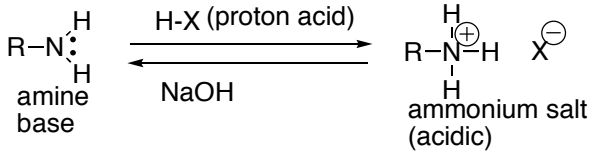
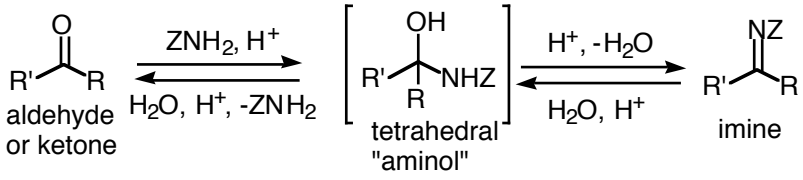
Reactions of Amines

1. **Reaction as a proton base** (Section 19-5 and 19-6)



- 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 for both the amine and the ammonium
    - N lone pair: $sp^3 > sp^2 > p$
    - For sp^3 nitrogens, 3º > 2º > 1º

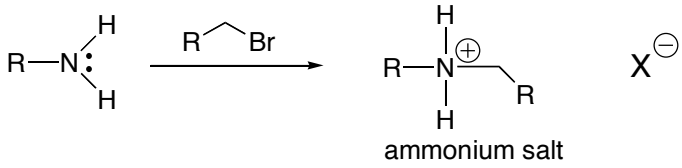
2. **Reaction with Ketones or Aldehydes** (Section 18-16,17 and 19-10)



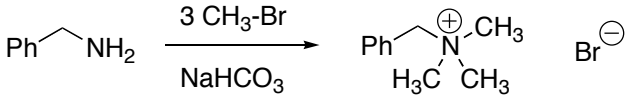
Notes:

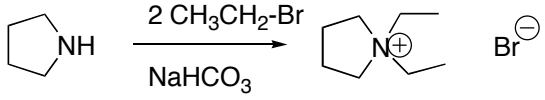
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2º, 3º amines can't do this

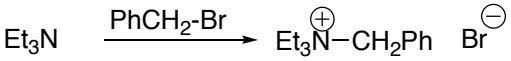
1. **Alkylation of 1º Alkyl Halides** (Section 19-12, 19-21A)



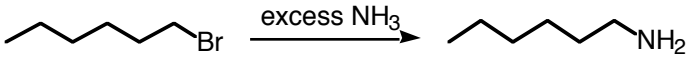
- **3a. Polyalkylation** is routine.
  - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below) .
  - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S_N2 alkylation-deprotonations.



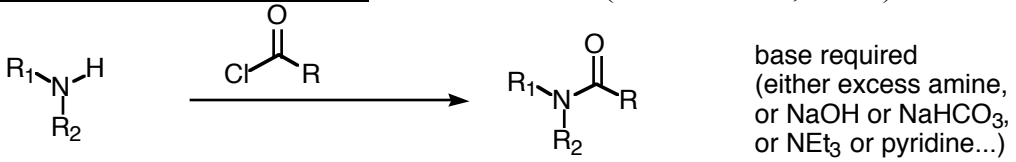




- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple S_N2, followed by deprotonation by the excess amine.

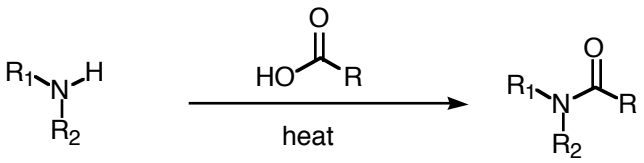


2. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)



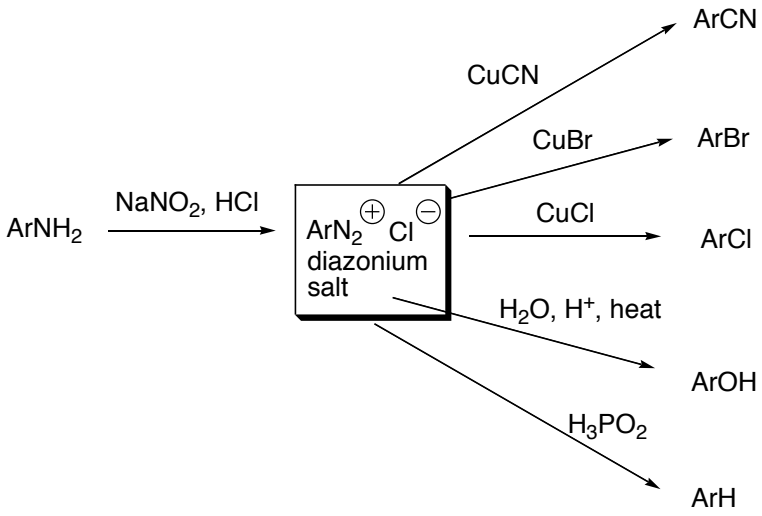
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

4b. **<u>Acylation with Carboxylic Acids</u>** 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

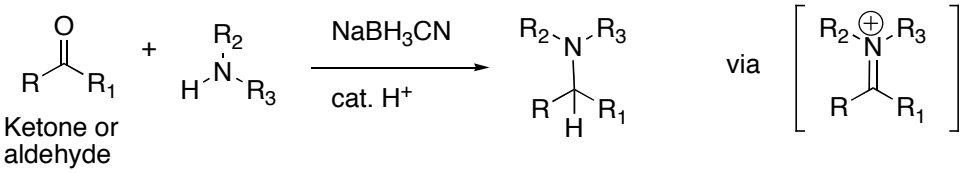
3. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)



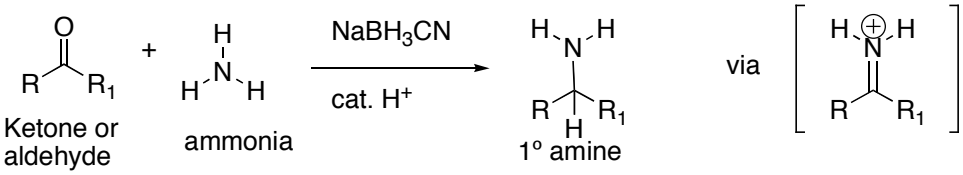
- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces N_2, a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). 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.

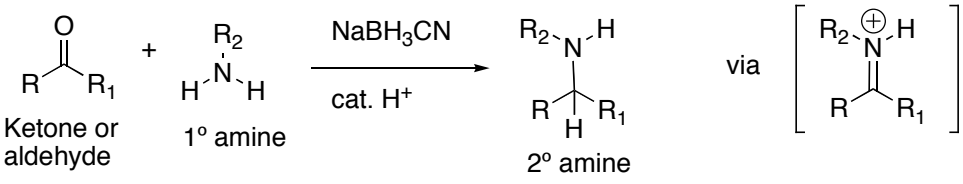
Synthesis of Amines

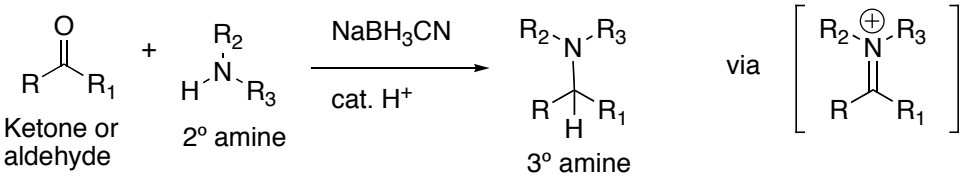
6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)



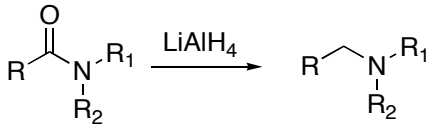
- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R_2 and/or R_3 can be either a carbon or a hydrogen. Thus:
  - NH_3 → 1º RNH_2
  - 1º RNH_2 → 2º R_2NH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





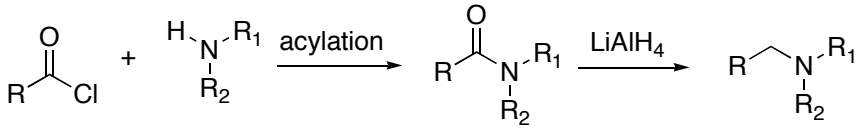


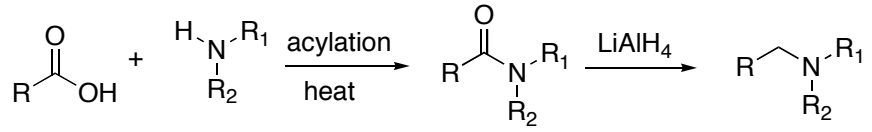
7. **Via Amides**: (Section 19-20)



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

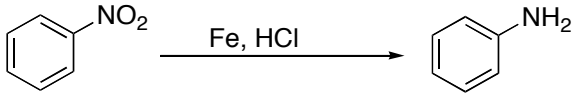
8. **From Amines via Amides**: (Section 19-20)





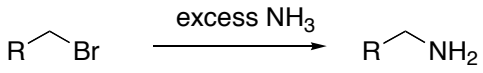
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 19-21C)



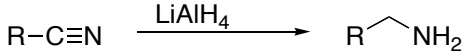
- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H_2, Ni/H_2, Pt/H_2,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).



