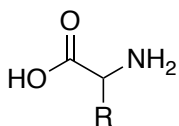
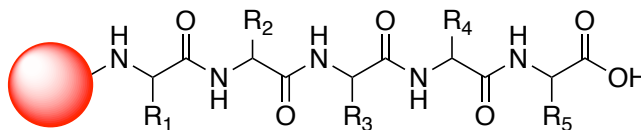


CHAPTER 22: Amines

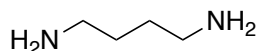
Amines are Biologically Important



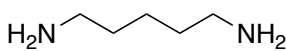
amino acids



peptides/proteins

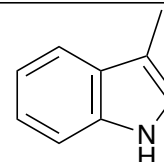


putrescine



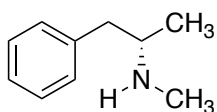
cadaverine

foul smelling constituents from rotting flesh

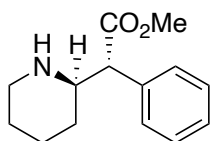


3-methyl-1H-indole
aka. skatole

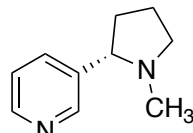
Some biologically active compounds



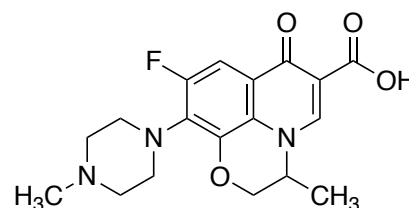
methamphetamine



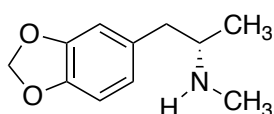
Dexamethylphenidate
(ritalin)



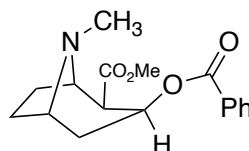
nicotine



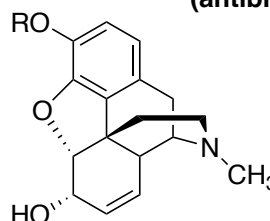
ofloxacin
(antibiotic for anthrax treatment)



ecstasy (MDMA)



cocaine



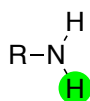
R = H: morphine
R = CH₃: codeine

Amine Substitution

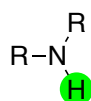
Primary, secondary, and tertiary amines refer to the amount of alkyl substitution on the Nitrogen atom (not the carbon as is the case with other functional groups).



