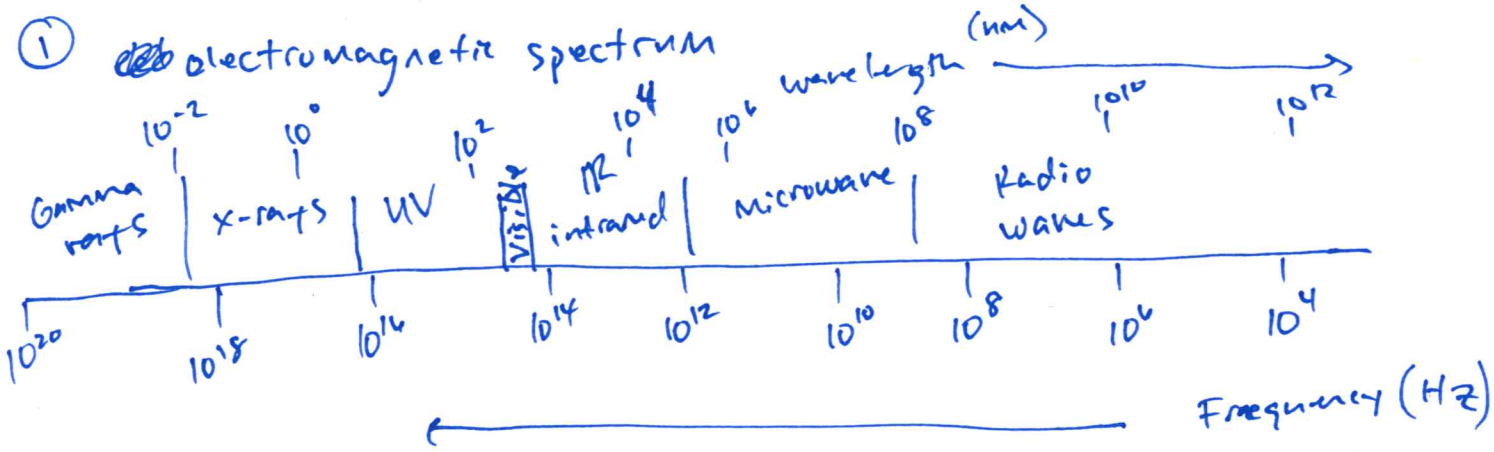
Spectroscopy

definition: a branch of science concerned with the investigation of spectra produced when matter interacts or emits electromagnetic radiation.

① electromagnetic spectrum



$E = h\nu$

ν = frequency, E = energy, h = Planck's constant

Frequency is directly proportional to energy, so higher ν → higher energy

② How does this apply to organic molecules? Why should I care?

- Molecules are too small to be seen by the naked eye
- we need a way of "seeing" molecules to know their structure.
- we use the spectroscopic data of organic molecules to snap "photos" of the molecules and their structure.

i.e. "Molecular snapchat"

Spectroscopy

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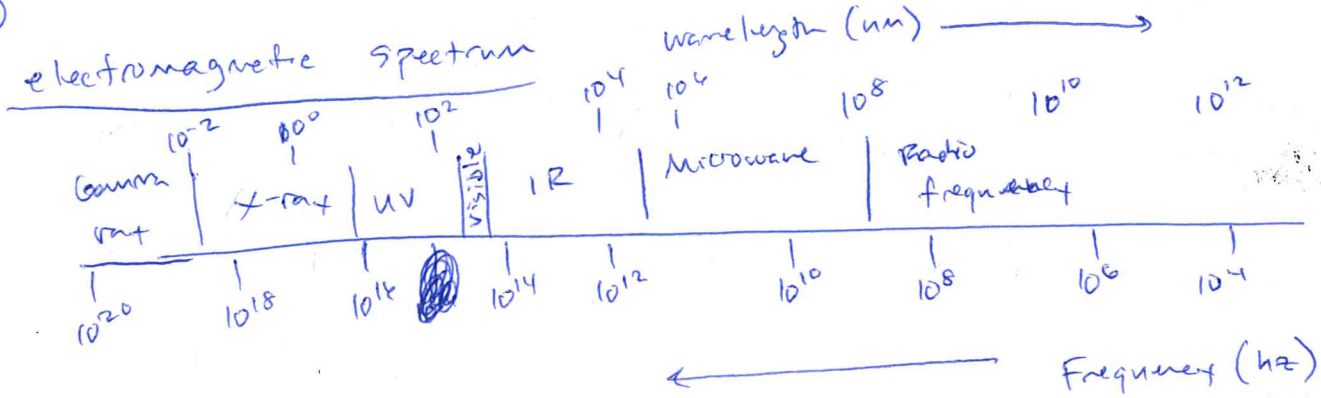

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- molecules are too small to be seen by the naked eye.
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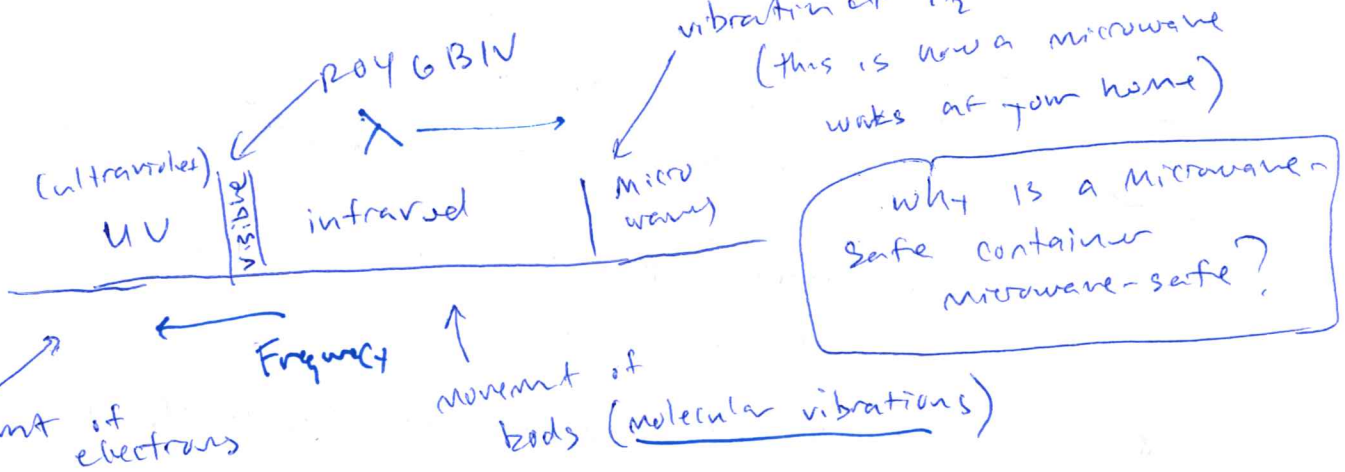
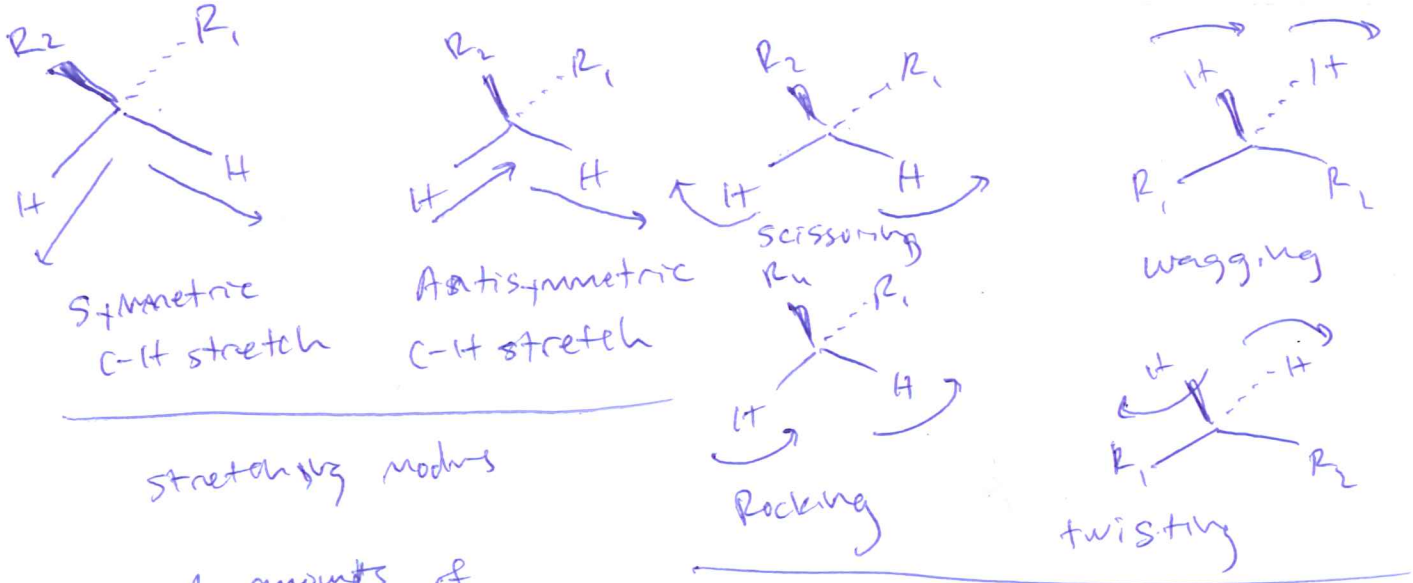
→ i.e. Molecular snap chart.

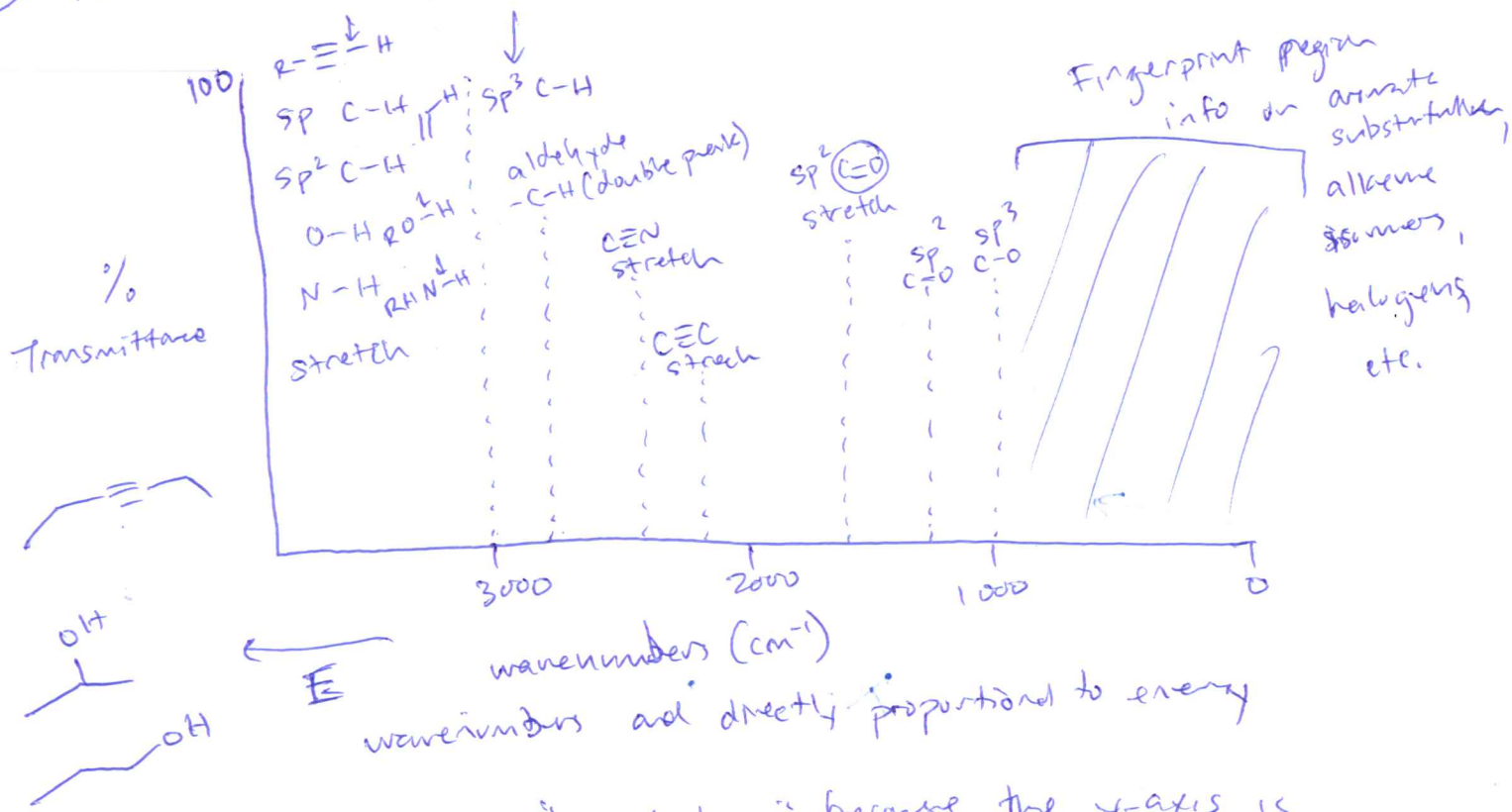


③ IR spectroscopy – stretching and bending



Different amounts of energy are needed for each type of bond in a molecule!

④ Functional Group identification via IR spectroscopy

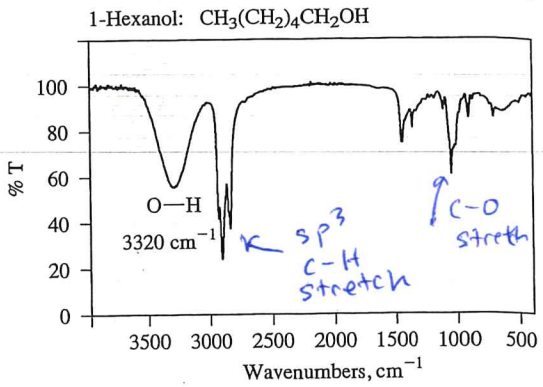


Spectrum looks "upside down" because the y-axis is transmittance and not absorbance

* You will not be able to determine absolute structure from IR alone!!

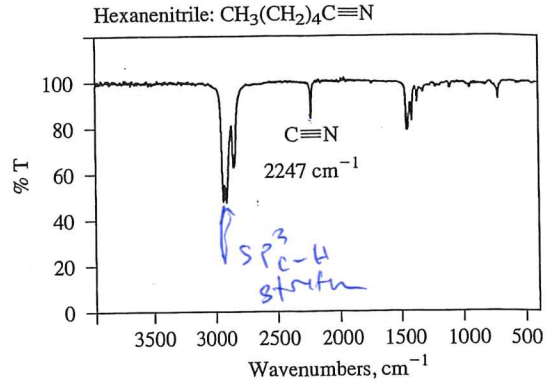
(*a*) **Alcohols:** A broad peak at 3200–3400 cm^{-1} is characteristic of hydrogen-bonded OH groups. In dilute solution, hydrogen bonding is less, and a sharp second peak for "free" OH groups appears near 3600 cm^{-1}.

The peak at 1070 cm^{-1} lies in the range given in Table 14.3 (1025–1200 cm^{-1}) for C—O stretching and can be assigned to it.

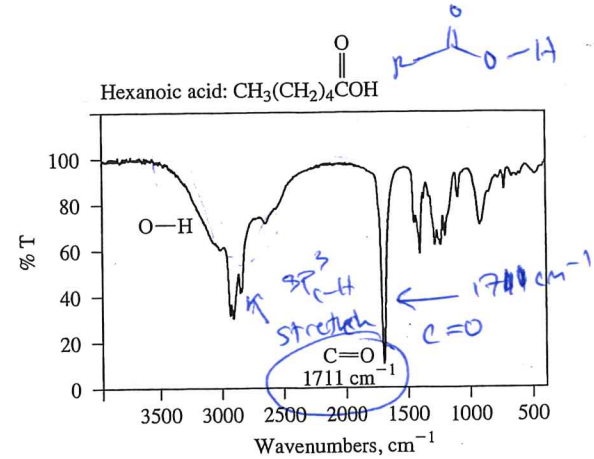


(*b*) **Nitriles:** The C≡N triple bond absorption is easily identifiable in the IR spectrum of a nitrile as a sharp peak of medium intensity at 2240–2280 cm^{-1}.

Very few other groups absorb in this region, the most notable being C≡C triple bonds (2100–2200 cm^{-1}).



(*c*) **Carboxylic acids:** Carboxylic acids have two characteristic absorptions: a broad peak for O—H stretching in the range 2500–3600 cm^{-1} and a strong peak for C=O stretching at 1700–1725 cm^{-1}.



(*d*) **Aldehydes and ketones:** As in other carbonyl-containing compounds, the C=O stretching vibration gives the strongest peak in the IR spectra of aldehydes and ketones.

The C=O stretching frequencies of aldehydes are similar to those of ketones.

The C—H stretch of the CH=O group in aldehydes appears as a pair of bands in the range 2700–2900 cm^{-1}.

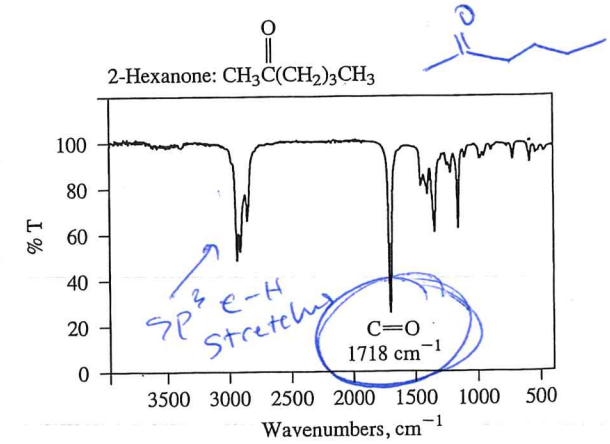
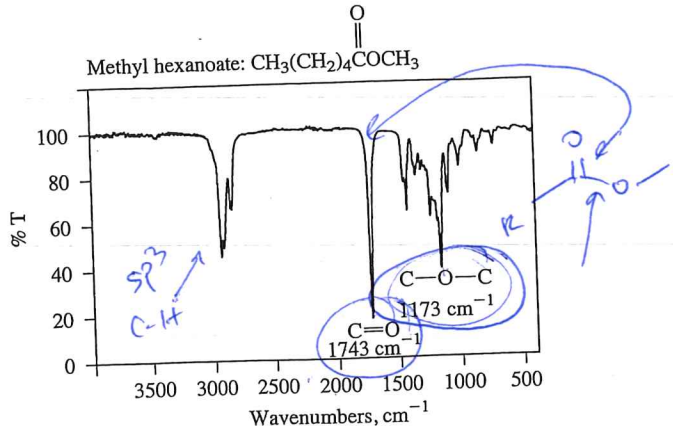


Figure 14.35

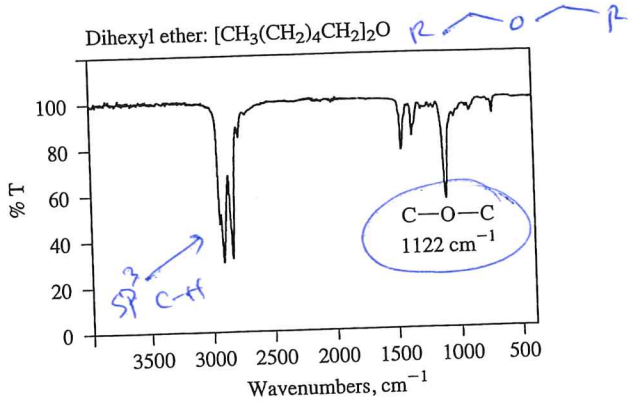
IR spectra of (*a*) 1-hexanol, (*b*) hexanenitrile, (*c*) hexanoic acid, (*d*) 2-hexanone, (*e*) methyl hexanoate, (*f*) dihexyl ether, (*g*) hexylamine, and (*h*) hexanamide.

(*Continued*)

(*e*) **Esters:** In addition to a strong C=O absorption (1730–1750 cm^{-1}), esters exhibit peaks for symmetric and antisymmetric C—O—C stretching at 1050–1300 cm^{-1}.



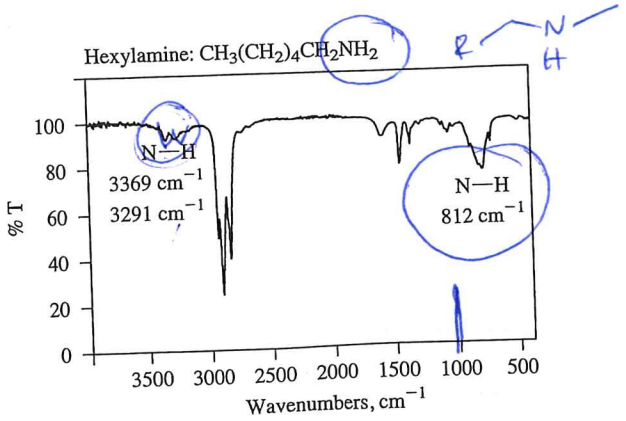
(*f*) **Ethers:** Peaks for C—O—C stretching in ethers appear in the range 1070–1150 cm^{-1}. Ethers of the type ROR′ where R and R′ are different have two peaks in this region.



(*g*) **Amines:** Primary amines (RNH_2) have two peaks for the NH_2 group in the 3300–3500 cm^{-1} region, one for symmetric and the other for antisymmetric N—H stretching. Secondary amines (RNHR′) have only one peak (3310–3350 cm^{-1}).

An NH bending peak at 650–900 cm^{-1} occurs in both RH_2 and RNHR′. Primary amines also have an NH bending absorption at 1580–1650 cm^{-1}.

C—N stretching peaks are found at 1020–1250 cm^{-1}.



(*h*) **Amides:** Amides of the type $RC(O)NH_2$ have peaks for both symmetric and antisymmetric N—H stretching in the 3400–3150 cm^{-1} region.

The C=O absorption for amides appears at slightly lower frequency (1650–1700 cm^{-1}) than for ketones. Amides have a peak for NH_2 bending at a slightly lower frequency (1600–1650 cm^{-1}) than C=O.

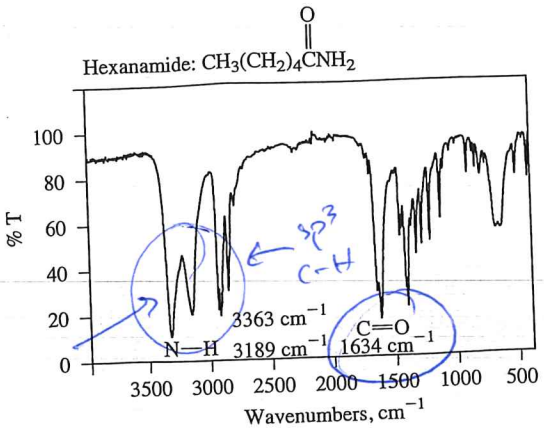


TABLE 14.3 Infrared Absorption Frequencies of Some Common Structural Units

Structural unit	Frequency, cm^{-1}	Structural unit	Frequency, cm^{-1}
Stretching vibrations			
Single bonds		**Double bonds**	
—O—H (alcohols)	3200–3600	C=C	1620–1680
—O—H (carboxylic acids)	2500–3600	C=O	
N—H	3350–3500	Aldehydes and ketones	1710–1750
sp C—H	3310–3320	Carboxylic acids	1700–1725
sp^2 C—H	3000–3100	Acid anhydrides	1800–1850 and 1740–1790
sp^3 C—H	2850–2950	Acyl halides	1770–1815
sp^2 C—O	1200	Esters	1730–1750
sp^3 C—O	1025–1200	Amides	1680–1700
		Triple bonds	
		—C≡C—	2100–2200
		—C≡N	2240–2280
Bending vibrations of diagnostic value			
Alkenes:		***Substituted derivatives of benzene:***	
$RCH{=}CH_2$	910, 990	Monosubstituted	730–770 and 690–710
$R_2C{=}CH_2$	890	Ortho-disubstituted	735–770
cis-RCH=CHR′	665–730	Meta-disubstituted	750–810 and 680–730
trans-RCH=CHR′	960–980	Para-disubstituted	790–840
$R_2C{=}CHR'$	790–840		

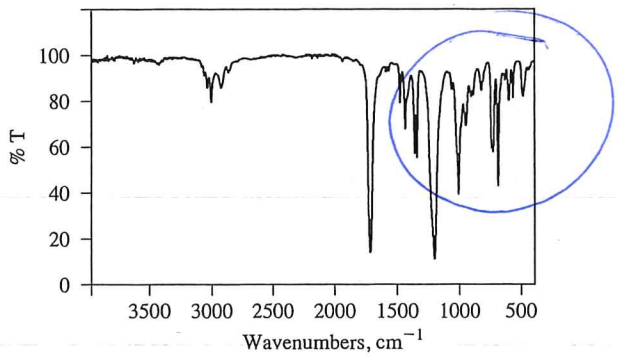
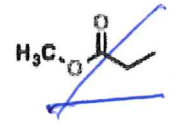
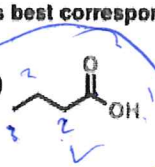


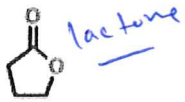
Figure 14.36

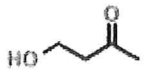
The IR spectrum of the unknown compound in Problem 14.24.

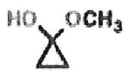
Which of these molecules best corresponds to the IR spectrum below?

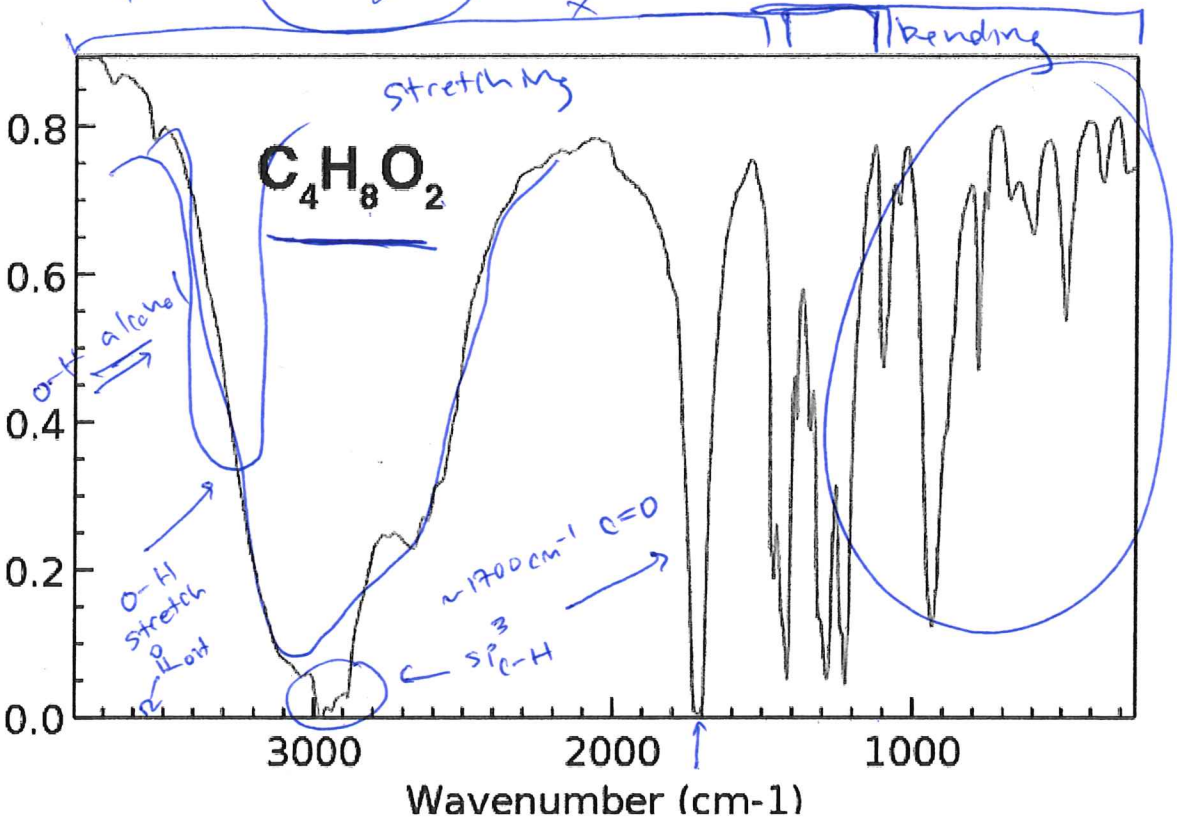
a) 

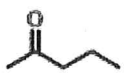
b) 

c) 

d) 

e) 



a) 

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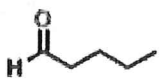
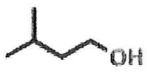
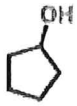
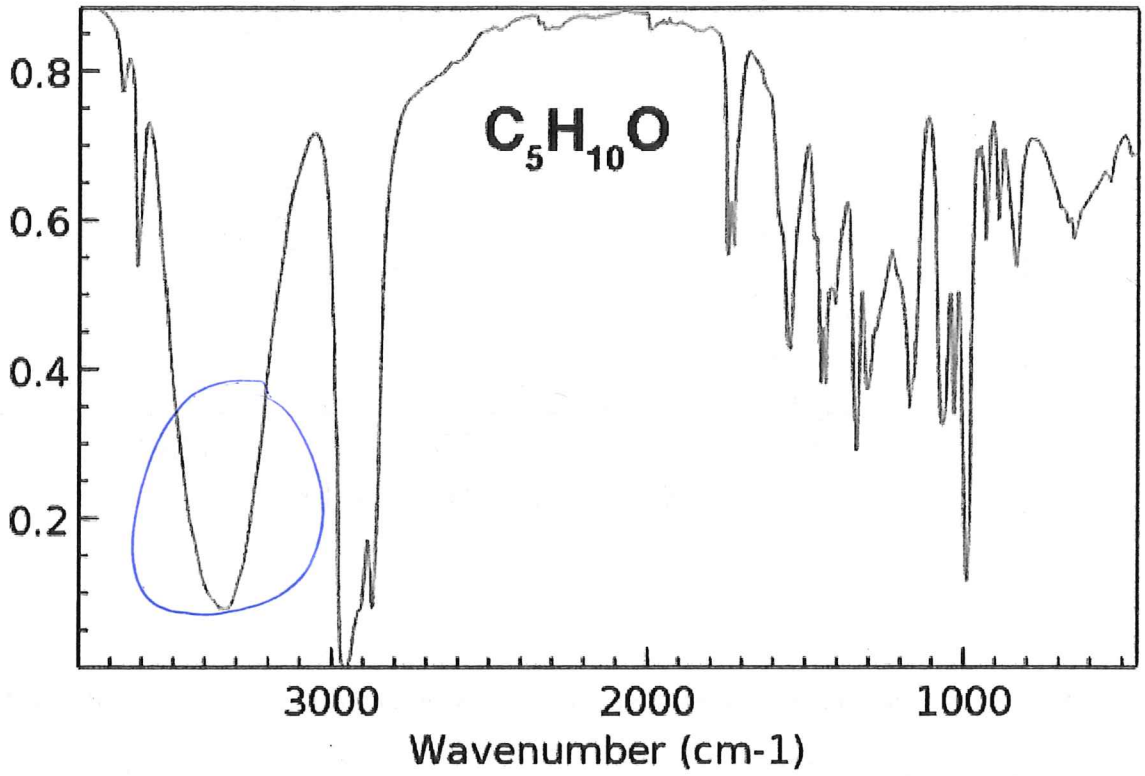
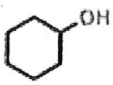
c) 

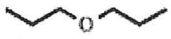
d) 

e) 

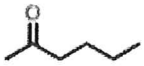


Which of these molecules best corresponds to the IR spectrum below?

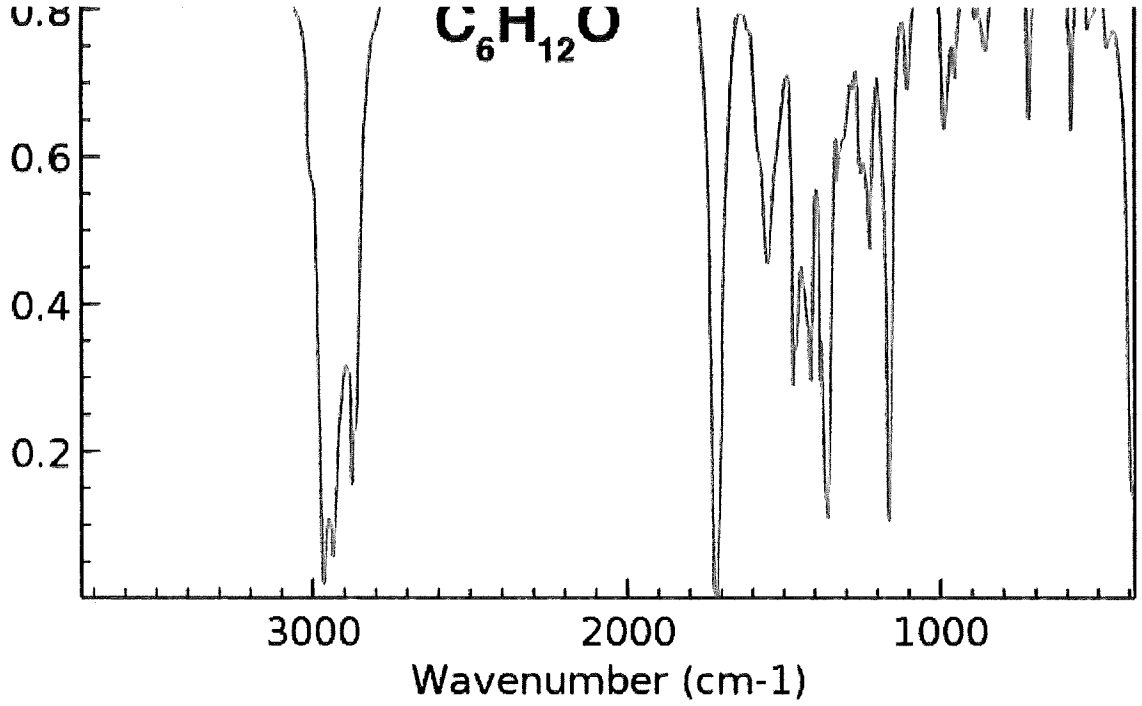
a) 

b) 

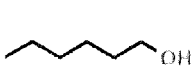
c) 

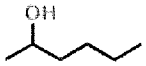
d) 

e) 



Which of these molecules best corresponds to the IR spectrum below with molecular formula $C_6H_{14}O$?

a) 

b) 

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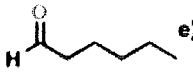
d) 

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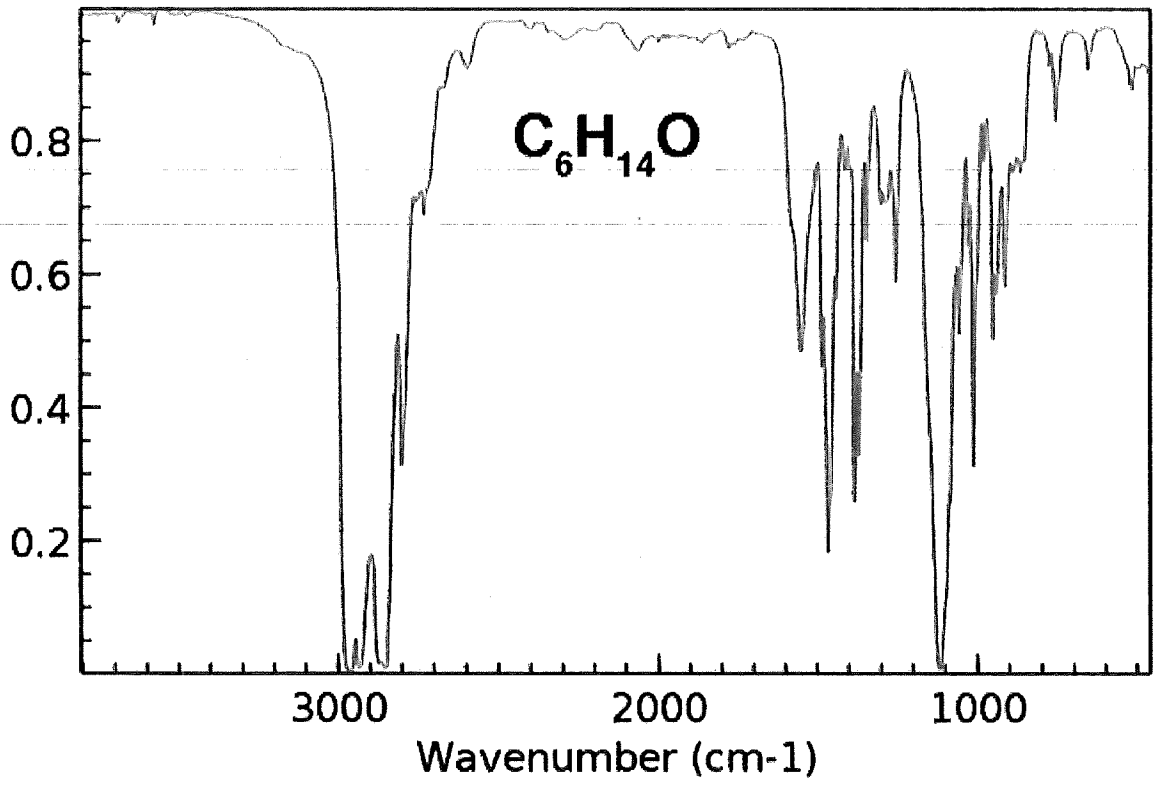
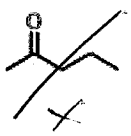


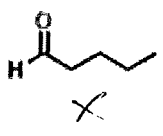
carbonyl

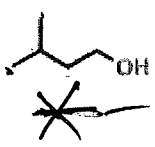
Carbonyl

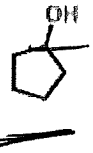
12 H !

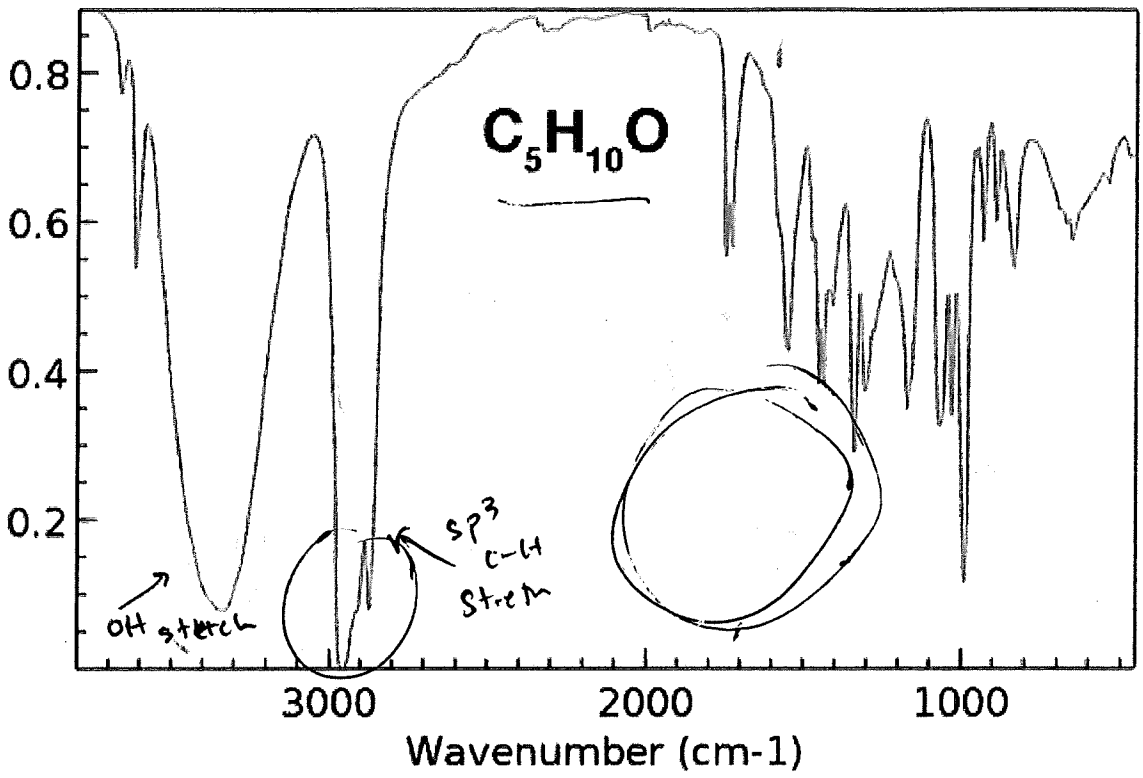
a) 

b) 

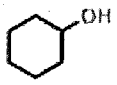
c) 

d) 

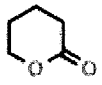
e) 

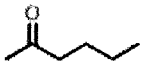


Which of these molecules best corresponds to the IR spectrum below?

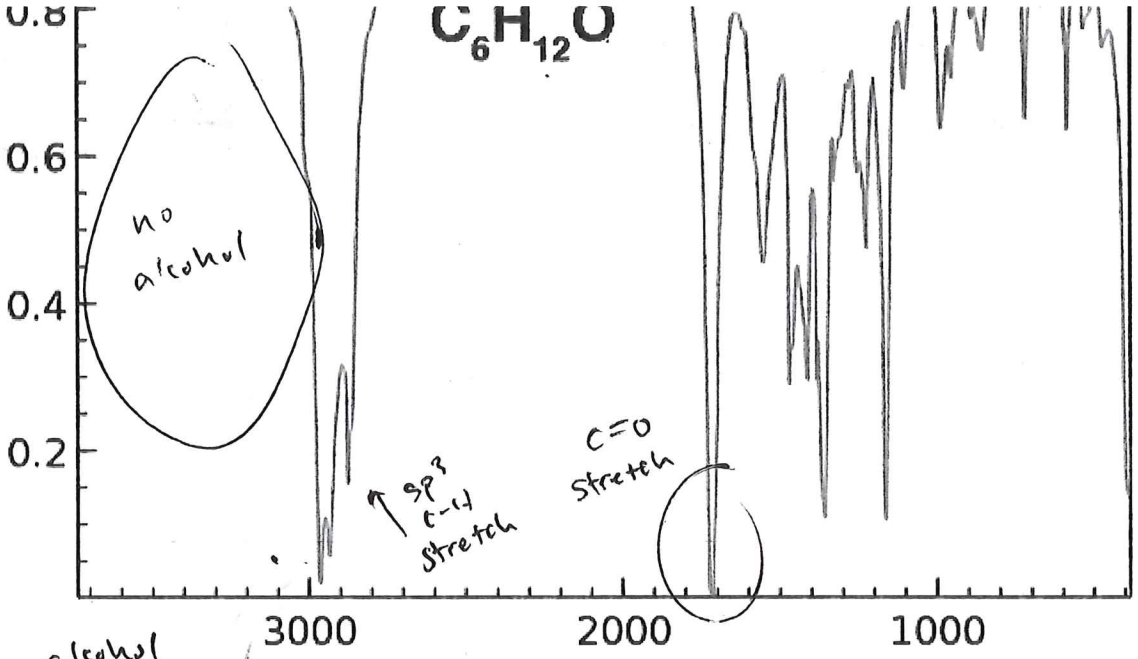
a) 

b) 

c) 

d) 

e) 



alcohol OH — C-O stretch — carbonyl — carbonyl — alcohol HO

a — b — c — d — e

X X X C X

Which of these molecules best corresponds to the IR spectrum below with molecular formula $C_6H_{14}O$?

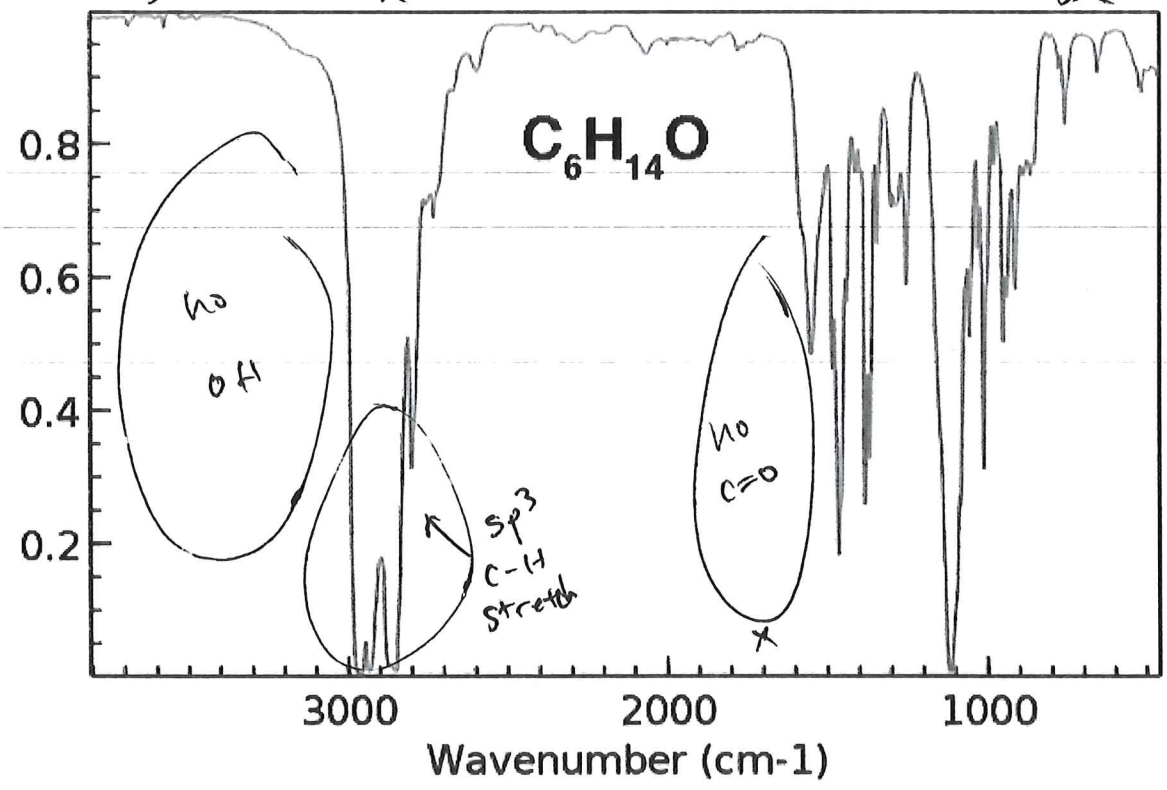
a) OH — alcohol — X

b) OH — alcohol — X

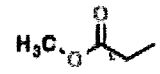
c) O — ether C-O stretch

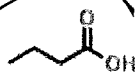
d) O, H — carbonyl — X

e) O — C-O Stretch — X

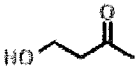


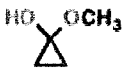
Which of these molecules best corresponds to the IR spectrum below?

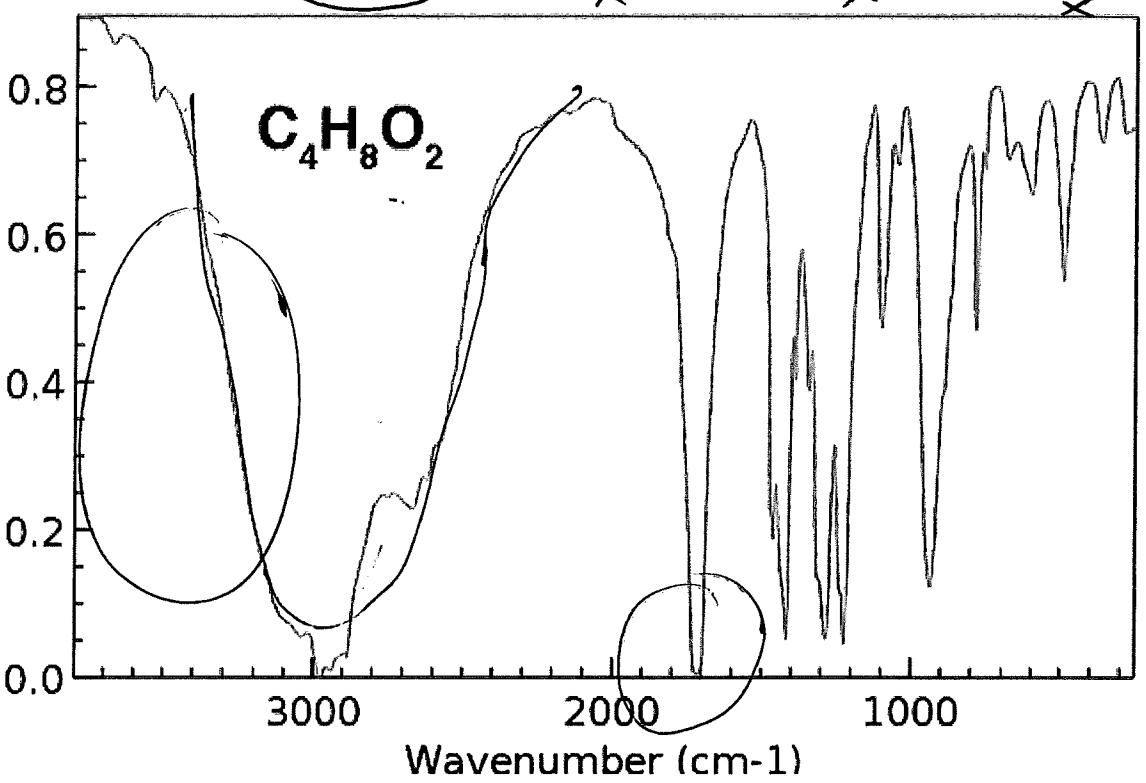
a)  carbonyl

b)  acid

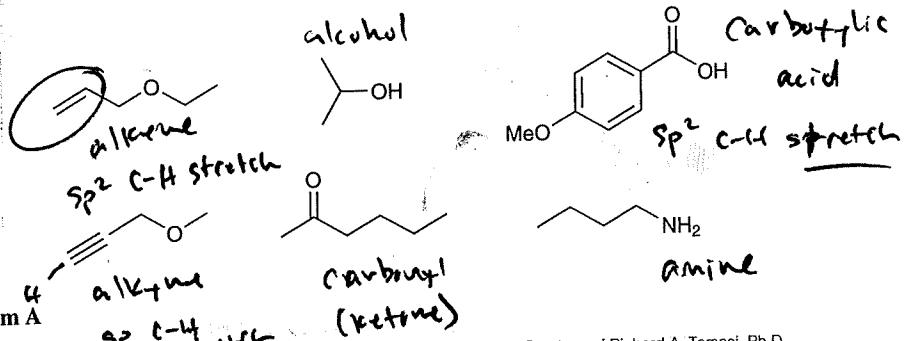
c)  cyclic ester ✗

d)  alcohol ✗

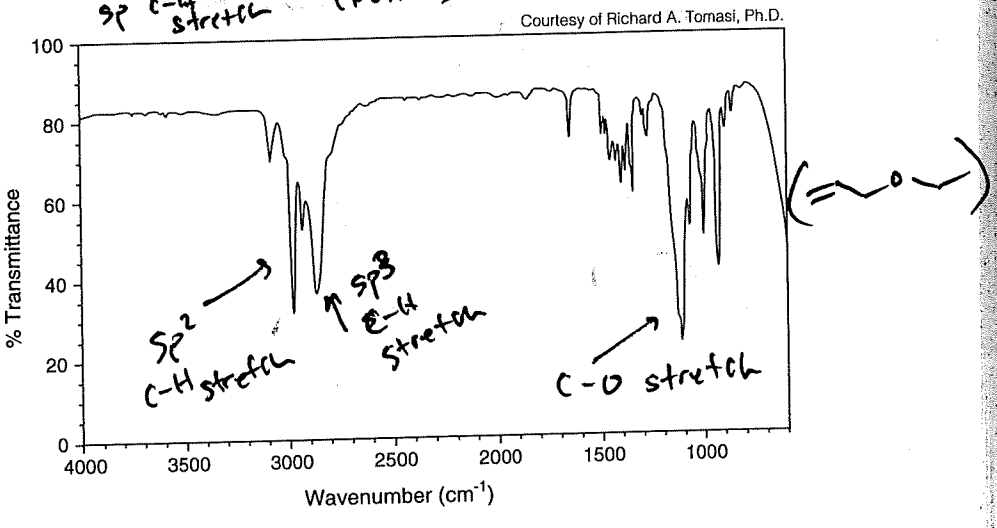
e)  alcohol ✗



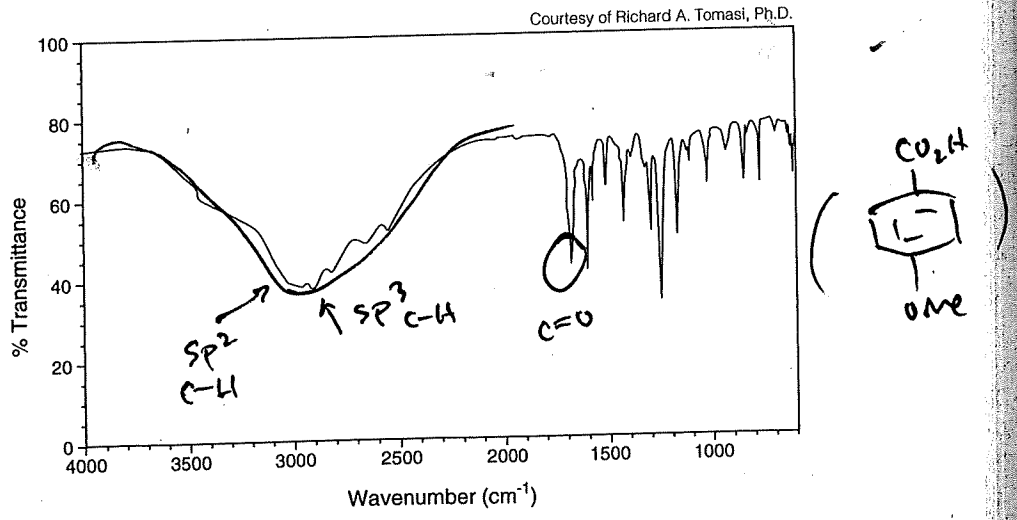
PROBLEM 2.22 Match each compound with the appropriate spectrum



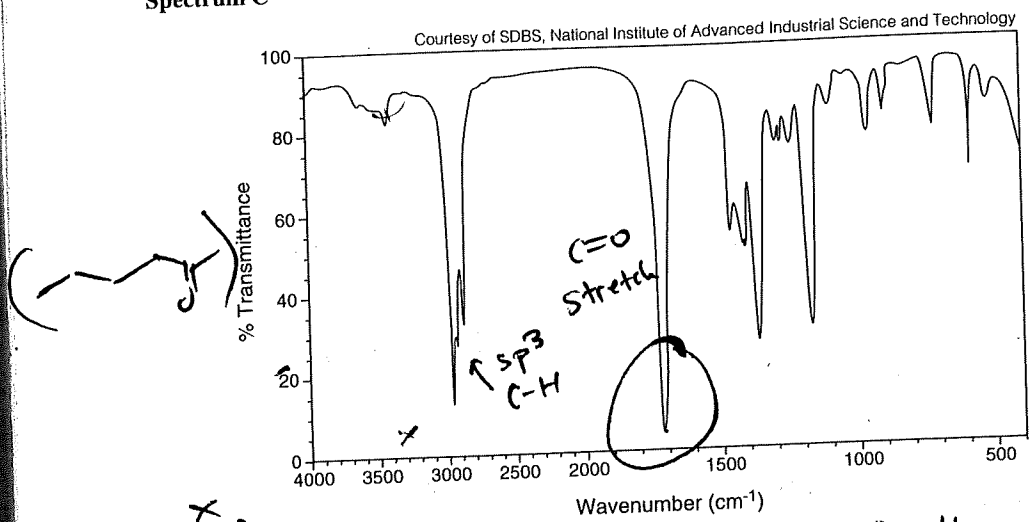
Spectrum A



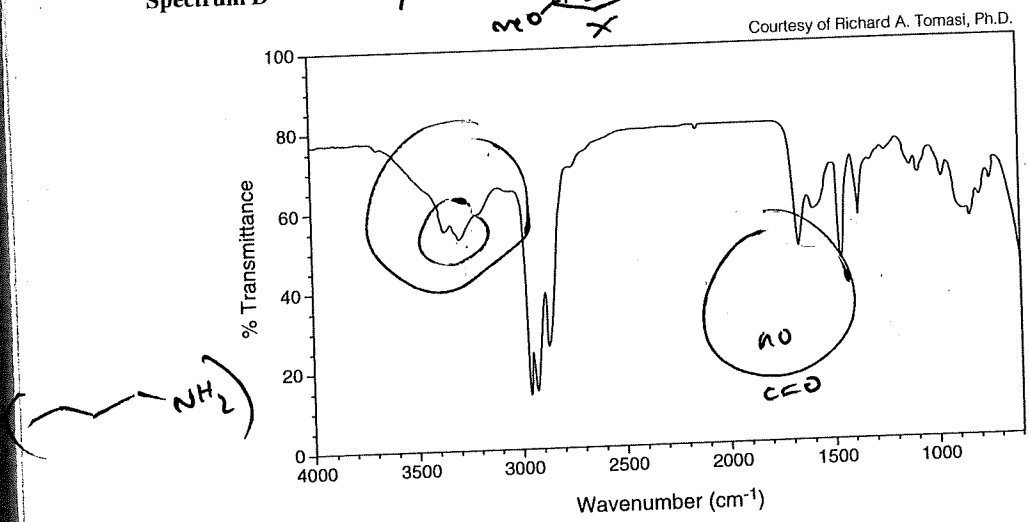
Spectrum B



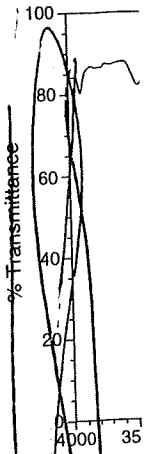
Spectrum C



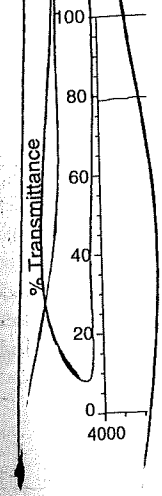
Spectrum D



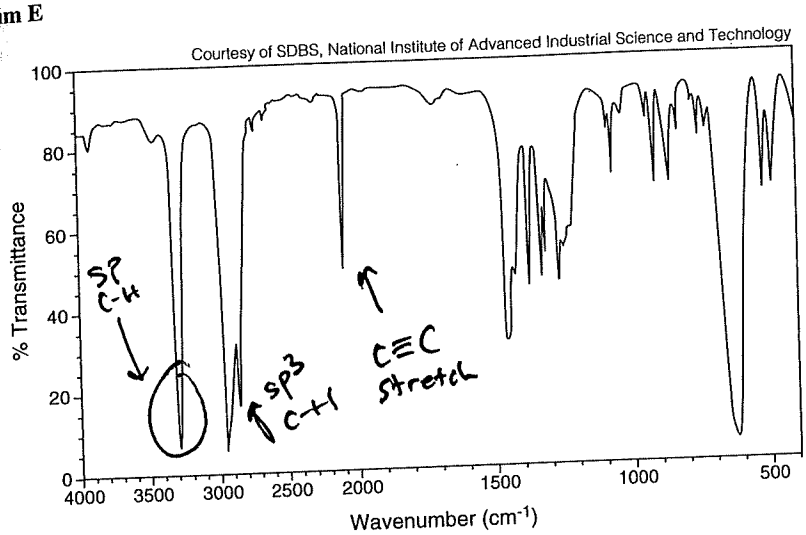
Spectrum E



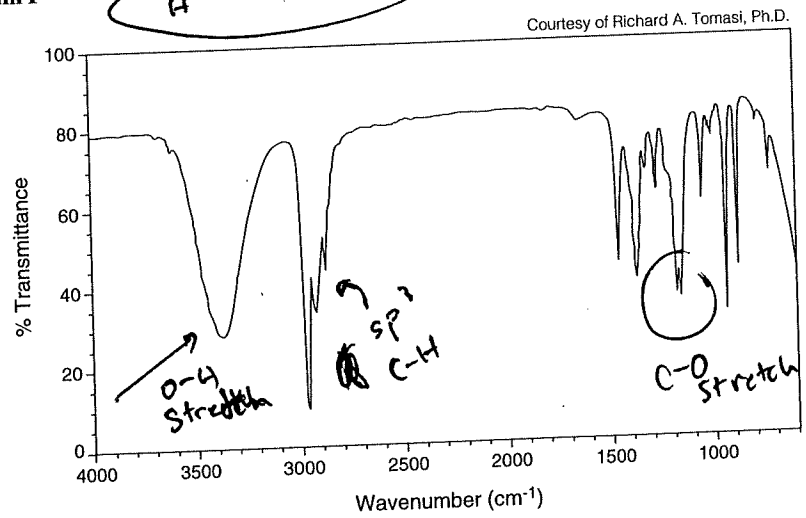
Spectrum F



Spectrum E



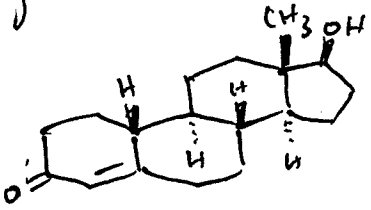
Spectrum F



Mass Spectrometry

① definition: An analytical tool useful for measuring mass-to-charge ratio (m/z) of one or more molecules in a sample.

Mass spectrometry is used regularly for the detection of doping agents in athletics. For example:

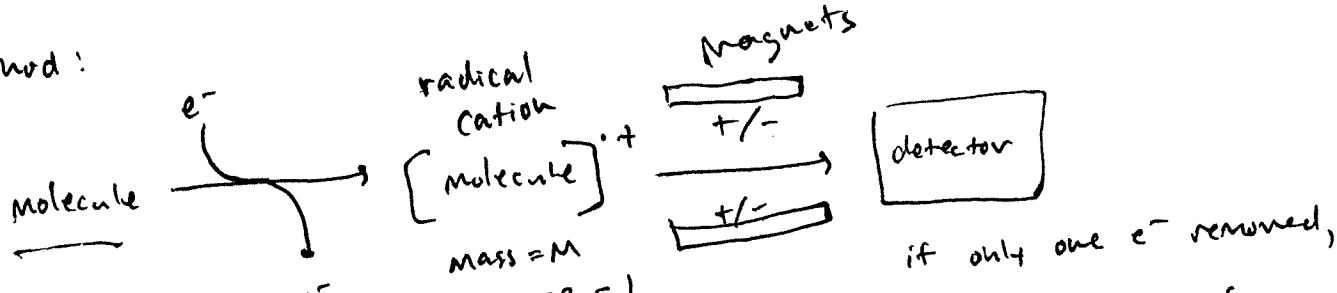


nandrolone (mass (mw) = 274)

only 2 μg/L in urine is allowed by International Olympic committee

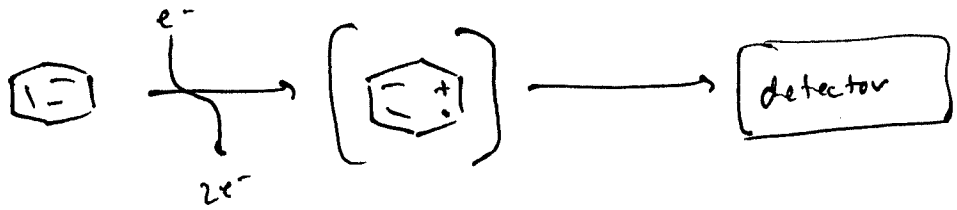
* in 2007, Marion Jones admitted use of nandrolone and was sentenced to 6 mo. in jail for perjury.

② method:



if only one e⁻ removed, the M/z = mass of compound.

for benzene (see p. 564 in book)



why are there those small peaks at 79 and 80?

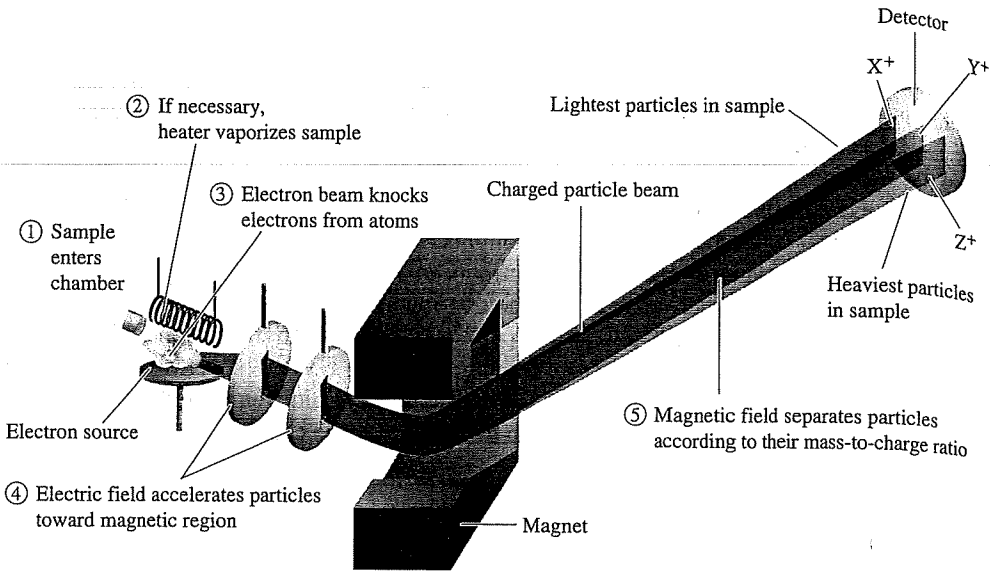
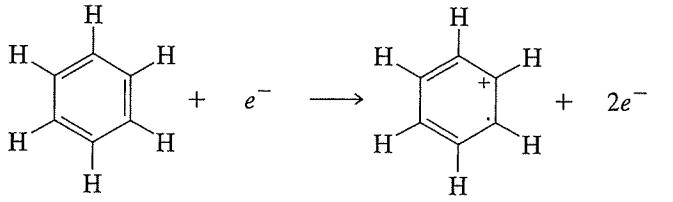


Figure 14.39

Diagram of a mass spectrometer. Only positive ions are detected. The cation X^+ has the lowest mass-to-charge ratio and its path is deflected most by the magnet. The cation Z^+ has the highest mass-to-charge ratio and its path is deflected least. (Adapted, with permission, from M. Silberberg, *Chemistry* 7th ed., McGraw-Hill Higher Education, 2015, p. 288.)

The mass spectrum of benzene is relatively simple and illustrates some of the information that mass spectrometry provides. The most intense peak in the mass spectrum is called the **base peak** and is assigned a relative intensity of 100. Ion abundances are proportional to peak intensities and are reported as intensities relative to the base peak. The base peak in the mass spectrum of benzene corresponds to the molecular ion (M^+) at $m/z = 78$.



Benzene does not undergo extensive fragmentation; none of the fragment ions in its mass spectrum are as abundant as the molecular ion.

There is a small peak one mass unit higher than M^+ in the mass spectrum of benzene. What is the origin of this peak? What we see in Figure 14.40 as a single mass spectrum is actually a superposition of the spectra of three isotopically distinct benzenes. Most of the

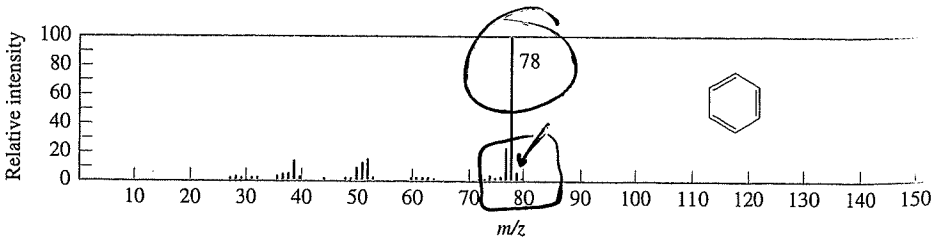
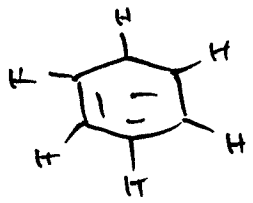


Figure 14.40

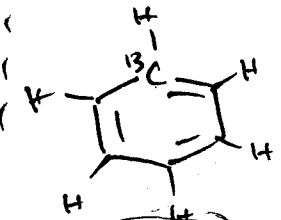
The mass spectrum of benzene. The peak at $m/z = 78$ corresponds to the C_6H_6 molecular ion.



→ mass = 78

all carbons are ^{12}C

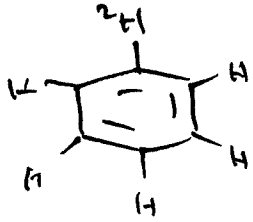
93.4 %



4.5 %

mass = 79

or



0.1 %

— ^{13}C accounts for about 1.1 % of all carbon isotopes

— The likelihood of there being two ^{13}C in a small molecule is low

what about other isotopes that have an effect on Spectrum?

for chlorine: $\frac{^{35}Cl}{^{37}Cl} = \frac{100}{32.7} \approx \frac{3}{1}$

for bromine: $\frac{^{79}Br}{^{81}Br} = \frac{100}{97.5} \approx \frac{1}{1}$

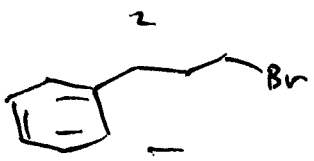
therefore the mass spectrum for chlorobenzene is:

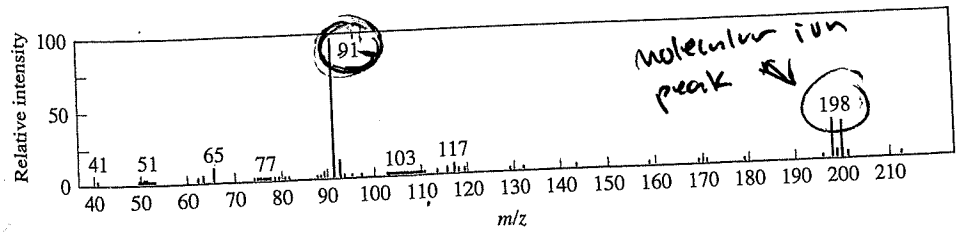
(see page 565 in book)

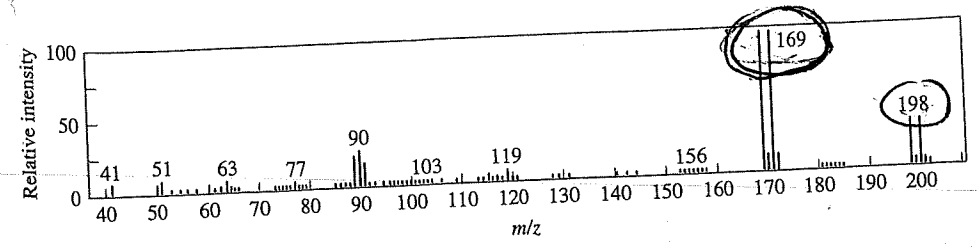
notice how the peak at 114 is about 1/3 the size of the peak at 112.

Consider the mass spectra for

and

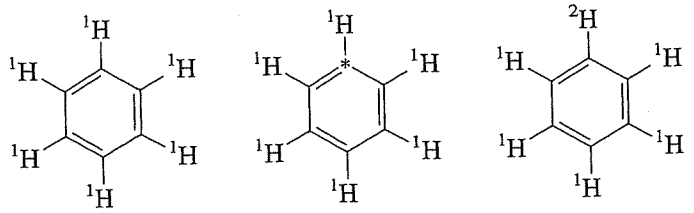






same MW, so why not same Spectrum?

benzene molecules contain only ^{12}C and ^{1}H and have a molecular mass of 78. Smaller proportions of benzene molecules contain ^{13}C in place of one of the ^{12}C atoms or ^{2}H in place of one of the protons. Both these species have a molecular mass of 79.



93.4% (all carbons are ^{12}C) Gives M^+ 78

6.5% (* = ^{13}C) Gives M^+ 79

0.1% (all carbons are ^{12}C) Gives M^+ 79

Not only the molecular ion peak but all the peaks in the mass spectrum of benzene are accompanied by a smaller peak one mass unit higher. Indeed, because all organic compounds contain carbon and most contain hydrogen, similar **isotopic clusters** will appear in the mass spectra of all organic compounds.

Isotopic clusters are especially apparent when atoms such as bromine and chlorine are present in an organic compound. The natural ratios of isotopes in these elements are

$$\frac{^{35}Cl}{^{37}Cl} = \frac{100}{32.7} \qquad \frac{^{79}Br}{^{81}Br} = \frac{100}{97.5}$$

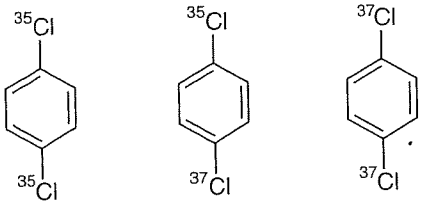
Figure 14.41 presents the mass spectrum of chlorobenzene. There are two prominent molecular ion peaks, one at *m/z* 112 for $C_6H_5{}^{35}Cl$ and the other at *m/z* 114 for $C_6H_5{}^{37}Cl$. The peak at *m/z* 112 is three times as intense as the one at *m/z* 114.

Problem 14.27

Knowing what to look for with respect to isotopic clusters can aid in interpreting mass spectra. How many peaks would you expect to see for the molecular ion in each of the following compounds? At what *m/z* values would these peaks appear? (Disregard the small peaks due to ^{13}C and ^{2}H.)

(a) *p*-Dichlorobenzene
(b) *o*-Dichlorobenzene
(c) *p*-Dibromobenzene
(d) *p*-Bromochlorobenzene

Sample Solution (a) The two isotopes of chlorine are ^{35}Cl and ^{37}Cl. There will be three isotopically different forms of *p*-dichlorobenzene present. They have the structures shown as follows. Each one will give an M^+ peak at a different value of *m/z*.



m/z 146 *m/z* 148 *m/z* 150

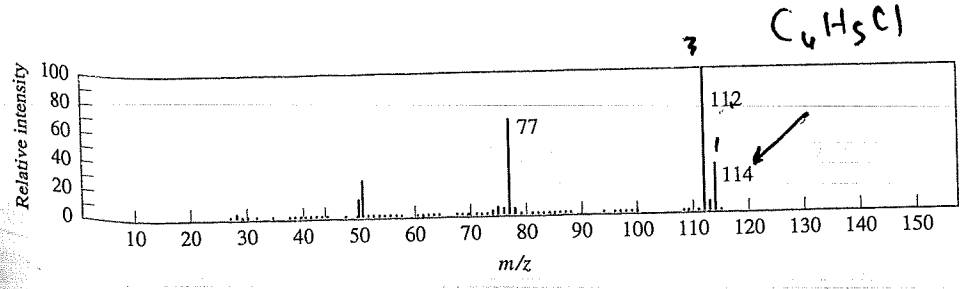
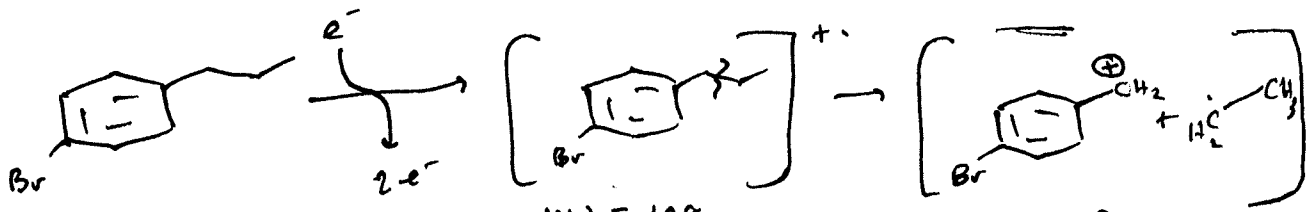
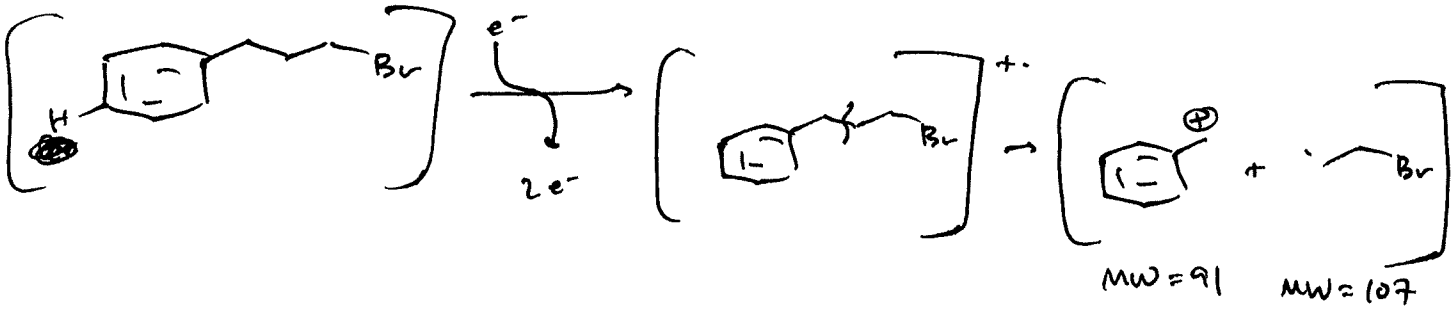


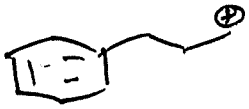
Figure 14.41
The mass spectrum of chlorobenzene.

The answer lies in the phenomenon of fragmentation.





other minor masses include 117 [redacted]

corresponding to  + Br·

What about molecules that contain nitrogen

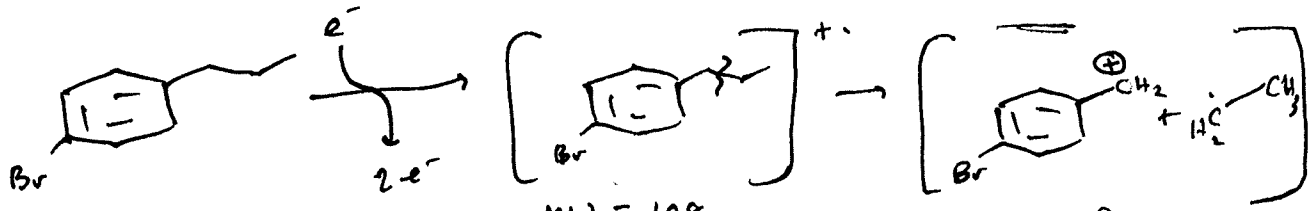

benzene $M/z = 78$

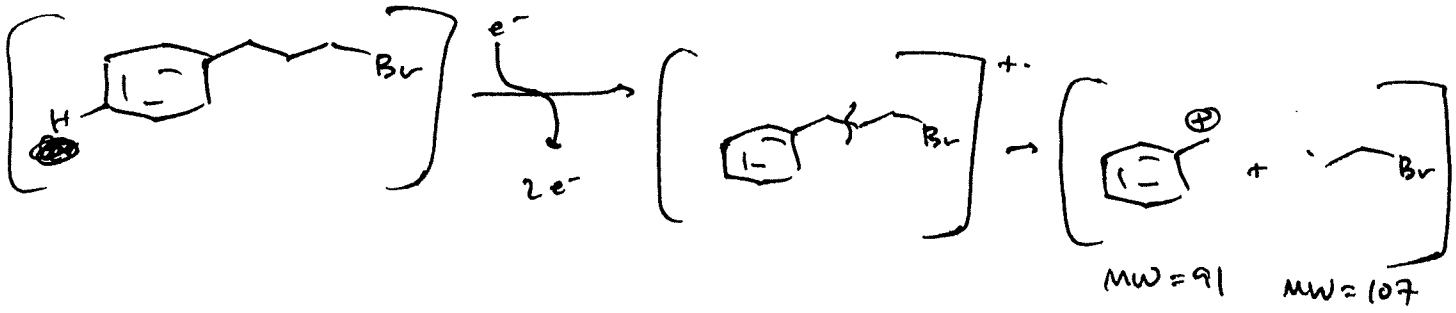

pyridine $M/z = 79$ → This odd number is significant


pyrazine $M/z = 80$ → even # of N means even mass

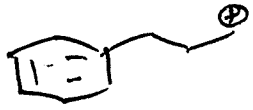
take-away: If a molecule has an odd mass and does not have halogens, it has an odd number of nitrogens.

The answer lies in the phenomenon of fragmentation.





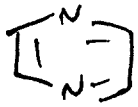
other minor masses include 117 [redacted]

corresponding to  + Br·

What about molecules that contain nitrogen

 benzene $M/z = 78$

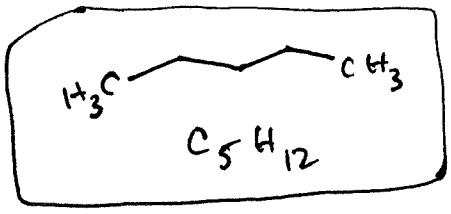
 pyridine $M/z = 79$ → This odd number is significant

 pyrazine $M/z = 80$ → even # of N means even mass

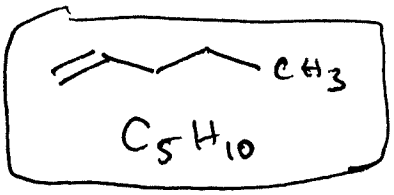
take-away: If a molecule has an odd mass and does not have halogens, it has an odd number of nitrogens.

Degrees of unsaturation and Molecular formulas:

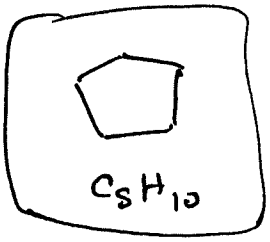
typically, a compound has C_nH_{2n+2} if saturated



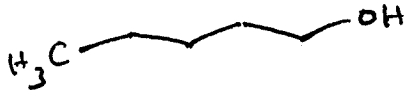
if we take away H_2, we get degree of unsaturation!



we can also make a ring →



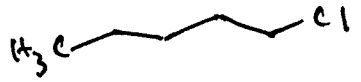
— adding oxygen or sulfur does not change the number of hydrogens

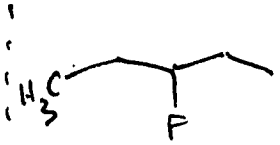


$C_5H_{12}O$ ⋮ 

$C_5H_{12}S$

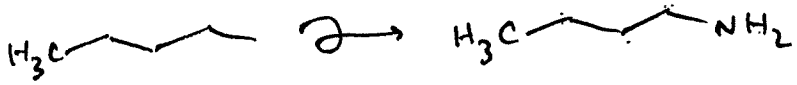
— adding halogens replaces a hydrogen, but is still saturated



$C_5H_{11}Cl$ ⋮ 

$C_5H_{11}F$

— adding a nitrogen for a carbon while still saturated, lacks 1 H



C_5H_{12} $C_4H_{11}N$

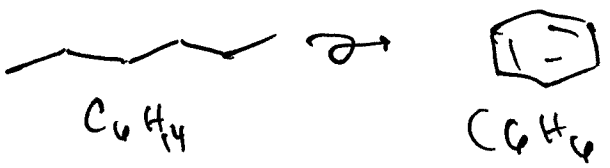
so for a molecular formula like C_6H_6, we do the following:

for 6 C, theoretical # of Hs for saturated is $2n+2 = 14$

the actual number of Hs in the compound is 6 so we are "missing" 8 Hs from being saturated.

since we lose 2 Hs for each unsaturation, $\frac{8}{2} = 4$

* we have four degrees of unsaturation



C_6H_{14} → C_6H_6

three alkenes and one ring is four degrees of unsaturation.

* Consider $C_8H_{13}Br$, how many degrees of unsaturation?

- Br is in place of H, so we act like it is "C_8H_{14}"
- theoretical is C_8H_{18}, and $18-14 = 4$, $4/2 = 2$ degrees of unsaturation.

* consider C_5H_5N,

for compound with N, subtract one H from number of Hs and then do the math. So C_5H_5N → like "C_5H_4"

- theoretical is C_5H_{12}, so $12-4 = 8$, and $8/2 = 4$ degrees of unsaturation

e.g.  C_5H_5N

C_5H_4NBr ≡ 

one ring
three alkenes

C_5H_4NBr

$-H$ for N

↓

"C_5H_3Br"

$+H$ for Br ⟶ "C_5H_4" (4)

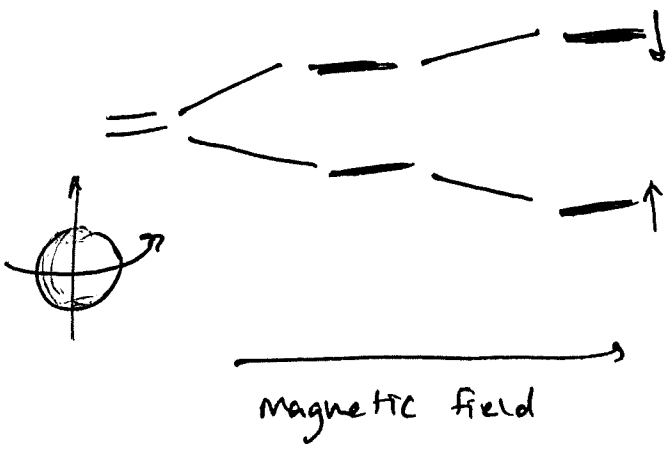
Theoretical for "C_5"

is C_5H_{12} (12)

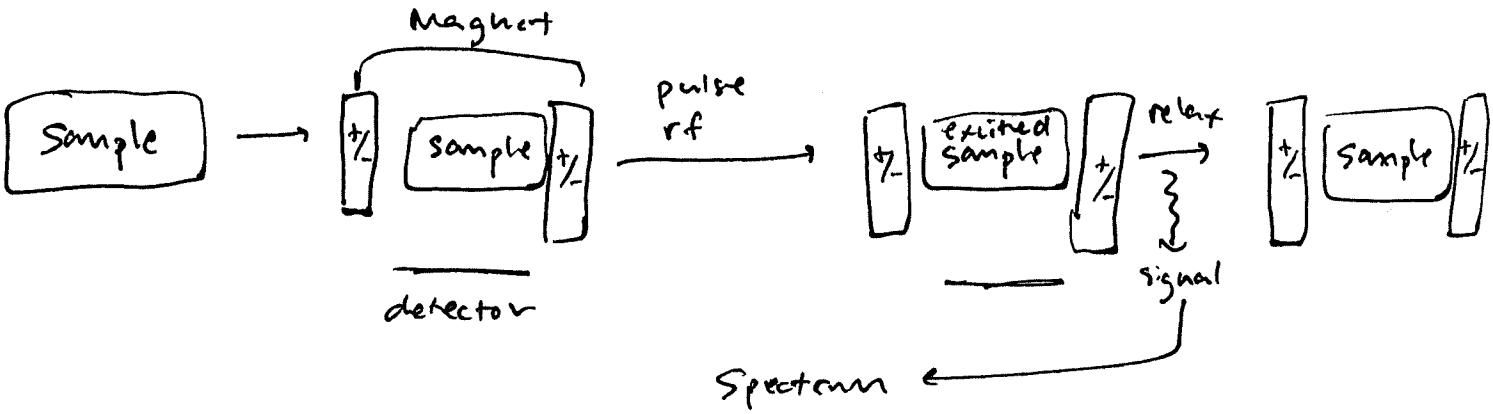
$12 = 2(5) + 2$

$12 - 4 = \frac{8}{2} = 4$ degrees of unsaturation

① We talked about adding energy to bonds earlier with IR spectroscopy, which allowed them to bend and stretch. Now, we will discuss adding energy to atomic nuclei.



upon irradiation with radio waves, the spin of nuclei is altered into differing vectors. They relax and return to their original state and emit a signal (Hz).



the two most informative nuclei in organic molecules are ^{1}H and ^{13}C!

②

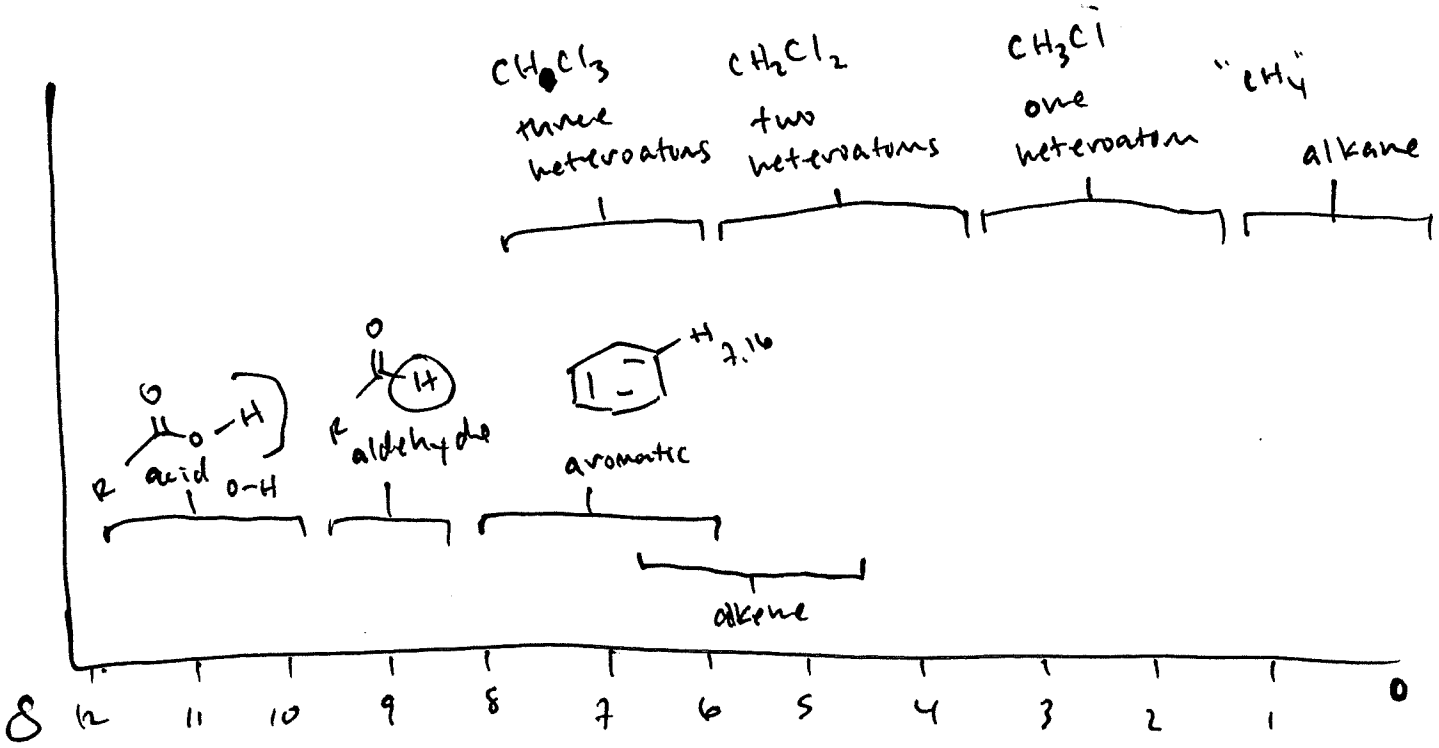
^{1}H NMR

The signal given by a particular ^{1}H nucleus if affected by its electronic environment. This is referred to as "shielding". The more shielded a proton is, the more "upfield" the signal occurs in the spectrum. The range for ^{1}H signals is about 0–15 ppm relative to Me_4Si (TMS) which is situated at 0 ppm.

ppm is a normalized unit for different spectrometer strengh

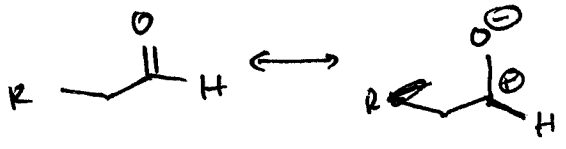
Hz ∝ ppm

③ A ^1H NMR spectrum (chemical shift)



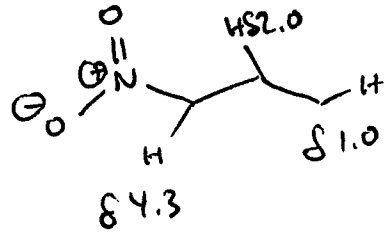
more "deshielded"

more "shielded"



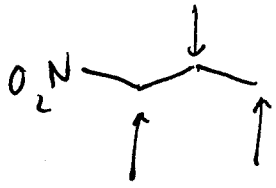
hydrogen connected to [redacted]
electron deficient carbon

Consider:



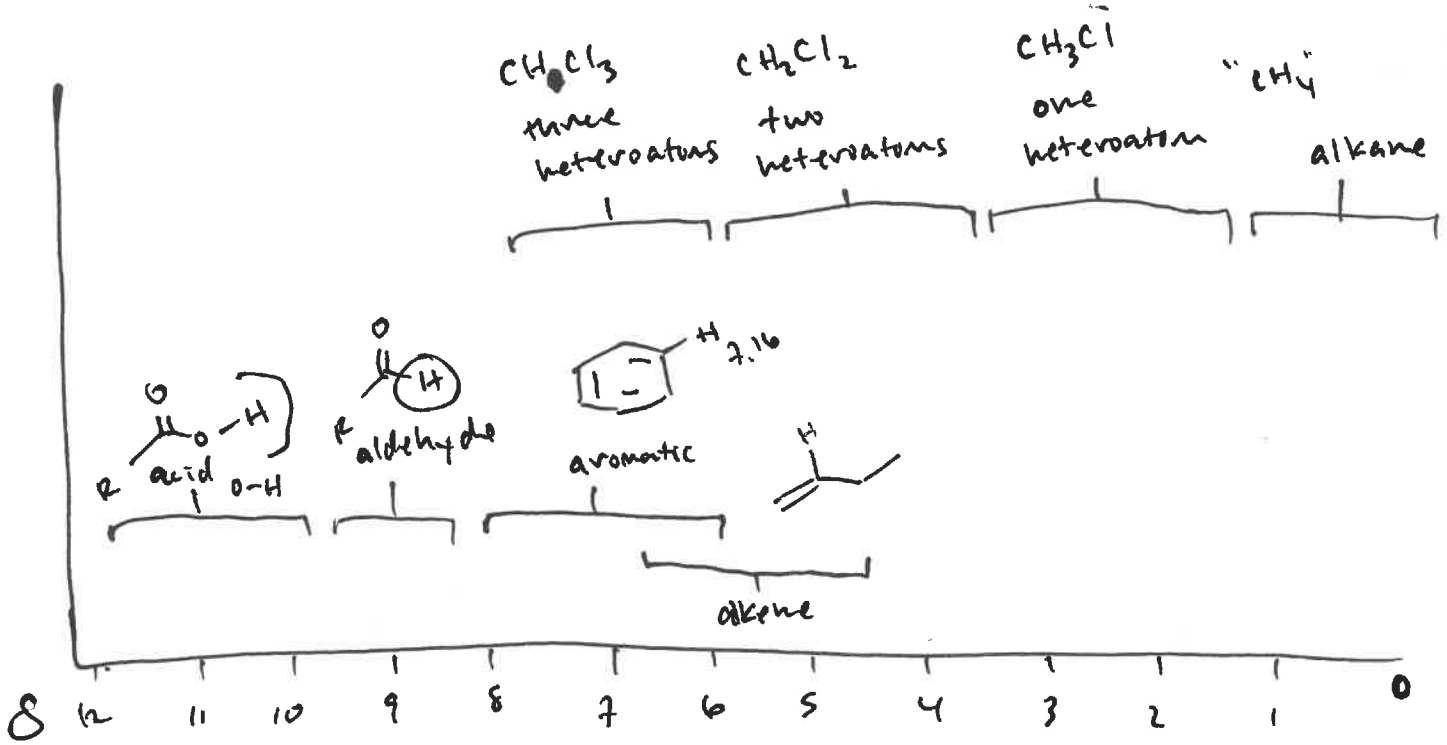
Shielding increases when farther away from e⁻-withdrawing group like $-NO_2$

^1H equivalency and signals



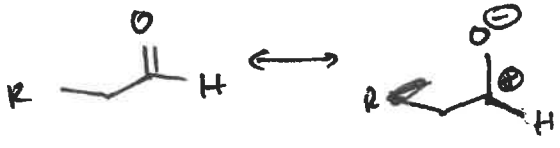
the hydrogens on each of these carbons are different, but hydrogen on same carbon in nitro propane are equivalent

③ A ^1H NMR spectrum (chemical shift)



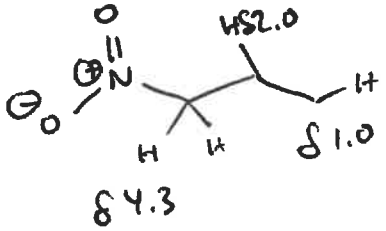
more "deshielded"

more "shielded"



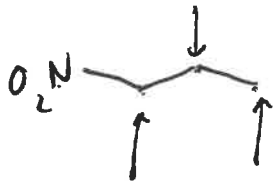
hydrogen connected to [redacted] electron deficient carbon

Consider:



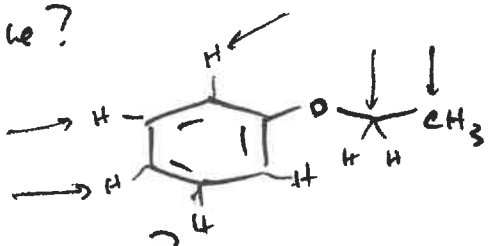
Shielding increases when farther away from e⁻-withdrawing group like $-NO_2$

^1H equivalency and signals



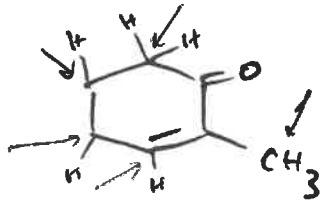
the hydrogens on each of these carbons are different, but hydrogen on same carbon in nitro propane are equivalent

example: how many chemically distinct hydrogens are in this molecule?



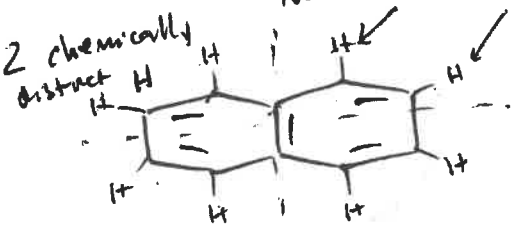
5 chemically distinct protons

how about this one?



5 distinct hydrogens

or this one? Mothballs

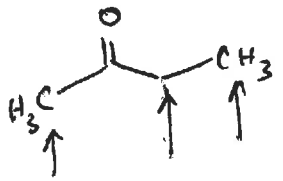


2 chemically distinct H

thus, recognizing molecular symmetry is essential!

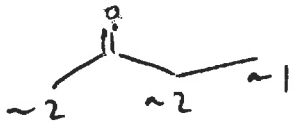
(4) Combining and predicting distict 'Hs with chemical shift

Consider:



how many distinct hydrogens? 3

what is the expected chemical shift?



~~how~~ ~~does~~ what does the spectrum look like?

why are some signals split and others not?

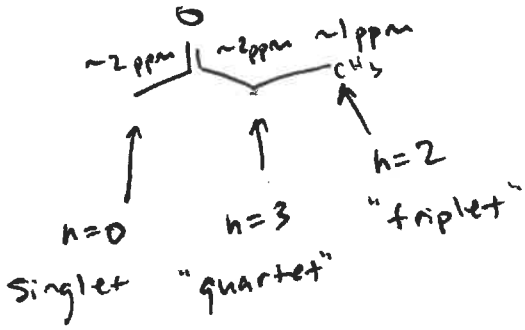
(5) the answer lies in chemical splitting.

The neighboring hydrogens to a chemically distinct hydrogens will "split" a peak.

thus, for each neighboring hydrogen, the n+1 rule applies for the particular peak in question. in this expression, n is the number of neighboring hydrogens, and n+1 is the splitting pattern of the peaks.

as a result: 0 neighboring H → peak is "singlet"
1 neighboring H → peak is "doublet"
2 " H → " is "triplet"
3 " H → " is "quartet"

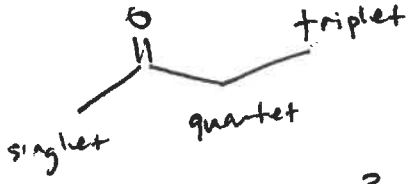
so, if we return to our earlier example:



so then the spectrum has three peaks, identifiable as a singlet, a quartet, and a triplet.

(6) There is also another aspect as well, though. Did you notice the line that looked like a calculus integral?

The area underneath each peak in the spectrum corresponds to the number of hydrogens encompassed by that peak. so in the prior example



relative integration: 3 2 3

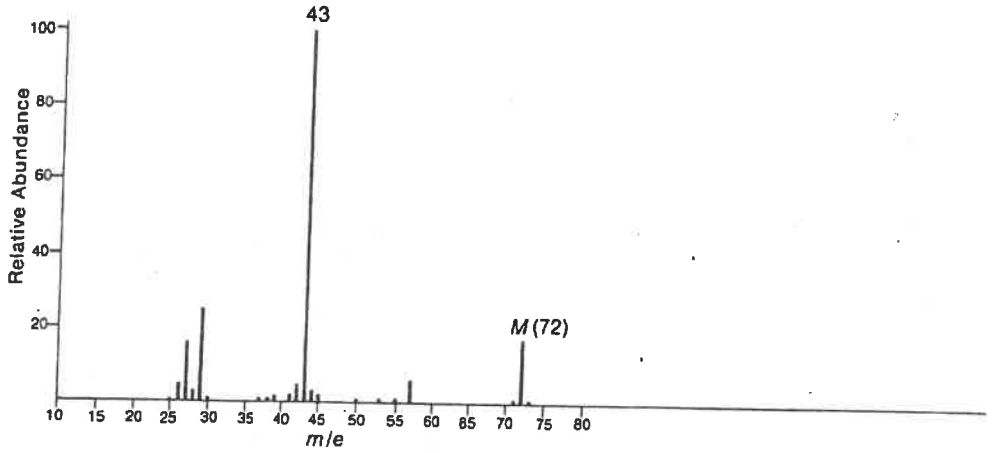
so, in all we have several levels of information in one spectrum:
- chemically distinct Hs (# of peaks)
- chemical shift
- splitting pattern (neighboring Hs)
- integration (# of hydrogens)

PROBLEMS

(*1.) The UV spectrum of this compound is determined in 95% ethanol: λ_{max} 290 nm (log ε 1.3).

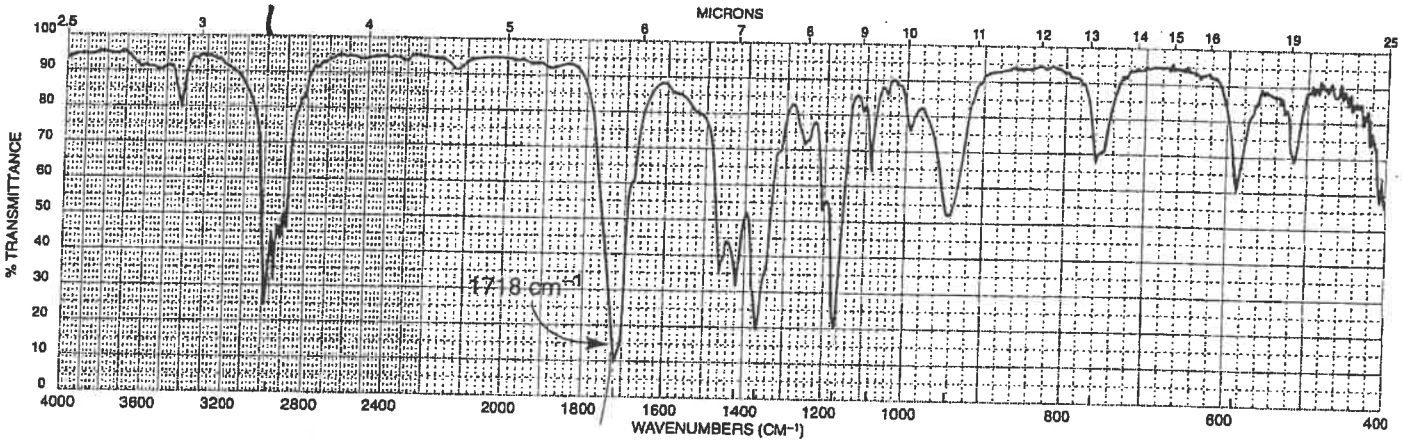
a)

Mass Spectrum

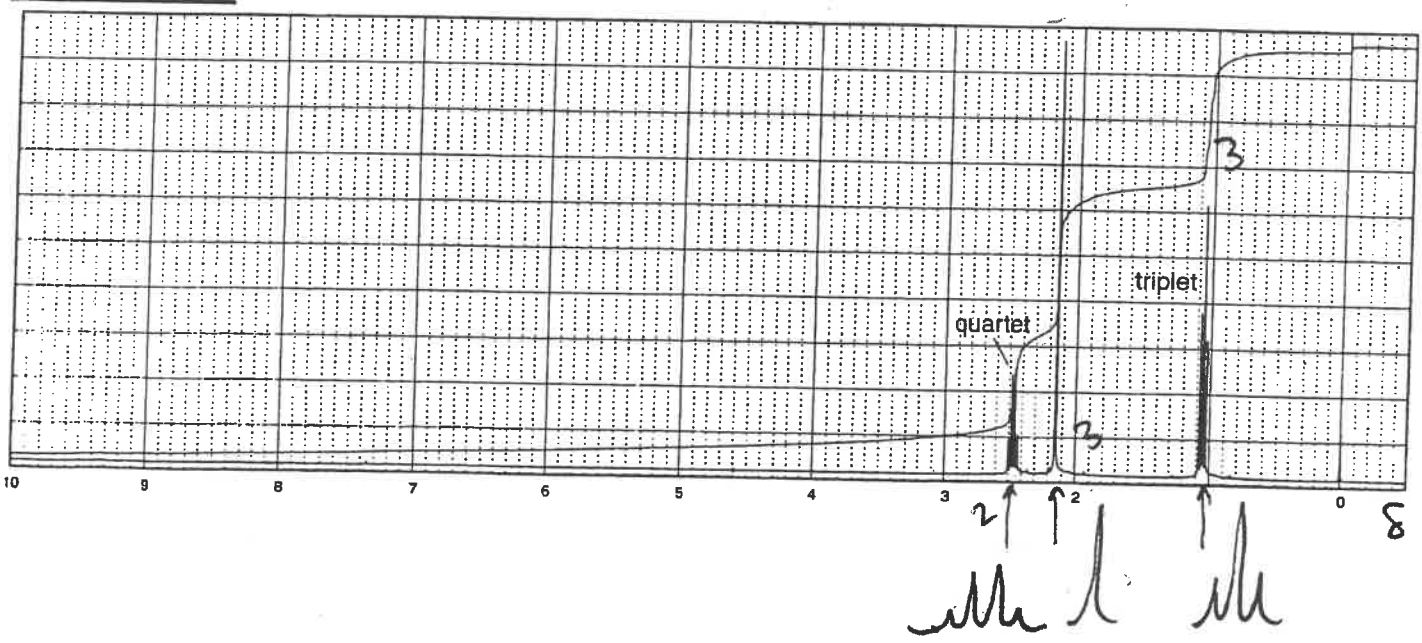


IR

b) 3000 cm⁻¹



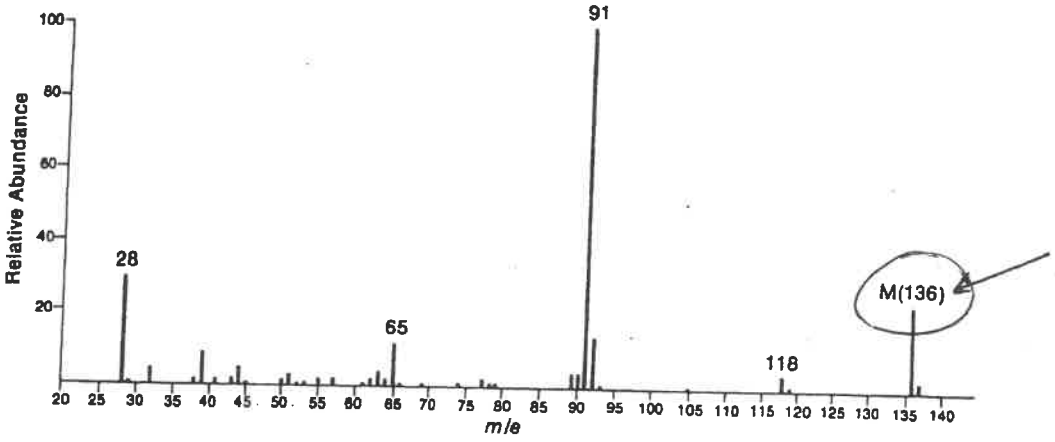
H-1 NMR c)



(*5.) ~~The UV spectrum of this compound is determined in 95% ethanol~~: strong end absorption and a band with fine structure appearing at λ_{max} 257 nm (log ε 2.4). The IR spectrum was obtained as a Nujol mull. The strong bands at about 2920 and 2860 cm^{-1} from the C–H stretch in Nujol overlap the broad band that extends from 3300 to 2500 cm^{-1}.

