Pericyclic Reactions and Organic Photochemistry
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Module No. #04
Lecture No. #20
Pericyclic Reactions – Sigmatropic rearrangements continued… [2,3] sigmatropic shifts

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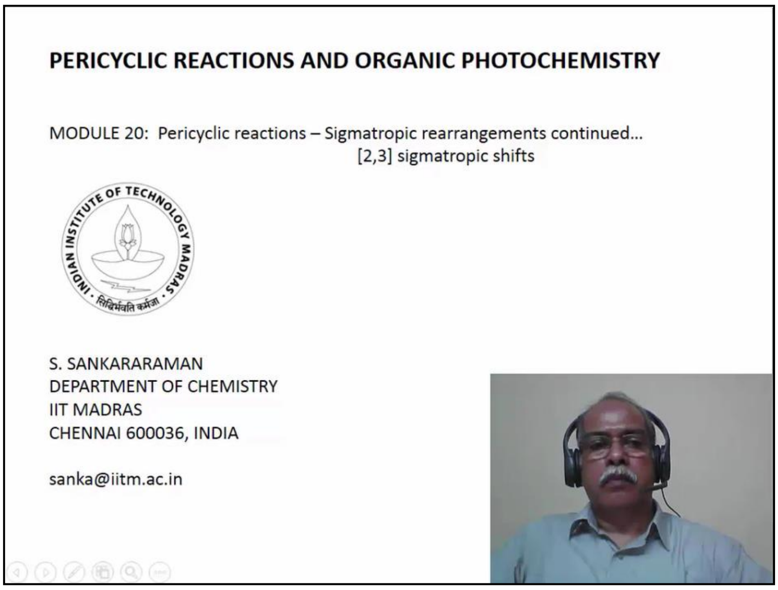

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 20: Pericyclic reactions – Sigmatropic rearrangements continued…
[2,3] sigmatropic shifts

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Hello, welcome to Module Twenty, of the course on Pericyclic Reactions and Organic Photochemistry. In this module, we will consider [2,3]-Sigmatropic rearrangement. [2,3]-Sigmatropic rearrangement is a very important rearrangement. Because, it allows you to synthesize, several different types of molecules, as we can see, in some of these examples here.

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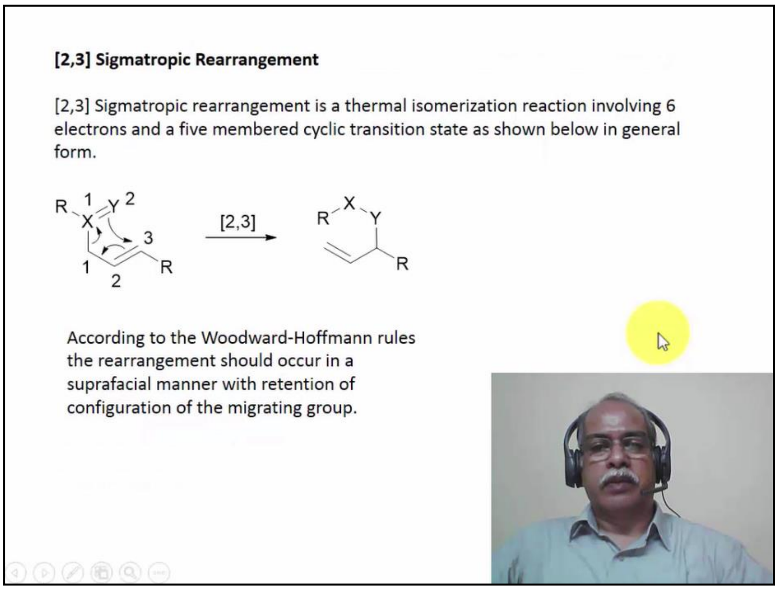

[2,3] Sigmatropic Rearrangement

[2,3] Sigmatropic rearrangement is a thermal isomerization reaction involving 6 electrons and a five membered cyclic transition state as shown below in general form.

According to the Woodward-Hoffmann rules the rearrangement should occur in a suprafacial manner with retention of configuration of the migrating group.

Now, what is a [2,3]-Sigmatropic rearrangement is explained, in a generic manner, in this particular scheme. If, X and Y group, are Heteroatom group. You can consider, for example, an Allyl Sulfoxide, or Allylamine oxide kind of a system, when they undergo the rearrangement, by breaking of the CX bond here, resulting in the migration of the Y group onto the 3 position, that constitutes a [2,3]-Sigmatropic rearrangement.

These are, 6-Electron cyclisation. 2 Sigma electrons of the bond, that is breaking. 2 PI electrons of the XY bond, and the 2PI electrons of the [2,3]-Carbon-Carbon bond, in this particular instance. So, overall, they are 6 electrons, involving 6-Electron rearrangement. According to the Woodward-Hoffmann rule, they should occur in a Suprafacial manner, with retention of stereo chemistry of the migrating group, as we saw in the earlier examples of, [3,3]-Sigmatropic rearrangement also.

These reactions, take place through a 6-Electron, 5-Membered cyclic transition state. Because, you can see, the connectivity is between 2 and 3. So, overall, it will be a 5-Membered ring cyclic transition state, in the general form, it is shown in this particular example.

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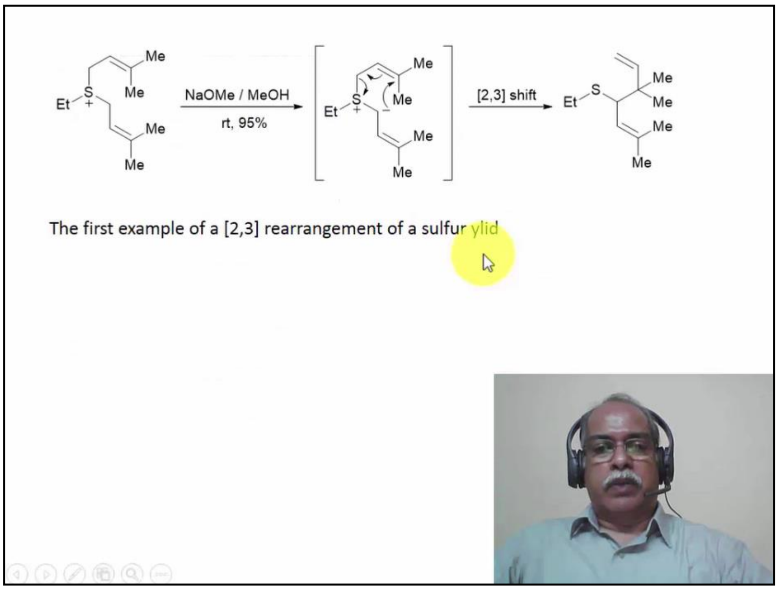

The first example of a [2,3] rearrangement of a sulfur ylid

Now, the most interesting example, or most common example, which is also the first example of the rearrangement, of the type [2,3]-Rearrangements, is of Sulphur ylide. If you consider a Sulfonium salt, which is a Diallyl Sulfonium salt, in this particular case. This is a symmetrical molecule. Because, both the groups are Allyl groups, Dimethyl substituted Allyl group. When, it is treated with Sodium Methoxide, it generates an ylide, which is this particular deprotonation, from this particular Carbon, results in the formation of a Sulphur ylide.

