Pericyclic reactions and Organic Photochemistry
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Module No. #05
Lecture No. #21
Pericyclic reactions – Sigmatropic rearrangements continued… Wittig rearrangement and higher order Sigmatropic shifts.

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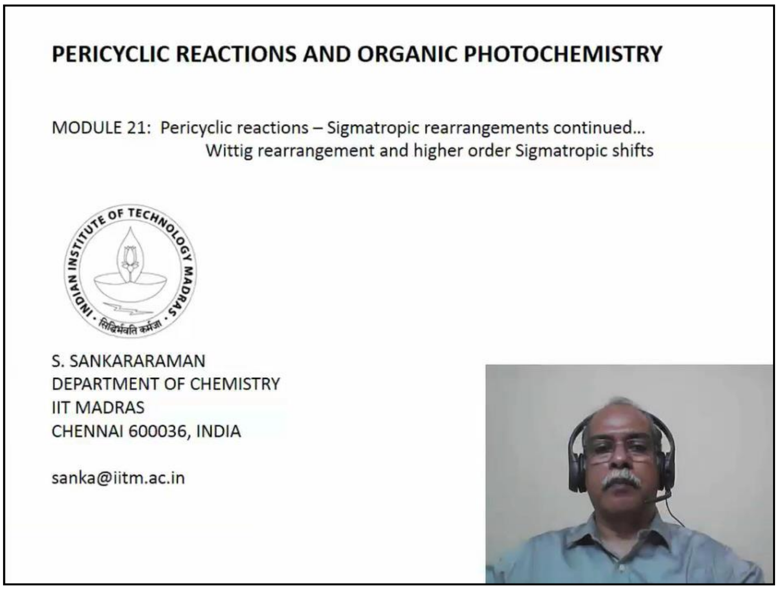

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 21: Pericyclic reactions – Sigmatropic rearrangements continued…
Wittig rearrangement and higher order Sigmatropic shifts

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Hello, welcome to the online course on, Pericyclic Reactions and Organic Photochemistry. We are in Module Number Twenty-One. We continue with Pericyclic reactions, in Sigmatropic rearrangement, there is a small portion under Wittig rearrangement, and a higher-order Sigmatropic shifts, we will be considered in this particular module. Now, let us first consider, what is Wittig rearrangement. This should not be confused with Wittig reaction, which involves Phosphorus ylide, for the synthesis of Olefins.

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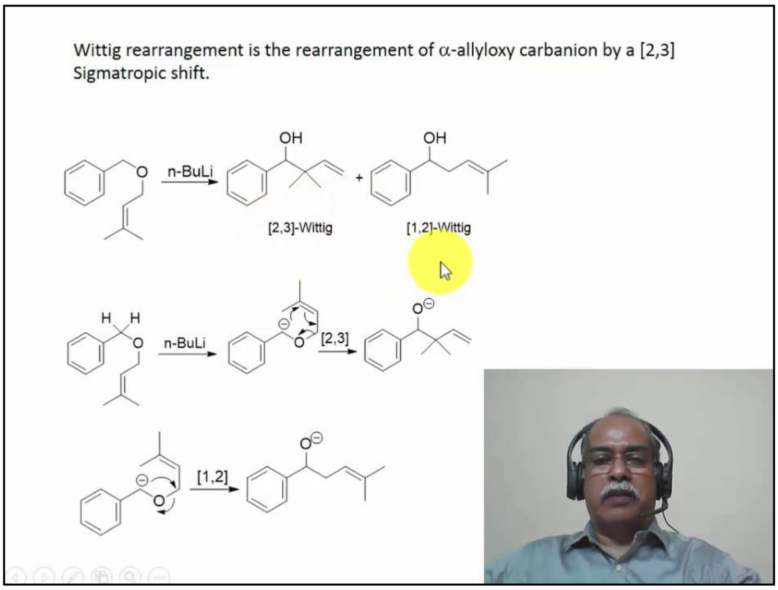

Wittig rearrangement is the rearrangement of α-allyloxy carbanion by a [2,3] Sigmatropic shift.

Wittig reagent is a, [2,3]-Sigmatropic rearrangement, of an Alpha Allyl Oxycarbanion. If you consider, this Benzyl Allyl Ether, when you treat it with Butyllithium, for example, it undergoes rearrangement, to give [2,3]-Rearrangement, as well as [1,2]-Rearrangement. We will look into the mechanism of this two rearrangement processes, as follows. If, Butyllithium is treated with this particular Benzyl Allyl Ether, the most acidic Hydrogens are mentioned as, the Benzylic Hydrogen.

So, the deprotonation of the acidic Hydrogen in the Benzylic position, leads to the Benzyl anion. That Benzyl anion, is capable of undergoing a [2,3]-Sigmatropic rearrangement, which is represented by the cyclic arrows, that are shown here. Now, this is a 6-Electron, 5-Membered ring transition state type of a rearrangement, where the Carbanion that is generated, reacts to the terminal position of the Allyl group, followed by rearrangement, with the breaking of the Carbon-Oxygen bond of the Ether, in this particular instance.

That, corresponds to the [2,3]-Sigmatropic rearrangement, corresponding to this particular product formed, upon workup by treatment of this anion, Alkoxy anion with an acid. Now, how is this [1,2]-Wittig product formed. [1,2]-Wittig product is formed, by the same Carbanion reacting, not in the allylic terminal position, but in the allylic position, in this position here, in this Carbon here, there by undergoing a [1,2]-Shift kind of a rearrangement, resulting in the formation of a [1,2]-Wittig product.

Often times, a mixture of [2,3]-Wittig products, as well as [1,2]-Wittig products, are formed. There is some control over the [1,2] versus [2,3], using the polarity of the solvent. Normally, the charged polarization, or the charged delocalization, is much higher in the [2,3]-Sigmatropic rearrangement, compared to a [1,2]-Sigmatropic rearrangement, of this type.

