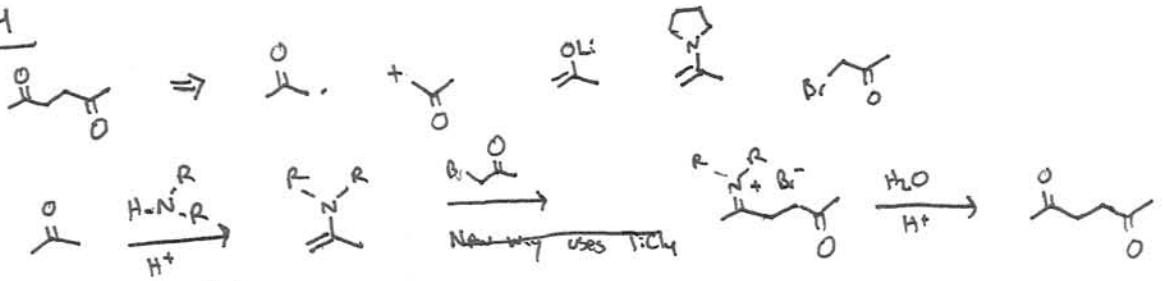
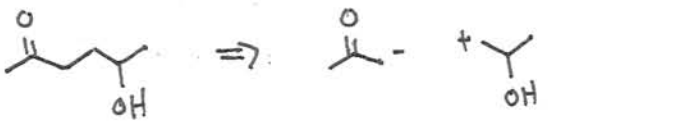
1/10

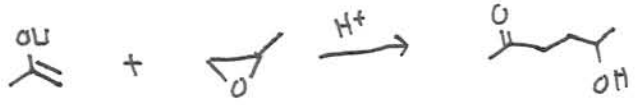
1,4



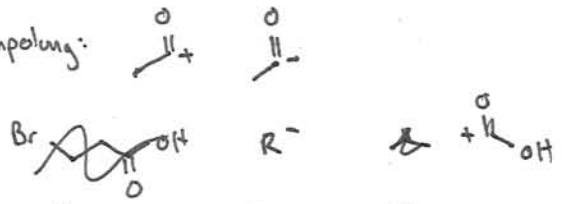
Dean Stark

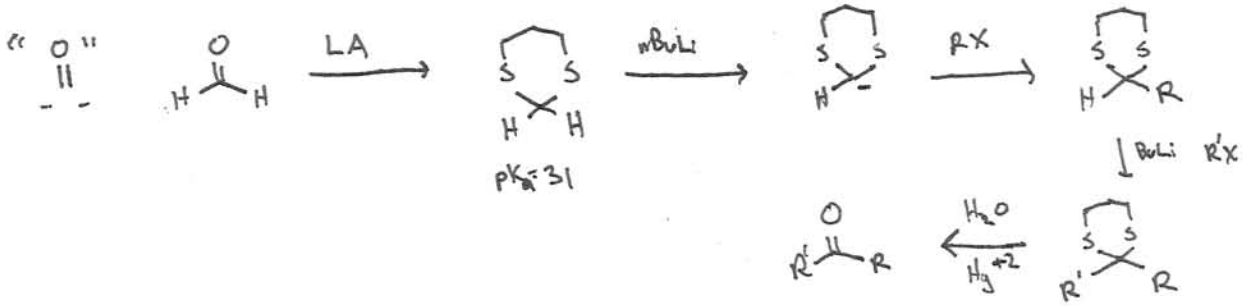
New way uses TiCl4



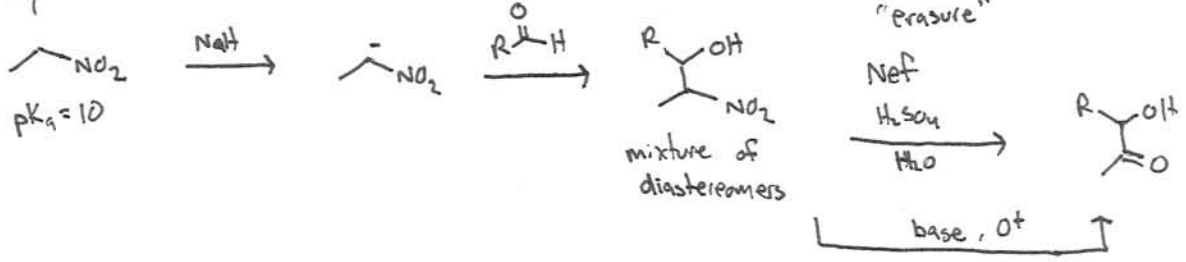


Umpolung:

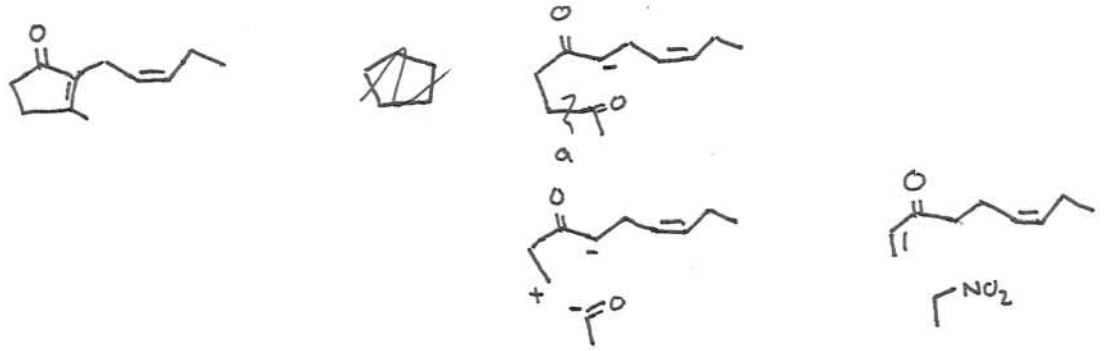




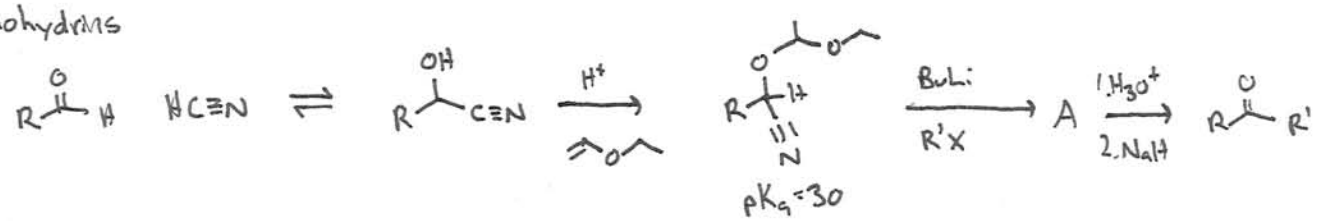
Henry

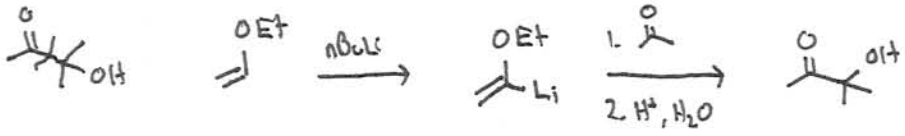


Example : Jasmone

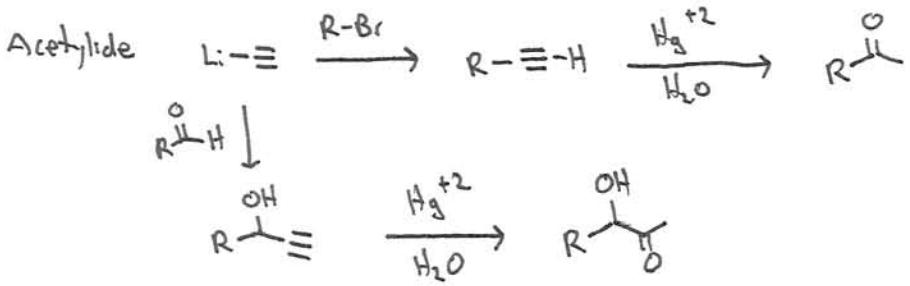


Cyanohydrins





Acetylide



Plan a synthesis : 1. C-C bond formation

- Organometallic Chemistry
- CN^-, enolate
- Dieckman, Claisen Cond., Aldol, Michael, Friedel Crafts, Wittig, HEW, Diels Alder, RCM

1) Choose reliable disconnections

2) # of disconnections

3) Near FG

4) Break branching points

5) Use preferred

6) Recognize FGI

7) Look of symmetry

8) Activating groups
last resort

9) Break alkenes

10) Do not carry mixtures forward

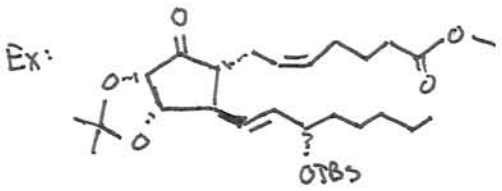
Key rxn: 1,2 addition, 1,3 addition, SN2, Aldol, Claisen, Michael

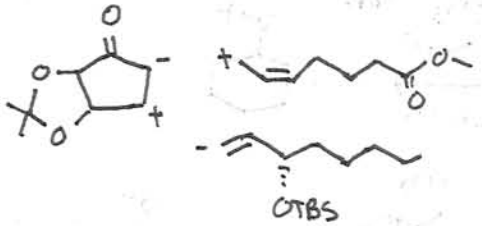
Table 1.4

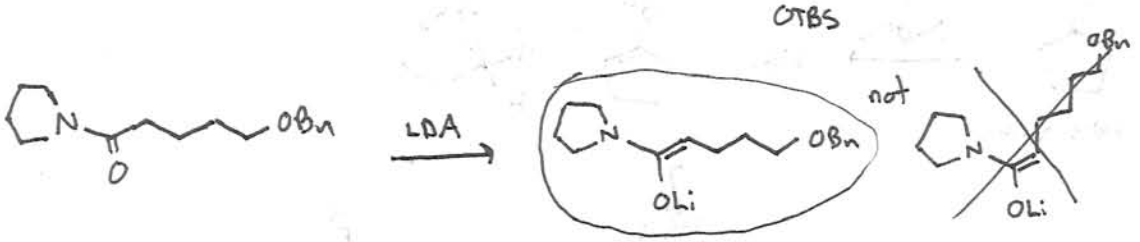
Stereospecific Stereoselective

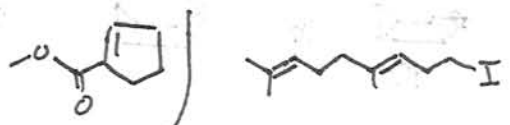
SN2, Alkyne reduction, dihydroxylation, epoxidation, enolate chem, cyclopropanation

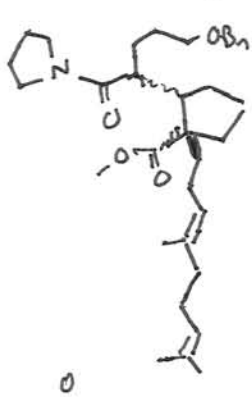
Ex:

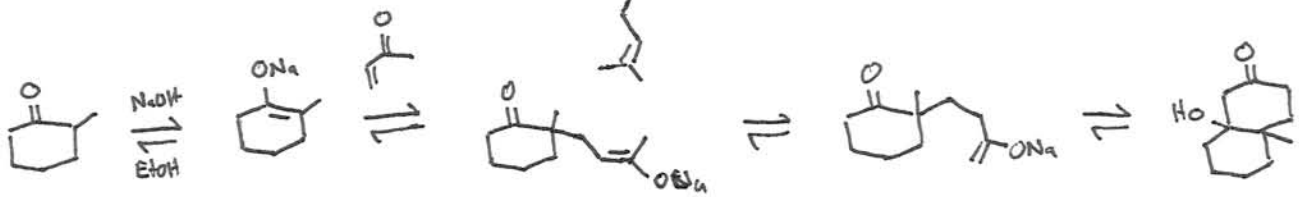




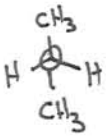








Stereochemistry



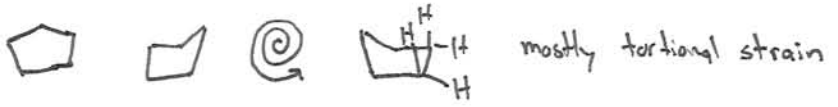
most stable form

eclipsed 5.4 kcal

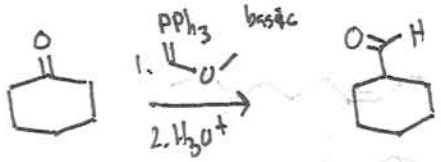
gauche .9 kcal

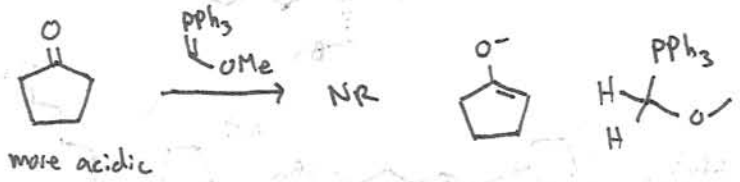
2.1 kcal difference isolable distinct compound

Δ torsional strain

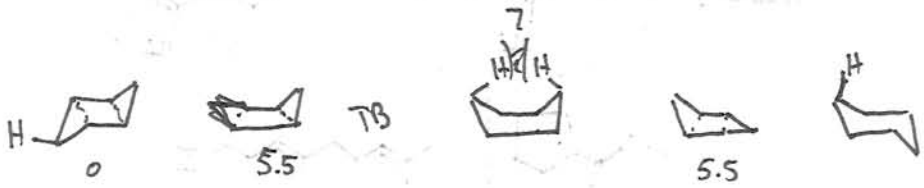


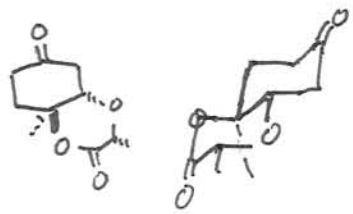
pseudo rotation
(rotating coin)

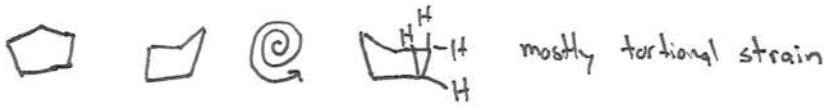




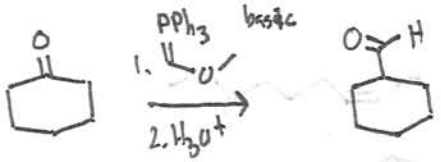
more acidic

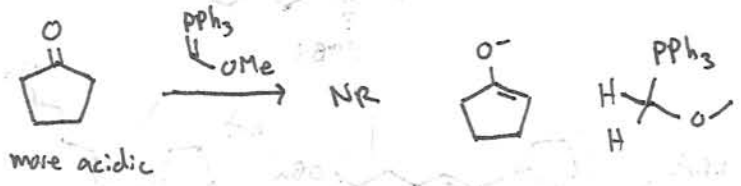


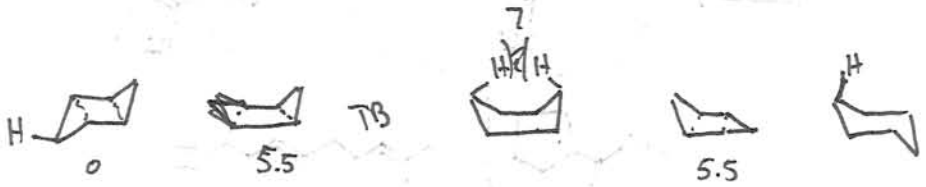


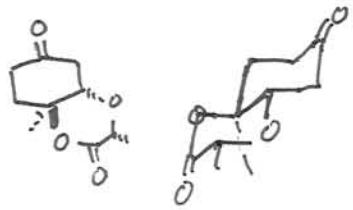


pseudo rotation
(rotating coin)



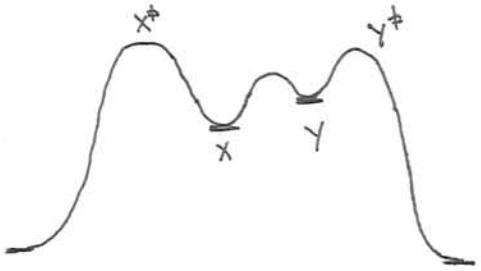






1/15

Curtin Hammond Principle

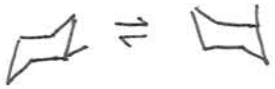


1) conf. energy of SM and TS energies are unrelated

2) However $\Delta G^{\ddagger_X} \neq \Delta G^{\ddagger_Y}$

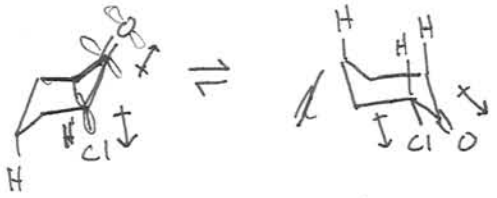
3) $\Delta G^{\circ} \approx \Delta G^{\ddagger}$

Then conformer energy reflect product distribution



CH_3 = 1.73 kcals
1.8 kcals

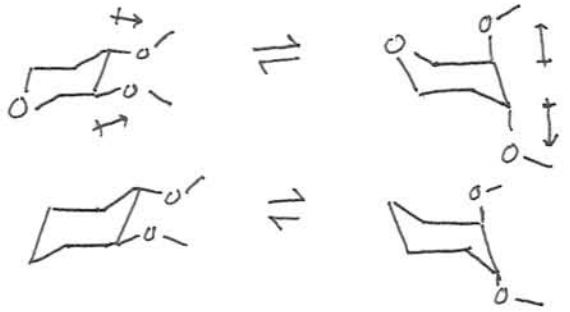
ΔG = 1800 cal
$-RT \ln K_{eq}$
$-(1.987)(298)$
$\ln K_{eq} = 3.04$
$K_{eq} = 21$



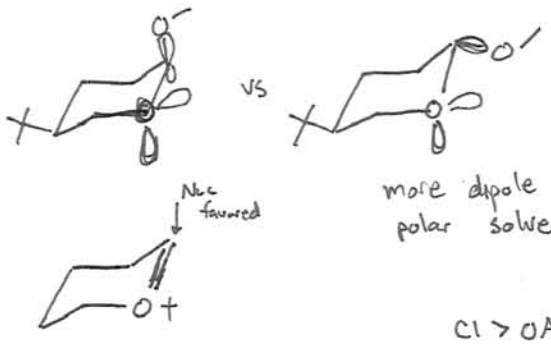
preferred in less polar solvent near O dipole

big dipole

lead to Cornforth model addition to carbonyls Predated Felkin Ahn



Anomeric Effect σ^*-n stabalization



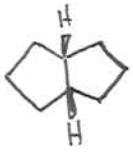
more dipole needs polar solvent

anomeric stabalization

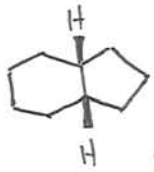
Cl > OAc > OMe > OH

weird effects associated with hydrogen bonding

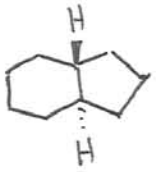
★ Spiroketal: draw prefered



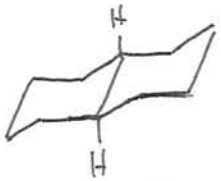
3.3.0 must be cis bicyclo octane



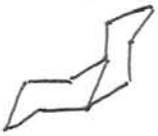
4.30



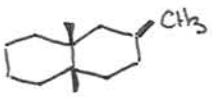
1 kcal difference



trans decaline locked

★ 

cis decalin will ring flip

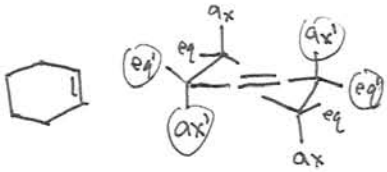


2.2.1

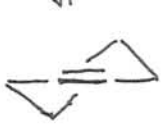
bridge head olefin very unstable

Bredt's rule: (8) or greater

OK



pseudo axial
pseudo equitorial

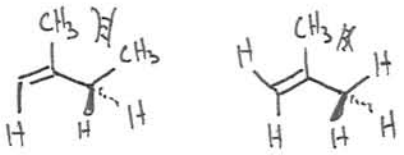


Allylic strain

- A 1,3

2 kcals higher

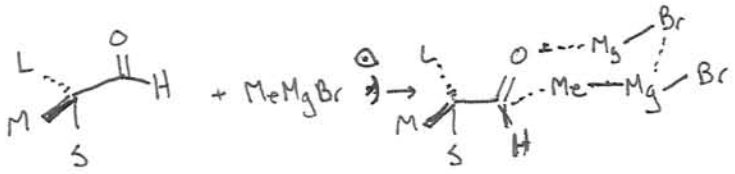
A 1,2



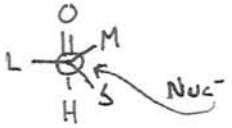
Closed transition state

open transition state

cation transfer

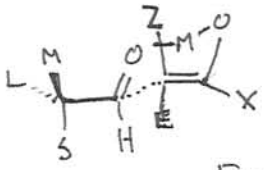


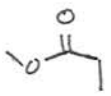
dimer lower in energy

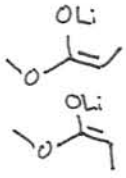


Felkin - Ahn

Consider Zimmerman-~~Traxler~~ Traxler





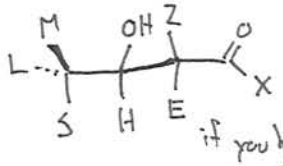


Z enolate

E enolate

E → anti

Z → syn



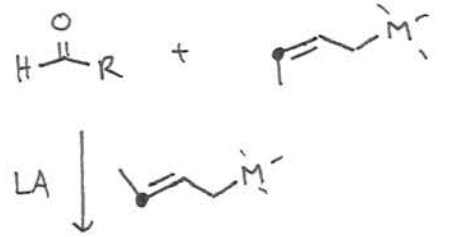
if you have control over E & Z enolate

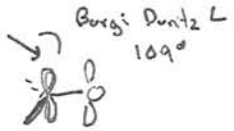
B	1.51	most selective
Li	1.92	
Zn	2.18	least selective

open transition state

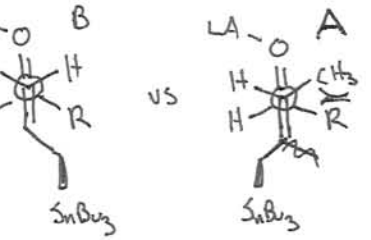
no coordination sites

closed TS





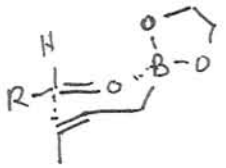
Burgi Dunitz ∠ 109°

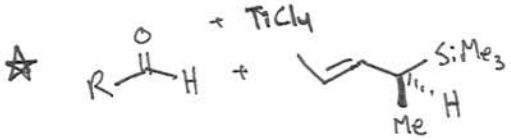


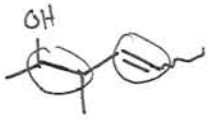
favored

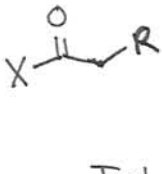
favored

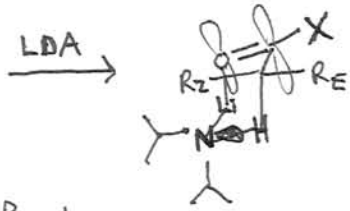
closed TS







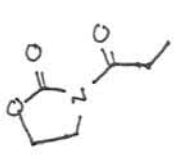


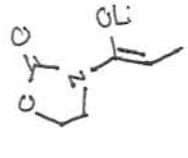


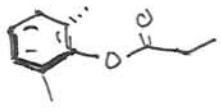
Ireland Paradigm

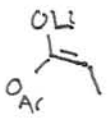
if X is big ⇒ then R_Z

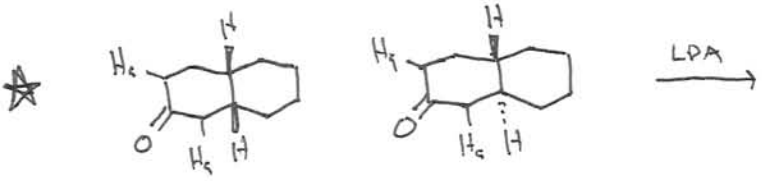
if X is small ⇒ then R_E

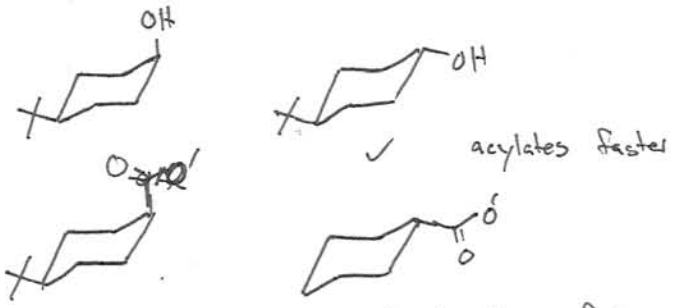




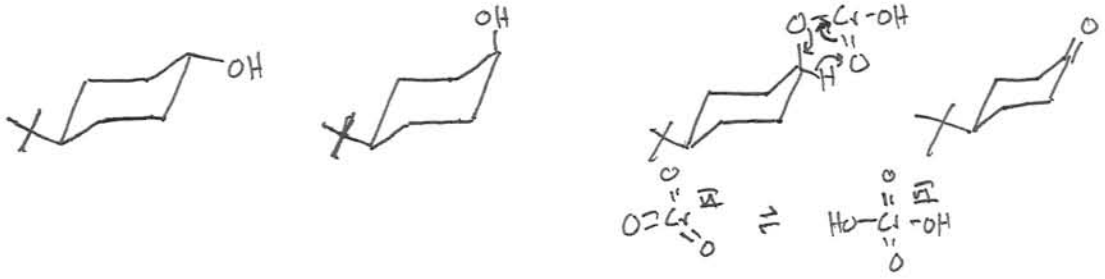





LDA

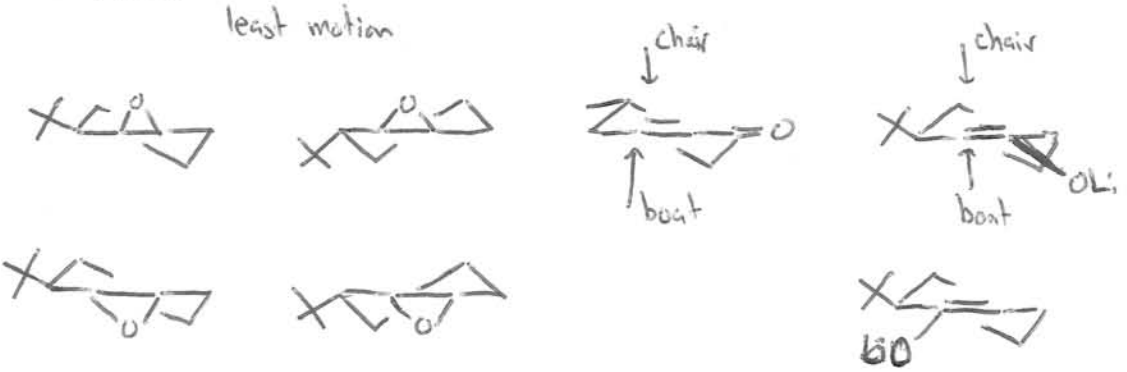

OH
OH
acylates faster
hydrolyzes faster

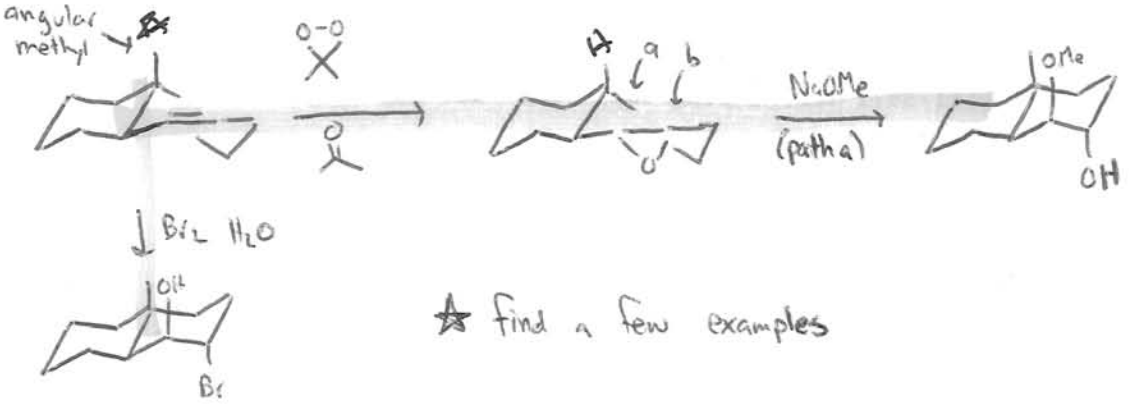

Br
Br
nucleophilic displacement


OH
OH

First - Platner

least motion



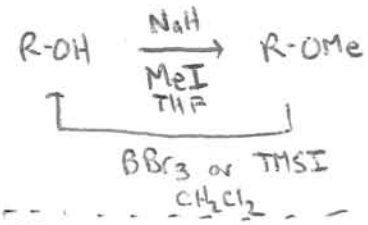


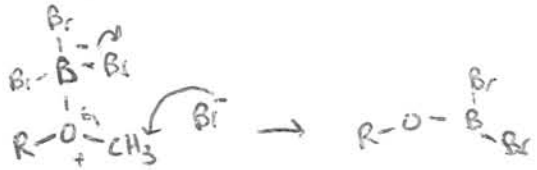
★ find a few examples

Protecting groups

- Alcohols (easy)

— Methyl ethers R-OMe

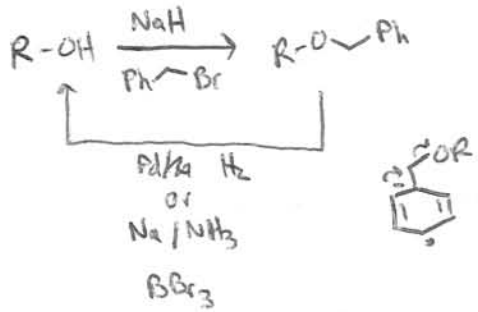


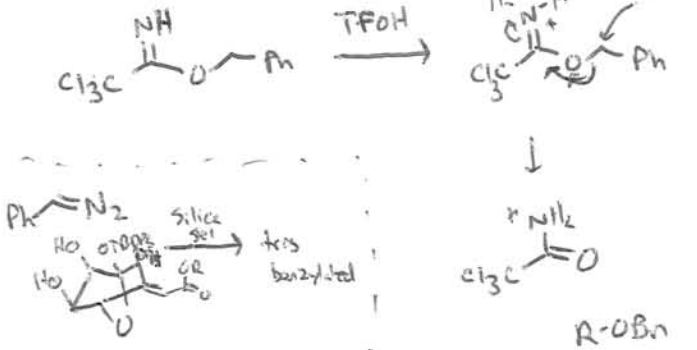


for base sensitive compounds:

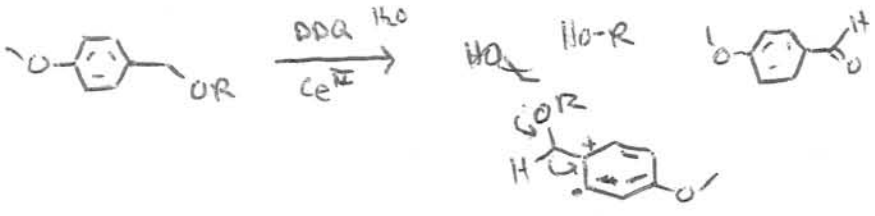
$R\text{-}OH \xrightarrow[MeI]{Ag_2O} R\text{-}OMe$ cationic mechanism

— Benzyl ethers R-OBn



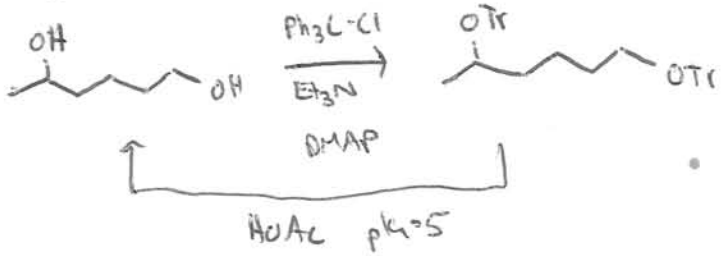


- PMBOR



- Trityl Ph_3C-OR

Ph_3C very fragile



- Silyl ethers

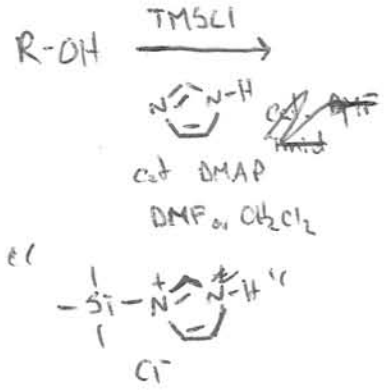
TMS R-O-Si-

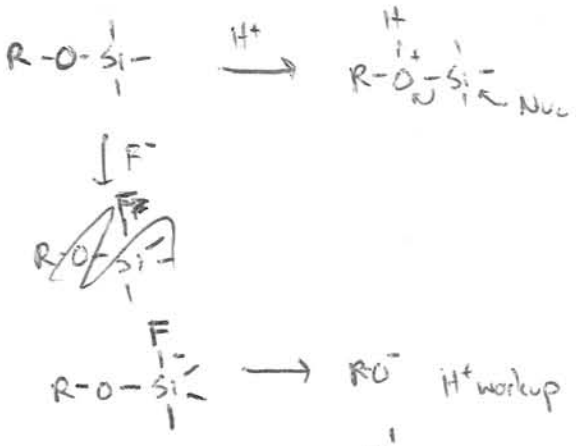
TES R-O-Si(Et)(Et)-Et

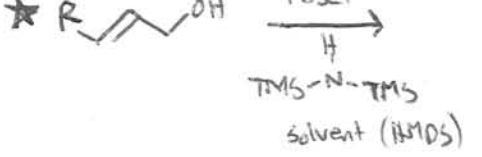
TBS RO-Si+

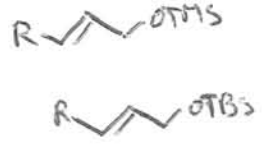
TIPS R-O-Si(Y)(Y)-Y most base stable

TBDPS BPS R-O-Si(Ph)(Ph)+ most acid stable



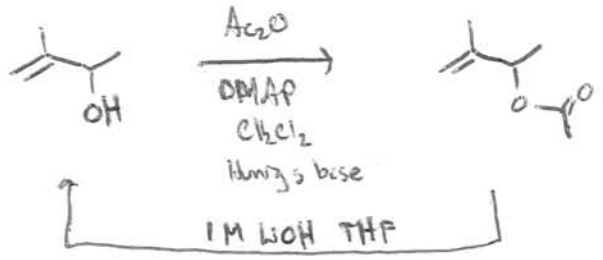


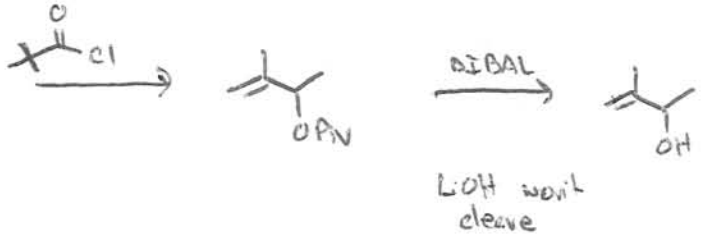


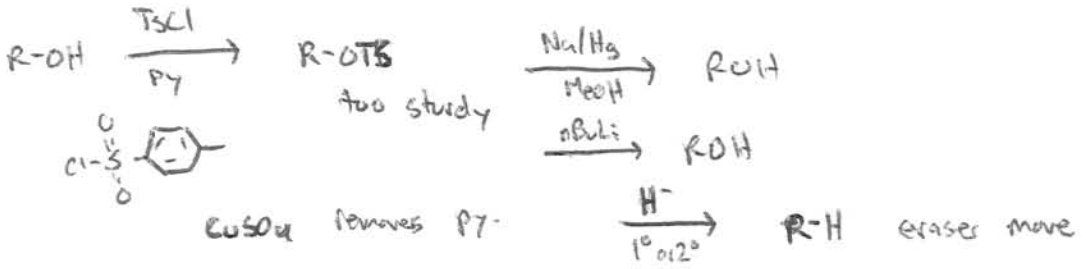


mechanism?

- Ester

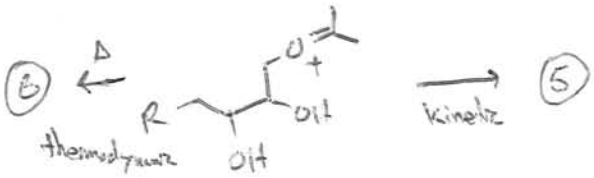


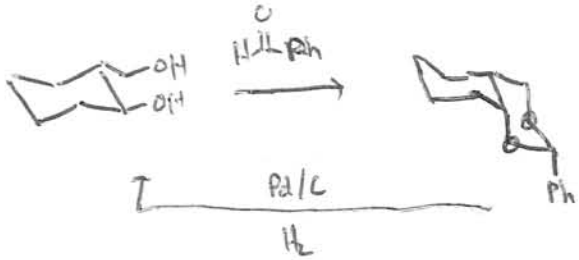




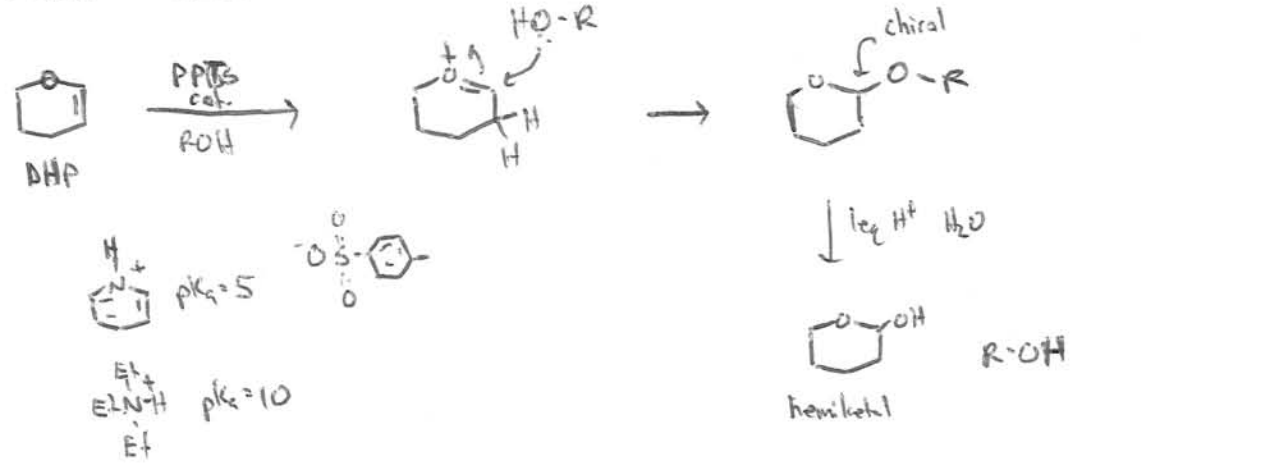
~~Diols~~

- Diols

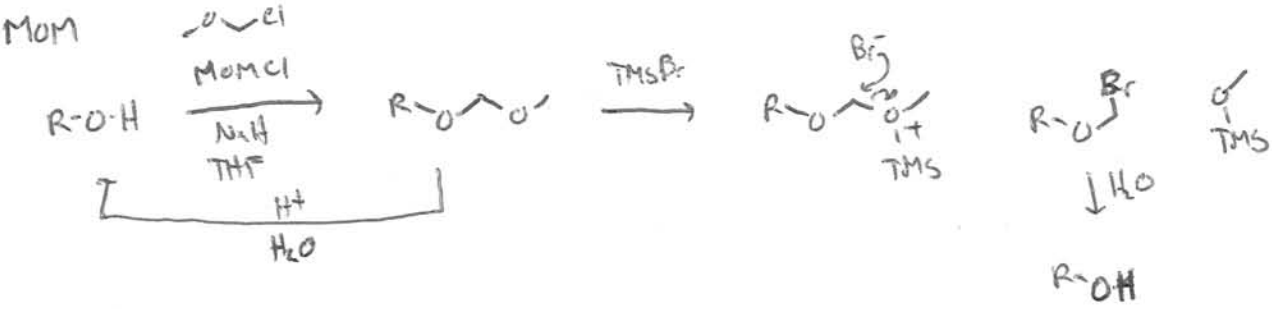




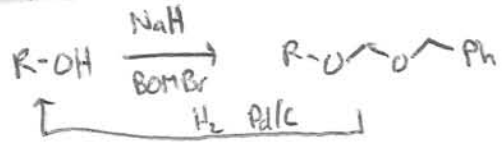
- Acetal ketal

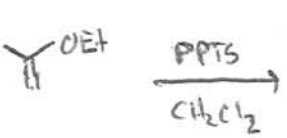


- MOM



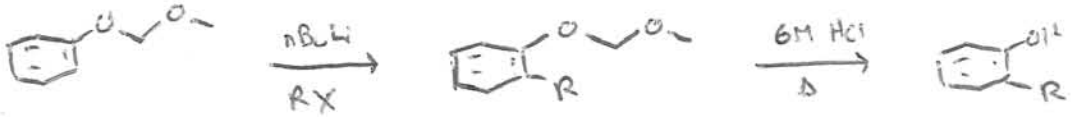
- BOM

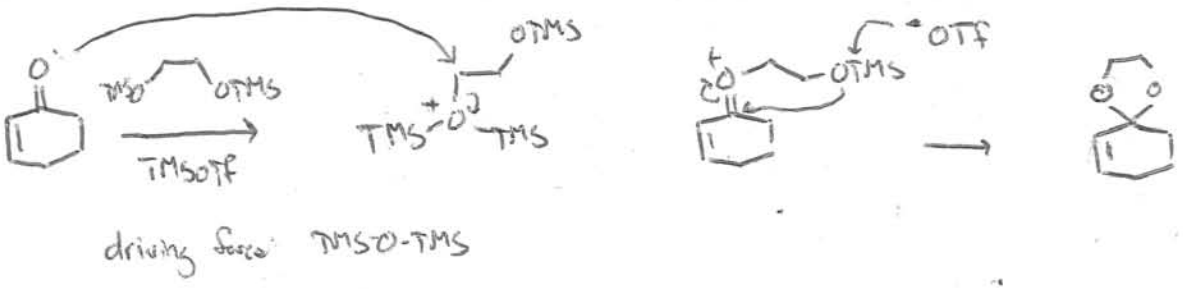




very very very fragile
silica will cleave,
not base bathed glassware,
not pH=7 buffers, pinch

- BOM



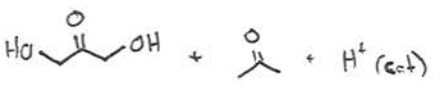


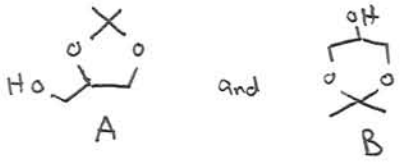
driving force: TMSO-TMS

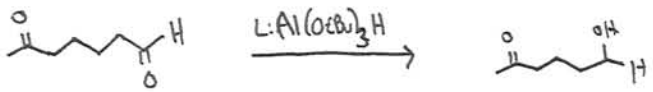
1/22

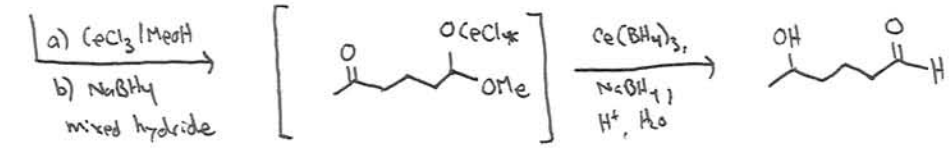
Test Tuesday 8:00 am

1-3 + stuff covered

★? Draw energy diagram 



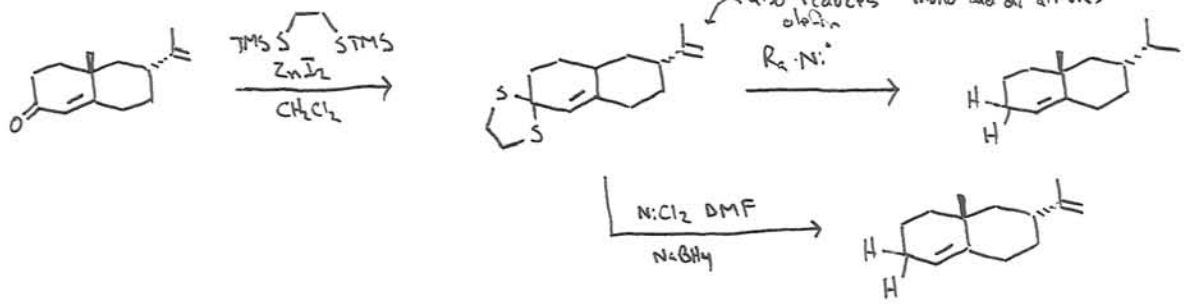




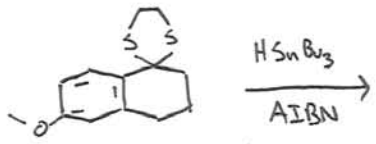
- S,S thio acetals and ketals

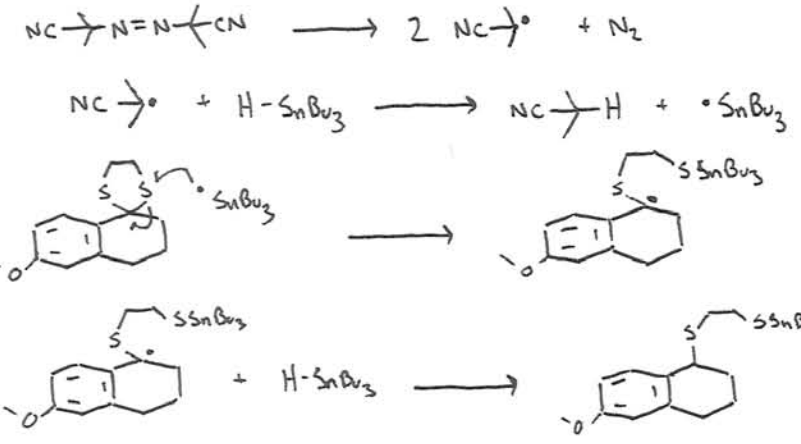
much easier to make, hard to cleave I^{III} Hg^{+2}

Evans



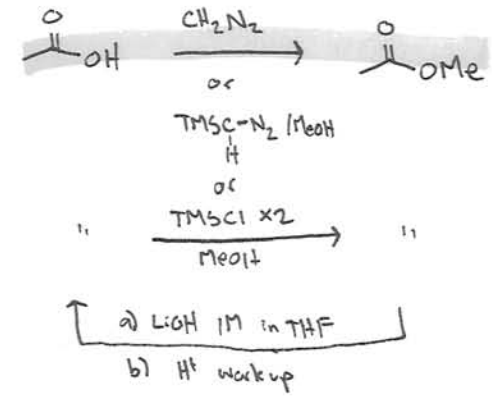
Radical Chem.

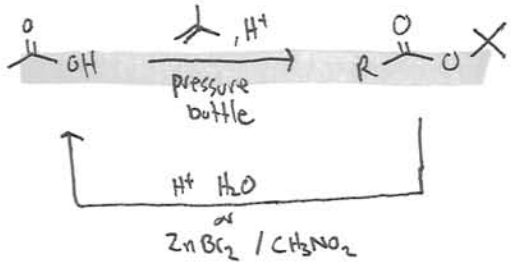


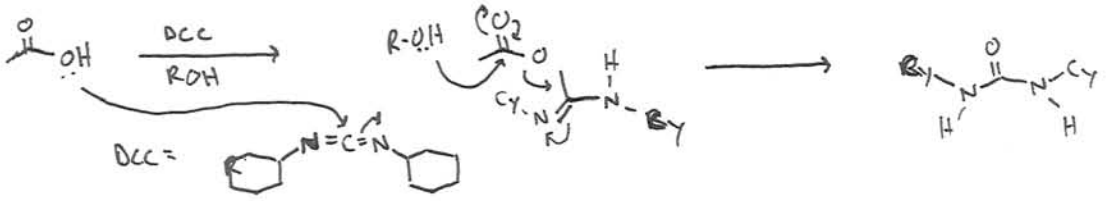


★ Clemson Red, Wolfe Kishner, Bamford Stevens

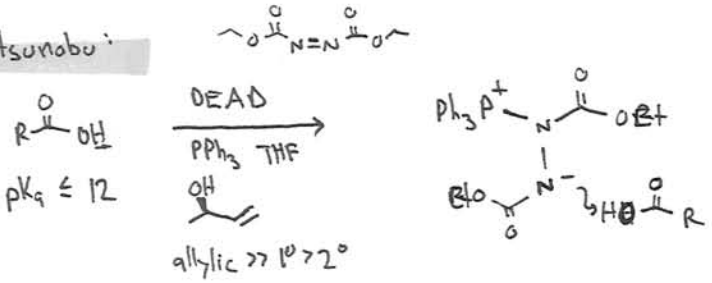
Esters





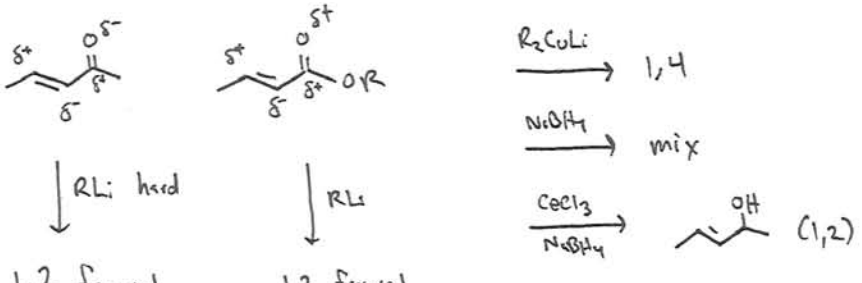


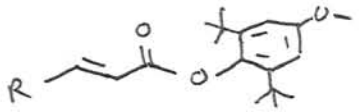
Mitsunobu:

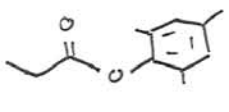


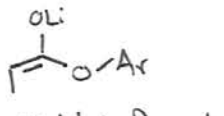
Hard / Soft

Matched HOMO/LUMO



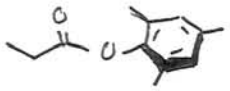


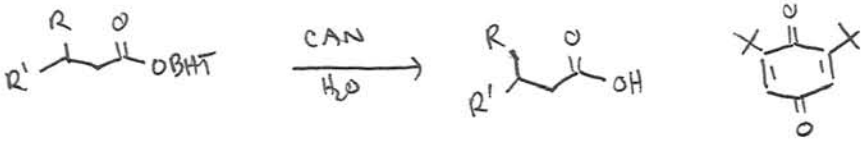




enolate formed

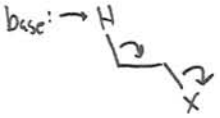
R'L: ↓ 1,4 reduction because sterics block 1,2 add





How to make Double bonds

E and Z is a big problem



E2 elimination X = ^-OAc, ^-OTs, ^-Br, $^+NR_4$

not so good

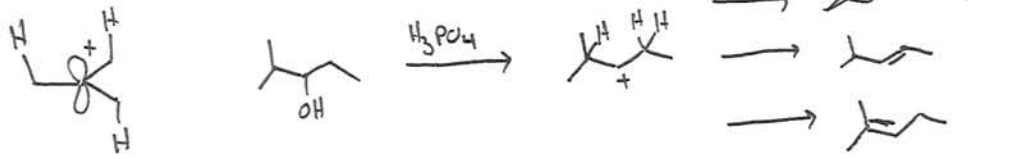
base: DBU, Et_3N, Py ~ hardly used

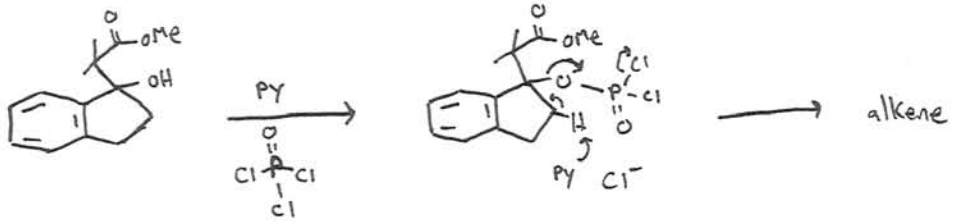
	H^+DBU	H^+TEA	H^+Py
pK_a:	11	9	5

poor geometry control

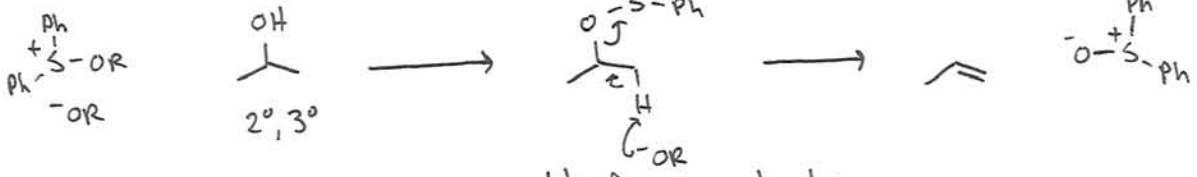
okay for rings, terminal olefins

E1 - cation



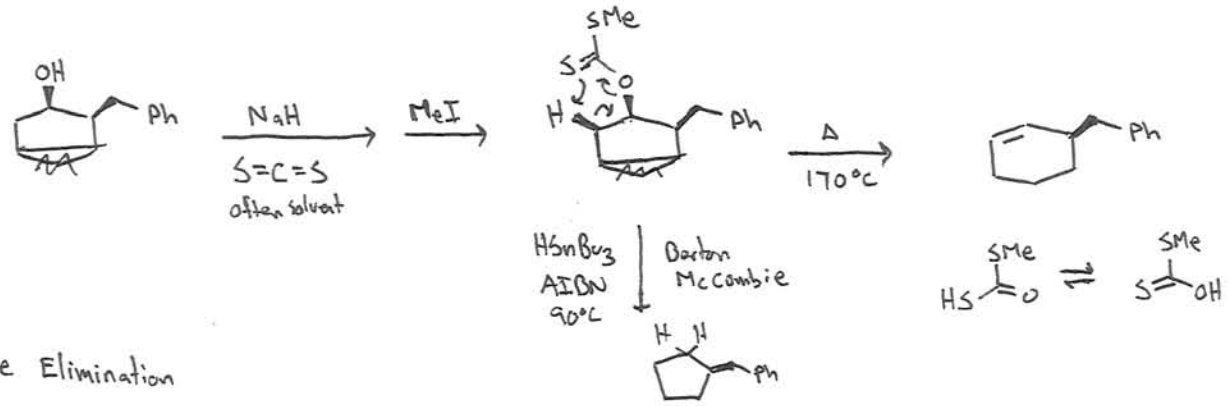


Martin Sulfurane

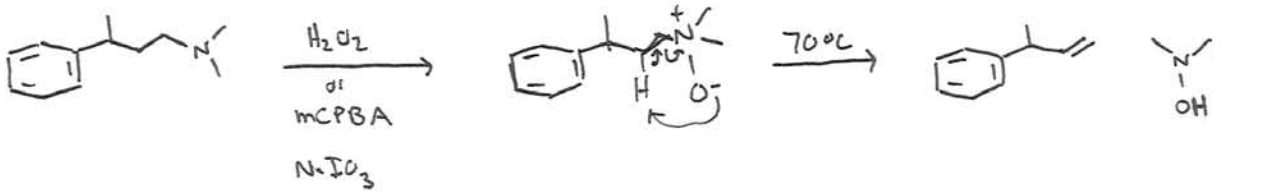


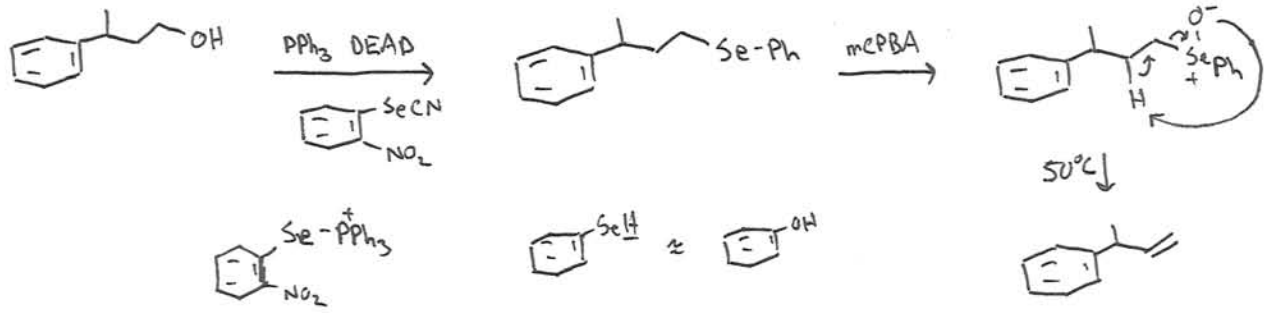
lots of cation character

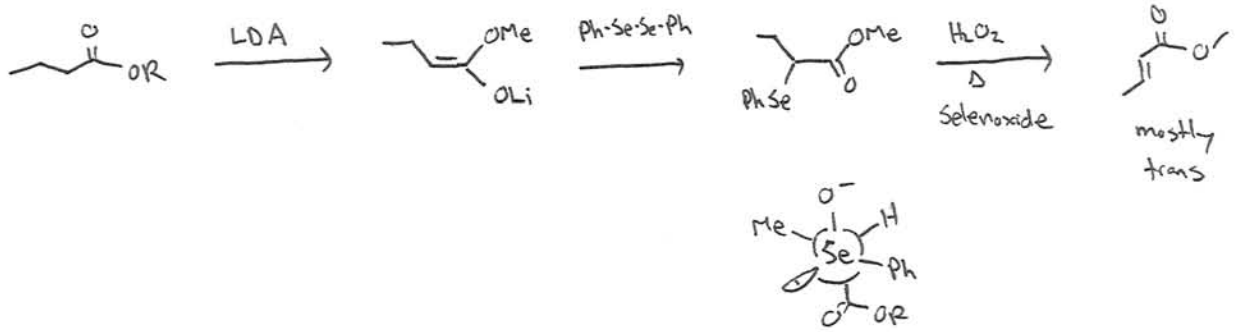
Syn Elimination



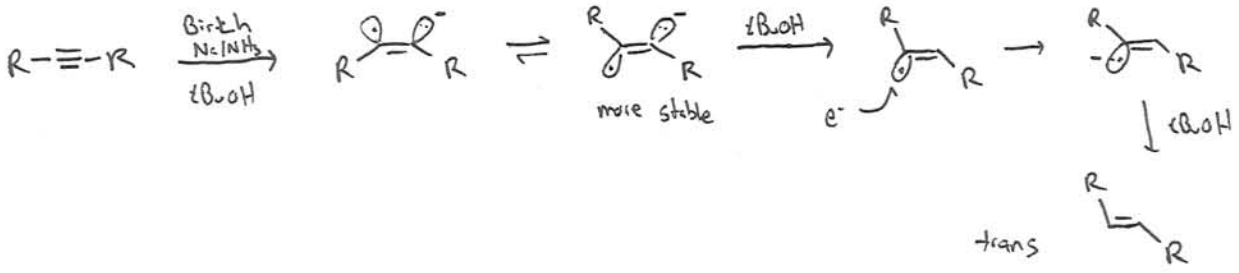
Cope Elimination



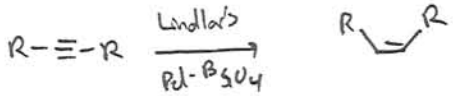




Alkynes



Cis:



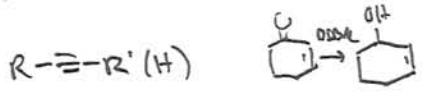
1/24

Test 1 Tuesday 8:00

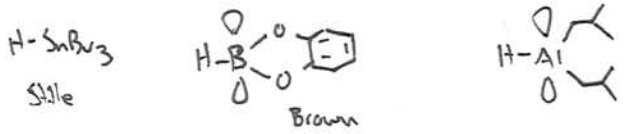
PS3 due Feb 2 (8,7)

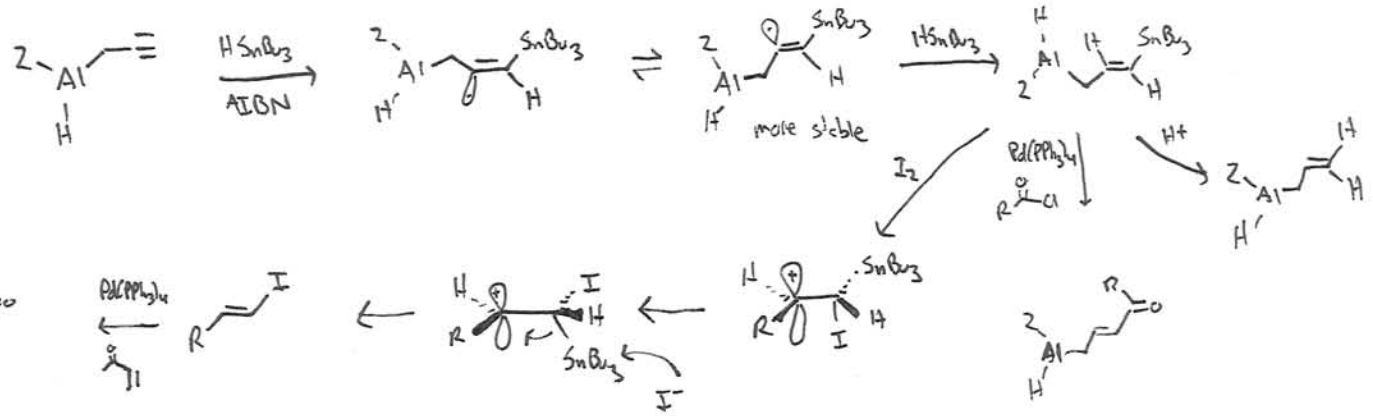
chem 233 read alkenes
enlightenment

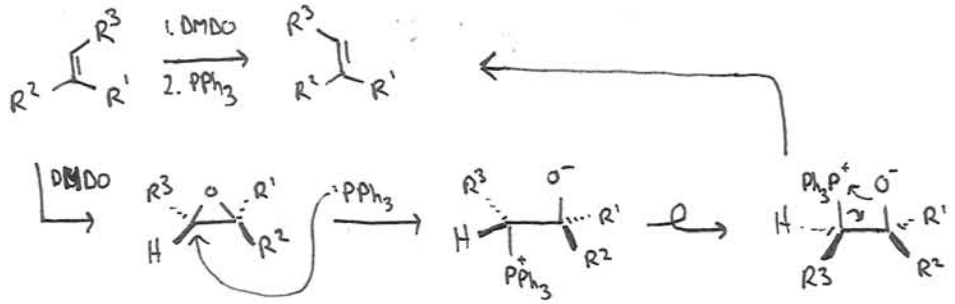
hydrometallation

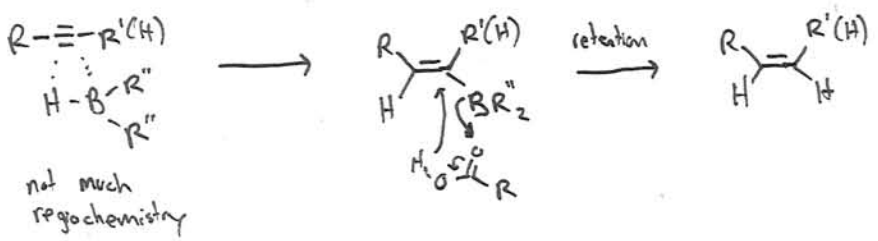


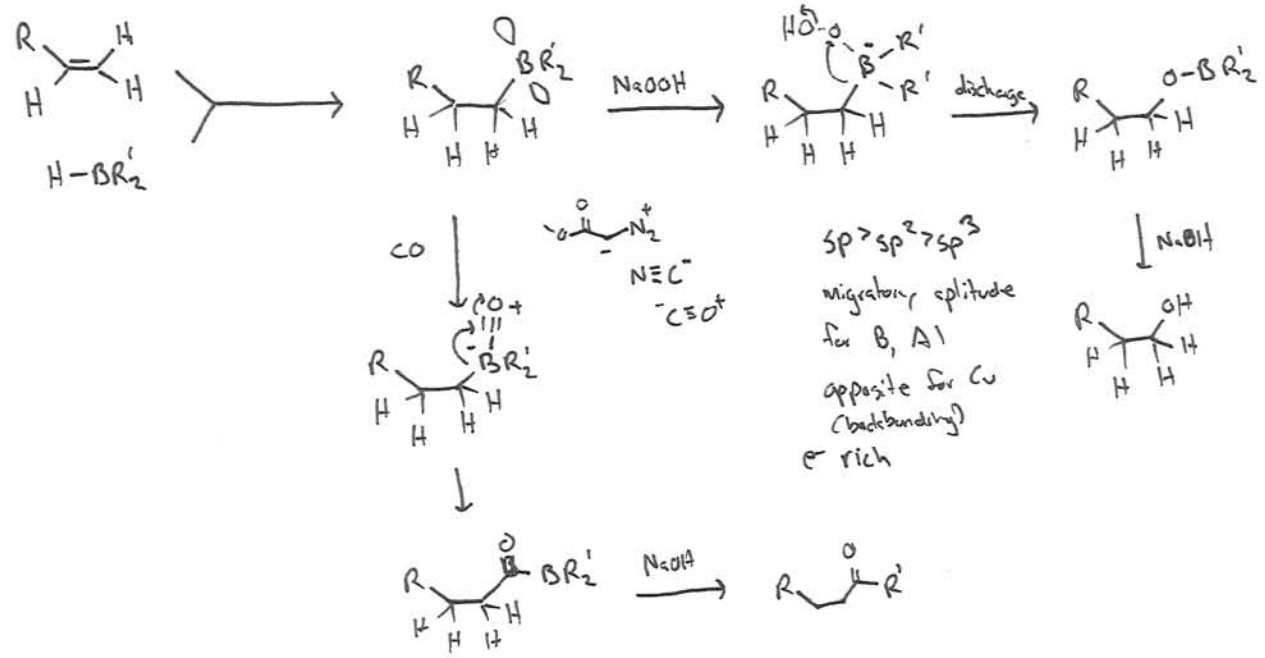
internal alkenes have regiochemical issues unless directing group

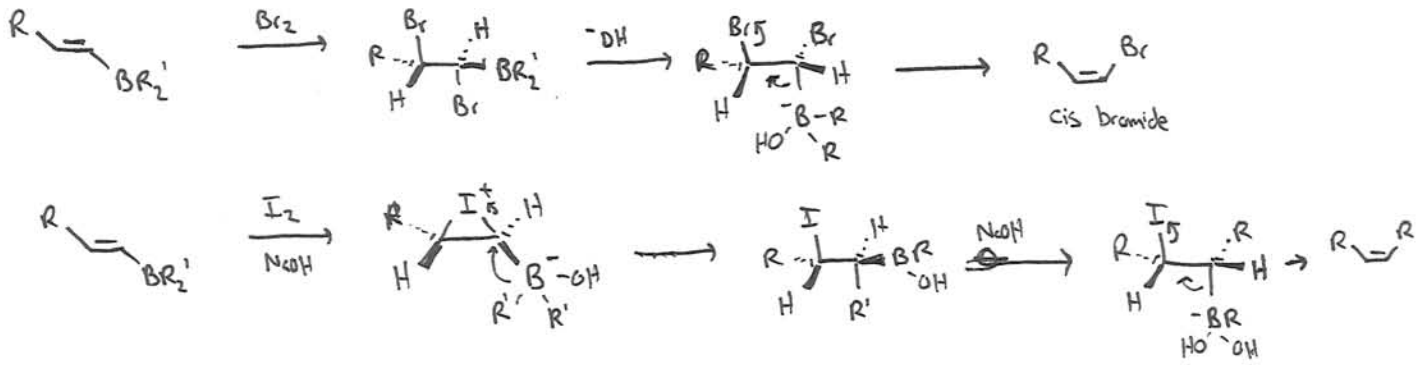


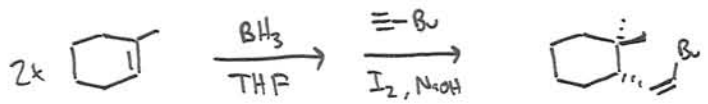




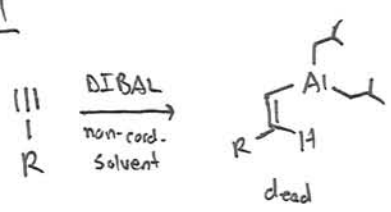




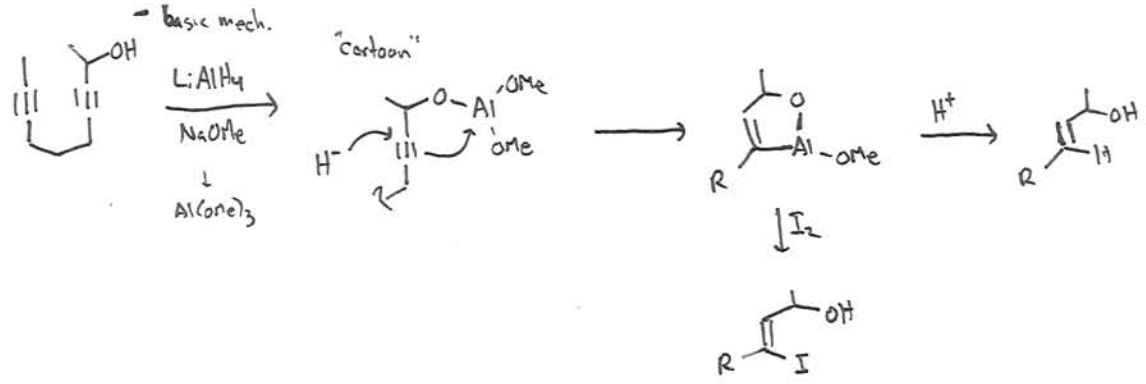


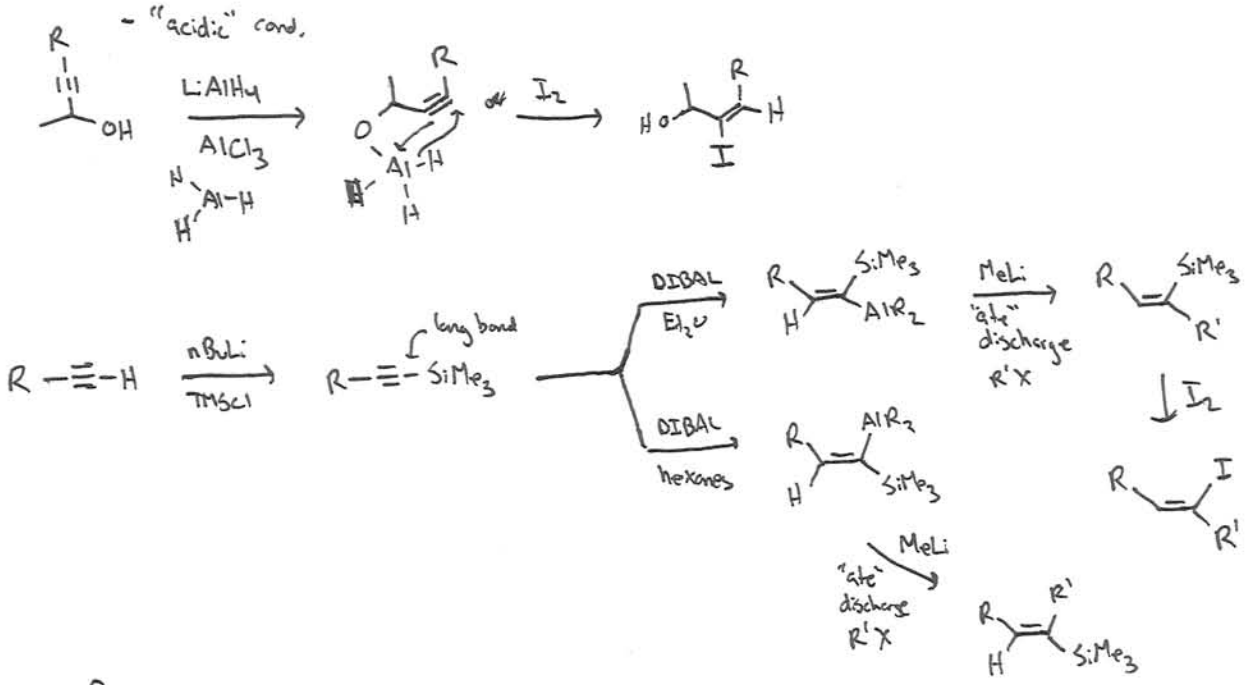


Al



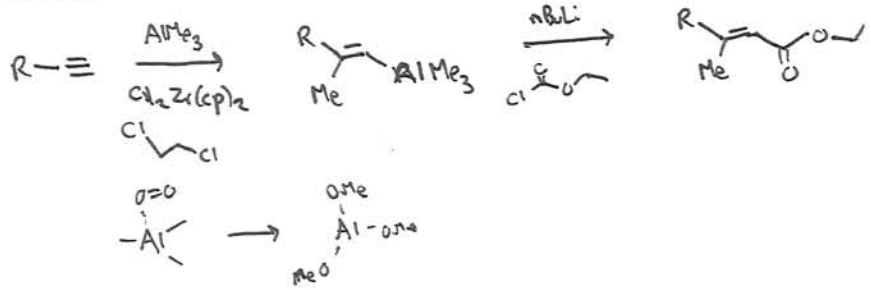
- basic mech.



