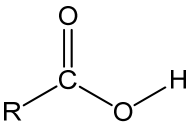
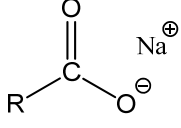
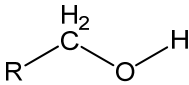
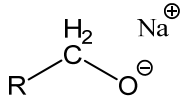
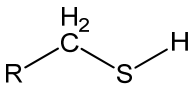
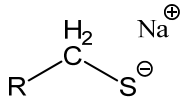
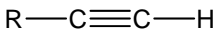
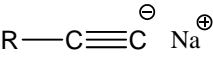
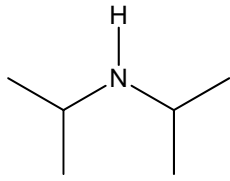
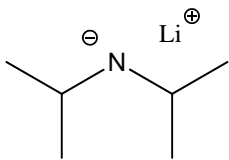
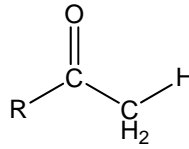
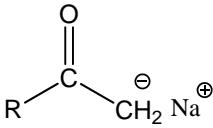
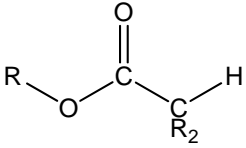
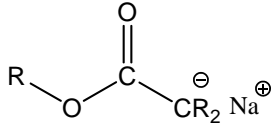
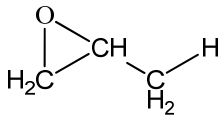
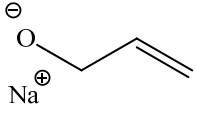
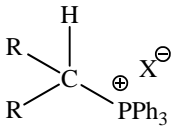
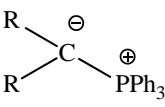
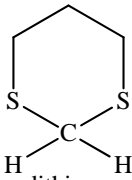
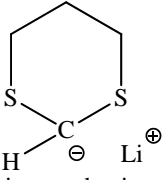
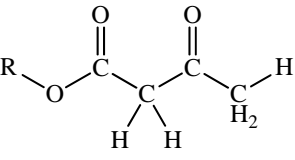
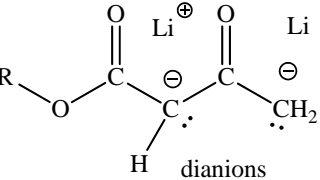
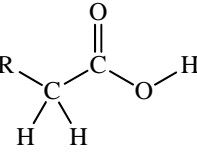
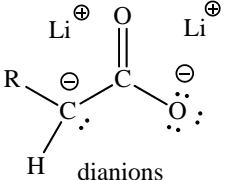

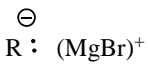


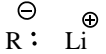
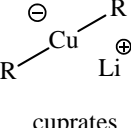


Important preparative reactions (acid/base and organometallic reactions) used in the examples below. These are sometimes necessary to set up reaction conditions.

<u>Acid</u>	<u>Base</u>	<u>New Base</u>	<u>Comments</u>
 carboxylic acids	sodium hydroxide $\text{Na}^{\oplus} \ominus \text{O}-\text{H}$ $K_{\text{eq}} = \frac{K_a(\text{RCO}_2\text{H})}{K_a(\text{H}_2\text{O})}$ $K_{\text{eq}} = \frac{10^{-5}}{10^{-16}} = 10^{+11}$	 carboxylates	Carboxylates are good nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me, 1° and 2° RX, only E2 at 3° RX.
 alcohols	sodium hydride $\text{Na}^{\oplus} \ominus \text{H}$ $K_{\text{eq}} = \frac{K_a(\text{ROH})}{K_a(\text{H}_2)}$ $K_{\text{eq}} = \frac{10^{-17}}{10^{-35}} = 10^{+18}$	 alkoxides	alkoxides are OK nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me, 1° RX and 2° allylic/benzylic centers. They are strong bases, $\text{E}2 > S_{\text{N}}2$ at 2° and only E2 at 3°RX.
 thiols	sodium hydroxide $\text{Na}^{\oplus} \ominus \text{OH}$ $K_{\text{eq}} = \frac{K_a(\text{RSH})}{K_a(\text{H}_2\text{O})}$ $K_{\text{eq}} = \frac{10^{-8}}{10^{-16}} = 10^{+8}$	 thiolates	thiolates are good nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me, 1° and 2° RX, and bases, $\text{E}2 > S_{\text{N}}2$ at 3°RX.
 terminal alkynes	sodium amide $\text{Na}^{\oplus} \ominus \text{NR}_2$ $K_{\text{eq}} = \frac{K_a(\text{RCCH})}{K_a(\text{HNR}_2)}$ $K_{\text{eq}} = \frac{10^{-25}}{10^{-37}} = 10^{+12}$	 terminal acetylides	terminal acetylides are OK nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me and 1° RX, and strong bases, $\text{E}2 > S_{\text{N}}2$ at 2° and only E2 at 3°RX.
 diisopropylamine	n-butyl lithium $\text{Li}^{\oplus} \ominus \text{n-Bu}$ $K_{\text{eq}} = \frac{K_a(\text{HNR}_2)}{K_a(\text{H-C}_4\text{H}_9)}$ $K_{\text{eq}} = \frac{10^{-37}}{10^{-50}} = 10^{+13}$	 LDA = lithium diisopropylamide	LDA is a very strong base that is also very sterically hindered, it always acts as a base in our course. We use LDA to remove C_{α} -H protons from carbonyl compounds to make enolates and epoxides to make allylic alcohols.
 ketones / aldehydes	LDA = lithium diisopropylamide: $\text{Na}^{\oplus} \ominus \text{NR}_2$ -78°C $K_{\text{eq}} = \frac{K_a(\text{RCOCH}_3)}{K_a(\text{HNR}_2)}$ $K_{\text{eq}} = \frac{10^{-20}}{10^{-37}} = 10^{+17}$	 ketone enolates	enolates are good nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me, 1° and 2° RX, and strong bases, $\text{E}2 > S_{\text{N}}2$ at 3°RX. Low temperature (-78°C) is important to prevent other reaction possibilities.
 esters / 3° amides	LDA = lithium diisopropylamide: $\text{Na}^{\oplus} \ominus \text{NR}_2$ -78°C $K_{\text{eq}} = \frac{K_a(\text{ROCOCH}_3)}{K_a(\text{HNR}_2)}$ $K_{\text{eq}} = \frac{10^{-25}}{10^{-37}} = 10^{+12}$	 ester enolates	enolates are good nucleophiles, $S_{\text{N}}2 > \text{E}2$ at Me, 1° and 2° RX, and strong bases, $\text{E}2 > S_{\text{N}}2$ at 3°RX. Low temperature (-78°C) is important to prevent other reaction possibilities.

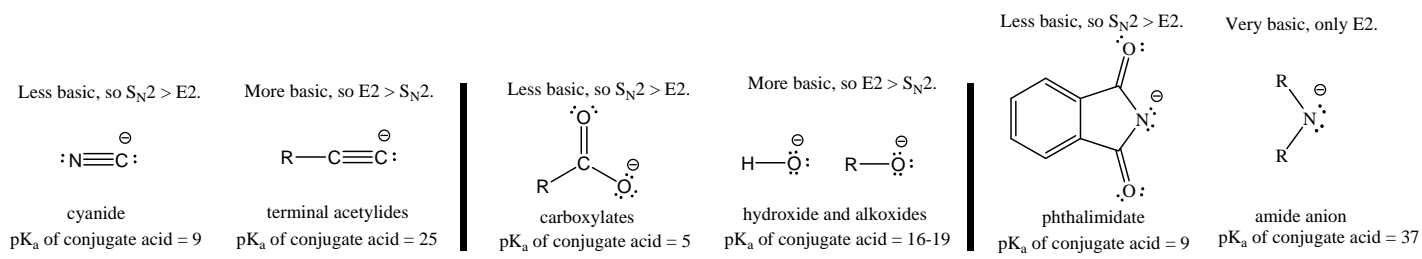
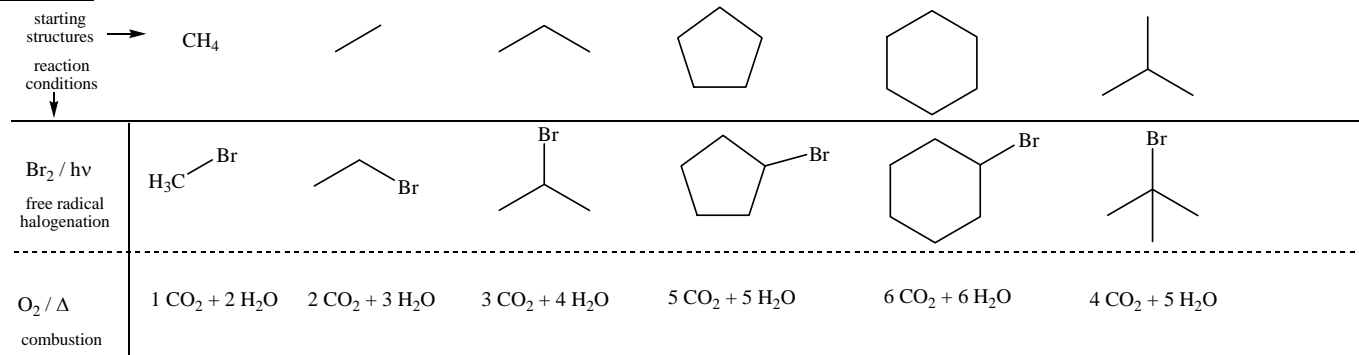
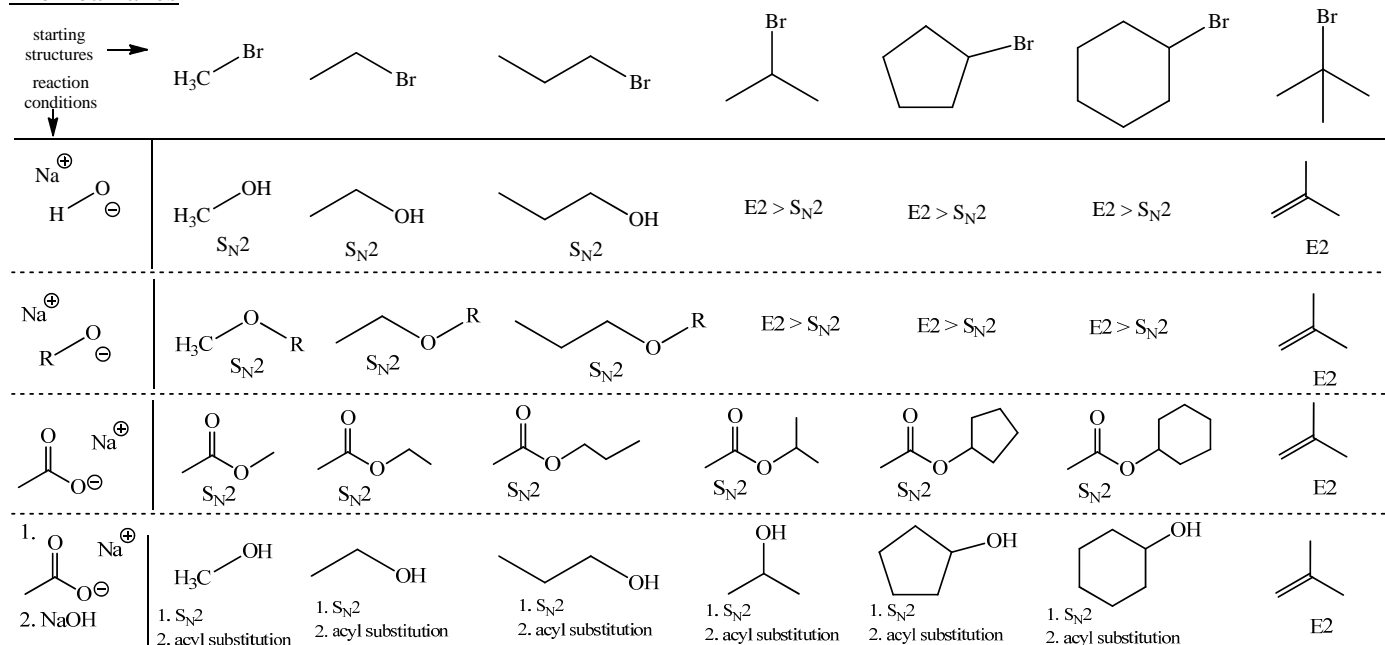
 <p>epoxides</p>	<p>LDA = lithium diisopropylamide</p> $\xrightarrow{\text{Na}^{\oplus} \ominus \text{NR}_2 \text{ } -78^{\circ}\text{C}}$	 <p>allylic alkoxide (further chemistry)</p>	<p>enolates are good nucleophiles, $S_N2 > E2$ at Me, 1° and 2° RX, and strong bases, $E2 > S_N2$ at 3° RX. Low temperature (-78°C) is important to prevent other reaction possibilities.</p>
 <p>Wittig salt = ylid</p>	$\xrightarrow{\text{Li}^{\oplus} \ominus \text{n-Bu}}$ $K_{\text{eq}} = \frac{K_a(\text{HCR}_2\text{PPh}_3)}{K_a(\text{H-C}_4\text{H}_9)}$ $K_{\text{eq}} = \frac{10^{-33}}{10^{-50}} = 10^{+17}$	 <p>betaine</p>	<p>n-butyl lithium removes proton from Wittig salt and makes a good nucleophile at ketones and aldehydes, forming alkenes.</p>
 <p>dithiane</p>	$\xrightarrow{\text{Li}^{\oplus} \ominus \text{n-Bu}}$ $K_{\text{eq}} = \frac{K_a(\text{dithiane})}{K_a(\text{H-C}_4\text{H}_9)}$ $K_{\text{eq}} = \frac{10^{-33}}{10^{-50}} = 10^{+17}$	 <p>dithiane carbanion</p>	<p>n-butyl lithium removes proton from dithiane and makes a good nucleophile at RX compounds. Can react once or twice in S_N2 reactions. Sulfur acetal forms carbonyl group after hydrolysis. Makes aldehydes and ketones.</p>
 <p>esters / 3° amides</p>	<p>2 eqs. LDA</p> $\xrightarrow{\text{Na}^{\oplus} \ominus \text{NR}_2 \text{ } -78^{\circ}\text{C}}$ $K_{\text{eq}} = \frac{K_a(\text{ROCOCH}_3)}{K_a(\text{HNR}_2)}$ $K_{\text{eq}} = \frac{10^{-25}}{10^{-37}} = 10^{+12}$	 <p>dianions</p>	<p>dianions are good nucleophiles, $S_N2 > E2$ at Me, 1° and 2° RX, epoxides and C=O groups.. Low temperature (-78°C) is typical. They react at the less stable position first.</p>
 <p>carboxylic acids</p>	<p>2 eqs. LDA</p> $\xrightarrow{\text{Na}^{\oplus} \ominus \text{NR}_2 \text{ } -78^{\circ}\text{C}}$ $K_{\text{eq}} = \frac{K_a(\text{ROCOCH}_3)}{K_a(\text{HNR}_2)}$ $K_{\text{eq}} = \frac{10^{-25}}{10^{-37}} = 10^{+12}$	 <p>dianions</p>	<p>dianions are good nucleophiles, $S_N2 > E2$ at Me, 1° and 2° RX, epoxides and C=O groups.. Low temperature (-78°C) is typical. They react at the less stable position first.</p>
 <p>bromoalkanes, alkenes and aromatics</p>	$\xrightarrow{\text{Mg}}$	 <p>carbanion equivalents</p>	<p>Grignard reagents are very strong bases and very powerful nucleophiles. They react well with carbonyl compounds (aldehydes, ketones, esters, 3° amides & nitriles) and epoxides, but not with other RX compounds.</p>
 <p>bromoalkanes, alkenes and aromatics</p>	$\xrightarrow{2 \text{ Li}}$	 <p>carbanion equivalents</p>	<p>Organolithium reagents react similarly to Grignard reagents, except if you use 2 equivalents with carboxylic acids you will get ketones. We also use them to make cuprates (in our course).</p>
 <p>carbanion equivalents</p>	$\xrightarrow{0.5 \text{ CuBr}}$	 <p>cuprates</p>	<p>We react cuprates with other RX, in an S_N2-like reaction, conjugate addition to α,β-unsaturated C=O compounds and acid chlorides to make ketones, all reactions not possible with Grignard and organo-lithium reagents, above.</p>

S_N2 versus E2 choices at 2°RX.

At secondary RX (X= OTs, I, Br, Cl) S_N2 and E2 products are in close competition with each other. Anions whose conjugate acids have higher pK_a's (stronger bases have weaker acids) generally produce more E2 relative to S_N2. The two examples that we will emphasize at 2°RX centers are carboxylates (S_N2 > E2) vs hydroxide and alkoxides (E2 > S_N2), and cyanide (S_N2 > E2) vs terminal acetylides (E2 > S_N2). Any additional steric hindrance in RX or the electron pair donor tends to the proportion of E2 > S_N2.

Similar looking base/nucleophiles (used in our course) that react differently with 2°RX structures. (They all react by S_N2 at methyl and 1°RX and they all react by E2 at 3°RX.)

At 2° RX structures the less basic anion type prefers S_N2 reaction and the more basic anion type prefers E2 reaction.



