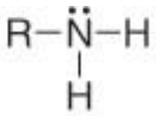
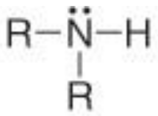
Amines

Introduction



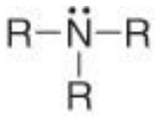
$R-\ddot{N}(H)-H$

1° amine
(1 R group on N)



$R-\ddot{N}(R)-H$

2° amine
(2 R groups on N)



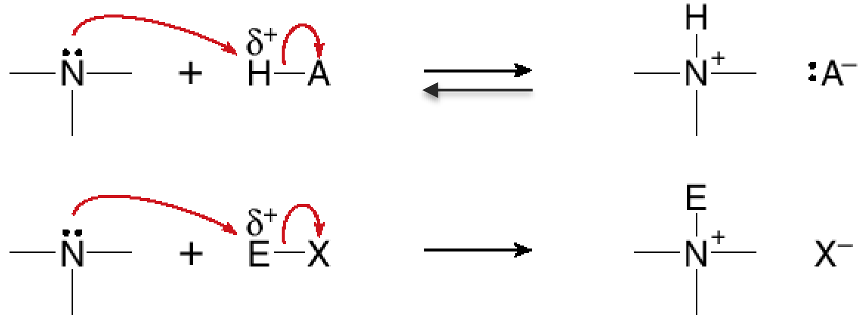
$R-\ddot{N}(R)-R$

3° amine
(3 R groups on N)

Amines are stronger bases and better nucleophiles than other neutral organic compounds.

Reaction as a base

Reaction as a nucleophile



E = an electrophilic site

quaternary ammonium salt

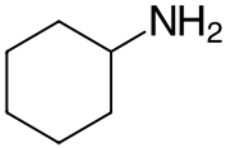
- **The chemistry of amines is dominated by the nonbonded electron pair on the nitrogen atom.**

Nomenclature

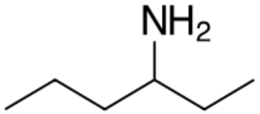
1ry Amines are named using either systematic or common names.

CH_3NH_2

methanamine
(methylamine)

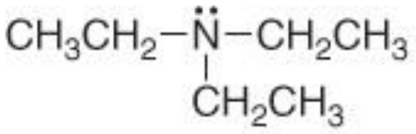


cyclohexanamine
(cyclohexylamine)



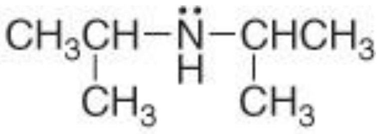
3-hexanamine

Secondary and tertiary amines having identical alkyl groups are named using the prefix di- or tri- with the name of the primary amine.



$CH_3CH_2-\underset{\underset{CH_2CH_3}{|}}{\ddot{N}}-CH_2CH_3$

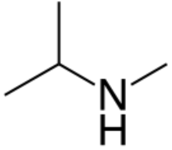
triethylamine



$CH_3\underset{\underset{CH_3}{|}}{CH}-\underset{H}{\ddot{N}}-\underset{\underset{CH_3}{|}}{C}HCH_3$

diisopropylamine

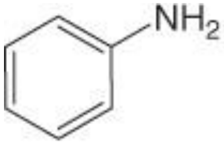
Secondary and 3° amines having more than one kind of alkyl group are named as *N*-substituted primary amines:



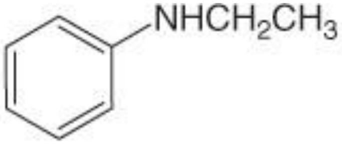
N-methyl-2-propanamine

Nomenclature

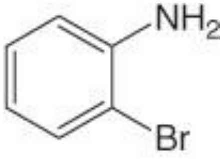
Aromatic amines are named as derivatives of aniline.



aniline

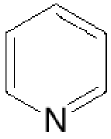


N-ethylaniline

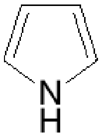


o-bromoaniline

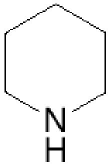
There are many different nitrogen heterocycles, each with a different name. The N atom is considered to be at position “1”.



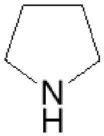
pyridine



pyrrole



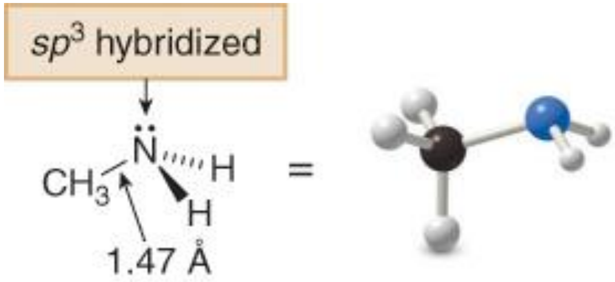
piperidine

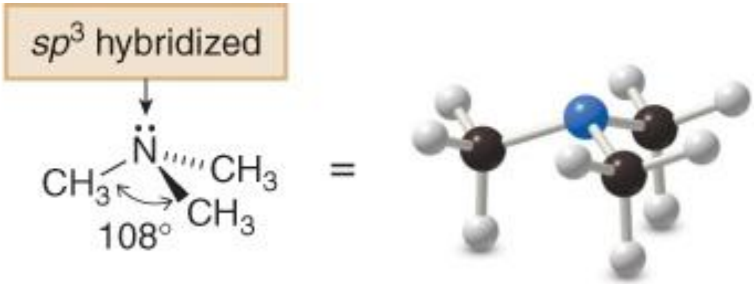


pyrrolidine

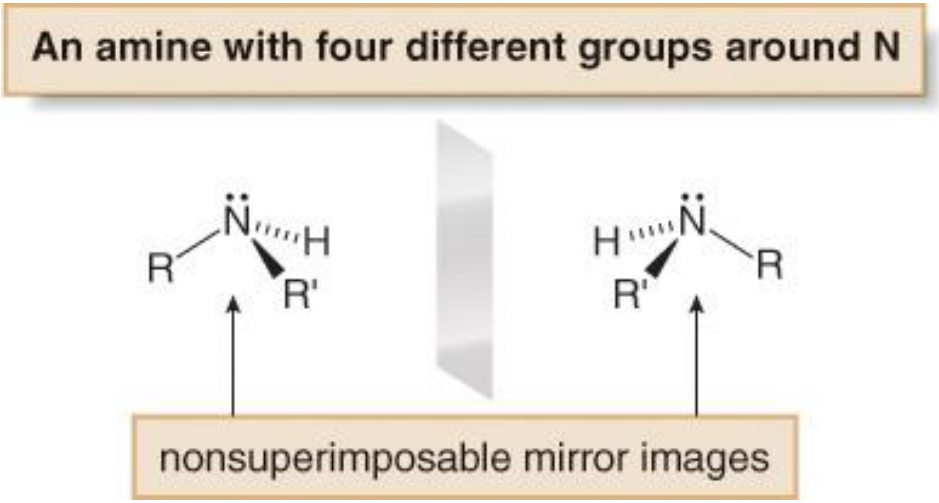
Structure and Bonding

An amine N atom is *sp*^{3} hybridized with trigonal pyramidal geometry, with bond angles of approximately 109.5°.



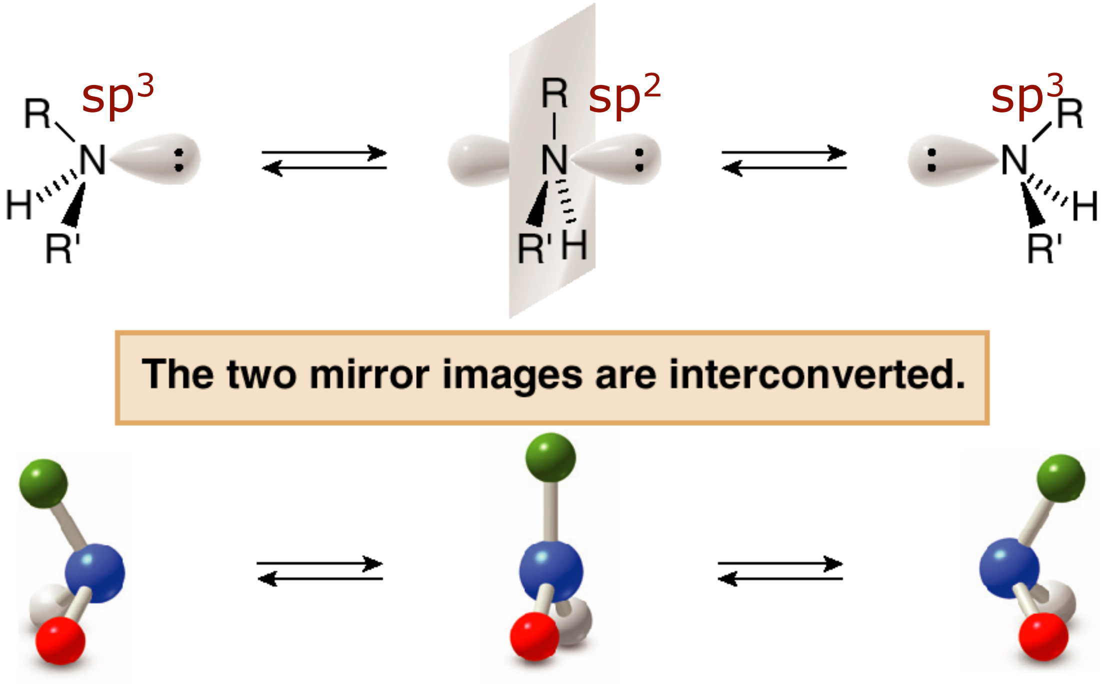


In case an amine nitrogen has four different groups around it, it is technically a stereogenic center.



Structure and Bonding

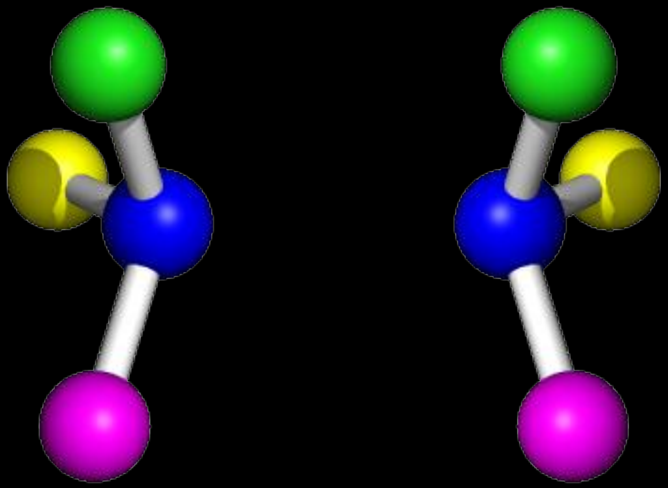
However, the chirality of the amine nitrogen can be ignored because the two enantiomers interconvert by passing through a trigonal planar (achiral) transition state.



The two mirror images are interconverted.

planar transition state

Inversion of Configuration in Amines

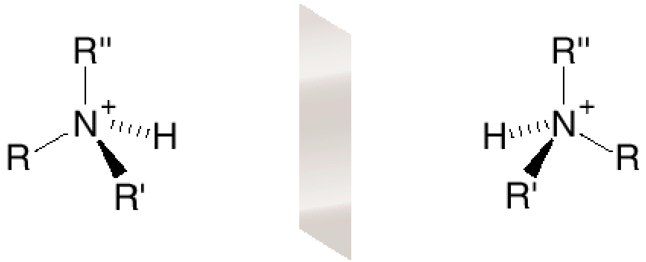


Ammonia inversion

Structure and Bonding

In contrast, the chirality of a quaternary ammonium salt with four different groups cannot be ignored. Because there is no nonbonded electron pair on the nitrogen atom, interconversion cannot occur, and the N atom is just like a carbon atom with four different groups around it.

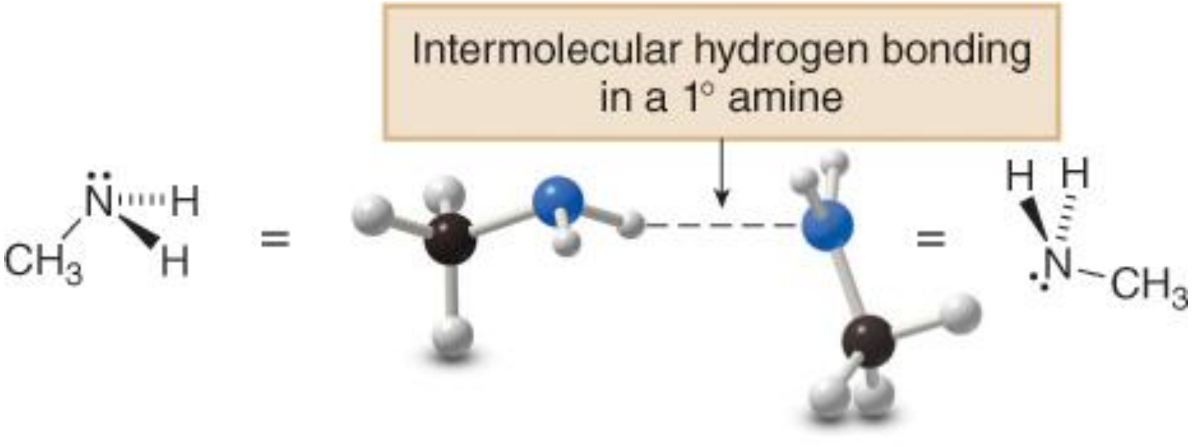
Two enantiomers of a quaternary ammonium salt



- The N atom of a quaternary ammonium salt is a stereogenic center when N is surrounded by four different groups.

Physical Properties

- Amines exhibit dipole-dipole interactions because of the polar C—N and N—H bonds.
- Primary and 2° amines are capable of intermolecular hydrogen bonding because they contain N—H bonds.



