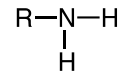
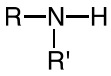
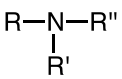
Chapter 22
Amines

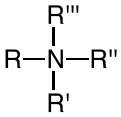
Amines are very important in biological chemistry. Most of the bases in biological acid-base reactions are amines. They are also very important nucleophiles in biochemical reactions.

Nomenclature
Amines are classified according to the degree of substitution at nitrogen.


primary (1°) amine

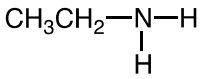

secondary (2°) amine


tertiary (3°) amine

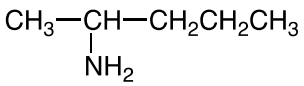

quaternary (4°) amine

There are two ways to name amines: (1) As alkyl amines (2) as alkanamines.

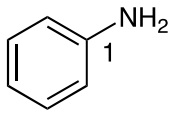
To name as alkyl amines, attach "-amine" to the name of the group that bears the nitrogen.

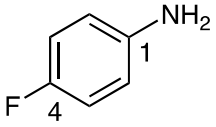

ethylamiane
(or ethanamine)

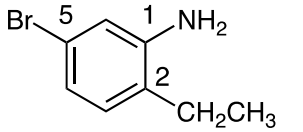

cyclohexylamine
(or cyclohexanamine)


1-methylbutylamine
(or 2-pentanamine)

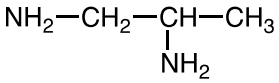
Aniline derivatives are numbered so that the amine bearing carbon gets number 1. The other substitutents are listed in alphabetical order and the direction of numbering is such that the lowest number occurs at the first point of difference.

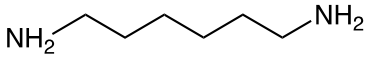

aniline


4-fluoroaniline

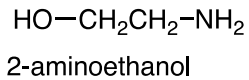

5-bromo-2-ethylaniline

Diamine compounds: use "diamine" with the alkane, retaining the "-e' of the alkane.

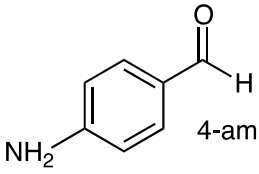

1,2-propanediamine


1,6-hexanediamine

Hydroxyl and carbonyl groups take precedence over amines.

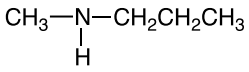


2-aminoethanol

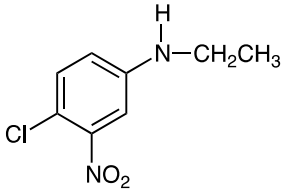


4-aminobenzaldehyde

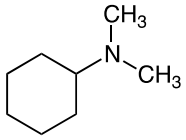
Secondary and tertiary amines are named as N-substituted derivatives of primary amine. The parent primary amine is the one with the longest chain. The prefix N- is added to identify substituents on the amine nitrogen as needed. The substituents are listed in alphabetical order. If two substituents are the same, use N,N-dialkyl.



N-methylethylamine

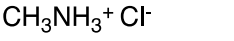


4-chloro-N-ethyl-3-nitroaniline

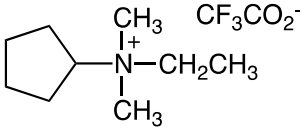


N,N-dimethylcyclohexylamine

Nitrogen with four substituents is named as an "ammonium ion" with the counter-ion named last.



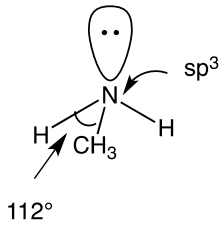
methylammonium chloride



N-ethyl-N-methylcyclopentylammonium trifluoroacetate

Structure and Bonding

Alkylamines are pyramidal, like ammonia.



112°

H—N—H angle = 106 slightly smaller than 109.5 because the lone pair is large

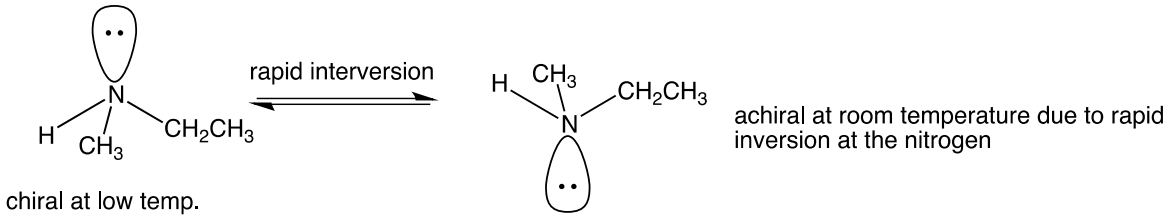
C—N—H angle = 112

C—N bond length = 1.47 A°

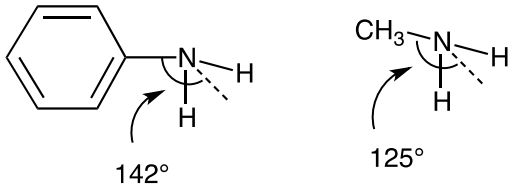
C—C bond length = 1.53

C—O bond length = 1.43

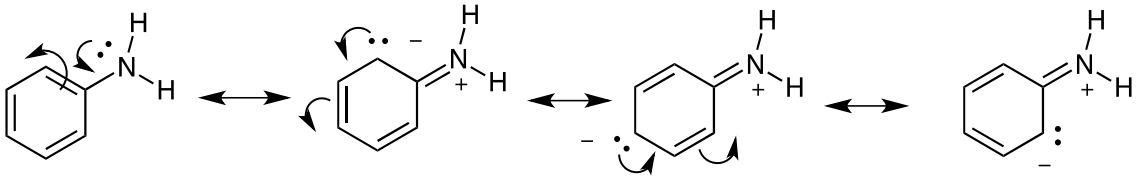
Nitrogen with four different substituents – counting the lone pair as a substituent – would be chiral at very low temperature but at room temperature there is rapid inversion at the nitrogen center and so the amine is achiral.



Arylamines have much flattened bond angles. This is due to donation of the amine lone pair onto the π–system of the aromatic ring.



The normal bond angle for an sp^3 nitrogen is about 125° whereas for an sp^2 nitrogen it would be 180°. Therefore the C-N bond is somewhere between an sp^2 and sp^3 bond. A lone pair orbital that is more p in character (i.e. sp^2) is better at overlapping with the π–orbitals of the benzene ring but an sp^3 orbital, with more s character is better for the electrons to interact with the nitrogen nucleus. Therefore the actual orbital for the lone pair is a compromise of these two opposing trends.

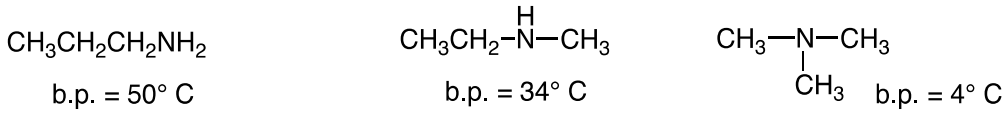


Physical Properties

Amines are more polar than alkanes but less polar than alcohols. Because nitrogen is less electronegative than oxygen, the N-H bond is less polarized than the O-H bond and hydrogen-bonding is weaker.

$CH_3CH_2CH_3$	$CH_3CH_2NH_2$	CH_3CH_2OH
μ = 0; b.p. = -42° C	μ = 1.2; b.p. = 17° C	μ = 1.7; b.p. = 78° C

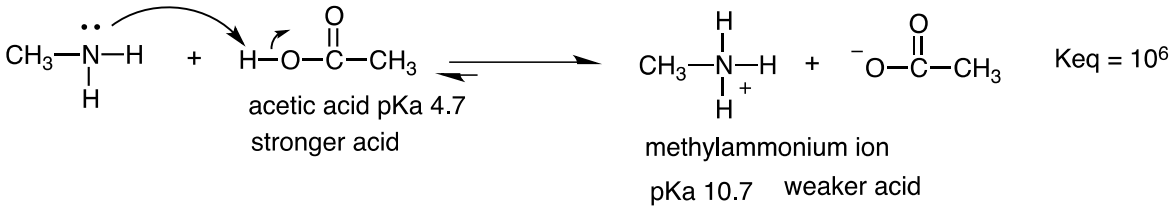
Among isomeric amines, primary amines have the highest boiling points, tertiary have the lowest.



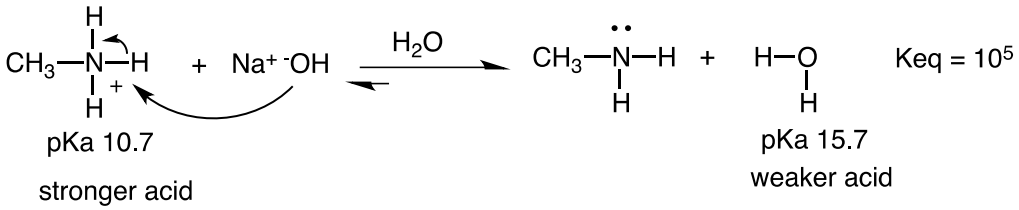
Amines with less than six or seven carbons are miscible in water.

