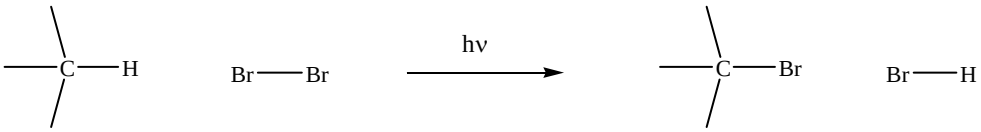
These same reaction schemes are available without the mechanistic details, so you can practice filling in those details.

Problems - In the following reactions each step has been written without the formal charge or lone pairs of electrons and curved arrows. Assume each atom follows the normal octet rule, except hydrogen (duet rule). Supply the lone pairs, formal charge and the curved arrows to show how the electrons move for each step of the reaction mechanism. Identify any obvious nucleophiles and electrophiles in each of the steps of the reactions below (on the left side of each reaction arrow). Let me know when you find errors.

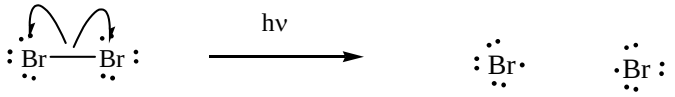
Free radical substitution at sp^3 C-H (overall reaction)



sp^3 C-H bonds The weakest bonds react the fastest.

Mechanism - fill in all necessary details (lone pairs, formal charge, curved arrows, resonance structures = best plus one other)

step 1 = initiation - the halogen bond is the weakest bond and most reactive to cleavage by hν.



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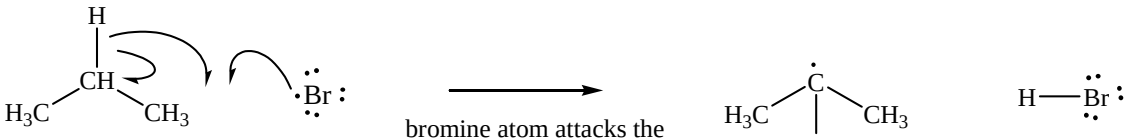
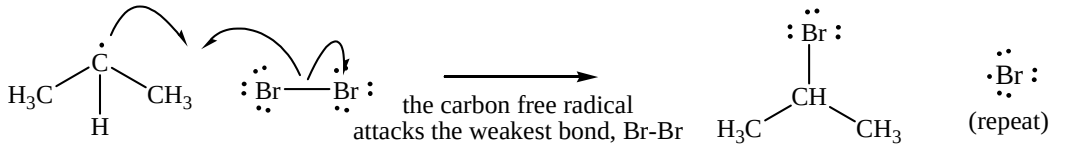
step 2a = propagation - these steps happen 100's to 1000's of times per initiation



step 2b = propagation



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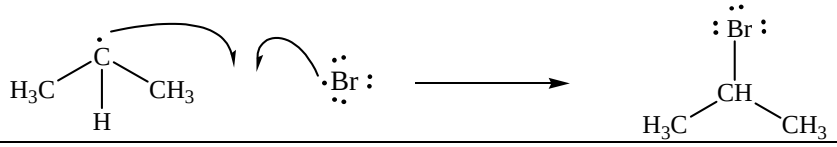
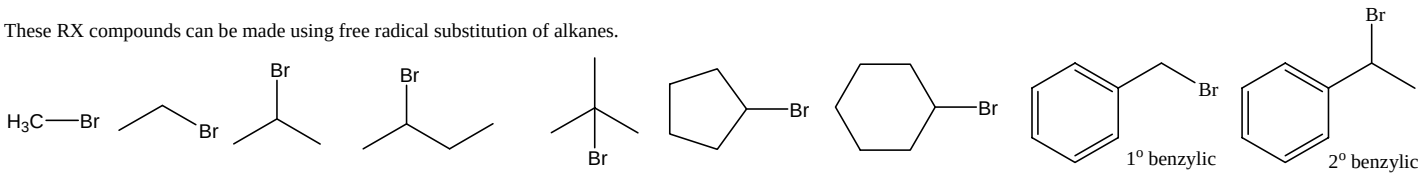
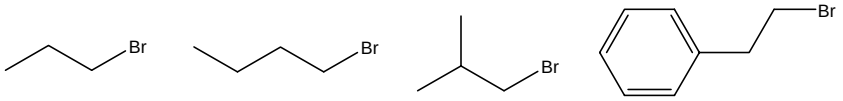
step 3 = termination - two free radicals encounter on another, pure release of energy, this is a rare event



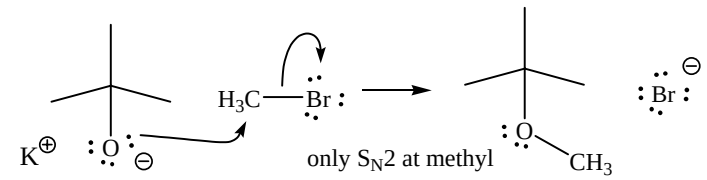
These RX compounds can be made using free radical substitution of alkanes.

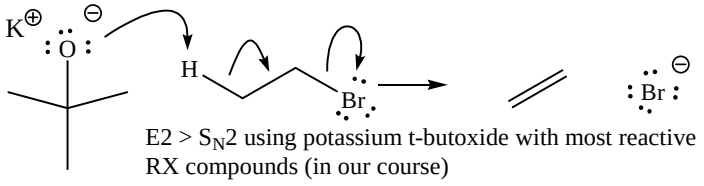


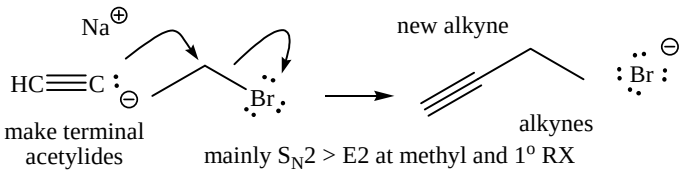
These RX compounds cannot be made using free radical substitution of alkanes.

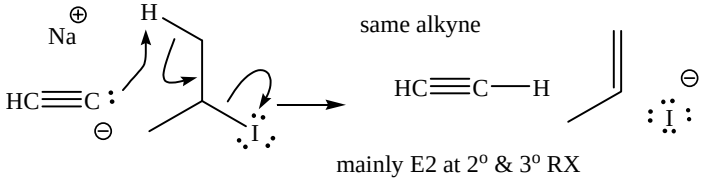


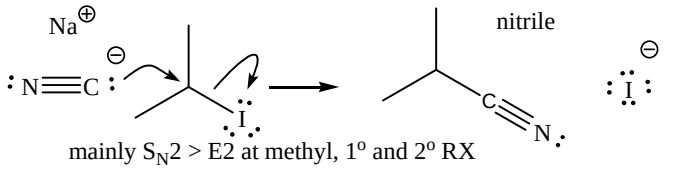
S_N2 reactions with R-X patterns (above): methyl, 1°, 2° (sometimes), allylic and benzylic are very good for S_N2, (R-X = RCl, RBr, RI, ROTs), E2 is the competition. You add all necessary mechanistic details (lone pairs, charge, curved arrows). If no reaction or a different reaction occurs, indicate this. Shown below are syntheses of alcohols, esters, ethers, nitriles, alkynes, thiols, thioethers and amines. Alkenes and alkynes can be made using E2 reactions. That's 10 different functional groups from RX compounds, and we left out using S_N2 chemistry using ketone and ester enolates, dithianes and cuprate chemistry.

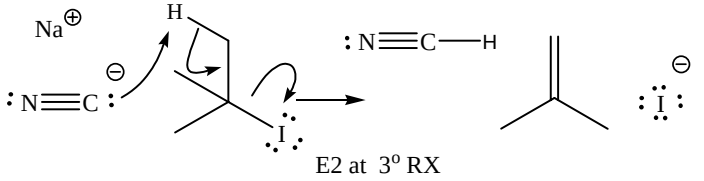


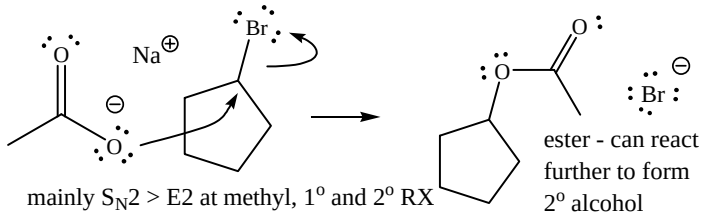


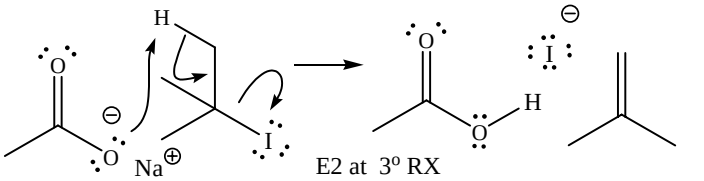




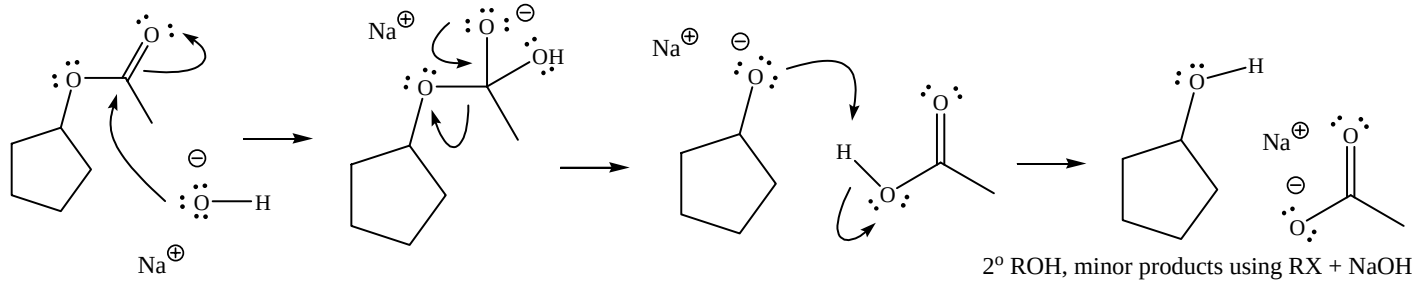


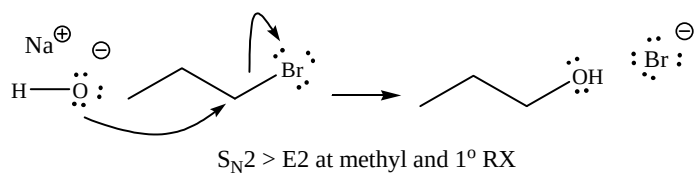


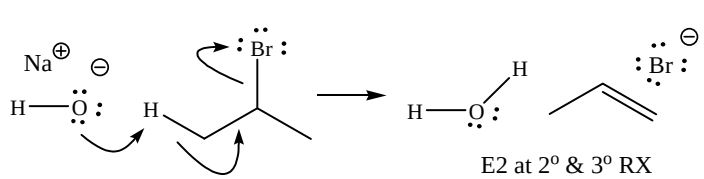




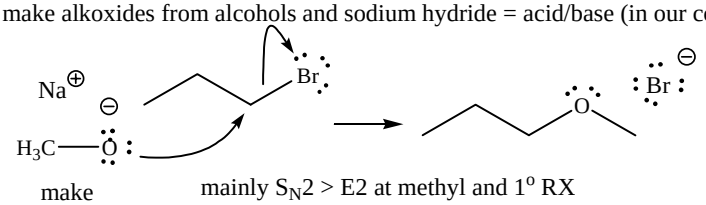
acyl substitution - further reaction with NaOH at ester can be used to make secondary alcohols = base hydrolysis (see imides on next page)

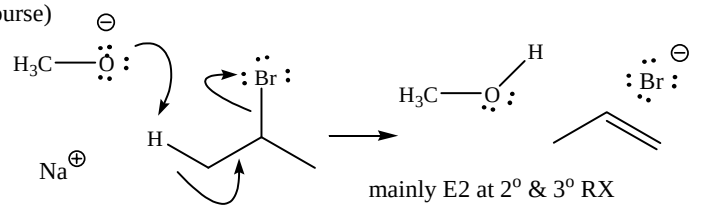




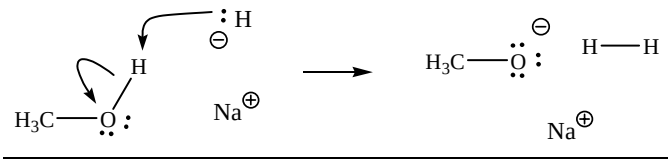


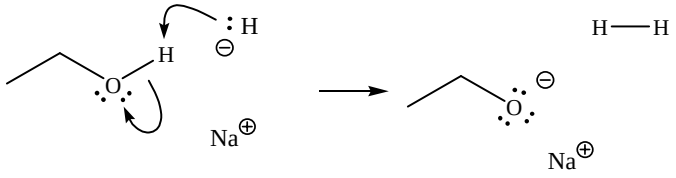
alkoxides are similar to hydroxide, except the S_N2 products are ethers instead of alcohols (potassium t-butoxide is our big exception = E2)
make alkoxides from alcohols and sodium hydride = acid/base (in our course)





make alkoxides from alcohols and sodium hydride

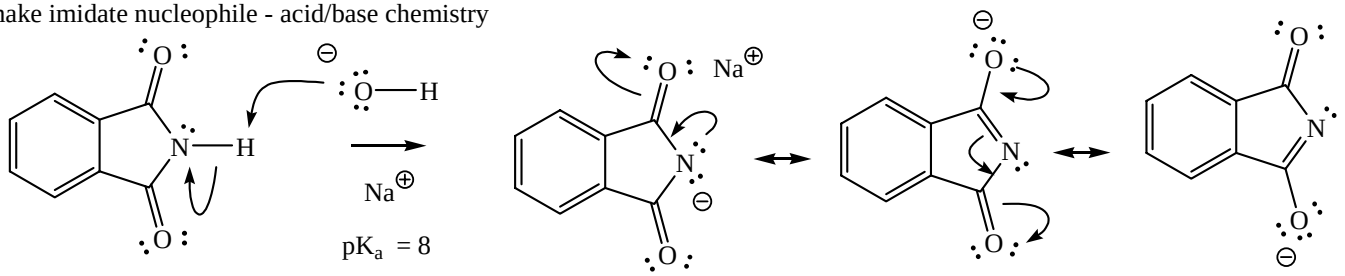




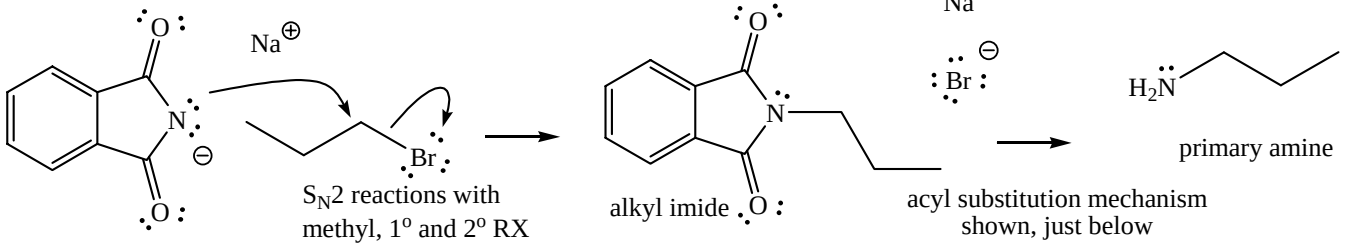
Using S_N2 reaction to make primary (1^o) amines

a. Gabriel amine synthesis

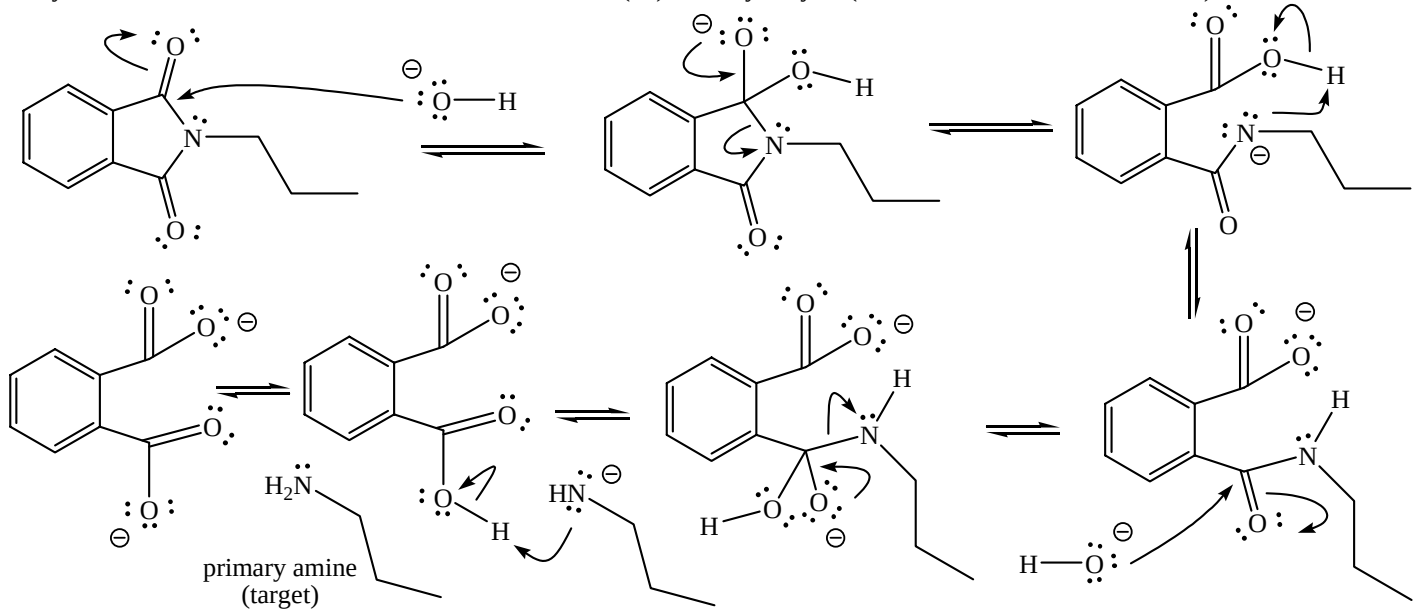
make imidate nucleophile - acid/base chemistry

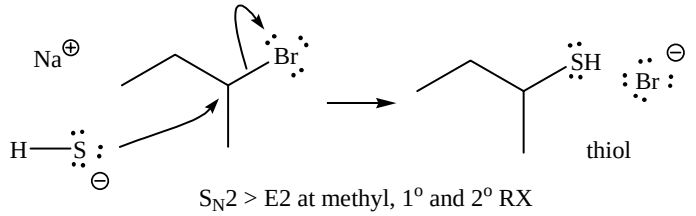


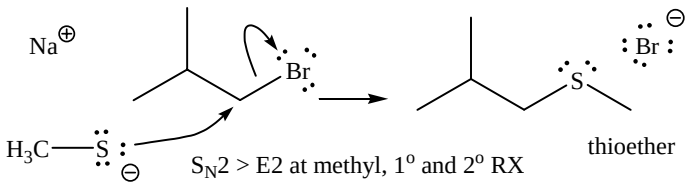
S_N2 reaction of imidate anion at methyl, 1^o and 2^o RX



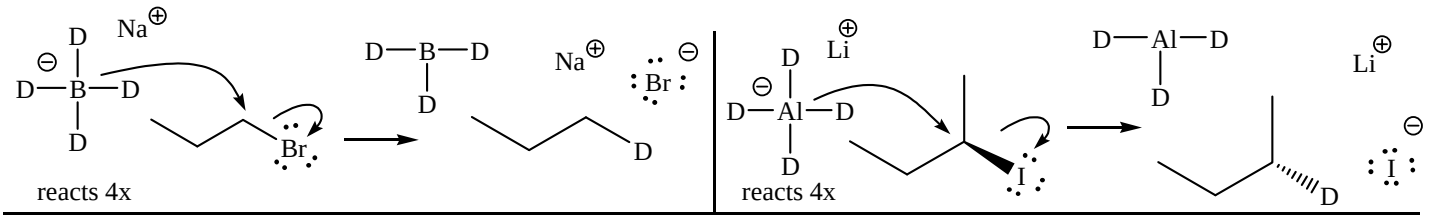
acyl substitution - further reaction with NaOH at imide (2x), base hydrolysis (similar to esters above, but twice)



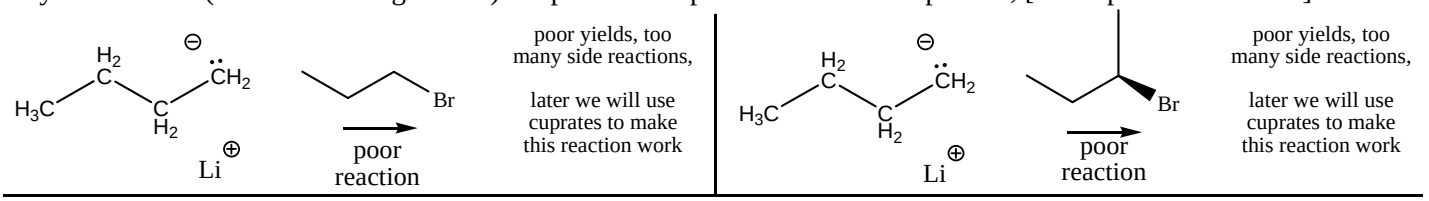




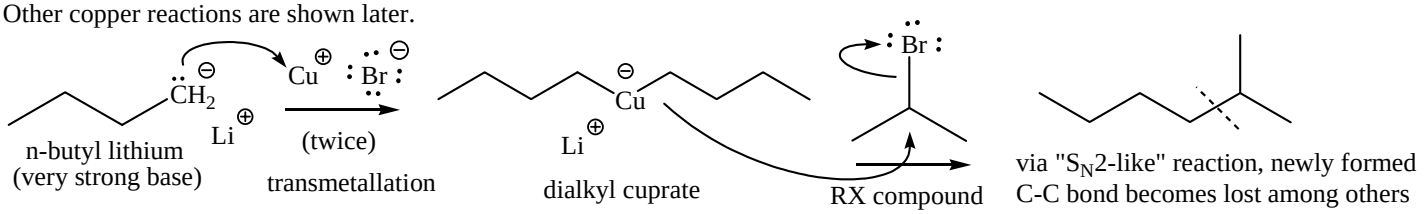
Nucleophilic hydride = sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$ = LAH), [deuterium is used below to show reaction site] – S_N2 reaction at Me, 1^o and 2^o RX.



Alkyl carbanions (lithium and magnesium) are poor nucleophiles with RX compounds, [but cuprates work well]

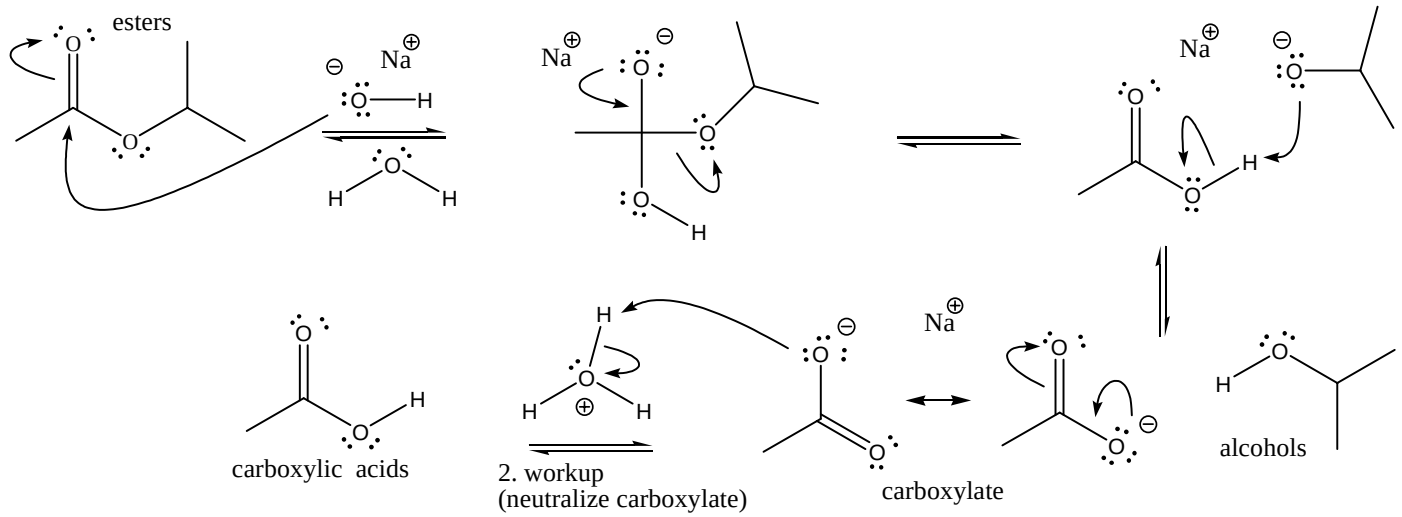


Other copper reactions are shown later.