Physical Properties

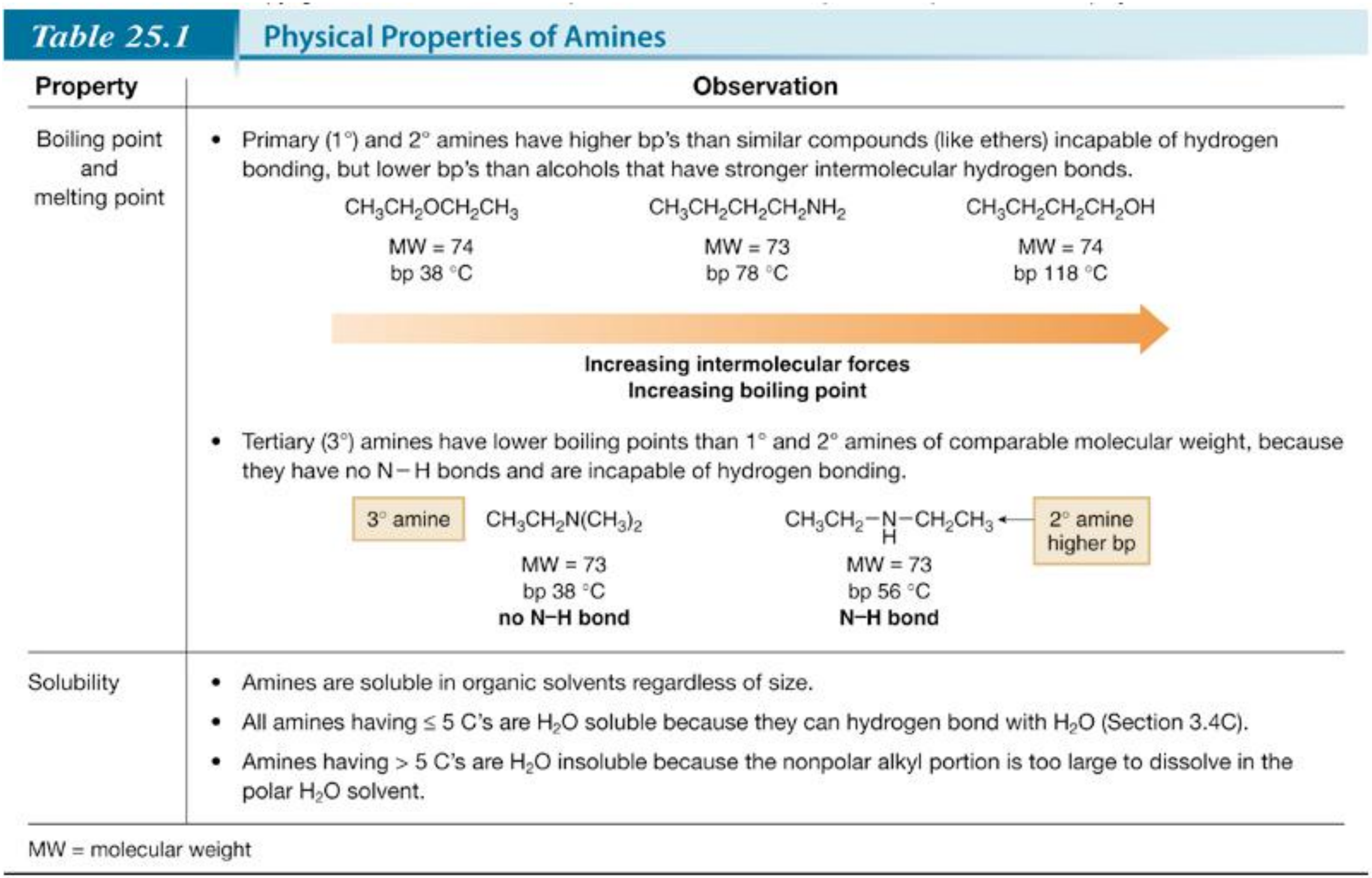


Table 25.1 Physical Properties of Amines

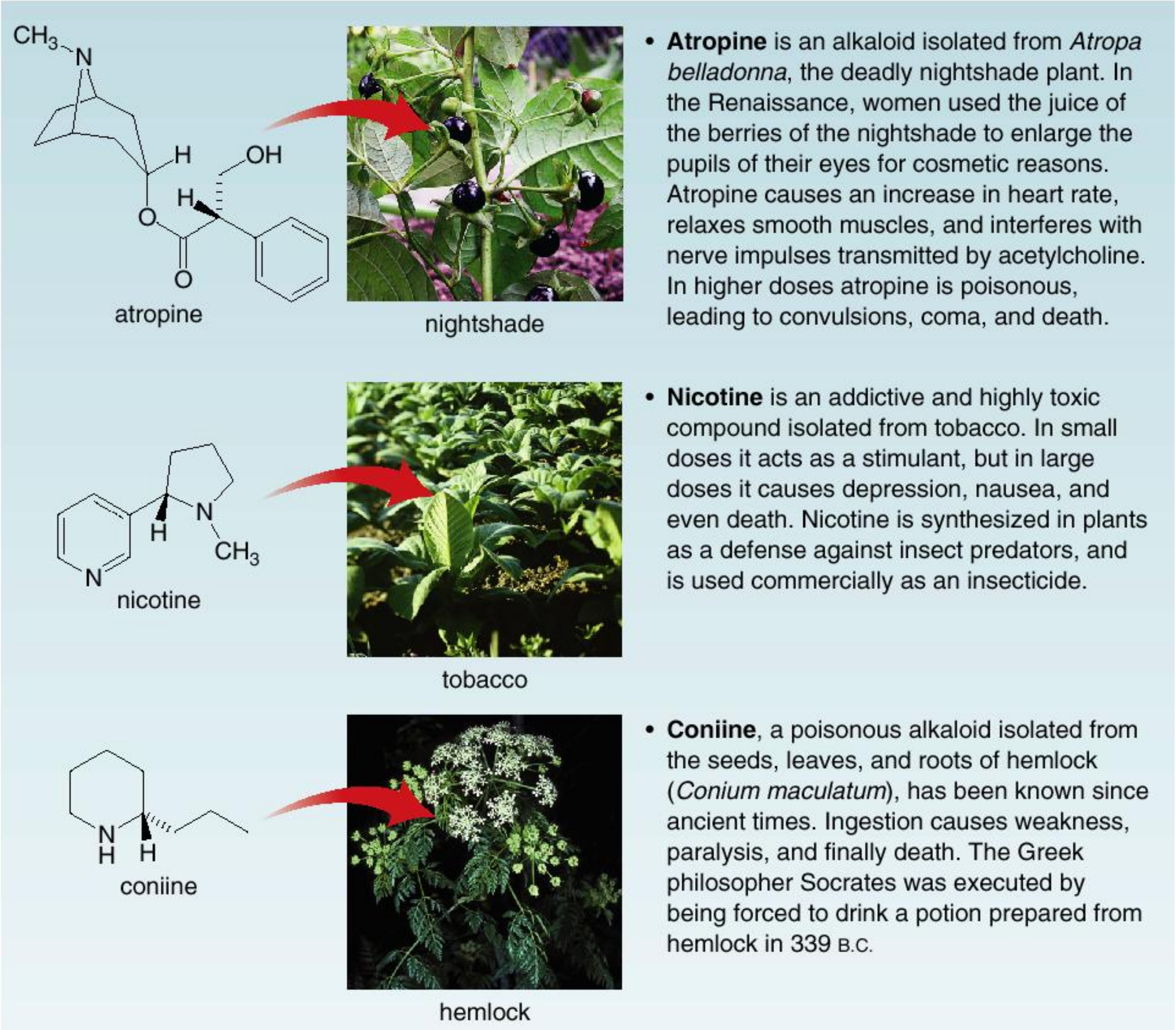
Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amines have higher bp's than similar compounds (like ethers) incapable of hydrogen bonding, but lower bp's than alcohols that have stronger intermolecular hydrogen bonds. $CH_3CH_2OCH_2CH_3$ MW = 74 bp 38 °C $CH_3CH_2CH_2CH_2NH_2$ MW = 73 bp 78 °C $CH_3CH_2CH_2CH_2OH$ MW = 74 bp 118 °C **Increasing intermolecular forces** **Increasing boiling point** • Tertiary (3°) amines have lower boiling points than 1° and 2° amines of comparable molecular weight, because they have no N–H bonds and are incapable of hydrogen bonding. 3° amine $CH_3CH_2N(CH_3)_2$ MW = 73 bp 38 °C **no N–H bond** $CH_3CH_2-\underset{H}{N}-CH_2CH_3$ MW = 73 bp 56 °C **N–H bond** ← 2° amine higher bp
Solubility	• Amines are soluble in organic solvents regardless of size. • All amines having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • Amines having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

MW = molecular weight

Interesting and Useful Amines

- Many low molecular weight amines have foul odors.
- Trimethylamine [$(CH_3)_3N$], formed when enzymes break down certain fish proteins, has the characteristic odor of rotting fish.
- Putrescine ($H_2NCH_2CH_2CH_2CH_2NH_2$) and cadaverine ($H_2NCH_2CH_2CH_2CH_2CH_2NH_2$) are both poisonous diamines with putrid odors. They too are present in rotting fish, and are partly responsible for the odors of semen, urine, and bad breath.
- Naturally occurring amines derived from plant sources are called alkaloids.

Interesting and Useful Amines



atropine

nightshade

- **Atropine** is an alkaloid isolated from *Atropa belladonna*, the deadly nightshade plant. In the Renaissance, women used the juice of the berries of the nightshade to enlarge the pupils of their eyes for cosmetic reasons. Atropine causes an increase in heart rate, relaxes smooth muscles, and interferes with nerve impulses transmitted by acetylcholine. In higher doses atropine is poisonous, leading to convulsions, coma, and death.

nicotine

tobacco

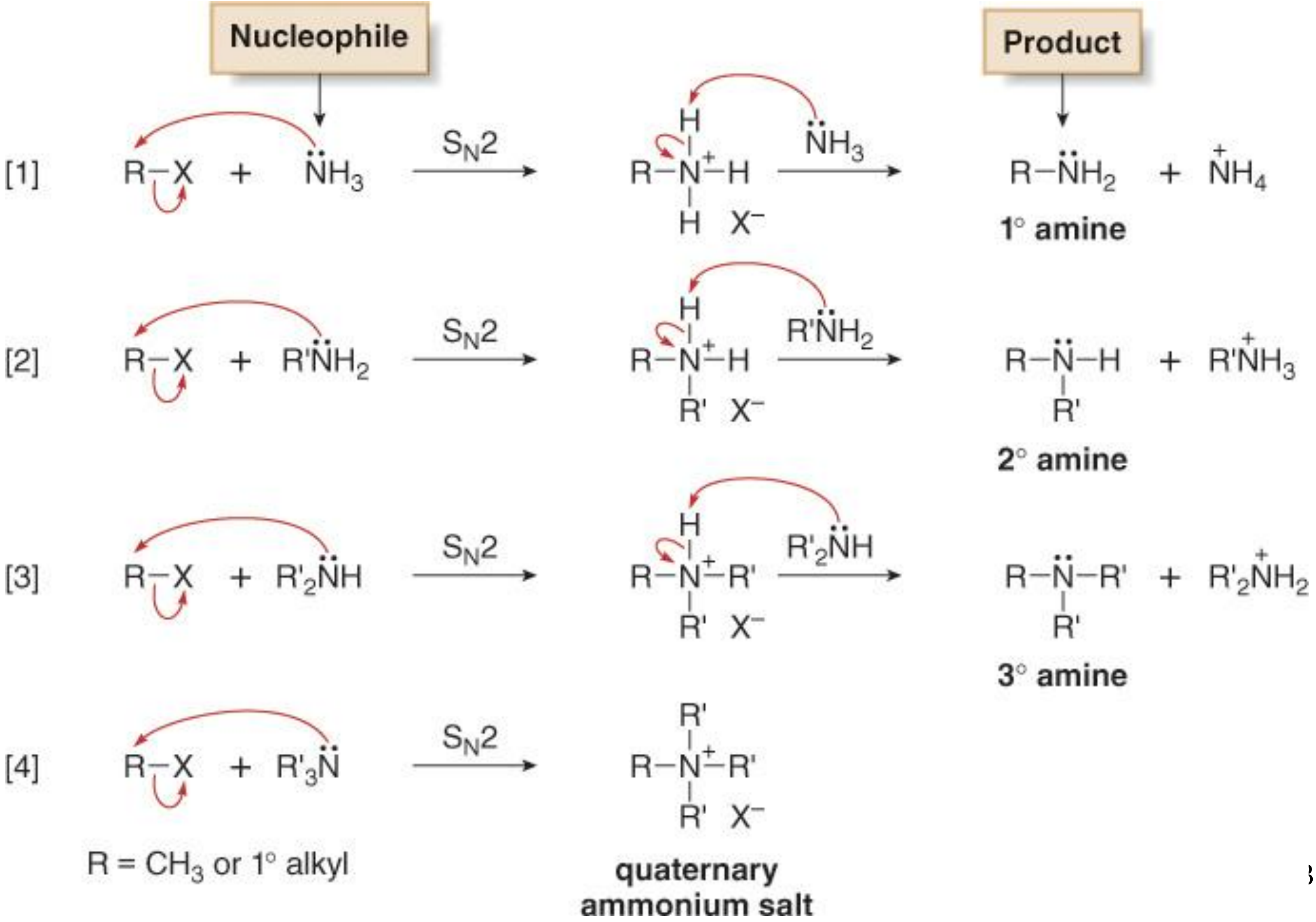
- **Nicotine** is an addictive and highly toxic compound isolated from tobacco. In small doses it acts as a stimulant, but in large doses it causes depression, nausea, and even death. Nicotine is synthesized in plants as a defense against insect predators, and is used commercially as an insecticide.

coniine

hemlock

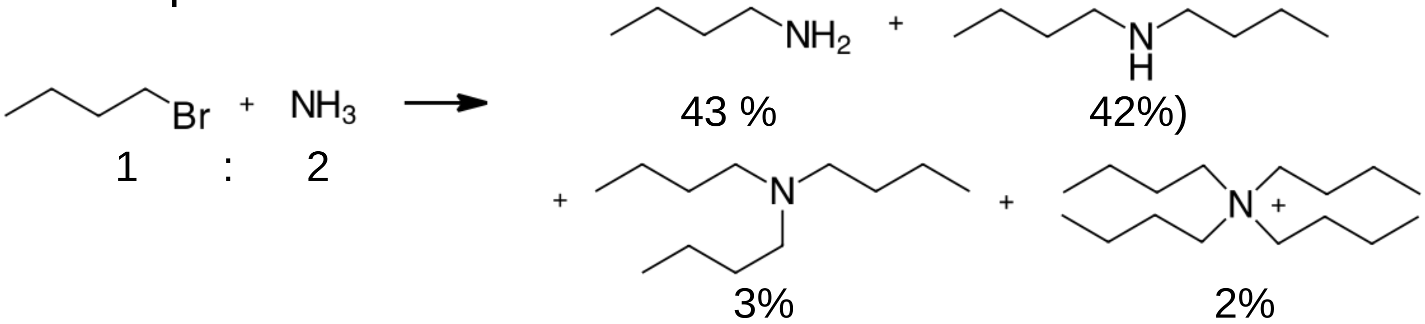
- **Coniine**, a poisonous alkaloid isolated from the seeds, leaves, and roots of hemlock (*Conium maculatum*), has been known since ancient times. Ingestion causes weakness, paralysis, and finally death. The Greek philosopher Socrates was executed by being forced to drink a potion prepared from hemlock in 339 B.C.

Preparation of Amines—Direct Nucleophilic Substitution



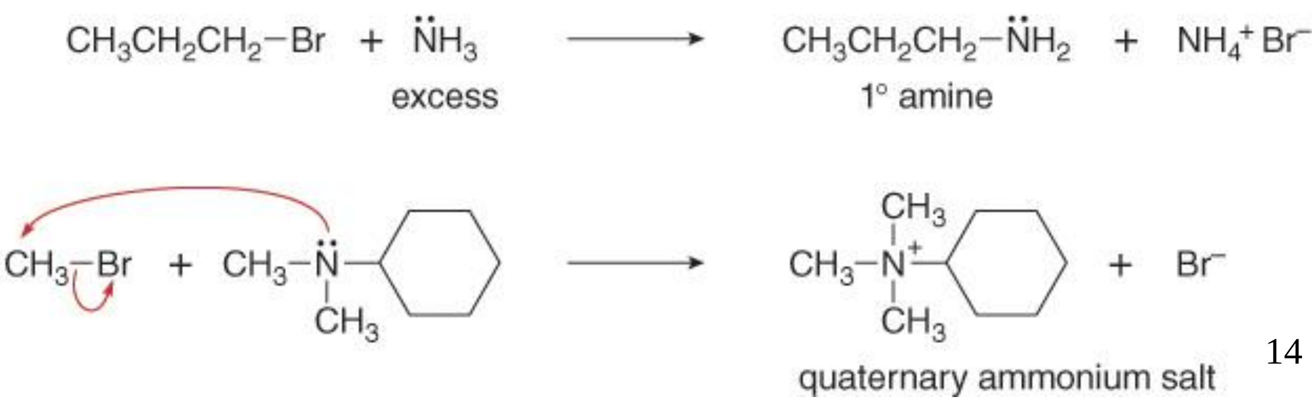
Preparation of Amines—Direct Nucleophilic Substitution

Although the process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness.



