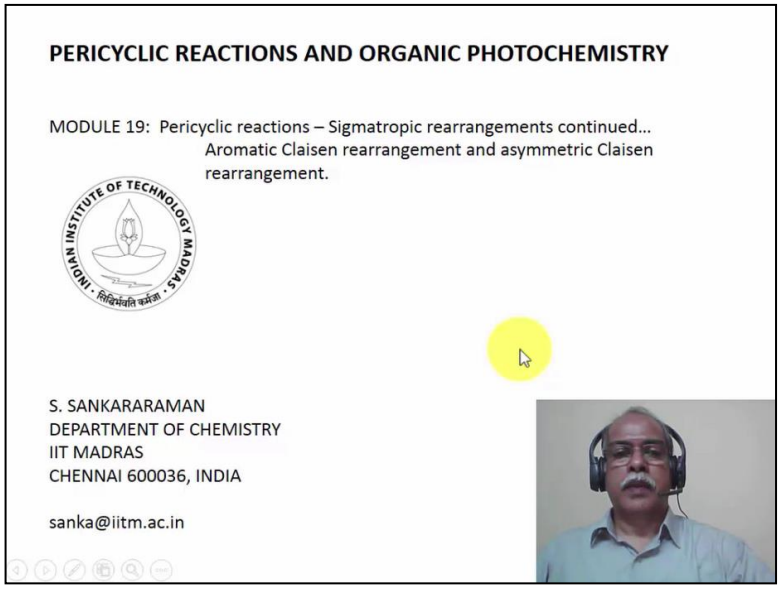
Pericyclic Reactions and Organic Photochemistry

S. Sankararaman
Department of Chemistry
Indian Institute of Technology, Madras

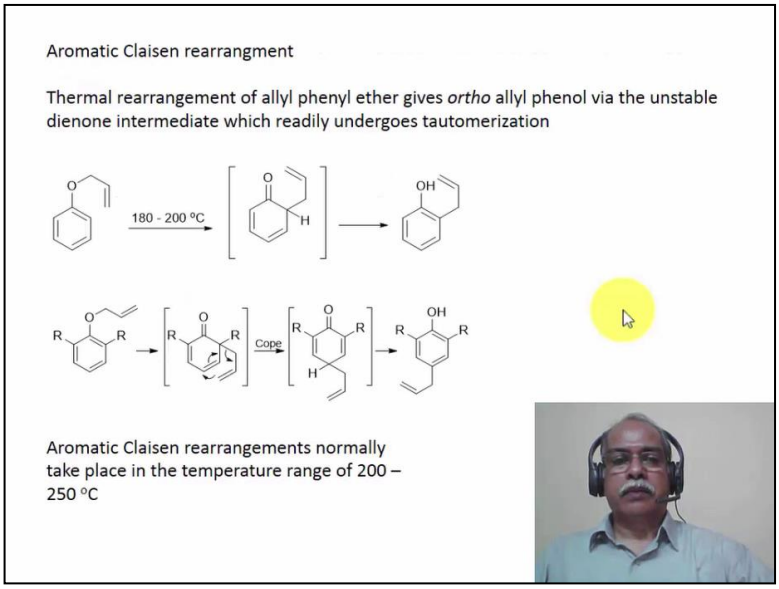
Module No. #04
Lecture No. #19
Pericyclic Reactions – Sigmatropic rearrangements continued…
Aromatic Claisen rearrangement and Asymmetric Claisen rearrangement.

(Refer Slide Time: 00:11)



Hello, welcome to Module Nineteen. This is on the course on, Pericyclic Reaction and Organic Photochemistry. We will continue with the Sigmatropic rearrangement. In this module, we have some portions left, which are the Aromatic Claisen rearrangement, and Asymmetric Claisen rearrangement, in the portions of Sigmatropic rearrangement.

(Refer Slide Time: 00:30)



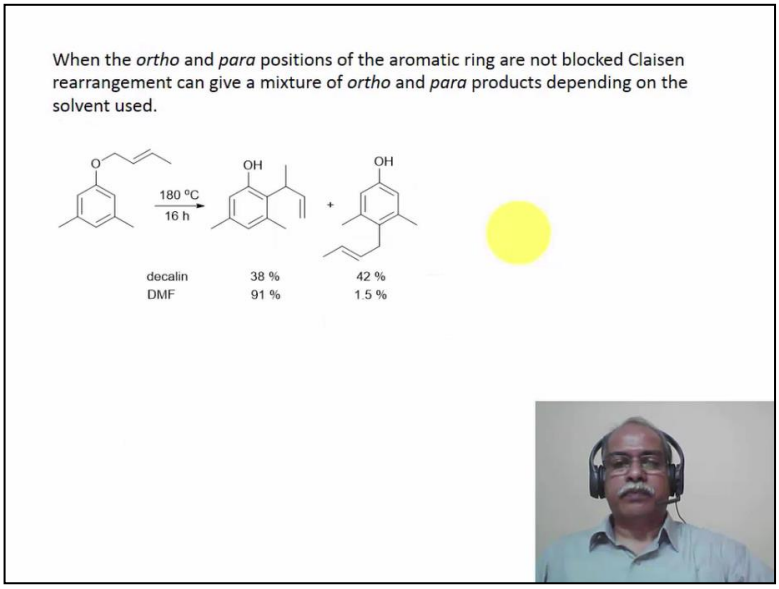
Now, an Aromatic Claisen rearrangement is nothing but, the Allyl Ether of Phenol, undergoing a rearrangement, to give Ortho Allyl Phenol as the product. This is a thermal rearrangement. This is a [3,3]-Sigmatropic rearrangement. If you consider, this Carbon-Oxygen bond to be broken, then it is 1-2-3-1-2-3. So, the Ortho position of the Phenolic group, and the terminal position of the Allyl group, are joined together in a CC bond forming reaction, forming an intermediate, which is this Ketone.