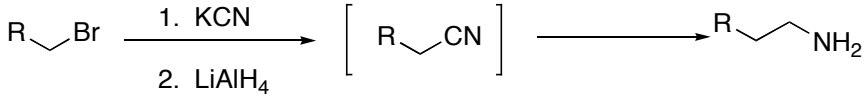
- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)



- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)



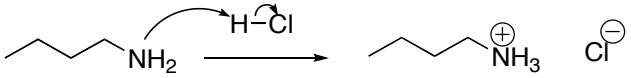
- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

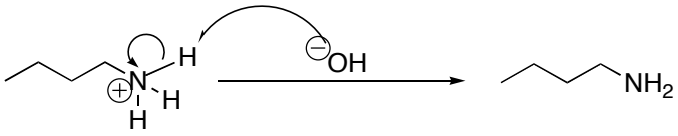
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH, H^+ $NaBH_3CN$,	1º, 2º, or 3º Amines	
2	#7, #8	Amides	$LiAlH_4$	1º, 2º, or 3º Amines	
3	#7, #8	Amines (via Amide)	1. RCOCl (or RCO_2H, heat) 2. $LiAlH_4$	1º $ArNH_2$	
4	#7, #8	Acid Chlorides or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

Mechanisms

1. **Protonation**

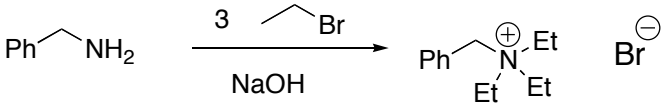


1.-**Reverse. Deprotonation**

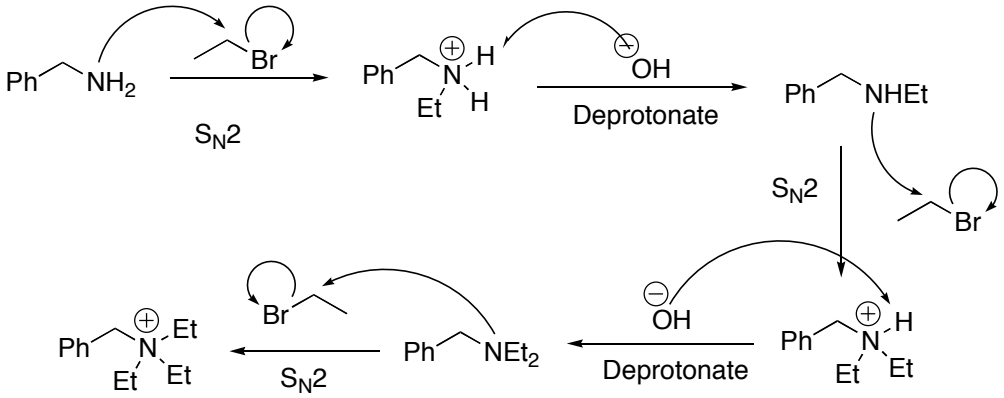


3. Polyalkylation

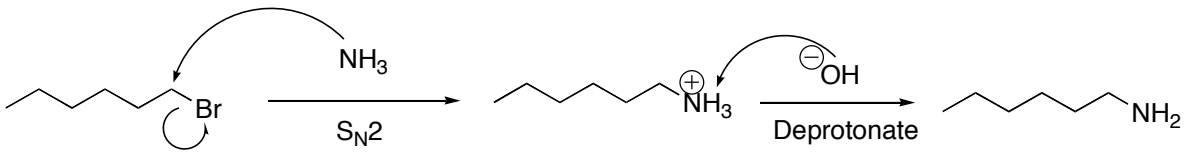
Ex:



Mech:

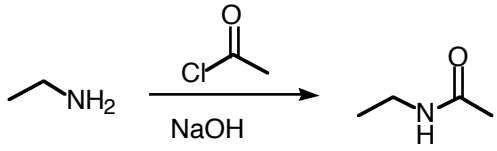


3b. Monoalkylation

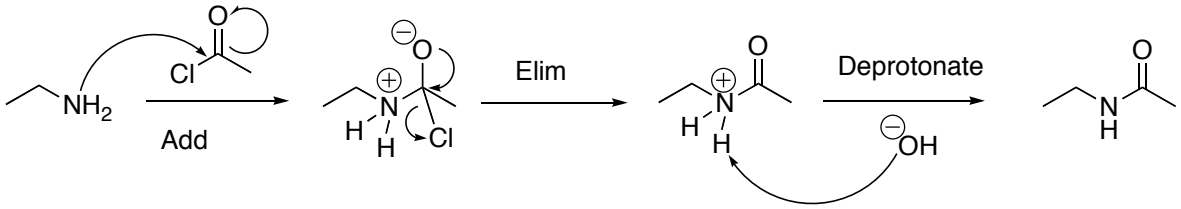


4. Acylation

Ex:



Mech: 3 steps: Addition-Elimination-Deprotonation



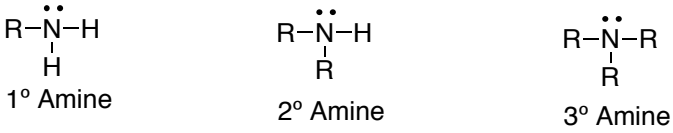
Chapter 19 Amines

A. Miscellaneous

19.1 Intro, Terms

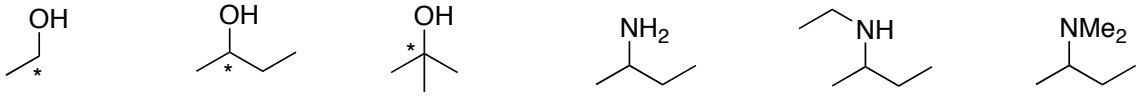
Amines versus Amides

1º, 2º, 3º classification: based on how many of the three nitrogen attachments are carbons:

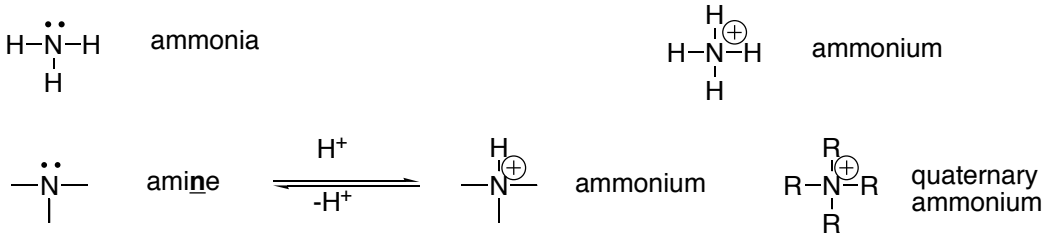


Note: 1º, 2º, 3º has a different sense than with alcohols.

1. In an alcohol, it's based on how many carbon groups are attached to the hydroxy-bearing carbon.
   - The alcohol oxygen always has one carbon group.
2. But in amines, it's how many carbon groups are attached to the nitrogen itself.
   - Because the nitrogen could have 0, 1, 2, or 3 carbon groups attached.