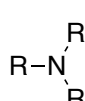
ammonia



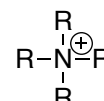
1°



2°

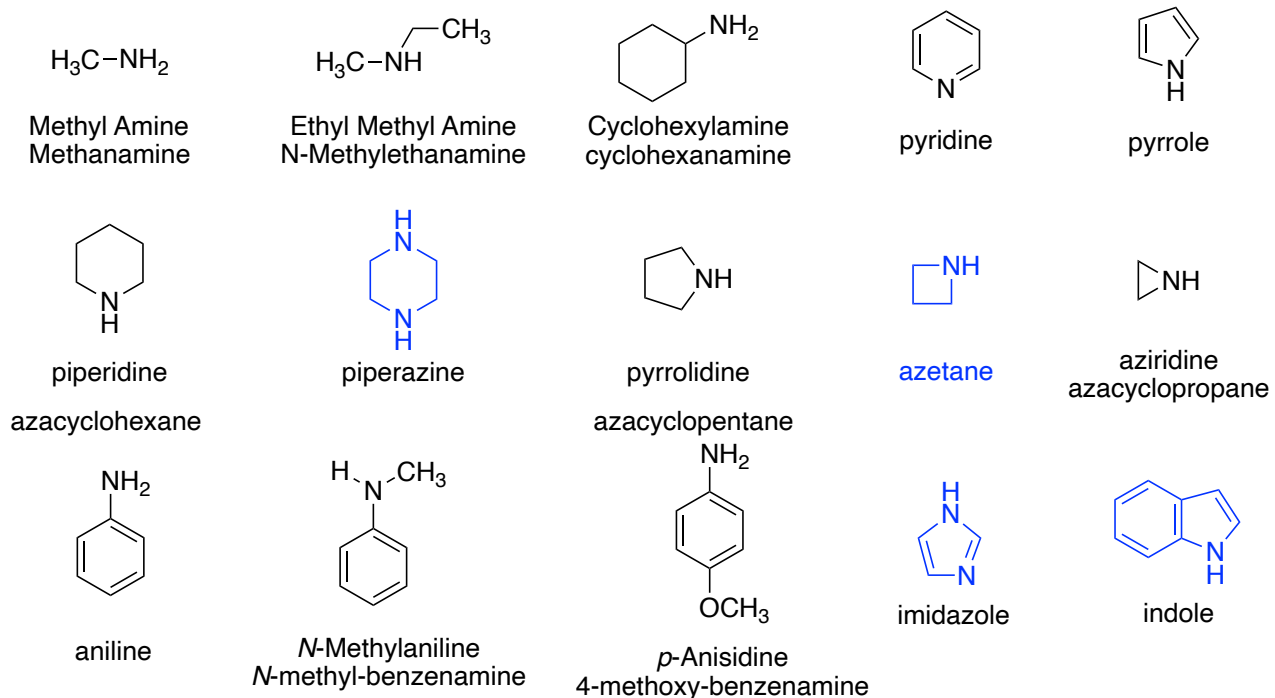


3°



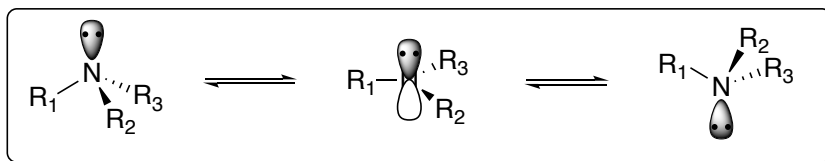
4° (quaternary ammonium salt)

Amine Naming

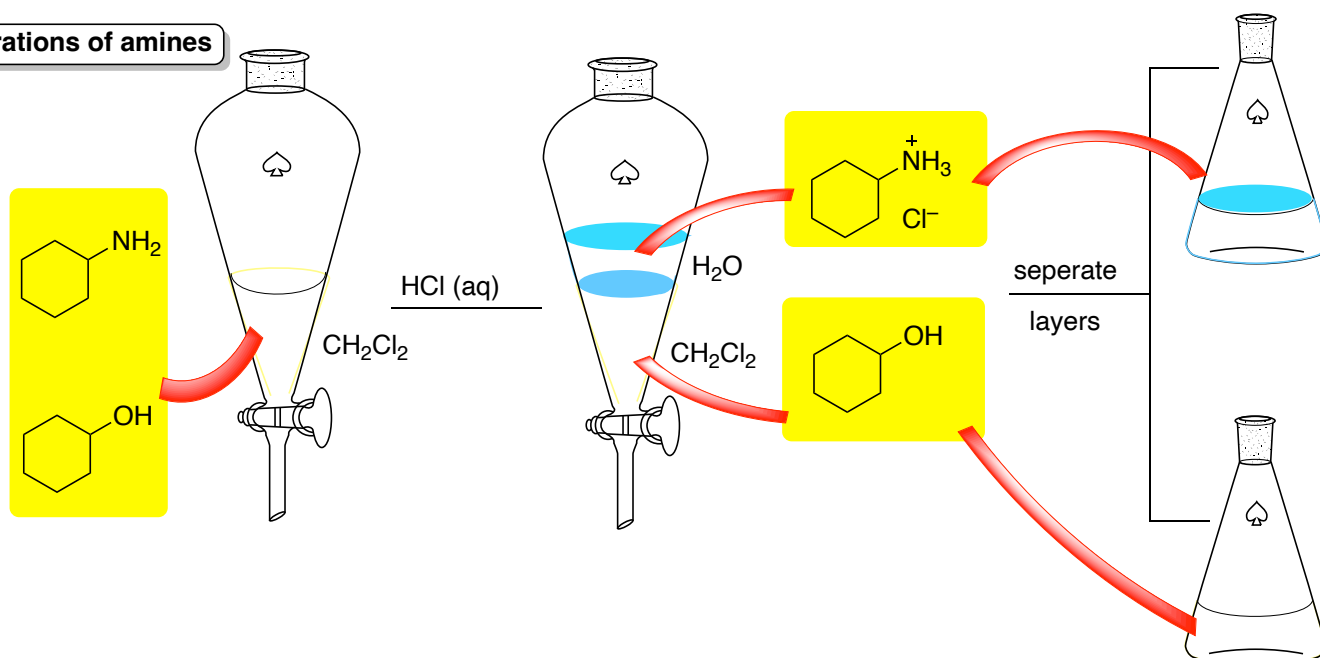


Amine Structure

Amines are sp^3 -hybridized and tetrahedral with the lone pair taking up one of the four positions. Amines are inherently chiral; however, they undergo rapid inversion at room temperature (requires the same energy as rotation around an sp^3 - sp^3 bond). Thus, they are always racemic.



Separations of amines


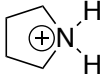
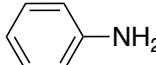
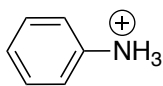
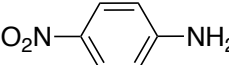
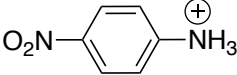

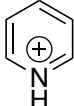

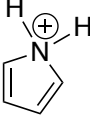
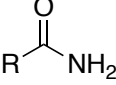
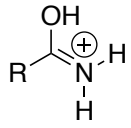


Amines are Good Bases

Amines are very good bases - more basic than oxygen-containing compounds like alcohols or water. One way to measure the base strength is to look at the pK_a of the protonated amine (conjugate acid). The weaker the acid is, the stronger was the base that generated it.

