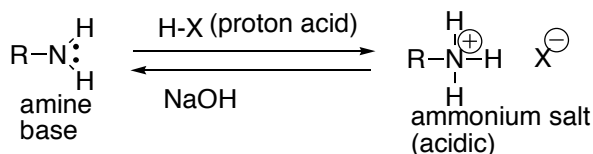


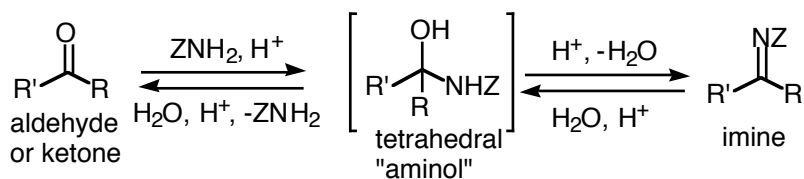
Reactions of Amines

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

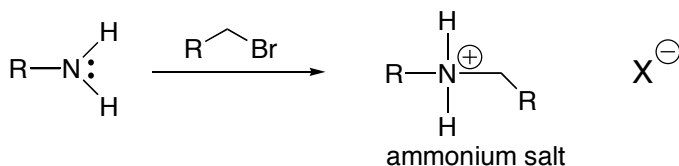
2. Reaction with Ketones or Aldehydes (Section 18-16,17 and 19-10)



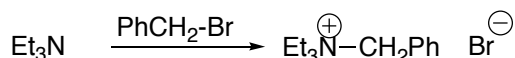
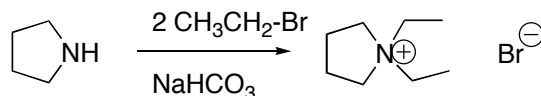
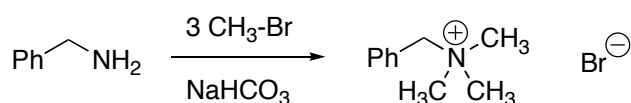
Notes:

- “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 \rightarrow 2° , 3° amines can’t do this

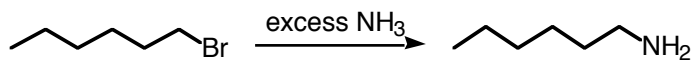
3. Alkylation of 1° Alkyl Halides (Section 19-12, 19-21A)



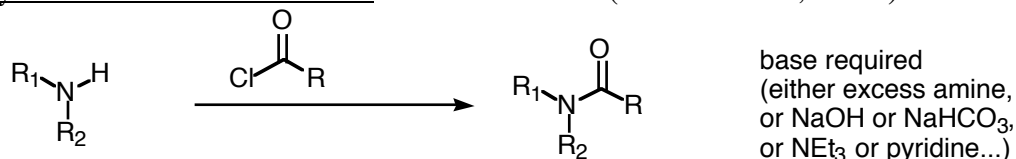
- **3a. Polyalkylation** is routine.
 - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H's on nitrogen, examples below).
 - Mechanism required for polyalkylations. The mechanism involves repetitive sequential $\text{S}_{\text{N}}2$ alkylation-deprotonations.



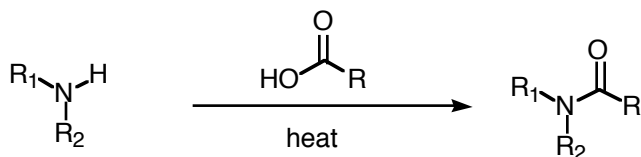
- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
 - Mechanism for monosubstitution required. This involves simple $\text{S}_{\text{N}}2$, followed by deprotonation by the excess amine.



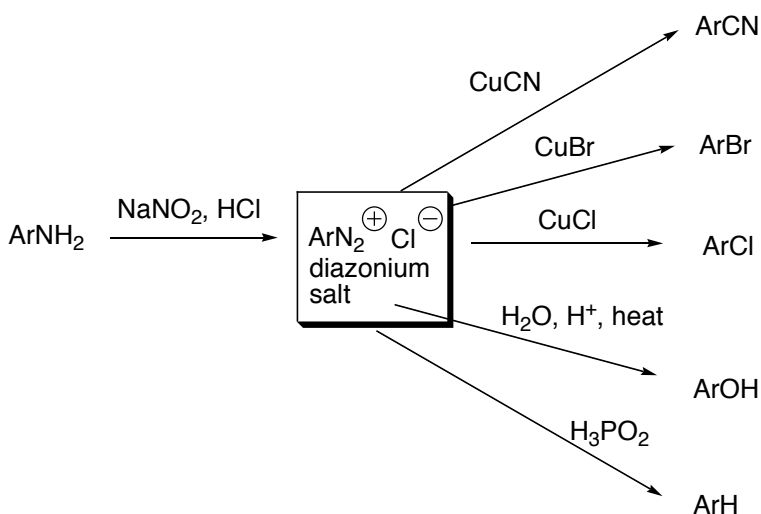
4. Acylation with Acid Chlorides to Form Amides: (Section 19-13, 20-15)



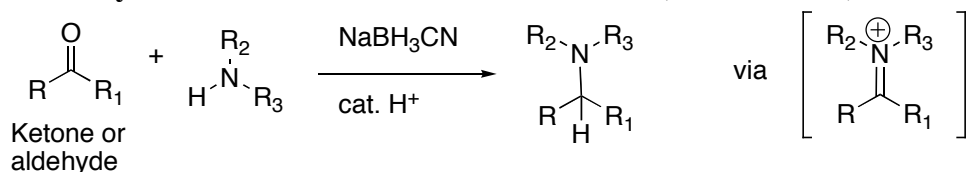
- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1°, 2°, or NH₃ all react well.
- But 3° amines can't work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H's (triethylamine, pyridine) can be used. Or else NaOH or NaHCO₃ can be used.