The intermediate is Ketone, does not survive under the reaction condition. It readily undergoes Keto-Enol-Tautomerism, to give the corresponding Phenolic product, which is Ortho Allyl Phenol, in this particular case. When the Ortho positions are blocked by Methyl group, or some substituent groups, that are present in the Ortho position, in the [2,6] position, for example, this could be simply [2,6]-Dimethylphenyl Allyl Ether.

Initially, it undergoes the Claisen rearrangement, to give the Ortho Alkyl Allyl substituted derivative. Since, there is no Hydrogen here, this cannot undergo the Keto-Enol-Tautomerism to the corresponding Phenol. However, it can undergo further Cope rearrangement, under the reaction condition, to the Para position. In other words, the Allyl group is shifted to the Para position.

And, from the Para position, of course, you have a Hydrogen, which can undergo Keto-Enol-Tautomerism, to give the Para Allyl substituted Phenol. Suppose, if there is no Hydrogen in the Para position also, then the Dienone systems that are formed, are isolated as the product. Claisen rearrangement, the Aromatic Claisen rearrangement, normally take place in the temperature range of, 200 to 250 Celsius.

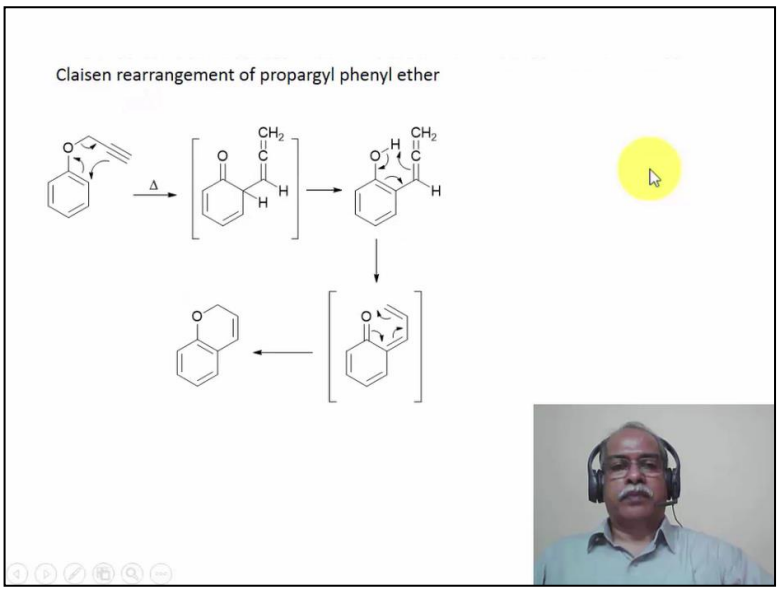
(Refer Slide Time: 02:08)



Now, in the case of the [3,5] Dimethyl Phenyl Allyl ether, case for example, the initial Claisen rearrangement gives the Ortho Allyl derivative. You can see here, this is a Carbon, that is connected to the Ortho position, with the Methyl substituent. And, that Methyl substituent appears here. Subsequently, further reaction leads to the, depends on the temperature, as well as the solvent polarity, in this particular case.

So, the rearrangement essentially can proceed, either through a [3,3]-Sigmatropic rearrangement, or a [3,5]-Sigmatropic kind of a rearrangement, which forms the Para substituted product, in this particular case. In Decalin, they are formed in nearly equal amount. Whereas, in DMF, the [3,3]-Sigmatropic rearrangement product is the major product, that is formed under the reaction condition.

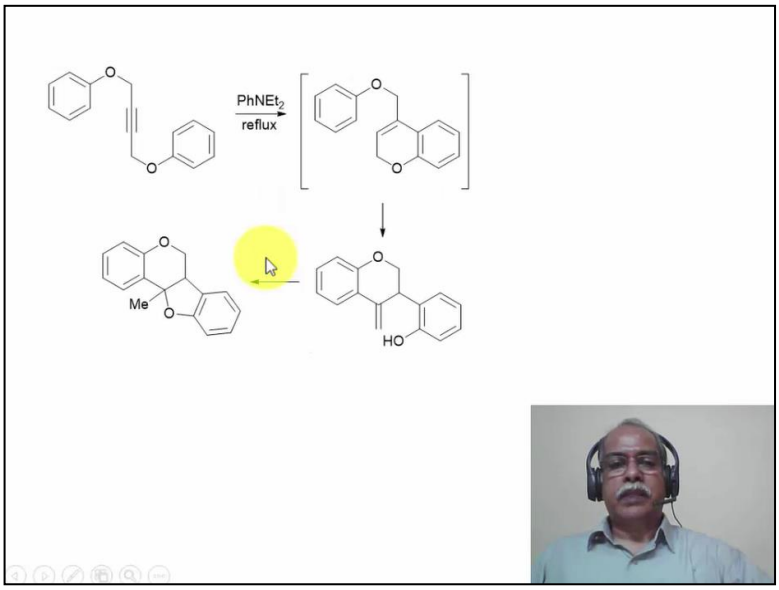
(Refer Slide Time: 02:58)



Now, instead of an Allyl derivative, if you take a Propargyl derivative, the Propargyl derivative also undergoes the Claisen rearrangement. In other words, this is Phenyl Propargyl ether, is what is undergoing the Claisen rearrangement. Initial rearrangement, essentially gives you this Ortho allenyl derivative. This is an Allene derivative. The Ortho Allenyl derivative, undergoes the Keto-Enol-Tautomerism, to give the Phenylallene kind of a, Ortho Hydroxy Phenylallene derivative, is what is formed in this particular case.

