Principles of Organic Synthesis
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Lecture 18: Nucleophilic Aromatic Substitution

Welcome you all to Principles of Organic Synthesis. Presently, we study the nucleophilic aromatic substitution. In this topic, so far, we had two lectures, where we studied the addition-elimination, elimination-addition, aryldiazonium fluoroborate to aryl fluoride, reaction aryl halides (via radical intermediate), cross-coupling reaction of aryl halides and C-H functionalization of arenes. In continuation, in this lecture, we cover nucleophilic substitution of aromatic systems bearing strong electron withdrawing group, amination and alkylation of pyridine and related heterocycle, reactions with rearrangement (von Richter, Smiles, Bamberger and Bucherer) and C-C cross-coupling reactions.

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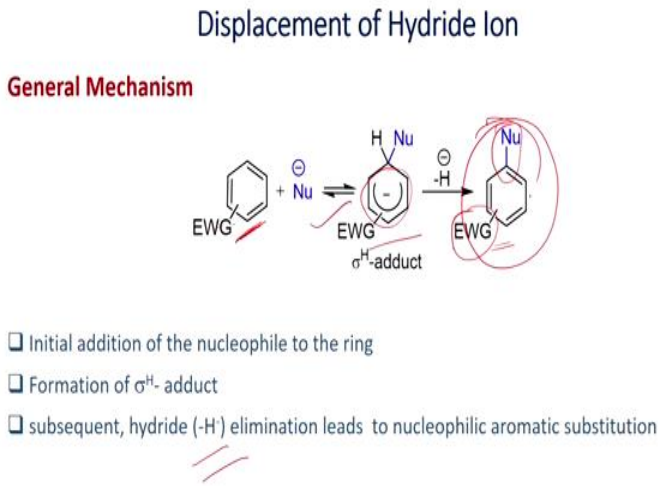

As we discussed in the earlier class, if the aryl ring has the electron withdrawing group, the nucleophile can react at *para* or *ortho* position to give the carbanion intermediate that can lose the hydride ion, which is the high energy species to produce the substitution product.

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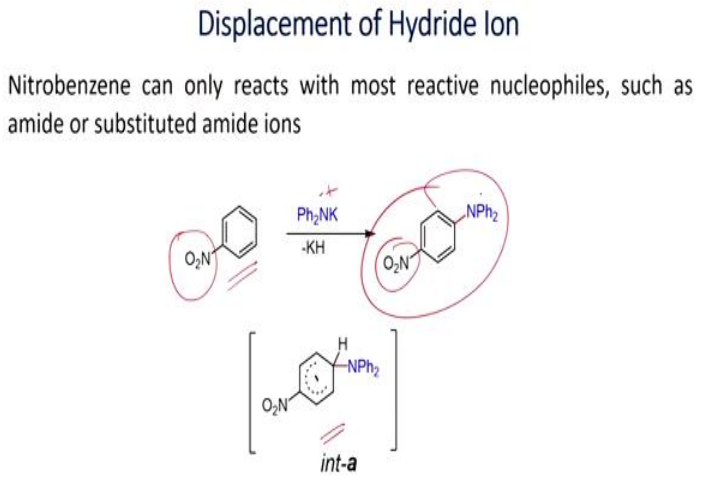

For example, let us look at nitrobenzene, which reacts with potassium diphenylamide to give 1-amino-4-nitrobenzene. The reaction takes place at the *para* position with respect to the nitro group. The addition gives a carbanion, which loses the hydride ion.

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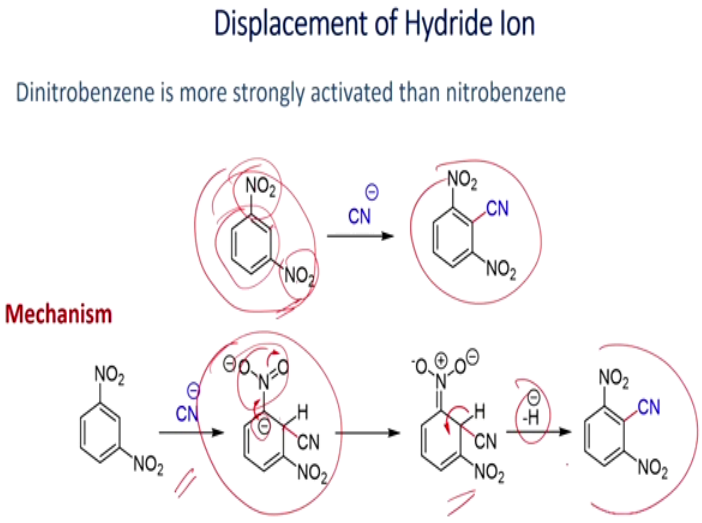

Here the reaction of 1,3-dinitrobenzene with nitrile ion is shown. 1,3-Dnitrobenzene is more reactive compared to nitrobenzene due to the presence of two nitro groups. Nitrile ion reacts at *ortho* position with respect to the nitro group to give 2,6-dinitrobenzonitrile.

