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

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Lecture - 50
Zwiiterionic-Claisen Rearrangement, Overmann Rearrangement, Bamford-Stevens and Shapiro Reactions and Synthetic Applications

Hello and welcome you all to today's class. Last class we looked at some aspects of Claisen rearrangement.

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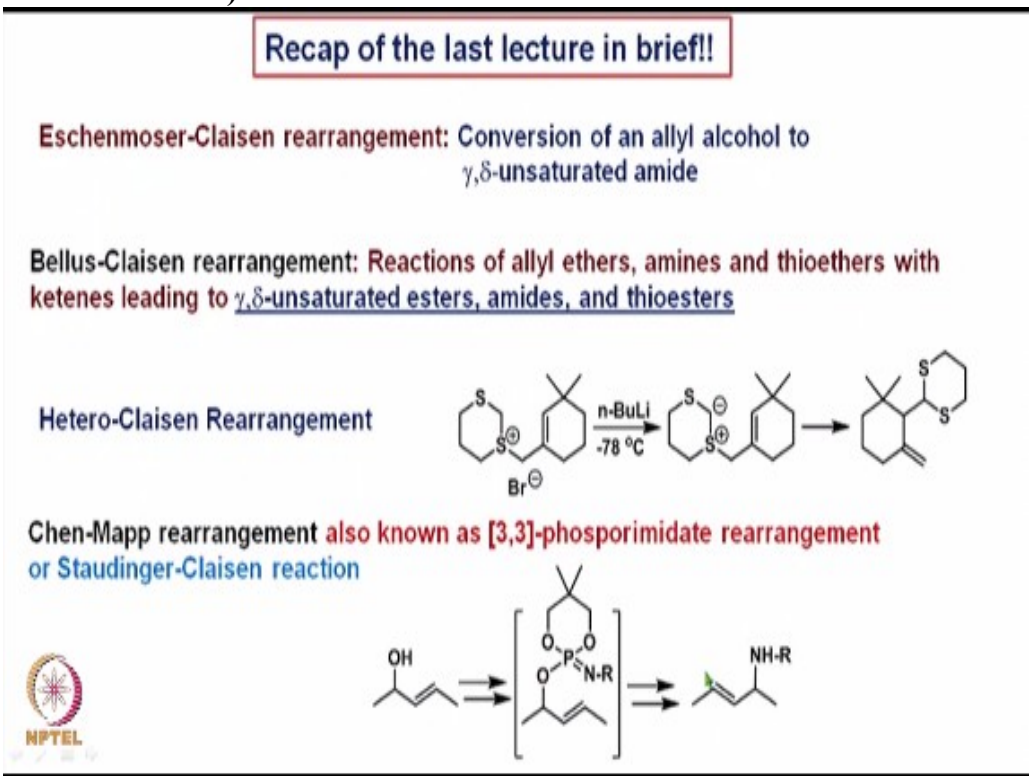

Particularly we looked at the Eschenmoser-Claisen rearrangement, which involve conversion of an allyl alcohol to gamma, delta unsaturated amide. We also looked at Bellus-Claisen rearrangement, where reactions of allyl ethers, allyl amines and allyl thioethers with ketenes were discussed, which led to the formation of the responding gamma, delta unsaturated esters, amides and thioesters respectively.

We also looked at Hetero-Claisen rearrangement both involving nitrogen and sulfur and also we saw some interesting reactions of thio base rearrangements like this, starting with a thio salt like this. If we treat this with butyllithium we generate this anion which undergoes an interesting rearrangement to cleave this carbon-sulfur bond and make this carbon- carbon bond to get this interesting thioketal based compound.

Finally we looked at Chen-Mapp rearrangement, which is also known as 3,3-phosporimidate rearrangement or Staudinger-Claisen reaction. This involves the rearrangement of this phosporimidate in 3,3-phosporimidate rearrangement, which is like a Claisen rearrangement in which we start with an allyl alcohol and form the corresponding allyl amine by the rearrangement of the double bond from here to here with the formation of a carbon-nitrogen bond here finally leading to the product like this.