Amines versus Ammoniums: Neutral versus protonated/cationic



19.2 Formal **Amine Nomenclature**: X-alkanamine, N-alkyl-X-alkanamine, etc.

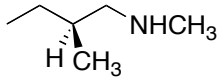
1. For core name, choose longest C-chain to which nitrogen is attached, and call it X-alkanamine
   - Number from end nearer N
   - Be sure to specify with a number which **carbon** has the nitrogen
   - The nitrogen does ****not**** count as a number itself.
2. Substituents on the nitrogen (rather than on carbon) are designated as "N-alkyl"
   - The position of substituents on a carbon are always designated by the carbon's number
   - this is the first time we've had a substituent on something other than carbon, so it's location is designated by "N-" rather than by a number
3. NH_2 as a Substituent: "Amino"

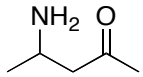
Draw the structure or provide the name for the following.

1. N-methyl-3-phenyl-2-octanamine

2. Z-3-penten-1-amine

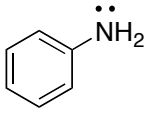
3. 3-hexanamine

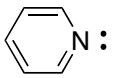
4. 

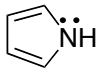
5. 

Common Naming (for simple amines): Alkylamine, dialkylamine, trialkylamine….

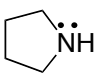
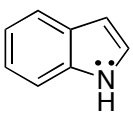
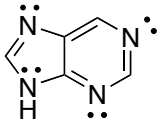
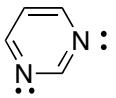
Three Common Amine Names to Memorize (Review from Aromatics Chapter)

Aniline 

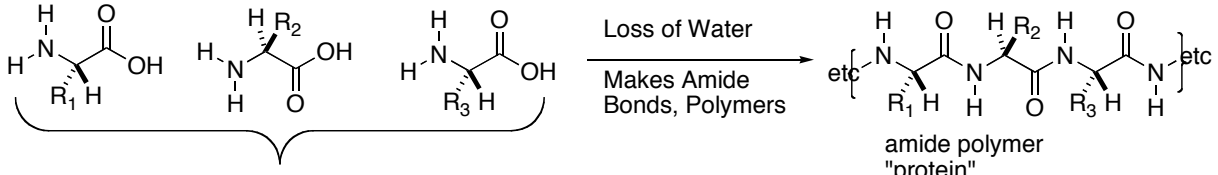
Pyridine 

Pyrrole 

Some Other Famous Common Amine Names (No memory requirement)

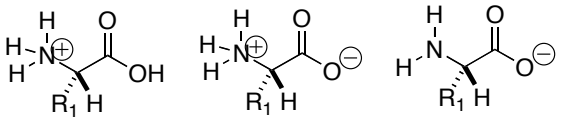
Name	Structure	Name	Structure	
Pyrrolidine		Pyridine		
Purine		Pyrimidine		RNA, DNA, ATP, and ADP are made from derivatives of Purine and Pyrimidine

"Amino Acids"



amide polymer
"protein"
"polypeptide"

-The major natural amino acids all have "S" configuration
-20 major natural amino acids
-Under neutral conditions, the amine actually deprotonates the acid to give not an "amino acid" but actually an "ammonium carboxylate"
-The side groups "R" can be acid, basic, hydrophilic, or hydrophobic.
-The sequence or R groups on thepolymer essentially spells out the biological activity of the protein.



acidic pH neutral pH basic pH

Test Keys:

1. Understand that amino acids are the building blocks for polymeric proteins, and that the biological information is specified by the identity and sequence of the side groups
2. Understand what form an "amino acid" exists in, depending on whether the conditions are acidic, neutral, or basic pH
   - Is the nitrogen neutral (base form) or protonated and cationic (acid form)?
   - Is the carboxylic acid anionic (base form) or protonated and neutral (acid form)?

   a. Acidic pH: both are in protonated acid forms — Overall Charge: POSITIVE
      - nitrogen is cationic and carboxylic acid is neutral

   b. Neutral pH: one in acid form, the other in base form — Overall Charge: NEUTRAL
      - One acidic H between the two of them
      - The amine is in its acid form (protonated, cationic); while the carboxylic acid is in its base form (deprotonated, anionic)
      - The amine is more basic than the carboxylate, the carboxylic acid more acidic than the ammonium cation. Acid base drives the equilibrium to the ammonium carboxylate form

   c. Basic pH: both are in deprotonated base form — Overall Charge: NEGATIVE
      - Nitrogen is neutral, carboxylic acid is anionic

19.3 Structure and Hybridization

1. **N <u>atoms</u>** are typically either sp^3 hybridized (normal) or sp^2 hybridized
   a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
   b. sp^2 in either of two cases:
      - N atom is itself double bonded
      - N atom is conjugated to a double bond

2. **<u>N lone pair</u>** is either:
   a. sp^3 is the default (when no double bonds/conjugation require a p orbital)
   b. sp^2 when the N atom is itself double bonded
      - the p orbital is used to make the double bond
      - the lone pair is left in an sp^2 hybrid
   c. p when the N atom is conjugated to a double bond but is not itself double bonded
      - the lone pair sits in the p orbital so that it can overlap with the adjacent p orbital/π bond

<u>Practice</u>: For the nitrogens on page 10, identify the lone pair hybridization and bond angles.

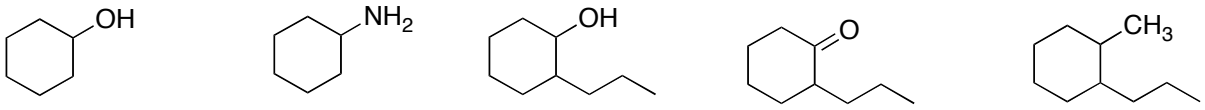
19.4 Physical Properties

Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

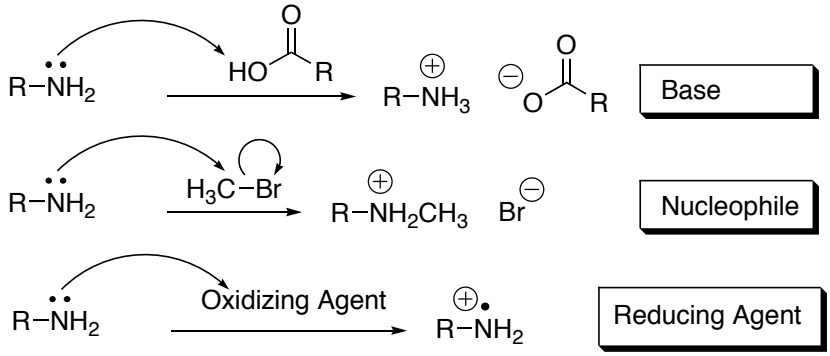
1. **Water Solubility**: All amines hydrogen-bond water → impacts solubility
   a. Because R_3N---HOH bond is stronger (due to amine lone-pair basicity) than ROH---HOH, amines tend to better H-bond water and are more soluble than oxygen analogs
   b. Based on basicity (the acidity of water's hydrogen is common)
2. **Boiling Point:** 1º and 2º amines hydrogen bond themselves, but 3º amines don't
   a. Boiling point for similar mw amines: 1º, 2º amines > 3º amines
   b. amines generally have lower boiling points than analogous oxygen compounds
      - Boiling point for similar mw: RCO_2H > RCH_2OH > RCH_2NH_2
   c. for boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.
3. Amines stink! (ammoniums don't)

1. Boiling Points. Rank the following in terms of boiling point, 1 being highest, 4 being lowest.

2. Water Solubility. Rank the following in terms of water solubility, 1 being most water soluble, 5 being least water soluble.