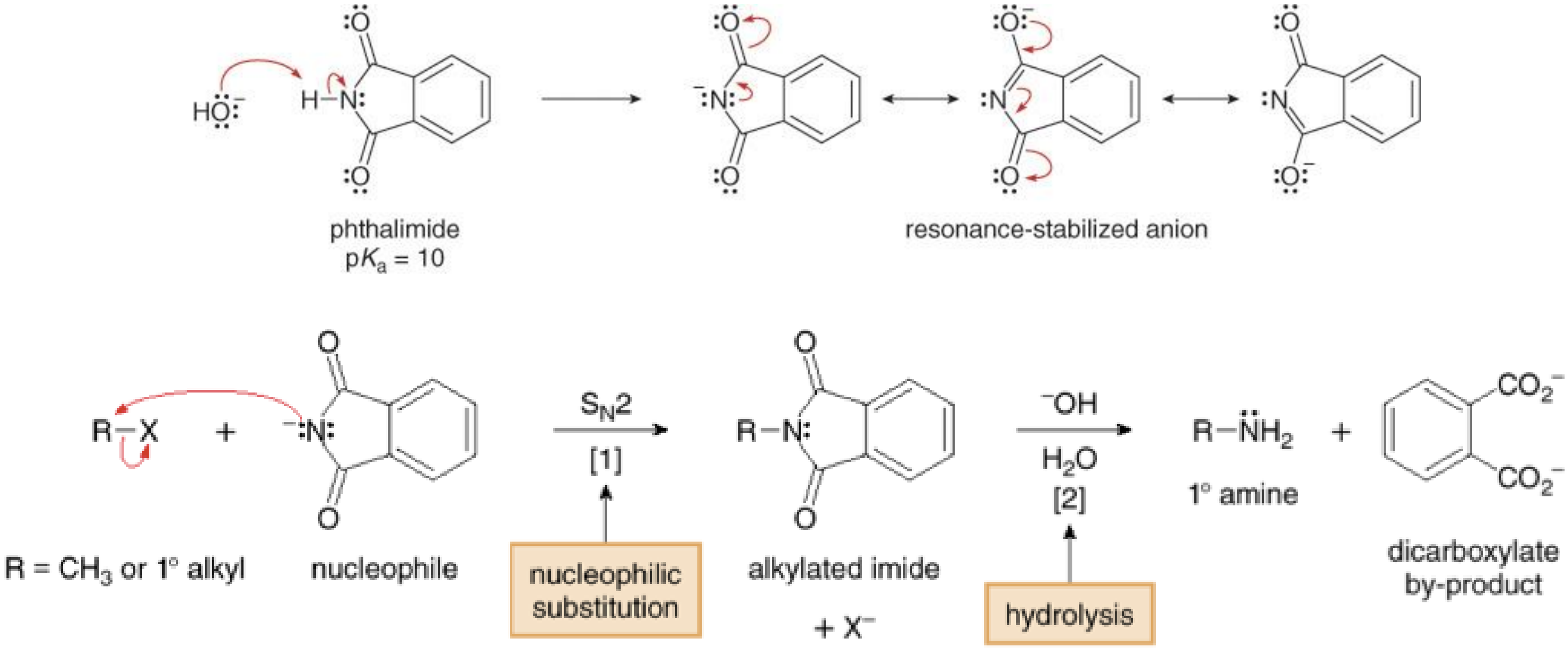
Consequently, the reaction is most useful in preparing 1^{ry} amines by using a large excess of NH_3, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.

Useful S_N2 substitutions



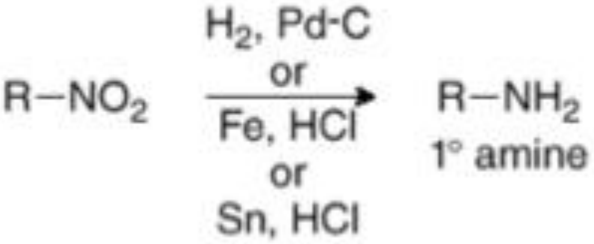
Preparation of Amines—Gabriel Synthesis of 1^{ry} Amines

The Gabriel synthesis is comprised of two steps and uses a nucleophile derived from phthalimide to synthesize 1^{ry} amines via nucleophilic substitution.



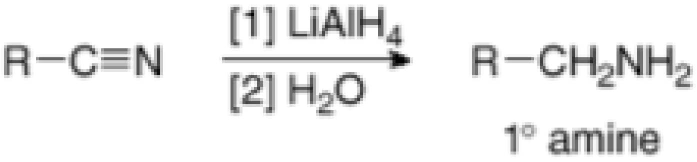
Preparation of Amines—Reduction of N-Containing Functional Groups

Nitro groups are reduced to 1° amines using a variety of reducing agents.



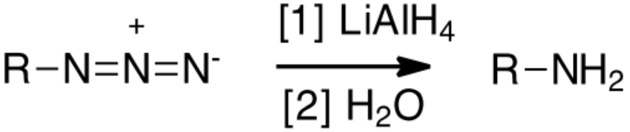
$$R{-}NO_2 \xrightarrow[\text{Fe, HCl or Sn, HCl}]{H_2\text{, Pd-C or}} \underset{\text{1° amine}}{R{-}NH_2}$$

Nitriles are reduced to 1° amines with LiAlH$_4$.



$$R{-}C{\equiv}N \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} \underset{\text{1° amine}}{R{-}CH_2NH_2}$$

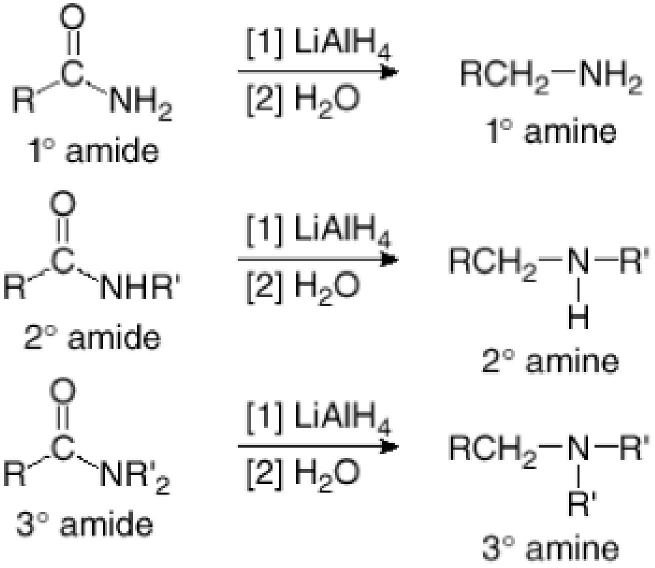
Azides are reduced to 1° amines with LiAlH$_4$



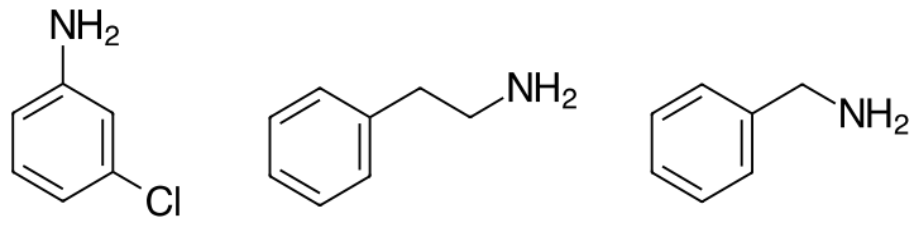
$$R{-}N{=}\overset{+}{N}{=}N^{-} \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} R{-}NH_2$$

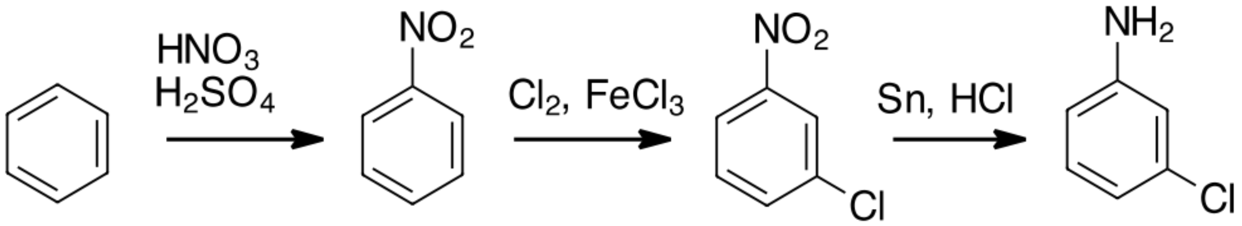
Preparation of Amines—Reduction of N-Containing Functional Groups

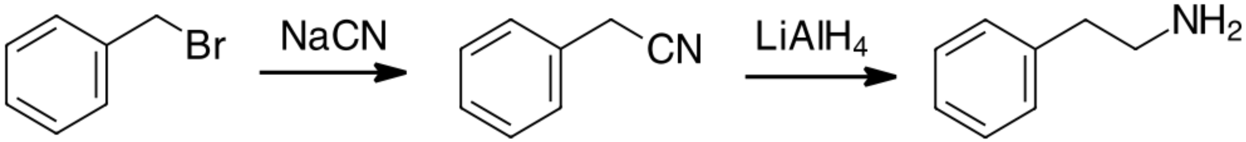
Primary (1°), 2°, and 3° amides are reduced to 1°, 2°, and 3° amines, respectively, by using $LiAlH_4$.

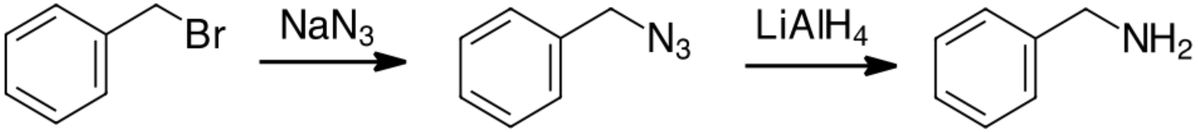


Preparation of Amines—Reduction of N-Containing Functional Groups



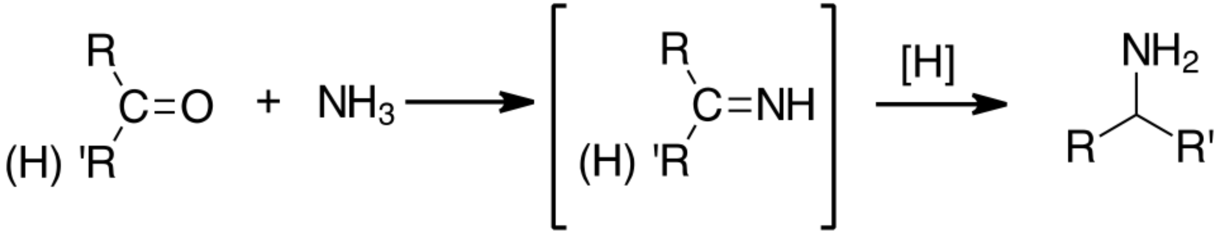




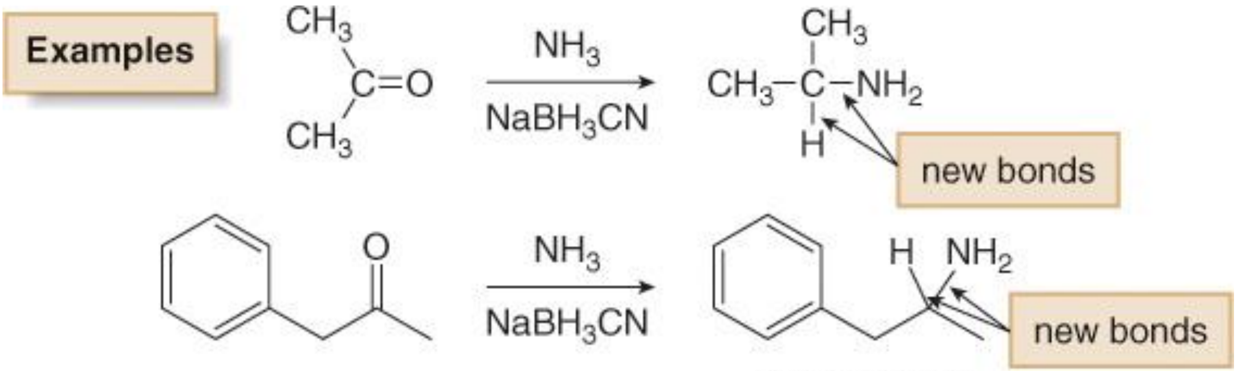


Preparation of Amines—Reductive Amination

Reductive amination is a two-step method that converts aldehydes and ketones into 1^{ry}, 2^{ry}, and 3^{ry} amines.



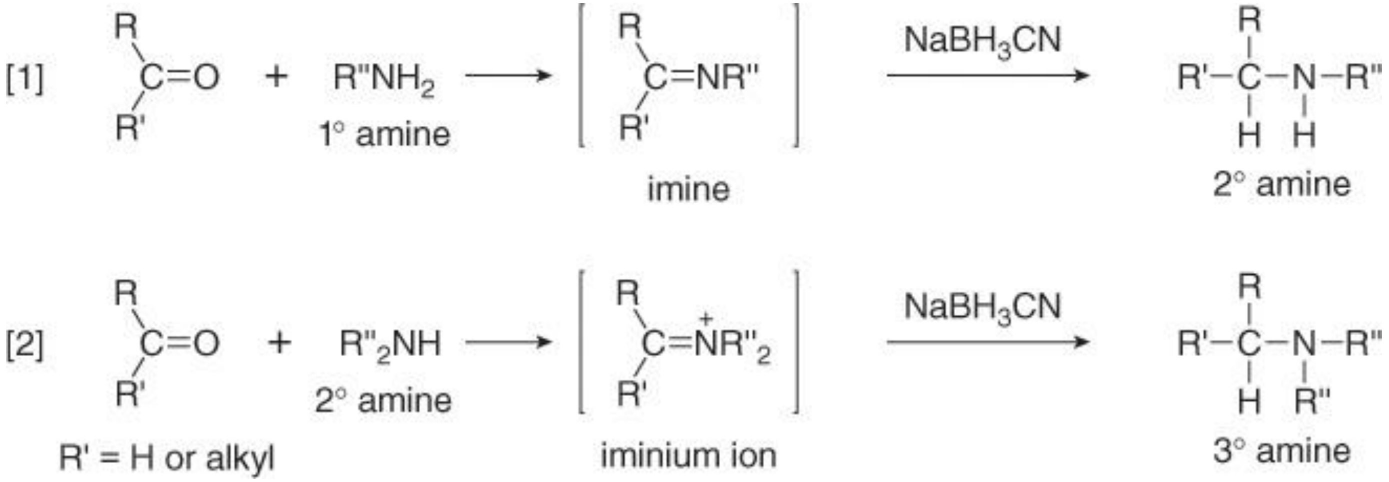
imine



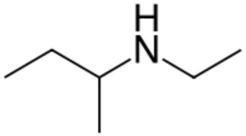
amphetamine
a powerful stimulant

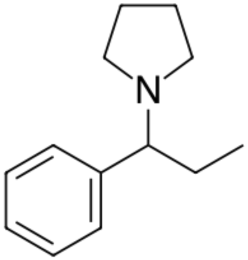
Preparation of Amines—Reductive Amination

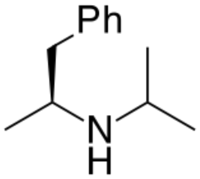
With a 1^{ry} or 2^{ry} amine as starting material, reductive amination is used to prepare 2^{ry} and 3^{ry} amines respectively.



