Principles of Organic synthesis
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Molecular Rearrangements
Lecture 24
Rearrangement to Electron-Rich Carbon

Welcome you all to principles of organic synthesis. So far we had two lectures on the molecular rearrangements, where we studied the rearrangement to the electron deficient carbon, nitrogen and oxygen. With respect to the migration to the electron deficient carbon, we covered the Wagner-Meerwein, pinacol and benzilic acid rearrangements, and homologation of the carboxylic acid.

In case of the migration to the electron deficient nitrogen, we focused on the Hofmann, Curtius, Schmidt, Lossen and Beckmann rearrangements, while for the migration to the electron deficient carbon, we studied the Baeyer-Villiger and hydroperoxide rearrangements.

In this lecture, let us focus on the rearrangement to the electron rich carbon and the migration in the aromatic substrates.

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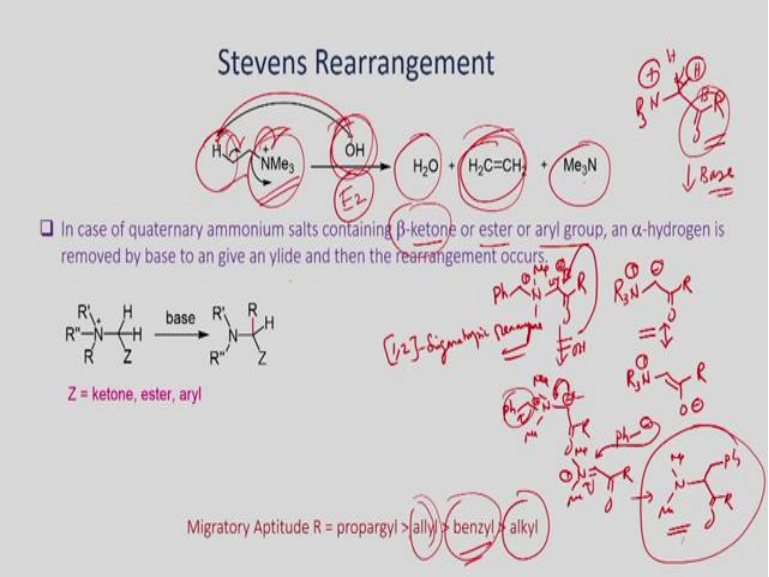

Let us begin with the Sevens rearrangement, where the quaternary ammonium salts with strong base converts to the amine via E_2 elimination. If an ester, keto and aryl group is present at the β-

carbon, an α-hydrogen is removed by the base to produce an ylide. Which is stabilized by the carbonyl or aryl group, and the [1,2]-sigmatropic rearrangement takes place from nitrogen to α-carbon. If you look at the substituent in ammonium salt, propargyl shows the greater migratory aptitude compared to benzyl, which exhibits more migratory aptitude in comparison to the alkyl group.

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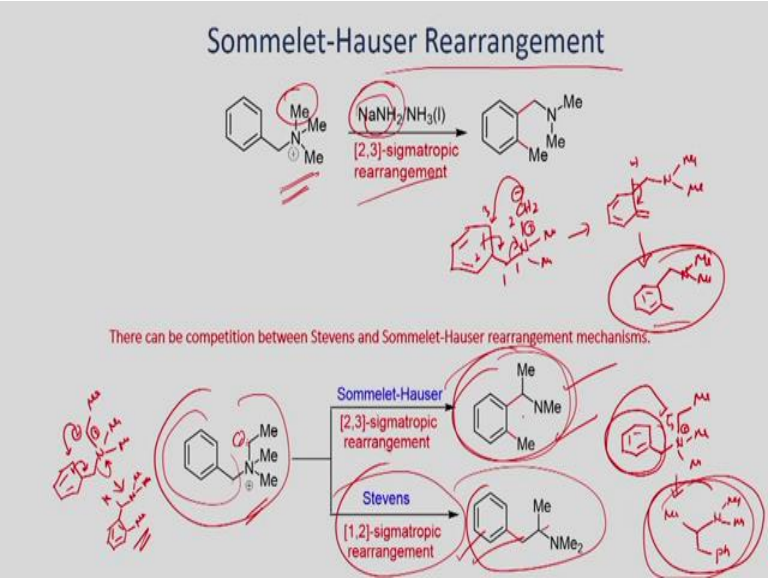

Now let us focus on the Sommelet-Hauser rearrangement, which involves the reaction of certain benzyl quaternary ammonium salt using strong base. For example, benzyltrimethylammonium iodide with sodamide leads [2,3]-sigmatropic rearrangement to produce *ortho*-methyl derivative of N,N-dimethylbenzylamine. Deprotonation of the benzylic hydrogen produces benzylic ylide, which leads [2,3]-sigmatropic rearrangement and aromatization to give the product. If you change the substrate to benzyldimethylethylammonium iodide, there can be competition between Stevens and Sommelet-Hauser rearrangements that can lead two different products.