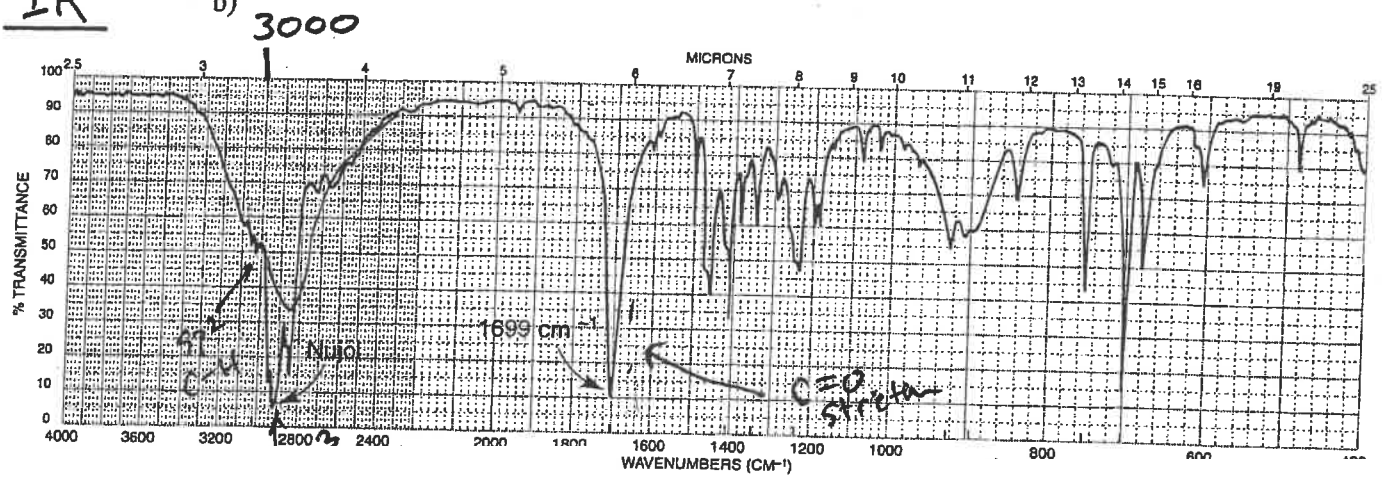
a)

Mass Spectrum

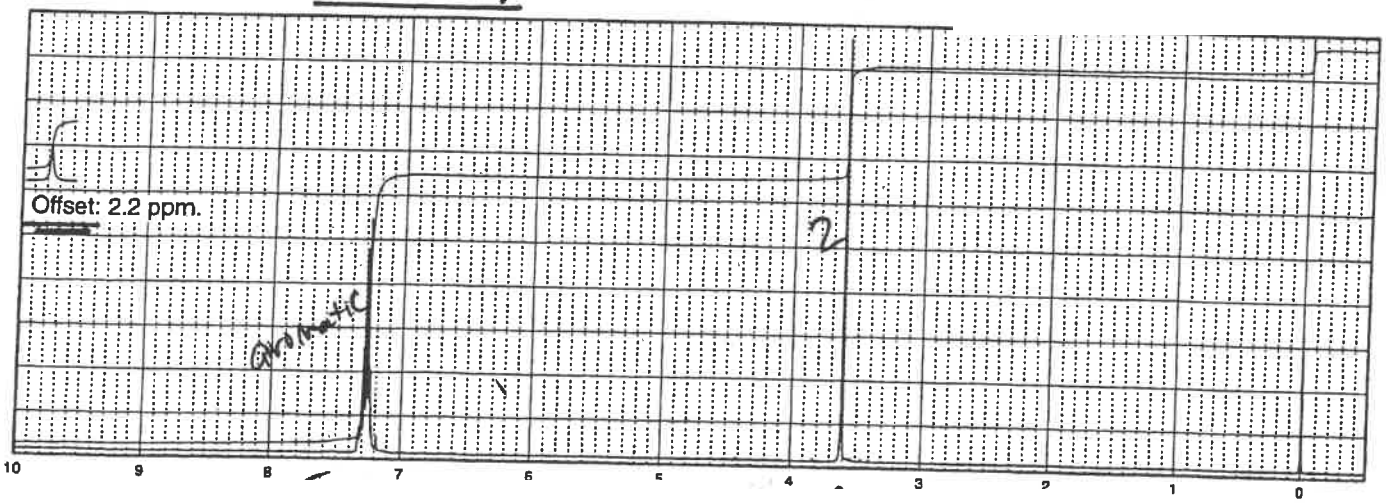


IR

b)

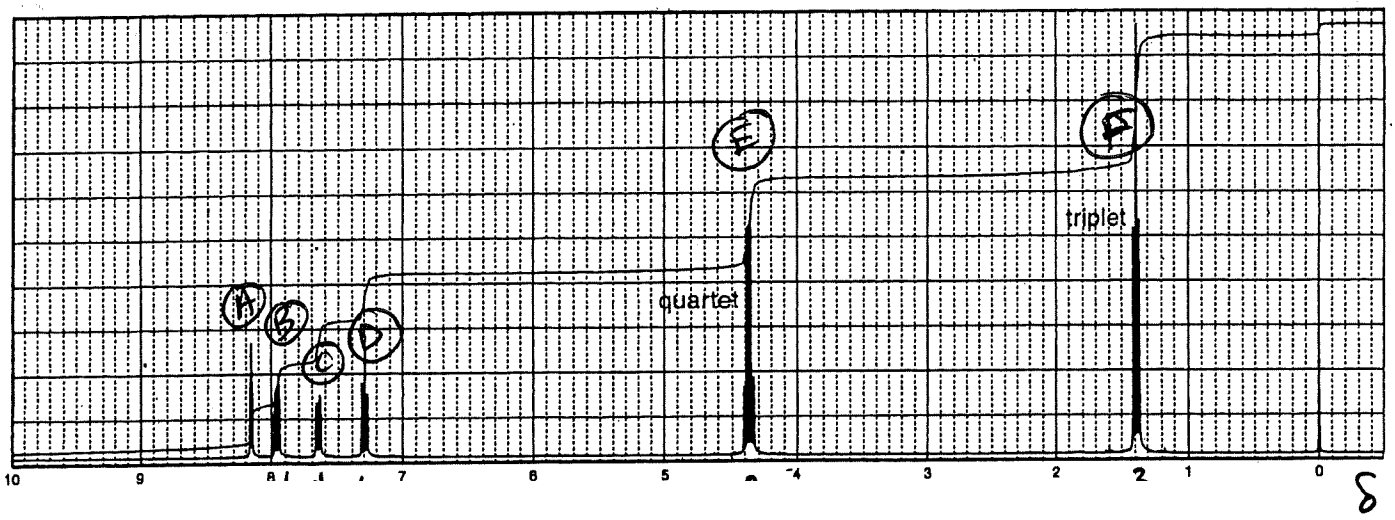


c) H-1 NMR

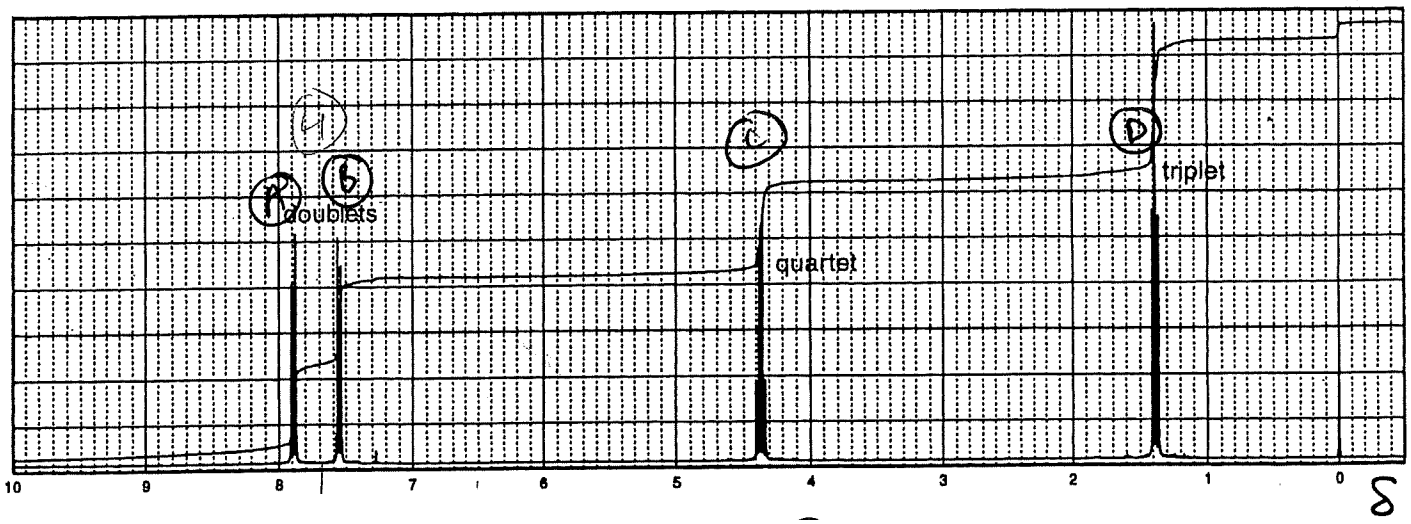


*8. Determine the structures of the isomeric compounds that show strong infrared bands at 1725 cm^{-1} and several strong bands in the range 1300–1200 cm^{-1}. Each isomer has the formula $C_9H_9BrO_2$. Following are the proton NMR spectra for both compounds, ***A*** and ***B***. Expansions have been included for the region from 8.2 to 7.2 ppm for compound ***A***.

H-1 NMR (A.)



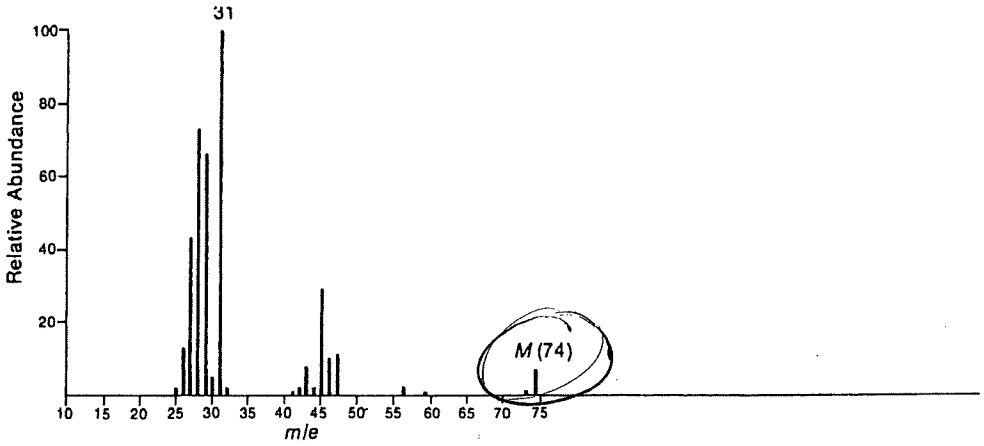
H-1 NMR (B.)



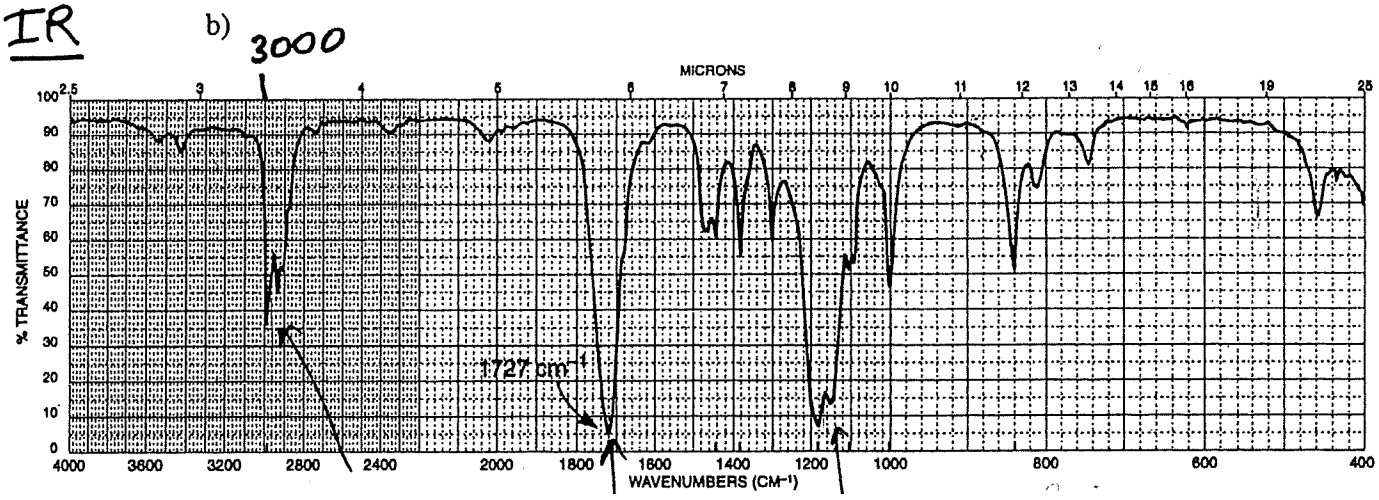
*11 This compound has the formula $C_3H_6O_2$. The UV spectrum of this compound shows no maximum above 205 nm. The carbon NMR spectrum shows peaks at 14, 60, and 161 ppm. The peak at 161 ppm appears as a positive peak in the DEPT-90 spectrum.

a)

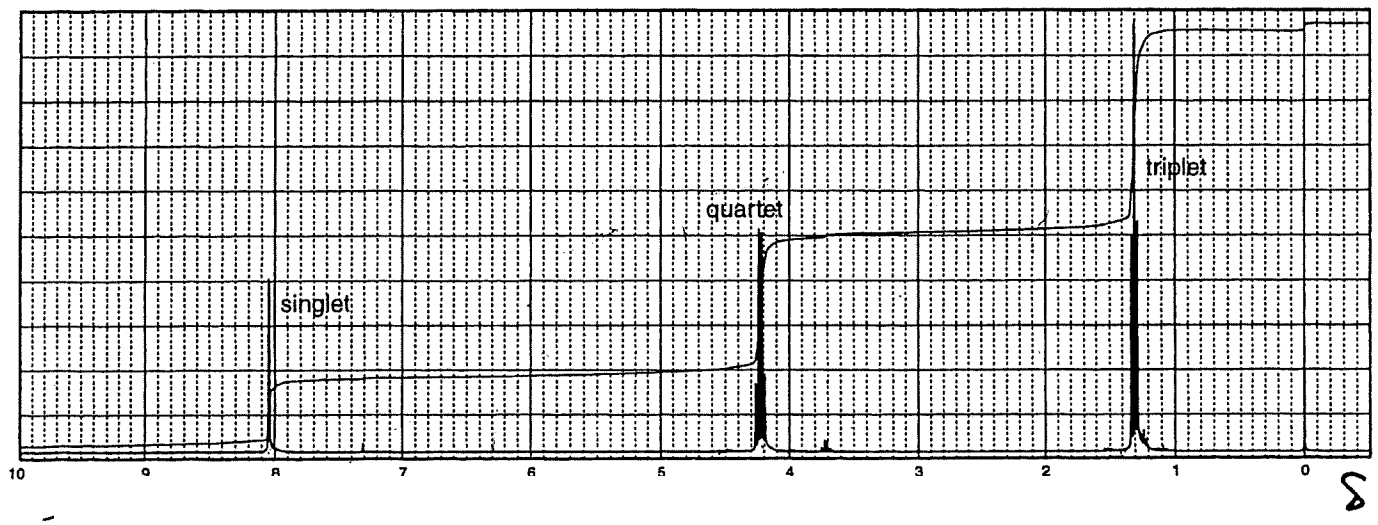
Mass Spectrum



IR b)

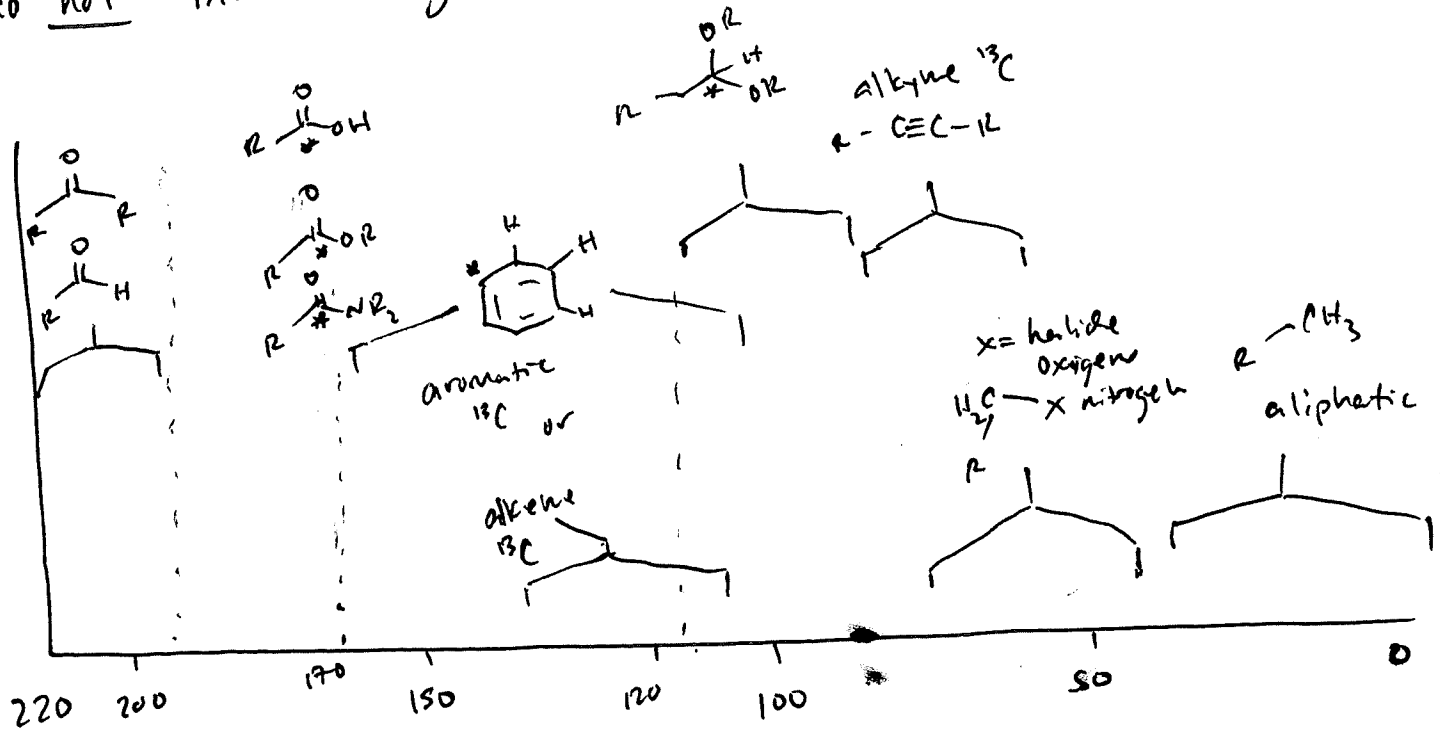


H-1 NMR c)

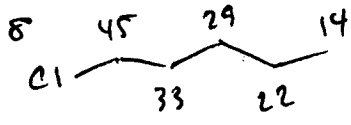


^{13}C NMR

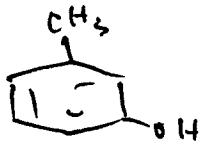
^{13}C NMR is very similar to ^{1}H NMR in that each chemically distinct C has a particular peak in a spectrum. However, ^{13}C NMR spectra do not typically have splitting patterns and do not involve integration.



There will be one sharp peak in the spectrum for each chemically distinct carbon in the molecule.

e.g. 

the electron-withdrawing Cl has a "distance-effect" on ^{13}C shift.

Consider this molecule:  meta-cresol

* carbons that have H attached to them tend to have "stronger" signals in the ^{13}C NMR spectrum.

We will have more to say about ^{13}C chemical shifts in later chapters when various families of compounds are discussed in more detail.

14.16 ^{13}C NMR and Peak Intensities

Two features that are fundamental to ^{1}H NMR spectroscopy—integrated areas and splitting patterns—are much less important in ^{13}C NMR.

Although it is a simple matter to integrate ^{13}C signals, it is rarely done because the observed ratios can be more misleading than helpful. The pulsed FT technique that is standard for ^{13}C NMR has the side effect of distorting the signal intensities, especially for carbons that lack attached hydrogens. Examine Figure 14.26, which shows the ^{13}C NMR spectrum of 3-methylphenol (*m*-cresol). Notice that, contrary to what we might expect for a compound with seven peaks for seven different carbons, the intensities of these peaks are not nearly the same. The two least intense signals, those at δ 140 and δ 157, correspond to carbons that lack attached hydrogens.

Problem 14.20

To which of the compounds of Problem 14.16 does the ^{13}C NMR spectrum of Figure 14.27 belong?

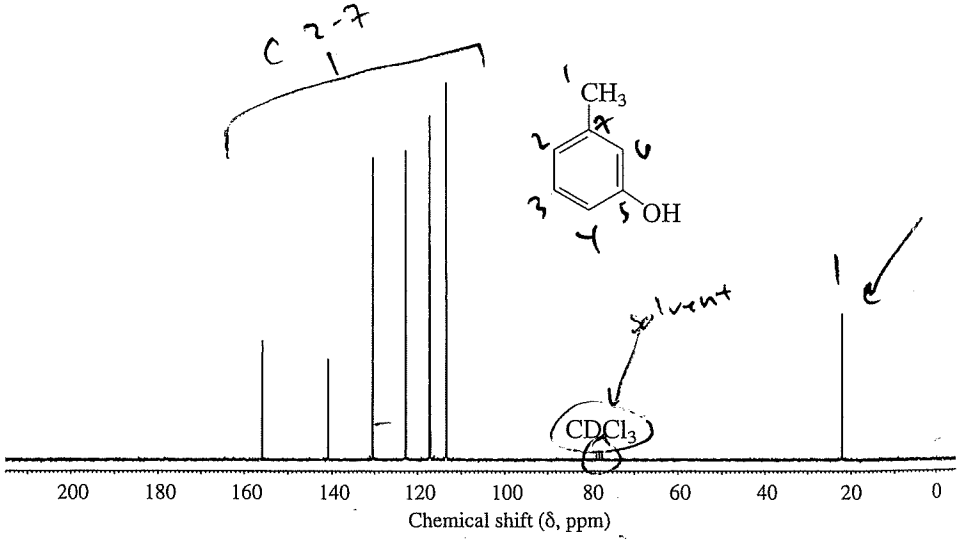


Figure 14.26

The ^{13}C NMR spectrum of *m*-cresol. Each of the seven carbons gives a separate peak. Integrating the spectrum would not provide useful information because the intensities of the peaks are so different, even though each one corresponds to a single carbon.

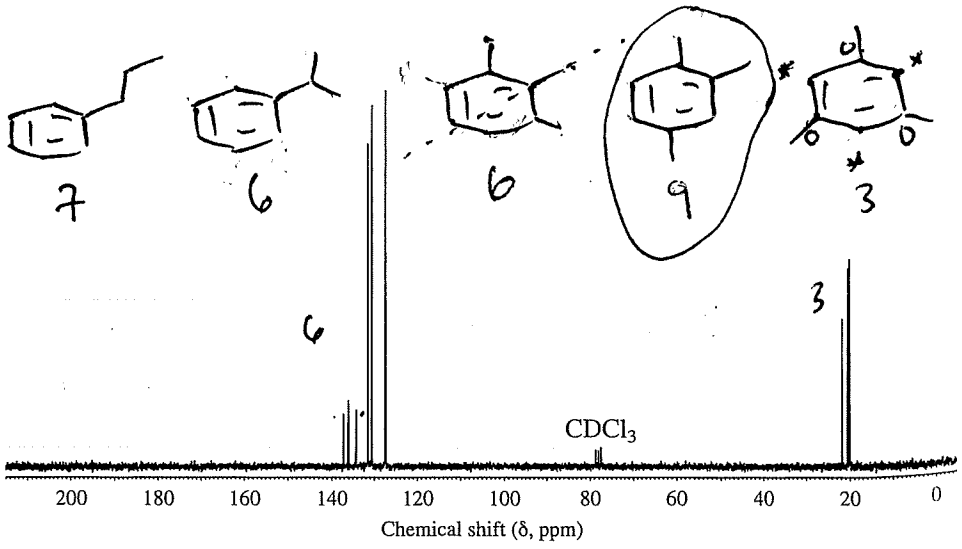


Figure 14.27

The ^{13}C NMR spectrum of the unknown compound of Problem 14.20.

TABLE 14.2 Chemical Shifts of Representative Carbons

Type of carbon	Chemical shift (δ) ppm*	Type of carbon	Chemical shift (δ) ppm*
Hydrocarbons		**Functionally substituted carbons**	
RCH_3	0–35	RCH_2Br	20–40
R_2CH_2	15–40	RCH_2Cl	25–50
R_3CH	25–50	RCH_2NH_2	35–50
R_4C	30–40	RCH_2OH and RCH_2OR	50–65
$RC{\equiv}CR$	65–90	$RC{\equiv}N$	110–125
$R_2C{=}CR_2$	100–150	$RCOH$ and $RCOR$	160–185
	110–175	RCH and RCR	190–220

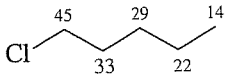
*Approximate values relative to tetramethylsilane.

Likewise, for functionally substituted methyl groups:

	CH_3F	CH_3OH	CH_3NH_2	CH_4
Chemical shift (δ), ppm:				
H	4.3	3.4	2.5	0.2
C	75	50	27	−2

Figure 14.25 compared the appearance of the ^1H and ^{13}C NMR spectra of 1-chloropentane and drew attention to the fact each carbon gave a separate peak, well separated from the others. Let's now take a closer look at the ^{13}C NMR spectrum of 1-chloropentane with respect to assigning these peaks to individual carbons.

^{13}C chemical shift (δ), ppm:

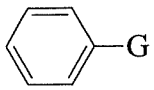


The most obvious feature of these ^{13}C chemical shifts is that the closer the carbon is to the electronegative chlorine, the more deshielded it is. Peak assignments will not always be this easy, but the correspondence with electronegativity is so pronounced that *spectrum simulators* are available that allow reliable prediction of ^{13}C chemical shifts from structural formulas. These simulators are based on arithmetic formulas that combine experimentally derived chemical-shift increments for the various structural units within a molecule.

Problem 14.17

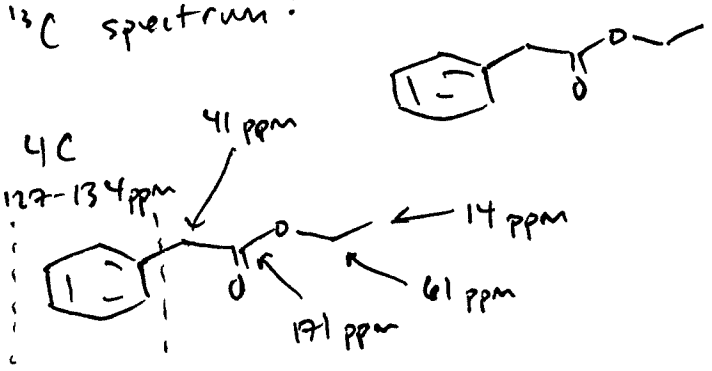
The ^{13}C NMR spectrum of 1-bromo-3-chloropropane contains peaks at δ 30, δ 35, and δ 43. Assign these signals to the appropriate carbons.

The effects of substituents on rate and orientation in electrophilic aromatic substitution described in Chapter 13 find parallels in their effect on the chemical shifts of aromatic ring carbons. For the group of compounds represented as



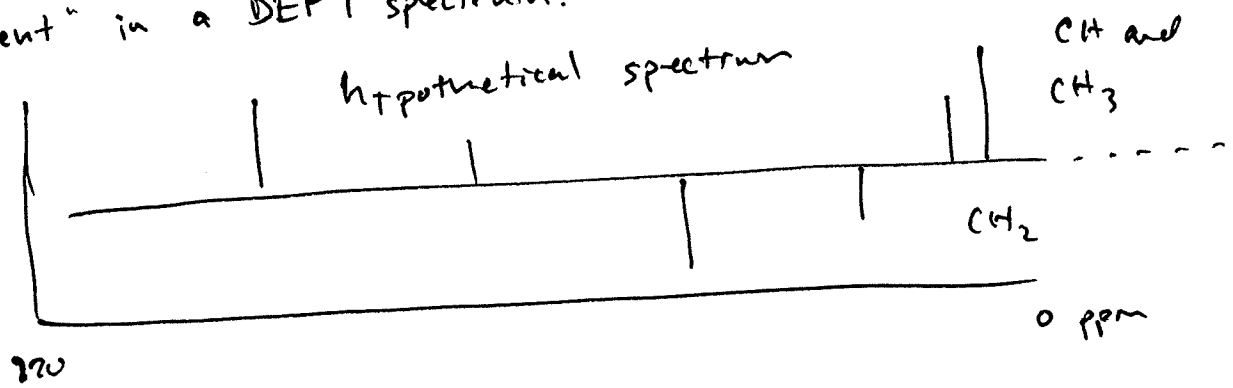
the ^{13}C chemical shift of the para carbon is observed to correlate with the *o-p* versus *m*-directing effects of substituent G. Since shielding in NMR results from the local magnetic

predict the NMR shifts for the following molecule for its ^{13}C spectrum:



DEPT NMR

a variant of ^{13}C NMR is DEPT NMR where a correlation between the number of hydrogens on a carbon can be observed. Carbons that have no hydrogens connected are "silent" in a DEPT spectrum.



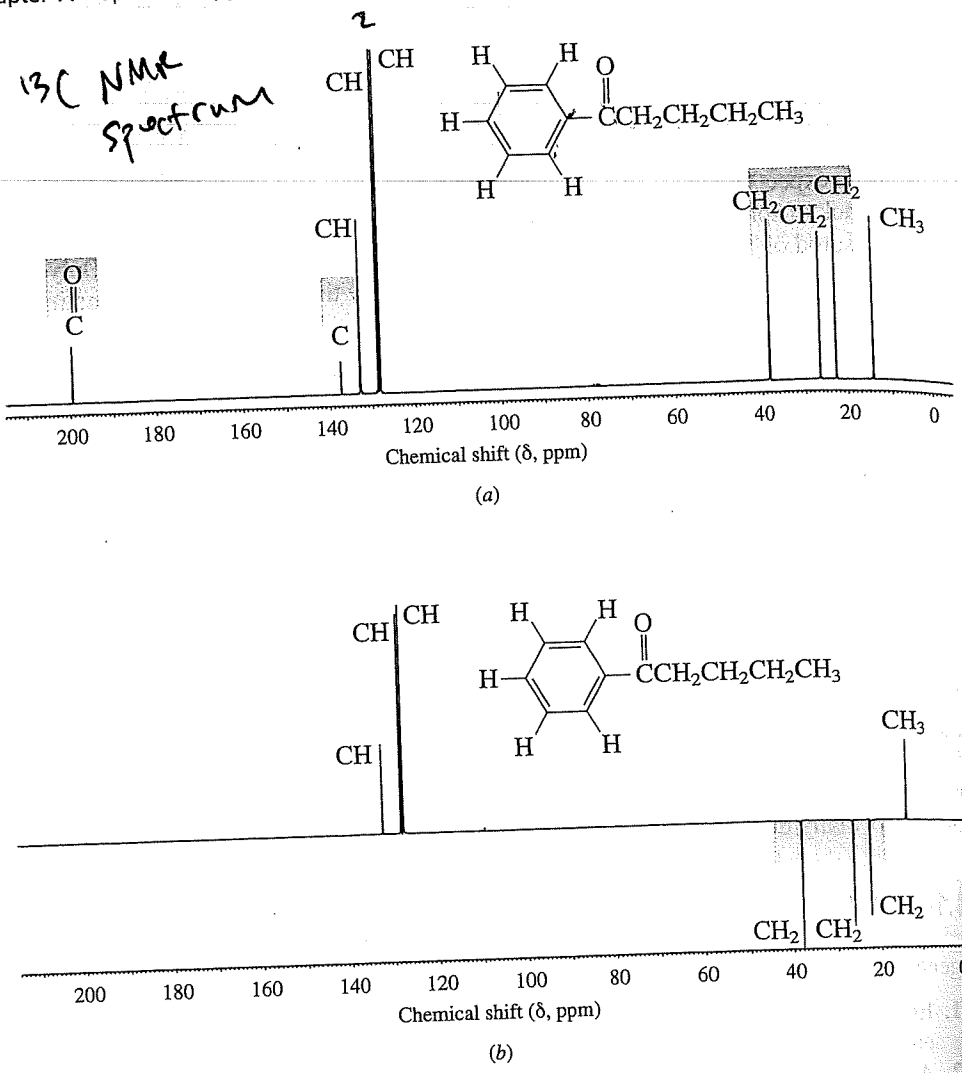


Figure 14.28

^{13}C NMR spectra of 1-phenyl-1-pentanone. (*a*) Normal spectrum. (*b*) DEPT spectrum recorded using a pulse sequence in which CH_3 and CH carbons appear as positive peaks, CH_2 carbons as negative peaks, and carbons without any attached hydrogens are nulled.

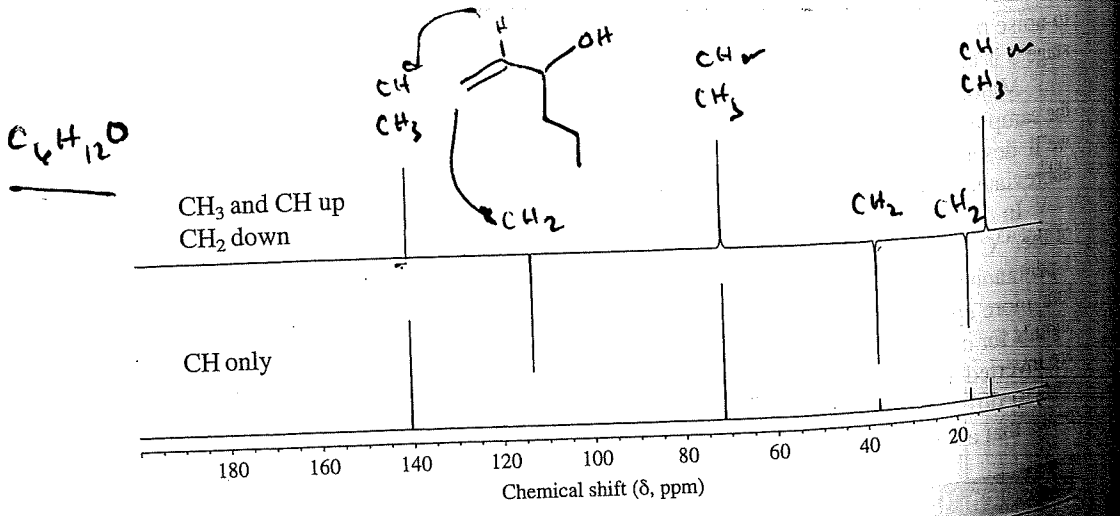


Figure 14.29

DEPT spectra for Problem 14.21.

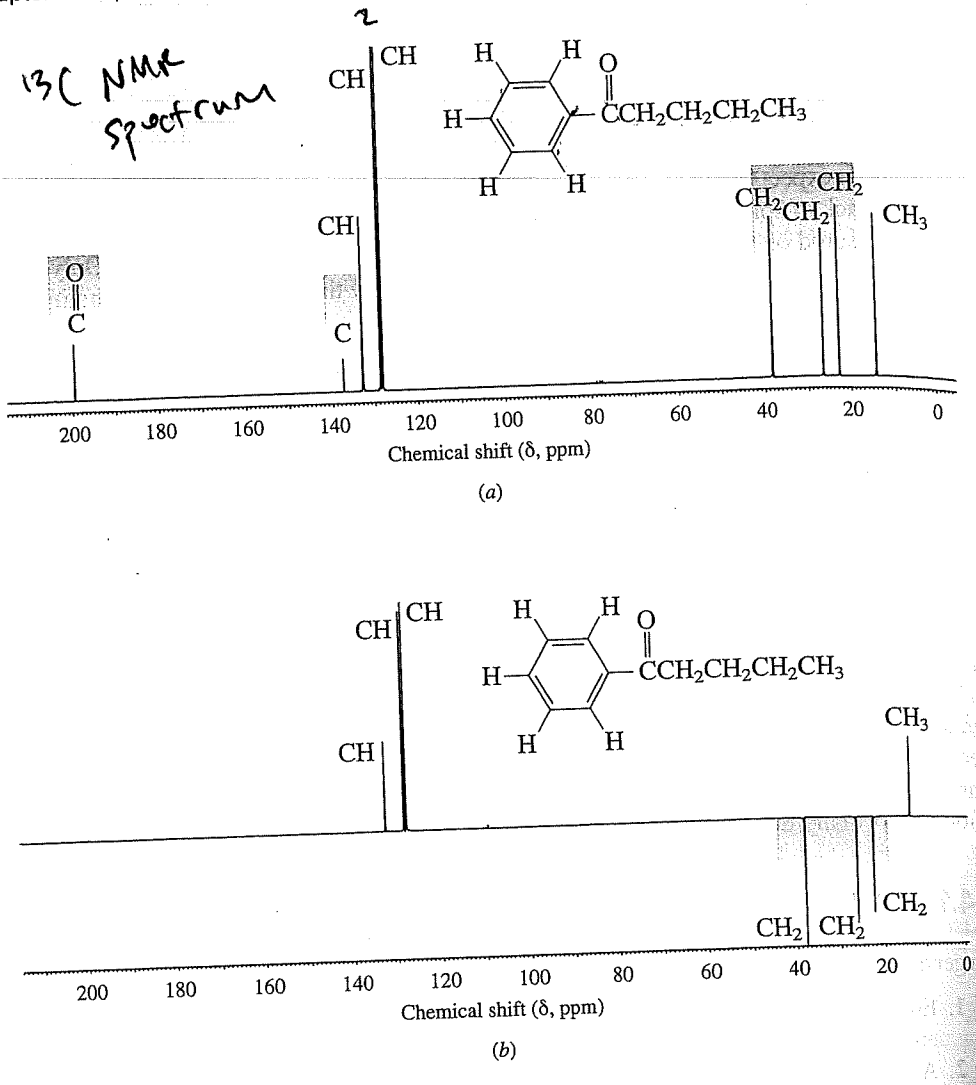


Figure 14.28

^{13}C NMR spectra of 1-phenyl-1-pentanone. (*a*) Normal spectrum. (*b*) DEPT spectrum recorded using a pulse sequence in which CH_3 and CH carbons appear as positive peaks, CH_2 carbons as negative peaks, and carbons without any attached hydrogens are nulled.

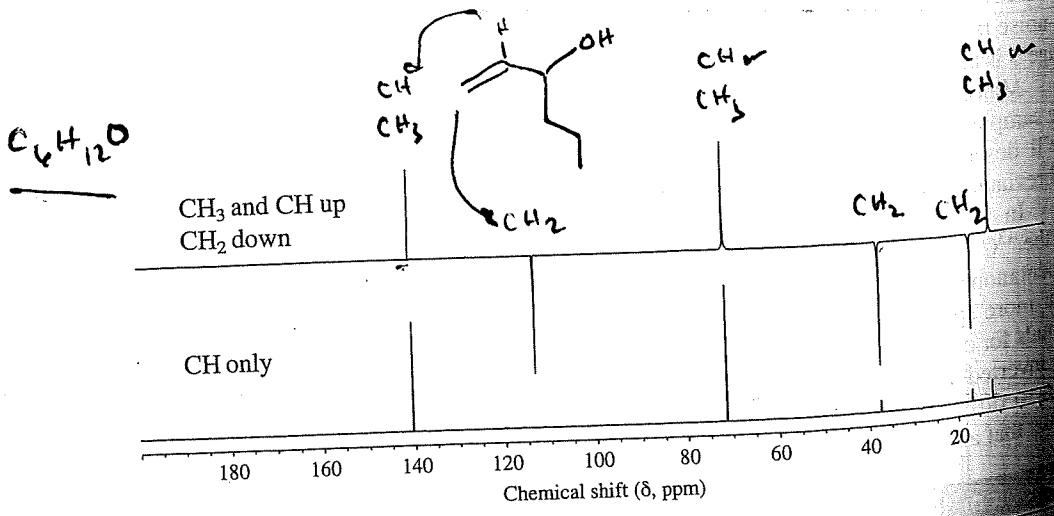
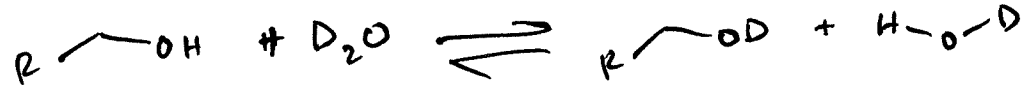


Figure 14.29

DEPT spectra for Problem 14.21.

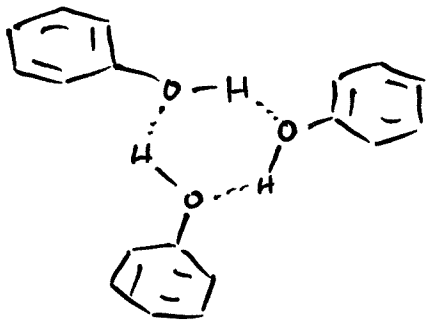
^{1}H NMR – The finer details

Most protons connected to heteroatoms have an equilibrium with protons on other molecules around them.



D = deuterium, ^{2}H

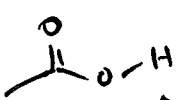
alcohols can also hydrogen bond with each other...



as a result, Hs connected to heteroatoms (O, N, S...) usually do not split with neighboring hydrogens.

these usually just show up as broad singlets.

generally, chemical shift will correspond with pka



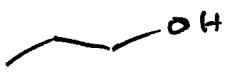
↑

δ = ~12-13

pka = 5

δ = ~8-10

pka = 9



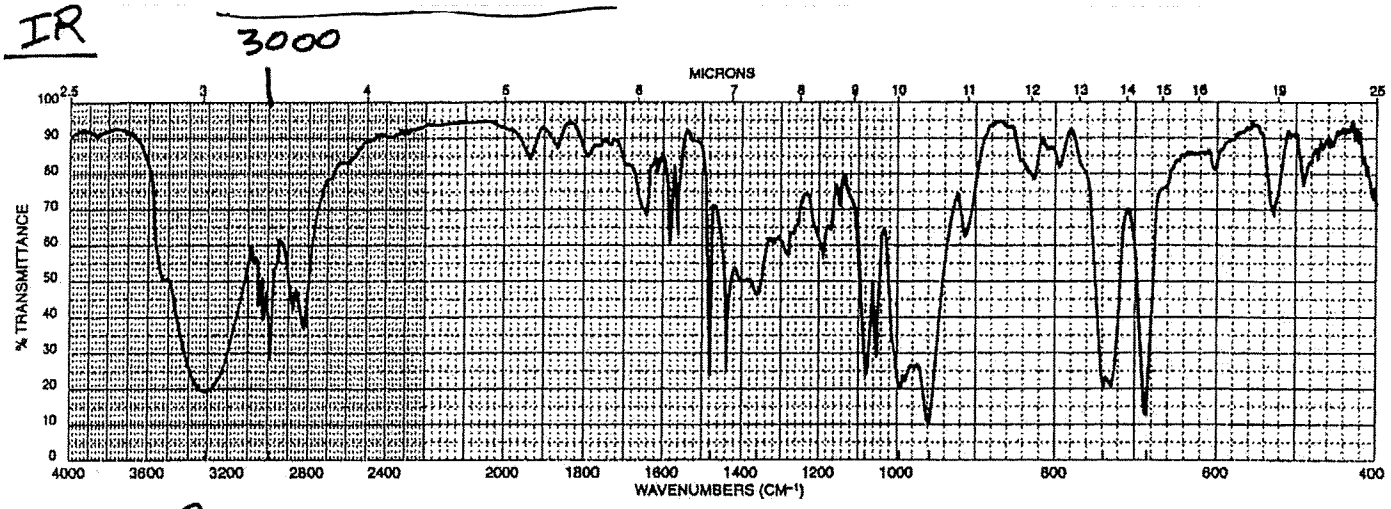
δ = ~1-5

pka = 16

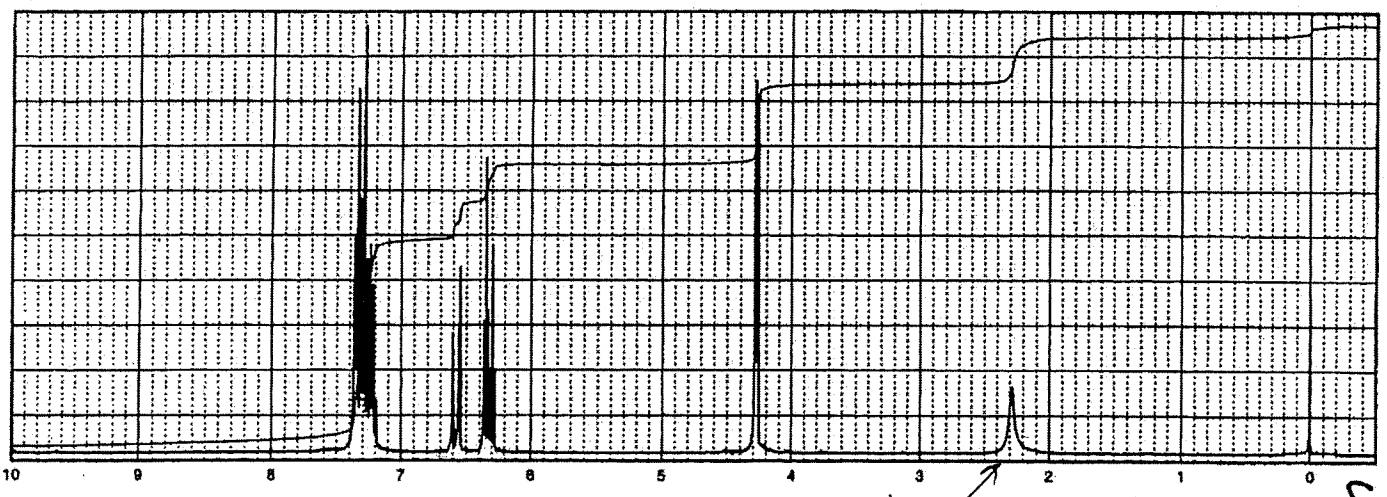
amine N-H peaks appear very similarly in most cases.

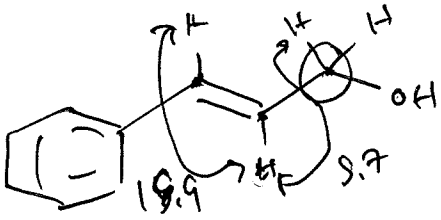
21. This compound has the molecular formula $C_9H_{10}O$. We have supplied you with the IR and proton NMR spectra. The expansions of the interesting sets of peaks centering near 4.3, 6.35, and 6.6 ppm in the proton NMR are provided, as well. Do not attempt to interpret the messy pattern near 7.4 ppm for the aromatic protons. The broad peak at 2.3 ppm (one proton) is solvent and concentration dependent.

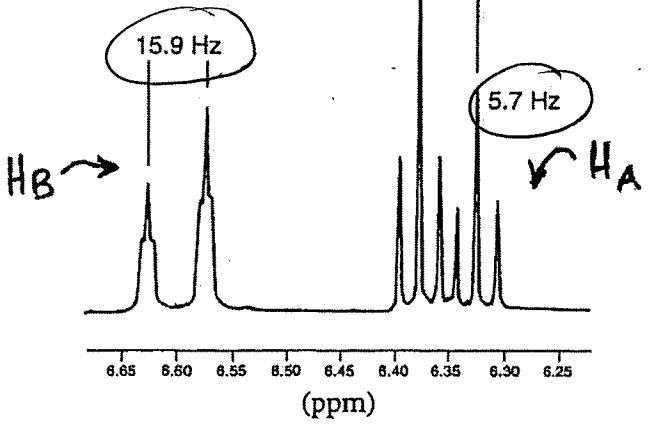
IR

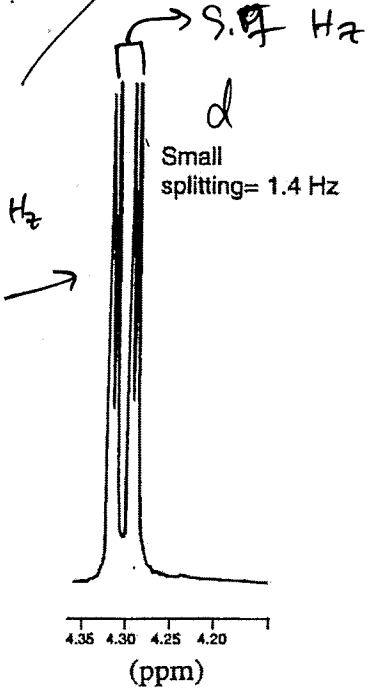


H-1 NMR



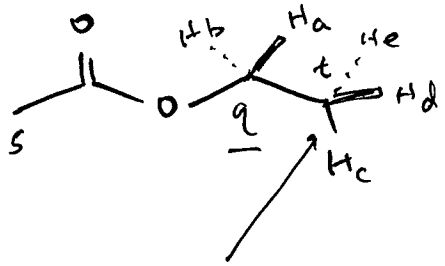


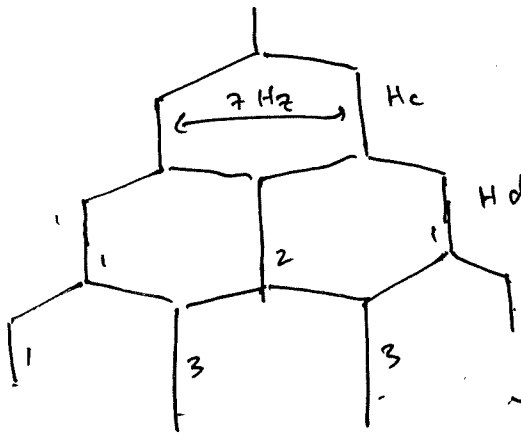




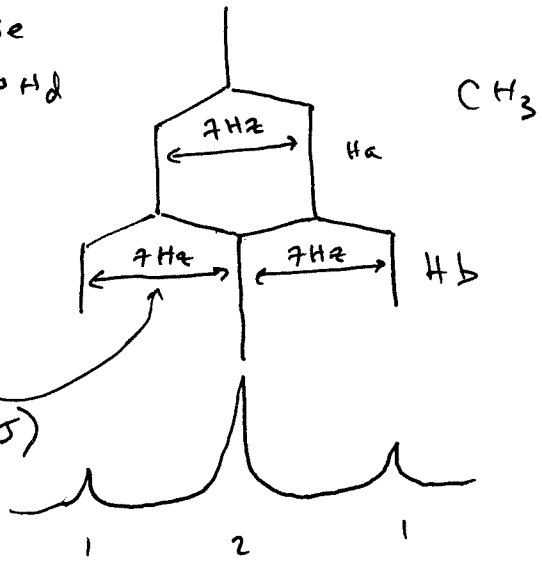
Complex splitting patterns (hybridization)

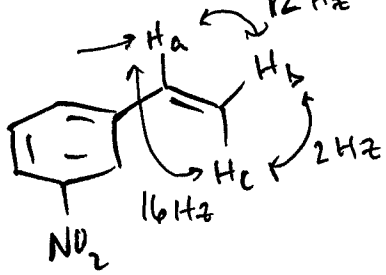
Consider:





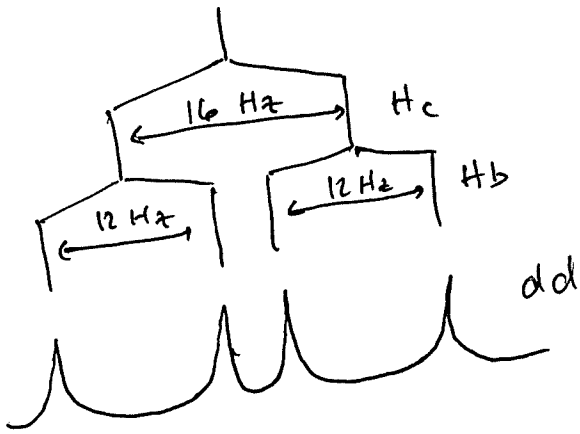
Coupling constants (J)





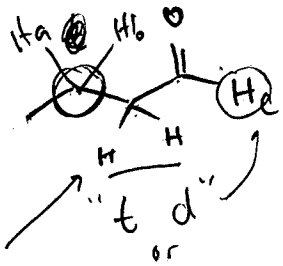
Now consider:

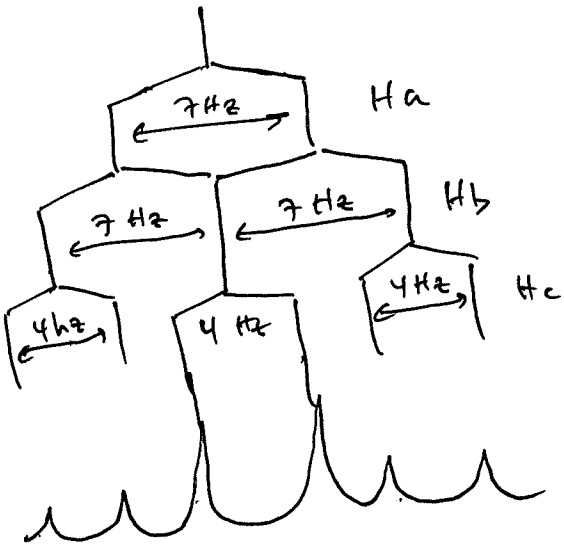
Consider the splitting pattern for Ha



"doublet of doublets"

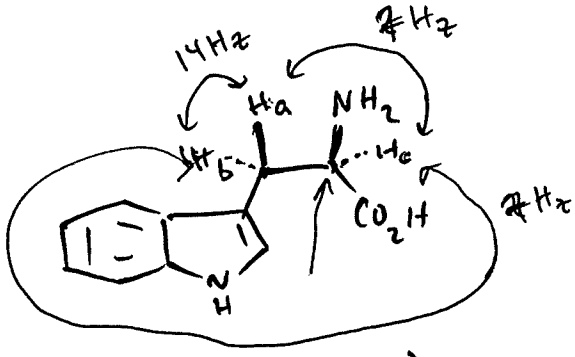
Consider:





Complex splitting patterns (stereocenters)

consider:

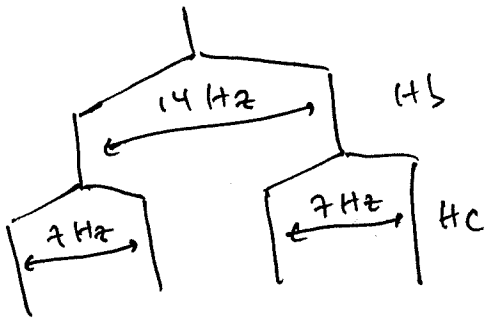


tryptophan (amino acid)

These hydrogens will have different environments.

As a result they will split each other!

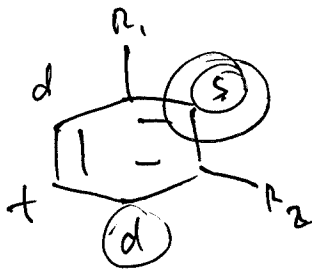
for Ha:



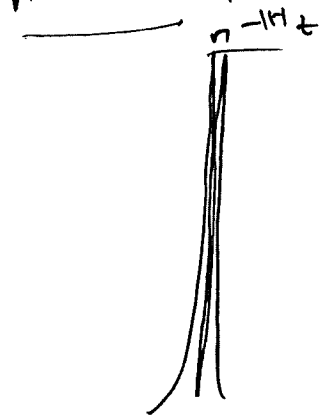
dd

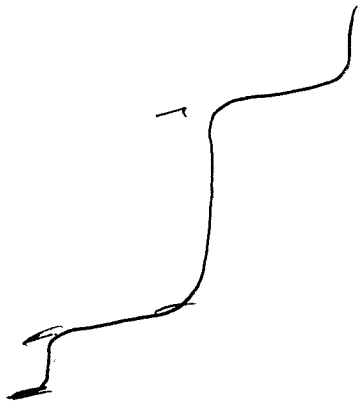
Hb will also have a similar splitting pattern.

Hc will also have a very similar splitting pattern.



meta-coupling





Retrosynthetic Analysis

The process by which a target molecule is "reverse-engineered" into simpler fragments by logical disconnections or fragmentations.

Consider: when building a house, what is the last thing you would construct or put in place?

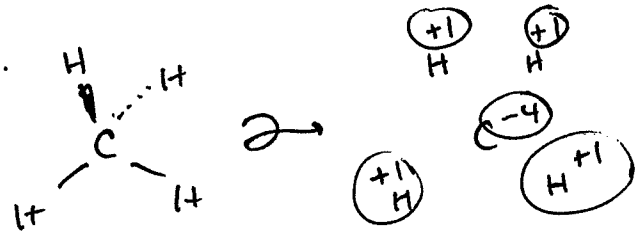
– Paint? Furniture? The point is that one would not put the roof or foundation in last!

– It would be like designing the IKEA furniture assembly instructions if presented with the final product!

① Understanding oxidation levels in organic chemistry.

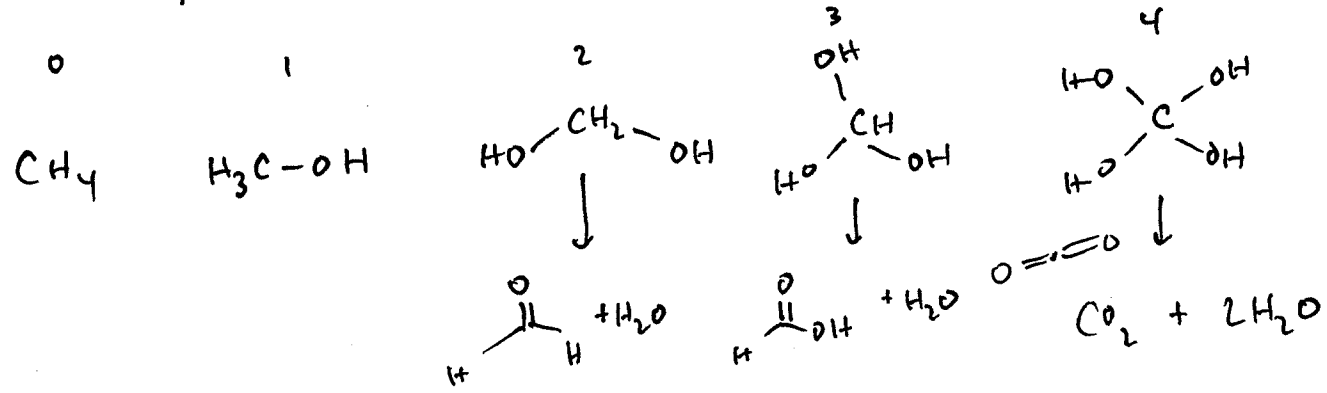
typically when we think of oxidation state C and H are treated differently.

Consider methane:

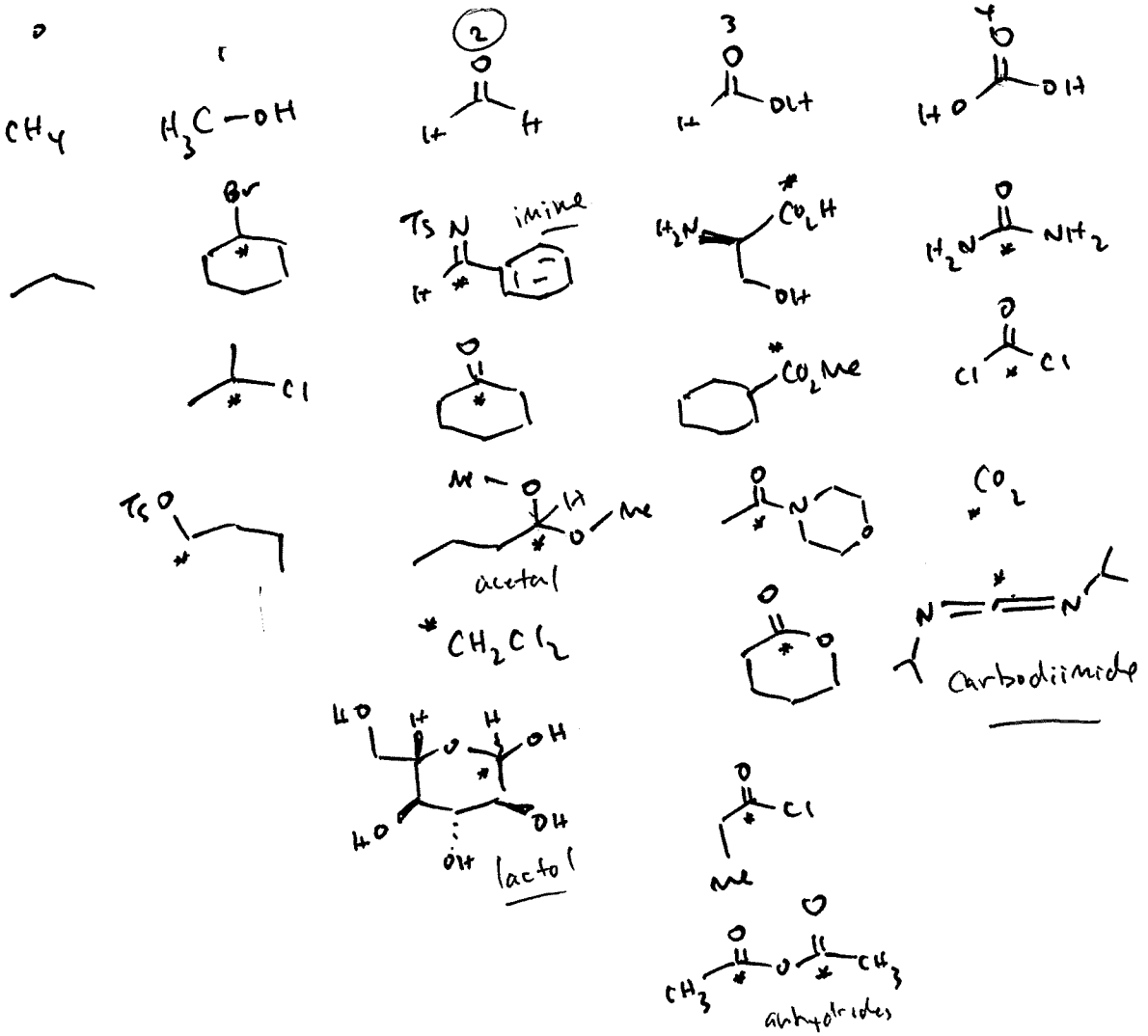


This gets confusing pretty quickly and is not so useful.

Alternatively, if we treat C and H as "oxidatively equal"...

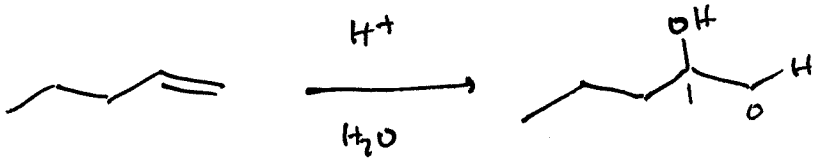


- Thus we can treat particular carbons based on their oxidation levels as behaving relatively similarly. This is based on ~~[illegible]~~ how many heteroatoms a carbon is attached to.



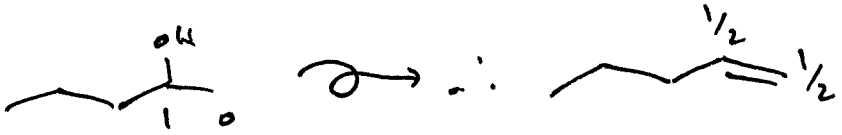
- what about pi systems?

consider:

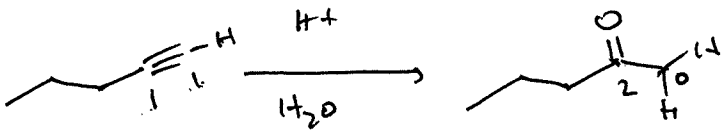


No oxidation or reduction has occurred, just hydration!

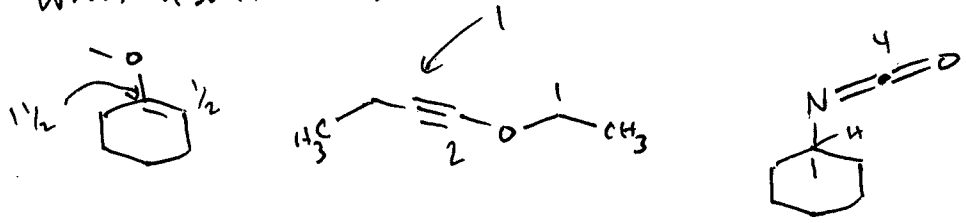
In the two carbons of interest, the oxidation levels are 1 and 0, so the oxidation levels of the alkene have to add up to 1.



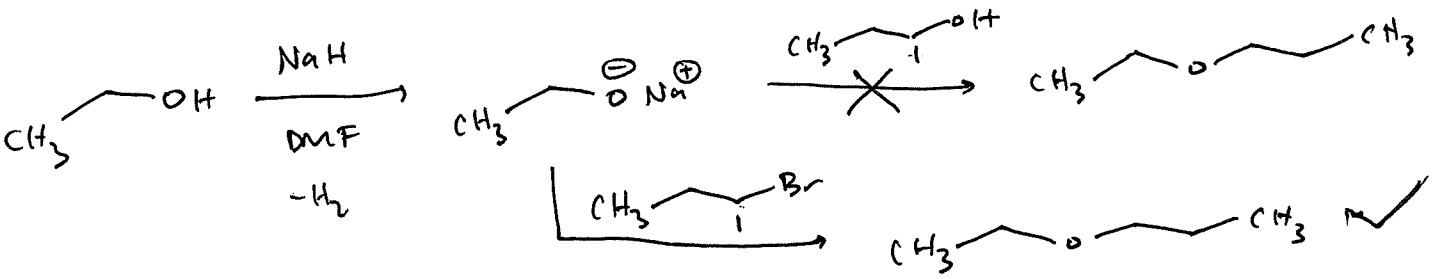
what about an alkyne?



as a result, each carbon of the alkyne bears an oxidation level of 1. what about these?

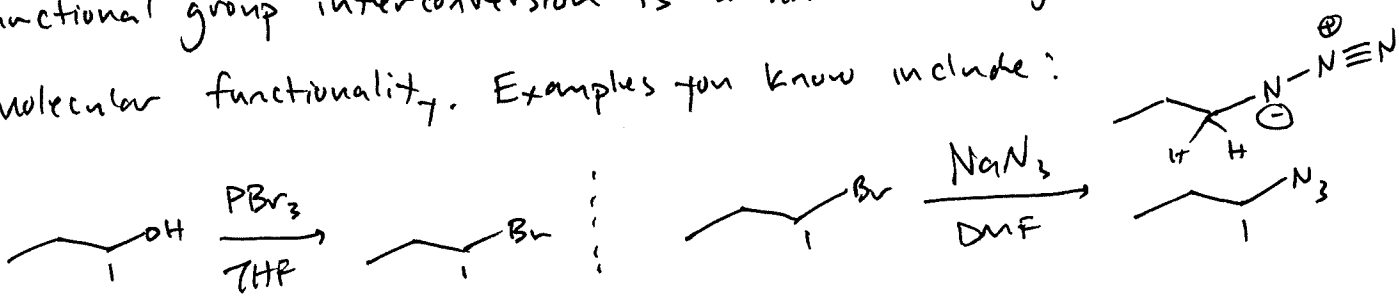


This a way of categorizing functional groups into large groups with similar relation with regard to retrosynthesis.

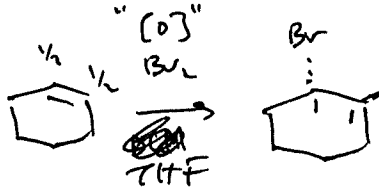


Thus, changing OH to Br did not change the oxidation level of the electrophile, but made the desired transformation functional through <u>functional group interconversion</u>.

Functional group interconversion is a non-redox adjustment of molecular functionality. Examples you know include:



don't include: eg.

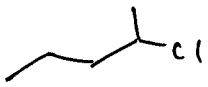


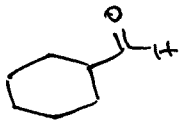
this is an oxidative functionalization!

Simple vs. composite functionality

simple functional groups.

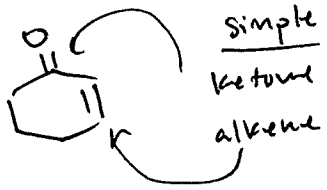

alcohol


choride


aldehyde

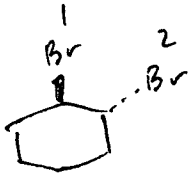

ketone etc.

composite functional groups consider the distance, orientation, and/or conjugation between functional groups.



simple
ketone
alkene

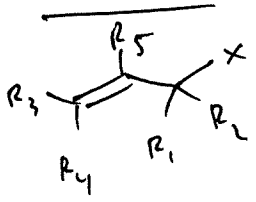
composite
enone ← considering composite functionality has an effect on retrosynthetic analysis.



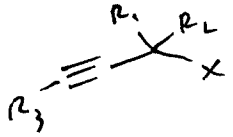
simple
bromide

composite
1,2-trans-dibromide (anti)

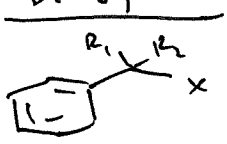
allylic

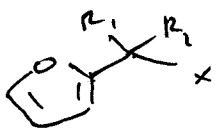


propargylic

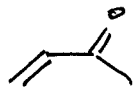


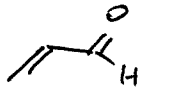
benzylic

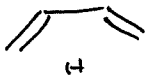


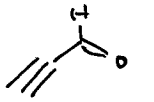


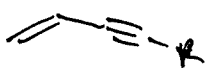
conjugated


"enone"


"enal"


diene

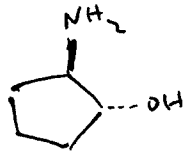

"ynal"


"enyne"

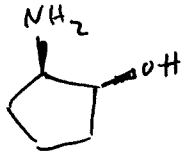
X can be an alcohol, halide, etc....

"allylic alcohol", "allylic bromide", "propargylic chloride", "benzylic tosylate" etc....

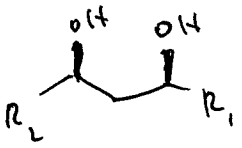
positioning of functional groups



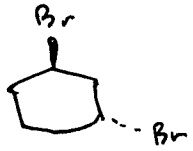
1,2-anti-amino alcohol



1,2-syn-aminoalcohol



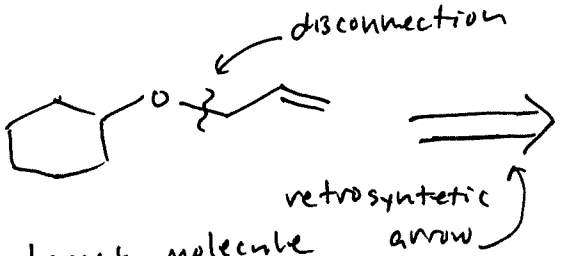
syn-1,3-diol or
1,3-syn-diol



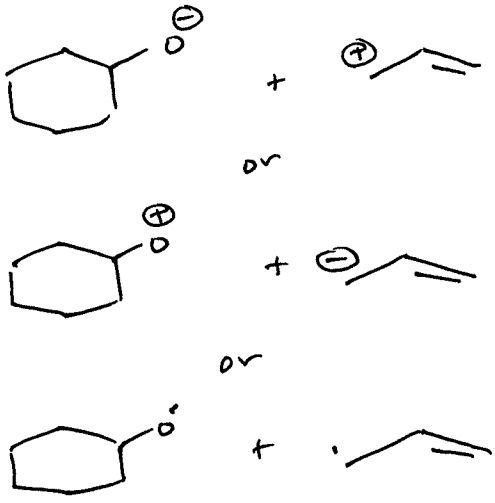
1,3-anti-dibromide

the key here is not to get the name right, but to see functionality as related to each other and not separate!

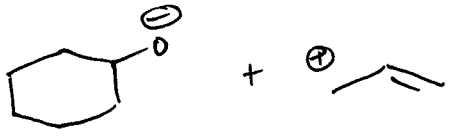
The process of retrosynthesis



synthons

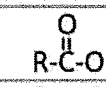
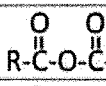
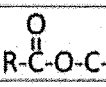
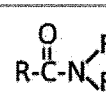
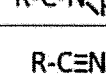
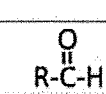
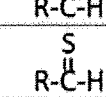
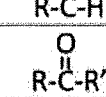
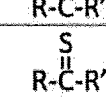
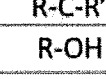
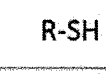
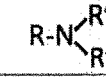
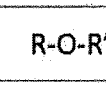
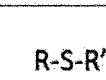
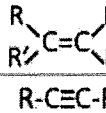
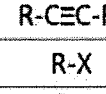
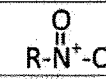
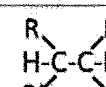


the first set of synthons look easiest to access:



nucleophile electrophile

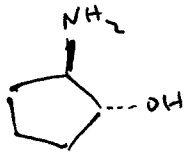
what would be the synthetic equivalents of these pieces? what functional groups could impart this desired reactivity?

Functional groups listed in *decreasing priority order* for nomenclature			
Functional group	**Prefix***	**Suffix**	**Formula****
Carboxylic Acids	carboxy-	-oic acid -carboxylic acid	
Acid anhydrides		-oic anhydride -carboxylic anhydride	
Esters	*alk*oxycarbonyl	-oate -carboxylate	
Acyl halides	halocarbonyl-	-oyl halide carbonyl halide	
Amides	carbamoyl-	-amide -carboxamide	
Nitriles	cyano-	-nitrile -carbonitrile	
Aldehydes	formyl-	-al -carbaldehyde	
Thioaldehydes	thioformyl-	-thial	
Ketones	oxo-	-one	
Thiones	thioxo-	-thione	
Alcohols	hydroxy-	-ol	
Thiols	mercapto- sulfanyl-	-thiol	
Amines	amino-	-amine	
Ethers	*alk*oxy- oxa-	-ether -ane	
Sulfides	*alk*ylsulfanyl- *alk*ylthio- thia-	sulfide	
Alkenes	*alk*enyl	-ene	
Alkynes	*alk*ynyl	-yne	
Alkyl halides	halo-	-ane	
Nitro	nitro-	-ane	
Alkanes	*alk*yl-	-ane	

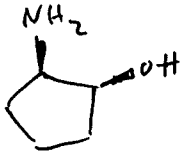
* *alk*- in the prefix, represents the number of carbon atoms in the root carbon chain. See list below.

** R, R', R'' and R''' are used to represent generic groups based on C (such as a methyl group) or just H.

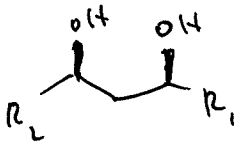
positioning of functional groups



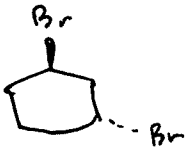
1,2-anti-amino alcohol



1,2-syn-aminoalcohol



syn-1,3-diol or
1,3-syn-diol

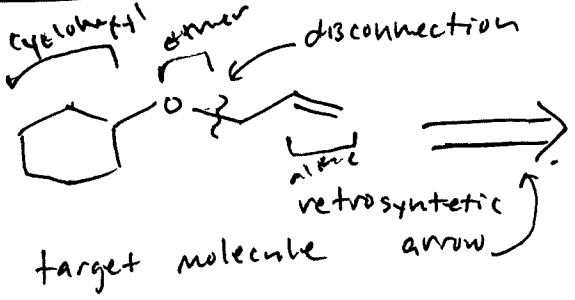


1,3-anti-dibromide

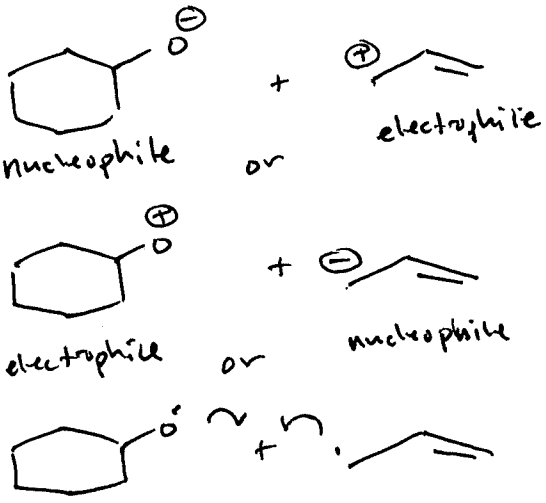
the key here is not to get the name right, but to see functionality as related to each other and not separate!

→

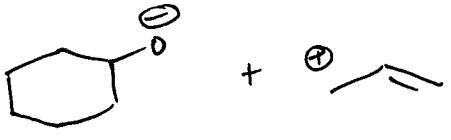
The process of retrosynthesis



synthons

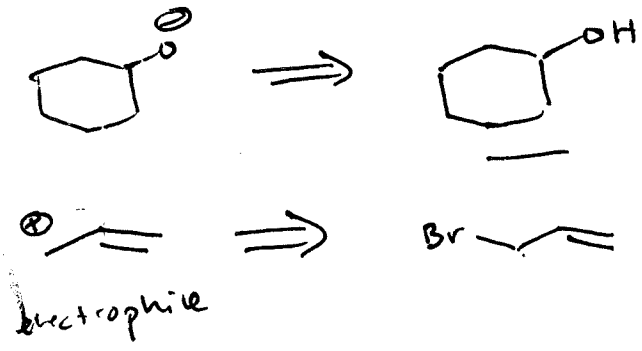


the first set of synthons look easiest to access:



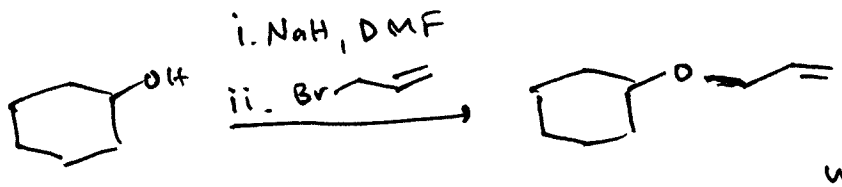
nucleophile + electrophile

what would be the synthetic equivalents of these pieces?
what functional groups could impart this desired reactivity?



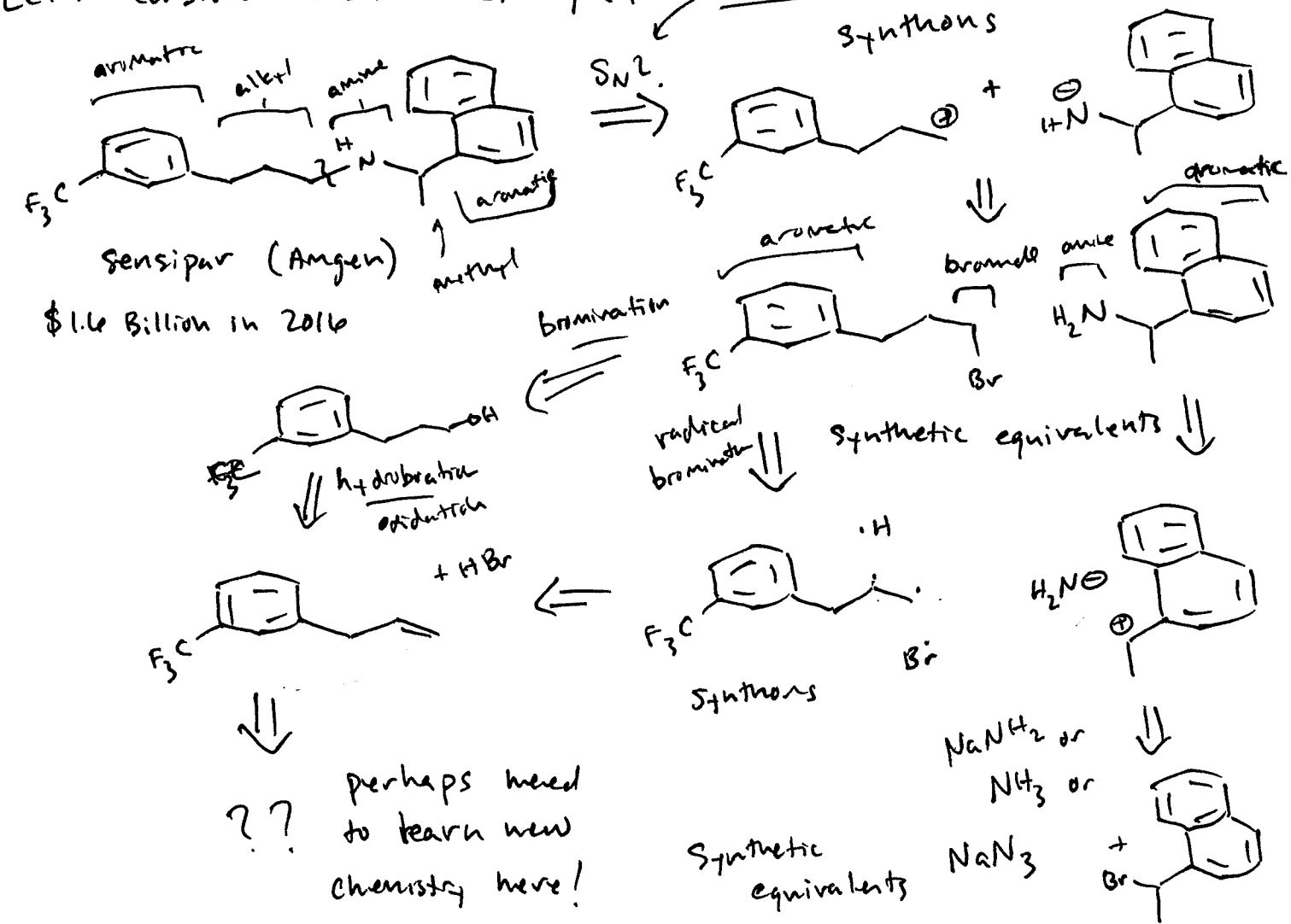
these are called synthetic equivalents. These are not theoretical, but things you can easily store, make and/or buy.

∴ the forward synthesis would proceed as such

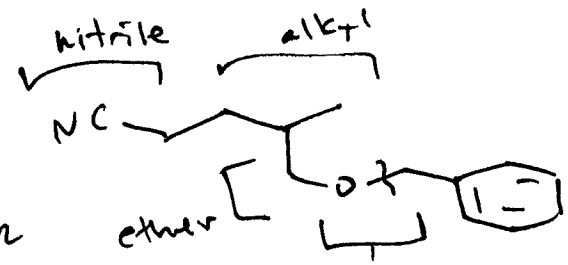


this reaction is an S_N2 reaction and a Williamson ether synthesis!

Let's consider another example: transform

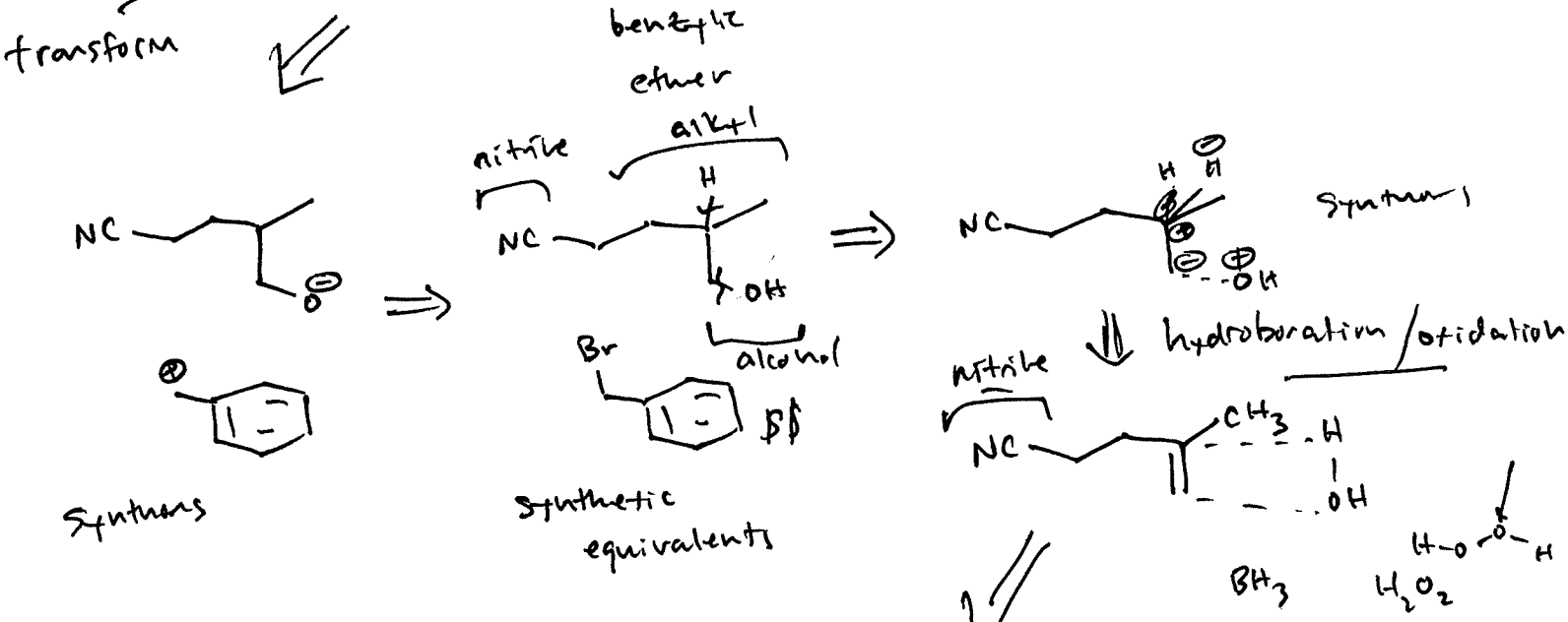


Consider a retrosynthesis of the following:

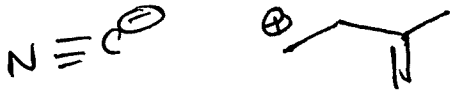


① define functionality (functional groups)

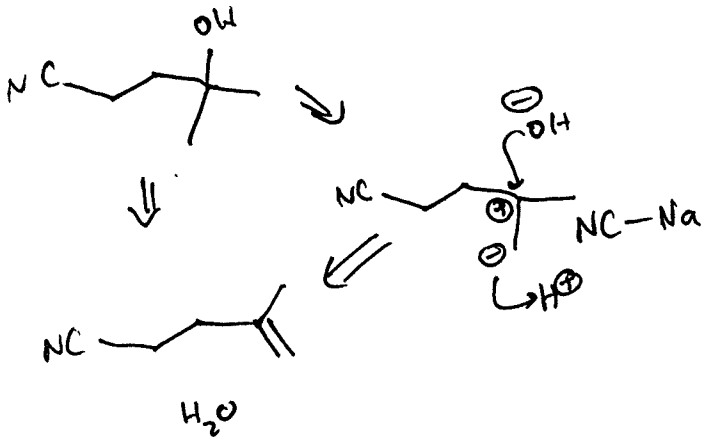
transform → S_N2

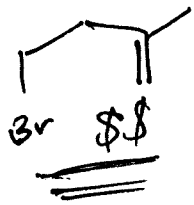


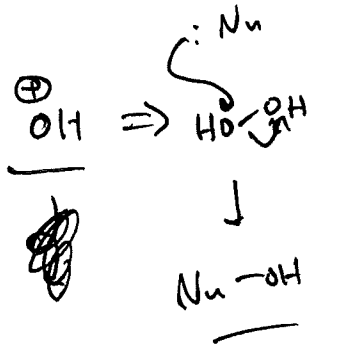
synthons



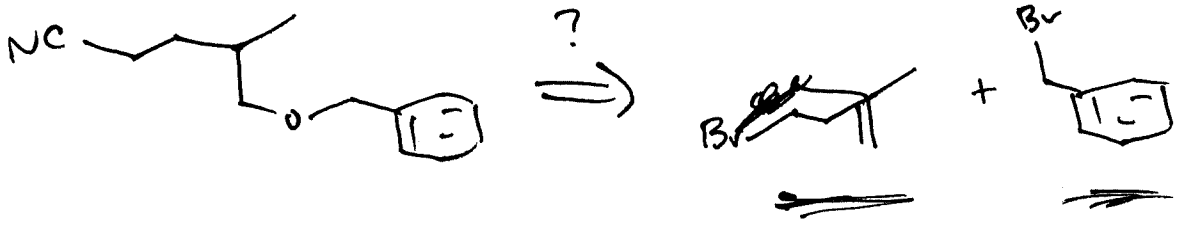
S_N2





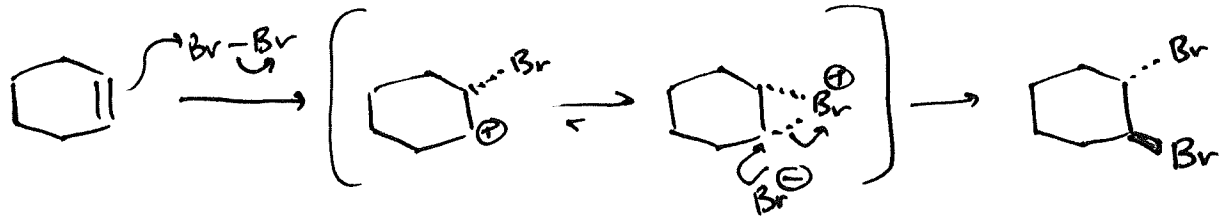


exam question



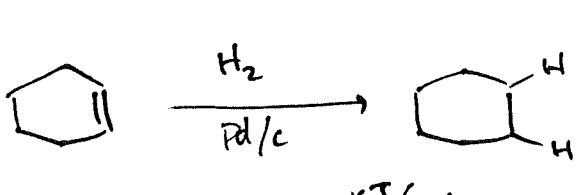
Arenes + Aromaticity

Consider:



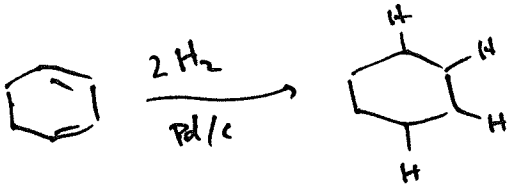
In this situation, alkene is nucleophile, Br_2 electrophile

Consider:



$\Delta H = -120\ KJ/mol$

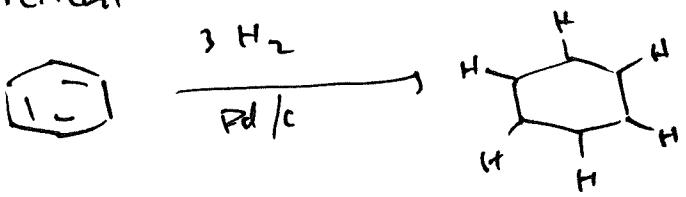
$= -28\ kcal/mol$



$\Delta H = -231\ KJ/mol$

$= -55\ kcal/mol$

theoretical

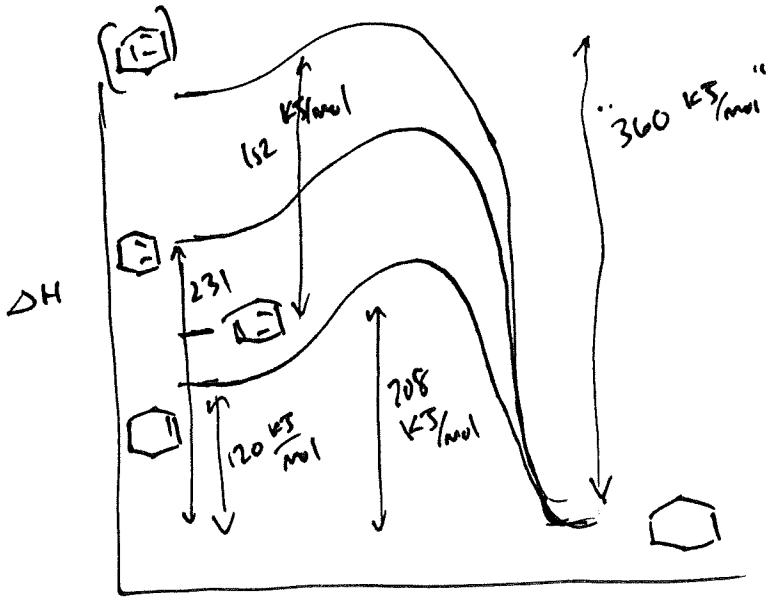


should be $\Delta = -360\ KJ/mol$

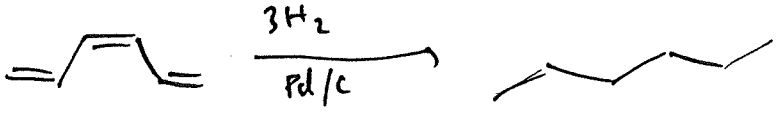
$= -85\ kcal/mol$

actually $\Delta H = -208\ kcal/mol$

$= [illegible]$



Benzene is 152 KJ/mol (36 kcal/mol) more stable than the imaginary cyclohexatriene!



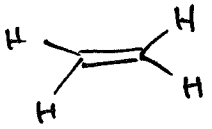
$\Delta H = -337\ KJ/mol$

$= -80.5\ kcal/mol$

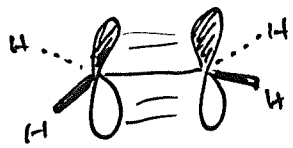
→ This is because benzene has resonance stabilization and delocalization of electrons.

Bonding in aromatic systems (pi systems)

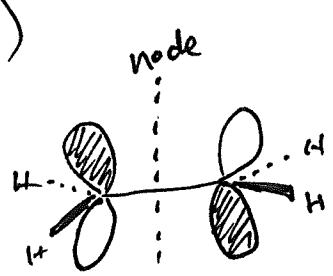
Consider:



≡

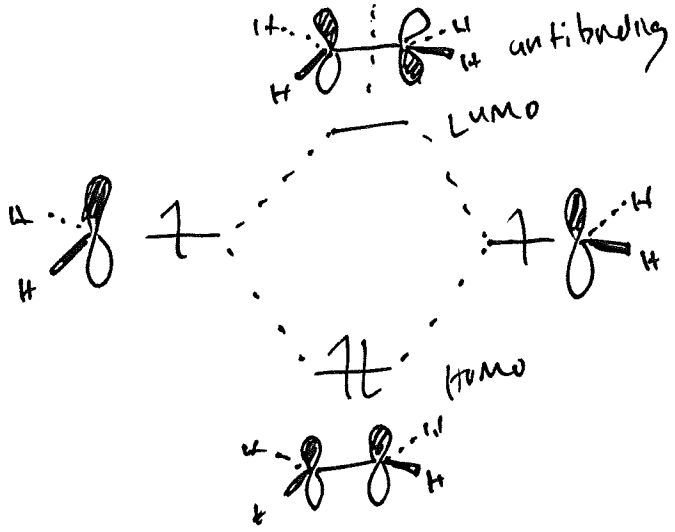


pi system
(bonding orbital)
π



pi system
(antibonding orbital)
π^*

when considering the molecular orbital diagram of the pi system:



in a pi system like ethylene, there are two total orbitals, one is a bonding orbital, and one is antibonding.

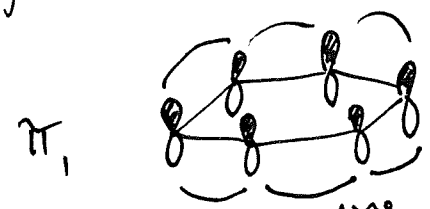
In the ground state, the electrons reside in the bonding molecular orbital (it is lower in energy). If we add a lot of energy (light) to the system, we can promote one electron to the antibonding orbital. The bonding orbital is the Highest Occupied Molecular Orbital (HOMO). The antibonding orbital in this example is the lowest unoccupied Molecular orbital (LUMO).

In chemistry, all electron movement occurs between the HOMO and the LUMO of a system!

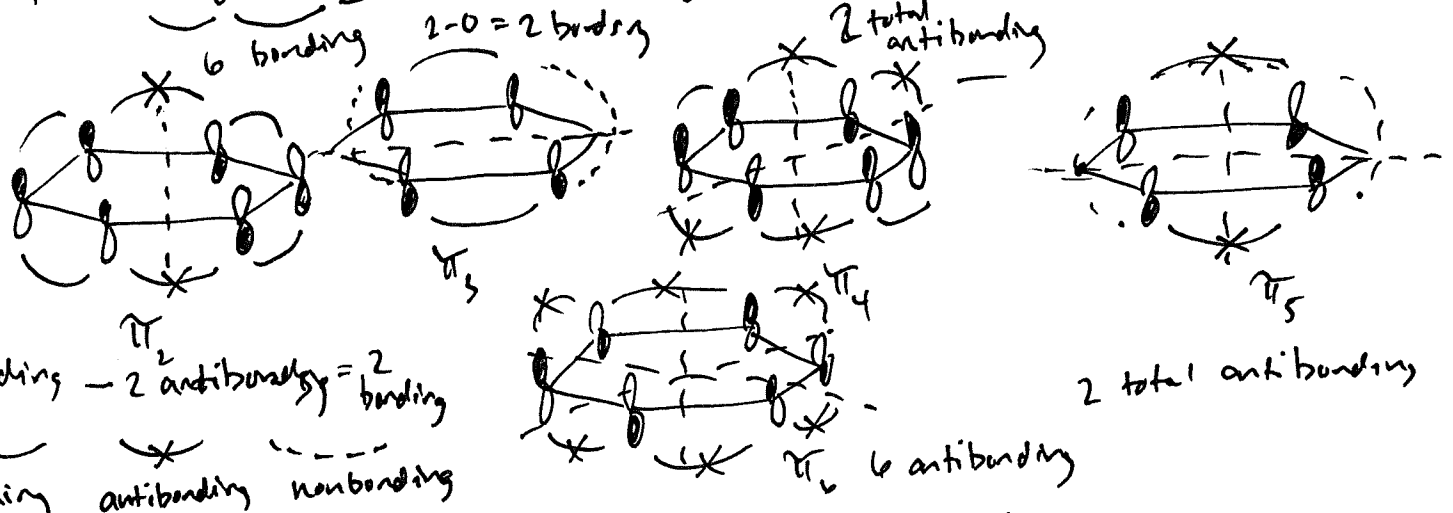
Bonding in Benzene

delocalized pi system ...
extra stability ∴ thermodynamic sink!

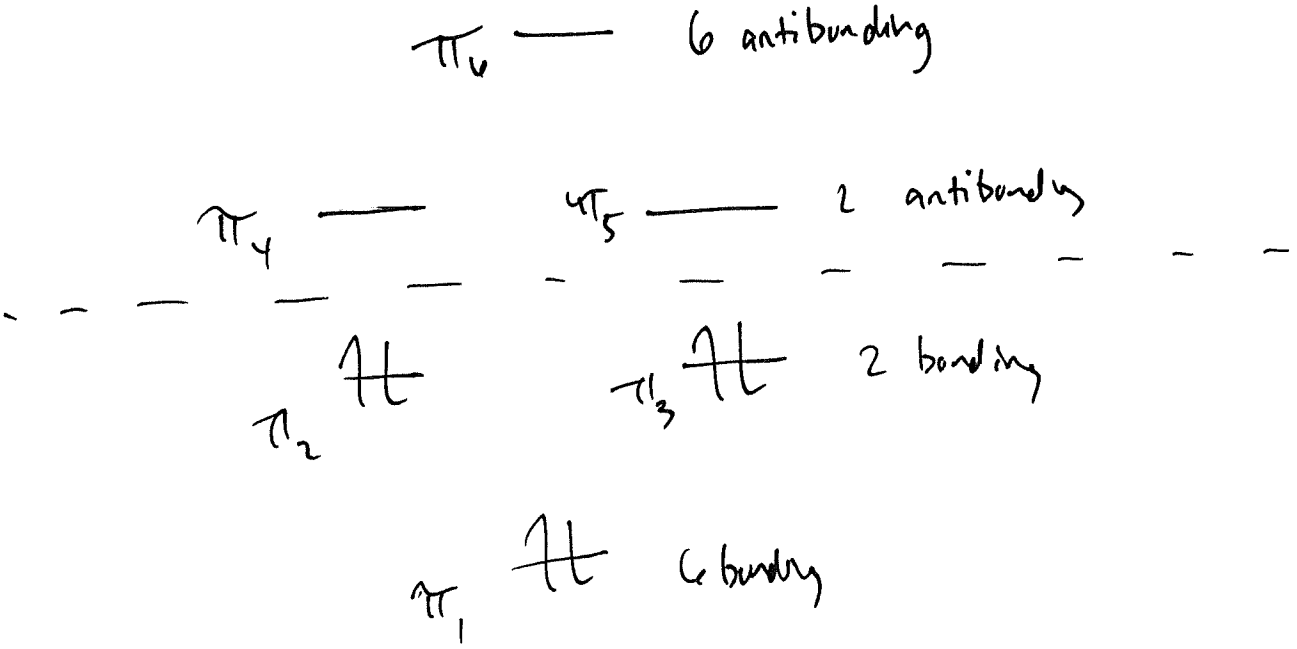
just like with ethylene we can draw all p orbitals in phase.



but we have 6 electrons to place and not just two this time. Need more orbitals!

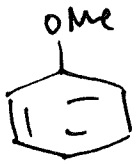


∴ The molecular orbital diagram looks like this:



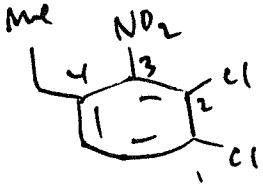
A brief overview of nomenclature in aromatic systems:

"benzene"



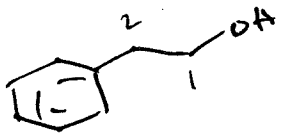
"methoxybenzene"
"anisole"

1-fluoro-3-methyl benzene



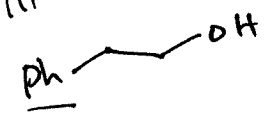
1,2-dichloro-4-ethyl-3-nitrobenzene

~~When~~ when benzene is a substituent, it is referred to as phenyl (Ph)



2-phenyl ethanol

III or



The highest priority substituent gets the number 1.

In this course, nomenclature will never be directly asked of you.

Hückel's rule

consider benzene:  6 carbons, 6 hydrogens, 6 π electrons

is there a general rule for determining whether a molecule is aromatic or not?

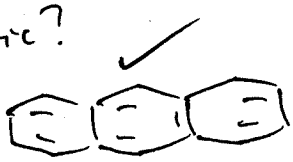
Hückel says: An aromatic compound must be planar, fully conjugated and contain $(4n+2)$ π electrons where n is a whole number.

for benzene: 6 π electrons, $\therefore 6 = 4n+2$, $n=1$

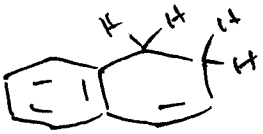
1 is a whole number so benzene is aromatic.

consider naphthalene:  10 π electrons!

according to Hückel — $10 = 4n+2$, $n=2$ so naphthalene is aromatic!

aromatic? 

anthracene $14 = 4n+2$, $n=3$



not aromatic! (planar)

$8 = 4n+2$?

Cyclooctatetraene $8 = 4n$ $n=1.5$

If in a continuous, planar system the number of electrons in the pi system is equal to $4n$ then it is "antiaromatic"

example: cyclobutadiene  4 π electrons

$4 = 4n$, $n=1$ so antiaromatic!

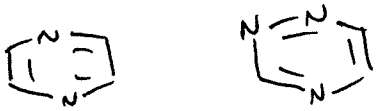
What about heterocyclic molecules?

benzene pyridine

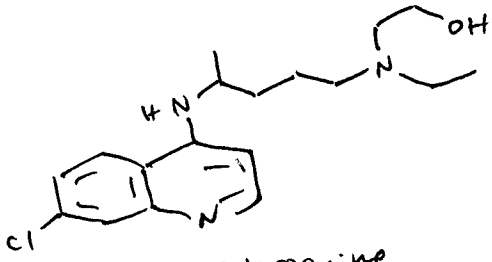
lone pair is orthogonal to aromatic π system!

other heteroaromatics similar to pyridine:

quinoline isoquinoline



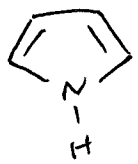
pyrazine 1,2,4, triazine



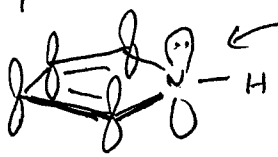
hydroxychloroquine

(malaria treatment, not a COVID-19 treatment)

other kinds of heterocycles:



pyrrole



lone pair in plane of ring

∴ takes part in aromaticity!

pyrrole has 6 π electrons including N lone pair

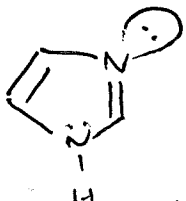
∴ $6 = 4n+2$, $n=1$ so aromatic!

other heteroaromatics similar to pyrrole:

indole

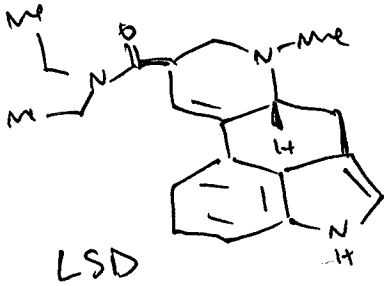
furan

thiophene

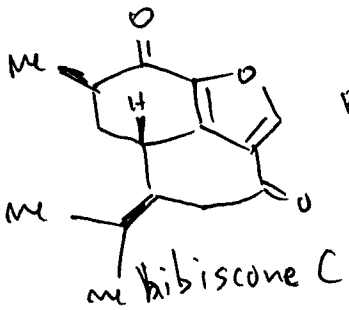


imidazole

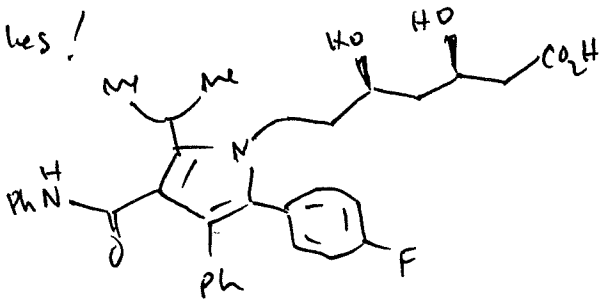
these are found in important molecules!



LSD



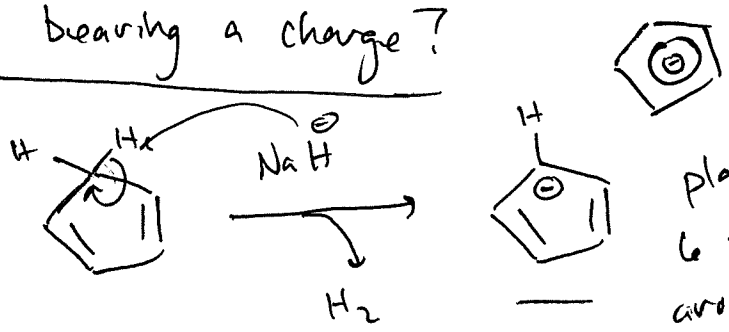
me hibiscone C



Lipitor

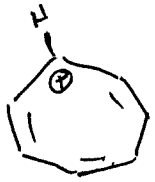
What about Molecules bearing a charge?

consider cyclopentadiene:



planar!
6 π electrons!
aromatic!

what about tropylium?



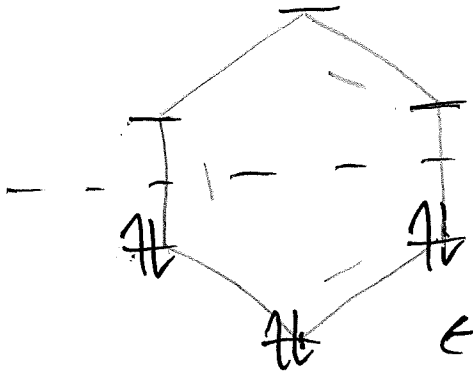
planar and has 6π electrons!
aromatic cation!

even the cyclopropenyl cation is aromatic!

4n + 2 = 2
n = 0 !