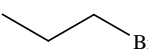

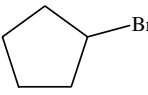
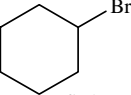
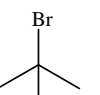


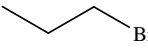

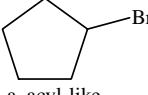
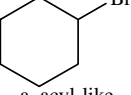
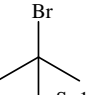
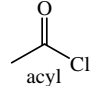


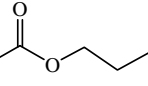
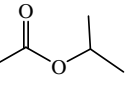
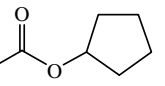
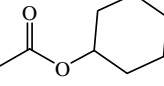
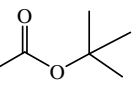
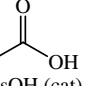


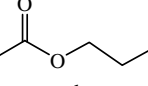
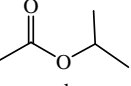
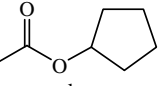
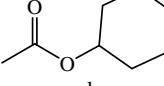
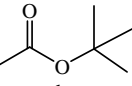
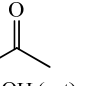
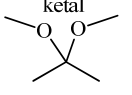
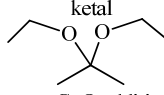


AlkanesBromoalkanes

S_N2	S_N2	E2	E2	E2	E2	E2	E2
starting structures reaction conditions ↓							
Na^+ $H-O^-$				E2 > S_N2	E2 > S_N2	E2 > S_N2	
Na^+ $R-O^-$				E2 > S_N2	E2 > S_N2	E2 > S_N2	
S_N2	S_N2	S_N2	S_N2	S_N2	S_N2	S_N2	E2
1. 2. NaOH							
1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	1. S_N2 2. acyl substitution	E2
S_N2	S_N2	E2	E2	E2	E2	E2	E2
	N.R.	N.R.	N.R.				
				S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement
	N.R.	N.R.	N.R.				
				S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement
	N.R.	N.R.	N.R.				
				S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement	S_N1 , possible rearrangement
							E2 > S_N2
S_N2	S_N2	S_N2	S_N2	S_N2	S_N2	S_N2	
				E2 > S_N2	E2 > S_N2	E2 > S_N2	E2 > S_N2
S_N2	S_N2	S_N2	S_N2				

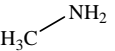
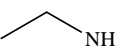
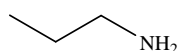

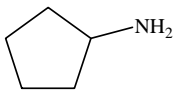
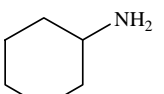
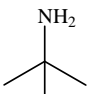
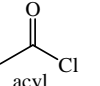


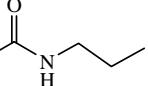
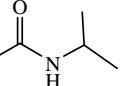
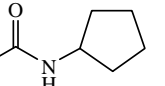
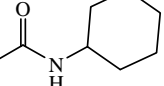
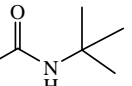
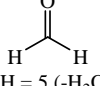


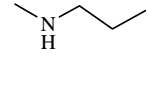
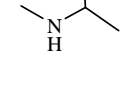
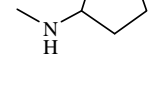
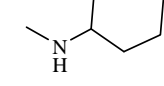
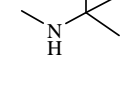
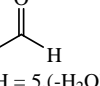


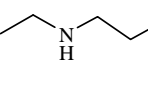
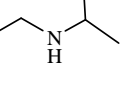
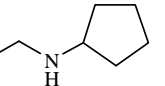
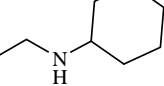
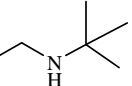
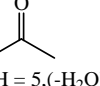


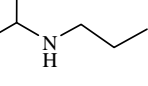
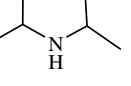
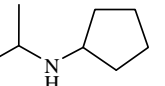
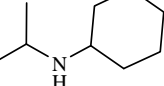
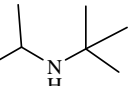
$\text{H}_3\text{C}-\text{C}\equiv\text{C}^-$ Na^+				$\text{E2} > \text{S}_{\text{N}}2$	$\text{E2} > \text{S}_{\text{N}}2$	$\text{E2} > \text{S}_{\text{N}}2$	$\text{E2} > \text{S}_{\text{N}}2$
1. NaN_3 2. LiAlH_4							$\text{E2} > \text{S}_{\text{N}}2$
1.							$\text{E2} > \text{S}_{\text{N}}2$
NaOH 2. R-Br 3. NaOH "Gabriel"	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	1. acid/base 2. $\text{S}_{\text{N}}2$ 3. acyl substitution	
$\text{Na}-\text{S}^-$							$\text{E2} > \text{S}_{\text{N}}2$
$\text{Na}-\text{S}^-$							$\text{E2} > \text{S}_{\text{N}}2$
Mg Grignard reagents							
Li organolithium reagents							
R : $(\text{MgBr})^+$	poor result with RX	poor result with RX	poor result with RX	poor result with RX	poor result with RX	poor result with RX	poor result with RX
R : Li^+	see cuprates for a workable alternative (next example), make cuprates from organolithiums + CuBr						
$\text{R}-\text{Cu}-\text{R}$ Li^+							poor at tertiary RX

Alcohols



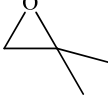
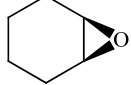
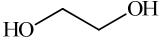
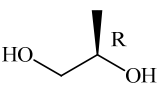
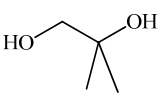
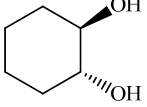
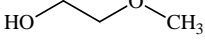
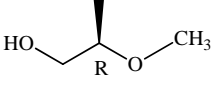
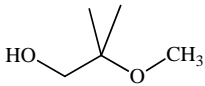
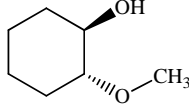
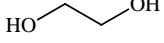
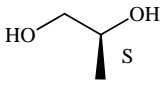
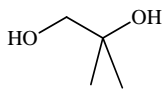
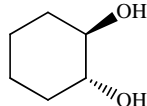
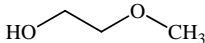
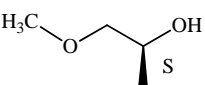
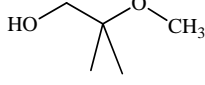
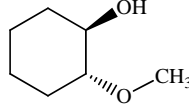
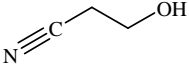
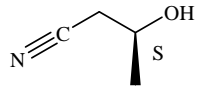
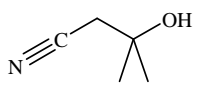
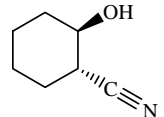
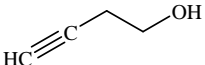
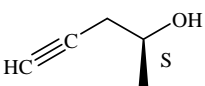
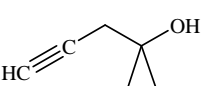
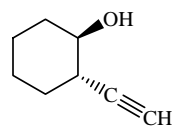
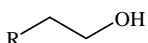
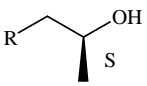
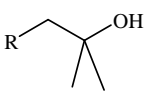
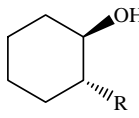
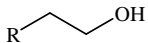
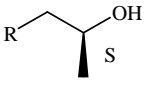
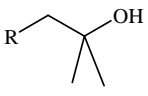
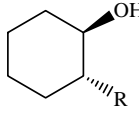
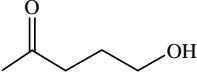
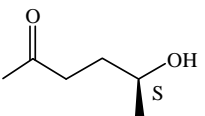
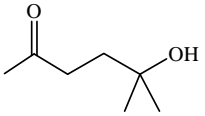
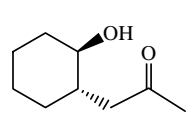
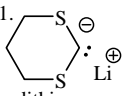
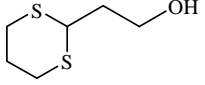
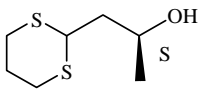
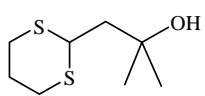
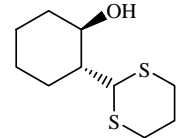
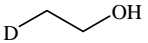
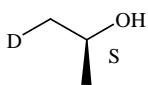
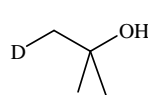
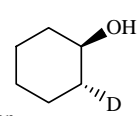
starting structures reaction conditions ↓							
Na^+ H^- acid/base							
1. Na^+ 2.							$\text{E2} > \text{S}_{\text{N}}2$

HBr SOBr ₂ PBr ₃							
	S _N 2	S _N 2	S _N 2	S _N 1 rearrangement possible	S _N 1 rearrangement possible	S _N 1 rearrangement possible	S _N 1 rearrangement possible
a. Ts-Cl / py b. NaBr							
use when rearrangement is a problem	a. acyl-like substitution b. S _N 2	a. acyl-like substitution b. S _N 2	a. acyl-like substitution b. S _N 2	a. acyl-like substitution b. S _N 2	a. acyl-like substitution b. S _N 2	a. acyl-like substitution b. S _N 2	S _N 1 rearrangement possible
 acyl substitution							
 TsOH (cat) (-H ₂ O)	 acyl substitution	 acyl substitution	 acyl substitution	 acyl substitution	 acyl substitution	 acyl substitution	 acyl substitution
 TsOH (cat) (-H ₂ O)	 ketal a. C=O addition b. S _N 1	 ketal a. C=O addition b. S _N 1	use 2 equivalents of "ROH"		 HO-CH ₂ -CH ₂ -OH commonly use ethylene glycol (diol)	 TsOH (cat) (-H ₂ O)	H ₂ O (remove forms ketal, add H ₂ O forms ketone)

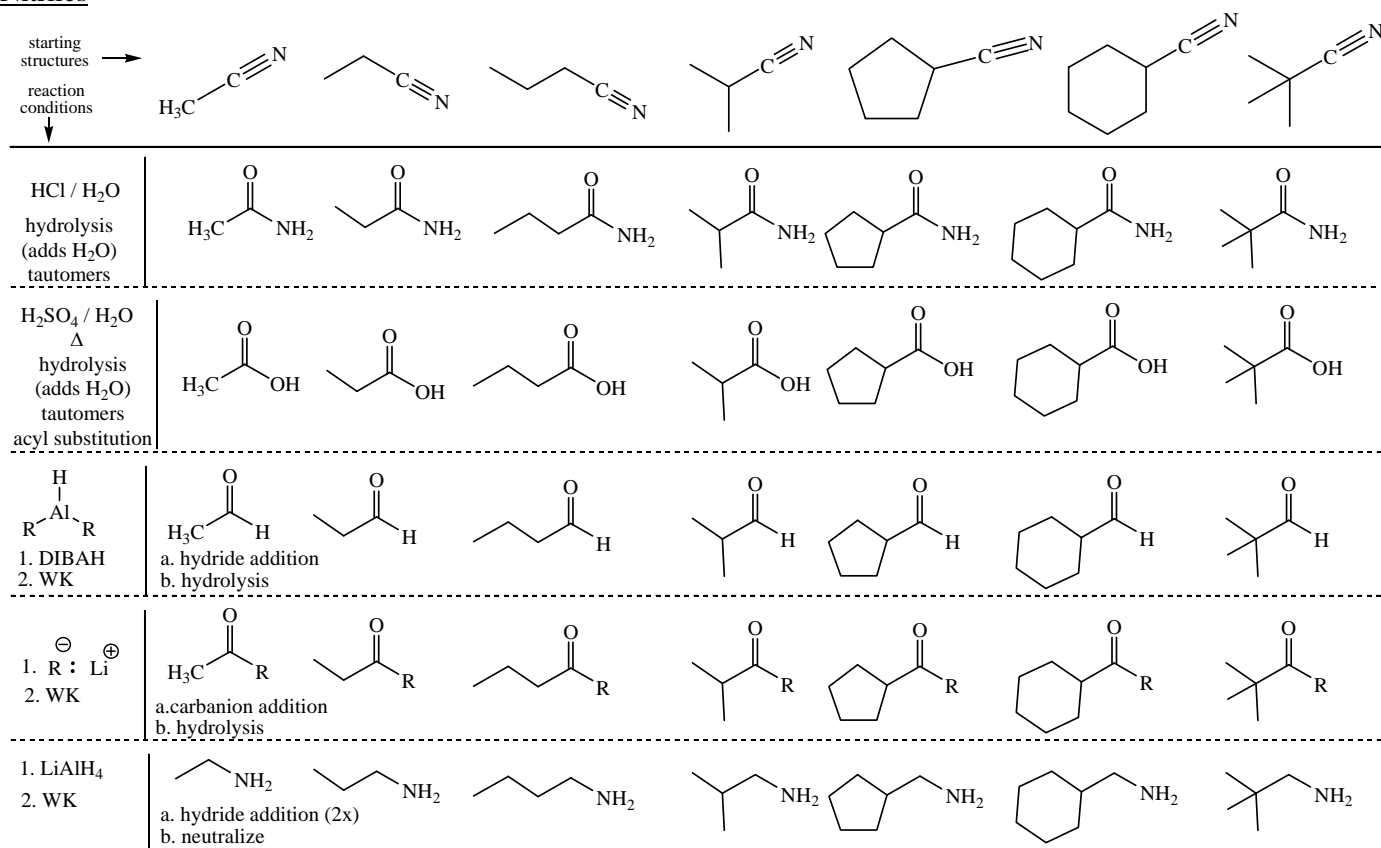
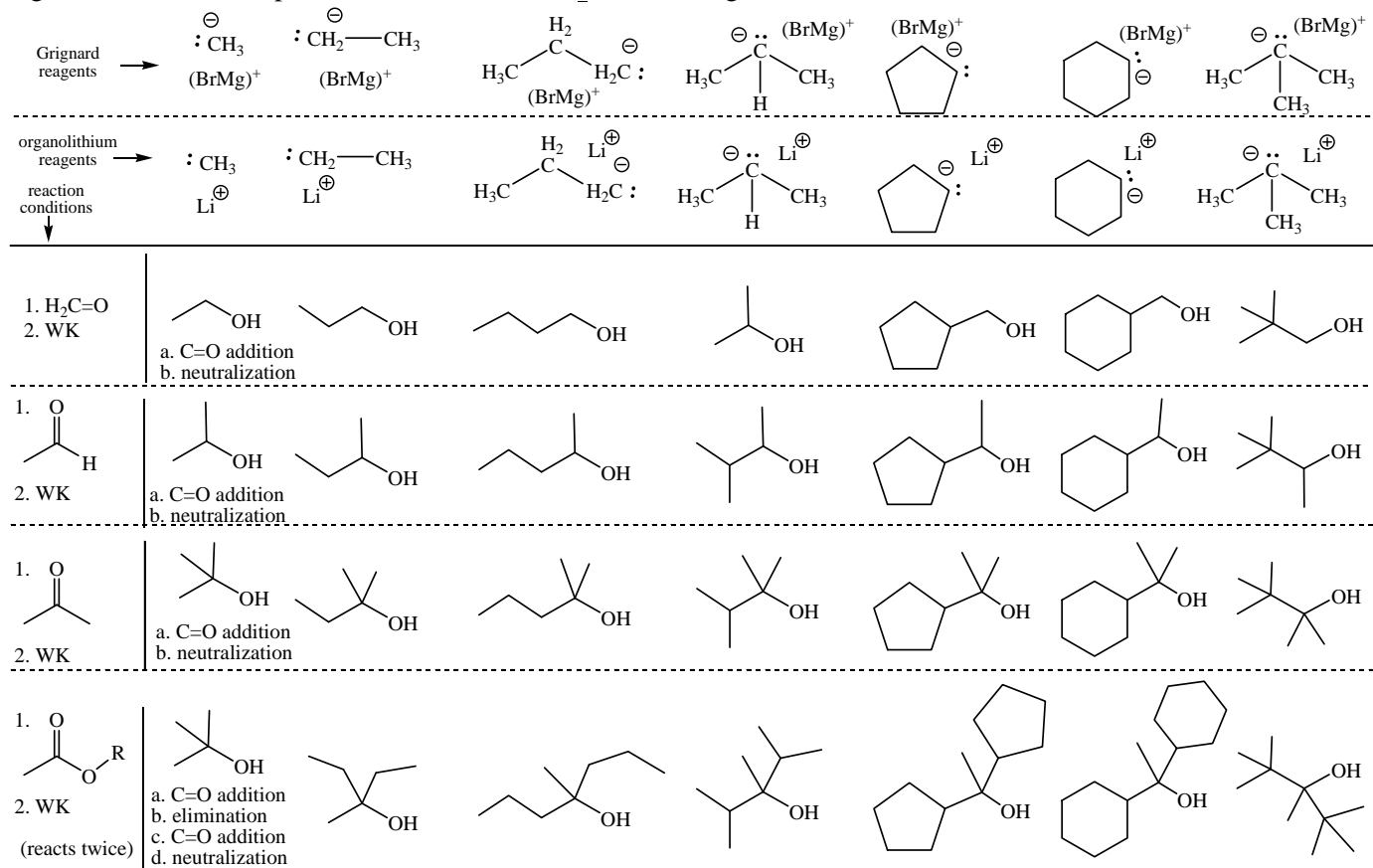
Amines