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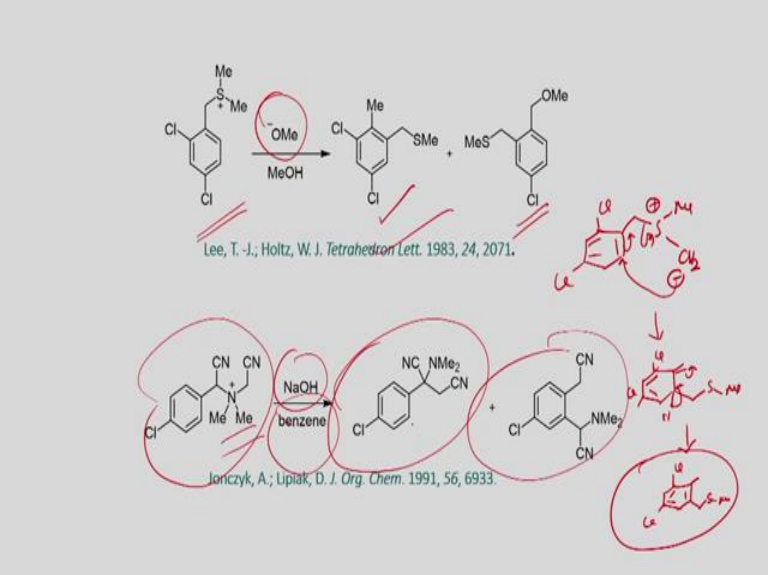

Here, the first example leads [2,3]-sigmatropic rearrangement to give benzyl methyl thioether, while the next example shows [1,2] and [2,3]-sigmatropic rearrangements to produce a mixture of products.

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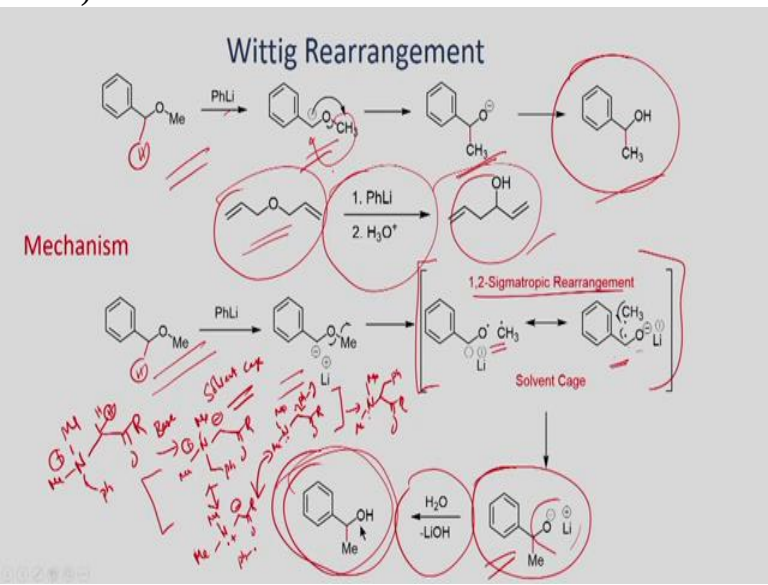

Now, let to focus on the Wittig rearrangement, where benzyl and allyl ethers with base leads [1,2]-sigmtropic rearrangement to produce benzyl and homoallylic alcohols. For example, benzyl

methyl ether with phenyllithium generates benzyl carbanion, which converts to free radical pair and [1,2]-sigmatropic rearrangement occurs to yield α-methyl benzyl alcohol. Similarly, diallyl ether with phenyllithium rearranges to vinyl alcohol.

If you remember the Stevens rearrangement, where we have seen the involvement [1,2]-sigmatropic rearrangement. Similar to the Wittig rearrangement, the Stevens rearrangement may also involve free radical pair intermediate that can be not be ruled out.

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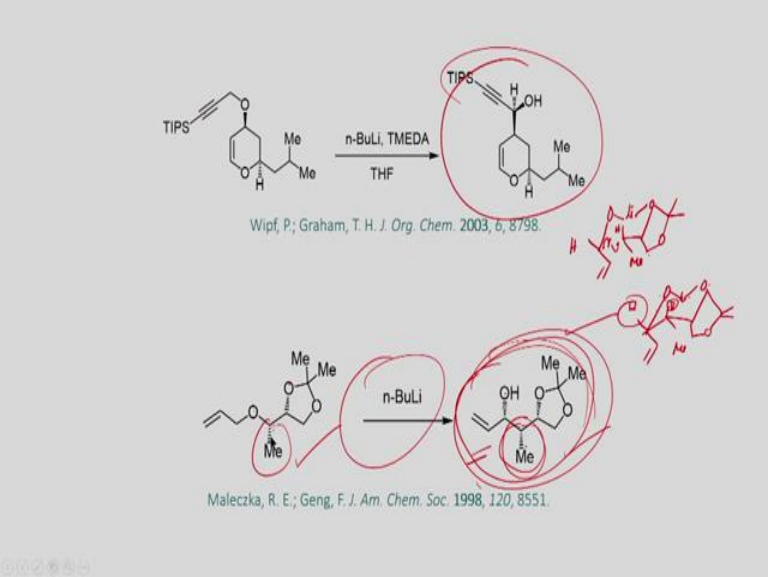

Here allyl proparyl ether with n-butyllithium leads [1,2]-sigmatropic rearrangement to yield propargyl alcohol. Similarly, the allyl ether reacts with n-butyllithium to produce vinyl alcohol in which the stereochemistry is retained.