This does not survive the reaction condition. It undergoes a Hydrogen transfer. In other words, this is a [1,5]-Hydrogen shift, is what is taking place, to generate the intermediate, which is shown here, for example. This intermediate, essentially undergoes cyclisation, to give this Chromene derivative, which is the final product of the Propargyl Phenyl Ether rearrangement. So, this is one convenient way to synthesize, the Chromene derivatives of several kinds.

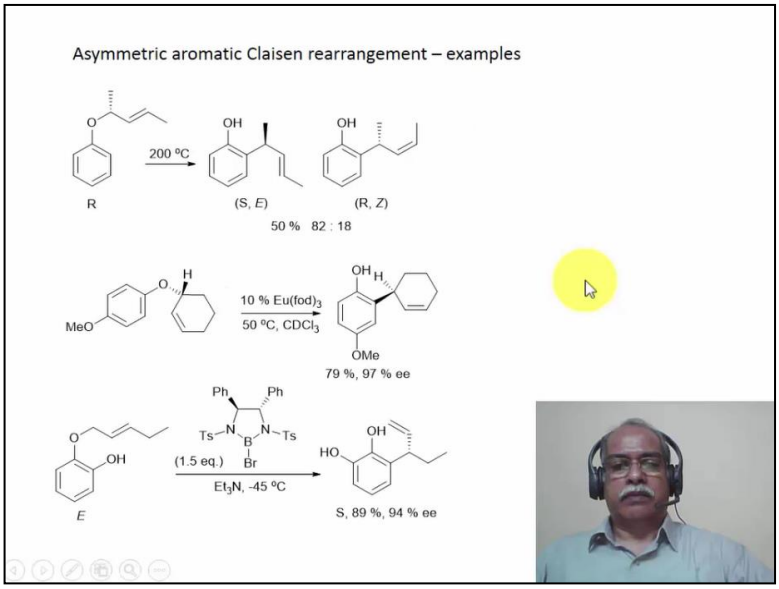
(Refer Slide Time: 03:56)



Suppose, if you take the Bis Phenyl Propargyl derivative, of this kind, when it is heated in Diethyl Aniline as the solvent, which is a high boiling solvent, the Chromene derivatives is initially formed. The Chromene derivative, is further set up for a [3,3]-Sigmatropic rearrangement, in this particular instance. This is essentially undergoing a [3,3]-Sigmatropic rearrangement, to give this particular product.

This product is now, it is undergoing an addition of a Hydroxy functional group, across this double bond in a Markovnikov fashion, to give the Benzopyran-Benzofuran fused system of this kind. So, it is an elegant way of synthesizing, a fairly complex heterocyclic, benzannulated heterocyclic derivative, of this kind.

(Refer Slide Time: 04:43)



Now, the Asymmetric Claisen rearrangement examples, are shown here. Remember, in the case of Claisen rearrangement, if we have a substituent in the Alpha position, or in the substituent in the double bond, it will create a Chiral center. And, the reaction is again proceeding through a 6-Membered cyclic transition state. So, there should be a high stereoselectivity for this reaction. When the pure R isomer, which is corresponding to this R isomer here, configuration here, with the E isomer of the double bond is taken, and heated to 200°.

The product formed are, these 2 products. The major product formed is the, S configurated isomer, with the E as the stereochemistry of the Vinyl group, that is being present here. The R substituted isomer, has the Z stereochemistry. This can be explained again, by the 6-Membered cyclic transition state. The reaction yield is not that great. It is only about 50%. But, the Diastereo selectivity is very good, in this case. 82% of the SE isomer, and 18% of the RZ isomer, is what is formed, from the RE isomer of the corresponding starting material.

Now, this is an experiment, probably that was done in an NMR tube. You can see here, $CDCL_3$ is used as a solvent, which is a typical NMR solvent. Europium FOD_3 is a shift reagent. This is essentially acting as a Lewis acidic reagent, in this particular case. So, catalytic amount of Europium FOD_3, FOD is a ligand, which is a Beta Diketonate ligand, is attached to the Europium center. So, it is a Beta Diketonate salt of the Europium, which is a Lewis acid, because Europium is in the 3+ oxidation state.

So, it probably coordinates with the Oxygen, and accelerates the reaction. The reaction is essentially, this is a Phenyl Allyl Ether. So, the Carbon-Carbon bond formation takes place, between this Carbon, which is Ortho Carbon, to this particular Carbon, which is the Allelic Terminal Carbon of the Allelic system. In the process, you can see here, this is a well-defined

stereochemistry of the starting material, resulting in the formation of a very well-defined stereochemistry, of only one enantiomer.

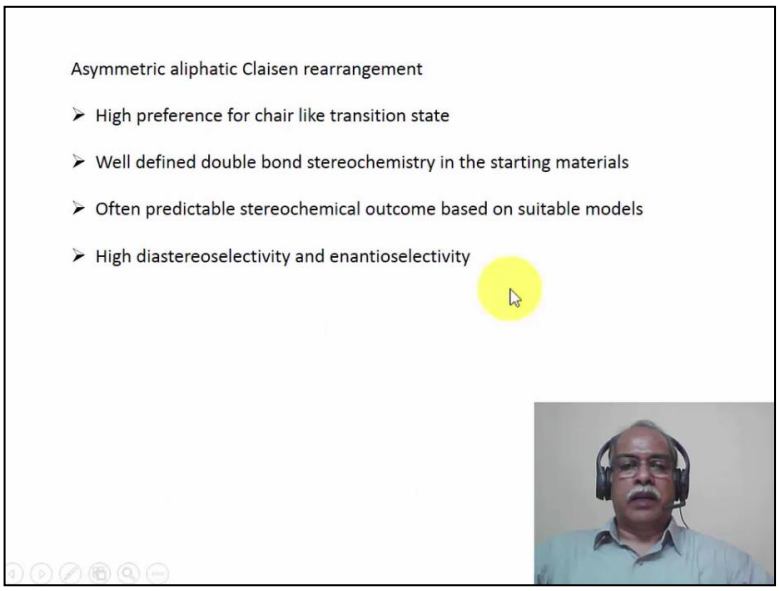
The reaction yield is about 79%, Enantioselectivity is about 97%, corresponding to this particular configuration, which can be explained on the basis of a [3,3]-Sigmatropic rearrangement, involving a suprafacial migration of the Carbon over here, to generate the new Chiral center at this particular position. Now here, the Boron reagent is used as a Lewis acid, Specifically. 1.5 equivalent of this Lewis acidic compound is used. You can see here; the Lewis acid is a Chiral Lewis acid.