Therefore, Polar solvent should favor, the formation of the less delocalized structure of this kind, which will result in the higher amount of formation of the [1,2]-Wittig reaction. Non-Polar solvents, would gently favor the [2,3]-Wittig creation, in general.

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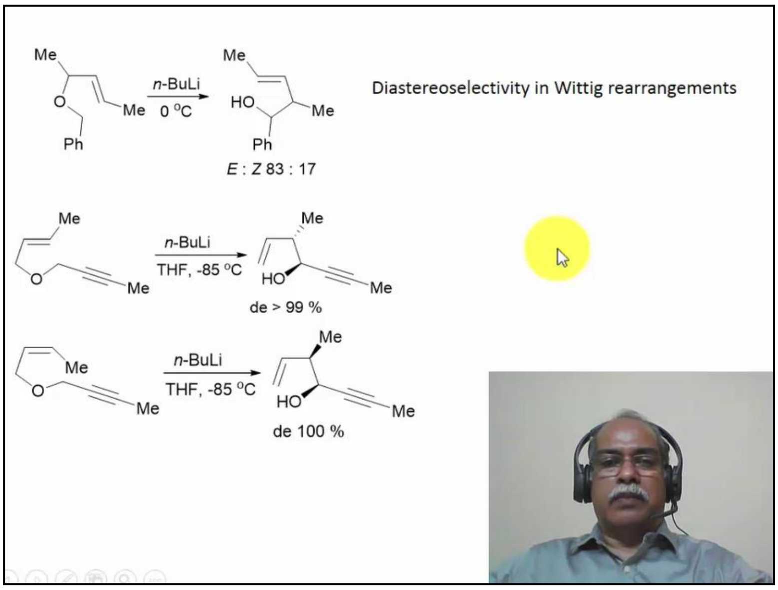
Diastereoselectivity in Wittig rearrangements

Now, the Wittig arrangements are, highly Diastereoselective in nature. You can see here, by taking the E-Olefin, in this particular instance. And, ZE-Olefin mixture, to the extent of about 83:17 is formed, for the Homo Allyl alcohol, that is formed, in this rearrangement. Here again, the Benzylic anion is generated. That, undergoes the [2,3]-Rearrangement, with the breaking of the Carbon-Oxygen bond, resulting in the formation of this Homo Allyl alcohol.

Suppose, if you take two Diastereo isomeric system, with a Propargyl Ether. In other words, this is an Allyl Propargyl Ether kind of a system, is what is represented, in these structures. This is the E isomer of the Propargyl Allyl Ether. And, this is the Z isomer of the Propargyl Allyl Ether. Upon treatment with Butyllithium, the Carbanion that is generated in the propargylic position, which is the most acidic Hydrogen, in this particular case.

Undergoes, [2,3]-Sigmatropic rearrangement, even at -85 degrees, quite rapidly to give, to an extent of 99% of the Diastereo isomer, which is the Anti Diastereo isomer, as indicated by the stereochemistry of the Methyl and Hydroxy being, Anti with respect to each other. On the other hand, when the Z isomer is treated with Butyllithium, again the Propargyl anion is generated, which undergoes the [2,3]-Sigmatropic rearrangement, at a very low temperature.

You get exclusively, only the Syn Diastereo isomer, to an extent of about 100% Diastereoselectivity. So, these two examples, clearly illustrate two things. One is that, the [2,3]-Sigmatropic rearrangement is a predominant process, in these cases. And, the rearrangement is highly stereospecific in nature, in the sense that, the starting material double bond stereochemistry really matters, in terms of the stereochemistry of the product, Homo Allyl alcohol product, that is being formed, in this particular system.

And, this involves essentially a tight 5-Membered, 6-Electron transition state, which leads to the high Diastereoselectivity, in this kind of reactions.

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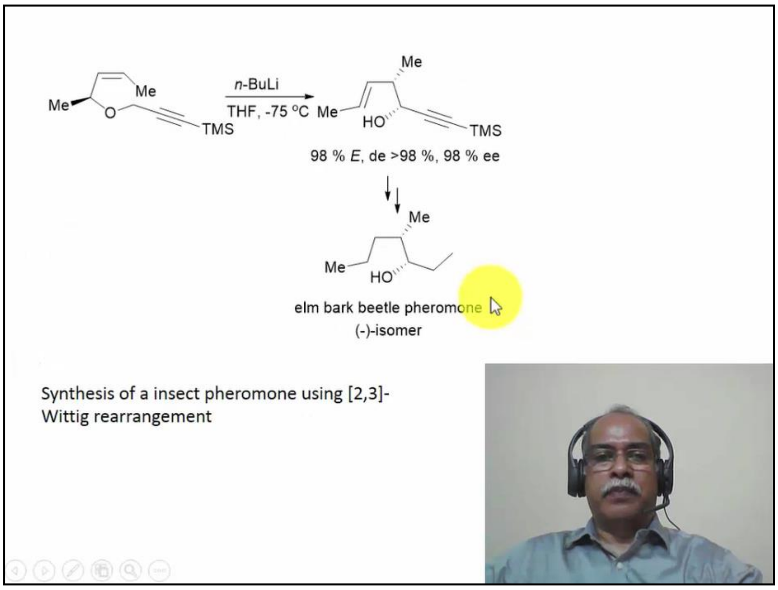

98 % *E*, de >98 %, 98 % ee

elm bark beetle pheromone
(-)-isomer

Synthesis of a insect pheromone using [2,3]-Wittig rearrangement

Now, the [2,3]-Wittig rearrangement has been put to use, in the synthesis of an insect Pheromone. Insect Pheromone are chemical substances, that are secreted by insects, for communication purposes, among the same species. For example, it could be attracting a male, the female may be excreting the Pheromone, which is this particular Pheromone, and so on. So, these are essentially signaling chemicals, which are secreted by insects.

In this particular instance, this optically pure isomer of this particular Propargyl Allyl Ether, is treated with Butyllithium. Again, a Alkoxy anion is generated here, which undergoes the [2,3]-Sigmatropic rearrangement. In doing so, there is a Chiral induction, that is takes place. Because, this is the first order Asymmetric transformation. Your starting material is optically pure, with this particular configuration.

