Principles of Organic Synthesis

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Nucleophilic Aromatic Substitution

Lecture 16

Welcome you all to principles of organic synthesis. So far, we had 15 lectures, of them, the lectures 1-9 focused on the aliphatic C-C and C-N bond formation, and the lectures 12-15 covered the electrophilic aromatic substitution. Today we will start new module on the nucleophilic aromatic substitution.

If you remember, the electrophilic aromatic substitution, the electrophile reacts with aromatic system, whereas, in the nucleophilic aromatic substitution, nucleophile reacts with aromatic system.

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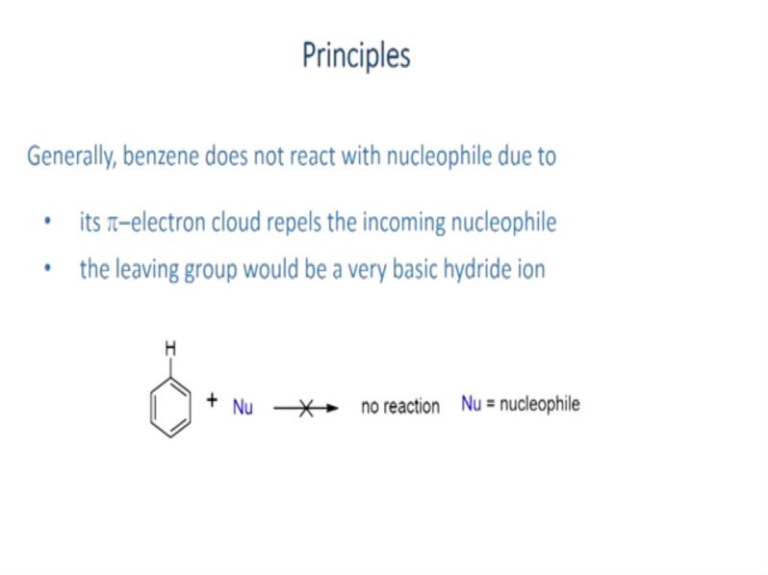

If you look at the electron density of aromatic system, which is electron rich and, thus, generally inert to undergo reaction with the nucleophilic species. As you can see, π-electron of the aromatic system repels the incoming nucleophile and the leaving group would be very basic hydride ion, which is high energy species. Thus, under normal conditions, the reaction does not take place, however, if you have activated aromatic system, the reaction can be facilitated.

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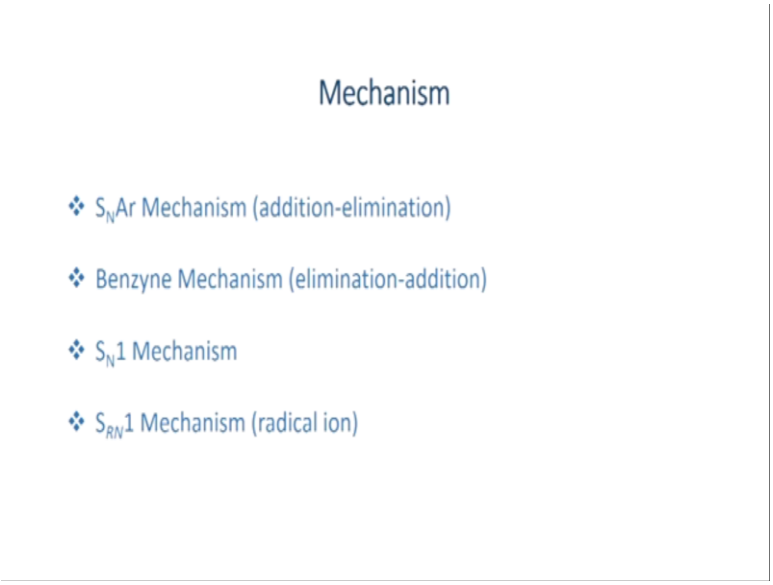

The reactions can be classified into four groups. The first one involves addition followed by elimination reaction. The second focuses on the elimination followed by addition. The next two covers the reaction that involves S_N1 pathway. In this class will cover the first two types.

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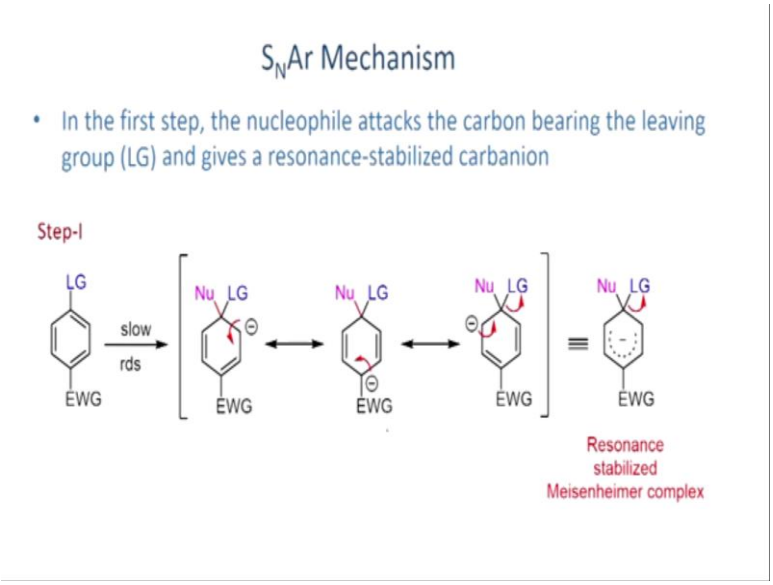