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

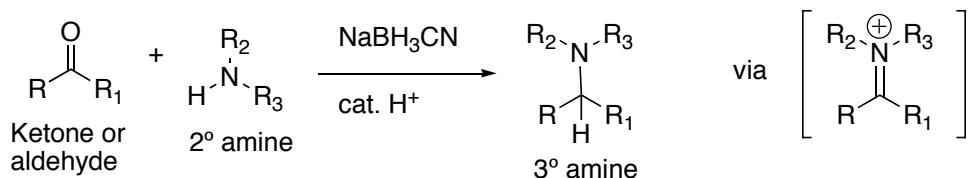
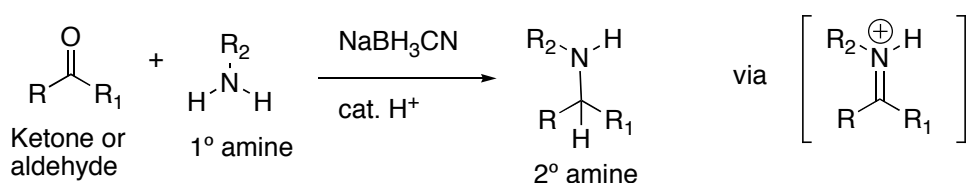
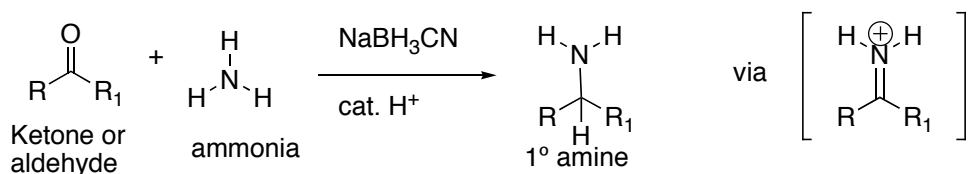
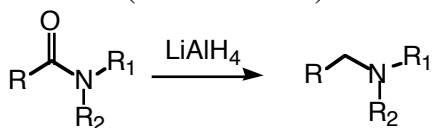
- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren't as good as with acid chlorides
- Biologically amine + acid \rightarrow amide is routine, and is facilitated by complex enzyme mechanisms

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.

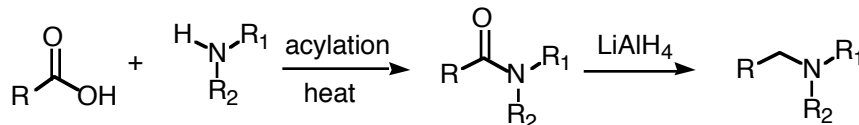
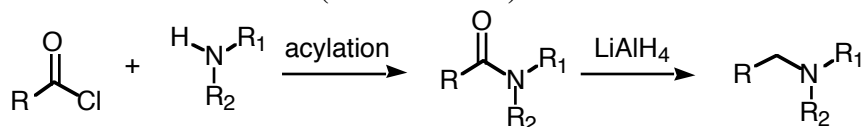
Synthesis of Amines**6. From Aldehydes or Ketones: Reductive Amination** (Section 19-19)

- Access: 1°, 2°, or 3° 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 R₂ and/or R₃ can be either a carbon or a hydrogen. Thus:
 - NH₃ → 1° RNH₂
 - 1° RNH₂ → 2° R₂NH
 - 2° R₂NH → 3° R₃N
 - 3° R₃N don't react

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

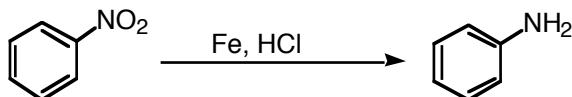
- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- R₁ and R₂ can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
 - RCONH₂ → 1° RCH₂NH₂
 - RCONHR → 2° RCH₂NHR
 - RCONR₂ → 3° RCH₂NR₂

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



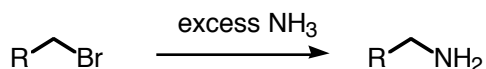
- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

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



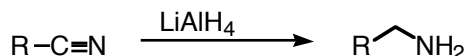
- Access: 1° Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
 - Pd/H₂, Ni/H₂, Pt/H₂,
 - Fe/HCl, Zn/HCl, Sn/HCl

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



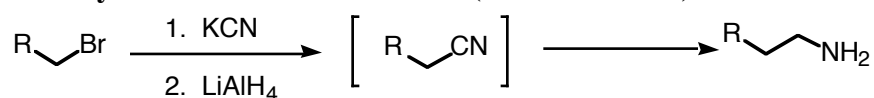
- Access: 1° Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH₃ prevents polysubstitution.

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



- Access: 1° amines
- Mechanism not required.

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



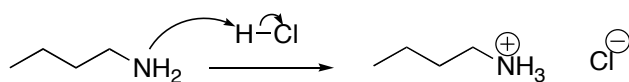
- Access: 1° Amines only
- Mechanism not required.
- One-Carbon chain extension!

Summary of Amine Syntheses

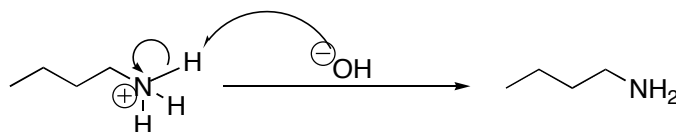
Route	Reaction Number	Source/ Precursor	Reagent	Available Amines	Comments
1	#6	Aldehydes or Ketones	R_2NH , H^+ $NaBH_3CN$,	1°, 2°, or 3° Amines	
2	#7, #8	Amides	$LiAlH_4$	1°, 2°, or 3° Amines	
3	#7, #8	Amines (via Amide)	1. $RCOCl$ (or RCO_2H , heat) 2. $LiAlH_4$	1° $ArNH_2$	
4	#7, #8	Acid Chlorides 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

