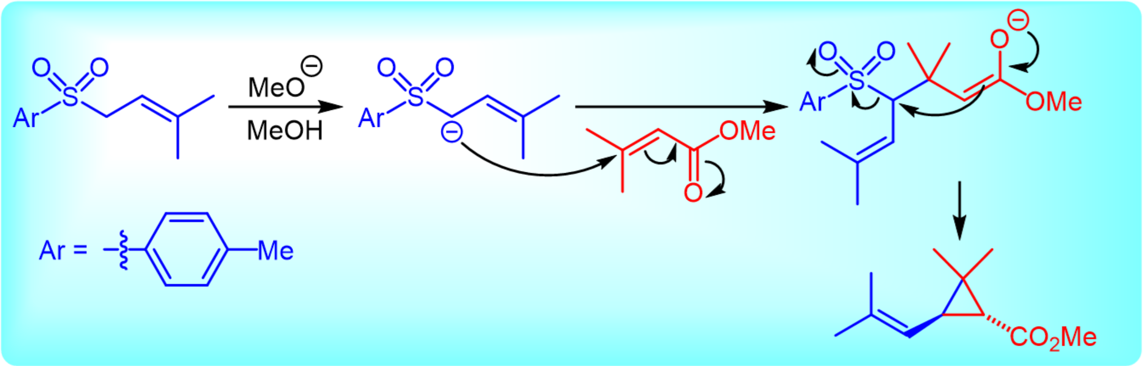




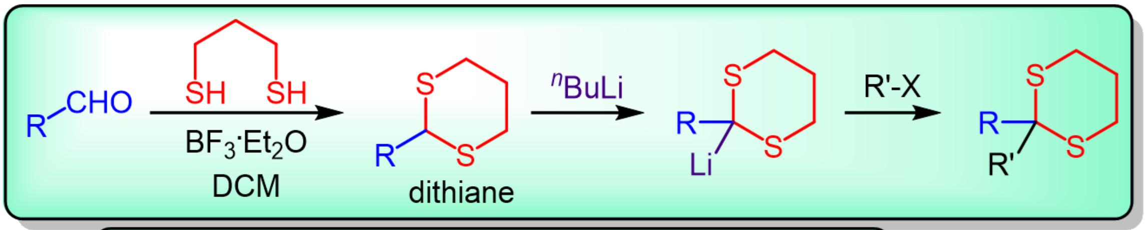
this is going to protonate the epoxide there will be ring expansion happening to form the cyclobutane and further, the positive charge will be neutralized by formation of cyclobutanone. I think you understand the first S_N2 then there is an internal formation of the carbanion then again there is an internal S_N2 type reaction then the Corey-Chaykovsky reaction and finally, there is a ring expansion to get to the product.

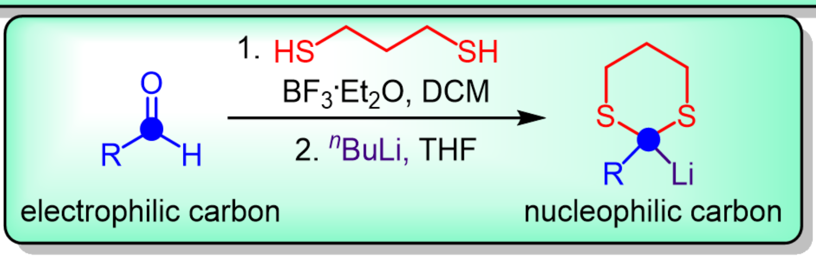
So, what will be the product in the following reaction? So, if you look into the structure again if you see we are using sodium methoxide in methanol. So, this is the base and if you look into this molecule you can see these are the protons that are next to a sulfoxide and these are allylic. So, this can be stabilized in both ways. So, this will generate this corresponding carbanion first and now this carbon ion is a stabilized carbanion going to participate in a 1,4-addition here. Again as I mentioned to you if you have a stabilized versus unstabilized carbanion, a stabilized carbanion goes for a 1,4-addition, and an unstabilized carbanion goes for a 1,2-addition. So, that is why 1,4-addition going to happen here and finally, after the 1,4-addition, the ester is going to form this compound, the O^- will come back and the double bond going to attack here. So, this enolate will come back and attack to get rid of the corresponding sulfoxide to get to the corresponding cyclopropane.