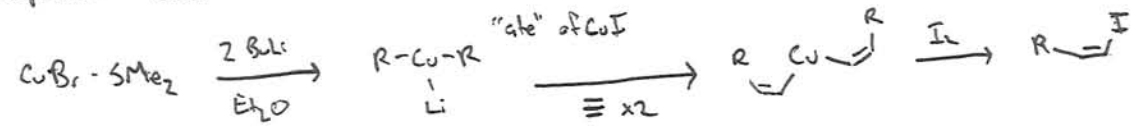


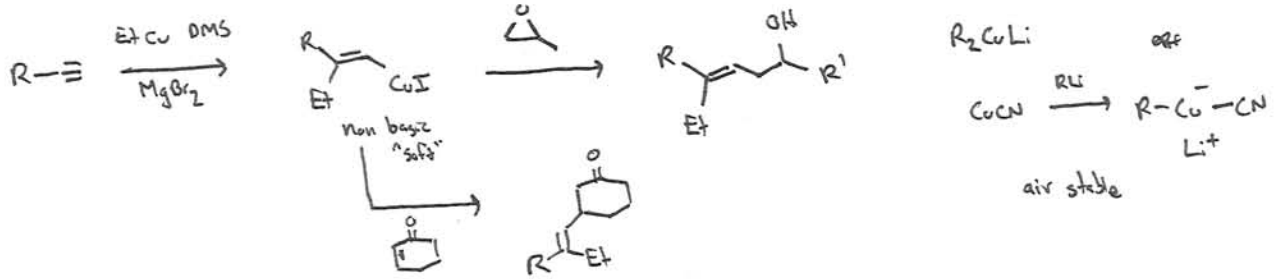
Carbometallation

Aluminction

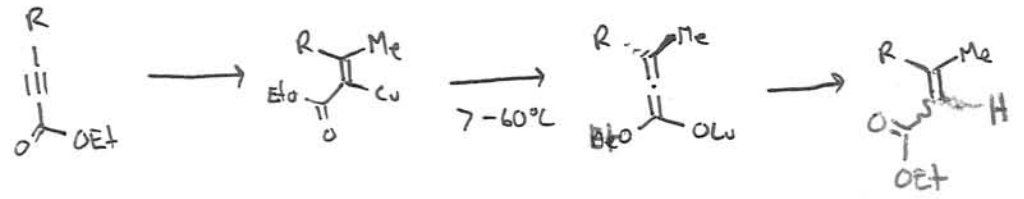


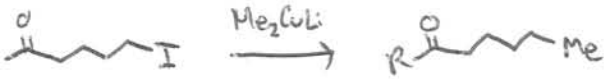
Cupration CuI



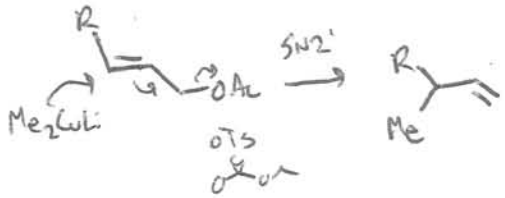


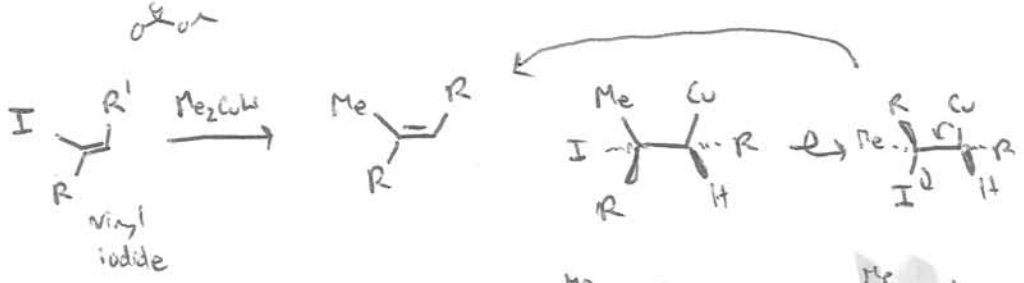
Me_2CuLi

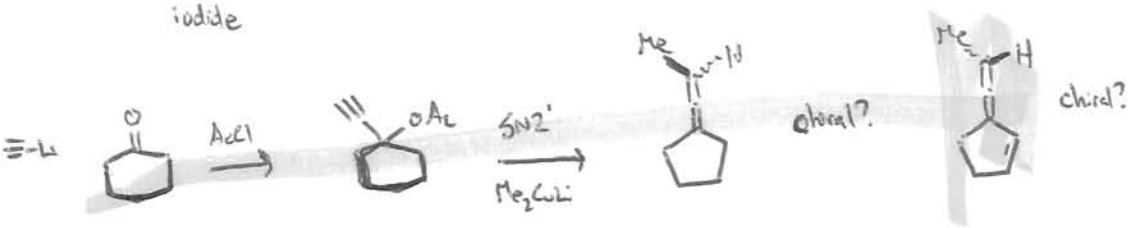



Me2CuLi

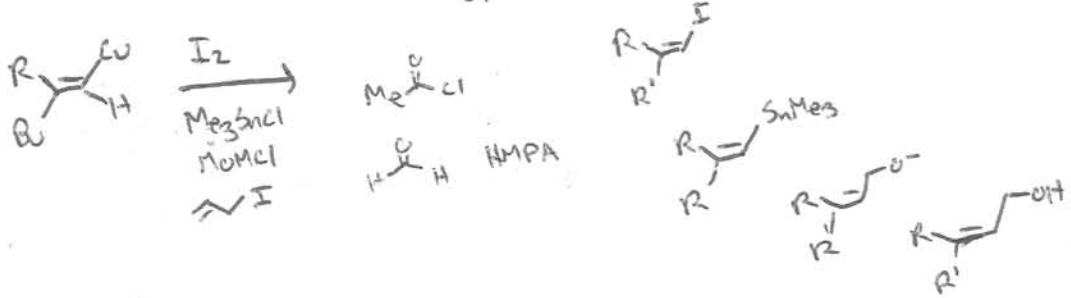

Me2CuLi
80% conversion
not clean


Me2CuLi
SN2'
OTs


Me2CuLi
vinyl iodide


AcCl
SN2'
Me2CuLi
chiral?
chiral?

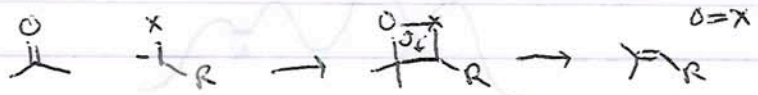

Me2CuLi


I2
Me3SnCl
MOMCl
HMPA

1/30

Class noon 4606 Saturday

Wittig, HEW, Peterson, Takai, Petasis, Tebbe, Julia



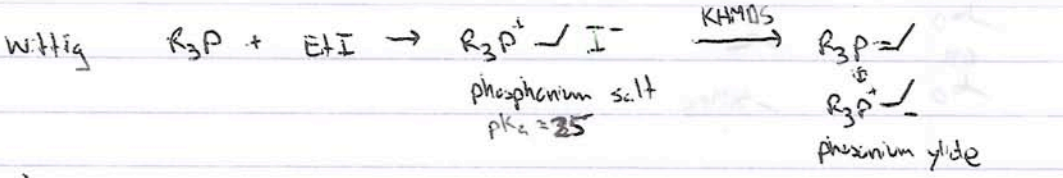
Si=O 110

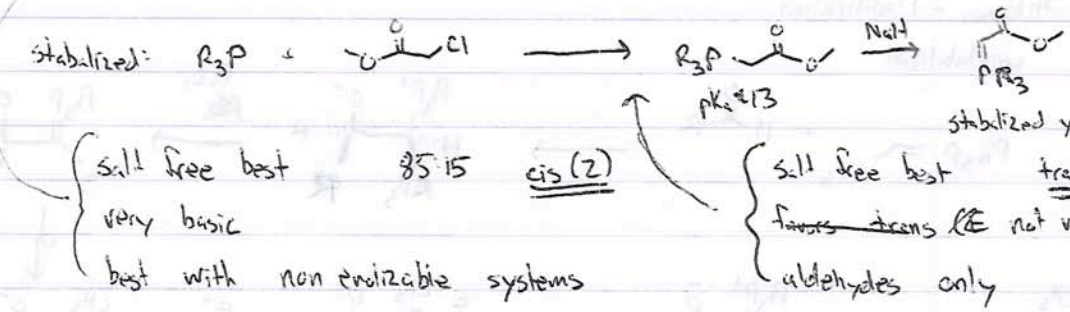
P-O 95

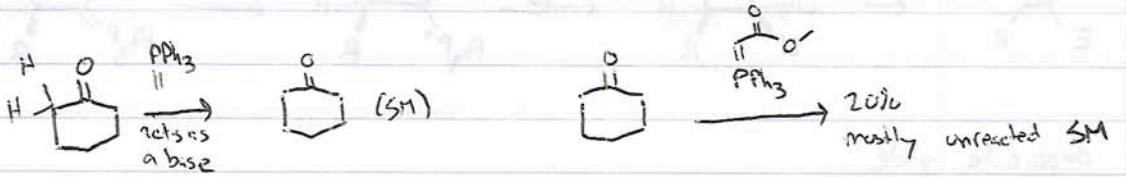
C-O

Ti-O

Ce-O

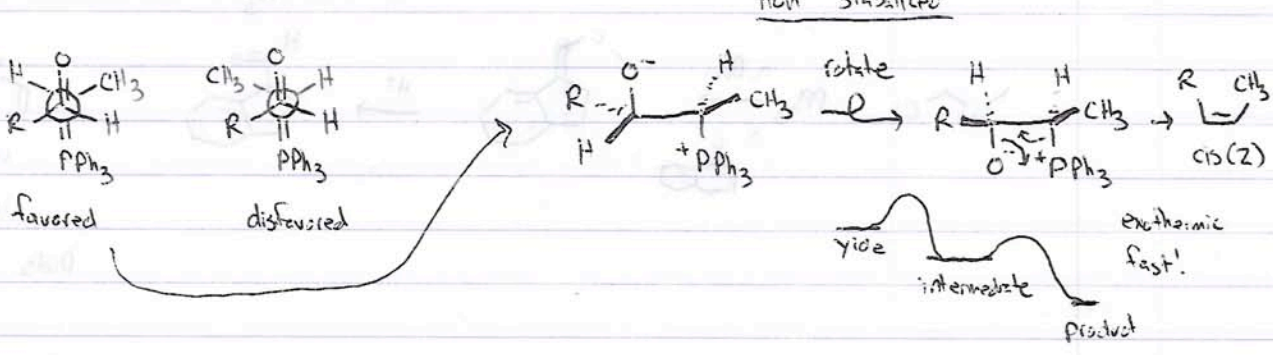


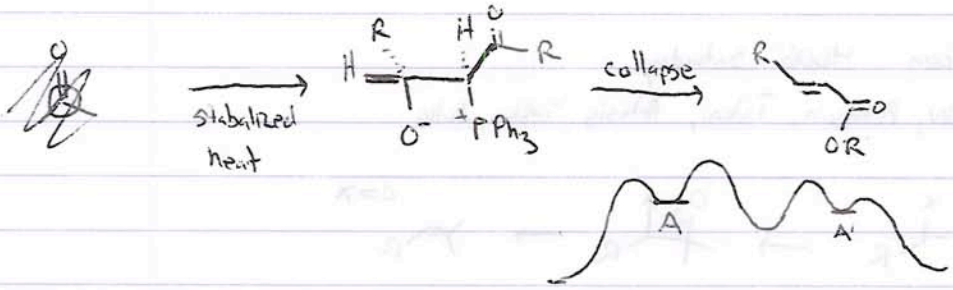




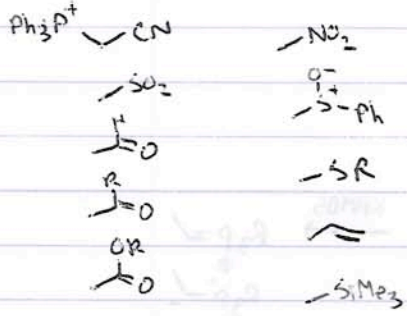
in nonstabilized systems must be non enolizable (PPh_3)

Mechanism asynchronous [2+2]

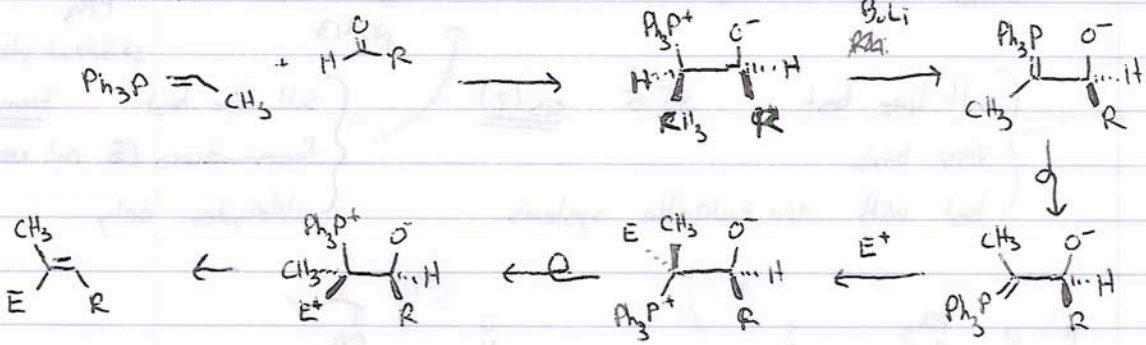




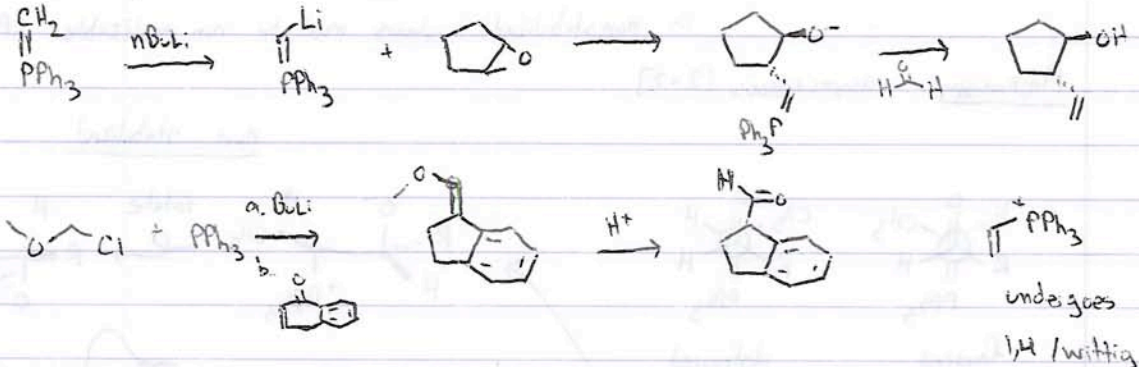
Stabalizing groups:



Schlosser - Modification
unstabilized



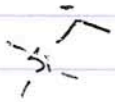
deprotonate ylide



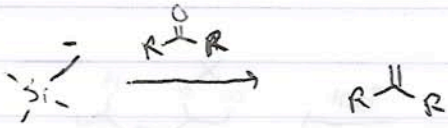
undergoes
1,4 / wittig
Diels Alder rxn Wittig

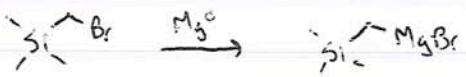
Peterson olefination

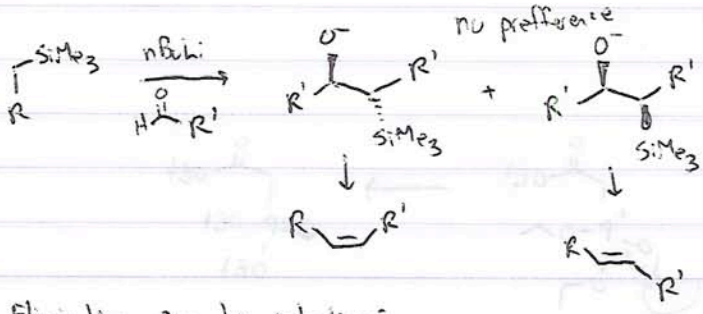
mostly only good for terminal olefin



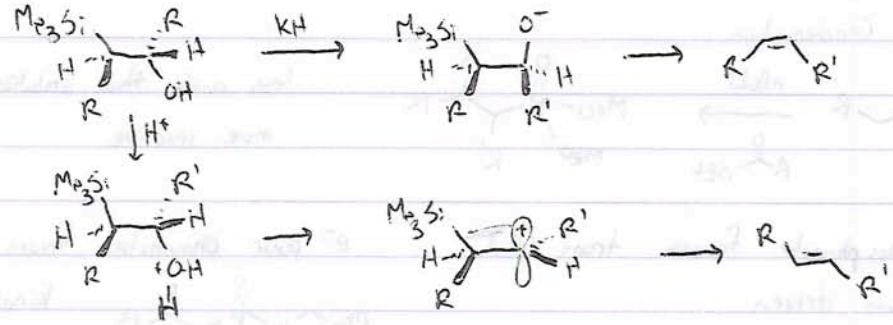
no conformational preffeience



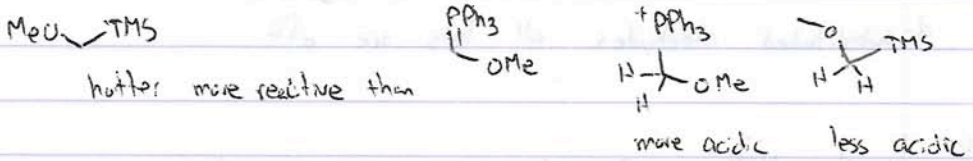


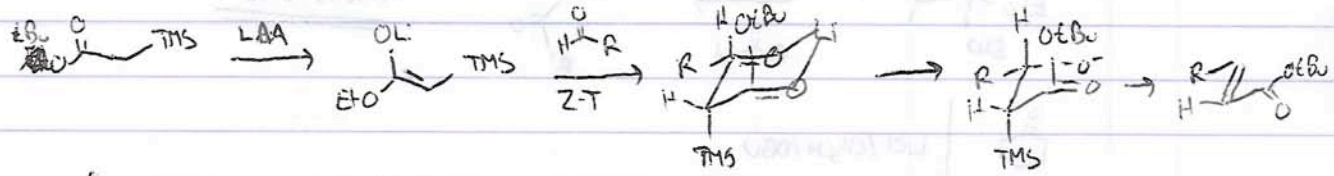


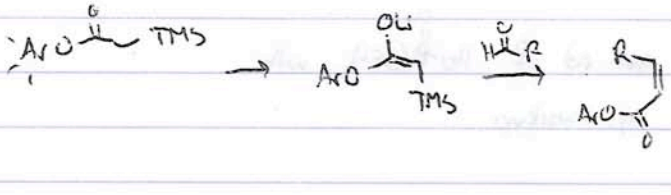
Elimination can be selective:

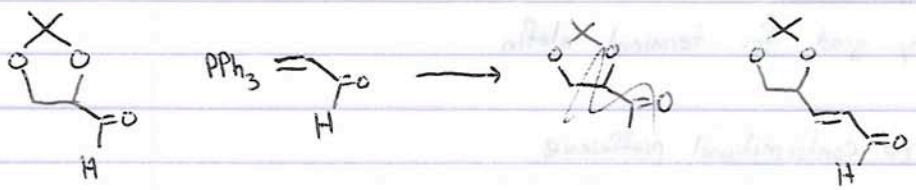


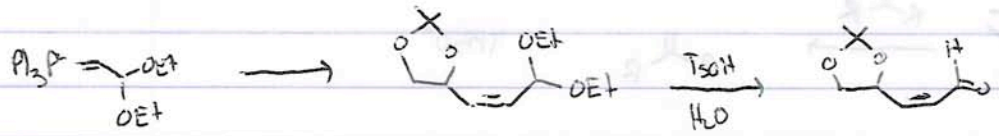
β stabilized conformational preffeference







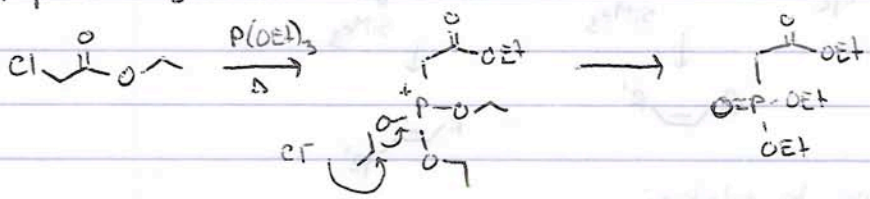




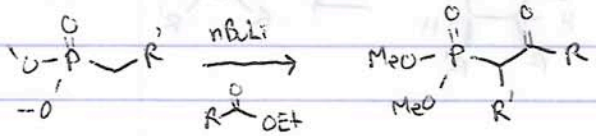
Bestmann

HWE

prep of reagent



Claisen Condensation



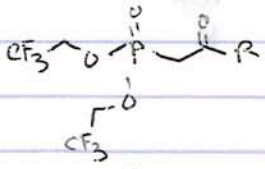
less acidic than stabilized ylide

more reactive

big phosphonate favors trans (E)

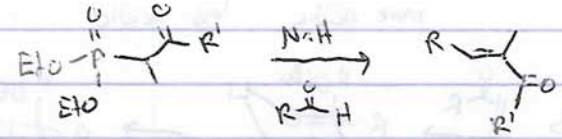
equilibrium driven

e⁻ poor phosonate favors cis (Z)

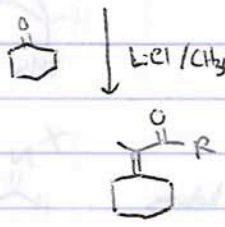


kinetically driven

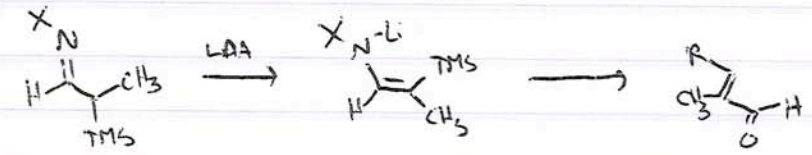
α-substituted aldehydes: all bets are off

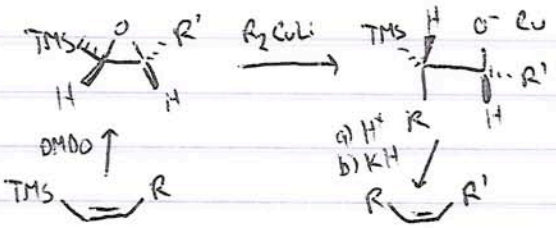


trisubstituted!



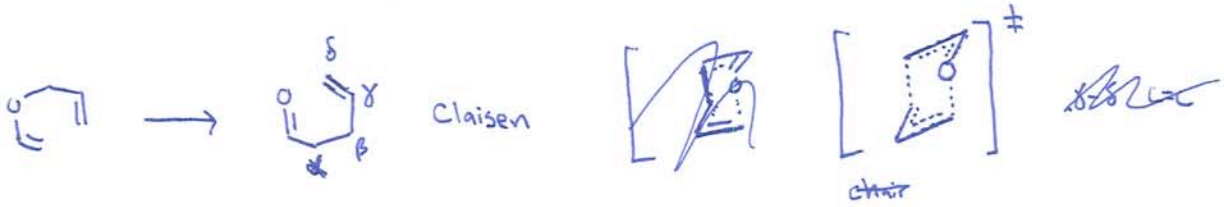
get rid of $HO-P(=O)(OEt)_2$ with aq. workup

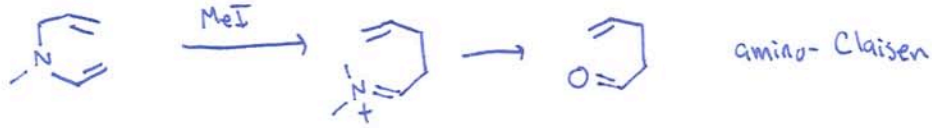

LDA
TMS
TMS


TMS
R'
R2CuLi
TMS
R'
DMDO
TMS
R
a) H+
b) KH
R
R'

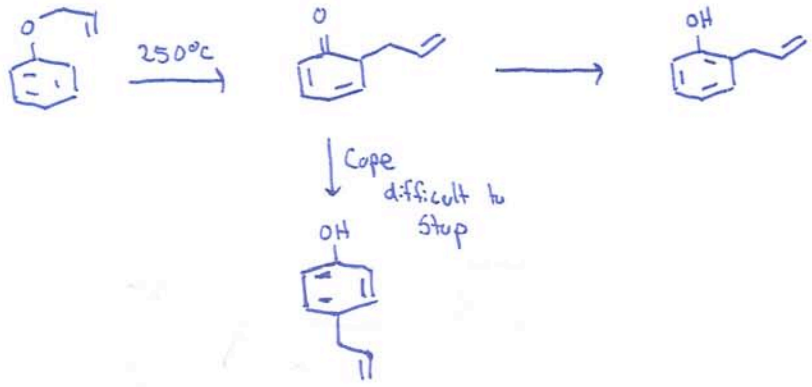
2/2/08

3,3 Sigmatropic Rearrangements

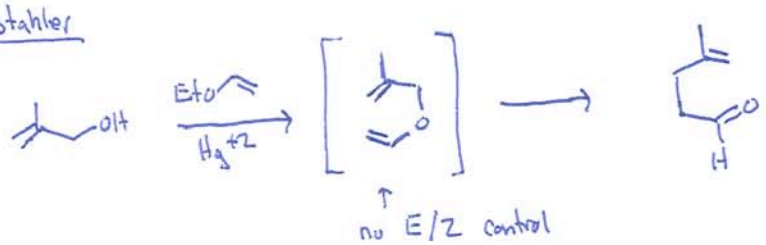




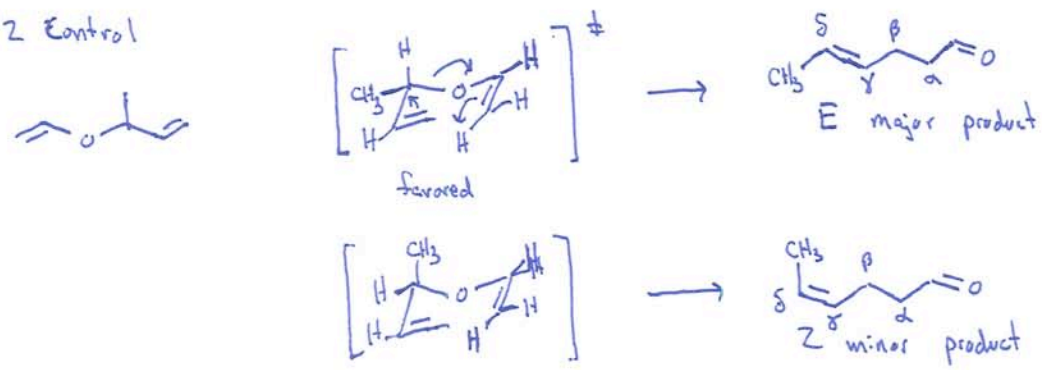
Aryl Claisen



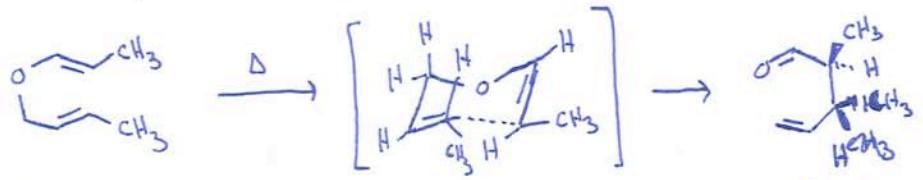
Burgstahler



E/Z Control

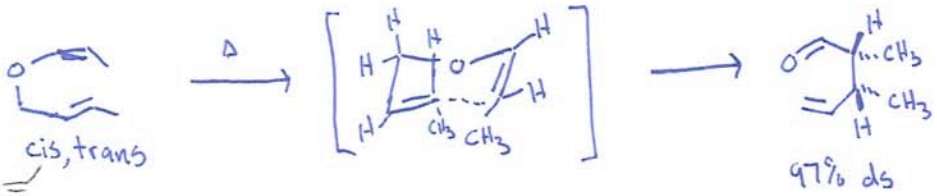


Stereochemistry of new single bond



trans, trans

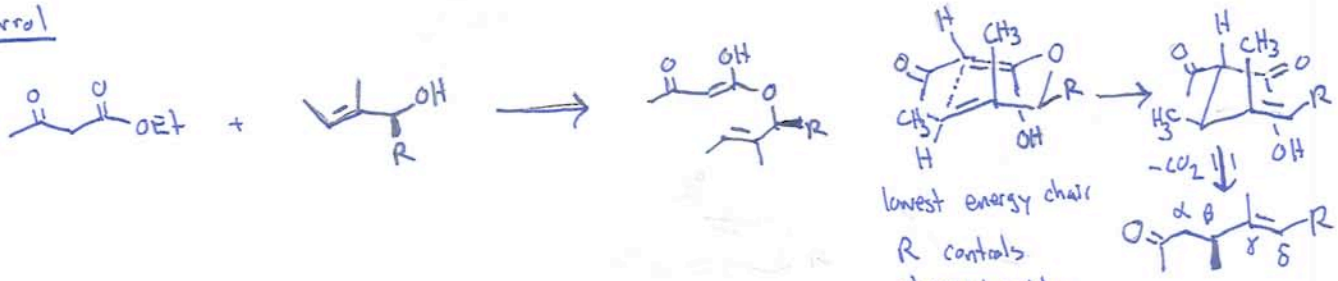
97% ds



cis, trans

97% ds

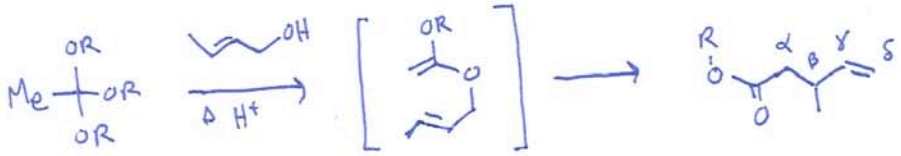
Carrol



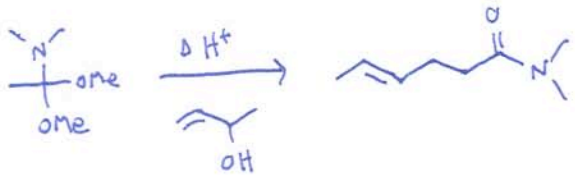
lowest energy chair

R controls stereochemistry

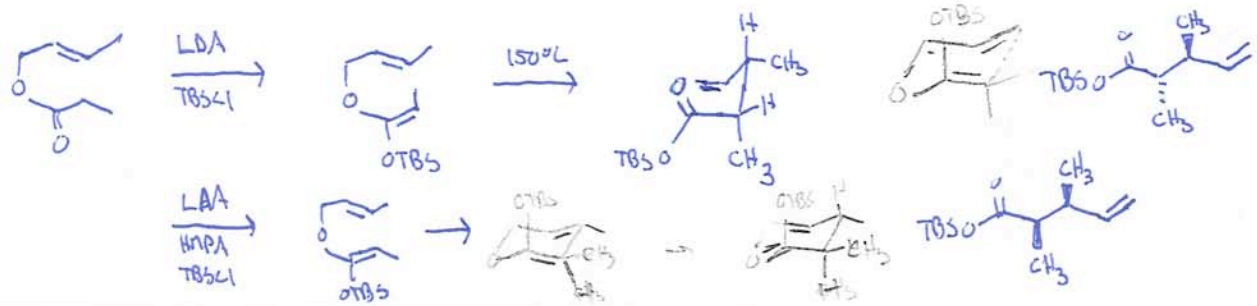
Johnson



Esther Mosher Eschenmoser

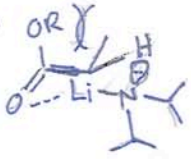


Ireland E-Z control with enolate and alcohol

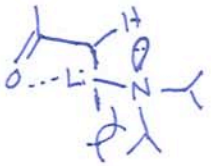


Ireland

LDA →

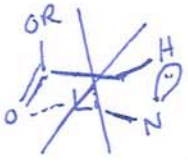


small A-strain (favored)



large A-strain

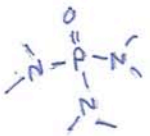
LDA in HMPA →



no ordered TS.

E enolate is favored

strongly lithium coordinating



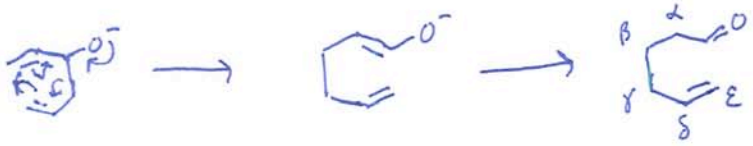
HMPA

DMPU

Cope

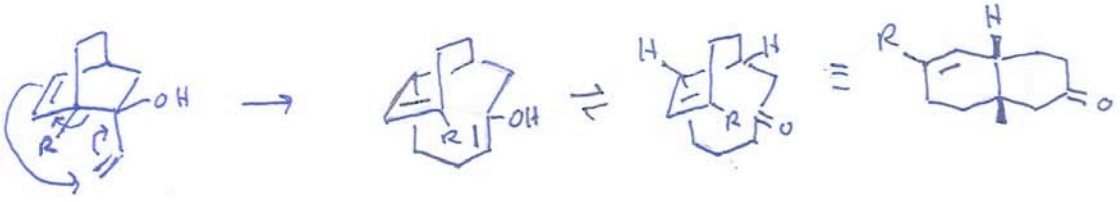
not much driving force to go: 1. conjugation
2. make a ketone
3. release ~~cation~~ strain
4. discharge cation

extended conjugation



oxy Cope

release strain



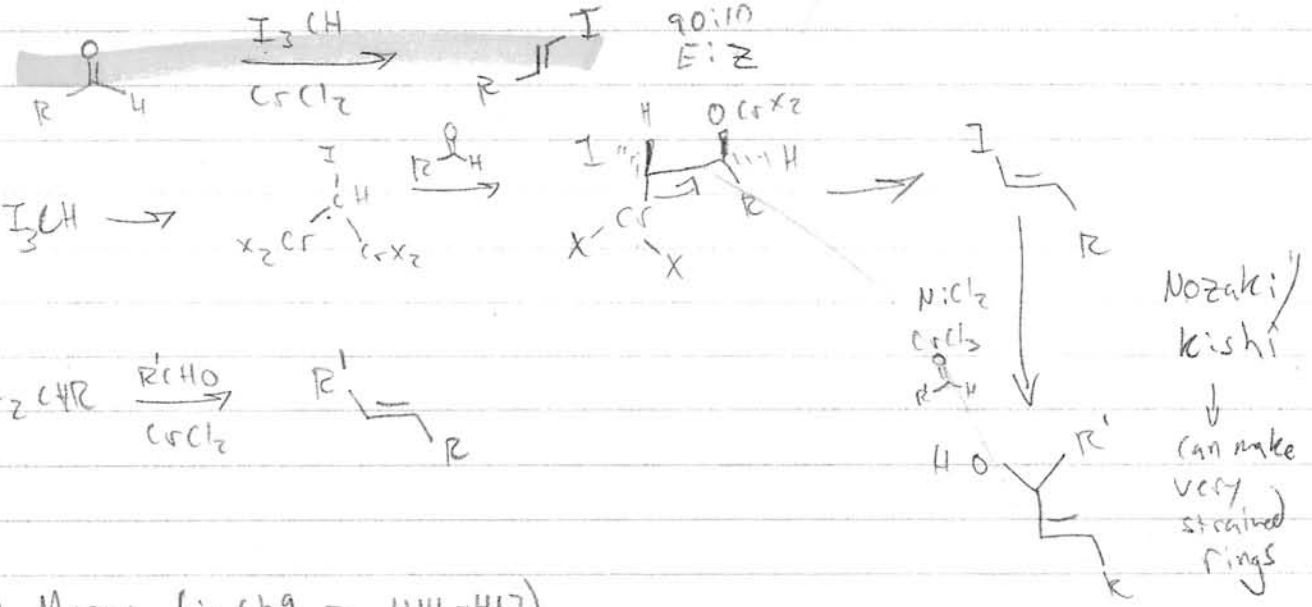
Another ~~3,3~~ sigmatropic

Another 3,3 sigmatropic rearrangement

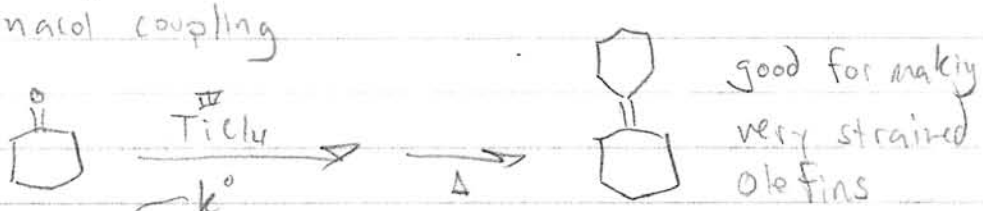
2/5

Feb 9, 16 12-2pm T.W. Chapter 4
Test #2 Ch 8, 7, 4 Feb 21 8:00 am
P.S. 3 Due Sat + pdf
Feb 26, 28 Todd ch 5 Gordan Conference

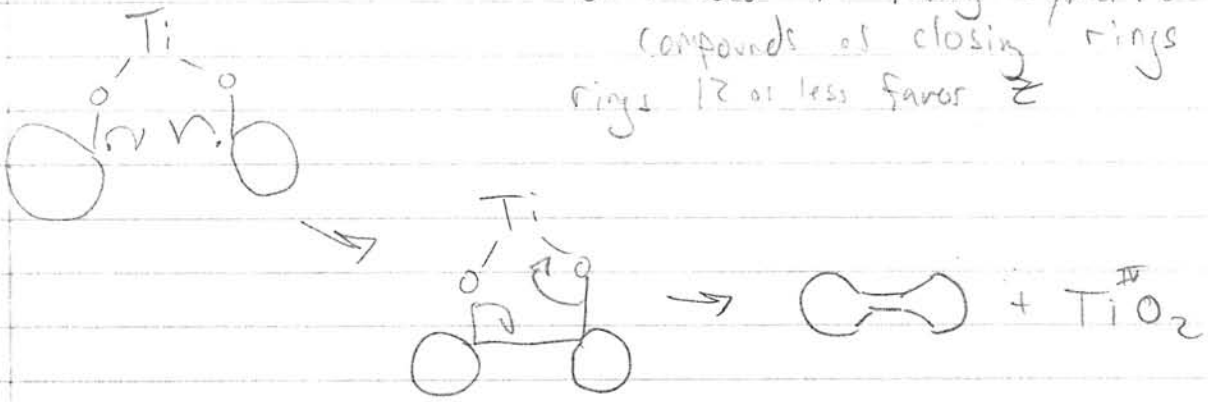
Takai gives a vinyl Iodide



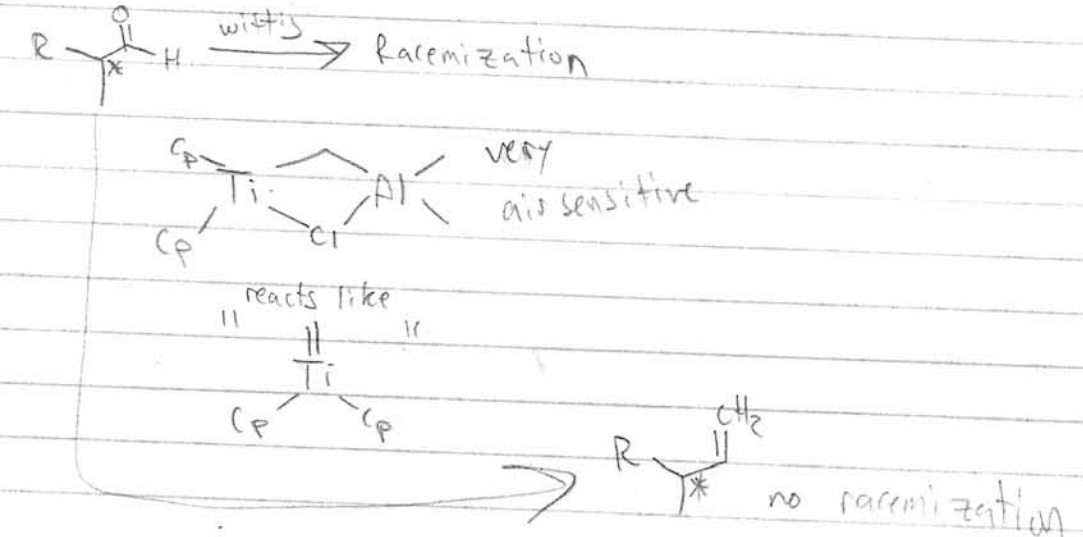
McMurry (in ch9 PS 414-417)
pinacol coupling



not good for E/Z control
often used for making symmetric compounds of closing rings
rings 12 or less favor Z



Tebbe (not in book) – nice to prepare for Claisen
non basic methylation

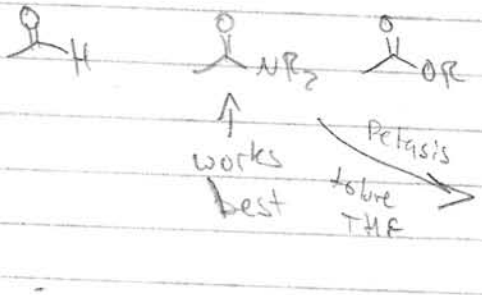


works on:

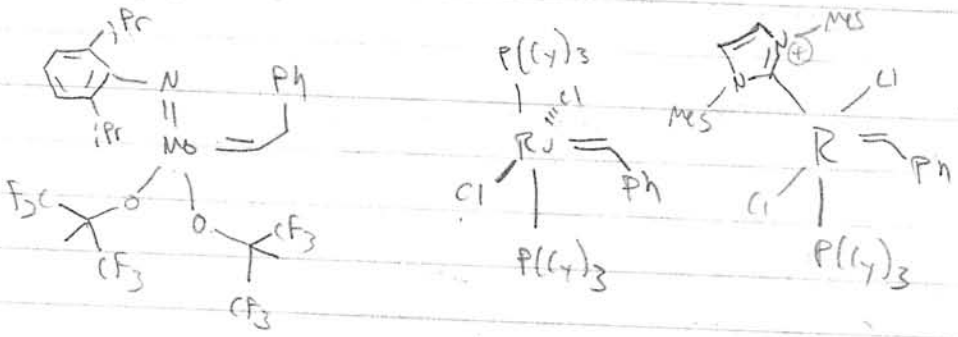
X = H, OR, NR_2, works best with esters

Petasis → nice to prepare for Eschenmoser

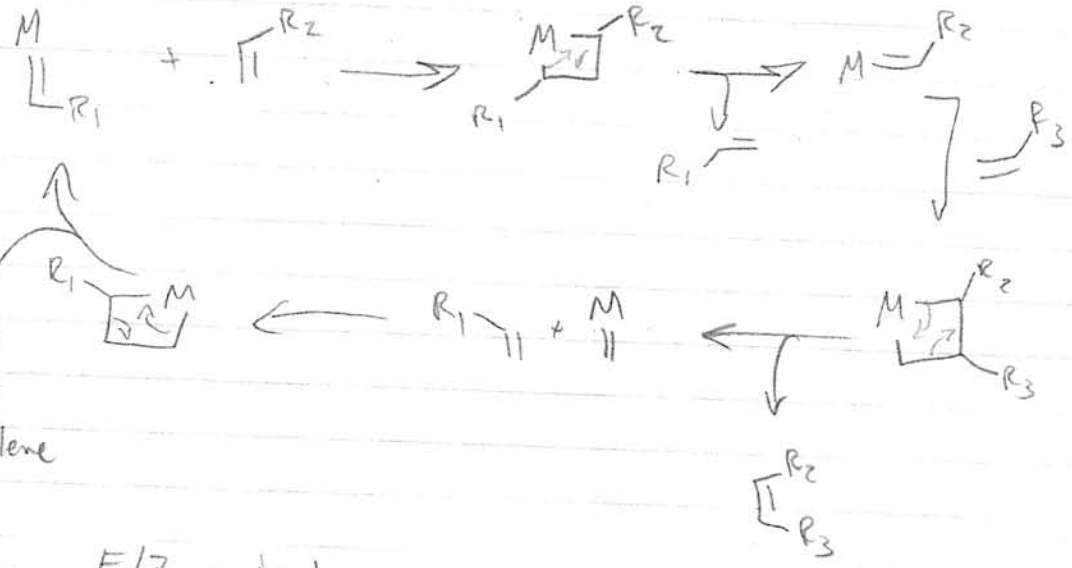
$Cp_2TiCl_2 + 2MeLi \longrightarrow Cp_2Ti$ ≃



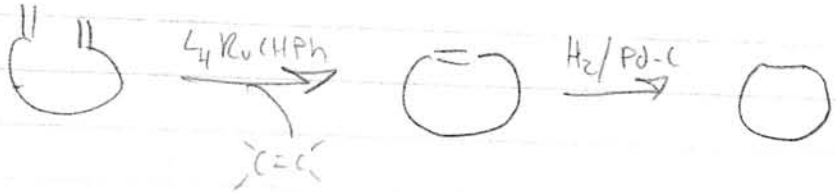
RCM PS 433-435



Grubbs 1 Grubbs 2

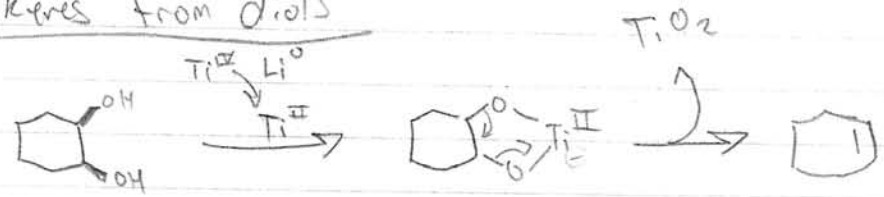


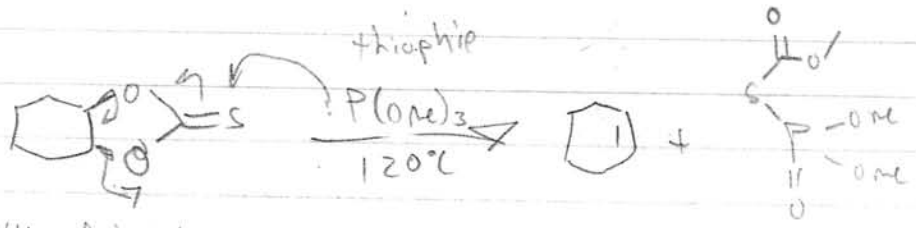
poor E/Z control
gives (Z) in rings < 12



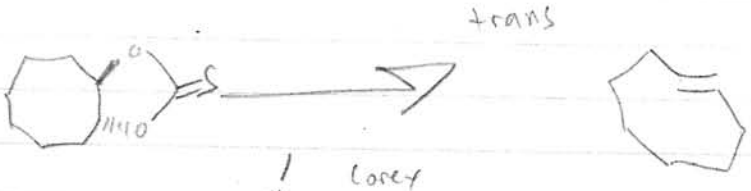
tolerates
esters, alcohols, epoxides, ketones

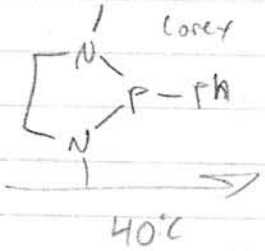
Alkenes from diols





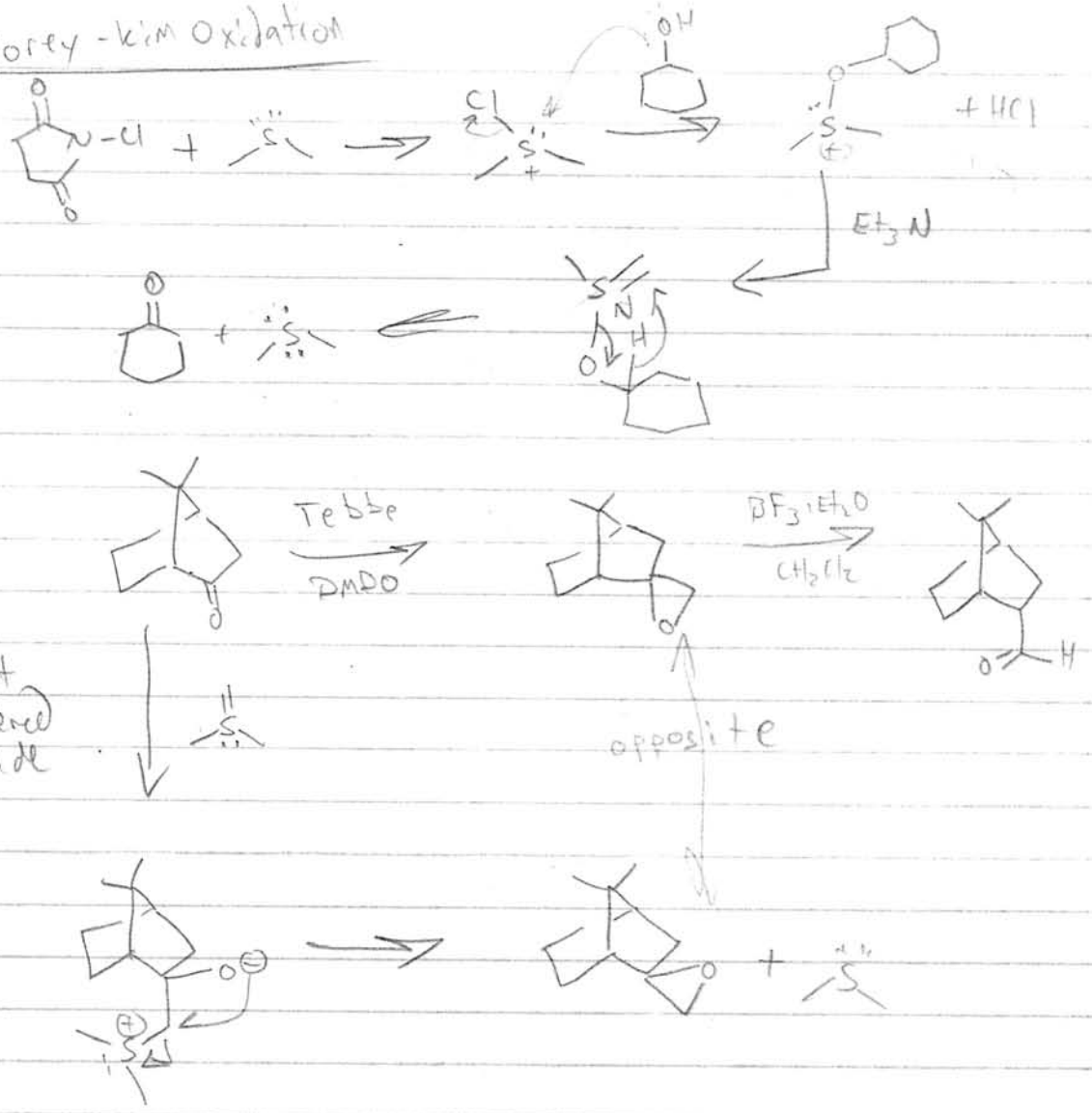
like Arbuzov



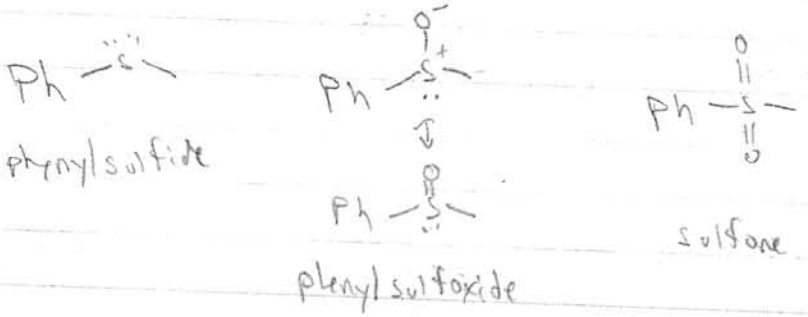


McMurry will work on large rings as well

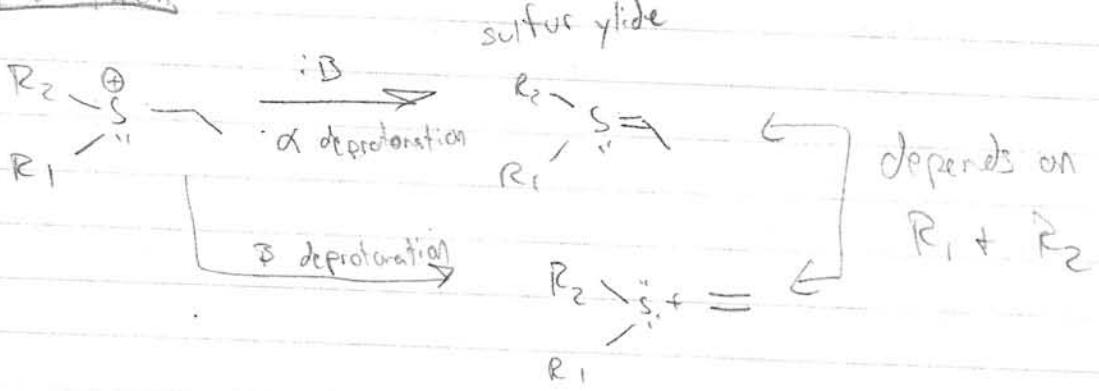
Corey-Kim Oxidation

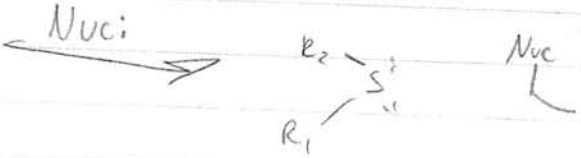


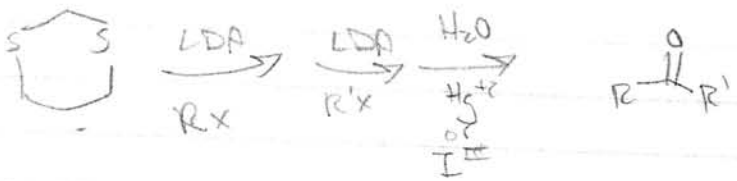
Sulfur Chemistry important to understand hypervalency