As shown here, addition of nitrile ion can generate the carbanion, which is stabilized by the nitro group. Removal of the hydride ion produces the product.

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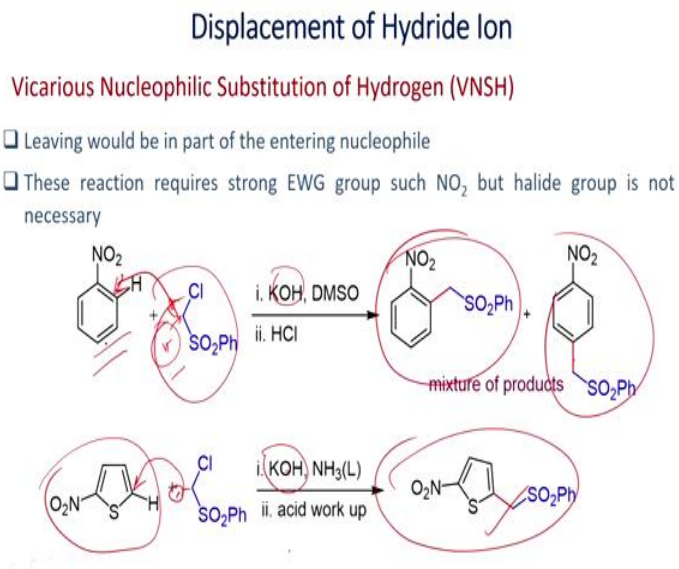

Here the reaction of carbon nucleophiles is shown. Nitrobenzene reacts with carbanion of chlormethyl phenyl sufone to produce a mixture of *ortho* and *para* aryl methyl phenyl sufones, whereas 2-nitrothiophene reacts with carbanion of chloromethyl phenyl sulfone to produce 2-nitro-5-((phenylsulfonyl)methyl)thiophene.

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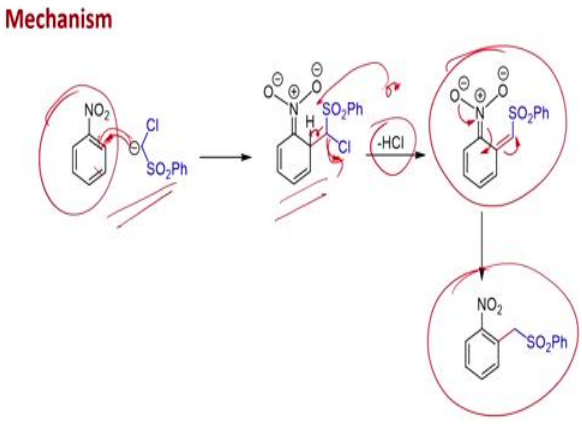

Deprotonation of chloromethyl phenyl sulfone produces the carbanion, which reacts with nitrobenzene to produce aryl carbanion that is stabilized by nitro group. Base mediated elimination of HCl followed by aromatization gives the carbanion that is protonated during the work up.

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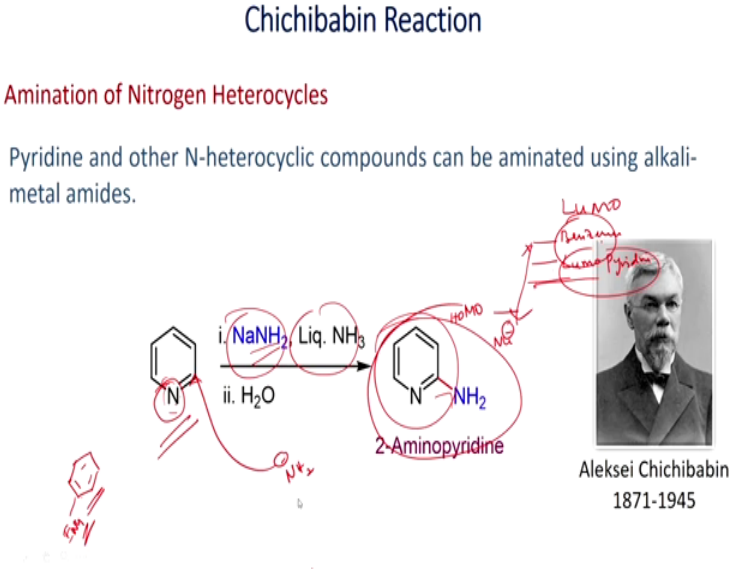

Now us look at the amination of pyridine using sodamide in liquid ammonia, which is known as the Chichibabin reaction. This method can be utilized for the amination of *N*-heterocyclic compounds.