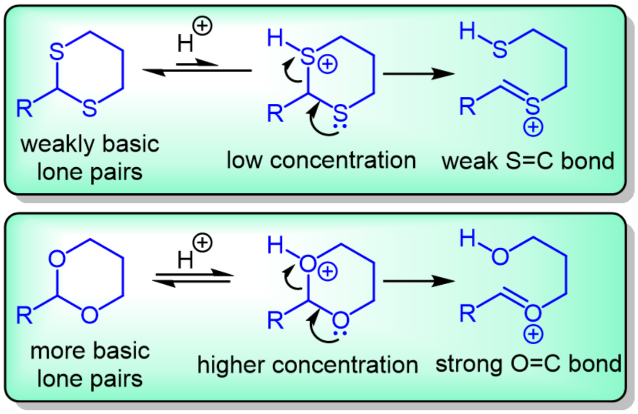


So, now we are going to talk about some of the chemistry of dithiane and umpolung reactivity. I think you have heard about dithiane before and if you remember again I think we have learned it when we talk about the protection of aldehyde. So, once you see the protection of aldehyde using dithiane you have to use a Lewis acid to activate the carbonyl oxygen that can allow the sulfur to attack the carbon and then it will form the dithiane after the elimination of water. So, now, once you have a dithiane, if you have this proton here again there are two sulfur there. So, previously you have seen that if you have a single sulfur then this CH_2^- has pKa around 48. Now if you have two sulfur you can understand the pKa will be even lower. So, using *n*-butyllithium you can comfortably able to go for this deprotonation. So, now, this is a stabilized organolithium that is going to participate in an S_N2 reaction to form this compound and then later you can also able to deprotect and get to the corresponding ketone. The other thing that you are seeing about the umpolung reactivity here because it is an electrophilic carbon at the beginning. So, this carbonyl was electrophilic carbon, but once you make a dithiane, this particular carbon in the dithiane now becomes nucleophilic. You can able to generate a carbanion here. So, which was electrophilic at the beginning now become a nucleophilic carbon. So, this type of reactivity is called umpolung reactivity. Again by using umpolung reactivity, there are several different reactions were developed, and we are going to discuss some of these also. So, I should also include that umpolung means a reversal of polarity. So, you see the electrophilic carbon is changing to a nucleophilic carbon.

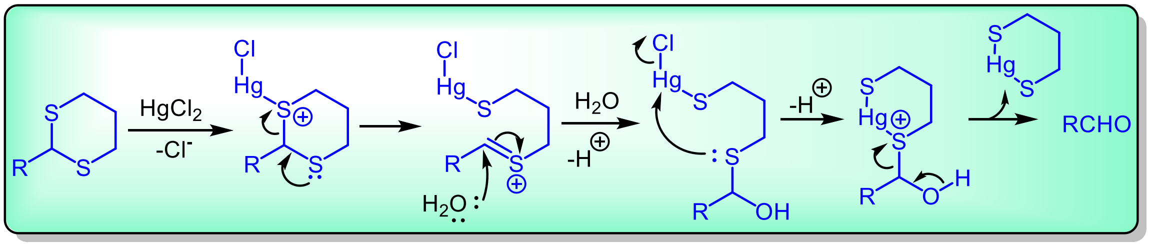




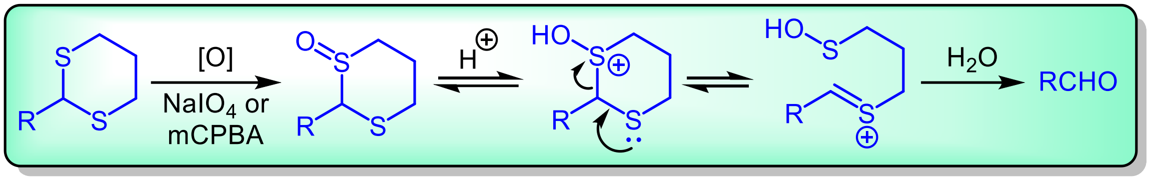
So, we already talk about the protection. Now, we are talking about the deprotection, how to remove them? what is the deprotection strategy of dithiane? Now, if you have seen that the dithianes are more stable than the corresponding acetal that is why dithianes are more popular than acetal protection. Because you can use some of the other reaction conditions and if you have a mild acid the dithianes are still stable. Acetal will be not stable, acetal will be immediately converted to the the corresponding aldehyde. So, that is why you can see that the dithiane are more important and used for natural product synthesis. So, now, the question is why the dithiane is not getting hydrolyzed in the case of the acid. The important thing is the protonation. Now if you compare the electronegativity of sulfur and oxygen which is more electronegative? If you remember we have talked about electronegativity which is around 3.5 and this is 2.58 very close to carbon. So, if use an acid and if there is a carbon CH_3 do you think it is going to get protonated? Of course, if it is a very very strong acid otherwise it is very difficult for the methane to form. So, if you think about the electronegativity, the sulfur takes a proton to form SH, so this step is not very favorable. That is why you will see a very low concentration of this forming. That is why majorly you will see the equilibrium is lying toward the starting material.