If you look at here, the aryl ring has an electron withdrawing as well as a leaving groups. The substrate reacts with the nucleophile at the carbon bonded to the leaving group to generate the carbanion, which is stabilized by the resonance. Of the three resonance structures, one of them has the carbanion, which is bonded with the EWG that is more stabilized.

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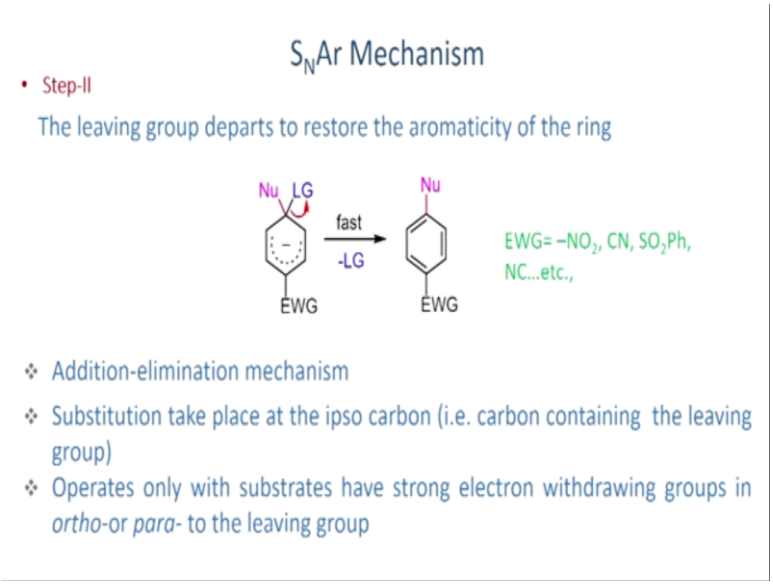

Now the leaving group departs to restore the aromaticity of the ring. So, the reaction involves addition (slow) followed by elimination (fast). The addition gives the carbanion intermediate, and the leaving group then departs to restore the aromaticity. In this way you can introduce the nucleophile at the *ipso* carbon. Thus, whenever you have the strong electron withdrawing substituent (such as nitro, cyano and sulfonyl), at *ortho* or *para* position of the leaving group, you can introduce nucleophile at the *ipso* carbon of the leaving group. If the EWG is at the *meta* position, that reaction is not facilitated, which can be understood drawing the resonance structures. If the reaction takes place at the *ortho* or *para* position, you will be able to have the more stable carbanion resonance structure bonding with the EWG.

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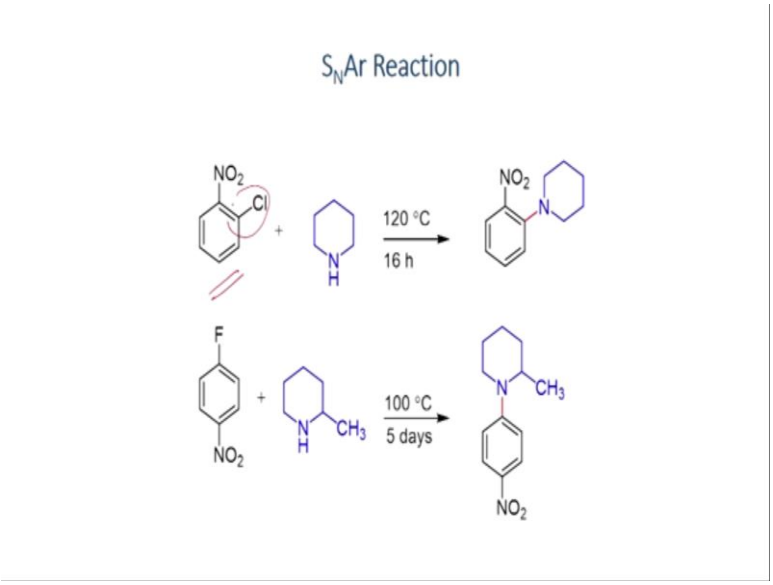

Here the first example involves the reaction of 2-nitrochlorobenzene with piperidine to produce 1-(2-nitrophenyl)piperidine. Nitro group activates the aromatic ring and piperidine reacts at the carbon bonded to chloro substituent to give the substituted product.

The next example covers the reaction of 4-nitrofluorobenzene with 2-methylpiperidine to produce *ipso* substitution, where fluoro substituent acts as the leaving group. If you look at the reaction, you have to carry out under high temperature for long reaction time to get the product in reasonable yield.