It does not matter, whether you deprotonate from this Carbon, or this Carbon, it will essentially yield the same ylide. On the other hand, deprotonation from the Alpha Hydrogen of the Ethyl group, will give another ylide, which is not a [2,3]-Sigmatropic system. So, this is a [2,3]-Sigmatropic system. This is an Allyl Sulphur ylide, is what we are considering.

If you consider the XY group here, we can call the XY group to be, Carbon and Sulphur. Instead of writing as a zwitter ionic structure like this, one can always write a Carbon Sulphur double bond here, (Refer Slide Time: 02:41) to illustrate the point, that you have a XY double bond, in this particular case. The Carbon Sulphur double bond can also be used, as a representation of this ylide.

[2,3]-Sigmatropic rearrangement takes place, by the attachment of this Carbon, to this Carbon, with a simultaneous breaking of this Carbon-Sulphur bond, in this particular case, resulting in the formation of a Sulfide. So, this is the [2,3]-Sigmatropic rearrangement of Diallyl Ethyl Sulfonium salt, going through an ylide. The ylide, is what is undergoing the [2,3]-Sigmatropic rearrangement.

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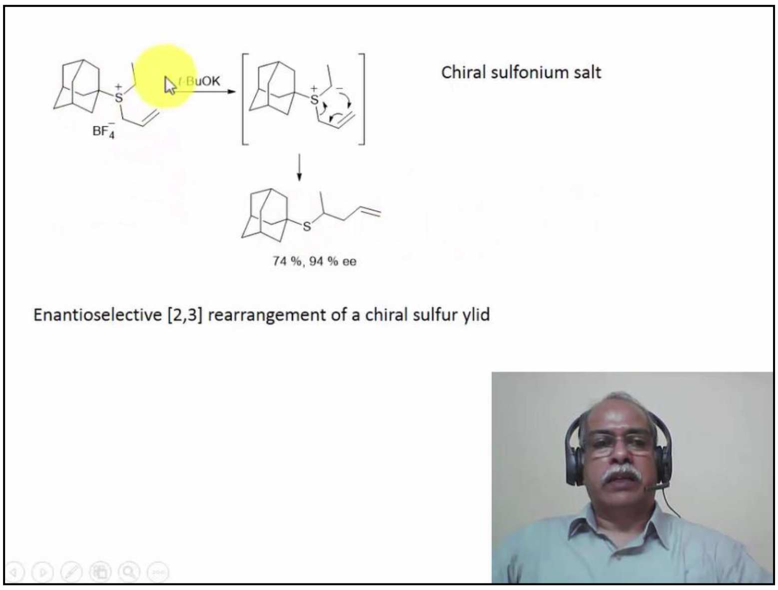

Chiral sulfonium salt

Enantioselective [2,3] rearrangement of a chiral sulfur ylid

Now, this is a Sulfonium salt, with 3 different Alkyl group substituted. This, one of the Alkyl group is an Allyl group. Another Alkyl group is an Ethyl group. The third Alkyl group is a 2-Adamantyl group, for example. When the reagent is treated with Tertiary Butoxide, the ylide is formed, with respect to the Ethyl group here, which constitutes a [2,3]-Sigmatropic Shift system, here.

This Alpha position, does not have, any kind of a Hydrogen. So, there is no problem here. This is a chiral Sulfonium salt, because of the fact, there are 3 different Alkyl groups, attached to the Sulphur center. So, the ylide that is generated, is undergoing a very Enantioselective. This is a first order kind of a chiral induction, is what is taking place. Because, an optically pure compound, is undergoing the [2,3]-Sigmatropic rearrangement, to give the Sulfide.

The Sulfide, that is formed, is formed in about 94% enantiomeric excess, in this particular case of the chiral centers, that is generated in this particular Carbon, here. So, this is a first example of an Enantioselective [2,3]-Sigmatropic rearrangement of a chiral Sulphur ylide. The Sulfonium salt itself is chiral, that is why the induction of chirality, takes place quite readily, in a first order manner, in this particular case.

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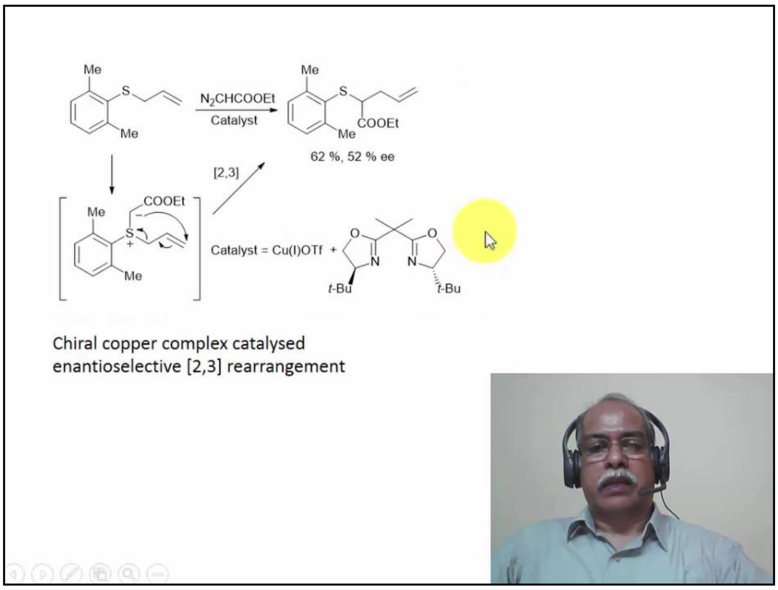

Chiral copper complex catalysed enantioselective [2,3] rearrangement

Now, here is an example of generation of a Sulfonium ylide, by the Carbene transfer. In other words, for example, in this particular case, you have an Alpha Diazo ester as the reagent. The catalyst used is Copper Triflate. Initially, the Nitrogen is lost, and the Carbene, that is generated, is attached to the metal. So, you get a Metal-O-Carbene species. Metal Carbenoid is a species, that is formed. And the Metal Carbenoid, transfers the Carbene onto the Sulphur, in generating the ylide.

When the neutral Sulphur, and the Carbene, react together, this Sulphur donates the electron, to the electron deficient Carbene. So, the Sulphur acquires the positive charge, and the Carbene center Carbon acquires a negative charge, in this particular case, this particular Carbon, so automatically, the ylide is formed, by transfer of a Carbene onto a Sulphur center. And, that constitutes a [2,3]-Sigmatropic shifts system. The skeleton is suitable for a [2,3]-Sigmatropic shift. So, [2,3]-Sigmatropic shifts takes place, essentially.