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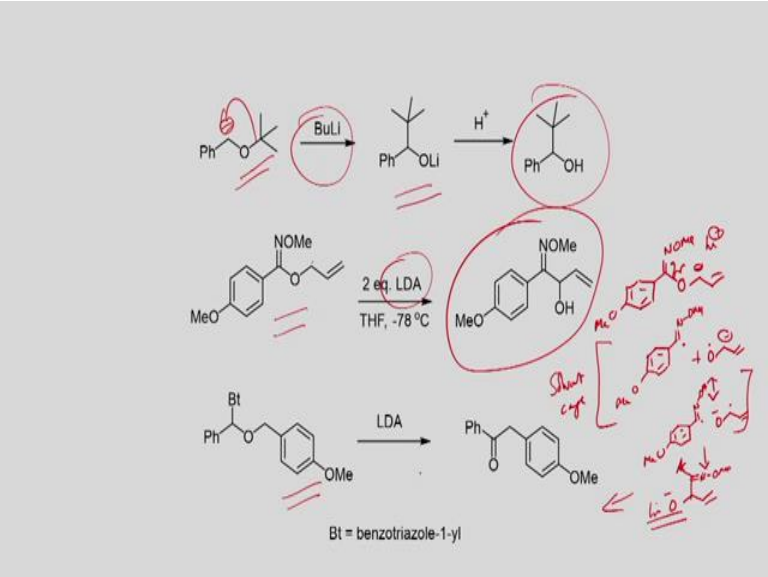

Here are some more examples. Benzyl t-butyl ether rearranges using n-butlyllithium to produce α-t-butyl benzyl alcohol. Likewise, allyl ether utilizing LDA rearranges to produce vinyl alcohol, whereas benzyl ether bearing good leaving benzotriazole rearranges to ketone.

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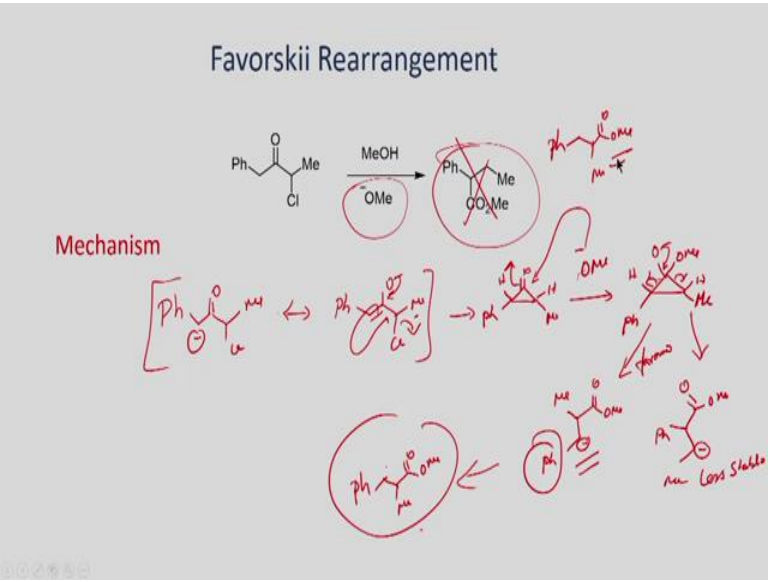

Now let us look at the Favorskii rearrangement that involves the rearrangement of α-haloketone to carboxylic acid derivatives. The reaction using hydroxide produces the carboxylic acid, while

the reactions of alkoxide and amine yield the ether and amide, respectively. For example, the deprotonation of the α-chloro ketone followed by substitution reaction leads to cyclopropanone, which reacts with methoxide to give the linear alkyl ester via addition followed by ring opening.

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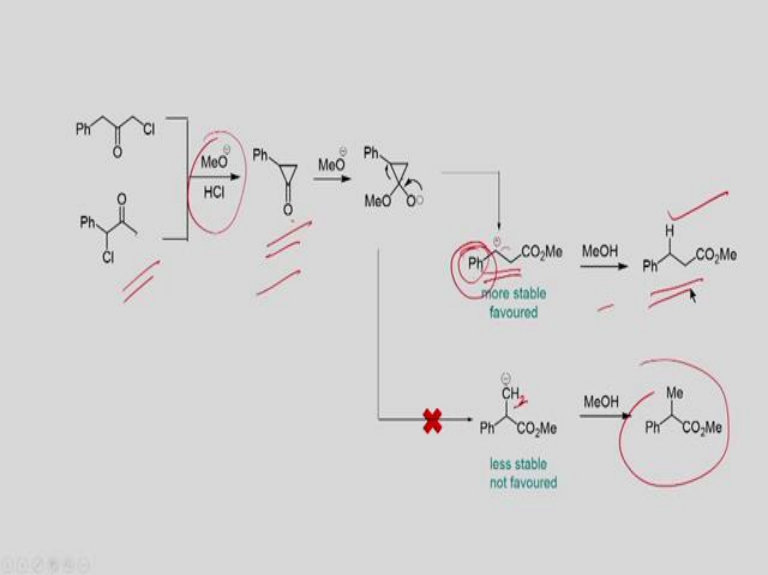

Let us look at the rearrangement of the α-haloketones. Deprotonation followed by intramolecular S_N2 substitution produces cyclopropanone. Addition of the methoxide to the carbonyl group followed by opening of the cyclopropyl ring gives the benzylic carbanion that protonates to give the product. The formation of benzylic carbanion is favoured as it can be stabilized by the aromatic ring.

