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

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Lecture - 48

Aromatic Claisen rearrangement, Johnson-Claisen Rearrangement and Eschenmoser-Claisen Rearrangement and Synthetic Applications

Hello everyone, I would like to welcome you all to today's class. In the last class that we discussed various aspects of the Ireland-Claisen Rearrangement, where the geometry of the enolates played a very important role. Of course, the geometry of the enolates plays a very important role otherwise also, that we saw in the Evans oxazolidinone case and other cases.

Here in the Ireland-Claisen Rearrangement how the formation of the enolates is affected by the solvent that we discussed in detail.

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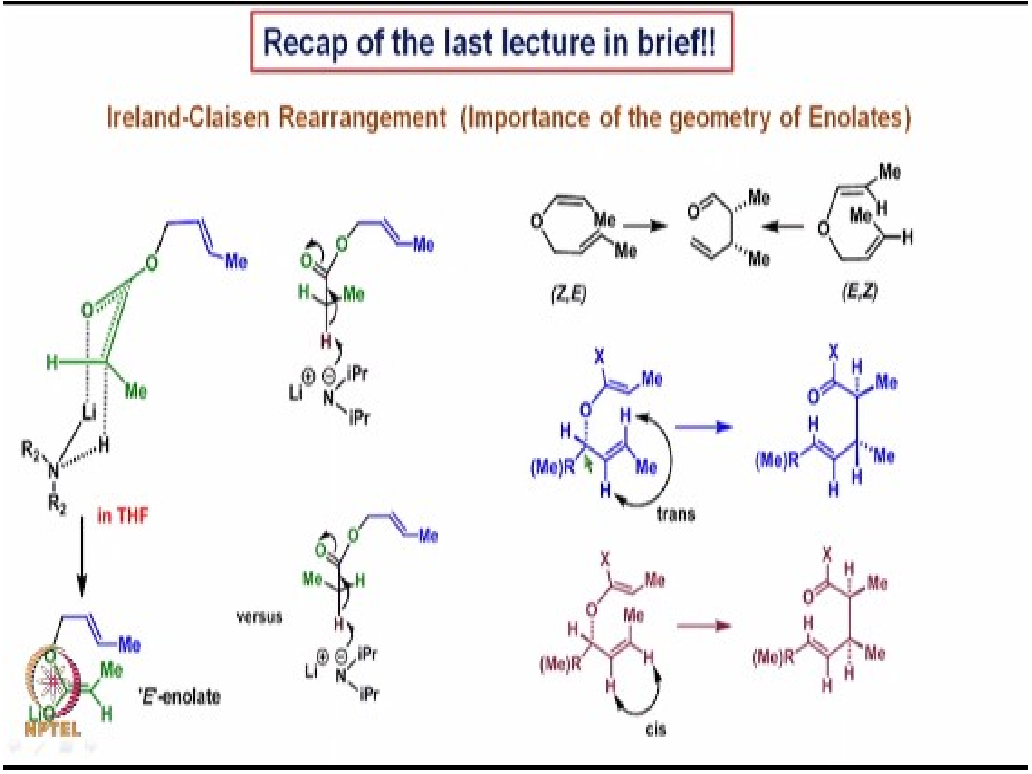

Recap of the last lecture in brief!!

Ireland-Claisen Rearrangement (Importance of the geometry of Enolates)

And of course we saw that in Ireland-Claisen Rearrangement, the geometry of the enolates depends on the transition state that we invoke. Now if we see the transition state in THF solvent, then we invoked the chelation between the oxygen and the lithium of LDA.

And we saw that in order to avoid the interaction between this R2 group and large group at this particular center, the transition state which is favoured would have the smaller group on this side that is the hydrogen on this side. And that is to the deprotonation of this hydrogen, which then leads to the formation of an enolate in which this methyl group and the enolate are trans to each other or this is an E enolate that is formed.

But in THF HMPA combination, this chelation is not possible, because the HMPA removes this chelation and then the deprotonation of this starting material occurs in such a fashion that the large group, the methyl group here in this particular case is away from this large group. So this arrangement here is not feasible for the deprotonation because methyl and the large group are on the same side.

