Transcriber's Name Angela
Pericyclic Reactions and Organic Photochemistry
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Module No. #03
Lecture No. #13
Pericyclic Reactions – 1,3-Diploar Cycloaddition reactions continued……

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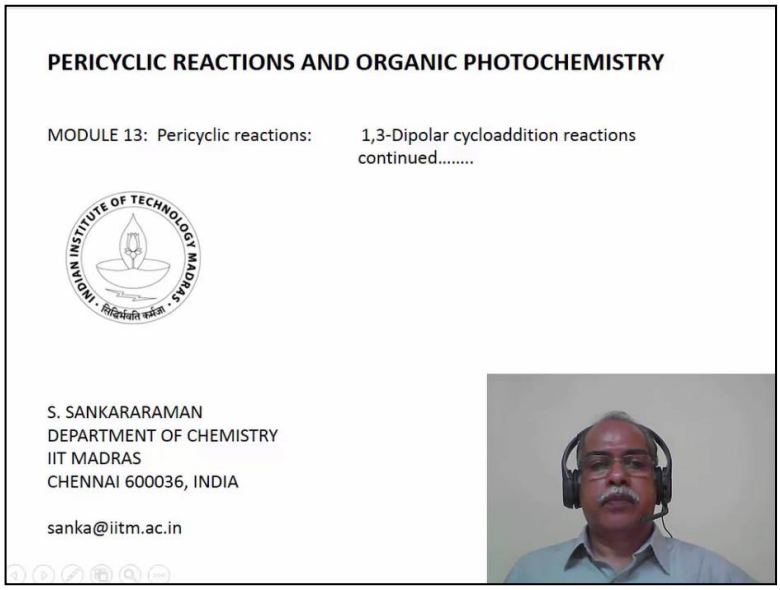

Hello, welcome to Module Thirteen of the course on Pericyclic Reactions and Organic Photochemistry. We will continue with 1,3-Dipolar Cycloaddition reactions, in this module also. In the earlier module, that is in Module Twelve, we consider the 1,3-Dipolar Cycloaddition reactions of Azomethine ylide and a Nitrile oxide, which belong to the category of Allyl anion type of 1,3-Dipolar systems. Now, we will consider the Propargyl Allenyl type of 1,3-Dipolar system, in this particular module.

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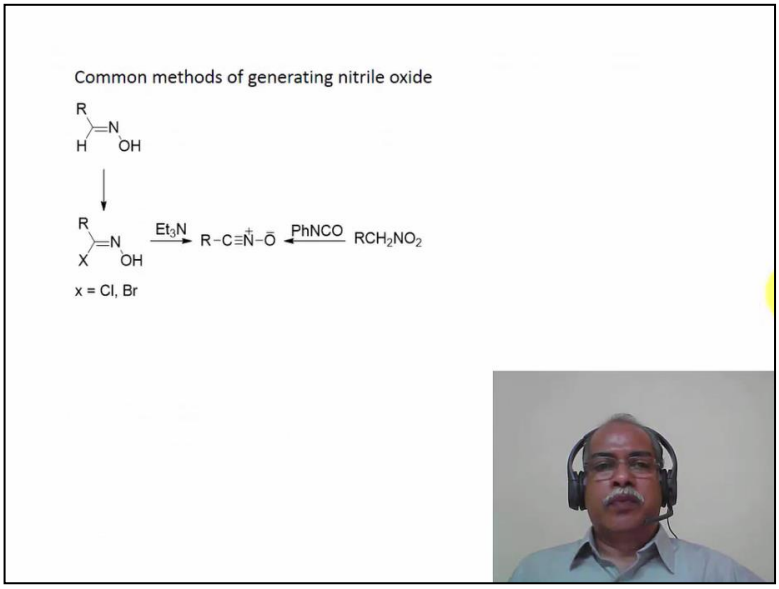

To start with, let us start with the Nitrile oxide system, as the 1,3-Dipolar system. Nitrile oxides are generated in, by the methodology, that is shown here. An Oxime is taken. An Aldoxime is taken. The Aldoxime is made to undergo a halogenation reaction, either chlorination or bromination is carried out, using bleaching powder like Sodium Hypochlorite, or similar chlorinating agent. N-Bromosuccinimide kind of a brominating agent can be used, in this particular case.

And, once the Alpha Bromo Aldoxime is formed, it is made to undergo an elimination reaction, in the presence of a base, to give the corresponding Nitrile oxide. Alternatively, Nitrile oxides can also be synthesized, by dehydration of a primary Nitro derivative, Alkyl Nitro derivative. You can see here, loss of water produces the corresponding Nitrile oxide derivative, by treatment with Phenyl Isocyanate in this particular case, as the dehydrating agent.