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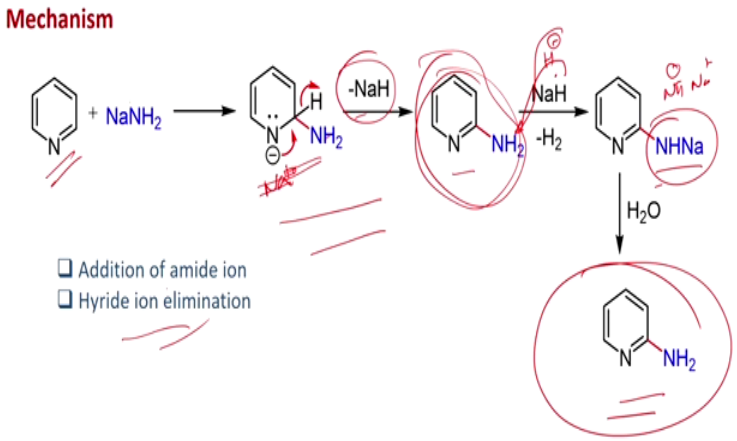

Addition of amide ion at 2-position of pyridine gives salt, which loses NaH to produce 2-aminopyridine.

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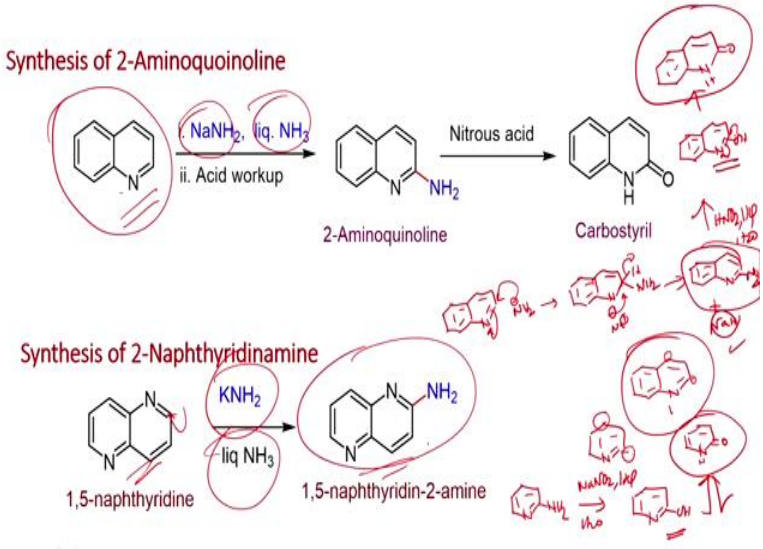

Here are some more examples. Quinoline reacts with sodamide to give 2-aminoquinoline, which can be readily reacted with nitrous acid to produce carbostyril. The amination can be understood as we have seen in 2-aminopyridine synthesis. Sodamide can add at 2-position of quinoline to give the salt, which can lose NaH to give 2-aminoquinoline. Reaction with nitrous acid will produce the diazonium salt, which can react with water to produce 2-hydroxyquinoline that exists as carborstyril.

Similarly, potassium amide reacts with 1,5-naphthyridine in liquid ammonia to give 1,5-naphthyridin-2-amine. The reaction can be understood as we have seen above.

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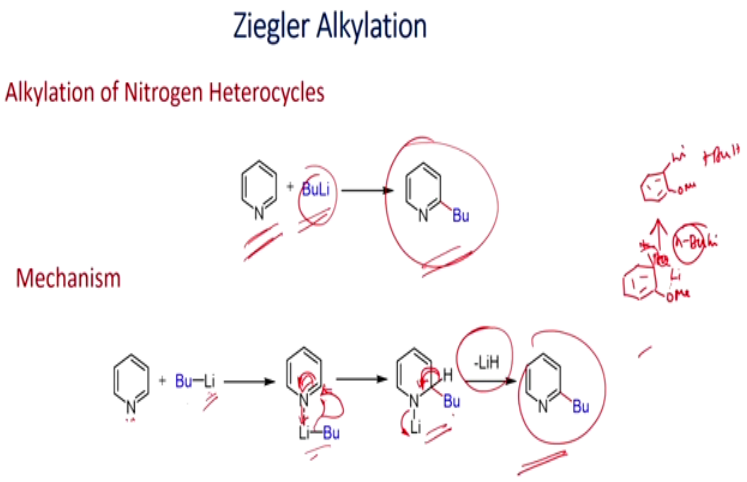

Now let us see the alkylation of pyridine, which is known as Ziegler alkylation. Here the reaction of pyridine with n-butlylithium give 2-butylpyridine. Already, we have seen that chelating group can lead to the *ortho* lithiation. For example, anisole, in which the lone pair of oxygen can make chelation with n-BuLi and can assist for the formation of *ortho* lithiation. Similarly, pyridine nitrogen can make chelation with n-BuLi, which can intramolecularly transfer butyl group to pyridine 2-position via addition that can lose LiH to give 2-butylpyridine.

