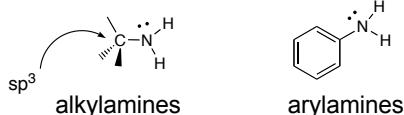
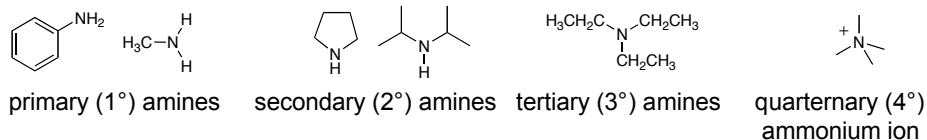


**Chapter 22: Amines.** Organic derivatives of ammonia,  $\text{NH}_3$ . Nitrogen atoms have a lone pair of electrons, making the amine both basic and nucleophilic.

**22.1: Amines Nomenclature.** (please read)



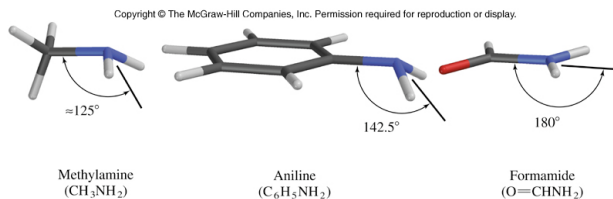
Amines are classified according to the degree of nitrogen substitution:  $1^\circ$  ( $\text{RNH}_2$ ),  $2^\circ$  ( $\text{R}_2\text{NH}$ ),  $3^\circ$  ( $\text{R}_3\text{N}$ ) and  $4^\circ$  ( $\text{R}_4\text{N}^+$ )



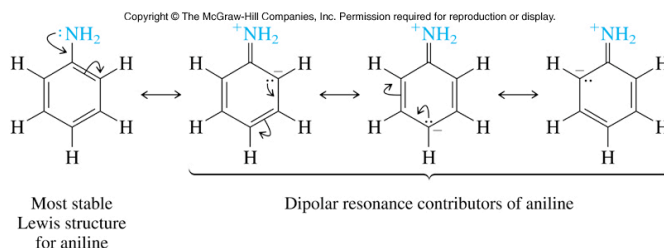
Note: Although the terminology is the same, this classification of amines is different from that of alcohols.

203

**22.2: Structure and bonding.** The nitrogen of alkylamines is  $sp^3$  hybridized and tetrahedral.

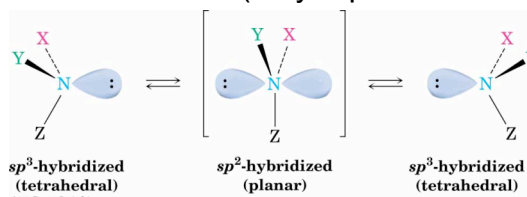


The nitrogen of arylamines (aniline) is slightly flattened, reflecting resonance interactions with the aromatic ring.



204

In principle an amine with three different substituents on the nitrogen is chiral with the lone pair of electrons being the fourth substituent; however, for most amines the *pyramidal inversion* of nitrogen is a racemization mechanism. The barrier to nitrogen inversion is about 25 KJ/mol (very rapid at room temperature).



### 22.3: Physical Properties. (please read)

**22.4: Basicity of Amines.** The basicity is reflective of and is expressed as the  $pK_a$ 's of the conjugate acid.

The conjugate base of a weak acid is a strong base:

Higher  $pK_a$  = weaker acid = stronger conjugate base

The conjugate base of a strong acid is a weak base

Lower  $pK_a$  = stronger acid = weaker conjugate base 205

*Table 22.1* (p. 915):  $pK_a$  values of ammonium ions

Alkyl ammonium ions,  $R_3NH^+ X^-$ , have  $pK_a$  values in the range of 10-11 (ammonium ion,  $H_4N^+ X^-$ , has a  $pK_a \sim 9.3$ )