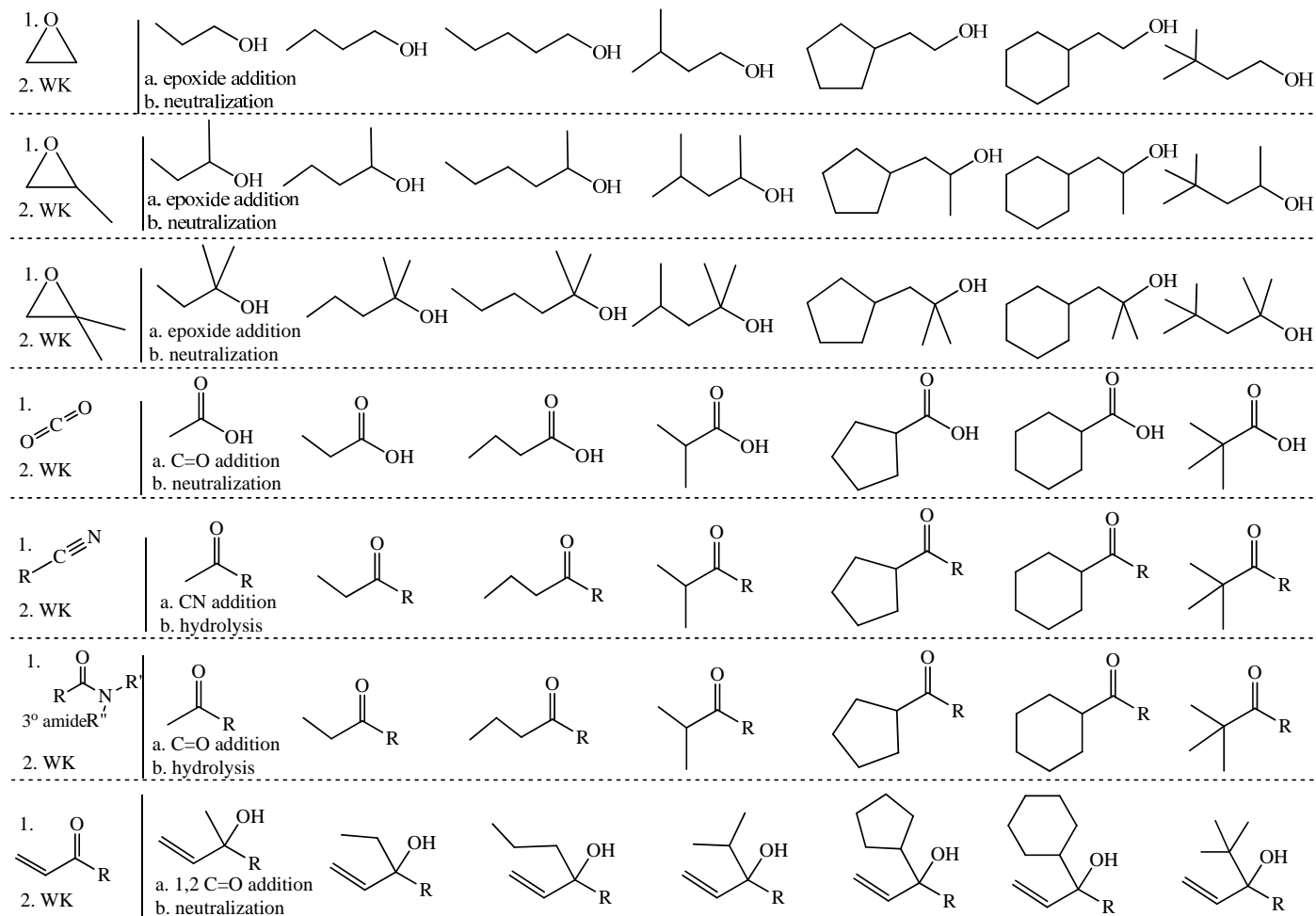
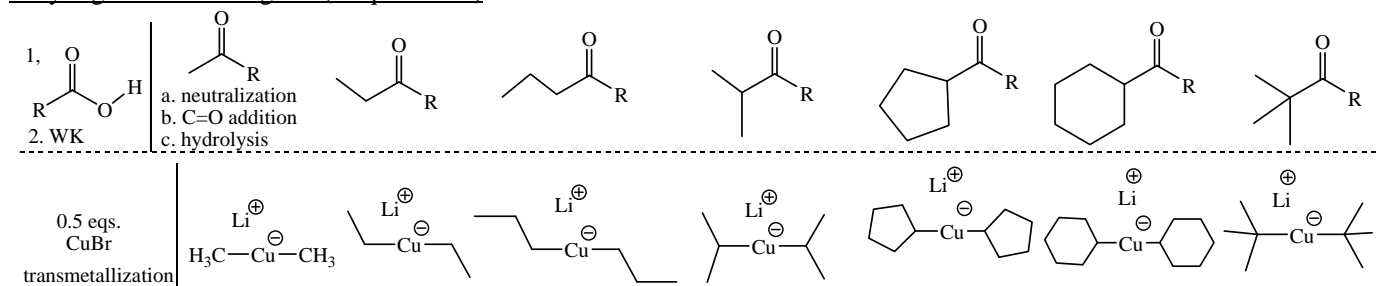
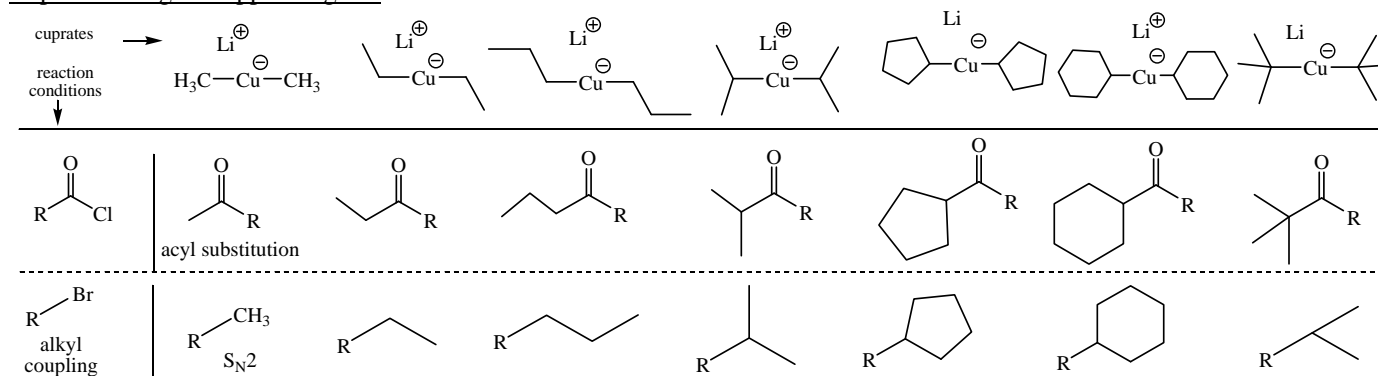
starting structures reaction conditions ↓							
 acyl substitution							
 pH = 5, (-H ₂ O) NaH ₃ BCN							
pH = 5, (-H ₂ O) NaH ₃ BCN	a. imine forms b. hydride reduction						
 pH = 5, (-H ₂ O) NaH ₃ BCN							
pH = 5, (-H ₂ O) NaH ₃ BCN	a. imine forms b. hydride reduction						
 pH = 5, (-H ₂ O) NaH ₃ BCN							
	a. imine forms b. hydride reduction						

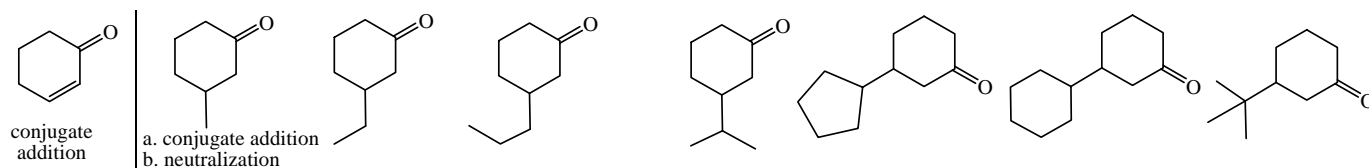
Epoxides

starting structures reaction conditions				
$\text{H}_3\text{O}^+ / \text{H}_2\text{O}$ hydrolysis (adds H_2O)	 a. $\text{S}_{\text{N}}1$ - like b. acid / base	 a. $\text{S}_{\text{N}}1$ - like b. acid / base		
$\text{CH}_3\text{OH}_2^+ / \text{HOCH}_3$	 a. $\text{S}_{\text{N}}1$ - like b. acid / base			
$\text{HO}^- / \text{H}_2\text{O}$ hydrolysis (adds H_2O)	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
$\text{CH}_3\text{O}^- / \text{HOCH}_3$	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. $\text{Na}^+ \text{C}\equiv\text{N}^-$ 2. WK	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. $\text{Na}^+ \text{HC}\equiv\text{C}^-$ 2. WK	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. $\text{R}^- \text{Li}^+$ 2. WK organolithium reagent	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. $\text{R}^- (\text{MgBr})^+$ 2. WK Grignard reagent	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. $\text{H}_3\text{C}-\text{C}(\text{O})\text{Li}^+ \text{CH}_2^-$ enolate 2. WK	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1.  dithiane 2. WK	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			
1. NaBD_4 or LiAlD_4 nucleophilic hydride 2. WK	 a. $\text{S}_{\text{N}}2$ - like b. acid / base			

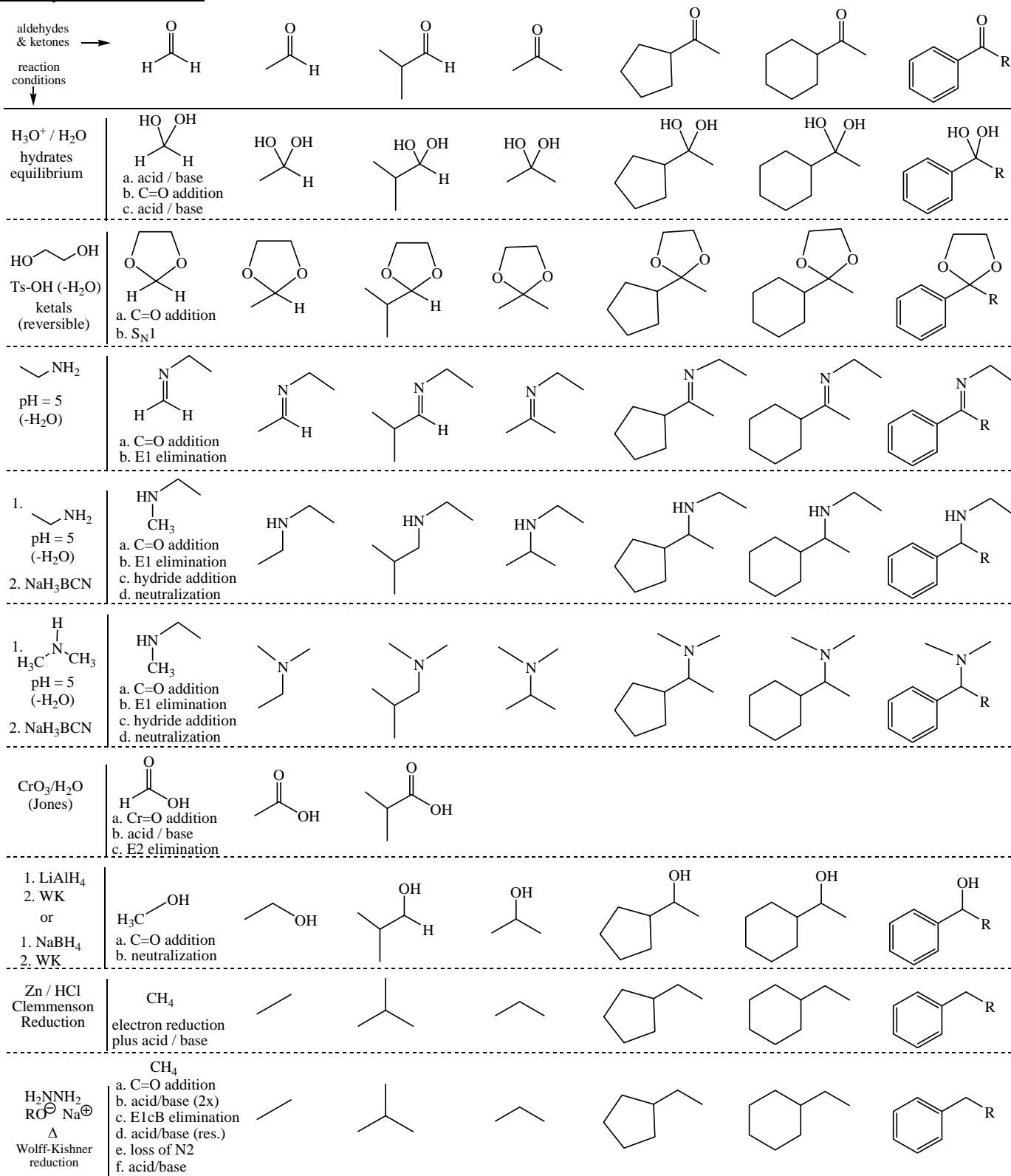
"D" used in these examples to show where attack occurs. "H" is more common.

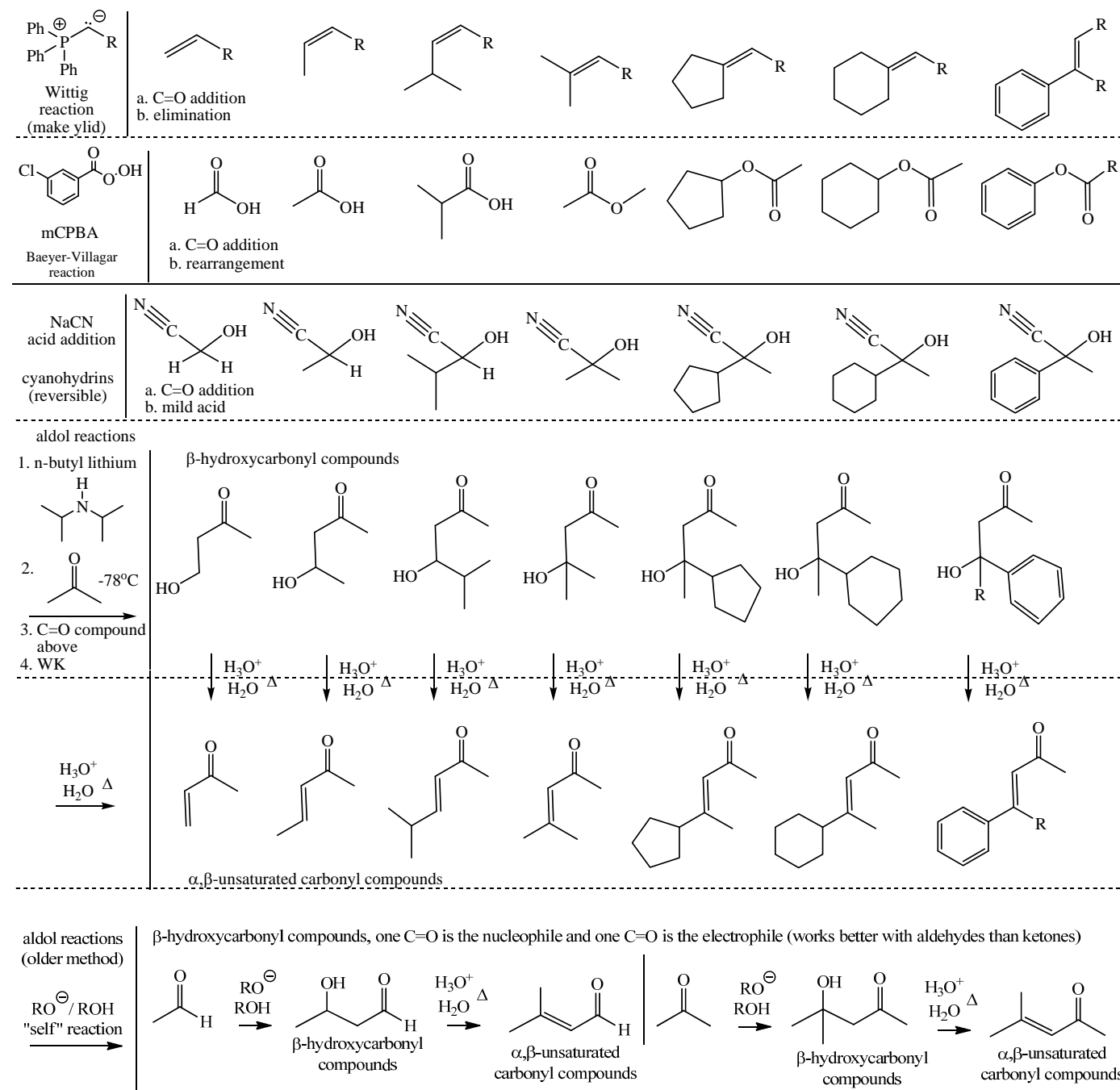
Nitriles**Organometallics – except for reactions with RCO₂H, these reagents react in a similar manner (in our course)**

**Only organolithium reagents (2 equivalents)****Cuprates – Organocopper reagents**

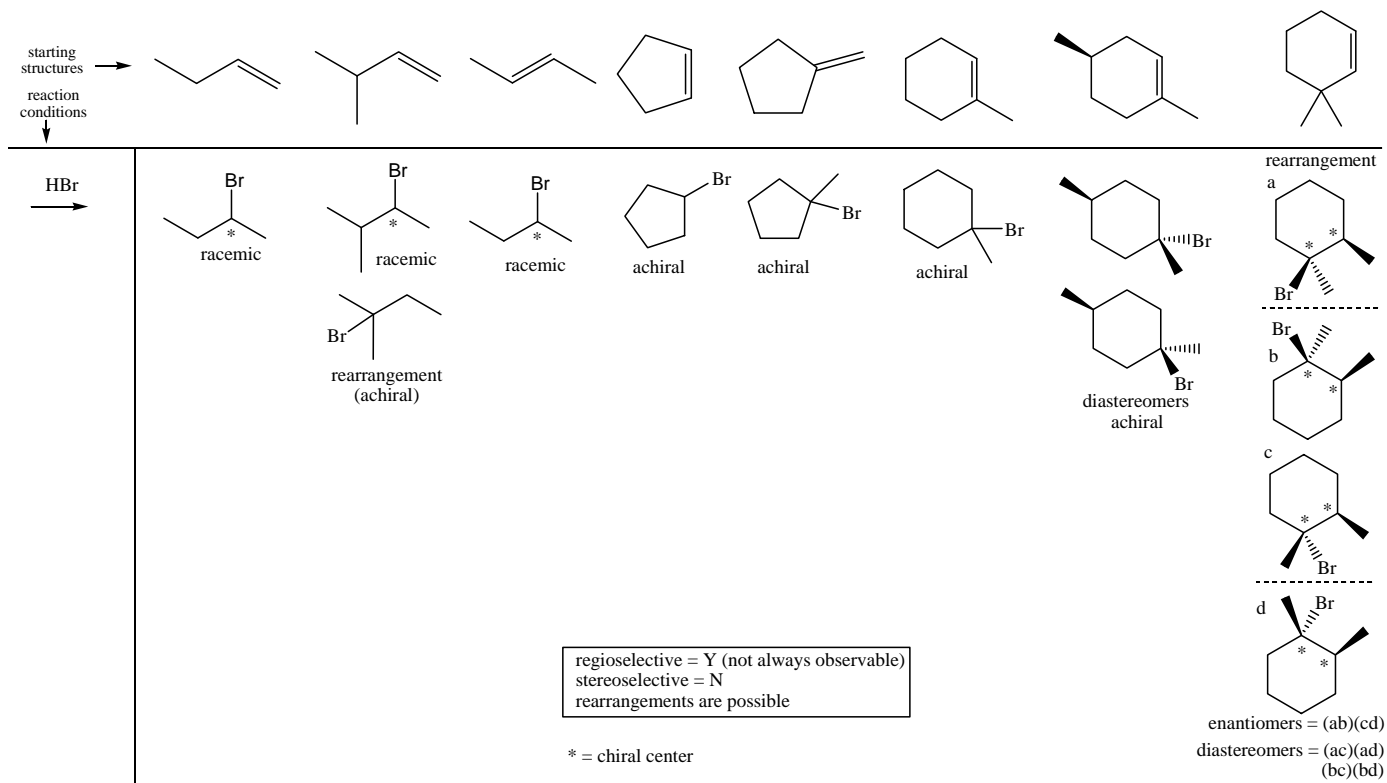
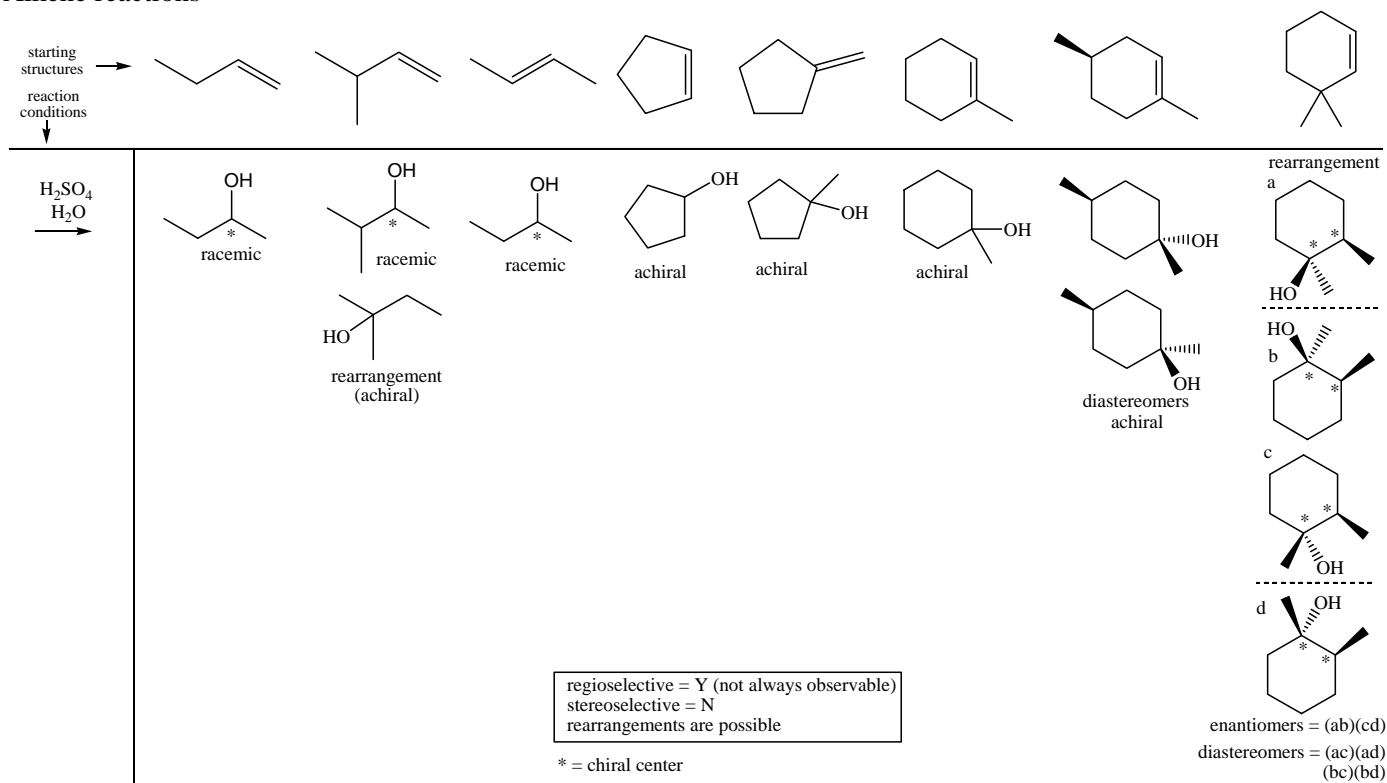