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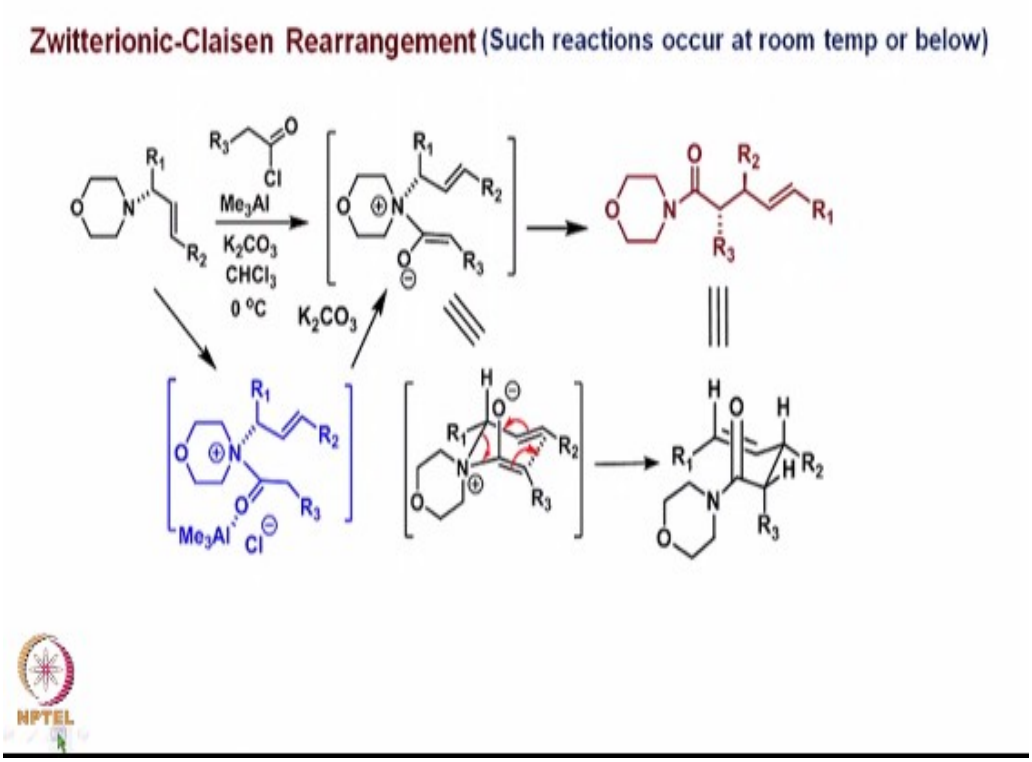

So today, we look at another rearrangement, which is called as Zwitterionic-Claisen rearrangement. And again, as we saw last time that when we did the ketene based reactions, the reactions took place at room temperature. And here also we will see that reactions take place at room temperature or below.

Thus for example, if we take an allyl amine of this kind and react with an acid halide like this, in the presence of a Lewis acid like trimethyl aluminum and of course potassium carbonate as a base in chloroform at zero degrees what is formed eventually is this particular kind of product.

Now what is believed that this particular allyl amine interacts with the acid halide in this particular fashion, because there is a nitrogen-carbon bond formation between this nitrogen and this carbon to lead to such an intermediate where the Lewis acid is interacting with the oxygen. Then, we of course can expect under basic conditions to form the corresponding enolate of this kind, which can be written up in this particular fashion.

And of course, this transition state which is a six member transition state then allows a rearrangement of Claisen type and since it is all along involving a Zwitterion, therefore it is called as Zwitterionic-Claisen rearrangement. And this rearrangement leads to the formation of this particular product here, which can be written up in this particular fashion.

Now depending on different kinds of substitutions and the number of substitutions one can get different kinds of products. Like in this particular case, we have started with this particular double bond being trans. And therefore, we have got a product of this kind which is an anti product. But one can take different kinds of substitutions and get different kinds of products syn or anti and variously substituted.

So this is a variation of the ketene based reaction. Of course, you can put as many substituents as they are allowed.