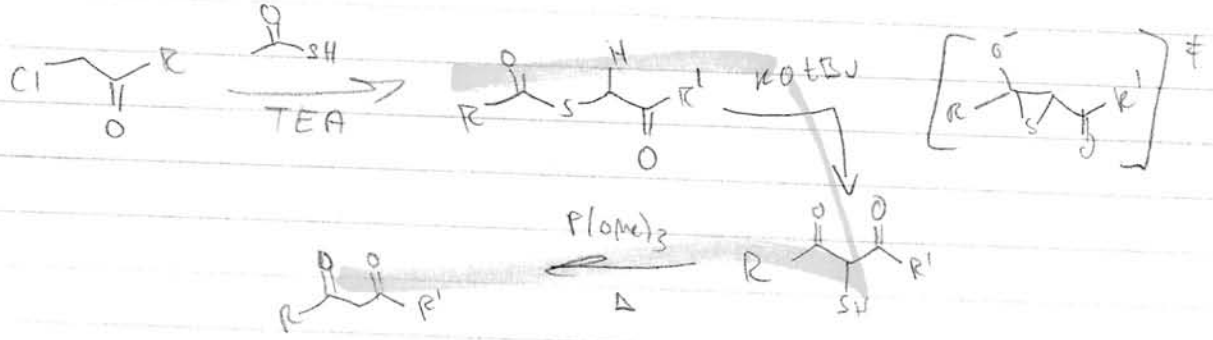


Basic Mech

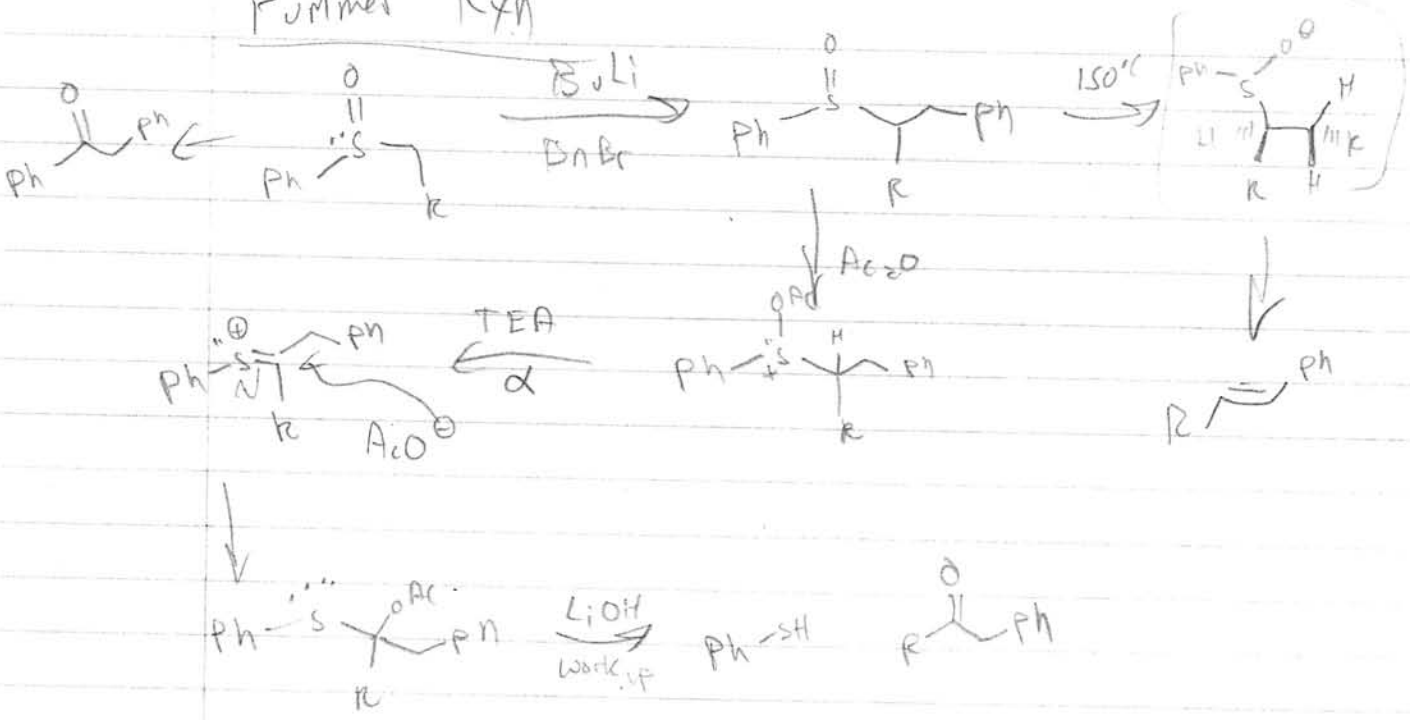




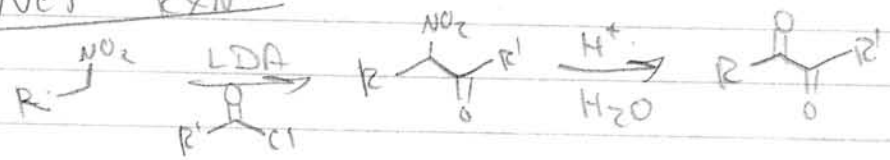


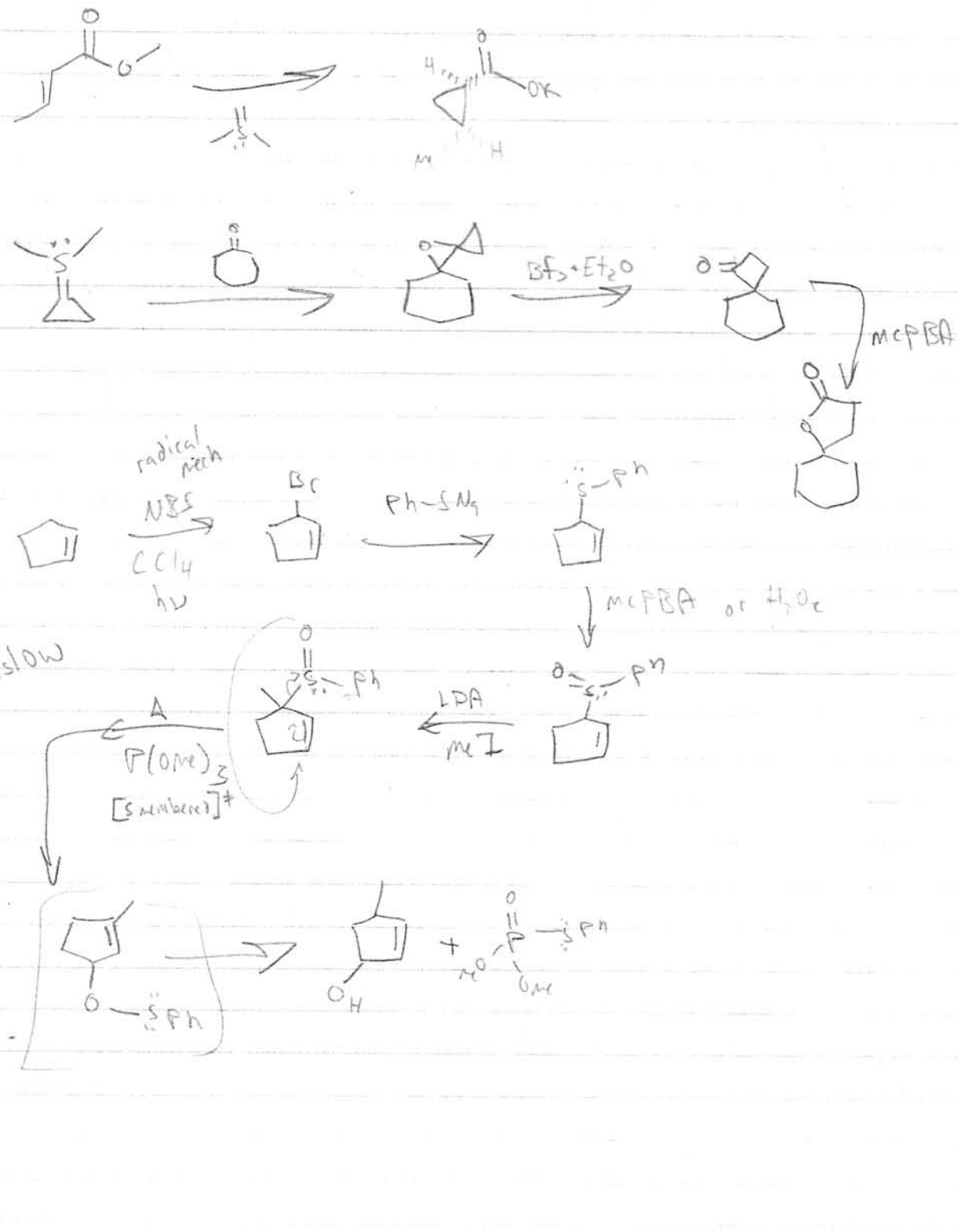


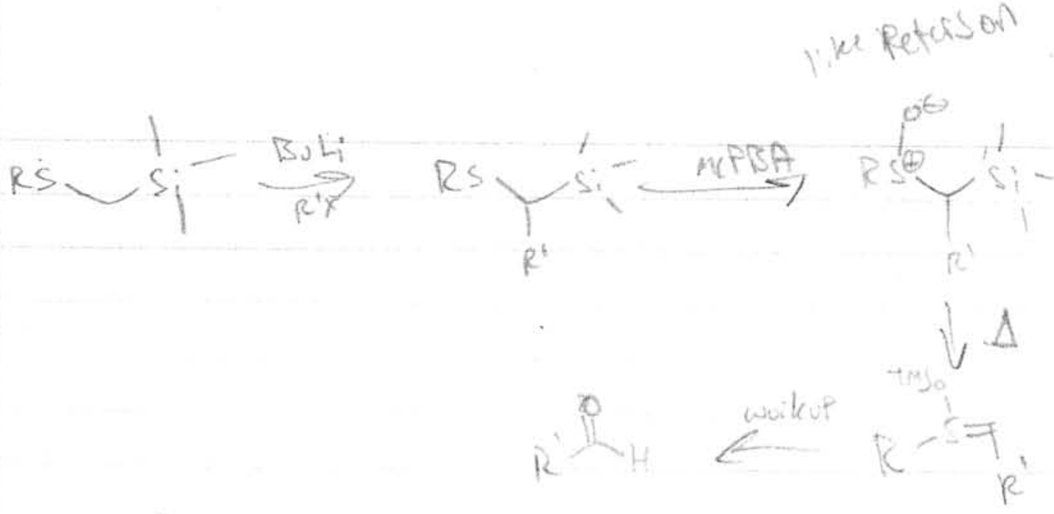
Pummer Rxn

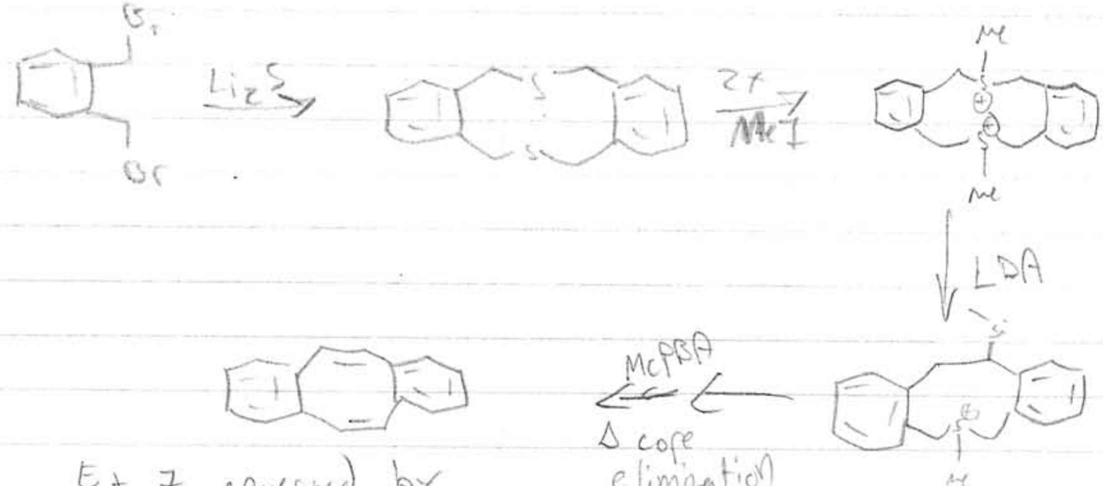


Nef Rxn




BF3•Et2O
mCPBA
radical mech
NBS
CCl4
hν
Br
Ph–SNa
mCPBA or H2O2
LDA
MeI
A
P(OMe)3
[5 membered]‡
Evans-Mislow
OH

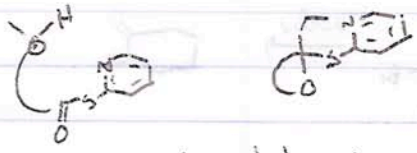




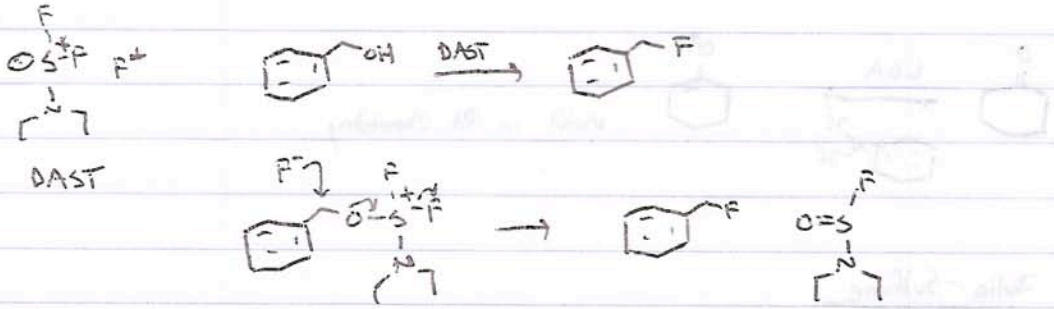
E + Z governed by
Newman projections

2/7 Problems Due Next Thurs.

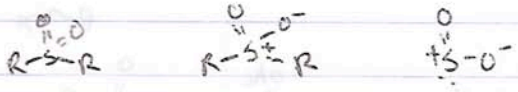
{ 1b, 1e, 1f, 1g
{ 2c, 2d, 2e

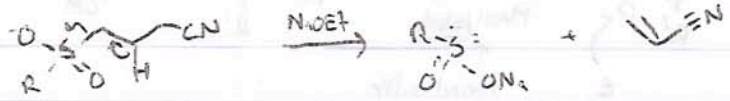


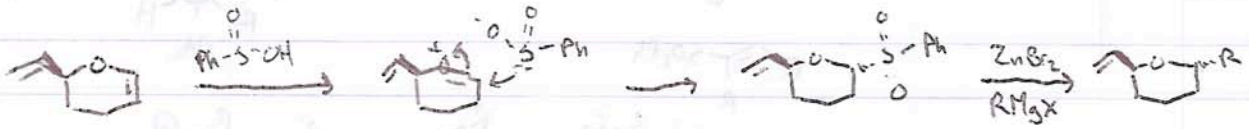
macrolactonization



sulfone

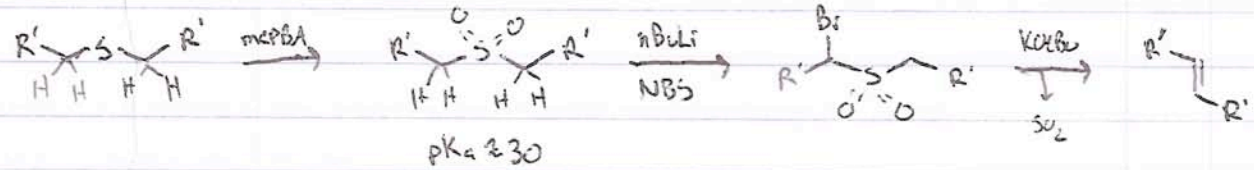






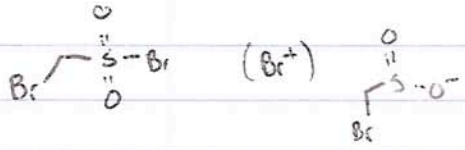
Ramberg Bicklund

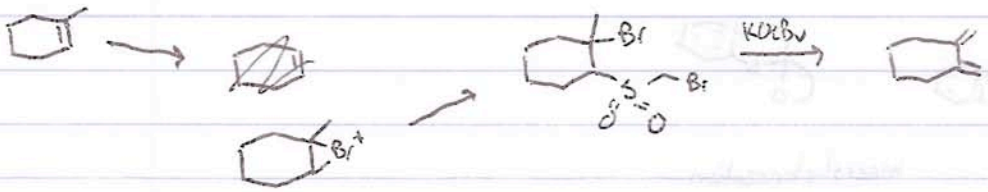
RX + Li$_2$S ⟶ R-S-R

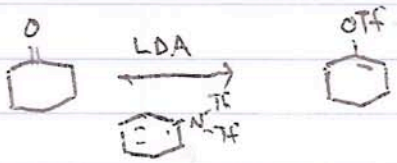


pKa ≈ 30

use BuLi

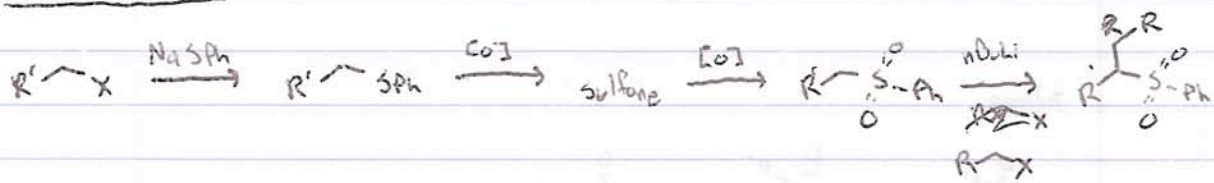


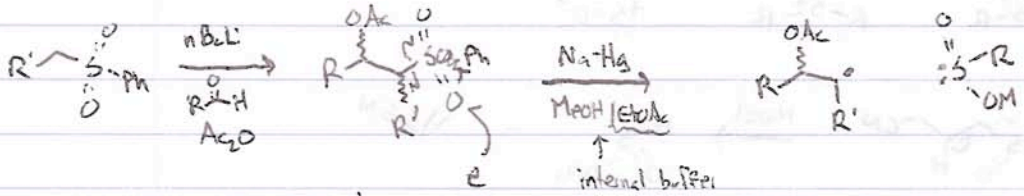




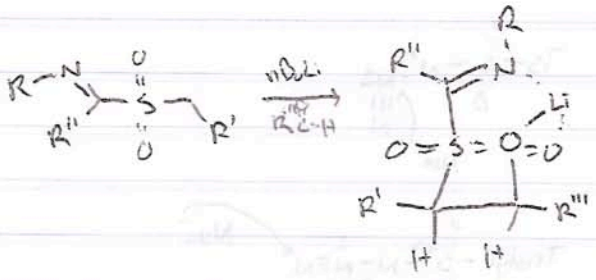
useful in Pd chemistry

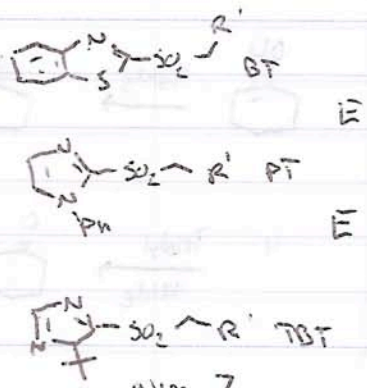
Julia - Sulfone



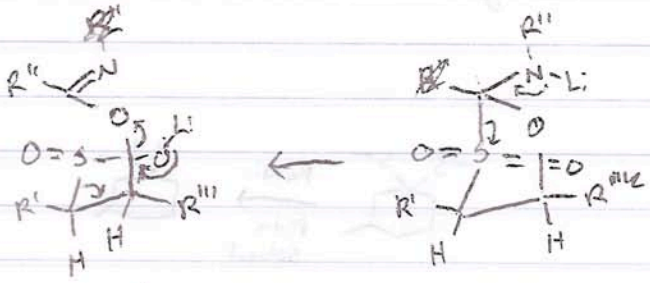


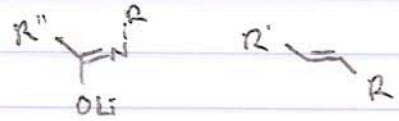
Modified Julia Sulfone



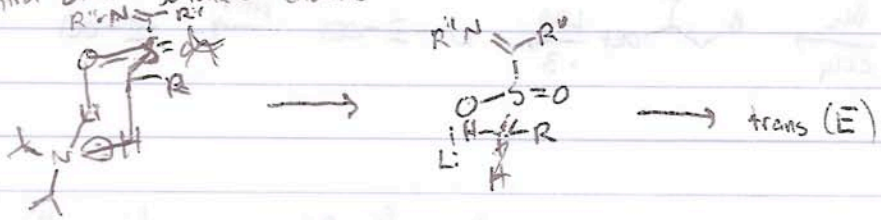


gives Z



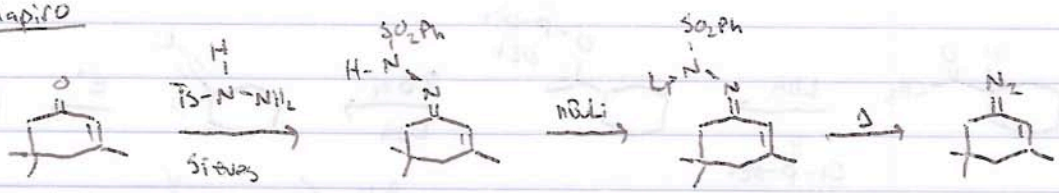


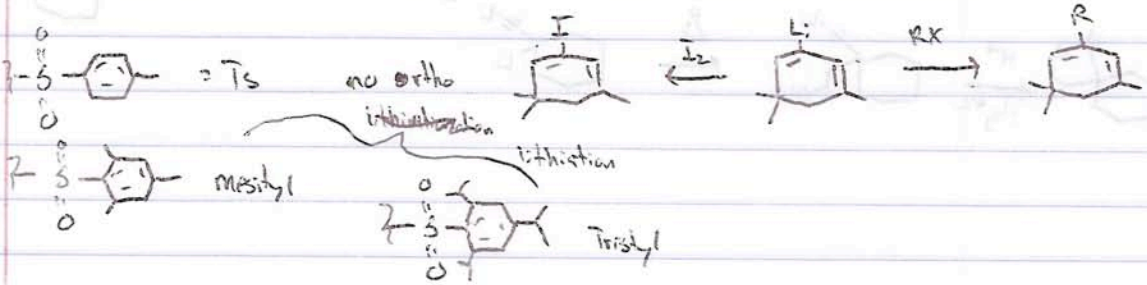
Control over sulfonate enolate

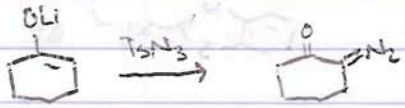
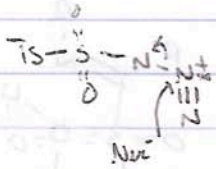
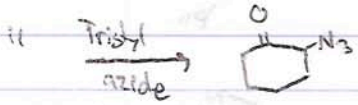
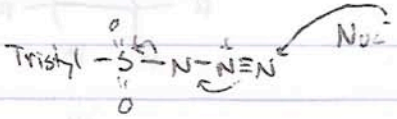


R' = tBu other enolate

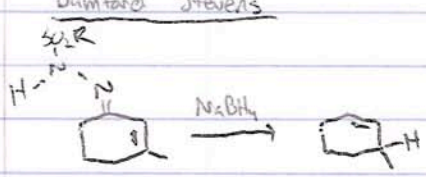
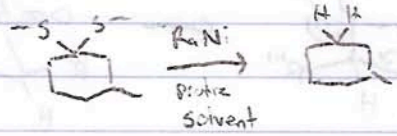
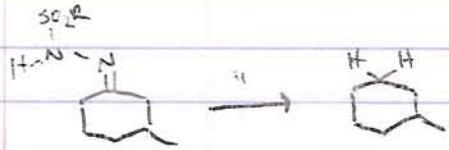
Shapiro



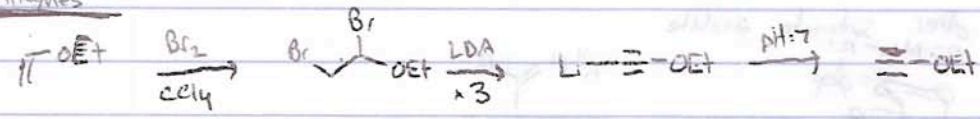


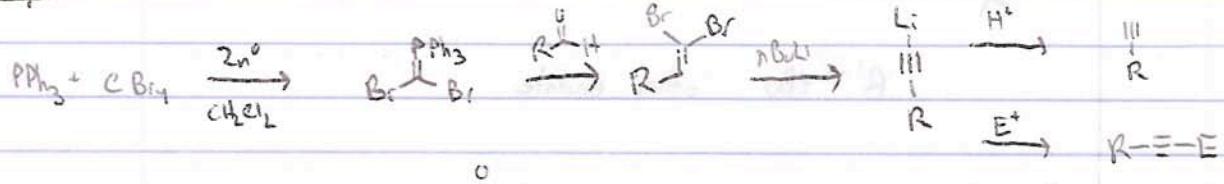
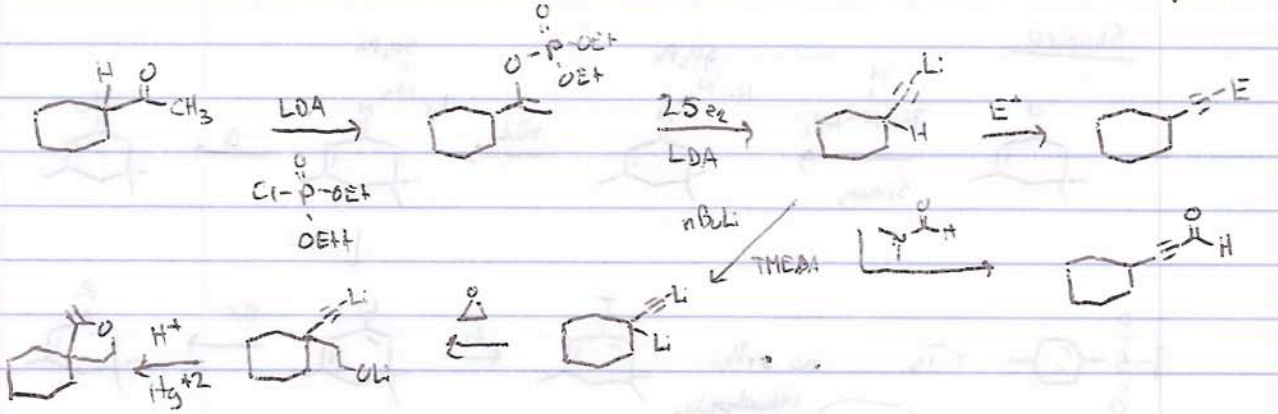
Bamford Stevens

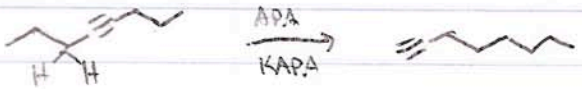
Alkynes



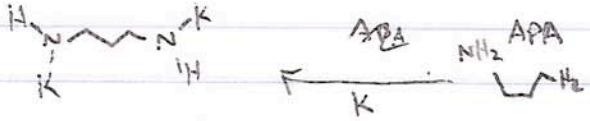
Corey Fuchs

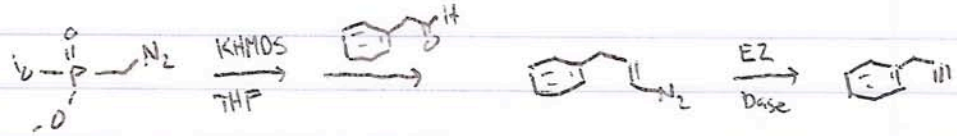
Alkyne walk

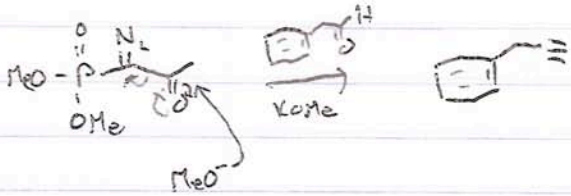


KAPPA



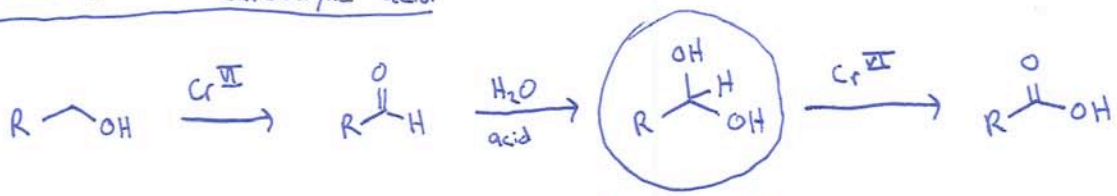
Gilbert Reagent





2/9 Oxidations

1° alcohol → carboxylic acid



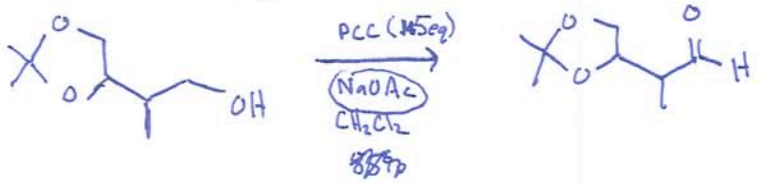
hydrate is oxidized to acid

1° alcohol → aldehyde

★ non acidic, anhydrous conditions

- Pyridinium Chlorochromate (PCC)

soluble in CH_2Cl_2



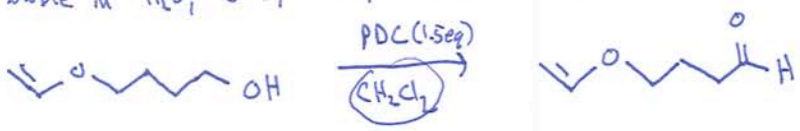
NaOAc neutralizes PCC, avoids deprotection of ketal

MS gives higher yields of aldehyde

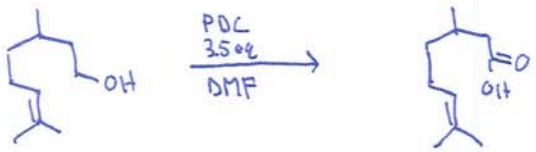
- Pyridinium Dichromate (PDC)

less acidic than PCC

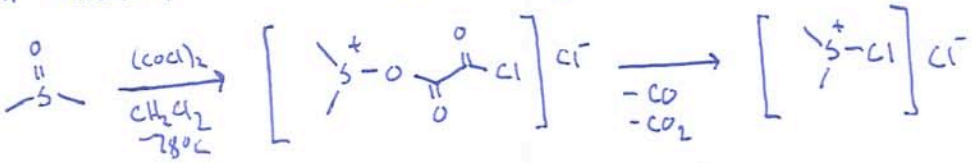
soluble in H_2O, DMF, DMSO, ~ CH_2Cl_2, $CHCl_3$

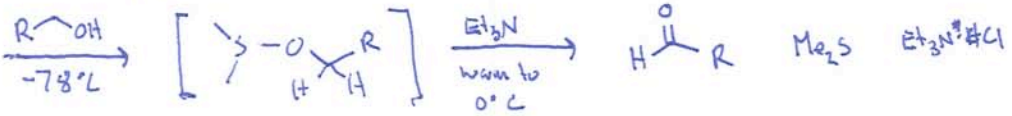


in DMF and excess PDC, alcohols are oxidized to acids

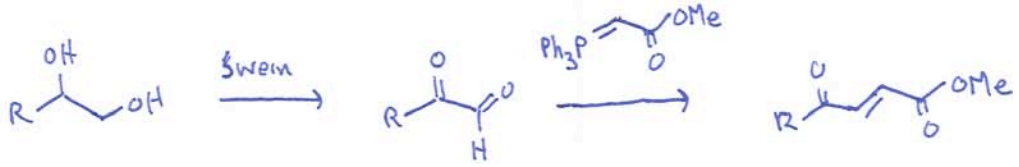


- Swern oxidation DMSO, $(COCl)_2$; alcohol; Et_3N in CH_2Cl_2



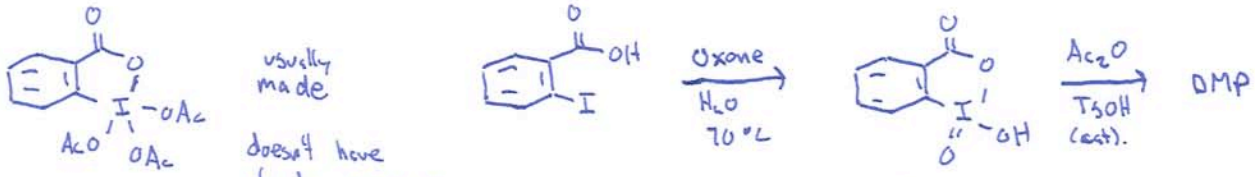
then: 

ex.



α-keto aldehyde
prone hydration, polymerization, air oxidation

- Dess Martin Periodinane

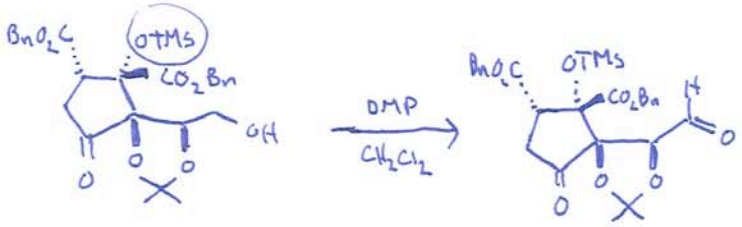


usually made

doesn't have to be super dry

IBX explosive

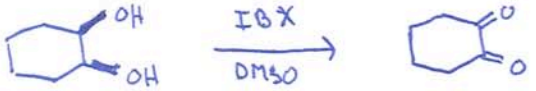
Oxone = $KHSO_5$, $KHSO_4$, K_2SO_4



Works well on ~~not~~ acid sensitive groups
trace H_2O accelerates reaction

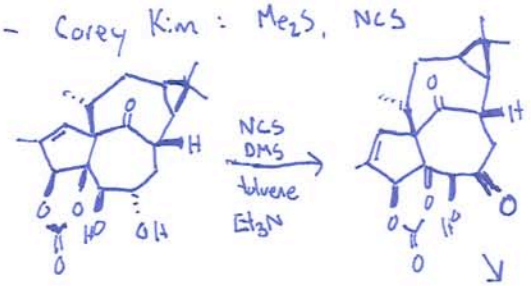
~~IBX~~ ★ cleaves 1,2 diols

- IBX



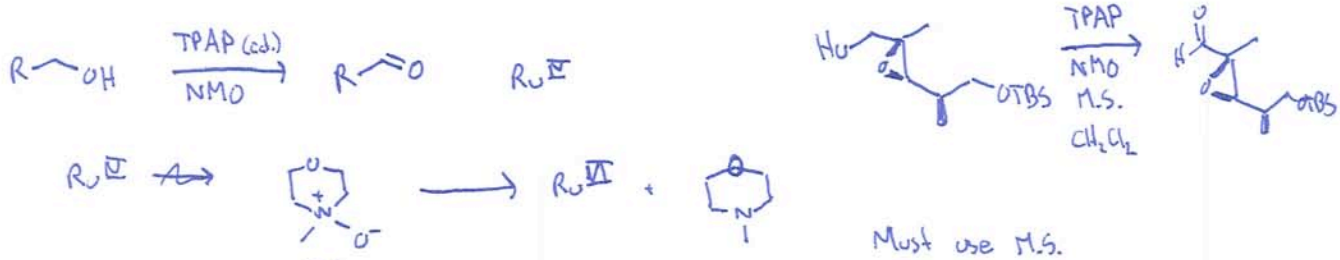
- IBX is soluble only in DMSO
- Cleavage can be a problem Corey Kim, Swern okay

- Corey Kim : Me_2S, NCS



Ingenol

- TPA (Tetrapropyl ammonium perruthenate) $Pr_4N^+ RuO_4^-$



Must use M.S.

2° alcohols in the presence of 1°

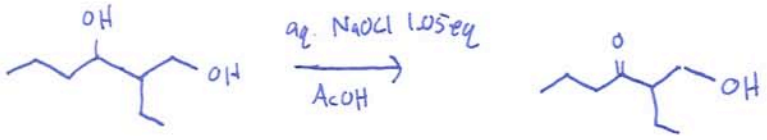
- CAN $(NH_4)_2Ce(NO_3)_6$, $NaBrO_3$

  no double bonds

- Triphenyl carbenium tetrafluoroborate ($Ph_3C^+ X^-$)

Selectivity: $R_2^+C\text{-}OTr$ formed faster than $RH^+C\text{-}OTr$

- $NaOCl$

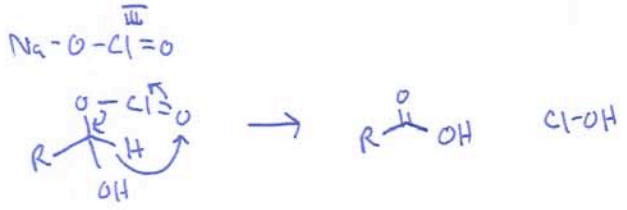


Aldehydes → Acids

- ~~Lindregn Lindgren~~ Lindgren

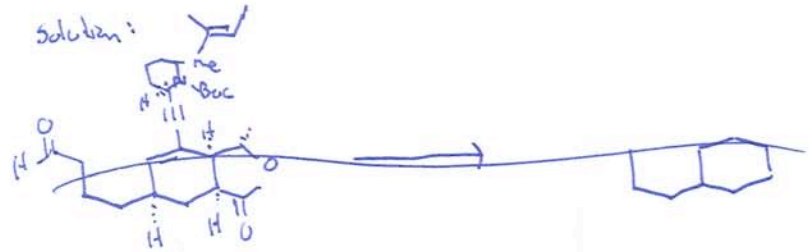
  Pinnick oxidation

  $NaClO_2$, sulfamic acid H_2NSO_3H, NaH_2PO_4 buffer, HClO scavenger

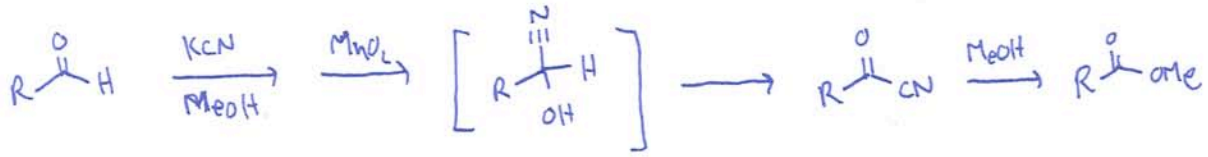


double bond can chlorinate

Solution:



Aldehyde → ester



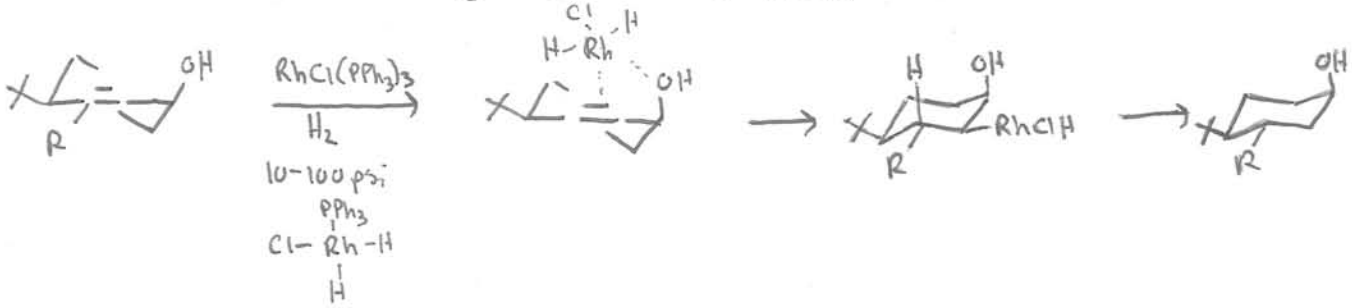
2/16 Reductions

By transformation, not reagent

Olefins → alkanes

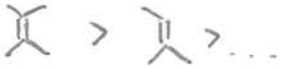
a. Pd/C H_2 EtOH (some steric control)

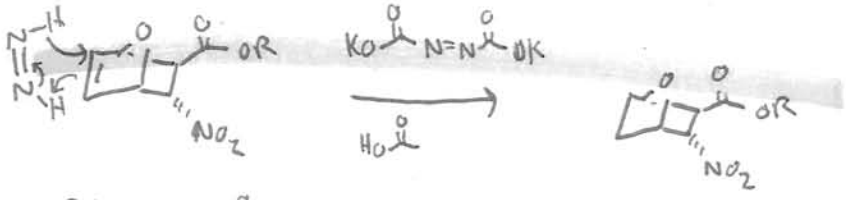
b. Wilkinsons catalyst (homogeneous) can be directed



c. Crabtree's catalyst also directed $[R_3PIr^{I}(COD)py]^{+}PF_6^{-}$

100 psi – 1000 psi H_2

d. Diimide (sterically conjested, electron rich) 



e. BH_3 / can be directed

Alkynes → cis alkenes

a. Lindlar's catalyst (cyclohexene)

b. diimide

c. BH_3 /

d. for  : $HSnBu_3$, AIBN

Alkynes → trans alkenes

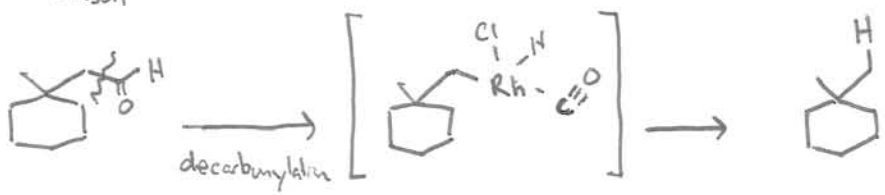
a. Na/NH_3

b. DIBAL

~~~~

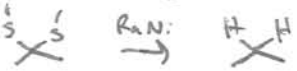
Aldehyde → H

a. Wilkinson



b. Clemmensen $Zn\text{-}Hg$ & HCl

c. Wolff Krishner H_2N_2 KOH

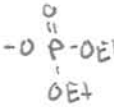
d. Mozingo 

R–X → R–H

a. Super hydride $LiEt_3BH$ (S_N2)

b. X = Br, Cl, I,  $H\text{-}SnBu_3$ / AIBN (radical)

c. $LiAlH_4$

d. X = vinyl (OTf),  OTs $HSnBu_3$, Pd^0

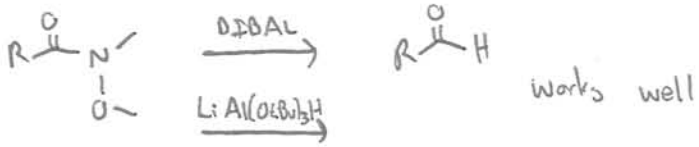
a. Rosemund Reduction Pd^0/H_2

b. $LiAl(OtBu)_3H$
~~~~

a. DIBAL HOT!

hexanes, toluene, CH_2Cl_2, THF

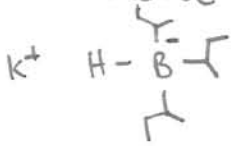
hot ——— cold



works well

Enone → enolate

a. K-Selectride



b (SET) Na / NH_3 SmI_2

Enone ~~to~~ ketone (no enolate)

a. $RhCl(PPh_3)_3$ TESH

b. Stryker PPh_3CuH

c. $NaHFe_2(CO)_8$

a. DIBAL

b. Lucke $NaBH_4$, $CeCl_3$

want wet selective over aldehyde

Nitrile → amine

$LiAlH_4$ difficult

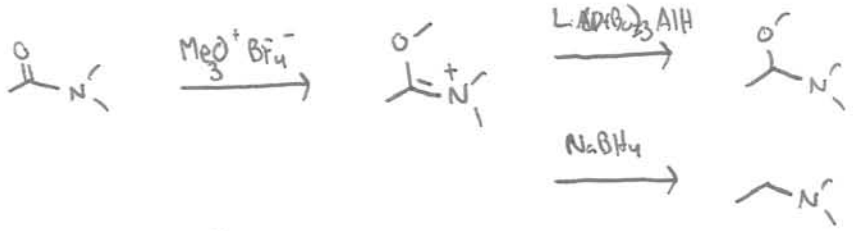
Amide → amine

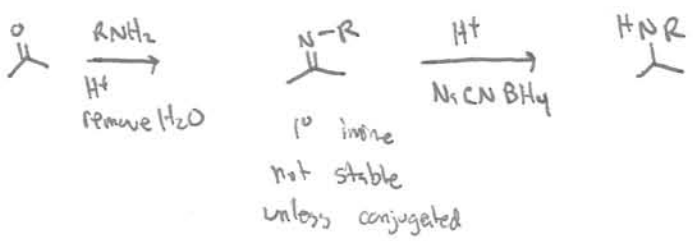
a. $LiAlH_4$

b. R_2BH

c. $Me_3O\ BF_4^-$

add $L{:}(OtBu)_3AlH$ → aldehyde add $NaBH_4$ → amine





1° imine not stable unless conjugated

Nitro → amine

a. $NaBH_4$ / $CoCl_3$

b. $LiAlH_4$

 →

a. $LiAlH_4$

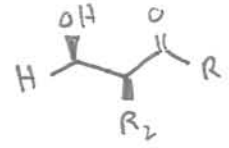
b. BH_3

ketones → alcohols

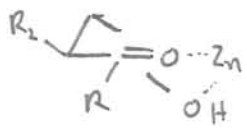
LAH, $NaBH_4$

SmI_2, MeOH (SET) most selective

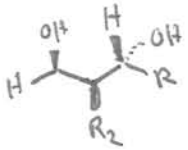
DIBAL, TIBAL, L-Selectride

Ex. 

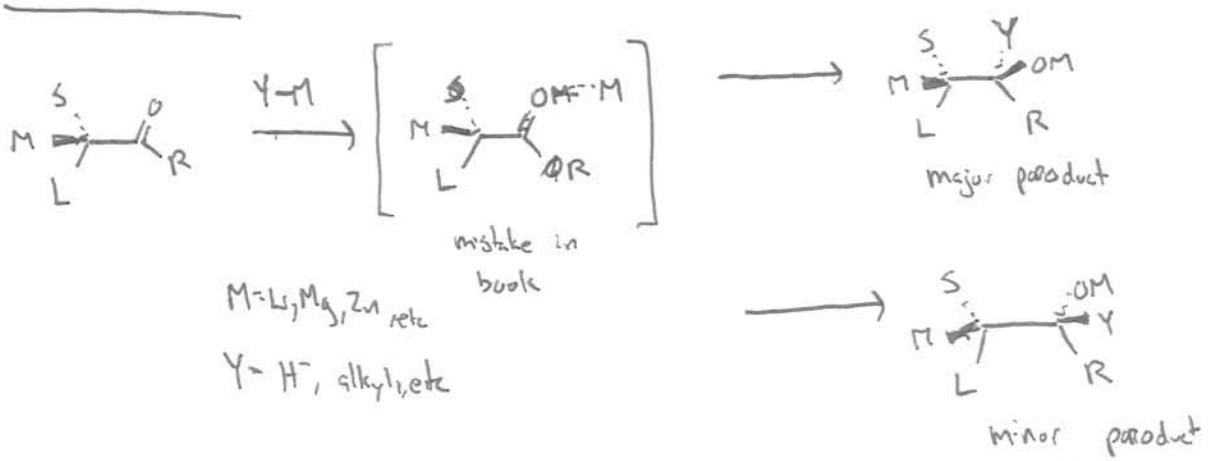
$Zn(BH_4)_2$ selective ketones only for free hydroxyl group or ether



R = OMe
OBn
OMOM
$OSiR_3$ not good

→ 

Cram's rule

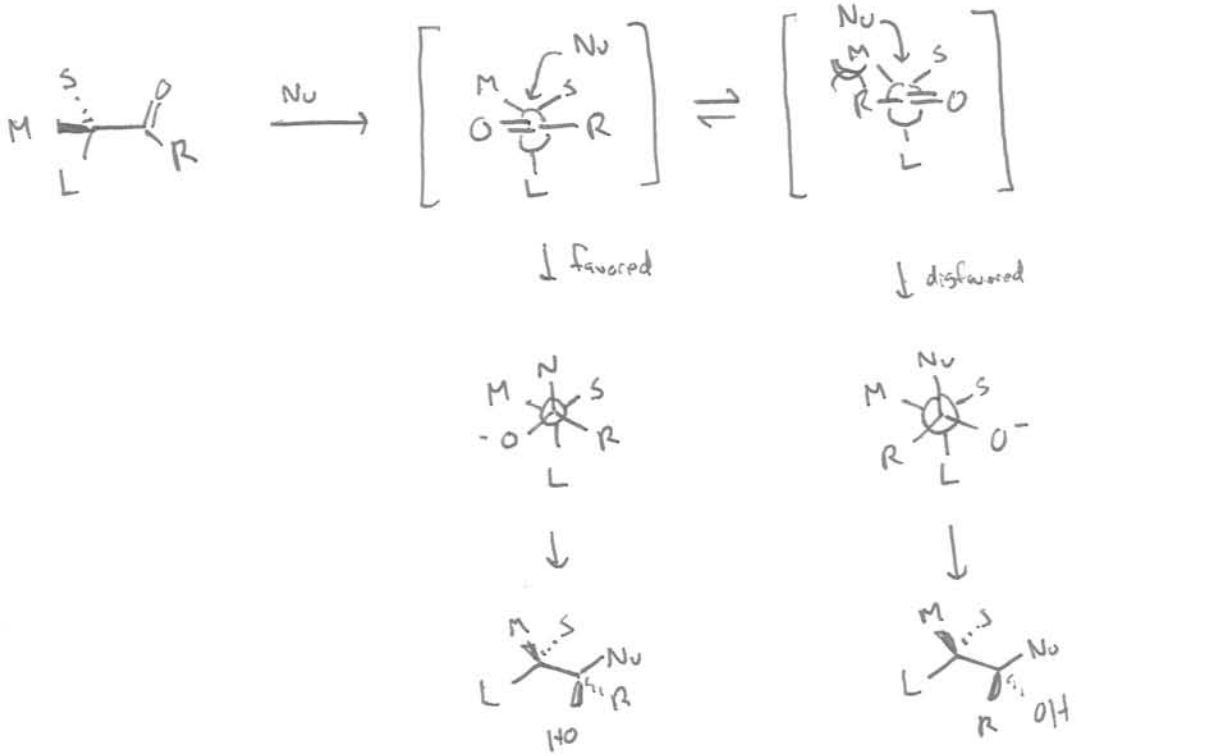


M = Li, Mg, Zn etc

Y = H^-, alkyl, etc

- only valid for no chelating groups
- torsional strain between L and R

Felkin-Anh



2/12

Organometallic Chemistry

Transition metals (Hegedus book) $18e^-$ in outer most shell

Pd^0 s^2d^8 → s^0d^{10} $Ph_3P{=}Pd(PPh_3){=}PPh_3$ $d^{10}+8 = 18\,e^-$

Pd^{+2} s^0d^8

$Ph_3P(PPh_3)Rh^{I}(Cl)PPh_3$ $(OC)_4Mn^{I}(H)$ charge Mn^I

neutral ligands: ROR PPh_3 R-OH $C{\equiv}O$ $h=1$

$= \equiv$ $h=2$

-1 ligand: -Cl, -Br, -H $h=1$ ⇌ $h=3$

-2 ligand: $=O$

$4e^-$ neutral: $h=4$ Mg

$6e^-$ -1: (Cp) $h=5$

Basic mechanism:

I. Oxidative insertion

a) concerted, agostic

M···H 3 center

H 2e⁻ bond

ex: R–Br $\xrightarrow{Pd^0}$ R–$Pd^{II}L_4$–Br → R–$Pd^{II}L^0_2$–Br

retention of geometry

b) S_N2 or S_N2' mechanism CH_3

$M^0L_4^0 + CH_3X \longrightarrow L^0M^{II}L^0$ (X)

ex: OAc + PdL_4^0 → AcO–Pd(II)–L^0 ⇌ L^0–Pd–OAc

X, III

L^0–Pd^{II}

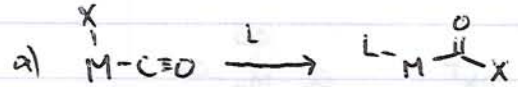
c) cycloaddition 2+2+1

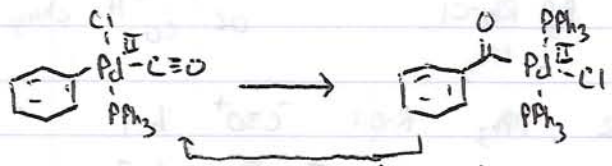
$\xrightarrow{M^0}$ M^{II}

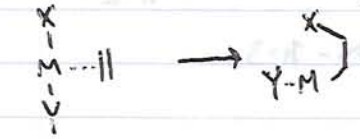
σ donor ligands facilitate oxidative insertion

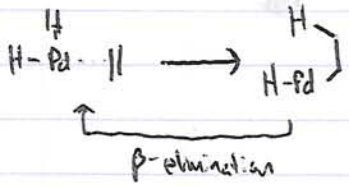
π acceptor ligands supress oxidative insertion

II. Migratory insertion or its reverse

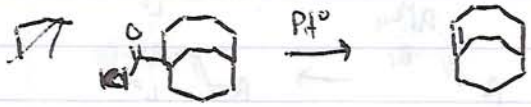
a) 



b) 

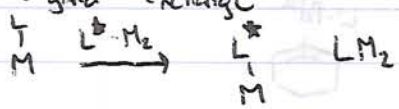


aptitude : allyl > alkyl > vinyl > aryl > hydride

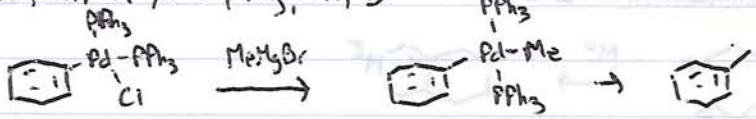


III. Nucleophilic attack

IV Ligand exchange



M_2 = Cu, Zn, Tl, Mn, Mg, Sn, B



V. Reductive elimination

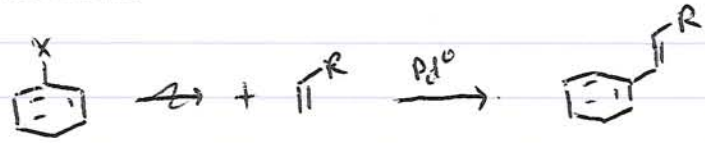
reverse of oxidative addition

σ donor ligands supress red. elim.

π acceptors facilitate red. elimin.

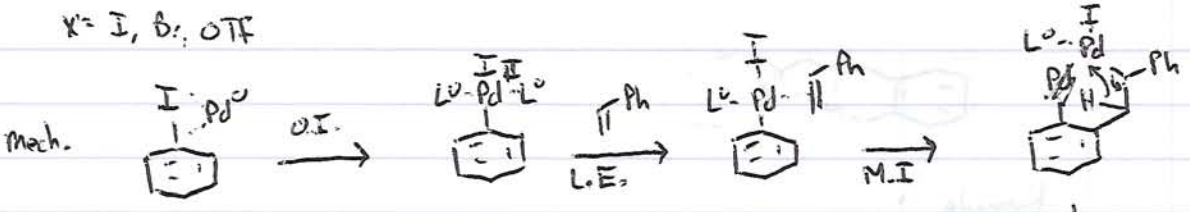
groups must be cis

Heck reaction

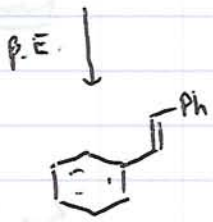


X = I, Br, OTf

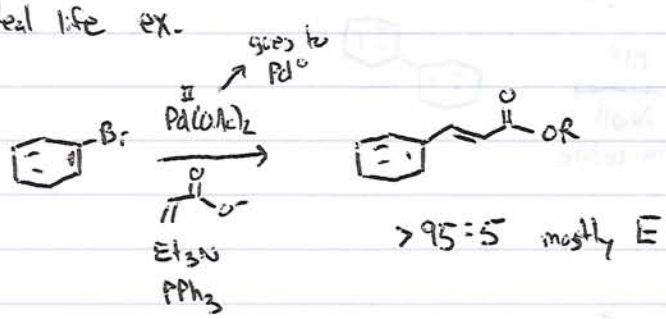
mech.



Sterics and electronics

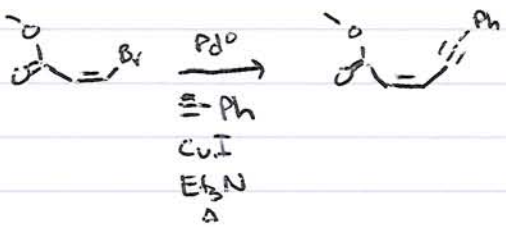


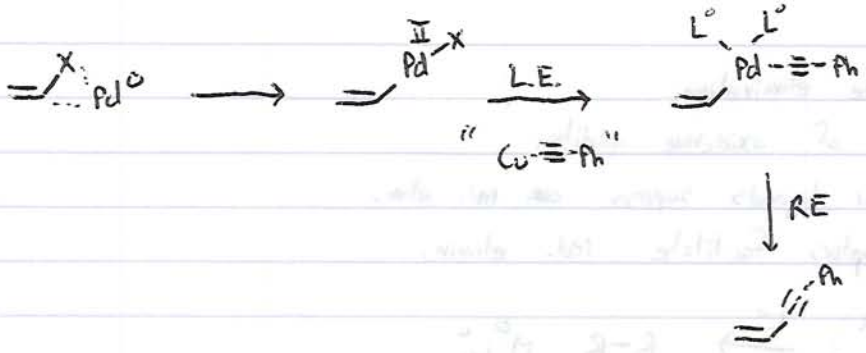
Real life ex.