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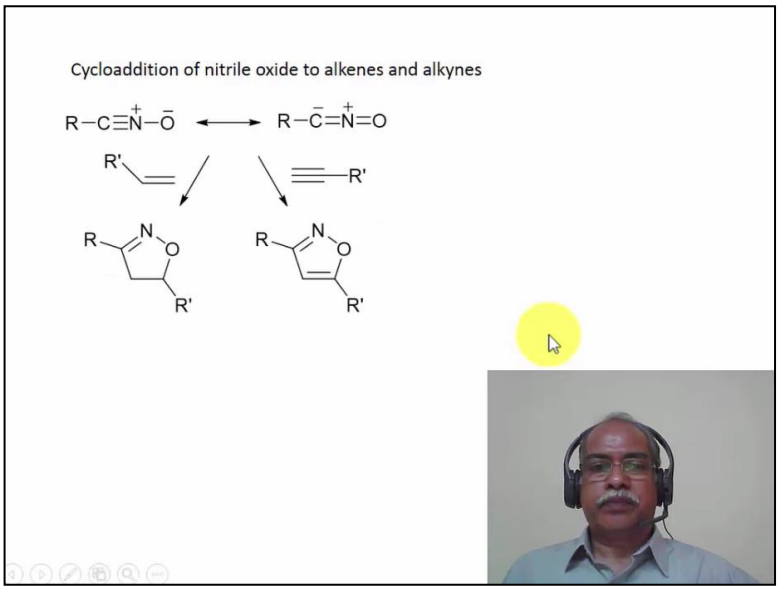

The Cycloaddition reactions of Nitrile oxides with Alkenes and Alkynes, is shown here. It produces Isoxazoline or Isoxazole as the derivative, as the final Heterocyclic compound, that is formed. Reaction of a Nitrile oxide with an Alkene, produces Isoxazoline. Whereas, the reaction of the Nitrile oxide with the Alkyne, produces Isoxazole as the product, in this particular case, which is an Aromatic Heterocyclic system, during the course of the Cycloaddition reaction.

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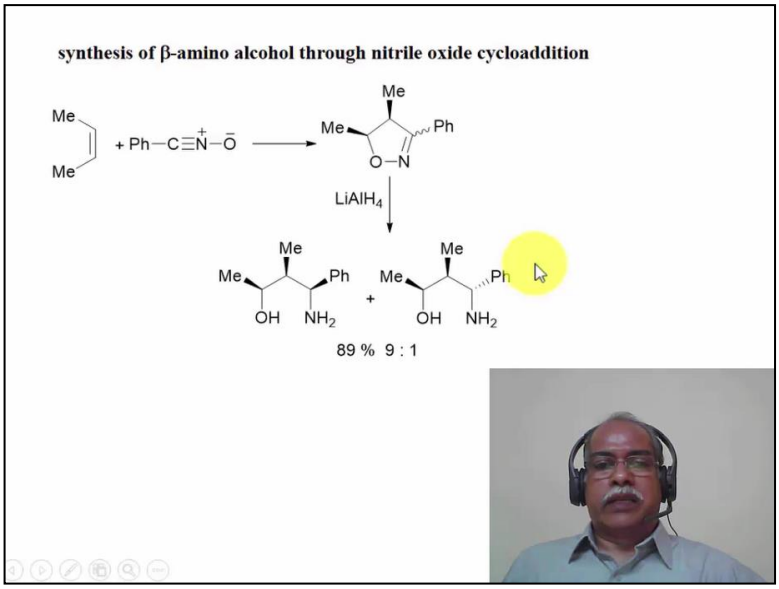

Now, the synthetic utility of the Isoxazoline, that is formed during the course of this 1,3-Dipolar Cycloaddition reaction between the Alkene and Nitrile oxide, is what is shown here. The Nitrile oxide undergoes reaction with Cis-2-Butene, in this particular case, in a stereo selective manner. We can see here, the two Methyl groups are Cis with respect to each other,

and it is retained as Cis in the product also. It produces a Diastereomeric mixture of compounds, as far as this stereo center is formed, for example.

And, what is important here is, the reductive cleavage of the Nitrogen-Oxygen bond, to produce a 3-Amino alcohol, in this particular case, in a stereo selective manner. the initially formed cycloadduct, has a stereoselectivity of probably 9:1. And, that is retained during the course of the Oxygen-Nitrogen bond cleavage, using Lithium Aluminium hydride, to produce the beta Amino alcohol derivative, that is shown here, in a highly stereo selective manner, in this particular example.