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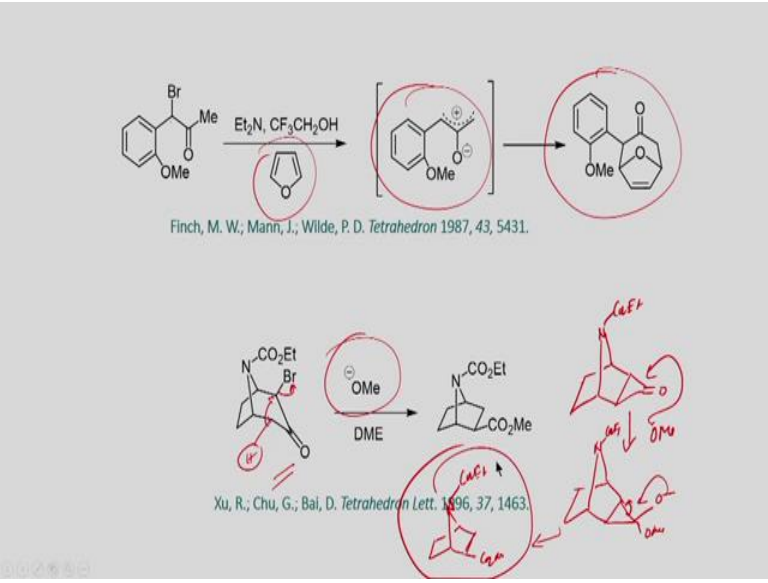

The first example involves the deprotonation followed by cycloaddition with furan to give the bicyclic compound. The second example shows the rearrangement via deprotonation followed by cyclopropanone formation and the ring opening to give the bicyclic ester. So far we have seen the migration to electron rich carbon where we covered Stevens, Sommelet-Hauser, Wittig and Favorskii rearrangements. In these reactions, strong base deprotonates the acidic hydrogen and the rearrangement takes place.

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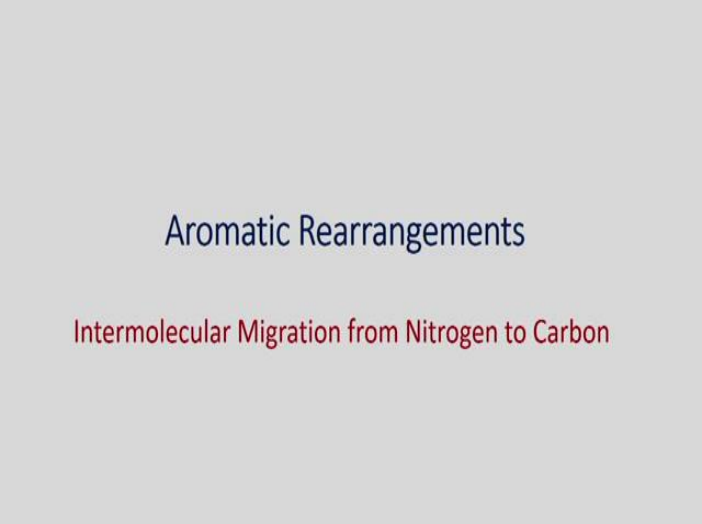

Now let us move to the rearrangement in the aromatic systems. These reactions are catalyzed by the acids. First let us see the rearrangement from nitrogen substituent to aromatic ring.

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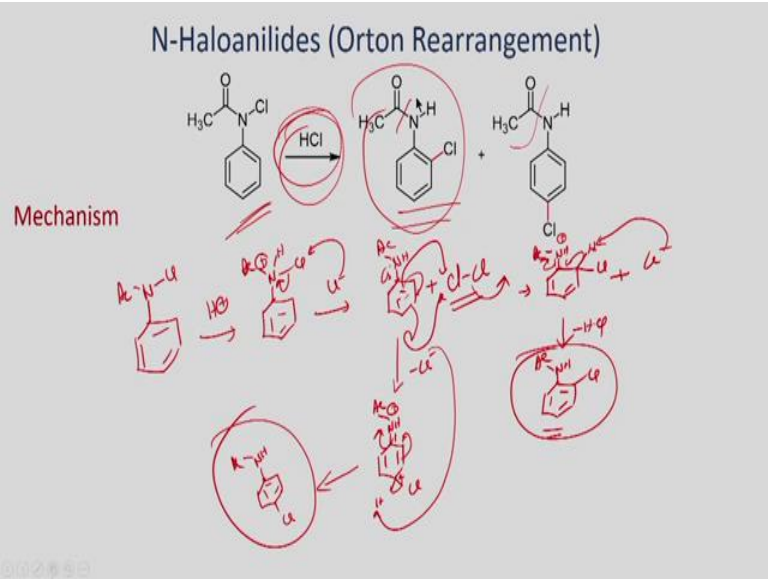

N-Haloanilides rearrange to 2- and 4-haloanilides in the presence of the acid. For example, N-chloroacetanilide with HCl gives a mixture of 2- and 4-chloroacetanilides. Protonation followed by substitution by chloride ion gives acetanilide and Cl_2, which undergoes electrophilic aromatic substitution to produce a mixture of 2 and 4-chloroacetanilides.