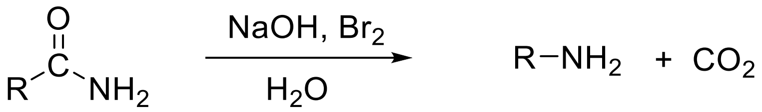
Preparation of Amines—Reductive Amination



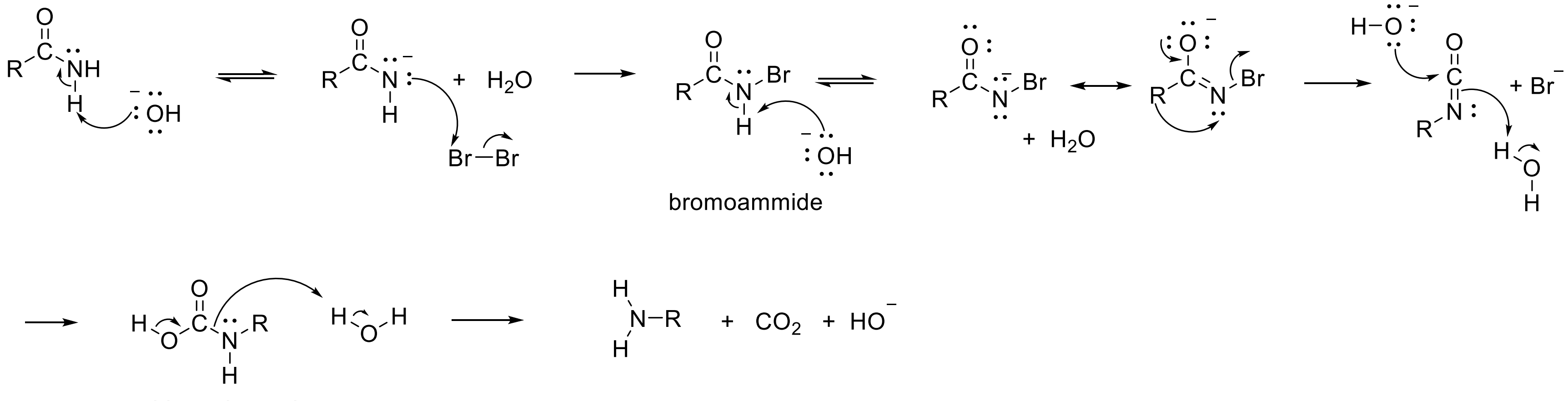




TRASPOSIZIONE DI HOFMANN



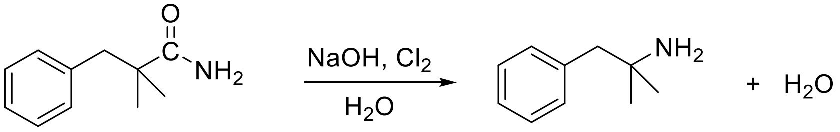
meccanismo



bromoammide

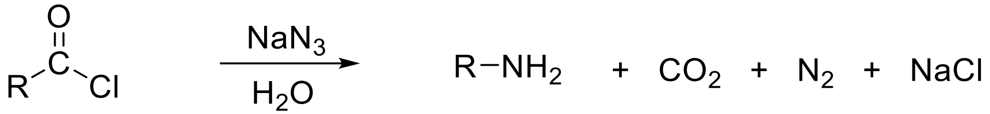
acido carbammico

esempio

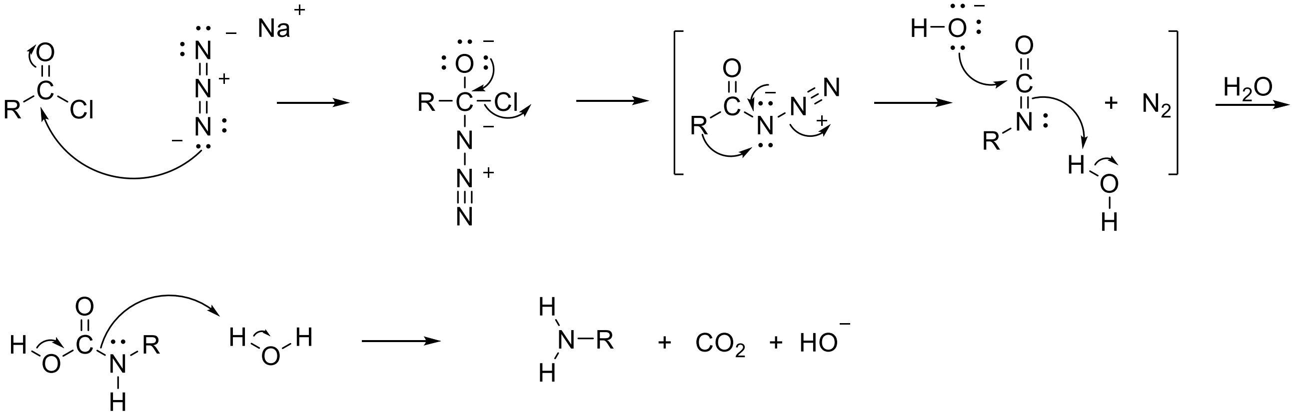


fentermina

TRASPOSIZIONE DI CURTIUS



meccanismo

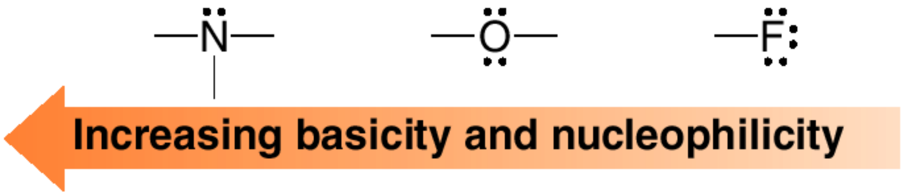


acido carbammico

Reactions of Amines—General Features

- The chemistry of amines is dominated by the lone pair of electrons on nitrogen.

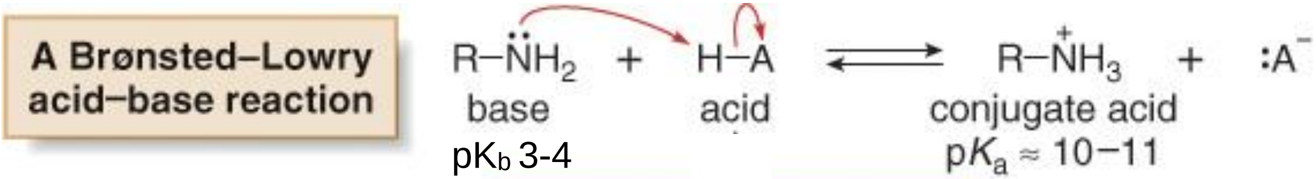
- Only three elements in the second row of the periodic table have nonbonded electron pairs in neutral organic compounds: nitrogen, oxygen and fluorine. Because basicity and nucleophilicity decrease across a row, nitrogen is the most basic and the most nucleophilic.



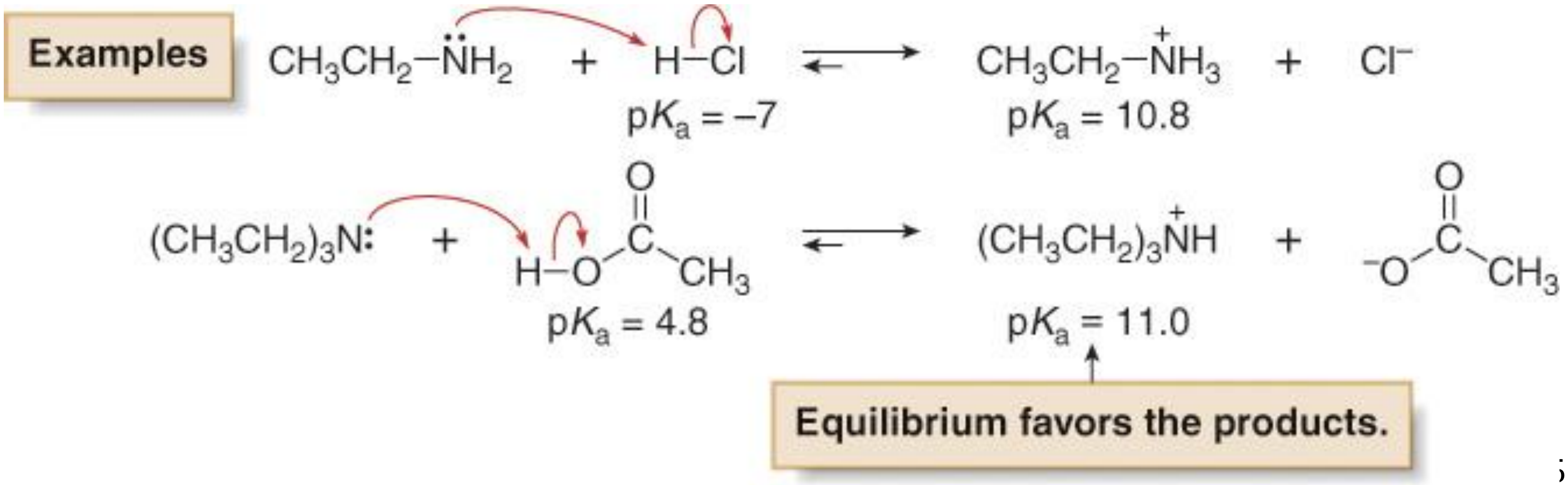
- Amines are stronger bases and nucleophiles than other neutral organic compounds.

Amines as Bases

Amines react with a variety of organic and inorganic acids.

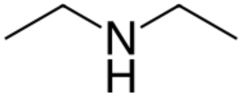
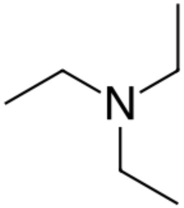


pK_b 3-4



Structural Effects on Amine Basicity
1. Inductive Effects

1°, 2°, and 3° alkylamines are more basic than NH_3 because of the electron-donating inductive effect of the R groups.

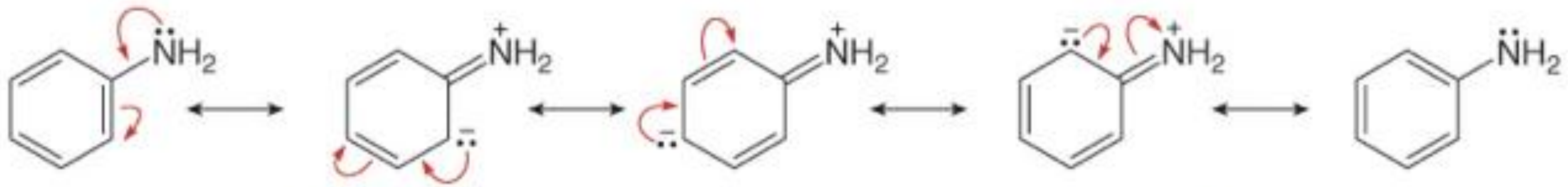
	NH_3			
pK_a (conjugate acid)	9.3	10.8	11.1	11.0

Amines as Bases

Arylamines are less basic than alkylamines because the electron pair on N is delocalized.

The electron pair is localized on the N atom.

$CH_3CH_2NH_3^+$:   pK$_a$ 10.8

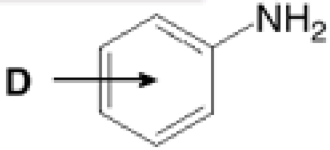


The electron pair is delocalized on the benzene ring.

$C_6H_5NH_3^+$:   pK$_a$ 4.6

Substituted Anilines

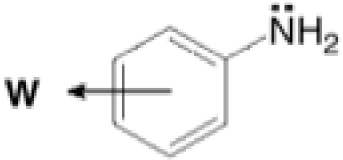
D = electron-donor group



D makes the amine more basic than aniline.

D
$-NH_2$
$-OH$
$-OR$
$-NHCOR$
$-R$

W = electron-withdrawing group

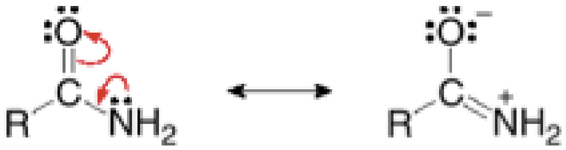


W makes the amine less basic than aniline.

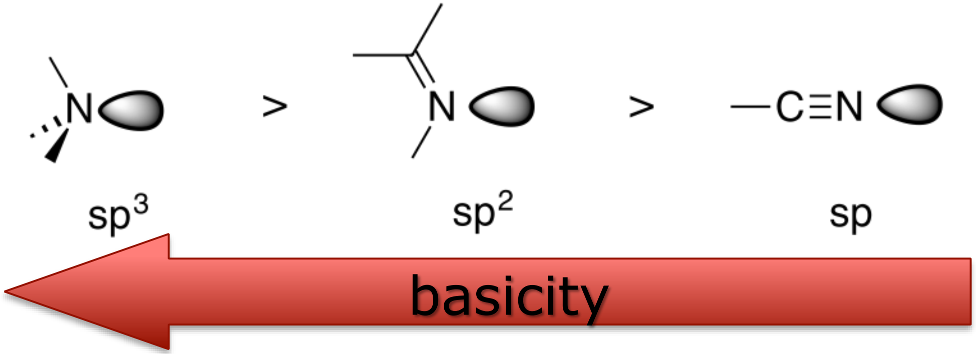
W
$-X$
$-CHO$
$-COR$
$-COOR$
$-COOH$
$-CN$
$-SO_3H$
$-NO_2$
$-NR_3^+$

Amides, Imines, Nitriles

Amides are much less basic than amines because the electron pair on N is delocalised



Imines and nitriles are less basic than amines because the electron pair on N is in an sp^2 and sp orbital, respectively.