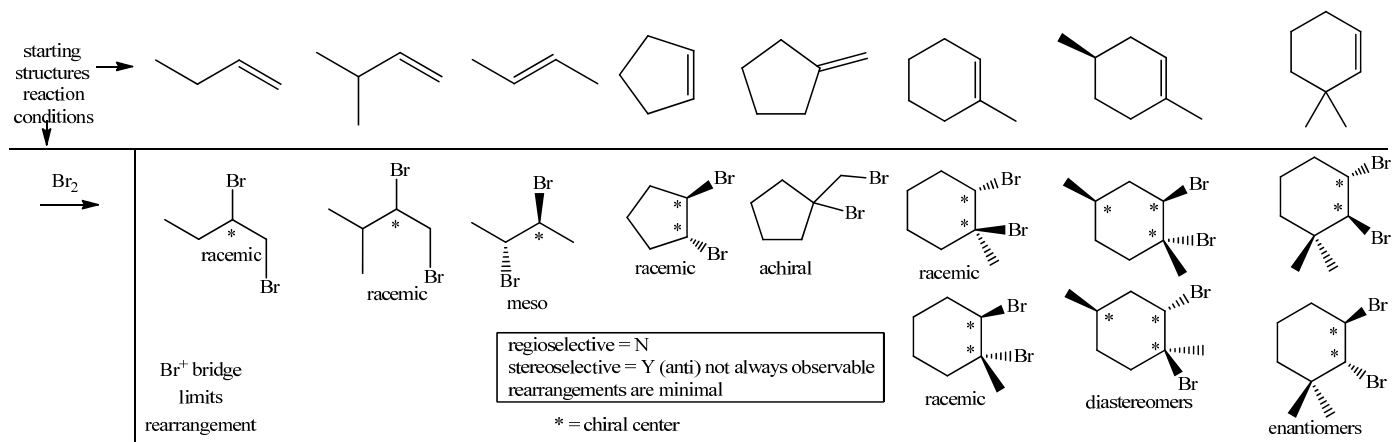
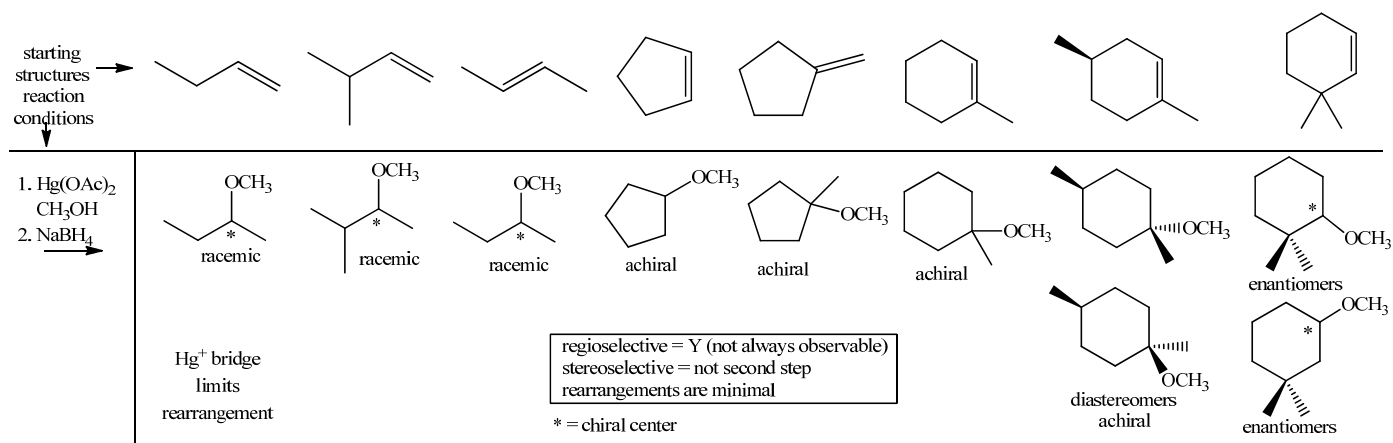
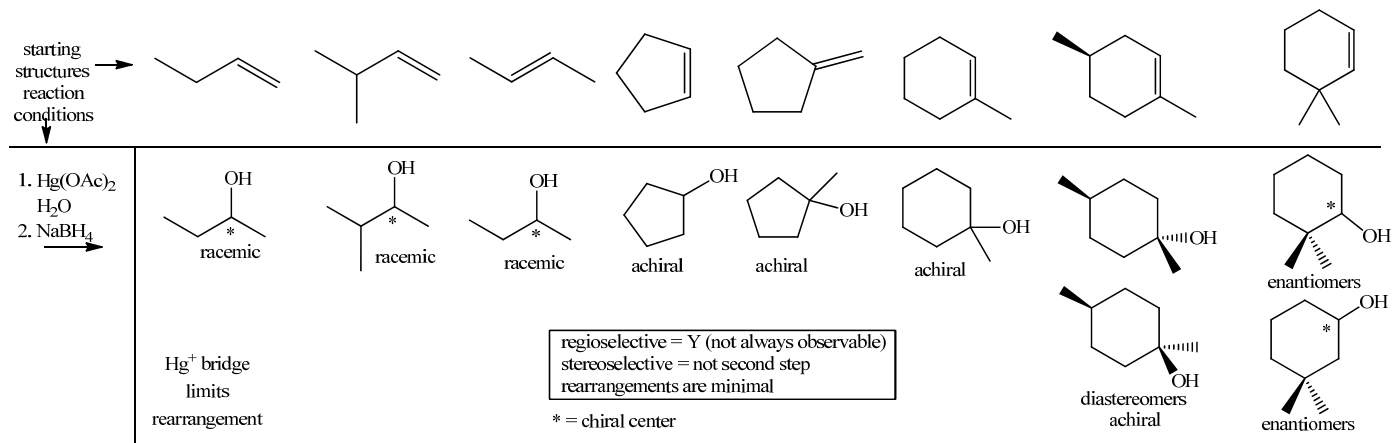
Aldehydes and Ketones

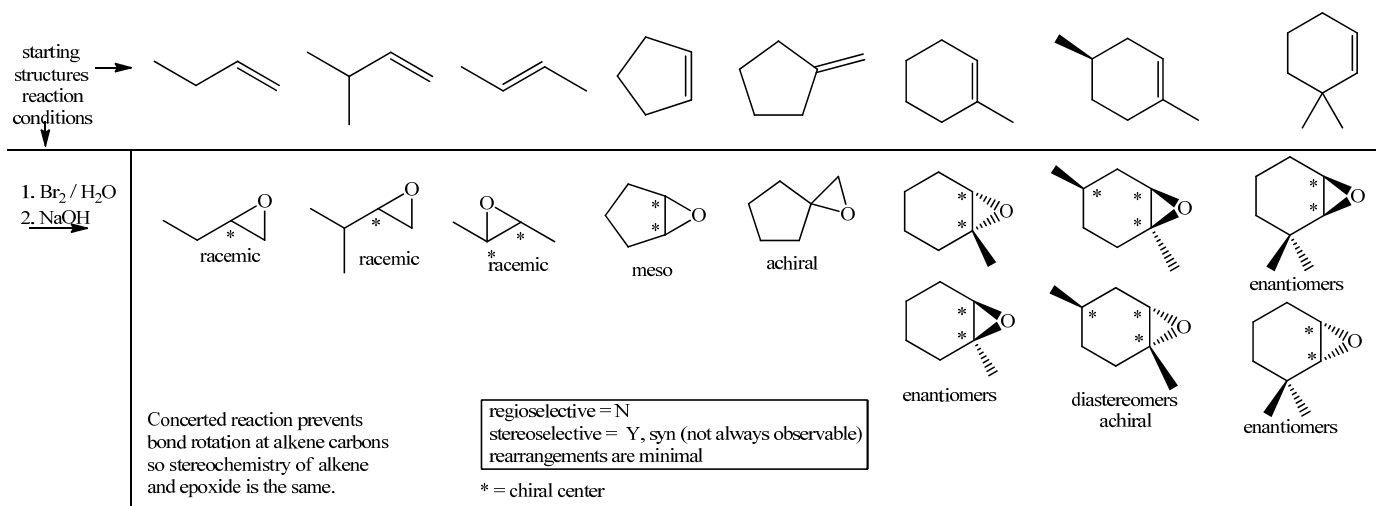
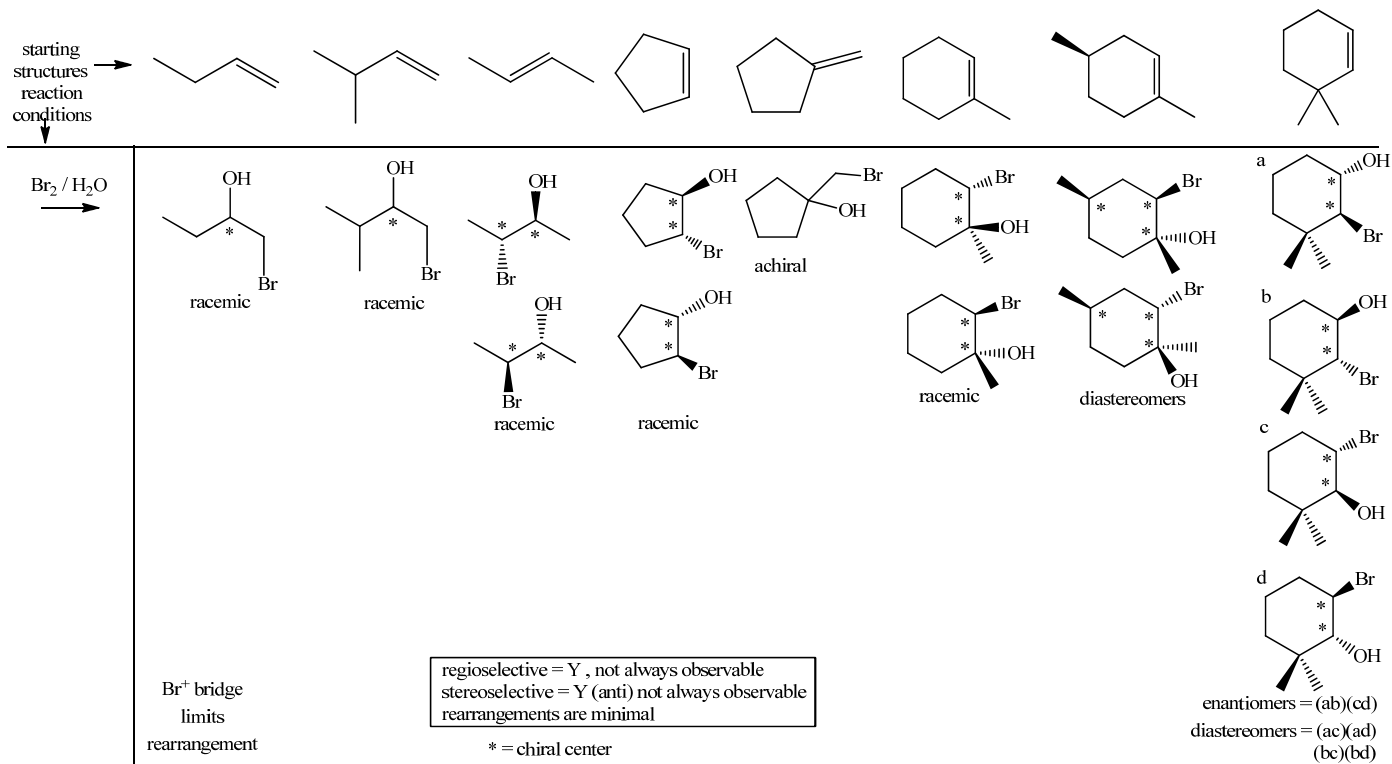


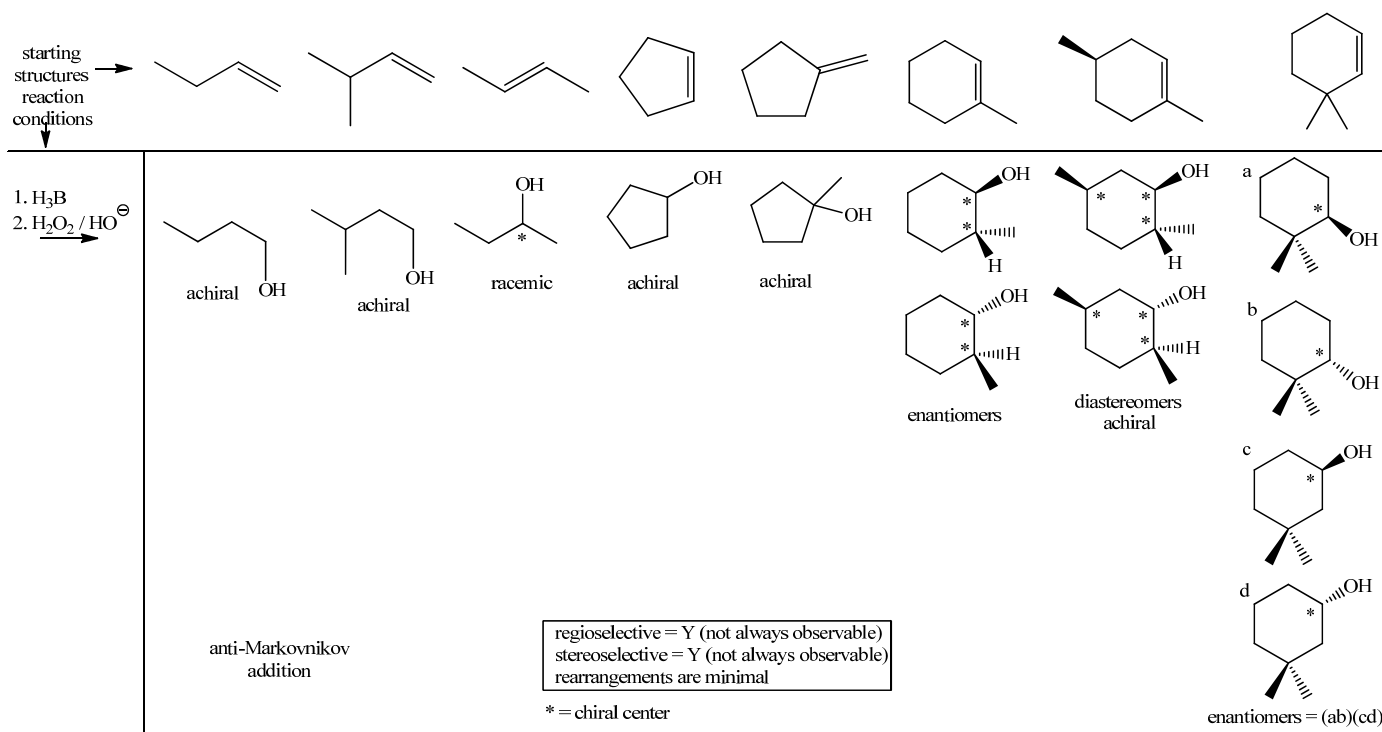
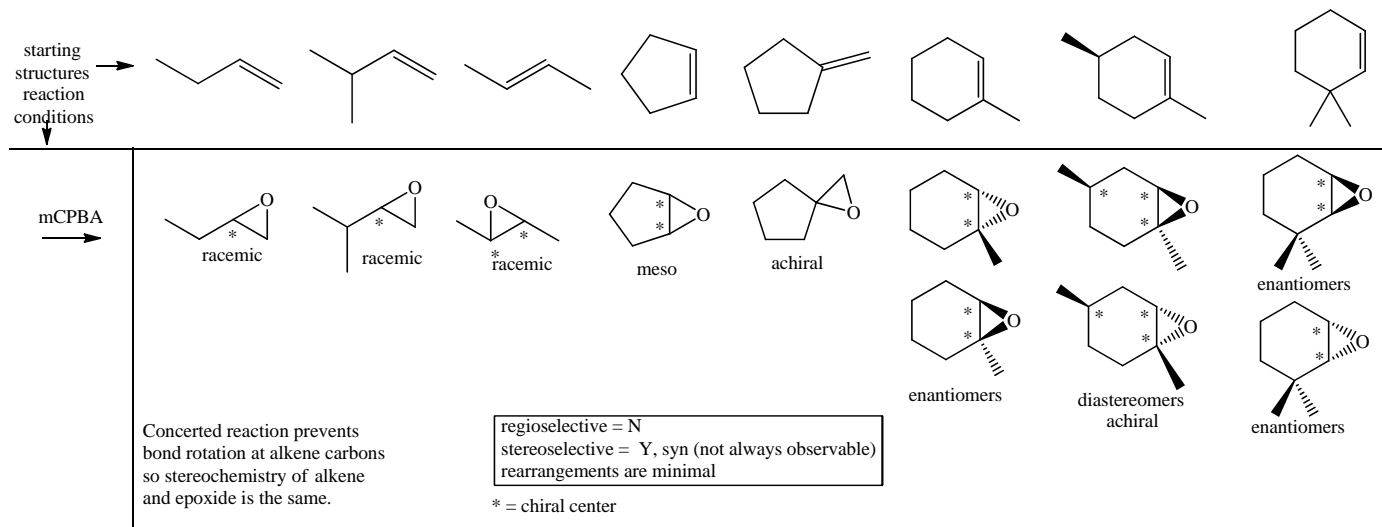