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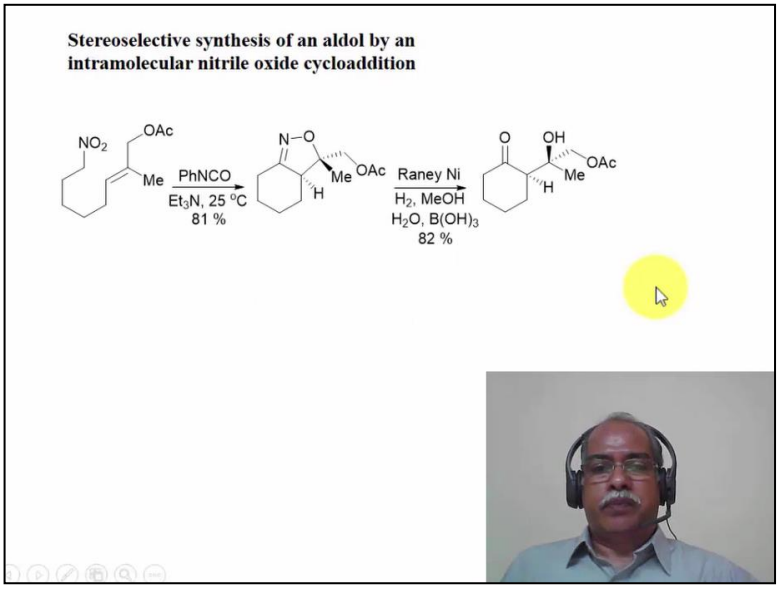

In addition to, having the beta Amino alcohol synthesis carried out in this particular manner, one can also do the synthesis of an Aldol, by an Intramolecular Nitrile Cycloaddition reaction. And, that is illustrated in this particular example. The Nitrile oxide itself is produced in-situ, by the reaction of this primary Nitro derivative with Phenyl Isocyanate, for example, producing the intermediate Nitrile oxide, which is not shown in the slide.

And, that intermediate Nitrile oxide, undergoes the Cycloaddition reaction with this double bond here, resulting in the formation of the Isoxazoline derivative, which is this particular derivative, which is a cycloadduct of this reaction. Dynamical Hydrogenation of this derivative, produces a corresponding imine, which is a beta Hydroxy imine. The beta Hydroxy imine is hydrolyzed, to produce the corresponding beta Hydroxy Ketone, in this particular case, which is nothing but an Aldol.

What is important about this reaction is, the stereoselectivity of this reaction. You can see here, the Hydrogen and the Methyl are Trans with respect to each other, and that is retained as Trans during the course of the reaction.

And, the cleavage of the Nitrogen-Oxygen bond is also carried out in a stereo selective manner, without the racemization of this particular center, here. alternative stereochemistry is not possible, in this particular case. So, overall it constitutes a stereo selective synthesis of an Aldol derivative, by means of an Intramolecular Diels-Alder reaction of a Nitrile oxide, with this Olefin, that is in-built in the molecule.

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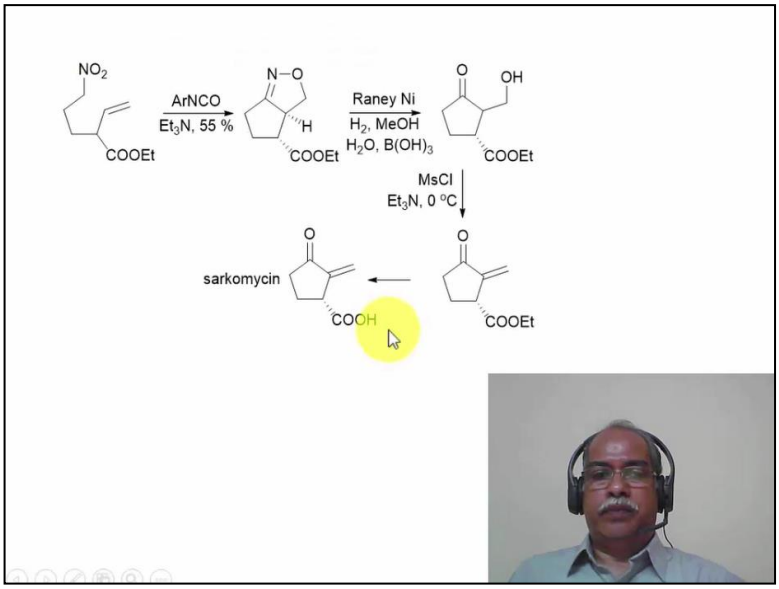

Another example of a Nitrile Oxide Cycloaddition reaction, is shown here. This Nitro derivative, when it reacts with Phenyl Isocyanate, produces the corresponding Nitrile oxide, which undergoes the Cycloaddition reaction with this Vinyl derivative here, to produce the Isoxazoline. And, reductive cleavage of the Nitrogen-Oxygen bond here, produces the ((evinol)) (05:23). The imine is hydrolyzed to the corresponding Ketone, in this particular case. And, this constitutes a synthesis of Sarkomycin, which is this particular molecule. So, this derivative is essentially used for the synthesis of Sarkomycin, which is this particular structure, that is shown here.