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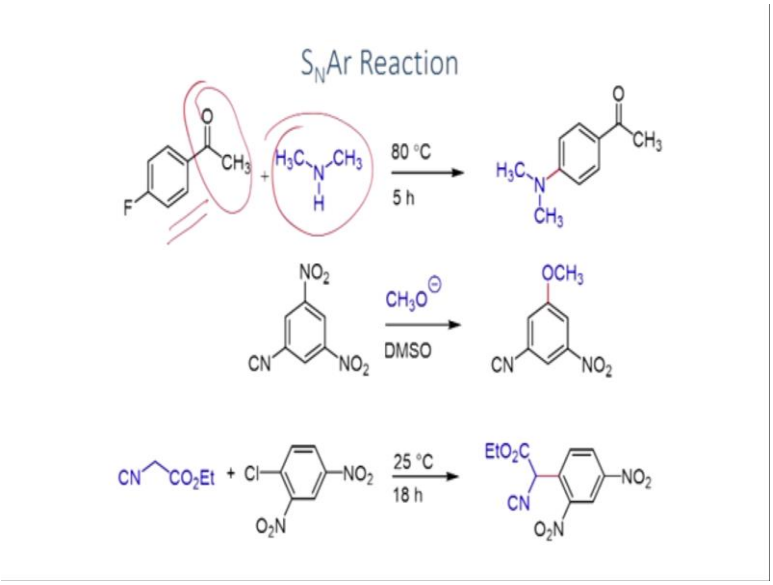

Here the first example involves the reaction of 4-fluoroacetophenone with dimethylamine to give 4-dimethylaminoacetopheone, while 3,5-dinitrobenzonitrile reacts with methoxide to produce 3-methoxy-5-nitrobenzonitrile. Further, 2,5-dinitrochlorobenzene reacts with ethyl 2-cyanoacetate. Deprotonation of the active methylene can generate the carbanion, which acts as the nucleophile to produce the substituted product.

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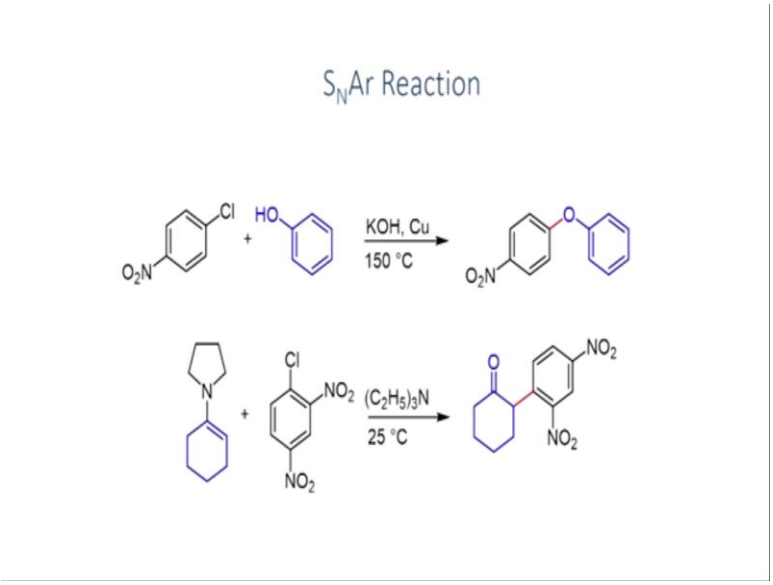

Here some more examples are shown. 4-Nitrochlorobenzene reacts with phenoxide to give diaryl ether, while the reaction of 2,4-dinitrochlorobenzene with enamine to produces the substituted compound.

So far we have discussed the nucleophilic aromatic substitutions, which are effective when you have strong the electron withdrawing group with respect to the leaving group at *ortho* or *para* position.

Now let us the reactions that involve elimination-addition pathway (benzyne intermediate).

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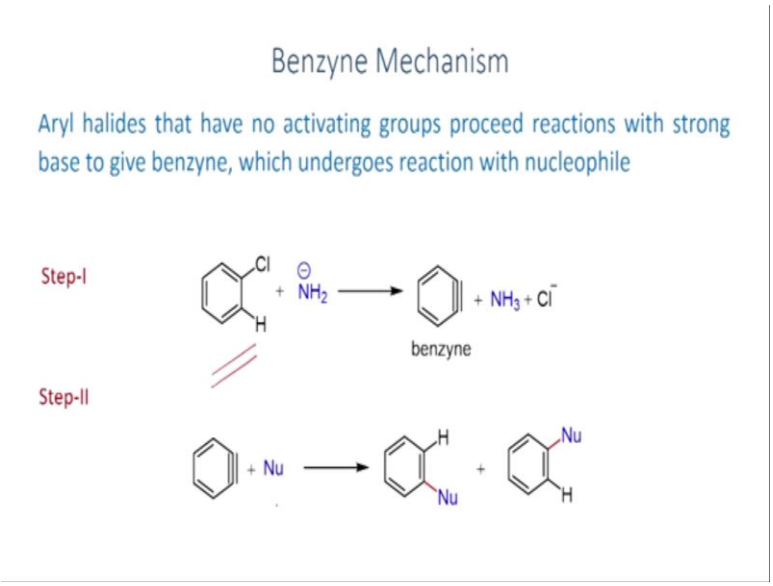

Aryl halide that does not have activating substituent reacts with strong base to generate benzyne, which readily reacts with nucleophile to give substituted products. Thus, the

reaction involves elimination-addition to produce the substituted compound. For example, chlorobenzene converts to benzyne via elimination in the presence of sodamide in liquid ammonia, which then reacts with nucleophiles via addition reaction.