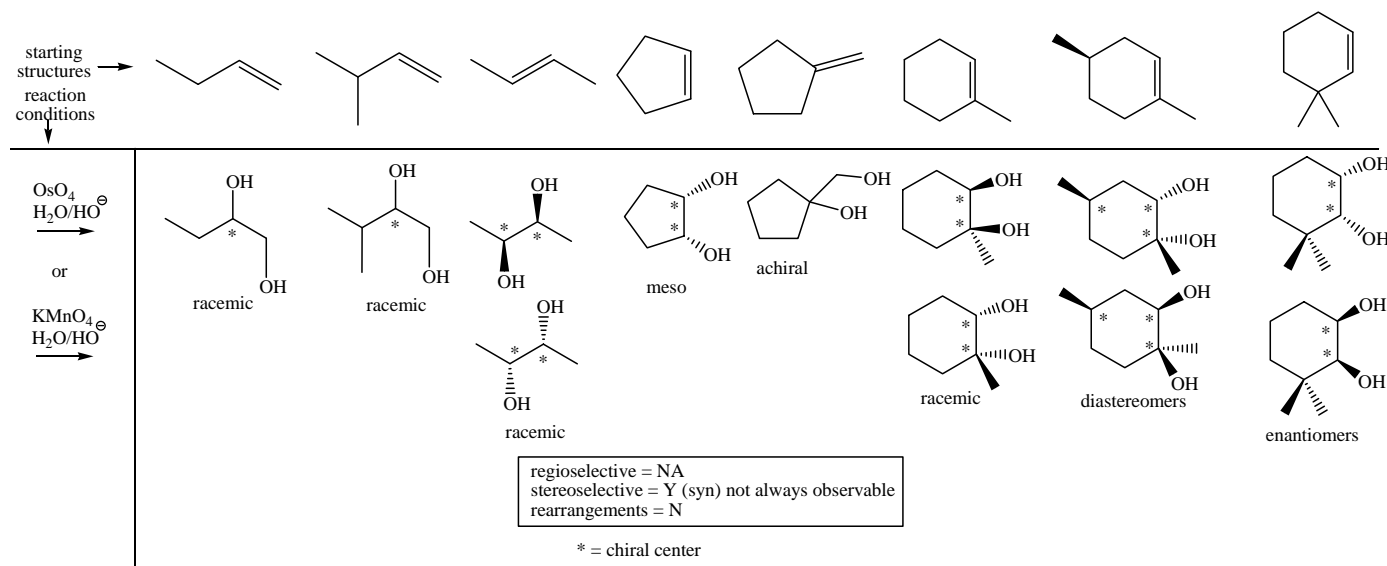
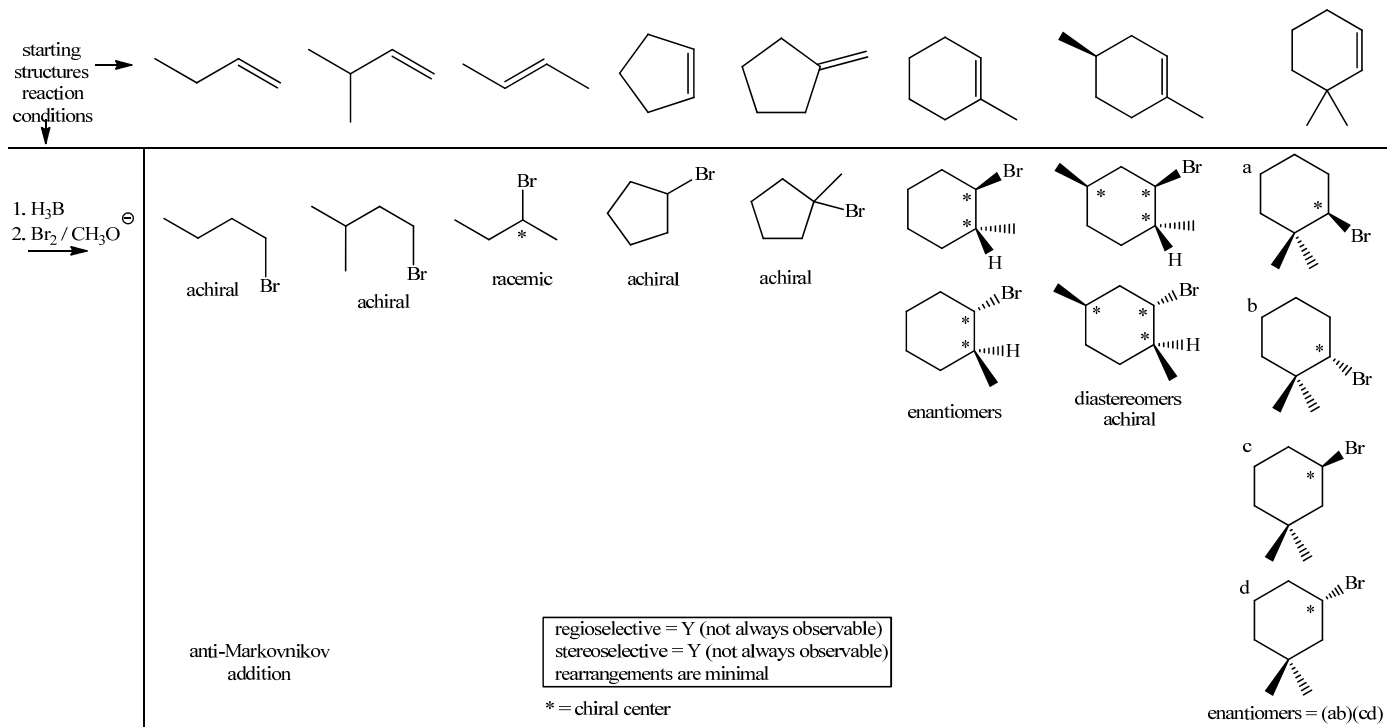
Alkene reactions

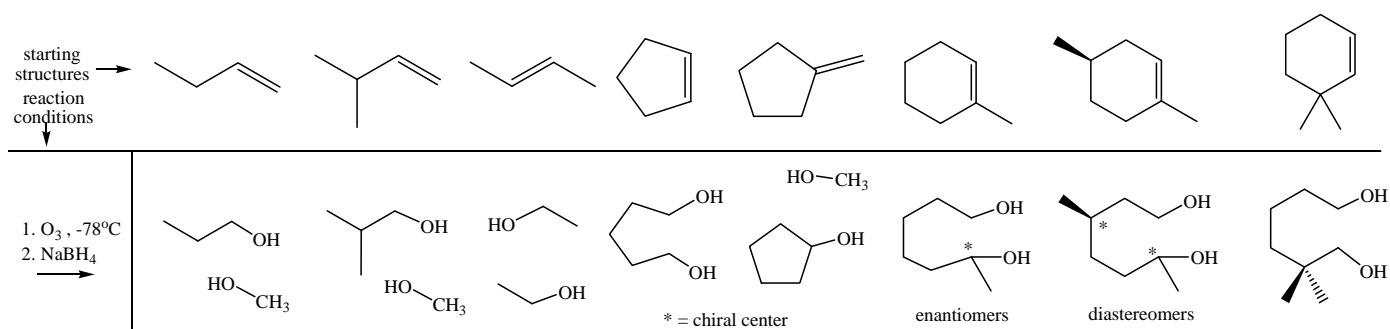
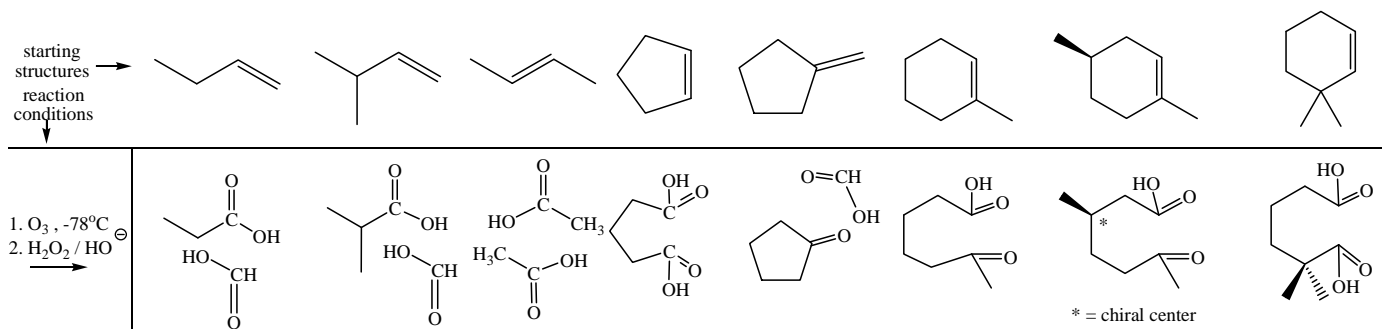
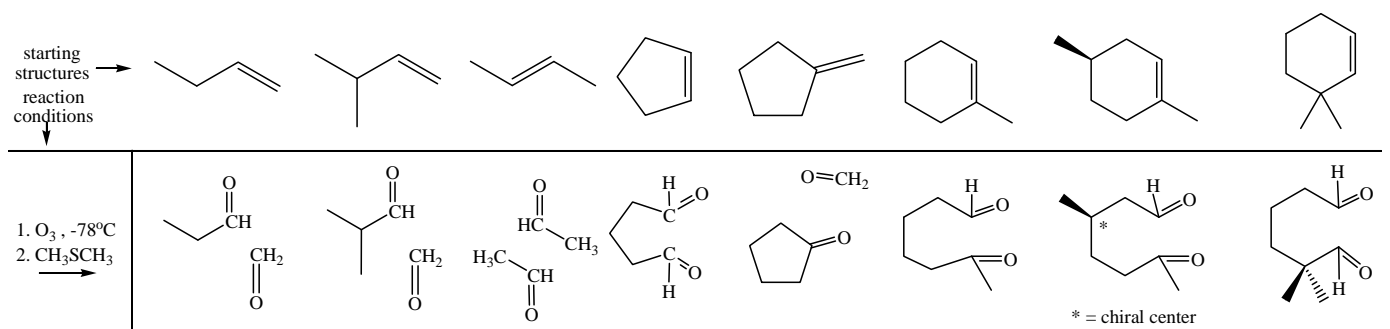
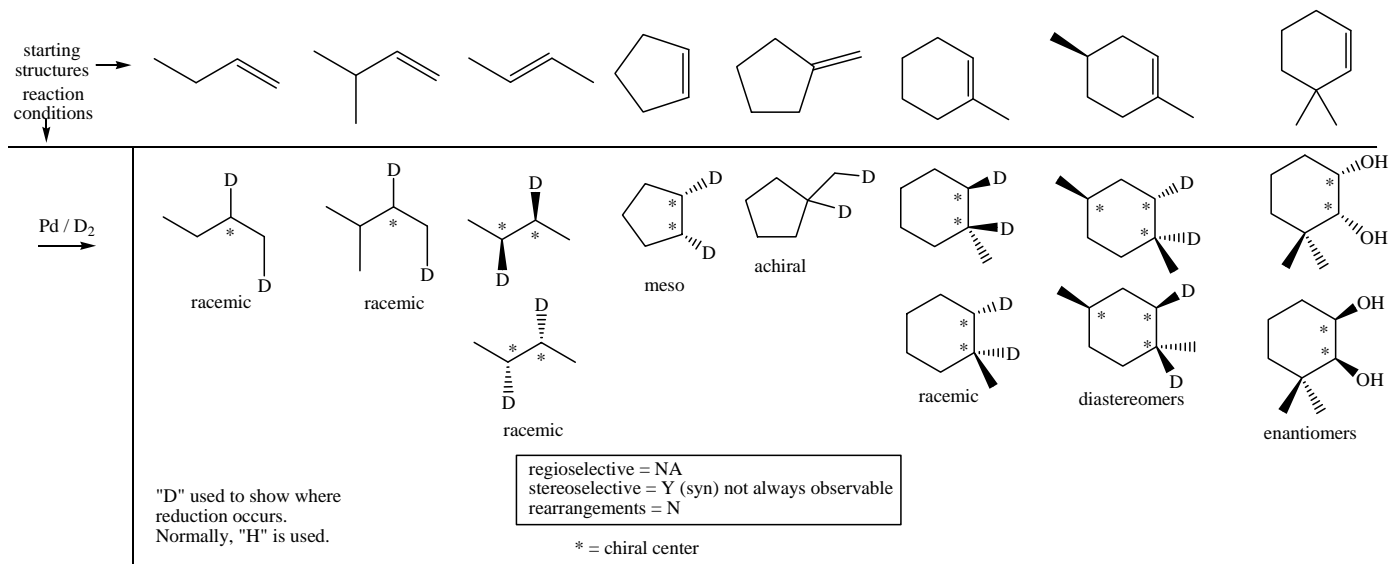








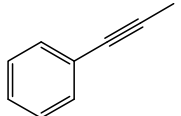
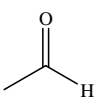

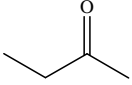
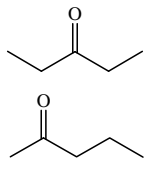
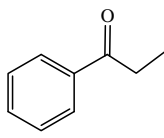
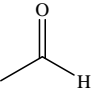
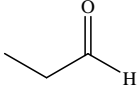
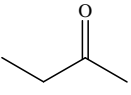
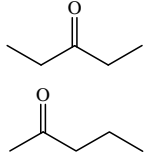


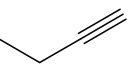
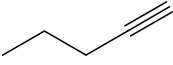
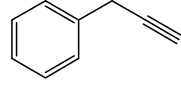


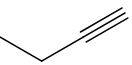
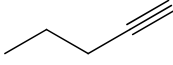
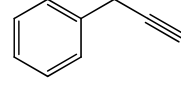


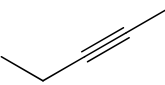
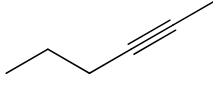
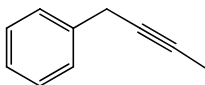
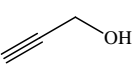
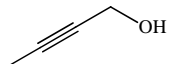


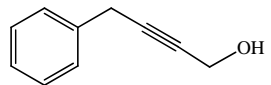

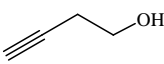
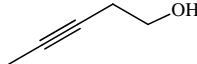
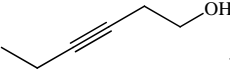

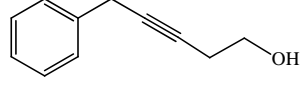



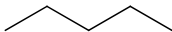
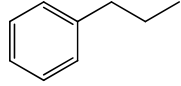
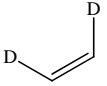
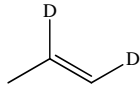
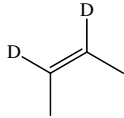
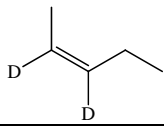
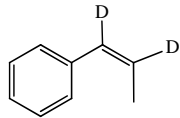

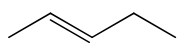
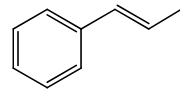




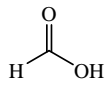

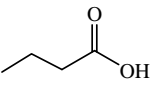
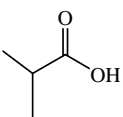
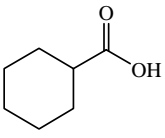
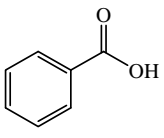
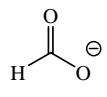

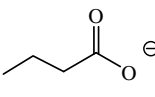
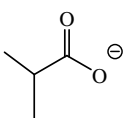
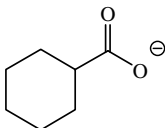
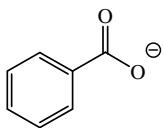
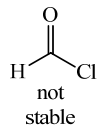

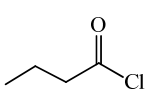
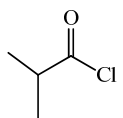
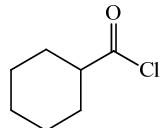
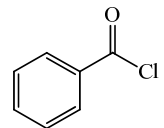
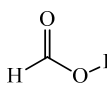

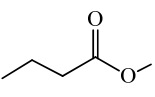
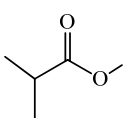
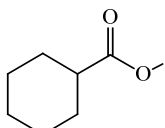
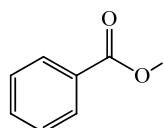
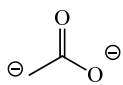
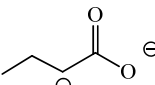
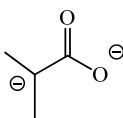
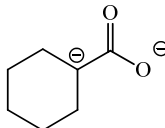
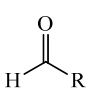

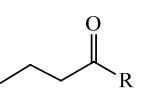
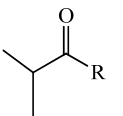
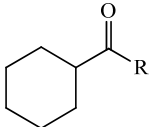
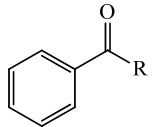
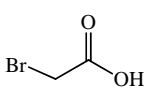
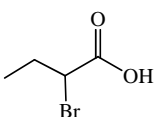
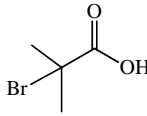
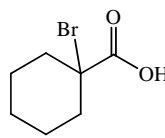
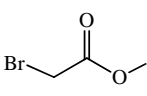
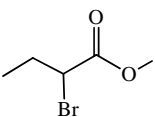
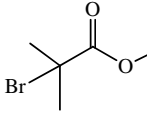
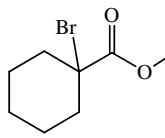