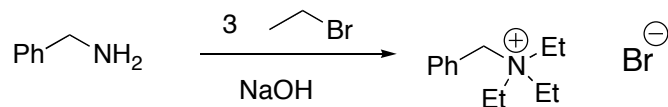


1.-Reverse. Deprotonation

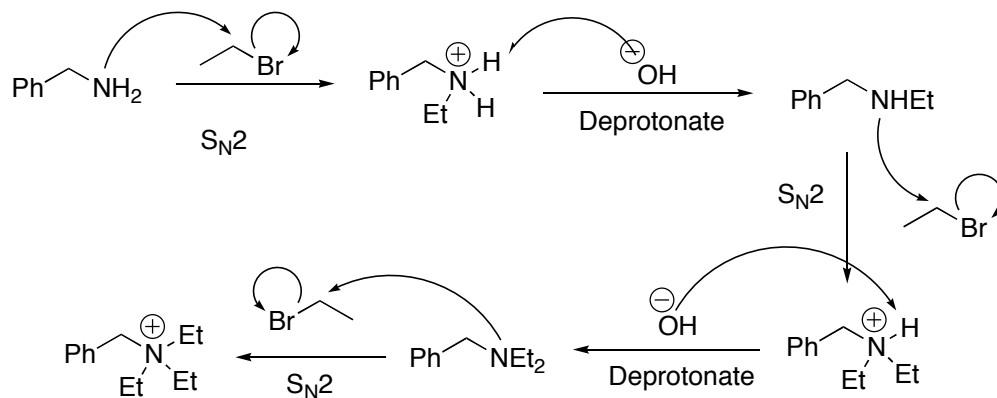


3. Polyalkylation

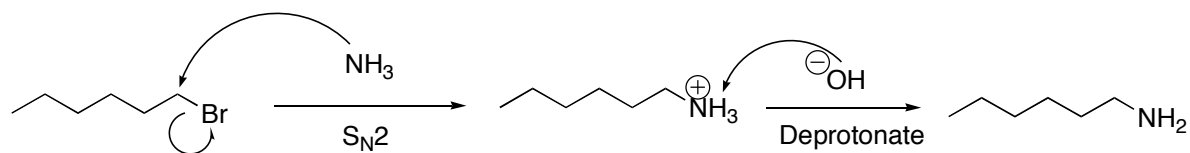
Ex:



Mech:

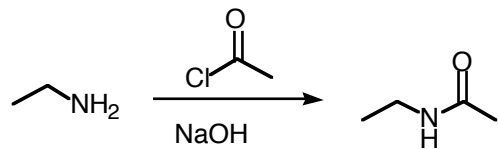


3b. Monoalkylation

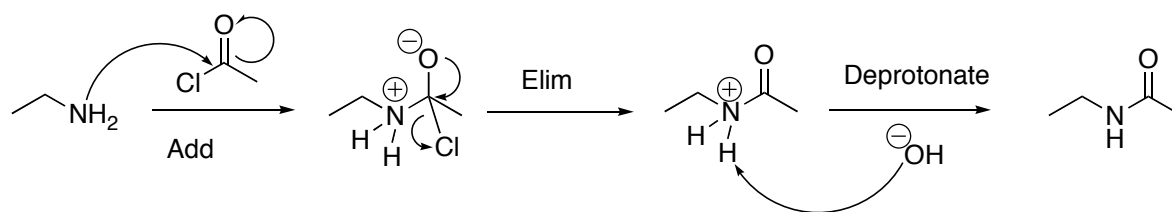


4. Acylation

Ex:



Mech: 3 steps: Addition-Elimination-Deprotonation

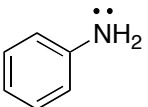
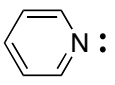



Formal Amine Nomenclature: X-alkanamine, N-alkyl-X-alkanamine, etc.


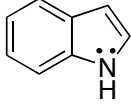
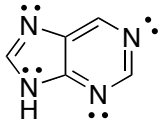
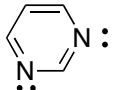
- Choose longest C-chain to which nitrogen is attached, and number from end nearer Nitrogen
- The nitrogen does ****not**** count as a number itself. An alkyl substituent is "N-alkyl"...
- Be sure to specify with a number to indicate which carbon has the nitrogen
- NH_2 as a Substituent: "Amino"

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

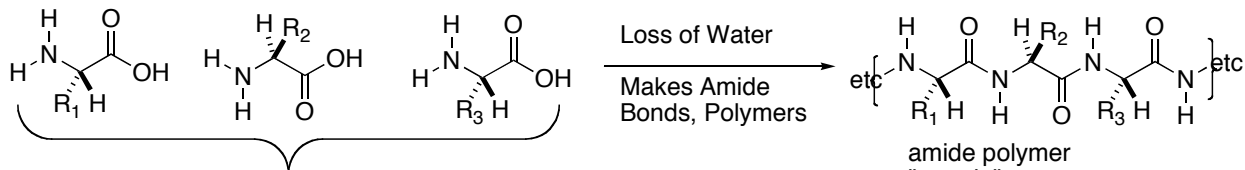
Three Common Amine Names to Memorize

Name	Structure	N Atom Hybrid	Lone-Pair Hybrid
Aniline		sp^2	p
Pyridine		sp^2	sp^2
Pyrrole		sp^2	p

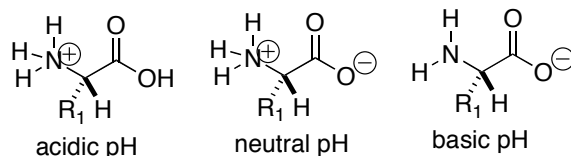
Some Other Famous Common Amine Names (No memory requirement)

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

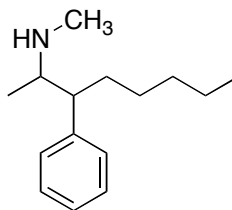
"Amino Acids"



- 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 the polymer essentially spells out the biological activity of the protein.

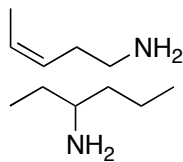


Nomenclature. Draw the structure or provide the name for the following.