B. Basicity of Amines: Reactivity of the Nitrogen Lone Pair (19.5,6)



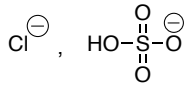
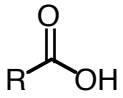
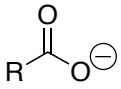
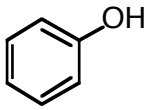
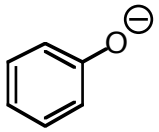
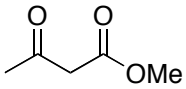
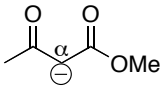
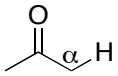
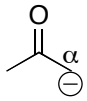
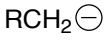
•The nitrogen lone pair dominates amine reactivity

•Trends in base strength, nucleophile strength, and redox strength follow similar patterns, based on lone pair stability/reactivity

Neutral amine bases are stronger than:
1. Neutral oxygens (water, alcohol, ketones…)
2. Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:
1. Anionic hydroxide or alkoxides
2. Anionic nitrogen or carbon bases

Acidity/Basicity Table 19.1: Neutral Acids and Anionic Bases

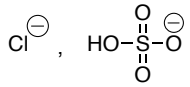
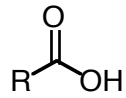
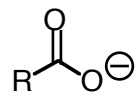
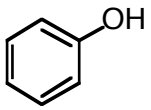
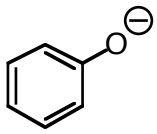
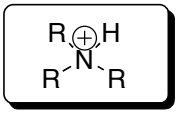
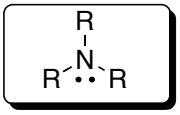
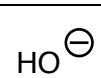
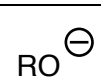
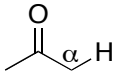
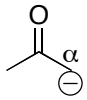
Class	Neutral Acid Structure	Ka	Acid Strength	Anion Base	Base Strength
Strong Acids	H-Cl, H_sSO_4	10^2			
Carboxylic Acid		10^{-5}			
Phenol		10^{-10}			
1,3-Dicarbonyl		10^{-12}			
Water	HOH	10^{-16}			
Alcohol	ROH	10^{-17}			
Ketones and Aldehydes		10^{-20}			
Amine (N-H)	$(iPr)_2N$-H	10^{-33}			
Alkane (C-H)	RCH_3	10^{-50}			

Quick Checklist of Acid/Base Factors

1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**

- **When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.**
- **When a neutral acids are involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.**

Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

Class	Structure	Ka	Acid Strength	Base	Base Strength	
Strong Acids	H-Cl, H_2SO_4	10^2				**S**mell **A**wful!
Hydronium	H_3O^+, ROH^+ cationic	10^0		H_2O, HOR neutral		**H**umans
Carboxylic Acid		10^{-5}				**C**uz
Phenol		10^{-10}				**P**eople
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	**10^{-12}**		 Neutral, but basic		**A**gainst
Water	HOH	10^{-16}				**W**orking
Alcohol	ROH	10^{-17}				**A**re
Ketones and Aldehydes		10^{-20}				**K**ingdoms
Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$		**A**nimal
Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$		**A**ll

Notes to remember

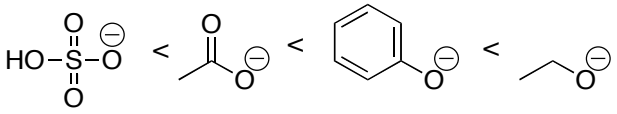
1. Average neutral amine a thousand billion times **more basic than a neutral oxygen** (**electronegativity** factor)
2. An average neutral amine is thousands of times **less basic than** non-resonance stabilized **hydroxide or alkoxide anions** (**charge** factor)
3. But average neutral amine **millions** of times **more basic** than highly resonance-stabilized **carboxylate anion** (**resonance** factor trumps charge factor in this case)
4. **Ammonium cations** are million of times **less acidic than** neutral **carboxylic acids**, but are **more acidic than neutral water/alcohol**!
5. Neutral amine can completely deprotonate carboxylic acids, but not water or alcohols.
6. Therefore hydroxide can deprotonate ammoniums, but carboxylates cannot.

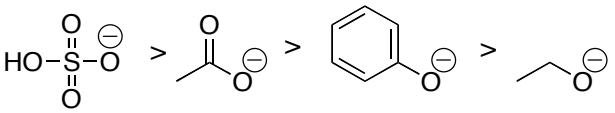
More Detailed Discussion of Acid/Base Patterns/Factors to remember

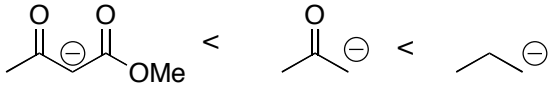
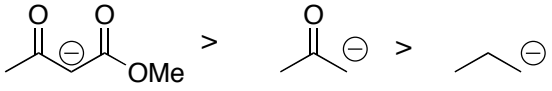
1. Charge
   - Nonfactor on Table 19.1, since all of the "acids" have the same charge (neutral)
   - In Table 19.1, all of the "bases" have the same charge (anion, single negative charge)
   - **Normally, all else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 19.2)**

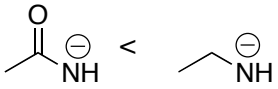
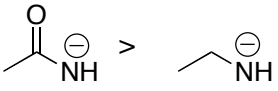
2. Electronegativity:
   - Acidity: H-X (halogen) > H-O > H-N > H-C
   - Basicity: $X^{\ominus} < O^{\ominus} < N^{\ominus} < C^{\ominus}$
   - Anion Stability: $X^{\ominus} > O^{\ominus} > N^{\ominus} > C^{\ominus}$

3. Resonance/Conjugation:
   - Oxygen Series:
     Acidity: sulfurice acid > carboxylic acid > phenol > alcohol

     Anion Basicity: 

     Anion Stability: 

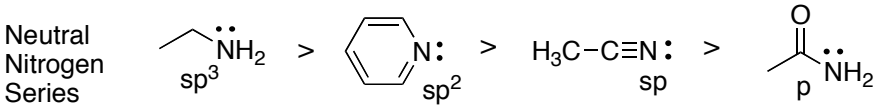
   - Carbon Series:
     - Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane
     - Anion Basicity: 
     - Anion Stability: 

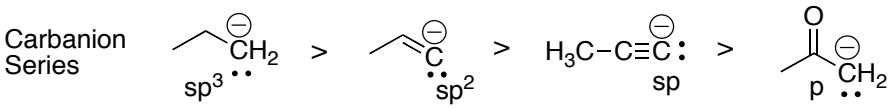
   - Nitrogen Series:
     - Acidity: amide > amine
     - Anion Basicity: 
     - Anion Stability: 

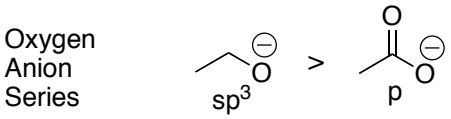
   - Note: Resonance is often useful as a tiebreaker (for example, molecules in which both have O-H bonds and both have equal charge, so that neither the charge factor nor the electronegativity factor could predict acidity/basicity)
   - NOTE: Resonance can sometimes (not always) trump electronegativity or even charge.
     - Example of resonance versus electronegativity: a C-H with carbonyl resonance (ketone/enolate case) is more acidic than an N-H with no resonance help but less acidic than an O-H with no resonance help. A C-H with two carbonyl resonances (a 1,3-dicarbonyl case) is more acidic than even an O-H that has no resonance help.

- Example of resonance versus charge: A carboxylate anion, with serious resonance stabilization, ends up being so stabilized that it is even less basic than a neutral, uncharged amine! A hydrogen sulfate anion from sulfuric acid is less basic than not only neutral amines but also neutral oxygen (water, etc.)

4. Hybridization:
   - For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$

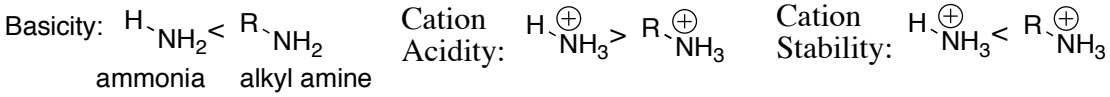




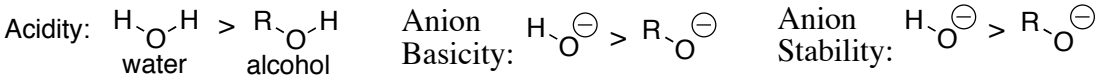


   - This means that for acidity, alkynes > alkenes > alkanes

5. Electron donating/electron withdrawing substituents:
   - Electron withdrawing substituents will stabilize negatively charged anions, but will destabilize positively charged cations.
     - This means a withdrawer will increase the acidity of a neutral acid because it will stabilize the resulting anion.
     - This means a withdrawer will decrease the basicity of a neutral base because it will destabilize the resulting cation
   - Electron donating substituents will stabilize positively charged cations, but will destabilize negatively charged anions.
     - This means a donor will increase the basicity of a neutral base because it will stabilize the resulting cation. The resulting cation will be less acidic.