NH_4OH is a base

NH_4Cl is an acid

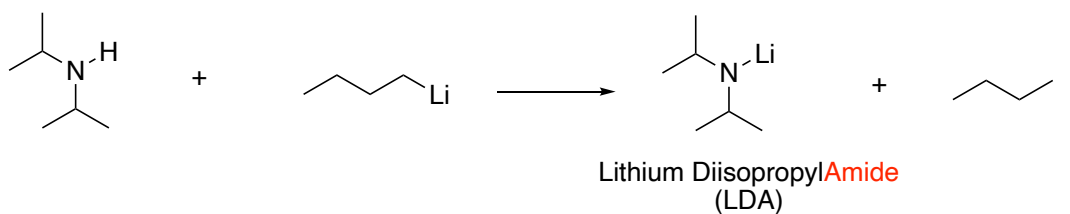
AMINE	AMMONIUM	pK_a (ammonium)
NH_3	NH_4^+	9.3
H_3C-NH_2	$H_3C-NH_3^+$	10.8
		11.2
Et_3N	Et_3NH^+	11.0
		4.6
		1.0
		5.3
		0.4
		-1

Note that the conj. acid of aliphatic amines have a $pK_a \sim 10$

Note aniline is less basic than Et_3N

Amines are very poor acids

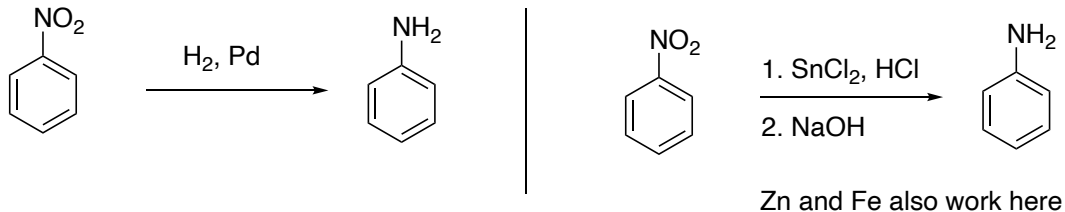
But they can be deprotonated with very, very strong bases like butyl lithium. For example, this is how chemists prepare LDA.



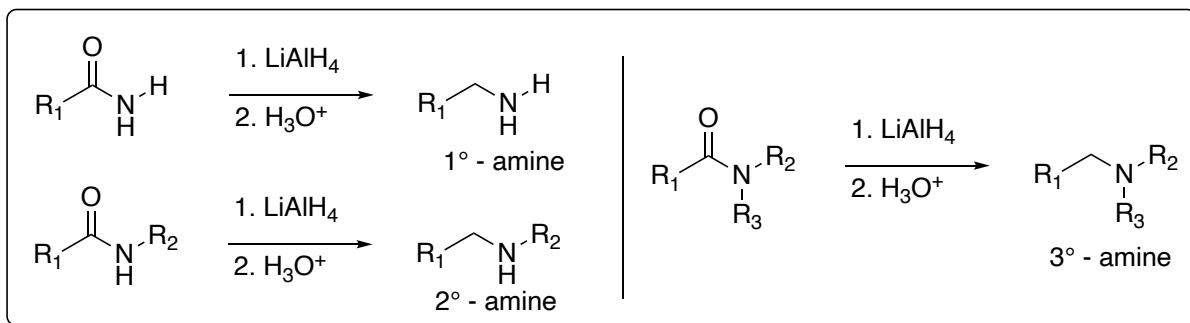
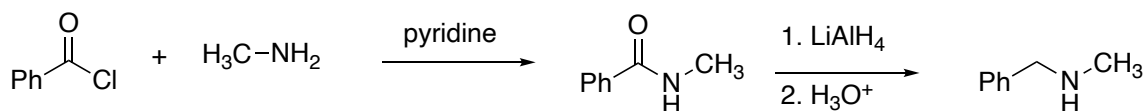
Note the term **amide** as applied here is a deprotonated amine

Preparation of Amines - From previous chapters

Aromatic nitro compounds can be reduced to afford anilines and amides can be reduced to form amines.

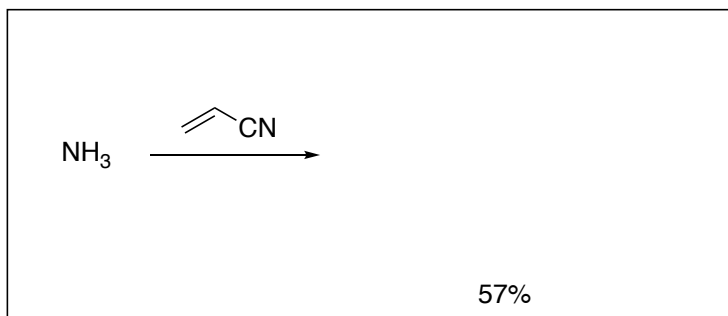
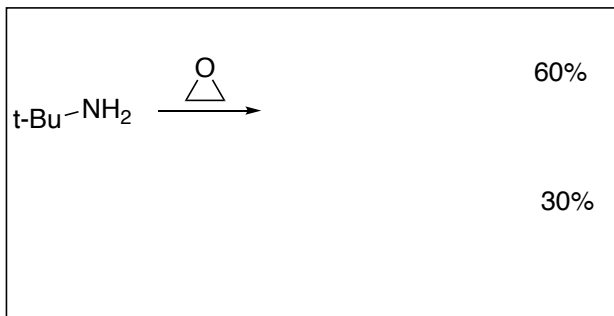
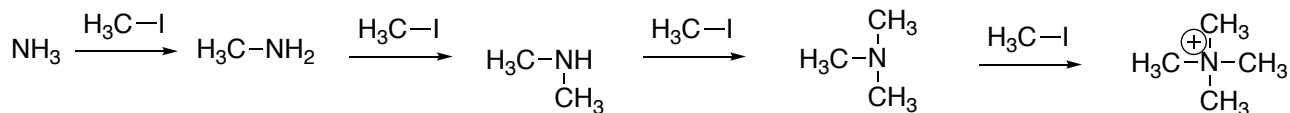