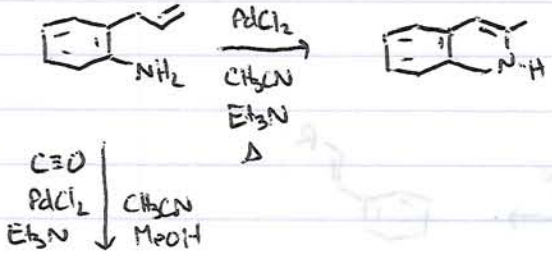
>95:5 mostly E

Sonogichira / Stevens-Castro

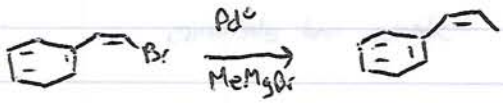




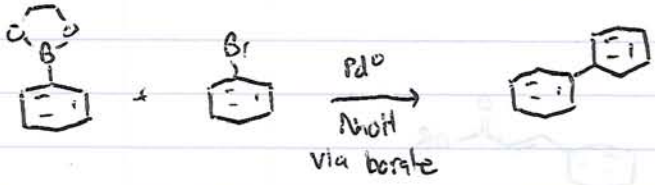
Hetero Heck



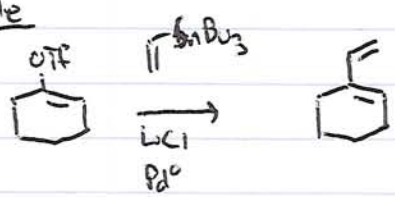
Kumada



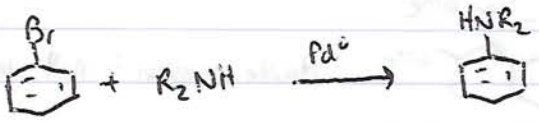
Suzuki



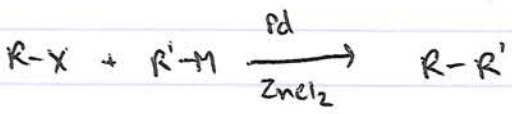
Stille



Buchwald-Hartwig

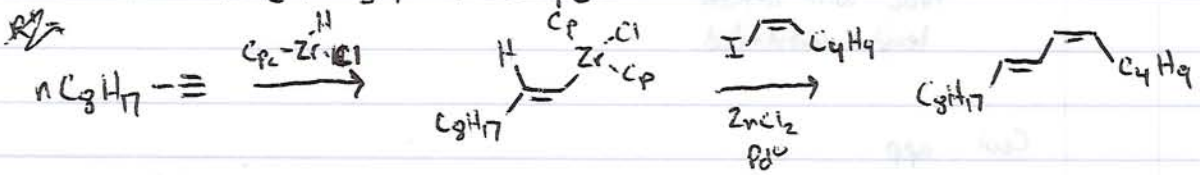


Negishi Modification

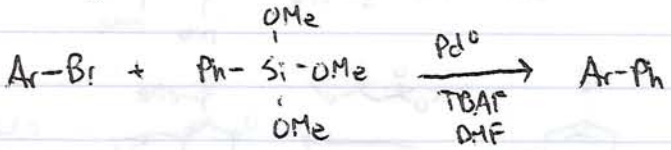


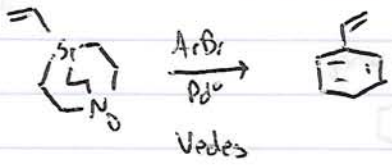
R: vinyl, acetylene

M= ~~aluminum~~ AlR_2, MgX, Li, $ZrClCp_2$

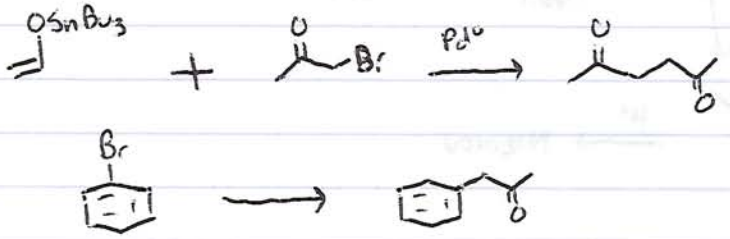


Deshong

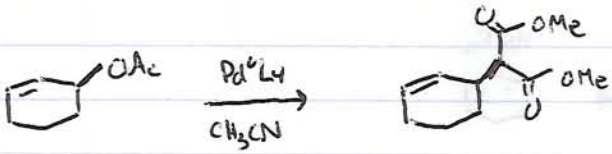




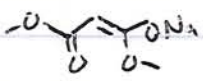
Migita



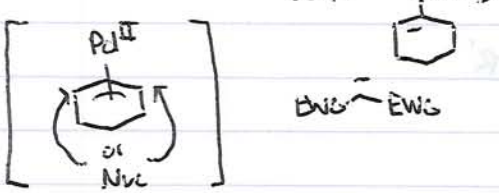
Trost allylation



double inversion = net retention

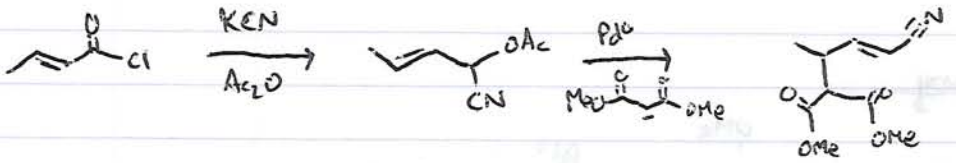


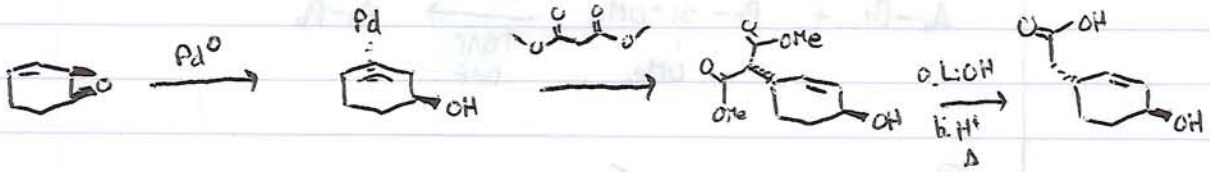
soft

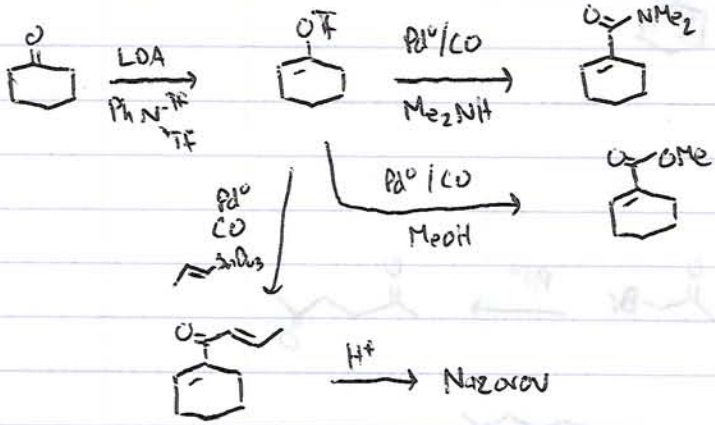


Nuc will attack least substituted

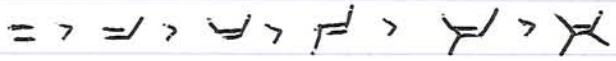
Cooi app

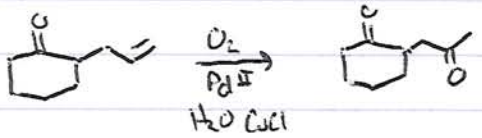




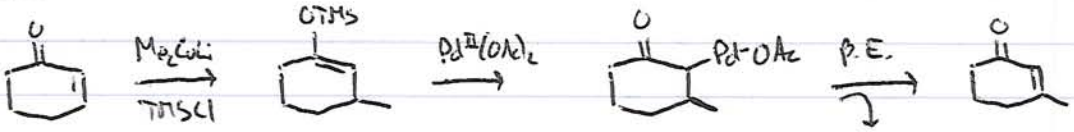


Wacker





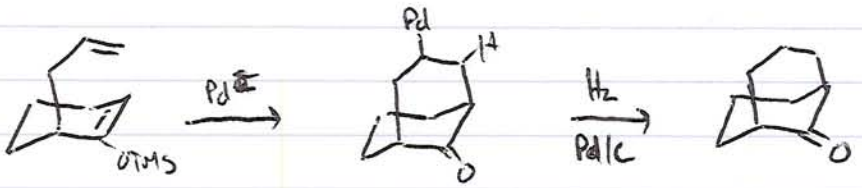
Segusa



typically uses stoichiometric Pd^{II} or ½ eq Pd^{II}, DDQ

$Pd^{0} \xrightarrow{DDQ} Pd^{II}$

Rawle Closure

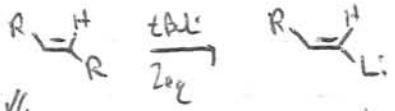


Chapter 7 problem set due Tuesday

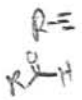
2/14

Lithiation (deprotonation, LHE)

LHE fast rxn vinyl > 1° more stable 2° > 3°



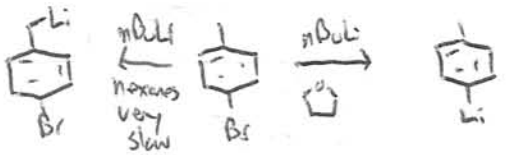
geometry control



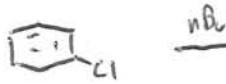
1° R-Br or RI

CO_2 DMF RCHO R_2CO

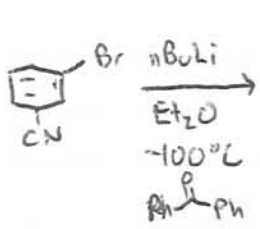
trap mixture 4:1:1 THF : Et_2O : Pentane

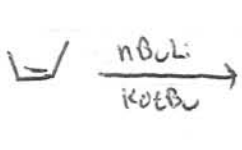


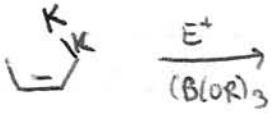
TMEDA



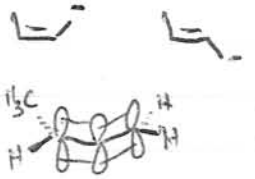
benzyne







geometry lock



anion next to π is sp^2

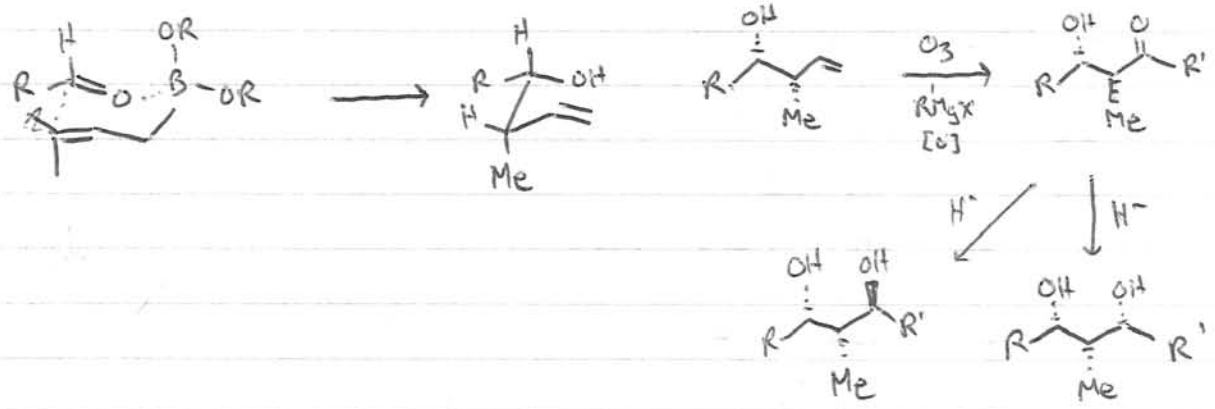
deprotonation

$R_3CH + R'Li \longrightarrow R_3CLi + R'H$

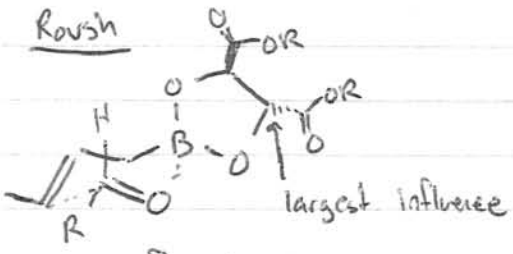
R_2NH	30-37
aliphatic	45-50
vinyl	44
R-≡-H	25

Z → syn

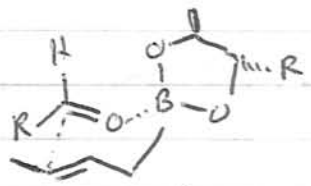
E → anti



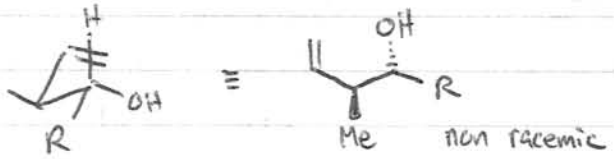
Roush



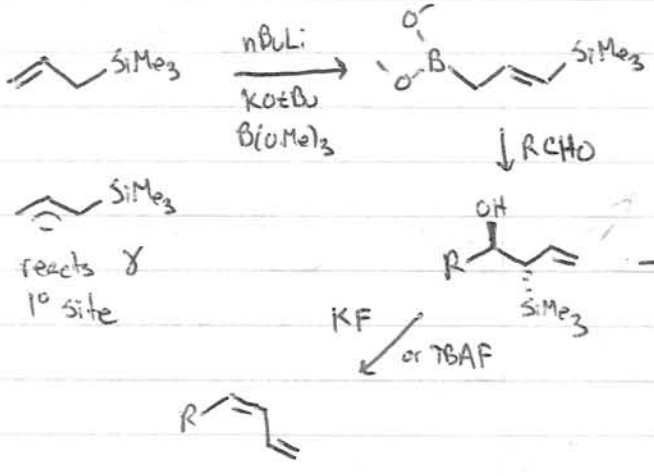
favored



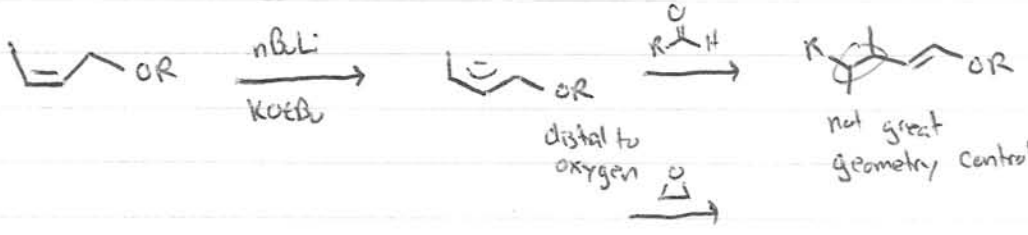
not favored

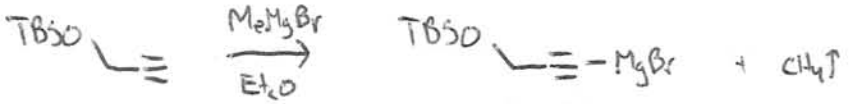


ex



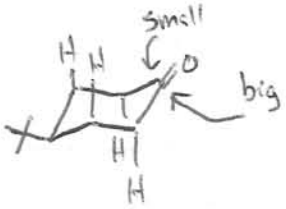
ex





Titanium reagent

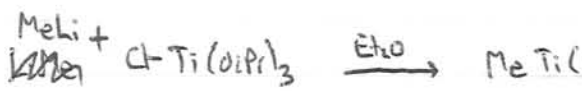
non basic, very bulky



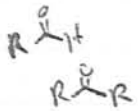
~~Small: MeLi~~

Small: MeLi

large: use titanium reagent



give equitorial addition only



Cerium non basic 1,2 adds to   

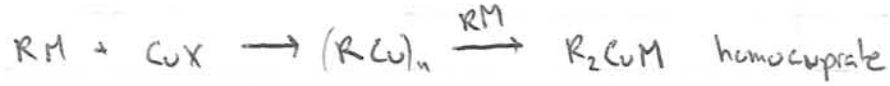
Iwamoto

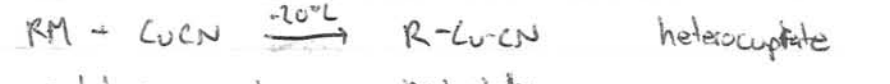
one polymorph to work

remarkable example

~~Organo Copper~~

Organo copper

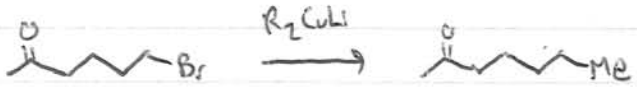




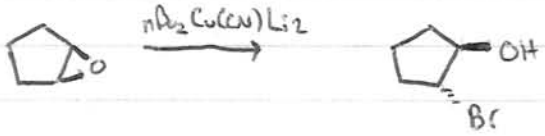
Higher order

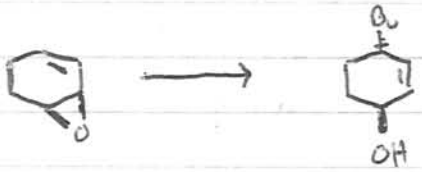
$CuCN + 2RLi \longrightarrow R_2Cu(CN)Li$

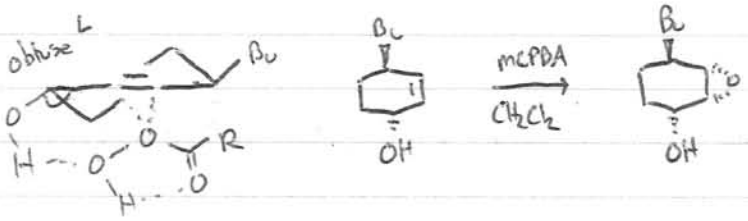
Cuprates displacement of 1° RX very soft



opening epoxides

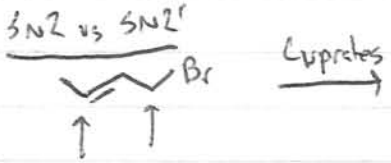




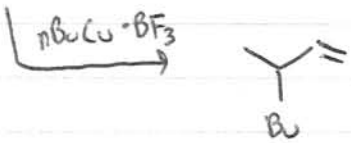


Henbeck

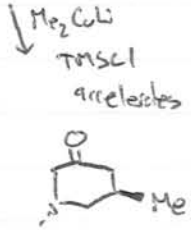
S_N2 vs S_N2'



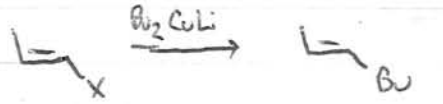
Cuprates → S_N2 or S_N2'



Conjugate addition

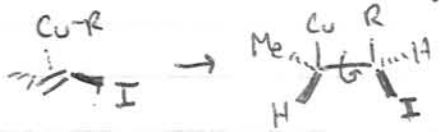


Also good for:



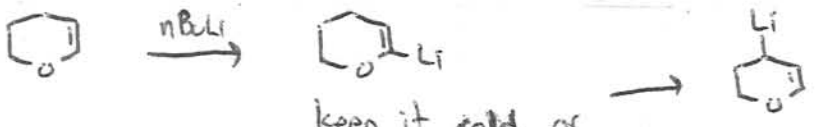
X = I, Br, OTf, OTs

carbocu



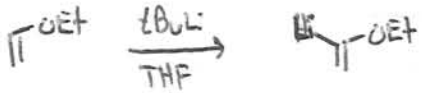
rotate and Eliminate

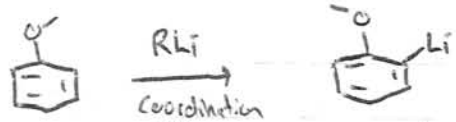
inductive effect S >> O > N



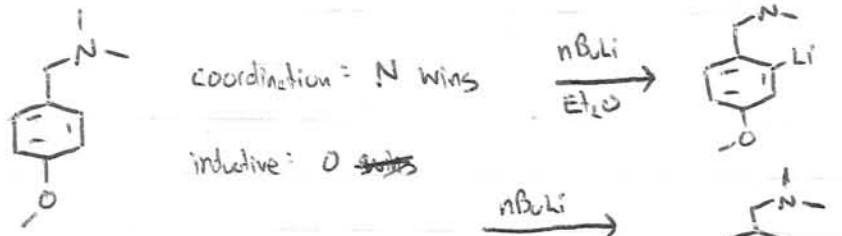
keep it cold or

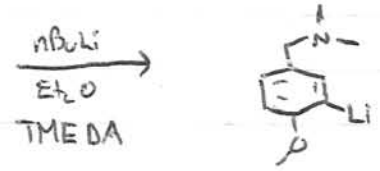
can trap as bromide, then regenerate under milder conditions

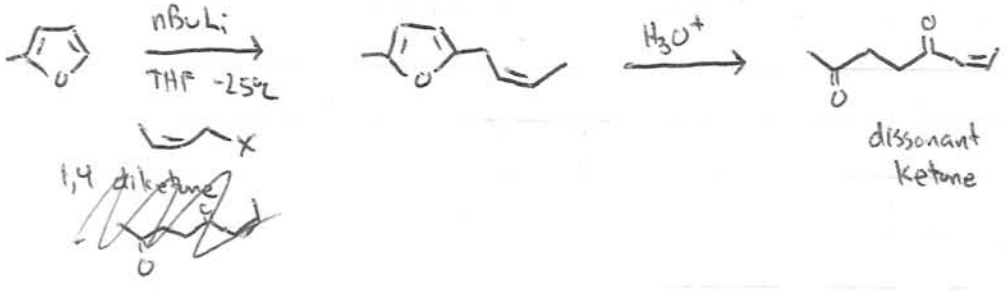




reacts ortho ~~to~~



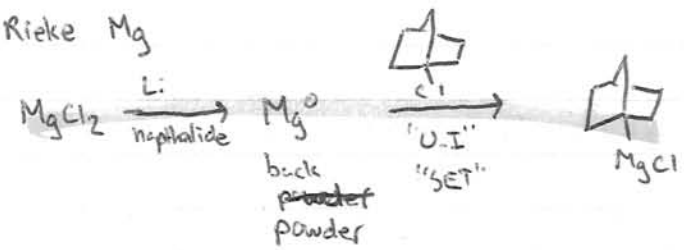


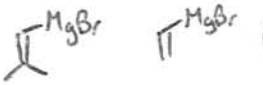


dissonant ketone

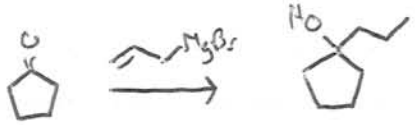
Magnesium

Rieke Mg



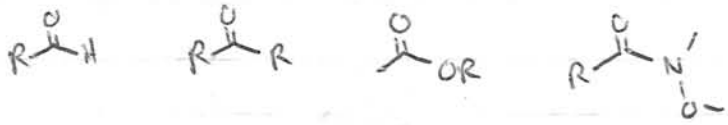


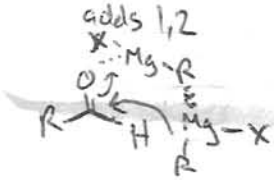
(geometry doesn't matter)



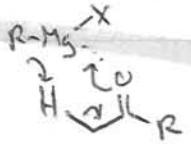
SET character

prone to wurtz  side product





can act as base



not as basic as RLi

Reduction

β hydride Rondorph

Meerwein V Verley Reduction

adds 1,2 1,4

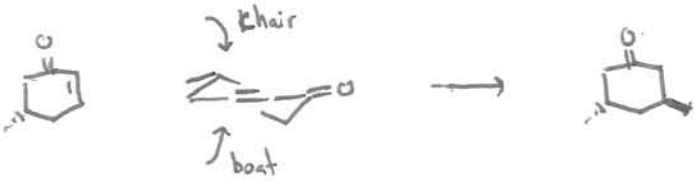
enolization and red

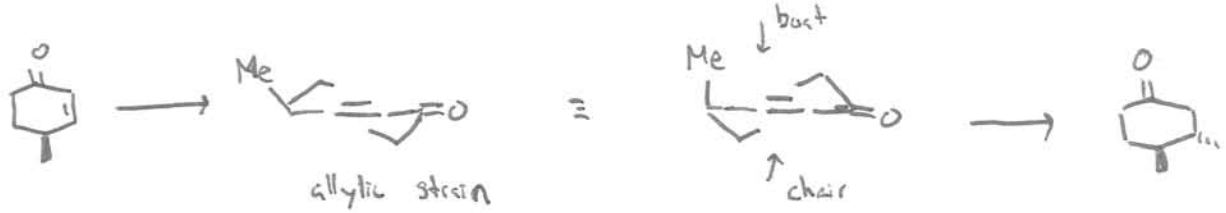
enolization only

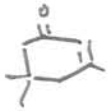
acts as base

2/19

Conjugate addition of cuprates





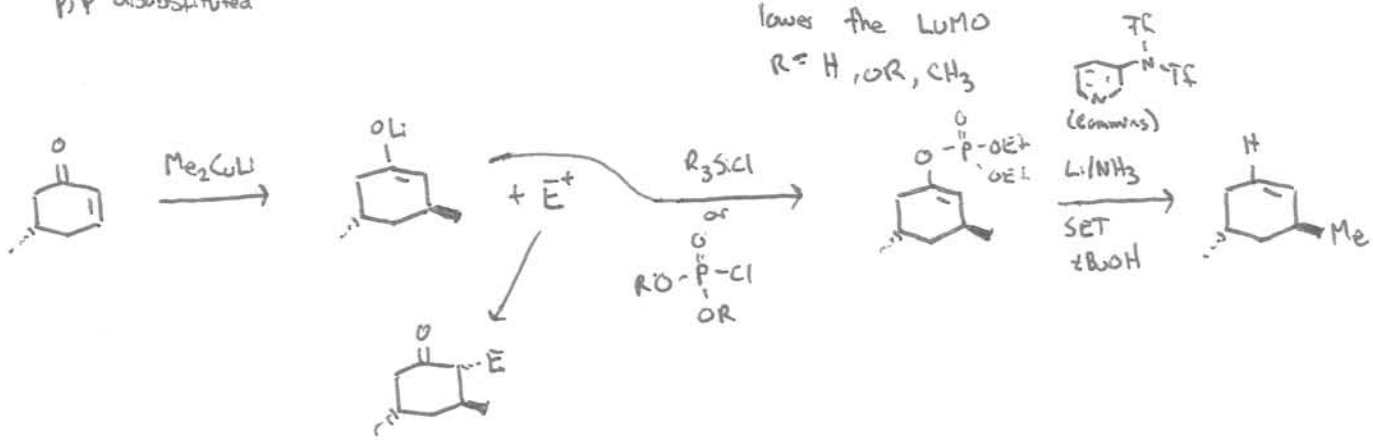


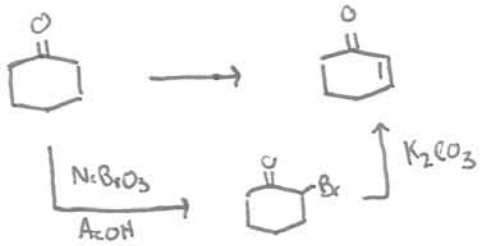
very unreactive

β,β disubstituted

lower the LUMO

R = H, OR, CH_3

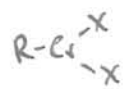


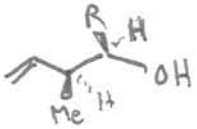


1. a) N_aBrO_3, AcOH
   b) K_2CO_3
2. Pd^{+2}, a) TMSOTf, DBU
   b). Pd^{+2} DDQ
3. a) IBX DMSO

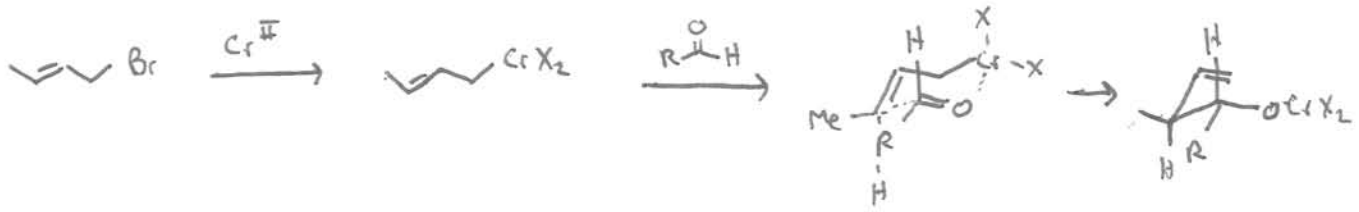
Chromium

$2CrCl_3 \xrightarrow{LAH} 2Cr^{II} \xrightarrow{R\text{-}X} R\text{-}Cr^{III}$



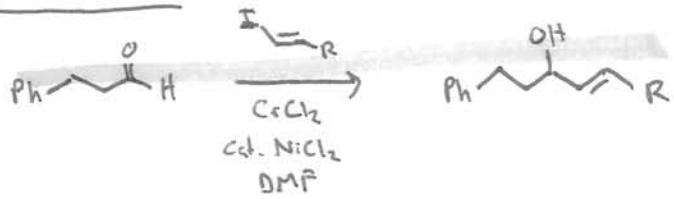


III



Nozaki-Kishi

Br, OTf, I



will close strained rings

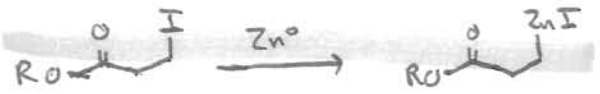
SE character

works in the presence of ketones

Zinc reagents

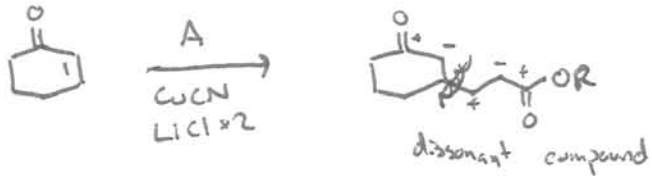
$Zn^0 \xrightarrow{R\text{-}X} R\text{-}Zn\text{-}X$

tolerates  , $\text{-}C{\equiv}N$

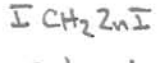


homo enolate

use in Pd cpl

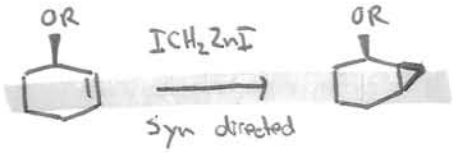


dissonant compound

$CH_2I_2 \xrightarrow[\text{or } Zn\text{-}Cu]{Zn^0}$ 

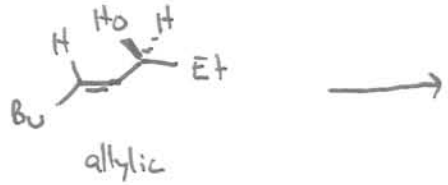
carbenoid

" $CH_2^{\pm}$ "



Syn directed

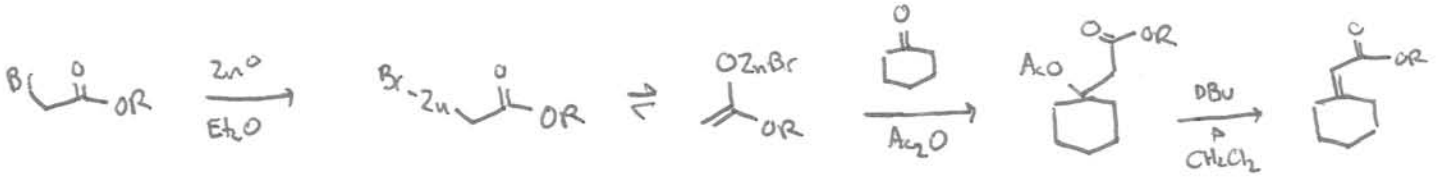
prefers e^- rich systems



allylic

→ stereochemistry of product cyclopropanation

Reformatsky Reaction



phosphonate okay

Stabilized with ketone not okay

Boron Reagents

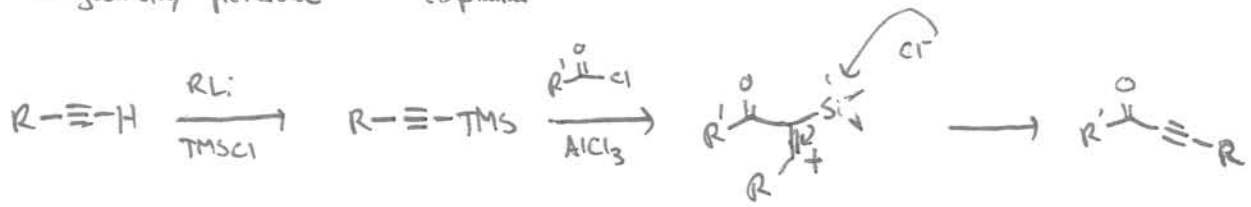
Silicon

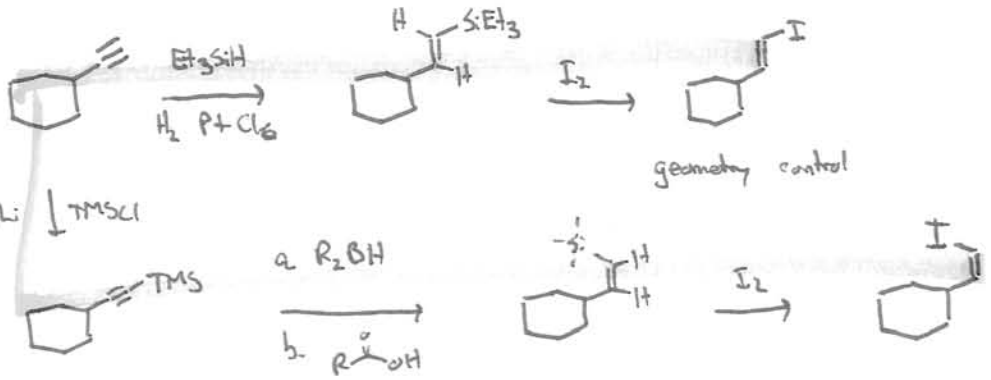
α anions

no geometry preference

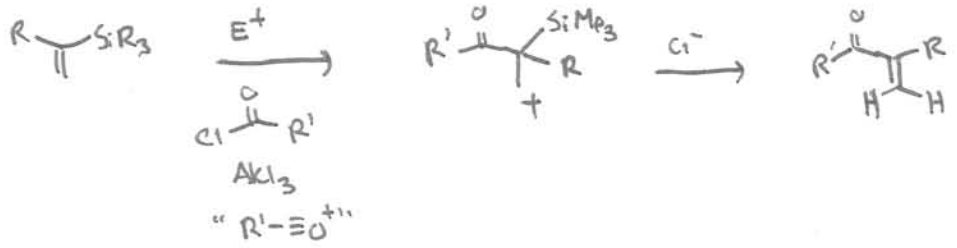
β cation

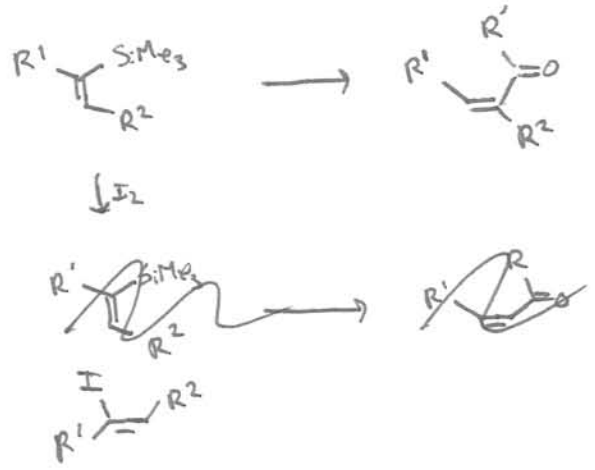
coplanar





geometry control

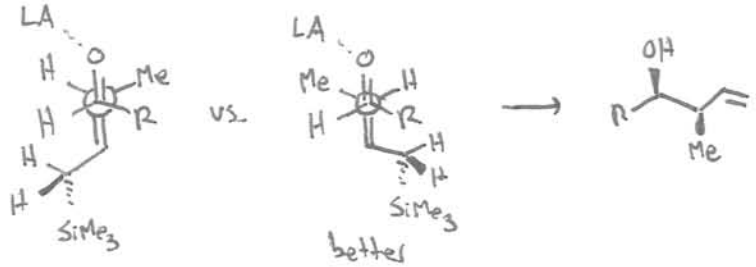




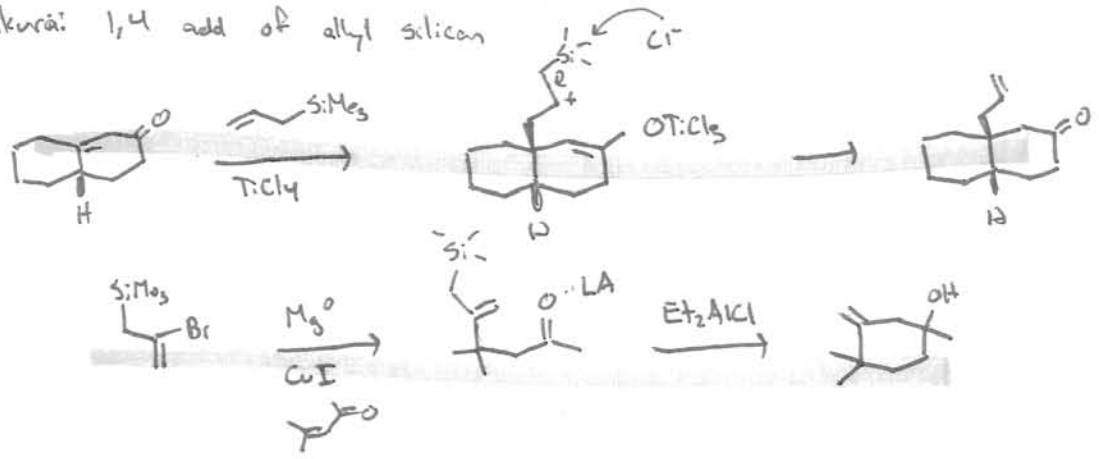
Allyl silanes

Open T.S.

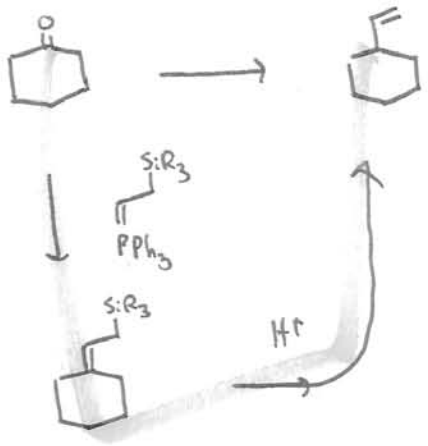
better selectivity — worse selectivity



Sakurai: 1,4 add of allyl silicon



Universal vinylation



2/26

Heterogeneous hydrogenation

Low pressure: 1-30 atm Pt, Pd, Rh, Ru

High pressure: 100-300 atm Ni

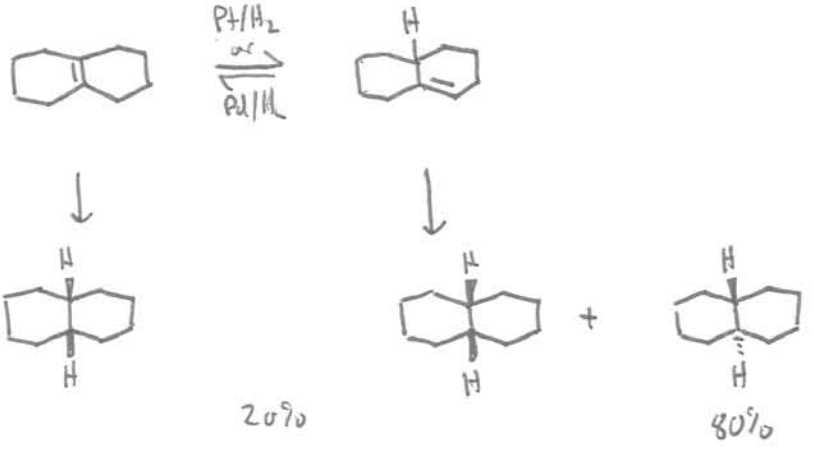
order of reactivity: Pt > Pd > Rh ~ Ru > Ni

Ni_2B

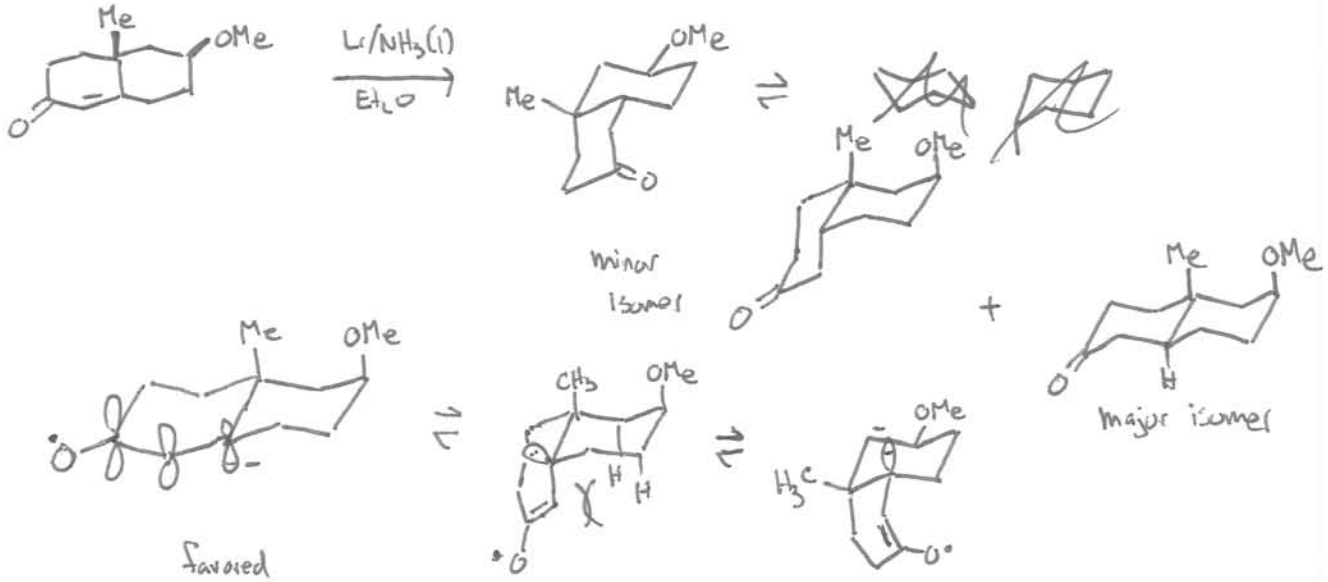
$NiCl_2 \cdot 6H_2O + NaBH_4 \longrightarrow Ni_2B$

1,4-reduction of aldehydes and ketones

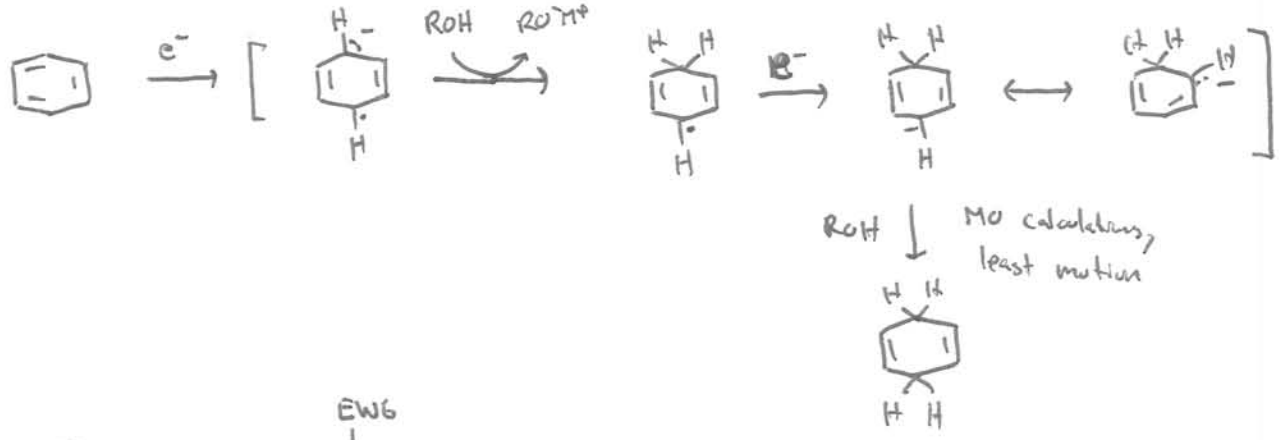
Isomerization



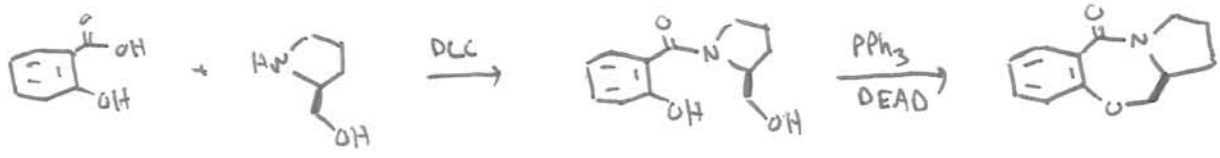
Li/NH_3

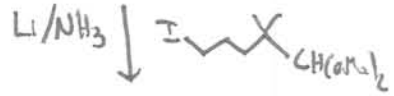


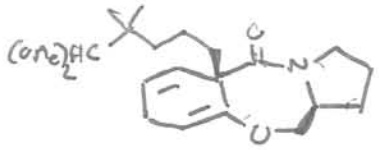
Birch reduction



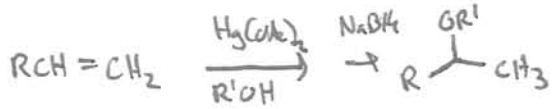
ex: chiral quaternary carbon

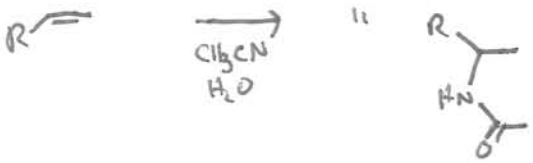




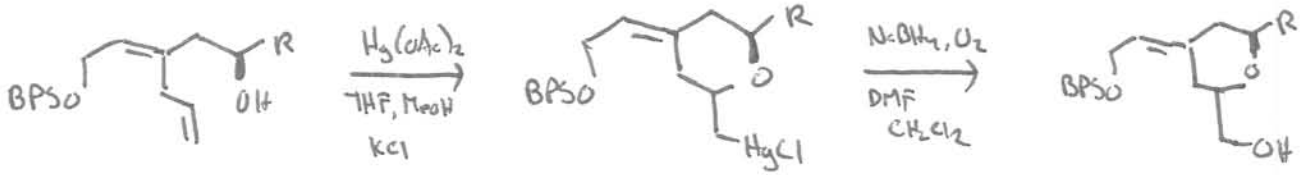


Solvomercuration- demercuration

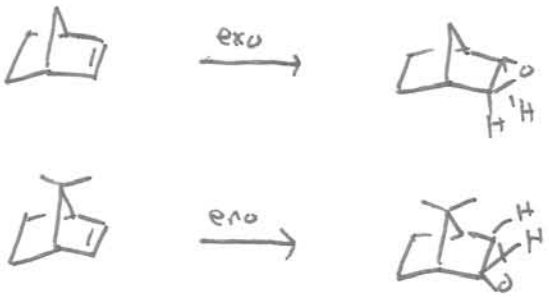




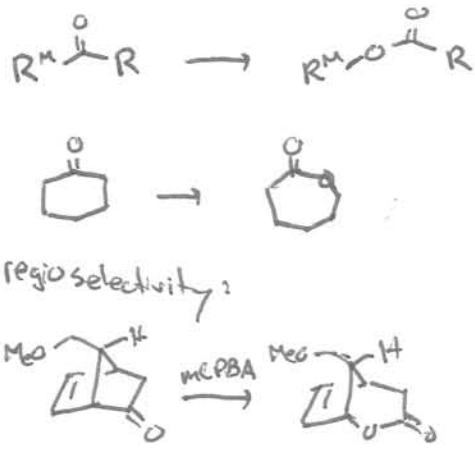
Oxidation of $RHgX$



Epoxydation

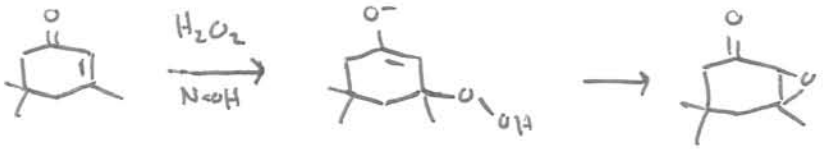


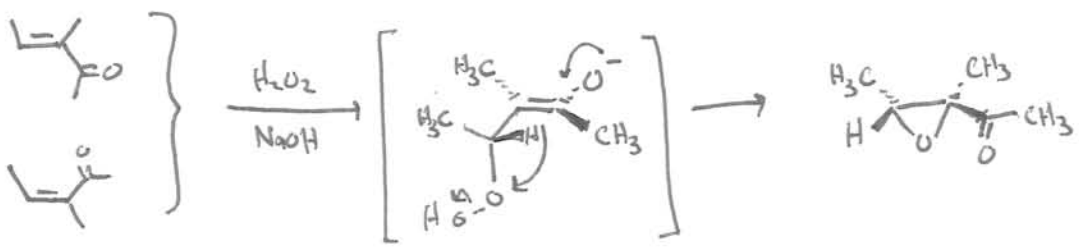
Bayer-Villiger



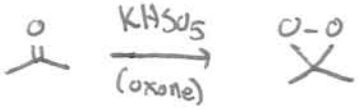
~~epoxydation~~

epoxidation of α,β unsaturated ketones using H_2O_2 / base

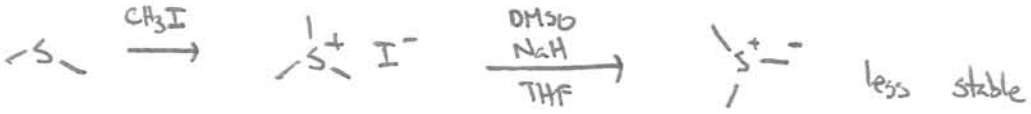


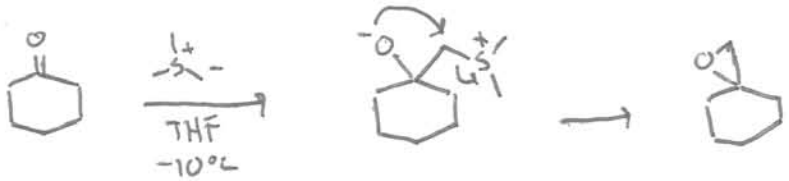


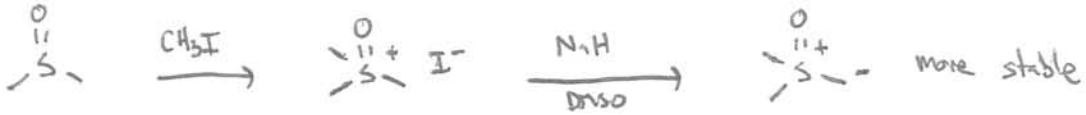
DMDO mild

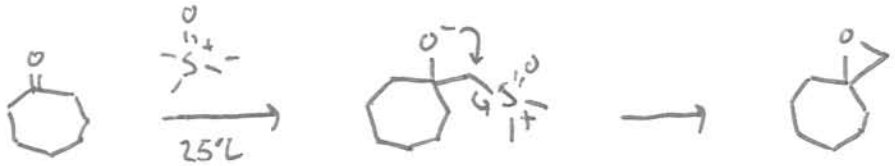


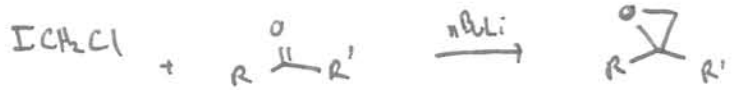
epoxides from ketones



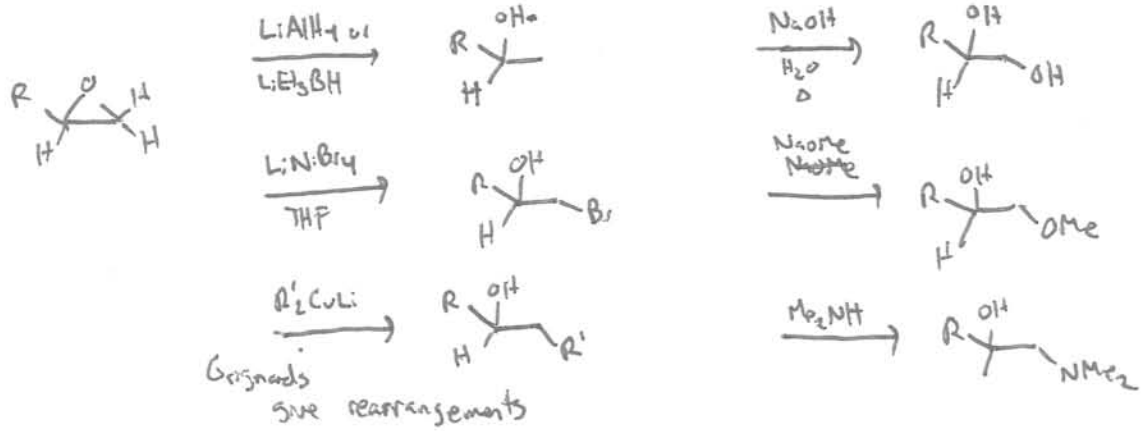




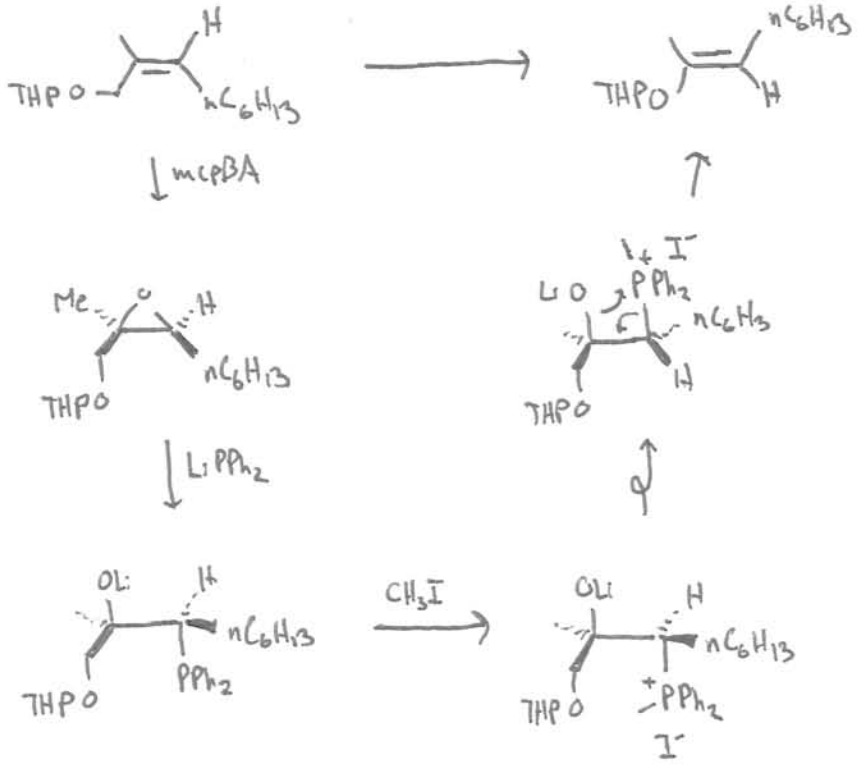




Reactions of epoxides

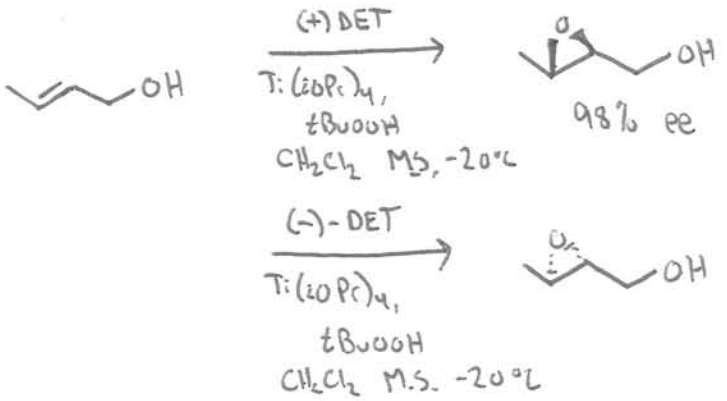


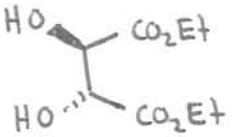
Inversion of olefin geometry

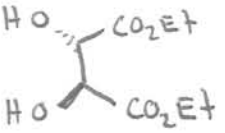


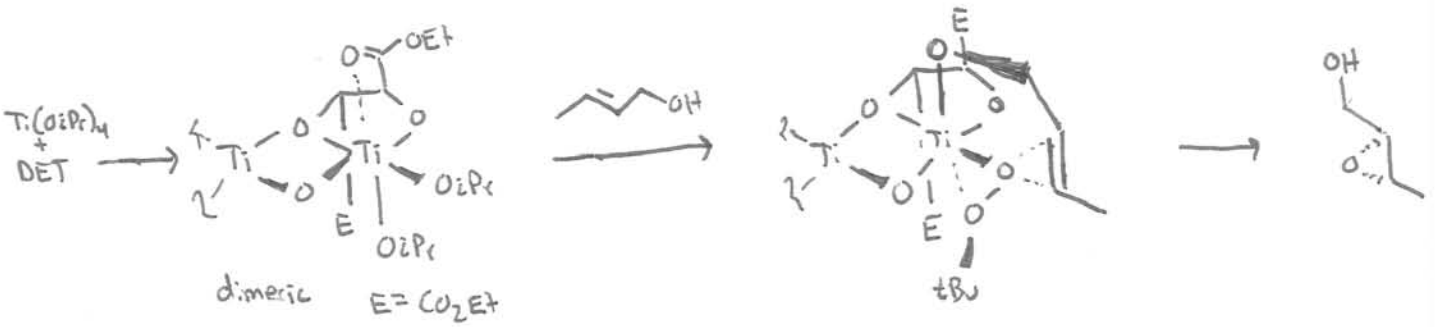
Sharpless Asymmetric Epoxidation

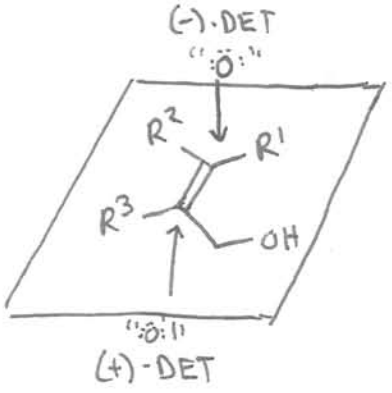
Nobel Prize 2001



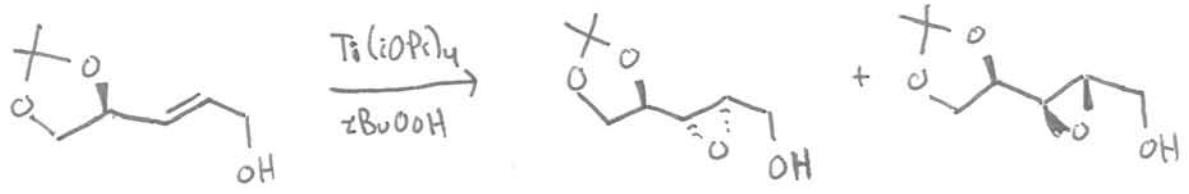
(+) DET = 

(-) DET = 



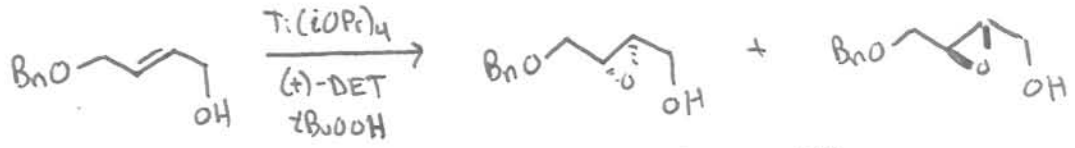


- Diastereoselectivity



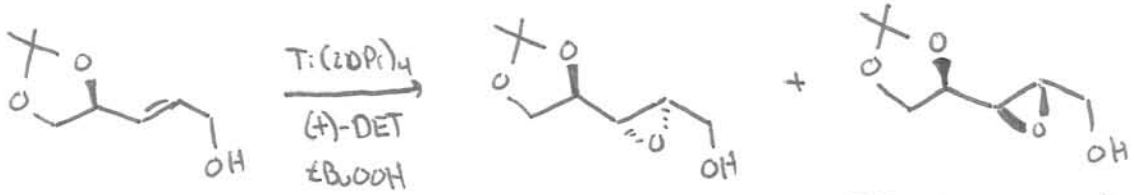
2.3 : 1

- Achiral S.M.



1 : 99

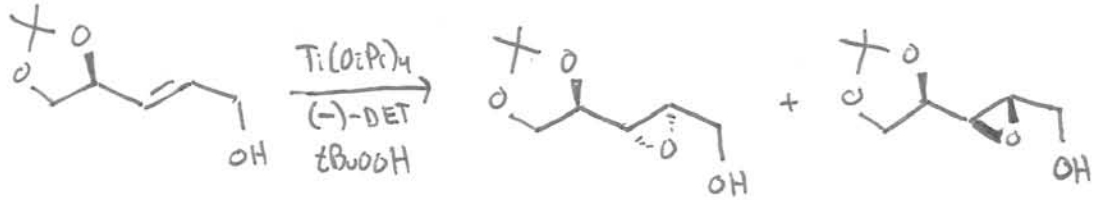
- Matched / mismatched



1 : 22 (mismatched)

Enantioselectivity competes with diastereoselectivity

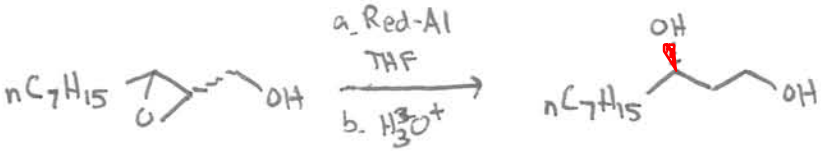
Enantioselectivity usuudly wins



90 : 1 (matched)

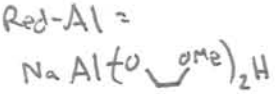
Enantioselectivity works together with diastereoselectivity

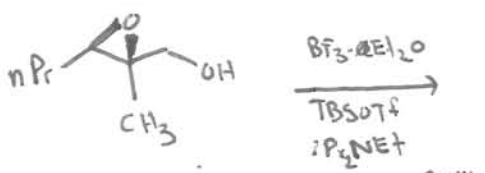
A few applications:



1,3-diol

Red-Al =



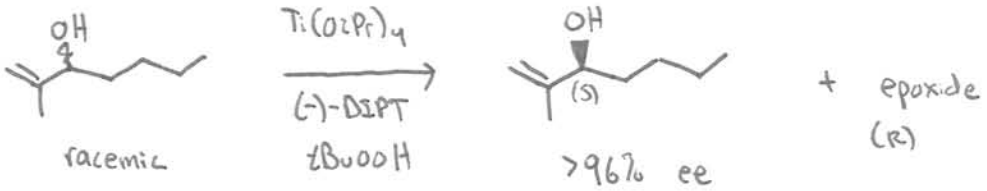


syn-

"aldol" product

anti-

Kinetic resolution

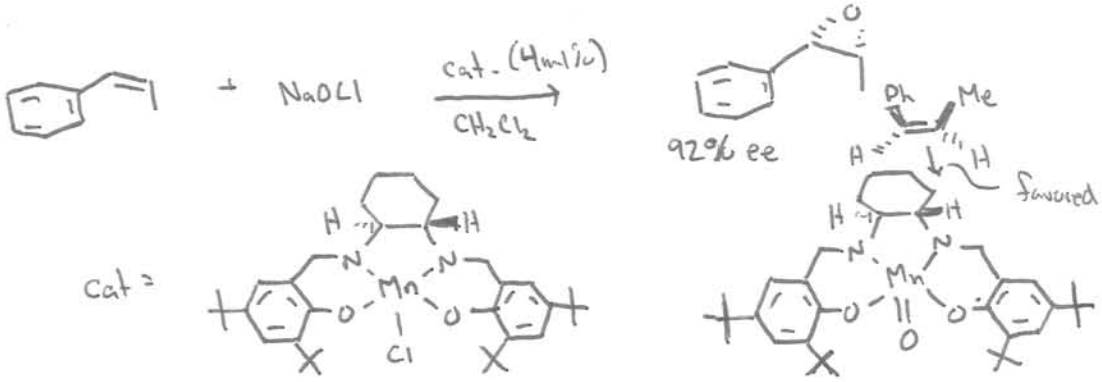


racemic

>96% ee

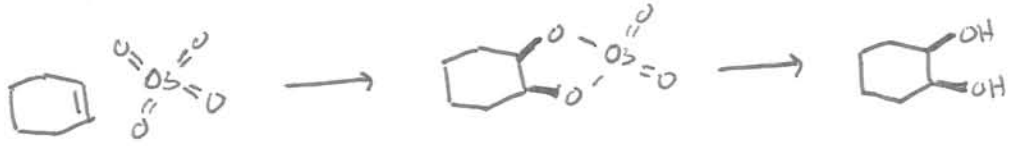
(R) is matched, so it reacts faster, leaving (S) unreacted

Jacobsen Epoxidation



chiral (Salen) Mn III complex

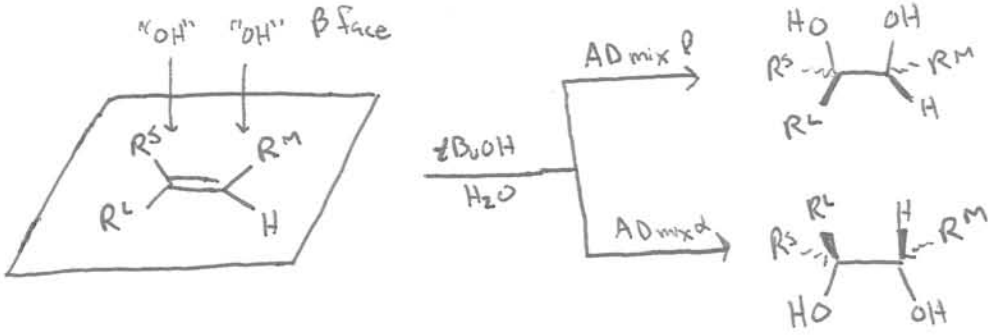
Dihydroxylation



OsO_4 is toxic and expensive

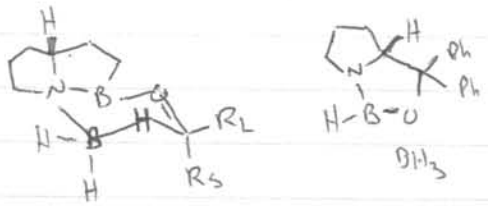
can use cat. with stoichiometric NMO, tBuOOH, etc.