Frost circles, a mnemonic that can help with MO diagrams

for benzene, remember: 6 molecular orbitals



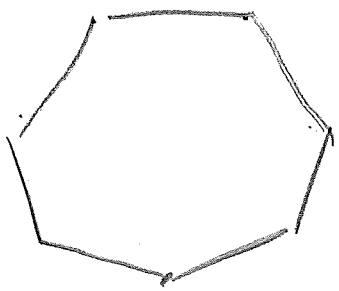
antibonding MO orbitals

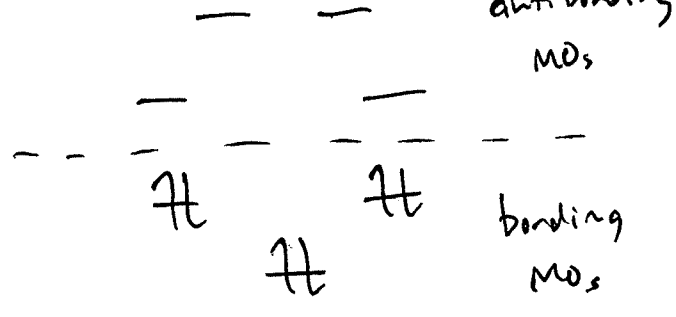
bonding MO orbitals

need a carbon at the bottom (alone) place a vertex!

for tropylium:

frost circle → MO diagram (tropylium)

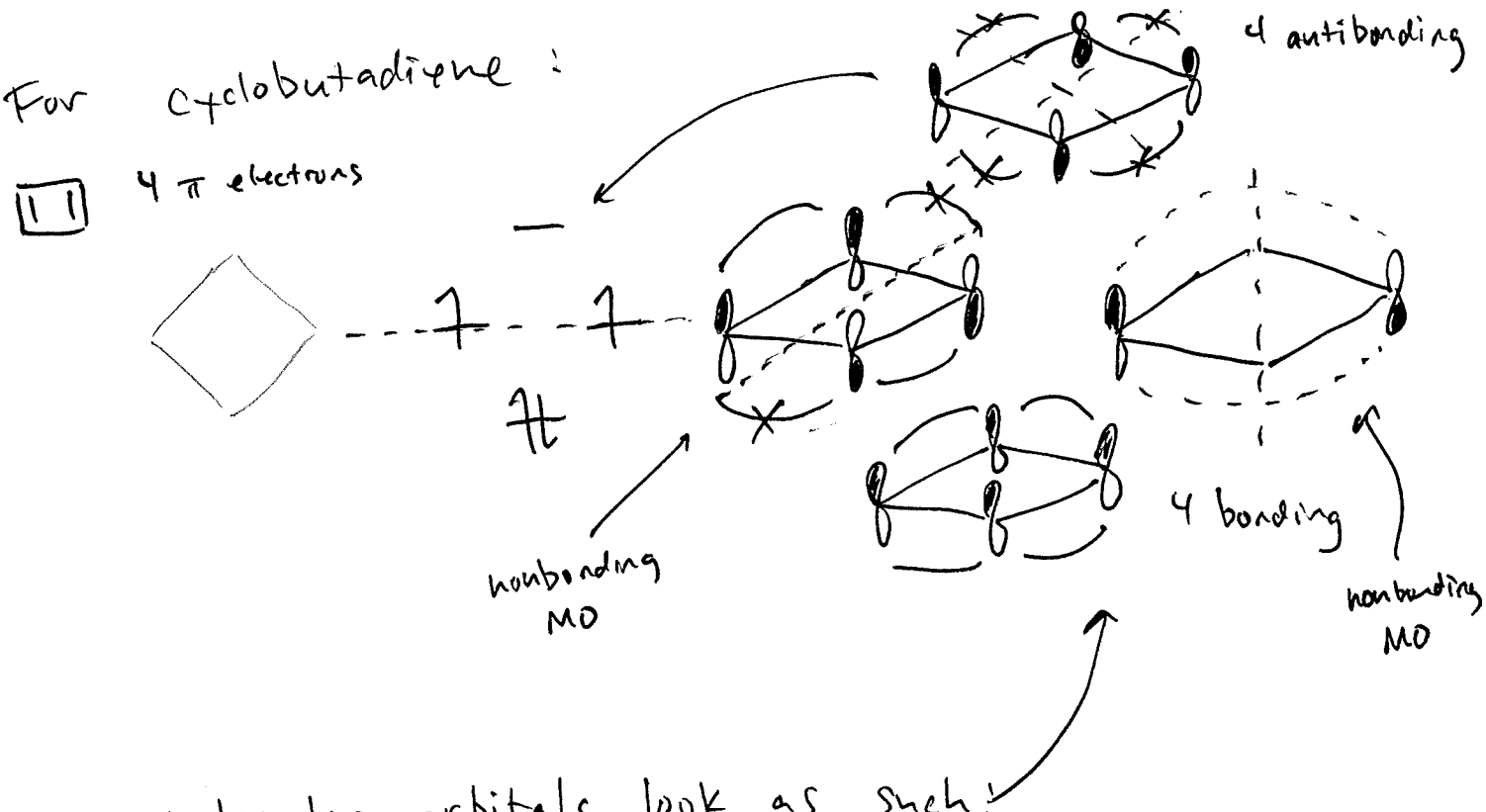




antibonding MOs

bonding MOs

For cyclobutadiene:



and, the Molecular orbitals look as such!

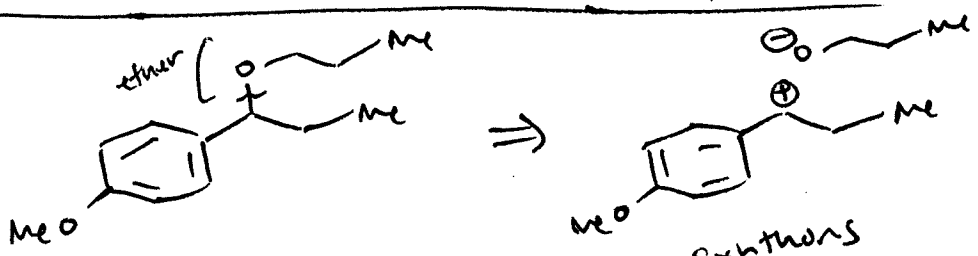
As a result of the unpaired electrons in cyclobutadiene's MO, this molecule has "diradical" character.

For frost circles, only monocyclic aromatics work.

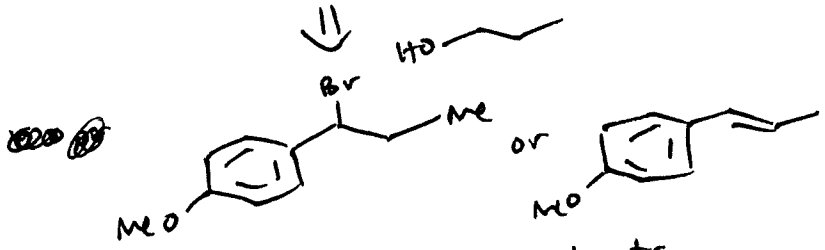
put on carbon as a vertex at the bottom and symetrically construct the ring (Molecular orbitals) from the bottom up. Then, fill electrons following Hund's rule starting from the lowest energy MO.

Reactions of arenes at the benzylic position

Consider:

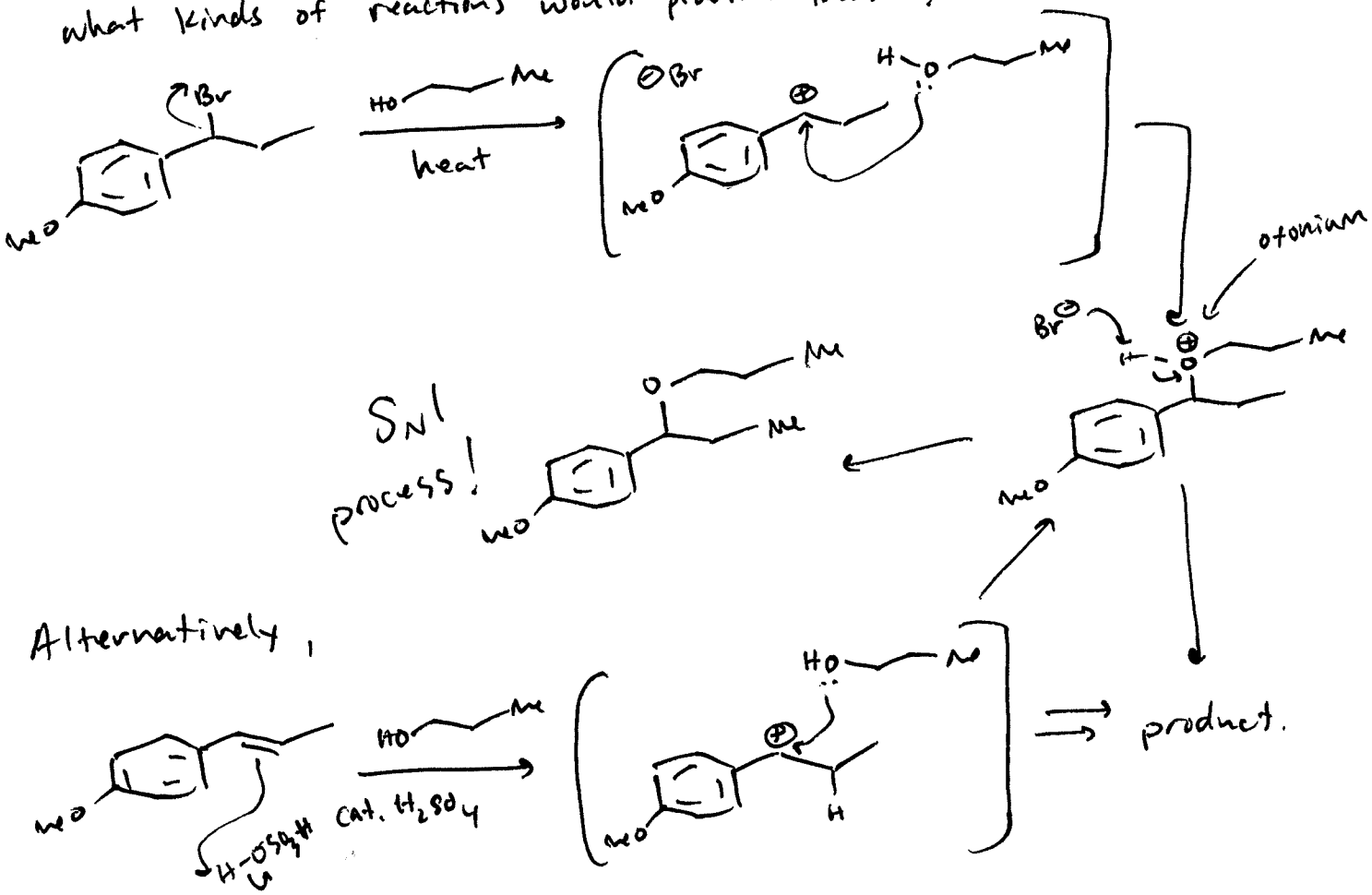


Synthons



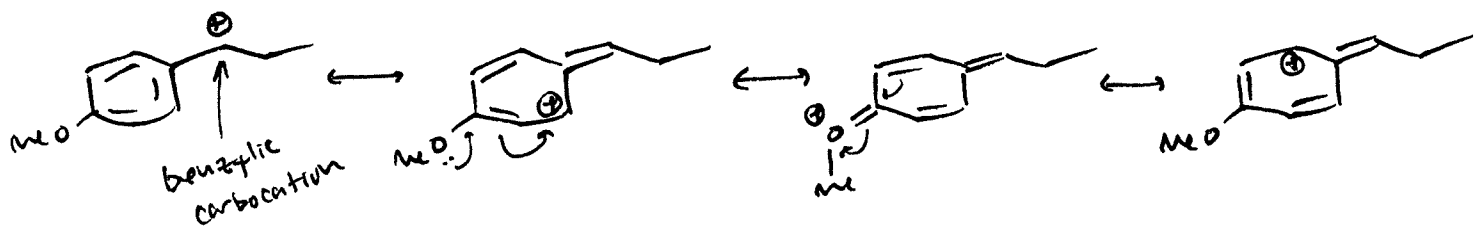
Synthetic equivalents

What kinds of reactions would provide these?

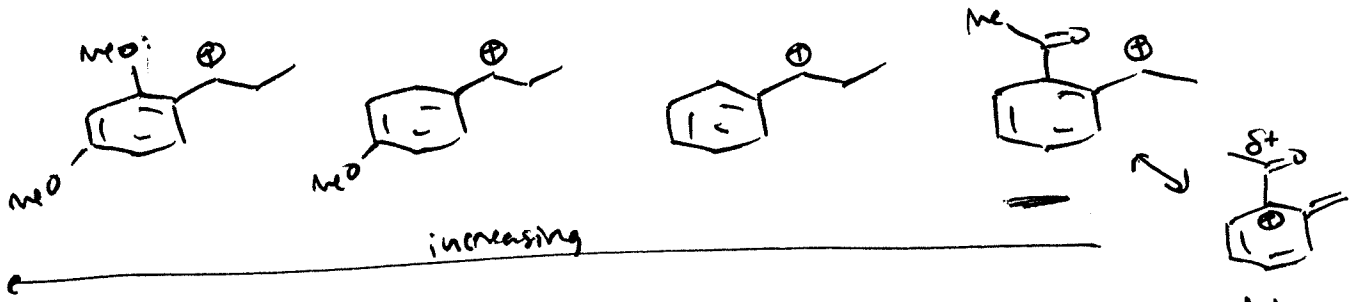


Alternatively,

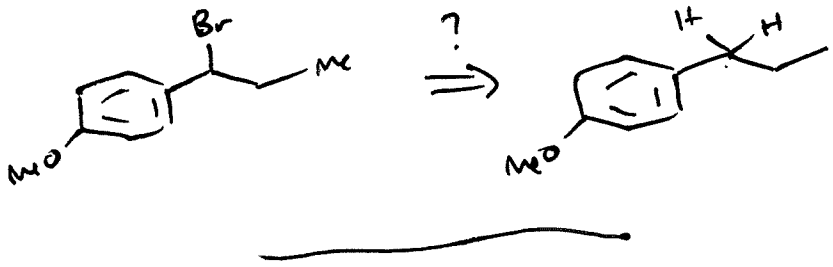
The secret lies in the stability of the benzylic cation!



electron donating groups stabilize carbocations much easier:

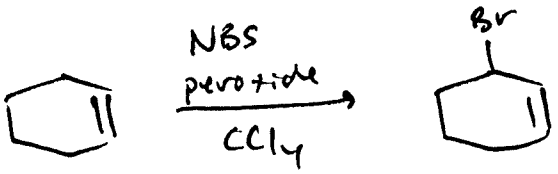


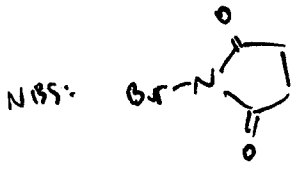
now consider the synthesis of the bromide in the last example.



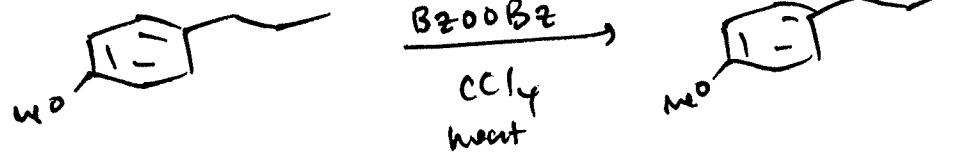
what if the bromide could be introduced at the benzylic position in place of an H?

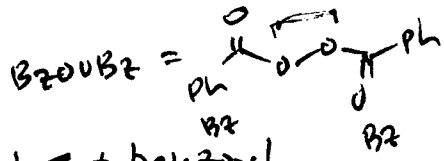
In the past you learned about "radical allylic bromination"



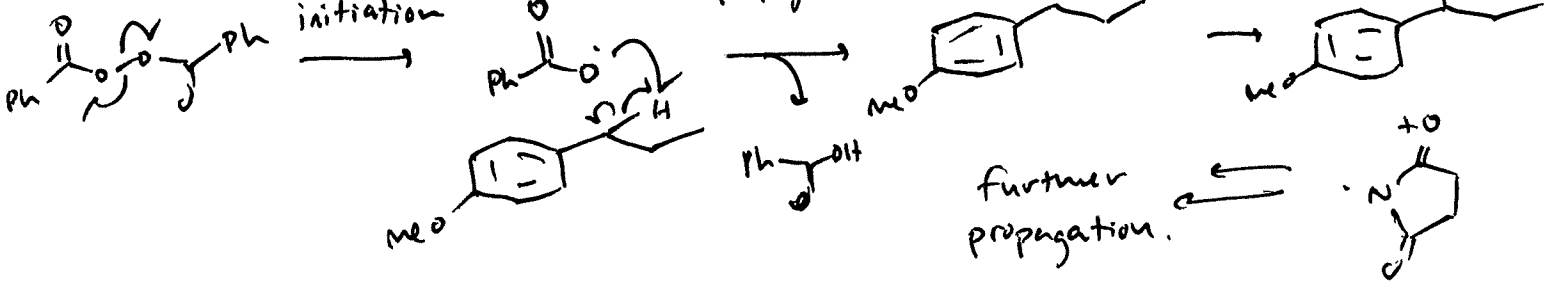


The same is true when an aromatic ring is present



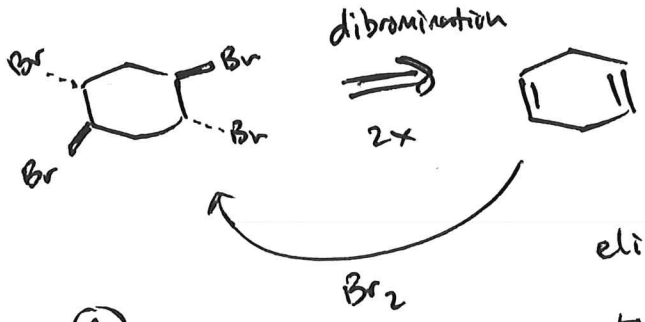


Mechanism



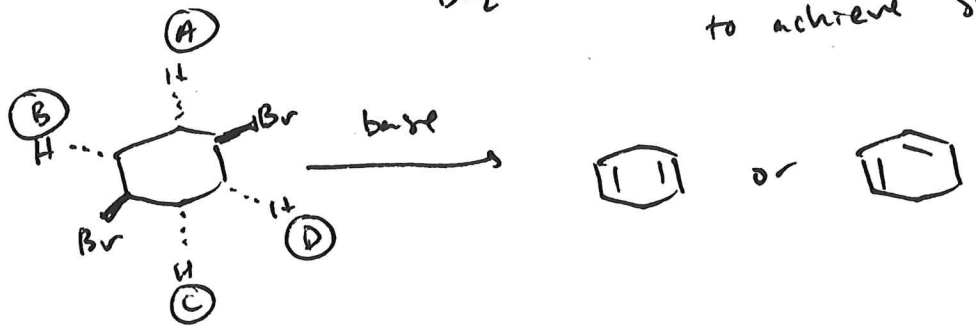
The Birch Reduction of Arenes

consider:



how would you make this?

eliminations may be tough to achieve selectivity.



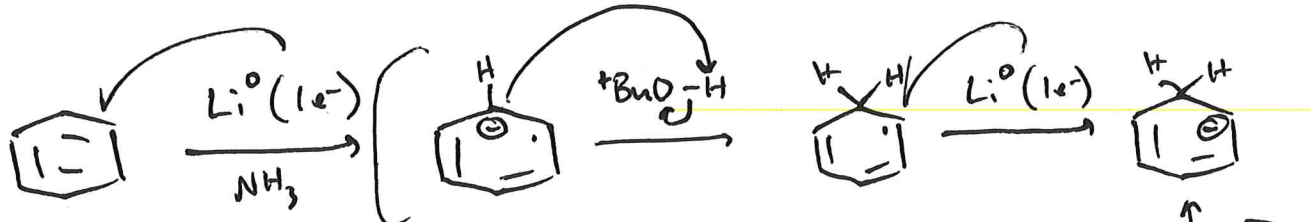
what if we tried to derive this from an arene?

for benzene, oxidation level → 3 (3 alkenes)

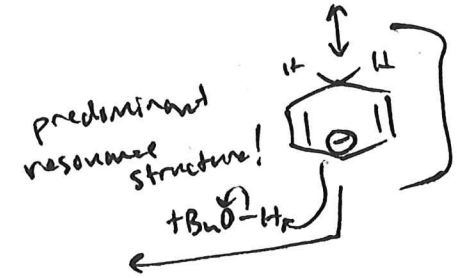
for 1,4 cyclohexadiene, ox. level → 2 (2 alkenes)

Needs reductive process!

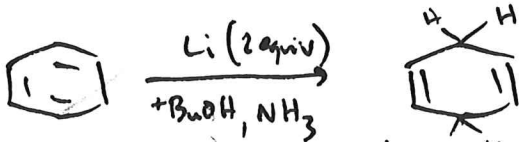
what if we could just simply add electrons directly to the LUMO of benzene?



7 electrons in ring now! unstable!



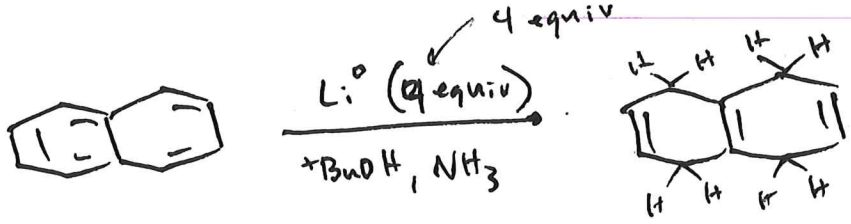
overall reaction:



dearomatization!

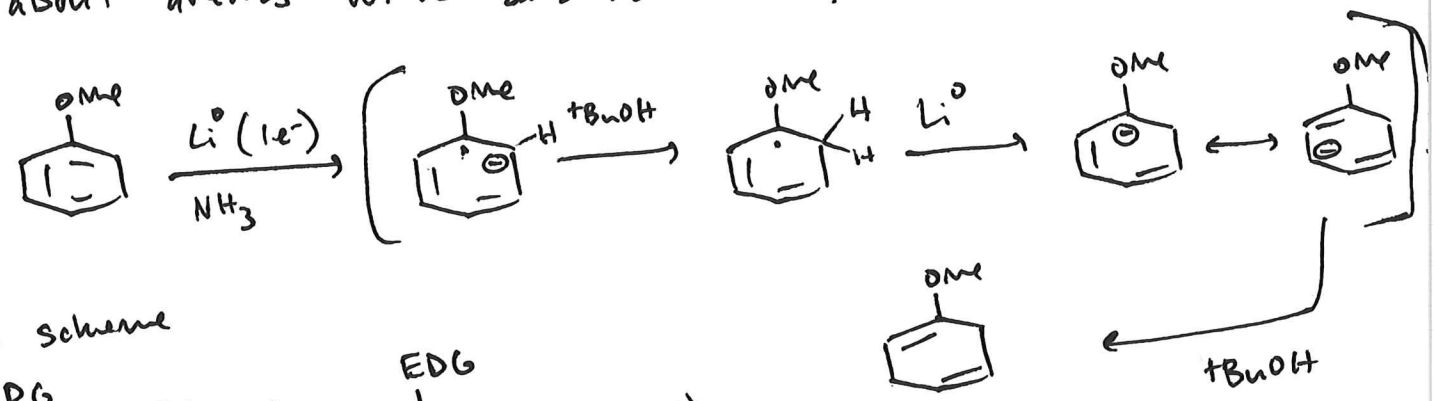
1,4-Cyclohexadiene

This reaction works on bicyclic arenes too!

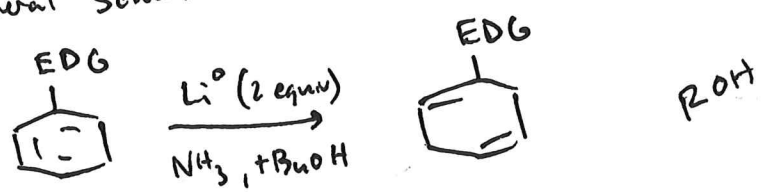


try mechanism to rationalize this selectivity! ←

what about arenes with ~~~ substitution?

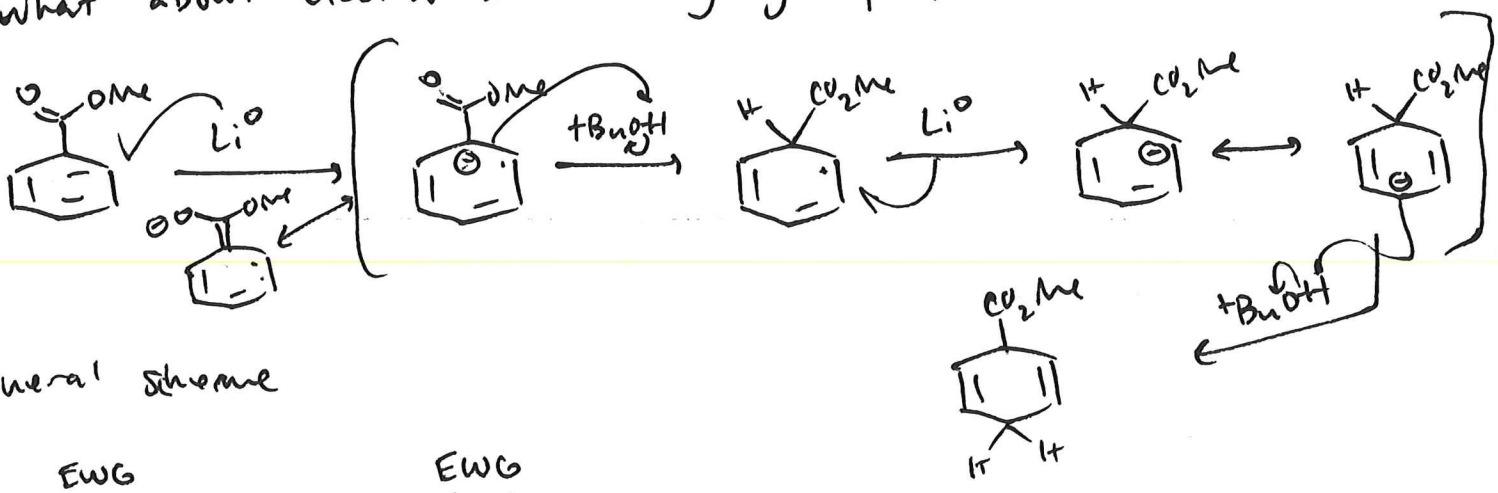


general scheme

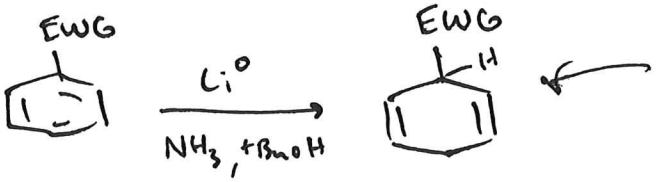


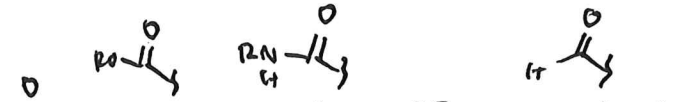
EDG = electron-donating group. e.g. OH, OMe, NH_2, NHR, SR

what about electron-withdrawing groups?



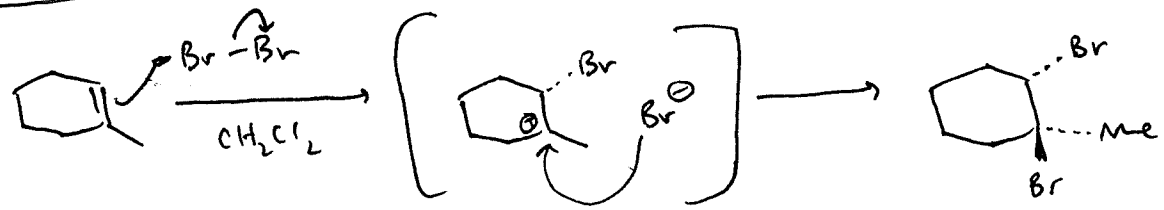
general scheme



EWG = electron-withdrawing group. e.g.  , ester, amide, CF_3, aldehyde

Electrophilic Aromatic Substitution

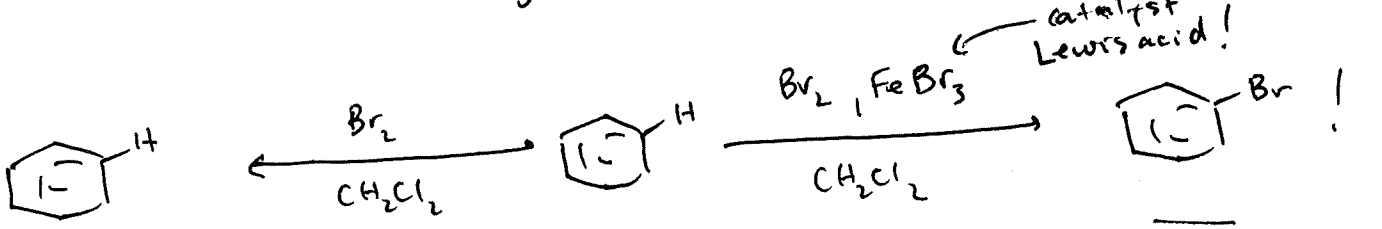
recall:



consider:

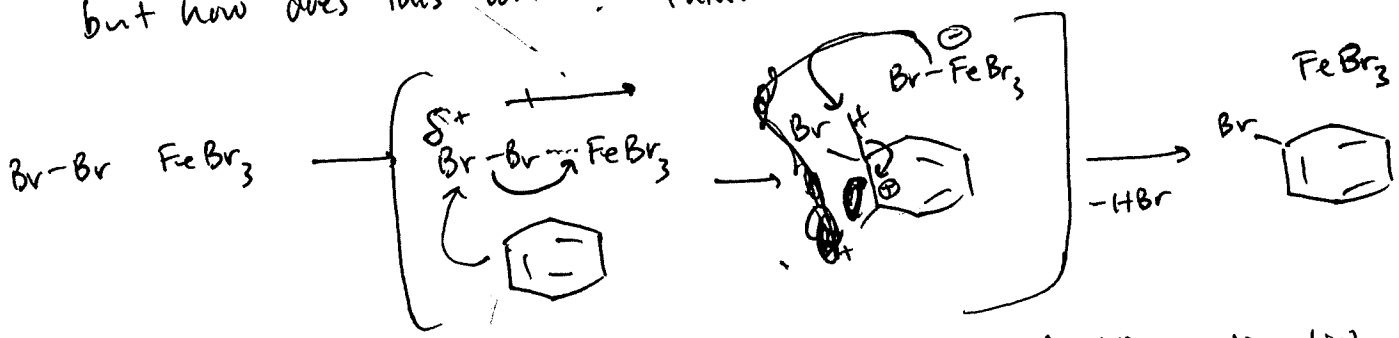
How might one accomplish this replacement of H with Br?

can we learn something from what we used to do with alkenes?



no reaction

but how does this work? Think the acronym AAA...

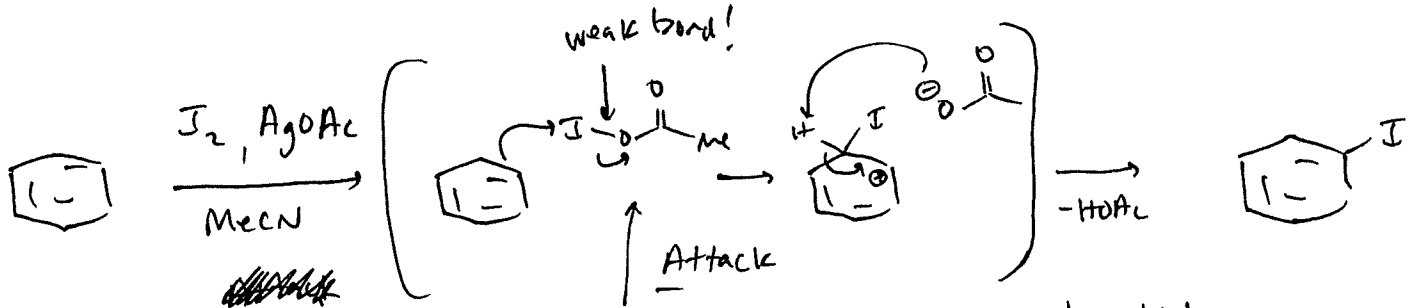


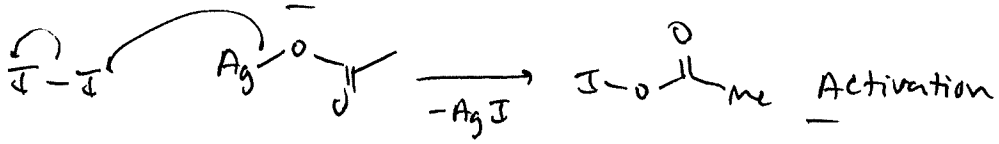
Activation

Attack

(Re)Aromatization

Iodination works similarly but with slightly different reagents.

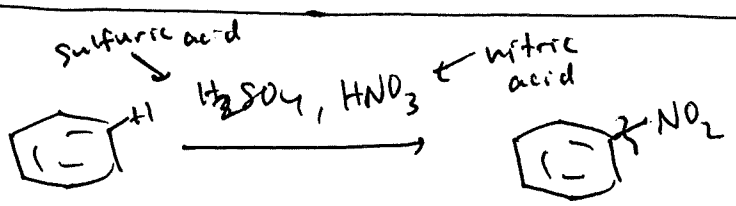


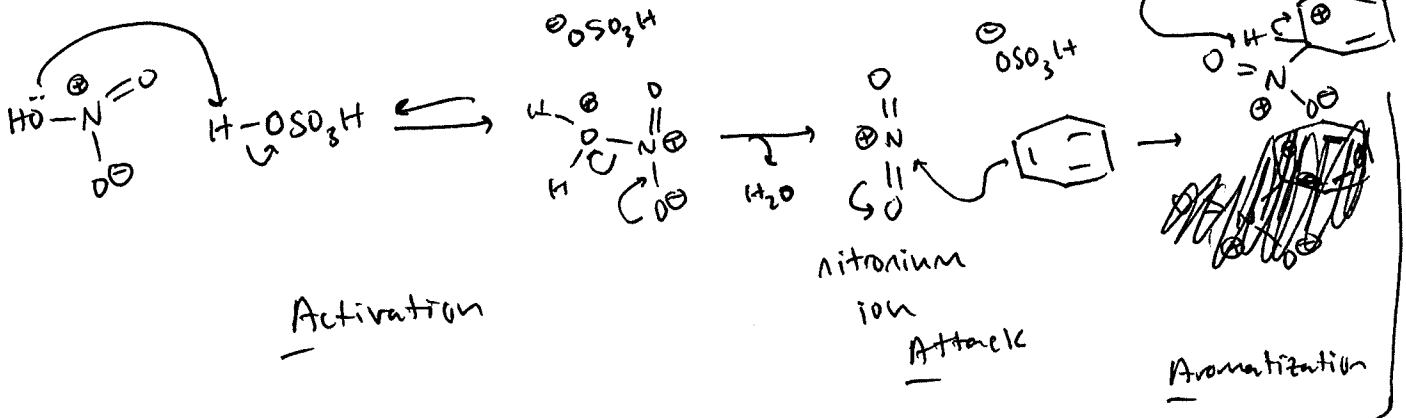


Activation

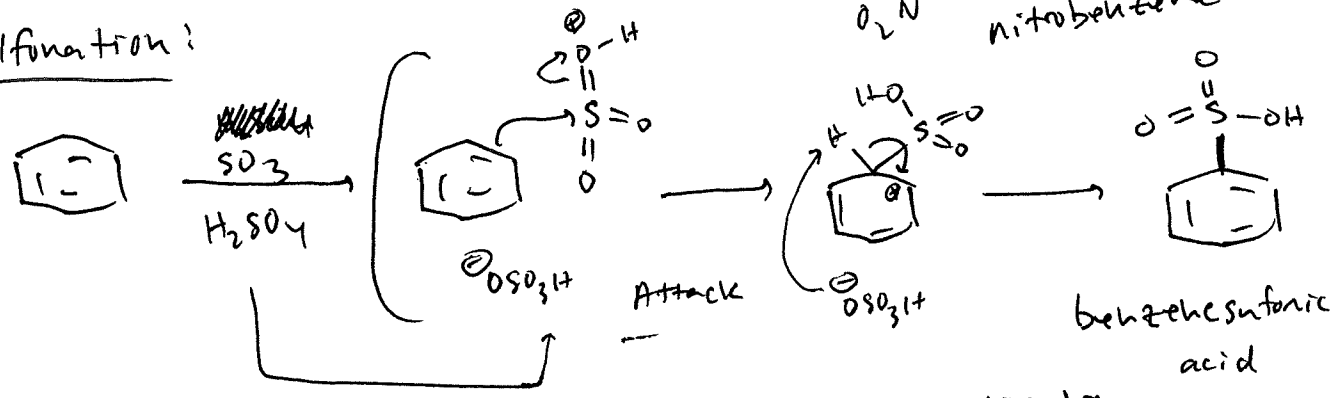
Installation of other heteroatoms on an aromatic ring

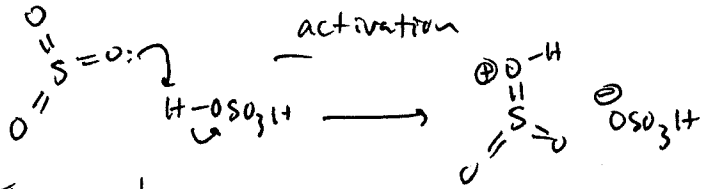
Nitration:



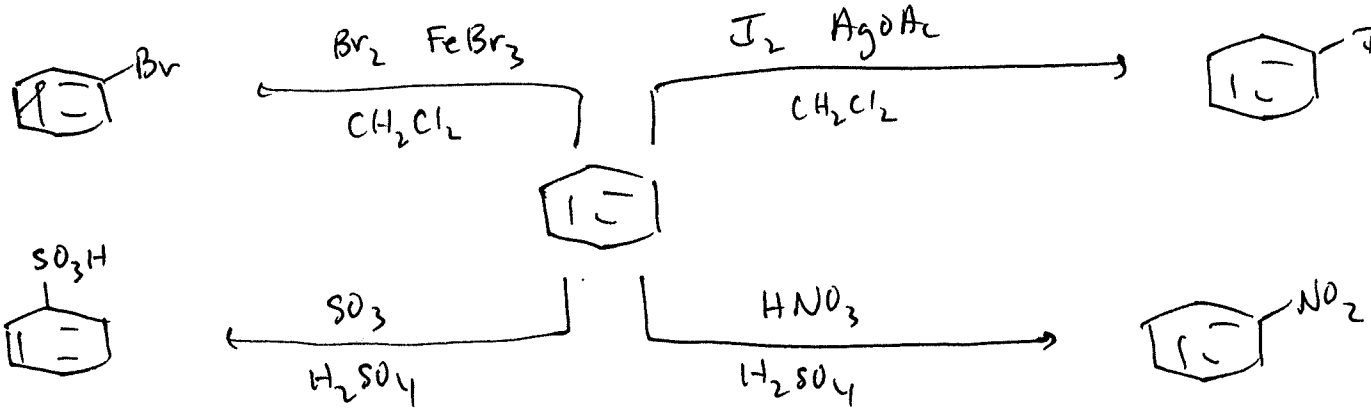


Sulfonation:

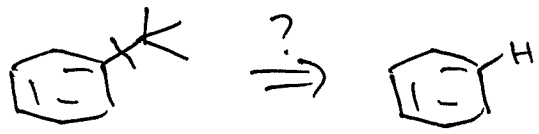




The only thing that really changes in each of these transformations is the activation step. (Look at page 465!)



What about carbon-carbon bond formation?

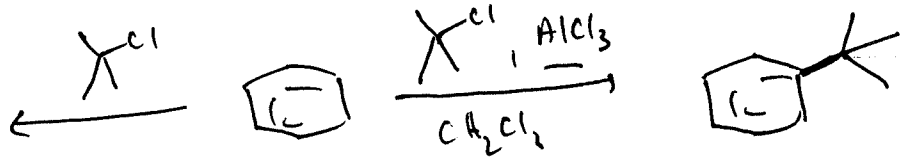
consider:  how could we do this using what we learned today?

Synthons

Synthetic equivalents

could this work?

First we need to activate the electrophile ... maybe?

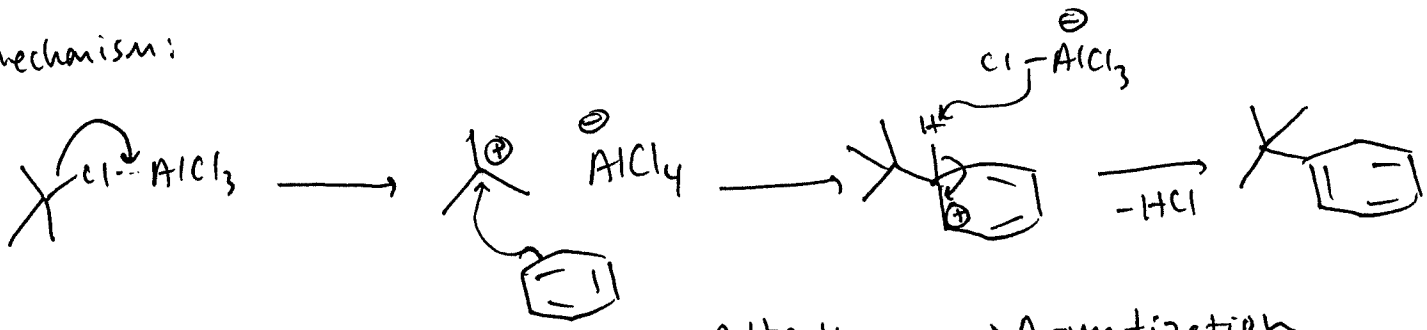


no reaction

CH_2Cl_2

success!

mechanism:



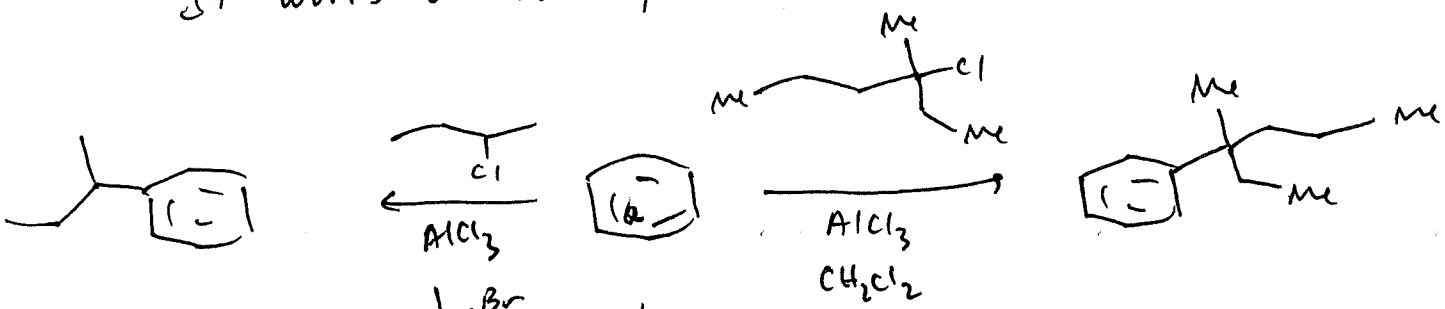
Activation

Attack

(re) Aromatization

This reaction is called a Friedel-Crafts Alkylation.

It works on tertiary halides as well as secondary.



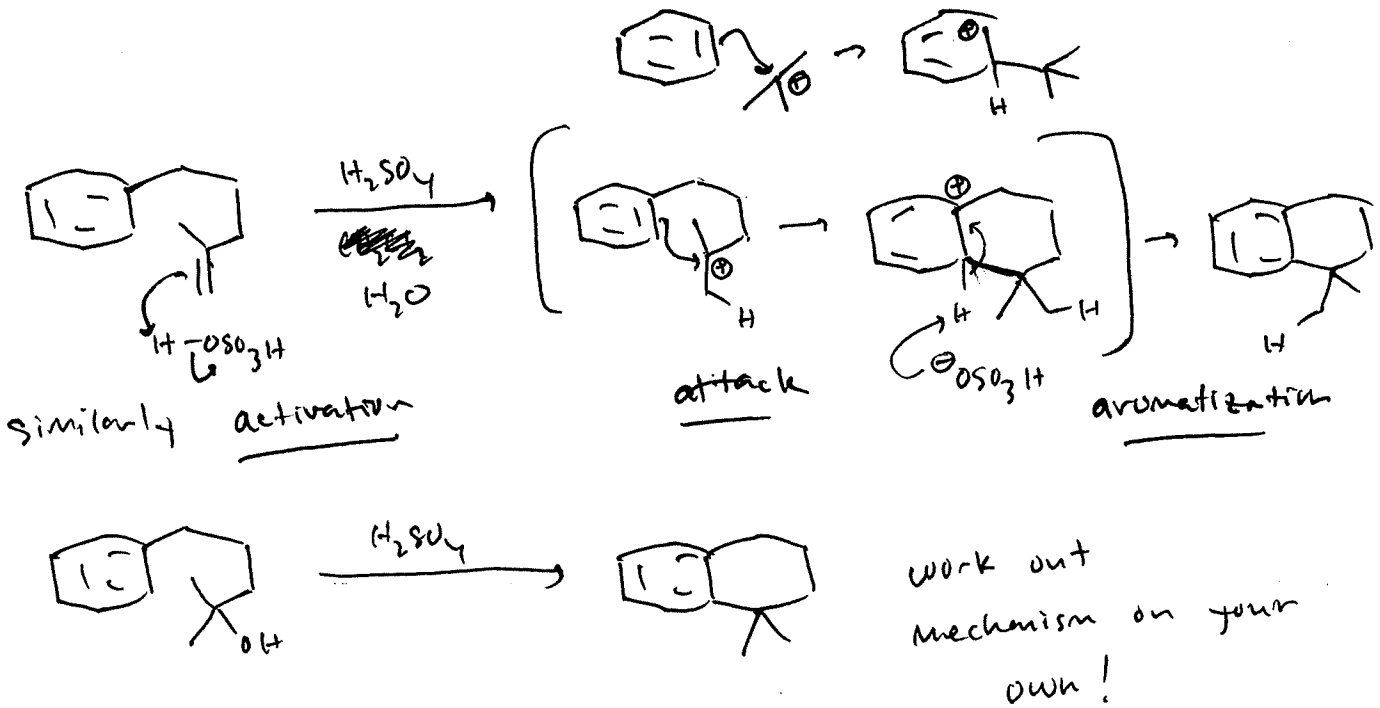
$AlCl_3$

CH_2Cl_2

$FeBr_3$ or $AlBr_3$

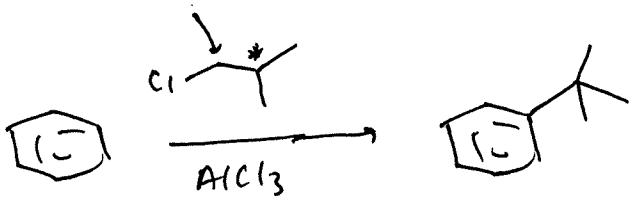
$FeBr_3$ or $AlBr_3$

One can also forge Friedel-Crafts type transformations from alkenes!



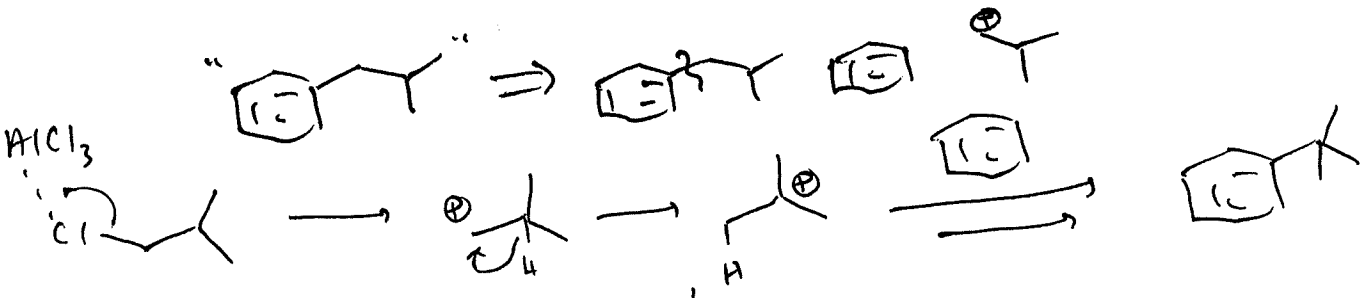
work out mechanism on your own!

[primary halides do not work in ~~alkylation~~ alkylation!



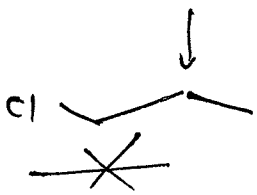
only observed product.

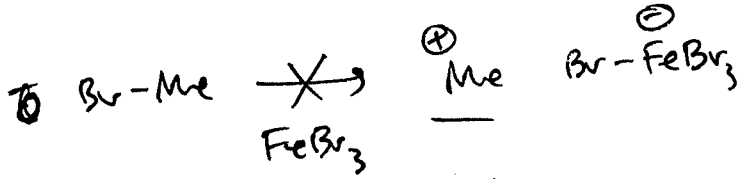
how does this work?



hydride shift!

primary carbocations undergo rearrangement!

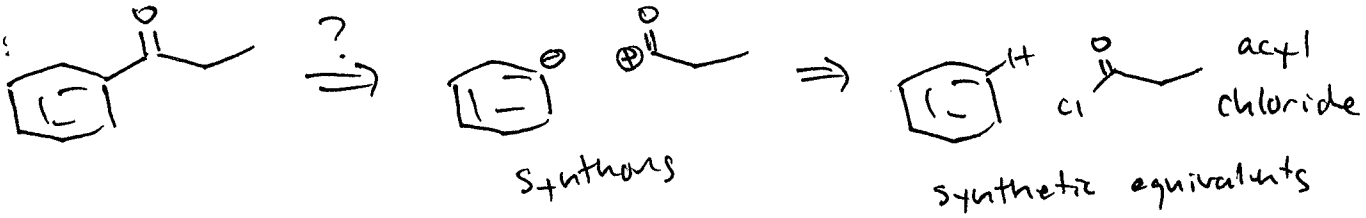




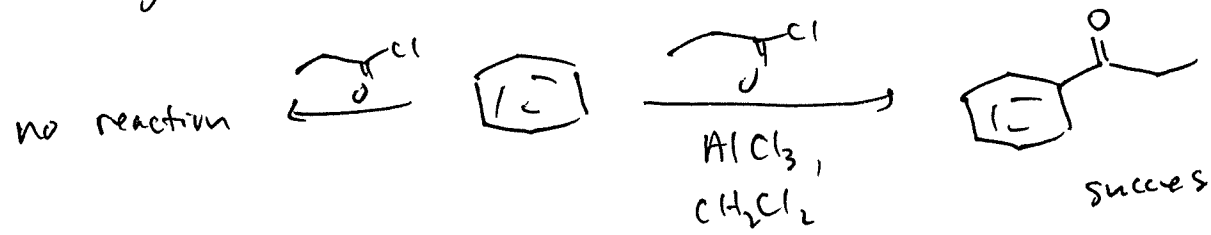
does not proceed.

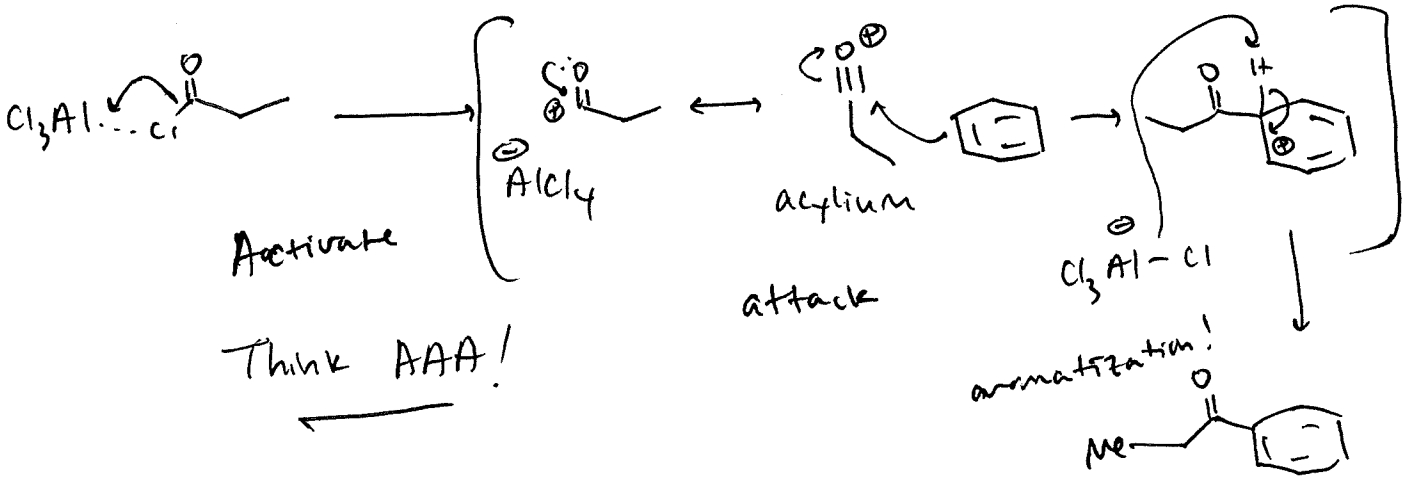
what about other carbon-carbon bond formations?

consider:

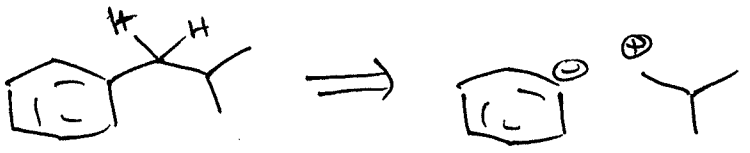


once again, need activation!

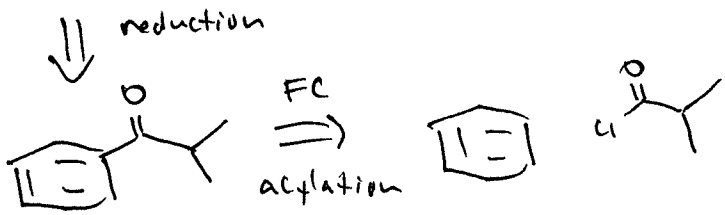




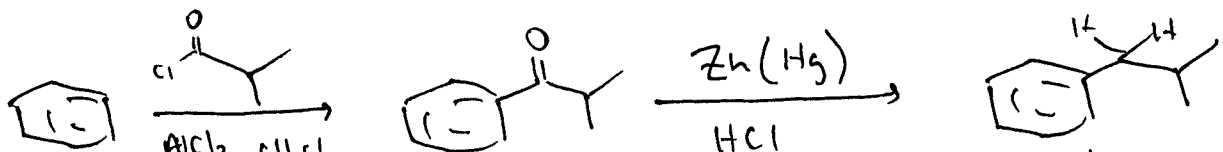
what if we absolutely needed the product of a "primary FC alkylation"?



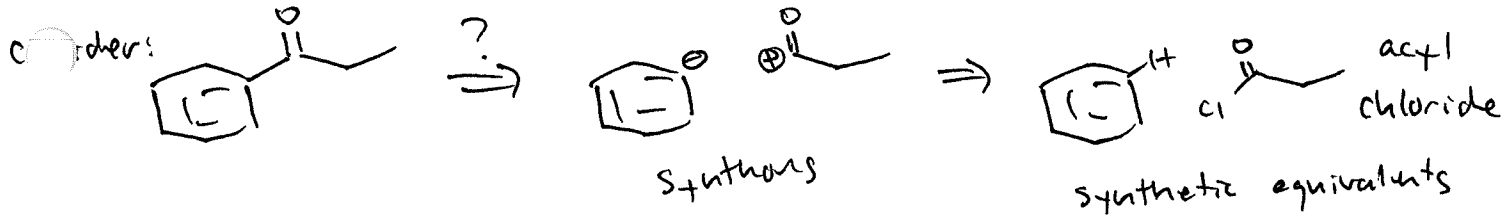
ideal, but not functional due to hydride shift...



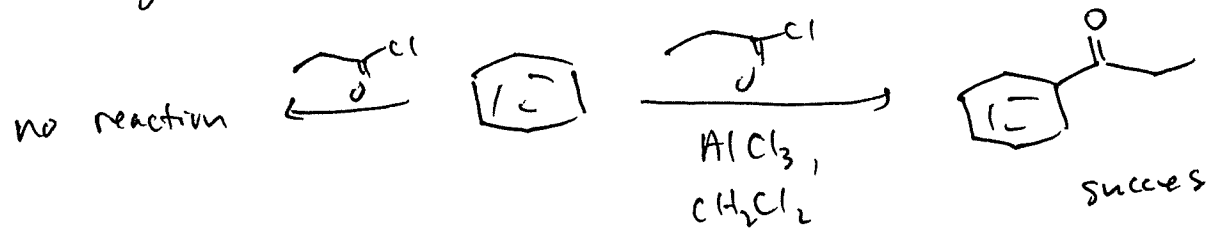
∴

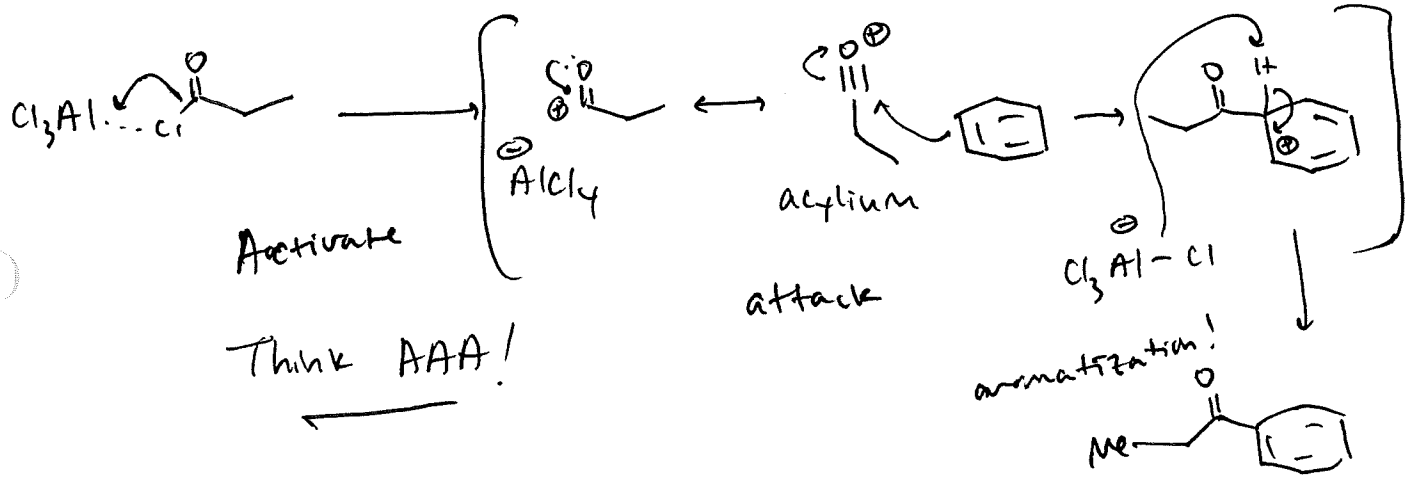


what about other carbon-carbon bond formations?

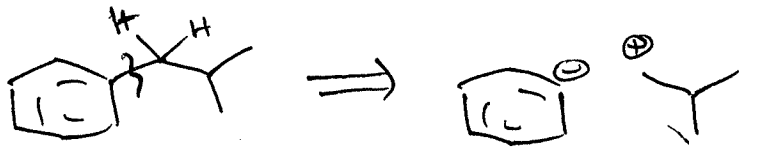


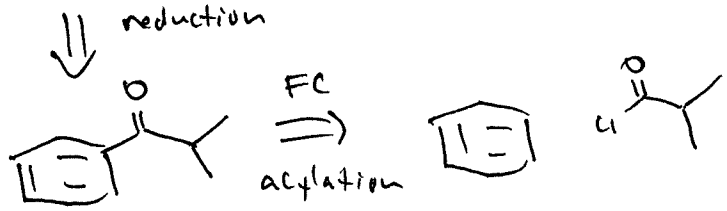
once again, need activation!

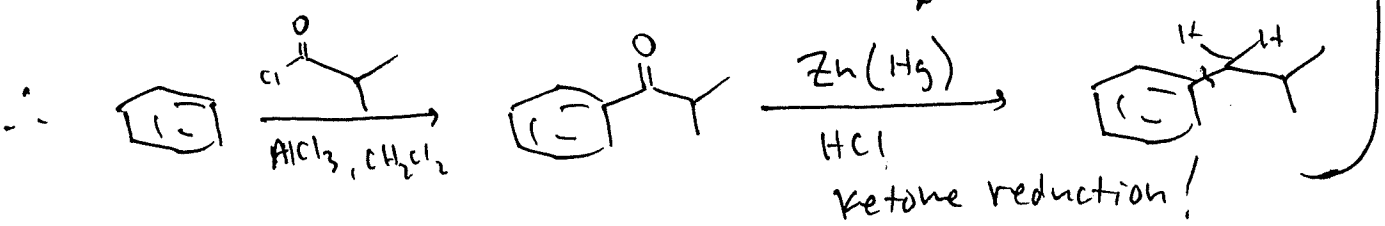




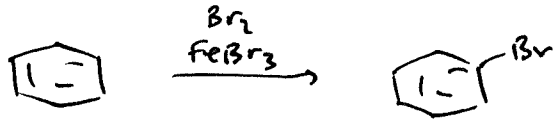
what if we absolutely needed the product of a "primary FC alkylation"?







Electrophilic Aromatic Substitution with substituted Arenes

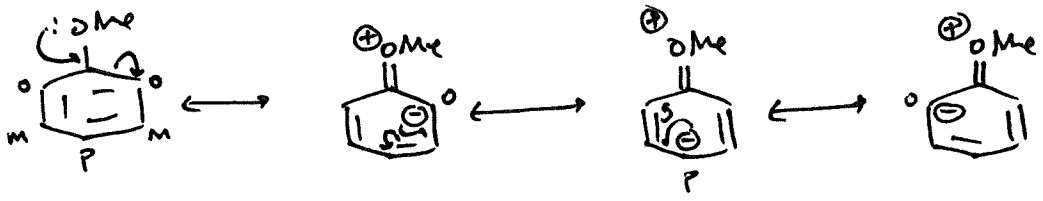
recall : 

all 6 sites are equal.

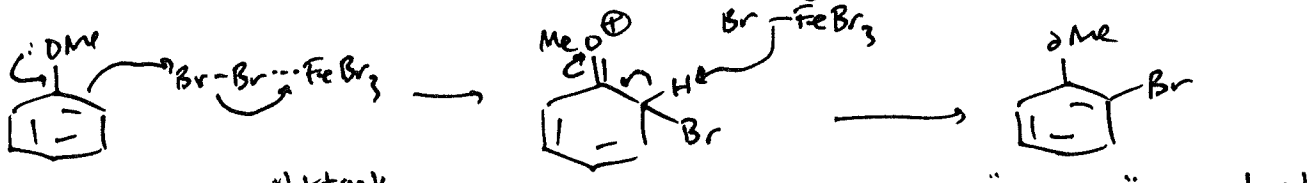
consider: 

anisole
Br_2, $FeBr_3$ → ? where will the Bromine end up?

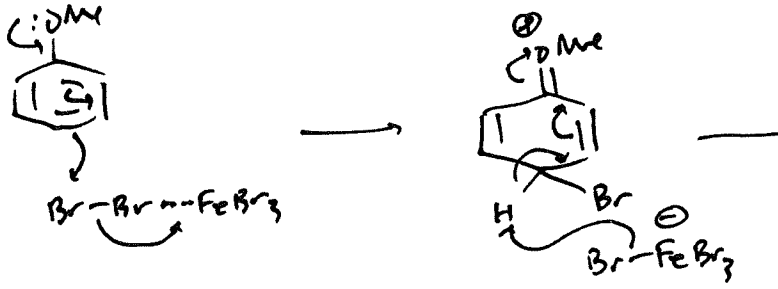
Think about resonance structures.



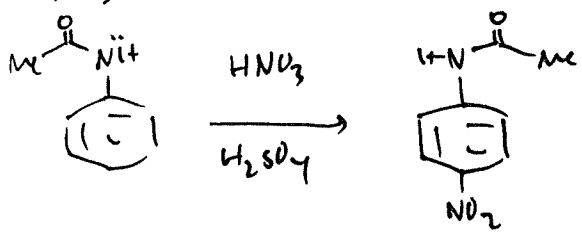
notice how the negative charge only can exist at certain positions. This dictates the reactivity!

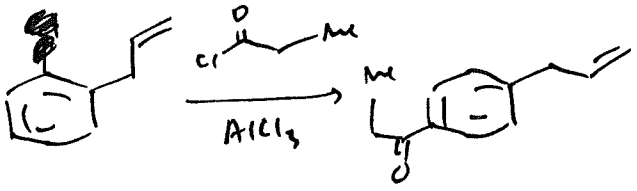


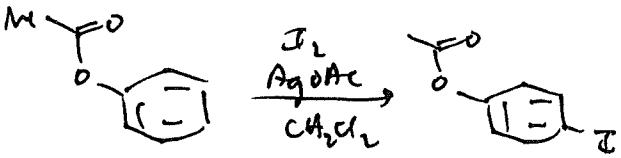
or

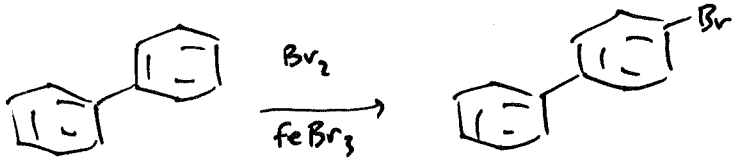


This behavior holds true for electron-donating substituents:



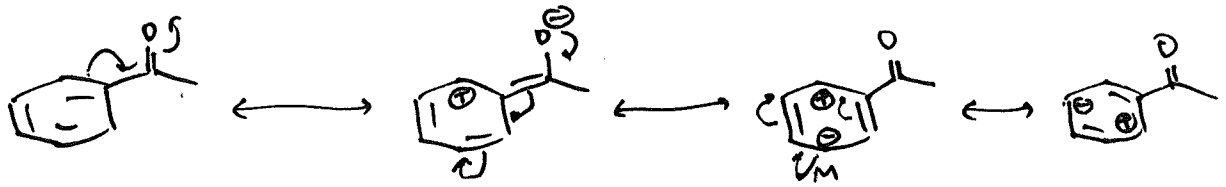






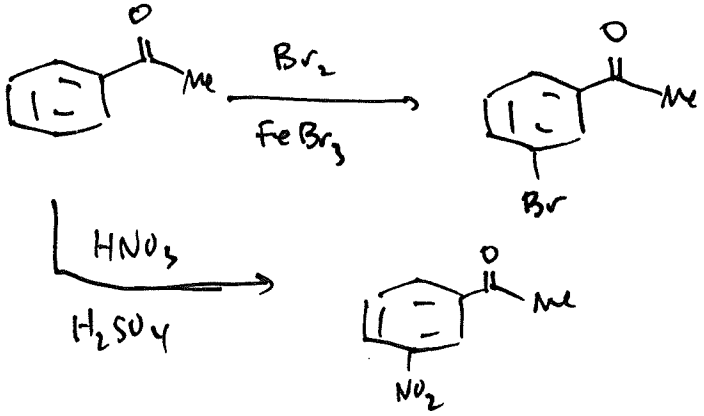
Effect of Electron-withdrawing groups

consider:

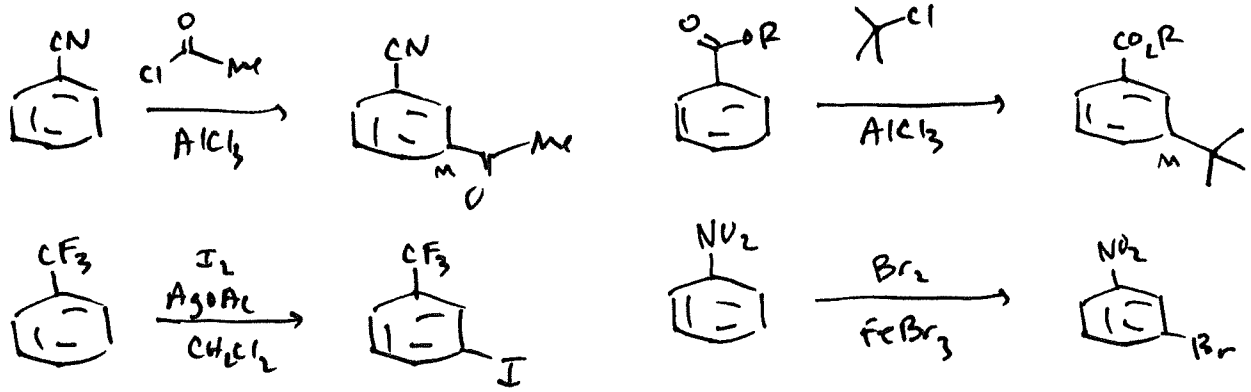


resonance dictates that negative charge is at "meta" position.

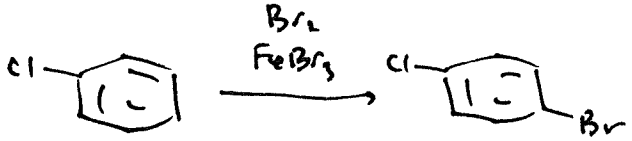
therefore,



other electron-withdrawing groups have the same effect.

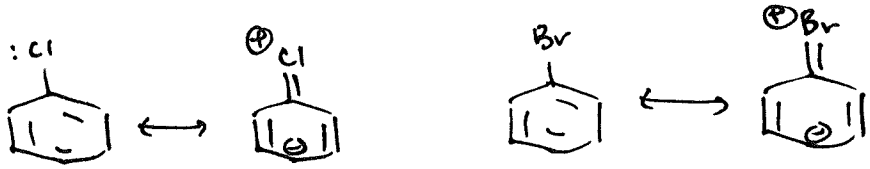


Halogens: Electron withdrawing, but o/p activating



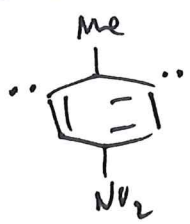
Major product.

halogens are o/p directors because of resonance.



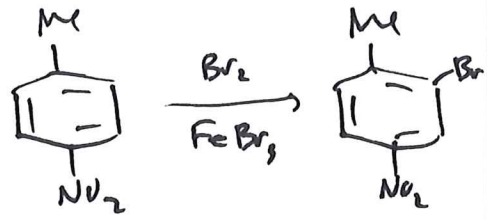
Additive Substituent Effects

Consider:



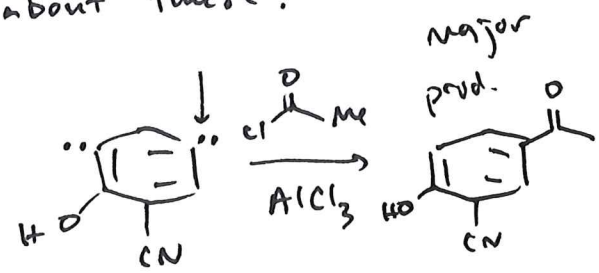
Me is o/p activating

NO_2 is m activating ∴

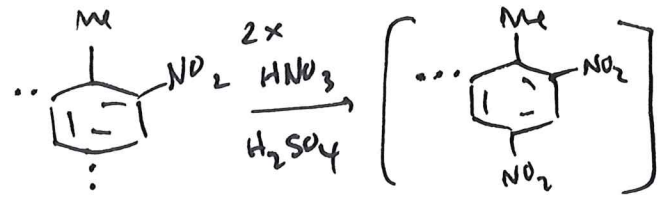


What about these?

- OH is o/p
- CN is m

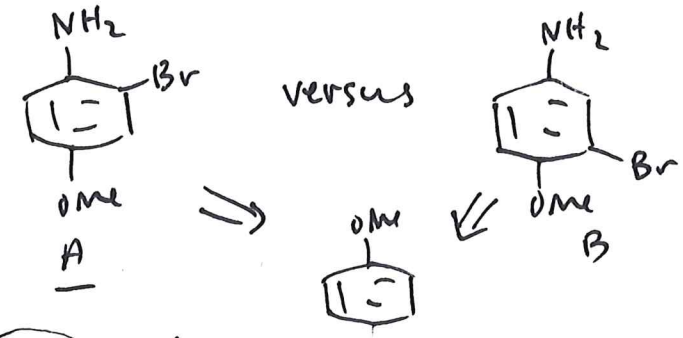


sterically driven outcome as well as electronic.



Functional group interconversion can be your friend!

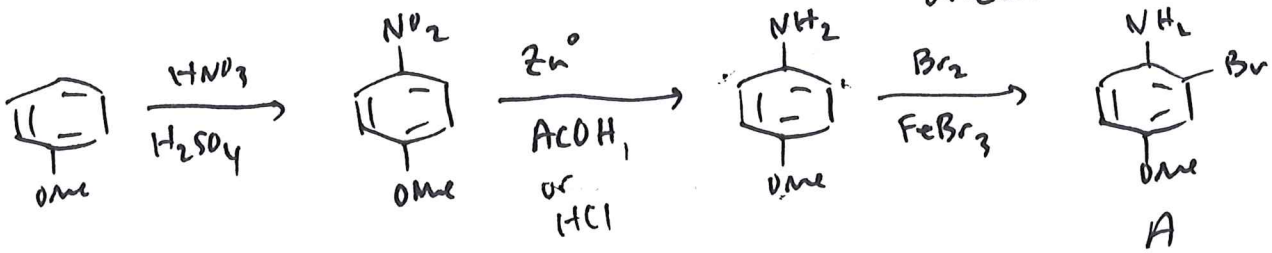
Consider:



How would you synthesize each of these compounds?

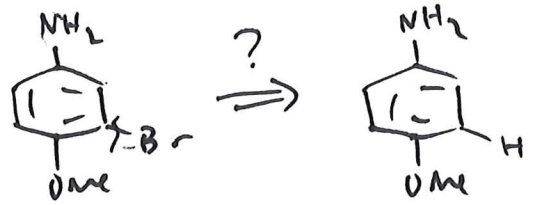
A

Forward Synthesis:

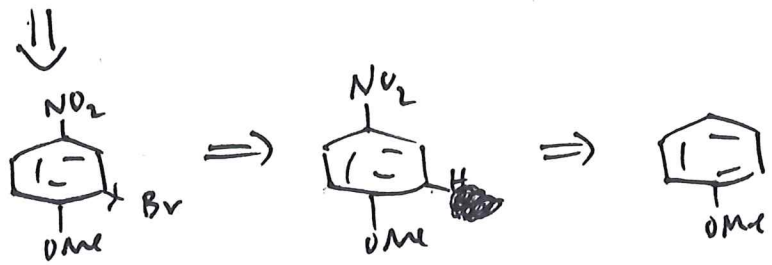


A

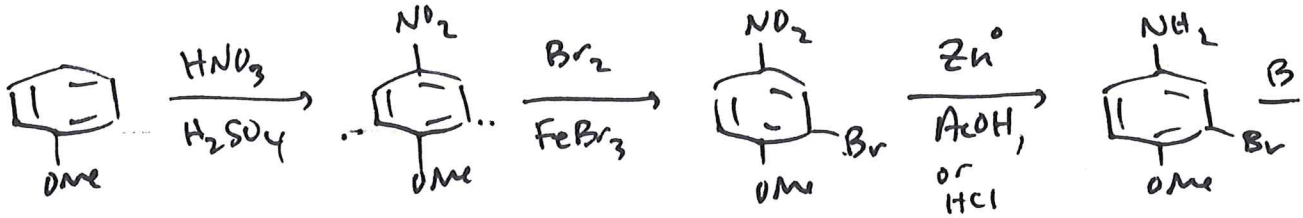
What about compound B?



not accessible, not possible because of directing effects of groups.

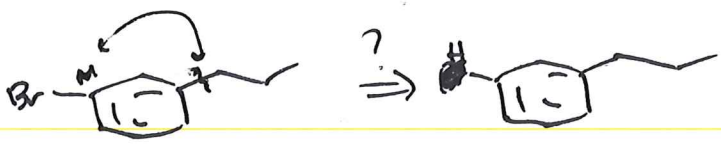


Forward synthesis:

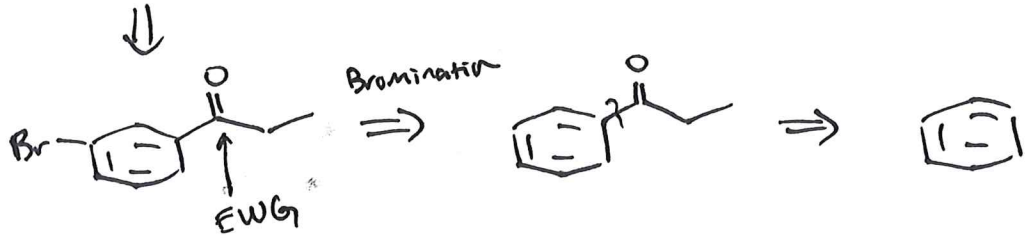


Consider:

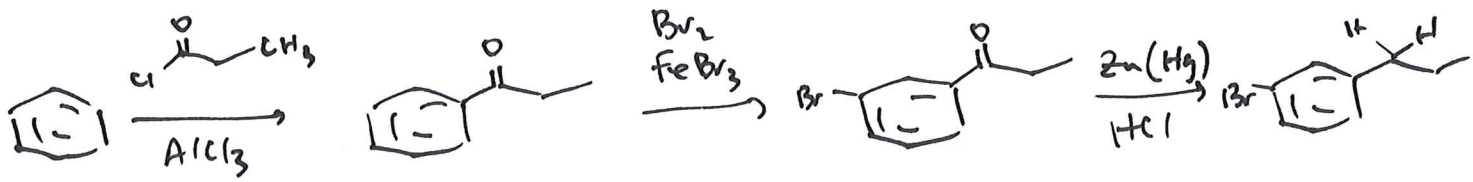
How would one synthesize this compound from benzene?



not possible because of substituent effects.

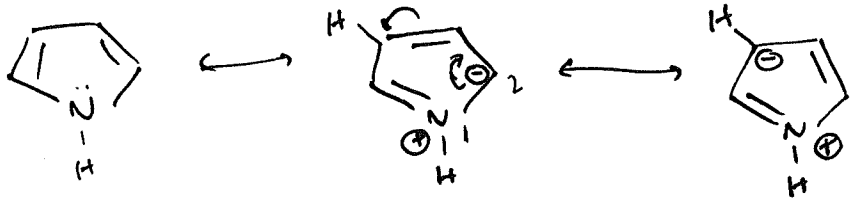


Forward synthesis:



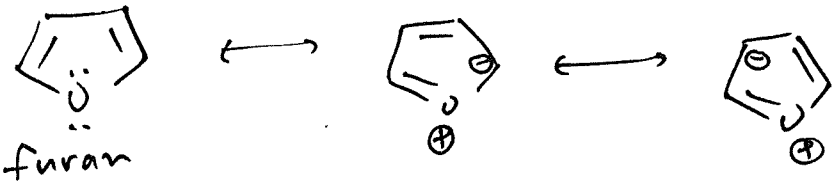
Electrophilic aromatic substitution on heterocycles

Consider:

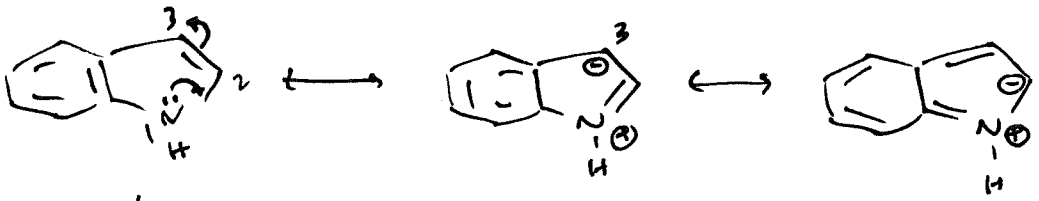


2 potential spots for addition

pyrrole

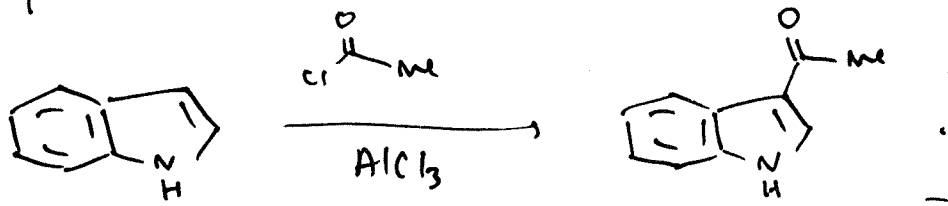


furan

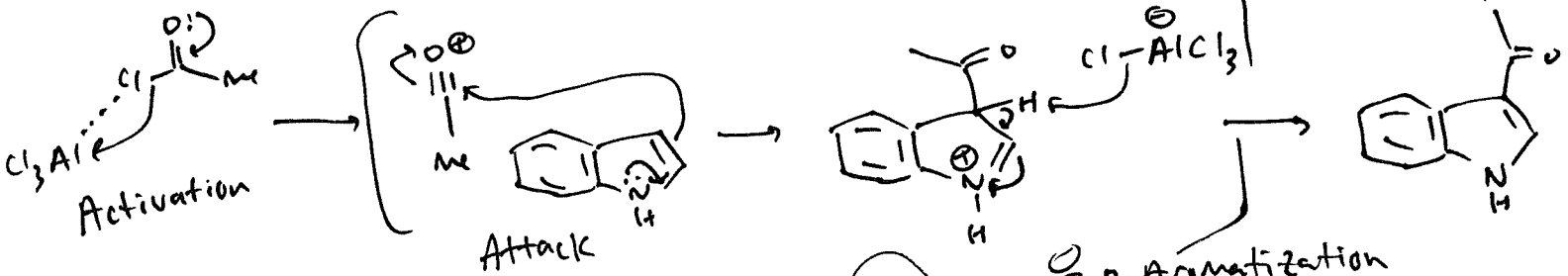


indole — major contributor — minor contributor.

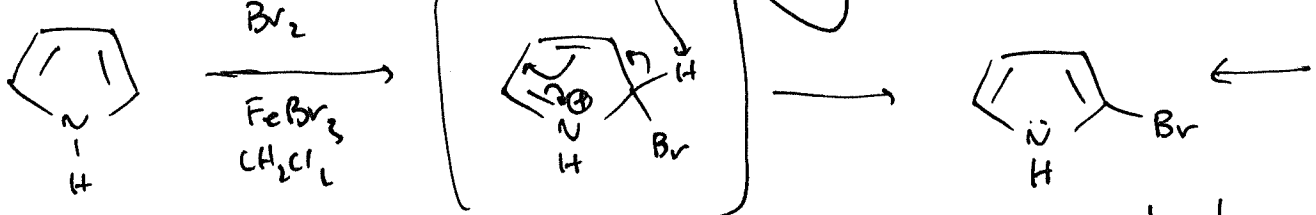
example:



AAA mechanism!



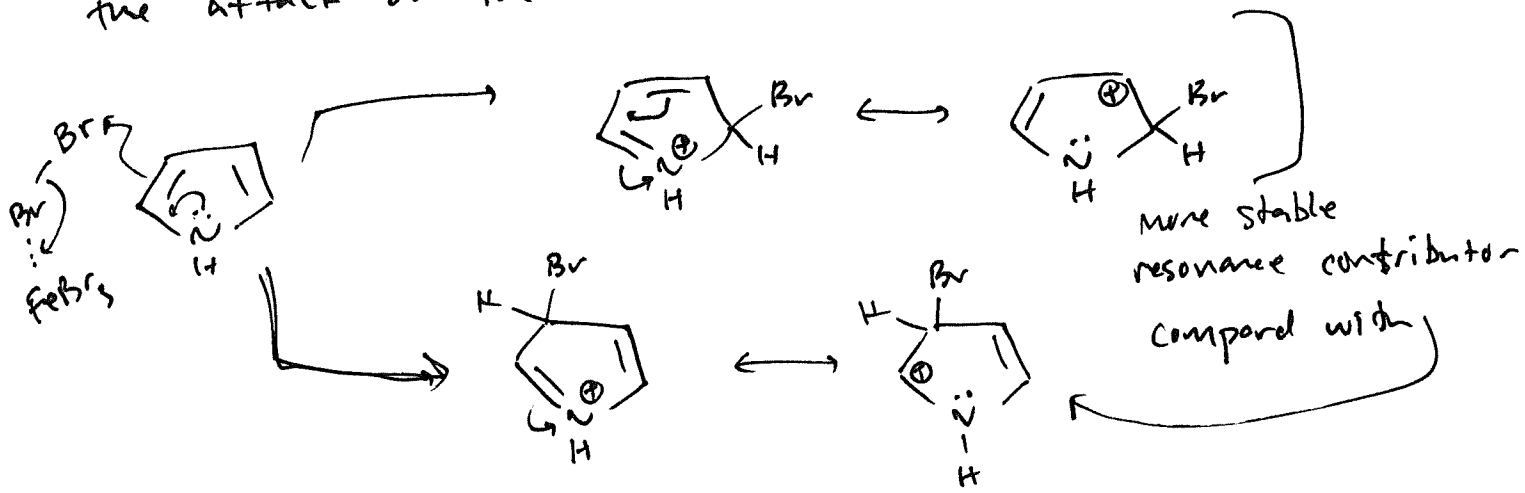
Activation — Attack — Aromatization



major product

but why?

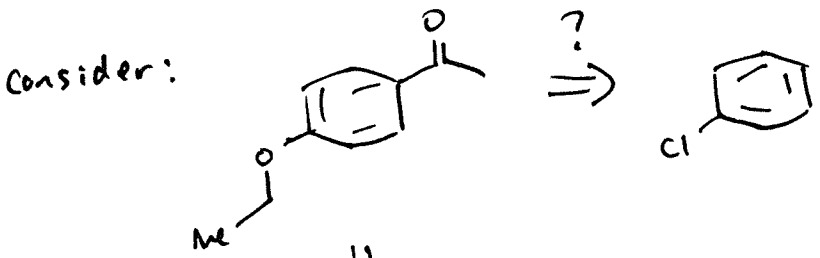
If we consider the two possible intermediates after the attack on the bromine...



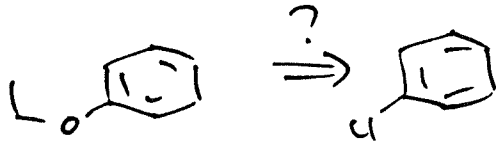
Always consider stability of resonance structures when considering regioselectivity outcomes!

Nucleophilic Aromatic Substitution

consider:

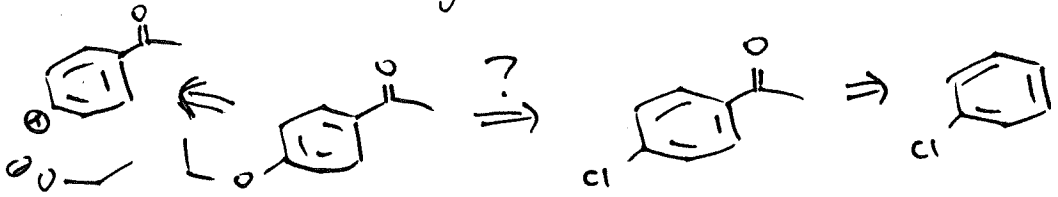


how would we construct this from chlorobenzene?

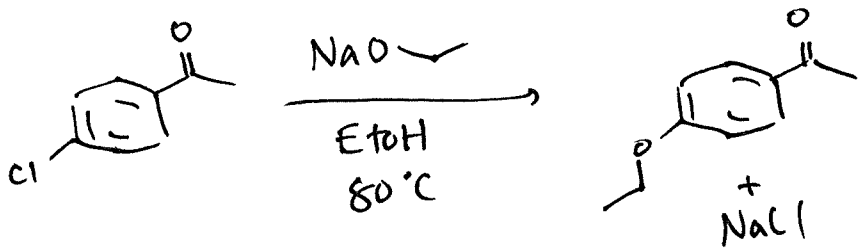


this might be a tricky substitution.

what about using the chloride differently?



what kind of reaction could we employ for the first disconnection?

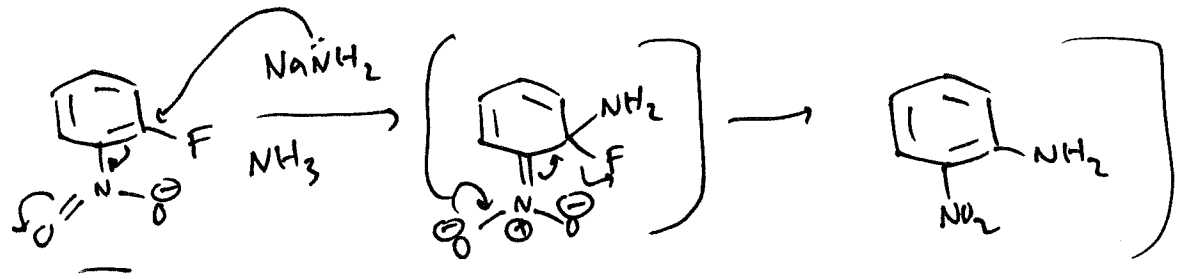


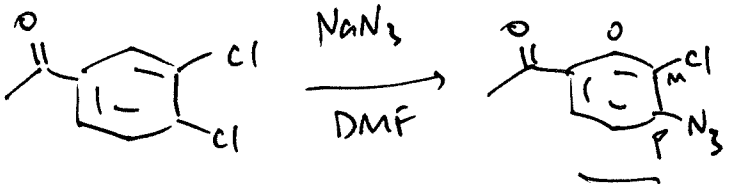
success! but how?

mechanism: addition elimination

$Cl^{\ominus}$ is leaving group!

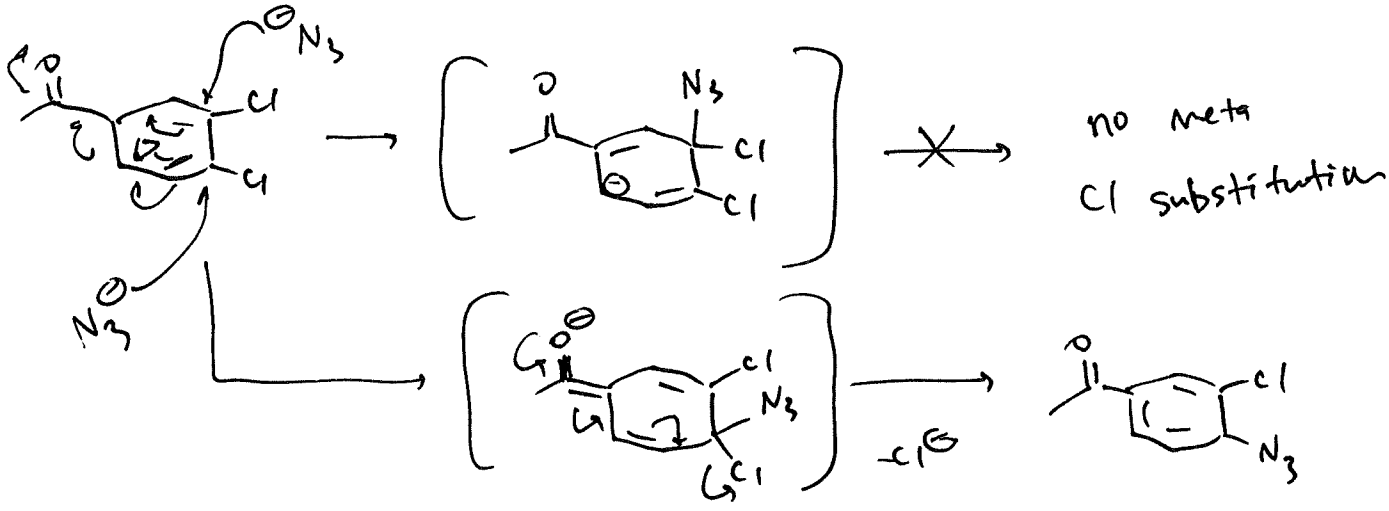
For this type of reaction, you need an EWG either ortho or para to the leaving group!





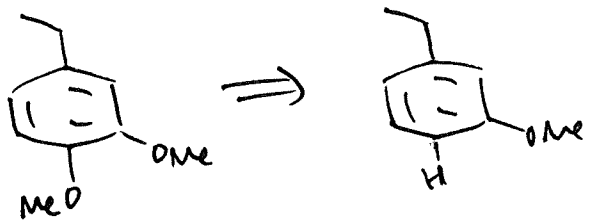
← this halide remains because it is meta to EWG

If we try substituting the "meta" chloride, mechanism fails!

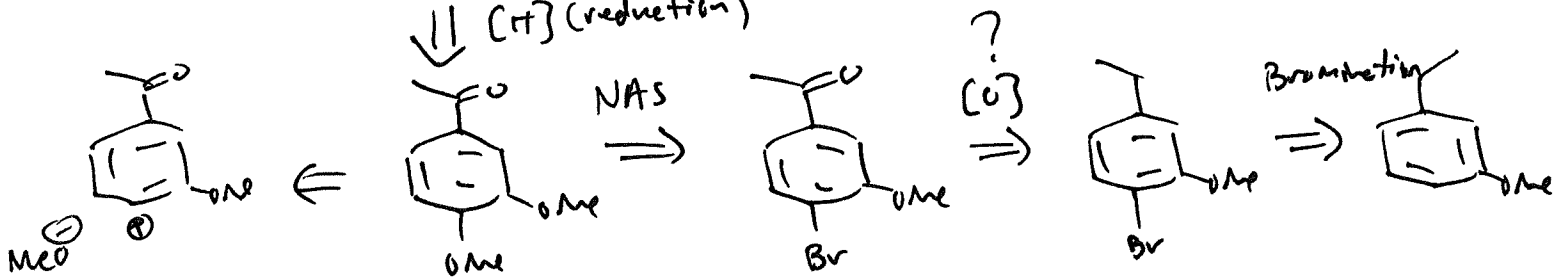


lower energy pathway

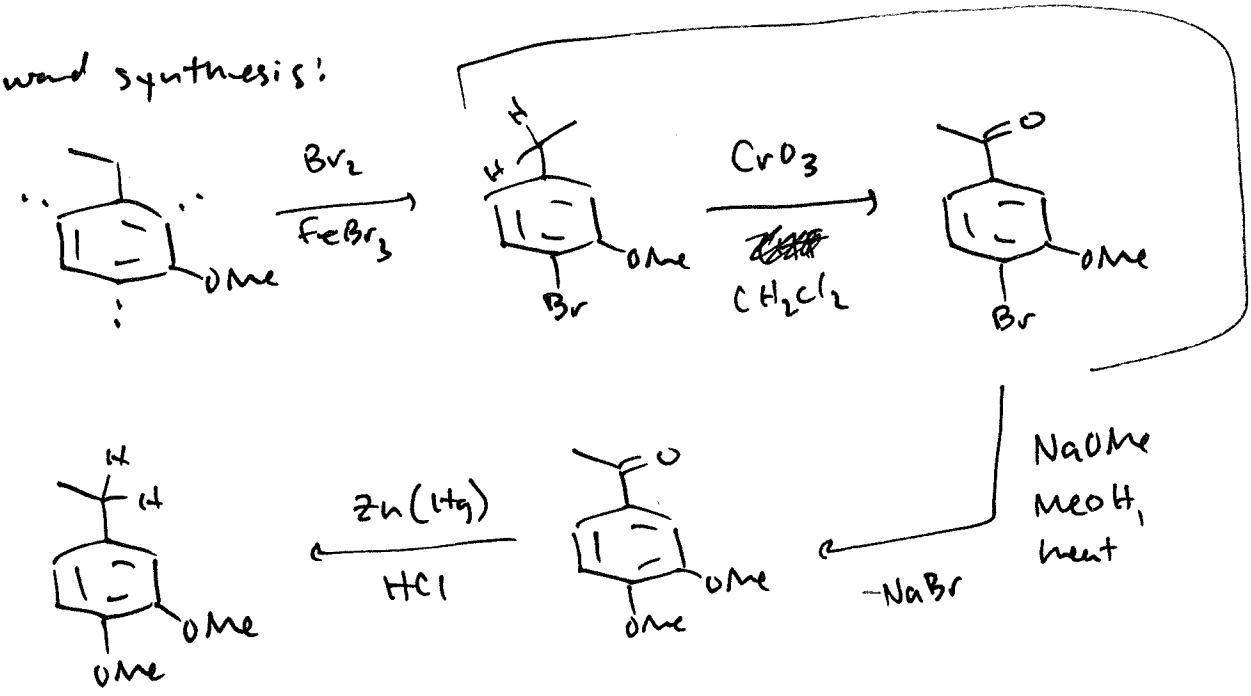
consider:



how would we install this methoxy group?



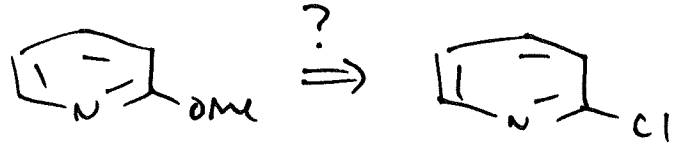
Forward synthesis:



Electrophilic Aromatic Substitution and Nucleophilic Aromatic Substitution can be used in conjunction with one another!

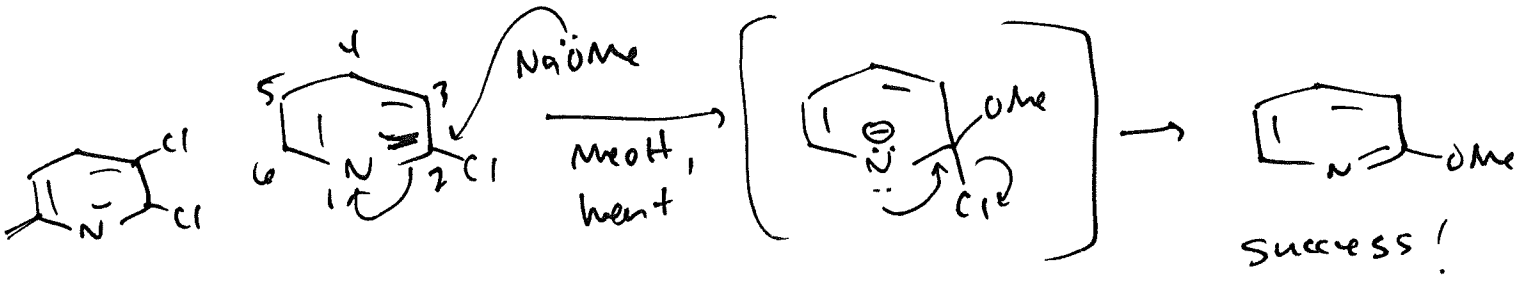
What about nucleophilic aromatic substitution on heterocycles?

consider:



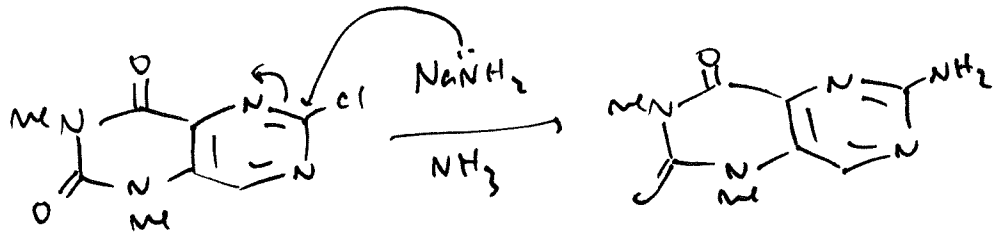
2-methoxy pyridine

can we do this OMe ← Cl replacement directly?

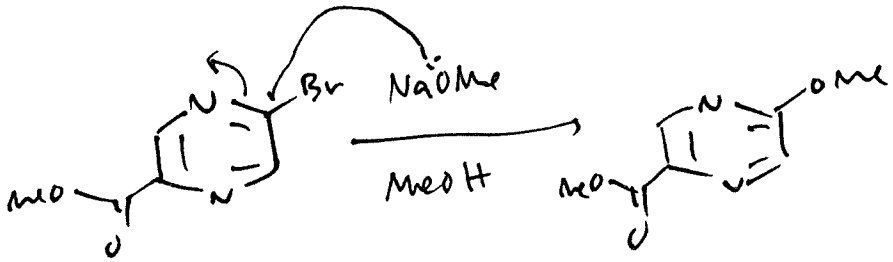


typically for NAS on pyridines, the LG has to be at either the 2 position ("ortho" to N) or the 4 position ("para" to N), or the 6 position (also "ortho" to N)

This NAS also works on other six-membered heterocycles:

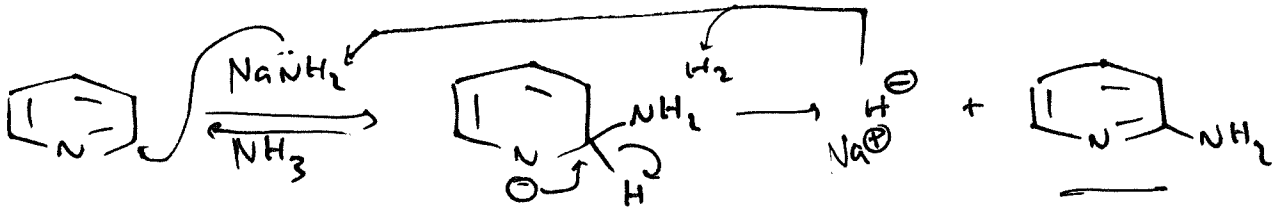


mechanism is analogous to the one above!



Note: Most of the nucleophiles used in S_N2 reactions are operable in NAS rxns!

The chichibabin reaction!

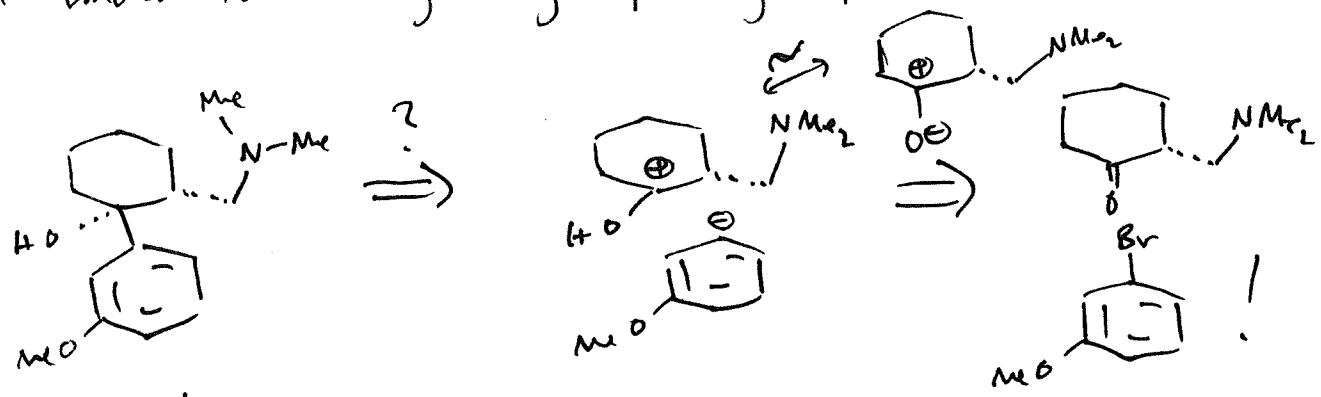


The pka of H_2 is 38 and the pka of NH_3 is 36 so they are similar. The thermodynamic driving force of this reaction is that the $H^\ominus$ leaving group is lost as H_2! This reaction only makes 2-aminopyridines however!

Organometallic Chemistry

organometallic - pertaining to a compound containing a metal atom bonded to an organic group or groups.

consider:



tramadol
(pain relief)

Dear Prof. Smith, Halides are electrophiles and could not be used as synthetic equivalents for a ⊖ synthon. You've lost your mind, go home, you're done.

Sincerely,

Upset Student

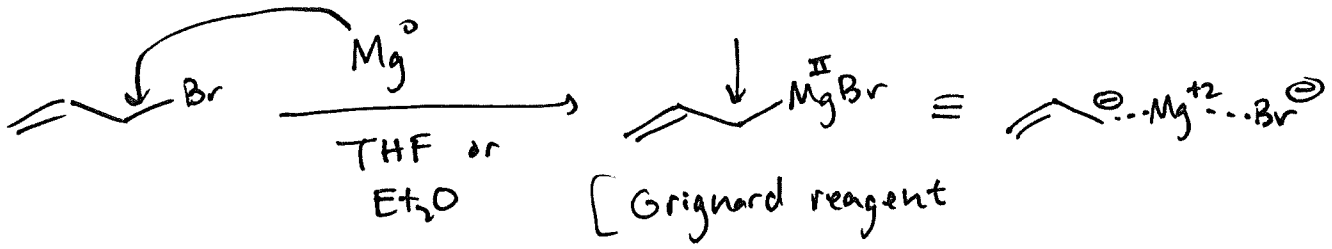
The reality is that we can use halogens as precursors to nucleophilic carbons.

Consider:

Suddenly My electrophilic halide has become a nucleophilic anion!

nucleophile!

How is this done in practice?

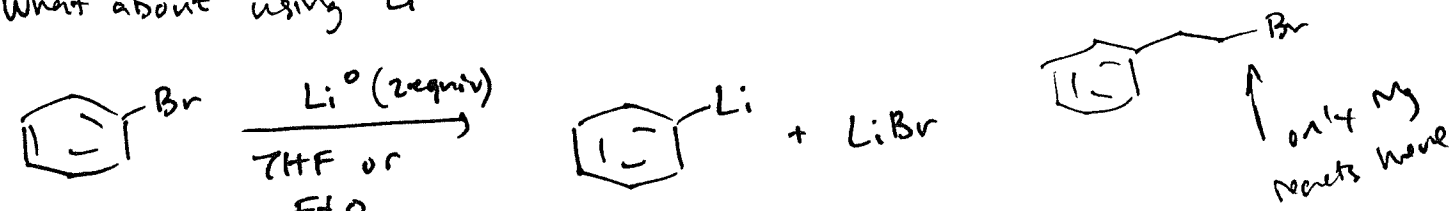


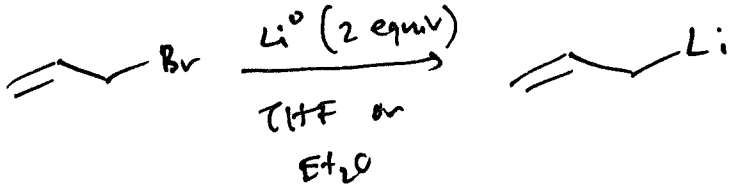
[Grignard reagent

remember how a metal halide can be made:

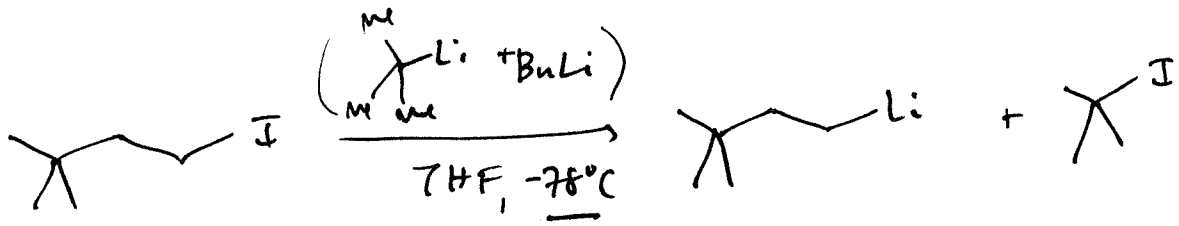
$Mg^0 + Cl_2 \longrightarrow Mg^{II}Cl_2$ this is the analogous process!

what about using Li^0

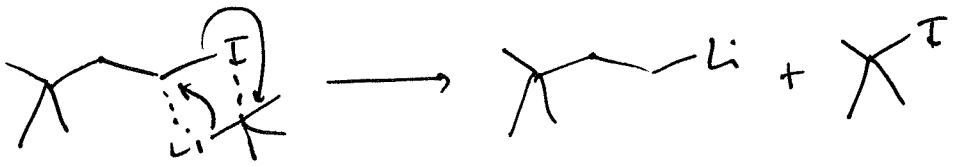




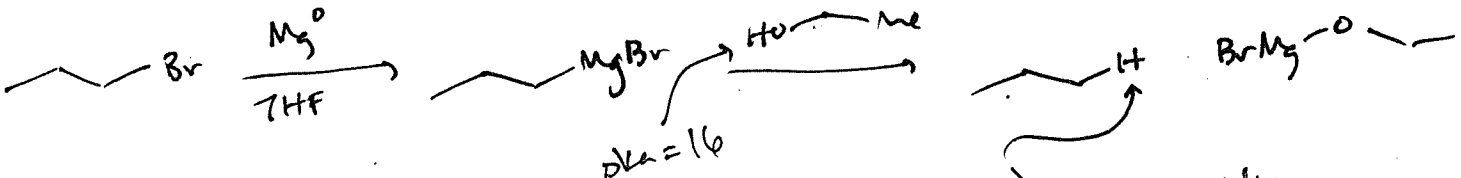
You can also make an organolithium reagent from a process called Li/x exchange (Lithium/halogen exchange):



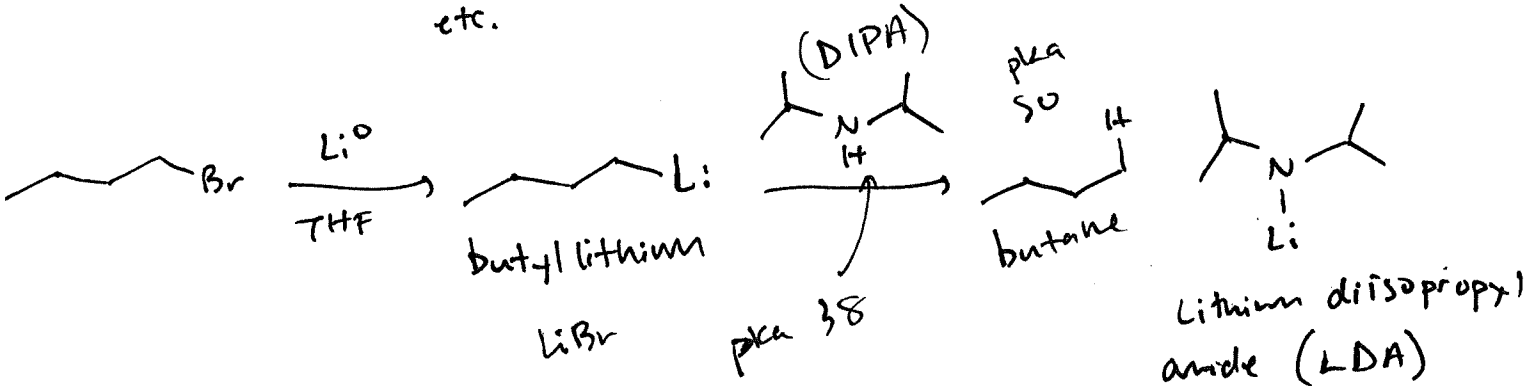
The primary lithiate is more thermodynamically stable, so the lithium jumps from the tertiary center.