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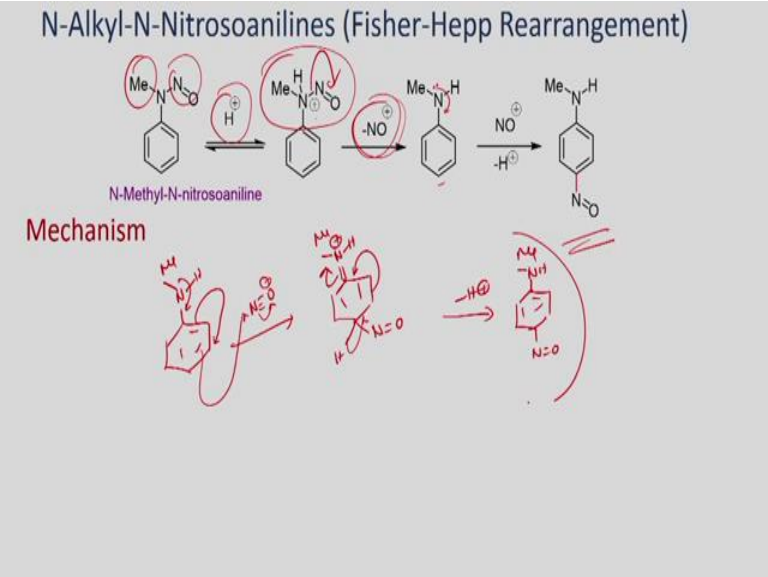

N-Nitrosoaniline rearranges to 4-nitrosoaniline in the presence of acid. For example, N-methyl-N-nitrosoniline with HCl produces 4-nitrosoaniline derivative. In this reaction, protonation leads to the formation N-methylaniline and nitrosonium ion, which undergoes electrophilic aromatic substitution.

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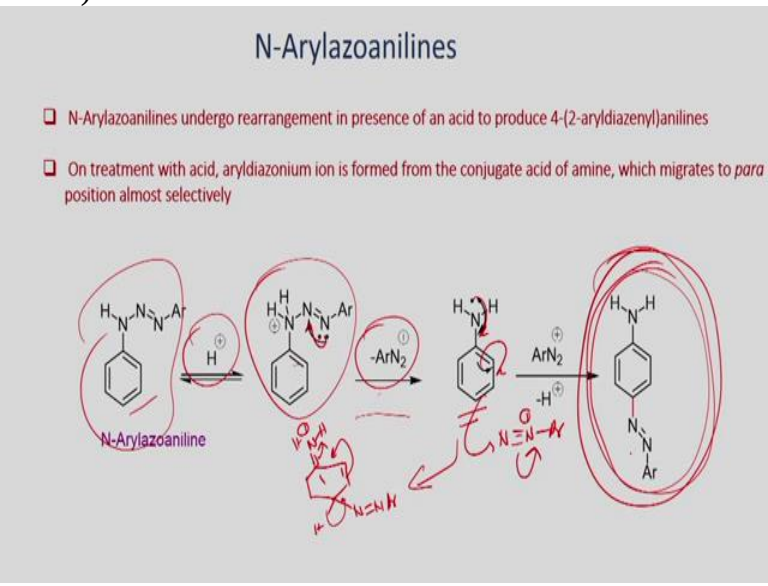

As above, N-arylazoaniline rearranges to 4-(2-aryldiazenyl)aniline. In this reaction, protonation leads to the formation of aryldiazonium ion, which migrates to the 4-positon via the electrophilic aromatic substitution.

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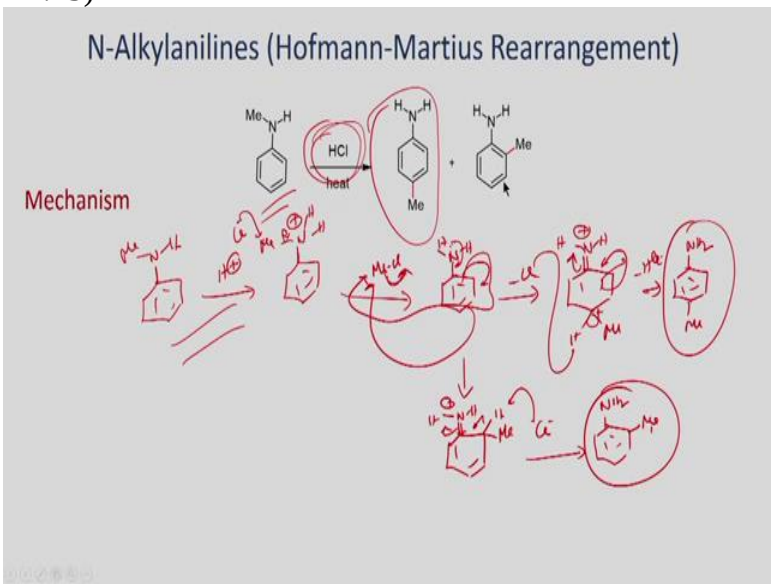

When you treat N-alkylaniline with acid, the alkyl group migrates to 2- as well as 4-position of the aryl ring. For an example, N-methylaniline with HCl produces a mixture of 2- and 4-methylanilines. Protonation followed by S_N2 reaction with the methyl group by the chloride ion gives aniline and chloromethane. Electrophilic aromatic alkylation with chloromethane produces a mixture of 2- and 4-methylaniline.