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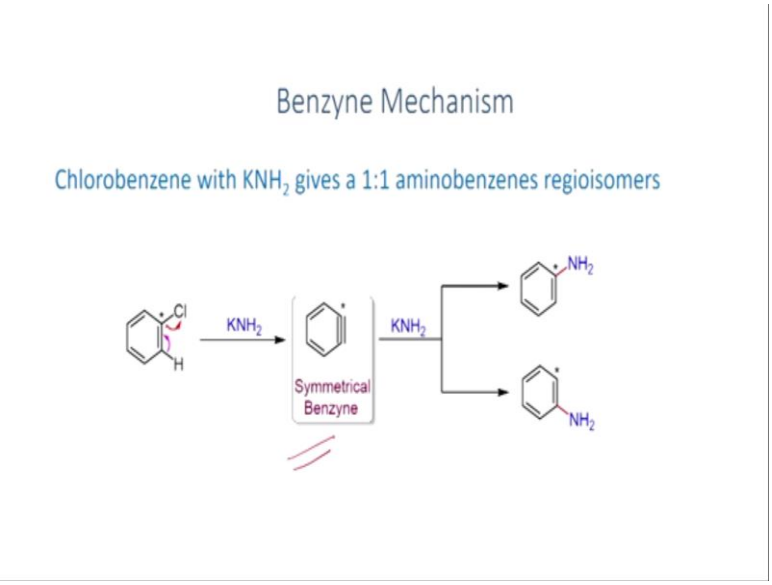

Here the mechanism is shown. The labelled chlorobenzene with potassium amide gives benzyne via elimination. Which further undergoes addition reaction with potassium amide to give a 1:1 mixture of regioisomers. In this reaction, potassium amide first acts as the strong base to form benzyne. In the second step, potassium amide acts as the nucleophile and undergo addition to give the carbanion, which is then protonated.

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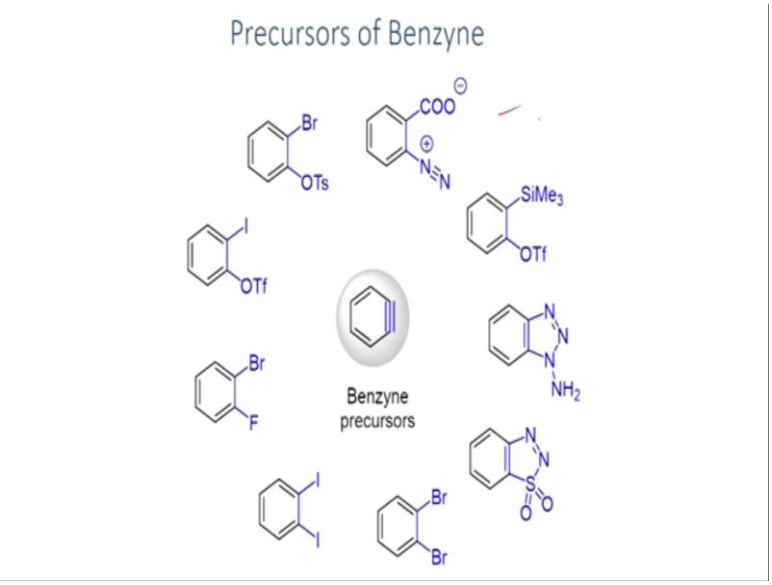

These are some of the compounds that we use as the precursor for the preparation of benzyne.

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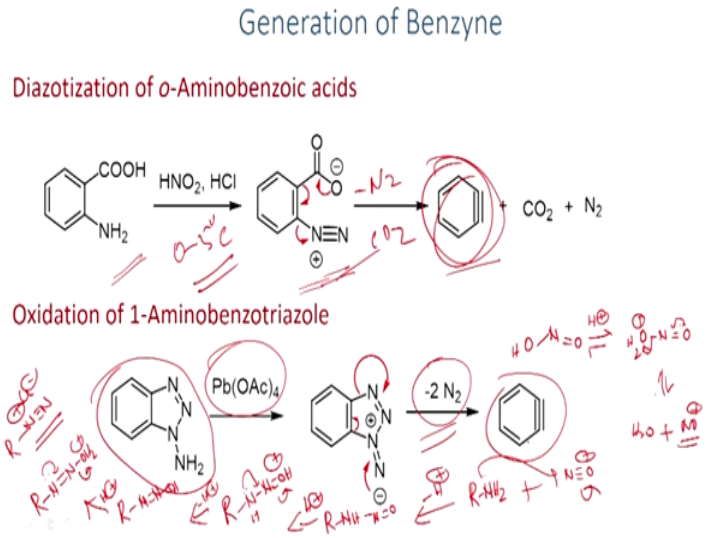

The first example involves the transformation of anthranilic acid to diazonium salt, which converts to benzyne. We have already studied the diazodization of aniline to diazonium salt. In this reaction, protonation of HNO_2 gives nitrosonium ion and water molecule. Addition of aniline to nitrosonium ion followed by removal of water molecule gives the diazonium salt.

