Pericyclic Reactions and Organic Photochemistry
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Module No. #03
Lecture No. #11
Pericyclic Reactions - Diels-Alder Reaction (continued) – Intramolecular – Hetero Diene and Dienophile – Lewis acid mediated – Asymmetric

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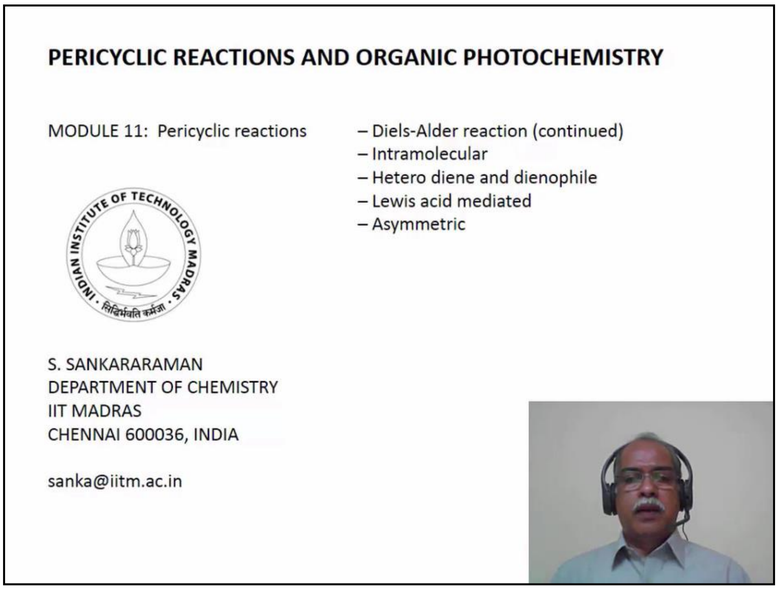

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 11: Pericyclic reactions

– Diels-Alder reaction (continued)
– Intramolecular
– Hetero diene and dienophile
– Lewis acid mediated
– Asymmetric

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Hello, welcome to the course on Pericyclic Reactions and Organic Photochemistry. We are on the third week of this course. And, we will start with Module Number Eleven, on the Pericyclic Reaction. We have few more topics, to cover under the Diels-Alder reaction, namely the Intramolecular Diels-Alder reaction, Diels-Alder reactions involving Hetero Dienes and Dienophiles, Lewis acid mediated or Lewis acid catalyzed Diels-Alder reaction. And, finally, Asymmetric Diels-Alder reaction, which is a very important topic, in the case of Diels-Alder reaction.

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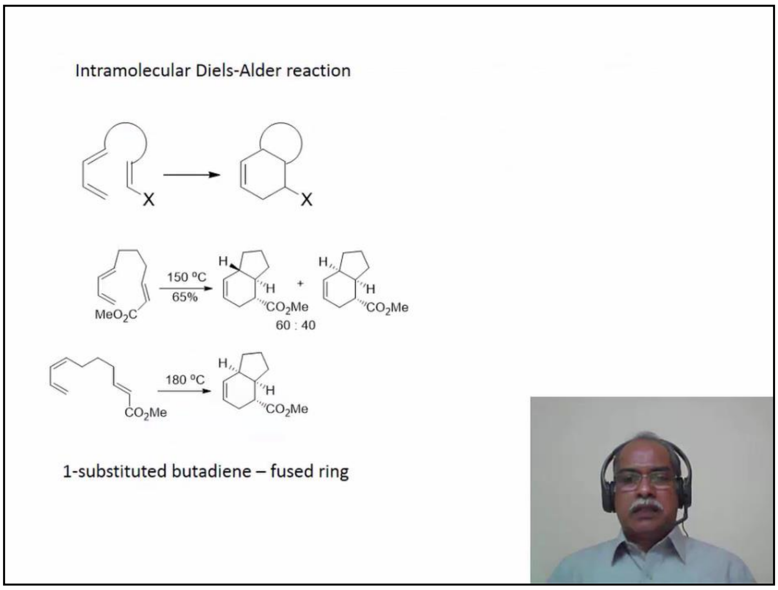

Intramolecular Diels-Alder reaction

1-substituted butadiene – fused ring

Now, Intramolecular Diels-Alder reactions are those reactions, where the 4+2 cycloaddition takes place, within the same molecule. If you look at this particular structure here, the Diene and the Dienophile are built-in within the same molecule. And, hence the reaction takes place within the single molecule, which is known as the Intramolecular Diels-Alder reaction. There are many examples of Intramolecular Diels-Alder reactions known. Let us consider, a few examples in this particular module.

If you take this particular molecule, in this molecule, the pendant group is attached in the form of a Dienophile, from the one position of the Diene. In so much, so that, the stereochemistry of this particular double bond is E, in this particular case. And, the stereochemistry of the Dienophile is also E, in this particular case. So, when this reaction is carried out at 150 degrees, these two adducts are formed.

And, you can tell from the stereochemistry of this particular ring junction, where this Hydrogen, here on the one position of the Diene, and the two position of the Dienophile, are Trans with respect to each other, is possible, only when there is an Endo kind of an approach. So, this adduct is arising out of the Endo approach. And, this particular adduct is arising out of the Exo approach, in the ratio of 60:40 ratio.

The Exo, Endo adducts are formed, as a mixture in this particular case. Now, here is a substituent, which is attached to one position, but the stereochemistry is reversed. Here, it is a E stereochemistry. Now, it is a Z stereochemistry, in this particular case. In the case of the Z stereochemistry, if you look at, based on the stereochemistry of these two Hydrogens, you get exclusively only the Endo adduct, in this particular case.

So, depending upon the stereochemistry of the attachment of the pendant group, which is the Dienophile group, in this case. Otherwise, the pendant group, length wise number of Carbons, and the kind of Dienophile, they are essentially same, except for the stereochemistry of attachment at this position one, in this particular Diene, here. So, depending upon the stereochemistry of the Carbon-Carbon double bond of the Diene, in this particular case, the Exo-Endo ratio varies quite dramatically.

In this case, you get exclusively the Endo adduct, compared to the case where, here we get a mixture of Exo, as well as the Endo adduct, in this case.

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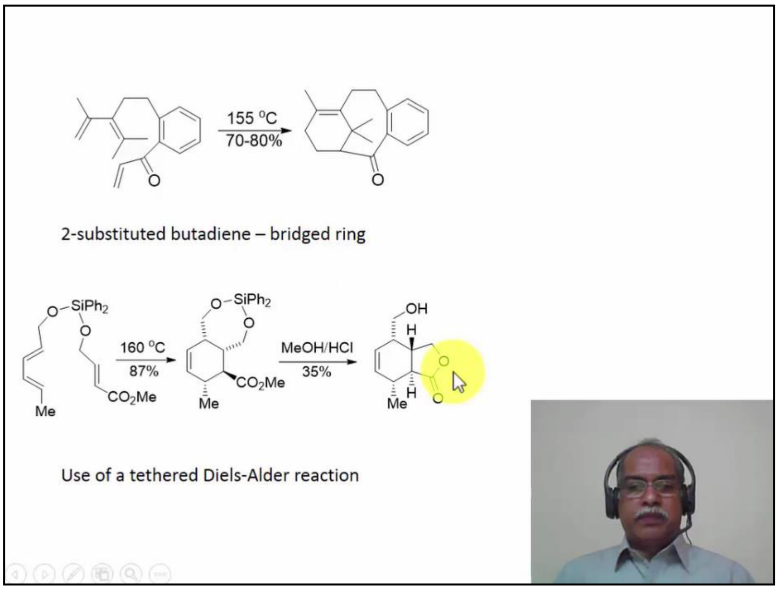

2-substituted butadiene – bridged ring

Use of a tethered Diels-Alder reaction

Here is another example of an Intramolecular Diels-Alder reaction, except the pendant group is now attached to the two position of the Diene, not at the one position, like the earlier example. When the pendant group is attached to the two position of the Diene, with this much length of the Dienophile, there is only one possibility of orientation of this Dienophile. The Dienophile essentially orients in this particular fashion, as it is shown.

And, the reaction proceeds to give the adduct, which is the bridged bicyclic adduct. In the case of these two systems, you get the fused bicyclic adduct. Whereas, in the case of the two-substituted Butadiene, you get a bridged bicyclic system, as one would expect in this particular case. Now, it is possible to attach the Diene and Dienophile, through a temporary connector like the Silicon connector, in this particular case.

The Diene is an alcohol. The Dienophile is also an alcohol. The alcoholate is reacted with the Diphenyl Silyl Dichloride to get this Silicon bridged system. In other words, this is a tethering that is used, which is removable tethering in this particular case. So, heating this particular Diene-Dienophile combination, essentially results in the formation of the adduct, which is shown here.

This adduct is essentially, the Endo adduct of this particular molecule. From this, the Silicon can be cleaved off by acid catalyzed hydrolysis, of this particular lactol kind of a derivative, that you have here. So, the hydrolysis essentially leads to the formation of the Di-alcohol, under the conditions of acidic condition, the esterification takes place in this particular case.

So, the esterified product, which is the Lactone product, is what is obtained during the course of the Intramolecular Diels-Alder reaction, followed by the work up, which is the acidic ethanol methanol work up. Acidic methanol work up is essentially, an alcoholysis of this particular Silicon derivative. And, that essentially results in the formation of the alcohol here, which undergoes the lactonization process, to give this particular Lactone, that is shown here.

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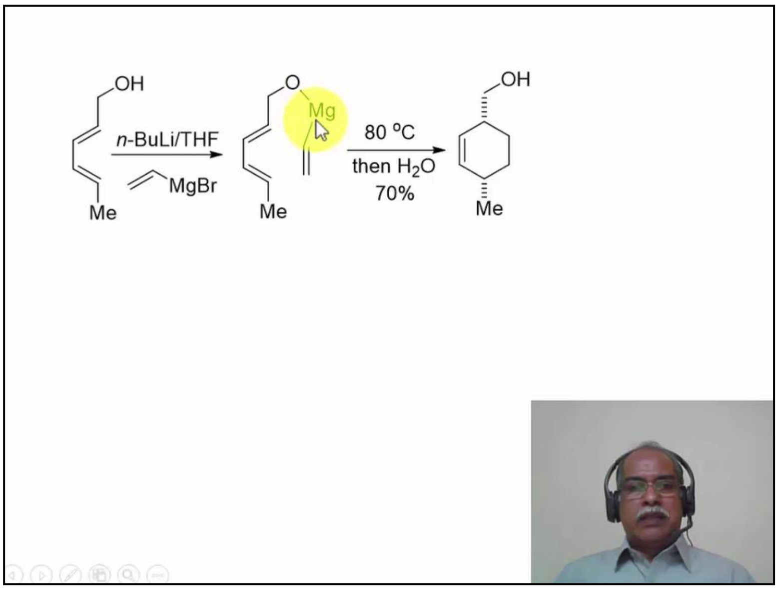

Here is an interesting example. The alcohol is first treated with Butyllithium, to get the corresponding Lithium salt. And then, it is treated with Vinyl Magnesium Bromide. The intention here is to exchange, the Lithium with the Magnesium. Such that, the Magnesium, Vinyl, Bromide, gets attached to the alcoholate, forming the Magnesium alcoholate. Such that, it brings the Diene and the Dienophile close together.