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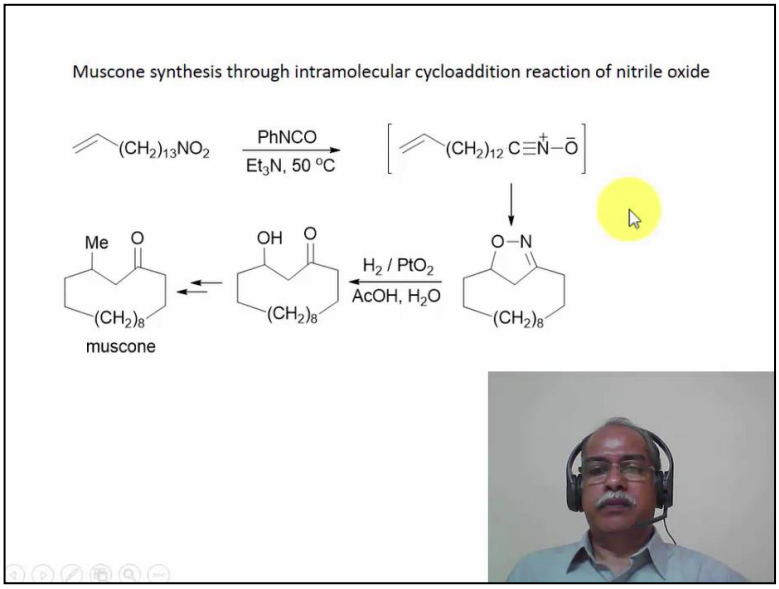

Muscone is a very important product in fragrance industry. Muscone synthesis, through Intramolecular Cycloaddition reaction of Nitrile oxide, is what is shown in this particular slide. Muscone has the structure, which is this 15-Membered ring system, with the ketonic system, with the Chiral center in the beta position, here. The starting material is a 15-Membered linear chain, with a Nitro functional group at one end, and a Vinyl functional group at the other end.

So, the reaction of this Nitro compound with Phenyl Isocyanate, produces the corresponding Nitrile oxide derivative. The Nitrile oxide derivative, undergoes an Intramolecular Diels-Alder reaction, with the terminal Vinyl group, to produce the Isoxazoline derivative. The Isoxazoline is now, Hydrogenolysis of the Nitrogen-Oxygen single bond, produces the corresponding beta Hydroxy Ketone.

The beta Hydroxy Ketone, is further transformed into the beta Methyl Ketone, which is the Muscone. So, overall it constitutes a synthesis of Muscone, from the 1,3-Dipolar Cycloaddition reaction of an inbuilt Nitrile, with an inbuilt Vinyl derivative, which is coming from a Linear 15-Carbon long chain, in this particular instance.

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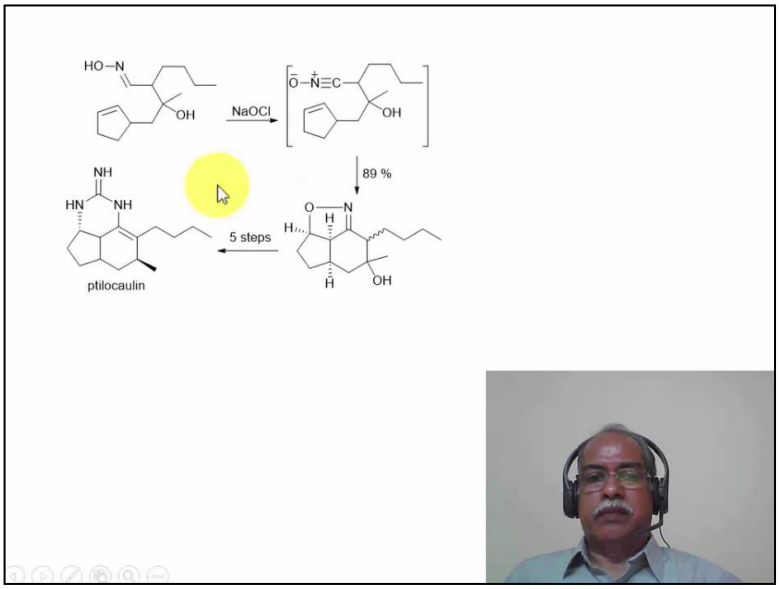

Here is an example of the halogenation using bleach, which is a Sodium Hypochlorite, for example. The alpha halogenation, followed by loss of Hydrochloric acid, produces the Nitrile oxide. The Nitrile oxide is undergoing an in-situ, or Intramolecular Cycloaddition reaction, with this double bond here, resulting in the formation of this particular derivative.

This particular derivative is converted into Ptilocaulin, which is this derivative here, by several steps. So, overall it constitutes a synthesis of a product, which is known as the Ptilocaulin, which is this particular structure, that is shown here.