"Basic" reactivity of organolithiums and Grignard reagents

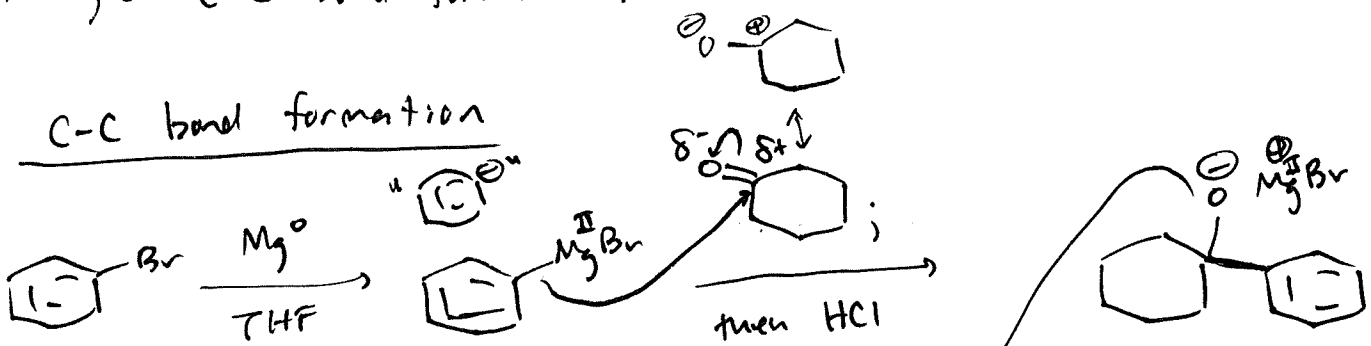


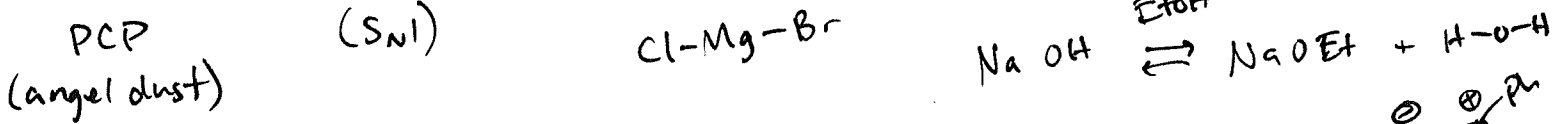
because it is an effective carbanion (pka ~ 50) any acidic alcohol, thiol, amine, etc. will react with the Grignard reagent or lithiate.



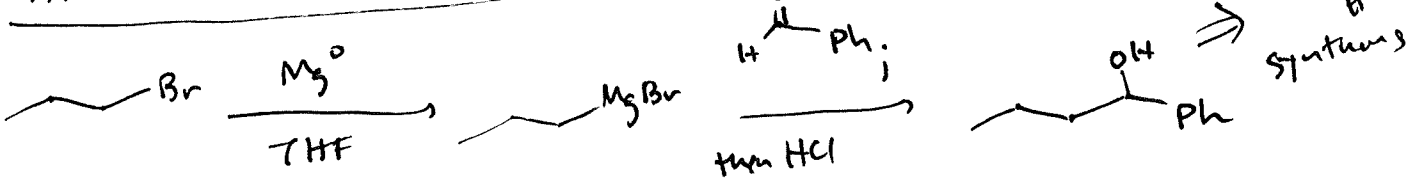
This acid/base reaction will happen first before any strategic C-C bond formation.

C-C bond formation

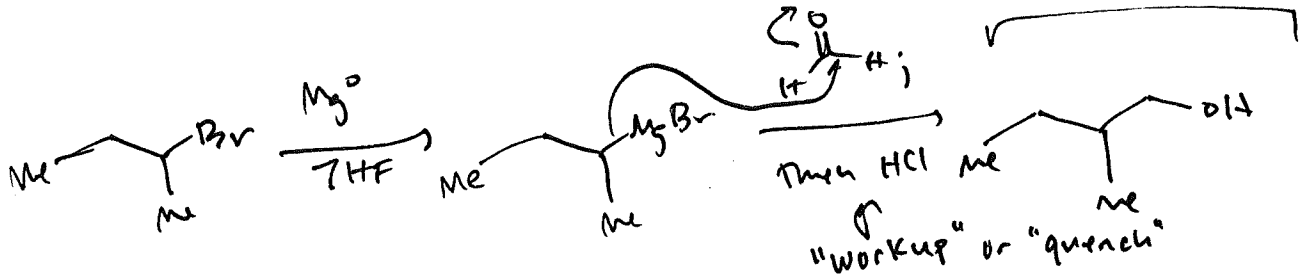




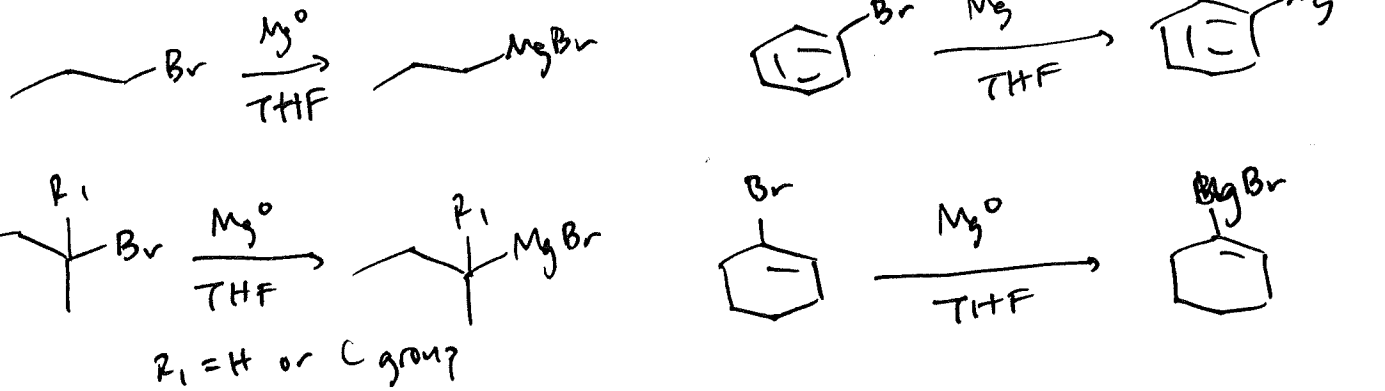
Addition to aldehydes

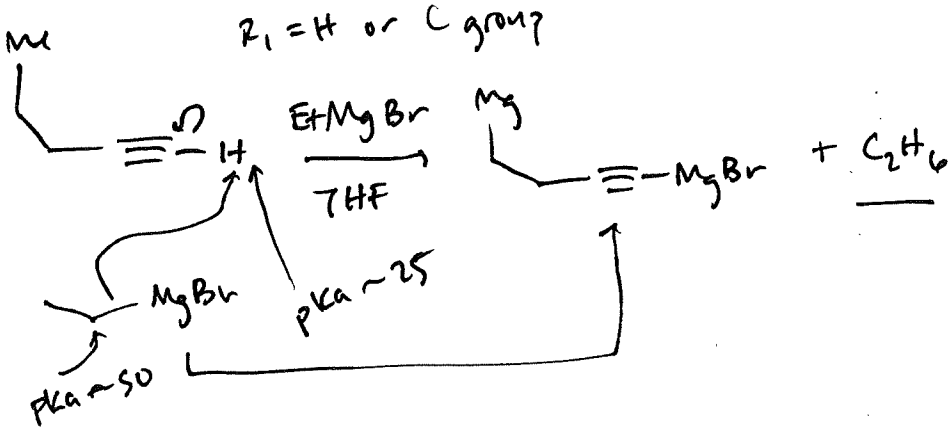


addition to formaldehyde



Grignard reagents can be made from almost any halide, but Br is the most popular, along with I. Chlorides are more rare.

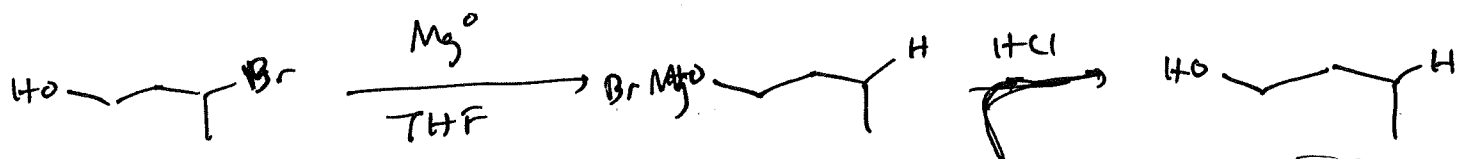




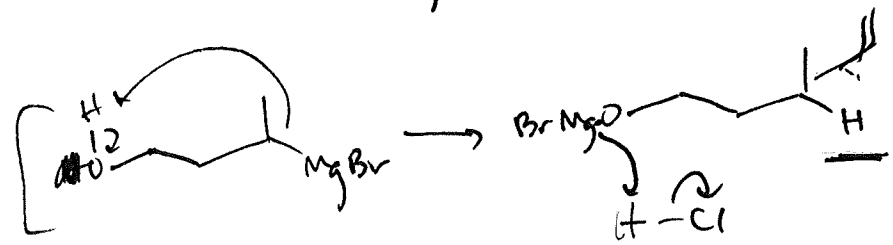
+ C_2H_6

alkynyl Grignards are made through an acid/base rxn with another Grignard.

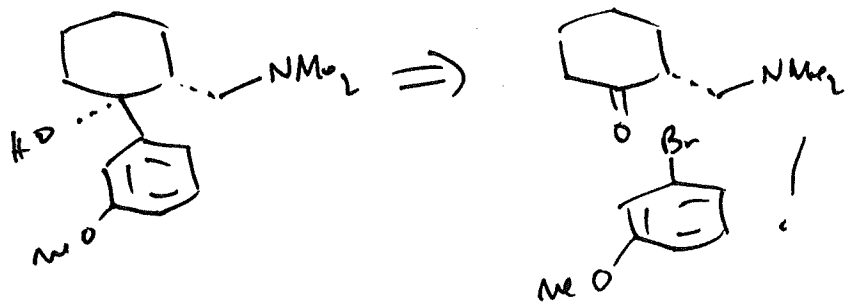
Draw a mechanism for the outcome of this reaction!



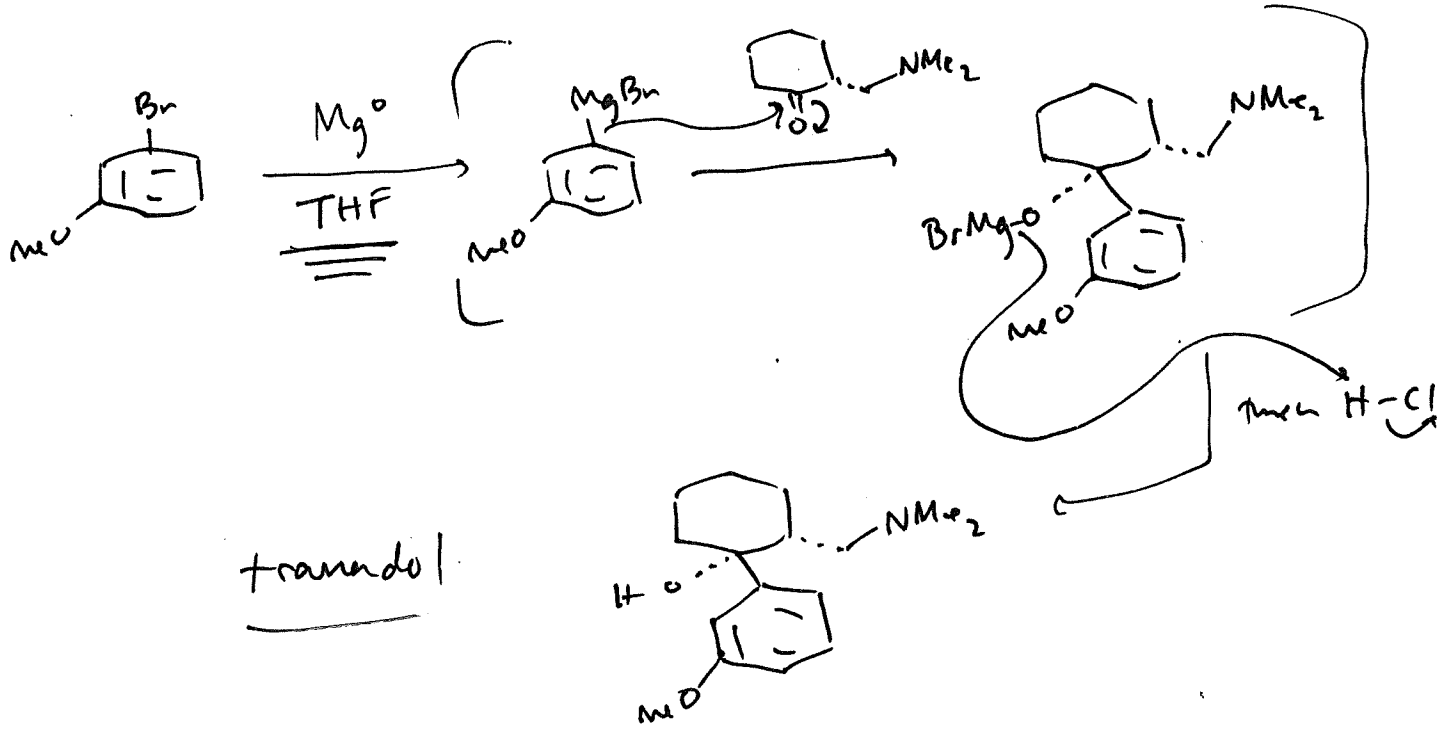
having an alcohol in your halide exposed is bad!



Back to the original problem



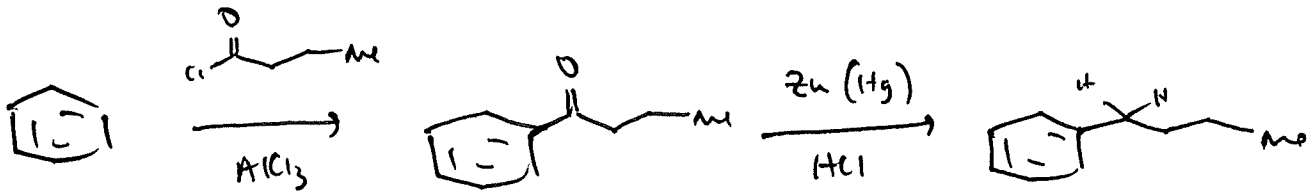
Forward synthesis



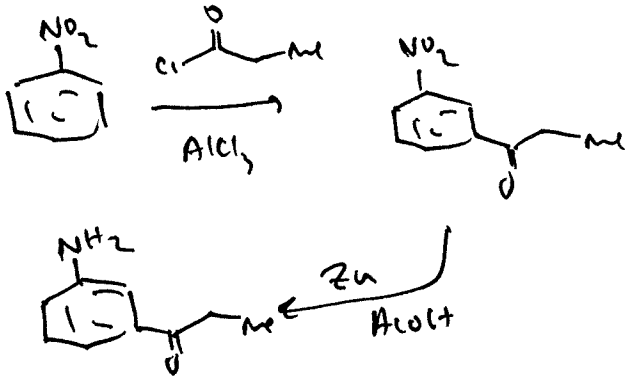
tramadol

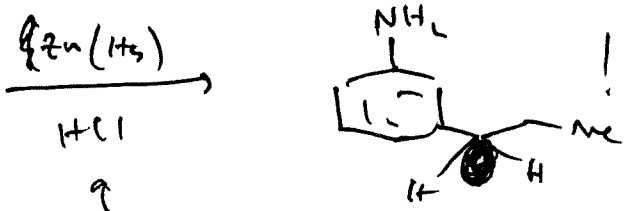
Tying up a loose end...

recall...



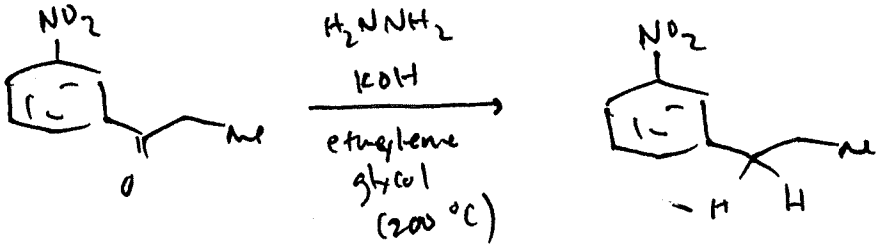
Consider:





This reduction will reduce both NO_2 groups and carbonyl groups.

∴



chemoselective reduction of carbonyl.

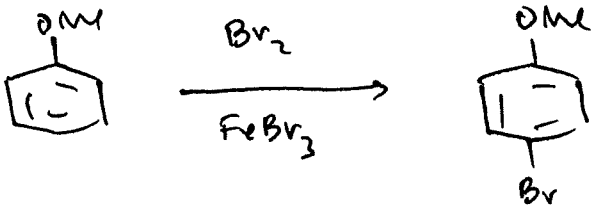
This reaction is called a Wolff-Kishner reduction.

The mechanism of this reaction will become important later.

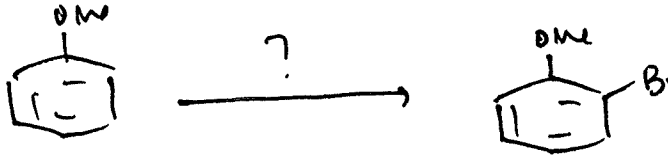
[redacted]

Ortho Lithiation

Consider:

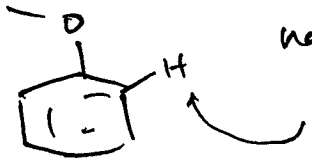


Major product due to steric effect of OMe.

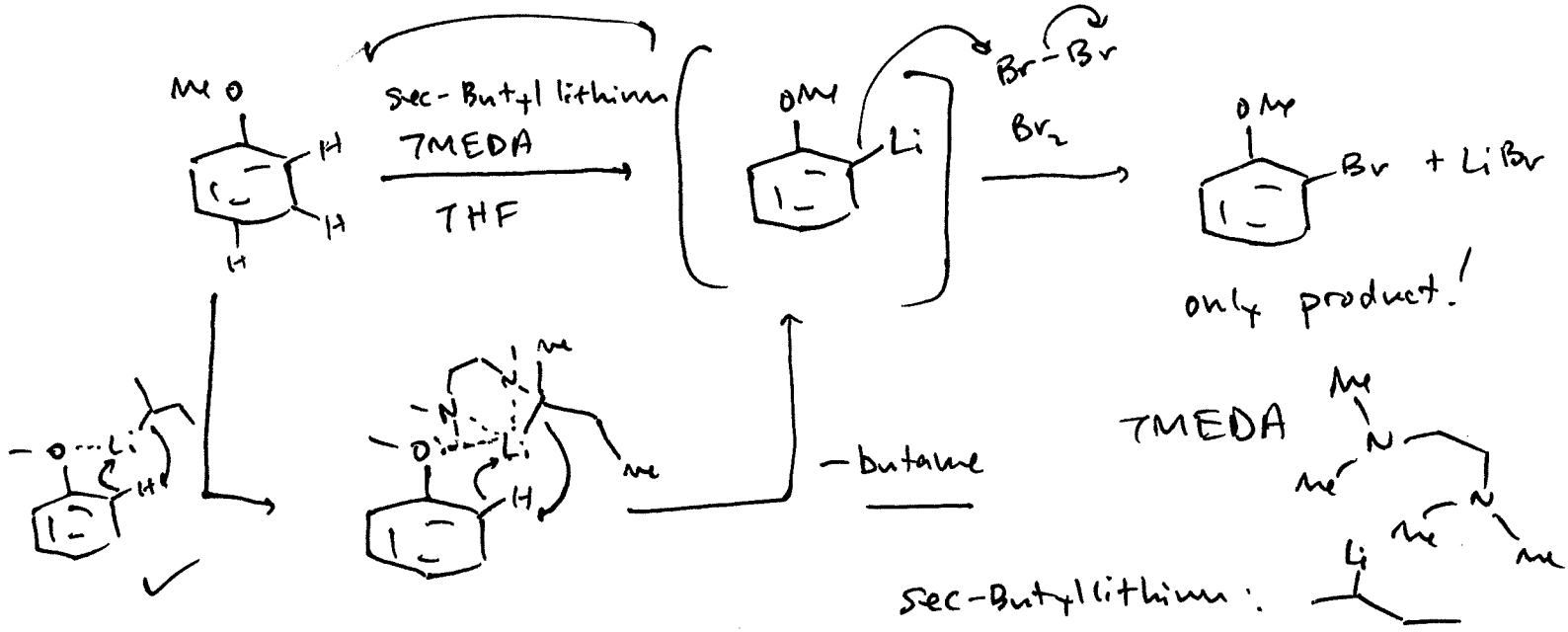


Major product. How?!

The answer lies in a process called "ortho lithiation"

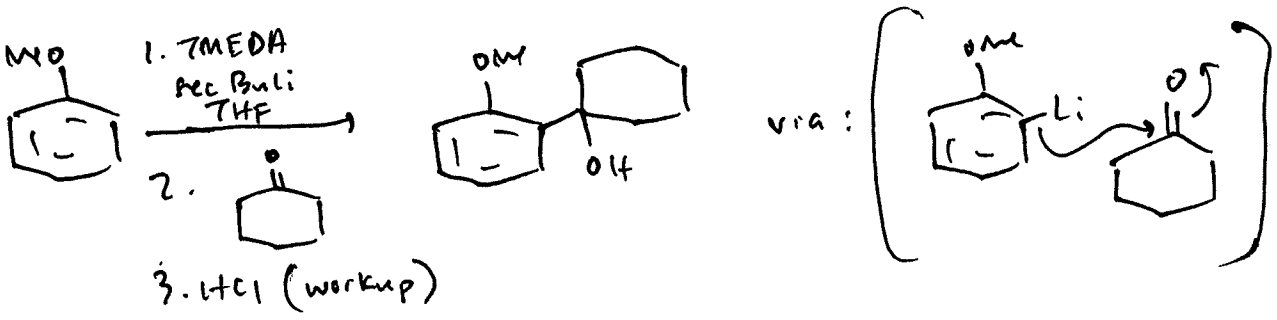


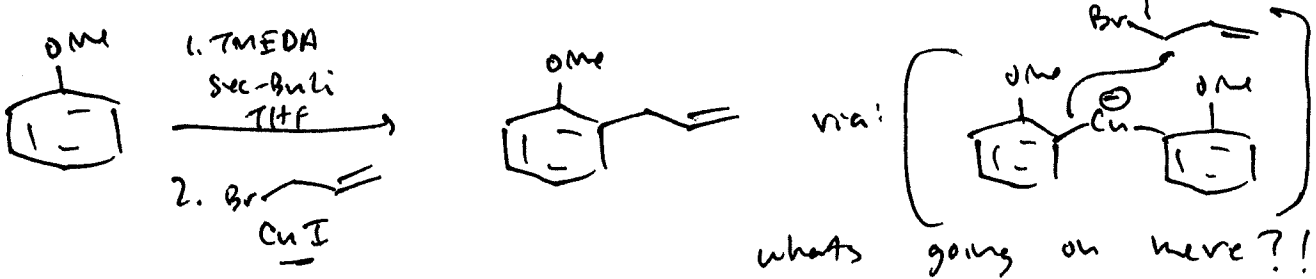
naturally these hydrogens are not especially acidic on their own. But, what if we could bring a strong base close enough...

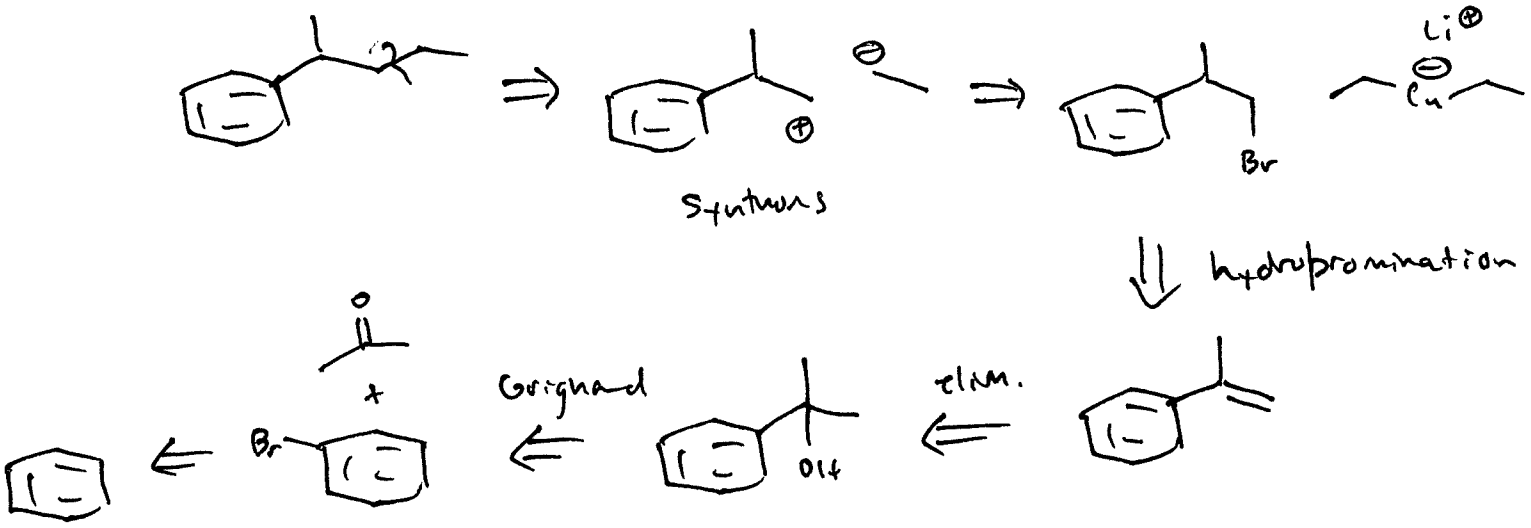


The methoxy group "directs" the removal of the ortho hydrogen to selectively give the "ortho-lithiated" arene.

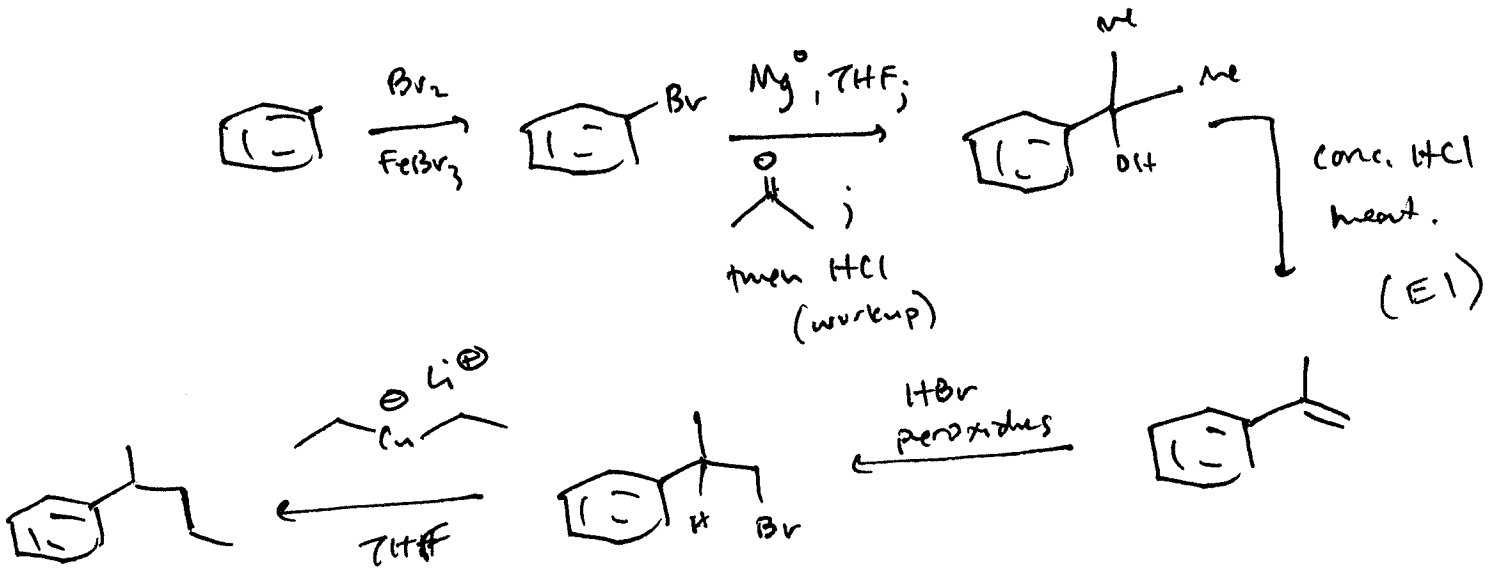
These lithiates can be used to trap a variety of electrophiles.



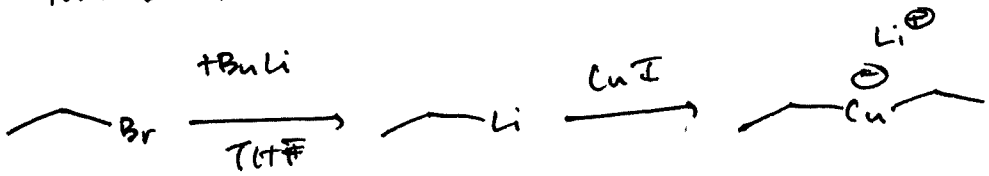




Forward synthesis:



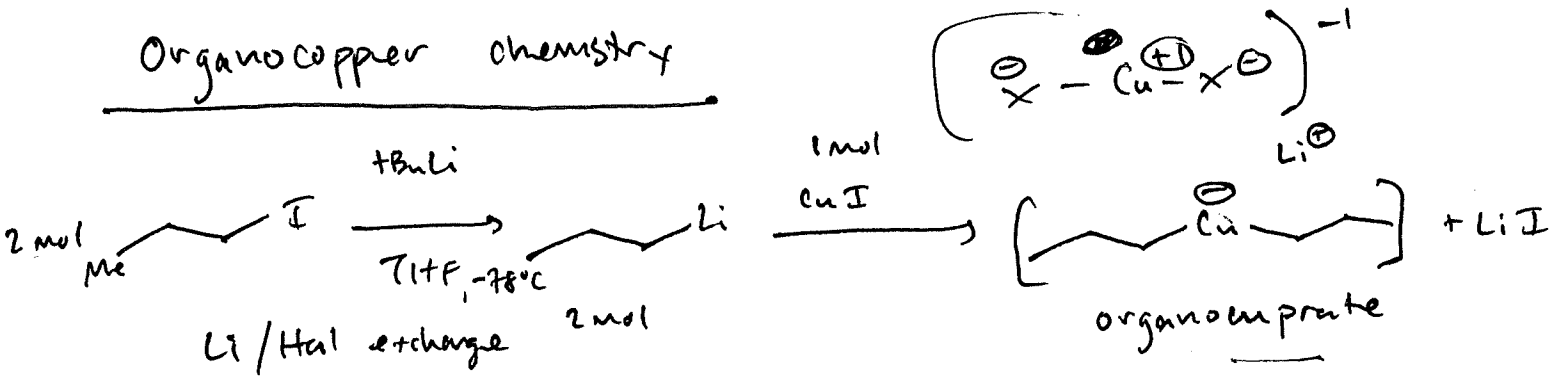
organocuprate formed from:



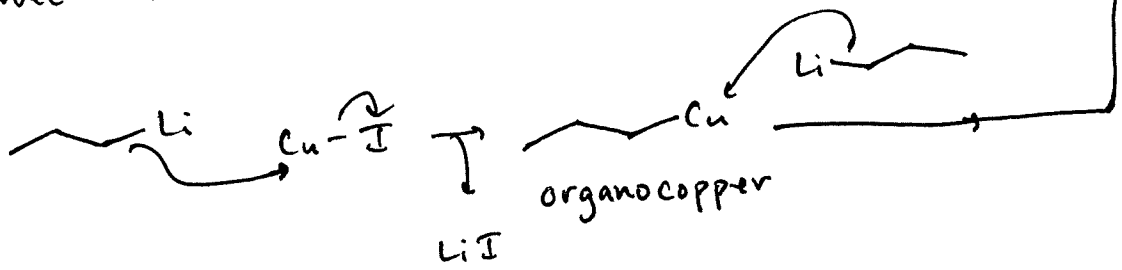
with Grignard and organocopper species in your toolbag, you can make a plethora of new C-C bonds!

* In general these organocuprates react best with primary halides. Tertiary halides don't work really at all.

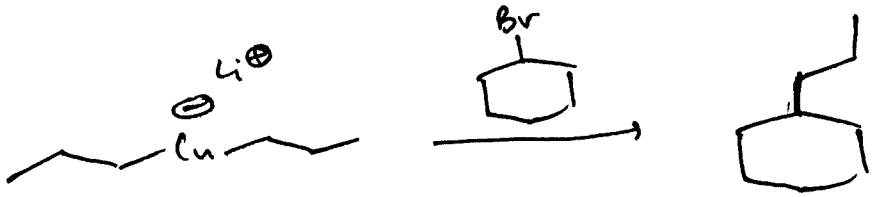
Organocopper chemistry



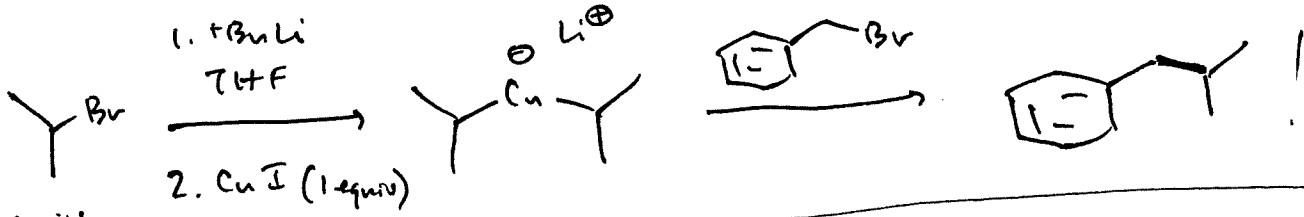
mechanism of formation:



why is this important?

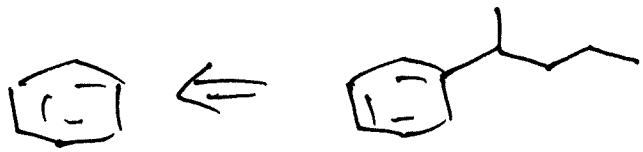


S_N2 type C–C bond formation!



This process only is operable when starting with organolithium species, not Grignard reagents.

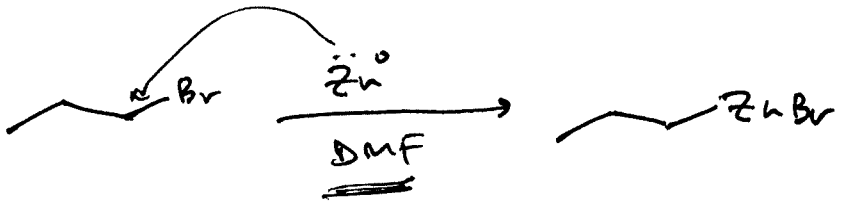
let's consider its use in synthesis!



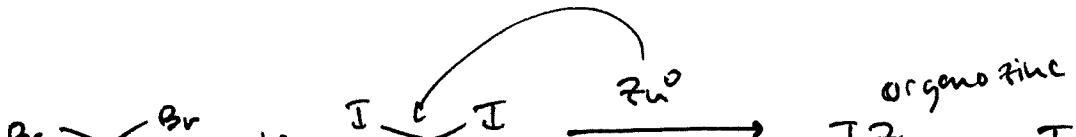
How would you make this from benzene and units of 3 carbons or fewer?

Organozinc reagents and cyclopropanation

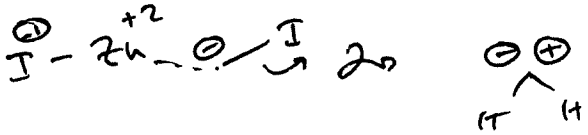
Zn can do insertion into C–X bonds similar to Mg



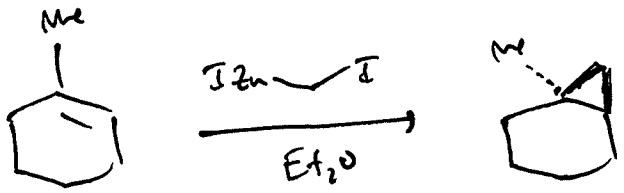
when we use a particular dihalide, this becomes very useful...



you can think of this as both a $Nu^{\ominus}$ and $E^{\oplus}$

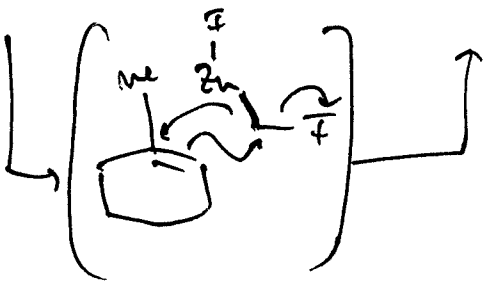


As a result, this special organozinc intermediate can be employed to create the cyclopropane functional group.



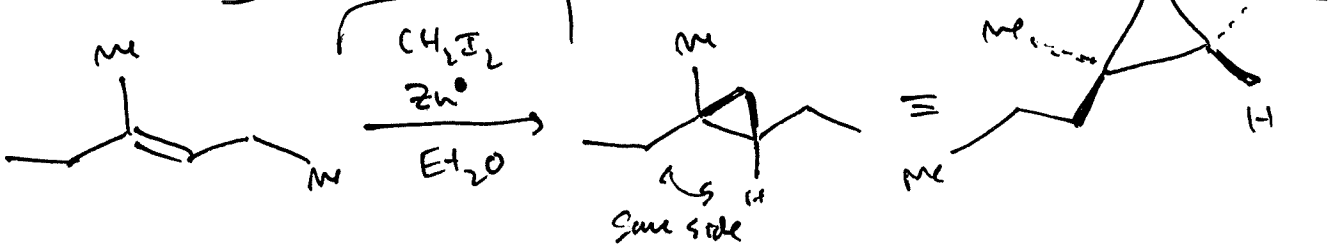
The geometry of the alkene dictates the stereochemistry of the cyclopropane!

mechanism:



Syn addition

Simmons-Smith cyclopropanation!



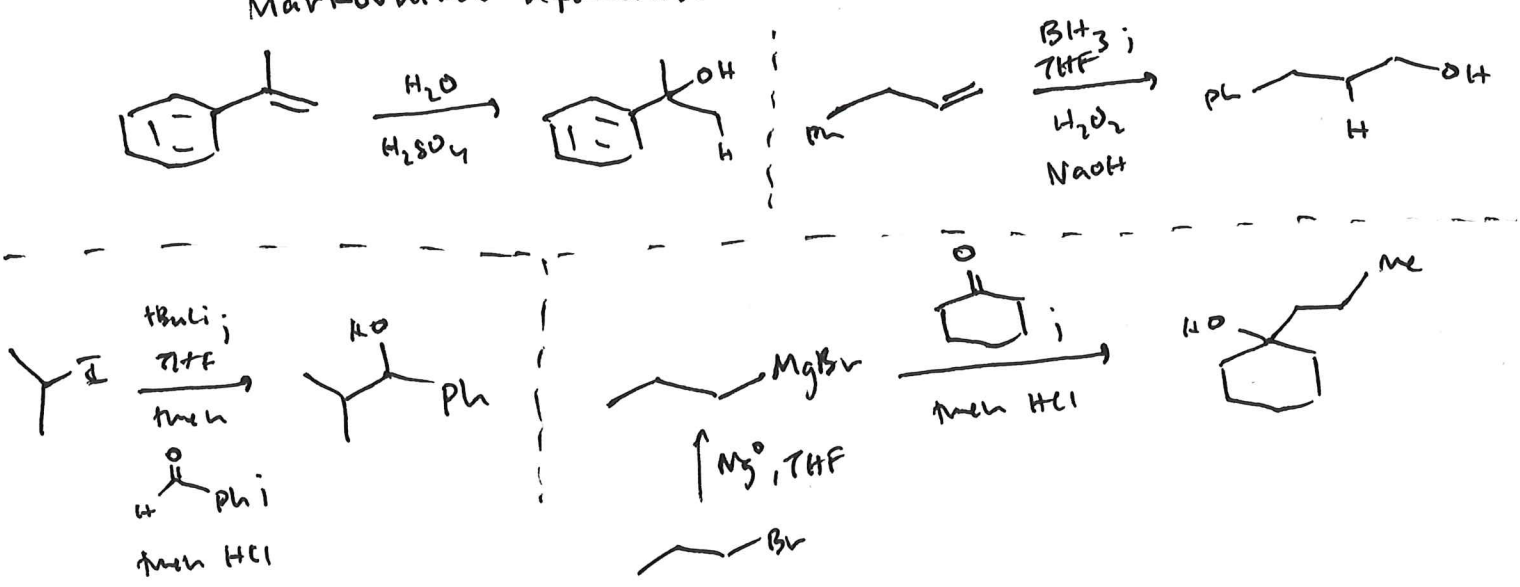
Reduction of Carbonyl Compounds

Recall:

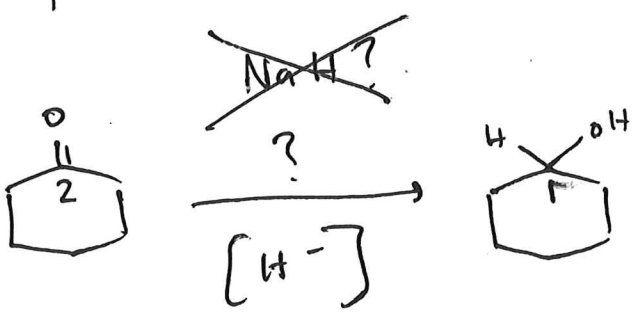
ox. level 1 2 3 4

How do we navigate accessing these oxidation levels from each other? Don't we need oxidation and reduction reactions?

The answer is yes. Remember the ways you accessed alcohols before:

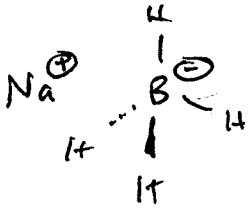


what if you needed to access an alcohol directly?



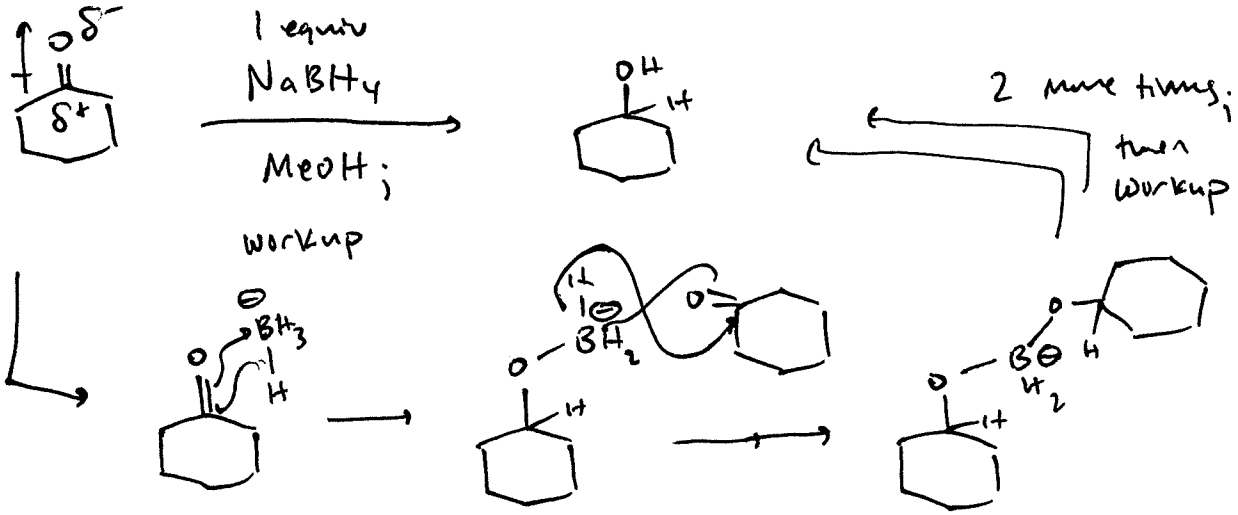
need a source of nucleophilic hydride!

one reagent capable of doing this is $NaBH_4$ → $NaH + BH_3$

structure: 

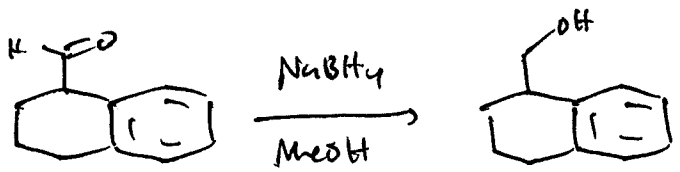
there are technically multiple hydrides that $NaBH_4$ can donate.

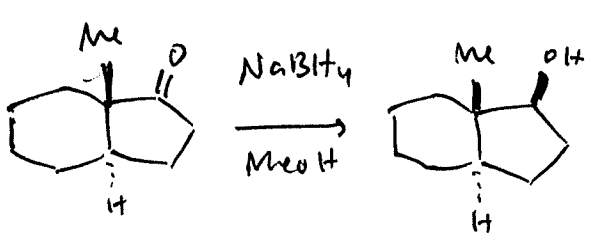
The reaction proceeds like this:

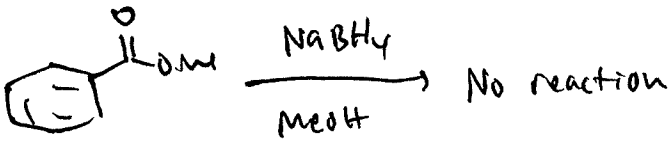


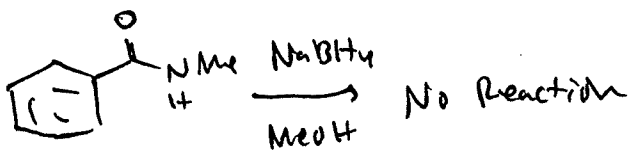
we typically will use one equivalent of $NaBH_4$ in a reaction even though we technically only need 0.25 equivalents. The point is to illustrate that multiple hydrides can come from $NaBH_4$!

$NaBH_4$ reduces aldehydes and ketones:



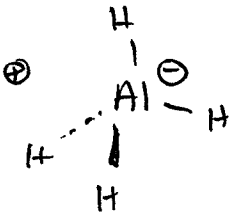






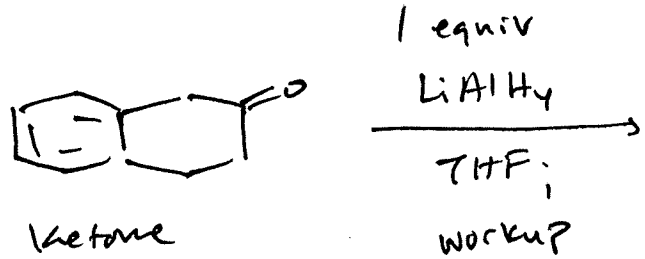
chemoselectivity profile!

As we go down the periodic table, Elements tend to become much more reactive. Introducing $LiAlH_4$!

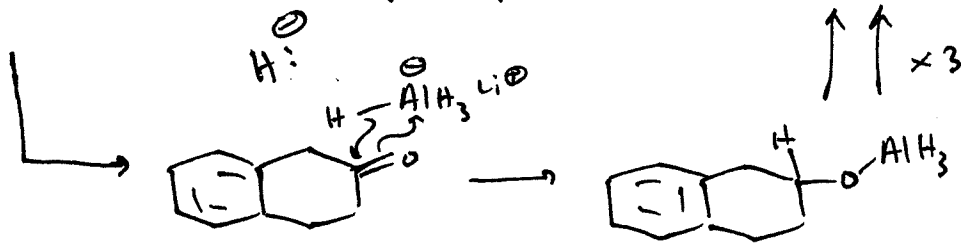
Structure: 

AlH_3: Alane

Because of the Al center, $LiAlH_4$ (LAH) is more reactive than $NaBH_4$

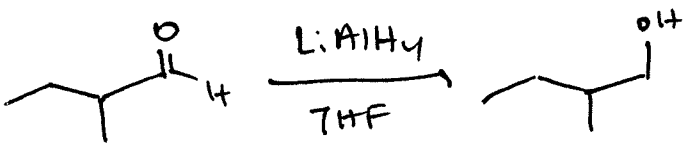


LAH requires an aprotic solvent b/c of its reactivity.

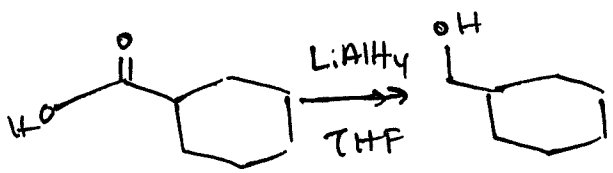


analogous to $NaBH_4$ mechanism.

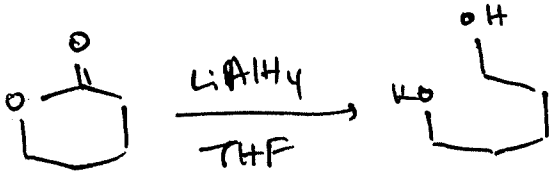
LAH can also reduce other carbonyl compounds:

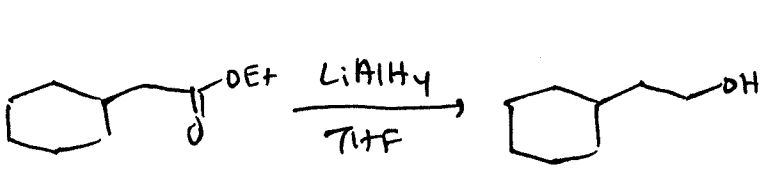


aldehydes



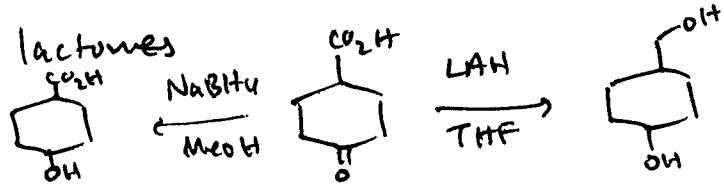
carboxylic acids



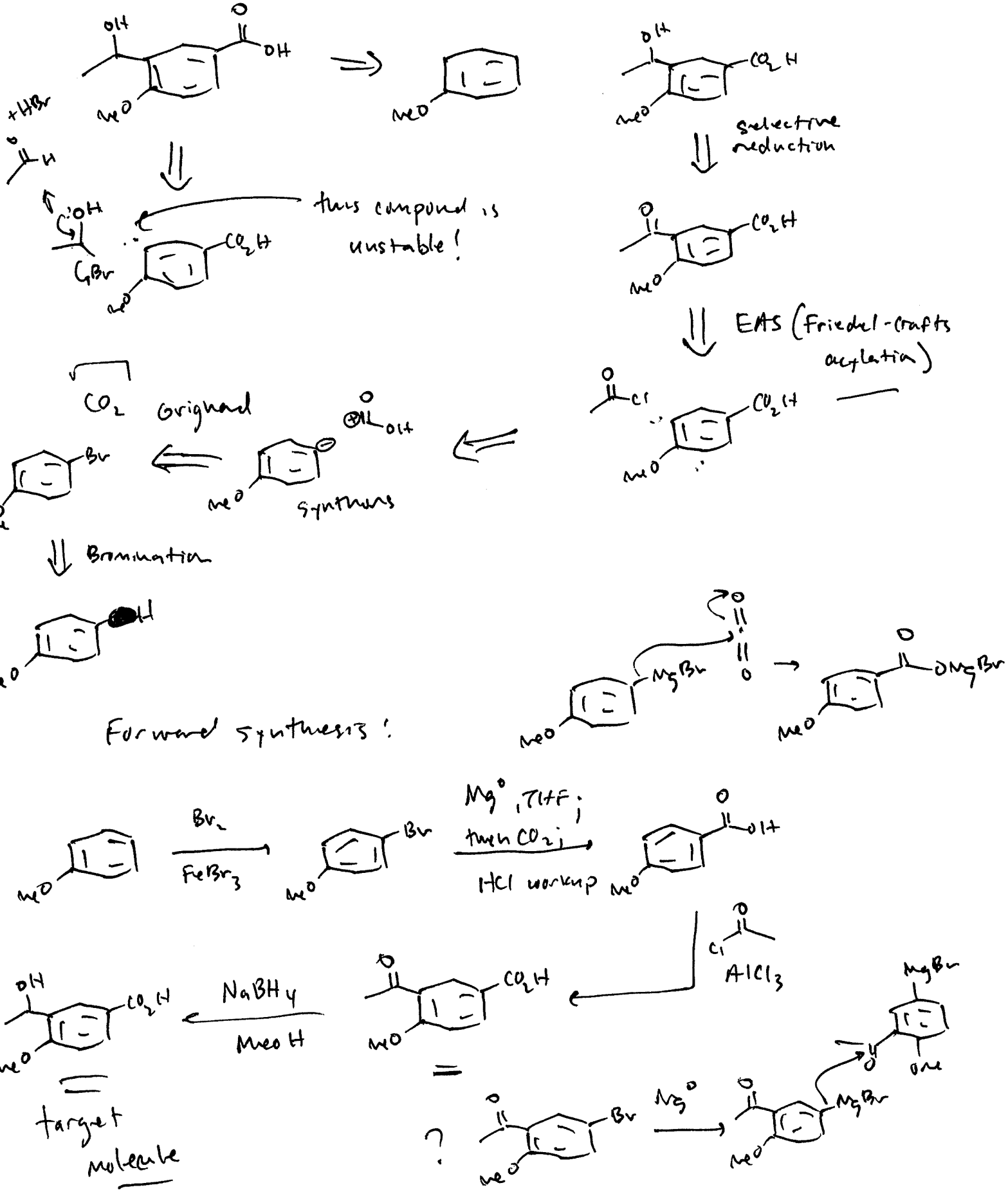


lactones

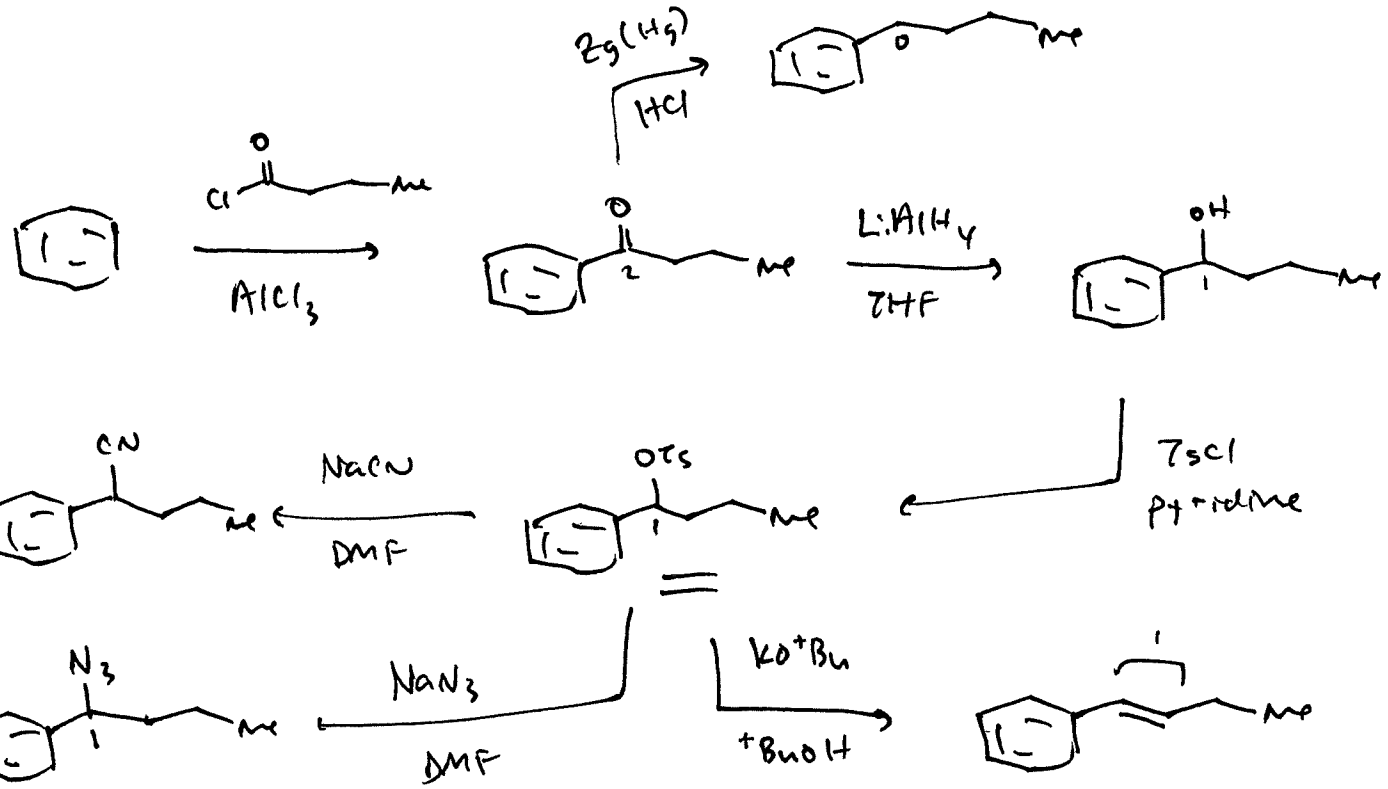
esters

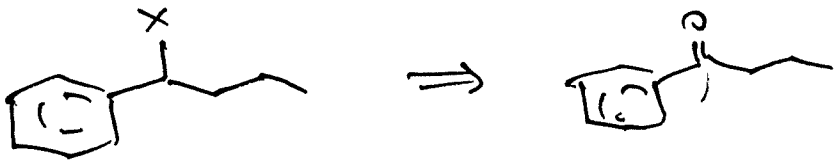


How would you synthesize this compound?



These reductions can also be used in sequences to convert carbonyl's (ketones, aldehydes mainly) to other functionality.



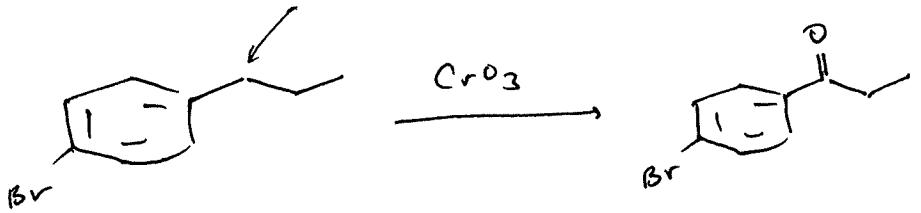


X = N_3, CN, Br, Cl

R-⊕

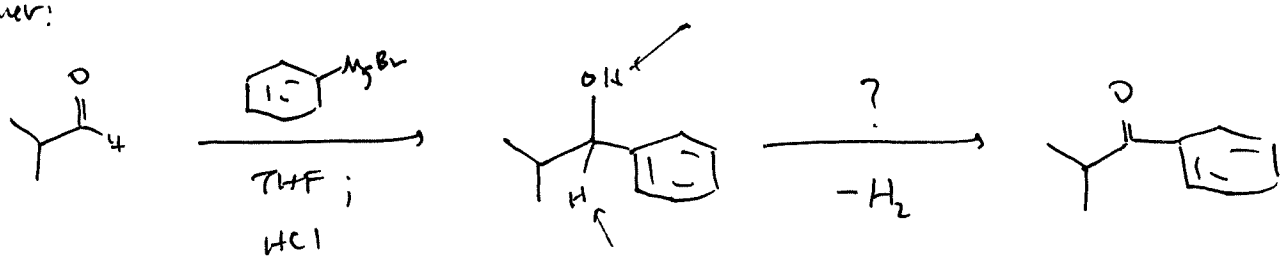
Oxidation of alcohols

recall:



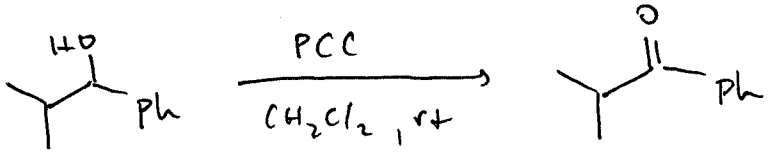
benzylic oxidation!

consider:



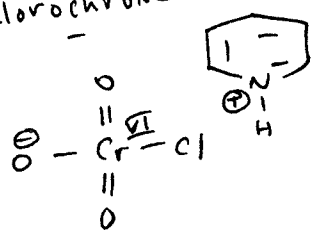
what if I wanted the carbonyl again?

Corey, Suggs, 1975:

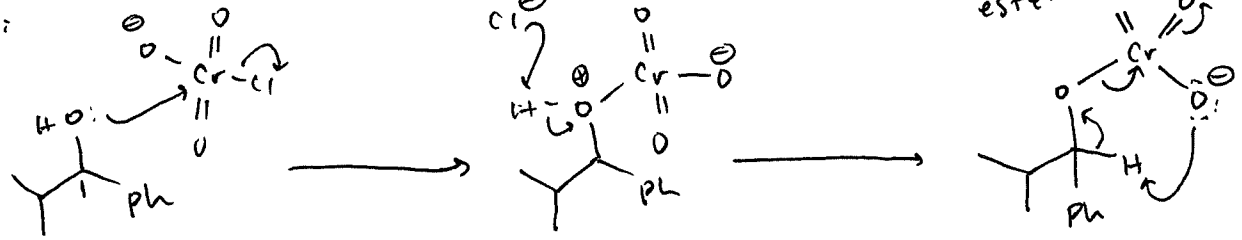


(pyridinium chlorochromate)

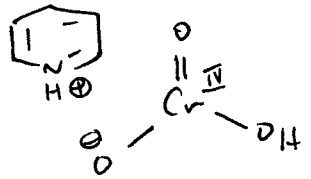
PCC:



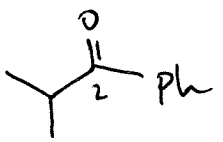
Mechanism:



chromate ester

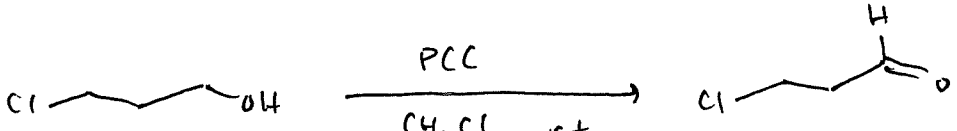


Chromium IV!



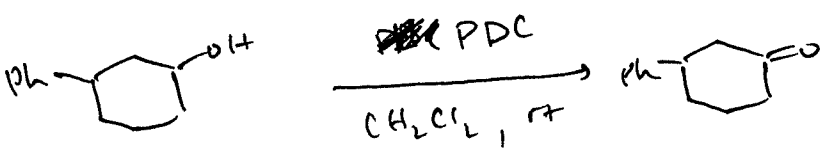
ketone product!

PCC can also oxidize alcohols to aldehydes!

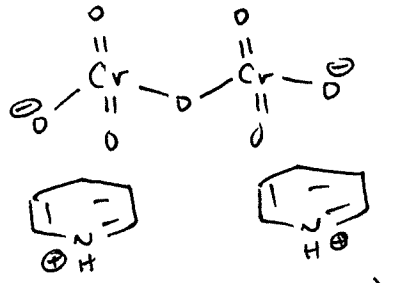


mechanism is the same.

One can also use Pyridinium dichromate to do the same thing: (PDC)



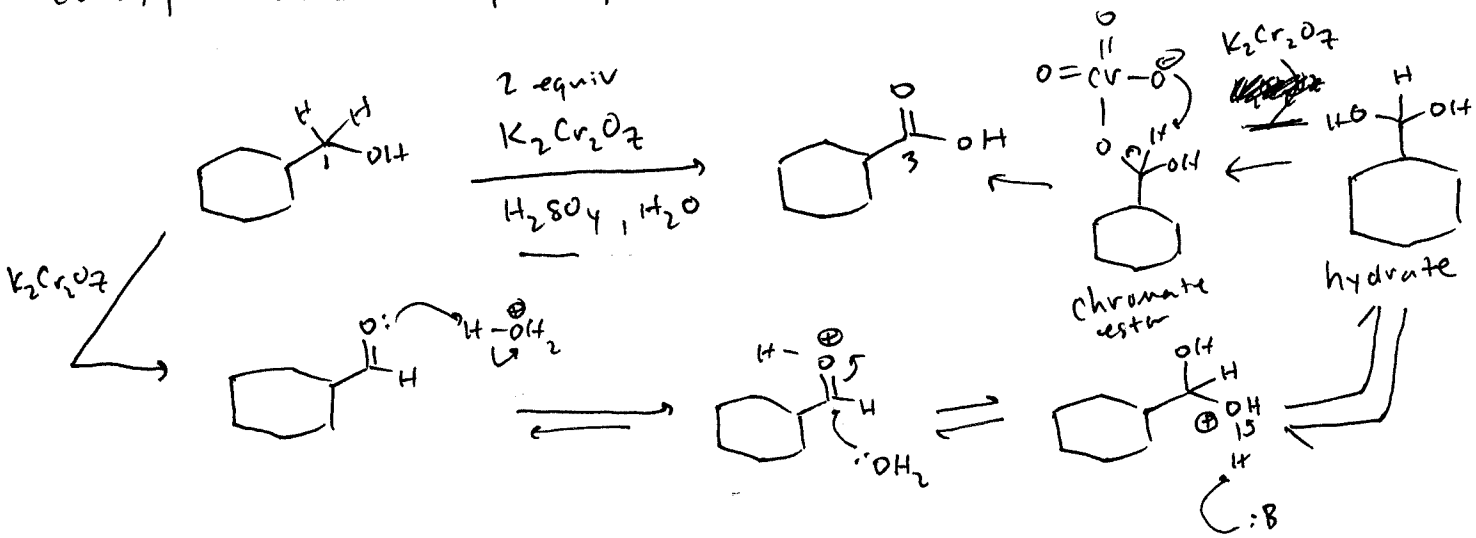
PDC:



also oxidizes 1° alcohols to aldehydes

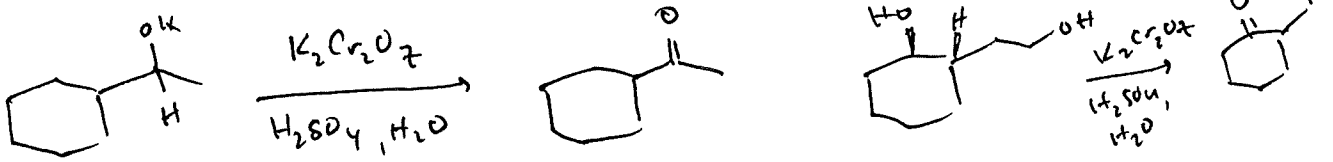
(corey-fuchs reagent)

However, in acid, the related $K_2Cr_2O_7$ (potassium dichromate) gives oxidation to carboxylic acids for primary alcohols.

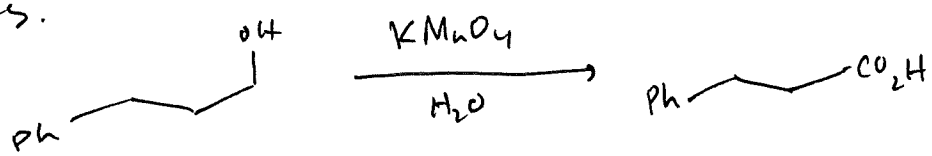


The presence of acid and $K_2Cr_2O_7$ allows for oxidation to acid.

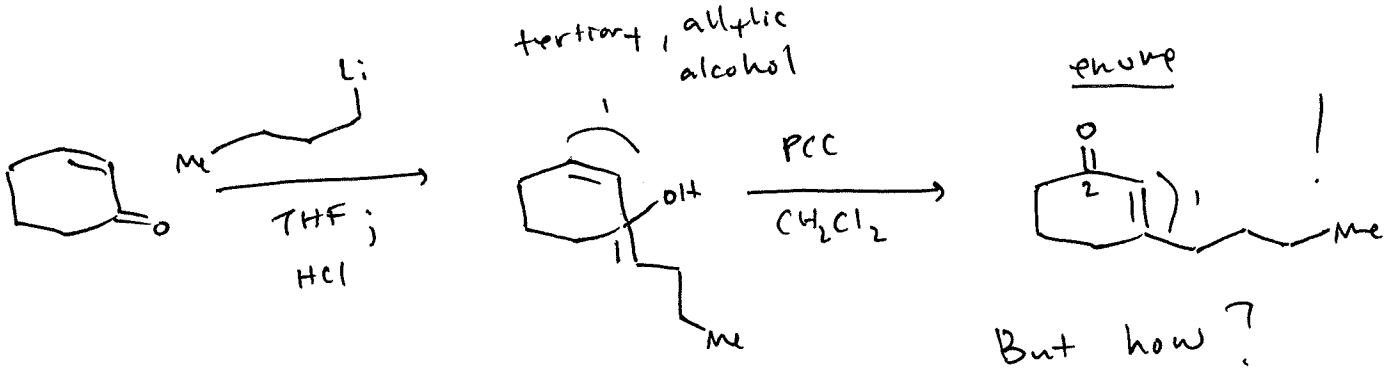
These conditions can also oxidize alcohols to ketones, however.



$KMnO_4$ is also a strong oxidant capable of oxidizing alcohols to acids.

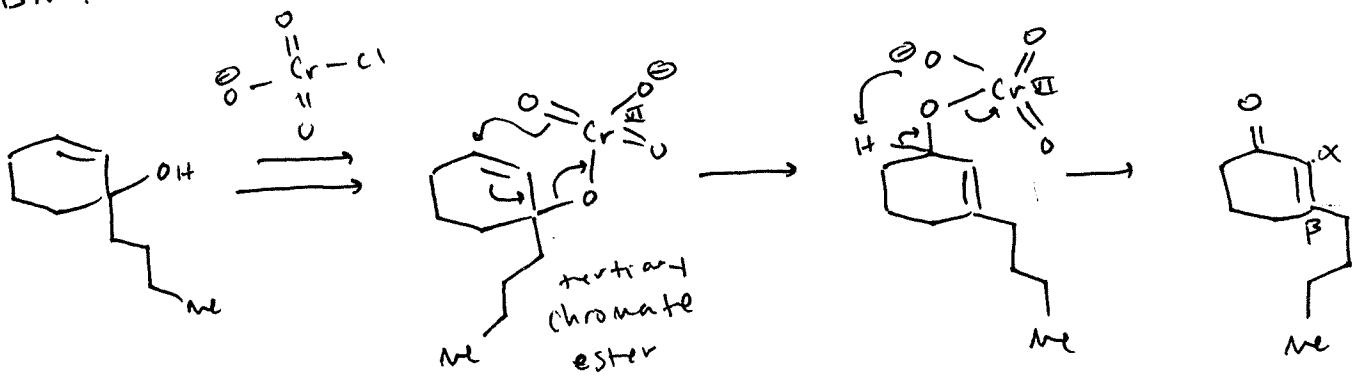


Consider this scenario:



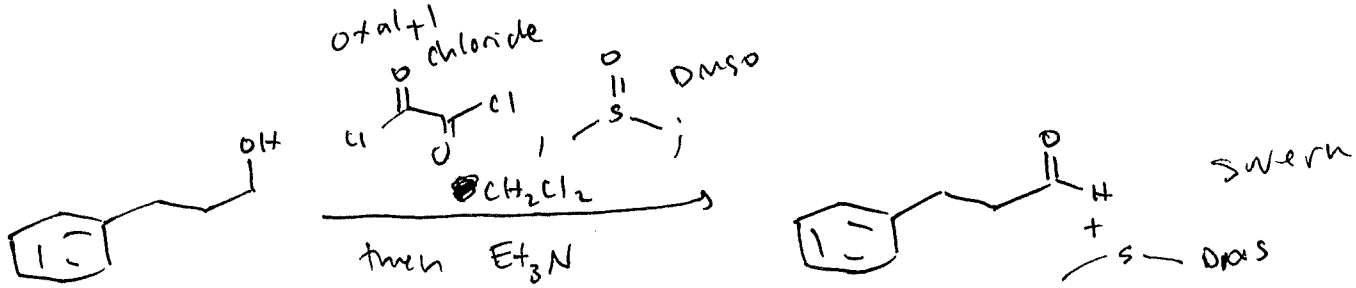
But how?

Mechanism:



This oxidative rearrangement of tertiary allylic alcohols is called the Babler oxidation. It is a very effective way to make Beta-substituted enones.

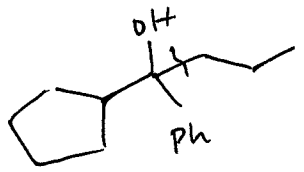
While Chromium-based oxidations are useful and versatile, Cr^{VI} is toxic to both you and the environment around you! There is an alternative called the Swern oxidation.

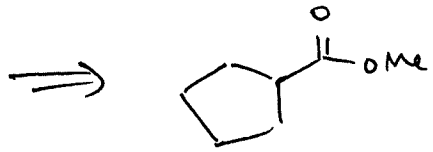


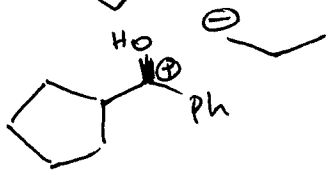
The swern oxidation converts alcohols to aldehydes (1° alcohols) and ketones (2° alcohols)

Consider:

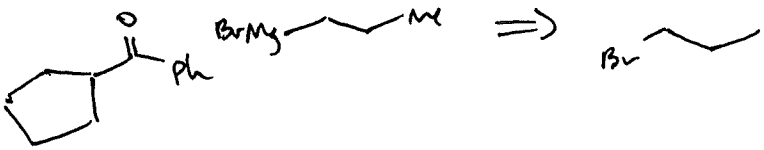
target

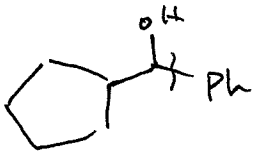


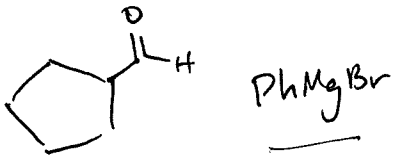




Synthons

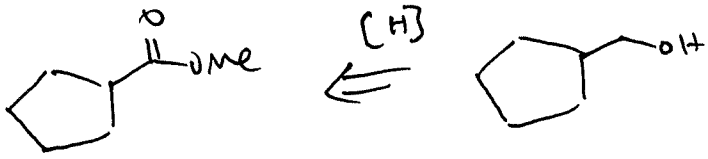




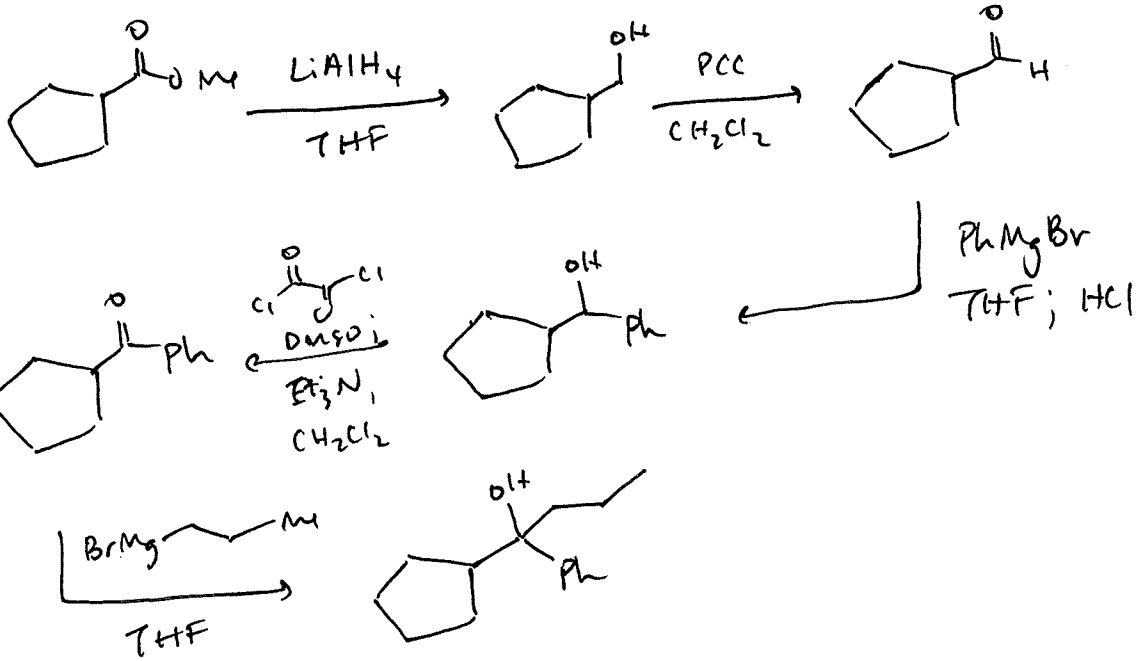


PhMgBr

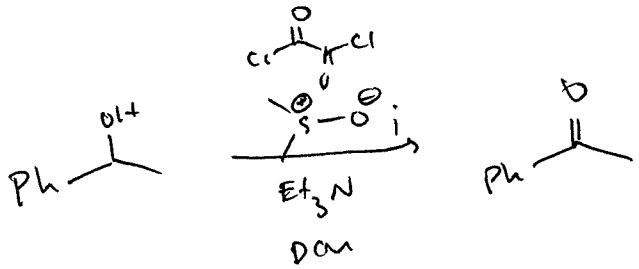
Retrosynthesis:



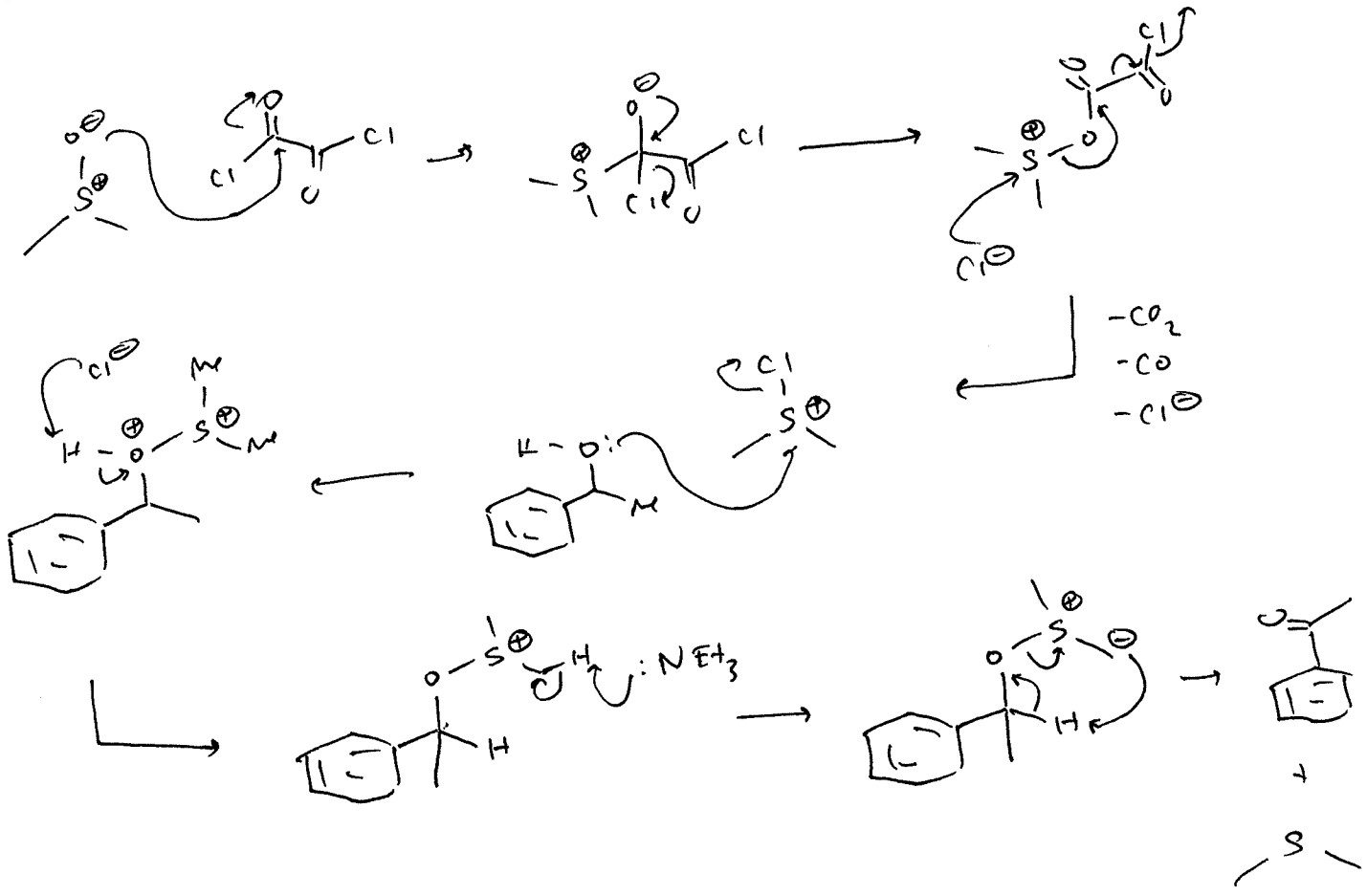
Forward Synthesis:



Swern Mechanism

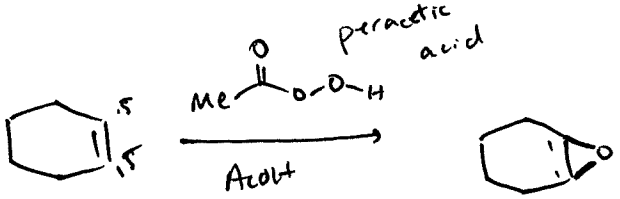


Mix oxalyl chloride and DMSO



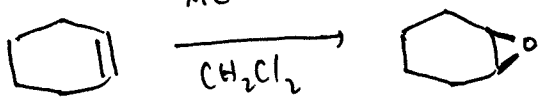
other oxidation reactions

Recall:

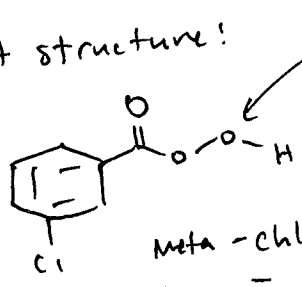


what are other common reagents for this reaction?

introducing mCPBA:

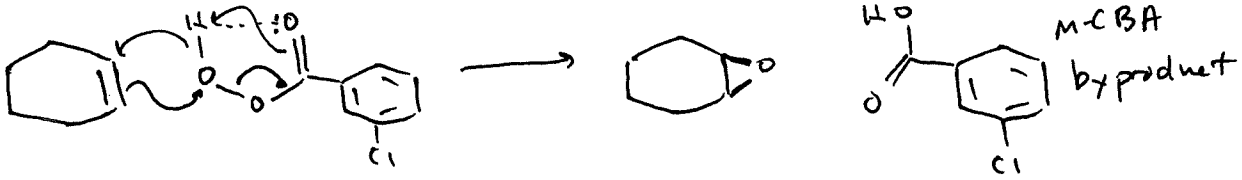


mCPBA structure:

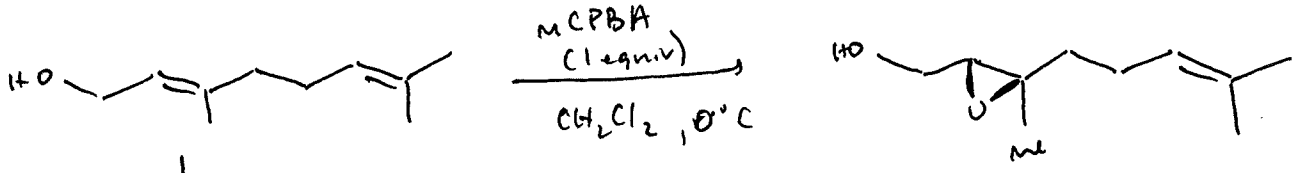


meta-chloro perbenzoic acid

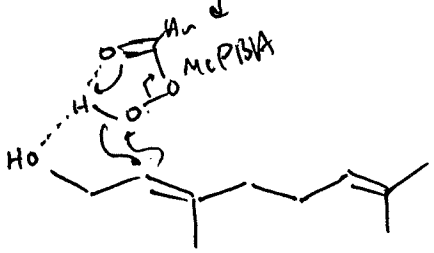
mechanism:



regioselectivity:

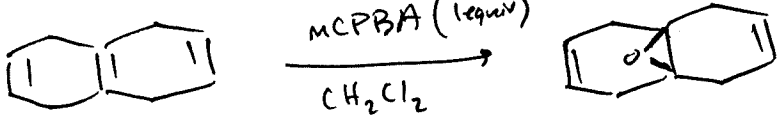


why?



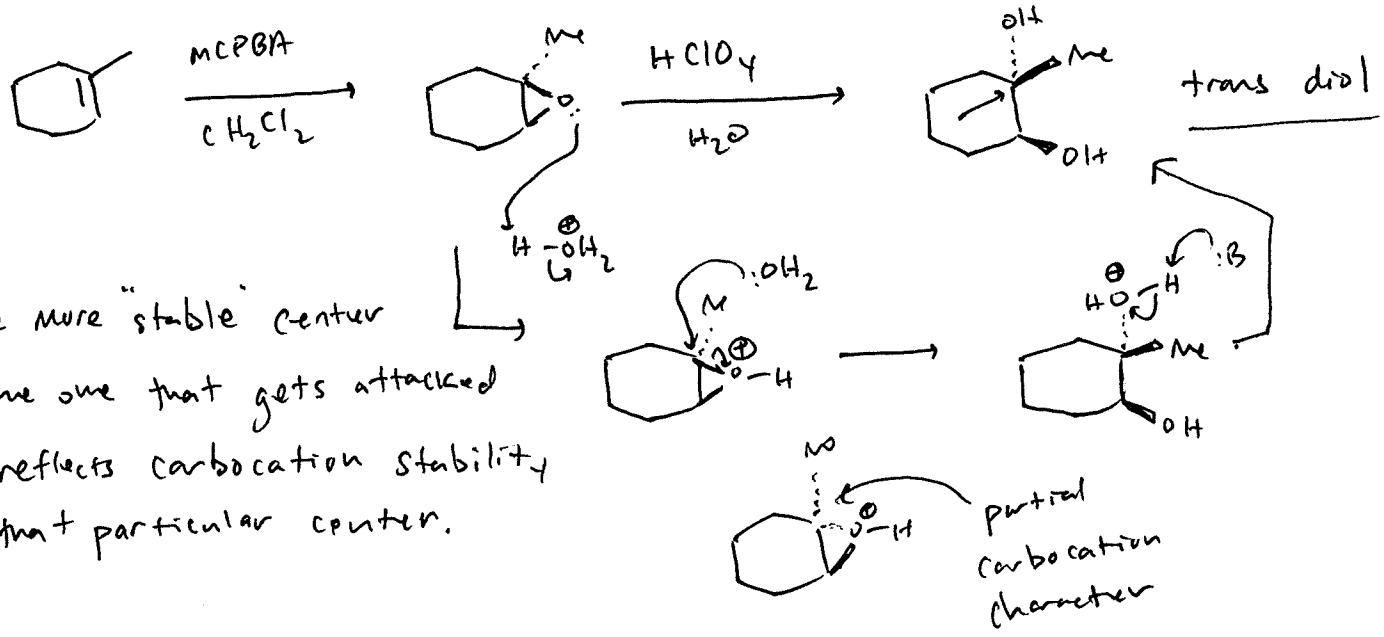
hydrogen bonding providing for selectivity

electronics matter!

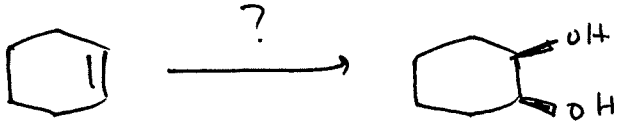


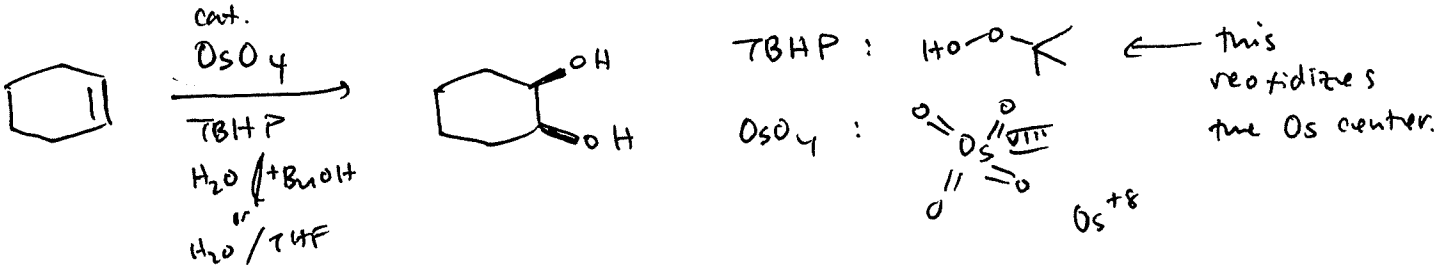
most electron rich (most substituted) alkene reacts first

Opening of epoxides to diols

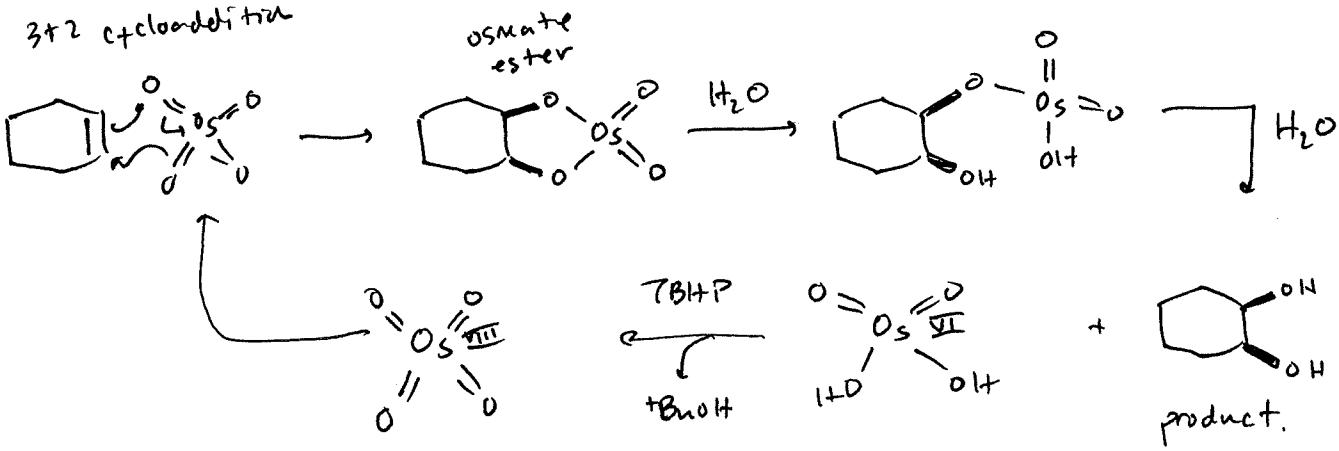


what about forging syn diols?

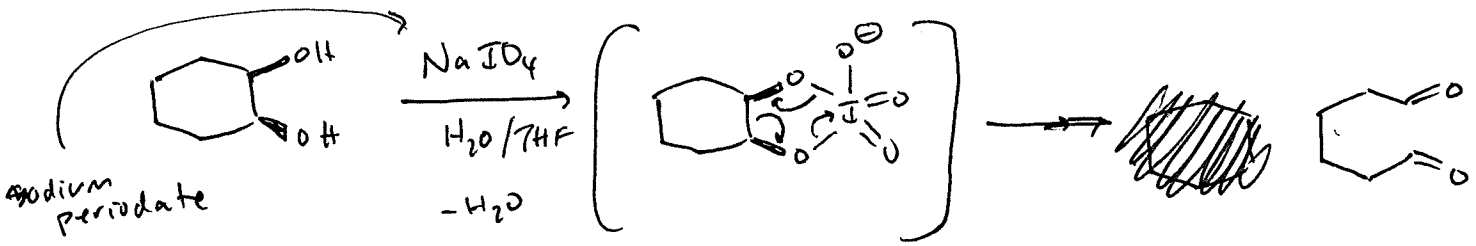




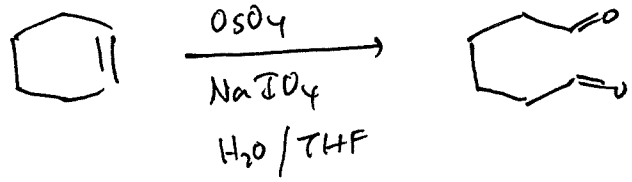
Mechanism:



Diols can be converted to dialdehydes through oxidative cleavage



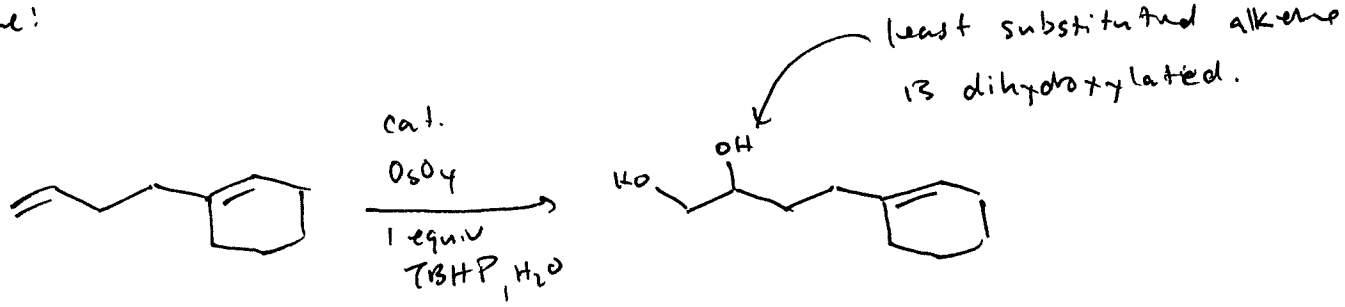
This can also be done in one reaction:



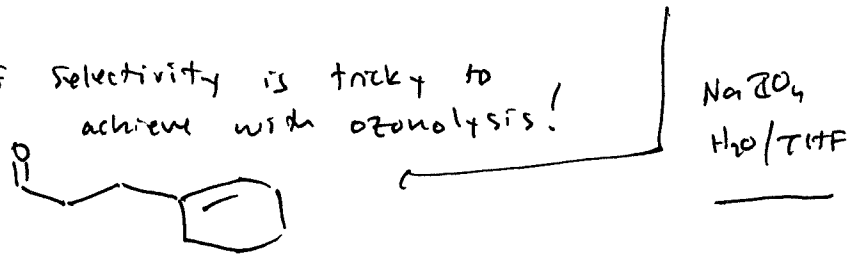
similar result to ozonolysis and then treatment with Me_2S

Name: Lemieux – Johnson oxidation

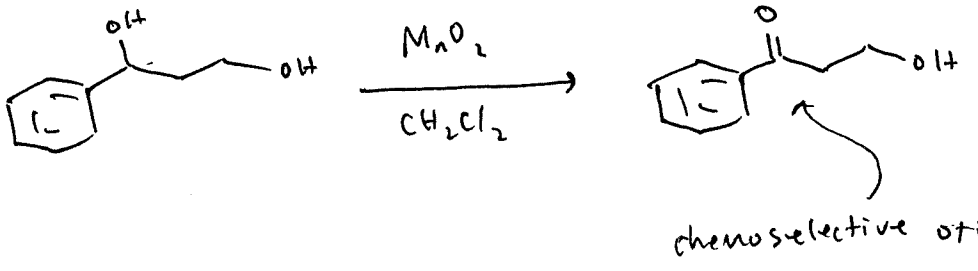
Generally OsO_4 is sensitive to the steric environment of an alkene:

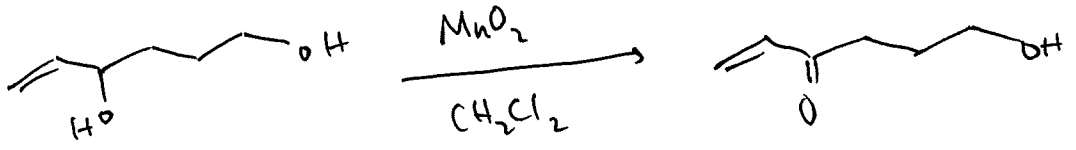


This type of selectivity is tricky to achieve with ozonolysis!

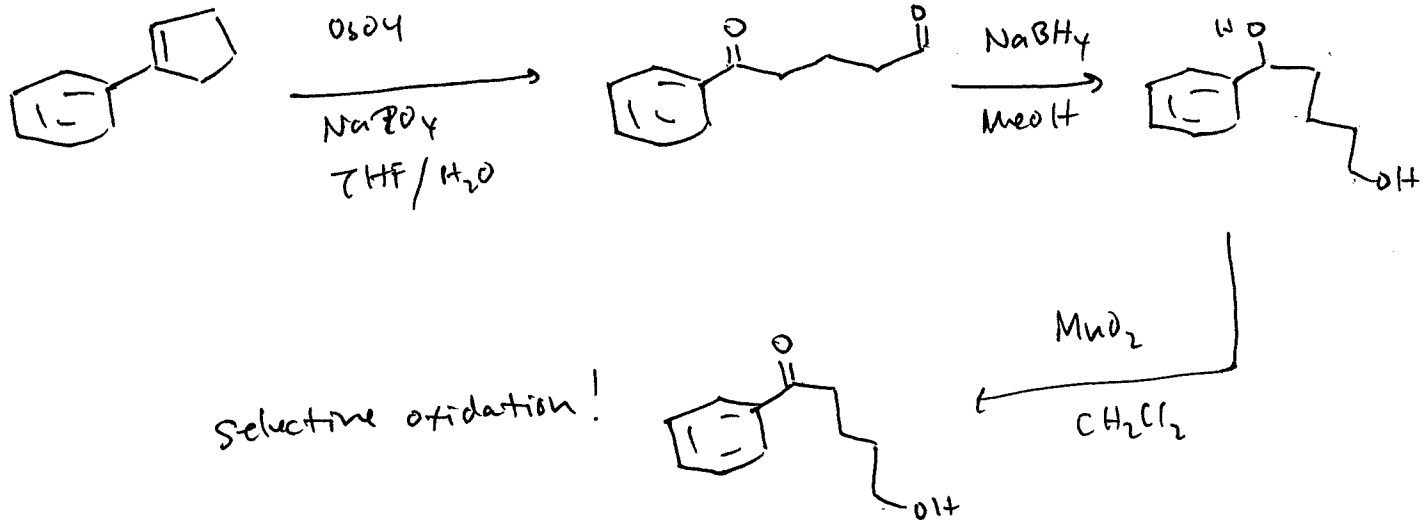


There is one more type of useful oxidation reaction that provides an exquisite selectivity profile!



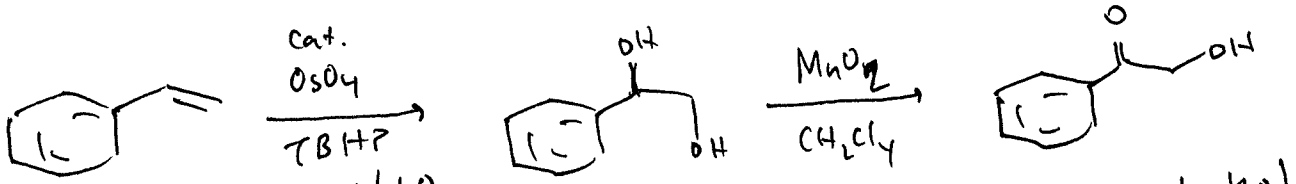


only allylic alcohol oxidized.



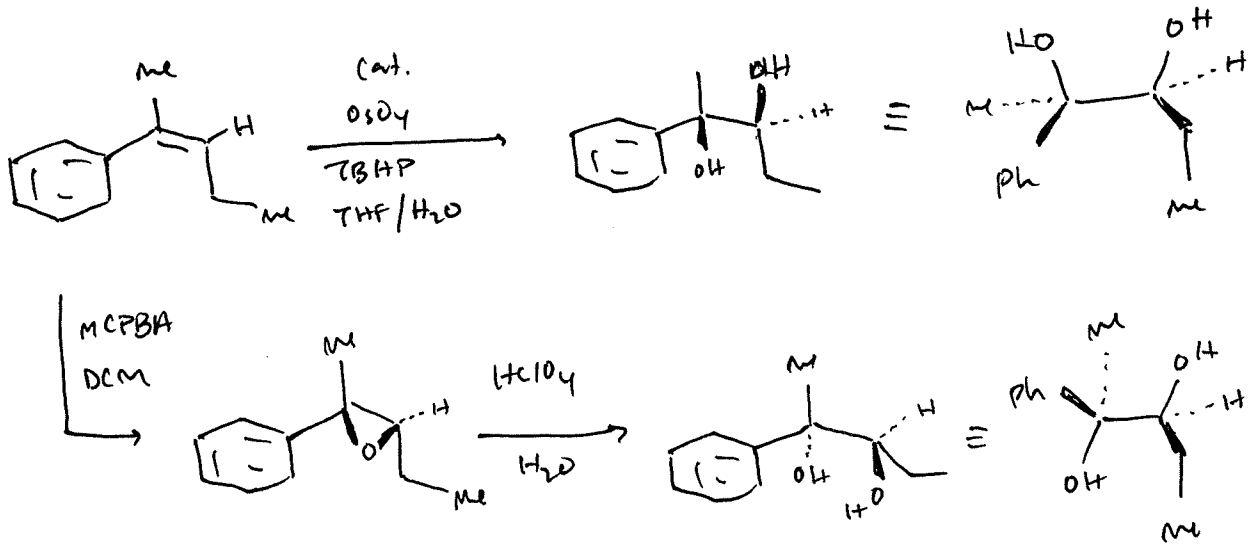
selective oxidation!

another example:

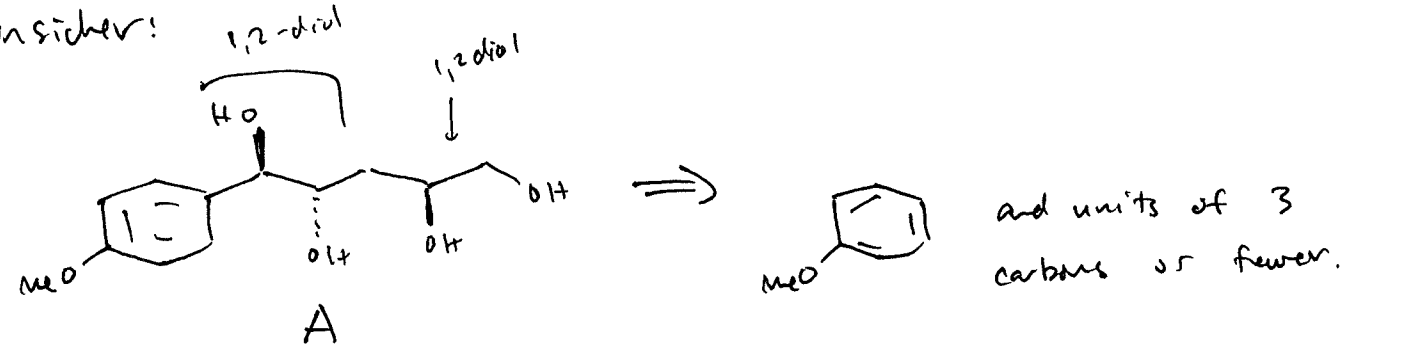


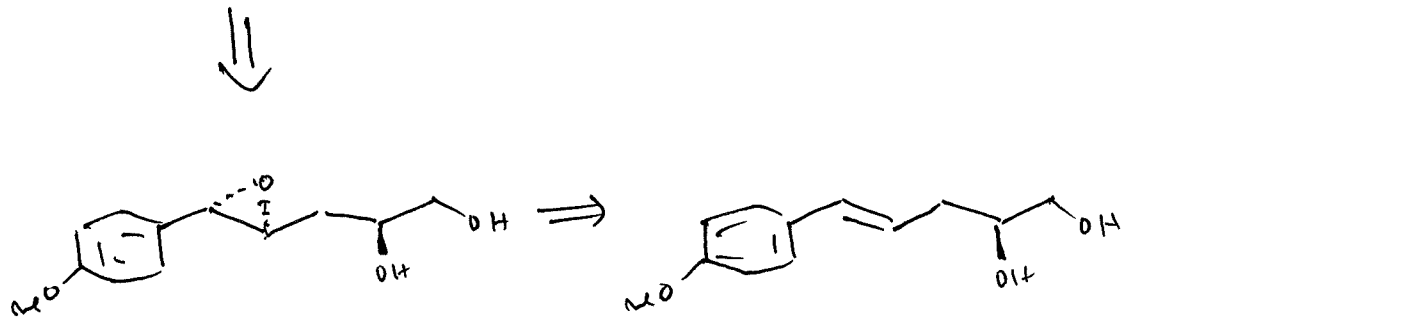
keto-alcohol

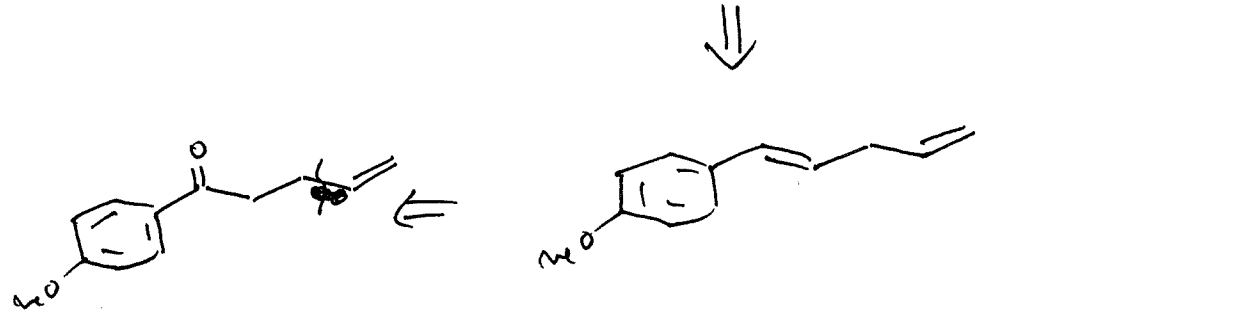
the stereochemistry of a diol is reminiscent of the alkene it was derived from!