Upon rearrangement, it undergoes a highly Diastereoselective, Syn type of a product, is what is obtained, through a 5-Membered cyclic transition state, involving 6-Electron, in this species. The chemical yield is 98%. The Diastereoselectivity is 98%, of this particular Diastereo isomer. If you call this as a Syn isomer, the Anti-isomer is not formed, more than 2% extent, in this particular instance.

And, the major Diastereo isomer, which is the Syn isomer is formed, in 98% of Enantiomeric excess. In other words, this particular configuration of the molecule is obtained, in about 98%. The other configuration molecule, where you have these two Chiral centers, in a different configuration, for example, with thick lines of representation. That would correspond, to about 2% of the material, that is formed, in this case.

This material, is a starting material, for the Elm Bark Beetle Pheromones Minus isomer, which is this particular structure here. So, this is an instance of the [2,3]-Wittig rearrangement, being put to use, for the synthesis of an insect Pheromone, which is useful, for example, in naturally eliminating the insects. A natural way of eliminating the insect, for example, as a natural insecticide, it can be used.

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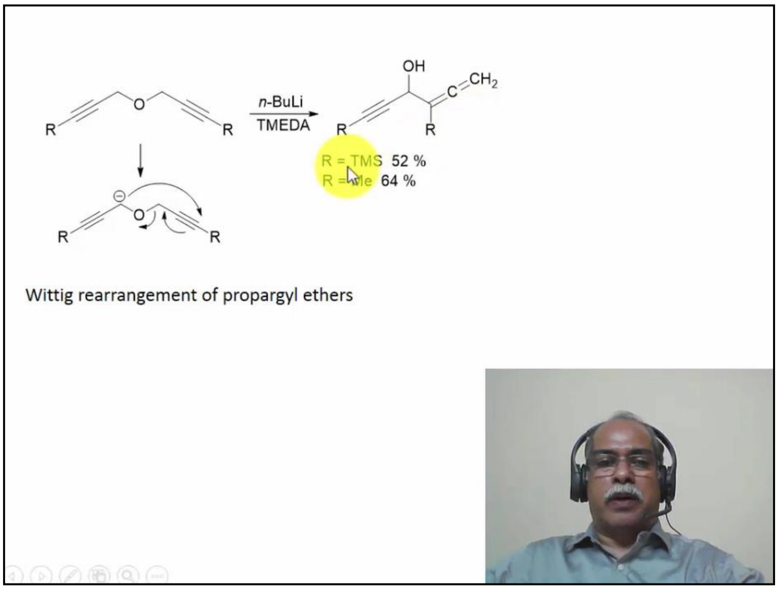

Wittig rearrangement of propargyl ethers

Dipropargyl Ethers also undergo, Wittig rearrangement. Here is an example of a Dipropargyl Ether, treated with N-Butyllithium, and Tetramethyl Ethylenediamine. Now, N-Butyllithium Tetramethyl Ethylenediamine, is a powerful combination, in terms of making the Butyllithium, even a stronger base, than it is. The NN-Tetramethyl Ethylenediamine, is essentially complex to the Lithium, as a result of that, free Butyl anion is generated, under this condition.

In other words, the Lithium is chelated by the Tetramethyl Ethylenediamine, resulting in the formation of a, highly ionized form of the N-Butyllithium, which is a stronger base than Butyllithium, itself. That, results in the generation by deprotonation of the Hydrogen from this position, generation of this Alkoxy Propargylic anion, which undergoes the [2,3]-Sigmatropic rearrangement, as shown by this arrow, involving a 6-Electron, 5-Membered cyclic transition state, resulting in the formation of this Allene derivative, which is the final product of this particular reaction.

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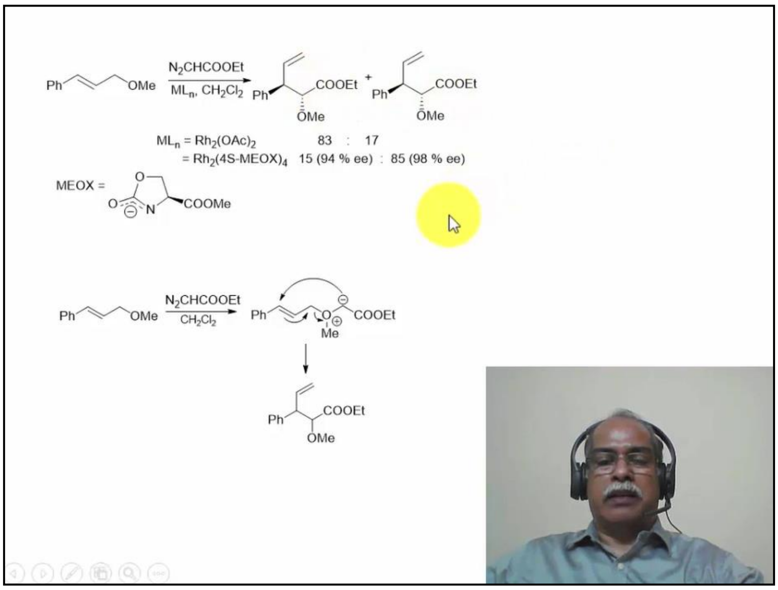

Now, the Alkoxy anion, that is generated in the previous example, Propargylic and Allylic-Oxy anion, they undergo the Wittig rearrangement. One can also generate in-situ, an Oxygen based ylide, that will undergo the [2,3]-Sigmatropic rearrangement. Here is an example, of an Alpha Diazo ester, being decomposed in the presence of Rhodium, to generate the Carbene. That Carbene, reacts with the Oxygen lone pair, to give the corresponding Oxygen ylide.