The next example involves the oxidation of 1-aminobenzotrizole to benzyne in the presence of iodobenzene diacetate.

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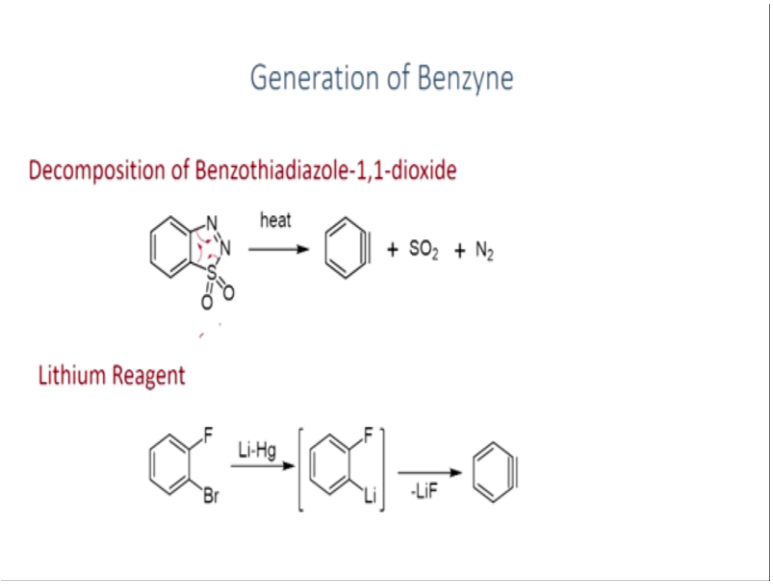

Here the first example shows the thermal decomposition of benzothiadiazole-1,1-dioxide to benzyne, while 2-fluorobromobenzene can be reacted with Li-Hg to produce benzyne via aryl lithium intermediate.

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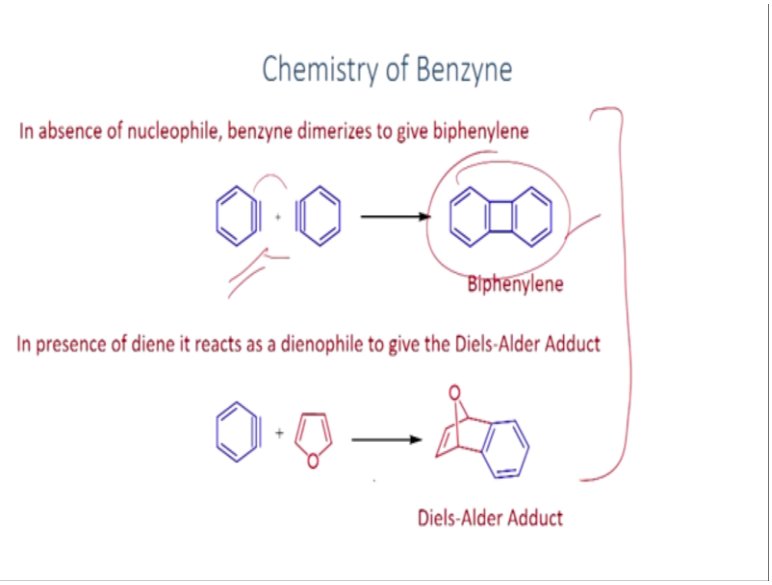

Now let us look at the reaction of benzyne. In the absence of nucleophile, benzyne undergoes dimerization to produce biphenylene. Benzyne is an excellent dienophile and reacts with diene via [4+2]-cycloaddition. For example, furan reacts with benzyne to give the bicyclic compound.

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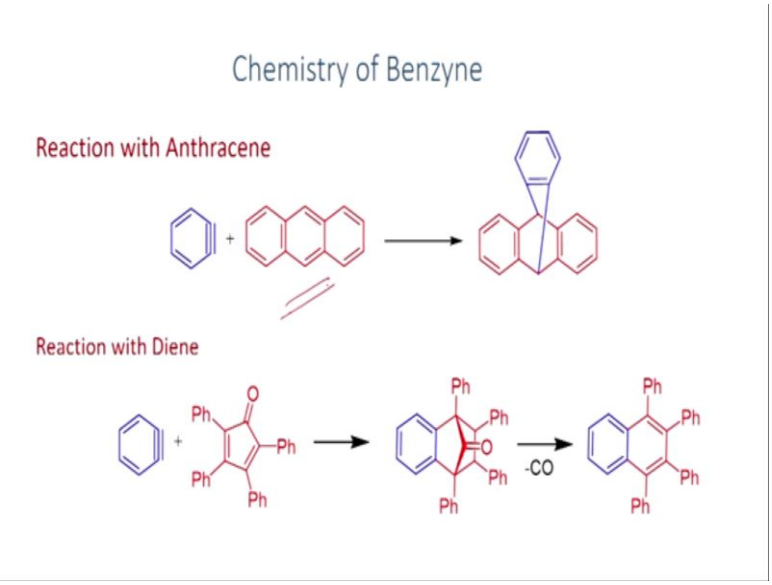

Benzyne with anthracene undergoes [4+2]-cycloaddition. Similarly, the [4+2]-cycloaddition of benzyne with tetraphenylcyclopentadienone affords the tricyclic compound, which loses CO to give 1,2,3,4-tetraphenlnaphthalene.