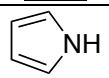
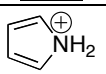
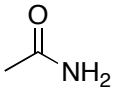
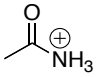
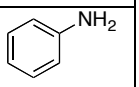
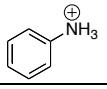


     - This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion



6. Ammonium Cations as Acids and Neutral Amines as Bases
   - Neutral amines are more basic than any neutral oxygen (electronegativity factor)
   - Neutral amines are less basic than most anionic oxygens, including alkoxides, hydroxides (charge factor)
   - However, neutral amines are more basic than highly resonance-stabilized carboxylate anions (in this case, resonance factor trumps the charge factor).

Table 9.3 Relative Basicity of Different Classes of Neutral Nitrogen Compounds.

Entry	Structure of Amine Base	Base Strenth	Lone Pair Hybrid		Impact On Base Strength	Structure of Ammonium Acid	K_a	Acid Strenth
1			P	Aromatic, Conjugated	Decrease		10^{1}	
2			P	Conjugated, Electron-Withdrawing Carbonyl	Decrease		10^{0}	
3			P	Conjugated	Decrease		10^{-4}	
4			sp^2				10^{-5}	
5	**NH_3**		**sp^3**	**Reference**		$\oplus NH_4$	**$10^{-9.3}$**	
6	$EtNH_2$		sp^3	Alkyl Donor	Increase	$Et\overset{\oplus}{N}H_3$	$10^{-10.6}$	
7	Et_2NH		sp^3	Alkyl Donor	Increase	$Et_2\overset{\oplus}{N}H_2$	$10^{-10.8}$	
8	Et_3N		sp^3	Alkyl Donor	Increase	$Et_3\overset{\oplus}{N}H$	$10^{-11.0}$	

General Amine Basicity Patterns.

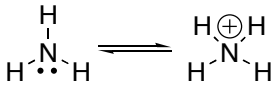
a. Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) > sp^2 (entry 4) > p (entries 1-3) (hybridization factor)
b. Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): 3º > 2º > 1º > NH_3 (electron donating group factor)

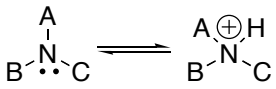
Note: patterns (a) and (b) essentially cover everything.

c. Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because or the electron-withdrawing group factor).
d. Conjugated nitrogens are in general less basic than isolated nitrogens (both hybridization and conjugation factors)

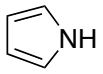
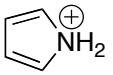
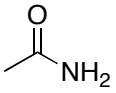
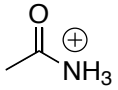
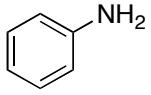
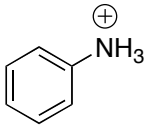
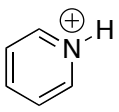
- Note: The **acidity of conjugate ammonium cations (conjugate acids relative to the amines) is directly and inversely related to the basicity of the neutral amines**.
- Key: remember patterns (a) and (b) above. That should help you solve relative basicity problems. If given ammoniums, draw the related conjugate neutral amines, rank them as bases, and realize that the strongest amine base relates to the weakest ammonium acid.
- You should be able to handle any ranking problems involving either amines as bases or their conjugate ammoniums as acids. This should include relative to non-nitrogen acids and bases.

Explanation for Basicity Pattern: Acidity/Basicity is an equilibrium measurement, and thus reflects both product stability and starting material stability.



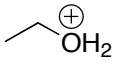
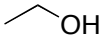


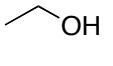
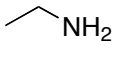
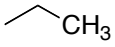
- Anything that **stabilizes the cation increases the basicity** of the nitrogen
- Anything that **destabilizes the cation decreases the basicity** of the nitrogen
- Anything that **stabilizes the amine decreases the basicity** of the nitrogen (especially if that stabilizing factor is sacrificed upon protonation)
- Anything that **destabilizes the amine** increases it's basicity
- When lone pair is p, that always reflects stabilizing conjugation and reduced basicity. This is the origin of both the p-hybridization factor and the resonance/conjugation factor.

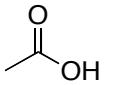
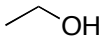
Entry	Base	Conjugate Cation	Substituent And it's Impact	Why: Which Side Is Stabilizied or Destabilized?
5	NH_3	NH_4^+	Reference	
6-8	Et_3N	Et_3NH^+	Alkyl Groups Increase Basicity	**Cation** side stabilized by alkyl groups (electron donors, cation stabilizers)
1			Being part of Aromatic ring Reduces Basicity	**Neutral** side is stabilized by aromaticity. (Aromaticity is lost following protonation.)
2			Acyl/Amide Conjugated To Carbonyl	**Neutral** side is stabilized by conjugation to the carbonyl. That conjugation is lost following protonation. Second, the **cation side is destabilized** by the strongly electron withdrawing carbonyl group.
3			Conjugated To Aromatic	**Neutral** side is stabilized by conjugation. (That conjugation is lost following protonation.)
5			Aromatic. Part of Aromatic Ring	**Amine** side is stabilized by the sp^2 hybridization of the lone pair. An sp^2 lone pair is shorter than an sp^3 orbital. The shorter sp^2 orbital means the electrons are nearer and held more tightly by the nitrogen nucleus, and are thus more stable.

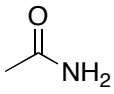
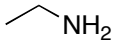
Choose the More Acidic for Each of the Following Pairs: Single Variable Problems

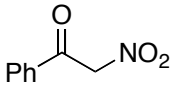
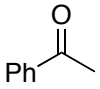
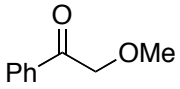
1. NH_3 $\oplus NH_4$

2.  

3.   

4.  

5.  

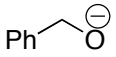
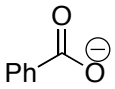
6.   

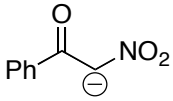
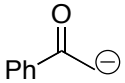
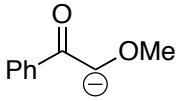
Choose the More **Basic** for Each of the Following Pairs (Single Variable)

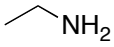
7. NH_3 $NaNH_2$

8. NaOH H_2O

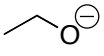
9. NH_3 H_2O

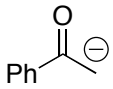
10.  

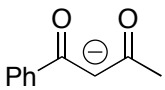
11.   

12.  NH_3 O_2N-NH_2

Choose the More **Basic** for Each of the Following (Multiple Variables, apples and oranges…)

13. NH_3 

14.  

15.  

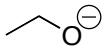
Choose the More Basic for Each of the Following Pairs

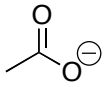
16. NH_3 $NaNH_2$

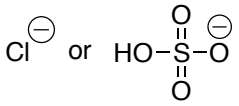
17. NH_3 NaOH

18. NH_3 H_2O

19. NH_3 CH_3OH

20. NH_3 

21. NH_3 

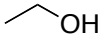
22. NH_3 

23. NH_3 CH_3MgBr

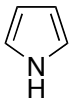
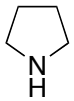
24. NH_3 CH_3NH_2

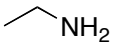
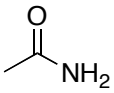
25. For the following sets of bases, rank them, 1 being the most basic.

a. CH_3MgBr CH_3NHNa CH_3NH_2 CH_3OH

b.   CH_3NH_2 

26. Amine Basicity. For the following pairs or sets of bases, rank them, 1 being the most basic.

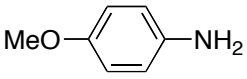
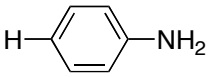
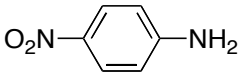
a.  