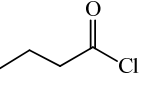
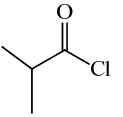
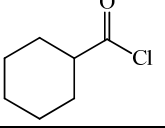
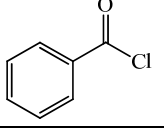
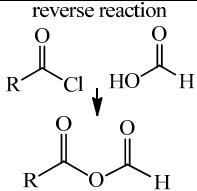
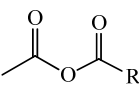
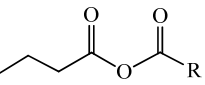
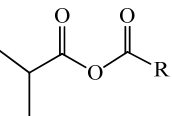
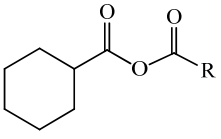
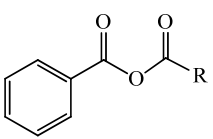
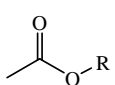
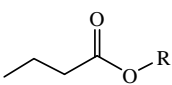
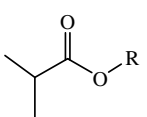
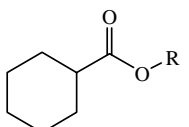
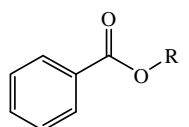
Alkyne reactions

starting structures reaction conditions					
$\text{H}_2\text{SO}_4 / \text{H}_2\text{O}$ Hg^{+2}					
1. R_2BH 2. $\text{H}_2\text{O}_2 / \text{HO}^-$					NA
1. excess NaNR_2 2. WK					
1. excess NaNR_2 2. WK					
1. excess NaNR_2 2. $\text{CH}_3\text{-Br}$					
1. excess NaNR_2 2. $\text{CH}_2=\text{O}$ 3. WK					
1. excess NaNR_2 2.  3. WK					
Pd / H_2 \rightarrow					
Pd / D_2 quinoline (Lindlar's cat.) \rightarrow					
Na / NH_3 (Birch Reduction)	poor yields on terminal alkynes	poor yields on terminal alkynes			

Acid reactions

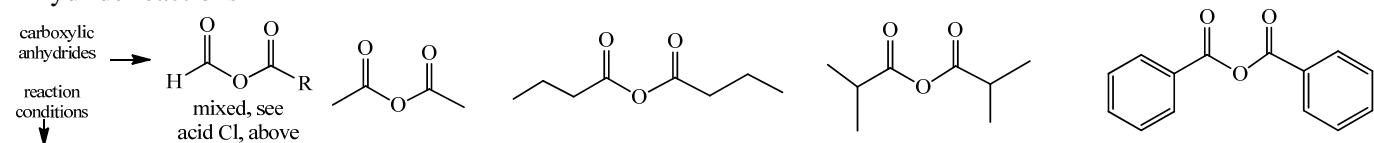
carboxylic acids reaction conditions						
NaOH acid / base reaction						
SOCl ₂ thionyl chloride	 not stable					
ROH TsOH (-H ₂ O) Fischer ester syn.						
1. 2 eqs. LDA makes dianions 2. react with electrophile	NA					NA
1. 2 eqs. R-Li 2. WK makes ketones						
Hell-Volhard-Zelinsky reaction (HVZ) - makes acid bromide and C _α -Br.						
1. Br ₂ 2. H ₂ O	NA					NA
1. Br ₂ 2. ROH	NA					NA

Acid chloride reactions


acid chlorides reaction conditions	not stable					
R-COOH make anhydrides	reverse reaction 					
R-OH make esters	NA					

$\text{R}-\text{NH}_2$ 1° amines make 2° amides	NA					
$\text{R}-\text{N}(\text{H})-\text{R}$ 2° amines make 3° amides	NA					
$\text{R}-\text{SH}$ thiols make thioesters	NA					
1. $\text{R}_2\text{Cu}^\ominus \text{Li}^\oplus$ 2. WK cuprates make ketones	NA					
1. $\text{R}_2\text{Al}-\text{H}$ -78°C 2. WK DIBALH make aldehydes	NA					
AlCl_3 Lewis cat. Friedel-Crafts acylation	NA					
$\text{H}-\text{O}-\text{H}$ usually an undesired side rxn	NA					

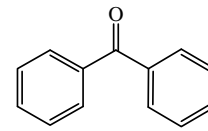
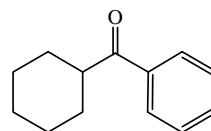
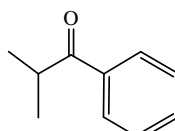
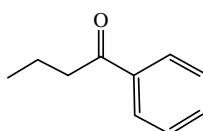
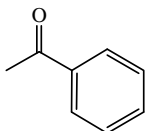
Anhydride reactions



$\text{R}-\text{OH}$ make esters	NA					
$\text{R}-\text{NH}_2$ 1° amines make 2° amides	NA					
$\text{R}-\text{N}(\text{H})-\text{R}$ 2° amines make 3° amides	NA					

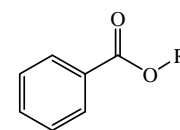
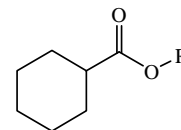
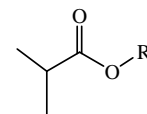
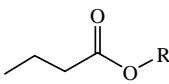
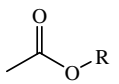
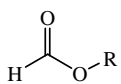
AlCl₃
Lewis cat.

Friedel-Crafts
acylation

NA



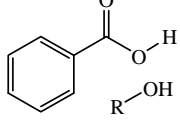
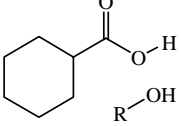
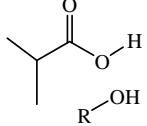
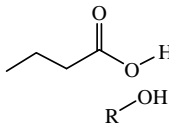
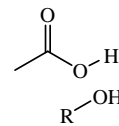
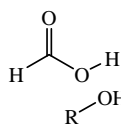
Ester reactions

esters →
reaction
conditions ↓



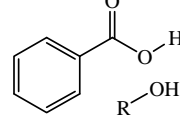
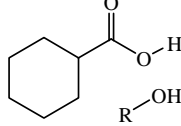
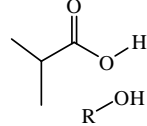
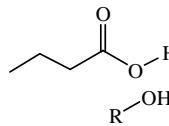
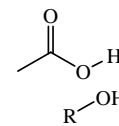
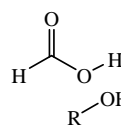
acid hydrolysis

H₃O⁺/H₂O
make
acids &
alcohols

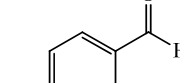
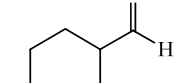
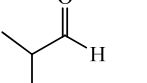
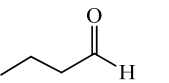
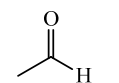
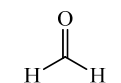


base hydrolysis

1. H₂O/HO[⊖]
2. WK
make
acids &
alcohols

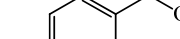
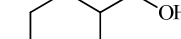
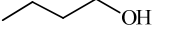
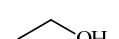
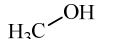


1. R₂Al-H
-78°C
2. WK
DIBAH
make
aldehydes



1. 2 eqs LiAlH₄
2. WK

LAH makes
1° ROH

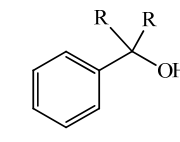
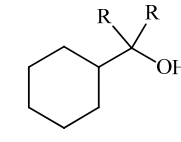
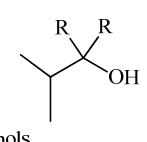
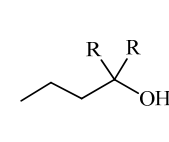
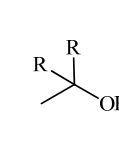
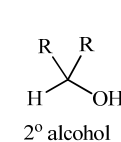


primary alcohols

1. 2 eqs NaBH₄
2. WK

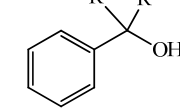
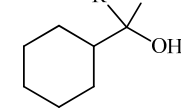
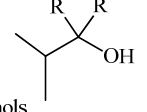
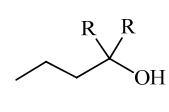
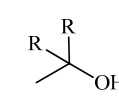
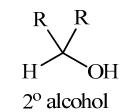
no
reactionno
reactionno
reactionno
reactionno
reactionno
reaction

1. 2 eqs RMgBr
2. WK

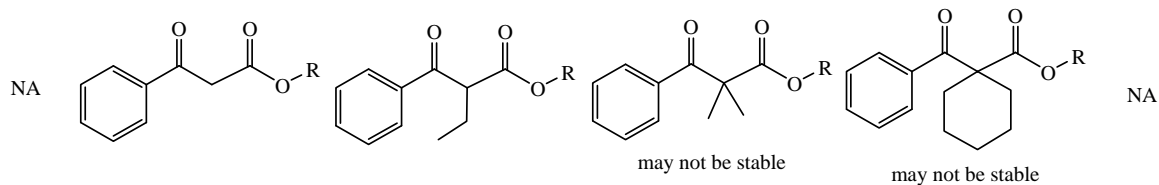
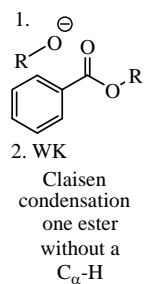