When it is heated to 80 degrees, and then, quenched with water, essentially the Magnesium salt is hydrolyzed, when it quenched with water. Heating to 80 degrees itself, in the formation of the Diels-Alder adduct, which is shown here. And, the stereochemistry of these two ring junctions, that are this particular junction, this particular Carbon, and this Carbon essentially, Cis with respect to each other, as one would expect in the Diels-Alder reaction.

So, this is an example, where the Magnesium, Vinyl Magnesium Bromide, is essentially chelated to the Oxygen of the alcoholate, resulting in the formation of the Diels-Alder reaction, which is an Intramolecular Diels-Alder reaction, of a Magnesium tethered compound.

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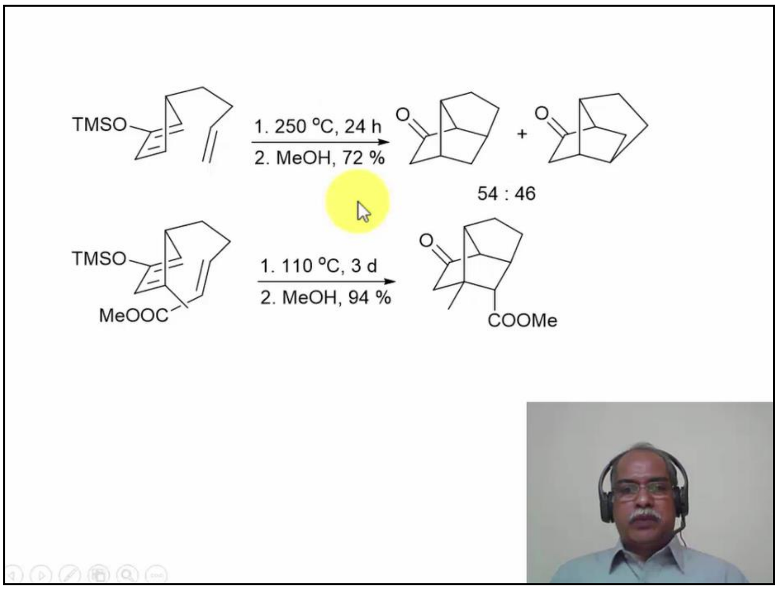

These are examples of Intramolecular Diels-Alder reaction, where the pendant group attached, is a vinyl group in this particular case. And, the Diene is essentially a very reactive Diene, which is an Enol Trimethylsilyl Ether kind of a Diene. When it is heated at 250 degrees for example, there are two possible orientations, this Dienophile can take with respect to the Diene. And, in one case, one orientation, as it is shown for example, gives you the Diels-Alder adduct, which is this particular Diels-Alder adduct.

If you orient in the other way around, in other words, if you bring this Carbon over here, and this Carbon over here, that would give this other orientation, which results in the formation of this particular Diels-Alder adduct. On the other hand, when the Dienophile is biased by an electron withdrawing group, then only the Para kind of a substitution pattern is obtained. If you look at the orientation of this Diene and the Dienophile, this is an Endo orientation, and also it is an orientation, where the OTMS group, and the COOME group, are Para with respect to each other. You can see here, the Para relationship.

So, the Para like product is, what is initially formed. The TMS Silyl group is hydrolyzed by Methanol, in both cases. The top equation, as well as the bottom equation, the work up is done by methanol, essentially to cleave up the O-Trimethylsilyl group, to get the Ketone back. The Enol will essentially undergo Keto Enol Tautomerism to give the Ketone, which is a cyclic adduct, which is eventually formed during the course of this reaction.

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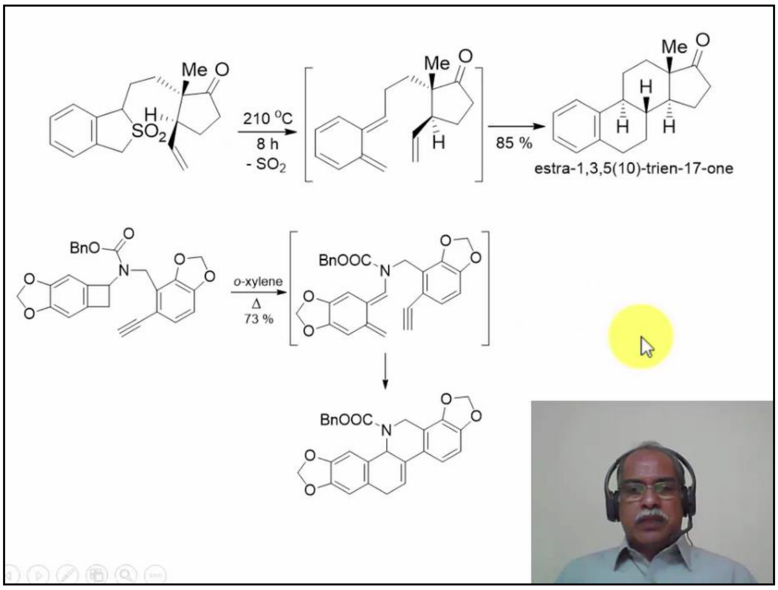

These are some interesting examples of, the Diene being generated In-situ, during the course of the heating. In this particular case, this Sulfolene, the Benzo Sulfolene is heated, Sulfur-dioxide is eliminated. It is a chelotropic reaction. We will see, some examples of chelotropic reaction, at a later stage. For the time being, assume that the Sulphur-dioxide elimination, results in the formation of the Ortho Quinodimethide, in this particular case.

This vinyl group is a built-in vinyl group. So, this tether essentially brings a vinyl group, in close proximity to the Diene. And, as a result of that, the Diels-Alder reaction takes place to give an Estrone as the product, in this particular case. This Benzcyclobutene derivative is heated in Ortho-xylene, refluxing Ortho-xylene for example, to produce this Ortho Quinodimethide as the intermediate.

The Ortho Quinodimethide has an acetylene group, which is a built-in acetylene group. And, the pendant group brings the acetylene group in close proximity to the Diene, resulting in the formation of a 4+2 cycloaddition reaction, to give this particular adduct, which is the Diels-Alder adduct, in this case.

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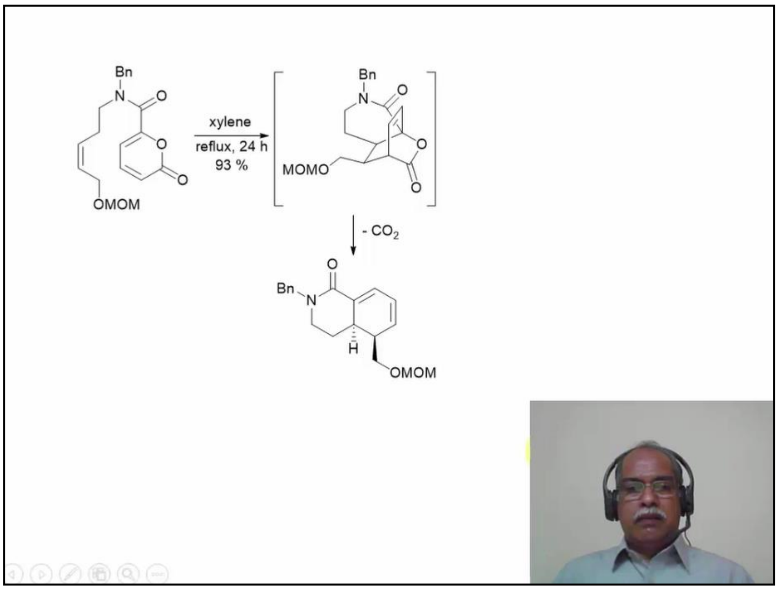

Here, the Diene is actually an alpha Pyrone derivative. The alpha Pyrone derivative can undergo Diels-Alder reaction, with this particular vinyl derivative, which is attached through a pendant group, which is this particular pendant group, in the form of an amide linkage. Diels-Alder reaction in refluxing xylene, produces this particular adduct. This adduct is not stable under the reaction condition. It undergoes the loss of CO2. By means of loss of CO2, you generate this Diene fragment, in this particular system.

This kind of CO2 bridged systems are angle strained, because one cannot maintain 120 degrees' angle of the Carbonyl SP2 Carbon, in this particular case. So, such an angle strain is released by means of elimination of Carbon-dioxide, in this case. And, as a result of that, Carbon-dioxide elimination, this adduct is formed, which is the Diels-Alder adduct of the pyrone, with respect to the Diels-Alder reaction with the vinyl derivative, that is the pendant group, here.

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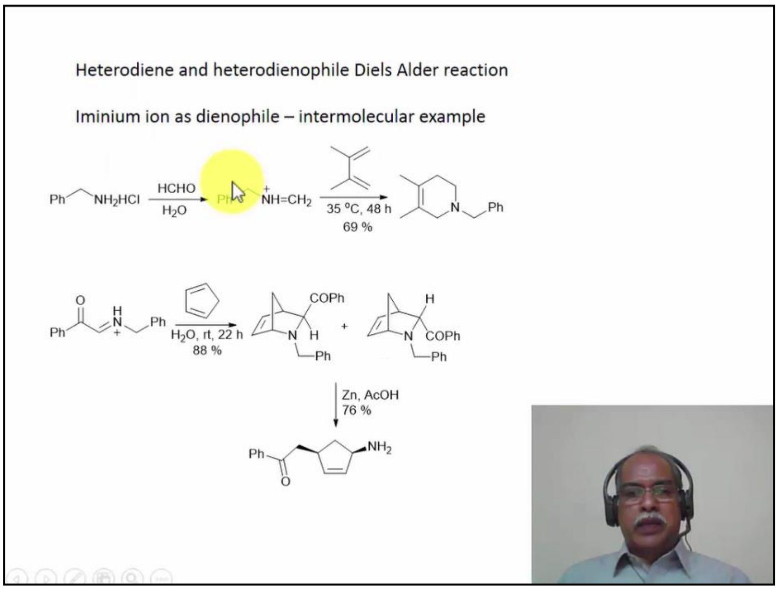

Heterodiene and heterodienophile Diels Alder reaction

Iminium ion as dienophile – intermolecular example

Let us move on to the Hetero Diels-Alder reaction, using a Hetero Diene, or a Hetero Dienophile. In this particular case, we are dealing with Iminium ion as a Dienophile, and Intramolecular examples are shown here. The Iminium ion is produced In-situ, by a reaction of a primary Amine Hydrochloride with formaldehyde, with the loss of water for example, resulting in the formation of an Iminium ion.

If the synthesis of the Iminium ion is carried out in the presence of a Diene, which is in this particular case, 2,3-Dimethyl Butadiene, then the 4+2 cycloaddition reaction, essentially gives you a Tetrahydropyridine derivative, in this particular case You can see here, this is a four PI component, and a two PI component, which is an Iminium ion, which is an electron deficient in nature.

And, that is why, the reaction essentially proceeds at room temperature or so, giving this particular derivative, which is the Tetrahydropyridine derivative. Here is an Iminium ion, which is generated from the Aldehyde and the primary Amine. And, that reacts with Cyclopentadiene, to give two types of adducts, the Exo adduct, and the Endo adduct. This is Exo, with respect to the Carbonyl functional group, and the bridge here.