The Oxygen ylide, undergoes the [2,3]-Sigmatropic rearrangement, to produce these products, that are formed, during the course of the process. So, this ester fragment, essentially comes from the Alpha Diazo ester, by the decomposition. The mechanism, is shown here. The Alpha Diazo ester, transfers a Carbene onto the Oxygen, resulting in the formation of this particular Oxygen-based ylide. Oxygen-based ylide, undergoes the [2,3]-Sigmatropic rearrangement, to produce this product.

And, you can see also here, the Diastereoselectivity is extremely high for this rearrangement, because of the well-defined stereo chemistry, which is the Trans stereochemistry of the double bond, and the well-defined 5-Membered cyclic transition state, which results in the high Diastereoselective formation of only one isomer, in this particular instance. The Diastereoselectivity is also high, when the Rhodium is complex, to this particular Chiral ligand.

The Chiral ligand, induces the Chiral induction of the product, that are being formed. The high Enantiomeric excess, that is obtained for these two products, and high Diastereoselectivity obtained for these two products, are synthetically very useful transformation, in terms of making such molecules, using a [2,3]-Wittig rearrangement reaction.

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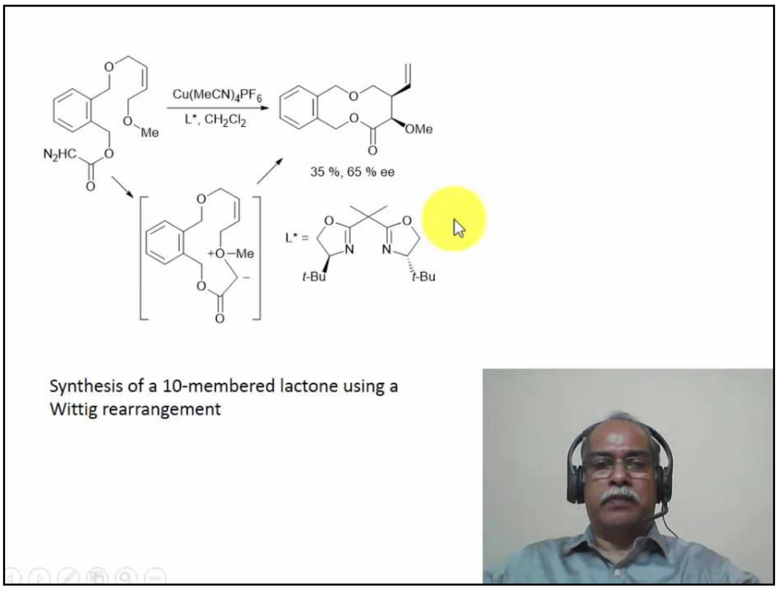

Synthesis of a 10-membered lactone using a Wittig rearrangement

Here is an example, of an Intramolecular transfer of a Carbene, from the Alpha Diazo ester. This is an Alpha Diazo ester, with the Oxygen, which is this particular Oxygen lone pair, is capable of trapping the Carbene, that is generated by the decomposition of the Alpha Diazo ester, in the presence of Copper Tetrafluoro Phosphate, for example. Now, the ligand that is used, is a Chiral ligand.

So, Asymmetric induction again, it is a Chiral Lewis acid catalyzed Asymmetric induction, is what is taking place, in this particular instance. This is a proposed intermediate, which is the Oxygen-based ylide intermediate, which undergoes [2,3]-Sigmatropic rearrangement. So, you can see here, this is the Allelic Ether part of it, and this is the ylide part of it.

So, if you take the Carbanion, and react it in this position, and the concomitant rearrangement of the PI bond, with the breaking of the Carbon-Oxygen bond, will result in the formation of this ring contracted product, which is a 10-Membered Lactone, using the [2,3]-Sigmatropic rearrangement, or the Wittig rearrangement, in this particular instance.

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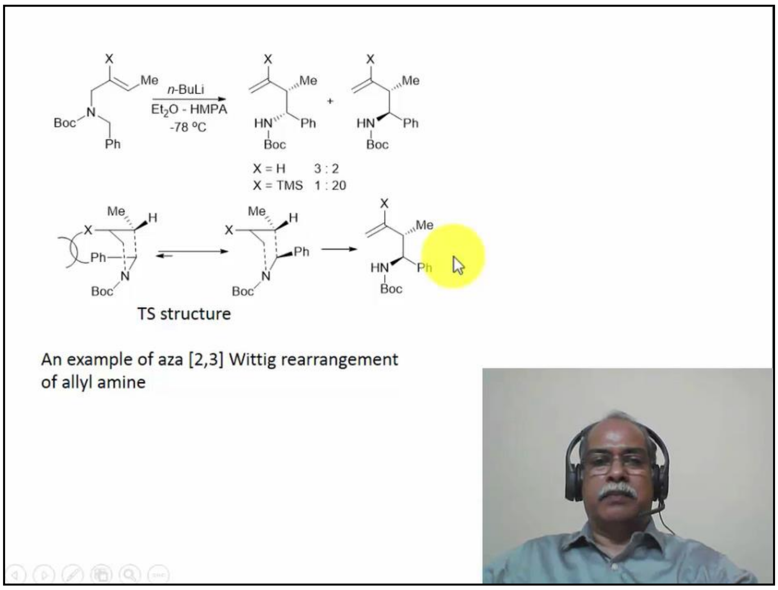

TS structure

An example of aza [2,3] Wittig rearrangement of allyl amine

Here is an example, of an Aza [2,3]-Wittig rearrangement. Instead of an Oxygen, if you have a Nitrogen, that is present in the Allyl Benzyl Amine kind of a system, instead of Allyl Benzyl Ether kind of a system, then it is called the Aza [2,3]-Wittig rearrangement. The Aza [2,3]-Wittig rearrangement is also triggered, by the generation of the Alpha anion of the Amine, by treatment of the Amine with N-Butyllithium, in HMPA as a solvent.

Hexamethyl Phosphoric Triamide is a solvent here, at -78° Centigrade, the rearrangement is essentially occurring from the Carbanion, that are generated in the Benzylic position, which attacks the allelic terminal position, with the concomitant rearrangement, followed by the Carbon-Nitrogen bond cleavage, resulting in the formation of this Boc protected secondary Amine, in this particular case. And, once again, the Diastereoselectivity is very high, because of the well-defined stereochemistry, which is the Trans stereochemistry, in this particular.