On the other hand, in this particular arrangement, the methyl group and this large group are away from each other and therefore deprotonation of this particular hydrogen leads to the enolate to be formed in which the methyl group and the enolate part are actually Z to each other. So therefore this particular deprotonation in THF HMPA gives Z enolate. Whereas, deprotonation in THF gives E enolate.

Then we also look at the Claisen rearrangement of these two types and some other types. For example in this case, if the geometry of the double bonds are different from each other, that means this is Z and E and this is E and Z. And they give the same product in which the relative stereochemistry remains the same. Now we also looked at two more examples in which the double bond geometry was changed.

For example, here it is trans and here it is cis. And there is an asymmetric center which is present and these molecules are chiral. So when this rearrangement is done, we get the products which are having different stereochemistry at these two centers. Like for example, here they are trans to each other and here they are cis to each other or they are anti to each other, here syn to each other.

And the molecules are chiral because starting material is chiral. So we now look at some other aspects of the Claisen rearrangement.

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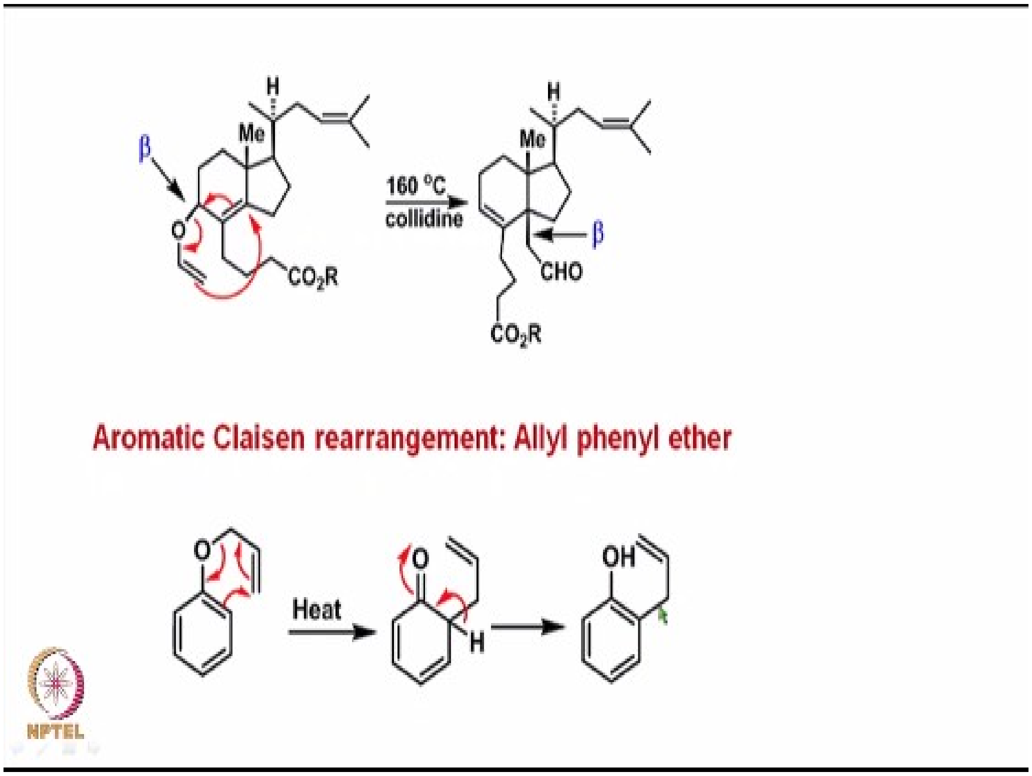
Aromatic Claisen rearrangement: Allyl phenyl ether

For example, if we do not use the high this Lewis acids or such kind of hydrogen bonding aided solvents, then of course, we need very high temperature for the Claisen rearrangement to occur.