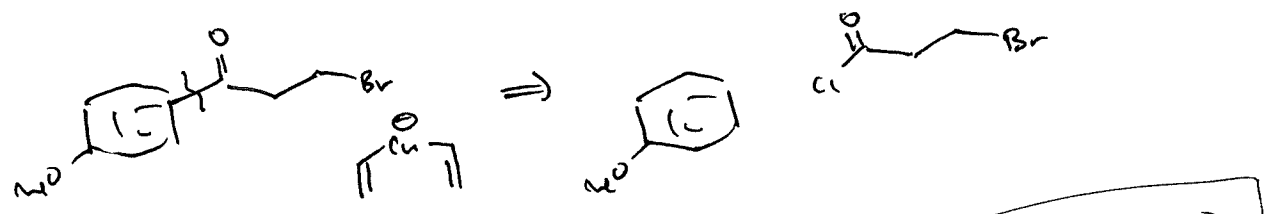


consider:

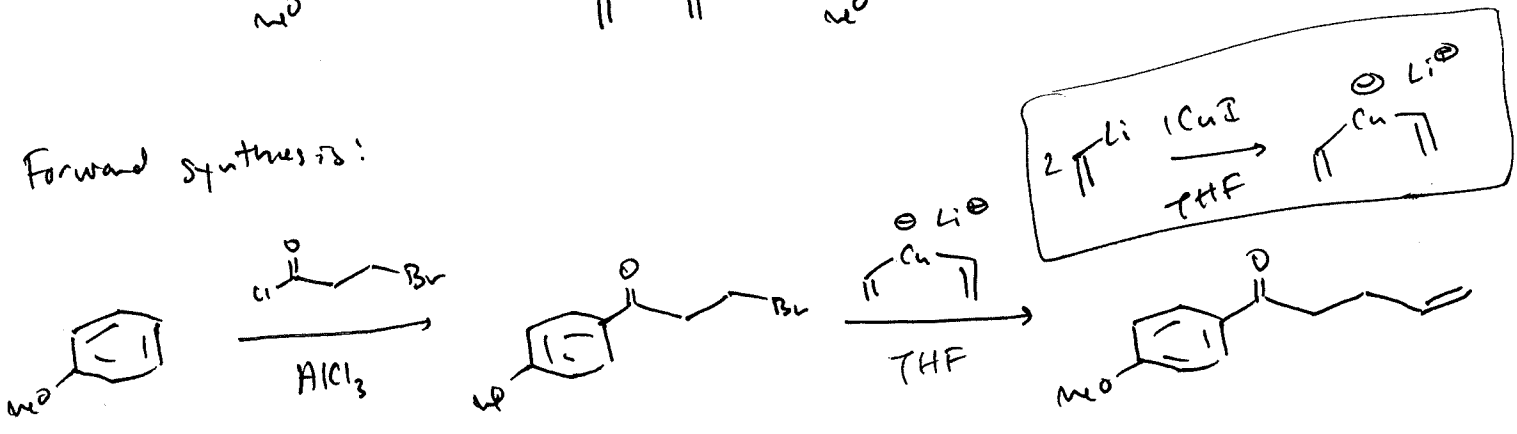


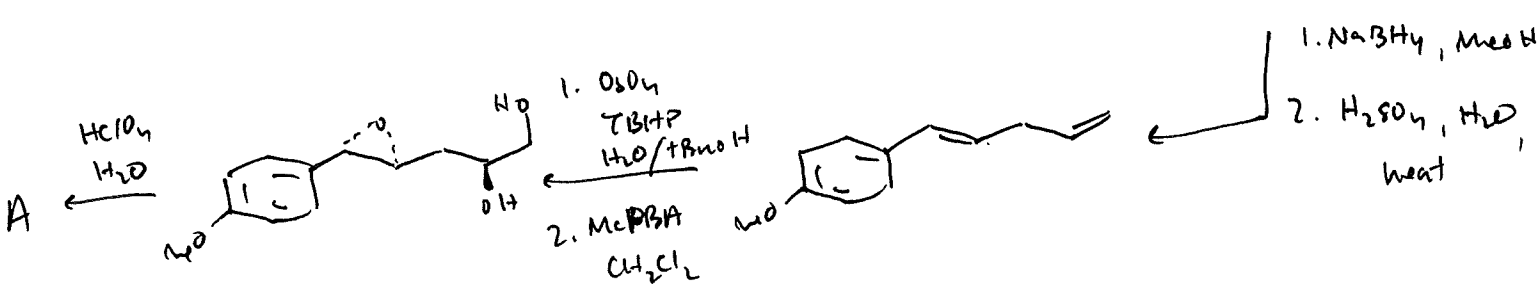






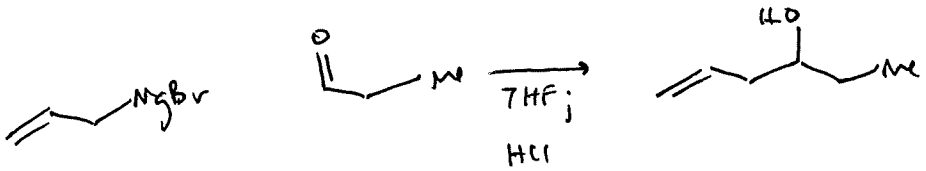
Forward synthesis:



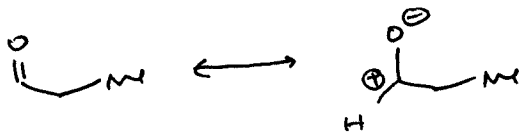


Reactivity of Aldehydes and Ketones

recall :



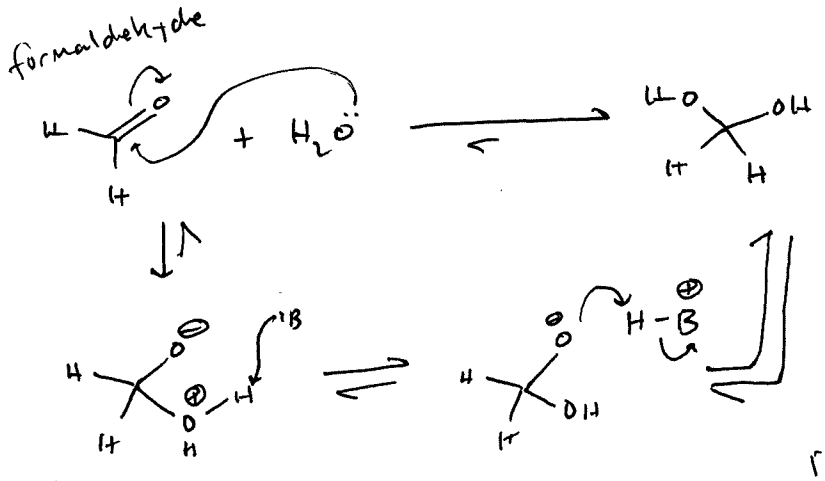
This reactivity occurs because of this resonance structure



In general, aldehydes are more reactive than ketones

If we analyze the ~~charged~~ charged resonance for their "carbocation" stability, the ketone is clearly a "tertiary carbocation", thus more stable.

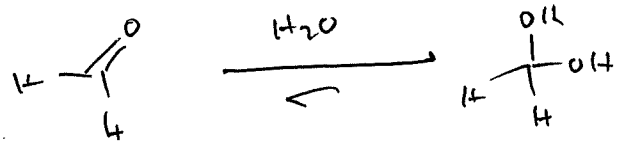
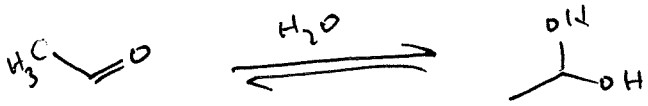
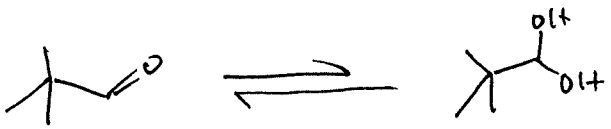
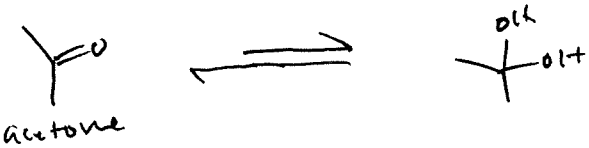
Aldehydes and Ketones also have an equilibrium with H_2O

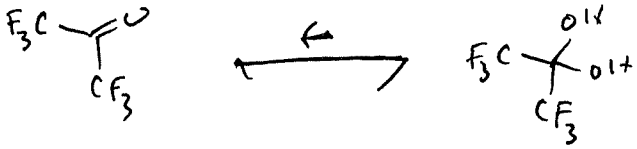


notice how every arrow is an equilibrium arrow

the ratio of hydrate : carbonyl is a thermodynamically driven process.

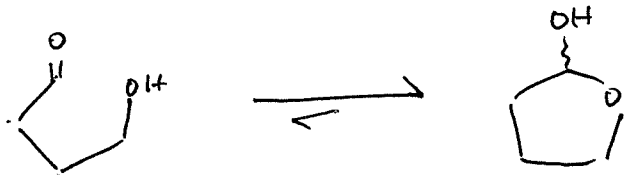
proton transfer

	percent hydrate	percent carbonyl
	>99.9	< .1
	50	50
	17	83
 acetone	.14	99.86



ratio hydrate : ketone :: 22,000 : 1

*hydrates can also exist in cyclic scenarios



this is called a <u>lactol</u> and is the predominant species for 5-6 membered rings

this is called a <u>hemiaminal</u> and is the predominant species for 5-6 membered rings.

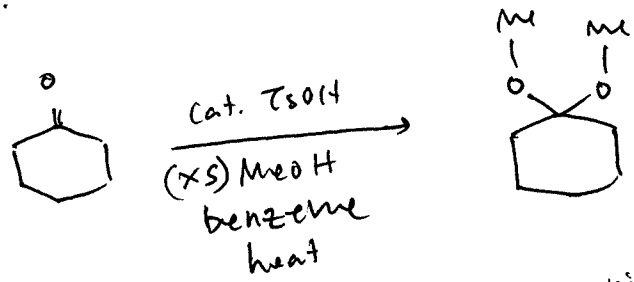
How can we use this phenomenon to our advantage?

We can "mask" carbonyls by turning them into "acetals" or "ketals."

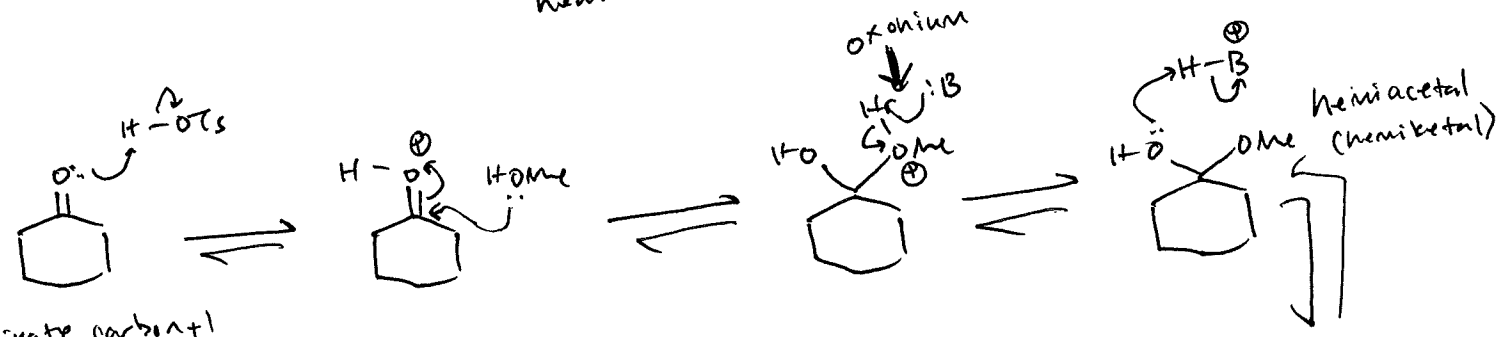
↳ ketones

↳ aldehydes

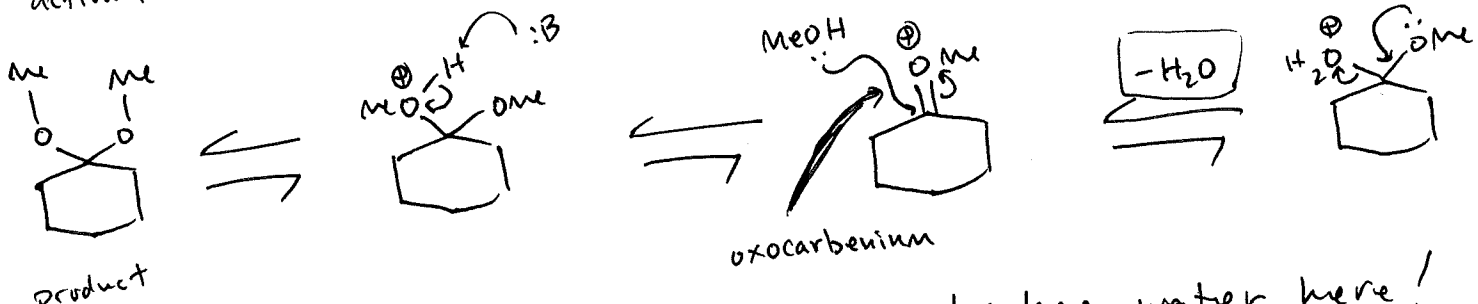
consider:



this is a ketal and is a stable product.



activate carbonyl



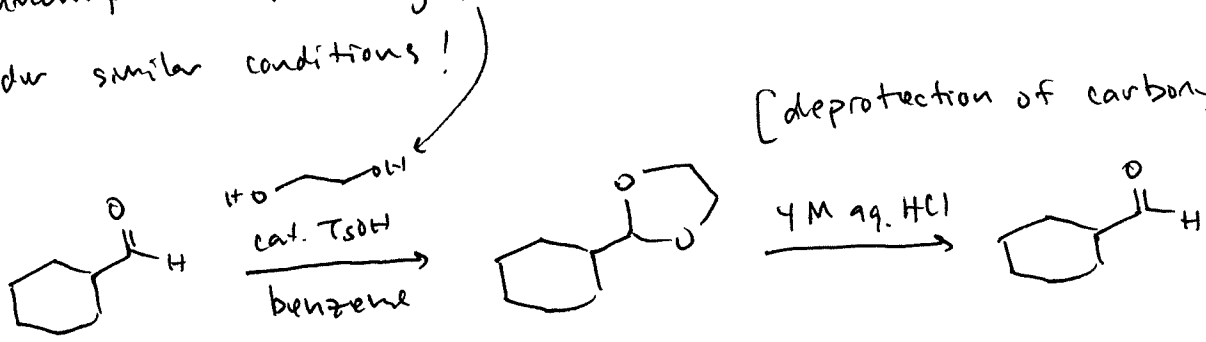
product

oxocarbenium

Never perform an S_N2 reaction to displace water here!

an SN2 reaction does not occur under acidic conditions!!

commonly ethylene glycol is used as diol to react under similar conditions!

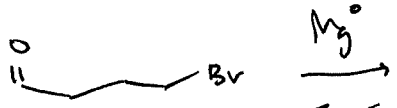
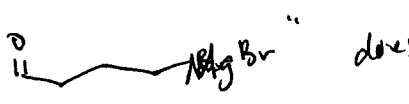


[protection of carbonyl]

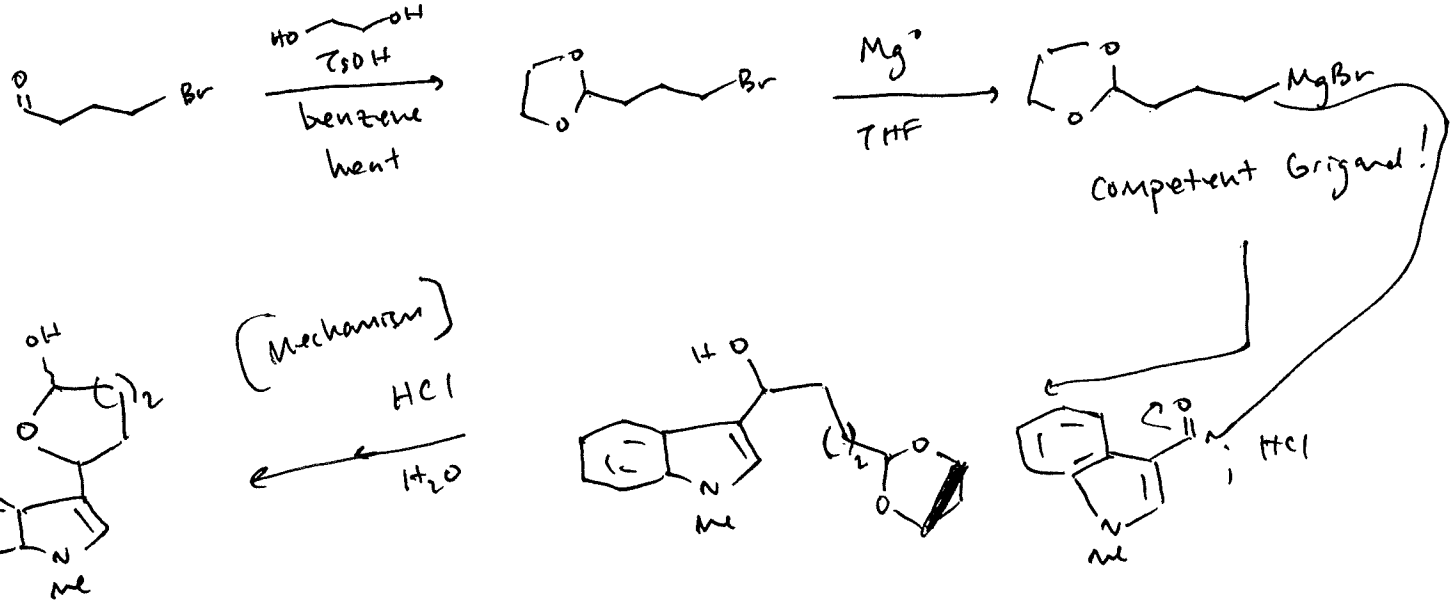
[deprotection of carbonyl]

try the mechanism of ketal/actal cleavage with $H_3O^{\oplus}$

We can use these acetals and ketals to our advantage in synthesis.

recall:  "  " does not exist because cannot make Grignard in presence of aldehyde.

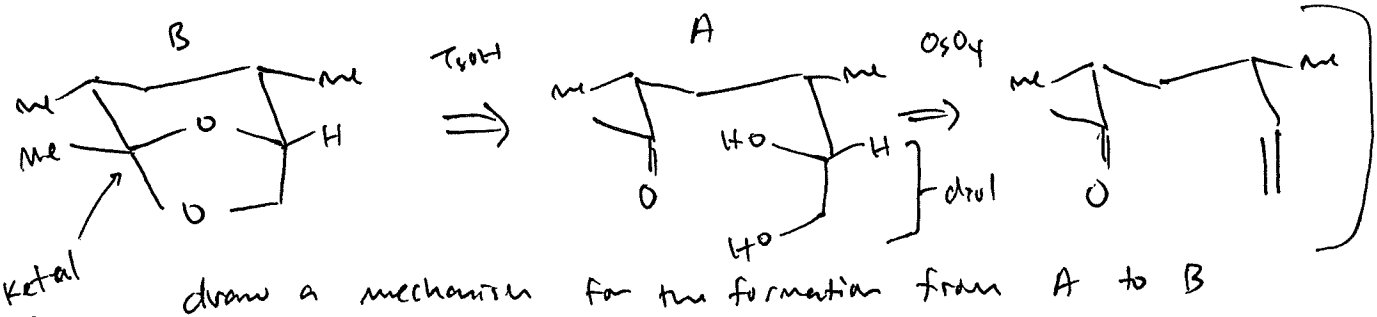
However.



formation of lactol

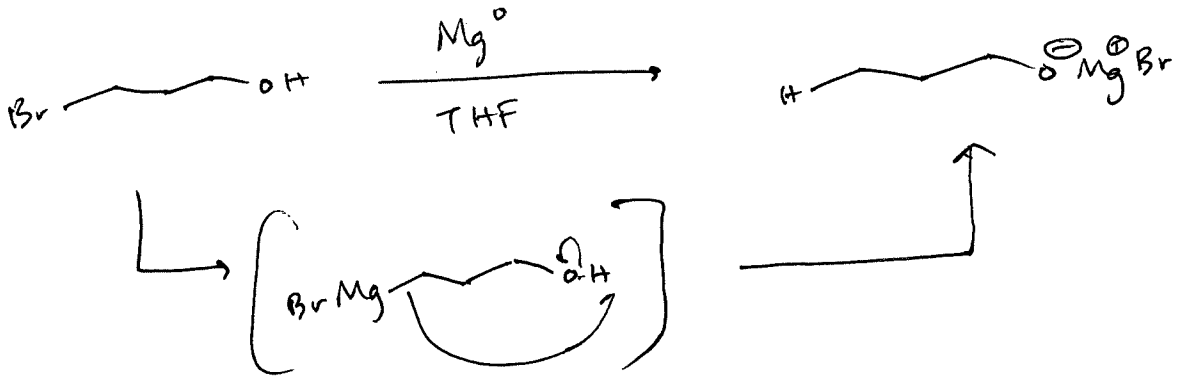
I encourage you to draw out the mechanism of the first transformation depicted in the above sequence for practice. Also the last.

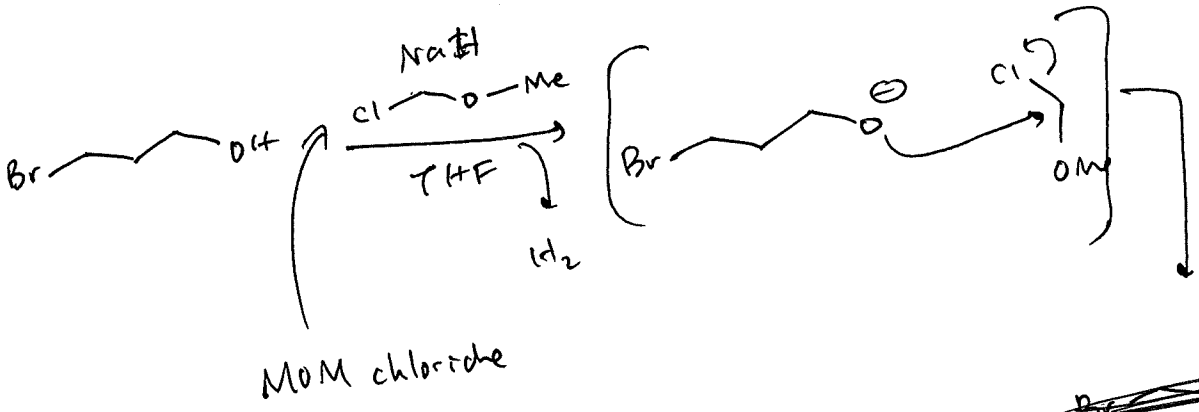
consider the beetle pheromone multistratin

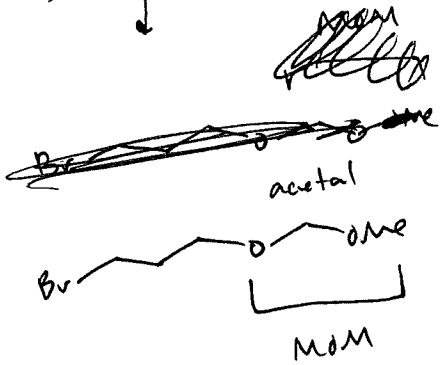


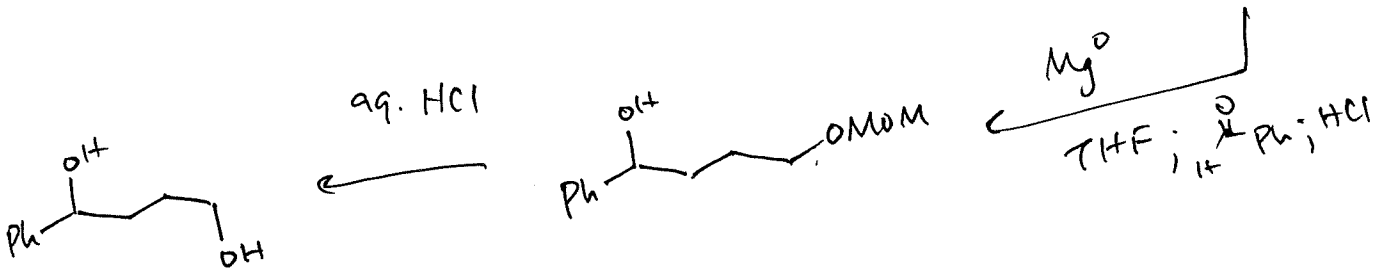
draw a mechanism for the formation from A to B

Alcohol protection with acetals ??



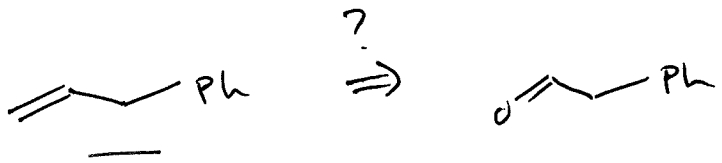




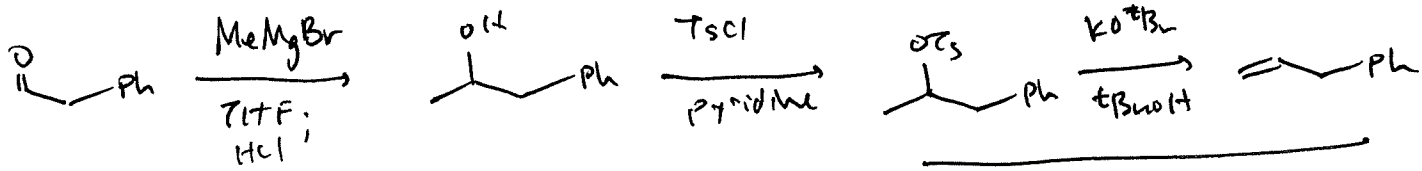


Alkene synthesis from aldehydes and ketones

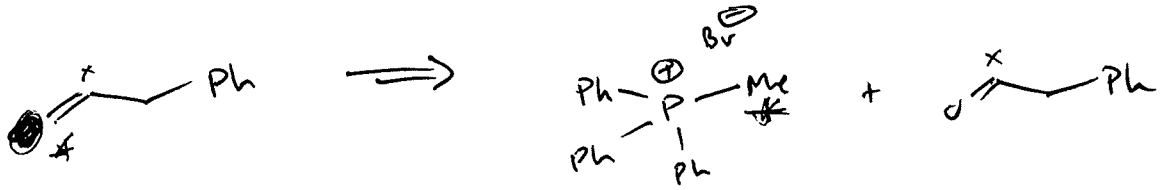
recall:



using a Grignard:

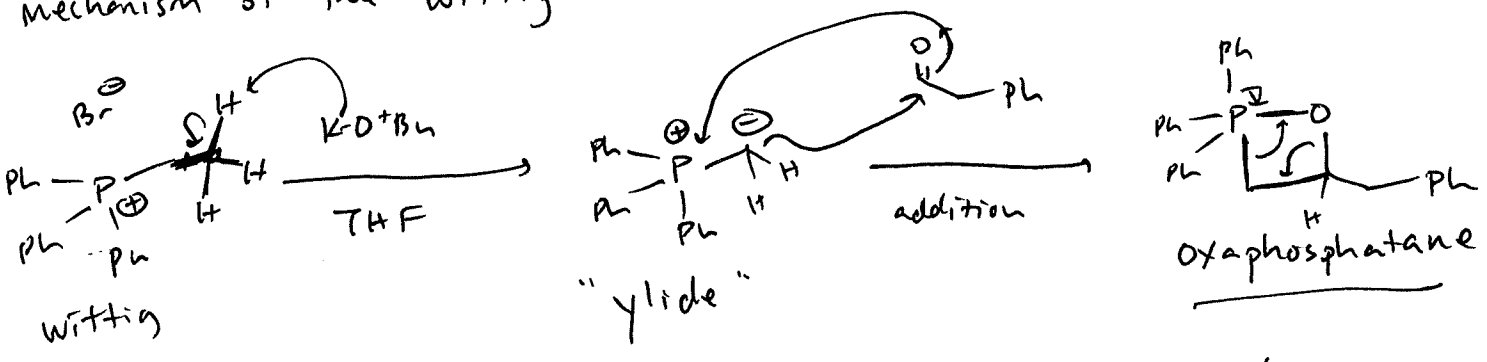


up until now, elimination was one of the only ways you've known how to make alkenes. what if it were possible to combine the nucleophilic addition and the elimination into 1 step?



wittig salt

mechanism of the witting reaction:

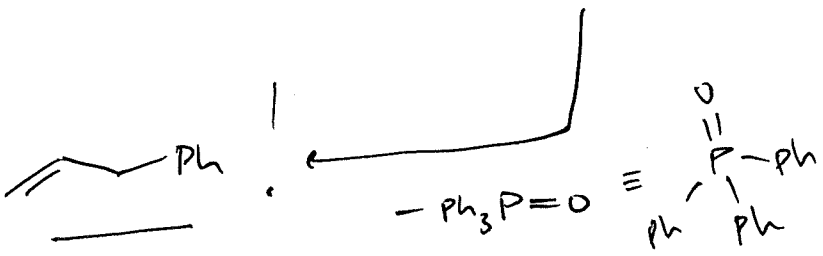


witting salt

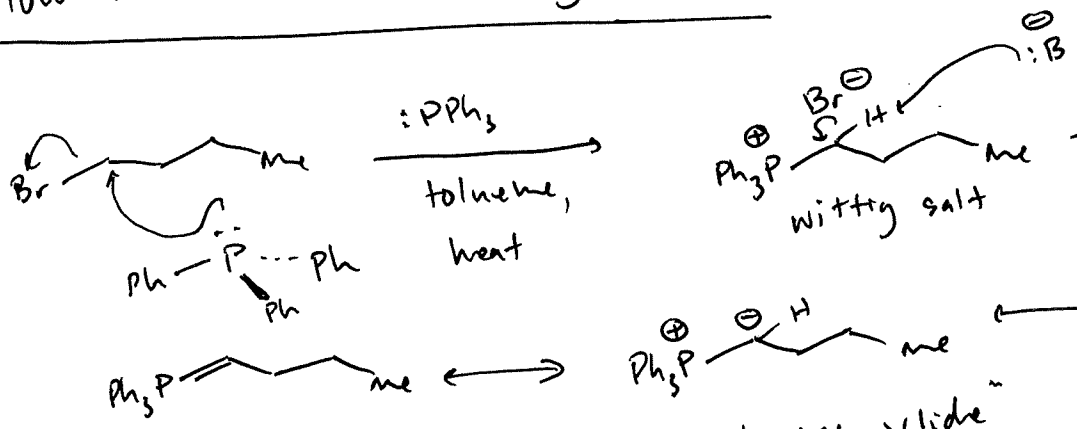
"ylide"

oxaphosphatane

phosphorous is very oxophilic!

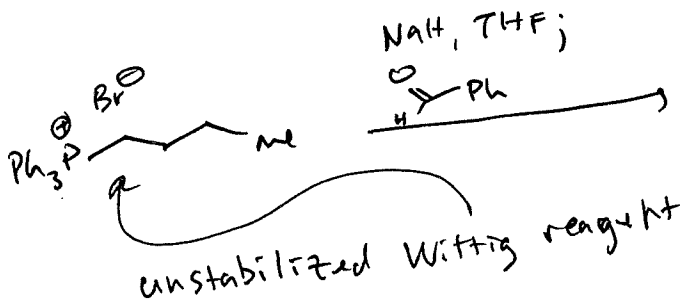


How to make a witting salt!



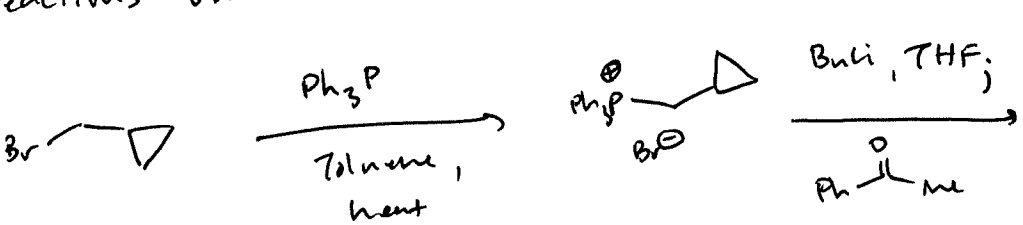
ylide: molecule with opposing charges on adjacent atoms.

Stereochemical outcomes of witting reactions:



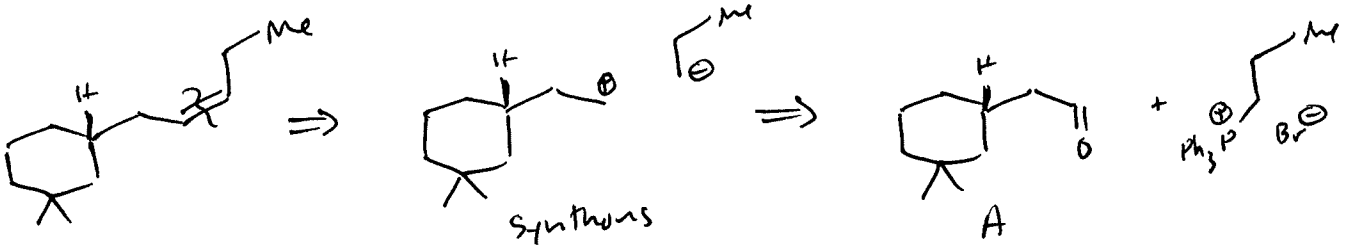
Z alkene is the major product.

reactions on ketones!

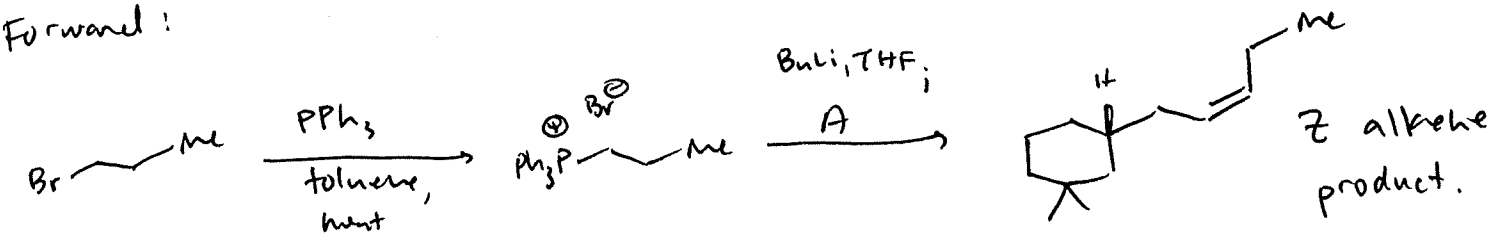


low selectivity!

How to disconnect an alkene with a witting transform!

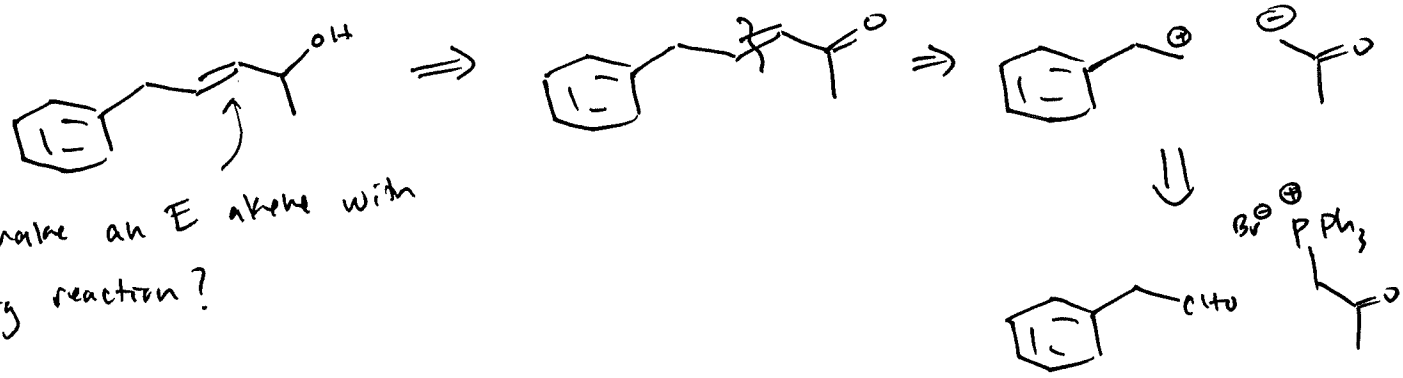


Forward!

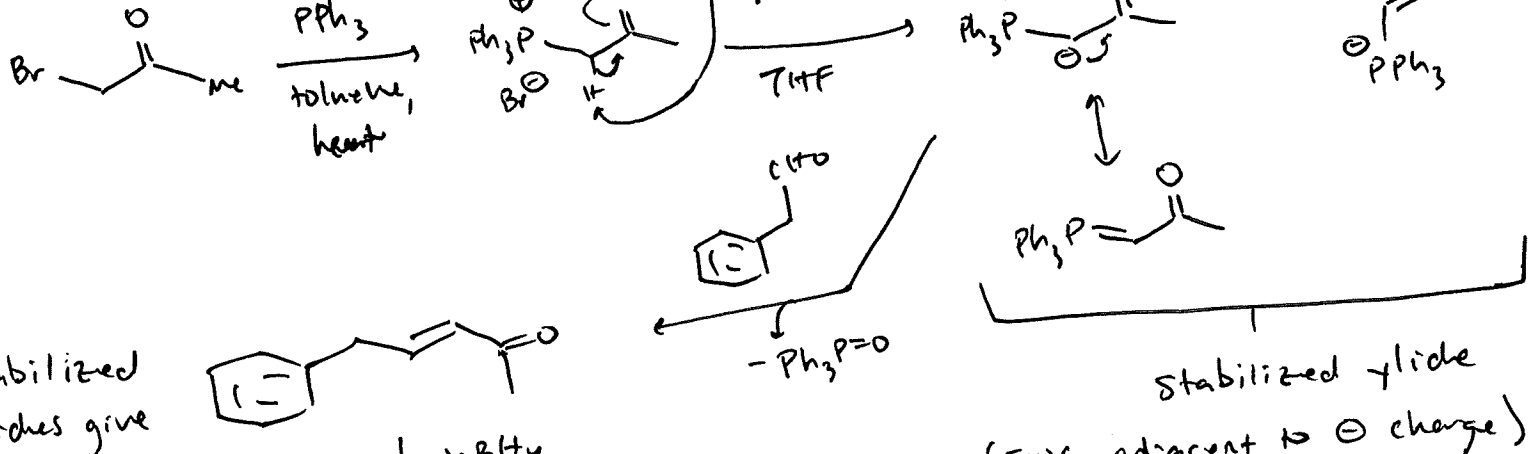


Z alkene product.

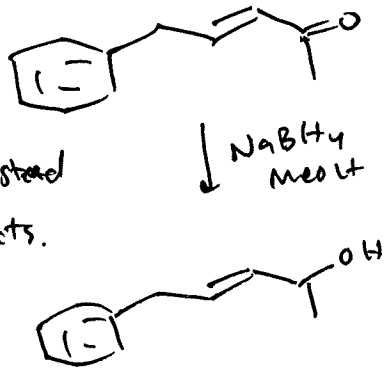
consider!



how to make an E alkene with a wittig reaction?

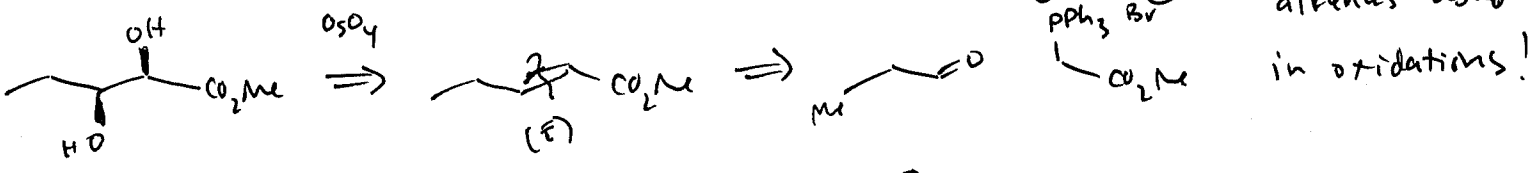


stabilized ylides give E products instead of Z products.

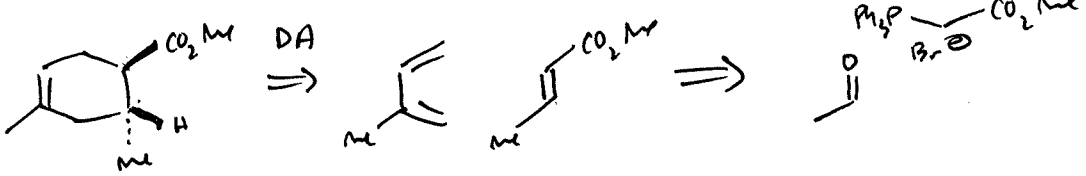


examples of EWG: NO_2, CO_2R, ketone, CN, not aldehyde!

Many composite functionality can be traced back to a wittig disconnection!



alkenes used in oxidations!



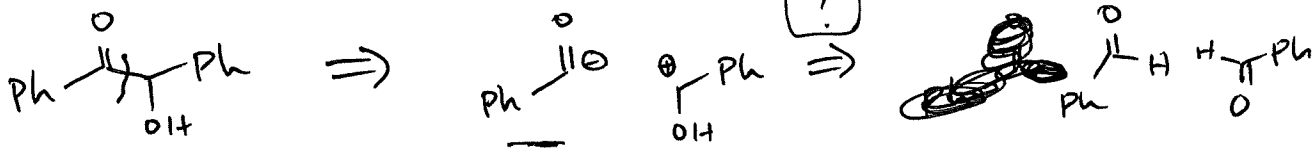
Alkenes used in Diels-Alder Reactions!

Umpolung chemistry

"umpolung" is a german word meaning polarity inversion.

we will look at umpolung reactivity of carbonyl compounds, specifically aldehydes.

consider:

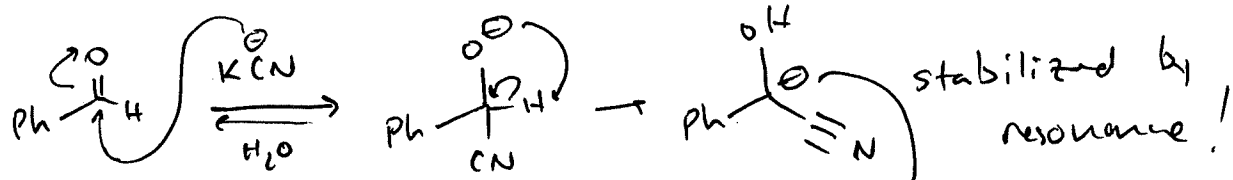


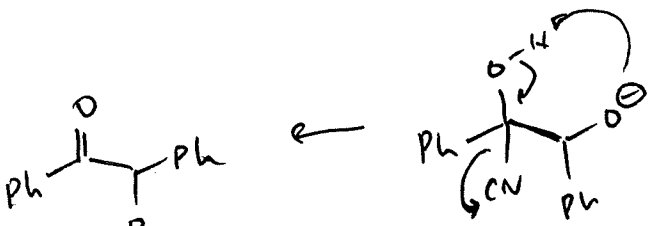
benzil

recall:

cyanohydrin

consider:

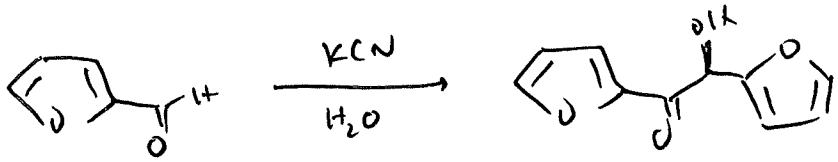


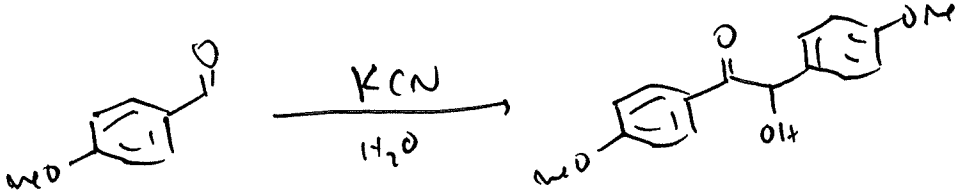


benzil

this reaction is called the benzoin condensation!

It is best used for dimerizations of aldehydes to form hydroxy ketones. Works best with aromatic aldehydes.

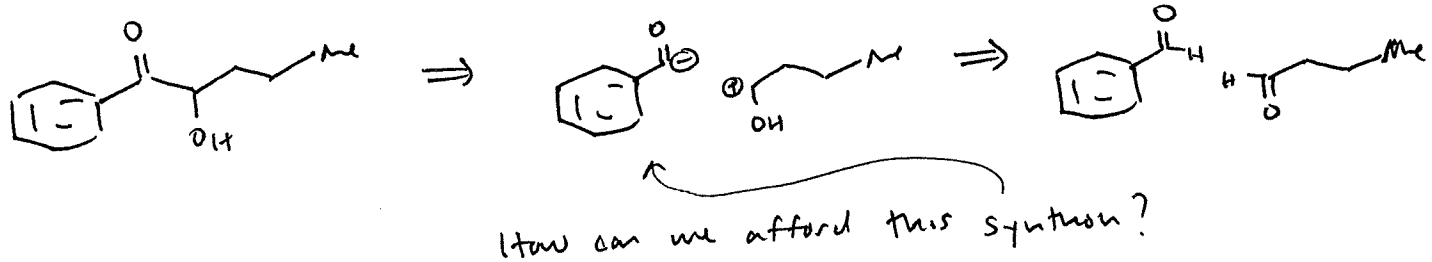




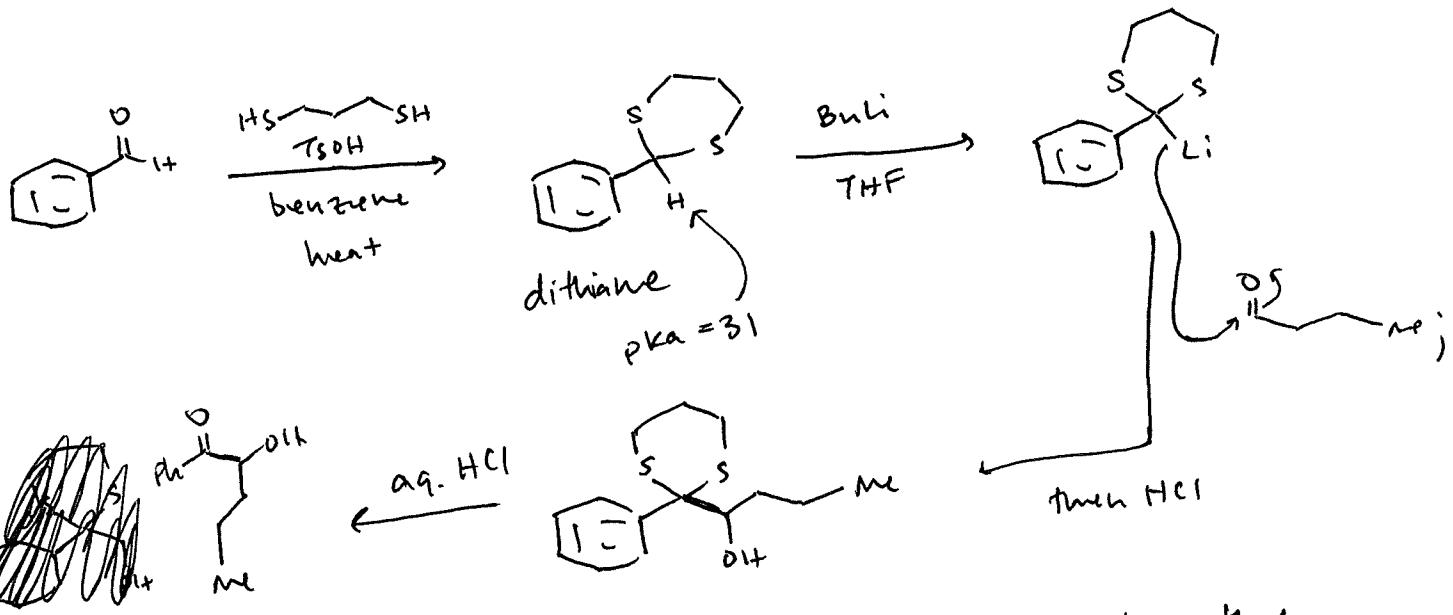
benzoin condensation products!

Umpolung Reactivity ..... using dithianes

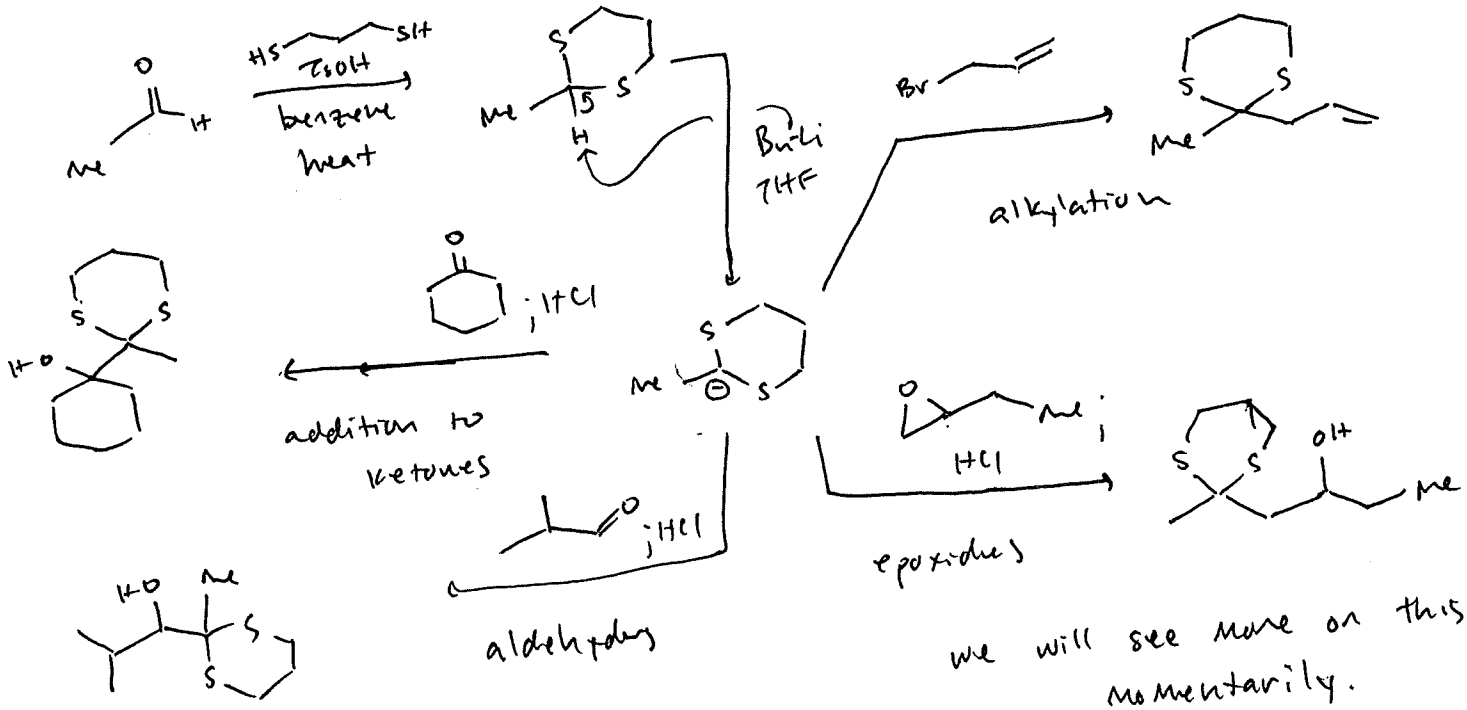
consider:



How can we afford this synthon?

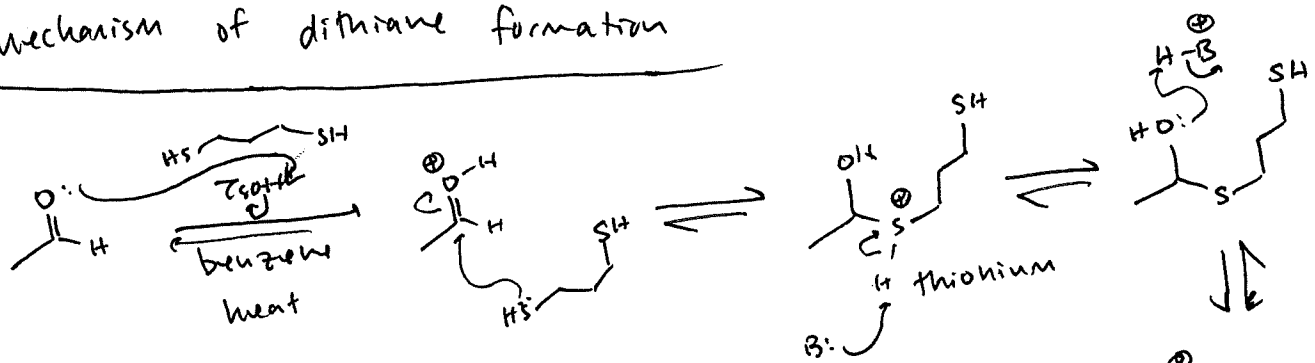


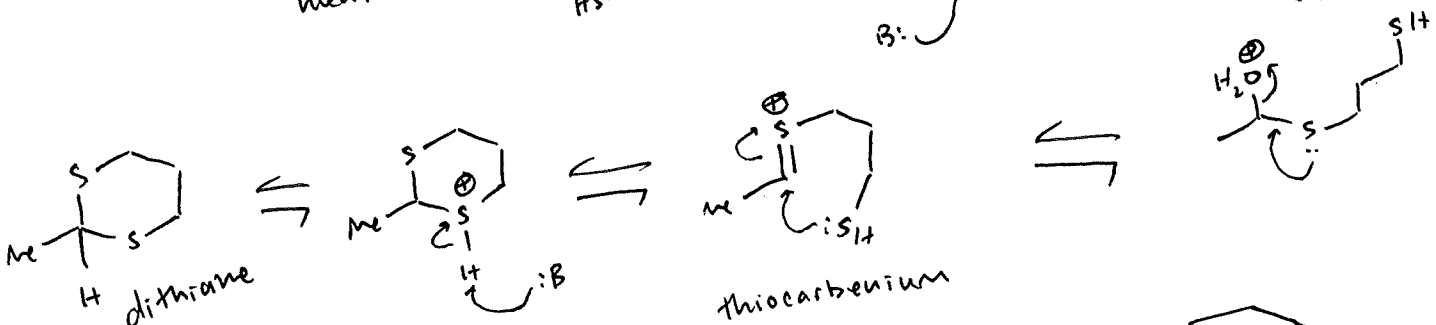
whereas the cyanohydrin can afford dimeric products, the dithiane allows the coupling of any type of electrophile.

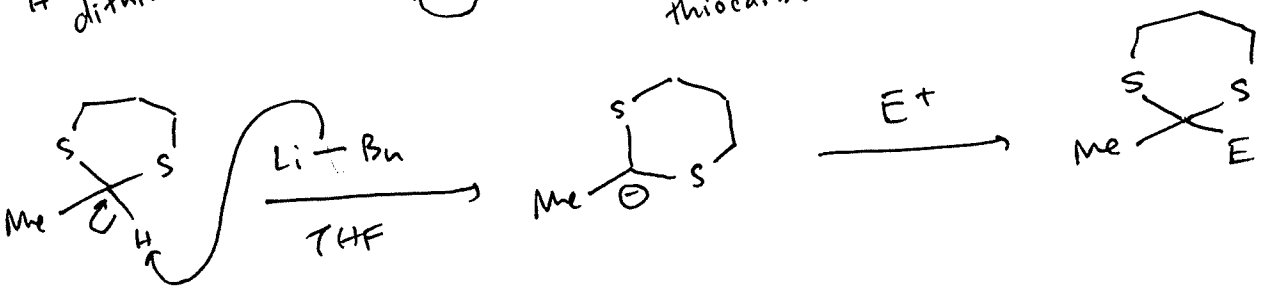


we will see more on this momentarily.

Mechanism of dithiane formation

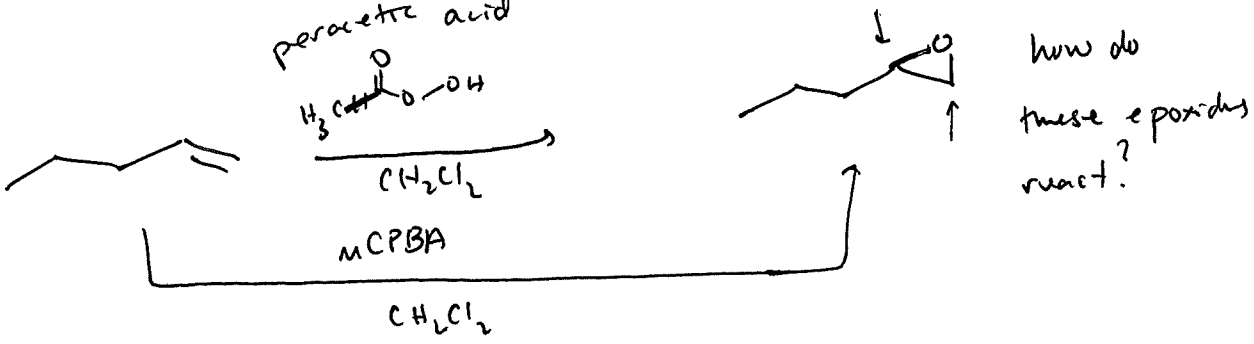






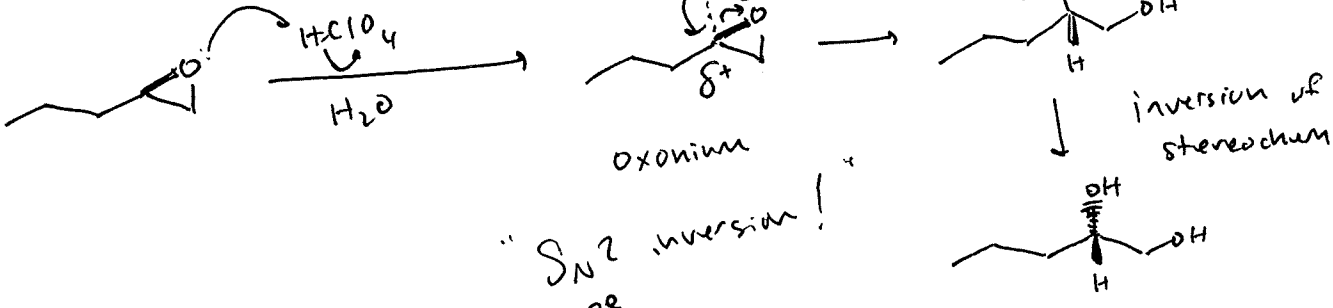
We will revisit sulfur the next time we meet. for now, let's expand upon our knowledge of epoxide reactivity.

recall:



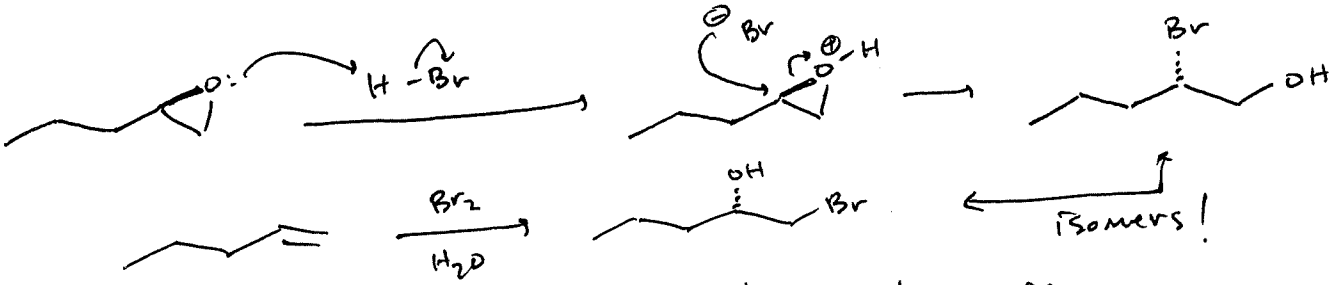
how do these epoxides react?

under acidic conditions:

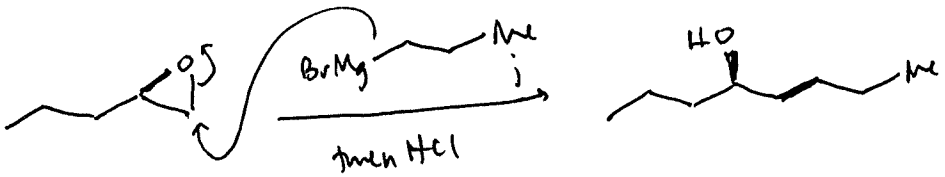


"S_N2 inversion!" type

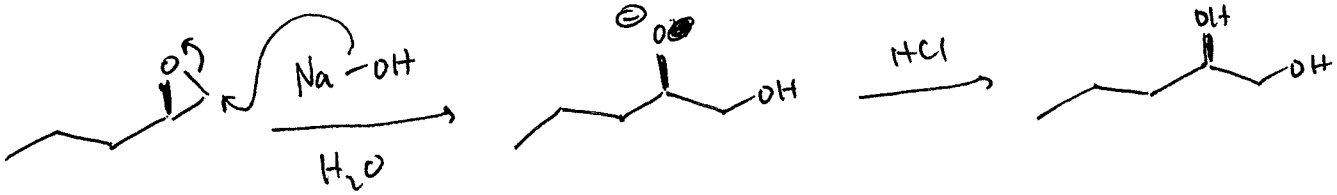
what about other nucleophiles under acidic conditions?

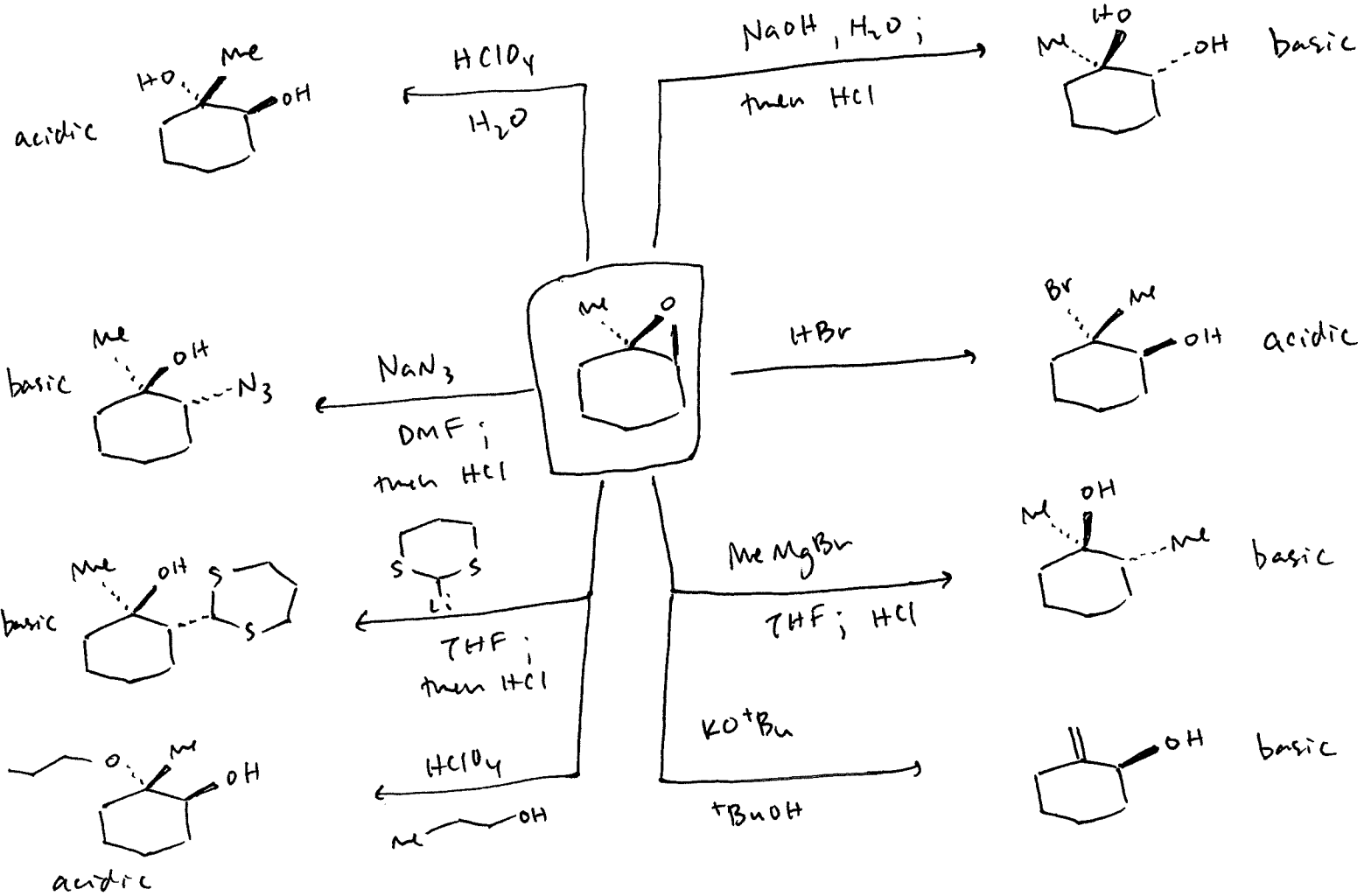


with basic conditions, we can do much more...

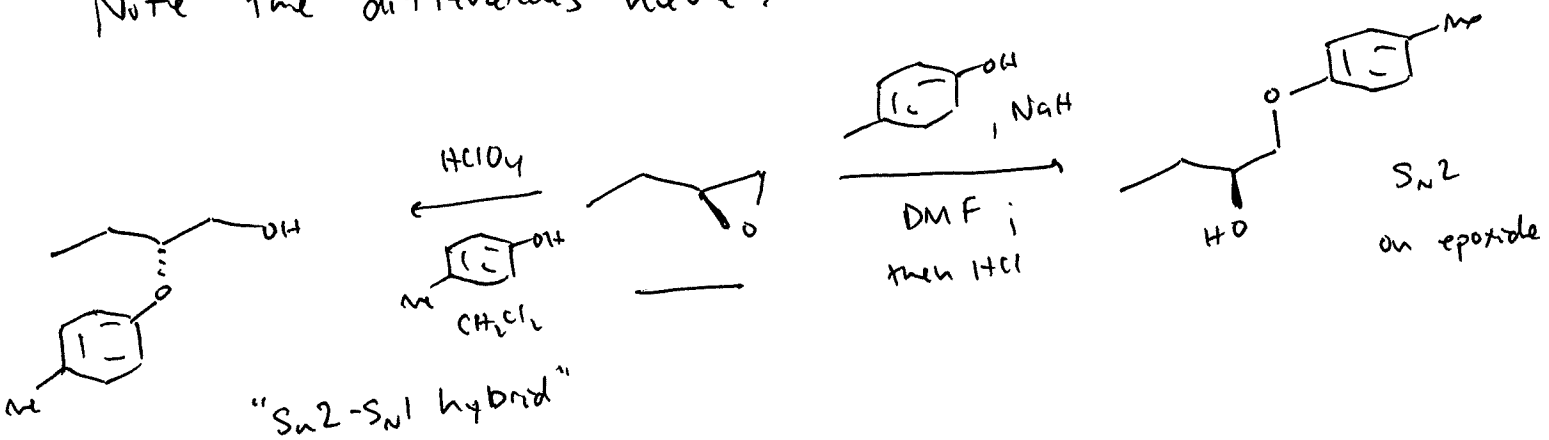


addition to less hindered side



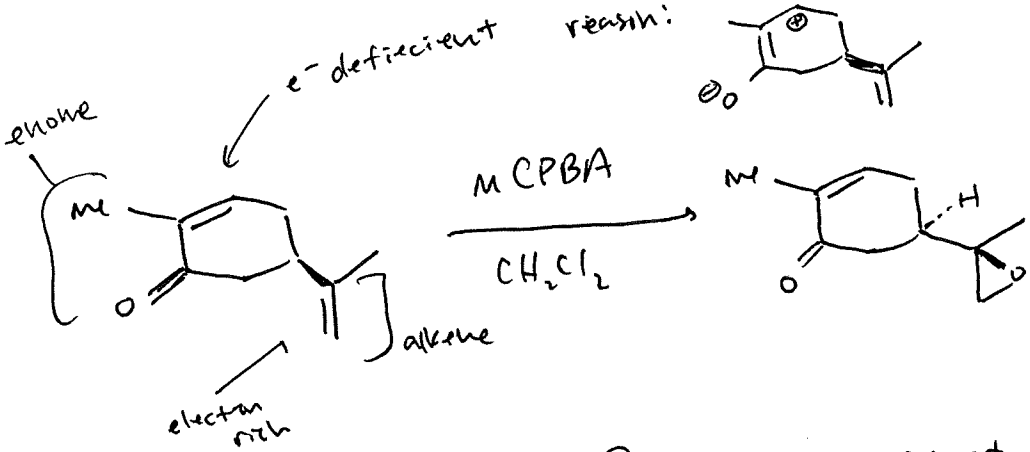


Note the differences here:

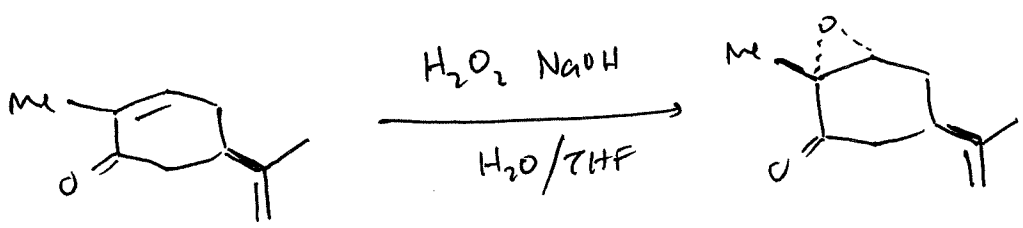


Not all alkenes are true some towards epoxidation.

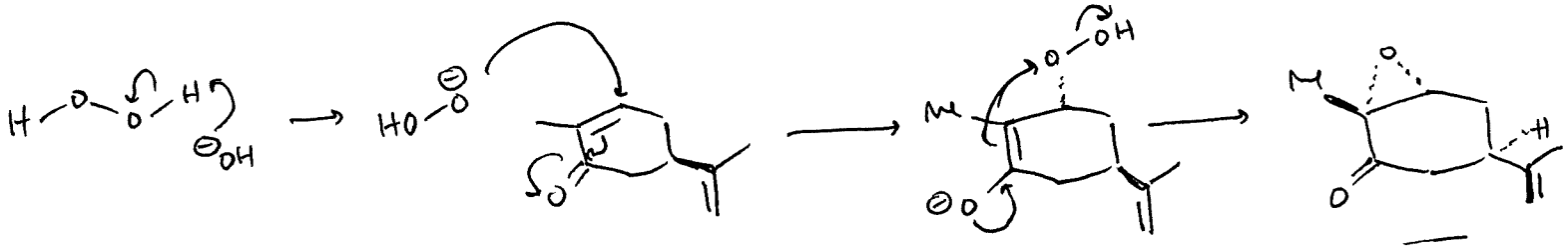
why does only one alkene react?



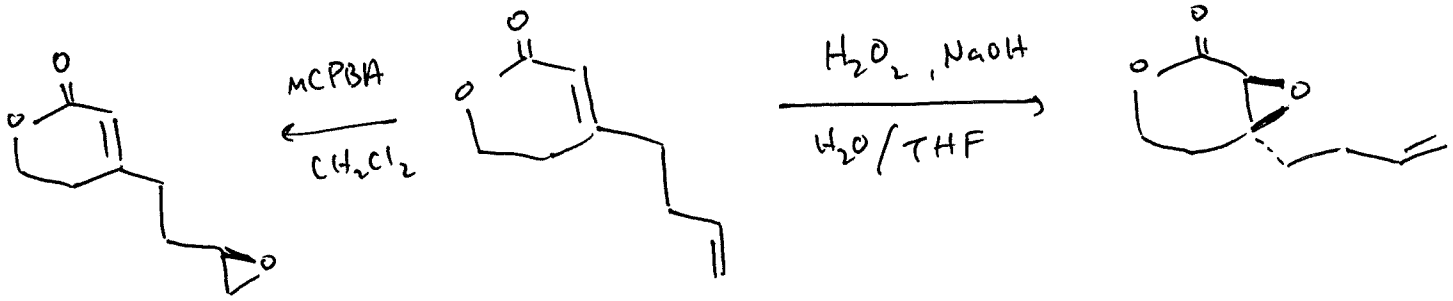
how can we react the other alkene? can we react it selectively?



success! but how?



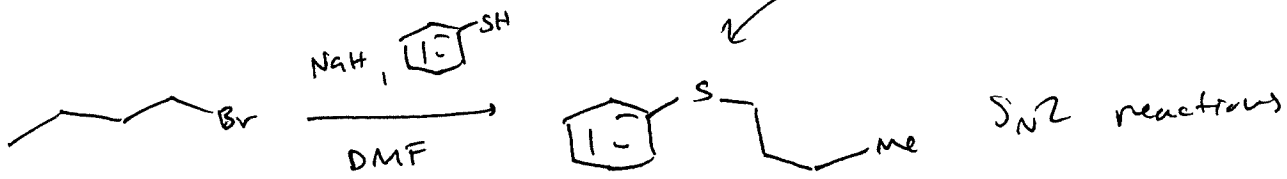
this is a nucleophilic epoxidation. only electron-deficient alkenes react under this mode of epoxidation.



both reactions are chemoselective! An electron deficient alkene must have an EWG (usually a carbonyl) adjacent to it.

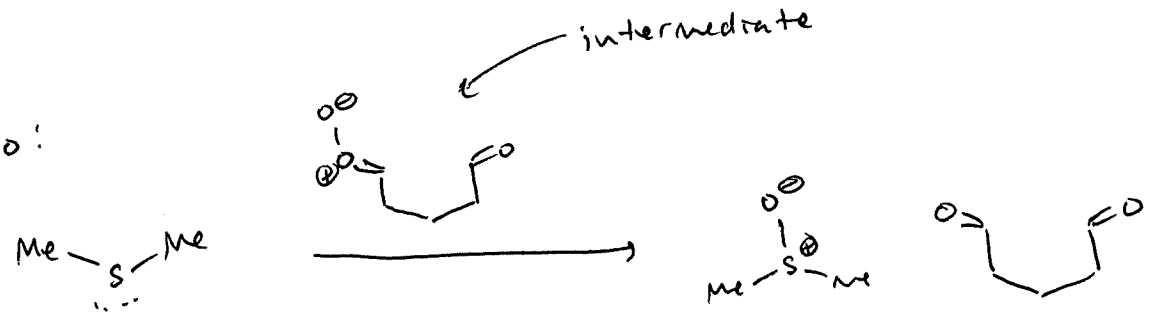
Utility of sulfides/thiols

recall:

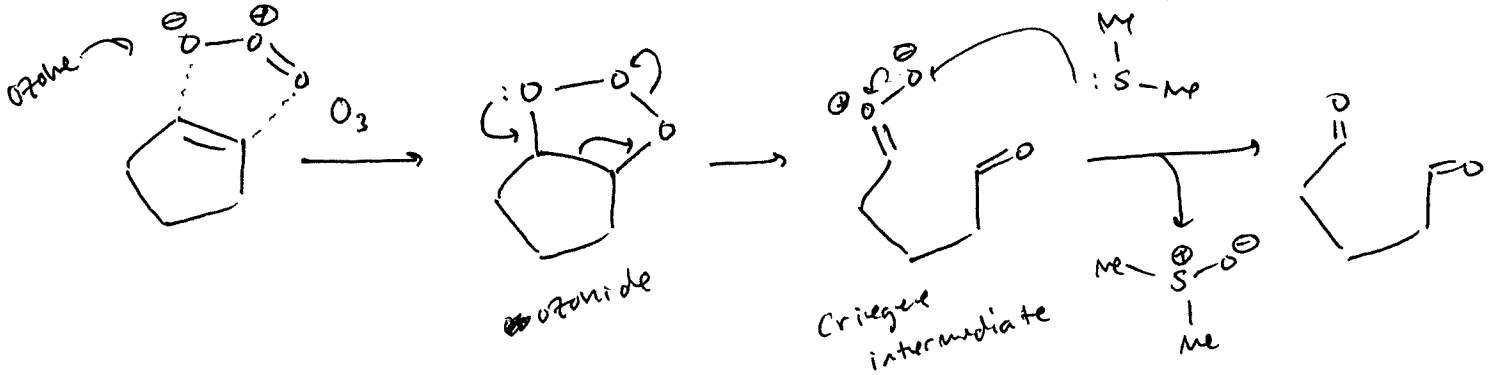


sulfides can be deprotonated and used in substitution reactions like alcohols.

But, also:

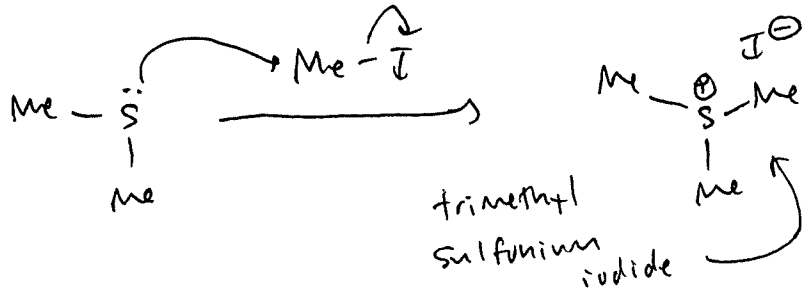


This is what is happening in the second step of ozonolysis.



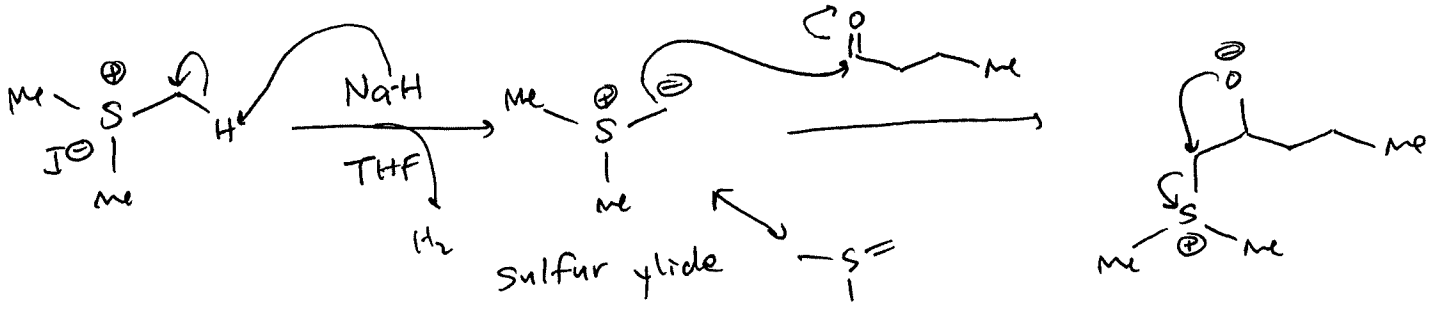
The take away point here is that sulfides are nucleophilic and that sulfur can accomodate an expanded octet, unlike oxygen.

We can also use sulfides to alkylate them.

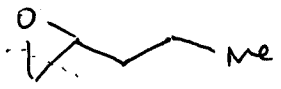


this is similar to a phosphonium! Forged by S_N2 reaction.

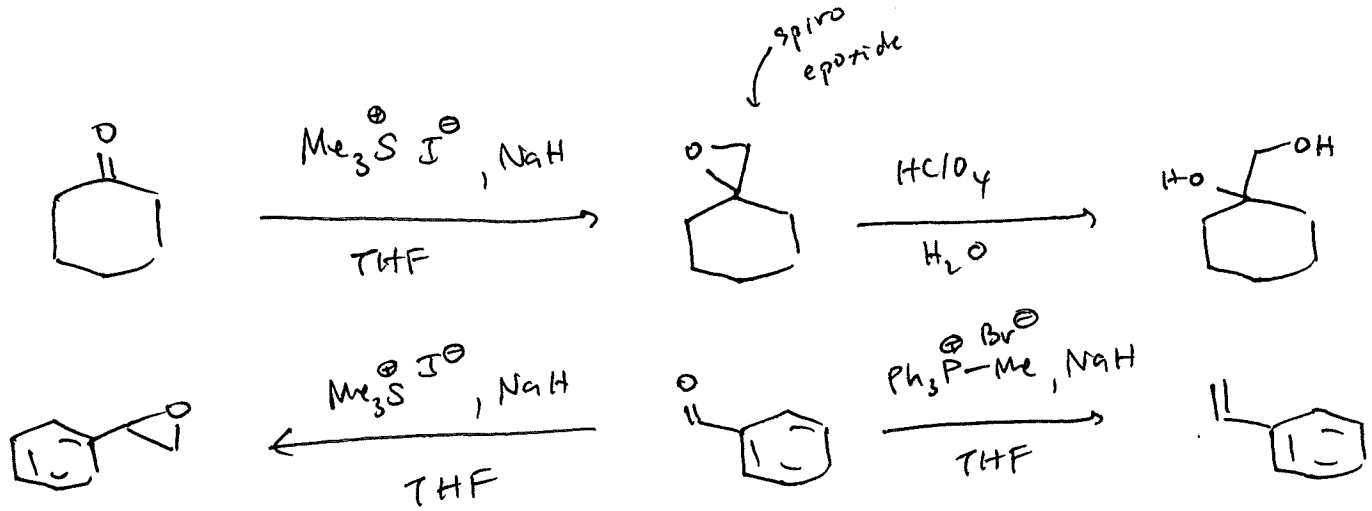
If its similar to a phosphorium, can we deprotonate it?



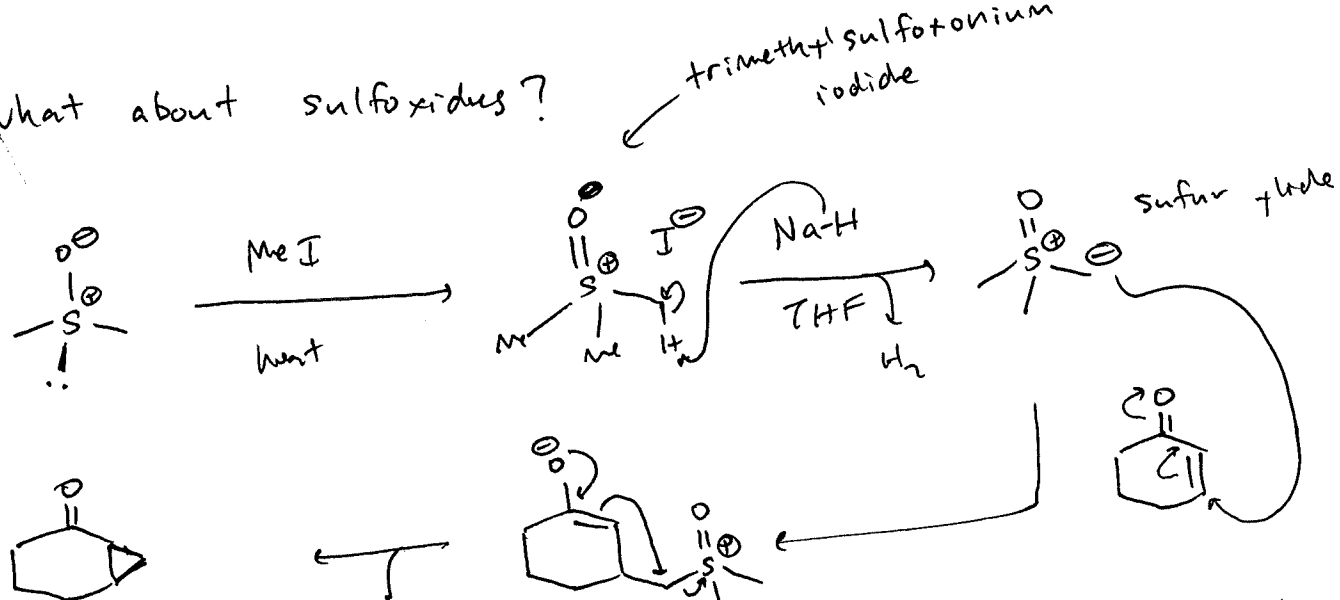
This is called the Corey-Chaykovsky epoxidation



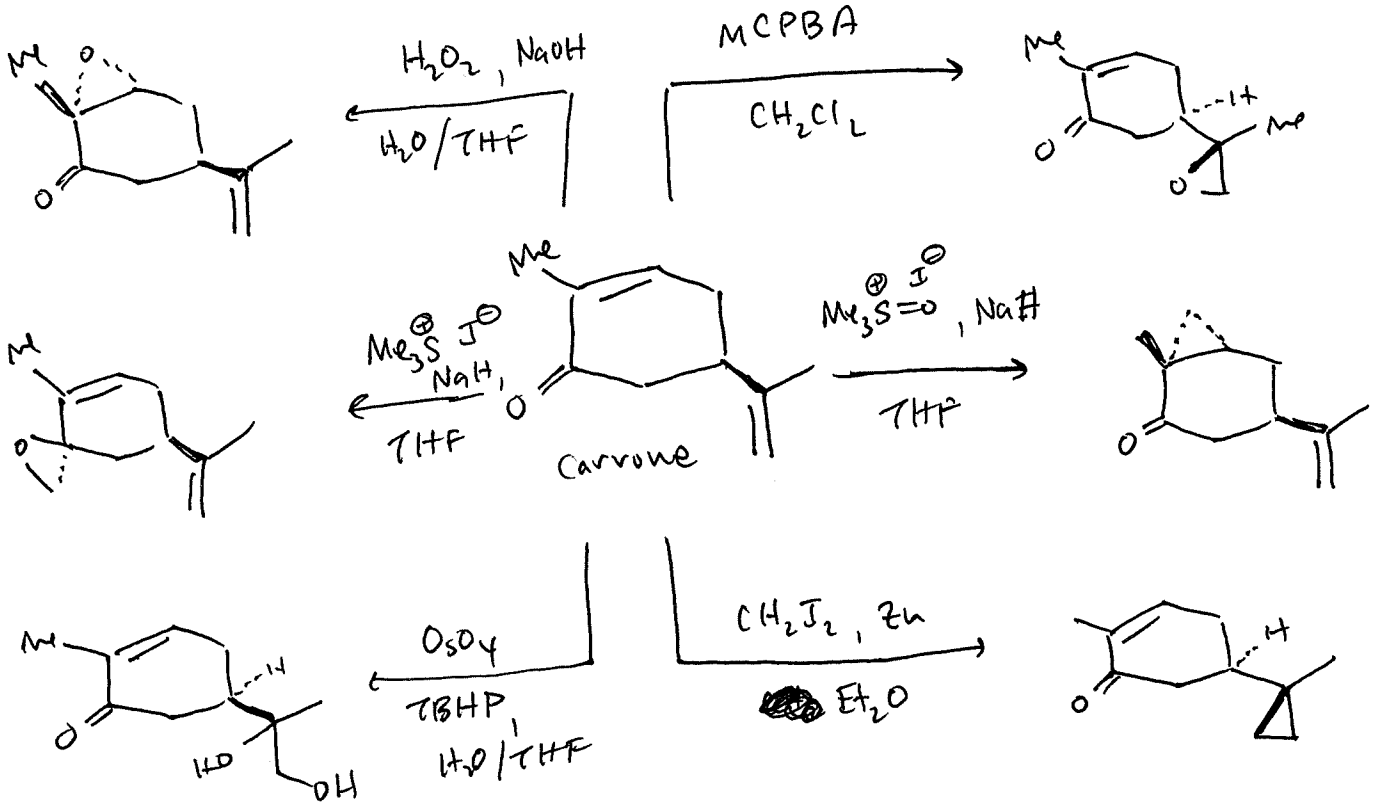
epoxide!



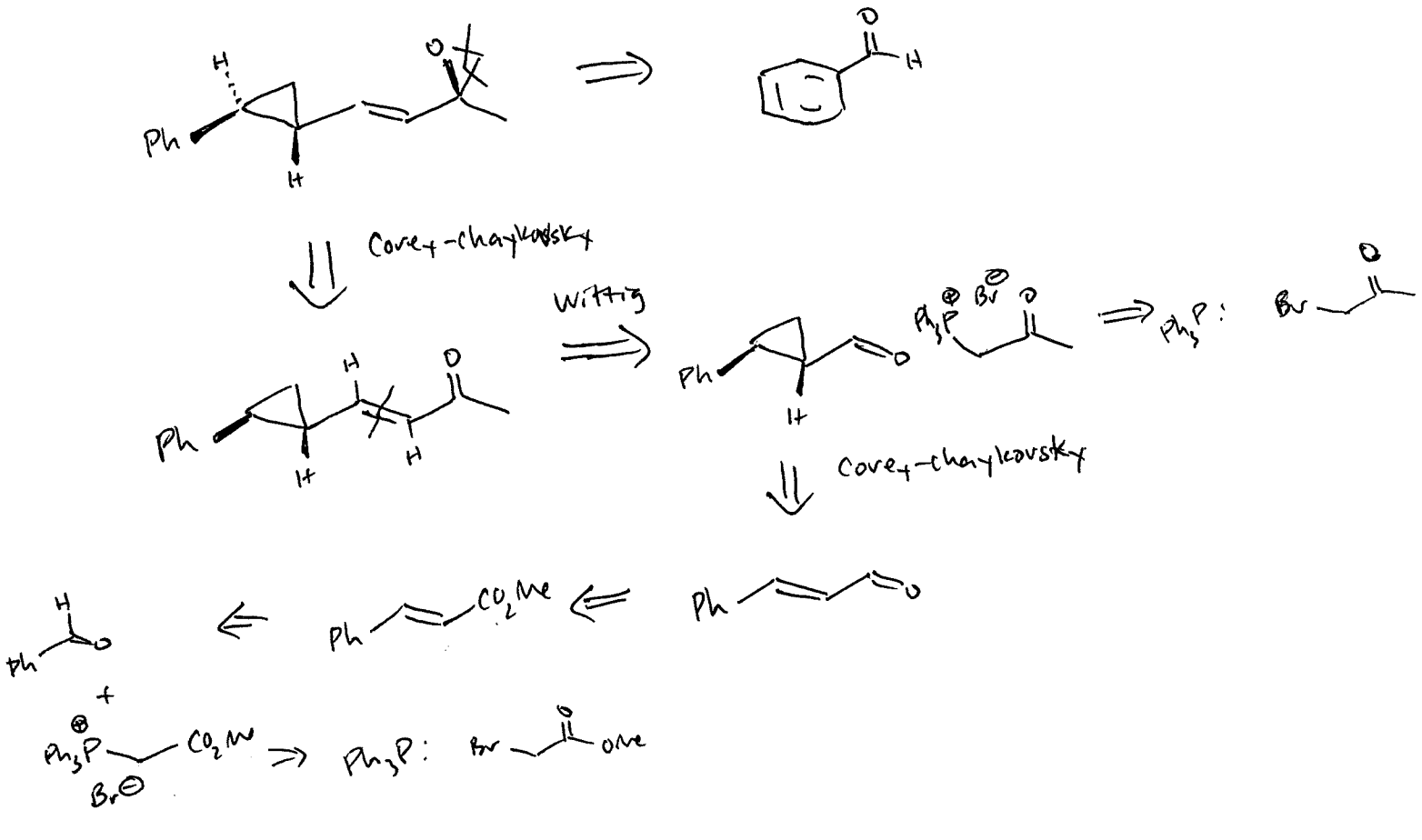
What about sulfoxides?



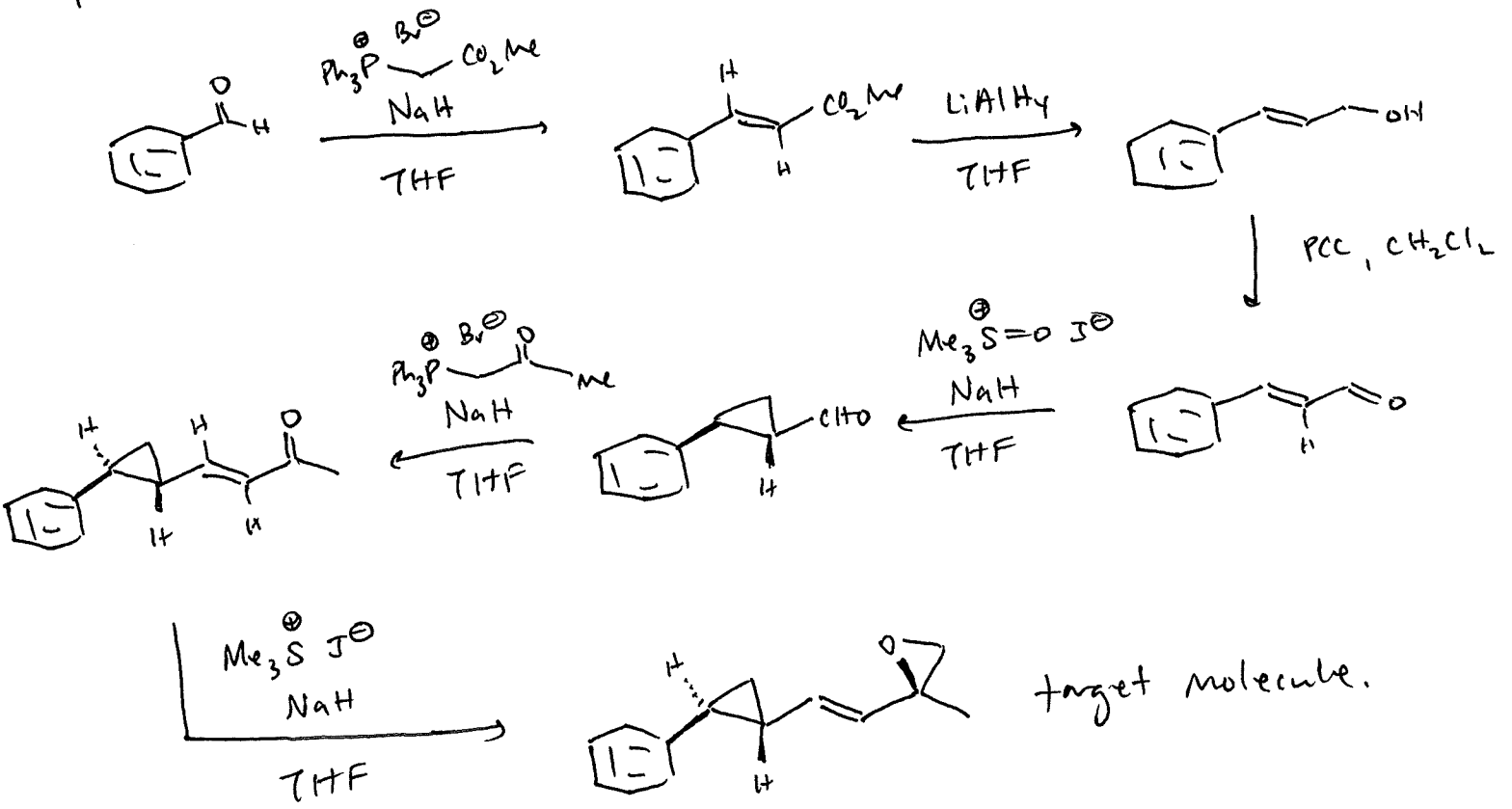
How to differentiate alkenes, enones, etc.



How would we make this compound?

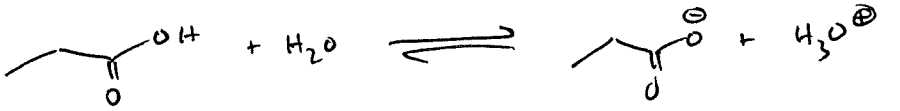


Forward synthesis

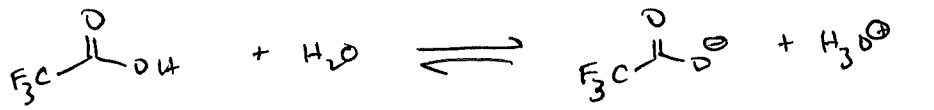


Chemistry of carboxylic acids

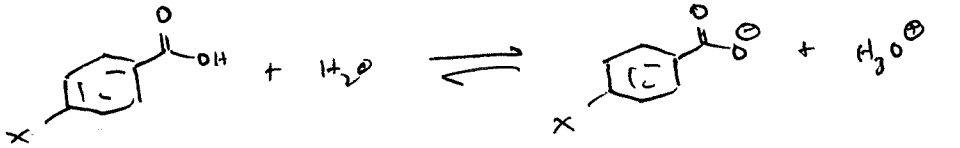
how acidic are carboxylic acids?



pka ~ 5 (acid)



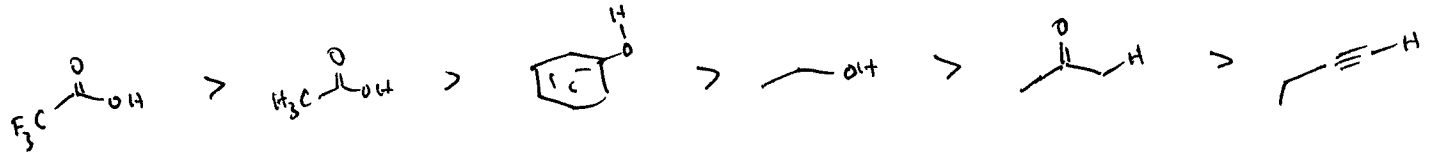
pka ~ 0 (acid)



X	pka
H	4.2
Me	4.4
NO_2	3.4
F	4.1
OMe	4.5

the x substituent can provide for inductive effect on acidity of carboxylic acid

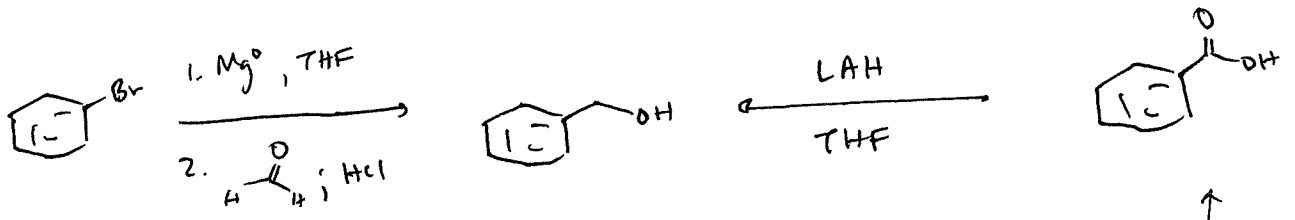
For reference!



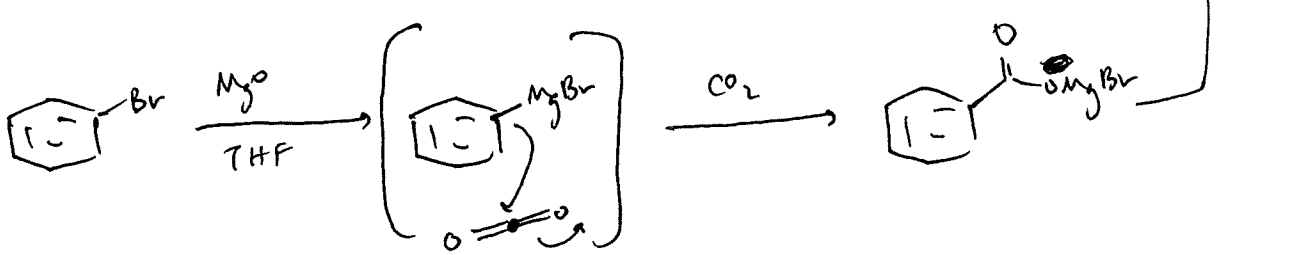
pka 0 5 9 16 20 25

Synthesis of carboxylic acids - from Grignards

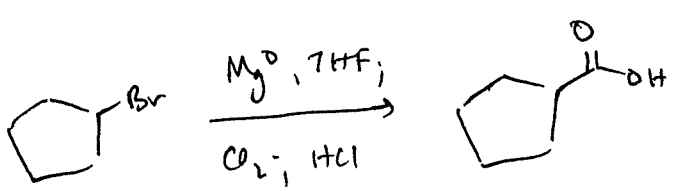
recall:

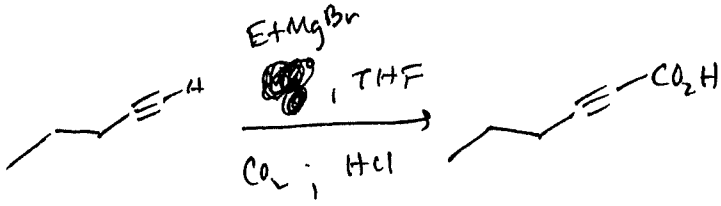


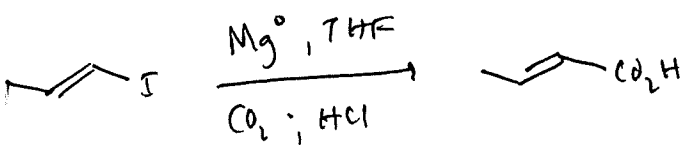
consider



This can be done for almost any Grignard reagent!

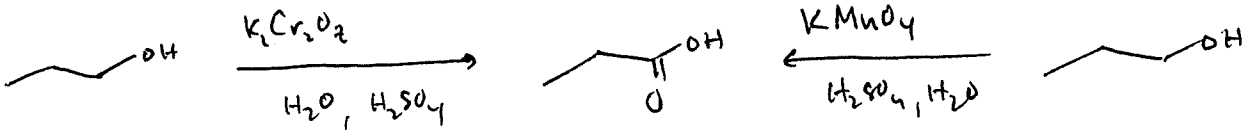


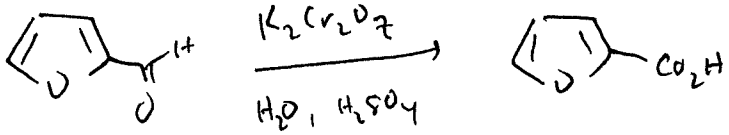




Carboxylic acids can also be made via oxidation:

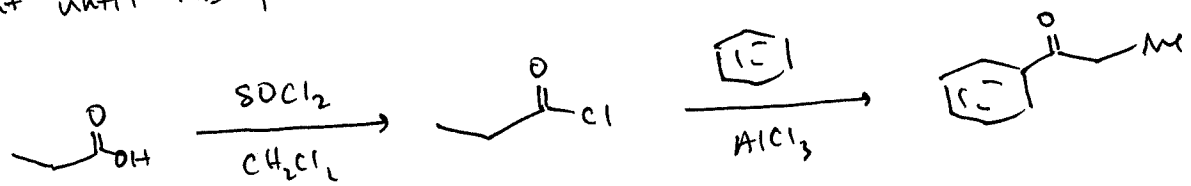
recall:



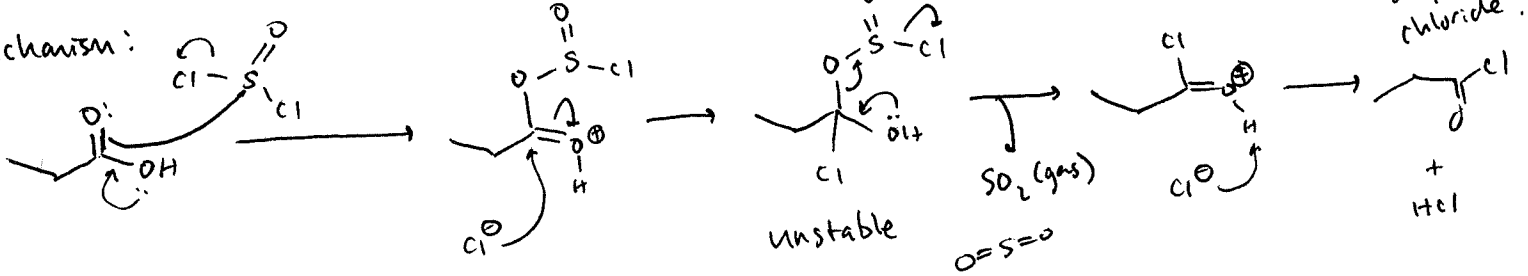


Reactions of carboxylic acids: synthesis of acyl chlorides

We know the utility of acyl chlorides in Friedel-Crafts reactions, but until this point their synthesis has been assumed.

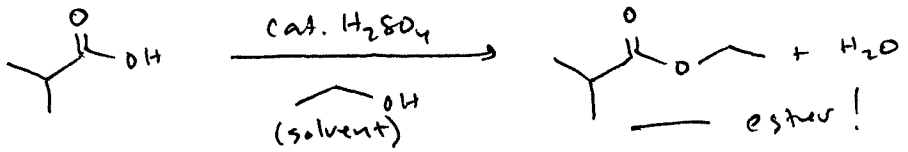


mechanism:

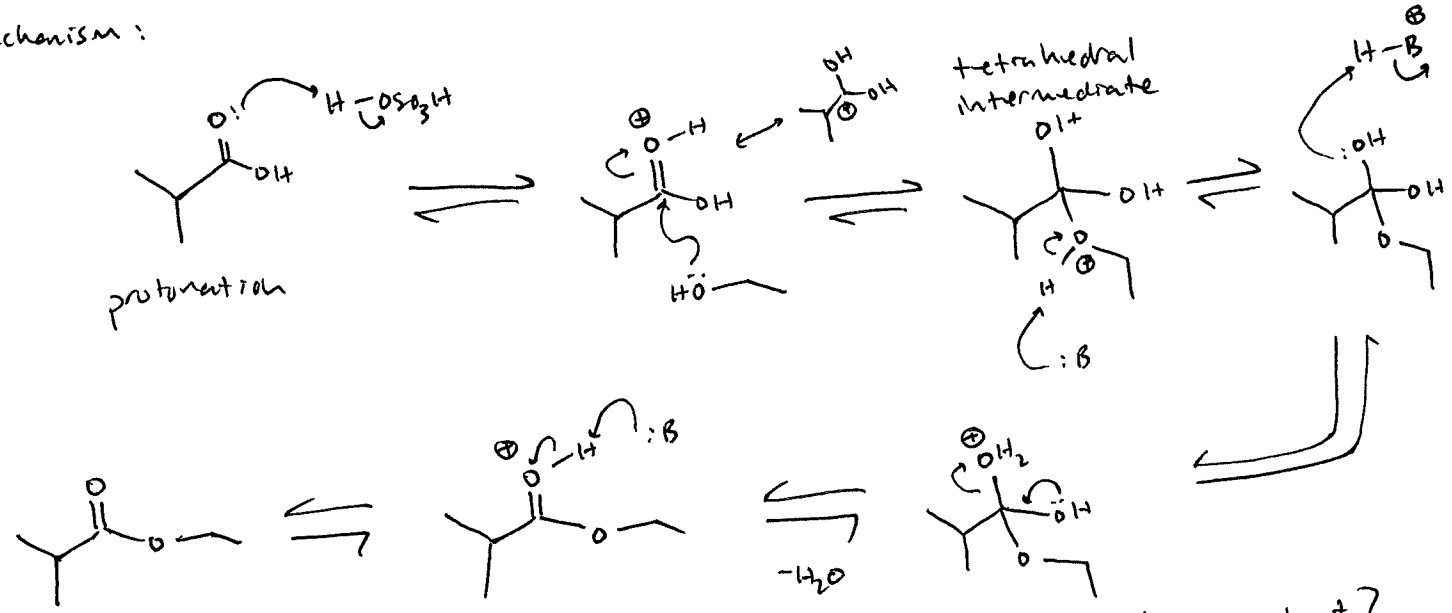


The fischer esterification – Emil Fischer

Consider:



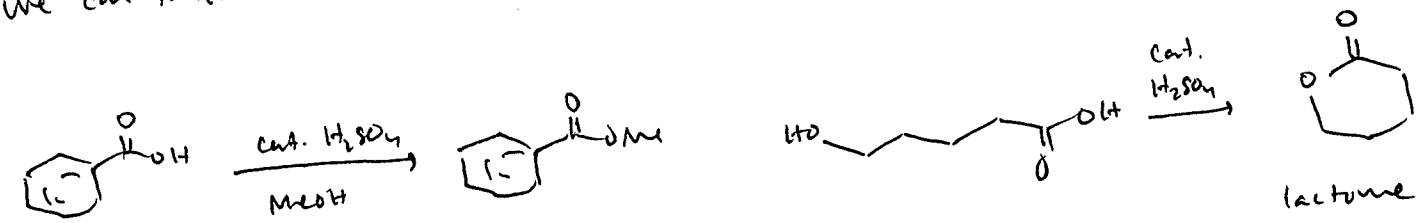
Mechanism:



If all steps are in equilibrium, how do we obtain the product?