And, this adduct is an Endo adduct, with respect to the Carbonyl functional group and the bridge, that is given here, for example. The Carbon-Nitrogen bond in this kind of an adduct, can be easily reductively cleave, to give the primary amino derivative of this kind. And, that has been exploited in the synthesis of the amino alkyl substituted cyclopentene derivative, with the stereo selective formation of the Cis isomer of the 1,3-Disubstituted Cyclopentene derivative, from the adductive cleavage of the Carbon Nitrogen bond, from this kind of an adduct.

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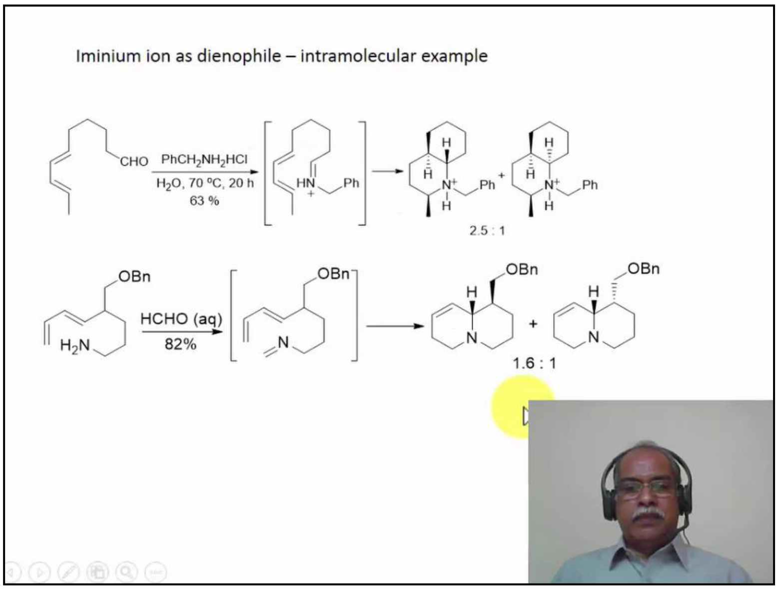

Iminium ion as dienophile – intramolecular example

Here are some interesting examples of Intramolecular versions of the Iminium ion Diels-Alder reaction. This particular aldehyde, which has a built-in Diene, is reacted with Benzylamine Hydrochloride. Upon reacting with Benzylamine Hydrochloride, it forms the corresponding Iminium ion. The Iminium ion, undergoes the Diels-Alder reaction, which is an Intramolecular Diels-Alder reaction. Here, both the Exo, as well as the Endo adducts, are formed in 2.5:1 ratio, for example. So, the corresponding Diels-Alder adduct, is what is formed.

There is a double bond missing, in this particular structure. So, please correct it that. This would essentially result in the formation of an adduct, with a double bond in this position, and a double bond in this position, in this case. Now, the Iminium ion is formed In-situ, by reacting this primary amine. Here, aldehyde is taken and reacted with the primary amine. Aldehyde is part of the Diene. Now, the amine can be part of the Diene. And, it can be made to undergo reaction with formaldehyde, to produce the corresponding Imine, in this particular case.

So, the primary amine and the formaldehyde reacts together, to form the Imine. And, the Imine undergoes the Diels-Alder reaction, which is a Hetero Diels-Alder reaction, to produce the corresponding bicyclic derivative, which is this bicyclic derivative. The orientation of the Imine, and this Diene, can be Exo or Endo, that would result in the relative stereochemistry, to be either Cis or Trans, as the case may be, in these two cases.

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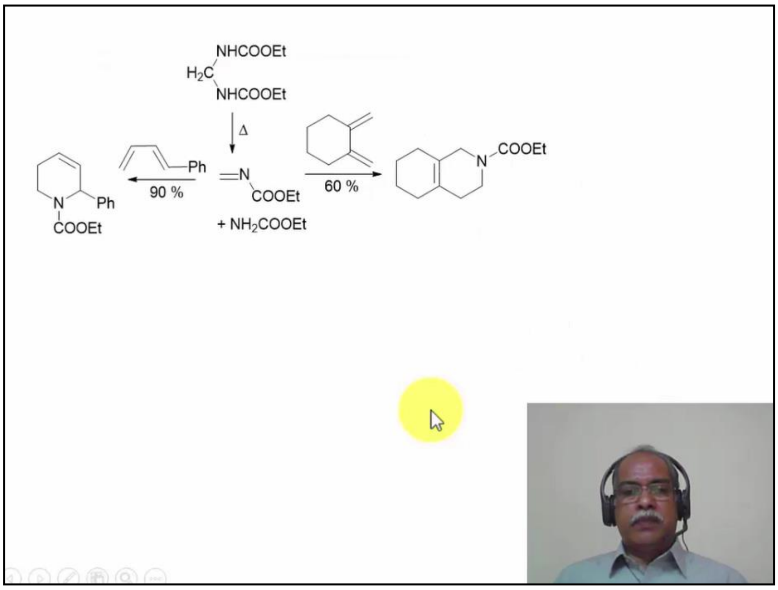

Now, in this example, this Carbamate is heated initially. The Carbamate undergoes the loss of Ethyl Carbamate, in this particular case, resulting in the formation of an Imine, which is an Ethyl Carboxylate substituted Imine. And, this is essentially an Imine Carbamide kind of a derivative, is what is generated. And, that reacts with one Phenyl substituted Butadiene, to produce the corresponding Phenyl substituted Tetrahydropyridine derivative, in this particular case.

On the other hand, it reacts with this particular Diene, to produce the bicyclic system, which is this particular bicyclic system, which is a Diels-Alder adduct, arising from the, this Intramolecular Diels-Alder reaction between the Diene and the Dienophile, producing this kind of Diels-Alder adduct, in this case.

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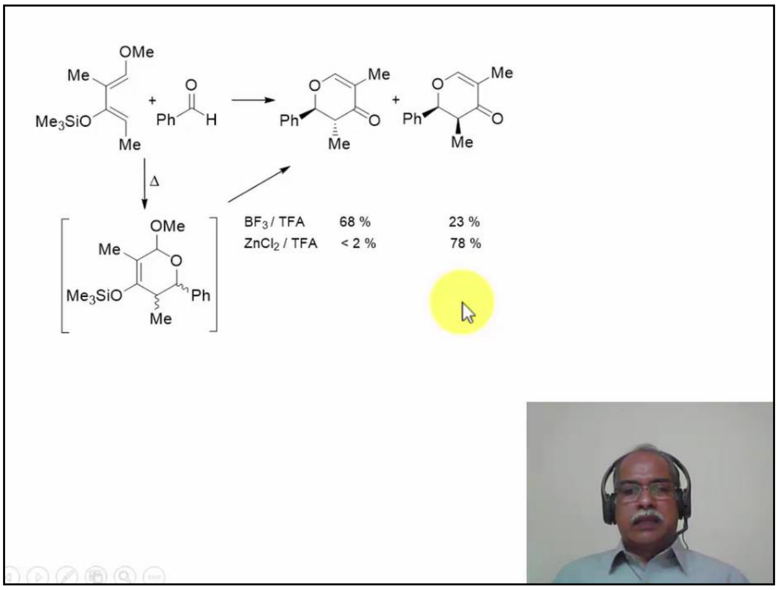

BF_3 / TFA	68 %	23 %
$ZnCl_2$ / TFA	< 2 %	78 %

Now, these are interesting examples of synthesis of Gamma Pyrone derivatives, from the so-called Diene, that is this particular Diene. This Diene is known as Danishefsky’s Diene. Danishefsky’s Diene does not have, this two methyl group. So, it is actually a Dimethyl derivative of the Danishefsky’s Diene. You can see here, this Diene is endowed with electron rich functional group, namely the Methoxy and the Trimethylsilyl-Oxy derivative.

It reacts with the aldehyde, which is Benzaldehyde, in this particular case, in a Diels-Alder fashion, to initially give a regio selective adduct, which is this particular adduct. You can see here, this is an Ortho-Para kind of a product, is what is Ortho, with respect to the Methoxy, and Para with respect to the Trimethyl-Oxy derivative. And, this particular adduct is exclusively formed, during the course of the Hetero Diels-Alder reaction. It is a Hetero Diels-Alder reaction, because the Dienophile is a Carbon-Oxygen double bond, and not a Carbon-Carbon double bond, as in the case of earlier examples.

So, this is a Hetero Atom substituted Dienophile. The Hetero Diels-Alder reaction, essentially produces, this Oxygen heterocycle. This Oxygen heterocycle can be made, to further undergo desilylation reaction, with the loss of Methanol for example, in the presence of Boron Trifluoride TFA mixture, or Zinc-chloride TFA mixture, to essentially produce this two adducts, which are arising out of this particular stereochemistry of the two orientations, that are possible for the Diene and the Dienophile.

The Exo-Endo orientation essentially determines, the stereochemistry of this two junctions, that are two Carbons, that are produced during the course of this particular reaction.

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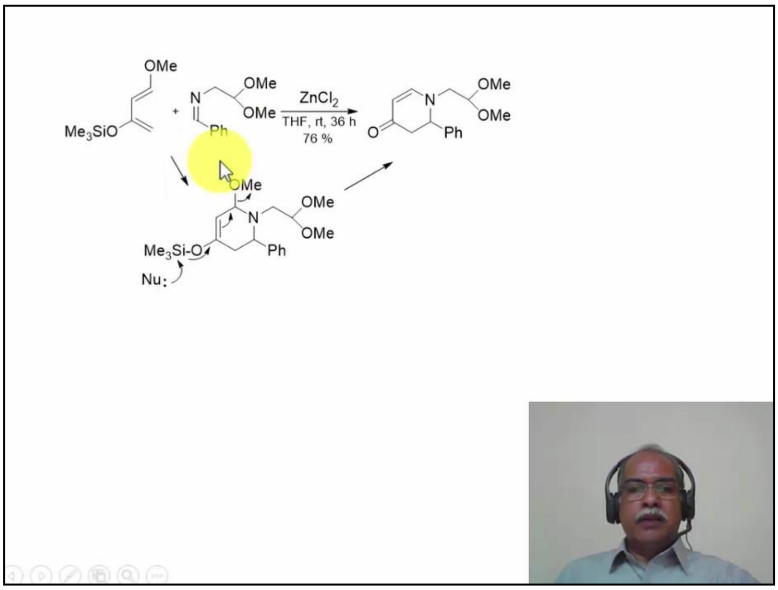

This is another example of a Danishefsky's Diene, reacting with an Imine. The earlier case, it was a reaction with an aldehyde. This particular case, it is a reactant with an Imine. And, the Danishefsky's Diene is this particular Diene, which is a 1-Methoxy,3-Trimethylsilyl Butadiene, in this particular case. The initial Diels-Alder adduct structure is shown here. And, the mechanism of loss of Methanol with the Trimethylsilyl group, is what is shown, to yield this Gamma Pyridine derivative, in this particular case.

A Nucleophile, which could be for example, Methanol, or Chloride, or Fluoride ion, for example, reacts with the Silicon center, with the loss of the Carbon Silicon bond cleavage, with a simultaneous loss of the Methoxy group in the third position of the molecule, resulting in the formation of the Gamma Pyridine derivative, which is shown as a final product, during the course of this particular reaction.