Make an amide, then reduce:



Alkylation of amines

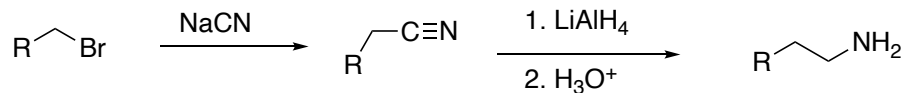
Amines are very good nucleophiles. Too good as a matter of fact. It is difficult to stop the reaction at just one alkylation.



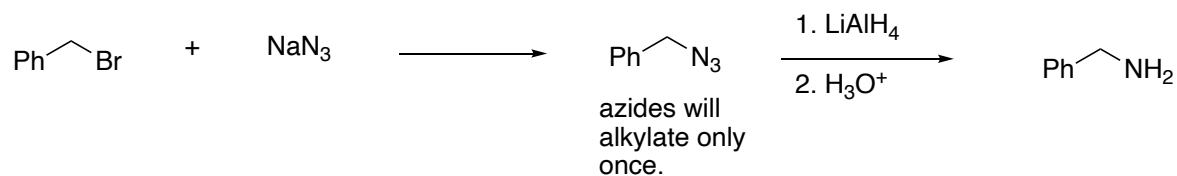
Controlling the Alkylation of Amines

In order to avoid problems with over alkylation (shown above), there are several strategies that can be undertaken:

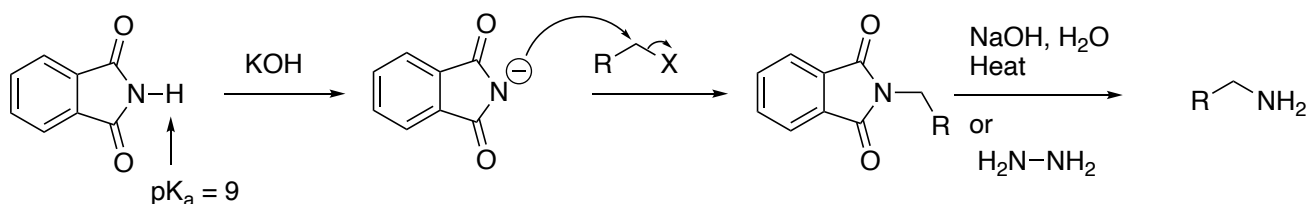
Reduce a nitrile to a primary amine:



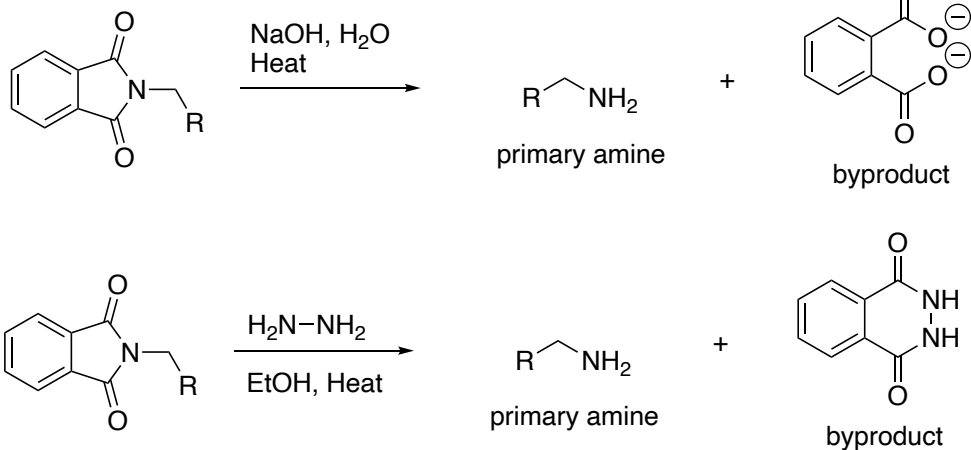
Use azide as a nucleophile, then reduce:



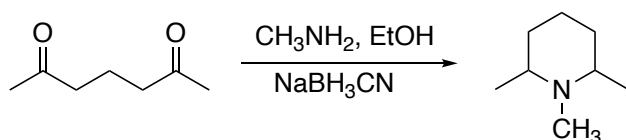
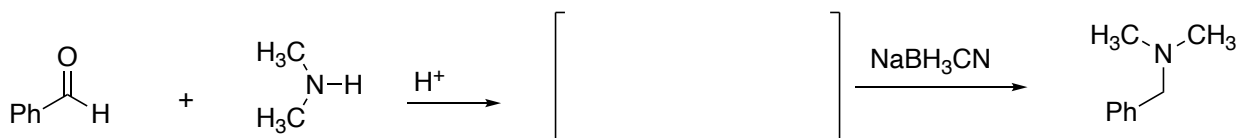
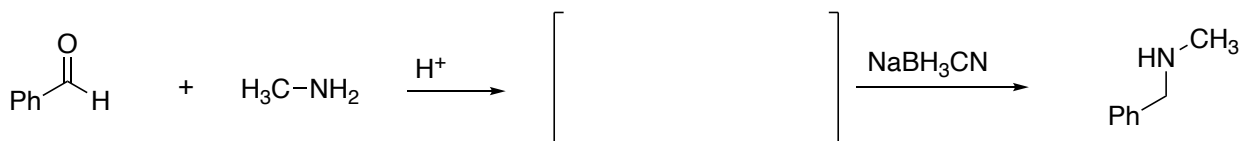
Use Phthalimide as a Nucleophile, then deprotect (Gabriel Synthesis):



Conversion of phthalimide to amine:



Reductive Amination with Amine and Aldehyde

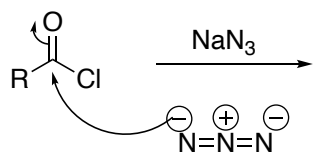


NaBH₃CN (derived from NaBH₄) is very effective for reductive aminations.

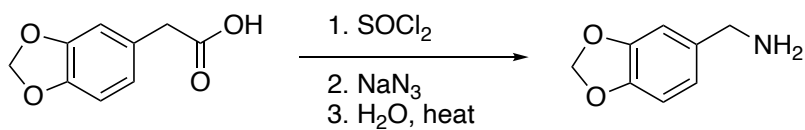
H₂/Pd can be substituted for NaBH₃CN

Note imines reduce faster than ketones, aldehydes, and before enamines can form

Curtius Rearrangement (not in Klein)

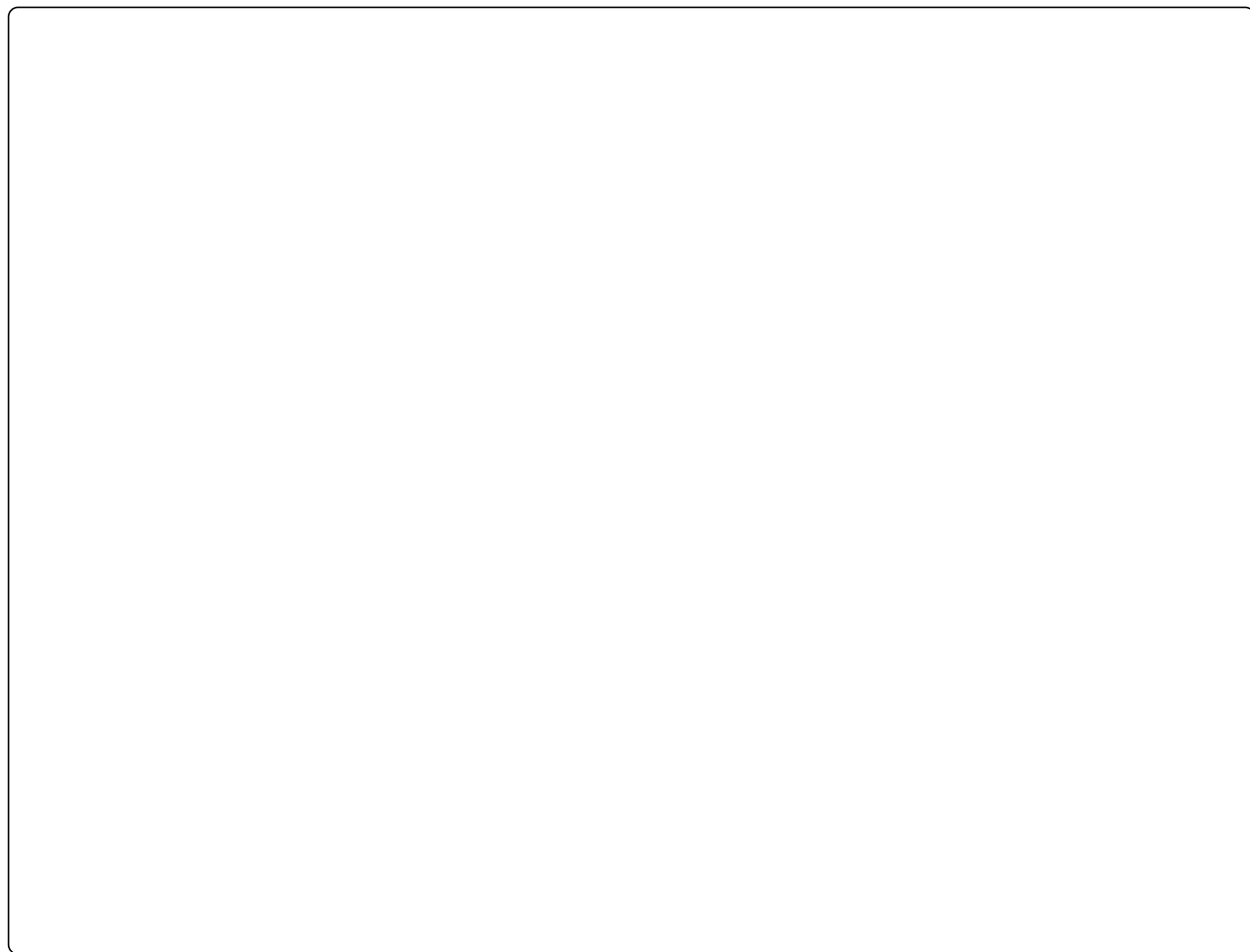
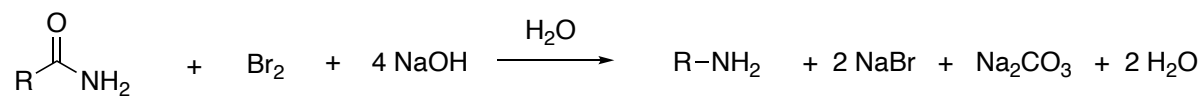