For example, if we start with ally vinyl ether of this kind, in which this carbon-oxygen bond is beta oriented and heat the reaction mixture at 160 degrees in collidine, then what we get is this particular type of product in which as we can see, that the newly formed carbon-carbon bond is also beta oriented because this carbon-oxygen bond was beta oriented. Now it means that the chirality here has been transformed to the corresponding C-C bond here.

Now if we take aromatic Claisen rearrangement what we discussed earlier for allyl phenyl ether type of molecules then we can write the mechanism in this particular fashion in which this particular allyl phenyl ether upon heating would form an intermediate or this particular kind in and where the regaining of the aromaticity is accompanied by the formation of the corresponding phenol.

Now from the starting material as you can see that there is a new C-C bond formed at the ortho position.

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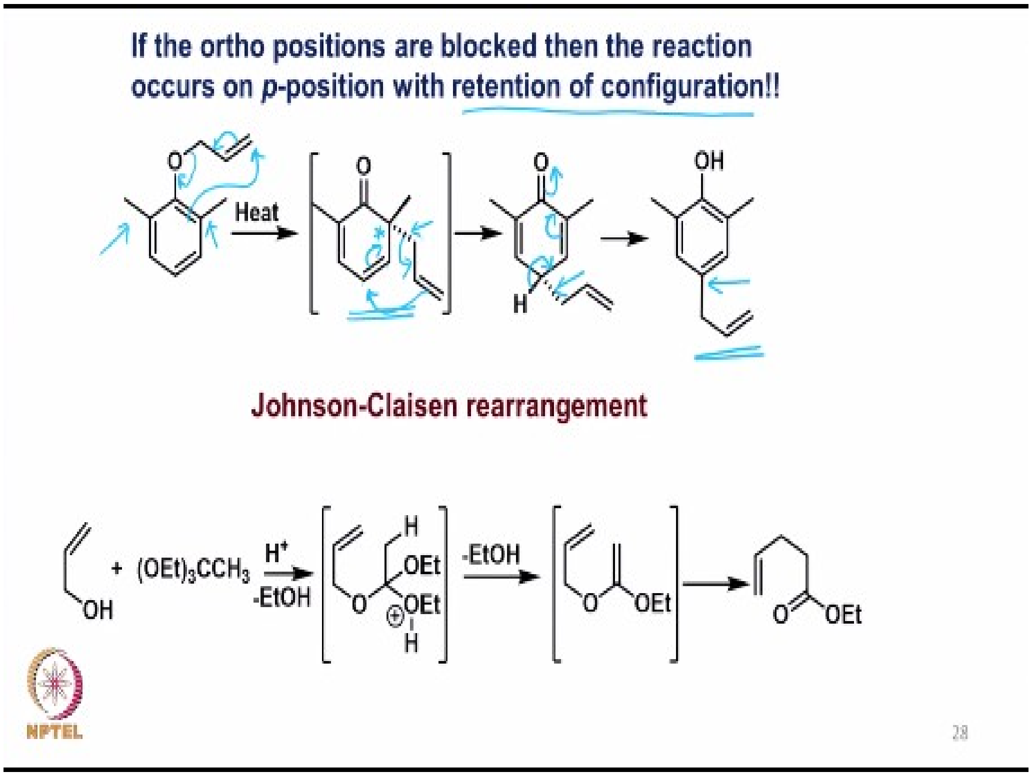

If the ortho positions are blocked then the reaction occurs on *p*-position with retention of configuration!!

Johnson-Claisen rearrangement

Now if the starting allyl phenyl ether is somewhat differently substituted, for example the ortho position are blocked, in that case for example here if they are blocked, then one can expect that the when the heating is done, the substituent goes into the para position as you can see here. But it proceeds via two types of reactions.

One is of course the Claisen rearrangement where we can say that okay, now this is what is happening here. And then you generate a species like this. Now here for the sake of clarity, it is written that this particular bond is alpha oriented. But it really does not matter. But supposing if the product does form there, this asymmetric center here has alpha orientation of the allyl group, then it is understood that since it is a now it is a Cope rearrangement.