Basicity of Amines

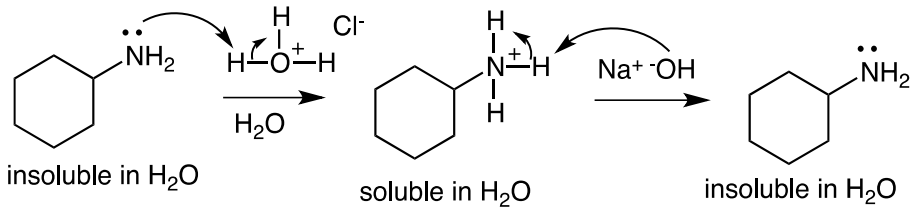
Amines are the strongest neutral bases in chemistry. As we have learned, we measure the base strength by looking at the pKa of the conjugate acid. The higher the pKa of the conjugate acid of a base, the stronger the base. And, the stronger acid is converted to the weaker acid.

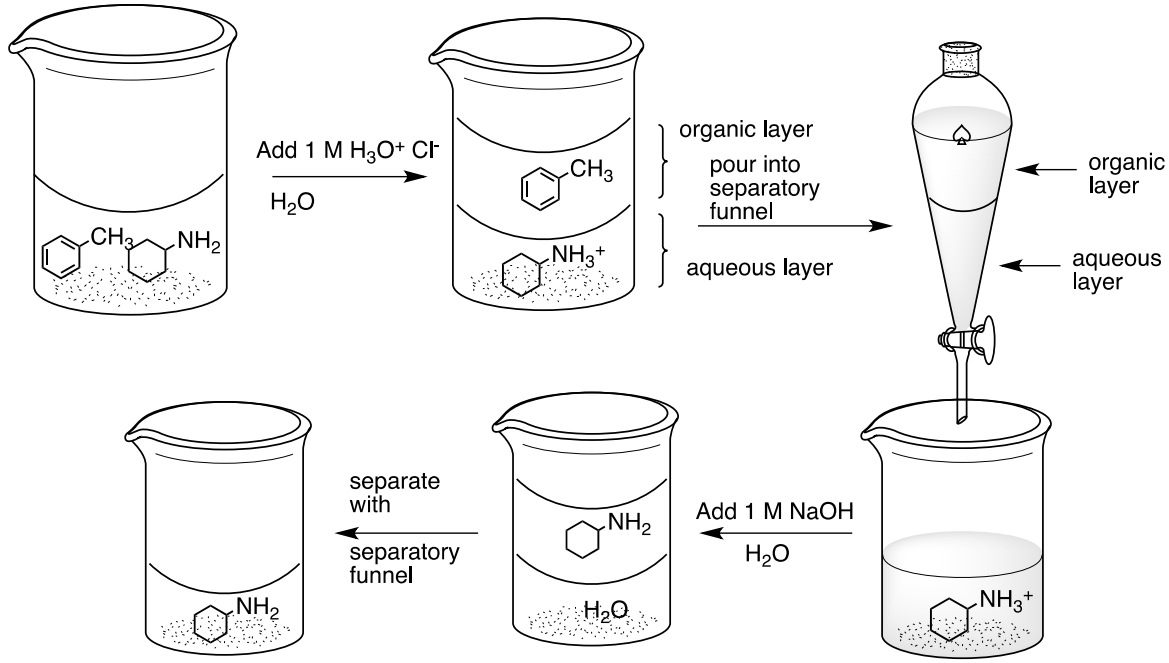


Treating the ammonium salt with sodium hydroxide converts it to the free amine, since sodium hydroxide is a strong base than the amine.

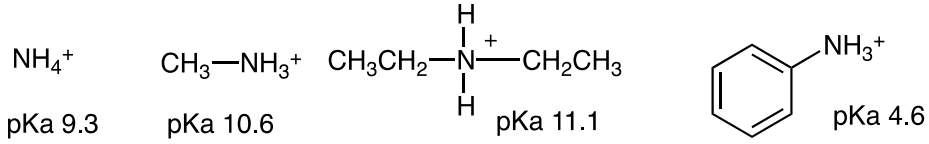


We can take advantage of the basic properties of amines to separate them from other organic compounds using simple laboratory techniques. For example, if we have a mixture of cyclohexyl amine and toluene, we can easily extract the cyclohexyl amine into an aqueous layer by adding 1 M HCl. The amine will become protonated and the ammonium salt will be soluble in the aqueous layer. By pouring the mixture into a separatory funnel, draining off the aqueous layer and then neutralizing with sodium hydroxide to give back the free amine, which then forms an organic layer. These two layers can then be separated using a separatory funnel.

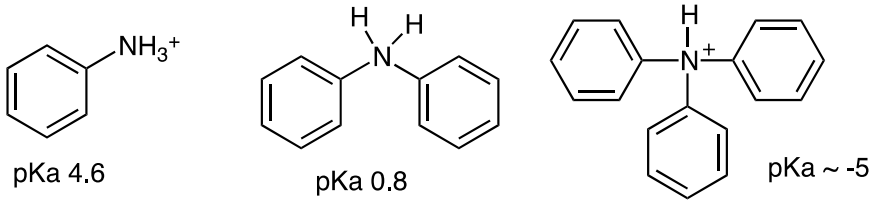




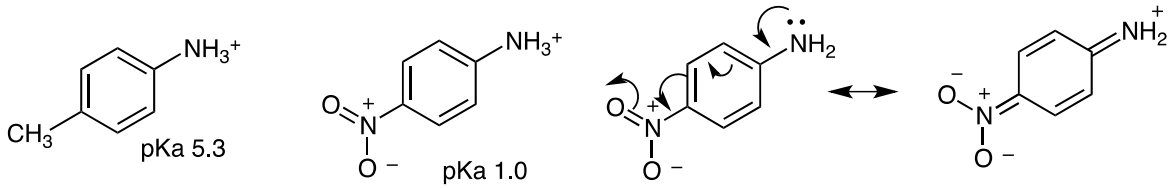
Look at the effect of substituents on the pKa of the conjugate acids of amines. Electron donating alkyl groups increase the basicity slightly. There is a huge decrease in the basicity of aniline versus methylamine. Anile is 10^6 times less basic. This is due to the delocalization of the nitrogen lone pair onto the π–system as discussed above. The aromatic ring is made much more electron rich but the nitrogen is much less basic.



As more aromatic rings are added to the nitrogen, the basicity decreases further to the point that triphenylamine is not basic at all.

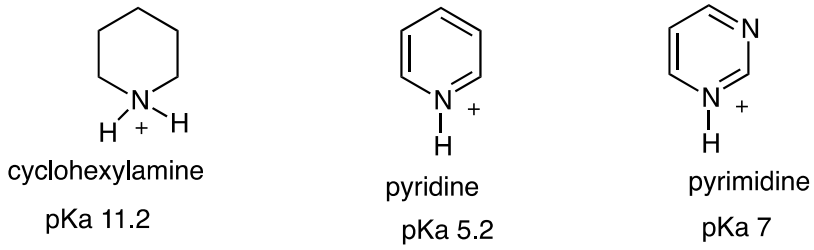


In general, electron donating substituent on the aromatic ring will increase the basicity slightly and electron withdrawing groups will decrease the basicity and can have fairly large effects.



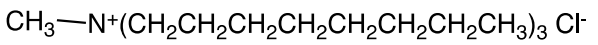
If there are two electron withdrawing groups on an aniline derivative, it is only weakly basic and it is not easily extracted into aqueous acid. So a protocol for separating aniline from 2,4-dinitroanilne would be to wash the mixture with 1 M aqueous HCl to protonate the aniline and make it soluble in the aqueous layer. The 2,4-dnitroaniline will not be protonated to any significant extent and will not go into the aqueous layer. The two layers can then be separated using a separatory funnel.

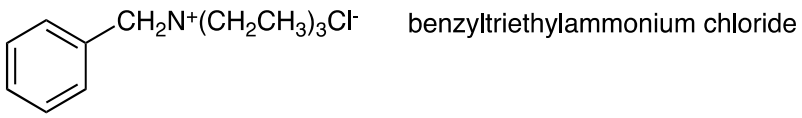
Pyridine is also a weak base like aniline. The diamino derivative, pyrimidine, is slightly more basic since the second oxygen donates electrons to the first nitrogen.