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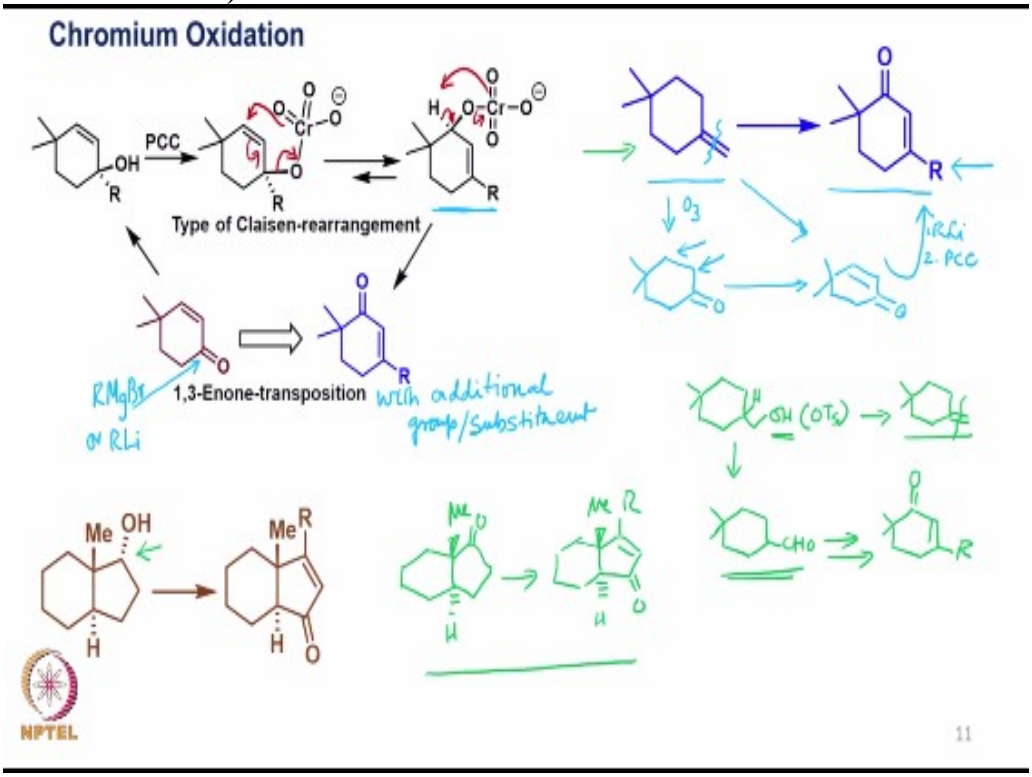

Now we have another reaction, which is chromium trioxide based reaction which is somewhat similar to what we have earlier discussed is a kind of is a type of Claisen rearrangement as you can see, that one can expect this thing to happen in this way. And of course, once this happens, then you can expect the oxidation to take place and something that we have already discussed earlier.

Now this is something that one can think about as an enone transposition. That means, if we take a substrate of this kind here and react it with RMgBr or RLi, then we can expect the R group to attack and form the corresponding tertiary alcohol which when reacts with pyridinium chlorochromate this is what is going to be intermediate. And that undergoes as you can see it is a kind of Claisen type rearrangement.

And then of course, you can get this intermediate which of course, undergoes oxidation to form this. So this is 1,3-enone transposition with an additional group, with additional group attached at the position where the carbonyl group with additional group or substituent. So this kind of reaction can be made use of it.

Say for example, if in the examination or as an home assignment, if I gave a transformation to be carried out like this to this, then we have to think about it that how are we going to go. There can be of course several ways by which one can think about it. But one of the ways that one can anticipate that is that if in case we are in a position to cleave this, because we have to bring here a double bond and of course an R group here.

So R group can easily come if we can convert this into the corresponding ketone by cleaving. So suppose if you do ozonolysis here and cleave it here, so you can get the corresponding ketone. And now if we add here RLi or RMgBr and of course this is a symmetrical molecule. So it does not matter, there are two methylene groups here, two methylene groups here. So it does not really matter which direction the elimination goes.

But what we would get is we can attach the R group here, get the corresponding tertiary alcohol here, and then we can do the dehydration. But we will not get extra double bond here and also how do we get the corresponding carbonyl group here. So this is something, is something it is an exercise that is important to look at it.

However, we if we can convert this particular ketone, which is a symmetrical ketone, so if we are in a position to convert this into something like this, which we have already studied earlier, that we can convert a ketone into an alpha, beta unsaturated ketone by using sulfur based chemistry or even by selenium based chemistry.