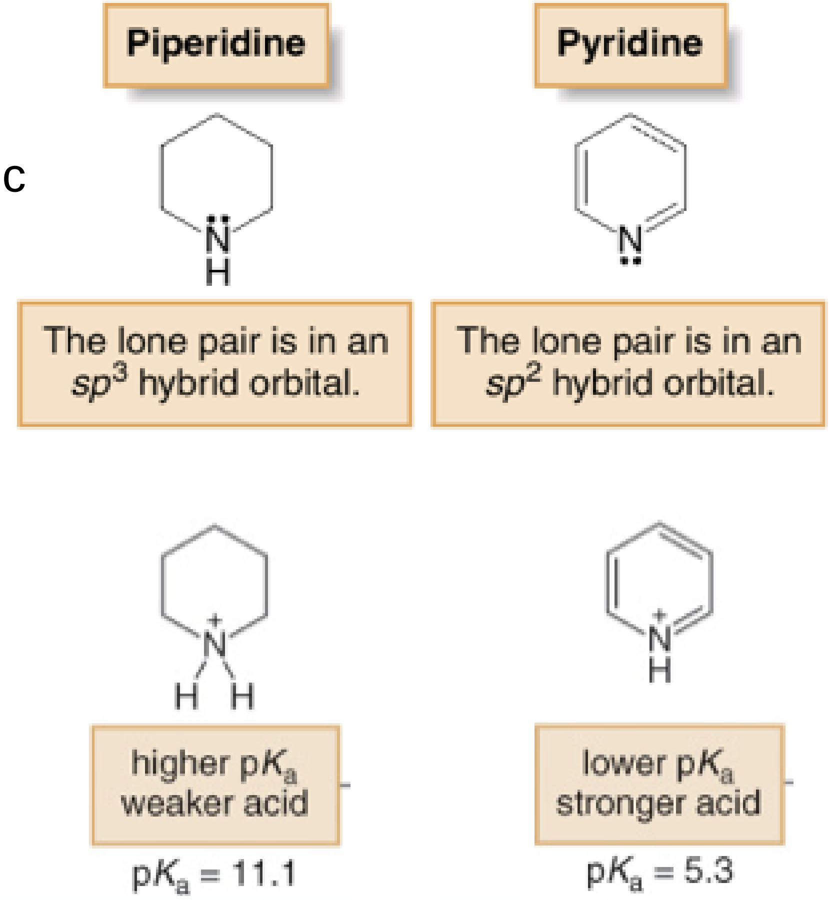
sp^3 orbitals are farther from the nucleus and therefore more available; sp orbitals are nearer to the nucleus and therefore less available.

Heterocyclic Amines

1. Hybridization

more basic

less basic



Piperidine

The lone pair is in an *sp*^{3} hybrid orbital.

higher pK_a
weaker acid

pK_a = 11.1

Pyridine

The lone pair is in an *sp*^{2} hybrid orbital.

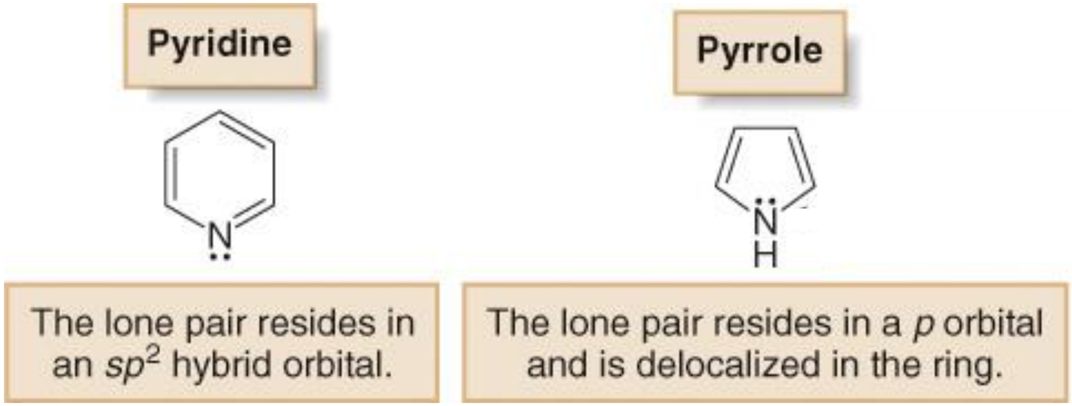
lower pK_a
stronger acid

pK_a = 5.3

- **The higher the percent *s*-character of the orbital containing the lone pair, the more tightly the lone pair is held, and the weaker the base.**

Heterocyclic Amines

2. Aromaticity



Pyridine

The lone pair resides in an *sp*^{2} hybrid orbital.

Pyrrole

The lone pair resides in a *p* orbital and is delocalized in the ring.

pK_a 5.3

pK_a 0.4

- **Pyrrole is much less basic than pyridine because its lone pair of electrons is part of the aromatic π system.**

Amines as Bases

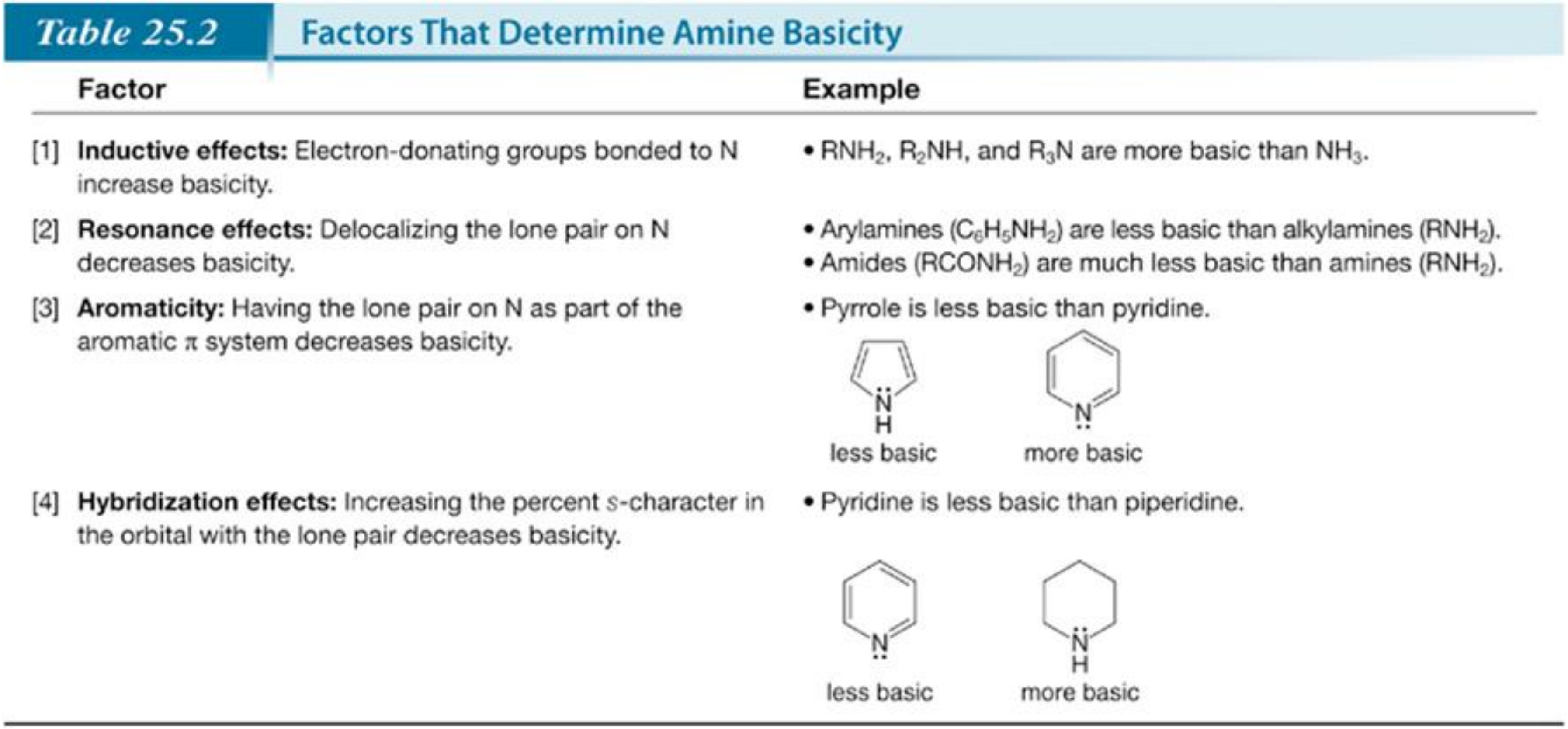


Table 25.2 **Factors That Determine Amine Basicity**

	Factor	Example
[1]	**Inductive effects:** Electron-donating groups bonded to N increase basicity.	• RNH_2, R_2NH, and R_3N are more basic than NH_3.
[2]	**Resonance effects:** Delocalizing the lone pair on N decreases basicity.	• Arylamines ($C_6H_5NH_2$) are less basic than alkylamines (RNH_2). • Amides ($RCONH_2$) are much less basic than amines (RNH_2).
[3]	**Aromaticity:** Having the lone pair on N as part of the aromatic π system decreases basicity.	• Pyrrole is less basic than pyridine. less basic more basic
[4]	**Hybridization effects:** Increasing the percent *s*-character in the orbital with the lone pair decreases basicity.	• Pyridine is less basic than piperidine. less basic more basic

Amines as Bases

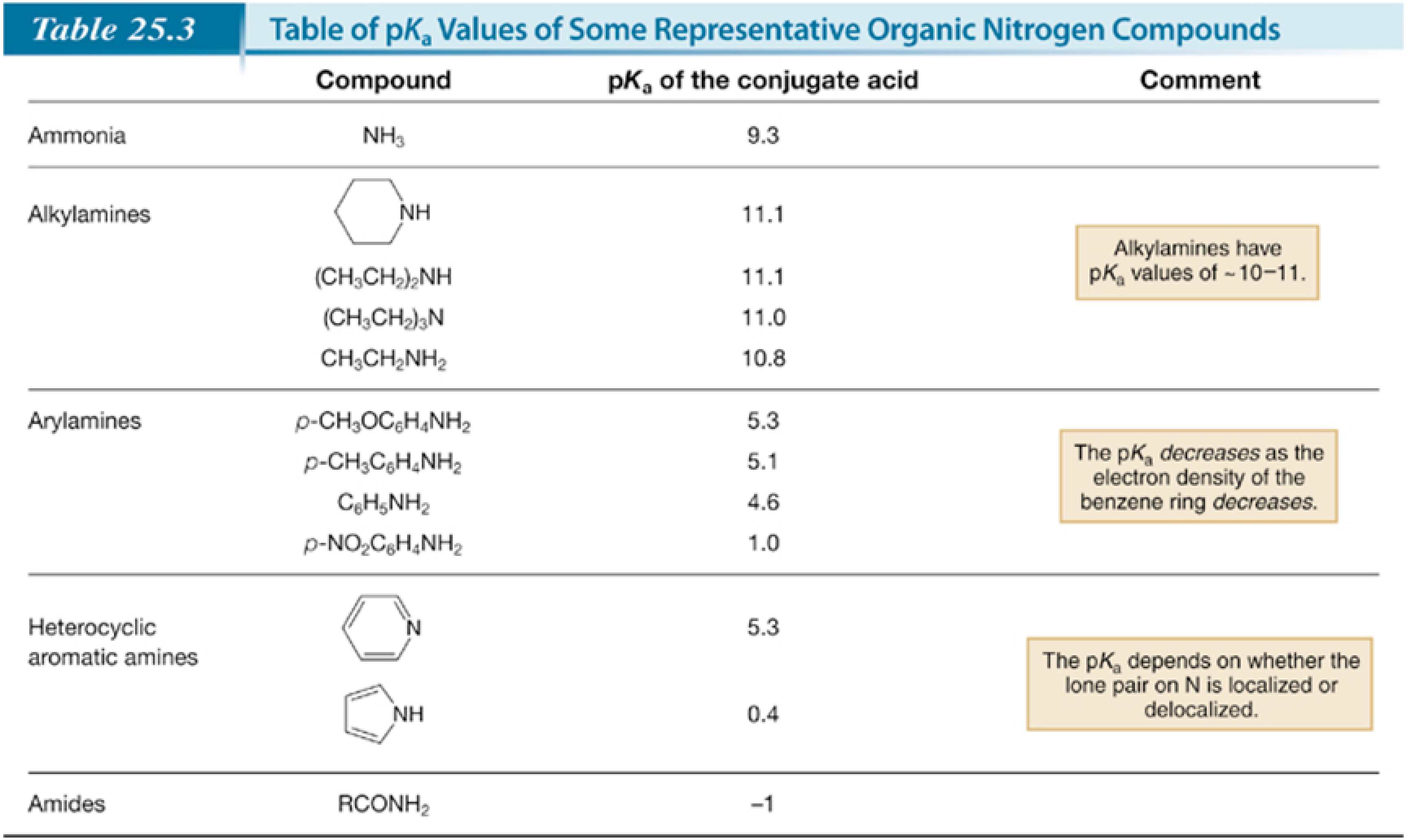
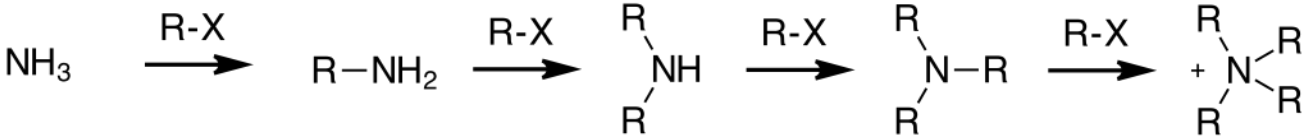


Table 25.3 Table of pK_a Values of Some Representative Organic Nitrogen Compounds

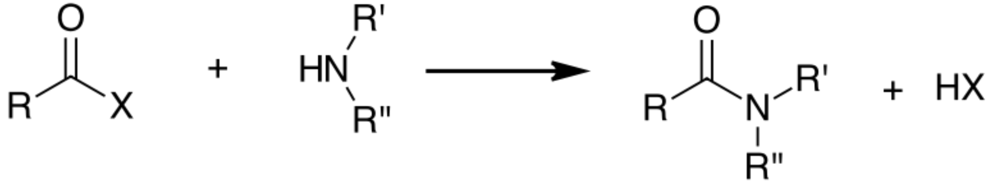
	Compound	pK_a of the conjugate acid	Comment
Ammonia	NH_3	9.3	
Alkylamines	NH	11.1	Alkylamines have pK_a values of ~10–11.
	$(CH_3CH_2)_2NH$	11.1	
	$(CH_3CH_2)_3N$	11.0	
	$CH_3CH_2NH_2$	10.8	
Arylamines	*p*-$CH_3OC_6H_4NH_2$	5.3	The pK_a *decreases* as the electron density of the benzene ring *decreases*.
	p-$CH_3C_6H_4NH_2$	5.1	
	$C_6H_5NH_2$	4.6	
	p-$NO_2C_6H_4NH_2$	1.0	
Heterocyclic aromatic amines	N	5.3	The pK_a depends on whether the lone pair on N is localized or delocalized.
	NH	0.4	
Amides	$RCONH_2$	−1	

Amines as Nucleophiles

alkylation (any amine):

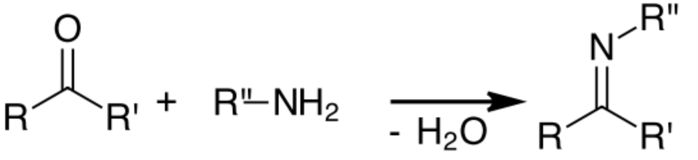


acylation:



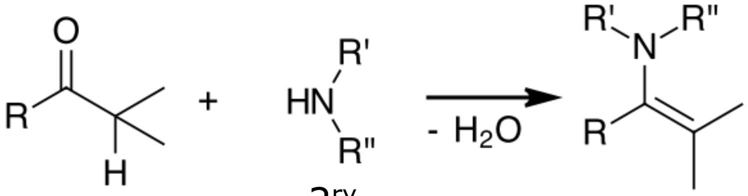
X = Cl, OCOR, OR', OH NH_3, 1^{ry}, 2^{ry} 1^{ry}, 2^{ry}, 3^{ry}

condensation with aldehydes and ketones:



NH_3, 1^{ry}

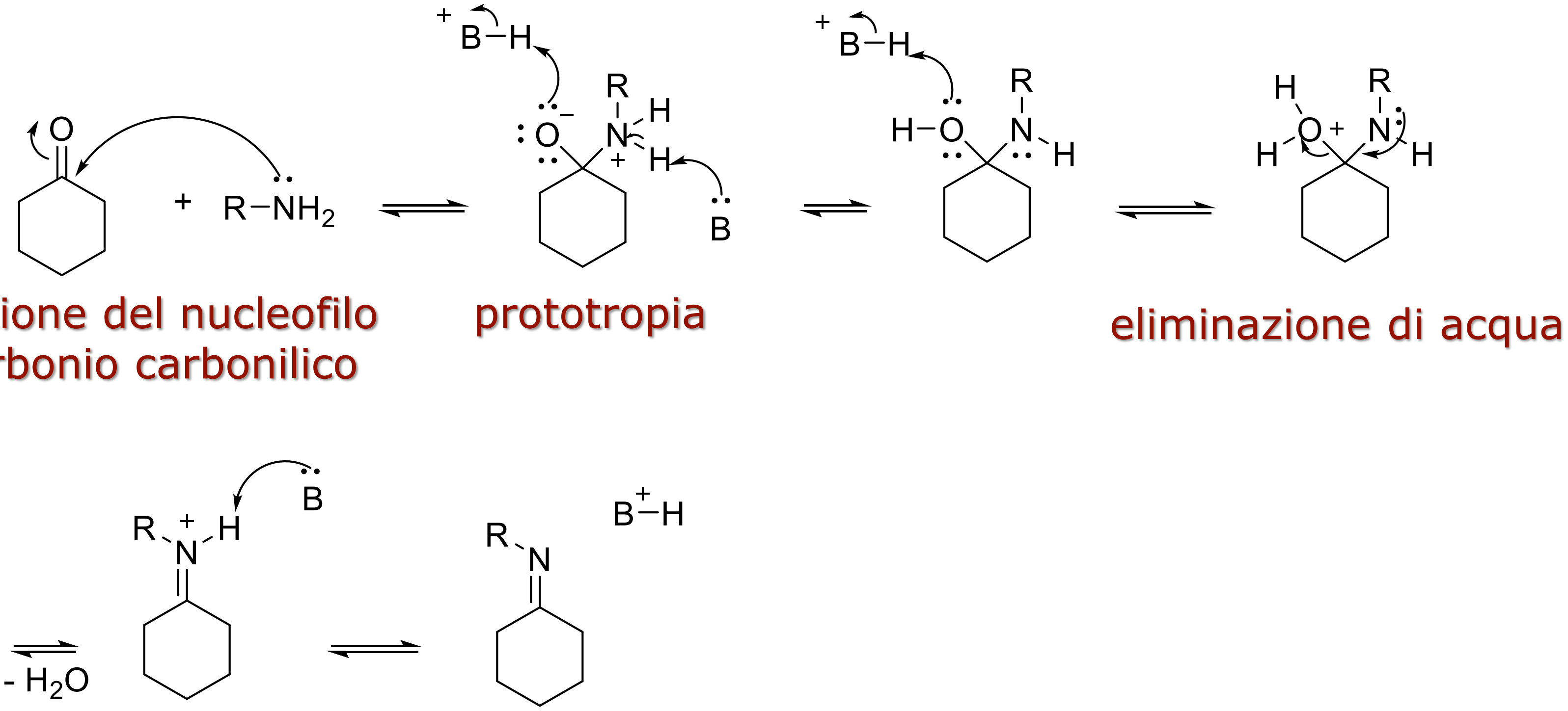
immina



2^{ry}

enammina

meccanismo con ammine primarie



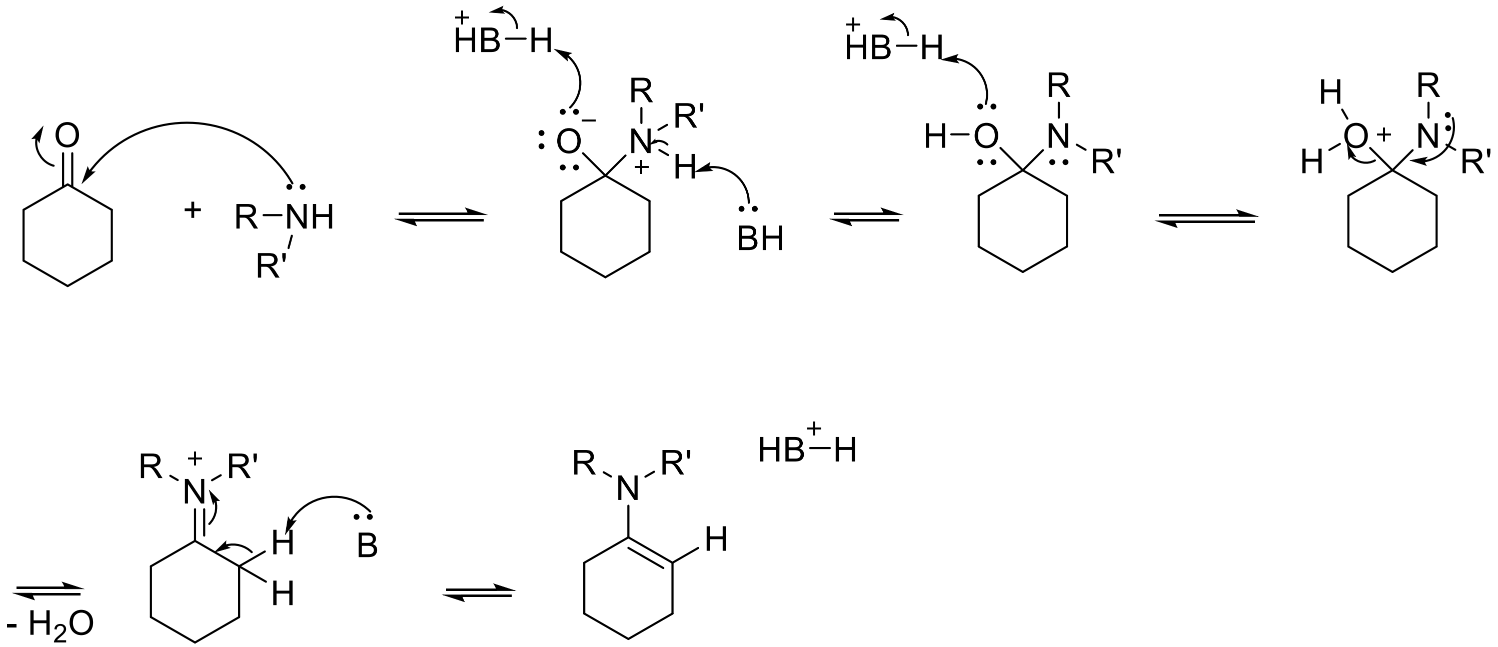
addizione del nucleofilo al carbonio carbonilico

prototropia

eliminazione di acqua

immina

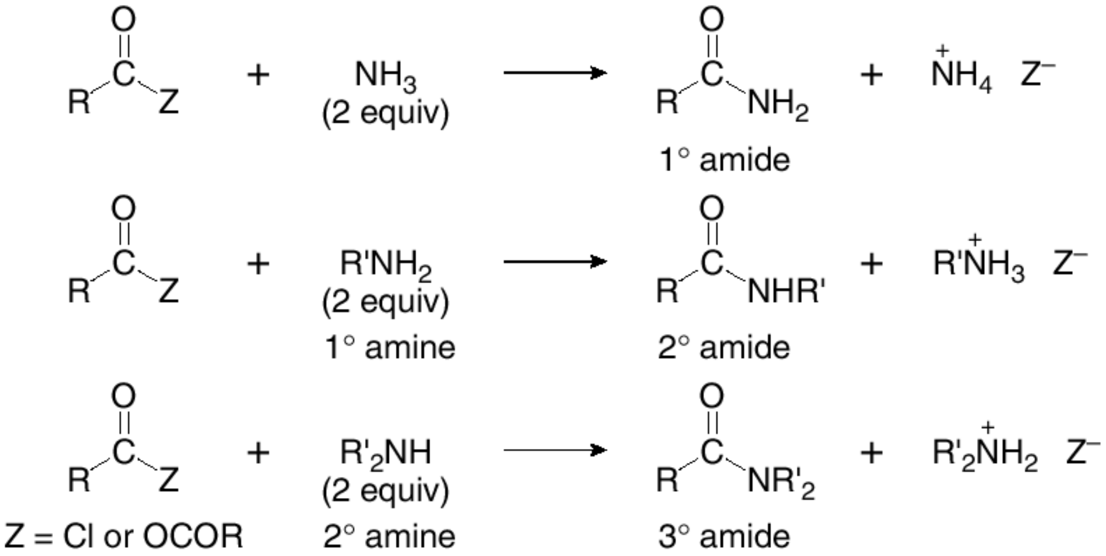
meccanismo con ammine secondarie



enammina

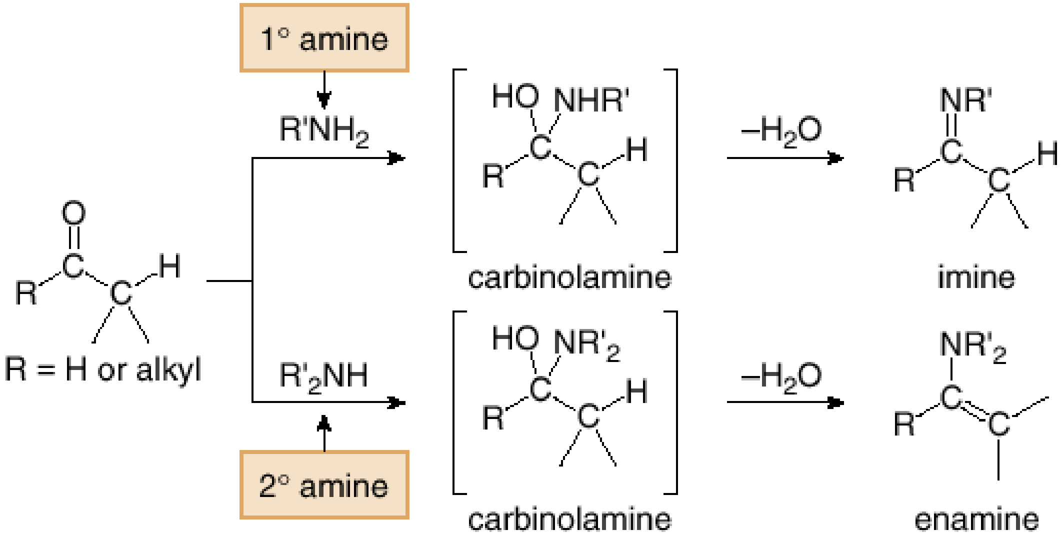
Amines as Nucleophiles. Acylation

Acid chlorides and anhydrides react with NH_3, 1° amines, and 2° amines to form **1°, 2°, and 3° amides,** respectively. These reactions involve attack of the nitrogen nucleophile on the carbonyl group followed by elimination of a leaving group (Cl^- or $RCOO^-$). The overall result of this reaction is substitution of the leaving group by the nitrogen nucleophile.



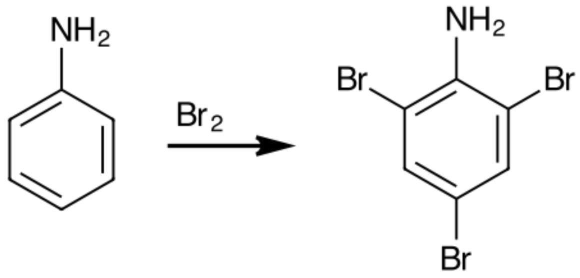
Amines as Nucleophiles. Reaction with Aldehydes and Ketones

Aldehydes and ketones react with 1° amines to form **imines** and with 2° amines to form **enamines.** Both reactions involve nucleophilic addition of the amine to the carbonyl group to form a carbinolamine, which then loses water to form the final product.



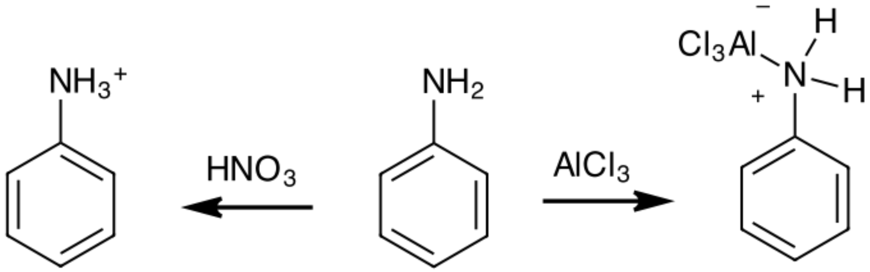
SEAr of Aromatic Amines

The amino group is the strongest neutral activating group



1. It is impossible to stop the reaction at the monobromination step

The amino group reacts with electrophiles

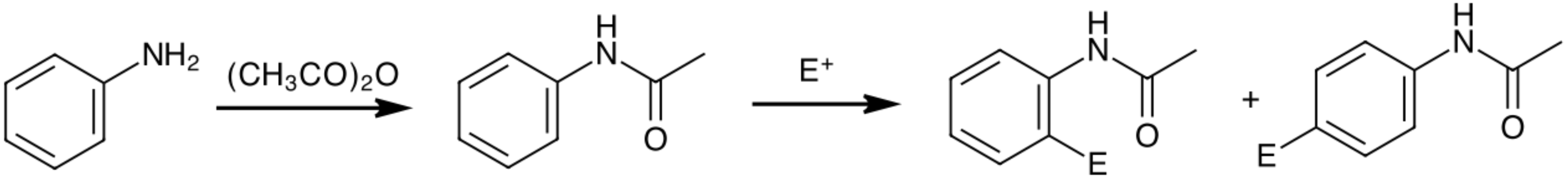


strongly deactivated

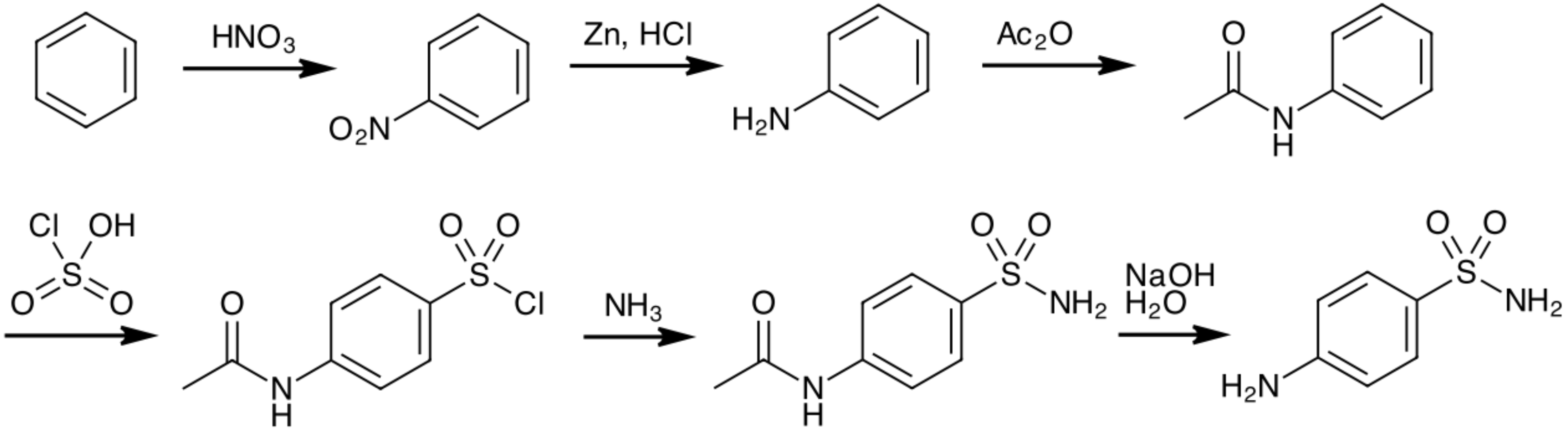
2. Aniline does not react under acid (Broensted or Lewis) conditions

SEAr of Aromatic Amines. Protection

- The conversion of amines to amides is useful in the synthesis of substituted anilines.