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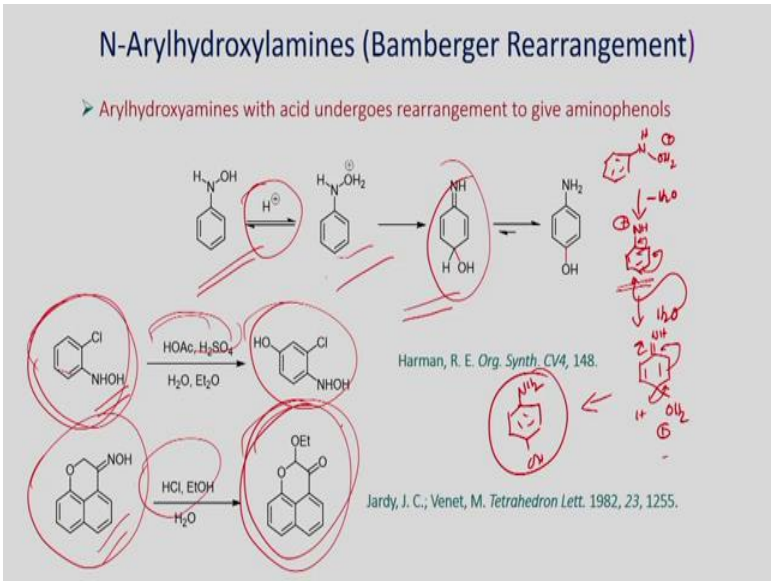

Now let us look at the rearrangement of phenylhydroxylamine with strong acid to produce 4-aminophenol. Protonation using strong aqueous acid gives the nitrenium ion, which reacts with water nucleophile to produce 4-aminophenol. The next example involves the rearrangement of 2-chloroarylhydroxylamine to produce 4-amino-2-chlorophenol. Similarly, oxime rearranges to produce ether substituent at 2-position when the reaction is performed using a mixture of HCl and EtOH in water.

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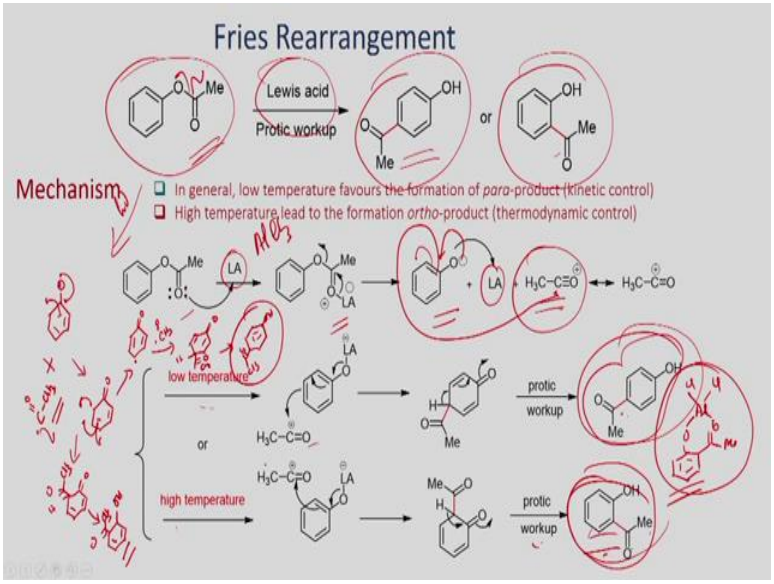

Here phenolic ester undergoes rearrangement using the Lewis acid to produce hydroxyl alkyl aryl ketone. For example, methyl benzoate with Lewis acid gives a mixture of 2- and 4-acetylphenol. In this reaction, Lewis acid makes chelation with the ester group and facilitates the formation of acetyl ion, which as the electrophile undergoes substitution with phenoxide at 2- and 4-positions to give a mixture of compounds. Low temperature favours the formation of 4-substitution, whereas higher temperature gives the 2-substitution as the major product due to complex formation with Lewis acid.

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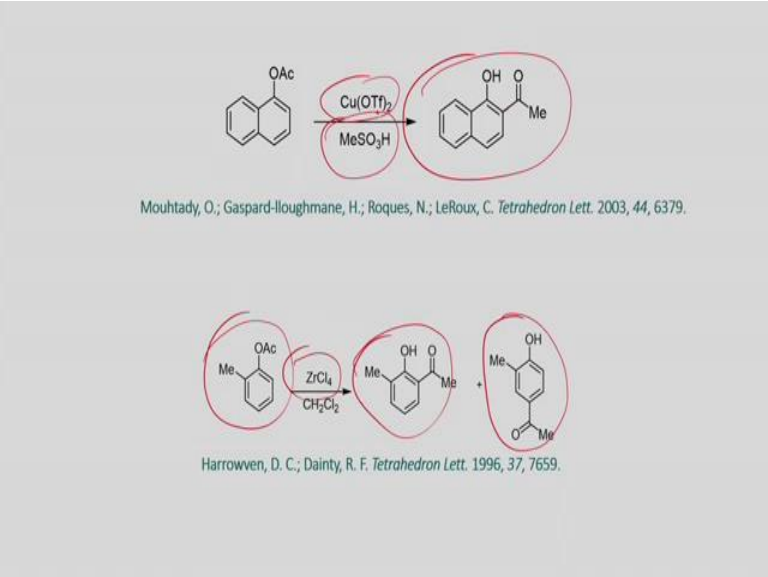

The first example involves the copper(II)-catalyzed rearrangement of 1-acetoxynaphthalene to 2-acetyl-1-naphthol. Similarly, 2-acetoxytoluene rearranges using zirconium(IV) chloride to give a mixture of 2- and 4-acetyl aryl derivatives.