The Copper salt, that is used as a Copper Triflate, that is complex to a chiral ligand, like this. So, the Carbene transfer takes place, in a very Enantioselective manner, to produce a particular enantiomer, of this particular Sulphur ylide. That undergoes, Enantioselective [2,3]-Sigmatropic rearrangement, to give in 62% chemical yield, and 52% enantiomeric excess of this particular Sulfide, where this chiral center is the configuration, that we are Enantioselectively producing, in this particular rearrangement.

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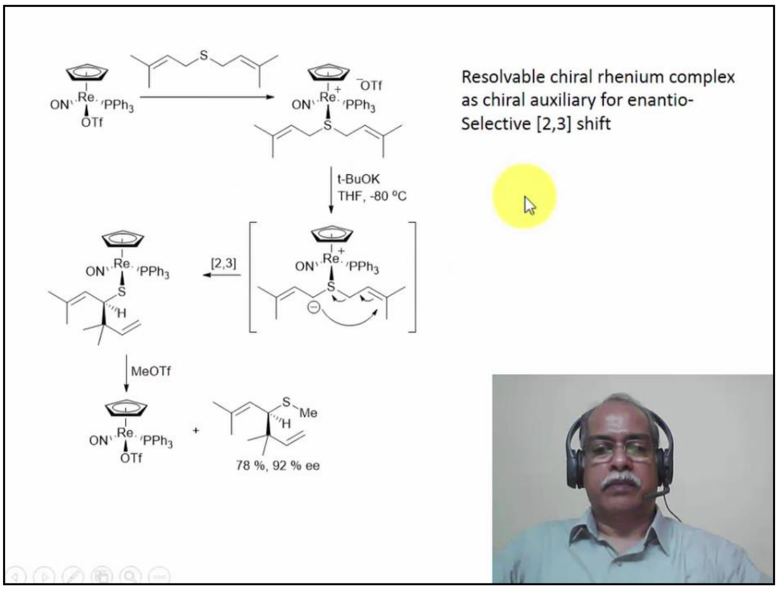

Resolvable chiral rhenium complex
as chiral auxiliary for enantio-
Selective [2,3] shift

One can also use, several different types of metal complexes, to generate. We can use Ruthenium, Rhenium, any kind of Copper, Rhodium, kind of metals, to transfer the Carbene, from a Diazo derivative, to the corresponding Sulphur center. In this particular case, a resolvable Chiral Rhenium complex, is used as a chiral auxiliary. This Rhenium center is a chiral center, and it is a resolvable complex. So, enantiomerically pure compound can be taken, in this particular case.

And, that is coordinated to the Sulphur, to produce essentially, this Sulfonium kind of a salt. This is a Diallyl Sulfonium kind of a salt, except it is instead of Sulphur bearing the positives charge, the Rhenium is bearing the positive charge. The oxidation state of Rhenium here, is different from the oxidation state here. And, the oxidation state here is +2, and probably here, the oxidation state is again +2. If you represent it, as a Sulfonium ion, it would be +2, in this particular case also. The Rhenium center is a chiral center.

So, the ylide that is generated, is undergoing a stereoselective [2,3]-Sigmatropic rearrangement, to produce this Sulfide. The Sulfide can be made into a Triflate, by treatment with Methyl Triflate, for example, with a simultaneous methylation of the Sulphur. So, the treatment of this complex with Methyl Triflate, produces the S-Methyl derivative, in an optically pure form, to the extent of about 92% energy enantiomeric excess, with a chemical yield of about 78%, in this particular case.

So, here is an example, where the resolvable Chiral Rhenium complex, is used as a chiral auxiliary. It is initially attached to the Sulfur. And, after methylation, it is removed in the form of a Triflate salt, and it is regenerated to get the starting material back, in this particular case. So, it is truly used in a stoichiometric amount, as a resolvable chiral auxiliary, is what is used, in this particular case, the Rhenium salt.

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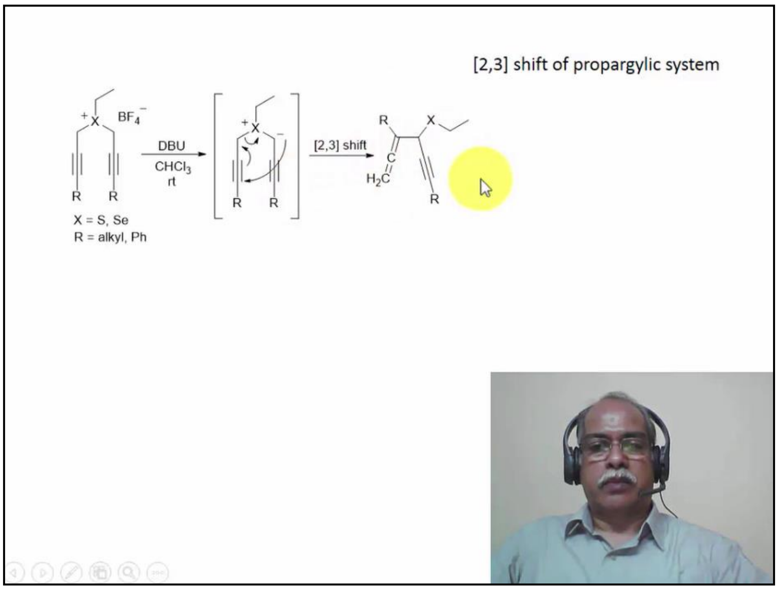

[2,3] shift of propargylic system

X = S, Se
R = alkyl, Ph

[2,3]-Shift of Propargylic system, is illustrated in this particular example. Instead of having Diallyl Sulfide, you can have Dipropargyl Sulfide, or Selenide, as the case may be. When it is reacted with Diazabicylo-undec-ene, which is a base, the ylide is generated. The ylide generated, undergoes [2,3]-Sigmatropic rearrangement, to produce an Allene derivative. In other words, Alpha Alkenyl substituted Allene derivative, is what is produced, as a result of the [2,3]-Sigmatropic rearrangement of the system.

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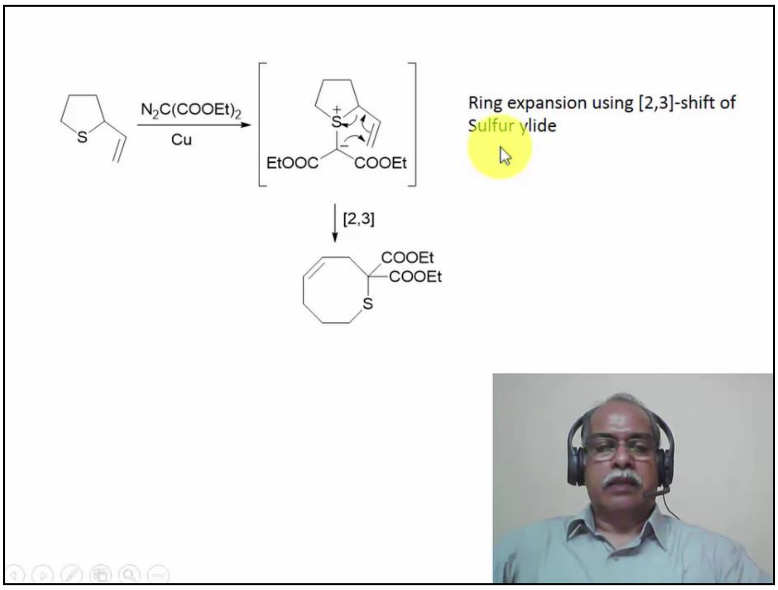

Ring expansion using [2,3]-shift of Sulfur ylide

Here is another example, of a ring expansion reaction, using [2,3]-Sigmatropic rearrangement. Once again, the Copper Carbenoid is generated, by the reaction of the Alpha Diazo ester, in this particular case. The Copper transfers the Carbene, that is generated on to the Sulphur, to produce the corresponding Sulphur ylide.