Tetraalkylammonium Salts as Phase Transfer Reagents

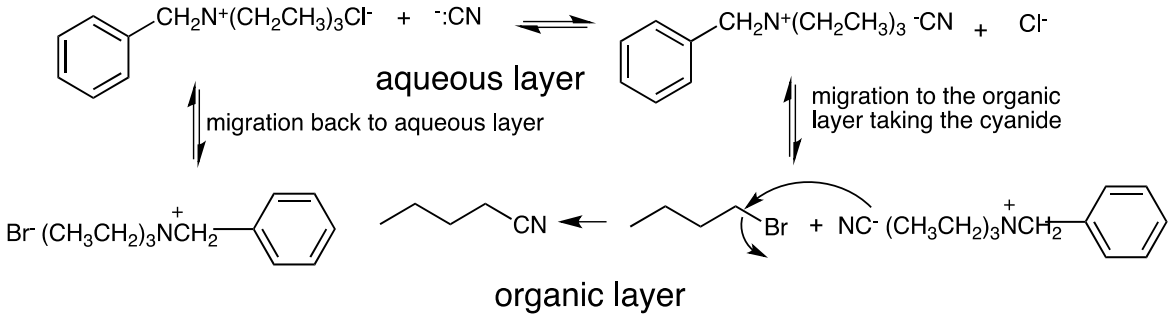
Many quaternary ammonium salts will dissolve in organic solvents of fairly low polarity such as methylene chloride (CH_2Cl_2), benzene, acetonitrile and they are also at least partially soluble in water.

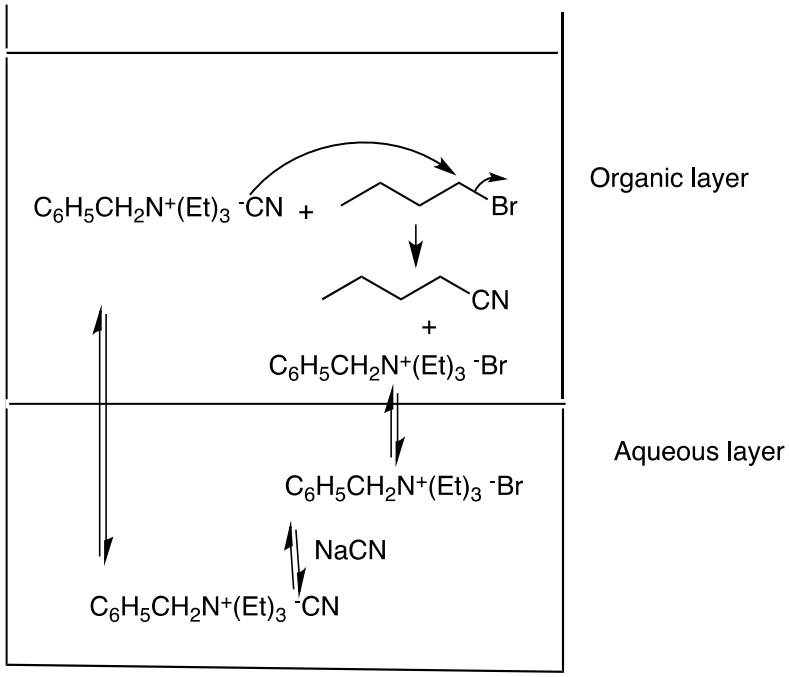




These compounds are very useful in phase transfer catalysis. This is a reaction that is done in two immiscible solvents, water and an organic phase. The function of the phase transfer catalyst is to transfer a water soluble reagent from the aqueous phase to the organic phase where is can react. For example, look at the following reaction:

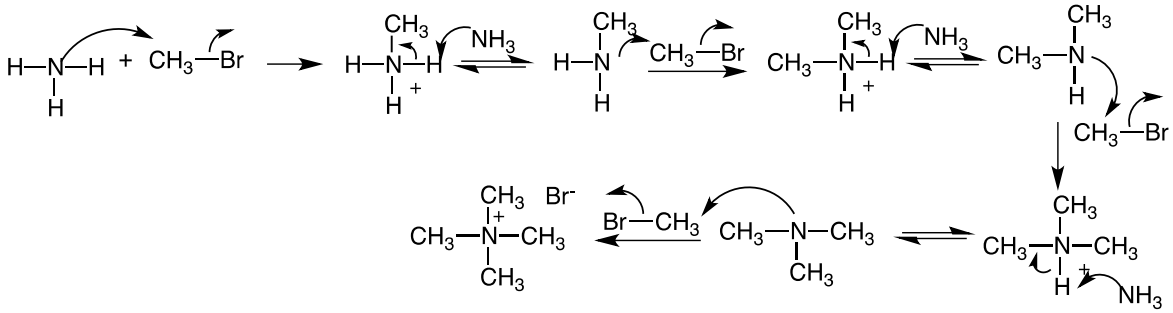
Sodium cyanide does not dissolve in organic solvents but is soluble in water. But 1-bromobutane is not soluble in water. In order for the reaction to occur the cyanide nucleophile must come into contact with the bromobutane electrophile. A biphasic solution with a phase transfer catalyst can accomplish this. Hexane and water can be used for the biphasic solution and benzyltriethylammonium chloride as the phase transfer catalyst. This will move from the aqueous layer to the organic layer where it will exchange anions. The cyanide anion will be very reactive in the organic layer since it will be weakly solvated. Once the reaction occurs, the benzyltriethylammonium salt will now have bromine anion as the counterion. This will then transfer back to the aqueous phase to repeat the process.





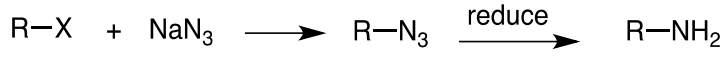
Methods for Preparing Amines

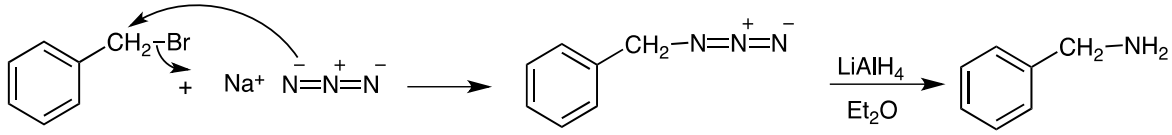
Amines are very good nucleophiles and so the obvious method for preparing alkyl amine derivatives is by simple alkylation of alkyl halides. But this is not a good synthetic method because the amine is too reactive and it is difficult to control the reaction. Up to four products can occur, giving complex reaction mixtures. For example, consider the reaction of ammonia with methyl bromide. The first product, methyl amine, is more electron rich, more basic and a better nucleophile than the starting ammonia so it will react again to give dimethyl amine which will react again to give trimethylamine which can then react a fourth time to give the quaternary ammonium salt. Usually it is possible to stop the reaction before the formation of the quaternary ammonium salt but mono-alkyl and di-alkyl amines are difficult to obtain using simple alkylation chemistry.



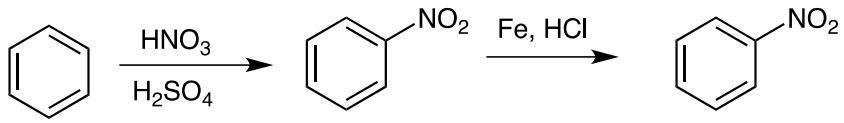
Synthetically Useful Methods

(1) Nucleophilic substitution of alkyl halides with azides followed by reduction. The azide will react only once with the alkylating agent. It can be reduced by lithium aluminum hydride ($LiAlH_4$) or catalytic hydrogenation (H_2, Pd) to give the free mono-alkylated amine.



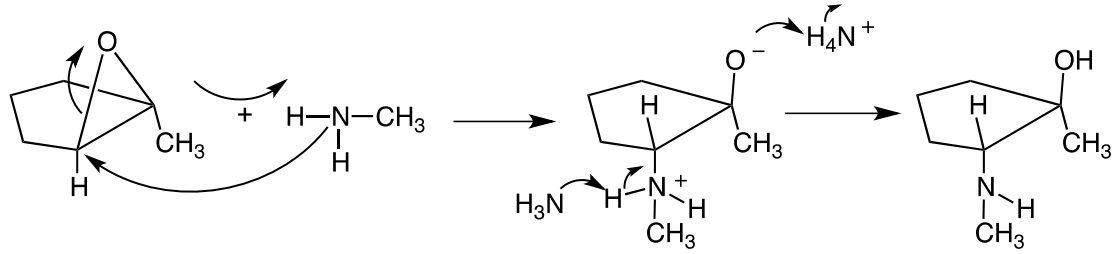


(2) Nitration of benzene derivatives followed by reduction. This is one of the best methods for putting an amine onto a benzene ring.