So you have 1, 2, 3, 4, 5, 6. So it is also a kind of concerted reaction. And therefore, this undergoes a 3,3 sigmatropic rearrangement and there is a retention of configuration here. That is what is being said here. Although you cannot really see it in this particular case easily because this will be immediately regaining the aromaticity leading to this particular product.

But it implies that when we say retention of configuration means that the first asymmetric center that is being created, if that has an particular orientation alpha or beta, then in the next Cope rearrangement it undergoes a kind of same with the same configuration and finally enolization leads to the aromatic product.

So this is how the Claisen rearrangement the original aromatic ally phenyl ether based aromatic Claisen rearrangement occurs.

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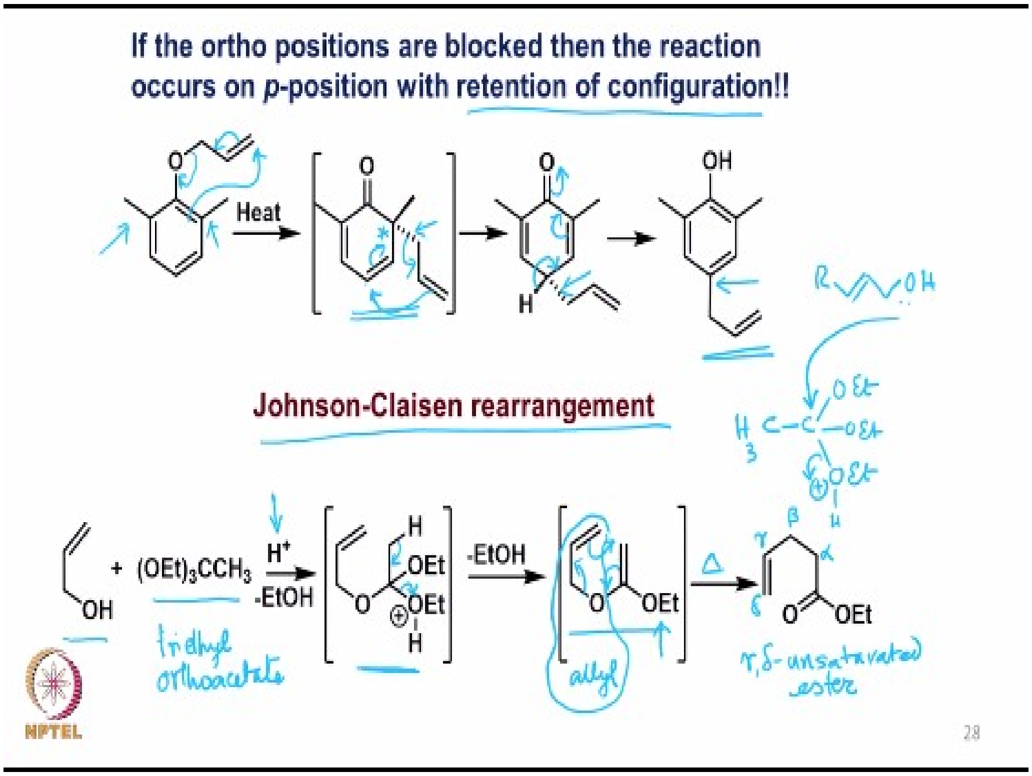

If the ortho positions are blocked then the reaction occurs on *p*-position with retention of configuration!!

Johnson-Claisen rearrangement

Very interesting Johnson-Claisen rearrangement which is very useful from various angles is like if you start with an allyl alcohol and if you react with this triethyl orthoacetate, this triethyl orthoacetate. So essentially it is something like this. What you have is 3-ethyl ethoxy groups are attached to this and in the presence of a protic acid as a catalyst at a high temperature you react it.

Then allyl alcohol basically reacts. So if you have something like this here, then this alcohol attacks because you get protonation of this particular one of the species here and this goes off and then it will form the intermediate of this kind, which of course will lose proton from here like this. And then you get a ethanol loss. The two ethanols are lost and then what we get is a this allyl like this kind of situation comes in.

So this part is the allyl part of it. And of course the other part is the vinyl ether part. But it is coming from a substrate in which you have an extra ethoxy group here, ROR group here. And when the reaction occurs in the Claisen rearrangement fashion in this way, then what you get is alpha, beta, gamma, delta. So you get gamma delta unsaturated ester.