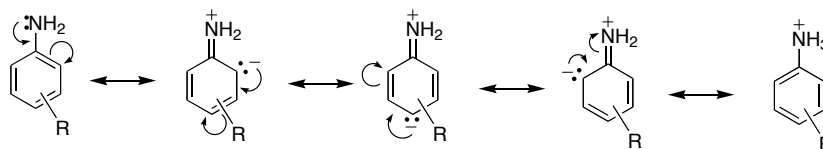
The ammonium ions of aryl amines and heterocyclic aromatic amines are considerably more acidic than alkyl amines ( $pK_a < 5$ ). The nitrogen lone pair is less basic if it is in an  $sp^2$  hybridized orbital (versus an  $sp^3$ )

$NH_4^+$	$pK_a = 9.3$		$pK_a = 4.6$
$(H_3CH_2C)NH_3^+$	10.8		5.2
$(H_3CH_2C)_2NH_2^+$	11.1		0.4
$(H_3CH_2C)_3NH^+$	10.8		7.0
			- 1.0

206

Arylamines are much less basic than alkylamines. The lone pair of electrons on the nitrogen of aniline are conjugated to the  $\pi$ -electrons of the aromatic ring and are therefore less available for acid-base chemistry. Protonation disrupts the conjugation.

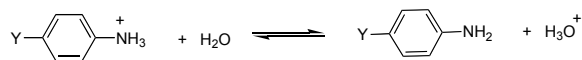
Substituents can greatly influence the basicity of the aniline. The effect is dependent upon the nature and position of the substituent.



207

Electron-donating substituents ( $-\text{CH}_3$ ,  $-\text{OH}$ ,  $-\text{OCH}_3$ ) make the substituted aniline more basic than aniline itself (the  $\text{p}K_a$  of the anilinium ion is higher than 4.6)

Electron-withdrawing substituents ( $-\text{Cl}$ ,  $-\text{NO}_2$ ) make the substituted aniline less basic than aniline itself (the  $\text{p}K_a$  of the anilinium ion is lower than 4.6)

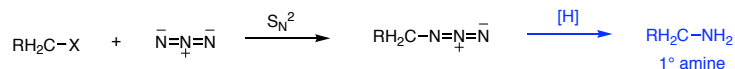


Y= $-\text{NH}_2$	$\text{p}K_a = 6.2$	less acidic (more basic)
$-\text{OCH}_3$	$\text{p}K_a = 5.3$	
$-\text{CH}_3$	$\text{p}K_a = 5.1$	more acidic (less basic)
$-\text{H}$	$\text{p}K_a = 4.6$	
$-\text{Cl}$	$\text{p}K_a = 4.0$	
$-\text{CF}_3$	$\text{p}K_a = 3.5$	
$-\text{CN}$	$\text{p}K_a = 1.7$	
$-\text{NO}_2$	$\text{p}K_a = 1.0$	

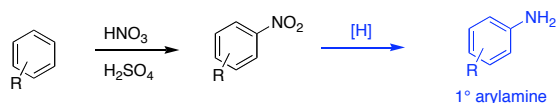
208

**22.5: R<sub>4</sub>N<sup>+</sup> Salts as Phase-Transfer Catalysts** (please reads)  
**22.6: Reactions That Lead to Amines: A Review and Preview**  
 Formation of C-N bonds:

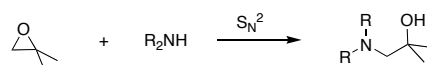
a. Nucleophilic substitution with azide ion (Ch. 8.1, 8.11)



b. Nitration of arenes (Ch. 12.3)

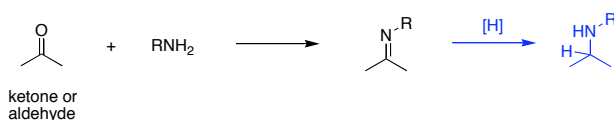


c. Nucleophilic ring opening of epoxides with NH<sub>3</sub> (Ch. 16.12)