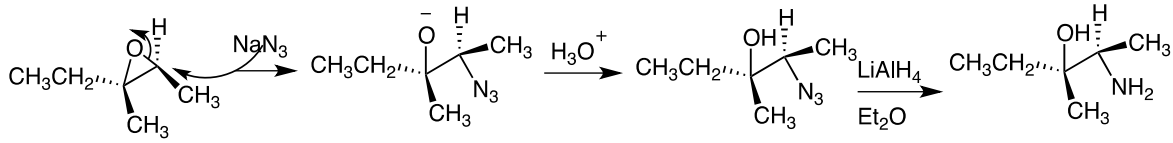


can also use $LiAlH_4$, H_2/Pd,

(3) Nucleophilic ring opening of epoxides with amines. Recall that attack is at the less hindered/less substituted position to give the trans product.



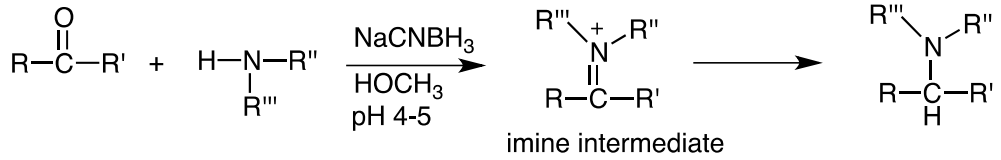
Azides also react with epoxides. Reduction gives the primary amine.

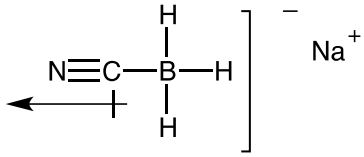


(4) Reductive Amination. This is a two step process, done in one pot, in which a primary or secondary amine reacts with an aldehyde or ketone to give an imine intermediate which is ten reduced *in situ* to the amine. The carbonyl carbon is also reduced to a methylene (-CH_2) or methenyl (-CH) group. Imines are generally easier to reduce than ketones or aldehydes so a

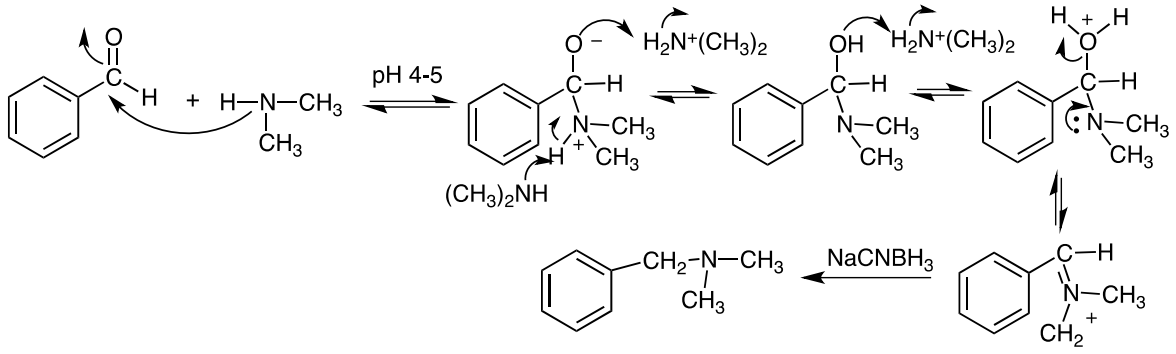
reducing agent that reduces ketones and aldehydes slowly is needed. One such reducing agent is sodium cyanoborohydride. It is similar to sodium borohydride, which does reduced aldehydes and ketones, but it is less reactive due to electron withdrawal by the cyano group, removing some of the electron density from the hydrides and making them less nucleophilic. Other reducing agents can also be used.

Overall reaction:

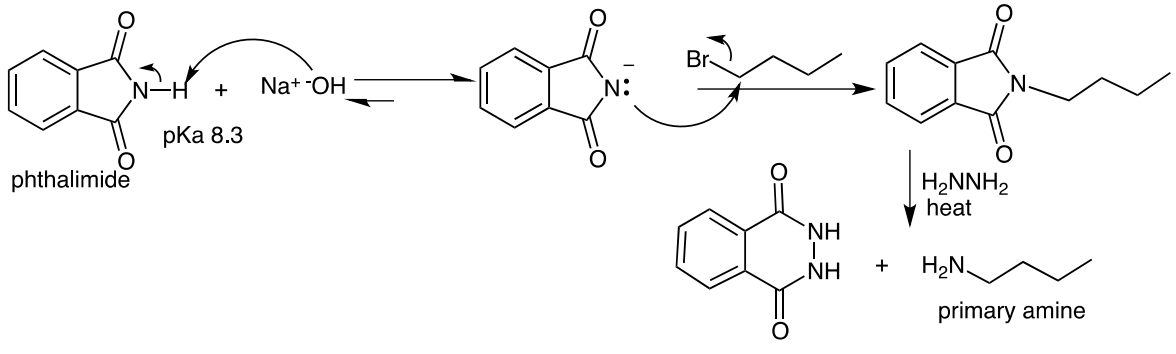




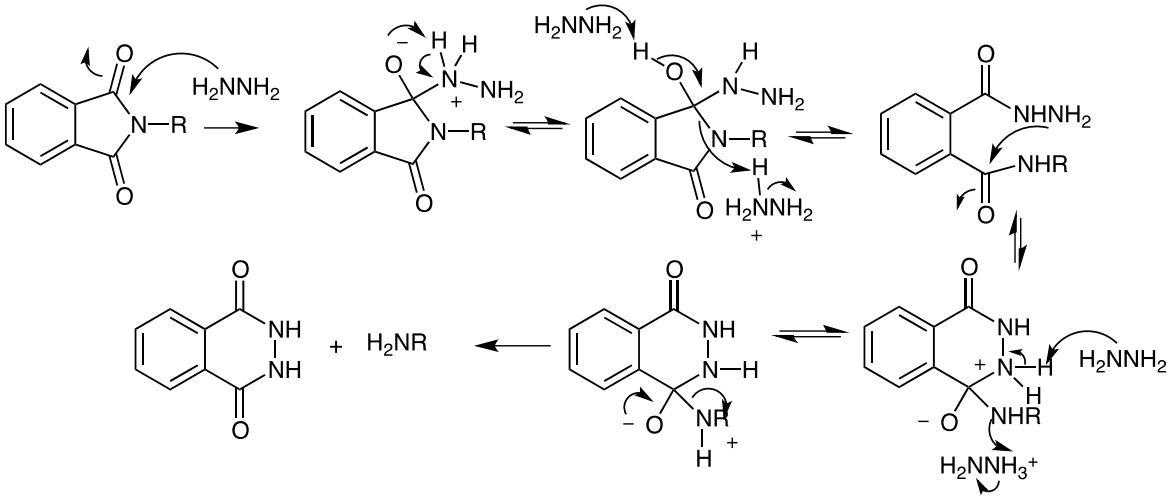
The cyano group withdraws electron density from the hydrides, making them less nucleophilic and more selective for imine reduction as opposed to reduction of the starting carbonyl.



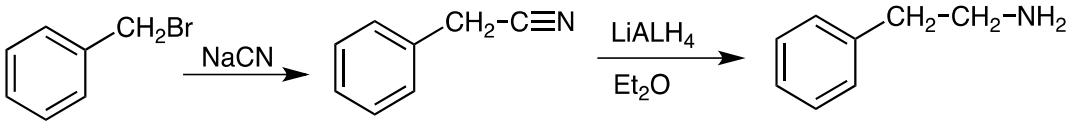
(5) Gabriel synthesis of primary amines. Another strategy for achieving mono-alkylation of amines is to use a protected amine. Phthalimide is a useful starting material. It is deprotonated in mild conditions using aqueous sodium hydroxide. The equilibrium for the deprotonation lies to the right (Keq ~ $10^{7.4}$) due to the two carbonyl groups attached to the nitrogen. The phthalimide anion can then be alkylated with a primary or secondary alkyl halide. The alkyl amine is then liberated by treatment with hydrazine.



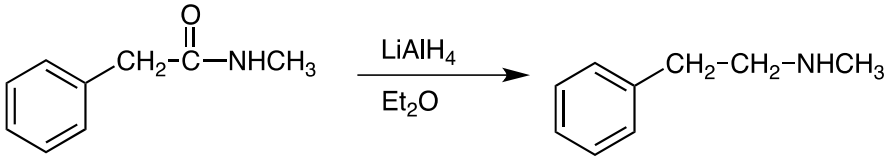
Hydrazine is a good nucleophile and replaces the amine in the phthalimide in a trans amination reaction. The mechanism is similar to that of amide formation.



(6) Amines can be prepared by reduction of nitriles using a strong reducing agent such as lithium aluminum hydride. The nitriles are prepared from alkyl halides. So the overall process adds one carbon and a primary amine.

