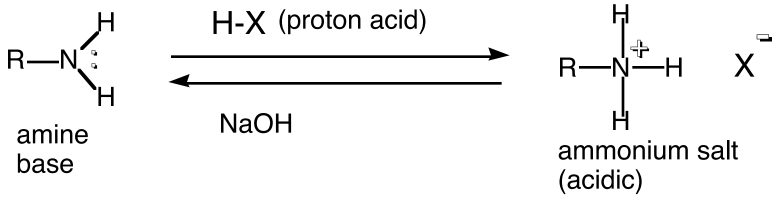
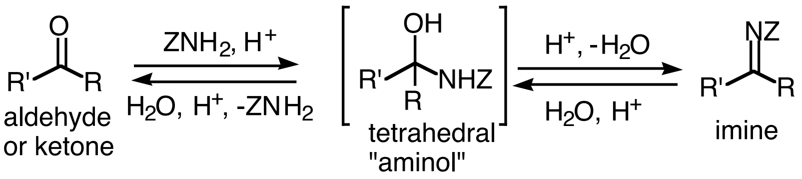
Reactions of Amines

1. **Reaction as a proton base** (Section 19-5)



- Mechanism: Required (protonation)
- Reverse Mechanism: Required (deprotonation)
- Amines are completely converted to ammonium salts by acids
- Ammonium salts are completely neutralized back to amines by bases
- Patterns in base strength: Reflect stabilization/destabilization factors on both the amine and the ammonium
    - N lone pair: $sp^3 > sp^2 > p$
    - For sp^3 nitrogens, 3° > 2° > 1°

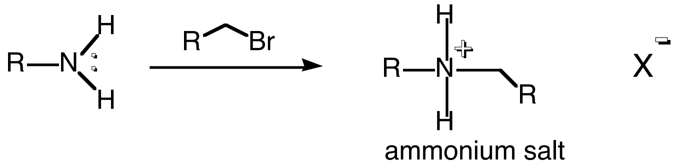
2. **Reaction with Ketones or Aldehydes** (Section 18-16,17)



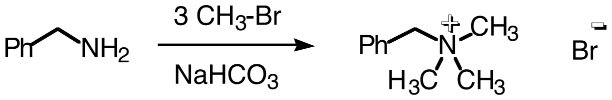
Notes:

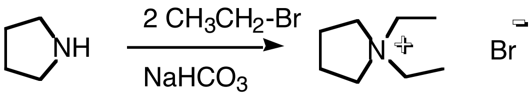
- “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The “aminol” can’t be isolated, it’s only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test

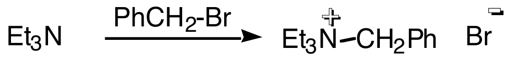
3. **Alkylation of 1° Alkyl Halides** (Section 19-12, 19-22)



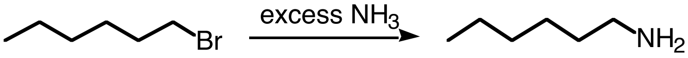
- **3a. Polyalkylation** is routine.
    - o With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
    - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



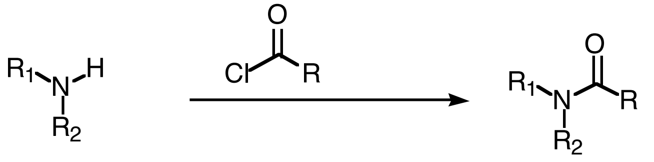




- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
    - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.



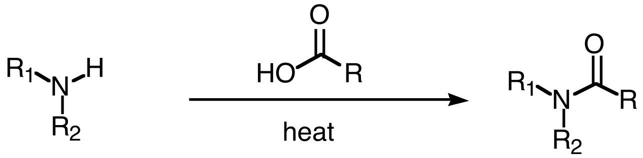
4. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-11)



base required
(either excess amine,
or NaOH or $NaHCO_3$,
or NEt_3 or pyridine...)

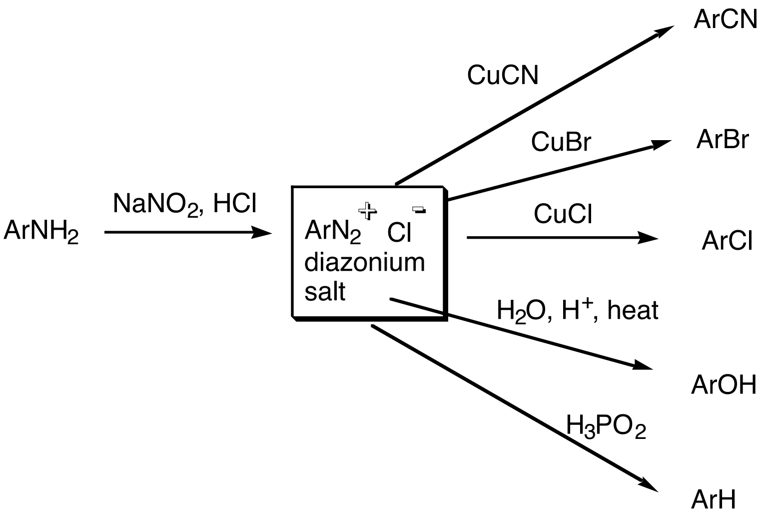
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1°, 2°, or NH_3 all react well.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