Acyl substitution, and similar to imide hydrolysis on page 3

base hydrolysis of ester to from alcohol, including acid neutralization of the carboxylate to recover the carboxylic acid (if desired)

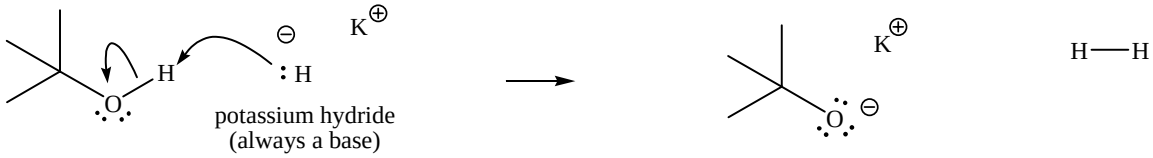


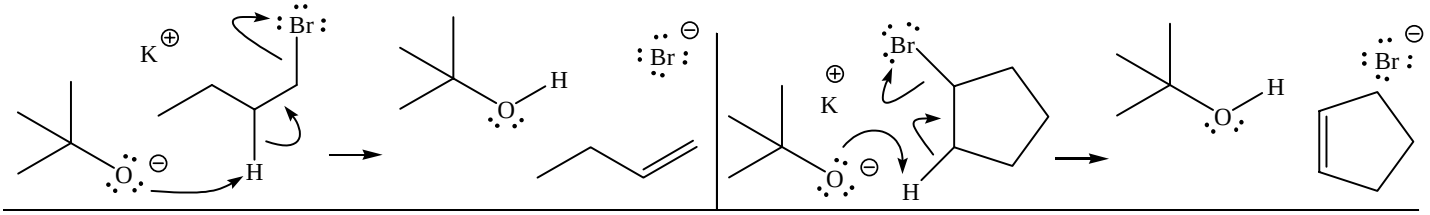
Sometimes we want the acid, sometimes we want the alcohol and sometimes we want both of them.

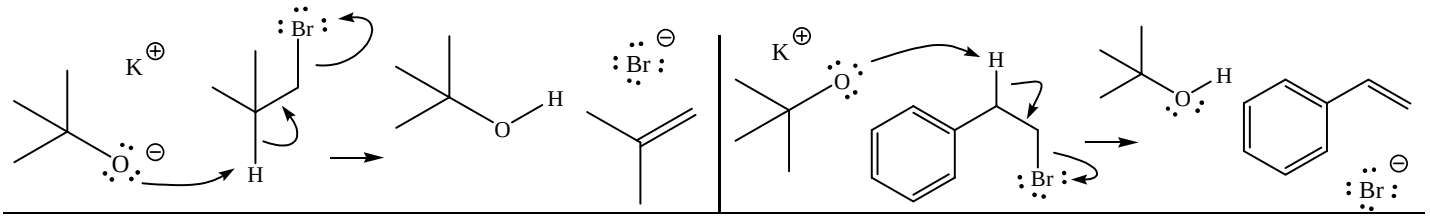
E2 reactions with R-X patterns, usually with potassium t-butoxide (in our course) as the base (to make alkenes) and $NaNR_2$ as the base (in our course) with dibromoalkanes (to make alkynes). S_N2 can be very weak competition (that we ignore). Remember, C_β-H and C_α-X should be "anti".

a. potassium t-butoxide with 1^o, 2^o and 3^o RX compounds to make alkenes (in our course)

make potassium t-butoxide using t-butyl alcohol and potassium hydride (in our course)

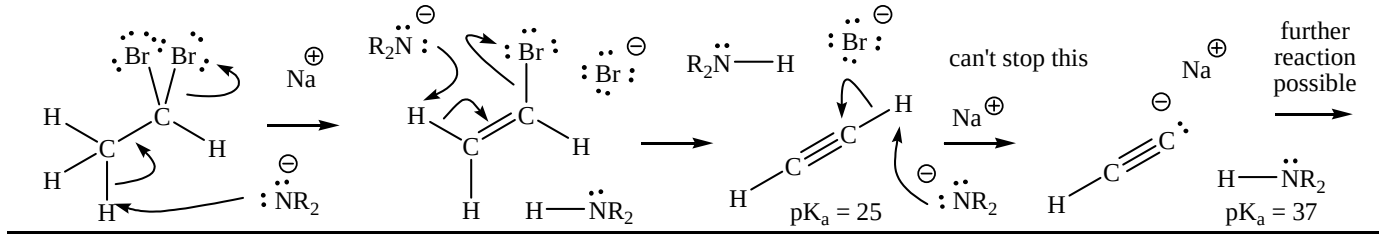


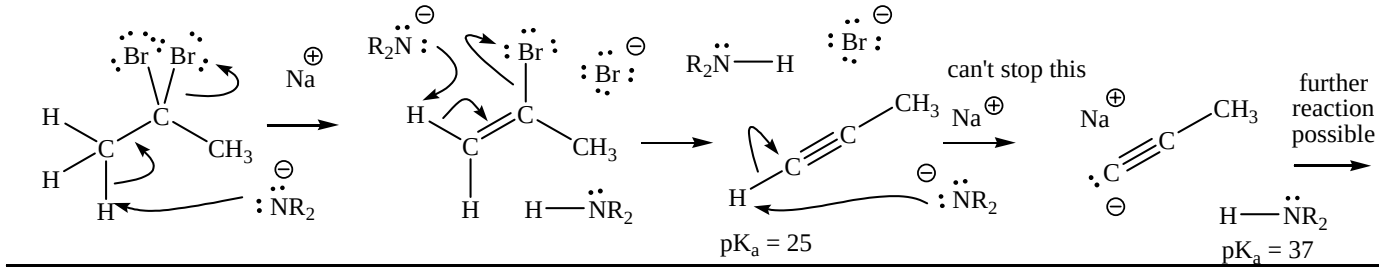




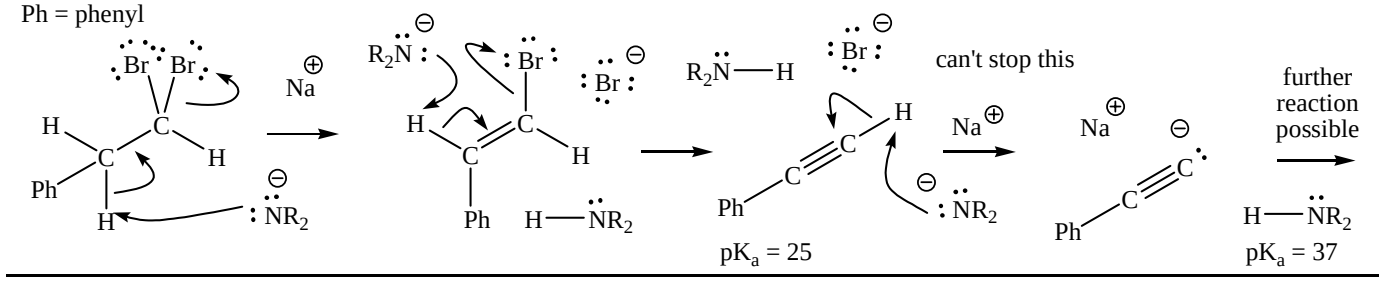
b. sodium amide with dialkyl RX_2 compounds to make alkynes (in our course).

make the alkyne (two E2 reactions and terminal sp C-H (pK_a = 25) is lost to the amide anion (conj. acid, NH_3, pK_a = 37)



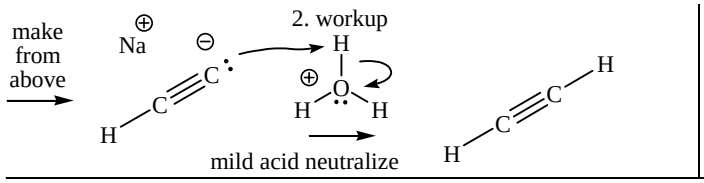


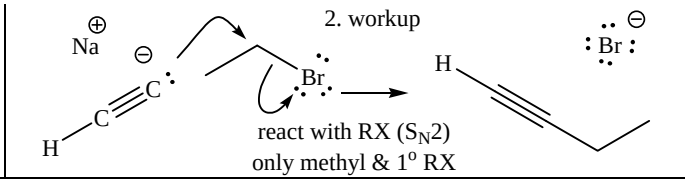
Ph = phenyl

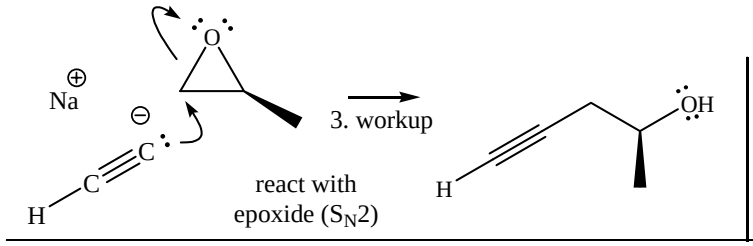


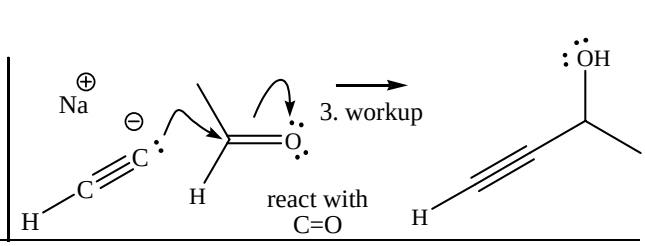
Four workup reactions with terminal acetylides available in our course (Step 2).

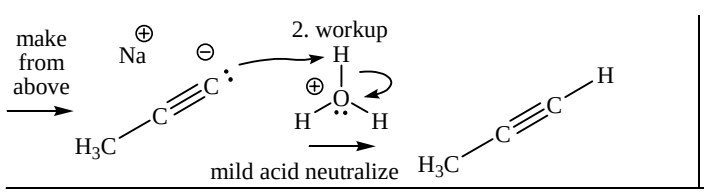
Step 2 = Neutralize with mild acid to get a terminal alkyne, or
Step 2 = react with methyl or 1° RX (S_N2), or
Step 2 = react with epoxide (best S_N2 site reacts fastest) followed by mild acid to protonate the alkoxide, or
Step 2 = react with aldehyde or ketone (carbonyl addition), followed by mild acid to protonate the alkoxide.

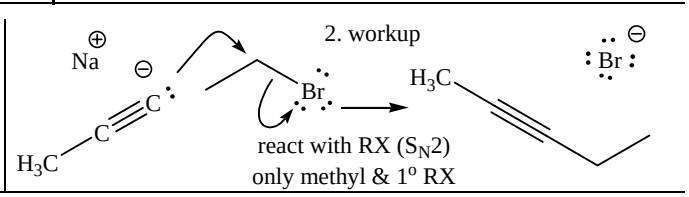


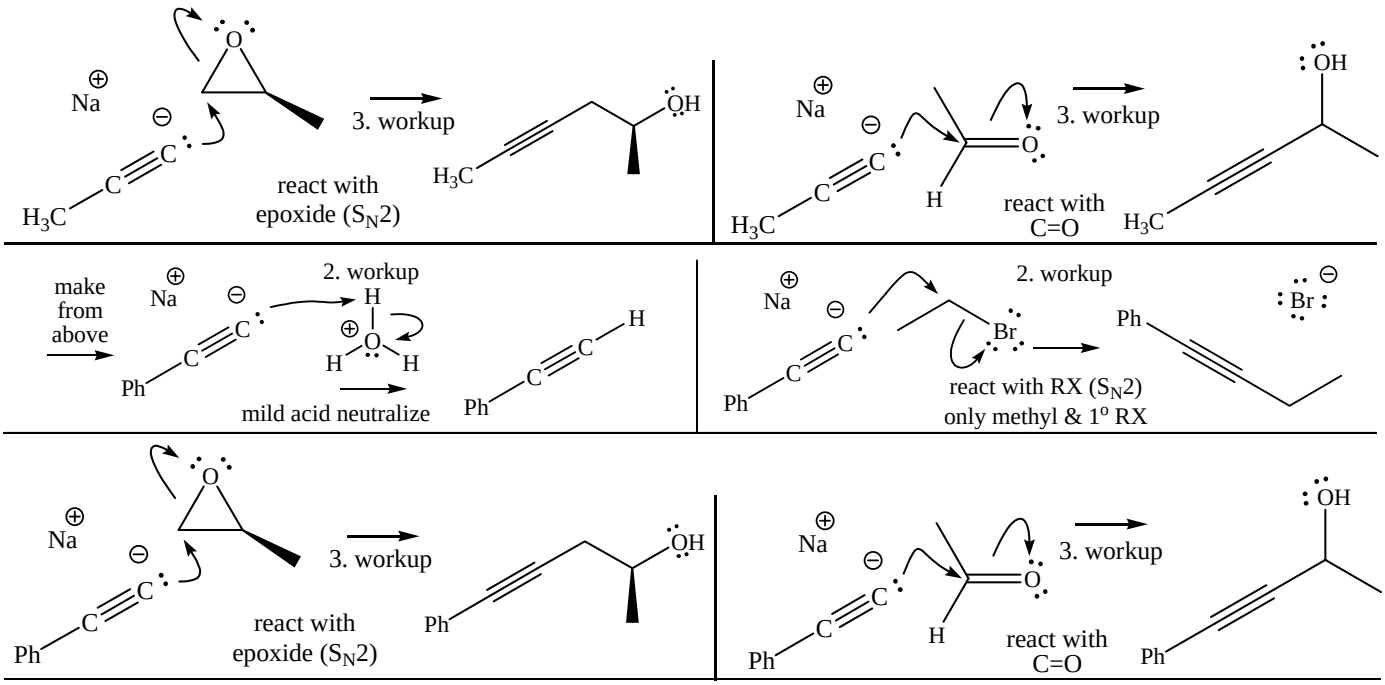






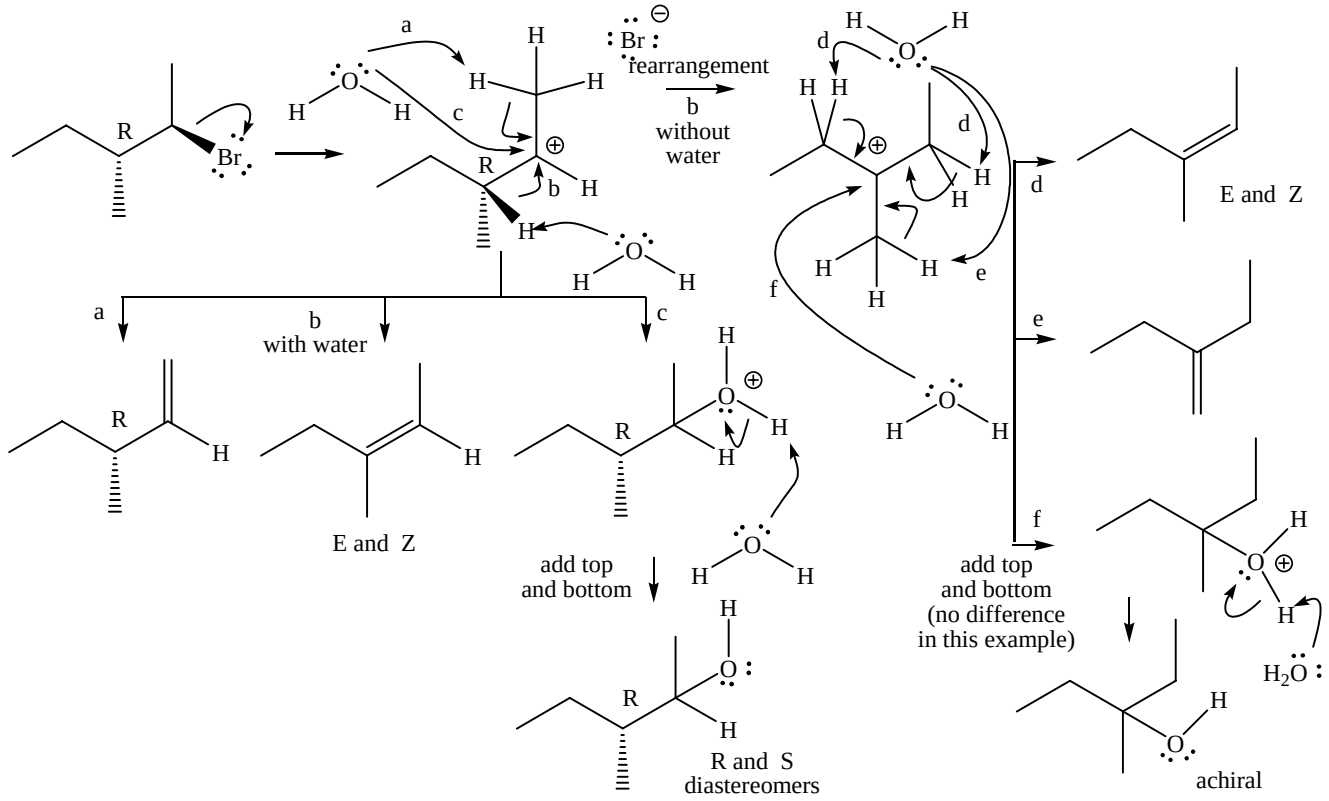


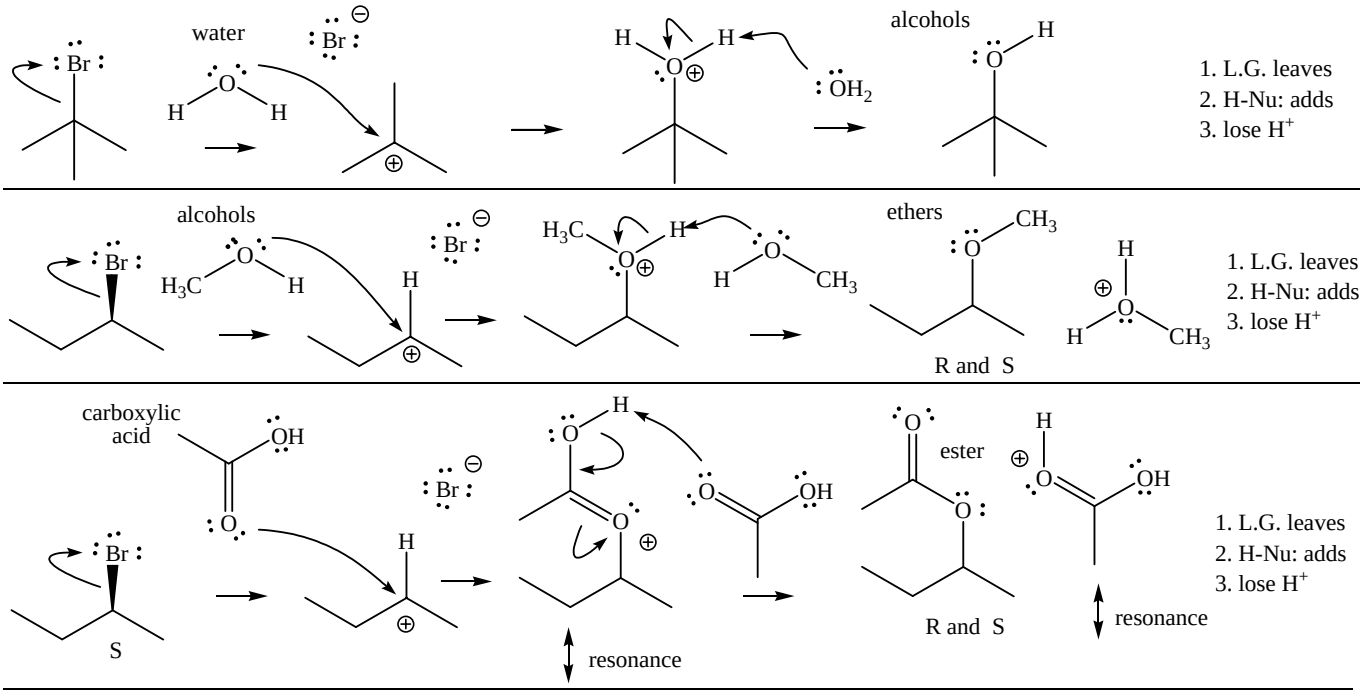




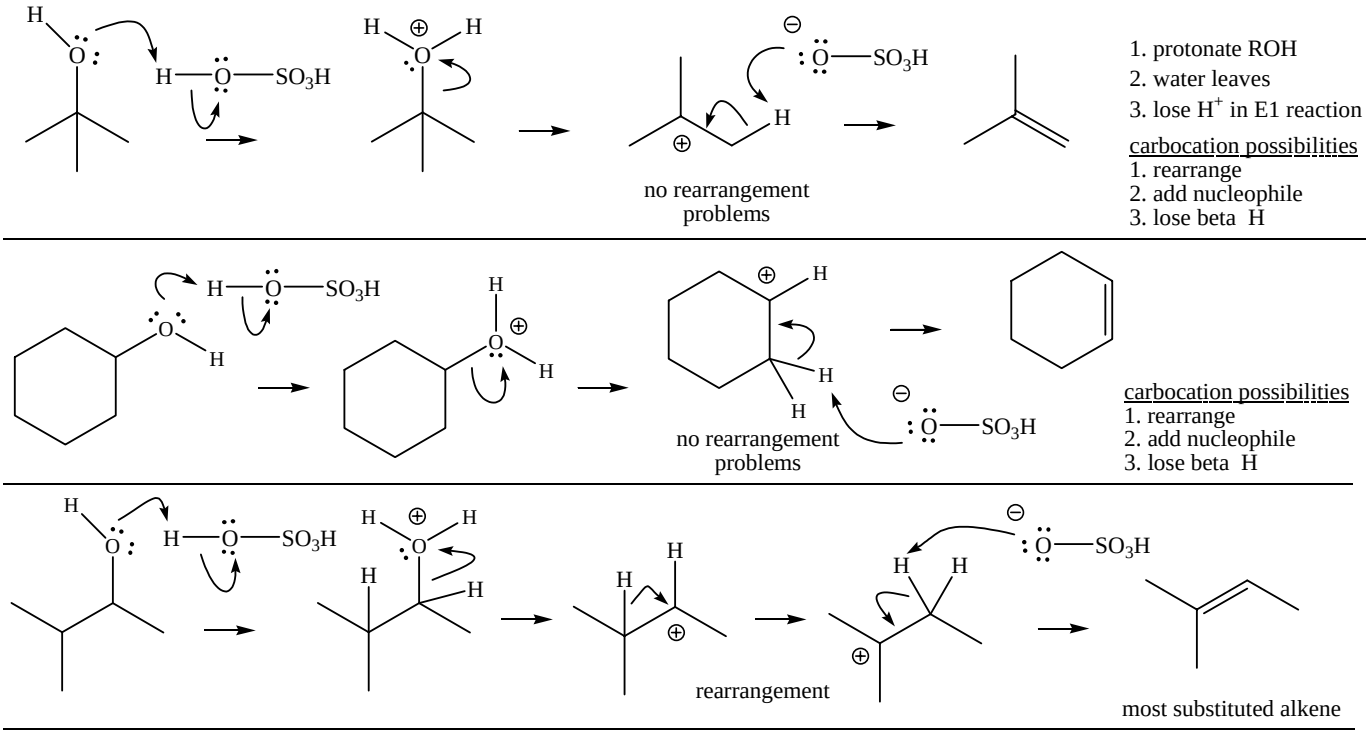
Examples of useful S_N1 reactions – S_N1 and E1 reactions require 2°, 3°, allylic or benzylic RX so that an energetically stable carbocation can form. Useful reactions should not have rearrangement possibilities. We assume S_N1 > E1. Our only synthetically useful reaction is: ROH + H_2SO_4 / Δ → alkenes.