The Sulphur ylide, is now located to undergo the [2,3]-Sigmatropic rearrangement, as it is shown by means of arrows, in this particular scheme, resulting in the formation of, breaking of this Carbon-Sulphur bond, and formation of this Carbon-Carbon bond, resulting in an enlarged structure, ring expanded structure, in this particular case, an 8-Membered ring with the Sulphur, is what is generated, during the course of the [2,3]-Sigmatropic rearrangement.

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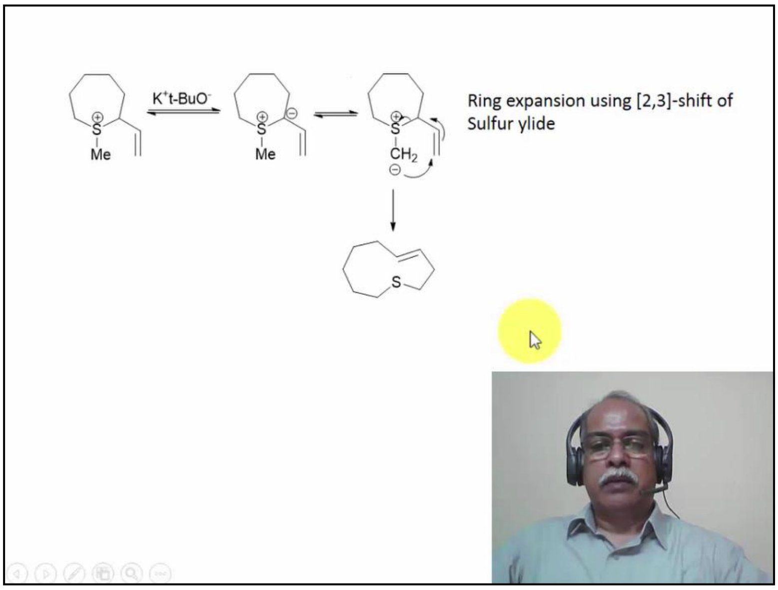

Ring expansion using [2,3]-shift of Sulfur ylide

Here is another structure, which is a 7+3, 10-Membered ring, is what is generated here. Initially, this particular Sulfonium salt with an Allyl derivative, which is this Vinyl derivative, is actually a S-Allyl derivative, when it is treated with the Potassium Tertiary Butoxide, it generates the Sulphur ylide, in the Alpha position, that cannot undergo any rearrangement.

The ylide that is generated, from the deprotonation of the Methyl Hydrogen, of course, can undergo [2,3]-Sigmatropic rearrangement. So, this two Sulphur ylides are in equilibrium. One of the ylide is undergoing a [2,3]-Sigmatropic shift, pushing the equilibrium towards the right side, towards the formation of this particular derivative, which is a 10-Membered ring system, in this particular case, by a [2,3]-Sigmatropic rearrangement of the Sulphur ylide.

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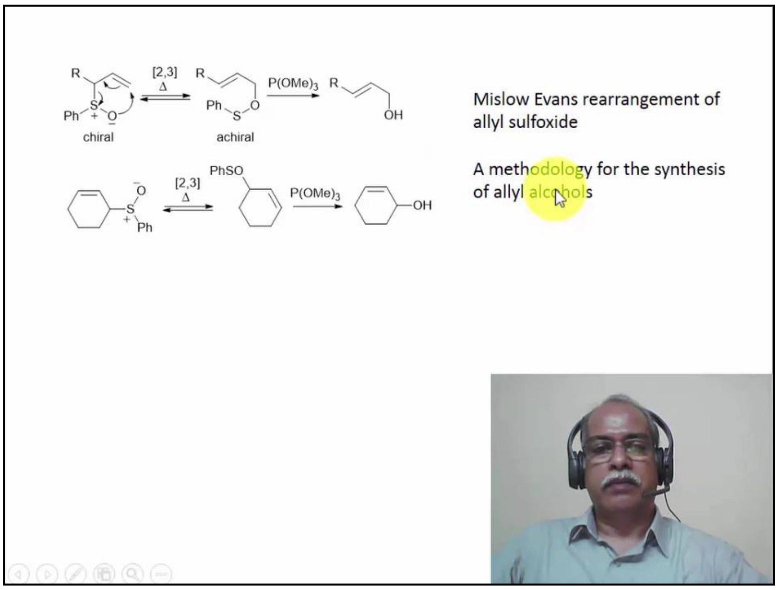

Mislow Evans rearrangement of allyl sulfoxide

A methodology for the synthesis of allyl alcohols

Sulfoxides also undergo [2,3]-Sigmatropic rearrangement, provided, they are Allyl Sulfoxides. Here is an example of an Allyl Sulfoxide, undergoing a [2,3]-Sigmatropic rearrangement. The Allyl Sulfoxide, undergo [2,3]-Sigmatropic rearrangement, at a much lower temperature, compared to the Allyl Sulphur ylide derivative. This is known as the, Mislow-Evans rearrangement of Allyl sulfoxides.

You can see here, the Allyl Sulfoxide, undergoes [2,3]-Rearrangement. The Carbon-Sulphur bond is broken. And, the Oxygen-Carbon bond is formed, to give a Sulfinate ester. The Sulfinate ester, of course undergo desulfurization, when it is treated with Trimethyl phosphate, produce the Trimethyl, the corresponding Trimethyl Phosphorus Sulfide, is what is produced here. And, the corresponding Allyl alcohol is produced.

So, the Allyl Sulfoxide, actually acts as a precursor, to produce the Allyl alcohol. So, this constitutes a synthesis of an Allyl alcohol, through the formation of an Allyl Sulfoxide, undergoing a rearrangement, followed by desulphurization, to give the Allyl alcohol. So, this methodology is known as the, Mislow-Evans rearrangement of Allyl Sulfoxide. It is also a methodology, for the synthesis of Allyl alcohol derivatives, using this particular rearrangement.