So, it is actually a Chiral Lewis acid catalysts reaction. This probably forms, initially a Boronate ester, using this particular Phenolic ester in this particular, Free Phenolic-OH, is what is generated here. The rearrangement takes place at this Carbon, which is the Ortho Carbon. Because, the other Ortho Carbon is occupied, by the Hydroxy functional group. So, Chirality induction takes place, up to 94% Enantioselectivity of the S isomer is formed, from the E isomer of the Allyl derivative, in this particular case, because of the Chiral nature of the catalyst, that is being used.

It is really not a catalyst, it is used in psychometric amount, to form the corresponding Boron Phenolate of this kind, in this particular instance. And, the rearrangement is essentially, breaking of this Carbon-Oxygen bond. This is 1-2-3, and 1-2-3, in the Ortho position. On the other side, the free Ortho position, is what is undergoing the [3,3]-Sigmatropic rearrangement, in this particular instance.

So, what we have seen here is, the Aromatic Claisen rearrangement, Asymmetric versions. The first instance, this is a first-generation Asymmetric induction. Because, this is a Chiral substrate, is what is undergoing the rearrangement. The second case, a Chiral catalyst is used. In the third case, a more or less a Chiral auxiliary, is what is used. So, there are 3 different kinds of examples, are shown for the Asymmetric induction, during the course of the Aromatic Claisen rearrangement.

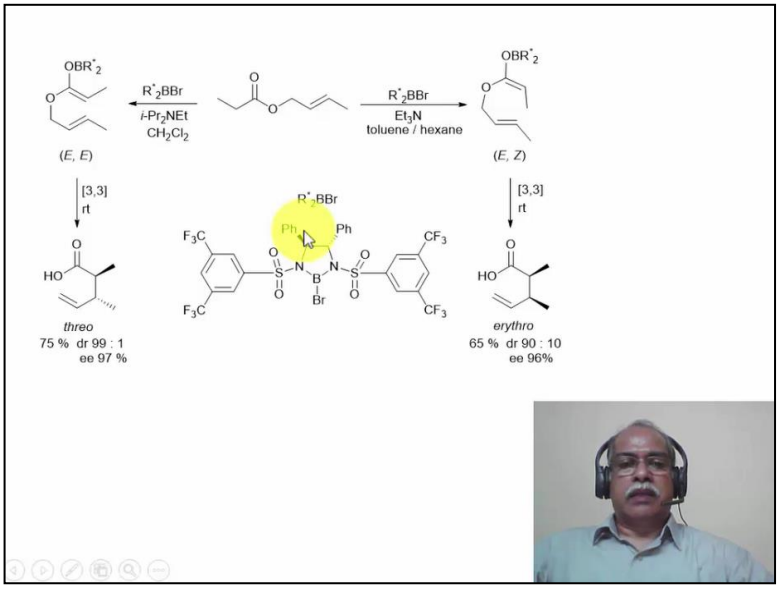
(Refer Slide Time: 08:31)



There are, not that many examples of Aromatic Claisen rearrangement. However, there are several examples of Aliphatic Claisen rearrangement, which are Asymmetric Aliphatic Claisen rearrangement, that is taking place. These are the favorable situation for the high Enantioselectivity, or high Diastereo selectivity, as the case may be, observed for the Asymmetric Claisen rearrangement. First of all, the reaction has a very high preference to, chair like a transition state. It is a very well-defined transition state.

And, well-defined double bond stereochemistry in the starting material, also helps in the stereoselectivity of this reaction. The stereochemistry is often predictable, because of the fact that, you have a chair type of a transition state, with a very well-defined double bond stereochemistry. Therefore, the high Diastereo selectivity, and Enantioselectivity, observed in the Aliphatic Asymmetric Claisen rearrangement, is not a very surprising factor, in view of the following points, which are favorable towards the high Enantio, and Diastereo selectivity of these reactions.

(Refer Slide Time: 09:28)



This is an example, that is reported by E. J. Korey. This particular Boron derivative, is used as the reagent, in this particular case. It is actually used as a catalyst, in this particular case. This is a Chiral Lewis acid catalyst, is what is used. This particular configuration of the Chiral Lewis acid, when treated with this particular ester, which is an Allyl ester. The Allyl ester is enolized in the Alpha position, with 2 different base. Diisopropylethylamine or Triethylamine, as a base. Depending upon, the kind of base that is used, the 2 different Diastereo isomers are produced.