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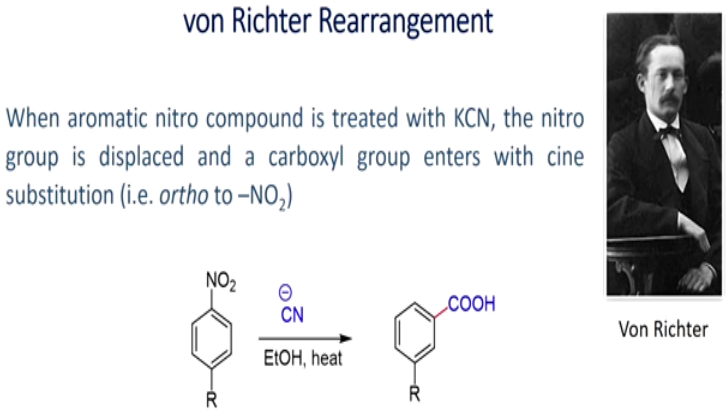

Now, let us look at the reaction of nitrobenzene with the cyanide ion in ethanol under heating, which is known as von Richter rearrangement. When aromatic nitro compound is treated with potassium cyanide, the nitro group is displaced and a carboxyl group enters with cine substitution (*ortho* to the nitro group). This reaction often gives a mixture of compounds with less yield, however, interesting with respect to the mechanism.

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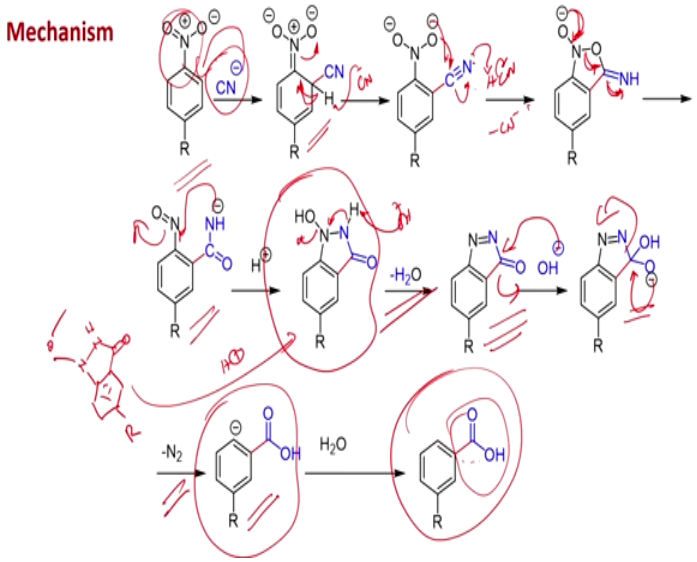

Cyanide ion adds at the *ortho* position and the resultant carbanion is stabilized by the nitro group. Deprotonation leads to the formation of 2-nitrobenzonitrile, which undergoes intramolecular cyclization to give the imine derivative. Cleavage of the N-O bond, followed by addition of the amide ion to nitroso group gives N-hydroxyl intermediate, which loeses water molecule to give the aza heterocycle. Addition of hydroxyl group to the carbonyl followed by loss of nitrogen molecule gives the carbanion that protonates to give the aryl carboxylic acid.

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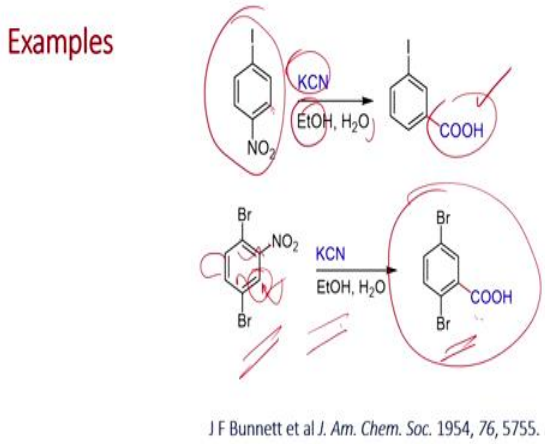

Let us see some examples. 4-Iodonitrobenzene with KCN produces 3-iodobenzoic acid. Similarly, 2,5-dibromonitrobezene can react with KCN to yield 2,5-dibromobenzoic acid.

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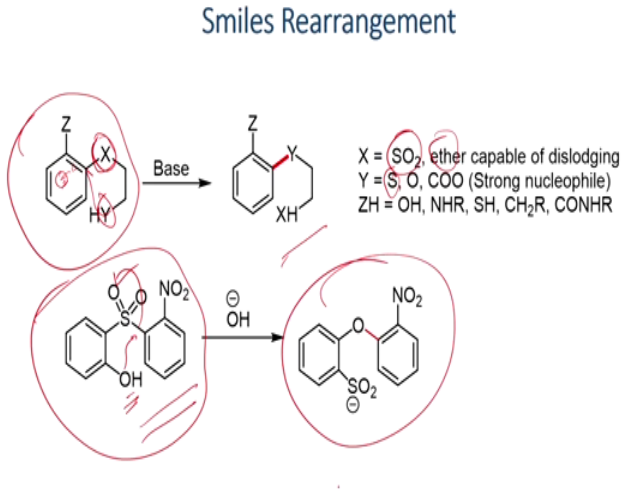

Now, let us look at the Smiles rearrangement. Aromatic compounds bearing substituents with X=SO_2 and O, Y= strong nucleophile and Z= O, NH, S and CHR can undergo rearrangement in the presence of base.