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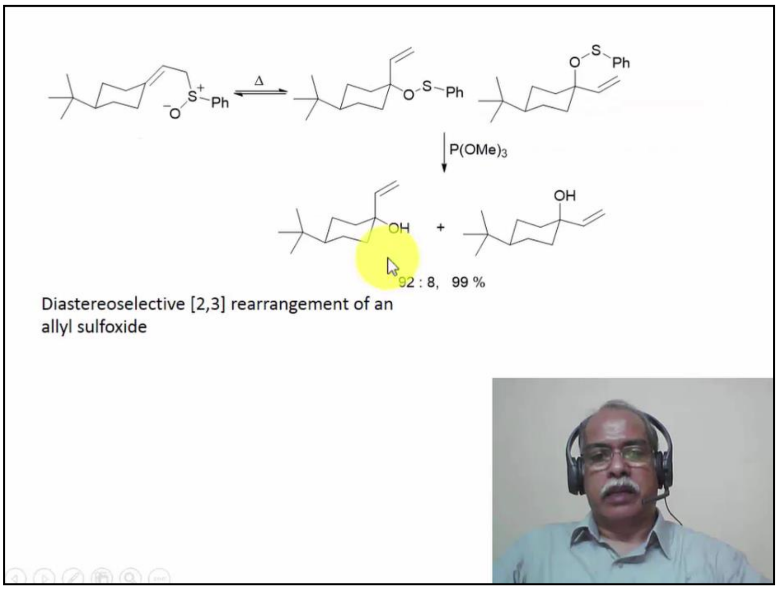

Diastereoselective [2,3] rearrangement of an allyl sulfoxide

And, that is illustrated in a Diastereoselective manner, in this particular case. This Allyl Sulfoxide, which is an Hexamethylene derivative of the 4-Tertiary Butyl Cyclohexyl derivative. The Sulfoxide can approach this double bond, either from the Equatorial face, or swing it around, and get it from the Axial face. Of course, swinging it around, and getting it through the Axial face, will be a sterically more hindered.

So, these are the two Sulfinates, that are produced by a [2,3]-Sigmatropic rearrangement. This is the Carbon-Sulphur bond, that is broken. And, the Carbon-Oxygen bond, that is formed, is this particular bond. So, this is 1-2, 1-2-3, [2,3]-Sigmatropic rearrangement, produces these two Sulfinates. Desulphurization, using Trimethyl phosphate, gives the Tertiary alcohols, which are shown here.

The Equatorial approach to rearrangement, is the predominant rearrangement, occurring to an extent of about 92%. The Axial approach produces, 8% of the other product. Overall, yield is about 99%. So, this constitutes a Diastereoselective synthesis of an Allyl alcohol, Tertiary alcohol, in a very Diastereoselective manner. Only the Equatorial alcohol is formed, in major amount. The Axial alcohol is produced, in a very small amount, in this particular case.

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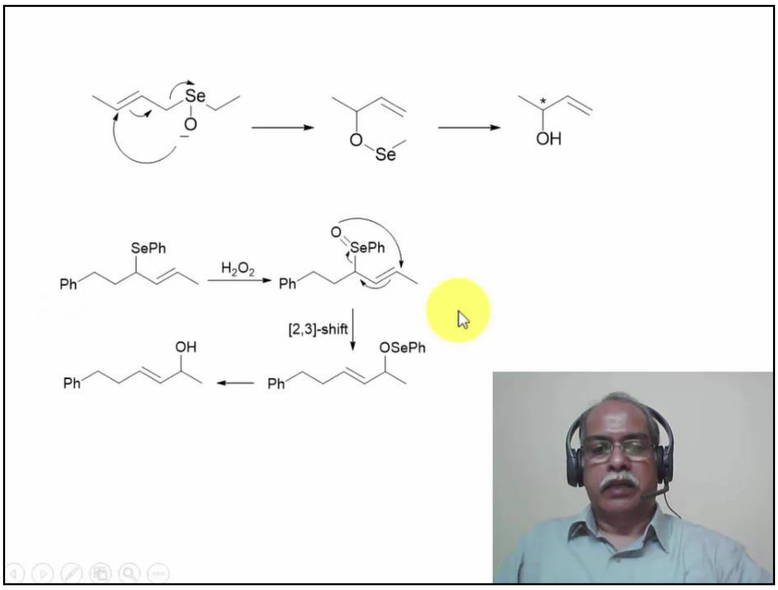

Instead of Sulphur, one can also use Selenium oxide, to make it undergo the [2,3]-Sigmatropic rearrangement, as it is shown here. The Selenium oxide, in fact, undergo [2,3]-Sigmatropic rearrangement, at much lower temperature, compared to the Allyl Sulfoxide. So, here is an example of an Allyl Selenoxide, undergoing a rearrangement, to give the Selenide. The Selenide is hydrolyzed, to give the corresponding Allyl alcohol. This is illustrated, by making use of this reagent.

This Selenide, is treated with Hydrogen peroxide, to produce the corresponding Selenoxide. The Selenoxide, undergoes [2,3]-Sigmatropic rearrangement, to give the Selenide. The Selenide is hydrolyzed, to give the corresponding Allyl alcohol. So, you can see the functionalization of this position, which is three Carbon away from the Selene. Carbon-Selenium bond is essentially used, for the synthesis of this type of Allyl alcohol, in a stereo selective manner.

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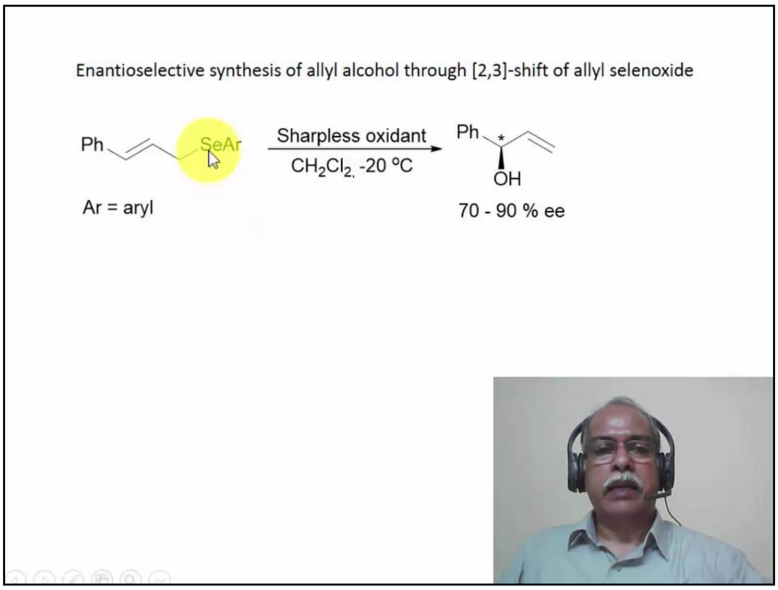

Enantioselective synthesis of allyl alcohol through [2,3]-shift of allyl selenoxide

If the Sulfoxide can be generated, in an enantio specific manner, using sharpless kind of a reagent. Sharpless oxidation, is nothing but, the oxidation of an Olefin, using a Titanium Tetraisopropoxide as a metal templates, Diethyl Tartrate as a chiral template, and then Tertiary Butyl Hydroperoxide as an oxidizing agent. The same reagent can be used, for the oxidation of the Selenide, to the corresponding Selenoxide, in an Enantioselective manner.