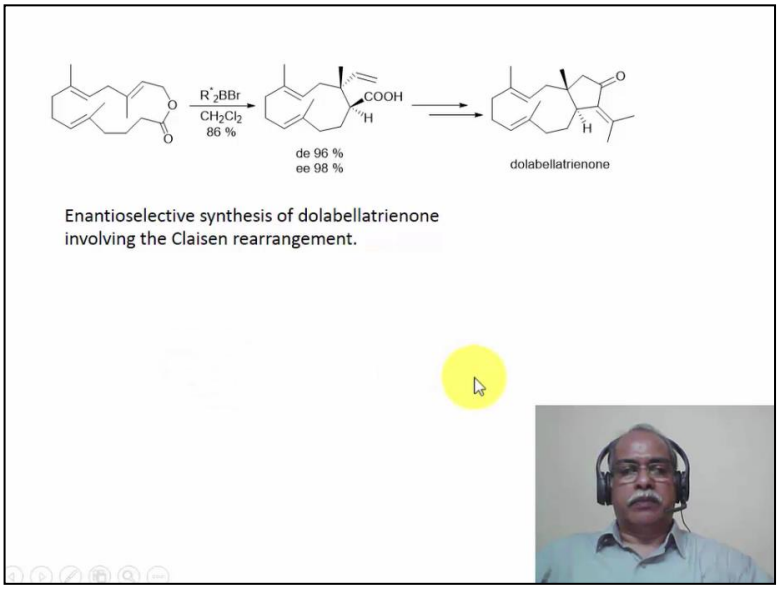
In the case of Diisopropylethylamine, which is a bulky base. The Boron reagent, generates the corresponding E-Boron enolate, which is this particular Ketene Silyl Acetal kind of a Boron enolate, is what is formed. Whereas, Triethylamine base, gives you the Z type of a stereochemistry, of this. So, what we have, here is a EE isomer of the Boron enolate. And, in this particular case, the EZ isomer of the Boron enolate, is what is formed.

So, Diastereoselective [3,3]-Sigmatropic rearrangement, produces the corresponding Gamma Delta Unsaturated Carboxylic acid, in this particular case. This is very similar to Ireland Claisen type of a rearrangement, except that, it is a Boron enolate, not a Silyl Enol Ether enolate. So, you can see here, the Diastereo selectivity is nearly 90:10, with respect to the Erythro isomer, that is formed. The Enantioselectivity of the particular isomer is 96. In other words, the Erythro Threo ratio is 90:10, in this case.

The Erythro isomer, which is a major product, is formed in 96% Enantioselective, because you are using a Chiral derivative, which induces the Chiral induction in the, during the course of the [3,3]-Sigmatropic rearrangement. The EE isomer produces a Threo isomer. You can explain the formation of the Threo isomer, from the EE, using a chair type of a cyclic transition state, which we have already seen, in the earlier module.

So, use the same logic to draw the transition state, which is the chair type of a transition state, to go from the EE, to the Threo, and the ZE, to the Erythro isomer. The Threo isomer is also formed, in very high Diastereo selectivity. The Threo Erythro ratio is 99:1. And, after that, we get rid of the Boron enolate, to the corresponding Gamma Delta Unsaturated Carboxylic acid, that Carboxylic acid is produced, in about 97% Enantioselective manner. The major isomer, which is a Threo isomer, is formed in 97% enantio pure form of the isomer.

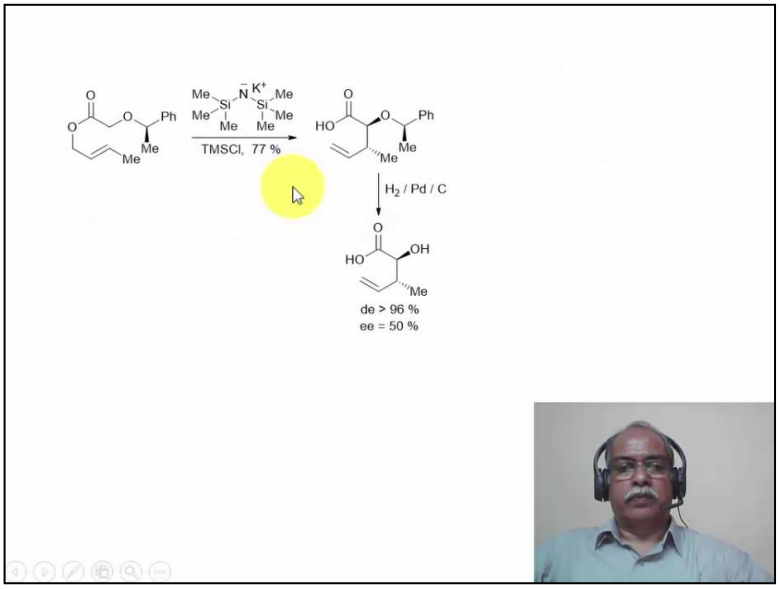
(Refer Slide Time: 11:58)



The Enantioselective synthesis of the Dolabellatrienone, which is this particular molecule, is a terpenoid molecule. It is essentially obtained by the same strategy, which is described in this particular slide. The Boron Enolate is stereo selectively synthesized, first. The Boron Enolate that is generated, undergoes the [3,3]-Sigmatropic rearrangement, to produce this. This is transformed further into this terpenoid molecule, by means of various transformations, which are not relevant to the Claisen rearrangement.

The first step is the Claisen rearrangement, that is formed, in about 96%. Diastereomeric Diastereo selectivity is 96%. The major isomer is formed in an Enantioselective manner, to an extent of about 98%. Using the same Boron enolate, which is this particular Boron reagent being used, to generate the Boron enolate, in this particular case also.