Sharpless dihydroxylation



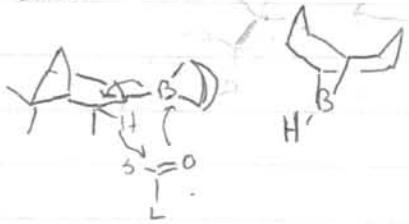
3/34

CBS

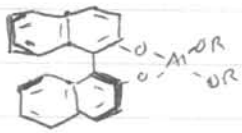


Alpine borane

9BBN



DINAL-H



Birch reduction

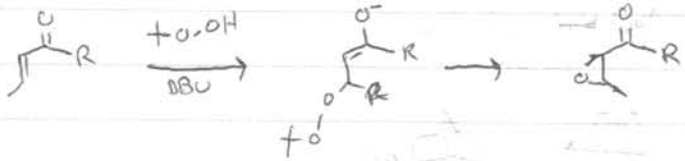
aromatic

enones

Epoxidation

acidic

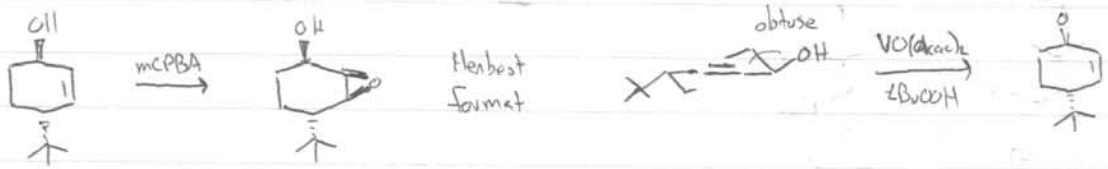
basic



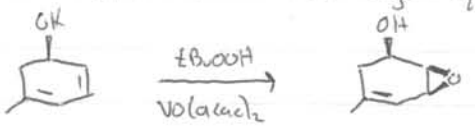
Woodward Prevost

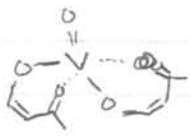
Convex face with mCPBA

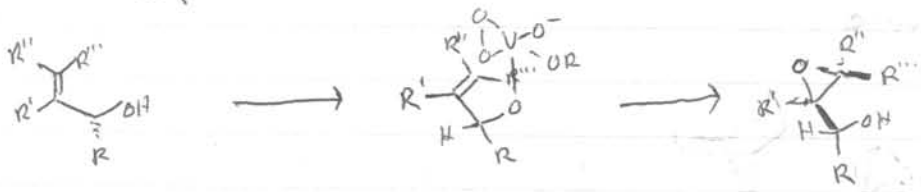
concave with Woodward / Prevost



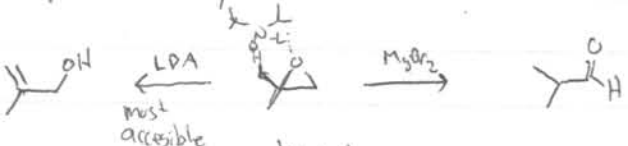
$VO(acac)_2$ / tBuOOH strict angle requirement





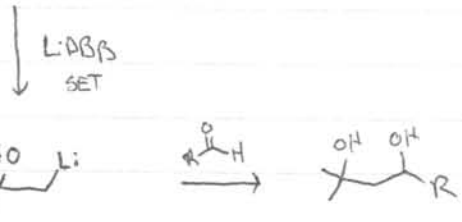


epox reactivity



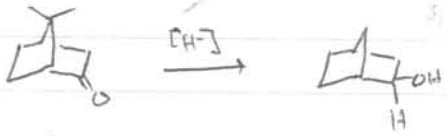
must accessible H

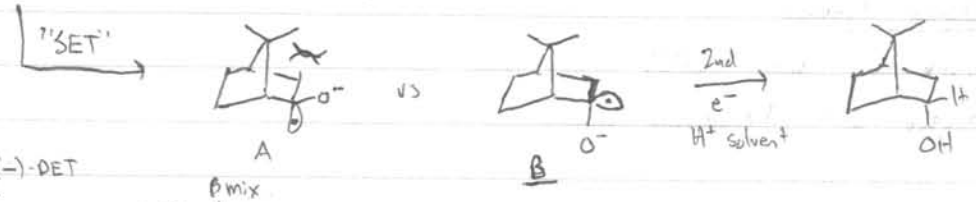
terminal

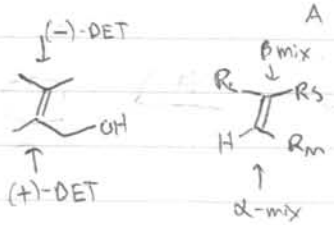


dianion

least ~~most~~ substituted carbon

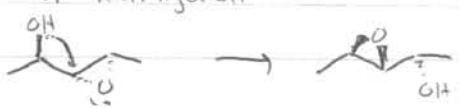


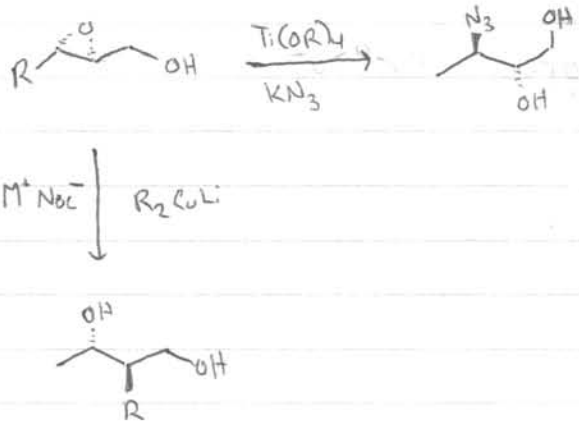




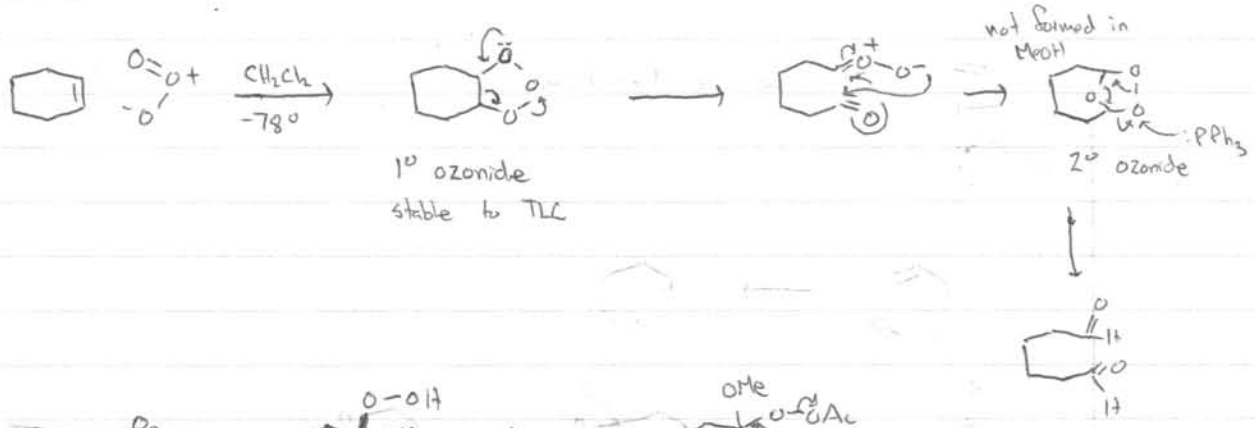
watch out for rearrangement

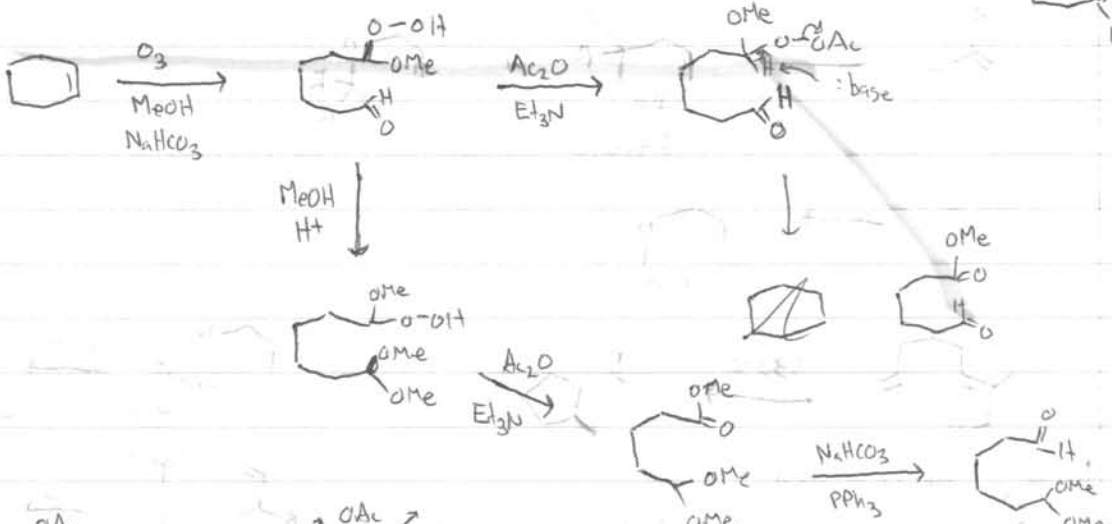
Payne rearrangement

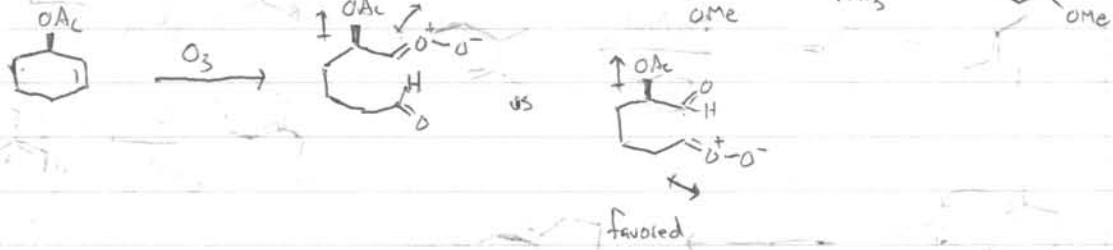


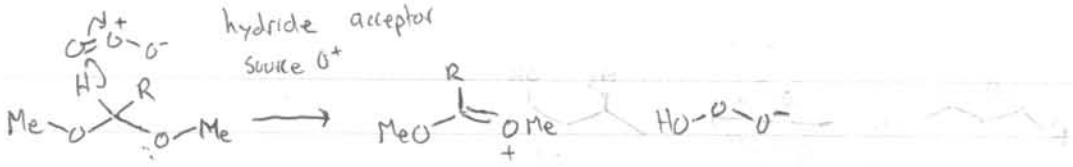

Ti(OR)4
KN3
M+ Nuc−
R2CuLi

Ozone (3+2)

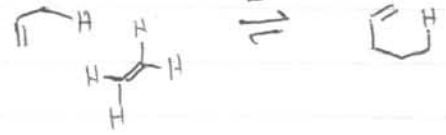

CH2Cl2
-78°
1° ozonide
stable to TLC
not formed in MeOH
PPh3
2° ozonide


O3
MeOH
NaHCO3
Ac2O
Et3N
base
MeOH
H+
Ac2O
Et3N
NaHCO3
PPh3

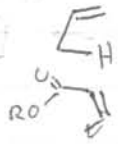

OAc
O3
vs
favored



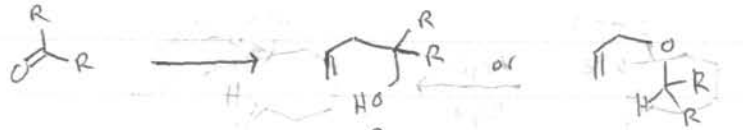
Ene reaction

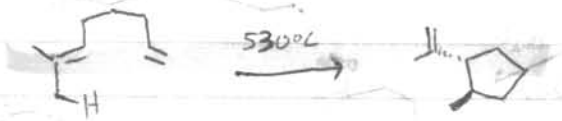


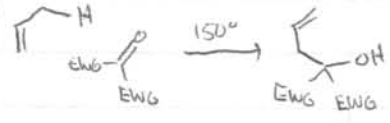
enophiles: X = C, N
Y = C, O, S, N



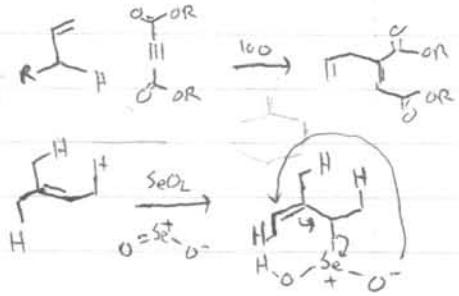
T.S. looks like Diels Alder







low temp: use Lewis acid



3/6
Saturday noon-3 DA, [3+2]

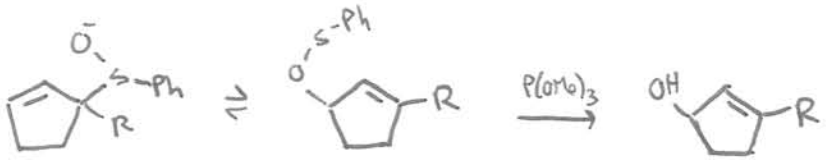
next
P.S. due Friday

Ene reactions

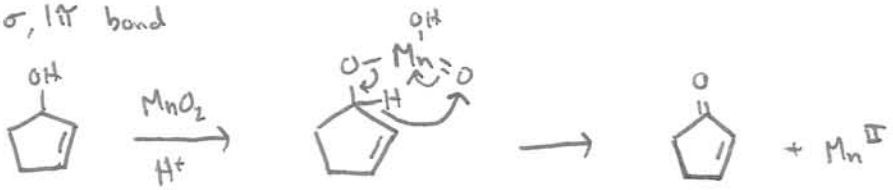
a) ene
b) 2,3 sigmatropic shift

2,3 sigmatropic

Evans Mislow



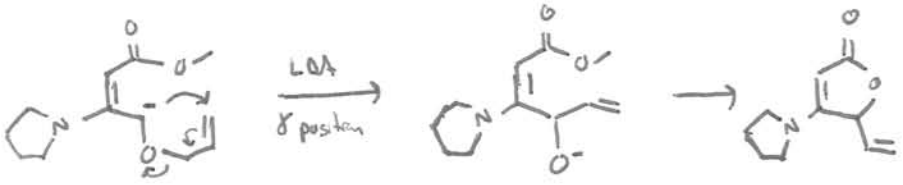
3σ, 1π bond

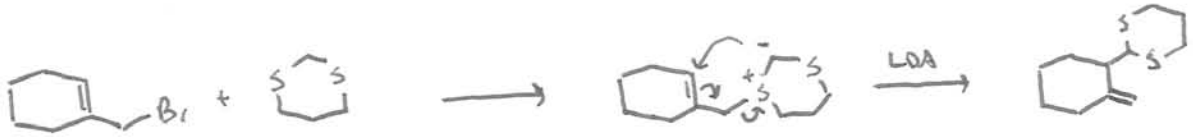


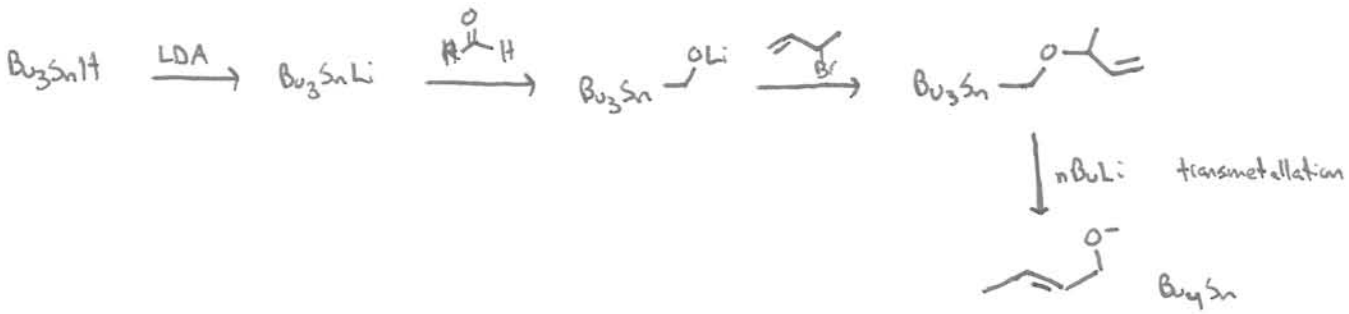
allylic alcohol 2,3 sigmatropic

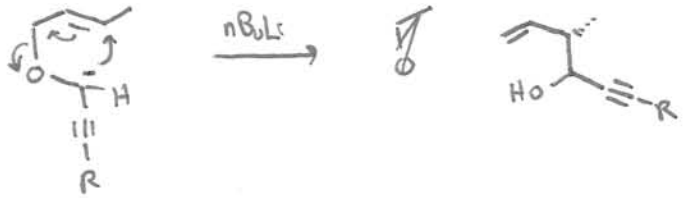
Swern oxidation

2,3 Wittig reaction charged







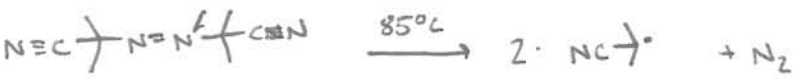


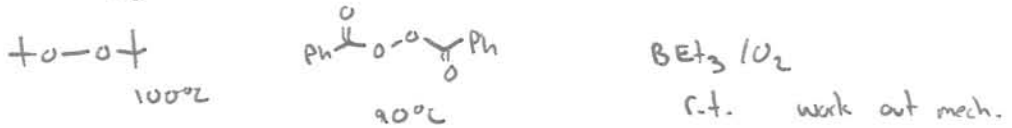
Radical tolerates wide range of functional groups

neutral conditions R·

mechanism

1. Initial B-B' ⟶ B· + B'·





2. propagation

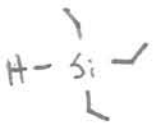
a B· A-X ⟶ A· + B-X

Propagation

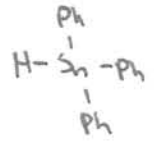
$\bullet SnBu_3 + R\text{-}I \xrightarrow{K_X} R\bullet + ISnBu_3$ $\quad I > Br > Cl$

$R\bullet \quad H\text{-}SnBu_3 \xrightarrow{K_H} R\text{-}H + \bullet SnBu_3$

b) $A\cdot \xrightarrow{K_c} C\cdot$



c) $A\cdot + D \xrightarrow{K_c'} A\text{-}D\bullet$



3. Termination

$R\bullet + R'\bullet \longrightarrow R\text{-}R'$

if K_H is faster than K_a it ~~dominates~~ dominates

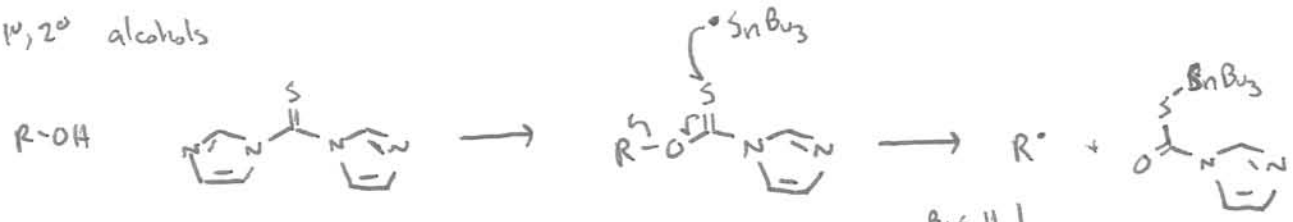
Reduction

$RX \xrightarrow{n Bu_3SnH} R\text{-}H$ $\quad X =$ halogen, $-SR$, $-SeR$, $-NO_2$, $-\overset{+}{N}\equiv C^-$, $-HgX$

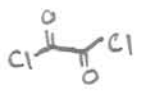
$X = \cdot OH$, $R\overset{O}{\overset{\|}{C}}OH$ tricks are required

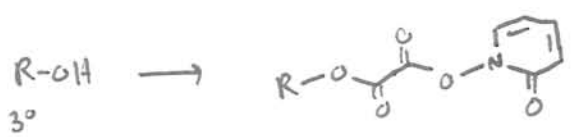
Barton McCombie

1°, 2° alcohols



if 3° add

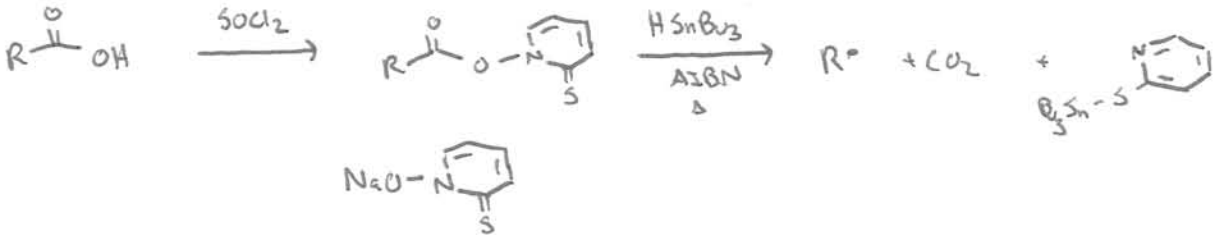


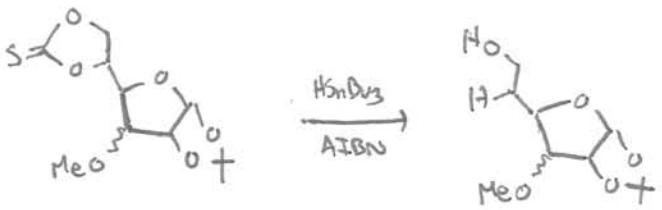


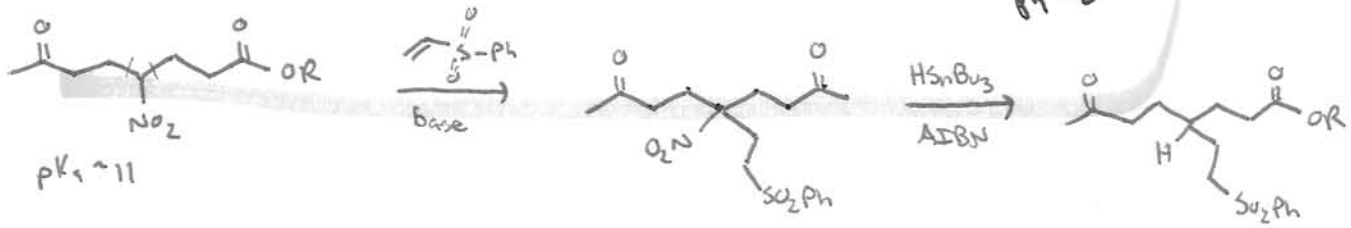
$R\bullet \xrightarrow{Bu_3SnH} R\text{-}H + \bullet SnBu_3$

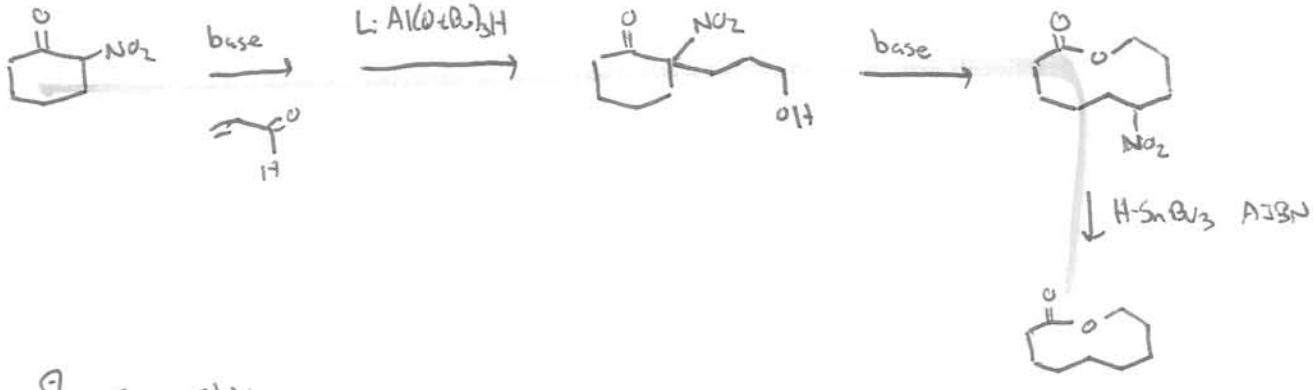
Acid

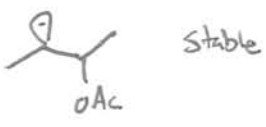
Barton Motherwell carboxylate erasure



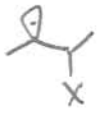








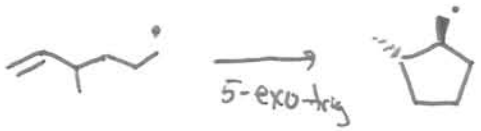
Stable



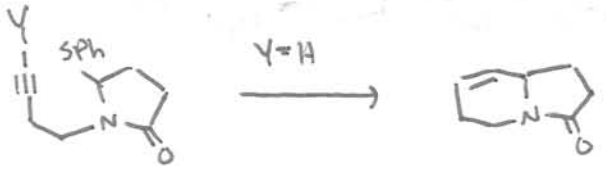
not stable

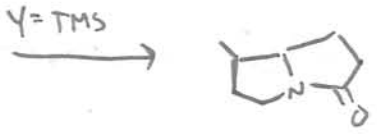
if X= Δ,  , NO_2, SPh, SO_2Ph, $SePh$ $\overset{+}{N}\equiv C^-$

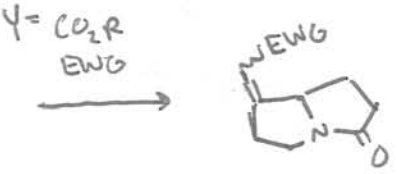
Intramolecular reaction



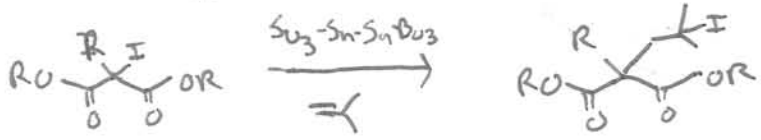
Sometimes substituents can override

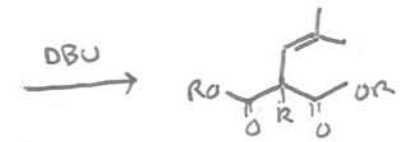


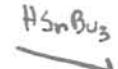


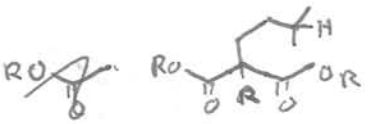


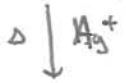
Atom transfer

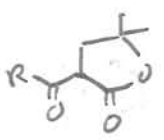




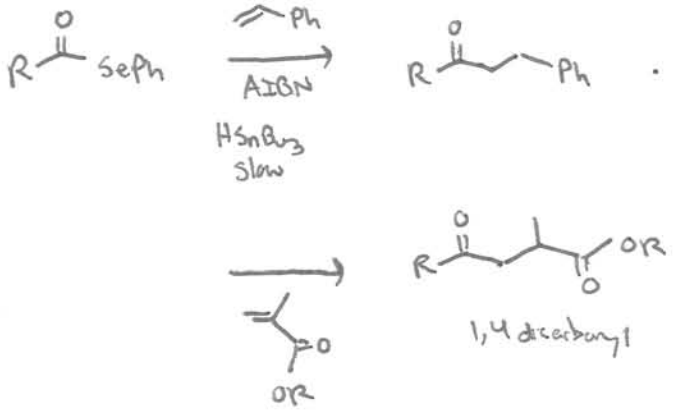


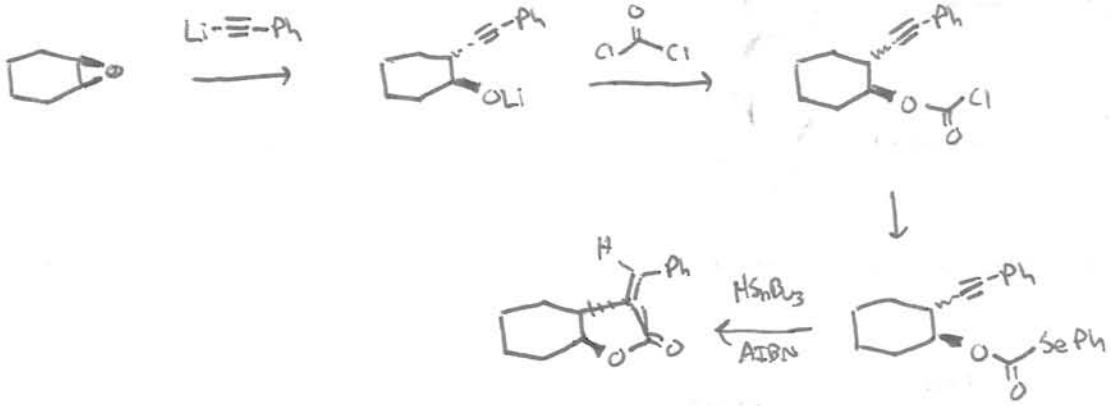




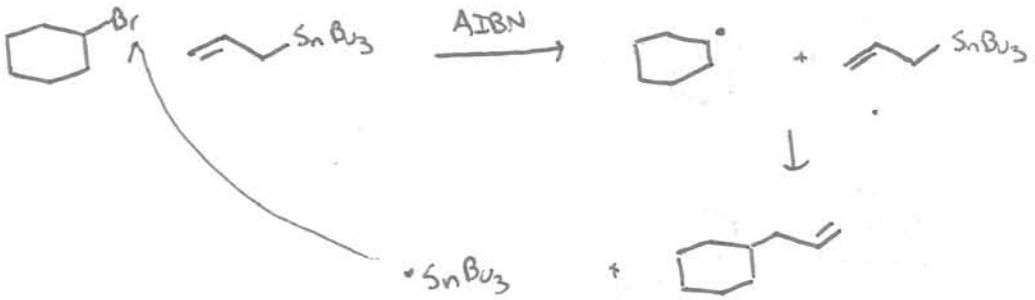


Acyl radicals



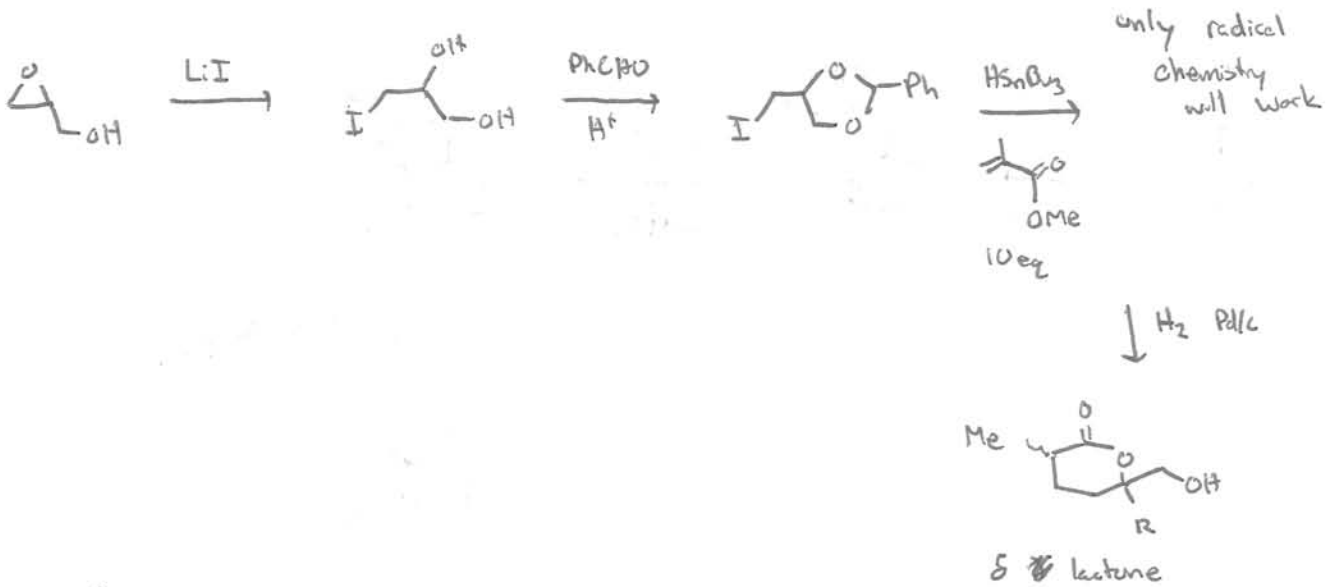


~~Atom~~

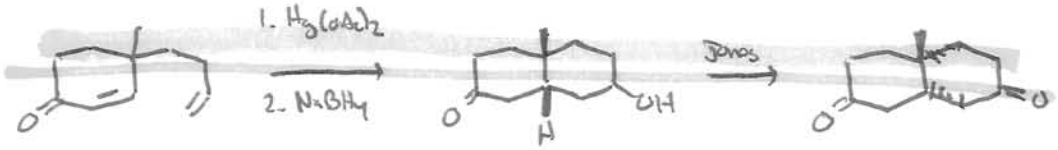


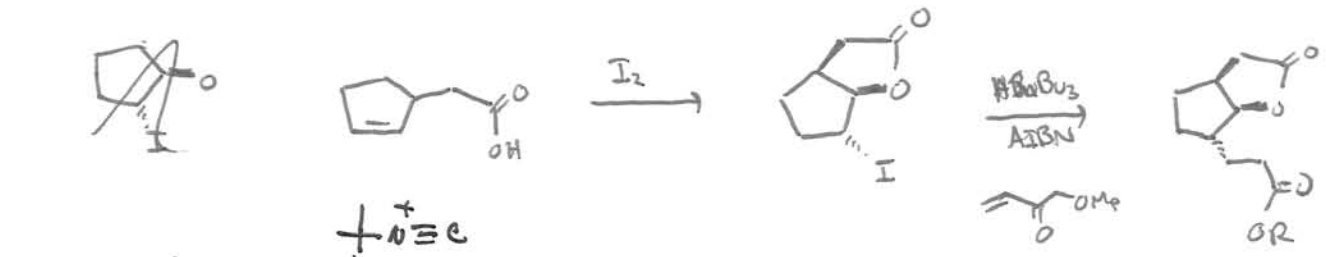
trans favored
Polar R activates

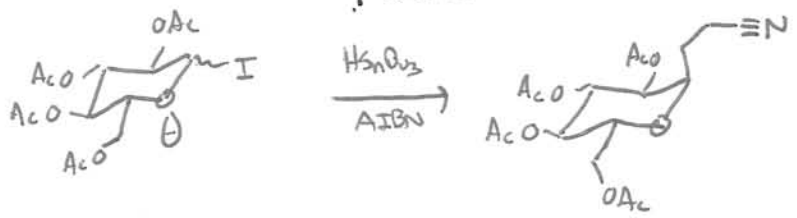
cis favored

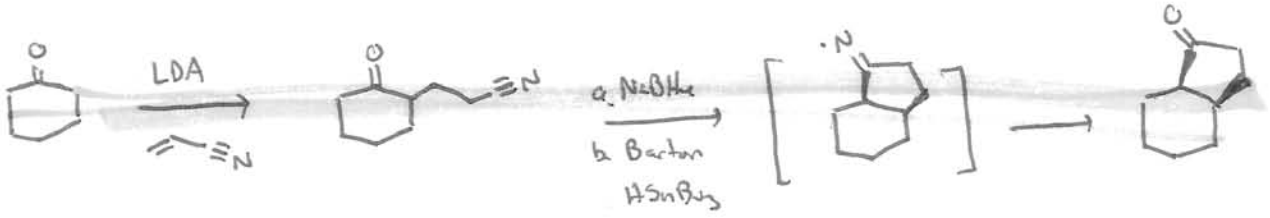

LiI
PhCHO
H+
HSnBu3
only radical chemistry will work
OMe
10 eq
H2 Pd/C
Me
OH
R
δ lactone

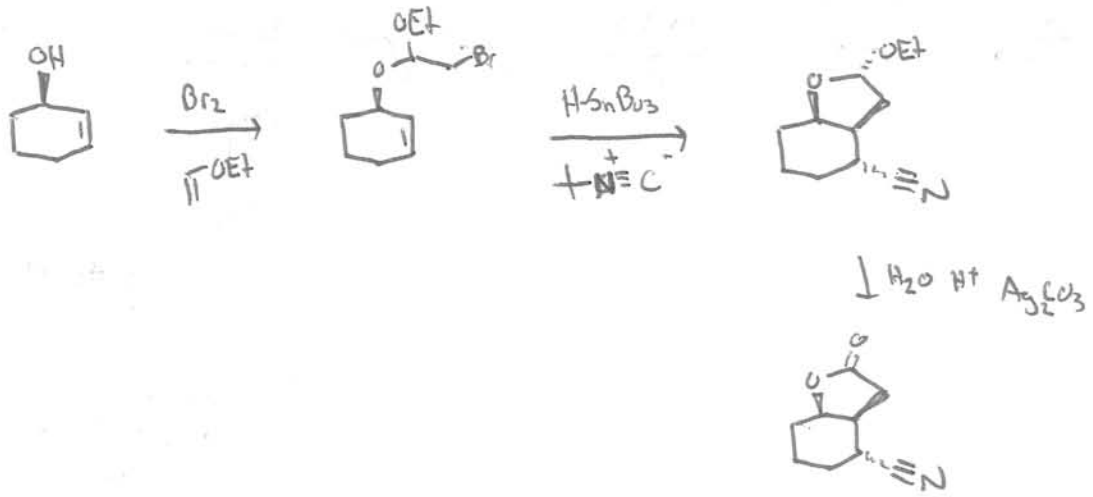

Br
HSnBu3
AIBN


1. Hg(OAc)2
2. NaBH4
OH
Jones


I2
OH
I
HSnBu3
AIBN
OMe
OR


OAc
AcO
I
HSnBu3
AIBN
N
OAc


LDA
N
a. NaBH4
b Barton
HSnBu3


OH
Br2
OEt
OEt
O
Br
H-SnBu3
+N≡C-
OEt
O
N2
H2O H+ Ag2CO3
O
O
N2

Cyclo additions

$4e^-$: 2+2

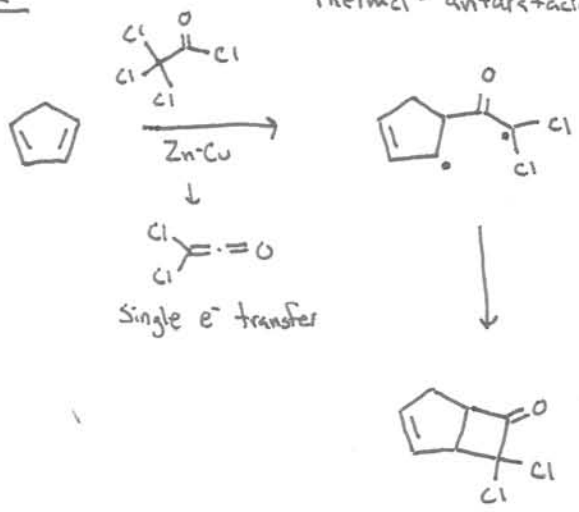
$6e^-$: 3+2 

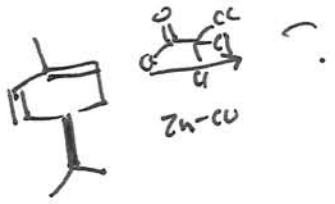
4+3 

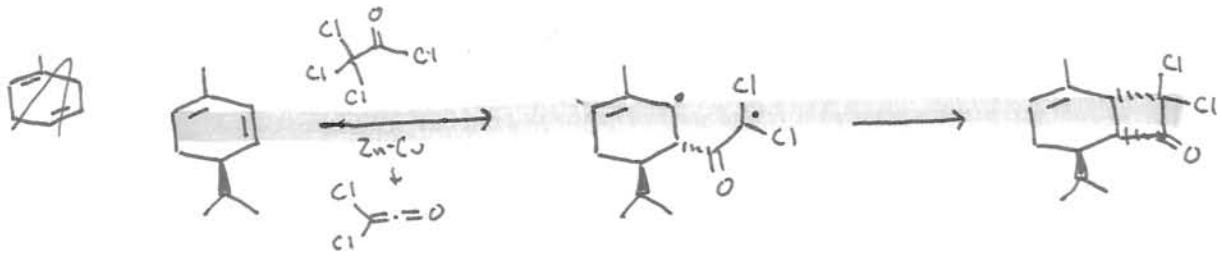
5+2 

2+2

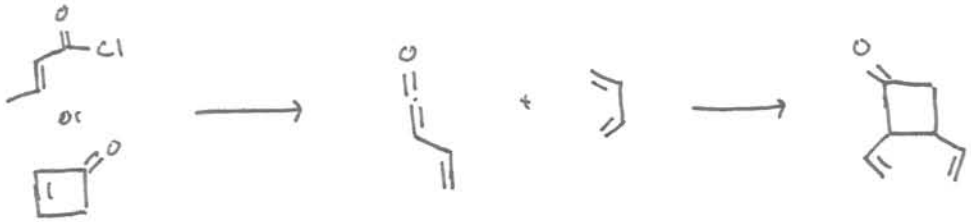
Thermal: antarafacial Photo: suprafacial or stepwise

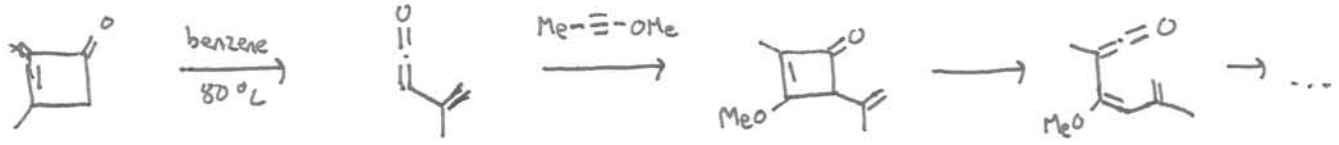


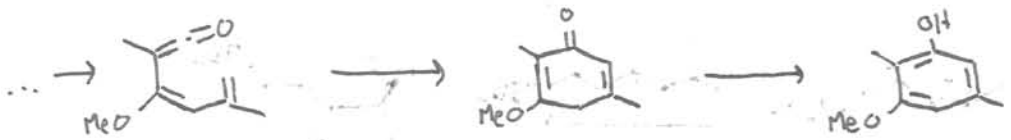




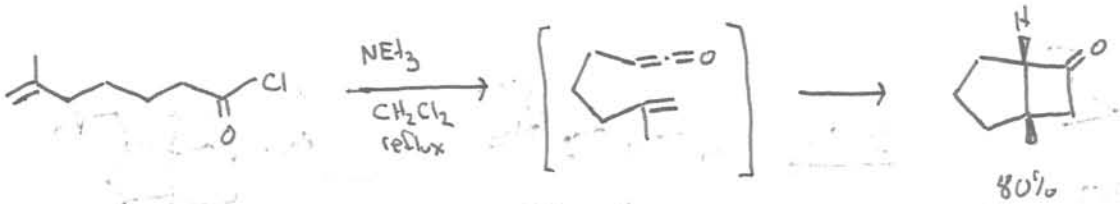
Other ketene precursors:



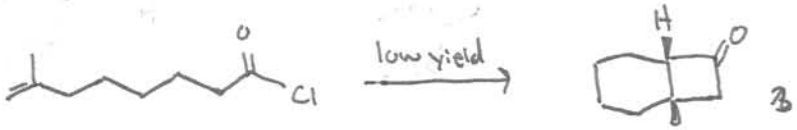




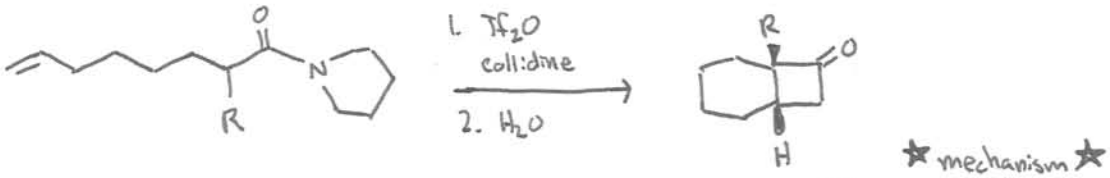
92%



80%



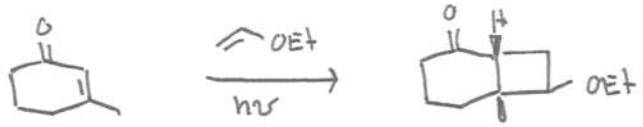
3%

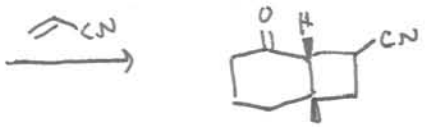


★ mechanism ★

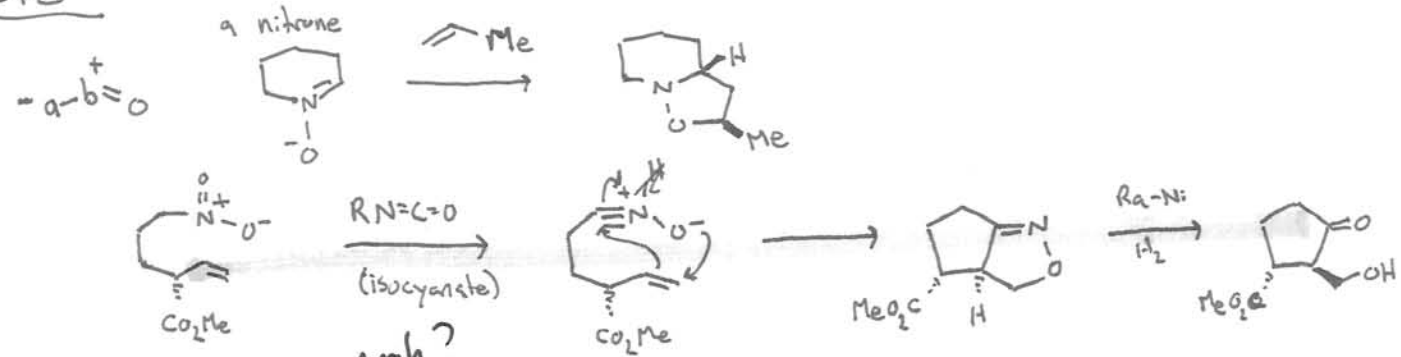
R=Me 89%
R=H 65%

Photocycloaddition to enones

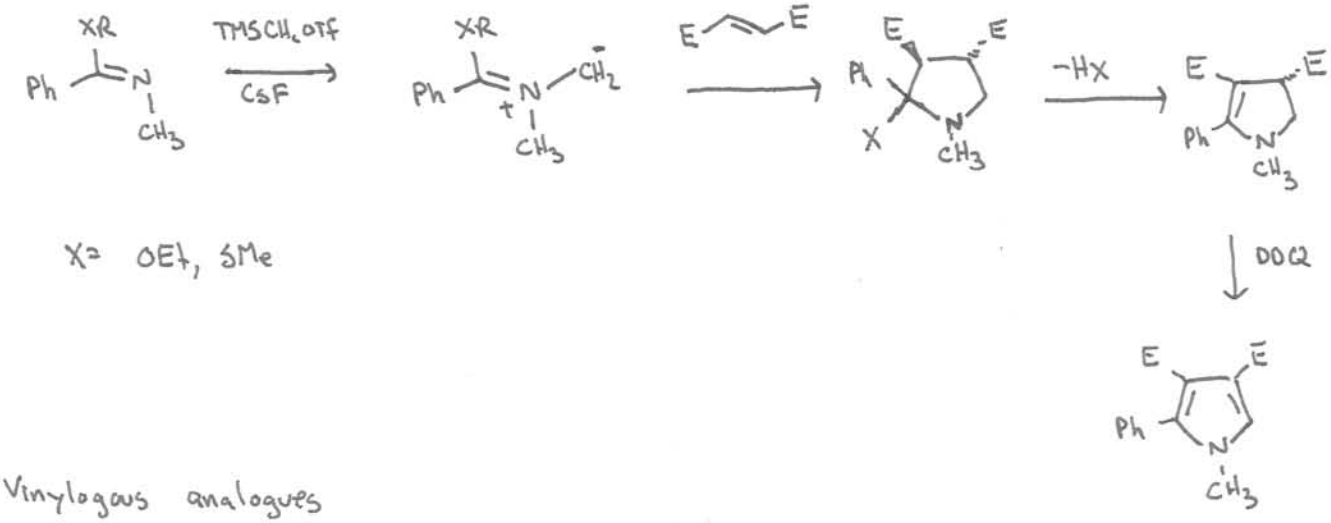




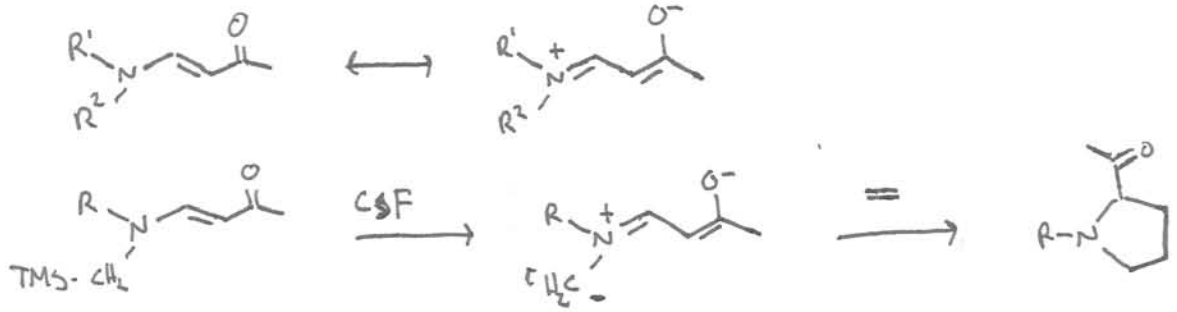
3+2



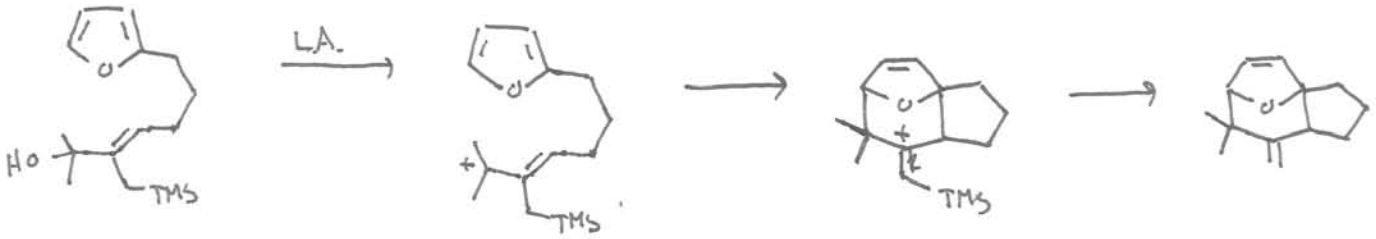
(back)



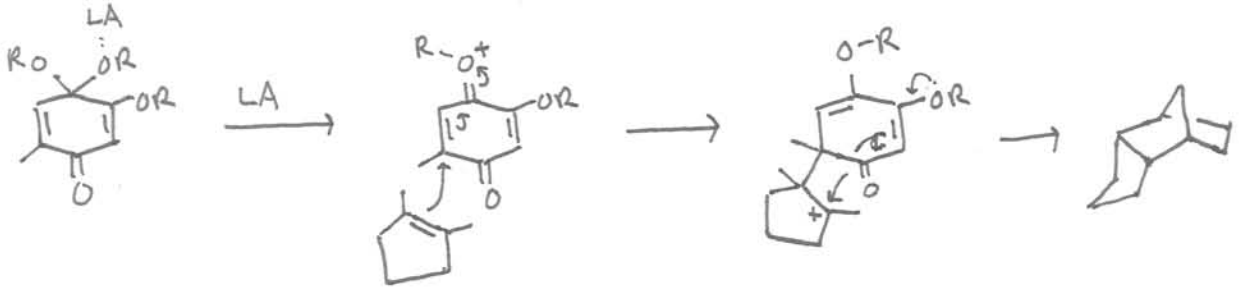
Vinylogous analogues



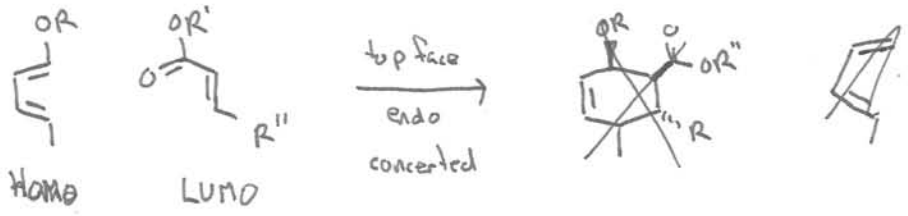
4+3

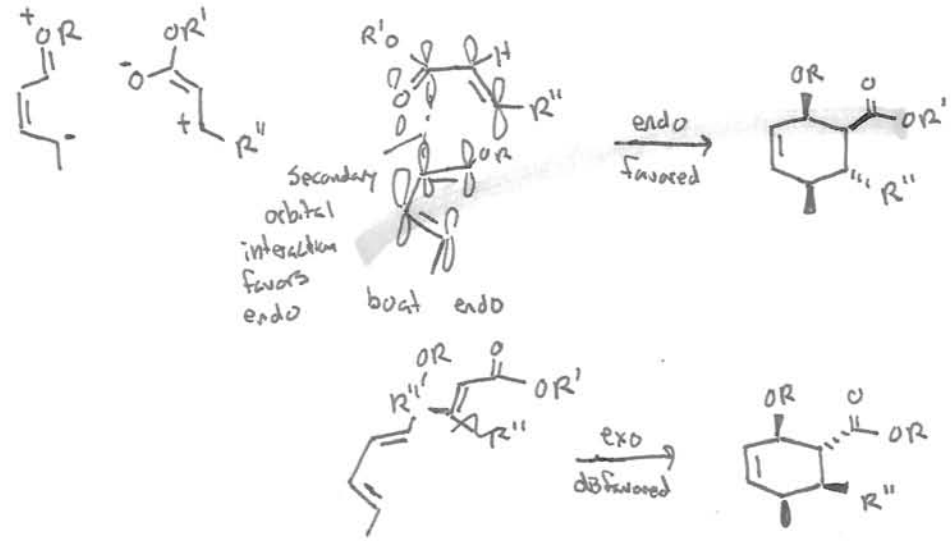


5+2

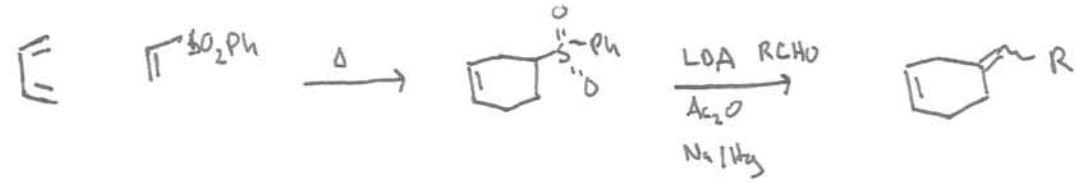


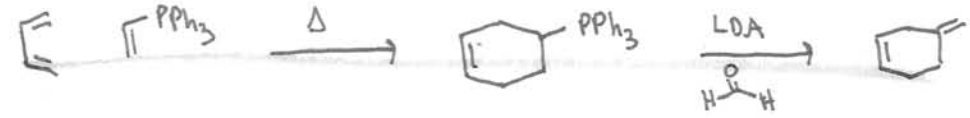
4+2 Diels Alder (Pericyclic) endo-exo selectivity

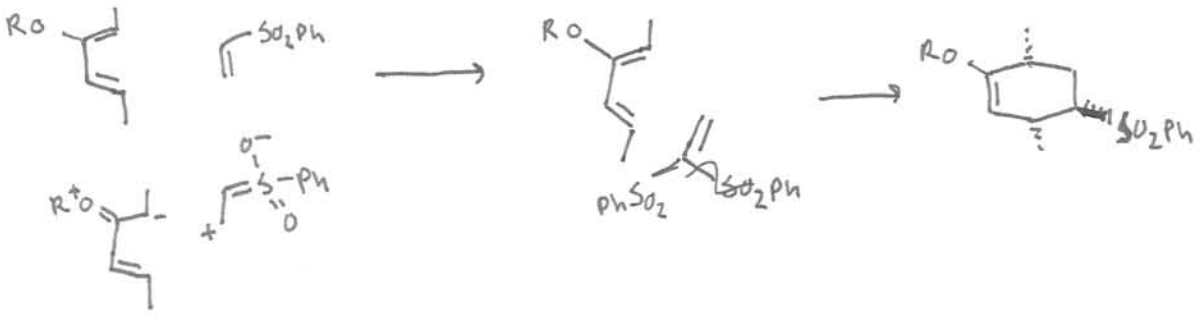


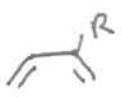


ex.

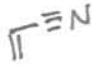




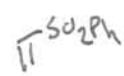




H > CH_3 > OCH_3 endo selectivity



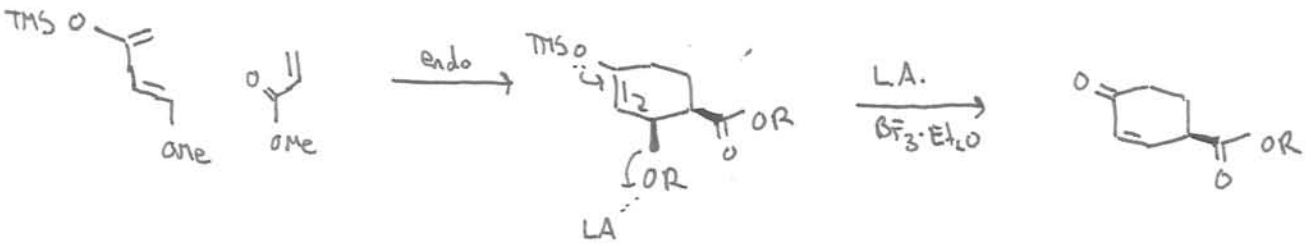
3:1

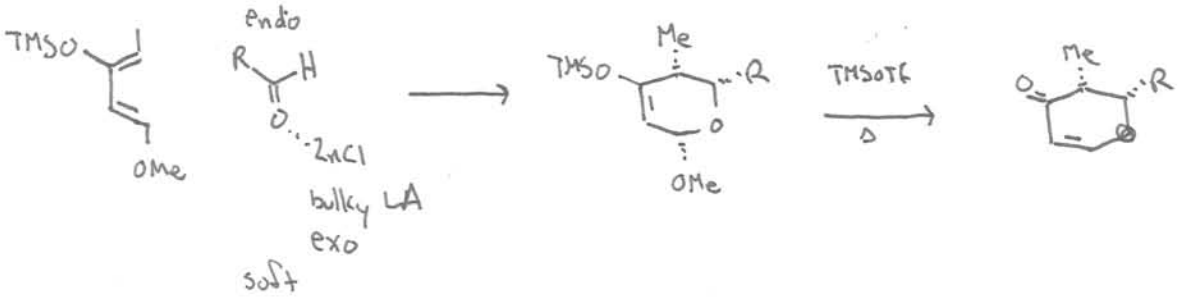


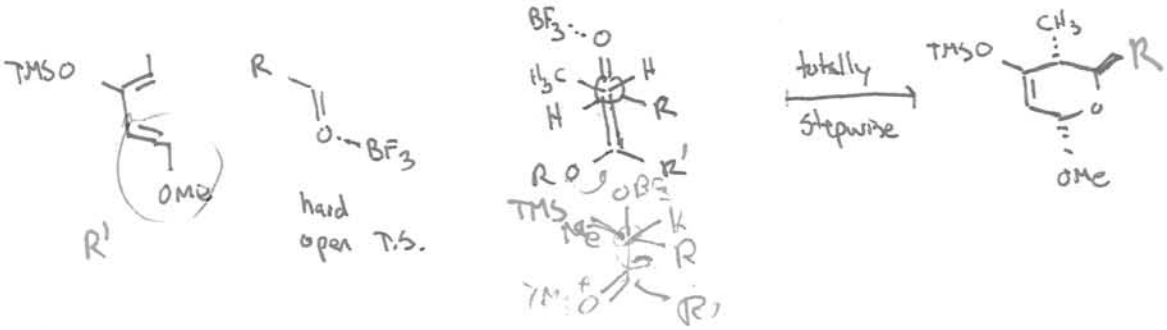
1:1

exo favored

Danishefsky diene



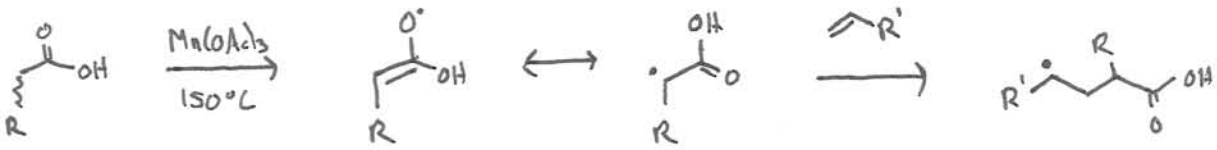


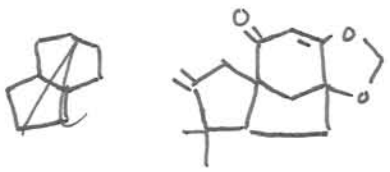


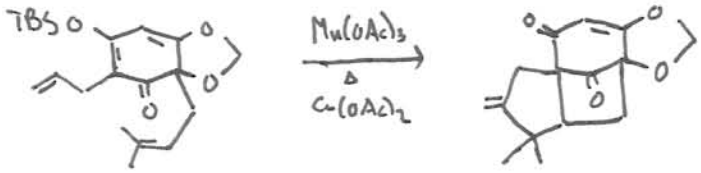
3/11

Radicals continued

Snider

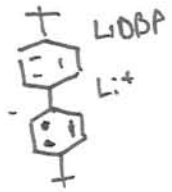


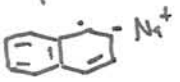




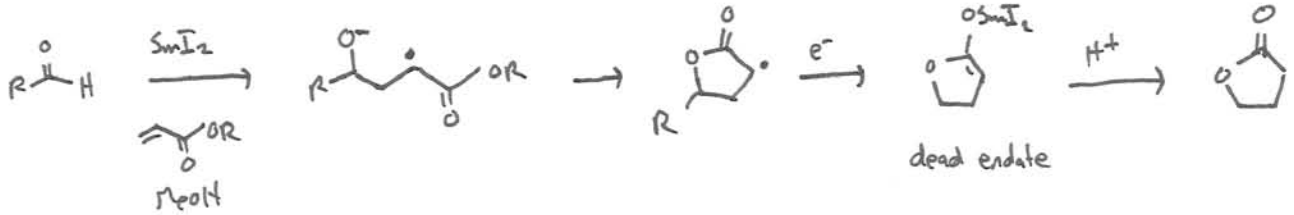
SET

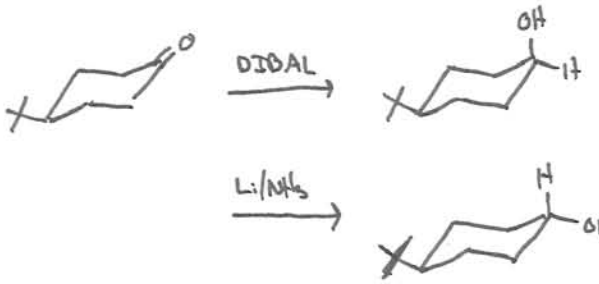
SmI_2 ~~LiDBP~~ Na naphthalide Li/NH_3

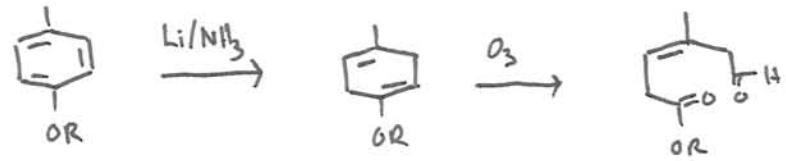


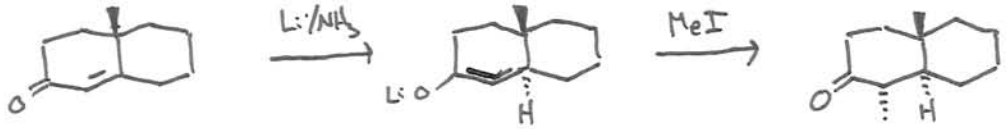


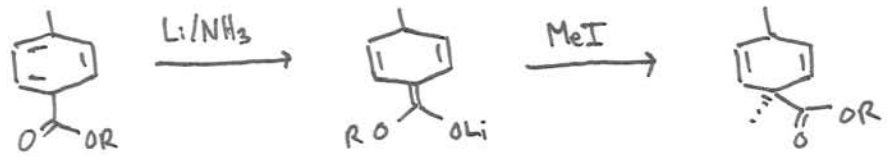
Y = H, Alk











Asymmetric Chem.

e.e. entiomeric excess = optical purity

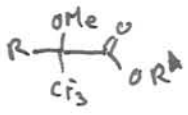
d.e. ~~diasterioselective~~ diastereomeric excess

master rule optical activity beget optical activity

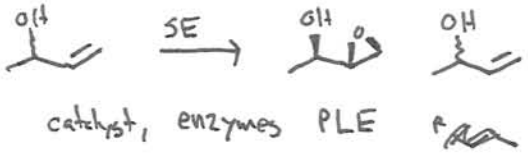
a. start from chiral pool "chiral app"
terpenes, amino acids, carbohydrates

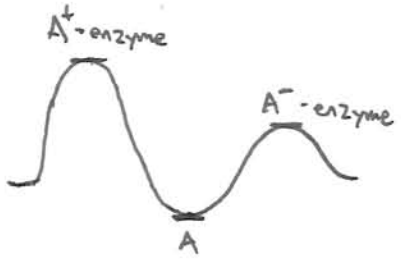
b) resolution of racemate

1. (±) acid and (±) base crystallization
2. c e Mosher ester



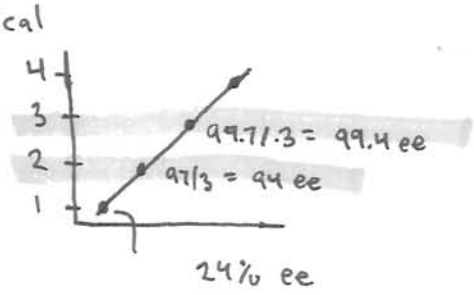
3. chiral chromatography
4. kinetic resolution





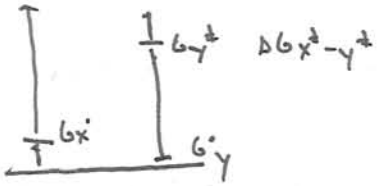
c. asymmetric synth.

1. chiral aux
2. catalyst
3. chiral system



1 Product distributions and ground state stability are ~~unrelated~~ unrelated

A less stable conformer may lead to a T.S.‡ of lower energy



However

if $\Delta G_x^{\ddagger} \geq \Delta G_y^{\ddagger}$

or

if $\Delta G^{\circ}_{xy} \geq \Delta G^{\ddagger}_{xy}$

than distribution based on ~~conformation~~ conformer distribution

Determination of ee

1. optical rotation

$[\alpha]_D^{25^\circ} = +27$ enriched

concentration same $+37$ pure

Same solvent $ee = {}^{27}/_{37}$

easily distorted by concentration, solvents

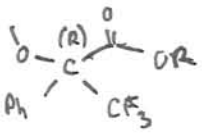
follows Beer's law

2. Chiral Column

HPLC IGC

must have racemic standard

3. Covalent derivative



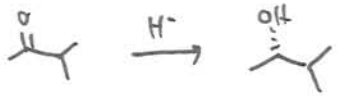
4. non covalent derivatives

a) chiral shift reagent

$Eu(fod)_3$

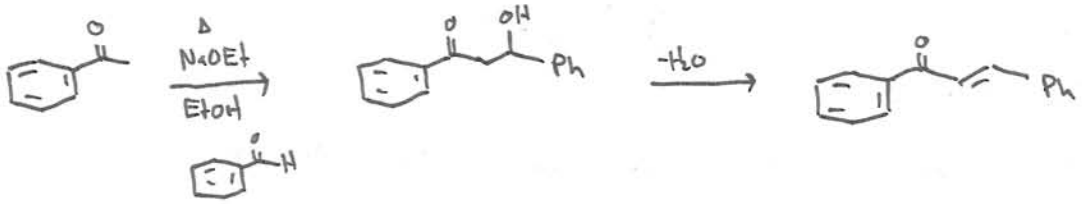
b. chiral solvents

when building (don't combine chiral reagents)



matched and mismatched pairs

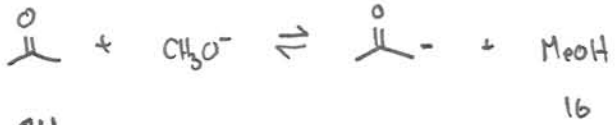
Aldol reactions / enolate alkylations / enamine / enol



conditions: kinetic or thermodynamic

- low T
- inverse addition (excess base strong base)

- Δ
- mix
  less base
  weak base
  non enolizable RCHO

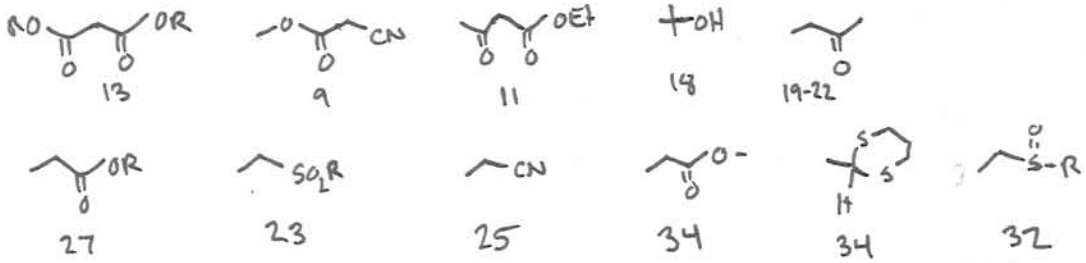


24 16

10^{24-16}

10^8

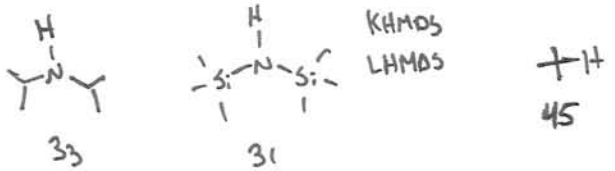
activated methylenes



13 9 11 18 19-22

27 23 25 34 34 32

bases



KHMDS
LHMDS

+H
45

Heterogeneous base

NaH Na°
KH K°
21

big M
small R

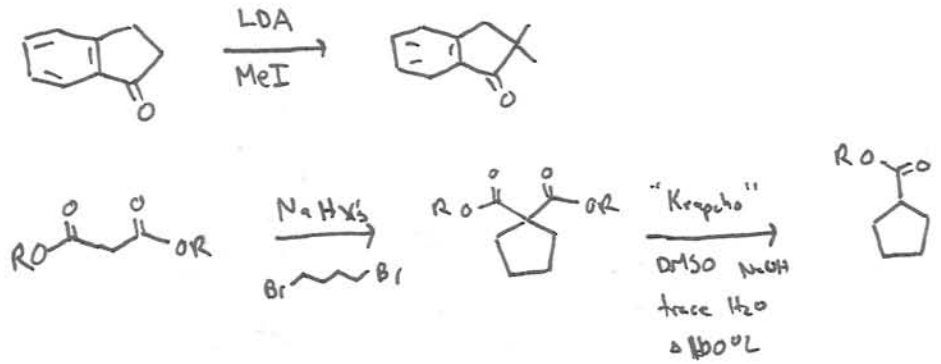
small M
big R

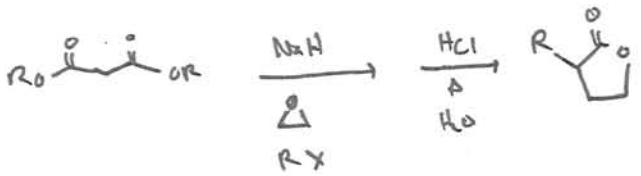
enolate geometry!