Once, you have synthesized the Selenoxide, in an Enantioselective manner, the rearrangement can also be expected to undergo, in an Enantioselective manner. In fact, the rearrangement of the Selenoxide that is produced, the chiral Selenoxide that is produced, from the Selenide, using sharpless oxidant. The sharpless oxidant, is same as the reagent, that is used for sharpless oxidation.

So, please look it up, it is a combination of Diethyl Tartrate with Titanium Tetraisopropoxide, and Tertiary Butyl Hydroperoxide, as the oxidant. So, the chiral Selenoxide, undergoes the [2,3]-Sigmatropic rearrangement. The Carbon-Selenide bond is broken. The Oxygen-Selenide bond is formed here, in this particular case, resulting in the formation of an Enantioselective formation, of this Allyl alcohol.

So, Asymmetric synthesis of Allyl alcohol is possible, by means of a Selenoxide, or a Sulfoxide rearrangement, by a [2,3]-Sigmatropic rearrangement. Synthetically, extremely, useful rearrangement. You can see here, the temperature at which, the reaction takes place. It is a very low temperature. So, one can expect a very high Enantioselectivity, in this kind of a situation.

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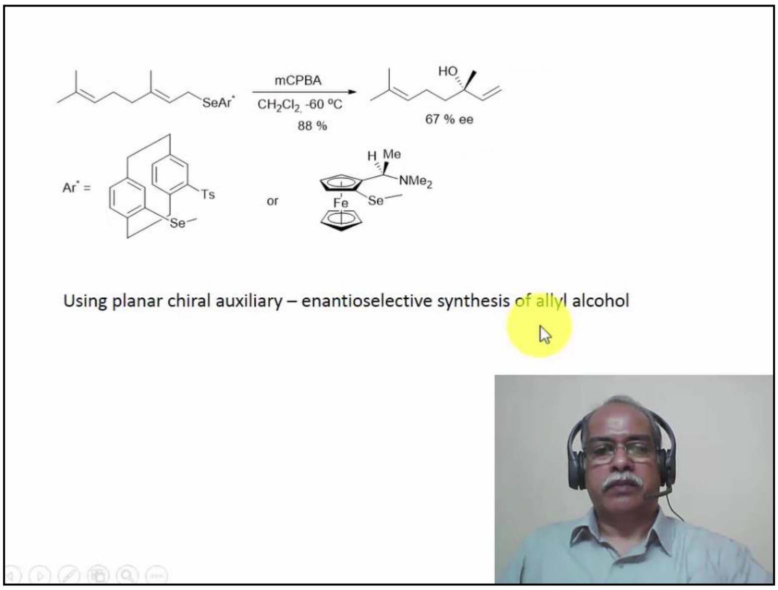

Using planar chiral auxiliary – enantioselective synthesis of allyl alcohol

Instead of using a Sulfoxide, which is a chiral Sulfoxide, the chiral auxiliary is used, in the form of a planar chiral auxiliary, which is a [2,2]-Paracyclophane derivative, or the [1,2]-Disubstituted Ferrocene derivative, which is a Selenide, in this particular case. So, the Aryl group, that is present in the system, is essentially this group, which forms a Diselenide bridge. In other words, there is a Selenium, already present in the Allyl Selenide. The Aryl group, also has a Selenide. So, it will be a Diselenide kind of a derivative, here.

MCPBA oxidation of the Selenium, to the corresponding Selenoxide, followed by [2,3]-Sigmatropic rearrangement, enantioselectively produces this particular Allyl alcohol. In this case, rearrangement is very specific, to only this allylic position, not to this double bond here, resulting in the formation of the terminal Allyl alcohol, in this particular case. So, the planar chiral auxiliary are the [2,2]-Paracyclophane derivative, or the Ferrocene derivative, which are used for chiral induction, in this particular instance of rearrangement.

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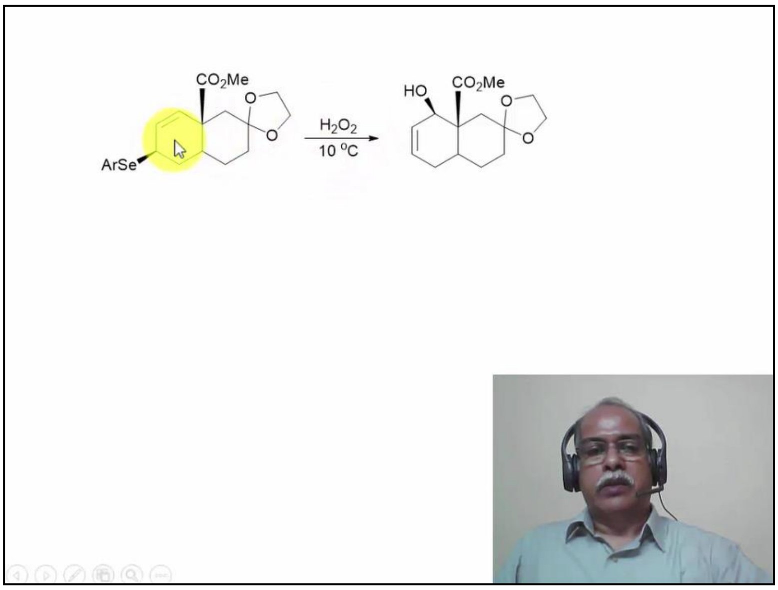

Another example of a, Diastereoselective Selenoxide rearrangement, is shown here. This Selenide, under the reaction conditions of Hydrogen peroxide as an oxidant, produces a corresponding Selenoxide. That Selenoxide, is an Allyl Selenoxide. So, it undergoes [2,3]-Sigmatropic rearrangement, to produce a corresponding Selenide, which can be hydrolyzed, to give the corresponding hydroxy functional group.

You can see here, the stereochemistry is Beta, in this particular case. The alcohol, that is produced, is also Beta, which indicates the Suprafacial migration has taken place, resulting in the formation of a particular Diastereo isomer, which is shown in this case. Again, the reaction is carried out at a very low temperature, ensuring the high diastereoselectivity of this particular reaction, in this particular case.

