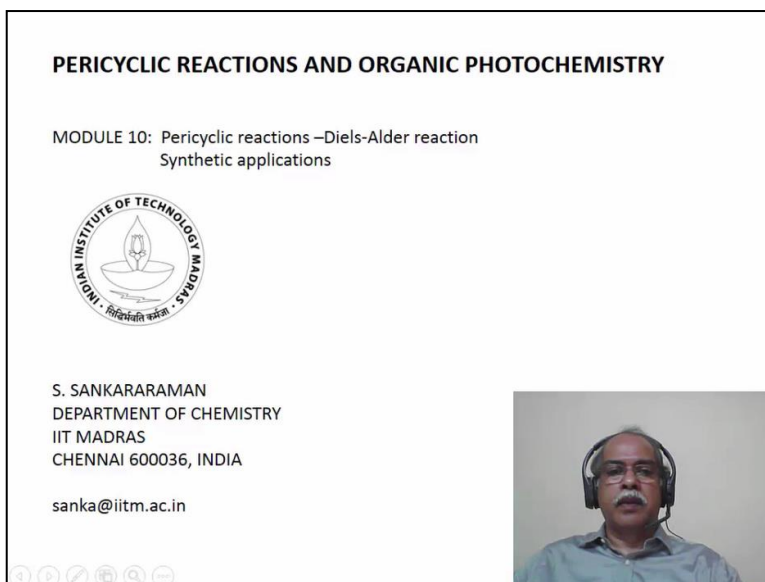


**Pericyclic Reactions and Organic Photochemistry**  
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**Module No. #02**  
**Lecture No. #10**  
**Pericyclic Reactions – Diels-Alder Reaction**  
**Synthetic Applications**

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**PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY**

MODULE 10: Pericyclic reactions –Diels-Alder reaction  
Synthetic applications



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Hello, welcome to the online course on Pericyclic Reactions and Organic Photochemistry. We are now, in Module Ten. We are, so far seen, Diels-Alder reaction, the basic aspects of Diels-Alder reaction. The regio and stereo selectivity aspects also, we have seen. Now, it is time to see some examples of, how Diels-Alder reactions are used in synthetic applications, in the synthesis of, some fascinating organic molecules.

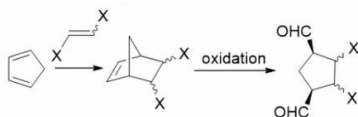
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### Synthetic applications of Diels-Alder reactions

Useful for stereoselective and regioselective synthesis of 6 membered carbocycles and heterocycles and bicyclic compounds.

The products of Diels-Alder reactions, namely cyclohexene and cyclohexadiene can be aromatized by dehydrogenation using various reagents

Bicyclic compounds that are products of Diels-Alder reaction can be converted to cis-1,3-disubstituted cycloalkenes



Now, Diels-Alder reaction initially gives a six-membered Carbo cyclic ring, or a six-membered heterocyclic ring, depending upon, whether we are doing a Carbon-based Diene and Dienophile, or Heteroatom based Diene and Dienophile. Now, it can also produce bicyclic compounds, if the Diene or the Dienophile is already cyclic in nature. Now, the product of Diels-Alder reaction namely Cyclohexene and the Cyclohexadiene, can be aromatized by dehydrogenation reaction, using various reagents.

So, it is not that, it produces only a six-membered ring, which is a Cyclohexene ring. It can also produce a six-membered ring, which is a Benzene ring, by a suitable mechanism of dehydrogenation, using various reagents. The bicyclic compound, that are produced by Diels-Alder reaction, can also be converted in to Cis-1,3-Disubstituted-Cycloalkenes. Here is a nice example of that. Let us assume that, the Diels-Alder reaction between this Dienophile and the Diene proceeds to give this particular 2,2,1-Bicyclic Norbornene type of a structure.

Now, upon oxidation or by ozonolysis, this double bond can be cleaved, and that will result in the formation of a 1,3-Cis-Dialdehyde, Cyclopentane-Dialdehyde, of such sort. Now, depending upon the Stereochemistry of the two X groups in this Dienophile, the two X groups can be either Cis or Trans, or they can be Endo or Exo. Assume, they are Cis, and they are Endo in nature. Then, all this four functional groups in the Cyclopentane, will be having the same Stereochemistry, relative Stereochemistry, namely Cis, All-Cis Stereochemistry, is what one would have.

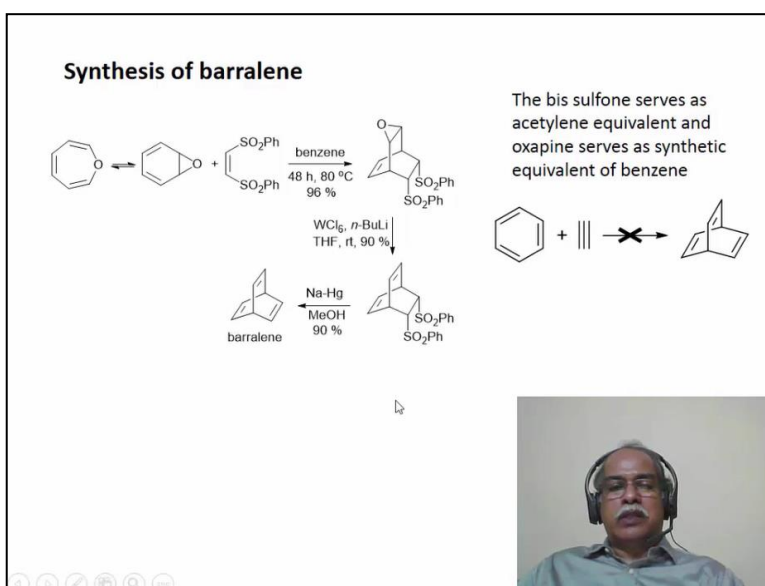
So, it is not that, Diels-Alder reaction can produce only, stereo selectively six-membered ring system. That six-membered ring system, so produced can be manipulated, to a five-membered

ring system, in a stereo selective manner. Now, why does this ozonolysis produce, the Cis Isomer of the Dialdehyde. That is because, the two Carbon-Carbon bonds are pointing in the same direction downwards. And, as a result of that, the ozonolysis essentially produce the relative Stereochemistry of the two Aldehydes, to be Cis with respect to each other.

Now, the relative Stereochemistry between the Aldehyde and the X group will depend upon, whether you have an Endo selective addition, or an Exo selective addition. All likelihood, the Endo selective addition will be the predominant product. So, that would mean, this Aldehyde and the two X group, and the other Aldehyde will be, all Cis with respect to each other, in this type of a situation.

On the other hand, if it is an Exo selective product formation, then the aldehydes and the two X groups, will be Trans with respect to each other. So, both the Stereo Isomers, it is possible to produce, using the Diels-Alder reaction.

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Now, let us take a beautiful example of Barrelene. This molecule is called Barrelene. Because, it is supposed to look like a barrel. It is essentially a 2,2,2-Bicyclic system, Bridged Bicyclic System. Retro Synthetic Analysis will tell you that, this molecule can be produced by a Diels-Alder reaction, between Benzene and Acetylene. Of course, Benzene does not undergo Diels-Alder reaction, readily. And, so does Acetylene. It does not undergo the Diels-Alder reaction, quite readily. Both of them are very inert compound, and they do not undergo the Diels-Alder reaction between and themselves, to produce Barrelene.

So, how do we produce Barrelene, in an indirect manner, as shown in this particular scheme. Now, take the balance Isomerization of Oxepine to Benzene oxide. So, this is essentially an electrocyclic ring closing reaction. Under thermal condition, certain amount of the concentration of the Benzene Oxide form, exist in the Oxepine structure. So, that undergoes Diels-Alder reaction, much faster than the Oxepine, itself.

So, this behaves like a Diene. And, the Endo selective Diels-Alder reaction, essentially produces this 2,2,2-Bicyclic framework, that is necessary for the Barrelene synthesis. Now, this is a Disulfone substituted derivative, Sulfonyl substituted derivative. And, that is acting as an equivalent of Acetylene, in this particular synthesis, as we will see soon. Now, all we need to do is, get rid of the functional group, and introduce a double bond in this position.

And, also introduce a double bond, at this position. Now, deoxygenation is what is necessary, to be done of the Epoxide, to produce this Olefin. And, this is best performed by Low Valent Tungsten kind of a compound, the Tungsten Hexachloride. Tungsten is in the maximum valence. When it is reduced with a strong Butyllithium kind of a reducing agent, it will go to Low Valent Tungsten. And, the Low Valent Tungsten is very oxophilic, and it is capable of removing this oxygen, and go to Tungsten Oxide.

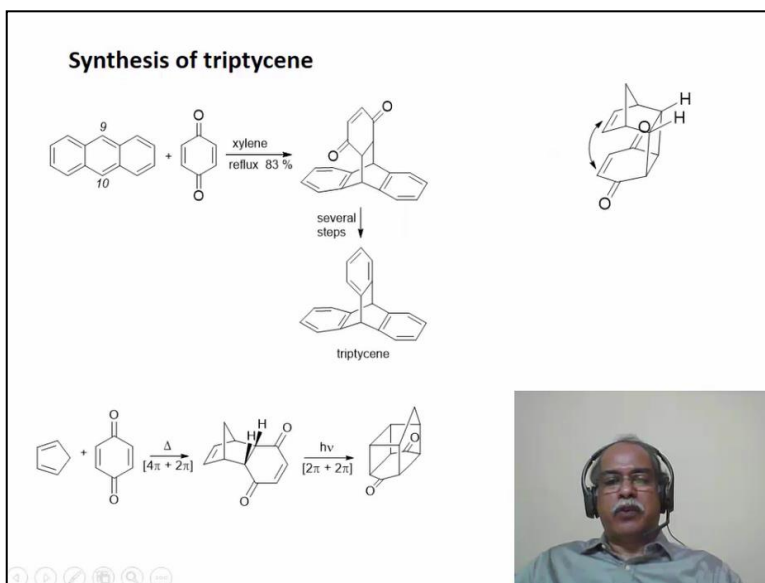
So, the Low Valent Tungsten, that is produced by the reaction between Tungsten Hexachloride and Butyllithium at low temperature, essentially deoxygenates this Epoxide, to produce this Olefin. Now all you have to do is, do the desulfurization reaction, or the desulfonation reaction, is what it needs to be done. This is best.