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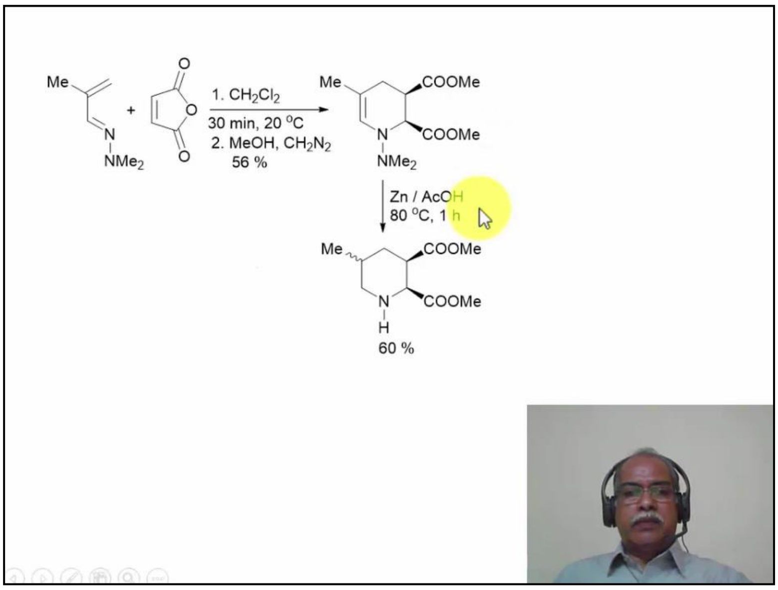


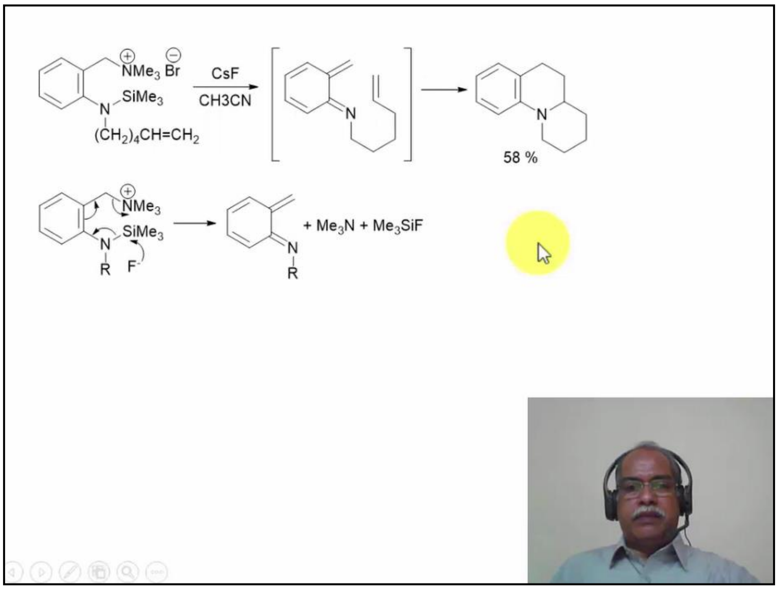
Here is an example of a Hetero Diels-Alder reaction, where the Diene is having the Hetero atom, and not the Dienophile. Until now, we had an Imine and Aldehyde as the Hetero Dienophiles. Now, we are dealing with a Diels-Alder reaction, where the Diene possesses a Hetero atom, in this particular case, Nitrogen. If you look at this derivative, this is nothing but an Alpha Methyl Acrolein, which is the aldehyde forming a hydrozone with NN-Dimethylhydrazine, for example. So, if you react Alpha Methyl Acrolein with NN-Dimethylhydrazine, this is a hydrozone, that one would produce.

And, that hydrozone is acting as the Hetero Diene, reacting with Maleic Anhydride as the Dienophile. The reaction is essentially taking place at room temperature, resulting in the formation of the Diels-Alder adduct. The Diels-Alder adduct is now undergoing hydrolysis with Methanol, to produce the corresponding Carboxylic acid. The Anhydride is hydrolyzed to Carboxylic acid. Then, it is treated with a Diazomethane, to produce the corresponding Ester. So, this is part of a natural product synthesis, for example.

The Piperidine derivative that is produced, is highly stereo selectively produced in this manner. The final reaction is essentially a Nitrogen-Nitrogen reductive bond cleavage, by treating this hydrous Hydrazine derivative with the Zinc and Acetic acid, where the reductive cleavage of the Nitrogen-Nitrogen bond results in the formation of the piperidine derivative, that is shown here. The stereochemistry of the two Carboxylic acid groups are Cis with respect to each other. Essentially because, it is coming from a, initially an Anhydride system, which are Cis with respect to each other.

So that, Cis stereochemistry is retained, during the course of the reaction. This relative stereochemistry between this Carbon center, and this Carbon center, would essentially depend upon, whether it is an Exo adduct, or Endo adduct, that is not properly defined, in this particular case. Because, it could be a mixture of Exo or Endo adduct, that is formed. Sorry, these three mesenteries, essentially produced by a reduction of the Carbon-Carbon double bond.

So, that can be, both the enantiomers can be produced, under the conditions of Zinc Acetic acid reduction of the Carbon-Carbon double bond, in this particular case. The Enamine is reduced to the corresponding Imine, if you look at the reaction carefully. This is essentially an Enamine kind of a system. It is not only a Nitrogen-Nitrogen bond reductive cleavage takes place, the Carbon-Carbon bond is also reduced, during the course of the Zinc Acetic acid reduction, in this reaction.



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Now, here is a generation of a Diene In-situ, from this derivative. This derivative can undergo 1,4-Elimination reaction. The mechanism of the 1,4-Elimination reaction is shown, in this particular case. The Trimethylsilyl Amine, and the Ammonium group, are the leaving groups, in this particular case.

When, these molecule is treated with Cesium Fluoride, the fluoride ion essentially being, highly Silicon affinity nature of the fluoride ion, results in the formation of the attack of the Silicon by the fluoride ion, resulting in the formation cleavage of the Nitrogen Silicon bond, leading to the elimination of the Trimethylamine as the leaving group, in this particular case, results in the formation of this particular Diene, which is a Hetero Diene.

A built-in Dienophile, which is this vinyl group, essentially traps the Diene, that is being produced in this particular case, resulting in the formation of the Diels-Alder adduct, which is this particular Diels-Alder adduct that is shown, in the final structure of the product, that is shown in this scheme.

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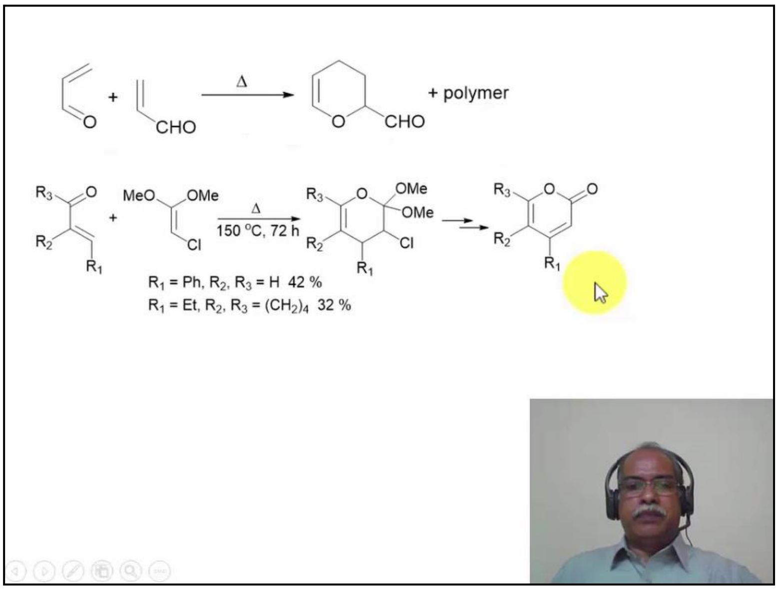

R_1 = Ph, R_2, R_3 = H 42 %

R_1 = Et, R_2, R_3 = $(CH_2)_4$ 32 %

Acrolein itself, can undergo Diels-Alder reaction, where one molecule of Acrolein reacts as a Diene, another molecule of Acrolein reacts as a Dienophile, resulting in the formation of a Pyrone derivative with an aldehyde substituent. This reaction is not synthetically very useful, because it also produces polymer. As you can imagine, Acrolein is a polymerizable material. Under thermal condition, it can undergo polymerization reaction, to produce the polymer also. Nevertheless, Acrolein derivatives can be successfully made use of, in the Diels-Alder reaction.

Here is an example of a Acrolein derivative, which is undergoing a Diels-Alder reaction, with a Ketene Silyl Acetal, Alpha Chloro Ketene Silyl Acetal, resulting in the formation of an initial Diels-Alder adduct, which is this Diels-Alder adduct. From this Diels-Alder adduct, loss of Hydrochloric acid, loss of HCL, essentially produces a double bond.

And, hydrolysis of this particular Ortho Ester, results in the formation of the Lactone, which is shown here. So, subsequently, after the Diels-Alder reaction is produced, it is treated with a base to eliminate the HCL, followed by an aqueous treatment to hydrolyze the Ortho Ester to corresponding Lactone, which is the Alpha Pyrone derivative that is produced, during the course of the final hydrolysis step.

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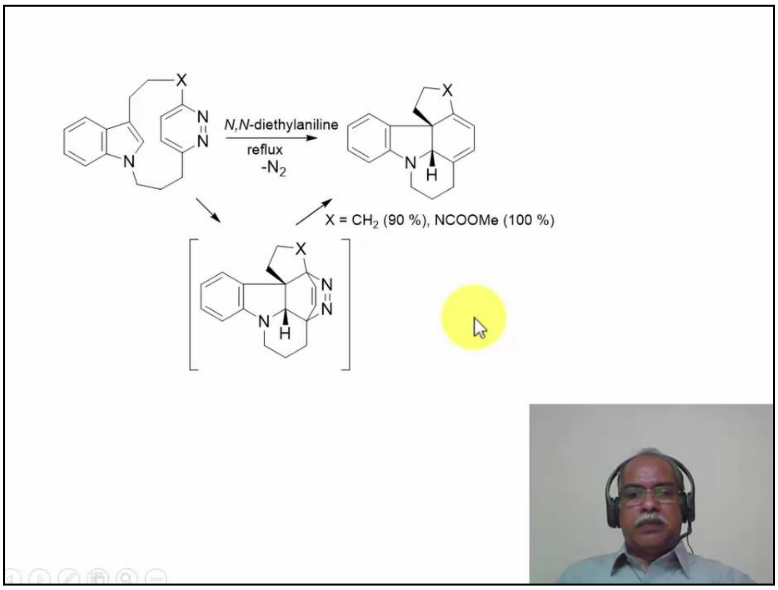

This reaction is an interesting reaction, for the simple reason that, this is a Transannular reaction. If you look at the ring, which is this particular ring. This is a medium sized ring. Medium sized ring, as you know, they undergo Transannular reaction. This Diene and the Dienophile are close proximity say, they undergo. This is essentially an indole derivative, is a cyclophoric indole derivative.

And, it undergoes the Diels-Alder reaction with the Diene, which is the Intramolecular version of the Diels-Alder reaction. Diels-Alder reaction, followed by loss of Nitrogen as sagacious Nitrogen, is the overall reaction. The initial Diels-Alder reaction is shown here, for example. You can see here, this stereochemistry is Cis, because it is a Cis stereochemistry, to start with. And, that results in the formation of this particular adduct.