Example:

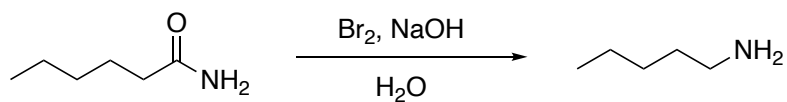
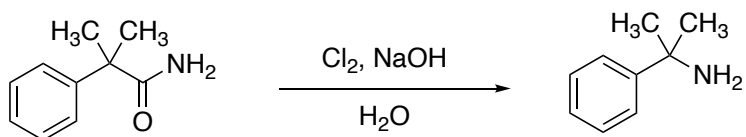


Hofmann Rearrangement (not in Klein)

Amides with no substituent on the nitrogen react with solutions of bromine or chlorine in sodium hydroxide to yield amines through a reaction known as the Hofmann Rearrangement.

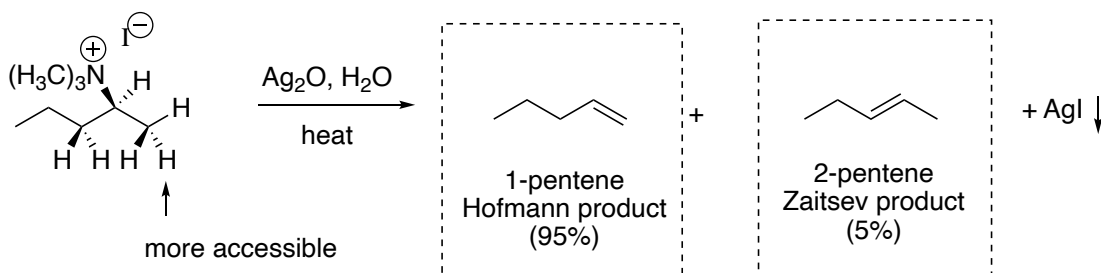


Examples:



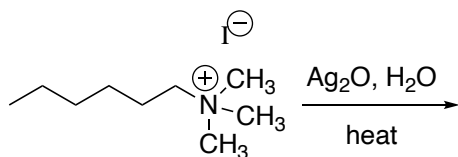
Eliminations: Hofmann Elimination

Amines can undergo eliminations too, like alcohols and alkyl halides, however they cannot eliminate directly. First, the amine must be converted into a good leaving group by exhaustive methylation (using methyl iodide), creating an ammonium ion that can leave as a neutral amine.