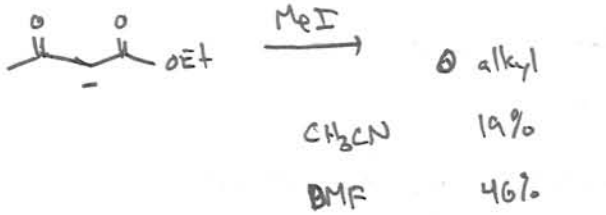
O alkylation - hard Me_2SO_4 metal dependent M=K HMPA

C alkylation - soft MeI M=Li Et_2O

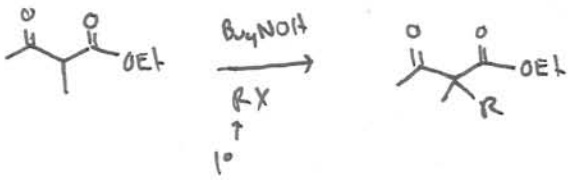
bis alkylation



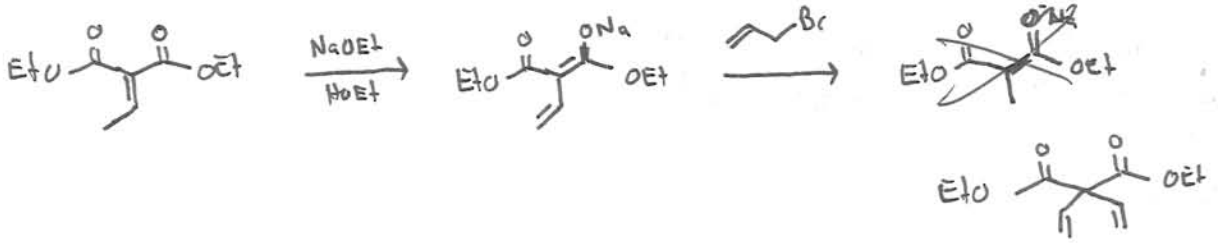


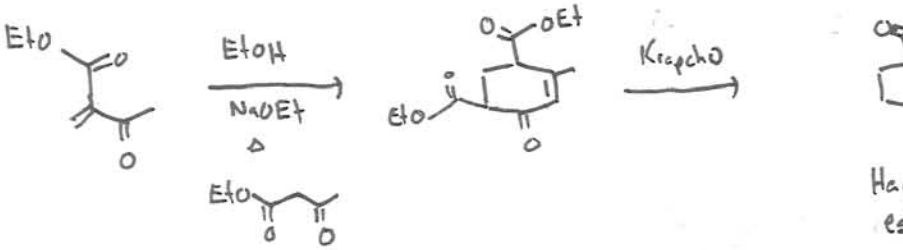


	O alkyl	C-alkyl
CH_3CN	19%	81%
DMF	46%	54%



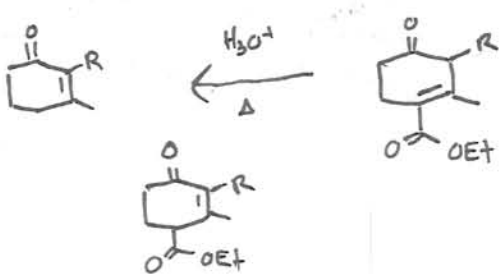
cool vinyl systems





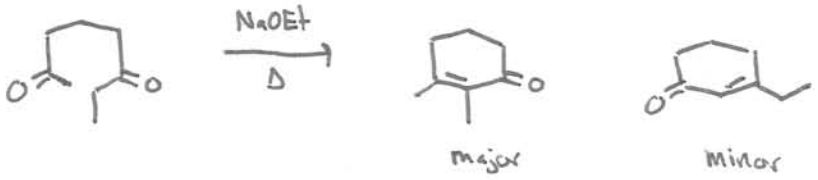
1,4 addition faster than 1,2

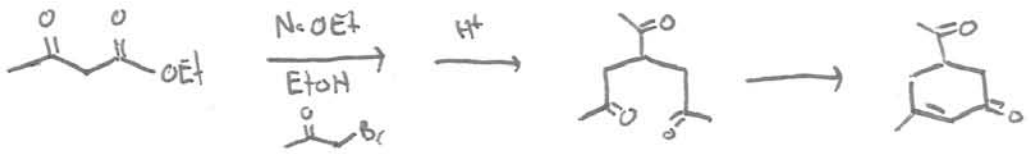
Hagmans ester

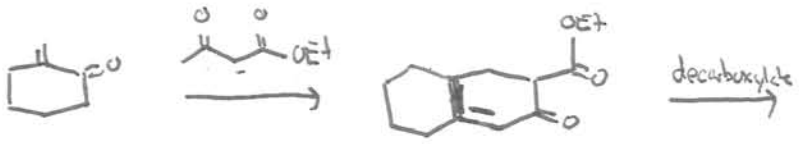


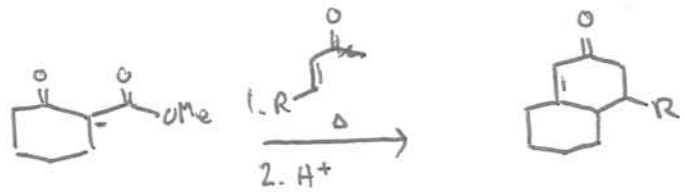
3/13

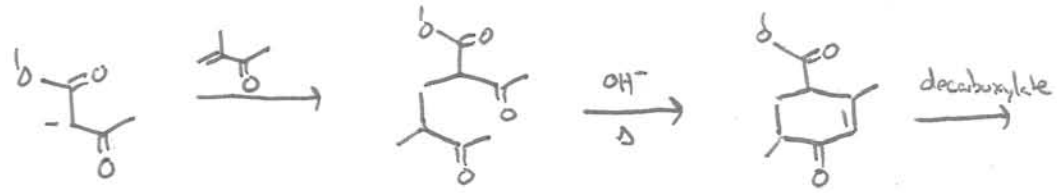
Aldol - pre LDA

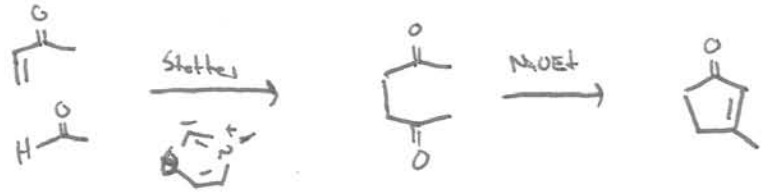




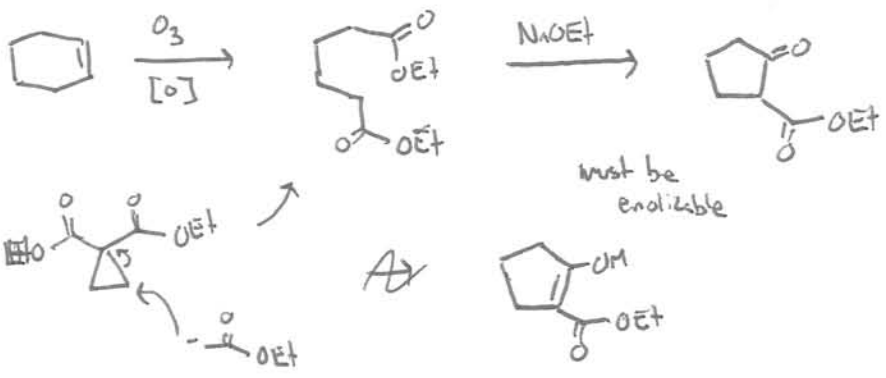




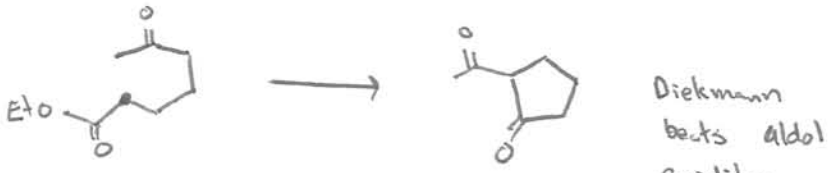




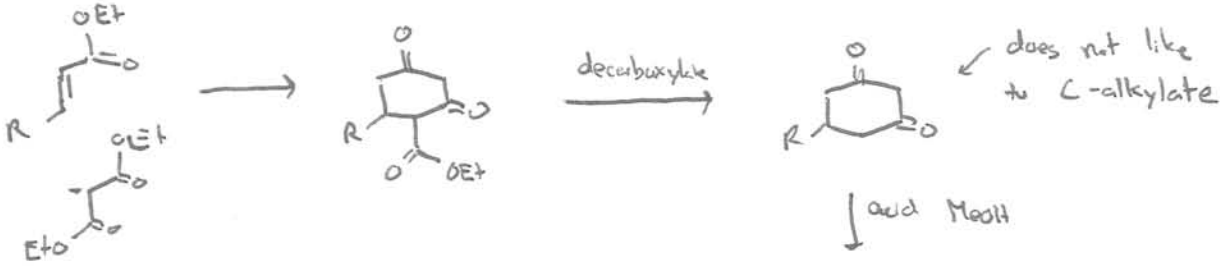
Claisen Condensation Dieckmann (ring closed)



other product
~~is~~ not enolizable

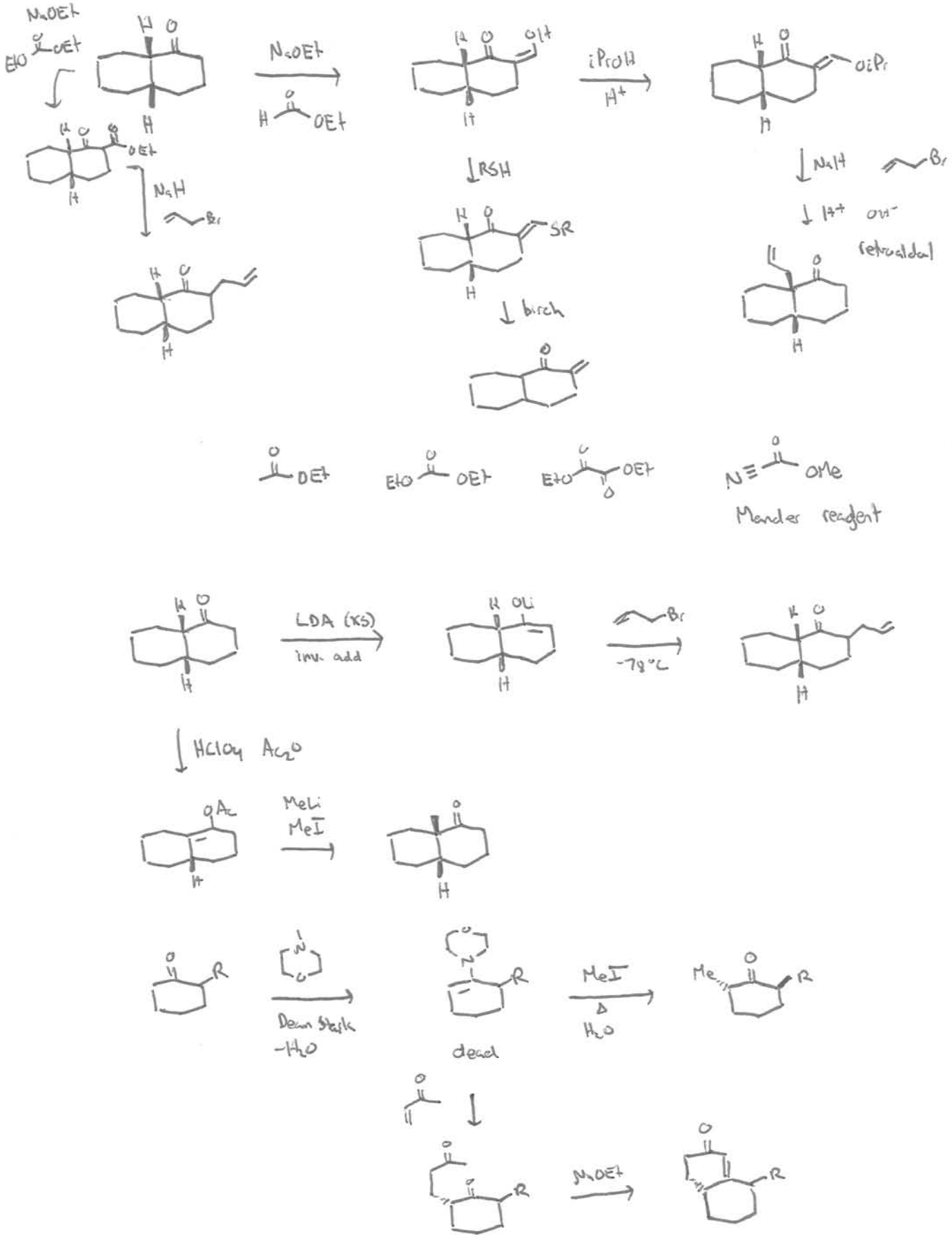


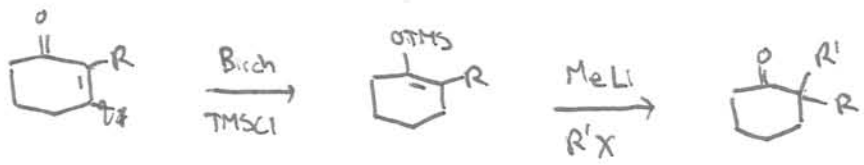
Diekmann beats aldol acidity



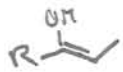
thermodynamic conjugate

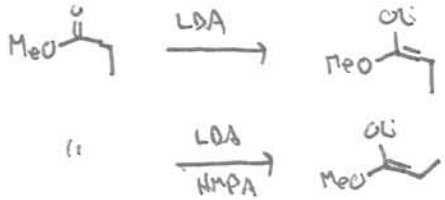
Cross conjugate kinetic

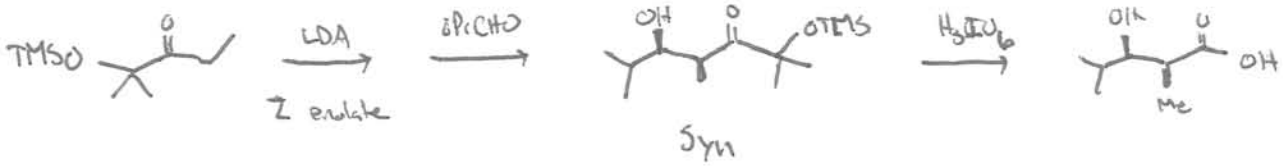

NaOEt
EtO
OEt
NaOEt
H
OEt
RSH
SR
birch
iPrOH
H+
OiPr
NaH
Br
H+ OH-
retroaldol
OEt
EtO
OEt
EtO
OEt
O
N
OMe
Meander reagent
LDA (XS)
imm. add
Br
-78°C
Li
HClO4 Ac2O
OAc
MeLi
MeI
R
Dean Stark
-H2O
decal
MeI
Δ
H2O
Me
R
NaOEt
R

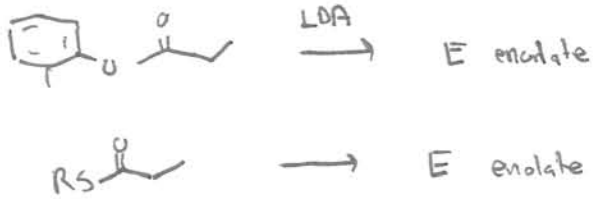

Birch
TMSCl
MeLi
R'X

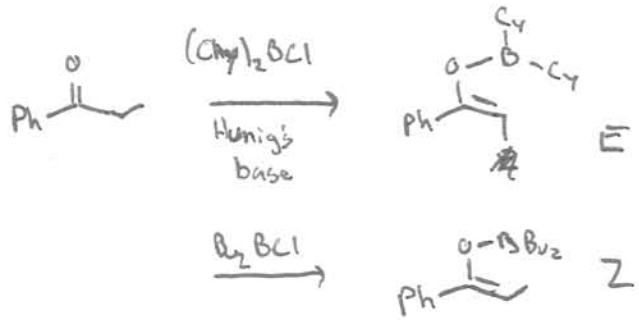

E
gives
anti in a closed TS

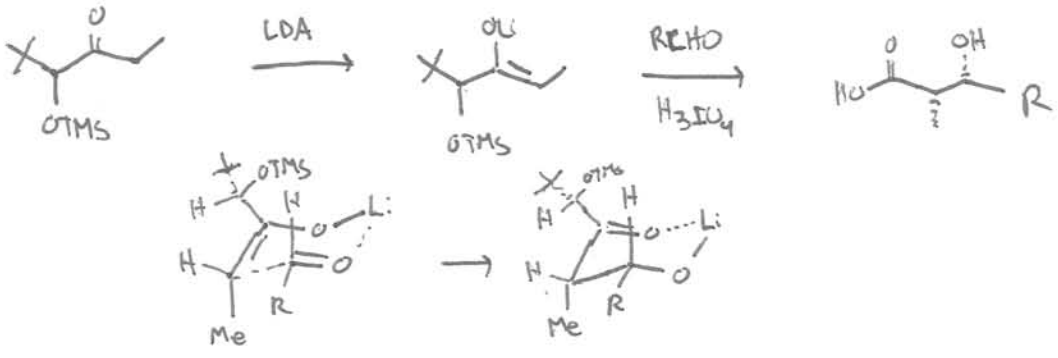

Z
gives
syn via closed T.S.

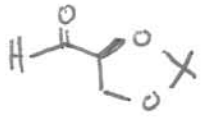

LDA
LDA
HMPA


LDA
Z enolate
iPrCHO
Syn
H3IO6
Me


LDA
E enolate
E enolate

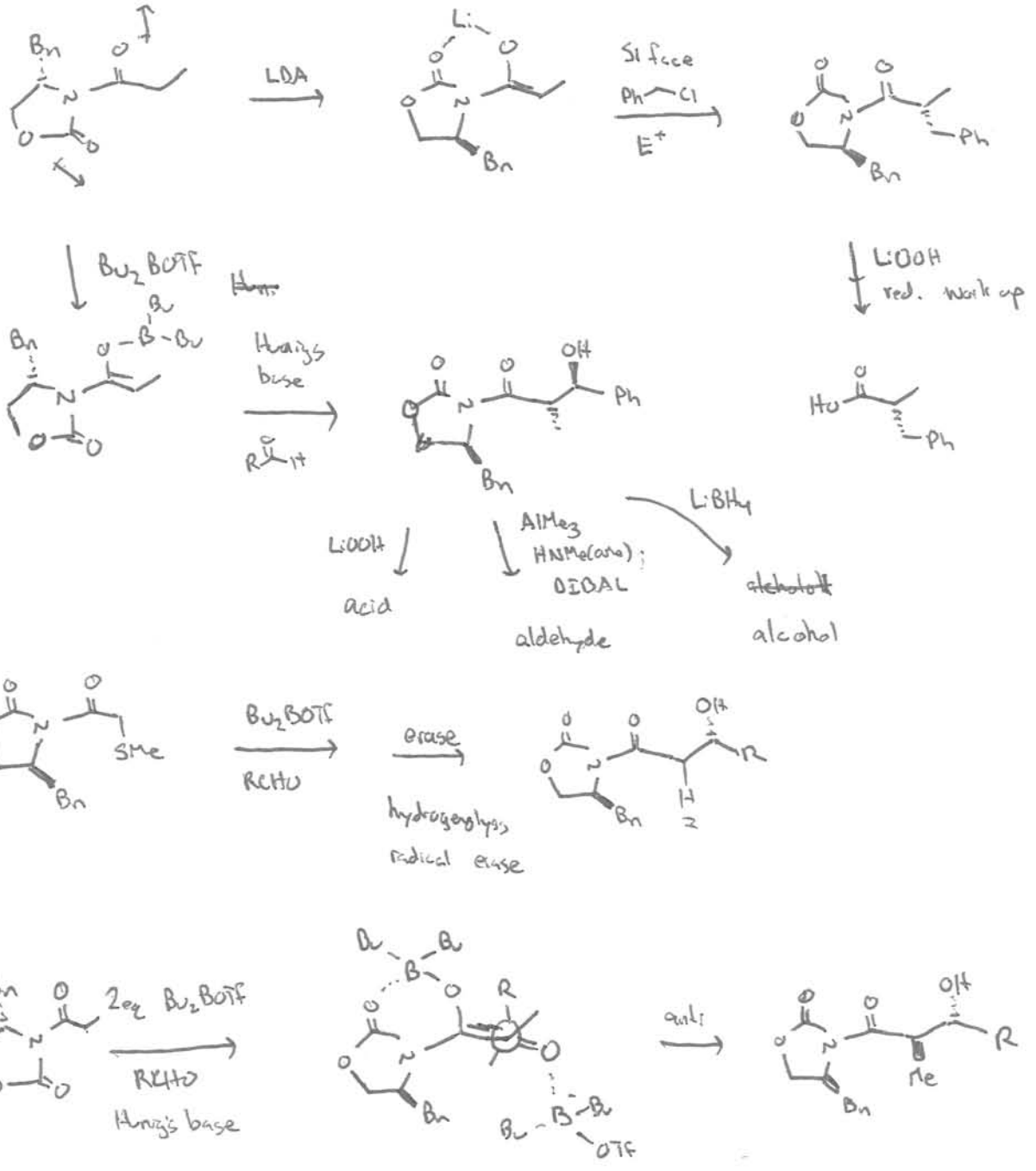

Hunig's base
E
Z


LDA
RCHO
H3IO4
OTMS
Me
R



Felkin Ahn

Cram Chelation

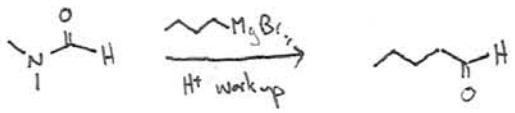


Name: KEY

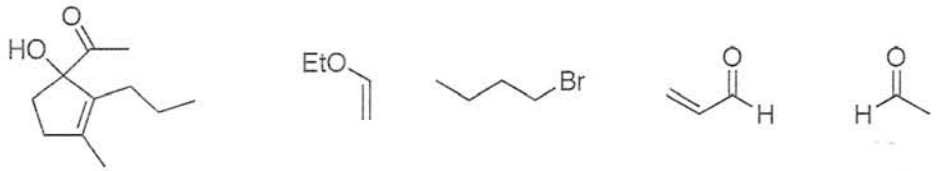
Chem 133/233
Exam 1
January 29, 2008
8:00 – 10:45 am

1. Give the reagent that is equivalent to the respective synthon and use it in a reaction. Provide all reagents and solvent.

ex:

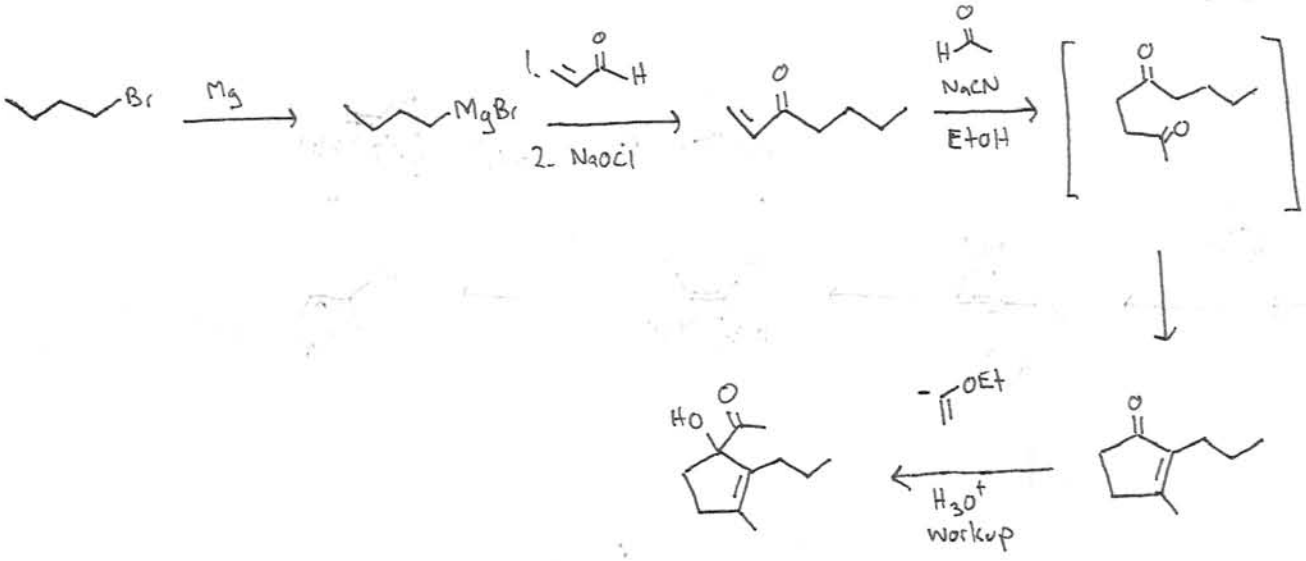


2. Propose a synthesis of the target molecule from the available building blocks and any necessary reagents. Higher marks will be given to those with fewer steps.



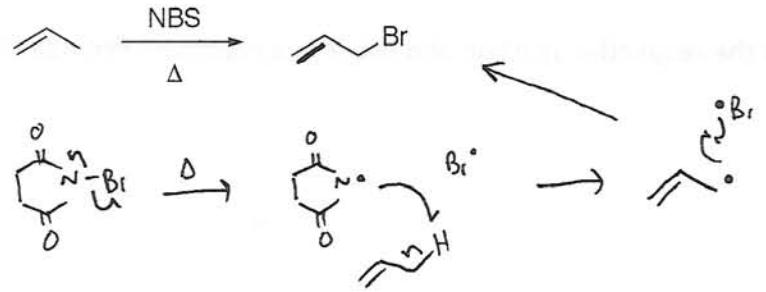
Target molecule

Available building blocks

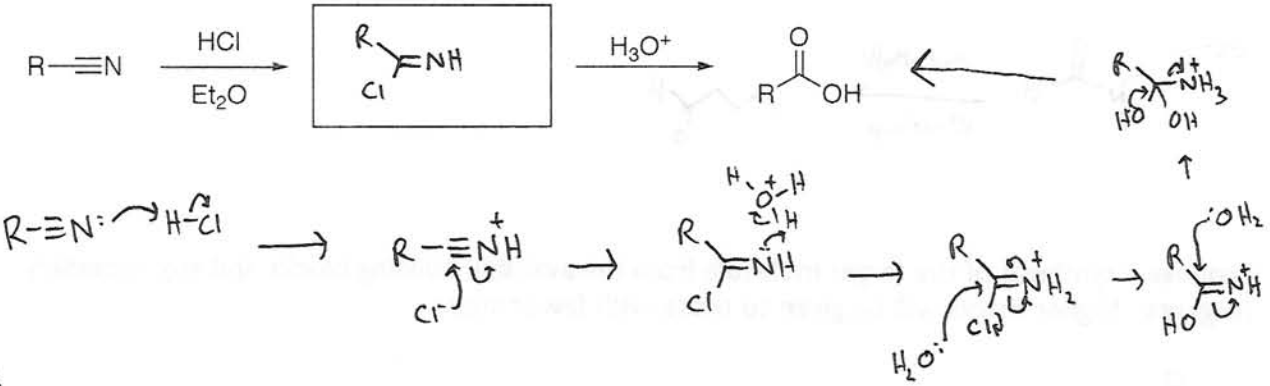


3. Choose four out of the following six and give the mechanism. If applicable, provide and any missing intermediates in the empty boxes:

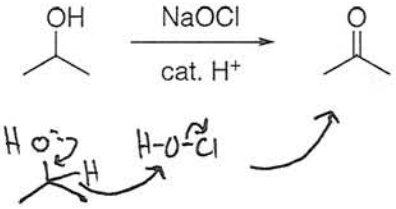
A.



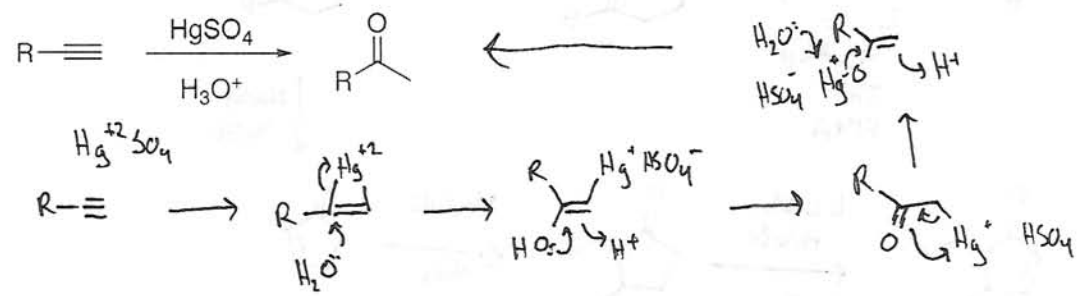
B.



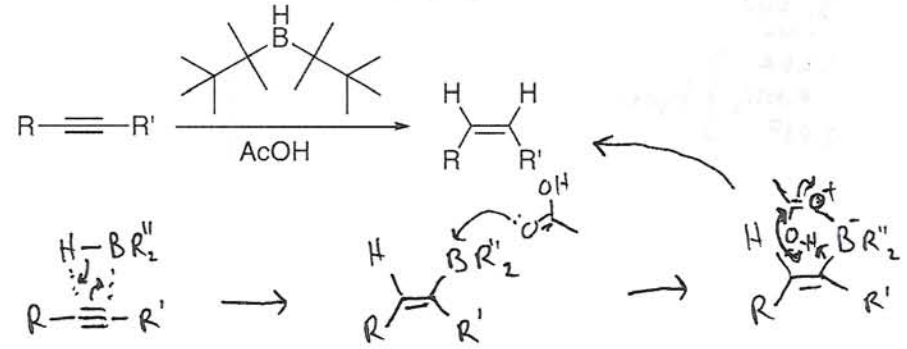
C.



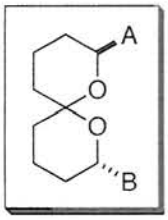
D.



E.



5. Draw all four conformations of the spiroketal shown below, in the assigned boxes. Which conformer is the most stable?



See last page

invert A ring

invert B ring

1 anomeric effect

no anomeric effects

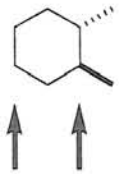
2 anomeric effects

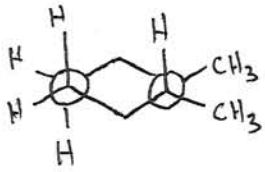
invert B ring

invert A ring

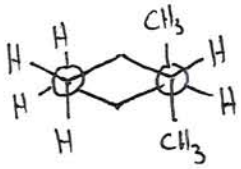
1 anomeric effect

6. Draw a Newman projection looking down the indicated bond, of both chair conformations of the molecule shown below.





vs.



7. Given the following A, G, and U data, calculate the energy difference between the two conformations drawn in #6: A_{Me}= 1.8, G_{Me}= 0.4, U_{Me}= 1.8 (kcal/mol).

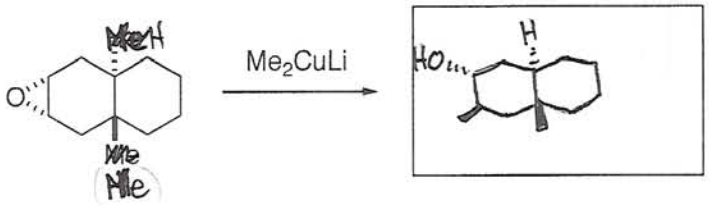
2 (1.8 kcal/mol) = 3.6 kcal/mol (diaxial)

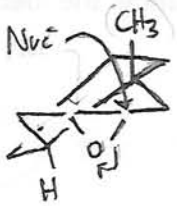
2 (.4 kcal/mol) = .8 kcal/mol (diequitorial)

$\Delta = (3.6 - .8)$ kcal/mol

Δ = 2.8 kcal/mol

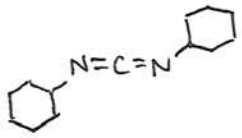
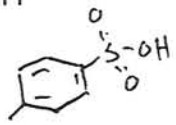
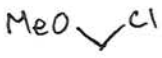
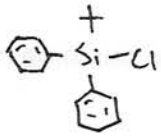
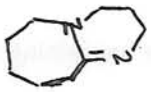
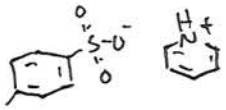
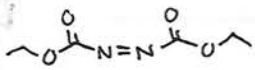
8. Give the product of the reaction, and explain the regiochemistry using a 3D drawing.



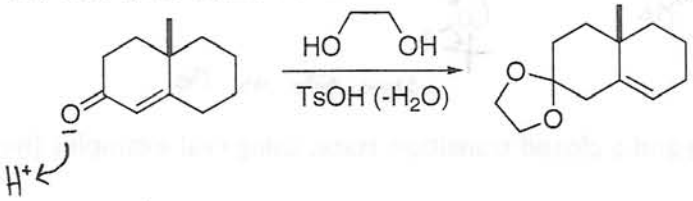


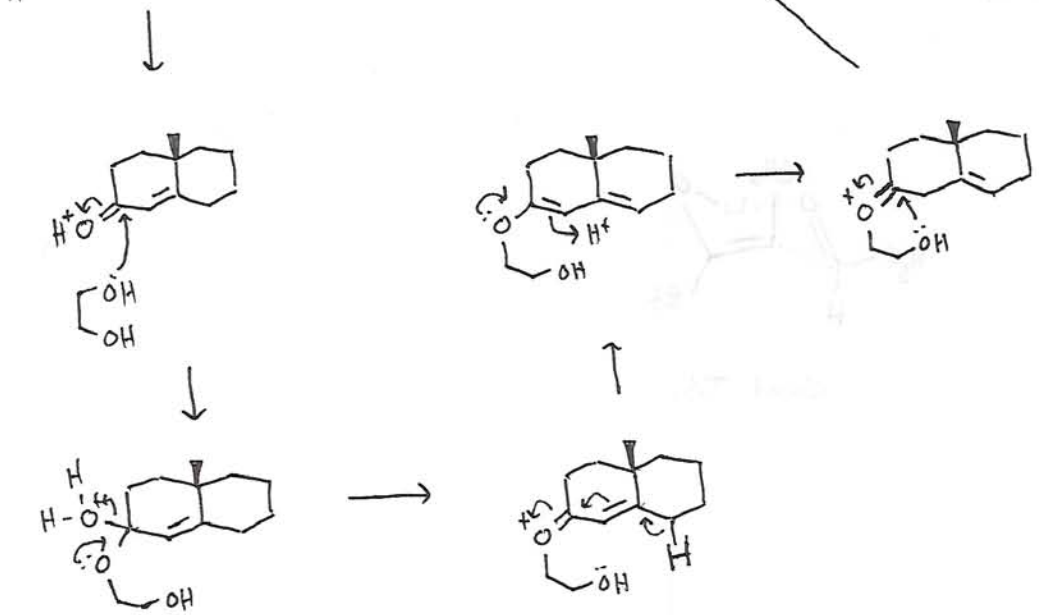
must be chair T.S.

9. Give the structure of each of the following

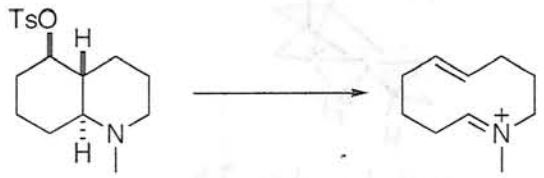
DCC 	TsOH 	MOMCl 
BPSCl 	DBU 	2,6-lutidine 
PPTS 	DMAP 	DEAD 

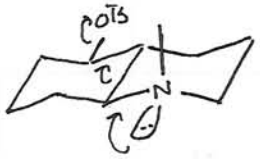
10. Give a mechanism that accounts for the following observation:



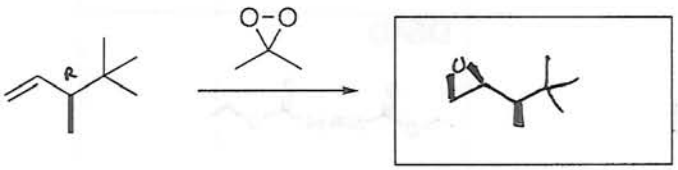


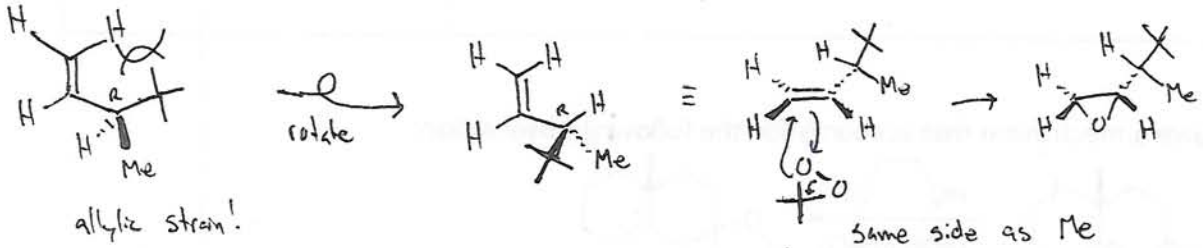
11. Draw the starting material in 3D showing the necessary orbital alignment for the following Grobb fragmentation (also show the mechanism in your drawing).



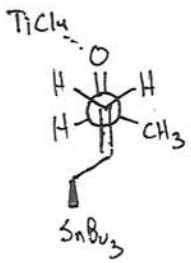


12. Give the product and draw a 3D transition state explaining the stereochemical outcome of the following:

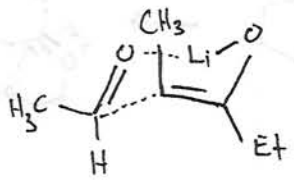




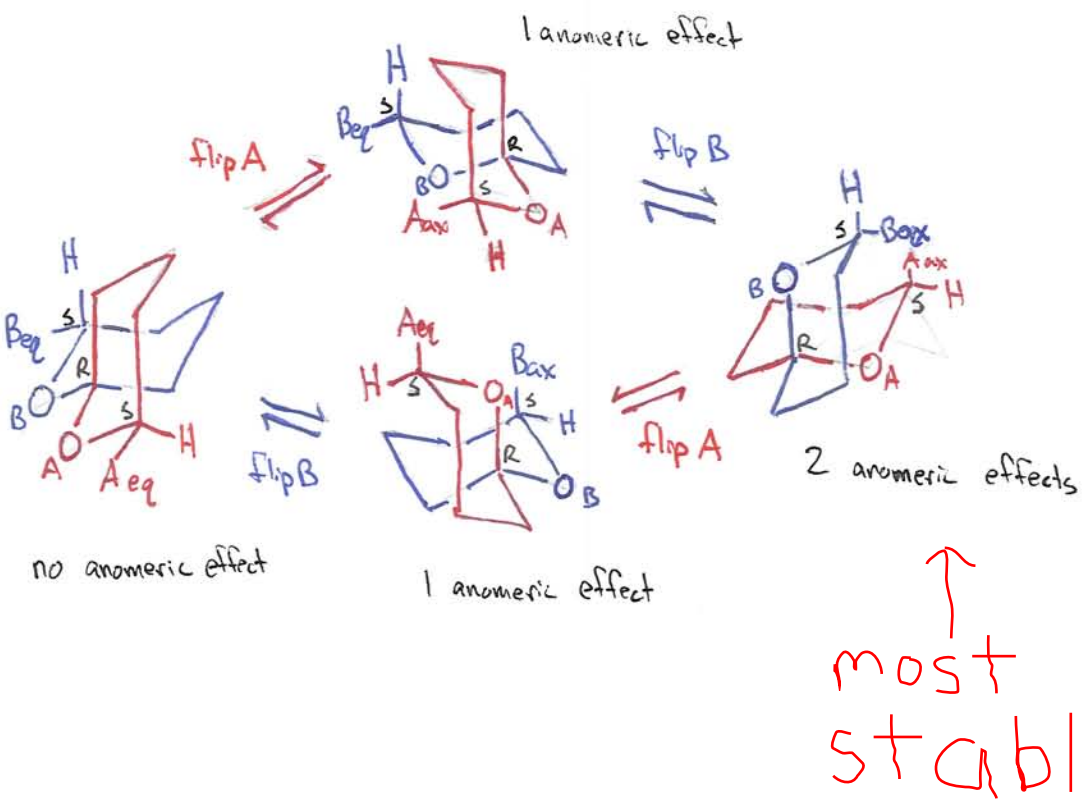
13. Give an example of a an open transition state and a closed transition state, using real examples (no "R" abbreviations, etc.)



open T.S.



closed T.S.

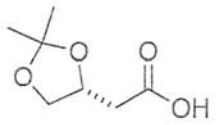

1 anomeric effect
flip A
flip B
flip B
flip A
no anomeric effect
1 anomeric effect
2 anomeric effects

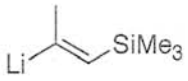
most stable

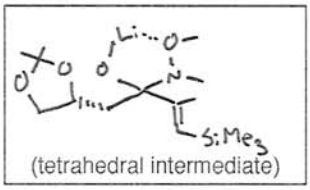
Name: KEY

Chem 133/233
Exam 2
February 21, 2008

1. Provide the products and/or intermediates of each set of conditions (28pts). 2pts each

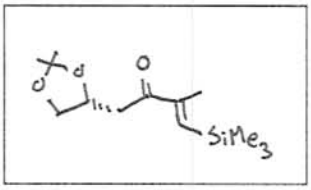
a. 

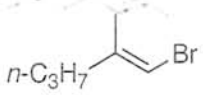
1. DCC, (MeO)MeNH•HCl
NEt_3, CH_2Cl_2
2. 



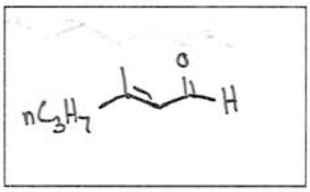
(tetrahedral intermediate)

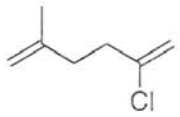
NH_4Cl wkup



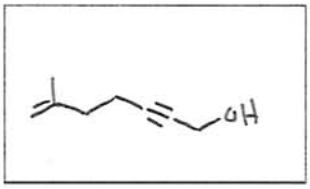
b. 

1. *t*-BuLi (2.1 eq)
2. DMF
3. H_3O^+ wkup

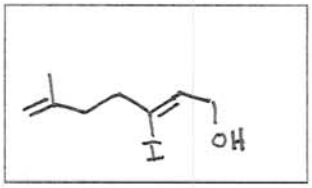


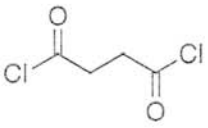
c. 

a) LDA (2.1 eq), -78 °C to rt
b) $(CH_2O)_n$
c) H_3O^+

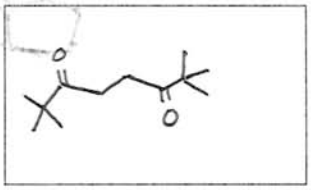


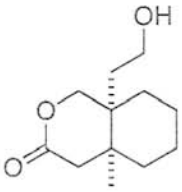
1. $LiAlH_4$, NaOMe, THF
2. I_2



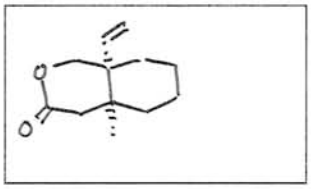
d. 

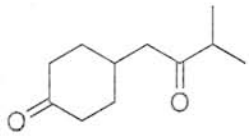
t-BuMgCl (2.1 eq)
cat. CuI, THF, -78 °C



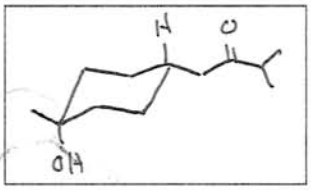
e. 

1. TsCl, pyr, cat. DMAP
2. NaSePh, EtOH
3. mCPBA (1 eq); then Δ

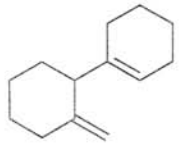


f. 

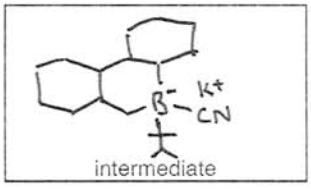
Me-Ti(O*i*-Pr)$_3$
Et_2O



show relative stereochemistry

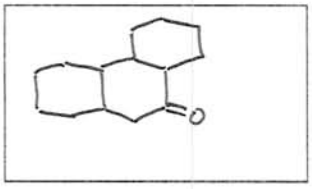
g. 

a) $ThxBH_2$, THF
b) KCN

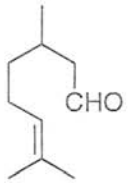


intermediate

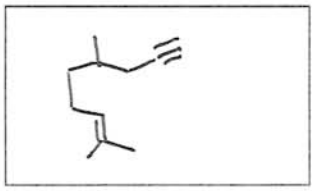
$(CF_3CO)_2O$
c) ~~$(CF_3O)_2O$~~
d) NaOH, H_2O_2

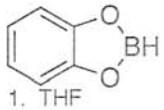


h.



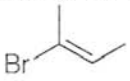
a. CBr_4, Ph_3P, Zn
b. *n*-BuLi (2.1 eq)
c. H_3O^+ wkup

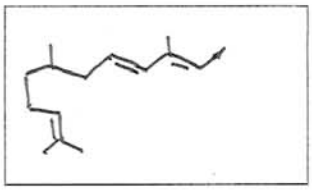




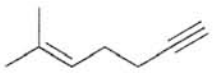
1. THF
2. $Pd(PPh_3)_4$, NaOEt

toluene, 80 °C

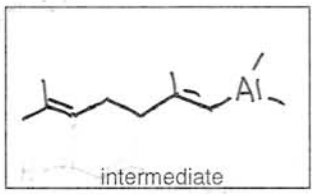




i.

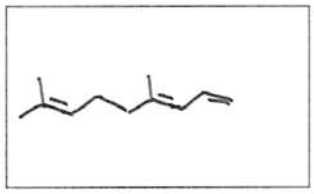


a. $AlMe_3$, cat. Cp_2ZrCl_2, 1,2-DCE



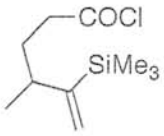
intermediate

b. , $ZnCl_2$
Pd(0) (cat.)

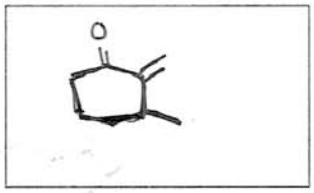


2. Give the product of each transformation (12pts).

a.



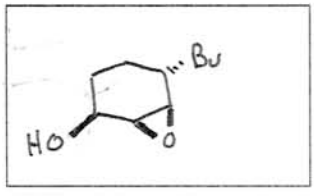
$AlCl_3$, CH_2Cl_2



3 pts

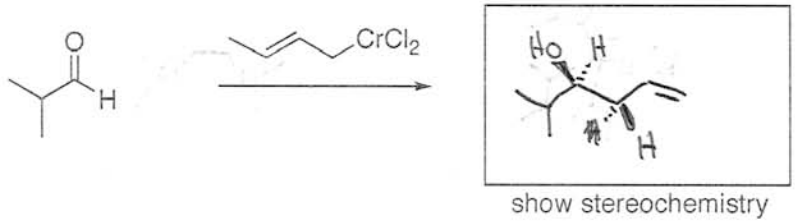
b.

1. $Bu_2(CN)CuLi_2$
2. mCPBA



3 pts

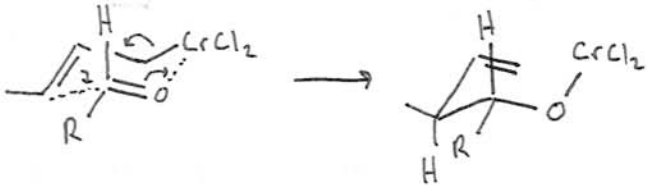
c.



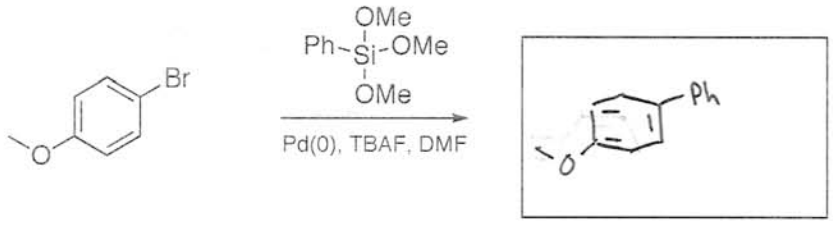
show stereochemistry

3pts

III

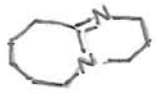
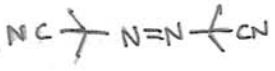
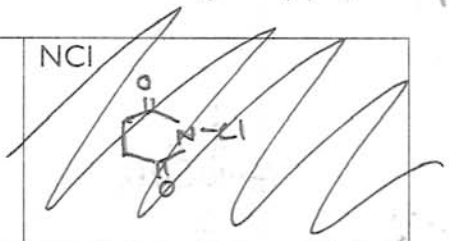
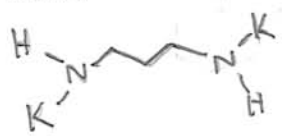
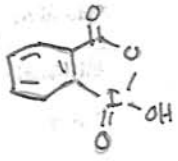
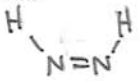


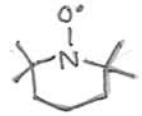
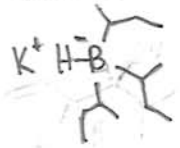
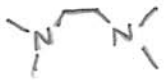
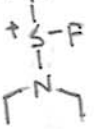
d.



3pts

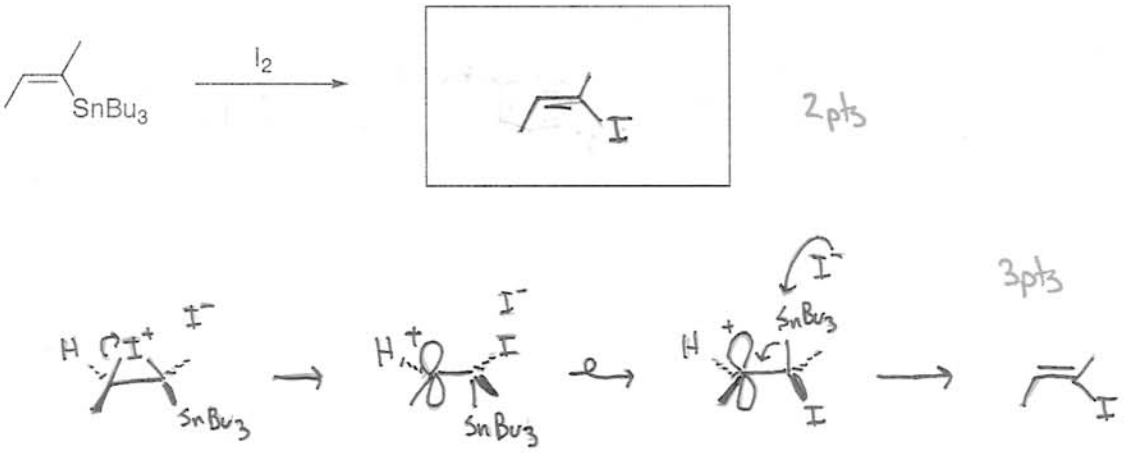
3. Choose six from the following twelve and draw the structures of the reagents (6pts). 1pt each

DBU 	AIBN 	NCI 
KAPA 	IBX 	Diimide 

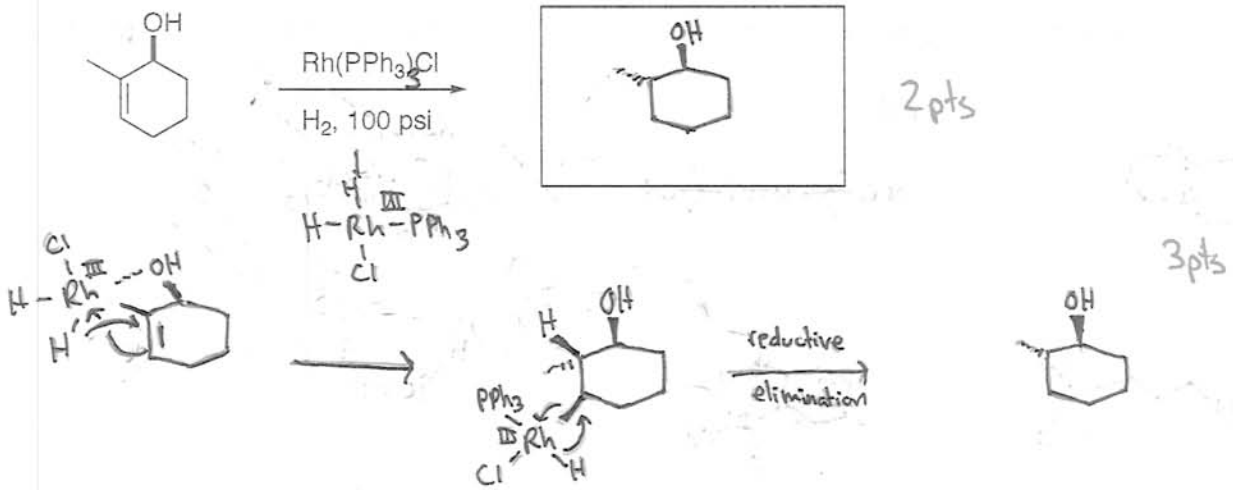
Tempo	K-Selectride	TMEDA
		
Superhydride	DAST	Imidazole
$LiHBEt_3$		

4. Choose four of the following six. Give the mechanism for the following reactions. Use sawhorse or Newman projections for all intermediates, where applicable (20pts).

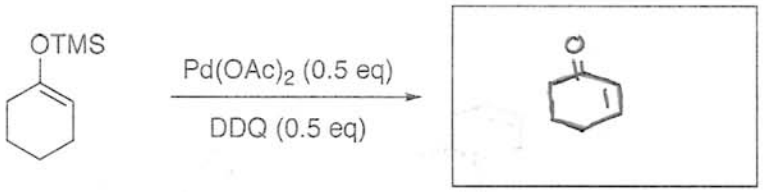
a.



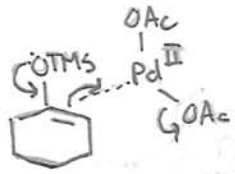
b.



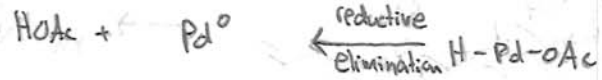
c.

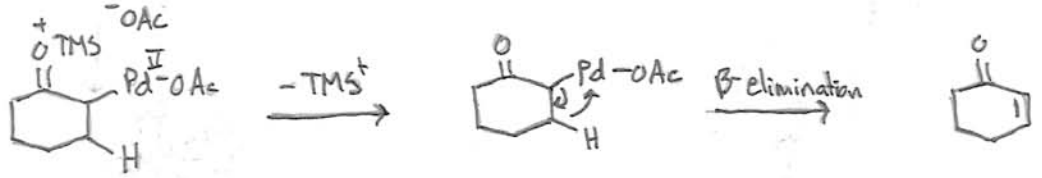


2 pts

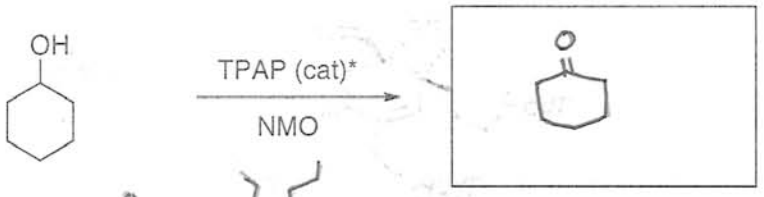


3pts



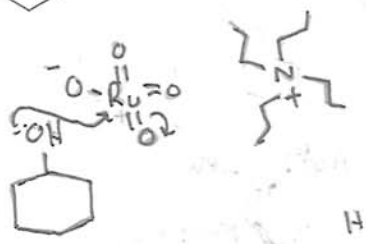


d.

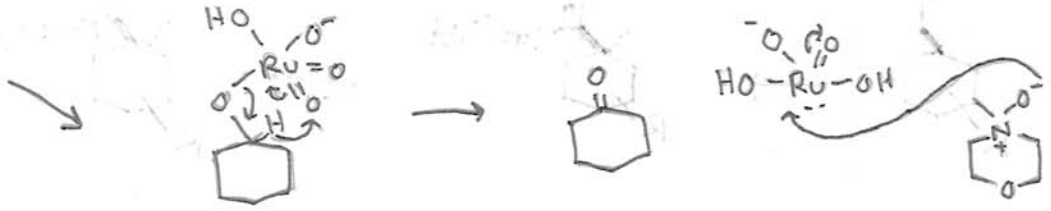


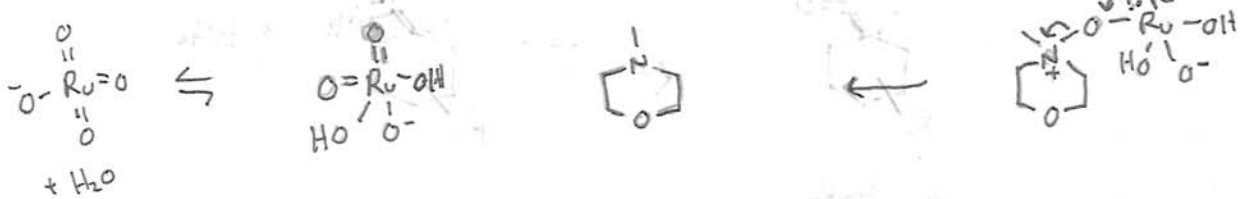
2pts

*Also show the re-oxidation of the catalyst

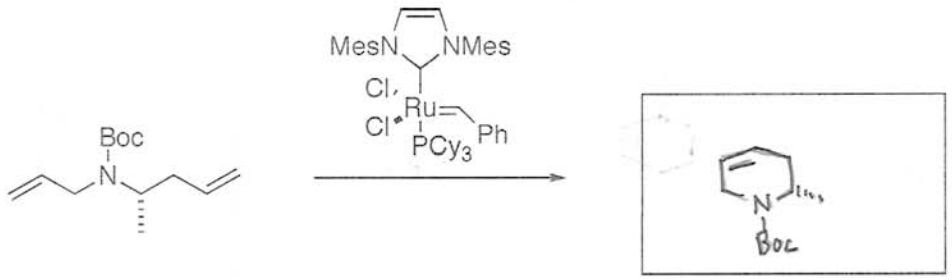


3pts

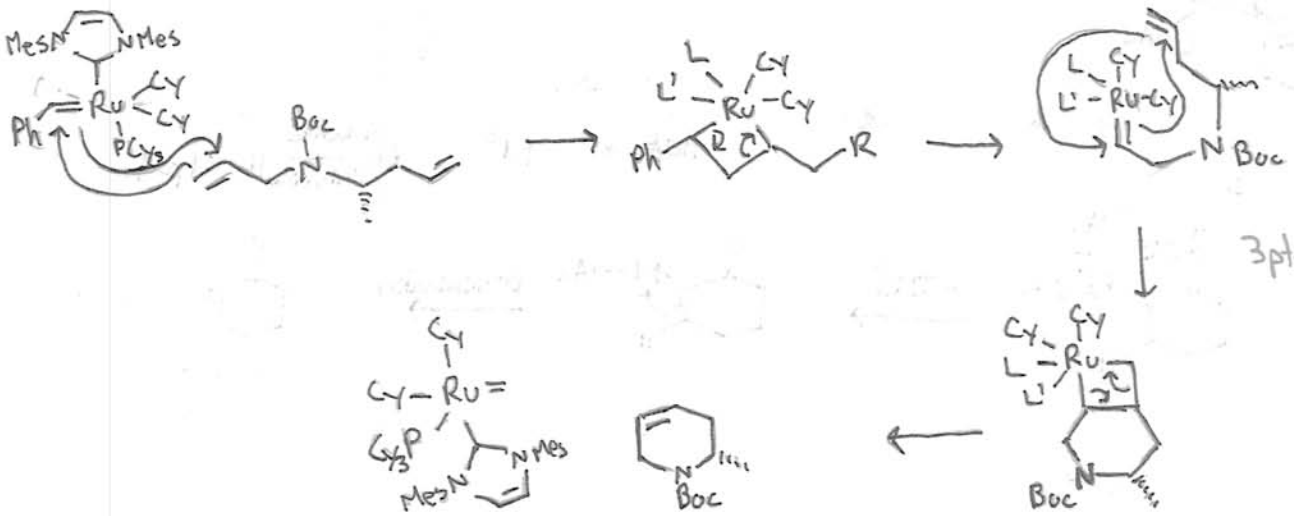




e.

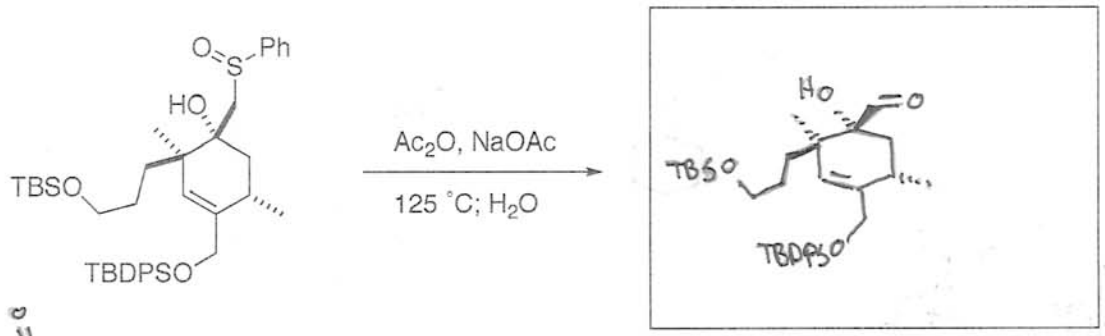


2 pts

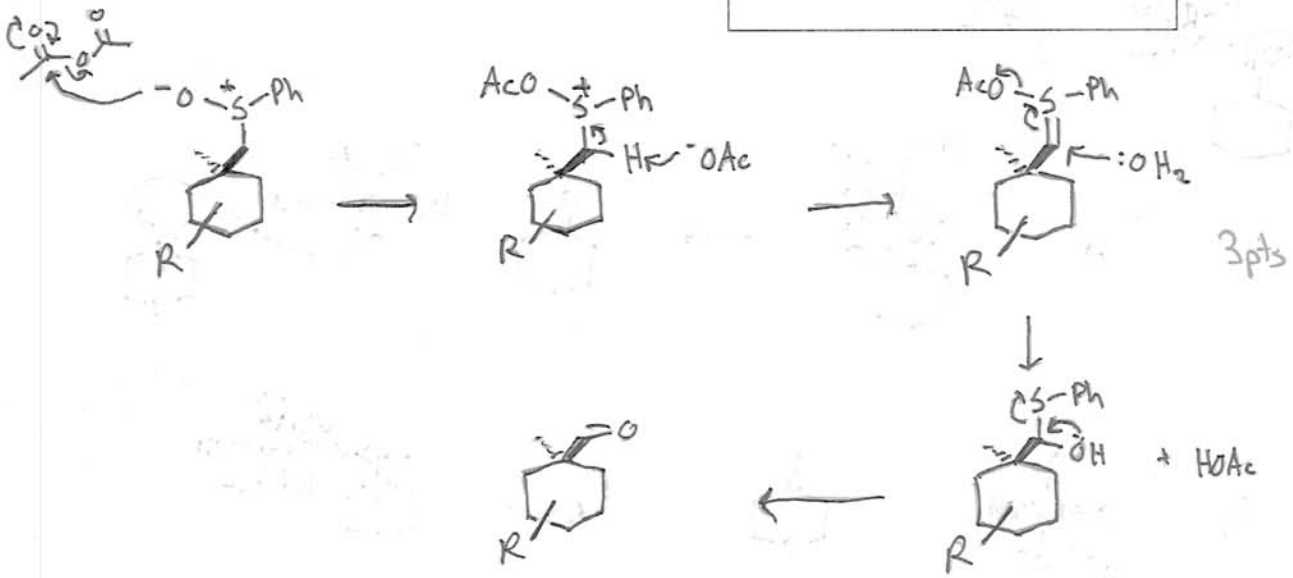


3 pts

f.