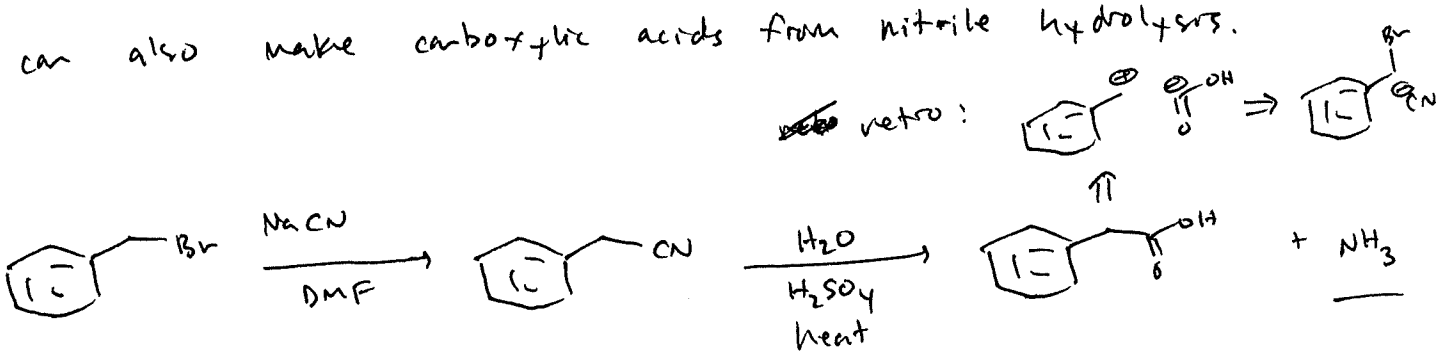
One has to use an excess of the alcohol in order to drive the reaction to completion. This is the utilization of Le Châtelier's principle

We can make all kinds of esters this way:

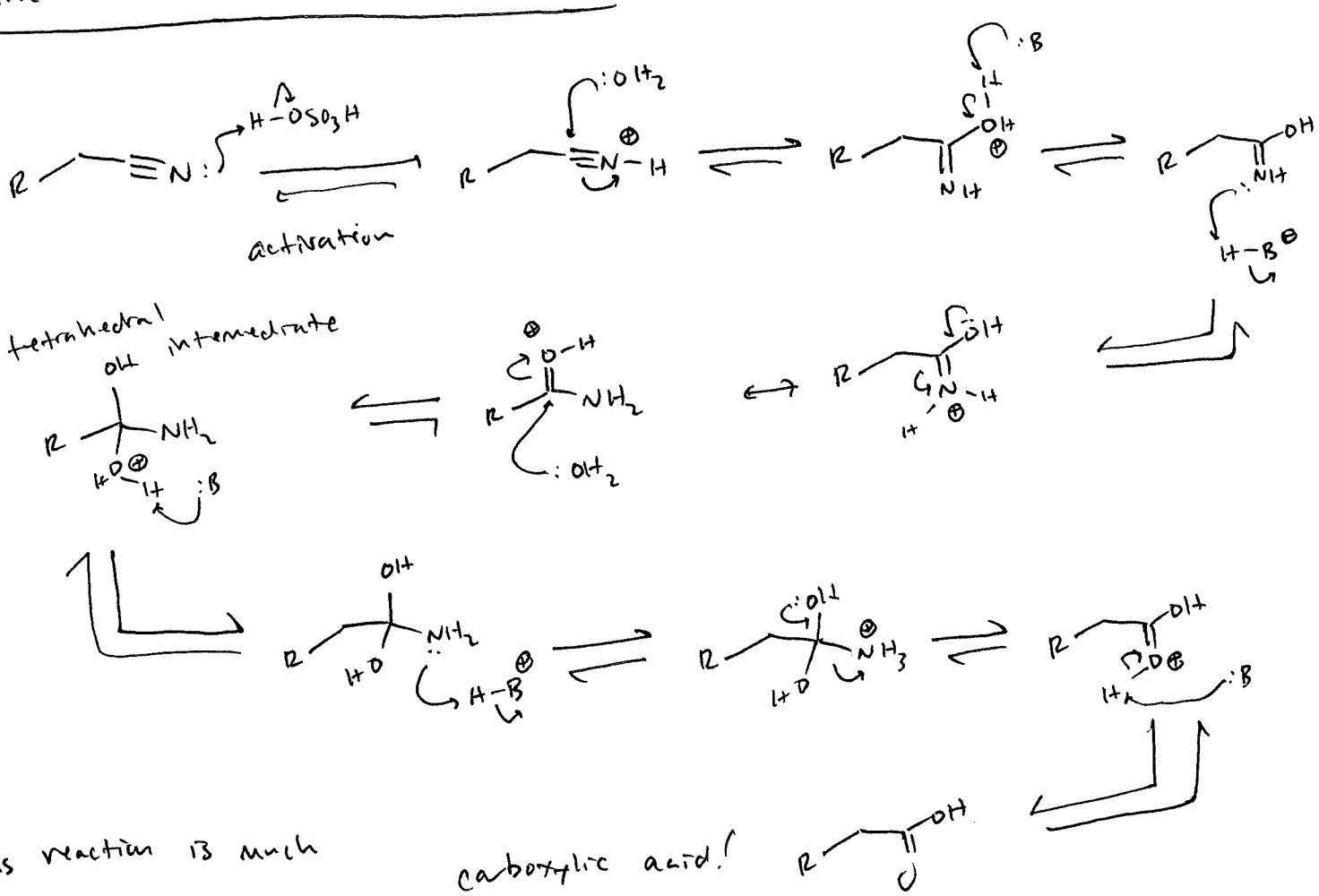


We can also make carboxylic acids from nitrile hydrolysis.

~~retro~~ retro:



Mechanism of nitrile hydrolysis

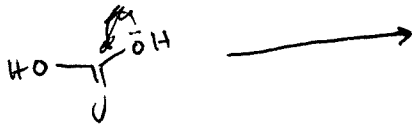


This reaction is much more difficult because of the many equilibrium steps it has beyond Fischer esterification.

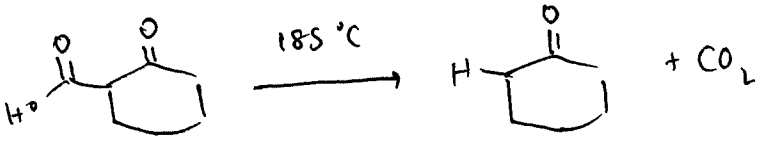
carboxylic acid!

Decarboxylation reactions of carboxylic acids

consider:

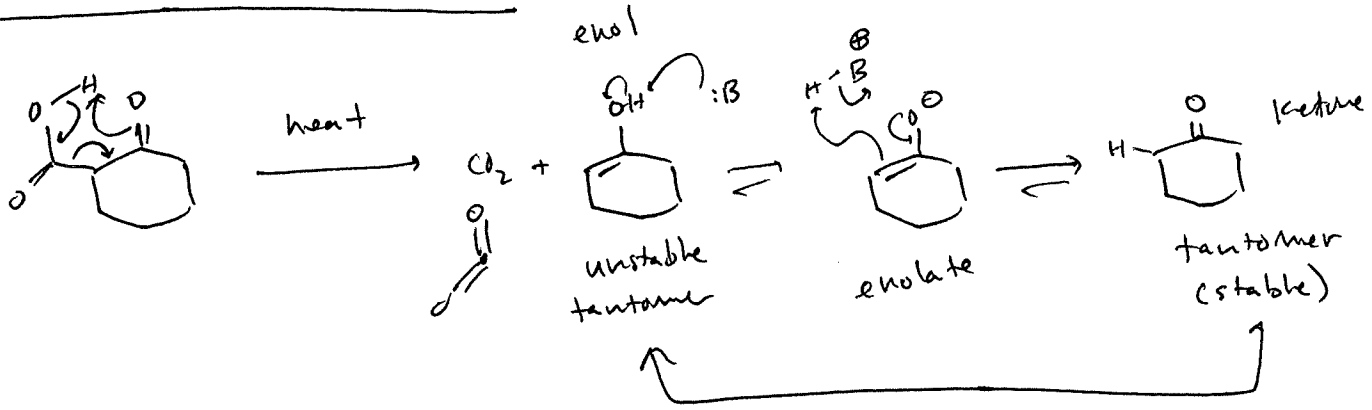


Can this type of decarboxylation happen on organic molecules?

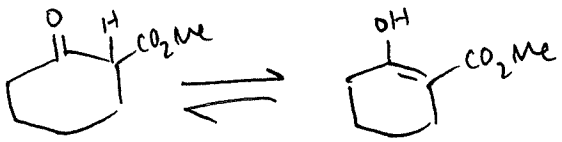


but how does this occur mechanistically?

Mechanism of decarboxylation



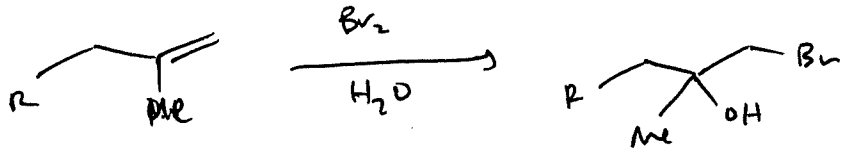
tautomers: molecules with the same molecular formula and atom connectivity with the exception of a hydrogen atom. Usually the hydrogens involved in two tautomers are sufficiently acid to undergo proton transfer processes.



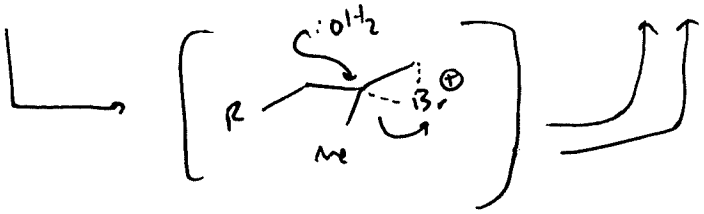
tautomers

tautomers are not resonance structures !!!

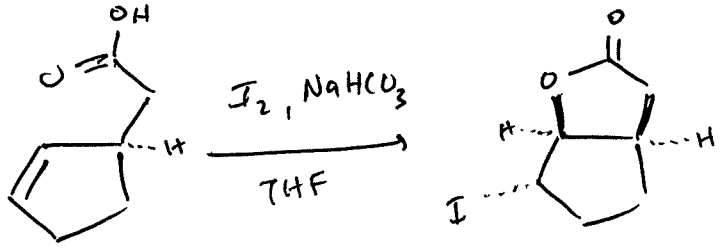
one last reaction with carboxylic acids

recall: 

Bromoalcohol product

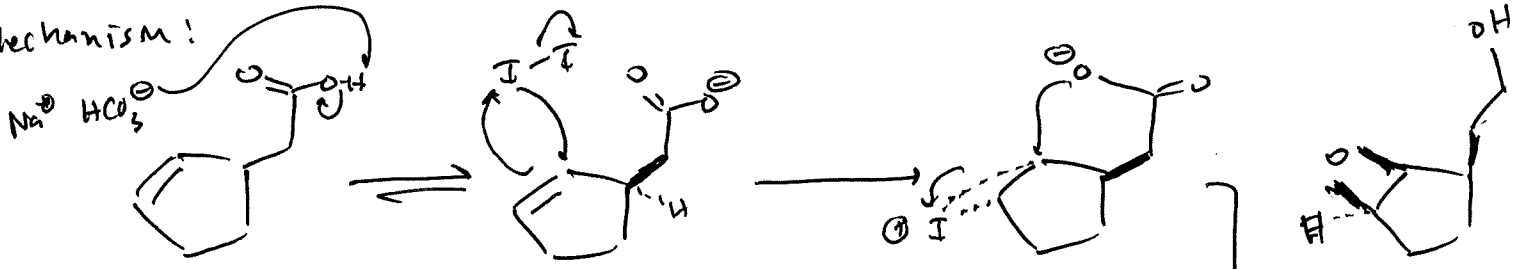


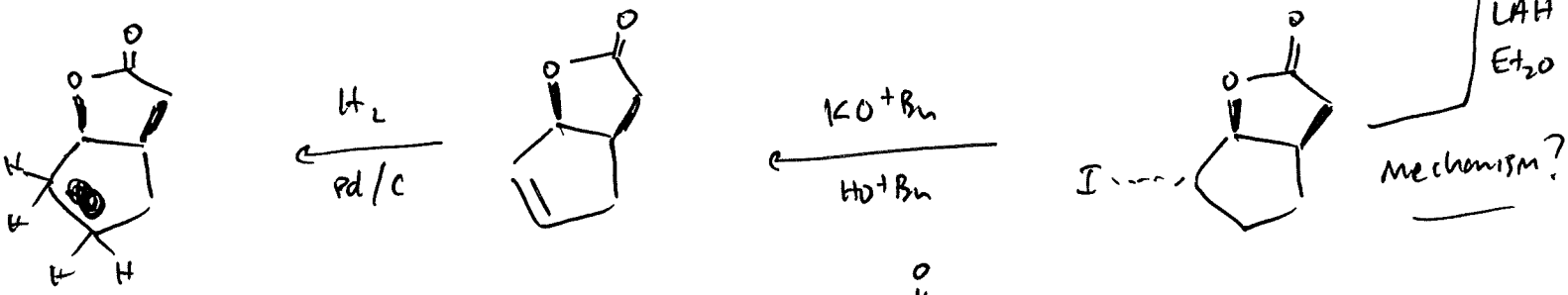
Carboxylic acids can do a similar type of reaction. This reaction is called "iodolactonization." It is an intramolecular reaction.



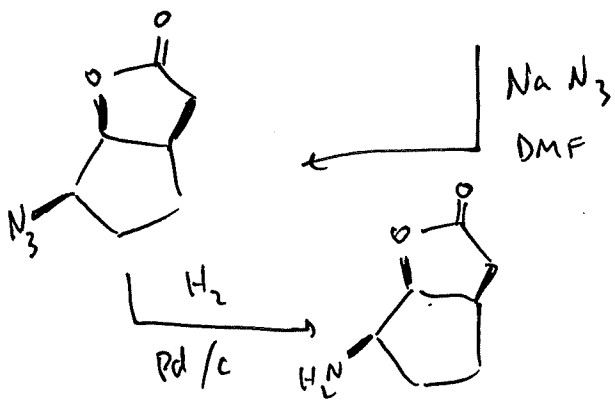
generates 3 stereocenters selectively in one reaction!

Mechanism!



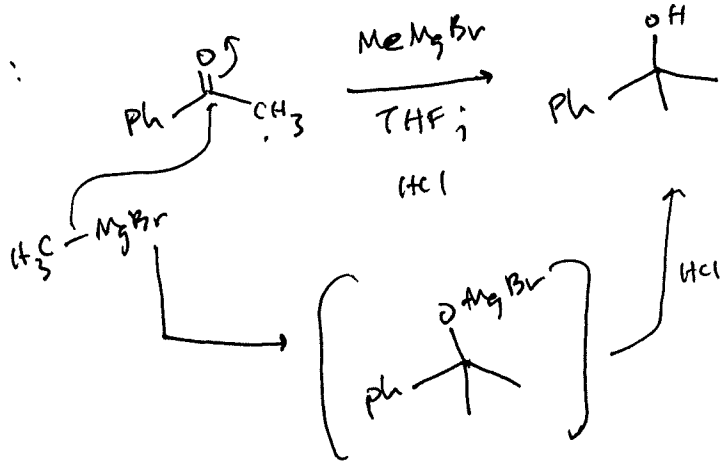


the Iodide and the lactone can be transformed in canonical ways



Carboxylic Acid Derivatives

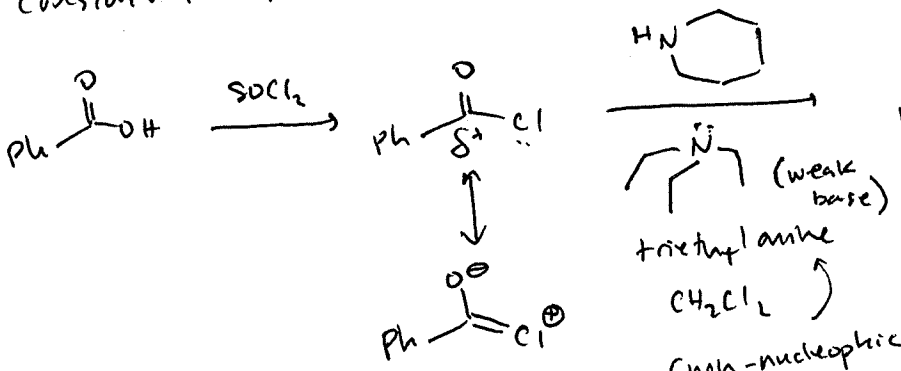
recall:



carbonyls, generally speaking, are electrophiles.

what happens when the CH_3 on this ketone is different?

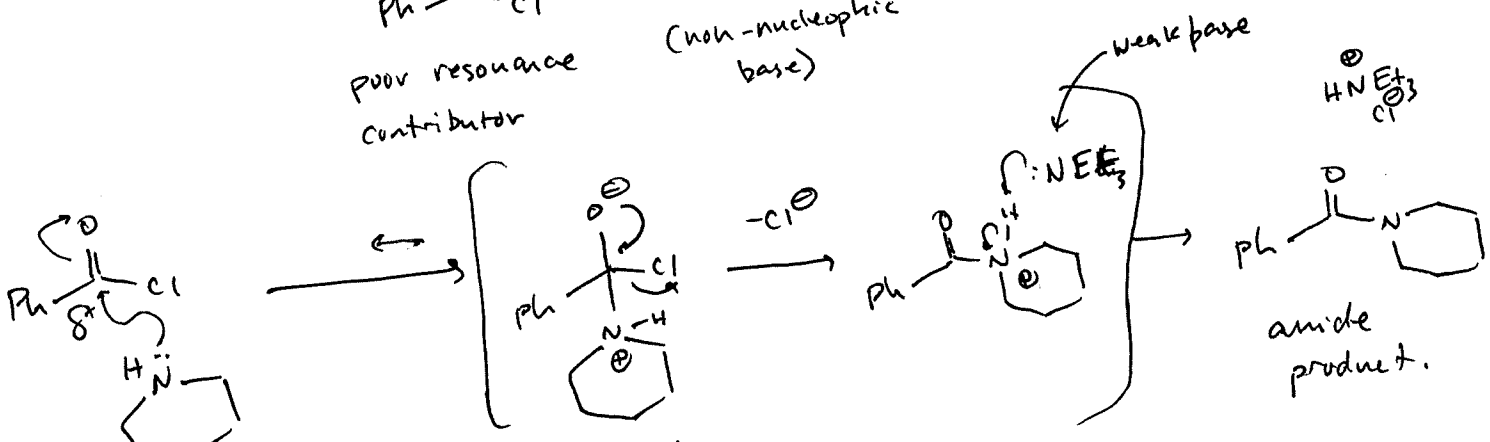
consider: an acid chloride



amide product.

how does this occur?

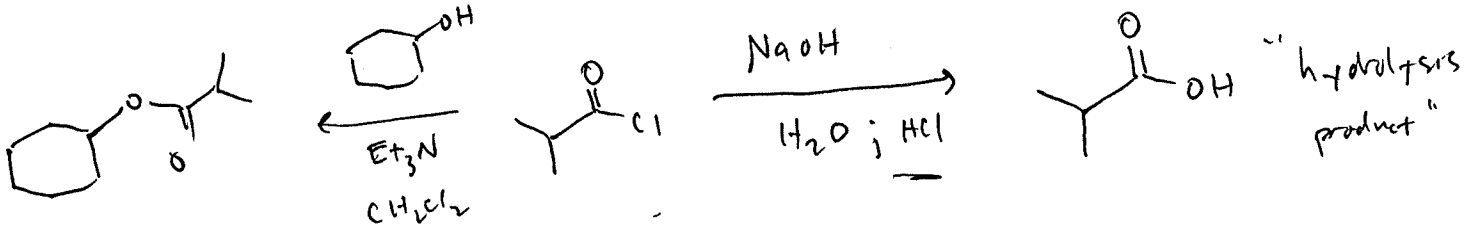
poor resonance contributor



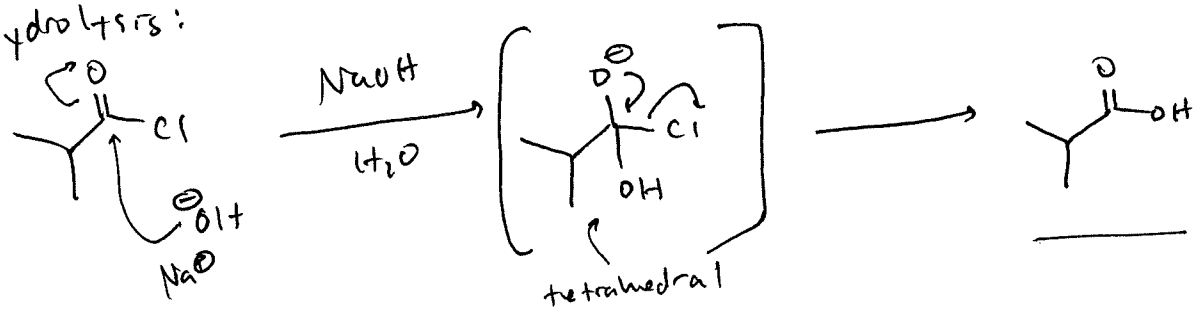
unstable tetrahedral intermediate

basic conditions!

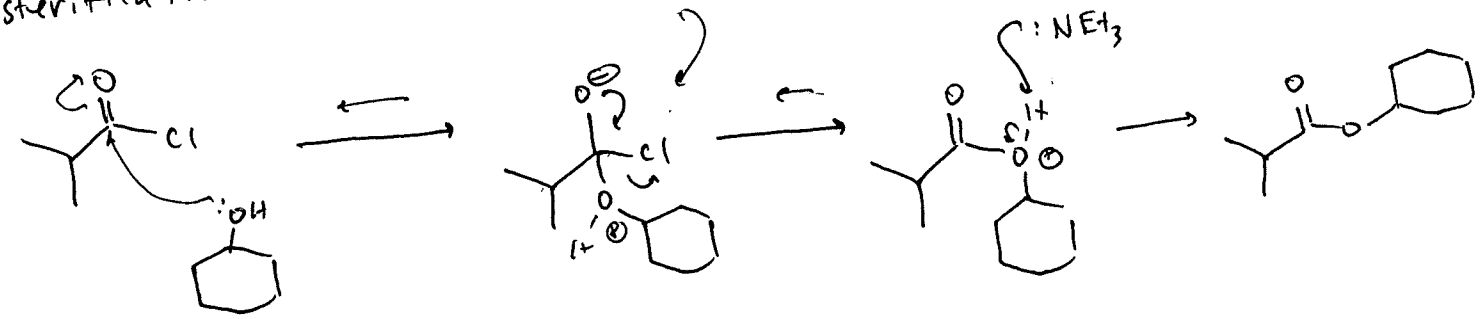
This mechanism will resurface again and again and again.



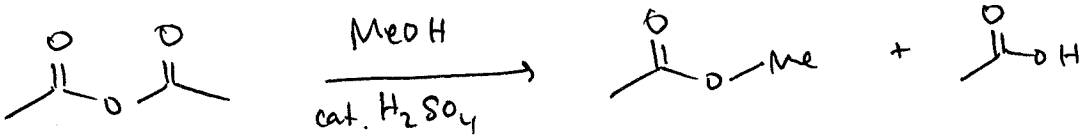
hydrolysis:



esterification:

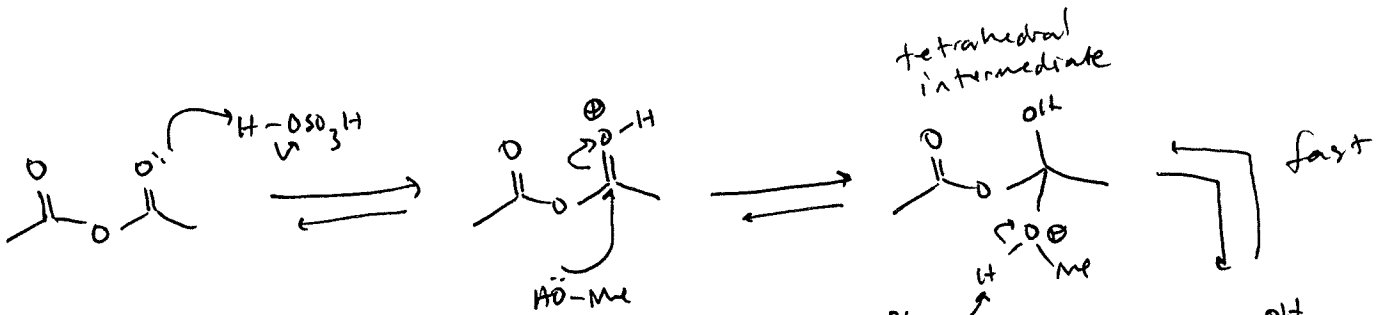


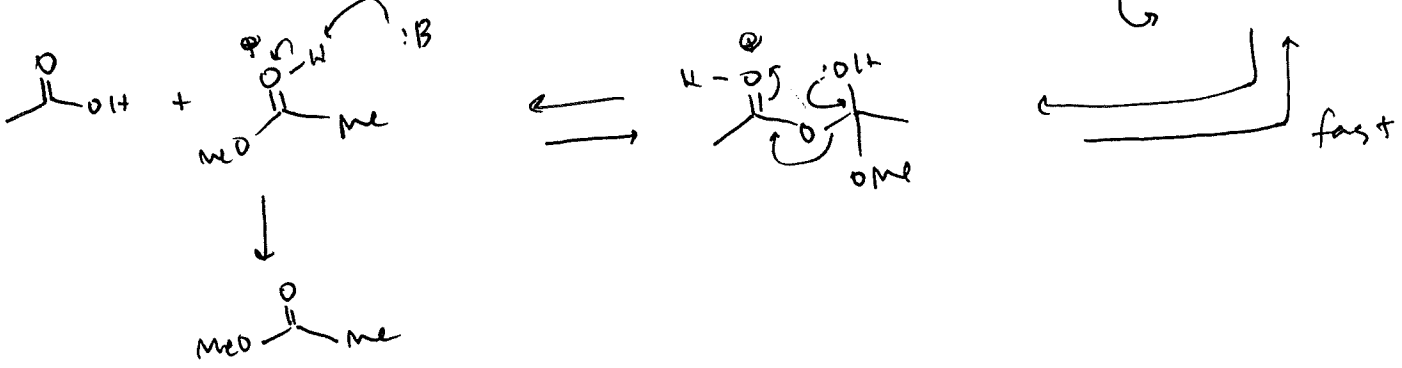
acid anhydrides function very similarly.

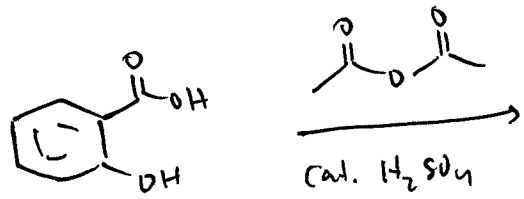


acetic ~~anhydride~~ anhydride

why use catalytic acid? what is the mechanism here?



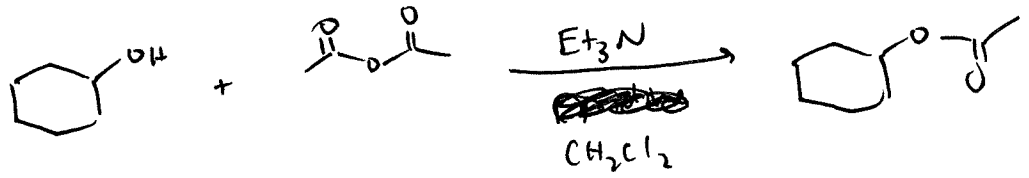




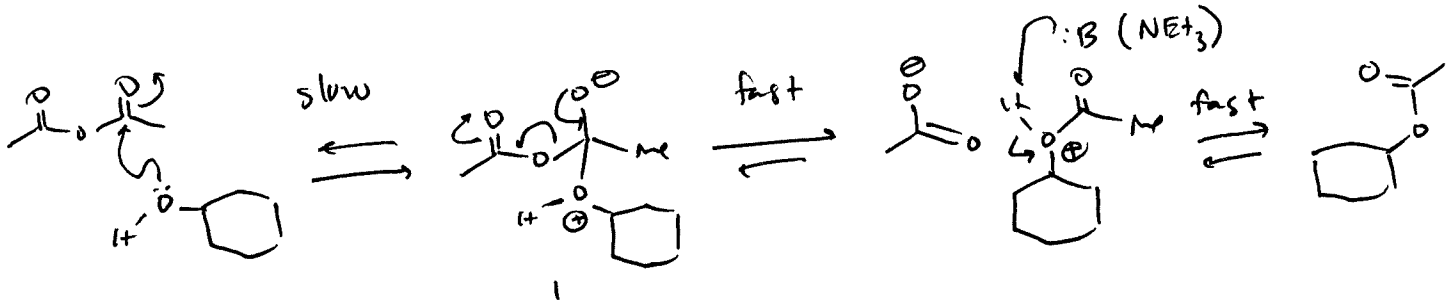
Salicylic acid

acetyl salicylic acid (aspirin - pain reliever)

You can also employ anhydrides under basic conditions!



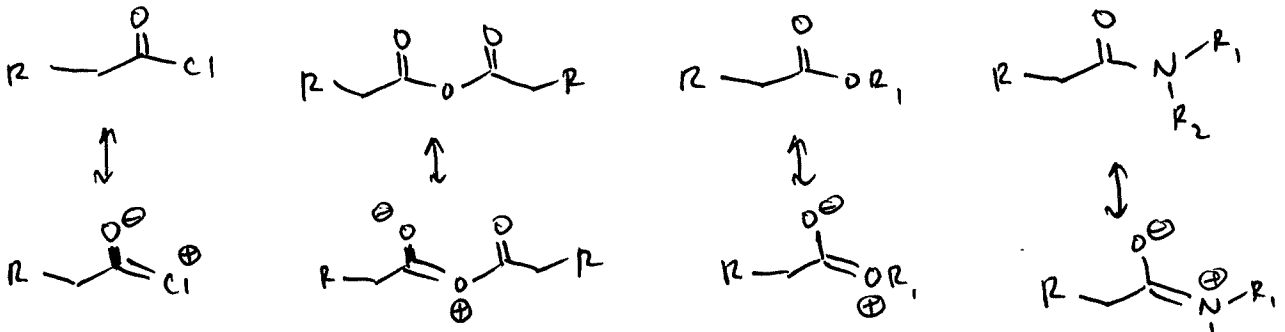
Mechanism:



1

Resonance is key to understanding acyl substitution trends.

electronegativity of X substituent (i.e. $R{-}\overset{O}{\overset{\|}{C}}{-}X$)

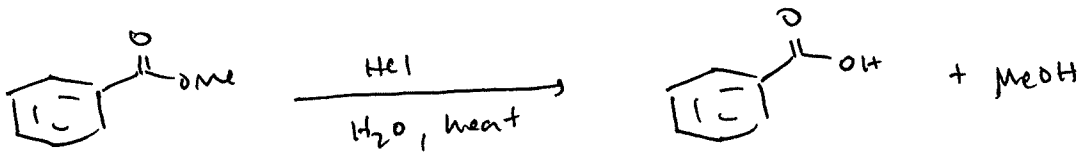


contribution to structure by charged resonance form

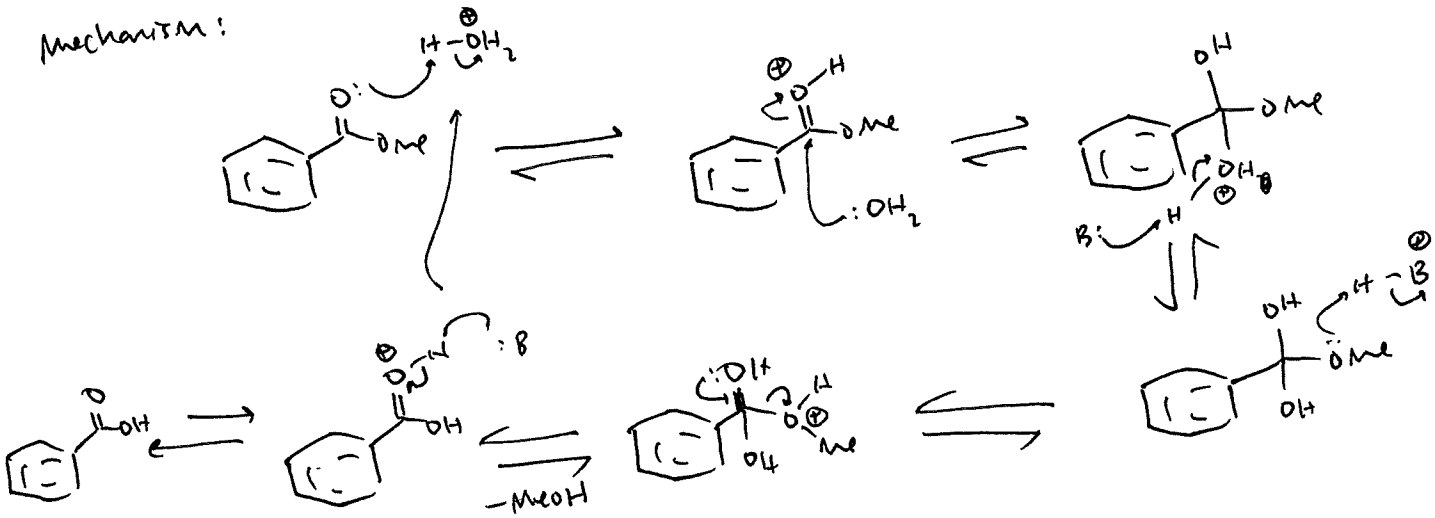
reactivity towards acyl substitution

acid-catalyzed hydrolysis of esters

consider:



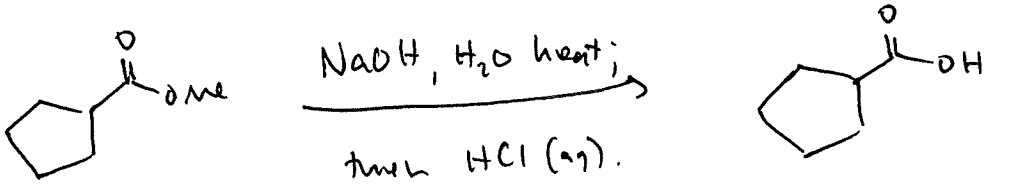
Mechanism:

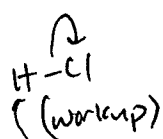


prodnd.

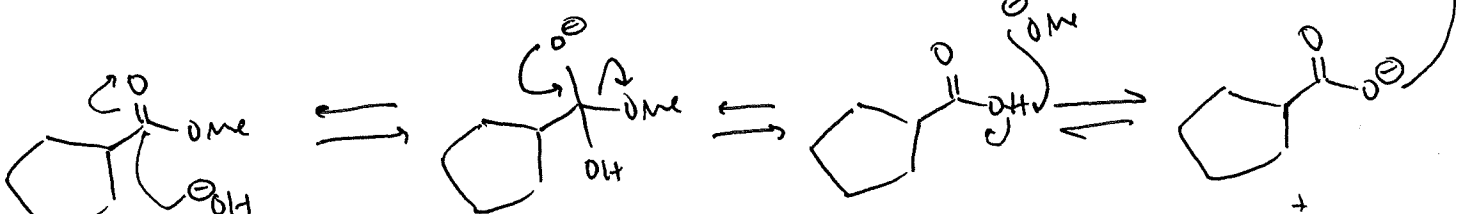
Compare this mechanism with the acid-catalyzed formation of esters. what are the factors driving Le Châtelier's principle here?

base-~~catalyzed~~ mediated hydrolysis of esters (saponification).

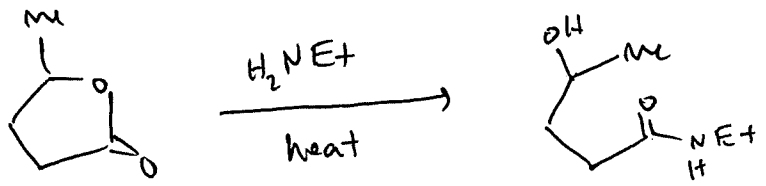




Mechanism:

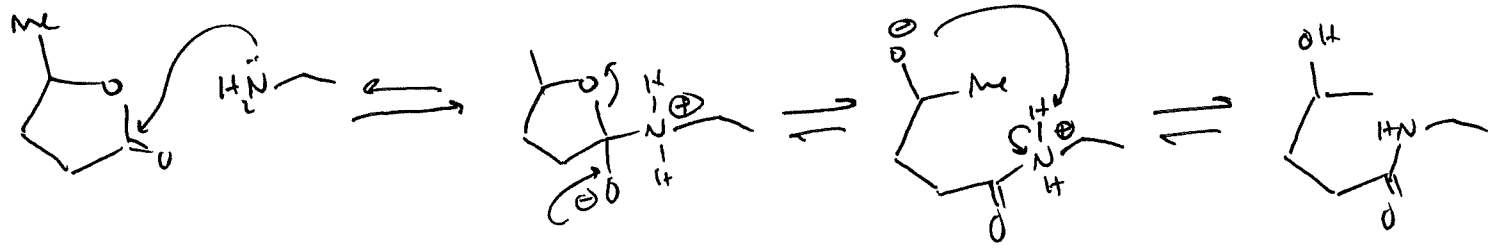


Reactions of amines with esters

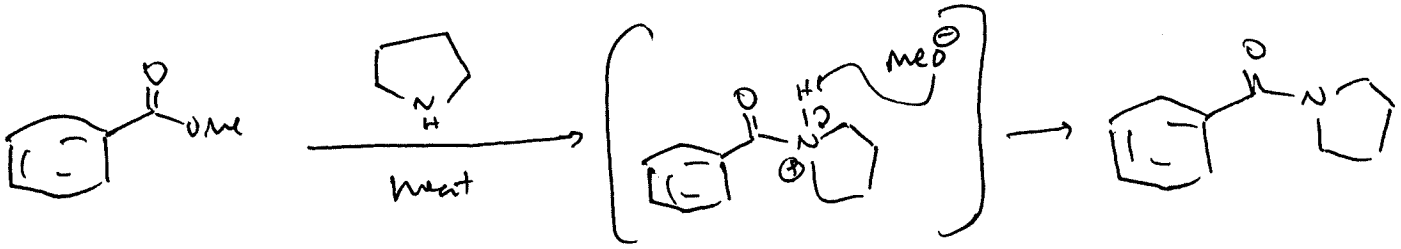


reaction needs heat because ester is far less reactive than acyl chloride or anhydride.

Mechanism:

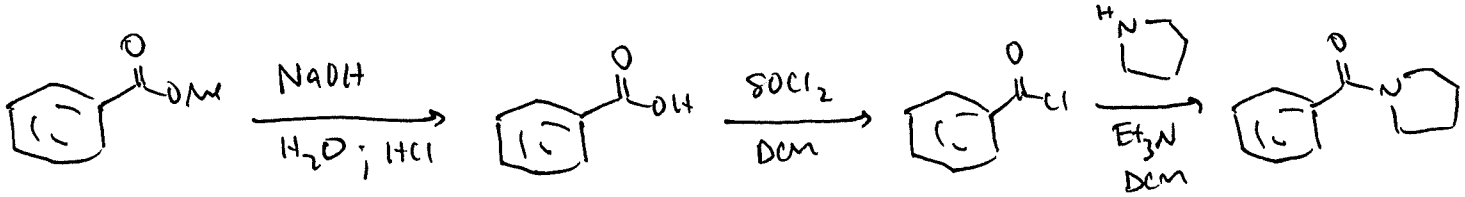


In general, these reactions are reasonably slow.

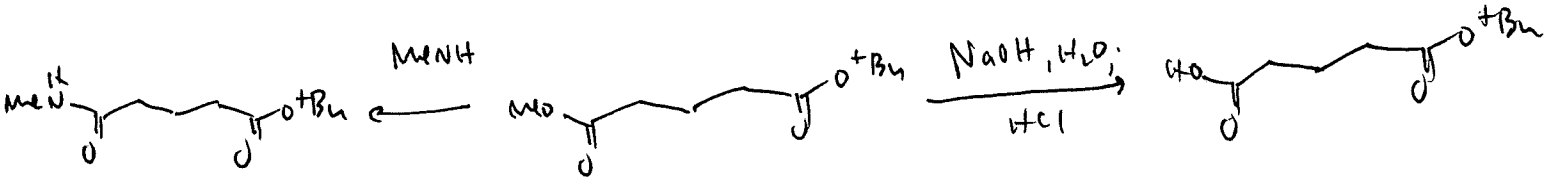


A possible workaround, and one that is common, is to go through the acyl chloride.

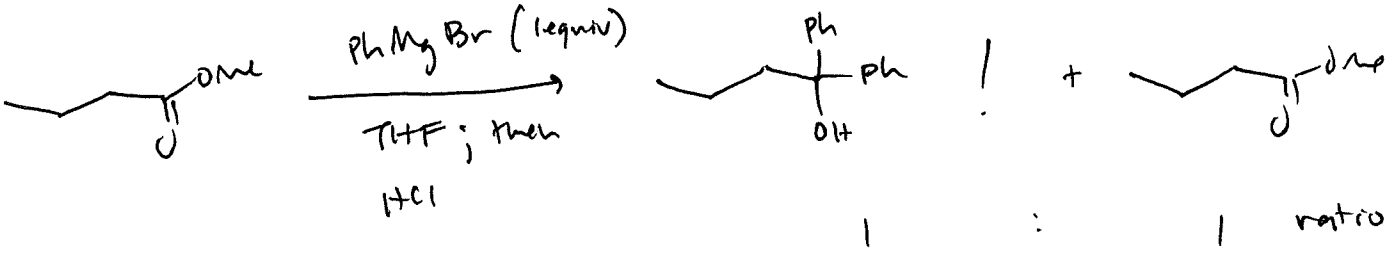
α—Cl CH_2Cl_2 = DCM



Different kinds of esters (depending on sterics) will react at different rates

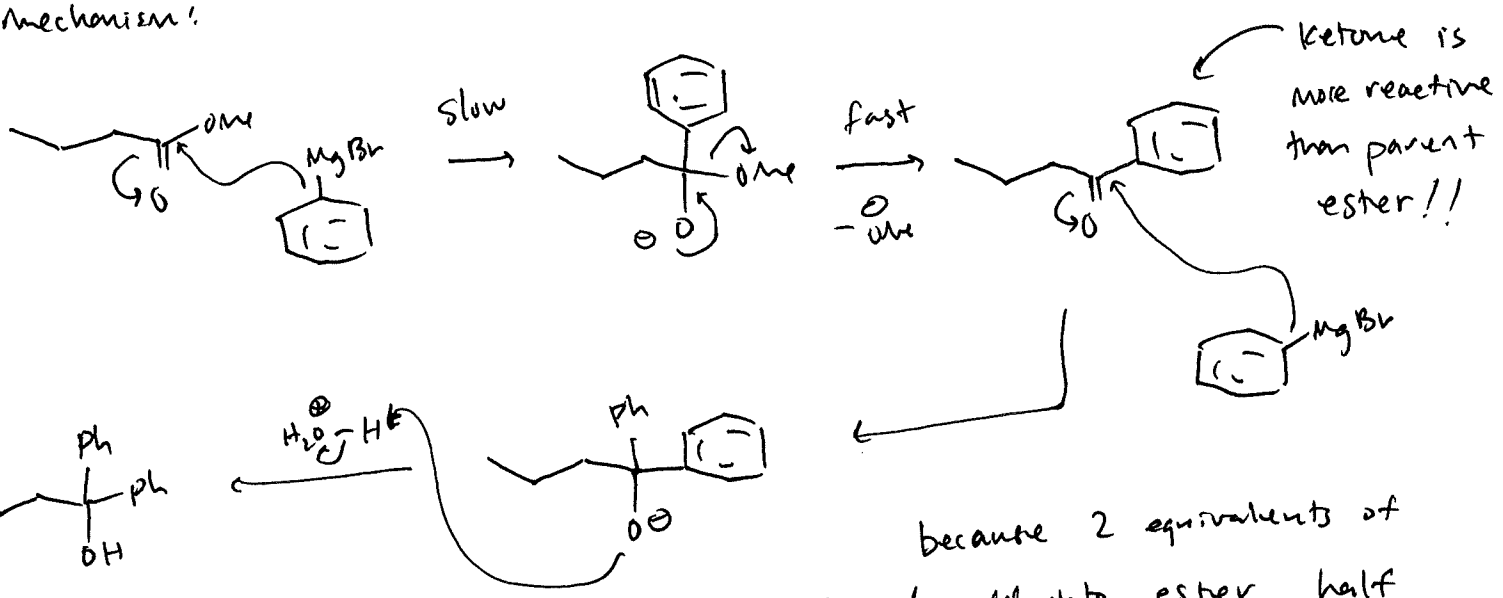


Reactions of Organometallic Reagents with Esters



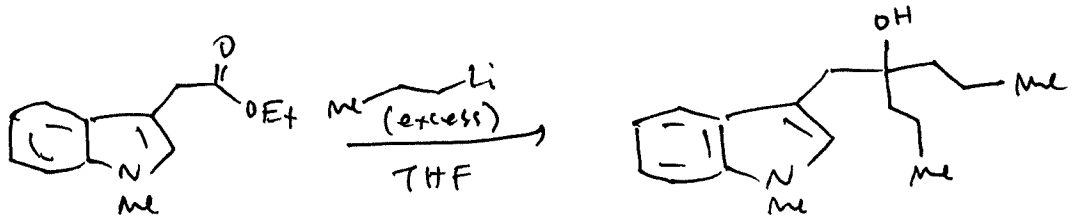
how does this occur?

mechanism:

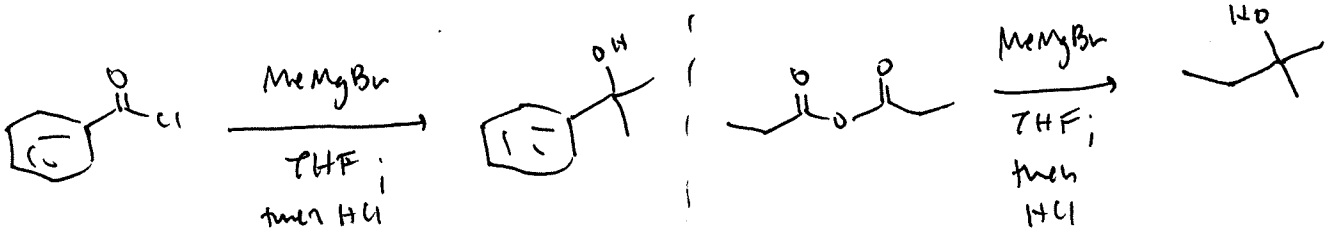


because 2 equivalents of grignard add into ester, half of the starting material remains!

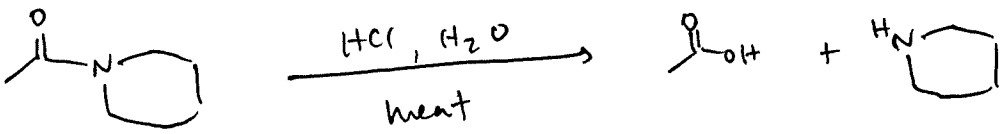
The same thing occurs when using organolithium reagents!



The same is true for acyl chlorides and anhydrides.

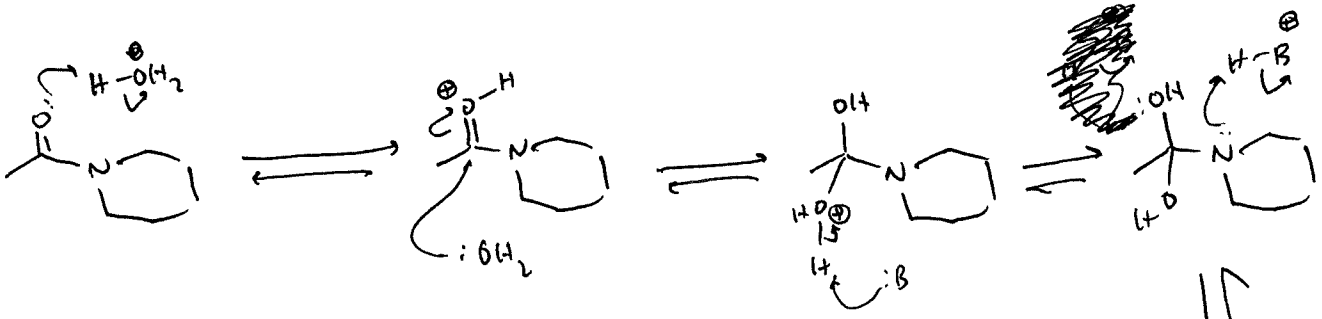


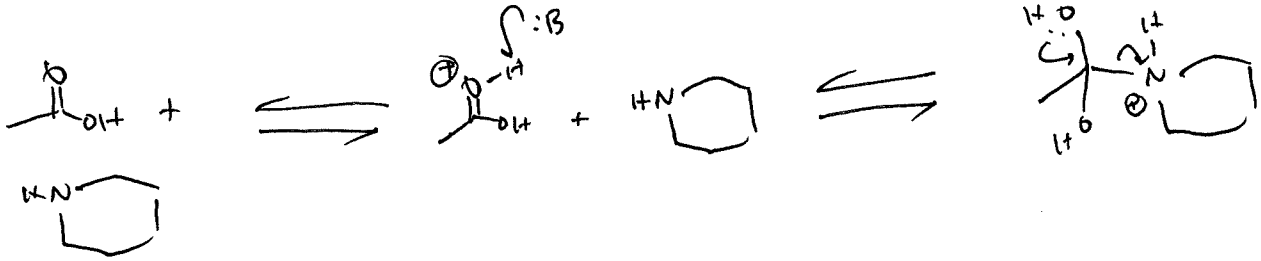
acid-catalyzed hydrolysis of amides



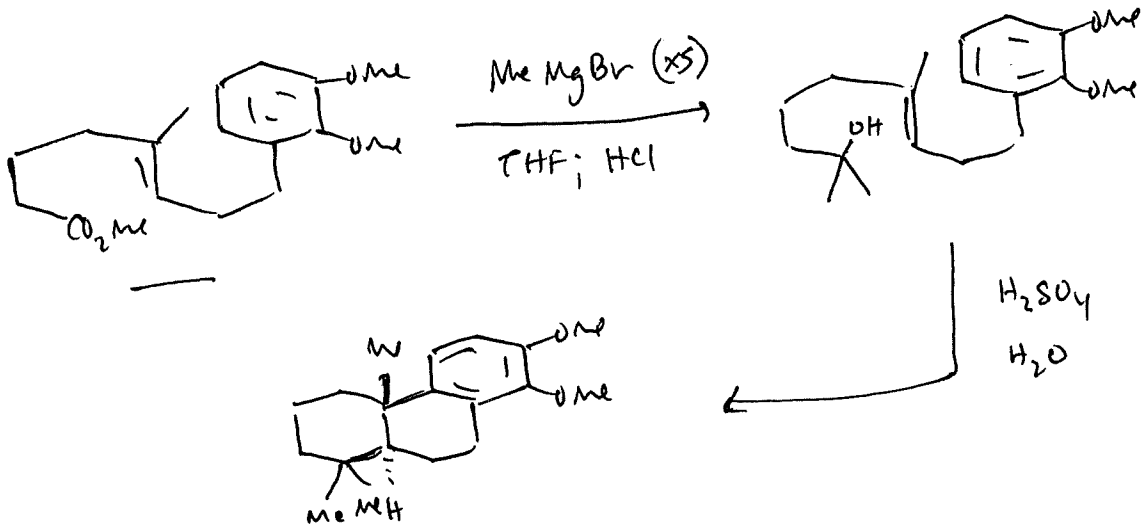
in general, these reactions can be quite slow.

Mechanism:



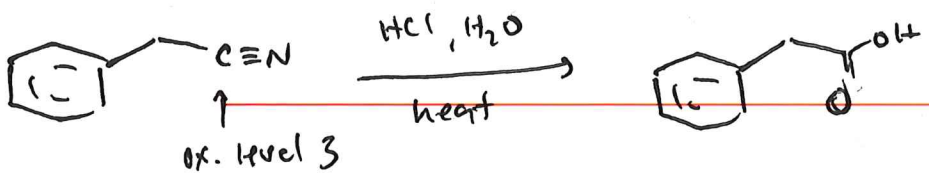


Utility of these phenomena in synthesis



The chemistry of nitriles

Recall!



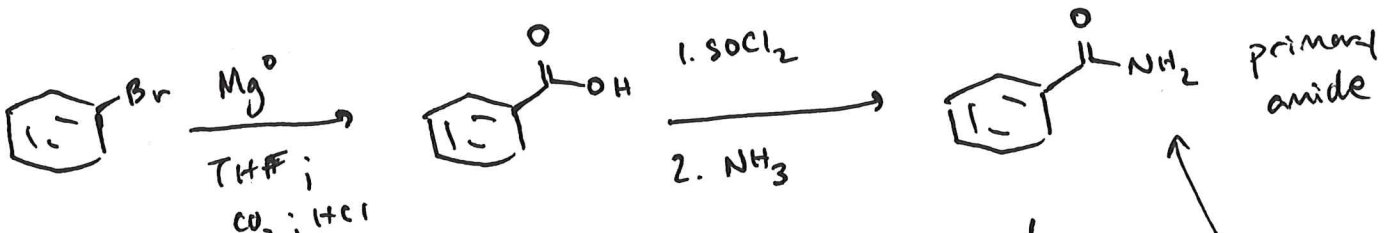
we can hydrolyze nitriles to afford carboxylic acids.

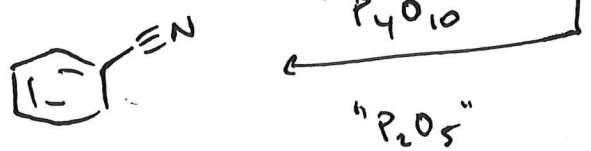
One way to forge nitriles was to perform an S_N2 reaction with a cyanide salt:

Another way to forge nitriles is through the dehydration of amides.

Consider:

how would you convert an aryl bromide to an aryl nitrile?



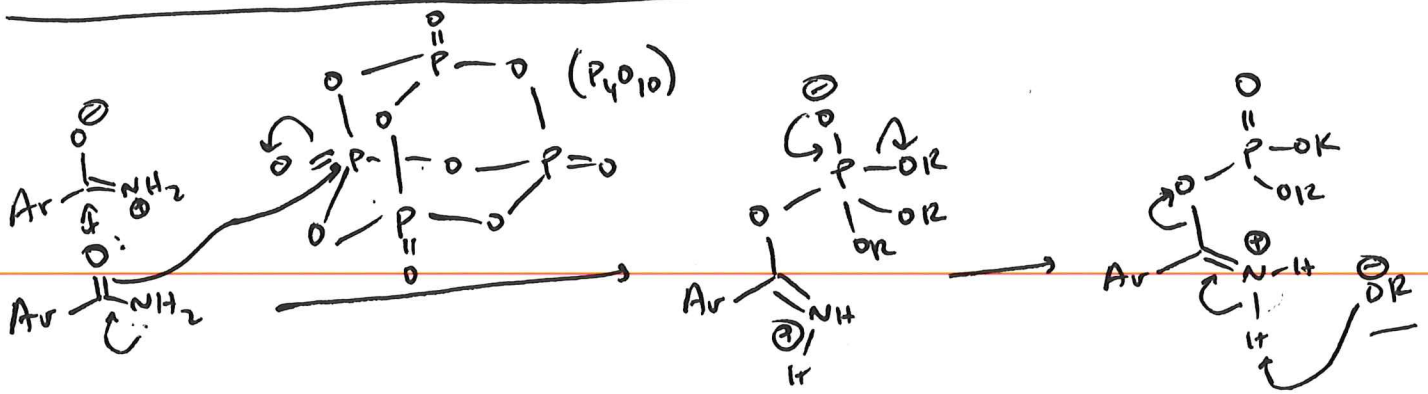


P_4O_{10} removes water from the primary amide to afford the nitrile

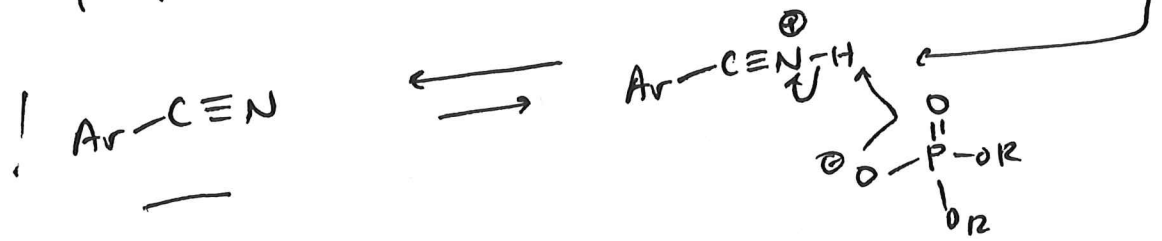
this intermediate is just a nitrile plus H_2O!

This is important because it is a situation where an S_N2 reaction would not be suitable for nitrile installation!

Mechanism of primary amide dehydration

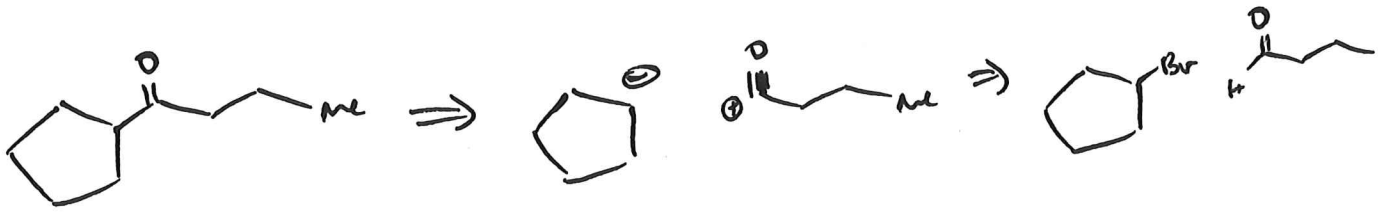


phosphates are great at removing H_2O !

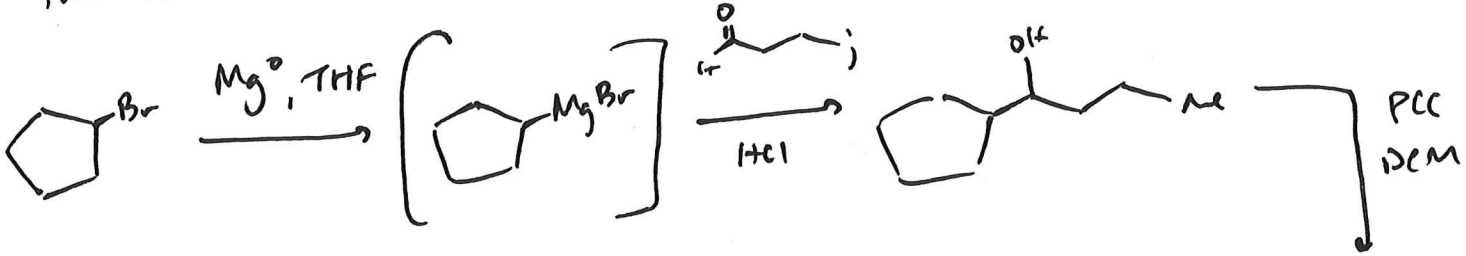


How would one make unsymmetrical ketones without a redox step?

recall:

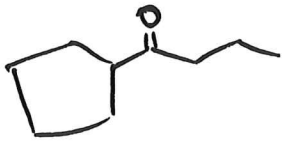


forward:

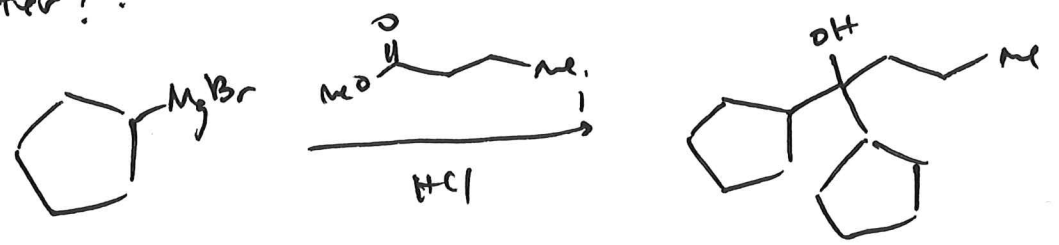


how might we avoid this by using an electrophile in a higher oxidation level?

needs redox step!



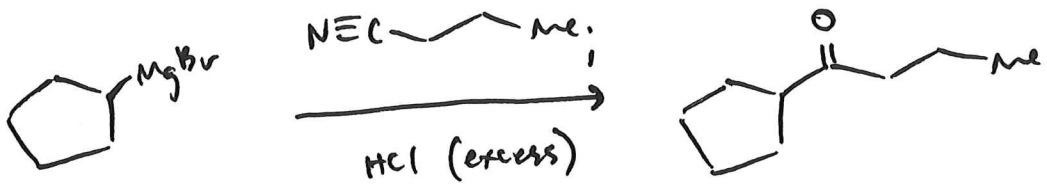
ester?:



tertiary alcohol!

overaddition!

Nitrile?

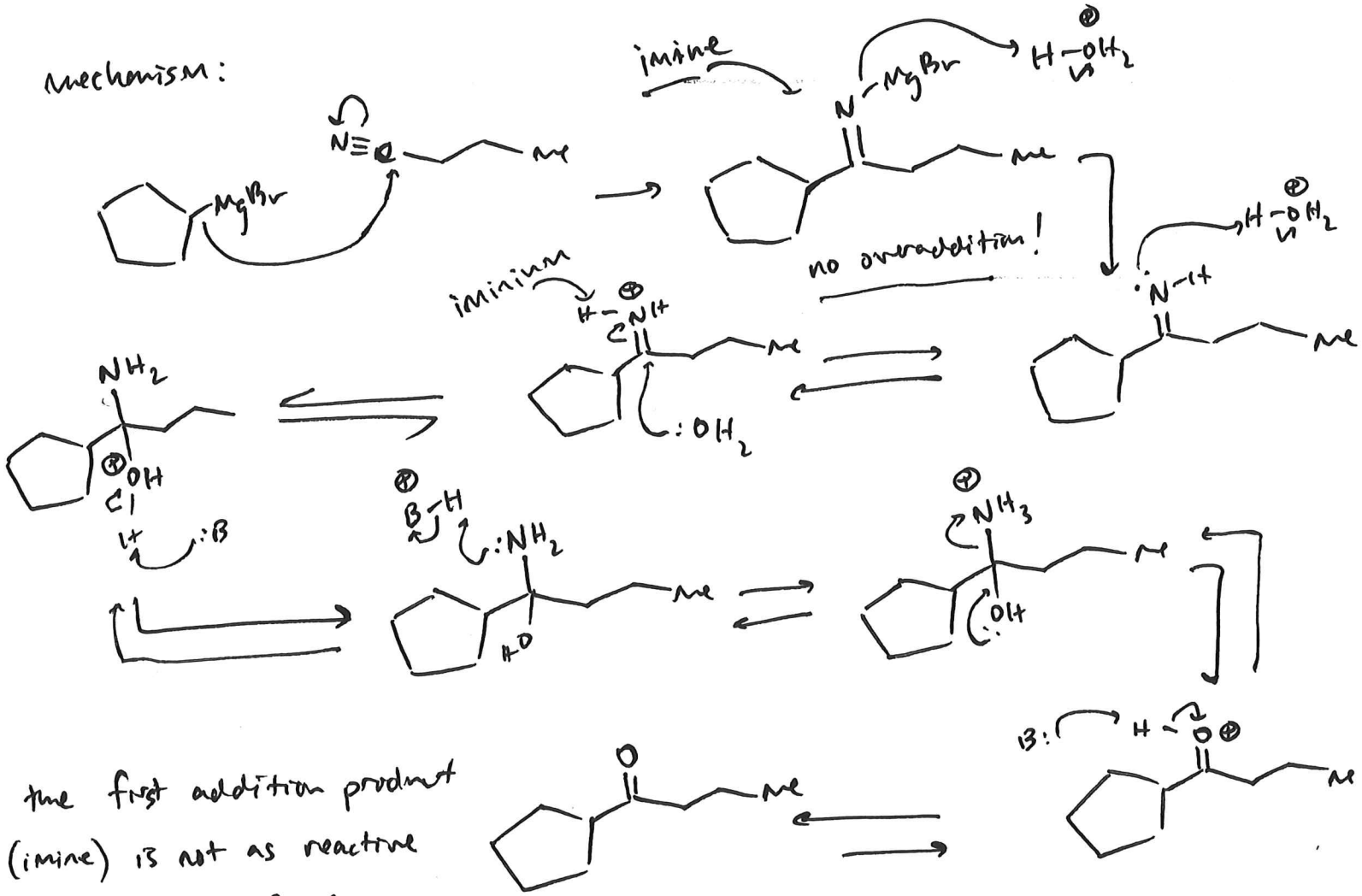


ketone product!

success?

but how does this work? why don't we get overaddition?

mechanism:



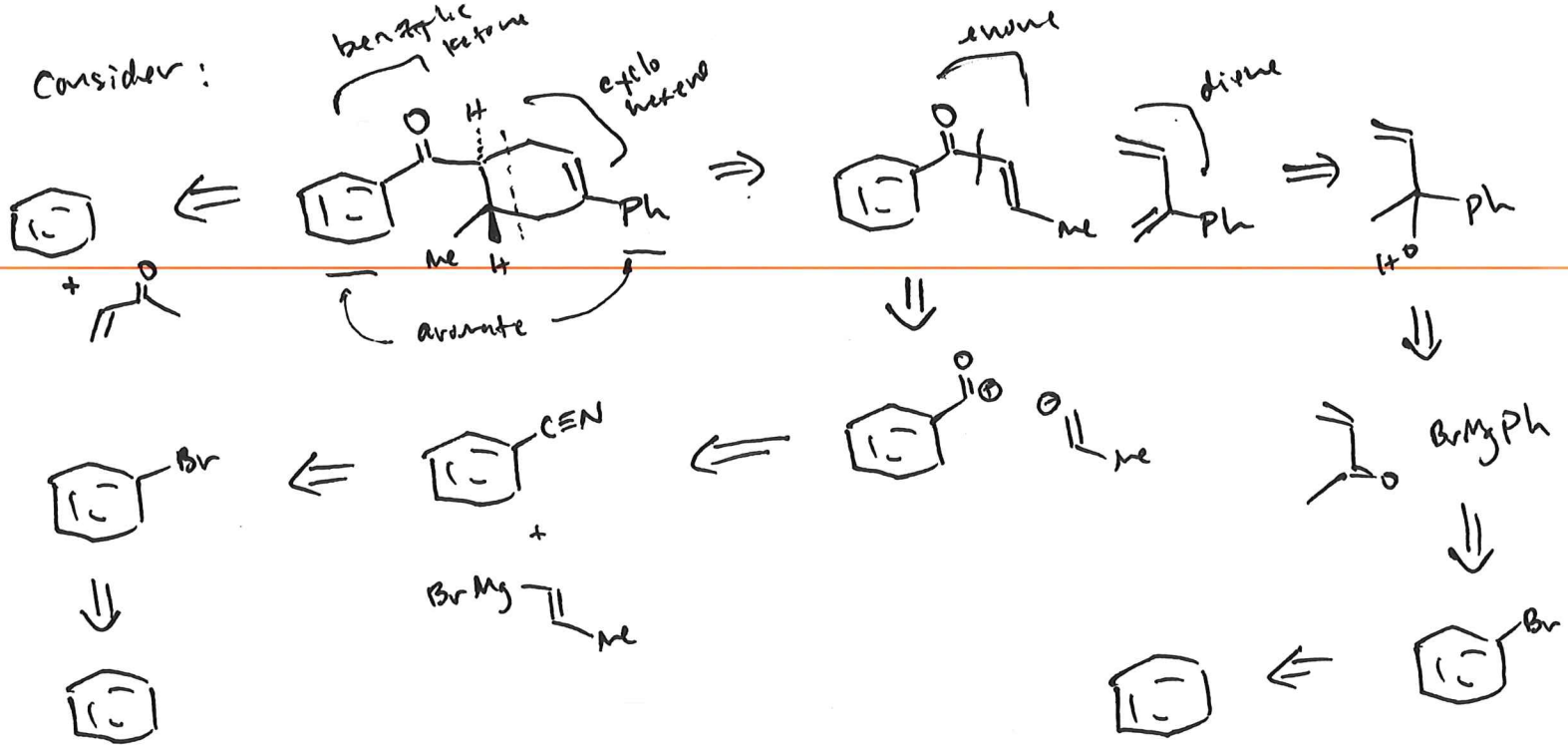
the first addition product (imine) is not as reactive as a ketone, so a second Grignard doesn't add into it!

ketone product.

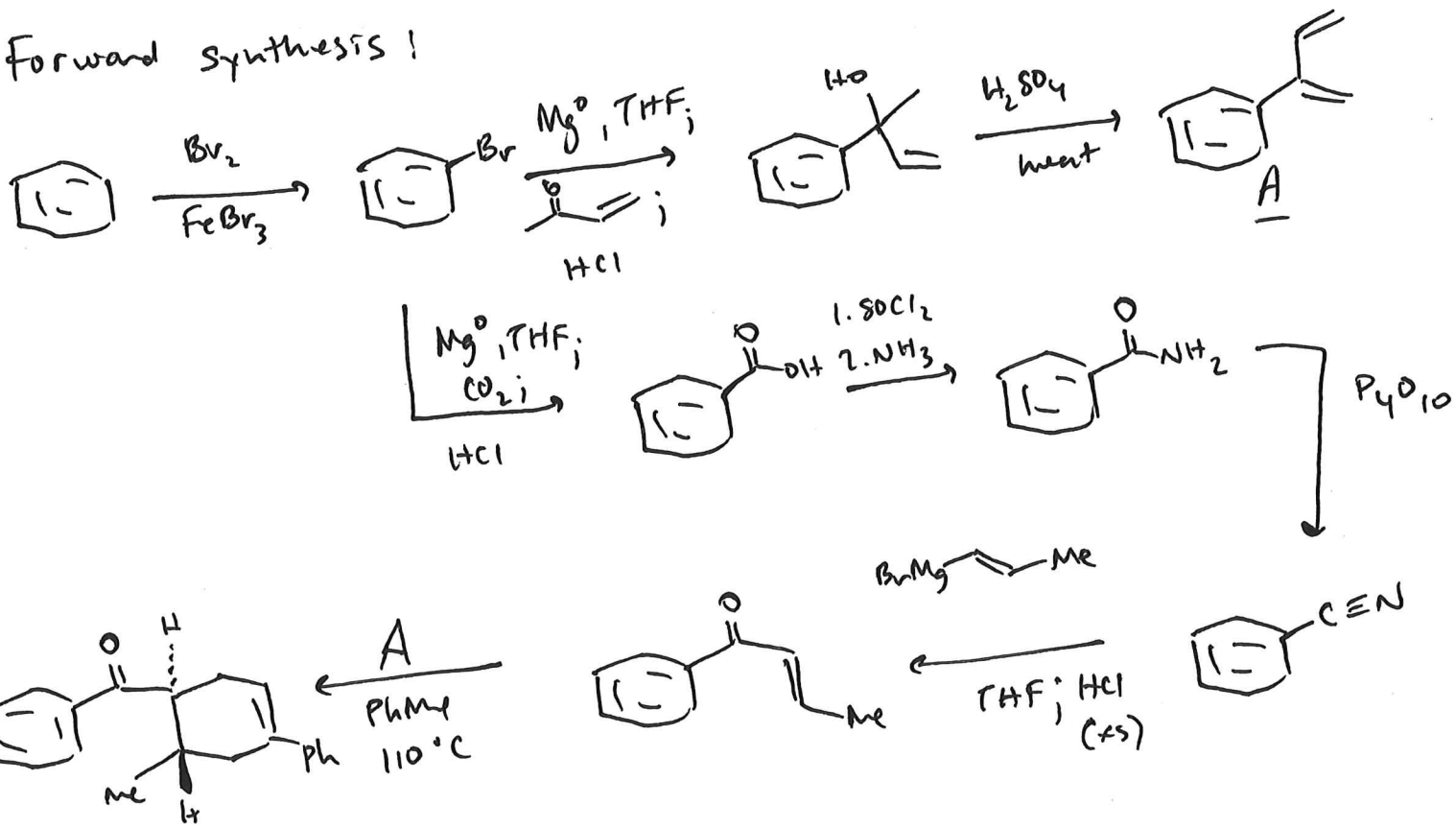
works best for acyclic ketones

How can we employ these phenomena in synthesis?

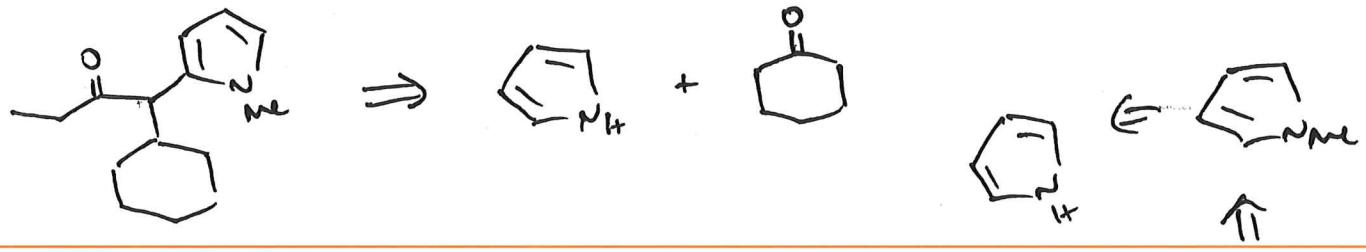
Consider:

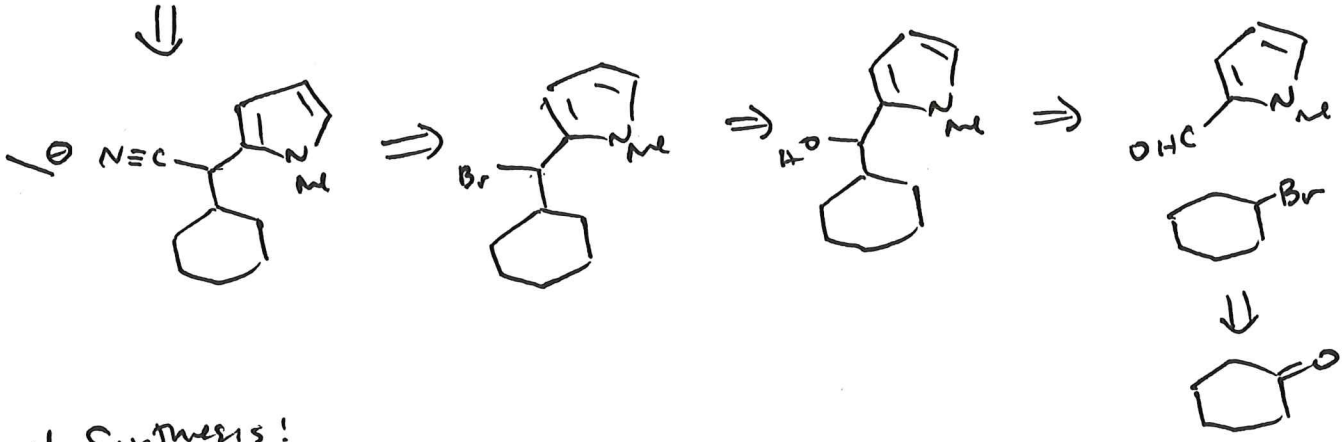


Forward synthesis!

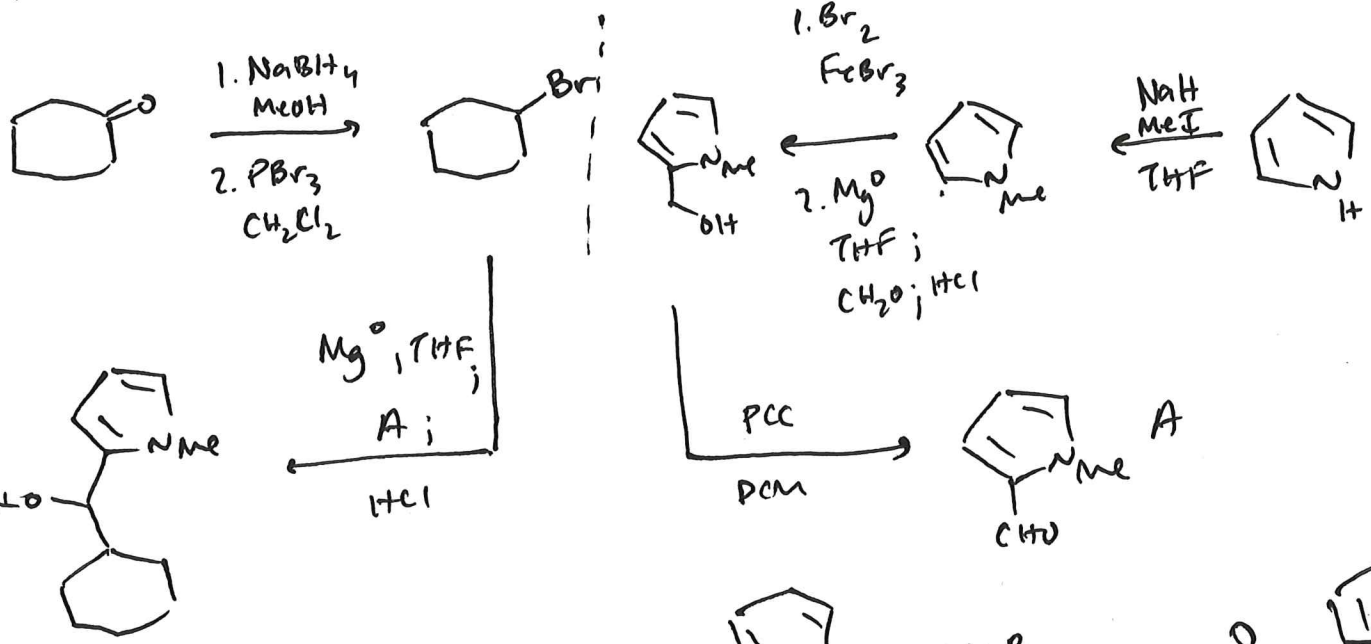


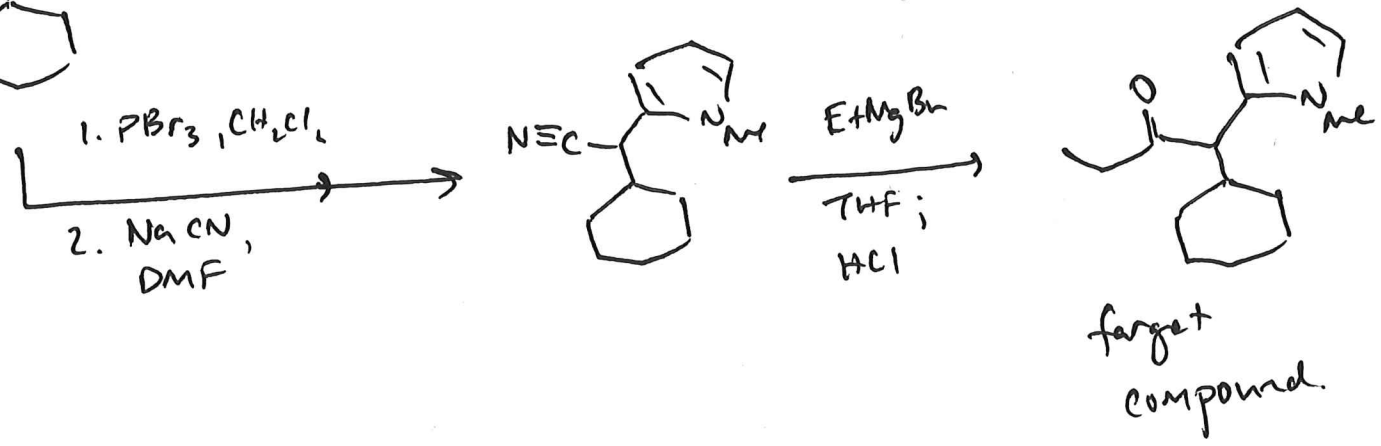
Consider this molecule!





Forward Synthesis!





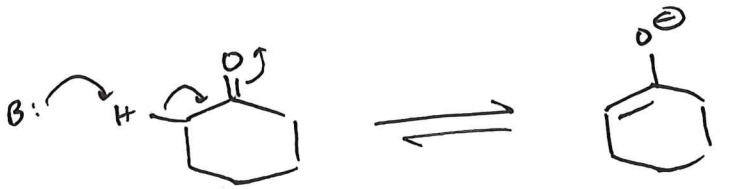
target compound.

Enols and Enolates

recall:

this occurs because the carbonyl carbon is electron deficient.

It turns out, that because of the electron deficient carbon the alpha protons relative to the carbonyl become acidic.

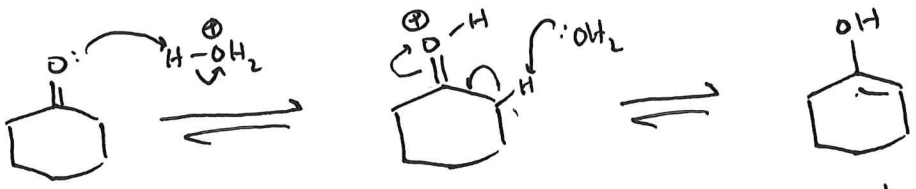


enolate

this species is electron-rich and is thus nucleophilic.

pka of proton is 20

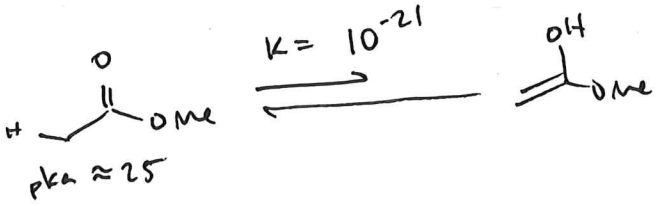
Enols can be forged under acidic conditions

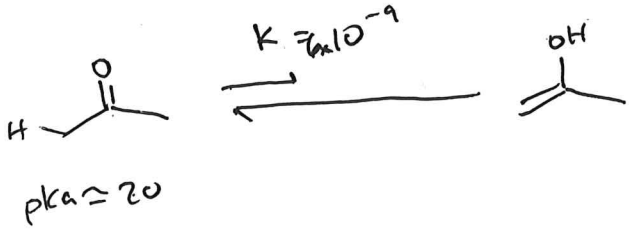


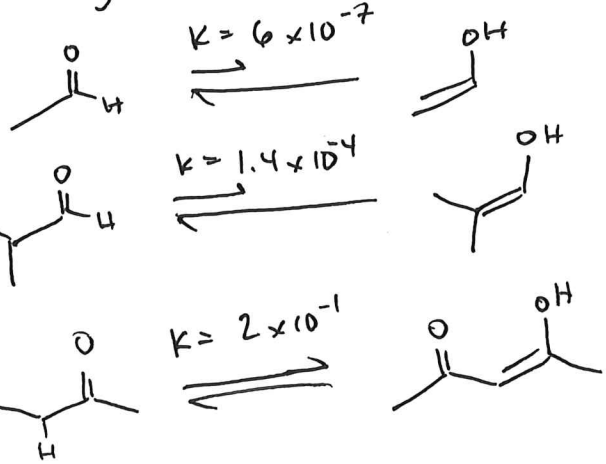
enol

this species is also electron rich and can be used as a nucleophile

The equilibrium for certain carbonyl species lies more or less to the side of its enol tautomer depending on its structure.

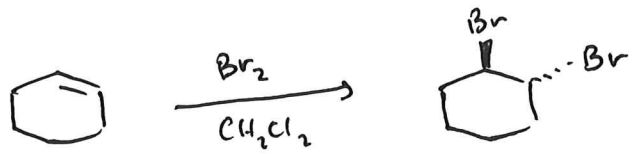




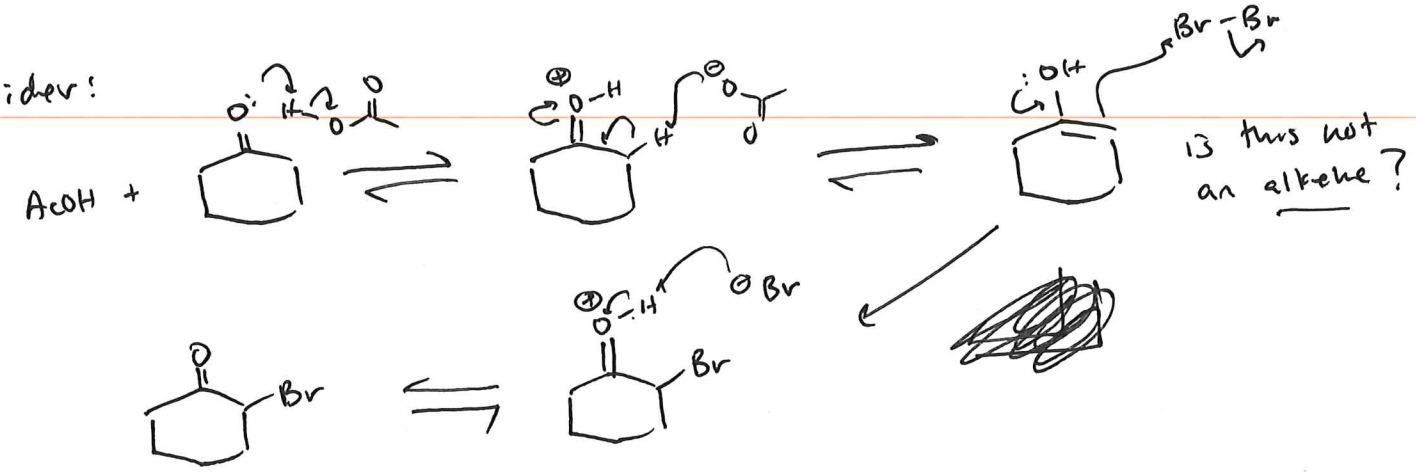


One reaction that employs enols is the bromination of carbonyls.

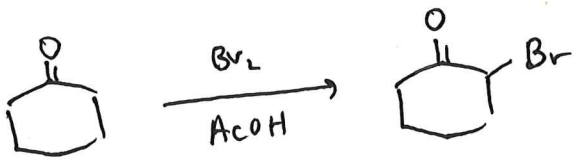
recall:



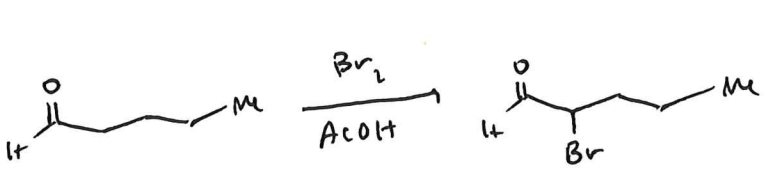
consider:

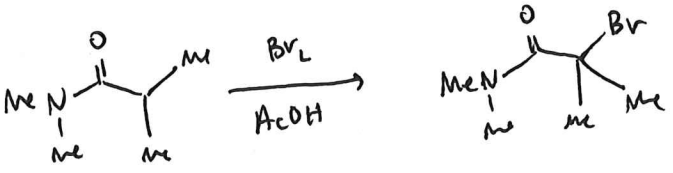


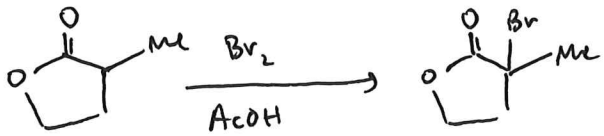
The overall reaction looks like this:

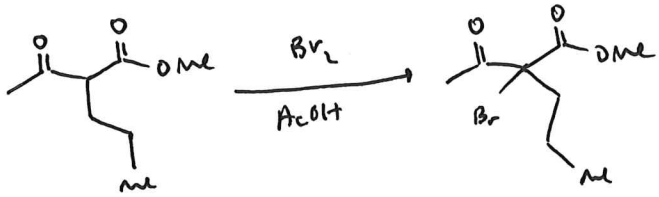


this type of reaction can be used for the bromination of many different types of carbonyls

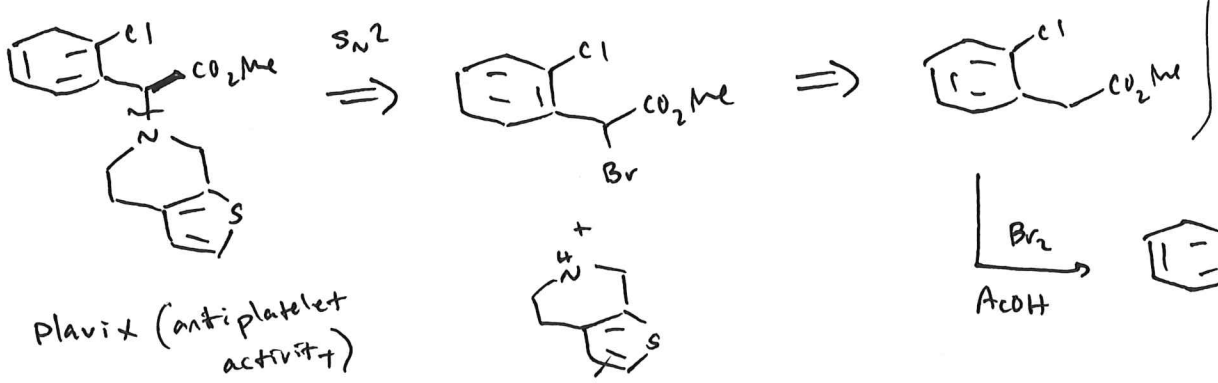






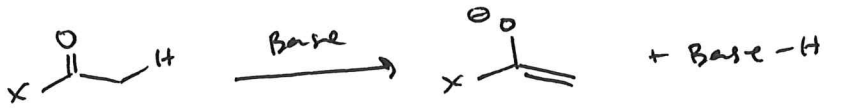


Synthesis of Plavix

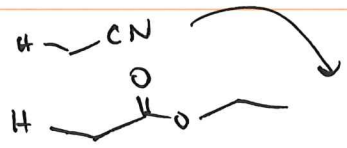


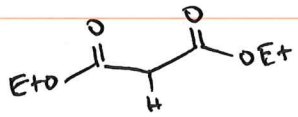
Plavix (antiplatelet activity)

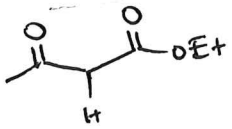
Let's return to the pka of alpha-hydrogens...

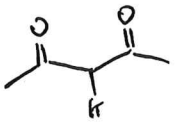
general reaction 

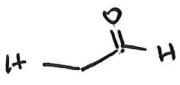
pka's for certain functional groups.







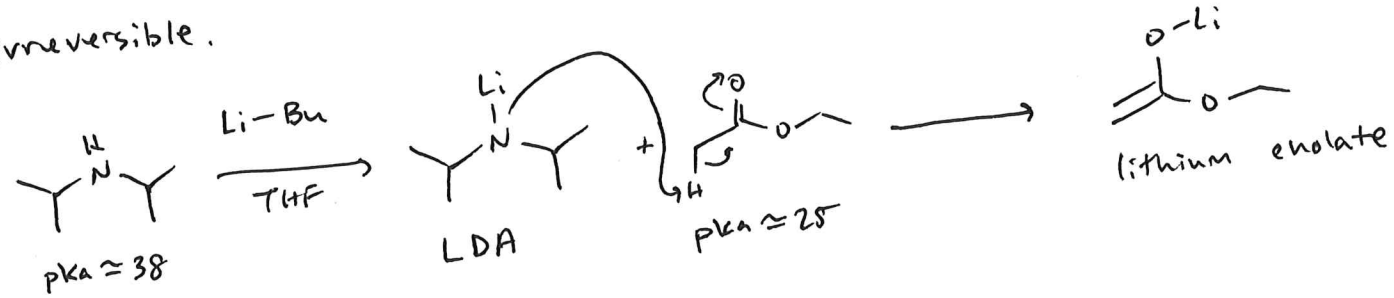




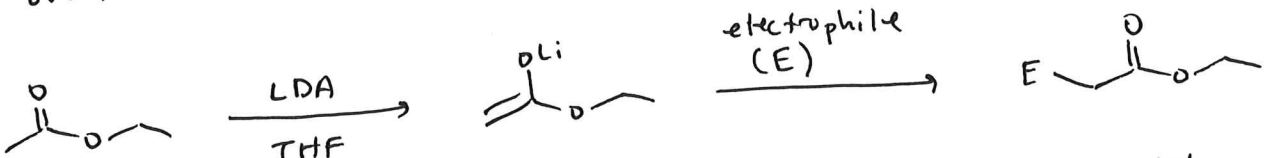
Consider the use of hydroxide as base

the equilibrium here lies to the left, but not by a massive margin

There are also stronger bases one can employ that are effectively irreversible.

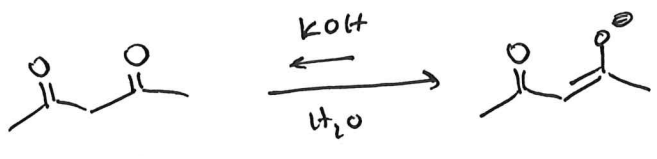


the overall reaction can be drawn like this as well!



this enolate can react with a variety of electrophiles.

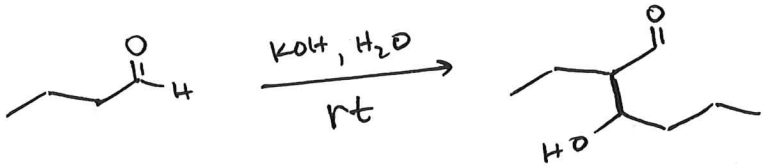
For dicarbonyl species, the equilibrium lies towards the enolate



equilibrium lies to the right!

How can we utilize enols / enolates to make new strategic bonds?

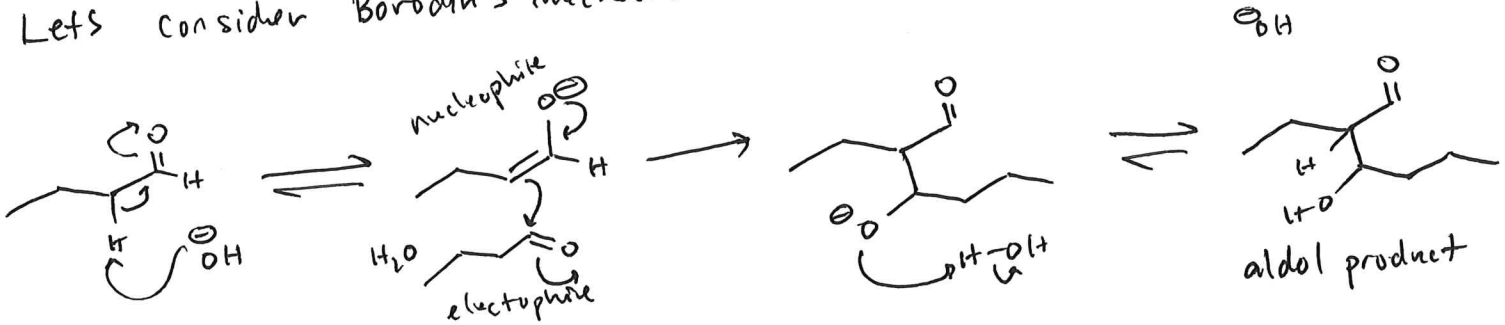
Consider



new carbon-carbon bond!

this reaction is called the aldol reaction and was discovered by the chemist/composer/doctor Aleksander Borodin.

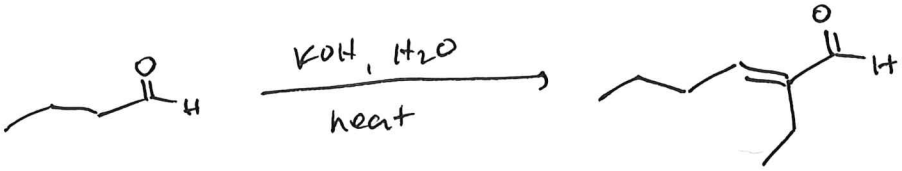
Lets consider Borodin's mechanism of the aldol reaction:



this reaction readily happens a room temperature.

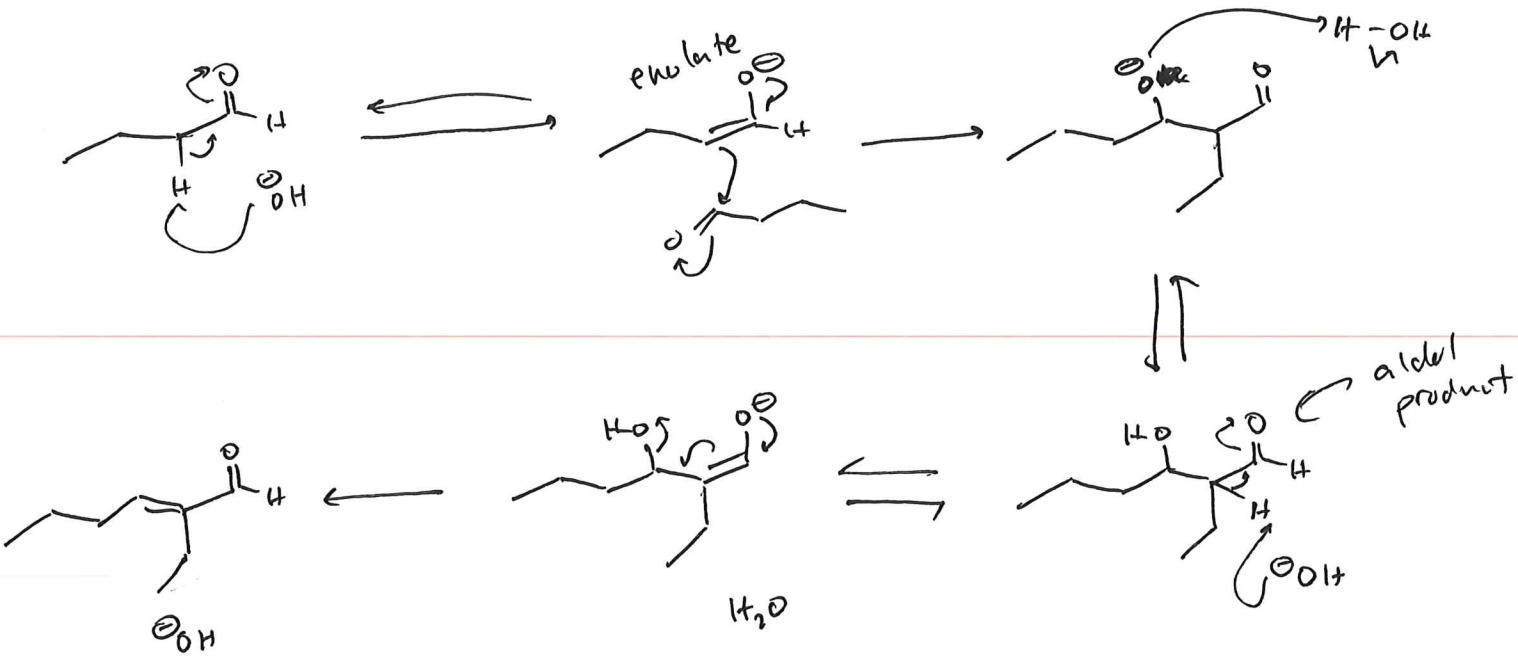
this reaction is considerably more difficult with ketone substrates.

What happens in these reactions when we expose them to more heat?



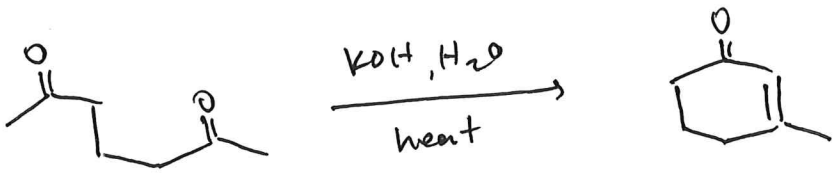
aldol condensation product!

let's look at the mechanism of how this works!



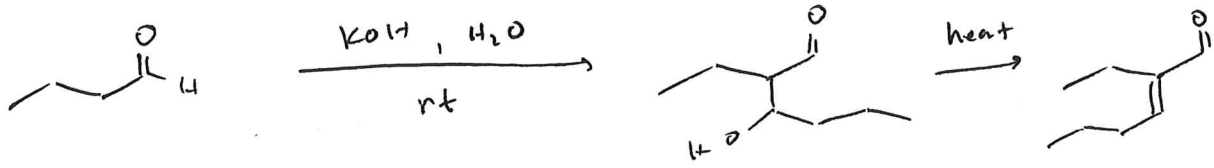
aldol condensation product.

draw the mechanism of this transformation.



Cross Aldol reactions and condensations

recall:

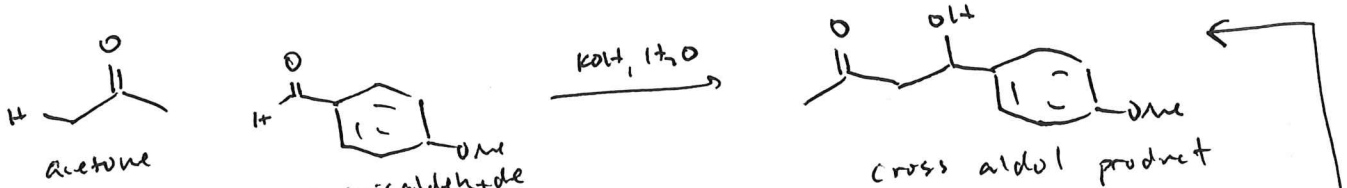


aldol product

condensation product.

what if we wanted to do an aldol with two different carbonyl's?

consider: option 1: only have one enolizable carbonyl

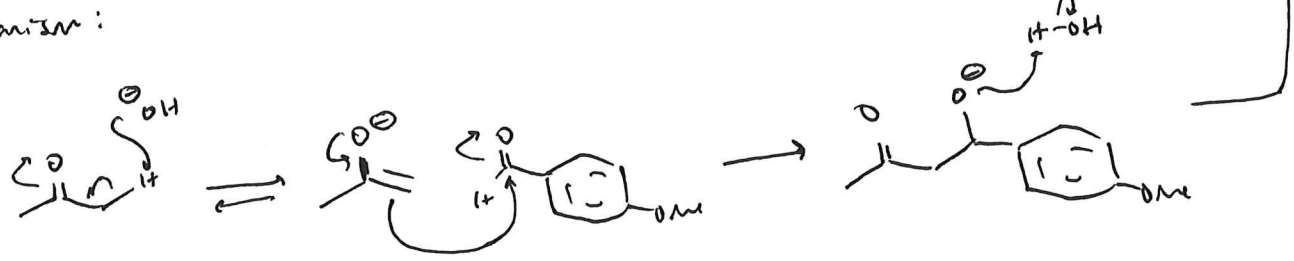


acetone

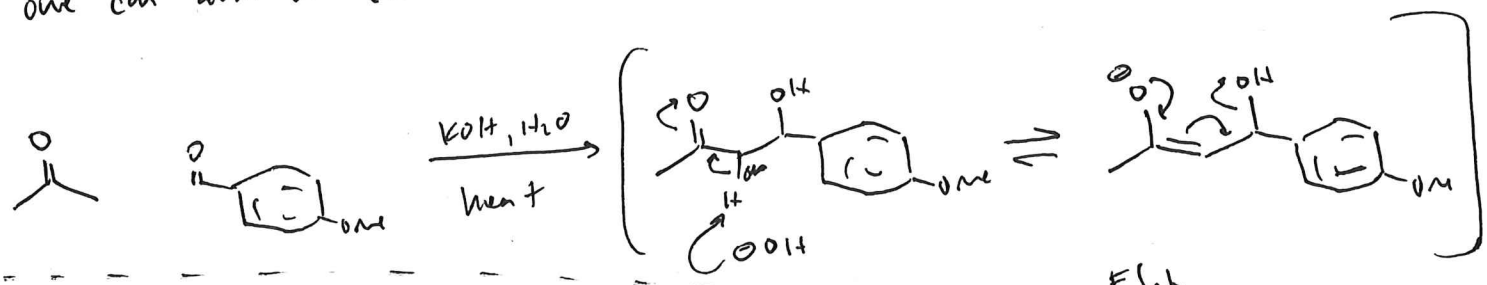
p-anisaldehyde

cross aldol product

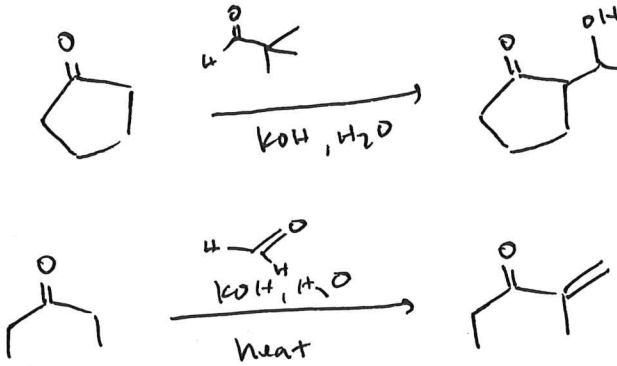
mechanism:



one can also do cross aldol condensations:

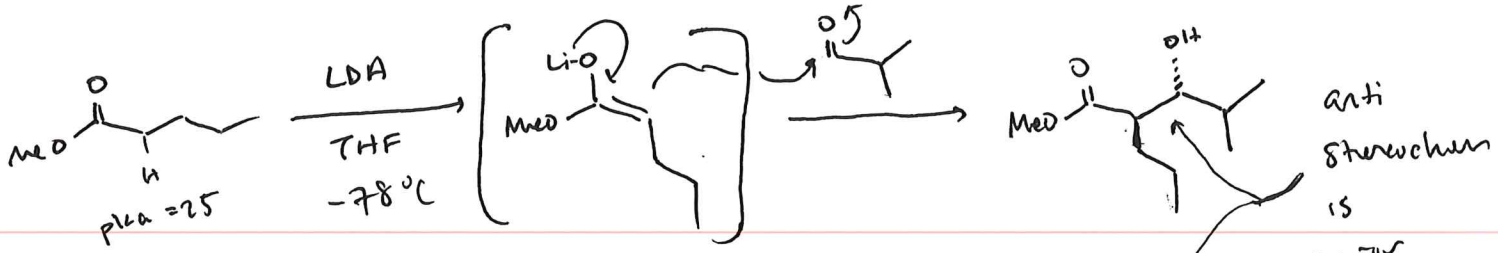


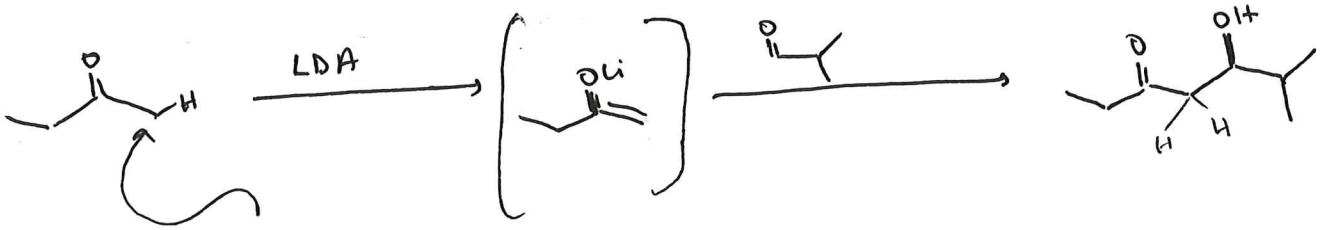
E1cb



more thermodynamically stable E olefin is product!