So we can introduce sulfur here or this particular position or selenium, make sulfoxide or selenoxide and then we can bring the corresponding double bond here. The moment double bond is brought in here that means there has to be a thought process that allows you to think that okay, I will convert this into this. If I convert into this into this, then of course, I can easily convert this into this by following that chromium based oxidation.

So you have here RLi followed by say PCC based oxidation. So this is how the 1,3-enone transposition can be carried out. So what it simply means, that from your home assignments and later on from the examination point of view, one can give different types of starting materials.

For example, here instead of giving this double bond here, which becomes relatively easy to kind of anticipate that how the ketone will come, one can even think about putting here an OH here. So if OH is put here, then that means that one can convert this into the and the moment you start thinking about it, there could be many different ways by which you can do it.

However, if you convert this into O tosylate and do the elimination here, from this particular position, you get the double bond here. So you can convert this into the olefin and then you can carry it out. Alternatively of course, you can convert this into the corresponding aldehyde and then think alternative ways of converting this into the final product say for example, if we have something like this.

So it is not necessary that you have to stick to what has been specifically given, talked or discussed in this particular course. However, as long as the procedures are correct, there is no

problem. But I thought that we can start with this and convert directly into the olefin here, then cleave the ketone, then we go further.

In a similar fashion and start with this alcohol to the corresponding enone. It is very obvious that we take the corresponding ketone by oxidation of this particular alcohol here and once we get the corresponding alcohol, then once we get the corresponding ketone, then we are in a good shape to convert that into this particular intermediate or the product that we are anticipating here.

So it is just a kind of extension of how this rearrangement can be exploited in organic synthesis. Now we have another very interesting rearrangement, which is also related to the kind of Claisen rearrangement type.

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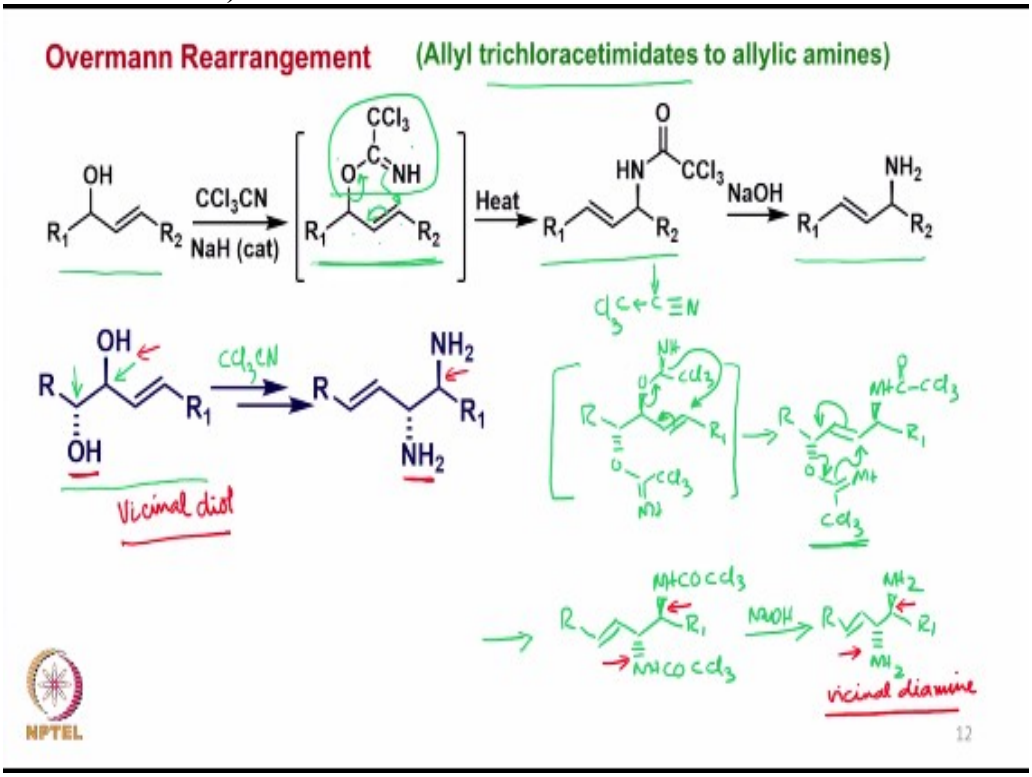

Is called Overmann rearrangement or allyl trichloracetimidates to allyl amines. So it is very similar to what we saw using Staudinger type of reaction or Chen-Mapp rearrangement where we have an allyl alcohol here and this allyl alcohol is converted to the corresponding allyl amine where the same situation is there in a inverted way that is rearranged way. The amine goes into the carbon where there is a double bond.