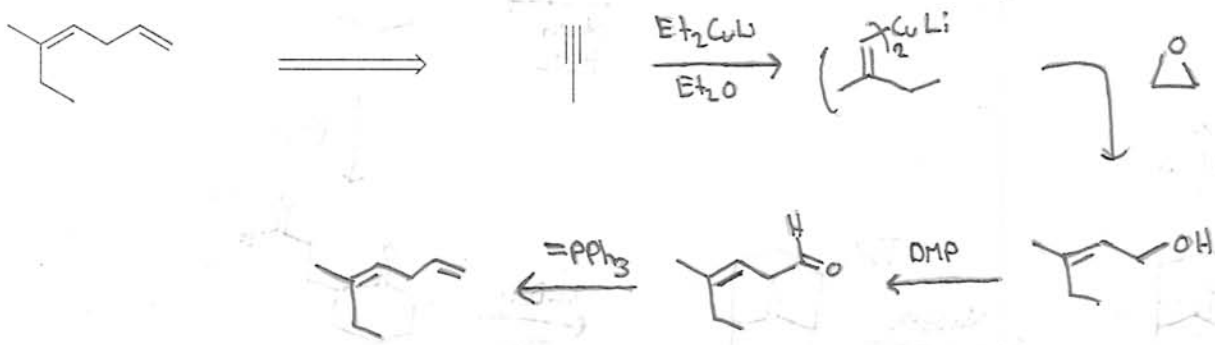


2 pts

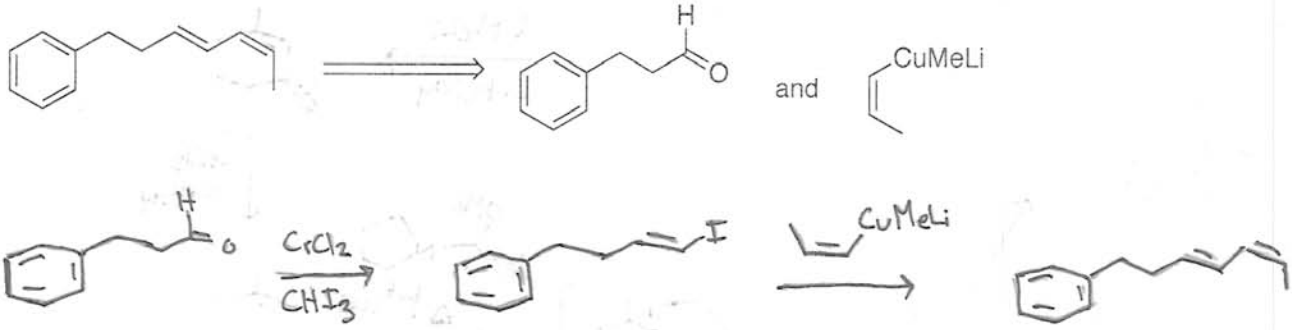


5. Propose a synthesis from the given starting material and any necessary reagents (35pts). 5 pts each

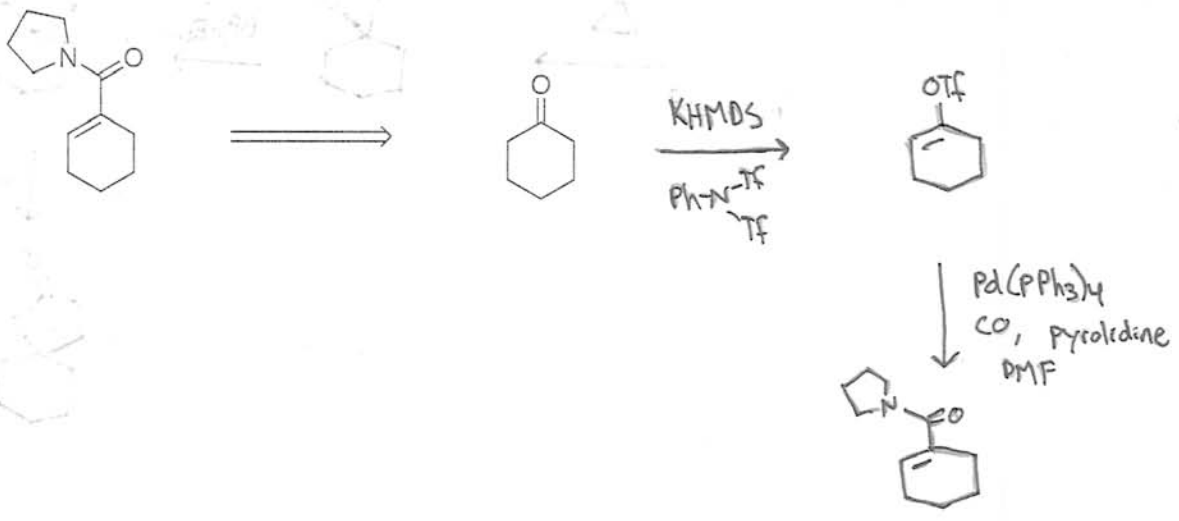
a.



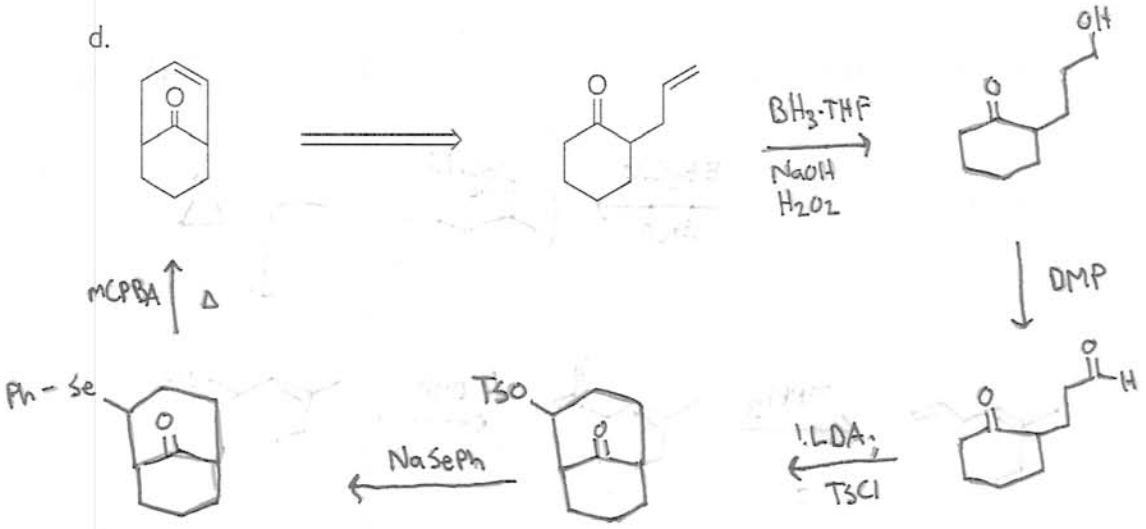
b.



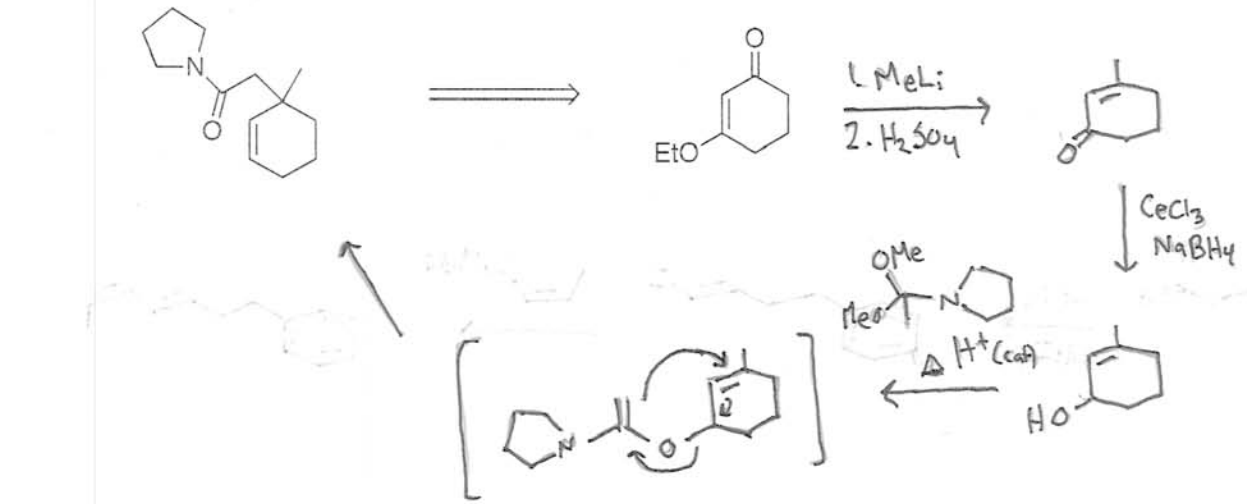
c.



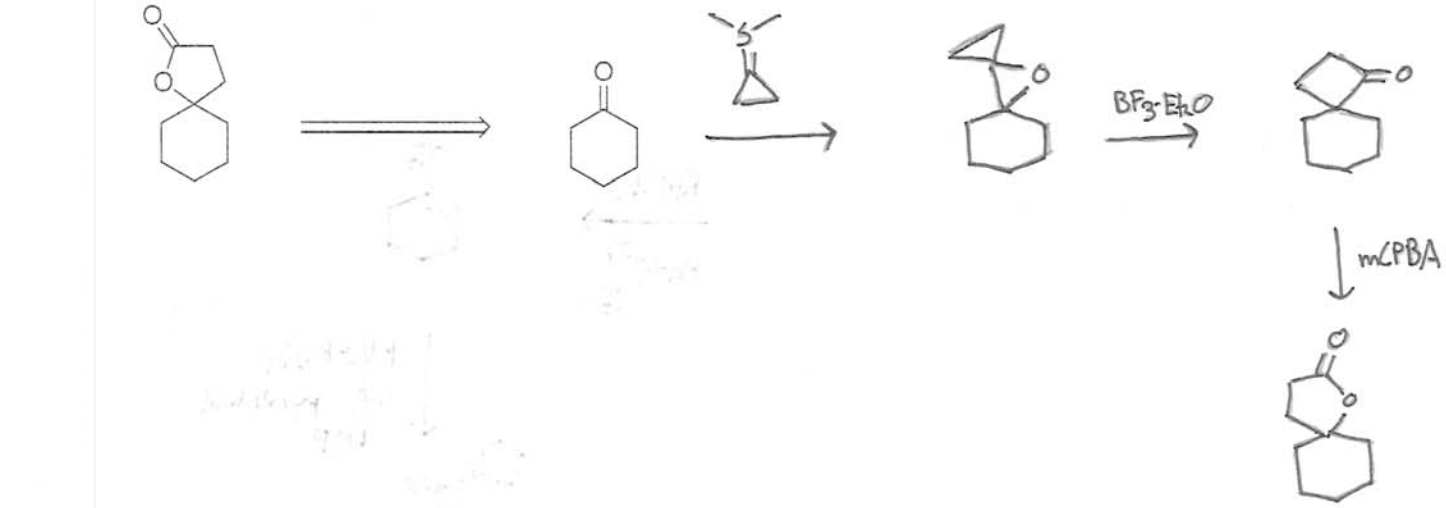
d.


BH3·THF
NaOH
H2O2
DMP
1. LDA;
TsCl
NaSePh
mCPBA
Δ
Ph – Se
TsO
OH
H

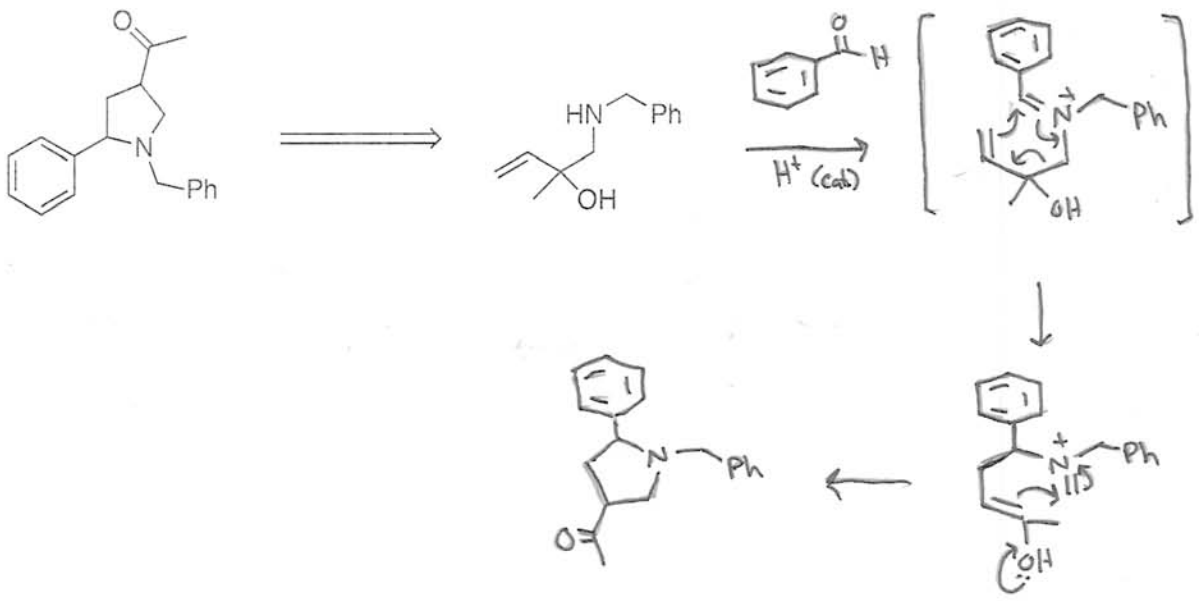
e.


1. MeLi;
2. H2SO4
CeCl3
NaBH4
EtO
OMe
MeO
N
Δ H+ (cat)
HO
O

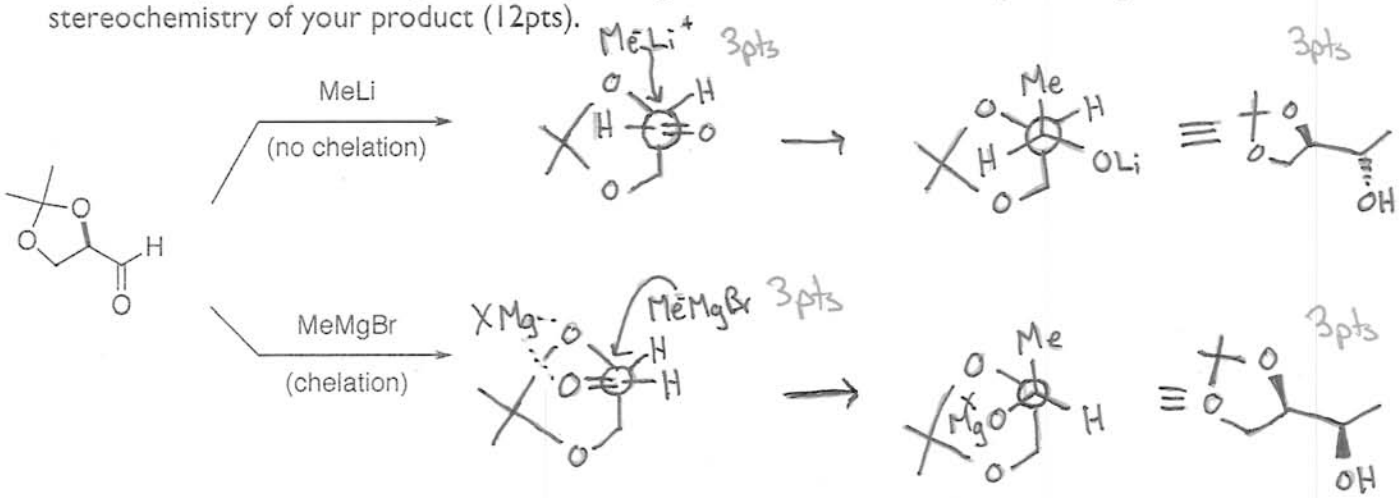
f.


S
BF3·Et2O
mCPBA
O

g.



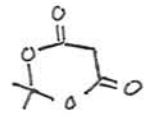
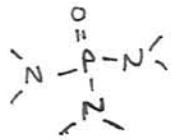
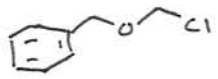
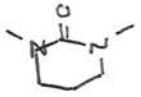
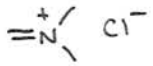
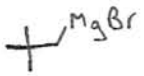
6. Predict the product resulting from the following.. Give a transition state predicting the stereochemistry of your product (12pts).



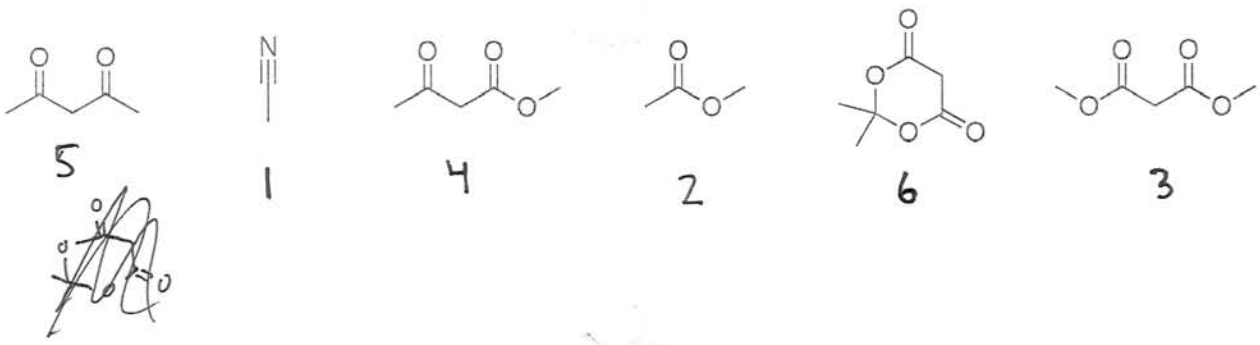
Name: KEY

Chem 133/233
March 19, 2007
Final Exam

1. Draw the structure of each reagent (6pts)

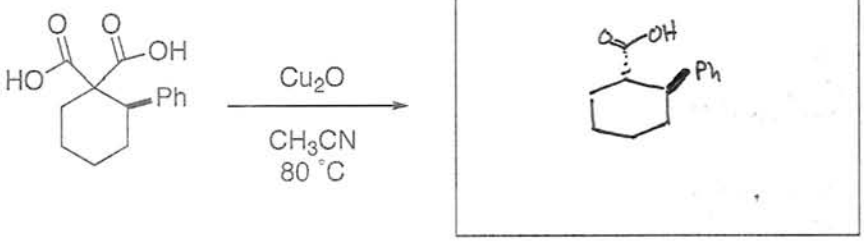
Meldrum's acid 	HMPA 	BOMCl 
DMPU 	Mannich reagent 	A non-reducing basic Grignard 

2. Rank the following compounds in order of decreasing pKa (4pts):

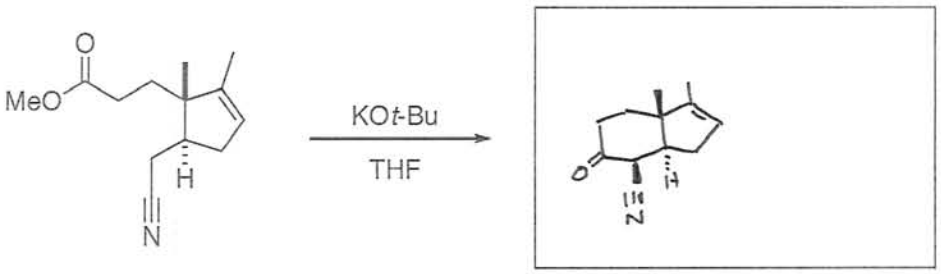


3. Give the product or reagents for each of the following reactions (2pts each, unless noted):

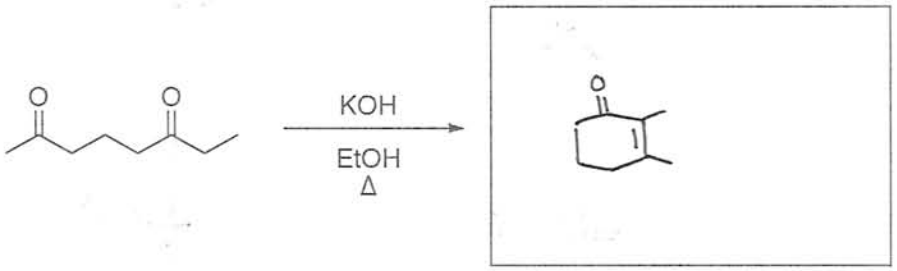
A.



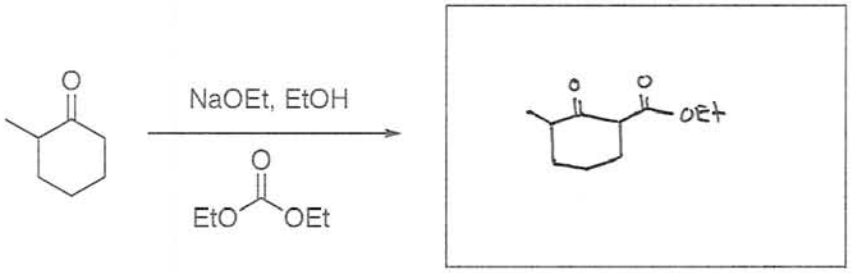
B.



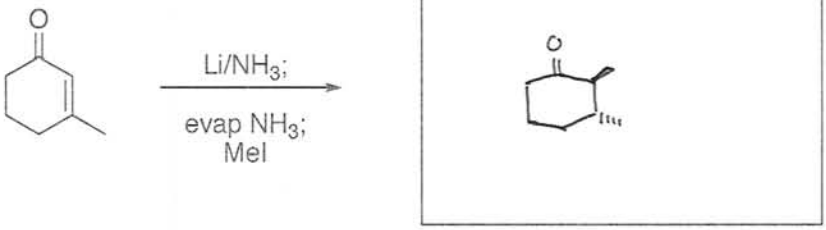
C.



D.

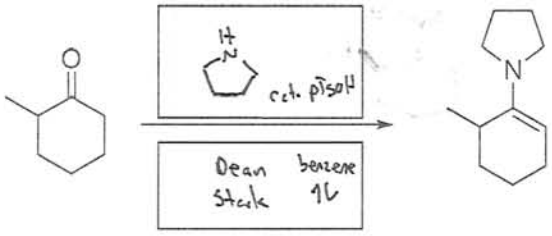


E.

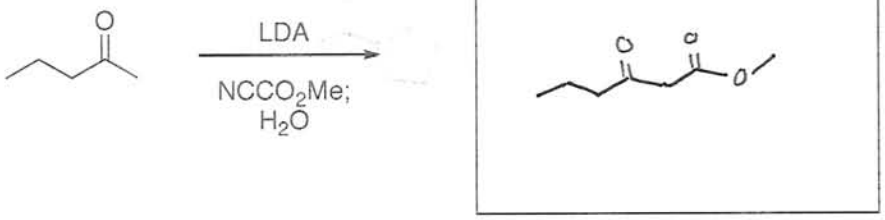


(show relative stereochemistry)

F.

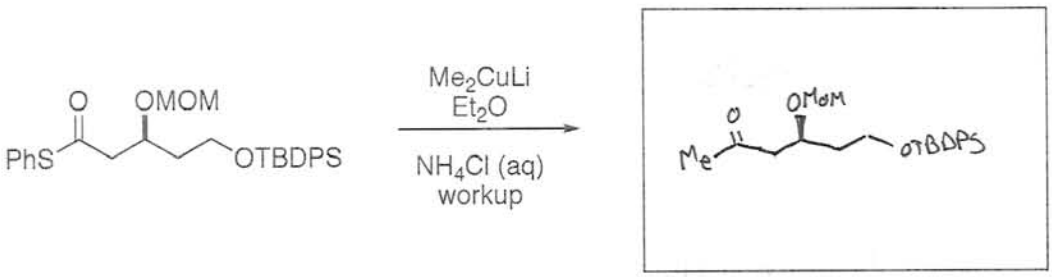


G.

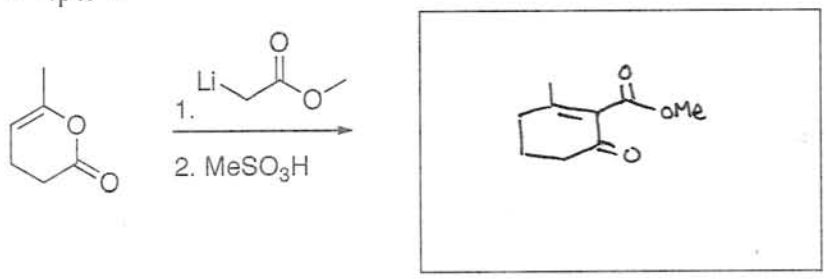


(kinetic)

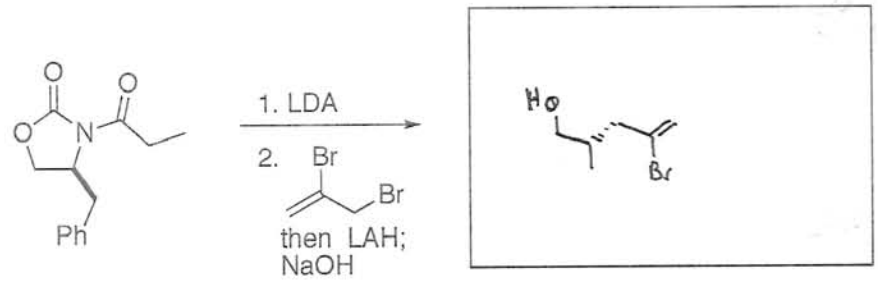
H.



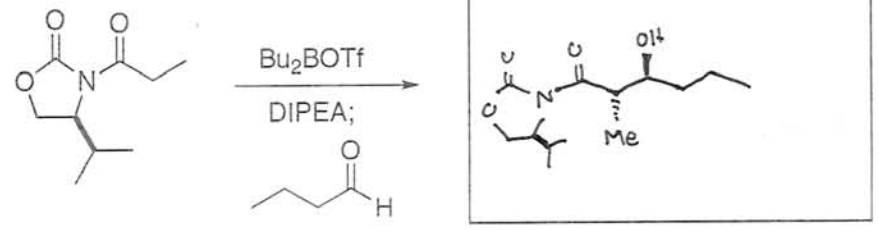
I. ★ 4pts ★



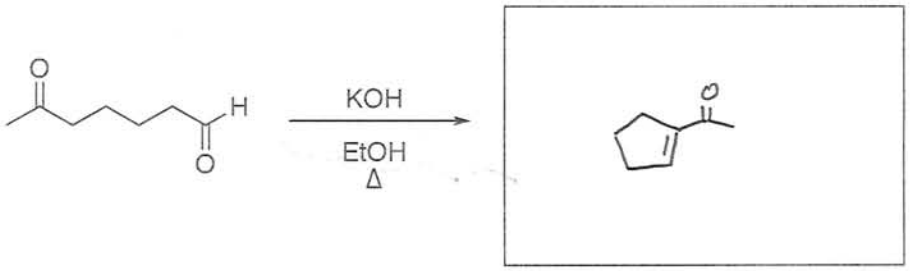
J. ★ 4pts ★



K. ★ 4pts ★

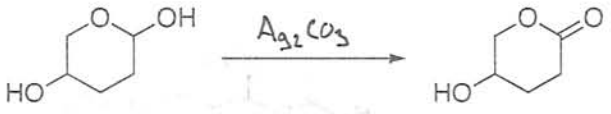


L.

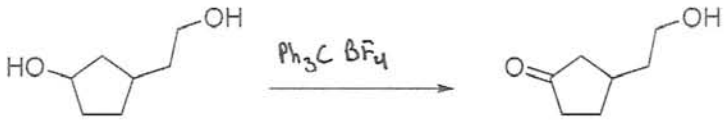


4. Give an appropriate reagent for each of the following transformations (2pts each):

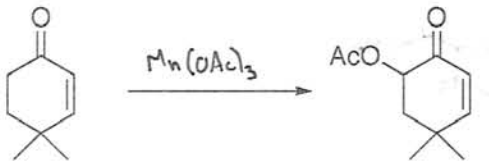
A.



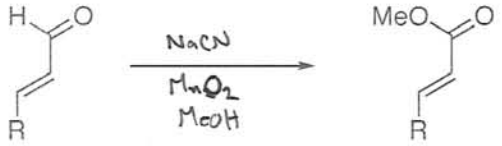
B.



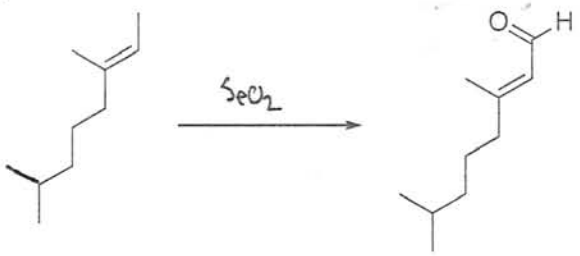
C.



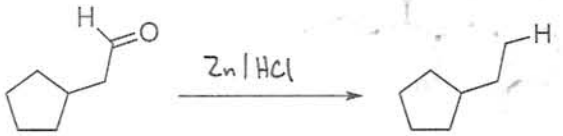
D.



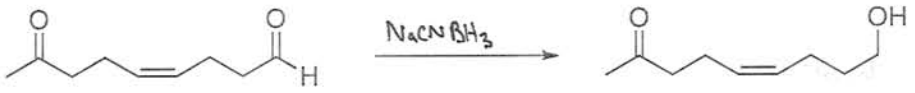
E.



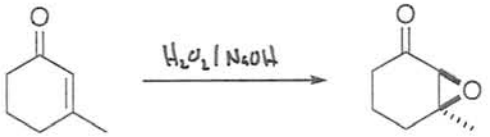
F.



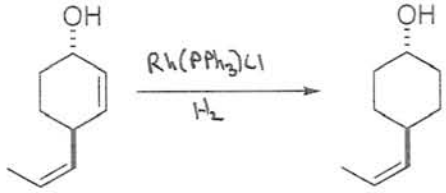
G.


O
O
H
NaCNBH3
O
OH

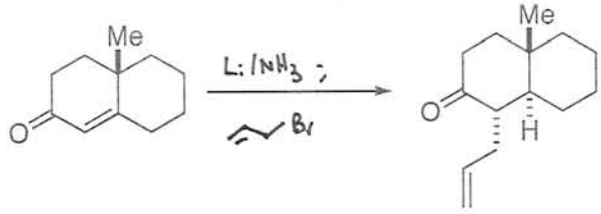
H.


O
H2O2 / NaOH
O
O

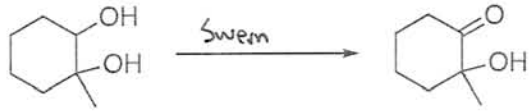
I.


OH
Rh(PPh3)Cl
H2
OH

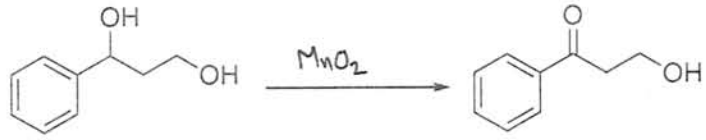
J.


Me
O
L: / NH3 ;
Br
Me
O
H

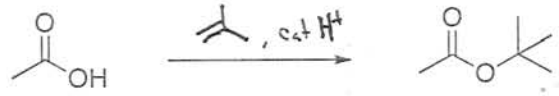
K.


OH
OH
Swern
O
OH

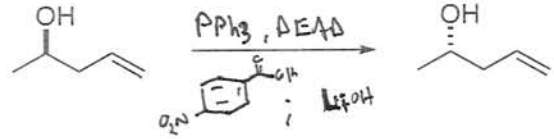
L.


OH
OH
MnO2
O
OH

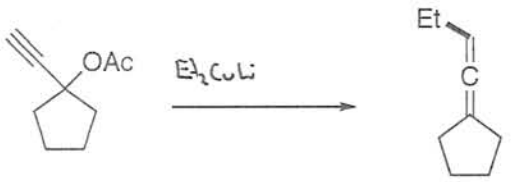
M.


O
OH
, cat H+
O
O

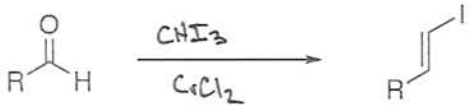
N.


OH
PPh3 , DEAD
O2N
LiOH
OH

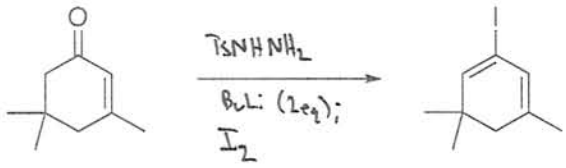
O.



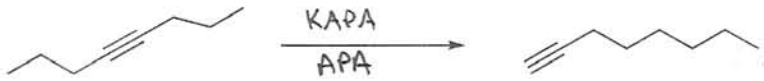
P.



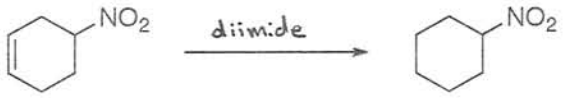
Q.



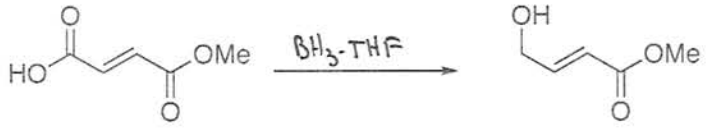
R.



S.

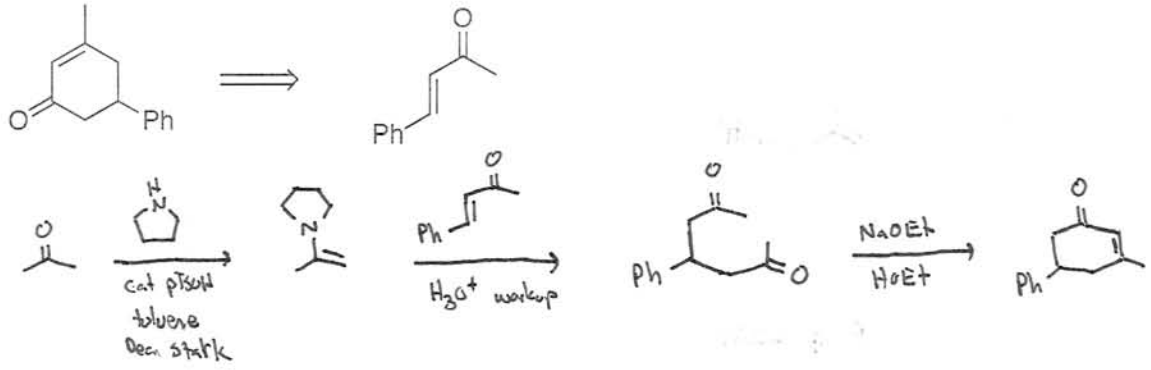


T.

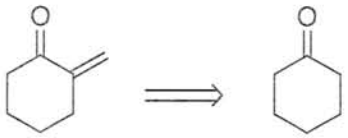


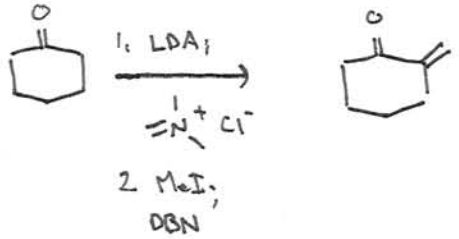
5. Propose a synthesis from the given starting material and any necessary reagents (5pts each)

A.

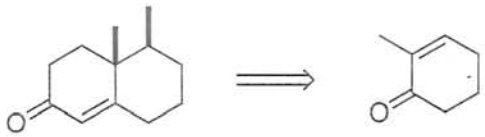


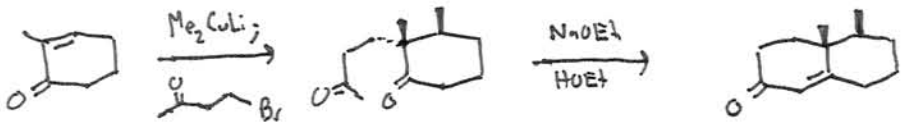
B.



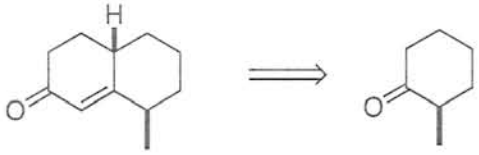

1. LDA;
2. MeI;
DBN

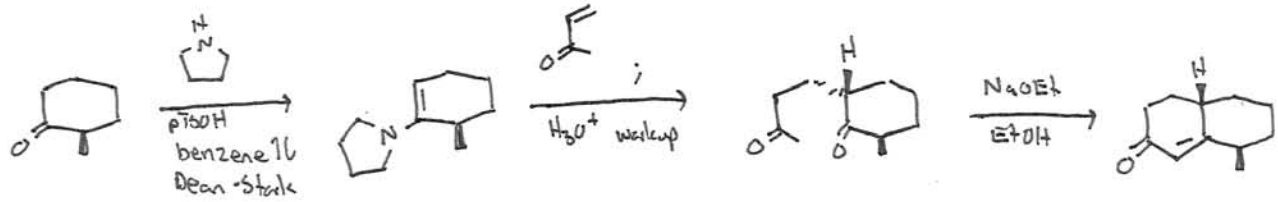
C.



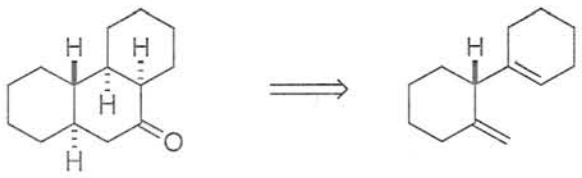

Me2CuLi;
NaOEt
HOEt

D.



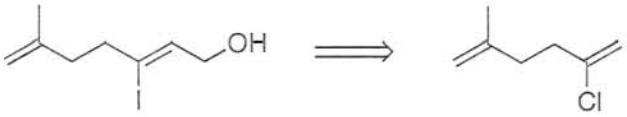

pTsOH
benzene 76
Dean-Stark
H3O+ workup
NaOEt
EtOH

E.

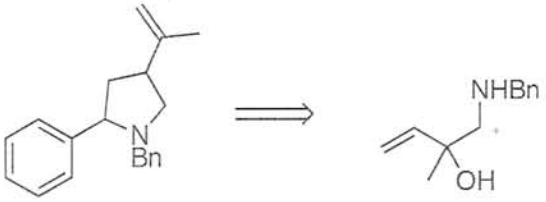


See exam #2

F.

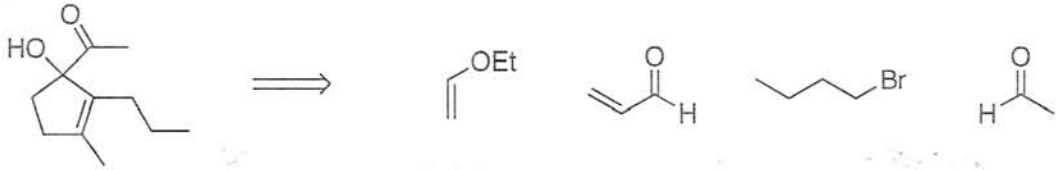


G.



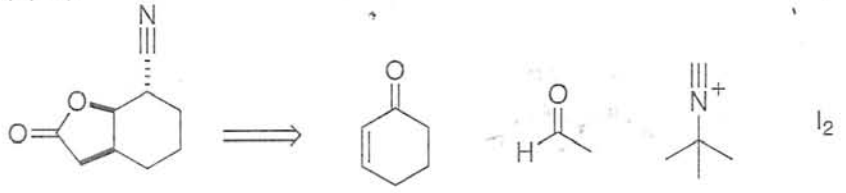
6. Propose a synthesis of the target molecule from the available building blocks

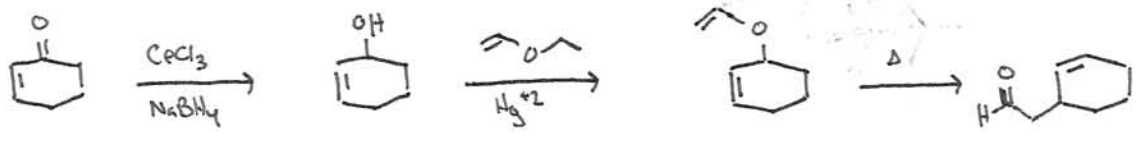
A. (5pts)

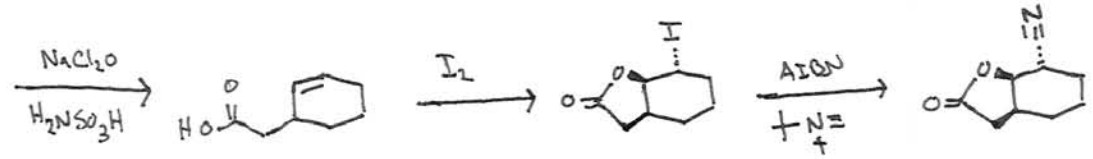


See exam #1

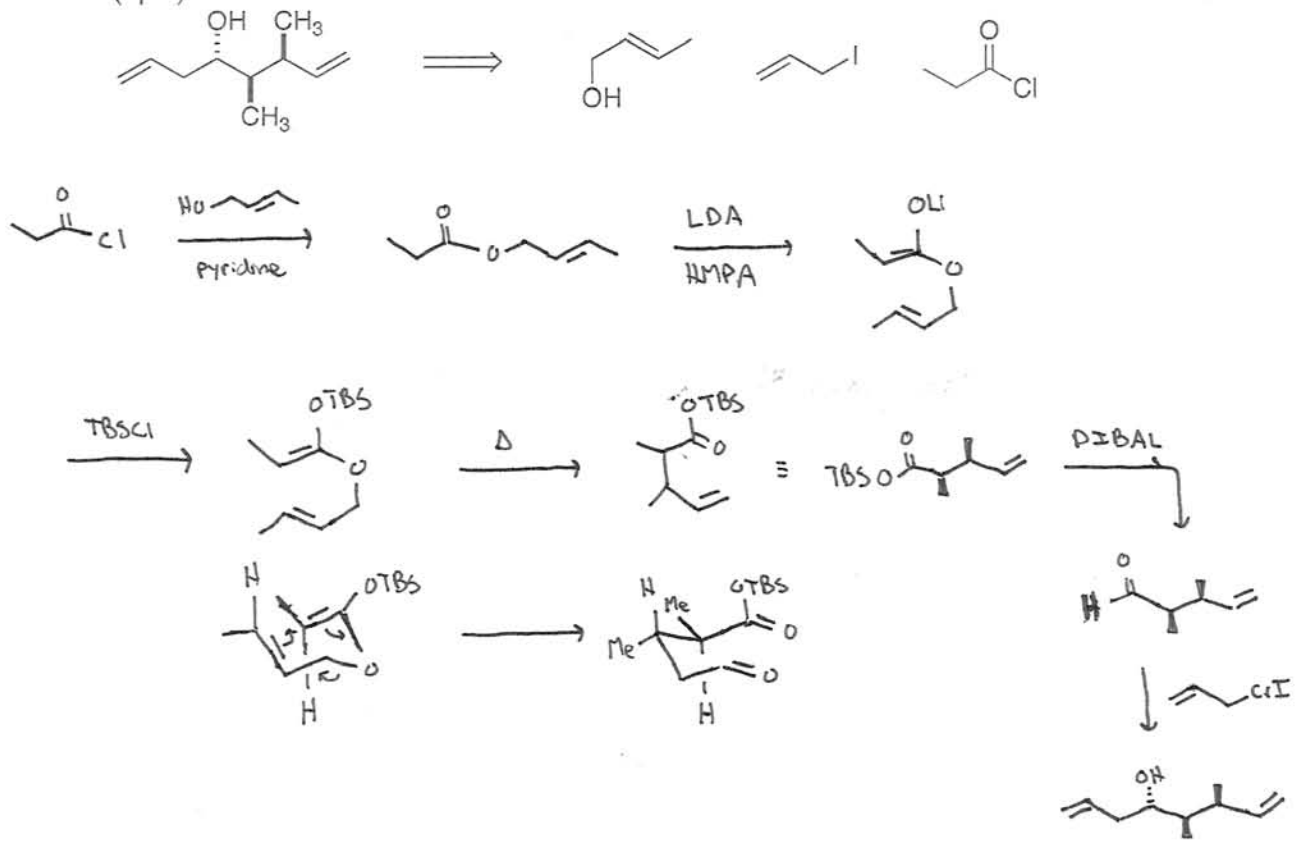
B. (8pts)





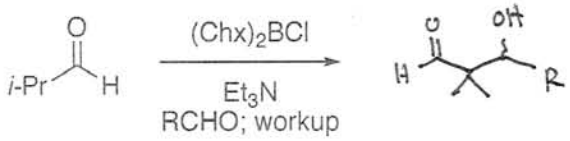


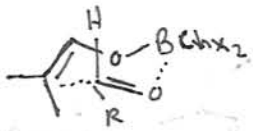
C. (8pts)



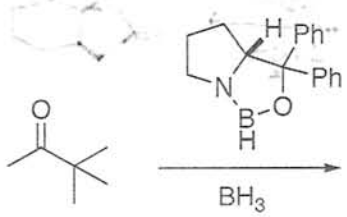
7. Give the product for each of the following. Use a 3D drawing that explains predicts stereochemistry (5pts each).

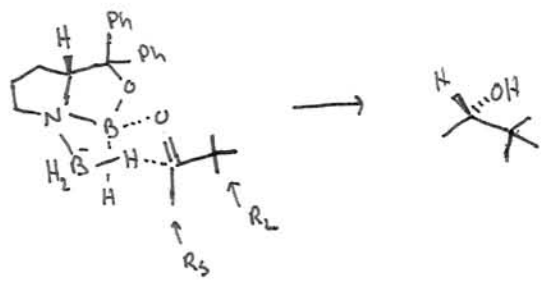
A.



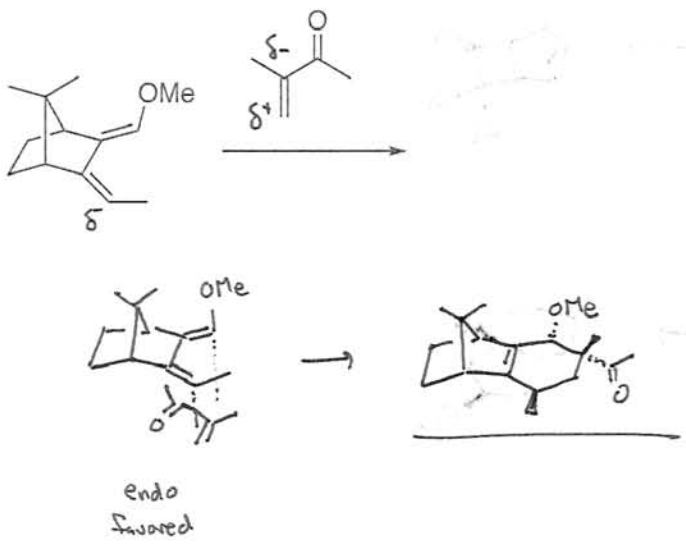


B.

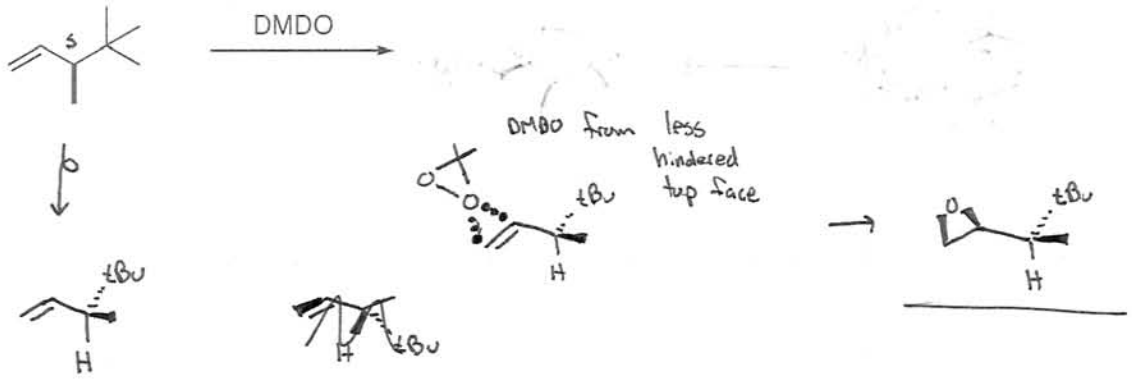




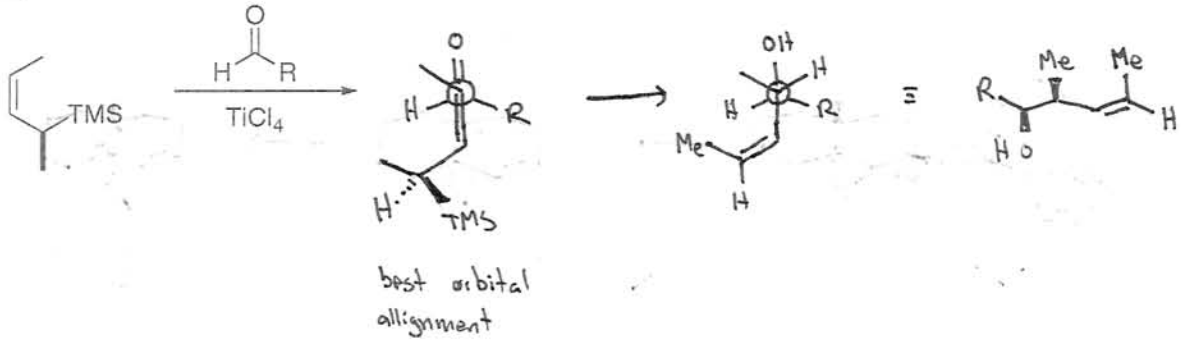
C.



D.

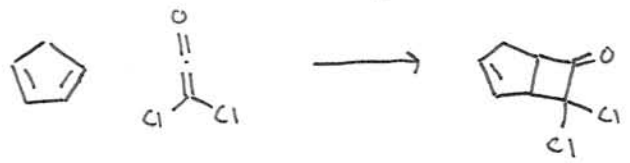


E.



8. Give an example of each of the following named reactions (3pts each)
   A. A 2,3 sigmatropic rearrangement

B. A 2+2 of a diene and a dichloroketene

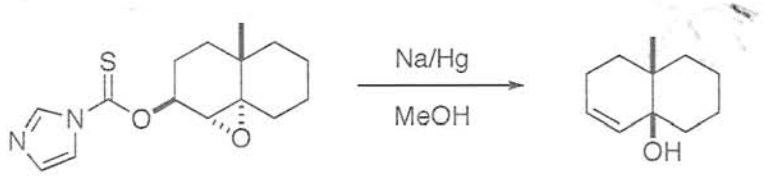


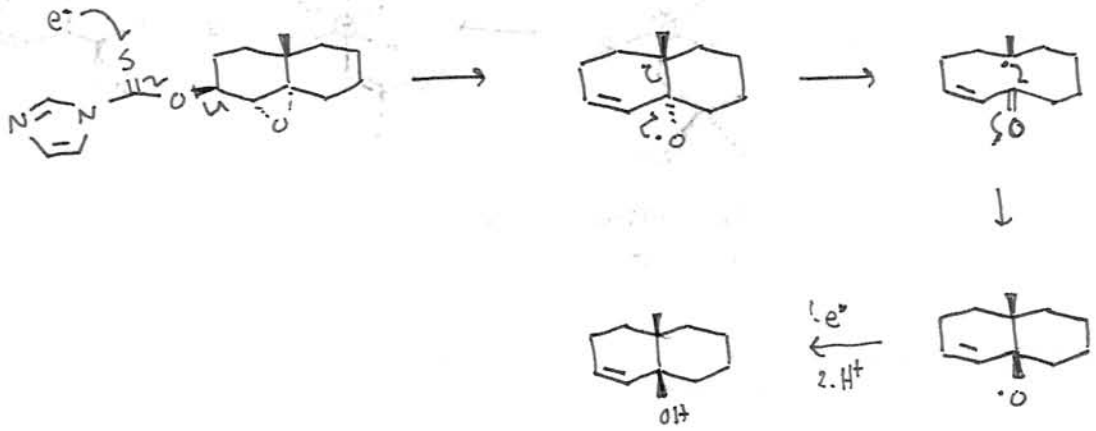
C. A 3+2 (other than ozone)

D. An ene reaction (other than S or Se)

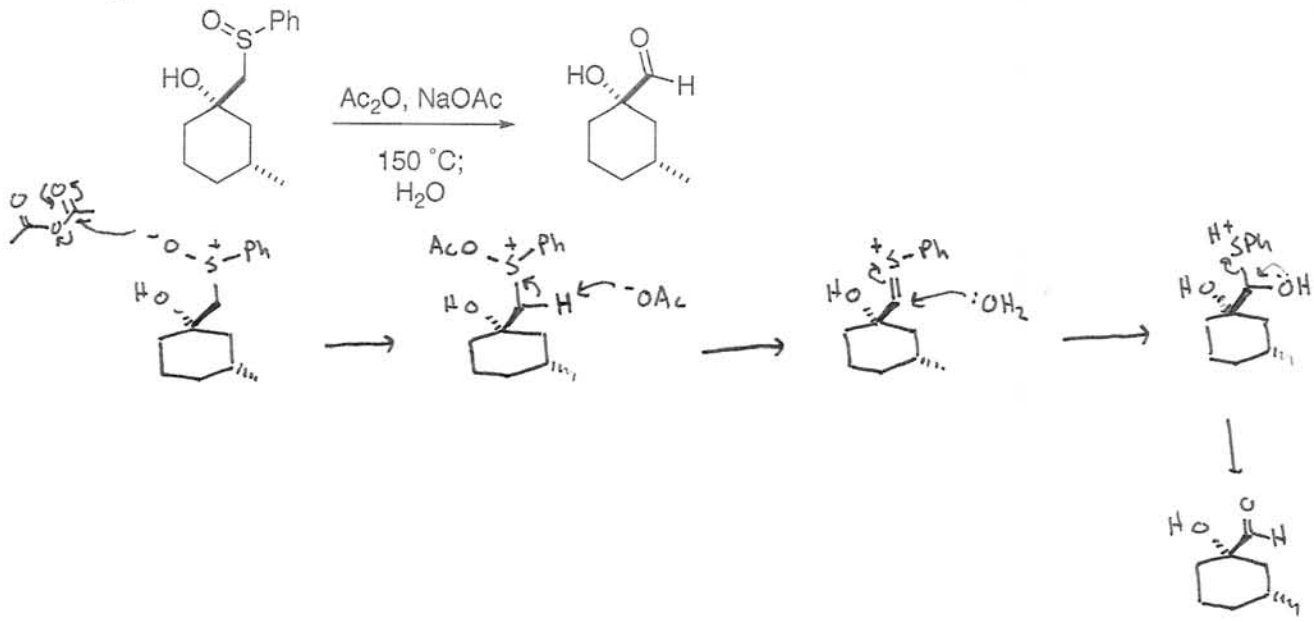
9. Give the mechanism for each of the following transformations (5pts each)

A.

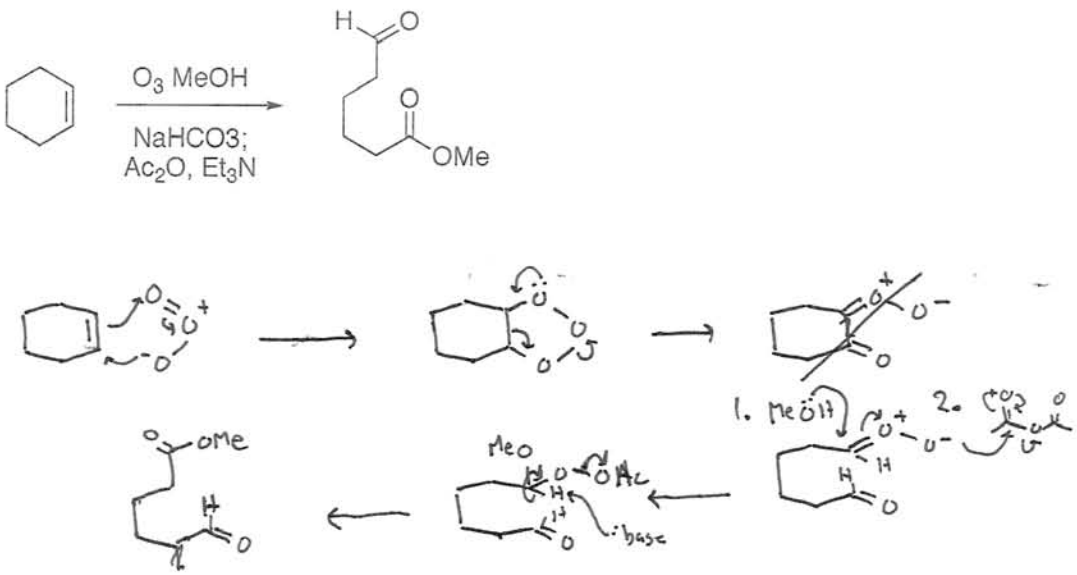




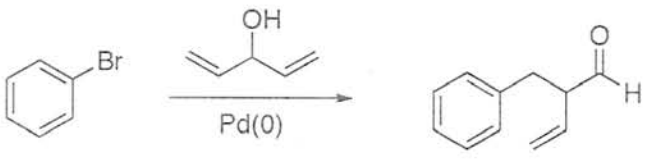
B.



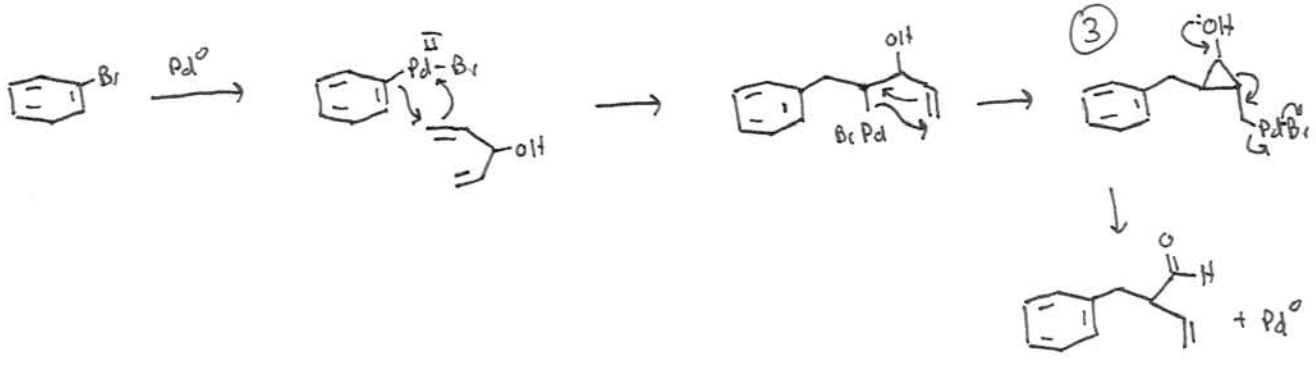
C.



D.



Hint: 3 membered ring intermediate



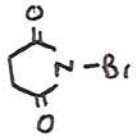
Show the mechanisms of the following transformations:

1. $ROH \xrightarrow{SOCl_2 + ZnCl_2} R\text{-}Cl$

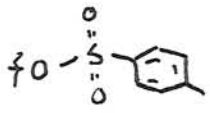
2. $ROH \xrightarrow{Ph_3P,\ CBr_4} R\text{-}Br$

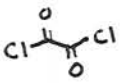
3. $RCH{=}CH_2 \xrightarrow[\text{free-radical initiator}]{HBr} RCH_2CH_2\text{-}Br$

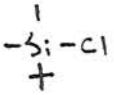
4. $RCH{=}CH_2 \xrightarrow[\text{b. } Br_2, NaOMe]{\text{a. } BH_3\cdot THF} RCH_2CH_2\text{-}Br$

5. alkene $\xrightarrow[\text{free-radical initiator}]{NBS}$ allylic bromide NBS = 

6. $RCH{=}CHCH_2OH \xrightarrow{NBS,\ Me_2S} RCH{=}CHCH_2Br$

7. $ROTs \xrightarrow{NaI} R\text{-}I$ OTs = 

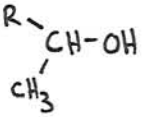
8. $RCH_2CONH_2 \xrightarrow[DMF,\ \text{acetonitrile}]{\text{oxalyl chloride}} RCH_2\text{-}CN$ oxalyl chloride = 

9. $RCH{=}NOH \xrightarrow[\text{imidazole}]{TBSCl} R\text{-}CN$ TBSCl =  imidazole = 

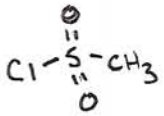
10. $R'_2C{=}O \xrightarrow[t\text{-}BuOK]{TsCH_2NC} R\text{-}CN$ VICIOUS!

11. $RCH_2COOH \xrightarrow{BH_3\ THF} RCH_2CH_2OH$

12. $RCH_2C{=}CH_2 \xrightarrow[\text{b. } NaOH,\ H_2O_2]{\text{a. } BH_3\ THF} RCH_2CH_2OH$

13. $RCH{=}CH_2 \xrightarrow[\text{b. } NaBH_4,\ NaOH]{\text{a. } Hg(OAc)_2,\ H_2O}$ 

14. $RCHO \xrightarrow[EtOH]{NH_3,\ NaBH_3CN} RCH_2NH_2$

15. $RCH_2OH \xrightarrow[\text{c. } Ph_3P,\ H_2O]{\text{a. } MsCl,\ \text{b. } NaN_3} RCH_2NH_2$ $\quad Ms\text{-}Cl =$ 

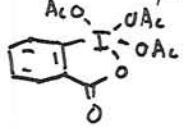
16. $DMF \xrightarrow[\text{b. } H_3O^+]{\text{a. } RCH_2MgX} RCH_2CHO$

17. $RCH_2CH_2OH \xrightarrow[\text{or Dess-Martin}]{PCC,\ Swern,} RCH_2CHO$

show all three mechanisms

17. PCC = pyridinium chlorochromate $C_5H_6NClCrO_3$

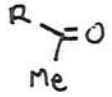
18. Swern = trifluoroacetic anhydride, DMSO

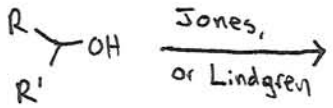
19. Dess-Martin = Periodinane 

20. $RCH_2COCl \xrightarrow{H_2,\ Pt/BaSO_4} RCH_2CHO$

21. $RCH_2CN \xrightarrow[\text{b } H_3O^+]{\text{a. } iBu_2AlH} RCH_2CHO$

22. $RCOCl \xrightarrow[\text{b. } H_3O^+]{\text{a. } Me_2CuLi}$ 

23. $RC{\equiv}CH \xrightarrow{HgSO_4,\ H_3O^+}$ 

24. 

25. Jones = CrO_3 or $Cr_2O_7^{-2}$ / acid

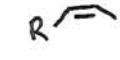
26. Lindgren = $NaClO_2$, H_2O

26. $RCH_2COOR' \xrightarrow[\text{b. } H_3O^+]{\text{a. } LiOH,\ THF/H_2O} RCH_2COOH$

27. $RCH_2Ph \xrightarrow{RuO_4} RCH_2COOH$

28. $RC(O)CH_3 \xrightarrow{LiOCl,\ chlorox} RCOOH$

29. $R\text{-}X$ or $R\text{-}OTs \xrightarrow{tBuOK,\ or\ DBU}$ alkene

30. $RC{\equiv}CR' \xrightarrow[H_2]{Lindlar\ cat.}$ 

31. $RCHO$ or $R_2CO \xrightarrow{\text{Wittig}}$ alkene

32. $HC\equiv CH \xrightarrow[\text{b. R-Br (1° only)}]{\text{a. nBuLi}} RC\equiv CH$

33. $RCHO \xrightarrow[t\text{BuOK}]{(MeO)_2P(O)CHN_2} RC\equiv CH$

or

a. CBr_4, Ph_3P, Zn dust; nBuLi

b. H_2O

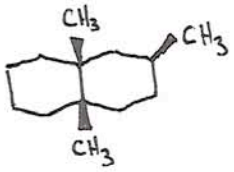
33. $(MeO)_2P(O)CHN_2$ = Seyferth - Gilbert Ohira & Bestmann modification

34. CBr_4, Ph_3P, ... = Corey - Fuchs

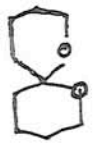
Problem Set 2

- Also do the questions in Chapters 2 and 3 of the text
- Draw bond angles in boats, chairs, etc. accurately. ~~and~~ All rings should be in 3D
- Wrong enantiomer = no credit
- Do not work with others. You must hand-draw your answers.

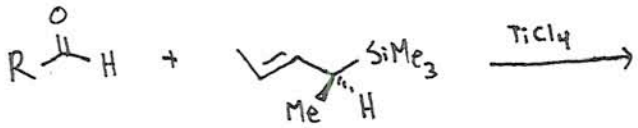
1. Draw both chair-chair forms of the following compound:



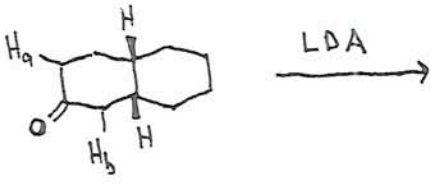
2. Draw the preferred conformation of the spiroketal shown below:

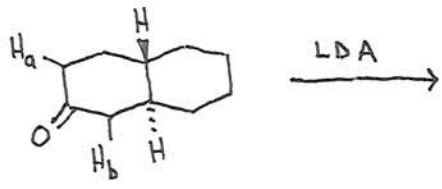


3. Draw the transition state and major product that results from the following reaction:

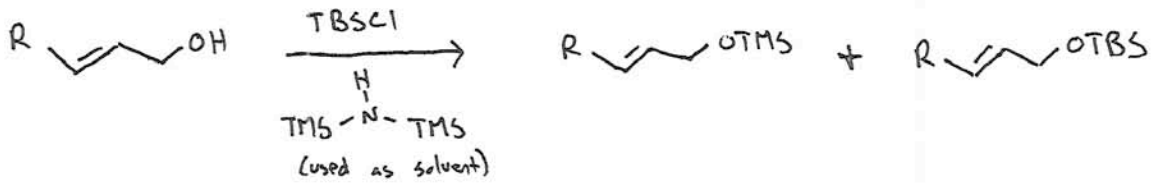


4. Draw the transition state that illustrates the selectivity in deprotonation of the following compounds:





5. The reaction shown below resulted in a mixture of two products. Give a mechanism that explains this result.



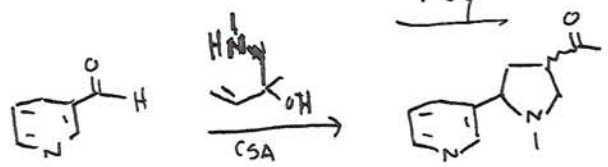
6. Give the mechanism for each of the named reactions. Use real molecules / examples (no "R", etc.).