The Carbon Sulfur bond is best treated with, reductively cleaved by usage of the Sodium amalgam in Methanol. So, reduction of Sodium amalgam in Methanol, produces a Carbanion at the center, by the cleavage of the Carbon Sulphur bond. And, the Carbanion so produced, undergoes 1,2-Elimination of the other sulfone derivative, as a Phenyl Sulfinat. So, the elimination of Phenyl Sulfinat, two moles of Phenyl Sulfinat, essentially produces a double bond over here. So, this is a beautiful synthesis of 2,2,2-Bicyclic compound, which is called Barrelene.

What could not be accomplished in a direct manner, is accomplished in an indirect manner, quite elegantly so. We can see here; the yields of the individual steps are nearly quantitative. 90 plus yields, is what is obtained. So, Barrelene can be conveniently synthesized, by this particular

methodology. So, here is an example of the power of Diels-Alder reaction, in terms of producing the basic framework of the Barrelene, which is a 2,2,2-Bicyclic framework.

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Here is an example of, a propeller shaped molecule called a Triptycene. This molecule is a three-blade propeller shaped molecule. This has a C<sub>3</sub> axis of rotation, passing through the front SP<sup>3</sup> Carbon, and the backside SP<sup>3</sup> Carbon. Such a molecule, can be produced by a Diels-Alder reaction, as illustrated in this particular example. Now, the basic propeller framework is designed and synthesized by, the cycloaddition reaction of Anthracene and Benzoquinone. Anthracene is a very reactive Diene.

The 9, 10 positions of Anthracenes, are quite reactive. They behave like a typical Diels-Alder Diene. And, they undergo Diels-Alder reaction, across the 9, 10 positions. In doing so, they produce a double bond at this position, which completes the sextet of this particular ring. So, instead of an Anthracene having only one sextet, upon Diels-Alder reaction, it produces two sextets, or two individual Benzene rings, which is probably having a higher resonance energy, than Anthracene itself.

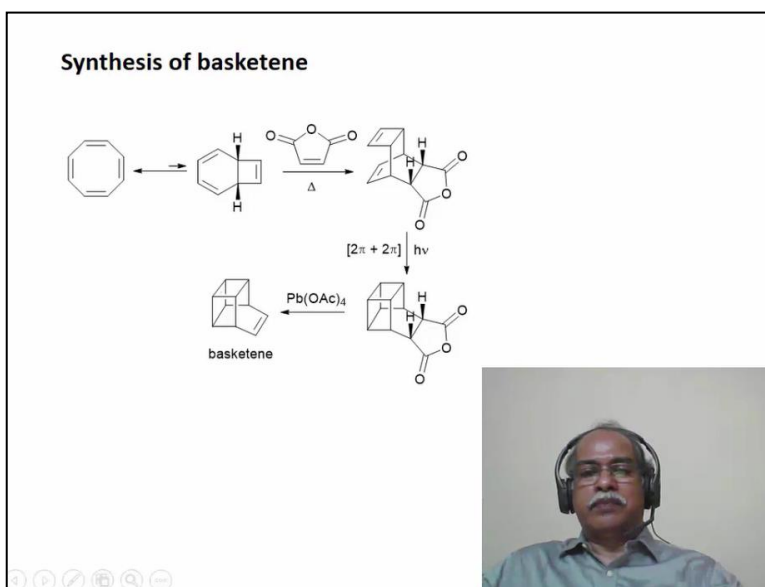
That is one of the reasons, why the 9, 10 positions of Anthracene are extremely reactive, towards Diels-Alder reactions. The reaction of this molecule with the Benzoquinone, essentially produces the necessary framework, for this molecule. And, the reduction and elimination of Hydrogen Peroxide in this molecule, essentially produces a Triptycene molecule, which is the tribenzene Benzannulated 2,2,2-Bicyclic system of this kind. Now, this is a cage type of a molecule.

That is also can be produced by a Diels-Alder reaction, in combination with a 2PI-2PI cycloaddition reaction. So, the initial thermal 2+4 cycloaddition reaction, or the 4PI-2PI cycloaddition reaction in a Suprafacial manner, and in an Endo selective manner, will produce this particular molecule.

The 2,2,1-Bicyclic framework is essentially produced, because of the fact that, your Diene is a cyclic Diene. And, a cyclic Diene produces a bridged bicyclic system. And, the structure of this is, shown here. This is an Endo product. In other words, the Benzoquinone moiety, essentially lies underneath the 2,2,1-Bicyclic framework, that brings this double bond, in close proximity to this double bond, with the distance separation of less than 3.5 angstroms or so. And, as a result of that, the 2PI-2PI cycloaddition reaction, between these two Olefinic system is quite facile.

So, under photochemical condition, this molecule undergoes a 2+2 cycloaddition reaction, forming the Cyclobutane ring, which is this particular Cyclobutane ring, in this molecule. And, now Decarbonylation followed by elimination of one of the methylene group, essentially can produce a Cubane kind of a structure, which is a caged molecular structure, that we have here.

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A similar cage molecular structure, is also known as Basketene. It is a very interesting molecule. This double bond is supposed to be the handle of a tilted basket, as it is drawn in this particular shape. Now, this molecule is synthesized, using this particular methodology, shown in this particular slide. The Cyclooctatetraene undergoes valence Isomerization, by means of an electrocyclic ring closing reaction under thermal condition, to give this fused bicyclic system, where you have a Cis fusion of the bicyclic system. And, this is again a Diene.

So, this can undergo a Diels-Alder reaction. Compared to Cyclooctatetraene, this will undergo Diels-Alder reaction, much faster. Because, this is a six-membered Diene, compared to an eight-membered ring system, which is this particular ring system. Cyclooctatetraene does not undergo Diels-Alder reaction. So, the Valence-Isomer, which is a Cyclohexadiene unit bicyclic compound, undergoes Diels-Alder reaction with Maleic Anhydride, in an Endo selective fashion, upon heating. And, this Endo adduct, is what is necessary, for the formation of the caged compound.

Because, in the Endo adduct, this Cyclobutene ring and the Cyclohexene ring, these two double bonds are face-to-face, with respect to each other. So, they undergo a very facile 2PI-2PI cycloaddition reaction, under photochemical condition. So, the first step Diels-Alder reaction is a 4PI Suprafacial-2PI Suprafacial cycloaddition reaction. The second stage is a photochemical 2PI Suprafacial-2PI Suprafacial cycloaddition. Such a cycloaddition, essentially builds this Cubane structure, in this molecule.

Now, all you need to do is, Hydrolyze the Anhydride to the Dicarboxylic acid. And, the Dicarboxylic acid can be oxidatively decarboxylated, to give this Olefin, using Lead Tetra Acetate as an oxidizing agent. Lead Tetra Acetate is a powerful oxidizing agent. So, it oxidizes the Carboxylic acid, to the corresponding radical by decarboxylation. So, as a result of that, the decarboxylative, oxidative decarboxylation of this Diacid, essentially produces this Olefin, which is the Basketene, in this structure.

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**Synthesis of [2,2]paracyclophane derivatives**

X = CN, COOEt

The first step is a Diels-Alder reaction between bis-allene and disubstituted acetylene. *p*-quinodimethide is the proposed intermediate which dimerizes (probably through radical pathway) to [2,2]paracyclophane derivative.

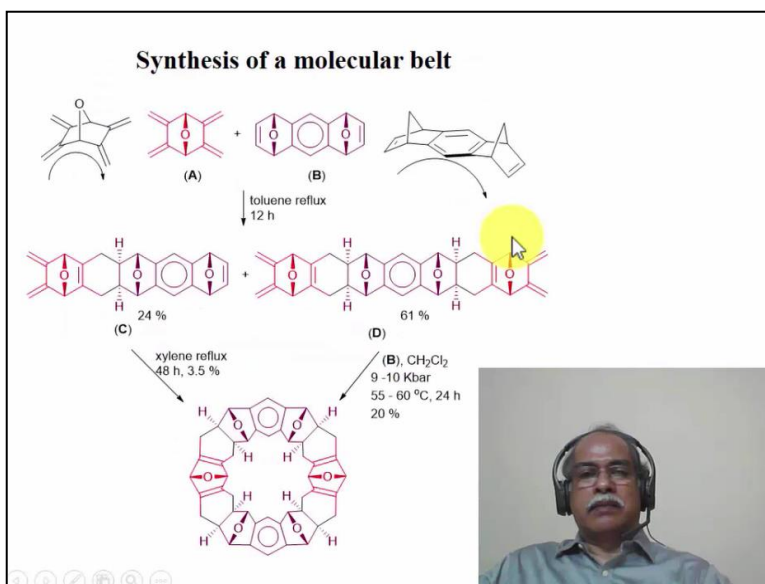
Only the Diels-Alder step is pericyclic in this case.

This is a very elegant synthesis of a 2,2-Paracyclophane derivatives. Several 2,2-Paracyclophane derivatives, have been synthesized using strategy. The starting material is essentially a Bisallene. This is a Hexatetraene, is what is the starting material. And, it behaves like a Diene, Diels-Alder Diene, and reacts with Acetylene, to produce the Para Quinodimethide derivative. Now, this is the concerted step, that we are talking about, namely the 4PI-2PI-Suprafacial cycloaddition reaction, between the Bisallene and the Acetylene moiety, produces this disubstituted Quinodimethide derivative.

The Quinodimethide derivative, Para Quinodimethide derivative, undergoes a dimerization reaction, to produce this particular 2,2-Paracyclophane derivative. This Quinomethide dimerization itself, could be a radical path way, because considerable amount of polymer is also produces the byproduct, in this reaction. So, the only step, that is pericyclic in nature, is this particular step, where the 4PI-2PI cycloaddition reaction is taking place, between the Bisallene and the Acetylene. So, this is a very elegant synthesis of a fairly complex structure, which is a 2,2-Paracyclophane derivative, in this particular case.