This is a structure of, or this is a structural scaffold of Strychnine, which is a naturally available alkaloid molecule. So, the naturally available alkaloid Strychnine scaffold, is synthesized using the Intramolecular Diels-Alder reaction, between this Diene and this Dienophile. The reaction is carried out at high temperature in N,N-Diethyl Aniline, which is refluxing N,N-Diethyl Aniline, more than 150 degrees or so, during the course of this reaction.

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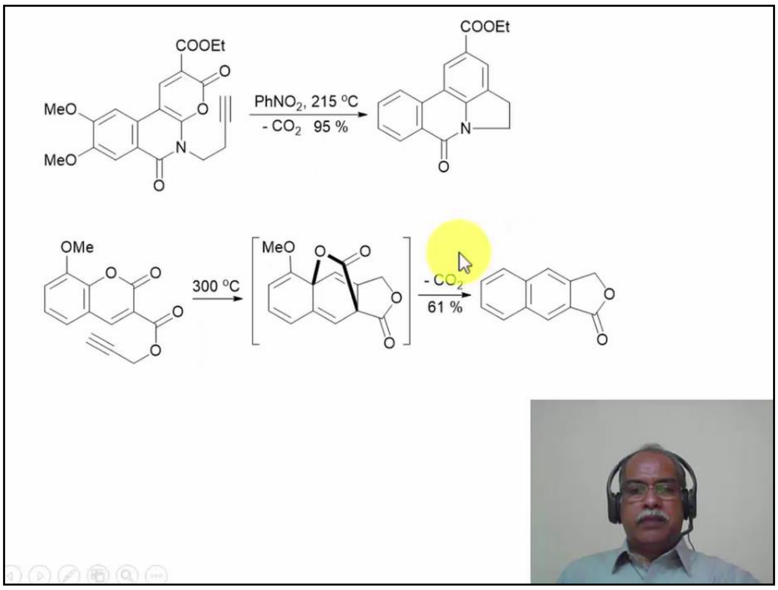

These are some examples of Alpha Pyrone, undergoing Diels-Alder reaction. Alpha Pyrones undergoes Diels-Alder reaction, to give initially an adduct, where the Carbon-dioxide bridge is being present. Carbon-dioxide bridge is not a very stable bridge, for the reason that, you have an angle strain associated with the CO, Carbonyl Carbon, which cannot accommodate 120 degrees, in this particular case. So, loss of CO2, essentially produces the adduct, which is this particular adduct.

So, initial Diels-Alder reaction between the Alpha Pyrone Diene, which is this particular fragment as a Diene, and the Dienophile, which is Acetylene in this particular case, results in the formation of the adduct, which is unstable, under the reaction conditions of 300 degrees. Loss of Carbon-dioxide, essentially produces this aromatic unit, here. Similarly, the Diels-Alder reaction between this Alpha Pyrone Diene, and this Dienophile, which is the built-in Acetylene Dienophile, in refluxing Nitrobenzene as a solvent. It is a high boiling solvent, reflexed at 250 degrees are so.

Initially, the Diels-Alder adduct structure is not shown here. But, one can imagine a similar structure of the Diels-Alder adduct, in this particular case also. This is a product, arising out of the loss of Carbon-dioxide, is what is shown, which produces this particular aromatic ring, by the loss of CO2, from the initially formed Diels-Alder adduct. So, try practicing, writing the Diels-Alder adduct, in this particular case, following the scheme of things, that are shown for this example.

A very similar structure has to be drawn, with the CO2 bridged adduct, which will lose CO2, to produce this particular compound, which is this final adduct of this reaction.

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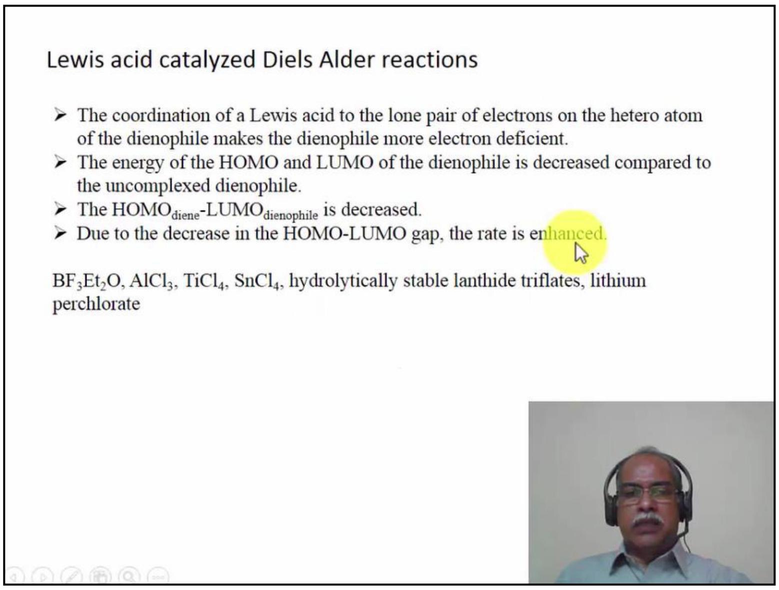

Lewis acid catalyzed Diels Alder reactions

- The coordination of a Lewis acid to the lone pair of electrons on the hetero atom of the dienophile makes the dienophile more electron deficient.
- The energy of the HOMO and LUMO of the dienophile is decreased compared to the uncomplexed dienophile.
- The $HOMO_{diene}$-$LUMO_{dienophile}$ is decreased.
- Due to the decrease in the HOMO-LUMO gap, the rate is enhanced.

BF_3Et_2O, $AlCl_3$, $TiCl_4$, $SnCl_4$, hydrolytically stable lanthide triflates, lithium perchlorate

Let us move on to, Lewis acid catalyzed Diels-Alder reaction. Now, when a Lewis acid is coordinated to the lone pair of electrons, on the hetero atom of the Dienophile, it makes the Dienophile more and more electron deficient. You can imagine that, something like an Aluminium-chloride, or a Zinc-chloride, or a Titanium-tetrachloride, or Tin-tetrachloride for example, they are all Lewis acidic in nature. The association of the Lewis acid to the lone pair of electrons on the hetero atom, is what is responsible for the electron deficient nature of the Dienophile.

Now, the energy of the Homo and Lumo of the Dienophile is decreased, in comparison to the un-complexed Dienophile, that brings the Homo-Lumo gap between the Diene and the Dienophile closer together. As a result of the decrease in the Homo-Lumo gap of the Diene and the Dienophile, the rate is enhanced, because the activation barrier is reduced. So, it is a fairly simple explanation to offer, why lewis acid addition to Diels-Alder reaction, catalyzes the reaction. There are two conditions, that one needs to meet, in this reaction.

The Dienophile should have a lone pair of electron, where the Lewis acid can be forming a complex. And, as a result of that, the catalysis takes place, because of the decrease in the Homo-Lumo gap, between the Diene and the Dienophile of the Diels-Alder reaction components. The commonly used Lewis acids are Boron-trifluoride, Aluminium-chloride, Titanium-tetrachloride, Tin-tetrachloride for example. Or, hydrolytically stable lanthanide triflates such as, Scandium triflate, or Ytterbium triflate, and so on. Lithium triflate are also has been used as a Lewis acid, in many Diels-Alder reaction.

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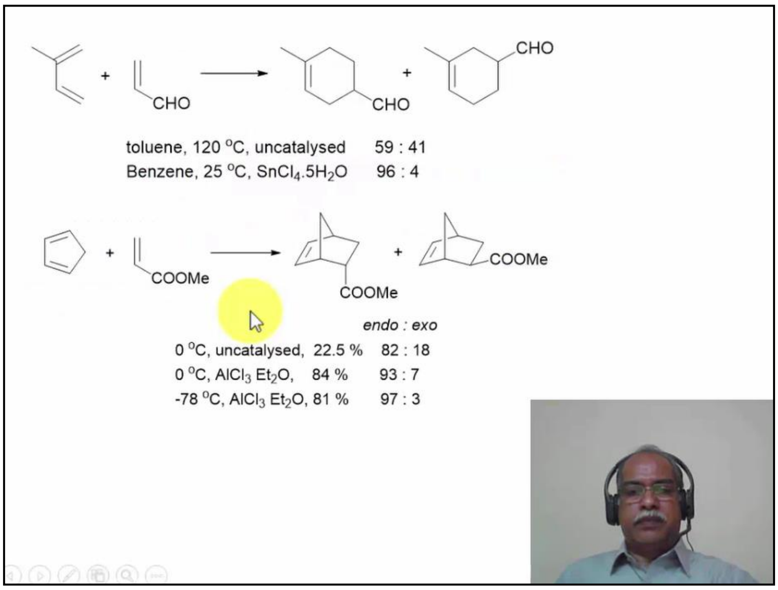

toluene, 120 ^{o}C, uncatalysed 59 : 41
Benzene, 25 ^{o}C, $SnCl_4.5H_2O$ 96 : 4

endo : exo
0 ^{o}C, uncatalysed, 22.5 % 82 : 18
0 ^{o}C, $AlCl_3$ Et_2O, 84 % 93 : 7
-78 ^{o}C, $AlCl_3$ Et_2O, 81 % 97 : 3

Some examples, to highlight the importance of Diels-Alder reaction, from the point of view of both the rate of the reaction, as well as the stereoselectivity of the reaction. Remember, the stereoselectivity, in terms of the Ortho-Para ratio can be changed, by means of using a Lewis acidic component in the Diels-Alder reaction. Here is an example of 2-Methyl Butadiene and Acrolein, undergoing a Diels-Alder reaction. Normally, when this reaction is carried out, the uncatalyzed reaction has to be heated in toluene at 120 degrees.

And, you can see here, the Meta and Para isomers, that are Diels-Alder adduct formed are in about 59:41 ratio, is what it is formed. When the reaction is carried out in Benzene, using Tin-tetrachloride as a Lewis acid catalysts. What is the role of Tin-tetrachloride? It will essentially form a complex, with a lone pair of electrons on the Oxygen of the Dienophile, in this particular case. And, there by decrease in the Homo-Lumo energy levels of the Dienophile, bringing the Homo-Lumo energy level closer together, between the Diene and the Dienophile.

We can see here, first of all the reaction temperature is reduced to room temperature. The reaction takes place at room temperature, in the presence of a Lewis acid catalyst, which means that, it is really a catalyzed reaction. Because, the activation barrier has been brought down. In addition to that, the added benefit is that, the Para isomer is almost exclusive product, in this particular case. In the absence of a Lewis acid, for example, you have a mixture of Para-Meta isomer. Whereas, in the presence of the Lewis acid, only the Para isomer is formed, more or less exclusively, in this particular case.

The meta isomer is a very small amount of 4%, is what is formed. The Endo-Exo isomer ratio can also be affected, by the Lewis acid catalysis. It is a reaction between Cyclopentadiene and Methyl Acrylate. And, the uncatalyzed reaction at zero degrees, it takes place to an extent of about only 22.5% or so, the conversion. The Endo-Exo ratio is 82:18. The Endo is still the predominant product, in this particular case. However, when Aluminium-chloride is added to this reaction mixture, the reaction proceeds to give 84% yield at zero degrees, at certain period of reaction.