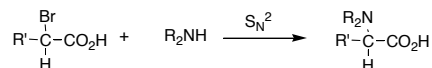


209

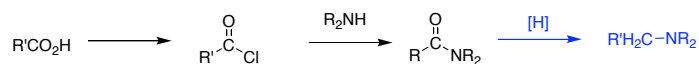
d. Reaction of amines with ketones and aldehydes (Ch. 17.10)



e. Nucleophilic substitution of α-halo acids with NH<sub>3</sub> (Ch. 19.16)



f. Nucleophilic acyl substitution (Ch. 20.4, 20.5, 20.11)

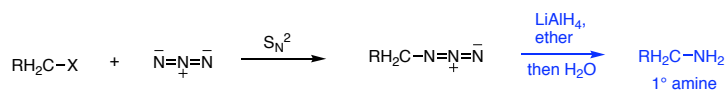


210

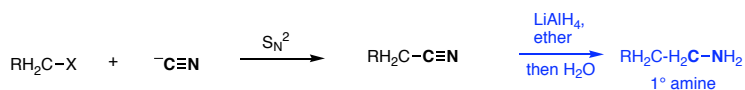


**22.9: Preparation of Amines by Reduction.** Alkyl azides, nitriles, amides, and nitroarene can be reduced to the corresponding amines.

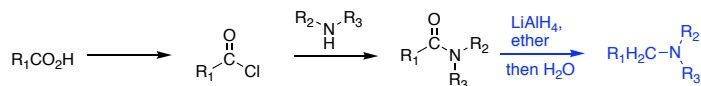
LiAlH<sub>4</sub> reduces alkyl azides to 1° amines



LiAlH<sub>4</sub> reduces nitriles to 1° amines

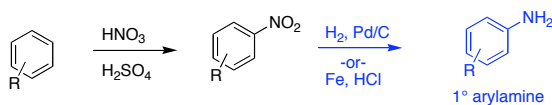


LiAlH<sub>4</sub> reduces amides to 1°, 2° or 3° amines

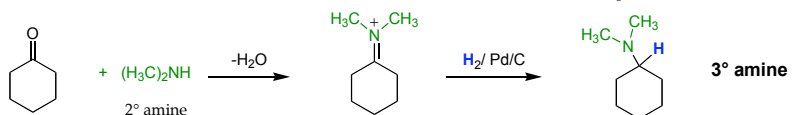
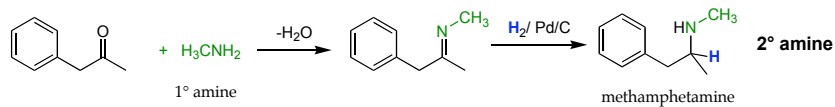
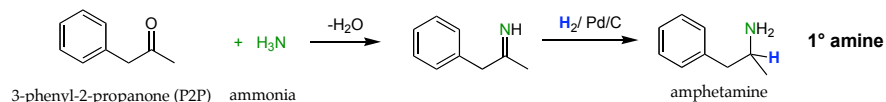


213

Nitroarenes are reduced to anilines



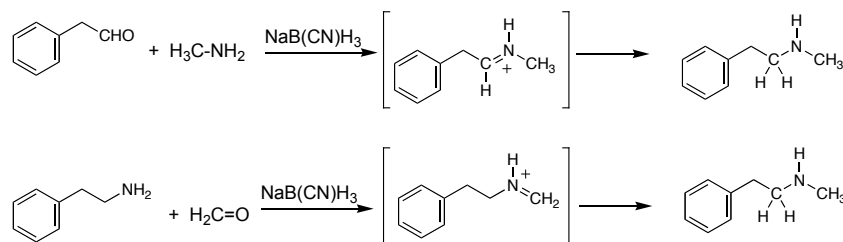
**22.10: Reduction Amination.** Imines and iminium ions are easily reduced to amines.



214

Sodium cyanoborohydride,  $\text{Na}^+ \text{N} \equiv \text{C} - \text{BH}_3^-$ : the cyano ligand makes cyanoborohydride a weak hydride source and it will react with only the most easily reduced functional groups, such as an iminium ion.  $\text{NaB}(\text{CN})\text{H}_3$  reduces ketones and aldehydes slowly.