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Here is a very fascinating example of a belt shaped molecule. This molecular structure, as although it is drawn in a planar form, it actually is a belt kind of a molecule, a loop kind of a molecule, where all these Oxygen atoms are protruding out of the belt. In other words, this particular molecule has a belt shape, in its structure. And, that can be synthesized using the strategy, that is shown here.

The starting materials are A and B. These two molecules, are the starting material molecule. These molecules, because of the Oxo-Bridged-2,2,1-Bicyclic framework, they have a curved shaped curvature of the molecular structure. The arrow, essentially shows the curvature of this particular molecule. Similarly, this molecule B, which also has two Oxa-2,2,1-Bicyclic framework. The oxygens are missing here. I am sorry, this should be oxygen, here.

And, that is also a curve shaped molecule. So, when this behaves like a Diene, and this behaves like a Dienophile. So, this can undergo, two times Diels-Alder reaction. This can also undergo, two times Diels-Alder reaction. So, if the molecule undergoes Diels-Alder reaction in a 1:1 ratio, this will essentially produce molecule C.

You can see here, the red colored portion of the molecule, is coming from compound A. And, the violet color portion of the molecule, essentially comes from molecule B. So, this is a 1:1 cycloadduct, Diels-Alder adduct of the two compounds, is what is shown as structure C. On the other hand, a 2:1 cycloaddition product is also shown here. This product is formed in 24% yield, and this product is formed in 61% yield, when these two molecules are reflexed in toluene for 12 hours.

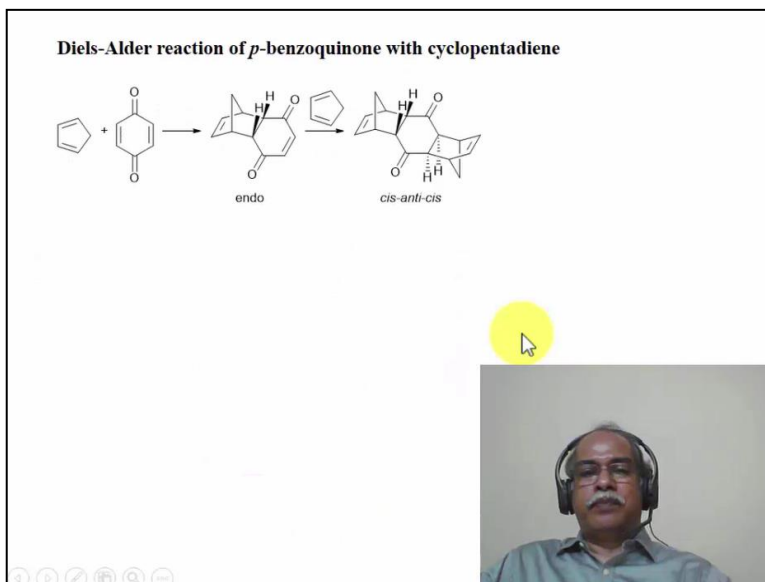
Here, you can see here, the molecule A, two equivalence of the molecule A has undergone, twice Diels-Alder reaction. Once in this side of the Dienophile, once on the other side of the Dienophile, resulting in the formation of the Bis adduct, in this particular case. Now, this molecule can undergo dimerization. A cyclodimerization, is what is taking place. This portion has a Diene, and this portion has the Dienophile.

So, two molecules should line up such that, the Dienophile portion of the second molecule should lie close to this, and the Dienophile portion of the second molecule should lie close to this. Such a Diels-Alder reaction is very unlikely to happen, because it is a orientational problem, that you have in this particular structure. Nevertheless, it produces the beltane in about 3.5% yield.

On the other hand, if one takes this molecule, and treats it with further one equivalent of the compound B, it can undergo Diels-Alder reaction, on this side, as well as on this side. Because, this molecule is already having a large curvature, it can undergo cyclisation. And, such a Diels-Alder, double Diels-Alder reaction on either side of the molecule, which are behaving like Diene, with this molecule, which is behaving like a Dienophile, this portion, as well as this portion, behaves like a Dienophile, it produces this cyclic structure, in about 20% yield. Although, this Diels-Alder reaction is carried out at a high pressure, and around 60 degrees or so, with a 9 to 10 kilobar pressure, is what this Diels-Alder reaction is carried out.

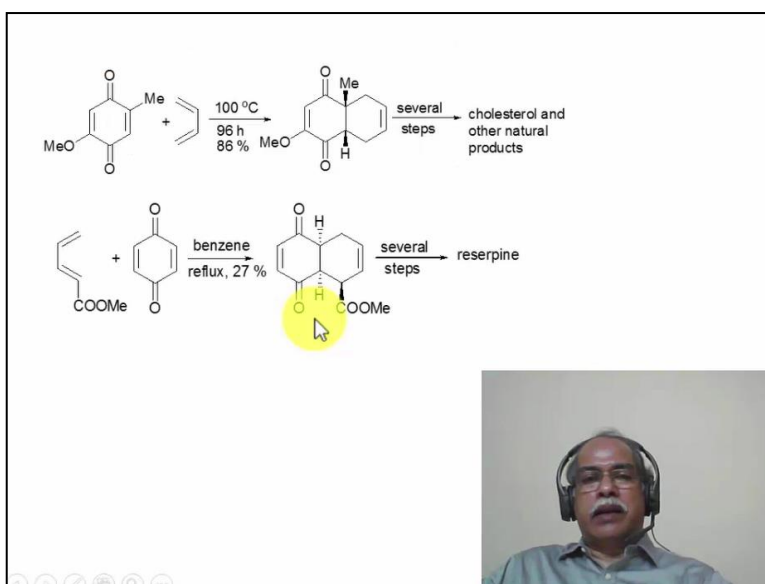
So, such a fascinating molecule has been generated, by a multiple Diels-Alder reaction, in this particular example.

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Now, when Cyclopentadiene undergoes Diels-Alder reaction with Para Benzoquinone, the Para Benzoquinone can actually undergo Diels-Alder reaction, twice. Once, on this particular side. Another time, on this side. In doing so, it initially produces an Endo Isomer of the mono adduct. The Endo Isomer of the mono adduct, in the presence of excess of Cyclopentadiene, can undergo once more Diels-Alder reaction to produce, the other side to be an Endo Isomer of the product. So, essentially produces, a Cis, anti Cis, kind of a fusion, in this Bis-adduct of the Benzoquinone molecule with Cyclopentadiene, as the Diene.

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If you take the Para Benzoquinone, which is differentially substituted. One side is substituted with the Methoxy. The other side is substituted with the Methyl. It undergoes Diels-Alder

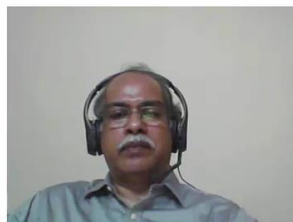
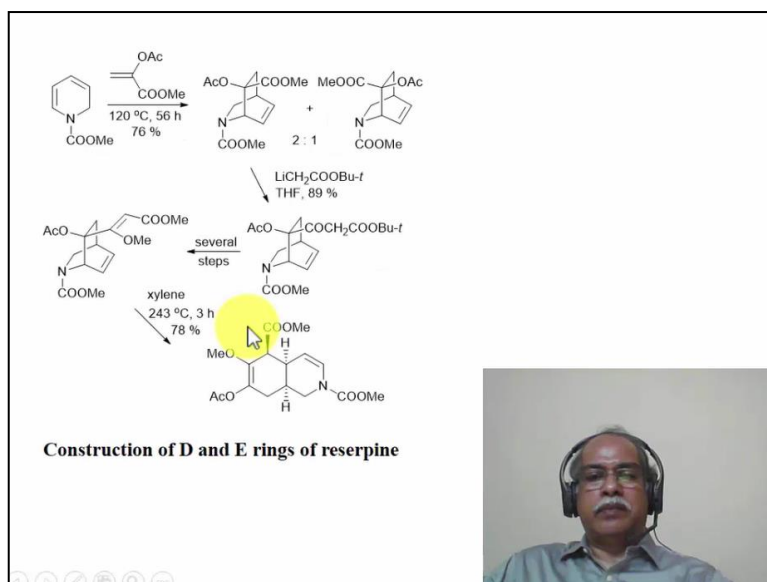
reaction with the Butadiene, for example, on heating to 100 degrees. Now, between this Dienophile, and this Dienophile, this is a more reactive Dienophile. Because, this is electron deficient, in relation to the electron rich Dienophile, which is this particular Dienophile. The lone pair present in the oxygen of the Methoxy functional group, can delocalize itself on to this double bond, there by rendering this to be a, relatively speaking, electron rich Dienophile, compared to this Dienophile, on the other side.

So, the Diels-Alder reaction takes place in a very regio selective manner, only on this particular side, resulting in the formation of the corresponding Diels-Alder adduct, which is shown here, for example. This molecule is taken as an intermediate, in several steps synthesis of cholesterol and other natural product, by Woodward. Here is another example of a Diels-Alder reaction, where you have an electron withdrawing substituted Diene, as well as Dienophile, the reaction proceeds in refluxing Benzene, although in very poor yield, for example, only 27% yield or so.

Because, this is a deactivated Diene. It is not an electron rich Diene. Unlike for example, Butadiene, this has electron withdrawing functional group. That may be the reason, why the reaction is very sluggish, in this particular case. It also produces the Endo adduct, which is shown here, for example. And, this molecule is a key intermediate in the several step syntheses of Reserpine, which is a naturally occurring alkaloid molecule.

So, the rest of the synthesis is fairly complex, which is very well known in the literature. All i wanted to do here is, to point out the fact that, the intermediate can be converted into several other natural products, in these two examples, from the Diels-Alder reaction of a Diene, with Para Benzoquinone as the Dienophile.