You start with an allyl alcohol, you add triethyl orthoacetate in the presence of an H+, then you get an intermediate of this kind, which of course, can be prepared in this way by some other means also, but it is an easy way. And of course you heat it, then what you get is a gamma delta unsaturated ester. Now there are very many applications of such kind of substrates in the literature and a couple of them we will try and look at it.

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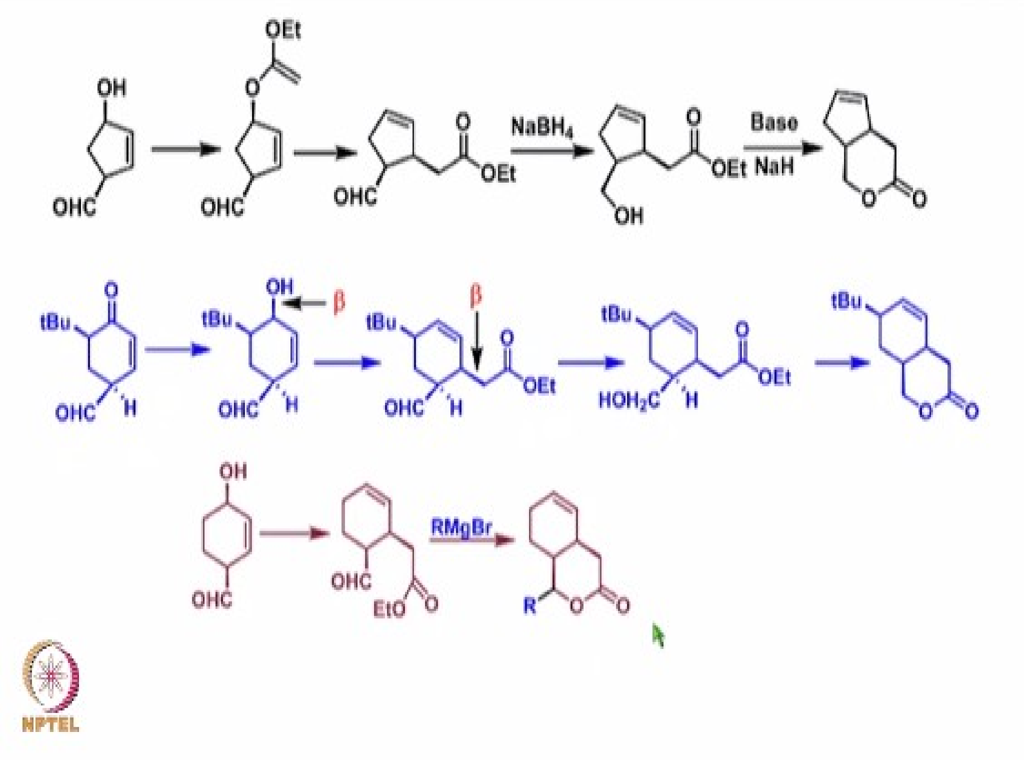

For example, if you start with a substrate like this and allow it to react under the Johnson-Claisen rearrangement type of conditions, then we expect this type of intermediate to form first, which will undergo Claisen rearrangement to lead to the formation of this gamma delta unsaturated ester. This is alpha, this is beta, this is gamma, this is delta.

And the stereochemistry which is shown in the starting material, this carbon hydroxy bond being beta leads to the formation of this carbon-carbon bond also in the beta orientation. Now reduction of this particular aldehyde with sodium borohydride leads to the formation of this primary alcohol which upon treatment with a base allows lactonization to take place and form this kind of bicyclic lactone molecule.

Now similarly, if we take this type of substrate in which there is an aldehyde group and an enone moiety and reduce under Luche reduction conditions, so that the known is reduced in preference to aldehyde to form this type of allyl alcohol. And this allyl alcohol upon treatment with conditions of Johnson-Claisen type will lead to the formation of this gamma delta unsaturated ester.