3° alcohols

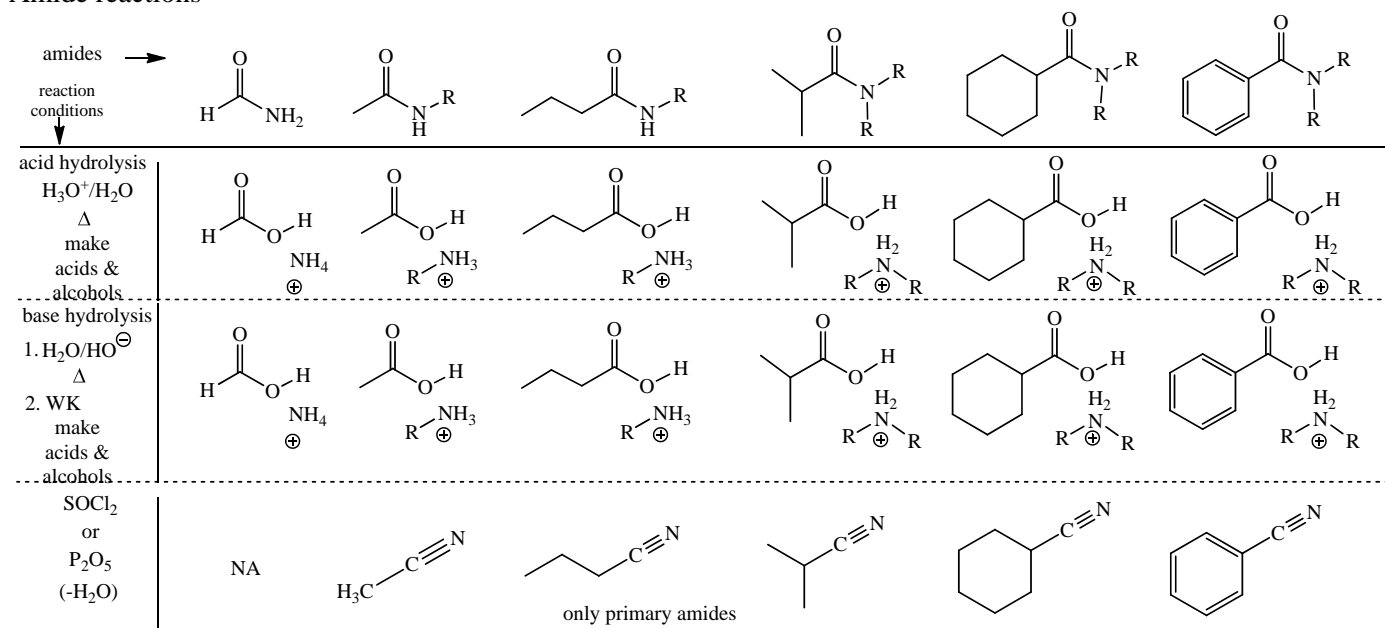
1. 2 eqs RLi
2. WK



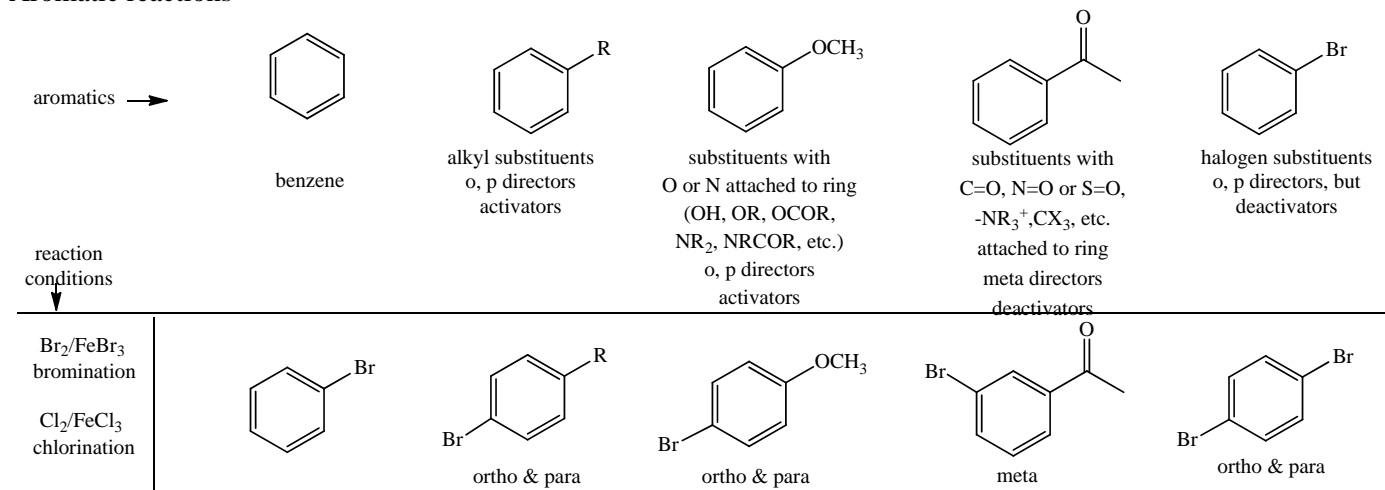
3° alcohols

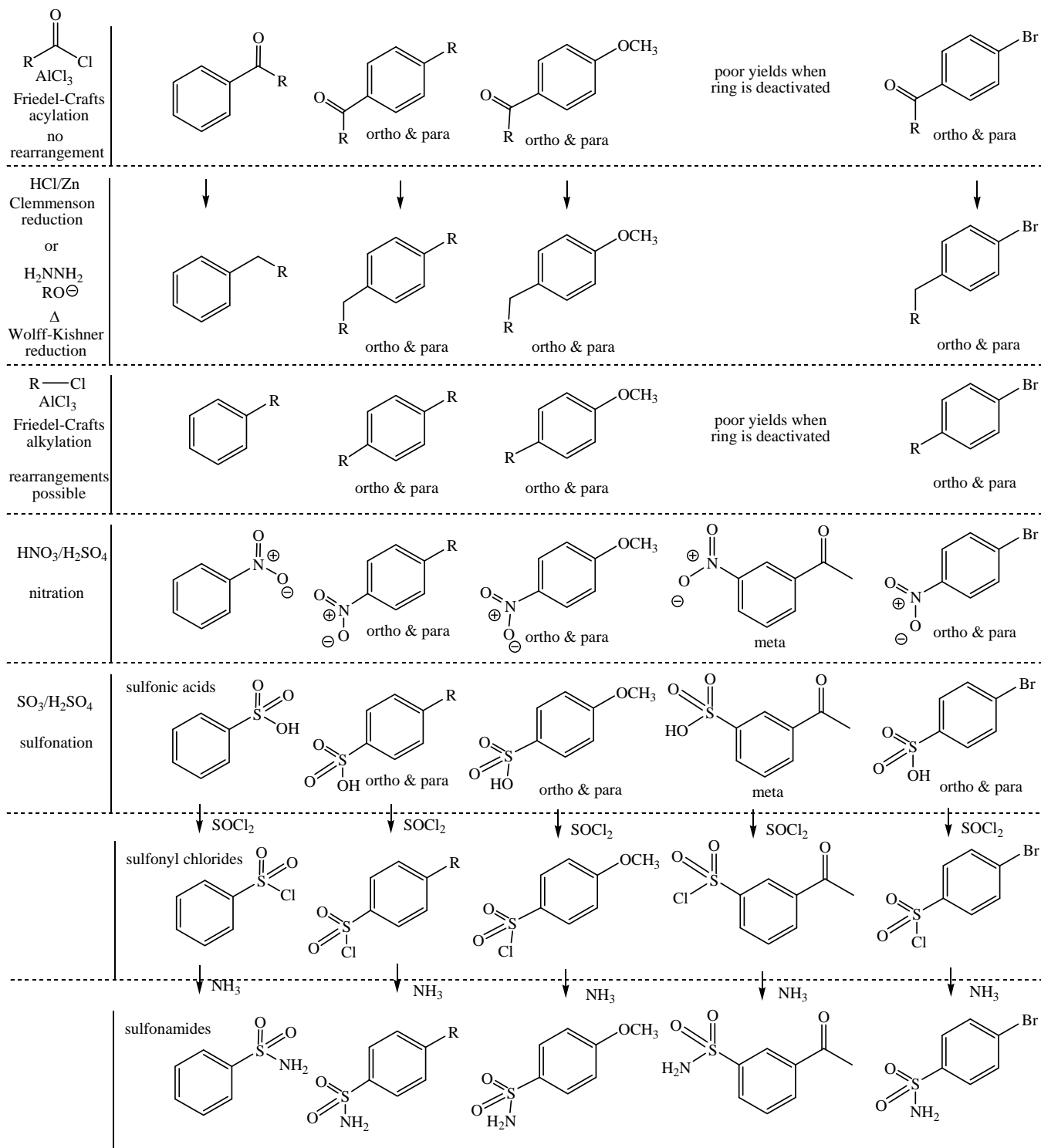


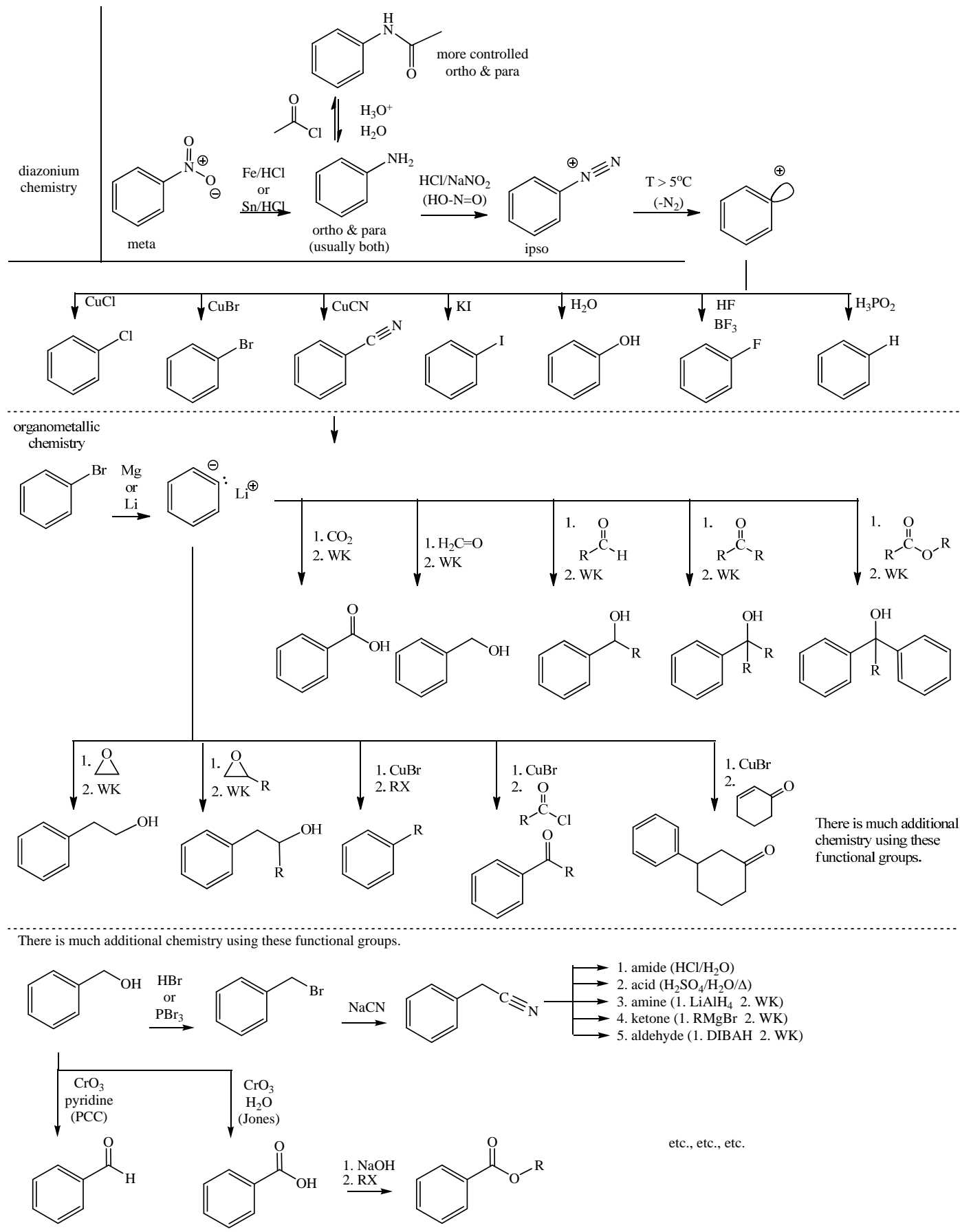
Amide reactions

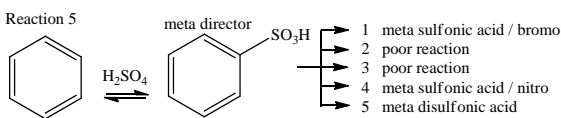
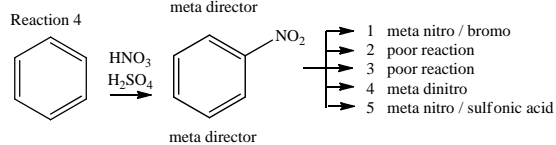
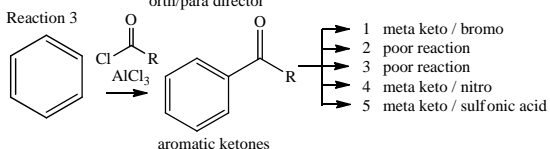
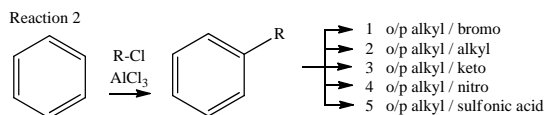
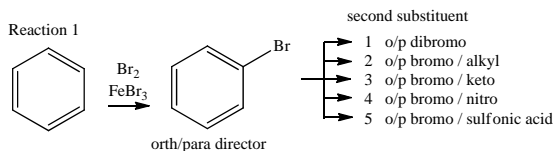


Aromatic reactions

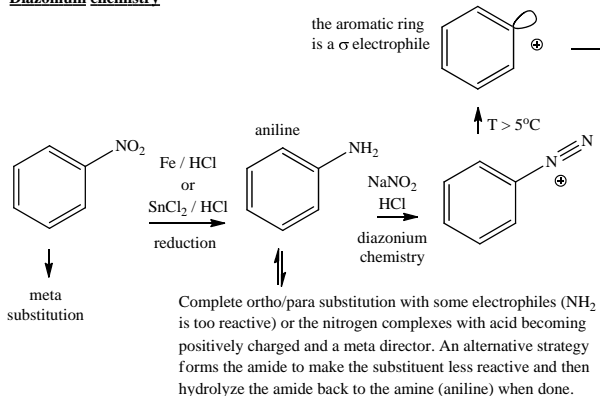
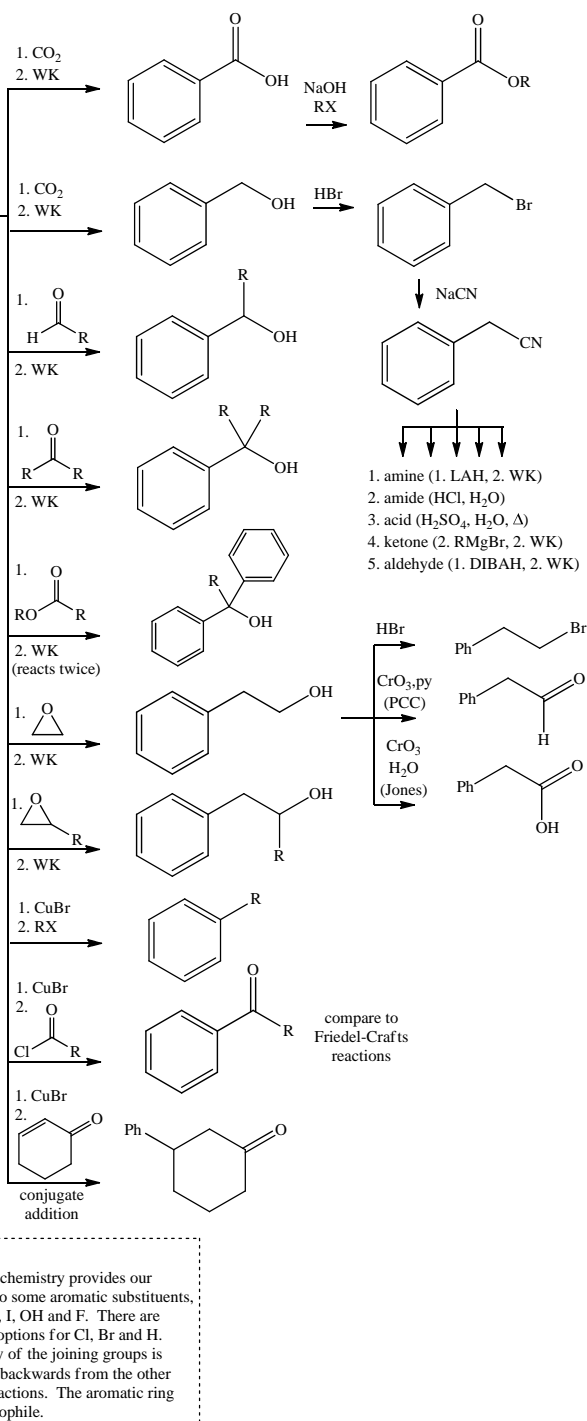
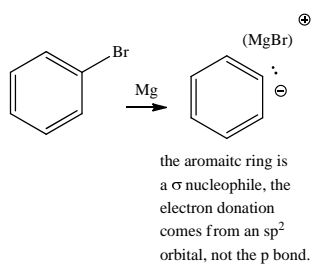
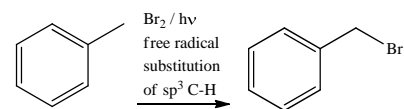
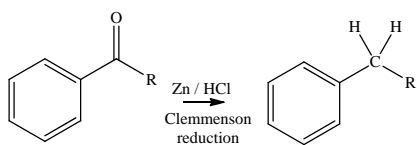
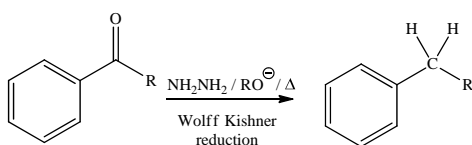
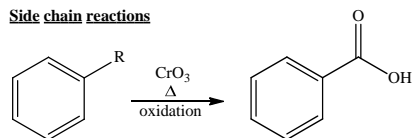






Electrophilic aromatic substitution reaction (aromatic ring is a π nucleophile).

benzene sulfonic acids and this reaction can be reversed with the addition of water

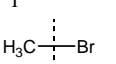
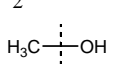
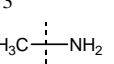
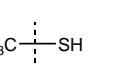
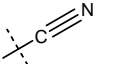


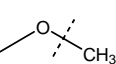
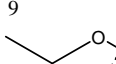
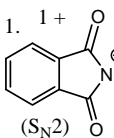
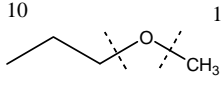
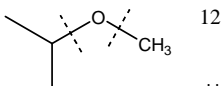
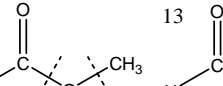
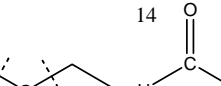
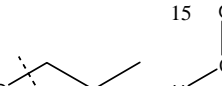
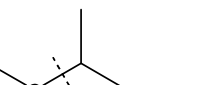
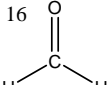
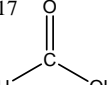
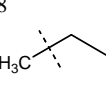
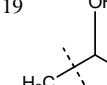
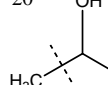
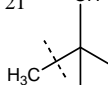
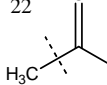
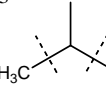
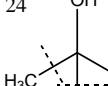
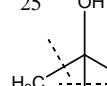
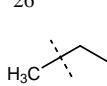
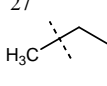
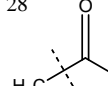
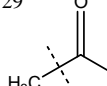
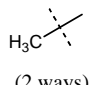
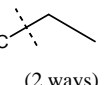
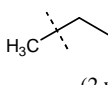
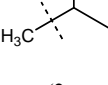
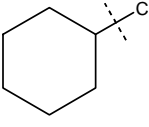
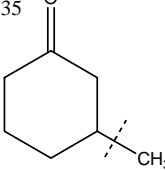
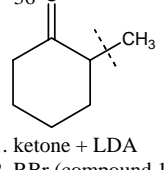
Diazonium chemistry**Organometallic reactions****Side chain reactions**

Miscellaneous C=O reactions (1,3-dicarbonyl compounds, dianions, Robinson's annelation, sulfur ylids, etc.)

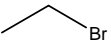
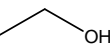
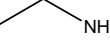
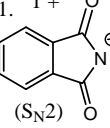
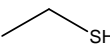
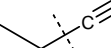
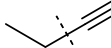
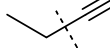
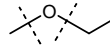
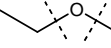
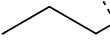
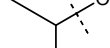
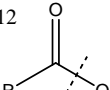
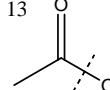
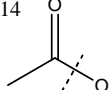
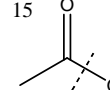
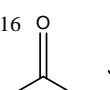
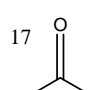
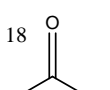
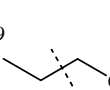
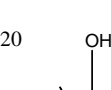
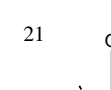
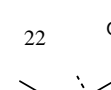
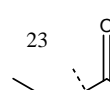
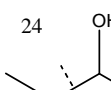
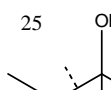
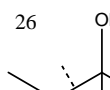
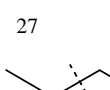
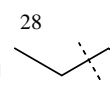
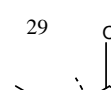
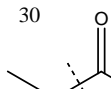
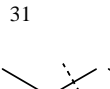
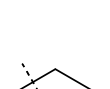
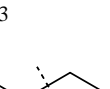
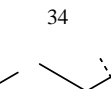
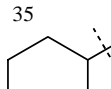
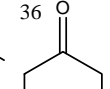
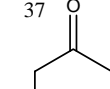

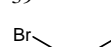

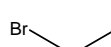

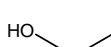
Propose synthetic reactions for the indicated target structures from the given starting materials. Show the starting material (methane, ethane and propane), a reaction arrow with the reagent and a product for each synthetic step of your synthesis. If a compound has been prepared earlier you do not need to remake it (just refer to the part where you made it). Common organic reagents may be used as needed. Additional "carbon" compounds available include bromobenzene, cyclohexane, carbon dioxide and sodium cyanide.

1. Given starting material = methane, (CH₄)

Target molecules (the part from methane has the "C" written out).

1 	2 	3 	4 	5 	6 	7 	8 	9 
methane + Br ₂ /hν 2 + HBr 2 + PBr ₃ 2 + SOBr ₂ 2 + a. TsCl/py b. NaBr	a. 1 + ester (S _N 2) b. ester + NaOH 31 + H ₃ O ⁺ , H ₂ O a. 31 + HgX ₂ /H ₂ O b. NaBH ₄ a. 13 + NaBH ₄ b. WK	1. 1 +  (S _N 2) 2. NaOH	1 + NaSH (S _N 2)	1 + NaCN (S _N 2)	a. 40 + NaNR ₂ b. bromomethane	a. propyne + NaNR ₂ b. bromomethane	(2 ways) RO [⊖] + RBr (S _N 2)	(2 ways)
10 	11 	12 	13 	14 	15 			
(2 ways) RO [⊖] + RBr (S _N 2)	(2 ways) RO + RBr (S _N 2) ROH + RBr (S _N 1)	(2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	(2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	(2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	(2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)			
16 	17 	18 	19 	20 	21 	22 	23 	
2 + CrO ₃ /py (PCC)	2 + CrO ₃ /H ₂ O (Jones)	a. 1 + Mg (or Li) b. methanal c. WK	a. 1 + Mg (or Li) b. ethanal c. WK	a. 1 + Mg (or Li) b. propanal c. WK	a. 1 + Mg (or Li) b. propanone c. WK	a. 1 + Mg (or Li) b. CO ₂ c. WK	a. 1 + Mg (or Li) b. alkyl methanoate c. WK	
24 	25 	26 	27 	28 	29 			
a. 1 + Mg (or Li) b. alkyl ethanoate c. WK	a. 1 + Mg (or Li) b. alkyl propanoate c. WK	a. 1 + Mg (or Li) b. 2C epoxide c. WK	a. 1 + Mg (or Li) b. 3C epoxide c. WK	acid chloride + cuprate a. 1 + Mg (or Li) b. ethanenitrile ethanoic acid + 2 eqs methyl lithium	acid chloride + cuprate a. 1 + Mg (or Li) b. propanenitrile propanoic acid + 2 eqs methyl lithium			
30 	31 	32 	33 	34 	35 	36 		
(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + enone (conjugate addition)	1. ketone + LDA 2. RBr (compound 1) a. enamine + 1 b. H ₂ O (hydrolysis)		

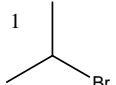
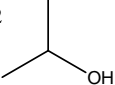
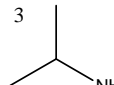
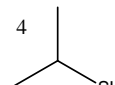
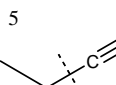
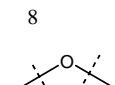
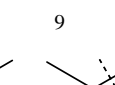
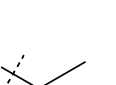
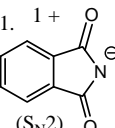
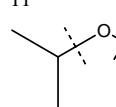
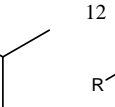
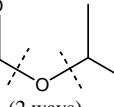
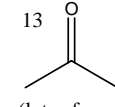
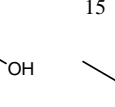
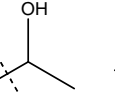
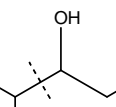
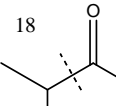
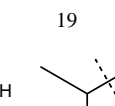
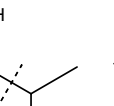
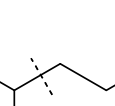
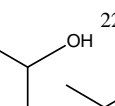
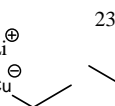
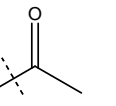
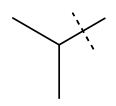
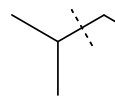
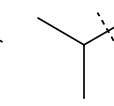
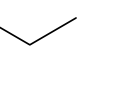
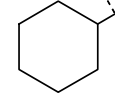
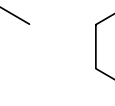
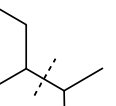
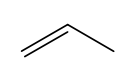
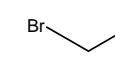
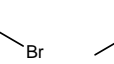
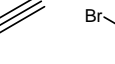
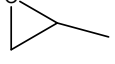
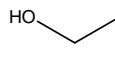
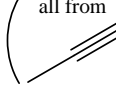
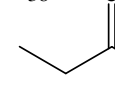
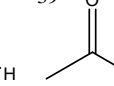
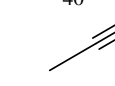
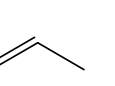
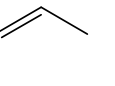
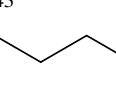
2. Given starting material = ethane, (CH₃CH₃)