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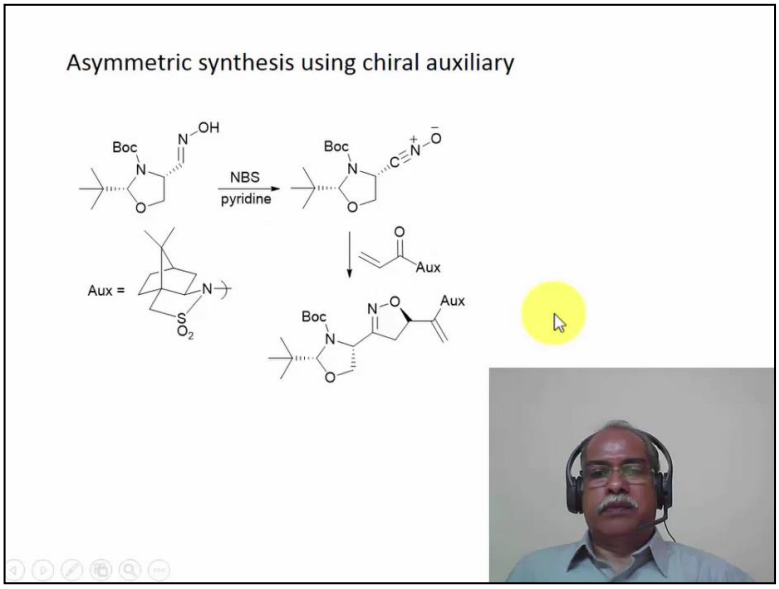

Asymmetric synthesis using a Chiral auxiliary, is what is illustrated here. Now, Asymmetric synthesis in the sense that, the Cycloaddition process is in an Asymmetric manner is carried out, using a Chiral auxiliary. The Chiral auxiliary, that is used is camphor based Sultam, which is this particular derivative. The Oxime is made to undergo, Alpha bromination with

N-Bromosuccinimide, followed by treatment with Pyridine, results in the HBR elimination to produce a Nitrile oxide.

The Nitrile oxide is treated with the Acrylate, which is this Acrylamide derivative, which is the Chiral auxiliary, which is this particular auxiliary. So, because it is enantiomerically pure Chiral auxiliary is taken, Asymmetric induction takes place, resulting in the formation of a stereo selective formation of this particular derivative, which is Isoxazoline derivative, in this particular case.

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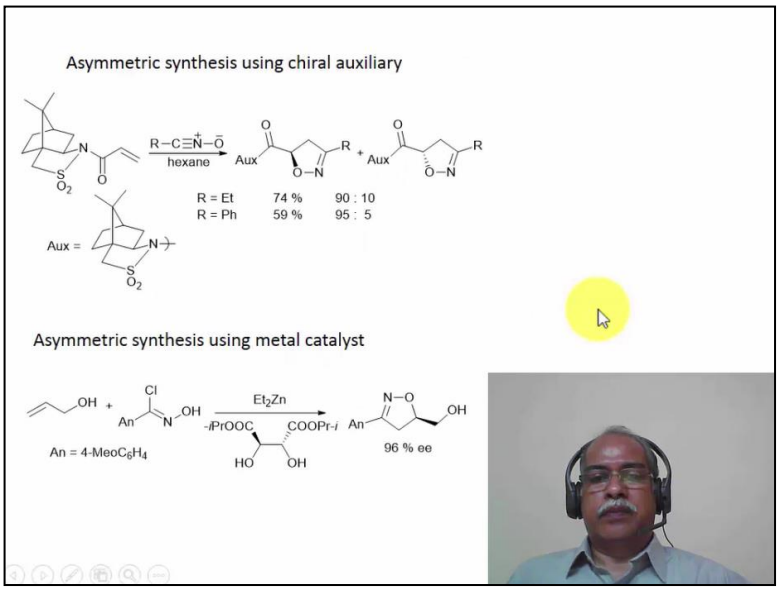

Another example of an Asymmetric synthesis, using Chiral auxiliary. Again, the same Sultam is being used, in this particular case. The Cycloaddition reaction with the Nitrile oxide, with this particular derivative is shown here. For two different derivatives, when R is equal to Ethyl, and R is equal to Phenyl, you get a high diastereo selectivity in this reaction. 90:1 and 95:5 is the diastereo selectivity of this two compounds, that are formed.

Once the Nitrogen-Oxygen bond is cleaved, and the Imine, resulting Imine is hydrolyzed, you get the corresponding beta Hydroxy derivative in an enantioselective manner. So, overall it constitutes an Asymmetric synthesis of a beta Hydroxy Ketone kind of a derivative, or an Aldol kind of a derivative, using this particular methodology. Here, Asymmetric synthesis using a metal catalyst, is what is illustrated. This is a Tartaric acid derivative.