It is done in the presence of this trichloracetonitrile. This trichloracetonitrile is a very interesting molecule, which is somewhat like this and the three chlorine groups here pull electron density under this carbon and therefore from this carbon and therefore this carbon is fairly electrophilic. In the presence of a base like sodium hydride, when an anion is formed here, the anion attacks on to this triple bond and you form this what is called as a trichloracetimidate.

This is what is as acetimidate. This is imidate. It is a kind of trichloracetimidate. And now as you can see, you have 1, 2, 3 1, 2, 3, so you have a 3,3-sigmatotropic rearrangement taking place.

And this immediately undergoes rearrangement upon heating, and it forms this particular substrate which can be hydrolyzed and the amine can be formed.

So it is a very interesting reagent or the or a substrate which can be utilized in the synthesis of this molecule. Now I am showing an interesting example here, where we take say, for example a 1,2-diol and this 1,2-diol with defined stereochemistry here. If we treat this with trichloracetonitrile, so if we use more than two equivalents of trichloracetonitrile, so both the alcohols would get converted into the corresponding trichloracetimidate.

So we can think about having this substrate as one of the intermediates and then what we have is double bond here. And now the first reaction that will occur is obviously this one coming in here, this coming in here, and this coming in here. So that gives the first rearrangement, where we can write something like this. And then what will happen, we transform this into say you have NH-CO-C-Cl_3 and then you have an R1.

Now this has been particular allyl alcohol and there is a homo allyl alcohol. Now that has been converted into an ally amine. And also now it is an allyl alcohol, which is now in the form of trichloracetimidate. So this undergoes second rearrangement as you can see here. And of course, then we can expect that you have a product which is somewhat like this. This is CCl_3 $COCl_3$. It should be CCl_3.

So now if we hydrolyze it by means of sodium hydroxide or potassium hydroxide, one can get the corresponding. Now in this reaction as you can easily appreciate that the geometry of the OH group is converted to the corresponding amine, same is here. So in the final product that we get the geometry is reflected into the final product.

But except that the position of the hydroxy group has been changed and eventually the amine comes at a carbon which is on the other side of the double bond. So we get, we start with a vicinal diol which is a vicinal diol and we get the vicinal diamine, but with a stereochemistry is well defined. So this is an very interesting Overmann rearrangement which is extremely useful in organic synthesis.

Now we have something called as Bamford-Stevens and Shapiro reactions. Although they are not directly C-C bond forming reactions, but at the first look, but then they build a case to make C-C bond formation.