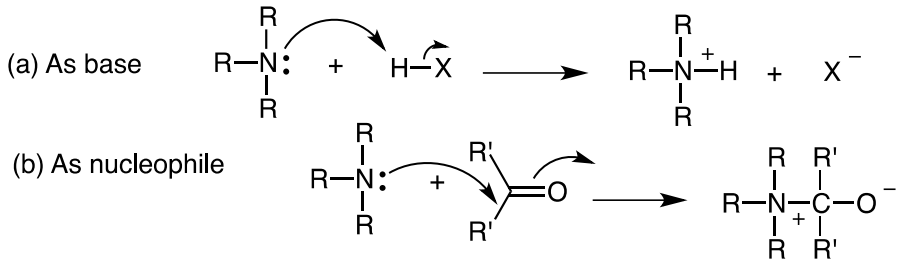


(7) Amines can also be prepared by reduction of amides using lithium aluminum hydride. Primary, secondary or tertiary amines can be obtained, depending on the substitution pattern of the amide.

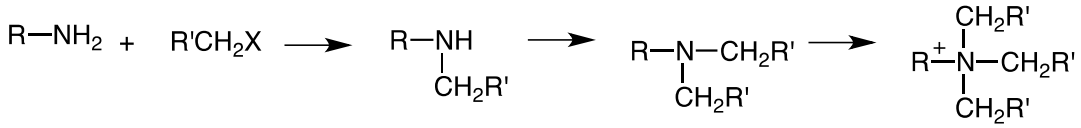


Reactions of Amines

As we have seen amines are good nucleophiles and moderately strong bases.

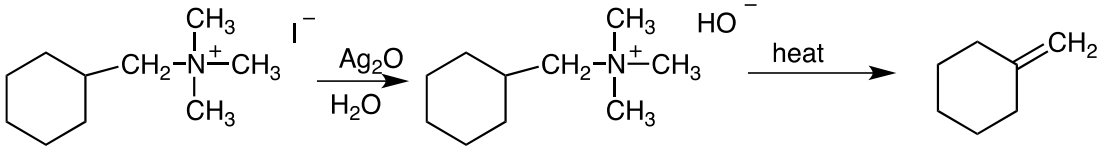


Reaction with amines. Mixtures of several products are obtained.

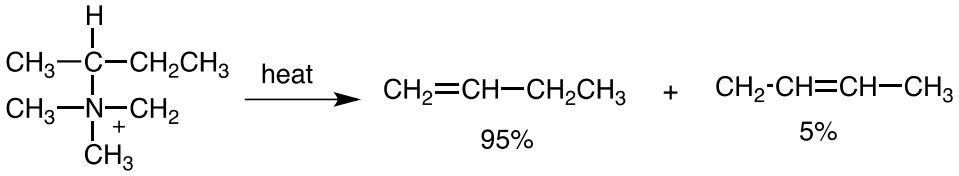


Hoffman Elimination

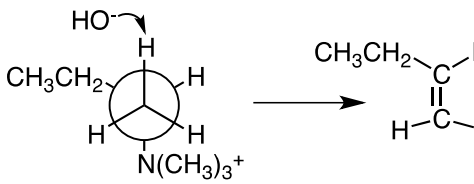
The halide of quaternary ammonium halides may be replaced by hydroxide by treatment with silver oxide. On heating, the quaternary ammonium hydroxide undergoes β−elimination.



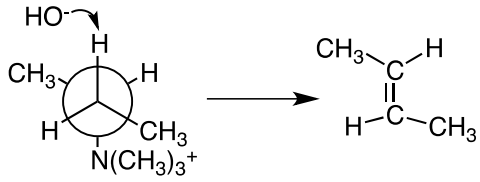
The less substituted alkene is usually formed.



This is opposite to Zaitsev's rule. The reason for this is that there is actually considerable negative charge building up in the transition state. This prefers to be on the less substituted carbon. Usually the less hindered β−carbon is removed. The $N(CH_3)_3^+$ group is fairly large and the less hindered transition state is formed for the E2 reactions.



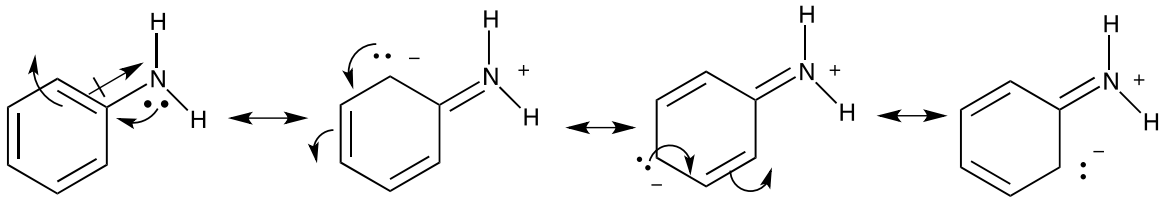
less hindered transition state



more hindered transition state

Electrophilic Aromatic Substitution of Aryl Amines

The amino group is a strong electron donating group due to the donation of the lone pair into the π–system of the benzene ring. Even though the amine nitrogen is more electronegative than carbon and has an electron-withdrawing inductive effect that pulls electrons away from the benzene ring, the π–donation effect is much stronger. The amino group is an *ortho/para* director, like all electron donating groups.

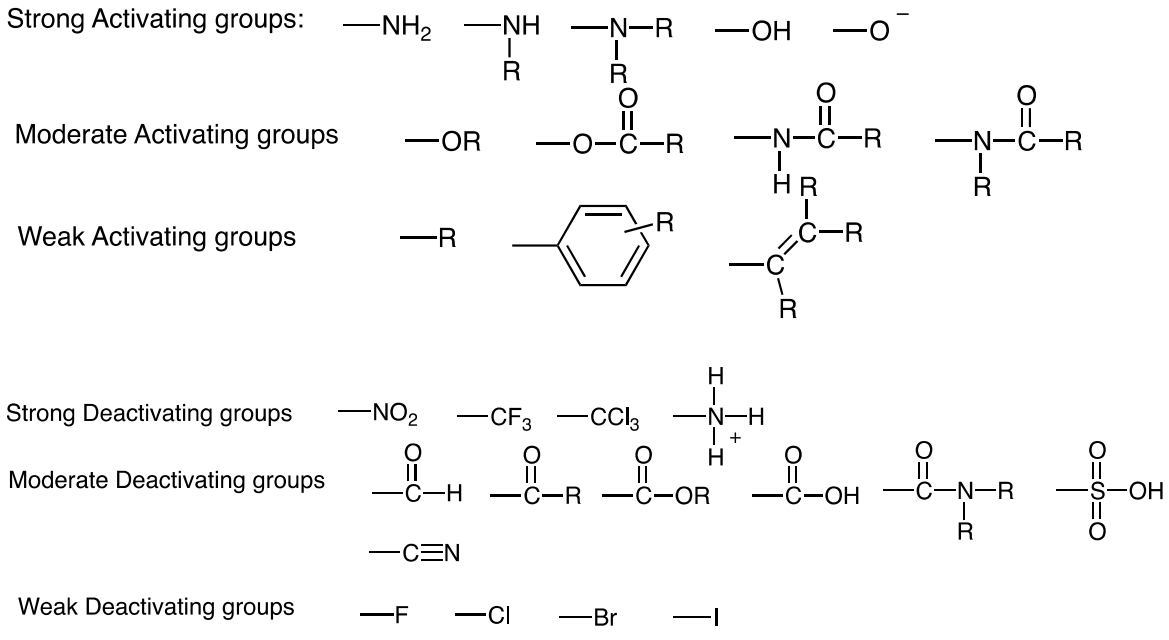


Induction withdrawal by the nitrogen due to electronegativity but larger π–donation due to lone pair

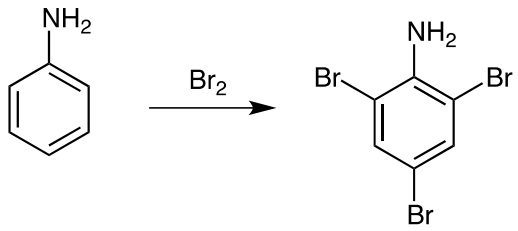
Note that the negative charge is located at the *ortho and para* positions.