Again one can see that the carbon hydroxy stereochemistry here was beta oriented and the same one is now here this carbon-carbon bond is also beta oriented. Once again we can reduce the aldehyde to the corresponding alcohol and then allow the lactonization to take place in a similar fashion as we did it here to form a bicyclic lactone molecule like this.

And the third example illustrates that if we take a allyl alcohol of this kind and treat the molecule under Johnson-Claisen type of rearrangement conditions, then we get this gamma delta unsaturated ester. Now instead of reducing the aldehyde if we react with say a Grignard reagent like our RMgBr then of course that will first react with the aldehyde because aldehyde is more electrophilic than the ester.

And then the corresponding secondary alcohol will undergo cyclization to form this type of substituted bicyclic lactone.

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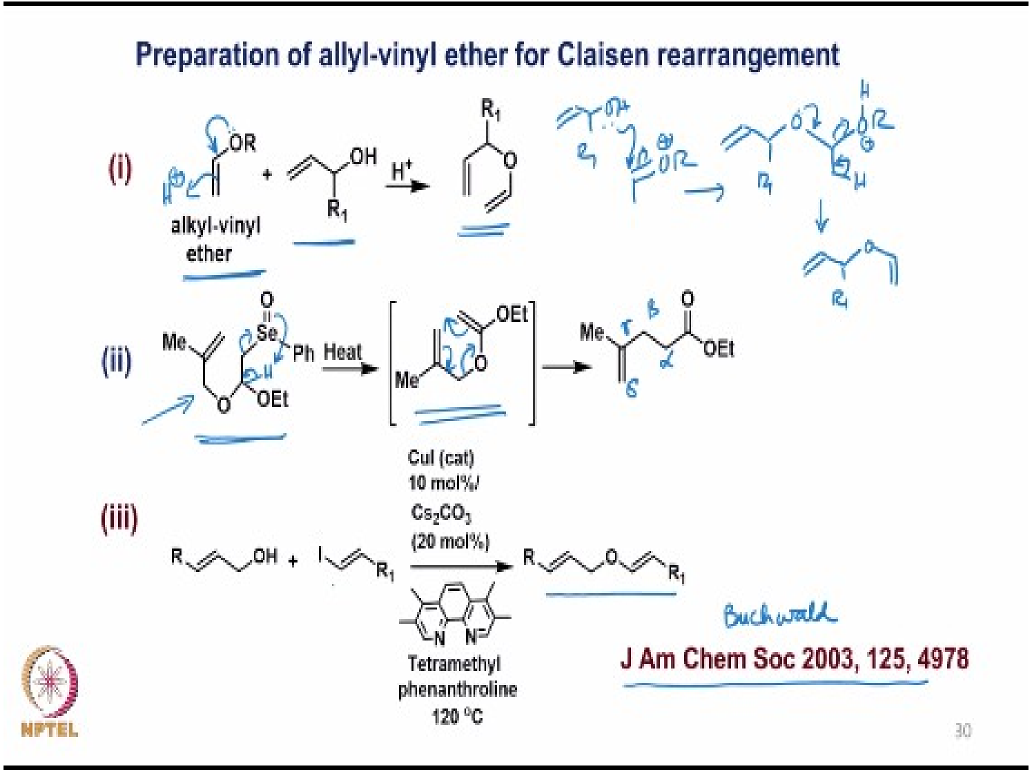

Preparation of allyl-vinyl ether for Claisen rearrangement

J Am Chem Soc 2003, 125, 4978

Now we look at how are these allyl vinyl ether for Claisen rearrangement are actually made. So there are the different methods by which allyl vinyl ethers are made. For example, of course we are talking about allyl vinyl ethers for Claisen rearrangement not for the just Johnson-Claisen rearrangement. For example here if we take a alkyl vinyl ether something like this, here like this.

And if you react with allyl alcohol in presence of H+ as one can anticipate very easily that the protonation of the double bond would occur first with H+ being here. And then of course, the lone pair of electron is going to push the electron density here to form an intermediate of this type. And of course, the allyl alcohol will then add on to add on to this and it would allow R1 to attack it here.