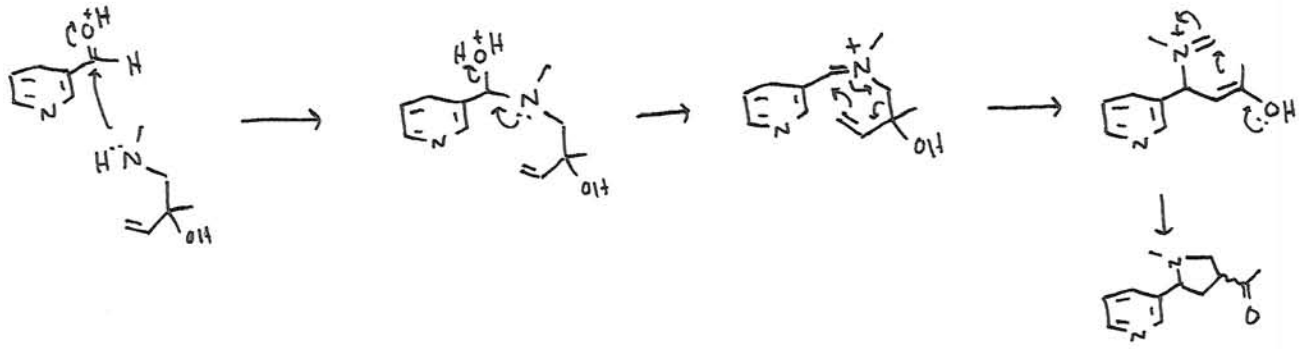
a. Clemmensen Reduction
b. Wolff- Kishner
c. Bamford- Stevens

Key

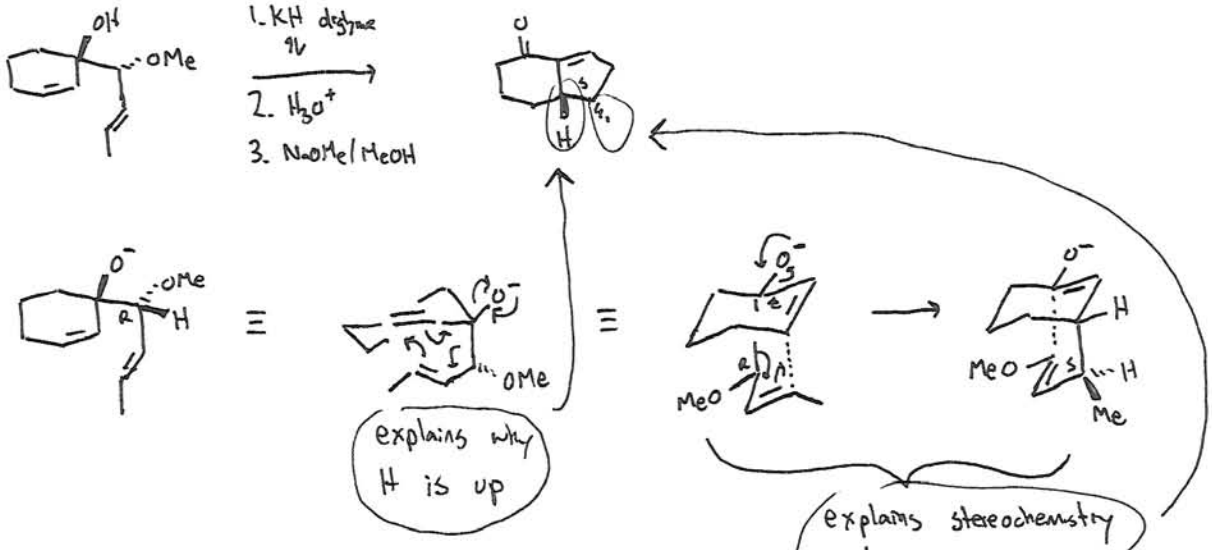
Hand written questions:

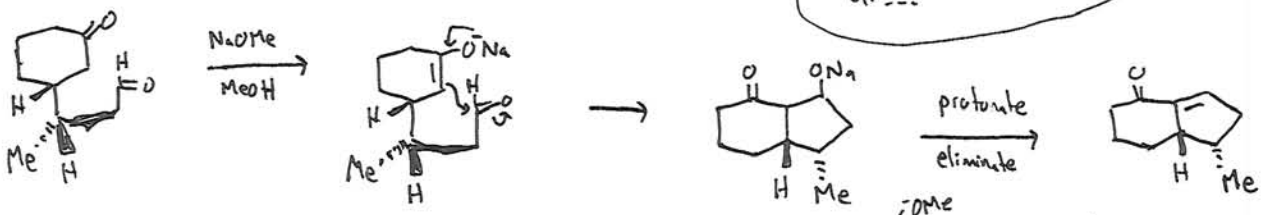
1.

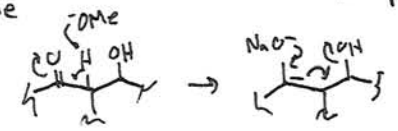




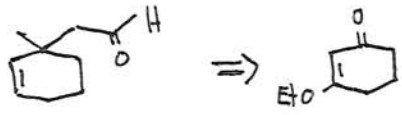
2.

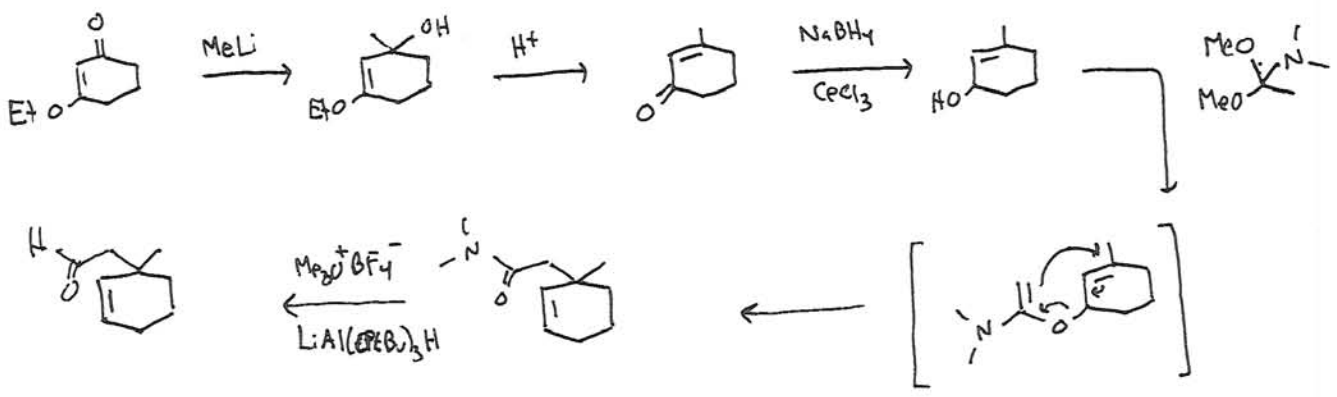




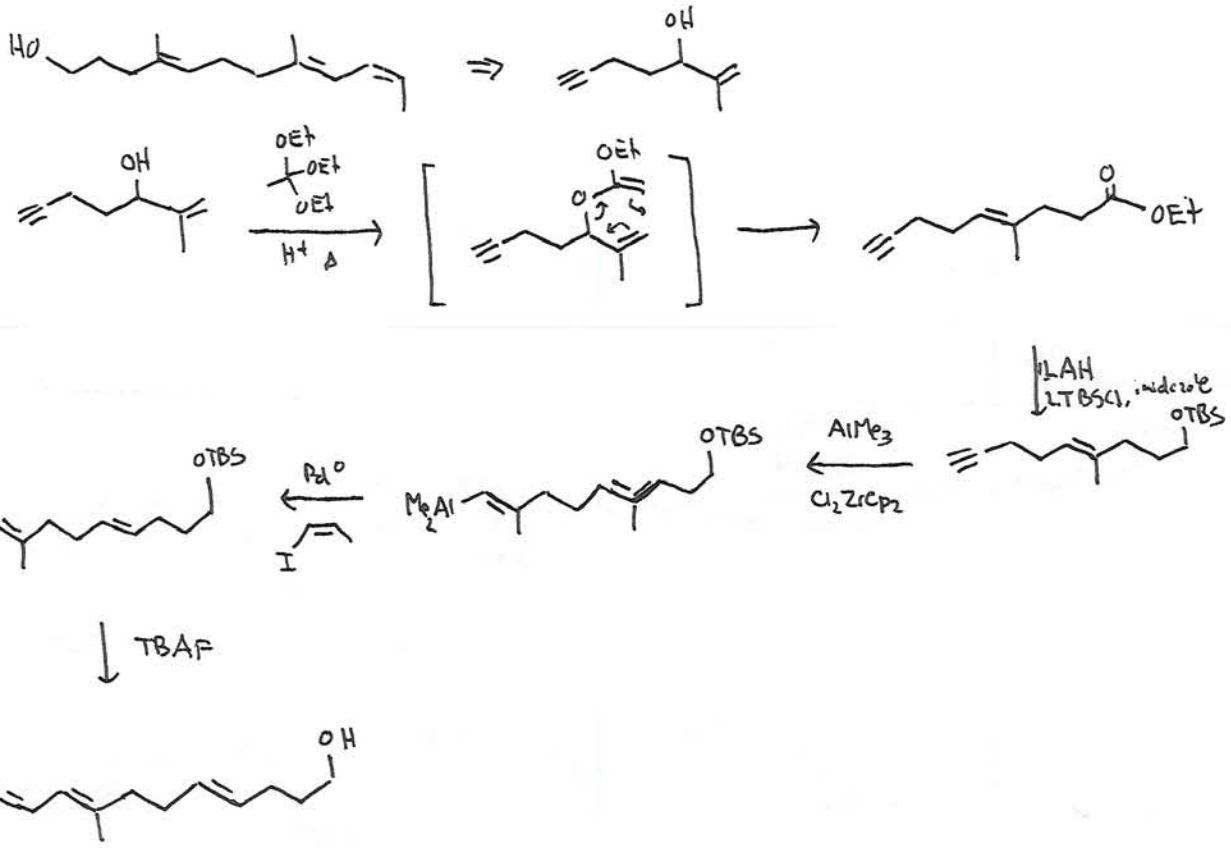


3.

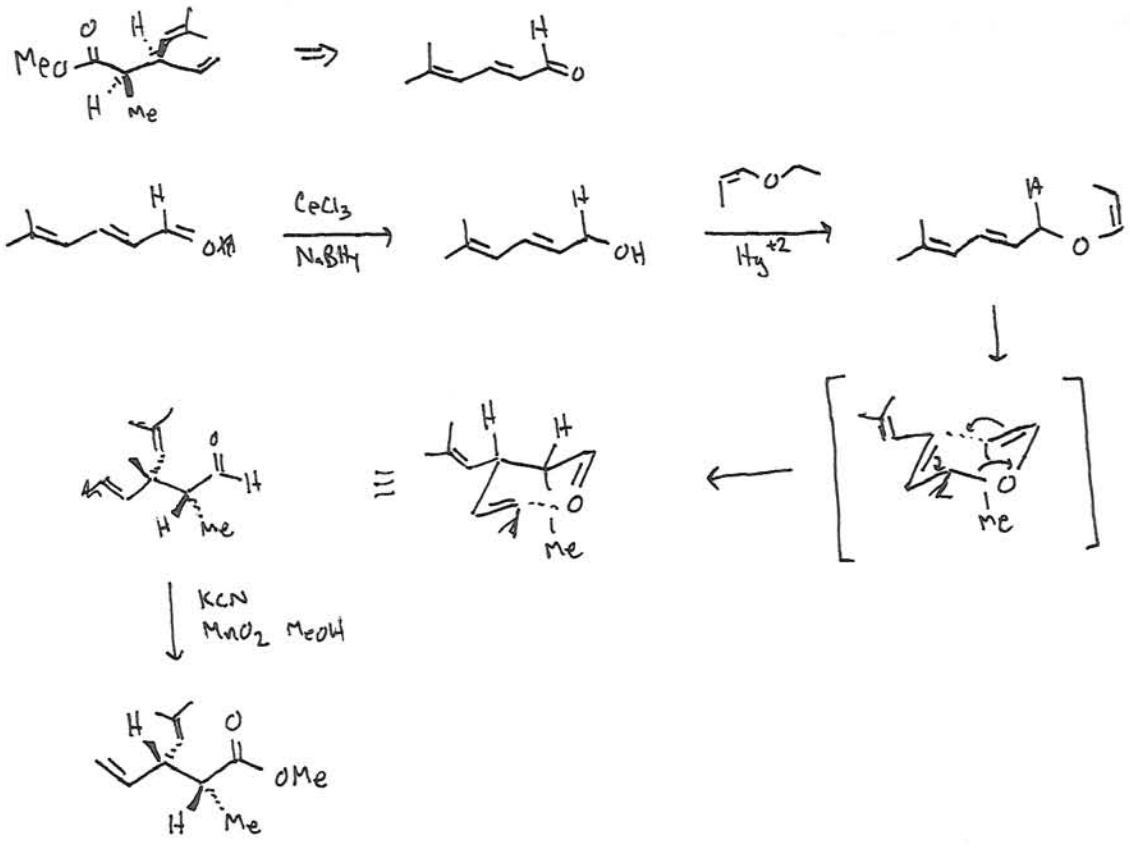




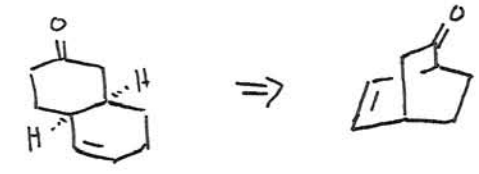
4.

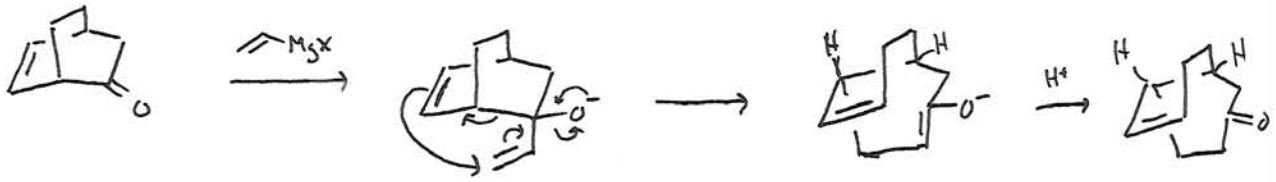

HO
OH
OEt
OEt
OEt
H+ Δ
O
OEt
1. LAH
2. TBSCl, imidazole
OTBS
AlMe3
Cl2ZrCp2
Me2Al
OTBS
Pd°
I
OTBS
TBAF
OH

5.

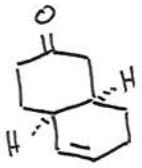

MeO
O
H
H
Me
CeCl3
NaBH4
OH
Hg+2
O
O
H
Me
KCN
MnO2 MeOH
OMe
H
Me

6.

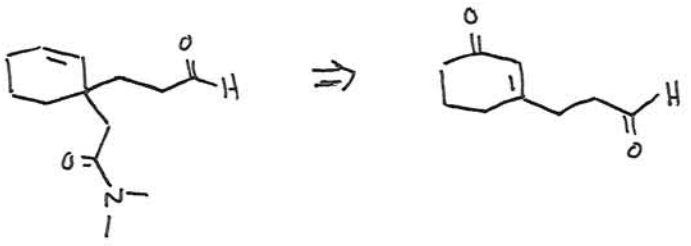


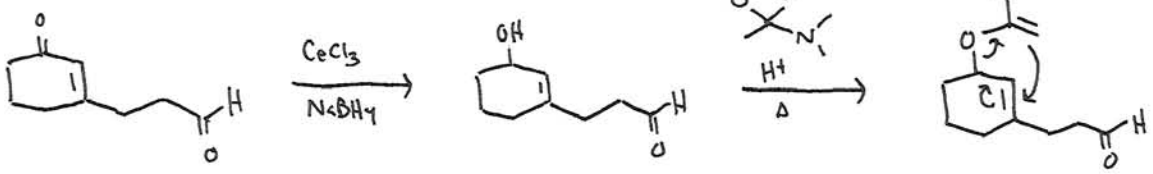


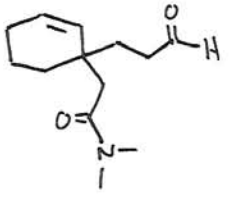
III



7.

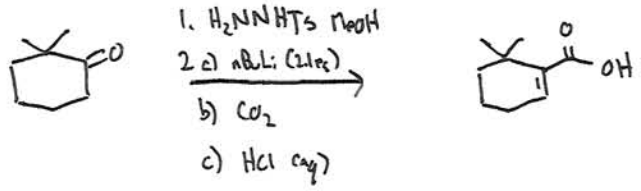




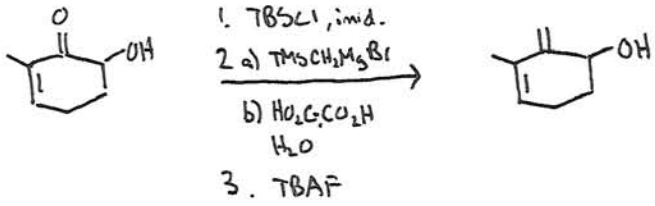


Answers to questions in text (Chapter 8)

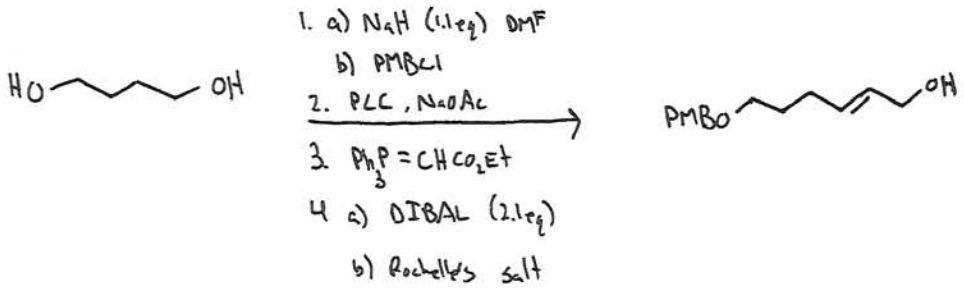
1. b)



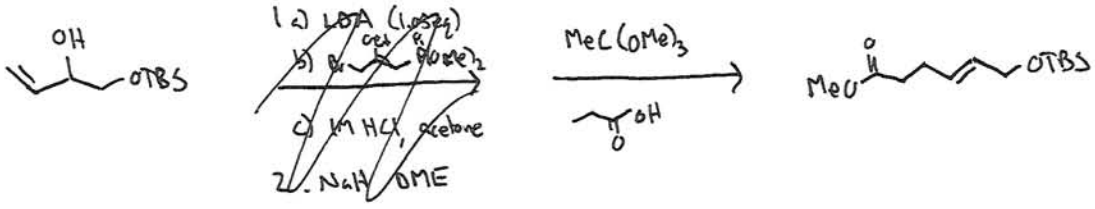
d)



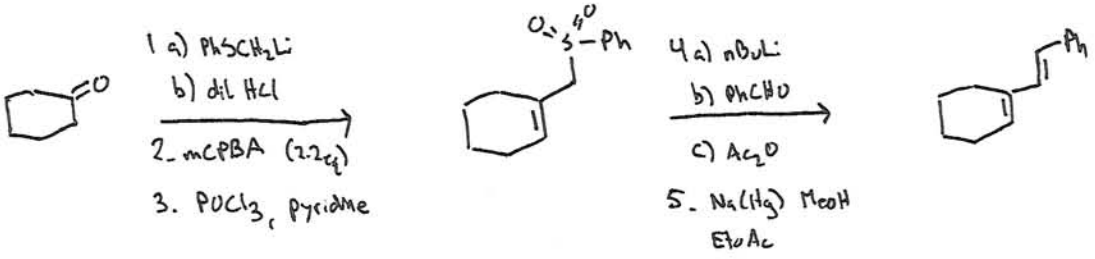
f)



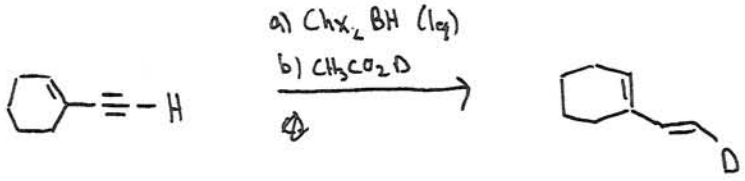
h)



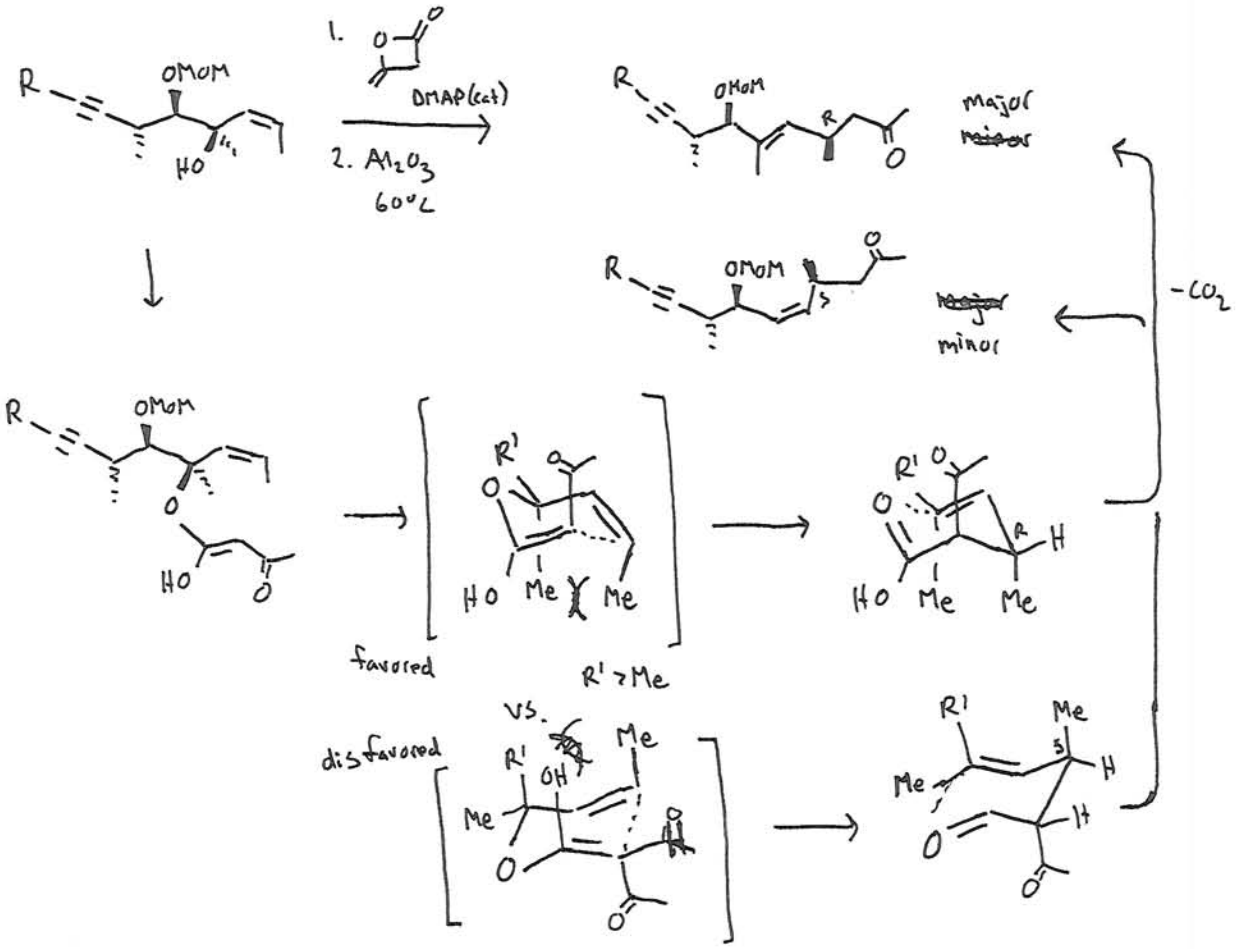
j)



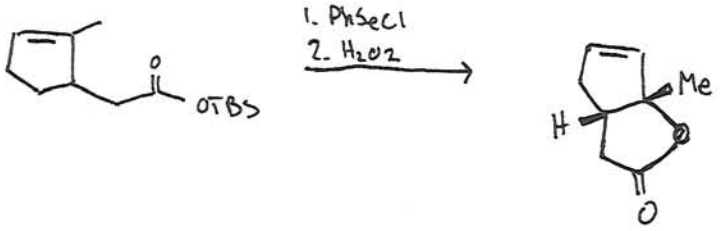
2. d)



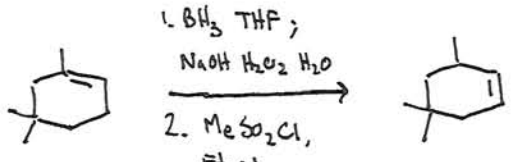
3. b)

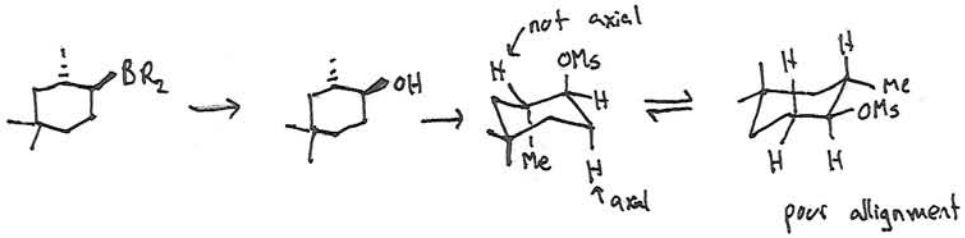

1.
DMAP(cat)
2. Al_2O_3
60°C
OMOM
R
HO
major
minor
$-CO_2$
favored
disfavored
vs.
$R' > Me$
Me
OH
H

d)

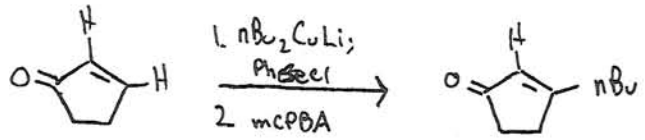

1. PhSeCl
2. H_2O_2
OTBS
Me
H

9. a)

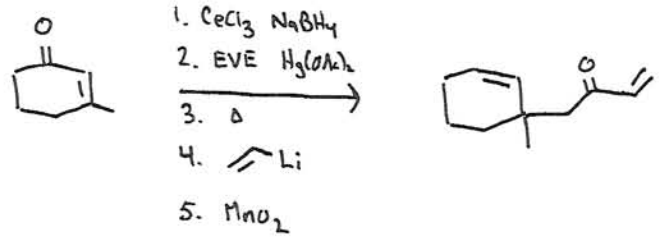

1. BH_3 THF;
$NaOH$ H_2O_2 H_2O
2. $MeSO_2Cl$,
Et_3N


BR_2
OH
not axial
OMs
H
Me
axial
poor alignment

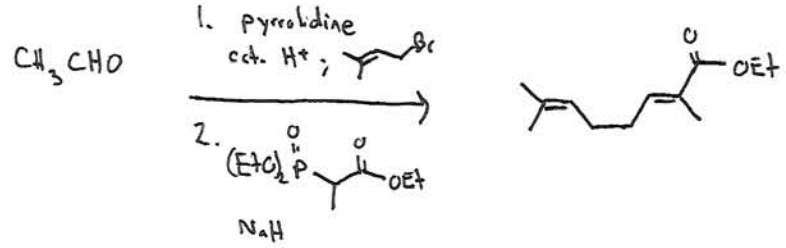
5. b)


1. nBu_2CuLi;
PhSeCl
2. mCPBA
nBu

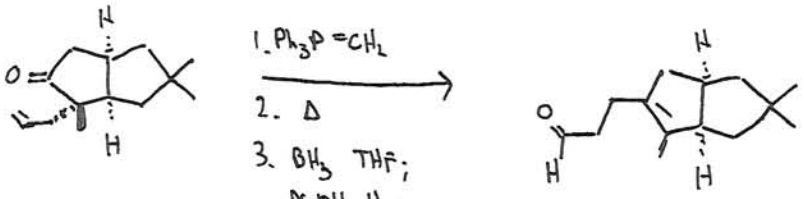
d)


1. $CeCl_3$ $NaBH_4$
2. EVE $Hg(OAc)_2$
3. Δ
4. Li
5. MnO_2

e)

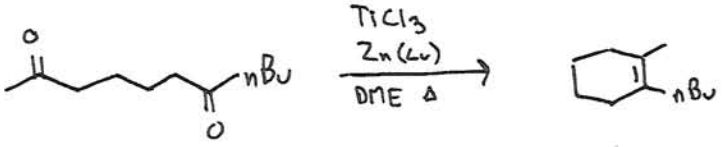

CH_3CHO
1. pyrrolidine
cat. H^+;
Br
2.
$(EtO)_2P$
OEt
NaH
OEt

h)

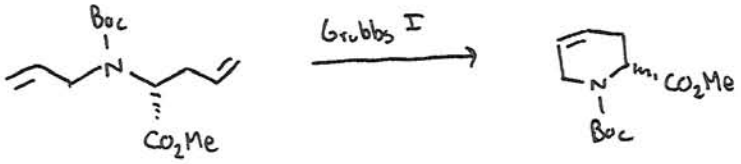

1. $Ph_3P=CH_2$
2. Δ
3. BH_3 THF;
$NaOH$ H_2O_2
4. DMP

Key to Chapter 9 problems

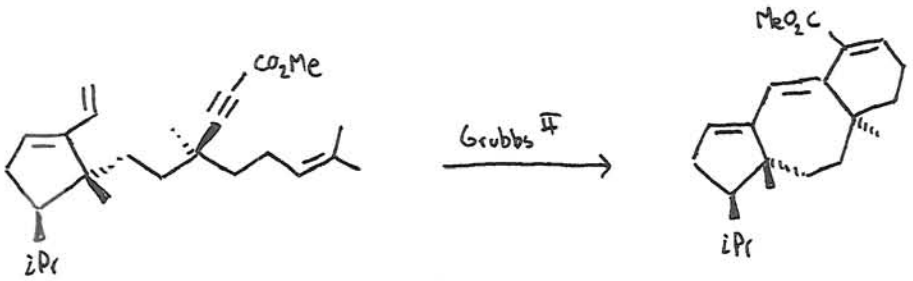
1. b)



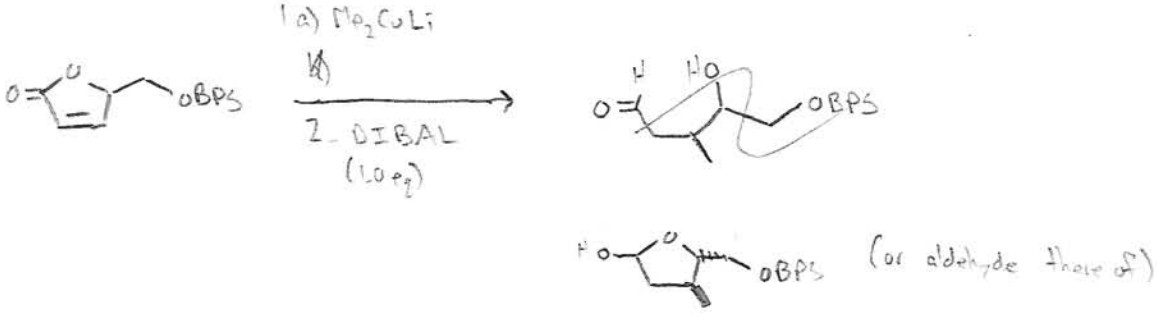
f)



2. d)

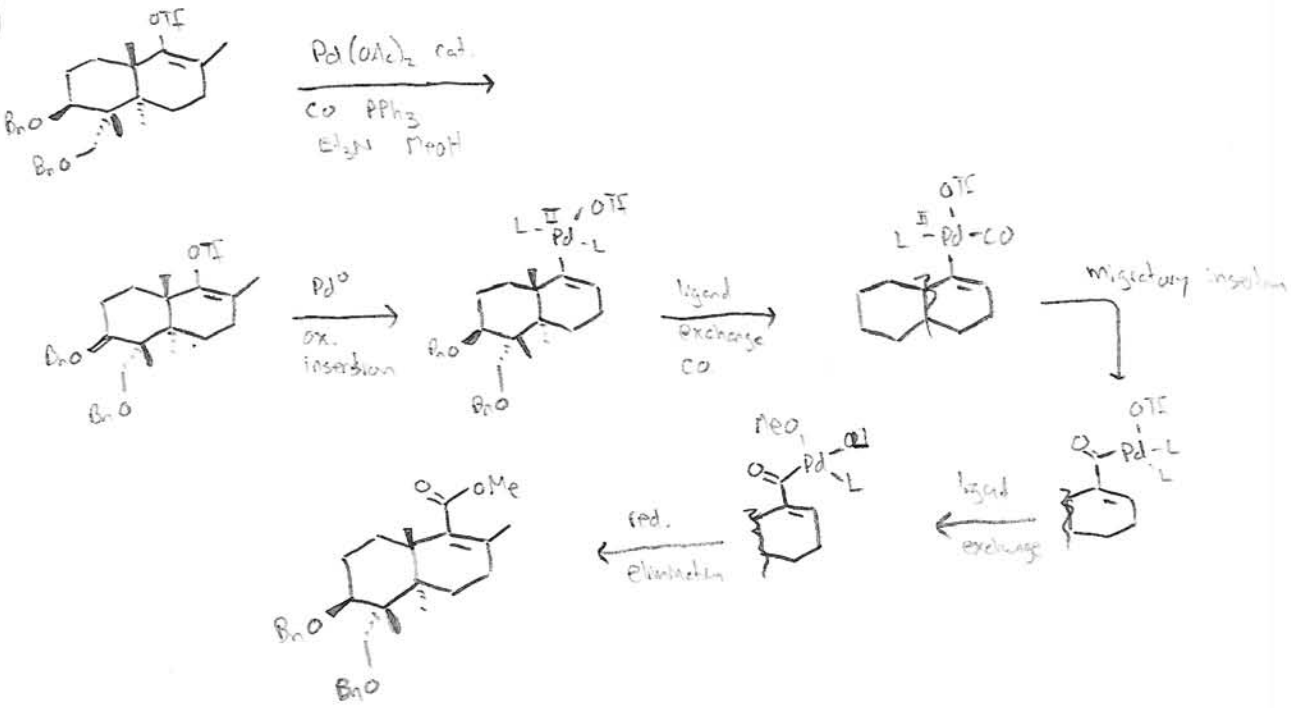


1b)

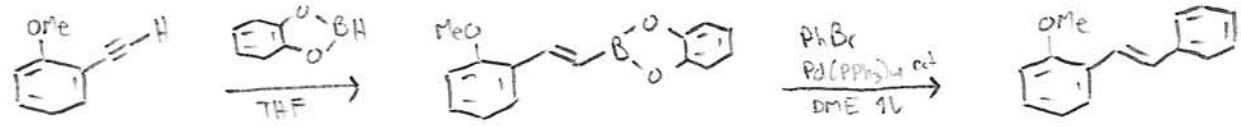


(or aldehyde there of)

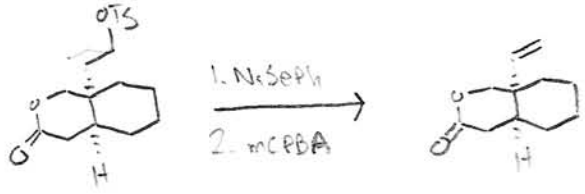
d)



g)



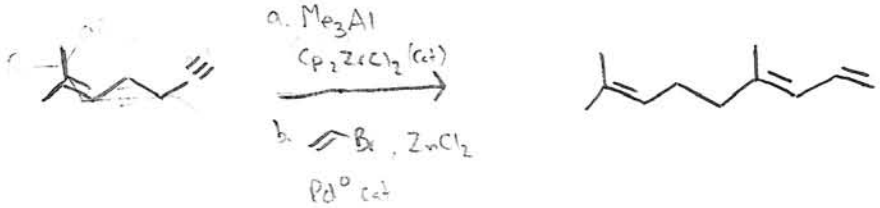
m)



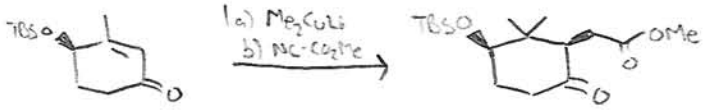
2. a)

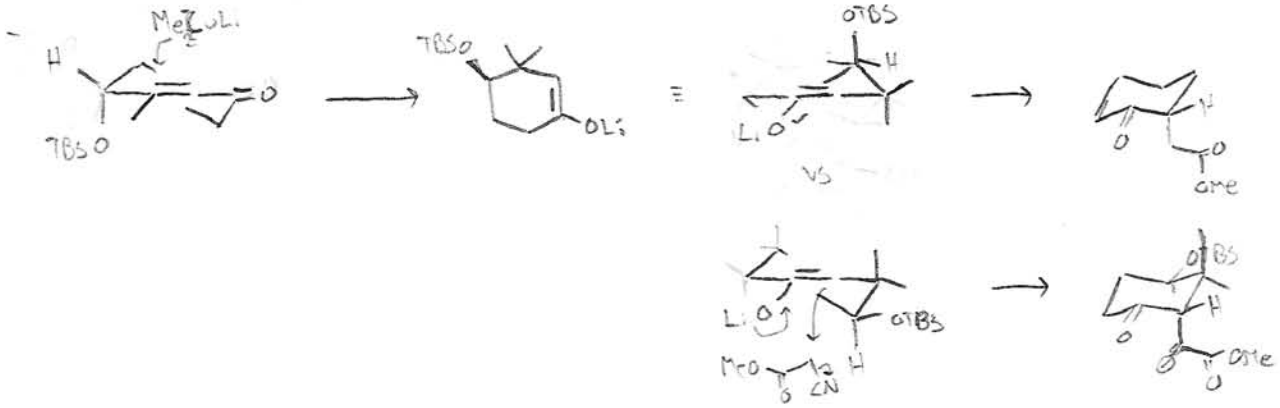

MeTi(OiPr)3
HO

3 b)

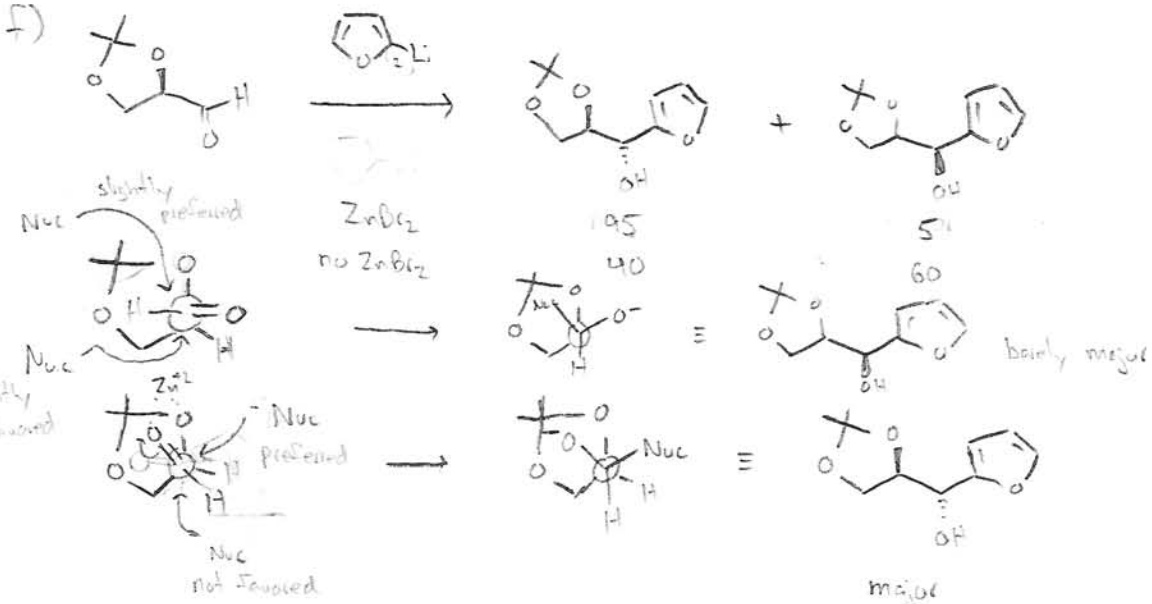

a. Me3Al
Cp2ZrCl2 (cat)
b.
Br , ZnCl2
Pd° cat

d)


TBSO
1a) Me2CuLi
b) NC-CO2Me
TBSO
OMe
O


Me2CuLi
H
TBSO
O
TBSO
OLi
OTBS
H
Li O
vs
OMe
Li O
OTBS
MeO
CN
OTBS
H
OMe

f)

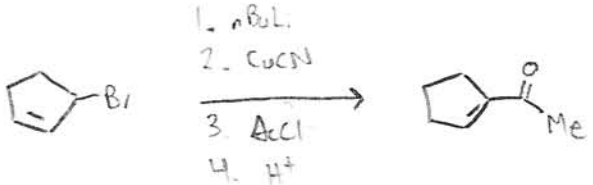

H
Li
ZnBr2
no ZnBr2
95
40
5
60
slightly preferred
Nuc
Nuc
slightly disfavored
Zn+2
Nuc
preferred
H
Nuc
not favored
Nuc
H
H
OH
OH
barely major
major

4 c)

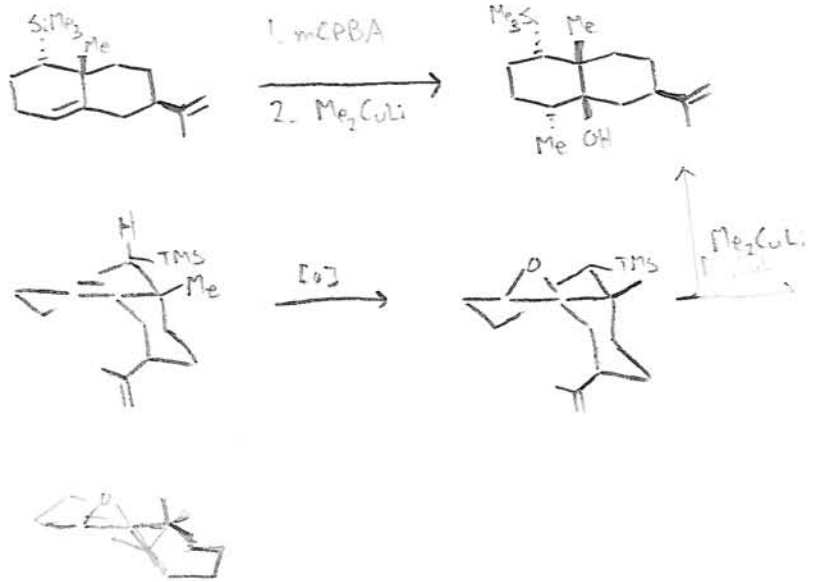

F⁻
SiMe3
TBAF
DMF, HMPA
Me
H
O


O
favored
SiMe3
H
O

5 b)

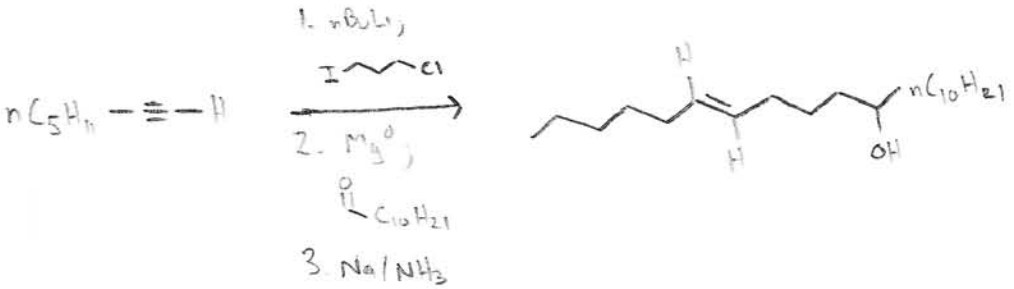

Br
1. nBuLi
2. CuCN
3. AcCl
4. H+
O
Me

f)

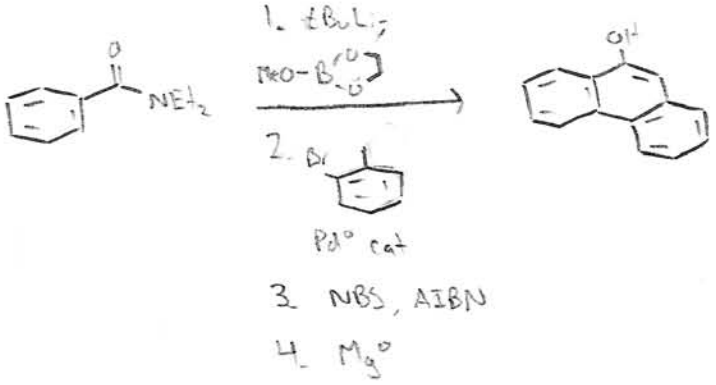

SiMe3
Me
1. mCPBA
2. Me2CuLi
Me3Si
Me
Me
OH
H
TMS
Me
[O]
O
TMS
Me2CuLi

O

h)

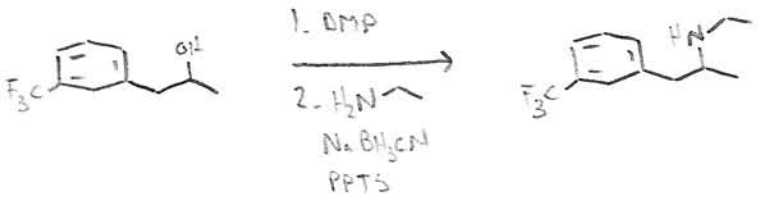

nC5H11
H
1. nBuLi,
I
Cl
2. Mg⁰,
O
C10H21
3. Na/NH3
N
nC10H21
H
OH

5 j)

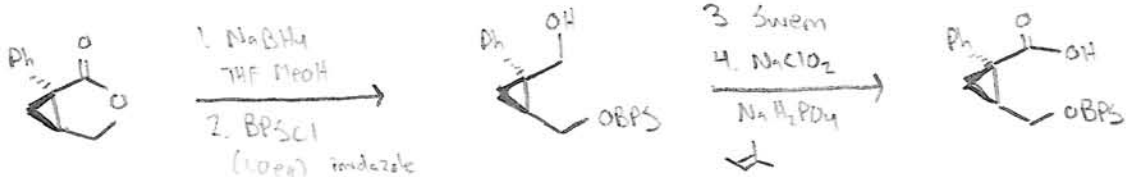


Chapter 4

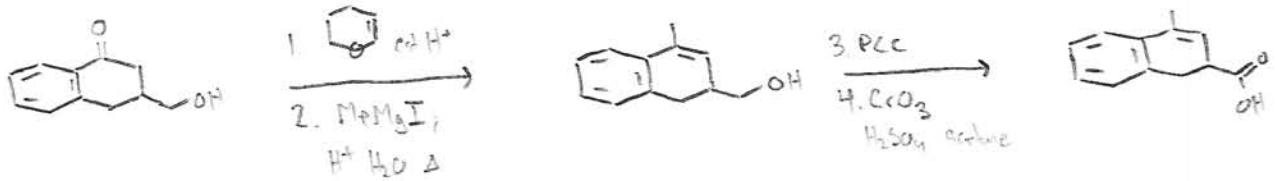
1 a)



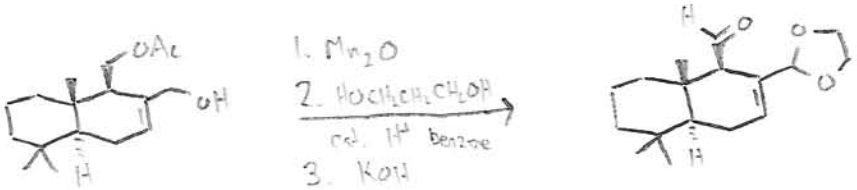
c)



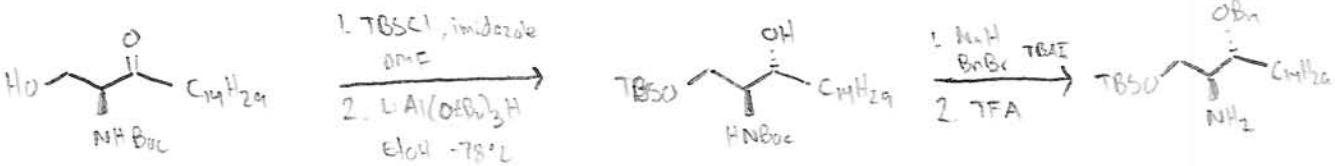
e)



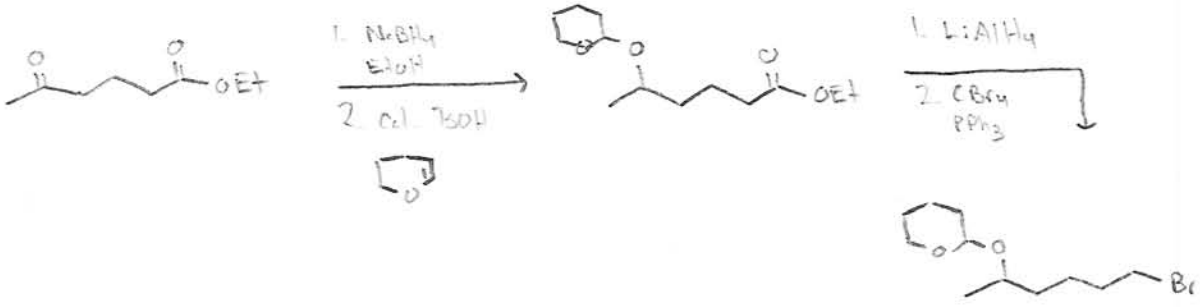
g)



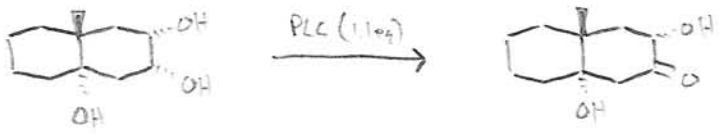
h)

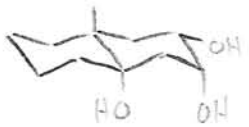


2. b)



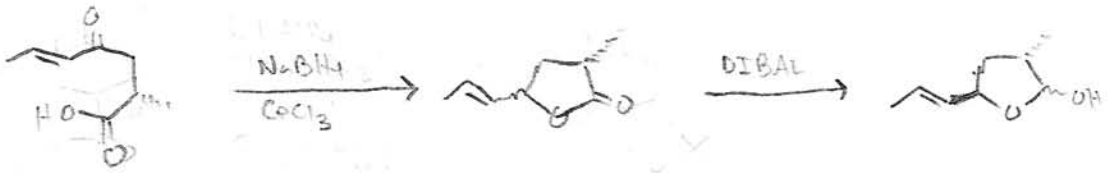
2. d)



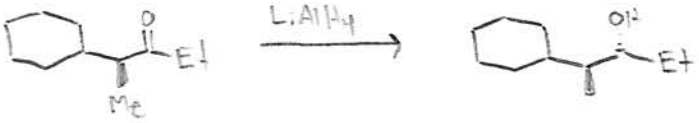


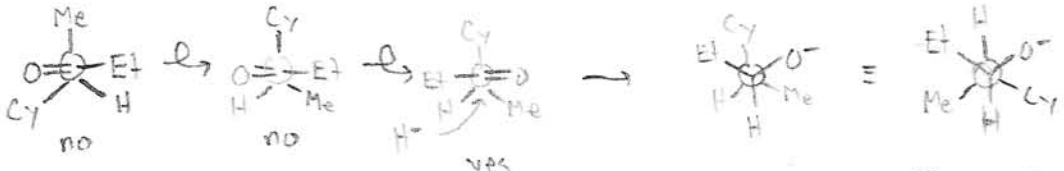
axial -OH oxidizes faster than equatorial (relieve strain)

f)



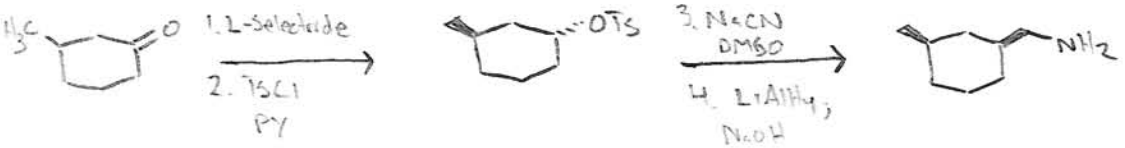
3. a)



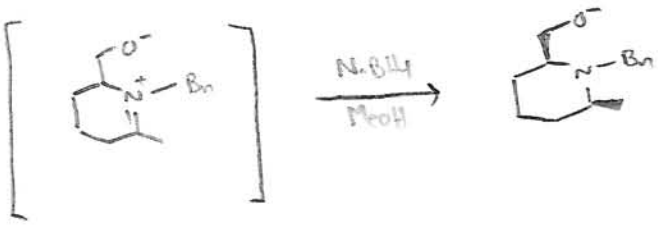


OH and Me are anti

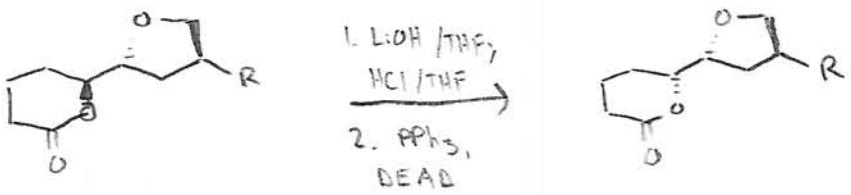
e)



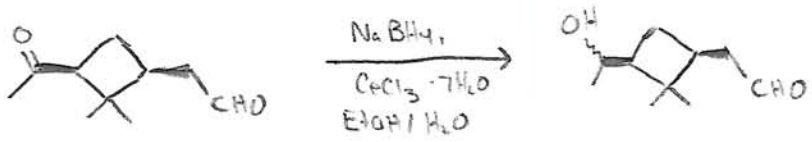
g)



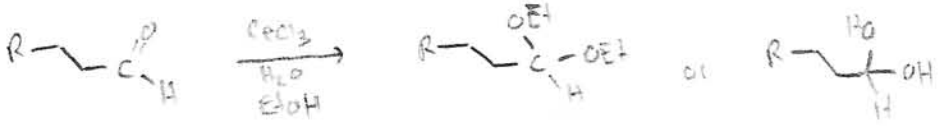
3 i)



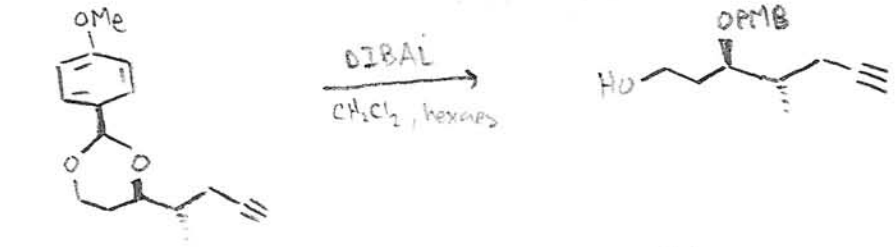
4 b)

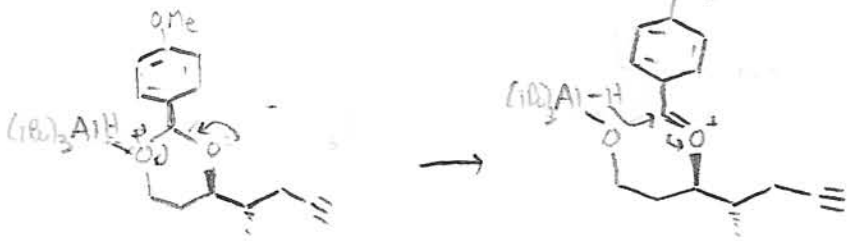


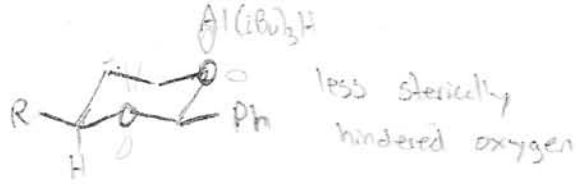
The acetal is formed (from the aldehyde) in the presence of $CeCl_3$ and is favored by the presence of water



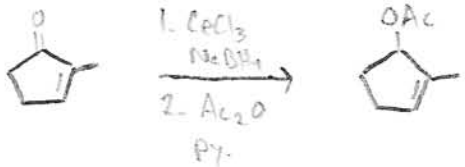
d)



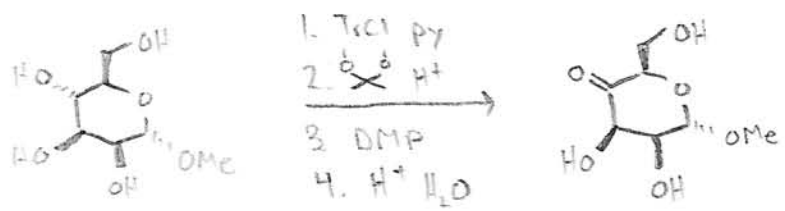




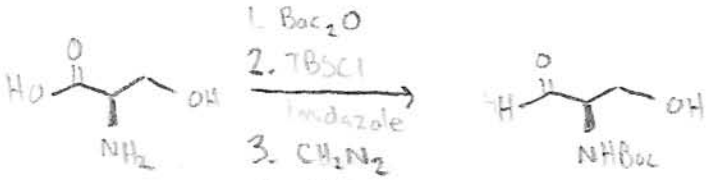
5 b)


1. $CeCl_3$
$NaBH_4$
2. Ac_2O
Py.
OAc

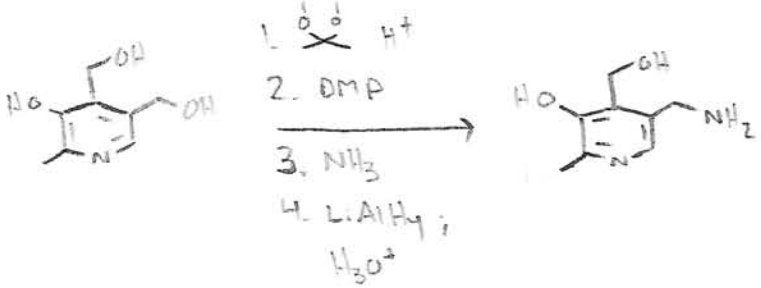
e)


1. TsCl Py
2. H^+
3. DMP
4. H^+ H_2O
OMe
OMe

g)


1. Boc_2O
2. TBSCl
Imidazole
3. CH_2N_2
4. DIBAL
5. TBAF
NH_2
NHBoc

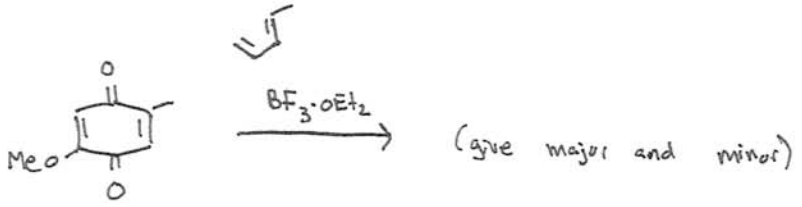
i)


1. H^+
2. DMP
3. NH_3
4. $LiAlH_4$;
H_3O^+

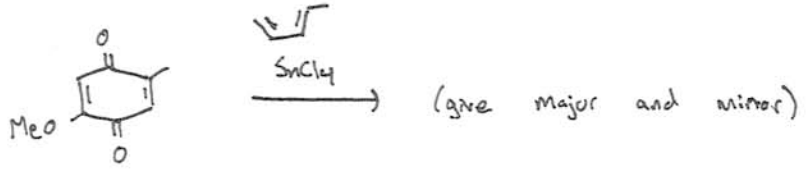
Final Problem Set (Hand written portion)

Give the product for each of the following. Include a drawing or explanation for the stereochemistry of your answer. Wrong enantiomer = no credit

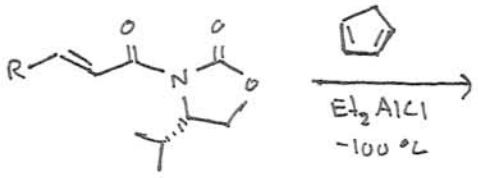
1. a)



b)

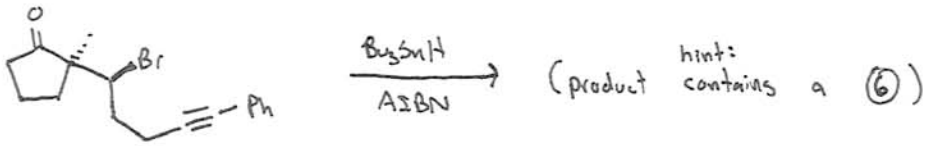


2.

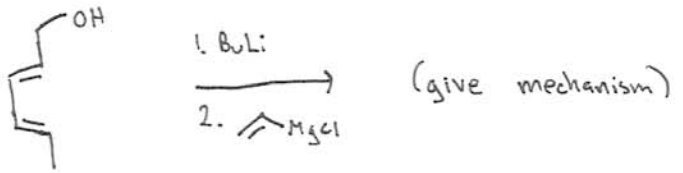


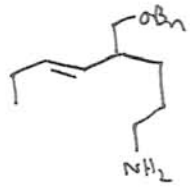
3.

4.

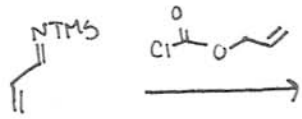


5.

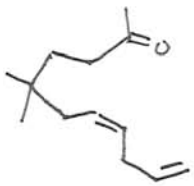


6. 

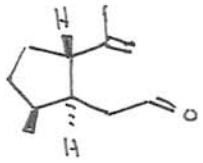
HCHO (aq)
65°C
(give major and minor)

7. 

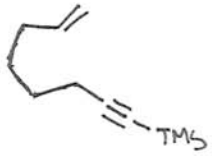
(give intermediate) xylenes, reflux

8. 

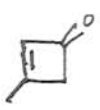
335 °C
60 hrs
(give mechanism)

9. 

$SnCl_4$

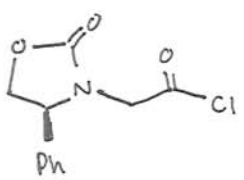
10. 

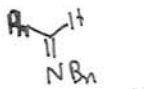
1. $sBuLi$
2. $ZnBr_2$
(Hint: allenyl intermediate)
(give mechanism)

11. 

Me–≡–OMe
benzene
1V

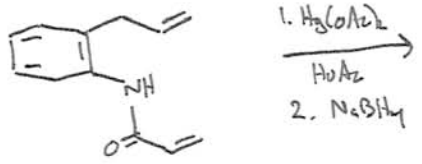
12. 

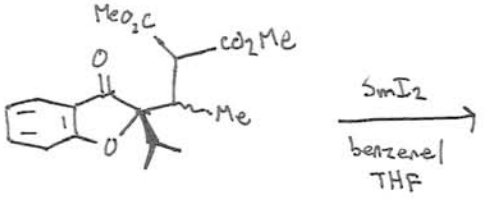


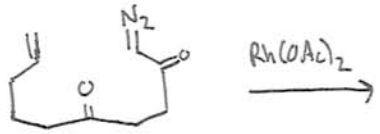


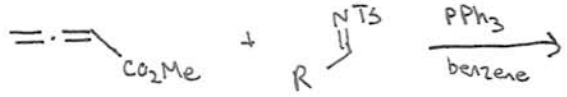
Et_3N
CH_2Cl_2

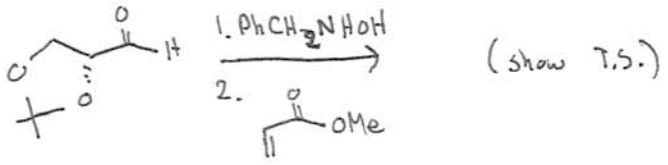
13. 

14. 

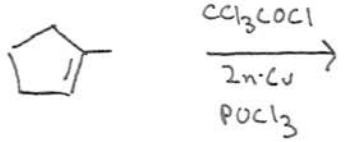
15. 

16. 

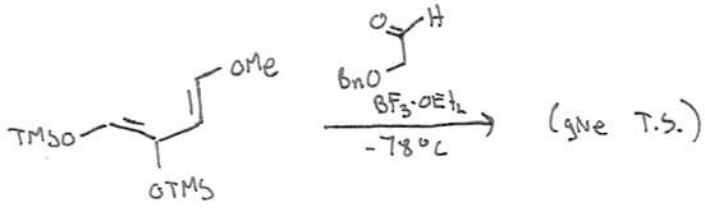
17. 

18. 

(show T.S.)

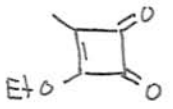
19. 

20.



(gNe T.S.)

21.



1. R−≡−Li
2. H^+
3. benzene ⅂

22.