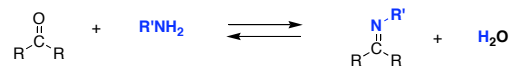
Reductive amination with  $\text{NaB}(\text{CN})\text{H}_3$  is a one-pot reaction



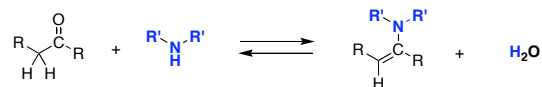
215

### 22.11: Reactions of Amines: A Review and a Preview.

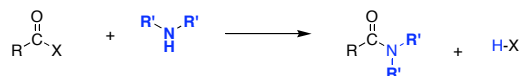
Reaction of ammonia and  $1^\circ$  amines with aldehyde and ketones to afford imines (w/ loss of  $\text{H}_2\text{O}$ ) (Ch. 17.10-17.11)



Reaction of  $2^\circ$  amines with aldehyde and ketones (w/ an  $\alpha$ -proton) to afford an enamine (w/ loss of  $\text{H}_2\text{O}$ ) (Ch. 19.16)



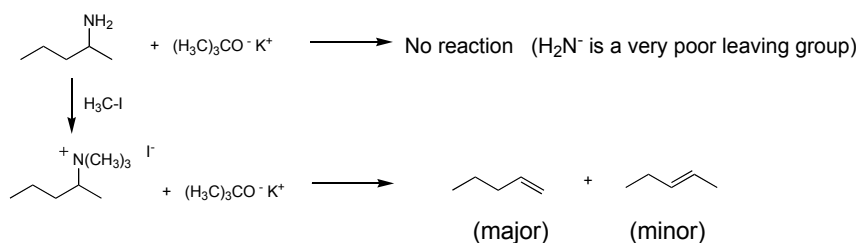
Reaction of ammonia,  $1^\circ$ , and  $2^\circ$  amines with acid chloride, anhydrides and esters to afford amides. (Ch. 20.4, 20.5, 20.11)



216

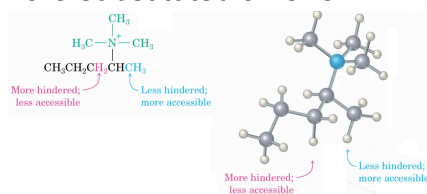
**22.12: Reaction of Amines with Alkyl Halides.** Amines react with alkyl halides and tosylates by nucleophilic substitution ( $S_N^2$ ). Products from multiple alkylation often results.

**22.13: The Hoffmann Elimination.**  $1^\circ$  amine react with excess methyl iodide yield quarternary ( $4^\circ$ ) ammonium salts. E2 elimination of the resulting trimethyl ammonium group to give an alkene.



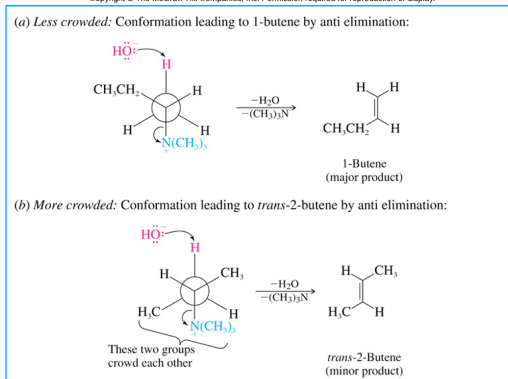
217

Hofmann elimination gives the less substituted alkene, where E2 elimination of an alkyl halide or tosylate will follow Zaitsev rule to give the more substituted alkene



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Fig 22.4,  
p.933



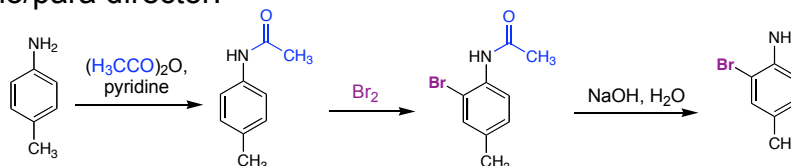
218



### 22.14: Electrophilic Aromatic Substitution in Arylamines.

The amino group is strongly activating, ortho/para director; however, it is largely incompatible with Friedel-Crafts reactions.