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

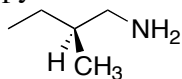
2. Z-3-penten-1-amine



3. 3-hexanamine

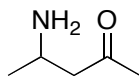


4. pyridine



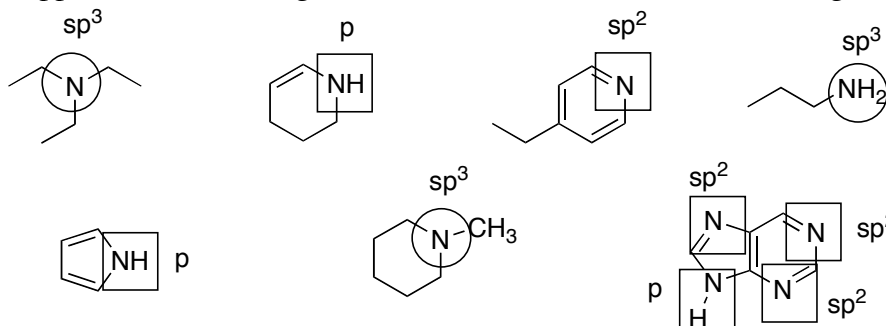
5. 2-methyl-1-butanamine

6. 4-amino-2-pentanone (here, amino is substituent, ketone priority)

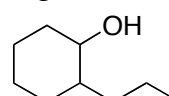
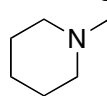
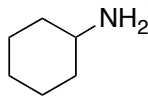
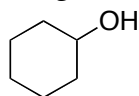


7. Structure and Hybridization. For each of the Nitrogens in structures below:

- circle the Nitrogen atom if the atom is sp^3 hybridized; but a box around the Nitrogen atom if it is sp^2 hybridized.
- Then beside each Nitrogen atom write in the hybridization of the Nitrogen lone pair,
- and the approximate bond angles (180, 120, 109, or 90) about the nitrogen atom.



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

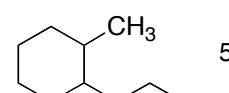
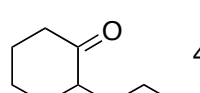
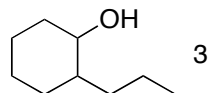
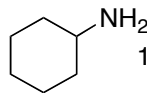
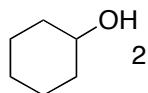


Alcohols H-bond themselves better than amines (because amine H is less positive)

no H-bonding

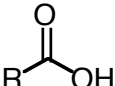
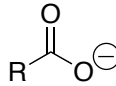
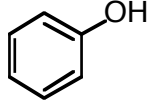
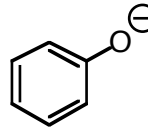
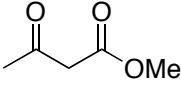
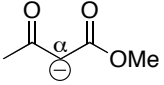
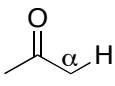
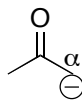
H-bonding + molecular weight

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



Basic amines H-bond water-H's better

Acidity/Basicity Table 19.1: Neutral Acids and Anionic Bases

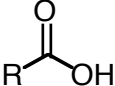
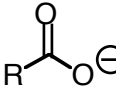
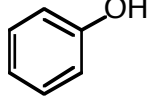
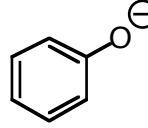
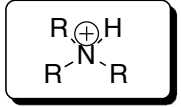
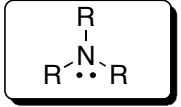
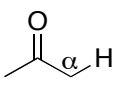
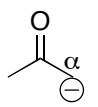
<u>Class</u>	<u>Neutral Acid Structure</u>	<u>K_a</u>	<u>Acid Strength</u>	<u>Anion Base</u>	<u>Base Strength</u>
Strong Acids	H-Cl, H _s SO ₄	10 ²		Cl [⊖] , HO-S(=O) ₂ -O [⊖]	
Carboxylic Acid		10 ⁻⁵			
Phenol		10 ⁻¹⁰			
1,3-Dicarbonyl		10 ⁻¹²			
Water	HOH	10 ⁻¹⁶		HO [⊖]	
Alcohol	ROH	10 ⁻¹⁷		RO [⊖]	
Ketones and Aldehydes		10 ⁻²⁰			
Amine (N-H)	(iPr) ₂ N-H	10 ⁻³³		(iPr) ₂ N [⊖] Li [⊕]	
Alkane (C-H)	RCH ₃	10 ⁻⁵⁰		RCH ₂ [⊖]	

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

<u>Class</u>	<u>Structure</u>	<u>K_a</u>	<u>Acid Strength</u>	<u>Base</u>	<u>Base Strength</u>	
Strong Acids	H-Cl, H ₂ SO ₄	10 ²		Cl^{\ominus} , $\text{HO}-\text{S}(\text{O})_2^{\ominus}$		<u>S</u>Smell <u>A</u>Awful!
Hydronium	H ₃ O ⁺ , ROH ⁺ cationic	10 ⁰		H ₂ O, HOR neutral		<u>H</u>Humans
Carboxylic Acid		10 ⁻⁵				<u>C</u>Cuz
Phenol		10 ⁻¹⁰				<u>P</u>People
Ammonium Ion (Charged)	 Charged, but only weakly acidic!	10⁻¹²		 Neutral, but basic		<u>A</u>gainst
Water	HOH	10 ⁻¹⁶		HO^{\ominus}		<u>W</u>orking
Alcohol	ROH	10 ⁻¹⁷		RO^{\ominus}		<u>A</u>re
Ketones and Aldehydes		10 ⁻²⁰				<u>K</u>ingdoms
Amine (N-H)	(iPr) ₂ N-H	10 ⁻³³		(iPr) ₂ N [⊖] Li [⊕]		<u>A</u>nimal
Alkane (C-H)	RCH ₃	10 ⁻⁵⁰		RCH ₂ [⊖]		<u>A</u>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.

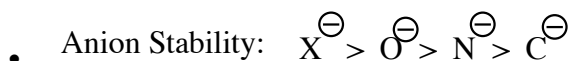
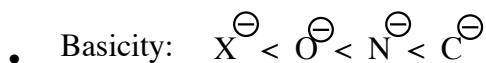
More Detailed Discussion of Acid/Base Patterns/Factors to remember

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:

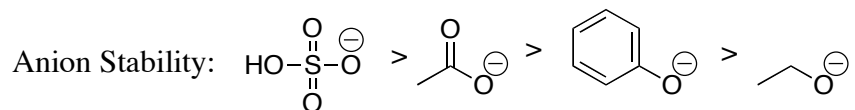
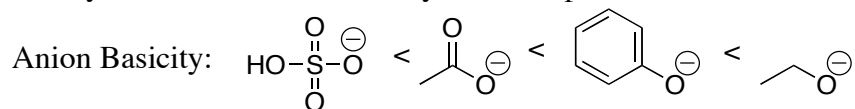
- Acidity: H-X (halogen) > H-O > H-N > H-C