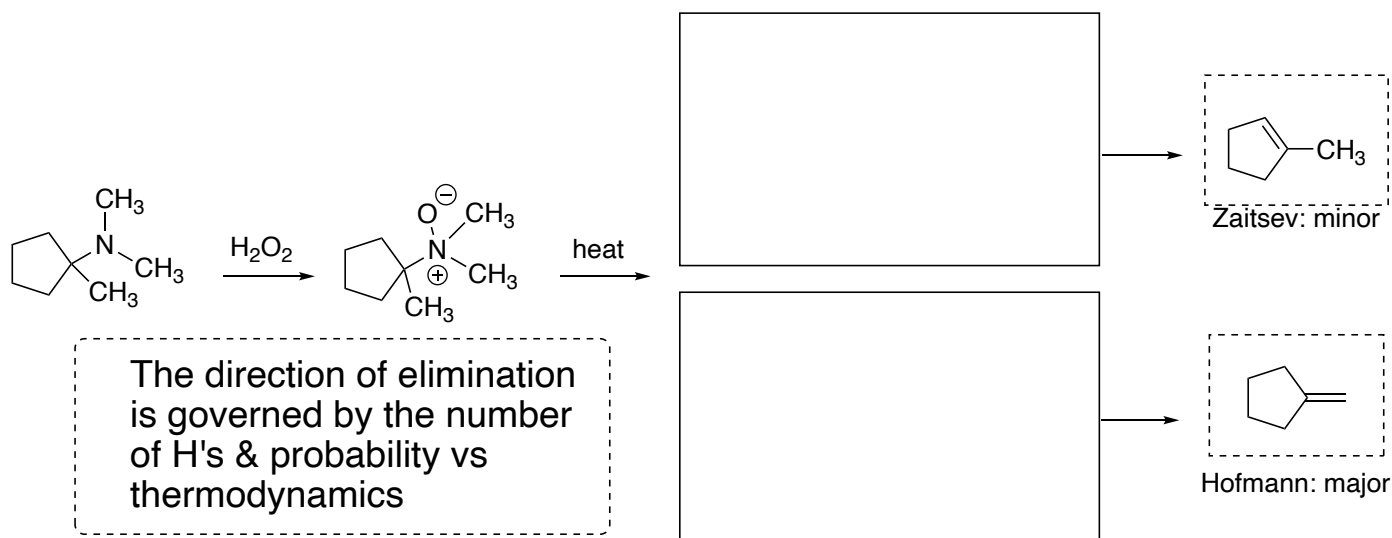
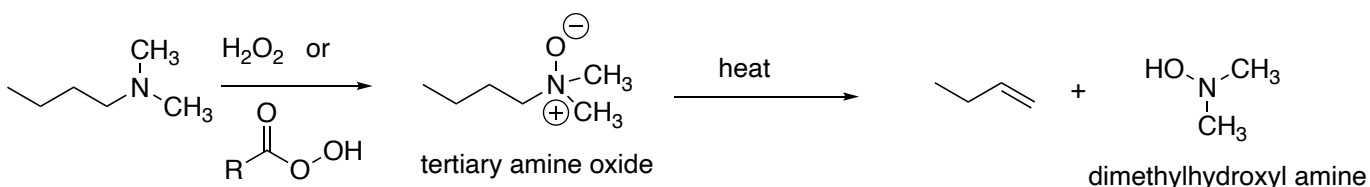


The Hofmann elimination prefers the least substituted alkene. This is mostly due to the sterics of the quaternary ammonium ion.

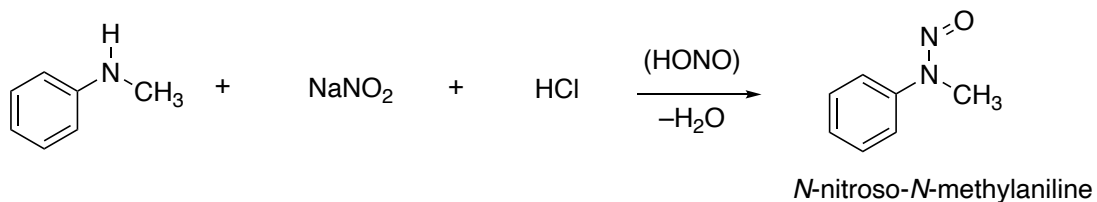
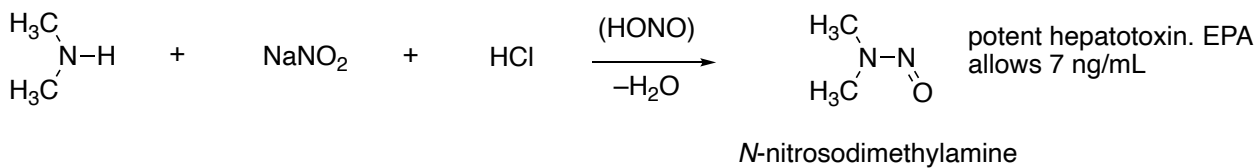
Elimination of the quaternary ammonium salt generally takes place by the E2 mechanism, which requires a strong base. To provide the base, the quaternary ammonium iodide is converted to the hydroxide salt by treatment with silver oxide followed by heating.