4b. **Acylation with Carboxylic Acids** to From Amides: (Section 20-12)



- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid → amide is routine, and is facilitated by complex enzyme mechanisms

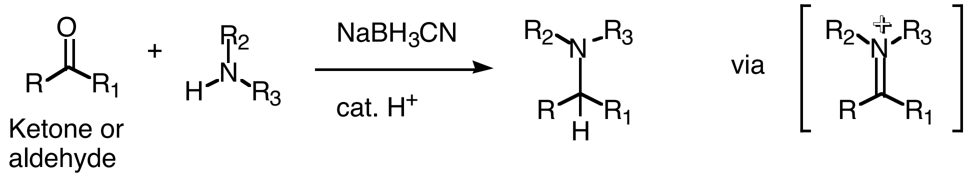
5. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)



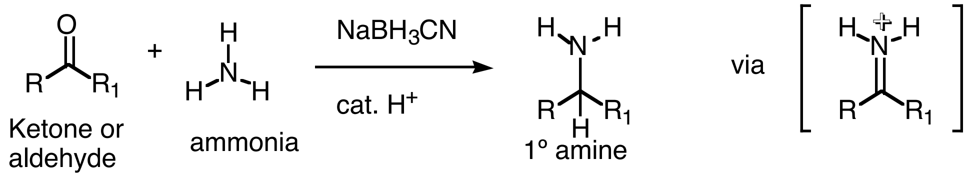
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven't been able to make before.

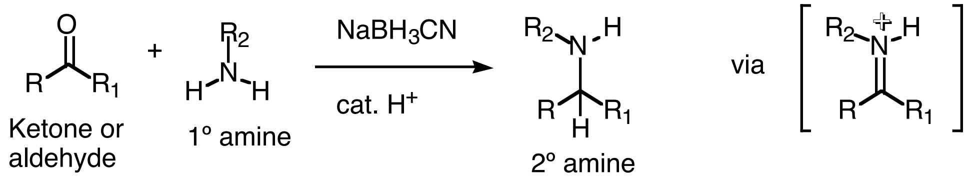
Synthesis of Amines

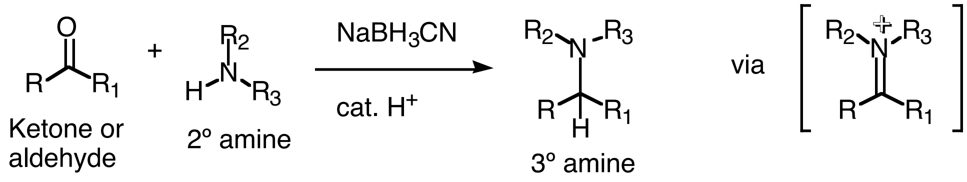
6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19A)



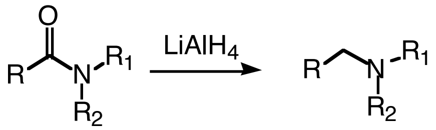
- Access: 1°, 2°, or 3° Amines
- Mechanism: Not required.
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - NH_3 → 1° RNH_2
  - 1° RNH_2 → 2° R_2NH
  - 2° R_2NH → 3° R_3N
  - 3° R_3N don't react





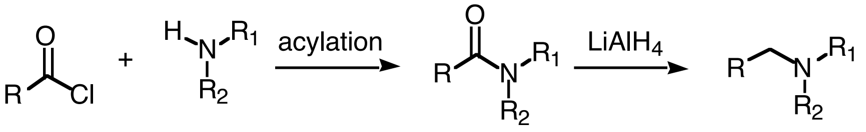


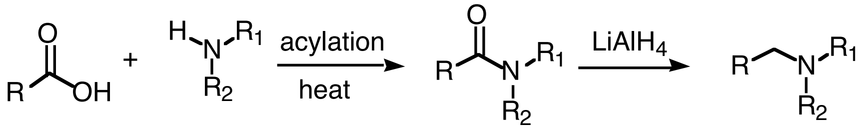
7. **Via Amides**: (Section 19-20)



- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines
- R_1 and R_2 can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - $RCONH_2$ → 1° RCH_2NH_2
  - $RCONHR$ → 2° RCH_2NHR
  - $RCONR_2$ → 3° RCH_2NR_2

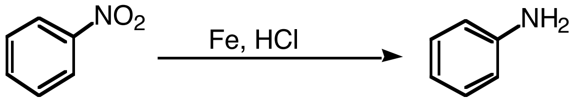
8. **From Amines via Amides**: (Section 19-19B)





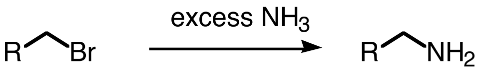
- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 19-19C)



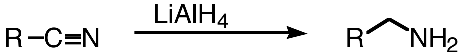
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
    - Pd/H_2, Ni/H_2, Pt/H_2,
    - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1° Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-22) (See reaction 3).