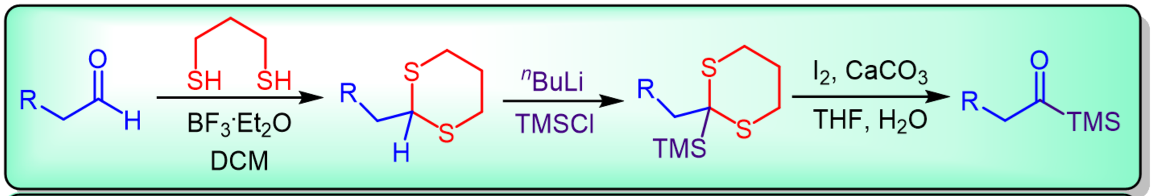
That is why the decomposition of this dithiane is happening in a very small amount. Even if this is happening also this can again come back to the original starting material. So, if it is forming here can you able to convert this compound to something else and then get rid of this R from there? So, mercury plays a very important role. That is why $HgCl_2$ and then acid condition H_2SO_4, so now it can able to do the job, the dithiane deprotection to the corresponding aldehyde group. So, we trying to learn the mechanism of this reaction of course, sulfur can act as a very good nucleophile than oxygen. So, it will react with $HgCl_2$ to form HgCl here with a positive charge on the sulfur. Now, once you have a positive charge there this can allow you to open up this dithiane to form this. So, you can think that carbon-sulfur double bond plus is some sort of a compound called thial. So, once you have this thial this can have a sulfur with the positive charge now this H_2O can attack here or you can also say this is the sulfonium type thing because we have learned that once you have a sulfur with three methyls and a positive charge, we call this a sulfonium. So, now, the water can attack here to this carbon-sulfur double bond. Then it is going to form this compound again the sulfur is free here. So, sulfur can attack the mercury to get rid of the chloride. Sulfur are very good nucleophile it will attack there to get it of this corresponding chlorine to form this very important compound it is called the cyclic mercury dithiolate.

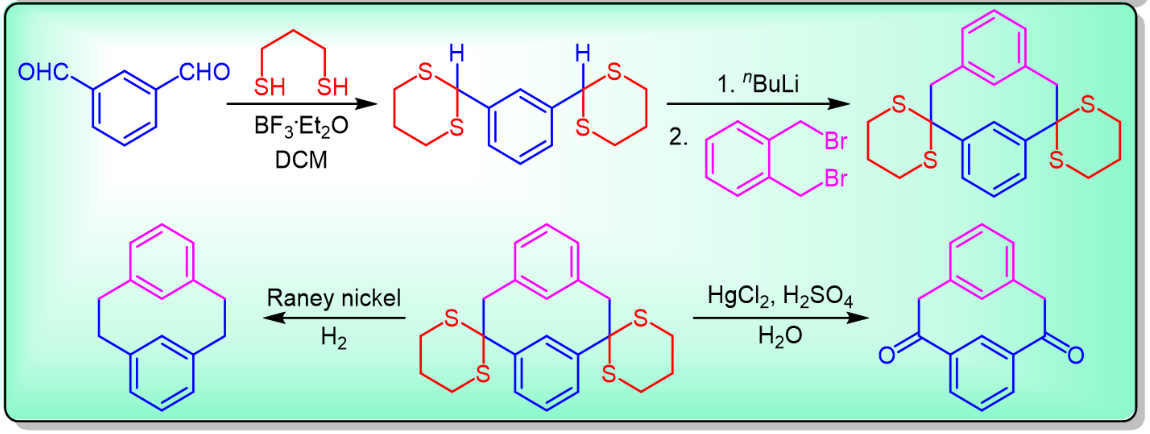


Once it is forming this sulfur with a positive charge now it is going to form the corresponding aldehyde and get rid of this cyclic mercury dithiolate. Sulfur is kind of getting out and this RCHO coming out. So, that is why this reaction is irreversible this cannot go back to the starting material. That is why mercury chloride plays a very important role in this deprotection. Again there is another approach if you have a dithiane, first you do the oxidation with periodate to form the sulfoxide. Once you have a sulfoxide you can use a H^+ because now oxygen can get protonated. Once the oxygen is protonated that will allow the rapture of this dithiane ring and then further if you treat it with water it can able to get to the corresponding aldehyde.