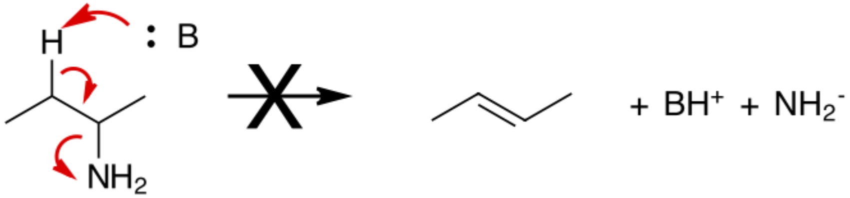
less basic
less nucleophilic
sufficiently activating



sulfanilamide

Amine as Leaving Group

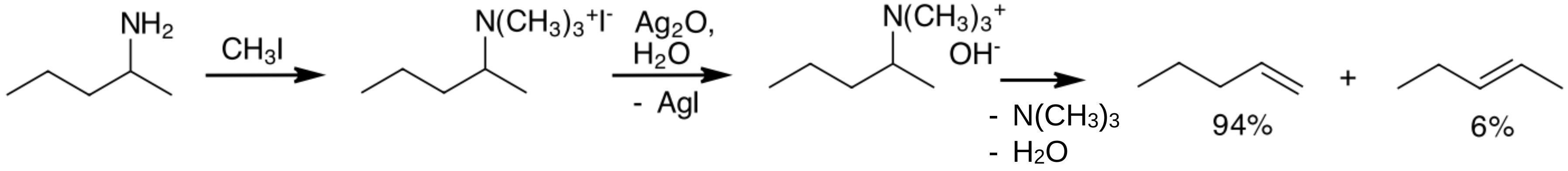
NH_2^- is not a good leaving group



Hoffman elimination:

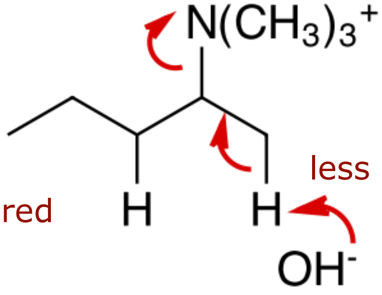
better leaving group

better leaving group



E2 mechanism:

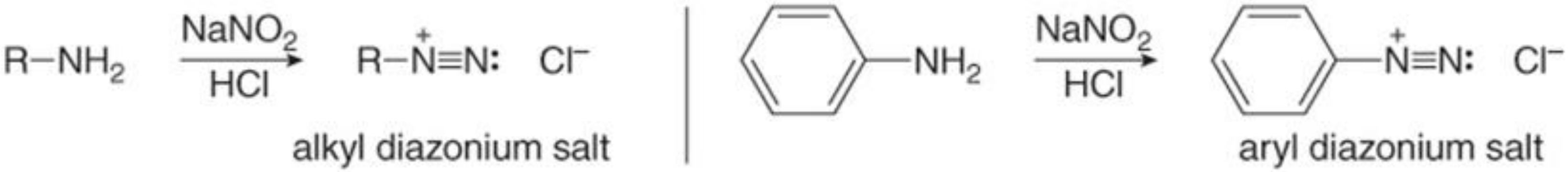
very bulky L.G.



more hindered

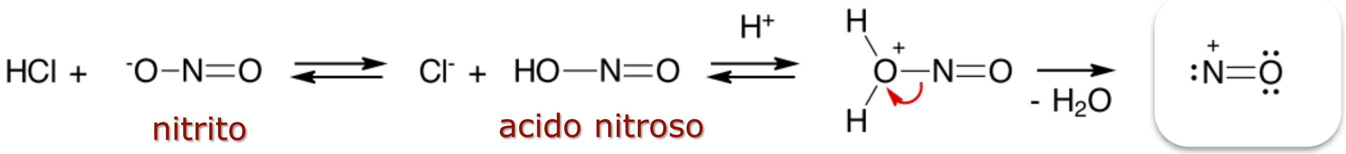
less hindered

Reaction of Amines with Nitrous Acid



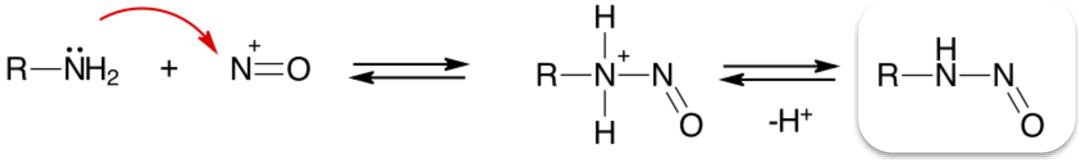
Reaction of Amines with Nitrous Acid

1. generation of the electrophile



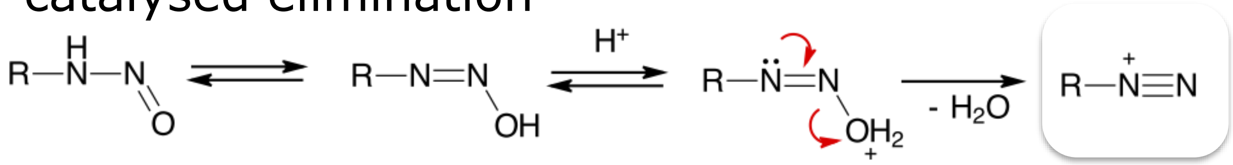
nitrosonium ion

2. nitrosation



N-nitrosamine

3. acid-catalysed elimination

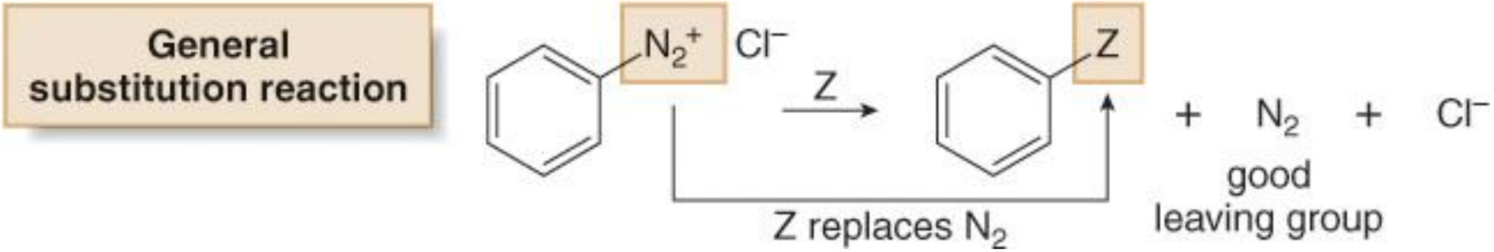


diazonium ion

Substitution Reactions of Aryl Diazonium Salts

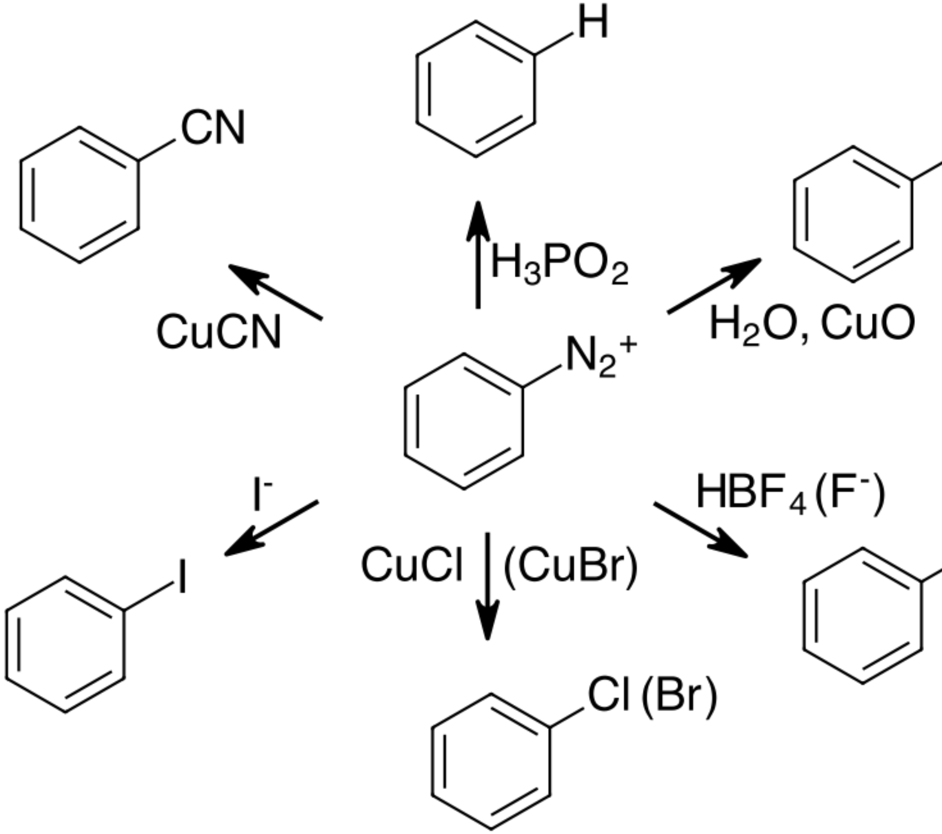
- Aryl diazonium salts react with a variety of reagents to form products in which a nucleophile Z replaces N_2, a very good leaving group.

- The mechanism of these reactions varies with the identity of Z.



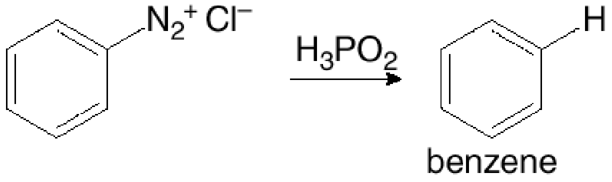
Substitution Reactions of Aryl Diazonium Salts

Reactions often take place in the presence of Cu(I) salts (Sandmayer reaction)



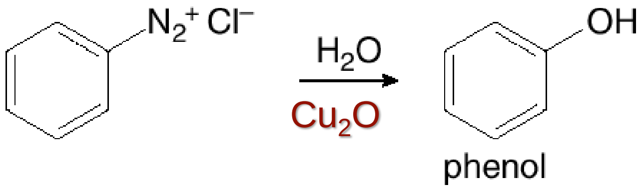
Substitution Reactions of Aryl Diazonium Salts

Substitution by H—Synthesis of benzene



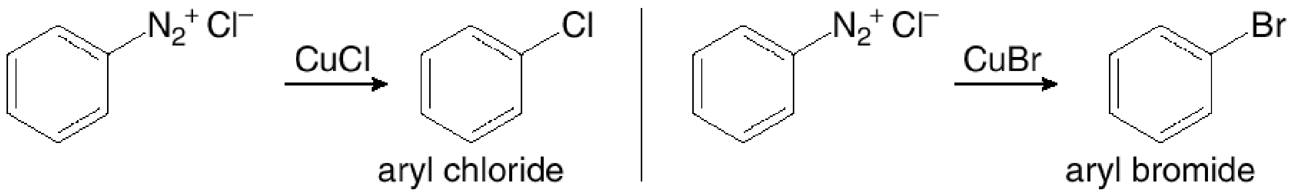
A diazonium salt reacts with hypophosphorus acid to form benzene. This reaction is useful in synthesizing compounds that have substitution patterns that are not available by other means.

Substitution by OH—Synthesis of phenols



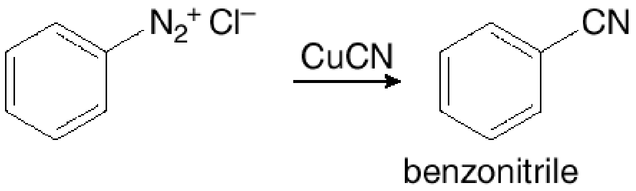
Substitution Reactions of Aryl Diazonium Salts

Substitution by Cl or Br—Synthesis of aryl chlorides and bromides



This is called the Sandmeyer reaction. It provides an alternative to direct chlorination and bromination of the aromatic ring using Cl_2 or Br_2 and a Lewis acid catalyst.

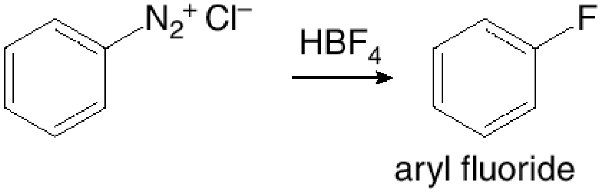
Substitution by CN—Synthesis of benzonitriles



Since the cyano group can be converted into a variety of other functional groups, this reaction provides easy access to a wide variety of benzene derivatives.

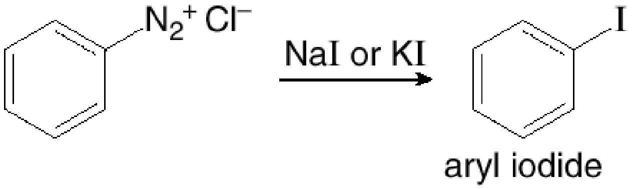
Substitution Reactions of Aryl Diazonium Salts

Substitution by F—Synthesis of aryl fluorides



This is a useful reaction because aryl fluorides cannot be produced by direct fluorination with F_2 and a Lewis acid catalyst.

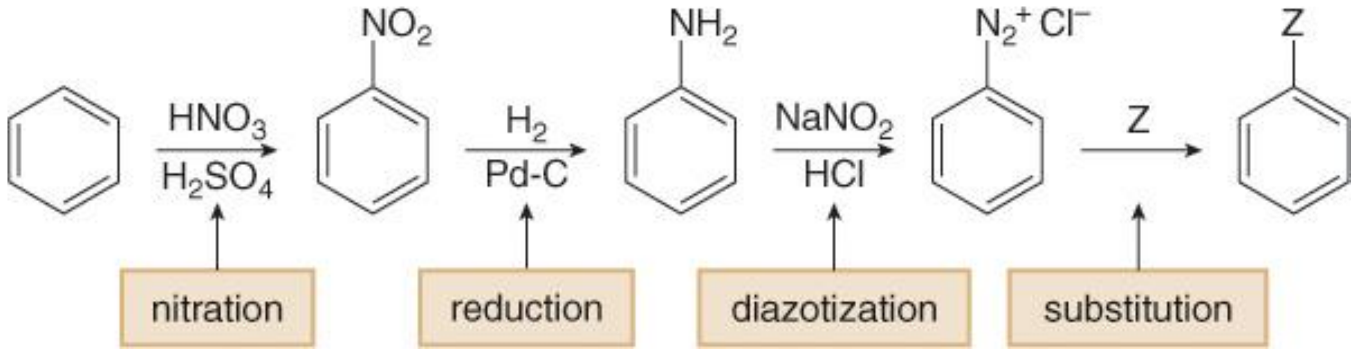
Substitution by I—Synthesis of aryl iodides



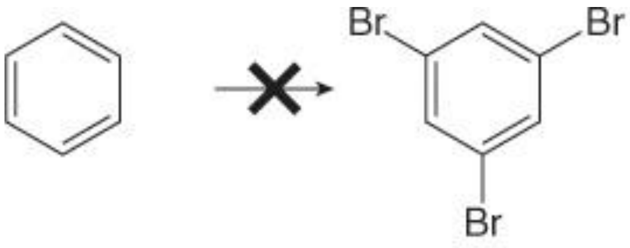
This is a useful reaction because aryl iodides cannot be produced by direct iodination with I_2 and a Lewis acid catalyst.