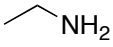
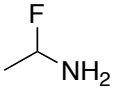
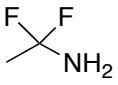
b.  

c. benzamide [$PhC(O)NH_2$] aniline ($PhNH_2$) pyridine triethylamine

d. triethylamine ethylamine ammonia

e. dimethylamine methylamine aniline ($PhNH_2$)

f.   

g.   

h. triethylamine NaOH

i. methanol methylamine methane

j. CH_3MgBr CH_3NHNa CH_3ONa CH_3NH_2 CH_3CO_2Na CH_3OH

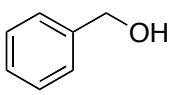
27. Rank the <u>acidity</u> of the following compounds, 1 being most acidic.

a. H_3O^+ $NH_4^+Cl^-$ water acetic acid (CH_3CO_2H) NH_3

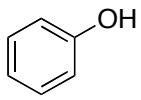
b. H_3O^+ acetic acid (CH_3CO_2H) $Me_3NH^+Cl^-$ ethanol

c. $NH_4^+Cl^-$ $Me_3NH^+Cl^-$ $PhNH_3^+Cl^-$

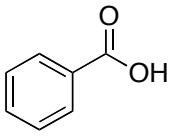
28. Suppose all of the molecules **A-D** are dissolved in diethyl ether.



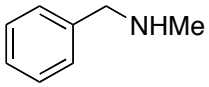
A



B



C



D

a. Which one or ones will extract (dissolve) into aqueous sodium hydroxide? (And why?)

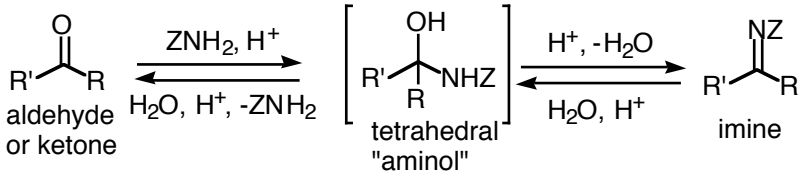
b. Which, if any, will extract into aqueous hydrochloric acid? (And why?)

c. Which, if any, will extract into neutral water? (Why or why not?)

d. Explain how you could use an extraction scheme to separate **D** from **A.**

C. Reactions of Amines (other than as bases)

2. Reaction with Ketones or Aldehydes (Section 19.10)



Notes:

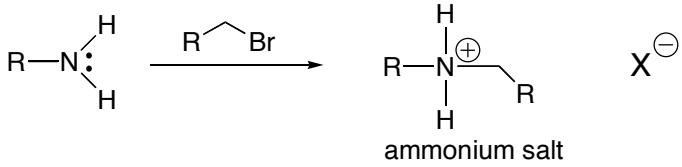
- "Z" can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The "aminol" can't be isolated, it's only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H's on nitrogen → 2º, 3º amines can't do this

Draw the Products of the following Amine reactions.

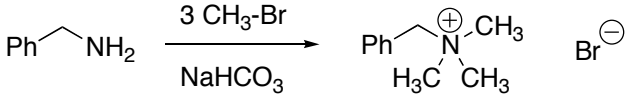
1. $PhNH_2$ —(4-phenyl-2-hexanone, H^+)→

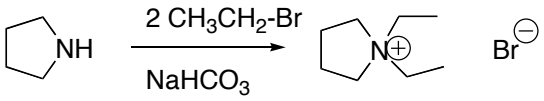
2. Cyclohexanone + H_2NNH_2 →

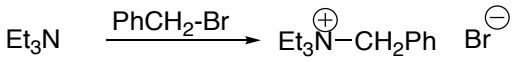
3. Alkylation of 1º Alkyl Halides (Section 19.12)



- **3a. Polyalkylation** is routine.
  - 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.



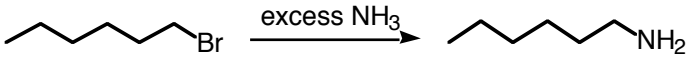




Notes

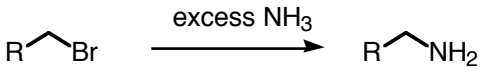
1. All amines are nucleophilic
   - $3^o > 2^o > 1^o > NH_3$
   - structural effects parallel basicity
2. Limited synthetic utility, due to frequent overalkylation
3. Due to S_N2 mechanism, limited to alkylation of 1^o R-X

- **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.



Synthetically Useful Alkylation Scenarios:

1. Exhaustive Alkylation to Intentionally produce quaternary ammonium salts
2. Reaction 10. **From 1^o Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A)

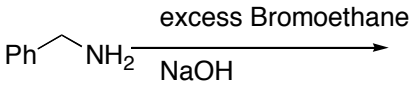


   - Access: 1^o Amines only
   - Mechanism required. (see reaction 3b)
   - No change in number of carbons.
   - Excess NH_3 prevents polysubstitution.

3. Cyclization reactions in which a 5 or 6-membered ring can form.

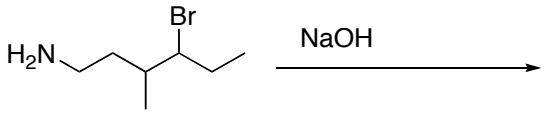
Draw the Products and mechanisms of the following Amine reactions.

1. $Me_3N + PhCH_2I \longrightarrow$

2. 

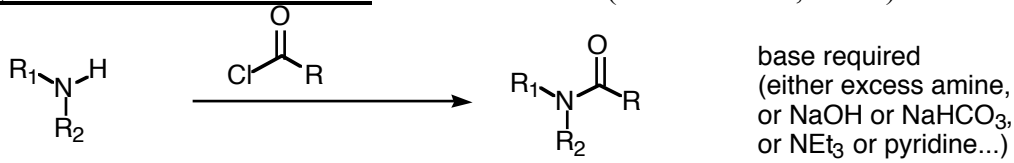
Draw the Products and mechanisms of the following Amine reactions.

1. $PhCH_2Br$ —(Excess NH_3)→

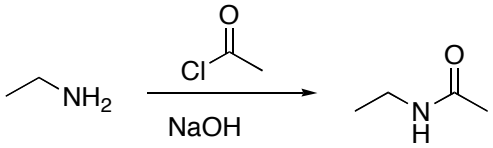
2. 

Why do you **not** get clean monoalkylation if you do a 1:1 mixture of RNH_2 and R-X?

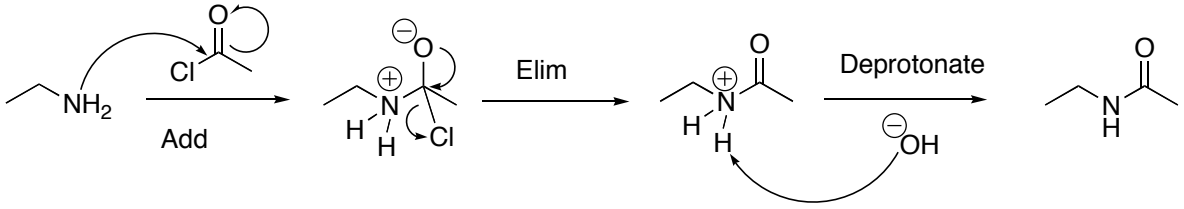
4. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)



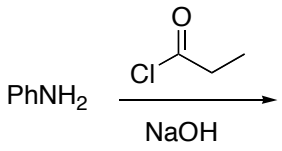
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH_3 all react well.
- But 3º amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or $NaHCO_3$ can be used.

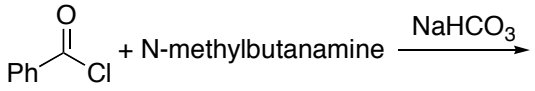


Mech: 3 steps: Addition-Elimination-Deprotonation

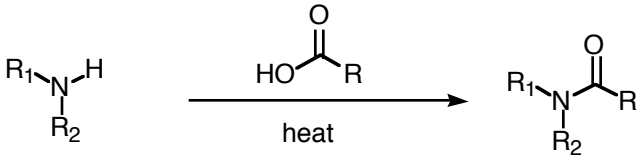


Draw the Products of the following Amine reactions, and the mechanism for the first one.

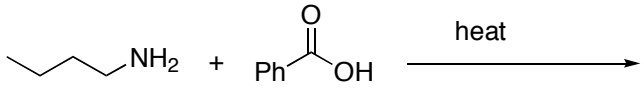
1. 

2. 