The cyclic transition state structures, are indicated here. There are two possible conformers, which can exist in a cyclic transition state. In this conformer, the X group, and the Phenyl group, are sterically interacting with each other, in a hindered fashion, which is absent in the case of this particular transition state, resulting in the formation of the Anti, this particular Anti isomer of the product, that is formed using the Aza Wittig rearrangement, in this particular instance.

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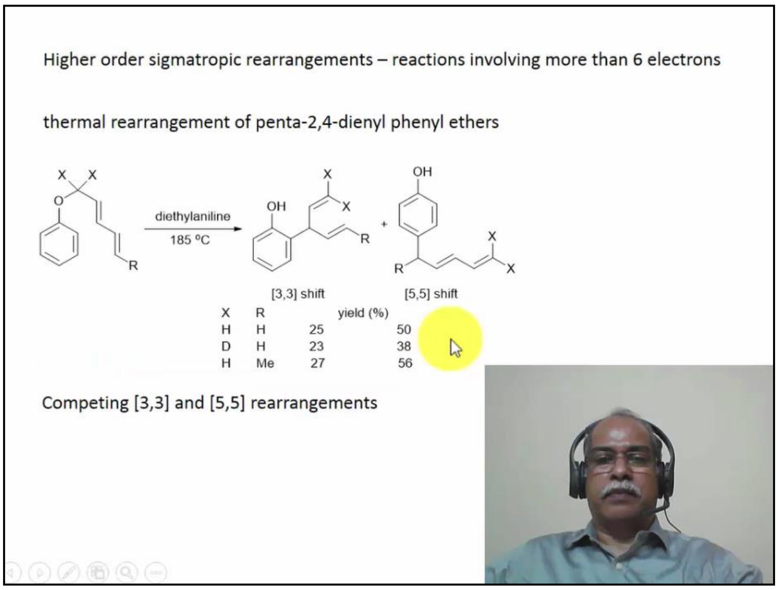

Higher order sigmatropic rearrangements – reactions involving more than 6 electrons

thermal rearrangement of penta-2,4-dienyl phenyl ethers

X	R	yield (%)	
		[3,3] shift	[5,5] shift
H	H	25	50
D	H	23	38
H	Me	27	56

Competing [3,3] and [5,5] rearrangements

Now, let us move on to, higher order Sigmatropic rearrangement. These are rearrangements, which involve 6-Electron or more. So far, we have looked at, 4-Electron, and 6-Electron involvement, of the Sigmatropic rearrangement. In this particular section, we will look at the higher-order Sigmatropic rearrangement, that involve, more than 6-Electrons.

The very typical example of a 10-Electron system, involving a [5,5]-Sigmatropic rearrangement is the, Pentadienyl Phenyl Ether. If you look at this molecule here, this is a Phenyl Ether, and Pentadienyl Ether. So, it is a Pentadienyl Phenyl Ether, is what we are referring to. When, this is refluxed in Dimethylaniline, which is a high boiling solvent up to 185° Celsius, there are two products, that are formed.

The first product, is resulting from a [3,3]-Sigmatropic rearrangement. You can see here, this is something like, Allyl Vinyl Ether. So, it can undergo a [3,3]-Sigmatropic rearrangement, resulting in the formation of this product. It can also react in the Para position, which would be a [5,5]-Sigmatropic shift.

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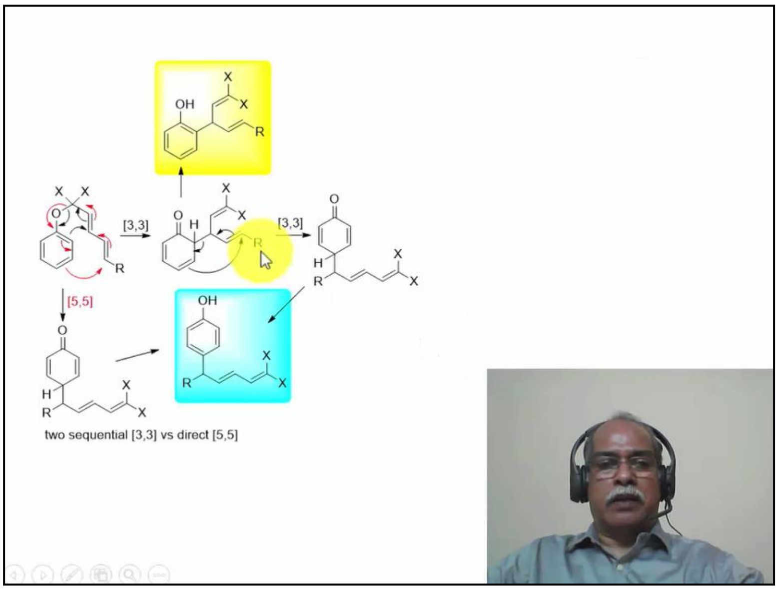

two sequential [3,3] vs direct [5,5]

These two mechanism are depicted, in this slide here. The black arrows essentially indicate, the [3,3]-Sigmatropic process. So, if you just to follow the black arrows, that is shown in this particular structure, that will lead to this particular product. This particular product, can further undergo a [3,3]-Sigmatropic rearrangement, to give this product. Or, it can undergo, simply a Keto Enol Tautomerism, to the observed product, which is a [3,3] product.

This particular product, is what is obtained here. And, that is a same product, that is mentioned here, arising out of a [3,3]-Sigmatropic rearrangement. Now, if you consider the red arrows, which involves 10-Electron system, this is a Pentadienyl Phenyl Ether kind of a system, that will essentially rearrange the Pentadienyl group, to the Para position, by reacting the terminal Carbon of the Pentadienyl system, with the Para position of the aromatic system. The chain is long enough, to reach the Para position. That is why, such a reaction is a facile reaction.