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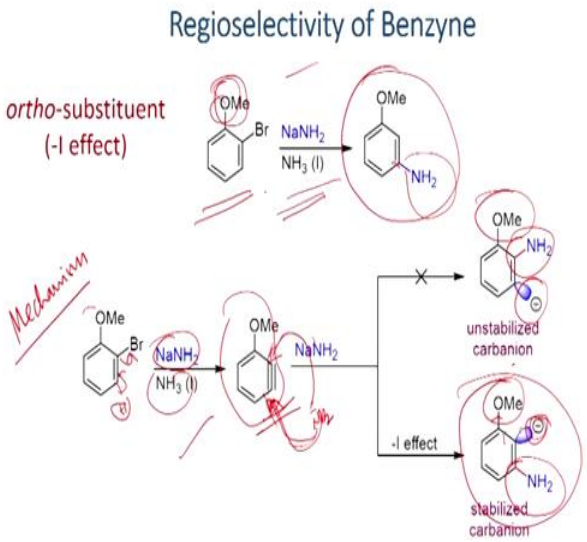

Now let us look at the regioselectivity. The reaction of 2-bromoanisole with sodamide in liquid ammonia produces 3-aminoanisole and not 2-aminoanisole. This is because if the nucleophile adds at *meta* position, you will generate the stabilized carbanion at *ortho* position due to –I effect of oxygen. On the other hand, if the nucleophile adds at *ortho* position, you will generate an unstabilized carbanion at *meta* position.

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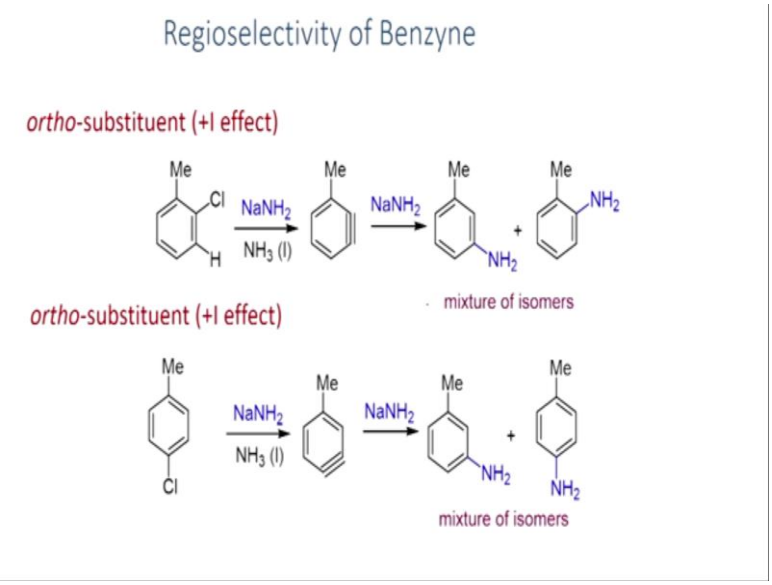

Here the reaction of 2-chlorotoluene with sodamide produces a mixture of 1,2- and 1,3-diaminobenzene. This is due to +I effect of methyl group and the addition takes place at *ortho* as well as *meta* position to give a mixture of regioisomers. Similar results are observed with 4-chlorotoluene producing a mixture 1,3- and 1,4-diaminobenznes as the products.

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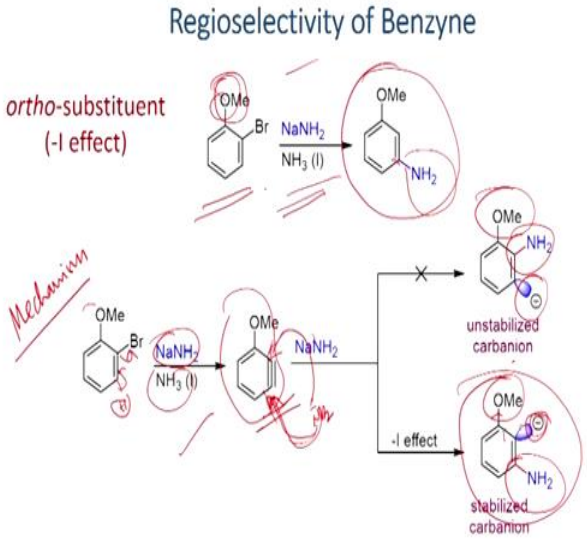

Just we have seen the regioselectivity in the reaction of 2-bromoaniaole with sodamide to produce 3-aminoanisole due to –I effect of oxygen.