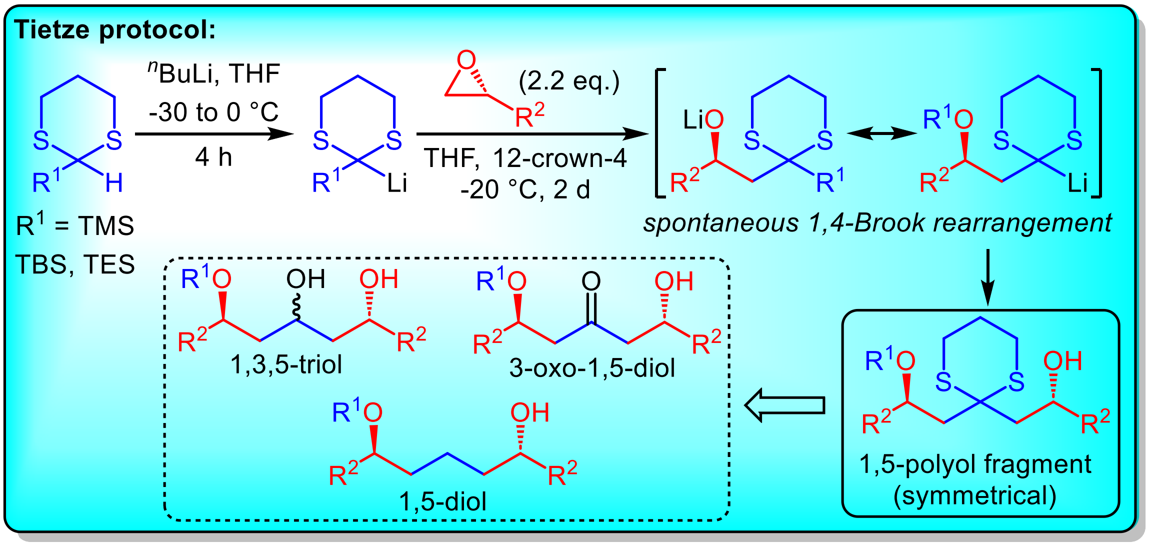
Again the dithianes are known as acyl anion equivalents and they can be useful for the synthesis of acyl silane. I think I talked about this compound in the Brook rearrangement, if you remember we are talking about acyl silane means this is the functional group we are talking about a CO with TMS. So, this type of compound synthesis can be done using this dithiane protection. So, we started from the corresponding aldehyde, this hydrogen was replaced by silicon. So, this group was introduced by replacing H. So, first, you do a dithiane protection and then there is a reversal of polarity. So, umpolung, *n*-butyllithium can generate the carbanion which is stabilized and reacts with TMS chloride. So, it can react here. Again I think if you remember this is some sort of S_N2 at silicon. So, if you remember that is forming some sort of a pentavalent silicon species, then at the end this chlorine will get out to form this corresponding compound here. Now, once you treat with I_2 and calcium carbonate; again this I_2, calcium carbonate is another reagent which can be also useful to break this dithiane ring here to convert to the corresponding carbonyl. Again here I think if you understand what we are doing here we are converting the sulfur because sulfur is a good nucleophile. So, it is from sulfur iodine bonds which will allow them to cleave the dithiane. So, sulfur will be positive. So, what is happening here? You are forming sulfur with iodo which will be positive sulfur that will allow you to open up. Once this is opened up you have water and you have calcium carbonate that can do the the rest of the job to get to here. The thing is you are not using a very harsh condition because if you have a harsh condition then this acyl silane like the one we have shown here, the mercury chloride and this condition cannot be used here because that can



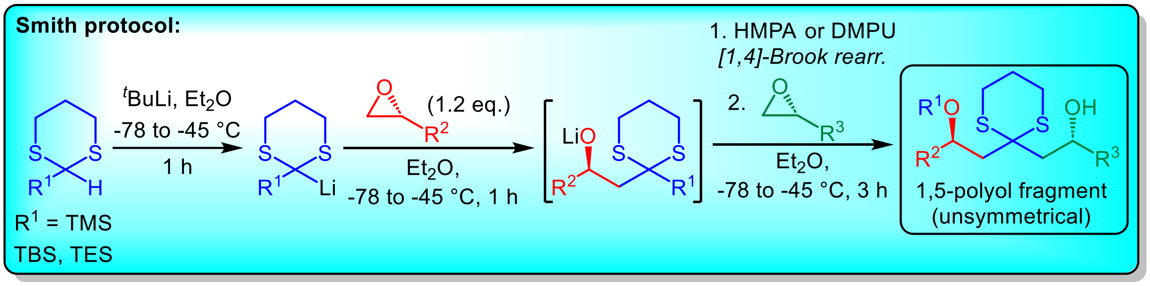


destroy the corresponding acyl silane. That is why you have to use a milder condition to open up. Again there is another example here you have the two CHO groups, first, there is a dithiane protection then *n*-butyllithium going to from the corresponding lithium. So, there are two benzylic bromide groups here, they are in 1,2-position. So, they can react to form these cyclic compounds here. Then the deprotection using $HgCl_2$ can form this corresponding carbonyl compound or if you use raney-nickel, the raney-nickel can cleave this carbon-sulfur bond and generate a carbon-hydrogen bond using this H_2 gas that can able to generate this compound.

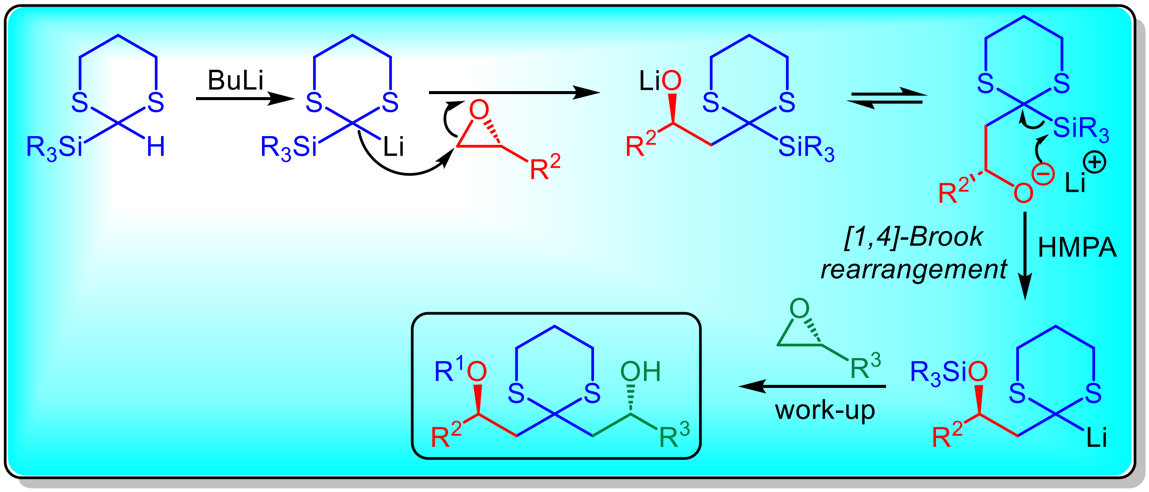
So, now, we are going to talk about this Smith-Tietze coupling, I think as I told you that there are very important reactions because of this umpolung reactivity. So, this is a one-pot and multi-component coupling of 2-silylated-1,3-dithiane with epoxide. So, what it is doing actually at the beginning it is forming a silylated-1,3-dithiane. So, we are talking about one particular class of 1,3-dithiane. So, this is not going to happen with any dithiane, this reaction is limited to a silylated 1,3-dithiane means we are talking about a compound where the dithiane will be starting from aldehyde and then we are talking about there will be a SiR_3. So, you can think about that you started with an acyl silane. So, you take an acyl silane and then do a dithiane protection. So, as I mentioned, you first make the dithiane protection, and then once you have that compound now you can use it for this reaction. There is another option you can also start with this dithiane. You can start with the dithiane and generate a carbanion and then react with the TMS chloride that can also comfortably generate this compound. So, once you have this starting material you treat it with *n*-butyllithium that can generate a corresponding lithium here, the lithium can attack the epoxide and it will attack the corresponding terminal position. Once it is going to attack the terminal position it will going to form this compound. Now, if you remember your R^1 is silicon. So, what is going to happen? If you remember we talk about this 1,4-Brook rearrangement. So, that means, this O^- going to take the silicon



to generate another lithium, another umpolung going to happen here, you generate this lithium again here. So, that is going to react with another epoxide. So, now you have this 1,5-polyol fragment because you are generating two hydroxy groups in the 1- and 5-position and you have a carbonyl group in the 3-position. So, the deprotection of this dithiane can generate a corresponding carbonyl compound. So, if you do the reduction then you can generate 1,3,5-triol or you can get rid of the carbonyl group to introduce a CH_2 group by some sort of Wolff-Kishner reduction.

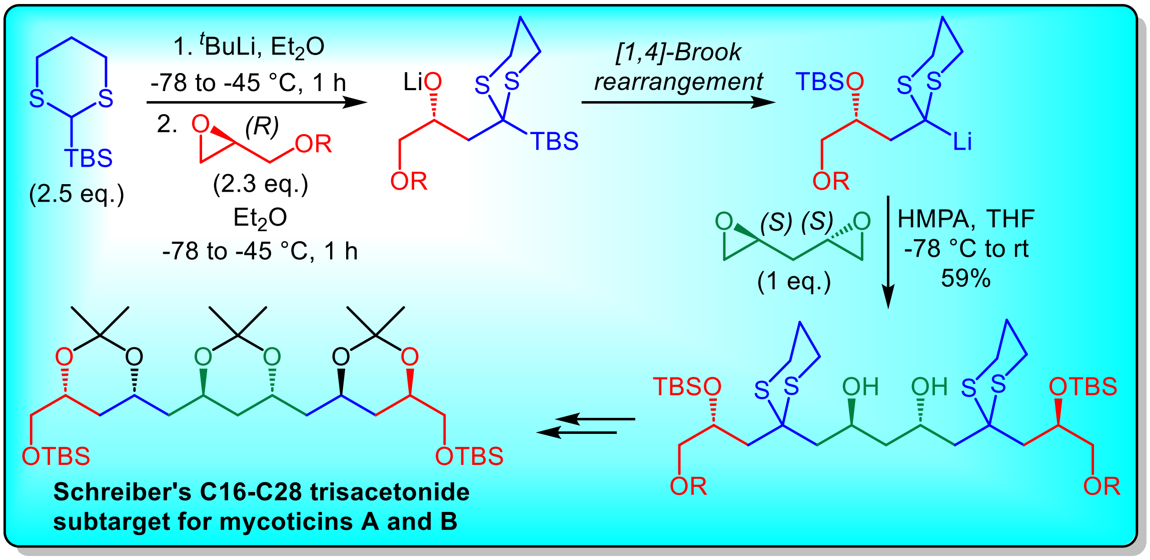


So, now we are talking about the Smith-Tietze protocol, the Smith protocol is useful for the synthesis of unsymmetrical enantiopure 1,5-diol using the two different epoxides. So, in the previous slide if you see this is the protocol which was the Tietze protocol. They are synthesizing C2-symmetrical enantiopure 1,4-diol and here the same epoxide reacts two times. But in the case of the Smith protocol, A. B. Smith developed this protocol using HMPA or DMPU as an additive in the solvent which significantly increased the rate of the reaction and allowed the two different epoxides to be coupled. That is the important thing. What the Smith group is doing is first there is one epoxide forming this and then the Brook rearrangement is happening and then they are introducing the second epoxide into the reaction. By controlling the equivalent of epoxide they can able to react and the additives play a very important role in stabilizing the corresponding lithium which can now react with another epoxide. Now, you can make this 1,5-polyol fragment which is unsymmetrical. So, if you need a symmetrical 1,5-polyol, then you can use the



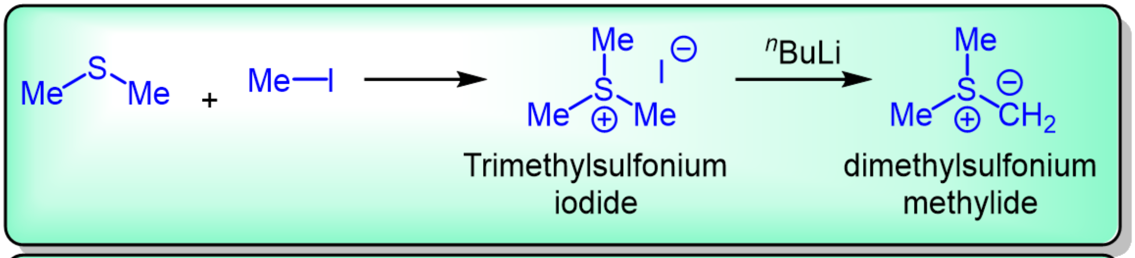
Tietze protocol, and in the other case, you use the Smith protocol. The mechanism here again the umpolung reactivity generation of lithium attacking the epoxide. Then the 1,4-Brook rearrangement and now the HMPA again going to stabilize this corresponding lithium which can react with another epoxide to get to the unsymmetrical fragments.

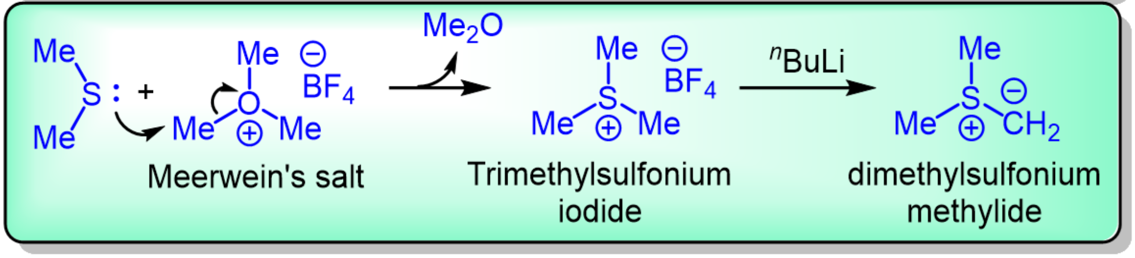
There is a synthetic application here first *tert*-butyllithium can able to generate a carbanion here, then attack the epoxide, 1,4-Brook rearrangement to generate the corresponding lithium. So, now, you are attacking both sides. So, one equivalent of these can attack both of these sites to generate this compound. So, it is a polyhydroxy fragment you can able to control the stereochemistry. So, you can get a very high stereoselective product. And that can be used for the Schreiber's C16-C28 trisacetonide sub-target synthesis for the mycoticins A and B. So, this is the natural product and this is the particular fragment that was synthesized using the Smith-Tietze coupling protocol.



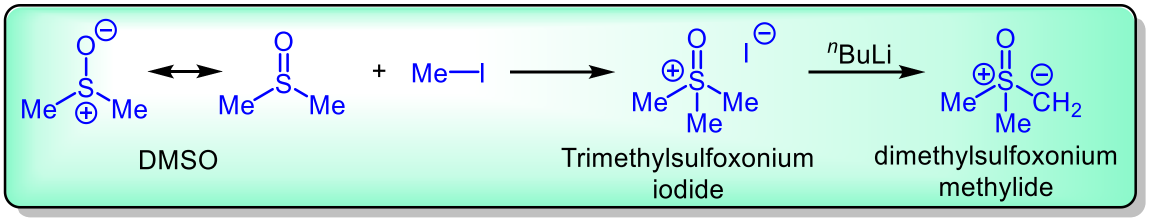
Schreiber's C16-C28 trisacetonide subtarget for mycoticins A and B

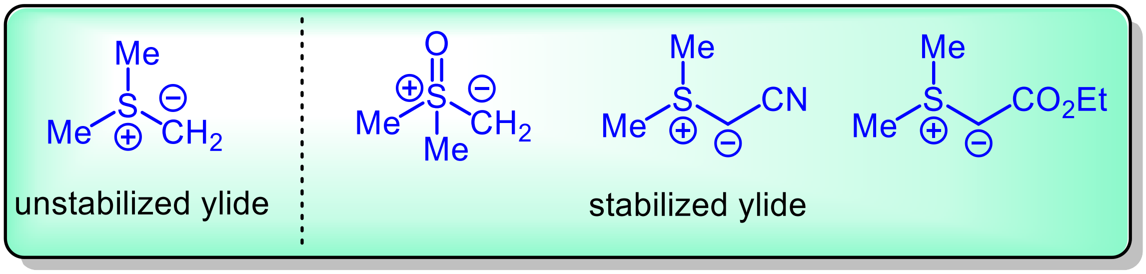
Again, regarding sulfonium salt and the sulfonium ylides, I think we already talked about that if you have the dimethyl sulfide, these are nucleophilic, so go for an S_N2 reaction with MeI to generate trimethyl sulfonium iodide and if you use butyllithium or sodium hydride, these protons are acidic, can be abstracted to generate corresponding dimethylsulfonium methylide. So, now, you can use them. So, again there is no stabilizing group here. So, these are not very stabilized, but in this synthesis, there is one problem. The problem is the first step when you treat with methyl iodide you are forming this trimethyl sulfonium iodide. So, you have an iodide that can also attack the methyl to get back to the starting material. So, this this reaction will have some reversibility, to stop that if can use Meerwin's salt which is this compound there you do not have this problem. Now, that can take a methyl group and you have a dimethyl ether and this BF_4^-. So, there is no way to get back to the starting mixture which can be comfortably now able to generate the dimethyl sulfonium methylide.





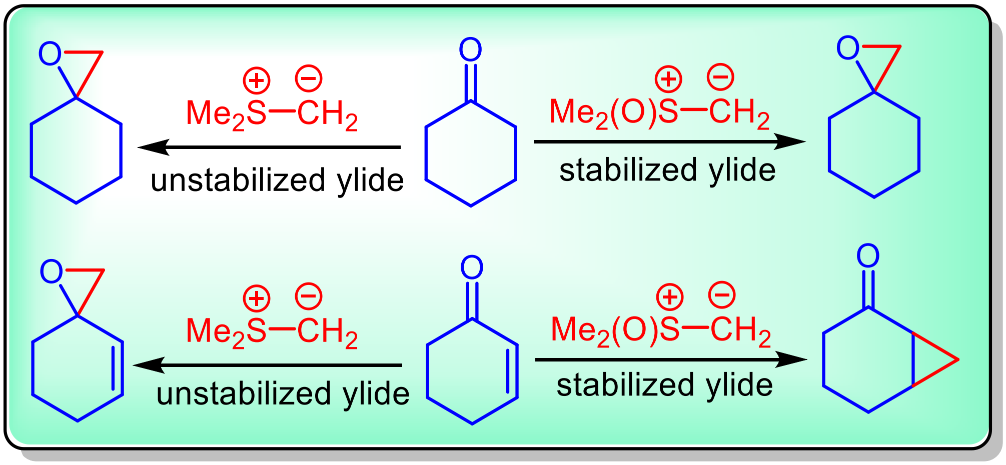
So, now we are talking about the sulfoxonium salt. So, you can think about DMSO you can able to do the resonance structure by putting sulfur plus because if you remember if you try to draw DMSO one thing you should always think about is the electronegativity of sulfur and oxygen, 3.5 versus 2.5 and I am telling you again and again because what that is telling you that all the electron density is lying on the oxygen, not on the sulfur.