Review of Electrophilic Aromatic Substitution:

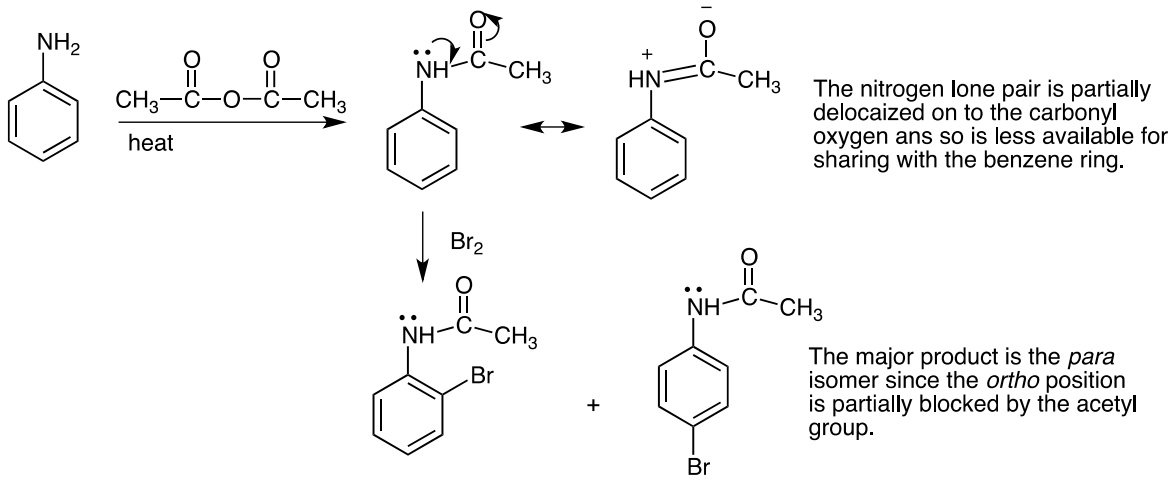
Recall: (1) All activating groups (electron donating groups) direct *ortho/para*. (2) All deactivating groups (electron withdrawing groups) direct *meta* except the halogens, which are deactivating (strong electron withdrawal though the inductive effect since they are electronegative) but weak electron donation through the π–donation of their lone pair.



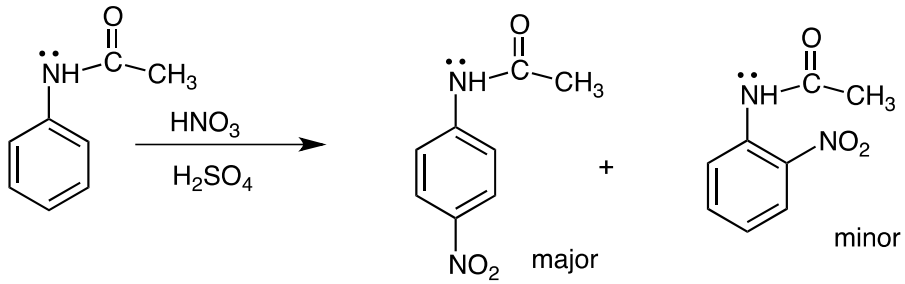
The amino group is so strongly activating that mono-bromination of aniline is not possible. No catalyst is needed and the tribromo-derivative is formed.



We can weaken the electron donating effect of the nitrogen lone pair by putting on an electron withdrawing acetyl group on the nitrogen. The acetyl group withdraws electrons both through resonance and the inductive effect.

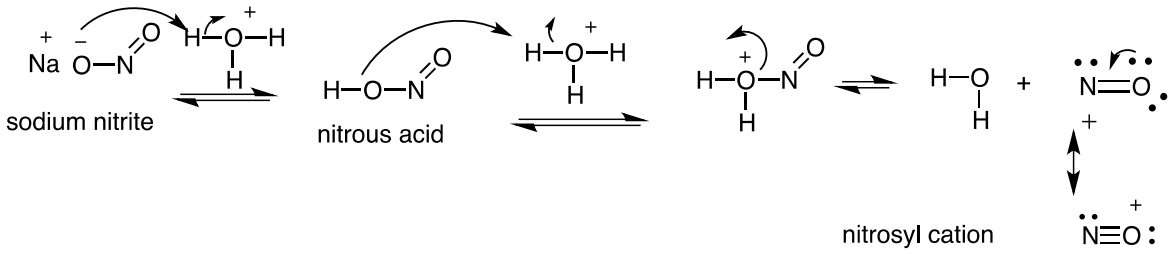


For nitration, the amino group must be protected against oxidation and protonation by nitric acid.

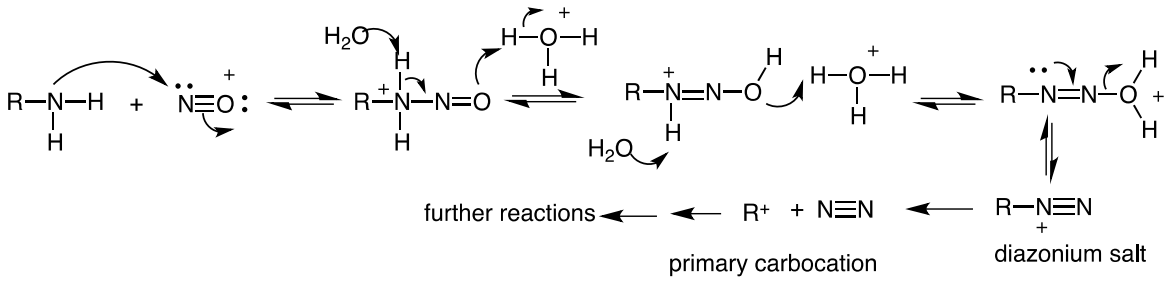


Nitrosation of Alkylamines

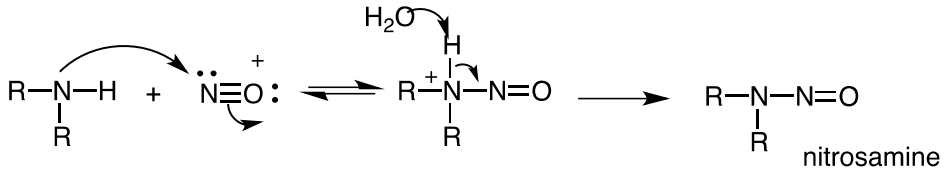
When sodium nitrate is treated with acid, a solution of nitrosyl cation is formed. This is a powerful electrophile and will react with other amines.



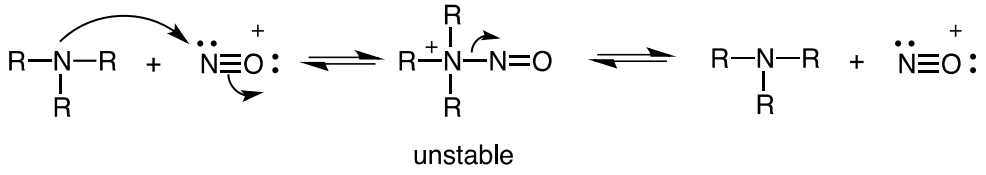
The nitrosyl cation can react with primary amines to form a diazonium salt. The diazonium salts of primary amines are unstable and decompose to give carbocations with loss of N_2, one of the best leaving groups in chemistry.



With secondary amines, stable N-nitrosoamines are formed. These are highly carcinogenic compounds. They are found in preserved meats and tobacco smoke.



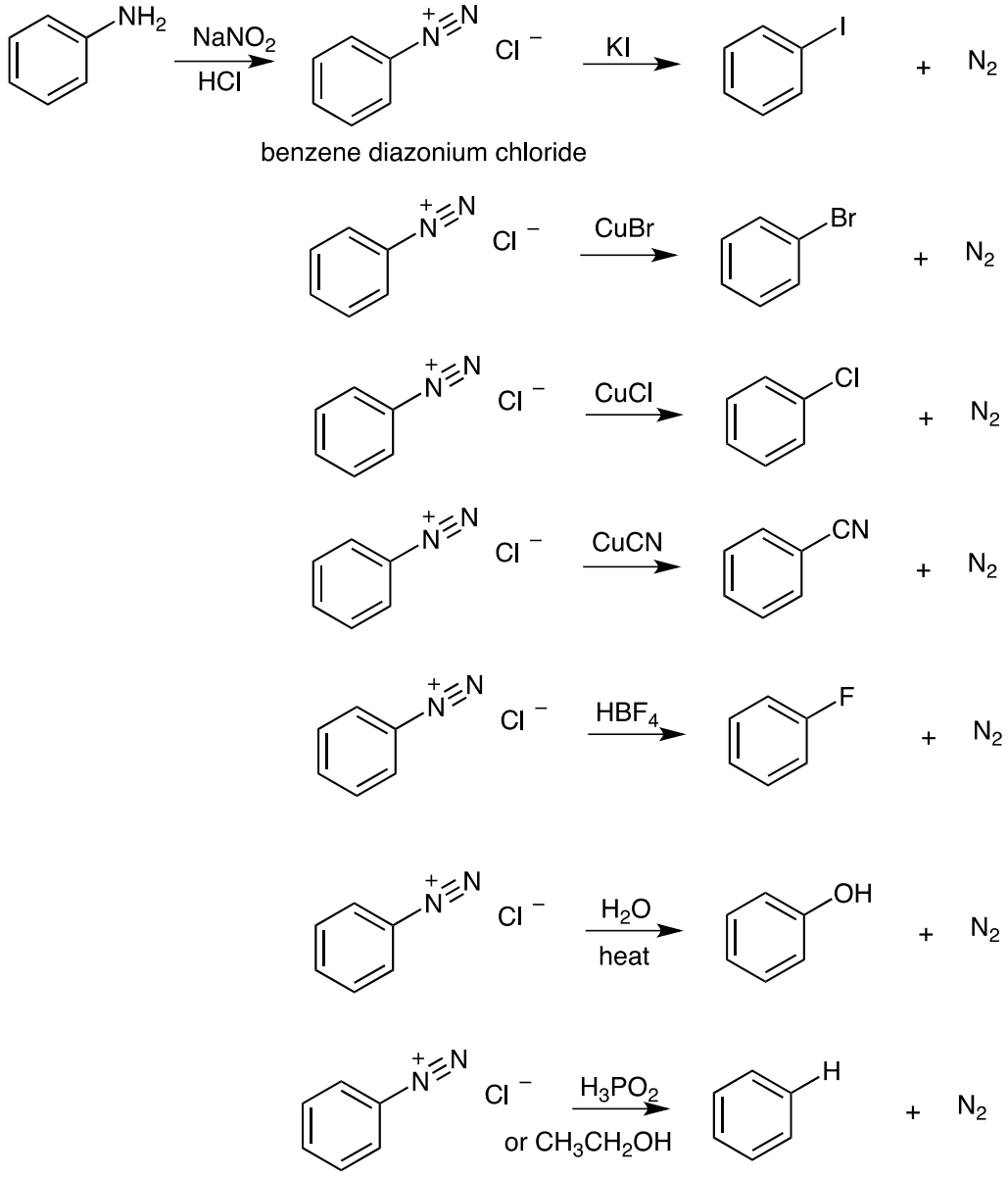
With tertiary amines the initially formed adduct with the nitrosyl cation is unstable and decomposes to give the starting tertiary amine.