S_N1 and E1 possibilities (make carbocation → 1. rearrangement, 2. add nucleophile, 3. lose beta proton). This example shows all three possibilities and would not be synthetically useful. Three weak nucleophiles in our course are H_2O, ROH and RCO_2H



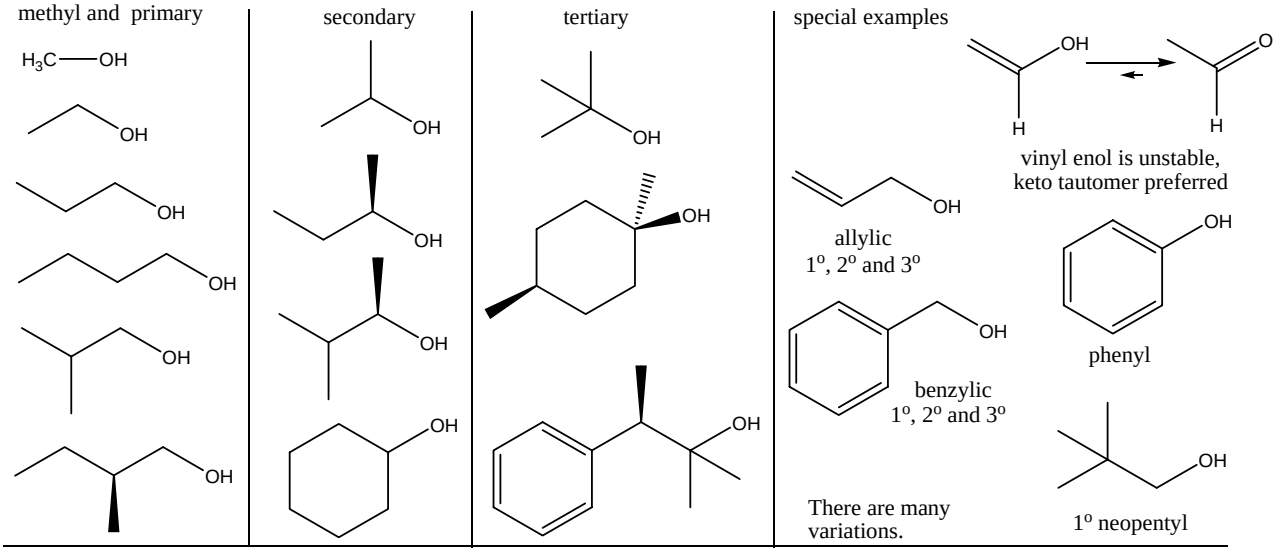


Examples of useful E1 reactions – The only example in our course is H_2SO_4/Δ conditions with alcohols. We propose that 1^o, 2^o and 3^o alcohols all work. The less stable the carbocation, the higher the temperature required. This E1 reaction works because the alkene is distilled away from the reaction mixture, continually shifting the equilibrium in the E1 direction until the starting material is used up. A diabolical trick on the S_N1 reaction, the usual winner. Rearrangements are possible, with the most stable carbocation usually leading to the major alkene product (most substituted alkene).

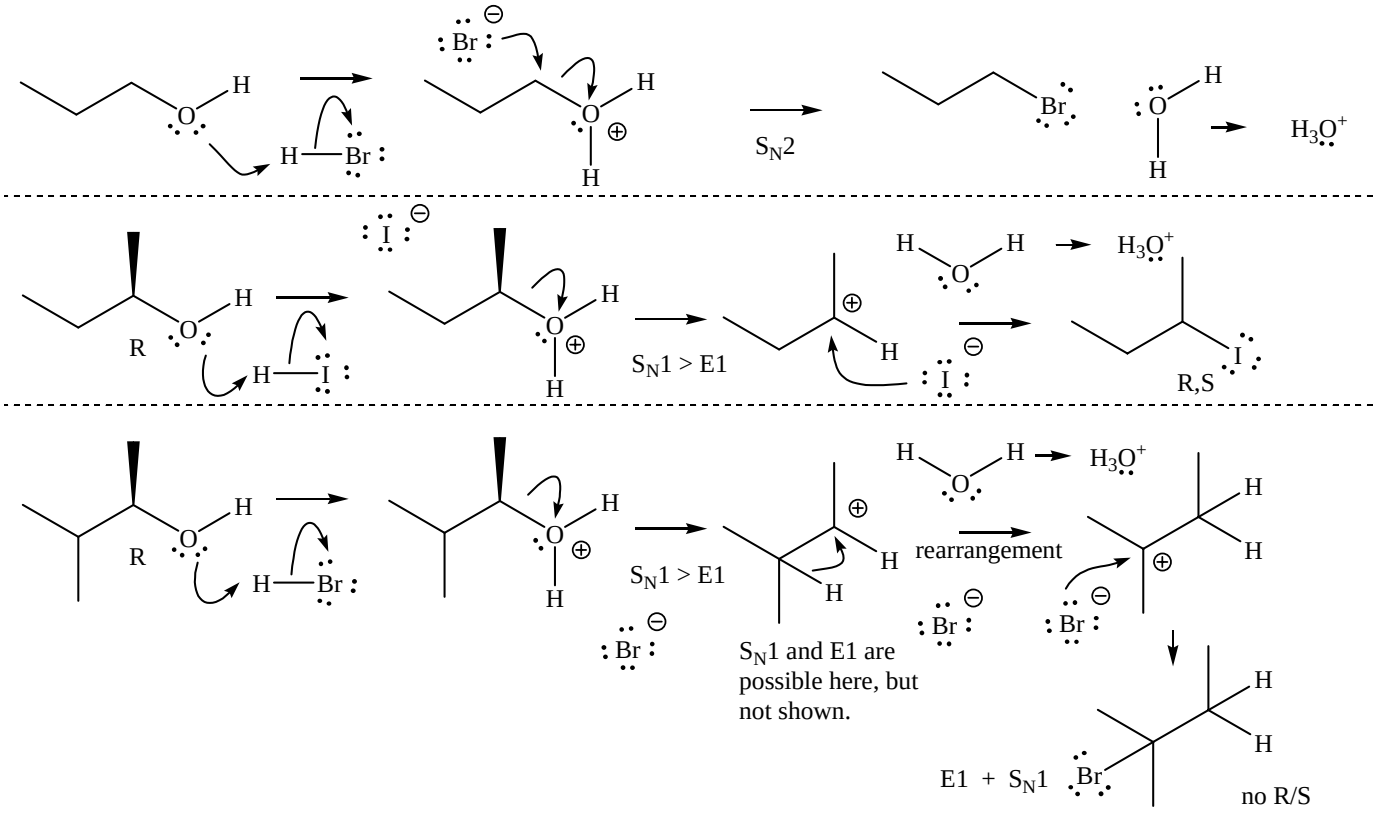


Alcohol Reactions (S_N and E reactions) (Acid/base with HX acids → S_N2 & S_N1 reactions) (1. tosylate synthesis 2. S_N2 with NaBr → RBr) ($SOCl_2$,/ $SOBr_2$, PCl_3/PBr_3 → RX compounds from alcohols, can also make acid halides) (formation of alkoxides with NaH which can form ethers and esters – S_N2 above and acyl substitution with acid chlorides), (oxidation reactions using CrO_3 + water → acids and ketones and without water → aldehydes and ketones)

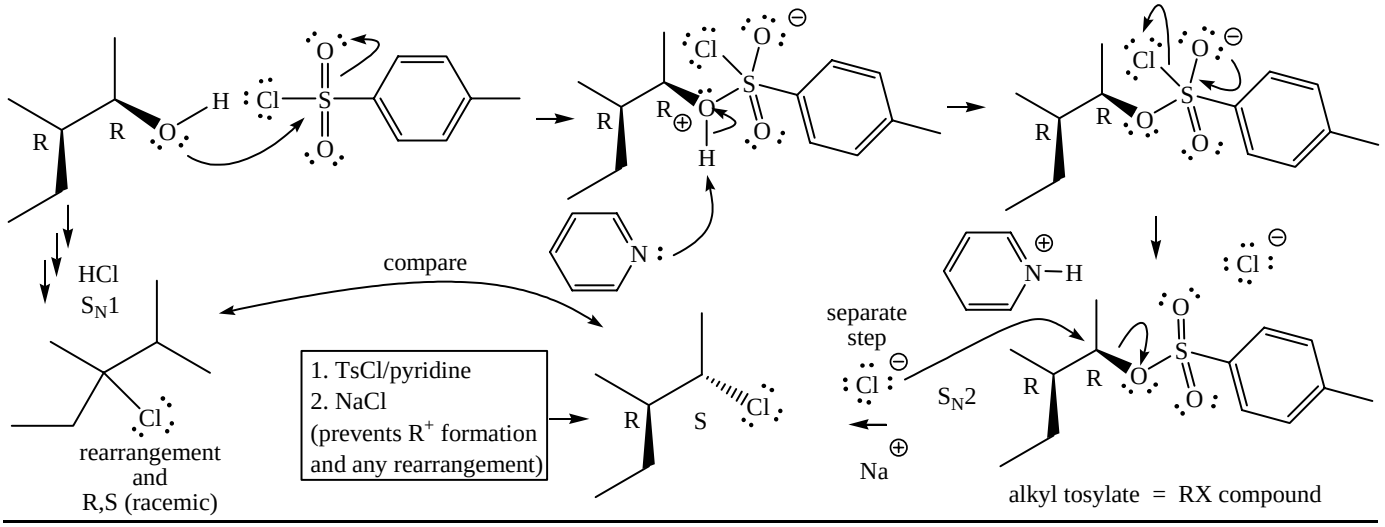
Examples of important patterns to know in our course (plus a few others).



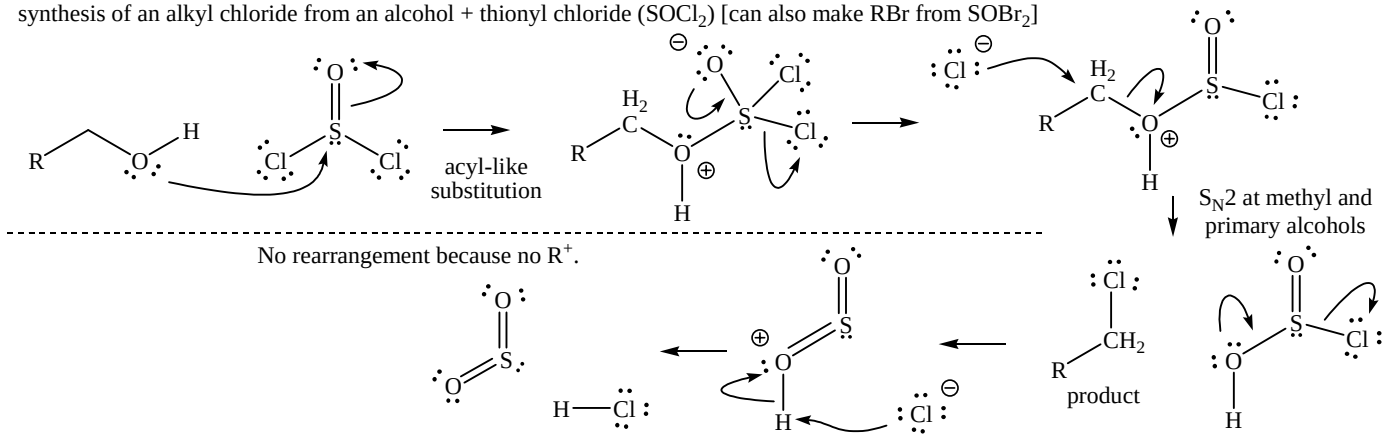
a. HX + ROH (S_N2 at methyl and primary ROH and S_N1 at secondary, tertiary, allylic and benzylic ROH in our course, HX = HCl, HBr, HI)



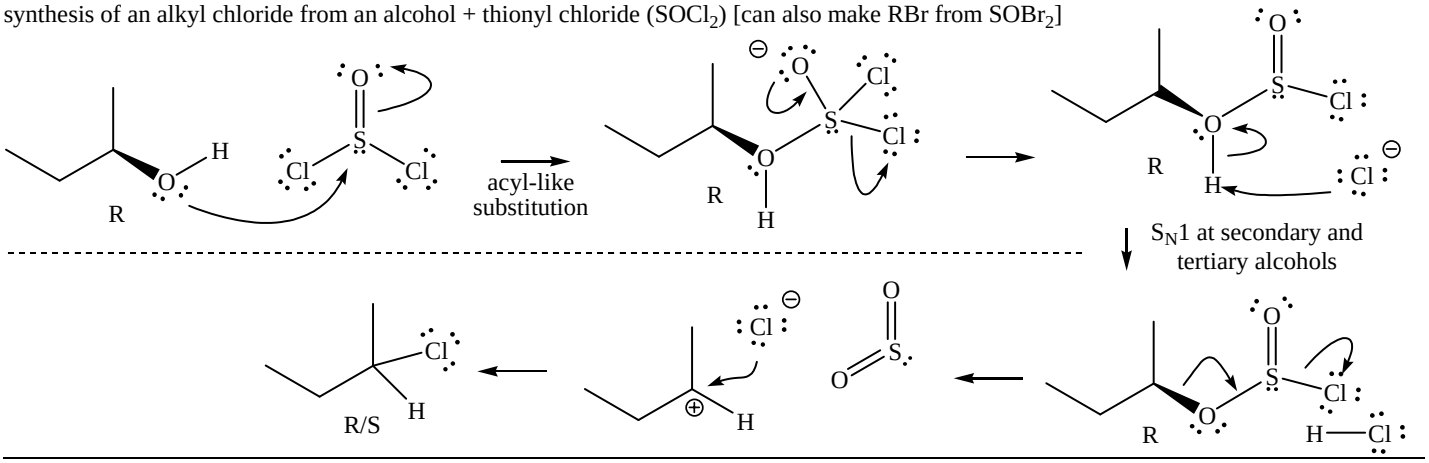
b. Formation of tosylates from ROH + TsCl (toluenesulfonyl chloride = tosyl chloride), S_N/E chemistry is possible



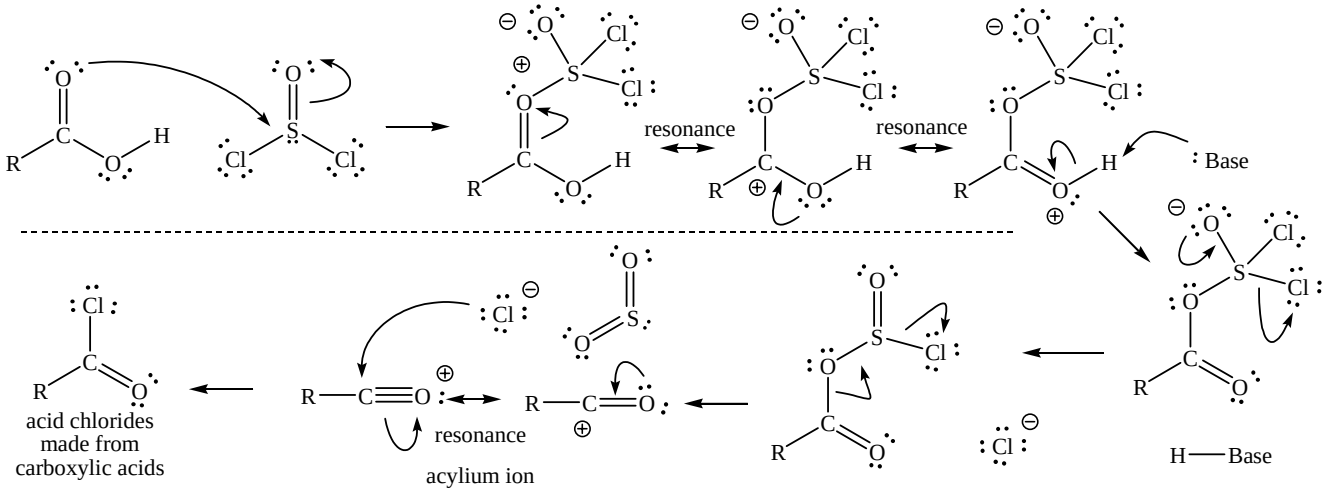
c. Thionyl chloride with methyl, 1° ROH = acyl-like substitution at $SOCl_2$, then S_N2 at methyl and primary RX. $SOBr_2$ is also available.



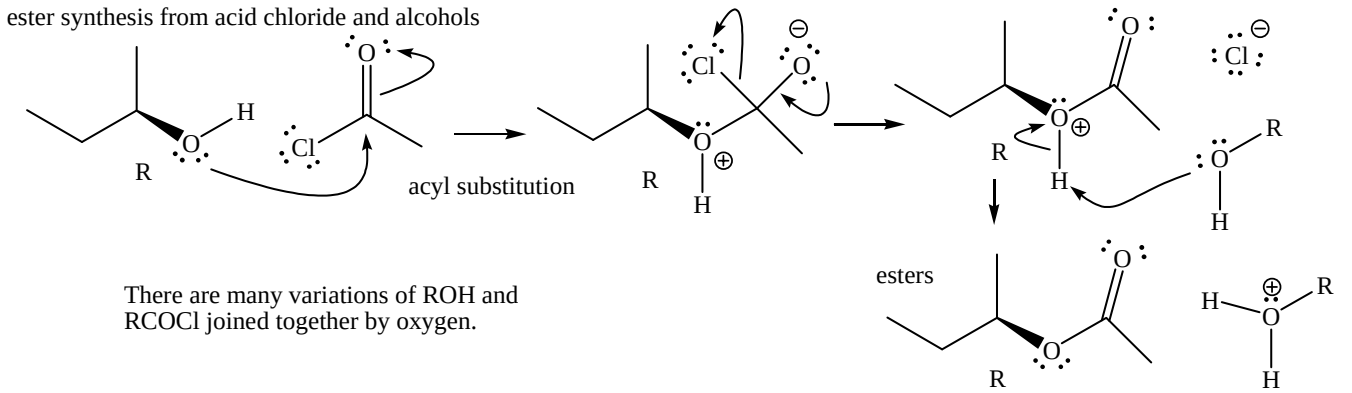
Thionyl chloride with 2° and 3° ROH = acyl substitution, then S_N1 (there are various ways you can write this mechanism)

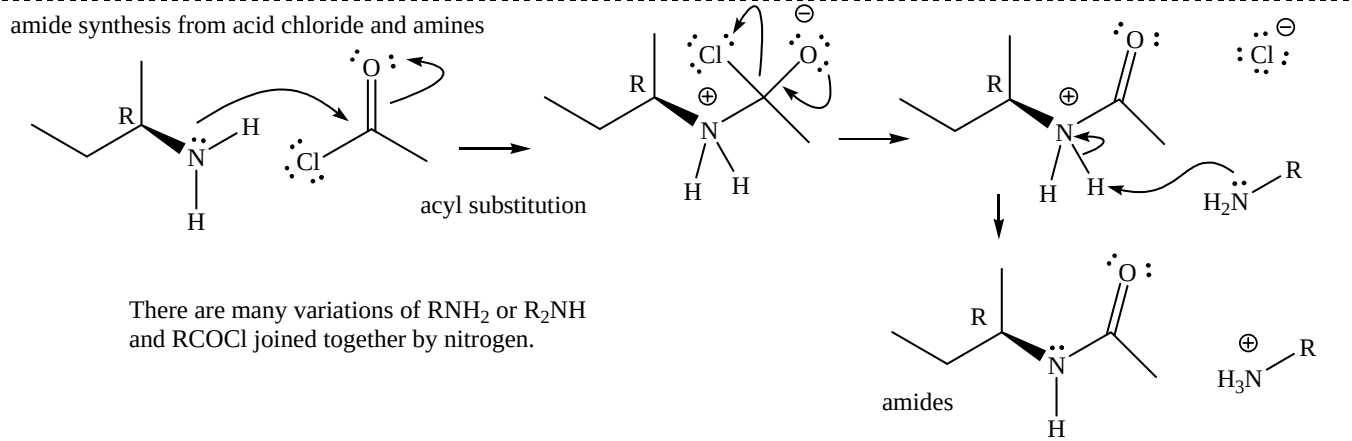


Synthesis of acid chlorides from acids + thionyl chloride ($SOCl_2$), use the carbonyl oxygen over the OH.

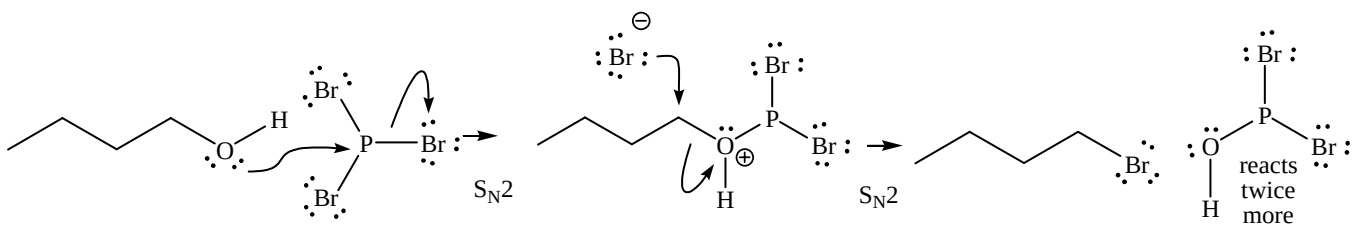


d. Formation of esters from ROH + acid chlorides and amides from RNH_2 or R_2NH + acid chlorides

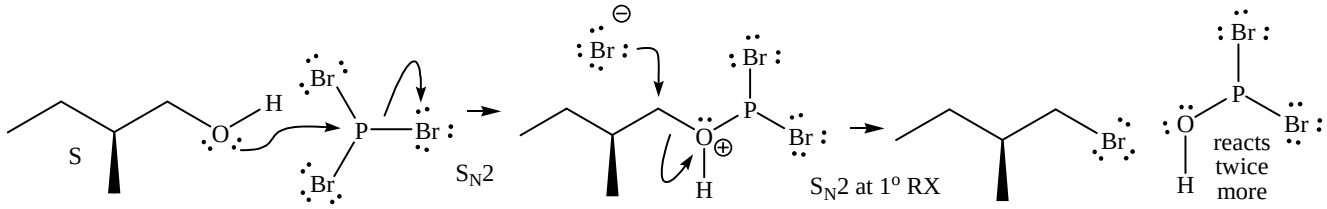


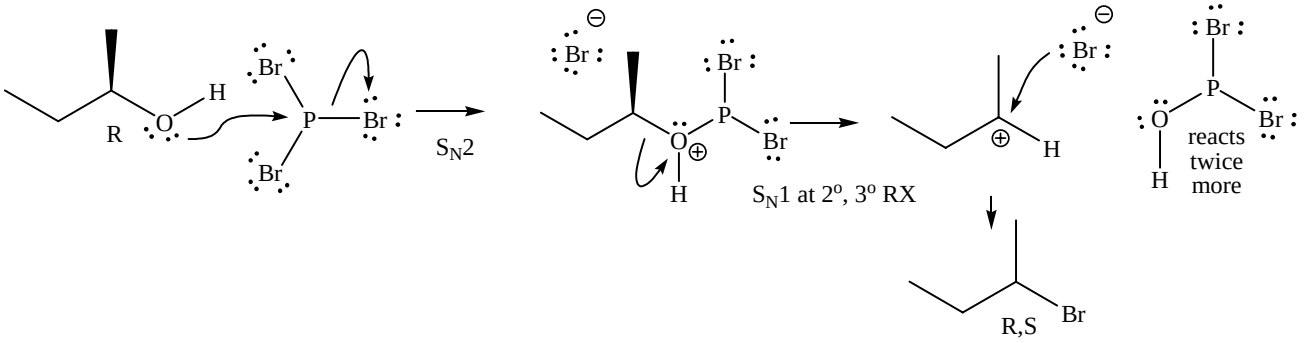


e. Phosphorous tribromide (PBr_3) = S_N2 at PBr_3, then S_N2 (at methyl and primary ROH)