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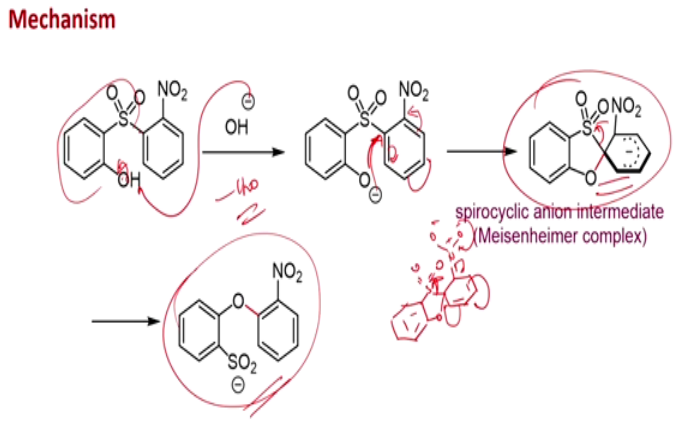

Deprotonation gives phenoxide that is strong nucleophile, and undergoes intramolecular addition to the carbon of the aromatic ring bearing SO_2 to give the spirocyclic anion, which dislodges SO_2 to give the diaryl ether as the product.

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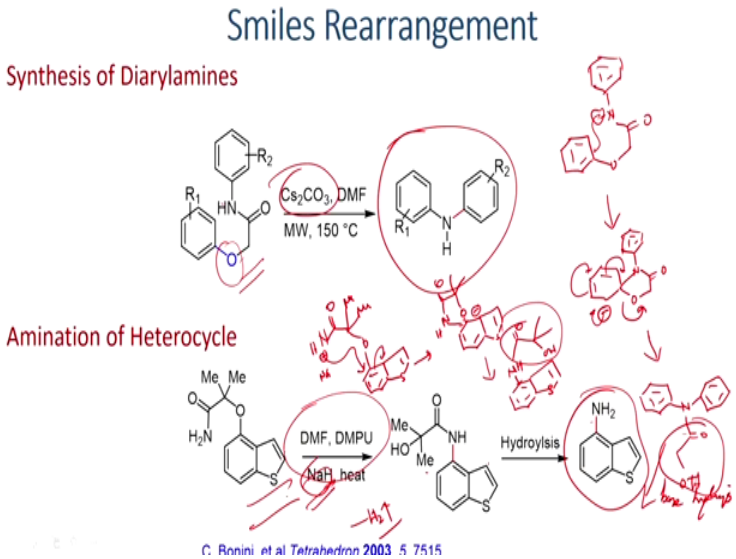

Here the first example involves the deprotonation of amide to produce the anion, which undergoes an intramolecular addition to the carbon bonded to ether to give the spirocyclic anion, which opens up to furnish diarylamine. The reaction is effective under microwave

irradiation. Similarly, the next example undergoes deprotonation of the amide, which undergoes intramolecular addition to the carbon bonded to ether oxygen to yield the spirocyclic anion, which dislodges the oxygen to yield amide that is hydrolyzed to give the amine derivative.

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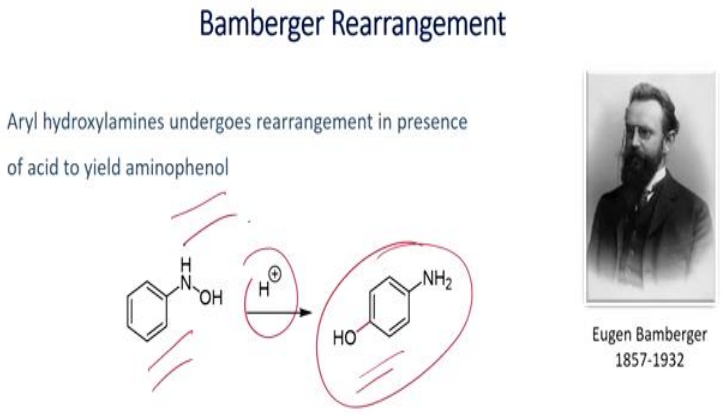

Here the acid-catalyzed rearrangement of arylhydroxylamine is shown, which is known as Bamberger rearrangement. For example, phenylhyroxylamine rearranges to afford 4-aminophenol in the presence of acid.