And, the Endo-Exo ratio is now, more in favor of the Endo adduct, which is 93:7 ratio. When the reaction is carried out even at lower temperature, the reaction essentially goes to completion to 81%. And, the Endo-Exo ratio is further enhanced to about 97:3 ratio. So, the advantage of the lewis acid catalyzes not only a rate enhancement, it also enhances the Exo-Endo ratio, or the Ortho-Para, Ortho-Meta ratio, kind of a regio isomeric ratios, are also improved, during the course of the catalysis of the Diels-Alder reaction.

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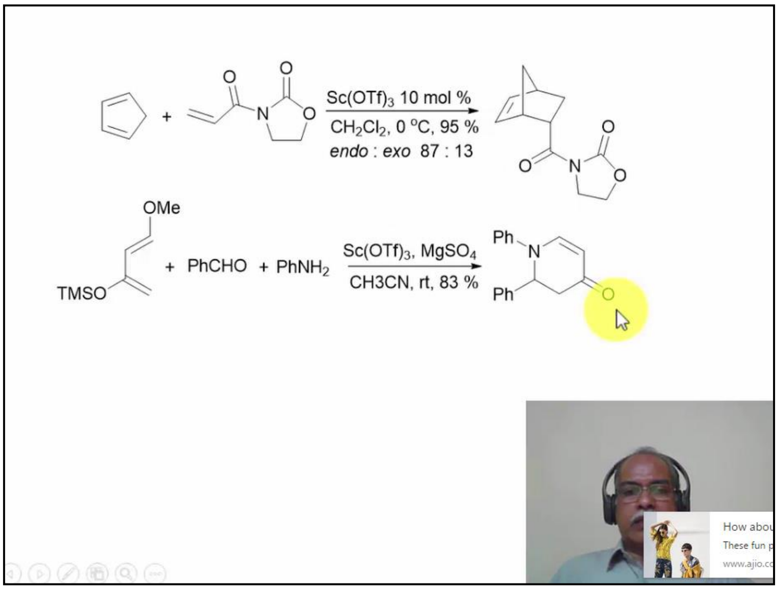

Here are two examples, where Scandium triflate is used as a Lewis acid. Scandium is in Scandium-3-Oxidation state. And, it can undergo chelation between these two Oxygens of the Carbonyl functional group, of this particular pendant group, that is shown in this particular structure. The reaction is the, Scandium triflate is used only to an extent of ten mole percent. So, it is truly a catalytic reaction. The reaction between Cyclopentadiene, and this particular Dienophile, results almost exclusively in the formation of Endo product as a major product, in this particular case, in the ratio 87:13 ratio.

Now, here is an example, where the Hetero Diels-Alder reaction, the Imine is formed In-situ. This is something, we have seen. Except, this is now catalyzed by a Scandium triflate, and Magnesium sulfate, as the Lewis acid combination in Acetonitrile. So, the Iminium ion, that is produced initially, can coordinate to the Scandium triflate, in making the Scandium triflate coordinated Iminium ion, to be a much more reactive Dienophile. And, that undergoes a

Diels-Alder reaction, to give this Pyridone derivative, after the hydrolysis of the Trimethylsilyl group, and loss of Methanol from the Diels-Alder adduct, of this particular molecule.

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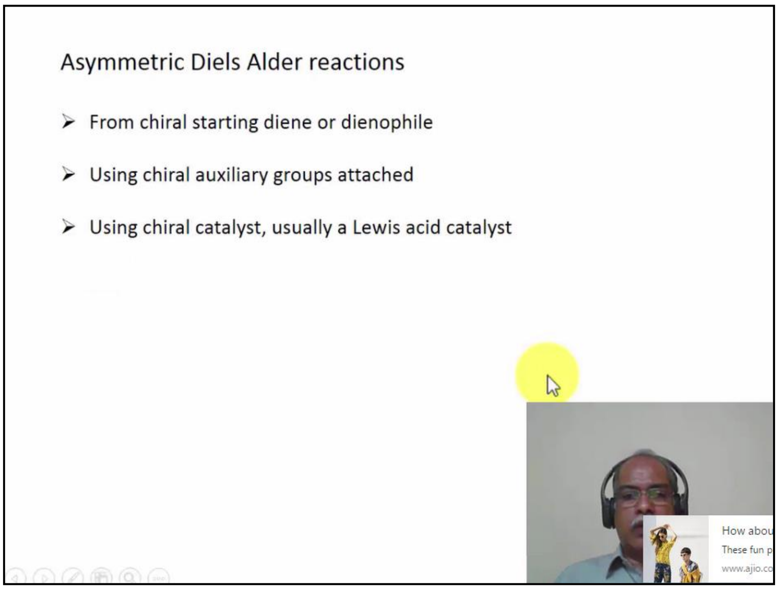

Asymmetric Diels Alder reactions

- From chiral starting diene or dienophile
- Using chiral auxiliary groups attached
- Using chiral catalyst, usually a Lewis acid catalyst

Finally, we will touch up on the Asymmetric Diels-Alder reaction. The Asymmetric Diels-Alder reaction can be carried out, in three different ways. It could be from chiral starting materials, where optically pure isomer of the Diene or the Dienophile is taken. And, it is reacted with the counterpart, to give the corresponding asymmetric induction. Or, a chiral auxiliary, can be used. Chiral auxiliaries are temporarily attached to chiral pendant groups, to the Diene or the Dienophile, which can be removed by cleavage, or by hydrolysis kind of a reaction.

So that the, after the chiral induction takes place, the auxiliary can be removed and recycled. Last and the most popular methodology, is to use a Chiral Lewis acid. The Chiral Lewis acid essentially is, as simple as a Lewis acid catalysis. Except that, in the case of the Chiral Lewis acid, the Lewis acid is initially coordinated to a chiral ligand, which makes the Chiral Lewis acid, which in turn catalyzes the reaction of the Diels-Alder reaction.

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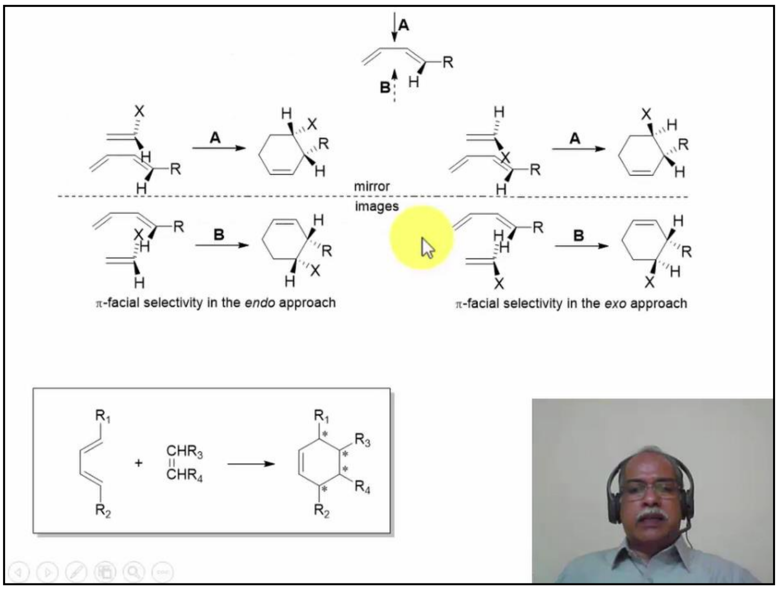

Let us, first of all, try to understand the basic principle behind the Asymmetric Diels-Alder reaction. Now, if you consider the Diene, the Diene is a planar unit. The Dienophile can either approach from the top face, or from the bottom face. And, these two faces are enantiotopic faces of the Diene. If it approaches from the top face, it will produce one enantiomer. If it approaches from the bottom face, it will produce another enantiomer. In this example, what we have taken is, a one substituted Diene. The substituent is R group, for example.

And, one substituted Dienophile, where the substituent is X. Now, in addition to the approach from side A and side B, either from the top face or from the bottom face, the approach can be also Endo or Exo. So, there are four possible approaches. Top face A approach with Endo-Exo, and B side approach with an Endo-Exo kind of an approach. So, all the four types of approaches are shown here, producing the corresponding stereo isomer, in each case. Now, when the approach is taking place, from either A side or B side, and if it is controlled as an Endo approach, then you will produce a pair of enantiomers.

So, these two isomers are enantiomers of each other. Similarly, if the approach from the A side or B side is taking place, with an exclusive Exo approach of the Diels-Alder Dienophile, you can see here, the X-group is Exo, and here also the X-group is Exo. And, that produces the corresponding diastereo isomer of this molecule. Now, these two structures, which are divided by this dash line, which is the mirror plane, for example. These are mirror images of each other. So, they are enantiomers. So, A and B are truly enantiotopic faces, produces an enantiomer.

Similarly, these two molecules are also enantiomer. But, if you take this molecule, and compare it with this molecule, here. In other words, the Endo approached molecule, and the

Exo approached molecule, they are diastereo isomeric in nature. Now, let us assume that, the control is possible that, we approach only from the A side, and only through the Endo side. Then, this is the only molecule, that would be produced, or predominantly produced, which is the basic principle of the asymmetric synthesis, where you induce asymmetric chiral center, chirality by asymmetric induction, for example, produce a particular stereoisomer.

So, by nature, the Endo approach is a most preferred approach, in a Diels-Alder reaction, particularly, when it is a Lewis acid catalyzed Diels-Alder reaction. And, if the Lewis acid also promotes the approach, either from the A side or B side selectively, then you would have produced only single enantiomer, or predominantly a single enantiomer of the adduct, that is formed. This is illustrated for a simple two-chiral center system.

This can be extended to a four-chiral center system also, as it is shown, in this particular case, where you have four consecutive chiral centers, that are produced by Diels-Alder reaction, between a disubstituted Diene and a disubstituted Dienophile, as a generic example, in this case.

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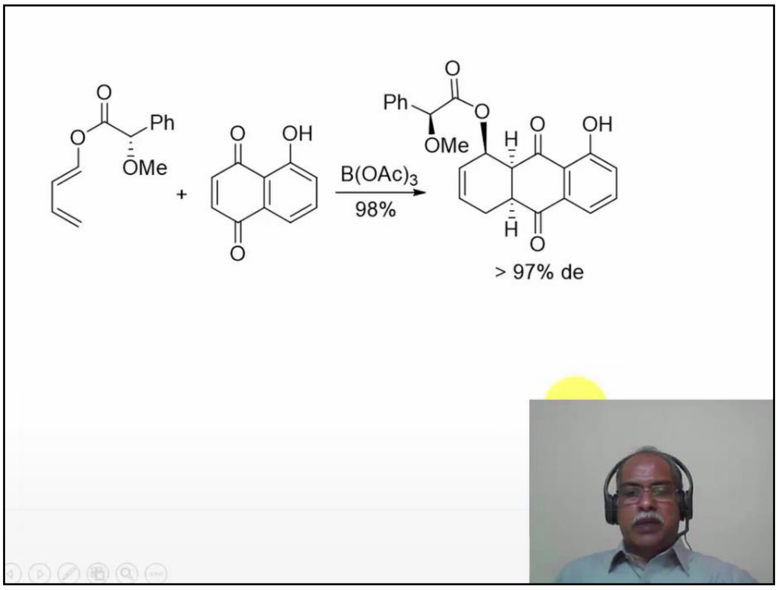

here is an example, where Methyl Mandelate is used as a chiral auxiliary, or you can call the starting material, to be optically pure isomer. Because, only one enantiomer of the Methoxy Mantellic acid derivative is formed, with this particular Enol Ether, for example. Now, the Diels-Alder reaction with this particular Naphthoquinone derivative, produces 97% diastereo selectively, this particular adduct, where the Pendant group and the Hydrogen are Trans with respect to each other. In other words, the approach is an Endo approach.