So, under these condition, if you count the number of atoms involved, this is the Carbon-Oxygen bond, that is going to break. So, if you start counting from there, this is 1 and 1. Oxygen is 1. And, this Carbon is 1. Then, 2-3-4-5. So, this is 1-2-3-4-5 on the Pentadienyl system. And, 1-2-3-5 up, to the Para position of the Phenyl, from the Oxygen. So, the Carbon-Oxygen bond, is what is breaking, in this particular system. So, the nomenclature wise, this would correspond to a [5,5]-Sigmatropic rearrangement.

After the [5,5]-Sigmatropic rearrangement, the Keto-Enol-Tautomerism will essentially produce this particular phenol. You can see here, the terminal R group, is now attached directly to the Benzene ring, that Carbon is directly attached to the Benzene ring. Detailed mechanistic studies have indicated that the, this particular product is obtained only from a

[5,5]-Sigmatropic rearrangement, ruling out the possibility of sequential [3,3], followed by a [3,3]-Sigmatropic rearrangement.

if you look at this particular product, this would rather undergo a Keto-Enol-Tautomerism, to give this particular product, than to undergo, further the [3,3]-Sigmatropic rearrangement, under the reaction condition. so, Deuterium substitution labelling, as well as the kinetic measurements very clearly tell, that this is a product arising out of a [3,3]-Sigmatropic rearrangement.

and, this is a product, that is arising out of a [5,5]-Sigmatropic rearrangement, involving 10-Electrons, during the course of the rearrangement. the sequential, the [3,3]-Sigmatropic rearrangement, although it can also principle yield this product, that has been ruled out, based on mechanistic studies. So, this particular process, that is shown by this arrow here, it is a ruled-out process, based on the mechanistic study, by the scientists.

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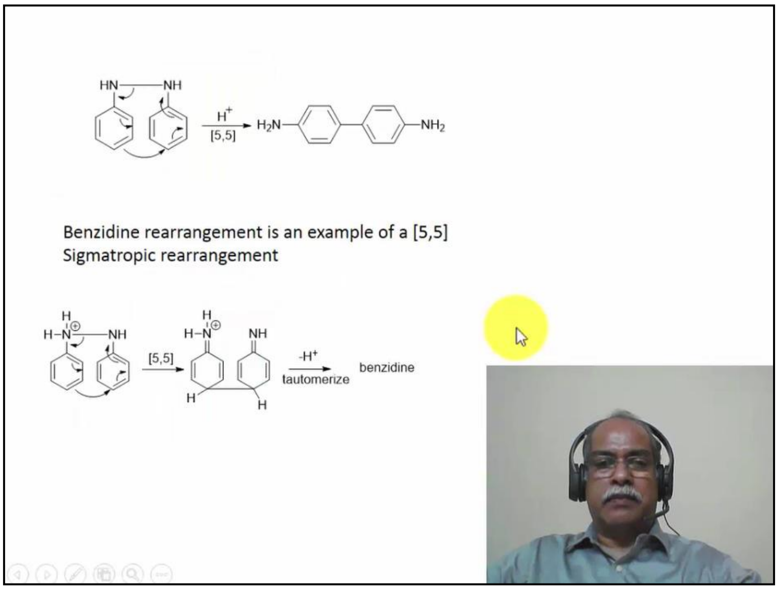

Benzidine rearrangement is an example of a [5,5] Sigmatropic rearrangement

Now, the most famous [5,5]-Sigmatropic rearrangement in Aromatic Chemistry, is the rearrangement of Hydrazobenzene, under acidic condition, to Benzidine. This is the rearrangement, where the Hydrazobenzene is under, concentrated hydrochloric acid condition. When, it is heated, it undergoes a [5,5]-Sigmatropic rearrangement, to give the Para Benzidine, as the product.

The suggested mechanism is that, the protonated Hydrazobenzene, essentially the two Benzene rings lie parallel to each other, bringing the Para positions in close proximity together, as if they are PI-PI interaction is there, between the two-aromatic ring, resulting in the interaction between the Para positions, and formation of a sigma bond, here.

If you consider the breaking of the Nitrogen-Nitrogen bond, then from this Nitrogen, it will be a 5th Carbon, and from this Nitrogen, this again will be a 5th position. So, overall, it is a [5,5]-Sigmatropic rearrangement. Such a rearrangement, essentially produces this molecule, which is an intermediate, in this particular case. This is a [5,5]-Sigmatropic strip. From here, Tautomerism essentially results in the formation of Benzidine, which is a final product, in this particular instance.

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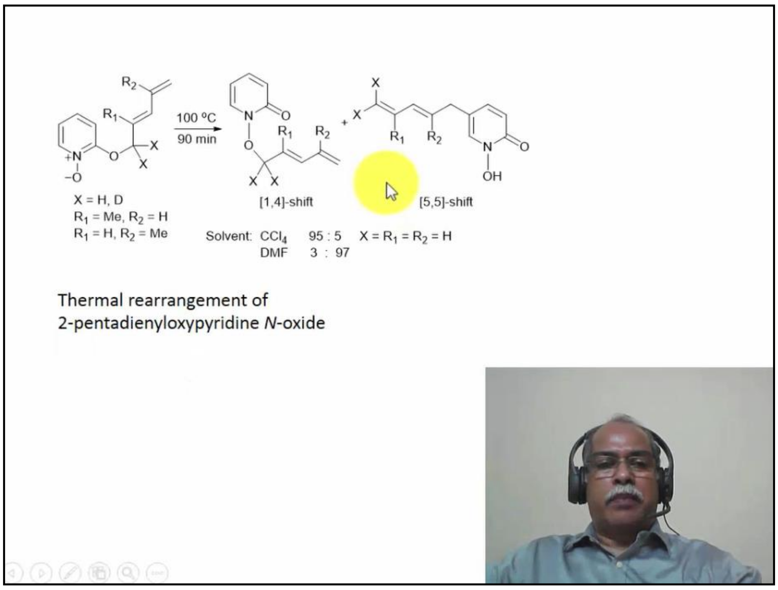

X = H, D
R_1 = Me, R_2 = H
R_1 = H, R_2 = Me

Solvent: CCl_4 95 : 5 $X = R_1 = R_2 = H$
DMF 3 : 97

Thermal rearrangement of
2-pentadienyloxypyridine *N*-oxide

Now, here is an example of a Pentadienyl Oxy Pyridine N Oxide as a substrate. There are two reactions, that are taking place here. One of the product is obtained, by a formal [1,4]-Shift of the Pentadienyl group. The other product is obtained by, a [5,5]-Shift of the Pentadienyl group. On to this particular position. The mechanism of those reactions, are very clearly indicated here. This is by the reaction of the Oxygen, on to this position here, with the cleavage of the Carbon-Oxygen bond.