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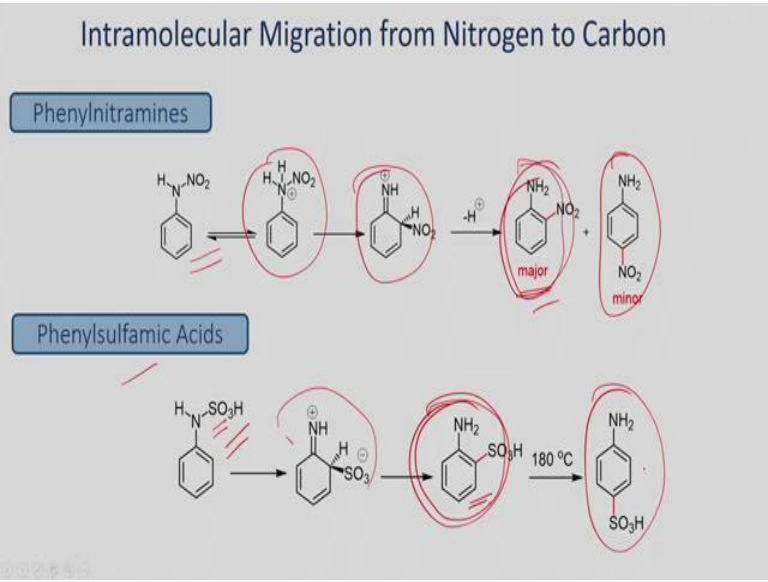

Here the acid catalyses the rearrangement of phenylnitramines to a mixture 2- and 4-nitroaniline in the presence of acid. Protonation leads to the formation of the nitronium ion, which reacts with aniline at 2- and 4-position to give the rearranged products. Similarly, arylsulfamic acid rearranges to aniline2-sulfonic acid, which on heating migrates to 4-position.

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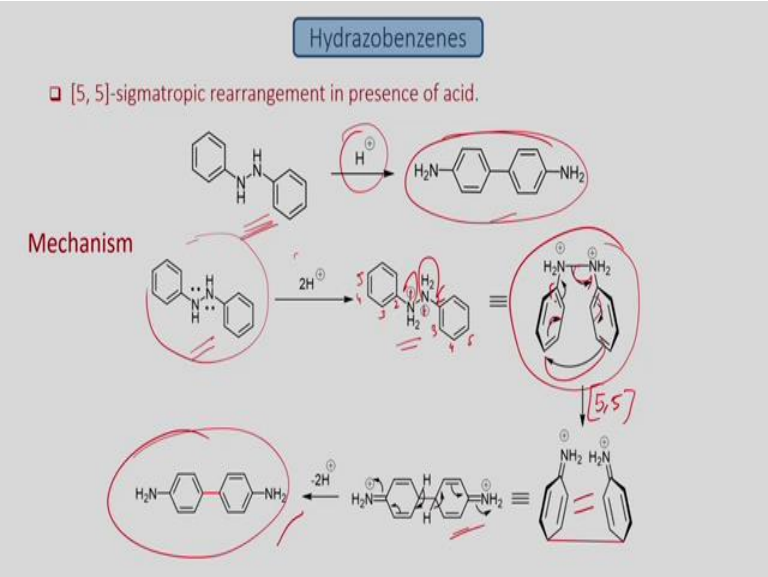

Now let us look at the rearrangement of hydrazobenzene, which with acid undergoes [5,5]-sigmatropic rearrangement to give the biphenyl derivative. Protonation followed by sigmatropic rearrangement gives the product.

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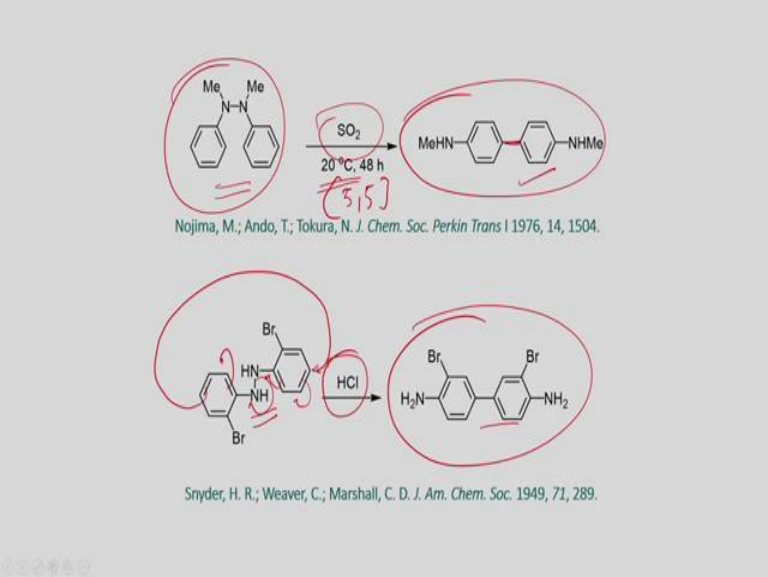

The first example leads [5,5]-sigmatropic rearrangement in sulfur dioxide to give the biphenyl derivative. Similarly, the next example using HCl rearranges to produce the biphenyl derivative via [5,5]-sigmatropic rearrangement.