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Here is an example, of a synthesis of a naturally occurring molecule, Reserpine. Reserpine, is again an alkaloid. This is construction of ring D and E of Reserpine, is what is being shown in this particular case. Now, the Diels-Alder reaction is essentially between the Dihydropyridine, this particular molecule, which is a starting material, acts as a Diene. And, this acts as a Dienophile. This is Alpha Acetoxy Acrylate, is Methyl acrylate, is what is acting as a Dienophile.

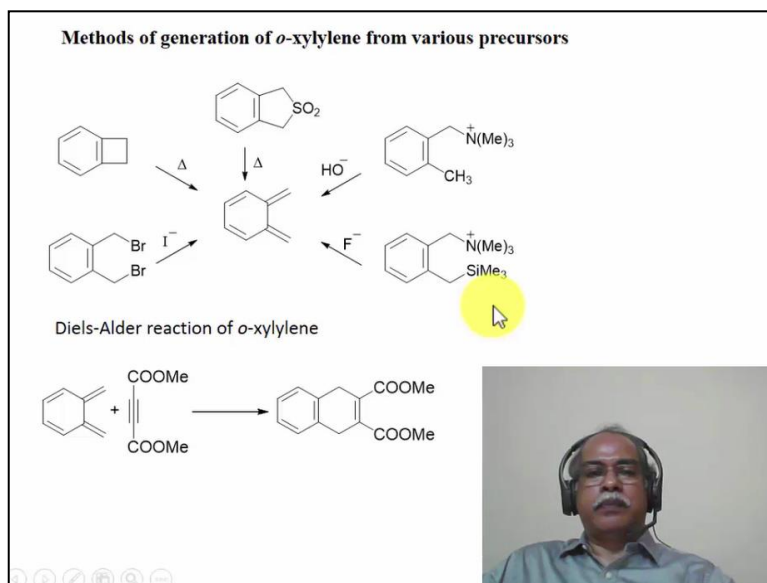
It produces a 2:1 ratio of the two Isomers, that are possible for the Diels-Alder reaction. Depending upon, the orientation of the Acetate and the Carbomethoxy functional group, one is an Endo, other one is an Exo type of an adduct. With respect to the Carbomethoxy group, this is an Endo product. With respect to the Acetoxy, this is an Endo product, for example. In a 2:1 ratio, this is produced. This undergoes a Claisen Schmidt kind of a condensation reaction, to produce the Beta-Keto Ester.

You can see here, the Lithium Enolate, that is generated from Tert-Butyl Acetate, for example. By treatment of Tert-Butyl Acetate with the LDA, this can be produced. This reagent, essentially adds on to the Carbonyl functional group of the Ester, to produce the corresponding Beta-Keto Ester, in this particular case. The Beta-Keto Ester can be converted into, the corresponding Methyl Ether. And now, this molecule is set up to undergo a 3,3-Sigmatropic rearrangement.

We will consider the 3,3-Sigmatropic rearrangement, at a later stage. But, this crucial intermediate is essentially obtained by the Diels-Alder reaction of this two molecules, to produce these two Diels-Alder adduct. And, the two Diels-Alder adduct can be converted into the corresponding 3,3-Sigmatropic system, which undergoes 3,3-Sigmatropic system rearrangement,

to produce this fused bicyclic compound. This portion of the reaction, we will consider it, when we come to the 3,3-Sigmatropic rearrangement. I will explain it properly, at that time.

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Now, Ortho Quinodimethide is an extremely reactive Diene. This portion of the molecule, can essentially react as a Diene, in producing a Benzene type of a structure. In other words, driving force is essentially, the aromaticity of this particular ring, aromatic ring, that is produced by the Diels-Alder reaction. The Ortho Quinodimethide itself, can be generated in several ways. Starting from here, let us consider the thermolysis of a Benzocyclobutene, which is already seen in the electrocyclic reaction, to produce the corresponding Ortho Quinodimethide.

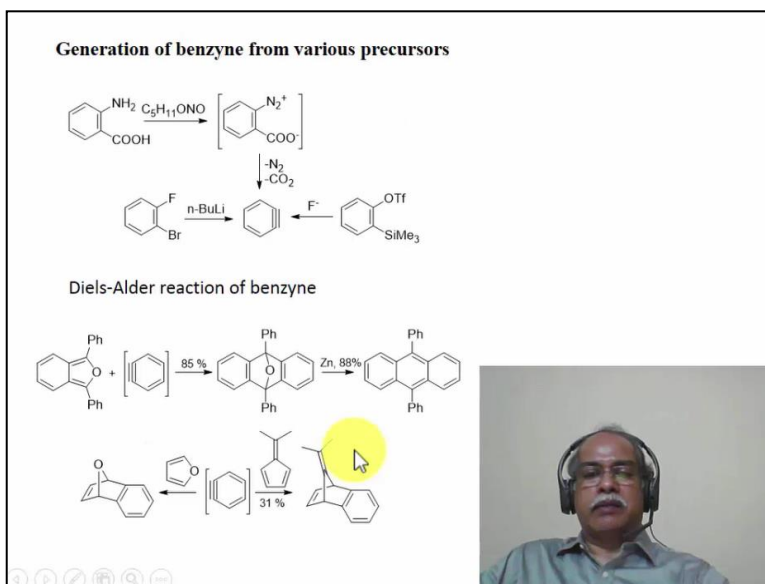
In this particular case, the dehalogenation reaction is promoted by Sodium Iodide, or Potassium Iodide. So, when this Ortho Dibromo Methyl compound is taken, and reflux with Sodium Iodide in Acetonitrile kind of a solvent, it triggers the elimination of Bromine, by the 1,4-Elimination of Bromine, for example, to produce the Ortho Quinodimethide. This Sulfolene molecule, which is a Benzo fused Sulfolene molecule, undergoes thermolysis, to eliminate chelotropic elimination of Sulphur dioxide, to produce the.

So, essentially the chelotropic elimination will be dealt with, in the last portion of the pericyclic portion. And, for the time being, assume that, this is also a concerted reaction, to produce the Ortho Quinodimethide. Here is an example of a Hoffmann elimination. This is essentially a 1,4-Elimination of the Amine. The Hydroxide base, abstracts the Hydrogen from this Methyl, producing a Carbanion here. That Carbanion, undergoes rearrangement with the elimination of the Trimethylamine, for example, to produce the Ortho Quinodimethide.

Finally, this is an Ortho Xylylated Ammonium salt. The Fluoride ion essentially attacks the Silicon, because Silicon is fluorophilic in nature. So, the Fluoride ion attacks the Silicon producing Trimethyl Xylyl Fluoride, and in the process, it undergoes the elimination of the Amine, to produce the Ortho Quinodimethide. Ortho Quinodimethide's reaction with the Diels-Alder fashion, with the Dimethyl Acetylene Dicarboxylic acid, is shown here. It produces the Dihydro Naphthalene derivative.

The Dihydro Naphthalene derivatives are easily, generally converted into the Naphthalene derivative, by reaction with DDQ, which causes the dehydrogenation of this particular molecule. So, the Ortho Quinodimethide, which is also termed as Ortho Xylylene, can be produced in several methods, as shown in this slide. And, it can, in see to be trapped by a Dienophile, which is the Dimethyl Acetylene Dicarboxylic acid in this case, to produce the Diels-Alder adduct, which is shown here.

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Now, Benzyne is a very reactive Dienophile. Benzyne is, can be produced in several ways. Some of the methods are shown here, starting from Anthranilic acid, for example. When Anthranilic acid is treated with Pentyl Nitrite, or Isoamyl Nitrite, it undergoes diazotization, to produce this Zwitter Ionic Carboxylate Diazonium salt. This, on strong heating, eliminates Nitrogen, as well as Carbon dioxide, to produce Benzyne, as the intermediate. The Benzyne, so produced, can be trapped. We will see the trapping by Diels-Alder reaction, a little while.

The Benzyne can also be produced, by the treatment of Ortho Bromobenzene, for example, using Butyllithium. When this molecule is treated with Butyllithium, initially a Halogen exchange

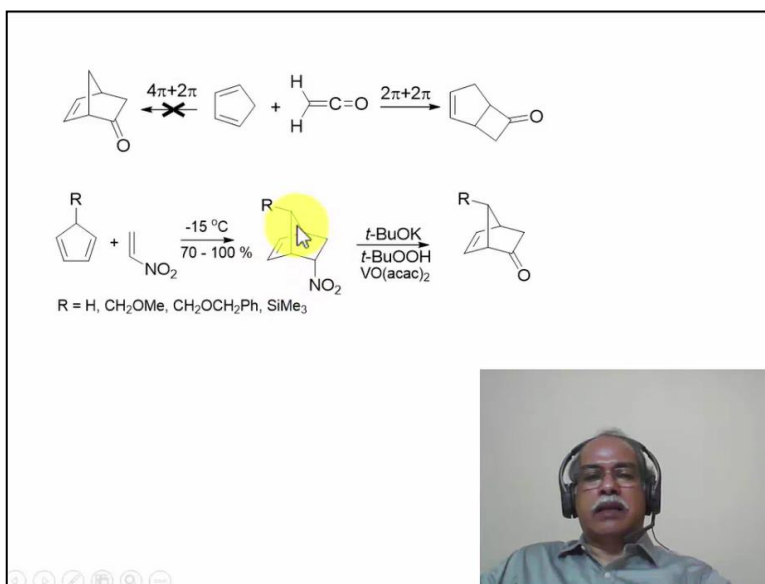
reaction with the Lithium takes place. So, the CBR bond is broken. And, you generate a Carbanion, which is the Lithium Carbanion salt, is what is produced. That Carbanion, undergoes elimination of the Fluoride, to produce the Benzyne as the product. Alternatively, Ortho Trimethyl Xylylated Phenol Triflates can be made to undergo 1,2-Elimination process. The Fluoride essentially attacks, the Silicon producing Trimethyl Xylyl Fluoride

In that process, the Triflate is eliminated, to give the corresponding Benzyne as the intermediate. The Benzyne, that is produced using this methodology, if it is produced, in the presence of a Diene, then it is capable of undergoing a Diels-Alder reaction. In fact, the Diels-Alder reaction between Anthracene and the Benzyne is known, to produce the Triptycene, which we have seen earlier, for example. In this particular case, the Diphenyl substituted Iso Benzofuran undergoes the Diels-Alder reaction, to produce this oxo bridged bicyclic system.