Diisopropyl tartrate, is what is used. And, it is initially reacted with the Diethyl zinc, to produce the corresponding Zinc chelated derivative. The Zinc chelated would be a Chiral derivative. And the Zinc chelate is made to undergo, chelation with the Nitrile oxide derivative, or the Dipolarophile, which is Allyl alcohol, in this particular case.

The Alpha Chloro Oxime is made to undergo hydrohalogenation, to give the corresponding Nitrile oxide. The Nitrile oxide derivative thus formed, is undergoing the Cycloaddition reaction with the Allyl alcohol, to produce the corresponding derivative, which is this particular derivative. It is produced in 96% enantioselective manner, because of the Chiral auxiliary, that is being used to induce the chirality of this particular center, that is formed during the course of the reaction.

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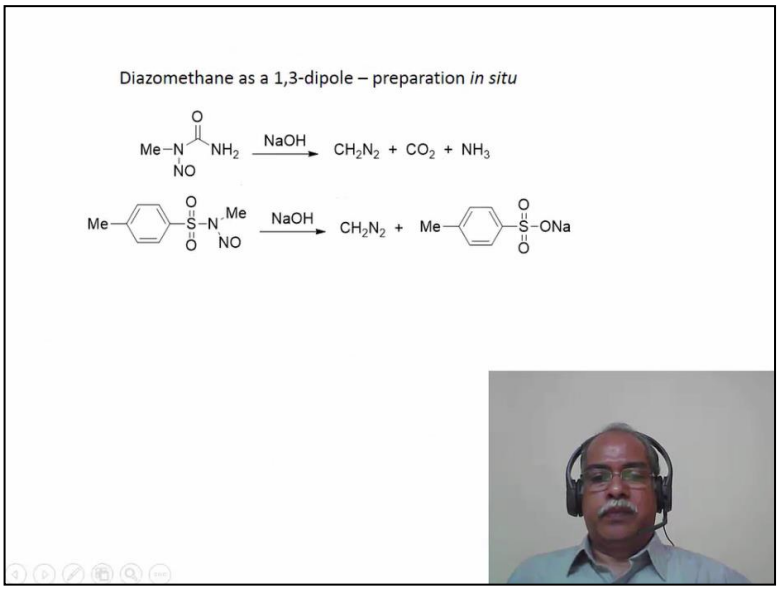

Diazomethane is an excellent 1,3-Dipole. And, it is very widely used in the synthesis of a Heterocyclic system. Diazomethane itself, is a very reactive intermediate. It has to be formed in-situ. And, it cannot be prepared and stored, for example. It undergoes slow decomposition. The N-Nitroso-N-methylurea is made to undergo reaction with Sodium Hydroxide, to produce Diazomethane, Carbon-dioxide, Ammonia.

The Diazomethane, thus produced can be dissolved in Ether kind of a solvent, for further reaction. Or alternatively, N-Methyl-N-Nitroso-para-Toluenesulfonamide is hydrolyzed, using Sodium Hydroxide, to produce Diazomethane and Sodium-para-Toluenesulfonate, for example. The Diazomethane, thus produced can be dissolved in organic solvents, and it can be made to react with other components also.

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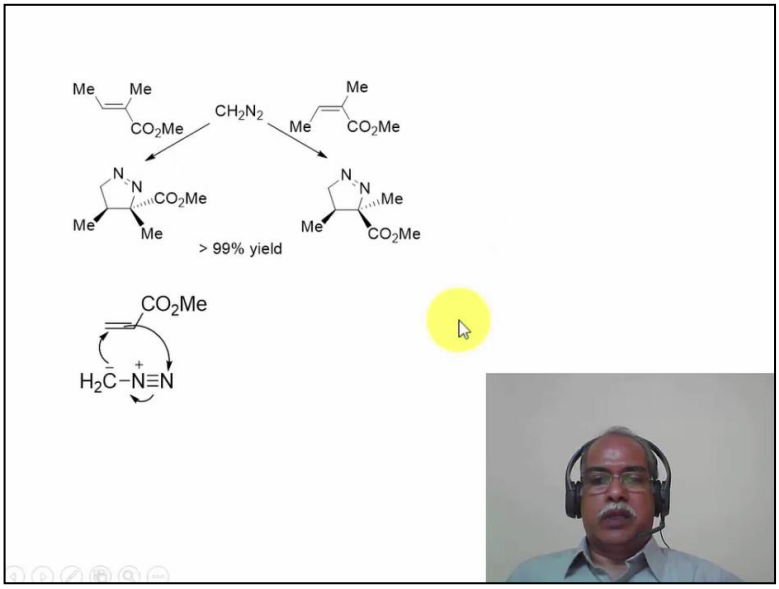

Reaction of Diazomethane with Dipolarophile, is highly stereo selective in nature. You can see here, the Trans isomer of this Ester is undergoing the Diels-Alder reaction, to produce the corresponding Trans derivative, where the Ester functional group and the Methyl group are Trans with respect to each other. Or, alternatively, the two Methyl groups are Cis with respect to each other.