Then we have, that means alcohol will attack on to this and you get OR here and of course methyl group here. And this then under acidic condition, again this gets protonated here and of course this can push this out and eventually this will push it out and then what you will get is allyl vinyl ether. This is what is this. Of course in this case this is also going to push it and again that it will deprotonate and finish it off.

The other possibility is that were the Johnson-Claisen rearrangement type of substrate can be obtained is somewhat like this where you can have a kind of selenoxide type of compound to be prepared. In fact, this is a very good home assignment for all of you that you can try and see how you can make this small molecule which is kind of very useful because of you, the moment you do this selenoxide elimination here there is a hydrogen here.

So 1, 2, 3, 4, 5 we have discussed this kind of thing, where you can anticipate that this comes in here, this comes in here, and this goes off. And you get this intermediate. Now this is the same intermediate which Johnson-Claisen rearrangement case it is and therefore you can anticipate that this kind of rearrangement will take place. And therefore, you have alpha, beta, gamma and delta unsaturated system.

Now there is another way of making allyl vinyl ether, which is somewhat more recent is by Buchwald here who has evolved this particular method, where he uses the allyl alcohol with vinyl iodide in the presence of cuprous iodide and cesium carbonate and in the at 120 degrees with phenanthroline. So now this is an interesting reaction. How does this reaction occur is something that we need to look at it little more carefully.

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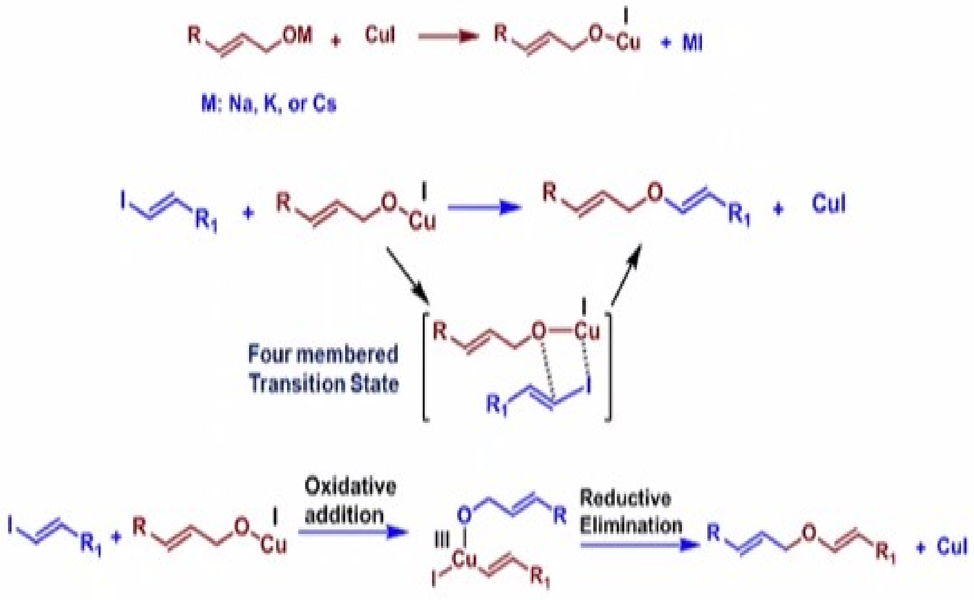

Tetrahedron 1992, 48, 2681-2690

So if we start looking at this way that if we start with a salt of allyl alcohol like this in which M is sodium, potassium or cesium, depending on the kind of base that we start with and reacted with cuprous iodide then we expect to form this kind of copper I species. And now this copper I species reacts with vinyl iodide via this kind of four member transition state in which now we form a new oxygen-carbon bond and thus copper iodide that is the cuprous iodide then gets released.

And this cuprous iodide then acts as a catalyst to continue the reaction in this particular fashion. Alternatively, what has been proposed that this copper I species which is formed here, reacts with vinyl iodide in such a fashion that there is first a oxidative addition that takes place to form this copper III species and which undergoes reductive elimination of cuprous iodide and release the allyl vinyl ether.