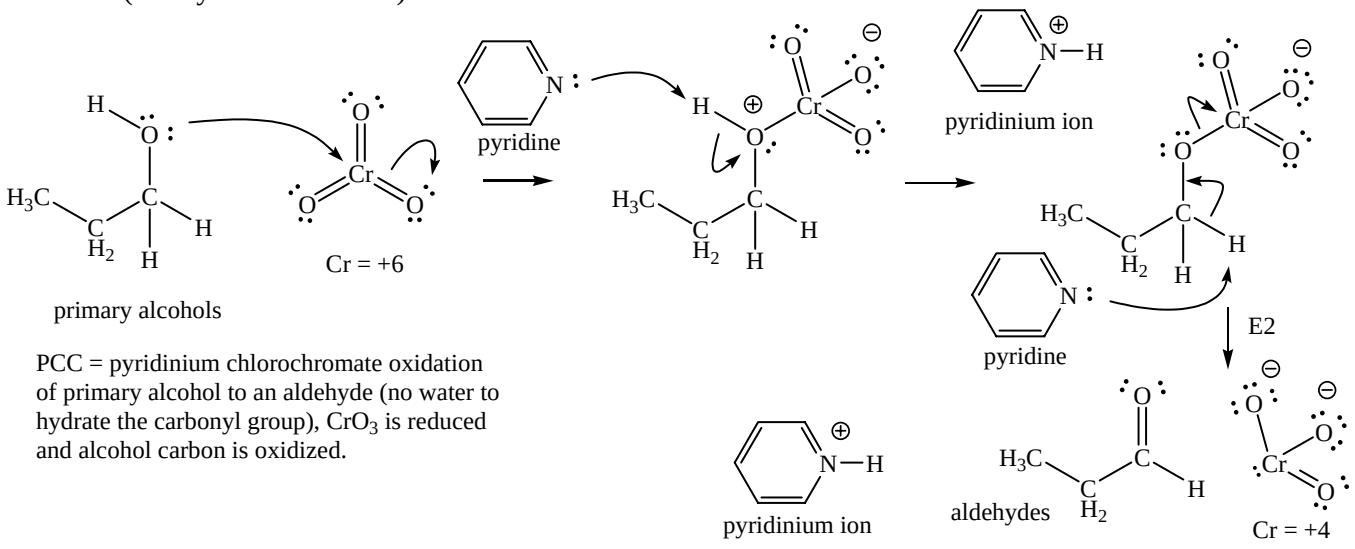


Phosphorous tribromide (PBr_3) = S_N2, then S_N1 (at secondary, tertiary, allylic and benzylic ROH)



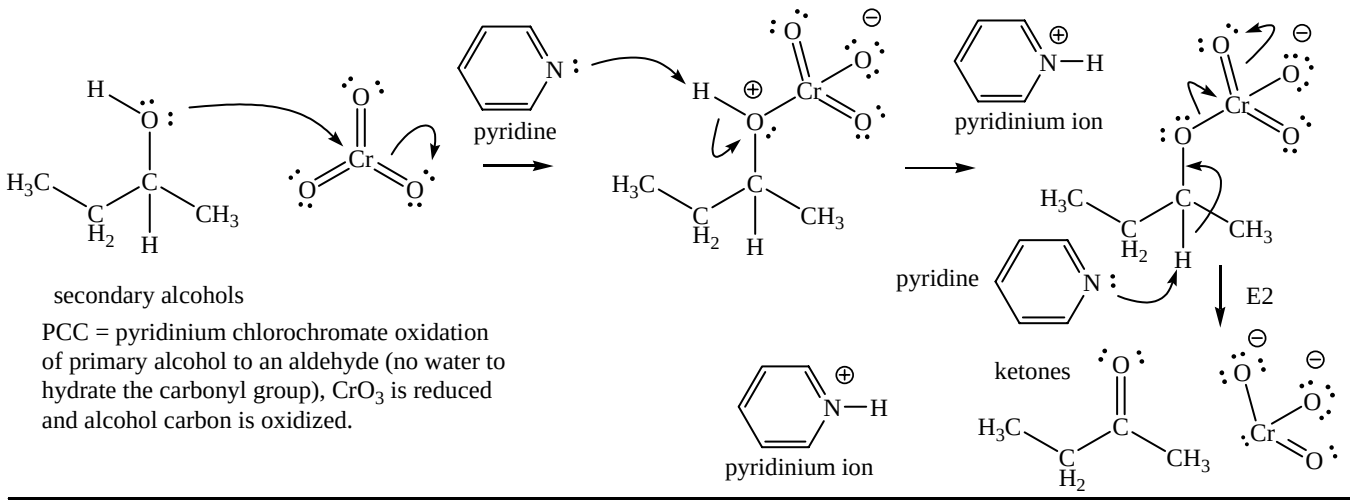


f. CrO_3 oxidations of alcohols (methyl, 1° and 2° ROH) without water & acid = PCC, Cr=O addition, acid/base and E2 to form C=O (aldehydes and ketones)



primary alcohols

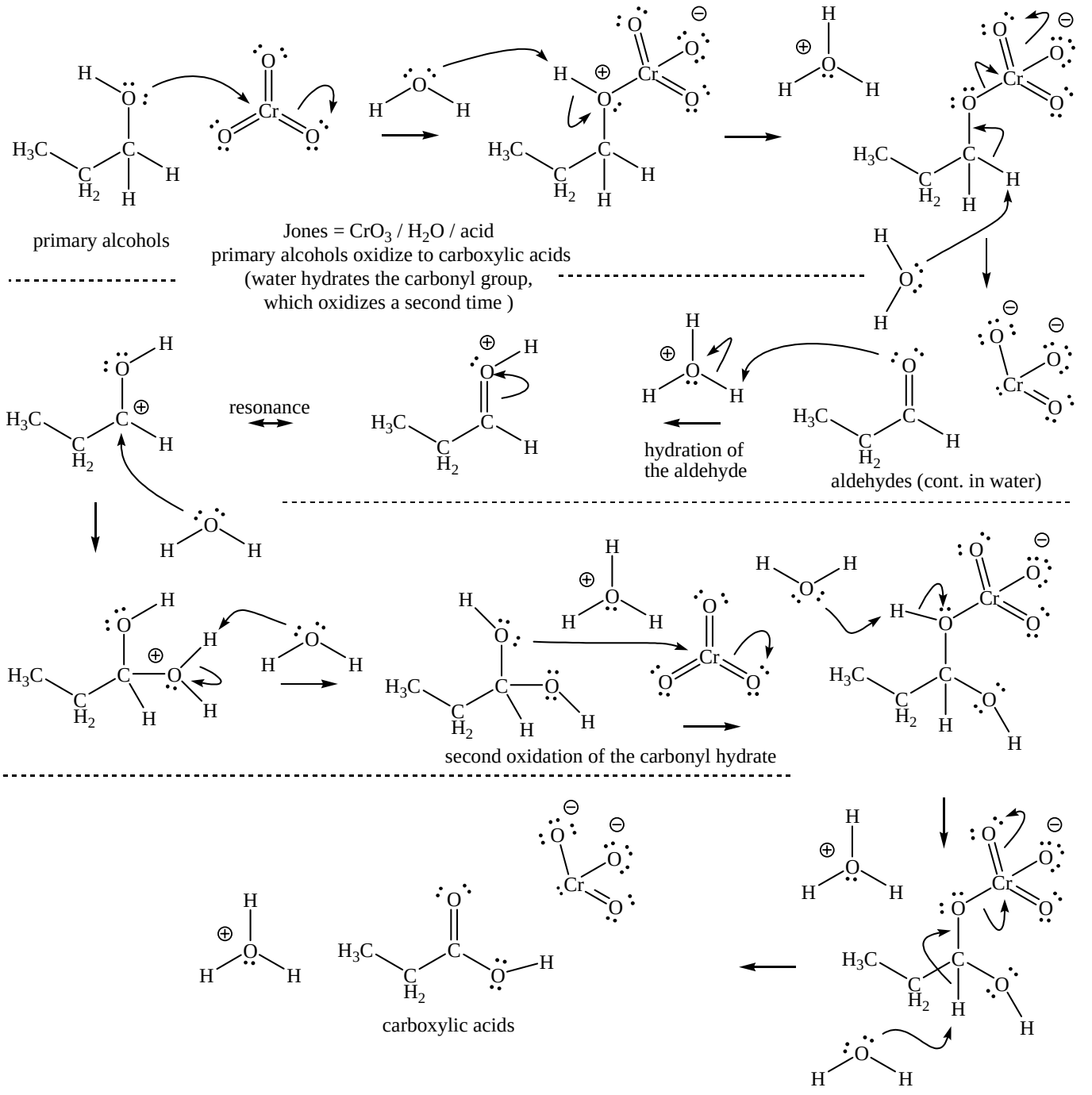
PCC = pyridinium chlorochromate oxidation of primary alcohol to an aldehyde (no water to hydrate the carbonyl group), CrO_3 is reduced and alcohol carbon is oxidized.



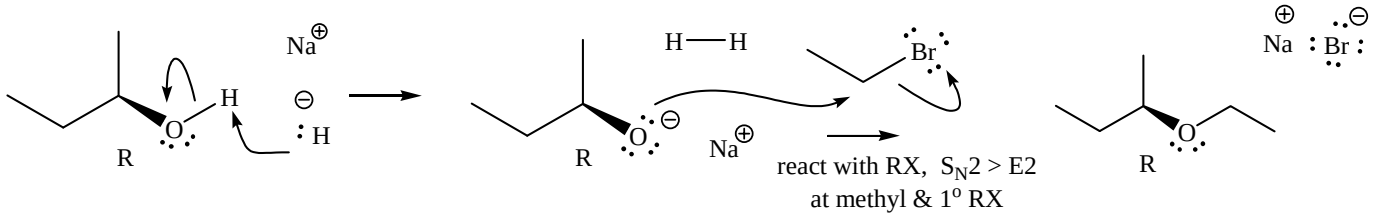
secondary alcohols

PCC = pyridinium chlorochromate oxidation of primary alcohol to an aldehyde (no water to hydrate the carbonyl group), CrO_3 is reduced and alcohol carbon is oxidized.

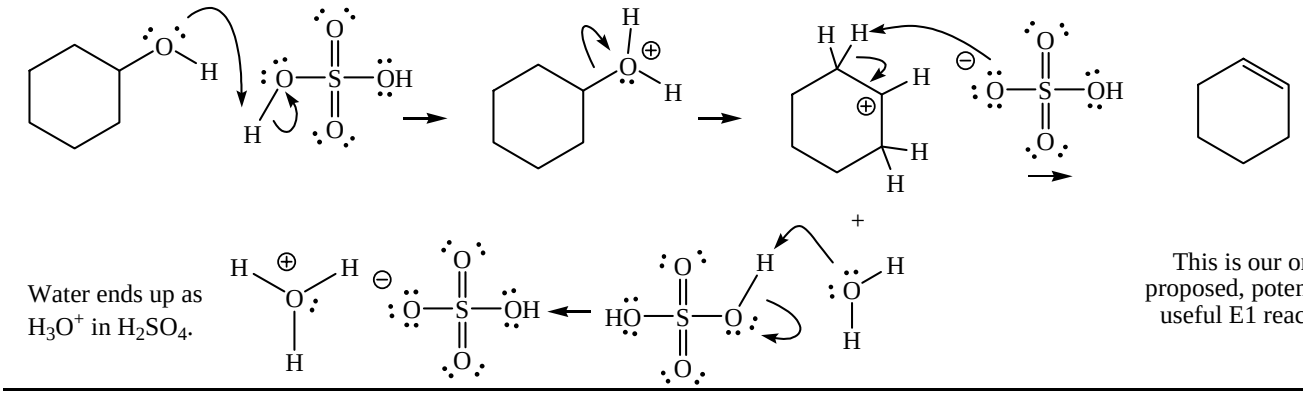
CrO_3 oxidations of alcohols (methyl, 1° and 2° ROH) with water & acid = Jones reagent, Cr=O addition by alcohol, acid/base and E2 to form C=O, then hydration of C=O and repeat reactions when 1° alcohol (forms carboxylic acids from primary alcohols and ketones from secondary alcohols)



g. Formation of alkoxide from ROH + NaH or KH (acid/base reaction)

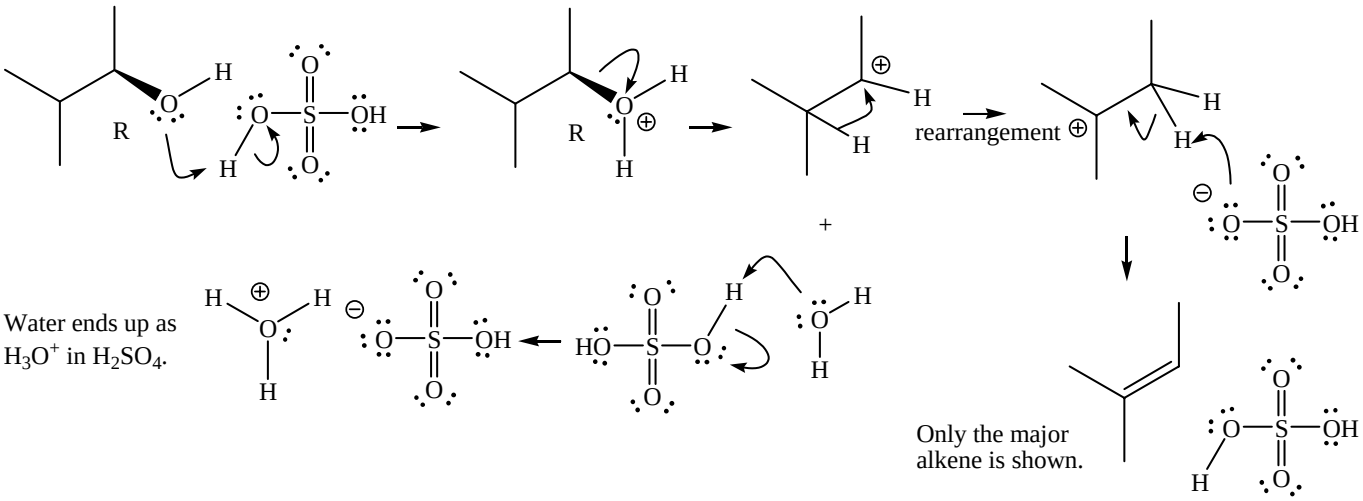


h. Dehydration to alkene (E1) from ROH + H_2SO_4/Δ (possibility of rearrangements)



Water ends up as H_3O^+ in H_2SO_4.

This is our only proposed, potentially useful E1 reaction

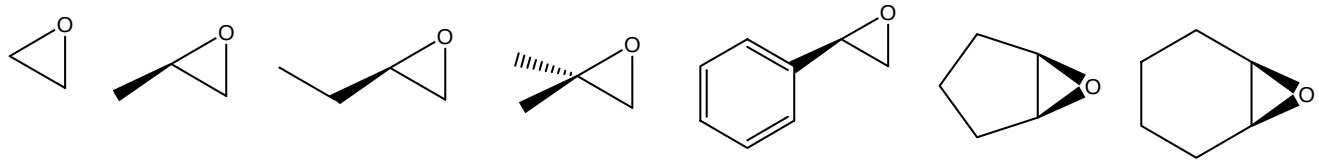


Water ends up as H_3O^+ in H_2SO_4.

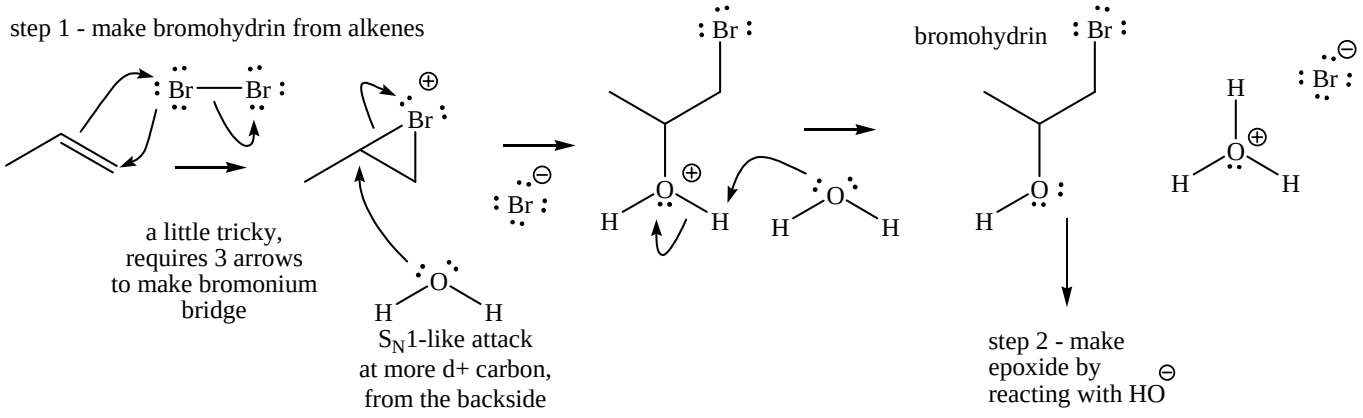
Only the major alkene is shown.

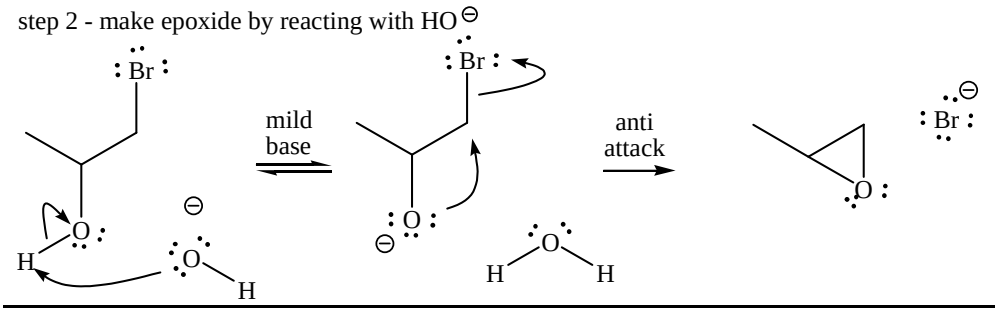
Epoxide reactions

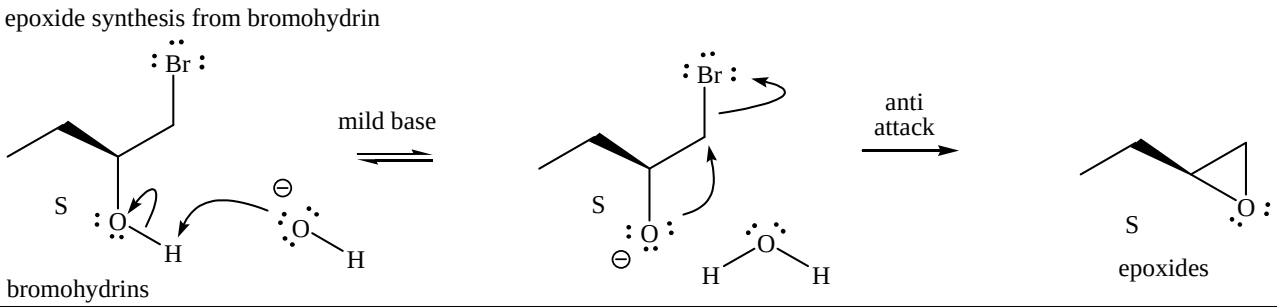
a. Examples of important patterns to know from our starting materials.



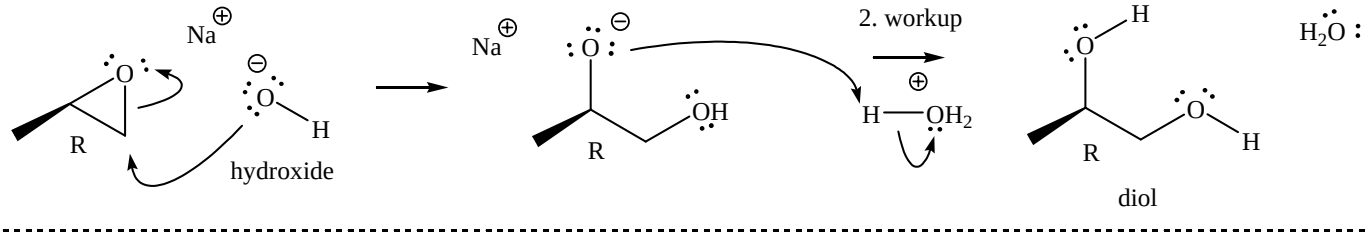
We can make epoxides from alkenes using either 1. Br_2/H_2O, 2. NaOH. or we can make epoxides using mCPBA.

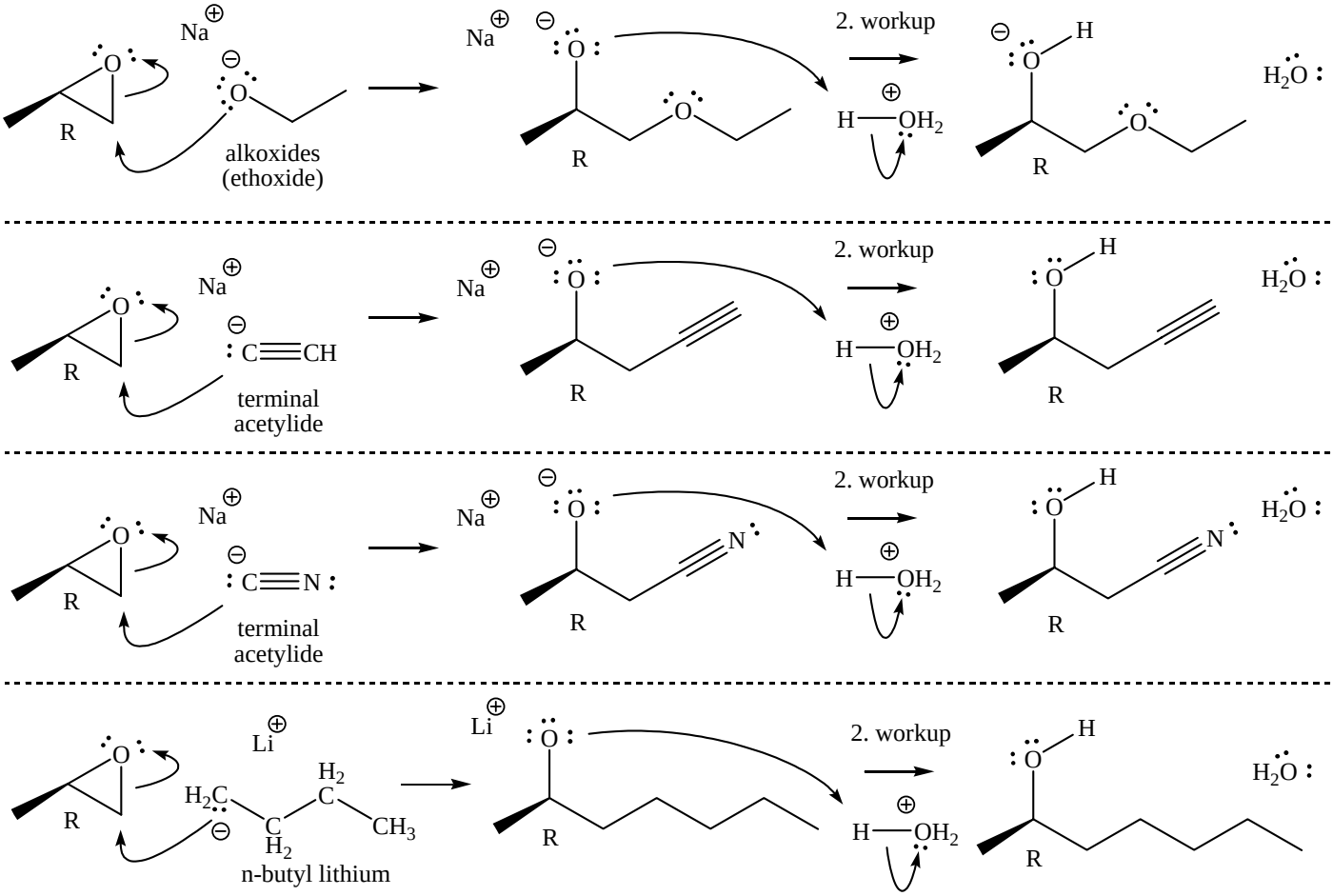




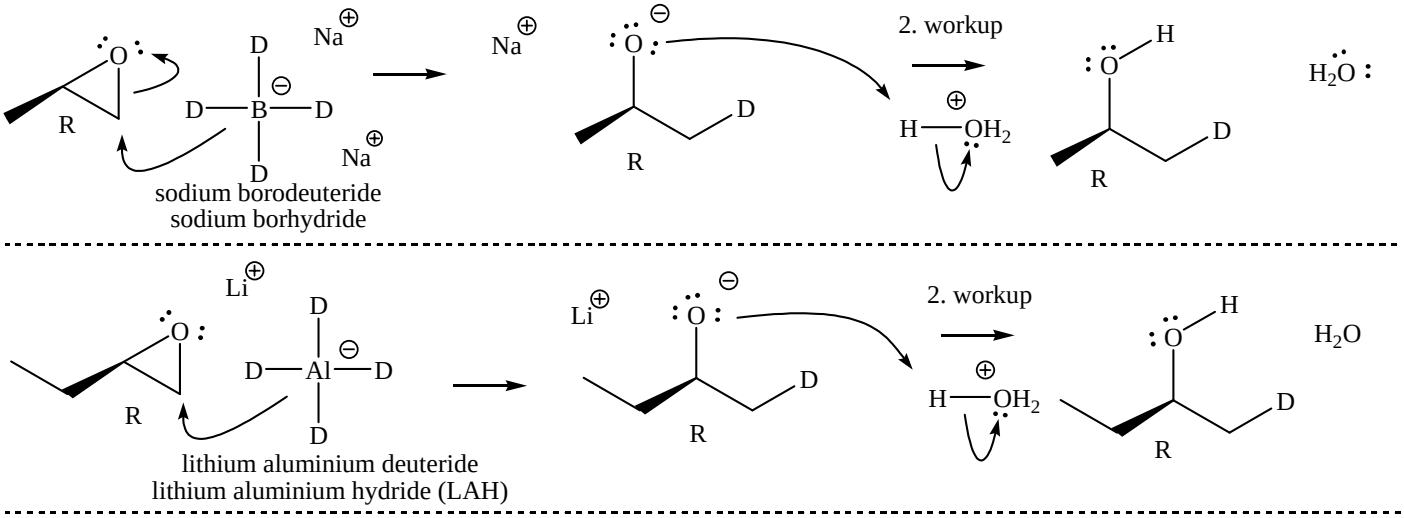


Strong nucleophile conditions - S_N2 like attack at less hindered epoxide carbon, and workup (overall addition)