So, it is a highly stereoselective reaction. When the two Methyl groups are Trans with respect to each other, Cycloaddition reaction produces the Trans isomer, whether the two Methyl groups are Trans with respect to each other. So, the mechanism of the reaction is essentially a 1,3-Dipolar Cycloaddition kind of a mechanism, where these Carbon adds to the beta position of the carboxylate, resulting in the formation of a cycloadduct in a regio selective manner, which is shown in this particular slide.

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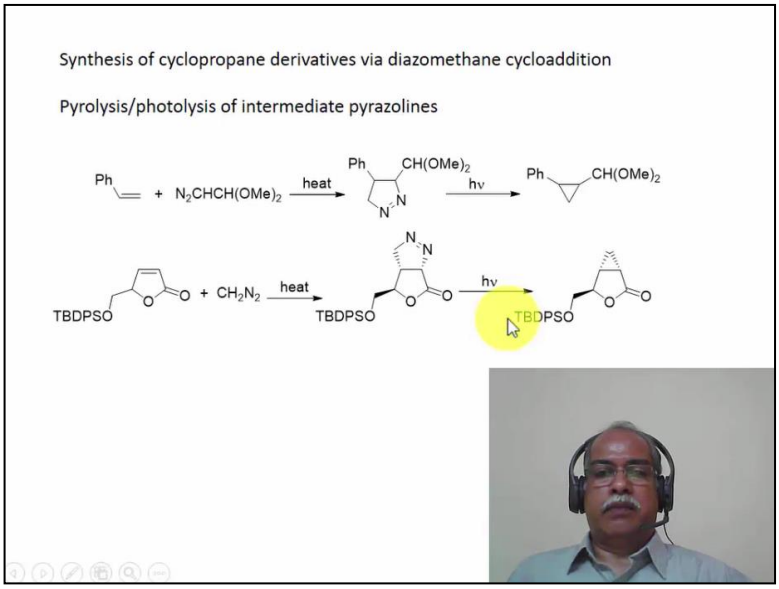

Cyclopropane derivatives can be prepared, by pyrolysis or photolysis of the intermediate that is formed, by the Cycloaddition reaction of Diazomethane with Olefins. The Pyrazoline, that is formed can be made to undergo loss of Nitrogen, to form the Cyclopropyl derivative. Two examples are given here. This is a general methodology about preparing Cyclopropane derivatives. Styrene is made to undergo reaction with this Diazomethane derivative.

And, the intermediate Pyrazoline that is formed, is photolyzed to give the corresponding Cyclopropyl derivative, in this particular case, by the loss of Nitrogen in this reaction. Alternatively, this Lactone is made to undergo reaction with a Diazomethane, to produce the corresponding Pyrazoline derivative. Pyrazoline derivative is fertilized to undergo the loss of Nitrogen, to produce the corresponding Cyclopropyl derivative.

So, cyclopropanation is a reaction, that can be made to occur by the initial Cycloaddition reaction of the Diazomethane to Olefin, followed by the photolysis of the Pyrazoline derivative, to produce the Cyclopropyl derivative, which is illustrated in this particular example.

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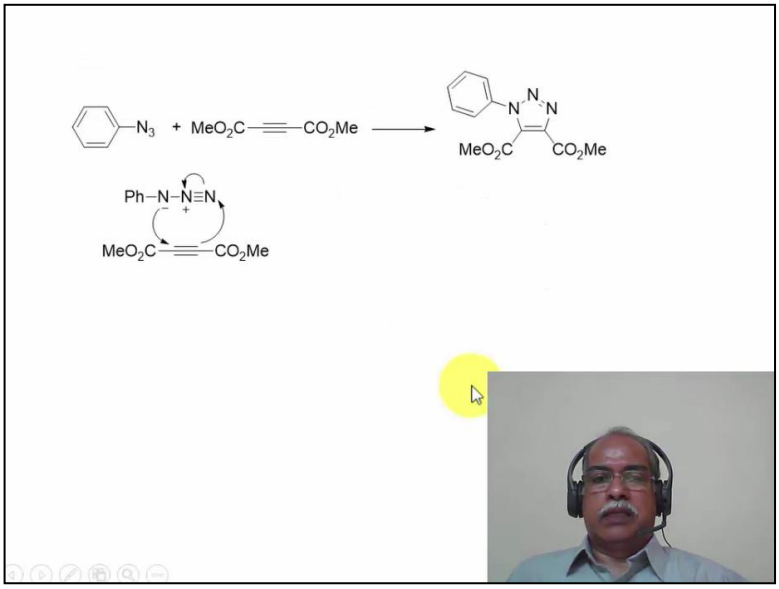

Now, let us come to the Azide Cycloaddition reaction. This is Phenyl Azide. Phenyl Azide is made to undergo Cycloaddition reaction, with the Dimethyl Acetylene Dicarboxylic acid. The reaction mechanism is a concerted mechanism of a 1,3-Dipole, adding to a Dipolarophile in this particular case, which is the Olefins. This produces a Triazole derivative. So, it is a 1-Phenyl Triazole, is what is being formed in this reaction. This is known as the Huisgen reaction. The Triazole formation can be easily accomplished, by the Cycloaddition reaction of Azides, with various types of Acetylenic compounds.