This kind of mechanistic considerations have been discussed in detail in this particular journal Tetrahedron 1992.

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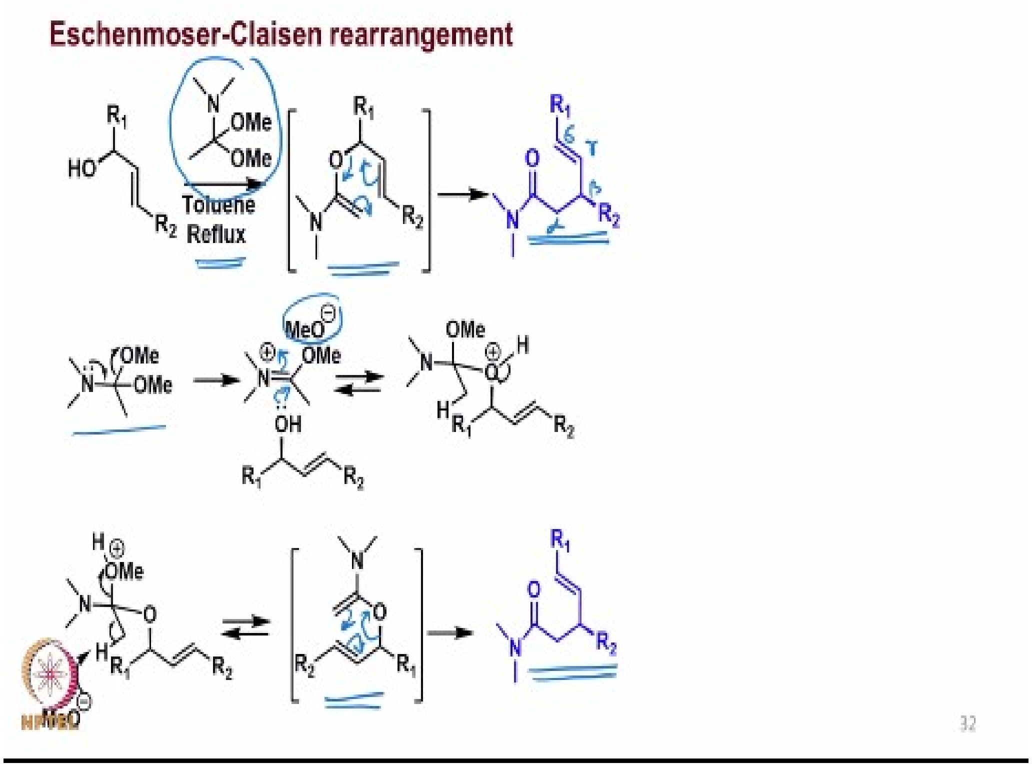

Eschenmoser-Claisen rearrangement

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So in addition to this, there is another rearrangement, which is known as Eschenmoser-Claisen rearrangement, and that involves reaction of the allyl alcohol like this with species of this kind, which upon heating forms disintermediate and this is also having a similar orientation of the double bonds.

So this of course, goes in this way to form this intermediate, which is again like alpha, beta, gamma, delta unsaturated amide type of system. So how does this form and then further aspects of it we will discuss it in the next time, but right now how does it form?

If this is your starting material where there are two dimethoxy methyl and NN dimethyl, they upon heating they breakoff to form this intermediate which then reacts with this ionic species to form this particular intermediate from where the proton is lost. And of course, the methoxide ion which is come out from here then takes up the proton in this fashion and methanol is lost of course.

And then this is how the reaction then leads to the formation of this intermediate which is similar to this intermediate. And this intermediate then undergoes kind of Claisen rearrangement or we can put the orientation in a slightly different way. And then we can say that the reaction occurs to form this particular product. So this is what is called as Eschenmoser-Claisen rearrangement.

It has been modified by Eschenmoser. And then we will look at some other aspects of the Claisen rearrangement and related reactions next time. Till then you can look at whatever I have discussed it today. And if you have any questions then of course you can keep that in mind and then post it to me when the course is being run. And till then take care and bye. Thank you.