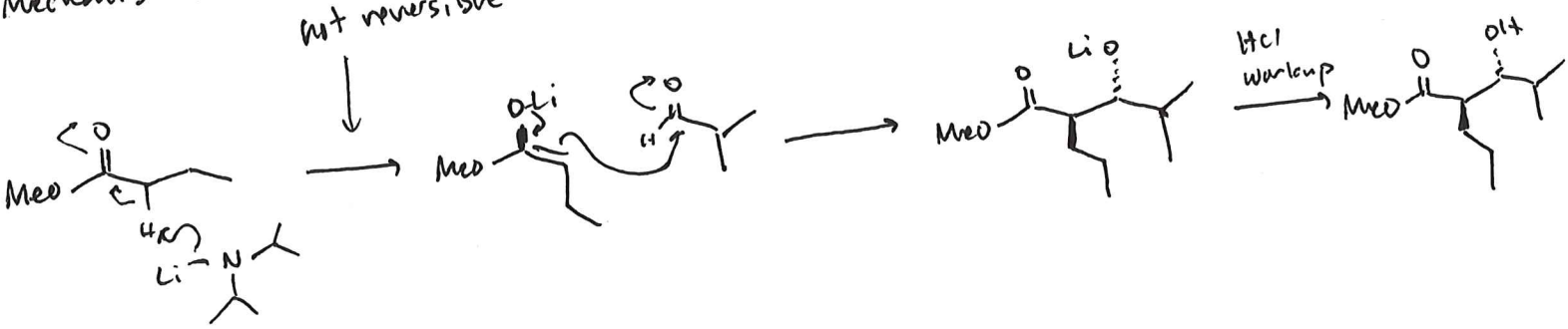
Option 2: independent enolate formation followed by quenching



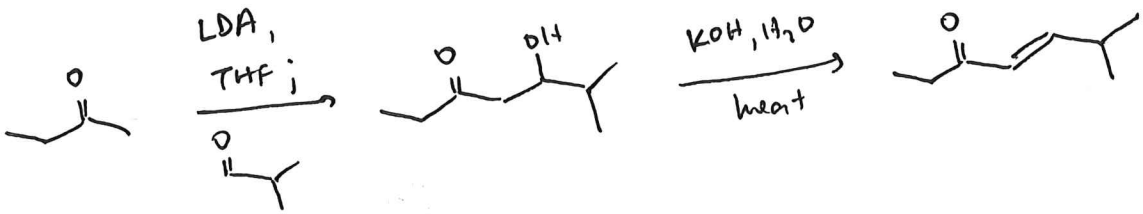


deprotonation happens on least hindered side of ketone

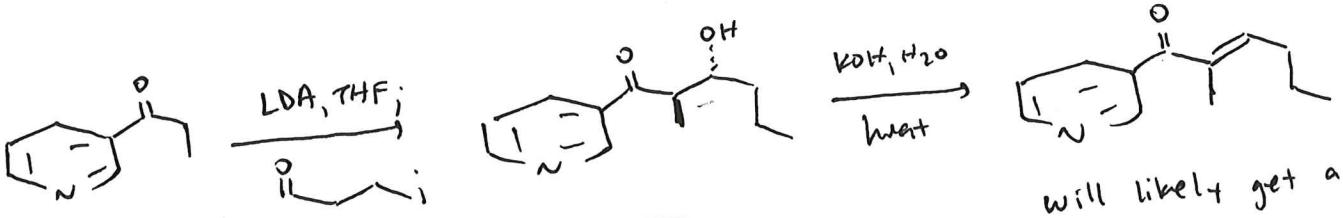
mechanism!



You can also do a stepwise cross-aldol condensation!



Cross aldol Condensation.

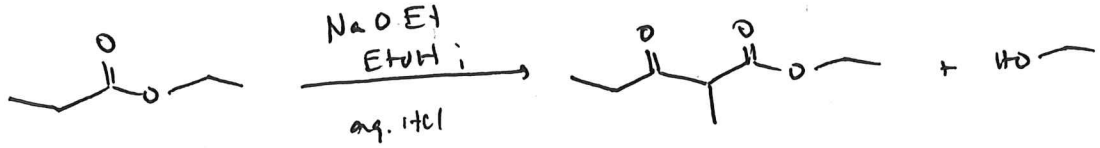


tricky!

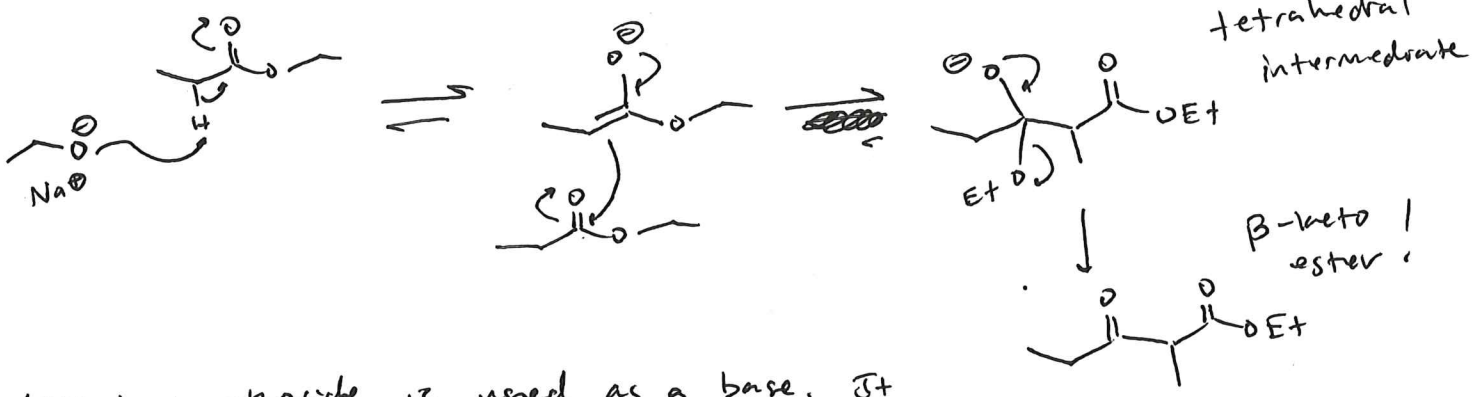
will likely get a mixture of alkene isomers.

Enolate reactions with ester electrophiles – the Claisen condensation

Consider:

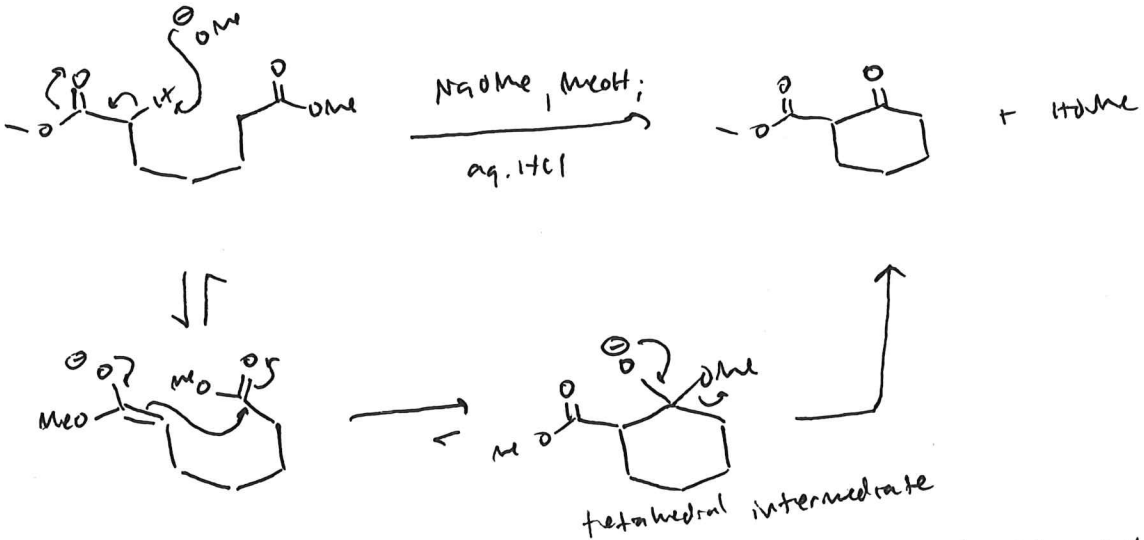


Mechanism:

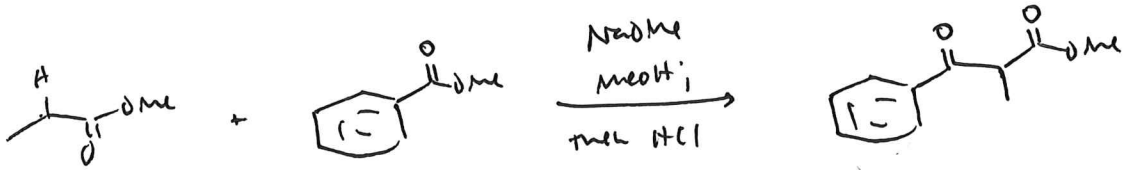


Notice how ethoxide is used as a base. It is the same as the type of ester so mixtures of esters are not afforded!

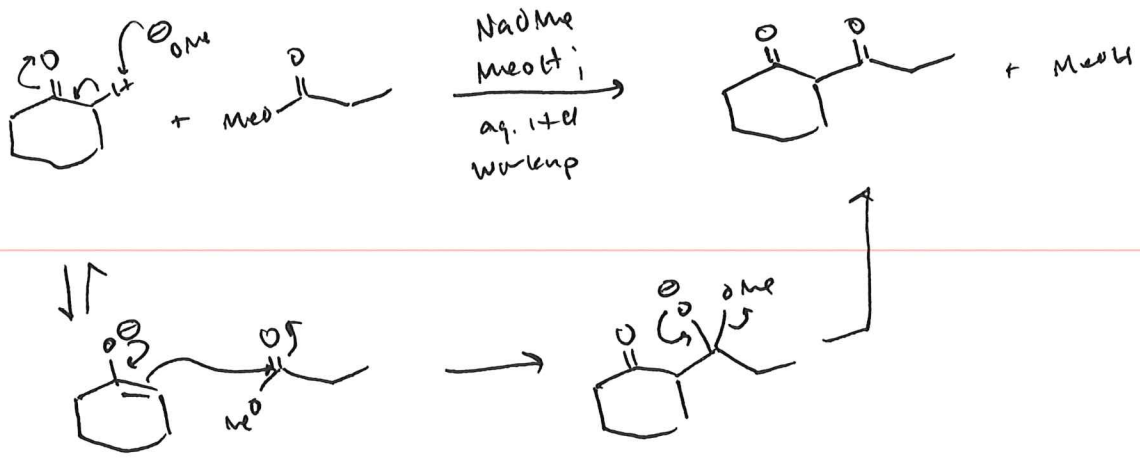
Intramolecular Claisen: the Dieckmann condensation



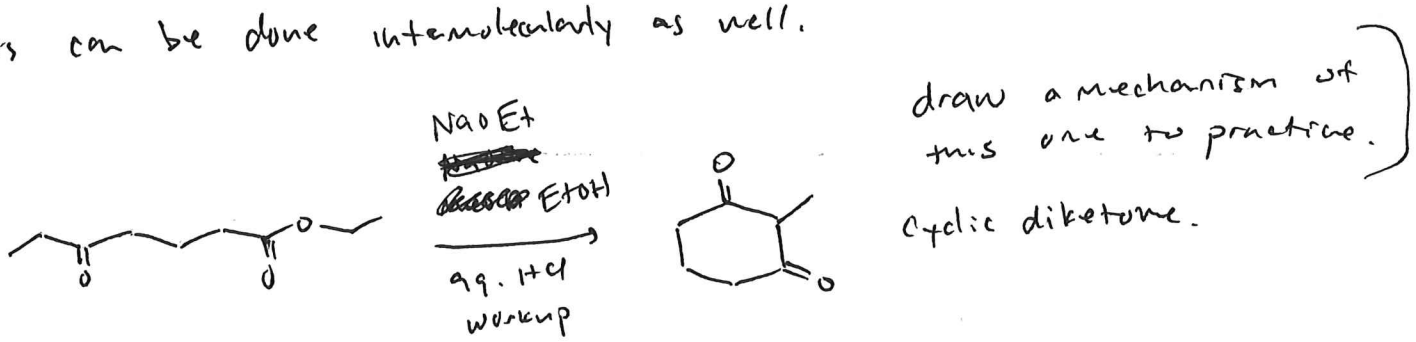
Esters with non-enolizable protons can be used as well:



Ketones can also be used in claisen reactions.



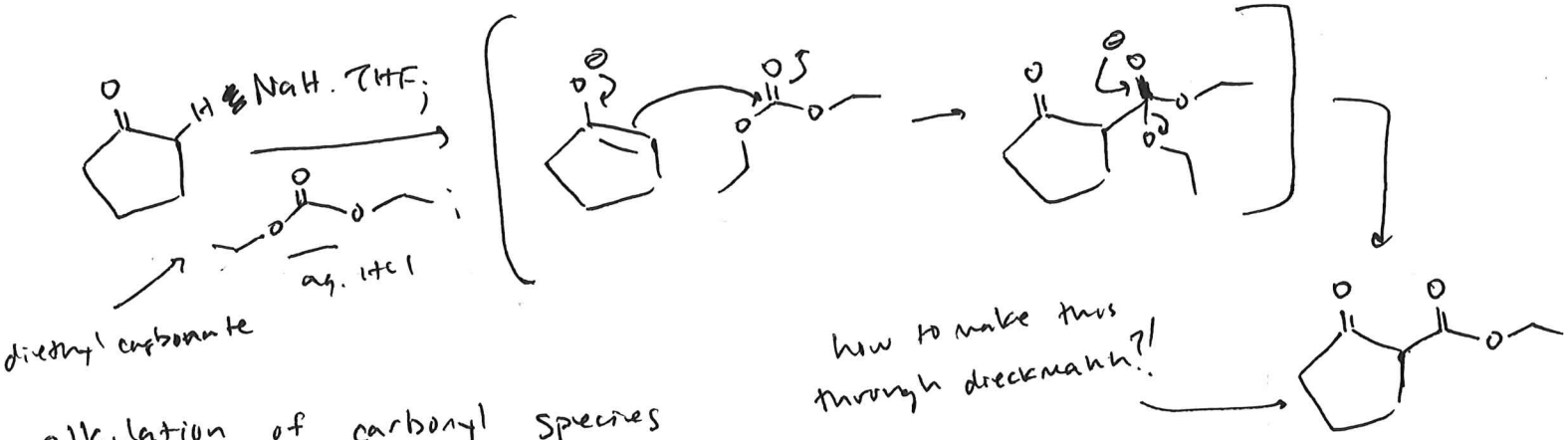
this can be done intermolecularly as well.



draw a mechanism of this one to practice.

cyclic diketone.

Carbonates can also be used to make β-keto esters. Stronger base is needed

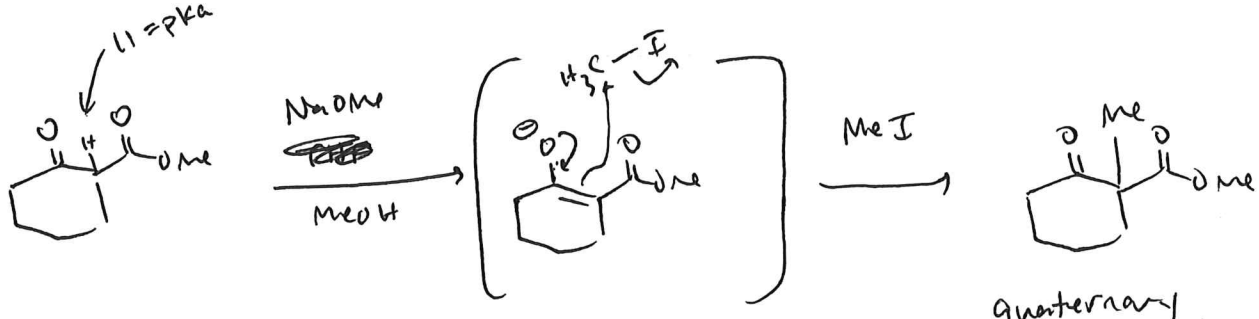


how to make this through dieckmann?!

alkylation of carbonyl species

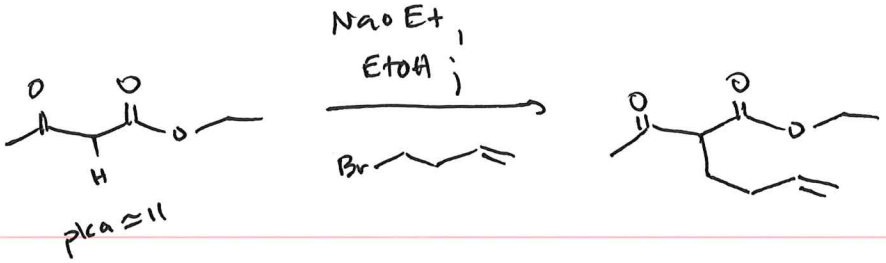
β-keto esters are the easiest species to use to make new C-C bonds

Consider:



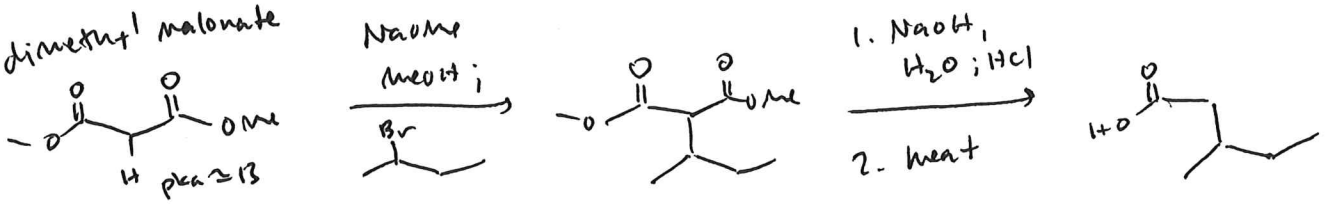
quaternary center!

The S_N2 reaction with dicarbonyl species is quite general

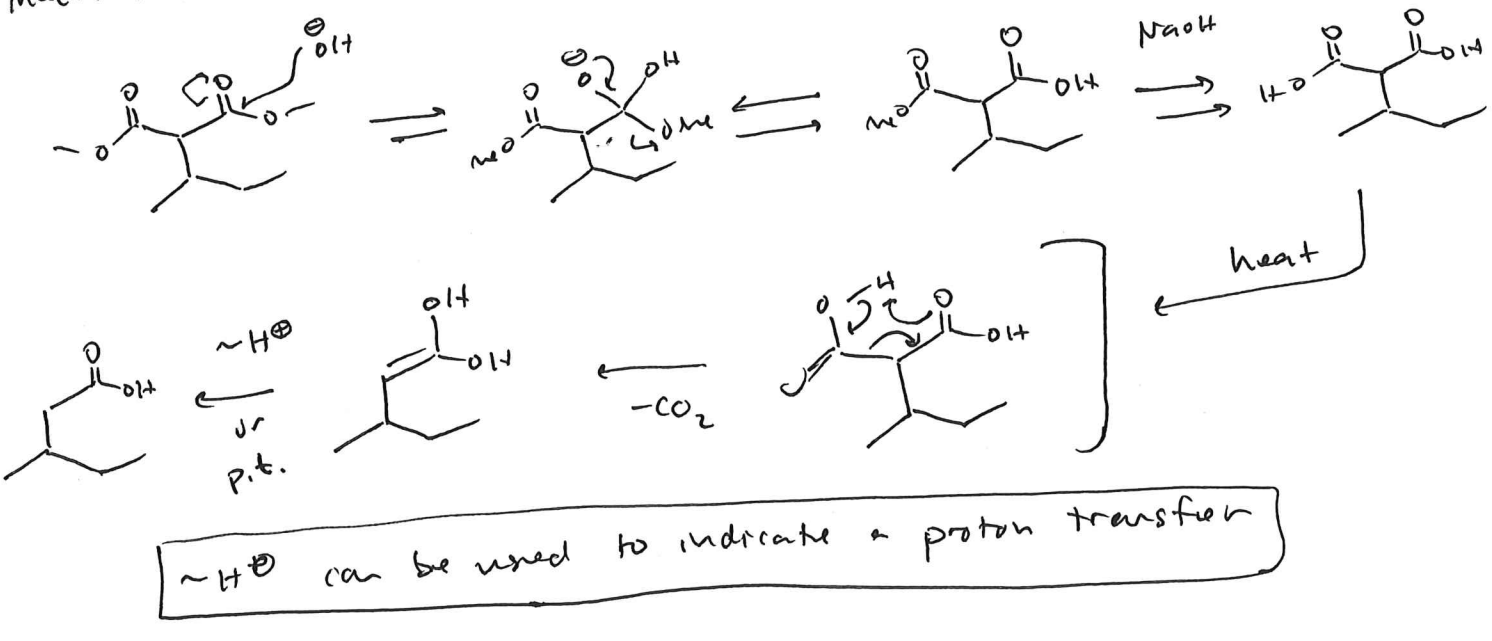


always alkylates between carbonyls!

We can also use diesters like dimethyl malonate!

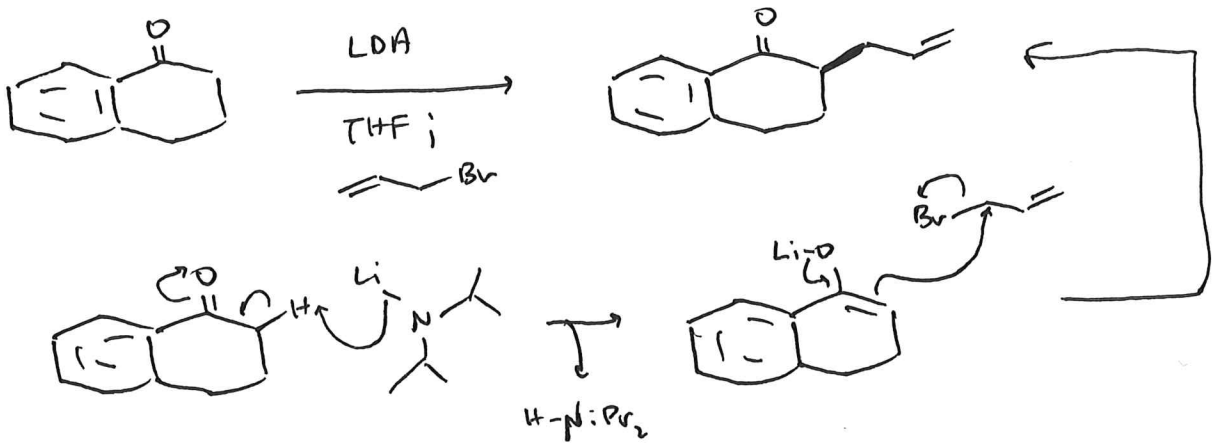


Mechanism:

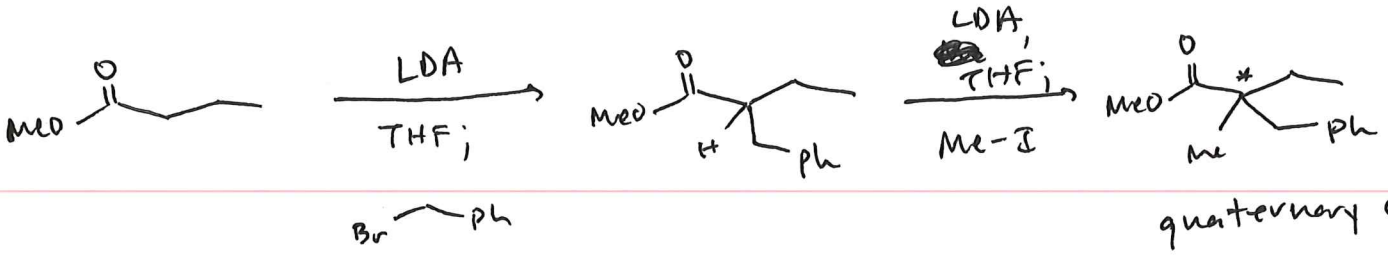


~H⊕ can be used to indicate a proton transfer

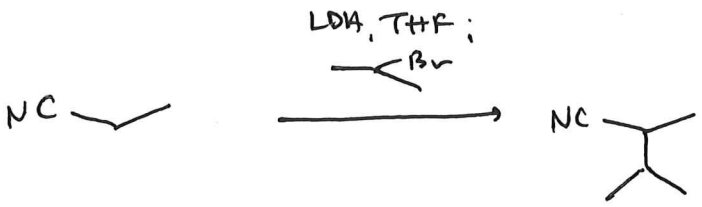
Use of strong bases in alkylation reactions!



other carbonyl species can be used in alkylations with LDA

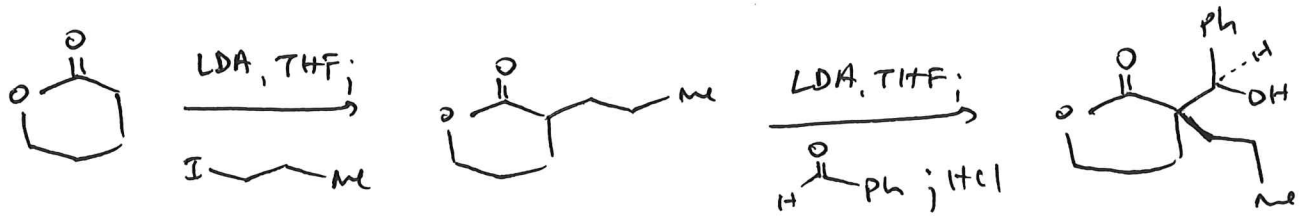


quaternary center!



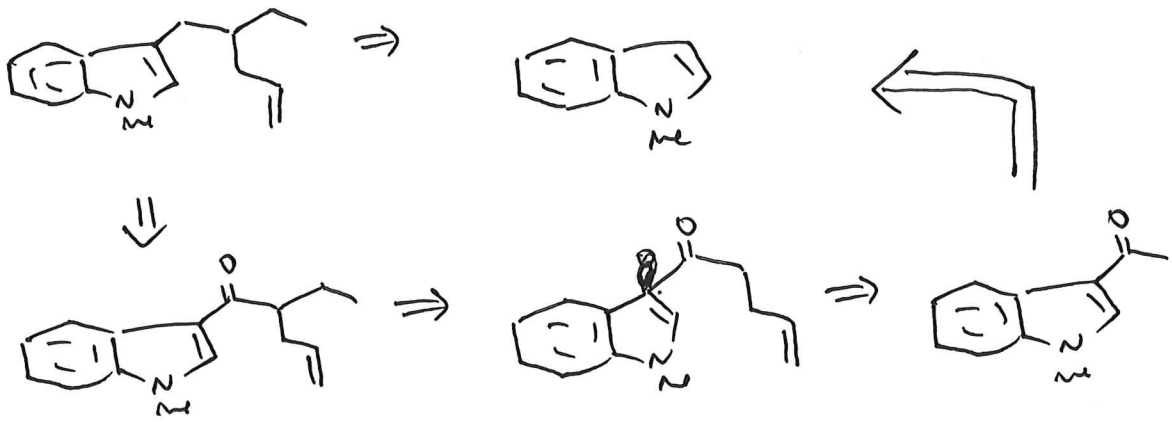
Nitriles can be used.

2° carbon electrophiles are not great, but can be utilized.

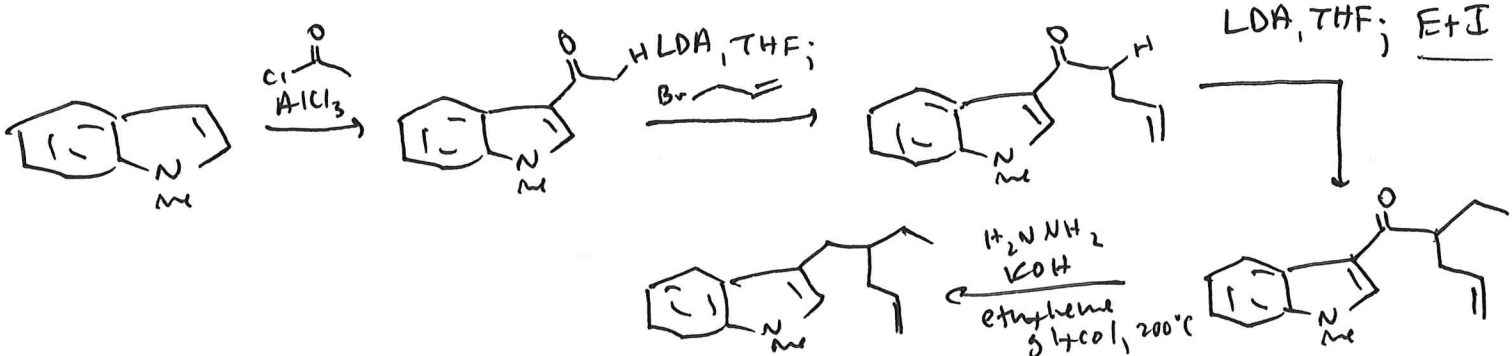


alkylation can be followed by an aldol reaction.

consider:

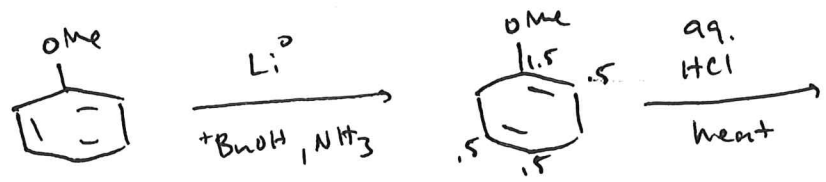


Forward synthesis:



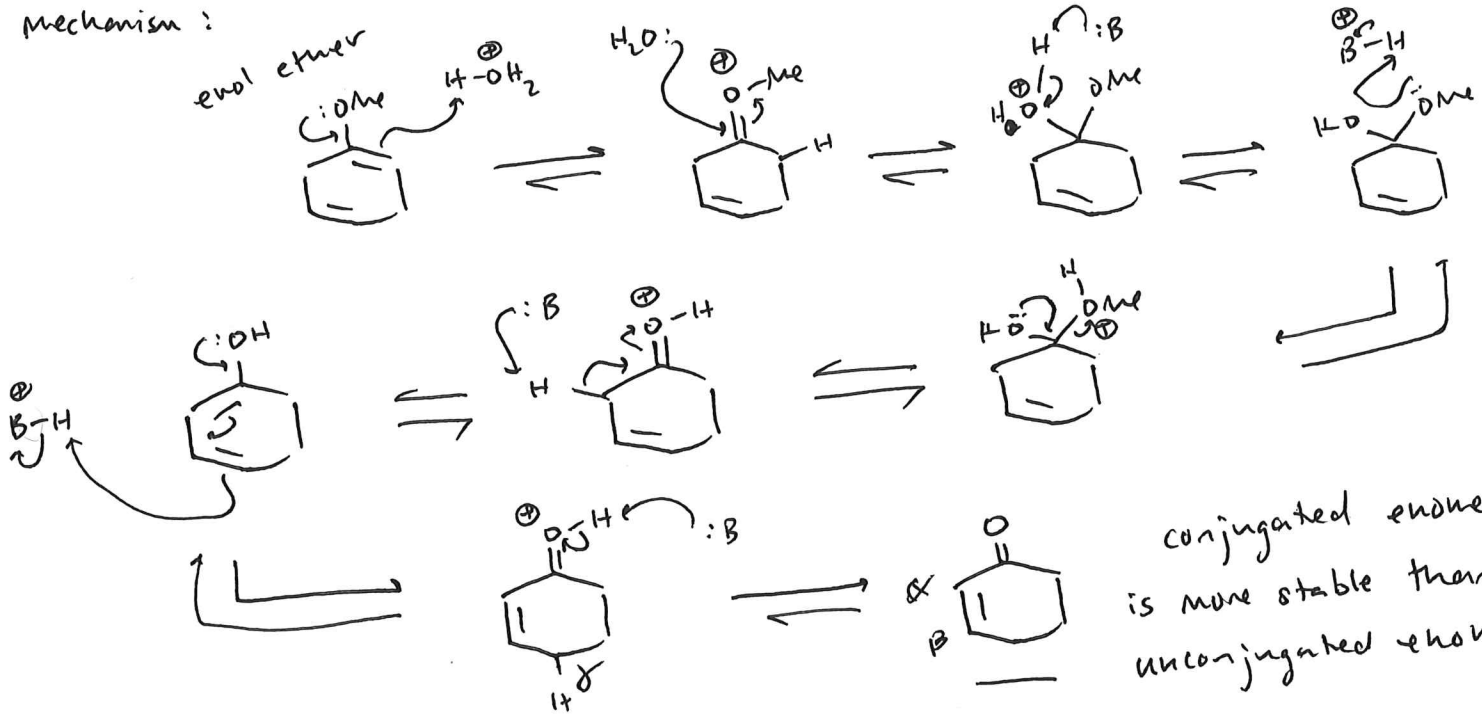
Conjugation in unsaturated carbonyl compounds

Consider:

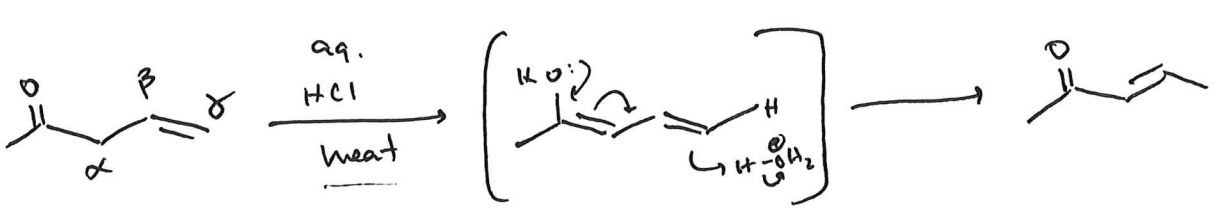


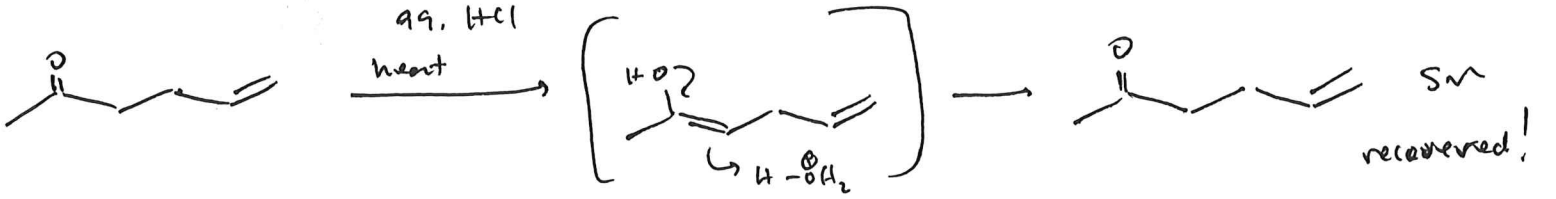
how does this happen?

Mechanism:



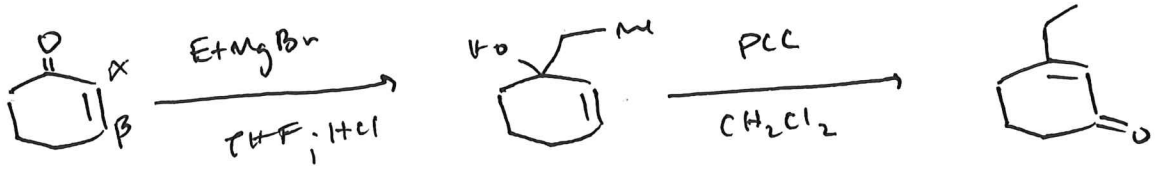
This is common amongst many unsaturated carbonyls:



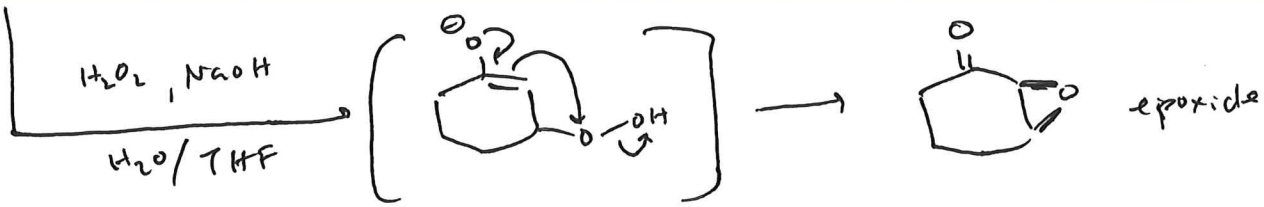


Enones are fantastic synthetic equivalents

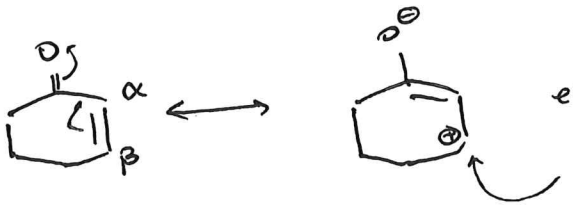
recall:



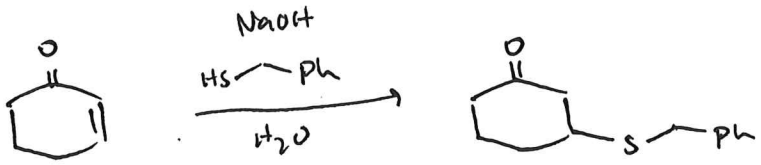
recall:



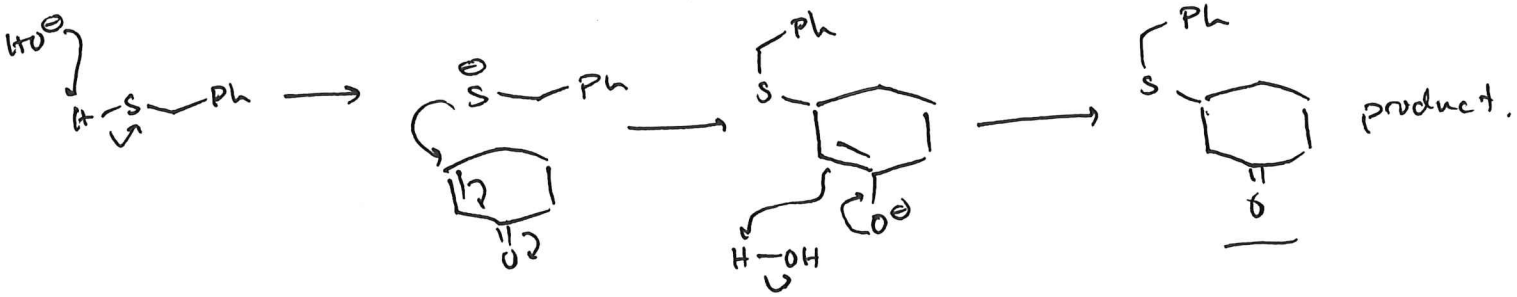
consider:



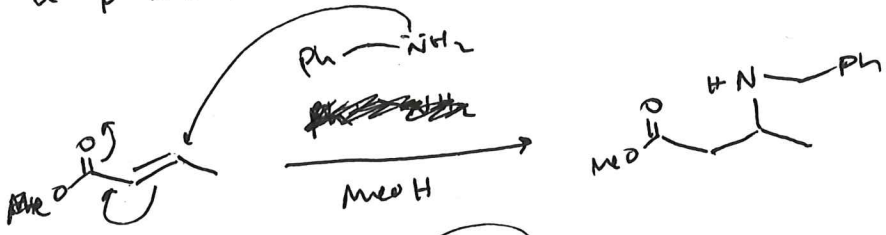
thus, weakly basic nucleophiles can add to the β position!



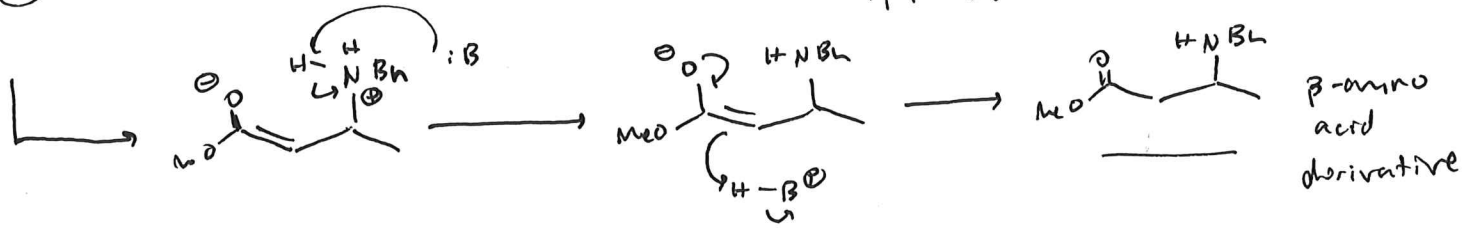
how does this occur..?!



α-β unsaturated esters can have similar reactivity:

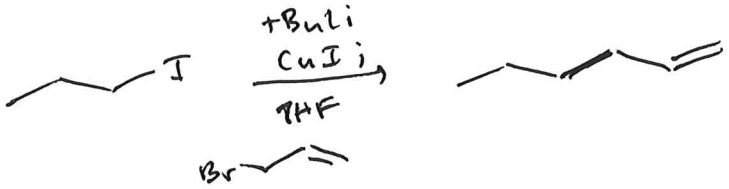


these reactions are called conjugate additions or 1,4 additions.

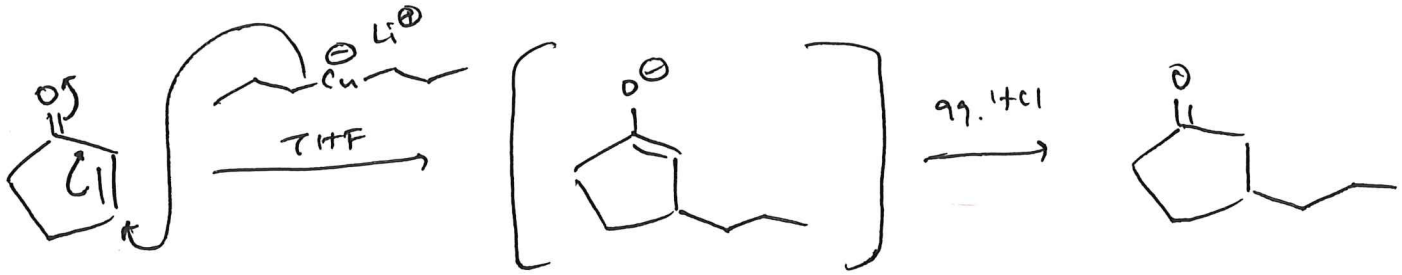


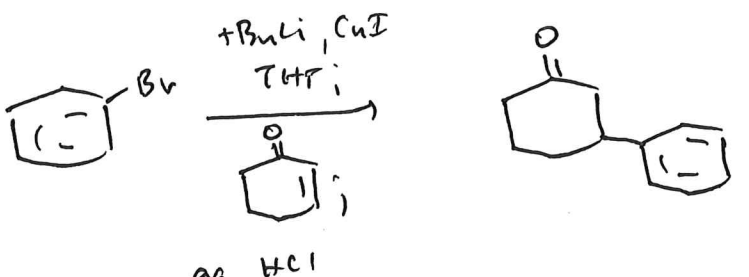
We can also use carbon nucleophiles!

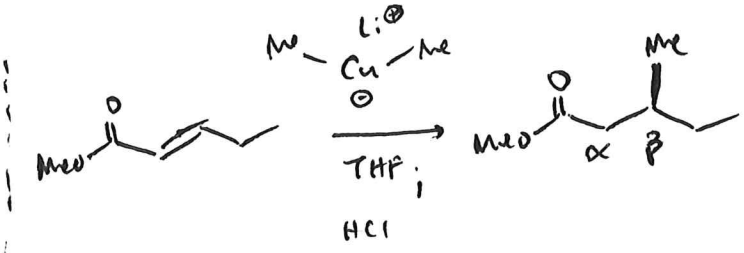
recall:



organocuprates can also be used to add into α,β unsaturated systems!

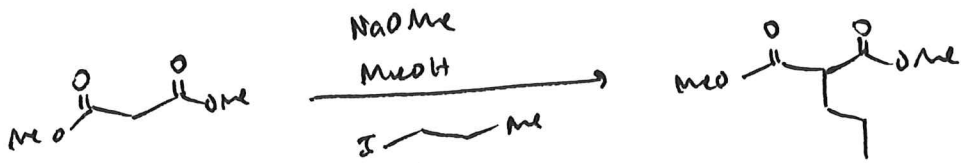






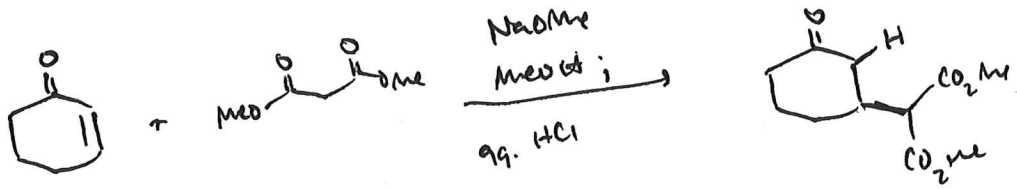
The Michael addition reaction:

remember that we can use malonates to do alkylation reactions quite efficiently.

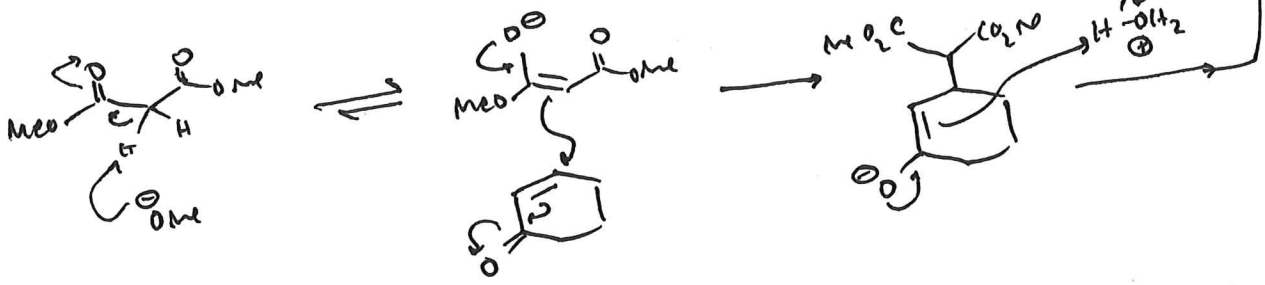


we can also use these enolate nucleophiles to add 1,4!

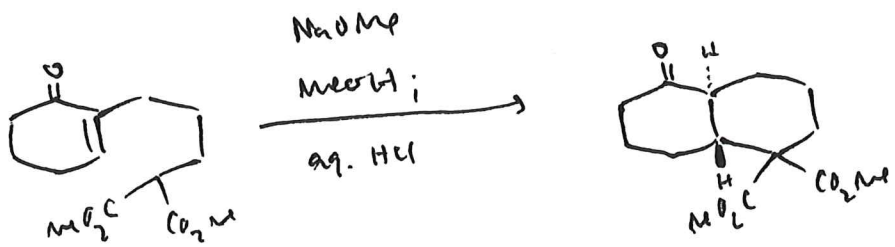
prototypical michael addition:



Mechanism:

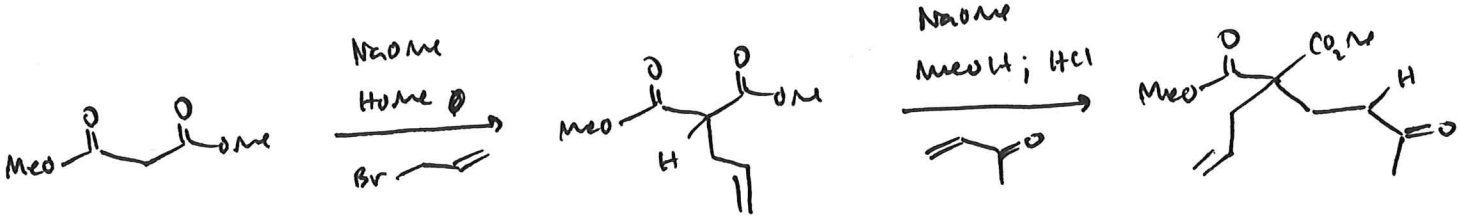


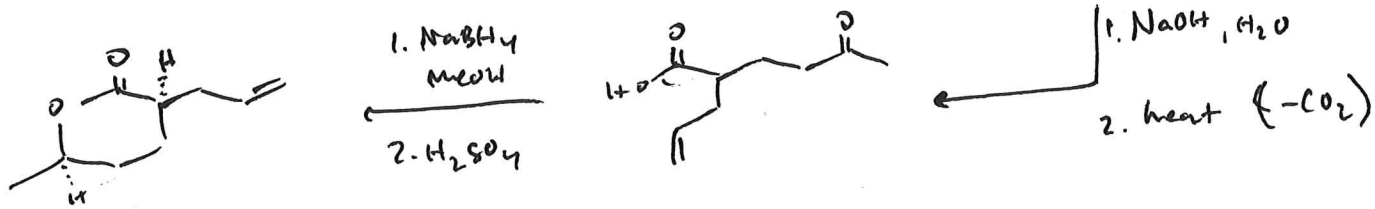
This reaction can be done intramolecularly as well.



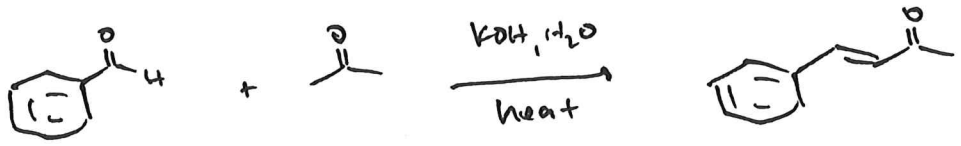
try mechanism on your own!

It can also be coupled to alkylation events and decarboxylations





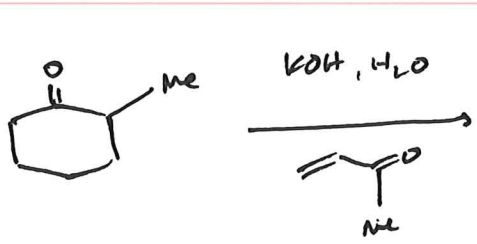
disubstituted lactone.

Recall: 

aldol condensation product.

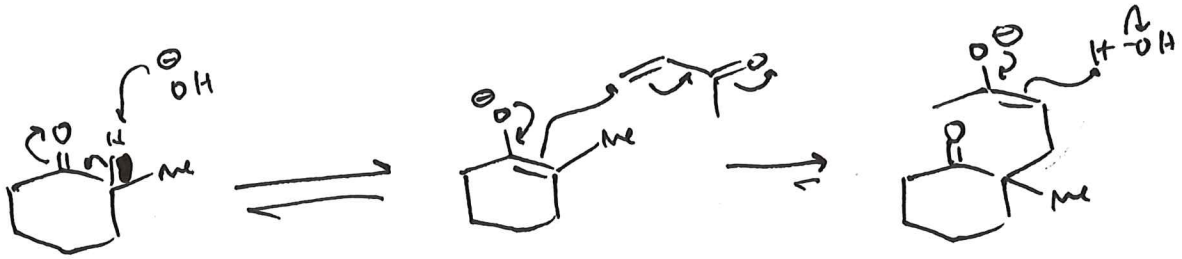
what if this was first part of a Michael addition?

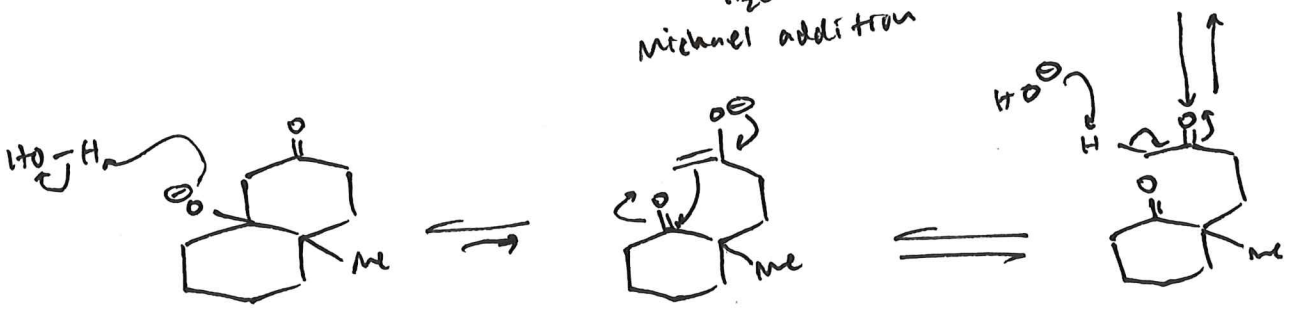
---

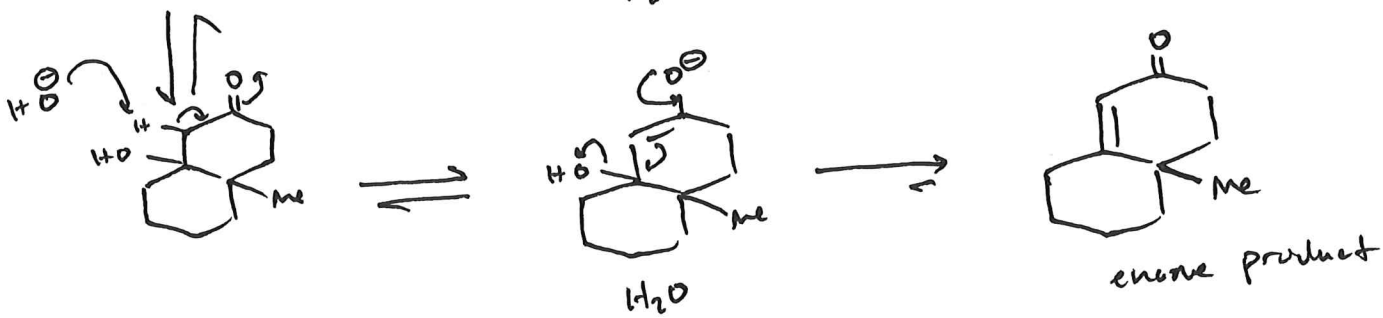
consider: 

! what happened here?

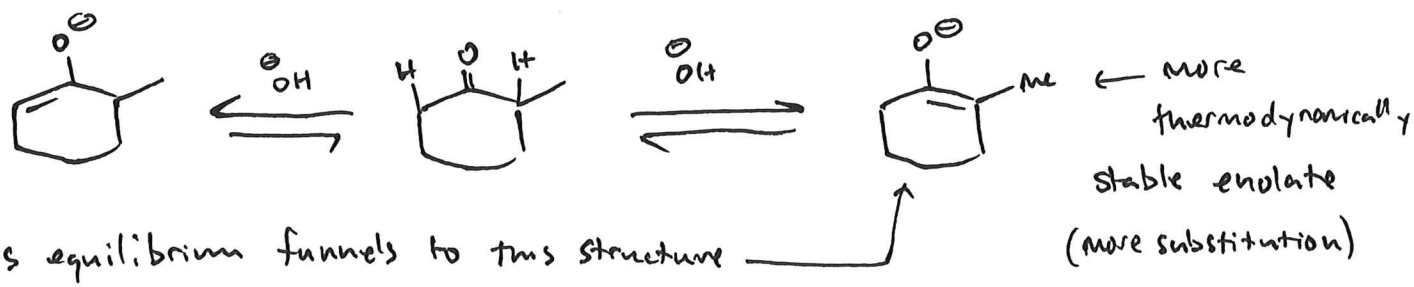
this is called a Robinson annulation

mechanism: 

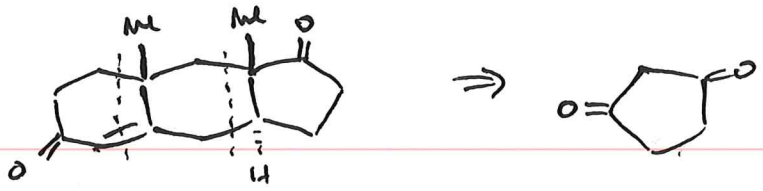




A couple of questions.

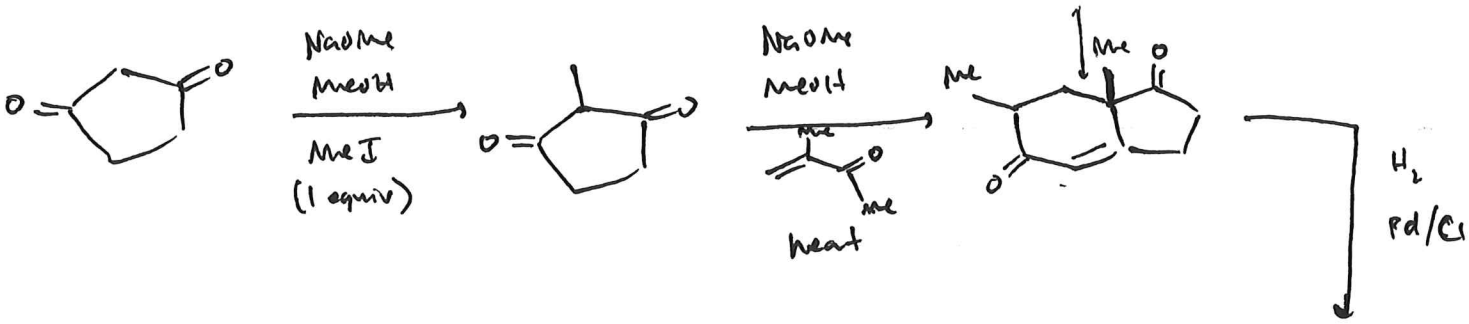


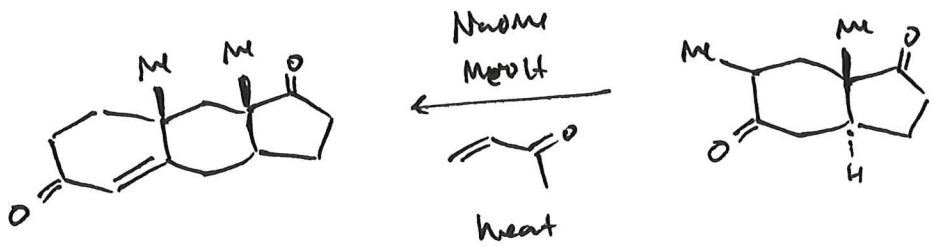
Robinson annulations can be performed iteratively. SP?



How can we make the target molecule from this diketone starting material?

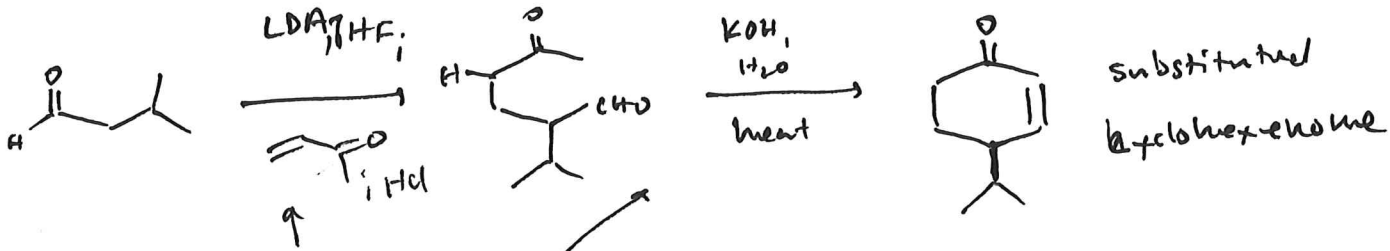
Forward synthesis:





facile way to access multicyclic systems!

This annulation method (Robinson annulation) can also be applied to aldehydes!



substituted cyclohexenone

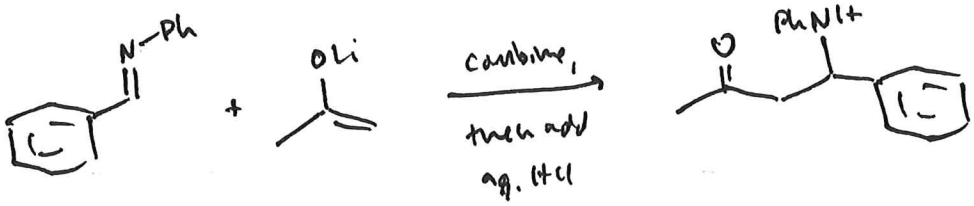
Stepwise Robinson annulation can also be employed when concerned with multiple sites of deprotonation.

The Mannich reaction

recall:

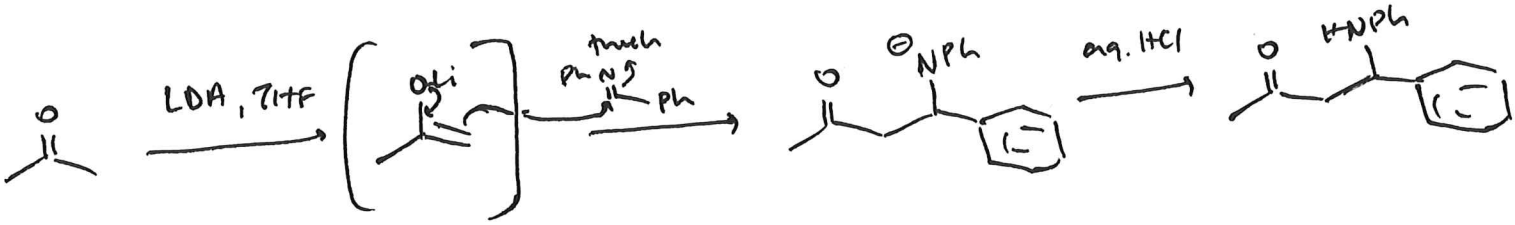
aldol product.

what if we replaced the aldehyde for an imine instead?

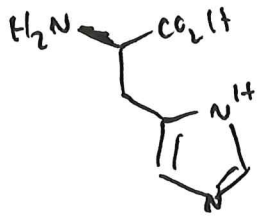


Mannich product.

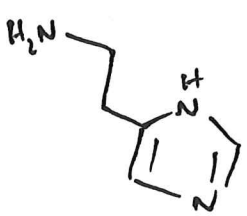
overall reaction looks like this.



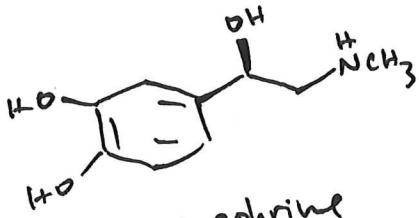
Amines



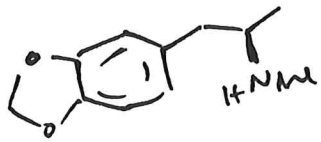
histidine
(amino acid)



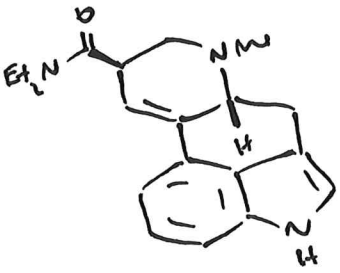
histamine
(signaling molecule)



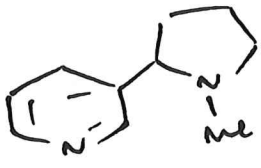
epinephrine
(adrenaline)



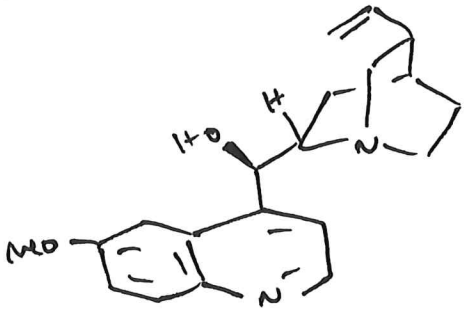
MDMA
(ecstasy)



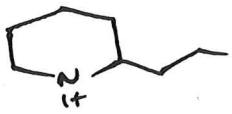
LSD
(acid)



nicotine
(addictive toxin)



Quinine
(malaria treatment)



Coniine
(poison that killed Socrates)

Basicity of amines

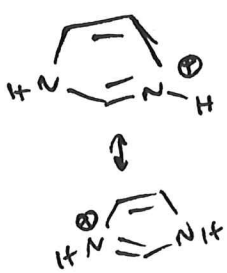
Amine basicity is based on the pka of its protonated form.

For example, consider:

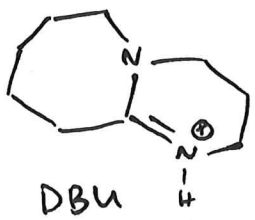
pka = 5

pka = 11

pka = 11

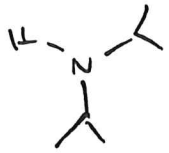


pka = 7



DBU

pka = 20

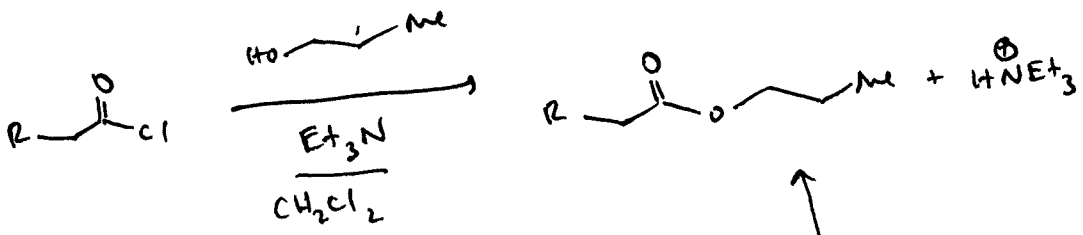


DIPA
diisopropylamine

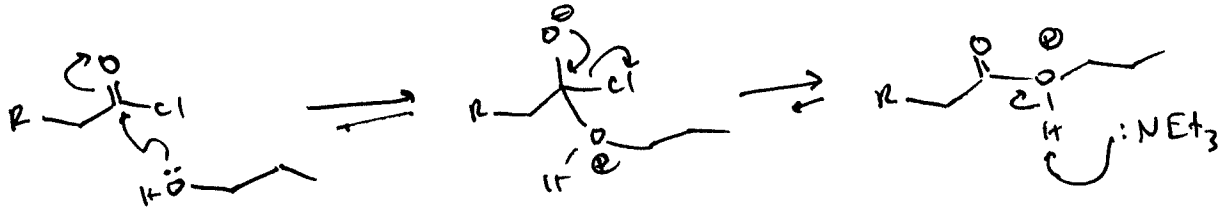
pka = 36

use of amines as a stoichiometric base

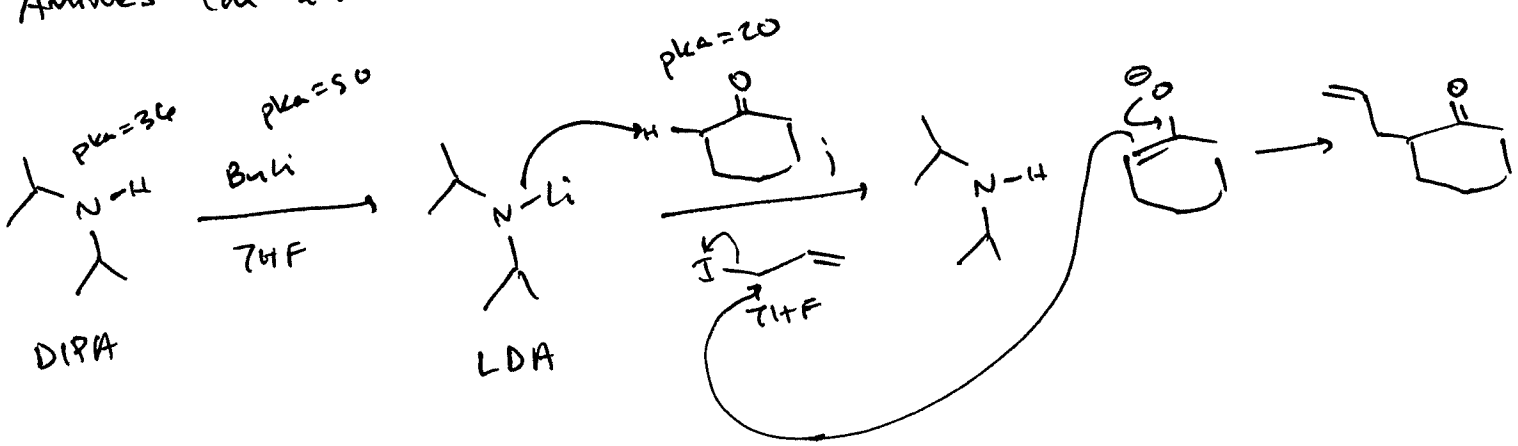
recall:



mechanism:

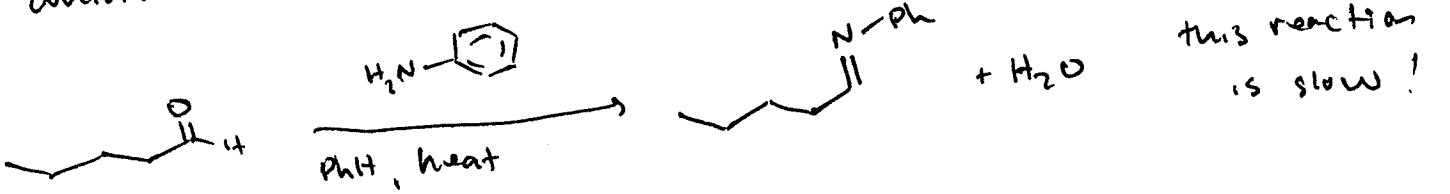


Amines can also be used as a strong base

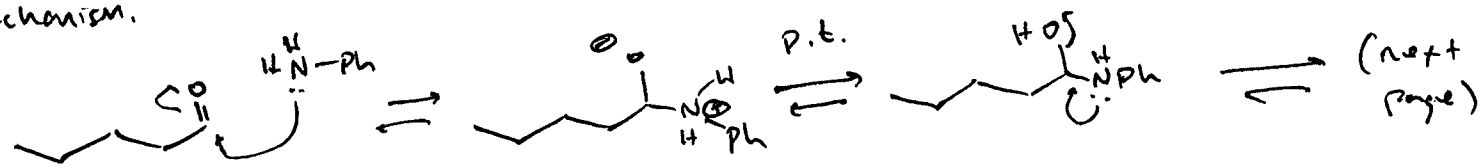


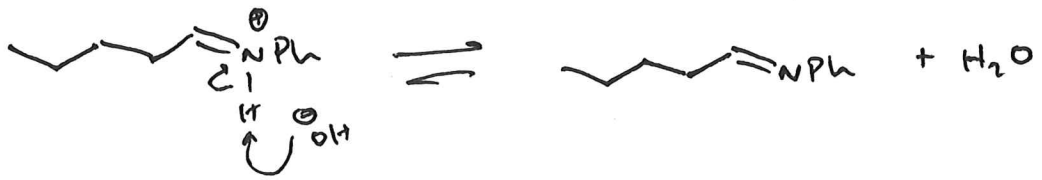
Amines can also react with carbonyl compounds in several ways.

amine condensation on an aldehyde:



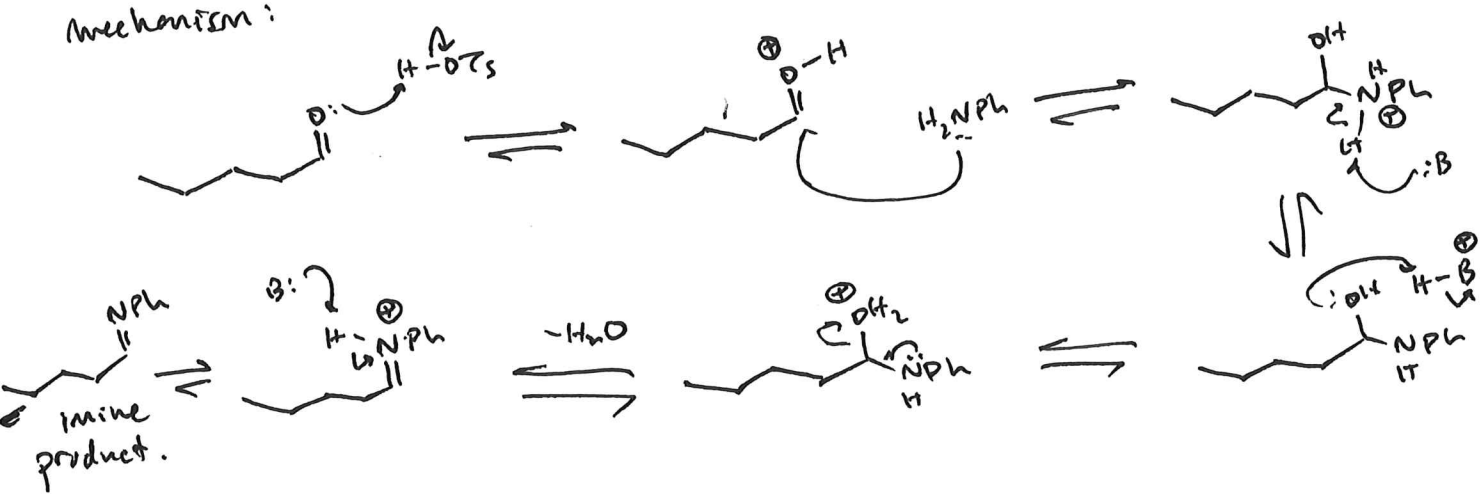
mechanism.



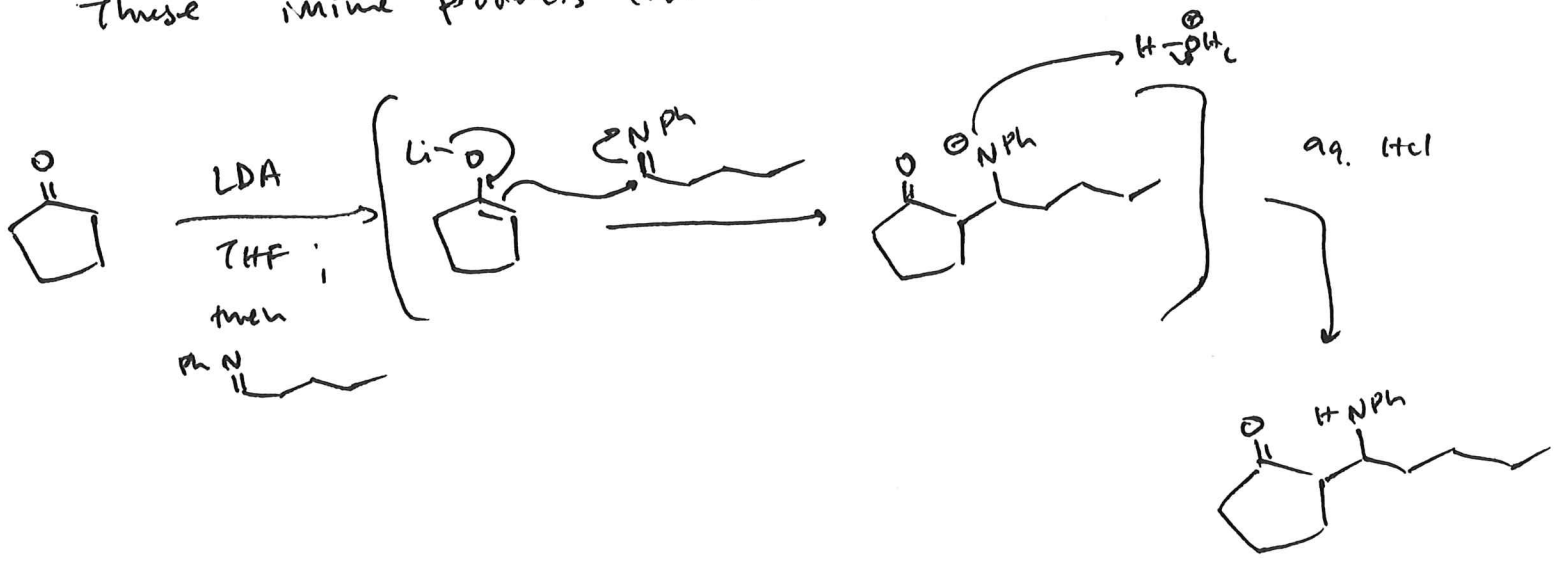


If we add catalytic acid, however, the reaction goes much faster.

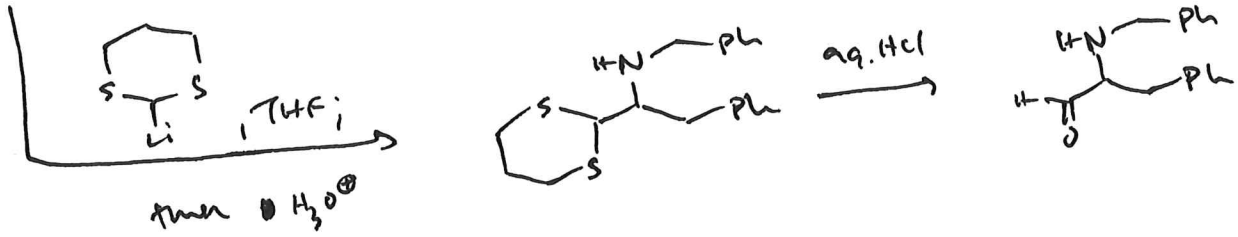
Mechanism:



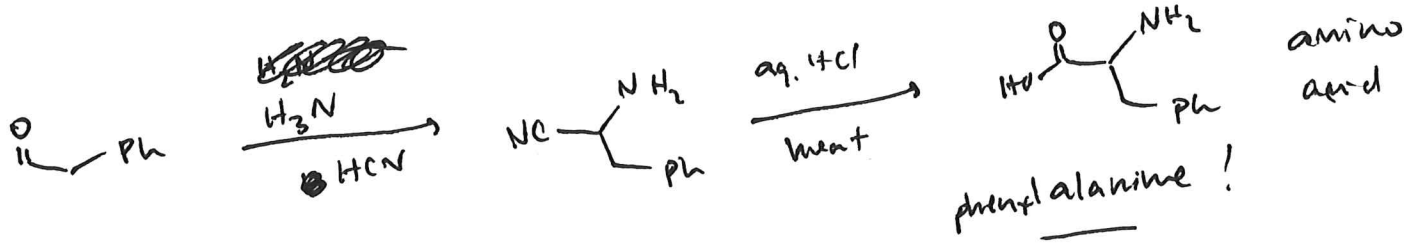
These imine products can be used in Mannich reactions.



imines can also behave as electrophiles to many nucleophiles

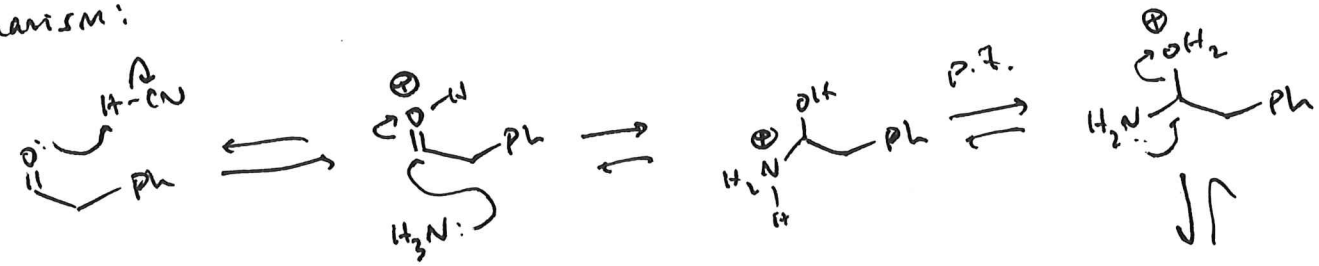


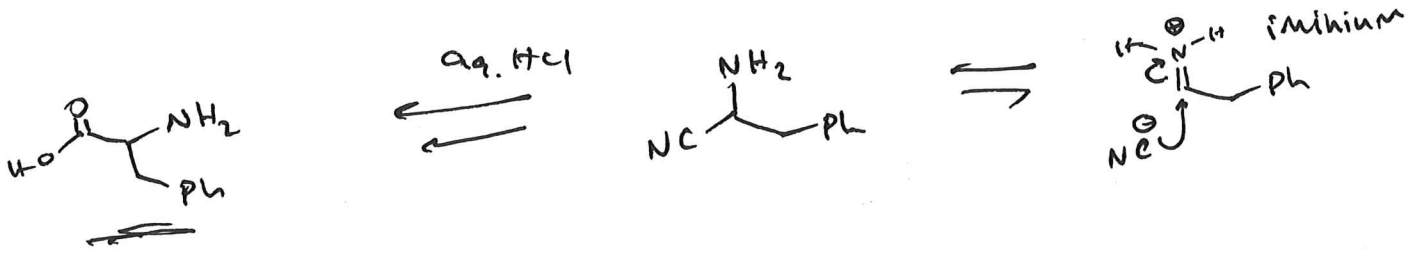
reaction with cyanide (strecker reaction)



phenylalanine !

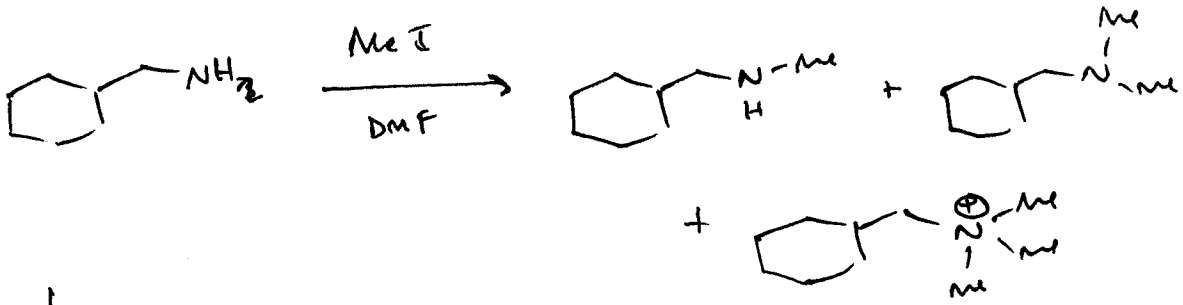
Mechanism:

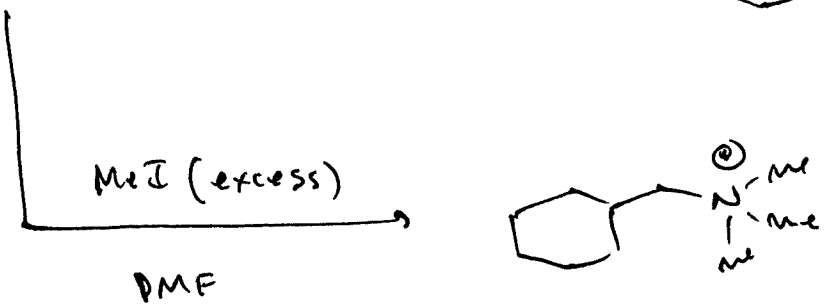




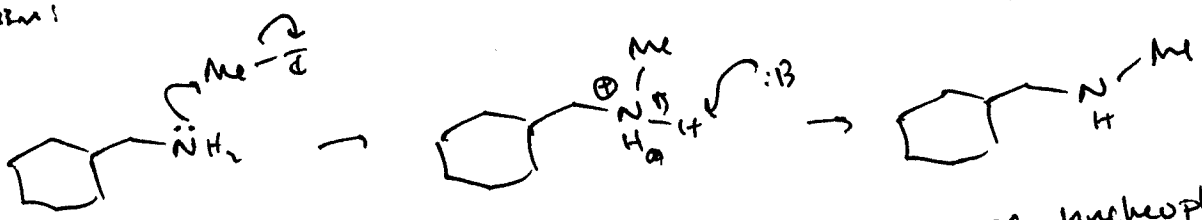
Alkylation of Amines

Consider:

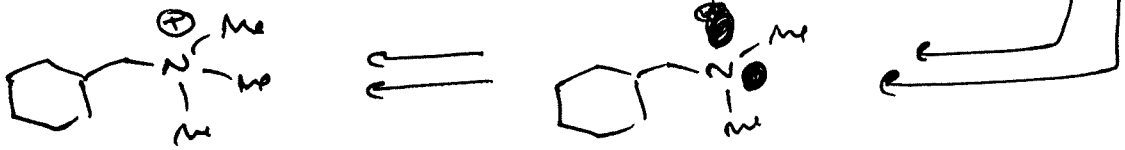




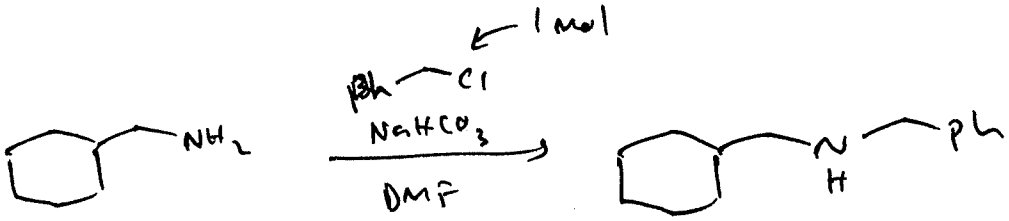
Mechanism:



more nucleophilic or equally nucleophilic to SM.



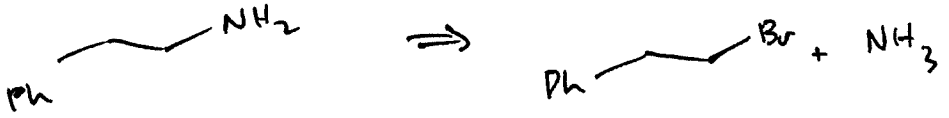
How can one accomplish the monoalkylation of an amine?



Mono alkylation through control of stoichiometry.

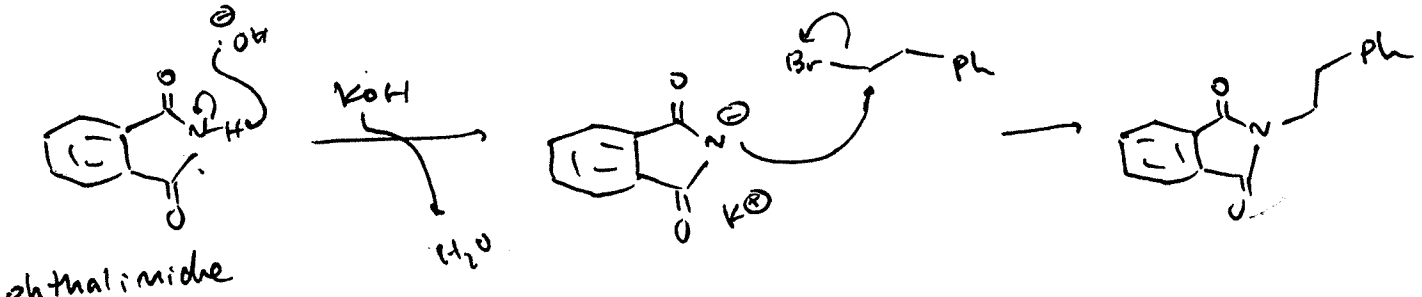
We will discuss another strategy soon.

Synthesis of primary amines (Gabriel amine synthesis):



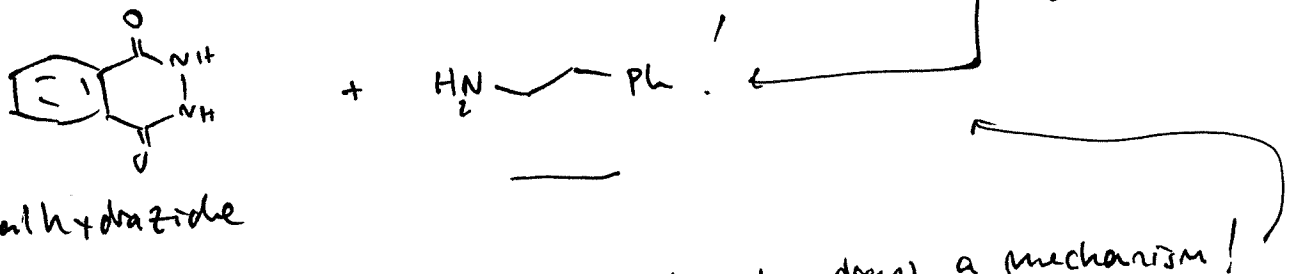
however, how do we avoid overalkylation?

we can used an engineered version of ammonia that can alkylate only once.



phthalimide

pka ≃ 8.3

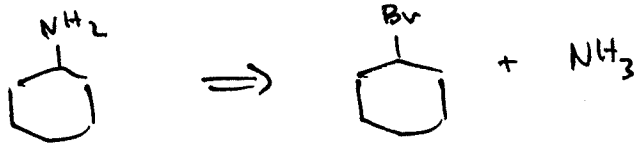


phthalhydrazide

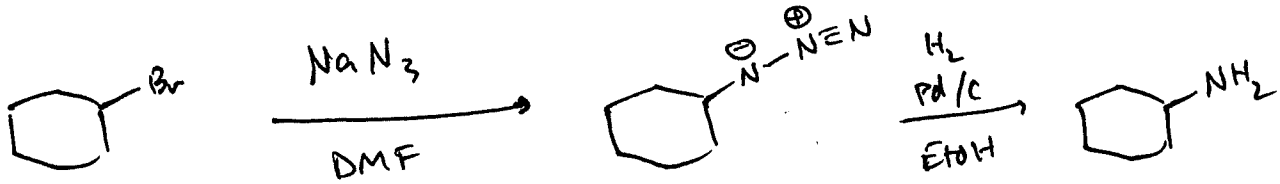
use your knowledge of amide chemistry to draw a mechanism!

the Gabriel amine synthesis is the canonical way to make amines!

utilization of azides:

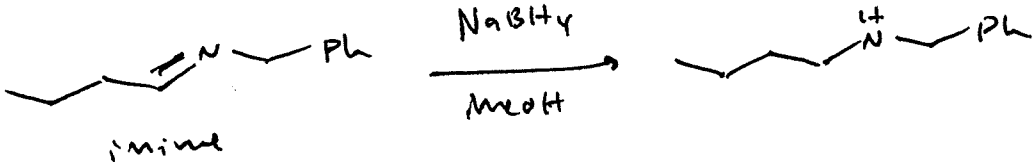


we still run into the overalkylation issue here! we can use azides followed by reduction to access these amines.

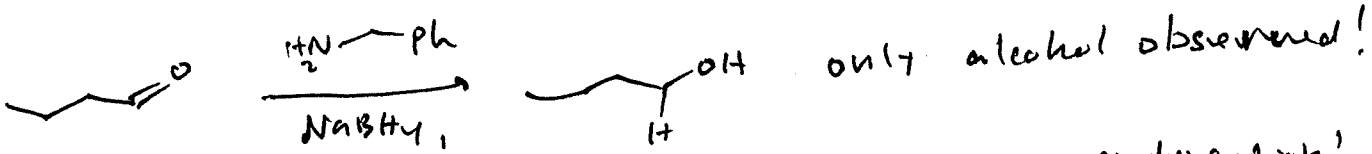


Synthesis of secondary amines:

Consider:



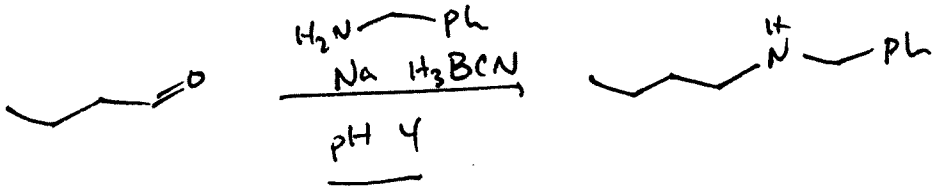
this reaction works but what if we wanted to do the condensation and reduction in one reaction?



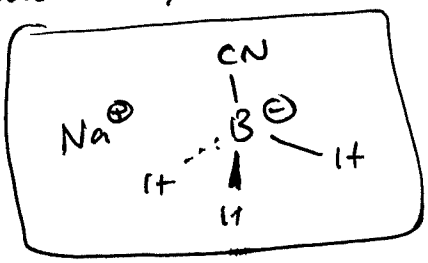
only alcohol observed!

reduction outcompetes condensation!

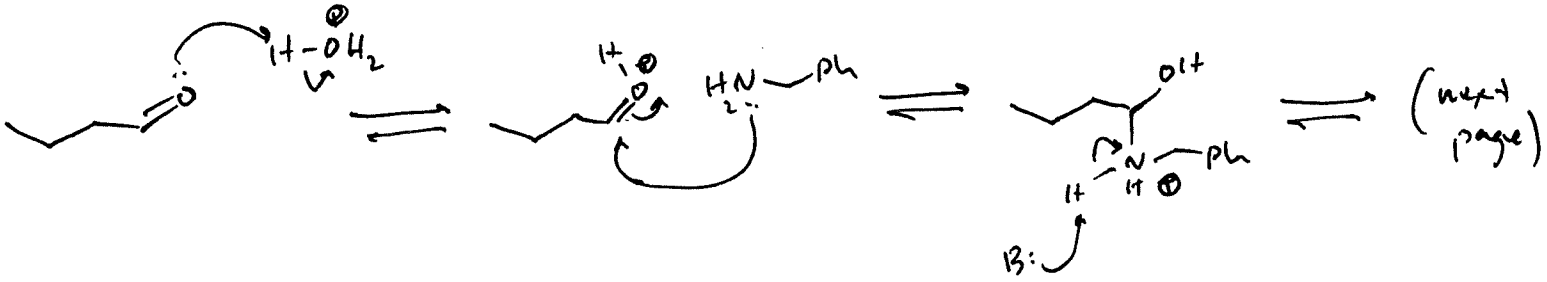
what if we add acid (by lowering pH), and make a weaker reducing agent.

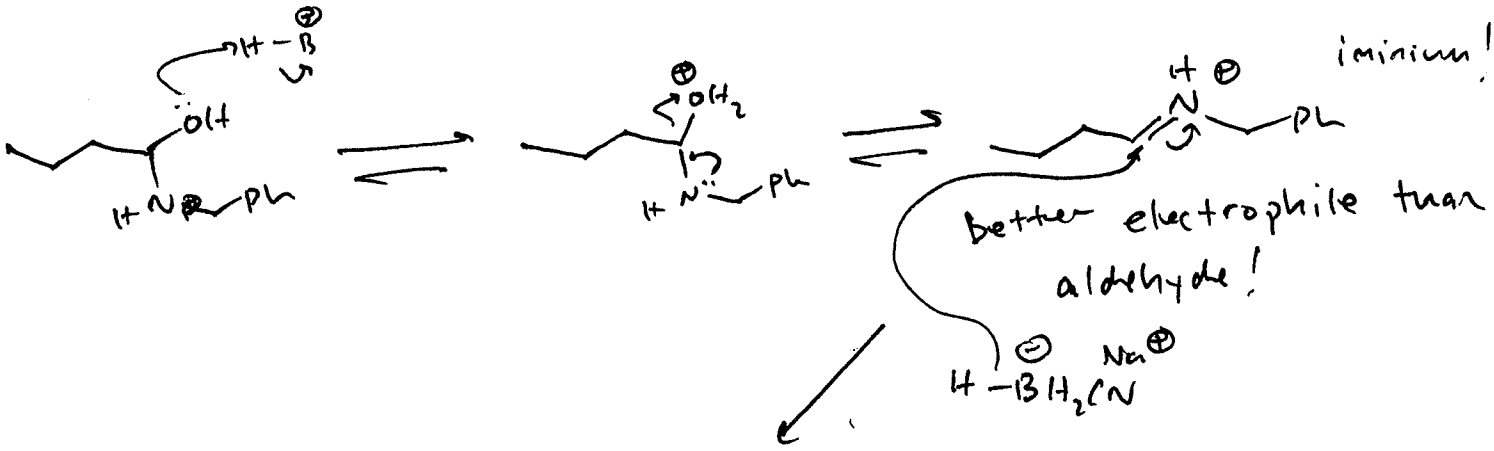


success!



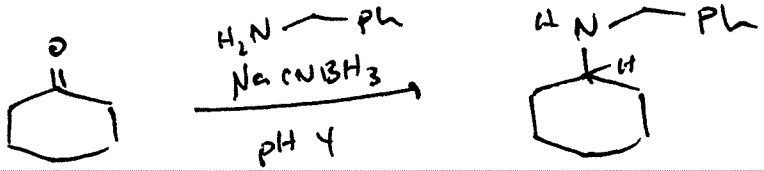
How does this work?



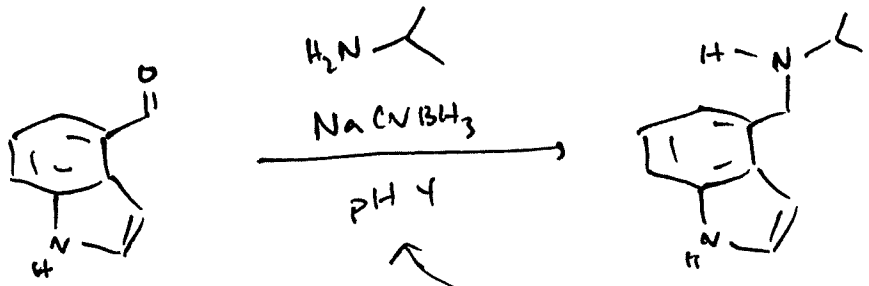

iminium!
better electrophile than aldehyde!
Na CNBH3 is too weak to reduce aldehydes directly. Thus, condensation can happen to allow for chemoselective reduction of the iminium.
Secondary amine product accessed through simple reductive amination!

Reductive Amination, part 2

recall:

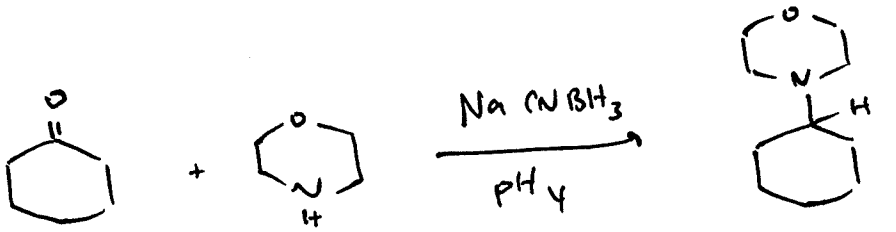


reductive amination can be done on aldehydes and ketones



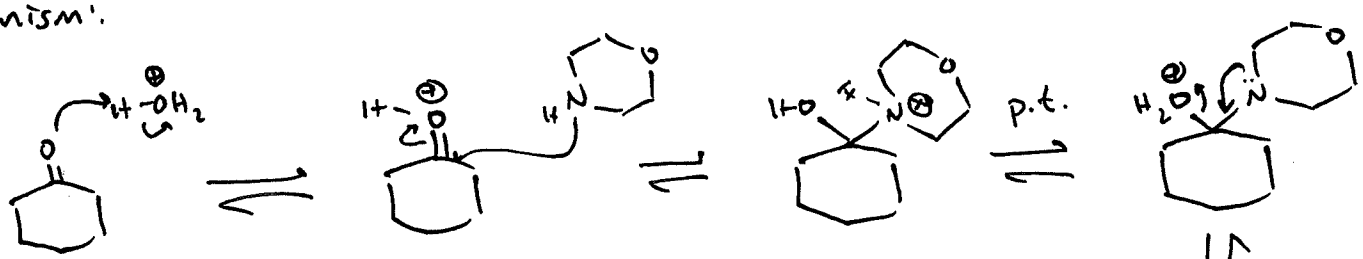
acidic protons are compatible as conditions are acidic already.

reductive amination of secondary amines:



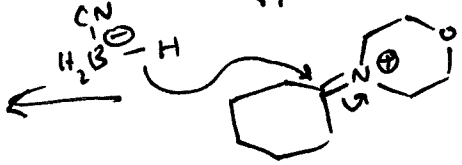
this is also a way to synthesize tertiary amines.

Mechanism:



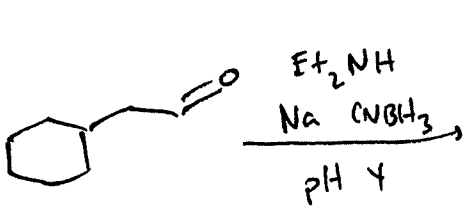
here, the iminium is a dialkyl iminium and has similar reactivity to the iminiums we saw earlier.

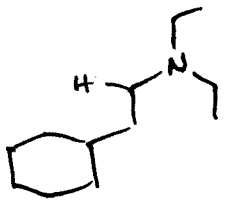
product.

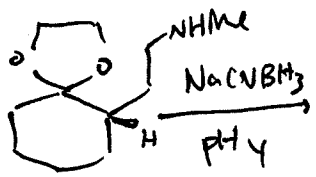


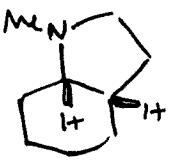
iminium

This can be used to make a variety of tertiary amines.



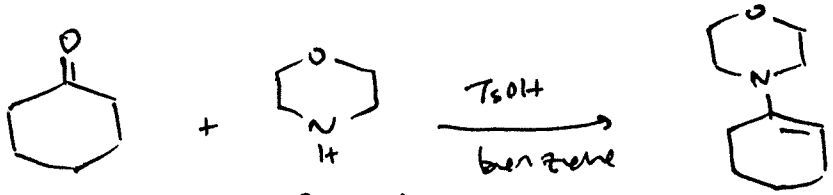






mechanism?

what happens if we exclude the hydride source?

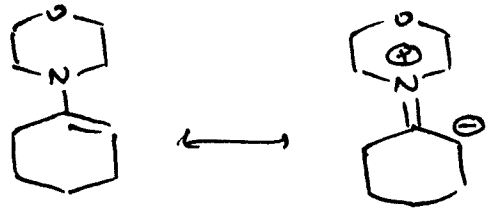


2° amine crucial

this is called an enamine

enamines are similar to enolates, but without the charge

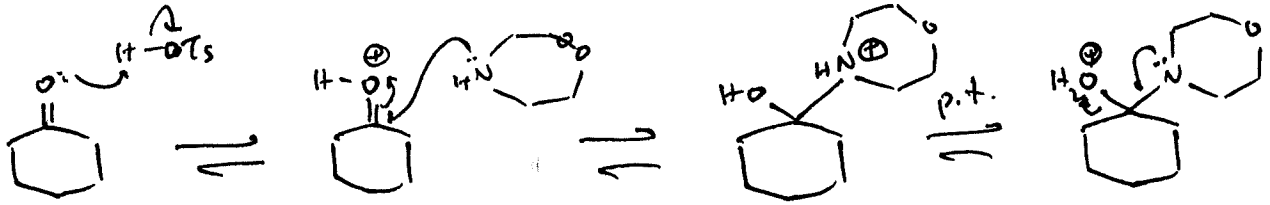
enolate



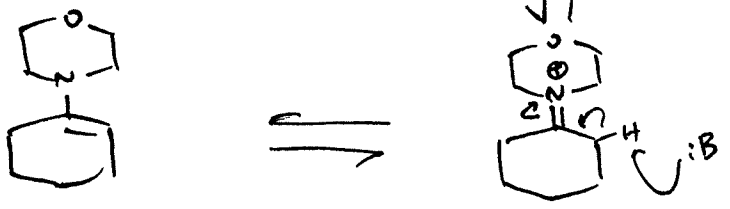
enamine

(still nucleophilic at "alpha" carbon.

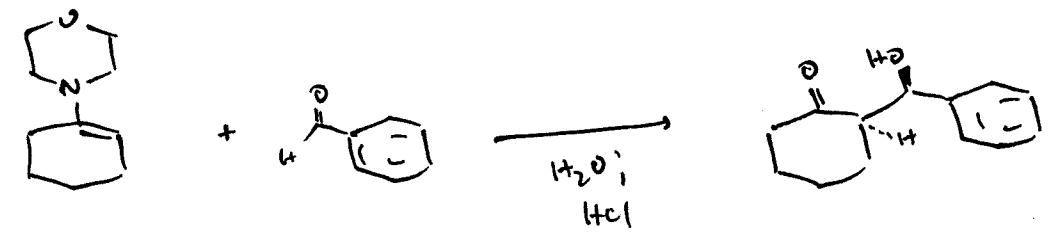
Mechanism of enamine formation:



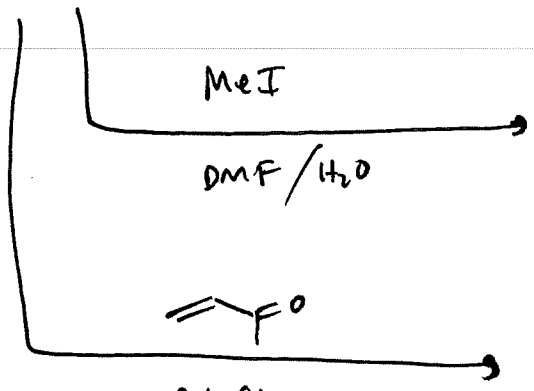
now, the enamine product can be used as a nucleophile!

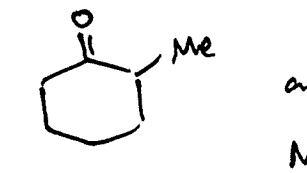


Stork enamines

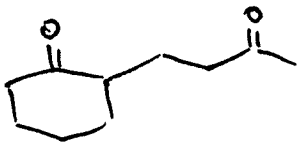


aldol product.



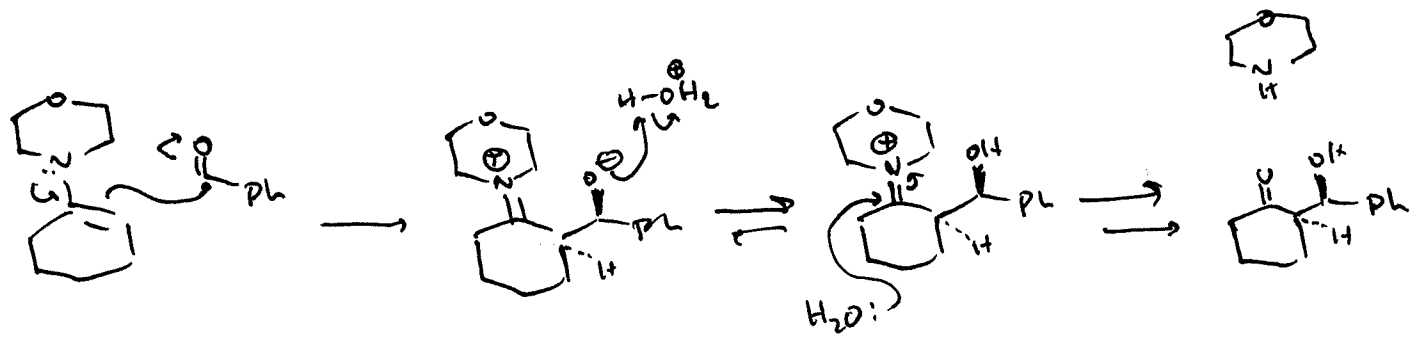


alkylation product. Only MeI works, however.



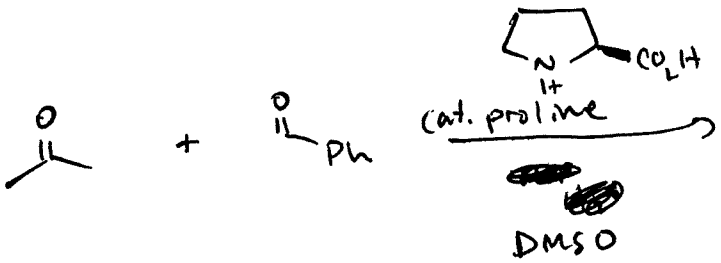
Michael addition product.

Mechanism:



I encourage you to draw mechanisms for the other additions for practice in using enamines.