(Refer Slide Time: 12:50)

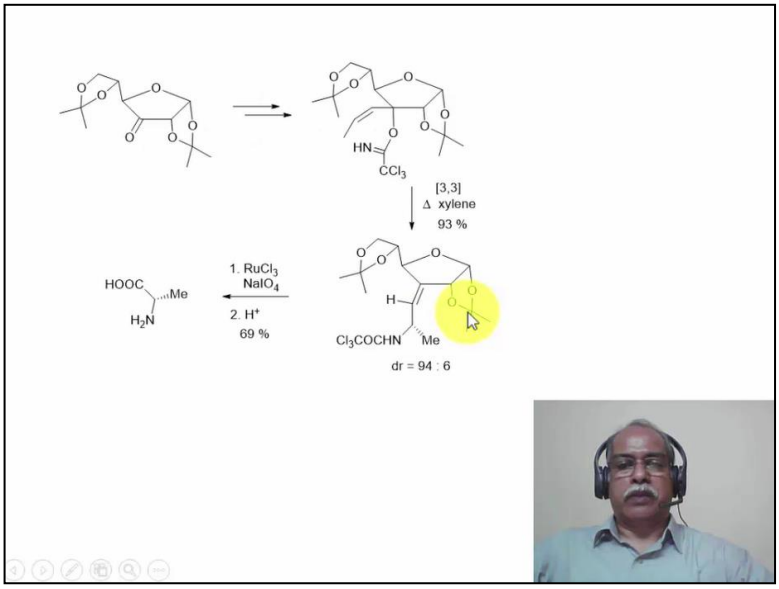


Here is an example of the, first-generation Asymmetric transformation of Claisen rearrangement. This is an Alpha Methyl Benzyl alcohol. The Alpha Methyl Benzyl alcohol, this particular isomer is taken. And, it is forming the corresponding enolate, by treatment with this Potassium Dimethyl Xyloside, in this particular case. And, Trimethylsilyl chloride captures the Enolate that is formed, in the form of Ketene Silyl Acetal.

The Ketene Silyl Acetal, undergoes the Ireland Claisen rearrangement in a stereo selective manner, to generate this particular isomer, which is the Erythro isomer, in this particular case. After get rid of the Chiral auxiliary, which is this particular, by means of Hydrogenolysis reaction. Because, it is a Benzyl Ether, it can be cleaved by Hydrogenolysis, to produce the corresponding alcohol.

The Carbon-Oxygen bond is hydrogenalized, to give the corresponding Hydroxy derivative, Alpha Hydroxy derivative. This is obtained in a Diastereo selective manner, in this configuration, to the extent of about 96%. The major isomer is formed in an Enantioselective manner, to an extent of about 50% of an enantiomeric excess, is what is formed, in the major isomer of this molecule.

(Refer Slide Time: 14:03)



Here is an example, where the Carbohydrate in the furanose form, is used as a Chiral auxiliary. The Ketone, which is an Alpha Hydroxy Ketone, in this particular case, is undergoing an addition of a Vinyl Grignard reagent, to produce the Tertiary alcohol. The Tertiary alcohol is captured, in the form of a Trichloroacetimidate kind of a derivative. The Trichloroacetimidate derivative, undergoes [3,3]-Sigmatropic rearrangement.

It is more or less a Claisen rearrangement, except, instead of a Vinyl derivative, Iminol kind of a derivative, is what is formed, in this particular case. Imino-Ether is the derivative, that is formed, in this particular case. The [3,3]-System is that, the Carbon-Oxygen bond is broken, and the Nitrogen-Carbon bond is formed, which is the [3,3]. This is 1-2-3, similarly it is 1-2-3.

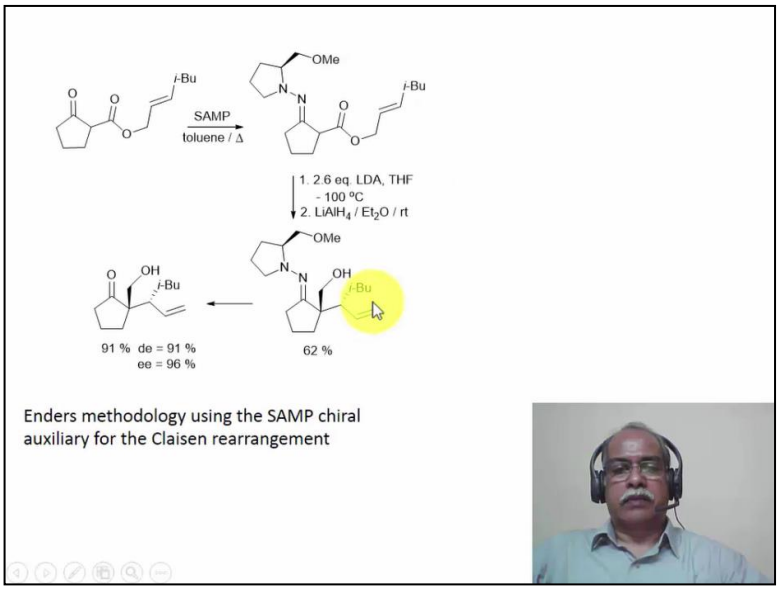
So, the Carbon-Nitrogen form, essentially forms the corresponding, this particular Amine derivative, is what is formed after the Claisen rearrangement. Now, cleavage of this particular Carbon-Carbon double bond, to get rid of the Chiral auxiliary, essentially produces an Amino acid. Because, this Acetate can be cleaved, to give the corresponding Amine. And, this Carbon-Carbon bond is cleaved, to give the corresponding Carboxylic acid.

So, this constitutes the synthesis of an optically pure Amino acid, in this particular case, Alanine as the product, through a Claisen rearrangement of this type, to give this derivative. The Trichloroacetimidate is a very crucial intermediate, which generates the system for the Amino acid synthesis. It generates the, secondary Amine system. The secondary Amine system, is in the form of an Acetate, in this particular case.

And, that undergoes the cleavage of the Trichloroacetimidate. Amide, is what is formed, here. The Trichloroamide is hydrolyzed under acidic condition, to give a primary Amine, which is

part of the Alpha Amino acid derivative, obtained from Ruthenium catalyst oxidation of the Carbon-Carbon double bond, in this case.

(Refer Slide Time: 16:12)



Now, Enders have developed a methodology, to use the S isomer, as well as the R isomer, of N-Amino Methoxy Methyl Proline derivative. The N-Amino Methoxy Methyl Proline derivative, is essentially Hydrazine derivative. In the presence of a Ketone, when it is reacted with a Ketone, SAMP-S corresponds to the S isomer, RAMP-R corresponds to the corresponding configuration, of this particular Chiral center.