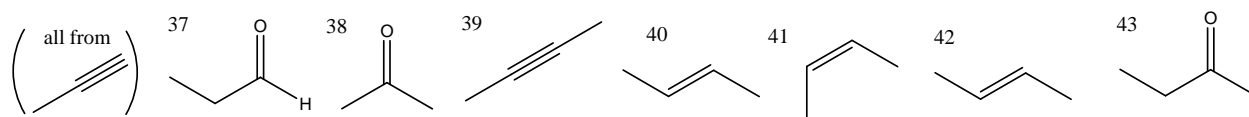
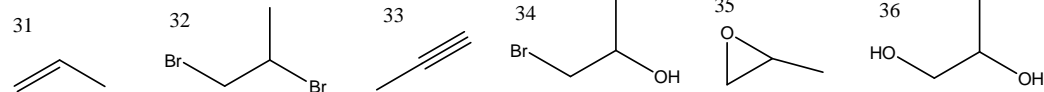
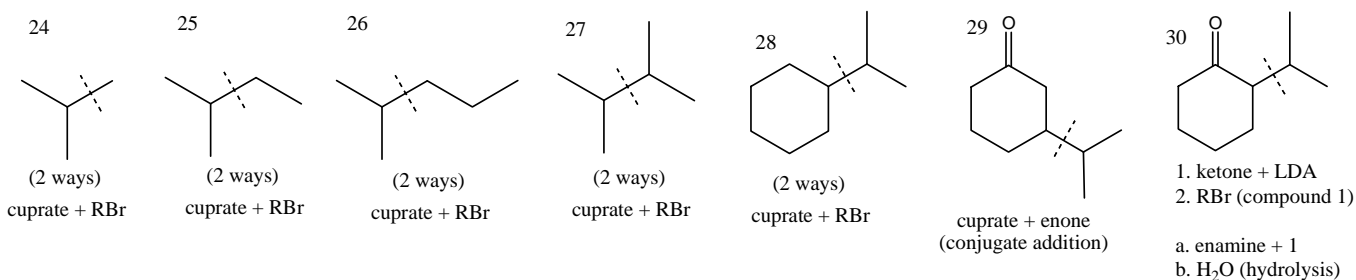
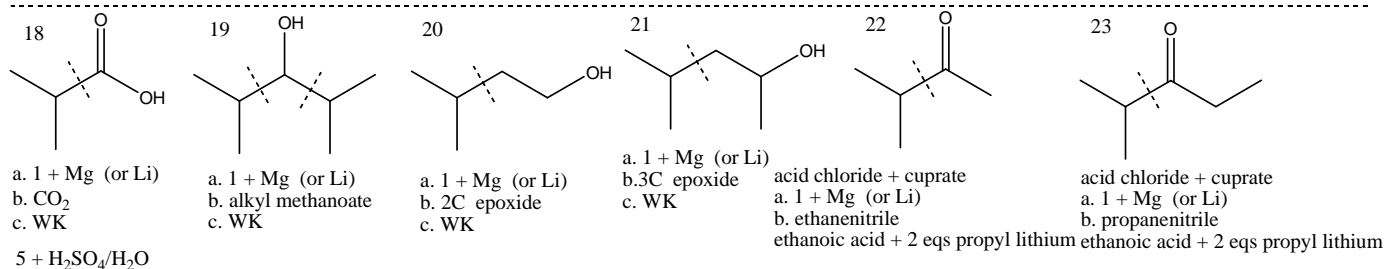
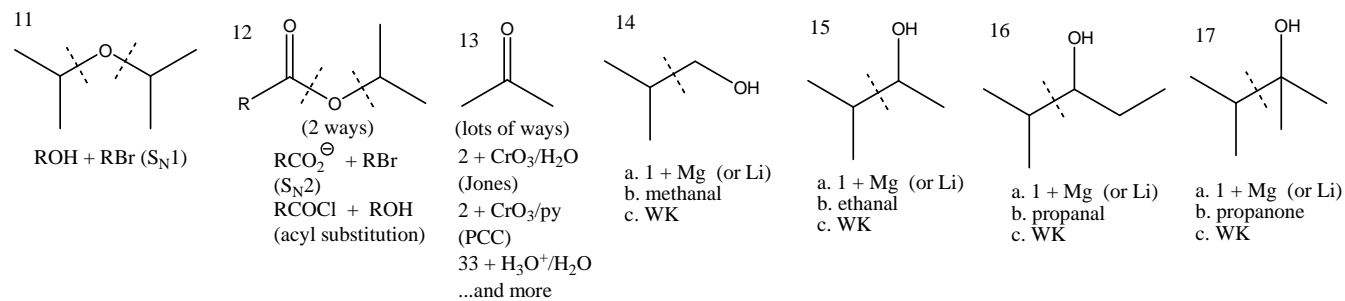
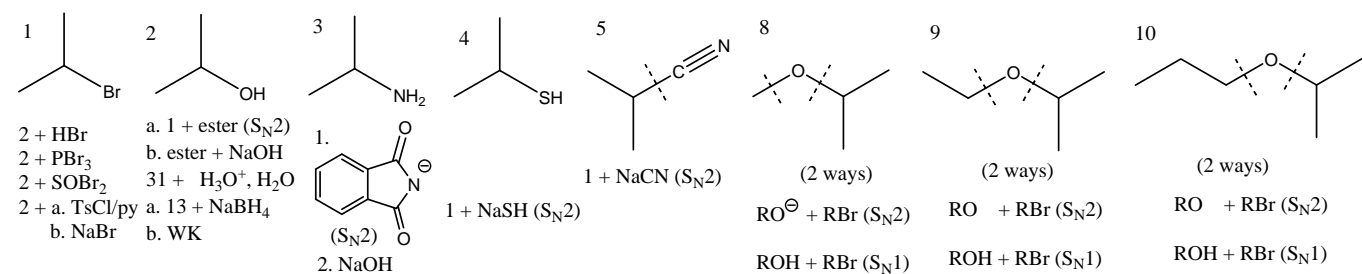
1  ethane + Br ₂ /hν 2 + HBr 2 + PBr ₃ 2 + SOBr ₂ 2 + a. TsCl/py b. NaBr	2  a. 1 + ester (S _N 2) b. ester + NaOH 31 + H ₃ O ⁺ , H ₂ O a. 31 + HgX ₂ /H ₂ O b. NaBH ₄ a. 13 + NaBH ₄ b. WK	3  1. 1 +  (S _N 2) 2. NaOH	4  1 + NaSH (S _N 2)	5  1 + NaCN (S _N 2)	6  a. 40 + NaNR ₂ b. bromoethane	7  a. propyne + NaNR ₂ b. bromoethane	8  (2 ways) RO [⊖] + RBr (S _N 2)	9  (2 ways)
10  (2 ways) RO [⊖] + RBr (S _N 2)	11  (2 ways) RO + RBr (S _N 2) ROH + RBr (S _N 1)	12  (2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	13  (2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	14  (2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	15  (2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)			
16  (2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	17  a. 40 + R ₂ BH b. H ₂ O ₂ / HO [⊖] 40 + H ₃ O ⁺ /H ₂ O 2 + CrO ₃ /py (PCC)	18  2 + CrO ₃ /H ₂ O (Jones) a. CH ₃ Br/Mg b. CO ₂ c. WK	19  a. 1 + Mg (or Li) b. methanal c. WK	20  a. 1 + Mg (or Li) b. ethanal c. WK	21  a. 1 + Mg (or Li) b. propanal c. WK	22  a. 1 + Mg (or Li) b. propanone c. WK	23  a. 1 + Mg (or Li) b. CO ₂ c. WK 5 + H ₂ SO ₄ /H ₂ O	
24  a. 1 + Mg (or Li) b. alkyl methanoate c. WK	25  a. 1 + Mg (or Li) b. alkyl ethanoate c. WK	26  a. 1 + Mg (or Li) b. alkyl propanoate c. WK	27  a. 1 + Mg (or Li) b. 2C epoxide c. WK	28  a. 1 + Mg (or Li) b. 3C epoxide c. WK	29  acid chloride + cuprate a. 1 + Mg (or Li) b. ethanenitrile ethanoic acid + 2 eqs ethyl lithium			
30  acid chloride + cuprate a. 1 + Mg (or Li) b. propanenitrile ethanoic acid + 2 eqs propyl lithium	31  (2 ways) cuprate + RBr	32  (2 ways) cuprate + RBr	33  (2 ways) cuprate + RBr	34  (2 ways) cuprate + RBr	35  (2 ways) cuprate + RBr	36  cuprate + enone (conjugate addition)	37  1. ketone + LDA 2. RBr (compound 1) a. enamine + 1 b. H ₂ O (hydrolysis)	
38  1 + K ⁺ t-butoxide 2 + H ₂ SO ₄ /Δ	39  Br ₂	40  a. 39 + NaNR ₂ b. WK	41  Br ₂ / H ₂ O	42  38 + mCPBA 41 + NaOH	43  38 + OsO ₄ (or KMnO ₄)			

Wittig =
methanal + ylid

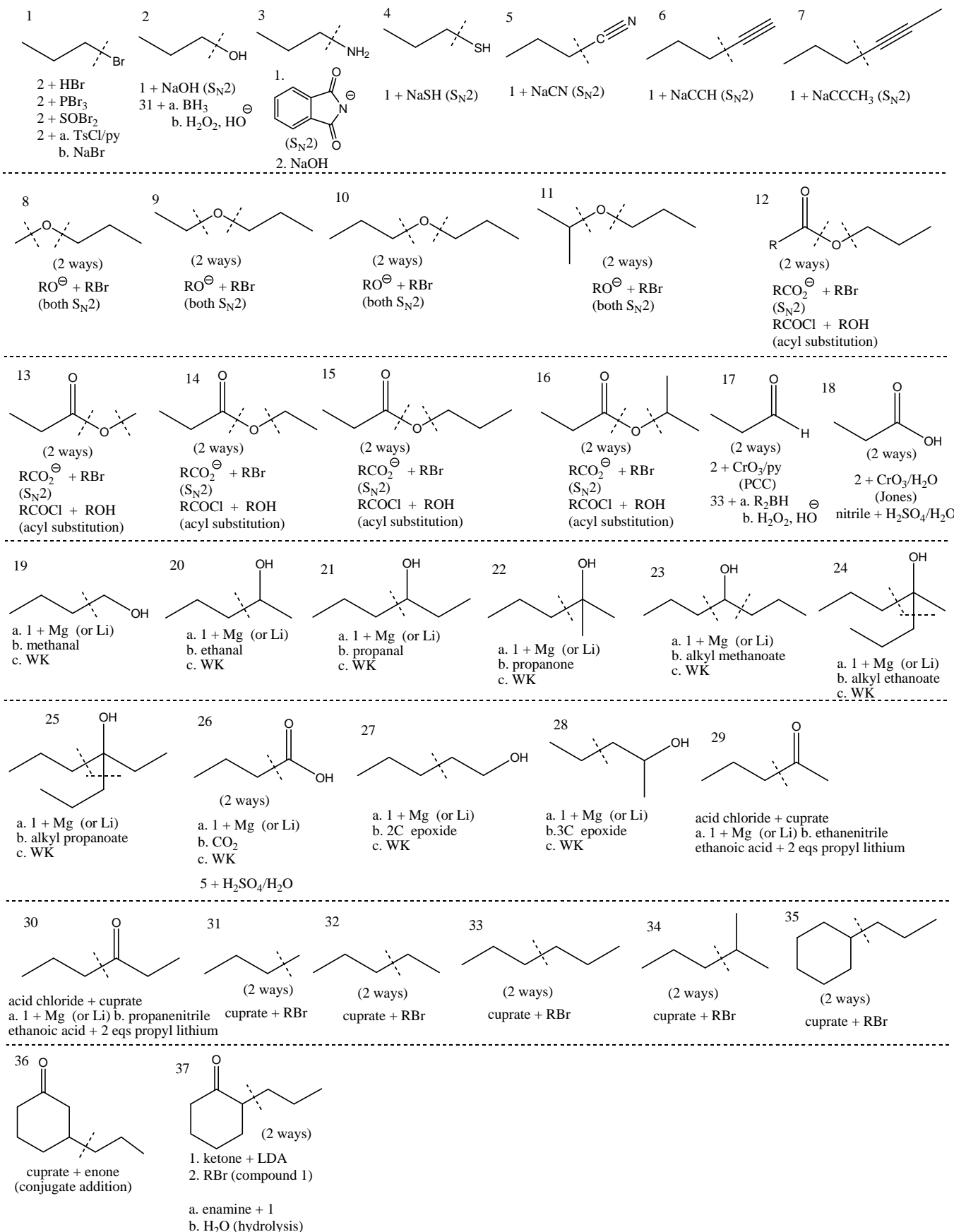
3. Given starting material = propane, (CH₃CH₂CH₃)

a.

1 	2 	3 	4 	5 	8 	9 	10 
propane + Br ₂ /hv 2 + HBr 2 + PBr ₃ 2 + SOBr ₂ 2 + a. TsCl/py b. NaBr	a. 1 + ester (S _N 2) b. ester + NaOH 31 + H ₃ O ⁺ , H ₂ O a. 31 + HgX ₂ /H ₂ O b. NaBH ₄ a. 13 + NaBH ₄ b. WK	1.  (S _N 2) 2. NaOH	1 + NaSH (S _N 2)	1 + NaCN (S _N 2)	(2 ways) RO [⊖] + RBr (S _N 2) ROH + RBr (S _N 1)	(2 ways) RO + RBr (S _N 2) ROH + RBr (S _N 1)	(2 ways) RO + RBr (S _N 2) ROH + RBr (S _N 1)
11 	12 	13 	14 	15 	16 	17 	
ROH + RBr (S _N 1)	(2 ways) RCO ₂ [⊖] + RBr (S _N 2) RCOCl + ROH (acyl substitution)	(lots of ways) 2 + CrO ₃ /H ₂ O (Jones) 2 + CrO ₃ /py (PCC) 33 + H ₃ O ⁺ /H ₂ O ...and more	a. 1 + Mg (or Li) b. methanal c. WK	a. 1 + Mg (or Li) b. ethanal c. WK	a. 1 + Mg (or Li) b. propanal c. WK	a. 1 + Mg (or Li) b. propanone c. WK	
18 	19 	20 	21 	22 	23 	24 	
a. 1 + Mg (or Li) b. CO ₂ c. WK 5 + H ₂ SO ₄ /H ₂ O	a. 1 + Mg (or Li) b. alkyl methanoate c. WK	a. 1 + Mg (or Li) b. 2C epoxide c. WK	a. 1 + Mg (or Li) b. 3C epoxide c. WK	cuprate 2RLi + CuBr	acid chloride + cuprate a. 1 + Mg (or Li) b. ethanenitrile ethanoic acid + 2 eqs propyl lithium	acid chloride + cuprate a. 1 + Mg (or Li) b. propanenitrile ethanoic acid + 2 eqs propyl lithium	
25 	26 	27 	28 	29 	30 	31 	
(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + RBr	(2 ways) cuprate + enone (conjugate addition)	1. ketone + LDA 2. RBr (compound 1) a. enamine + 1 b. H ₂ O (hydrolysis)	
32 	33 	34 	35 	36 	37 		
1 + K ⁺ t-butoxide	31 + Br ₂	a. 32 + NaNR ₂ b. WK	31 + Br ₂ /H ₂ O	31 + mCPBA 34 + NaOH	31 + H ₂ O ₂ / HO [⊖]		
(all from) 	38 	39 	40 	41 	42 	43 	
	1. R ₂ BH b. H ₂ O ₂ / HO [⊖]	(lots of ways) 2 + CrO ₃ /H ₂ O (Jones) 2 + CrO ₃ /py (PCC) 33 + H ₃ O ⁺ /H ₂ O ...and more	a. NaNR ₂ b. CH ₃ -Br	39 + Na / NH ₃	39 + Pd / H ₂ quinoline	39 + Pd / H ₂	

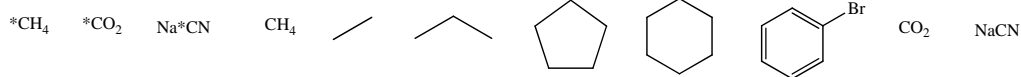


b.

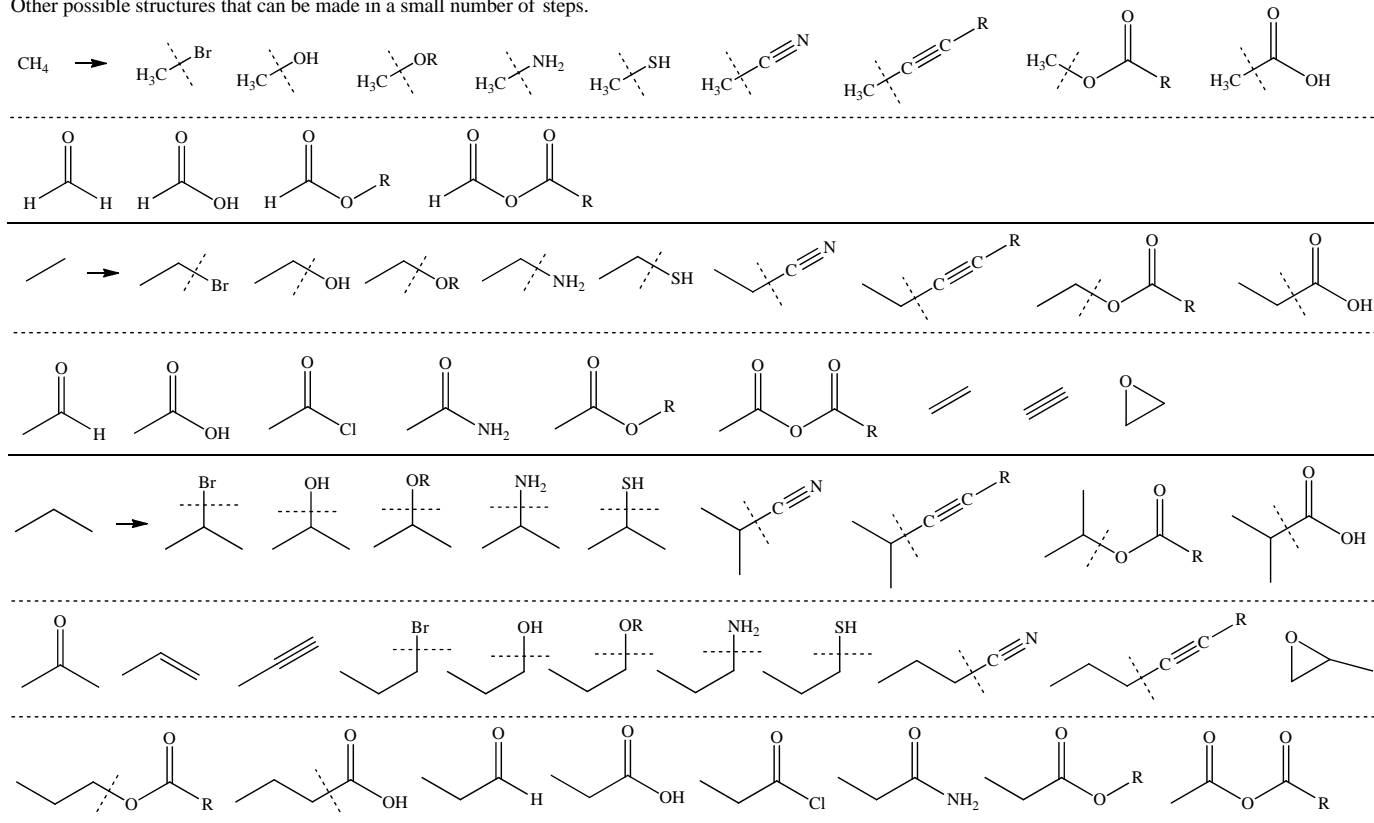


Propose a synthesis for the following compounds using only *CH_4 , Na^*CN , and *CO_2 as your source of radioactive ^{14}C isotope. Bromobenzene, methane, ethane, propane and cyclohexane are also available. Work backwards from the target. The last step of the synthesis should be your first step. Show the reagents and reactant for each backwards step until you reach one of the ^{14}C compounds above and the other allowed starting structures. If a specific functional group or type of reaction is listed, try to use that group or reaction in your synthesis. For many of the target structures, there is more than one possible approach and for some there may be several possible approaches. Any approach is acceptable for this problem as long as the steps are reasonable and any necessary conditions are met. Do not show mechanisms.

Allowed ^{14}C precursors: Use any typical reagents from our course and limited sources of carbon.



Other possible structures that can be made in a small number of steps.



Synthetic Targets

Put "*" at various carbon positions to make problems more challenging (* = ^{14}C).