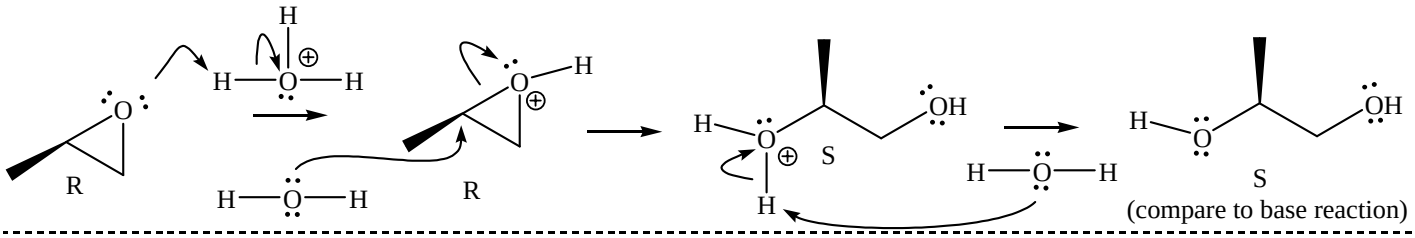


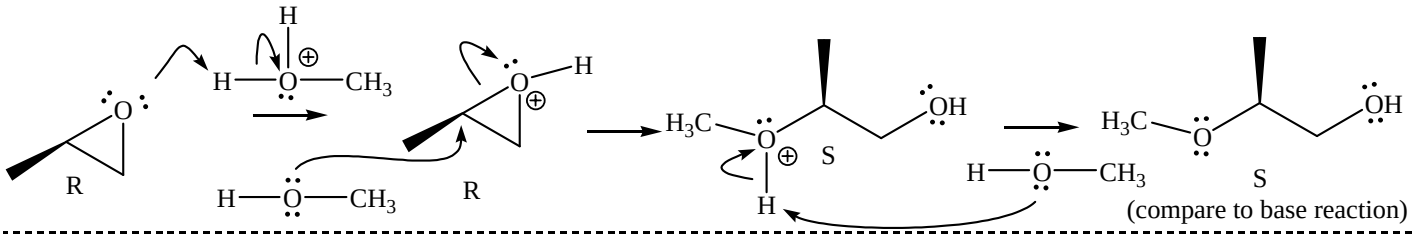


Nucleophilic hydride = sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$ = LAH), [deuterium is used below to show reaction site]



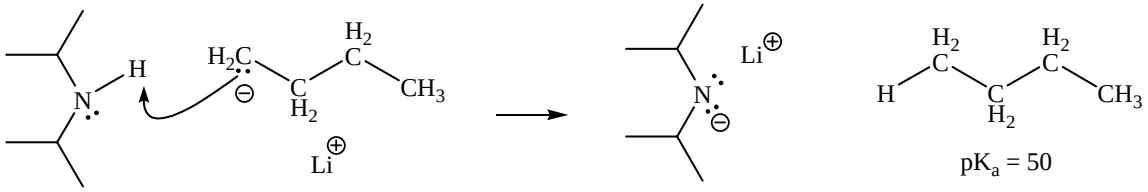
Epoxide reactions in acid conditions – S_N1-like conditions, attack at more δ+ carbon.

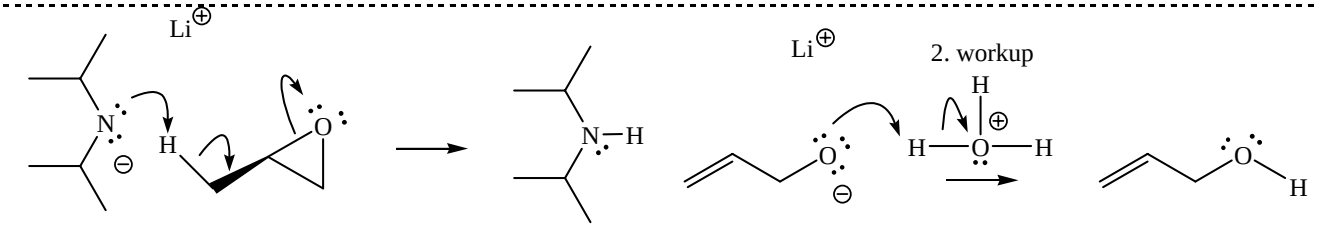


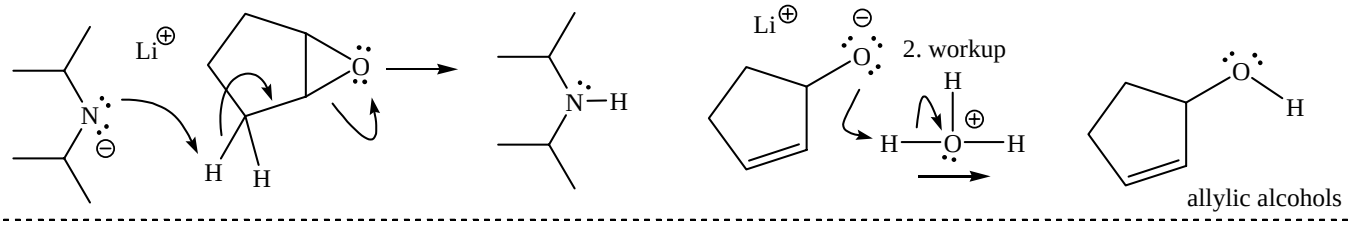


Our only E2 reaction for epoxides. Uses very basic, sterically bulky LDA (always a base).

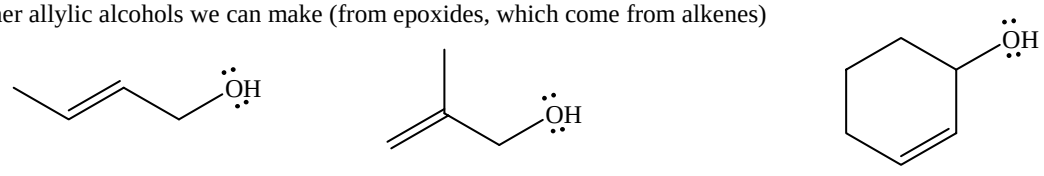
Make LDA = lithium diisopropylamide (a very strong base)





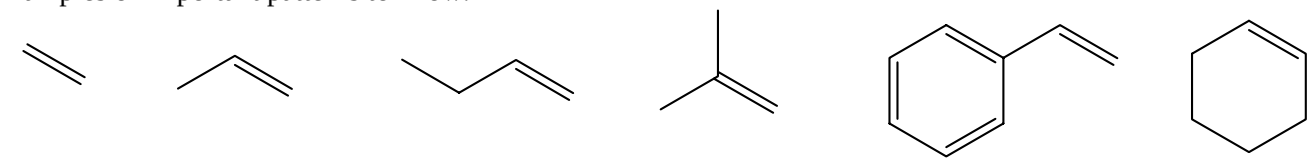


other allylic alcohols we can make (from epoxides, which come from alkenes)

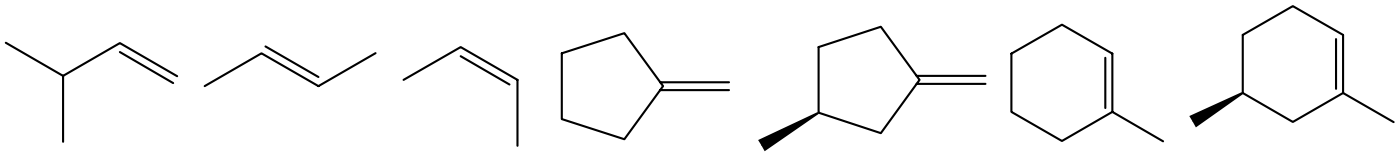


Alkene and Alkyne reactions

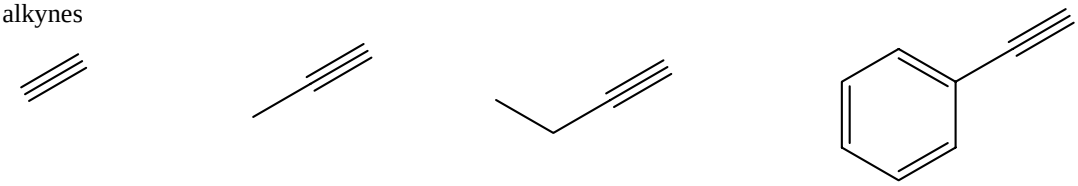
Examples of important patterns to know.



other patterns showing regioselectivity and stereoselectivity



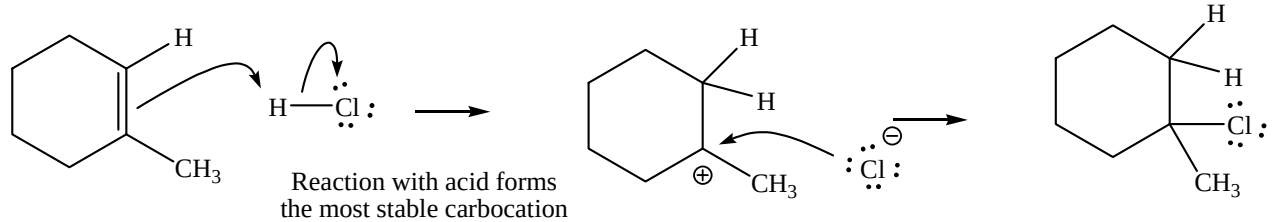
alkynes



We can make alkenes from RX (E2 reactions) and ROH (H_2SO_4/Δ = E1), and alkynes from RX_2 ($NaNR_2$), for now.

a. C=C addition reaction with H-Cl (H-Br and H-I are similar), Markovnikov addition forms most stable carbocation

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.

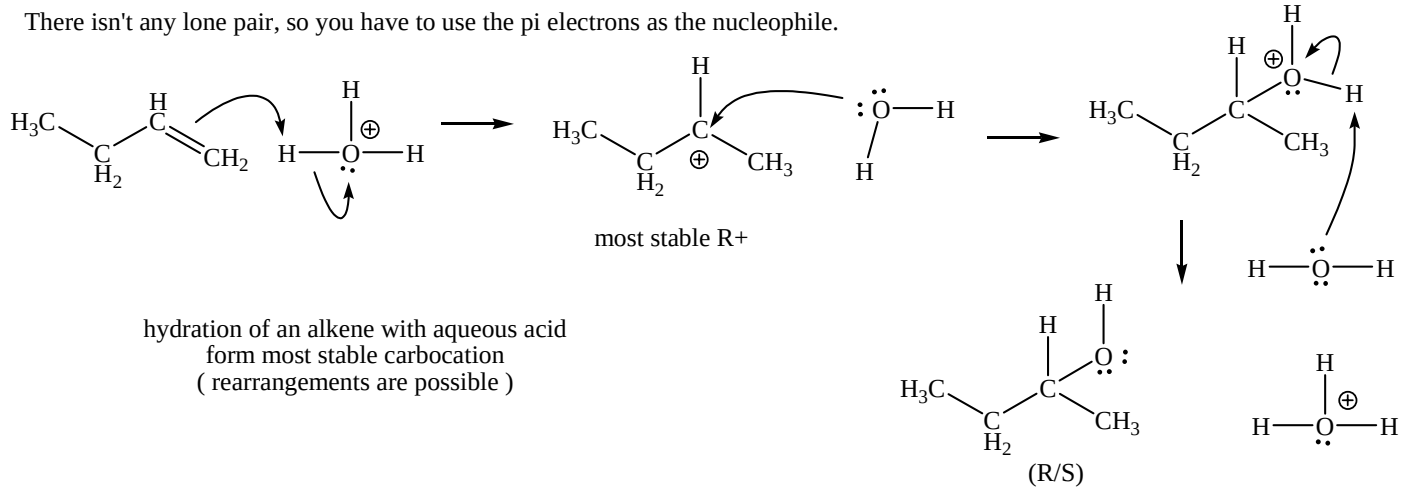


Reaction with acid forms
the most stable carbocation
(rearrangements are possible)

$Cl^{\ominus}$ adds to top and bottom, but no difference in this example

b. C=C aqueous acid hydration reaction, goes via top/bottom addition (hydration of an alkene)

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.



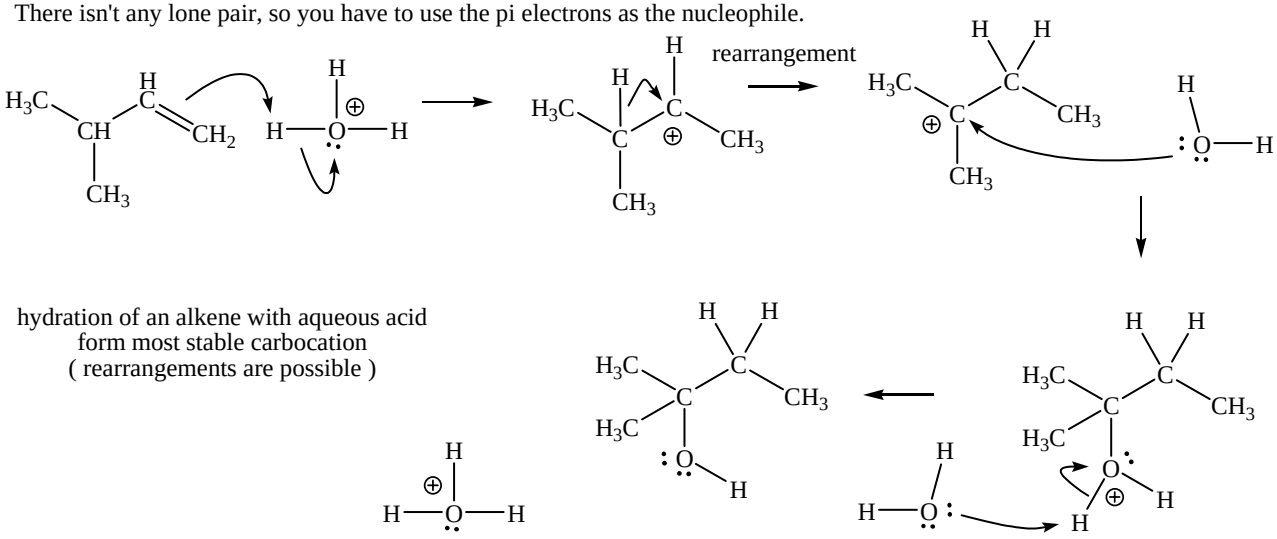
most stable R+

hydration of an alkene with aqueous acid
form most stable carbocation
(rearrangements are possible)

(R/S)

C=C addition reaction (hydration of an alkene), with rearrangement

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.

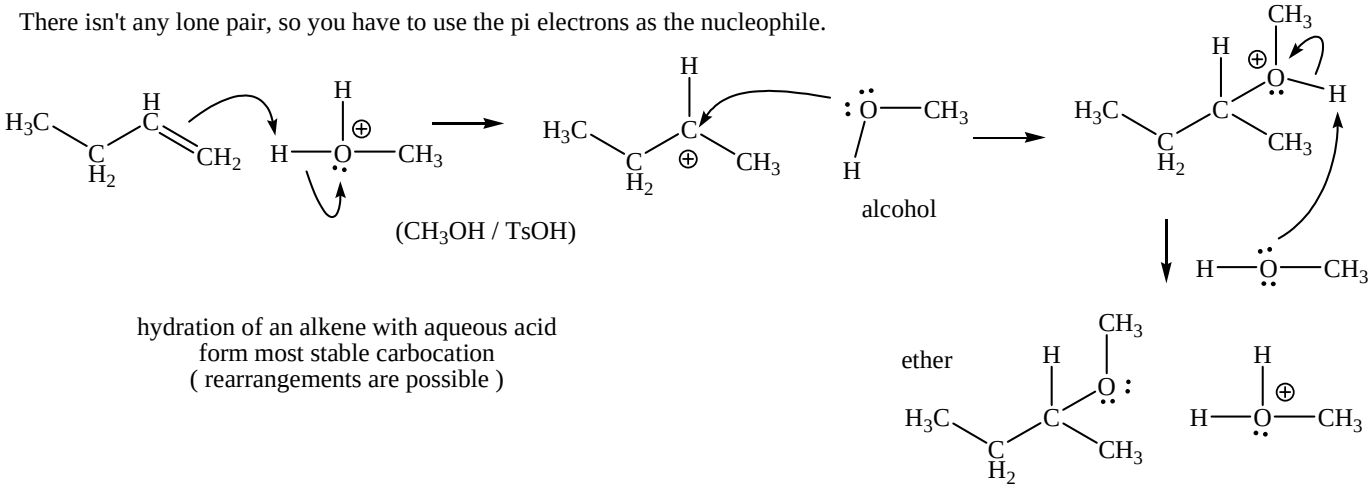


hydration of an alkene with aqueous acid
form most stable carbocation
(rearrangements are possible)

---

c. C=C addition reaction (ether synthesis from an alkene by addition of alcohols)

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.

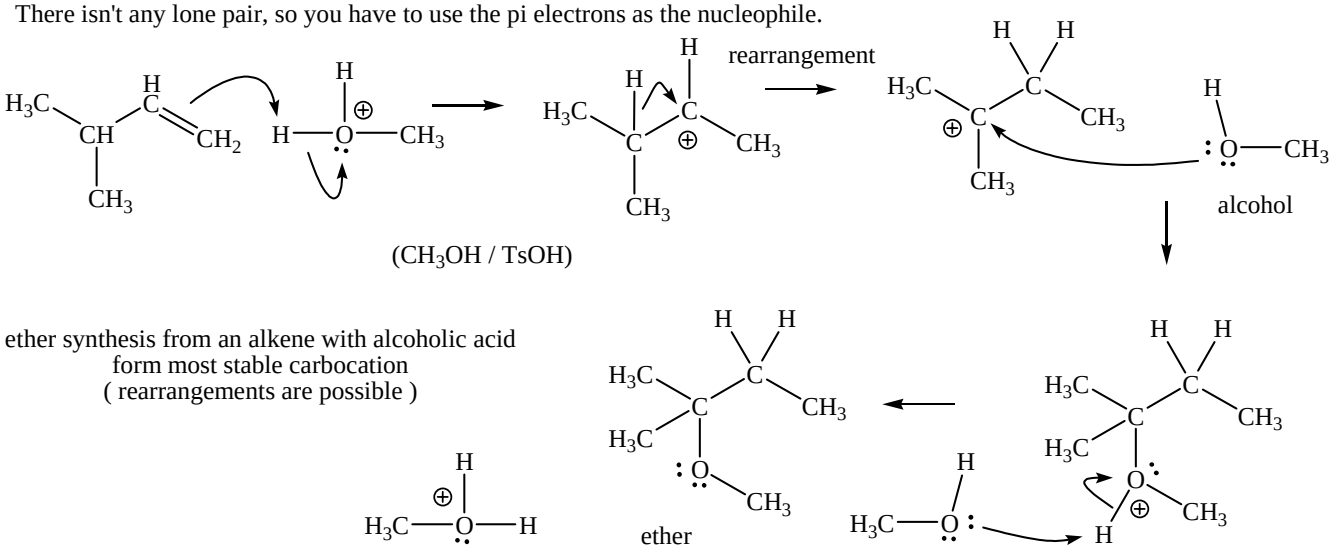


hydration of an alkene with aqueous acid
form most stable carbocation
(rearrangements are possible)

---

d. C=C addition reaction (ether synthesis from an alkene by addition of alcohols), with rearrangement

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.



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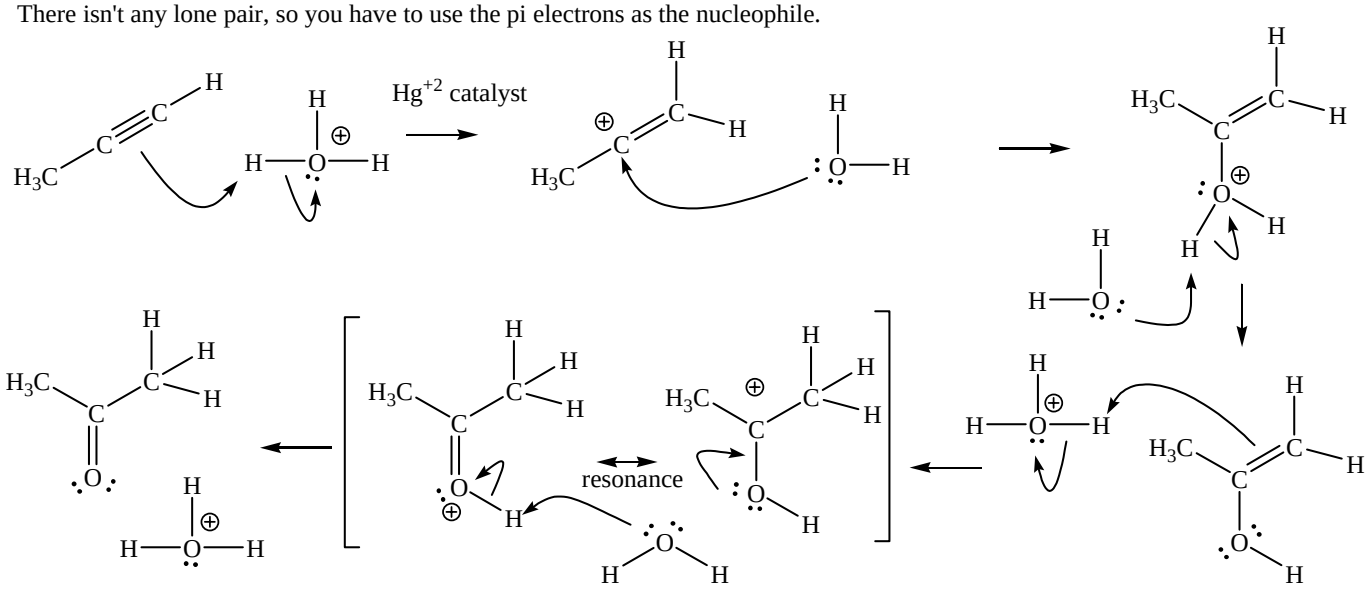
e. Mercuration, reduction – minimizes rearrangements

f. Hydration of alkynes (Markovnikov addition forms most stable carbocation), enol intermediate tautomerizes to keto tamtomer. (The Hg^{+2} has been left out of the mechanism to simplify the mechanism.)

There isn't any lone pair, so you have to use the pi electrons as the nucleophile.