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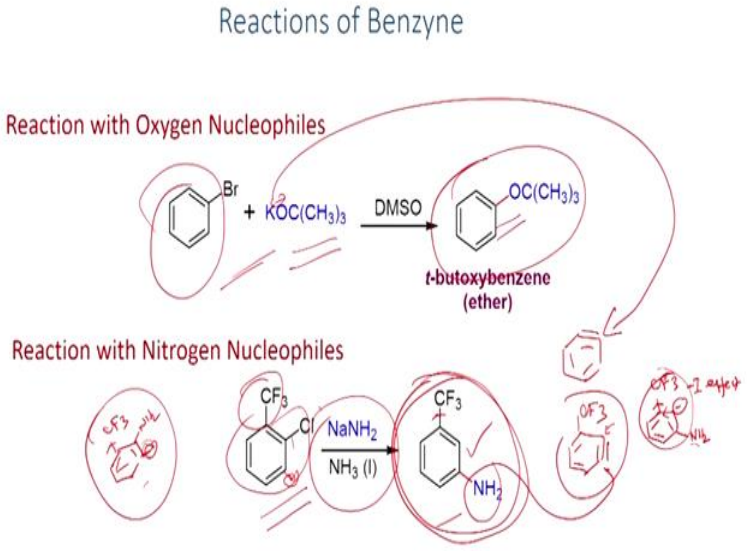

Here an example is shown where bromobenzene with the potassium t-butoxide produces t-butoxybenzene. The next example involves the reaction 2-trifluoromethylchlorobenzene with sodamide to produce 3-trifluoromethylaniline. This is due to –I effect of trifluoromethyl group. As we have seen, if the nucleophile adds at *meta* position, the carbanion at *ortho* position can be stabilized by the trifluoromethyl group.

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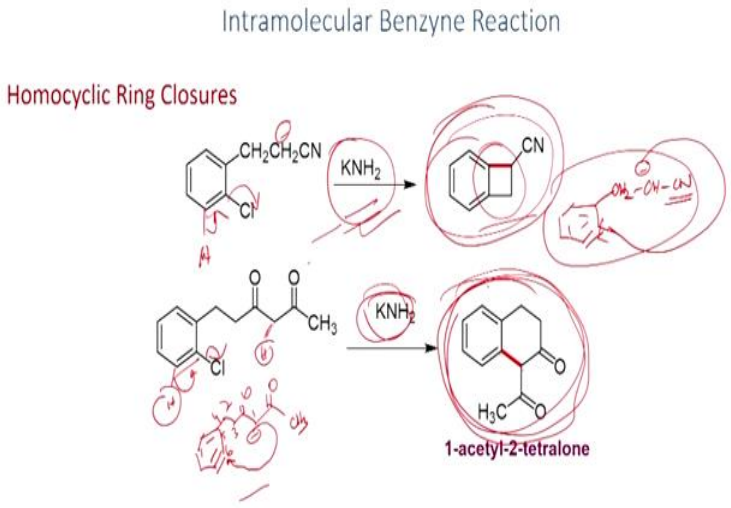

So far we have seen the intermolecular reactions. Now let us look at the intramolecular reactions. Reaction of chlorobenzene derivative with KNH_2 produces benzyne, which undergoes addition with the carbanion to produce the bicyclic nitrile derivative via C-C bond formation.

Similarly, the next example forms benzyne, which undergoes addition reaction with the enolate that can be generated from the activated methylene to give the bicyclic ketone via C-C bond formation.

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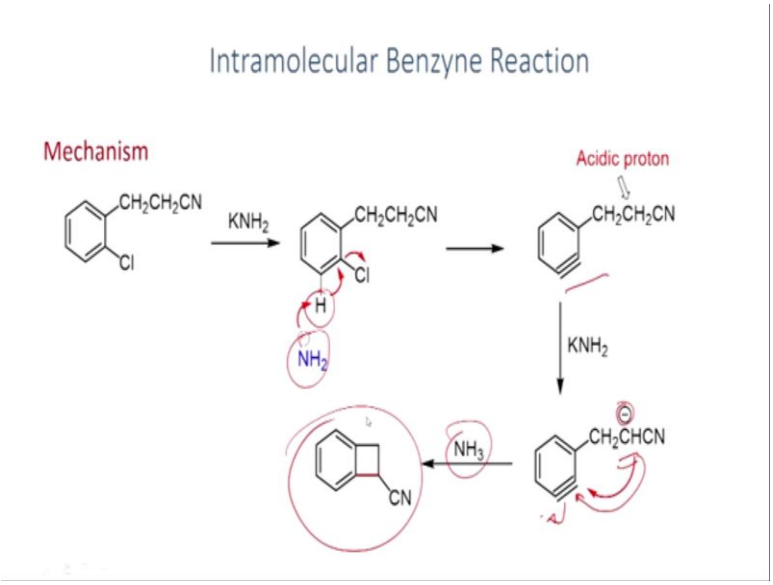

Here the mechanism is shown. Base mediated elimination of HCl produces benzyne. Further, the deprotonation of acidic hydrogen from alkyl side chain can produce the nitrile stabilized

carbanion, which undergoes intramolecular cyclization. Protonation of the carbanion can produce the bicyclic nitrile derivative.