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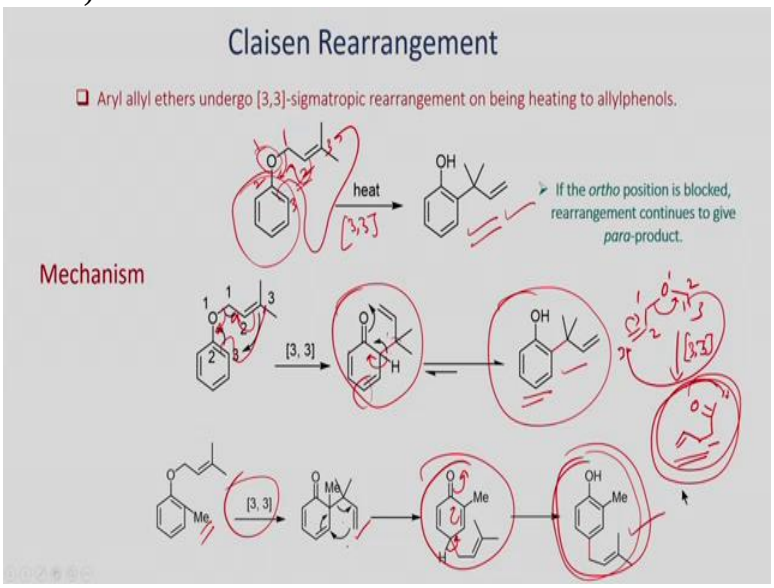

Allyl phenyl ether undergoes [3,3]-sigmatropic rearrangement to produce 2-allyl phenol. Which can further rearrange to 4-allyl phenol.

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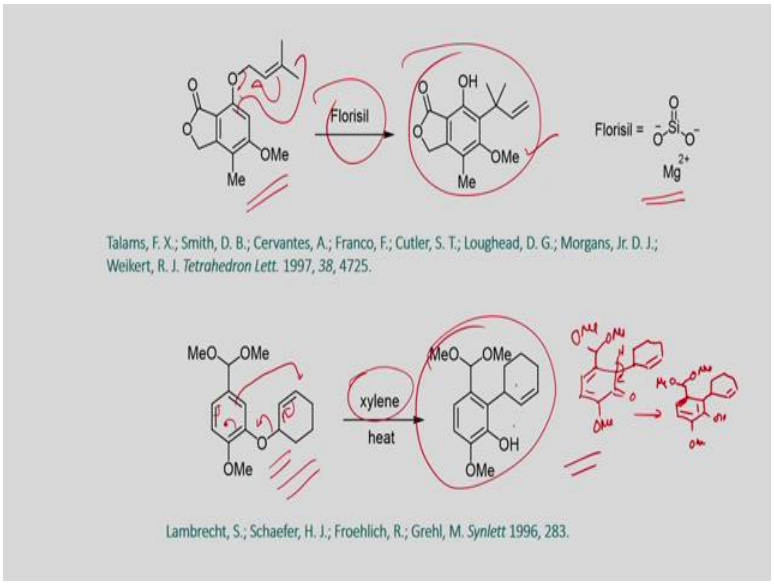

For example, the aryl allyl ether rearranges to 2-allyl aryl in the presence of florisil. Similarly, the aryl allyl ether on heating rearranges to produce 2-allyl phenol derivative.

So far have seen a series of rearrangements in the aromatic substrates. These reactions include the electrophilic and nucleophilic aromatic substitution, and sigmatropic rearrangements.

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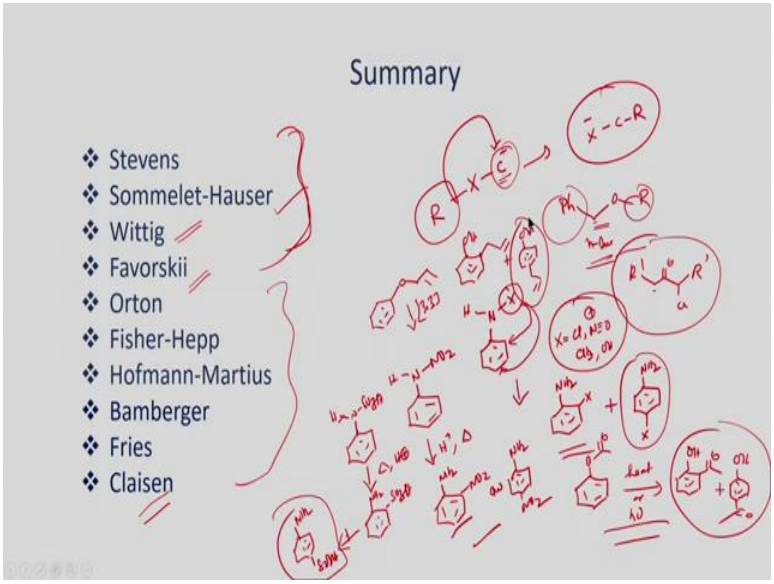

In summary, in the first part, we have seen the reactions that involve rearrangement to the electron rich carbon. In these reactions, strong base deprotonates the acidic hydrogen and the carbanion involves in the rearrangement.

In the second part, we have seen a series of reactions where the substituent from nitrogen migrates to the aromatic ring via electrophilic as well nucleophilic aromatic substitution. Then, we have seen the rearrangement of esters. These reactions are catalyzed by acids.

Finally, we have seen [5,5] and [3,3]-sigmatropic rearrangements.

If you look at these reactions, they find broad utilities in synthetic chemistry with this we conclude this lecture. Thank you very much.