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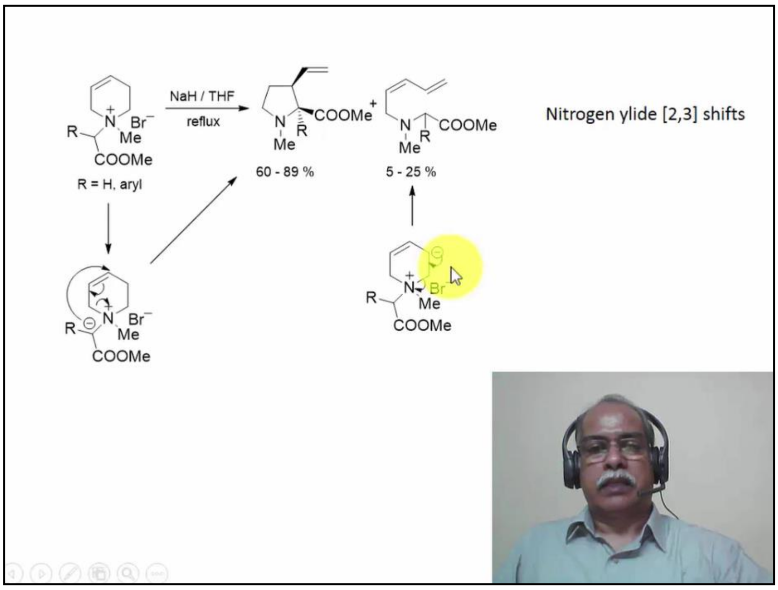
Nitrogen ylide [2,3] shifts

Instead of Sulphur and Selenium, one can also use Nitrogen center. Nitrogen ylides also, undergo the [2,3]-Sigmatropic rearrangement. These are examples of Nitrogen ylide, undergoing [2,3]-Sigmatropic rearrangement. When, this Ammonium salt is treated with Sodium hydride, two reactions takes place. The first reaction is the generation of an ylide, followed by a [2,3]-Sigmatropic rearrangement, to form this particular product, which is arising from the skeletal rearrangement of the piperidine ring, to the corresponding pyrrolidine ring system, in this particular case, by a ring contraction.

Alternatively, this Beta Hydrogen can also be removed, and an elimination can take place, as it is shown here. So, this is something like a Hoffmann elimination product, is what is formed. So, when the reaction is carried out, under basic condition, the competing elimination product is formed, in about 5 to 25% yield. Whereas, the [2,3]-Sigmatropic rearrangement, through the ylide is formed, to an extent of over, 60 to 89% or so.

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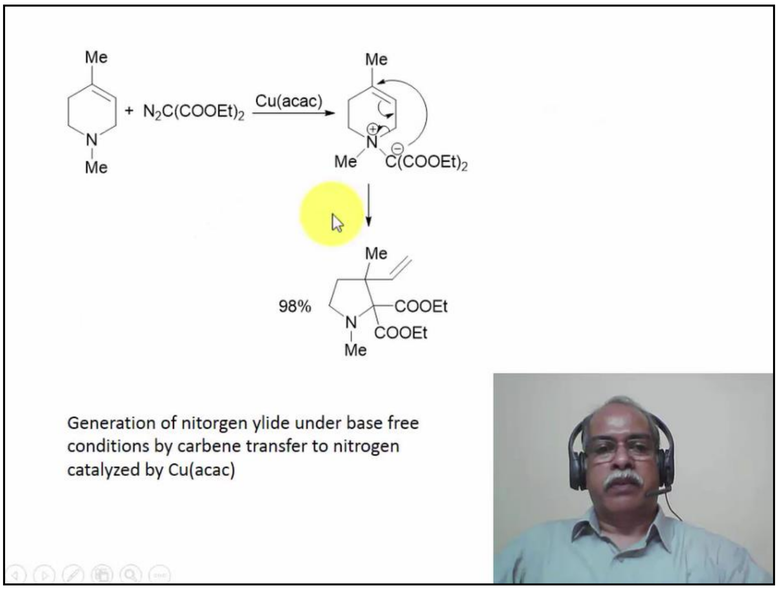

Generation of nitorgen ylide under base free conditions by carbene transfer to nitrogen catalyzed by Cu(acac)

If the same reaction can be carried out, in the absence of any base, in other words, if the ylide can be generated, in the absence of base free condition, by a Carbene transfer reaction. Here, the Diazo ester is transferring, the Carbene to the Copper. And, Copper in turn, transfers the Carbene onto the Nitrogen, resulting in the formation of a Nitrogen ylide.

Now, this Nitrogen ylide is formed in the absence of any base, so there is no problem of elimination reaction, Hoffmann elimination reaction, taking place. Only a [2,3]-Sigmatropic rearrangement takes place, to produce the product, in very high yield of about, 98% or so.

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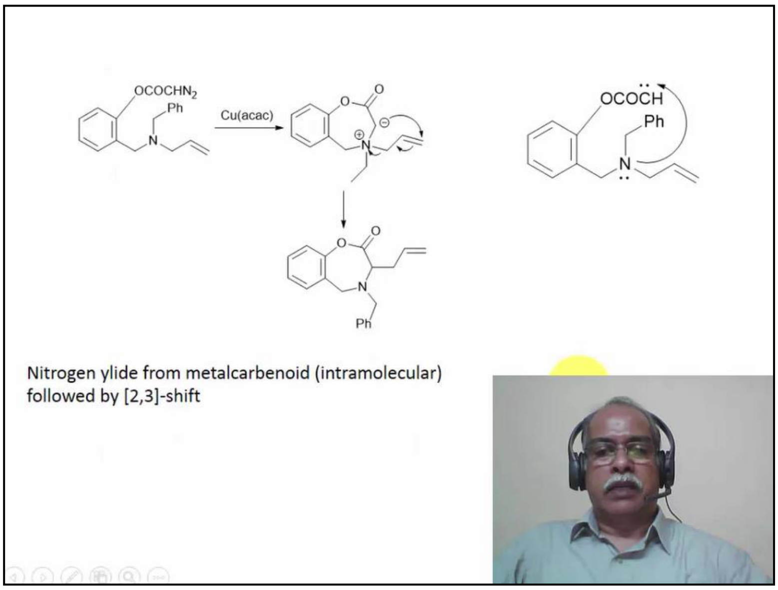

Nitrogen ylide from metalcarbenoid (intramolecular)
followed by [2,3]-shift

So, that is advantage of generating the Nitrogen ylide, without the presence of a base. Another example of a Copper mediated, Intramolecular Carbene transfer reaction, is what is shown here. This Alpha Diazo ester undergoes decomposition, in the presence of Copper Acetylacetonate, resulting in the formation of a Copper Carbenoid system. The Carbene, that is generated is now added to the Nitrogen, to produce the corresponding ylide. This is already substituted with an Allyl group, here.

So, the ylide undergoes the [2,3]-Sigmatropic shift, resulting in the formation of the Alpha Allyl substituted Amine derivative, which is the final product, in this particular case. The Intramolecular Carbene transfer, is shown by this mechanism. Nitrogen is electron rich, whereas Carbene is electron deficient. So, the Nitrogen pair is added to the Carbene, resulting in the formation of the ylide, which has a structure, zwitter ionic structure, where the Nitrogen possesses the positive charge, and a Carbene center possesses the negative charge, in this particular case.