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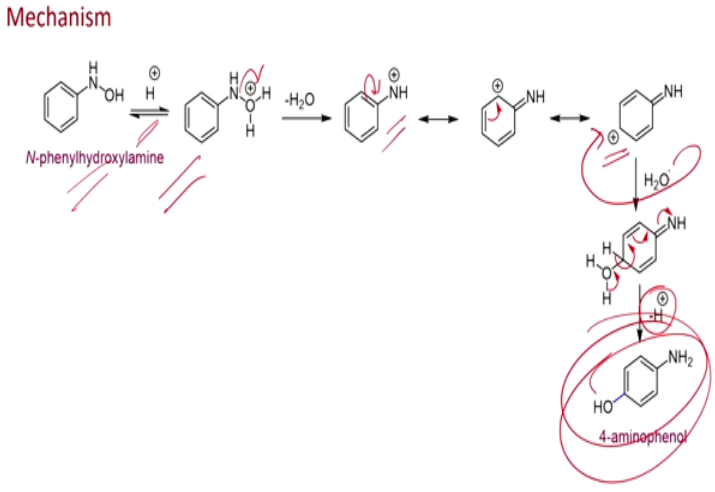

Protonation of the hydroxyl group followed by removal of water molecule gives the nitrenium ion that reacts with water molecule to produce 4-aminophenol.

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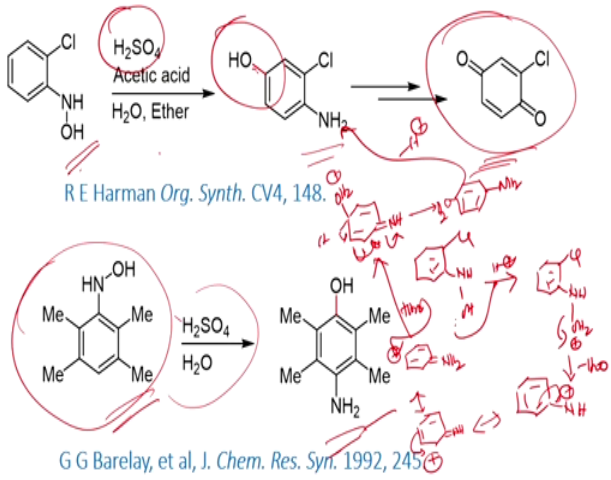

Now, let us look at some examples. 2-Chlorophenylhydroxylamine rearranges to 3-chloro-4-aminophenol in the presence of H_2SO_4 in AcOH. Which can be readily oxidized to 2-chlorobenzoquinone. Protonation of the hydroxyl group followed by removal of water molecule gives nitrenium ion, which reacts with water molecule. Similarly, 2,3,5,6-tetramethylphenylhydroxylamine rearranges in the presence of H_2SO_4 in water.

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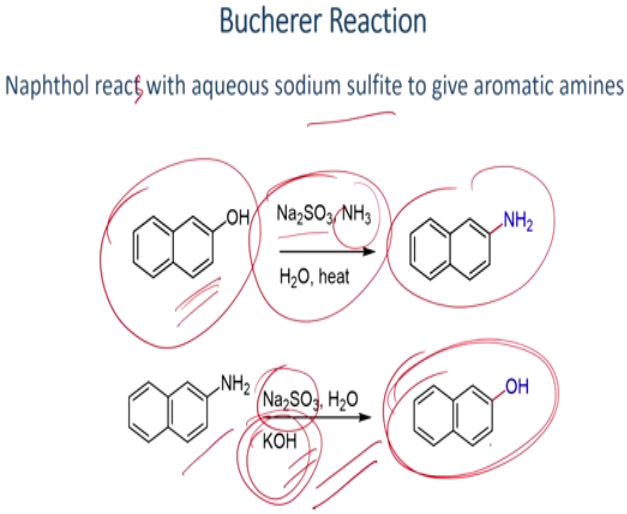

Here the Bucherer reaction is shown. In which, 2-naphthol converts to 2-naphthylamine using ammonia in the presence of aqueous sodium sulfite. Similarly, 2-naphthylamine can be converted to 2-naphthol using aqueous sodium sulfite and KOH.

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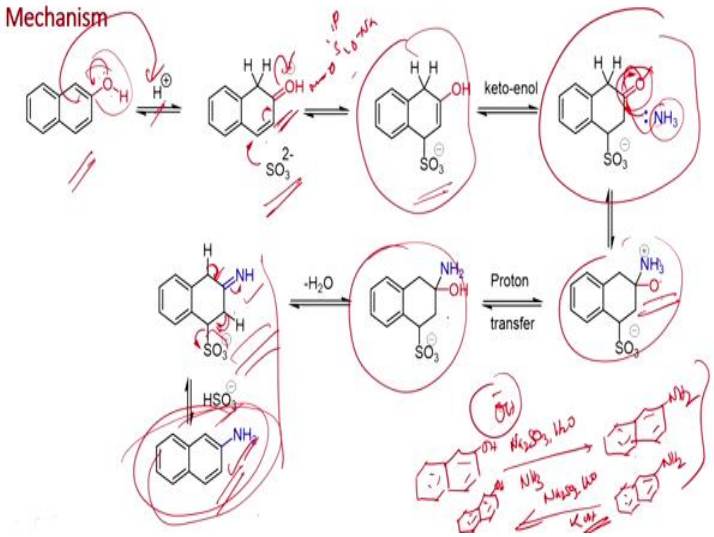

Addition of proton to the high electron density carbon gives the dearomatization ring, which leads to addition at C4 with bisulfite anion that tautomerizes to ketone. Addition with ammonia and proton transfer gives amino alcohol, which loses water to give imine, which eliminates sodium bisulfite to give 2-naphthylamine.

