Synthesis of Amines

I. Amine Alkylation by SN2 reaction
Amines can be alkylated in SN2 fashion by alkyl halides; primary halides are best for this purpose. This is not a practical reaction for formation of mono-alkylated amines, because the quaternary ammonium salts formed in the reactions are deprotonated by the starting amines and then undergo further alkylation.

II. Reductive Amination
Reductive Amination involves condensation of an amine with a ketone or aldehyde, followed by reduction. This procedure is general for amine synthesis and over alkylation is avoided. 1°, 2°, and 3° amines can all be prepared in straightforward fashion. N-methylation may be accomplished by treating an amine with formaldehyde followed by in-situ reduction of the iminium ion with sodium triacetoxyborohydride.
III. Amide reduction
Reduction of amides with LiAlH₄ gives amines. Note that the carbonyl oxygen is removed and replaced with two hydrogens, giving a methylene unit:

IV. Methods to make 1° Amines: a. The Gabriel Amine Synthesis
The Gabriel amine synthesis is a method for preparation of primary amines. The compound phthalimide has an acidic NH group which can be deprotonated by KOH; phthalimide anion is a strong nucleophile which can undergo SN2 reaction with an alkyl halide. The alkylated phthalimide product is treated with hydrazine (NH₂NH₂) to release the primary amine product.
b. **Azide as a Nucleophile; Reduction of Azides leads to Primary Amines**

Azide ion (N$_3^-$) is a strong nucleophile which can displace halides and epoxides to form alkyl azides. Reduction of alkyl azides to primary amines is accomplished via catalytic hydrogenation or LiAlH$_4$.

c. **Nitrile/Nitro reduction to amines**

Nitriles are easily introduced by SN2 alkylation of halides with cyanide ion. Reduction of nitriles to amines is accomplished via catalytic hydrogenation of LiAlH$_4$ reduction. Aromatic nitro groups are reduced to anilines by hydrogenation or by metal/aqueous acid solutions.

d. **One carbon degradation of carboxylic acid derivatives: The Hoffmann and Curtius Rearrangements**

The Hoffmann rearrangement involves treatment of amides with bromine in the presence of aqueous base, and involves the formation of an intermediate nitrene species (a low valent nitrogen species similar to a carbene). The Curtius rearrangement involves heating an acyl azide to produce an analogous acyl nitrene which undergoes the same rearrangement. The products are primary amines lacking the carbonyl unit of the amide. This method is particularly useful for preparing very hindered amines.
V. Reactions of Amines
   a. Hoffmann elimination
Quaternary ammonium halides, when treated with silver oxide in water, undergo E2 elimination to produce alkenes. This process always results in the production of the less substituted alkene, the Hoffman product. Crowding in the transition state for anti-periplanar elimination of H-X to give the more substituted alkene is responsible for the contra thermodynamic selectivity.
Note that the Hoffmann elimination gives the least substituted alkene by abstraction of the least hindered proton available:

VI. Amine Oxidation and the Cope Rearrangement
Amines are readily oxidized in the presence of air, H₂O₂, and peracids. Ammonium salts are resistant to oxidation. Primary and secondary amines give low yielding mixtures of hydroxylamines, nitroso compounds and nitro compounds upon oxidation with H₂O₂. A practical process is the formation of amine N-oxides from tertiary amines.
The Cope elimination is an E2-like process which proceeds by a cyclic transition state; no strong base is required. Abstraction of the proton syn to the leaving amine oxide leads to the alkene product. Note that again the Hoffmann product predominates.

Notice the different stereochemical outcomes in the minor products of the following eliminations performed by either the Hoffman elimination (anti elimination of H and X) or the Cope elimination (syn elimination of H and X).