Electrophilic aromatic substitution of phenyl acetamides (amides of aniline). The acetamide group is still activating and an ortho/para director.



The acetamide group acts as a protecting group for the arylamine.

Anilines are so activated that multiple substitution reactions can be a problem. The reactivity of the acetamide is attenuated so that mono substitution is achieved.

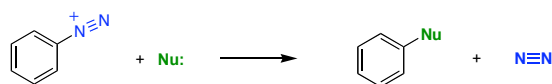
The acetamide group is compatible with the Friedel-Crafts reactions

219

### 22.15: Nitrosation of Alkylamines. (please read)

**22.16: Nitrosation of Arylamines.** Reaction of aniline with *nitrous acid* (NaNO<sub>2</sub> + H<sup>+</sup> → HONO) leads to an aryl diazonium cation, which are valuable precursors to other functional groups.

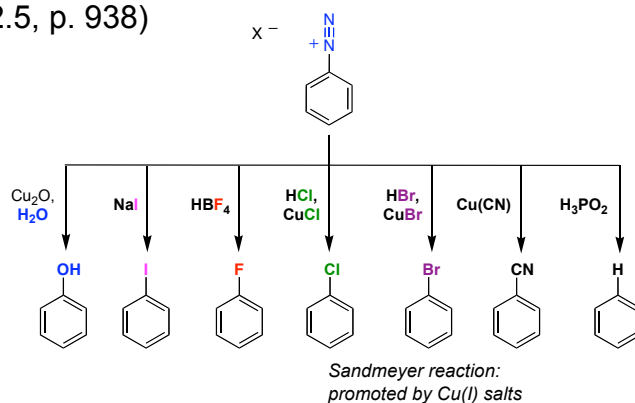
Aryl diazonium salts react with nucleophiles in a substitution reaction. N<sub>2</sub> is one of the best leaving groups.



220

## 22.17: Synthetic Transformations of Aryl Diazonium Salts.

(Fig. 22.5, p. 938)



Advantages of the aryl diazonium salt intermediate:

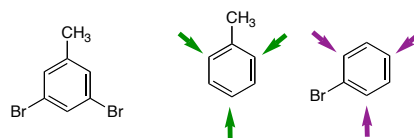
- 1) Introduces aryl substituents that are not otherwise accessible, such as -OH, -F, -I, and -CN.

221

Advantages of the aryl diazonium salt intermediate:

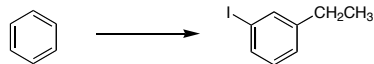
- 2) Allows preparation of substituted arenes with substitution patterns that can not be prepared by other means.

Synthesis 3,5-dibromotoluene



222

Synthesize 2-iodoethylbenzene from benzene:

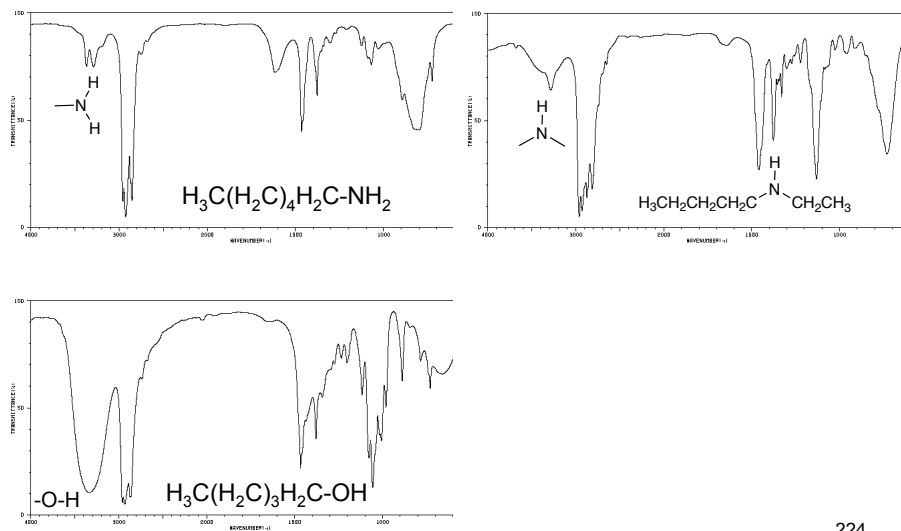


**22.18: Azo Coupling. (please read)**

223

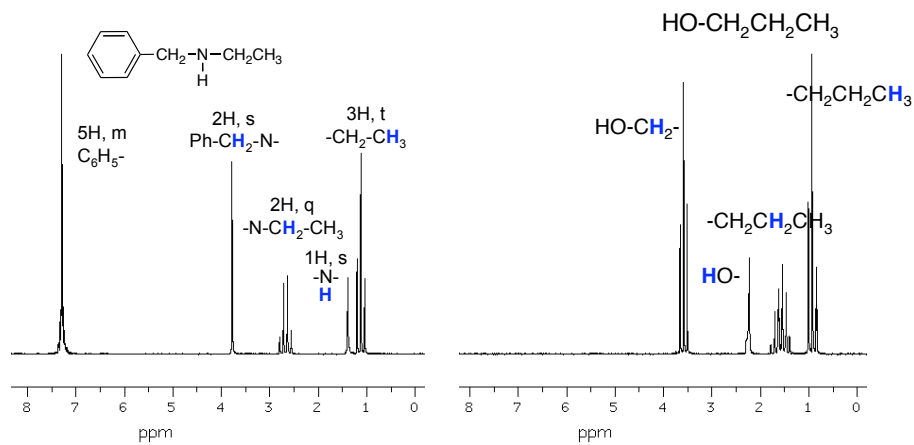
**22.19: Spectroscopic Analysis of Amines.**

*IR:* N-H stretches in the range of 3300 - 3500  $\text{cm}^{-1}$ ; this is the same range as an O-H stretch, but N-H stretches are less intense.



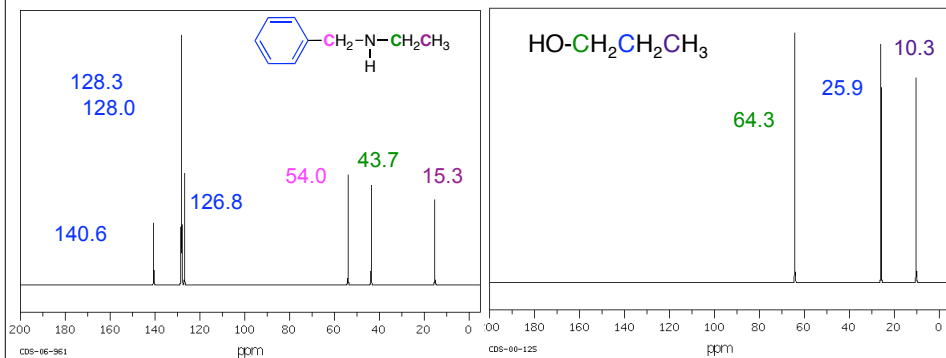
224

**<sup>1</sup>H NMR:** Nitrogen is less deshielding than oxygen. Hydrogens on the carbon attached to the amino nitrogen have a typical chemical shift of  $\delta$  2.2 - 3.0



225

**<sup>13</sup>C NMR:** The resonances of carbon attached to a nitrogen of an amine are deshielded about 20 ppm downfield from those of an alkane.



**Mass Spectrum: Nitrogen rule:** small organic compounds with an odd number of nitrogen atoms have an odd mass; compounds with an even number of nitrogen atoms have an even mass

226