And, the Endo approach is essentially producing this particular molecule. This is essentially an Anhydride of Boric acid, and Acetic acid. Boron acetate, you can call it. The correct terminology that, this is an anhydrous of Boric acid, and Acetic acid mixture. And, this is essentially acting as a Lewis acid, because Boron is a Lewis acidic center, that will coordinate to this two Oxygen, chelate these two Oxygen, and thereby catalyzing the reaction to produce this particular devious diastereo isomer. If this pendant group can be cleaved, then only one enantiomer of this molecule would be produced, during the course of the Diels-Alder reaction.

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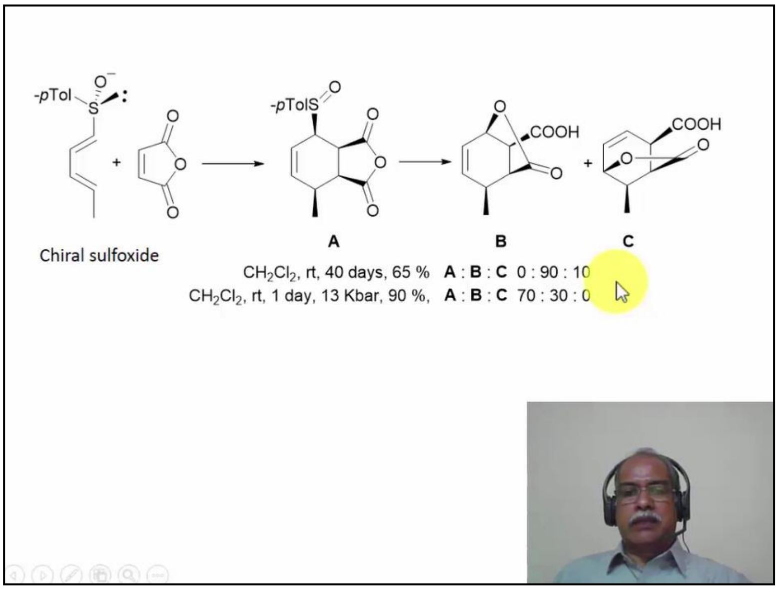

Chiral sulfoxide

CH_2Cl_2, rt, 40 days, 65 % **A** : **B** : **C** 0 : 90 : 10

CH_2Cl_2, rt, 1 day, 13 Kbar, 90 %, **A** : **B** : **C** 70 : 30 : 0

Another example, a Chiral Sulfoxide is taken. Optically pure isomer of the Chiral Sulfoxide, of course, it is enantiopure Diene, reacting with the Dienophile, which is Maleic Anhydride. The initially formed Diels-Alder adduct is essentially a, in this particular case, an Exo kind of an adduct is what is formed, during the course of the reaction. This is an Allyl Sulfoxide. Allyl Sulfoxides undergo rearrangement by a 2,3-Sigmatropic rearrangement, to give the corresponding Allyl Sulfonate. The Allyl Sulfonate undergoes a lactonization with Anhydride.

And, that is responsible, it can undergo a lactonization, with either this Carbonyl functional group, or with this Carbonyl functional group, for example, producing two types of Lactone derivative, which is a bridged Lactone derivative, in this particular case. The reaction is not catalyzed by any Lewis acid. The reaction takes place, either at room temperature, for 40 days, at yielding 65%. Or, it is carried out under high pressure of 13 kilobars pressure, yielding the product to be about 90% yield or so.

Diels-Alder reaction can also be promoted by high-pressure, because the orientation of the two Diene and the Dienophile, would be favored under high-pressure. Because, we have a tight compact transition state that is being formed, during the course of this reaction.

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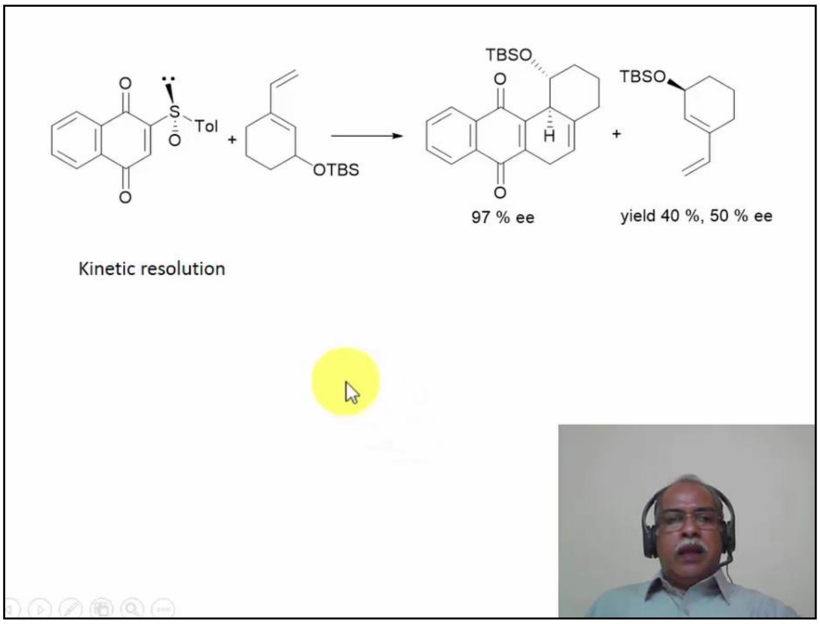

97 % ee

yield 40 %, 50 % ee

Kinetic resolution

Another example, where the sulfoxide is actually attached to a Dienophile. In the earlier case, it was attached to a Diene. Now, it is attached to a Dienophile. Now, let me first say something, about the kinetic resolution. Kinetic resolution is a reaction, where you take racemic mixture of compound, and only one enantiomer reacts preferentially, or one enantiomer reacts much faster than the other enantiomer.

And, thereby producing the cycloadduct, or the reaction product, from one enantiomer, leaving the other enantiomer intact. So, you consider the mixture of enantiomers. This is a racemic mixture of the Diene, is what is taken. You can see, this is a chiral center. So, racemic mixture of this Diene, reacts with the optically pure isomer of the Sulfoxide.

The reaction proceeds with only one of the enantiomers of the Diene, with this particular configuration, the enantiomer is used for the Diels-Alder reaction, is results in the 97% yield of this particular Diels-Alder adduct. The Trimethyl Sulfoxide group is eliminated, after the Diels-Alder reaction is over. Leaving the other Diene, which is this particular configuration Diene, which is an unreactive Diene under this case, in about 50% enantiomeric excess, and 40% yield.

In other words, if you take 1:1 mixture of the enantiomers of the racemic mixture of this particular Diene, only one of the Diene is reacting with this configuration in the chiral center. The other Diene, with this configuration, the chiral center is unreactive, under these conditions. And, that is the basic principle of the kinetic resolution, which is illustrated by this particular example.

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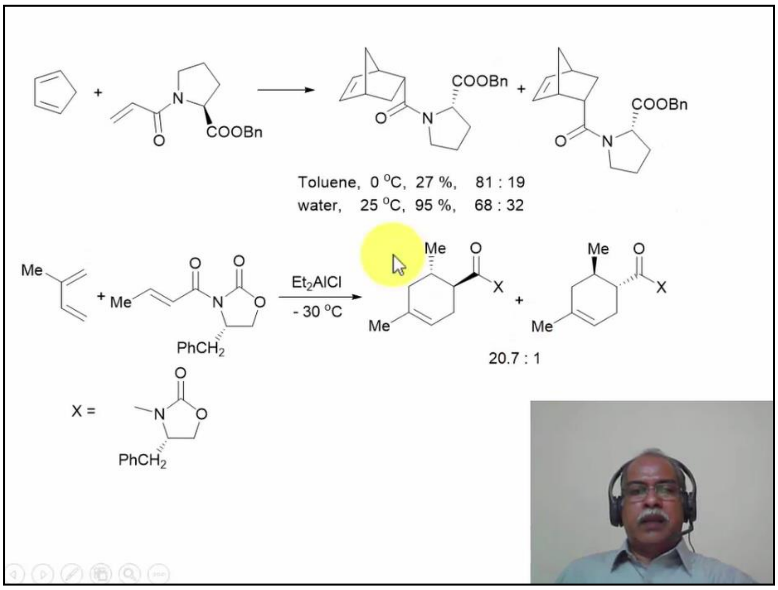

Toluene, 0 °C, 27 %, 81 : 19
water, 25 °C, 95 %, 68 : 32

20.7 : 1

These are some examples of Diels-Alder reaction, either catalyzed by a Lewis acid, just like the Lewis acid, that is shown here. So, let us consider these reactions, carefully. This Cyclopentadiene reacts with this Acrylamide derivative, in the presence of water, for example. Water can catalyst Diels-Alder reaction, through Hydrogen bonding interaction, resulting in the formation of the two isomers of the, diastereo isomers of the product, that has been formed in this particular case.

And, the reaction, when it is catalyzed by a Diethyl Aluminium-chloride, which is a Lewis acid, the Aluminium can coordinate to, or chelate to this particular derivative. This is a chiral derivative. So, when Aluminium coordinates to this, it catalyzes the reaction. Because, the Lewis acid catalysis, which enhances electrophilicity of the Dienophile, for example.

Under these conditions, the Exo-Endo ratio of the isomer is 20:1, almost exclusively, the Endo isomer is formed, during the course of the reactions. This is a chiral auxiliary, that is coordinated to the aluminium center, for example. So, this is an asymmetric catalysis of the Diels-Alder reaction, is what we are referring to, in this particular case.

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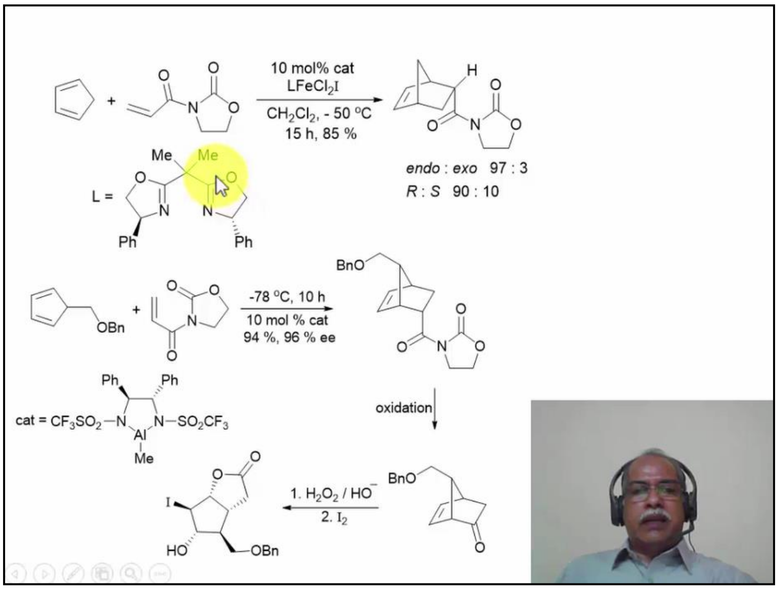

This is a ligand, which is a chiral ligand. It can coordinate to the Iron, which in turn can coordinate to the chelate, to the two Carbonyl Oxygens, in this particular molecule. And, it is a Lewis Acid Catalyst Asymmetric Diels-Alder reaction, where the Lewis acidic nature of the Iron, and the chiral nature of this particular ligand, makes the entire Lewis acid as a Chiral Lewis acid. And, catalysis by Chiral Lewis acid gives exclusively one enantiomer, in this particular case, an R isomer is formed, in about 90% yield.