3. Resonance/Conjugation:

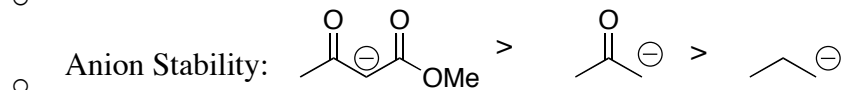
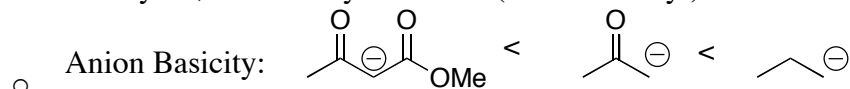
- Oxygen Series:

Acidity: sulfuric acid > carboxylic acid > phenol > alcohol



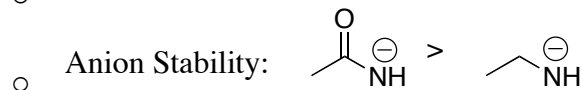
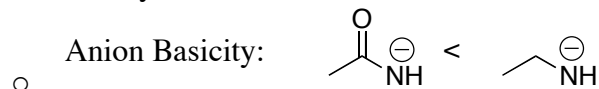
- Carbon Series:

○ Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane



- Nitrogen Series:

○ Acidity: amide > amine



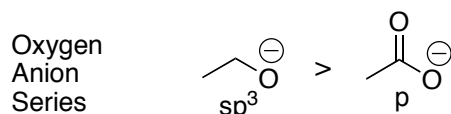
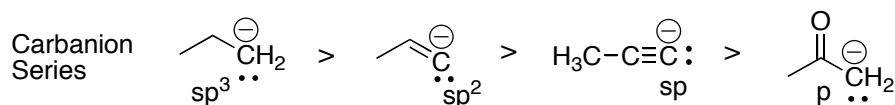
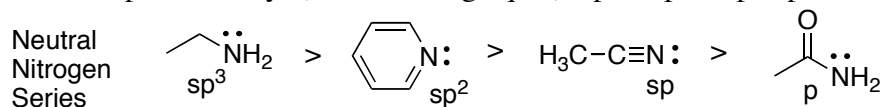
- Note: Resonance is often useful as a tiebreaker (for example, molecules in which both have O-H bonds and both have equal charge, so that neither the charge factor nor the electronegativity factor could predict acidity/basicity)
- NOTE: Resonance can sometimes (not always) trump electronegativity or 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:

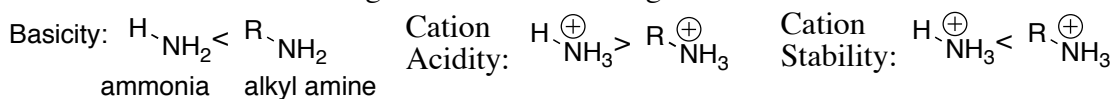
- For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$



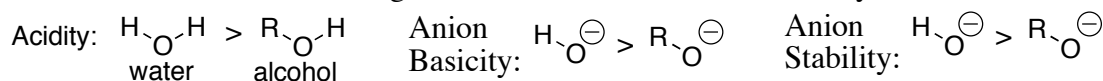
- This means that for acidity, alkynes > alkenes > alkanes

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 Strength	Lone Pair Hybrid		Impact On Base Strength	Structure of Ammonium Acid	K_a	Acid Strength
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		NH_4^+	$10^{-9.3}$	
6	EtNH_2		sp^3	Alkyl Donor	Increase	EtNH_3^+	$10^{-10.6}$	
7	Et_2NH		sp^3	Alkyl Donor	Increase	Et_2NH_2^+	$10^{-10.8}$	
8	Et_3N		sp^3	Alkyl Donor	Increase	Et_3NH^+	$10^{-11.0}$	

General Amine Basicity Patterns.

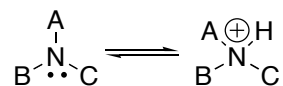
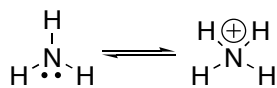
- Relative basicity correlates Lone pair hybridization: sp^3 (entries 5-8) > sp^2 (entry 4) > p (entries 1-3) (hybridization factor)
- Within the sp^3 amines, increasing alkyl substitution increases basicity (entries 5-8): $3^\circ > 2^\circ > 1^\circ > \text{NH}_3$ (electron donating group factor)

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

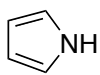
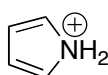
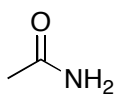
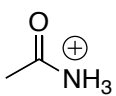
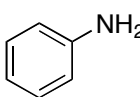
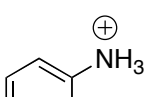

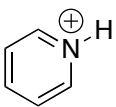
- Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because of the electron-withdrawing group factor).
- Conjugated nitrogens are in general less basic 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 its 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 Stabilized or Destabilized?
5	NH ₃	NH ₄ ⁺	Reference	
6-8	Et ₃ N	Et ₃ NH ⁺	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

10. NH_3 NH_4^+ The ammonium. Charge factor.
11. The cation. Charge factor.
12.
 1 2 3
 Electronegativity factor.
13. The acid. Resonance factor.
14. The amide. Resonance factor.
15.
 1-2-3. Electron donor/withdrawer factor. Nitro withdrawer stabilizes anion; methoxy donor destabilizes anion.
 1-2-4.

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

16. NH_3 NaNH_2 Charge factor, second structure
17. NaOH H_2O NaOH , charge factor.
18. NH_3 H_2O Ammonia. Electronegativity factor.
19. Alkoxide. Resonance factor.
20.
 3-2-1. Donor/withdrawer factor. Nitro withdrawer stabilizes, methoxy donor destabilizes.
21. NH_3 $\text{O}_2\text{N-NH}_2$
 1 - 2 - 3 Donor/withdrawer. Alkyl is donor, nitro is withdrawer.

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

22. NH_3 Alkoxide. Charge trumps electronegativity.
23. Enolate. Resonance isn't enough to outweigh electronegativity.
24. Alkoxide. Resonance is so good that even a C anion beats the O anion.