Deoxygenation using Zinc, produces the Diphenyl substituted Anthracene, as the final product. So, the Anthracene can be made by the deoxygenation, of this particular intermediate here. Alternatively, the Benzyne can be trapped with the Furan, as a Dienophile. Furan is not a very reactive Dienophile. But, this not a very reactive Diene, but with a reactive Dienophile such as Benzyne, it can undergo Diels-Alder reaction, to produce the 2,2,1-Oxa Bridged Bicyclic system of this kind.

Fulvene can be made to react with the Benzyne, for example, in a Diels-Alder fashion, to produce the molecule, that is shown on the right-hand side of this sequence of reaction, that are shown here.

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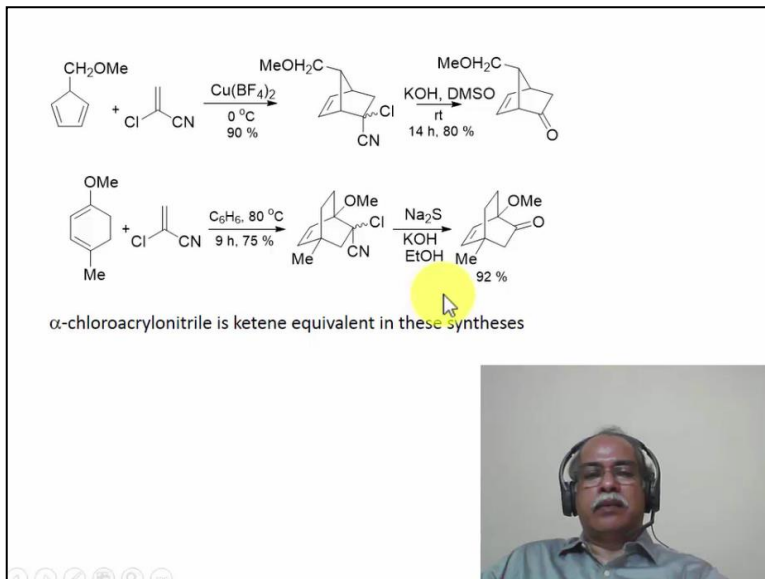
We already seen that, the Ketene does not undergo Diels-Alder reaction with Cyclopentadiene, for example, to produce the 2,2,1-Bicyclic Ketone of this kind. It rather undergoes, a 2PI-2PI cycloaddition reaction. In other words, 2PI Suprafacial-2PI Antarafacial cycloaddition reaction to produce a Cyclobutanone derivative, which is shown here. So, one cannot make the Bicyclic Ketone of this type, by means of a Diels-Alder reaction, with the Ketene as a methodology. Alternatively, one can use Ketene equivalence. One such example is shown here.

A mono substituted Cyclopentadiene, for example, reacts with Nitro Ethylene, at a very fairly low temperature. Because, this is a very reactive Dienophile. Nitro substituted Ethylene is an extremely reactive Dienophile. It undergoes Diels-Alder reaction, to produce the Endo selective Diels-Alder adduct, which is shown here.

With the several derivatives, this has been tried. And, this Diels-Alder adduct can be made to undergo Oxidative NEF reaction, using Tert-Butyl Hydroperoxide, Vanadyl ACAC as the catalyst, for example, using Tert-Butoxide. What happens is essentially, in the presence of Tert-Butoxide, this Hydrogen, which is an acidic Hydrogen, is removed, and you form the Nitronate. The Nitronate undergoes, this will be C double bond N kind of a compound, is what is going to be produced, when the anion is generated here. That Nitronate anion is essentially oxidize the, Carbon Hydrogen bond is oxidized to the, corresponding Ketone. So, if you look under NEF reaction, you will be able to see, N E F, NEF reaction, you will be able to see the mechanism of this particular reaction.

This is an oxidative cleavage of a secondary Nitro compound, to the corresponding Ketone, under basic condition, under oxidizing condition. So, Nitro alkene is actually, acting as a Ketene equivalent. Because, it produces a Ketone, which would have otherwise been obtained, from the reaction of the Ketene with the Cyclopentadiene.

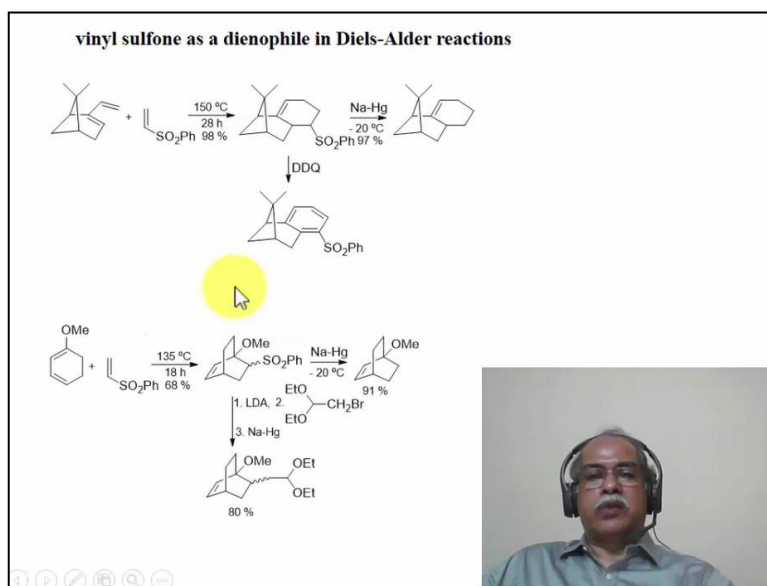
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These are again, two examples of Ketene equivalent. Alpha Chloro Acrylonitrile can be used as a Ketene equivalent. It is a fairly strong Dienophile. It reacts with cyclic dienes like Cyclopentadiene, and Cyclohexadiene, and so on, producing the corresponding Diels-Alder adducts, which are shown here. In the Diels-Alder adduct, when it is treated with Potassium Hydroxide in DMSO, or using Sodium Sulfide and Potassium, essentially under basic conditions, the Carbon Halogen bond is removed by OH substitution reaction.

Once the OH is produced, is essentially a Cyanohydrin, is what is produced. The Cyanohydrin is nothing but, a most form of the Ketone. So, under basic condition, the Cyanohydrin undergoes the loss of Cyanide, to produce the corresponding Ketone. So, 2,2,1-Bicyclic, as well as 2,2,2-Bicyclic Ketones, can be easily synthesized, using Alpha Chloro Acrylonitrile as a Ketene equivalent, by choosing the corresponding Diene, which is either Cyclopentadiene or Cyclohexadiene, as shown in these two examples.

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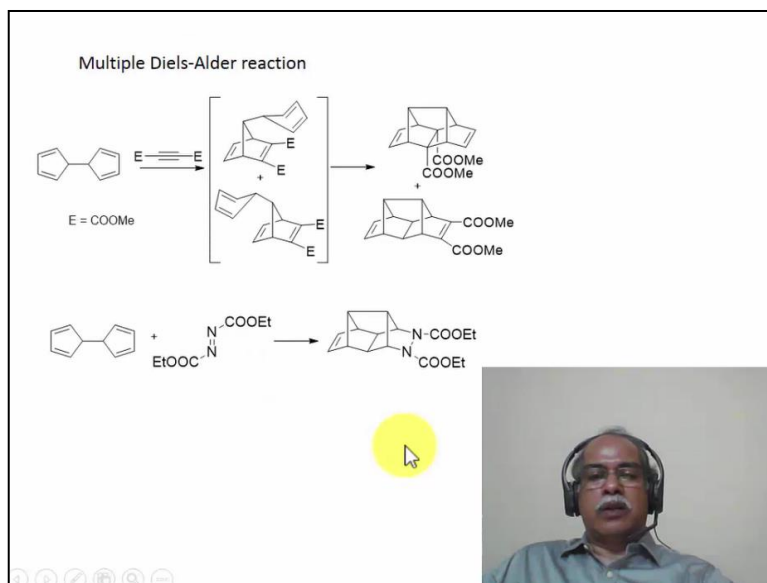


Vinyl Sulfones are also fairly powerful dienophiles. Because of the electron withdrawing nature of the sulfone group, they act as dienophiles in Diels-Alder reaction. Couple of examples are shown here, for example. The Diene, which is this particular Diene, derived from Alpha Pinene, undergoes Diels-Alder reaction with Phenyl Vinyl Sulfone at 150 degrees, nearly quantitative yield of the corresponding Diels-Alder adduct is formed. This can be either dehydrogenated, to made to undergo aromatization of this ring, to produce the benzannulated system, which is this particular system here.

Or, the Carbon-Sulfur bonds, can reductively cleaved by desulfonation reaction. Phenyl Sulfonic Acid is produced. And, as a result of that, the Carbon Sulfone bond, is replaced by a Carbon Hydrogen bond, which is a reductive elimination of the Phenyl Sulfonate, in this particular case. Similarly, when the reaction is carried out with the Cyclohexadiene of this kind, the corresponding Diels-Alder reaction is produced. Reductive cleavage gives you, this particular molecule in high yields.

Alternatively, a Carbanion can be generated at this Carbon, because of the acidic nature of the Carbon Hydrogen bond, next to the Sulfone group, here. So, the Carbanion, so produced is trapped by an electrophile, which is this particular Bromide, producing the substituted derivative. Finally, the Carbon Sulfur bond is cleaved reductively, to give this molecule, in about 80% yield. These are molecules, which are used for further synthesis as intermediate stages, in the total synthesis of some compounds.

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Now, let us go into multiple Diels-Alder reaction. We have already seen that, Benzoquinone can undergo multiple Diels-Alder reaction, to give products of multiple Diels-Alder reaction. Now, this Diene is nothing but, a dimer of Cyclopentadiene. It can undergo Diels-Alder reaction, two-fold, once here, as well as, once here. The initial Diels-Alder adducts are, two products can be formed, depending upon, whether it is endo selective or hexo selective, with respect to the second Cyclopentadiene.