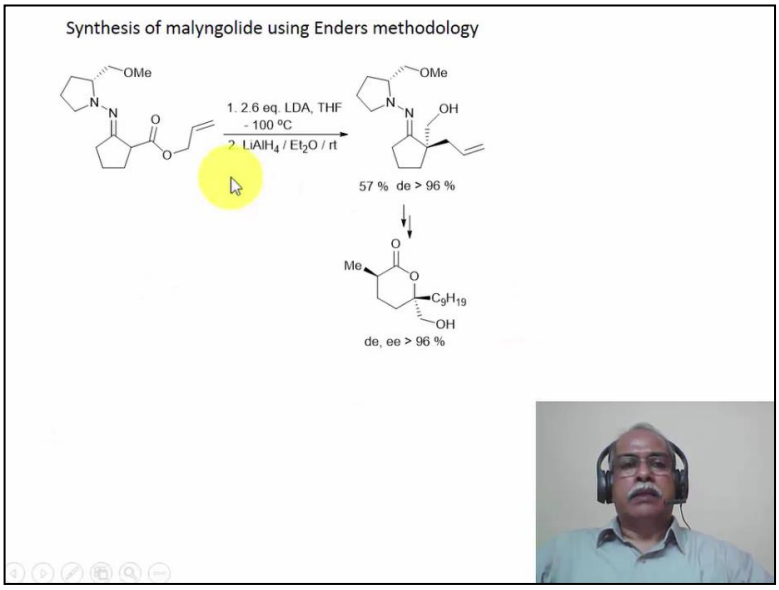
So, the S isomer of Proline, is what is the derivative, that is talking about. This is an Amino group, that is here. Methoxy Methyl Proline, is what, we are talking about. SAMP as the Chiral auxiliary. The Hydrozone that is formed, has this particular structure, with the configuration, which is the enantiomerically pure configuration, at this particular center.

So, this is an optically active compound. When the Enolate is generated, from this particular Carbon here, and the Enolate generated, is essentially going to have a [3,3]-Sigmatropic character. The enolate, that is generated, you consider this to be the enolate, then this would constitute an Allyl Vinyl Ether kind of a derivative. We can see here, the Enolate to be the Vinyl derivative.

So, the [3,3]-Sigmatropic rearrangement takes place between this Carbon, which will be the Enolic Carbon, and this Carbon, which will be the Allylic Terminal Carbon. So, [3,3]-Sigmatropic shift brings the Isobutyl substituted Carbon, to this particular position, releasing this acid. That acid is reduced with Lithium Aluminium Hydride, to the corresponding alcohol. And, after we get rid of the Chiral auxiliary, you get the Diastereomeric ratio to be 91%.

The major Diastereo isomer, which is shown here, is formed in about 96% Enantiomeric excess. So, the S-SAMP, or the RAMP, is used as a Chiral auxiliary. And, the Enolate, that is generated, will be Chiral, because of the Chiral auxiliary in nature. And, a stereo selective [3,3]-Sigmatropic rearrangement essentially produces, these 2 Chiral centers, in a very Diastereo selective, as well as Enantioselective manner, which is reported in this particular work.

(Refer Slide Time: 18:27)



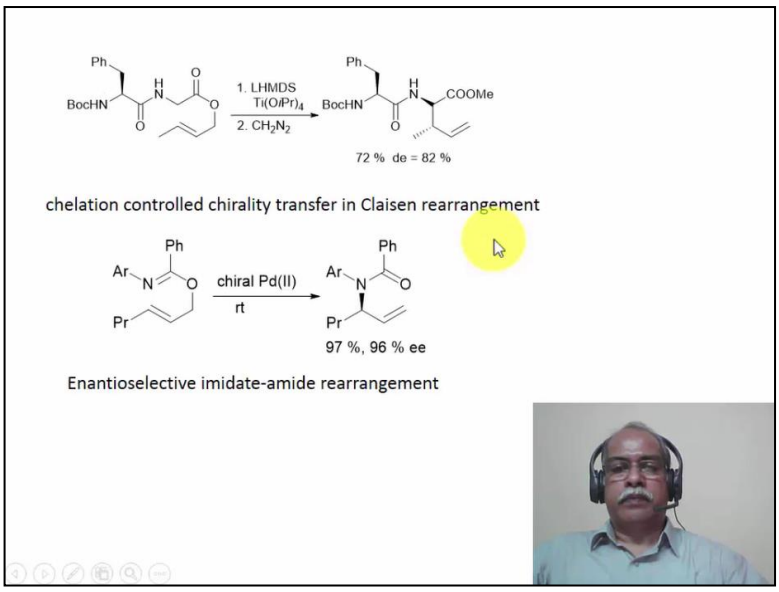
The same strategy has been used for, synthesis of this particular molecule, which is Malyngolide. Malyngolide is this particular molecule, which is synthesized by the same methodology. In this particular case, RAMP is used as the Chiral auxiliary. Here, you will see the stereochemistry is S, so it corresponds to SAMP.

In this case, the stereochemistry is R, so it would correspond to RAMP isomer. R configuration, is what is reported, in this particular case. The Methoxy Methyl Proline derivative, which is forming the Hydrozone, with this Ketone, and is enolized. This Alpha Hydrogen to the ester is enolized, in this particular case. And, this [3,3]-Sigmatropic rearrangement, produces a Carboxylic acid. That Carboxylic acid, is reduced by Lithium Aluminium Hydride.

So, there are 2 steps, which are built-in in this particular scheme. The first step is the generation of the Enolate, followed by [3,3]-Sigmatropic rearrangement, to produce the Carboxylic acid. The Carboxylic acid is reduced with the Lithium Aluminium Hydride. So, this Hydroxy functional group, is essentially coming from the Carboxylic acid functional group, which was originally present, which is being reduced by the Lithium Aluminium Hydride.