So, if the Carbon-Oxygen bond is being cleaved, then it will be 1 and 1. This is 1-2-3-4, between the two Oxygen, there are four atoms. And, between the C, substituted with the 2X groups here. Essentially, this is a [1,4] kind of a rearrangement, is what is taking place. You can see here, solvent has a major effect, on the distribution of this two types of products. In the [1,4]-Rearrangement essentially, there is a delocalization of the charges.

In other words, the charge is dispersed, between these 5 atoms, that are involved in the reaction. So, the low polarity solvent, essentially favors the solvent of low polarity, or dielectric constant favors the [1,4] shift. Whereas, the [5,5]-Rearrangement, which is the Pentadienyl rearrangement, undergoing a rearrangement at this position here, resulting in the formation of this particular product.

The charge dispersion is bare minimum. So, Polar solvents essentially favors, that particular product formation, under this condition. So, solvent polarity plays a huge role, in promoting [1,4] in the Non-Polar solvents, and [5,5] in the Polar solvents, as CCL4 and DMF4 used in this particular reaction, to illustrate this particular point.

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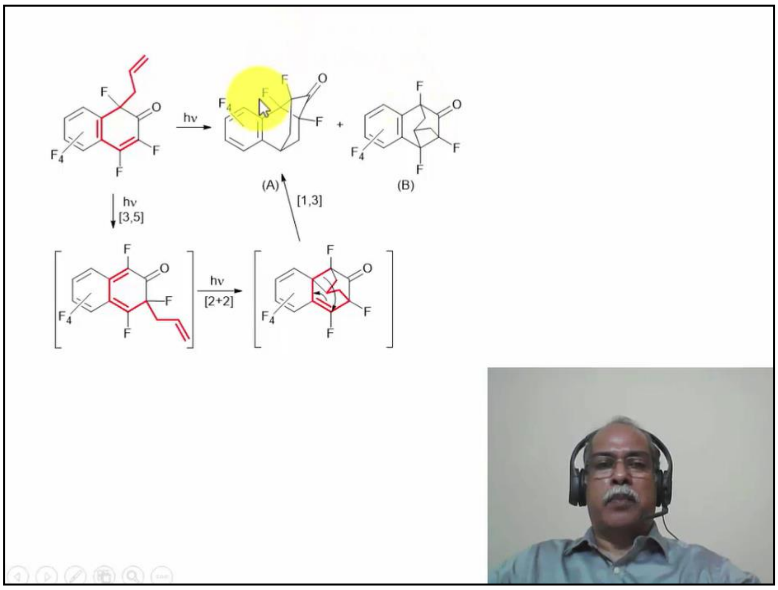

Here is a very interesting, photo chemical [3,5]-Sigmatropic rearrangement. [3,5]-Sigmatropic rearrangement, under photochemical condition, should be suprafacially favored. It is an 8-Electron system, essentially. 8-Electron system, under photochemical condition, should be suprafacial. Under thermal condition, it should be Antarafacial, like a 4N-Electron system, that we normally discuss.

The system, that is undergoing the rearrangement is clearly, the skeleton is shown in this particular case. This is a Carbon-Carbon bond, that is going to break. If the Carbon-Carbon bond is breaking here, then it will be 1-2-3, and this will be 1-2-3-4-5. So, the terminal of this Carbon, and this Carbon containing this Fluorine, or the Carbons, that are interacting during the course of the rearrangement. The rearranged product, which is the [3,5]-Rearrangement product, is shown here.

The rearranged product, is under the photochemical conditions, also undergoes a 2+2 Cycloaddition reaction, leading to the formation of the Cyclobutene derivative, which is this particular derivative. The Cyclobutene is a Vinyl Cyclobutane. It readily undergoes [1,3]-Sigmatropic rearrangement, to give this particular product. The arrows very clearly indicate, the [1,3]-Sigmatropic rearrangement. And, the other product is essential formed by a 2+2 Cycloaddition reaction, straightforward 2+2 Cycloaddition reaction, of the starting material.

In fact, Product A arises by a sequence of [3,5]-Sigmatropic rearrangement, followed by [1,3]-Sigmatropic rearrangement. Whereas, Product B arises by a 2PI-2PI Cycloaddition reaction, between this double bond and this double bond here, resulting in the formation of the Cyclobutene, by a 2+2 process. It has also been shown, that the product B, under the photochemical condition, does not isomerize to product A, which rules out the possibility of the product B as an intermediate, for the formation of product A, in this particular case.