So, the first Cyclopentadiene has undergone a Diels-Alder reaction, in a hexo selective fashion, in this particular case, and in an endo selective fashion, in this particular case. Now, that puts this Diene in close proximity to this particular Dienophile. So, that Diels-Alder reaction between, this 1 and 4 Carbon, and this 1 and 2 Carbon, essentially produces this bridged bicyclic system. On the other hand, the Diels-Alder reaction between this Diene, and this Dienophile, essentially produces the second Bridged Bicyclic Tetracyclic system of this kind, for example.

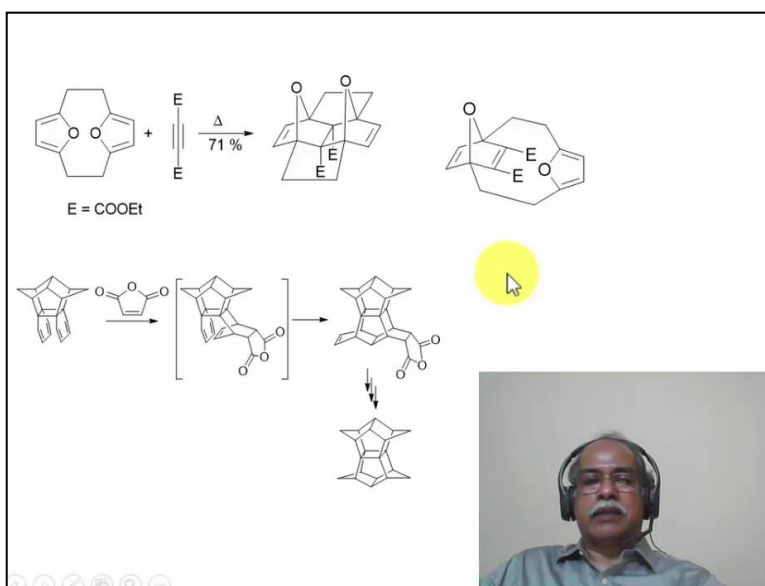
Now, you can see here, where the Dimethyl Acetylene Dicarboxylate units are placed. Here, it is placed between the two Cyclopentadiene ring. So, it is undergone two times, the Diels-Alder reaction. The Acetylene Dicarboxylic acid has undergone, two times Diels-Alder reaction. Once with the Cyclopentadiene on this side, another time with the Cyclopentadiene on this, as if the Dimethyl Acetylene Dicarboxylic acid has come in between these two Cyclopentadiene rings, to undergo twice the Diels-Alder reaction.

On the other hand, in this particular case, it has undergone only once the Diels-Alder reaction, to produce this bridged cyclic system of this kind. Instead of Carbon Dienophiles, one can have

also Heteroatom Dienophile, as illustrated in the case of Diethylaceto-Dicarboxylate. The Diethylaceto-Dicarboxylate, of course produces only one kind of a Diels-Alder adduct, which is structure of, which is shown here.

So, the first Diels-Alder reaction essentially produces something like, similar to this intermediate. Except here, we have a Nitrogen-Nitrogen single bond, instead of the Carbon-Carbon double bond, that further undergoes Diels-Alder reaction, to produce the second bridged bicyclic system, that is shown in this particular case. So, these are examples of multiple Diels-Alder reaction.

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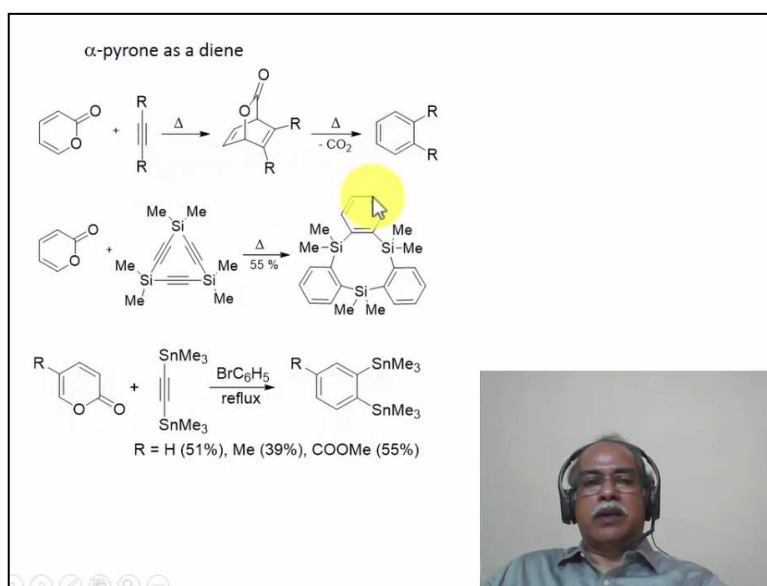
That is one more example. Here, the Bis Furan-2,2-Cyclophane undergoes Diels-Alder reaction, tries with the Dimethyl Acetylene Dicarboxylic acid, to produce this fairly complex bridged dioxo bridged derivative, in this case. You can see here, the Dimethyl Acetylene Dicarboxylate essentially lies between the two Furan ring, so that, this Furan ring can initially undergo Diels-Alder reaction. in the second Furan ring, can also undergo the Diels-Alder reaction, with the remaining double bond arising out of the first Diels-Alder reaction, to essentially saturate these Carbon-Carbon triple bond, into a saturated SP3 Carbon, in this particular instance.

So, this must be the intermediate, that is produced. This intermediate, so produced, can now undergo Diels-Alder reaction, further with the Furan and the Diethyl Acetylene Dicarboxylic acid residue, that is present in this molecule, in this case. It is a very fascinating example of synthesis of a molecule called Pagodane. Pagoda are the structures, that you see in South-East Asia. And, this is one structure, molecular structure, which resembles the pagoda. One can look

at the internet and see, what pagoda actually is, in terms of the structural feature. It will resemble something, architecture would resemble something, similar to this particular structure.

This molecule has been synthesized, after several steps, involving several steps. This has two Diene unit, pointing face-to-face to each other. The Diels-Alder reaction with Maleic Anhydride, essentially produces the Diels-Alder adduct, which puts this double bond in close proximity to the Diene. Once again, the Diels-Alder reaction between the Diene and the Dienophile, essentially produces this complex framework, which is further transformed into the Pagodane structure by Prince Bagh in his synthesis, elegant synthesis of this very fascinating molecule.

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Now, so far, we have seen the Diels-Alder reaction to give bicyclic systems, and so on. Here is an example, where the Diels-Alder reaction initially produces a bicyclic system. But, the bicyclic system is not the stable system. It readily undergoes elimination of Carbon dioxide, to give an aromatic target molecule. So, Alpha Pyrone is used as the starting material here, as the Diene. Alpha Pyrone is this particular molecule. It undergoes Diels-Alder reaction with Acetylenic systems of this kind, essentially producing a CO<sub>2</sub> bridged bicyclic system, like this.

Elimination of CO<sub>2</sub> of this molecule, is very facile for two reasons. One, it releases the strain of this bridge. Secondly, the gain of aromaticity is the main driving force, in this particular case. A chelotropic elimination of CO<sub>2</sub>, essentially produces the aromatic ring, which is ortho disubstituted aromatic ring, in this particular case. Now, when the Acetylene is part of a fancy structure like this, which is the Xylyl capped Triacetylene structure of this kind, you can imagine

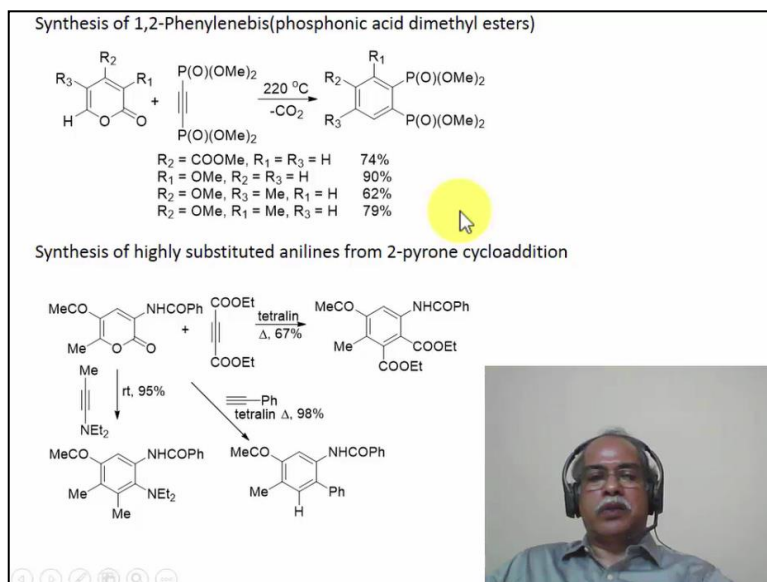
that, the molecule can undergo Diels-Alder reaction three times, once here, once here, and once here.

Three times, it can undergo Diels-Alder reaction, with the elimination of Carbon dioxide, in each Diels-Alder adduct to produce. So, essentially, this is the portion, which comes from the Pyrone derivative. This is the portion, which comes from the Pyrone derivative. And, Carbon dioxide elimination, essentially results in the formation of this Xylyl Cyclophane, which is a very nice molecule, here.

So, this Carbons, between the two Silicones, whatever the Carbons that you see, is actually the triple bonded Carbon, the Acetylenic Carbons are present here, in this molecule. So, essentially, the reaction proceeds three times, like it is shown in the top portion. Because, the molecule has three Acetylenes, to produce this nice cyclic Cyclophane, which is Xylyl bridged Cyclophane of this kind. Pyrone can also undergo Diels-Alder reaction, with Bis Trimethylstannyl Acetylene, to produce the corresponding ortho disubstituted Bis Trimethylstannyl substituted Benzene derivative, in this particular case.

And, this is essentially carried out in refluxing Bromobenzene, at high temperature. So, the reaction leads to a Diels-Alder adduct, which eliminates Carbon dioxide to give the aromatic system, as in the case of the top reaction, that is shown here.