Substitution Reactions of Aryl Diazonium Salts

- Diazonium salts provide easy access to many different benzene derivatives. Keep in mind the following four-step sequence, because it will be used to synthesize many substituted benzenes.

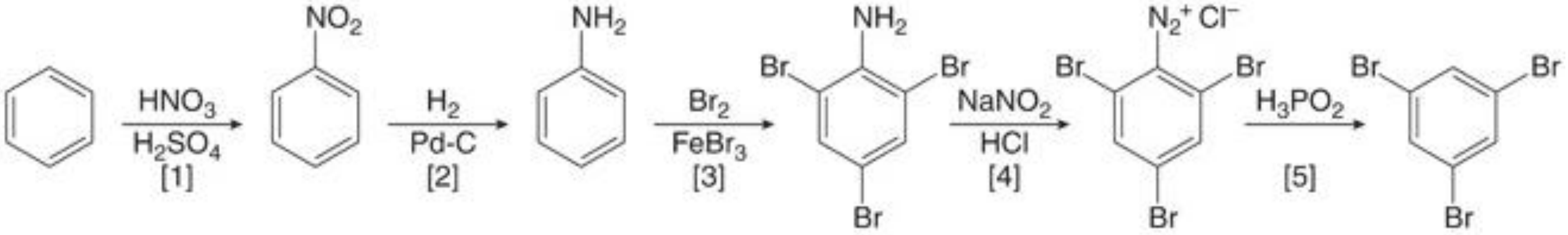


Substitution Reactions of Aryl Diazonium Salts



1,3,5-tribromobenzene

The Br atoms are ortho, para directors located meta to each other.

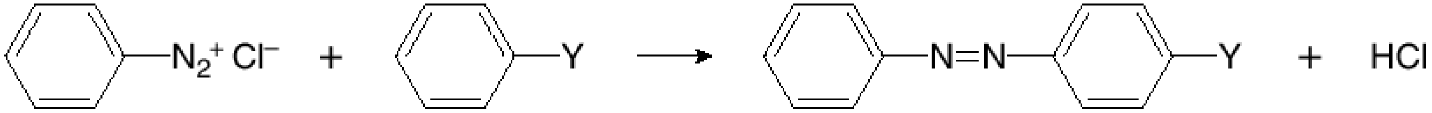


- Nitration followed by reduction forms aniline ($C_6H_5NH_2$) from benzene (Steps [1] and [2]).
- Bromination of aniline yields the tribromo derivative in Step [3].
- The NH_2 group is removed by a two-step process: diazotization with $NaNO_2$ and HCl (Step [4]), followed by substitution of the diazonium ion by H with H_3PO_2.

Coupling Reactions of Aryl Diazonium Salts

When a diazonium salt is treated with an aromatic compound activated by a strong electron-donor group, a substitution reaction takes place giving an azo compound.

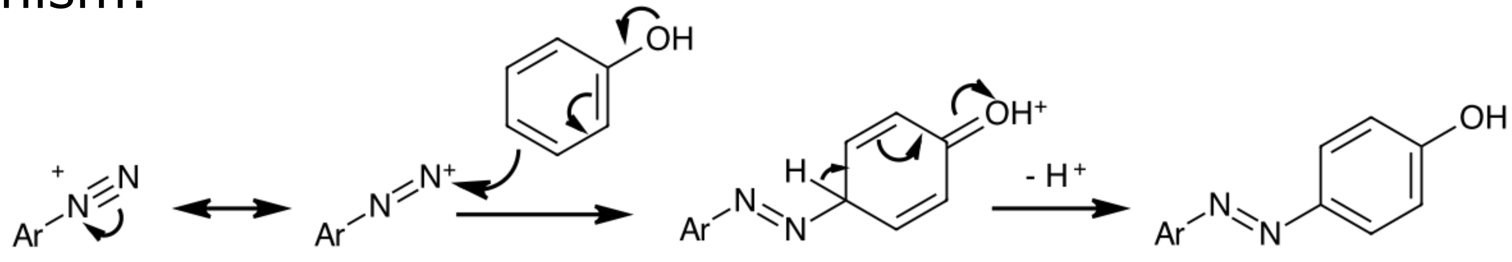
Azo coupling



$Y = NH_2, NHR, NR_2, OH$
(a strong electron-donor group)

azo compound

Mechanism:

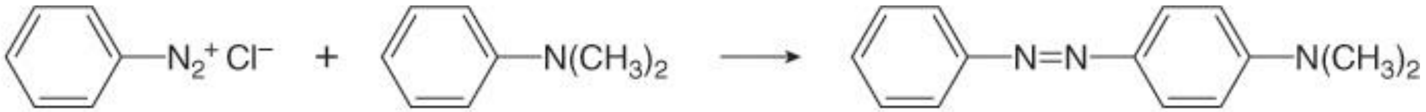


The para position is preferred for steric reasons

Azo Dyes

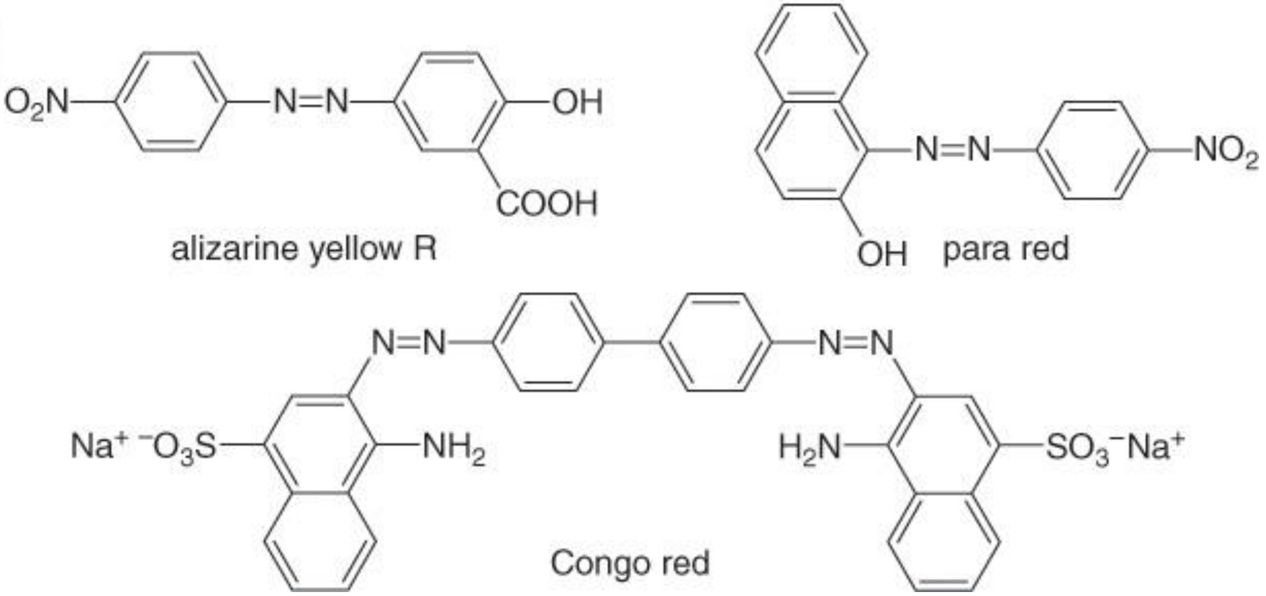
Azo compounds are highly conjugated, rendering them colored. Many of these compounds are synthetic dyes. Butter yellow was once used to color margarine.

Example



a yellow azo dye
“butter yellow”

Three azo dyes



alizarine yellow R

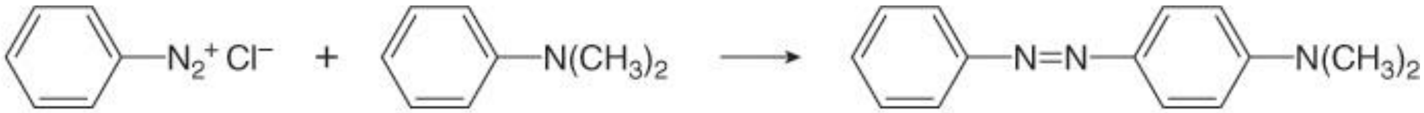
para red

Congo red

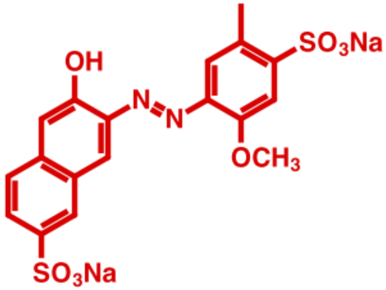
Azo Dyes

Azo compounds are highly conjugated, rendering them colored. Many of these compounds are synthetic dyes. Butter yellow was once used to color margarine.

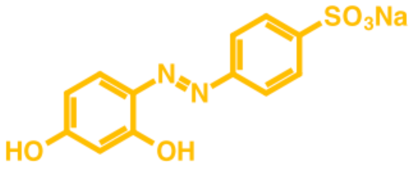
Example



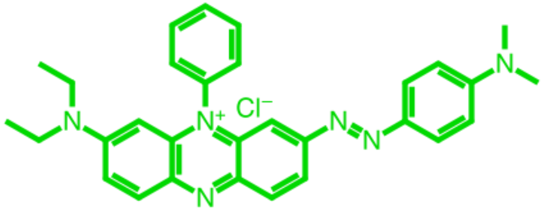
a yellow azo dye
"butter yellow"



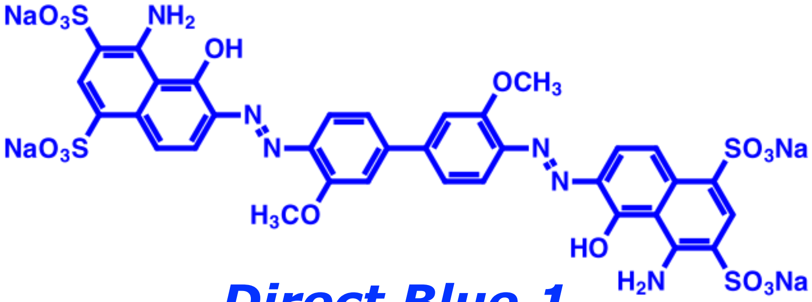
Allura Red



Chrysoine Resorcinol



Janus Green B

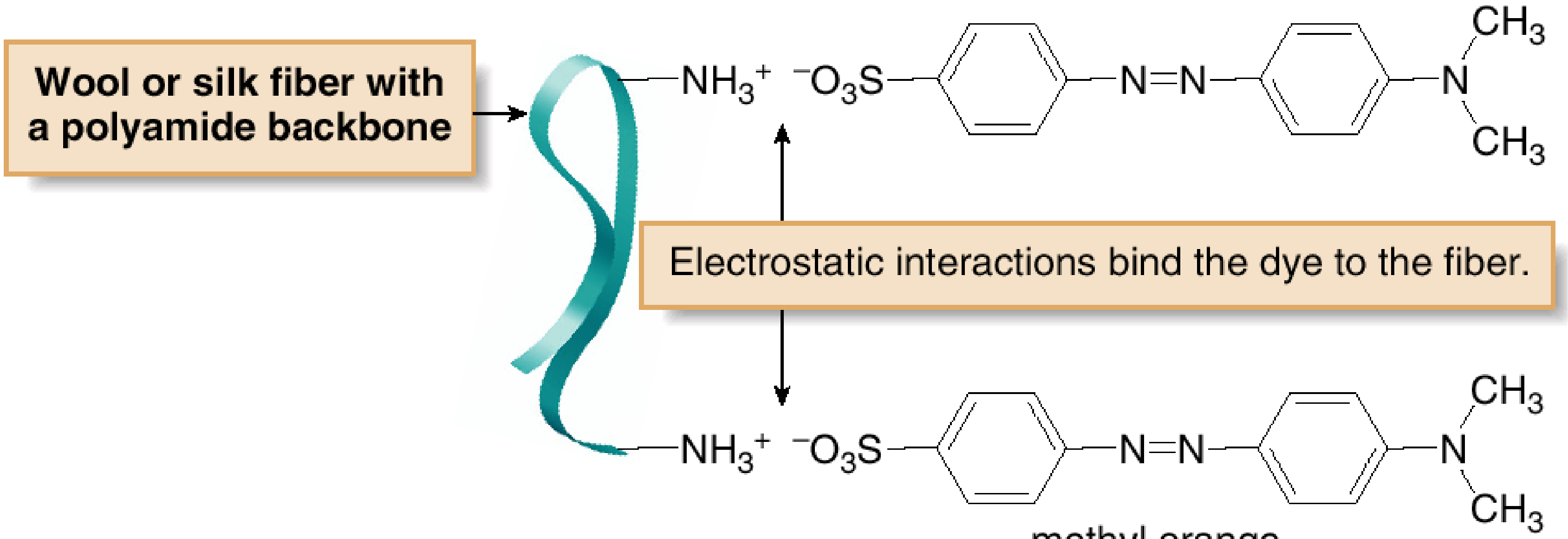


Direct Blue 1

Natural and Synthetic Dyes

- Wool and silk contain charged functional groups, such as NH_3^+ and COO^-. Thus, they bind to ionic dyes by electrostatic interactions.

- Positively charged NH_3^+ groups bonded to the protein backbone are electrostatically attracted to anionic groups in a dye like methyl orange.



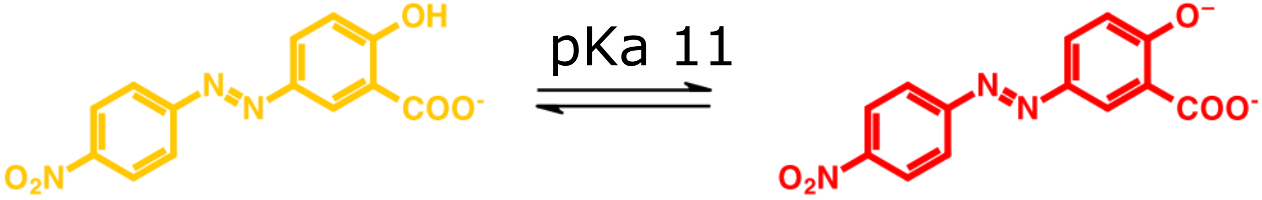
Wool or silk fiber with a polyamide backbone

Electrostatic interactions bind the dye to the fiber.

methyl orange

Indicators

Alizarine yellow



Methyl red