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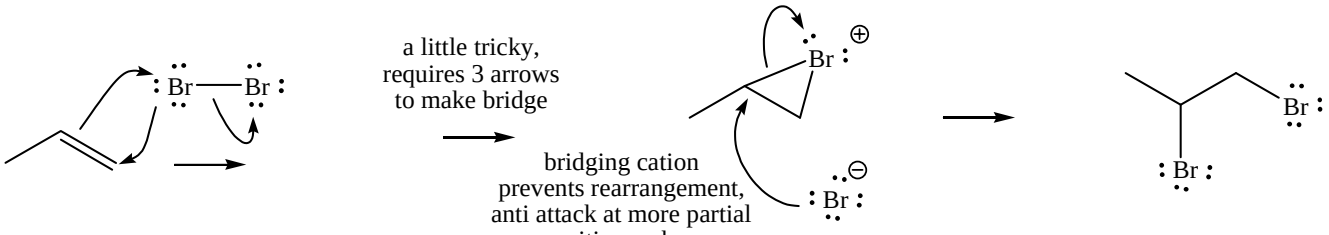
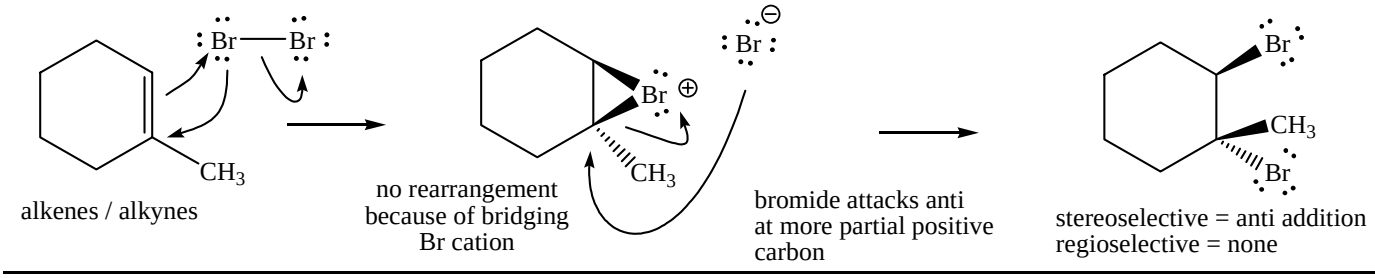
g. Bromination of alkenes, goes via anti addition



C=C addition reaction



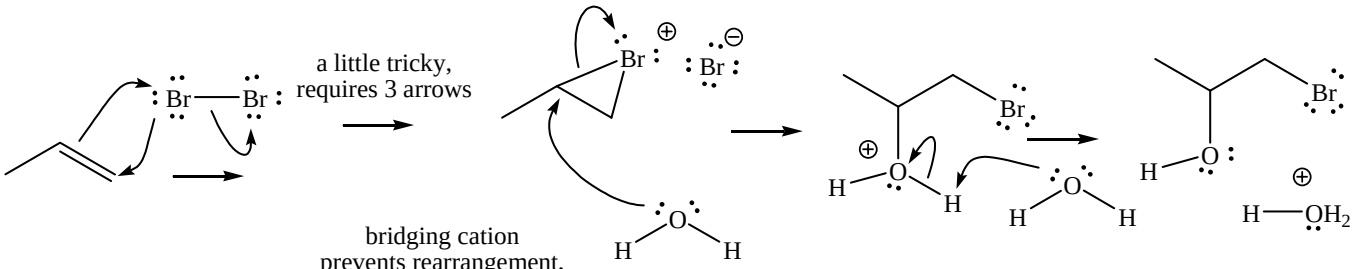
alkenes / alkynes

no rearrangement because of bridging Br cation

bromide attacks anti at more partial positive carbon

stereoselective = anti addition
regioselective = none

h. Bromhydrin formation from alkenes, goes via anti addition

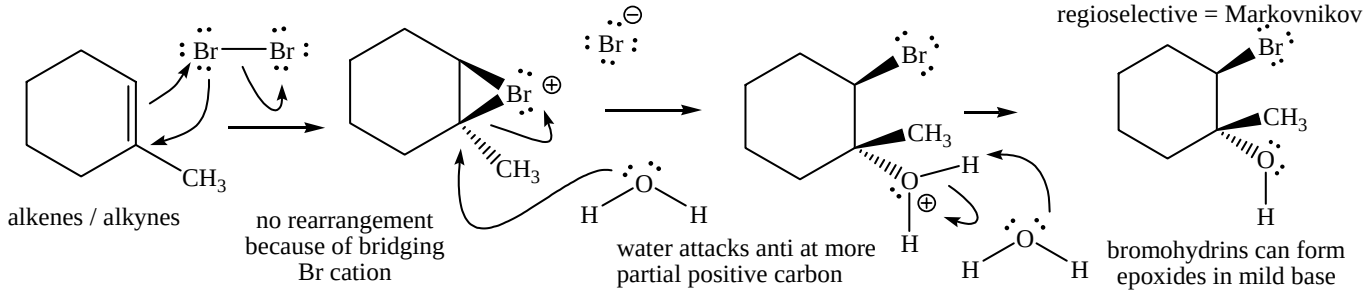


bridging cation prevents rearrangement, attack at more partial positive carbon

water attacks anti at more partial positive carbon

bromohydrins can form epoxides in mild base

C=C addition reaction



stereoselective = anti addition
regioselective = Markovnikov

alkenes / alkynes

no rearrangement because of bridging Br cation

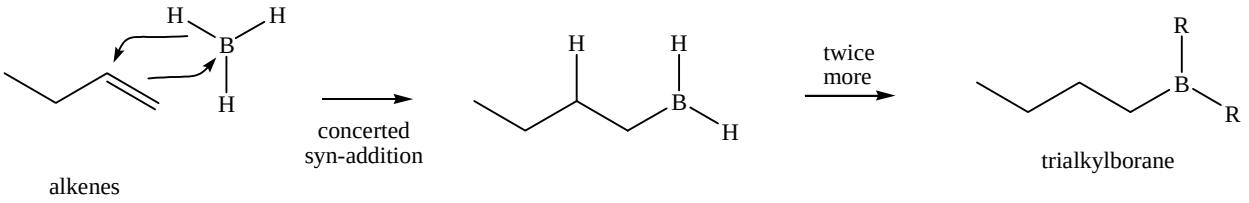
water attacks anti at more partial positive carbon

bromohydrins can form epoxides in mild base

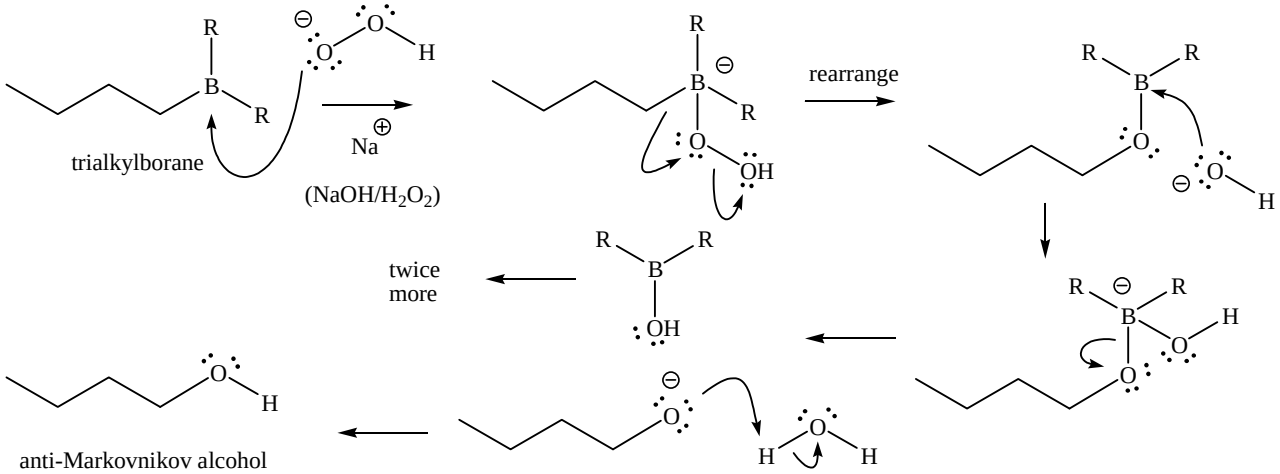
i. Hydroboration of alkenes = anti-Markovnikov addition (opposite regioselectivity to normal hydration conditions)

anti-Markovnikov addition to C=C (hydration makes alcohols), two steps: 1 BH_3 2. H_2O_2/HO

step 1 = concerted addition to C=C by borane



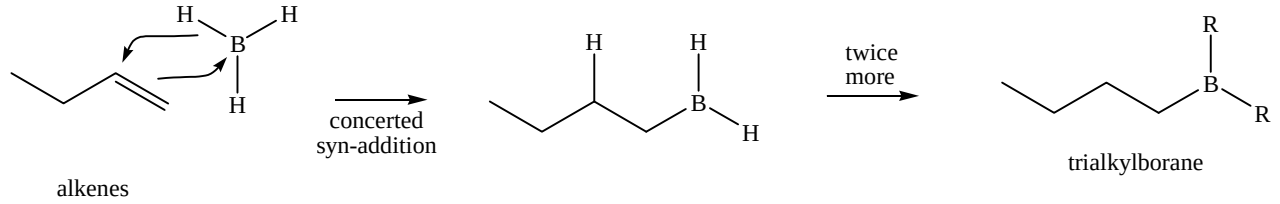
step 2 = oxidation by hydrogen peroxide and rearrangement to anti-Markovnikov alcohol



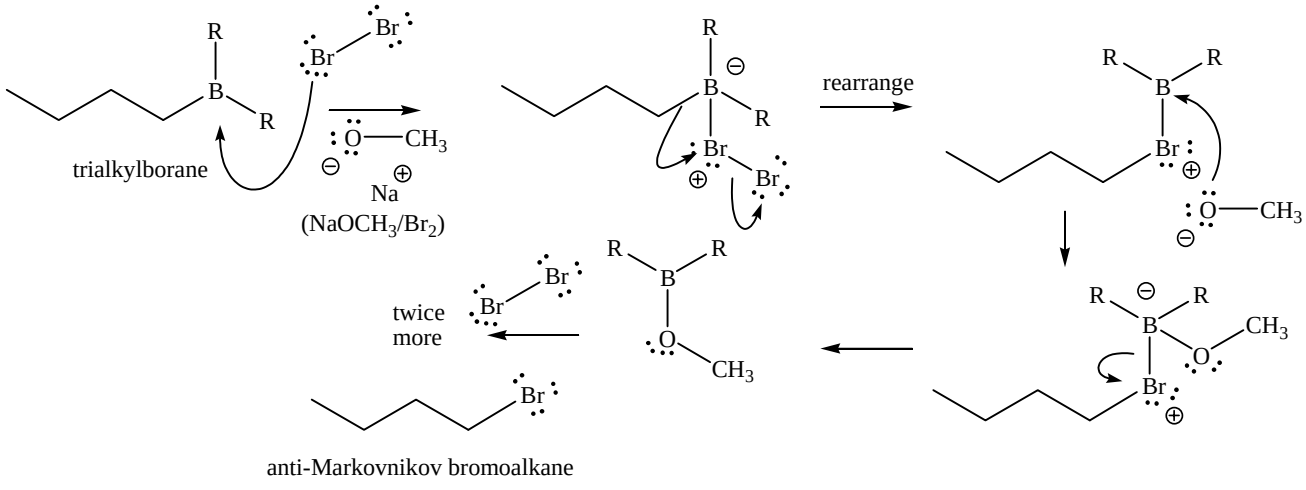
j. bromination "anti" – looks very similar to hydration reaction, just above

anti-Markovnikov addition to C=C (bromination makes R-Br), two steps: 1 BH_3 2. $Br_2/CH_3O^{\ominus}$

step 1 = concerted addition to C=C by borane



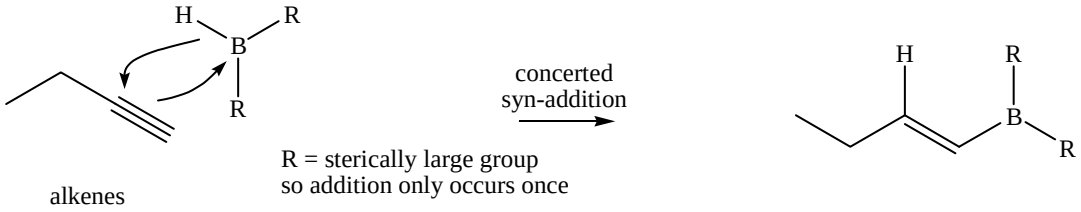
step 2 = oxidation by bromine and rearrangement to anti-Markovnikov R-Br



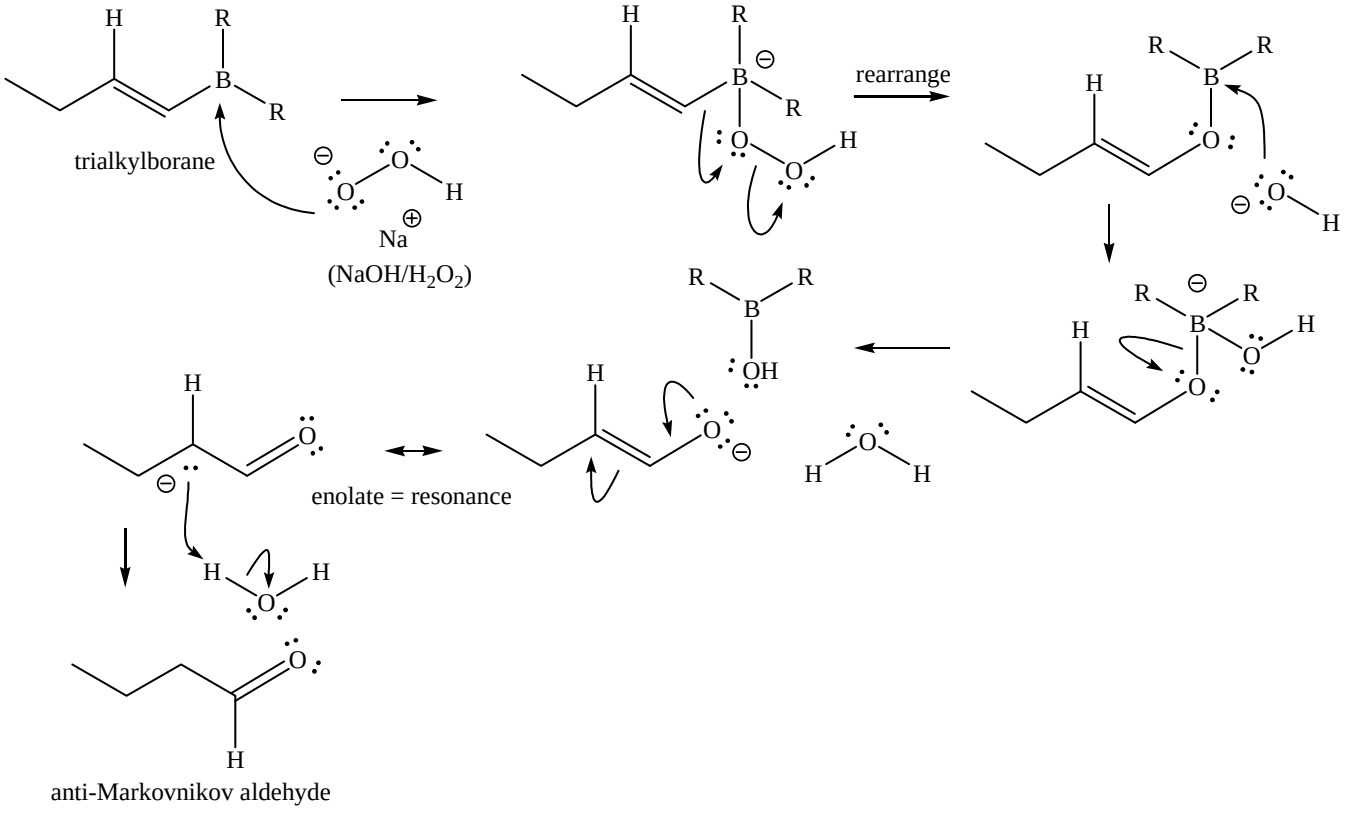
k. Hydroboration of alkynes = anti-Markovnikov addition (opposite regioselectivity to normal conditions)

anti-Markovnikov addition to CC (hydration makes aldehydes), two steps: 1 R_2BH 2. $H_2O_2/\overset{\ominus}{HO}$

step 1 = concerted addition to CC by dialkylborane

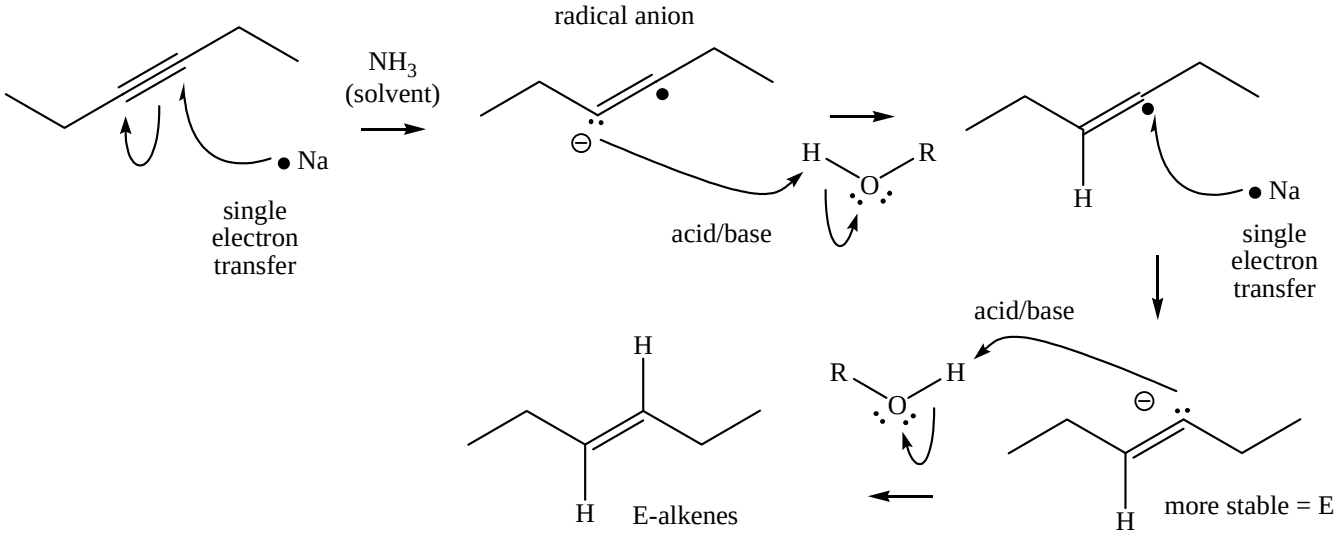


step 2 = oxidation by hydrogen peroxide and rearrangement to anti-Markovnikov aldehyde

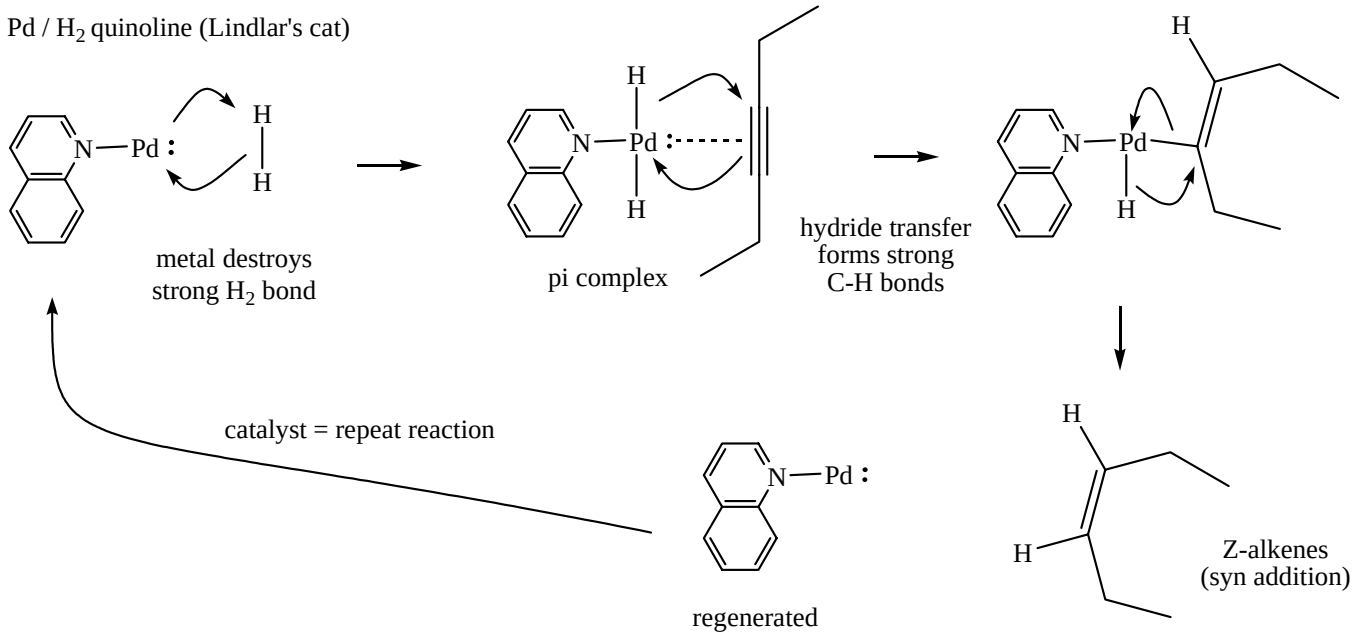


Reduction of alkynes (Z and E alkenes)

Birch conditions (Na / NH_3)

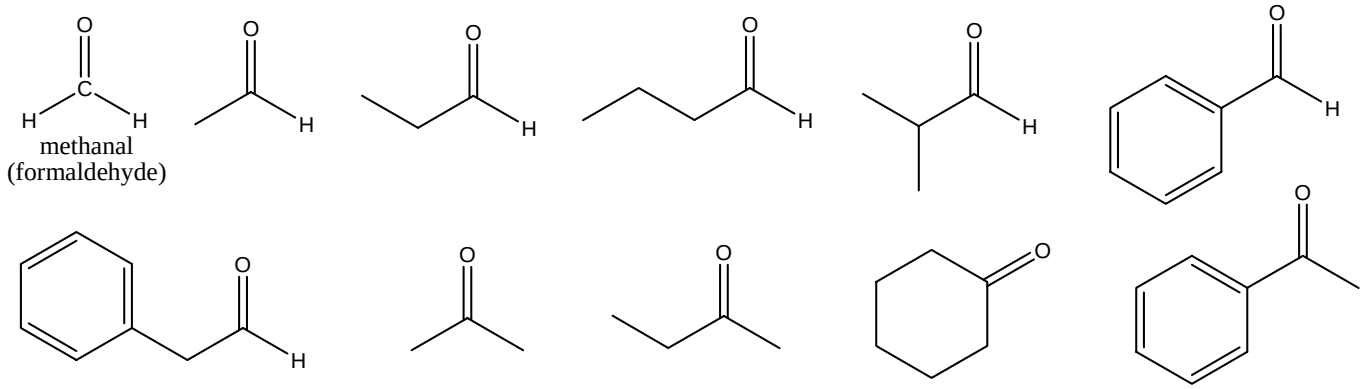


Pd / H_2 quinoline (Lindlar's cat)



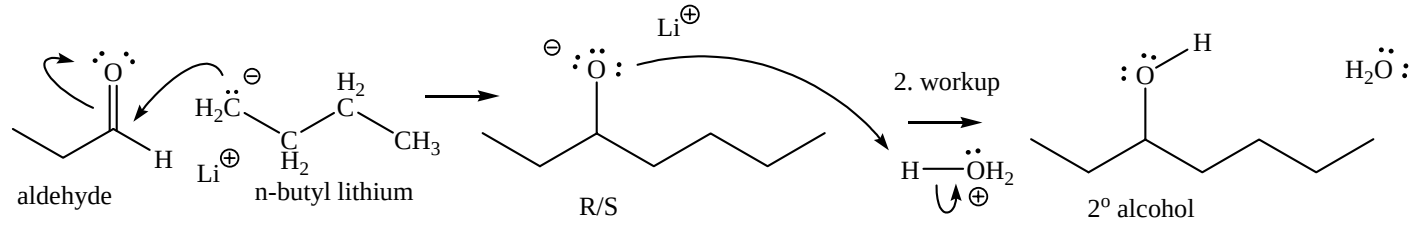
Aldehyde and Ketone reactions

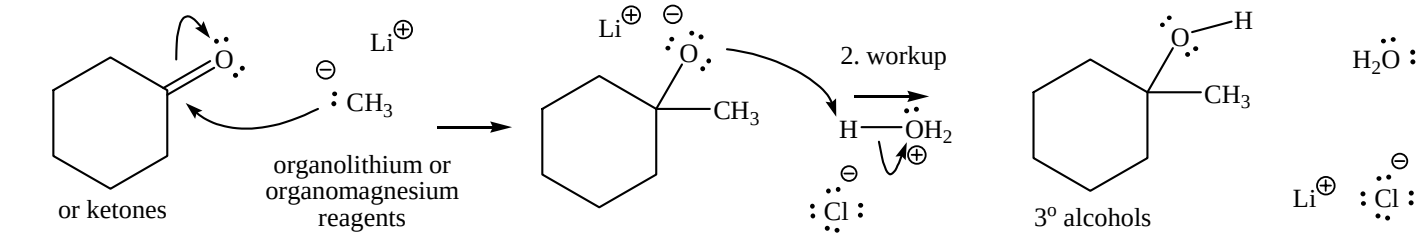
Examples of important patterns to know from our starting materials.