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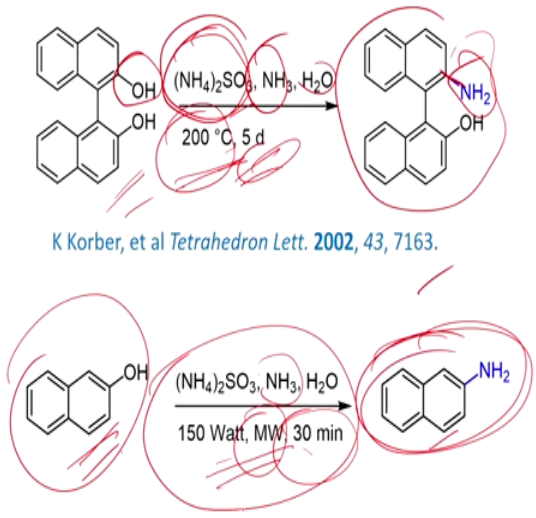

Let us look at some examples. One of the "OH" groups of BINOL converts to "NH_2" using aqueous ammonium sulfite and ammonia at elevated temperature. Under similar conditions, 2-naphthol is converted to 2-naphthylamine.

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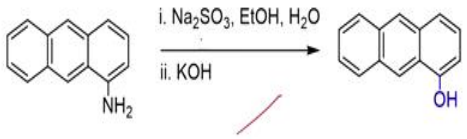
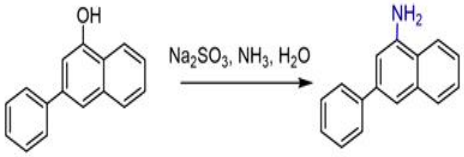


R S Coleman, *Tetrahedron Lett.* **2003**, *44*, 1215.



S Vyskocil, *et al, J. Org. Chem.* **2001**, *66*, 1359.

Here the first example shows the reaction of 2-aminoanthracene to 2-hydroxyanthracene using sodium sulfite and KOH. The next example presents the conversion 3-phenyl-1-naphthol to 2-phenyl-1-naphthylamine using sodium sulfite and ammonia.

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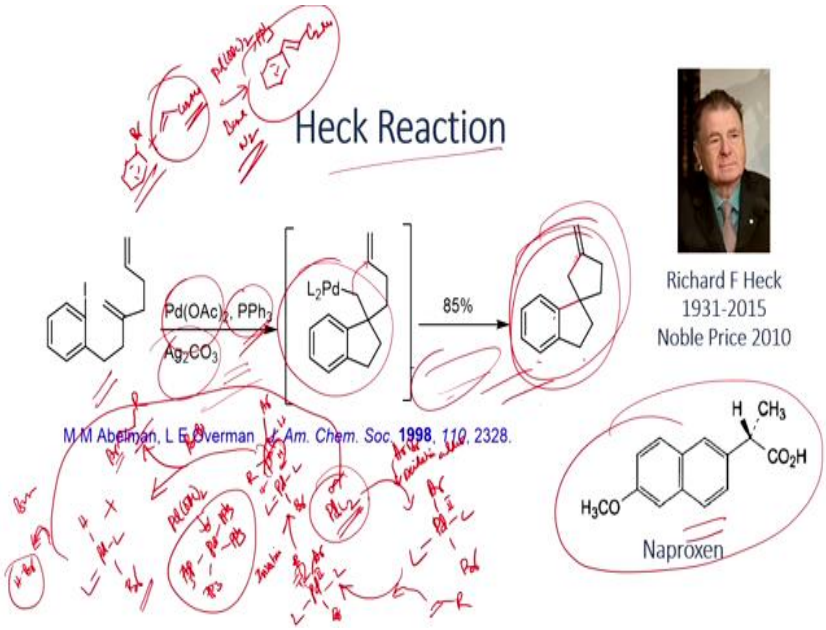

Now, let us look at the C-C cross-coupling reactions. If you remember the Negishi coupling, where we studied the C-C coupling of the aryl halide with organozinc using Pd and Ni-based catalytic system. At the same time, Heck showed the coupling of alkenes with aryl halides using Pd-catalysis. Here an example is given for the intramolecular double Heck reaction. Aryl iodide undergoes oxidative addition with Pd(0) to give Pd(II), which makes π-complex with the double bond and inserts into the carbon-Pd(II) bond via *syn* addition. β-Hydride elimination gives Pd(II)–π-complex, which gives the C-C cross coupled product and HBr to complete the catalytic cycle. Thus, base is needed to pursue the reaction and Pd(II) is used as the catalyst, which is reduced *in situ* to catalyze the reaction.

Heck reaction finds wide applications in pharmaceuticals. For an examples it is used in the synthesis of the anti-inflammatory drug naproxen.