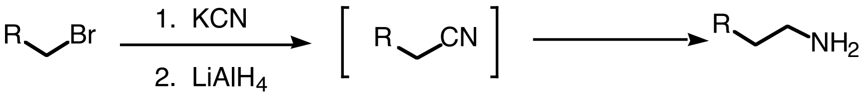
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)

11. **From Nitriles: Reduction of Nitriles** (Section 19-23B)



- Access: 1° amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-23B)



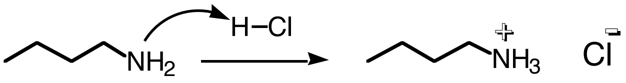
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

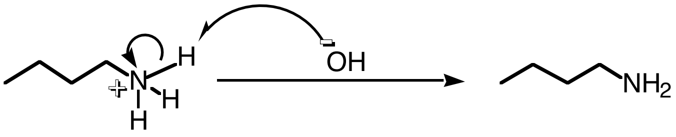
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1°, 2°, or 3° Amines	
2	#7, #8	Amides	$LiAlH_4$	1°, 2°, or 3° Amines	
3	#7, #8	Amines (via Amide)	1. RCOCl (or RCO_2H, heat) 2. $LiAlH_4$	1° $ArNH_2$	
4	#7, #8	Acid Chlorides or Acids (via Amide)	1. RNH_2 2. $LiAlH_4$		
5	#9	$ArNO_2$	Fe/HCl	1° $ArNH_2$	
6	#10	1° RCH_2Br	NH_3 (excess)	1° only, with CH_2 next to nitrogen	Original carbon chain is not extended
7	#12	1° RCH_2Br (via nitrile)	1. 2. KCN 3. $LiAlH_4$	1° only, with CH_2 next to nitrogen	Original carbon chain is extended by one carbon
8	#11	RCH_2CN	$LiAlH_4$	1° only, with CH_2 next to nitrogen	

Mechanisms

1. **Protonation**

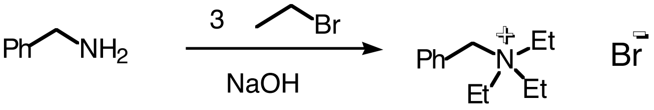


1.-**Reverse. Deprotonation**

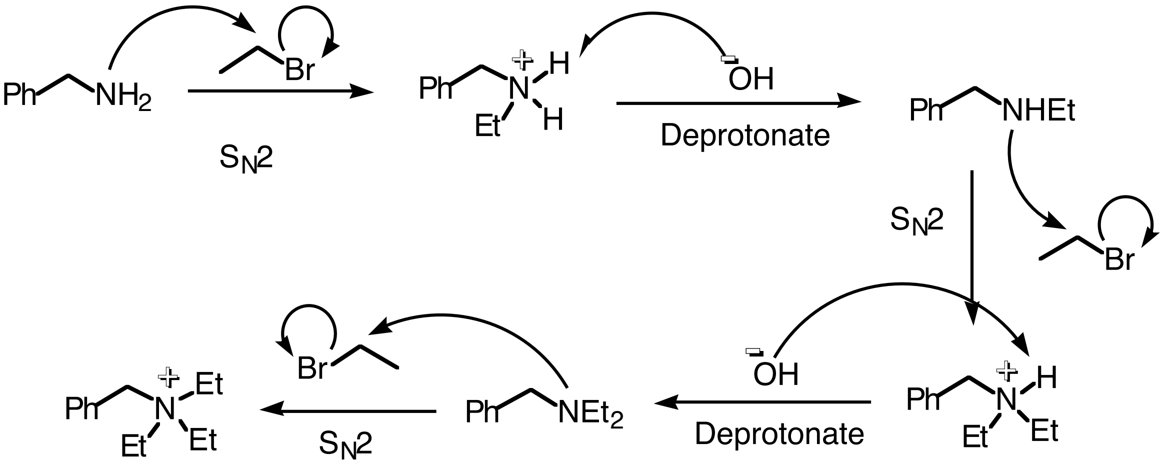


3. Polyalkylation

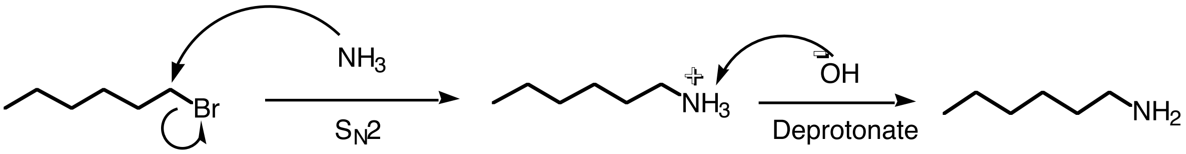
Ex:



Mech:

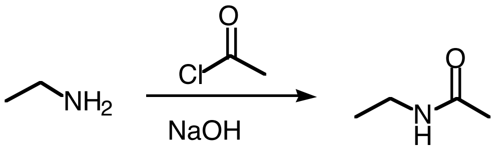


3b. Monoalkylation



4. Acylation

Ex:



Mech: 3 steps: Addition-Elimination-Deprotonation