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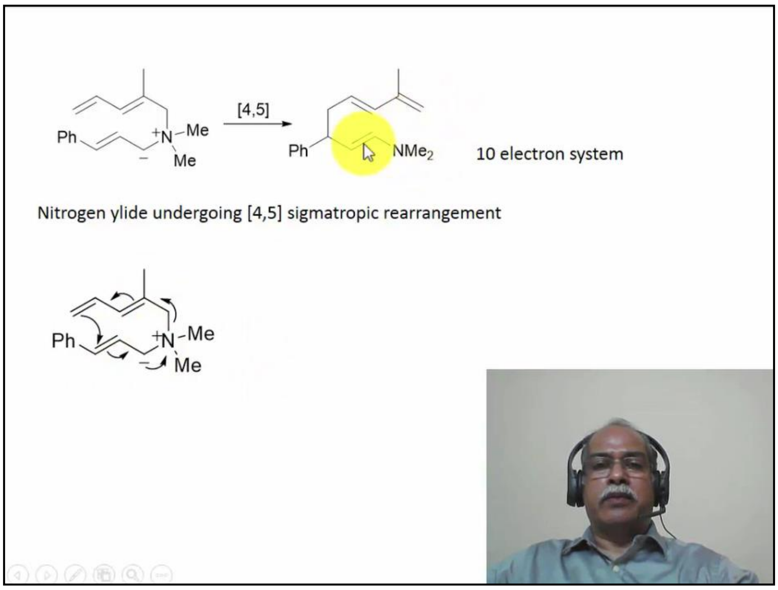

10 electron system

Nitrogen ylide undergoing [4,5] sigmatropic rearrangement

Nitrogen ylides, undergo a [4,5]-Sigmatropic rearrangement, is involving 10-Electron system. And, this is an illustrated example of that, particular rearrangement. The Nitrogen ylide is generated, by deprotonation of the Quaternary Ammonium salt, in this particular instance. And, you can see here, the mechanism of this reaction, essentially involves 10-Electrons. If you count the number of arrows, that will be 5 arrows, corresponding to 5 x 2, 10-Electron system.

So, it is a 9-Membered ring transition state, involving a 9-Membered ring, with a [4,5]-Sigmatropic rearrangement. Why is it [4,5]? This is the Carbon-Nitrogen bond, that is undergoing the cleavage. So, the it will 1-2-3-4-5. This is a 5-Carbon chain, that is undergoing the rearrangement. From the Nitrogen, it is Nitrogen 1-2-3-4. This is the terminal position, where the Carbon-Carbon bond is formed.

So, overall, it is a [4,5]-Sigmatropic rearrangement, involving a 10-Electron system, as shown by the arrows, in this particular case, leading to the formation of this Tertiary Amine, which is an Allelic Tertiary Amine, in this particular instance.

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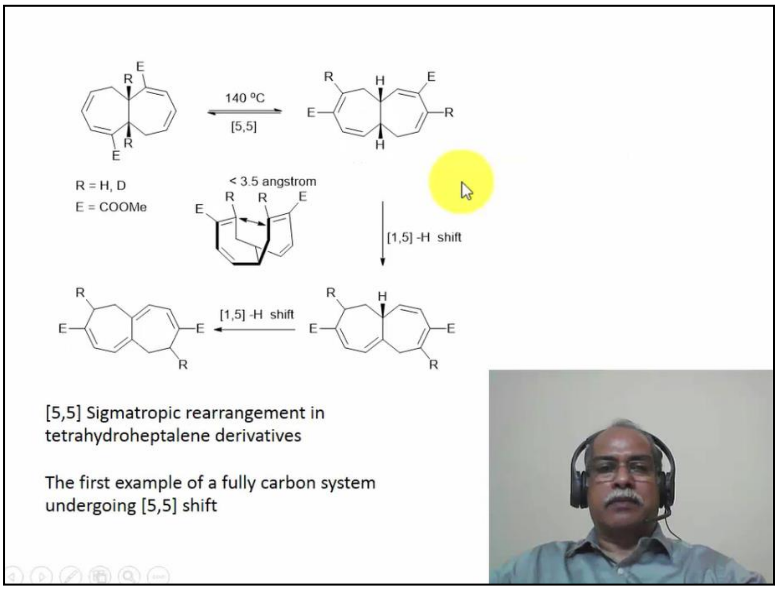

[5,5] Sigmatropic rearrangement in tetrahydroheptalene derivatives

The first example of a fully carbon system undergoing [5,5] shift

Finally, we will conclude the session with an, All Carbon [5,5]-Sigmatropic rearrangement. So far, we have considered the [2,3]-Sigmatropic rearrangement, and [5,5]-Sigmatropic rearrangement. And, they are all, not involving All Carbon system. At least, one Heteroatom, in the form of Oxygen or Nitrogen, is involved. Here is an example, of a [5,5]-Sigmatropic rearrangement, of Tetra Hydro Heptalene derivative.

This particular derivative, this undergoes isomerization back and forth, through a [5,5]-Sigmatropic rearrangement. The [5,5]-Sigmatropic rearrangement is essentially facilitated by the interaction of this two Carbon, which is the Carbon R substituted Carbon, with the R substituted Carbon, resulting in the formation of a [5,5]-Sigmatropic rearrangement. Why is it, a [5,5]-Sigmatropic rearrangement?

If you look at this Carbon-Carbon bond here, this is Carbon number 1-2-3-4-5. So, this will be essentially, the breaking of this Carbon-Carbon bond, is what is taking place. 1-2-3-4-5. This is 1-2-3-4-5. So, the resulting, the Carbon-Carbon bond that is breaking, is this particular Carbon-Carbon bond, resulting in the formation of this particular product.

This product, as it is not stable under the reaction condition, it rapidly undergoes a [1,5]-Hydrogen shift. A sequence of [1,5]-Hydrogen shifts, also take place under this condition. So, this is a first example of a fully Carbon substituted system, that undergoes a [5,5]-Sigmatropic rearrangement, as an illustration of these example. Now, in this module, what we have seen is, the specific reaction of Wittig rearrangement, which is a [2,3]-Sigmatropic rearrangement.

Rearrangement of some Nitrogen ylides and the Oxygen ylides, which are also constituting a [2,3]-Sigmatropic rearrangement. Then, we moved on to higher order Sigmatropic rearrangement involving, [3,5]-Sigmatropic rearrangement, involving 8-Electrons. Then, we had a system of [4,5]-Sigmatropic rearrangement, involving 10-Electron. And, finally, an all Carbon system of Sigmatropic rearrangement, involving 10-Electron, which is a [5,5]-Sigmatropic rearrangement. Thank you, for your kind attention.