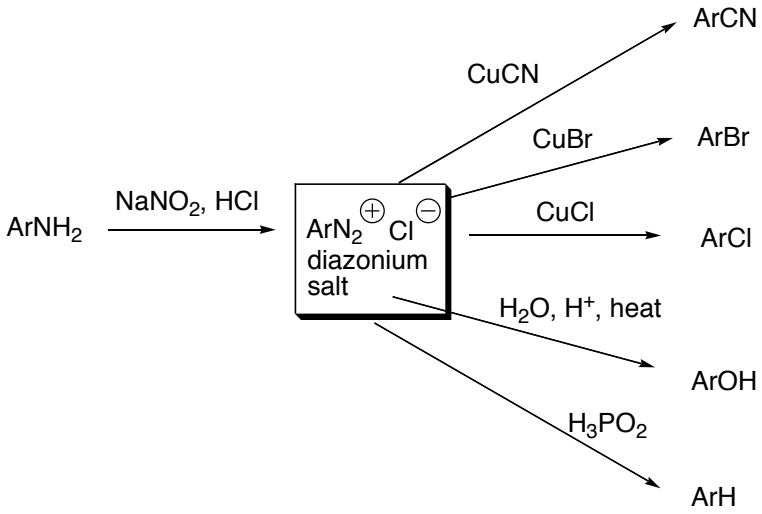
4b. **Acylation with Carboxylic Acids** to Form Amides: (Section 20-12)



- 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

1. 

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.

Lewis bases (lone pair electron donors) all function as:

1. Bases (give electrons to H^+)
2. Nucleophiles (give electrons to some other electrophile)
3. Reducing agents (give electrons to oxidizing agents)

Amines can be oxidized

$NaNO_2$/HCl is a strong oxidizing agent, converts RNH_2 to RN_2^+, and $ArNH_2$ to ArN_2^+

- "Diazonium salts"

RN_2^+ has the best leaving group known, because the leaving group is highly stable, neutral N_2 gas

1. Alkyl RN_2^+ are highly unstable, give cations, and usually give mixtures of E1, S_N1, and cation rearrangement product mixtures
2. Not much use synthetically
3. However, N_2 is such a great leaving group that even 1º carbocations can be formed/studied

Reactivity: $RN_2^+ > ROH_2^+ >$ ROTs > RI > RBr > RCl
Leaving group ability: N_2 > H_2O > TsO anion > Iodide anion > Bromide anion > Chloride anion

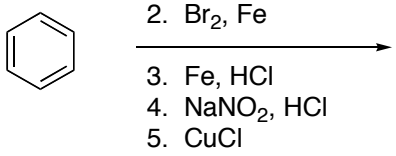
1. Unlike Alkyl diazoniums RN_2^+, aryl ArN_2^+ are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms

Synthetic Use:

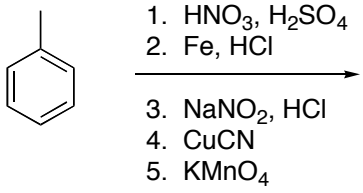
1. NO_2 (meta director) → NH_2 → N_2^+ → Cl, Br, OH, CN, H
2. Easy to get meta relationships, even when you end with things that are not meta directors

Draw the products

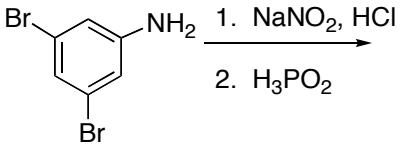
1.



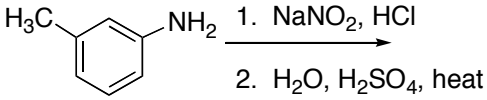
2.



3.

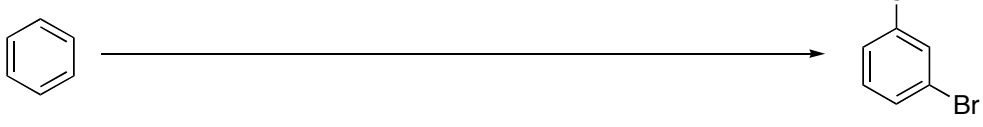


4.

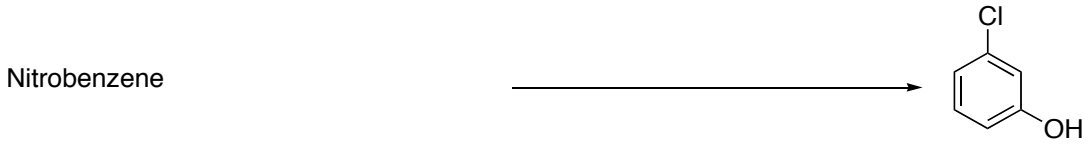


Design Synthesis

5.



6.

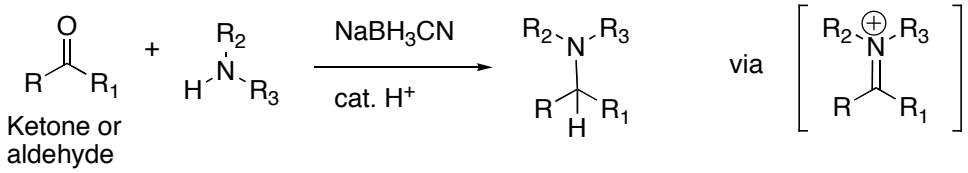


19.14 Reaction with Sulfonyl Chlorides (Not tested)

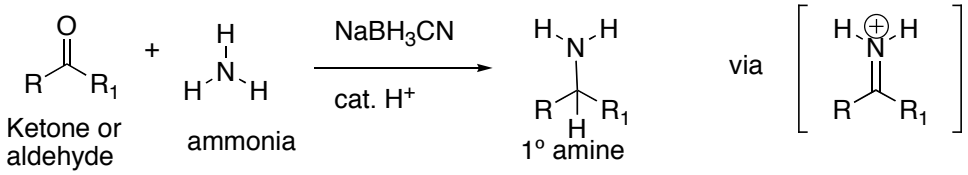
- Exactly as for amide formation
- Many antibiotic drugs: sulfonamides are so similar to amides that they occupy enzyme active sites → prevent bacterial growth

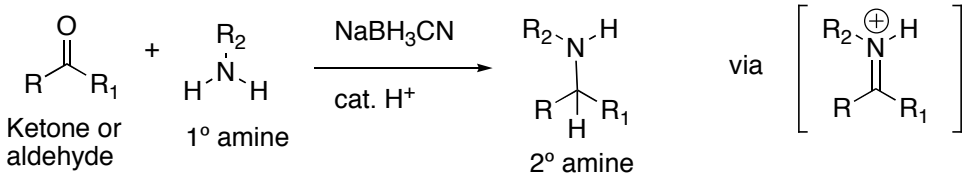
D. Synthesis of Amines

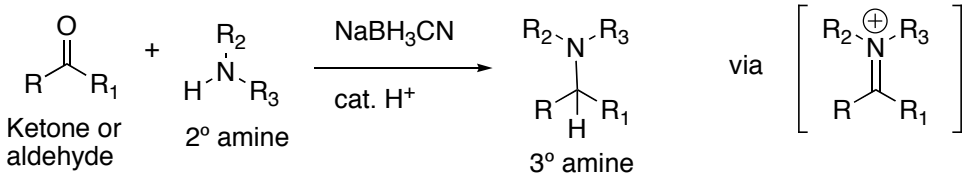
6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)



- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- 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:
  - $NH_3 \rightarrow$ 1º RNH_2
  - 1º $RNH_2 \rightarrow$ 2º R_2NH
  - 2º $R_2NH \rightarrow$ 3º R_3N
  - 3º R_3N don't react

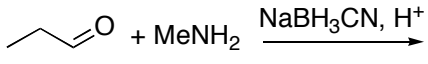


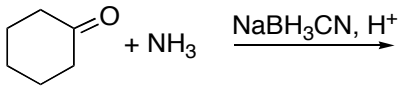


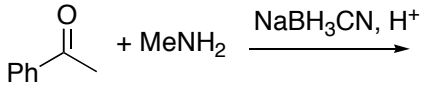


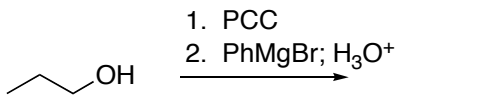
Note: book gives several other variants, but this is really the one universal method, and the one I'll use for my tests.

Synthesis of Amines: Draw the products for the following reactions.