Choose the More Basic for Each of the Following Pairs


25. NH_3 NaNH_2
Charge factor. NaNH_2 .

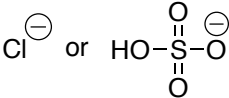
26. NH_3 NaOH
 NaOH . Charge factor outweighs electroneg.

27. NH_3 H_2O
 NH_3 . Electroneg factor.

28. NH_3 CH_3OH
 NH_3 . Electroneg factor.

29. NH_3 
Alkoxide. Charge factor.

30. NH_3 
Ammonia. The anion is so stabilized by **resonance** that the neutral amine is more basic.

31. NH_3 Cl^- or 
Ammonia. Both of these "strong acid" anions are so stable that they don't function as bases.



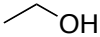
32. NH_3 CH_3MgBr
Grignard. C anion. Charge factor.

33. NH_3 CH_3NH_2
 CH_3NH_2 . Donor effect.

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

a. CH_3MgBr	CH_3NHNa	CH_3NH_2	CH_3OH
1	2	3	4
Carbanion	N anion	N neutral	O neutral

So we see both the charge factor and the electronegativity factors at play.

b. 		CH_3NH_2	
1	3	2	4
Anion, no res	Anion, with res	Neutral, Nit	Neutral, Ox

Alkoxide with charge is stronger than neutral nitrogen. But carboxylate with resonance is weaker than neutral nitrogen. Neutral oxygen is weakest (loses all charge and electroneg wars)

36. Rank the acidity of the following compounds, 1 being most acidic.

a.	H_3O^+	NH_4^+Cl^-	water	acetic acid ($\text{CH}_3\text{CO}_2\text{H}$)	NH_3
	1	3	4	2	5

Charge factor, electronegativity factor, and resonance factor all impact.

Of the three neutrals, acetic acid is most due to resonance, ammonia least due to electroneg.

Of the two cations, hydronium is stronger than ammonium (electronegativity).

Ammonium ion is weaker than carboxylic acid (due to carboxylate resonance trumping charge factor)

b.	H_3O^+	acetic acid ($\text{CH}_3\text{CO}_2\text{H}$)	$\text{Me}_3\text{NH}^+\text{Cl}^-$	ethanol
	1	2	3	4

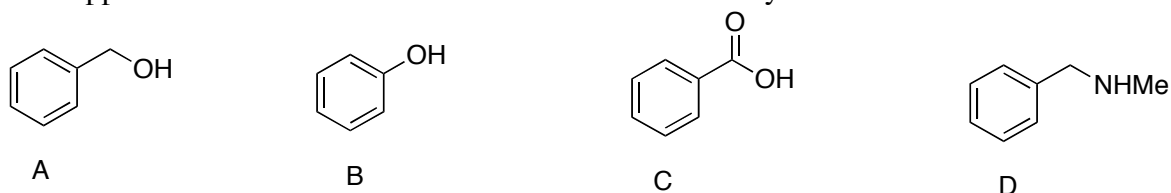
Charge, electroneg, and resonance.

Acetic acid is stronger than ammonium due to resonance on resulting carboxylate.

c.	NH_4^+Cl^-	$\text{Me}_3\text{NH}^+\text{Cl}^-$	$\text{PhNH}_3^+\text{Cl}^-$
	2	3	1

Hybridization and donor effect. #1 wins because it produces aniline, which has p hybridization and is stabilized by conjugation. #2 and #3 both produce sp^3 lone pairs. #3 is least acidic because of the alkyl donors, which stabilize the cation.

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



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

Answer: B and C.

Key: An organic will move into the organic phase if it is ionized.

Why: B and C give resonance stabilized anions that are more stable than hydroxide. Hydroxide is unable to deprotonate A and D, since that would result in anions less stable than hydroxide.

Since they stay neutral, they stay in the organic layer.

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

Answer: D.

Key: An organic will move into the organic phase if it is ionized.

Why: Amine D is protonated in acid to give a water soluble ammonium ion. The oxygen compounds are not protonated and ionized by acidic water; since they stay neutral, they stay in the ether layer.

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

Answer: None.

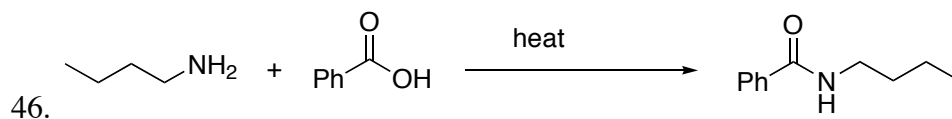
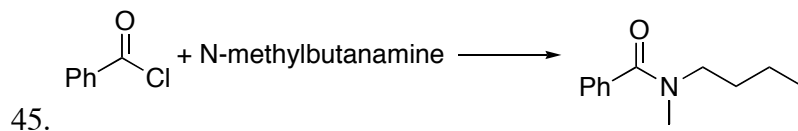
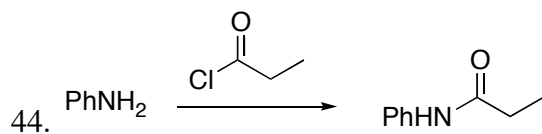
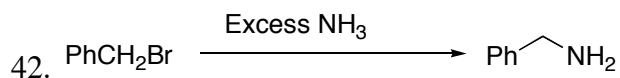
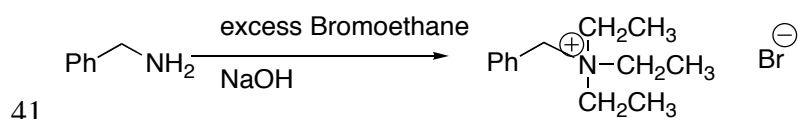
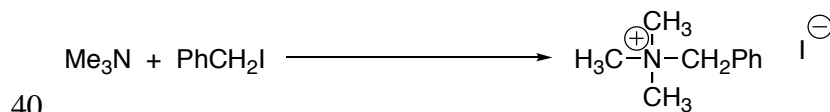
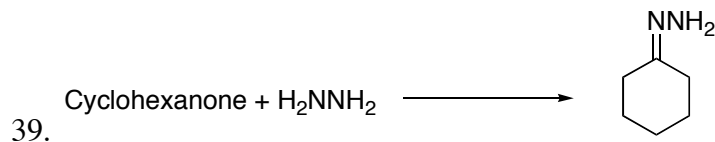
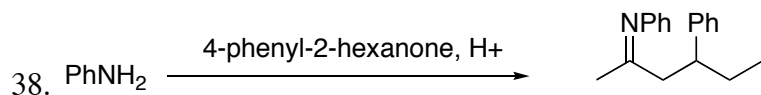
Key: an organic will move into the organic phase if it is ionized.