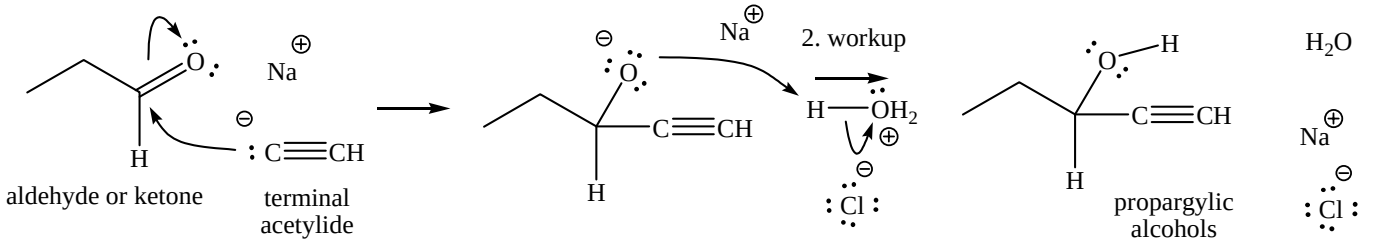
We can make aldehydes and ketones from alcohols and alkynes (for now). There are many other possibilities.

a. C=O addition with organolithium and organomagnesium (Grignard) reagents, and workup (use n-butyl lithium, methyl lithium or phenyl lithium, others are coming, with esters, nitriles, 3° amides and acids).

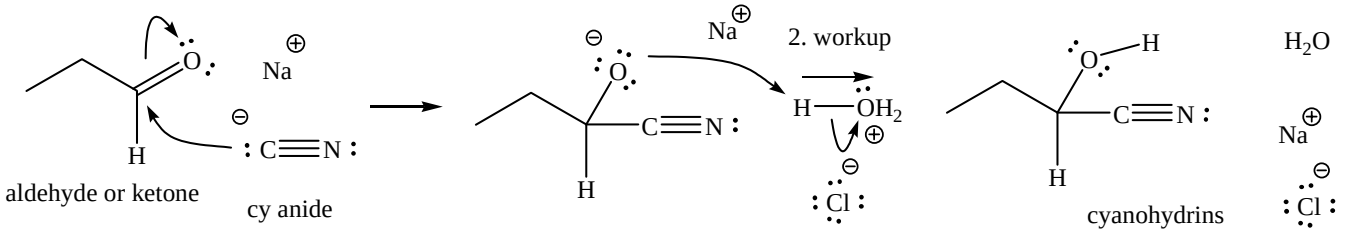




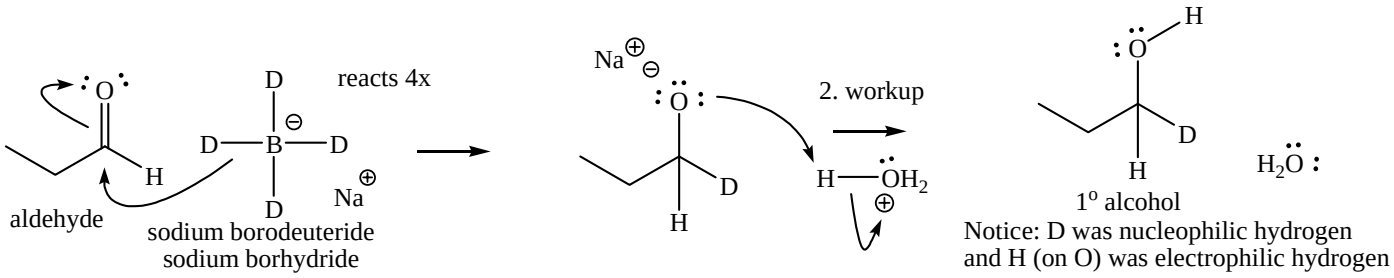
b. C=O addition with terminal acetylides to form propargylic alcohols or with cyanide to form cyanohydrins

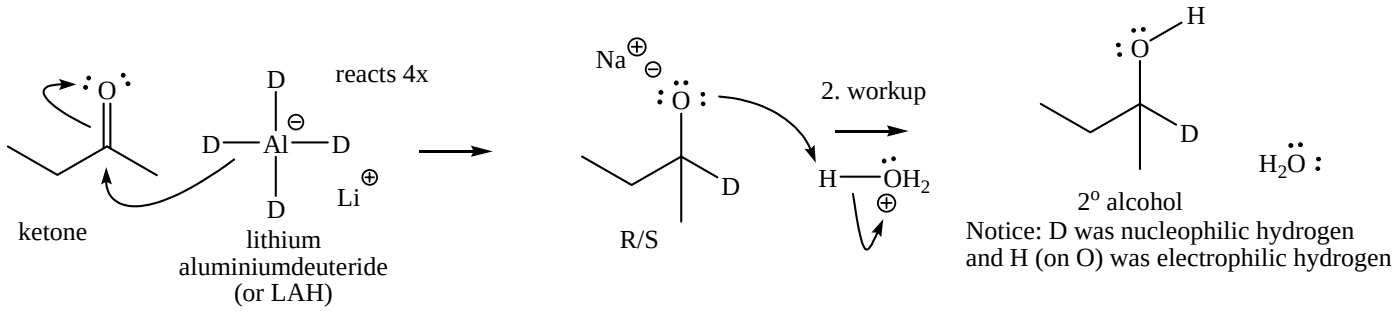


C=O addition with cyanide forming cyanohydrin



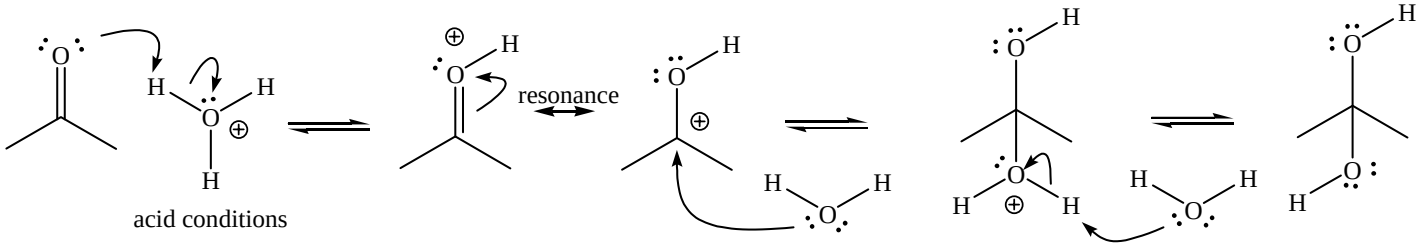
c. Nucleophilic hydride = sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$ = LAH), [deuterium is used below to show reaction site]

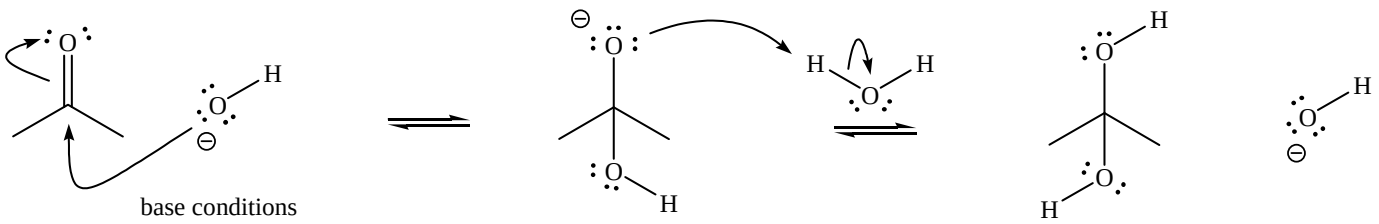




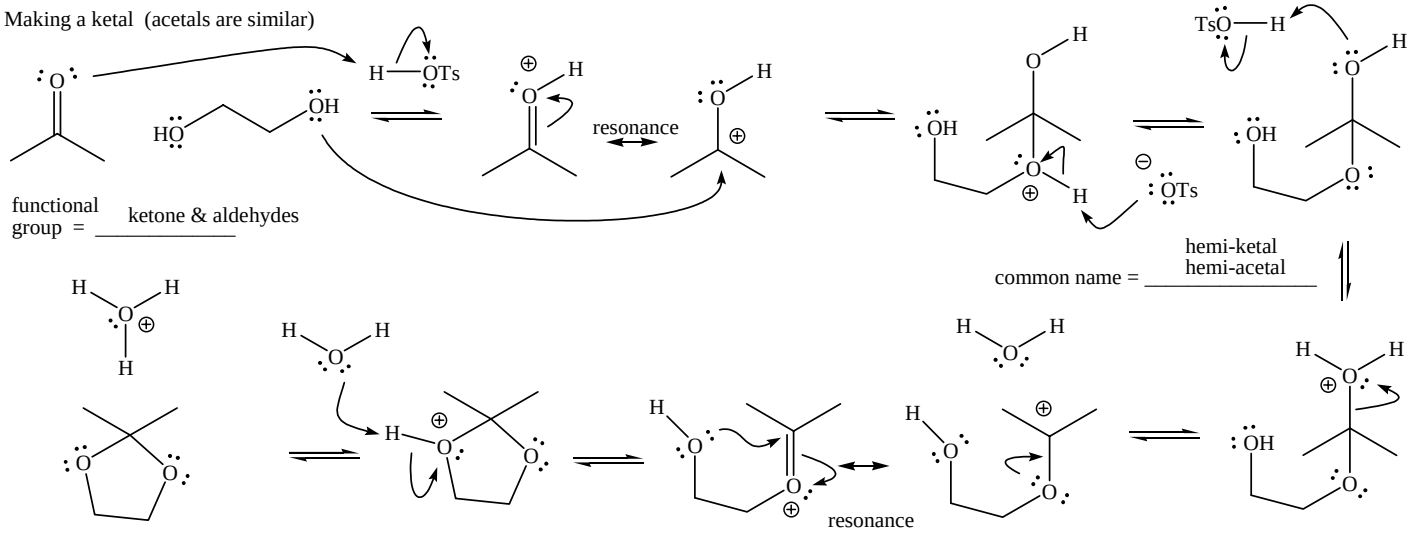
d. Hydration of C=O in acid or base conditions (also tautomerization conditions, a competing reaction)

Hydration of C=O is similar to making acetals and ketals and hydrolysis of esters



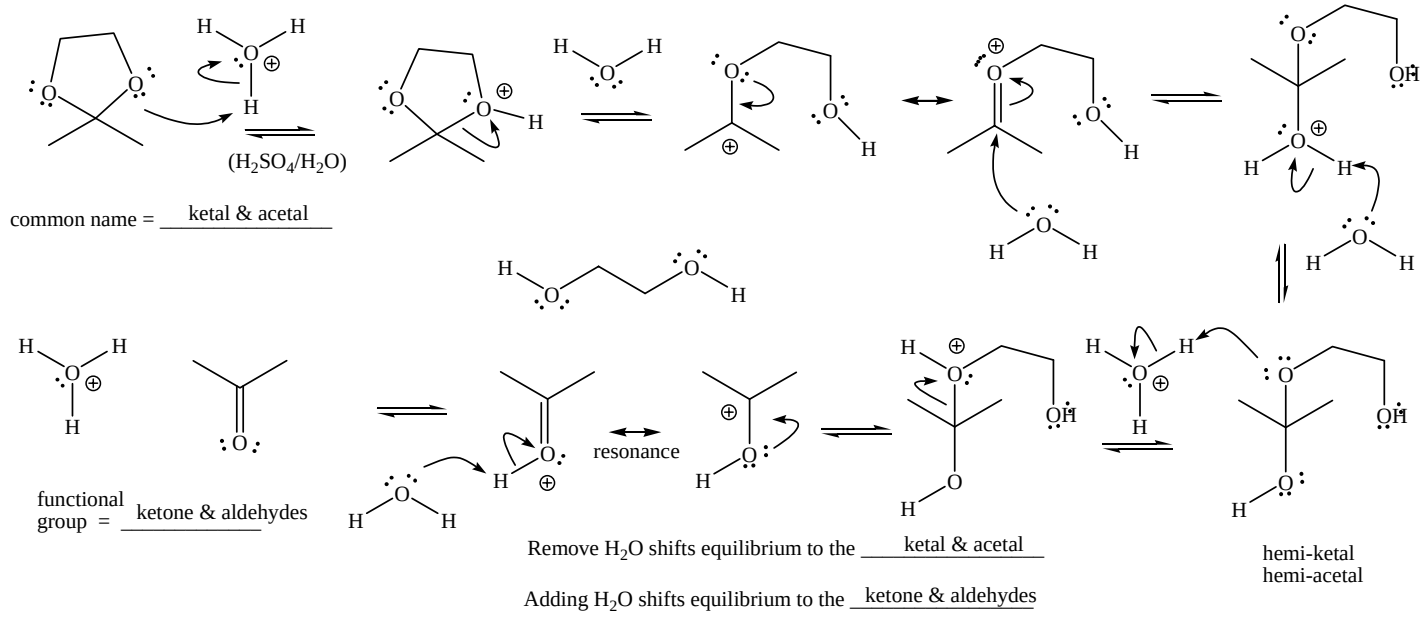


e. Ketone to hemi-ketal to ketal and aldehyde to hemi-acetal to acetal (protects C=O as di-ether during neutral and basic reactions conditions). Ketals and acetals revert back to C=O in aqueous acid conditions.



Deprotection of ketal (acetal) to regenerate ketone or aldehyde, S_N1 reaction, then E1 reaction to form C=O (deprotection of a ketone or aldehyde)

l Hydrolysis of a ketal back to a ketone and ethylene glycol (acetals are similar and go back to aldehydes and ethylene glycol)



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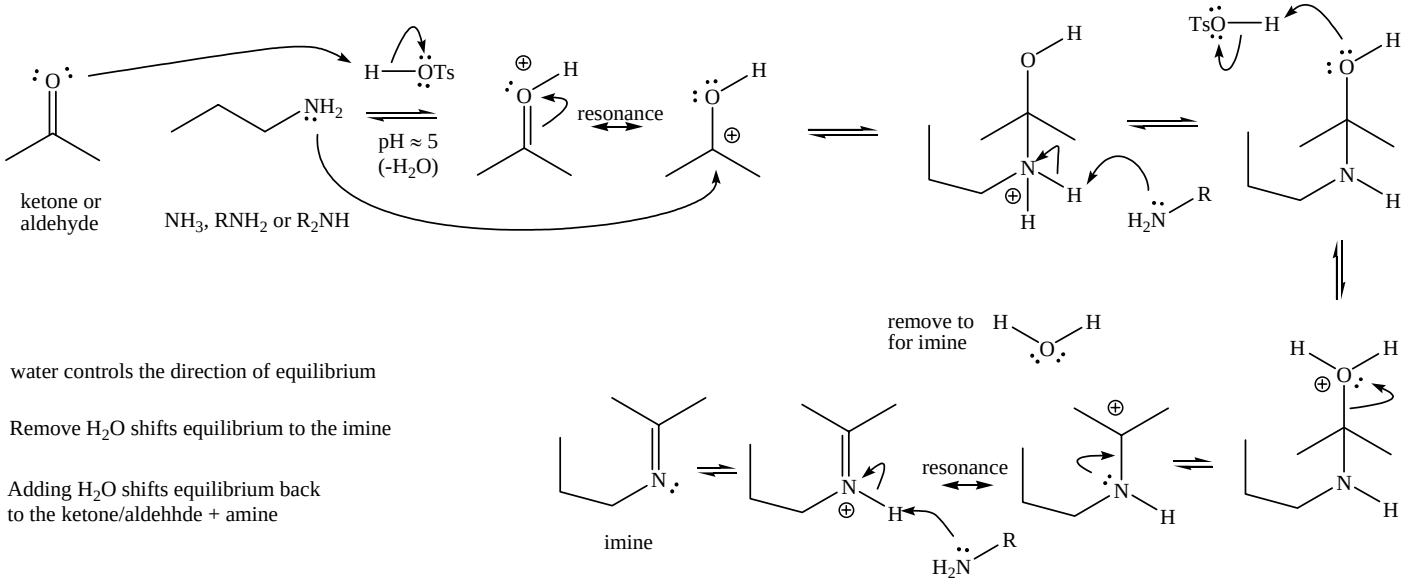
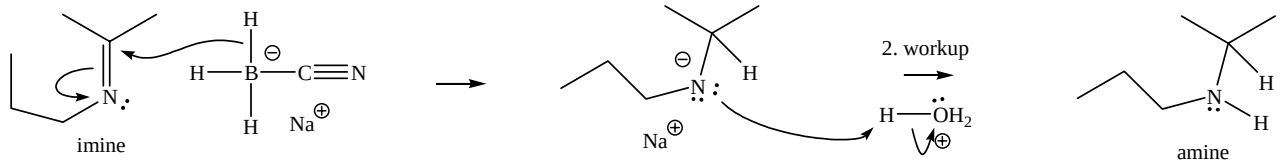
f. Primary amines → imines → reduced to amines with sodium cyanoborohydride (can form 1°, 2°, 3° amines)

Making an imine from a ketone or aldehyde and NH_3, RNH_2 or R_2NH. Then making the imine into a 1°, 2° or 3° amine using NaH_3BCN and workup.

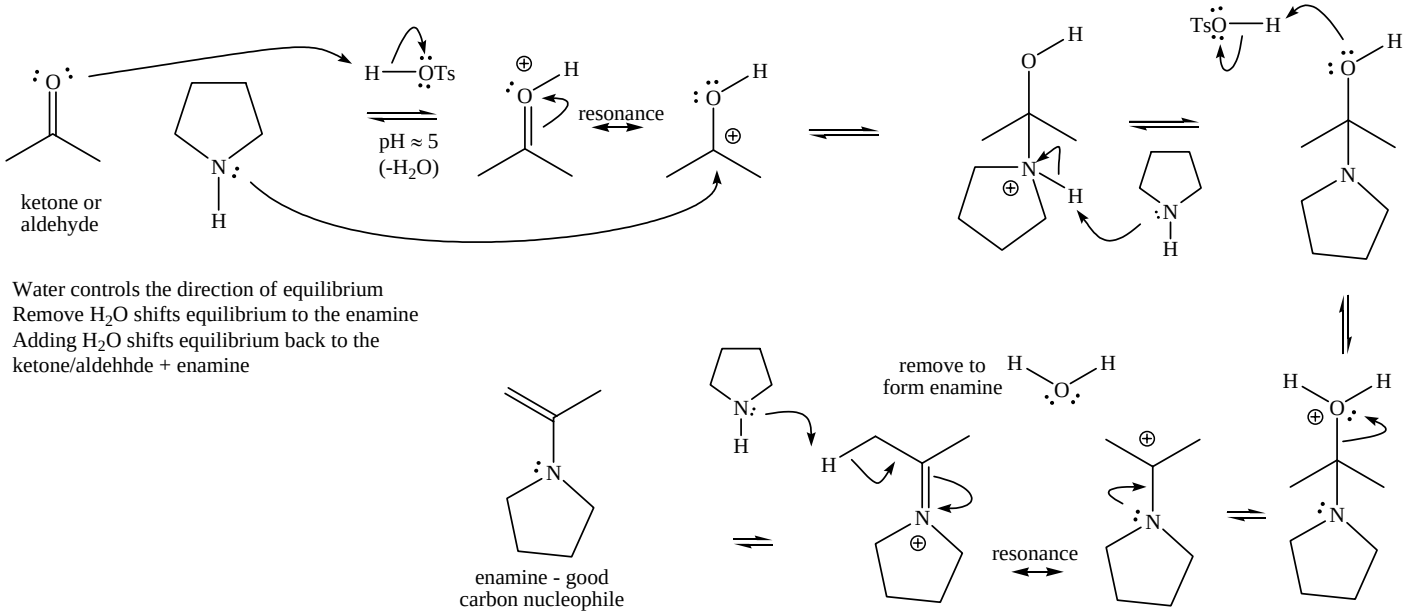


Reduce imine to amine with 1. sodium cyanoborohydride and 2. workup

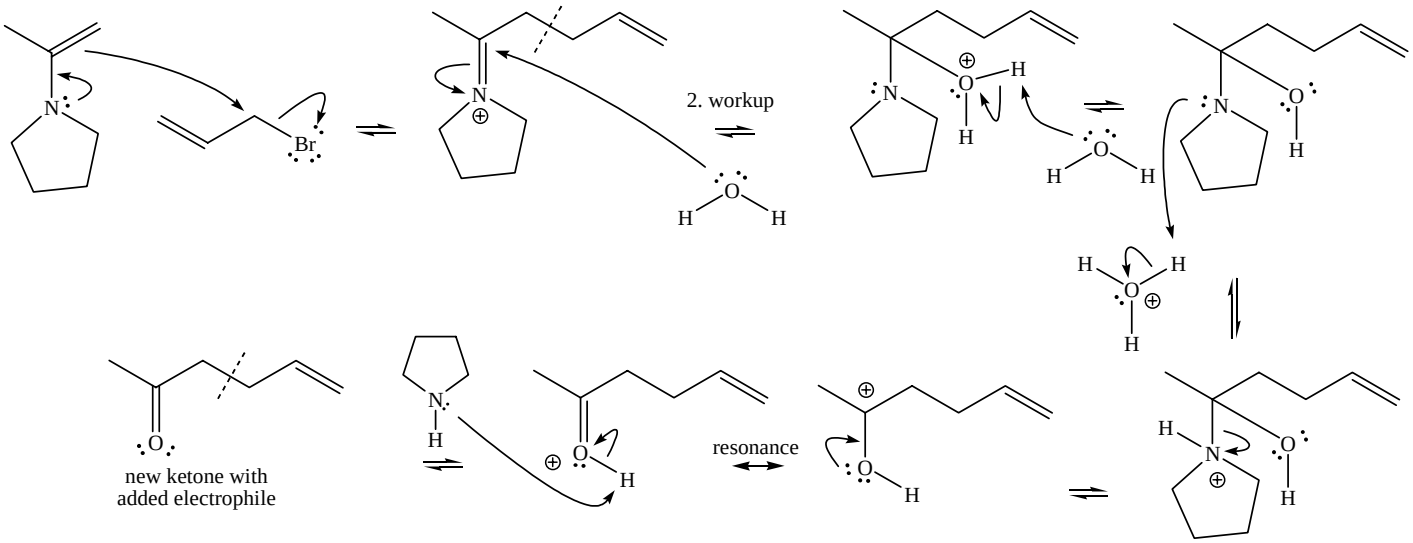


Transformations
C=O + NH_3 → primary amines
C=O + 1° amines → secondary amines
C=O + 2° amines → tertiary amines

g. Secondary amines → enamines → react with electrophiles + hydrolyze → ketones with new bonds