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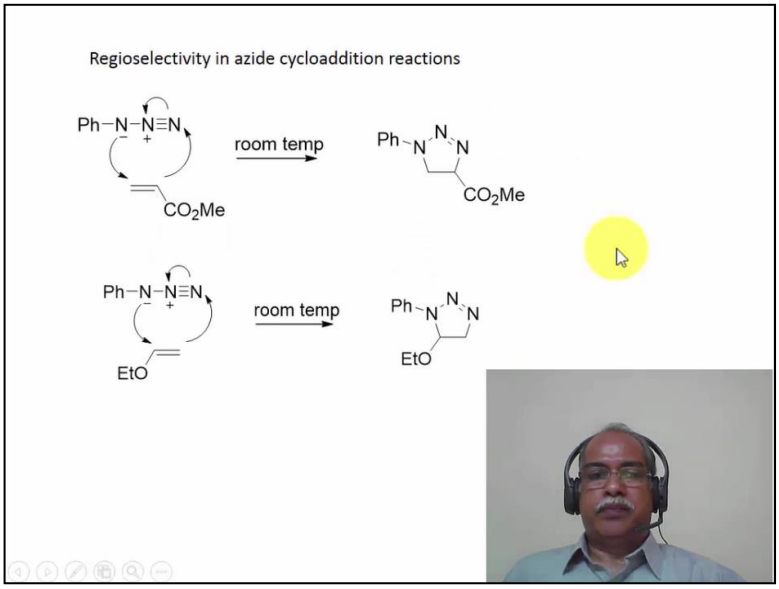

Regio selectivity in Azide Cycloaddition reaction, is what is given here. For, electron deficient Olefin and an electron rich Olefin, you can see here, the regio selective formation of a four-substituted isomer, in the case of electron deficient Dipolarophile, is given here. Whereas, a five-substituted derivative is what is formed, in the case of an electron rich

Dipolarophile, which is this particular Enol-Ether derivative. The mechanism is very clearly shown here, to account for the regio selectivity of this two reactions, that are formed during the course of the Cycloaddition reaction.

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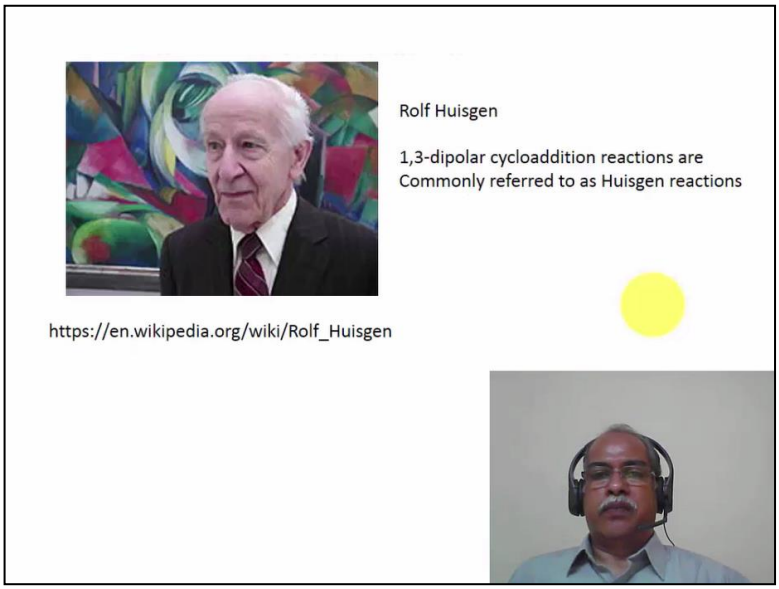

Now, the 1,3-Dipolar Cycloaddition reactions are largely explored by Rolf Huisgen, who is a German scientist. So, these reactions are collectively known as Huisgen reactions. Rolf Huisgen have a long career in Chemistry Department, at the University of Munich, for example. And, he is the, sort of father of the 1,3-Dipolar Cycloaddition reaction. And hence, the credit is given to him, by calling this reactions as Huisgen reactions. I hope you enjoyed this module, thank you very much, for your kind attention. Thank you.