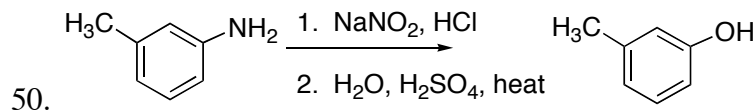
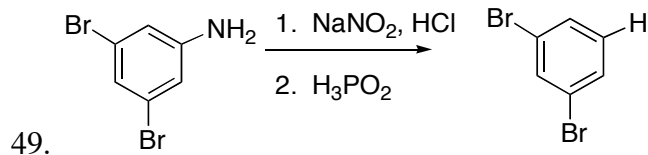
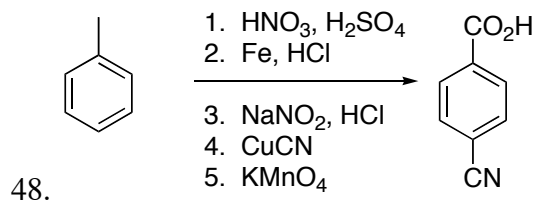
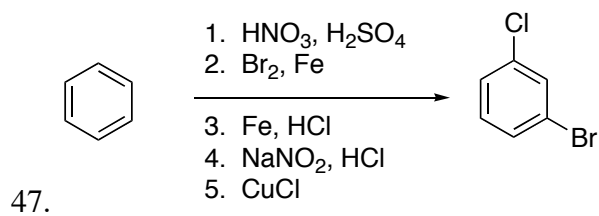
Why: Neutral water neither protonates nor deprotonates the compounds. They all stay neutral, so they all stay in the organic layer.

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

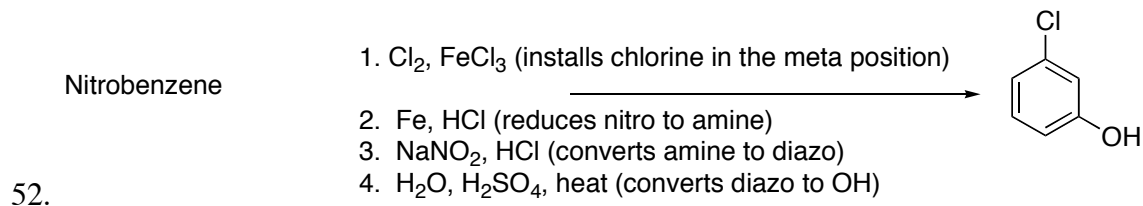
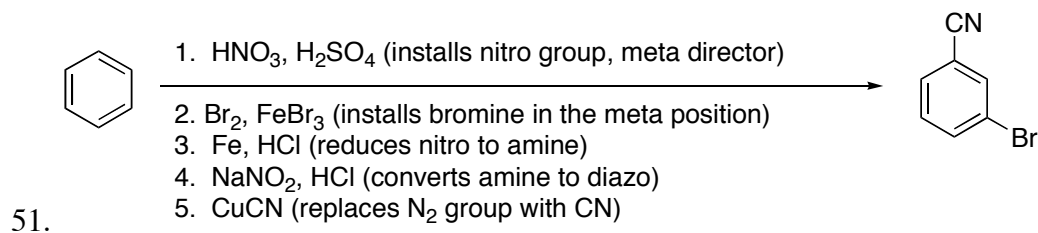
- Dissolve in ether.
- Treat with aqueous acid, which protonates/ionizes D but not A.
- Separate layers.
- Concentrate the organic phase; get pure A.
- Add base to the aqueous layer, to convert DH^+ back to neutral D. In its neutral form, amine D will no longer be soluble in water, and will either crystallize out or can be extracted out with an organic solvent.

Draw the Products of the following Amine reactions.

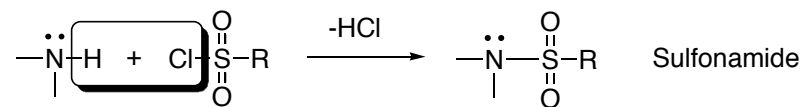




Design Synthesis



19.14 Reaction with Sulfonyl Chlorides: and the Hinsberg Test

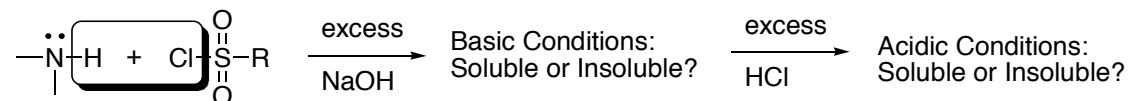


- Exactly as for amide formation
- Many antibiotic drugs: sulfonamides are so similar to amides that they occupy enzyme active sites → prevent bacterial growth