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It is another example, where the Phosphonate substituted Acetylene, is undergoing Diels-Alder reaction with alpha Pyrone. Various substituted Alpha Pyrenes, have been made to undergo this Diels-Alder reaction, in producing the Ortho Diphosphonile Benzene derivatives, in this

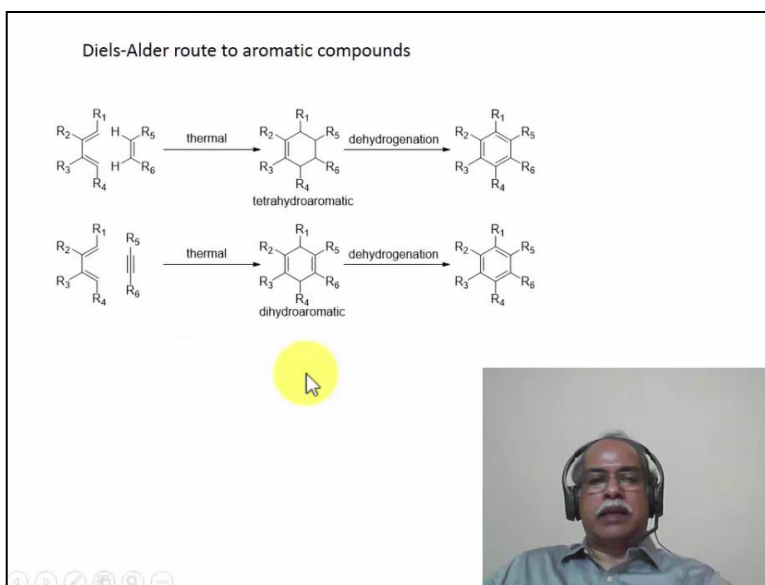
particular case. The alpha Pyrone is also called two Pyrones, this particular molecule, has been used to make a highly substituted aniline derivative, as it is shown in this particular example.

The Alpha Pyrone undergoes Diels-Alder reaction, with the Acetylene, Diethyl Acetylene Dicarboxylate, which produces the Diels-Alder adduct, which subsequently eliminates the Carbon dioxide, to produce the disubstituted derivative, which is this particular derivative. Alternatively, it can also undergo Diels-Alder reaction with this Enamine. The Enamine portion undergoes diels, Dienophile is the, this is an inwards electron demand Diels-Alder reaction.

In other words, this is an electron rich Acetylene, and this is an electron poor Diene. So, this is electron rich Dienophile, and electron poor Diene. So, it is an inverse relationship, in terms of the electronic nature of this. Diels-Alder adduct, undergoes a Carbon dioxide elimination, to produce the corresponding highly substituted Aniline derivative, in this particular case.

On the other hand, with Phenyl Acetylene, you can undergo Diels-Alder reaction, to produce the corresponding Phenyl substituted derivative. Important thing is that, these are highly substituted Aniline derivative, which can be further used for organic synthesis. And, this is a general methodology to produce, such highly substituted Aniline derivatives, from two Pyrone as the Diels-Alder components, in these reactions.

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Now, let us, we have already seen the Diels-Alder route to the aromatic system. Because, the Diels-Alder reaction with an Olefin, produces a Dihydro aromatic system, which can be dehydrogenated using DDQ, to produce the aromatic system. Or, the Diels-Alder reaction with an Acetylene, can produce a Dihydro aromatic derivative. This is a Tetra Hydro aromatic

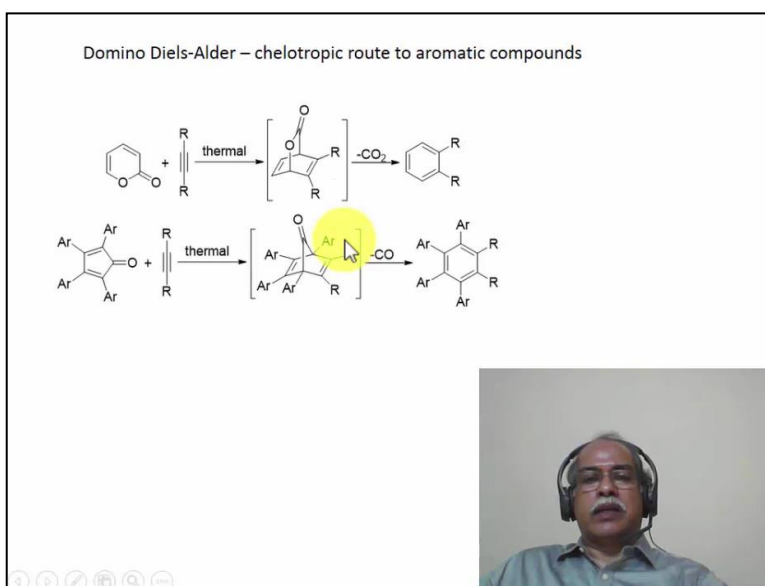


derivative. And, this is a Dihydro aromatic derivative. Again, dehydrogenation using reagents like, DDQ or Selenium Dioxide, can result in the formation of the corresponding aromatic derivative.

Let us see some examples of applications, of this two types of reactions, in organic synthesis. Now, alternatively, what you can have is, you can have substituents, which are leaving group substituents like, the Chloro, Bromo, Methoxy, and Acetoxy, on the Diene, such that, the Diels-Alder reaction with an Olefin, produces a Tetra Hydro aromatic derivative. This can undergo, 1,4-Elimination of the HX molecules twice, to give the corresponding aromatic derivative.

Or, this Di Hydro aromatic derivative, can undergo the elimination of HX molecule, to produce this aromatic derivative. So, instead of doing a dehydrogenation, you are doing a dehydrohalogenation reaction in these cases, to produce the corresponding aromatic derivatives.

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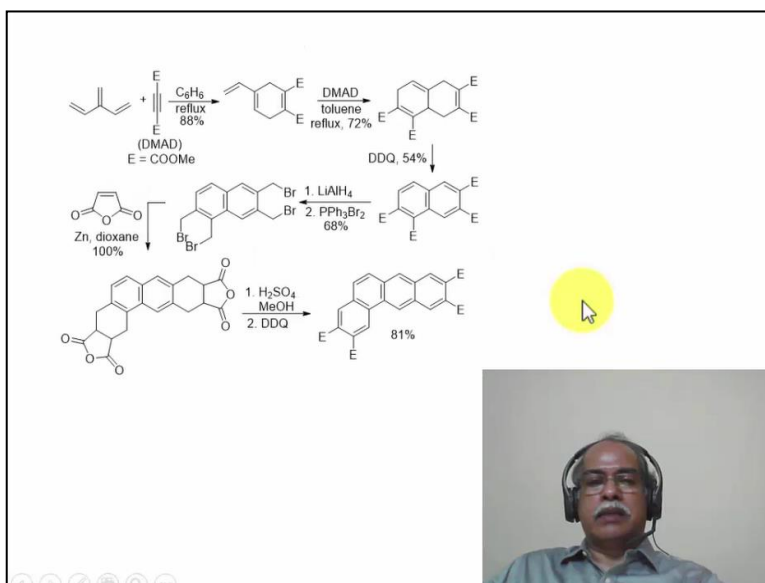


This is something, we have already seen.  $\alpha$ -Pyrone undergoing Diels-Alder reaction, followed by elimination of Carbon dioxide, to produce this. On the other hand, Tetraphenyl Cyclopentadienone, which is known as Tetracyclone, can also undergo Diels-Alder reaction with an Acetylene. The intermediate 2,2,1-Bicyclic system is very unstable. It undergoes Decarbonylation reaction, by the loss of Carbon monoxide.

This is a chelotropic reaction. So, under the thermal heating condition, this is an unstable compound. The driving force here, is again aromatization, and the loss of strain, because of the elimination of the Carbon monoxide molecules. So, it is a chelotropic elimination of Carbon

monoxide, to produce the corresponding Hexa-Aryl, or Hexa-Substituted Benzene derivative, can be synthesized using this methodology.

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We will see some examples of this methodology, in a few minutes. This is called 3-Dentralene. These are cross conjugated molecule. You can see the Diene portion here, as well as a Diene portion here. It undergoes Diels-Alder reaction, to produce the corresponding Diels-Alder adduct, which is a Vinyl substituted Ene derivatives. So, this is again, can act as a Diene derivative. So, with the Dimethyl Acetylene Dicarboxylic acid, it again, once again undergoes a Diels-Alder reaction, to produce a very specifically substituted Naphthalene, Tetrahydronaphthalene derivative.

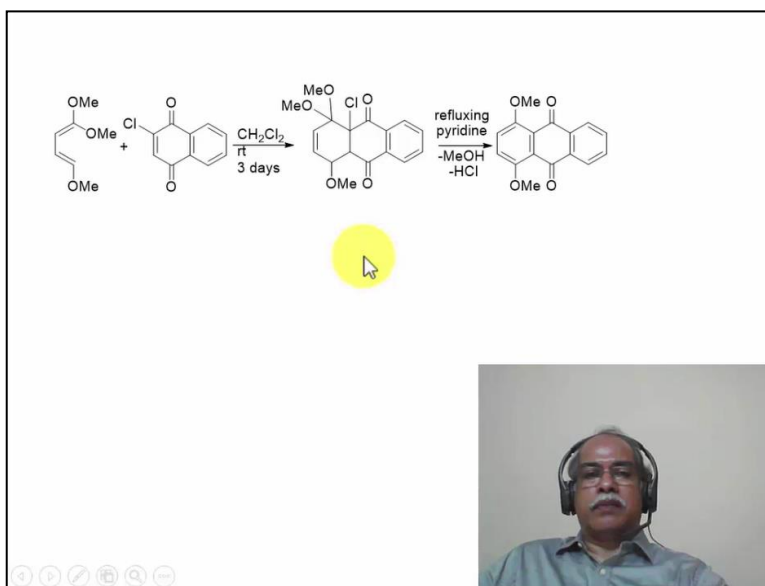
The Tetrahydronaphthalene derivative can be made, to undergo dehydrogenation using DDQ, to produce this particular substitution pattern of the naphthalene derivative, which is very important in organic synthesis. Now, this can, the Ester can be reduced with Aluminium Hydride. And, in the alcohol so obtained, can be converted into the corresponding Tetrabromide. So, the Tetra alcohol, which is produced by the Lithium Aluminium Hydride, is converted into the Tetrabromide, using Triphenyl Phosphene, Bromine combination, as the brominating agent.