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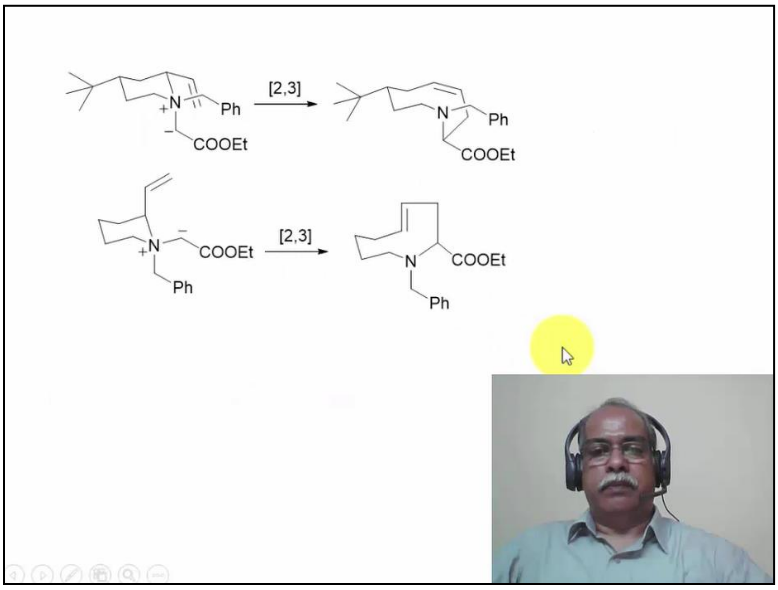

Now again, Diastereoselective 5-Membered cyclic transition state, is what is illustrated in this particular example. If you have an Equatorial isomer of the Allyl Nitrogen ylide, and the Axial isomer of the Nitrogen ylide, the Diastereoselective rearrangement produces this particular Diastereo isomer, from the Equatorial isomer.

And, this particular isomer, where you have a E isomer of the double bond, from the Axial isomer of the starting material. So, essentially, this is selectively formed, because of the 5-Membered cyclic transition state. This is also 5-Membered cyclic transition state, except the substituent is in Axial substituent. So, resulting in the formation of this particular product, in this particular case.

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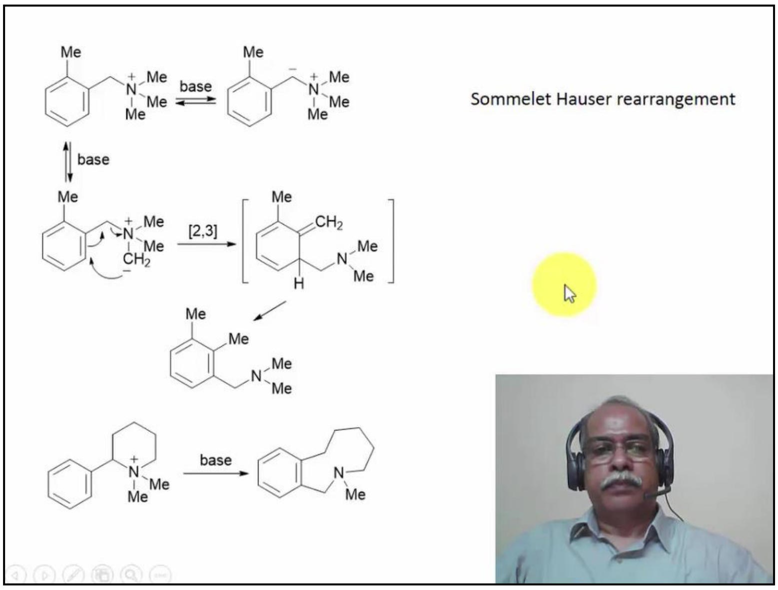
Sommelet Hauser rearrangement

Now, the Benzyl Ammonium salts, undergo [2,3]-Sigmatropic rearrangement, which is known as Sommelet–Hauser rearrangement. If you take a Benzyl Ammonium salt of this type, which is shown here. This is Trimethyl Benzyl Ammonium salt, or Ortho Methyl substituted Trimethyl Benzyl Ammonium salt, is what is treated with the base. When you treat it with the base, it produces the corresponding Nitrogen ylide.

The Nitrogen ylide, undergoes the [2,3]-Sigmatropic rearrangement, with the breaking of the Carbon-Hydrogen bonds, and forming of the Carbon-Carbon bond, which produces this intermediate here. This undergoes tautomerization, under basic conditions, to give the corresponding primary Tertiary Amine, which is shown here, by a Hydrogen migration reaction.

The same reaction, is used for synthesis of a medium-sized ringed Tertiary Amine, in this particular case. The base abstracts the Hydrogen, from the Methyl proton, and which generates the Nitrogen ylide, followed by attack in the ortho position, resulting in a [2,3]-Sigmatropic rearrangement, to produce this particular Tertiary Amine, is also constitutes an example of a Sommelet-Hauser kind of a rearrangement reaction, in this case.

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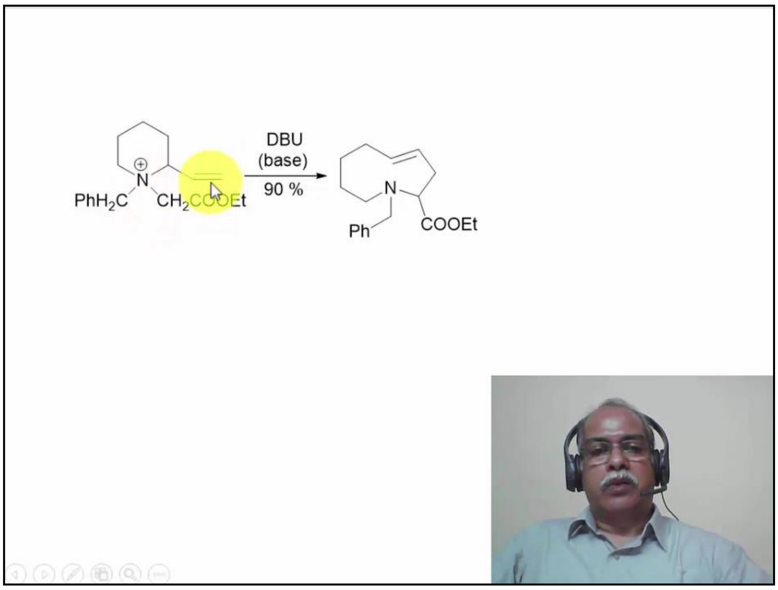

Here is another example, of a Nitrogen ylide being produced. Alpha to the Nitrogen, which is this acidic Hydrogen here, resulting in the formation of an ylide. The ylide undergoes [2,3]-Sigmatropic rearrangement, to produce a medium-sized ring, which is a Tertiary Amine, in this particular case. What we have seen in the examples, that are shown in the particular module, is examples of [2,3]-Sigmatropic rearrangement.

First, we defined the [2,3]-Sigmatropic rearrangement. How it occurs. And, what is the Woodward-Hoffmann rule, for the corresponding sigmatropic rearrangement. And, the Nitrogen, Sulphur, and Selenium systems, which undergo the [2,3]-Sigmatropic rearrangements are illustrated, with a lot of examples, in this module. Hope you enjoyed the module, thank you very much, for your kind attention.