Sulfonamides and the Hinsberg Test for 1°/2°/3° Amines

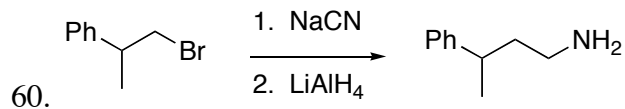
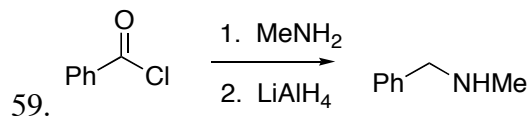
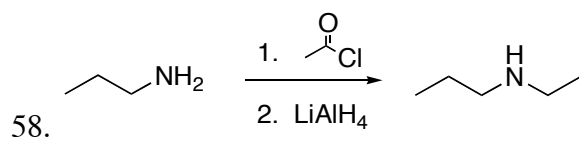
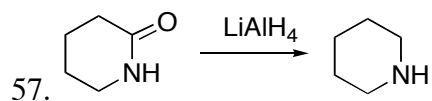
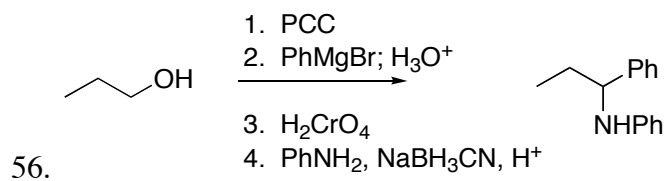
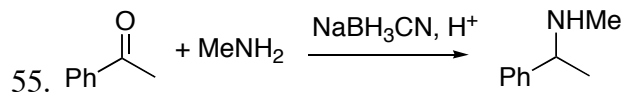
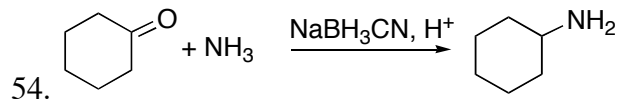
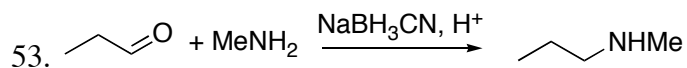
Keys:

- Sulfonamides are Nonbasic
- Sulfonamides in which the nitrogen has a hydrogen are acidic

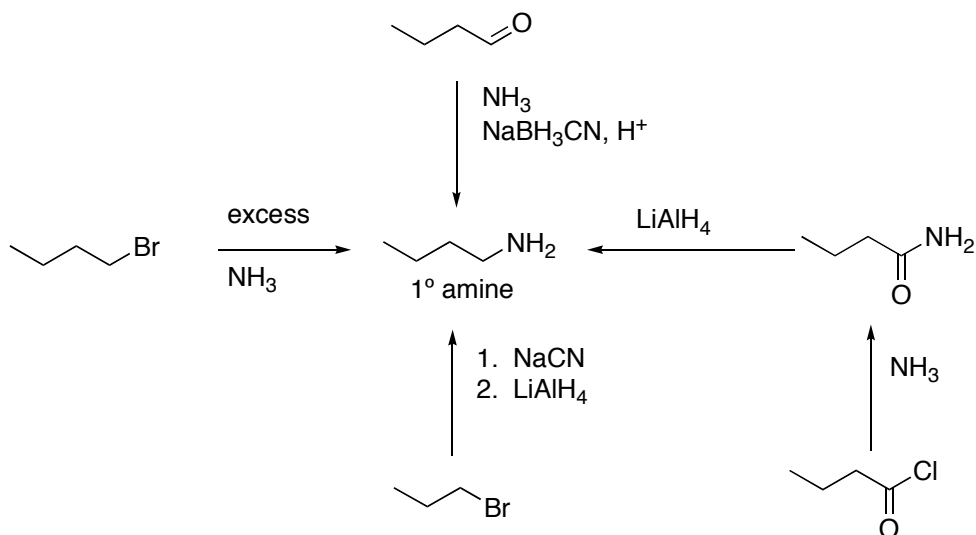


Starting Amine	Derived Sulfonamide	Basic Conditions	Acidic Conditions
1° Amine	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N---S(=O)}_2\text{---R} \\ \\ \text{H} \end{array}$	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N}^{\ominus}\text{---S(=O)}_2\text{---R} \\ \\ \cdot\cdot \end{array}$ <u>Soluble</u>	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N---S(=O)}_2\text{---R} \\ \\ \text{H} \end{array}$ <u>Insoluble</u>
2° Amine	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N---S(=O)}_2\text{---R} \\ \\ \text{R} \end{array}$	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N---S(=O)}_2\text{---R} \\ \\ \text{R} \end{array}$ <u>Insoluble</u>	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N---S(=O)}_2\text{---R} \\ \\ \text{R} \end{array}$ <u>Insoluble</u>
3° Amine	None Can Form	$\begin{array}{c} \cdot\cdot \\ \\ \text{R---N}^{\ominus}\text{---R} \\ \\ \text{R} \end{array}$ <u>Insoluble</u>	$\begin{array}{c} \text{H} \\ \\ \text{R---N}^{\oplus}\text{---R} \\ \\ \text{R} \end{array}$ <u>Soluble</u>

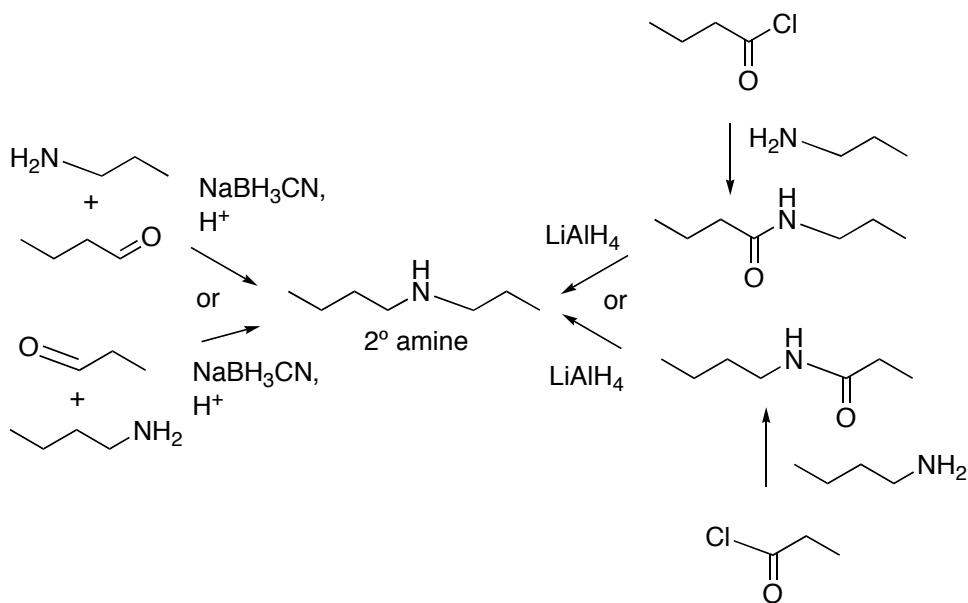
Synthesis of Amines: Draw the products for the following reactions.



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



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



Provide Reagents for the following Transformations.