The world's smallest enzyme

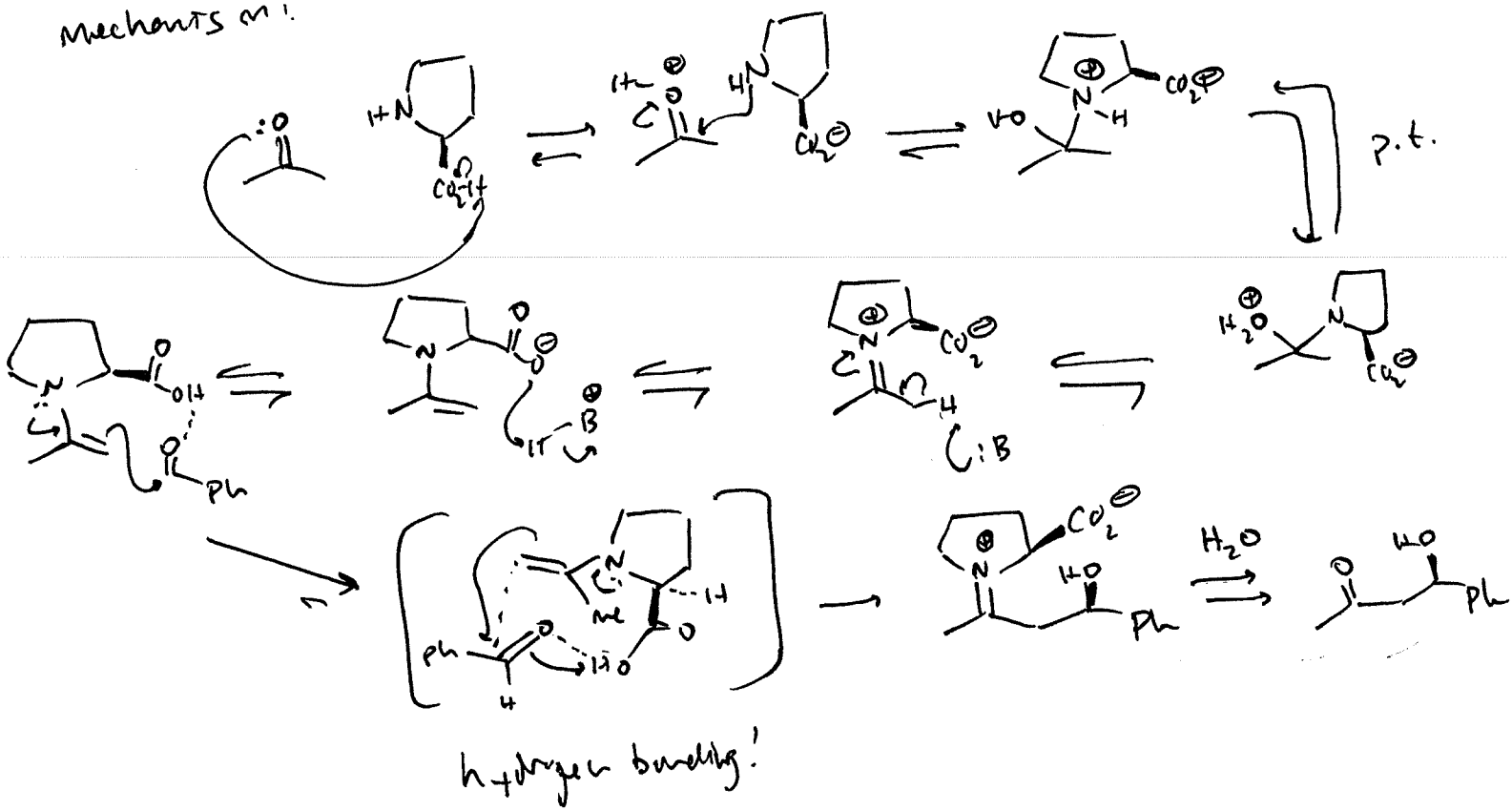


enantioselective aldol reaction!

60% ee = 80/20 ratio of enantiomers.

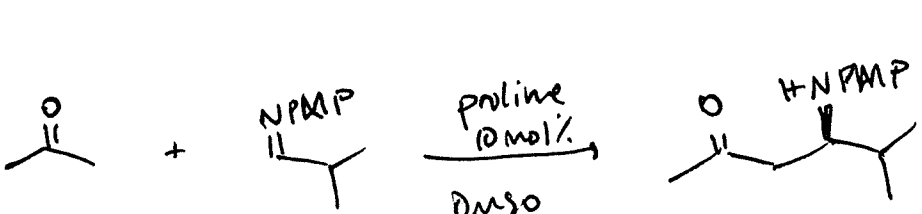
ee stands for enantiomeric excess

Mechanism:



hydrogen bonding!

proline can also be used in Mannich reactions!

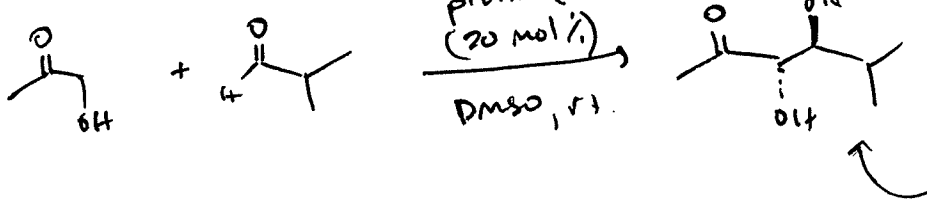


PMP = 

para methoxy phenyl

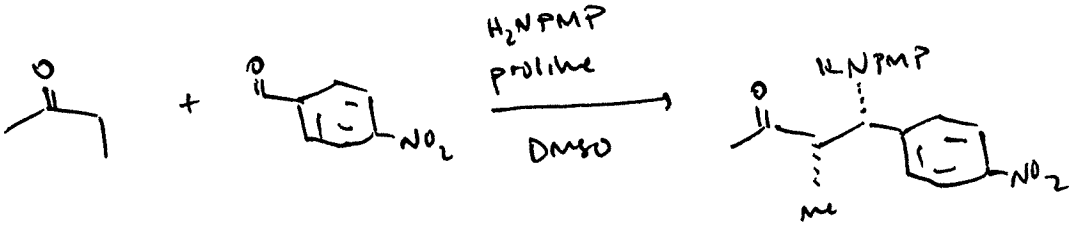
70% ee

alpha substituents can also be used.



"anti" product is Major

99% ee = 99.5 : .5 ratio of enantiomers.

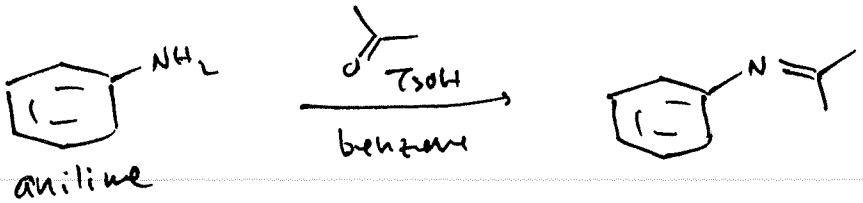


>20:1 syn, 99% ee

draw out entire mechanism for your practice!

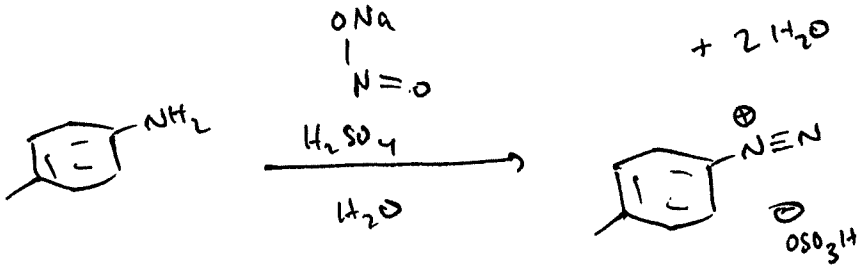
Reactions of aromatic amines (anilines)

recall:



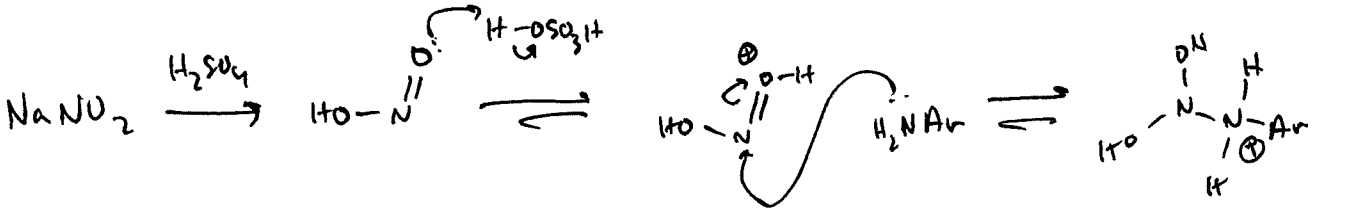
imine synthesis via condensation.

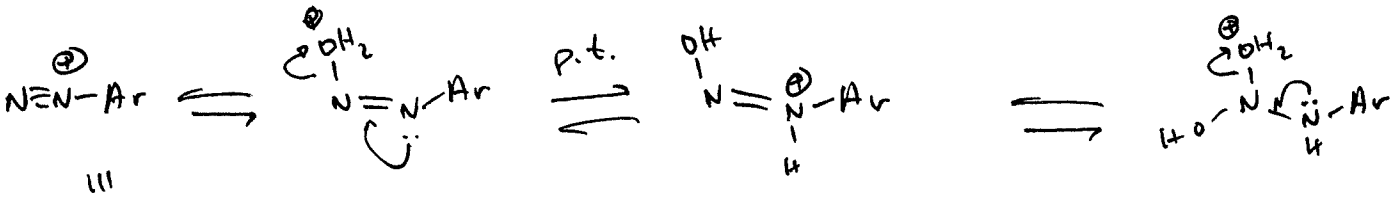
consider:

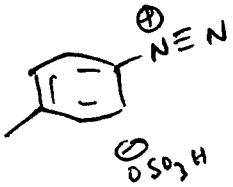


This is called a diazonium salt

mechanism:

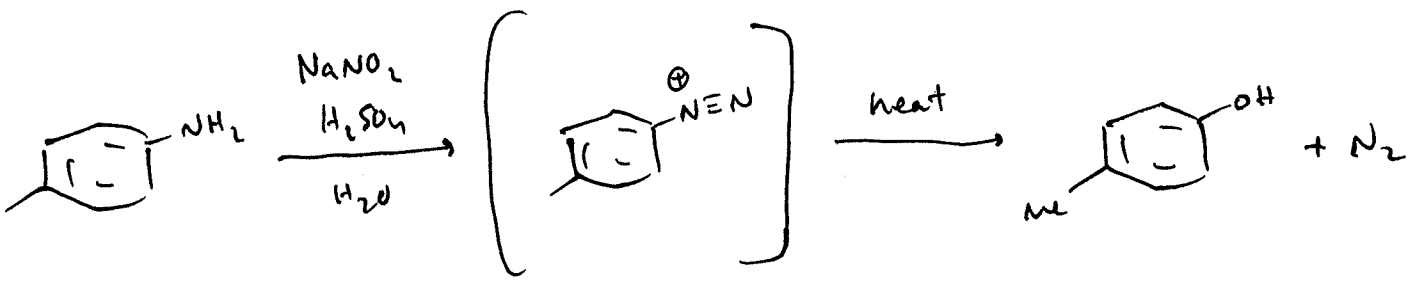






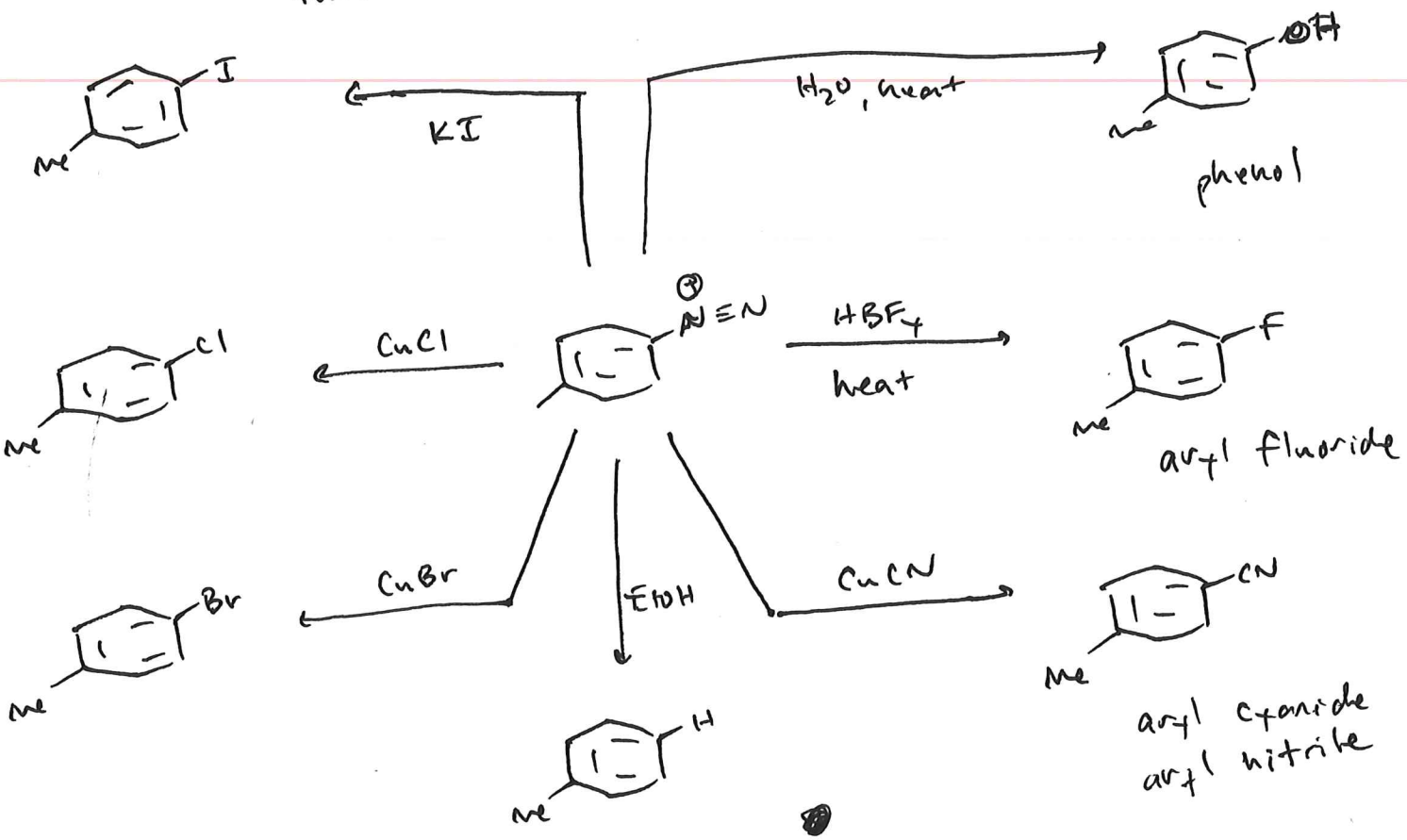
notice how this is an aryl group with an extremely good leaving group! the leaving group is N_2!

If we heat the solution a bit, we get a displacement!

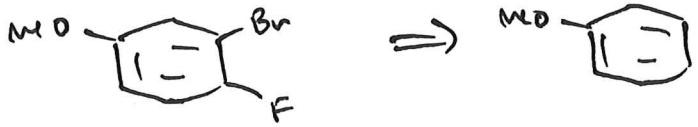


We can employ diazonium salts in a whole host of direct aromatic substitution reactions!

these are called Sandmeyer reactions!



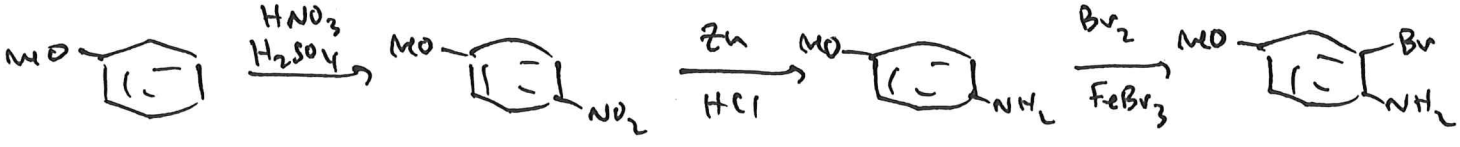
utilization in synthetic sequence:



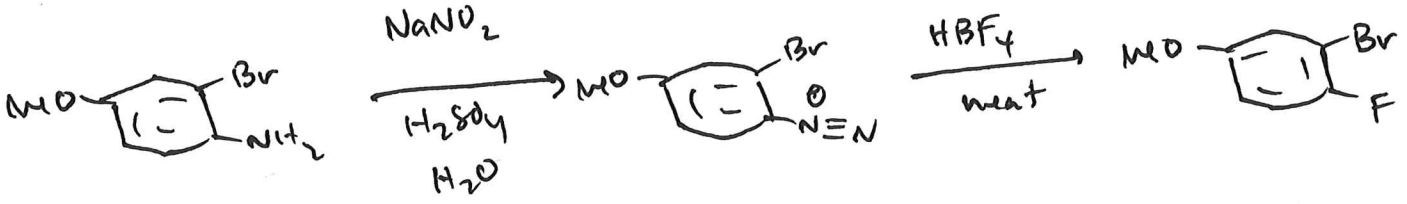
~~type reaction here~~

We can utilized the intermediates for other functionalizations!

Forward synthesis:

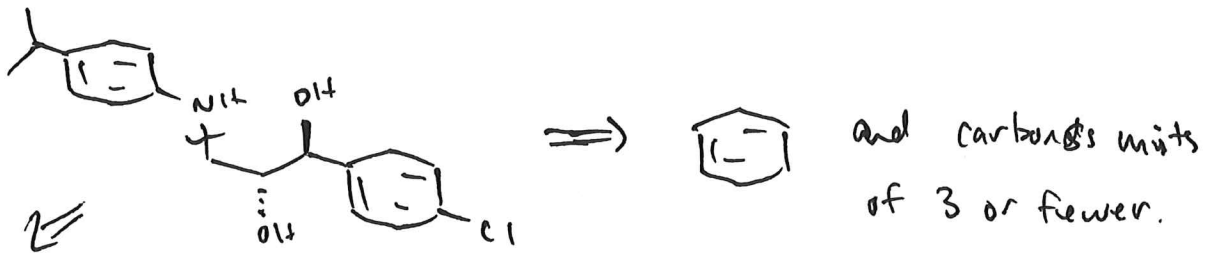


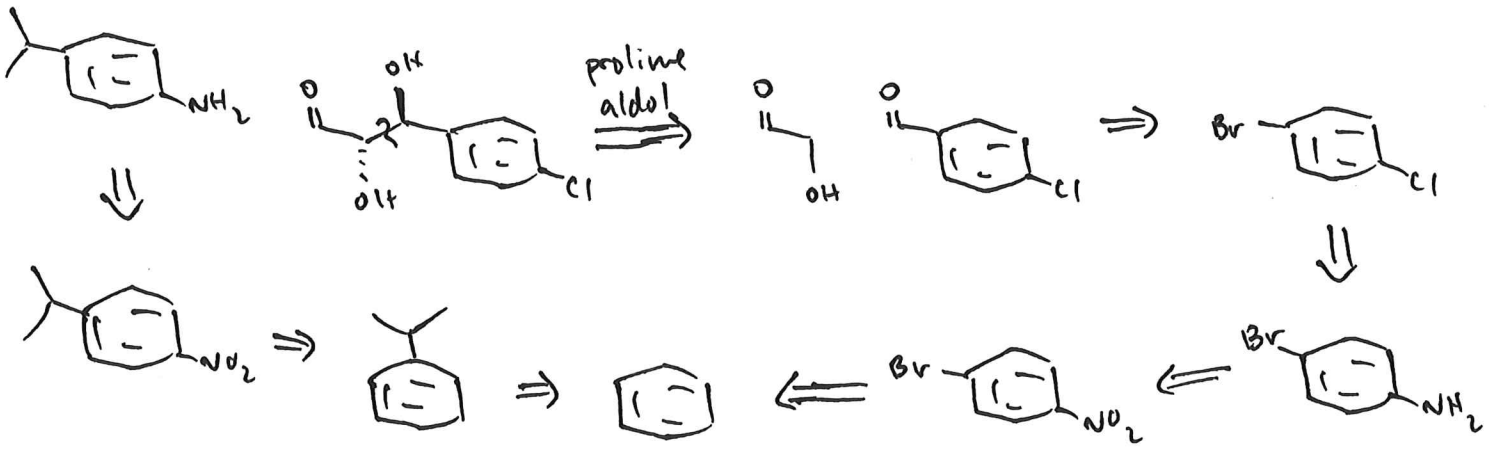
(continued)



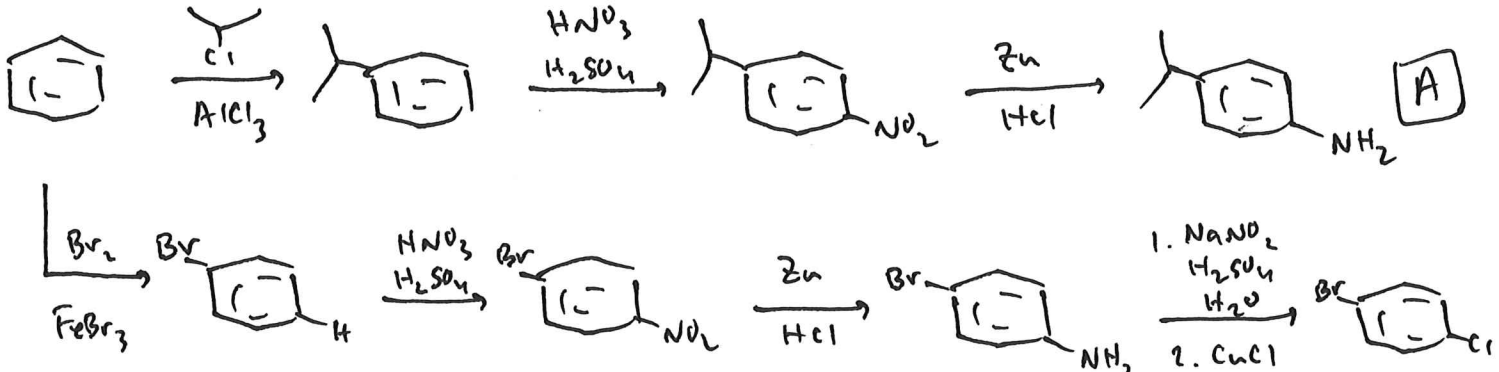
Let's do some synthesis using many different amine reactions.

Consider:

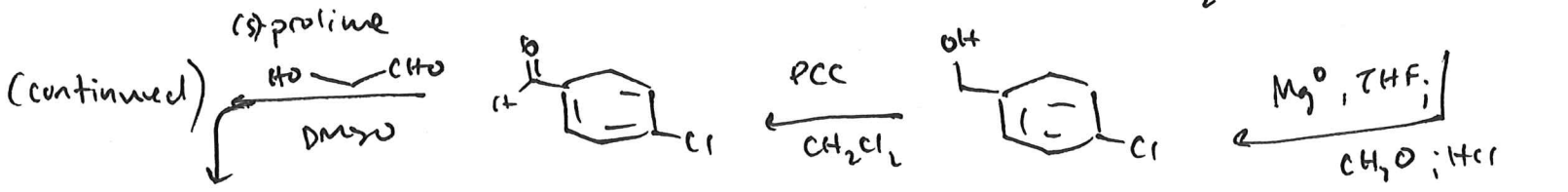


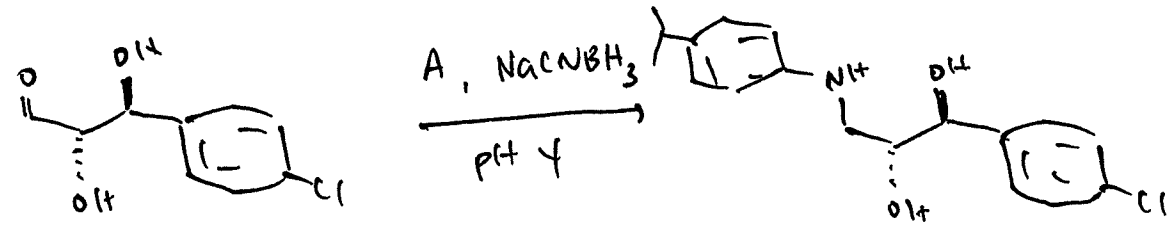


Forward synthesis:

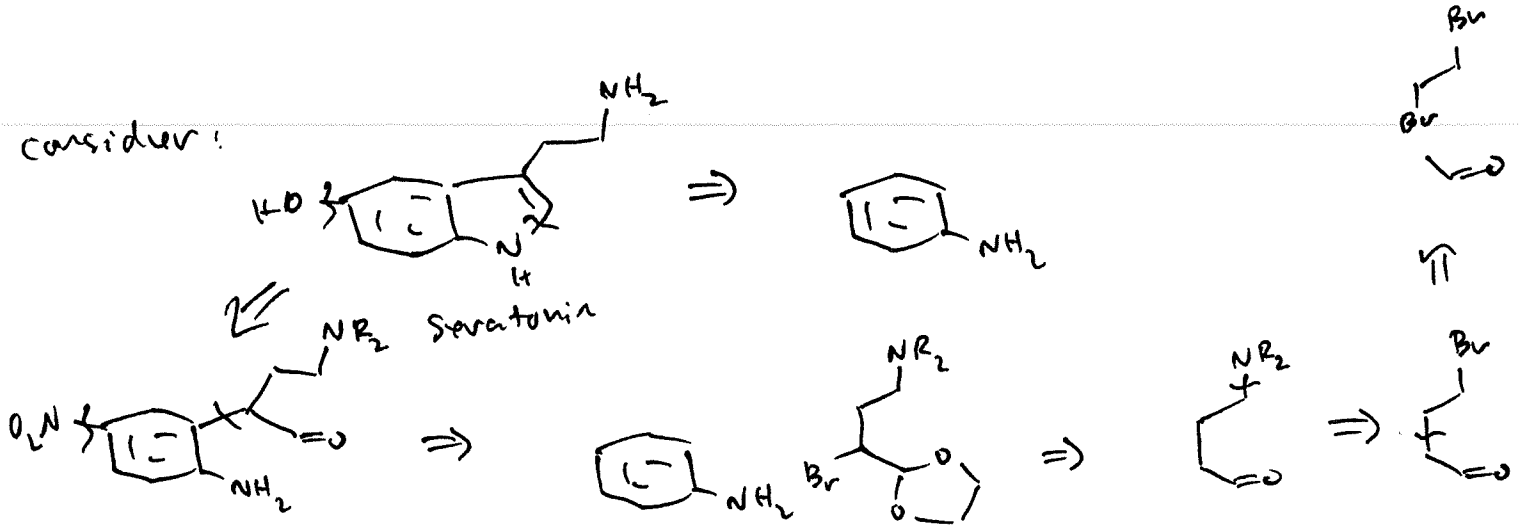


(continued)

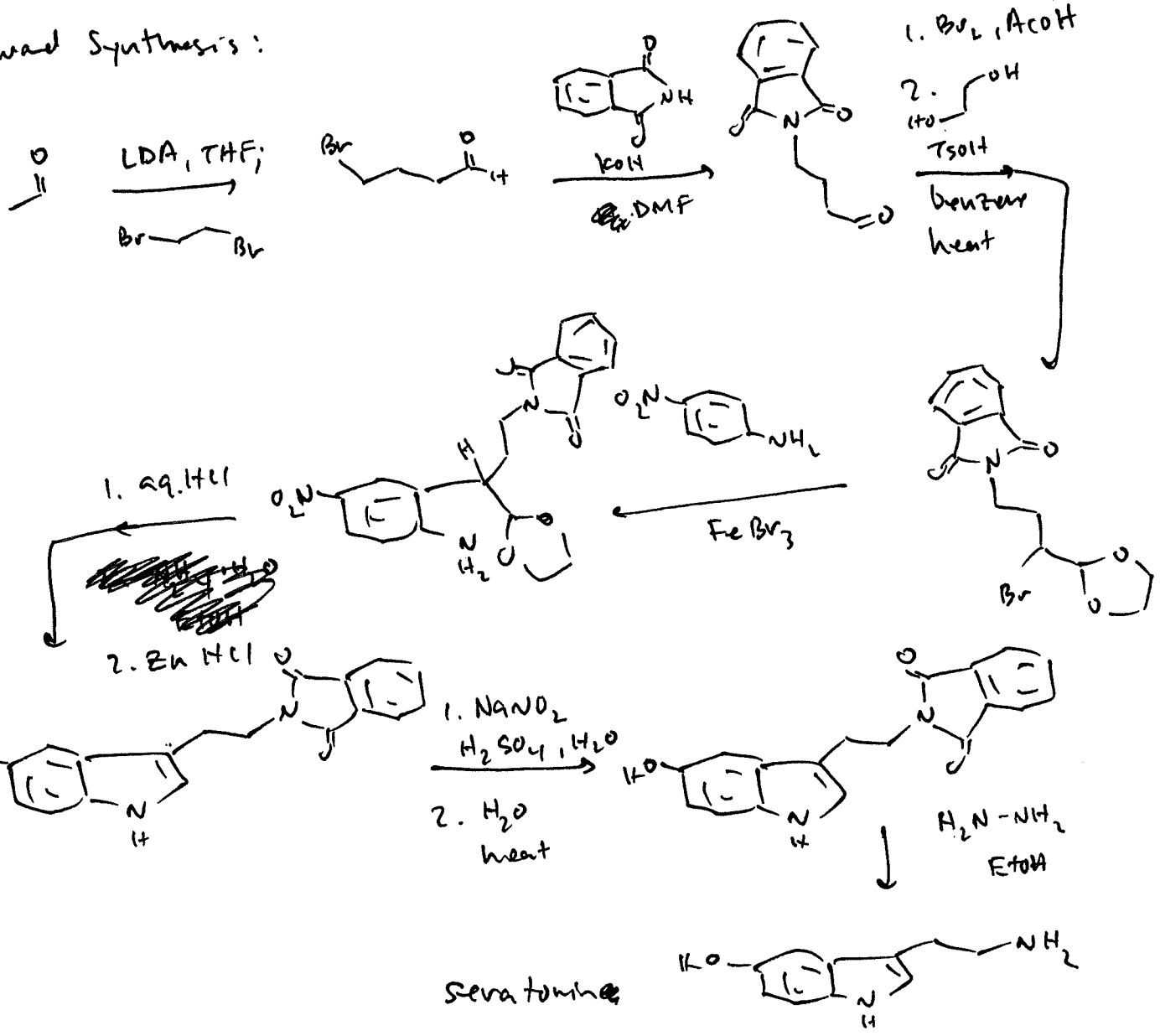




consider:

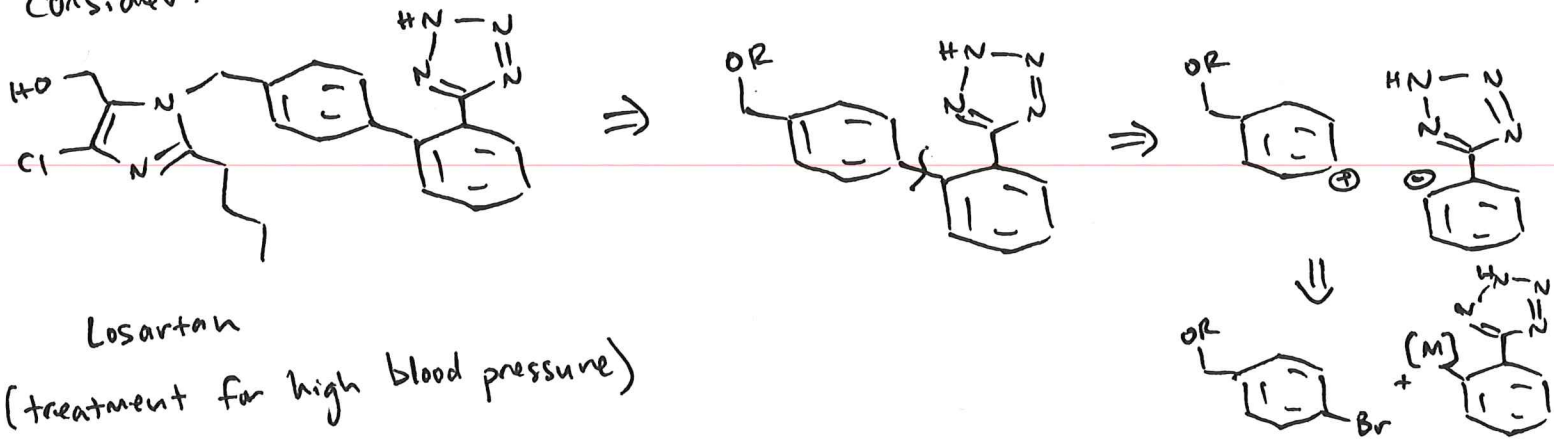


Forward Synthesis:



Cross-Coupling reactions (Nobel Prize, 2010)

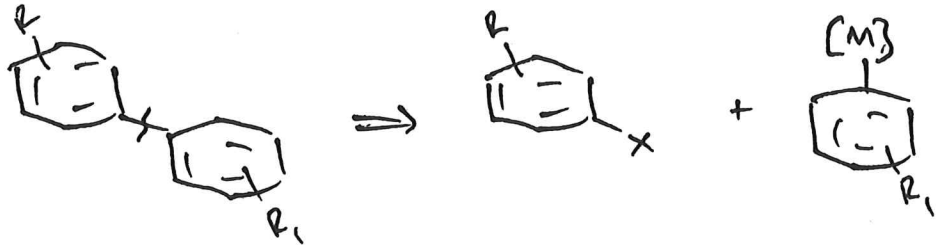
Consider:



Losartan
(treatment for high blood pressure)

Bromide + organo metallic.

If we generalize this, we can consider the following:



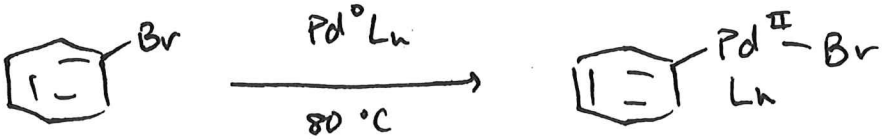
[M] = -MgX
= -ZnX
= -B(OH)$_2$
= -SnBu$_3$

But how can we just stick two aryl groups together like this?

We need a catalyst to do this!

recall:

Palladium can do the same thing! (and much more)



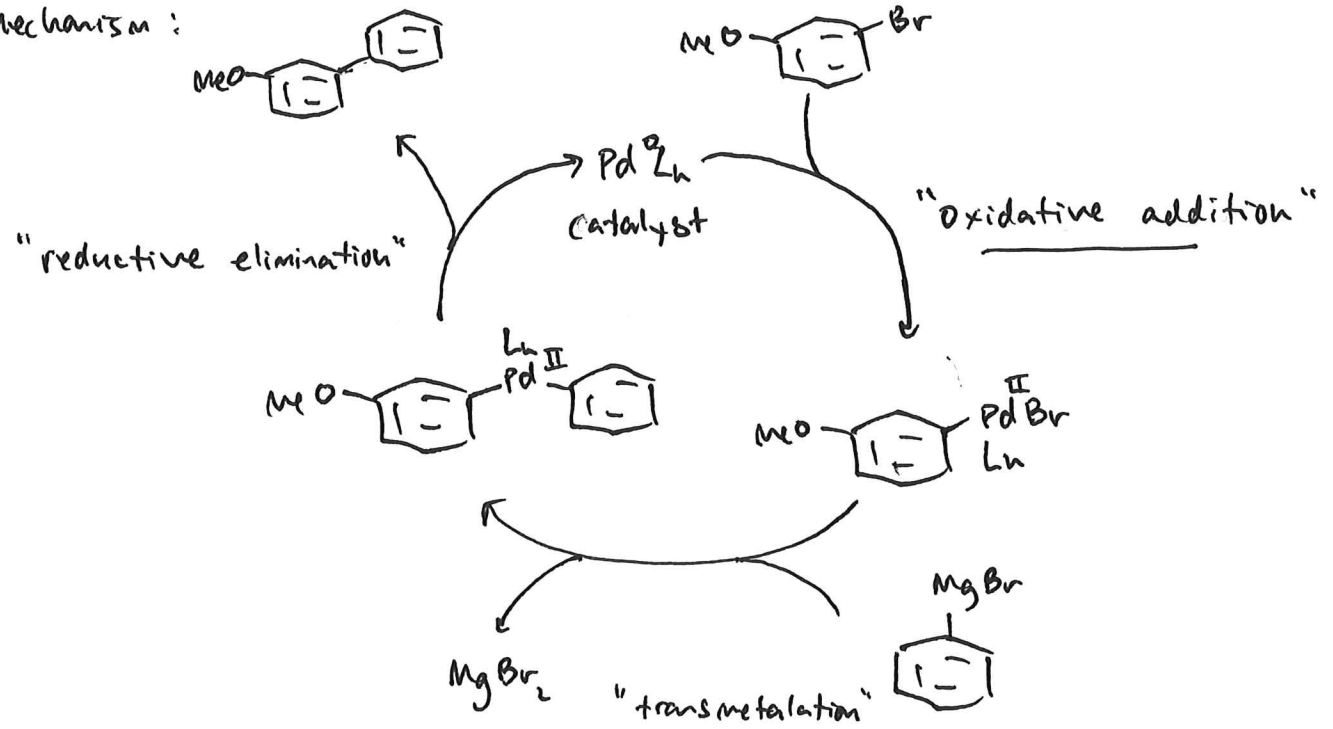
but, Pd is expensive, so how can it be catalytic?

Consider the following reaction:

!

This reaction is called a "Kumada coupling" how does this happen?

Mechanism:

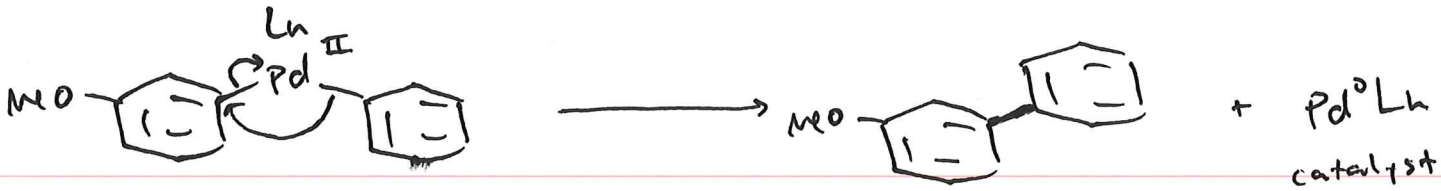


the transmetalation step is similar to reactions you've seen before:

"double replacement"

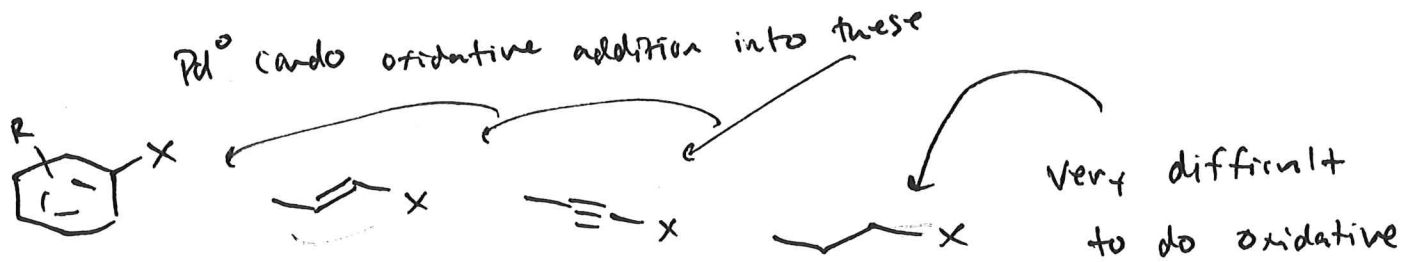
"transmetalation"

Reductive elimination is the main difference here:



electrons end up on Pd so it returns to Pd^0 from Pd^{II}

Limitations on oxidative addition:



rates of oxidative addition vary based on nature of X:

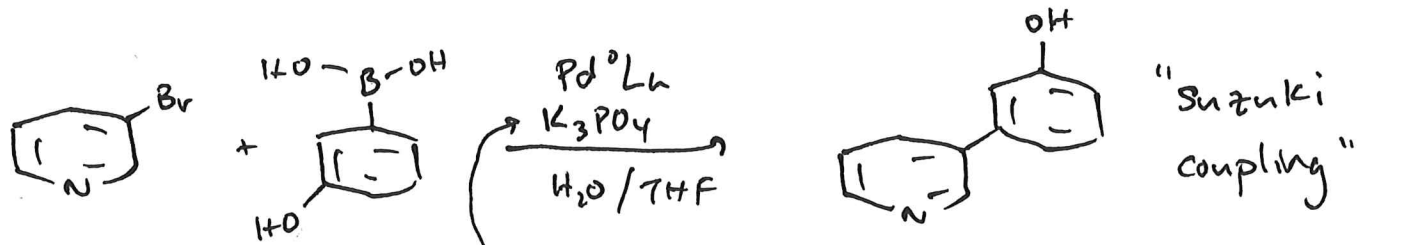
rate:

$$I > Br >> Cl$$

this because the weaker C–X bond is more susceptible to ox. add.

Nucleophile can be any hybridization!!

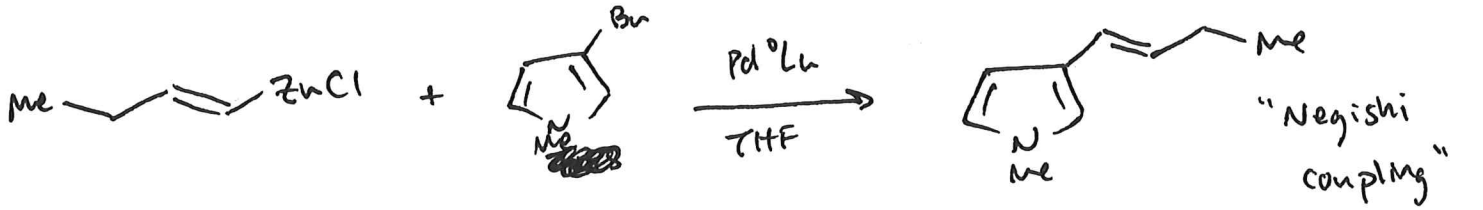
other related reactions to the Kumada coupling:

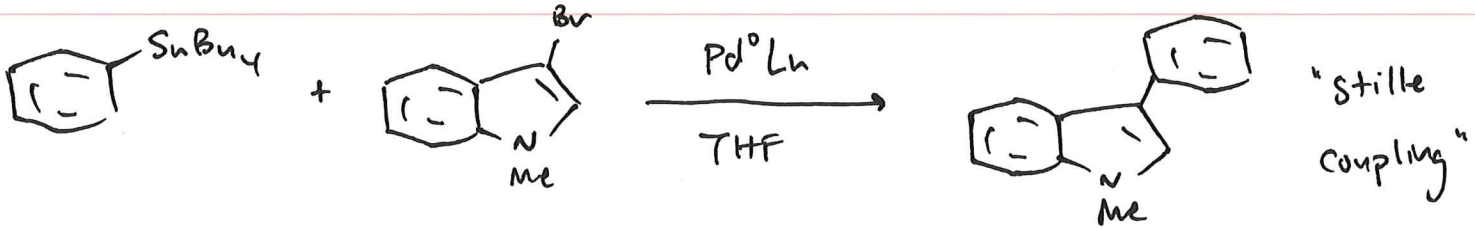


boronic acid

base needed to promote reaction.

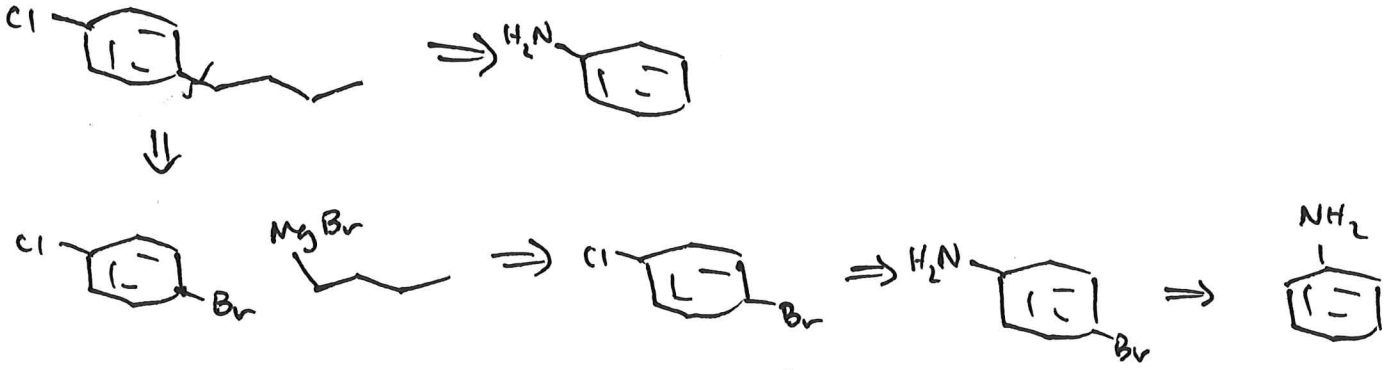
can be done in the presence of acidic hydrogens!



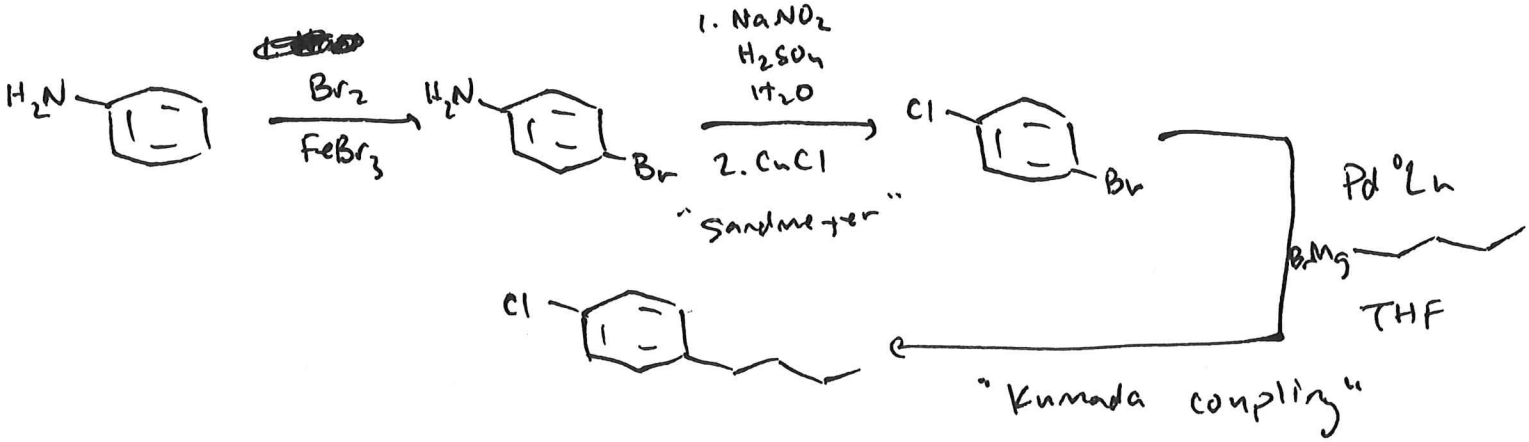


The mechanisms of these reactions are the same, with the exception of the transmetalation step being slightly different in that the metal changes in each example.

Consider the following:

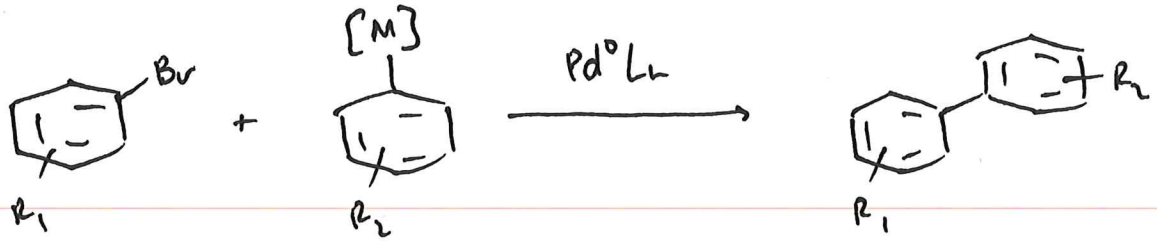


Forward synthesis:



The nucleophiles of cross-coupling reactions

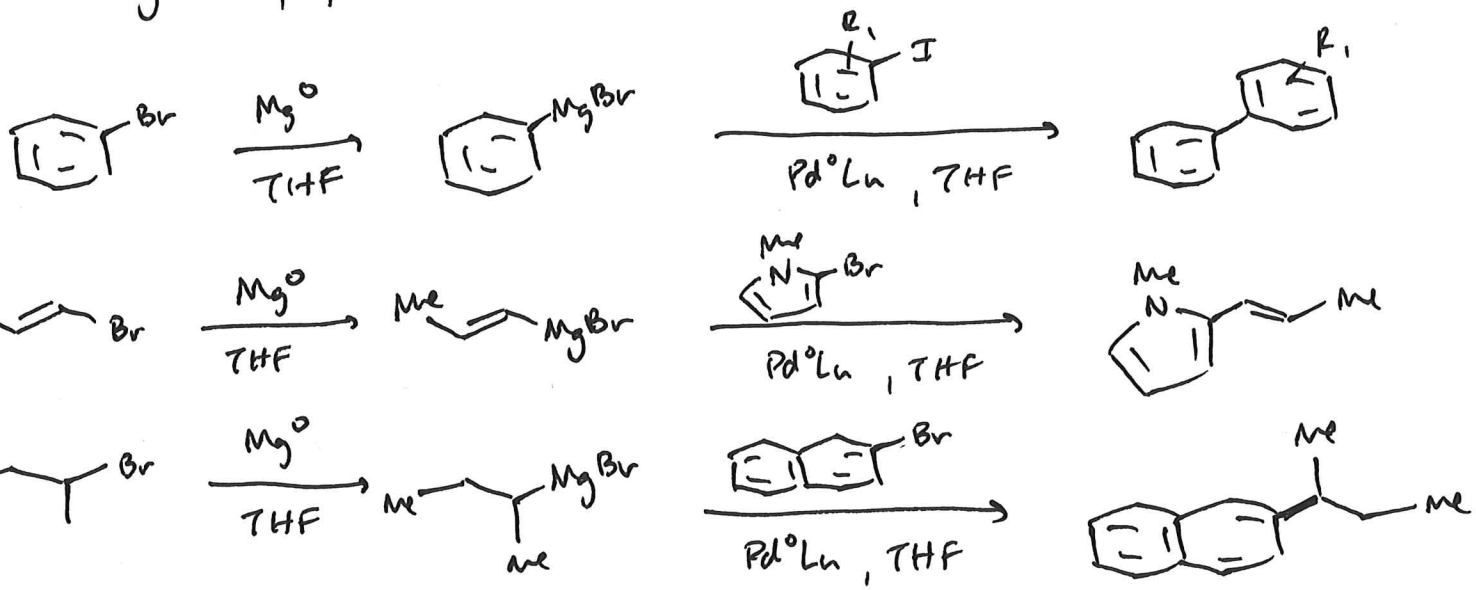
recall:



For these reactions: [M] can be MgX, ZnX, $B(OR)_2$, SnR_3

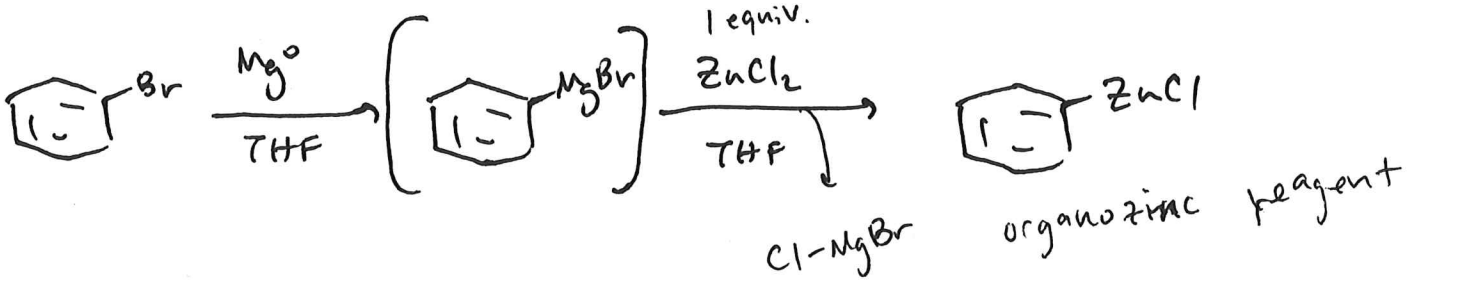
In order to use these reactions effectively, one must know how to synthesize each of these nucleophiles.

For Grignards, you already know!

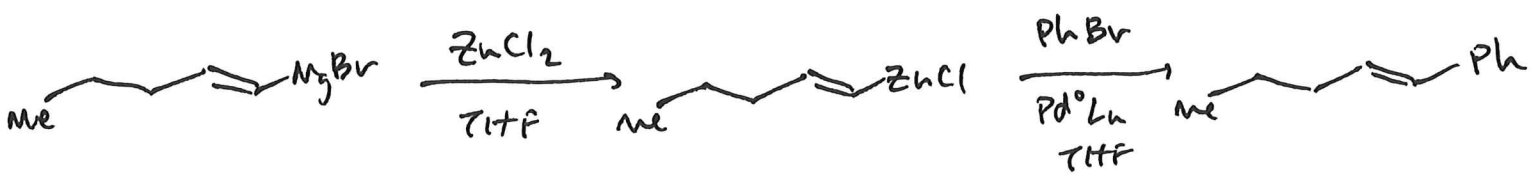


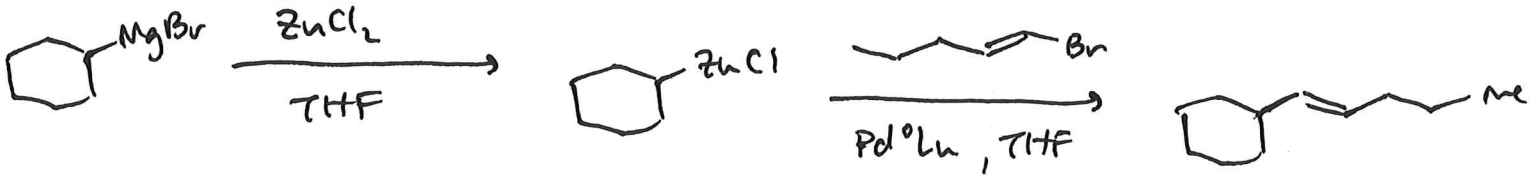
All of these are Kumada couplings.

For Zn reagents, a simple transmetalation is needed!

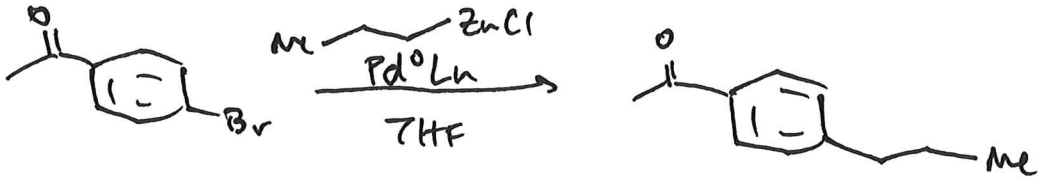


This can work for other grignard reagents as well:

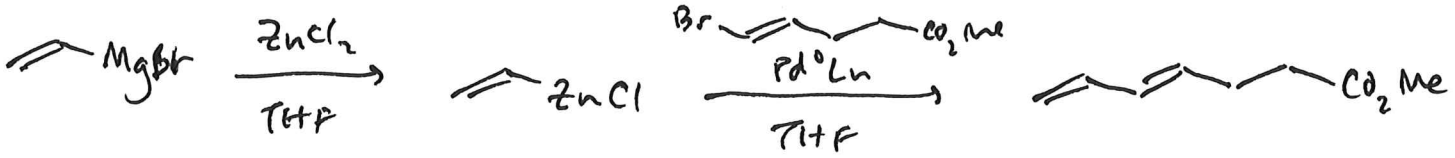




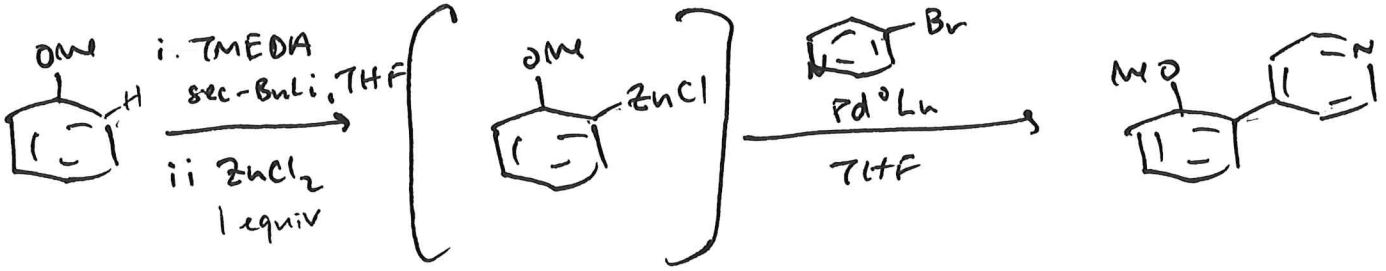
The advantage of doing Negishi couplings over Kumada couplings is that carbonyl species are tolerated.



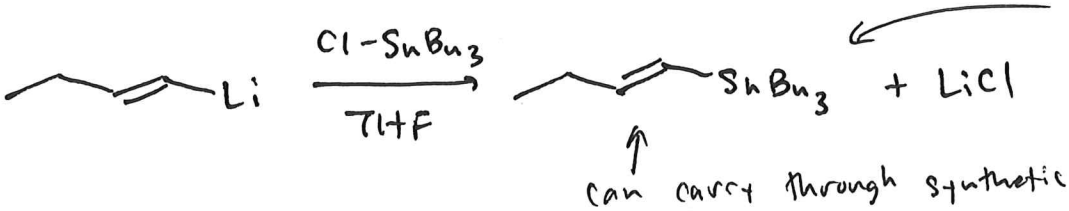
using the Grignard would have selectivity issues with ketone

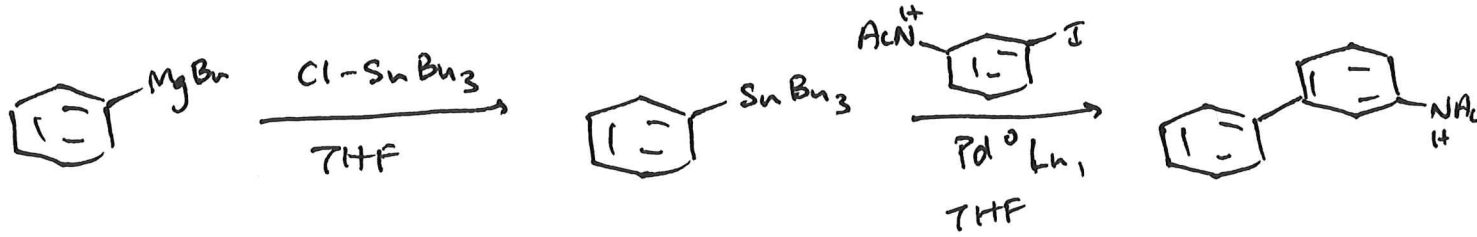


Organozinc reagents can also be synthesized from lithiates



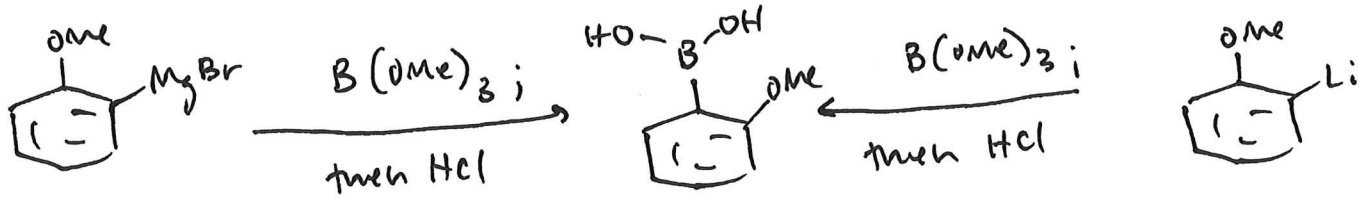
organotin reagents are also typically made from Grignard reagents and organolithium reagents.





Stille couplings can tolerate acidic hydrogens in molecule. This is the advantage of using these couplings. Also tolerates carbonyls.

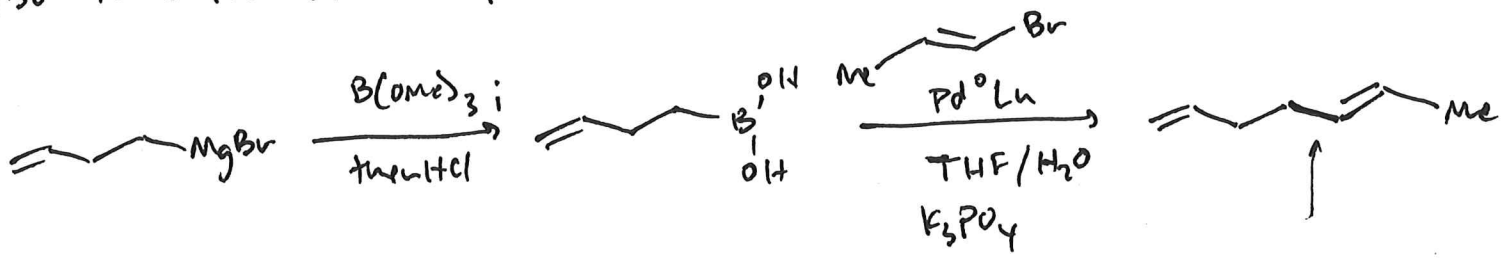
Synthesis of Boron nucleophiles for Suzuki couplings



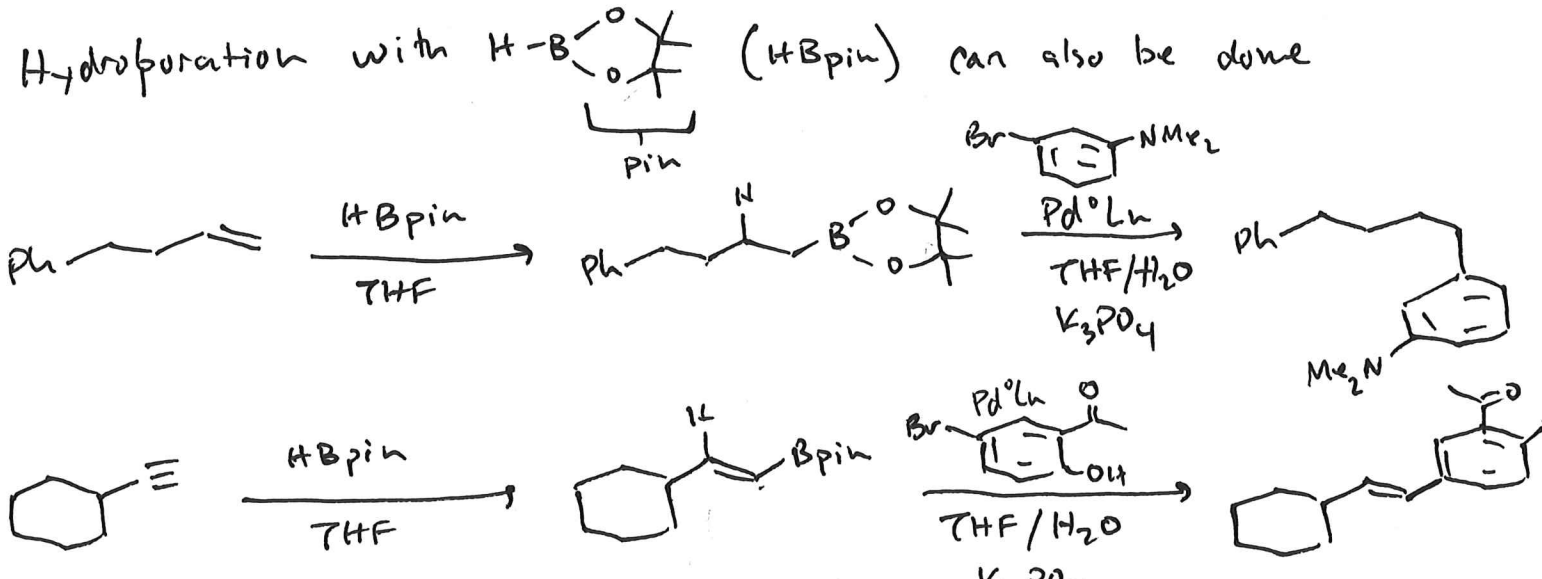
From Grignard reagents

From organolithiums

Also true for other hybridizations (sp^3)



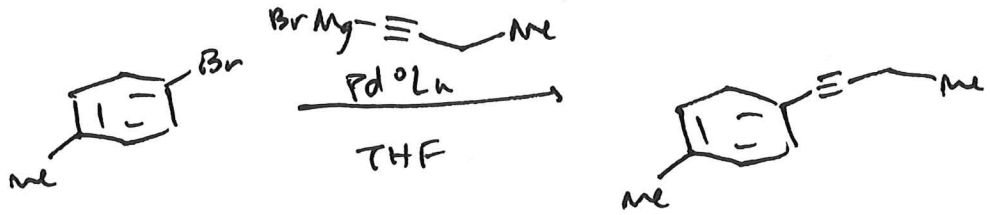
Hydroboration with H-B(pin) (HBpin) can also be done



tolerates carbonyls and acidic hydrogens!

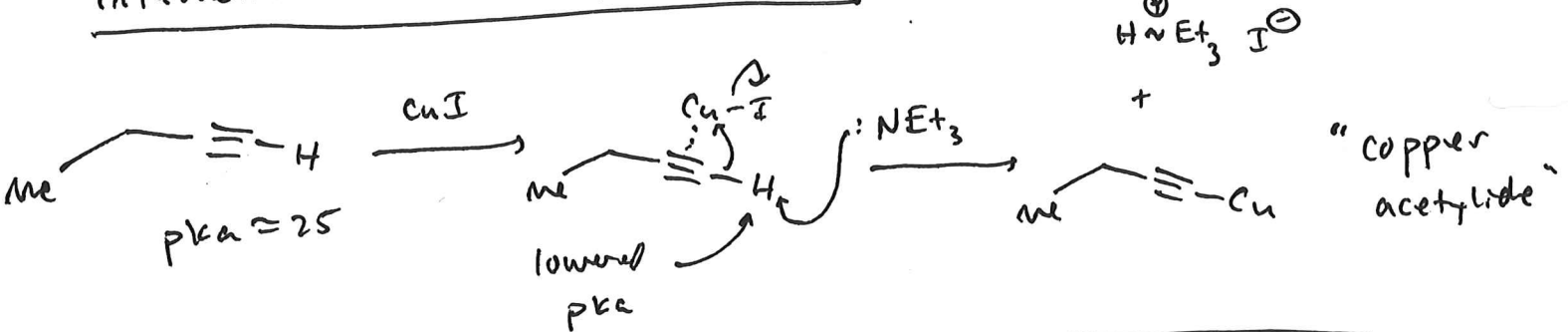
Alkyne Nucleophiles – the Sonagashira coupling

consider!



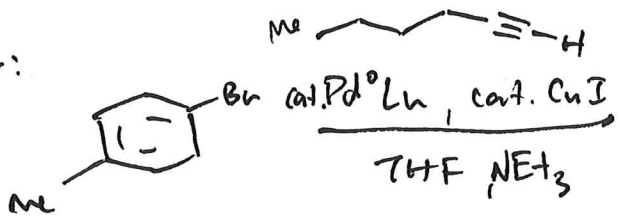
what if we didn't have to make the alkynyl Grignard? increased tolerance? operationally more simple?

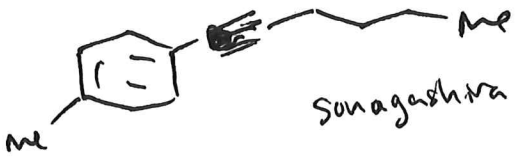
interaction between alkynes and Cu



what if you could merge this with the Pd° cycle?

consider:

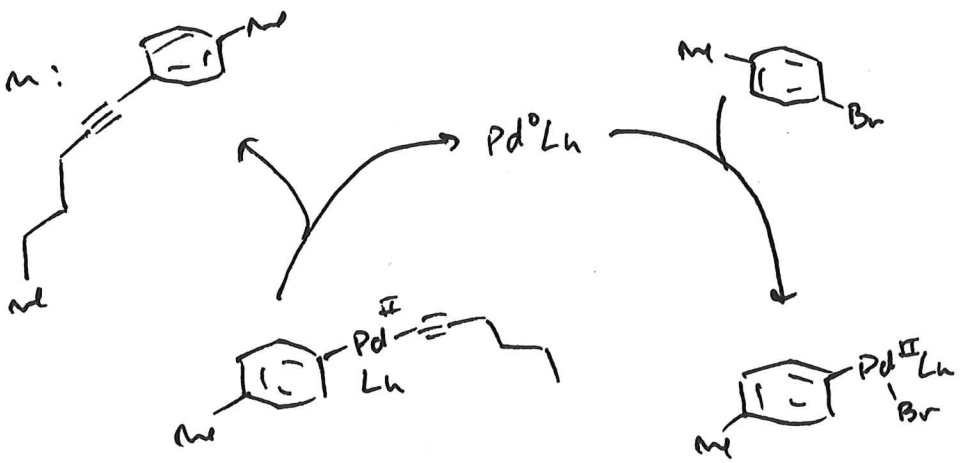




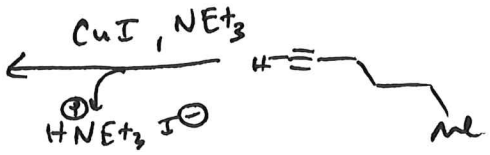
Sonagashira product

two catalysts working together!

mechanism:

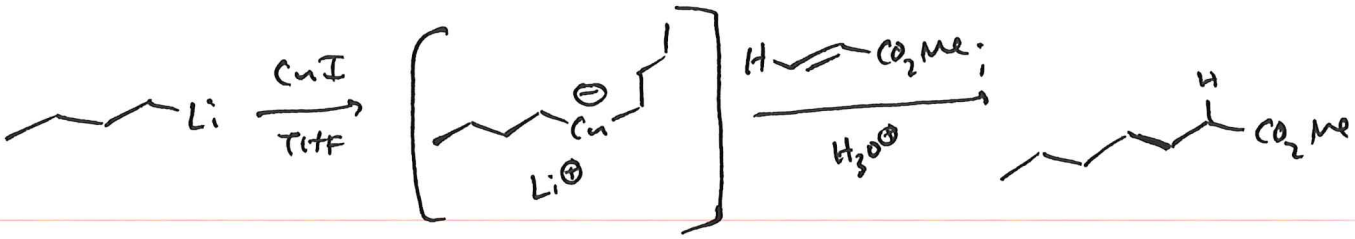


then reacts with another alkyne!



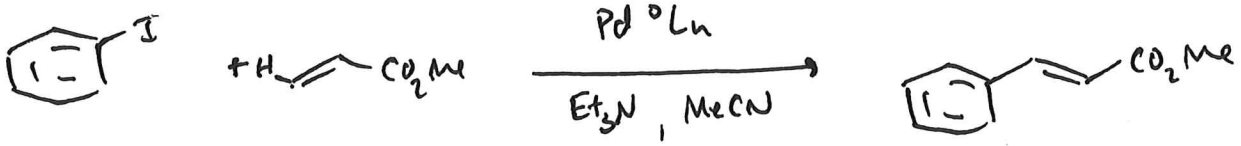
The Heck Reaction

recall:



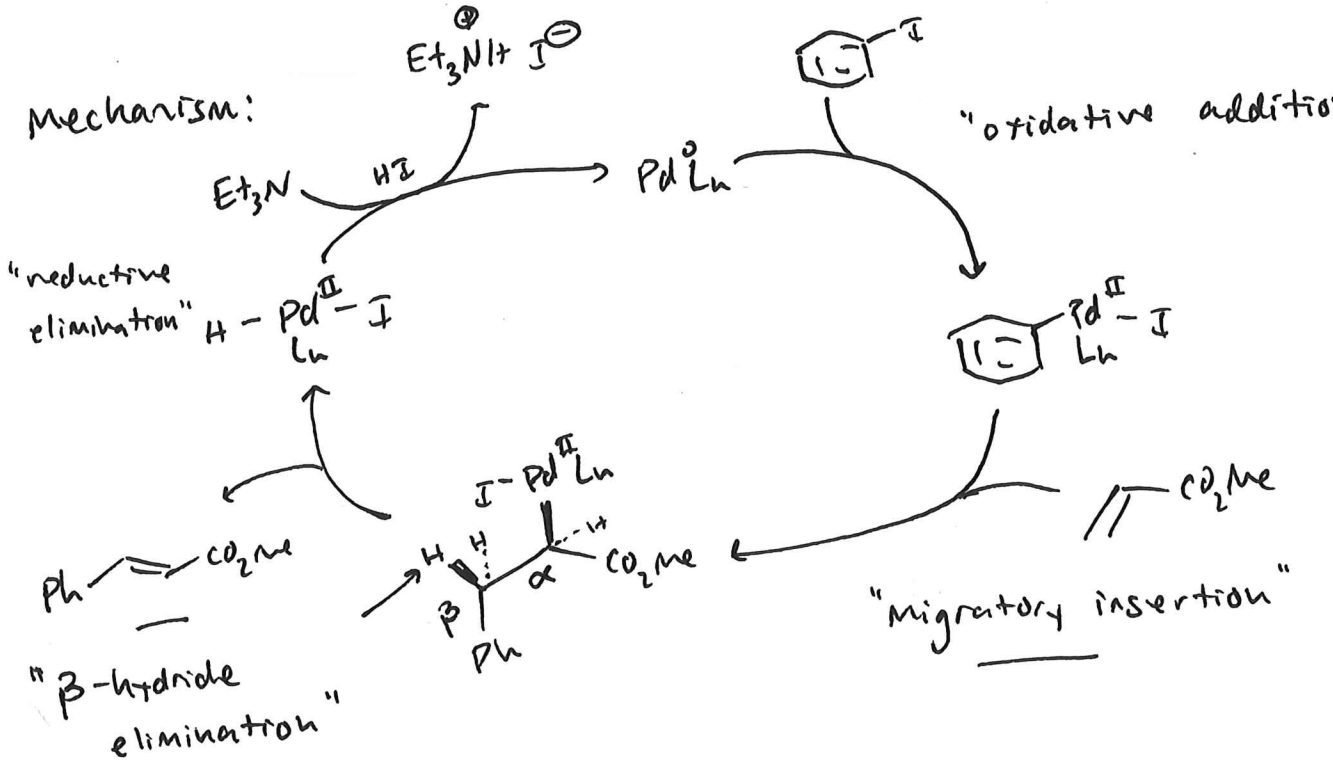
Consider making a similar type of bond, but then having the alkene of the α,β-unsaturated ester restored. How?

Consider:



what is happening here?! we just replaced a C-H bond with Ph!

Mechanism:

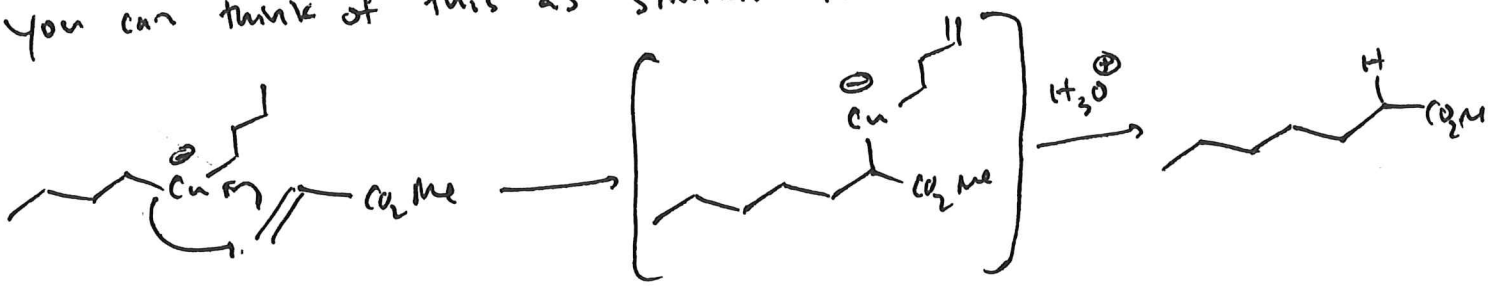


Let's take a closer look at these these two new mechanistic steps of the Heck reaction:

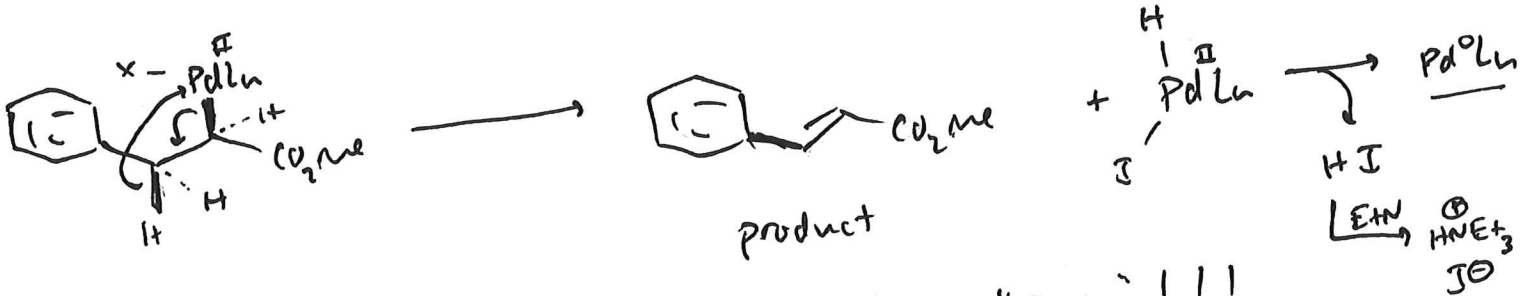
Migratory insertion.

"ox. add. intermediate" "coordination"

You can think of this as similar to the Cu reaction:



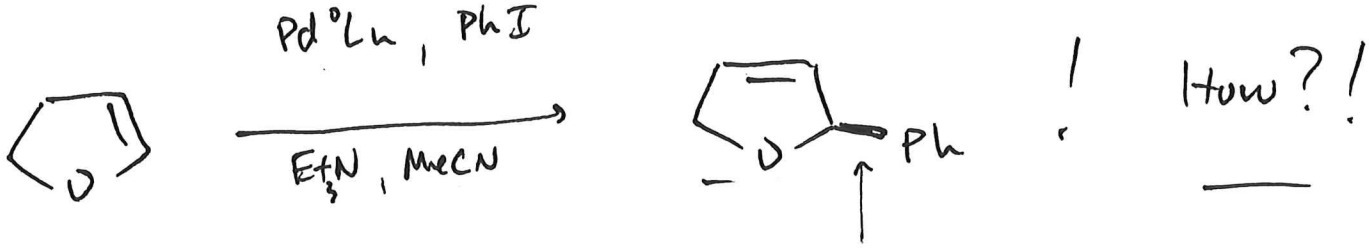
β-hydride elimination



product

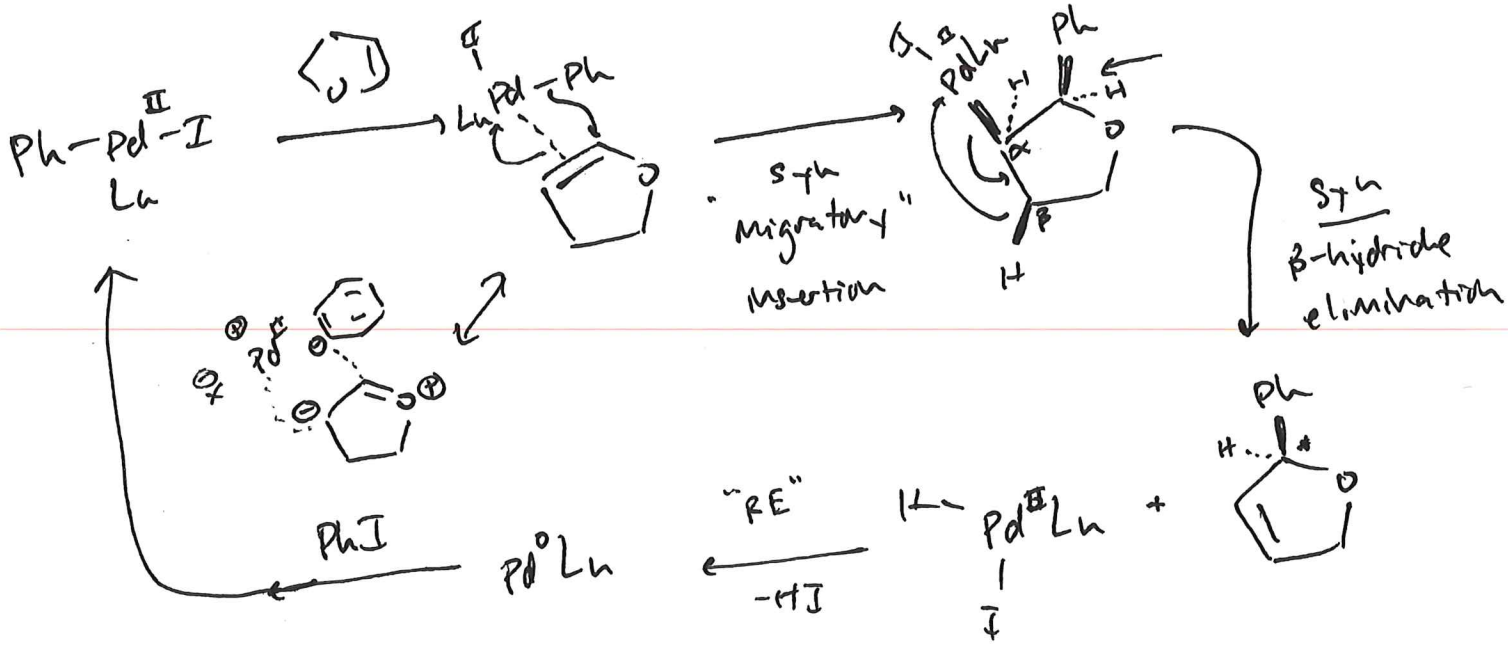
Hydride and Palladium catalyst must be "syn"!!!

Consider:



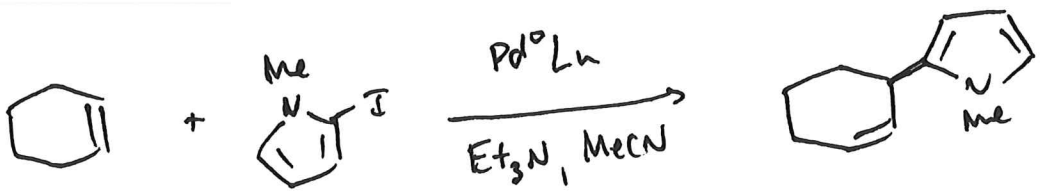
! How?!

consider the mechanism following oxidative addition...

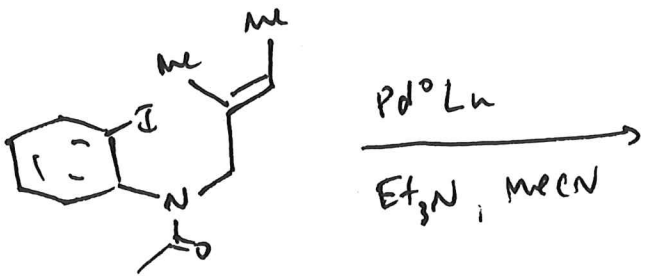


The nature of the syn Migratory insertion and the syn β-hydride elimination is very evident in cyclic systems.

Consider the following scenarios:

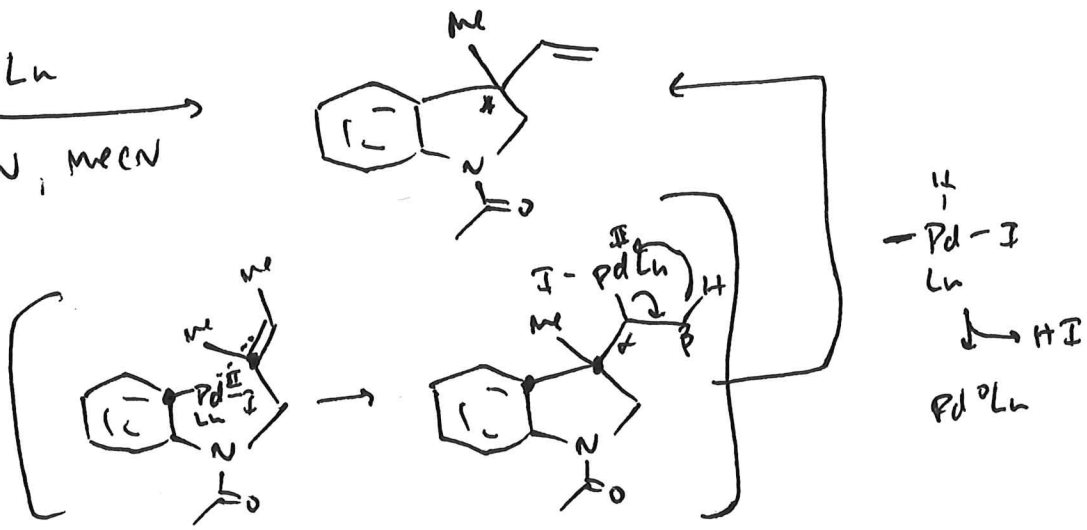


notice how the alkene is in a different spot.

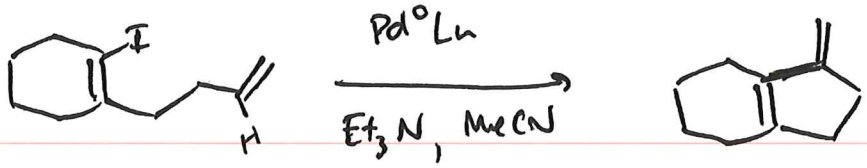


Kinetically, 5 membered rings form faster than 6

Via:

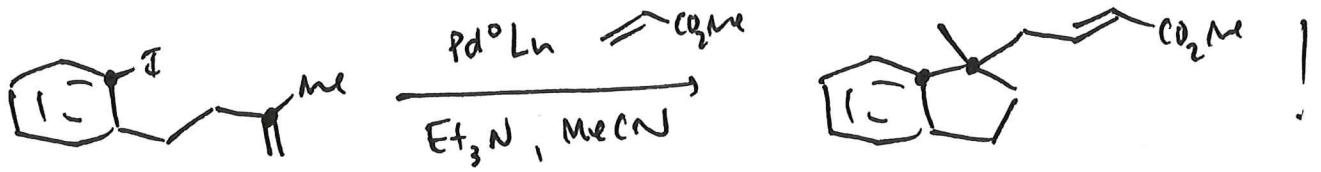


alkenyl halides are also operable:



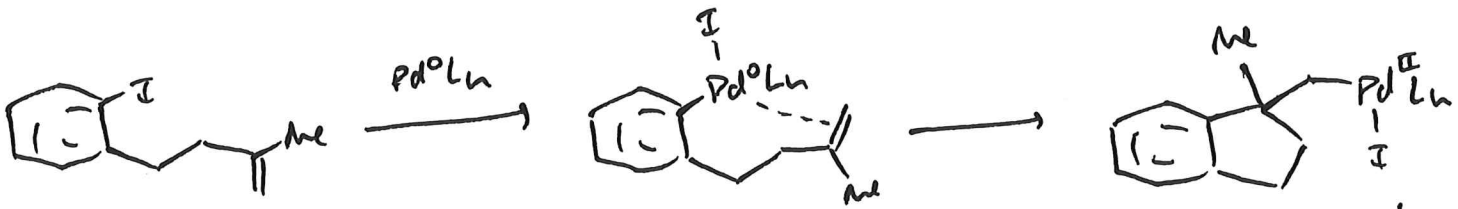
Try writing a mechanism for this reaction.

Intramolecular migratory insertions will occur before intermolecular migratory insertions.

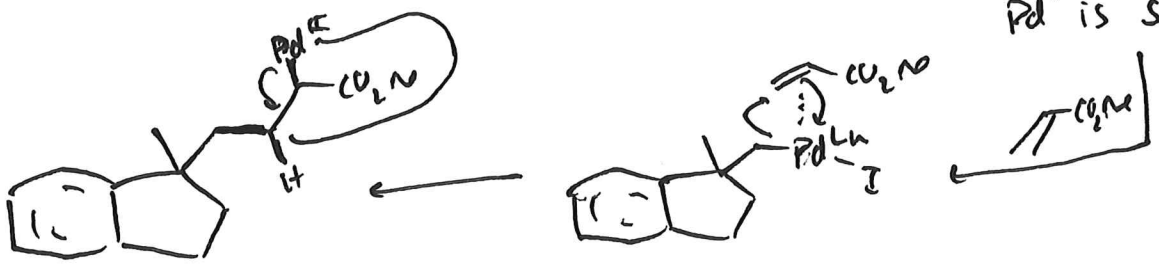


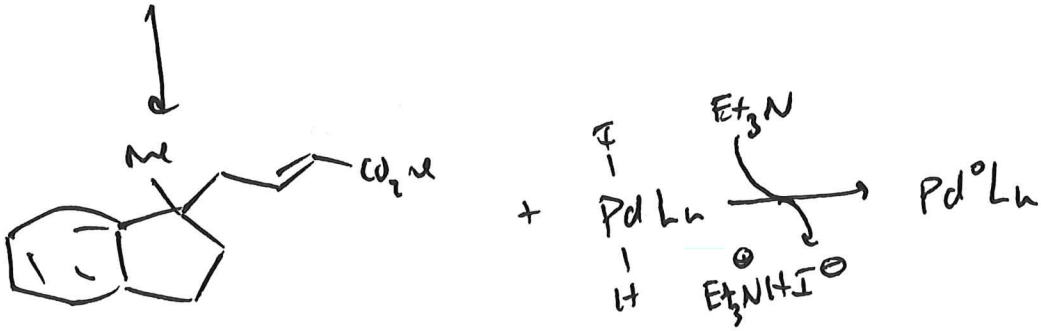
!

How?



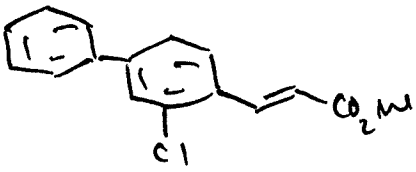
No β-hydride!
Pd^{II} is stuck!



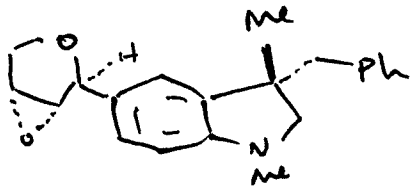


Cross-coupling in synthesis

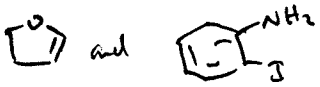
Today we will do retrosynthesis and forward synthesis of several targets. The three targets are depicted below.

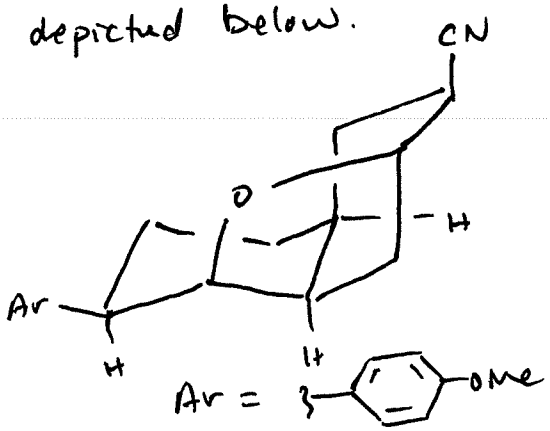


from benzene



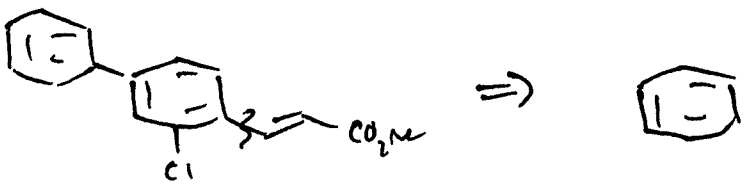
from benzene and

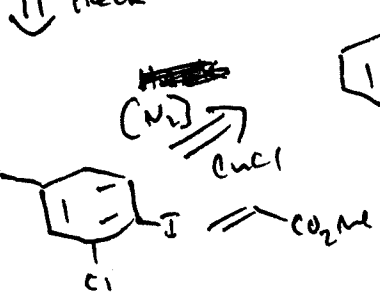


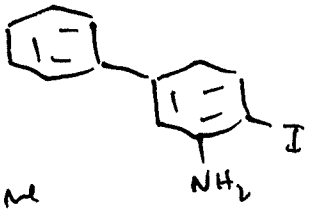


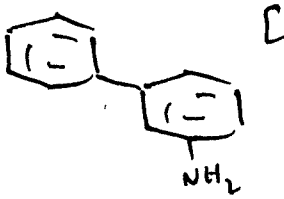
from anisole

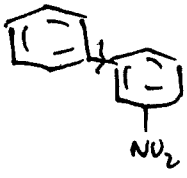
let's consider the first target:

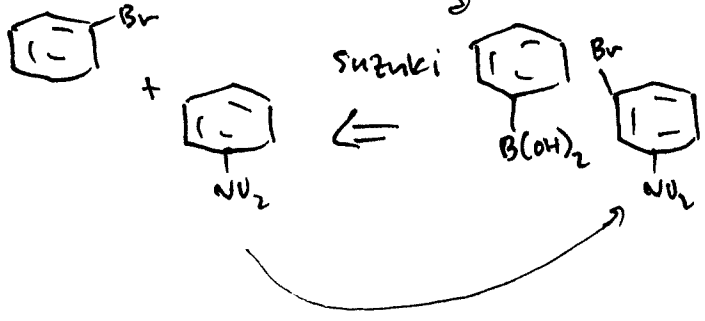






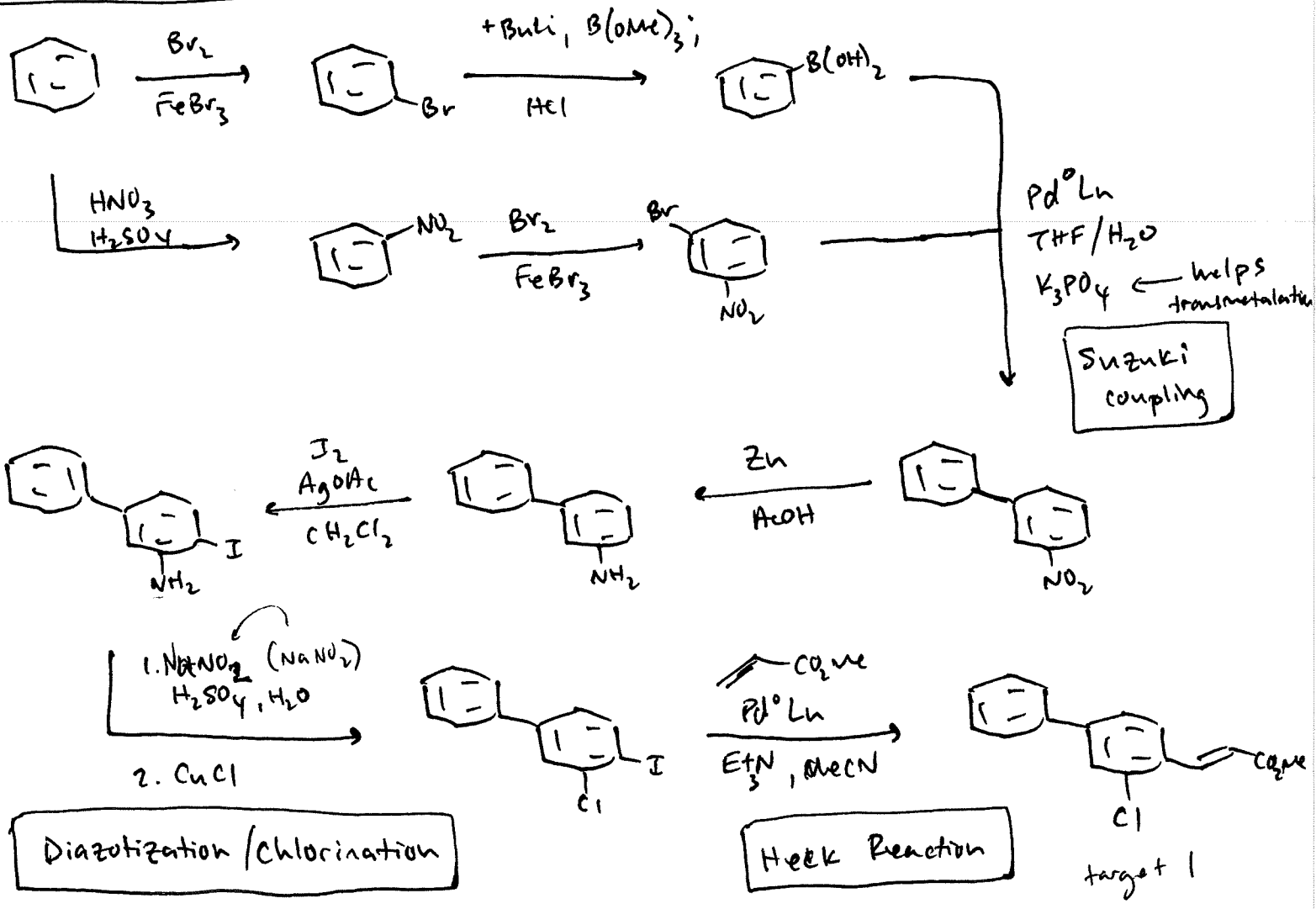




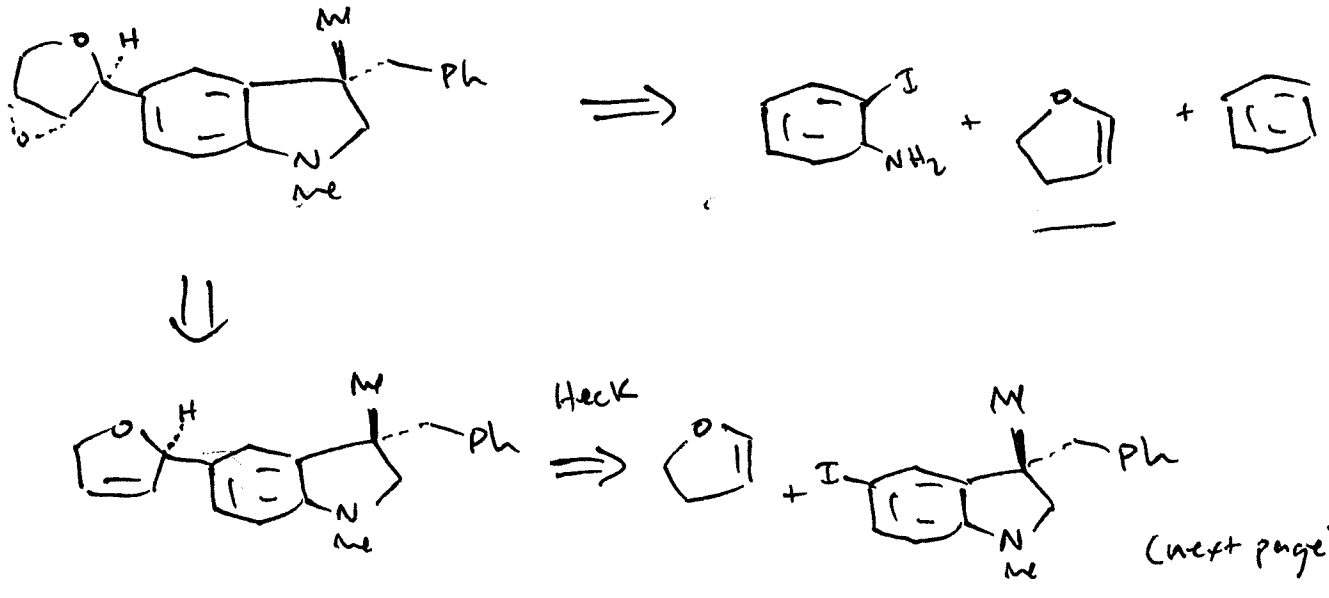


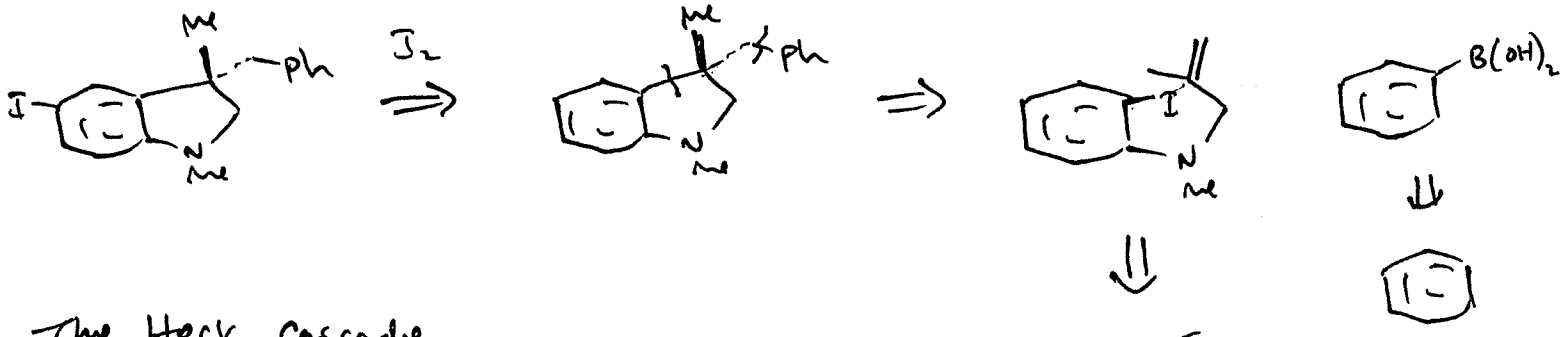
This disconnections here are reasonably straightforward, the challenge is finding the chemoselectivity in the synthetic equivents.

Forward Synthesis !



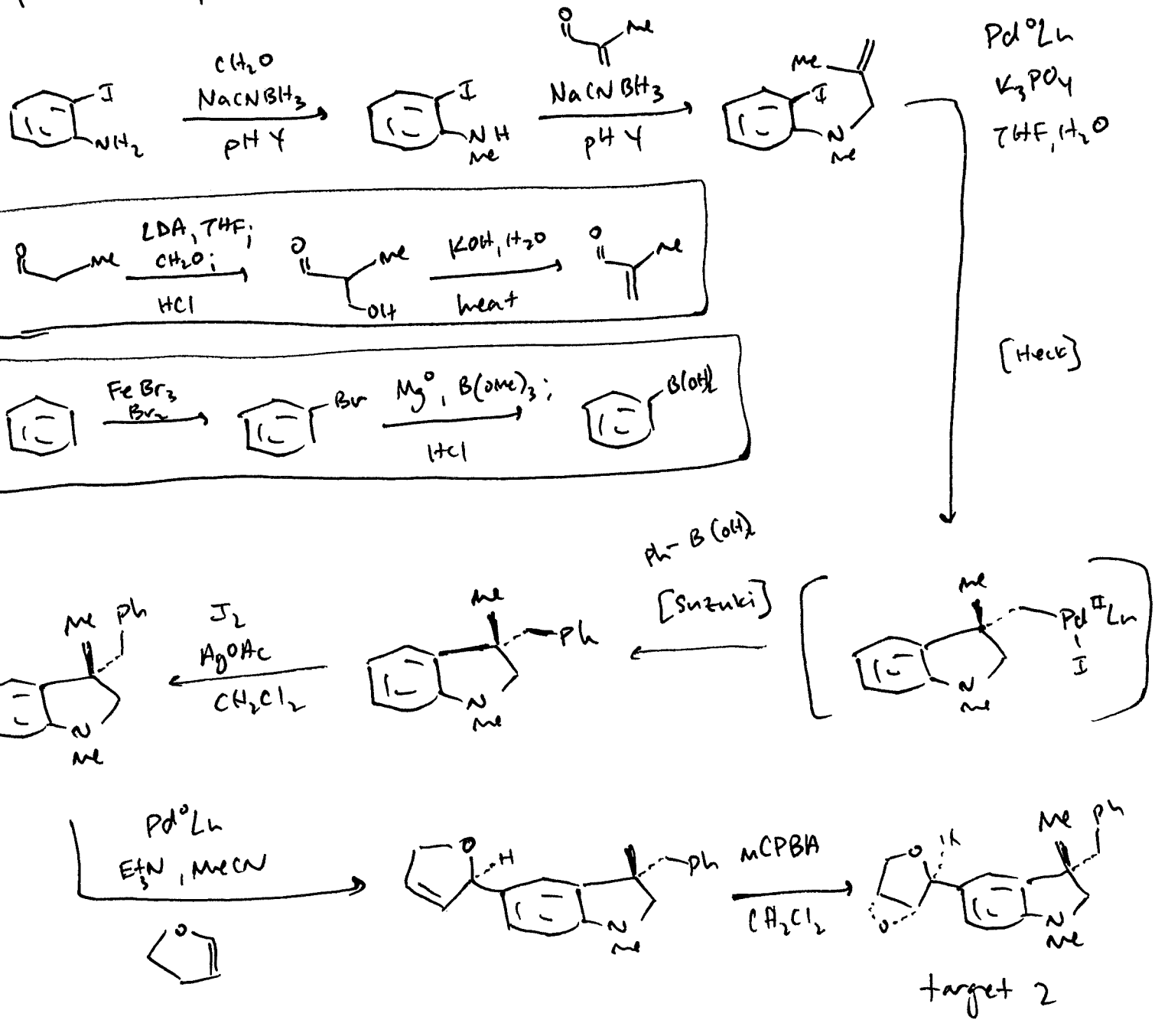
Now, let's consider ~~the~~ second target:





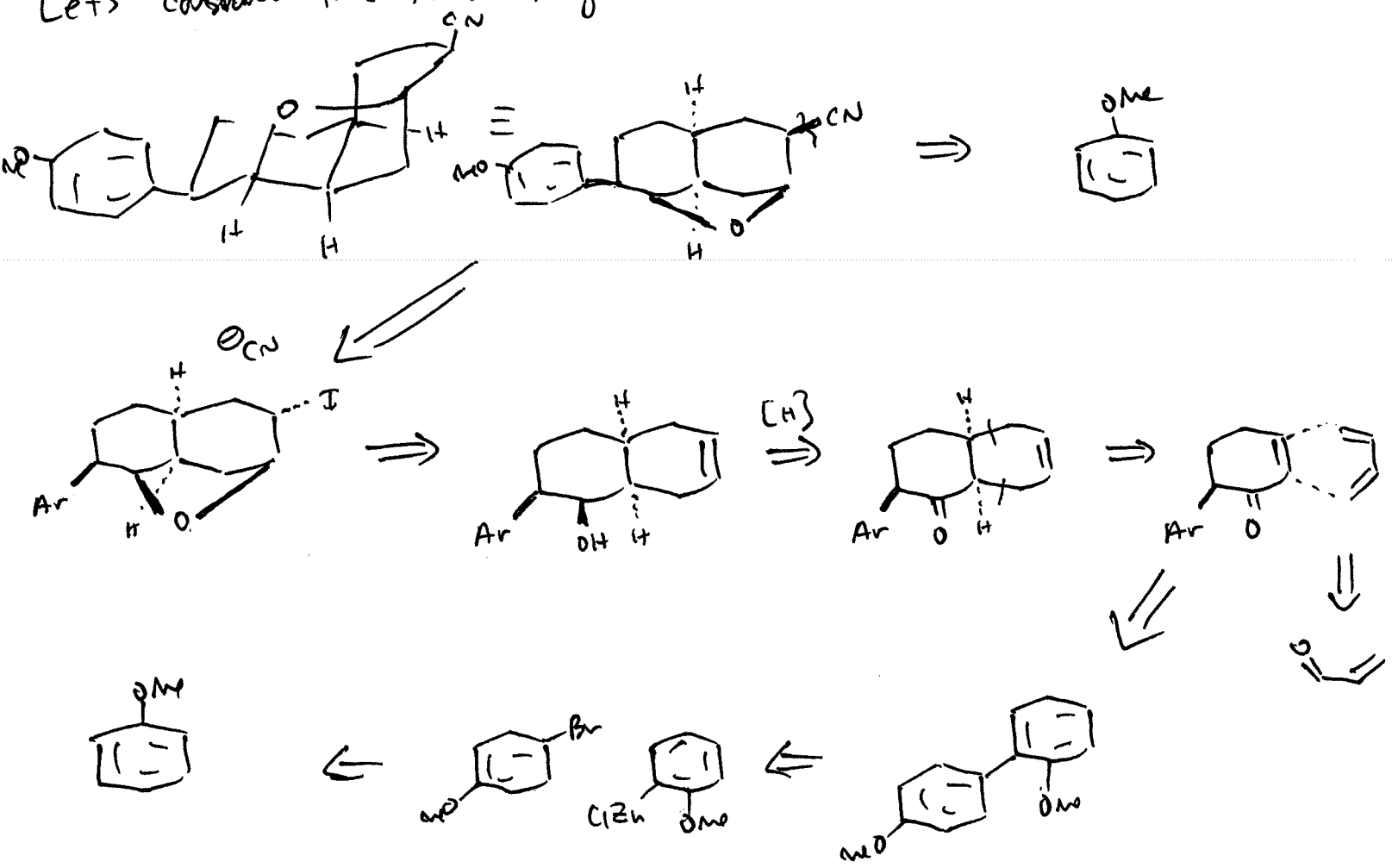
The Heck Cascade is the key to building the right side of the molecule.

Forward Synthesis:



target 2

Let's consider the final target:



Forward Synthesis: