Reagents in Organic Synthesis
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Lecture 16
S BASED REAGENTS INORGANIC SYNTHESIS

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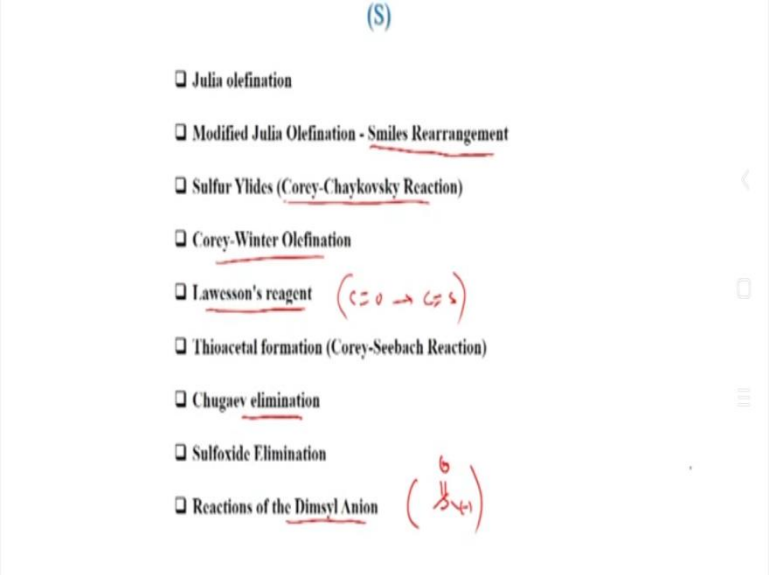

Welcome again. Today we will discuss sulphur based reagents in organic synthesis. So there, today we will cover Julia olefination, modified Julia olefination which is Smiles Rearrangement, Sulphur Ylides (Corey-Chaykovsky Reaction), Corey-Winter Olefination. Also, Lawessons reagent, we will discuss carbon C=O to C=S conversion this, with this reagent. Thioacetal formation (Corey-Seeback Reaction), Chugaev elimination, we will discuss, the olefin formation. Sulfoxide Elimination where also olefin is there. Reaction of the Dimsyl Anion so this is negative charge on the alpha carbon of the S-O bond.

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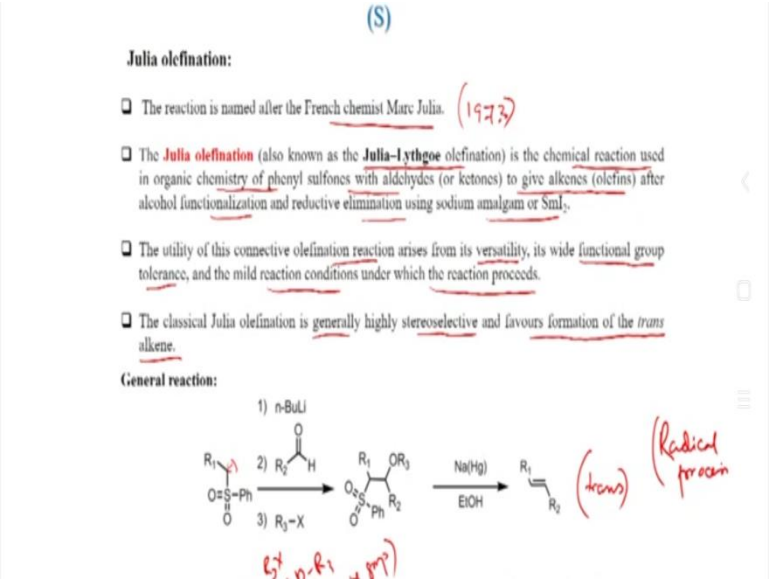

So, first we will discuss Julia Olefination. The reaction named after the french chemist Marc Julia. In 1973, this reaction was discovered. The Julia Olefination, also as the Julia Lythgoe olefination, is the chemical reaction used in the organic chemistry of phenyl sulfones with aldehydes or ketones to gives alkenes. After alcohol functionalization reductive elimination using Sodium amalgam or samarium iodide.

The utility of this connective olefination reaction arises from its versatility, its wide functional group tolerance, and the mild reaction conditions under which the reaction proceeds. The classical Julia olefination is generally highly stereo selective and favors formation of the trans alkene. So, this is very important. The trans alkene is formed. And the general reaction is that, the sulfonyl compound, first will be deprotonated with n-Butyl lithium, you get an anion there. And that will react with the aldehyde to give the beta-hydroxy sulfone. And that OH, OH will be protected with R3X, so O become R3 and this X is a leaving group.

After NaHg treatment, this trans alkene is formed. So, this is trans. So here a few steps are there. First, the treatment with n-Butyl lithium, to generate the anion then the reaction with aldehyde. And then activation of the hydroxy group for the leaving group ability and after that, final elimination with Na(Hg). Also, this process is a radical process here. This step, Sodium amalgam.

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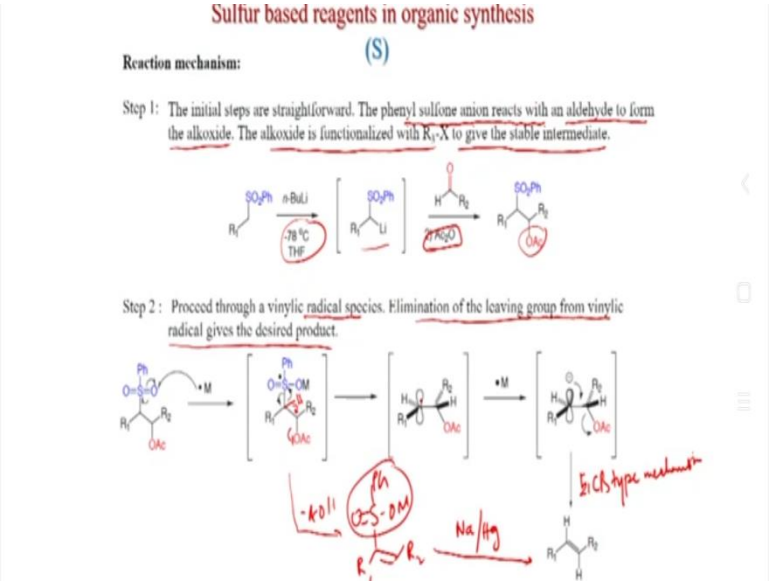

So, what will be the reaction mechanism. The initial steps are straightforward. The phenyl sulfone anion reacts with an aldehyde to form the alkoxide. The alkoxide is functionalized with R3X to give the stable intermediate. We have already seen the n-butyl lithium minus 78 degree centigrade THF generates this negative charge here and this reacts with aldehyde to give the alkoxide which is treated with acetic anhydride generate the acetate. And in the state to, this proceed through the vinylic radical species elimination of the leaving group from vinylic radical gives the desired product.

So here, the metal first reacts with the sulfonyl group and then radical is formed, then this bond cleaved. And after cleave, you get a radical here, and this radical here can take another electron to generate the anion, and this anion then, E1CB, like E1CB type mechanism. The elimination happens, and you get the E alkene. Alternatively, that this elimination can happen first also. If there is a hydrogen, then this elimination can happen. And then, you get this one. This one treatment with NaHg can also give this, olefin. Trans olefin. So the first elimination after that SOPh group removal.

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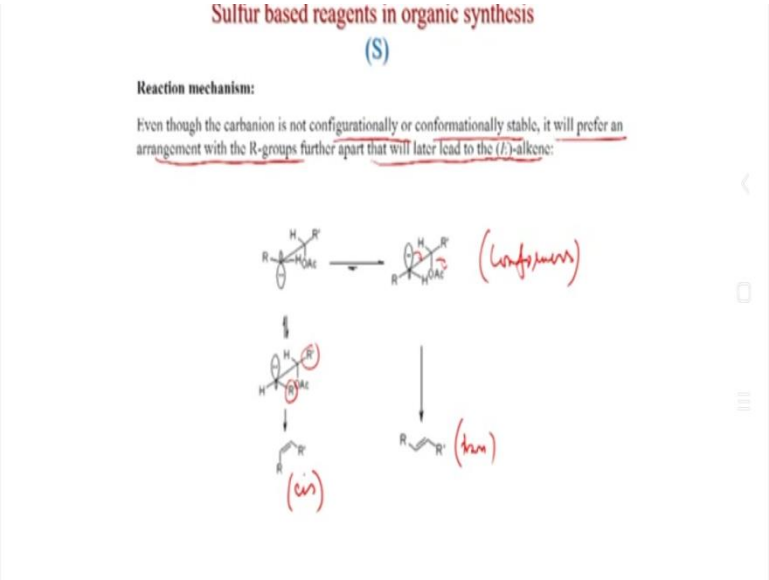

Even though the carbon anion is not (configure) congurationally or conformationally stable, it will prefer an arrangement with the R-groups further apart that will later lead to the E-alkene. So there are two possibilities this, if you rotate along the C-C bond, you get these two conformers. So, these are conformers. And this one will be stable because here, the negative charge is trans with the acetate and this one after elimination, you get this trans-alkene.

On the other hand, this conformer where this negative charge anion and O-acetate are the same side, this has to give another rotation so that negative charge goes to the trans. And when you give the rotation, then this R dash become same side of the R and after elimination you get the cis-alkene. So, this is very important in Julia olefination because of the, though they are conformers are possible, but because of this steric region, the trans-alkene is forming as the major product.

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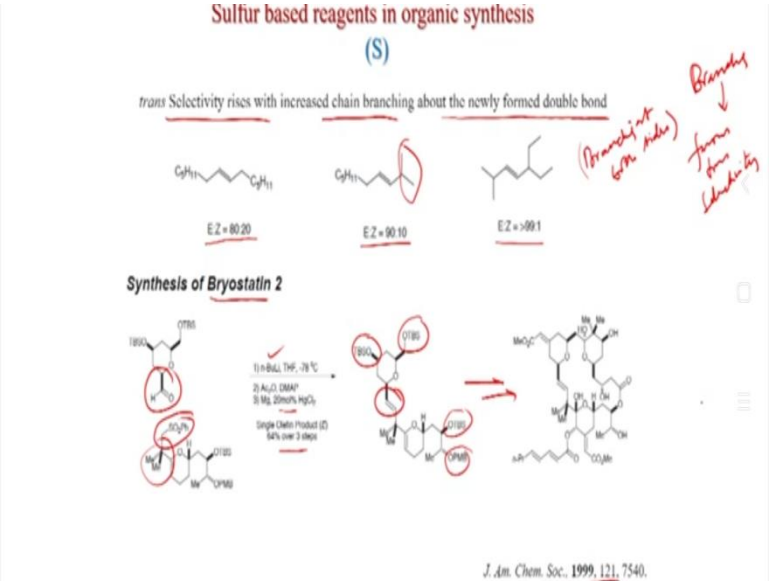

Trans-selectivity rises with increased chain branching about the newly formed double bond. Like here, there is no branching so the E/Z ratio is 80 is to 20. There are two long chains are there. Now if you put branching in one side, the selectivity increases to 90 is to 10. And if you put branching at both side, branching at both sides, it gives a selectivity greater than 99 is to 1. So, Branching, branching is favours, branching is favours trans-selectivity.

This method has been applied in many national products. One example is, synthesis of Bryostatin 2. So, here is an aldehyde and here sulfonate group is present. And this is the active methylene group where it can be deprotonated with n-butyl lithium. Also, there is a branching here and with acetic anhydride, DMF treatment, followed by magnesium, HgCl2, you get a single olefin product and with this, trans geometry. At this condition, other protecting group, TBS, PMB groups, they are untouched and this can be further converted to the intermediate Bryostatin 2. This was published in JACS 1999.

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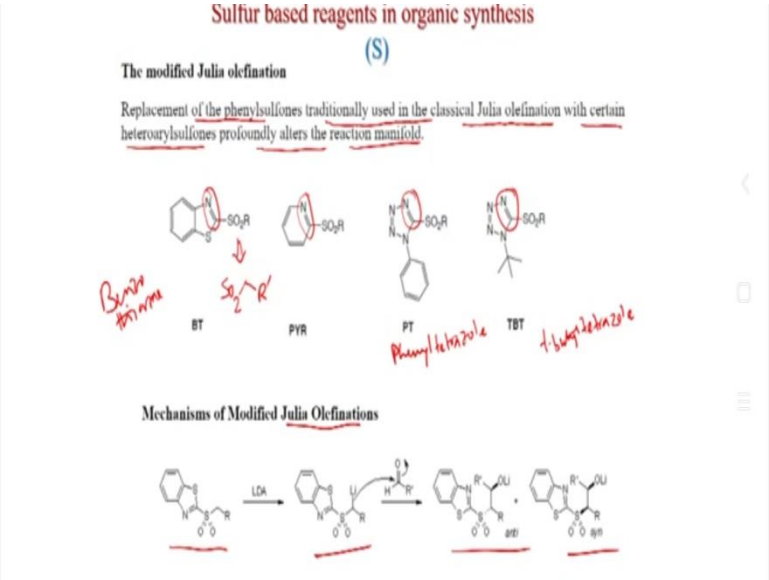

The modified Julia olefination, the replacement of phenylsulfones traditionally used in the classical Julia olefination with certain heteroarylsulfones profoundly alters the reaction manifold. Like here, this is benzothiazole. So BT is benzothiazole and this SO2R, it is better to write like this, SO2R dash, so there is an active methylene group you can see. And this pyridine. This is phenyl tetrazole. And this is tert-butyl tetrazole. So, different instead of phenyl, there can be different heterocyclic motif and all of these, this is very common. This one, this C double bond N is present in all these cases. So we will see the importance of this one in the mechanism.

So, mechanism of the modified Julia olefination. So, here this benzothiazole group is present with the sulfonyl. And this is the active methylene group which can be deprotonated with LDA. You generate the anion. Anion is reacting with the aldehyde and there are two possibilities, the anti and syn. And we will see that in this case both anti and syn are forming and which can of course give two different types of products, one is trans, another is cis.

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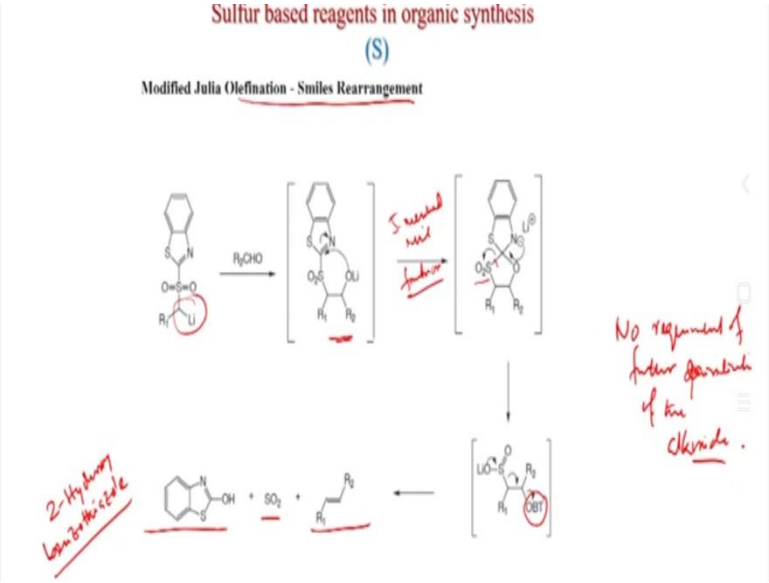

And in the modified Julia olefination, Smiles Rearrangement is happening. That is the importance of the C=N bond. So here this anion is reacting with the aldehyde, R2CHO, generating this alkoxy compound. And now, if you see, this C double bond N is there. And this one is a negative charge and 1, 2, 3, 4, 5. So, 5 membered ring formation will be facile, 5 membered ring formation. Though this is aromatic but this aromatization will regain again that we will see. So, this ring is not aromatized here. And now this oxygen is reacting with this carbon so you get this intermediate. After that, aromatization again will gain. And the benzothiazole group will migrated to oxygen here. So you see here, OBT is there. And this is a, this bond is breaking.

So, benzothiazole is not in the part of sulfonyl group now. And a lithium charges there. And this will eliminate in situ to generate this 2-Hydroxy benzothiazole. So, these are the by-product. SO2 will be formed and with alkene, generally Trans. So, this is important that what we have seen that here, no requirement of further protection or further derivatization of the alkoxide.

So, this is important. In Julia olefination we have seen that that alkoxide we have to treat with acetic anhydride so that it will act as leaving group. But when you functionalize this pH with hetero cycle, replacement of the phenyl with the hetero cycle that this modified Julia olefination, you do not need the another leaving group. So here the itself this benzothiazole, OBT will act as a leaving group and you get this olefin.

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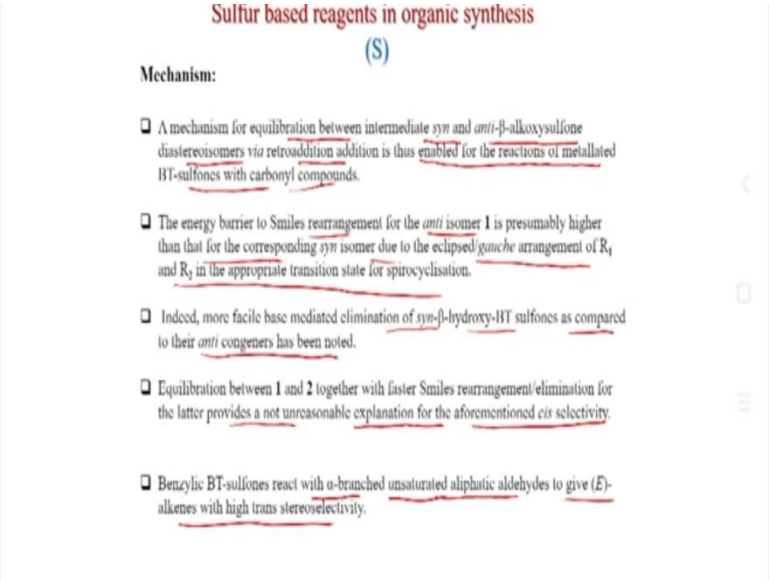

In mechanism for equilibrium between intermediate syn and anti-beta-alkoxysulfone diastereoisomers via retroaddition is thus enabled for the reactions of metallated Benzothiazole-sulfones with carbonyl compounds. And the energy barrier to Smiles rearrangement for the anti-isomer is presumably higher than that for the corresponding syn isomer due to the eclipsed gauche arrangement of R1 and R2 in the appropriate transition state for spirocyclisation.

So, this we will see in the next slide. And indeed more facile base mediated elimination of syn-beta-hydroxy-benzothiazole sulfones as compared to their anti-congeners has been noted. And this provides that unreasonable, not unreasonable explanation for the aforementioned cis- selectivity.

Benxylic benzonthiaxole sulfones react with alpha branched unsaturated aliphatic aldehydes to give E-alkenes with Trans selectivity. So, if alpha branched unsaturated, even alpha branched unsaturated aliphatic aldehydes are there, then also it gives a trans-selectivity.

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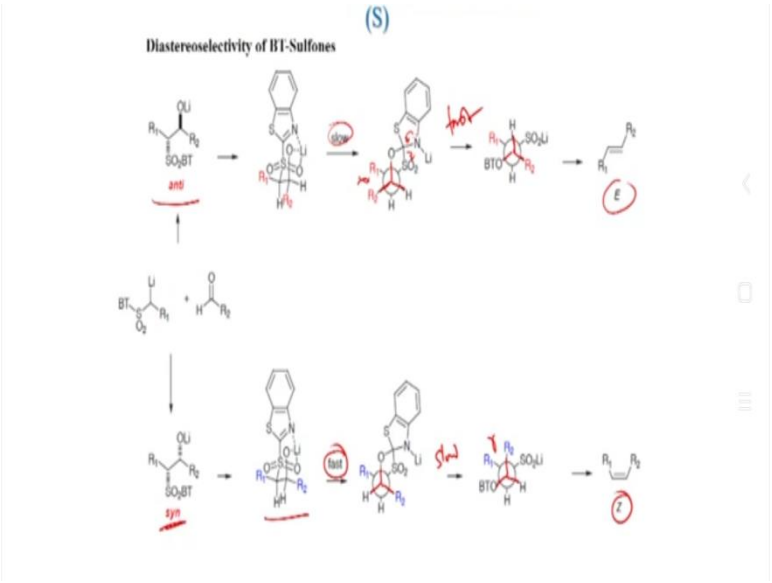

So, this is the mechanism that two are formed. First, we are showing for the anti. So this is the anti alkoxide is forming and after that, this benzothiazole takes orientation like this. So, this one, the R2 aldehyde you can see, in this one, if we see this new N projection, this R1-R2, they are facing steric repulsion. Because they are in the cis-orientation.

When this O oxygen attacks to this C=N bond, this intermediate is forming. This process is slow for anti because of the steric repulsion. On the other hand, when it, the rearrangement happens. So, this one, this SO2Li, when which forms like this, then this will be In the R1-R2, will be in the trans-orientation and this will gives the E isomer. So, this process will be very fast because the steric repulsion is no more in this intermediate.

For the syn case, so syn will be like geometry and after that the 5 membered ring formation you have to draw like this. And in this case, in this case, R2CHO, is the aldehyde. When this 5 membered ring is the formation, then this R1-R2 are trans to each other. So, this process will be very fast. On the other hand, after rearrangement, this R1 and R2 comes to the syn. So, this process will be slow because now steric repulsion is increasing and this will give the Z-alkene. So, both possibilities, cis and trans alkene is possible and depending on the substrates, you get this selectivity.

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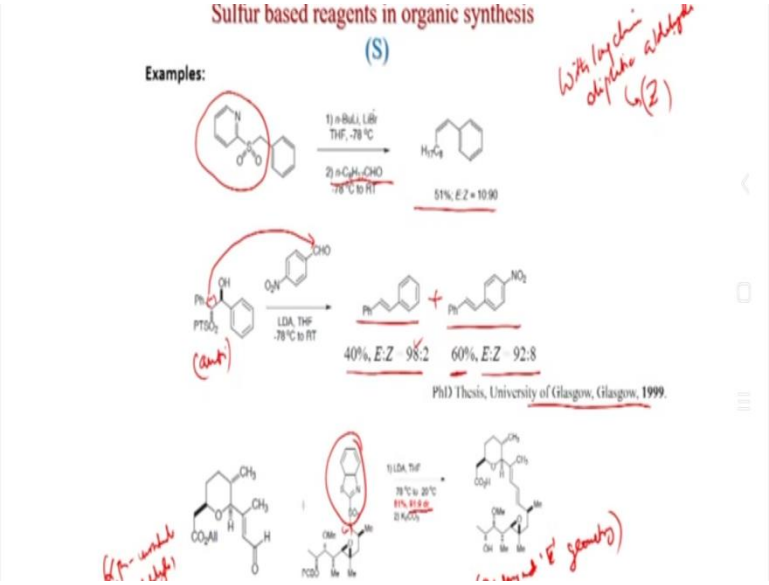

Examples like, here the pyridine sulfonyl group is present and here, first it will n-Butyl lithium and Lithium bromide, followed by treatment with this long chain aliphatic aldehyde. And here, so, with long chain aliphatic aldehydes. Here you get major Z, 90 percent Z and E only 10 percent.

Also, if you treat this intermediate, the alkoxide, this is the trans or anti. This one, if you treat with aldehyde, para-Nitrobenzaldehyde, then LDA so what will be possible? So, this one (elimination) can be possible that this can eliminate by this Smiles rearrangement and you get this product. And this product is formed in 40 percent E-Z, 98 is to 2.

And this anion can also react with the aldehyde, and after that you can get this product, para-Nitro phenyl group present. And this product is formed in 60 percent E-Z ratio, 90 is to 2. So both elimination as well as the reaction with aldehyde, they are both competitive process, that is why you are getting a mixture of products. And this was in the PhD thesis, University of Glasgow.

And one application of the this one also with this alpha beta unsaturated aldehyde, here this, benzothiazole sulfonyl group is there and this is active methylene group. Here, LDA will generate an anion and this will react with this. And here, you get the E-Z, 91 is to 9, so this is the preferred E geometry. This was published in Archilnstance 1999.

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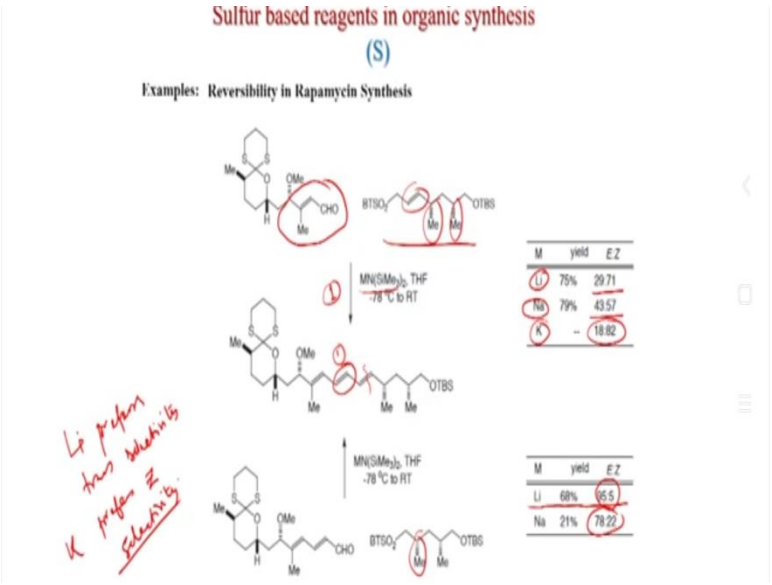

Reversibility in Rapamycin Synthesis. So, here we will see the how the substitution is giving different product. Suppose here, you have this Beta branch, alpha beta unsaturated aldehyde and with this one, Benzothiazole sulphonyl group, also there double bond is present and some branching is present but further.

So here, what happens, you do not get so much selectivity. With different metals, this is the disilazane, so lithium- hexamethyldisilazane you get 29 is to 71 E-Z mixture. With Sodium disilazane, you get almost equal amount, 43 is to 57. And with potassium you get more Z selectivity.

Now, so this is the product and this is the product and you see this bond is forming here. So, this is the 1, this is the 1. This is the first case this double bond is forming. Now, if you focus on this double bond formation, so for this double bond formation we have to use this substrate.

So here, you see the branching is closed with the sulfonyl group now. And there is also alpha beta unsaturated aldehyde. This is actually diene. And in this case, the selectivity is good.

Suppose with lithium-hexamethyldisilazane, you get 68 percent yield and the E selectivity 95 percent. On the other hand, sodium cases you get 78 percent. So, lithium prefers, prefers trans-selectivity and potassium prefers Z-selectivity here. And also you can see, if the branching is close to the sulfonyl then the preference for the E-selectivity is more.

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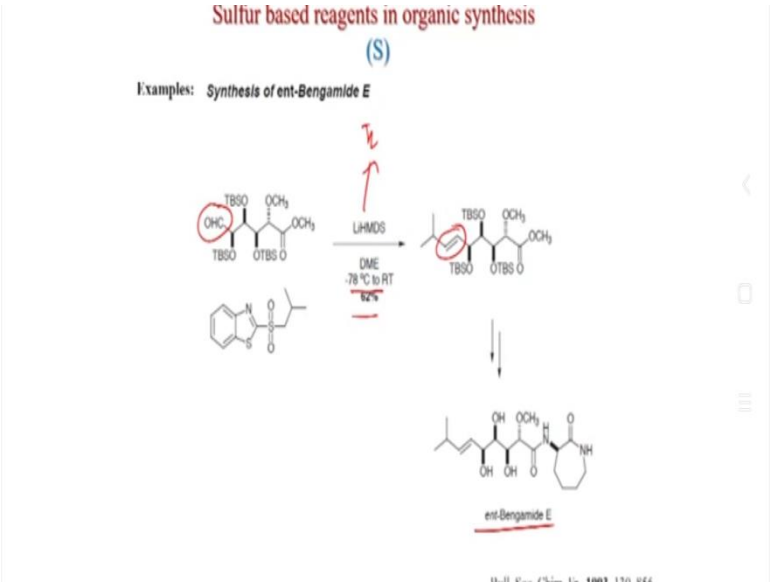

Some example, so here this Sulfonyl benzothiazole is present and this is the aldehyde. And after that with Lithium-hexamethyldisilazane. So, we told that lithium prefers the E-selectivity with this solvent minus 78 degree to room temperature, you get 62 percent yield of this product with this E olefin. And this E olefin can be further converted to the natural product, ent-Bengamide E. This was published in Bulletin of chemical society kim France, 1993.

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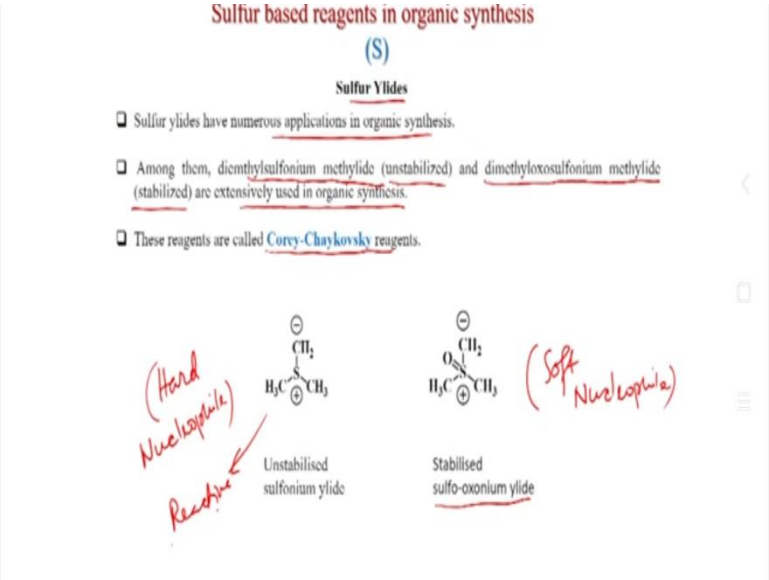

So, Sulfur ylides now we will talk. Sulfur Ylides have numerous applications in organic synthesis. Among them, dimethylsulfonium methylide which is unstabilized and simethyloxosulfonium methylide, stabilized, are extensively used in organic synthesis. These reagents are called Corey-Chaykovsky reagents.

Like this one is unstabilized sulfonium ylide. So, here positive charge on sulfur and negative charge on CH2, that is the carbon, and stabilized sulfo-oxonium ylide because there is an oxygen with sulfur. So, this is stabilized and that's why this is soft actually. This is soft nucleophile. We will see for these different kind of reaction happens. And this is hard nucleophile because this is not stable so this is reactive.

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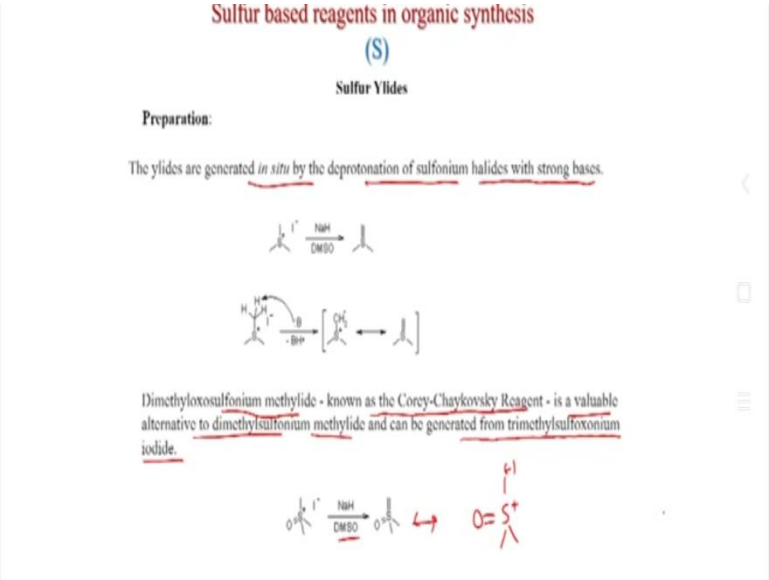

Preparation, the ylides are generated in situ by the deprotonation of sulfonium halides with strong bases. Like here, dimethylsulfonium iodide with sodium hydride, DMSO, you get this. So, what will be the mechanism? Because this sulfur is positive charge, this is activated methylene group and with base, strong base this can be deprotonated and this will be resonating structure. Dimethyloxosulfonium methylide, known as Corey-Chaykovsky reagent, is a valuable alternative to dimethylsulfonium methylide and can be generated from trimethylsulfoxonium iodide. So this is trimethylsulfoxonium iodide and with NaH, DMSO, you get this one. So, this is resonated structure.

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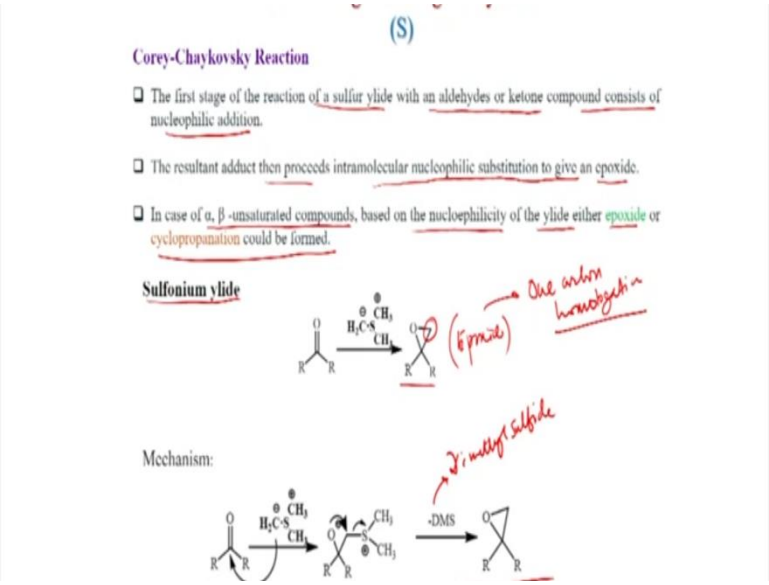

The first stage of the reaction of a sulfur ylide with an aldehyde or ketone compound consists of the nucleophilic addition. Resultant adduct then proceeds intramolecular nucleophilic substitution to give an epoxide. In case of alpha beta - unsaturated compounds, based on the nucleophilicity of the ylide either epoxide or cyclopropanation could be formed. So, this we will see, depending on the nature of this hard soft different product could be formed.

So, first we will discuss sulfonium ylide, which is hard, and with carbonyl compound, generally the epoxide is formed. And also you can see this is actually 1-carbon homologation, because this carbon is coming from this carbon, from this ylide. So, 1-carbon homologation is happening. What is the mechanism? First, this nucleophilic addition will happen to the carbonyl compound. After that, elimination of dimethyl sufide, dimethyl sulfide. You get this epoxide.

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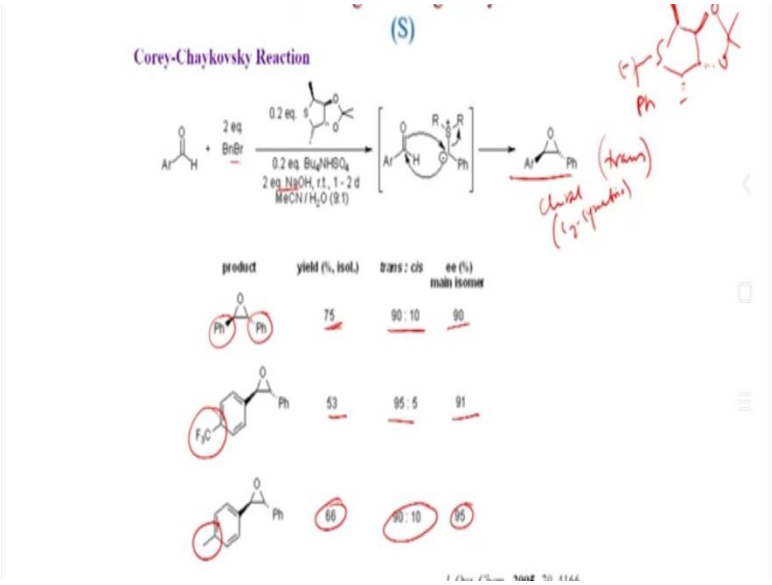

So, some examples like here, if you use a C2 symmetric sulfide and which in reacted with the benzyl bromide, and so, this will be the chiral reagent. And this is situ symmetric as we can see here. And this, after sodium hydroxide, this anion will generate. So, this is the anion. And after that it will react with the aldehyde and elimination will give this trans-epoxide. So, this is important because of the steric also, like Julia olefination, we can see here also, the trans product is major.

So, when two phenyls are present, you will get 75 percent isolated yield. Trans cis is 90 is to 10 and 90 percent yield for the major enantiomer. So, this is chiral. This is also situ symmetric. With CF3, if you put the CF3 group in the phenyl ring then you get a little less yield but better selectivity is 95 is to 5 and 91 percent yield for the major diastomer. And if you put a methyl group, that s the para tolyl group, you get 66 percent and 90 is to 10, and 95 percent, the (enhanced) selectivity gets increased when you put a methyl group to 95 percent. This was published in JOC.

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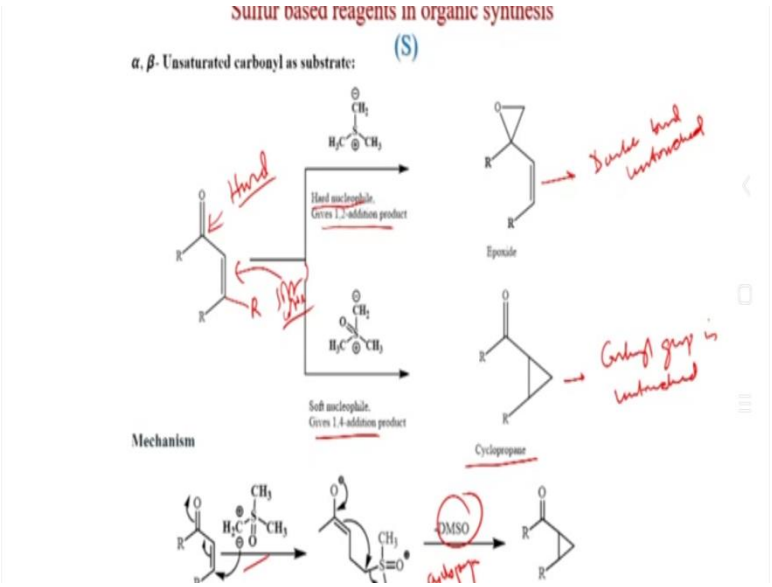

With alpha beta-unsaturated carbonyl compound, depending on the hard or soft reagent, you get different products. So, this alpha beta-unsaturated ketone can be trans or cis, trans, this side also possible. And when you put this hard nucleophile, it gives 1,2-addition product.

So, in alpha beta-unsaturated ketone, we known for the Grignard addition also and 1,2 additions. The Grignard has to 1,2 because Grignards are hard nucleophile and cuprate adds to 1,4 fashion So similarly here also, because this is a hard centre and this is soft centre, the double bond. So, hard nucleophile will prefer to react with the hard electrophile, that is the carbonyl group, and you get the epoxide and the double bond which will be untouched.

On the other hand, if you put the soft nucleophile, it gives 1,4-addition product. So, cylcopropanation, so here, double bond is reacting and carbonyl group is untouched. So, this is very selective and the mechanism is like this. First the 1,4-addition will happen with this oxosulfonium methylide. Then the cylcopropanation will happen. So, this is cyclopropanation. And DMSO will eliminate, you get this cyclopropanated carbonyl compound.

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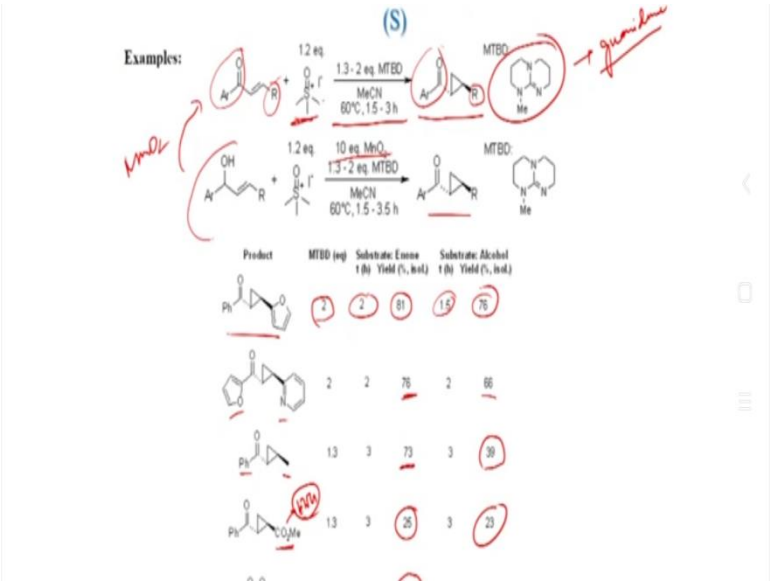

So examples. So because this is acidic this and not only sodium hydride, simple organic base like guanidine. So, these are guanidine can also be used to deprotonate this one. And after that, it is reacted with this alpha beta-unsaturated ketone in acetonile solvent, 60 degree centigrade, you get this cyclopropanated carbonyl compound. And because of this geometry, this is trans and this also trans.

So, this geometry is retained in the cyclopropanation reaction. Also, this allylic alcohol can also be used which with MnO2, it is getting oxidized in situ to the alpha beta carbonyl compounds. So, with MnO2 you can get, the alpha beta-unsaturated carbonyl compound. And with this also, similar condition you get this product. So, this is the yield.

Suppose this substrate, if you use with the furyl group and this side phenyl carbonyl then two equivalent of this MTBD, that is the base you have to use and substrate is two enone. So, in the enone case you get, 81 percent yield after two hours reaction. And when alcohol is there, with extra MnO2 you get 76 percent yield. 1.5 hours.

So, yield got little bit reduced also, both sides heterocyclic, you get 76 percent yield and in this case, alcohol case, you get 66 percent. Also, phenyl, methyl you get 73 percent yield and this case you get very less yield, 39 percent. And when CO2Me

group is present then you get 25 percent yield, the yield gets reduced because this is acting as a EWG.

So, that is a problem and the yield also get reduced for this case. And when the sulfonyl group is there, the yield again got enhanced. You get 72 percent yield. So, this was published in singlet 2007. So, this is an important method for cyclopropanation. This method is very simple and the reagents are commercially available and very useful way for the cyclopropanation of alpha beta-unsaturated ketones.

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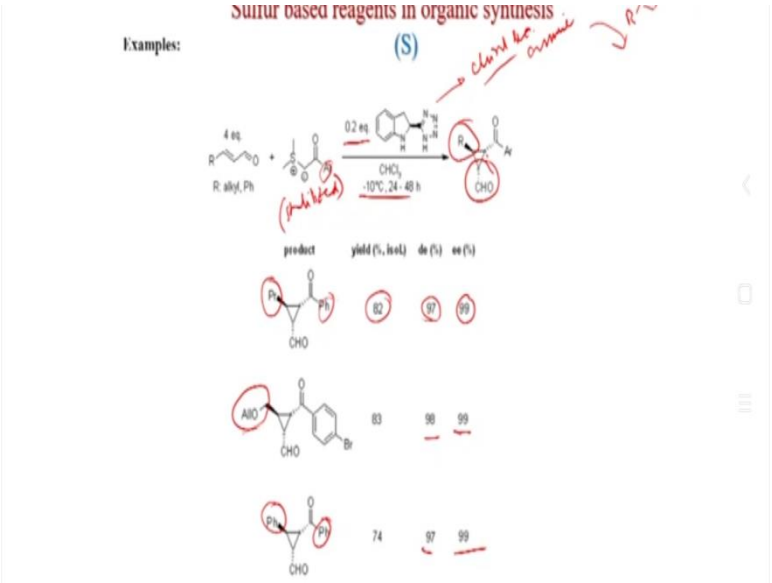

Also, asymmetric variants is possible and this is also stabilized yilide, stabilized because there is a carbonyl group. And this is alpha beta-unsaturated aldehyde so, this chiral secondary amine. So this is chiral secondary amine and this will react first with the alpha beta-unsaturated aldehyde to generate an iminium ion. So, iminium ion will form first and then the conjugated addition. After that, the cyclopropanation will happen. And this geometry, you can see here, R and CHO are trans so here also they are trans, and a newly generated chiral centre is forming. This is newly generated chiral centre.

So, cyclopropanation along with a newly generated chiral centre. And this method only 0.2 equivalent of this catalyst is enough to give these products in chloroform and at minus 10 degree centigrade. When this is propyl group, this is phenyl then you get

82 percent yield and 97 percent diastromeric excess and 99 percent enantiomeric excess.

So, all chiral centres, relative as well as absolute configuration is very high. Also, if you have a O-Allyl group here and para-bromobenzyl also you get 98 percent diastereoselectivity and 99 percent ee. Also, this is phenyl and this is also phenyl case, you get 97 percent diastromeric excess and 99 percent enantiomeric excess. So, this process is very good giving the products in high diastereomeric and enantiomeric ratio. So this was published in JOC 2007.

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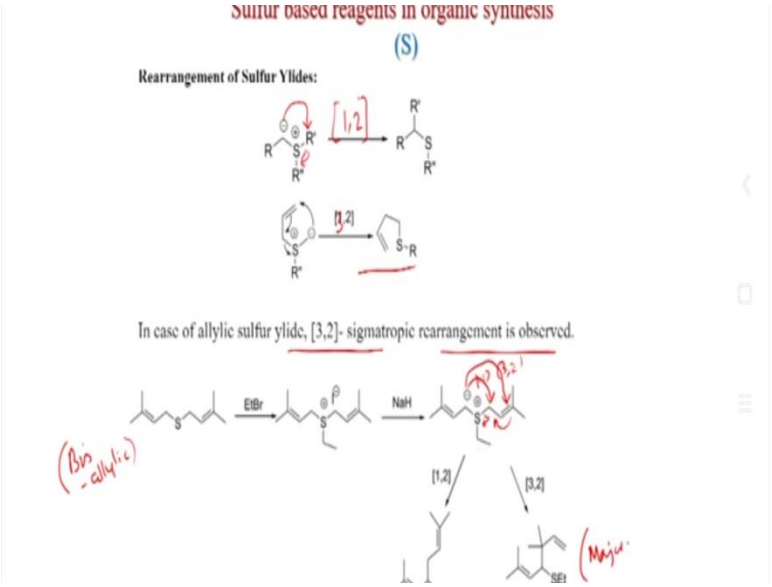

Now, we will discuss rearrangement of sulfur ylide. So, rearrangement sometimes possible if you heat it and this negative charge can react here. In this case, it is reacting here, this bond is breaking and you get this is the (1,2) - rearrangement. And this is actually (3,2). So, for allylic system, allylic sulfur ylide, 3 2-sigmatropic rearrangement is formed because in allylic, instead of here, it reacts at the double bond and the double bond is migrating here and this bond is breaking, you get this product.

Suppose this is Bis-allylic system. Bis-allylic. Now, you react with Ethyl bromide to react with this sulfonium salt and after sodium hydride treatment, you get this ylide. And this one, now, if it reacts in the 1,2 fashion. So, 1,2 means it will react here. So in this case, this bond is breaking and you get the 1,2 product. On the other hand, 3, 2 case, this will react here. So, this is 3,2 and this is 1,2. 3,2 case you get this product.

This is the quaternary carbon atom here and in 1,2 case you get this. So, in allylic system, this will be of course major 3,2 is favourable.

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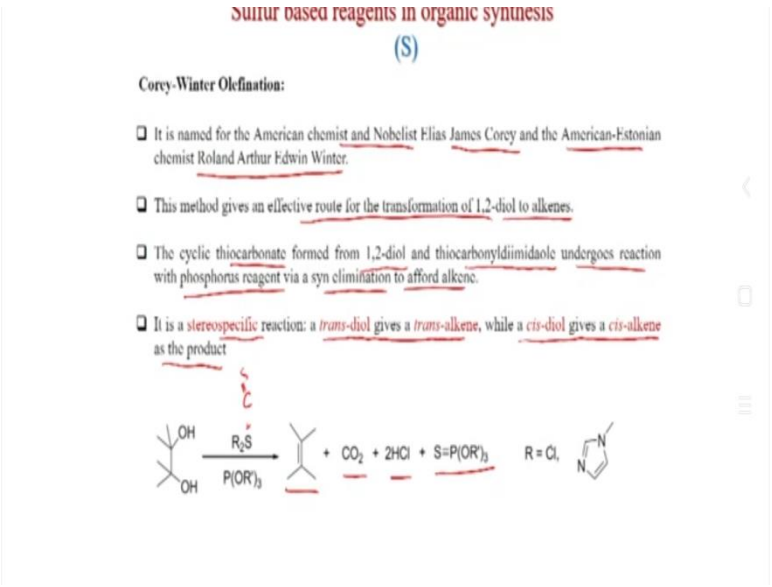

Now we discuss Corey-Winter olefination. It is named for the American chemist and Nobelist Elias James Corey and the American-Estonian chemist Roland Arthur Edwin Winter. This method gives an effective route for the transformation of 1,2-diol to alkenes. So, we have seen that the osmium tertaoxide gives the alkene to diol. But Core-Winter olefination, you will get the diol to alkene.

So it is reverse osmylation. The cyclic thiocarbonate formed from 1,2-diol and thiocarbonyldiimidazole undergoes reaction with phosphorus reagent via a syn elimination to afford alkene. So this is the syn elimination. Osmylation we have seen that is the syn dihydroxilation. So here also the syn elimination.

It is stereospecific, a trans-diol gives trans-alkene while a cis-diol gives a cis-alkene as the product. Suppose here, if you have a diol and (generally) phosphites are used and with this activated C=S. So here C=S is there and now the elimination will give the olefins, CO2 , 2 HCl and this one, phosphorous sulphur bond will form and R is equal to chlorine or imidazole.

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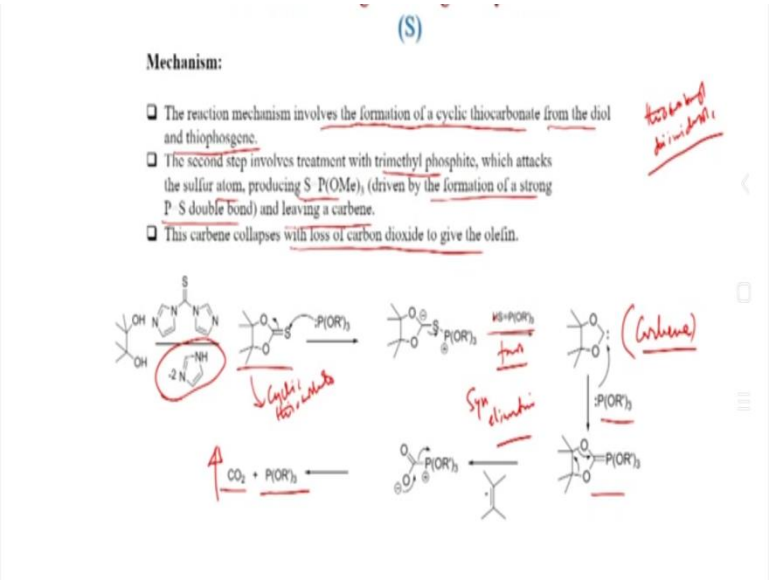

So, what is the mechanism? The mechanism involves formation of a cyclic thiocarbonate from the diol and thiophosgene, or Thiocarbonyldiimidazole. Thiocarbonyldiimidazole. The second involves treatment with trimethyl phophite which attacks sulfur atom, producing S double bond P(OMe) driven by the formation of a strong P double bond S, and leaving a carbene. This carbene collapses with loss of carbon dioxide to give the olefin. So this is the reaction first. This diol has to be treated with this. This can be imidazole or chlorine, so this is the thiocarbonyldiimidazole.

Then this intermediate will form after elimination of two molecules of imidazole, Cyclic thiocarbonate. So this is Cyclic thiocarbonate. Now this phosphite will react with this sulfur and you get this intermediate which after elimination of this, you get a carbene. So, there are few steps are there. Then the carbene reacts with this phosphite again to generate this double bond. After elimination, after elimination so this syn elimination.

After syn elimination, you get the olefin and this intermediate which collapses to carbon dioxide and phosphite, alkyl phosphite. So, this is very important. In this reaction, carbon dioxide is eliminating, that is also driving the equilibrium. And here also, this is also stable, this also fast. Because this, P double bond s bond is forming actually.

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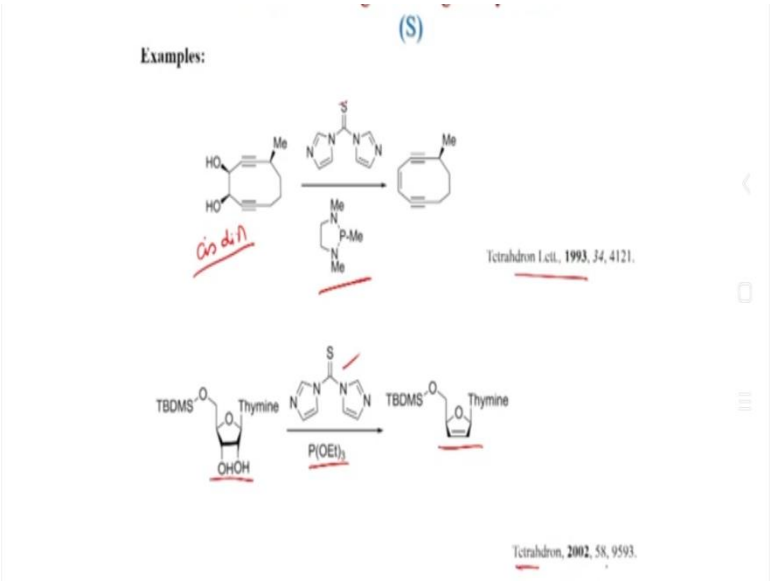

So examples. This is cis-diol cyclic system and with this thiocarbnyldiimidazole you get this Z. This was published in Tetradron Lett. And this is a phosphine. So you to use a phosphine and thiocarbonyl compound. Also here, this is also cyclic system, cis-diol is here and this is the thiocarbonyl compound. This is the phosphite and you get this double bond, cis. So this process is also very efficient. It was published in Tetrahedron.

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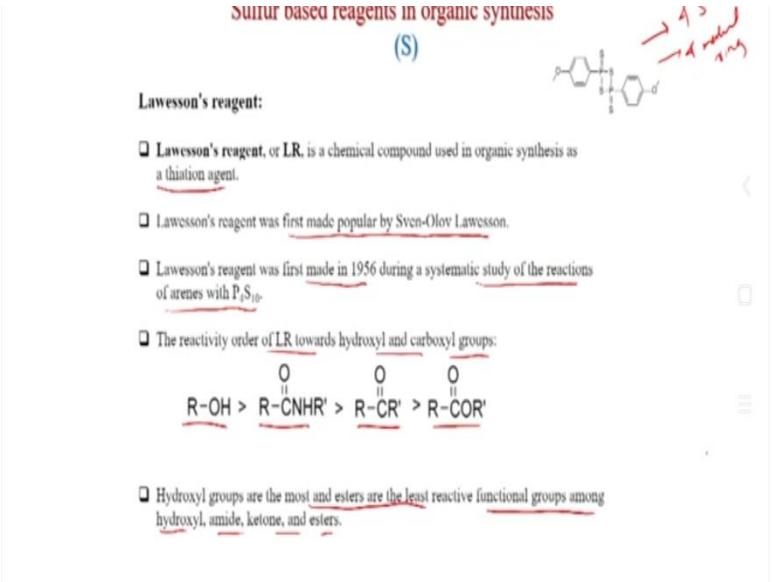

Now, we will discuss Lawesson reagent. So, in Lawesson reagent, you can see 4 sulfur atoms is present. And also, a 4 membered ring is there. Lawesson reagent or LR is a chemical compound used in organic synthesis as a thiation reagent. Lawesson reagent was first made popular by Sven-Olov Lawesson. Lawesson agent was first made in 1957 during a systematic study of the reactions of arenes with P4S10. Reactivity order of LR towards hydroxyl and carbonyl groups are alcohol is better than amide that is better than ketone that is better than esters. So, hydroxyl groups are the most and the esters are the least reactive functional groups among hydroxyl, amide, ketone and esters.

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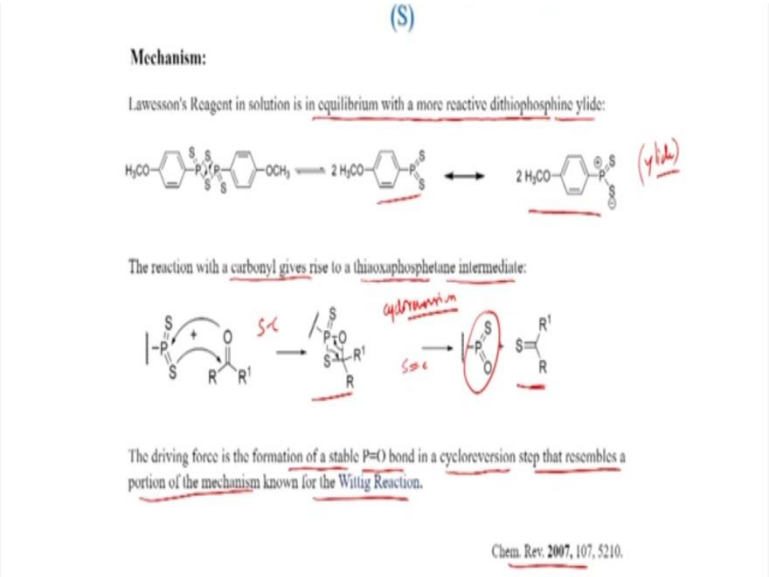

So, what is the mechanism? Now Lawesson reagent in solution is in equilibrium with more reactive dithiophosphine ylide. Because this ring in solution, it breaks and you get this one, dithiophosphine and this will be with the ylide. This is ylide. And this is active, that is reacting.

The reaction with the carbonyl gives rise to a thiaoxophosphetane intermediate. So, this one is reacting with the carbonyl so this sulfur is attacking to carbon and this oxygen is attacking to phosphorus so you get this 4 membered ring formation. And then, then cyclo reversion. So, this cycle will break, and interestingly, you see first this sulfur carbonyl bond here. S-C bond is forming. And now S-C double bond form. So, S-C double bond forming here. And after elimination of this, oxygen goes to

phosphorus and sulfur goes to carbon, you get, your carbonyl compound is got to thiocarbonyl now.

The driving force is the formation of a stable P double bond O bond in a cycloreversion step that resembles a portion of the mechanism known for the Wittig reaction. So in the Wittig reaction also we have seen this kind of mechanism. Maybe 5 membered ring is forming there. And this is the Chemical Review which tells about this reagent.

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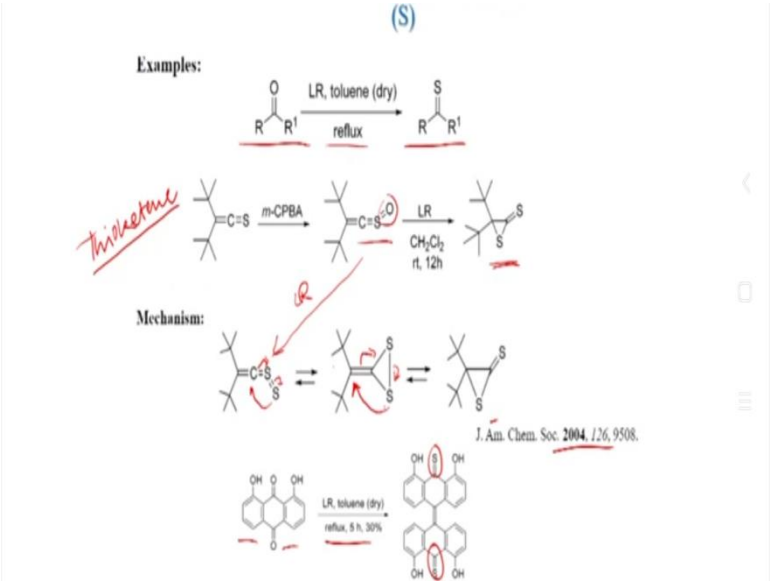

Examples, simple carbonyl compound can go to thiocarbonyl with Lawesson reagent, toluene, reflux condition. This is an thioketene. So, this thioketene if you treat with m-CPBA, now this ketene sulfoxide is forming. Now if you treat with Lawesson reagent, you are getting this. 3 membered sulfur ring is forming. So, what will be the mechanism? Now first this will go to this that oxygen will be replaced by sulfur.

Now, what will happen. This sulfur-sulfur bond will be formed so this will react like this. So you get a sulfur-sulfur as well as this carbon react with 1 sulfur here. Both sulfur. This carbon is bonded with both sulfur so that is the possible this way. And now, this is forming, so what could be the possible. Possible is that, this one, double bond is migrating to here.

This bond is breaking and this is attacking here. So you get this one. This was published in JACS 2004. Also, if you have this kind of a di-carbonyl compound,

aromatic system with Lawesson reagent, you get a dimerization. So, this is very interesting. Dimerization is happening along with this thiocarbonyl formation. This is in reflux condition you get aqueous 30 percent yield. And this was published in hetero [atom] chemist in 1999.

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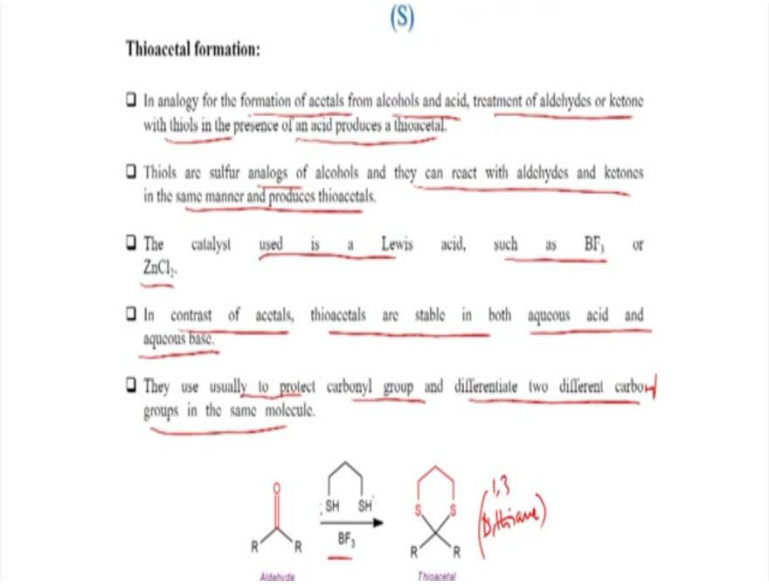

Thioacetal formation is also an important reaction of sulfur based reagent. In analogy for the formation of acetals from alcohols and acid, treatment of aldehydes or ketone with thiols in the presence of an acid produces a thioacetal. Thiols are sulfur analogs of alcohols and they can react with aldehydes and ketones in the same manner and produces thioacetals. The catalyst used is a Lewis acid, such as BF3 or ZnCL2. in contrats to acetals, thioacetals are stable in both aqueous acid and aqueous base. So this is very important. For acetals they generally clipped with acid but thioacetals are very stable to acid as well as base. So they are very useful protecting you from carbonyl compound.

They use usually to protect carbonyl group and differentiate two different carbonyl groups, this will be carbonyl groups, in the same molecules. Like here, an aldehyde and ketone is reacting with this. 2 sulfur atoms are present with BF3 you get this thioacetal or this is called dithionol. So, 1,3-dithiane. So, bis-thiol is reacting with BF3 and you get this thioacetal or 1,3-dithiane.

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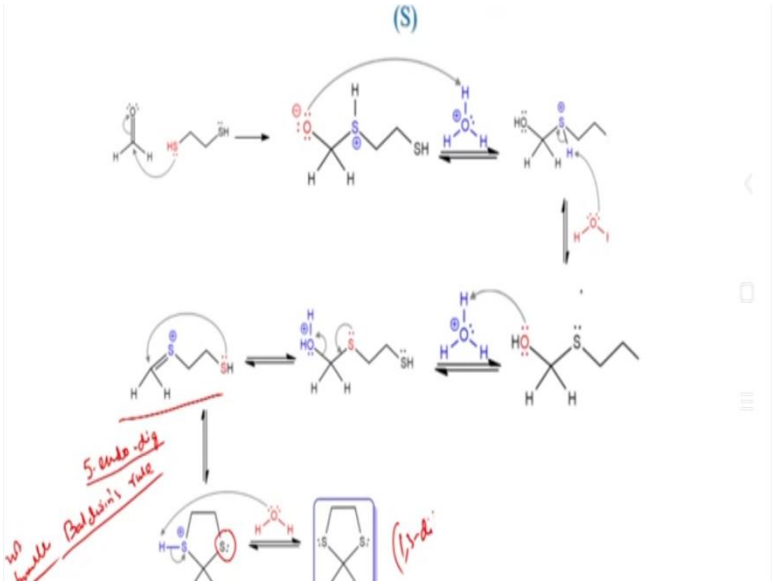

And these are the possible mechanism. This thiol is reacting with the aldehyde first to generate this intermediate. Then the protonation happens, deprotonation. Again, alcohol will be protonated to get the, so that water will be eliminating. This oxygen is getting a positive charge. Now, this double bond will form, carbon-sulfur double bond is forming and this is interesting if we show this mechanism. This is actually 5-endo-dig and this according to Baldwins rule, this is disfavoured. But because of the sulfur systems, sulfur is heavy atom. So this is not favourable according to Baldwin rule. Because of this heavy atom, this process might occur. The cyclisation, 5-endo-dig cyclisation and after that, this proton is deprotonated by water, you get this 1,3-dithiane.

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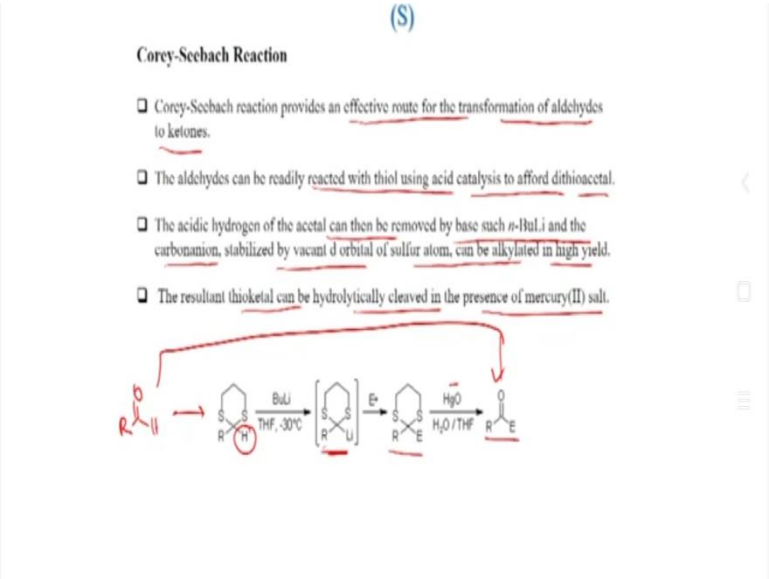

Corey-Seebach reaction. Corey-Seebach reaction provides an effective route for the transformation of aldehydes to ketones. The aldehydes can be readily reacted with thiol using acid catalysis to afford dithioacetal. The acidic hydrogen of the acetal can then be removed by base such n-Butyl lithium and the carboanion stabilized by vacant d orbital of sulfur atom can be alkylated in high yield. The resultant thioketal can be hydrolytically cleaved in the presence of mercuric salt.

So this is the usefulness, not only the protecting group, this is also usefulness to convert aldehydes to ketones. So, that is the Corey-Seebach reaction. Here, this dithiane, this hydrogen can be deprotonated with Butyl lithium and this is stabilized because the sulfur atoms are present vacant the orbital stabilized the carboanion. And this carboanion can be reacted with electrophile, also alkene group other electrophiles and then mercuric oxide treatment gives back carbonyl. So, this is ultimately, this you can get from aldehyde. So ultimately, aldehyde is converting to a ketone. This is the method, Corey-Seebach reaction.

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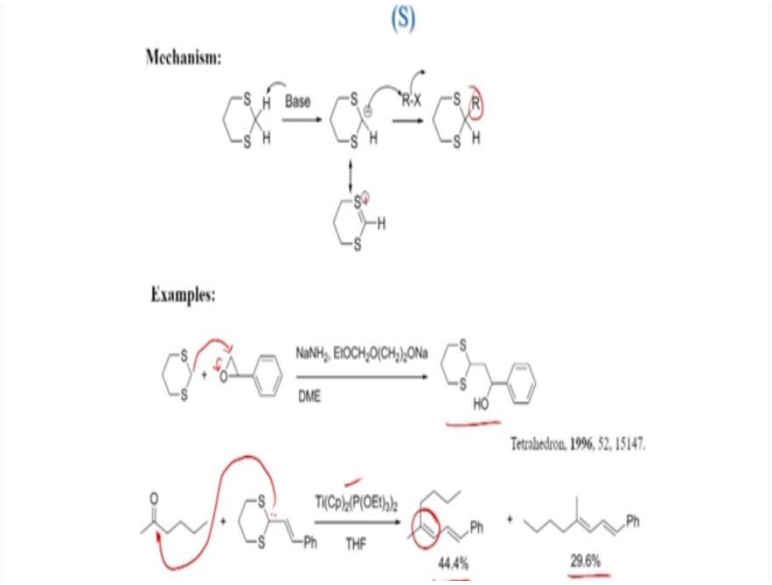

So, mechanism is same that you will be deprotonated and this anion will be stabilized with the sulfur. The positive charge is there. And R3X, you can get, this alkylation. Also, this can act as a nucleophile like epoxide this is terminal carbon is reacting giving this intermediate This is published in Tetrahedron. Also, it can react with carbonyl compound. So, carbonyl compound it can react and generate olefin here. With titanium reagent, you get 44 percent yield of this diene. And this diene is forming furthur this group is here, methyl group is here, you get 29 percent yield of this diene. This was published in JACS,1997.

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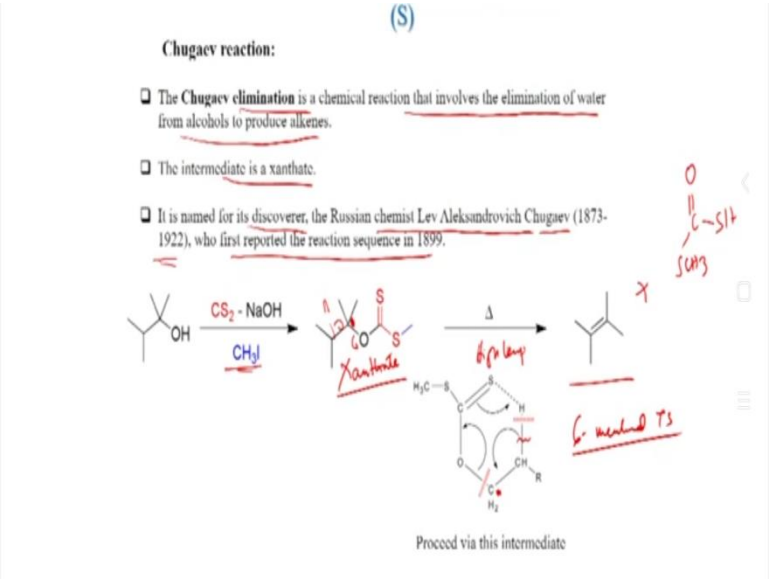

Chugaev reaction. The Chugaev elimination is a chemical reaction that involves the elimination of water from alcohols to produce alkenes. Thus intermediate is xanthate. This is an old chemistry. This, it is named for the its discoverer, the Russian chemist Lev Aleksandrovich Chugaev (1873 to1922), who first reported the reaction sequence in 1899. so, this is important. Carbon disulphide, sodium hydroxide followed by treatment with methyl iodide, you get this xanthate ester or xanthate. After heating, you get this so high temperature you have to put. Then you get elimination of this, so this will eliminate.

So what will be the mechanism? This carbon is actually this carbon here which is connected to the oxygen and if you see, the 6 membered transition state is forming. So if you see, this C=S bond is activating this hydrogen, beta hydrogen, so the elimination will happen. So this is reacting with this one and now this bond will break. Double bond will form and this carbon-oxygen bond will break and it will go to this carbon. And after that, you get this olefin and you get this also, CHSCH3. So this is the side product of this reaction.

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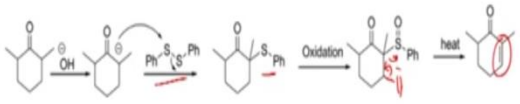
Sulfoxide Elimination:

- The compound containing an activated C-H bond can undergo reaction with diphenyl or dimethyl disulfide in the presence of base to give substituted sulfide that could be readily oxidized to sulfoxide.
- The latter readily undergoes elimination on heating to give **α, β**-unsaturated carbonyl compound.



Sulfoxide elimination. The compound containing an activated C-H bond can undergo reaction with diphenyl or dimethyl disulfide in the presence of base to give substituted sulfide that could be readily oxidized to sulfoxide. The latter readily undergoes elimination on heating to give alpha, beta-unsaturated carbonyl compound. Like here, 2,6-Dimethylcyclohexanone treated with OH minus generate the anion and then this disulfide is reacted with this one, you get this alpha sulfonylation after oxidation you get this sulfoxide. And now after heat, this will eliminate and you get an olefin.

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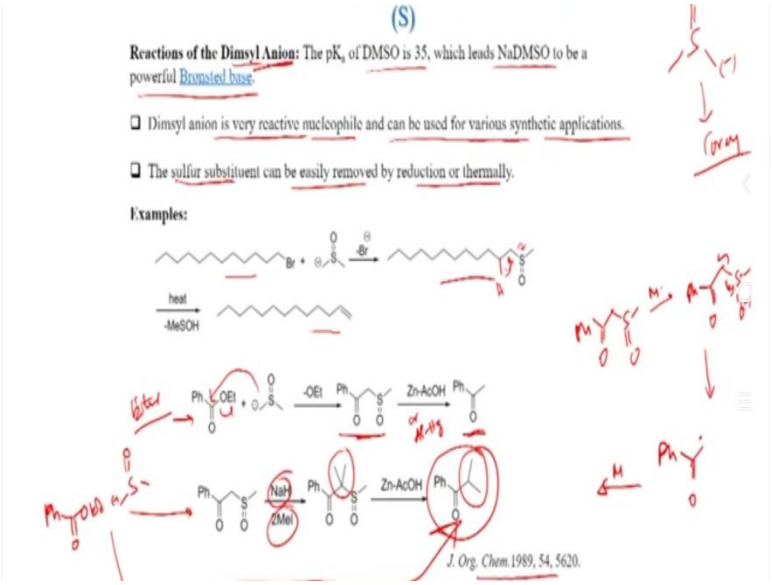

Now lastly we will see, reactions of Dimsyl anion. So this is the anion of DMSO and this was first discovered by Corey. So the pK of DMSO is 35, which leads NaDMSO to be a powerful Bronsted base. Dimsyl anion is very reactive nucleophile and can be used for various synthetic applications. The sulfur substituent can be easily removed by reduction or thermally. Examples, like here, long chain aliphatic bromide with treated with this one, dimsyl anion.

You get this, sulfoxide and after heating you get this elimination. You get the elimination and you get a double bond. So this is a method to generate alkyl bromide to olefin with dimsyl anion. And if you react with an ester, so this is ester, ester what will happen. You get, first this reaction here and you get this intermediate and interestingly, if you put this intermediate in zinc acetic acid or aluminium mercury also, this reaction will happen. You get this ketone.

So, what will be the possible mechanism? Possible mechanism is that, first this metal will come here, gives an electron. So this we have already seen. O minus. Now this single electron will migrate to this carbon and other to this sulfur. You get this one, radical is formed here. And this radical is stable because this is alpha to the carbonyl. Now because this one is activated carbon, if you put sodium hydride and methyl iodide, you can put two methyl groups also, this is very interesting that you convert this to this with this. And now if you put 2 equivalent methyl iodide, you get this 2 methyl groups and after treatment with zinc acetic acid, you get this. So, you convert an ester to a carbonyl compound with a substitution. You bring an isopropyl group here. This was published in J.Org Chemistry, 1989.

So, today we have seen sulfur based reagents. First we have discussed Julia olefination. In Julia olefination, you have to react a sulfonyl compound with an aldehyde or ketone and then you have to add an electrophile so that the leaving group, generally the acetic anhydride, is added. And after sodium amalgam treatment, you can generate a trans-olefin. So, the mechanism is mostly radical process. Though radical can conformer possible but because of the steric repulsion, this alkyl groups or 2 subtituents will be trans to each other and you get the trans-olefin.

Now in the Julia variant, the benzothiazole motif also phenyl tetrazole motif, have been used. And the major difference is the Similes rearrangement will happen to give 5 membered ring formation, which collapses and after that, you get an olefin. And interesting thing that you don't need the alcohol activation. Like we have seen the acetal formation in Julia case, here the elimination happens. And 2-hydroxybenthiazole, sulfur dioxide and olefin will be your product. And in this case, because in the anti case this formation of this Smiles rearrangement will be sterically hindered because 2 groups come close in the cis-orientation, so they will feel a steric repulsion. But after rearrangement they become trans and that becomes more stable. So, that's why this products depending on the subtituents give either E or Z. Simply the aliphatic aldehydes we have seen the Z isomer major and if you put branching and if the alpha beta unsaturation is there then the trans isomer is formed.

Also, in one cases we have seen that depending on the potassium or lithium cases, you can get different products depending on the substitution also. So generally, Lithium favors trans-geometry product and potassium favors the Z-geometry products.

Then we have seen the Corey-Chaykovsky reactions. So in the Corey-Chaykovsky reaction, the hard nucleophile we have seen this, sulfonium ylide. And also, oxosulfonium ylide is a soft nucleophile. So, this cases we have seen in the alpha, beta-unsaturated cases. The hard nucleophile, the sulfonium ylide is reacting as a carbonyl carbon giving the epoxide. On the other hand, with oxosulfonium ylide you get the cyclopropanation.

Then we have seen the Lawesson reagent. Lawesson reagent and its method for the conversion of carbonyl compound to C=S. This method is very useful and different carbonyl compound can be converted to C double bond S form. Also, we have seen the Corey-Winter olefination. In Corey-Winter olefination, the diol has to be converted to olefin and the diol is treated with an phosphite and also activated C double bond S compound, generally phosgene or thiocarbonyldiimidazole is used and which gives the olefin. And this method is very stereoselective. The trans-diol gives the trans-olefin, the cis-diol give the cis-olefin.

Then, we have seen the thioactal formation. This method is very useful for converting aldehydes to carbonyl compound and that is the Corey-Seebach method. Also it is a useful method for the alkylation, that you can treat with different electrophile and you can get the different products.

And lastly, we have seen the Chugaev olefination. In the Chugaev olefination, a xanthate ester will be formed and which on the high temperature will gives the olefin. And in the dimsyl anion we have seen that this dimsyl anion is very effective base as well as nucleophile. Simple alkyl bromide, it can be treated with dimsyl anion, then the olefin wil be formed. And in the ester cases, we have seen that ester will give an intermediate which after zinc acetic acid treatment, it gives the substituted ketone. Also this alpha carbon can be alkylated so that more substitution can be brought to this ketone. Thank you.