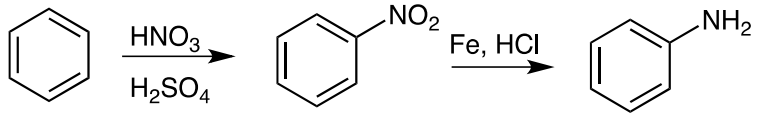
Aryl Diazonium Salts

The diazonium salt formed from an aryl amine is relatively stable at low temperature (< 5°C) and can be transformed into a variety of other derivatives with loss of nitrogen gas. This is a

very useful series of reactions and allows formation of benzene derivatives that would otherwise be inaccessible.

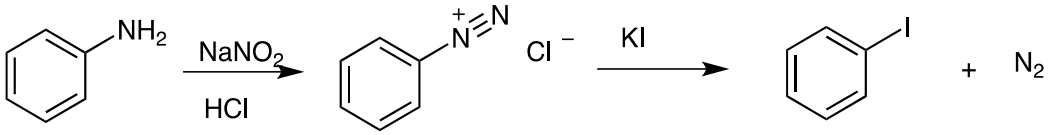


The amino group is first put on by nitration followed by reduction.

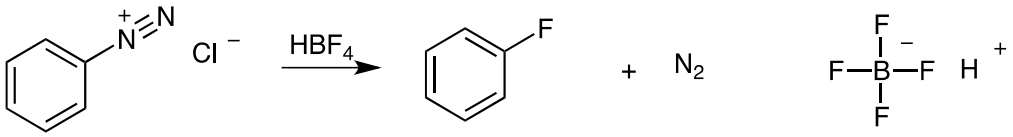


To make the aryl iodide, the diazonium slat is formed and then treated immediately at low temperature with a solution of potassium iodide in water. This is the standard method for

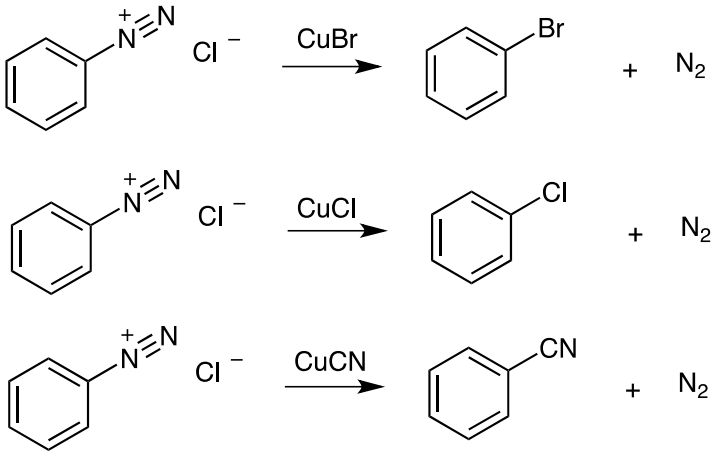
introducing an iodine onto a benzene ring since direct iodination is not thermodynamically a favorable reaction.



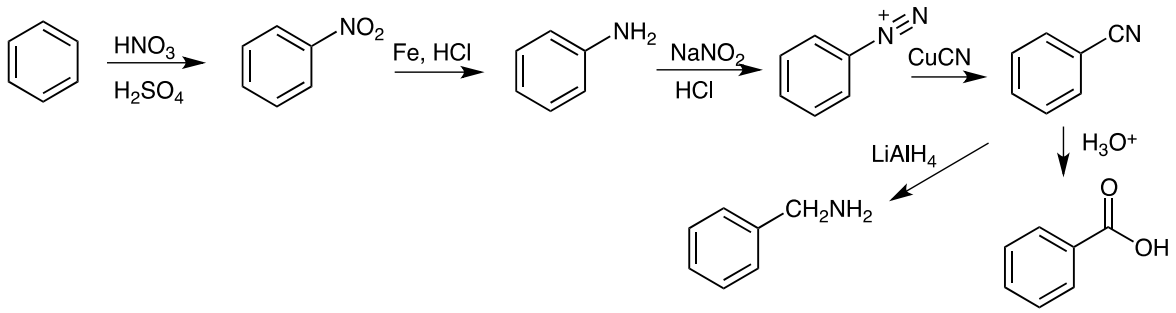
To make aryl fluorides, the diazonium salt is treated with fluoroboric acid. Direct treatment with molecule fluorine is not a practical reaction since it is violently exothermic and difficult to control.



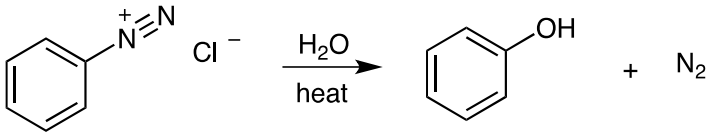
The amino group can be replaced with –Cl, -Br, -CN using copper (I) reagents. These reactions are called the Sandmeyer Reactions.



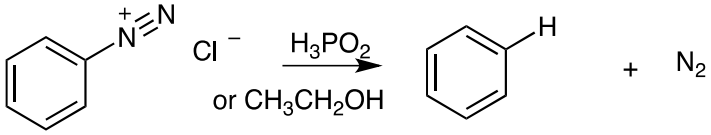
Using copper cyanide, the nitrile group can be installed with the formation of a new C-C bond. The nitrile group can be hydrolyzed to a carboxylic acid or reduced to a $–CH_2NH_2$ group.



The amino group may be replaced by hydroxyl by allowing the diazonium salt to warm up in aqueous solution.

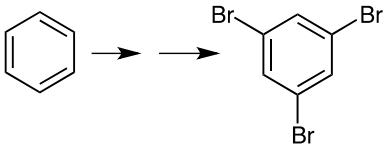


The amino group may be replaced with a hydrogen using hypophosphorus aci (H_3PO_2) or ethanol. This can be a useful transformation in synthesis, since the nitro- or amino- group can be added and used as a directing group and then removed.



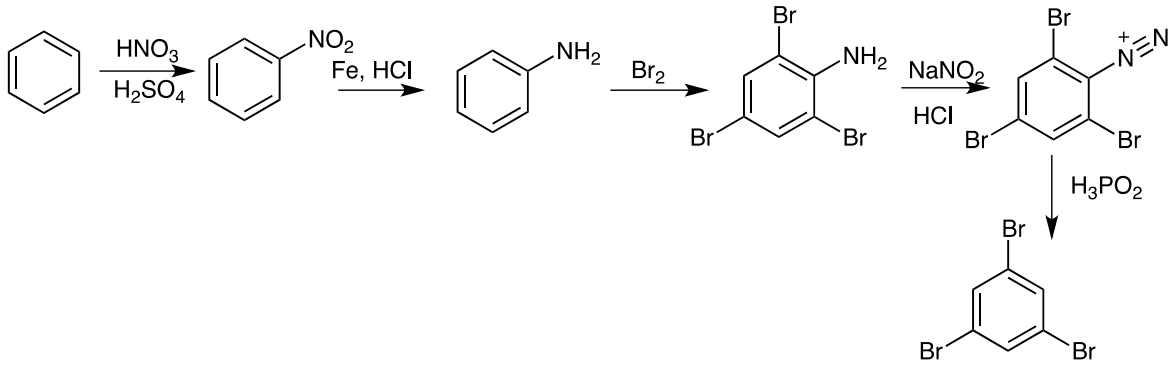
Synthetic Applications

For the following synthesis:

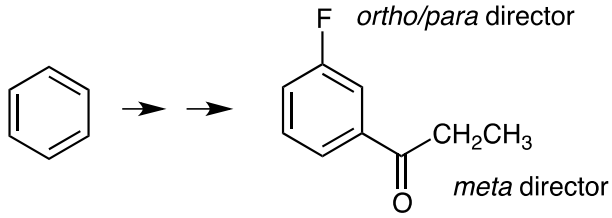


Since the Br is *ortho/para* directing we can not simply brominate directly.