Subsequent Hydrolysis of this molecule, followed by transformation, by means of a Baeyer-Villiger oxidation, essentially produces a necessary skeleton. Then, the Alpha alkylation at this position, produces this Methyl group. And, further elaboration of this molecule, into a long chain, is what produces the Malyngolide synthesis, in this particular case.

(Refer Slide Time: 19:58)



Now, here is an example of a Chelation Controlled Chirality Transfer of the Claisen rearrangement. What is seen here is the, optically active Amine derivative, which is a BOC protected Amine derivative. This is used as a Chiral center. Now, when you produce a Enolate, by means of Lithium Hexamethyldisilazane, the Enolate is generated here. That Enolate will be now, tied up by the Titanium center.

So, in other words, Titanium chelates between, this Oxygen, and the Enolate Oxygen, forming a tight chelate, which is a well-defined chelate. So, as a result of that, the [3,3]-Sigmatropic rearrangement, between these 2 centers, proceeds very stereo selective manner, to an extent of about 82% of Diastereo selective manner, to give this particular product. And, the initial product that is formed will be an acid, Carboxylic acid.

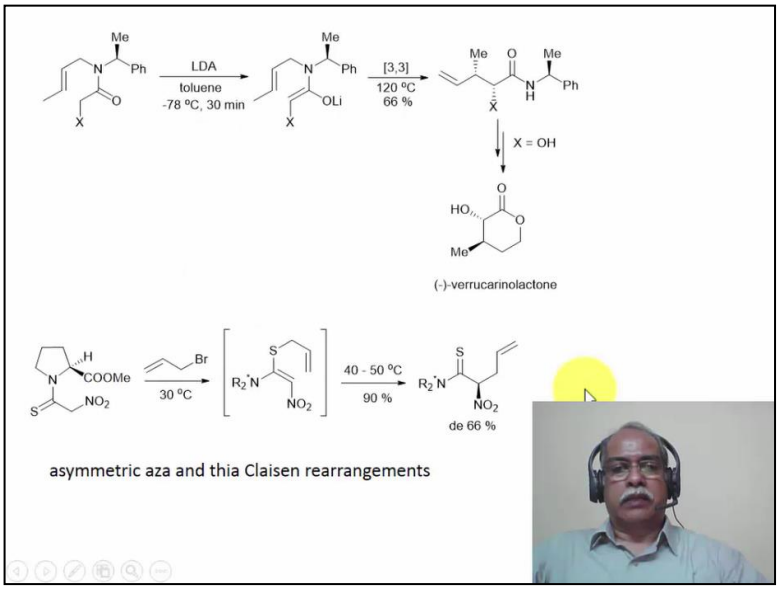
Because, Ireland Claisen rearrangement of this type, will produce a Carboxylic acid, coming from this moiety, which is esterified into a Methyl ester, by treatment with the Diazomethane. So, this is an example. This Oxygen here, in the form of an Enol, and this Oxygen here, in the form of an Amide, is undergoing a chelation with the Titanium. Titanium is acting as a metal template essentially, to trigger this reaction, to go in a Diastereo selective manner, in this particular case.

There are several examples, reported by Larry Overman, which are Palladium catalyzed [3,3]-Sigmatropic rearrangement. The Chiral Palladium complex is what is used, in this

particular case. So, the Chirality of the Palladium complex essentially, the coordination of the Palladium onto the Oxygen essentially, induces the Chirality of the rearrangement itself.

The [3,3]-Sigmatropic rearrangement of this particular derivative, gives this Tertiary Amine. The Tertiary Amide, in this particular case, in a highly Enantioselective manner, because of the Chiral nature of the Palladium catalyst, that is used. So, this is an example of an Enantioselective Imidate. This is a Imidate. Amide, which is a product. Imidate-Amide rearrangement, which is a [3,3]-Sigmatropic rearrangement, in this particular case.

(Refer Slide Time: 22:07)



Examples of Asymmetric Aza and Thia Claisen rearrangement, are given here. This is an example of Asymmetric, first order Asymmetric system. Because, this is an optically pure starting material, is what is taken. Once you generate the Enolate, using LDA in Toluene, at a very low temperature, the Enolate is highly reactive. So, when it undergoes a [3,3]-Sigmatropic rearrangement at 120°, it produces, this particular Diastereo isomer of the compound. So, when X is equal to Hydroxy functional group, it can be made into a Lactone.

This Hydroxy functional group is in Alpha position, which we are talking about. And, this particular Lactone is a natural product. Verrucarinolactone, is what the structure of this compound is. If you take this example, this is a Nitro substituted Thioamide, is what is present here. Allylation, using a base, and Allyl bromide will essentially generate, the S-Allyl derivative. Because, a Sulphur is a much more nucleophilic center. So, S-Alkalization takes place.

So, the deprotonation of the Proton from this position, results in the formation of a Ene Thiol. The Ene Thiol is trapped by this Silyl Bromide, to generate the corresponding Vinyl Allyl sulfide derivative, in this particular case. This undergoes, Claisen [3,3]-Sigmatropic Thia

Claisen rearrangement, at about 50°C, to generate this corresponding center. Here, if the Chiral auxiliary group is the Proline group, which is shown here. Then, it is a Proline template is acting as a Chiral auxiliary group, that induces the Enantioselective of this particular compound.

Because, there is a Chiral center here, the Diastereo selectivity, is what is reported for this compound, to be about 66%, in this particular instance. So, what we have seen in this module is, Asymmetric Claisen rearrangement of Aliphatic type, Aromatic Claisen rearrangement, as well as the Asymmetric version of Aromatic Claisen rearrangement, in the module.

Hope, you enjoyed the module. Thank you very much, for your attention.