Now, this Tetrabromide, is treated with Zinc dust, when it undergoes reaction, which is a dehalogenation reaction. It forms an Ortho Quinodimethide derivative here, and an Ortho Quinodimethide derivative here, which can undergo double Diels-Alder reaction, once on this side. The ortho Quinodimethide derivative is not shown, in the scheme of things. That is an intermediate, that is produced, by the reduction of Zinc, the dehalogenation reaction of Zinc,

with this dibromo compound. And again, this dibromo compound will also produce the Ortho Quinodimethide.

So, the Diels-Alder adduct of the Bis ortho Quinodimethide, is what is shown here. This, upon Esterification by treating the Anhydride with Methanol and Sulphuric acid, the corresponding Tetra Ester is produced. The Tetra Ester is actually a Tetra Hetero Benzo Anthracene derivative, Benz Anthracene derivative. And, that is oxidized to the corresponding aromatic derivative, is in DDQ. So, overall, it allows you to produce very specifically substituted Naphthalene, or this kind of a Tetracene derivative, angularly fused Tetracene derivative, very nicely, with high yields, in all the steps.

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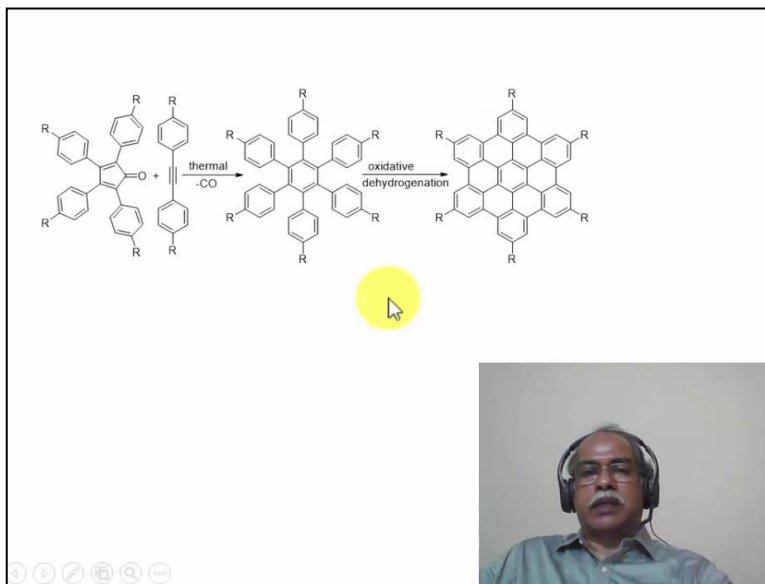


Here is an example, where the dehydrohalogenation and the elimination of Methanol, is taken as an advantage, to aromatize this compound. The Diels-Alder reaction, between this Tri Methoxy substituted Butadiene, and the Chloro substituted Naphthoquinone, for example, takes place at room temperature, to produce the corresponding Diels-Alder adduct. Now, there is a Hydrogen here, which can undergo dehydrohalogenation, for example, to produce the double bond over here.

There is a Hydrogen here, which can undergo methanol loss, 1,4-Methanol loss, in refluxing Pyridine, for example, the dehydrohalogenation produces HCL. The HCL can catalyze, the loss of the methanol, by protonation of one of the Methoxy groups, followed by a proton loss, from this position over here. 1,4-Elimination of Methanol, is what is responsible for the aromatization of this particular ring. So, initially, the dehydrohalogenation produces a Cyclohexadiene.

And, from the Cyclohexadiene, you lose 1,4-Methanol in a 1,4 position, to give the corresponding aromatic ring system. So, from a Naphthoquinone ring system, now you have produced an Anthraquinone ring system, by a benzoylation reaction, in this particular case.

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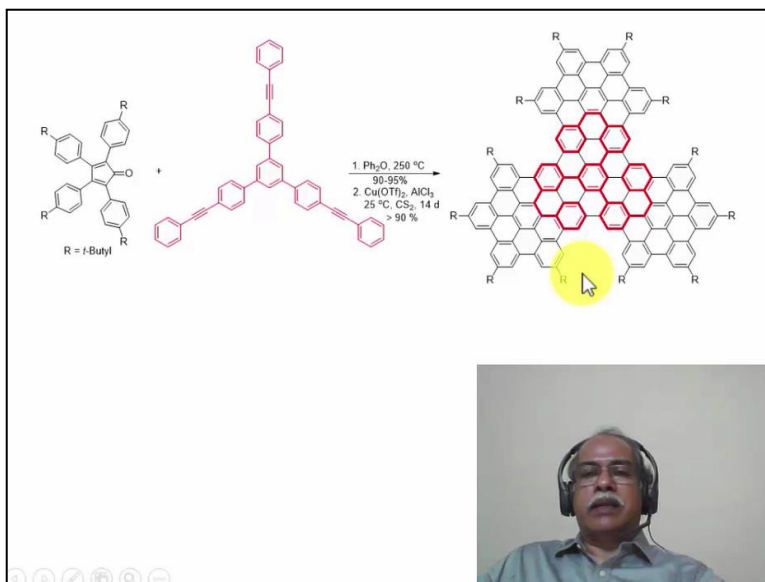


These are some fascinating examples, of producing large cyclic compounds, of this kind polycyclic aromatic, polycyclic aromatic compounds of this type. This is Tetraphenyl Cyclopentadiene, which is otherwise known as Tetra-Cyclone, undergoes Diels-Alder reaction, to produce the corresponding Diels-Alder adduct, which will be a Carbonyl Bridged 2,2,1-Bicyclic system, as it is shown here, for example.

The Carbonyl bridged 2,2,1-Bicyclic system, is shown here. This undergoes decarbonization reaction, to give the Tetra Aryl substituted derivative. That is exactly, what is happening in this particular example. They initially formed Diels-Alder adduct, with the loss of Carbon monoxide, aromatizes the central ring to the aromatic core. And, Hexa-substituted aromatic derivatives can be easily synthesized.

The oxidative cross coupling of this Carbon-Carbon bond, by dehydrogenation reaction, in the presence of oxidizing agents like Ferric chloride, essentially fuses these rings, to produce the Hexa-Benzo Coronene as the final product, in this particular case.

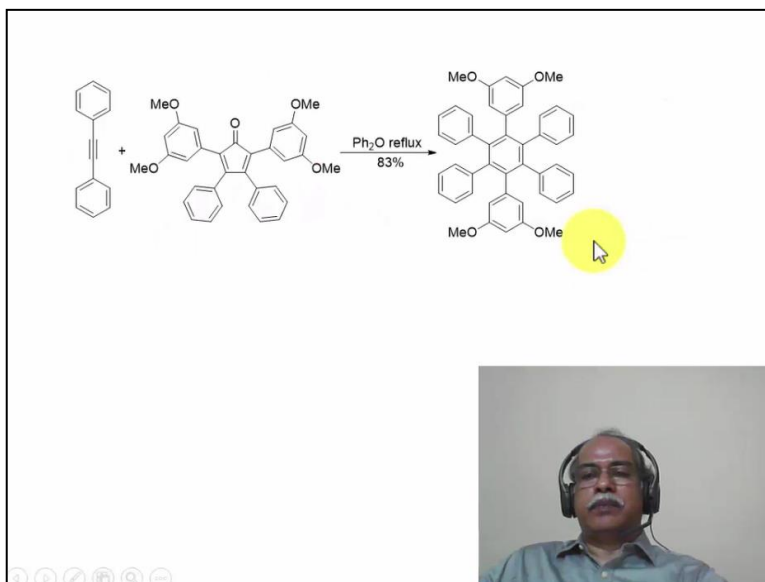
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These are very fascinating molecule. Because, one's imagination can be used, for example, to produce large polycyclic aromatic ring. This is called Super-Triphenylene kind of a molecule. This is essentially produced by the Triacetylene, which is shown here, with three equivalence or more of the Tetracyclone, as the derivative. The red portion in this particular structure, essentially corresponds to this molecule. And, the black portion essentially corresponds to the Tetracyclone unit here, for example. So, you can trace this, Carbon-Carbon triple bond.

This is originally a Carbon-Carbon triple bond. This was originally a Carbon-Carbon triple bond. Similarly, this was also originally a Carbon-Carbon triple bond. The molecule undergoes, 3 times Diels-Alder reaction, with the loss of Carbon monoxide, which gives a Diels-Alder adduct. The Diels-Alder adduct itself, is not shown in this slide. Instead, the fully aromatized cyclist compound, is what is shown. The aromatization and the cyclisation takes place, in the presence of Copper Triflate as an oxidizing agent, in the presence of Aluminium Chloride as a Lewis acid, in a non-nucleophilic solvent like Carbon disulfide, in this particular step.

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A similar reaction, is what is taking place here. The Cyclopentadienone, undergoes the Diels-Alder reaction, with this particular Acetylene, to produce the 2,2,1-Bicyclic system, which loses Carbon monoxide, in refluxing Diphenyl ether as a product. So, you can see here, this portion essentially comes from the Diphenyl Acetylene derivative, in this particular case. So, the consecutive rings, which are this particular four rings, for example, essentially come from the Tetracyclone. And, this portion has essentially come from the Diphenyl substituted Acetylene, in this particular case.

So, what we have seen in this module, is the synthetic application of Diels-Alder reaction, by several examples that are highlighted. Some of the reactions like, the Beltane, and the Triptycene, and the kind of polycyclic aromatic Hydrocarbons, are very-very fascinating molecules. Of course, they have potential application in many areas, also. I have not touched upon that. I hope, you enjoyed this particular module. Thank you very much, for your kind attention.