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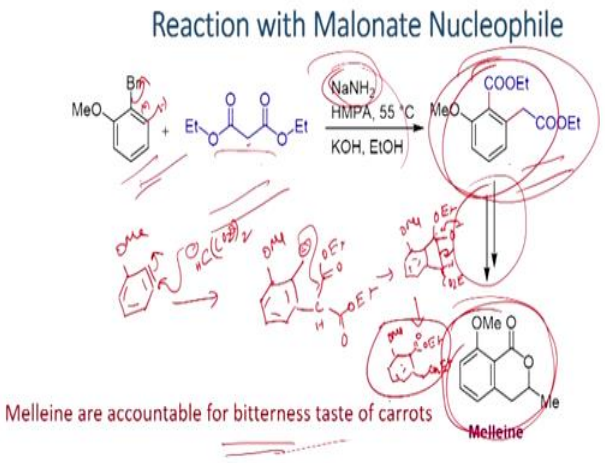

Here an another example is shown. In this case, reaction of 2-bromoanisole with sodamide produces benzyne. Deprotonation of active methylene of diethylmalonate gives the enolate. Addition to benzyne at *meta* position gives the *ortho* stabilized carbanion, which reacts with ester group intramolecularly to give the bicyclic lactone, melleine that is accountable for the bitterness of carrots.

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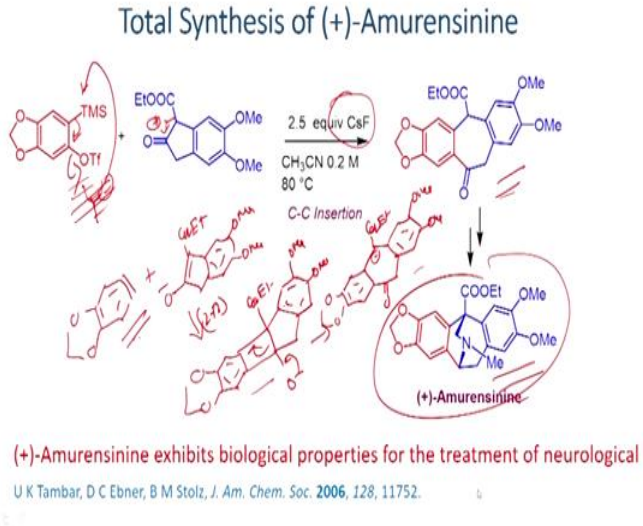

The next example involves the reaction of the silyl ether having triflate at *ortho* position with CsF to give benzyne, which undergoes [2+2]-cycloaddition with the enolate of β-ketoester

that opens up to give the seven membered cyclic system. Which has been further converted to (+)-amurensinine that is used to treat neurological problems.

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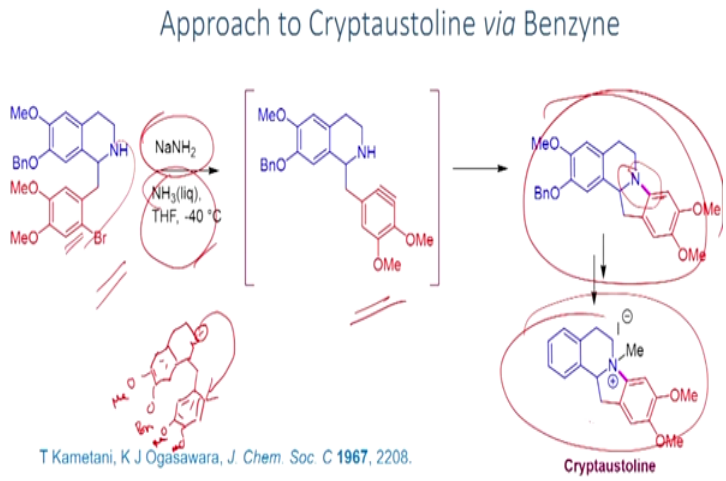

The next example involves the benzyne formation followed by the intramolecular cyclization to produce the cyclic compound, which has been converted to cryptaustoline. Thus, benzyne chemistry finds broad utilities in organic synthesis to make complex molecules.

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In summary, we have seen the principles of the nucleophilic aromatic substitution. The reaction takes place when the aromatic ring has the strong electron withdrawing group and

the leaving group is present at *ortho* or *para* position. Nucleophile adds at the carbon bonded to the leaving group. These reactions involve the carbanion intermediate and the substitution occurs at the *ipso* carbon. Thus, these reactions involve addition (of nucleophile) and elimination (of leaving group).

The second part focused on benzyne. We have seen the common precursor that we use for the preparation of benzynes and their reactions. We have seen several examples for the C-N, C-O and C-C bond formation. If the substrate has –I group, *meta* substitution is favoured. On the other hand, if +I group, a mixture regioisomers is formed. Thus, elimination reaction gives benzyne, which undergoes addition with nucleophile to give the carbanion that is protonated, with this, we conclude this lecture. Thank you very much.