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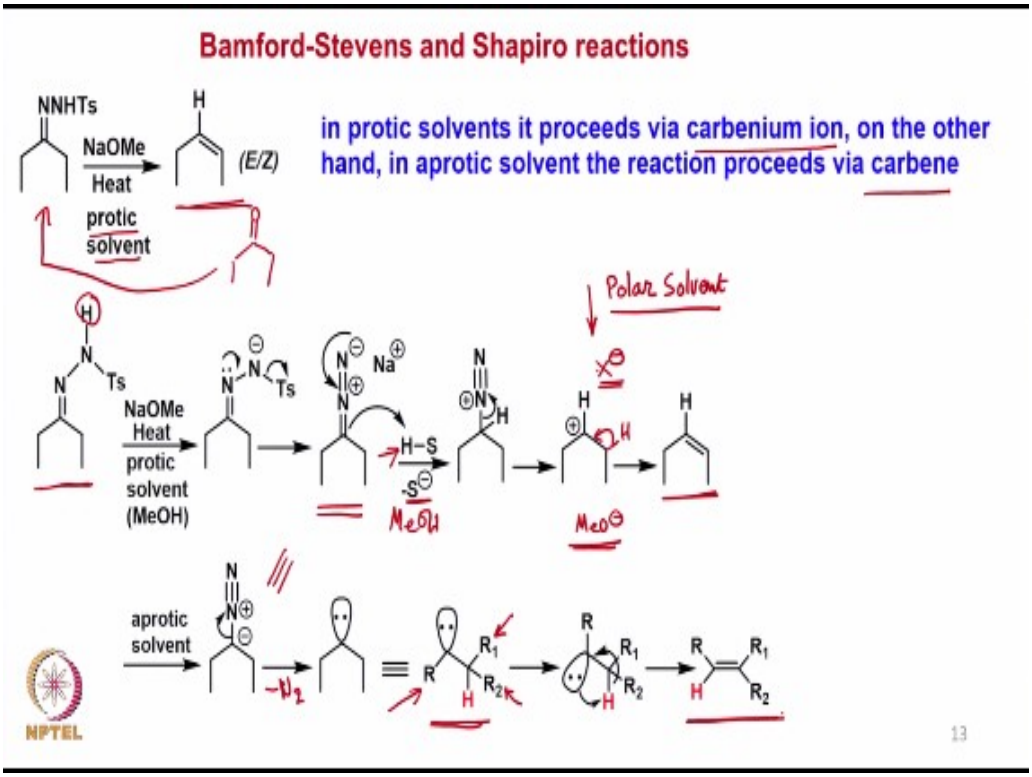

So for example, if you start with a ketone and convert that into a tosylhydrazone. So if we have a ketone of this kind and convert this into a tosylhydrazone and then treat with sodium methoxide and heat it in a protic solvent, then we get an olefin. Now in protic solvent it proceeds via carbenium ion. But on the other hand, if it is aprotic solvent, then what happens is it proceeds via a carbene reaction.

So let us see the mechanism how this happens. This is the tosylhydrazone. When it is treated with sodium methoxide and heated in a protic solvent like methanol, first there is a deprotonation of this hydrogen because that is directly attached to the nitrogen here.

And then there is a lone pair of electron pushing it and forming this kind of diazo species which then looses the negative charge from here, moves and takes the proton from the solvent, this solvent, H-S is actually a solvent. So you have a methanol, so methanol will give you a proton from here and methoxide will come here. And then once that happens, this loses from here and generates a positive charge.

Because this positive charge and of course, there will always be a negative charge here, whatever the negative charge is, that methoxide. For example, in this case it will be methoxide ion. So this positive charge or the charged species is possible because of the polar solvent. So the polar solvent allows the formation of this particularly charged species and then you have a loss of proton from here to form the corresponding olefin.

On the other hand, if it is a aprotic solvent, then what is proposed is that this particular intermediate then breaks directly from here and since there is a negative charge at this particular part, that means the moment this particular diazo compound comes in, this can be written up in this fashion.

And therefore, at this stage when this nitrogen is lost, so instead of this negative charge, taking up a proton from the protic solvent, since protic solvent is not present here, this particular carbon-nitrogen bond breaks and then you loose nitrogen from here and then you generate a carbene. And then this carbene could be written up in this fashion with proper substituents around here, here like this.

And then there is a migration of the hydrogen and eventually forming a double bond like this. So these are two different Bamford-Stevens reactions, which are essentially done in two different solvents and they give the olefins. And the geometry of the olefin also is somewhat influenced by which path the reaction proceeds. Now of course, in these cases the thermodynamically more stable products generally form.