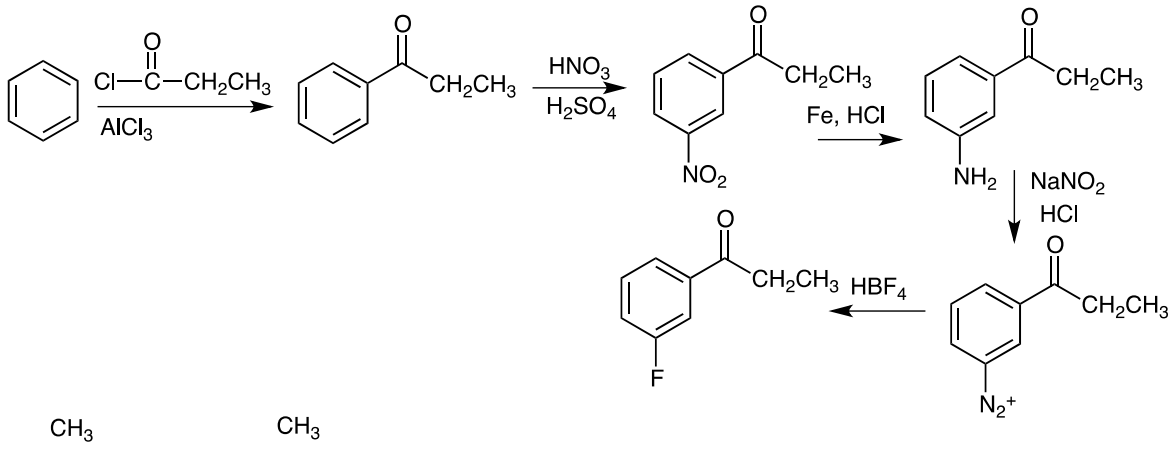
Since the Br- group is *ortho/para* directing we cannot simply brominates directly since we would get the 1,2,4-tribromospceies instead of the desired 1,3,5-derivative. We need to use the amino group as a directing group. We put this on by nitration followed by reduction. Then we brominates and then remove the amino- group by means of the diazonium salt.



For:

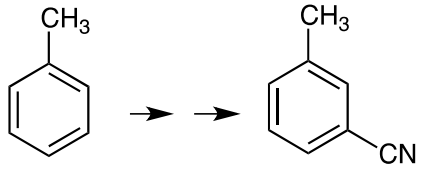


Here the order of events is critical. The fluorine must be put on by means of the diazonium salt but it is an *ortho/para* director so the carbonyl substituent should be put on first since it is a *meta* director.



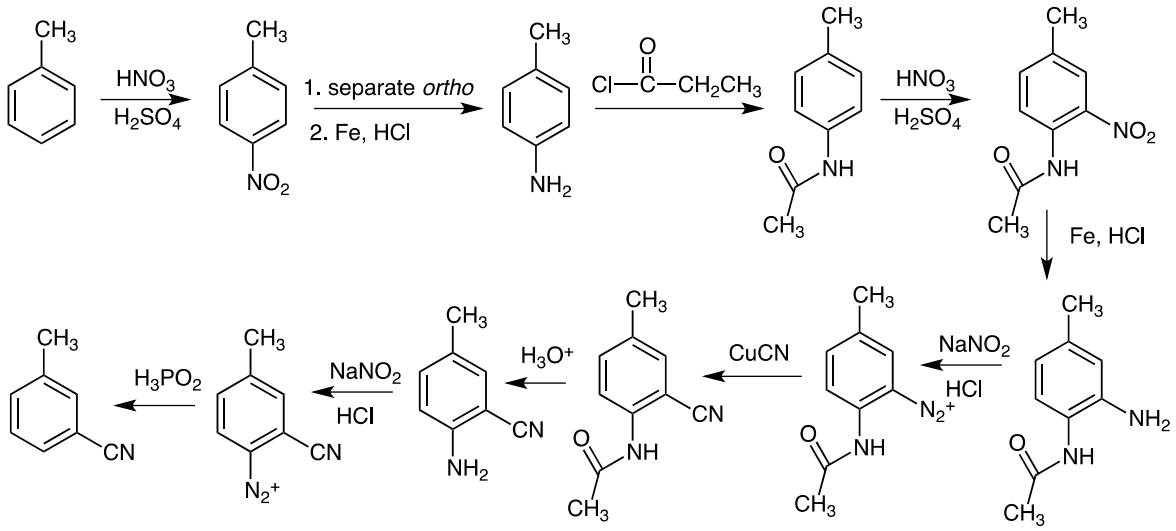
CH3 CH3

And the amino group can be used as a blocking and directing group as in the following synthesis.



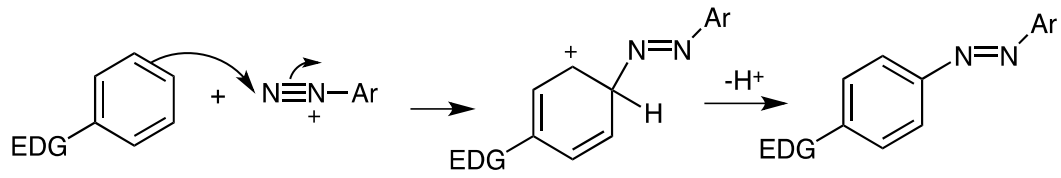
The -CH_3 group is an *ortho/para* director so the para position must be blocked with an amino group.

The first step is nitration. This will give a mixture of *ortho* and *para*, which must be separated. The desired *para* isomer is then reduced and protected as the acetyl amide. The next step is nitration. The amide will be a strong directing group than the methyl substituent and so the nitration will go *ortho* to it. The sequence of reduction, diazonium salt formation and treatment with copper cyanide will install the cyano group in the desired position *meta* to the methyl group. The amide is then replaced by hydrolysis and diazonium slat formations.

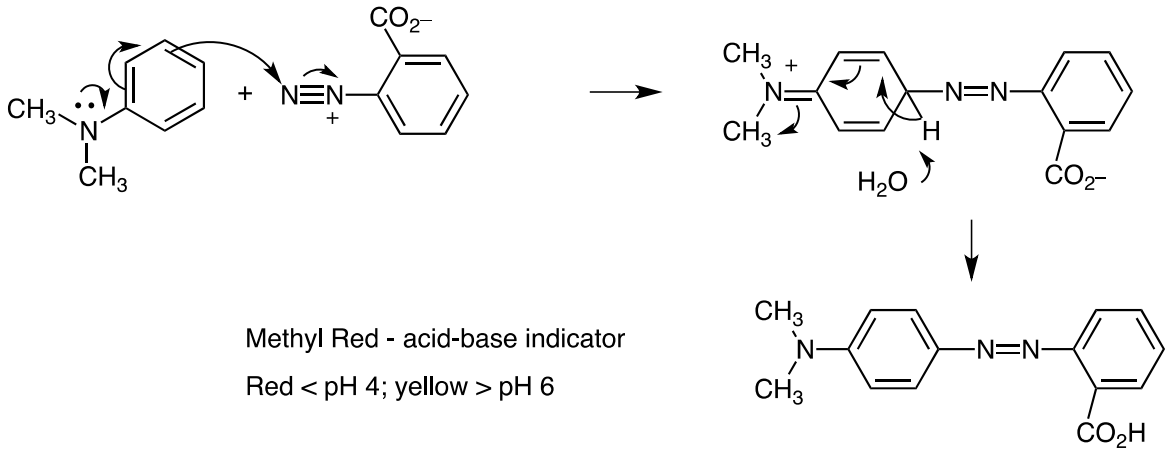


Azo Coupling

Aryl diaxonium salts are also weak electrophiles and will react with strongly activated aromatic rings to give azo compounds. These molecules are very useful dyes and food coloring compounds.



For example:



Methyl Red - acid-base indicator

Red < pH 4; yellow > pH 6