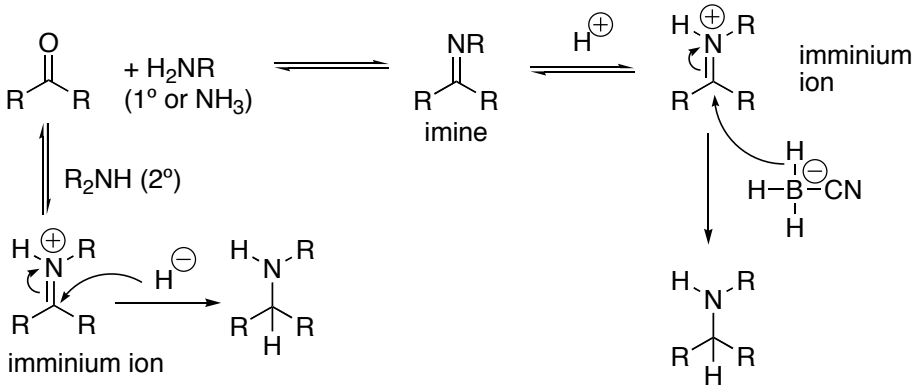
1. 

2. 

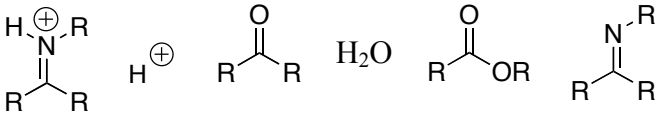
1. 

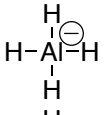
2. 

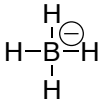
Mechanism (not for test) and some related notes

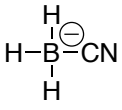


1. $NaBH_3CN$ functions as a hydride $H^{\ominus}$ source, similar to $NaBH_4$ and $LiAlH_4$
2. Formation of imminium cation is key
   - Highly electrophilic, much more so than neutral imine
3. $NaBH_3CN$ is a special, mild $H^{\ominus}$ source, much more stable and less reactive than $NaBH_4$ and $LiAlH_4$
   - So much so that it can coexist with acid (thus enabling imminium ion formation)
   - So much so that it does not reduce neutral ketones and aldehydes (thus allowing the aldehydes and ketones to sit around and equilibrate with imminium ion)

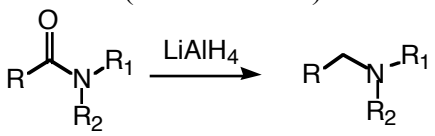
Hydride Stability	Hydride Reactivity	

$LiAlH_4$ 

$NaBH_4$ 

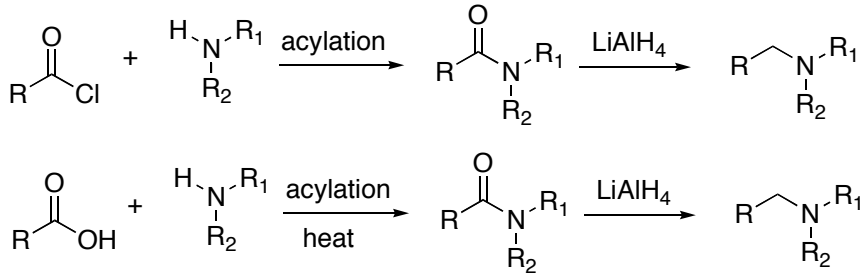
$NaBH_3CN$ 

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

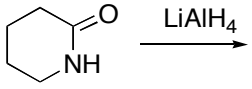


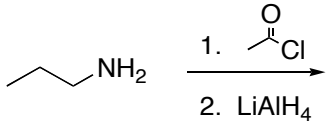
- No mechanism required for the reduction
- Access: 1º, 2º, or 3º Amines.
- R_1 and R_2 can be either H or C. Thus, you can produce either 1º, 2º, or 3º amines in this way:
  - $RCONH_2 \rightarrow$ 1º RCH_2NH_2
  - $RCONHR \rightarrow$ 2º RCH_2NHR
  - $RCONR_2 \rightarrow$ 3º RCH_2NR_2

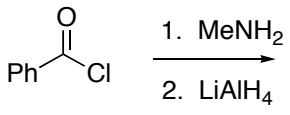
8. **From Amines via Amides**: (Section 19-20)



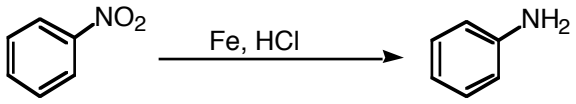
- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

1. 

2. 

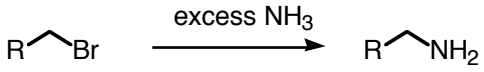
3. 

9. **Reduction of nitro compounds**: (section 19-21C)



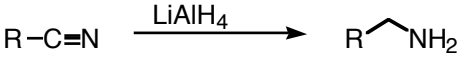
- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H_2, Ni/H_2, Pt/H_2,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).



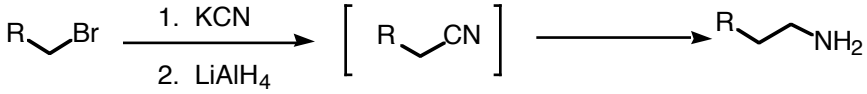
- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH_3 prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)

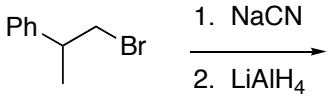


- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)



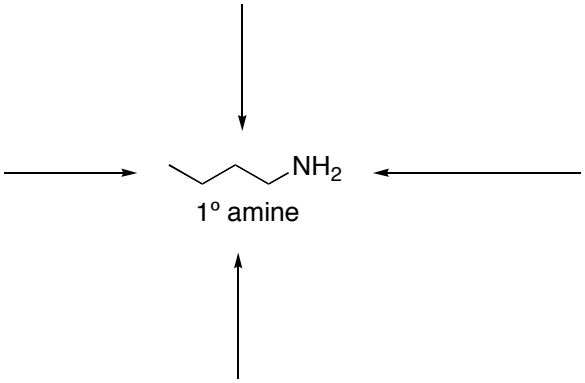
- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!



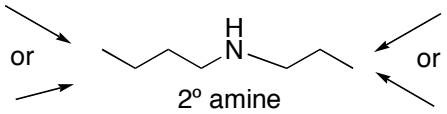
Summary of Amine Syntheses

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

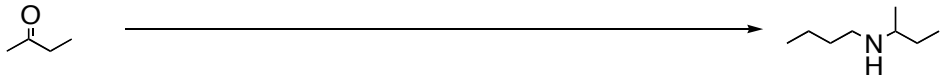
1. Come up with various pathways (4 good ones) to the following 1º amine:

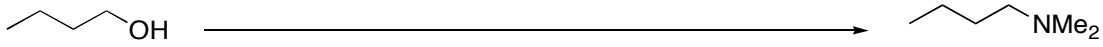


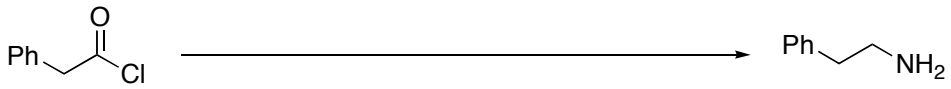
2. Come up with pathways (4 good ones) to the following 2º amine:

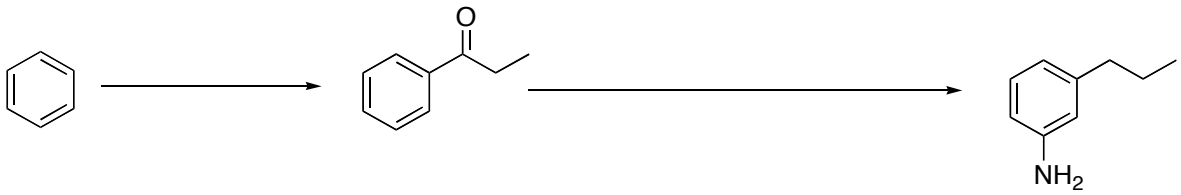


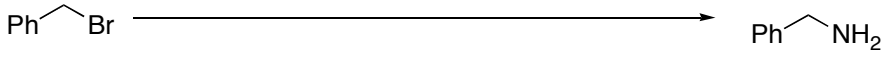
Provide Reagents for the following Transformations.

1. 

2. 

3. 

4. 

5. 

6.