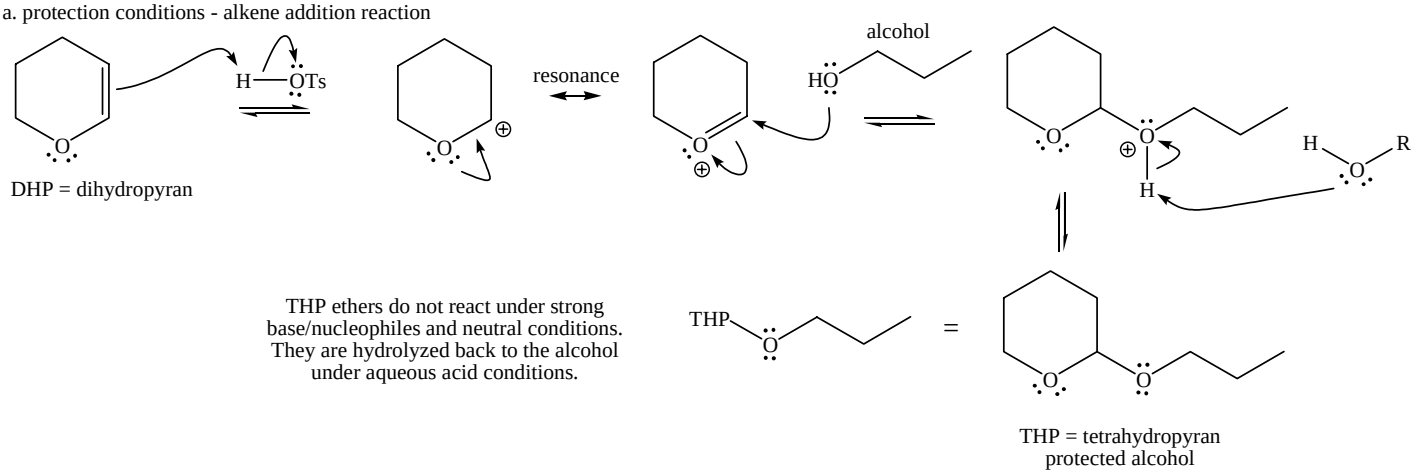


React enamine with 1. electrophile and 2. workup to reform C=O, joined with the electrophile

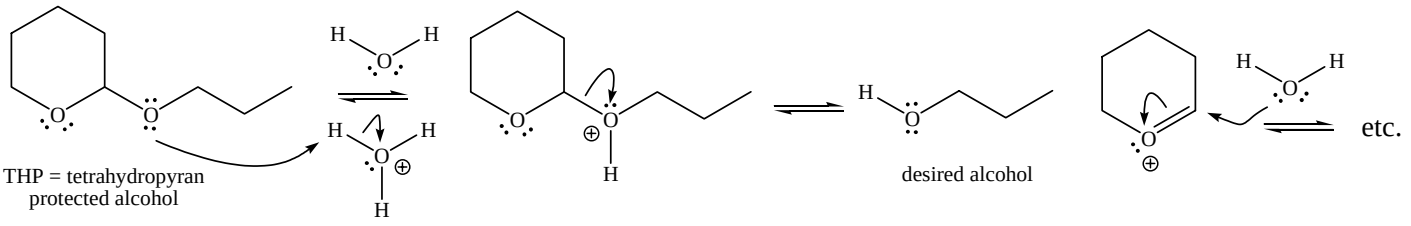


h. THP protection of alcohols & deprotection

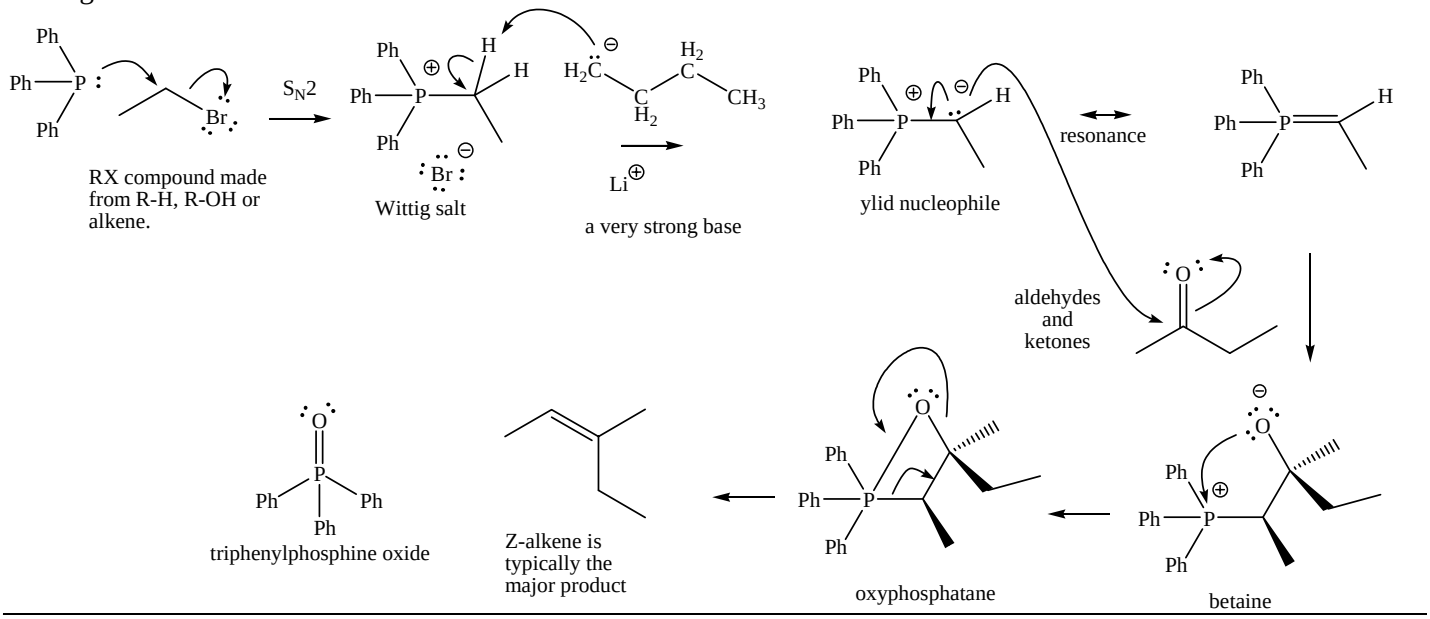
a. protection conditions - alkene addition reaction



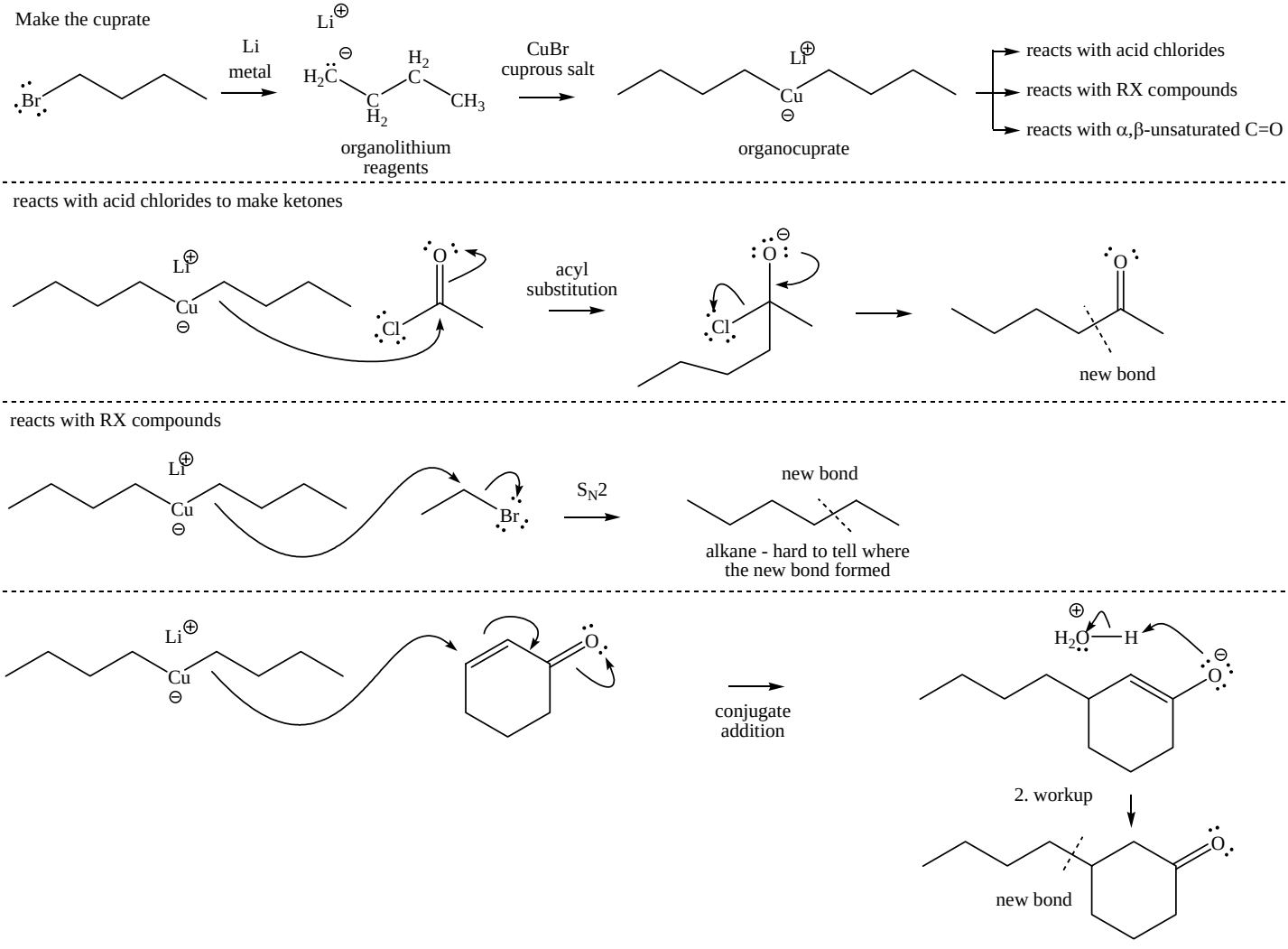
b. deprotection conditions - aqueous acid conditions hydrolyzes acetal back to alcohol



i. Wittig reactions

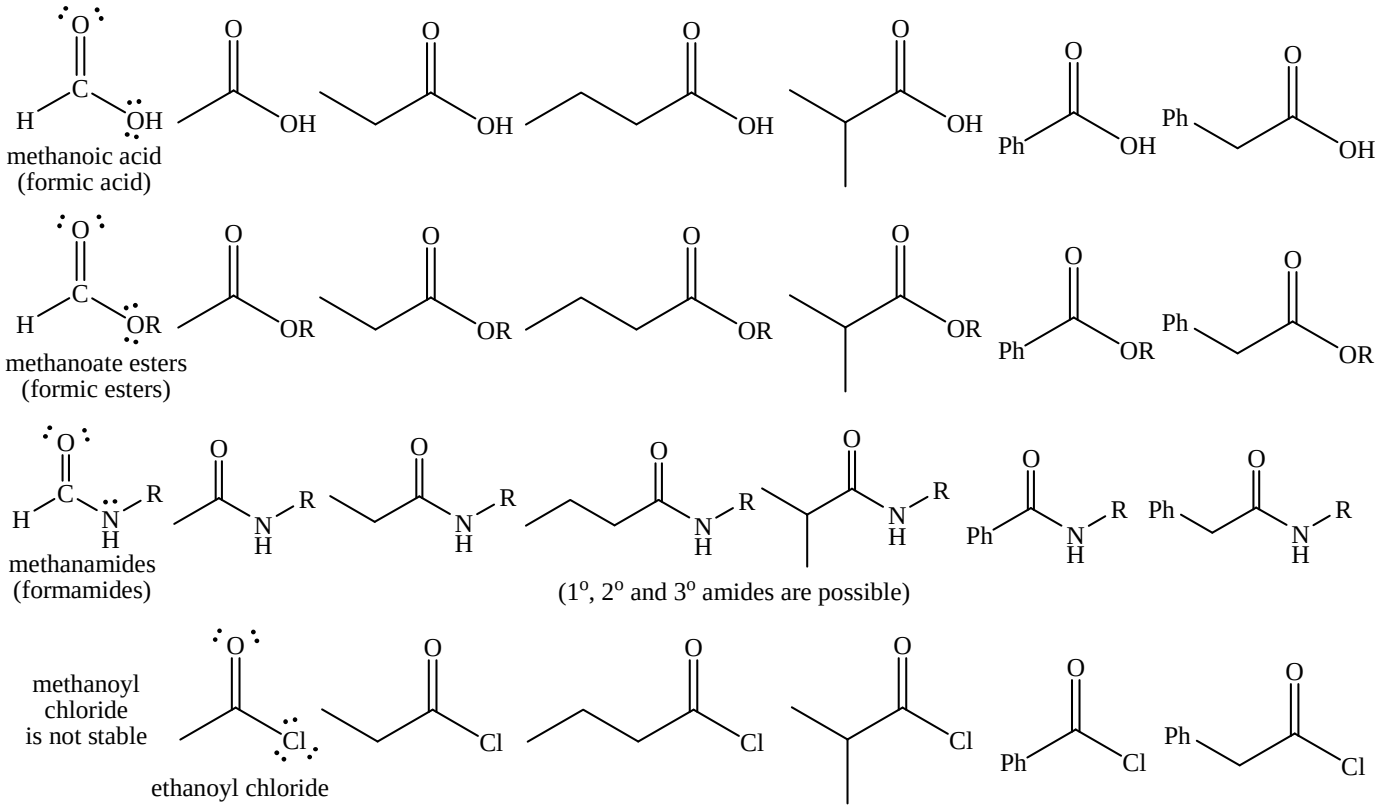


j. Cuprate reactions (with RX, with acid chlorides, with α,β-unsaturared C=O)



Carboxylic acids and derivatives – reactions

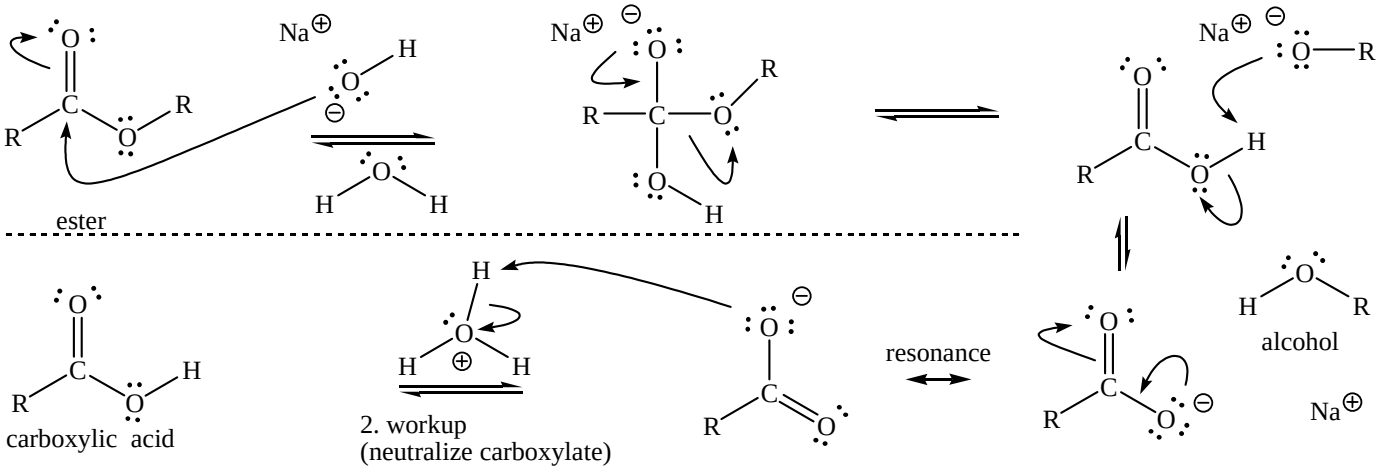
Examples of important patterns to know from our starting materials.



We can make carboxylic acids from 1° alcohols, aldehydes and nitriles (for now).

a. Base hydrolysis of esters

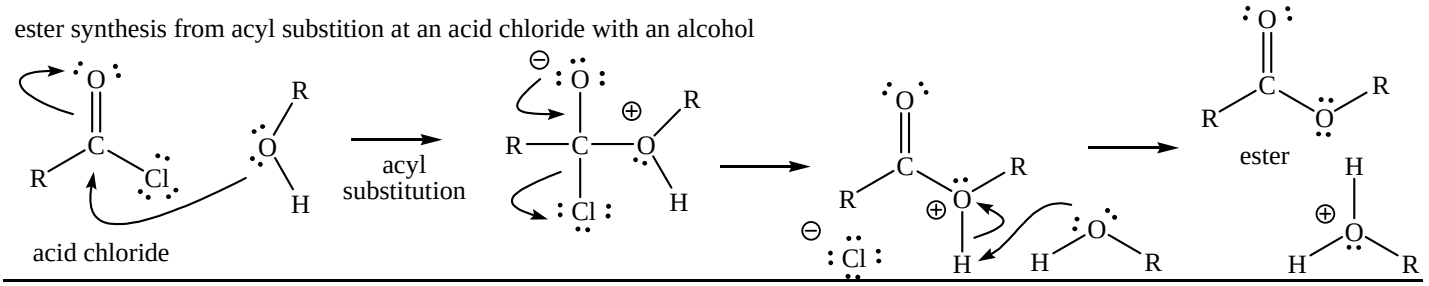
ester base hydrolysis = saponification = acyl substitution



Sometimes we want the alcohol part of the ester, sometimes the acid part of the ester and sometimes both parts.

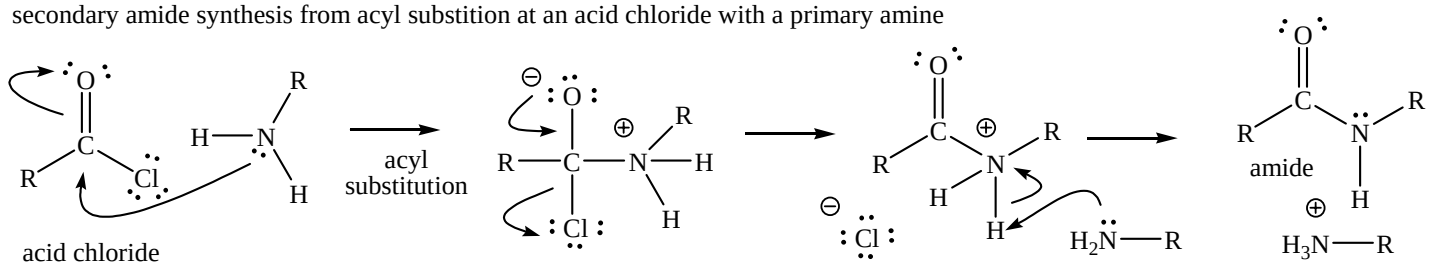
b. acid chloride + ROH = esters (notice two different R groups joined together by an oxygen)

ester synthesis from acyl substition at an acid chloride with an alcohol

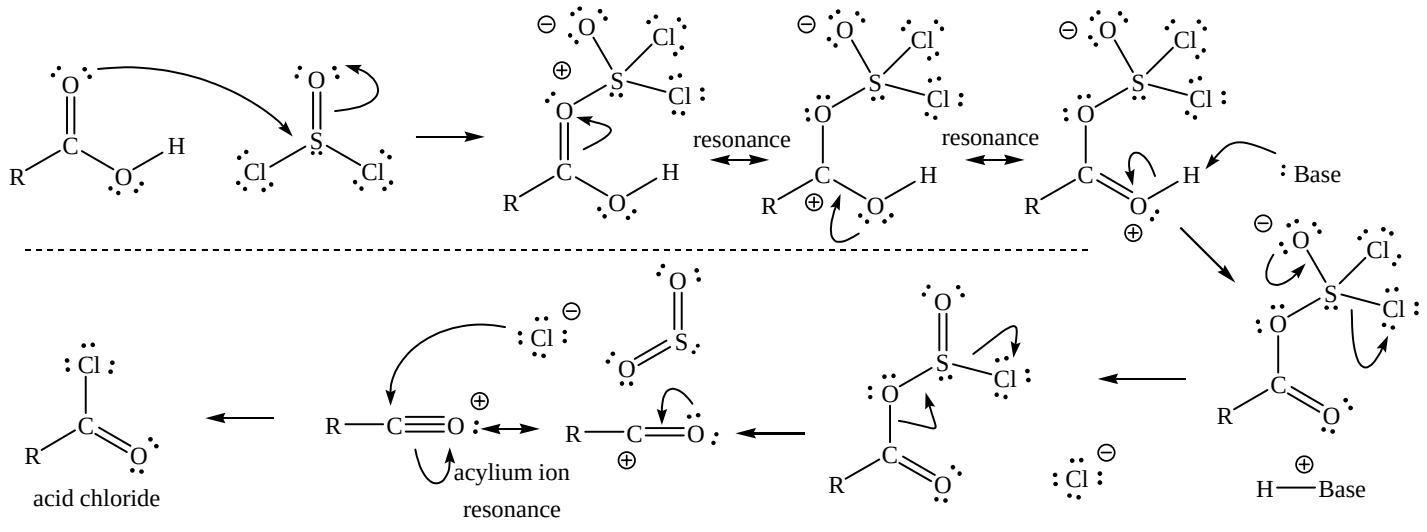


c. acid chloride + RNH_2 = 2^o amides (notice two different R groups joined together by a nitrogen)

secondary amide synthesis from acyl substition at an acid chloride with a primary amine

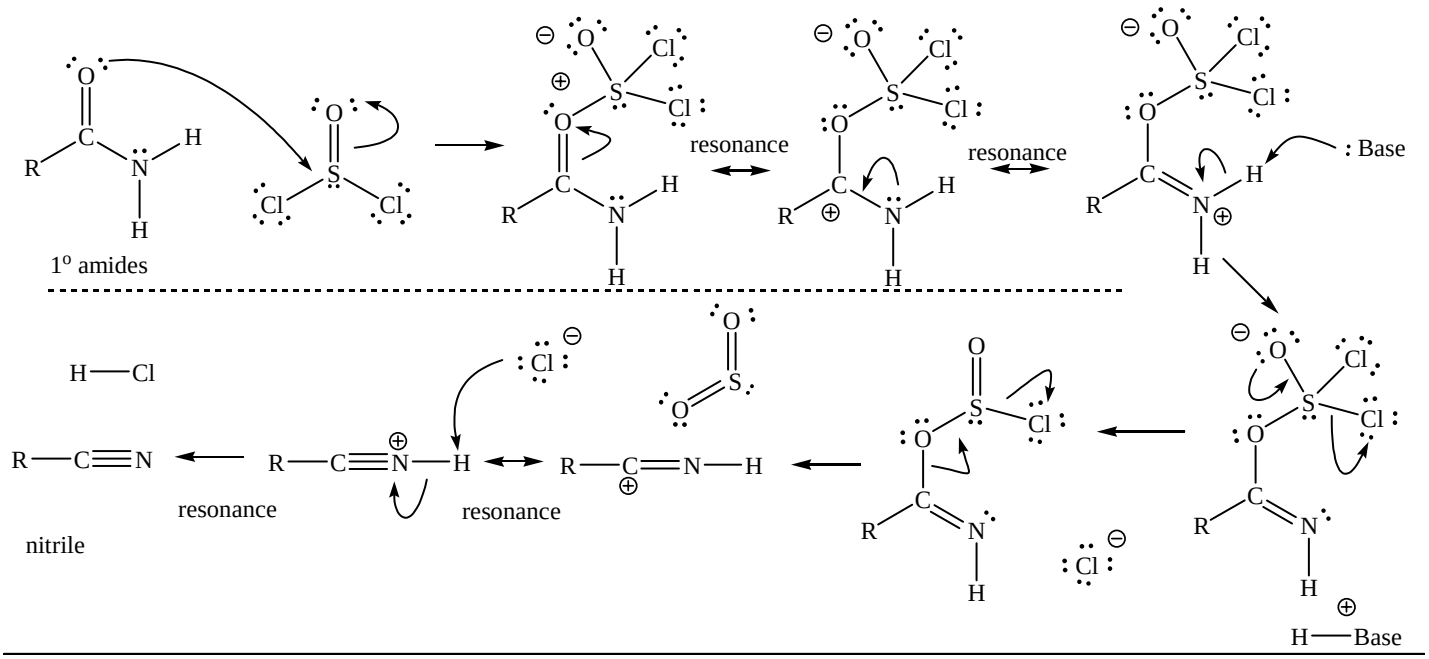


d. Synthesis of acid chlorides using thionyl chloride + carboxylic acids, acyl substitution, twice



e. acyl substitution, then two elimination reactions

synthesis of a nitrile from an 1° amide + thionyl chloride ($SOCl_2$)



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f. addition reaction (hydration) to imidate, tautomers to amide, acyl substitution to carboxylic acid

HCl / H_2O hydrolysis of a nitrile to an amide (in H_2SO_4 / H_2O / Δ hydrolysis continues on to a carboxylic acid)