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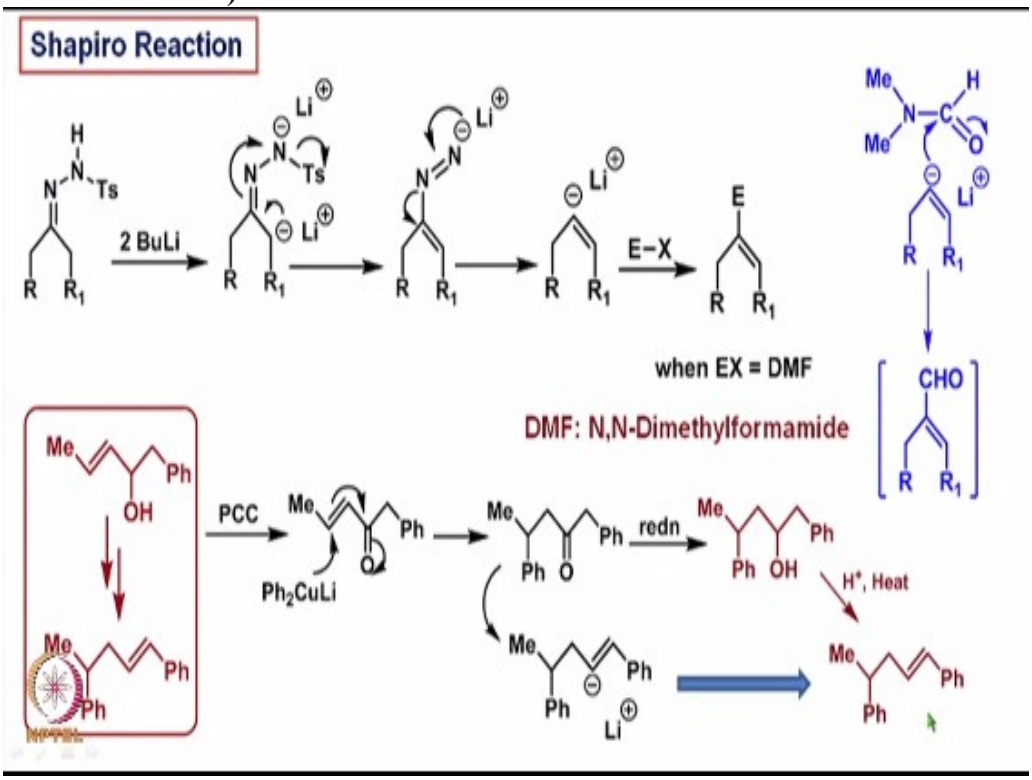

Now what is Shapiro reaction? The Shapiro reaction is an extension of Bamford-Stevens reaction, which is done in a solvent like THF or ether and you use two equivalents of butyllithium. Now if we take a tosylhydrazone of this type and use two equivalents of butyllithium, we expect to form a dianion of this kind, because the butyllithium will deprotonate this NH proton here.

And also deprotonate the hydrogen which is here to form this kind of dianion, which will then allow the removal of the tosylate by the formation of this carbon-nitrogen double bond and movement of this double bond to this particular part of the molecule where N double bond N is formed. Now this particular anion can undergo expulsion of nitrogen to form this vinyl lithium.

And this vinyl lithium can react with the different kinds of electrophiles to form this kind of vinylated product. If EX happens to be dimethylformamide of this kind, which is also known as

NN dimethylformamide, then the anion can react onto this carbonyl carbon and expel eventually this dimethyl amino part to form the corresponding vinyl aldehyde. Now this is what is Shapiro reaction.

So basically starting with a tosylhydrazone we can generate a vinyl anion and then introduce any electrophile that we want to react with. How do we make use of it in a conversion like this? For example, if you take this allyl alcohol and we want to convert into this particular olefin then how do we go about it? One of the ways is of course, is to oxidize this alcohol to the corresponding ketone, which is now an alpha beta unsaturated ketone.

And since, at the end of the double bond, we have a phenyl group here for example, therefore we can react it with lithium diphenylcuprate, which will allow a Michael addition of the phenyl part to get this particular product which can be reduced to the corresponding alcohol and this alcohol under acidic condition should undergo dehydration to form this double bond on this side, because this is conjugated with the phenyl ring.

Of course, one can expect the double bond to be formed on this side, but major product should form on this side. So from this ketone, one can get to this particular olefin in two steps, the reduction followed by dehydration. Other possibilities by using Shapiro reaction.

So if we take this ketone and make the corresponding tosylhydrazone and then react with two equivalents of butyllithium, then since this proton which is benzylic as well as alpha to the carbonyl group, therefore this side deprotonation will occur and eventually we would get vinyl lithium of this kind, which can then simply by protonation lead to the formation of this type of olefin in the target molecule.

So this is how these reactions occur. So we will stop it here today and take up the other aspects of such reactions where C-C bond formation occur and therefore, we will take those other examples in the next class. Till then take care and bye.