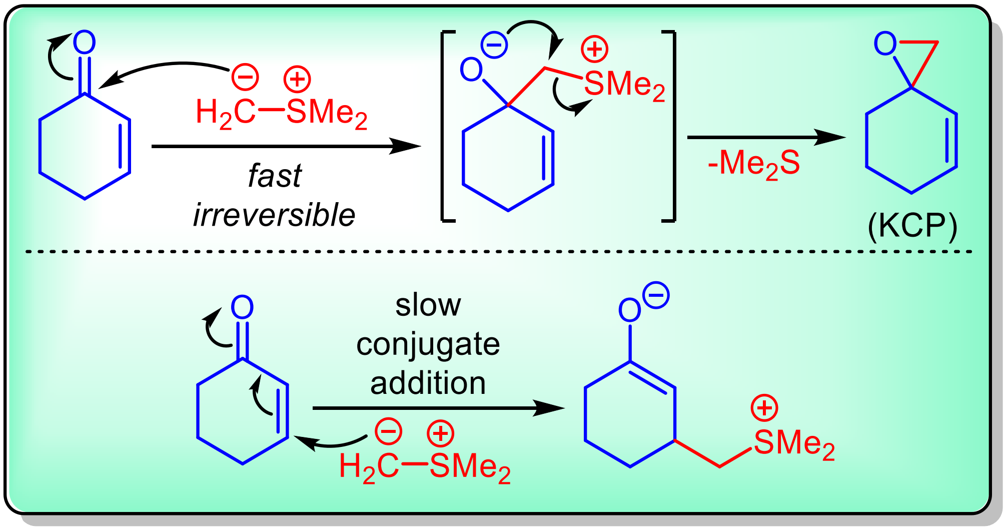




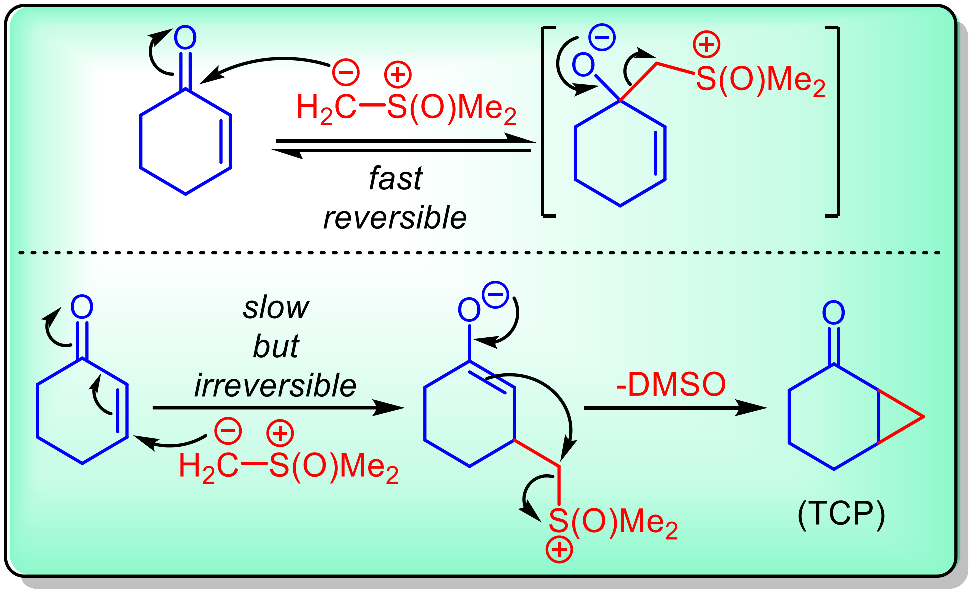
So, you can write comfortably this structure that O- and S^+. Then if you treat with methyl iodide you can able to generate this trimethyl sulfoxonium iodide. Again the sulfur can react with the methyl iodide to generate this corresponding sulfoxonium iodide and now you can use *n*-butyllithium to abstract this proton to generate the dimsyl carbanion or dimethyl sulfoxonium methylide. Again this is a stabilized ylide because you have this SO group to stabilize this corresponding carbanion. So, these are called unstabilized because there is no stabilizing group, but once you have a SO. I am going to bring back to SO_2-based carbanion, or if you have some sort of a stabilizing group like cyano or ester these are called stabilized ylide.

So, there is a difference between the stabilized and the unstabilized ylide. Now once you think about the reaction of carbonyl compound what is going to happen? Once you react with this one versus this one, the sulfonium versus sulfoxonium ylide. So, one is stabilized. So, if you have an unstabilized ylide then it will go for 1,2-addition this is the bottom line here. So, 1,2-addition going to happen first. So, if you see the mechanism what is happening here? there is a 1,2-addition formation of O^- and then you have this SMe_2^+; O^- going to come back and get rid of this to generate the corresponding epoxide. So, from the carbonyl compound, you can comfortably generate the corresponding epoxide, but again the stabilized ylide also can do the same job because there is no 1,4-addition possibility. So, it will go for the 1,2-addition. But as soon as you come to enone, there is a possibility of 1,2- versus 1,4-addition. So, stabilize ylide will go for a 1,4-addition. So, attacking here and then it will be going to come back. So, you end up generating this sort of enolate intermediate where you have CH_2 and you have $S(O)Me_2^+$. So, this can come back here and get rid of this that can generate the corresponding cyclopropane here. In the case of unstabilized ylide it will directly go for 1,2-addition to





generate the epoxides. So, 1,2-addition of ylide to an enone is a very fast reaction. What they are saying the reaction is a very fast reaction, but in case of unstable ylide this reaction is irreversible in nature. That means, this is a kinetic control product. So, once you have an unstable ylide this is fast and irreversible going to the product and there is no way to come back and then this is the conjugate addition that will be a slower reaction because this is going to be the thermodynamic control one. But now once you come to a stabilized ylide what they are saying is because of stabilized ylide this 1,2-addition can happen, but this reaction is reversible which means, once this is forming this can also come back to the starting material. So, in that case, the slow addition the other one which is that the 1,4-addition is slow but irreversible to give you to the thermodynamically controlled product. So, that is why what is going to happen again there is another thing you can compare that this is softer. So, the so, this is a soft nucleophile and this is a softer position. So, that is why the 1,4-addition going to be preferable here and it is going to end up giving you the thermodynamically control product.



So, in this part I talk about sulfur stabilized carbanion, I talk about what is the reason for their stabilization, I talk about the nonbonding to the σ* electron donation, I talk about dithiane, Smith-Tietze coupling, there are several things that can be symmetrical or unsymmetrical polyols, sulfonium salt, and sulfonium ylide, sulfoxonium ylide and salt generation, and also I talk about their reactivity difference. These are the references, of course, you can get lot more about this chemistry from Jonathan Clayden's books. Again you know thank you so much for coming to the class and I am going to see you guys in the next class. Thank you.