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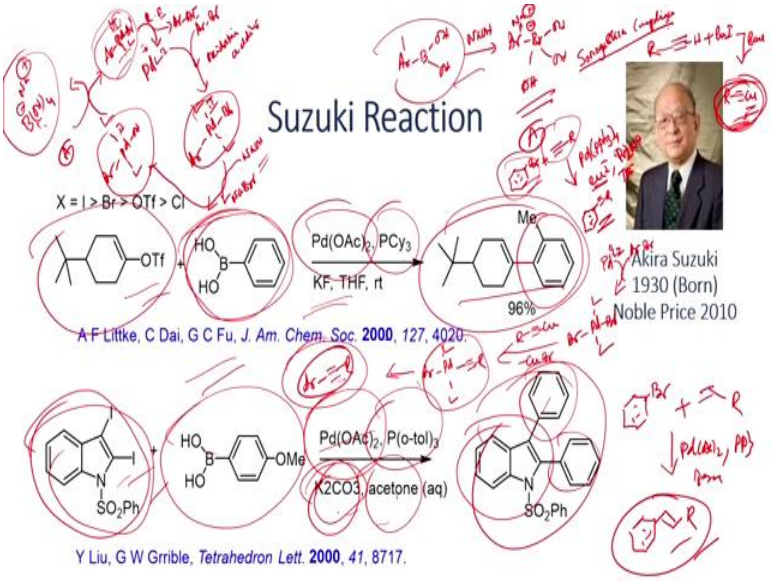

Here the Suzuki C-C cross-coupling of aryl boronic acid with vinyl triflate is shown. The reaction is carried using Pd-catalysis. The next example focuses on the C-C coupling of N-sulfonyl-2,3-diiodoindole with 4-methoxyphenylboronic acid. Suzuki coupling also finds broad utilities as Heck and Negishi couplings. All three together got the 2010 Noble price for chemistry.

The aryl halide or vinyl triflate undergoes oxidative addition with Pd(0) to give Pd(II) species, which reacts with base. Similarly, base activates the boronic acid, which reacts with the Pd(II) intermediate through transmetalation. Reductive elimination gives the C-C cross-coulpled product with Pd(0) to complete the catalytic cycle.

During this period Sonogashira also showed C-C coupling of terminal alkynes with aryl halides using Pd-catalysis. Here base deprotonates alkyne, which undergoes reaction with copper(I) iodide to produce copper(I)-alkyne species that reacts with Pd(II) that is derived from Pd(0) and aryl halide by oxidative addition. Reductive elimination gives the C-C coupled product with Pd(0) to complete the catalytic cycle.

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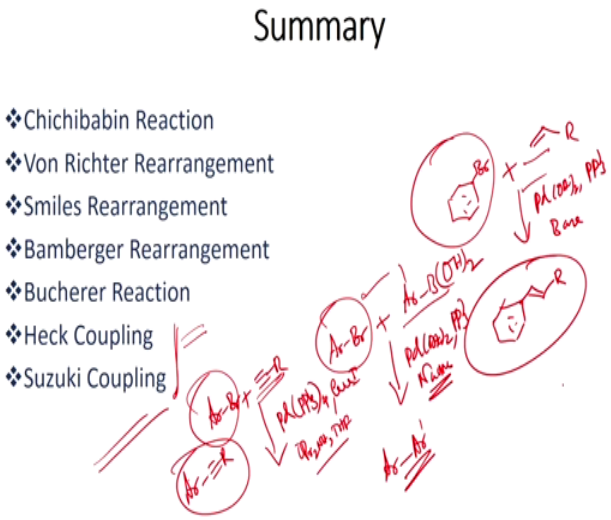

In summary, we have seen the reaction of aromatic system bearing strong electron withdrawing group with nucleophile. The nucleophile reacts at *ortho* or *para* position with respect to the electron withdrawing substituent. In these reactions the high energy hydride ion departs.

Then, we have seen the amination of pyridine and related compounds, which is known as Chichibabin reaction.

We have seen the alkylation of pyridine using alkyl lithium, which is known as Ziegler alkylation.

Then, we have seen the dislodge of nitro group and introduction of carboxyl group at cine carbon when aromatic compound reacts with KCN, which is known von Richter rearrangement.

We have discussed the Smile rearrangement, if the aryl system has the good leaving group like sulfur dioxide, and strong nucleophile, it rearranges in the presence base.

Then, we have seen acid-catalyzed rearrangement of aryl hyroxylamine to 4-aminophenols, which is known as the Bamberger rearrangement. We have then seen the Bucherer reaction where 2-naphthol converts to 2-aminonaphthalene using aqueous bisulfite and ammonia. This reaction is reversible, thus, 2-naphthylamine can convert to 2-naphthol.

Finally, we discussed the C-C cross-coupling of aryl halide with alkenes (Heck), boronic acid (Suzuki) and alkyne (Sonogashira) using Pd-catalysis. These reactions find broad utilities in synthetic chemistry, with this we conclude the lecture, thank you.