Eliminations: Cope Elimination (not in Klein Book)

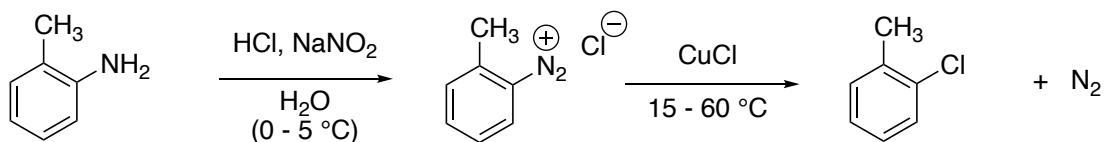


Reactions of Secondary Amines with Nitrous acid (HONO)

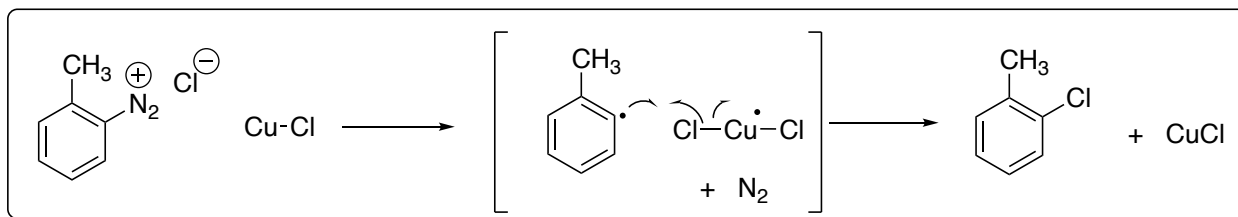


Replacement Reactions of Arenediazonium Salts

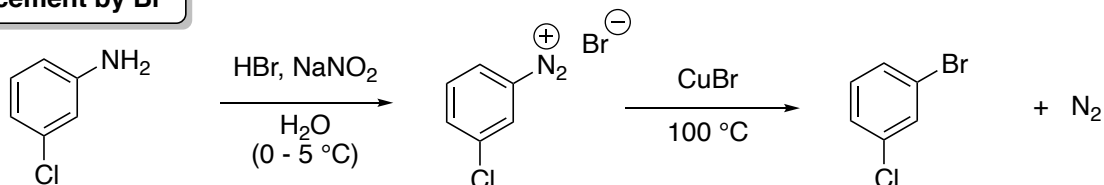
Replacement by Cl



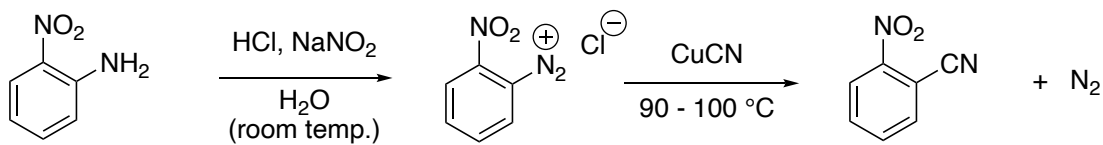
Mechanism: Radical



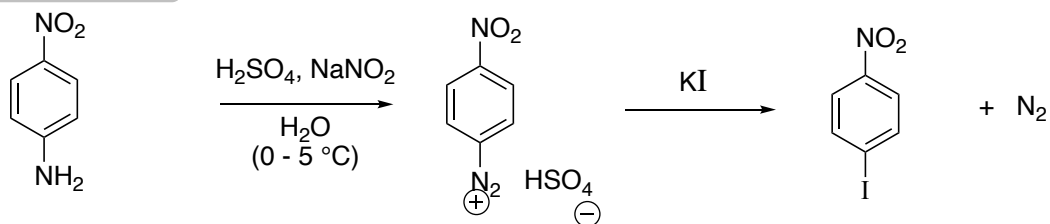
Replacement by Br



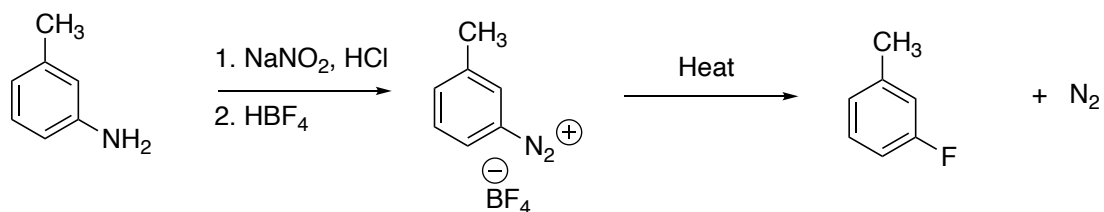
Replacement by CN



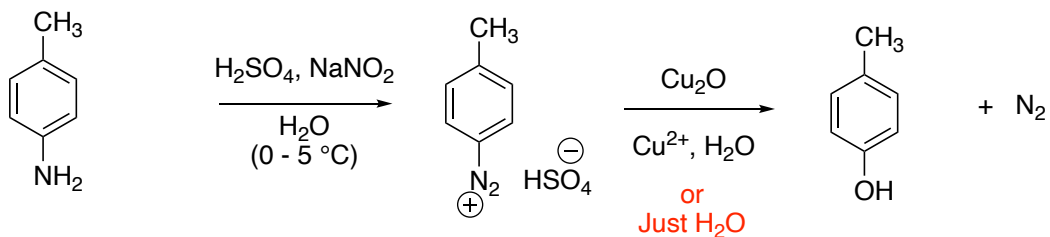
Replacement by I



Replacement by F



Replacement by OH



Replacement by H (deamination)

hypophosphorous acid