Here is another example of a Diels-Alder reaction, where this Chiral Aluminium reagent is used as a catalyst, for example. So, ten mole percent of this catalyst is used. The Aluminium will essentially coordinate to this two Carbonyl Oxygens, catalyzing this reaction. Reaction takes place essentially at -78 degrees, to give exclusively the Endo adduct, which is shown here. The Endo adduct is oxidized by means of an oxidizing agent, to produce this Ketone. In other words, this Carbon-Carbon bond is oxidized to the corresponding Ketone.

The Ketone undergoes, a Baeyer Villiger kind of an oxidation, to form a Lactone. And, the Lactone undergoes further iodolactonization, to give this particular product. The relative stereochemistry of the iodolactonization, you can see is anti, as one would expect. The Iodine, to be forming an Iodonium ion, followed by attack of the Oxygen of the Lactone from the Endo side, leaving the Iodine in the Hexo side, for example, resulting in the formation of the Trans isomer. The Iodine, and the OBN group- the Benzyl Oxy group, for example, they would be Cis with respect to each other.

Because, Iodine will be Exo. And, this is also in the same side. So, those two are relatively speaking, they are Cis with respect to each other. And, finally the hydroxy functional group, that is produced by the lactonization reaction, becomes Anti with respect to the hydroxy functional Iodine, which is adjacent position, for example. So, the entire stereochemistry can be explained on the basis of the Lactone, that is being formed, by the Diels-Alder reaction. Cleavage of the Lactone, followed by the attack of the Lactone by iodolactonization, to form the Iodolactone, that is shown in this particular stereochemistry of the product, that is shown here.

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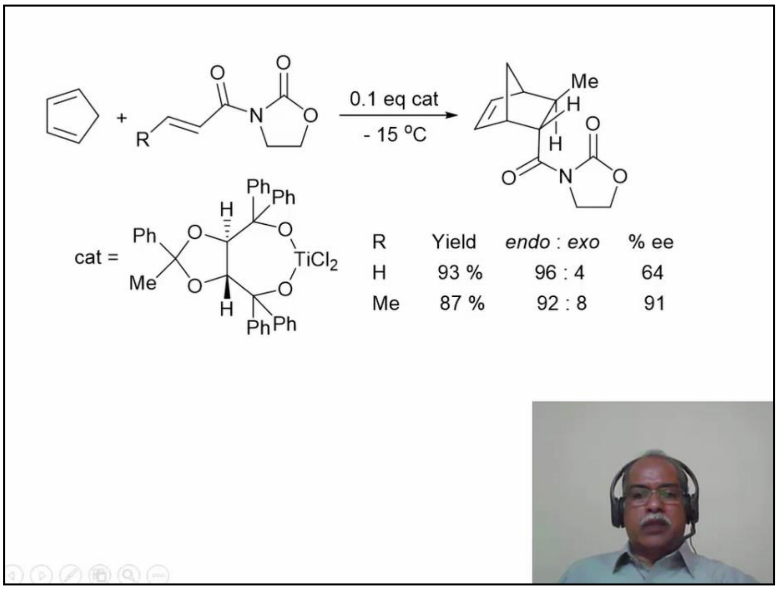

R	Yield	*endo* : *exo*	% ee
H	93 %	96 : 4	64
Me	87 %	92 : 8	91

Here is an example, where the derivative of Tartaric acid, which is known as Tadol, is used to complex the Titanium dichloride. This is produced from, reaction of the Diol with Titanium-tetrachloride, or Titanium Dichloride Diisopropoxide as the starting material. That is used as a catalyst 0.1 equivalent. In other words, ten mole percent, is what is used as a catalyst. And, that affects the Exo-Endo ratio, as well as, one enantiomers of the product is formed, during the course of the catalysis of this Chiral Lewis acid, for this Diels-Alder reaction.

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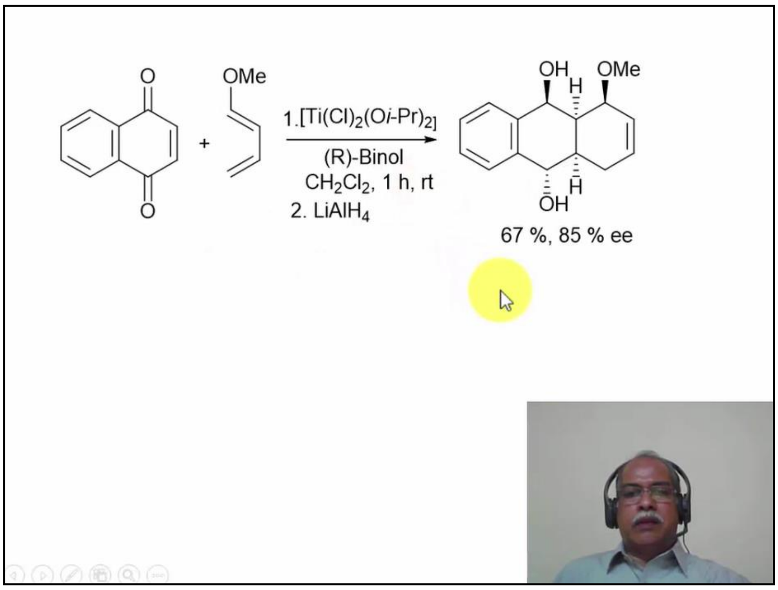

Another example, where Binal is used. Binal is, 1,1-Binaphthol is Binal. And, the R isomer of Binal is a chelating agent. That can chelate the Titanium, to the Titanium-dichloride derivative. The two isopropoxide groups, can be substituted by a Binal derivative. A Diels-Alder reaction essentially, initially produces the Diketone, which is reduced by Lithium Aluminium hydride, to the corresponding Diol.

You can see, very high enantiomeric excess of this particular isomer, can be formed. We have essentially generated, five stereo centers in one shot, in this particular reaction, by means of a Diels-Alder reaction, followed by reduction of the Carbonyl to the corresponding hydroxy functional group.

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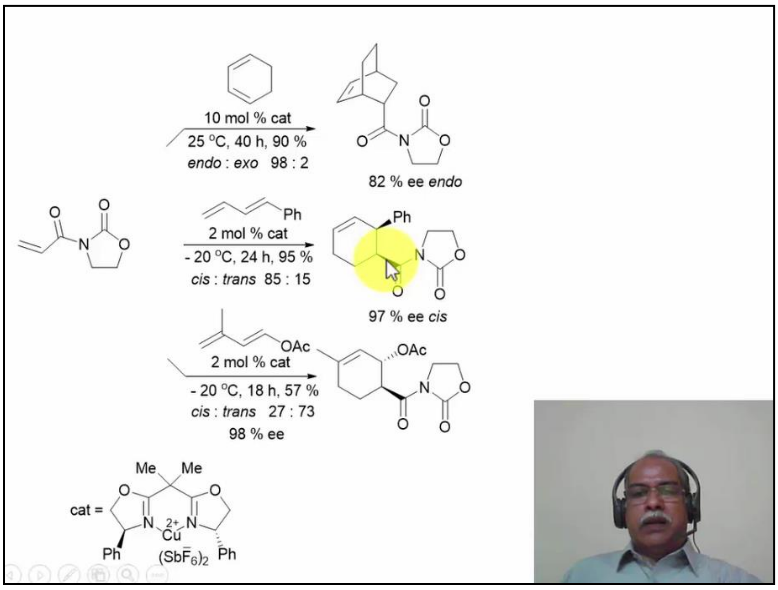

These are again, some more examples of the Diels-Alder reaction, produced by catalysis, using this Copper Bisoxazoline derivative as the Lewis acid catalyst. In Lewis acid catalyst essentially coordinates are, chelates to this two Oxygens of the Dienophile. In this case, the Cyclohexadiene, or 1- Phenyl substituted Butadiene, or this particular Enol Acetate Diene, is what is used as a Diene component, resulting in the formation of very high Endo selectivity, with a high enantiomeric excess of the product that is formed, during the course of the Diels-Alder reaction, in this case.

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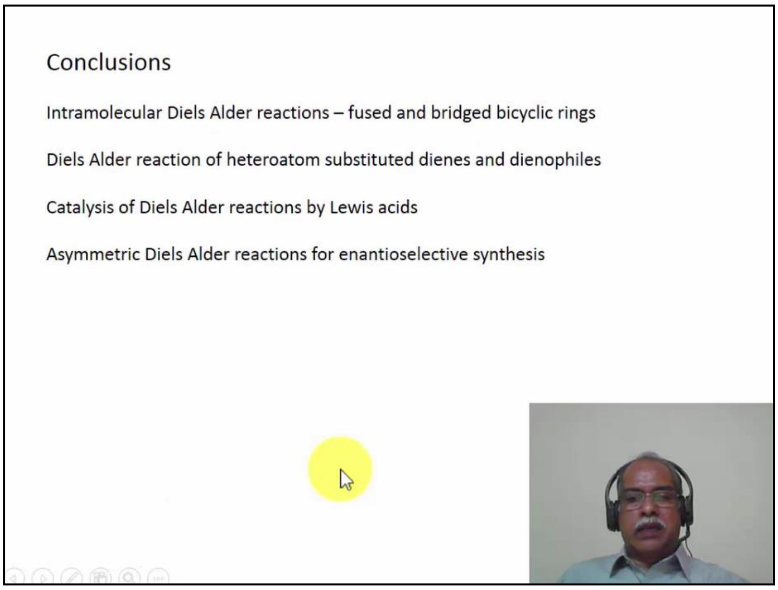

Conclusions

Intramolecular Diels Alder reactions – fused and bridged bicyclic rings

Diels Alder reaction of heteroatom substituted dienes and dienophiles

Catalysis of Diels Alder reactions by Lewis acids

Asymmetric Diels Alder reactions for enantioselective synthesis

So, let us conclude this particular module. What we have seen in this module is, the Intramolecular versions of Diels-Alder reaction, to produce fused and bridged bicyclic system. If it is a one substituted derivative, then it will be a fused bicyclic system. If it is a two substituted Diene derivative, then it will be a bridged bicyclic system. We have also seen, Diels-Alder reactions of Heteroatom substituted Dienes and Dienophiles, predominantly Oxygen and Nitrogen Hetero atoms are, what is illustrated in the examples.

Catalysis by Diels-Alder reaction by Lewis acid catalyst, has some examples, have been seen. Where a Lewis acid coordinates, to the lone pair of electron in the Dienophile, reducing the Homo-Lumo energy levels of the Dienophile, bringing the Homo-Lumo energy gap of the Diene-Dienophile combination closer together, and thereby reducing the activation barrier.

Finally, the basic principle behind the asymmetric Diels-Alder reaction, and some examples of Enantioselective, Asymmetric Diels-Alder reaction, particularly those had catalyzed by Chiral Lewis acid, have been illustrated in this particular module. I hope, you enjoyed the molecule module. Thank you very much, for your kind attention. Thank you.